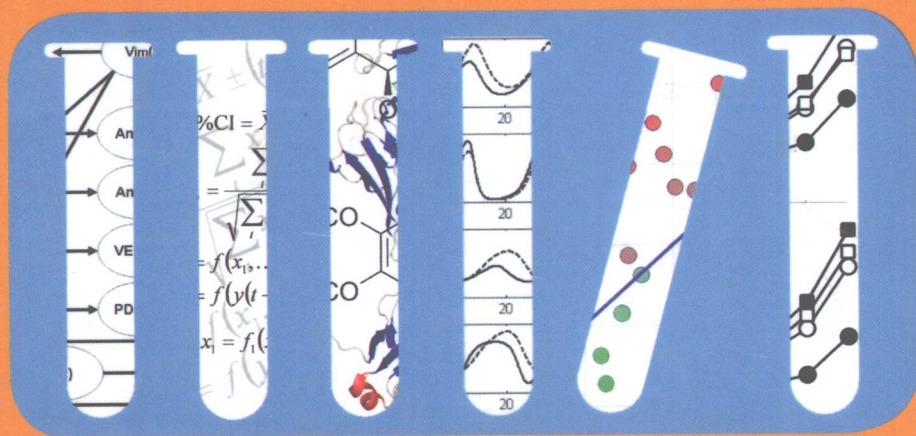


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Systems Biology in Drug Discovery and Development



Edited by
Daniel L. Young and Seth Michelson

SYSTEMS BIOLOGY IN DRUG DISCOVERY AND DEVELOPMENT

Edited by

Daniel L. Young
Seth Michelson



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PREFACE

Despite the wealth of data describing mechanisms underlying health and disease in living systems, health care costs continue to rise, and there is a growing need for improved and more affordable treatments. Efficient drug discovery and development requires methods for integrating preclinical data with patient data into a unified framework to project both efficacy and safety outcomes for new compounds and treatment approaches.

In this book we present the foundations of systems biology, a growing multidisciplinary field, applied specifically to drug discovery and development. Systems biology formally integrates knowledge and information from multiple biological sources into a coherent whole by employing proven engineering and mathematical modeling approaches. The integrated system allows rapid analysis and simulation that can inform and optimize the drug research and development processes, by formalizing, and testing, the set of acceptable hypotheses *in silico*, thereby reducing development time and costs and ultimately improving the efficacy of novel treatments.

This book is the first systems biology text to focus on how systems biology can be specifically applied to enhance drug discovery and development, with particular emphasis on real-world examples. Other texts on systems biology to date have focused on particular subdisciplines of systems biology (such as cellular networks) and have not specifically addressed drug discovery and development. This book introduces key methodologies and technical approaches for helping to solve many of the current challenges facing the pharmaceutical and biotechnology industries.

The target audience for the book includes those training or currently involved in all phases of drug discovery and development. Specific examples include life scientists, pharmacologists, computational and systems biology modelers, bioinformaticians, clinicians, and pharmaceutical/biotech management. The methods and case studies presented here will help researchers understand the diverse applications of the systems approach and integrate these technologies into their drug discovery and development programs. Those who incorporate these approaches successfully should increase their organization's competitiveness to address unmet market needs as well as more complex diseases and therapies.

The book is divided into four complementary parts. Providing a foundation for the techniques of systems biology, Part I provides an introduction to

engineering and mathematical methods employed to characterize biological systems. In particular, Chapter 2 overviews model construction and analysis, focusing on model building, parameter estimation, model validation, and sensitivity analysis. Chapter 3 presents general statistical modeling approaches as well as methods for representing and analyzing nonlinear dynamical biochemical networks, of which feedback and feedforward loops are central players. In addition to modeling fundamental biological interactions and dynamics, an essential element of the systems biology approach is the study and simulation of population-level variability. To this end, Chapter 4 presents how drug pharmacokinetics is affected by variations in drug absorption, distribution, metabolism, and excretion, illustrating methods for predicting interindividual variability essential for rationale compound evaluation.

Part II highlights systems biology techniques aimed at enhancing the drug discovery process. An essential component of drug discovery is target identification and validation. To tackle many of the challenges inherent in these processes, Chapter 5 introduces a variety of complementary systems approaches, including text-mining, disease and therapeutics modeling, large multicontext data sets, regression modeling, and network and dynamic pathway modeling. In Chapter 6, systems biology approaches are applied to lead identification and optimization disciplines. In particular, systems approaches are shown to enable building bridges between compounds' chemical and biological activities. In this way, lead identification and optimization are enhanced by the systematic quantification of the optimal pharmacokinetic and pharmacodynamic compound profiles, defined potentially for specific patient populations. Chapter 7 addresses drug safety by exploring the role of biological motifs, in particular switchlike circuits, critical for dose-response models. Such models help uncover complex emergent behaviors and reveal factors driving variable patient responses to drugs that could limit efficacy or even lead to low-incidence adverse responses. Finally, Chapter 8 presents the use of mechanistic systems models for the study of pharmacokinetics and pharmacodynamics during discovery and early development. These models integrate a mechanistic understanding of biology and disease processes into a framework to aid in the selection of lead compounds, evaluation of dosing regimens, and support of optimal study design for specific patient populations.

Part III addresses particular applications of systems biology to drug development. Illustrating practical drug development challenges, Chapter 9 details the development and validation of a multiscale mathematical model for angiogenesis, integrating molecular and tissue-level processes. Here the exemplary model is applied for treatment personalization, and results suggest that an arrested drug candidate can be efficacious if applied in combination with current standards of care. Chapter 10 presents methods for applying systems biology to candidate biomarker identification. In particular, the chapter highlights the biomarker discovery process, its application to drug development, and the utility of mechanistic systems modeling to biomarker development in cardiovascular disease and rheumatoid arthritis. Finally, to aid in the design

and execution of costly clinical programs, essential aspects of clinical trial simulations are presented in Chapter 11, where both clinical efficacy and safety are essential considerations.

In the final section of the book, Part IV, we address how systems biology technologies can synergize with other approaches. To this end, Chapter 12 presents how biological pathway analysis can be integrated into drug discovery systems approaches. Chapter 13 addresses aspects of personalized medicine and how functional mapping aimed at understanding genes and genetic networks can be used to help predict drug responses in patients. The book concludes in Chapter 14 with a broad overview of opportunities and challenges in systems biology that should ultimately help to extend both its reach and its acceptance, thereby further enhancing pharmaceutical productivity and the success of drug discovery and development for the benefit of patients.

In addition to the contributing authors of this book, we would like to thank our collaborators and colleagues throughout the years who have helped develop and apply systems biology approaches to drug discovery and development. We look forward to future advances and successes in the coming years as these approaches are applied and extended by dedicated researchers for enhanced drug discovery and development and ultimately, better care for patients.

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 PART I

INTRODUCTION TO SYSTEMS BIOLOGY IN APPROACH

Introduction to Systems Biology in Drug Discovery and Development

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Summary

Over the last several decades, medical and biological research has opened vast windows into the mechanisms underlying health and disease in living systems. Integrating this knowledge into a unified framework to enhance understanding and decision making is a significant challenge for the research community. Efficient drug discovery and development requires methods for bridging pre-clinical data with patient data to project both efficacy and safety outcomes for new compounds and treatment approaches. In this book we present the foundations of systems biology, a growing multidisciplinary field applied specifically to drug discovery and development. These methods promise to accelerate time lines, to reduce costs, to decrease portfolio failure rates, and most significantly, to improve treatment by enhancing the workflow, and thus the competitiveness, of pharmaceutical and biotechnology organizations. Ultimately, these improvements will improve overall health care and its delivery.

SYSTEMS BIOLOGY IN PHARMACOLOGY

Discovering a new medicine is a multistep process that requires one to:

- Identify a biochemically based cause–effect pathway (or pathways) inherent in a disease and its pathophysiology

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