# Contents

<table>
<thead>
<tr>
<th>Preface</th>
<th>page xi</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Notations</td>
<td>xv</td>
</tr>
</tbody>
</table>

1 Introduction 1

2 Enzymatic Adaptation 3

2.1 Enzyme Balance 4

2.2 Metabolic Reaction Rate 5

2.3 The Cybernetic Variables 6

2.3.1 The Control of Enzyme Synthesis 6

2.3.2 The Control of Enzyme Activity 9

3 Early Development of Cybernetic Models 13

3.1 Modeling of Diauxic Growth 13

3.2 Growth and Maintenance in Low Substrate Environments 18

3.3 A Model for the Production of a Bacterial Metabolite 27

3.4 More on Growth on Mixed Carbon Substrates: Simultaneous Utilization 36

3.4.1 Cybernetic Models of Mixed Substrate Growth: Sequential and Simultaneous Utilization of Substrates 37

3.5 Toward Metabolic Networks 42

3.5.1 Elementary Pathways 42

3.5.2 Growth on Complementary Nutrients: Interactive and Noninteractive Substrates 46

3.5.3 Modeling of Bacterial Growth under Multiple Nutrient Limitations 50

3.6 Concluding Remarks 63

4 Revisiting Cybernetic Laws via Optimal Control Theory 64

4.1 System Variables and the Optimal Control Problem 64

4.2 The Matching Law 66

4.3 The Proportional Law 69

4.4 Tandem Treatment of Matching and Proportional Laws 71

4.5 Retrospection of Past Cybernetic Models 72

4.6 Computational Assessment of Different Cybernetic Control Laws 74
## Contents

### 4.6.1 Comparison of Different Cybernetic Models
- Page 76

### 4.6.2 Analysis of an Evolutionary Scenario
- Page 82

### 4.7 Concluding Remarks
- Page 85

### 5 Toward Modeling of Metabolic Networks
- Page 86
  5.1 Cybernetic Modeling of Metabolic Networks
    - Model Formulation
      - Page 88
  5.1.2 Modeling of a Simple Linear Pathway
    - Page 92
  5.1.3 Modeling of Anaerobic Metabolism of *Escherichia coli*
    - Page 95
  5.2 Concluding Remarks
    - Page 103

### 6 The Hybrid Cybernetic Model (HCM)
- Page 105
  6.1 Modeling of Regulation
    - Page 106
  6.2 Anaerobic Growth of *E. coli*
    - Page 110
    - HCM Simulations for Glucose Limited Growth
      - Page 111
    - HCM Simulations for Growth on Glucose-Pyruvate Mixtures
      - Page 118
  6.3 A Mode Reduction Technique for Lower Order HCM
    - Page 124
  6.3.1 A General Formulation of Metabolic Yield Analysis
    - Page 126
  6.4 HCM of Yeast Co-Consuming Glucose and Xylose for Ethanol Production
    - Page 131
    - Parameter Determination
      - Page 135
    - HCM simulations of Co-Consumption of Glucose and Xylose by Recombinant Yeast. Comparison with Other Models
      - Page 136
  6.5 HCM of Carbon Storage Molecule Accumulation: Poly(β-hydroxybutyrate)
    - Page 140
  6.6 HCM for a Mixed Culture of Yeasts for Bioethanol Production
    - Page 144
  6.7 Concluding Remarks
    - Page 149

### 7 The Lumped Hybrid Cybernetic Model (L-HCM)
- Page 150
  7.1 Modeling Concept
    - Page 151
    - Elementary Mode (EM) Families: A Classification of EMs
      - Page 151
    - Uptake Flux Distribution to EM Families
      - Page 153
    - Modeling of Regulation in L-HCM
      - Page 154
    - Nature of Flux Distribution in L-HCM
      - Page 157
  7.2 L-HCM for Aerobic Growth of *Saccharomyces cerevisiae*: The Crabtree Effect
    - Page 158
    - Metabolic Network for *S. cerevisiae*
      - Page 159
    - EMs and EM Lumps
      - Page 159
    - L-HCM Equations
      - Page 161
    - A Lumped Cybernetic Model (LCM) for the Crabtree Effect
      - Page 162
    - Performance of L-HCM on Aerobic Growth of *S. cerevisiae*
      - Page 164
  7.3 More on Lumping EMs
    - Page 167
  7.4 L-HCM of Multiple Strains of *E. coli*
    - Page 169
    - EM Lumpings: Anaerobic Growth of *E. coli* on Glucose
      - Page 170
    - L-HCM Equations: Anaerobic Growth of *E. coli* on Glucose
      - Page 170
Table of Contents

7.4.3 Dynamics of Anaerobic Growth of *E. coli* on Glucose: L-HCM Predictions 171
7.4.4 Effect of Yield Data on EM Lumping 171
7.4.5 On Other EM Lumpings in the Literature 176
7.5 L-HCM of Aerobic Growth of *Shewanella oneidensis* 176
   7.5.1 Metabolic Network for *S. oneidensis* 178
   7.5.2 L-HCM Equations for *S. oneidensis* 180
7.6 Concluding Remarks 184

8 Predicting Dynamic Behavior of Mutant Strains with L-HCM 186
   8.1 Prolegomena 186
      8.1.1 L-HCM Approach to Predicting KO Strain Behavior 187
      8.1.2 Illustration with a Toy Example 189
   8.2 L-HCM Predictions of Single Gene Knockouts of *E. coli*: Anaerobic Growth 191
      8.2.1 Reflections on L-HCM Predictions of Single KO Strains 196
   8.3 Toward Genome Scale Modeling 198
      8.3.1 Optimization-Based Approaches for EM Computation 200
      8.3.2 Basic Formulation 201
      8.3.3 Typical MILP-Based Approach 202
      8.3.4 AILP-Based Algorithm 203
      8.3.5 Basic Properties of AILP 205
      8.3.6 Computation of EMs from Genome-Scale Networks 208
      8.3.7 EM Sampling by AILP 209
      8.3.8 Summary 212
   8.4 Concluding Remarks 212

9 Nonlinear Analysis of Cybernetic Models 213
   9.1 Introduction 213
      9.1.1 Multiple Steady States in a Continuous Bioreactor: The Chemostat 215
      9.1.2 HCM Prediction of Steady-State Multiplicity in a Continuous Reactor Fed with Pyruvate-Glucose Mixtures 221
      9.1.3 LCM Prediction of Steady-State Multiplicity in Hybridoma Cultures 222
   9.2 Oscillatory Behavior with Cybernetic Models 229
      9.2.1 Oscillations in Continuous Cultures of Yeast (*S. cerevisiae*) 230
      9.2.2 Oscillations in Bacterial Cultures 230
   9.3 Concluding Remarks 234

10 Metabolic Modeling Landscape 235
    10.1 Introduction 235
    10.2 Fully Structured Dynamic Models 236
       10.2.1 Conventional Approaches. Kinetic Formalisms 237
       10.2.2 The Cybernetic Model: Young’s Model 238
# Contents

10.3 Quasi Steady State (QSS) Models .......................... 239
  10.3.1 Steady-State Network Analysis: FBA and EM Analysis ............. 240
  10.3.2 Conventional Approaches: DFBA and MBM ..................... 241
  10.3.3 The Cybernetic Approach: HCM and L-HCM .................... 242
10.4 Unstructured Dynamic Models ............................ 244
10.5 Nexus of Metabolic Models ................................ 245
10.6 Model Selection ............................................. 246
  10.6.1 Modeling Goals ......................................... 247
  10.6.2 Systematic Model Evaluation Based on Information Theoretic Tools 247
  10.6.3 Prediction of Emergent Properties .......................... 249
10.7 Concluding Remarks ....................................... 251

References ......................................................... 252

Index .............................................................. 266