SECOND EDITION

COMPUTATIONAL SYSTEMS BIOLOGY

FROM MOLECULAR MECHANISMS TO DISEASE

Edited by
Roland Eils
and Andres Kriete

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ROLAND EILS

ANDRES KRIETE

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Preface

Computational systems biology, a term coined by Kitano in 2002, is a field that aims at a system-level understanding by modeling and analyzing biological data using computation. It is increasingly recognized that living system cannot be understood by studying individual parts, while the list of molecular components in biology is ever growing, accelerated by genome sequencing and high-throughput omics techniques. Under the guiding vision of systems biology, sophisticated computational methods help to study the interconnection of parts in order to unravel complex and networked biological phenomena, from protein interactions, pathways, networks, to whole cells and multicellular complexes. Rather than performing experimental observations alone, systems biology generates knowledge and understanding by entering a cycle of model construction, quantitative simulations, and experimental validation of model predictions, whereby a formal reasoning becomes key. This requires a collaborative input of experimental and theoretical biologists working together with system analysts, computer scientists, mathematicians, bioengineers, physicists, as well as physicians to contend creatively with the hierarchical and nonlinear nature of cellular systems.

This book has a distinct focus on computational and engineering methods related to systems biology. As such, it presents a timely, multi-authored compendium representing state-of-the-art computational technologies, standards, concepts, and methods developed in this area. If compared to the first edition published in 2005, the second edition has been specifically extended to reflect new frontiers of systems biology, including modeling of whole cells, studies of embryonic development, the immune systems, as well as aging and cancer. As in the previous edition, basics of information and data integration technologies, standards, modeling of gene, signaling and metabolic networks remain comprehensively covered. Contributions have been selected and compiled to introduce the different methods, including methods dissecting biological complexity, modeling of dynamical properties, and biocomputational perspectives.

Beside the primary authors and their respective teams who have dedicated their time to contribute to this book, the editors would like to thank numerous reviewers of individual chapters, but in particular Jan Eufinger for support of the editorial work.

It is often mentioned that biological systems in its entirety present more than a sum of its parts. To this extent, we hope that the chapters selected for this book not only give a contemporary and comprehensive overlook about the recent developments, but that this volume advances the field and encourages new strategies, interdisciplinary cooperation, and research activities.

Roland Eils and Andres Kriete
Heidelberg and Philadelphia,
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Contents

13. Stochastic Simulations of Cellular Processes: From Single Cells to Colonies

JOHN COLE, MICHAEL J. HALLOCK, PIYUSH LABHSETWAR, JOSEPH R. PETERSON, JOHN E. STONE, ZAIDA LUTHEY-SCHULTEN

14. Advances in Machine Learning for Processing and Comparison of Metagenomic Data

JEAN-LUC BOUCHOT, WILLIAM L. TRIMBLE, GREGORY DITZLER, YEMIN LAN, STEVE ESSINGER, GAIL ROSEN

15. Systems Biology of Infectious Diseases and Vaccines

HELDER I NAKAYA

16. Computational Modeling and Simulation of Animal Early Embryogenesis with the MecaGen Platform

JULIEN DELILE, RENÉ DOURSAT, NADINE PEYRIÉRAS

17. Developing a Systems Biology of Aging

ANDRES KRIETE, MATHIEU CLOUTIER

CHAPTER

1

Introducing Computational Systems Biology

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CONTENTS

We need to turn data into knowledge and we need a framework to do so. **S. Brenner, 2002.**

1 PROLOGUE

The multitude of the computational tools needed for systems biology research can roughly be classified into two categories: *system identification* and *behavior analysis* (Kitano 2001). In molecular biology, system identification amounts to identifying the regulatory relationships between genes, proteins, and small molecules, as well as their inherent dynamics hidden in the specific kinetic and binding parameters. System identification is arguably one of the most complicated problems in science. While behavior analysis is solely performed on a model, model construction is a process tightly connected to reality but part of an iterative process between data analysis, simulation, and experimental validation (Figure 1.1). A typical

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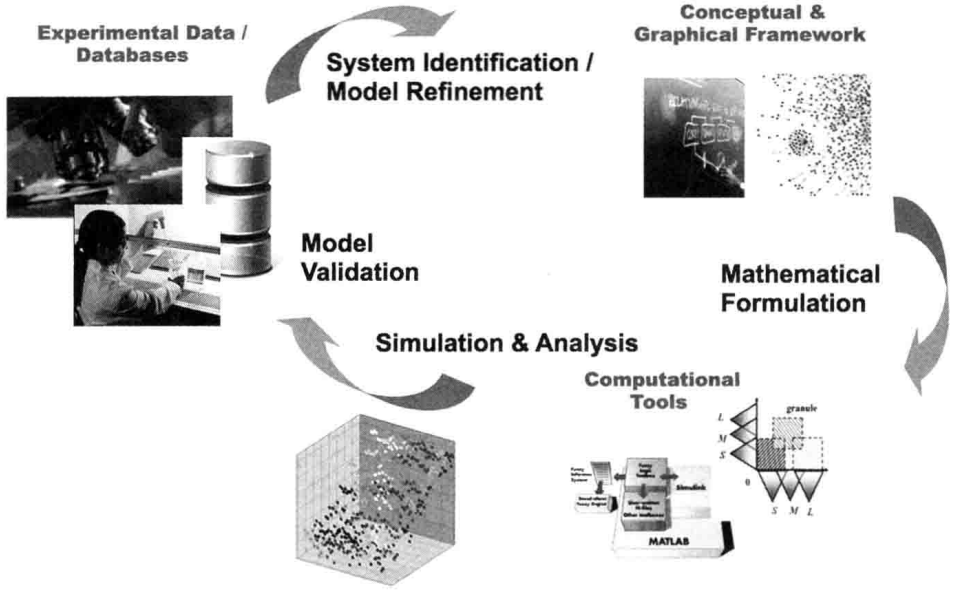

FIGURE 1.1 Key to systems biology is an iterative cycle of experimentation, model building, simulation and validation.

modeling cycle begins with a reductionist approach, creating the simplest possible model. The modeling process generates an understanding of the underlying structures, and components are represented graphically with increasing level of formalization, until they can be converted into a mathematical representation. The minimal model then grows in complexity, driven by new hypotheses that may not have been apparent from the phenomenological descriptions. Then, an experiment is designed using the biological system to test whether the model predictions agree with the experimental observations of the system behavior. The constitutive model parameters may be measured directly or may be inferred during this validation process, however, the propagation of errors through these parameters present significant challenges for the modeler. If data and predictions agree, a new experiment is designed and performed. This process continues until sufficient experimental evidence in favor of the model is collected. Once the system has been identified and a model constructed, the system behavior can be studied, for instance, by numerical integration or sensitivity analysis against external perturbations.

Although the iterative process is well defined, the amount of data to be merged into this process can be immense. The human genome project is one of the hallmarks indicating a turn from a reductionistic approach in studying biological systems at increasing level, into a discovery process using high-throughput techniques (Figure 1.2). Ongoing research increases the wealth of contemporary biological information residing in some thousand public databases providing descriptive genomics, proteomics and enzyme information, gene expression, gene variants and gene ontologies. Refined explorative tools, such as new deep sequencing, along with the emergence of new specialized -omics (metabolomics, lipidomics, pharmacogenomics) and phenotyping techniques, constantly feed into this data pool and accelerate its growth.

Given the enormous and heterogeneous amount of data, computational tools have become indispensable to mine, analyze, and connect such information. The aggregate of statistical