Preface

Systems biology could be defined as the *quantitative* analysis of the *dynamic* interactions among several components of a biological system and aims to understand the behavior of the system as a *whole*. R&D in systems biology involves the development and application of systems theory concepts for the study of complex biological systems through iteration over *mathematical modeling* and *computational simulation* and *biological experimentation*. Systems biology could be viewed as a tool to increase understanding of biological systems and to develop more directed experiments and finally allow predictions.

The field of systems biology arose out of a biological problem which is essentially entailed by the complexity of biological life. It was created because of the limitations of conventional (reductionistic) biology in the investigation and understanding of complex biological phenomena arising from the dynamic interaction of many biological compounds. At present, a large number of individual genes or proteins which play key roles in essential physiological processes are known. For many of these, structural data and detailed mechanistic descriptions at a molecular level are available. In most cases, however, the individual characterization of these molecules is not sufficient to fully understand their immediate or their superordinate physiological function. Similarly, large networks of genes, proteins and other organic molecules have been discovered, mapped and characterized. While underlying mechanisms have been regarded as a promising base for explaining the multitude of cellular functions and phenomena observed in vivo, there is still a fundamental gap between the knowledge of a molecular mechanism and the understanding of the corresponding cellular or higher-level function.

The growing field of systems biology promises to bridge our current gap in understanding. Systems biology views biological function and macroscopic behavior as an emergent or supervenient property – i.e., a property that a collection of components or complex system possesses but which the individual constituents do not have. The properties of individual elements, such as proteins, are investigated in the context of the whole, complex system of interactions. The different spatial and temporal scales involved in biological processes – ranging from the level of molecules through to organisms and, ultimately, to the level of entire populations or ecosystems – permit upward and downward causation in complex arrangements of feedback loops. Systems-level properties arise from interconnected processes on multiple

scales of temporal and spatial organization. Understanding such complexity is a major challenge to the unaided human brain. Thus, using mathematical and computational models, systems biologists integrate elementary processes of systems into a coherent description that allows them to predict and characterize the systems-level properties and behavior of complex biological phenomena.

As the field of systems biology matures, we are beginning to see practical answers to real biological problems. We believe it is now time to step back and review some of the approaches of systems biology to concrete problems. This volume introduces some of the main methods and techniques of systems biology and assesses their pros and cons based on concrete case studies. The investigated biological phenomena include tissue organization, hormonal control, bacterial stress response, tumor growth and cellular metabolism. Each chapter and the book as a whole is intended to simultaneously serve as *design blueprint*, *user guide*, *research agenda*, and *communication platform*.

As *design blueprint*, the book is intended for biologists, mathematicians and systems scientists, computer scientists and technology developers, managers, and other professionals who consider adopting a systems biology approach.

As *user guide*, this volume addresses the requirements of scientists and researchers to gain an overview and a basic understanding of key systems biology methodologies and tools. For these users, we seek to explain the key concepts and assumptions of the various techniques, their conceptual and computational merits and limitations, and, where possible, give guidelines for choosing the methods and tools most appropriate to the task at hand. Our emphasis is not on a complete and intricate formal and technical treatment of the presented methodologies. Instead, we aim at providing the users with a clear understanding and practical know-how of the relevant methods in the context of concrete life science problems.

As *research agenda*, the book is intended for computer and life science students, teachers, researchers, and managers who seek to understand the state of the art of the methodologies used in systems biology research and development. To achieve this, we have attempted to cover a representative range of life science areas and systems biology methodologies, and we have asked the authors to identify areas in which gaps in our knowledge demand further research and development.

The book is also intended as a *communication platform* to bridge the cultural, conceptual, and technological gap among the key systems biology disciplines of biology, mathematics, and information technology. To support this goal, we have asked the contributors to adopt an approach that appeals to audiences from different backgrounds.

Providing a representative overview of current research, this book aims to illustrate the insights gained by adopting a systems biology approach. While systems biologists typically apply mathematical, statistical, and computational methods, these insights are presented in the context of current life science research. As a result, this book is targeted at an interdisciplinary audience comprising life scientists, mathematicians, system and computer researchers, and developers. In pursuing these goals, the book seeks to bridge the cultural, conceptual, and technological gap among the key disciplines that contribute to systems biology.

Table 1 Classification of modeling formalisms: examples

	Deterministic	Stochastic
Continuous	ODE, PDE	SDE
Discrete	Boolean network, cellular automaton	Agent-based simulation

In recent years, the increased interest of computer scientists in systems biology has led to an explosion of novel systems methodologies for modeling, analysis, and validation, but also for model representation and exchange. In this book, we do not intend to cover a wide variety of these methods, but we aim to present illustrative applications of systems biological methods in a representative overview.

In any modeling discipline, modeling formalisms may be classified according to the type of representation chosen to model *time*, *space*, and *entities* (such as the cell, proteins, or genes) of the system. These entities or dimensions can be modeled as continuous variables, so that the model can cope with any value within a meaningful range. Table 1 illustrates this. *Continuous* means that the model may output a simulation result at any given time point, t (continuous time) and location, x (continuous space), and that the output of the model may assume any value within a predefined range. In contrast, *discrete* refers to a modeling strategy that uses distinct values from a predefined set to represent time, space, and the entities of the modeled system. The output of a time-discrete model is limited to certain time intervals; a space-discrete model can explore only certain points in a given space; and discrete variables express levels or predefined states (*on*/*off*, *low*/*high*, cell cycle phase) of the modeled entities. Clearly, any of the combination of discrete and continuous methods is possible. An agent-based simulation can be backed by a time-continuous, space-discrete model with agents that are represented using both continuous and discrete variables. Discrete methodologies sometimes deviate from the classification shown in Table 1. The most common cases are shown in the table.

Systems biology modeling methodologies may also be divided into deterministic and stochastic formalisms. Consider a set of interacting cells which behave according to certain rules. In reality, the observation of randomly picked single cells may lead to grossly varying observations; although when looking at a large number of cells, they all share the same characteristic behavior. Deterministic simulations deal with this problem by modeling only those characteristics; the stochastic approach, in contrast, considers a large number of individual simulations and uses statistical analysis to draw conclusions.

Below we provide a brief overview of the contributed chapters in terms of the modeling methodology used and the biological problems addressed.

The modeling framework that was probably the first to be adapted for systems biological modeling – before the term systems biology was even coined – is the mathematical framework with the longest tradition: differential equations modeling, or more concrete, *ordinary differential equations* (*ODEs*). The ODE methodology offers a variety of basic, mathematical, and computational tools for modeling, simulation, and qualitative and quantitative analysis.

Chapter 1 presents two elementary case studies that illustrate ODE-based model definition as well as timescale analysis and sensitivity analysis. These analysis methods can be used to extract biologically meaningful information from the model. In the study, the authors measure the efficiency of the simulated cell's protein-folding machinery under various conditions using timescale analysis.

While ODEs offer a general and flexible approach to modeling, this methodology relies on a qualitatively and quantitatively exact definition of the molecular network or system to be represented. Chapter 2 illustrates some of the most common mathematical tools in an ODE-based case study relating to folate metabolism.

Chapter 3 presents a delay differential equations (DDE) model of hormonal control of the menstrual cycle. This study demonstrates that it is sometimes more interesting to characterize the behavior of a system in relation to its inputs and parameters, than to just reproduce its outputs using concrete parameter values.

Pharmacokinetic models, most of which are ODE-based, have become an established tool in pharmacology. Such models have become an important tool in drug development to predict the fate of drugs or toxins taken in by the human body. Chapter 4 introduces this field and highlights the problem of investigating active transport phenomena.

The studies presented in Chaps. 3 and 4 rely on a reasonably well-established body of quantitative data. However, in the majority of cases, sufficient amounts of data are currently not available to systems biologists. The need to abstract from concrete sets of parameters has therefore led to the development of different modeling methods. *Piece-wise linear* (*PL*) *equations*, introduced in Chap. 6, are one example. Based on ODEs, they divide the entire parameter space into parts that share the same qualitative behavior. This behavior is approximated using only simple, linear equations, as opposed to the nonlinear equations that typically arise in complex ODE systems. This property makes PL models mathematically more tractable.

Flux balance analysis (*FBA*) is another useful tool in pharmacological applications of systems biology. An FBA model can predict metabolic activities (fluxes) under homeostatic conditions. Knowing the relevant metabolites and the stoichiometry of all reactions in the system is sufficient for performing such an analysis. FBA permits comprehensive studies of qualitative structural changes in the network, such as deletion of arbitrary genes throughout the genome. Chapter 5 presents an FBA case study concerned with the metabolism and pathogenicity of *Mycobacterium tuberculosis*. The overall goal of the effort is to systematically and efficiently design anti-tuberculosis drugs. Toward this goal, this chapter also illustrates how other techniques, besides FBA, can be used. The use of graph-theoretical techniques are illustrated for analyzing the protein–protein interaction networks, to gain insights about strategic hub proteins and possible of routes of information flow in triggering drug resistance. Boolean network modeling, another technique gaining popularity for studying biological systems, has been used for studying host–pathogen interactions, in this case leading to qualitative understanding of the complex interplay of the bacterial components with the human immune system.

Another modeling technique which is growing in popularity is the *agent-based model* (or individual-based model). Chapter 7 illustrates this methodology with an

application to the problem of bacterial antibiotic resistance. In this model, each cell is represented as an agent, which moves and interacts with other agents according to a defined set of rules. The agent paradigm is well suited to investigating the mechanisms of emergent spatial patterns. This is also discussed in Chap. 8, where an agent-based model is used to mimic the assembly of microtubules into the mitotic spindle at cell division.

Since different modeling methodologies are typically suited for different scales of time and space, it is an appealing proposition to build multi-scale models, where multiple modeling techniques applied to different aspects of the same biological problem integrate into a single, integrated model. The agent-based modeling approach permits the use of arbitrary modeling methods for defining the rule sets by which the agents are governed. This is illustrated in Chap. 9, where agents are used to model the behavior of epithelial tissue.

Finally, Chap. 10 uses an entirely different approach to investigate a problem in synthetic biology. In this discipline, biological molecules are used to engineer functional entities such as logic circuits. In this study, a domain-specific programming language helps to model and define the behavior of this engineered component.

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August, 2010

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http://www.springer.com/978-1-4419-7963-6

Understanding the Dynamics of Biological Systems
Lessons Learned from Integrative Systems Biology
Dubitzky, W.; Southgate, J.; Fuß, H. (Eds.)
2011, XIV, 238 p., Hardcover
ISBN: 978-1-4419-7963-6