Modelling and Optimisation of Mechanical Ventilation for Critically Ill Patients

Submitted by Anup Das, to the University of Exeter as a thesis for the degree of Doctor of Philosophy in Engineering,
March 2012.

This thesis is available for library use on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgment.

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.

Signature:  ----------------------------------------
Abstract

This thesis is made up of three parts: i) the development of a comprehensive computational model of the pulmonary (patho)physiology of healthy and diseased lungs, ii) the application of a novel optimisation-based approach to validate this computational model, and iii) the use of this model to optimise mechanical ventilator settings for patients with diseased lungs.

The model described in this thesis is an extended implementation of the Nottingham Physiological Simulator (NPS) in MATLAB. An iterative multi-compartmental modelling approach is adopted, and modifications (based on physiological mechanisms) are proposed to characterise healthy as well as diseased states.

In the second part of the thesis, an optimisation-based approach is employed to validate the robustness of this model. The model is subjected to simultaneous variations in the values of multiple physiologically relevant uncertain parameters with respect to a set of specified performance criteria, based on expected levels of variation in arterial blood gas values found in the patient population. Performance criteria are evaluated using computer simulations. Local and global optimisation algorithms are employed to search for the worst-case parameter combination that could cause the model outputs to deviate from their expected range of operation, i.e. violate the specified model performance criteria. The optimisation-based analysis is proposed as a useful complement to current statistical model validation techniques, which are reliant on matching data from in vitro and in vivo studies.

The last section of the thesis considers the problem of optimising settings of mechanical ventilation in an Intensive Therapy Unit (ITU) for patients with diseased lungs. This is a challenging task for physicians who have to select appropriate mechanical ventilator settings to satisfy multiple, sometimes conflicting, objectives including i) maintaining adequate oxygenation, ii) maintaining adequate carbon dioxide clearance and iii) minimising the risks of ventilator associated lung injury (VALI). Currently, physicians are reliant on guidelines based on previous experience and recommendations from a very limited number of in vivo studies which, by their very nature, cannot form the basis of personalised, disease-specific treatment protocols. This thesis formulates the choice of ventilator settings as a constrained multi-
objective optimisation problem, which is solved using a hybrid optimisation algorithm and a validated physiological simulation model, to optimise the settings of mechanical ventilation for a healthy lung and for several pulmonary disease cases. The optimal settings are shown to satisfy the conflicting clinical objectives, to improve the ventilation perfusion matching within the lung, and, crucially, to be disease-specific.
Acknowledgements

First and foremost, I would like to thank Professor Declan Bates, whose vision and boundless enthusiasm continues to be the driving force behind our project and my work. I am thankful to Professor Jonathan Hardman from University of Nottingham, whose work and knowledge in the field of physiology and physiological modelling has been the cornerstone of this thesis. I would like to kindly thank Dr Prathyush Menon from the University of Exeter, for his ever-reliable and extensive guidance. All my supervisors have shown incredible patience and support towards me, for which I will be forever grateful.

I would like to thank my friends and family for their understanding and care. I would like to thank my colleagues and the staff at University of Exeter for the numerous instances they have provided me help.

Finally, I would like to dedicate this thesis to my father, mother and my sister, whose love and encouragement have been a source of inspiration throughout my life.
# Table of Contents

Abstract............................................................................................................................................... 1

Acknowledgements............................................................................................................................. 3

Table of Contents ............................................................................................................................... 4

List of Figures ...................................................................................................................................... 7

List of Tables ...................................................................................................................................... 11

Abbreviations and Nomenclature ....................................................................................................... 13

Chapter 1: Introduction....................................................................................................................... 16
  1.1 Motivation..................................................................................................................................... 16
  1.2 Thesis organisation ...................................................................................................................... 18
  1.3 Main contributions of this study ................................................................................................. 20

Chapter 2: Modelling of pulmonary physiology .............................................................................. 23
  2.1 Pulmonary physiology – key concepts ....................................................................................... 23
   2.1.1 Lungs ..................................................................................................................................... 23
   2.1.2 Lung volumes and capacities ............................................................................................... 24
   2.1.3 O₂ and CO₂ movement across the alveolar membrane ...................................................... 27
   2.1.4 The airways and the blood vessels ....................................................................................... 29
   2.1.5 Distribution of ventilation and perfusion ............................................................................. 30
  2.2 Modelling and implementation of a pulmonary physiology simulator ................................. 32
   2.2.1 Modelling of pulmonary systems - background ................................................................ 32
   2.2.2 Simulation model initialisation ............................................................................................. 45
   2.2.3 Program Structure ................................................................................................................ 46
  2.3 Model development and utilisation ............................................................................................. 48
   2.3.1 Simulating a healthy lung....................................................................................................... 50
   2.3.2 Simulating diseased lungs .................................................................................................... 51
   2.3.3 In silico behaviour of diseased lungs ................................................................................... 53
   2.3.4 Simulating alveolar volumes ................................................................................................. 54
   2.3.5 The effect of PEEP ............................................................................................................... 58
   2.3.6 Clinical validation of the modified model ............................................................................ 61
# Table of Contents

## Chapter 3: Validation of Pulmonary Physiology Models ........................................... 64
  3.1 Current methods ........................................................................................................ 64
  3.1.1 Disadvantages of current methods ................................................................. 68
  3.2 Model validation using optimisation methods ......................................................... 71
    3.2.1 Sequential Quadratic Programming ................................................................. 74
    3.2.2 Mesh Adaptive Direct Search (MADS) ............................................................... 74
    3.2.3 Genetic Algorithms (GA) .................................................................................... 76
    3.2.4 Differential Evolution (DE) ................................................................................ 79
  3.3 Validation of pulmonary physiology simulator for clinical applications .......... 81
    3.3.1 Introduction ......................................................................................................... 81
    3.3.2 Modelling of uncertain parameters ................................................................. 82
    3.3.3 Formulation of the model validation problem .................................................. 83
    3.3.4 Results ................................................................................................................ 86
    3.3.5 Discussion ........................................................................................................... 95

## Chapter 4: Optimising Mechanical Ventilator Settings .............................................. 99
  4.1 Introduction ............................................................................................................... 100
    4.1.1 Mechanical Ventilation ..................................................................................... 100
    4.1.2 Ventilator Associated Lung Injury (VALI) ......................................................... 103
    4.1.3 Current approaches to deciding mechanical ventilation settings ................... 104
  4.2 Problem introduction ............................................................................................... 107
  4.3 Multi-objective optimisation .................................................................................... 108
    4.3.1 Introduction ......................................................................................................... 108
    4.3.2 Methods for multi-objective optimisation ......................................................... 111
  4.4 Problem description .................................................................................................. 117
    4.4.1 Mechanical ventilator settings ........................................................................... 117
    4.4.2 \textit{In silico} setup ................................................................................................. 119
  4.5 Modelling healthy and diseased lung states .......................................................... 122
  4.6 Multi-objective optimisation of mechanical ventilation ....................................... 123
    4.6.1 Weighted Aggregate Objective Function approach ........................................... 125
    4.6.2 Comparison of the WAOF approach to NSGA-II .............................................. 126
  4.7 Computing optimised ventilator settings ............................................................... 129

## Chapter 5: Conclusions and Future Work ................................................................. 136
  5.1 Conclusions .............................................................................................................. 136
5.2 Future work

Appendix

A – Pre and post-intervention ventilator settings to validate modified model

B – Termination conditions for optimisation algorithms - TolFun and TolX

Bibliography