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

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier

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525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
225 Wyman Street, Waltham, MA 02451, USA
The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK
32 Jamestown Road, London, NW1 7BY, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands

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Library of Congress Cataloging-in-Publication Data

Computational systems biology (Kriete)
Computational systems biology / edited by Andres Kriete, Roland Eils. -- Second edition.
p. ; cm.
Includes bibliographical references and indexes.
ISBN 978-0-12-405926-9 (alk. paper)
I. Kriete, Andres, editor of compilation. II. Eils, Roland, editor of compilation. III. Title.
[DNLM: 1. Computational Biology. 2. Systems Biology. QU 26.5]
QH324.2
570.1'13--dc23

2013045039

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

ISBN: 978-0-12-405926-9

Printed in the United States of America
14 15 10 9 8 7 6 5 4 3 2 1

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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,
September 2013

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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

http://dx.doi.org/10.1016/B978-0-12-405926-9.00001-0

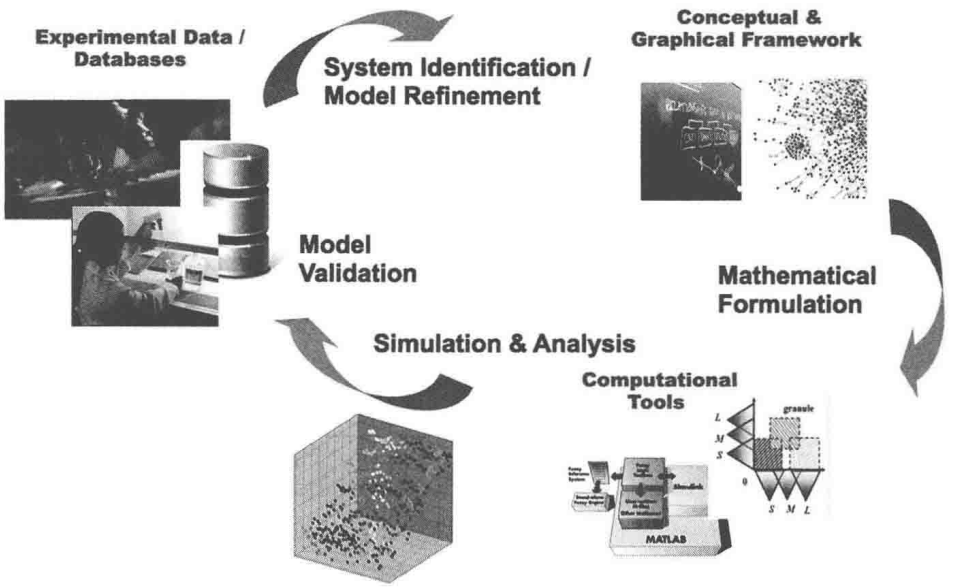

FIGURE 1.1 Key to systems biology is an iterative cycle of experimentation, model building, simulation and validation.

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

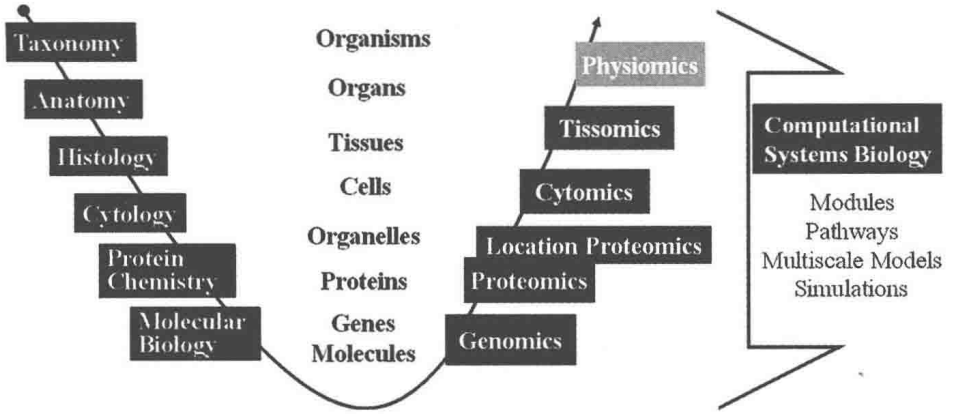

FIGURE 1.2 By the evolution of scientific disciplines in biology over time, ever-smaller structures have come into focus and more detailed questions have been asked. With the availability of high-throughput sequencing techniques in genetics a turning point was reached at the molecular basis of life. The frontiers of research extended to hypothesis-free data acquisition of biological entities, with genomics becoming the first in a growing series of "-omics" disciplines. Although functional genomics and proteomics are far from being completed, "omics" -type approaches addressing the phenotypical cellular, tissue and physiological levels constitute themselves as new scientific disciplines, filling up an otherwise sparse data space. Computational systems biology provides methodologies to combine, model, and simulate entities on diverse (horizontal) levels of biological organization, such as gene regulatory and protein networks, and between these levels by using multiscale (vertical) approaches.

bioinformatics tools to collect, store, retrieve, visualize, and analyze complex biological data has repeatedly proven useful in biological decision support and discovery. Deciphering the basic building blocks of life is a necessary step in biological research, but provides only limited knowledge in terms of understanding and predictability. In the early stages the human genome project stirred the public expectation for a rapid increase in the deciphering of disease mechanisms, more effective drug development and cure. However, it is well recognized that the battery of mechanisms involved in the proliferation of complex diseases like cancer, chronic diseases, or the development of dementias cannot be understood solely on the basis of knowing all its molecular components.

As a consequence, a lack of system level understanding of cellular dynamics has prevented a substantial increase in the number of new drugs available for treatment, drug efficacy, or eradication of any specific diseases. In contrast, pharmaceutical companies are currently lacking criteria to select the most valuable targets, R&D expenses skyrocket, and new drugs rarely hit the market and often fail in clinical trials, while physicians face an increasing wealth of information that needs to be interpreted intelligently and holistically.

Analysis of this dilemma reveals primary difficulties due to the enormous biomolecular complexity, structural and functional unknowns in a large portion of gene products and a lack of understanding of how the concert of molecular activities transfers into physiological alterations and disease. It has been long recognized that the understanding of cells as open systems, interacting with the environment, performing tasks and sustain homeostasis, or better homeodynamics (Yates 1992), requires the development of foundations for a general systems theory that started with the seminal work of Bertalanffy (Von Bertalanffy 1969).

It appears that with the ever increasing quality and quantity of molecular data, mathematical models of biological processes are even more in demand. For instance, an envisioned blueprint of complex diseases will not solely consist of descriptive flowcharts as widely found in scientific literature or in genomic databases. They should rather be based on predictive, rigorously quantitative data-based mathematical models of metabolic pathways, signal transduction cascades, cell-cell communication, etc. The general focus of biomedical research on complex diseases needs to change from a primarily steady-state analysis at the molecular level to a systems biology level capturing the characteristic dynamic behavior. Such biosimulation concepts will continue to transform current diagnostic and therapeutic approaches to medicine.

2 OVERVIEW OF THE CONTENT

This completely revised, second edition of this book presents examples selected from an increasingly diverse field of activities, covering basic key methods, development of tools, and recent applications in many complex areas of computational systems biology. In the following, we will broadly review the content of the chapters as they appear in this book, along with specific introductions and outlooks.

The first section of this book introduces essential foundations of systems biology, principles of network reconstruction based on high-throughput data with the help of engineering principles such as control theory. Robert B. Russell, Gordana Apic, Olga Kalinina, Leonardo Trabuco, Matthew J. Betts, and Qianhao Lu provide an introduction (Chapter 2) on "*Structural Systems Biology: modeling interactions and networks for systems studies.*" Molecular mechanisms provide the most detailed level for a mechanistic understanding of biological complexity. The current challenges of a structural systems biology are to integrate, utilize, and extend such knowledge in conjunction with high-throughput studies. Understanding the mechanistic consequences of multiple alterations in DNA variants, protein structures, and folding are key tasks of structural bioinformatics.

Principles of protein interactions in pathways and networks are introduced by Hans V. Westerhoff, Fei He, Ettore Murabito, Frédéric Crémazy, and Matteo Barberis in Chapter 3. Their contribution is entitled "*Understanding principles of the dynamic biochemical networks of life through systems biology*" and discusses a number of basic, more recent and upcoming discoveries of network principles. The contributors review analytical procedures from flux balance in metabolic networks to measures of robustness.

In Chapter 4, Ursula Klingmüller, Marcel Schilling, Sonja Depner, and Lorenza A. D'Alessandro review the "*Biological foundations of signal transduction and aberrations in disease.*" Signaling pathways process the external signals through complex cellular networks that regulate biological functions in a context-dependent manner. The authors identify the underlying biological mechanisms influential for signal transduction and introduce the mathematical tools essential to model signaling pathways and their disease aberrations in a quantitative fashion.

Further acceleration of progress in pathway reconstruction and analysis is contingent on the solution of many complexities and new requirements, revolving around the question of how high-throughput experimental techniques can help to accelerate reconstruction and

simulation of signaling pathways. This is the theme of the review in Chapter 5 by Christina Kiel and Luis Serrano on the *"Complexities underlying a quantitative systems analysis of signaling networks."* Chapter 6 by Seiya Imoto, Hiroshi Matsuno, Satoru Miyano presents *"Gene networks: estimation, modeling and simulation."* The authors describe how gene networks can be reconstructed from microarray gene expression data, which is a contemporary problem. They also introduce software tools for modeling and simulating gene networks, which is based on the concept of Petri nets. The authors demonstrate the utility for the modeling and simulation of the gene network for controlling circadian rhythms.

Section 2 provides an overview of methods, mathematical tools, and examples for modeling approaches of dynamic systems. *"Standards, platforms, and applications,"* as presented by Herbert Sauro and Stanley Gu in Chapter 8, reviews the trends in developing standards indicative of increasing cooperation within the systems biology community, which emerged in recent years permitting collaborative projects and exchange of models between different software tools. *"Databases for systems biology,"* as reviewed in Chapter 9 by Juergen Eils, Elena Herzog, Baerbel Felder, Christian Lawerenz and Roland Eils provide approaches to integrate information about the responses of biological system to genetic or environmental perturbations. As researchers try to solve biological problems at the level of entire systems, the very nature of this approach requires the integration of highly divergent data types, and a tight coupling of three general areas of data generated in systems biology: experimental data, elements of biological systems, and mathematical models with the derived simulations. Chapter 10 builds on a classical mathematical modeling approach to study patterns of dynamic behaviors in biological systems. *"Computational models for circadian rhythms - deterministic versus stochastic approaches,"* Jean-Christophe Leloup, Didier Gonze and Albert Goldbeter demonstrates how feedback loops give rise to oscillatory behavior and how several results can be obtained in models which possess a minimum degree of complexity. Circadian rhythms provide a particular interesting case-study for showing how computational models can be used to address a wide range of issues extending from molecular mechanism to physiological disorders.

Reinhard Laubenbacher and Pedro Mendes review *"Top-down dynamical modeling of molecular regulatory networks,"* Chapter 11. The modeling framework discussed in this chapter considers mathematical methods addressing time-discrete dynamical systems over a finite state set applied to decipher gene regulatory networks from experimental data sets. The assumptions of final systems states are not only a useful modeling concept, but also serve an explanation of fundamental organization of cellular complexities. Chapter 12, entitled *"Multistability and multicellularity: cell fates as high-dimensional attractors of gene regulatory networks,"* by Joseph X. Zhou and Sui Huang, investigates how the high number of combinatorially possible expression configurations collapses into a few configurations characteristic of observable cell fates. These fates are proposed to be high-dimensional attractors in gene activity state space, and may help to achieve one of the most desirable goal of computational systems biology, which is the development of whole cell models. In Chapter 13 John Cole, Mike J. Hallock, Piyush Labhsetwar, Joseph R. Peterson, John E. Stone, and Zaida Luthey-Schulten review *"Whole cell modeling strategies for single cells and microbial colonies,"* taking into account spatial and time-related heterogeneities such as short-term and long-term stochastic fluctuations.

Section 3 of this book is dedicated to emerging systems biology application including modeling of complex systems and phenotypes in development, aging, health, and disease. In Chapter 14, Jean-Luc Bouchot, William Trimble, Gregory Ditzler, Yemin Lan, Steve Essinger,

and Gail Rosen introduce *"Advances in machine learning for processing and comparison of metagenomic data."* The study of nucleic acid samples from different parts of the environment, reflecting the microbiome, has strongly developed in the last years and has become one of the sustained biocomputational endeavors. Identification, classification, and visualization via sophisticated computational methods are indispensable in this area. Similarly, the deciphering immune system has to deal with a large amount of data generated from high-throughput techniques reflecting the inherent complexity of the immune system. Helder I. Nakaya, in Chapter 15, reports on *"Applying systems biology to understand the immune response to infection and vaccination."* This chapter highlights recent advances and shows how systems biology can be applied to unravel novel key molecular mechanisms of immunity.

Rene Doursat, Julien Delile, and Nadine Peyrieras present *"Cell behavior to tissue deformation: computational modeling and simulation of early animal embryogenesis,"* Chapter 16. They propose a theoretical, yet realistic agent-based model and simulation platform of animal embryogenesis, to study the dynamics on multiple levels of biological organization. This contribution is an example demonstrating the value of systems biology in integrating the different phenomena involved to study complex biological process. In Chapter 17, Andres Kriete and Mathieu Cloutier present *"Developing a systems biology of aging."* The contribution reviews modeling of proximal mechanisms of aging occurring in pathways, networks, and multicellular systems, as demonstrated for Parkinson's disease. In addition, the authors reflect on evolutionary aspect of aging as a robustness tradeoff in complex biological designs.

In Chapter 18, Hang Chang, Gerald V Fontenay, Ju Han, Nandita Nayak, Alexander Borowsky, Paul Spellman, and Bahram Parvin present image-based phenotyping strategies to classify cancer phenotypes on the tissue level, entitled *"Morphometric analysis of tissue heterogeneity in Glioblastoma Multiforme."* Such work allows to associate morphological heterogeneities of cancer subtypes with molecular information to improve prognosis. In terms of a multiscale modeling approach the assessment of phenotypical changes, in cancer as well as in other diseases, will help to build bridges toward new spatiotemporal modeling approaches. Stefan M. Kallenberger, Stefan Legewie, and Roland Eils demonstrate *"Applications in cancer research: mathematical models of apoptosis"* in Chapter 19. Their contribution is focused on the mathematical modeling of cell fate decisions and its dysregulation of cell death, contributing to one of the ramifications of the complexities in cancer biology.

3 OUTLOOK

It is commonly recognized that biological multiplicity is due to progressive evolution that brought along an increasing complexity of cells and organisms over time (Adami et al. 2000). This judgement coincides with the notion that greater complexity is "better" in terms of complex adaptive systems and ability for self-organization, hence robustness (Csete and Doyle 2002 Kitano 2004). Analyzing or "reverse" engineering of this complexity and integrating results of today's scientific technologies responsible for the ubiquitous data overload are an essential part of systems biology. The goals are to conceptualize, abstract basic principles, and model biological structures from molecular to higher level of organization like cells, tissues, and organs, in order to provide insight and knowledge. The initial transition requires data