

Contents



UNIVERSIDAD NACIONAL DE ENTRE RÍOS
FACULTAD DE INGENIERÍA
CENTRO DE MEDIOS
BIBLIOTECA

1737

1. INTRODUCTION 1
 - 1.1 Aims 1
 - 1.2 The Scientific Context 2
 - 1.3 Readership 5
 - 1.4 Organization of the Book 5

2. METABOLIC AND ENDOCRINE SYSTEMS 9
 - 2.1 Introduction 9
 - 2.2 Overview of Metabolic Systems 9
 - 2.3 Overview of Endocrine Systems 11
 - 2.4 Systemic Framework for the Description of Metabolic and Endocrine Systems 12
 - 2.4.1 *Compartmental Models* 13
 - 2.4.2 *Chemical Reactions* 14
 - 2.4.3 *Transport Processes* 17
 - 2.4.3.1 *Diffusion* 19
 - 2.4.3.2 *Compartment Washed by Fluid* 19
 - 2.4.3.3 *Transport by Fluid Circulation* 20
 - 2.4.4 *Controlled Processes* 21
 - 2.5 Summary 22

3. THE PURPOSES OF MODELING METABOLIC SYSTEMS 23
 - 3.1 Purposes of Modeling 23
 - 3.2 Identification of System Structure 24
 - 3.3 Estimation of Internal Parameters 27

- 3.4 Predictive Dose-Response Models 31
- 3.5 Predictive Models for Patient Management 32
- 3.6 Diagnostic Models 33
- 3.7 Teaching Models 33
- 3.8 Summary 34

4. THE MODELING PROCESS 37

- 4.1 The Modeling Process 37
- 4.2 The Basis of the Model in Theory and Data 37
 - 4.2.1 *Empirical Models* 39
 - 4.2.2 *Theoretical Models* 39
 - 4.2.3 *Empirical-Theoretical Models* 39
- 4.3 The Representational Property of the Model 40
- 4.4 Model Formulation 40
 - 4.4.1 *The Conceptual Model* 40
 - 4.4.1.1 *Aggregation* 41
 - 4.4.1.2 *Abstraction* 41
 - 4.4.1.3 *Idealization* 41
 - 4.4.2 *Mathematical Realization* 41
 - 4.4.3 *Model Solution* 43
- 4.5 Model Identification 43
- 4.6 Model Validation 43
 - 4.6.1 *Validity Criteria* 44
 - 4.6.1.1 *Internal Criteria* 44
 - 4.6.1.2 *External Criteria* 44
- 4.7 Levels of Modeling 45
 - 4.7.1 *Global Models* 45
 - 4.7.2 *Organ Models* 48
 - 4.7.3 *Cellular and Subcellular Models* 49
- 4.8 Model Reduction 50
- 4.9 Summary 54

5. APPROACHES TO MODELING METABOLIC SYSTEMS 55

- 5.1 Classes of Mathematical Representation 55
 - 5.1.1 *Lumped Deterministic Models* 56
 - 5.1.1.1 *Linear Models* 58
 - 5.1.1.2 *Nonlinear Models* 59

- 5.1.2 *Distributed Models* 59
- 5.1.3 *Stochastic Models* 60
- 5.2 Compartmental Models 63
 - 5.2.1 *Mathematical Representation* 63
 - 5.2.2 *The Steady State (Dynamic Equilibrium)* 64
- 5.3 Control System Models 66
 - 5.3.1 *Mathematical Representation* 67
 - 5.3.2 *The Steady State* 70
- 5.4 Perturbation Schemes 72
 - 5.4.1 *Tracer Perturbation* 72
 - 5.4.2 *Small-Signal Perturbation* 77
 - 5.4.3 *Gross Perturbation* 79
- 5.5 Some Properties of Compartmental Models 80
 - 5.5.1 *Non-Negativity of Compartmental Variables* 80
 - 5.5.2 *Stability* 81
 - 5.5.3 *Oscillations* 83
- 5.6 Noncompartmental Approaches 86
 - 5.6.1 *Introduction* 86
 - 5.6.2 *The Integral Equation (Convolution) Approach* 87
 - 5.6.3 *Steady State Applications of the Convolution Integral and Model-Independent Parameters* 88
 - 5.6.3.1 *Rate of Appearance* 89
 - 5.6.3.2 *Initial Volume of Distribution* 90
 - 5.6.3.3 *Clearance Rate* 91
 - 5.6.3.4 *Recirculating Volume* 92
 - 5.6.4 *Time Parameters and Rates of Movement of Material Using Tracer Methods* 92
 - 5.6.4.1 *One Accessible Compartment* 92
 - 5.6.4.2 *Two Accessible Compartments* 94
 - 5.6.4.3 *Mean Transit Time, True Total Distribution Volume, and Compartmental Structure* 94
 - 5.6.5 *Rate of Appearance in the Nonsteady State* 95
- 5.7 Case Studies 97
 - 5.7.1 *Bilirubin Metabolism* 97
 - 5.7.2 *Glucose Metabolism* 101
- 5.8 Summary 111

- 6. MODEL IDENTIFICATION: A GENERAL FRAMEWORK 113**
- 6.1 The Nature of Identification 113
 - 6.2 Model Structure Determination 114
 - 6.2.1 *Available Approaches* 114
 - 6.2.2 *Mathematical Description of Model Structures* 115
 - 6.3 Test Signals and Measurement 117
 - 6.4 Theoretical Identifiability and Experimental Design 119
 - 6.5 Parameter Estimation 120
 - 6.5.1 *Sources of Error* 120
 - 6.5.2 *Estimation Procedures* 122
 - 6.5.3 *Goodness of Fit and Practical Identifiability* 124
 - 6.6 Approaches to Improved Experimental Design 124
 - 6.7 Summary 127
- 7. THEORETICAL (A PRIORI) IDENTIFIABILITY AND ITS RELATION TO EXPERIMENTAL DESIGN 129**
- 7.1 Introduction 129
 - 7.2 Basic Concepts and Equivalences, with Examples 130
 - 7.3 Formal Definitions: Constrained Model Structures and Theoretical Identifiability 141
 - 7.3.1 *The Constrained Model* 141
 - 7.3.2 *Definitions* 142
 - 7.4 Ambiguities in Model Prediction 145
 - 7.5 Methods for Testing for Identifiability 149
 - 7.5.1 *Linear Models* 149
 - 7.5.1.1 *The Markov Parameter Matrix Approach* 150
 - 7.5.1.2 *Transfer Function Matrix Approach* 151
 - 7.5.2 *Linear Strictly Compartmental Models* 154
 - 7.5.2.1 *Transfer Function and Markov Parameter Matrix Approaches* 155
 - 7.5.2.2 *Normal-Mode Approach* 155
 - 7.5.2.3 *Explicit Identifiability Results* 156
 - 7.5.2.4 *Topological Identifiability Conditions* 161
 - 7.5.3 *Nonlinear Models* 171
 - 7.6 Theoretical Identifiability and Experimental Design 175
 - 7.7 Summary 176

8. PARAMETER ESTIMATION, PRACTICAL (A POSTERIORI) IDENTIFIABILITY, AND ENHANCED EXPERIMENTAL DESIGN 179

- 8.1 The Parameter Estimation Problem 179
- 8.2 Estimators and Their Desirable Properties 181
 - 8.2.1 *Unbiasedness* 182
 - 8.2.2 *Minimum Variance* 182
 - 8.2.3 *Efficiency* 182
 - 8.2.4 *Consistency* 183
- 8.3 Parameter Estimation 183
- 8.4 Least Squares Estimation 183
 - 8.4.1 *Linear Least Squares Estimation* 183
 - 8.4.2 *Nonlinear Least Squares Estimation* 189
 - 8.4.2.1 *Principles of Nonlinear Least Squares Estimation* 190
 - 8.4.2.2 *General Comments on Available Algorithms* 193
 - 8.4.3 *Practical Aspects of Nonlinear Least Squares Estimation* 194
 - 8.4.3.1 *Initial Parameter Estimates* 194
 - 8.4.3.2 *Gradient-Type and Direct Search Methods* 194
 - 8.4.3.3 *Solution of the Model Differential Equations* 195
 - 8.4.3.4 *Computation of Derivatives and Sensitivity Equations* 195
 - 8.4.3.5 *Robustness* 199
- 8.5 Maximum Likelihood Estimation 199
 - 8.5.1 *Equivalence of the Maximum Likelihood and Least Squares Estimators* 201
 - 8.5.2 *Measurement Noise* 202
- 8.6 Goodness of Fit, Residual Errors, and Practical *A Posteriori* Identifiability 203
 - 8.6.1 *Goodness of Fit (Residual Sum of Squares)* 203
 - 8.6.2 *Examination of Residuals* 203
 - 8.6.3 *Accuracy of Parameter Estimates (Practical *A Posteriori* Identifiability)* 204
- 8.7 Approaches to Improved Experimental Design 204
 - 8.7.1 *General Principles* 204
 - 8.7.2 *Determination of Optimal Sampling Schedules* 206

- 8.7.3 *Determination of Minimal Sampling Schedules* 210
- 8.8 Summary 216
- 9. THE VALIDATION OF MODELS OF METABOLIC AND ENDOCRINE SYSTEMS 217**
 - 9.1 Validation and Validity 217
 - 9.1.1 *Validity Criteria* 218
 - 9.1.1.1 *Internal Criteria* 218
 - 9.1.1.2 *External Criteria* 218
 - 9.2 Validation within the Modeling Process 219
 - 9.3 Validation of the Completed Model 219
 - 9.3.1 *General Principles* 219
 - 9.3.2 *Model Testability* 220
 - 9.3.3 *Validation Procedure* 220
 - 9.4 The Validation of Metabolic Models Where Formal Identification Techniques Can Be Adopted (Theoretically Identifiable Models) 221
 - 9.4.1 *Quantitative Criteria Based on the Results of Identification* 221
 - 9.4.1.1 *Theoretical (A Priori) Identifiability* 221
 - 9.4.1.2 *Practical (A Posteriori) Identifiability* 221
 - 9.4.1.3 *Goodness of Fit* 222
 - 9.4.1.4 *Statistics of the Residual Errors* 222
 - 9.4.2 *Model Plausibility* 223
 - 9.4.2.1 *Plausibility of the Estimated Parameters* 223
 - 9.4.2.2 *Plausibility of Other Features of Structure, Parameters, and Behavior* 223
 - 9.4.2.3 *Overall Physiological Plausibility* 223
 - 9.5 The Validation of Theoretically Unidentifiable Models of Metabolic Systems 224
 - 9.5.1 *Approaches to Increasing Model Testability* 224
 - 9.5.1.1 *Model Simplification* 224
 - 9.5.1.2 *Improved Experimental Design* 224
 - 9.5.1.3 *Model Decomposition* 224
 - 9.5.1.4 *Reevaluation of Model Testability* 225
 - 9.5.2 *Adaptive Fitting* 225
 - 9.5.2.1 *Qualitative Feature Comparison* 226
 - 9.5.2.2 *Quantitative Feature Comparison* 226

9.5.2.3	<i>Time Course Prediction</i>	227
9.5.3	<i>Model Plausibility</i>	227
9.5.3.1	<i>Quantitative Assessment</i>	227
9.5.4	<i>Final Assessment of Model Validity</i>	230
9.6	<i>Case Study 1—Glucose—Insulin Model to Estimate Insulin Sensitivity</i>	230
9.6.1	<i>Insulin Sensitivity</i>	230
9.6.2	<i>The Development of Models of Optimal Complexity</i>	231
9.6.3	<i>Model Decomposition</i>	232
9.6.4	<i>Models of Glucose Utilization</i>	236
9.6.5	<i>Model Comparison</i>	242
9.6.5.1	<i>Theoretical Identifiability</i>	242
9.6.5.2	<i>Practical Identifiability</i>	242
9.6.5.3	<i>Goodness of Fit, Number of Parameters, and Residual Errors</i>	242
9.6.5.4	<i>Overall Physiological Plausibility and Final Selection</i>	242
9.6.6	<i>Insulin Sensitivity Index</i>	244
9.7	<i>Case Study 2—Validation of Compartmental Models</i>	245
9.7.1	<i>The Role of Model-Independent Parameters</i>	245
9.7.2	<i>Model-Independent Parameters, Experimental Design, and Model Validity</i>	246
9.7.2.1	<i>The Effect of Neglecting a Fast Transient</i>	246
9.7.2.2	<i>The Effect of Neglecting a Small Time Delay</i>	248
9.7.3	<i>The Validation of Nonuniquely Identifiable Compartmental Models</i>	249
9.7.4	<i>Evaluation of Alternative Compartmental Model Structures</i>	251
9.7.4.1	<i>Riphamycin Kinetics</i>	251
9.7.4.2	<i>Bilirubin Kinetics</i>	252
9.8	<i>Case Study 3—A Model of Insulin Secretion</i>	254
9.8.1	<i>A Model for the Threshold Secretory Mechanism</i>	254
9.8.2	<i>Experimental Data and Preliminary Evaluation of Candidate Models</i>	255
9.8.3	<i>The Model</i>	260
9.8.3.1	<i>First-Phase Insulin Secretion</i>	261
9.8.3.2	<i>Second-Phase Insulin Secretion</i>	264
9.8.3.3	<i>Model Equations</i>	265
9.8.4	<i>Remarks on Model Validity</i>	272

- 9.9 Case Study 4—A Model of Glucose Regulation 272
- 9.9.1 *Model Equations* 273
- 9.9.2 *Model Testing* 276
- 9.9.2.1 *Normal Metabolic State* 276
- 9.9.2.2 *Pathological States and Other Conditions* 281
- 9.9.3 *Assessment of Model Validity* 283
- 9.10 Summary 291

10. CASE STUDIES 293

- 10.1 Case Study 1—The Role of Models in Evaluating Alternative Schemes of Closed-Loop Insulin Infusion in Diabetes 293
- 10.1.1 *Mathematical Model of Type I Diabetes* 294
- 10.1.2 *Control Algorithms for the Artificial Pancreas* 296
- 10.1.2.1 *Biostator–Miles Algorithm* 296
- 10.1.2.2 *A Modified Biostator–Miles Algorithm* 297
- 10.1.2.3 *Albisser Algorithm* 297
- 10.1.3 *Simulation of the Closed-Loop Control System* 298
- 10.2 Case Study 2—Mathematical Models for the Description of Insulin Secretion and Kinetics *In Vivo* 303
- 10.2.1 *Global Models Based on Cellular Mechanisms* 304
- 10.2.1.1 *The Ličko and Silvers Model* 304
- 10.2.1.2 *Other Models Based on Cellular Mechanisms* 308
- 10.2.2 *Global Models Derived from an Organ Approach* 309
- 10.2.3 *Model Comparison* 309
- 10.2.4 *Use of the Minimal Model to Estimate Secretion Parameters* 311
- 10.3 Case Study 3—A Clinical Model to Describe the Carbohydrate Metabolic State 313
- 10.4 Case Study 4—A Model of the Kinetics of Ketone Bodies 317
- 10.5 Case Study 5—The Clinical Use of a Model of Unconjugated Bilirubin Metabolism 325
- 10.6 Case Study 6—A Model of Bilirubin Metabolism as an Aid to Physiological Insight 328
- 10.7 Case Study 7—Models of Galactose Kinetics and Their Role in Testing Liver Function 334

- 10.7.1 *The Proposed Models* 336
 - 10.7.1.1 *The Complete Tygstrup Model* 336
 - 10.7.1.2 *The Simplified Tygstrup Model* 336
 - 10.7.1.3 *A Model Incorporating Michaelis-Menten Dynamics* 338
- 10.7.2 *Model Comparison* 338
- 10.8 Case Study 8—A Distributed Model of Galactose Uptake by the Liver 342
- 10.9 Case Study 9—Models of BSP Kinetics and Their Role in Assessing Hepatobiliary Disease 345
 - 10.9.1 *The Two-Compartment Model* 345
 - 10.9.2 *The Four-Compartment Model* 347
 - 10.9.3 *The Six-Compartment Model* 349
 - 10.9.4 *Remarks on Model Selection* 353
- 10.10 Case Study 10—A Model of the Human Thyroid Hormone Regulatory System 355
- 10.11 Case Study 11—A Clinical Model of Thyroid Hormone Regulation 362
- 10.12 Summary 368

REFERENCES 369**INDEX 387**