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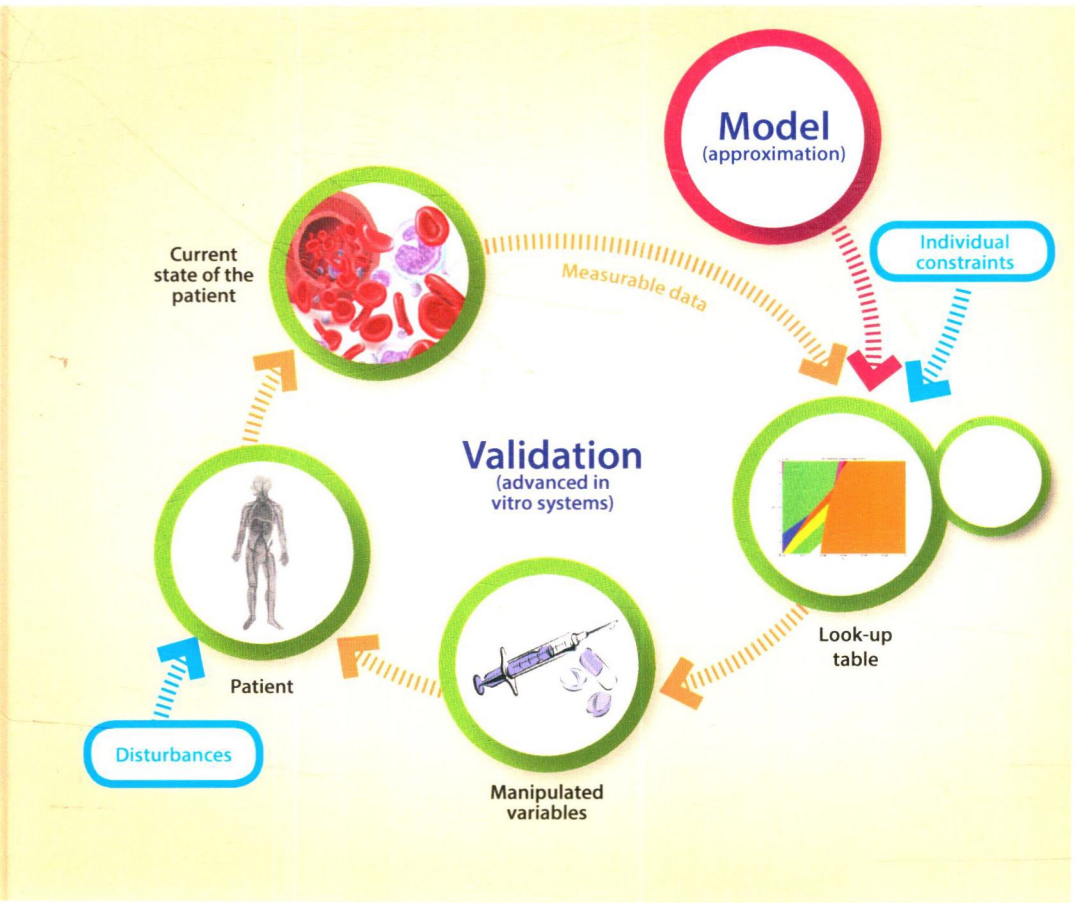
Modelling Optimization and Control of Biomedical Systems



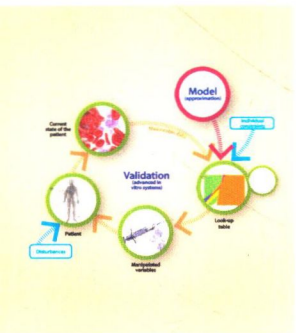
Shows the Newest Developments in the Field of Multi-Parametric Model Predictive Control and Optimization and their Application for Drug Delivery Systems

This book is based on the Modelling, Control and Optimization of Biomedical Systems (MOBILE) project, which was created to derive intelligent computer model-based systems for optimization of biomedical drug delivery systems in the cases of diabetes, anaesthesia, and blood cancer. These systems can ensure reliable and fast calculation of the optimal drug dosage without the need for an online computer—while taking into account the specifics and constraints of the patient model, flexibility to adapt to changing patient characteristics and incorporation of the physician's performance criteria, and maintaining the safety of the patients.

Modelling Optimization and Control of Biomedical Systems covers: mathematical modelling of drug delivery systems; model analysis, parameter estimation, and approximation; optimization and control; sensitivity analysis & model reduction; multi-parametric programming and model predictive control; estimation techniques; physiologically-based patient model; control design for volatile anaesthesia; multiparametric model based approach to intravenous anaesthesia; hybrid model predictive control strategies; Type I Diabetes Mellitus; in vitro and in silico block of the integrated platform for the study of leukaemia; chemotherapy treatment as a process systems application; and more.

- Introduces readers to the Modelling, Control and Optimization of Biomedical Systems (MOBILE) project
- Presents in detail the theoretical background, computational tools, and methods that are used in all the different biomedical systems
- Teaches the theory for multi-parametric mixed-integer programming and explicit optimal control of volatile anaesthesia
- Provides an overview of the framework for modelling, optimization, and control of biomedical systems

This book will appeal to students, researchers, and scientists working on the modelling, control, and optimization of biomedical systems and to those involved in cancer treatment, anaesthsia, and drug delivery systems.



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Cover Design: Wiley
Cover Image: Courtesy of Efstratios N. Pistikopoulos

ISBN 978-1-118-96559-7

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Also available as an e-book

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This edition first published 2018

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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Library of Congress Cataloging-in-Publication data applied for

ISBN: 9781118965597

Cover design by Wiley
Cover image: Courtesy of Efstratios N. Pistikopoulos

Set in 10/12pt Warnock by SPi Global, Pondicherry, India
Printed and bound in Malaysia by Vivar Printing Sdn Bhd

10 9 8 7 6 5 4 3 2 1

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Preface

A great challenge when dealing with severe diseases, such as cancer or diabetes, is the implementation of an appropriate treatment. Design of treatment protocols is not a trivial issue, especially since nowadays there is significant evidence that the type of treatment depends on specific characteristics of individual patients.

In silico design of high-fidelity mathematical models, which accurately describe a specific disease in terms of a well-defined biomedical network, will allow the optimisation of treatment through an accurate control of drug dosage and delivery. Within this context, the aim of the Modelling, Control and Optimisation of Biomedical Systems (MOBILE) project is to derive intelligent computer model-based systems for optimisation of biomedical drug delivery systems in the cases of diabetes, anaesthesia and blood cancer (i.e., leukaemia).

From a computational point of view, the newly developed algorithms will be able to be implemented on a single chip, which is ideal for biomedical applications that were previously off-limits for model-based control. Simpler hardware is adequate for the reduced on-line computational requirements, which will lead to lower costs and almost eliminate the software costs (e.g., licensed numerical solvers). Additionally, there is increased control power, since the new MPC approach can accommodate much larger – and more accurate – biomedical system models (the computational burden is shifted off-line).

From a practical point of view, the absence of complex software makes the implementation of the controller much easier, therefore allowing its usage as a diagnostic tool directly in the clinic by doctors, clinicians as well as patients without the requirement of specialised engineers, therefore progressively enhancing the confidence of medical teams and patients to use computer-aided practices. Additionally, the designed biomedical controllers increase treatment safety and efficiency, by carefully applying a "what-if" prior analysis that is tailored to the individual patient's needs and characteristics, therefore reducing treatment side effects and optimising the drug infusion rates. Flexibility of the device to adapt to changing patient characteristics and incorporation of the physician's performance criteria are additional great advantages.

There were several highly significant achievements of the project for all different diseases and biomedical cases under study (i.e., diabetes, leukaemia and anaesthesia). From a computational point of view, achievements include the construction of high-fidelity mathematical models as well as novel algorithm derivations. The methodology followed for the model design includes the following steps: (a) the derivation of a high-fidelity model, (b) the conduction of sensitivity analysis, (c) the application of parameter estimation techniques on the derived model in order to identify and estimate the sensitive model parameters and variables and (d) the conduction of extensive validation studies based on patient and clinical data. The validated model is then reduced to an approximate model suitable for optimisation and control via model reduction and/or system identification algorithms. The several theoretical (*in silico*) components are incorporated in a closed-loop (*in silico–in vitro*) framework that will be evaluated with *in vitro* trials (i.e., through experimental evaluation of the control-based optimised drug delivery). The outcome of the experiments will indicate the validity of the suggested closed-loop delivery of anaesthetics, chemotherapy dosages for leukaemia and insulin delivery doses in diabetes. It should be mentioned that this is the first closed-loop system including computational and experimental elements. The output of such a framework could be introduced, at a second step, in phase 1 clinical trials.

Chapter 1 is an overview of the framework for modelling, optimisation and control of biomedical systems. It describes the mathematical modelling of drug delivery systems that usually requires a pharmacokinetic part, a pharmacodynamic part and a link between the two. Model analysis, parameter estimation and approximation are used here in order to obtain an in-depth understanding of the model. Mathematical optimisation and control of the biomedical system could lead to a better prediction of the optimal drug and/or therapy treatment for a specific disease.

Chapter 2 presents in detail the theoretical background, computational tools and methods that are used in all the different biomedical systems analysed within the book. More specifically, Chapter 2 focuses on describing the computational tools, part of the developed multiparametric model predictive control framework presented in Chapter 1. It also presents the theory for multiparametric mixed-integer programming and explicit optimal control. This is part of the larger class of hybrid biomedical systems (i.e., biomedical systems featuring both discrete and continuous dynamics).

Chapters 3 and 4 aim at applying the presented framework to the process of anaesthesia: both volatile as well as intravenous. They present the procedure step by step from the model development to the design of a multiparametric model predictive controller for the control of depth of anaesthesia. Chapter 3 focuses on the process of volatile anaesthesia. A detailed physiologically based pharmacokinetic–pharmacodynamic patient model for volatile anaesthesia is presented where all relevant parameters and variables are analysed. A model

predictive control (MPC) strategy is proposed to assure safe and robust control of anaesthesia by including an on-line parameter estimation step that accounts for patient variability. A Kalman filter is implemented to obtain an estimate of the states based on the measurement of the end-tidal concentration. An on-line estimator is added to the closed control loop for the estimation of the PD parameter C50 during the course of surgery. Closed-loop control simulations for the system for conventional MPC, explicit MPC and the on-line parameter estimation are presented for induction and disturbances during maintenance of anaesthesia.

In Chapter 4, we describe the process of intravenous anaesthesia. The mathematical model for intravenous anaesthesia is presented in detail, and sensitivity analysis is performed. The main objective is to develop explicit MPC strategies for the control of depth of anaesthesia in the induction and maintenance phases. State estimation techniques are designed and implemented simultaneously with mp-MPC strategies to estimate the state of each individual patient. Furthermore, a hybrid formulation of the patient model is performed, leading to a hybrid mp-MPC that is further implemented using several robust techniques.

Chapter 5 is focused on type 1 diabetes mellitus, more specifically on modelling, model analysis, optimisation and glucose regulation. The basic idea is to develop an automated insulin delivery system that would mimic the endocrine functionality of a healthy pancreas. The first level is the development of a high-fidelity mathematical model that represents in depth the complexity of the glucoregulatory system, presents adaptability to patient variability and demonstrates adequate capture of the dynamic response of the patient to various clinical conditions (normoglycaemia, hyperglycaemia and hypoglycaemia). This model is then used for detailed simulation and optimisation studies to gain a deep understanding of the system. The second level is the design of model-based predictive controllers by incorporating techniques appropriate for the specific demands of this problem.

The last three chapters are focused on the development of a systematic framework for the personalised study and optimisation of leukaemia (i.e., a severe cancer of the blood): from *in vivo* to *in vitro* and *in silico*. More specifically, Chapter 6 is a general description of the independent building blocks of the integrated framework, which are further analysed in the next chapters. Chapter 7 focuses on the detailed description of the *in vitro* building block of the framework. More specifically, it includes analysis of the disease, analysis of the experimental platform and environmental (stress) stimuli that are monitored within the platform, and a description of cellular biomarkers for monitoring the evolution of leukaemia *in vitro*. Chapter 8 focuses on the *in silico* building block of the framework. It describes the pharmacokinetic and pharmacodynamic models developed for the optimisation of chemotherapy treatment for leukaemia. Finally, the simulation results and analysis of a patient case study are presented.

The main outcome of this work is to develop models and model-based control and optimisation methods and tools for drug delivery systems, which would ensure: (a) reliable and fast calculation of the optimal drug dosage without the need for an on-line computer, while taking into account the specifics and constraints of the patient model (personalised health care); (b) flexibility to adapt to changing patient characteristics, and incorporation of the physician's performance criteria; and (c) safety of the patients, as optimisation of drug infusion rates would reduce the side effects of treatment. The major novelty introduced by mobile technology is that it is no longer necessary to trade off control performance against hardware and software costs in drug delivery systems. The parametric control technology will be able to offer state-of-the-art model-based optimal control performance in a wide range of drug delivery systems on the simplest of hardware. All of this will lead to some very important advantages, like: enhancing the confidence of medical teams to use computer-aided practices, increasing the confidence of patients to use such practices, enhancing safety by carefully applying a "what-if" prior analysis tailored made to patients' needs, a simple "look-up function," an optimal closed-loop response and cheap hardware implementation.

The book shows the newest developments in the field of multiparametric model predictive control and optimisation and their application for drug delivery systems.

This work was supported by the European Research Council (ERC), that is, by ERC-Mobile Project (no. 226462), ERC-BioBlood (no. 340719), the EU 7th Framework Programme (MULTIMOD Project FP7/2007-2013, no. 238013), the Engineering and Physical Sciences Research Council (EPSRC: EP/G059071/1 and EP/I014640), the Richard Thomas Leukaemia Research Fund and the Royal Academy of Engineering Research Fellowship (to Dr. Ruth Misener).

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