Pattern selection: the importance of "how you get there"

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We all developed from an embryo: along this long way many billions of cells were making decisions on how to differentiate, proliferate or undergo apoptosis. Along the way, these cells take cues from each other in order to differentiate into different tissues, organs and patterns. Pattern formation is one of the most visible forms of decision making and has been widely studied; for example, in chemotactic pattern formation (1). The seminal work of Turing (2) showed the basic principle that patterns can form in homogeneous tissue through a generic instability in a system that involves at least two interacting chemical species. Although cells are much more complicated, it is well-accepted that a cell's decisions about pattern formation are controlled by gene regulatory networks that coordinate the action of many genes involved in the decision making, in conjunction with signals from other interacting cells or external media. But precisely which factors affect these decisions? In particular, if there are several stable patterns, which emergent pattern will be "selected" by the cells that make up a tissue?

A common belief is that the eventual pattern chosen depends primarily on initial conditions. Palau-Ortin et al. (3) suggest a different view, from a theoretical study of pattern-formation for the Notch signaling pathway in the *Drosophila* embryo. Surprisingly, their research shows that the pattern chosen may depend more on the dynamical mechanism of spatio-temporal changes of the control parameters than on the initial conditions; a dynamical path in the space of signals may steer the system into one of a number of possible stable patterns. Indeed, according to Palau-Ortin et al. (3), pattern formation seems to be as much about "how you get there" as "where you start"!

Decisions in biological systems often need to be made rapidly and consistently, for example during the development of an embryo, and the outcome may depend not only on the path taken but on how fast you traverse the path. A mechanism explaining how the final state can depend on the speed is illustrated in Fig.1. Let us consider a system governed by the asymmetric bifurcation scenario: if we start in state A and change the control parameter slowly, state B will be reached. However, a fast change of the control parameter will move a system into the state D. This simple example illustrates that rate of the decision making can be just as important as any bifurcation scenario or initial conditions. In this case, the selection of final state can be understood in the context of a rate-induced tipping point in an open system (4).

Cellular decisions are fundamental for key cellular processes, including developmental pattern formation, cell differentiation and the maintenance of pluripotency. In the presence of several stable conditions (and the absence of any clear mechanisms to set initial conditions), these decisions must somehow depend on the form and rate of the dynamical path in the space of controlling parameters. For example, a common genetic switch that sustains decision making consists of two mutually inhibiting genes under the action of two external signals. Such a switch, because of its bistability (where stable states correspond to the genes in the states “On-Off” or “Off-On”), can be considered as a simple model of the cell differentiation. This genetic switch may be engineered by tools of Synthetic Biology and there are many possible implications for biotechnology, biocomputing or gene therapy. When the external signals are sufficiently symmetric, the circuit may exhibit bistability which is associated with two distinct cell fates chosen with equal probability because of noise involved in gene expression. If, however, the input signals provide a transient asymmetry, the switch will be biased by the rate of the external signals and the effect of speed-dependent cellular decision making can be observed (5), in which slow and fast decisions will results in a different probability to choose the corresponding cell fate. The speed at which the system crosses a critical region strongly influences the sensitivity to transient asymmetry of the external signals. For high speed changes, the system may not notice a transient asymmetry but for slow changes, bifurcation delay may increase the probability of one of the states being selected (6).

Palau-Ortin et al. (3) study a number of scenarios in their paper that enable them to control the system into a target pattern that may be homogeneous (H), periodic "salt-and-pepper" (P) or stripe (S) patterns in an idealized 2D tissue. They consider three types of control, (1) the control is homogeneous, (2) the control acts locally in space and (3) the control propagates across the tissue. By a number of computational experiments the authors give recipes of how to rapidly and reliably move the system into one of the three target patterns by a path that may be transient. As Palau-Ortin et al. (3) state; "the key elements for pattern selection are the destabilization of the initial pattern, the subsequent exploration of other patterns determined by the spatio–temporal symmetry of the parameter changes and the speeds of the path compared to the time scales of the pattern formation process itself".

Study of time-dependent bifurcation problems has long history and there is a considerable literature on noise and rate induced escape from attractors in dynamical models. To mention a few of these, Kondepudi et al. (7) considered the combined effect of noise and parameter changes on the related problem of "attractor selection" in a noisy system, while Nicolis and Prigogine described a mechanism enabling symmetry breaking and pattern selection in non-equilibrium systems (8). Dynamic bifurcations (9) are a useful approach to the quantitative description of solutions to systems of stochastic differential equations evolving on well-separated timescales. Symmetry breaking and state selection have been shown to play an important role in noisy electronic systems (7) while Alagha et al. considered an interplay between asymmetry and noise in erythroid-myeloid differentiation switch and have shown that timing in a binary cell-fate decision may have important contributions to the immune system when the bias is in favor of the cell fate which gives rise to non-immune cells (10).

The finding of Palau-Ortin et al. (3) that dynamics and shape of the parameter path can crucially affect the selection of the final pattern seems to be an important and generic mechanism. These effects should allow us to account for rapid pattern formation in developmental biology, clinical diagnostics and synthetic biology. A next step in the study of path dependent pattern formation (3) will be a testing of these theoretical findings into experimental and practical applications. Questions that need to be addressed include: Which signals give rise to a specific patterned outcome? How are they generated by the cell? How can parameter paths through bifurcations suggest engineering principles underlying biological systems? Taking parameter paths and timing into account may explain many features of dynamic pattern formation and gives us a hope of new methods, for example, to treat diseases associated with malfunctioning of these mechanisms. Many related interesting questions are ripe for exploration, including, for example, counter-intuitive behavior resulting from the interplay between the system and input asymmetries, the noise and the spatio-temporal features of the path in parameter space.

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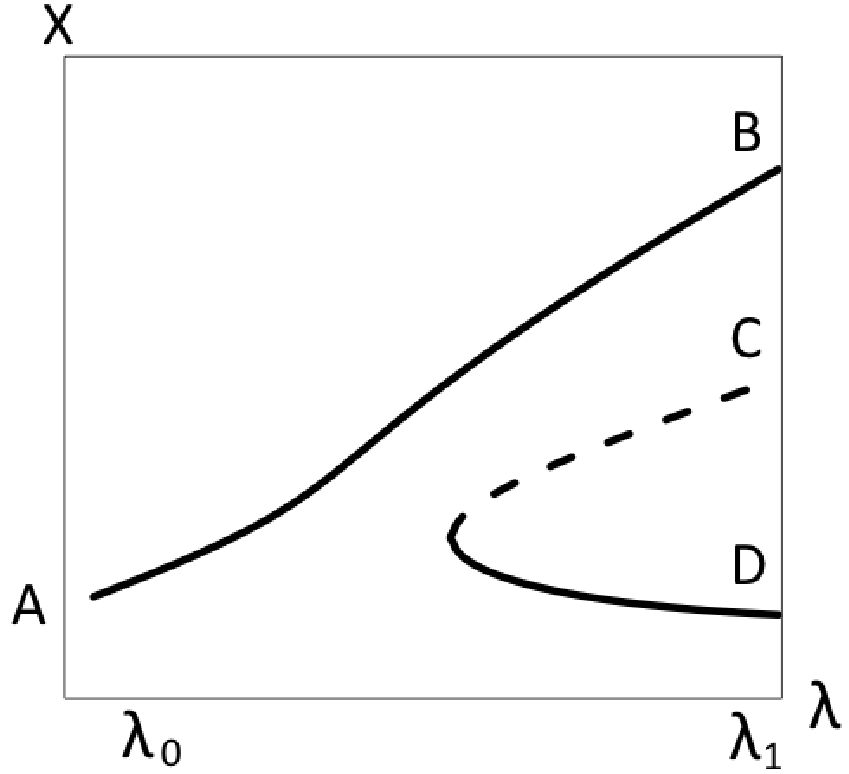

Figure 1 An illustration of a simple mechanism responsible for speed dependent decision making in terms of a bifurcation diagram where the horizontal axis represents a time-dependent input that changes from $\lambda = \lambda_0$ to λ_1. The vertical axis represents the state of the system X; in this illustration the system for λ_0 has only one attracting state, while for λ_1 there is bistability. If the control parameter λ changes slowly enough, the system will move from state A to state B. If the change is sufficiently fast, then the system will move to state D; for intermediate rates of change the details of noise in the system will become significant.