Contents

List of Contributors  xiii
Preface  xv

Part I  1

1 Framework and Tools: A Framework for Modelling, Optimization and Control of Biomedical Systems  3
Eirini G. Velliou, Ioana Naşcu, Stamatina Zavitsanou, Eleni Pefani, Alexandra Krieger, Michael C. Georgiadis, and Efstratios N. Pistikopoulos

1.1 Mathematical Modelling of Drug Delivery Systems  3
1.1.1 Pharmacokinetic Modelling  3
1.1.1.1 Compartental Models  3
1.1.1.2 Physiologically Based Pharmacokinetic Models  5
1.1.2 Pharmacodynamic Modelling  5
1.2 Model analysis, Parameter Estimation and Approximation  7
1.2.1 Global Sensitivity Analysis  8
1.2.2 Variability Analysis  8
1.2.3 Parameter Estimation and Correlation  9
1.3 Optimization and Control  9
References  11

2 Draft Computational Tools and Methods  13
Ioana Naşcu, Richard Oberdieck, Romain Lambert, Pedro Rivotti, and Efstratios N. Pistikopoulos

2.1 Introduction  13
2.2 Sensitivity Analysis and Model Reduction  14
2.2.1 Sensitivity Analysis  14
2.2.1.1 Sobol’s Sensitivity Analysis  16
2.2.1.2 High-Dimensional Model Representation  17
2.2.1.3 Group Method of Data Handling  18
2.2.1.4 GMDH–HDMR 19
2.2.2 Model Reduction 20
2.2.2.1 Linear Model Order Reduction 21
2.2.2.2 Nonlinear Model Reduction 22
2.3 Multiparametric Programming and Model Predictive Control 24
2.3.1 Dynamic Programming and Robust Control 28
2.4 Estimation Techniques 33
2.4.1 Kalman Filter 34
2.4.1.1 Time Update (Prediction Step) 34
2.4.1.2 Measurement Update (Correction Step) 34
2.4.2 Moving Horizon Estimation 34
2.5 Explicit Hybrid Control 39
2.5.1 Multiparametric Mixed-Integer Programming 40
2.5.1.1 Problem and Solution Characterization 40
2.5.1.2 Literature Review 42
2.5.1.3 A General Framework for the Solution of mp-MIQP Problems 48
2.5.1.4 Detailed Analysis of the General Framework 50
2.5.1.5 Description of an Exact Comparison Procedure 54

References 57

3 Volatile Anaesthesia 67
Alexandra Krieger, Ioana Naşcu, Nicki Panoskaltsis, Athanasios Mantalaris, Michael C. Georgiadis, and Efstratios N. Pistikopoulos
3.1 Introduction 67
3.2 Physiologically Based Patient Model 69
3.2.1 Pharmacokinetics 69
3.2.1.1 Body Compartments 72
3.2.1.2 Blood Volume 73
3.2.1.3 Cardiac Output 73
3.2.1.4 Lung Volume 74
3.2.2 Pharmacodynamics 74
3.2.3 Individualized Patient Variables and Parameters 74
3.3 Model Analysis 75
3.3.1 Uncertainty Identification via Patient Variability Analysis 75
3.3.2 Global Sensitivity Analysis 77
3.3.3 Correlation Analysis and Parameter Estimation 81
3.3.4 Simulation Results 83
3.4 Control Design for Volatile Anaesthesia 86
3.4.1 State Estimation 87
3.4.1.1 Model Linearization 88
3.4.2 On-Line Parameter Estimation 90
3.4.2.1 Control and Algorithm Design 91
4 Intravenous Anaesthesia 103
Ioana Naşcu, Alexandra Krieger, Romain Lambert, and Efstratios N. Pistikopoulos

4.1 A Multiparametric Model-based Approach to Intravenous Anaesthesia 103
4.1.1 Introduction 103
4.1.2 Patient Model 104
4.1.3 Sensitivity Analysis 108
4.1.4 Advanced Model-based Control Strategies 110
4.1.4.1 Extended Predictive Self-adaptive Control (EPSAC) Strategy 111
4.1.4.2 Multiparametric Strategy 111
4.1.5 Control Design 112
4.1.5.1 Case 1: EPSAC 115
4.1.5.2 Case 2: mp-MPC Without Nonlinearity Compensation 116
4.1.5.3 Case 3: mp-MPC With Nonlinear Compensation 117
4.1.5.4 Case 4: mp-MPC With Nonlinearity Compensation and Estimation 118
4.1.6 Results 118
4.1.6.1 Induction Phase 119
4.1.6.2 Maintenance Phase 123
4.1.6.3 Discussion 125
4.2 Simultaneous Estimation and Advanced Control 130
4.2.1 Introduction 130
4.2.2 Multiparametric Moving Horizon Estimation (mp-MHE) 130
4.2.3 Simultaneous Estimation and mp-MPC Strategy 132
4.2.4 Results 134
4.2.4.1 Induction Phase 135
4.2.4.2 Maintenance Phase 138
4.3 Hybrid Model Predictive Control Strategies 142
4.3.1 Introduction 142
4.3.2 Hybrid Patient Model Formulation 143
4.3.3 Control Design 144
4.3.3.1 Hybrid Formulation of the Control Problem: Intravenous Anaesthesia 144
4.3.3.2 Robust Hybrid mp-MPC Control Strategy: Offset Free 146
4.3.3.3 Control Scheme 147
4.3.4 Results 147
4.3.4.1 No Offset Correction 147
4.3.4.2 Offset Free 150
4.3.5 Discussion 150
4.4 Conclusions 153
References 153

Part II 157

5 Part A: Type 1 Diabetes Mellitus: Modelling, Model Analysis and Optimization 159
Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, and Efstratios N. Pistikopoulos

5.a Type 1 Diabetes Mellitus: Modelling, Model Analysis and Optimization 159
5.a.1 Introduction: Type 1 Diabetes Mellitus 159
5.a.1.1 The Concept of the Artificial Pancreas 160
5.a.2 Modelling the Glucoregulatory System 162
5.a.3 Physiologically Based Compartmental Model 162
5.a.3.1 Endogenous Glucose Production (EGP) 167
5.a.3.2 Rate of Glucose Appearance (Ra) 168
5.a.3.3 Glucose Renal Excretion (Excretion) 168
5.a.3.4 Glucose Diffusion in the Periphery 168
5.a.3.5 Adaptation to the Individual Patient 169
5.a.3.5.1 Total Blood Volume 169
5.a.3.5.2 Cardiac Output 170
5.a.3.5.3 Compartmental Volume 170
5.a.3.5.4 Peripheral Interstitial Volume 171
5.a.3.6 Insulin Kinetics 171
5.a.4 Model Analysis 172
5.a.4.1 Insulin Kinetics Model Selection 172
5.a.4.2 Endogenous Glucose Production: Parameter Estimation 176
5.a.4.3 Global Sensitivity Analysis 177
5.a.4.3.1 Individual Model Parameters 178
5.a.4.4 Parameter Estimation 182
5.a.5 Simulation Results 183
5.a.6 Dynamic Optimization 185
5.a.6.1 Time Delays in the System 185
5.a.6.2 Dynamic Optimization of Insulin Delivery 188
5.a.6.3 Alternative Insulin Infusion 189
5.a.6.4 Concluding Remarks 192
Part B: Type 1 Diabetes Mellitus: Glucose Regulation 192
Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, and Efstratios N. Pistikopoulos

5.b Type 1 Diabetes Mellitus: Glucose Regulation 192
5.b.1 Glucose–Insulin System: Typical Control Problem 192
5.b.2 Model Predictive Control Framework 194
5.b.2.1 “High-Fidelity” Model 194
5.b.2.2 The Approximate Model 195
5.b.2.2.1 Linearization 195
5.b.2.2.2 Physiologically Based Model Reduction 196
5.b.3 Control Design 199
5.b.3.1 Model Predictive Control 199
5.b.3.2 Proposed Control Design 200
5.b.3.3 Prediction Horizon 200
5.b.3.4 Control Design 1: Predefined Meal Disturbance 202
5.b.3.5 Control Design 2: Announced Meal Disturbance 202
5.b.3.6 Control Design 3: Unknown Meal Disturbance 202
5.b.3.7 Control Design 4: Unknown Meal Disturbance 204
5.b.4 Simulation Results 204
5.b.4.1 Predefined and Announced Disturbances 204
5.b.4.2 Unknown Disturbance Rejection 204
5.b.4.3 Variable Meal Time 207
5.b.4.4 Concluding Remarks 207
5.b.5 Explicit MPC 208
5.b.5.1 Model Identification 209
5.b.5.2 Concluding Remarks 211
Appendix 5.1 212
Appendix 5.2 215
Appendix 5.3 215
References 217

Part III 225

6 An Integrated Platform for the Study of Leukaemia 227
Eirini G. Velliou, Maria Fuentes-Gari, Ruth Misener, Eleni Pefani, Nicki Panoskaltsis, Athanasios Mantalaris, Michael C. Georgiadis, and Efstratios N. Pistikopoulos

6.1 Towards a Personalised Treatment for Leukaemia: From in vivo to in vitro and in silico 227
6.2 In vitro Block of the Integrated Platform for the Study of Leukaemia 228
6.3  *In silico* Block of the Integrated Platform for the Study of Leukaemia  229

6.4  Bridging the Gap Between *in vitro* and *in silico*  231

References  231

7  *In vitro* Studies: Acute Myeloid Leukaemia  233

*Eirini G. Velliou, Eleni Pefani, Susana Brito dos Santos, Maria Fuentes-Gari, Ruth Misener, Nicki Panoskaltsis, Athanasios Mantalaris, Michael C. Georgiadis, and Efstratios N. Pistikopoulos*

7.1  Description of Biomedical System  233
7.1.1  The Human Haematopoietic System  233
7.1.2  General Structure of the Bone Marrow Microenvironment  235
7.1.3  The Cell Cycle  236
7.1.4  Leukaemia: The Disease  238
7.1.5  Current Medical Treatment  239
7.2  Experimental Part  240
7.2.1  Experimental Platforms  240
7.2.2  Crucial Environmental Factors in an *in vitro* System  241
7.2.2.1  Environmental Stress Factors and Haematopoiesis  241
7.2.3  Growth and Metabolism of an AML Model System as Influenced by Oxidative and Starvation Stress: A Comparison Between 2D and 3D Cultures  244
7.2.3.1  Materials and Methods  244
7.2.3.2  Results and Discussion  247
7.2.3.3  Conclusions  254
7.3  Cellular Biomarkers for Monitoring Leukaemia *in vitro*  255
7.3.1  (Macro-)autophagy: The Cellular Response to Metabolic Stress and Hypoxia  255
7.3.2  Biomarker Candidates  256
7.3.2.1  (Autophagic) Biomarker Candidates  256
7.3.2.2  (Non-autophagic) Stress Biomarker Candidates  257
7.4  From *in vitro* to *in silico*  257

References  258

8  *In silico* Acute Myeloid Leukaemia  265

*Eleni Pefani, Eirini G. Velliou, Nicki Panoskaltsis, Athanasios Mantalaris, Michael C. Georgiadis, and Efstratios N. Pistikopoulos*

8.1  Introduction  265
8.1.1  Mathematical Modelling of the Cell Cycle  266
8.1.2  Pharmacokinetic and Pharmacodynamic Mathematical Models in Cancer Chemotherapy  268
8.1.2.1  PK Mathematical Models  269
8.1.2.2 PD Mathematical Models 273
8.2 Chemotherapy Treatment as a Process Systems Application 273
8.2.1 Physiologically Based Patient Model for the Treatment of AML With DNR and Ara-C 275
8.2.2 Design of an Optimal Treatment Protocol for Chemotherapy Treatment 277
8.2.3 Mathematical Model Analysis Using Patient Data 278
8.2.3.1 Model Sensitivity Analysis 278
8.2.3.2 Patient Data 279
8.2.3.3 Estimation of Patient-specific Cell Cycle Parameters 280
8.3 Analysis of a Patient Case Study 282
8.3.1 First Chemotherapy Cycle 282
8.3.2 Second Chemotherapy Cycle 282
8.4 Conclusions 285
Appendix 8A Mathematical Model 286
Appendix 8B Patient Data 290
References 296

Index 301