
Table of Contents

About the Authors, xvii	
Introduction, xix	
CHAPTER 1 ■ Systems Biology, Biological Knowledge and Kinetic Modelling	1
DEPENDENCE OF ENZYME REACTION RATE ON THE SUBSTRATE CONCENTRATION	3
WHAT ARE THE MODEL LIMITATIONS? OR, IN OTHER WORDS, WHAT CAN BE MODELLED?	8
CHAPTER 2 ■ Cellular Networks Reconstruction and Static Modelling	13
PATHWAY RECONSTRUCTION	13
THE HIGH-QUALITY NETWORK RECONSTRUCTION: DESCRIPTION OF THE PROCESS	14
VISUAL NOTATIONS: THREE CATEGORIES	17
Communication between Diagrams	22
Tools and Methods for Static Modelling	24
Databases, Ontology and Standards for Pathway Reconstruction	25
SBML	27
SBGN: A Visual Notation for Network Diagrams	28
	<hr/>
	ix

CHAPTER 3 ■ Edinburgh Pathway Editor	29
INTRODUCTION	30
FEATURE SUMMARY OF EPE	31
A FLEXIBLE VISUAL REPRESENTATION	35
CONCLUSION	47
CHAPTER 4 ■ Construction and Verification of Kinetic Models	49
INTRODUCTION	49
BASIC PRINCIPLES OF KINETIC MODEL CONSTRUCTION	50
Development of a System of Ordinary Differential Equations Describing the Dynamics of a Metabolic System	51
Derivation of Rate Law of Enzymatic Reactions	58
BASIC PRINCIPLES OF KINETIC MODEL VERIFICATION	60
Verification of Kinetic Model Using <i>in Vitro</i> Experimental Data Measured for Purified Enzymes	60
Verification of the Kinetic Model Using <i>in Vitro</i> and <i>in Vivo</i> Experimental Data Measured for a Biochemical System	61
STUDY OF DYNAMIC AND REGULATORY PROPERTIES OF THE KINETIC MODEL	63
CHAPTER 5 ■ Introduction to DBSolve	65
CREATION AND ANALYSIS OF THE MODELS USING DBSOLVE. FUNCTIONAL DESCRIPTION	66
A General Look at the Interface	67
Description of the Example	67
The 'Metabolic Network' Tab: Creation of ODE System (Simple Method)	69
Creation of the ODE System Using RCT Format (The Alternative Method)	71
DBSolve Editors: RHS, Initial Values, Pools	72
<i>RHS Editor</i>	72
<i>Initial Values</i>	73
<i>Pools</i>	73

ODE Tab: Solving the ODE System. Model Integration or <i>in Silico</i> Experiments	73
Explicit Tabbed Page. Calculating Dependencies Determined Explicitly	77
The Implicit Solver Tabbed Page. The Study of the System in a Steady State	79
Experimental Data Tab: Creation of the Table with Experimental Data	81
The Fitter Tabbed Page: Automatic Parameter Fitting	84
<i>Options Tab</i>	86
<i>Advanced User Tab</i>	87
<i>Example of Fitting</i>	87
The 'Options' Tabbed Page	90
Some Examples from the CD	92
CHAPTER 6 ■ Enzyme Kinetics Modelling	95
INTRODUCTION	95
BASIC PRINCIPLES OF MODELLING OF INDIVIDUAL ENZYMES AND TRANSPORTERS	96
Methods to Derive Rate Equation on the Basis of Enzyme Catalytic Cycle	97
<i>Quasi-Equilibrium Approach</i>	98
<i>Quasi-Steady-State Approach</i>	100
<i>Combined Quasi-Equilibrium, Quasi-Steady-State Approach</i>	102
How to Express Parameters of the Catalytic Cycle in Terms of Kinetic Parameters	107
Examples of Rate Equations Expressed in Terms of Kinetic Parameters	109
<i>Random Bi Bi Mechanism</i>	109
<i>Ordered Uni Bi Mechanism</i>	110
<i>Ping Pong Bi Bi Mechanism</i>	111

'HYPERBOLIC' ENZYMES	113
Kinetic Model of Histidinol Dehydrogenase from <i>Escherichia coli</i>	113
Available Experimental Data	113
Construction of the Catalytic Cycle	114
Derivation of Rate Equations	118
Estimation of Kinetic Parameters of the Rate Equations Using in Vitro Experimental Data	121
Kinetic Model of <i>Escherichia coli</i> Isocitrate Dehydrogenase and Its Regulation by Isocitrate Dehydrogenase Kinase/Phosphatase	124
Available Experimental Data	126
Kinetic Model of Isocitrate Dehydrogenase	126
Kinetic Model of IDH Kinase/Phosphatase	128
Model Predictions	136
Kinetic Model of β -Galactosidase from <i>Escherichia coli</i> Cells	139
Catalytic Cycle of β -Galactosidase Construction	139
Derivation of the Rate Equation of β -Galactosidase	141
Identification of the Parameters of the β -Galactosidase Rate Equation	147
Model Predictions	147
Kinetic Model of Imidazologlycerol-Phosphate Synthetase from <i>Escherichia coli</i>	150
Experimental Data	150
Catalytic Cycle	153
Derivation of the Rate Equations	153
Evaluation of Parameters of the Rate Equations	158
Application of the Model to Predict How the Synthetase and Glutaminase Activities of Imidazologlycerol-Phosphate Synthetase Depend on Concentrations of the Substrates and Effectors	166
ALLOSTERIC ENZYMES	168
Principles Used for Description of the Functioning of Allosteric Enzymes	168

Kinetic Model of Phosphofructokinase-1 from <i>Escherichia coli</i>	170
<i>Available Experimental Data</i>	172
<i>Reconstruction of a Catalytic Cycle of Phosphofructokinase-1</i>	173
<i>Derivation of a Rate Equation</i>	175
<i>Verification of the Model against Experimental Data</i>	178
<i>Predictions of the Model</i>	180
TRANSPORTERS	187
Kinetic Model of Mitochondrial Adenine Nucleotide Translocase	187
<i>Experimental Data for Model Verification</i>	188
<i>Antiporter Functioning Mechanism</i>	188
<i>Kinetic Scheme</i>	189
<i>Derivation of Rate Equation</i>	190
<i>Dependence of Kinetic Constants on Membrane Potential</i>	194
<i>Estimation of Parameters</i>	198
<i>Model Verification</i>	200
<i>Model Predictions</i>	202
CHAPTER 7 ■ Kinetic Models of Biochemical Pathways	207
MODELLING OF THE MITOCHONDRIAL KREBS CYCLE	208
Model Development	208
Description of Individual Enzymes of the Krebs Cycle	210
α -Ketoglutarate Dehydrogenase	212
Aspartate-Glutamate Carrier (AGC)	214
Aspartate Aminotransferase (AspAT)	219
Succinate Thiokinase (STK)	221
Succinate Dehydrogenase	225
Fumarase (FUM)	227
Malate Dehydrogenase (MDH)	228
α -Ketoglutarate-Malate Carrier (KMC)	229
Estimation of Model Parameters from <i>in Vivo</i> Data	231

MODELING OF THE <i>ESCHERICHIA COLI</i> BRANCHED-CHAIN AMINO ACID BIOSYNTHESIS	233
Model Development	233
Derivation of the Rate Equations	235
Detailed Description of Pathway Steps	237
Influxes	237
Threonine Dehydratase (TDH)	239
Acetolactate Synthase (AHAS)	239
Acetohydroxy Acid Isomeroreductase (IR)	241
Dihydroxy-Acid Dehydratase (DHAD)	243
Branched-Chain Amino Acid Transaminase (BCAT)	245
NADP Recycling and Effluxes	246
Evaluation of Maximal Reaction Rates	246
CHAPTER 8 ■ Modelling of Mitochondrial Energy Metabolism	249
OXIDATIVE PHOSPHORYLATION AND SUPEROXIDE PRODUCTION IN MITOCHONDRIA	249
DEVELOPMENT OF KINETIC MODELS	251
DESCRIPTION OF INDIVIDUAL PROCESSES OF THE MODEL	262
MODEL PREDICTIONS	269
CHAPTER 9 ■ Application of the Kinetic Modelling Approach to Problems in Biotechnology and Biomedicine	277
STUDY OF THE MECHANISMS OF SALICYLATE HEPATOTOXIC EFFECT	277
Kinetic Description of the Influence of Salicylates on the Krebs Cycle	278
Impacts of Different Mechanisms of Salicylate Inhibition on the Total Adverse Effect on the Krebs Cycle	283
Prediction of Possible Ways to Recover Krebs Cycle Functionality	285

MULTIPLE TARGET IDENTIFICATION ANALYSIS FOR ANTI-TUBERCULOSIS DRUG DISCOVERY	287
Construction of a Kinetic Model of the Glyoxylate Shunt in <i>Mycobacterium tuberculosis</i>	288
Application of the Model to Identify Potential Targets for Therapeutic Drug Intervention	292
APPLICATION OF THE KINETIC MODEL OF <i>ESCHERICHIA</i> <i>COLI</i> BRANCHED-CHAIN AMINO ACID BIOSYNTHESIS TO OPTIMISE PRODUCTION OF ISOLEUCINE AND VALINE	293
Prediction of Possible Genetic Changes That Should Maximise Isoleucine and Valine Production	294
Conclusion and Discussion	299
REFERENCES	303
INDEX	323