Synthetic Biology in a Fractiversal World:

On Novel Biologies and Modest Geographies

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

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Abstract

The object of inquiry of this thesis is synthetic biology. In this thesis I ask what is this 'thing' that is synthetic biology (Latour, 2005) and what might it mean for synthetic biology to inhabit the world and to inhabit it well? Synthetic biology's coming into being has been accompanied by a considerable amount of 'hype' and 'hyperbole' (Marris and Rose, 2012) – by what the philosopher Annemarie Mol (1999) would describe as a noisy 'perspectivalism.' My aim in this thesis is to contribute to the telling of different kinds of less-perspectival and less-technologically-deterministic stories about the development of this burgeoning approach to biological engineering. In drawing on a combination of empirical material from over 30 1-2 hour interviews with leading synthetic biologists and ethnographic materials generated from working alongside the UK's Health and Safety Executive (the UK regulatory authority responsible for overseeing the development of synthetic biology), I aim to multiply outwards registers for understanding what synthetic biology is and what it might become. I highlight, for example, how synthetic biology is not simply a hubristic endeavour (Lewens, 2013) but is also about processes of learning and apprehension. What's more, depending on how synthetic biology takes shape(s) in different practices, 'time' also becomes aleatory and freed from its modernist shackles (Serres, 2008). I use the lens of regulation as a means of addressing the question of what it might mean for synthetic biology to inhabit the world well. Synthetic biology's regulatory provocations have been largely underexplored within STS and human geography literatures. The thesis is informed by and builds upon, theoretical notions of multiplicity (Mol, 2002) and of syncretisms (Law and Mol, 2013). The thesis contributes to a broader shift in social theory from critique towards compositionism and concludes by arguing for the development of a modest geography of novel biologies.

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ANT	Actor Network Theory
BAU	Biological Agents Unit
FFI	Fee for Intervention
FMDV	Foot and Mouth Disease Virus
GM	Genetic Modification
GMO	Genetically Modified Organism
HID	Hazardous Installations Directorate
HSE	Health and Safety Executive
SFAIRP	'So Far as is Reasonably Practicable'
STS	Science and Technology Studies

Chapter One

Introduction

1. Synthetic Biology – Beyond the ‘Hype’ and ‘Hyperbole’

Synthetic biology is a developing approach to biological engineering that promises to heal us, feed us and fuel us (Nature Reviews Microbiology, 2014). It is an emergent modality of scientific practice that aspires to bring an engineering approach to bear on the ‘design and construction of new biological parts, devices and systems’ (Schmidt, 2009 in Bailey et al 2012: 1). Synthetic biology practitioners are working to create novel genetic parts and devices and to redesign existing natural biological systems for useful purposes (NRM, 2014). The concepts of modularity, standardisation and interoperability are routinely employed by practitioners in order to facilitate and intensify possibilities for the design and modification of genetic and biological materials.

Proponents of a synthetic biology approach envisage a future world or field of biological engineering whereby ‘interchangeable’ biological and genetic parts can be ‘slotted’ together and implanted into microbial hosts in order to create biological systems and devices of increasing levels of complexity (see, for example, Purnick and Weiss, 2009; Prescott and Papachristodoulou, 2014). Microorganisms that detect and degrade mercury; genetic and biological circuitry that ‘open up’ and expand the quality and range of biopharmaceutical compounds; segments of DNA that have been ‘streamlined’ and ‘stripped’ of their ‘frivolities’ so as to enhance their functional efficacy – these are just some of the developments or ‘artefacts’ arising from the bringing of an engineering approach to bear on the mutable materialities of the stuff of the biological.

Synthetic biology practitioners endeavour not only to bring into the world a proliferating repertoire of biological parts that are generative of a dazzling array of novel biological functionalities when implanted into varying microbial ‘chassis,’ but are working also to transform biology into an engineering discipline (Cameron et al, 2014). Synthetically engineered organisms are being increasingly fine-tuned and reconfigured, for example, so as to meet specific kinds of performance based criteria. Practitioners place a distinct emphasis on the integration of pathways and regulatory systems into the design procedure. ‘Toggle switches,’ ‘repressilators’ and ‘logic gates’ are all examples of biological ‘parts’ and ‘devices’ that are being implanted into the very fabric of synthetically engineered organisms in order to control the timing and frequency of the transcriptional process – that is, the process of the conversion of DNA sequence information into a corresponding protein chain and specific biological functionality. Precision, control, and efficacy are amongst the key leitmotifs of a synthetic biology approach (Weber and Fussenegger, 2012; Cheng and Lu, 2012).

The development of synthetic biology and the drawing together of the sensibilities of an engineering ethos into the doings of the manipulation of biology can be attributed in part to a range of enabling technologies including computational modelling, infrastructures for the sharing of biological data and materials and advances in gene synthesis technologies. More recently, advanced assembly and editing techniques have been heralded as pivotal developments in helping to realise the potential of synthetic biology. Notable examples include ‘Multiplex Automated Genomic Engineering’ (MAGE) which allows for up to 50 genomic modifications to be made in parallel and the ‘Clustered Regularly Interspaced Short Palindromic Repeats’ system (CRISPR/Cas), which, through its use of RNA guided nucleases purports to enhance the precision of genomic modification at targeted sites in complex organisms.

Although the following list is by no means exhaustive and is likely to change as the field continues to develop, current subsets of synthetic biology can be broadly delineated into the following key areas which utilise a combination of in vivo, in vitro and in silico approaches:

1. **Metabolic engineering.** Synthetic biologists in this area are working to enhance the complexity and precision of biosynthetic pathways for the production of a range of useful products and materials including biofuels and speciality chemicals. Perhaps the most commonly cited example is the production of the anti-malarial drug artemisinin. Much metabolic engineering employs optimised gene sequences with recent research proposing to use the whole genome instead of a gene-by-gene approach. Faulon (in Pauwels et al, 2013: 218) has recently distinguished between 'natural heterologous' approaches to metabolic engineering which use an 'insert or pathway from one donor organism in a host organism;' 'non-natural' approaches which use a 'pathway with different parts from different donor organisms' and 'new chemistry approaches' where enzymes are evolved to allow 'new reactions with slightly different products. Genes coding for these enzymes are then inserted into a host organism.
2. **Regulatory circuits.** Regulatory circuits have been defined by the European Academies Science Advisory Council (2010) as the insertion of 'well-characterised, modular, artificial networks to provide new functions in cells and organisms.' Whilst this definition might not seem too dissimilar to conventional genetic engineering undertakings, a distinct emphasis is placed upon regularity and predictability with practitioners incorporating functional

devices such as oscillators into the engineering process in order to attain new levels of sophistication. The development of a toggle switch by Gardner et al in 2000 and a biological clock by Elowitz and Leibler, also in 2000, are regarded as two prominent early examples of functional experimentation heralding the dawn of synthetic biology (ESC, 2015: 11).

3. **Orthogonal biosystems/xenobiology.** Orthogonality within synthetic biology refers to the design and enrolling of non-overlapping or independent variables into broader biological systems such as the insertion of prokaryotic DNA into a eukaryotic cell. The overarching goal of an orthogonal approach is described by the Chin Laboratory (2015) as bringing 'a level of molecular, spatial and temporal precision – more typically associated with *in vitro* biochemistry – to the study of complex biological systems in their native, *in vivo*, context.' Xenobiology, as a particular subset of an orthogonal approach, is concerned with expanding the canonical 20 amino acid repertoire through the construction and use of artificial DNA (XNA). As noted by the European Scientific Committees (ESC, 2014: 15), XNA brings with it the potential to enhance the biochemical functionality of proteins and 'may offer new opportunities for the development of novel biocontainment systems.'
4. **Protocells.** Protocell research aims to develop synthetic cells that perform functions and various compartmentalised reactions that we would expect to find in a biological cell. Current research involves the examination of lipid and vesicle the ways in which these structures five rise to cellular behaviour. The ESC (2014) has recently stressed that much of this work is currently in its early stages and exists in the domains of nanotechnology and chemistry. However, the ESC has further noted that the potential of protocells as

precursors to synthetic cells qualifies protocellular research as part of synthetic biology practice.

5. **Synthetic genomics.** This area of research involves the synthesis of DNA and its subsequent insertion into a host organism. Developments in synthesis technologies mean that it is now possible to chemically synthesise DNA on the scale of entire bacterial genomes. Minimal genomics is a particular subset of synthetic genomics that refers to the stripping down of microbial DNA to the lowest possible level that is required to sustain life.

In 2014, the UK Minister of State for Universities and Science described synthetic biology as one of the 'eight great technologies' of the twenty first century (Willetts, 2014). The applications of synthetic biology are projected to cut across multiple industrial sectors ranging from the development of biofuels to synthetic chemicals, bioremediation technologies and medicinal products. Overall market forecasts for synthetic biology are predicted to grow to a sizable USD 11.8 billion by 2018 (ESC, 2014: 11). The molecular biologists-come-synthetic biologists David Savage, Jeffrey Way and Pamela Silver (2008: 14) have recently described how synthetic biology will 'transform' the production of biofuels such that the continuing development of this burgeoning field will 'enable a transition to a sustainable energy economy that is largely independent of fossil fuels.' Priscilla Purnick and Ron Weiss (2009), also synthetic biologists, have described how synthetic biology will revolutionise the ways in which we interact with and approach human health and the environment.

'Revolutionary time' – that is, the modernist striving towards a 'progressive' and necessarily 'better' future (Latour, 2005), very much courses through and suffuses predominating narrations of the coming into being of synthetic biology. Take, for example, the recent assertions of Professor George Church, a prestigious scientist at the very forefront of synthetic biology whose visions and practices are doing much to shape the shifting frontiers and contours of this developing approach to biological engineering. Church has described how synthetic genomics – a particular subset of the doing of synthetic biology which involves the chemical synthesis and re-assembling of DNA sequences in a variety of host organisms has the potential to:

> ‘recapitulate the course of natural genomic evolution, with the difference that the course of synthetic genomics will be under our own conscious deliberate control instead of being directed by the blind and opportunistic processes of natural selection.’ (Church and Regis: 2012: 12-13)

In reflecting upon the long-term societal ‘impacts’ and ‘benefits’ of this burgeoning approach to biological engineering, Church has further emphasised that:

> ‘these technologies have the power to improve human and animal health, expand our life span, increase our intelligence, and enhance our memory, among other things.’ (Church and Regis, 2012: 13)

In addition to being underpinned by a lingering sense of ‘revolutionary time,’ the assertions as delineated above are also underpinned by a rather pervasive and powerful notion of the societal good. Advancing the societal good is, to be sure, a rallying call that underpins many accounts of and rationalities for the development of synthetic biology. In 2015, for example, the CEO of Twist Bioscience - a biotech company that produces synthetic DNA for health and sustainability purposes, described how synthetic biology will lead ‘to a range of positive outcomes for the world as a whole’ (Leproust, 2015). Johnjoe McFadden (2012), a professor of molecular genetics and renowned science writer at the University of Surrey has relatedly and fervently proclaimed that synthetic biology is perhaps ‘the best hope’ yet for ‘the future of mankind.’

And yet, to reify the notion of the 'societal good,' without attending to the specificities of context and the intricacies of practice, is to contribute to the generation of what the philosopher of science Annemarie Mol (1999: 76) would describe as a noisy 'perspectivalism' - a perspectivalism which oscillates, for example, between accounts of synthetic biology as a 'monstrous' endeavour which defiles the integrity of species existence, to accounts which posit that synthetic biology is but the latest and salvational iteration of human ingenuity (cf Gschmeidler and Seiringer, 2012; Ancillotti et al, 2015). Rather problematically, the brashness and unrelenting circularity of these proclamations serves all too readily to drown out and delimit the possibilities of cultivating and opening up what the philosopher of science Isabelle Stengers (2005) would describe a somewhat different awareness of the situations that mobilise us.

In a commentary on the framings of synthetic biology in wider deliberative forums and cultural fora the sociologists of science Claire Marris and Nikolas Rose (2012: 28) have argued that the pervasiveness and prevalence of the epistemic circularity that has surrounded synthetic biology is such that 'Utopias and dystopias seem to be the only scenarios possible.' Marris and Rose highlight, for example, how commentators tend to focus on the 'potential reckless use or misuse' of synthetic biology, its 'pathogenic possibilities' and pose deep questions including whether or not synthetic biologists have the right to play God. As Marris and Rose (2012: 28) explain, these are 'the flip side of grand claims about synthetic biology's imminent ability to solve challenges in health, environment and energy.'

In light of the epistemic circularity that has so readily surrounded the coming into being of this developing approach to biological engineering, the aim of this thesis is to contribute to the effort of multiplying synthetic biology's *reals* rather than simply its surrounding eyes (cf Mol, 1999). I am interested, in other words, in generating some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. As Stengers (2015: 35) puts it:

> 'It's not that conflict is pointless or "old hat," it is its link with the production of intelligibility that is in question, which threatens to give answers before having learned to formulate questions, of offering certainties before having had the experience of perplexity.'

More specifically, I ask in this thesis; what is this 'thing' (Latour, 2005) that is synthetic biology and what other kinds of less-perspectival and less-technologically-deterministic stories might it become possible to tell, by tending to the ways in which synthetic biology is done in action and in process – that is, in practice. I am interested in multiplying outwards registers for understanding what this thing that synthetic biology is and what it might become.

Cultivating a sensibility towards the messiness and complexities of things done in action and in practice is a key hallmark of an ontopolitical sensibility. An ontopolitical sensibility is a social scientific approach to the doing of research that is associated with the Dutch philosopher Annemarie Mol (1999). It is an approach to the doing of research which acknowledges that rather 'than being seen by a diversity of watching eyes while itself remaining untouched in the centre, reality is manipulated by means of various tools in the course of a diversity of practices' (Mol, 1999: 77). An ontopolitical approach insists, therefore, that we trace the ways in which synthetic biology is being done in, and is intersecting with, different kinds of actions, practices and doings.

In this thesis I work to generate some ontological curiosity by tracing the ways in which synthetic biology is being done in and through the practices of over thirty leading synthetic biology practitioners and by teasing out and tracing the ways in which synthetic biology is intersecting in, and interfering with, extant modalities of regulatory organising. I work to bring a *geographical sensibility* to bear on this developing field of scientific endeavour.

A geographical sensibility starts out from the premise that synthetic biology's engineering rhetorics and languages are necessarily scrambled as they touch down in and through varying practices. It is a sensibility which acknowledges that synthetic biology can never be alone in the world – that its coming into being depends on 'everything and everyone that is active while it is being practiced' (Mol, 2002: 32). A geographical sensibility is attuned towards encounterings, tensions, turbulences, fictions and entanglements. It is a sensibility which is alive and attentive towards difference in the world and which acknowledges that the 'progressive' and 'promissory' narrations that have surrounded the coming into being of synthetic biology are by no means the only stories to be told. A geographical sensibility is committed, in this vein, to the art of disorientation. It is a sensibility which endeavours to unsettle as much as it endeavours to orientate. It is a sensibility that works, in Stengerian terms, to call into question who we are and what we know.

The nature of the synthetic biology regulatory encounter is a particular site or suite of actions, practices and doings that has been largely underexplored within social scientific engagements interested specifically in the question of synthetic biology. Social scientists who have addressed synthetic biology as a matter of social scientific 'concern' (Latour, 2004) have sought instead to focus on questions of 'governance' and 'responsible innovation' (cf, Calvert and Frow, 2015; Li et al, 2015). The lingering legacy of the 'Ethical, Legal and Social Implications' paradigm is such that, as I explain in chapter two of the thesis, STS scholars interested in synthetic biology's coming into being have sought to distance themselves from the 'site' of the doing of regulation and from the lingering presumption amongst their scientific colleagues that the role of the social scientist is to 'foretell' any regulatory and public relations 'hurdles' that might forestall the coming into being of this burgeoning field of scientific endeavour (cf Balmer et al, 2015).

Regulation, however, like any other doing or 'site' of social scientific inquiry, is an important part of a broader suite of practices through which certain realities and relations are brought into being. There are, I suggest, idiosyncrasies and empirical specificities associated with the doing of the business of regulation that might have much to teach us about how certain kinds of reals and relations are engendered, foreclosed, brought into being or otherwise marginalised. As Latour (2005) usefully reminds us, all organisations and institutions have their own architectures and their own complex set of procedures and protocols which are generative of certain kinds of effects and reals.

Through negotiating a research relationship with the UK's Health and Safety Executive - the UK competent authority responsible for overseeing the developing trajectories of synthetic biology and for delimiting risks to human health and the environment posed by the undertaking of synthetic biology practice - I was able to gain access, as part of my PhD research, to a developing community of synthetic biology practitioners and to open up to social scientific inquiry, a relatively underexplored set of (regulatory) reality making practices. My affiliation with HSE would provide me with a route into the synthetic biology community and enable me to engage with the doings of synthetic biology as it is done in, and intersects with, varying kinds of practices. It would provide me with the resources necessary to contribute to the telling of less perspectival stories about what this thing that synthetic biology is and what it might become.

2. Research Aims

This is a thesis that is about difference and multiplicity. It is a thesis that seeks to go beyond narrow and technologically deterministic accounts of synthetic biology as a ‘progressive’ and ‘promissory’ thing that is but the latest iteration of human ingenuity. The primary aim of this thesis is to generate some ontological curiosity surrounding the developing ‘thing’ (Latour, 2005) that is synthetic biology. I ask in this thesis; what is this ‘thing’ that is synthetic biology and what might it mean for synthetic biology to inhabit the world and to inhabit it well? I use the lens of the synthetic biology – regulatory encounter as a) an entry point into the developing field of synthetic biology and b) as a focal point of analysis or a particular web or set of ‘reality making’ practices (Law, 2004) through which to target my efforts of addressing the aim of the thesis of generating some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. The objectives of the thesis can be broken down as follows:

a) To develop an empirically informed and less perspectival account of the doing of synthetic biology and the bringing of an engineering approach to bear on the stuff and substances of the biological.

This objective is designed to enable me to explore the ways in which synthetic biology is being done in and through varying practices and to go beyond the narrow, technologically deterministic and economistically freighted accounts of synthetic biology that we encountered at the very outset of this chapter. The objective is underpinned by the recognition that, by attending to the complexities and nuances of things done in action and in process, it becomes possible to generate the material resources necessary to contribute to the telling of less-perspectival and less-technologically deterministic stories about what this developing 'thing' (Latour, 2005) that synthetic biology is and what it might become. In addressing this objective, I am interested in:

- tracing the frictions and tensions that arise as the sensibilities of an engineering ethos are brought into an encountering(s) with the mutable materialities of the stuff of the biological;
- exploring the ways in which engineering rhetorics and languages are necessarily scrambled as they touch down in and through varying practices;
- giving breath to difference – that is, in tending to the ways in which synthetic biology is done differently by different practitioners in what the STS scholar Kristin Asdal (2012) would describe as different 'contextings.'

b) To develop an empirically informed account of the ways in which synthetic biology is intersecting in, and interfering with, extant modalities of regulatory organising.

This second objective of the thesis provides a specific and relatively underexplored set of reality making practices (Law, 2004) through which to further explore and address the aim of the thesis of generating some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. In this vein I am interested in:

- developing an empirically informed account of the regulatory provocations posed by synthetic biology's coming into being;

- contributing unique empirical material to this relatively underexplored site where synthetic biology is forcing thought;
- exploring the skills and sensitivities that are required to empower the situation that is the coming into being of synthetic biology and contribute to the bringing of synthetic biology into a governable world.

c) To develop further conceptual resources from STS, geography and social theory that enable us to grapple more affirmatively with the coming into being of biotechnological developments such as synthetic biology.

This third objective of the thesis is designed to enable me to mobilise the empirical materials that I generated throughout the course of the fieldwork period in order to ‘speak back’ to prevalent theoretical registers and repertoires that are interested in the coming into being of biotechnological developments such as synthetic biology. In this vein I am interested in exploring:

- the nature of the cross fertilisations, the hybridisations and the connections between STS and biopolitics, for example, that work to compel and to move in their insistence that things could be otherwise;
- the generativities that arise from the retooling and the recombining, the sharpening and the softening, of different conceptual innovations.

3. Thesis Structure

The structure of this thesis is largely conventional consisting of an introductory chapter, a review of relevant literatures, a methodology chapter, two substantive empirical chapters and a conclusion. The structure of the thesis is such that it affords considerable space and room for the empirical materials in chapters four and five to breathe – that is, to begin to force thought on their terms and to contribute an empirical richness and an in-depth texturing to the complexities and nuances of a) synthetic biology done in-practice and b) the ways in which synthetic biology is forcing thought for HSE. Affording the space and the room for the empirical materials that I generated throughout the course of my fieldwork period to do the 'leading' (Mansnerus and Wagenknecht, 2015) is a critical prerequisite in contributing to telling of less-perspectival and less-technologically-deterministic stories about the coming into being of the developing approach to biological engineering that is synthetic biology.

Chapter two forms the literature review chapter of the thesis. It situates the thesis within its broader intellectual context. The chapter begins by highlighting how social scientists have, over the years, sought to bring technoscience 'down to earth' (Law and Mol, 2001) – to render its shifting contours simultaneously political, economic, cultural and social. The chapter then turns towards a number of post-ANT conceptual tools and sensitivities that are attentive and acutely attuned towards difference in the world. I highlight in this chapter how the thesis synthesises and builds upon these literatures, bringing them into an encounter with the empirical specificities of synthetic biology and its regulatory provocations.

Chapter three forms the methodology chapter of the thesis. The chapter engages with ontopolitical methodological frameworks as a means of exploring multiplicity and complexity in the world. I explain in this chapter how my interest in synthetic biology led me to the Health and Safety Executive (HSE) – the UK competent authority responsible for regulating this developing approach to biological engineering. I describe how I came to work ethnographically alongside HSE as a Major Hazards Policy Researcher over the course of a one year period. I explain how working as a Major Hazards Policy Researcher provided me with a) a unique gateway into the synthetic biology community and b) a relatively underexplored set of (regulatory) reality practices through which to examine what it might mean for synthetic biology to inhabit the world well. The nature of the synthetic biology regulatory encounter is a particular lens or site of social scientific inquiry that, as I noted in the earlier stages of this chapter has been relatively underexplored within social scientific literatures.

Chapter four is the first of the two substantive empirical chapters. The chapter is entitled 'Synthetic Biology: Beyond Biologism, Beyond Emergence.' It contributes an in-depth, geographically inflected, empirical texturing to the term synthetic biology. It weaves together insights and materials generated from over 30 one to two hour interviews with leading practitioners in the field. The chapter is the outcome of an extended and iterative process of coding and qualitative analysis that enabled me to identify three prominent modalities of the doing of synthetic biology – the 'cellular engineer,' the 'controlled experimentalist' and the 'multidisciplinary scientist.' These three modalities of doing are modalities of doing that diffract and interfere. Tracing the contours of these three modalities of doing and the ways in which they work together syncretically, enables me to decentre in this chapter the prevalence or predominance of economistically freighted narrations of the doing of synthetic biology. It enables me to multiply outwards stories about what synthetic biology is and what it might become. The stories that I open up in this chapter are stories of learning, resistance, apprehension, 'epistemic things' (Rheinberger, 1997) and much more besides.

Chapter five turns towards synthetic biology's regulatory provocations. It builds upon the fuller, thicker and more variegated account of the doing of synthetic biology that I flesh out and develop in the first empirical chapter of the thesis. The chapter is entitled 'Bringing Synthetic Biology into a Governable World.' In the second empirical chapter of the thesis I develop an empirically informed account of the ways in which synthetic biology is interfering with extant modalities of regulatory organising. I reflect in this chapter on the kinds of skills and affordances that might be necessary to empower the situation that is synthetic biology and to contribute to the effort of the bringing of synthetic biology into a governable world. I mobilise the insights and materials that I generated whilst working alongside HSE in order to develop a conceptualisation of the present regulatory moment. The time that I spent working ethnographically alongside HSE provides me with a unique insight into how this organisation thinks, feels and senses and how it is reconfiguring, and being reconfigured by, the coming into being of synthetic biology.

Chapter six is the final chapter of the thesis. The chapter is entitled 'Towards a Modest Geography of Novel Biologies.' Here I draw together the key findings of the thesis. I highlight how by thinking fractiversally – that is, by tending to the taking of shape(s) of things in the fractiverse, it becomes possible to open up different-kinds-of-stories and different-kinds-of-accounts of the coming into being of synthetic biology and the doing of the business of regulation for HSE. Crucially, these are stories that are not so much concerned with diagnosing any kind of power-over or hubris even, but which work instead to give breath to the busyness, to the diffractions and the interferences of synthetic biology and regulation as it is done in action and in process. I argue in this chapter that if the task of a 'modest sociology' is to loosen the constraining push of grand explanatory forces, to recover difference and to let the world show up differently (Law, 1994), then perhaps we might describe the task of a 'modest geography' as endeavouring to multiply outwards possibilities for living together and for living together well. I conclude the chapter by providing suggestions for future areas of research that build upon the key findings of the thesis.

This introductory chapter has set the scene for the thesis, making clear my personal interest in the topic and introducing the field of synthetic biology. In order to move beyond the noisy perspectivalism and epistemic circularity that has accompanied synthetic biology's coming into being I argue that there is a need attend to the complexities and nuances of synthetic biology done in action and in process. In the next chapter of the thesis I turn now to situate the thesis within the context of a rich and multifaceted tradition of intellectual inquiry that has sought to open up to social scientific inquiry, the 'objects' of science and technology.

Chapter Two

Literature Review

1. Chapter Overview

In this chapter I set out the literature of relevance to the thesis. I highlight how the thesis synthesises and builds upon these literatures, drawing them into an encounter with the empirical specificities of synthetic biology and its regulatory provocations. The literatures that I engage with in this chapter of the thesis are attendant to a) the complexities and the scrambling propensities of practice b) the agential vitalities of the other-than and more-than-human and c) the existence of difference and multiplicity in the world. Together, these literatures provide a number of orientational cues once we acknowledge that the hyped and perspectival narrations that have surrounded synthetic biology's coming into being are by no means the only stories to be told. They make room for the opening up of different kinds of less perspectival and less technologically deterministic stories about what this thing that synthetic biology is and what it might become.

The chapter proceeds in three main sections. The first section 'Bringing (Techno) Science Down to Earth' highlights how social scientists have, over the years, sought to open up to social scientific inquiry the 'black boxes' (Latour, 2003: 36) of science and technology. I trace the ways in which early philosophical meditations on the delineation and demarcation of a scientific 'proper,' contributed to the seeding of a rich lineage of sociological scholarship that rendered science and technology as simultaneously political, social and economic. In this section of the chapter I also discuss the development and significance of a material-semiotic or actor-network theory (ANT) sensibility – a sensibility which endeavours to make room for the agential vitalities of a plethora of other-than and more-than human things. An ANT sensibility insists that the taking shape of technoscience in practice cannot be attributed simply to human orderings alone, but is patterned and reconfigured by the affordances, texturings and pre-discursive forcings of nonhuman things.

In the second section of the chapter, 'Post-ANT Approaches: Shape Shifting and Syncretisms,' I turn towards a number of conceptual tools and sensitivities, which, beyond making room for other kinds of 'things,' or pointing towards the complexities and scrambling propensities of practice, work instead to foreground multiplicity, difference and noncoherence(s) in the world. These conceptual tools and sensitivities – including Annemarie Mol's (2002) notion of the 'multiple' – inform the ways in which I approach and apprehend synthetic biology in this thesis.

In the third section of the chapter, 'Synthetic Biology and the Regulatory Encounter,' I turn towards a number of literatures which are interested specifically in the site that is the doing of regulation. The synthetic biology regulatory encounter is the lens through which, in the second empirical chapter of the thesis, I work to generate some ontological curiosity surrounding the coming into being of synthetic biology. I am interested in how synthetic biology is forcing thought for the UK Health and Safety Executive (HSE) and in the kinds of skills and affordances that might be necessary to contribute to the bringing of synthetic biology into a governable world. The literatures that I engage with in this section of the chapter insist that the doing of regulation, like any other practice or doing, is an important suite or site of practices and doings where relations are formed, dis-assembled and re-configured.

Throughout the course of this chapter I focus on the different kinds of 'goods' that are engendered by the mobilisation and reconfiguring of different conceptual tools and sensitivities. I tend, for example, to the ways in which certain kinds of conceptual tools are particularly effective in helping to make certain kinds of political arguments, in generating a 'loudness' or an 'overtness' even in political critique. I highlight how others are better equipped to more subtly 'disorientate' - to call things into question in gentler yet equally important ways. A number of the conceptual tools that I draw on and mobilise in this chapter of the thesis originate in the fields of science and technology studies (STS) and sociology. There is, however, a fundamentally geographical inflection to these literatures in their *making room* for the agential vitalities of other-than and more-than human things and their attentiveness towards the processual and *multi-directional unfolding* of things done in action and in process. I conclude this chapter by pointing to the need to explore synthetic biology as it is done in, and becomes imbricated within, practice.

2. Bringing (Techno) Science 'Down to Earth'

2.1. Opening up the 'Black Box' of Science

There is a lengthy and rich tradition of intellectual work in the sociology of scientific knowledge (SSK) that has played an invariably critical role in helping to bring 'down to earth' (Law and Mol, 2001: 609) and to 'wrest open,' (Latour, 2003) the 'black boxes' of science and technology. One of the core aims of this research – to generate some ontological curiosity surrounding the coming into being of synthetic biology and to contribute to the telling of less perspectival and less technologically deterministic stories about synthetic biology – draws on a number of conceptual tools and innovations seeded by the early logics and trajectories of

SSK. It is for this reason that I begin this review of the relevant literature by tending to the sensibilities, sensitivities and contemporary significance of the sociology of scientific knowledge. The conceptual tools and innovations that emerged from the field of SSK inform the ways in which I approach and apprehend synthetic biology in this thesis.

SSK emerged as a distinctive subset of Anglophone sociology in the early-mid 1970s – partly in response to the arguments made by Robert K Merton, one of the earliest sociologists to approach science as an object of social scientific inquiry. Merton (1973: 27) was a 'structural-functionalist' – that is, he sought to examine how the 'structure' of science enabled it to meet its societal 'function' of providing 'certified knowledge.' Merton (1973) theorised that science's behavioural ideals – most notably, its 'disinterestedness,' 'universalism,' 'communism' and 'scepticism' – were critically important in enabling science to perform its social function of delivering 'certified knowledge.' Merton (1973) argued that the flourishing of society depended upon the functioning of 'unified' and 'overarching' institutions including religion, science and government.

Merton's sociological reflections, however, left the content of scientific knowledge untouched. The division between the social and the technical remained largely intact. David Bloor, writing in 1976, expressed considerable dissatisfaction at Merton's division between the social and technical. Not only did Merton's theorisations seem to bear a tenuous relation to the doing of science in practice (see, for example, the work of Mitroff (1974), who pointed to generativities of bias and secrecy amongst prominent scientists working on the Apollo moon project), but they also worked to constrain the *scope* of sociological inquiry. Bloor sought to recast the terms of the debate and to refigure scientific knowledge itself as a new object of social scientific inquiry. Bloor was interested not simply in the organisation of scientific knowledge but also in its content:

> 'Can the sociology of knowledge investigate and explain the very content and nature of scientific knowledge? Many sociologists believe that it cannot… They voluntarily limit the scope of their own enquiries. I shall argue that this is a betrayal of their disciplinary standpoint. All knowledge, whether it be in the empirical sciences or even in mathematics, should be treated, through and through, as material for investigation.' (Bloor, 1991 [1976]: 1)

In calling for social scientists to open up and tend to the nature(s) of scientific knowledge itself, Bloor's provocation set into motion the coming into fruition of a vibrant terrain of scholarly practice that began to bring into focus and to make explicit, the social dimensions and inflections of scientific knowledge. The influential work of Bloor (1976), Shapin (1975), MacKenzie (1978) and others, contributed to a recasting of scientific knowledge as a thoroughly social endeavouring. Shapin (1975), for example, explored the relationship between class struggles and the development of phrenology in Edinburgh. MacKenzie (1978: 35) sought to shed light on the social qualities 'of statistical theory by revealing connections between statistics and wider social and ideological issues.' Shapin and MacKenzie insisted – somewhat provocatively at the time - that scientists were not simply 'accessing' the natural world through neutral and unbiased means, but were engaged in a social enterprise shot through with ideology.

The implications of the so-called 'strong programme' of the sociology of scientific knowledge were hugely significant. They began to challenge the notion that scientific knowledge was an 'apolitical' entity that straightforwardly represented and accounted for the objective reality of things in nature. They contributed to the realisation that:

> ‘The ‘pure’ universe of even the ‘purest’ science is a social field like any other, with its distribution of power and its monopolies, is struggles, interests and profits...’ (Bourdieu, 1975: 19)

SSK, in other words, began the process of opening up to social scientific inquiry, a new territory for sociological exploration – a territory or ‘universe,’ to use the language of the anthropologist and cultural theorist Pierre Bourdieu, which had remained largely shielded by the presumption that science was an ‘objective’ endeavouring distinct from the idiosyncrasies, particularities and convolutions of culture and politics.

But, the strong programme of the sociology of scientific knowledge was not without its critics. Whilst, for example, the sociologist of science Steve Woolgar (1981: 366) acknowledged the importance of replacing ‘passive, contemplative accounts of the character of knowledge generation’ with a ‘more active sociological conception of the relation between knowledge producer and reality,’ Woolgar simultaneously cautioned against replacing the ‘natural’ with a deterministic ‘social.’ Class interests, for Woolgar (1981), were simply too diffuse and too flexible to be invoked as explanatory devices. As the contemporary scholar of science and technology Sergio Sismondo (2010: 54) puts it, the strong programme of SSK, in its earliest of instantiations, appeared ‘too committed to the reality and hardness of the social world.’ SSK adopted a ‘foundationalism in the social world to replace the foundationalism in the material world that it rejects’ (Ibid., 54).

The strong programme also fed into and fuelled the circularity between realism and relativism, or, what Hacking (1999) refers to as the ‘science wars’ – a series of tumultuous exchanges between scientific realists and postmodernist critics concerning the nature of scientific knowledge. It was suggested by some that SSK was engaged in a trashing orthodoxy that served to undermine the practice and significance of the scientific enterprise. Shapin (1995: 291) has described how SSK developed into one of academy's 'most centrifugal, most argumentative' and 'at times uncivil' terrains where the 'interpretation of our culture's most highly valued form of knowledge' became 'fraught and bitter.'

And yet, in spite of its limitations, the strong programme of the sociology of scientific knowledge has done a great deal to facilitate and to open up social scientific engagements with science. SSK continues to offer important resources for thinking through and engaging with scientific enterprises and developments today. Throughout the course of this thesis I exhibit an attentiveness towards the sensibilities and sensitivities of the sociology of scientific knowledge. Synthetic biology, for example, can be described as a thoroughly 'social' endeavouring in the sense that it is imbued with particular kinds of hopes, imaginaries, fears and aspirations. I delineated some of these hopes, imaginaries and fears at the outset of the introductory chapter to this thesis.

But rather than simply emphasising the social qualities of the scientific, I am interested instead, in this thesis, in the intersections and interferences between the social *and* the material. It is for this reason that I turn now towards a further series of conceptual tools and developments that direct our attention towards questions of practice and materiality. Attending to questions of practice and materiality is of critical importance to this thesis, in that it is through the doing of things in *practice*, that the vision of an engineerable and economistically orientated biology is put to work and is subject to deviations and mutual reconfigurations of varying kinds along the way.

2.2. Science as Practice

The turn towards 'science as practice' can be attributed in part to a growing recognition of the limitations of the earliest instantiations of SSK. It can also be attributed to the influential work of Thomas Kuhn (1962) and the publication of *The Structure of Scientific Revolutions.* One of the fundamental premises of this thesis is that, by attending to the complexities and the messiness of things done in practice, it becomes possible to multiply outwards synthetic biology's *reals* rather than simply its surrounding *eyes* (Mol, 1999). It is for this reason that, in chapter four of this thesis, I explore what happens when synthetic biology's engineering rhetorics are scrambled as they touch down in and through the practices of over thirty leading synthetic biology practitioners. Practice poses a significant challenge to abstract theorisations and broad descriptors in that it throws into relief the messiness of realities that are always in the *making.* This is an important methodological point that I discuss in chapter three of the thesis.

Kuhn's 1962 *The Structure of Scientific Revolutions* marked a critical moment in adding to and shaping the sensitivities of intellectual engagements with science and technology. Whilst the philosophy and sociology of science had, up until that point, tended to focus on what Law (2008: 628) describes as 'formalisms, laws and theories,' Kuhn sought instead to recast the scientific endeavour as a thoroughly practical and pragmatic puzzle solving exercise. Kuhn's recasting of science as a laborious and pragmatic exercise stemmed in part from his disciplinary background not only as a philosopher, but also as a historian and physicist (Marcum, 2015). Kuhn was familiar with and attuned towards the convolutions and the pragmatics of experimental protocols, and the significance of professional allegiances and institutional politics, in shaping the knowledge generations of science done in action.

For Kuhn, it was not so much abstract behavioural ideals that defined and organised scientific communities but the specificities of scientific ideas, practices and politics. Kuhn's work, in this regard, undoubtedly did much to further facilitate what Law and Mol (2001: 609) describe as the bringing of the sciences 'down to earth.' But crucially, Kuhn's work did much more than simply shift what Law (2008: 628) describes as the 'epistemological centre of the gravity of science' away from abstract formalisms towards the laborious, material and embodied qualities of scientific puzzle solving in action. In tracing the ways in which science flits between and moves from one 'more or less adequate [scientific] paradigm to another' (Sismondo, 2010: 16), Kuhn called into question the then prevalent notion of a Whiggish history – a history where knowledge develops in an accumulative and progressive fashion over time.

Kuhn's work on the politics and pragmatics of paradigm shifts contributed to the recognition that, as the contemporary science and technology policy scholar Andy Stirling puts it:

> 'the form and orientation taken by science and technology are no longer seen as inevitable, unitary, and awaiting discovery in Nature. Instead, they are increasingly recognised to be open to individual creativity, collective ingenuity, economic priorities, cultural values, institutional interests, stakeholder negotiation, and the exercise of power.' (Stirling, 2008: 263)

It is important to acknowledge here that Kuhn's account of the 'discontinuities' and 'breaks' between scientific paradigms have themselves become subject over the years to the scrutiny of practice. The work of Peter Galison (1997), for example, has highlighted how the taking shape of a new scientific theory does not always involve the development or the use of new scientific equipment. Continuities, in other words, persist and traverse the purported 'incommensurabilities' between different types of scientific paradigms.

But, regardless of the limitations of Kuhn's approach, what makes Kuhn's work so important is that it insists that we attend to the specificities and complexities of science done in action and in process. It acknowledges that there are texturings and intricacies associated with the doings of things in practice that are all too readily effaced by an over-reliance or emphasis on abstract explanatory tools and devices.

Kuhn's work also reminds us that the present within which we live is open to multiple trajectories of becoming – that science does not simply unfold along any kind of 'natural' or 'linear' and 'progressive path.' This is a critical sensibility that I pursue and mobilise throughout the course of this thesis. In both chapters four and five of this thesis, for example, I highlight how synthetic biology and the doing of regulation are practices that are unfolding along multiple trajectories. I mobilise and enrol two further conceptual tools and sensitivities; namely that of actor network theory and ontological politics, in order to open up and to throw into relief, the specificities of how and why synthetic biology and the doing of regulation are taking different kinds of shape(s) in different sets of relations.

In spite of its significance, it is important to note that the 'practice turn' in social scientific engagements with science has, in more recent years, been criticised for refraining from theorising what scientists actually do (see, for example, Soler et al, 2014). In chapter four of this thesis although I exhibit an attentiveness towards the texturings of synthetic biology done in practice, I also attend to what synthetic biologists are doing in terms of a) contributing to the development of what is commonly referred to as the 'knowledge economy' b) opening up new spaces of learning and apprehension and c) knitting together what the historian of science Sophia Roosth (2010) describes as particular kinds of 'species' as well as 'socialities.' It became clear in my research that there is a multiplicity to the practices and doings of the synthetic biologist that exists in tension. Biology might no longer be straightforwardly an 'ology' of the bio in the sense of a study of 'life,' but neither, I argue, is it simply the case that biology has become a discipline orientated simply towards what Calvert (2008) refers to as the 'commodification' of emergence.

2.3. Technology in Practice

Technology too, similarly to science, has also become subject over the years to the scrutiny of practice. Synthetic biology can be described as a 'technoscience' in the sense that it is both a science *and* a technology. I explore the multiform configuring of synthetic biology as a simultaneous science and technology in chapter four of the thesis. The philosopher of science and technology Don Ihde (2009: 28) has explained how early theoretical engagements with technology tended to be transcendental – that is, technology was treated as though 'it were a single, reified thing.' Technology was often cast not only in homogenous terms but also in dystopian mode. In his 2009 contribution, Ihde provides an illustrative account of how, particularly during the mid-1900s, the literary figures of Faust and Frankenstein were often invoked within sociological and philosophical analyses of technology. Technology, in the language of Ihde, was:

> 'blamed for human alienation from *nature*, it was seen as the cause of the decline of *Kultur*, that is, elite culture, it stimulated the rise of mass man and popular culture, and it pointed to a levelling of all things. In its sociological form, derived from the thought of Max Weber, it also was thought to play a role in the *disenchantment* of nature and the desacralization of the earth.' (Ihde, 2009: 28, emphasis in original)

Idhe's account of technology 'out of control' resonates with some of the dystopic headlines of synthetic biology that we encountered in the preceding chapter of the thesis. Martin Heidegger's 'The Question Concerning Technology' (1977) is perhaps one of the most widely-renowned examples of technology theorised in transcendentalist and dystopian mode. Heidegger presents an account of technology as disrupting proper relations to Being – as instigating an objectifying process that instrumentalises and disenchants the world. Heidegger explains in Paramenides, a lecture course delivered in 1942 that:

> 'It is not accidental that modern man writes "with" the typewriter and "dictates" (the same word as "poetize" [Dichten]) "into" a machine. This "history" of the kinds of writing is one of the main reasons for the increasing destruction of the word. The latter no longer comes and goes by means of the writing hand, the properly acting hand, but by means of the mechanical forces it releases. The typewriter tears writing from the essential realm of the hand, i.e. the realm of the word. The word itself turns into something "typed"… Today, a hand-written letter is an antiquated and undesired thing; it disturbs speed reading. Mechanical writing deprives the hand of its rank in the realm of the written word and degrades the word to a means of communication…The typewriter makes everyone look the same…' (Heidegger, 1998: 80-81)

There is, in many respects, a coarse determinism that suffuses Heidegger's theorisations of modern technology – a determinism that regards technology as driving and engendering societal and cultural change. For Heidegger, technology was generative of relations of alienation and exploitation (Lewis, 2014). Technology's fundamental essence was an essence of objectification. Timothy Campbell (2011), a biopolitical theorist and romance studies scholar at Cornell University, explains that, for Heidegger, the 'hand' and the 'word' constituted the essential distinction of man. Campbell (2011) describes how the 'occlusion' of the character of man that stemmed from 'improper' or 'mechanical' writing contributed, for Heidegger, to a domination over beings and an undermining of the possibility of caring for others.

Perhaps unsurprisingly, Heidegger's technologically determinist rendering of modern technology has been critiqued for obscuring the recognition that technologies can enable as much as they constrain – that they are generative of different kinds of effects in different webs of relations. This is an important point that I develop further in the latter stages of this chapter. It is a critical sensibility that informs the ways in which I approach and apprehend synthetic biology in this thesis.

But, it is nevertheless important to acknowledge here that Heidegger's thanatopolitically inflected rendering of modern technology emerged at a time when technology was being mobilised and instrumentalised in large part for military-industrial purposes. Heidegger's theorisations were influenced by the distinctive industrial context of inter-war and post-war Europe. Similarly to the ways in which Heidegger's theorisations were shaped by the political and cultural milieu within which he was writing, I highlight in the latter stages of this chapter how synthetic biology is often swept up and theorised through the lens of contemporary political concerns surrounding bioterrorism and biopolitical securitisation. In 2005, for example, the European Commission proclaimed that:

> "The possibility of designing a new virus or bacterium *a la carte* could be used by bioterrorists to create new resistant pathogenic strains or organisms, perhaps even engineered to attack genetically specific sub-populations." (European Commission 2005, p. 18)

It is perhaps unsurprising, therefore, that a number of social scientific analyses of synthetic biology have sought to emphasise and address the security implications of synthetic biology's coming into being (cf Jefferson et al 2014; Cirigliano et al, 2017). But, whilst the intersection of synthetic biology with biopolitical discourses of securitisation is undoubtedly an important object or area of social scientific inquiry, I highlight in this thesis how it is by no means the only story to be told. By tracing the ways in which synthetic biology is being done in and through varying local practices, I open up in this thesis a collection of much smaller 'little narratives' (Lyotard, 1984) surrounding the coming into being of this developing approach to biological engineering. These 'little narratives' are narratives that are obscured by the broad strokes of biopolitical analyses or theorisations of securitisation and preparedness.

In drawing inspiration from the turn to practice in social scientific analyses of science that I outlined in the preceding section of this chapter, the STS scholars Pinch and Bijker's (1987) seminal work on the 'social construction of technological systems' has done much to undercut and dismantle technological determinisms of varying kinds. Pinch and Bijker (1987) argue, contra Heidegger, that technologies do not have fundamental essences. In drawing on empirical research in a variety of different contexts, Pinch and Bijker highlight how technologies are reconfigured in all manner of ways as they touch down in and amidst the thickness of practice. Whilst technologies might well have affordances and dispositions of varying kinds, there is, for Pinch and Bijker (1987), no deterministic essence that underpins what a technology is or what it might become – technologies are redefined by their users and put to use in often unexpected and unanticipated ways.

The work of Kline and Pinch (1996), for example, in building upon the insights of Pinch and Bijker (1987), has accounted for the ways in which the automobile was re-composed and refigured by farmers whose 'tinkering' (Jacob 1977, Knorr Cetina, 1981) and 'bricolage' (Latour and Woolgar, 1986) practices would ultimately contribute to the making of the contemporary tractor. Kline and Pinch's analysis disrupts notions of a linear innovation process. It points to the importance of context and place in the co-constitutive shaping of what a technology does and what it might become. It is important to note here that the term 'place' should not be read as constituting any kind of fixed or immutable locale. Place refers instead to the specificities of the relationalities that constitute particular kinds of shifting space-times, or, 'contextings,' to use the language of the STS scholar Kristin Asdal (2012). Although Kline and Pinch are sociologists, there is, I suggest, a fundamentally geographical inflection to their analysis. A geographical inflection or sensibility acknowledges that, in a processually unfolding world, technology is subject to morph and mutate in unexpected and non-linear ways.

Recent and related work by the geographers Carol Morris and Lewis Holloway (2014) has examined the ways in which different farms in the UK implement and negotiate genetic breeding technologies. Morris and Holloway (2014) provide a particularly illustrative example of the continued utility of the insights generated by examining the unfolding trajectories of technologies in practice. The attentiveness exhibited by Morris and Holloway towards the ways in which things are scrambled as they become imbricated within particular webs of relations is an attentiveness that I pursue and mobilise throughout much of the course of this thesis. Morris and Holloway's recent contribution problematises the 'innovation adoption' model that continues to persist within policy and scientific domains. Morris and Holloway describe the innovation-adoption model as:

> 'tend[ing] to view farmers as either 'adopters' or 'non-adopters' of innovations, i.e. with identities that are coherent and singular in relation to a particular technology or policy initiative and in which the attributes and attitudes of individual humans alone are seen as determining the decision to adopt or not adopt.' (Morris and Holloway, 2014: 151)

In providing a more nuanced examination of the uptake of genetic breeding technologies, Morris and Holloway (2014: 155) develop an empirically informed account of how different farmers with 'distinct sets of experiences, skills and knowledge-practices, and working with particular groups of animals,' come to differentially engage with genetic breeding technologies on the farm. In chapter four of this thesis I examine in a manner that is akin to the approach of Morris and Holloway, the ways in which different synthetic biology practitioners, working in different contexts, come to perform and do synthetic biology differently. I trace the ways in which synthetic biology takes different shape(s) in different sets of relations.

Rather than simply pointing, therefore, to the intentional decision making capacities of the farmer, Morris and Holloway attend instead to the complex imbrication of factors that come together, often in novel ways, to contribute to the convoluted patterning of the uptake of genetic breeding techniques on UK farms. Included in this complex imbrication of things are the fleshed and bodily affordances and dispositions of different types of cattle – many of which are differentially suited to the application of estimated breeding values or 'EBVs,' as they are otherwise known. It is in this sense that the uptake of genetic breeding techniques on the farm can perhaps best be described as a 'co-constructionist' (Murdoch, 2001) affair – that is, as a heterogeneous and relational achievement.

Morris and Holloway's attentiveness towards the role of the non-human and the fleshed and bodily affordances of different types of cattle in 'shaping the use and non-use of technology' (2014: 152) usefully leads me into a discussion of a further theoretical tool or sensibility that has done much to contribute to social scientific engagements and interventions with the development of science and technology – that of material semiotics or actor-network theory as it is more commonly known. Actor network theory is a social scientific toolkit that is of particular relevance to this thesis in that it draws attention to the manifold nature and intricate texturings of the often non-human ‘things’ that contribute to the scrambling and branching out of logics and ideas in practice.

Synthetic biology is an emergent technoscientific endeavour that enrols organismal parts and self-replicating biological substances into the doing of technoscientific practice. Actor-network theory helps to shed light, therefore, on the ways in which the agential vitalities of non-human things, might work to push and pull the vision of an engineerable biology into different kinds of directions. Actor-network theory is a social scientific toolkit that is attentive towards the affordances, texturings and the recalcitrant propensities of organismal ‘hosts,’ biological processes, experimental apparatus and much more besides.

2.4. Heterogeneous Networks – Making Room for Other Kinds of ‘Things’

Actor-network theory (ANT) is a social scientific toolkit that, as the sociologist of science John Law (2007) explains, borrows from the work of Kuhn and the sociologists of scientific knowledge. The term actor-network theory first appeared around 1982 when it was devised by the French sociologist Michel Callon (Law, 2007). But, as Law (2007: 3) has sought to emphasise, ANT is ‘itself a network that extends out in time and place, so stories of its origins are necessarily in part arbitrary.’ Actor-network theory is not so much a ‘theory’ as it is an ‘approach’ to the tending of ‘things’ and relations in practice (Mol, 2010). ANT builds upon the work of Kuhn (1962) in that it is committed to exploring the complexity of things done in *practice*. It builds upon the work of the sociologists of scientific knowledge in that it is similarly concerned with opening up and expanding the space of social scientific inquiry. But, in stark contrast to SSK, an ANT approach insists that:

> 'there is nothing specific to social order; that there is no social dimension of any sort, no 'social context,' no distinct domain of reality to which the label 'social' or 'society could be attributed.' (Latour, 2005b: 4)

An ANT approach can be best be described, therefore, as constituting a 'sociology of *associations* rather than a sociology of the social' (Latour 2005b: 7, emphasis added). An ANT approach is interested, in other words, in foregrounding and tending to the 'busyness' of the mix of the animate and inanimate 'things' that are imbricated within the taking shape of certain kinds of activities and reality making practices.

Latour and Woolgar's (1986) seminal study 'Laboratory Life: The Construction of Scientific Facts' is perhaps one of the most prominent forebearers of an ANT sensibility. Latour and Woolgar sought to open up to social scientific scrutiny, the busyness and the fullness of the doing of scientific practice in the neuroendocrinology laboratory of the Nobel Prize winner Roger Guillemin. Through conducting a two year period of ethnography at Guillemin's neuroendocrinology laboratory in San Diego, California, Latour and Woolgar (1986) documented in intricate detail, the importance of laboratory equipment, blackboards and paperwork in contributing to the stabilisation of scientific facts. Similarly to the SSK theorists Steve Shapin and Donald Mackenzie, Latour and Woolgar insisted that it is insufficient and inaccurate to describe scientists as working simply to 'access' or to 'represent' an objective natural world through neutral and unbiased means.

But, for Latour and Woolgar, it was not simply the 'social' that was shaping the unfolding of activities in Guillemin's laboratory. Science was shaped as much by non-human things and materialities as it was by human hands, ideas and orderings. Latour and Woolgar's study began to make room, therefore, for a proliferating range of other kinds of 'things,' – things such as bioassays, inscription devices and test tubes, which, together, worked to generate alliances and associations that brought into the world particular kinds of (provisional) accomplishments and achievements. Michel Callon (1986), also a sociologist of science, similarly pointed to the significance of non-human things in his study of the domestication of scallops and fisherman in St Brieuc Bay, northwestern France. Callon developed an empirically informed account of how scallop larvae and the fishermen of St Brieuc Bay worked to simultaneously domesticate each other in a relational configuring where 'agency' was anything but given or distributed in advance (Callon 1986). Callon sought to emphasise the 'precarity' of things-in-relation and similarly to Latour and Woolgar (1986), extended ontological agency well beyond the realm of the human.

ANT's commitment to the ontological levelling of agency - its giving breath to other kinds of more-than and other-than-human things, has contributed to the taking shape of a vibrant and lively body of work in the area of more than human geography. Inspired in part by the dispositions and sensibilities of ANT, much work in this area of geography has attended to the agential vitalities of a diverse and variegated range of non-human 'things' including viruses (cf Hinchliffe et al, 2016), mice (Davies, 2012) and technological artefacts (Kinsley, 2015) of varying kinds. Similarly to an ANT approach, much work in this area of geography is concerned with unsettling ontological distinctions in kind between 'humans' and 'nature.' More than human geographies espouse a relational worldview and work to decentre the role and significance of the human by pointing to the role of non-human things in disrupting and reconfiguring 'human' orderings. As the geographers Steve Hinchliffe and Nick Bingham (2008: 1541) have emphasised, 'all kinds of things become more interesting once we stop assuming that 'we' are the only place to begin and end our analysis.'

In an empirically informed study into the use of mice in laboratory research settings the geographer of science and technology Gail Davies (2012: 623) provides an illustrative example of the ways in which the agential vitalities of non-human things are unsettling some of the 'human' orderings and foundational principles applicable to the organisation of experimental research. Davies has argued that the differential capacities of genetically altered mice constitute a 'multitude.' Davies (Ibid., 623) traces the ways in which the 'indefinite number and irreducible multiplicity' of genetically altered mice are threatening the international institutional principles of the so-called '3R's' – principles which aim to 'reduce, replace and refine' the use laboratory animals in biomedical research. The proliferation of these genetically altered mice, for Davies (2012: 626), is working to 'open up the existing ethico-political settlements around animal welfare, revealing international and disciplinary tensions.' Davies' paper presents an illuminating example of how other-than-human things are working to exert their agential forcings in the formation and unsettling of world making processes.

Geographers interested in the agential vitalities of other-than and more-than-human things have called for social scientific analyses to open up and to tend to the different types and kinds of relations that exist between humans and non-human others. These relations might, as in the case of Davies' paper, be relations of interference, but they might also be relations of antagonism or co-existence. In a recent paper on the science and practices of biocontrol in invasive species management, the geographer Jennifer Atchison (2015: 1697) has recently argued that although 'biosecurity scholars have argued for looser, more flexible approaches to securing life, this work is yet to examine how life might be lived where invasive species are entrenched.' Atchison works to recast biocontrol as a site where it becomes possible to explore the ways in which human and nonhuman others might collaborate and work together in different ways. As Atchison (2015: 1709) puts it, 'biocontrol offers up the possibility of a different kind of science, one done in recognition of human involvement and without the prospect of human mastery.'

It emerged during the course of this research that the agential vitalities of self-replicating biological substrates are deflecting and diffracting the vision of an engineerable biology in a number of different ways. By tracing what happens when synthetic biology's engineering rhetorics encounter the stuff and substances of the biological, I highlight in this thesis how the doing of synthetic biology in practice is working to generate new kinds of associations and relationalities. I highlight, for example, how the material specificities of the liverwort Marchanita, have enabled a particular group of synthetic biologists to "eke out a space" away from the pressure of commercial interests. I explicate how the organismic texturings of this liverwort have enabled it to emerge as an important actant in the formation of certain webs of relations. I develop an account of how the contours and texturings of this non-vascular plant are contributing to the taking shape of a version of synthetic biology that is somewhat different from the economistic and end-goal orientated version of synthetic biology that we encountered at the very outset of the thesis. In chapter five of the thesis I highlight how the emergent propensities of the biological are intersecting with the desire of synthetic biologists to construct hybrid organisms in ways which require the cultivation of new modalities of relating, apprehending and organising – particularly in terms of the assessment of risk.

In its ‘single minded commitment to relationality,’ ANT ‘makes it possible to explore strange and heterogeneous links and follow surprising actors to equally surprising places: ships, bacilli, scallops and scientific texts’ (Law, 2007: 7-8). It also works to undercut and erode ontological distinctions-in-kind between the human and non-human, the social and the technical and the natural and cultural. This is, as Law (2007: 8) emphasises, politically ‘obnoxious to those who take people to be morally special, and intellectually flawed for those who frame the social in terms of meaning and intersubjectivity.’ Given that the generation of certain kinds of ‘effects’ and ‘reals’ requires the assembling of many differing things, an ANT approach or sensibility endeavours to foreground these effects as being always provisional and precarious. This ethos of provisionality and precarity is an ethos that I pursue throughout much of the course of this thesis. Whilst, for example, it may well be the case that the guiding rationality suffusing developments in the life sciences today is predominantly ‘instrumental’ (Rabinow and Bennett, 2012), we must take care, I suggest, not to attribute to this particular rationality a solidity or firmness that isn’t necessarily there (cf Law, 1994).

Although ANT is described as constituting a sociology of associations it might also be described as a geography of associations in that a) it endeavours to make room for a plethora of other-than and more-than-human things b) it foregrounds the contextual specificities of place and practice and c) it endeavours to disorientate in its insistence that there is no such thing as pre-existing ‘reals’ – that there exists only reals that are made and generated through the formatting and re-formatting of particular sets of relations.

2.5. Synthetic Biology Brought Down to Earth

Most social scientific engagements with synthetic biology have thus far tended to be embedded within the field of STS and have mobilised a combination of the conceptual tools and sensitivities that I have outlined above. In this section of the chapter I explore the ways in which social scientific engagements specifically with synthetic biology have sought to bring this developing field of scientific endeavour 'down to earth' (Law and Mol, 2001: 609) – to render its shifting contours simultaneously political, cultural, economic and social. I highlight how the thesis builds upon and departs from these recent contributions.

2.5.1. Synthetic Biology and its Social Dimensions

STS scholars Jane Calvert and Emma Frow (2013: 70) have called for social scientists to open up and to foreground, 'the 'social, political and economic influences on the nature of scientific and technological work' in the developing field of synthetic biology. In their recent contribution 'The Social Dimensions of Microbial Synthetic Biology,' Calvert and Frow make clear their intention to redress what they regard to be the still counterintuitive notion that 'society' is always already part of 'science.' Calvert and Frow (Ibid., 70) propose a series of shifts in the 'framing and language used for discussing the social aspects of synthetic biology.' Instead of speaking of synthetic biology's social 'implications,' Calvert and Frow insist that we should rather be discussing its social 'dimensions.' Calvert and Frow (Ibid., 70) posit that 'seemingly subtle changes in vocabulary' can help to open up 'a new and productive space' for approaching synthetic biology that challenges 'familiar ways of thinking.'

In drawing upon the work of the sociologist and information scholar Susan-Leigh Star (1991: 52), who famously asserted that 'Power is whose metaphors bring worlds together,’ Calvert and Frow (2013) question whether, by endeavouring to engineer genetic and biological parts so that they might “boot up” in microbial ‘chassis,’ synthetic biologists are mobilising a language that encourages us to forget that we are working with living things. Calvert and Frow suggest that the adoption of distinctively engineering rhetorics and languages by synthetic biology practitioners might have very real and tangible implications in terms of the type of research that is pursued and the types of organisms that are brought into the world. As Calvert and Frow explain:

> ‘The metaphors that organise a discipline can prove very consequential. Indeed, it seems that the central metaphors and analogies that are used in the daily workings of synthetic biologists are shaping the types of research questions they are pursuing and thus the types of products and applications that are likely to emerge.’ (Calvert and Frow, 2013: 72)

In chapter four of this thesis I develop an empirically informed account of the ways in which different synthetic biologists are differentially mobilising and engaging with engineering rhetorics and languages in their own working practices. I draw Calvert and Frow’s hypothesis into an empirically grounded engagement with over thirty leading synthetic biology practitioners. It became apparent during the course of my research that the metaphors that are being mobilised and deployed by synthetic biologists are indeed shaping the ways in which practitioners are engaging with (and bringing into the world) synthetically engineered organisms of varying kinds. But it also became clear in my research that the encounter between the discipline of engineering and the mutable materialities of the stuff of the biological is anything but seamless and is branching out in different ways with different kinds of effects in practice. Synthetic biology, in other words, is not simply or straightforwardly transforming biology into an engineering discipline.

Calvert and Frow's 2013 contribution insists that there is a need to make 'space' for a new kind of discussion – that there is a need to bring the tools and insights of social science into a productive engagement with this emergent field of scientific endeavour. In this thesis I endeavour to contribute to the making space for a new kind of discussion by staging an encounter between synthetic biology and a number of conceptual tools and sensitivities that are alive and attentive towards difference in the world. These tools and sensitivities are attuned not only towards the 'social dimensions' of synthetic biology, but also to the interferences and intersections that exist between the social and the material. More specifically, I draw together a commitment to exploring the complexities of practice with material-semiotic and ontopolitical sensibilities in order to generate some ontological curiosity surrounding what this thing that synthetic biology is and what it might become.

2.5.2. Synthetic Biology and its Social Noisiness

If Calvert and Frow have called for social scientists to attend to the social 'dimensions' of synthetic biology, then the STS scholar Claire Marris and social theorist Nikolas Rose have sought instead to draw attention to what might be described as the social 'noisiness' that has surrounded synthetic biology's coming into being. Marris and Rose (2012) urge commentators to 'get real' on synthetic biology and have called for social scientists and commentators to turn their attention towards the intricacies and nuances of the doing of synthetic biology in practice. Marris and Rose (2012: 28) argue that the 'ability of synthetic biologists to overcome serious scientific and technological challenges' is often taken for granted in wider deliberations with the 'economic, legal, social and political conditions for the uptake of these technologies' routinely ignored. This is particularly the case, Marris and Rose argue, in ethical, policy and media discussion forums.

As Marris and Rose (2012: 28) continue to explain, commentators tend often to 'focus on [the] potential reckless use or misuse [of synthetic biology], overestimate the pathogenic possibilities, and worry about deep questions such as: "Do we have the right to play God?" Marris and Rose (2012: 29) emphasise that 'the prospects for synthetic biology are likely to be both less sensational and less forbidding than is generally acknowledged.'

Marris and Rose are taking issue here with the noisy 'perspectivalism' (cf Mol, 1999) or the epistemic circularity that I outlined at the very outset of chapter one of the thesis. They too, like Calvert and Frow (2013), are acknowledging the need to open up and to grapple in more affirmative terms, with the coming into being of this developing approach to biological engineering. Marris and Rose insist that practice based analyses are likely to play a key role in helping to inform more nuanced discussions.

In spite of Marris and Rose's (2012) call for social scientists to investigate the doing of synthetic biology in practice there have been comparatively few social scientific or ethnographic examinations of the varying doings and practices of synthetic biology. This can be attributed, in part, to the relative infancy of the field and is a point that Finlay (2013) has recently sought to emphasise. It can also be attributed, I suggest, to the opacities and qualities of synthetic biology as an 'object' of social scientific inquiry. Synthetic biology is an object of social scientific inquiry that requires an appreciation of and an engagement with the biological and scientific basis of organismal and genetic processes. In chapter three of the thesis I reflect on the methodological implications of grappling with the technicalities of a complex and intricate field of scientific endeavour. I mobilise the Stengerian figure of the 'idiot' in order to argue that partiality in knowledge, depending on how it is mobilised, can be affirmatively productive. It is perhaps unsurprising, in some respects, that a number of STS scholars grappling with the developing trajectories of synthetic biology, such as Marris and Frow, hold PhDs in plant science and biochemistry respectively.

2.5.3. Synthetic Biology and Biopolitical Securitisation

A notable social scientific exception to the tending-to of synthetic biology in practice can be found in the recent work of Catherine Jefferson, Filippa Lentzos and Claire Marris (2014). Jefferson et al (2014) address Marris and Rose's call to turn towards the complexities and the nuances of synthetic biology done in action and in process. Jefferson et al (2014) focus specifically on some of the biosecurity 'challenges' associated with the development of synthetic biology. Jefferson and Lentzos are both sociologists based in the Department of Global Health and Social Medicine at Kings College London, with long standing interests in the intersection between science, security and international relations.

Jefferson et al's paper intersects with broader trends in contemporary social theory which identify what Cooper (2006) describes as a 'biological turn' in the 'war on terror.' The biological turn in the war on terror refers to the ways in which notions of 'biological emergence, resistance and pre-emption' have crossed over and become insinuated within international governmental discourses such that the future evolution of life is now defined by catastrophe risk and 'permanent warfare' (Cooper, 2006: 114). As Cooper (2006: 13) explains, 'For US defence, it seems, the frontier between warfare and public health, microbial life and bioterrorism, had become strategically indifferent.'

Jefferson et al (2014) delineate in their paper a number of prominent threat narratives and biosecurity ‘challenges’ associated with the development of synthetic biology. Included in these threat narratives and biosecurity challenges are; the potential role of synthetic biology in contributing to the facilitation of the ‘de novo’ (from scratch) chemical synthesis of viral genomes; the de-skilling of certain areas of biological practice through the development of automative techniques; and the mobilisation of synthetic biology for nefarious (bioterrorist) purposes.

Jefferson et al (2014) draw on a number of publications and policy documents which exemplify these threat narratives. They refer, for example, to the work of Tucker and Zilinskas, who have described how:

> ‘The reagents and tools used in synthetic biology will eventually be converted into commercial kits, making it easier for biohackers to acquire them. Moreover, as synthetic biology training becomes increasingly available to students at the college and possible high-school levels, a ‘hacker culture’ may emerge, increasing the risk of reckless or malevolent experimentation.’ (Tucker and Zilinskas, 2006: 42)

Jefferson et al (2014) also draw on the work of Maruer and Zoloth who emphasise that:

> ‘Synthetic biologists have already shown how terrorists could obtain life forms that now exist only in carefully guarded facilities, such as polio and 1918 influenza samples.’ (Maurer and Zoloth 2007: 16)

Jefferson et al endeavour to add a further texturing to these bio-security ‘threat narratives’ by subjecting them to the scrutiny of practice. They do this by zoning in on a number of so-called ‘experiments of concern.’ The 2002 chemical synthesis of the poliovirus, for example, by researchers at the State University of New York Stony Brook, is perhaps one of the most widely renowned ‘alarmist anchors' surrounding the development of synthetic biology. The synthesis of the virus raised a number of concerns surrounding the extent to which synthetic biology technologies might be simultaneously mobilised for nefarious purposes. And yet, as Jefferson et al have emphasised in their paper, the de novo synthesis of viral genomes is an incredibly intricate and delicate task. Jefferson et al describe how:

> 'even specialized DNA synthesis companies cannot easily synthesize de novo any desired DNA sequence… the process is error prone, and some sequences are recalcitrant to chemical synthesis.' (Jefferson et al, 2014: 8)

Jefferson et al provide a compelling illustration of how making good HeLa cell extracts (extracts which are critical to the material cultivation of the poliovirus) is an arduous technique - a task that requires a great deal of craftwork-like skill and which is notoriously difficult to transfer between different laboratory facilities. What's more, in spite of it being well over ten years since the poliovirus was first chemically synthesised, Jefferson et al highlight how attempts to replicate the de novo synthesis of the virus continue to remain 'non-trivial' - even in cutting edge laboratories.

In weaving together a historical account of the weaponisation of biological agents, Jefferson et al (2014: 6) further posit that even 'well-resourced state biological weapons programmes of the past [have] faced critical challenges in over-coming problems of aerosolisation and [the] delivery of biological agents.' For example, Jefferson et al (2014) describe how the Soviet bioweapons programme and the Japanese Aum Shunrikyo regime failed to produce a working bioweapon in spite of having spent many years endeavouring to weaponise different kinds of biological agents. They illustrate how the scale-up process and experimental attempts to disseminate pathogenic organisms worked to destroy the virulence and pathogenicity of the biological agent in question. This is because, unlike nuclear and chemical weapons which are more likely to hold their material properties, biological substrates are subject to morph and mutate in different ways (Jefferson et al, 2014).

Jefferson et al (2014: 60) emphasise that, in spite of the portrayal of bioterrorists as pursuing capabilities ‘on the scale of twentieth century state biological weapons research and development programs,’ past bioterrorism attacks have ‘typically been small-scale, low casualty events.’ The mutabilities of the biological, in other words, cannot simply be ‘written out’ or overcome by technological innovations. Tacit knowledges and social factors are just some of the other-than or more-than-technical factors that remain critical to the doing of the engineering of biology when mobilised for nefarious purposes (see also Vogel, 2013).

Jefferson et al’s (2014) paper can be said to resonate with an ANT approach in its foregrounding of the agential vitalities of the non-human. It contributes to an unsettling of technologically deterministic and dystopic renderings of synthetic biology that are evident in the work of Maurer and Zoloth (2007) and Tucker and Zilinskas (2006).

It is important to make clear here that Jefferson et al (2014) are by no means arguing that the threat narratives that have surrounded synthetic biology are unfounded. Rather, Jefferson et al’s contribution works instead to foreground the importance of social scientific sensibilities in helping to open up, and to apprehend in more nuanced and empirically grounded terms, contemporary developments in the life sciences today. In response to these hyped biosecurity threat narratives, Jefferson et al (2014: 26) argue that there is a subsequent and urgent need to map out ‘what exactly is getting easier, and what might remain difficult.’ Jefferson et al (Ibid., 26) emphasise that mapping out the doings and recalcitrances associated with the engineering of biology may well allow for a ‘more refined assessment of the biosecurity threats posed by synthetic biology’ to emerge.

Similarly to the sentiment as espoused in the work of Jefferson et al (2014), I map out in this thesis a more nuanced account of synthetic biology done as it is done in and through varying local practices. In contrast, however, to Jefferson et al’s (2014) analysis, I attend to the intricacies and complexities of synthetic biology outside of the biopolitical discourses of securitisation which have conditioned and influenced how Jefferson et al (2014) approach synthetic biology as an object of social scientific inquiry. This is a point that I discussed in the earlier stages of this chapter in light of the emergence of Heidegger’s theorising of the form and effects of modern technology. HSE’s regulatory responsibilities are concerned more with biosafety than with biosecurity.

2.5.4. Synthetic Biology and Biopolitical Critique

The recent work of the STS scholar Pablo Schyfter (2012) has sought to call into question the developing trajectories of synthetic biology by staging an encounter between synthetic biology and the philosophical theorisations of Martin Heidegger. In section 2.3 of this chapter I highlighted how Heidegger theorises modern technology as a dystopian and thanatopolitically inflected enterprise. Schyfter (2012: 203) describes how, for Heidegger, modern technology is constitutive of a form of ‘enframing’ (Gestell) – a form of enframing that ‘presences’ non-human natures in such a way so as to render them ‘intelligible as a raw material for human utility.' As Schyfter (2012: 203) continues to explain, this form of enframing 'reduces the entities brought forward to a mere "skeleton" (or "frame") of their actual existence.' In Heidegger's own terms "Nature becomes a gigantic gasoline station, an energy source for modern technology and industry" (Heidegger 1969 [1959]: 50 in Schyfter, 2012: 204).

Whether it be the development of tools to quantify rates of genetic transcription – tools such as 'PoPS' or 'RiPS' – polymerase per second or ribosomes per second, Schyfter (2012: 206) identifies a 'zeal for calculability' within the undertaking of synthetic biology endeavourings. Schyfter highlights how 'that which is not calculable is not accepted; that which is not quantifiable is not real' (Ibid., 206). Schyfter argues that, for the synthetic biologist, vitalism is regarded as a form of unscientific 'mysticism,' with the 'proper scientific perspective' being 'based in quantification' (Ibid., 206). Nature, in short, is 'set upon' by 'technology [/synthetic biology] as a repository of usable resources' (Schyfter, 2012: 204). For Schyfter (2012: 205), synthetic biology is working to render 'the living world intelligible as a standing reserve of function – as 'something to be used' for human utility and consumption rather than as something in and of itself.

These standing reserves of 'function' include the development and use of synthetically engineered organisms to target and invade cancerous cells; the use of genetic material to store and archive data; and the use of synthetically engineered organisms to degrade toxic pollutants in wider ecological environments. Perhaps most illuminatingly of all, Schyfter highlights how, when it comes to the functional use of synthetic biology to develop chemical products in microbial hosts, some of the generated chemicals are toxic even to 'wild-type' strains. Schyfter describes how synthetic biology is engaged in a 'setting upon' the substrates of the biological such that:

> 'natural regulatory mechanisms are generally disabled or transformed. Like the mechanization of cultivation, here, the harvesting is not respectful of natural limitations. It is a coercive challenging forth… Within synthetic biology, living entities are set upon, challenged, and brought forth as components of a productive technological system. They are rendered intelligible as things to be exhausted of their products.' (Schyfter, 2012: 210)

Schyfter's (2012) mobilisation of the philosophical explications of Heidegger presents a powerful framework through which to apprehend the coming into being of this developing approach to biological engineering. There is a certain clarity and lucidity to Schyfter's analysis that compellingly works to call into question, and to place centre-stage, a hubrism and instrumentality that undergirds this developing field of scientific endeavour.

In this thesis, however, whilst I am sympathetic towards the clarity and the overtness in critique that Schyfter's mobilisation of Heidegger's framework offers, I work to bring a geographical as opposed to a predominantly philosophical or sociological sensibility to bear on this developing field of scientific endeavour. A geographical sensibility starts out from the presumption that, in a full and busy world (Bingham, 2006), there is always more that is going on – that there always exists other kinds of stories to be told. I turn now, in this next section of the chapter, towards a number of conceptual tools and sensitivities which are attentive towards difference and multiplicity in the world.

3. Post-ANT Approaches: Shape Shifting and Syncretisms

Thus far in this chapter I have provided an account of some of the conceptual tools and sensitivities that have helped to bring the sciences 'down to earth' (Law and Mol, 2001: 609) and to 'wrest open' the 'black boxes' (Latour, 2003: 36) of science and technology. These conceptual tools and sensitivities insist that we attend to the complexities and the scrambling propensities of practice. In this next section of the chapter I turn towards what Law and Singleton (2005), Gad and Jensen (2010) and Michael (2016) describe as a series of 'post ANT' conceptual tools and devices. These are tools and sensitivities, which, beyond making room for other kinds of 'things,' or acknowledging the complexities of things done in action and in process, foreground multiplicity and non-coherence in the world.

3.1. What are Multiples and Why Do They Matter?

Actor-network theory's thick descriptions of how heterogeneous assemblages of more-than-human 'things' come together and associate in ways which are generative of provisional and precarious alliances contributed to a reshaping of the question of ontology. Actor-network theory insisted, amongst other things, that ontologies are never apriori givens but are always already in process and in-the-making. As the philosopher and anthropologist of the body Annemarie Mol (1999) puts it, actor network theory pulled down iconoclastically, the traditional divisions between 'ontology' and 'politics.' Annemarie Mol (1999, 2002), however, has 'pushed this logic one step further by washing away a single and crucial assumption: that successful translation generates a single co-ordinated network and a single coherent reality' (Law, 2007: 13). Mol (1999, 2002) is interested in *multiples* – that is, in how different objects are performed in and through different practices. As Mol explains:

> 'if reality is *done*, if it is historically, culturally and materially *located*, then it is also *multiple*. Realities have become multiple.' (Mol, 1999: 75, emphasis in original)

Mol's notion of multiplicity developed through her empirical engagements with anaemia and lower limb atherosclerosis. In 'Ontological politics: a word and some questions,' Mol traces three different but related versions of the performance of anaemia: anaemia as an embodied and visible set of symptoms; anaemia as laboratory practice (the tapping of blood and the generation of blood haemoglobin levels) and anaemia as pathophysiological method. Mol (1999: 78) explains that it is often the case that in textbooks these three performances of anaemia are typically understood as constituting 'aspects of a single deviance.' A low haemoglobin level is meant to fall outside of the normal statistical range and to surface in the form of problematic symptoms.

But this is not always the case. As Mol highlights, things are often messier in practice. Some patients have a low haemoglobin level without exhibiting any symptoms. Others might have organs that lack oxygen because their haemoglobin level has 'just dropped' (Mol, 1999: 78) but which nevertheless still reside within the normal range. These three ways of diagnosing anaemia then, each diagnose something *different*. They are not different perspectives but are different *enactments* of anaemia. As Mol (1999: 78) explains, 'The objects of each of the various diagnostic techniques do not necessarily overlap with those of the others.'

There is an important spatial-temporal dimension to Mol's theorising of the 'multiple' that is somewhat different to an ANT or constructivist approach. Mol emphasises that:

> 'constructivist stories suggest that alternative 'constructions of reality' might have been possible. They have been possible in the past, but vanished before they ever fully blossomed. So there is plurality again. But this time it is a plurality projected back into the past.' (Mol, 1999: 76-7)

Thinking in terms of multiples helps to resist what Latour (2013: 64) describes as one of the key challenges of an ANT approach – namely, its retention of 'some of the limitations of critical thought' in that it 'risked succumbing' to the 'unification of all associations.' As the sociologist of science John Law (2008: 636) puts it, to think in terms of multiples is to 'bring difference in from the cold.' Anaemia, in other words, is an unsettled object – it *shifts its shape* as it is performed in and through different practices. It is worth quoting Mol at length here:

> 'reality is manipulated by means of various tools in the course of a diversity of practices. Here it is being cut into with a scalpel; there it is being bombarded with ultrasound; and somewhere else, a little further along the way, it is being put on a scale in order to be weighted. But as a part of such activities, the object in question varies from one stage to the next.' (Mol, 1999: 77)

Mol (2002: 82) borrows from the anthropologist Marilyn Strathern (1991) when she describes anaemia as being 'more than one, and less than many.' For Mol (2002: 84) the question of how any multiple – anaemia, synthetic biology or otherwise - might 'hang together,' is a thoroughly empirical question – a question which demands a thoroughly empirical response. As Mol (2002: 83) puts it 'The question of how objects, subjects, situations and events are differentiated into separate elements and how they are coordinated together is opened up for study.'

The work of Hinchliffe (2010) provides an illustrative example that draws Mol's framework into an engagement with the taking shape(s) of a community garden in Birmingham. Hinchliffe (2010: 304) highlights how the garden is 'done in more than one place and with a variety of different things.' In departing from a more conventional ANT approach, the garden, for Hinchliffe, is far from exhausted by its relations. Hinchliffe reminds us that in its being of the world, it is always in-the-making and in process. As Hinchliffe explains:

> 'The multiple is already indeterminate by virtue of its being made up of things that are making other things, and that are therefore elsewhere too…

> [things] never lend themselves fully to a relation, a network or to an association. They are as Strathern has put it, partially connected (Strathern 1991).' (Hinchliffe, 2010: 317)

It is for this reason that Hinchliffe (2010), following Deleuze and Guattari (1998), prefers to speak of 'involutions' rather than involvements. Involution, in contrast to involvement, is suggestive instead not of any kind of 'seamless mix' (Hinchliffe, 2010: 310) but of a much messier and far from integrative touching or coming together of things. The garden, in this sense, is an unsettled object – an object with 'frayed' and fraying edges (Hinchliffe, 2010: 309). Tracing the ways in which different objects are being pushed and pulled into different kinds of shapes is, I suggest, critically important in thinking through the kinds of reals and the kinds of shape(s) of things that we might want to nurture and to help bring into the world. It is for this reason that I mobilise Mol's ontological politics as a sensitising device when approaching and apprehending the developing trajectories of synthetic biology as it is done in and through practice.

More recently, a number of geographers have begun to engage with Mol's understanding of ontological politics and multiplicity in order to stage a number of critical interventions in what some would describe as a 'post-political' (Žižek, 1999; 2011) world. Simon and Randalls (2016: 3), for example, have deployed the concept of multiplicity in order to open up and re-politicise the concept of 'resilience' – a term which 'is tightly bound to the adage that we now live in a 'time of crisis.'' As Simon and Randalls (2016: 3-4) explain, resilience has 'come to stand for the ability to absorb, withstand, persist and even thrive and reorganize in the face of the shocks and disturbances of always uncertain becoming.' And yet, whilst Simon and Randalls (2016: 15) are attentive and sympathetic in their paper towards the ways in which resilience 'has been and can be deployed toward profoundly conservative ends,' Simon and Randalls insist that:

> 'This is one ontological siting, where resilience is supposedly found in the survival of the unavoidable and never-ending turbulence of speculative capitalism. There are, however, many other ontological locations of resilience, and this flexibility and generality is what makes it an effective and slick frame for mobilizing interventions (or not) without really having to articulate agendas, values and desires. Our aim is not to resuscitate or rescue resilience but to offer a framework for assessing the implications of this concept so widely wielded to arrange present relations in the name of such divergent visions of the future. Critical assessments of resilience can cut across the generality and evasiveness of the term by nailing it down and forcing the question of specifics when it is summoned, which we maintain is perhaps the only universal moment for politicizing the concept.' (Simon and Randalls, 2016: 15)

The significance, then, of thinking in terms of multiples is that it alerts us to the ways in which things might always already be different. It demands that we attend to the specificities and intricacies of thigs done in and through practice. Thinking in terms of multiples helps to make room, therefore, for the opening up of different kinds of stories about what things such as resilience, community gardens, anaemia and synthetic biology are and what they might become.

The significance of the multiple to this thesis is that it helps to cultivate an attentiveness towards difference in the world. It is an approach to social scientific inquiry that resists the tendency to 'evacuate reality' from what Law (2015: 134) describes as 'non-dominant reals.' It emerged during the course of this research that there are indeed a number of non-dominant reals associated with the doing of synthetic biology in practice and that these reals are all too readily effaced by broad descriptors of synthetic biology as working simply to transform the efficacies of biotechnological production.

3.2. Towards an Ecology (Geography) of Syncretisms

There is more to theorising and thinking with multiples than simply identifying the ways in which different objects are performed in and through different kinds of practices. Moser (2008) reminds us, in her exploration of the Alzheimer's disease multiple, that it becomes important to ask how (and why) different realities relate or co-exist. In drawing on the work of the feminist scholar and theorist Donna Haraway (1996, 1997), Moser (2008: 99) posits that 'All enactments make a difference, but sometimes they make the same difference, or one that supports other enactments and so contributes to reproduce a pattern rather than diffract and make something new.' Like Mol (1999, 2002), Moser argues that it is not simply the case that we can *choose* between different practices and enactments. Instead, different enactments are caught up in and intersect with, complex webs of relations of varying kinds.

The recent work of Law et al (2013) has sought to foreground the importance of tending to the ways in which different realities relate. For Law et al (2013), it becomes important to trace syncretisms and syncretic associations. Law et al (2013) mobilise the term 'syncretism' from the disciplinary tradition of religious studies where it is often used in either a normative or a descriptive fashion. As Law et al (2013: 176) explain, used 'normatively, the focus has been on (the importance of) maintaining boundaries to protect the purity of doctrine and/or practice.' Used descriptively however, Law et al (2013: 176) emphasise that 'the interest has been in characterizing more or less messy processes that combine or perhaps secure the temporary coexistence of practices and doctrines from a variety of dissimilar research backgrounds.'

In drawing on six empirical case studies ranging from the implementation of the Cattle Tracing System in the UK to end-of-life medical caregiving, Law et al (2013) trace six different ways in which multiple realities work together syncretically. In the case of the Cattle Tracing System, Law et al identify what they regard as the syncretic modality of ‘denial.’ They highlight how this state programme, which places stringent demands on cattle farmers, is ultimately in ‘denial about its essential noncoherence’ (Law et al, 2013: 178). The system ignores, for example, the complexities and challenges of tagging aggressive cattle and fails to recognise that farmers might not always be present on the farm. As Law et al (Ibid., 178) progress to explain, ‘Farmers have no choice: they must comply. But the system itself is dependent on no *particular* farm and can carry on even if some of them fail to conform’ (emphasis in original).

In moving on to discuss the example of biomedical care giving towards the end of a patient’s life, Law et al (2013) regard ‘care’ as further example of a modality of syncretism. In tracing the tensions between a ‘biomedical’ and ‘social’ logic – logics which Law et al (2013) acknowledge are themselves internally differentiated – the authors highlight how a caregiver must negotiate the tensions between delivering medical care at the end of a patient’s life whilst simultaneously providing the room and space for family interactions and engagement with the dying patient. Law et al (2013: 183) emphasise that this modality of syncretism involves being sensitive to ‘nuances, hints, and needs, for what is right at one moment may not be right a few hours later.’

Law et al (2013) draw on a number of other empirical case studies in their attempts to theorise and to open up to critical reflection different modalities of syncretism. The six modalities of syncretism that Law et al identify throughout the course of their paper are: denial, domestication, separation, care, conflict and collapse. Significantly, these are not mutually exclusive modalities of syncretism and often get blended together in a number of different ways. The critical question that Law et al (2013) pose, concerns whether it might be possible to say anything about what might count as a 'good' mode of syncretism. As Law et al (2013: 188) remind us 'Any response to such questions will be contingent on context, location, commitments, and the issue at hand.' Indeed, in true STS fashion Law et al (2013: 189) posit that 'In the abstract there are no good (or bad) modes of syncretism, in part because there is no "abstract." Instead, there are concrete and noncoherent practices that need to be held together in practice and in particular locations.'

Law et al (2013) call for an attentiveness towards the ways in which different syncretic relationships (within different contexts) are generative of different kinds of 'goods' and 'bads.' As Law et al (2013) explain:

> 'In its religious context, the term *syncretism* has been understood both as negative and positive. Negatively, it has been taken to connote sloppiness: a failure to be clear. It has been treated as a theologically and intellectually suspect eclecticism, as an attempt to throw everything into one pot. But positively, it has been understood as an expression of vitality, tolerance, and inclusiveness – as an indication of a fluid willingness and ability to draw on the power of many traditions by finding ways of holding them together… hegemony is not the only syncretic mode available. We need to explore the different ways in which these modes work and transmute them into a resource for thinking about how to do noncoherences well. There will be no analytical or normative guarantees, but then we have never been modern, and the guarantees that we once believed we had were always empty. There is no need to be scared, for if noncoherence is not incoherence, then neither is incomplete success a failure.' (Law et al, 2013: 192)

In this thesis I respond to the call of Law et al (2013) by tracing the ways in which different performances of the doing of synthetic biology in practice diffract and interfere. I also trace the ways in which this 'thing' that is synthetic biology intersects and interferes with extant modalities of regulatory organising. I am interested in what kinds of reals and relationalities are brought into being as this emergent approach to biological engineering encounters the sensibilities and sensitivities of HSE.

4. Synthetic Biology and the Regulatory Encounter

The synthetic biology regulatory encounter is the lens through which, in chapter five of the thesis, I grapple empirically with synthetic biology's coming into being. Latour (2005) emphasises that all organisations and institutions – regulatory or otherwise - have their own complex sets of procedures and protocols which are generative of certain kinds of effects and reals. Tracing, therefore, the ways in which synthetic biology is imbricated within the regulatory reality practices of HSE provides an important focal point of analysis through which to explore, empirically, some of the tensions and provocations associated with synthetic biology's coming into being. Here I draw on a number of literatures and conceptual tools and sensitivities which inform the ways in which I approach and apprehend the doing of regulation in this thesis.

4.1. Regulation in a Post-ELSI Context

Asdal and Hobæk, (2016) describe science STS as a field of study that is concerned with politics. And yet, as Asdal and Hobæk, (2016: 96) have recently argued, STS has tended to 'disregard the work of conventional political institutions such as parliaments, especially in the politics of nature, which is often seen as delegating 'nature' to 'science.'' Asdal and Hobæk, (2016) suggest that the comparative lack of attention that has been afforded by STS scholars to ‘conventional’ political institutions can be attributed to a number of recent trends in political and social theory. In drawing on the work of prominent contemporary theorists including that of Beck (1997), Habermas (2001), Callon et al (2011) and Latour (2007), Asdal and Hobæk, (2016) highlight how the question of the ‘where’ of politics has undergone something of a radical transformation.

Simply put, politics, Asdal and Hobæk, (2016) explain, is no longer to be found solely within ministries or the parliamentary practices of the nation state even, but has been pushed beyond its conventional moorings and resides within all kinds of other fora and non-conventional political spheres. Citizen juries (Dryzek et al, 2011), patient interest-groups (Callon and Rabeharisoa, 2008) and citizen science initiatives (Mamo and Fishman 2013; Silvertown 2009) – these are just some of the latest manifestations of the reconfiguring of the ‘where’ of the ‘political.’ Asdal and Hobæk, (2016: 97) posit that one of the implications of this reconfiguring in the where of the political is that STS engagements with science and technology have tended to look ‘for the politics of nature anywhere but traditional sites, such as parliaments.’

STS engagements specifically with the biotechnological nature-culture that is synthetic biology have similarly afforded considerably less attention to the question or the ‘site’ of the doing of the regulation of synthetic biology. Calvert and Frow (2015), leading STS scholars working in the field of synthetic biology, have gone as far as to emphasise that:

> ‘As researchers in STS, our primary concern is not with regulation, nor in attempting to draw a line between permissible and prohibited research.’ (Calvert and Frow, 2015: 37)

There are a number of reasons, both theoretical and pragmatic, as to why STS scholars interested specifically in the coming into being of synthetic biology have sought to decentre or to shift their attention away from the question of regulation. A collaborative paper co-authored by Balmer et al in 2015 entitled 'Taking roles in interdisciplinary collaborations: Reflections on working in post-ELSI spaces in the UK synthetic biology community,' is particularly instructive in helping to shed some light on why this is the case.

Balmer et al (2015) are prominent social scientists engaged in the field of synthetic biology. In their 2015 contribution, Balmer et al weave together and reflect on their experiences of endeavouring to collaborate with synthetic biologists in a 'Post-ELSI' context. 'ELSI' is an acronym which refers to the 'ethical, legal and social implications' that stem from the development of new scientific enterprises and technologies (Jasanoff, 2011). ELSI was mandated in 1990 under the provisions of the Human Genome Project. The US National Institutes of Health and the US Department of Energy devoted 3-5% of the Human Genome Project budget specifically to the undertaking of 'ELSI' research (Sateesh, 2008).

A significant number of STS scholars, however, have expressed considerable dissatisfaction with the fundamental premises of the ELSI paradigm. Not only has it been argued that the 'ELSI' paradigm obfuscates the realisation that science is always already social, but it also presumes that the risk and ethical 'implications' of a new technology can be simply 'read off' the scientific and/or technological artefact (Williams, 2006 in Balmer et al, 2015: 7). The ELSI paradigm works to constrain social scientific intervention to the 'downstream' end of novel technoscientific innovations.

STS scholars have endeavoured, therefore, to move into a number of “post ELSI” spaces – to engage ‘upstream’ with the development of technoscientific innovations and to cultivate a series of techniques and tools that help to ‘open up’ (Stirling, 2008) the innovation process to the ‘fruits’ (Callon, 1999) of lay and non-scientific knowledges. And yet, in spite of these developments, Balmer et al (2015: 6) posit that the ‘lasting legacy’ of ELSI logics and practices remains ‘obdurate.’ Balmer et al (2015: 3) provide an illustrative account of how, although they have been ‘offered roles in technical projects and as part of scientific research centres,’ they are rarely regarded as ‘co-investigators’ in their engagements with synthetic biology practitioners. Instead, they are often positioned as either ‘administrators,’ ‘representatives of the public,’ ‘trophy wives’ or ‘foretellers’ of any regulatory and public relations hurdles that might forestall the realisation of the coming into being of novel technoscientific artefacts.

Significantly, it is not simply Balmer et al (2015) whose attempts to open up and to move into ‘post-ELSI’ spaces have been fettered by some of the lingering presumptions that underpin the ELSI paradigm. The prominent anthropologist Paul Rabinow and the STS scholar Gaymond Bennett (2012: VII) similarly found that, throughout the course of their engagements with prominent synthetic biologists in the United States, they did not regularly encounter a ‘warm glow of solidarity, curiosity and reciprocity' from those that they were attempting to collaborate with.

Both Balmer et al (2015) and Rabinow and Bennett (2012) highlight how the lingering presumption that social science exists to identify the ‘downstream’ implications of technoscientific developments is continuing to impact upon the ability of social scientists to push into, and to open up, post ELSI modalities of scientific/social scientific engagement. It is in part for this reason that a number of STS scholars interested specifically in the development of synthetic biology have sought to distance themselves from the question of regulation. Regulation, in other words, all too easily feeds conventional renderings of the social scientist as existing simply to remediate what Bock and Buller (2013: 403) describe as 'the barriers and pathways [to] scientific innovation adoption.' There is a politics to the decision of STS scholars interested in synthetic biology to foreground, at present, certain sites of inquiry over others.

It is my aim in this thesis, to complement and extend the work of Balmer et al (2015) by turning explicitly towards synthetic biology's regulatory provocations – particularly in terms of biosafety and the risks posed by the undertaking of synthetic biology practice to human health and environment. I turn now to consider the ways in which the question of regulation has been theorised and approached within wider social scientific literatures. I provide an account of the conceptual tools and sensitivities which shape the way in which I think about and approach the question of regulation in this thesis.

4.2. Regulation Beyond Foucault

The term regulation is often linked to and associated with the work of the French philosopher and social theorist Michel Foucault. For Foucault (2007), regulation is about the tempering of risk and the securing of circulation. In chapter five of the thesis I trace the ways in which synthetic biology is intersecting in, and interfering with, extant modalities of regulatory organising for the UK Health and Safety Executive (HSE). I provide an account of how I came to work ethnographically alongside HSE in the methodology chapter of this thesis.

HSE's regulatory remit is to delimit risks to human health and the environment posed by the undertaking of synthetic biology practice and work with biological agents more generally. HSE endeavours to temper the excessive propensities and risky proclivities of synthetic biology in a manner that simultaneously enables synthetic biology work to go ahead. HSE's approach to the doing of regulation is concerned, therefore, with what Foucault would describe as 'modulation' and 'optimisation' – that is, with facilitating <u>and</u> suppressing. This is exemplified by HSE's mobilisation of the principle 'so far as is reasonably practicable' (SFAIRP). SFAIRP is a principle which acknowledges that regulation cannot afford to be all encompassing – that too much regulation stifles innovation and impedes the flow of circulation.

Foucault's work provides a useful departure point for this thesis in that it alerts us to some of the key tensions faced by authorities tasked with the doing of regulation today. But, as a number of scholars have sought to emphasise, when we tend to the doing of the regulation of in practice, we can begin to see that there is a thickness and busyness to the doing of the business of regulation that is obscured by accounts or descriptions of regulation as working simply to 'optimise' and to 'modulate.' Regulation might be about modulation and optimisation, but it is also about attuning, apprehending, negotiating, relating, engaging and much more besides.

The regulatory scholars Farrell et al (2013) usefully capture the dynamism and busyness of the doing of regulation in their recent review of the intersection of regulation and new health technologies. Farrell et al (2013: 3) describe how regulatory environments are becoming increasingly 'more complex and crowded,' with a 'range of actors, institutions and interests advocating particular positions and demanding that certain courses of action be taken.' In this thesis I am interested in the intricacies and the specificities of the ways in which HSE is attuning towards, apprehending and engaging with this thing that is synthetic biology. I noted in the earlier stages of this chapter that HSE's regulatory remit is concerned more with questions of biosafety than it is with biosecurity. HSE's regulatory remit usefully provides, therefore, a focal point of analysis that resists the tendency to apprehend synthetic biology solely in light of biopolitical discourses of securitisation.

There are also numerous examples of the doing of regulation in practice, where the question of who or what is being 'optimised' is not always clear and where regulatory practices work to unsettle, rather than to simply perpetuate, neoliberal regimes of governing (see, for example, Demeritt et al, 2015). Regulation, in other words, takes on different kinds of shapes in different sets of relations. In her work on 'bioconstitutionalism,' for example, Sheila Jasnaoff (2011) usefully points to the 'co-constructedness' of law and science. By tending to the different 'civic epistemologies' that exist between the United States and Europe, Jasanoff draws on and mobilises the 'multiplicity' of space as a means of throwing into relief and making explicit, the 'constructedness' of varying regimes of regulatory governance.

This is not to say that Foucault's account of regulation is not alive towards the thickness of things or the different trajectories along which the doing of regulation unfolds in practice. Latour (2005b: 86) writes of Foucault that 'no one was more precise in his analytical decomposition of the tiny ingredients from which power is made and no one was more critical of social explanations.' But what this is to suggest is that when addressing and thinking through the question of regulation, it is important to bring an *empirical specificity* to bear on our analyses. This means approaching regulation as a complex set of practices rather than as a pre-formatted 'site' that is oriented towards particular kinds of pre-specified ends.

The ways in which geographers have approached and engaged with the doing of regulation in practice is particularly instructive in this regard. The work of the geographers Nick Bingham, Steph Lavau and David Demeritt informs the way in which I approach and apprehend the site that is the doing of regulation in this thesis. In their engagement with the regulatory challenges of the securing of food safety, Bingham and Lavau (2012) approach the doing of regulation in a manner that departs from a strictly Foucauldian lineage. For Bingham and Lavau (2012: 1590), there is an 'abundance' to the typical inspection visit – an abundance 'from which we have much to learn.' In their 'paying attention' to the 'paying attention' of a food safety inspector, Bingham and Lavau (2012) trace the ways in which the typical inspection visit involves a thickness of things.

This thickness or abundance of things includes the folding together of multiple versions of the future and an acknowledgement that food businesses 'cannot be all about food safety' (Bingham and Lavau, 2012: 1602). Food products are simultaneously expected to be tasty, healthy and affordable, amongst other things. The significance of this busyness or multifactedness of the doing of regulation for Bingham and Lavau (2012: 1589) is that the securing of meat as a material object of regulation involves a great deal of 'underrecognised, undervalued, and untheorized articulation work.' Bingham and Lavau posit that:

> 'Yes, security, "unlike the law that works in the imaginary and discipline that works in a sphere complementary to realities, tries to work within reality" (Foucault, 2007, page 45), but that 'reality has a rather more complex present and presence than Foucault was able to acknowledge, and a more complex present and presence than much (though by no means all) of the biopolitics literature that has been generated since.' (Bingham and Lavau, 2012: 1603)

Bingham and Lavau are directing our attention here towards the complexities and multifacetedness of regulatory attempts to make matters safe. Bingham and Lavau emphasise the skilful articulation work and the careful modalities of apprehension that contribute to the 'tending' of the 'tensions' of food safety (Bingham and Lavau, 2012). Similarly to Bingham and Lavau, I ask in this thesis; what kinds of skills and affordances might be necessary to contribute to the bringing of synthetic biology into a governable world? I am interested in where and how synthetic biology is forcing thought for HSE. I ask; how might this emergent 'thing' that is synthetic biology be pushing and pulling HSE in different directions and how and where might HSE and synthetic biology be mutually reconfiguring one another in the process?

David Demeritt (2015), like Bingham and Lavau, has similarly brought an empirical specificity and a geographically inflected approach to bear on the question of regulation in a number of different contexts. In a 2015 paper 'Mobilizing risk: explaining policy transfer in food and occupational safety regulation in the UK,' Demeritt and colleagues (2015: 373) trace the ways in which the regulatory regime for food safety has been 'less receptive to risk based reforms of its organising principles and practices' in comparison to the regulatory regime for the oversight of occupational health and safety. In drawing on policy mobilities literature Demeritt et al (2015) argue that the persistence of a non-risk based approach to the doing of the regulating of food safety can be attributed to a number of factors including the Food Standard Agency's (FSA) institutionally distinct responsibilities for standard setting and for enforcement. Demeritt et al conclude their paper by arguing that:

> 'The complexity and unevenness of these policy transfers challenge arguments that suggest risk-based regulation reflects either a coherent

> Anglo-Saxon style of regulation (Rothstein et al., 2013) or the globalising forces of neo-liberalisation (Gray, 2009).' (Demeritt et al, 2015: 386)

What makes Demeritt et al's paper of particular relevance to this thesis is that insists, following Law (2015: 127), that there is 'no overarching.' Demeritt et al (2015) foreground the importance of *context* and are attendant to the ways in which general principles such as 'risk based' regulation are reworked and refigured anew, as they are 'translated' (Callon 1986) into the particularities of practice. It is these sensitivities and sensibilities that I mobilise in endeavouring to trace the regulatory provocations associated with the coming into being of synthetic biology. Rather than starting out from the presumption that regulation today is characterised by either a power over or a power vacuum (cf Tombs and Whyte, 2013), I am interested instead in opening up an empirically informed account of what happens when this emergent thing that is synthetic biology and the sensitivities and sensibilities of HSE meet.

5. Opening up 'Little Narratives' in a 'Fractiversal' World

In this chapter I have set out the literature of relevance to this thesis. The conceptual tools and sensitivities that I have engaged with in this chapter remind us that the world within which we live and the objects that populate it are anything but singular or settled. To foreground difference and multiplicity in the world is to acknowledge that we live in what the sociologist of science John Law (2015) describes as a *fractiverse*. The fractiverse refers, in the broadest possible sense, to a world of things and sensibilities that are enacted (and not simply perceived) in different and multiple (but not unrelated) ways.

Thinking fractiversally does not so much constitute any kind of theoretical straitjacket as it does a point of *departure* – a point of departure which insists that the prevailing stories of progress and perspecitvalism that have so readily surrounded the coming into being of synthetic biology are by no means the only stories to be told. It is a point of departure which, in its attentiveness towards the scrambling propensities and the busyness of practice, interferes with singularity and the pretence of set trajectories. I turn now towards some of the methodological implications of endeavouring to trace the taking of shape(s) of synthetic biology in a fractiversal world.

Chapter Three

Methodology

1. Chapter Overview

In this chapter, I provide an account of the methodological and ethnographic (or what Mol (2002) would term as the 'praxiographic') approach that underpinned the fieldwork component of the thesis. I reflect on how my interest in synthetic biology led me to the Health and Safety Executive (HSE) - the UK competent authority responsible for regulating this developing approach to biological engineering. I provide an account of how I came to work ethnographically alongside HSE's Biological Agents Unit as a Major Hazards Policy Researcher over the course of a one year period from April 2014 – April 2015. Working alongside HSE provided me with a critical entry point into the developing field of biological engineering that is synthetic biology. It enabled me to gain access to, and to interview, over thirty leading practitioners in this developing field of technoscientific endeavour. It also enabled me to trace the ways in which this emergent 'thing' is intersecting in, and interfering with, extant modalities of regulatory organising for HSE.

In this chapter I reflect on the conceptual sensitivities underpinning the fieldwork component of the thesis. I engage with ontopolitical methodological frameworks as a means of exploring complexity in the world. I discuss, in what follows, the pragmatics of the doing and unfolding of research in practice and the challenges of working with the abundant nature of field notes, ethnographic materials and interview transcripts. I also describe my approach to the doing of data analysis. Analytical tools such as coding are part of a creative process – that is, they contribute to the generation of certain kinds of reals and to the telling of certain kinds of stories (Law, 2004). I reflect in this chapter on the kinds of stories and the kinds of reals that I endeavoured to give breath to throughout the course of the unfolding of this research project. Through attending to the specificities of the unfoldings of things done in action and in process, ontopolitical methodological frameworks allow for the thickness and complexities of practice to be brought to the fore.

2. Approaching the Research Aims of the Thesis

Synthetic biology aims to design and construct new biological parts, systems and devices and to redesign existing natural biological systems for useful purposes (Roberts et al, 2013; Zhao 2013; Engelhard 2016). I highlighted at the very outset of the thesis that this is a field that has become surrounded by what Marris and Rose (2012) describe as a considerable amount of 'hype' and 'hyperbole.' There is, in other words, a noisy 'perspectivalism' (Mol, 1999) that has accompanied synthetic biology's coming into being – a perspectivalism which oscillates, for example, between accounts of synthetic biology as a 'monstrous' endeavour which defiles the integrity of species existence, to accounts which posit that synthetic biology is but the latest and salvational iteration of human ingenuity (cf Gschmeidler and Seiringer, 2012; Ancillotti et al, 2015). This is a perspectivalism that drowns out the possibilities for a more nuanced discussion (Marris and Rose, 2012). It is a perspectivalism that distracts us from 'less exciting but more pressing questions' such as 'what are synthetic biologists actually doing? How easy, or difficult, is it proving? What applications are they realistically going to develop in the short to medium term? What is their intended purpose, and to what extent could these contribute to the public good?' (Ibid., 29).

The aim of this thesis, in light of the epistemological circularity as diagnosed by Marris, Rose and others, was to contribute to the effort of multiplying synthetic biology's reals rather than simply its surrounding eyes (Mol, 1999). I wanted, in other words, to generate some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. But what might a less perspectival account of the coming into being of synthetic biology look like? What kinds of 'forums' or sites of doing, might help to throw into relief some of the key tensions and trajectories associated with the taking of shape(s) of synthetic biology as it comes to inhabit the world in action and in process? What sites of inquiry, in other words, might help to provide an insight into the ways in which synthetic biology shifts its shape(s) and shifts the shape(s) of other things, as it becomes imbricated within, and intersects with, different practices and webs of relations? And, perhaps most importantly, what kinds of lessons might we learn from teasing out and tracing the nature of these encounters and imbrications?

Within the UK context, the taking of shape(s) of synthetic biology is intertwined with the regulatory practices of HSE, the UK competent authority responsible for delimiting risks to human health and environment posed by the undertaking of work with genetically modified organisms and biological agents more generally. The question of what it might mean to regulate synthetic biology and to regulate it well, is a question that has been largely underexplored within science and technology studies (STS) literatures. This can be attributed, in part, to what Balmer et al (2015: 6) have described as the 'lasting legacy' of ELSI (ethical, social and legal 'implications') logics and practices – a legacy which continues to position social scientists (particularly those interested in the developing field of synthetic biology) as either 'representatives of the public' or 'foretellers' of regulatory and public hurdles. This is a legacy that has led STS scholars such as Calvert and Frow (2015) to explicitly distance themselves from examining the question or the site of the synthetic biology regulatory encounter.

Attending then, to the nature of the synthetic biology regulatory encounter would provide me with a relatively underexplored avenue of engagement or set of reality making practices, through which to address the aim of the thesis of generating some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world well. It would also, I hypothesised, provide me with an entry point or access route into the synthetic biology community more generally. Engaging with practitioners involved in the doing of synthetic biology in practice would prove critically important in enabling me to address the aim of the thesis of contributing to the telling of what Lyotard (1984) would describe as 'little narratives' surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. 'Little narratives' are multiplicitous and heterogeneous narrations whose 'conflictual multiplicity and heterogeneity' (Carroll, 2006: 42) interferes with singularity and the pretence of set trajectories.

In the discussion that follows, I explain how my interest in the reals of synthetic biology – in how synthetic biology takes shape(s) as it becomes imbricated within different kinds of practices and webs of relations, led me to HSE, the UK competent authority responsible for contributing to the regulatory oversight of this developing approach to biological engineering. I provide an account of how I went about establishing a research secondment with HSE and how this enabled me to establish contact with over 30 leading practitioners in the field of synthetic biology. Working alongside HSE enabled me to develop a sense of what the doing of the business of regulation feels like for HSE - to trace the nature(s) of the mixings of the varying 'things' and space-times that are imbricated within, and which intersect with, HSE's approach to the doing of regulation. It also provided me with access to a range of materials, practices and processes that enabled me to trace the forcings of thought and the regulatory provocations posed by the coming into being of this developing approach to biological engineering.

3. Approaching Synthetic Biology in Action: Ontopolitical Methodological Frameworks

Methodological approaches to the doing of research are performative – they contribute to the generation of certain kinds of reals. Law (2004) has powerfully argued that there is an urgent need for 'messy' method – for methods that are better able to engage with the kaleidoscopic, diffuse and processual nature of realities that are never simply made, but which are always already in-the-making. Latour (2005) and Mol (2002) similarly argue that we need to experiment with the methodological tools that enable us to map out the making of realities in action and in process. The sentiment espoused here by Law (2004), Latour (2005) and Mol (2002), resonates with the ethos or sensibility of actor-network theory that I delineated in the preceding chapter of the thesis. Latour (2005), for example, describes the importance of teasing out and making explicit the hidden geographies of the 'gathering' – that is, the ways in which the assembling and association of certain 'things' contributes to the patterning and taking shape(s) of certain realities.

Law and Mol (2002) similarly speak of 'complex' presents – of how presents are patterned and configured differently by the mixing and coming together of varying practices, space-times, materialities and sensitivities. Mol (2002) describes the tracing of complex presents as 'praxiography.' Praxiography refers to the cultivation of an attentiveness towards the relatedness and the taking shape(s) of things in practice and in relation. 'To be is to be related,' as Mol (2002: 53) puts it. Underpinning the arguments of Latour (2005), Law and Mol (2002) and others, is an attentiveness towards and an endeavouring to make explicit, the politics of ontology – that is, the 'way in which 'the real' is implicated in the 'political' *and vice versa'* (Mol, 1999: 74, emphasis in original). Praxiography is interested in the intricacies and the specificities of reality making practices.

In order to map out the ways in which synthetic biology was intersecting and imbricated within the practices of HSE, and in endeavouring to tell different kinds of less-perspectival and less-technologically-deterministic stories about the coming into being of synthetic biology, it was clear that some form of ethnography, some way of getting at the messiness and the complexities of things done in action and in process, was a critical perquisite or a critical entry point rather, in gathering and generating the kinds of resources that might be required to multiply synthetic biology's reals.

Ethnography is a methodological tool that is especially attentive towards the doings of things in action and in process (Falzon 2016; Latour and Woolgar 1986). It is an approach to the doing of research that tends to involve an 'immersive' period of study (Latour and Woolgar 1986; Cambrosio, Limoges and Pronovost 1990) whereby a researcher will endeavour to situate themselves in the 'midst' of a particular 'community' or 'institution' or perhaps even within the midst of a 'gathering' that surrounds a particular 'matter of concern' (Latour, 2004). Ethnography, in this vein, is a critical component of an ontopolitical methodological framework.

Traditionally speaking, ethnography tended to conjure notions of a 'scientist' or 'specialist' venturing 'out' into the world with a view to collecting (as opposed to generating) passive segments of ‘data’ that were simply waiting to be unveiled by an ‘expert’ figure (Massey, 2003). As Goodley (2007: 16) explains, this can be attributed, in part, to the emergence of ethnography within the context of the sub-discipline of ‘descriptive anthropology’ – an approach to the doing of research whereby research participants were regarded as ‘passive elements of a culture’ that could be understood by an ‘all-knowing researcher.’ Since then, however, the discipline of anthropology has become increasingly self-reflexive (Kearney, 2004; Kim 2002). Ethnography as a methodological tool has begun to take different kinds of shape(s). Its contours have become reworked and refigured anew by different kinds of conceptual sensitivities and by different objects of social scientific inquiry.

Stemming in part from what is widely described as anthropology’s ‘crisis of representation’ (Marcus and Fisher, 1986) – a formative period in the discipline of anthropology where the role and significance of the expert researcher was called into question - anthropologists have sought instead to foreground the partiality and incompleteness of their ethnographic representations, acknowledging, for example, that all representations are necessarily re-presentations and that such re-presentations are not only generative of certain kinds of effects but are imbued with political implications and power relations of varying kinds (Grimshaw and Hart 1993; Benthall, 2013).

In the field of science and technology studies, sociologists of science, particularly during the early 1970s, similarly began to mobilise an ethnographic approach not as a means of documenting pre-existing ‘realities,’ but as a means of tending to the ways in which realities are being made, or, better yet, are always already in process and in the making. I developed an account of the significance of ethnography to the sensibilities and sensitivities of STS in the preceding chapter of the thesis.

In more recent years, ethnography has also had to shift its shape in order to engage with the complexities of an increasingly networked and 'globalised' world. George Marcus's (1995: 95) pioneering work on multi-sited ethnography, for example, has called for social scientists to attend to the 'circulation of cultural means, objects and identities in diffuse time-space.' Social scientists such as Martin (1994), Tsing (2011; 2015) Rahm (2010) and others have subsequently sought to 'follow people connections, associations, and relationships' across different forms and instantiations of space-time (Falzon: 2009: 1-2). In many ways Marcus's call for multi-sited ethnography and multi-sited methods resonates with the recent work of Law (2004: 3) who posits that ethnography needs to 'work differently if it is to understand' and to intervene in 'a networked or fluid world.' Law's (2004) work, however, is also somewhat different to Marcus's in that it is much more explicit in its foregrounding of incoherences, fractionalities and multiplicities.

But, it is also important to note here that it is not simply the case that ethnography has become refigured anew in order to better attend to the disparate space-times of a more networked and globalised world. Ethnographic research practices have also had to learn to become attendant to what Kirksey and Helmreich (2010) describe as different kinds of multispecies encounter – encounters which acknowledge that the world within which we live is brimming with a plethora of more-than-human and other-than-human critters and things. As the anthropologist Donna Haraway (2008: 244) puts it, any 'becoming is always becoming with – in a contact zone where the outcome, where who is in the world, is at stake.' Multi-species ethnographies thus acknowledge and exhibit an attentiveness towards the agency of different species and other kinds of more-than and other-than-human things in the making and re-making of worlds.

Multisited, single sited and multispecies approaches to the doing of ethnography are methodological tools that require the investment of a considerable amount of time. They tend to include the undertaking of some form of participant observation. The idea behind this is that by attuning carefully towards the messiness and the complexities of things done in action, it becomes possible to develop a richer, nuanced and more textured account of different kinds of things as they unfold processually and take different kinds of shape(s). Latour and Woolgar's (1986) *Laboratory Life* was the outcome of a two year period of ethnography and participant observation. In addition to including some form of participant observation, ethnography tends also to include the patching together of other methodological tools and devices which might include, for example, interviews, desk-based background research and focus groups (O'Reilly, 2012; Crang and Cook, 2007; Falzon 2016).

Depending on how ethnography is done, it becomes possible to generate what Law et al (2013) would describe as a number of different 'goods.' These 'goods' might include, for example, the amplification of what Hinchliffe (2010) terms as the fraying edges of a particular object or matter of concern. They might also include the unsettling of predominating ways of thinking about things. In this regard then, depending on how ethnography is done, an ethnographic approach might help to open up new possibilities for thinking and doing things differently. It can work to equip social scientists with the material generations, for example, to tend to what Derrida (1978) describes as the disjunctions between worlds and words. In addition to unsettling however, ethnography can also help to develop a richer and fuller appreciation of how and why certain practices take or are pushed into certain kinds of shapes.

In endeavouring to ascertain how synthetic biology is taking shape and is imbricated within the practices of HSE, and in endeavouring also to multiply synthetic biology's reals, it was clear that an ethnographic approach – an approach that foregrounds the doing of things in action and in process, would be an essential tool in generating the resources required to address the research aims of the thesis. The methodological approach of this thesis cannot, however, be described as a conventional ethnography in the traditional sense of the word. The fieldwork materials that appear throughout much of the course of chapters four and five are largely derived from interview transcripts and excerpts. The methodological approach can nevertheless be described as ethnographic in that these materials emerged as a direct result of my being present at, and embedded within, HSE's Biological Agents Unit. These materials were shaped and patterned by the encounters, insights and connections that I developed at HSE.

It was through, for example, the process of being able to attend policy deliberations and team meetings of varying kinds, that I was able to more effectively probe the regulatory challenges associated with the development of synthetic biology through interviews and more informal conversations with BAU team members. Meetings, draft regulations and off site trips to containment facilitates all worked to provide moments or instances that 'forced thought' (Stengers, 2005) and which necessarily contributed to shaping my understanding of what it might mean and what it might take, to bring synthetic biology into a governable world. The positive rapport that I developed with members of the BAU contributed to the types and kinds of interview materials and responses that I was able to generate.

Furthermore, it is unlikely that I would have been able to access and interview such a prominent and varied range of synthetic biology practitioners without being affiliated with HSE and positioned as a Major Hazards Policy Researcher. Many synthetic biology practitioners are not only acutely aware of the regulatory challenges surrounding synthetic biology, but are also keen to share their practices and experiences and to contribute to the responses that surround the question as to what it might mean and take to bring synthetic biology into a governable world.

It is important to acknowledge here that interviewing in itself does not constitute an 'ethnographic' methodology. Interviews in particular have been criticised for their limited ability to access and apprehend the thickness and grittiness of practice. Nevertheless, in the latter stages of this chapter I argue that people *can* talk powerfully and with nuance about their practices. It is not simply the case that practice necessarily becomes sedimented down into unreflexive or unthinking habit (see Hitchings, 2012).

In short, the methodological approach of the thesis can be described as ethnographic in that a) the interview materials that take centre stage in chapters four and five of the thesis emerged directly from and were patterned by the very process of being embedded within HSE and b) underpinning the thesis is a commitment to exploring the thickness of practice. The thesis starts out from the recognition that in a busy and processual world the progressive and economistic narrations that have surrounded synthetic biology are by no means the only stories to be told. Acknowledging the thickness and complexities of practice is a key hallmark of an ethnographic sensibility. I turn now towards the specificities and pragmatics of the ethnographic and methodological design of the thesis in practice.

4. **Research in Practice**

4.1. Establishing Contact with HSE

I first approached HSE in late November 2013 to establish whether it might be possible to set up an informal fieldwork relationship where, at the same time as conducting my own research into the field of synthetic biology, I could also look into any specific matters of concern for HSE. I was aware at the time that HSE were endeavouring to keep a 'watching brief' (HSE, 2012) on this developing approach to biological engineering. My initial contact with HSE was met with a positive and enthusiastic response. This was an exciting moment in the coming together of the methodological design of the thesis. It was a moment that reaffirmed the assertion of Cook and Crang (2007) that places that might seem to be far away or out of reach even, are often closer than we might initially realise – that there are no isolated or discrete organisations, goings on or doings that are not suffused with, or separated from, sociabilities and relationalities of varying kinds.

Establishing a research arrangement with HSE would turn out to be a lengthy and fragile process that extended over a 6 month period[1]. And yet, in spite of the fragility and lengthiness of the process, the ultimate relationship that I was able to develop with HSE was incredibly rewarding. During my time at HSE I was fully

[1] This was a period where, on many occasions, it looked increasingly unlikely that any kind of relationship or engagement even with HSE was going to be possible. Throughout the course of negotiations with HSE and the ESRC, it ultimately transpired that I could only establish a research relationship with HSE if I worked with HSE on the basis of a secondment. This required that I have the status of an employee rather than a student. In the end, it was down to the perseverance and skilful contractual work of the University of Exeter and HSE that I was eventually able to be seconded to HSE.

integrated (by way of a 'secondment') into HSE's Biological Agents Unit as a 'Major Hazards Policy Researcher' and was able to attend and participate in the fullness of the doing of the business of regulation for HSE. I was able to tap into, and to access, the wider synthetic biology community as well as HSE resources and networks. In the subsequent section of this chapter I elaborate upon the specifics of what my time at HSE looked like. I provide a descriptive account of a typical week at HSE.

Whilst negotiating my secondment to HSE, the policy lead of HSE's Biological Agents Unit (BAU) placed a submission to HSE's Corporate Efficiency Board (CEB) in order to secure the funding and resources required for the secondment to go ahead. Section 4.2 of this chapter provides a detailed account of the role and responsibilities of the BAU. The stated purpose of the secondment was to 'gather intelligence and analyse the resultant data for the purpose of developing HSE policy within the area of synthetic biology.' It was noted on the submission to the Corporate Efficiency Board that:

> 'Synthetic biology presents a number of challenges to HSE, which include assessment of novel hazards, exposure of diverse workforces to new and unfamiliar hazards and how to regulate activities outside the work environment (in a proportionate and responsible manner). These are complicated by the political environment, in which, the Minister for Universities & Science (BIS) is a vociferous advocate of ensuring that synthetic biology is regulated in an enabling manner and the Convention on Biological Diversity, has identified synthetic biology as a new and emerging issue for biodiversity, with significant concern raised by green pressure groups.'

The secondment was to be a mutually beneficial arrangement and it was agreed that I would produce a written report for HSE that would weave together the empirical materials and insights that I would generate throughout the course of a series of interviews and engagements with synthetic biology practitioners. Being affiliated with HSE would help me to gain access to these practitioners and it would also enable me to tap into HSE resources and materials including, for example, the responses that HSE had recently received from its UK wide consultation on the consolidation of the Genetically Modified Organisms (Contained Use) (GMO CU) Regulations.

The consolidation of the GMO regulations was an outcome of the 2011 Lofstedt Review. Led by Professor Ragnar Lofstedt, Chair of Risk Management at Kings College London and commissioned by the then Employment Minister Chris Grayling, the review examined over 200 health and safety regulations and 53 Approved Codes of Practices or 'ACOPS,' as they are more commonly known. It called for a 35% reduction in health and safety legislation – a sizeable figure by all accounts. The review culminated in a number of recommendations which it felt would not only help to make the regulatory landscape less 'voluminous' but which would also help to 'reposition' health and safety legislation as a vital part of doing 'good business.'

In the process of consolidating and updating the GMO regulations, HSE initiated a UK wide consultation process. This included a questionnaire which was sent out to more than 700 stakeholders across the biotech community. A further 4000+ individuals were alerted to the questionnaire through HSE's Biological Agents eBulletin. The questionnaire made specific reference to the development of synthetic biology and it provided respondents with an opportunity to reflect on whether they felt synthetic biology raised any particular regulatory provocations and on what kinds of regulatory models they felt might be suitable for the effective and responsible regulation of this developing field of technoscientific practice. Forty-two responses were received by HSE.

In addition to providing me with an insight into what the doing of regulation looks and feels like for HSE, the secondment would also help HSE to achieve a number of different things. This became most clearly apparent to me after having accompanied a BAU team member on a cross government visit to BIS - the Department for Business, Innovation and Skills (now known as the Department for Business, Energy and Industrial Strategy) to discuss a number of overlapping areas of regulatory interest. BEIS or BIS as it was known at the time, is a UK government department that is responsible for contributing, in part, to the freeing up of innovation and for enhancing UK economic efficacies and competitiveness.

This early meeting between HSE and BIS was particularly useful in helping me to develop an understanding of the different priorities and sensitivities of these two governmental organisations. HSE, unlike BEIS, is a non-departmental public body of the UK – that is, as a regulatory authority, it carries out its work at an 'arm's length' from ministers. The BAU team member that I accompanied on the visit, however, was unsure just how interesting or useful I might have found this meeting. They explained that even if the usefulness of this meeting was not immediately apparent to me, it was important in adding to the relationship between these different bodies – in letting BIS know that HSE were indeed taking the regulation of synthetic biology seriously.

A number of weeks later, in a ministerial write-round, HSE were commended for their pro-active engagement with the coming into being of synthetic biology. This was shared at HSE as an example of good practice:

> 'We welcome the further work that HSE is currently initiating to better understand the risks associated with the potential applications of synthetic biology which should help to inform future regulations in a similarly responsible and proportionate way.' (The Rt Hon David Willetts MP

[Minister for Universities and Science] to Rt Hon Nick Clegg MP [Chair of the Home Affairs Committee] and the Rt Hon Vince Cable MP [Chair of the Reducing Regulation sub-Committee].

Being present, therefore, at HSE provided me with a means of learning about how the different parts and components of government get done and performed in practice. It provided me with an insight into what it looks and feels like to be a non-departmental regulatory authority working within a broader ecosystem of regulatory and governmental practices, activities and initiatives.

In short, by working as a Major Hazards Policy Researcher for HSE's Biological Agents Unit, I would be provided with an entry point into the worlds of regulation and into the field of synthetic biology. HSE, on the other hand, would be provided with an opportunity to enhance their evidence base and to continue to keep a 'watching brief' on this developing field of scientific endeavour. This collaborative approach to the doing of research would ultimately afford me with a lens through which to examine a particular set of practices where synthetic biology is being done and taking shape(s). It would enable me to depart from the epistemic circularity that I outlined at the very outset of the thesis and to zone in on a particular suite or set of practices where synthetic biology is forcing thought. It would enable me to open up and to tend to the skills and affordances that might be necessary to contribute to the effort of the bringing of synthetic biology into a governable world.

4.2. Specifics of the Fieldwork Approach

Throughout the course of the fieldwork period which ran from April 2014 to April 2015, I spent one week per month based at the BAU's offices at HSE's Headquarters in Bootle, Liverpool. The Biological Agents Unit is a policy and inspectorate division comprised of 26 staff which forms part of the Health and

Safety Executive's Hazardous Installations Directorate (HID). The remit of the Hazardous Installations Directorate is to implement and develop legislation and policy relating to 'major hazard industries whose products are essential to our everyday life, but where failures in safe management and risk control can lead to catastrophic harm to workers and the public at large.' These are industries which are typically regarded as involving 'complex processes with intrinsic hazards that need careful management.' HID itself is composed of two overarching divisions; the 'Chemicals, Explosives and Microbiological Hazards Division,' which includes the Biological Agents Unit, the Chemicals Unit and the Explosives Unit, and the 'Energy Division,' which covers the offshore industry, the gas and pipeline industry and the mining industry.

The Biological Agents Unit is largely composed of specialists in the fields of microbiology and biotechnology who have a 'broad collective experience' in the 'research, clinical and industrial bioscience sectors.' The BAU's policy team is responsible for ensuring that HSE's regulatory approaches are in line with broader government initiatives and in contributing to and shaping the direction of international negotiations concerning biological agents. The BAU's operational team consists of 15 specialist inspectors and two intervention managers. The operational team reviews and approves risk assessments received by HSE and is responsible for conducting proactive and reactive inspections at sites registered as working with biological agents and genetically modified organisms.

During the one week per month that I would spend in Bootle, Liverpool, I was allocated a desk amongst the policy team and would attend a range of meetings from the policy-specific to the project-specific. At the time of my fieldwork, the BAU were undertaking a number of workstreams including - but not limited to - the consolidation of the GMO Regulations; the development of a compendium of guidance to accompany the new regulations and the transfer of licensing responsibilities for work with specified animal pathogens from Defra to HSE. The BAU were also involved in contributing to the European Scientific Committees (ESC) consultation on synthetic biology and in shaping international policy negotiations concerning the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. The Cartagena Protocol is a supplement to the Convention on Biological Diversity which endeavours to ‘protect human health and the environment from the adverse effects of the products of modern biotechnology’ (CBD, 2000: 1).

Whilst at Bootle I would meet with and interview members of the BAU and civil servants working in different roles and capacities across HSE more widely. I would spend time at my desk simply attuning to the rhythms and the busyness of the goings-on of different things and doings for HSE. I would attend meetings relevant not simply to HSE’s BAU but also to HSE as a whole. This included, for example, a policy ‘away day’ that took place at a local college in Bootle. The policy away day examined what it means to be a ‘policy professional’ and to make and develop policy and legislative provisions within the current political climate. I was also able to engage in the doing of regulation in practice. I was provided, for example, with the opportunity to draft an EU position paper on the contained use of living modified organisms in light of the provisions of the Cartagena Protocol on Biosafety. This paper, which made reference to the developing trajectories of synthetic biology, was then presented at the European Commission in Brussels which I was able to attend.

Whilst at HSE I was also able to tap into and to use HSE’s networks to send out a survey to synthetic biology practitioners requesting information on a number of key questions devised in conjunction with a team member from the BAU. This survey requested information on; the type of work being undertaken by synthetic biology practitioners; whether or not practitioners foresaw any regulatory challenges associated with their work and who/where they would seek advice and support should they have any concerns about the risks posed by their project to either human health and/or the environment. A copy of the survey can be found in Appendix 1. This survey was sent out across HSE's network of registered premises. A total of 17 responses were received. The survey also provided room for practitioners to provide a more open ended reflection on synthetic biology's regulatory provocations.

Outside of my week at Bootle I accompanied members of the BAU on a number of visits ranging from the 'inspection' visit to dutyholder engagement events, to cross-government 'relationship building' visits. These visits and meetings provided me with a feel for, and an insight into, the busyness and the multi-facetedness of the doing of the business of regulation for HSE. The busyness of the doing of the business of regulation for HSE provides an important background context to the second empirical chapter of the thesis, where I turn to examine how synthetic biology is intersecting in, and interfering with, extant modalities of regulatory organising for HSE.

During my time at HSE I had to learn to attune towards and become comfortable with 'going with the flow.' This required, for example, taking the opportunity to ask questions as certain things 'came up' at unexpected moments, sitting in on impromptu meetings and accompanying BAU members on lunch time strolls around Bootle. Conducting fieldwork in this way was, at times, a slightly unsettling task. It was a task that required what Hinchliffe et al (2005) describe as getting a feel *for* things rather than a neat and tidy knowledge of them. Perhaps this is what Law (2004: 9) means when he asserts that when we engage in the doing of fieldwork - when we endeavour to attune towards fullness of a busy and abundant world we need 'to unmake our desire and expectation for security.'

The sources used to inform and construct chapter five on what it might mean and take to bring synthetic biology into a governable world were therefore diverse and varied. These sources included:

- Notes and interview materials from meetings with key figures in HSE. I met on a one to one basis with individuals including HSE's Biotech Portfolio Holder responsible for bridging the operational and policy divisions of the BAU; HSE's resident social scientist; the BAU intervention manager responsible for managing the BAU's team of inspectors; the BAU policy team leader responsible for developing HSE's policy and for ensuring that its regulations are in line with broader government objectives; a BAU inspector responsible for implementing regulations on the ground; a senior figure in HSE's Cross Cutting Interventions Division (CCID); a BAU policy team member responsible for contributing to the development of BAU policy and the Senior Civil Servant (SCS) responsible for overseeing policy work done across the whole of HSE's Hazardous Installations Directorate.
- Notes and materials from nine BAU meetings where a diversity of topics were discussed and deliberated including the consolidation of the GM regulations, potential challenges posed by synthetic biology and the regulatory provisions surrounding work with specified animal pathogens.
- Notes and documents from meetings of the Scientific Advisory Committee on Genetic Modification (Contained Use) (SACGM CU). During the course of the fieldwork period I was able to attend three SACGM meetings. At these meetings HSE received advice from scientific experts on contentious risk

assessments submitted to the BAU and discussed policy initiatives and developments with SACGM members including the European Scientific Committees consultation on synthetic biology.

- Notes and materials from off site visits to three containment facilities, the Health and Safety Laboratory (which is the research division of HSE), a BAU policy 'away day' and a cross-government policy meeting in London.
- Email correspondence and HSE strategy documents including HSE's intervention plans and HSE's commercial strategy plans.
- HSE documents including responses to the UK wide consultation on the consolidation of the GM regulations.

I used my time outside of Bootle to establish contact with and to arrange interviews with over 30 synthetic biology practitioners. These interviews were generally 1-2 hours long and were primarily conducted at the interviewees' place of work. This required travelling, often from Exeter, to a diverse range of locations across the country. These often lengthy journeys provided a useful time and space to begin to digest and reflect on the unfolding and content of the interview exchange.

I identified potential interviewees by working my way through the various institutional networks in synthetic biology that had been set up from 2009 onwards. These networks included the Centre for Synthetic Biology and Innovation or 'CSynBI,' as it is otherwise known, which was established in 2009 by a 5 year EPSRC Science and Innovation award and 'SynBiCITE' – an Imperial College led Innovation and Knowledge Centre. SynBiCITE's (2013) stated aims are to; act as an 'industrial translation engine'; to support 'small and medium UK companies'; and to engage in open dialogue with the 'public' and other interested stakeholders.

In addition to identifying and working through the key institutions networks in synthetic biology set up from 2009 onwards I also developed a list of universities and organisations in receipt of recent governmental grants including the ‘Flowers Consortium’ - a group of five universities aiming to develop platform technology and infrastructures for the advancement of synthetic biology and a number of recently established DNA synthesis centres including Edinburgh Genome Foundry and Liverpool GeneMill, which was awarded £2M in 2014 to develop a high throughput system for synthesising genes and DNA.

HSE also provided me with a number of additional contacts and put me in touch with the Biosciences Knowledge Transfer Network – a bioscience network which is supported by Innovate UK (previously the Technology Strategy Board). The Bioscience Knowledge Transfer Network and Innovate UK work with ‘people, companies and partner organisations to find and drive the science and technology innovations that will grow the UK economy’ (Innovate UK, 2015). This helped to ensure that the practitioners that I engaged with as part of this research were not simply or predominantly research based but were working also within the private and commercial sectors.

After having compiled this list of contacts I began to reach out to potential interviewees from my HSE email address, explaining that I was a PhD researcher seconded to HSE and that I was completing a research project on synthetic biology. I emphasised that the research project was interested in developing an in-depth understanding of how synthetic biology is being done in and through practice and in how synthetic biology might be intersecting in, and interfering with, extant modalities of regulatory organising. Following a suggestion from the head of the BAU’s inspection team, I explained that this was a policy project that was not linked to the enforcement side of HSE. HSE felt that my positioning as being both a part of but also simultaneously distant from HSE, might encourage practitioners to be more open in their responses.

It is important to briefly note here that it is likely that being affiliated with HSE may well have influenced the kinds of responses generated during the course of my interviews with synthetic biology practitioners. Berger (2015: 220) writes of the research process that research participants necessarily modulate and adjust their responses based on their perception of the positionality of the researcher and that, in turn, this may affect 'the information that participants are willing to share.' However, I feel that the potential impact of my being affiliated with HSE was lessened in part by making clear to research participants, and emphasising on a number of occasions, that I was as a research student on secondment to HSE.

Table 1 list the details and backgrounds of the synthetic biology interview participants. The names of the research participants have been replaced with pseudonyms and identifying factors have been removed.

<u>Table 1 – Research Interview Participants</u>

Name	Descriptor
Geoff	Professor and Chair of leading UK synthetic biology strategic research initiative, background plant biology, current practitioner of synthetic biology. Geoff is employed at a UK university.
Emmett	Molecular biology and biochemistry background, specialising in biofuels, shortlisted Biotechnology and Biological Sciences Research Council innovator of the year, current practitioner of synthetic biology. Emmett is employed at a UK university.
Lawrence	Biochemist and protein scientist, current practitioner of synthetic biology. Lawrence is employed at a UK university.

Nick	Biologist and Professor in Industrial Biotechnology, specialising in biofuels, current practitioner of synthetic biology. Nick is employed at a UK university and is heavily involved in a number of industry and commercially oriented partnerships.
Toby	CEO & founder of synbio start up, background in microbiology, current practitioner of synthetic biology.
Mark	Director of international gene synthesis consortium. Mark's company distributes genetic sequences and biological parts to a variety of commercial and research oriented organisations and institutions.
Dominic	Director of UK SynBio research network, specialist in protein design, current practitioner of synthetic biology.
Sandra	Scientific Manager, Synbio research centre, UK.
Sarah	Molecular biologist and biochemist, current practitioner of synthetic biology.
Mitch	Molecular biologist and biochemist, current practitioner of synthetic biology.
Hugh	Previously Strategic Programme Manager for Innovation at leading oil and gas company, key contributor to one of the UK's leading biotechnological forums and wider gov synbio strategy (technical background in biophysics). Current Director of UK synbio company.
Richard	Director of renowned genetics spin out. Technology Pioneer of World Economic Forum. Visiting Professor at UK university and current practitioner of synthetic biology.
Lester	CEO of leading UK synbio start-up, venture entrepreneur, background in biochemistry and physics, current practitioner of synthetic biology. Lester is working within the commercial sphere and is an active participant in two key industry forums.
David	Professor of Biotechnology, special interest in synbio, working in advisory capacity to UK government department, practitioner of synthetic biology.

Helen	Scientific Adviser, involved in UK government steering group for synbio. Helen does not have a scientific background.
Jess	Molecular biologist by training, co-founder of biocreative consultancy.
Sam	Molecular biologist, current practitioner of synthetic biology.
Alfosno	Molecular biologist, keen interest in computer science, founder of kickstarter tool to facilitate the undertaking of DIY bio experimentation.
Paul	Molecular biologist, current practitioner of synthetic biology.
Oliver	Geneticist, background in GM crops, government advisor, involved in orchestration of UK 2010 Synthetic Biology Public Dialogue.
Peter	Bioengineer, specialising in synthetic biology and synthetic genome engineering, leader of prominent UK synbio project, working on tools for the acceleration and scaling of biological design, practicing synthetic biology at present. Peter is employed at a UK University.
Mikel	Molecular biologist, specialising in bacteriophage based synthetic biology, current practitioner of synthetic biology. Mikel is employed at a UK university.
Tim	Molecular biologist, specialist in molecular parasitology, current practitioner of synthetic biology.
Owen	Background genetics and nanotech, current practitioner of synthetic biology.
Laura	Specialising in bioinformatics, current practitioner of synthetic biology.
Seth	Scientific adviser on significant synbio project.
Patricia	Microbiologist, principal synthetic biologist, government research organisation.
Kieran	Biosafety specialist, government research organisation.
Lisa	Senior Biological Adviser, Non-Proliferation, DSTL.
Rebecca	Co-founder, DIYbio organisation.
Adrian	Co-founder, DIYbio organisation, creative technologist.

Most of the interviews that I conducted were semi-structured and largely open ended in nature. By adopting a more conversational approach I wanted to provide practitioners with the opportunity to express, in their own terms, what the doing of synthetic biology looks like and means to them. Galletta (2013) argues that a more conversational approach to the doing of interviews can help to generate new insights by resisting or diminishing the potential for the researcher to impose any rigid or pre-determined framework on the 'data' generation process. The social and cultural geographer Robyn Longhurst (2003: 103) relatedly describes how 'semi-structured interviews unfold in a conversational manner offering participants the chance to explore issues they feel are important.'

I would begin the interview process by asking practitioners what they understood by the term synthetic biology. I would then ask practitioners to explain how synthetic biology features in their own working practices. This particular question would typically open up a conversational exchange that would meander in different kinds of directions as practitioners began to explain, often with a palpable sense of enthusiasm, what synthetic biology was enabling them to do and where they envisaged the field progressing. Given that most of the interviews were conducted at the interviewees' place of work it was not unusual for practitioners to enrol into the interview exchange material publications or near to hand documents that helped to exemplify and to illustrate practitioner descriptions and accounts of what synthetic biology looked like and meant to them in practice.

In an influential paper 'People can talk about their practices,' the social and cultural geographer Russell Hitchings (2012: 61) has described how, in spite of the framing of interviews as an inappropriate tool for investigating routine practices - because practices have either 'sedimented down into unthinking forms of embodied disposition,' or, because 'this method is out of step with a current enthusiasm for research styles that do not focus unduly on the representational,' people can nevertheless often talk, 'in quite revealing ways,' about their own working practices. This was certainly the case amongst the synthetic biology practitioners that I interviewed as part of this research.

The interviews that I conducted with synthetic biology practitioners would prove critically important in enabling me to tend to the ways in which the 'object' of synthetic biology is being enacted differently in different sets of relations. I noted at the very outset of this thesis that my initial aim in conducting these interviews was to unsettle the prevalent story of synthetic biology as a predominantly economistic endeavour that is framed in terms of either its 'promises' or 'perils' (see, for example, Tucker and Zilinskas, 2006).

Scientific practice has taken on a somewhat different set of forms and shapes since Latour and Woolgar published *Laboratory Life* in 1986 and it is important to make clear here that synthetic biology in particular is done not simply in the laboratory but also in computer algorithms, electronic exchanges and in multidisciplinary teams that span across a number of different institutions. Interviewing, in this regard, is a pragmatic and important tool in helping to explore and engage with contemporary forms of scientific practice today.

When discussing the regulatory challenges posed by synthetic biology's coming into being, I asked practitioners to reflect on where and how their own practices were working to trouble extant modalities of regulatory organising and whether they foresaw any tensions or challenges arising in the future. In chapter six of the thesis I highlight how the foregrounding and centering of certain kinds of regulatory provocations and challenges amongst practitioners can be linked, in part, to the different kinds of working practices and the different directions that different synthetic biology practitioners are endeavouring to push and pull the field into. I emphasise how the multifacetedness of synthetic biology as an object of regulatory governance requires the cultivation of particular sets of skills, affordances and dispositions on the part of HSE.

Without wanting to reify here the notion of the 'progressive' and 'economistic' synthetic biology that we encountered at the very outset of the thesis, I was aware that a considerable number of synthetic biology practitioners are engaged in the doing of the business of synthetic biology so as to contribute (in large part) to the furthering of what has come to be known as the 'knowledge economy.' There is, in other words, a considerable amount of commercial sensitivity surrounding their work and these are practitioners that are being pushed and pulled in a number of different ways to meet a number of different demands. The philosopher of science Isabelle Stengers (2015: 29) describes the knowledge economy not as an 'empty order word' used in 'reports on the challenges of our epoch but the strong reorientation of public research policy, making partnerships with industry a crucial condition for the financing of research.' These are practitioners, then, that are often pushed for time and who are working in competitive and fast paced environments where commercial sensitivity and 'getting ahead' are predominating orderings of the day.

With this in mind, I realised that if I was to going to successfully engage with these practitioners, then I would need to think carefully about how to manage and make the most of the research encounter. In particular, I spent a considerable amount of time at the earlier stages of the research design of the thesis, familiarising myself with key areas of research in the field of synthetic biology. I read up, amongst other things, on some of the key biological processes and materialities with which synthetic biologists are working. This was, at times, a challenging task not least because of my background as a social scientist (and not a biologist). This was also, however, a remarkably generative task in that learning about the mutable materialities of the stuff of the biological, the complexities of the signalling functions of metabolites and the convoluted patternings of biological emergence, worked to reaffirm my interest in the coming into this world of synthetic biology. From the very outset of the research design process, there seemed to be something geographically interesting about the bringing of an engineering approach to bear on the stuff and substances of the biological. By geographically interesting, I am referring here to the thickness and varieties of the relationalities and encounterings that are unfolding and playing out within and across the organismal milieu and how these are apprehended and understood by synthetic biology practitioners.

In addition to familiarising myself with the processes and practices of synthetic biology, I would also supplement the data generation process by regularly surveying peer-reviewed and popular accounts of synthetic biology. This helped me to keep attuned to the shifting contours of this developing field of scientific endeavour. It also provided me with an awareness of broader trends and happenings that facilitated the opening up of conversation at HSE and throughout the course of my engagements with synthetic biology practitioners. A particularly notable development in the field of synthetic biology that arose during the course of the undertaking of this research, was the synthesis of a fully functional yeast chromosome by a group of undergraduate researchers based in the United States. The synthesis of the functional chromosome marked a significant moment in the development of the field of synthetic biology, reaffirming the ambitions of practitioners to bring an engineering approach to bear on the stuff and substances of the biological.

It is important to note here that by taking the time to learn some of the languages and the technical basics of the doing of the business of synthetic biology, it was by no means my aim to develop any kind of ‘technical’ knowledge that would enable me to ‘represent’ more ‘accurately’ the doings of the synthetic biologist. On the contrary, I would argue that it is the differences in the understandings between, for example, the social scientist and the synthetic biology practitioner, that enable new kinds of questions to be asked and new kinds of provocations to be brought to the fore. Partiality in knowledge, in other words, is not only endemic but, depending on how it is mobilised, it is also affirmatively productive. Stengers (2005) captures this nicely when she reflects on the generativities associated with the Deleuzian figure of the ‘idiot.’ For Stengers (2005: 2), the figure of the ‘idiot’ (a term which is proximate to ‘idiom’) is a presence that produces an ‘interstice’ – an interstice that works to resist ‘the consensual way in which the situation is presented.’

In practice, this meant that I would often emphasise to research participants my background as a social scientist. I would ask, at times, practitioners to explain in greater detail what exactly they meant, for example, when they mobilised technical terms such as ‘morphogenetic’ or biological ‘chassis.’ By encouraging practitioners to switch and to (re)modulate their discursive repertoires, this presented a number of ‘openings’ where I was able to ask interviewees how their explanation fitted with other understandings or approaches to the doing of synthetic biology.

The timing of my getting in touch with these synthetic biology practitioners was helped by the fact that the European Scientific Committees (ESC) had recently issued a consultation on risk assessment challenges associated with the development of synthetic biology. This was something that many of the practitioners that I interviewed were not only aware of, but were also interested in contributing to. Synthetic biology, at the time of the undertaking of this thesis, was very much a live topic that appeared frequently in the news and in wider discussion forums.

It is important to emphasise here that interviews, like all methodological tools, do not provide any 'unmediated' access to the worlds of those engaged in the practice of synthetic biology. Neither can they be said to offer any kind of 'representative' or 'exhaustive' account of the contours and texturings of the developing thing that is synthetic biology. As Valentine puts it, 'the aim of an interview is *not* to be representative (a common but mistaken criticism of this technique) but to understand how individual people experience and make sense' of their own working practices (2005: 111, emphasis in original). That being said, I feel that the length and breadth of the interviews that I conducted, in conjunction with following developments in the field more generally, enables me to encapsulate in chapter four of the thesis, much of what it means, at the present moment, to bring an engineering approach to bear on the stuff and substances of biology. The empirical generations that emerged throughout the course of my interviews with these synthetic biology practitioners enable me to add a texturing to this emergent 'object' that has been so readily framed in an economistic and progressive fashion.

4.3. On Ethics and Being Care-full

The research project was approved by the University of Exeter's Geography ethics committee prior to research commencing. Informed consent was sought from all synthetic biology practitioners who were informed that I was a PhD student seconded to HSE as a Major Hazards Policy Researcher. It was explicitly written into the secondment contract developed between the University of Exeter and HSE that all fieldwork materials generated during my time working alongside HSE as a Major Hazards Policy Researcher could be used as part of my PhD thesis. In accordance with the University of Exeter's ethical procedures, I explicated in my initial correspondence with the practitioners that took part in this research they could withdraw from the research process at any stage.

It is important to note here that being welcomed into HSE with such openness necessitated not only a careful consideration of ethics but also a great deal of taking care – of being care-full and respectful towards those members of HSE and indeed the organisation of HSE as a whole that had made such an effort in inviting me 'in.' Eliss (2007: 4) writes of the research encounter that 'relational ethics recognises and values mutual respect, dignity, and connectedness between researcher and researched and between researchers and the communities in which they live and work' (see also Lincoln, 1995). Research, in other words, cannot and should not be reduced to a transactional exchange. This is a sensibility or disposition that I endeavoured to remain alert to throughout the entirety of the unfolding of the research process.

5. Approaches to Data Analysis

The fieldwork component of this thesis was generative of a considerable volume and quantity of fieldwork materials. These ranged from field notes and interview transcripts, to draft regulations, survey results, peer reviewed scientific journals, inspection plans and regulatory strategy documents of varying kinds. The anthropologist Rosalie Wax (1983) illustratively remarks that 'it's a horrible but inescapable fact that it takes more time to organise, write and present material well than it does to gather it' (Wax, 1983: 193-4, in Crang and Cook, 2007: 131).

Coding enabled me to begin to make sense of these material generations, to re-assemble them and to put them to work in speaking to the broader research aims of the thesis. Coding is an analytical tool that helps to throw into relief key themes and topics (Yates 2003; Creswell 2014). As Kottak (2006) explains, emic coding seeks to identify key idiosyncratic terms, whereas etic coding links these contextual understandings to their broader connotations and implications.

I began the coding process by engaging in an iterative re-reading of my fieldwork materials. During this iterative process of re-reading I would cultivate an attentiveness towards difference – that is, I would zone in on the different things that seemed to matter differently to different practitioners. I would tend to the specificities of how and where practitioners were engaging with and mobilising engineering rhetorics and languages in their own working practices. I would look out for particular moments, hesitations and descriptions which pointed to the ways in which synthetic biology is taking on different kinds of shape(s) in different sets of relations and where synthetic biology seemed to be unfolding along different kinds of trajectories amidst the thickness and complexities of practice.

In relation to the second aim of the thesis - to trace the ways in which synthetic biology is intersecting in, and interfering with, extant modalities of regulatory organising for HSE - I would tend to those instances and moments where synthetic biology was becoming imbricated within, and was rubbing up against, the regulatory reality practices of HSE. I would cultivate an attentiveness towards the qualities and particularities of the encounter. Were, for example, these instances and moments, instances of tension, or were they moments of co-existence and mutual accommodation?

It is important to emphasise here that, as posited by Tracy (2012) and Saldana (2015), coding is a thoroughly creative process. It is a process that would ultimately enable me to move from working with pages upon pages of verbatim transcripts to identifying three composite modalities of the doing of synthetic biology - namely, the ‘cellular engineer,’ the ‘controlled experimentalist’ and the ‘multidisciplinary scientist’ - that take centre stage in the first empirical chapter of the thesis. I argue that these three composite modalities encapsulate much of what it means, at the present moment, to bring an engineering sensibility to bear on the substances and the stuff of the biological. Given the centrality of these three composite modalities of doing to the first empirical chapter of the thesis, is important to elaborate further here upon the specificities of their analytical genesis.

I noted that I began the analysis process by cultivating an attentiveness towards difference. Whilst, for example, some synthetic biologists embraced with very few qualifiers, the importation of the rhetorics of engineering into the doings of biology, others were much more hesitant and reluctant. Whilst some practitioners emphasised the significance of DNA or ‘biobricks’ in culminating in a specific bio-functional ‘output,’ others would rather describe the organismic milieu in terms of a processual interweaving of entanglements and imbrications where particular kinds of outputs were anything but guaranteed. Attending to these differences enabled me to begin to identify a series of initial coding categories and headings. These initial categories were loose and exploratory. They included, for example, terms and phrases such as ‘emphasis on translation;’ ‘significance of an economistic end-goal;’ ‘significance of learning;’ ‘ambivalent-engineer;’ ‘cellular milieu = thick and noisy;’ ‘mechanistic rendering of relationality’ and ‘assemblage-oriented description.’

After having identified these initial descriptors I would then identify a series of further categories and headings that included broader umbrella terms such as 'agency,' 'systems' and 'control.' I would juxtapose and re-assemble these categories in order to discern patterns and trends amongst what Law (2004) would describe as the dazzle of worldly complexities. In terms of the juxtaposition and re-assembling of these coding headings, Schiellerup (2008) reminds us that coding can be done either manually or with the support of computational tools and aids, with computational and manual approaches each presenting their own affordances and challenges. I mobilised and deployed a manual system of coding in my approach to the doing of data analysis which involved dissecting, colour coding and re-assembling my field notes and interview transcripts in a manner not to dissimilar to Mann and Warr's (2016) description of montage. Mann and Warr (2016: 3) describe montage as an approach which enables the juxtaposition of opposing standpoints and perspectives such that 'meaning and interpretation is synthesised through the ways in which they are arranged to form sequences and layers of understanding.' I found this more hands-on approach to the doing of coding to afford greater flexibility in terms of visualising, making-sense of, and re-assembling the empirical generations that emerged throughout the course of the fieldwork process.

This approach to the doing of coding enabled me to begin the process of identifying a series of divergent yet interlinked performances of the biosocial. Morris and Holloway (2014: 156) describe biosocial collectivities as 'intentional groupings that come together because members have a shared concern for a fundamentally biological issue.' Morris and Holloway posit (2014: 152) that what is at stake in the formation of a biosocial collectivity 'is the 'problem of 'life itself' (Franklin 2000), and how that problem is defined and responded to.' The composite modalities of the doing of synthetic biology that I outline in the first empirical chapter of the thesis define and respond to the problem or rather the question of 'life' and the encounterings between the stuff of the biological and the sensibilities of engineering in a number of different ways – in ways which are much more complex, nuanced and, at times, affirmative, than the economistic or dystopian renderings of synthetic biology that we encountered in the earlier stages of this thesis.

It is important to note here that like all methodological and analytical tools, coding is a performative process – it amplifies certain signals at the expense of others (cf Law, 2004). As Pernille Schiellerup (2008: 169) puts it, 'writing up involves leaving all the theses that could have been written behind in favour of 'this one.' In quoting the sociologist Howard Becker, Schiellerup further remarks that 'one has to accept that 'some, perhaps a great deal, of your hard-won knowledge and material will end up, as film people used to say, on the cutting-room floor'' (Becker, 2007: 31 in Scheillereup, 2008: 169).

Coding then, is perhaps best thought of as part of a process of crafting – a process of assembling certain kinds of stories. The coding process that ultimately enabled me to arrive at the three modalities of the doing of synthetic biology that I delineate and flesh out in chapter four of the thesis was anything but neat, tidy or seamless. It is worth illustrating this point with a key example. Towards the latter stages of the coding process I had identified the following key performances of the biosocial:

- 'The Controlled Experimentalist and the Organism Refactored.'
- 'The Cellular Engineer and the Organism in Process'
- and 'The Multidisciplinary Scientist and the Organism as Epistemic Thing'

However, I had also identified a fourth performance of the biosocial. This fourth performance or modality of the doing of synthetic biology was entitled 'The Genetic Engineer and Organism Inherited.' This modality of doing did not make the final cut. Although the fieldwork materials that I dissected and re-assembled in montage fashion did indeed indicate that this fourth modality of doing was a part of synthetic biology's complex present, the fieldwork materials which pointed towards and illustrated this modality of doing were comparatively fewer. I also found that the insistence of the genetic engineer that synthetic biology and genetic engineering are similar in kind is a tension that more broadly maps onto and differentiates the controlled experimentalist from the cellular engineer.

The strength of the supporting fieldwork materials which speak to and illustrate these performances of the biosocial enable me to argue that these three modalities of doing encapsulate much of what it means, at the present moment, to engage in the doing of synthetic biology and to bring an engineering approach to bear on the stuff and substrates of biology.

By mobilising a methodological and philosophical commitment to difference I was able to (re)assemble and curate my fieldwork materials in such a way that would enable me to speak to the research aim(s) of the thesis and to craft a series of stories, or 'little narratives' as Lyotard (1984) would put it, about the coming into being of synthetic biology within the context of a fractiversal world. But, beyond exhibiting a sensitivity to difference, when drawing together and analysing my fieldwork materials I would also foreground and zone in on what Haraway (1991, 1996) would describe as those moments of diffraction and interference. I tended, in other words, to those moments and instances where particular practices, relations and doings rubbed up against and encountered one another in the thickness of a full and busy world – sometimes affirmatively and sometimes less so.

6. Departing the Field

At the end of my fieldwork period with HSE I delivered a 23 000 word report to HSEs Biological Agents Unit entitled ‘Building Competence and Safe Practice in the Developing Trajectories of Synthetic Biology Practice: Policy Orientations and Operational Considerations.’ I have attached a copy of this report to the appendix of the thesis (Appendix 2). Although the report was crafted in a different style to the PhD thesis, the process of writing the report was a useful exercise in helping to familiarise me with the empirical materials that I generated throughout the course of my interviews with synthetic biology practitioners. It also provided me with an opportunity to experiment with writing and communicating to a non-academic audience. During my final visit to HSE the head of the BAU policy unit orchestrated a meeting to examine HSE’s regulatory approach to the oversight of synthetic biology. The report was used as a key discussion document during this meeting. It was noted that HSE would follow up on a number of key points developed in the report. Appendix 3 provides an overview of the discussions and impact of the report and Appendix 4 provides a copy of HSE feedback on the secondment arrangement.

7. Conclusion

In this chapter I have explained how my interest in synthetic biology led me to the Health and Safety Executive, the UK competent authority responsible for overseeing this developing approach to biological engineering. I have provided an account of how, by working as Major Hazards Policy Researcher for HSE’s Biological Agents Unit (BAU), I was provided with an entry point or a gateway into this developing field of scientific endeavour. I have also described how, by working alongside HSE, I was provided with access to a relatively underexplored set of reality making practices where synthetic biology is working to force thought. Working alongside HSE provided me with a lens through which to generate some ontological curiosity surrounding the coming into being of this developing approach to biological engineering.

In terms of the structure of the chapters that are to follow, I begin the next chapter of the thesis by turning towards the developing 'thing' (Latour, 2005) that is synthetic biology. I mobilise a methodological and conceptual commitment to difference in order to multiply outwards registers for understanding not only what this thing that synthetic biology is, but also what it might become. In the second empirical chapter of the thesis I ask; what might it mean, and what might it take, to bring synthetic biology into a governable world?

Chapter Four

Synthetic Biology: Beyond Biologism, Beyond Emergence

1. Chapter Overview

In this first empirical chapter of the thesis I turn towards and open up to social scientific inquiry the developing 'thing' (Latour, 2005) that is synthetic biology. 'Synthetic biology' is a term that, for the STS scholars O'Malley et al (2008) 'conceals' more than it 'reveals.' It is, in other words, a homogenising term that effaces the intricacies and subtleties of what is ultimately a diverse and highly variegated set of apprehensions and working practices. By mobilising a methodological and conceptual attentiveness to difference, my aim in this chapter is to contribute an empirical texturing to the term synthetic biology and to bring a geographical sensibility to bear on this developing field of scientific endeavour. A geographical sensibility is a sensibility that is alive and attentive towards the contextual specificities of synthetic biology done in and through multiple practices. In drawing together insights and materials generated from over thirty 1-2 hour interviews with leading practitioners in the field, I trace, in this vein, the shifting contours of what the social theorist and feminist philosopher Annemarie Mol (1999, 2002) would describe as the 'synthetic biology multiple.'

The insights and empirical materials that I generated throughout the course of my interviews with leading practitioners in the field enables me to tease out and trace the shifting contours of three prominent modalities of the doing of synthetic biology – the 'cellular engineer,' the 'controlled experimentalist' and the 'multidisciplinary scientist.' These three modalities of doing emerged through an extended and iterative process of coding and qualitative data analysis that I outlined in chapter three, the methodology chapter of the thesis. The access that

I was able to gain to these differentially oriented modalities of doing was facilitated in large part through my affiliation with the UK's Health and Safety Executive (HSE). Working as a Major Hazards Policy Researcher for HSE's Biological Agents Unit (BAU) – a policy and operational division of HSE, provided me with an entry point or a 'gateway' into this developing field of scientific endeavour.

The three modalities of the doing of synthetic biology that I tease out and trace in this chapter; the cellular engineer, the controlled experimentalist and the multidisciplinary scientist encapsulate much of what it means, at the present moment, to bring an engineering approach to bear on the design and construction of novel biological parts, systems and devices. These three modalities of doing each occupy different space-times – that is, they are moving in different directions with different kinds of baggage. They foreground and prioritise different types and kinds of 'things,' relations and apprehensions over others. Significantly, however, these three modalities of the doing of synthetic biology are neither fixed nor discrete modalities of doing. They are not singular subject positions. Instead, they are perhaps best described as composite and distributed modalities of doing that 'diffract' and 'interfere' (Haraway, 1996, 1997; Strathern, 1996; Moser, 2008).

In the latter stages of this chapter I elucidate and reflect on the slippages and tensions that exist between these three modalities of doing. I highlight, for example, how practitioners are able to inhabit and to slip between more than one modality of doing. Mapping the movements and the moments of friction and tension that exist between these composite modalities is, I argue, critically important in opening up and developing a more nuanced understanding of how synthetic biology is taking different kinds of shape(s) in different sets of relations. It also enables me to turn, in the second empirical chapter of the thesis, to consider what it might mean, and what it might take, to contribute to the effort of the bringing of synthetic biology into a governable world.

On a conceptual level, the chapter works to depart from the freighted and promissory narratives of ‘progress,’ which, as we saw at the very outset of the thesis, have tended so readily to accompany synthetic biology’s coming into being. It is precisely these kinds of narratives which, as Bingham (2008: 113) and others have so powerfully posited, tend not to ‘leave any room for any-thing else. Any other trajectories, any other versions of becoming.’ Whilst, for example, in some sets of practices and relations, synthetic biology might well endeavour to ‘transform’ and to ‘revolutionise’ the purported efficacies of biotechnological production, I highlight in what follows how this is by no means the only story to be told. When we tend to the intricacies and the nuances of synthetic biology done differently by different practitioners in what Asdal (2012) calls different ‘contextings,’ it becomes possible to open up more modest accounts and storyings of synthetic biology that are concerned instead with different modalities of organismal apprehension and with the dis/re-assemblings of new kinds of associations and relationalities.

The chapter builds upon and extends the recent work of Schyfter and Calvert (2015) who have highlighted how different synthetic biologists are differentially committed to synthetic biology’s engineering principles. It also builds upon the work of the STS scholars O’Malley et al (2008), who have identified and differentiated between three different facets of synthetic biology - DNA based device construction, genome driven cell engineering and protocell creation. It contributes an empirical texturing to O’Malley et al’s (2008) largely theoretical discussion. The chapter is interested in the syncretisms – that is, the co-existences, diffractions and interferences that exist between the synthetic biologist as cellular engineer, the synthetic biologist as controlled experimentalist and the synthetic biologist as multidisciplinary scientist. The chapter works to open up a somewhat different awareness of what synthetic biology is and what it might become.

2. Assemblage Cultures: The Cellular Engineer and the Organism in Process

In this section of the chapter I trace the first of the patterned and composite modalities of the doing of synthetic biology that I identified throughout the course of my interviews with over thirty leading practitioners in the developing field of synthetic biology – that of the 'cellular engineer.' The cellular engineer refers to a constellation of practitioners for whom the doing of synthetic biology can perhaps best be described as constituting a "systems based approach rather than focussing on genetic modification" (Jess, Molecular Biologist). I open up and reflect in what follows on the distinct space-times and sensitivities that are being mobilised by the synthetic biologist-as-cellular engineer.

I highlight how, for the cellular engineer, proteins, metabolites and vesicles, amongst other things, emerge as important actants in the processual configuring of the organismic architecture. I argue that, beyond simply drawing our attention to the fluidities and indeterminacies of biological emergence and relationality, the cellular engineer is engaged in an apprehension of, and a tending-to, the thickness of biological sociabilities in action. Whilst the cellular engineer does indeed aspire to engage in the 'engineering of biology,' I trace the ways in which the cellular engineer nevertheless refuses to adopt the more programmatic languages and rationalities of an engineering approach. I highlight how the cellular engineer is engaged in a becoming attuned towards the disorientating proclivities of the noisiness of the biological.

For Alfonso, a molecular biologist with a keen interest in computer science, to engage in the doing of synthetic biology is to engage in something more than conventional genetic engineering. It is to engage in the doing of:

> "biological engineering… or cellular engineering… but to me it's in a way a more wholesome view of genetic engineering actually, of engineering biology."

Put differently, to conceive of the doing of synthetic biology in more "wholesome" terms, is to acknowledge that, as explicated by Geoff, a biochemist with a particular interest in plant synthetic biology, DNA encodes biological interactions "in concert with the physical system." It is, in other words, to give breath to the sociality of the biological – or rather, to the propensity of the biological to associate.

Geoff, who had recently been appointed as the Chair of a leading synthetic biology strategic research initiative was acutely attuned towards the socialities of the biological and was keen to emphasise that, in spite of the prominent 'plug and play' imaginaries which have so readily surrounded the development of synthetic biology - imaginaries which presuppose the 'insertion' of 'interchangeable' and 'discrete' biological and genetic parts within a organismal host, the doing of synthetic biology is seldom a straightforward endeavour.

The prevailing vision, in other words, of synthetic biology as a developing 'engineering' discipline – as a discipline that will ultimately engender and facilitate the interchanging of 'neatly' designed biological parts with smooth edges and clear cut connective joints, is a vision that neither resonates with, nor accounts for, the apprehensions and endeavourings of the synthetic biologist-as-cellular engineer.

The synthetic biologist-as-cellular engineer is alive instead to what might be described as the jaggedness and the very thickness of the cellular and organismic milieu. This is a thickness that troubles synthetic biology's functional ambitions. As Geoff explained:

> "things like cell expansion or division… and [the] geometry of the cells… [all] impinge back on the genetic processes… you have this huge network of interactions, many of which are not genetic at all, which produce morpho-genetic outputs…. DNA is not reduced in importance as such, but it's just not the master control…. the interaction between the processes creates a huge amount of complexity."

There is then, for Geoff, an intricate agential dance going on here - a suite of interactions between DNA and the stuff of the molecular that belies any ready account of the seamless, or rather, the frictionless insertion of a genetic or biological insert into a host organism. In referring to the tendency of a number of synthetic biologists to draw heavily on and to mobilise engineering languages and metaphors, Geoff sought to emphasise that:

> "the very fact that they're using the term chassis as opposed to the binomial is a certain… cavalier disregard for the complexity of the system that one is trying to work with which can also go pear shaped quite quickly, particularly if the person, the engineer is not a biologist."

'Chassis' is a term that is often mobilised by a number of synthetic biologists in order to refer to the 'biological cell' or the 'organismal host' into which an engineered biological part or sequence of parts can be inserted. It is a term that originates in the field of mechanical engineering where it is typically used to designate an unmalleable supporting structural framework that encases a functional or mechanical device (Atkins and Escudier 2013; Vogit, 2011).

For Geoff, who expressed a palpable sense of unease and disconcertment at the developing use of the term 'chassis,' the host organism is anything but an empty vessel. Much like Bingham (2008) has posited in relation to the wider ecological configurings of the Bt Cry protein and its unanticipated associations with the Monarch butterfly, there is an extant fullness to the world - a fullness which is demanding of a careful attentiveness. This is a fullness which, at times, and in the language of Geoff, can be generative of an unruliness, of "unexpected behaviour… [of] behaviour that is more than the sum of the parts." As Geoff continued:

> "small differences which get amplified by the interactions, result in completely unpredictable behaviour… tiny microscopic differences get amplified in the feedback of the system."

Geoff was by no means the only synthetic biology practitioner who was acutely attuned towards the 'unruliness' of the biological. Neither was Geoff the only synthetic biology practitioner who sought to call into question the utility of the bringing of a programmatic engineering approach to bear of the substances and the socialities of the stuff of the biological. Take, for example, the following assertion made by Paul. Paul, a molecular biologist who is working to develop and design a light sensitive biomolecular pathway that regulates the production of cellulose, explained that in spite of the rhetorics of control and rational design that surround the development of synthetic biology it is still "so hard to predict the outcome of any transformation you do…"

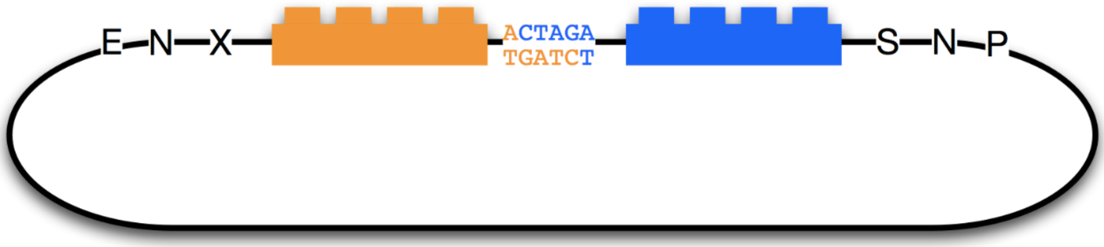
> "you can like look at it and theoretically read all the literature and you can say well this protein is supposed to do this, this protein is supposed to do

> this, but when you actually put it into an organism and all the proteins start interacting with all the other proteins then actually… you can't predict that."

Crucially, what Geoff and Paul's explications alert us to is a topological rendering of the biological – a being in the midst of interminglings and processual associations. This is not the 'neat' and 'tidy' spatiality that is suggested by the prevalent imagery of the so-called 'BioBrick'

The 'BioBrick' is a particular and indeed one of the more prevalent and widely recognised approaches to the doing of synthetic biology. The 'BioBrick' refers to a standard interchangeable genetic part that has been designed to conform to a restriction enzyme assembly standard. By conforming to a specific assembly standard, the BioBrick part is intended to facilitate a system of transgenic and social exchange whereby genetic 'bricks' can be shared freely amongst synthetic biology practitioners and put to work alongside other BioBrick parts in order to 'build up' novel biological devices and systems of increasing levels of complexity.

Researchers at University College London, for example, have recently created a BioBrick that is comprised of two genes – one of which degrades mercury and the other which produces antifreeze. By inserting these BioBricks into a microbial host it is intended that the resultant synthetic organism will take on the function of degrading mercury whilst surviving in ice-cold waters. Figure 1 provides a visual representation of how the assembling of BioBrick constructs can work to generate novel biological systems and devices.



[Figure 1] – A simplified schematics of a bacterial host complete with two 'BioBrick' inserts. Available from http://agapakis.com/hssp/biobricks.html; accessed 01/09/16.

Tom Knight, a prominent US synthetic biologist and one of the co-founders of the 'BioBrick' assembly method has described the BioBrick as being 'inspired by his love of Legos' (Restuccia 2009 in Roosth, 2010) and indeed, what we can begin to see here, in this particular visual representation, is how the spatial imaginary that underpins the 'BioBrick' vision stands in contrast to the sensitivities and working practices of Geoff and Paul.

In particular, for Geoff and Paul, the BioBrick vision doesn't quite add up in practice. Instead of the neat, discrete parts pioneered by the engineering and BioBrick vision, Geoff and Paul's explications rather alert us to a spatiality of varying encounters and intensities. This is a spatiality which refuses to speak of discrete objects or of neatly defined devices that can be slotted into any kind of vacuous space. It is a spatiality of processes and of contexts that are always in-the-making. As Geoff continued:

> "there's no master plan, there's no blueprint for how you organise these things, they just emerge… and that, of course, is how biological systems work…. interactions in a cellular context… produce extra features of complexity and it all feeds back on each other."

The recent work of the synthetic biologists Cardinale and Arkin (2012) who have examined the interrelations between compositional, host and environmental contextings on the functionality of heterologous organismic architectures (that is, on organisms which have been engineered to contain synthetic componentry) is particularly instructive here in further illuminating the sensitivities and apprehensions of the synthetic biologist-as-cellular engineer.

Cardinale and Arkin are prominent synthetic biologists. Their work, which sits at the intersection of functional genomics and bioengineering, is interested in mapping the importance of 'context' to the doing of synthetic biology and the circumstantial nature of much synthetic biology work at present.

Amongst other things, Cardinale and Arkin (2012) have highlighted how enzymes can promiscuously bind to non-specific segments of DNA and how changes in an organism's temperature can alter the curvature of an organism's DNA, which, by extension, can favour certain activators and repressors over others. Activators and repressors play an important role in 'tripping' certain switches and in initiating the activation of heterologous genetic parts. They have similarly explicated how, even the slightest of changes in an organism's pH can alter growth rates and impact upon the development of an organism's toxicity.

What's more, as Cardinale and Arkin (2012) continue, parasitic interactions between heterologous inserts and host organisms are by no means uncommon occurrences. In consuming resources that are typically required for endogenous processes - resources such as free floating ribosomes and nucleotides - heterologous genetic circuitry can impart a significant fitness cost on the host organism. This can have notable implications, particularly in terms of the performance and functionality of the engineered organism.

Although the language of Cardinale and Arkin might be read in terms of pathway 'logics' and in terms of 'causes' and 'effects,' it is important to note here that Cardinale and Arkin are not working to invoke any such sense of ready determinism in their account of the relational configurings of the organism in process. Far from dealing in determinisms, there is a 'dance' of agency that is going on here (Pickering, 2008) – a dance that is both loose and improvisational.

What we can begin to see here then, in the explications of Geoff and Paul and in the recent explorative contributions of Cardinale and Arkin, is an ontological levelling in the agential vitalities of the constituent components of the cellular milieu - a troubling in the very languages of control and rationality which have so readily surrounded the development of synthetic biology. Information and instruction is not so much something that is simply 'passed on.' The central dogma of molecular biology does not loom large here. Rather, there is an ongoing process of negotiation – a being in the midst of what we might describe as the noisiness of the biological where "the most complicated structures we know are driven by these local decision making processes" (Geoff).

It is in this way, I suggest, that tracing the synthetic biologist as cellular engineer contributes to a tempering of what Marris and Rose (2012) have described as the 'deterministic' and 'hyped' claims that synthetic biology will necessarily and inevitably revolutionise the efficiencies and predictabilities of biotechnological production. Synthetic biology is, quite simply, hard work. Biological processes do not always conform to the narratives we tell about them and neither do they necessarily acquiesce to the processes that we enrol them in.

Lester, a physicist turned biochemist and now CEO of one of the UK's leading synbio start-ups was acutely attuned towards the difficulties and challenges associated with attempts to engineer the biological. In reflecting on his experiences and engagements with the ‘scaling up’ of modified organisms designed to yield high value biological products and chemicals, Lester explained that “a lot of companies have found… these strains… when they try and put them into a 30 000 litre reactor they behave in completely different ways.” As Cardinale and Arkin (2012: 856) have emphasised:

> ‘Heterologous pathways have not had the advantage of long periods of co-evolution with other cellular substrates. There are generally subject to environments, such as bioreactors, that they have not experienced at length previously in the evolutionary history of the system.’

Richard, the Director of a renowned genetics spin out company and Professor and Group Leader of research into vector borne viral diseases who is also mobilising a synthetic biology approach in his own working practices similarly emphasised that:

> “we tend not to talk so much about cross talk which is a quite a big problem and modules are only modular up to an extent… this one works in this particular context but if you put this other one next to it you’ve changed its context and so you change the function of you know Part B because you have put Part A in front of it…. [it’s like] trying to make transistors smaller and smaller on silicon chips… you get more sort of quantum phase more interaction between them…. so it’s you know it’s hardly a unique problem to us but we’re starting from a lower base in terms of knowledge.”

Richard continued his reflections on the challenges of the doing of synthetic biology with a somewhat compelling sobriety and was keen to emphasise that “making things that perform as you design them is quite hard in biology… and quite a long way off.” Although Richard acknowledged that “we can make pretty amazing things” he nevertheless sought to caution that these “seem to be sort of one off creations… which I think is probably true of the artemisinin synthesis thing." Richard is referring here to the mobilisation of a synthetic biology approach to implant a complex sequences of genes into the bacterium *E.Coli* in order to produce a precursor to the drug artemisinin an antimalarial drug that is traditionally sourced from the wormwood *Artemisia annua.*

For Richard, whilst it may well be the case that "people such as Drew Endy have done a really good job of getting bright young people interested in this sort of area" that "doesn't mean that expectations are going to be fulfilled." Drew Endy is a prominent and vocal synthetic biologist in the United States. Along with Tom Knight, Endy is the co-founder and current director of the 'BioBricks' registry and is thus renowned for advancing a version and vision of synthetic biology that is underpinned by its use of standardised parts that can be slotted interchangeably between different host organisms.

Like Richard, Lawrence, who is working to bring together "modules of metabolism" from a range of different organisms to "make products that are hopefully useful from a health perspective" also sought to emphasise that engineering the biological is indeed hard work. Lawrence explained that:

> "what we're finding is that because what we're doing is very applied and we're trying to get them to do things for us we tend to make them [the organism] a lot less fit…. the genes that we're adding are imposing a quite significant fitness cost on the organism."

One of the implications of the challenges associated with the doing of the engineering of biology is that, for these practitioners, there is much more to synthetic biology than simply making and doing. Synthetic biology, for the cellular engineer, is in large part also about processes of apprehension - of becoming attuned towards the processual dance of the organism and of entering into a mutual reconfiguring of the thingness of the biological and the understandings of the practitioner. As Richard explained, for example:

> "I think you learn things from the process of building things and what you learn may be quite unrelated to ... or hard to draw a link between what you set out to build… but it doesn't mean that you won't learn things on the way... you challenge your notions of what you really understand by trying to use that knowledge for something other than explaining."

Emmett, a molecular biologist and biochemist who was mobilising a synthetic biology approach to develop coordinated metabolic networks similarly reflected on how:

> "the reason we're doing it is partly because it challenges you and the big challenges that we face but also because it does give us fundamental knowledge of how the cell is working so we learn a lot along the way."

And for Geoff:

> "most of the synthetic biology at this point has been done in microbes, so you can effectively ignore many of the morphogenetic cellular scale things, because you've only got a single cell, but as people start to grapple with multi-cellular systems it's becoming clear that these synthetic biology approaches provide also a way of directly grappling with some of the emergent processes that you see in living systems, so in a way it's helping fill out our understanding of these local processes which give rise to complex order by virtue of quite subtle or directive interactions which might be limited in their initial effect, but which propagate across the system and these are the same kind of systems that you see in any kind of networked process."

Far then from representing an intolerable hubris (see Lewens, 2013), tracing the synthetic biologist as 'cellular engineer' helps to open up a storying of learning and apprehension. Indeed, with reference to the development of the synthetic precursor to the anti-malarial drug artemisinin, the social scientist Maureen

O'Malley (2011) has highlighted how, in spite of being heralded as a clear indicator of the rationalistic prowess of synthetic biology, the development of this synthetic precursor was neither as 'engineered' nor as rationally designed as it is often depicted. In drawing on the work of Prather and Martin (2008), O'Malley highlights how, in addition to involving a complex orchestration of varying enzymes and protein scaffolds, the reaction steps that culminated in the development of this synthetic precursor are even now not yet fully understood.

It is perhaps unsurprising therefore that the storying of the artemisinin precursor - and in fact the storyings of synthetic biology endeavourings more generally - are, for O'Malley (2011), better described as 'kludges' – that is, as iterative, partially experimental and generative becomings, which are more akin to an explorative fumbling around than to any neat, pre-conceived and rationally orchestrated undertaking. As O'Malley (2011: 410) explains:

> 'The notion of kludging is reinforced by Max Delbrück's 'principle of limited sloppiness', Delbrück used this term to describe the importance of not being excessively rigorous or controlled in experimentation. He thought that too much precision would prevent novel insights, and that these might arise more readily if the researcher was flexible and responsive to the system of study and its variability.'

What O'Malley is alerting us to here, following the American biophysicist Max Delbrück (1979), is that the preference for 'rigour' and 'control' that is typically valorised and highly regarded by the engineer and 'rational designer' is an approach that might, in practice, work to deaden and to circumscribe the potentiality for the generation of novel insights and the development of novel biological parts, systems and devices. This is an important point that I will return to in the latter stages of this chapter.

For the cellular engineer then, to engage in the doing of synthetic biology is to embark on a processual venturing into the midst of things – a venturing into the thickness, or rather, the noisiness of the cellular milieu. This is a journey which is iterative, flexible and responsive – a journey where, as Emmett explained, “what we do in the lab, it’s a little bit of trial and error, but…that’s a bit too dismissive because it’s not an error, you learn from the data and then you iterate around several cycles.”

The cellular engineer directs our attention towards the qualities and complexities of the relations and encounterings that exist within, beyond and between organismic architectures and components. We can begin to see that, following Latour, the stuff of the biological is not made of ‘clearly delineated, discrete objects that would be bathing in some translucent space like the beautiful anatomical drawings of Leonardo, or the marvellous wash drawings of Gaspard Monge, or the clear-cut “isotypes” devised by Otto Neurath.’ (Latour, 2005: 13).

To trace the figure of the synthetic biologist as cellular engineer is to open up a different kind of geography. This is a geography which does not work to foreground the relationship between genetic code and specific functionalities. Neither does it afford an ontological primacy to certain components of the organismic architecture over others. Instead, it is interested in apprehending the noisiness of the biological and in grappling with a much fuller range of encounters - whether these be encounters between heterologous enzymes and protein scaffolds, or between the synthetic organism and its environmental contextings.

Such an approach requires what the scientists Andrianantoandro et al (2006: 5) describe as novel combinations of ‘rational redesign, parameter estimation, sensitivity analysis, and directed evolution.’ This is, in other words, a call for new modalities of assembling and expertise. It is a call to take seriously the textured specificities of biological encounterings and imbrications. The engineering rhetorics and the mechanistic, Euclidean spatialities of neat biological ‘chassis’ and smooth, interconnecting and discrete biological ‘parts’ simply won’t do for the synthetic biologist as cellular engineer.

In social scientific terms, we might say that the synthetic biologist as cellular engineer works to call for an attentiveness towards the multiplicitous qualities of being and relating. The synthetic biologist as cellular engineer is willing to and indeed expects to become lost even in the thickness and disorientating proclivities of the cellular milieu. As Stirling (2008) and social scientists and theorists have powerfully argued, it is precisely this kind of openness, this appreciation of multiplicity and of multiply unfolding trajectories that is in need of protecting.

3. Innovative Cultures: The Controlled Experimentalist and the Organism Refactored

I turn now to trace the second of the composite modalities of doing that I identified throughout the course of my interviews with leading practitioners – that of the ‘controlled experimentalist.’ The controlled experimentalist mobilises a somewhat different set of sensibilities and sensitivities than that of the cellular engineer. For the controlled experimentalist “the point of synthetic biology is to try and define things as well as possible” (Nick, molecular biologist and Professor in Industrial Biotechnology). It is an approach to the doing of biological engineering that is endeavouring to attain enhanced levels of “precision” and “regularity” (Nick) in the construction of novel biological parts, systems and devices.

I highlight in this section of the chapter how, in working to foreground and import the languages of engineering into the doings of biology, the controlled experimentalist is working to strip the synthetically engineered organism of the ‘complex ramblings bequeathed’ to it ‘by evolution’ (Roosth, 2010: 86). I argue that, for the controlled experimentalist, there is less of an openness or indeed a willingness to become sensitised to the disorientating proclivities of the thickness of biological sociality. At the same time however, I also argue that there are important divergences *and* synergies between the controlled experimentalist and the cellular engineer that we must be careful not to efface.

Hugh, a biologist by training, who had worked for many years as the Strategic Programme Manager for Innovation at a leading oil and gas company and who was now Director of a UK synbio company and a key contributor to one of the UK’s leading biotechnological forums, was palpably excited at the prospect of the coming into being of synthetic biology. Hugh explained that:

> “I think in biology we’ve actually been held back by the complexity of biological systems… although a lot of wonderful stuff has been done it’s been hard gained through a lot of empirical trial and error… but that doesn’t mean to say that achievements haven’t been made… things like insulin, for example, which are entirely synthetically made.”

For Hugh, the real salience of the coming into being of synthetic biology resides in its purported capacity to move beyond what Toby, molecular biologist and CEO of a nascent synbio start up described as the real “hard work and slog” associated with the development of technological innovations “where a biological solution could play a role.” As Hugh continued:

> “we’re translating… what has been a fairly empirical science into something which is much more predictive… so it’s understanding the fundamental building blocks and the modularity of biology… and then…

> bringing our understanding of biology into a more predictive less empirical realm."

Synthetic biology, in this particular modality of doing, endeavours not so much to apprehend or to give breath to but rather to 'black-box' biological complexity - to 'write it out' of the doing of biological engineering (Heinemann and Panke, 2006). Biological complexity, in this way, is posited as a hurdle to be overcome - a hindrance that constrains rather than enables.

Similarly to the synthetic biologist as cellular engineer, synthetic biology is positioned here as being about 'more than' the recombination or the bringing together of different genetic parts and constructs. For the controlled experimentalist however, this 'more than' does not involve an engagement with the unfolding dance of the organism in process. Rather, it involves processes of 'refactoring' and 'redesigning' in order to attain new levels of experimental efficacy and predictability. As Tim, a molecular biologist with a particular interest in molecular parasitology explained in relation to his own working practices:

> "what we did… is we took apart the violaceum operon and refactored it for expression in E.coli…. so we took it out of its normal context in terms of the gene arrangements and we put in specific elements to make it express better in E.coli…. this is definitely an engineered thing… it's not something where we've just tried to take the operon out of chromi bacterium and stick it into E.coli… that doesn't work very well as it turns out… so we're re-engineering the whole thing."

'Refactoring,' not too dissimilarly to the term 'chassis,' is a term that is being increasingly imported into the conceptual vocabulary of the controlled experimentalist – particularly over the past number of years. It is a term that is typically mobilised within the field of computer science where it used to refer to the process of the ‘cleaning out’ of computational code without changing external ‘outputs’ (Fowler et al, 2012; Bölker 2015).

Refactoring aims to identify and eliminate ‘redundancies’ – that is, elements of computer or genetic ‘code’ that are regarded as having little or no external effect on the desired functional ‘output.’ Significantly, refactoring presupposes that ‘informational pathways’ unfold along an identifiable and largely linear trajectory. Refactoring, in other words, is a term that leaves little room for the more convoluted and intricately folded spatial imaginaries that we encountered in the modality of doing encapsulated by the figure of the cellular engineer.

Tim continued to explain that, for him, synthetic biology is about “approaching bio-science research and developing bio technologies using engineering principles and an engineering framework.” More specifically, it is about developing “new things” by “building” in a “rational way.” In reflecting on his own attempts to bring a synthetic biology approach to bear on the development of novel biofuels, Nick described how:

> “[we’re bringing together] existing genes, pathways and things like that throughout the phylogeny…. and recombining them in ways which couldn’t just be bred or evolved… [and] what you’re trying to do as well is to streamline the process to make it more efficient.”

It is this very emphasis on streamlining and making the process ‘more efficient’ that, for the controlled experimentalist, differentiates synthetic biology from more conventional approaches to genetic modification. Whereas genetic modification is contrasted to synthetic biology for the cellular engineer in that the synthetic biologist-as-cellular engineer engages with a wider range of more-than-genetic components within the organismal milieu, the controlled experimentalist rather contrasts synthetic biology from genetic modification in terms of the emphasis that it places on tightening the 'efficiency' of the functional expression and performance of novel biological parts. Nick was at pains to underline that:

> "it's very clear what a GM organism is right it should be equally clear what a synthetically engineered organism is and it should be something that's more targeted, less hit and miss. GM in plants – it's pretty much hit and miss and there should have been an attempt at prediction about what's going on… synthetic biology should be about pathways… it should not just be gene-gene… it should be about regulatory systems and things like that….. Syngenta [a leading biotechnological agricultural company] are doing these things with artificial plant chromosomes… to me that's true synthetic biology."

Hugh similarly placed an emphasis on regulatory systems explaining that by "using synthetic biology to generate a whole load of very sensitive [health] sensors… you go into the trial with enormous confidence rather than slightly not sure if this is going to work and we have to wait three years for the answer."

In endeavouring to designate a 'true' synthetic biology or a synthetic biology 'proper,' many of the controlled experimentalists that I interviewed throughout the course of this research project emphasised the significance of the outcome or the 'output' of the engineering of biology. Nick, for example, was quick to assert that "synthetic biology really needs to be focussed on application" and Hugh similarly sought to emphasise that:

> "it's all about the industrial translation… you've got a wide range of potential applications… and synthetic biology will simply provide a mechanism for facilitating those applications."

This emphasis on industrial translation was much less explicit in the apprehensions and undertakings of the cellular engineer. Rarely did the cellular engineer foreground or draw attention to any cumulative end-point or output. The cellular engineer was content instead to be led more by the biological than by any rigidly pre-defined and economic endpoint. Toby, for example, controlled experimentalist, CEO and founder of a nascent synbio start up described how the short term goal of his company is to:

> "apply synthetic biology tools and techniques to the existing industrial biotechnology sector [to] increase [the] manufacturing efficiencies of useful proteins and other sort of protein derived products."

Toby went on to explain that in the longer term:

> "[this] really broadens into just being able to capitalise on the possibilities opened up by the engineering of life… to be able to build things with synthetic DNA and synthetic systems."

As Mark, the Director of an international gene synthesis consortium that stiches together and 'streamlines' bespoke sequences of DNA which are then mailed to commercial as well as more research orientated clients explained:

> "We provide services to pharmaceutical companies making new antibodies… biofuel companies who are developing novel ways to convert cellulose into gasoline… vaccine companies… chemical companies making novel chemical derivatives. We also have customers in academia doing basic research and developing new tools. DNA can of course be applied to a lot of different things… all these different things are always in need of pathways and more efficient ways to get there… and that's what we're trying to provide."

Mark's description is particularly useful here in gesturing towards the extent of the range of the applications through which synthetic biology tools and techniques are projected to play a part. Mark's description resonates with wider market forecasts and descriptions of synthetic biology that describe this burgeoning field of scientific endeavour as being one of the eight great technologies of the 21st century (see, for example, Willetts, 2013) and which purport that synthetic biology will herald effects not too dissimilar to that of the semi-conductor in the nineteenth century (cf Royal Academy of Engineering, 2009).

Given the emphasis of the controlled experimentalist on biotechnological outputs, it is perhaps unsurprising therefore that the controlled experimentalist tends often to mobilise certain kinds of languages and descriptors that foreground a rationality of optimisation.

Take, for example, the recent work of the synthetic biologists Jewett and Forster. In their 2010 paper an 'Update on Designing and Building Minimal Cells,' Jewett and Forester provide an overview of the development of 'minimal cells' in synthetic biology practice. Jewett and Forester trace the ways in which synthetic biology techniques have facilitated the transformation of minimal cells into biotechnological 'workhorses.'

Minimal cells, or, biotechnological 'workhorses,' to use the language of Jewett and Forster (2010) are organisms that have been stripped of the so-called evolutionary 'detritus' (Calvert, 2010) and the convoluted texturings that have accumulated over evolutionary time in the organismal architecture. By stripping out any 'redundant' and 'unnecessary' codings from the genomes of these 'minimal risk' organisms, the synthetic biologist as controlled experimentalist is working to minimise the metabolic burden that is placed on the cell, so that the 'remaining cellular energy can be directed towards the manufacture of a desirable industrial product, such as an industrial chemical or a pharmaceutical' (Pyne et al, 2011 in European Scientific Committees, 2014: 27).

What we can begin to see here then, is how a very particular version of synthetic biology and of the future more generally – a technologically rationalistic future -

is being folded into the dispositions and descriptions of this particular modality of the doing of synthetic biology.

In reflecting, for example, on what the coming into being of this rationalistic and end-goal orientated synthetic biology might mean in terms of his own interest and expertise in the development of innovative fuel sources, Hugh described how:

> "bio fuels to date are based on a very ancient technology of yeast fermentation to alcohol… there are many other potential ways that you could take bio feed stock and convert it to useful chemicals including bio fuels… understanding either ways that yeast could be modified or other organisms could be modified is really where synthetic biology comes in… you could do it more efficiently and you can start to design things… rather than producing ethanol you could, for example, produce a hydrocarbon, which looks more like a like a jet fuel."

There is then, a distinctive tightening in the remit of the doing of biological engineering that accompanies the endeavourings of the controlled experimentalist. In contrast to what might be described, following Max Delbrück, as the kind of creative 'sloppiness' that we saw being mobilised by the synthetic biologist as cellular engineer, there is less of a willingness here for the unfoldings of science in action to morph and mutate into something other than what these synthetic biologists had originally set out to achieve.

There is, in other words, less of a propensity here for the thickness of the sociabilities of the biological to do the leading. There is not so much a dismissal of, but rather, a deprioritisation of learning. As Mitch, a molecular biologist with a particular interest in biochemistry put it:

> "I'm going to be able to put these parts together… it won't be a matter of testing to find out what it does but how well it does it… systems biology that's characterising something… measuring it….. and seeing how it

> naturally acts… synthetic biology is more making… the work you do in the lab is more… a confirmation of your ideas. More than predicting you kind of already think you know."

Sarah, like Mitch, who is also a molecular biologist and biochemist similarly sought to emphasise that for her, synthetic biology is about:

> "taking something that's already been made or that's already out there but you almost control it… you sort of give it a regularity…. people have made new base pairs… if you put [them] in a mouse the mouse wouldn't know what to do with it… but we do."

And as Mitch continued:

> "[it's]creating a manmade system… that has changed so much the natural inputs wouldn't have any effect and you have complete control of it. That's what synthetic biology needs to be."

This account of the doing of biology is markedly different from the account of the molecular biologist Paul. Paul rather foregrounded the real difficulties associated with endeavouring to attribute any phenotypic qualities to the configuring of specific genetic sequences.

Whilst Paul sought to emphasise and give breath to the density of the entanglements and re-assemblings that arise in the processual transformation of DNA code into protein, Mitch and Sarah are much less attentive towards the meanderings that take place in the processual and unfolding space of the organismal milieu. For the cellular engineer, what it means to 'know,' looks much less clear cut.

Now, it is important to note here that this is not to suggest that the controlled experimentalist does not engage in a process of learning or adjust the parameters of the biotechnological endeavouring in any kind of iterative fashion – doing and learning are two processes that necessarily go together and indeed this is an important point that I expand upon and develop further in the latter stages of the chapter. But what this is to suggest however is that there is a privileging here of speed and a desire to move more quickly through the design-build-test cycle to reach a pre-specified and particular economistically orientated end goal.

More specifically, there is an endeavouring to develop the resources through which it might become possible to move more seamlessly (and with less friction) towards “some form of deployment and benefit realisation” (Curtis, governmental regulator). The controlled experimentalist is endeavouring to circumvent the stickiness and the explorative fumblings associated with the so called ‘kludge.’

In reflecting on the ways in which a number of nascent synthetic biology start-ups are endeavouring to move more quickly and with less friction through the design space of the biological, Hugh, Director of a UK synbio company and a key contributor to one of the UK’s leading biotechnological forums explained that:

> “Amyris [the company]… I talk to very regularly… they say well actually what you’ve got is a design-build-test cycle right.… the design is not yet perfect, but it’s not completely empirical… this isn’t like a directed evolution where you’d make a million things and see if there’s one that’s better than the others…. what we’re trying to do is to get to where the design-build-test cycle is done much more efficiently.”

There is an attempt here not only to speed up but also to straighten out the routes taken towards the development of an industrially relevant biotechnological output and certainly, for the controlled experimentalist, there was a sense that this might be achieved through enrolling and splicing together the tools of maths and informatics into the engineering of biology.

Lester, CEO of one of the UK's leading synbio start-ups – a key protagonist that we encountered in the preceding section of the chapter, described the work of his company as endeavouring to navigate "biological design space mathematically and applying synthetic biology protocols in order to demonstrate increases in productivity." Lester is a particular protagonist that inhabits or slips between the composite characters of cellular engineer and controlled experimentalist and I elaborate upon Lester's simultaneous subjective patterning in the latter stages of the chapter.

For the time being however, Lester emphasised, in the language of the controlled experimentalist, that in order to meet his company's aim of transforming cells into assembly lines for high value biological and chemical products, this would require a 'close coupling' of 'computational and experimental methods.' Lester's company's mission statement describes how:

> 'Our technical approach seeks to seamlessly integrate theory, computation, automation and sophisticated experimentation to give us exceptional levels of understanding and control of biological systems with an efficiency and a level of rigour suited to the demanding industrial environment.' (Company mission statement)

Lester explained that by mobilising computational techniques in this way it would become possible to tackle biological complexity which, in his own terms, has been a serious "bottleneck to progress." Biology, Lester continued, has "found its way down some cul de sacs."

Lester expressed a real sense of frustration at the "artistic" nature of biological experimentation as exemplified by "pipetting" and the conduct of laboratory practice in a "similar fashion" to the way it was conducted "a hundred years ago."

Lester asserted that not only is this “error prone” but it “costs too much [and] it takes too long.”

Lester sought to emphasise that “you cannot build on collective knowledge when only 10% of it is reproducible” and felt that “a big sea change is coming in terms of the development and advancement of standardised biological parts and protocols.” He explained that we are “still just scratching the surface in terms of what biology is capable of… I mean it can be exquisitely precise for making very complex chemicals and regulating intricate processes.” As Lester continued:

> “there was 89 billion dollars worth of life science research in the OECD countries last year and quite a few papers, academic papers have estimated that only 10% of it is reproducible ... you cannot build on collective knowledge when only 10% of it is reproducible… that’s got to change and it can only change with an increase in productivity based on standardised protocols and automation. Biologists don’t think of unit separation, the protocols they use aren’t standardised and if they’re not standardised you can’t build on top of them.”

The space-times that are being mobilised here speak of discrete ‘packages’ of information and ‘modular’ materialities that can be piled on top of each other. Progress is figured here in its most conventional of instantiations and time is figured as something that is not to be lost.

Nick, a Professor in Industrial Biotechnology, was keen to emphasise that the “one thing we don’t have is time on our side” and certainly, there was a palpable awareness amongst most of the controlled experimentalists that I interviewed, of the importance of synthetic biology to the development of a knowledge based bio-economy.

I defined the knowledge economy in chapter three of the thesis by drawing on the language of the philosopher of science Isabelle Stengers (2015: 29), for whom the knowledge economy is not an ‘empty order word’ used in ‘reports on the challenges of our epoch’ but in fact designates ‘a strong reorientation of public research policy, making partnerships with industry a crucial condition for the financing of research.’

For the controlled experimentalist there is more of a concerted effort (with fewer qualifiers) to map out and to navigate the pathways through which it might become possible to develop a range of biologically based products and outcomes. If, therefore, the cellular engineer is engaged in an apprehending of the multiplicity of organismal relations – of the ‘fullness’ (Bingham, 2008) of the organismal architecture and the multiple trajectories of biological becomings, then there is more of a tightness associated with the doings of the controlled experimentalist.

Time, for the controlled experimentalist, is figured in such a way that it exerts a palpable downwards pressure — there is a demand for immediate and profitable results. This, then, is a particular instantiation or modality of the doing of synthetic biology that resonates with the recent argumentation of Rabinow and Bennett (2012: 7) that ‘the dominant mode of rationality and purpose guiding the life sciences today is instrumental.’ This is the predominating version of synthetic biology that I outlined in the very introductory chapter to the thesis.

4. Collaborative Cultures: The Multi-Disciplinary Scientist and the Organism as Epistemic Thing

I turn now in this section of the chapter to trace the third modality of doing that I identified throughout the course of my interviews with practitioners in the developing field of synthetic biology. I trace, in what follows, the synthetic biologist as multi-disciplinary scientist. I argue in this section of the chapter that depending on how multidisciplinarity is done, it becomes possible to open up a further storying and account of synthetic biology that is somewhat different from a) the attentiveness towards the thickness of biological sociality and sociabilities that I teased out and traced in the figure of the synthetic biologist as cellular engineer and from b) the economistic and 'end-goal' orientated rendering of synthetic biology that I teased out and traced in the modality of doing that is the synthetic biologist as controlled experimentalist.

I highlight in this section of the chapter how inhering with the endeavourings of certain kinds of multidisciplinary working practices are the glimmerings of the makings of a synthetic biology that might be described, following the anthropologist and sociologist of science Bruno Latour (2003), as having 'outgrown progress.' I unpack precisely what I mean by this in the discussion that follows.

The empirical materials that I mobilise in this section of the chapter enable me to tease out and trace the ways in which the comings-together of different disciplinary traditions and sensitivities are contributing to an unsettling and reconfiguring of established regimes of making, knowing and understanding. There are, I argue, different kinds of intersections and imbrications of 'space' and 'time' that are taking shape within the endeavourings of the synthetic biologist as multidisciplinary scientist.

Most if not all of the synthetic biology practitioners that I interviewed throughout the course of this research project pointed to the importance of engaging with, and working across, different disciplinary boundaries and traditions. For Sarah, a molecular biologist and biochemist, "the multidisciplinary part of it [synthetic biology]… it's key." Sarah continued to explain that, for her, it is synthetic biology's multidisciplinarity that sets this developing approach to biological engineering apart from other kinds of scientific practices. As Sarah explained:

> "it's having the engineers and the math people… the people that haven't been taught about recombinant DNA their whole lives… and getting all those different people together I think that makes synthetic biology a bit different."

Nick, a molecular biologist and Professor in Industrial Biotechnology similarly sought to emphasise that:

> "synthetic biologists by their very nature are multidisciplinary… you have to want to engage… I think that the people that are being pulled into synthetic biology have got a different mindset… they want to engage with engineers, mathematicians and other disciplines… social scientists as well…"

Like Nick and Sarah, Oliver, a geneticist with a background in GM crops who works in an advisory capacity to the UK government on GM and synthetic biology related matters and who contributed to the orchestration of the UK 2010 Synthetic Biology Public Dialogue, also sought to draw attention to what he described as the "multidisciplinary atmosphere in which synthetic biology thrives." Oliver explained that:

> "I mean if you look at Imperial College for example, you have engineers, social scientists, mathematicians, physicists, and biologists all working together on these projects. And not just working on one project but working in a kind of integrated way on a whole raft of projects… so you have got social scientists buzzing between them and engineers being borrowed and leant within institutions, and they bring a completely different perspective to bear I think on the way in which the science if you can call it that is being done. It is very tempting to think of synthetic biology as simply a scientific endeavour. I think it's bigger than that I think it is it's not

> just a science there is a kind of deep social science interest in it and there is also a deeper intellectual interest…"

It is often the case that 'multidisciplinarity' is described being a critical prerequisite of the successful development of synthetic biology (see, for example, RCUK, 2012; Baldwin et al, 2012; Balmer et al, 2016) and indeed a growing number of policy reports and academic papers have recently sought to emphasise that the drawing together of different types and kinds of disciplinary expertise can help to increase the likelihood of the successful design and construction of synthetic organisms.

The question however, of what multidisciplinary working might actually look like in *practice* and the specificities of what multidisciplinary working might actually help to achieve, are questions that remain largely under explored and under theorised within the context of the doing of synthetic biology in practice.

Nick continued to explain that the significance of a multidisciplinary approach to the doing of synthetic biology in his own working practice is that "it forces you to actually be able to explain in simple terms what it is you're doing… I think that challenges you… which is a good thing." Nick emphasised that:

> "because we all speak different languages we all have different assumptions… we all have different foresight about what's important… things that seem easy to me… right I think okay can you do a fluid model of this bioreactor for instance… I say that to an engineer and they'll go you just don't know how hard that's going to be right… and then they'll say to me oh can you just like insert this thirteen gene pathway into that… and yeah you don't know how hard that's going to be…"

What Nick is alerting us to here is an appreciation of the different sensitivities and sensibilities of different disciplinary traditions. Nick is also alerting us to an appreciation of what we might describe as the 'hands on' or what the STS scholars and theorists Polyani (1958) and Collins (2010) would describe as the ‘tacit’ knowledge that emerges from different kinds of working practices.

However, as we saw in the earlier stages of this chapter, Nick is a synthetic biologist that, for the most part, falls into the category of the ‘controlled experimentalist.’ More specifically, Nick is interested in enrolling and developing a synthetic biology approach in order to develop certain kinds of biologically based and economistically orientated products. Nick’s working practices are, in other words, oriented in such a way that there is less of a willingness for Nick and his colleagues to engage in the more diffuse temporalities and the meanderings that we encountered in the approach to the doing of synthetic biology that is the cellular engineer.

It is perhaps unsurprising therefore to find that in spite of Nick’s commitment to engaging with the “different languages” and dispositions that are emerging in the developing multidisciplinary field of synthetic biology, Nick nevertheless sought to foreground and to privilege certain forms of multidisciplinary working over others. Nick explained, for example, that:

> “we work with anyone who’s willing to work with us… but it’s the economic modellers that are really really important because they tell you if something is going to be viable and unfortunately in this world you know people only pay for what is viable… so that’s just the way it works.”

Richard, Director of a renowned genetic spin out and Professor and Group Leader of research into vector borne viral diseases, like Nick, similarly foregrounded and expressed a real interest in engaging and working with economic modellers. Although Richard is a full time scientist and commercial director of a genetics spin out company, Richard described how he is spending an increasing amount of time nurturing and developing economic affiliations and connections in his own working practices. Richard explained, for example, that:

> "the reason I did an MBA recently was to learn about some of these other cultures and trying to understand where some of these people are coming from…"

This approach however, to the doing of multidisciplinary working as outlined by Nick and to a lesser extent Richard, is indicative more of a 'cooperative' as opposed to a 'collaborative' approach. To briefly elaborate upon the differences between 'cooperation' and 'collaboration,' the social scientists Paul Rabinow and Gaymond Bennett (2012: 5-6) have recently emphasised that whilst cooperation assumes 'specialization and a defined division of labor,' collaboration involves:

> 'the likely reworking of existing modes of reasoning and intervention, adjusting these modes to the topography of the emerging problem-space. Collaboration proceeds with the assumption that new capacities, skills, arrangements, and distribution of power may well be required to carry out a successful inquiry.' (Rabinow and Bennett, 2012: 6)

What I want to suggest here, in this section of the chapter, is that depending on how collaborative multidisciplinary working is done in synthetic biology practice, it becomes possible to refigure the organism as 'epistemic thing' (Rheinberger, 1997) – that is, as an unfolding entity open to multiple trajectories of becoming. Take, for example, the recent collaborative endeavourings of Geoff.

Geoff, a cellular engineer that we encountered in the earlier stages of the chapter, is working with colleagues from across a number of different disciplines in a distinctly collaborative approach to the doing of multidisciplinary working. In drawing together the expertise and multidisciplinary sensitivities of computer scientists, mathematicians, pathologists and plant biologists, Geoff is endeavouring to open up "a new generation of plant experimentation" that he hopes will contribute to the cultivation and taking root of a "plant synthetic biology."

Geoff explained that the coming together of these different disciplinary traditions is helping to provide new insights into the biological interactions that play out and reverberate across the architectures of multi-cellular eukaryotes. Geoff explained that due to the insights and tools offered by the coming together of these different disciplinary traditions it is now possible to:

> "apply [to plants] the same kind of tools that you can with yeast and bacteria…. which allow you to do quite radically different things… you've got the benefits of working with a microbe…"

Interestingly, Geoff also alluded to the agential capacities of Marchantia itself in helping to facilitate the holding together of this diverse constellation of practitioners. Geoff was particularly keen to emphasise how, by working with Marchantia which has a "very simple architecture," with "fewer genes of various types and less redundancy," this is a plant which is "about as far from a crop plant as you can get." For Geoff and his collaborators this means that:

> "there's less commercial interest in it, it means you can start to eke out a space which allows you freedom to work with systems without people slapping on patents… or worrying about commercial applications…."

Paul, a molecular biologist and current practitioner of synthetic biology who was aware of and who held in high regard the working practices of Geoff and his collaborators, similarly pointed to the ways in which the agential capacities and texturings of Marchantia are feeding into Geoff's approach to the doing of synthetic biology. In reflecting on what makes Marchantia good to work with Paul explained that:

> "I think it would be really nice to do some plant stuff here as well… [Marchantia] it's like a moss basically... slightly higher than a moss... it's small and compact… the nice thing about it is it's quite easy to grow basically… you just need a box with a light in it… [it's] easy to contain… and kind of nicer in terms of working in that you don't have to… the timeline is much like fuzzier you know plants grow slower than bacteria so whereas you have a bacterial protocol you need to do things sometimes like two or three days in a row… with the plant actually you know if other commitments get in the way it's okay because you can sort of delay the protocol by a day or two… also I guess if you're kind of showing the public you know or trying to get the public involved in stuff, there is less of an ickyness factor…"

For Geoff however, the significance of the texturings and agential qualities of Marchantia resides not so much in its 'user friendliness' or in its reduced 'ickyness factor,' but in the ways in which it is resonating and intersecting with, the comings-together of different disciplinary tools, traditions and processes. Geoff sought to emphasise that:

> "in the 80s things shifted towards the *Arabidopsis* as the model system which happened to be one of these higher plants systems [where] you can make links with crop systems… now, we're in a position where we've actually got to go back… reverting back to 150 years ago where the benefits that made Marchanita useful in those days… with the then primitive knowledge about plant culture…. now resonates with all of the molecular tools that we have on top of that."

There are differing versions of temporality that course through Geoff's collaborative approach to the doing of multidisciplinary working. These are versions of temporality which, following the social theorist and philosopher Michel Serres (1997), are less concerned with the straight forward march of progress, but which work instead to fold together and multiply outwards, past, present and future. As Serres (1997: 15) explains:

> 'far from flowing in laminar and continuous lines, like a well-behaved river under a bridge, upstream to downstream, time descends, turns back on itself, stops, starts, bifurcates ten times, divides and blends, caught up in whirlpools and counter-currents, hesitant, aleatory, uncertain and fluctuating.'

The contours of Marchantia are, in other words, being recast and refigured anew by the comings together of these different types of knowledge practices, tools and temporalities. In particular, Geoff's 'eking out' of a space that is free from the temporal or felt pressures of an economistic return, combined with Marchantia's 'distance' from a crop plant and the different and distanced sensitivities of the multiple disciplinary traditions that Geoff is drawing together, is opening up new insights into what Marchantia is and into what multi-cellular eukaryotes can do.

Similarly to Geoff, the multidisciplinary working practices of the evolutionary biologist Andres Moya (2008, 2009) and colleagues at the Institute of Biodiversity and Evolution and in the departments of Genetics and Molecular Biology at the University of Valencia is a further example of synthetic biology as multidisciplinary endeavour that helps to open up a somewhat different story about what synthetic biology is and what it might become – a story that stands in contrast to the sensitivities, dispositions and doings that were foregrounded in the figure of the synthetic biologist as cellular engineer and in the figure of the synthetic biologist as controlled experimentalist.

In their recent work on the development of minimal cells and genome reduction processes, Moya and colleagues have mobilised the tools of synthetic biology in order to 'open up to biological study,' an engagement with previously uncultivable endosymbionts. Endosymbionts are small symbiotic partners that live within an associate organism and which are integrated at the behavioural, metabolic or genetic level (Moya et al, 2008). The term 'symbiosis' or 'symbiont' refers to the process of 'living' (*biosis*) 'with' (*sym*) (Moya et al, 2008).

In leveraging the tools of synthetic biology and in drawing together the expertise of genomic scientists and molecular biologists specialising in transcriptomics and metagenomics, Moya et al have developed new insights into prokaryote – animal symbioses. In particular, their work has raised a number of important questions surrounding what this might mean in terms of 'learning how to live together.' Moya et al have highlighted, for example, how contrary to previous understandings, endosymbionts from the same prokaryotic lineage can take part in multiple symbiotic associations of a bewildering array of complexity. The minimal cell that is the endosymbiont bacteria is reconfiguring understandings of the manifold complexities of prokaryotic – eukaryotic associations.

Significantly, Moya et al have emphasised that the intersection of sequencing tools with different omic technologies and the disciplinary sensitivities of the evolutionary biologist, is playing a critical role in helping to open up a 'new field of research' into processes of symbiosis and symbiotic associations (Moya et al, 2008). For Moya and colleagues, instead of being simply a means to enhance the efficacy of industrial biotechnological endeavourings, the minimal cell – that is, the organism that has been stripped of the so called 'complex ramblings' bequeathed to it by evolution (Roosth, 2010: 86), resurfaces here in this particular storying of the doing of synthetic biology as an 'epistemic thing' (Rheinberger, 1997) – that is, as an unfolding entity open to multiple trajectories of becoming.

Similar multidisciplinary working practices and novel insights have been generated in the recent work of the prominent scientists and evolutionary biologists John McCutcheon and Nancy Moran (2012). McCutcheon and Moran are also working at the intersection of evolutionary biology and genomic science and are similarly leveraging the tools and techniques offered by synthetic biology in their own multidisciplinary working practices. Like Moya et al, McCutcheon and Moran are assembling different kinds of disciplinary expertise and techniques around symbiotic bacteria as an 'object' of multidisciplinary scientific inquiry.

McCutcheon and Moran (2012: 13) have emphasised that the 'minimal cells' that emerge at the intersection of evolutionary biology, genomic science and molecular biology 'are not models for replication efficiency and in fact are probably among the least efficient or robust bacterial genomes.' McCutcheon and Moran (2012: 13) highlight, for example, how the proteins generated by these organisms are susceptible to different kinds of misfolding and require 'a large investment in chaperones to preserve protein functionality.' As McCutcheon and Moran (2012: 13) continue to explain, the insights generated by the coming together of evolutionary biology, genomic science and synthetic biology are opening up and posing profound and significant 'implications for the concept of minimal genomes, the origins of cellular organelles, and studies of symbiosis and host-associated microbiota.'

What we can begin to see here then is a somewhat different story to the account of the refactored minimal cell that we encountered in the figure of the synthetic biologist as controlled experimentalist. McCutcheon and Moran describe the minimal cells that are the bacterial symbionts emerging at the intersection of evolutionary biology and genomic science as a 'conundrum' of biological classification. These are organisms that have fewer proteins than are found in certain kinds of organelles and viruses, but at the same time these are organisms which differ from organelles and viruses 'in that they retain many genes enabling the core processes for cellular life' (McCutcheon and Moran, 2012: 24). This is a particularly illustrative example of how the sensitivities of the evolutionary biologist are intersecting with computational logics and the laboratory techniques of different disciplines in ways which are working to recast the contours and understandings of intracellular bacterial symbionts. This assembling of things is working to call into question extant structures and modalities of understanding and indeed it is the coming-together and the intersecting of multiple disciplinary traditions, tools and techniques that are enabling these minimal cells, in the language of the philosopher and historian of science Isabelle Stengers (2005) to 'force thought.'

In short then, it is my suggestion in this section of the chapter that the differing modalities of and opportunities for multidisciplinary collaboration associated with the doing of synthetic biology are working to generate alliances which are not simply or narrowly about the development of a biotechnological solution. More significantly, these are alliances that are working to reconfigure what it means to 'know.' If the synthetic biologist as cellular engineer is alive to the agential dance of the organism in process then the synthetic biologist as multidisciplinary scientist is engaged in a dance or intercalation of disciplinary sensitivities. These disciplinary sensitivities, as they come together and encounter one another in a collaborative fashion, are opening up new possibilities for thinking and doing things differently. They are enabling biological process and materialities to force thought on their own terms.

5. Thinking With and Through the Multiple and Malleable Modalities of the Doing of Synthetic Biology

5.1. Recapitulation of Key Points So Far

In this chapter of the thesis I have sought to add an empirical texturing to the term 'synthetic biology' – a term which, for the social scientists O'Malley et al (2008), 'conceals' more than it 'reveals.' O'Malley et al (2012) are referring here, as I noted at the very outset of this chapter, to the homogenising propensity of 'synthetic biology' as an umbrella term. This is, in other words, a term that effaces the intricacies and the subtleties of what is ultimately a diverse set of apprehensions and working practices.

The insights and empirical materials that I generated throughout the course of my interviews with leading practitioners in the field has enabled me to bring a geographical sensibility to bear on this developing approach to biological engineering and to trace the ways in which synthetic biology is done differently in different sets of relations by different practitioners. I have identified three prominent modalities of the doing of synthetic biology – the 'cellular engineer,' the 'controlled experimentalist' and the 'multidisciplinary scientist.' To use the language of the anthropologist and feminist philosopher Annemarie Mol (1999, 2002) I have traced the contours of the 'synthetic biology multiple.'

The cellular engineer, controlled experimentalist and multidisciplinary scientist are three modalities of the doing of synthetic biology which occupy different space-times – that is, they are moving in different directions with different kinds of baggage. I have chosen to focus in on the different 'things' (Latour, 2005) and the different types and kinds of relations and apprehensions that underpin these different modalities of the doing of synthetic biology in practice.

Whilst, for example, the synthetic biologist-as-cellular engineer is attentive towards the rough edges and the thickness of biological sociabilities, I have highlighted how the controlled experimentalist is rather concerned with 'smoothing' and 'straightening out' the route taken towards a particular biotechnological outcome or output. If the cellular engineer is engaged in more of a 'feeling around' - in what the philosophers Deleuze and Guattari (1988) would describe as a 'diagrammatical' form of apprehension, then the controlled experimentalist is working instead to demarcate and to 'map' out the quickest and indeed the most efficacious route through which it might become possible to realise the qualities of predictability and efficacy in the doing of biological engineering.

Whilst the cellular engineer foregrounds and is sensitised towards the thickness and multiply unfolding trajectories of a processual biological, the controlled experimentalist is rather concerned with stripping back the thickness of biological sociabilities. Tim, for example, a controlled experimentalist, provided an illustrative account of how he is mobilising in his own working practices engineering mechanisms and strategies such as 'refactoring' that have been designed with a view to dampen and to modulate the noisiness of the improvisational dance of the organism in process.

The cellular engineer, with its attentiveness towards the noisiness of the biological, is interested in grappling with a much fuller range of biological encounters that are taking place within the cellular milieu - whether these encounters be between heterologous enzymes and protein scaffolds, or between the synthetic organism and its environmental contextings. In contrast, the controlled experimentalist is concerned instead with tending to the relationship between genetic code or biological 'part' and specific functionalities. The controlled experimentalist speaks of ‘discrete’ biological components that can be seamlessly slotted and integrated into different microbial ‘chassis.’ The cellular engineer however, adopts a more relational ontology – a modality of tending-to that is attentive towards the relations and touchings together of different constituent components within the organismal milieu.

In the latter stages of the chapter I then moved on to trace the figure of the multidisciplinary scientist – the third of the composite modalities of the doing of synthetic biology that I identified throughout the course of my interviews with practitioners in the field. I highlighted how different approaches to the doing of collaboration and multidisciplinary working differentially figure the organism as ‘epistemic thing’ (Rheinberger, 1997) – that is, as an unfolding entity open to multiple trajectories of becoming. More specifically, I highlighted how the comings together of different disciplinary traditions can, at times, help to open new ways for thinking about, and engaging with, biological materialites and organismic ontologies and orderings.

I used the example of Geoff’s multidisciplinary work on the liverwort Marchantia to illustrate how, in this particular modality of multidisciplinary working, time becomes freed from its ‘progressive’ march and can instead turn back on itself, becoming aleatory and fluctuating (Serres, 1997). Similarly to the ways in which the cellular engineer resists the tendency to afford any ontological primary to certain parts of the organismic architecture over others, I highlighted in this section of the chapter how the conditions of possibility that are seeded by the comings together of multiple disciplinary traditions can work also to generate some ‘ontological intrigue’ – to make room for varying biological processes and materialities to force thought on their own terms.

These three different modalities of the doing of synthetic biology are not however discrete, neat or self-contained doings and it is important to reflect here on the syncretisms and the tensions that exist between them. These are, in other words, composite and patterned modalities that diffract and interfere. Practitioners are able to inhabit more than one category and to transition between them. I will now conclude this chapter by reflecting on how these different modalities of the doing of synthetic biology 'hang together' (Mol, 2002) or, in the more recent language of Law et al (2013) work together syncretically. I will reflect on the implications posed by the nature of these syncretic associations, particularly in terms of thinking through what it might mean for synthetic biology to inhabit the world and to inhabit it well.

5.2. On Syncretisms, Co-Existences and Tensions or, How the Synthetic Biology Multiple 'Hangs' Together

Whilst the pointedness of the efforts of the controlled experimentalist is at times generative of varying forms of reductionism and mobilises a somewhat mechanistic rendering of relationality, the controlled experimentalist does not work simply in opposition to the cellular engineer. Far from solely endeavouring to 'write out' biological complexity of the doing of synthetic biology (Endy, 2005), there was a developing sense amongst a number of controlled experimentalists that becoming sensitised towards the processual nature of the organismal architecture might be important in making what Hugh, Director of a UK synbio company described as the "reactions that occur in nature more amenable to commercial processes."

This slippage between controlled experimentalist and cellular engineer was most clearly exemplified by Lester, a physicist turned biochemist and now CEO of one of the UK's leading synbio start-ups who simultaneously inhabited both of these subjective patternings. Take, for example, Lester's account of his company's approach to the doing of synthetic biology. Lester sought to emphasise that:

> "I think our methods are going to be quite transformative actually. We're doing things in a slightly different way, what I would call synbio 2.0…the big problem with what I would describe as synbio 1.0 is that it optimises genes and then the environment, whereas you're a product of your genes and your environment not genes then your environment…. it's this multifactorial approach which is key…. we've pushed our methods [up to] 30 factors where we look at the genetic factors and process factors at the same time…. first of all in small scale tanks… and then in the bigger scale tanks… all in parallel… and you do this multivariate analysis… and you get phenomenally higher yields phenomenally quickly. It's transformational the first time you do it you think somebody's been cheating or elves are doing it… it is… it's unbelievable… and biology has yet to professionalise, has yet to embrace this method of working… biology is incredibly complex so we have to… we have to address it in a multifactorial way and that message hasn't got through yet. I mean we're starting to preach it pretty loud and a few people are adopting it and it will happen. There's a new generation of students coming along who are a bit more switched on to it and software will help as well. We will have programming languages coming through which will enable us to increase our productivities significantly…. but it is the application of these multivariate methods which are the only way to progress."

Lester is explicitly acknowledging here the complexities and the thickness of biological sociality. Indeed, he is emphasising in this very extract that the doing of the engineering of biology might well require an engagement with, rather than simply a dismissal or deprioritisation of, the more convoluted sensitivities and apprehensions that are typically exhibited by the cellular engineer. Given Lester's attentiveness towards the processual nature of the biological, it is perhaps unsurprising therefore that a number of social scientists such as O'Malley (2011) and others have recently argued that biological design may well have to become biologically 'plastic' – that is, biological design may well have to become increasingly accustomed and attentive towards the agential forcings and intricate texturings of self-replicating biological substrates.

In a 2013 paper, for example, the philosopher and historian of science Tim Lewens has advanced a compelling critique of the purported efficacies of 'rational design.' Rational design is an approach to the doing of engineering and construction that is typically associated with the endeavourings of the controlled experimentalist. It refers to the decomposition of a specific problem into distinct sub-units. These distinct 'sub-units' are then slotted together with a view to addressing and remediating a pre-designated problem.

The 'BioBrick' approach to the doing of synthetic biology that I outlined in the earlier stages of this chapter – an approach to the doing of synthetic biology whereby 'interchangeable' and 'discrete' biological parts are 'hooked up' and 'joined together' with a view to creating novel biological systems which perform pre-designated and functional tasks, is a prominent example of how rational design based engineering techniques are being increasingly brought to bear on the substrates and substances of the stuff of the biological. But, the 'BioBrick approach' to the doing of synthetic biology is not the only example of where rational design based approaches are being incorporated into the developing trajectories of synthetic biology practice. The process of 'refactoring,' for example, as described by the controlled experimentalist Tim in the earlier stages of this chapter, is a further example of how rational design based approaches are being increasingly mobilised within the developing trajectories of synthetic biology.

In calling into question the very efficacies of 'rational design,' the historian and philosopher of science Tim Lewens (2013) has reflected on recent high profile work in the discipline of evolutionary electronics involving the development of a reconfigurable electronic chip designed to discriminate between two audio tones. Lewens (2013: 645) highlights how 'some sections of the best-performing evolved chip couldn't be altered without loss of function, even though they were not electrically connected (in the usual way, at least) to the output of the chip.' What this means, is that the evolved reconfigurable electronic chip had developed inscrutable yet highly fortuitous associations that arose from the ad-hoc specificities of its local contexting. These fortuitous inscrutable associations were damaged and lost when practitioners subsequently attempted to improve upon the electronic chip.

Significantly, for both Lewens and for the researchers working on this evolved reconfigurable chip, the findings of this study provide a powerful exemplification of how evolutionary design techniques – that is, design techniques which resist the tendency to 'decompose' a problem into distinct sub-units and which mobilise instead looser and less orientational experimental protocols can work to outcompete their rational design counterparts – the simple reason for this being that 'the unconstrained pathways of evolutionary design are free to take advantage of whatever fitness-enhancing effects may present themselves' (Lewens, 2013: 645). As the metaphysical theorist Andy Clark puts it:

> 'biological evolution is *liberated* by being able to discover efficient, but 'messy' or unobvious solutions: ones which may, for example, exploit environmental interactions and feedback loops so complex that they would quickly baffle a human engineer… Biological evolution is thus able to explore a very different solution space… than that which beckons to conscious human reason.' (Clark, 1999: 6, emphasis in original)

The co-founder of a company ‘Microbial Solutions’ – a company which uses non-genetically modified bacteria in order to detoxify and remediate industrial waste streams, has relatedly emphasised that whilst there might be a role for genetic modification and synthetic biology approaches to address ‘pinch points’ in the detoxification process, synthetic biology is nevertheless unable to outcompete, certainly at the present moment, 3.5 billion years of evolution (Ian Thompson in Marris and Jefferson, 2013).

Lewens has suggested that the implementation of a rational designed based approach can therefore paradoxically serve to constrain not only the efficacies of, but also the possibilities for, the generation of novel functionalities in other-than and more-than-human things – whether those things be biological organisms, electronic chips or segments of algorithmic code. Far then from being a hindrance that should be necessarily ‘written out’ (Heinemann and Panke, 2006) of the design process, what we can begin to see here is that biological complexity, particularly in the form of cross talk, can be incredibly ‘fortuitous’ (Lewens, 2013) in the development of novel functionalities in organisms. It is for precisely this reason that Lewens (2013), O’Malley (2011) and others have posited that ‘irrational design’ approaches to the doing of engineering – that is, approaches and experimental protocols which are premised upon techniques such as blind mutation and non-directed evolution might very well begin to take centre stage in the burgeoning approach to biological engineering that is synthetic biology.

What I want to suggest here then, in relation to the composite and patterned modalities that I have identified throughout the course of this chapter is that the controlled experimentalist might perhaps best be described therefore as being necessarily engaged in a becoming cellular engineer. It is not implausible to suggest here that it might well be the practices and endeavourings of the controlled experimentalist, as opposed to simply that of the cellular engineer, that work to decentre the old dogmas of molecular biology and which help to open up a repertoire of resources for thinking through and engaging with, the fullness and thickness of biological sociality.

Take, for example, the case of Toby. Although Toby, controlled experimentalist and CEO of a nascent start-up frequently mobilised reductive metaphors in his descriptions of the doing of synthetic biology, he also acknowledged that in order for synthetic biology to reach its full potential, considerable work will need to be undertaken with regards to exploring the complexities of biological relationality. Toby asserted that:

> "organisms are themselves hugely robust… they are you know very complex… there's a multiple feedback loop… you knock something out and you know they're okay because they'll use a different carbon source or whatever. It's important to recognise that any synthetic genetic network is obviously either operating orthogonally or disrupting natural homeostatic mechanisms which makes your chassis less robust…. understanding how chassis's interact with those sort of synthetic networks and how the synthetic networks themselves can be structured to be more robust… these are essential questions if you're ever going to translate anything into a complex environment..."

Toby, like Lester, is acknowledging here that it is not simply enough to 'black box' biological complexity. Biological complexity might instead have to become an object of inquiry in its own right if the controlled experimentalist is to successfully engage in the engineering of the biological. There are, then, important divergences *and* synergies between the cellular engineer and controlled experimentalist that we must be careful not to efface.

The explications of Lester and Toby open up here the glimmerings of what might be described a more hopeful and affirmative account of synthetic biology – an account of synthetic biology that is not so much about 'hubris' (Lewens, 2013) or any kind of human mastery even, but which is rather concerned with taking seriously the limits of human knowledge and with foregrounding (as opposed to simply black-boxing) the richness and the agential vitalities of non-human things in their full complexities and textured specificities.

But, it is not simply sufficient here to simply argue that the synthetic biologist as controlled experimentalist is necessarily engaged in a becoming cellular engineer. There are also more fraught and problematic relations that exist between the synthetic biologist as controlled experimentalist and the synthetic biologist as cellular engineer. Schyfter and Calvert (2015), for example, have recently argued that the noisiness and prevalence of the utterances of the controlled experimentalist might well be putting the long term viability of the development of synthetic biology as a whole at risk. As Schyfter and Calvert (2015: 380) explain, the 'convincing and successful discourse of engineering-based industrialisation and economic growth [associated with synthetic biology] can lead ironically to a shift away from the industrial developments' that might be critical to facilitating and securing the development of this burgeoning approach to biological engineering.

Schyfter and Calvert highlight in their 2015 paper how the deterministic proclamations and utterances that synthetic biology 'will' turn biology into an engineering discipline and 'will' culminate in revolutionary biotechnological outcomes might well have helped synthetic biology practitioners to secure funding and to attract government support – particularly within the context of the so-called knowledge based bio-economy (KBBE), but can paradoxically work to overshadow the investments and the infrastructural resources that are necessary to make these aspirational visions a reality.

This is an example then, of how the 'future' is being compressed into the 'present' in ways which can prevent and halt the realisation or the coming into being of certain kinds of realities (Schyfter and Calvert, 2015). To problematise matters even further, the failure of synthetic biology to culminate in any of its ambitiously projected 'outputs' can further work to push the coming into being of synthetic biology off-course by relegating to 'hype' and 'hyperbole' the aspirational visions of the field.

In terms of the relations between the cellular engineer and the multidisciplinary scientist, whilst the cellular engineer and the multidisciplinary scientist are both modalities of the doing of synthetic biology that can work to generate different kinds of ontological intrigue and curiosity, I have highlighted in this chapter how different kinds of multidisciplinary working practices afford different kinds of possibilities for opening up new ways of thinking and doing things differently. A 'cooperative' approach, for example, to the doing of multidisciplinary working does not afford the same propensity to 'open things up' and to call extant understandings into question in the same ways that a more 'collaborative' approach can (cf Rabinow and Bennett, 2012). The synergies then, between the cellular engineer and multidisciplinary scientist are wrapped up in the space and the room that is made available for genuinely collaborative approaches to the doing of multidisciplinary working.

In a recent paper O'Malley et al (2008: 63) have emphasised that the 'fate of synthetic biology hinges on its capacity to deal with the complex properties of highly variable biological systems.' The reduction of complexity O'Malley (2008:

63) posit, may well be 'necessary for proximate understanding, but it is a very limited manifesto for a field aspiring to be a new approach to biology.' For O'Malley et al (2008: 63), if synthetic biology is to realise its engineering ambitions and to become more than simply a 'modest contributor to 'analytic' biology,' then synthetic biology must do more than simply incorporate or mimic programmatic engineering principles into the doings of biological practice.

Significantly, what O'Malley et al (2008) are alerting us to or calling for here is a biologised approach to the doing of engineering – an approach to the doing of engineering that is alive not only to the contextual challenges and specificities of working with self-replicating biological substrates but also to the intricate texturings of different kinds of organismal architectures. This is, in other words, a call to drag the programmatic rhetorics and rationalities of an engineering approach into a rather different terrain and biologised habitat.

Geography as a discipline is well equipped to map out and trace the frictions and the twist and turns that emerge as the sensitivities of engineering become mutually reconfigured by the stuff and substances of the biological. It is important to make clear here that this is not simply a call for an attentiveness towards the ways in which the stuff of biological resists or pushes back against the implementation of an engineering logic. This is not another story of recalcitrant natures. Rather, there are important re-assemblings at play here between different disciplinary sensitivities and different apprehensions and engagements with the stuff of the biological that are in need of mapping out.

By mobilising a methodological and conceptual attentiveness to difference I have aimed in this chapter to contribute to the effort of mapping out these twists and turns and dis/re-assemblings. I have highlighted in this chapter how, by tending to the doings of synthetic biology in practice, we can begin to develop a more nuanced understanding not only of what synthetic biology is but also of what it might become – of how synthetic biology takes and shift(s) its shape in different sets of relations.

I have opened up a series of less-perspectival and less-technologically deterministic stories about the emergence of this developing approach to biological engineering and it is in this sense that I hope to have generated some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. In the next chapter of this thesis I turn now to reflect on the regulatory provocations posed by synthetic biology's coming into being. I ask; what might it mean to empower the situation that is the coming into being of synthetic biology and to contribute to the effort of bringing synthetic biology into a governable world?

Chapter Five

Bringing Synthetic Biology into a Governable World

1. Chapter Overview

In this final empirical chapter of the thesis I turn to address the regulatory provocations posed by the development of synthetic biology. I am interested in how synthetic biology is imbricated within, and is intersecting with, the regulatory reality practices of the UK's Health and Safety Executive (HSE). Regulation is a multifaceted endeavour. It is an endeavour or doing that takes on different forms as it is done in different locations and enforced by different organisations. There are many different types, kinds and approaches to the doing of regulatory governance (Foucault 2007; Jasanoff 2011). HSE's regulatory remit is concerned not with the development or enforcement of patent law or ethical guidelines (refs), but with delimiting risks to human health and the environment arising from work place practices.

HSE's Biological Agents Unit (BAU) is part of HSE's Hazardous Installations Directorate (HID). It is responsible for overseeing the undertaking of synthetic biology practice and work with biological agents in laboratory and containment facilities. The delimitation of risks arising from synthetic biology practice and work with biological agents more generally is known as 'biosafety.' HSE's approach to the doing of biosafety provides a specific lens through which to explore regulation as it is done in action and in process. There is, I argue, a specificity to the doing of biosafety that has much to teach us about how certain kinds of reals and relations are engendered, foreclosed, brought into being or otherwise marginalised. Regulation cannot be reduced to the development of prescriptive rules but is also about attuning, relating, learning and becoming.

In this chapter I draw on empirical materials generated whilst working alongside HSE's Biological Agents Unit as a Major Hazards Policy Researcher. I begin the chapter by providing an account of how HSE is encountering and tempering at present, associated risks to human health and environment posed by the coming into being of this developing approach to biological engineering. This is primarily through the legislative framework of the Genetically Modified Organisms (GMO) Contained Use (2014) Regulations. Synthetic biology then, the unsettled object that we encountered in the preceding chapter of the thesis, has become cast here in terms of a singular, stabilised and pre-established set of regulatory and reality practices. But this, I argue, is just one part of a much more complex story.

As HSE and a number of synthetic biology practitioners are acutely aware, synthetic biology is a somewhat 'slippery' regulatory object. Synthetic biology differs and departs from conventional genetic modification (GM) work in a number of important ways. In this chapter I highlight how synthetic biology's 'betwixt and between' of 'source species' and 'chassis' organism (Roosth, 2010: 99) – its splicing together of multi-species organismal parts and components, is contributing to a decentring of, and a departure from, extant templates and comparative frames of reference. I argue that synthetic biology is an emergent field of technoscientific endeavour that exemplifies and intensifies a shift away from life or biology rendered in informational terms (cf Caduff, 2012).

Bringing, therefore, synthetic biology into a governable world requires not simply the implementation of a regulatory *framework* that delineates fixed and neat Euclidean objects - but a shift towards a looser and more relational sense of *networking*. I use the term networking in the Stengerian (2005, 2015) sense of the opening up of synthetic biology to new connections and dynamics of learning.

As this chapter progresses I ask; what are the kinds and qualities of networks and relations that might help to govern the already-present and the virtual (to come) objects of synthetic biology? I consider the extent to which the bringing of synthetic biology into a governable world has involved the adoption of a more open regulatory frame. Beyond however, simply arguing for a shift from frameworks to networks, I argue that frameworks too have their own generative affordances and dispositions. They retain their value for a number of important reasons.

In addition to tracing the ways in which synthetic biology is forcing thought for HSE, I also highlight in this chapter how, for a number of synthetic biologists, questions and considerations of safety and risk have taken on a new found significance. I trace the glimmerings of what might be described as a less-modernistic-post-Promethean engineering subjectivity. I argue that the development of this less-modernistic-post-Promethean engineering subjectivity can be attributed, in part, to synthetic biology's inheritance from, and association with, some of the challenges and controversies surrounding the development of GM crops. I highlight how, inhering within some of the endeavourings of a number of synthetic biologists (most notably that of the controlled experimentalist), are relational and networked practices of working that contribute to the bringing of synthetic biology into a governable world. Different disciplinary knowledges, for example, are being spliced together by synthetic biologists in order to engage more affirmatively with the species of (non) knowledge that is scientific indeterminacy.

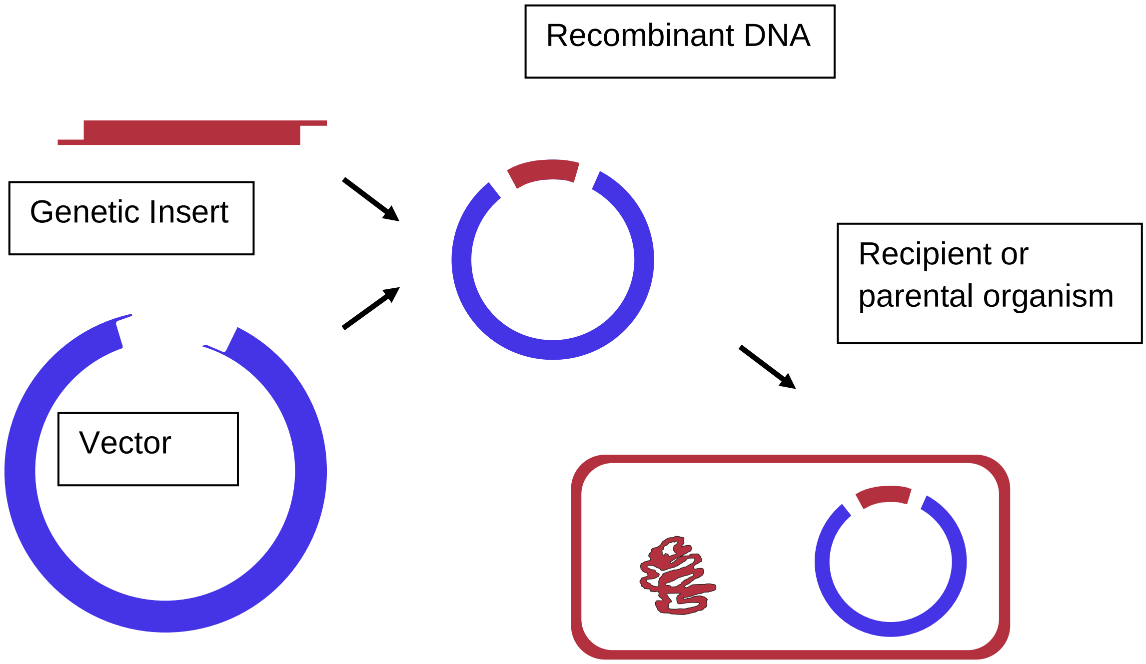
The chapter opens up a somewhat different story to a number of science and technology studies (STS) accounts of regulation that have rendered the site of the doing of regulation as a particular forum or agora that is marked by its propensity to externalise and excise varying kinds and forms of unknowns and complexities from the policy-making process (Stirling 2008, 2010; Wynne 1992; Zhang et al 2011). I highlight how HSE's 'complex present' is intersecting with the 'slipperiness' of synthetic biology as an 'object' of regulatory governance in ways which are opening up new kinds of regulatory settlements and shape(s) – settlements that are based not so much on habit or on any kind of orientational knowledge but on the cultivation of sentinel capabilities. There is, in other words, much more to the doing of regulation than simply the attempted pursuit of a scientifically informed bureaucracy (Zhang et al, 2011).

I argue that imbued within the reflexive practices and apprehensions of HSE, and the relational and networked practices of working of a number of synthetic biology practitioners, are the glimmerings of what might be described as a different kind of making governable. This is a making governable that involves the development of new sets of skills and affordances. It is a making governable which endeavours to work with, rather than against, inevitable gaps in scientific understandings of and evidence for risk. At the same time, however, I also argue that there is further work still to be done in terms of nurturing more networked orientated modalities of apprehension – particularly in terms of engaging with and opening up social conceptions of risk.

2. Synthetic Biology and the GMO CU Regulatory Framework

At present, HSE is encountering synthetic biology through the GMO (2014) Contained Use Regulatory framework. The GMO (CU) regulations stipulate that, prior to commencing any work which involves processes of genetic modification, practitioners must first assess whether their projected work poses any risks to either human health or the environment. Risk assessment is achieved through an evaluation of the characteristics of the GMO and its constituent parts which includes the recipient or parental organism, the host/vector system and the origins and intended functions of the genetic insert. Figure 2 presents a diagrammatical representation of key constituent components of the GMO risk assessment process. The parental organism and genetic insert are clearly identified.

[Figure 2] – Key constituent components to consider during the undertaking of the GMO risk assessment process.



The constituent components as delineated above contribute to the making of what the science and technology scholar Javier Lezaun (2006: 499) describes as a 'viable object' of regulatory governance – that is, they contribute to the taking shape of a process through which the 'GMO' regulatory object acquires 'concrete and material meaning' (Lezaun., Ibid). Figure 2 is also particularly useful in throwing into relief the spatiality of organismal intervention that underpins the GMO regulatory framework. This is a spatiality of organismal intervention that is premised upon a localised genetic ‘insert’ that is integrated into a distinctive ‘parental’ host.

During the process of evaluating the characteristics of the GMO and its constituent parts, practitioners are required to assess the host range of the micro-organism, its biological stability, the virulence of the strain and the availability/effectiveness of prophylactic or therapeutic measures. Practitioners must also take into account the nature of the work that they are undertaking and whether, for example, their projected work might enhance the virulence of the microorganism that they are working with or transform exposure routes through the generation of aerosols.

Subsequent to the identification of any biological hazards, practitioners then determine whether their projected work falls into risk classification level one, two, three or four. These classification levels ascend in conjunction with the level of risk. Class level one (Cl1) refers to activities that are regarded as posing nil or negligible risks to human health and the environment. This might include, for example, the use of an attenuated strain of *E.coli* that has been genetically modified in order to produce a particular biochemical product within a commercial fermenter. Class level 4 (Cl4), on the other hand, refers to activities that are regarded as posing high risk to either human health or the environment. Examples of Cl4 work include the genetic modification of Foot and Mouth Disease Virus (FMDV) or Rinderpest Virus for research purposes in a public or private Cl4 research facility.

The risk classification is then used to determine the implementation of a containment level. Containment levels are similarly divided into levels one, two, three and four. These levels typically correspond to the risk classification level and they require that practitioners implement a variety of mechanisms in order to delimit risks to human health and environment. Differential air pressure systems, protective clothing and waste inactivation procedures are just some examples of the physical, biological and chemical barriers that practitioners must enrol in order to provide for proportionate and practicable protection to human health and environment. These measures are documented in the accompanying Annex to the GMO CU regulations and are further outlined in a compendium of guidance produced by HSE.

The GMO CU Regulations (2014) are underlined by the recognition that whilst recombinatorial biotechnical organisms might well be laboratory-born, they share a biology and a propensity to interact with, and to transform, organisms and ecologies well beyond the laboratory - organisms which therefore maintain a very real stake in the 'production, containment and potential dispersal' of novel biologies and biotechnological endeavours (Roosth, 2010: 65).

In 2014, the GMO (CU) regulatory framework was consolidated and streamlined following the Löfstedt Review of 2011. The Löfstedt Review is widely regarded as constituting a deregulatory 'moment' in the doing of regulation for HSE. Led by Professor Ragnar Löfstedt of Kings College London, and commissioned by the UK government, the review culminated in a number of recommendations which it felt would not only help to make the regulatory landscape less 'voluminous' but which would also help to reposition health and safety as a vital part of doing 'good business.' HSE emphasised during the process of the consolidation of the GMO Regulations and indeed, they wrote into the very text of the new consolidated framework, that the GMO CU regulations sufficiently take into account the developing trajectories of synthetic biology practice. Section 7 of the 2014 consolidated GMO (CU) Regulations explicates that:

> ‘The requirements of the Regulations also apply to ‘synthetic biology,’ ie the use of techniques that involves incorporating synthesised DNA or RNA into an organism. It is inserting the synthetic material into an organism that makes it ‘contained use’ and not the process of the DNA synthesis.’

Early in the consolidation process, the Department of Business, Innovation and Skills (otherwise known as ‘BIS’) expressed a perceived need to ‘distance’ synthetic biology from its association with GM and to carve out a space for synthetic biology that was separate and distinct from the extant provisions of the GMO regulatory framework (Field Notes, 10/04/14). This was a position that was held by BIS in spite of BIS’s general preference for a ‘better’ regulatory agenda – a regulatory agenda that endeavours to strip back and to streamline the quantity and volume of extant regulatory provisions (see, for example, Tombs and Whyte, 2013).

And yet, in spite of the existence of competing understandings surrounding the question of where and how synthetic biology might be brought within the realm of regulatory oversight, HSE used the consolidation of the GMO CU regulations as an opportunity to address directly the development of synthetic biology – to bring this burgeoning approach to the doing of biological engineering within the realm of extant modalities of regulatory oversight. HSE used the consolidation process as an opportunity to provide ‘assurances’ to the public and wider government that synthetic biology is adequately covered by the GMO regulatory frame. Synthetic biology then, has become cast here in terms of a singular, stabilised and pre-established set of regulatory and reality practices. It has become cast as an ‘object’ of regulatory governance that can be corralled into extant ways of working.

The incorporation of synthetic biology into the GMO Regulatory framework is an example of what Frow (2013) would describe as the 'retrofitting' of extant ways of working in order to contain and to render more amenable to traditional modalities of oversight, this emerging field of biotechnological endeavour. It is an example of what Zhang et al (2011: 7) have described as a 'filling the prescription approach' to the doing of regulation – an approach that formats 'the problem to fit readily available solutions.'

But this, I argue, is just one part of a much more complex story. In drawing on a combination of empirical materials generated whilst working alongside HSE and from over thirty 1-2 hour interviews with a range of synthetic biology practitioners, I reflect in this chapter on the more subtle working practices of HSE that a 'filling the prescription' analysis is quick to efface. These practices, I argue, highlight how the successful implementation of the GMO CU Regulatory framework requires simultaneous processes and practices of *networking*. I also reflect in this chapter on the ways in which synthetic biology practitioners are addressing and tending to questions of safety and risk in their own working practices and in doing so, are contributing to the bringing of synthetic biology into a governable world.

3. Synthetic Biology: A Slippery Regulatory Object

In spite of its corralling of synthetic biology into the legislative framework for the regulation of GMOs, HSE and a number of synthetic biology practitioners are acutely aware that synthetic biology is a somewhat slippery object – that it both exceeds and departs in a number of ways from extant templates and frames of reference. Mike, for example, head of HSE's Biological Agent Unit's policy team, explained that the emphasis that synthetic biology places on 'functions' and on interchangeable biological parts and circuitry, doesn't really "map onto" the language of the 'parental organism' and the host/vector system that is integral to the GMO regulatory framework.

This was a point that was similarly raised by Peter, a prominent synthetic biologist specialising in genome engineering. When reflecting on his own working practices and on that of his colleagues, Peter described how:

> "People are making multiple modifications in parallel… and even getting to the point where they are creating systems which are almost 50/50 with parts from one organism and parts from another… that makes it a little more of a challenge to do things like fill out the forms that say I start with this organism and I modify these 3 things… the emphasis on saying what is the parent DNA of the construct… that might need to change to being what is the parent coding of this construct, whether it be amino acids or the way RNA folds, or, you know, the content of a phage… because if you just did a mechanical match DNA sequence to DNA sequence you can have especially for phage the entire genome being no match for the genome."

Al, head of HSE's BAU intervention team was similarly attuned towards this uneasy alignment of synthetic biology with the extant provisions and framings that underpin the GMO regulatory framework. Al emphasised that:

> "as it stands in GM at the moment you would know the characteristics of the parental organism… this is where I think synthetic biology is difficult."

What Mike, Peter and Al are alerting us to here is a departure from, or rather a decentering of, the relevance and/or necessity of the so-called 'parental organism' in determining the risks of any deleterious effects to human health and/or the environment. The central tenet of the GMO regulatory framework, in other words, does not straightforwardly or seamlessly apply to the developing trajectories of synthetic biology practice.

It is important to note here that the GMO Regulatory framework has itself occupied a somewhat uneasy relationship even when applied to the most conventional instantiations of genetic modification work. HSE has had to address and differentiate, for example, between GMO and non GMO organisms with so-called 'new techniques' including site directed mutagenesis working to call into question the coverage of the extant regulatory frame (Breyer et al, 2009). What's more, the purportedly 'localised' and 'targeted' nature of recombinant DNA modification work has also been known to effect unanticipated 'transformation induced' mutation events which have reverberated across the genome of modified organisms (Wilson and Chosewood, 2009).

Regulations, in other words, have to be made to work (Lezaun, 2006) – that is, they have to be 'translated' (Callon, 1986) into practical courses of action. Regulations are not immune from having to work with, and to attend to, the pre-discursive forcings of a world that neither conforms to the narratives we tell about it or acquiesces to the processes that we enrol it in.

But, the spatialities and modalities of organismic intervention that are being mobilised by the synthetic biologist, are adding a renewed intensity to the work required to effectively implement the provisions of the GMO regulatory frame – they are stretching the limits of the GMO regulatory framework in a number of different ways. Lawrence, a cellular engineer and protein scientist explained that:

> "the traditional genetic modification [legislation] I think was written for this view that people would be adding a gene or maybe two and that legislation was written in the 90s when that was what was technically possible. Now we're talking about… essentially rewriting a genome from scratch… and that's a very different ball game. For some of the things that I'm doing… we're already talking about can we put in 15 to 20 genes, could we put in

> 30 genes maybe… the effects you're going to have on the organism are, I think, quite unpredictable."

Oliver, a geneticist with a background in GM crops, who was involved in the orchestration of the UK 2010 Synthetic Biology Public Dialogue, similarly sought to draw attention to the different spatialities and modalities of intervention that are being prioritised and mobilised by the 'biological engineer' in contrast to that of the 'genetic' engineer – the conventional 'genetic' engineer being the original 'subject' of the GMO CU regulatory framework. Oliver described how:

> "synthetic biologists are thinking much more in the way of how can we design a chromosome or some other entity that works within a cell, but has nothing to do with the natural ancestor of that cell. We are just using the cell as a containment vessel for the thing that we want to put into it to work. So there won't be any wild ancestors, and therefore if you want to apply conventional risk assessment it is not going to work because you don't have any background by which you can assess things like ecological characteristics or just growth counters, simple stuff."

Oliver continued to explain that whilst the GMO regulatory framework "kind of works at the moment," synthetic biology's continued progression and migration towards the construction of 'designer organisms' would likely render increasingly untenable, the comparative ancestral frames that underpin the GMO framework. Oliver suggested that continuing with "business as usual" would run the risk of "slowing down" and halting the virtual (to come) objects of synthetic biology:

> "I mean one of the fundamental problems with risk assessments is assessing the hazard part of the equation... The hazard part of the equation is already a problem with GM organisms in many ways… but we will be designing crops in the future with completely different leaf form, completely different flower heads, and seed heads that may not look like our conventional crops... plants that will defend themselves in a different way as well. They will be designer crops. Well to my mind there's not

> going to be any wild ancestors, there's not even going to be any domesticated ancestors they will be quite different in the future…"

The explications of Peter, Lawrence and Oliver alert us here to the ways in which synthetic biology's mobilisation of a more patchworked and amalgamistic modality of organismic intervention is troubling and interfering with extant modalities of regulatory organising. Al, head of HSE's BAU intervention team further explained that:

> "you may be putting multiple things together that you think you understand on an individual level… but actually when you put them all together there may be interactions that you haven't anticipated between various proteins… they're all interacting with each other and also within a host… you can create something that's capable of infecting things in a way that you never anticipated... so that it can get into a completely different type of cell in the body."

Al described how, in its endeavouring to open up and to expand the largely uncharted terrain of 'chemical space' and the space of novel biological functionality, synthetic biology is drawing into an encounter different kinds of organismic components and oligonucleotide sequences – components and sequences that are now touching together with new kinds of frictions and intensities. Al emphasised that the very biological 're-assemblings' that are purported to herald the generation of 'novel' and 'new' biological products, can simultaneously work to engender and facilitate the conditions of possibility for unexpected and unanticipated outcomes – outcomes that may present a risk of deleterious effects (particularly in terms of allergenicity and toxicity) to human health and environment.

During a 2012 workshop convened and attended by biosafety advisory bodies and regulatory authorities across the EU including HSE, it was acknowledged, for example, that metabolites - the intermediary products and molecules of metabolism, have a 'signalling function in distinct metabolic pathways.' It was emphasised that these signalling functions – functions which play out and reverberate in often complex and non-linear ways - underscore a need to be attentive towards the onset of pleiotropic effects within the doing of synthetic biology practice (Pauwels et al, 2013: 221). 'Pleiotropy' refers to the propensity for single genes or biomolecular substances to influence two or more seemingly unrelated traits. The term is derived from the Greek 'more' (*pleion*) 'responses' (*tropy*) (Kavalipati et al, 2015). Participants acknowledged that the 'higher' the 'order of combination and complexity' associated with certain facets of the doing of synthetic biology practice, the greater the potential difficulties in terms of the assessment of risk (Pauwels et al, 2013: 221).

Kevin, one of the heads of HSE's Hazardous Installations Directorate (HID), like Al, was also attuned towards some of the challenges posed by synthetic biology's amalgamistic spatiality of organismic intervention. Kevin reflected on how:

> "I guess because you're making so many changes you've got something totally different or if you remain routed to that first step you're looking at the wrong thing really… because you'll be in such new territory I guess with some of this you won't necessarily know what the risks are… so how do you ask the questions and can you model it at all… it's all very interesting because if I'm right you could have say there are thirty stages and each of those in its own right are totally low level of risk but how would anyone ever know what the thirty together would do?"

Kevin's description of how synthetic biology is opening up and moving into a different kind of "territory" provides a further indication of how the orientating and sensitising device that is the comparator organism is much less relevant to the undertakings of the synthetic biologist – the frames of reference offered by the GMO CU Regulations take the synthetic biologist only so far.

James, a Biological Safety Officer at a leading public facing research facility, provided a particularly illustrative example of how synthetic biology is facilitating a departure from extant frames of reference in his own working practices. James described how:

> "we've been growing microalgae down here for years... the move towards synthetic biology and the increased capability we now have in being able to genetically modify microalgae has exposed a gap in our ability to assess the new risks… growth at 100-1000ml scale, whilst a useful starting point, is often irrelevant when the strains are being developed for industrial purposes… we can learn from the plant community that have been through this over the past decade, however there are microalgae specific factors that we need to be aware of: a plant is relatively easy to control because it doesn't move around too much; algae sloshing around in large volumes of water are surprisingly easy to disperse, including the generation of aerosols. And scale up is associated with loss of containment e.g. a raceway pond (millions of litres in volume) is commonly used in industry already for microalgal growth. But as soon as you start talking about GM algae in a raceway, environmental contamination (wind, storms, birds, leaks) is not feasibly avoidable… The potential problem is the inevitable impact of the release of such organisms. It may not be a problem, but it is very difficult to predict.'

Although the unpredictabilities, or rather, the indeterminacies associated with the scaling up of biological and experimental processes are by no means unique to synthetic biology, synthetic biology can be said to add a further intensity and layer of complexity to the 'scale up' process in that many of the synthetic organisms that are being 'scaled' up and put to use in raceway ponds or commercial fermenters, are themselves already amalgamised hybrids for which there is no clear comparator.

But, it is important to note here that it is not simply the scale and the different spatialities of organismic intervention associated with the doing of synthetic biology that are working to trouble extant modalities of regulatory organising. Protocell work, for example, is a particular subset of the doing of synthetic biology practice that aims to develop synthetic cells that perform functions and various compartmentalised reactions that we would expect to find in a biological cell. Current work involves the examination of lipid and vesicle structures and the ways in which these structures give rise to cellular behaviour.

Protocellular work interferes with and undercuts established modalities of regulatory organising in that aspects of the ‘transmissibility’ and ‘propagation’ of ‘information’ still apply even though protocell work tends not to involve or to enrol any genetic material (cf Pauwels et al, 2013). As Mike, head of HSE’s BAU policy unit explained, the GMO regulatory frame attributes the quality of communicability to genetic material – this is one of the key qualities that draws particular kinds of working practices within the remit of the regulatory oversight. And yet, as Bedau et al (2009) and Chen and Walde (2010) have recently highlighted, in spite of the absence of genetic information, protocells are still able to ‘communicate’ and to interact with biological materialities and substances. There is then, an ontological slipperiness to this particular facet of synthetic biology practice – a slipperiness that is working to undercut extant modalities of apprehension and regulatory organising.

3.1. Sorting Synthetic Biology Out

Perhaps unsurprisingly, the slipperiness of synthetic biology as a regulatory ‘object’ and its departure from extant templates and frames of reference, poses a number of challenges in terms of the bringing of synthetic biology into a governable world. Oliver, for example, sought to emphasise that:

> "So we do have a real challenge for the scientific and regulatory community. How do we assess the important characteristics of [synthetic biology innovations] in the future?... how do we assess them to the point we can actually apply regulations to them… how do we carry out the hazard assessment… what are we actually regulating, how do we define it, how do we bring it within the regulatory sphere, or keep it outside of the regulatory sphere, maybe we don't need to…"

As Oliver continued to explain:

> "we need to know the answer to that in order to build public confidence. Otherwise synthetic biology will not fly the way it should fly. It is going to be bogged down in the concerns, opposition and regulatory gloom basically and I think a lot of researchers feel like that… they feel a sense of trepidation about how regulation will be applied in the future, and maybe that is having an effect on the research agenda. People may be choosing easy stuff within the regulatory sphere rather than stuff that might be a bit of a challenge. So I think this is a key issue that needs to be addressed."

Oliver is alerting us here not only to the slipperiness of synthetic biology as an object of regulatory governance but also to the multiform functioning of the regulatory frame. He is pointing towards the role and significance of the regulatory set-up not only in tempering associated risks to human health and environment, but also in facilitating the undertaking or the doing of synthetic biology in practice. He is alerting us to the realisation that as Douglas and Stemerding (2014: 8-9) have argued, maintaining 'the current system of GMO regulation may thus discourage future SynBio innovation, nipping in the bud promising (health) applications with potential benefits for society, or pushing SynBio research out of the area of human health and into other areas with lower regulatory hurdles (e.g. cosmetics).'

Toby, CEO of a nascent synbio start up, similarly sought to emphasise the configuring of the regulatory frame in contributing to the taking shape(s) of synthetic biology in practice. Toby emphasised that "regulation can make a big difference… particularly in terms of whether or not certain work gets done… it's important not to forget but another risk comes from not doing particular research." This emphasis placed here by Oliver and Toby on the importance of the regulatory framework in enabling the undertaking or the doing of synthetic biology in practice, was an emphasis or understanding that was shared in part by HSE. Curtis, for example, a senior member of HSE working in a policy making capacity explained that:

> "HSE's position should always be in my view you know we're a facilitating and enabling regulator. Anything is possible as long as it's done safely and we're here to support [that]... we shouldn't be perceived as a blocker… if ever I hear the words Health and Safety won't allow us to do that my automatic response is why? Where is it saying that? What are you saying?"

Al, who manages the Biological Agent Unit's team of specialist inspectors, similarly sought to emphasise HSE's nurturing and facilitating role:

> "it's not saying you can't do something because it might not be safe… but you might have to do it in a certain way… so despite the public opinion of HSE I think we're there to facilitate people doing work that's important within the parameters of the law."

The question, however, of *how* synthetic biology might be nurtured in a manner that simultaneously ensures the effective delimitation of risks to human health and environment, is a question that is forcing thought for both HSE and for a number of synthetic biology practitioners. Oliver, in particular, was at pains to emphasise that synthetic biology's decentering of and departure from extant templates and frames of reference, does not necessarily mean that synthetic biology poses any enhanced or inherent risks to either human health or environment, but rather raises a number of important questions in terms of the mechanisms and procedures through which synthetic biology might be brought into a governable world. Oliver explained that:

> "If you see something that is unfamiliar you instantly think actually this might be a bit more risky. That is not necessarily the case and I think we have to get outside that mindset… there is a problem with novelty… and that is that if you are dealing with something that is very novel that means you are almost by definition dealing with something that you don't know what its characteristics are. You don't know what its ecological characteristics are… how it relates to its environment… whether it can mutate and if it mutates what it will mutate into… this is what we have to focus on… focusing on novelty is not necessarily the right focus…"

Oliver is emphasising here the need to develop the tools and techniques through which it might become possible to apprehend the potential risk implications associated with the development of synthetic biology. Hugh, a scientist by training with a background in biophysics, who is now Director of a UK synbio company, similarly asserted that:

> "an emerging technology means that you are moving into new areas… creating new opportunities and new solutions to maybe otherwise intransigent problems. By definition you are moving into areas which have not been done before so you have to understand that being innovative means you're doing something you haven't done before. So, if challenged with the basic question can you be sure exactly what's going to happen the answer is no because if you did know then it wouldn't be innovative…"

As Hugh continued to explain:

> "there is a language problem that says if it's uncertain therefore there is potential risk… if there's potential risk it is risky… therefore if it's risky you

> shouldn't do it… one of the things that we have to do is to untangle the tautology from what you're trying to do."

Bringing then, synthetic biology into a governable world, requires, as Oliver, Hugh and Toby have emphasised, an attentiveness towards and an engagement with, the 'slipperiness' of synthetic biology as an object of regulatory governance. It requires apprehending the contours of synthetic biology in a manner that facilitates the undertaking of synthetic biology practice whilst simultaneously delimiting associated risks to human health and environment.

This is, in many respects, a basic Foucauldian point. But, as I progress to highlight in the subsequent stages of this chapter, the question of how to simultaneously nurture and temper in practice, is a question that is met by a thickness of things – a thickness of sensibilities, contextings and materialities, which contribute to the patterning and emergence of different kinds of regulatory shapes and settlements.

It is also important to make clear here that, beyond tending to the slipperiness of synthetic biology as an object of regulatory governance, bringing synthetic biology into a governable world also requires tending to the tensions that stem from the realisation that, at present, synthetic biology both does and doesn't fit into extant modalities of regulatory organising. This is not simply a technical question but is a question that is politically and culturally inflected. Lawrence, a biochemist and protein scientist encapsulated this tension nicely when he explained that:

> "there are people who see [synthetic biology] really as something akin to traditional genetic modification but simply say there are better tools now and that we can do things on a more ambitious scale… and really in that idea the idea is that it's synthetic biology if you're bringing different genes

> from lots of different organisms together and if it's doing something that really is making something that wouldn't ever really be seen in nature then that really is synthetic biology… but when people are debating this I wonder whether they're coming at it with a very certain angle of where they want that debate to go and so I would be wondering what the underlying question behind that is… some people see synthetic biology as a new buzz word and therefore they think people are saying whatever they do is synthetic biology so they'll try and get funding… but others say well why isn't it just good old genetic modification just done at a slightly more ambitious scale… So I guess the usefulness of that topic depends on the context in which people are raising it…"

Lawrence is alerting us here to the social noisiness surrounding synthetic biology that we encountered in chapters two and four of the thesis. He is describing how, for a number of practitioners, the mobilisation of the term 'synthetic biology' as a new "buzz word" can help to gain institutional support and to attract funding – a process that sociologist of science John Law (2011: 7) describes as 'heterogeneous engineering.' The question, therefore, of how and where synthetic biology might differ from more conventional GM work is a question that is diffracted and reconfigured in light of political and cultural interests.

Geoff, a Professor and Chair of a leading UK Synthetic Biology Strategic Research Initiative, was similarly attuned towards the uneasy and at times rather unclear nature of the relationship between GM and synthetic biology. Geoff described how:

> "people look at synthetic biology and say... ah these guys are just doing the same stuff as GM… you know, maybe increasing the scale, but it's the same old stuff you know what's the problem… and in a sense they're correct [in that] the capabilities or the differences between the two systems in terms of what they can do is not that different…[but that's] because you've got sort of more mature technology on the one hand and the

> embryonic technology on the other… but then, you're on very different trajectories…"

Emmett, a molecular biologist specialising in biofuels also explained that:

> "if you speak to biologists and people who are doing it… I suspect like me they'll probably say well at the minute we're fine, because it's all in the lab, it's kind of what we've been doing all along… people who aren't working with it will tell you this is a new revolutionary thing… and it's both which is why it's really difficult…"

The differences that Emmett, Lawrence and Geoff describe here can be attributed in part to the multiplicity of the working streams, strategies and practices that I outlined in the preceding chapter of the thesis. They alert us to the difficulties faced by regulatory authorities in determining when and how to act. Indeed, whilst the corralling of synthetic biology into the regulatory framework for the oversight of GMOs has been described as constituting a 'filling the prescription approach' (Zhang et al, 2011) it is important to acknowledge that regulatory frameworks have their own generative affordances and dispositions.

Working, for example, within the parameters of extant regulatory frameworks can help to prevent 'regulatory churn' (Federation of Small Businesses, 2015). Regulatory churn refers to the process of the (regular) updating and transformation of regulatory and legislative provisions. Regulatory churn not only increases costs to businesses but can also lower levels of protection to human health and environment through increased levels of unfamiliarity amongst dutyholders.

The regulatory provocations that I have opened up in this section of the chapter point to the limits of regulatory frameworks or object centred modalities of regulatory intervention. I have highlighted how, certainly for a number of synthetic biology practitioners, bringing synthetic biology into a governable world requires, “inspiring confidence” amongst biotech, research and public communities that regulatory authorities such as HSE are not “working with old philosophies that don’t really apply to the research and development that’s going on now” (Oliver). Empowering, therefore, the situation that is the coming into being of synthetic biology requires a shift from the imposition of frameworks to more network like modalities of apprehension. But what kinds of skills and affordances and what kinds of regulatory shape(s), might contribute to the bringing of synthetic biology into a governable world?

4. On Sharp Lines and Shades of Grey

Thus far in this chapter I have highlighted how, although HSE is encountering synthetic biology through the regulatory and risk assessment practices associated with the GMO regulatory framework, it is aware that synthetic biology exceeds and departs from extant templates and frames of reference. I have suggested that synthetic biology’s ‘betwixt and between’ of ‘source species’ and ‘chassis’ organisms (Roosth, 2010: 99), renders increasingly troublesome regulatory attempts to place fixed grids upon, and to demarcate specifiable parameters around, synthetic biology as an ‘object’ of regulatory concern. But where then does this leave us in terms of the bringing of synthetic biology into a governable world?

HSE’s attentiveness towards and acknowledgement of the slipperiness of synthetic biology has played an important role in its contribution to wider policy negotiations. In 2015, for example, the European Scientific Committees (ESC), a group of three independent scientific advisory bodies that provide advice and guidance to the European Commission, suggested that competent authorities such as HSE might work to identify and afford enhanced levels of scrutiny to microorganisms that have been genetically modified by so-called ‘novel’ techniques through, for example, quantifying the percentage of a genome that has been chemically synthesised.

Al, however, head of HSE’s BAU intervention team, was quick to emphasise that “having a number on changes is a dangerous route to go down.” As Al continued to explain in a manner that no doubt drew upon his background and prior experience in the area of virology:

> “it’s difficult to quantify the level of change… if you’re changing more you could argue that it makes it more difficult… but I think having some kind of cut-off point where you know a couple of changes are okay but anything more than ten needs to be assessed is a simplistic way of… you know… [apprehending] a complex biological system”

For Al, whilst scrutinising synthetically engineered organisms in this way might well provide some level of ‘assurance’ to external stakeholders that HSE is indeed keeping a careful ‘watching brief’ on synthetic biology and is taking seriously its role as ‘enforcer’ and ‘protector’ of human health and environment, this particular approach to ‘sorting things out’ – to use the language of Bowker and Star (1999), would, for Al, likely channel the regulatory gaze too narrowly. Al emphasised that “there are examples of where you could make one single change that could have serious consequences.”

Lewis, a Biosafety Manager at a leading commercial biotech company similarly cautioned against what the social scientist McNamara (2014: 8) has described as the ‘comfort of assigning sharp lines in a sea of shades of grey.’ Lewis described how:

> ‘[whilst] novelty on face value could be a useful trigger to flag organisms which may pose a greater risk… using % genome change may not be a good indicator, e.g. the % difference in B subtilis & B anthracis is not great and does not reflect the difference in pathogenicity. Previous experience with numerical schemes (e.g. Brenner) showed that people like the ‘certainty’ of a numerical result with the temptation not to assess the risk holistically so a small % change below a threshold but with a significant potential for harm could be overlooked.’

Lewis was by no means alone in acknowledging the difficulties associated with tending to and scrutinising the substances and stuff of the biological through numerical schema and the sharp lines of regulatory frames. Tim, a molecular biologist specialising in molecular parasitology, also emphasised the arbitrariness of numerical schema and pointed to the propensity of biological materialities to confound and undermine framework orientated modalities of regulatory oversight. Tim emphasised that:

> “you’re too young to know what the old system was like… we used to put bloody numbers on these things like well… you know it’s 10 to the minus (laughs) this doesn’t make any sense you know… a lot of it was based on the old methods of looking at mutation frequencies and these sorts of things, but all that sort of stuff just got thrown out the window cos you realised you were just making up numbers and you really were making up numbers and it just didn’t make sense.”

What Lewis and Tim are suggesting here is that bringing synthetic biology into a governable world requires avoiding what Al described as “knee jerk” reactions and resisting the comfort of assigning sharp lines in a sea of shades of grey. Indeed, as Al continued to explain, “as an intelligent regulator [you] should be aware of what the technologies are… but it doesn’t mean you immediately react and say this is new so it needs to be regulated.”

Al pointed to the importance of listening to and engaging with synthetic biology practitioners. Al emphasised that "we've all been out of the lab for quite a while." But what kinds of practitioner-regulator relations and what kinds of more network-like modalities of regulation and apprehension might help to empower the situation that is the coming into being of synthetic biology? What kinds of less informationally-oriented regulatory modalities of oversight might contribute to the bringing of synthetic biology into a governable world? If the sociabilities of the biological are working to confound neat regulatory categorisations and demarcations, then what regimes of knowing and apprehending might help to identify and temper the risks posed to human health and environment by the coming into the world of these synthetically engineered organisms? These are some of the questions that I turn to address in the subsequent stages of this chapter.

4.1. Interlude: Synthetic Biology and 'Complex Presents' in the USA

Prior to considering the more networked and less object oriented modalities of regulatory oversight that might help to contribute to the bringing of synthetic biology into a governable world, it is useful to pause and reflect here on the recent work of the philosopher and historian of science Pierre Methot (2015). In his 2015 contribution 'Science and Science Policy: Regulating "Select Agents" in the Age of Synthetic Biology,' Methot develops an account of the US Centre for Disease Control's (CDC) and the Animal and Plant Health Inspection Service's (APHIS) institution of a legal and policy initiative known as the Select Agents Programme. The Select Agents Programme is an important part of the US regulatory approach to tempering the perceived risks associated with the developing trajectories of synthetic biology practice.

Reflecting on the specificities of the Select Agents Programme enables me to throw into relief the compositionist ethos of the chapter – that is, it provides me with a comparative lens or window of analysis through which to open up and make explicit, the ways in which the composition of different kinds of regulatory settlements works to generate different kinds of effects and 'reals' (Law 200; Law et al, 2013). The Select Agents Programme is a document which lists over 300 microorganisms that have been defined as 'pathogenic.' Any work with any organism or biological agent or toxin listed under the provisions of the Selects Agents Programme is subject to stringent controls. Possession of any listed organism or biological agent is a criminal offence unless appropriate approvals have been sought.

The Select Agents Programme was brought into being in the US following the anthrax attacks of 2001. In September 2001, anthrax spores which were presumed to have originated in a US laboratory facility, were posted with malicious intent throughout the US mail system. At the time, the US government were unaware as to which laboratory facilities were working with anthrax or who had access to laboratory facilities (Methot, 2015). The Select Agents Programme was further spurred into being by intensifying concerns surrounding the 'dual use potential' of biological research. Dual use research refers to the potential for biological research to be simultaneously used for beneficent as well as for nefarious purposes (see, for example, Rappert 2014 and chapter two of the thesis for more on dual use research of concern).

There is, one might argue, a certain common sense appeal that underpins the provisions of and the rationality for the institution of the Select Agents Programme. It certainly appears to make sense, upon initial observation, that the US CDC and APHIS would want to know where work with certain kinds of biological agents and materialities is taking place and to place controls upon work with organisms, agents or toxins that are associated with what Gomes et al (2006: 188) describe as ‘structural, biochemical or genetic traits’ that contribute to the production of disease in a host.

And yet, in drawing upon the work of the prominent scientists and immunologists Casadevall and Pirofski (2003), Methot (2015) compellingly unsettles any sense of ‘comfort’ that might be derived from the sharp lines that have been instituted as a result of the coming into being of the Select Agents Programme. In particular, Methot undercuts the ‘framework’ and ‘object’ oriented provisions of the Select Agents Programme by challenging its most fundamental of premises – namely, that there exists in the world such a thing as ‘pathogenic’ organisms.

Methot, following Casadevall and Pirofski, argues that pathogenicity is not something that is located *within* an organism but emerges instead from the suite of interactions that exist between a microbe and its host. In quoting the immunologist Irun Cohen and colleagues, Methot emphasises that all microorganisms are ‘pathogenic or commensal in a given context, under given conditions’ (Swiatczak et al, 2011: 985 in Methot, 2015: 290). For Methot, then, there is no intrinsic difference between microorganisms with or without weapon potential.

In tracing some of the implications associated with the regulatory dispositif that is the Select Agents Programme, Methot (2015) highlights how the programme itself has led to a 2-5 increase in the cost of doing research on select agents. Methot links this to the recent destruction of a number of microbial collections across the US. Paradoxically, for Methot (2015: 293-4), if the goal of constructing the select agent list is to enhance public health and public security, then restricting access to microorganisms ‘might make society as a whole more vulnerable to naturally occurring and bioterrorist attacks’ - by interfering, for example, with the ‘sharing of biological samples’ between labs and in ‘slowing down the production of vaccines.’

Methot’s (2015) paper provides a compelling example of how the engineering rhetorics that have surrounded the field of synthetic biology – rhetorics which point to the significance of synthetic biology in making biology ‘easier’ to engineer, have, within the US context, intersected with broader political sensitivities in ways which have framed synthetic biology as being a matter of considerable regulatory concern. As the cultural anthropologist Carlo Caduff (2014) has recently argued, apocalyptic thinking and visions of impending disaster have come to suffuse multiple registers and structures of modern American life. It is perhaps unsurprising, therefore, that synthetic biology has become wrapped up in the US within a particular kind of security orientated regulatory frame.

The kinds of ‘reals,’ then, brought into the world by this assembling of things – by the loudness of the engineering rhetorics that have surrounded synthetic biology and by a heighted security-centred affective sensibility in the US have generated what the social and legal theorist Roberto Esposito (2011) would describe as a kind of hypertrophic security. Returning then, to what this might mean for HSE and the synthetic biology practitioners that I engaged with throughout the course of this research, I ask in what follows; what might it mean to regulate synthetic biology and to regulate it well? What sensitivities, qualities and regulatory shape(s) might be necessary to empower the situation that is the coming into being of this developing approach to biological engineering? What might it mean to protect life without contributing to its simultaneous negation?

5. On Networkings and Dis/Re-Assemblings

I have suggested that bringing synthetic biology into a governable world requires, in part, a shift from frameworks to networking – a shift from a 'knowing of' to a more apprehensive and distributed sense of 'knowing around' (Hinchliffe et al, 2005). I have argued that there is a 'slipperiness' to synthetic biology as an object of regulatory governance that resists the delineations and demarcations that underpin the extant provisions of the GMO CU Regulations. In this next section of the chapter I turn now to reflect on the kinds of apprehensions and networking practices that might help to govern the already-present and the virtual (to come) objects of synthetic biology.

I begin this section of the chapter by turning towards the reflexive apprehensions and practices of a number of synthetic biology practitioners. I highlight how, for a number of synthetic biology practitioners, synthetic biology's 'inheritance' from the so-called GM 'debacle' (Marris, 2012) means that questions of safety and risk are taking on a new found significance and are bringing into politics that which 'was supposed to transcend it' – namely, 'progress resulting from the irresistible advances in science and technology' (Stengers, 2015: 41).

I argue that inhering within the practices and reflexive apprehensions of a number of synthetic biologists are a series of rich resources and dis/re-assemblings – that is, new alignments and organising practices which further contribute to the bringing of synthetic biology into a governable world. I argue that regulating synthetic biology and regulating it well requires taking seriously these resources and re-assemblings whilst simultaneously acknowledging and tending to their limits and vulnerabilities.

5.1. Reconciliations of Materiality and Morality: On the GMO Event and Safety-by-Design

Synthetic biology's 'complex present,' to use the language of the feminist theorist and philosopher of science Annemarie Mol (2002), is wrapped up in and has inherited from, some of the controversies and challenges surrounding the development of GM crops. This is particularly the case for the controlled experimentalist – a particular modality of the doing of synthetic biology that is mobilising engineering languages and practices primarily for economistic purposes. Toby, for example, CEO of a nascent synbio start up whose approach to the doing of synthetic biology resembles that of the controlled experimentalist, emphasised that there is a real "fragility" that surrounds synthetic biology's coming into being:

> "everyone is hugely keen that things are done in a responsible way… everybody working in synthetic biology is obviously already sold on its potential right but equally there's a huge amount of sort of sensitivity over how fragile it is because it's still a young discipline."

The perceived fragility described here by Toby could be attributed in not insignificant part to a lingering awareness amongst practitioners of what the STS scholar and social scientist Claire Marris (2012) has described as the GM 'debacle.' The GM 'debacle' refers to a somewhat tumultuous period in the development and deployment of GM technoscience – a period where the exclusion of lay knowledges and the patenting of presumed to be 'discrete' bits of GM biotech, worked to generate an event that 'made both scientific experts and State officials stutter' (Stengers, 2015: 39). As Stengers (2015: 37) puts it:

> ‘public research [was] called seriously into question, militant actions had begun and, in the wake of the so-called mad cow crisis, trust in scientific expertise was at its lowest ebb.’

Curtis, a senior member of HSE working in a policy making capacity similarly described how past experiences with GM have:

> “set back the governments wider aim of getting this technology more accepted through those early decisions and now we see the government investing in you know sense by science… we’re still trying to pick up the pieces.”

In what follows I suggest that the legacy of GM is a distinctive and critical part of synthetic biology’s ‘complex present’ (Mol, 2002) that is contributing to the glimmerings of the emergence of what might be described, following the sociologist of science Bruno Latour (2008), as a less-decisively-modernistic post-Promethean engineering subjectivity. The legacy of GM, in other words, is a legacy that is folded with a particular intensity into the current working practices and strategies of a number of synthetic biology practitioners. It is a legacy which is prompting practitioners to approach and to apprehend in more affirmative terms, the complexities and the thickness of biological sociabilities as well as the potential for unintended, unexpected outcomes.

Nick, for example, a controlled experimentalist and Professor in Industrial Biotechnology, explained that his more recent work is attempting to think in more explicit terms about questions of safety from the very outset of the project design process:

> “that’s the big difference between say GM crops and synthetic biology… actually it’s a shame… the problem with GM crops is that people weren’t thinking about things like that at the time… there was a rush to profit if you like rather than a rush to research and also there was a lot of vested

> interest in it and a lot of personalities involved... we need to be careful about what we choose to do..."

With specific reference to one of his current work streams, a work stream that involves the design and development of synthetically engineered organisms to function in industrial sized bioreactors, Nick described how:

> "in a sense we've been thinking ahead here and [we're] thinking right what we could do is put in say a light sensitive kill switch… so the light will switch on a gene and that gene will not only kill the bacteria but scrub the DNA… we'd get the bacteria to decompose themselves… so we can build in safeties… synthetic biologists can design bugs to the environment that they're intending to be in… so if you're designing something for release into say a waste purification plant…. you can build the safe guards in both in terms of the plant but also in terms of biology… we shouldn't be afraid of thinking if this doesn't work as planned what do we do… what do we do next… risk will always be there…a question that I think that should appear on [funding] forms is if you are successful right what is your ultimate aim and how would you envisage a safety system and it doesn't need to be a long answer right… it's to force people to think about it…"

Similarly to Nick, Lester, CEO of one of the UK's leading synbio start-ups also reflected on how his company is endeavouring to think in more pro-active terms, about some of the challenges and provocations posed by the development of synthetic biology:

> "so [it's] asking yourself you know what is novel about what we're doing, what unusual risks are there …. [practitioners] go oh yes yes we know all that… but when you ask the question what does an early warning look like… that's the one where they start staring at their shoes… it makes people realise that actually something may go wrong that they've not thought about and how would they recognise that… and I don't think as sort of industry the life science industry I'm not sure we're geared up to think about that… I've got to make sure as CEO this is what we're doing…"

Lester is explicitly drawing our attention here to the species of non-knowledge that is scientific indeterminacy. Lester is acknowledging that biological materialities and substrates do not always care for, or bend to, the wills of the synthetic biologist. He is acknowledging that the stuff and substances of the biological are only *partially connected* (Strathern, 1991) to the endeavourings of the synthetic biologist - that these are materialities that are, in part, always already elsewhere, doing other things.

In spite, therefore, of the instrumentalist ethos that is typically accentuated by the controlled experimentalist – an ethos that is concerned in large part with transforming the efficacies of biotechnological production, the explications of Nick and Lester alert us to a simultaneous slackening or a weakening even in a particular kind of modernist mastery – a mastery that, as Latour puts it (2008: 6), 'refused to include the mystery of unintended consequences.' As the controlled experimentalist and CEO Toby continued to explain:

> "you need to start off with the premise that containment isn't possible… I think any safety mechanism that you build in you have to assume it's not going to work… there are various kill switches and so on… they may delay the advent of something, but it's not certain you're going to stop them."

Lawrence, a biochemist and protein scientist, like Toby, Lester and Nick, also pointed to the importance of thinking about and approaching the safety and risk implications of synthetic biology with a renewed attentiveness towards the real possibility of unintended consequences. Lawrence explained that:

> "even if you have access to quite advanced tools nevertheless the models that you have still I don't think will ever be perfect to be honest. So therefore the effect of deleting a whole bunch of genes, the effect of throwing another ten, twenty, thirty genes is going to have an effect which before you start really isn't very predictable…"

The reference made by Toby and Nick to the practice of the "building in of safeties" is a process that is known within the synthetic biology community as safety by 'design.' Synthetic biologists interested in safety-by-design are working to develop switches and vulnerabilities including light sensitivities and nutrient dependencies that have been designed with a view to delimiting risks to human health and the environment should a synthetic organism escape from the confines of a containment facility or field site. Peter, a genome engineer mobilising the approach of the controlled experimentalist explained that:

> "[we're] looking into things like kill switches and timers that mean that over a certain amount of divisions these things can't propagate anymore."

Emmett, a molecular biologist and shortlisted Biotechnology and Biological Sciences Research Council innovator of the year similarly described how:

> "you [can] introduce new novel codons into the DNA such as XNA... there's also a slightly different one where it reads a different amino acid and puts that in instead… what it means is that that code can't be read by a natural system… it's very very much in its infancy at the minute, but the idea is that you start using that code instead of the other…"

Significantly, the concept of 'safety by design' was mobilised by participants in this research not so much as any kind of hubristic mastery trope but constituted instead an explicit engagement with non-knowledge – a centering of the agential vitalities of biological substrate and substances. The controlled experimentalist, in other words, acknowledged that it is no longer possible to 'hide behind the old protection of matters of fact' (Latour, 2008: 9) and that, as Mitch asserted, "you might think it will never happen but it might."

The sociologist of science Bruno Latour (2008) has recently argued that there is a 'humility' associated with the term and the practice of design. To design is never to create ex nihilo – it is to work *with* – it is to cultivate an attentiveness towards the texturings and the fabrics of all kinds of materialities and substrates and certainly, for a number of the participants in this research, safety-by-design is a particular facet of the doing of synthetic biology practice that necessitates a care-full tending-to the particularities and the specificities of different kinds of organismal processes and architectures.

What I want to suggest here then, following Latour (2008) and Sloterdijk (2005), is that safety-by-design does not so much represent an intolerable hubris (cf Lewens, 2013) as it does remind us that to be 'emancipated' and to be 'attached' are 'two incarnations of the same event' (Latour, 2008: 8). More specifically, the interest amongst synthetic biology practitioners in the tools and techniques of 'safety by design' cannot, in other words, simply be reduced to, or equated with, GM 'terminator tech.' Rather, there is a reconciliation here of what Latour (2008: 4) regards as 'two absolutely foreign sets of passions' – namely, that of the 'engineering tradition' and the 'precautionary principle.'

For Latour (2008: 3), the significance of design resides in its 'careful attention to detail, craft and skill' which 'was precisely what seemed reactionary as this would only have slowed the swift march to progress.' In 'slowing down' the swift march to progress, Mitch, a molecular biologist working within the modality of doing that is the controlled experimentalist who is incorporating safety-by-design principles into his own work explained that:

> "it's important that we don't make the mistakes of the past where people have gone too quick… obviously GMOs are already out there… it's better not to do anything rather than rush into something and have a bad impact..."

And for Sarah, also a molecular biologist adopting the controlled experimentalist approach:

> "GMO's are out there people have their opinions… synthetic biology is so new a lot of people haven't got the positive or negative opinions about it yet… if we do this right and it starts well then maybe it will go better"

It is perhaps unsurprising, therefore, that Emmett sought to emphasise that:

> "what I would like to see maybe more from the scientific community in terms of funding is more effort and resources into developing mechanisms to make these things safe… unnatural DNA, kill switches, these things are still in their infancy… things like that should be pushed up the agenda somewhat… especially if we're going to want to release these things."

The synthetic biologist as controlled experimentalist does not regard safety-by - design as a fail proof strategy. As Latour puts it, 'it's as though we had to imagine Prometheus stealing fire from heaven in a cautious way!' (Ibid.,) and indeed, as Oliver a geneticist with a background in GM crops explained, "I think there is some real thought being put into where this science is going."

The controversies, therefore, surrounding the development of GM crops are continuing to force thought for a number of synthetic biologists today and indeed, as the philosopher of science Isabelle Stengers (2015: 41) has recently argued, rather than simply bemoaning that the GM debacle is a past 'event' that has been 'recuperated,' it 'belongs to political struggle to invent the manner in which to make what has thus been learned count.' In terms of making what has been learned 'count,' I have signalled how, particularly for the controlled experimentalist, questions of safety and risk are taking on a new found significance.

Whilst, to some extent, the interest of synthetic biology practitioners in questions of safety-by-design can be linked to what some would describe as a strategic and instrumental desire to manage and to contain even potential public controversy, I suggest that inhering within the endeavourings of a number of synthetic biologists are the glimmerings of the makings of a less-decisively-modernistic engineering subjectivity which acknowledges the inevitable intertwinements and imbrications between materiality and morality.

To design is to attend to detail - it is to engage with the convoluted texturings of biological materiality. As Latour (2008) reminds us, to design is also to raise the question of whether sometime has been designed *well* – it allows for the opening up of a new political territory that is alive and attentive towards contextual specificities and the question of *where*. In a recent study into the use of synthetically engineered bacteria in the water industry, the sociologists and STS scholars Andrew Balmer and Susan Molyneux-Hodgson (2013) have powerfully thrown into relief the significance of attending to the contextual specificities of the development and deployment of synthetic biology. In tending to the ways in which ontologies of bacteria take on different forms and shape(s) as they become imbricated within the practices of laboratory scientists and water facility engineers, Balmer and Molyenux-Hodgson highlight how differently situated insights and knowledges can contribute a much needed texturing to the synthetic biology deployment process. As Balmer and Molyneux-Hodgson (2013: 72) explain:

> ‘In this manner, actors from publics of other sorts might be able to ask questions of engineers, make objections to assumptions, critically evaluate aspirations and innovations, and – perhaps more importantly – contribute to the process of innovation.’

To engage, therefore, in the doing of safety-by-design is to engage in a doing that is attentive towards context and the lively matter of non-human things. It is to engage in a doing that provides an opening for a diversity of actors to contribute to synthetic biology's taking of shape(s). Although these openings have yet to be realised given the embryonic nature of safety-by-design within the context of biological engineering, it will be critically important, I suggest, as this subset of the doing of synthetic biology develops further, to trace the ways in which different actants and actors are assembled together in order to develop and deploy synthetic biology in a less-modernistic and more affirmative post-Promethean fashion.

In the subsequent stages of this chapter I turn now towards a number of more specific measures and practices through which the new found attentiveness of the synthetic biology practitioner towards questions of safety and risk might help to contribute to the bringing of synthetic biology into a governable world.

5.2. Differentiated Knowledges

I have argued that in spite of the rhetorics of prediction and control that have so readily surrounded the developing field of synthetic biology, questions of safety and risk are taking on a new found significance for a number of synthetic biology practitioners. In this next section of the chapter I focus on some of the less-object-centred and more networked oriented practices of apprehension that might help to contribute to the bringing of synthetic biology into a governable world.

Within the developing body of policy literatures on synthetic biology it is often the case that the migration of physicists, mathematicians and computer scientists into the field of synthetic biology is regarded as constituting a threat to established practices of biological risk assessment (see, for example, Schmidt, 2008; HSE, 2012 and Pauwels et al, 2013). But, for a number of the practitioners that I interviewed throughout the course of this research there was a strong sense that synthetic biology's splicing together of different disciplinary traditions and sensitivities might work instead to enhance the robustness of a risk based approach.

Much in the way that the jarrings and frictions associated with the coming together of different disciplinary traditions contributed in the preceding chapter of the thesis to a rendering of the organism as 'epistemic thing' – that is, as an unfolding entity open to multiple trajectories of becoming, there was a strong sense amongst the practitioners that I interviewed that different disciplinary understandings of what a synthetically engineered organism is, and what it might become, might help to build capacity in engaging with the indeterminacies associated with the re-assemblings and socialities of the biological.

Toby, for example, CEO of a nascent start-up, reflected on how "communicating between highly specialised disciplines is such a challenge with each one having so much jargon… I think it can actually de-risk it" and for Nick, a Professor in Industrial Biotechnology:

> "…we are equally ignorant of each other's discipline but that's a good thing because it basically means that people have the confidence to ask the naïve or stupid questions that are never actually in fact stupid… with synthetic biology you have to explain it to other people all the time… people from different fields… you cannot make the assumption that they're thick because they're not right they're profs in other departments… they just don't have the same view or background as you…"

Naivety then, for Nick, is not regarded as a frailty or a weakness to be overcome, but as a generative force – as a condition or modality of being that takes on a new and more affirmative meaning within this developing field of scientific practice. As Nick continued to explain:

> "the difficult thing I mean is sometimes you don't know right and then people are a bit worried to admit that they don't know something okay… well again I think with synthetic biology because basically you never know what the hell's going on in engineering and stuff like that I think that attracts a certain calibre of person who's a lot more willing to admit ignorance and so they're a lot more willing to partner with people… I think that challenges you as well and I think it's a good thing."

Nick described how 'partnering' is a key means through which it becomes possible to subject ones knowledge and understanding to the scrutiny of different knowledge practices - to the scrutiny of what the STS scholar Knorr Cetina (1999) would describe as different kinds of 'epistemic cultures.'

Lester similarly emphasised that "it always helps to get a second opinion… ideally it should be somebody who thinks slightly differently from you" and for Richard, one of the few synthetic biologists whose work is currently being applied beyond the confines of a scientific laboratory or commercial containment facility, synthetic biology's drawing together of different disciplinary sensitivities can help to resist any quick and easy closures or "overly permissive" and "cautious" assessments of risk. Richard explained that:

> "a chemist might see things differently… it would be worth finding out what and why and taking that into account… without having the world run by chemists any more than having it run by biologists… I think probably the more different inputs and perspectives you have to risk assessment the better actually because you know, all those people looking at it the one way might miss things or be overly permissive or cautious of whatever relative to what some other people think…. I think probably a wider range of inputs or views would be good... it's good to have people who are very sceptical and look at something and pick as many holes in it as they can.

> Now they shouldn't be the final arbiters right any more than I should but it's still good to have it…"

Richard and Nick are gesturing here towards the ways in which differences in practitioner understandings can be used to enhance the robustness of a risk based approach.

Tim, a molecular biologist and current practitioner of synthetic biology who specialises in molecular parasitology, also pointed to the importance of the assembling of different disciplinary knowledges in terms of enhancing the robustness of a risk based approach. In reflecting on the use of synthetic biology to engineer biological devices that have been designed to manipulate and interfere with host immune responses Tim explained that:

> "if you're a doctor or pathologist or look at disease organisms you know pretty quickly whether or not [the project's] a good idea… if you think you have the ability to manipulate the immune system, you're insane ok. It's just too bespoke to the individual to think you can do something like that… and there are [synthetic biology] projects aimed that way that you're just thinking… nobody in their right mind should be even considering this project from the get go… and that comes from having people around that are professionals that do that kind of work… I'm not sure how to implement that because every institution isn't structured that way… diseases are what we're about so we get that… but if you don't have that in place you could make up all sorts of… stuff and it's pretty easy to just kind of dismiss the reality of it…"

Tim continued to describe how he and his colleagues had recently presented their own synthetic biology work before HSE's Scientific Advisory Committee on GM (SACGM (CU)). SACGM (CU) is a twelve-strong committee of expert scientists who meet on a quarterly basis and who provide advice and guidance to HSE's Biological Agents Unit. These quarterly meetings typically include the discussion of any contentious or ‘unusual’ risk assessments which have been submitted to HSE and they also provide an opportunity for committee members to comment on, and to review, HSE’s proposed inputs to wider cross governmental and international initiatives, including European and international consultations on emerging techniques and technologies.

In reflecting on his experience of presenting his work to SACGM – a process during which Tim’s work was scrutinised in light of the potential risks it posed to human health and environment, Tim further explained that:

> “going forward you have to have people on board, like the SACGM, they have doctors on their panel ok, and that was really amusing to watch because these guys, whilst they might not know a lot about [the] engineering [part of synthetic biology], they know a lot about disease organisms and you know, they can tell you oh yes, we know what pathologies are associated with that… have you looked at those things within your laboratory, your company, your university, your whatever? Do you know what would happen if this thing got out in the open? Who is it going to hurt? Will it hurt people… is it a zoonoses?”

Tim is alerting us to here to the ways in which different kinds of disciplinary knowledges and expertise can help to provoke new kinds of questions and to open up a somewhat different awareness of the nature and risks associated with the undertaking of synthetic biology in practice.

Whilst, for example, it might well be the case that a particular biological part might be benign within the context of a particular host organism, the question of what might happen when that biological part has been hooked up to another biological insert, integrated into a microbial chassis and put to work in a large-scale commercial fermenter operating above a particular temperature threshold, is a question that is much less straightforward.

This was a point that was similarly raised by Oliver, a geneticist with a background in GM crops who noted that the emphasis that synthetic biology places on processes of de/re-contextualisation is “unique to synthetic biology.” Oliver posited that whilst the drawing together of different disciplinary sensitivities might well generate tensions and uneasy differences in understanding, it can also help to expose the synthetic biology community to different sensibilities that, when brought together, contribute to the development of synthetically engineered organisms or biological parts that actually work. Oliver explained that:

> “the synthetic biology community by and large doesn’t understand evolution. That is probably a bit of a harsh thing to say but I don’t think they do. I have had these conversations with the synthetic biology community and that is why I say that.”

Oliver is emphasising here a missing temporal dimension to conventional engineering practice. The different sensitivities then, of the chemist, the biologist, the engineer and the ecologist can help practitioners to open up and to engage with the convolutions of the biological and the species of (non) knowing that is scientific indeterminacy. More specifically, the differential emphases that each of these epistemic cultures places on different processes and components within the organismic milieu can help to resist what Richard cautioned against as any “over permissive” or “cautious” assessments of risk.

Lawrence, a biochemist and protein scientist spent considerable time explaining how he and his colleagues are endeavouring to carve out a space within their own working practices where they are endeavouring to assemble and to benefit from the insights generated by the drawing together of different disciplinary sensitivities. Lawrence described how:

> "[we've] got people who are experts in competition looking at organisms in competition and coevolution and stuff like that… there are very good microbiologists in the department who have got a lot of expertise in working with really very nasty organisms so they understand the risks that can come with both natural organisms and genetically modified organisms very well, particularly with regard to things like toxins and to defences that microorganisms have… we have all these abilities already so why don't we use them? We've got good plant biology, we have good microbiology and we've even got good mathematical models as well. So I think we could come up with a really good set of tests that might be quite, quite attractive from that perspective… It's not a massive undertaking to do [this]… as part of a due diligence process."

But, as Lawrence continued to explain, there are a number of barriers hindering the drawing together and sharing of different disciplinary sensitivities and expertise. Lawrence acknowledged, for example, that although it "would be really helpful… if people could share understandings of what the risks are," the question of how to "persuade scientists to do that is quite tricky because that involves them taking some effort to share that information and also maybe giving up some information on what they're doing. It's always a bit tricky to get people to do that." Lawrence emphasised that this "might be something where the synthetic biology community needs to start talking."

The question then, of how to sustain the connections and frictions that arise from the encounterings of these different disciplinary traditions and sensitivities is, I argue, a critically important question to which we must attend. What I also want to suggest here is that HSE, as UK competent regulatory authority, might encourage and look for evidence of the differentiation (as opposed to the integration) of knowledge as a being a marker of good practice during the undertaking of the risk assessment process.

Indeed, as I have highlighted in this section of the chapter, assuring the safe practice of synthetic biology and ensuring containment requires, paradoxically, an increasingly wider engagement with and differentiation of knowledge. This is something that HSE are themselves acutely aware of and attuned towards. Kevin, for example, Director of the Policy Unit of HSE's Hazardous Installations Directorate emphasised that:

> "the [outdoor activities sector] were saying look your conventional approach to risk management is very industrial based and it tends to come from almost process engineering where you start a process and set it up and run it and you assume all things stay equal and you can work it out and do the risk assessment and put the controls in and away you go… [it's the same with synthetic biology] there must be some degree, there must be a sort of mindset perhaps where you're trying to get over to people that there isn't just going to be one answer or one process. It's probably different brains working in different ways but it would be a way of getting people to think multi-dimensions and at the same time it won't suit everybody but how are we going to that as a competence?... How much is that a science or an art I think is a judgement call…"

What I have endeavoured to illustrate in this section of the chapter is how synthetic biology's splicing together of multiple disciplinary traditions is opening up what might be described as a new dynamic of learning and apprehension. It is opening up a spatiality of encounter that embraces, rather than endeavouring to supress, inevitable gaps in scientific understandings of and evidence for risk and it is in this sense that synthetic biology's drawing together of differentiated knowledges and sensitivities might well be an important part in bringing synthetic biology into a governable world.

If it is the case, following the social scientists Law et al (2013), that there is less prejudice today against U turns, against inconsistencies and non-coherences, then mapping out the frictions and the tensions that emerge as different disciplinary traditions and sensitivities come together and encounter one another in the unfolding practices of synthetic biology is a critically important task. This more networked and less object-centred modality of apprehension can help to empower the situation that is the coming into being of synthetic biology. This is particularly the case, I suggest, when it comes to the development of synthetic biology applications that have been designed with a view to interacting in broader ecological environments and contextings beyond the confines of the scientific laboratory.

6. Limits and Vulnerabilities to the Practice of Self-Regulation

I began this chapter by developing an empirical account of how synthetic biology exceeds and departs from extant templates and frames of reference. I argued that there is a 'slipperiness' to synthetic biology as an 'object' of regulatory governance that undercuts the central tenets of the GMO CU Regulatory Framework. The GMO CU Regulatory Framework is a particular modality of regulatory organising that, as with most regulatory frameworks, externalises fixed protocols and procedures. It endeavours to work on and over discrete objects of regulatory concern.

Bringing then, synthetic biology into a governable world, requires much more than simply the implementation of object centred regulatory frames. It also requires internalised processes of apprehension on the part of synthetic biology practitioners. In the preceding sections of this chapter I have highlighted how questions of safety and risk have indeed taken on a new found significance for a number of synthetic biology practitioners. I argued that inhering within the working practices of a number of synthetic biologists are a number of rich resources and markers of good practice that further contribute to the bringing of synthetic biology into a governable world.

But, there are limits and vulnerabilities to these internalised and more networked practices and processes of apprehension. Lester, for example, who is endeavouring to enrol a novel approach to the assessment of risk in his company's working strategy, emphasised that:

> "it's a question of how much time again you've got to give. We could spend 50% of our time looking at those questions and answering those questions and we just don't have that amount of time…"

What Lester is alerting us to here is what Strathern (1991) would describe as the partial connectedness of his companies working strategy. Safety and risk considerations are an important part of Lester's company's work. But they are just one part of a bigger and busier range of activities.

Nick, who is also thinking in much more proactive terms about questions of safety and risk, similarly sought to emphasise that "the one thing that we don't have is time on our side." The sensitivities then, of Nick, Lester and other synthetic biology practitioners are not immune from the felt pressure of 'time' or from the economistic pressures of the 'knowledge economy.' In chapter three of the thesis, I described the knowledge economy, following the philosopher of science Isabelle Stengers (2015: 29), not as 'empty order word' used in 'reports on the challenges of our epoch but the strong reorientation of public research policy, making partnerships with industry a crucial condition for the financing of research.'

Geoff, however, a synthetic biology practitioner operating largely within the modality of doing of the cellular engineer, painted more of an affirmative picture.

Geoff explained that there is a growing realisation that by tending to the safety and risk implications associated with the doing of synthetic biology – that is, by directing one's attention towards the ways in which the re-assemblings of the biological can work to generate certain kinds of deleterious effects, it becomes possible to generate new kinds of insights that are useful in terms of "just getting things to work." As Geoff explained:

> "it's not… a positive versus negative yin and yang thing, if you could somehow, bridge those gaps that would be quite valuable in a sense but the crafty thing would be to try and find a way… a venue or an avenue of getting both things at once… so there would be a clear perceived benefit, so the same kind of process of canvassing incidents would also relate to the construction of the systems as well as their interaction with the environment or whatever. Not easy to do perhaps, but I think worthwhile… multi-factorial processes which would be impossible to predict… real experiences… and it seems to me…. that kind of approach has an appeal... not so much from a safety aspect, although that's part of it, but also from the point of view of just getting things to work."

Peter, a genome scientist working within the modality of doing of the controlled experimentalist, relatedly described how there is a growing commercial interest in safety-by-design which is attracting resources and directing momentum towards the safety and risk implications associated with the doing of synthetic biology:

> "in the first instance you think well you want to do that for a safety mechanism… but there is also a commercial interest in it in that if a company sells you a therapy you can't home brew it yourself and then give it to others."

Nevertheless, during a recent international meeting convened by regulatory authorities and biosafety committees across the EU, it was acknowledged that systems of self-regulation can 'only work until they are too time- or money-consuming and stand in the way of commercial interest.' (Pauwels et al, 2013: 224). There is, in other words, an important role for regulatory authorities such as HSE to play in bringing synthetic biology into a governable world. The internalised apprehensions of synthetic biology practitioners need to be accompanied in conjunction with the regulatory reality practices of competent authorities such as HSE.

But, as we have seen, regulation cannot suffice if it simply takes on the form of framework implementation. The important questions thus become; what kinds of regulatory shape(s) might help to empower the situation that is the coming into being of synthetic biology and how might practices and processes of regulation and self-regulation work together? I return now in what follows towards the subtler working practices and sensitivities of HSE that are helping to bring synthetic biology into a governable world.

7. Regulating Synthetic Biology and Regulating it Well

At present, the vast majority of synthetic biology work in the UK falls into containment levels 1-2. Under the provisions of the GMO CU Regulations HSE does not receive risk assessments for cl1 work. Such work is regarded as 'non-notifiable.' HSE's approach to focusing on higher hazard activities means that cl1-2 level premises are rarely visited by HSE inspectors. But, as HSE are themselves aware, this 'orientational' approach to the doing of regulation takes HSE only so far. Al, for example, described how:

> "by the very nature of the notification scheme we don't always know what's happening… and likewise there's probably lots of GM stuff at class one that you might say would be quite interesting to have a handle on because you don't know where it's going to go and you don't know how it's going to be applied to higher containment levels in the future… the argument is well

why would you need to know if it's nil or negligible risk which I agree with… but how do you know people are getting that right… it's quite a new technology… so are they getting the assessments right… I think that's a key question…"

Al further acknowledged that synthetic biology's slipperiness and evasiveness as an object of regulatory governance means that the question of getting assessments "right" is anything but a settled or straightforward affair:

> "if the people doing the work are struggling with it there's nothing to suggest that HSE's knowledge will be any better than theirs…"

In reflecting on the BAU's attentiveness towards the limits of this orientational approach to the doing of regulation Al described how the BAU is endeavouring to develop its presence and to engage in more networked practices of working that enable HSE to hone its sentinel capabilities:

> "at the minute it's down to the individual proactive desire [at HSE] to see networks exist… but I think we're quite engaged on lots of levels with the synthetic biology community… whether its leadership groups or various stakeholders… when I was portfolio biotech holder… there was a Royal Society group looking into this as well… there was a new techniques working group at the European Commission level... there were other groups as well which I was involved with not necessarily sitting on panels or anything but as an observer or just as an attendee at various conferences and discussions…"

Similarly to Al, Kevin, who is responsible for contributing to the managerial oversight of HID also sought to draw attention to the BAU's commitment to networking and to engaging with practitioners:

> "Mike's got a great grasp and understanding of how to get them networking and he's been a huge asset to the team… if you didn't do that then I think you could miss things… the biological agents team and the policy team, are far more plugged in with the community because it's quite a small

> community so you can have the luxury of knowing what's happening and who the stakeholders are in a way that you can't with the oil and energy sectors which are just bigger…"

HSE's commitment to networking and engaging with practitioners can be attributed in part to HSE's tripartite history which is an integral part of HSE's 'complex present.' Kevin explained that:

> "we've been very lucky… HSE was set up way back in the seventies, and it reflected thinking at the time… tripartite bodies that were mixtures of unions, employers and governments… and so for many many years HSE has been working on the basis we need to talk to the workers, we need to talk to the employers, we need to talk to government and within the organisation we had this… the HSE logo… above the HSE text there's that weird little, is it a flower, is it a triangle, is it praying hands…I don't know but we used to say it was a triangle and that the three sides were the field inspectors, the policy side and a base of technical specialists and only in working together do you get the result and so we've always been about communication… and I think it helps us to make effective judgements.'

Networking and developing good sets of relations between HSE and practitioners are particular facets of the doing of making governable that synthetic biology practitioners too regarded as being critically important in terms of the empowering of the situation that is the coming into being of synthetic biology.

Hugh, for example, a scientist by training, who had worked for many years as the Strategic Programme Manager for Innovation at a leading oil and gas company and who was now Director of a UK synbio company and key contributor to one of the UK's leading biotechnological forums explained that:

> "So, the question is how do we move forward and I think that's where in fact the [synthetic biology] sub group really is something which I'm experimenting with where we can bring together regulators and academics and social scientists and others together in a forum which is a safe area if

> you like to actually say hey look I'm not sure about this… I'm not sure if this is going to work or I wonder if we could do that… and then I think if you've got the right mix of people you can start to move forward and the risk is that if you formalise these things too early immediately everybody has to play to type and you get polarised… and you've destroyed that very sharing of ideas which can take us forward…"

As Hugh continued to emphasise:

> "It is about creating structures which are designed to allow us to deal with these issues in a way that we didn't have the right mechanism… and breaking down those barriers and how can I have regulators talking informally and I'm being exposed to ideas where people are actually willing to say I'm not sure if this is going to work I'd like to explore this difficult concept rather than being fearful of it in case they get the wrong answer… so, the key to policy is to recognise that there is an area that needs more work, but to create an environment in which that work can be carried out where the risk is managed…"

In a related vein, Tim reflected on how at conferences and varying synthetic biology events:

> "a lot of people meet and start talking about ideas and they go oh is this feasible, what would a regulatory body think about this, and these never go beyond that point because there's no one to talk to in the room to explore the idea further… it would really speed a lot of these new ideas forward if there was someone that they could talk to and answer questions and give demonstrations of concepts and ideas that are never a good idea… I'm not saying let's make it black and white, but show which side is the lighter grey…"

What Hugh and Tim are alerting us to here is that HSE's shape needs to be such that practitioners perceive HSE as an "open and friendly port of call if researchers have ideas or concerns" (Nick). There was much evidence to suggest that this was the case. Practitioners expressed, for example, an appreciation of HSE's regard for context and its technical capabilities. Nick, controlled experimentalist and Professor in Industrial Biotechnology explained that:

> "they're [HSE] really helpful they're really willing to discuss things. They don't come at things from a knee-jerk perspective either you know and I think that they're very reasonable… they were saying… you could improve safety by doing this sort of thing but to be honest it would be really difficult for you to do that so we understand why you've done this instead."

Tim, a molecular biologist and current practitioner of synthetic biology explained that "I can talk to [names removed] because they're biologists, they get it." Emmett similarly reflected on how:

> "it felt like there was someone who was thinking about what I was proposing, whereas had it been more automated tickbox where if you do this then you're alright… then things would creep through."

What we can begin to see here is how HSE's configuring of technical expertise is an important part of contributing to an empowering of the situation of synthetic biology. It is this technical expertise that enabled HSE to resist the call of the ESC, for example, to scrutinise organisms in terms of the % of a genome that has been chemically synthesised. But, the type and quality of the relations between HSE and its dutyholders needs to be carefully managed and configured. It is not as simple as to argue that HSE needs to work more closely with synthetic biology practitioners.

Hugh, for example, was quick to emphasise that "we need to have that constructive discussion whilst at the same time not making it look as though we're in cahoots because you do also need that independence as well… so it's always a balance… I think we need to be very careful that you don't confuse the interface with the core role." This attentiveness towards the importance of retaining independence was similarly espoused by HSE. Curtis, a senior civil servant working in a policy making capacity posited that “we’ve got to where we are because of our reputation and we need to protect that... we [cannot] undermine or compromise that.”

HSE’s unique configuring in terms of the extent and breadth of the sectors that it is responsible for regulating is a further part of HSE’s ‘complex present’ that is providing it with a number of sensitivities and sensibilities that are critically important in terms of apprehending the coming into being of the developing approach to biological engineering that is synthetic biology. Richard, for example, Director of a renowned genetics spin out, emphasised that “regulators tend to be a little more sort of pragmatic [on risk] than academics… possibility because they have to look at a whole bunch of other stuff.”

In terms of the breadth and variety of the sectors that HSE is responsible for regulating HSE is aware - and indeed has made explicitly clear - that experience is not always a benefit and that new processes can reduce the advantages and affordances otherwise presented by experience. This is a critical sensibility that HSE has emphasised over the years - particularly in light of its engagement with, and investigations into, health and safety failures including the Flixborough chemical plant explosion of 1974. It was noted, for example, during the investigative proceedings into the Flixborough chemical plant explosion, that new processes can contribute to the imposition of problems not only differing in magnitude but also in *kind* (Department of Employment, 1975).

HSE is acknowledging here that knowledge does not necessarily increase in any kind of linear fashion. It is acknowledging that whilst in some instances experience *can* be a benefit, it can work in others to constrain the possibilities for thinking and doing things differently. This is a regulatory sensibility, then, that is alive towards the multiform configuring(s) of the relations between knowledge and experience.

It is these less orientational approaches to the doing of regulation – approaches which acknowledge that it is not always possible or desirable to ‘accumulate knowledge’ or to know where is necessarily the right place to go which will play an important role in empowering the situation that is the coming into being of synthetic biology.

Getting comfortable, for example, with non-knowledge - that is, with inevitable gaps in scientific understandings of and evidence for risk is an important part of empowering the situation that is the coming into being of synthetic biology for regulatory authorities such as HSE. And yet, this is by no means a straightforward task. Kevin, who is responsible for contributing to the managerial oversight of HSE’s Hazardous Installations Directorate, explained that the ‘hype’ and ‘hyperbole’ that tends to surround the coming into being of new technologies such as synthetic biology can interfere in the doing of good regulatory practice:

> “it’s difficult and very hard to say this publicly but as a government regulator there’s an expectation that we will provide public reassurance and I think sometimes there’s a risk there that we then may not be as open as we might around what risk is actually involved in the process… If the debate is polarised in the extremes… I think sometimes we can react to the scare stories and you can perhaps go too far the other way saying there’s no risk… we don’t have all the answers or the knowledge and you know you start to get a bit nervous about being asked certain questions…”

What Kevin is alerting us to here, is that the perceived expectation that HSE will provide public assurance can exert a felt pressure upon the organisation such that HSE feels that there is a need to provide answers. Kevin continued to explain that:

> "when you go out in a bigger community it does get difficult and I think a lot of our people aren't necessarily trained or prepared for those sorts of discussions… it's the new stuff or the sudden discovery that tends to prompt the hardest debates… you come out and you try and put over some reasons, explanation or position and it's just swept away partly because it's boring and it doesn't make a good news story and the willingness to believe in a nightmare scenario is quite high…"

Empowering, therefore, the situation that is the coming into being of synthetic biology requires attuning towards the social noisiness that tends often to surround the coming into being of new technoscientific innovations and developing new sets of skills and affordances. Kevin explained that "what we have entered into perhaps more than we initially thought we would… is actually joining in that public debate." This is an example of how HSE is shifting its shape in order to cater for synthetic biology's coming into being.

I have suggested that the quality of the relations between HSE and its dutyholders and the cultivation of new sets of skills and affordances is an important part of the bringing of synthetic biology into a governable world. In more recent years, however, it is important to note that the relations between HSE and its dutyholders are being stretched and reconfigured anew in light of developments including the implementation of the 'Fee for Intervention' scheme, or, 'FFI' as it is otherwise known. FFI is an operational development which stipulates that HSE must recover the costs associated with investigating and remediating any breaches in dutyholder activities.

FFI was introduced in 2011 following the recommendations of the Employment Minister Chris Grayling. During the 2014 Triennial Review of HSE – a review which, every three years brings the spotlight of scrutiny to bear on the activities of HSE, Martin Temple, previously Director-General of the Engineering

Employer's Federation, expressed considerable concern at what he described as:

> 'the strength of feeling from stakeholders that FFI has damaged HSE's reputation for acting impartially and independently, and thereby its integrity as a regulator… [there] is a risk that inspector decisions will be, or be seen to be, skewed by the need to raise income.' (Temple, 2014: 11)

The UK Federation of Small Businesses (2015: 12) have similarly sought to emphasise that changes to the regulatory system must not 'create perverse incentives which could worsen the 'regulatory experience' and move it away from a more partnership based approach.' The FSB (Ibid.,) have cautioned against what they perceive to be the potential role of FFI in undermining the quality of the relationship between HSE and its dutyholders:

> 'We believe that since its introduction the Fees for Intervention (FfI) policy employed by the HSE has contributed to an undermining of the open and collaborative approach to compliance which, we believe the HSE had been trying to move towards and that the FSB wants to see more of. It has begun to drive a 'wedge' between some small businesses and the regulator.'

HSE have acknowledged some of the potential negative implications of FFI. In 2014 they emphasised that:

> 'we recognise that the transition to the FFI regime has been challenging and accept that there has been a cost to pay in terms of the relationship between dutyholders and inspectors, particularly with respect to the advice that inspectors feel able to offer businesses, and that they are motivated to seek from inspectors…' (HSE, 2014: 2).

This is a particularly illustrative example, I suggest, of how regulator-dutyholder relations are being put at risk by particular kinds of economistic and political pressures associated with the present regulatory moment. This is an example of how the skills and affordances required to empower the situation that is the coming into being of novel technoscientific developments such as synthetic biology are being simultaneously constrained and enabled by a multitude of *other* orderings and sensibilities. These are orderings which include the need for HSE to retain its financial income – particularly at a time when it is receiving decreasing levels of government funding. Whether HSE is able to implement the FFI regime in practice in a manner that guards against the becoming that is deteriorating regulator-dutyholder relations is a question that remains to be seen.

8. **Conclusion**

In this final empirical chapter of the thesis I have argued that empowering the situation that is the coming into being of synthetic biology and the bringing of synthetic biology into a governable world requires not simply the implementation of a regulatory *framework* that delineates fixed and neat Euclidean objects - but a shift towards a looser and more relational sense of *networking*. I used the term networking in the Stengerian sense of the opening up of synthetic biology to new connections and dynamics of learning.

I began the chapter by developing an account of how synthetic biology exceeds and departs from the extant provisions of the GMO CU Regulatory framework. I highlighted how synthetic biology’s mobilisation of a more patchworked and amalgamistic spatiality of organismic intervention is contributing to a decentering of, and a departure from, extant templates and frames of reference. The notion of the comparator organism, for example, is a key orientating and sensitising device that is much less relevant to the undertakings of the synthetic biologist. I highlighted how the dis/re-assemblings of the biological associated with the undertaking of synthetic biology in practice are working to generate new kinds of frictions and touchings together - the effects of which cannot always be known or anticipated in advance.

It is in this sense that synthetic biology can be described as a developing approach to biological engineering that exemplifies and intensifies a shift from life or biology rendered in informational terms (cf Caduff, 2014). This is, in other words, an emergent field of technoscientific endeavour that is working to undercut the demarcations and differentiations between ‘high’ and ‘low’ levels of risk. It is an approach to the doing of biological engineering that is unsettling the sharp lines and categorical preferences of extant modalities of regulatory organising. In sections 4 and 4.1 of this chapter, for example, I highlighted how the practice of scrutinising synthetic organisms in light of the percentage of their genome that has been chemically synthesised not only channels the regulatory gaze too narrowly, but can work also to generate a number of undesirable ‘reals’ (Law, 2004; Law et al, 2013) – reals which include the placing of prohibitive restrictions upon particular kinds of research processes and experimental work.

Although synthetic biology has been corralled into the extant provisions of the GMO CU Regulatory framework, I argued that it is not simply the case that the incorporation of synthetic biology into the GMO CU regulatory framework can be described as a ‘filling the prescription approach’ to the doing of regulation – an approach that formats ‘the problem to fit readily available solutions’ (Zhang et al, 2011: 7). I highlighted, for example, how HSE is not only alive and attentive towards the ‘slipperiness’ of synthetic biology as an object of regulatory governance but is simultaneously engaged in more networked practices of apprehension that contribute to the bringing of synthetic biology into a governable world.

HSE's ability to engage in more networked practices of apprehension is bound up in its organisational sensibilities and in what Mol (2002) would describe as its 'complex present.' HSE is an organisation or regulatory authority whose tripartite history and experiences of tempering the risks associated with a diverse variety of regulatory objects, places it in a unique position to apprehend the coming into being of this developing approach to biological engineering. In particular, HSE is a regulatory authority that places a distinct emphasis upon nurturing regulator-dutyholder relations and whose technical expertise has been shown to play a critically important role in helping to cultivate and sustain these connections and relationalities.

At the same time, however, the regulatory endeavour is an endeavour or 'doing' that is always in process. It is an endeavour that takes different kinds of shape(s) in light of its being composed of multiple sensibilities and orderings that are pushing and pulling in different directions. More recently, for example, the relations between HSE and its dutyholders are being stretched and pushed into new kinds of configurings by the introduction of government initiated policies and interventions such as the 'Fee for Intervention' scheme. FFI has been critiqued by stakeholders who have suggested that the introduction of the scheme may well impact upon the extent to which dutyholders feel that they are able to approach HSE for advice and guidance (HSE, 2014). Different kinds of regulatory settlements are generative, therefore, of different kinds of regulatory reals. This alerts us to the realisation that in a fractiversal world – that is, in a world that is patterned by multiple orderings and sensibilities, it becomes important to trace the ways in which different kinds of reals are composed or brought into being with particular kinds of effects.

In addition to tracing the ways in which synthetic biology is forcing thought for HSE, I also developed an account of how, for a number of synthetic biology practitioners, questions of safety and risk have taken on a new found significance. Different disciplinary sensitivities, for example, are being spliced together by synthetic biologists in order to engage more affirmatively with the species of non-knowledge that is scientific indeterminacy. I traced the contours of what might be described as a less-modernistic post-Promethean engineering subjectivity. I highlighted how the emergence of this less-modernistic-post-Promethean engineering subjectivity can be attributed, in part, to synthetic biology's inheritance from, and association with, some of the controversies and challenges surrounding the development of GM crops. At the same time, however, in spite of the emergence of these more affirmative practices of working, it is clear that there is more still to be done in terms of the opening up of synthetic biology not only to the scrutiny of different types and kinds of scientists, but also to the scrutiny of multiple kinds of publics and to the scrutiny of social conceptions of risk.

Throughout the course of this chapter I have argued that bringing synthetic biology into a governable world requires the opening up of synthetic biology to new connections and dynamics of learning. Tracing the generativities that arise from these new connections and dynamics of learning is critically important if we are to empower the situation that is the coming into being of this developing approach to biological engineering. As the scholars Claire Marris and Catherine Jefferson (2013: 17) put it, bringing synthetic biology into a governable world requires refusing to speak in 'routine ways' about this burgeoning approach to biological engineering. It requires refusing to take for granted the equation of genetic material with the quality of communicability. It requires acknowledging that synthetic biology confounds the ready demarcation between high and low levels of risk. It requires getting comfortable with the species of non-knowledge that is scientific indeterminacy. It requires calling into question what is understood and meant by the terms ‘organism,’ engineering, genetic material and biological sociality.

Imbued, therefore, within the reflexive practices of HSE and a number of synthetic biology practitioners are the glimmerings of what might be described as a different kind of making governable. This is a making governable that is premised upon the qualities of reflexivity, humility and relationality. Examining the ways in which these qualities and goods are not only brought into being but are also composed and placed at risk is, I suggest, an important part of mapping out what it might mean for synthetic biology to inhabit the world and to inhabit it well. This requires looking beyond the broad modernist inflected descriptors of the site of the doing of regulation as a site that is predisposed simply to excise varying forms of unknowns and non-knowledges from the policy making process. It requires tending to the thickness and the texturings of things done in action and in process – that is, in practice.

Chapter Six

Conclusion

Towards a Modest Geography of Novel Biologies

1. Introduction

I began this thesis by outlining my aim to generate some ontological curiosity surrounding the developing 'thing' that is synthetic biology. Through in-depth interviews and fieldwork engagements with leading practitioners in the field, I have explored the complexities and nuances of the process of the bringing of an engineering approach to bear on the stuff and substances of the biological. I have mobilised insights and materials generated whilst working alongside HSE, the UK competent authority responsible for regulating the developing trajectories of synthetic biology, in order to consider what it might mean and what it might take, to bring synthetic biology into a governable world.

The thesis has drawn from a variety of established areas of literature including more-than-human geographies; actor network theory; ontopolitical theory and the sociology of scientific knowledge. The thesis has responded to the call of Marris and Rose (2012) to map out a more nuanced cartography of synthetic biology's contours, trajectories and opacities. One of the key findings to have emerged from the process of this research is the recognition that synthetic biology is an intricately textured and highly variegated approach to the doing of the engineering of biology that is suffused by issues, tensions and contradictions of varying kinds. It also emerged during the course of this research that there is a 'slipperiness' to synthetic biology as an object of regulatory governance – a slipperiness that is contributing to a decentering of, and a departure from, extant templates and frames of reference.

In this chapter I focus on the key messages of importance to emerge in this thesis. I begin the chapter by returning to the aims of the thesis that I set out in chapter one. I discuss the key findings, contributions to the literature and future trajectories that have emerged in the process of exploring these aims.

2. Returning to the Aims of the Thesis

In the introductory chapter to the thesis I set out the aims for this research. I now return to these aims in order to demonstrate the ways in which the thesis has addressed these aims and in doing so has contributed to geographical and social scientific debates concerning the coming into being of novel biotechnological developments such as synthetic biology.

2.1. Aim One: To develop an empirically informed and less perspectival account of the doing of synthetic biology and the bringing of an engineering approach to bear on the stuff and substances of the biological.

To address this aim I explored the ways in which different practitioners are engaged in the doing of synthetic biology. I developed a typology of the ways in which synthetic biology is taking different kinds of shape(s) in different sets of relations. In approaching this aim a number of key findings emerged. I delineate the key findings that emerged in the process of exploring this aim below.

2.1.1. Synthetic Biology Multiplied Outwards

Synthetic biology is often described as being marked by the desire to take ‘even further’ yet (Calvert and Fujimura, 2011: 156) the drive towards predictability and instrumentality in the doing of the manipulation of biology. One of the key findings to have emerged in the course of this research, is the recognition that to engage in the drive to take ‘even further’ yet the qualities of predictability and instrumentality in the doing of the engineering of biology is to embark on what is ultimately an intensely processual venturing. Engineering languages and rhetorics are not simply *imposed* upon or seamlessly *incorporated* into the doings of the manipulation of biology. Rather, they are brought into an *encountering* with a number of differing 'things' including the sensibilities and sensitivities of different practitioners; the mutable materialities of the 'stuff' of the biological and the different contextings within which different practitioners are working.

Approaching, therefore, the doing of synthetic biology through a lens of analysis that is attentive towards the messy and at times jarring nature of the spatialities of the 'encounter,' has enabled me to open up a thick and textured account of the doing of synthetic biology that departs from prevalent and programmatic descriptions of synthetic biology as simply 'incorporating' (cf Weiss, 2009) engineering principles into the doings of the manipulation of biology. It has enabled me to multiply outwards registers for understanding not only what synthetic biology is but also what it might become. To describe synthetic biology as simply 'incorporating' engineering principles into the doings of biology is to efface and hide from view, the resistances, the mutual reconfigurings, the tensions and the turbulences, that arise when the ethos and sensibilities of an engineering approach are brought into an 'encounter' with the stuff and substances of the biological. The findings of this research thus resonate with the work of Hinchliffe and Bingham (2008: 1534) who posit that order is not something that is simply 'impressed on the world following a logic or idea' but that rather 'there are orderings and practices which are already impure and which become increasingly more complex as they meet more and more of the world.'

In exploring how synthetic biologists are differentially encountering and endeavouring to work with and mobilise engineering languages and rhetorics in their own working practices, I was able to tease out and trace in this thesis, through an extended process of coding and qualitative analysis, three prominent modalities of the doing of synthetic biology – the cellular engineer, the controlled experimentalist and the multidisciplinary scientist. These three patterned modalities can be said to offer a unique contribution to knowledge in that they open up and throw into relief, the micro-level politics and differences that inhere within the various undertakings of the doing of synthetic biology in practice. They can perhaps best be described as constituting a geographically inflected heuristics in that they foreground, amongst other things, the different directions within which different practitioners are moving and the different 'things,' materialities and sensitivities that matter differently to different practitioners.

The identification of these three modalities of the doing of synthetic biology extends the work of O'Malley et al (2008) who have differentiated between three facets of the doing of synthetic biology – DNA based device construction, genome driven cell engineering and protocell creation. The identification of the three modalities also responds to the call of the social anthropologist Sarah Pink (2009: 14) 'to bring local voices into academic representations.' Perhaps most importantly, however, the identification of these modalities has enabled me to 'open up' what Lyotard (1984) would describe as a series of 'little narratives' surrounding the coming into being of the developing approach to biological engineering that is synthetic biology. Little narratives are multiplicitous and heterogeneous stories whose 'conflictual multiplicity and heterogeneity' (Carroll, 2006: 42) interferes with singularity and the pretence of set trajectories. This was one of the core research objectives that I delineated at the very outset of chapter one of the thesis.

In attending to the ways in which synthetic biology is done in action and in process, I have multiplied outwards the 'fraying' edges (Hinchliffe, 2010) of synthetic biology as a matter of 'concern' (Latour, 2004). I have generated some ontological curiosity surrounding the coming into being of this developing approach to biological engineering. In this thesis synthetic biology became about; the disorientiating proclivities of the noisiness of the biological; the mobilisation of particular kinds of words and cues so as to create worlds and to exert certain kinds of gravitiational pulls and connectivities (e.g. between funders and practitioners); the layering and (dis)assembling of different kinds of disciplinary knowledge traditions; the drawing together of what Latour (2005) would describe as varying 'prostheses' including computational models and algorithms into the doing of the engineering of biology, and much more besides. To use the language of the social and cultural geographer Nick Bingham (2006), we might say that there is indeed a busyness or a 'plenitudal' abundance to the variegated and multifaceted process of the bringing of an engineering approach to bear on the stuff and substances of biology.

The process of the identification of the three modalities of the doing of synthetic biology that emerged during the course of this research was inspired, in part, by the conceptual tool or notion of the 'multiple' as developed by the feminist philosopher and theorist Annemarie Mol in the late 1990s. I introduced the concept of the 'multiple' in chapter two of the thesis. In spite of it being almost twenty years since Mol developed the notion of the 'multiple' as a means of staging an explicit encounter between ontology and politics, I have highlighted in this thesis how the notion of the multiple continues to remain a remarkably generative tool or sensitising device in helping to open up a different awareness of what varying ‘objects’ such as synthetic biology are and what they might become.

The findings that emerged in the process of exploring this aim throw into relief the continued importance and significance of tending to the existence of difference in the world. As the feminist theorist and philosopher Donna Haraway (1991: 172-173) puts it, the process of cultivating an attentiveness towards difference in the world is a critically important task, not least because, lurking within the micro-politics and doings of different ways of relating and becoming, are ‘emerging pleasures, experiences and powers with serious potential for changing the rules of the game.’ In terms of the ‘doings’ and ‘differences’ that came to the fore during the undertaking of this research, it quickly transpired during the course of this research that, initial appearances aside, synthetic biology is not simply a hubristic endeavour (see also Lewens, 2013), but that there are affirmative glimmerings and storyings of becomings, learnings and encounterings at play in the doing of synthetic biology that are about much more than simply stretching the productivities of life to new and unprecedented limits.

It is for this reason that the findings of this research lead me to suggest that there is a continued need to experiment with, and to put to work in different contexts, conceptual tools and sensitivities that are alive towards difference in the world and which might help us to develop further our capacities for living well, amongst and amidst, a full and plenitudal (Bingham, 2006) world of proliferating sensibilities, orderings, objects and things.

In chapter two of the thesis I noted that the ‘multiple’ is a conceptual tool that is interested not only in the ways in which different objects are performed differently in different sets of relations, but also in the ways in which different enactions of particular objects interact and interfere with one another. In terms of the diffractions and interferences that exist between the modalities of doing that took centre stage in chapter four of the thesis, it transpired during the course of this research that the utterances of the controlled experimentalist might well be putting the longevity of the field of synthetic biology as a whole at risk. This particular finding builds upon the work of Schyfter and Calvert (2015) who have posited that the promissory rhetorics that are being mobilised by synthetic biology practitioners might be contributing to the generation of a form of 'compressed foresight' that neglects to consider the infrastructural resources and the longer term funding strategies that might be necessary to realise the coming into fruition of this developing approach to biological engineering. But the findings of this research also extend the conclusions of Schyfter and Calvert (2015) in that they point towards the specificities of the more affirmative modalities of relating and becoming that might be endangered by the realisation of compressed foresight in the developing trajectories of synthetic biology practice.

One of the key differences or distinguishing variables that enabled me to differentiate between the three modalities of doing that emerged during the course of this research relates to the differential presencing of the agential vitalities and texturings of the stuff of the biological. The agential vitalities and texturings of the other-than and more-than-human is a particular facet or object of social scientific inquiry that is critically important to the disciplinary identity of human geography. It is for this reason that I reflect in what follows on how and where the findings of this research complement and extend geographical engagements with the other-than and more-than human.

2.1.2. Engaging with and Accounting for the Agential Vitalities of the Biological

A key finding of this thesis relates to the ways in which synthetic biologists are differentially attuned towards and engaging with the agential vitalities of the stuff and substances of the biological. The political geographer and nature-culture theorist Bruce Braun (2008) has argued that, once the point of the agential vitalities of the other-than or more-than-human has been made, then things become, quite quickly, very uninteresting. Braun has cautioned against what he describes as an unreflexive, unthinking 'romance' of matter and has insisted that there is an urgent need to reflect on how organisation occurs and on the ways in which the agential vitalities and propensities of the more-than and other-than human are registered, apprehended, neglected and much more besides. Braun has called for geographers to 'open up' and to 'map out,' the specificities of the webs of relations within which the agential vitialities of non-human things become imbricated and work to generate certain kinds of effects.

It emerged during the course of this research that practitioners are engaging with and apprehending the agential vitalities and texturings of the stuff and substances of the biological in ways which exceed narrow accounts of biological substrates as being *either* pliable manipulable materialities *or* recalcitrant lively things. It became apparent during this research that the agential forcings of biological materialities are generating effects and dis/re-assemblings that are branching out in a plethora of different ways. It is in this sense that this thesis can be said a) to respond to Braun's call and b) to open up to social scientific inquiry a particular set of relations or imbrications between microbial life and the discipline of engineering that have been unexplored within extant geographical scholarship interested in the agential vitalities of the more-than-human.

The agential texturings of the liverwort Marchantia enabled Geoff, for example, a cellular engineer, to “eke out a space” away from the felt pressures of a commercial return. Geoff’s engagements with the liverwort Marchantia provide a particularly illustrative example of how the ‘affordances’ of a non-human thing are working to resist the increasing encroachment between capital and life. More specifically, the presence of Marchantia in the developing trajectories of synthetic biology, is a presence that is working to resist synthetic biology’s economistic orientation. It is a presence that is pushing the field into different kinds of directions and which is helping to facilitate the ‘sticking together’ of multidisciplinary working practices. Marchanita became a key ‘locus’ or object of inquiry that is drawing together and intersecting with particular kinds of looser space-times and more affirmative relationalities.

It also transpired during the course of this research that the demarcation between the cellular engineer and the controlled experimentalist is perhaps not quite as clean or clear cut as it might initially appear. For the controlled experimentalists Lester and Toby, cultivating an attentiveness towards the thickness of biological sociabilities is quickly becoming an important part of realising the qualities of efficacy and precision in the doing of the engineering of biology. This raises the question of how to make sense of, and to account for, the nature of this slippage which, upon initial observation, appears to signal what Lorimer (2012: 603) would describe as the integration or the co-option of the ‘stochastic’ and emergent texturings of ‘non-human immanence’ by corporate and commercial interests.

If at one point the emergent propensities of lively materialities were being ‘celebrated’ for their ability to constrain and circumvent human hubris, then today it seems that new forms of domination and oppression are working to exploit the pre-discursive forcings of non-human life. To use the language of the political theorist Luigi Pellizzoni (2016), we might say that practitioners such as Lester and Toby are 'riding' the indeterminacies and emergent propensities of the becomings of the biological. It would certainly be plausible, in this regard, to argue that the engagements and attunements towards biological complexity that I teased out in chapter four of the thesis are but the latest examples of what the political theorists Michael Dillon and Julian Reid (2009: 148-9) would describe as a liberal biopolitical grasping at life's 'pluripotency or totipotency.'

But this, I suggest, would be too easy an argument. It would be to efface the intricate texturings and the non-dominant reals (Law, 2004; 2015) associated with the doing of synthetic biology in action and in process. It emerged, for example, during the course of this research that there are much more nuanced engagements with the lively materialities of the biological that inhere even within the endeavourings of those participants who exhibited a distinct hubrism in their desire to engage in the doing of the engineering of biology. To emphasise solely the exploitation and the pushing of the limits of the biological for instrumental purposes is to extinguish the more affirmative flickerings or configurings of synthetic biology that reverberate and extend beyond simply the manipulation of life and the intensification of 'human agency and the application of means-ends rationality' (Pellizzoni, 2016: 11).

As a case in point, in the very process of endeavouring to control the transcriptional process, synthetic biology practitioners are finding themselves increasingly confronted, head-on, with a myriad of biological associations that cannot simply be wished or willed away by the mobilisation of rhetorics of the black boxing of complexity. One of the implications of this resurfacing of biological complexity at the intersection of engineering and biology is an unravelling in particular regimes of knowing and doing. It emerged, for example, in chapter four of the thesis that synthetic biology tools and techniques are intersecting with the micro-spatialities of intracellular bacterial endosymbionts in ways which are calling into question extant modalities of relating and becoming. The findings of this research can be said to resonate in this vein with the work of the physicist and feminist theorist Evelyn Fox Keller (Keller, 2009: 8) who has argued that developments in the life sciences are enabling practitioners to 'fathom' the depths of life and to marvel 'not at the simplicity of life's secrets' but also its complexity.

There is, then, much more to the (re)centering of biological complexity than is encapsulated in the broad yet nevertheless compelling narrative of synthetic biologists as working to adventitiously 'ride' the becomings of the biological. The reconfigurings in regimes of knowing and doing that are emerging from synthetic biology done in action and in process throw into stark relief the realisation that I opened up this concluding chapter with – namely, that to engage in the doing of the engineering of biology, is to embark on a processual venturing – a venturing that is subject to branch out and to meander in unexpected and unanticipated ways.

Indeed, it emerged during the course of this research that, when done in particular kinds of practices and working environments, synthetic biology is enabling non-human things to begin to more powerfully force thought on their own terms. For a number of practitioners, the doing of synthetic biology is contributing to a reversal in hierarchical 'truth' claims concerning, for example, the purported 'centrality' of DNA and the genetic code. This was particularly the case for the figure of the cellular engineer.

The bringing of an engineering sensibility to bear on the stuff and substances of the biological can thus be said to be generative of new kinds of entanglements – of apparitions and new kinds of associations that extend and reverberate in different kinds of directions with different kinds of effects. Perhaps unsurprisingly, it is the very expansion of the space of the social and the bringing into sharp relief of new kinds of connectivities and associations between the human and the non-human, that, for the sociologist of science Bruno Latour (1993; 2005b), continues to make 'science' such an interesting site of social scientific inquiry.

The question of how the reconfigurings in regimes of knowing and doing associated with the bringing of an engineering approach to bear on the substances of biology might spill over and shape future research strategies or understandings of different kinds of biological processes and phenomena is a critically important question to which we must attend. Future research might usefully look to map out and trace the ways in which the desire to bring control and predictability into the doings of the engineering of biology is generative of new regimes of learning and becoming; and of how the intensity of the encounter between the logics and sensibilities of an engineering approach and the mutable materialities of the stuff of biology generates excessive apparitions and reverberations that provide new openings for non-human things to force thought more powerfully.

The findings of this research thus point to the need to ensure that our conceptual frames are not orientated or configured in such a way that they miss out on the intricate granularities and the specificities of micro-level practices and politics. There are, in other words, important dis/re-assemblings emerging in the doing of synthetic biology that we run the risk of marginalising when we mobilise or channel our empirical materials through the lens of particular kinds of theoretical repertoires.

Instead, therefore, of simply amplifying the hubristic propensities of synthetic biology it becomes important to ask; how might the splicing together of computational logics and visualisation tools and techniques enable practitioners to differentially apprehend the rugged contours and vast expanse of chemical space? What are the different kinds of navigational affordances offered by blind mutation and rational design, and what does this mean in terms of providing the space and room for non-human things and materialities to differentially force thought and to become a co-constituent actant in the formation of particular kinds of lived realities? What kinds of pressures, temporal or otherwise, might hinder or enable these kinds of openings up and closings down? This thesis has gone some way to addressing and opening up these questions.

Addressing these kinds of questions – questions which are concerned more with relationalities, layerings and encounterings is more useful, I suggest, than channelling or addressing synthetic biology's coming into being through the lens of philosophical and theoretical repertoires that are poorly attuned towards the micro-politics and intricate granularities of synthetic biology done in action and in process. To return briefly to the biopolitical reading of synthetic biology that I outlined in chapter two of the thesis, to argue that synthetic biology simply 'presences' biological materiality as a 'standing reserve' of 'function' (Schyfter, 2012), is to veer almost entirely on the side of the thanatopolitical. Synthetic biology, as this research has highlighted, can be both affirmative and thanatopolitically inflected in orientation.

I argue that, as social scientists, we have a responsibility to map out the differential configurings and webs of relations that are generative of affirmative and thanatopolitical modalities of relating and becoming. The important question thus becomes under what set of conditions, and in what sets of relations, are these different qualities and orientations brought in being and amplified? This is one of the reasons why I draw this chapter to its close by arguing for the development of a modest geography of novel biologies – a geography that is attentive towards, and which endeavours to 'map out,' the reverberations, the apparitions, the entanglements and the frictions that arise in the thickness of the morass of synthetic biology done in action and in process.

2.2. Aim Two: To develop an empirically informed account of the ways in which synthetic biology is intersecting in and interfering with, extant modalities of regulatory organising.

2.2.1 Shape Shiftings and Complex Presents

During the process of exploring this aim it became apparent that it is insufficient to argue that extant regulatory regimes have simply been 'retrofitted' (Frow, 2013) in order to render more amenable to traditional oversight, this developing field of scientific endeavour. Through negotiating a research relationship with HSE and embedding myself within HSE's Biological Agents Unit, I was able to develop in this thesis an account of the hesitations, the apprehensions and the forcings of thought, that are exerting their presence as HSE goes about the doing of the business of regulation in practice. These are important parts of the doing of regulation that cannot be discerned by external accounts or desk based analyses of the regulatory and legislative provisions applicable to the developing trajectories of synthetic biology practice.

It emerged during the course of this research that there is a slipperiness to synthetic biology as an object of regulatory governance. Synthetic biology is contributing to a departure from and a decentering of extant templates and frames of reference. Synthetic biology's splicing together of multiple organismal parts – that is, its 'betwixt' and 'between' of source species and chassis organism (Roosth, 2010: 99), is working to stretch and undercut, predominating regimes of regulatory organising. I highlighted, for example, in chapter five of the thesis, how synthetic biology is troubling the demarcation between 'high' and 'low' levels of risk. I developed an empirically informed account of how the manifold touchings together generated by the dis/re-assemblings of the biological resist regulatory attempts to scrutinise synthetic organisms through processes of quantification and/or the demarcation of species or biological agents of concern.

This thickness in the socialities of the biological means that the identification of 'organisms' or 'objects' of concern is an approach to the doing of regulation that is poorly suited to the task of bringing synthetic biology into a governable world. The findings of this research resonate in this vein with the work of Lowe (2010), Caduff (2012) and Cooper (2008) who have similarly foregrounded the ways in which microbial bodies are always in formation and are always already different from themselves. Synthetic biology is working to add a renewed intensity to these debates. Although Caduff (2012: 350) does not engage specifically with the question of synthetic biology, he highlights in a recent contribution how the iterability of the biological and the enormous level of strain diversity amongst micro-organisms means that practitioners may end up working with microorganisms that are defined as 'harmless' but which prove just as 'dangerous' as a designated select agent organism or organism of 'concern.'

But the findings of this research extend the work of Caduff, Lowe and Cooper in a number of important ways. In chapter five of the thesis I opened up and explored the more network based and less framework orientated modalities of apprehension that might help to contribute to the bringing of synthetic biology into a governable world. I argued that HSE's shape needs to be such that it is able to attune towards the indeterminacies and the non-knowledges emerging from the process of the dis/re-assembling(s) of the biological. This means acknowledging the limitations posed by an orientational approach to doing of high/low risk inspection work and ensuring that HSE's profile is configured in such a way that the delimitation of risks to human health and the environment emerges as a reflexive and mutual process of learning between HSE and its dutyholders.

I highlighted in chapter five of the thesis how HSE's cadre of specialist inspectors and its commitment to dutyholder engagement are important parts of HSE's complex present that are contributing to the ways in which HSE is apprehending and becoming sensitised towards the provocations posed by synthetic biology's coming into being. Thinking in terms of complex presents (Mol, 2002: 43) – that is, in terms of the space-times, sensitivities and materialities that are folded into the present, is a useful tool through which to open up, and throw into relief, the specificities of how and why certain kinds of things take certain kinds of shapes in certain sets of relations.

Health and safety considerations have typically been relegated within social scientific engagements and analyses of the coming into being of technoscientific developments such as synthetic biology. Jasanof, Hulburt and Saha (2015), for example, have recently argued that questions of 'biosafety' are generative of a narrowing effect in that they are typically 'expert' led and fail to speak to broader questions surrounding, for example, the desirability of technoscientific innovations and developments in the first place. It transpired, however, during the course of this research that whilst the doing of regulation and the securing of health and safety might well constitute a largely ‘conventional’ and ‘traditional’ site of the doing of politics (Asdal and Hobæk, 2016), there are nevertheless important reconfigurations and modalities of relating and becoming that are taking shape within HSE’s approach to the delimitation of risks to human health and the environment posed by the developing trajectories of synthetic biology practice. There are, in other words, important lessons to be learnt by tracing the ways in which synthetic biology is forcing thought at the thresholds of this regulatory milieu.

The findings that emerged in the process of exploring this aim build upon the work of Zhang et al (2011) who have recently posited that synthetic biology intensifies and dramatizes ‘some of the key challenges confronted by modern scientific governance.’ The thesis has provided an empirical exploration of the regulatory challenges and provocations posed by synthetic biology’s coming into being within the context of the remit of the UK’s Health and Safety Executive. It has explored the skills and affordances that might help to contribute to the bringing of synthetic biology into a governable world. Empowering the situation that is the coming into being of synthetic biology requires reconfigured modalities of attuning, learning, apprehending and relating. Many of these skills and reconfigured modalities of apprehension and intervention are, I argue, taking shape within the regulatory reality practices of HSE and in the apprehensions and practices of a number of synthetic biology practitioners.

2.2.2. Frictions and Tensions in Trajectories of Knowing and Doing

There was an acknowledgement amongst the participants in this research that multidisciplinarity is a key means through which it might become possible to build capacity and to engage in more affirmative terms, with the complexities and indeterminacies associated with the re-assemblings of the biological. The findings of this research thus resonate with the work of Barry et al (2008) and Szersynski and Galarraga (2013: 2817), who have pointed to the importance of the coming together of different disciplinary traditions in addressing complex issues and processes that cannot be effectively 'engaged,' or made 'tractable' from disciplinary silos alone.

But the findings of this research also extend the work of Szersynski and Galarraga (2013) in a number of important ways. In this research multidisciplinarity became not simply a means of providing 'answers' to questions that require the competencies of more than one discipline, but a form of 'encountering' that is helping to open up more affirmative ways or modalities of 'being' in the world. Nick, for example, a controlled experimentalist, described how synthetic biology's multidisciplinarity is providing practitioners with the "confidence" to ask the "naïve or stupid questions that are never in fact naïve." Naivety became framed not as a weakness to be overcome but as a generative force that is taking on a more affirmative meaning in this developing field of scientific endeavour.

It is easy to valorise the utility and generativities of a multidisciplinary approach on a rhetorical basis (Barry and Born, 2013). It is much harder to implement the doing of a multidisciplinary approach in practice (cf Choi and Pak, 2006). It emerged during the course of this research that it is easy for a genuinely ‘collaborative’ approach to the doing of multidisciplinary working to morph into a ‘cooperative’ approach and to retain and solidify hierarchical regimes of knowing and doing. Szersynski and Galarraga (2013: 2823) have relatedly posited in their own research into the doing of interdisciplinarity in geoengineering research that certain kinds and forms of interdisciplinarity can make processes of reflection, contestation and revision harder, by reifying disciplinary outputs and by ‘occluding the processes that shape the production of knowledge.’

And yet, in spite of the difficulties associated with the doing of multidisciplinarity in practice, both chapters four and five of this thesis contained glimmerings or moments where the drawing together of different kinds of knowledge practices worked to create frictions or ‘layering’ effects that unravelled and pulled into different directions, the processual unfolding (and the subsequent implications) of the doing of the engineering of biology.

Chapter four of the thesis, for example, illustrated how the tools and techniques of synthetic biology have facilitated the drawing together of insights and understandings from the fields of genomic science and evolutionary biology in ways which are unravelling long held assumptions about the structure and function of cellular life at its most fundamental of levels. Chapter five of the thesis highlighted how, for a number of practitioners, the juxtaposing and drawing together of different disciplinary sensitivities might help to resist any overly permissive or cautious assessments of risk. The touching together, in other words, of different disciplinary traditions can work not simply to ‘slow down’ (Whatmore, 2009) the developing trajectories of synthetic biology practice, but to ‘open up’ the practice and the process of the doing of the engineering of biology such that it unfolds in different directions, with different kinds of effects and reals.

The dissonances and frictions generated by the assembling or encounterings of different disciplinary traditions speaks to what the philosopher of science Isabelle Stengers (2005b) describes as an ‘ecology of practices.’ An ecology of practices refers to the production of “parts” that ‘are not submitted to [a] whole but [which] owe to their participation a power to think and act and resist, that they would not have been capable of without it.’ As Stengers (2005: 12-13) puts it:

> ‘The efficacy of the ritual is therefore not the manifestation of a Goddess who might inspire the answer, but that of a presence which transforms each protagonist’s relations with his or her own knowledges, hopes, fears and memories, and allows the whole to generate what each one would have been unable to produce separately.’

Stengers is alerting us here to the ways in which certain forms or ‘stagings’ and arts of address, can work to push and pull into different directions, the trajectories of certain kinds of practices and doings. For a number of the practitioners that took part in this research, the development of an ecology of practices is likely to become an important part of empowering the situation that is the coming into being of this developing approach to biological engineering. Research participants emphasised, for example, that the assembling of multiple knowledge traditions or ‘epistemic cultures’ (Knorr Cetina, 1999) is likely to play an important role not only in helping to realise the visions of an engineerable biology, but also in helping to build capacity in engaging with scientific indeterminacy.

Future research might usefully consider, therefore, under what sets of conditions it becomes possible to engage in the doing of multidisciplinary working in ways which open up more affirmative registers and potentialities for relating, knowing, becoming and doing. If, as Stengers (2005) puts it, certain forms of ‘stagings’ and arts of address are generative of a rich repertoire of different kinds of ‘goods’ and ‘reals’ (Law, 2004; Law et al, 2013), then teasing out the nature of these different kinds of goods and reals (and the ways in which these goods and reals might be brought into being) is a critically important area of research that social scientific analyses might usefully open up to further exploration.

Future research might ask; how do different disciplinary sensitivities intercalate and what are the kinds of goods that are engendered or brought into being by the encounterings of these different knowledge practices? How and where does the coming together of different disciplinary sensitivities work to generate 'hesitations' or what Stengers (2005: 2) refers to as 'interstices' – that is, moments which work to call into question who we are and what we know? Does the coming together and encountering of different disciplinary sensitivities reconfigure the objects of social scientific inquiry, such that, as we saw in chapter four of the thesis, non-human things are able to force thought on their own terms? What kinds of configurings might enable time to become unhinged from its forward march, or, to become 'fluctuating' and 'aleatory,' to use the language of the contemporary theorist and philosopher Michel Serres (1997: 15)?

When apprehended in this way, the practice of multidisciplinarity becomes a rich and generative lens through which to probe and consider the ways in which practices and processes of learning, listening and attuning are done differently in different sets of relations. It becomes a lens through which to explore the configurations and coordinates, or, the spatialities of encounter that call into question extant modalities of organising and understanding.

It is important to emphasise that I am not arguing here for simply an expansion in the range of 'inputs' and knowledges that might be taken into account in particular kinds of doings (cf Callon 1999; Callon et al, 2011). It is, by now, well established in social scientific literatures both within and beyond the discipline of human geography that the ‘fruits’ (Callon, 1999: 85) and texturings of lay and non-expert knowledges can work to enrich and to open up a somewhat different awareness of varying matters of concern (Barry and Born, 2013; Whatmore, 2009). Rather, I am arguing instead for an attentiveness towards the specificities of the ways in which different knowledge practices come together in particular ways to generate particular kinds of effects. I am interested in the spatialities of their encounterings. The metaphors of twists, turns, torques and turbulences might usefully help to throw into relief, and shed light on, the mechanisms through which multidisciplinary working might help to transform what Stengers (2005: 12-13) has described as ‘each protagonists’s relations with his or her own knowledges, hopes, fears and memories.’

These are theoretical questions. But they are also practical questions. They are questions that are likely to exert a very real and significant influence on the kinds of reals and goods that are brought into the world by the developing trajectories of synthetic biology practice. The Royal Academy of Engineering (RAE, 2009), for example, has recently emphasised that, in spite of the acknowledged importance of working across disciplinary divides, synthetic biology training programmes tend to remain committed to the cultivation of singular forms and modalities of disciplinary expertise. The Royal Academy of Engineering has acknowledged that much more is still to be done in terms of developing the infrastructural resources that might help to nurture the doing of multidisciplinary working in practice.

Multidisciplinary working can take on a number of different forms and generate a number of different effects. Bringing a social science perspective to bear on the development of a ‘mapping’ and ‘schematics’ of the spatialities of encounter that arise in the doing of multidisciplinary working is an important task. The sensibilities of sociological and geographical approaches can be used to map out what kinds of spaces of encounter are produced under what kinds of conditions and with what effects.

The findings of this research can be said to resonate with the work of the STS scholars Calvert and Frow (2013) who have pointed to the importance of 'inclusive' deliberation in shaping the developing trajectories of synthetic biology practice. But they also build upon and push Calvert and Frow's (2013) contribution in a different direction in that they emphasise the need to open up and to explore the less 'orientational' goods – that is, the frictions, the turbulences and the unravellings in regimes of knowing and doing that arise within the developing trajectories of this emergent field of scientific endeavour.

2.3. Aim Three: To develop further conceptual resources from STS, geography and social theory that enable us to grapple more affirmatively with the coming into being of biotechnological developments such as synthetic biology.

The social scientific stories and analyses that we bring into the world are generative of certain kinds of effects and reals. They are performative (Law, 2004; Pryke et al, 2003; Denzin, 2001). This is an important point that I developed in the methodology chapter and at the very outset of the thesis. This thesis was motivated by a desire to contribute to the telling of less-perspectival and less-technologically-deterministic stories about what this thing that synthetic biology is and what it might become. The thesis started out from the premise that synthetic biology's engineering rhetorics are necessarily scrambled as they touch down in, and intersect with, varying kinds of practices. The thesis sought to move beyond the noisy perspectivalism and epistemic circularity that has surrounded synthetic biology's coming into being.

In the process of exploring a) how synthetic biology is being done in and through varying practices and b) how synthetic biology is intersecting and interfering with extant modalities of regulatory organising, my aim in this thesis was to generate some ontological curiosity surrounding what it might mean for synthetic biology to inhabit the world and to inhabit it well. I sought to open up a series of 'little narratives' (Lyotard, 1984) surrounding the complexities and heterogeneities of synthetic biology done in action. I acknowledged that in a 'plenitudal' and busy world (Bingham, 2006), the 'progressive' and 'promissory' narrations that have so readily surrounded synthetic biology's coming into being are by no means the only stories to be told. Quite however, what the other kinds of stories that I endeavoured to give breath to in this thesis would look like, I couldn't be sure in advance.

It may well have been the case that my empirical generations would lead me to the conclusion that synthetic biology was indeed intensifying, and raising to a new level, the instrumentalisation and exploitation of life. On the contrary, my fieldwork materials rather enabled me to develop a much more multifaceted and variegated account of what this thing that synthetic biology is and what it might become. The access that I was afforded not only into the synthetic biology community but also into HSE, the UK regulatory authority responsible for overseeing the developing trajectories of synthetic biology, provided me with an in-depth insight into how the visions and aspirations of the doing of the engineering of biology are playing out in practice and on the ground.

The findings of this research suggest that there is a richness and multifacetedness to the doing of synthetic biology that cannot be encapsulated by the broad brush strokes of conventional biopolitical analysis or critique. There is an intricate set of dis/re-assemblings that are taking shape within the developing trajectories of synthetic biology practice. It is for this reason that I argue in this thesis for the development of a modest geography of novel biologies. If the task of a 'modest sociology' (Law, 1994: 14) is to loosen the constraining push of grand explanatory forces, to recover difference and to let the world show up differently, then perhaps we might describe the task of a modest geography as an exercise in mapping and multiplying outwards, repertoires and registers for living together and for living together well.

A modest geography is a geography that is alive and attentive towards the apparitions and reverberations that arise as things touch together and generate new kinds of alliances and dis/re-assemblings - no matter how small or slight. It is interested in the specificities of how things and practices might hold together. A modest geography deals in encounterings, tensions and frictions – it is interested in the thickness of the morass of practice. A modest geography might perhaps best be described therefore as constituting a particular kind of sensibility – a sensibility that is attuned towards the intricate granularities and manifold texturings of things done in action in a processually unfolding world. It is a sensibility which, following the sociologist of science John Law (2015: 128), insists that there is no 'overarching.'

The question of how things, practices and sensibilities might, for example, branch out in unexpected ways and create new kinds of alliances - these are the micro-geographies or the modest geographies that we need to give breath to if we are to consider what it might mean for technoscientific developments such as synthetic biology to inhabit the world and to inhabit it well. Being attentive towards the branching out of things done in action and in process is a critically important task, not least because, as the cultural geographer Catherine Phillips (2013) puts it, what is at stake in the ways in which varying relations, practices and doings cohere and divide, is nothing less than our collective possibilities for living together and for living together well. John Law (2004: 156), like Phillips, has emphasised that:

> 'After the subdivision of the universal we need quite other metaphors for imagining our worlds and our responsibilities to those worlds. Localities. Specificities. Enactments. Multiplicities. Fractionalities. Goods. Resonances. Gartherings. Forms of craftings. Processes of weaving. Spirals. Vortices. Indefinitenesses. Condensates. Dances. Imaginaries. Passions. Interferences.'

What Law (2004) is alerting us to here is the need to ensure that our conceptual frames are attendant to the taking shape(s) of things in a world where entanglements and relations are subject to disassemble and re-associate in a number of different ways. This is, to be sure, something that social scientists from across the disciplines and fields of STS, human geography and empirical philosophy have been arguing for quite some time. But, at a time when new kinds of innovations are proliferating and are accompanied by the glimmerings of new kinds of less-modernistic post-Promethean engineering subjectivities, there is, I suggest, a need to ensure that our social scientific toolkits are alive and attentive towards these transformations. Cultivating an attentiveness towards the ways in which things take shape and might be shaped otherwise is geography's way of making space for more generous and affirmative, life-sustaining futures.

3. Contributions of the Thesis to Contemporary Academic Debates

There are a number of theoretical areas and subsets of human geography that this thesis speaks to. I have gestured towards the ways in which the findings of this research resonate with and build upon extant social scientific engagements that have sought to 'open' synthetic biology up to social scientific scrutiny. Here I distil a series of further contributions and intersections of the thesis with a number of contemporary academic debates.

3.1. Contributing to Biopolitical Geographies

Since the term 'biopolitics' first appeared in Foucault's (1978) *The History of Sexuality*, there has been a profusion of academic endeavours attending to the convergences and intertwinings between life and politics. In spite of the undoubted salience of biopolitics and its efficacy in facilitating critical engagements with a plethora of contemporary issues, there is, however, a growing sense of unease that biopolitics is perhaps lacking in the 'ballast' required to make a difference (Campbell, 2011: vii). Indeed, as Wolfe (2013, 2014) and others have argued, many biopolitical endeavours are not only pervaded by homogenising terms such as 'life' and 'sovereignty,' but tend also to remain underpinned by formal divisions between 'bios' and 'zoe' and the 'human' and 'animal.' Such divisions are complicit in the flattening and stifling of emergent subjectivities and delimit the ethical and political purchase of subsequent analyses. They contribute to an impoverishing of the manifold possibilities of being in and relating to the world. They institute what John Law (2015: 132) would describe as a 'metaphysics by stealth.'

The limitations of the biopolitical endeavour, as currently figured, become acutely apparent when we turn, for example, to the recent work of the anthropologist

Stefan Helmreich (2011) who, in his study of 'limit biologies,' has argued that 'life,' – as the epistemic object of biology – has lost its self-clarity. Put differently, the 'bio' in biopolitics is becoming ever more strange and elusive. In a related vein, for the historian of science Hannah Landecker (2015), whose most recent work has attended to the microbiological transformations associated with the mass production of antibiotics, 'biopower' is becoming increasingly 'out of joint.' The fundamental languages of the biopolitical lexicon, including that of 'optimisation' and 'rationalisation,' are seemingly no longer adequate to the task in hand (see also Campbell and Sitze, 2013).

In this thesis I have highlighted how synthetic biology is an epistemically troubling instantiation of the 'bio' that is reconfiguring extant modalities of relating and becoming, organising and doing. I have pointed to the ways in which the shifting of shape(s) of the bio require a new kind of 'polis' and new forms of politics. It is increasingly clear that, whether we are thinking in terms of immunology, zoonoses or epidemiology, engaging with and opening up the space of the 'bio' is doing much to shift the debate away from fixed and discrete notions of individual 'subjects' to thinking instead about shared qualities such as 'vulnerabilities.' Beyond, therefore, simply offering a counter-narrative to biopolitical graspings of excess, I have signalled in this thesis the need to take seriously and develop further, the disciplinary subfield of biopolitical geographies.

By bringing the more-than and other-than-human into an encounter with the theoretical repertories and registers of the biopolitical, biopolitical geography is a subfield of social-cultural geography that is likely to play an important role in helping to multiply outwards registers for living together and for living together well (see, for example, Asdal et al 2016 and Hodgetts, 2017). As Rutherford and Rutherford argue (2013: 432), geographers are well placed to develop some of the most interesting and persuasive work in this domain not least because of a) their attentiveness 'to the manner in which biopolitics works (and does not) on the ground' and b) their engagements and long standing interest in vital geographies. In this thesis I have highlighted how vital geographies can indeed help to resist and reconfigure the thanatopolitical inflection of much biopolitical scholarship at present. I have highlighted how a vitalist sensibility contributes a much needed texturing to assessments and imaginations of the art and styles of the doing of governing today.

3.2. Contributing to Geographies of Science and Technology

Geographical scholarship has long tended to the agential vitalities of the more-than-human as a means of decentering the mantle of human exceptionalism. The political theorist Luigi Pellizzoni (2011: 802) has recently argued, however, that anti-essentialisms, indeterminacies and contingencies are overflowing 'from intellectual avant-gardes' and are being increasingly re-figured as an 'enabling' way to govern. One does not have to delve far into extant geographical scholarship in order to develop a sense of the ways in which indeterminate futures are now being folded into the present in ways that legitimate a power over (cf Braun, 2007; Amin, 2013). This is particularly the case when we turn towards the pre-emptive rationalities and the controversies that surround the stock-piling of vaccines and experimental work with highly pathogenic avian influenzas in the life sciences today.

In this thesis I have highlighted how whilst it is critically important that we attune and attend to these ontological re-figurings, there is a need to ensure that we do not efface heterogeneity and the generative interferences of multiplicity from the world. I suggest that, perhaps more than ever, we need to develop tools which are sensitive to these ontological reconfigurings - but tools which refuse to reify them - tools which are equipped with ‘goods’ and ‘qualities’ that work, amongst other things, to puncture the metaphysical grandeur of these claims and to provide new ways of articulating and joining things together differently. This is, I have suggested, geography’s way of making room and space for the cultivation of more affirmative and hopeful futures.

This thesis contributes to extant geographies of science and technology by opening up a series of ‘little narratives’ (Lyotard, 1984) or modest geographies of synthetic biology done in practice and in particular sets of relations. In tracing the meanderings, scramblings and branchings out of synthetic biology done in action and in process the thesis has reaffirmed the importance of tending to and giving breath to difference in the world. It has done this at a time when theorisations of preparedness and the biopolitics of security seem to leave little room for more affirmative and textured storyings of science in the making. Synthetic biology, as I highlighted in chapter two of the thesis, has found itself readily wrapped up in social scientific and biopolitical discourses of securitisation. This thesis has highlighted that this is by no means the only story to be told.

3.3. Contributing to Understandings of Regulation

Contrary to prevalent renderings of the ‘site’ of the doing of regulation as constituting either a ‘power over’ or a ‘power vacuum’ (Tombs and Whyte, 2013), I have argued in this thesis that there is a busyness to the doing of the business of regulation that we must be careful not to efface. I have argued that imbued within the busyness of the doing of the business of regulation, are rich resources for living together well. In chapter five of the thesis, for example, I highlighted how regulation is simultaneously about the delimitation of risk, the freeing up of innovation, the cultivation of relations, delimiting the spectre of the GM debacle and much more besides. In developing an account of the skills and affordances that are required to bring synthetic biology into a governable world, I have built upon the work of Bingham and Lavau (2012: 1589) who have posited that regulation is a task that requires a 'great deal of usually underrecognised, undervalued, and undertheorized articulation work.'

The prominent regulatory theorists Robert Baldwin, Martin Cave and Martin Lodge have recently argued that what makes the doing of regulation such an interesting practice and field of study is 'the rate of change that affects most affected regulated sectors' (Baldwin et al, 2012: 1993). This thesis complements and extends the work of Baldwin, Cave and Lodge by opening up a more spatialised account of the doing of regulation. It has highlighted how synthetic biology is contributing to a stretching and rescaling of regulatory responsibilities and distributions. The stretching and shifting of shape(s) of these responsibilities requires that HSE cultivate a rich repertoire of skills and affordances. Far then, from constituting any kind of power over or being undergird by a logic of constraint, this thesis has highlighted how regulation involves a much more intricate and lively suite of interactions, negotiations and goings on than many scholarly and biopolitical accounts of regulation have tended to acknowledge.

4. Final Thoughts and Future Areas of Research

Throughout this thesis accounts of the doing of synthetic biology in practice have been used to multiply outwards registers for understanding what this thing that synthetic biology is and what it might become. Synthetic biology in this thesis became about; the disorientating proclivities of the noisiness of the biological; the drawing together of different kinds of (multi)disciplinary sensitivities; the dis-assembling of hierarchical ‘truth’ claims; the development of new kinds of therapeutics and chemical products; the amplification of particular kinds of socio-technical imaginaries and much more besides. It is insufficient, therefore, to describe synthetic biology as simply constituting an intolerable hubris (Lewens, 2013).

This thesis has shed light on some of the more affirmative relationalities and dis/re-assemblings that are taking shape(s) within the developing trajectories of synthetic biology practice. To ‘keep pace’ with these dis/re-assemblings we must be ‘attuned’ to them (Roosth, 2010). We need to ensure, in other words, that our conceptual tools and theoretical repertoires are sufficiently equipped so as to be able to tease out and apprehend, the thickness and the intricate granularities of synthetic biology as it takes shape(s) within a busy and processually unfolding world. Our conceptual resources must work to add to, rather than to unduly prefigure, the form and the kind of the stories that we are able to tell.

The empirical generations that emerged during the course of this research enabled me to ‘map out’ an interesting set of geographies, entanglements and relationalities that are taking shape within the developing trajectories of synthetic biology practice. These are geographies that cannot be encapsulated or tended-to by the broad strokes of conventional biopolitical analysis alone. Neither can they be explored or apprehended by conceptual tools and sensitivities that gravitate towards and amplify what Sloterdijk (2005) refers to as the art and style of the moderns. Whilst, upon initial observation, synthetic biology might appear to extend even further yet, the drive for control and human mastery over the non-human world, the little narratives that I opened up during the course of this research tell a somewhat different story.

I have argued in this thesis that synthetic biology that presents a rich and fertile terrain through which to explore a number of contemporary issues of particular interest to the discipline of human geography and beyond. I have highlighted how it is insufficient, for example, to describe biological materialities as being simply 'recalcitrant' to the practices of synthetic biologists. Rather, there is a specificity and intensity to the nature of the encounterings between the sensibilities of an engineering approach and the stuff and substances of the biological that is generative of a number of different effects. These effects include the generation of a number of openings for new modalities of learning, apprehending and relating. Attending to these openings and reconfigurings is critically important, not least because, to return to the evocative language of the feminist philosopher and theorist Donna Haraway (1991: 172-173), lurking within these encounterings are 'emerging pleasures, experiences and powers with serious potential for changing the rules of the game.'

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Appendices

Appendix 1

Synthetic Biology Survey
HSE Policy Project

Please return to Katie.Ledingham@hse.gsi.gov.uk

Thank you for contributing to this survey which should take no more than 15 minutes of your time. This survey is part of a broader HSE policy project that is assessing the types of coordination and interaction that are necessary in order to realise the full potential of synthetic biology whilst ensuring its safe practice. All material submitted as part of this survey will be anonymised and held in accordance with the provisions of the Data Protection Act 1998.

SECTION 1: STAKEHOLDER INFORMATION

Title:	
Name:	
Email:	
Organisation Name:	

Organisation Type:

University [ ]; Research Institute [ ]; Commercial [ ]; Other [ ];

If 'Other' please specify: __________

SECTION 2: ACTIVITIES

1. Which area of synthetic biology best represents your current work?

Minimal Genomes [ ]; Synthetic Genomics [ ]; Orthogonal Biosystems/Xenobiology [ ]; Metabolic Engineering [ ]; Protocells [ ]; Regulatory Circuits [ ]; Other [ ];

In vitro [ ]; *In vivo* [ ]; *In silico* [ ]

If 'Other' please specify: _____________

2. What containment level are you working at?
Containment Level 1 [ ]; Containment Level 2 [ ]; Containment Level 3 [ ];
Containment Level 4 [ ];

3. **Will this change as your work progresses?**

Yes [ ]; No [ ]; Unsure [ ]

4. **If yes, how will this change?**

5. **Are you working with established organisms traditionally used in industrial processes?**

Yes [ ]; No [ ]; Unsure [ ]; Not Applicable [ ];

If you plan to work with novel alternatives please specify what these are:

____

6. **What is the end goal of your work?** [Please select all that apply]

Development of Synthetic Biology Parts [ ]; Building Information Networks and Databases [ ], Commercialised Product [ ]; Development of Synthetic Biology Techniques [ ]; Development of Synthetic Biology Tools [ ]; Other [ ];

If 'Other' please specify:_____________

7. **When do you intend to achieve this end goal?**

1-2 years [ ]; 3-4 years [ ]; 5-6 years [ ]; 7+ years [ ];

8. **Please list the role and academic discipline of the person responsible for conducting the risk assessment?** (e.g. Principal Investigator - Biochemistry) ______________

SECTION 3: RISK ASSESSMENT

9. **Is there a particular subset of synthetic biology which for you raises novel hazards?**

Yes [ ]; No [ ]; Unsure [ ];

If yes please specify which subset(s):______________

10. **How did you become aware of these hazards?**

Practical experience [ ]; Academic literature [ ];
Policy reports [ ]; Media [ ];
Other [ ];

If 'Other' please specify: ____________

Please list any key documents if applicable: _____________

11. Please select the extent to which you agree with the following statements:

Synthetic biology challenges one's ability to:

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Identify an appropriate risk comparator					
Assess the pathogenicity of the organism					
Determine any fitness costs to the organism					
Predict the extent of crosstalk					
Assess any potential deleterious effects to human health					
Assess any potential deleterious effects to the environment					
Determine credible mechanisms through which deleterious effects might be realised					
Assess any pleiotropic effects					
Identify appropriate containment measures					

If you have any comments on any of these statements please list them below:

12. Do you think that it is desirable to attempt to quantify 'novelty' as a means of assessing the risks associated with synthetic biology? *(E.g. the European Scientific Committee on Consumer Safety recently proposed that one way to do this is could be to establish a % threshold of the genome that has been chemically synthesised).*

Yes [ ];
No [ ];
Unsure [ ];

13. How would you attempt to quantify or ascertain the degree of novelty in your own work?

14. Can you think of alternative ways of identifying synthetic organisms whose risk assessment requires closer scrutiny?

SECTION 4: INTERACTIONS/CONNECTIONS

15. Pease select from the following options:

I seek guidance related to my work from:

	Almost always	Sometimes	Every once in a while	Rarely	Never
Departmental Safety Professional (e.g. Biological Safety Officer)					
Departmental Colleague					
Non-departmental Colleague					
GM Committee					
HSE					
Defra					
ISTR (Institute of Safety in Technology and Research)					
Synthetic Biology Networks					
Official publications					
Other					

If 'Other' please specify: ___________

16. Please list any resources that you have found particularly useful and their associated qualities (e.g. was it regularly updated?)

17. Is there a more effective way of delivering information to suit your needs?

18. Would you be happy for us to contact you for further information?

Yes [ ]
No [ ]

Thank you for your time.

Appendix 2

2015

Research Report for HSE

Building Competence and Safe Practice in Synthetic Biology:

Policy Orientations and Operational Considerations

Katie Ledingham, University of Exeter

Foreword:

This report has been prepared for HSE as part of a 12 month secondment from the University of Exeter to HSE's Biological Agents Policy Team, the Hazardous Installations Directorate's (HID) Policy Division. The report draws on a range of primary interview data and fieldwork materials generated during the course of the secondment.

Abstract:

This research report is a social scientific investigation into what it might mean for regulators and practitioners to work together to build competence and safe practice in the developing trajectories of synthetic biology. In drawing on a range of interview and fieldwork materials the report develops a more grounded understanding of synthetic biology and adds depth and texture to terms and categories such as 'risk' and 'novelty' which are frequently mobilised in synthetic biology discussions. The report argues that it is important to recognise that it is not always possible or desirable to 'reduce' risk simply through the 'accumulation' of knowledge. Rather, of greater importance are the qualities and nature of the connections and support mechanisms that exist between regulators and practitioners, the questions raised, knowing when to have a conversation and how to recognise and build upon experiences gained and lessons learned. In bringing these considerations to the fore, the report sets an agenda for considering how practitioners, regulators and interested parties might work together in order to cultivate and build confidence in a regulatory environment that is able to foster innovation in a safe, iterative and 'can do' manner. The considerations outlined in this report intersect with broader debates about what 'intelligent regulation' might look like within a goal setting framework when knowledge is indeterminate and incomplete.

Key terms: *synthetic biology, intelligent regulation, robustness in risk based approaches, scientific indeterminacy, knowledge, confidence, assurances, ownership of risk.*

Executive-Summary

1. In drawing on a range of interview and fieldwork materials, this report adds depth to and develops a more grounded understanding of the diverse and heterogeneous nature of synthetic biology work and the variable relationships between synthetic biology and risk.

2. Recognising this heterogeneity is an important first step in departing from understandings of 'synthetic biology' as a singular and homogeneous field of scientific practice and in disentangling a range of broader presuppositions such as the ready conflation of 'novelty' and 'risk.'

3. The report highlights, amongst other things, the propensity for synthetic biology to depart from existing comparative frames of reference and to enable non-proportionate and synergistic interactions between a range of biological parts and components.

4. The emergent propensities associated with synthetic biology do not necessarily make synthetic biology any more 'risky,' but rather raise interesting questions in terms of the assurances of competence and safe practice that we might subsequently expect to see enrolled in the undertaking of synthetic biology activities.

5. The report argues that it is important to recognise that it is neither possible nor desirable for risk to be 'reduced' simply through the 'accumulation' of knowledge. This is because there is an inherent indeterminacy and incompleteness that is endemic to and embedded within all scientific knowledge.

6. Indeterminacy and incompleteness in scientific knowledge stems from the contextual specificity of scientific experimentation and is amplified further in synthetic biology undertakings by the emergent and non-proportionate propensities of biological substrate.

7. Building confidence in synthetic biology means building capacity in the ways in which we acknowledge and address the inevitable gaps in scientific understandings of and evidence for risk. Where knowledge is necessarily incomplete, what becomes of critical importance are the nature of the connections and support mechanisms existent between practitioners, regulators and other interested stakeholders.

8. The connections as established throughout the course of this research helped to identify a proactive and safety conscious field of practitioners who are already thinking of ways to incorporate mechanisms for safe practice into their own work strategies.

9. ‘Intelligent regulation’ requires developing the methods, techniques and tools that allow for a productive engagement with practitioners and interested parties. This must be done in a manner that does not impinge upon the role and integrity of HSE as an independent regulator.

10. HSE’s long standing expertise in the legislative and practical implications of ‘inherently safer design’ places HSE in a unique position to engage with a number of developments in the field synthetic biology (e.g. safety switches).

Contents

Chapter 1: Introduction

1.1. The Need for this Report: Why 'Practice' Matters:

Since 2004 over 60 policy reports and in excess of 75 industry-led documents have been published on the topic of synthetic biology. The World Economic Forum Global Risks Report (2015) and the Council on Foreign Relations Risk Report (2015) are but the latest iterations of an increasing number of publications which have identified synthetic biology as an area of critical industrial and societal significance. Although many of these reports have played an important role in projecting some of the key issues associated with the development of synthetic biology, comparatively less attention has been afforded to developing a grounded sense of what it means to 'do' synthetic biology work in practice. Knowledge of what it means to undertake synthetic biology work in practice is critically important. Not only does it help to deepen our understandings of synthetic biology, but it also helps to assist regulators and interested parties in ensuring that their engagements with synthetic biology are proportionate, robust and rigorously informed. This report develops an attentiveness towards the undertaking of synthetic biology in practice and focuses specifically on the remit of HSE in delimiting the risks to human health and the environment posed by the undertaking of synthetic biology activities. In particular, it considers the mechanisms through which scientists and regulators might provide meaningful assurances of competence and safe practice as this area of life science experimentation continues to develop. In doing so, the report sets an agenda for considering how practitioners, regulators and other interested stakeholders might work together to cultivate and build confidence in a regulatory environment that is able to foster innovation in a safe, iterative and 'can do' manner. This is an important approach to take, particularly during a time when synthetic biology is becoming increasingly scrutinised by a wide range of institutions, organisations and international forums.

1.2. A Brief Introduction to Synthetic Biology:

Synthetic biology is a dynamic and powerful approach to biological engineering (RAE, 2014; ESC 2015). It has been described as one of the eight great technologies of the 21st century and its applications are projected to cut across multiple industry sectors ranging from the development of biofuels to synthetic chemicals, bioremediation technologies and medicinal products. Overall market forecasts for synthetic biology in 2018 are estimated to grow to USD 11.8 billion (BCC research in ESC, 2014: 11). As an emergent modailty of scientific practice, synthetic biology brings an engineering approach to bear on the 'design and construction of new biological parts, systems and devices' (Schmidt, 2009 in Bailey et al 2012). The concepts of modularity, standardisation and interoperability are routinely employed by practitioners in order to facilitate and intensify the possibilities for the design and modification of genetic and biological materials. Many scientists working in this area have described their work as attempting to enhance the predictability and efficacy of biological experimentation and are keen to emphasise the integration of pathways and regulatory systems into the design procedure. The development of synthetic biology can be attributed in part to a range of enabling technologies including computational modelling, infrastructures for the sharing of biological data and materials and advances in gene synthesis technologies. More recently, advanced assembly and editing techniques have been heralded as pivotal developments in helping to realise the potential of synthetic biology. Notable examples include 'Multiplex Automated Genomic Engineering' (MAGE) which allows for up to 50 genomic modifications to be made in parallel and the 'Clustered Regularly Interspaced Short Palindromic Repeats' system (CRISPR/Cas), which, through its use of RNA guided nucleases purports to enhance the precision of genomic modification at targeted sites in complex organisms (see, for example, Hisano et al, 2015).

Although the following list is by no means exhaustive and is likely to change as the field continues to develop, current subsets of synthetic biology can be broadly delineated into the following areas which utilise a combination of *in vivo, in vitro* and *in silico* approaches:

1. **Metabolic engineering.** Synthetic biologists in this area are working to enhance the complexity and precision of biosynthetic pathways for the production of a range of useful products and materials including biofuels and speciality chemicals. Perhaps the most commonly cited example is the production of the anti-malarial drug artemisinin. Much metabolic engineering employs optimised gene sequences with recent research proposing to use the whole genome instead of a gene-by-gene approach. Faulon (in Pauwels et al, 2013: 218) has recently distinguished between 'natural heterologous' approaches to metabolic engineering which use an 'insert or pathway from one donor organism in a host organism;' 'non-natural' approaches which use a 'pathway with different parts from different donor organisms' and 'new chemistry approaches' which mobilise 'evolving enzymes allowing new reactions with slightly different products and inserting genes coding for these enzymes into a host organism' (Pauwels et al, 2013: 218).

2. **Regulatory circuits**. Regulatory circuits have been defined by the European Academies Science Advisory Council (2010) as the insertion of 'well-characterised, modular, artificial networks to provide new functions in cells and organisms.' Whilst this definition may not seem too dissimilar to conventional genetic engineering undertakings, a distinct emphasis is placed upon regularity and predictability with practitioners incorporating functional devices such as oscillators into the engineering process in order to attain new levels of sophistication. The development of a toggle

switch by Gardner et al in 2000 and a biological clock by Elowtiz and Leibler, also in 2000, are regarded as two prominent early examples of functional experimentation which heralded the dawn of synthetic biology (ESC, 2015: 11).

3. **Orthogonal biosystems/Xenobiology**. Orthogonality within synthetic biology refers to the design and enrolling of non-overlapping or independent variables into broader biological systems such as the insertion of prokaryotic DNA into a eukaryotic cell. The overarching goal of an orthogonal approach is described by the Chin Laboratory (2015) as bringing 'a level of molecular, spatial and temporal precision – more typically associated with *in vitro* biochemistry – to the study of complex biological systems in their native, *in vivo*, context.' Xenobiology, as a particular subset of an orthogonal approach, is concerned with expanding the canonical 20 amino acid repertoire through the construction and use of artificial DNA (XNA). As noted by the European Scientific Committees (ESC, 2014: 15), XNA brings with it the potential to enhance the biochemical functionality of proteins and 'may offer new opportunities for the development of novel biocontainment systems.'

4. **Protocells**. Protocell research aims to develop synthetic cells that perform functions and various compartmentalised reactions that we would expect to find in a biological cell. Current research involves the examination of lipid and vesicle structures and the ways in which these structures give rise to cellular behaviour. The ESC (2014) has recently stressed that much of this work is currently in its early stages and exists in the domains of nanotechnology and chemistry so long as it does not produce living organisms. However, the ESC has further noted that the potential of protocells as precursors to synthetic cells and their ability to modify living organisms clearly qualifies them as part of synthetic biology research.

5. **Synthetic Genomics.** This area of research involves the synthesis of DNA and its subsequent insertion into a host organism. Developments in synthesis technologies mean that it is now possible to chemically synthesise DNA on the scale of entire bacterial genomes. Minimal genomes as a particular subset of synthetic genomics refers to the stripping down of microbial DNA to the lowest possible level that is required to sustain life.

A number of recent initiatives such as the Wilson Center's Synthetic Biology Project (2015) are attempting to develop a crowdsourced and regularly updated inventory of products and applications that enrol the emerging technology of synthetic biology.

1.3. Synthetic Biology's Regulatory Architectures:

The regulation of synthetic biology is covered in European Member States by the application of Directive 2009/41/EC of the European Council on the Contained Use of Genetically Modified Micro-Organisms and Directive 2001/18/EC of the European Council on the Deliberate Release into the Environment of Genetically Modified Organisms. European Directives 2009/41/EC and 2001/18/EC are implemented in GB through the GMO (Contained Use) Regulations (2014) and the GMO (Deliberate Release) Regulations (2002). Other regulatory frameworks of relevance to the development of synthetic biology include the Cartagena Protocol on Biosafety which specifically focuses on the transboundary movements of living modified organisms and the European Commission's (2000: 4) iteration of the Precautionary Principle as enshrined in the Rio Declaration 1992. This iteration has sought to avoid the 'unwarranted recourse to the precautionary principle, as a disguised form of protectionism' and has clarified that where a precautionary approach is applied, any precautionary measures must be proportional to the chosen level of protection, consistent with measures already taken and recognise that judging 'what is an "acceptable" level of risk for society is an eminently political responsibility.'

The central tenet of the GMO (Contained Use) and GMO (Deliberate Release) regulations concerns an assessment of the risks of a given activity to human health and the environment. Most synthetic biology work in GB is currently undertaken in accordance with the GMO (CU) regulations. Risk assessment of contained use activities is achieved through an evaluation of the characteristics of the GMO and its constituent parts which includes the recipient or parental organism, the host/vector system and the origins and intended functions of the genetic material involved.

Listed below is a brief account of the steps generally undertaken during the risk assessment procedure:

1. **Identification of biological hazards** – including an assessment of the host range of the micro-organism, its biological stability, the virulence of the strain and the availability/effectiveness of prophylactic or therapeutic measures.

2. **Consideration of the undertaken activity** – particularly in terms of exposure routes (e.g. potential for aerosolisation).

3. **Determination of risk class**– this involves assessing whether the GM activity falls into risk class level 1, 2, 3 or 4. Determination of risk class is informed by the control measures required to protect human health and the environment. Class level 1 refers to activities that are regarded as posing 'nil' or 'negligible' risk to human health and

the environment. Class level 4 refers to activities that are regarded as posing high risk to human health and the environment and includes, for example, work undertaken with Ebola virus and foot-and-mouth disease virus.

4. **Implementation of containment measures –** Containment levels 1, 2, 3 and 4 typically correspond with the class of risk. They require the implementation of mechanisms and processes to ensure protection to human health and the environment from any deleterious effects associated with the undertaken work.

(Source: European Scientific Committees, 2015)

The vast majority of synthetic biology work in GB at present typically falls into containment levels 1-2. HSE as part of GB's 'Competent Authority' is responsible for acting as an independent check on the assessment and undertaking of GM work. Under the provisions of the Health and Safety at Work etc. Act 1974, HSE is able to engage in enforcement action for any breaches which pose risks to human health and the environment. HSE typically focuses its resources at higher levels of risk and does not therefore individually review all risk assessments undertaken at the lower levels of containment. For the assessment and review of contentious or unusual GM work, the Scientific Advisory Committee on Genetic Modification (Contained Use) (SACGM (CU)) provides technical and scientific advice to HSE. It should be noted that the implementation of the GMO (CU) regulations operates within the context of a goal setting framework. This means that although the regulations stipulate a series of minimum requirements that duty-holders must achieve, there is flexibility in terms of the procedures and mechanisms through which duty-holders attain those requirements. In terms of the risk assessment process for deliberate release activities involving GM plants, the European Food Safety Authority (EFSA) provides guidance on and requires an assessment of the following considerations; hazard identification; hazard characterisation; exposure characterisation; risk characterisation; risk management strategies; overall evaluation and post market environmental monitoring. Hazard characterisation is typically informed by an assessment of the invasiveness of the GM plant and the potential for interaction with non-target organisms. This is determined in part through a consideration of the non-modified parental organism as a comparator. GMO derivatives are not organisms capable of continued propagation and are not therefore covered under these regulations.

1.4. Terms of Reference/Methodology:

The aim of this report is to consider what it might mean for scientists and regulators to provide assurances of competence and safe practice in the emerging field of synthetic biology.

Its objectives are to:

1. Develop a more grounded sense of what it means to carry out synthetic biology in practice.
2. Account for the implications that this poses in terms of the development of safe practice.
3. Consider what it might mean to build competence and confidence in synthetic biology from a scientific and regulatory perspective.

In order to meet the requirements of these objectives the report draws on a multi-method approach consisting of the following:

- Over 30 1-2 hour interviews with a variety of key stakeholders. This has included interviews with a diverse range of synthetic biology practitioners operating across commercial and academic sectors and with a variety of biological materials and approaches. Representatives from GB regulatory authorities including the Health and Safety Executive, the Department for Business Innovation and Skills and Defra have been interviewed, as have representatives from the UK's key synthetic biology infrastructures including the Synthetic Biology Leadership Council and the British Industry Association.
- Analysing the responses from a survey on synthetic biology sent out across GB GM registered premises and synthetic biology interest networks. This provided an opportunity for interested organisations and individuals to explain the nature of their work and to share their reflections on synthetic biology more broadly.
- Analysing the responses submitted to the consultation on the consolidation of the GMO (Contained Use) Regulations which came into force in October 2014.
- Attendance at key regulatory meetings including the Scientific Advisory Committee on Genetic Modification (CU) which has brought a broader regulatory perspective to bear on the issues under consideration.
- A review of recent policy and social science literatures concerned with examining the developing field of synthetic biology.

- Analysis of the above materials was determined through the categorisation of text into codes which reflect and summarise the content of the fieldwork material. These codes were continuously re-evaluated through an iterative process of review.

Chapter 2: Working with and Accounting for Variation in Synthetic Biology Practice

2.1. Recognising Heterogeneity in Synthetic Biology Practice

Section Overview:

- Synthetic biology is not a singular and homogenous field of scientific endeavour. This section of the report draws on a range of interview material in order to provide an overview of synthetic biology's heterogeneity.
- Starting the report in this way helps to add depth to and move beyond generic statements such as synthetic biology either 'reduces' risk through its utilisation of standardised, well characterised parts, or rather 'increases' risk through, for example, the unintended consequences of environmental release.
- The heterogeneity that underpins synthetic biology stems from the different understandings and approaches to synthetic biology which, in combination, enact different 'versions' of synthetic biology. These different versions of synthetic biology do not always overlap and prioritise different ways of approaching the work being undertaken.
- It is through developing an awareness of this heterogeneity that it becomes possible to shed light on some of the underpinning tensions associated with synthetic biology. These tensions include differences in understandings of and approaches to the nature and significance of the risks attributed to the practice of synthetic biology.
- An appreciation of these tensions is a critical prerequisite in enabling the report to open up and set an agenda for considering how regulators, practitioners and other stakeholders might work together in order to build confidence in the developing trajectories of synthetic biology.

2.1a) Differences in Practitioner Understandings of the Scope and Significance of Synthetic Biology:

Listed below are examples of differences in practitioner understandings of synthetic biology. These examples have been identified through an iterative coding of the interview transcripts and reflect the range of practitioner understandings as encountered throughout the duration of the research project. It is important to acknowledge these differences in practitioner understandings for a number of reasons. First, each of these understandings is imbued with different presumptions about the nature and implications of the development of synthetic biology. Second, these understandings are not simply matters of opinion, but are also enrolled in local approaches to the practice of synthetic biology. Recognising these differences is therefore an important starting point in opening up new questions about what it might mean to build competence and confidence in this developing area of life science experimentation.

Example One: Synbio as an Incremental Advance on GM

For Practitioner No.15 synthetic biology is *'genetic engineering under a new name.'* Practitioner No.12 relatedly noted that *'I don't see anything that strikes me as on a different dimension to conventional genetic engineering'* and Interviewee No.3 reflected on how *'I don't know if there's any specific new tool which would come under the sort of synbio definition which is some way different to what we've been seeing before.'* In these examples, synthetic biology is regarded as an incremental advance that builds upon an extensive lineage of genetic modification work that has been undertaken since the 1970s. Here, specific DNA fragments are inserted into a host genome with the intent to perform particular functions. As with conventional GM work, the nature of the recipient or parental organism and the origins and intended functions of the genetic insert retain their significance in determining the nature and implications of the work being undertaken. Synthetic biology is not therefore regarded in these instances as posing any unique risks or challenges to the assessment of potential deleterious effects to human health or the environment. Any challenges posed by synthetic biology exist more in the realm of administrative rather than scientific considerations. As, for example, was expressed by a respondent to the GB GMO (CU) consolidation consultation, it might be in some instances that the use of synthetic RNA or DNA in synthetic biology activities is better described in terms of the '*manipulation'* rather than the '*modification'* of genetic elements.

Example Two: Synbio as a Combination of GM and Systems Biology

Practitioner No.17 asserted that *'if you wanted synthetic biology to be something more than genetic engineering then you have to definitely include XNA and protocells and metabolic engineering because then it is not just genetic engineering, it's biological engineering… or cellular engineering… but to me it's in a way a more wholesome view of genetic engineering actually, of engineering biology.'* Practitioner No.14 similarly regarded synthetic biology as a *'systems based approach rather than focussing on genetic modification'* and Practitioner No.15 concluded *that 'if you want to engineer biology you consider all the options.'* The significance of this more 'wholesome' understanding of synthetic biology is that it decentres the overarching emphasis that Example One placed on the genetic component of synthetic biology work and rather gestures towards the broader relations that exist between wider biological parts and components. This particular understanding therefore provides a suggestive window onto the nature of synthetic biology's relationship with scientific and technical considerations including the wider interactions '*not just genetic, but also physical and chemical,*' which, as described by Practitioner No.1, *'play out'* and reverberate across the architecture of modified organisms. These wider interactions include cross talk and pleiotropic effects where one gene can be implicated in multiple phenotypic traits.

Example Three: Synbio as an Acceleration of GM

Practitioner No.19 positioned synthetic biology as increasing the 'scale' and 'speed 'of genetic engineering. This Practitioner noted that *'people are making multiple modifications in parallel at any one time and even getting to the point where they are creating systems which are almost 50/50 with parts from one organism and parts from another.'* Synthetic biology is rendered here as a widening of the scope and extent of genetic engineering. Implicit therefore to this understanding of synthetic biology is a departure from, or rather a decentering of, the relevance and/or necessity of the parental organism which, as noted previously, is one of the key components through which recombinant DNA work is understood and assessed. Practitioner No.19 further noted that the *'emphasis on saying what is the parent DNA of the construct… that might need to change to being what is the parent coding of this construct, whether it be amino acids or the way RNA folds, or, you know, the content of a phage… because if you just did a mechanical match DNA sequence to DNA sequence you can have especially for phage the entire genome being no match for the genome.'* Similar sentiment was also expressed by Practitioner No.7 who reflected on how *'the traditional genetic modification I think was written for this view that people would be adding a gene or maybe two and that legislation was written in the 90s when that was what was technically possible. Now we're talking about… essentially rewriting a genome from scratch… and that's a very different ball game.'* The scale of these changes gestures also towards what Practitioner No.7 described as the potential '*difficulties'* associated with determining the effects on these changes on the modified organism.

Example Four: Synbio as Controlled Experimentation

Practitioner No.8 understood synthetic biology in aspiring to achieve enhanced regularity and precision in biological endeavours, noting that '*the point of synthetic biology is to try and define things as well as possible.'* This practitioner expressed that *'it is very clear what a GM organism is, it should be equally clear what a synthetically engineered organism is and it should be something that's more targeted and less hit and miss…. it should be pathway…it should not just be gene gene and it should be about regulatory systems and things like that.'* Similarly, Practitioner No.10, who was combining a range of biological parts and components in order to optimise and streamline the degradation of TNT, explained that '*rather than testing to find out what it does, it's to see if it works as we think and if we can make it better.'* This practitioner further noted that *'more than* *predicting, you give it regularity.'* Synthetic biology in these circumstances is posited as being more than the recombination of genetic parts; it also involves 'refactoring' and processes of 'redesigning' in order to attain new levels of experimental efficacy. Similar sentiment was echoed by Practitioner No.9, the founder of a synthetic biology start-up company, who described the work of this company as *'engaging complexity through quantitative and systematic approaches to genetic design.'* Implicit to these understandings is the presumption that synthetic biology brings with it enhanced levels of predictability and control in biological endeavours. As Interviewee No. 2 explained *'synthetic biology is about bringing our understanding of biology into a more predictive and less empirical realm.'* Interviewee No.3 similarly posited that it's a *'much more accurate way of doing genetic engineering, genetic engineering which we've been doing for millennia… we understand it rather than just guess work or as I say mutagenesis.'*

Example Five: Synbio and Emergence

Not all practitioners regarded synthetic biology in terms of its propensity to enhance levels of control and predictability. Practitioner No.17, for example, asserted that '*it is still so hard to predict the outcome of any transformation you do…. you can like look at it and theoretically read all the literature and you can say well this protein is supposed to do this, this protein is supposed to do this, but when you actually put it into an organism and all the proteins start interacting with all the other proteins then actually… you can't predict that.'* It was also recognised by a significant number of practitioners that achieving the scientific objectives that underpin specific synthetic biology experiments is a laborious process, even with the added assistance of computational and automation tools and techniques. As Practitioner No.8 put it *'the funny thing about biology is that it's incredibly boring most of the time… it sounds like we're doing all this amazing stuff…. But it takes months and years and it's a daily job… you know a twelve hour day and things like that for an extended period of time...to actually get a meaningful result and it's not something you can easily do in your kitchen..'* Inherent to these particular understandings of synthetic biology is therefore an awareness of and appreciation for the challenges of working with self-replicating and emergent biological substrate. This is appreciation which co-exists alongside an acknowledgement of the wider aim of synthetic biology to facilitate the conducting of experiments in what Practitioner No.7 described as *'a more rigorous way'*.

2.1b) Differences in the Substances, Sites and Approaches to Synthetic Biology Practice:

The differences in understandings of synthetic biology as listed above are not simply a collection of varying perspectives on a singular 'synthetic biology.' Although practitioners of synthetic biology in GB have to work within the parameters of the legislative framework as outlined in Section 1.3 of this report, it is also important to recognise that there are different ways of practising synthetic biology which do not always overlap. This a realisation which becomes increasingly apparent upon attending to the differences that cut across the **substances** enrolled in the practice of synthetic biology, the **sites** where synthetic biology work is taking place and the **approaches** that shape the undertaking of synthetic biology experimentation. The following examples provide a brief and indicative illustration of some of these differences. The implications of these different practices and of the different understandings as outlined in Section 2.1a are discussed in the next section of the report.

Example One: Optimisation and Industrial Intensification

Practitioner No.9 foregrounded the commercial-industrial potential of synthetic biology and expressed a preference for bringing a synthetic biology approach to bear on substances and organisms traditionally used in industrial processes. This practitioner noted that *'there's a huge emphasis on using strains that are either E.coli you know generally recognised as safe…. it all boils down to consumer demand in a lot of instances.'* Similar sentiment has also been documented by Jewett and Forester (2010) who provide an account of the use of Biosafety Level 1 'minimal risk' organisms in a range of industrial endeavours and identify a movement towards stripping down the genomes of these organisms/'biotechnology workhorses' into 'minimal cells.' This minimises 'the metabolic burden on the cell, so the remaining cellular energy can be directed forwards the manufacture of a desirable industrial product, such as an industrial chemical or a pharmaceutical (Pyne et al, 2011 in ESCS, 2014: 27). In a related vein, Practitioner No. 7 described bringing a synthetic biology approach to bear specifically on thermophilic organisms. These are organisms which typically cannot be cultured below fifty degrees centigrade and which can be used to complement and extend biological work undertaken within existing chemical engineering infrastructures.

Example Two: Standardisation, Automation and Multivariate Approaches to Experimentation

Interviewee No.3, practitioner and CEO of a synthetic biology start-up is working to utilise synthetic biology in order to advance the professionalisation of biology. This practitioner expressed frustration at the *'artistic'* nature of biological experimentation as exemplified by '*pipetting'* and the conduct of laboratory practice in a similar fashion to the way it was conducted *'a hundred years ago… it's error prone, it costs too much, it takes too long.'* Above all, this practitioner expressed that *'you cannot build on collective knowledge when only 10% of it is reproducible.'* For this practitioner *'a big sea change is coming in terms of the development and advancement of standardised biological parts and protocols'* and we are *'still just scratching the surface in terms of what biology is capable of.'* This particular practitioner is working towards realising the professionalisation of biology through the enrolling of computational and automative tools into the experimental process and enhancing the interoperability and modularity of biological parts and protocols. Interviewee No.3 is also employing multifactorial approaches in order to optimise gene and environmental factors simultaneously. This practitioner critiqued conventional strategies to biological engineering for optimising genetics and then environmental variables, explaining that *'normally people use 5 maybe going up to 7 factors… we've pushed our methods as 30 factors where we look at the genetic factors and process factors at the same time.'*

Example Three: Orthogonal Systems

A number of practitioners are utilising the precision and efficacy associated with synthetic biology experimentation in order to develop organisms with a view to interacting in broader ecological environments. Practitioner No.12 is bringing a synthetic biology approach to bear on the design of GM mosquitos and noted that *'people are interested in genetic control because they haven't got other means of controlling the stuff that needs to be controlled… like mosquito borne disease… and major agricultural pests… there's a very clear need for more precise methods … a lot of chemicals as you probably know are under threat from a loss of registration… genetics has a whole load to offer in that area*.' Underpinning these developments is the concept of 'orthogonality' which refers to the construction and utilisation of non-overlapping, independent biological parts which are constrained in their ability to function outside of pre-defined parameters. Practitioner No.10 explained, for example, in relation to the development of novel base pairs that '*you're not controlling nature but creating a manmade system that has changed so much that you have complete control… if you put these into a mouse the mouse wouldn't know what to do with them but we would.'*

Example Four: Expansion

Practitioner No.7 reflected on how the precision associated with synthetic biology may facilitate a movement from work on '*well understood low ris*k' model organisms to '*more medically relevant organisms'* with greater metabolic potential. This practitioner expressed concern at recent experimental work undertaken on *Streptococcus* *agalactiae*, a pathogen of *'a not inconsiderable number of neonates and expectant mothers in the UK.'* Practitioner No.1 similarly reflected on the ways in which synthetic biology is transforming the substances and potentialities of biological experimentation with a particular reference to plants. This practitioner described how synthetic biology is opening up a *'new generation of plant experimentation'* where *'you can apply the same kind of tools that you can with yeast and bacteria because you've got these haploid genetic approaches and single cell handling which allow you to do quite radically different things… you've got the benefits of working with a microbe.'* For Practitioner No.1 synthetic biology allows practitioners to conduct experimental work on lower plants whose default is to regenerate and to produce *'millions of spores that you can collect and each one of them is the equivalent of a seed… you can handle individuals by liquid handling… you can use robotics and you have the ability to scale up the kind of genetic modification techniques developed in higher plants.'*

Example Five: Non-Conventional Spaces of Experimentation

Practitioner No.9 highlighted how synthetic biology is making the underpinning process of biological experimentation 'easier.' It is this purported 'deskilling' of biology that can be implicated in the movement of synthetic biology into non-conventional spaces of work such as community laboratories and/or private residences. It can also be implicated in what Practitioner No.9 identified as the development of an increasing number *'of young start-ups…myself a perfect example… people who don't know the first thing about the practicalities of getting GM approved.'* Chapter 3 of this report will come on to highlight the risk management implications that are posed by these developments. It is important to note, however, that the renderings of DIY bio as projected in wider discussions are considerably different to the accounts and versions of DIY bio that emerge from attending to what DIY bio looks like in *practice*. Section 3.1 addresses these considerations in further detail and attends also to the question posited by Interviewee No.10 - *'how does regulation keep up with the fact that these tools are becoming faster and cheaper and more accessible to people, whether they are formal researchers or whether they're informal researchers?'*

Example Six: Disciplinary Divergence

Local practices and approaches to synthetic biology activities are also influenced by the disciplinary backgrounds of those undertaking the work in hand. For Practitioner No.1 it is critical that biologists play a leading role in shaping and overseeing synthetic biology experimentation. This practitioner noted that *'the fact that the term chassis is used… is a certain cavalier disregard for complexity of system which can go pear shaped quite quickly, particularly if the person, the engineer is not a biologist.'* Similarly, Practitioner No.7 described collaborating with biologists who are *'migrating towards the chemistry* *engineering end rather than the other way.'* These particular examples stand in contrast to the working practices described by Practitioner No.20, who reflected on the tendency of one Principal Investigator to hire *'engineers not bioengineers but hard core engineers.'* Of the 23 respondents to the survey component of this research project, most if not all respondents had a background in molecular biology. Practitioner No.9 reflected on how *'you're going to see a lot of people entering the discipline… from other areas…I don't know but maybe the HSE stuff is aimed at microbiologists or so on and so forth. I'd be interested to know how anybody entering the field with say more of a physics slant or something like that would be able to utilise and interpret the documentation.'*

2.1c) What are the Implications of this Heterogeneity?

Sections **2.1a** and **2.1b** of the report have demonstrated that synthetic biology is not simply a singular field of scientific endeavour. Attending to synthetic biology's heterogeneity is important in highlighting the following:

i. Synthetic biology is understood and practised in different and occasionally non-overlapping ways. It is not as simple therefore as to assert that synthetic biology either 'reduces' risk through its utilisation of standardised, well characterised parts, or rather 'increases' risk through, for example, its role in the purported 'de-skilling' of biological experimentation.

ii. Wider deliberations must be informed by the undertakings of synthetic biology work in practice. Chapter 3 of this report considers how HSE might further develop its understandings of and awareness of synthetic biology in practice. It is only by attending to synthetic biology in practice that it becomes possible to develop a more grounded understanding of this developing field of life science experimentation.

iii. Acknowledging the complexity and variegated nature of synthetic biology as charted in Sections 2.1a and 2.1b is critically important in adding depth to wider discussions and in disentangling a number of wider presuppositions such as the ready conflation of novelty and risk.

    Interviewee No.10, for example, noted that '*novelty is perceived as a risky thing… that is not necessarily the case and I think we have to get outside that mindset*.' Similarly, as noted by a respondent in relation to the tentative proposal made by the European Scientific Committees that 'novelty' could be quantified through, for example, the percentage of a genome that has been chemically synthesised, *'I am not sure that attempts to quantify novelty in this manner are desirable. Y.pestis is 0% chemically synthesised, but not a desirable organism to* *manipulate! A mature risk assessment by experts seems a more sensible approach.'*

iv. The dynamic and proliferating nature of synthetic biology experimentation means that it is critically important that the responsibility for managing risks, as outlined in the Roben Review of HSE's approach to regulation of 1972, rests with those undertaking and most familiar with the work in hand.

v. As noted by Practitioner No.2 it is also important that *'you really have to just take it [the risk assessment process] as a case by case. That's hard, expensive, but if you're serious, you're going to have to have the mechanisms in place and spend the money to do it.'*

vi. HSE has considerable experience in assessing GM experimentation on a case by case basis and in inspecting the implementation of risk management strategies at premises conducting GM work.

vii. Nonetheless, given the considerable differences that surround practitioner understandings of the implications of synthetic biology it is important to examine these differences further and to consider what it might mean for regulators and practitioners to work together to provide assurances of competence and safe practice.

viii. The differences in understandings as charted in Sections 2.1a and 2.1b do not therefore need to be overcome but rather provide an important platform upon which to consider what it might mean to build confidence in this developing area of life science experimentation.

2.1d) Additional Considerations of Relevance to HSE:

Listed below are a number of additional considerations raised in Sections **2.1a** and **2.1b**:

Administrative Considerations:

i. These include the sufficiency of the legislative and regulatory frameworks in adequately capturing the diversity of synthetic biology experimentation.

ii. Whilst the consolidated GB GMO (Contained Use) Regulations 2014 recently clarified that contained use synthetic biology activities in the UK are covered under these regulations, it is likely that administrative and definitional questions will continue to shape national and international policy deliberations.

One respondent to the GMO (CU) 2014 consolidation noted that '*it might be possible that an entirely self-assembling and subsequently self-replicating construct derived solely from synthetic RNA or DNA with appropriate medium* *could escape the current definition of a GMMO as per abiogenesis research as it is not "modification" of any kind but rather is "creation."* This respondent posited that it might be more appropriate to describe the undertaken work as the '*manipulation'* rather than the '*modification'* of genetic elements.

Interviewee No. 10 similarly expressed with respect to the Cartagena Protocol on Biosafety that *'Cartagena talks about a living modified organism, but if you look at that you realise very quickly that many entities constructed in labs are not living modified organisms by that definition… they might be highly modified quasi biological systems, some of them may be self-replicating some of them may be printed onto circuit boards, some of them may be free living in a solution of some kind doing some industrial process… some may fall within the definition of a living modified organism others may not… they may be hybrids between biological systems and electronic systems… they may be biological systems that are based on different base pairs.'*

iii. Other relevant considerations include whether or not it will become necessary to incorporate more explicitly a risk-benefit analysis into the risk assessment process.

Interviewee No.10 asserted that *'there has to be a balance of risk against benefit because I think that is... it's honest'* and similarly Practitioner No.12 explained that *'I think if you only consider risk you are in effect comparing your actual use with a hypothetical risk free world.'*

Scientific and technical considerations:

i. These include the propensity for synthetic biology to raise scientific and technical considerations including the enabling or amplification of pleiotropic effects, cross talk and a distancing from the parental or recipient organism as a tool for determining the characteristics of the modified organism. There is considerable difference in practitioner understandings of the scope and significance of these variables.

ii. This raises a series of implications in terms of HSE's interest in the risks to human health and the environment posed by synthetic biology and is a key tension that is examined in Section 2.2 of the report.

Interviewee No.10 expressed that *'we do have a real challenge for the scientific and regulatory community. How do we assess the important characteristics of self-replicating entities in the future? How do we actually assess those to the point where we can actually apply regulations to them? In other words what is the minimum set of information that we require from those entities in order to apply regulatory systems?'*

Risk management issues:

i. These include the movement of synthetic biology into a number of increasingly differentiated environments including non-conventional spaces of work such as community laboratories and the release of synthetically engineered organisms into broader ecological environments. The undertaking of genetic engineering activities in community laboratories and/or ‘DIY’ workspaces is addressed in Chapter 3 of the report.

ii. Also of relevance here are the variable understandings of synthetic biology which influence practitioner approaches to the undertaken work. It is important for HSE to develop an appreciation of the understandings as charted in Section 2.1a. This is because these understandings are not simply matters of opinion - as highlighted in Section 2.1b they are also enrolled in local approaches to the practice of synthetic biology.

As, for example, Practitioner No.7 noted in relation to the construction of synthetically engineered organisms designed to function within the confines of a defined set of parameters *‘now maybe when we start talking about these very safe organisms where they’re disabled, their ability to survive outside culture is pretty much none existent in the wild then even their ability to be conjugating things between different organisms is quite low then we might feel that we have a much more latitude to be doing things without worrying about what’s going on.’*

2.2. Acknowledging the Emergent Propensities of Biological Substrate and Indeterminacy in Scientific Knowledge

Section Overview:

- Of particular interest to the remit of HSE are the differing understandings of and approaches towards the risk implications of synthetic biology. This section of the report draws on a range of empirical material in order to investigate this tension further.
- In particular, it highlights the propensity for synthetic biology to depart from existing comparative frames of reference and to enable non-proportionate and synergistic interactions between a range of biological and non-biological parts and components.
- What makes these propensities significant is that they cannot always be fully captured or addressed by risk based calculations alone. This is because 'risk' is a particular type of knowledge that relies upon the identification of specifiable parameters in order to define the likelihood of a particular hazard occurring.
- The 'emergent' nature of these propensities means that there is an inherent indeterminacy and fundamental limit to the amount of knowledge that can be accumulated in order to reduce these risks.
- Rather than being necessarily indicative of a 'risky' activity, an awareness of and proactive engagement with this indeterminacy can be used to enhance the robustness of a risk based approach. Indeed, as has been highlighted by an increasing number of social scientists, the limiting commitments and assumptions inherent to scientific practice only become a problem 'when external commitments are built on it as if such intrinsic limitations did not exist' (Wynne, 2006).
- This section of the report provides a brief account of the ways in which practitioners are addressing these propensities and considers what other mechanisms and approaches might be mobilised in order to build confidence in this developing area of life science experimentation.

Section 2.1 of the report highlighted how for some practitioners, synthetic biology does not pose any unique risks or challenges to the assessment of deleterious effects to human health or the environment but rather brings greater predictability into the experimental process. It also highlighted how for others, the scale and scope associated with this emerging approach to genetic engineering necessitates a precautionary approach. This section of the report opens up these differences in practitioner understandings and approaches towards the risks associated with the practice of synthetic biology. It has been suggested in a number of publications and wider deliberative forums that in order to address uncertainties surrounding the purported implications of synthetic biology there is a need to increase the characterisation of biological parts and to develop tools for the streamlining of relevant information. Whilst these are critically important undertakings, this section of the report provides an account of how and why it is important to recognise that there is an inherent indeterminacy and fundamental limit to the amount of knowledge that can be 'accumulated' in order to determine and 'reduce' risk. Building confidence in synthetic biology also means building capacity in the ways in which we acknowledge and address this indeterminacy.

2.2a) Practitioner Accounts of Difficulties in Predicting and Assessing the Risks Associated with Synthetic Biology:

The following examples provide a brief snapshot of issues raised by practitioners when predicting and assessing the risks associated with synthetic biology experimentation. These challenges associated with assessing the credible mechanisms through which deleterious effects to human health and environment might be realised do not necessarily make synthetic biology any more 'risky,' but rather raise interesting questions in terms of the assurances of competence and safe practice that we might subsequently expect to see enrolled in the undertaking of synthetic biology activities.

i. **Practitioner No.17** reflected on how, as with conventional genetic engineering approaches, it can be *'hard to predict the outcome of any transformation you do… you can like look at it and theoretically read all the literature and you can say well this protein is supposed to do this, this protein is supposed to do this, but when you actually put it into an organism and all the proteins start interacting with all the other proteins then actually… you can't predict that.'*

ii. **Interviewee No.6** expressed that *'I think synthetic biology has got the potential to make more significant changes whether that's in terms of numbers or just entire parts of a genome that could have effects that are a lot harder to predict…biological systems don't always behave like circuits do and electronics.'* This interviewee further noted that *'when you think about knocking something out or stopping the function of something… it might make it worse in terms of evolutionary fitness but not necessarily in terms of the damage it could do… I think having a number on changes is a dangerous route to go down.'*

iii. **Practitioner No.7** similarly noted that *'the number of genetic changes you're talking about making are really quite large and therefore the effects you're going to have on the organism are I think quite unpredictable and people have seen that one of the outcomes of systems biology has been that if you do a knock out on a certain gene you often see that the effects that you get are not the effects you expected to get,* *particularly where metabolism's concerned.'* This practitioner also expressed concern in terms of the stripping down of an organisms genome, noting that some of the most *'dangerous pathogens have significantly reduced genomes.'*

iv. **Practitioner No.12** emphasised difficulties in ascertaining the nature and implications of wider interactions between biological parts and components noting that *'we tend not to talk so much about cross talk which is a quite a big problem and modules are only modular up to an extent…this one works in this particular context but if you put this other one next to it you've changed its context and so you change the function of you know Part B because you have put Part A in front of it.'*

v. **Interviewee No.10** reflected on the construction of a partially synthetic bacterium by the Craig Venter Institute and remarked *'do we say Mycoplasma has a chromosome which is similar to its ancestor… even though it's fully synthetic… what if there is any epigenetic effects… do we actually know that a chromosome is going to behave like the ancestor even in the basal metabolic processes… we don't know that and have no way of knowing that really.'*

The following assertions were made in relation to the potential challenges associated with the enrolling of synthetic biology approaches in specific commercial and experimental undertakings:

vi. **Practitioner No.7** reflected on how difficulties in predicting the risks associated with synthetic biology may become more challenging as synthetic biology is brought to bear on higher risk organisms**,** explaining that '*I think the position now is people are mostly talking about this in model organisms…very well understood, low risk levels… once we have the tools that will change very quickly to potentially to medically relevant organisms that have a greater metabolic potential in the first instance and at that stage almost any form of regulation goes out the window because you have no idea what's going on.'*

vii. **Practitioner No.10** asserted that *'Craig Venter produced a chromosome a very simply chromosome which placed in a cell boots up and appears to work… that is a very conservative approach to synthetic biology… in the future synthetic biologists won't be thinking like that at all. They will be thinking much more in the way of how can we design a chromosome or some other entity that works within a cell, but has nothing to do with the natural ancestor of that cell... so there won't be any wild ancestors, and therefore if you want to apply conventional risk assessment it is not going to work because you don't have any background by which you can assess things like ecological characteristics of just growth counters, simple stuff.'*

viii. **Interviewee No.3** drew attention to the unpredictabilities associated with the industrial scale up of synthetic biology activities and reflected on how *'a lot of companies have found that… these strains… when they try and put them into a 30 000 litre reactor they behave in completely different ways.'*

ix. **Practitioner No.4** similarly reflected on the challenges associated with scale up noting that '*we've been growing microalgae down here for years... the move towards synthetic biology and the increased capability we now have in being able to genetically modify microalgae has exposed a gap in our ability to assess the new risks… growth at 100-1000ml scale, whilst a useful starting point, is often irrelevant when the strains are being developed for industrial purposes… we can learn from the plant community that have been through this over the past decade, however there are microalgae specific factors that we need to be aware of: a plant is relatively easy to control because it doesn't move around too much; algae sloshing around in large volumes of water are surprisingly easy to disperse, including the generation of aerosols. And scale up is associated with loss of containment e.g. a raceway pond (millions of litres in volume) is commonly used in industry already for microalgal growth. But as soon as you start talking about GM algae in a raceway, environmental contamination (wind, storms, birds, leaks) is not feasibly avoidable… The potential problem is the inevitable impact of the release of such organisms. It may not be a problem, but it is very difficult to predict.'*

x. **Interviewee No.10** felt that any difficulties in assessing risks to human health and the environment would be compounded further when it comes to the deliberate release of synthetically engineered organisms. This interviewee questioned '*How will these things behave if either we deliberately put them out or they get out in some way? We need to know the answer to that in order to build public confidence. Otherwise synthetic biology will not fly the way it should fly. It is going to be bogged down in the concerns, opposition and regulatory gloom basically and I think a lot of researchers feel like that they feel a sense of trepidations about how regulation will be applied in the future, and maybe that is having an effect on the research agenda. People may be choosing easy stuff within the regulatory sphere rather than stuff that might be a bit of a challenge. So I think this is a key issue.'*

xi. **Practitioner No.11** posited that '*our current activities and techniques can be adequately addressed using existing GM risk assessment techniques although it is foreseeable in the future, developments in synthetic biology, may need a more tailored approach. Assessment of potential risks following release into the environment could pose a particular challenge as there is less experience in this area.'*

The significance of the examples as listed above is that they are underpinned by an acknowledgement of the propensity for synthetic biology to a) enable non-proportionate and synergistic interactions between a range of biological parts and components and b) to depart from pre-existing comparative frames of reference. This can be partially attributed to the self-replicating qualities of biological substrate and to the embedding of synthetic biology activities within the broader relational architecture of a host organism where, as described by Practitioner No.1, the organismal traits and characteristics are '*not determined by the DNA alone, rather the DNA encodes the interactions in concert with the physical system.'* Pauwels et al (2013), for example, have recently drawn attention to the complexities of the signalling functions associated with metabolites and the wider interactions that exist between non-target biological components in genetic modification activities. Within the context of deliberate release activities, wider interactions with non-target species and positive selection pressures may also delimit the effectiveness of built in safeguards such as auxotrophy and kill switches (ESC, 2015). It is for these reasons that the ESC (2015: 6-7) has recently asserted that 'a blue print of a general strategy for designing inherently safe applications of SynBio is demanding, because of the stochastic and probabilistic character of the underlying biochemical SynBio processes.'

The propensity of synthetic biology to depart from pre-existing frames of reference does not simply relate to the de-centering of the parental organism. It also has relevance to other synthetic biology undertakings including the development of protocells where, for example, aspects of the transmissibility of information still apply even when there is no genetic material present. Further examples include the use of non-standard biochemical systems in living cells (ESC) and the enrolling of synthetically engineered organisms in industrial activities at unprecedented scales. It should be noted that both the significance of a) the emergent propensities of synthetic biology and b) the implications associated with synthetic biology's departure from pre-existing frames of reference are widely contested. The ESC (2015: 26), for example, have recently highlighted how 'even the most complex organisms created by humans are genetically close to their non-GMO parents with engineered organisms sharing 99-100% of their DNA with their parent organism.'

2.2b) On Synthetic Biology and the Drive to 'Accumulate' Knowledge:

An increasing number of reports and publications have argued that in order to address these propensities it is essential to 'accumulate' knowledge and to build up and enhance the evidence base that underpins the development of synthetic biology. More recently, the CBD has sought to develop and build up a repository of information pertaining to the Member States experiences of and engagements with synthetic biology. Similar initiatives are also being undertaken by individual practitioners themselves. As Practitioner No.19 explained, *'we're particularly putting emphasis on including as much data and metadata on our measurements of our systems in our publications… one thing my own group is very interested in is how growth rate is affected where there is engineering of things like E. Coli… it grows slower because its been given this extra work to do… so I can imagine that kind of data would be useful as well in terms of being something that informs regulation… it might help identify parts that are somehow toxic or somehow provide a growth benefit.'*

Listed below are further examples of this drive to accumulate knowledge. Also included in these examples are suggestions made by practitioners pertaining to the mechanisms and practices that they feel will help to deepen understandings of this developing approach to life science experimentation:

i. **Interviewee No.5** posited that we need *'close regulation at the lab level and we need to understand what the hazards are, how they can be controlled. As time goes on you can hopefully reduce the hazards and the risks by engineering those out.'*

ii. **Practitioner No.7** explained that what *'would be really helpful and I don't know how to achieve it would be if people could share understanding of what the risks are…. and also where people do these experiments down the line and start saying so we've tested this in an experimental model of safety and we demonstrated that this is safe.. or that when we do this we make the organism less pathogenic… sharing of that sort of information might be really important…what we're finding is that because what we're doing is very applied and we're trying to get them to do things for us we tend to make them a lot less fit…. the genes that we're adding are imposing a quite significant fitness cost on the organism rather than vice versa.'*

iii. **Interviewee No.6** highlighted how *'a lot of modification stops an organism from being able to do something you can find out lots of info as this tells you a lot about how that pathway works.'*

iv. **Practitioner No.1** explained that *'as people start to grapple with multi-cellular systems it's becoming clear that these synthetic biology approaches provide also a* *way of directly grappling with some of the emergent processes that you see in living systems, so in a way it's helping fill out our understanding of these local processes which give rise to complex order by virtue of quite subtle or directive interactions which might be limited in their initial effect, but which propagate across the system.'*

v. **Interviewee No.10** felt that *'in a way there is a lot of lost opportunity there because it should be possible for researchers to gain knowledge of the characteristics of the thing that they are working with that runs concurrent with their research. It doesn't take that much, it might not take that much more effort or that many more personnel to do that, but they don't know what kind of knowledge is needed by the regulatory system for example…are there things that we can do in simulated environments where we can actually test the entity itself within the environment that it is destined for, and what are the kinds of characteristics that we want to quantify.'*

vi. **Interviewee No.2** described the drive towards Responsible Innovation as advocated by a number of Research Councils as an important mechanism in addressing gaps in knowledge, asserting that '*you might be moving into an area that you genuinely have no idea what the consequences might be… and that's where you have to say well is that simply because you don't know but another expert does… in which case connect them up and that's what for me responsible innovation is thinking about.'*

vii. **Practitioner No.20** suggested that if experimental work undertaken on phages identified '*something very unusual… I think it should be a requirement to review an entire genome of that phage which is not a big requirement really... if you end up with a collection of genomes… you might have certain... sequences that they carry toxic genes or maybe some of the relatives or some other sequence that shouldn't be there in the first place.'*

viii. **Interviewee No.10** provided an account of how uncertainties surrounding the purported implications of synthetic biology are opening out new research agendas, explaining that '*a small sequence in conventional GM technology is easily understandable in the context of what the safety implications of that might be, but if you are dealing with massive oligos, great chunks of chromosomes you know that are being made in say Venter's lab and the chances of those getting out of the lab are miniscule and they're being contained but nobody is asking the question what if. You know what if they did actually get incorporated into another organism. So I think there might be some mileage in looking at the safety and risk implications of the science of oglionucleotides.'*

ix. **Practitioner No.17** relatedly noted that *'any synthetic genetic network is obviously either operating orthogonally or disrupting natural homeostatic mechanisms so it* *inherently it makes your chassis less robust… understanding how chassis's interact with those sort of synthetic networks and how they can be structured to be more robust… these are essential questions if you're ever going to translate anything into a complex environment like this one.'*

x. **Interviewee No.9** asserted that knowledge gained from contained use activities can be extrapolated and applied to deliberate release scenarios where a step by step form of release is employed *'as knowledge of the organism grows.'*

xi. **Practitioner No.17** reflected on how synthetic biology can draw on experiences gained and lessons learned from the outcropping of transgenic plants noting that '*I am interested in crop cross breeding and then planting out…. If it's not transgenic by official means…but if you are cross breeding two quite distant species of plant and then using that in mono cultures that will have environmental effects that are not necessarily predictable… that is the same process in many respects…. you are taking a quicker route … basically a different protocol but the outcome is kind of the same.'*

Figures 1 and 2 provide an additional overview of how organisations such as the European Scientific Committees and individual practitioners are attempting to develop and engage with relevant sources of information in order to facilitate the safe development of synthetic biology.

<u>Figure 1</u>: Recommendations made by the European Scientific Committees in Preliminary Opinion II in response to concerns associated with the development of synthetic biology:

The Scientific Committees suggest 'several improvements to ensure continued safety protection proportionate to risk, while enabling scientific and technological advances in the field of SynBio. These improvements include, 1) Support the characterisation of the function of biological parts and the development of computation tools to predict emergent properties of SynBio organisms, 2) Streamlining and standardise the methods for submitting genetic modification data and genetic parts information to risk assessors, 3) Encourage the use of GMOS with a proven safety record as acceptable comparators for risk assessment, 4) Aim to ensure that risk assessment methods advance in parallel with SynBio advances, and 5) Support the sharing of relevant information about specific parts, devices and systems to risk assessors.' (ESC, 2015: 6)

These suggested improvements made by the ESC are primarily concerned with attempting to characterise biological parts as a means of enhancing understandings of the risks associated with synthetic biology activities. HSE might wish to consider from its own experiences of assessing and reviewing GM work what kind of additional information (if any) that it feels would enhance the robustness of the risk assessment process as is currently applied to GM undertakings.

<u>Figure 2:</u> Practitioner suggestions made by survey respondents in response to the question:

- Can you think of alternative ways of identifying synthetically engineered organisms whose risk assessment may require closer scrutiny?

The suggestions as listed in the table below are derived from the survey component of this research project. It is important to note that a number of these suggestions place a distinct emphasis on using pre-existing information to define and demarcate hazards prior to the undertaking of synthetic biology experimentation.

i.	'An ad hoc evaluation of the nature of the product (relative to known metabolic pathways) and the new genetic elements. The greatest risk being unwitting creation of toxic compounds.'
ii.	'Not really sure but would look at percentage of new genes or genes that would not normally be there.'
iii.	'Perhaps a ratio of novel genes: host genes.'
iv.	'All our work is based on rationale design of predicted compounds and expected changes to our strains.'
v.	'Perhaps an assessment of % 'unknown' for host metabolic map and genome?'
vi.	'There may be a need to develop standardised approaches to assessing the fitness of the organism within the environment for which it is intended, especially for those organisms intended for medical and environmental use.'
vii.	'Yes, through pathogenic ID databases and biosecurity databases.'
viii.	'Inclusion of pathogenicity factors. Selection for Gain of Function, Dual Use Research of Concern experiments.'
ix.	'Any synthetic organism where there are new or different genes that you think may govern pathogenicity or tissue tropism or allow the organism to grow abundantly in an environment where it is not normally found.'
x.	'I would imagine that it is most important to examine the parent organism and its behaviour; to examine the level and scale of the changes that have taken place; and ultimately it will be necessary to develop new and robust methods for rapidly screening synthetic organisms for their novel behaviours.'
xi.	'Creation of a bank for synthetic organisms.'
xii.	'Context-dependent. Greater scrutiny will be applied to projects where there is a pathogenicity focus or clearer potential for harm to the human health or the environment.'
xiii.	'Expected scale of use e.g. geo engineering.'

Whilst these are undoubtedly useful and important suggestions for HSE to consider, it is also important to recognise that there is little room within these suggestions to engage with indeterminacy - that is, the inevitable gaps in understandings of and evidence for risk which cannot simply be filled in advance of scientific undertakings. The subsequent sections of this report will progress to consider how we might better engage with 'indeterminacy' where the causal hazard chains are open and unspecifiable, in addition to 'risk,' where the parameters of the causal hazard chains are typically identified in advance.

2.2c) Recognising Indeterminacy in Scientific Knowledge

A number of policy theorists and social scientists (see, for example, Stirling 2008 and 2010) have powerfully illustrated that it is neither possible nor desirable to 'reduce' risk simply through the accumulation of knowledge. This is because the emergent, processual and contextually specific unfolding of any scientific undertaking means that the exact outcome of that undertaking can a) never be known in advance or b) be seamlessly extrapolated and applied to other contexts. Indeed, as noted by Practitioner No. 16, *'management of risk and prediction of consequences of actions are highly context specific.'* As Section 2.2a of the report highlighted, scientific indeterminacy is amplified further in synthetic biology due to the self-replicating and non-proportionate propensities of biological substrate. This does not necessarily make synthetic biology experimentation any more 'risky.' Rather, it requires recognising that enrolled within the practice of synthetic biology are unmeasurable uncertainties where the causal hazard chains are both open and indeterminate.

For Stirling, reducing unmeasurable uncertainties to 'risk' is an inadequate response to indeterminate knowledge. This is because 'risk' is a particular type of knowledge which relies upon the prior identification of fixed hazard parameters. Stirling and others have documented the negative implications that stem from an overreliance on '*risk proper*,' which refers to the privileging of fixed identifiable hazard parameters. In particular, Stirling (2012: 1029) has highlighted how the slowness of regulatory authorities and scientific experts 'to acknowledge the possibility of novel transmission mechanisms for spongiform encephalopathies in animal breeding and in the food chain' during the BSE crisis of

> *'Conventional risk assessment methods tend to treat all uncertainties as if they were due to incomplete definition of an essentially determinate cause-effect system… in other words, they suggest that the route to better control of risks is more intense scientific knowledge of that system, to narrow the supposed uncertainties and gain more precise definition of it.'*
>
> (Wynne, 1992: 116)

the 1980s was because these sources of harm 'were not formally characterised as possible risks.'

An awareness of and proactive engagement with indeterminacy in scientific knowledge can be used to develop and enhance the robustness of a risk based approach. As, for example, has been highlighted by an increasing number of social scientists, 'the built-in ignorance of science towards its own limiting commitments and assumptions is only a problem when external commitments are built on it as if such intrinsic limitations did not exist' (Wynne, 1992: 116). Whilst it is important, therefore, to think about what Interviewee No.10 described as the *'minimum information'* required for practitioners and regulators to assess the characteristics of a genetically modified organism, it is also important to think about how we might address indeterminacy in knowledge in order to build confidence in, and develop a more rigorous engagement with, the undertakings of this developing area of life science experimentation.

Thinking about how scientific indeterminacy might be addressed is also critically important in helping to move away from what Interviewee No.8 described as the nervousness that surrounds being asked certain questions and the presumption that there is *'some scale of lack of knowledge in HSE.'* It helps to bring to the fore the realisation that as noted by Interviewee No.2 '*not knowing and being good and bad are two totally different concepts but they very quickly get muddled in the media either by misunderstanding or in some cases deliberately… the key to policy is to recognise that there is an area that needs more work, but to create an environment in which that work can be carried out.'* Thinking about how this indeterminacy might be addressed is also important in building public and duty-holder confidence. As noted by Interviewee No.10 *'otherwise it [synthetic biology] is going to be bogged down in the concerns, opposition and regulator gloom basically and a lot of researchers feel a sense of trepidation about how regulation will be applied in the future and maybe that is having an effect on the research agenda, people may be choosing easy stuff rather than stuff that might be a bit of a challenge.'*

2.2d) Building Capacity in Addressing Scientific Indeterminacy:

'There is a need for humility about science-based decisions' (Stirling, 2010:1030)

The examples listed below provide an account of the ways in which practitioners are addressing the emergent propensities of synthetic biology and engaging with scientific indeterminacy. Incorporated into these examples are further suggestions as to what other mechanisms and approaches might be mobilised in order to build confidence in this developing area of life science experimentation. These examples help to develop a space that proactively engages with scientific indeterminacy as a means of enhancing the robustness of a risk based approach. This is critically important in helping to avoid the sense of 'gloom' and 'trepidation' as described by Interviewee No.10.

Example One: Engaging Productively with 'Difference'

Sections 2.1a and 2.1b of the report highlighted how there are considerable differences in understandings of the nature and implications of synthetic biology work. Crucially, these differences do not need to be overcome but rather provide the very conditions necessary to enhance and facilitate the practice of synthetic biology in a competent, safe and assured manner. It is through, for example, an engagement with difference that it becomes possible to cultivate an iterative and sustained process of thought and reflection that is able to resist what Interviewee No.8 described as the '*desire in all organisations to stick in a steady state and assume that we've answered all the tough questions.'*

i. **Practitioner No.12**, for example, explained that it is important to '*challenge your notions of what you really understand,'* noting that *'the more different inputs and perspectives you have to risk assessment the better actually because you know, all those people looking at it the one way might miss things or be overly permissive or cautious or whatever relative to what some other people think... I think probably a wider range of inputs of views would be good… it's good to have people who are very sceptical and look at something and pick as many holes in it as they can.'*

ii. **Practitioner No.8** similarly posited that *'because we all speak different languages we all have different assumptions we all have different foresight about what's important and also err things that seem easy to me…right I think okay can you do a fluid model of this bioreactor for instance… I say that to an engineer and they'll go you just don't know how hard that's going to be right... and then they'll say to me oh can you just like insert this thirteen gene pathway into that… and yeah you don't know how hard that's going to be so we are equally ignorant of each other's discipline but that's a good thing because it basically means that people have the confidence to ask the naïve or stupid questions that are never actually in fact stupid. You have to explain to people all the time.'*

iii. **Practitioner No.2** reflected specifically on how '*if you're a doctor or pathologists or look at disease organism you know pretty quickly whether or not that's a good idea… if you think you have the ability to manipulate the immune system, you're insane ok. It's just too bespoke to the individual to think you can do something like that…and there are projects that are aimed that way you're just thinking… nobody in their right mind should be even considering this project from the get go because it's not useful* *and that comes from having people around that are professionals that do that kind of work…and I'm not sure how to implement that because every institution isn't structured that way… diseases are what we're about so we get that…but if you don't have that in place you could make up all sorts of weird and dangerous stuff and it's pretty easy to just kind of dismiss the reality of it… it's not reasonable just to do something because you can…'*

iv. **Practitioner No.2** further noted that *'going forward you have to have people on board, like the SACGM, they have doctors on their panel ok, and that was really amusing to watch because these guys, whilst they may not know a lot about genetic manipulation, and might not know a lot about engineering, they know a lot about disease organisms and you know, they can tell you oh yes, we know what pathologies are going to be that are associated with…have you looked at those things within your laboratory, your company, your university, your whatever? Do you know what would happen if this thing got out in the open? Who is it going to hurt? Will it hurt just people or is it zoonoses?'*

The above examples highlight how it's the **differentiation** rather than the **integration** of knowledge that is important here. Differences in the understandings and implications of synthetic biology work do not therefore need to be 'written out' of the risk assessment process but can a) rather be used to enhance the robustness of the assessment and b) help to establish a longer process of critical thought that extends into the very undertaking of the work in hand. As indicated in the above interview extracts, it is likely that SACGM (CU) with its bringing together of a range of different expertise and varied knowledges will become an important and valuable tool for addressing some of the key issues associated with the development of synthetic biology practice.

Example Two: Asking New Questions

In addition to using differences in practitioner understandings of synthetic biology as a means of enhancing the robustness of a risk based approach, it is also possible to open up and ask new types of questions which can help to cultivate a recognition that as noted by Practitioner No.7 *'even if you have access to quite advanced tools nevertheless the models that you have still I don't think will ever be perfect to be honest.'*

v. In addition to fulfilling the requirements of the risk assessment as outlined in the Section 1.3 of the report, Interviewee No.3 expressed a preference for considering what an early warning might look like. This interviewee noted that '*asking what is novel about what we're doing… what unusual risks are there… [scientists] go oh yes we know all that… but when you ask that question what does an early warning look like it makes people realise that actually something may go wrong that they've not* *thought about… and how would they recognise that and I don't think as a sort of industry… the life science industry… I'm not sure we're geared up to think about that.'*

vi. In reflecting on what these 'early warnings' might look like Practitioner No.19 explained that *'the easiest early warning I would think about would be our cells growing faster than wild type.'* Practitioner No.20 similarly drew attention to *'unexpected behaviour like unexpected tropism… or resistance unexpected resistance to multiple factors.'*

vii. The examples as listed above intersect with the assertion made by Interviewee No.6 who posited that '*if you remain routed to that first step you're looking at the wrong thing really.'* This interviewee was referring to the tendency for most risk assessments to focus on the nature of the recipient or parental organism and the origins and intended functions of the genetic insert. In this regard, considering what an early warning might look like begins to open up a slightly different terrain of analysis that is attentive towards the wider interactions '*not just genetic, but also physical and chemical*' which, as described by Practitioner No.1, *'play out'* and reverberate across the architecture of modified organisms. This might best be described as a mode of anticipation as well as prediction.

viii. It is important to also recognise that methods and tools used to conduct risk assessments do not simply 'represent' the risks, but are rather complicit in participating in the formation of risk. As a case in point, Practitioner No.7 noted that '*novelty on face value could be a useful trigger to flag organisms which may pose a greater risk – however using % genome change may not be a good indicator, e.g. the % difference in B subtilis & B anthracis is not great and does not reflect the difference in pathogenicity. Assessment must rely on a combination of factors; % of synthetic genome could be one but must also include the predicated activity of inserted parts and characteristics of the final organism. Previous experience with numerical schemes (e.g. Brenner) showed that people like the 'certainty' of a numerical result with the temptation not to assess the risk holistically so a small % change below a threshold but with a significant potential for harm could be overlooked.'*

ix. In terms of what a risk assessment might look like Practitioner No. 2 reflected on his experiences of working as a BSO and sought to emphasise that *'you can't make the process overly complicated, yet you want to have things in place where you can ask the right questions – previous forms have been overly complicated and still there are elements of that because they're so prescriptive and they don't allow you to explain things and you end up ticking a lot of boxes like not applicable.'*

Example Three: Acknowledging Current Practices

It is important to be aware of the mechanisms and undertakings that practitioners are already incorporating into their working practices. The following examples provide a brief snapshot of the ways in which practitioners are already thinking of ways to enrol relevant mechanisms for safe practice into their own work strategies.

x. Practitioners No.10 and 11 reflected on how during the undertaking of experimental work '*we did look into all the sort of different pathways… to check that there wouldn't be a metabolite that was dangerous or that it wouldn't make a product that was more harmful than TNT.'*

xi. Practitioner No.7 asserted that *'another thing that we might look at which we have the people in biosciences to do would be to see how these organisms work and how effective they are in their mixed culture… so can they survive and thrive in a mixed culture with wild type E.coli or even their parent strains?.'* This Practitioner also explained that *'there are very good mircobiologists in the department who have got a lot of expertise in working with really very nasty organisms so they understand the risks that can come with both natural organisms and genetically modified organisms very well, particularly with regard to things like toxins and to defences that microorganisms have.'*

xii. Practitioner No.7 further expressed *that 'if we started doing a larger number of things… I suspect the GM committee would be saying to us well you're going to have some sort of test at least to what's going on with the pathogenicity of these organisms to show that they're less, there's no sort of increase in pathogenicity... we'd also probably want to look at some sort of plant model as well to show that they're not more pathogenic in the environment… we've got good plant biology, we have good microbiology and we've even got good mathematical models as well… I think we could come up with a really good set of tests that might be quite, quite attractive from that perspective.'* This practitioner highlighted how *'for a reasonable balance of effort against time we could make a reasonable sort of thing part of a due diligence process'*

2.3. Key Points:

- Synthetic biology is a highly variegated field of life science experimentation. There is an equally heterogeneous relationship between synthetic biology and risk. It is not as simple therefore as to assert that synthetic biology either 'increases' risk through, for example, the consequences of unintended release, or rather 'decreases' risk through its use of standardised, well-characterised parts. It is precisely these kinds of statements which can be implicated in constraining the possibilities for meaningful action and nuanced debate.
- HSE must engage with the undertakings of synthetic biology in practice. This is important in ensuring that HSE's contributions to wider policy deliberations are informed by grounded understandings and that HSE can lead effectively in considering the nature of the assurances of competence and safe practice that can help to build confidence in the developing trajectories of synthetic biology.
- There are considerable differences in terms of practitioner understandings of the nature and implications of synthetic biology experimentation. One of the key tensions identified in this section of the report concerned the nature and extent of the risks posed to human health and the environment by the development of synthetic biology. Underpinning this tension is the propensity for synthetic biology to depart from existing comparative frames of reference and to enable non-proportionate and synergistic interactions between a range of biological and non-biological parts and components.
- Although most synthetic biology work undertaken in GB is currently class 1 or 2 and is regarded as constituting 'nil' and 'negligible' or 'low' risk to human health and the environment respectively, it is likely that the emergent propensities of synthetic biology practice may become of greater relevance as practitioners design organisms to interact within broader ecological environments and work with more hazardous organisms or organisms with increased potential for causing harm to humans and/or the environment.
- Crucially, **these propensities do not make synthetic biology necessarily any more 'risky'** but rather raise interesting questions in terms of the building of competence and safe practice.
- Although it is possible to build upon experiences gained and lessons learned, it is important to also recognise that there is a fundamental limit to the amount of knowledge that can be 'accumulated' in order to address scientific indeterminacy. This limit exists due to the emergent propensities of biological substrate and the contextual specificity of the work in hand.
- Many wider deliberations have tended not to foreground this limit in knowing and have rather placed an emphasis on how functional information can be used to decrease 'uncertainties.' This section of the report has rather argued that it is important to acknowledge **indeterminacy** in scientific knowledge and to build confidence in synthetic biology through building capacity in the ways in which regulators and practitioners work with and engage this indeterminacy.

Chapter 3: Principles of 'Intelligent Regulation' Within a Goal Setting Framework

3.1. Enhancing Assurances of Competence and Safe Practice through Networks and Partnerships

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Chapter Overview:

- The preceding chapter of this report highlighted how the emergent propensities of biological substrate and the contextual specificity of synthetic biology experimentation means that there will always be a fundamental incompleteness to knowledges of the risk implications associated with the doing of synthetic biology.
- 'Intelligent regulation' requires recognising that what becomes of critical importance in these circumstances are the qualities and nature of the connections and support mechanisms that exist between regulators, practitioners and other stakeholders.
- This section of the report highlights how, it is through these very connections and support mechanisms, that it becomes possible to build confidence in and provide additional assurances that the unfolding trajectories of synthetic biology are being undertaken in a safe and competent manner.
- In particular, the profile of HSE must be such that practitioners feel suitably empowered to approach HSE during the development and/or unfoldings of synthetic biology experimentation and HSE must ensure that it is sufficiently tapping into the developing trajectories of synthetic biology in practice.
- It should be noted that these connections cannot simply be about 'delivering' or 'receiving' information, but must rather consist of an iterative process of working together in a mutual process of reflexive learning.
- An intelligent regulatory approach therefore recognises the indeterminacy and incompleteness of scientific knowledge and builds capacity in productively engaging with this incompleteness through the avenues of engagement that connect regulators, practitioners and other stakeholders.

This section of the report highlights how it is through the very connections and support mechanisms that exist between practitioners, regulators and other interested stakeholders that it becomes possible to:

a) move beyond what Interviewee No.8 described as the '*dread'* that often surrounds '*something new and not understood and the assumption that it's probably not regulated'* and;

b) to address the fundamental question as posited by Interviewee No.5 *'how do you let the technology develop when you haven't got all the answers?'*

This section begins by using the example of DIY bio as a case study through which to tease out the importance of ensuring that HSE is sufficiently tapped into the undertakings of biological engineering in practice. It then progresses to consider the specific mechanisms through which HSE might develop its profile as a *'friendly and open port of call'* (Interviewee No.10) and engage with the undertakings and developing trajectories of synthetic biology in a manner that is both practicable and feasible.

3.1a) A Case Study in DIY Bio: Grounding Deliberations through an Attentiveness to Practice

Section 2 of the report highlighted how an attentiveness to practice is critically important in grounding understandings of synthetic biology and in helping to add nuance to wider deliberations. The importance of being tapped into practice becomes further apparent when we attend to the development of DIY bio. DIY bio is often associated with the rise of synthetic biology and can be broadly understood as the expansion of biological experimentation into non-conventional spaces of work such as community laboratories which span a range of educational and innovative purposes. At present and as noted in Chapter 2 of the report, there is a considerable disjunction between renderings of DIY bio as posing heightened safety and security concerns and the undertakings of DIY bio in practice. The interview materials as listed below provide a brief account of the ways in which engaging with the unfoldings of DIY bio in practice opens up a very different set of questions and considerations than have often been projected in wider deliberations.

All DIY biologists undertaking genetic modification work in the UK must conform to the legislative requirements as documented in Chapter 1 of the report. This includes the implementation of appropriate containment and control measures and the undertaking of experimental practices in accordance with the general principles of good microbiological practice and of good occupational safety and hygiene. At present there is one community laboratory in GB which has registered to undertake class 1 work although a number of organisations and individuals have expressed both an interest in, and agendas for, the undertaking of DIY bio work. Containment level 1 (Cl1) refers to the minimum containment requirements required for class 1 work - that is, work which is typically regarded as posing nil or negligible risk to human health and/or the environment. This is determined by an assessment of the hazards associated with the genetically modified organism (including pathogenicity and toxicity) and an assessment of the nature of the activity in hand, particularly in terms of the probability of exposure to potential hazards (including, for example, the potential for the generation of aerosols).

The examples listed below provide a brief **snapshot of the undertakings and aspirations** of a number of **'DIY biologists'** interviewed as part of this research project.

i. **Practitioner No.14** explained that '*we were a bit dubious [about] whether we would go ahead and do CL1, because… you know we're not interested in going too far…. CL1… you get a whole bunch of stuff that opens up… putting human proteins in bacteria I would regard as pretty out there you know beyond what I would need to do.'* Upon reflecting on the motivations that underpinned the attractiveness of DIY bio this practitioner noted that '*I was doing a chemistry degree and I hadn't done any lab work… I wanted some wet lab work… I don't want to do really crazy stuff here.'*

ii. **Practitioner No.15** described the ambitions of a number of DIY biologists as best being regarded as constituting *'Biosafety Level Point 5'* - that is, they exist below the limit of the types of activities that would typically fall into Containment level one. Practitioner No.14 and Practitioner No.15, for example, expressed an interest in self-cloning. Self-cloning, which is exempt from the majority of the requirements in the GMO (CU) Regulations except for the general principles of good microbiological practice and of good occupational safety and hygiene, refers to the 'removal of DNA or RNA from a cell of an organism, which may be followed by the reinsertion of all or part of it into the same species' (GMO CU Regulations, 2014).

iii. **Practitioner No.17**, reflected upon the type of work that is often discussed at DIY bio meetings and expressed that a number of DIY biologists would like to develop capacity in *'the kind of fun things to do with genetic engineering… you know bio-sensory things, right so it's just going to be basically grabbing the proteins and stuff expressed normally in one piece of bacteria, sticking it in E. coli.'*

iv. In terms of the framing of DIY bio in wider deliberations, **Practitioner No.15** asserted that '*anthropologists and sociologists are the only ones who mention bioterror and DIYbio*' and Practitioner No.16 acknowledged that whilst the term biohacking acts as a '*provocation,'* the phrase *'citizen science is such a condescending term*.'

In spite of the relatively low level nature of DIY bio undertakings at present in GB, wider deliberations have tended to regard DIY bio as being likely to 'increase the probability of harm' (ESC, 2015) and as intensifying the possibilities for the malicious and malevolent use of biological materials. However, as the Wilson Center (2013: 10) and a number of academics have recently highlighted, 'the link between synthetic biology and DIY bio, and the level of sophistication of the experiments typically being performed in DIY bio labs, is overstated.' Jefferson, Lentzos and Marris (2014) have similarly posited in relation to the linking of synthetic biology with heightened biosecurity concerns, that it is important to recognise that 'tacit knowledge and socio-technical factors limit the possibility of reproducing experiments based on the informational aspects of science alone.' The work of Jefferson, Lentzos and Marris (2014) has progressed to chart some of the key barriers associated with the weaponisation of biological agents, particularly in terms of 'finding a suitable means of dissemination that will not destroy the agents virulence or infectivity.' However, this is not to say that concerns surrounding DIY bio are not without their merit. Indeed, as noted by Practitioner No.1 it might be that DIY bio is a *'flash in the pan, it might come and it might go… or you can see it as a growing trend… a new way of doing things.'*

Rather, by tethering these considerations to an attentiveness to DIY bio in practice, a number of interesting **questions** open up **surrounding how** it is that **HSE might target its interventions and engagements with non-conventional sites of biological experimentation:**

i. **Practitioner No.14**, for example, pointed to the high turnover rate associated with community spaces and explained that the '[GMO CU] *regulations talk about workplaces… that isn't a very good mapping… the ability to force discipline and create sanctions is unquestionable in both private and academic setups… whereas am I in a position to throw someone out of the lab or ban them from it? It would require a series of steps here which doesn't map well on to the way the regulations expect the organisation to behave.'*

ii. **Practitioner No.14** further reflected on the challenges associated with both the development of contracts for individuals using equipment in the community laboratory and the appointment of a Biological Safety Officer. This practitioner explained that *'a group of people might go off and start a biotech, leave the lab empty… the people who are kind of in the lab downstairs most of the time now are not the same who were in the in the lab most of the time a year and a half ago… it tends to change quite quickly which makes it very hard to pin down any of this stuff.'*

iii. In a related vein, **Interviewee No.7** expressed that '*it would be nice to maybe try and describe what a Biosafety 0 facility looks like and what kind of organisms would a Biosafety 0 facility be allowed to work with… there's some selection plasmids that you are allowed to use to transport into E. coli and it's not classed as genetic engineering because it's just using something that's generally regarded as harmless...'*

In addition to the above, it should be noted that many of the practitioners interviewed during the course of this research project expressed both an interest in (and confusion surrounding) the undertaking of 'basic recombinant DNA work' in schools.

i. **Practitioner No.12**, for example, expressed that '*I'm more interested in… it's not synthetic biology specific… it's almost the opposite, about doing basic recombinant DNA work in schools, in home kits, in whatever and it's quite hard for me to see why you wouldn't allow that or even encourage it okay and yet again as I understand it it's quite incompatible with the current regulations.'*

ii. **Interviewee No.7** posited that *'so I think for a long time I was under the impression that you couldn't really do bacteria in a school or without sort of regulation…. without sort of notification… I think we recently worked out that wasn't the case.'*

iii. **Practitioner No.9** posed the question *'am I right in thinking that it's not okay to transform a plasmid say with GFP into a bacteria outside laboratory containment… in a classroom or something?'* This practitioner reflected on prior experience attempting to do this and noted that '*I remember there being sort of a grey area… initially what we wanted to do is we wanted to transform just some cells with some fluorescent proteins to show these guys look this is pretty cool… because there was uncertainty over whether the premises would be licensed or exempt we ended up having to run the whole thing through [academic institution], which was viable, but if there could be, I don't know, maybe there are maybe they're just not communicated… relaxed frameworks around very simple kind of synthetic biology experiments that could enthuse young people about the discipline… that would probably do more good for the discipline than anything else.'*

iv. **Practitioner No.1** similarly reflected on the emphasis on STEM (science, technology, engineering and maths) that is *'all the rage in British schools now'* and noted that *'HSE could make a concrete difference if they could… lower the activation energy… shifting from a more negative regulatory context to a more enabling context and trying to enable things… and that I think would be quite important if we can convey that at school level as well.'*

v. Although not specifically related to the undertaking of experimental work in schools, **Practitioner No.9** expressed that *'with synthetic biology you're going to have a lot of people who want to basically start laboratories right… the question is how do you start your lab in a safe and compliant way and you know what are the kind of facilities that you need… it's always cited as there's the odd DIY biologists who has a registered lab... how practical is that? Is that actually a viable model to go with? I guess that's kind of more horizon scanning looking ahead for the next sort of 10, 15 years as opposed to the next sort of 5 to 10.'*

An attentiveness to practice is therefore important for the following reasons:

i. In contentious and politically charged areas such as a DIY bio an attentiveness to practice helps HSE to differentiate between projected visions and actual doings of 'DIY bio' in practice. Similarly to the ready conflation of novelty and risk as discussed in Chapter 2 of the report, it is through an attentiveness to practice that it becomes possible to disentangle the ready association of synthetic biology with DIY bio.

ii. Developing a more grounded understanding of DIY bio helps to bring to light considerations such as the undertaking of low risk work in schools and helps to ensure that the questions and engagements that surround DIY bio are appropriately focused. Interviewee No.3, for example, posited that as a community *'we have to make sure [it] is included in the mainstream and isn't pushed out through trying to be, not being able to keep up with the regulations.'* Similarly, as posited by Interviewee No. 3 *'we can read DNA, we can write DNA, transformation protocols are pretty easy. High school kids do it… so yes by all means let's make sure that we don't make it too onerous for DIY bio people to tinker and play, because they will.'*

iii. Not only does an attentiveness to practice help to enhance HSE's evidence base but it serves also to provide assurances to practitioners that broader policy negotiations are informed by grounded understandings and are not based upon what Interviewee No.10 described as '*old philosophies that don't really apply to the research and development that's going on now.'*

iv. In short, it is through an attentiveness to practice that it becomes possible to engage in what Interviewee No.2 described as a more *'dynamic approach to regulation.'* This Interviewee noted that *'it might be that certain things have to be tightened and other things can be relaxed… it's all about the approach and showing that everything is being managed dynamically as we learn things… you can learn something you weren't sure about isn't a problem just as much as you can discover that something is new and gosh you need to think more.'*

3.2. Developing HSE's Capacity and Profile in its Engagements with Practitioners

> Synthetic biology is *'not just a science, it's a whole culture…. regulation needs to be part of that culture.'* Interviewee No.10

This section of the report considers how HSE might develop its profile as a *'friendly and open port of call if researchers have ideas or concern'* (Interviewee No.10) and tap further into the rapidly developing trajectories of synthetic biology. At present, most synthetic biology work currently operates at containment levels 1-2 and is of comparatively lesser concern to HSE than experimental work at higher levels of containment. As such, practitioners and organisations operating at CL1 only submit a sample of their risk assessments to HSE for review. The rationale behind this, as posited by Interviewee No.6, is *'why would you need to know if it's nil or negligible risk.'* However, as this Interviewee further went on to note, the important question that remains is *'how do you know [that] you are getting that right?"* Given that synthetic biology is a) altering the textures of established scientific practice through, for example, the increased scale of the undertaken work and that b) there is a fundamental and inherent incompleteness to the knowledge that underpins the development of synthetic biology, it is important to consider the ways in which HSE might ensure that it is adequately engaging with the developing trajectories of synthetic biology.

In terms of HSE's profile, it is critically important that practitioners feel suitably empowered to approach HSE during the development and/or unfoldings of synthetic biology experimentation. The examples as listed below provide an account of practitioner reflections on their relationship with HSE.

i. **Practitioner No.2** expressed an appreciation for the integration of technical knowledge into HSE's policy role, noting that *'I can talk to [names removed] because they're biologists, they get it.'*

ii. **Practitioner No.6** reflected on how when engaging with HSE, *'it felt like there was someone who was thinking about what I was proposing, whereas had it been more automated tickbox where if you do this then you're alright…. then things would creep through.'*

iii. **Interviewee No.10** expressed that for some, *'there is a wariness of HSE, most researchers think that HSE is concerned primarily with health and safety within lab practice. I don't really think they see HSE in the context of regulation so much, I think maybe HSE needs to up its game a bit in terms of its profile with researchers.'*

iv. **Interviewee No.10** pointed to the importance of having the right mechanisms in place so that concerns can be appropriately filtered through to HSE as *'an open port of call.'* This interviewee was specifically interested in how it is that regulation keeps *'up with the fact that these tools [genetic modification tools] are becoming faster and cheaper and more accessible to people, whether they are formal researchers or whether they're informal researchers.'*

v. **Practitioner No.3** felt that *'there has to be some level of greater transparency in seeing how things are progressing through the system.'* This comment was made in relation to the gaining of regulatory approval for deliberate release activities. Although deliberate release activities do not exist under the remit of HSE, Practitioner

No.7 relatedly reflected on the importance of the public register for contained use activities, noting that this is consulted often by practitioners for various reasons including *'to see what the public can see we're doing.'*

vi. Practitioners held in high regard HSE's appreciation of context and infrastructure. **Practitioner No.8**, for example, expressed that *'HSE… they understand more about what a general working day is'* and **Practitioner No.12** reflected on how *'I have to say in many cases I've found regulatory agencies better than academics on risk … a number of academics get really hung up on hypothetical risks.'*

vii. **Practitioner No.8** further described HSE as being *'really helpful they're really willing to discuss things. They don't come at things from a knee-jerk perspective either you know and I think that they're very very reasonable… they were saying … you could improve safety by doing this sort of thing but to be honest it would be really difficult for you to do that so we understand why you've done this instead and that's fine and they do have an appreciation of context and infrastructure.'*

viii. **Interviewee No.8** acknowledged that it might be necessary to enter into the public debate to provide level statements and to take on a *'public reassurance role,'* noting that *'it is the new stuff that prompts the hardest debates.'* As a particular example of this, Practitioner No.9 reflected on how *'everybody seems to be very comfortable with the organisms that exist at the moment and there are terrible organisms and there's so much more fear around things that don't exist, which may or may not exist in the future if that makes sense.'*

In terms of **how HSE might develop its profile as an 'open port of call' and tap further into the developing trajectories of synthetic biology** in a manner that is both feasible and practicable, many of the interviewed practitioners expressed a preference for HSE to attend synthetic biology conferences:

i. **Practitioner No.3**, for example, reflected on how HSE might add to its role as an enabling regulator, noting that at synthetic biology conferences '*a lot of people meet and start talking about ideas and they go oh is this feasible, what would a regulatory body think about this, and these never go beyond that point because there's no one to talk to in the room to explore the idea further.'* Interviewee No.10 relatedly noted that, '*I think HSE have a lot of useful things to say and they have a lot of useful things to listen to and putting ideas out there for people to discuss.'*

ii. **Practitioner No.2** similarly expressed a preference for HSE to attend synthetic biology conferences but rather placed an emphasis on the role of HSE in helping to share best practice and in tempering some of the more *'ambitious iGEM type proposals.'* This practitioner expressed the opinion that *'a lot of people in synthetic* *biology don't have a firm grasp on what's safe and what isn't and that's why I really feel that in these public forums where these ideas get discussed and a lot of new ideas are created by new people meeting and talking at these conferences, it would speed a lot of these new ideas forward if there was someone that they could talk to and answer questions and just give demonstrations of concepts and ideas that are never a good idea… I'm not saying let's make it black and white, but show which side is the lighter grey.'* Indeed, for Practitioner No.7 *'the big risk in all this is not that people do things that are actively malicious but that people do things that are thoughtless.'*

iii. **Practitioner No.12**, reflected on how *'I wouldn't say that the sort of requirements of the regulatory process are foremost in people's minds as they're thinking about what sort of problems could be addressed or methods used to solve them by synthetic biology means.'*

iv. In terms of the feasibility of attending and contributing to synthetic biology *conferences* **Practitioner No.18** noted that *'you could hit 50% of the UK synthetic biology community by attending just six conferences.'* It is, however, important to note that as Interviewee No.3 posited, *'getting these people together is great but we must be careful about workshop fatigue.'*

v. **Interviewee No.7**, a DIY biologist, explained that '*I've been to one of the iGEM meet ups here in Newcastle and there was someone from the Health and Safety Executive there talking to undergraduates but I don't know if there's been any sort of 'meet the Health and Safety Executive' for DIY bio yet which might be useful… 2016 Manchester.. there's a thing called the European Science Open Forum…it's next to go to Manchester so it might be an important date to work towards.'*

vi. **Interviewee No.10** posited that *'I feel very strongly that the only way to address these issues [surrounding synthetic biology] is to get researchers and regulators together as almost a continuous process. There ought to be some kind of at least annual global event where we get all researchers from throughout the world and regulators throughout the world together to try and thrash out some of these issues, and to do some foresight off the wall thinking. You know what is coming up on the horizon. Horizon scanning is you know it's a kind of trite thing really but in a way you do need to do it.'*

3.3. A Note on Practitioner Engagements with Wider Synthetic Biology Networks

The synthetic biology community in the UK is widely recognised as being one of the most *'joined up'* (Interviewee No.2) Committees in the world. This community is constituted by a growing number of organisations and structures which are bringing together complimentary areas of synthetic biology expertise and are helping to facilitate the commercial translation of synthetic biology applications. A number of practitioners were keen to stress that they should *'maintain their contact with networks and not disappear into the lab and not come out for six months'* and ensure also that they make the most of the support networks *'as put together by the BBSRC and EPSRC'* (Interviewee No.10). Section 2.3 of this report gestured towards the ways in which the divergent understandings and concerns that underpin synthetic biology experimentation do not need to be 'overcome' and are not necessarily indicative of a problem. Rather, it highlighted how it is through these very differences that the robustness of a risk based approach can be enhanced. It demonstrated how, for example, an engagement with difference enables practitioners to cultivate and engage in an iterative and sustained process of thought and reflection.

Practitioner involvement with wider synthetic biology networks provides an important avenue for those undertaking synthetic biology experimentation to enhance their exposure to the divergent understandings that surround the developing trajectories of synthetic biology. As, for example, Interviewee No.3 explained *'it always helps to get a second opinion… ideally it should be somebody who thinks different from you.'* Practitioner No.12 similarly reflected on how *'you challenge notions on what you understand… you find out pretty soon that story wasn't quite right.'* What an engagement with difference does is that it helps to open up and establish an iterative and critical process of thought. This is particularly important in helping to avoid what Interviewee No.8 described as the '*desire in all organisations to stick in a steady state and assume that we've answered all the tough questions.'*

Although practitioner engagement with synthetic biology networks cannot in itself provide assurances of competence and safe practice, HSE might encourage and look for evidence of the differentiation of knowledge as being a tool for the development of best practice in the risk assessment process. Practitioners No.10 and No.11, for example, relatedly noted that *'there are areas where scientists aren't the best judges, scientists can get very attached to their work and can be overly confident.'* Furthermore, in relation to the ready conflation of 'novelty' and 'risk' as discussed in Chapter 2 of this report, Interviewee No.10 asserted that *'to assume that because something is very novel it's going to pose a greater risk, especially where deliberate release is concerned is probably* *wrong. You need to go to the evolutionary biology community to get a view on that not the synthetic biology community… because the synthetic biology community by and large doesn't understand evolution.'*

3.4. Avoiding Regulatory Capture and Reaffirming the Ownership of Risk

'Regulatory capture' refers to instances where the regulatory process is unduly co-opted by wider influences. A number of social scientists have provided a range of influential accounts which have documented how regulatory capture can lead to diminished faith in both the credibility and integrity of regulatory structures and institutions. Whilst it is important for HSE to develop the avenues of engagement and connection as delineated above, it is also important that HSE maintains and protects its role and integrity as an independent regulator. Indeed, as noted by Interviewee No.5 *'it's the regulators job to do the sampling assessments or audits, to be the independent checker that the original assessment was valid.'*

It is particularly important, therefore, to take note of the following:

i. Given the dynamic and proliferating nature of synthetic biology work, responsibility for managing risk, as outlined in the Roben Review of the HSE's approach to regulation of 1972, must rest with those undertaking and most familiar with the work in hand. Interviewee No.5, for example, explained that *'because you own that risk you're looking to protect your reputation and the health and safety of you, your team and institute, you have a vested interest… the good thing about the HSE system is that it says this is what you need to achieve... here's some way of achieving it, here's the minimum you need to have but it's up to you how you want to do that… so you know there's minimum requirements about door seals etc but everything else is up to you'*

ii. It is important to recognise that synthetic biology and DIY bio, as with many emergent fields of scientific and industrial endeavour, are politically contentious and that wider speculation is often not tethered to the realities of practice (see, for example, Calvert and Frow, 2013). By tapping further into the undertakings of synthetic biology in practice, HSE can ensure that it is able to temper speculative claims and navigate wider political milieus and agendas.

iii. A number of interviewees made assertions throughout the duration of this research project which resonated with the statement made by Interviewee No.2 that *'if the answer is a block then maybe the person giving the answer isn't approaching it right.'* It is important to remember, however, that whilst most synthetic biology activities are at present typically low risk, there are nevertheless very real and serious implications that can stem from the undertaking of synthetic biology practice. Interviewee No.8 emphasised that *'you've got people who certainly in their own minds will know a lot about the subjects and possibly in some situations they're going to be tempted to push the boundaries or feel that they know more than others because they are experts and specialists.'*

Chapter 4: Conclusions

Chapter Overview:

- This concluding chapter draws together the key points and findings as developed throughout the report.
- It highlights how building confidence in synthetic biology means building capacity in the ways in which we think about synthetic biology and the tools and techniques of regulatory-practitioner engagement.
- In particular, it is important to recognise that synthetic biology is not simply a singular field of scientific endeavour but is understood and approached in a range of different ways which do not always overlap.
- There is also a fundamental 'incompleteness' to the knowledge that underpins the development of synthetic biology. This can be attributed, in part, to the emergent, self-replicating propensities of biological substrate and the contextual specificity of synthetic biology experimentation.
- Such incompleteness and indeterminacy does not necessarily make synthetic biology any more 'risky' but rather raises interesting questions in terms of the assurances of competence and safe practice that we might subsequently expect to see enrolled in the undertaking of synthetic biology activities.
- In particular, what becomes of critical importance in these circumstances are the connections and avenues of engagement that link regulators with practitioners and other interested stakeholders.
- This section of the report highlights how developing capacity in these areas not only helps to enhance the robustness of a risk based approach but helps HSE to ensure that the questions that are asked of synthetic biology and the regulatory engagements that surround synthetic biology are proportionate, pragmatic and appropriately informed.
- The points developed in this section intersect with broader debates about what 'intelligent regulation' might look like in dynamic fields such as synthetic biology where knowledge is necessarily indeterminate and incomplete.

> *'this isn't a side show, this is centre stage… it is going to transform the way we make things, manufacture things… [it's a] hugely transformative set of technologies.'*
>
> Interviewee No.10

The considerations outlined in this report are primarily informed by and focus in particular on the contained use of synthetic biology activities. It is important to note, however, that they also speak to and have relevance to broader regulatory contexts and challenges including those associated with the deliberate release of genetically modified organisms. The UK's Science and Technology Committee (2015), for example, has recently posited that the European regulatory framework on genetically modified crops is 'not fit for purpose' and that it is imperative to consider the characteristics of a genetically modified crop rather than presuming that because an organism has been made via GM techniques, it necessarily poses greater risks to human health and the environment. In their report, the Science and Technology Committee (2015) progress to note that there should be a consideration of the purported benefits of GM crops alongside the risk assessment process. This concluding chapter adds to these broader regulatory imperatives by providing a grounded account of what it might mean to enhance the robustness of a risk based approach in areas of scientific endeavour where knowledge is indeterminate and incomplete. This is particularly pertinent to areas of synthetic biology work where a) there is no clear parental organism; b) synthetic biology approaches are being brought to bear on organisms posing greater risks to human health and the environment and c) where organisms are being designed with a view to interact within broader ecological environments.

4.1. Enhancing the Robustness of a Risk Based Approach

Chapter 2 of this report charted the propensity of synthetic biology to depart from existing comparative frames of reference and to enable non-proportionate and synergistic interactions between a range of biological and non-biological parts and components. It highlighted how the significance of these propensities is that they cannot always be fully captured or addressed by risk based calculations alone. This is because 'risk' is a particular type of knowledge that relies upon the identification of specifiable parameters in order to pre-define the likelihood of a particular hazard occurring. As a developing area of life science experimentation, synthetic biology is characterised in part by the qualities of emergence and non-proportionality which stem from its enrolling of self-replicating biological substrate. The implication of this is that it is not always possible to identify hazards prior to the undertaking of synthetic biology experimentation. Chapter 2 progressed to highlight how, for some practitioners, this is an issue which scientists undertaking GM work have been dealing with for many years. It also highlighted how, for others, the scale and speed of the changes associated with synthetic biology means that this an approach to the doing of life science experimentation and research that warrants a precautionary approach.

Instead of suggesting that any one perspective on the implications of synthetic biology is more valid than another, or asserting that synthetic biology is inherently 'risky,' this report rather highlighted how synthetic biology's departure from existing comparative frames of reference raises interesting questions in terms of the assurances of competence and safe practice that we might subsequently expect to see enrolled in the undertaking of synthetic biology activities.

In particular, Chapter 2 of the report argued that there is a limit to the amount of knowledge that can be accumulated pertaining to the risks associated with synthetic biology practice. This section of the report also highlighted how there is considerable room to build capacity in the ways in which regulators and practitioners think about and engage with synthetic biology as a developing area of scientific endeavour.

More specifically, Chapter 2 and Chapter 3 of the report provided an account of how, enhancing the **robustness of a risk based approach,** in a dynamic and emergent field such as synthetic biology, requires the following essential components:

4.1a. It is important to acknowledge indeterminacy in scientific knowledge:

When we recognise indeterminacy in scientific knowledge, that is, the inevitable gaps in scientific understandings of and evidence for risk which cannot simply be 'filled' by the accumulation of scientific knowledge, it becomes possible to move beyond the presumption that there is some *'scale of lack of knowledge'* (Interviewee No.8) and to rather open up questions pertaining to how we might build capacity in engaging productively with scientific indeterminacy. Indeterminacy is not the same as uncertainty. As noted by Wynne (1992: 118), 'the distinction between uncertainty and indeterminacy is important because the former enshrines the notion that inadequate control of environmental risks is due only to *inadequate scientific knowledge*, and exclusive attention is focused on intensifying that knowledge, to render it more precise.' In particular, it is upon acknowledging scientific *indeterminacy*, which stems from emergence, non-proportionality and contextual specificity in scientific experimentation, that it then becomes possible to open up the realisation that gaps in scientific understandings of and evidence for risk are a) inevitable and b) do not necessarily make synthetic biology work more 'risky.' Instead, they require a recalibration of the processes and assurances of competence and safe practice that we might look for in the undertaking of synthetic biology experimentation. From a policy perspective, through recognising the inevitability of gaps in understandings of and evidence for risk, HSE is able to ensure that wider negotiations surrounding synthetic biology are not focused simply on the 'accumulation' of knowledge, but consider also what it might mean to engage in a productive and pragmatic manner with the limitations of knowledge itself.

4.1b. It is important to build capacity in engaging with scientific indeterminacy:

The concept of indeterminacy has very practical implications and opens up new types of operational questions. Chapter 2 of this report, for example, charted the range of differences in practitioner understandings of the scope and implications of synthetic biology. It highlighted how these differences do not need to be 'overcome,' but can rather be used to enhance the rigour of the risk assessment process. Indeed, instead of being 'written out' of the risk assessment process or being used to reach any definitive or singular perspective on the risks associated with a given synthetic biology activity, an engagement with difference can be used to establish a longer process of critical reflection that extends further into the undertaking of the work in hand and does not take for granted or presume that all of the important questions have been answered. Engaging with difference helps to build into the assessment process a space of critical reflection and recognises the endemic partiality rather than the singularity of any given outcome. Indeed, as has been noted by Stirling (2010: 1030) 'there is a need for humility about science-based decisions.'

Related to this, Interviewee No.3 in Chapter 2 of the report explained that instead of simply asking to what extent the undertaken work is 'novel,' it is also helpful to consider what it is that an 'early warning' might look like. It should be stressed that this is a consideration that exists *in addition to* the current requirements and considerations as typically addressed in the risk assessment process. The significance of this perspective is that it centres biological emergence and shifts the terrain of analysis towards a more iterative process of analysis. Indeed, as noted by Interviewee No.10 *'no matter how much information you have within the regulatory system in Europe at the end of the day it comes down to a judgement.'* The question, then, becomes how to make sure that such a judgement is rigorously informed, empirically grounded and recognises that there are inevitable gaps in scientific understandings of and evidence for risk which cannot simply be filled through the 'accumulation' of knowledge. These gaps can, however, as this report has demonstrated, be productively engaged through developing iterative ways of working with and thinking about synthetic biology experimentation. Building capacity in engaging with indeterminacy therefore helps HSE to ensure that work is handled in a measured and proportionate manner.

4.1c. In a field that is fast evolving and where knowledge can never be complete, the qualities of competence and safe practice must be built and enhanced through connections and partnerships:

Where knowledge is indeterminate, what becomes of critical importance are the connections and avenues of engagement that exist between regulators, practitioners and other interested stakeholders. In particular, Chapter 3 of the report highlighted how a) the profile of HSE must be such that practitioners feel able to approach HSE to raise any issues and concerns that they may have and that b) HSE must be sufficiently tapped into the undertakings of synthetic biology activities in a feasible and practicable manner. This ensures that HSE is able to develop a more grounded understanding of synthetic biology and is able to take a leading role in appropriately shaping and informing wider policy negotiations. Chapter 3 of the report suggested that HSE might achieve this through developing its presence at synthetic biology conferences. Not only would this help to develop HSE's understandings of synthetic biology but it would also help to position HSE as an *'open and friendly port of call if researchers have ideas or concerns'* (Interviewee No.10). Chapter 3 also provided an account of the qualities that practitioners held in high regard in terms of their relationship with HSE. In particular, practitioners expressed an appreciation for the linking of policy and technical knowledge. Some practitioners felt that there was more that HSE could do to raise its profile in terms of making clearer its role in wider policy negotiations. When considered in terms of partnerships, assuring the safe practice of synthetic biology therefore becomes an activity that is always beyond the lab and ensuring containment requires, paradoxically, an increasingly wider engagement with and differentiation of knowledge.

4.2 Final Remarks and Future Work

Through conducting over 30 1-2 hour interviews with a variety of key stakeholders and practitioners, analysing the responses from a) a synthetic biology survey sent out across GB's GM registered premises and b) from HSE's consultation on the consolidation of the GMO (Contained Use) Regulations which came into force in October 2014, and through attending key regulatory meetings including the Scientific Advisory Committee on GM (CU), this report sought to address the objectives as listed below. Accompanying these objectives is a brief account of the extent to which these have been successfully addressed. This is followed by a subsequent indication of future work/areas of reflection for HSE to consider.

Report Objective 1:

To develop a more grounded sense of what it means to carry out synthetic biology in practice.

Sections 2.1a and 2.1b of the report provided an account of the full range of practitioner understandings of the scope and implications of synthetic biology as encountered throughout the course of this research project. In drawing on a range of interview materials, this enabled Section 2.1c of the report to demonstrate that synthetic biology is not simply a singular field of scientific endeavour but is both *understood* and *practiced* in ways which do not always overlap. Chapter 2 of the report helped to add depth to and move beyond broad and generic statements such as synthetic biology either 'increases' or 'reduces' risk to human health and/or the environment through, for example, its respective role in the de-skilling of biological experimentation or its use of standardised, well characterised parts. Chapter 2 further highlighted how the significance of developing a more grounded understanding of synthetic biology is that it is only through developing an appreciation of synthetic biology's heterogeneity that it becomes possible to shed light on some of the key tensions that underpin the development of the field. In particular, these tensions were shown to include differences in practitioner understandings of the scope and implications of the emergent propensities of synthetic biology and the propensity of synthetic biology to depart from extant frames of reference.

Report Objective 2:

To account for the implications that this poses in terms of the development of safe practice.

Having developed a more grounded understanding of synthetic biology, Section 2.2 moved on to highlight how underpinning the range of understandings of the significance of synthetic biology is the propensity for synthetic biology to depart from existing comparative frames of reference and to enable non-proportionate and synergistic interactions between a range of biological and non-biological parts and components. Sections 2.2b and 2.2d provided an account of the ways in which practitioners are addressing the emergent propensities of synthetic biology and indeterminacy in scientific knowledge. These findings were drawn together in Section 4.1 'Enhancing the Robustness of a Risk Based Approach.' The significance of the examples listed in Section 2.2d and Section 4.1 is that they help to develop and build a space of critical reflection that proactively engages with the limitations of scientific knowledge.

Report Objective 3:

To consider what it might mean to build competence and confidence in synthetic biology from a scientific and regulatory perspective.

The interview materials that underpinned the development of this report pointed to the importance of productive and open avenues of communication between regulators and practitioners and highlighted the importance of the ways in which we understand synthetic biology as an emerging approach to scientific experimentation. It is upon recognising that synthetic biology is not simply a singular field of experimental endeavour that it becomes possible to ensure that the regulatory questions that surround synthetic biology are sufficiently focused and appropriately informed. This report demonstrated that building competence and confidence in synthetic biology from a scientific and regulatory perspective requires a) shifting the ways in which we think about synthetic biology; b) ensuring that built into the risk assessment and experimental process is sufficient space for critical reflection and that c) the avenues of connection that link regulators with practitioners must be open and effective.

In terms of **future areas of work** of relevance to HSE, HSE's long standing expertise in the both the legislative and practical implications of 'inherently safer design' places HSE in a unique position to engage with a number of developments in the field synthetic biology (e.g. safety switches).

i. Interviewee No.5 asserted that *'as soon as you start saying no that plant isn't good enough [in terms of containment and infrastructure] we need to start investing and that's when companies will make the commercial decision to say do we want to crack on and build this new lab this new containment this new lovely thing or do we just say right it's not for us at this time and I think HSE can have a role to play in that.'*
ii. Practitioner No.8 similarly posited that *'one of the things that we are aiming to do in the future is to have a bioreactor… that would contain these synthetically engineered bacteria… this would be a huge bioreactor… HSE would obviously be involved in building that right…. in a sense we've been thinking ahead here and thinking right what we could do is put in say a light sensitive kill switch.'*
iii. Finally, Practitioner No.19 reflected more speculatively that *'people are going to have products that need to be insured…. the actuaries who calculate risk will need to talk to people about what is risk specific in synthetic biology…. they will talk to HSE and it might not be so much about regulations, specific things it may be more about risk specific things.'*

On a more immediate basis, this report has demonstrated that HSE may wish to consider how it might tap further into the undertakings of synthetic biology in practice and develop its profile as a *'friendly and open port of call'* (Interviewee No.10). Building a presence at synthetic biology conferences was a preferred option that was expressed by many of the practitioners interviewed as part of this project.

These are important considerations, particularly during a time where synthetic biology is becoming scrutinised by an increasing number of international forums and non/governmental organisations. By considering what it might mean to engage productively with scientific indeterminacy, HSE is able to ensure that wider deliberations do not solely focus on the drive to accumulate scientific knowledge. Due to the emergent and non-proportionate propensities of biological substrate, it is important to recognise that it is simply not always possible to 'accumulate' scientific understandings of and evidence for risk. As such, it is critically important that attention is also afforded to building capacity in engaging with scientific indeterminacy through, for example, the connections and avenues of support that link regulators and practitioners. These considerations are especially important in ensuring that wider engagements with synthetic biology are proportionate and are not unduly swayed by the broader political milieu within which synthetic biology is unfolding and taking shape.

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Appendix 3

Notes from meeting on synthetic biology – regulatory approach

Room 5S2.020, Redgrave Court, HSE,
20 May 2015
13:30 – 15:00

Attendees: Lyndsey Baldwin (Policy Advisor, HID Policy), Peter Brown (Director, HID Policy), David Brown (Intervention Manager, CEMHD8), Katie Ledingham (Researcher, University of Exeter), Paul Logan (Director, CEMHD), Mike Paton (Policy Advisor, HID Policy), Simon Warne (Biotech Portfolio, CEMHD8)

Apologies: Richard Daniels (Head of Unit, CEMHD8)

Introduction & scene setting

1. Mike Paton introduced the topic with reference to the UKTI note[1] on investment in synthetic biology and the recent comment article in Nature on expression of opiates in yeast[2]. These articles illustrate the level of investment and some wider interest in the field.

2. In addition to being one of the eight great technological growth areas for the UK economy, synthetic biology is attracting international attention from the European Commission (through published opinions of its scientific committees)[3] and the United Nations Convention on Biological Diversity (CBD) (emerging topic discussion)[4].

3. MP explained that currently, most of the work in synthetic biology is encompassed by the genetically modified organism (GMO) legislation, which was confirmed in 2014, by the responses to the public consultation on the consolidation of the GMO contained use regulations[5]. While there has been considerable hype surrounding the proposed applications of synthetic biology for a number of years, the field is gaining some traction through delivery of products that were not previously feasible (eg biomanufacturing by altering the relevant biochemical pathways in yeast; and the expansion of databases containing subunits, parts, and components for assembly into synthetic systems).

4. Synthetic biology is also of interest to the security services, with particular reference to dual use research of concern, DIYBio and bioterrorism. The accessibility of 'biobricks' and ease of DNA synthesis has raised the potential, in the opinion of security services and commentators, for misuse of this technology.

5. MP explained that HSE is well positioned to contribute to this topic through:

    a) good policy links with Defra, BIS, Go Science;
    b) participation in the synthetic biology leadership council's (SBLC) governance subgroup;
    c) representation on the CBD on-line discussion forum and the future Ad-Hoc Technical Advisory Group meeting;
    d) participation in the Home Office led Biostrategy working group; and
    e) discussion papers at the Scientific Advisory Committee for Genetic Modification (SACGM).

Action 1 - Although not yet transformational, it was agreed that this is an area that HSE should continue to engage in at a policy level.

Summary & discussion of the report

6. Katie Ledingham briefly summarised the purpose of her secondment before explaining the key findings of her report entitled '*Building competence and safe practice in synthetic biology*'[6]. KL explained that she had been asked to conduct research to gather a more grounded understanding of synthetic biology. More specifically the research aimed to gain an insight into the breadth and scope of activities; practitioners understanding of the terms 'risk' and 'novelty'; and familiarity with existing risk management approaches. The research involved over thirty interviews (including practitioners, regulators, policymakers), circulation of a targeted questionnaire and participation in scientific advisory committee meetings.

7. The report identified the importance of the quality and nature of information and need for critical reflection to inform risk assessments, particularly where knowledge is indeterminate or incomplete. It highlighted the divergent nature of the actors involved in synthetic biology, which is significantly different from the traditional GMO field. The report considered the existing status of DIYBio in the UK, concluding that current activities are generally of negligible risk and that there is a considerable disjunction between renderings of DIY bio as posing heightened safety and security concerns and the undertakings of DIY bio in practice. It highlighted how engaging with the unfoldings of DIY bio in practice opens up a very different set of questions and issues (such as the high turnover rates and organisational structures associated with community laboratories). The 'community laboratories' interviewed as part of the research project were reassuringly tuned into biosafety considerations. The research recommended the need for an 'intelligent regulator' with productive and open avenues of communication between regulators and practitioners, to gather information on the range and pace of activities and to work together to build and ensure competence and safe practice in synthetic biology.

8. Given the current level of risk involved in synthetic biology activities, the type of frontline operational engagement that would be appropriate was discussed. Paul Logan explained that the primary focus of inspectors needed to remain on high containment facilities. Where such proactive inspections coincided at institutions undertaking synthetic biology activities, PL and David Brown considered it appropriate for inspectors to discuss risk assessment process and monitoring provisions with respect to synthetic biology. This would involve discussion on the risk assessment process (possibly including engagement with the institution biosafety committee). Both PL and DB explained that this was not a mandate to inspect lower containment laboratories but rather an instruction to explore the risk assessment management system and source of competent advice.

Action 2 – CEMHD8 to consider when visiting Universities/research Institutes as part of proactive CL3 inspection programme, Inspectors could discuss risk assessment management arrangements that encompasses synthetic biology

9. It was noted that this would only address academic and research institutions and would be unlikely to pick up industrial or commercial dutyholders. The UKTI note provides a list of companies involved in synthetic biology. Simon Warne suggested looking to see which of the companies was actually a registered GM centre. This would to give an indication of how many actually involve work with microorganisms.

Action 3 – CEMHD8 to cross check list of 5 or 6 start-up companies to check registration as GM centres

10. Peter Brown also suggested looking into an another secondee to follow up the industrial applications of synthetic biology. It was accepted that there may be a need to look at HSL are the primary source of research support, however there may be a case for the expertise only being available in Academia.

Action 4 – Policy to investigate possible secondment to follow up KL's project

11. A number of practitioners suggested that HSE could increase its profile with respect to synthetic biology via attendance at relevant conferences. Selection of one or two key conferences was considered an effective means of reaching non-traditional practitioners. Whilst the importance of this was recognised, it was emphasised that this needed to be considered on a cost-effective basis and as part of the wider training and conference budget.

Action 5 – CEMHD8/Policy to raise HSE profile by attendance at targeted synthetic biology conferences

12. Lyndsey Baldwin suggested increasing the profile by developing a webpage dedicated synthetic biology webpage, under the biological agents part of the HSE website. This would include reference to how it is regulated, links to risk assessment and some frequently asked questions to address the overlap between synthetic biology and GMOs.

Action 6 – Policy to develop a webpage for synthetic biology (possibly including an FAQ section)

13. MP also suggested that as the SACGM Compendium of Guidance is currently being revise, it would be an appropriate time to include a specific section on synthetic biology, either under the risk assessment section or as part of the introduction to the guidance, setting out how it can be applied to synthetic biology.

14. There are a number of emerging technologies that have the potential to create hazardous products (eg gene drives, gene editing and gain-of-function), which are often considered to be examples of synthetic biology. In some cases, there is uncertainty as to whether the products of these techniques fall within the definitions of the GMO legislation. These applications will need further consideration by SACGM and guidance as part of the revised Compendium.

Action 7 – CEMHD8 to include a section on synthetic biology in the revised SACGM Compendium of Guidance

15. MP raised the question of publication of the report and whether this might compromise KL's thesis submission hence whether publication should wait until after this was complete. KL confirmed that publication would not impact on her thesis. It was agreed that it was appropriate to publish the report, with particular interest in this field from other social scientists. MP agreed to discuss with the HSE editorial team as to the best means of doing this. PB expressed appreciation for the work that had gone into the report and the valuable information that had been provided.

Action 8 – Policy to investigate the most appropriate means of publishing the report

International perspective

16. As mentioned in the scene setting, there is growing national and international interest in synthetic biology with respect to investment and commercial growth, biosecurity concerns and regulatory oversight. The paper by Rhodes (2014)[7] provides a good

insight into the international debate on governance of synthetic biology including deliberations of CBD. MP highlighted some of the steps being taken in the USA as summarised by Gronvall (2015)[8]. These workstreams were considered in turn, to establish their relevance to the approach taken in the UK. These included:

- creation of a biosafety accident reporting system;
- engage (biosafety & biosecurity) beyond traditional laboratories (eg DIYBio, iGEM);
- explore 'safer by design' technologies;
- revise regulations and guidance to fill any gaps (eg Glowing plants); and
- focus on sectorial oversight (ie specific application based) rather than trying to regulate the entire field.

17. In the UK, there is already an accident reporting system in place (for GMOs, RIDDOR & SAPO). It was also felt that 'safety by design' was an integral part of the GMO risk assessment process and something that could be picked up by SACGM and the Compendium of Guidance. Where further advice on 'biological containment' was necessary, SACGM was considered to be an appropriate and effective route for doing so. One point raised was to ensure that the membership of SACGM remained current and encompassed the emerging field of synthetic biology.

Action 9 - SACGM to advise on synthetic biology risk assessment & and new techniques and also CEMHD8 need to check expertise of committee

18. As discussed previously, engagement with practitioners outside the traditional microbiology laboratories is important. The could be delivered via the approach of discussing synthetic biology at premises which coincide with the CEMHD8 proactive inspection programme. This would enable inspectors to gather intelligence, whilst ensuring a robust risk assessment process is in place for synthetic biology activities.

19. Whilst feedback from the recent public consultation on the consolidated GMO regulations indicated that the current regulations are deemed to encompass on-going synthetic biology work, it was recognised that this may not be the case for some future applications (eg protocells). It was recognised that any changes in regulations or definitions should be done through the EU rather than the UK doing something in isolation, to ensure a level playing field across the EU.

20. SW raised one gap in the current regulatory approach that relates to larger GMOs (eg plants, animals). Whilst there is a legislative requirement to undertake risk assessment, contain LGMOs and protect the environment (ie through Environmental Protection Act 1990 & associated regulations), there is no requirement for such work to be notified to the regulatory authority. In many cases, this work does not present a risk to the environment, however, there are examples where a release could cause environmental damage. Whilst this is not synthetic biology specific, there are applications of synthetic biology (eg gene drive) in LGMOs that could present a hazard to the environment.

21. HSE undertakes inspections of such LGMO work as part of an agency agreement with Defra and the Devolved Governments and is tasked with identifying where such work is undertaken and targeting inspections appropriately. It was agreed that further work was necessary to ensure HSE targets its inspections, as part of this agency agreement, in a manner that corresponds with LGMOs of greatest hazard.

Action 10 – CEMHD8 to review mechanism for prioritising LGMO visits - potential gap exists where greater hazard work involving synthetic biology (eg gene drive)

22. There has been an on-going debate in the EU about whether the GMO legislation, which defines GMOs based on the techniques used to modify them, should be changed to a definition entirely based on the novelty of the final GMO (ie whether it is different to the natural equivalent). It is unclear if the point raised by Gronvall is intended to reflect the 'product versus process' debate or more generally, the need to regulate the applications of synthetic biology on a case by case basis. The latter is reflective of the UK approach ie the products of synthetic biology may fall under the GMO regulations, chemical regulations or other relevant legislation and there is no imperative for overarching synthetic biology regulations.

Conclusions and Actions

PB summed up the key points from the meeting which included:

- Synthetic biology is an important growth area for the UK and HSE needs to be on the front-foot with respect to this emerging technology – it would be helpful to have a stakeholder map of the key players in this field (Action 11)
- Given the current level of hazard is low, the operational engagement with practitioners needs to be proportionate and targeted
- The existing mechanisms for seeking expert advice on risk assessment (ie through SACGM) on hazardous applications or microorganisms is appropriate provided the membership of SACGM has adequate expertise in synthetic biology
- There may be a gap with respect to target interventions in relation to LGMOs that should be reviewed
- The potential for inspectors to discuss synthetic biology as part of their existing programme of proactive inspections should be explored
- Given the appetite of practitioners to engage with HSE, participation in one or two key synthetic biology conferences should be investigated (eg SynBioBeta, Synthetic Biology Congress)
- HSE needs to reflect the growing area of activity on the HSE webpages and in the SACGM Compendium of Guidance
- Given the success of the project, HSE should investigate whether a future secondment from academia is feasible (taking account of expertise in HSL)

References

1. UK Trade & Investment (2015), UK science & innovation - synthetic biology (TRIM 2015/219666)
2. Oye et al (2015), Comment – Regulate 'Home Brew' Opiates, Nature, 521, 281-283 (TRIM 2015/219657)
3. European Commission (2014), The European Commission and the Scientific Committees on Consumer safety (SCCS), on Health and Environmental Risks (SCHER) and on Emerging and Newly Identified Health Risks (SCENIHR) – Final Opinion on synthetic biology I – definition
4. Convention on Biological Diversity (2015), CBD Technical Series No.82 - Synthetic Biology
5. HSE (2014), Summary report – Responses to HSE's consultation (CD263) on the proposed consolidation of the Genetically Modified Organisms (Contained Use) Regulations
6. Katie Ledingham, (2015), *Research Report for HSE - Building Competence and Safe Practice in Synthetic Biology: Policy Orientations and Operational Considerations*, University of Exeter (TRIM 2015/219700)

7. Catherine Rhodes, (2014), *Relevance of Genetic Resources Governance to Synthetic Biology,* Ethics in Biology, Engineering & Medicine - An International Journal, 5(2): 161–183 (TRIM 2015/219744)
8. Gigi Kwik Gronvall, (2015), *Mitigating the Risks of Synthetic Biology*, Center for Preventive Action Contingency Roundtable and Memoranda series, Council on Foreign Relations, February 2015 (TRIM 2015/219756)

Annex 1 – Table summarising of Actions and suggested timescales

No.	Action required	By Whom	By When
1	*HSE should continue to engage in at a policy level – revision of UK roadmap; participation in international discussions (EC, CBD)*	*MP*	*On-going*
2.	*CEMHD8 to consider when visiting Universities/research Institutes as part of proactive CL3 inspection programme, Inspectors could discuss risk assessment management system that encompasses synthetic biology*	*SW/DB*	*April 2016*
3.	*CEMHD8 to cross check list of 5 or 6 start-up companies to check registration as GM centres*	*SW*	*October 2015*
4.	*Policy to investigate possible secondment to follow up KL's project*	*MP*	*October 2015*
5	*CEMHD8/Policy to raise HSE profile at targeted synthetic biology conferences*	*SW/MP*	*April 2016*
6	*Policy to develop webpage for synthetic biology (possibly including an FAQ section)*	*LB/MP*	*December 2015*
7	*CEMHD8 to include section on synthetic biology to be included in the revised SACGM Compendium of Guidance*	*SW*	*March 2016*
8	*Policy to investigate the most appropriate means of publishing the report*	*MP/LB*	*October 2015*
9	*CEMHD8 to review SACGM expertise to include synthetic biology (may require recruitment of specific members)*	*SW*	*December 2015*
10	*CEMHD8 to review mechanism for prioritising LGMO visits*	*SW/DB*	*October 2015*
11	*Policy to develop a stakeholder map of the key players in synthetic biology*	*LB/MP*	*October 2015*

Appendix 4

Katie Ledingham - Secondment Feedback

Project: 'Building Competence and Safe Practice in Synthetic Biology: Policy Orientations and Operational Considerations.'
Division: Health & Safety Executive, Hazardous Installations Directorate (HID), HID Policy Division, Biological Agents Policy Team
Position: Researcher (secondment)
Line Manager: Dr Michael Paton
Duration: April 2014 – April 2015

HSE was fortunate to secure the services of Katie from 1 April 2014, initially for 6 months but extended to a very productive 12 months, finishing 31 March 2015.

During this time, Katie gained an insight into how policy is developed within the civil service (& across different Government Departments) and gained a comprehensive understanding of HSE's approach to regulating health and safety in Great Britain (including visits to high containment laboratories). In return, Katie undertook a research project to provide an understanding of what it means to undertake synthetic biology in practice and provide recommendations to inform HSE's policy deliberations in this area. Katie was able to produce a comprehensive report that:

- Engaged a range of stakeholders in the synthetic biology field.
- Provided an analysis of practitioner understandings and approaches to synthetic biology.
- Added depth and texture to terms such as 'risk' and 'novelty' which are frequently mobilised in synthetic biology discussions.
- Presented a number of recommendations for HSE to consider in how it engages practitioners and to include as part of developing policy in this area.

In addition, Katie was also able to research and draft a position paper on behalf of the European Commission, in relation to the contained use of living modified organisms, which also involved attendance at a Working Party on International Environmental Issues, at the European Commission in Brussels. The paper was presented by the European Presidency, at the Conference of the Parties to the Convention on Biological Diversity, in South Korea and resulted in a successful outcome for the UK and EU.

During the course of this research, Katie managed to immerse herself in the HSE organisational culture through participation in the HSE's performance management system, utilised the travel and subsistence system effectively, contributed to biological agents policy team meetings and attended the HID Policy Division Conference. Consequently, Katie has been able to demonstrate civil service core competencies including (i) delivery of quality work to challenging deadlines; (ii) establishing positive and professional working relationships with a wide range of people both within and outside civil service to improve HSE business; (iii) used sound judgement, evidence and knowledge to articulate reasoned decisions and opinions and; (iv) developed an excellent understanding and knowledge of how her work contributed to both HSE's business and the wider public needs. Katie has taken full advantage of the opportunities that her secondment offered.

A key development observed across the course of the secondment was Katie's willingness to discuss and ability to communicate complex and theoretical social science principles in a more practical and accessible manner such that it is anticipated that Katie's final report will be published by HSE to benefit the wider synthetic biology community.

Overall, the outputs from Katie's secondment have been extremely helpful in informing HSE's policy on synthetic biology. More importantly, Katie has demonstrated a professional, committed and effective performance that is a credit to both Katie and the University of Exeter.