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Systems Biology in Drug Discovery and Development



Edited by Daniel L. Young and Seth Michelson



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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 biological sources into a coherent whole multiple bv 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 help researchers studies presented here will case understand the applications of the diverse systems approach and integrate these technologies into their drug and development programs. Those discoverv 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 drua distribution. metabolism. absorption. 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. Chapter 6, In systems bioloav applied lead identification approaches are to 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 pharmacodynamic compound profiles. defined and potentially for specific patient populations. Chapter 7 addresses drug safety by exploring the role of biological motifs, in particular switchlike circuits, critical for doseresponse 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 broad overview of а 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 CHAPTER 1

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 preclinical 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
- Identify those cells and molecular entities (e.g., receptors, cytokines, genes) involved in the control of those pathways (typically termed *targets*)
- Identify an exogenous entity that can manipulate a molecular target to therapeutic advantage (typically termed a *drug*)
- Identify, with some level of specificity, how manipulation modulates the disease effects (termed the *mechanism of action* of the drug)
- Identify that segment of the patient population most likely to respond to manipulation (typically through the use of appropriate surrogates termed *biomarkers*)

Given these challenges, pharmaceutical drug discovery and development is an extremely complex and risky endeavor. Despite growing industry investment in research and development, only one in every 5000 new drug candidates is likely to be approved for therapeutic use in the United States (PhRMA, 2006). In fact, approximately 53% of compounds that progress to phase II trials are likely to fail, resulting in amortized costs of between \$800 million and \$1.7 billion per approved drug (DiMasi et al., 2003; Gilbert et al., 2003; Pharmaceutical Research and Manufacturers of America, 2006). Clearly, the crux of the problem is the failure rate of compounds, especially those in late-stage clinical development. To solve this problem, one must clearly identify the most appropriate compound for the most appropriate target in the most appropriate subpopulation of patients, and then dose those patients as optimally as possible. This philosophy forms the cornerstone of the "learn and confirm" model of drug development suggested by Sheiner in 1997.

For example, to address these three issues specifically, the Center for Drug Development Science at the University of California–San Francisco has developed a set of guidelines for applying one particular *in silico* technology, biosimulation, to the drug development process (Holford et al., 1999).

These guidelines define a three-step process. During step 1, the most relevant underlying biology describing the pathophysiology of the disease is characterized, as are the pharmacokinetics of any candidate compound aimed at its treatment. In step 2, the various clinical subpopulations expected to receive the compound are identified and characterized, including measures of interpatient variability in drug absorption, distribution, metabolism, and excretion, and compound-specific pharmacodynamics are established. Once steps 1 and 2 are complete, this information is used in step 3 to simulate and thus design the most efficient clinical trial possible.

We believe that the general principles outlined above should not be restricted to only one methodology (i.e., biosimulation) but should be extended to the entire spectrum of *in silico* technologies that make up the generic

discipline called systems biology. Systems biology is a rapidly developing suite of technologies that captures the complexity and dynamics of disease progression and response to therapy within the context of *in silico* models. Whether these models and their incumbent analytical methodologies represent explicit physiological models and dynamics, statistical associations, or a mix thereof, en suite they provide the pharmaceutical researcher with access to the most pertinent information available. By definition, that information must be composed of those data that best characterize the disease and its pathophysiology, the compound and its mechanism of action, and the patient populations in which the compound is most likely to work. With the advance of newer and faster assay technologies, the gathering of those data is no longer the rate-limiting process it once was. Rather, technologies capable of sampling the highly complex spaces underlying biological phenomena have made the interpretation of those data in the most medically and biologically reasonable context the next great hurdle in pharmaceutical drug discovery and development.

challenges adequately, To address these the pharmaceutical or clinical researcher must be able to understand and characterize the effects of diverse chemical entities on the pathways of interest in the context of the biology they are meant to affect. To accomplish that, research scientists and clinicians must have at their disposal the means to acquire the most pertinent and predictive information possible. We believe that systems biology is a particularly attractive solution to this problem. It formally integrates knowledge and information from multiple biological sources into a coherent whole by subjecting them proven engineering, mathematical, and statistical to methodologies. The integrated nature of the systems biology approach allows for rapid analysis, simulation, and

interpretation of the data at hand. Thus, it informs and optimizes the pharmaceutical discovery and development processes, by formalizing, and testing, the most biologically relevant family of acceptable hypotheses *in silico*, thereby enabling one to reduce development time and costs and improve the efficacy of novel treatments.

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CHAPTER 2

Methods for In Silico Biology: Model Construction and Analysis

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2.1. INTRODUCTION

increasing Despite investment research in and development, the productivity of the pharmaceutical has been declining, and this unfortunate industrv necessitates novel phenomenon approaches to drua discovery and development. Systems biology is an approach that shows great promise for identifying and validating new drug targets and may ultimately facilitate the introduction of personalized and preventive medicine. This interdisciplinary field integrates traditional experimental techniques from molecular biology and biochemistry with computational biology, modeling and simulation, and systems analysis to construct quantitative mathematical models of biological networks in order to investigate their behavior. The utility of such models depends on their predictive abilities. Although constructing models that can predict all phenotypes and perturbation responses is not feasible at present, it is