Preface

Systems Biology is an emerging, multi-disciplinary field that has attracted increasing attention over the last few years. The rapid development of new experimental technologies in biology and medicine results in an enormous amount of biological data not only on sequences and structures, but also on their dependencies and interactions for many prokaryotes and eukaryotes. Thus, new data bases on gene expression, protein-protein interaction, and pathways have been developed. This quantity of data allows scientists to investigate molecular cell processes in a large scale manner. With the help of such newly available experimental data, many qualitative as well as quantitative in silico models have been constructed in order to obtain new insights into the behavior of biochemical systems, leading to a better understanding of molecular processes.

The lack of computational methods to explore such experimental data has led to an explosion of method development in this area. Methods in computational systems biology cover discrete, continuous, and stochastic techniques. Many of them are based on principles and algorithms which have been known for more than 20 years. The mathematical formalism of Petri net theory can encompass all of these techniques. For about 15 years, Petri net models of biochemical systems have been successfully developed, simulated, and analyzed. In the last five years, many papers have been published applying Petri net theory to different types of biochemical systems which model gene regulation, signal transduction and/or metabolism in biologically different application fields. This development provided the motivation to produce a book which explains Petri net foundations and reflects the main applications of Petri nets in molecular biology.

Who Should Read This Book?

This book intends to provide a comprehensive overview on recent applications of Petri nets in systems biology. The text has been designed to reach students, graduates, scientists with biological or medical background as well as with mathematical or computer science background, and also lecturers. The book aims to enable the
interested reader to enter the field of modeling biochemical systems using Petri net concepts. The chapters have been divided into three parts, an introductory part, a methodological part, and an application-oriented part. The three introductory chapters comprise a general introduction on systems biology, biological foundations, and Petri net basics. As far as possible, we have unified the mathematical notations. We redraw the Petri nets in figures according to unifying drawing rules suggested by Wolfgang Reisig. Additionally, exercises are provided for each chapter, facilitating use of the book for lectures. Finally, cross references between chapters, a glossary and an index help in navigating the content and finding information quickly. We hope to spark interest not only in the application of Petri nets in modeling biochemical systems, but also in the fascinating and challenging fields of systems biology and of Petri nets.

**How to Read This Book?**

The book aims to introduce the latest research in Petri net applications in systems biology, but also to provide the necessary foundations of Petri net theory and of biochemical systems. The book can also be used as a textbook, as facilitated by the problems and their solutions provided for each chapter.

The book is organized into three parts each consisting of three to six chapters. The parts focus on theoretical foundations, basic modeling techniques, and special applications, respectively. Each chapter is self-contained and can be used as a unit of study. The first part introduces basic concepts. The second part discusses different modeling techniques, reflecting different levels of abstraction. The third part is dedicated to biochemical applications adopting a variety of different methods.

Part I introduces the field of systems biology, the foundations of biochemistry, and Petri net basics. This part should be read by newcomers to that field, but may be skipped, if the reader is already familiar with the foundations. Part I comprises three chapters. The first, Chap. 1, gives a general introduction into systems biology, also providing an overview of the main data resources, software tools, and visualization techniques. The second, Chap. 2, introduces the main biological principles of biochemistry comprising cell biology, metabolism, signal transduction, and gene expression. Chapter 3 explains basic principles of Petri nets, giving the necessary definitions and many examples.

Part II compiles basic Petri net modeling techniques for building and analyzing biological models. It starts with Chap. 4 on discrete modeling, comprising the classical Petri net modeling techniques as well as special new methods developed for application to biochemical systems. Discrete modeling techniques are particularly important for systems biology because often quantitative data is not available. Thus, a system’s behavior can only be explored on the basis of its topology. One focus in the chapter concerns invariant analysis, which is in particular important for analyzing biochemical systems. Other special discrete modeling techniques have been developed to handle gene regulatory networks, which are described in Chap. 5, and with a special biological application in Chap. 12 in Part III.
In cases where some quantitative data is additionally available, hybrid modeling techniques, which combine discrete and continuous modeling, become suitable. These methods are introduced in Chap. 6. Many biochemical processes follow stochastic rules. Chapter 7 describes how stochastic systems can be modeled by Petri nets.

For continuous modeling, we have to know a critical amount of quantitative (kinetic) data. Methods applied in continuous modeling are mainly based on solving ordinary differential equation systems. These methods, which have been known for many years, differ in accordance with the underlying kinetics. Thus, for modeling enzymatic reactions, Michaelis–Menten kinetics is used, whereas for reflecting cooperativity, Hill kinetics is applied. Both concepts and the underlying mass action kinetics as well as their translation into Petri net formalism is explained in Chap. 8.

A new interesting application is fuzzy reasoning in Petri nets, which is introduced in Chap. 9.

Part III covers special applications to biochemical systems with regard to the type of the network according to its biological classification. Chap. 10 considers applications to metabolic networks, reflecting the relationship to stoichiometry-based methods, in particular to the concept of elementary modes. We continue in Chap. 11 with modeling of signal transduction pathways. The following chapter considers the modeling of gene regulation based on logical networks, and its conversion into Petri nets, using logical regulatory modules applied to development in segments of Drosophila embryos. Chapter 13 considers the modeling of feedback loops in the circadian clock of mammals using the hybrid Petri net approach. Additionally, Part III contains a special chapter on network prediction. The prediction of possible network structures from experimental data is a very challenging approach. Chapter 14 introduces such an approach using Petri net formalism.

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**FTP Site for Supplementary Material**

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Modeling in Systems Biology
The Petri Net Approach
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