Mathematical modeling of metal ion homeostasis and signaling systems

Cui, J.

Citation for published version (APA):
Contents

1 General Introduction 1

1.1 System Biology and Its Grand Challenges 1
  1.1.1 A Bit History of Systems Biology 2
  1.1.2 Biological Complexity 2
  1.1.3 Computational Challenge and Other Challenges 3
  1.1.4 Prize for Efforts: The Golden Fleece 4

1.2 Mathematical Modeling 5
  1.2.1 The Role, Levels and Strategies of Modeling 5
  1.2.2 Approaches of Mathematical Modeling 6
  1.2.3 Multi-Scale Modeling 7

1.3 Metal Ion Homeostasis and Signaling Systems 7
  1.3.1 Functions of Main Essential Metals 8
  1.3.2 Metals-Related Human Diseases 10
  1.3.3 Metal Ion Homeostasis Systems 11
  1.3.3.1 Various Proteins Involved in Metal Ion Homeostasis 11
  1.3.3.2 Regulated Membrane Ion Transport 14
  1.3.3.3 Other Strategies of Maintaining Homeostasis 15
  1.3.4 Metal Ion Signaling Systems 16
  1.3.4.1 Versatility and Universality of Calcium Signaling 16
  1.3.4.2 Intracellular Calcium Signaling 18
  1.3.4.3 Extracellular Calcium Signaling 20
  1.3.4.4 Calcium Signaling Toolkit 20
  1.3.4.5 Spatial and Temporal Aspects of Calcium Signaling 21
  1.3.4.6 Calcium Signature Hypothesis vs. Chemical Switch Hypothesis 21
  1.3.4.7 Zinc Signaling 22

1.4 Feedback Control Theory and Network Motifs 23
  1.4.1 A Bit History of Feedback Control 23
  1.4.2 Basic Feedback Control System 23
  1.4.3 Negative Feedback 24
  1.4.4 Network Motifs 25

1.5 Enzyme Kinetics and Nonlinear ODE Modeling 26
  1.5.1 Michaelis-Menten Kinetics 27
  1.5.2 Reversible Competitive Inhibition 27
  1.5.3 Nonlinear ODE Modeling 29

1.6 Thesis Overview 30
2 The 1st Model for Yeast Calcium Homeostasis 32
  2.1 Introduction 32
  2.2 Methods 35
  2.2.1 Control Block Diagram 35
  2.2.2 Feedback Modeling 35
  2.2.3 Growth Modeling 38
  2.2.4 Protein Modeling 39
  2.2.5 Preliminary Model 40
  2.3 Results 42
  2.3.1 Steady-State Properties 42
  2.3.2 Transients and Mutant Behavior 44
  2.3.3 Parameter Sensitivity 47
  2.4 Discussion 48

3 Detection of A New Calcium Transporter on Yeast Plasma Membrane 52
  3.1 Introduction 52
  3.2 Methods 54
  3.2.1 Experimental Methods 54
  3.2.2 Mathematical Modeling 54
  3.2.2.1 Control Block Diagram 54
  3.2.2.2 Feedback Modeling 55
  3.2.2.3 Volume Evolution Modeling (under Hypertonic Shock) 55
  3.2.2.4 Protein Modeling 56
  3.2.2.5 A Concise Model 57
  3.2.2.6 Conversion to Aequorin Luminescence Unit (RLUs) 59
  3.2.3 Parameter Estimation Method 59
  3.3 Results 61
  3.3.1 Mg$^{2+}$ Blocks Ca$^{2+}$ Toxicity and Ca$^{2+}$ Influx in Yeast 61
  3.3.2 Computational Modeling of Ca$^{2+}$ Influx and Sequestration 63
  3.3.2.1 Steady-State Properties 63
  3.3.2.2 Transients and Mutant Behavior 64
  3.3.2.3 Flux Analysis and Cell Volume Evolution 66
  3.3.2.4 Extracellular Mg$^{2+}$ Depletion and Ca$^{2+}$ Challenge 66
  3.4 Discussion 67
4 Simulating Complex Calcium-Calcineurin Signaling Networks in Cardiac Myocytes  
4.1 Introduction  
4.2 Method  
4.2.1 Cellerator Software  
4.2.2 Representation of Relevant Reactions  
4.2.3 The Equations of the Model  
4.3 Results  
4.3.1 Steady-State Property  
4.3.2 Transients and Mutant Behavior  
4.4 Discussion  

5 Simulating In Vitro Transcriptional Response of Zinc Homeostasis System in E. coli  
5.1 Introduction  
5.2 Methods  
5.2.1 Representation of Relevant Reactions  
5.2.2 The Equations of the Model and the Numerical Solver  
5.2.2.1 Equations for Zur-DNA Interaction  
5.2.2.2 Equations for Zur Transcription Assay  
5.2.2.3 Equations for ZntR Transcription Assay (I)  
5.2.2.4 Equations for ZntR Transcription Assay (II)  
5.2.3 Translating the Model into CellML  
5.2.4 The Image Analysis Method  
5.3 Results  
5.3.1 Zur-DNA Interaction  
5.3.2 Zur Transcription Assay  
5.3.3 ZntR Transcription Assay (I)  
5.3.4 ZntR Transcription Assay (II)  
5.4 Discussion  

6 Network Motifs and Their Functions  
6.1 Introduction  
6.2 Network Motifs in Metal Ion Homeostasis and Signaling Systems  
6.2.1 Examples of Network Motifs  
6.2.2 Signaling Cycle Motif
6.3 Discussion

7 Final Discussion and Future Work

References
Acknowledgements
Publication List