Preface

You hold in your hand a volume devoted to systems biology of infectious disease. If you are new to the field, you may be asking "what is systems biology?" If you think you already know the answer, you may be wondering how such an approach can be applied to a problem as complex as infectious disease. Our goal is to address both of these questions, and we anticipate that this volume will be of great interest to investigators already engaged in systems biology research as well as to those scientists and clinicians who may be seeking an introduction to the field.

What is Systems Biology?

As you read through this volume, it will become apparent that while there is no single concise definition of systems biology, most authors will settle on several key points. First, systems biology is an inter-disciplinary approach, requiring the combined talents of biologists, mathematicians, and computer scientists. Second, systems biology is holistic, with the goal of obtaining a comprehensive understanding of the workings of biological systems. This is achieved through the acquisition of massive amounts of data by high-throughput technologies—oligonucleotide microarrays, mass spectrometry, and next-generation sequencing—and the analysis of this data through sophisticated mathematical algorithms (Fig. 1). It is perhaps the use of mathematics, to integrate abundant and diverse types of data and to generate models of interconnected molecular networks, that best characterizes systems biology.

An additional characteristic often attributed to the approach is the use of an iterative cycle of experimental perturbations. Once a model has been developed, subsequent perturbations of the biological system are used to yield refinements to the model and increase its predictive capacity. While the value of a clear understanding of complex molecular networks may seem readily apparent, proponents of systems biology argue that the approach is also the only way to understand the "emergent properties" of biological systems. As described in

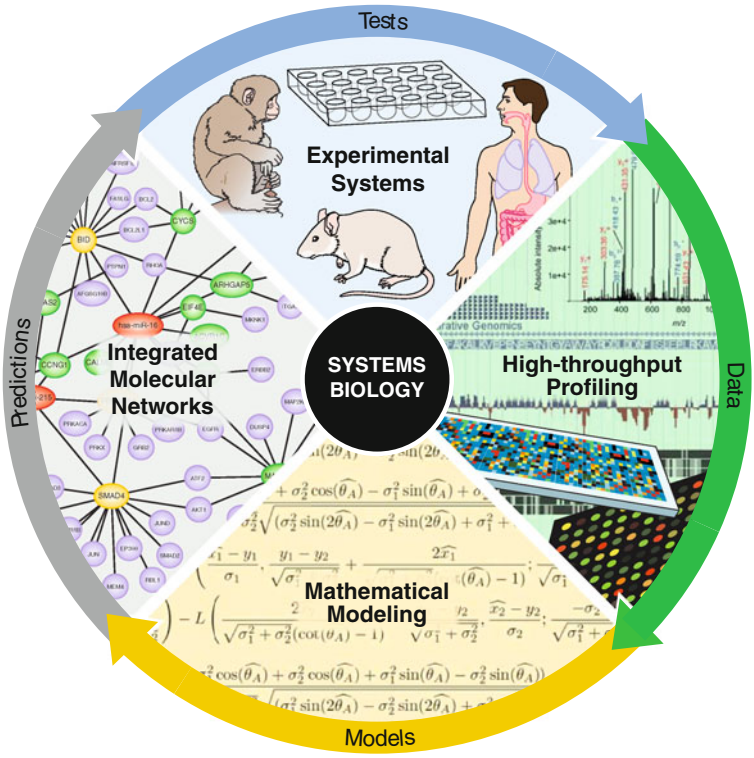

Fig. 1 The systems biology paradigm viewed as an iterative cycle of events leading to the generation of integrated models of molecular networks that serve to generate predictions for subsequent testing, model refinement, and a deeper understanding of biological processes

"Systems Approaches to Dissecting Immunity", these are properties—or biological outcomes—that cannot be predicted by an understanding of the individual parts of a system alone. Finally, systems biology typically seeks to capture information about changes in a biological system over time, providing unique insights into the dynamic nature of the system, a property that has particular relevance to infectious disease.

Why Focus on Infectious Disease?

Systems biology as we know it today was made possible by the human genome project and the advent of high-throughput technologies to measure global changes in gene transcription and protein and metabolite abundance. The first uses of this approach just over a decade ago focused on the systematic perturbation of yeast and the mathematical modeling of metabolic pathways (Ideker et al. 2001). Given

the complexity of even a single-cell organism, many would argue (and some still do) that the approach is ill-suited for multi-cellular organisms or mammalian systems. Yet the cancer field rapidly embraced the approach and has proven its utility for network-based classification and prognosis of breast cancer, the identification of oncogenes in B-cell lymphomas, and improvements to radiation therapy (Laubenbacher et al. 2009).

The infectious disease field, in contrast, has come rather late to the game. Although our own group published the first genomic analysis of HIV-infected cells in culture (Geiss 2000), and numerous reports of transcriptional profiling of virus-infected cells and tissues have followed, the application of a true systems biology approach to infectious disease has until only recently been considered too daunting. What has brought about the change in attitude? Recent and dramatic improvements to mathematical modeling (see "Studying Salmonellae and Yersiniae Host–Pathogen Interactions Using Integrated 'Omics and Modeling" and "Insights into Proteomic Immune Cell Signaling and Communication via Data-Driven Modeling") and the success of the approach in other fields are certainly contributing factors, but perhaps most important is the growing realization that the infectious disease field desperately needs to take new approaches to solve long unanswered challenges, particularly in the areas of vaccine and drug development.

Trying to understand the countless and complex pathogen–host interactions and intra- and inter-cellular signaling events that occur during the course of infectious disease is indeed a formidable task. Historically, a reductionist approach was both the most tractable and only available line of attack. But clearly a new approach is needed. Vaccines against numerous deadly diseases, most notably AIDS, malaria, and tuberculosis are still lacking. Drug-resistant viruses and bacteria continue to emerge, a trend that is likely to endure as long as microbial targets remain the focus of new drug development, and the focus on microbial targets also yields drugs that are typically narrow in spectrum. As described throughout this volume, systems biology offers a new and holistic approach to understanding pathogen–host interactions, the innate immune response, and the mechanisms that lead to disease, immunopathology, or protective immunity. The approach holds enormous potential, but there are challenges as well.

Risks and Rewards

No doubt everyone engaged in systems biology research has heard the criticism that the approach is nothing more than an expensive fishing expedition that takes funding away from individual investigators. The relative merits of big versus small science aside, if systems biology is a fishing expedition, the chapters in this volume show that the approach is beginning to make some nice catches. For example, systems biology is accelerating vaccine development by increasing our understanding of how protective immune responses are elicited "Systems Biology

of Vaccination in the Elderly". Similarly, by providing a better understanding of the host response to infection, the approach is facilitating the development of drugs that target the host side of the pathogen–host interaction "Systems Biology Analyses to Define Host Responses to HCV Infection and Therapy", an approach that will yield drugs that are broader in spectrum and less prone to microbial resistance. Moreover, systems biology is beginning to deliver on its much touted potential for yielding biomarkers for new diagnostic and prognostic applications "Systems Biology Approach for New Target and Biomarker Identification".

Nevertheless, the approach is expensive, and with ever-tightening budgets, more money for systems biology means less money elsewhere. Moreover, because the approach has been extensively hyped as being revolutionary, expectations have been set high, and many are understandably disappointed with the pace of progress. The extent to which systems biology represents a true paradigm shift has also been called into question (Bothwell 2006). And there are still plenty of technical, scientific, and mathematical hurdles to overcome. Even the choice of experimental systems can be a challenge. The jump from cell culture systems to nonhuman primates, for example, represents an enormous leap in system complexity that taxes every aspect of the approach, particularly computational and modeling techniques. Yet, as discussed in "The Role and Contributions of Systems Biology to the Non-Human Primate Model of Influenza Pathogenesis and Vaccinology" and "'Omics Investigations of HIV and SIV Pathogenesis and Innate Immunity", significant progress is being made, and the analysis of biologically relevant infection models is essential if we are to understand the processes of disease and immunity and translate findings into rational drug design and vaccine development.

In This Volume

We begin this volume with an engaging editorial by Dr. Valentina Di Francesco and colleagues, who oversee a broad portfolio of systems biology research contracts at the National Institute of Allergy and Infectious Diseases (NIAID). NIAID has made a substantial commitment to systems biology through the sponsorship of genomic, proteomic, and bioinformatic resource centers, and more recently through the funding of a systems biology for infectious disease research program. This program is aimed at using experimental and computational approaches to analyze, model, and predict the architecture and dynamics of the molecular networks underlying the initiation and progression of infectious disease (Aderem et al. 2011). Each of the primary investigators associated with this program have provided material for this volume.

The chapters of *Systems Biology* provide the reader with cutting-edge research from leaders in the systems biology field. The initial chapter provides both a concise overview of the systems biology paradigm as well as an excellent discussion of how this approach is being used to dissect the innate immune system.

Subsequent chapters are devoted to systems biology approaches to bacterial–host interactions (including *Salmonella*, *Yersinia*, and *Mycobacterium*), where molecular events within the pathogen are as important as the host response to the invading microbe; the application of high-throughput and computational approaches to nonhuman primate models of influenza and AIDS; and an overview of the emerging field of systems vaccinology, where systems biology is changing the way we think about vaccine design and testing. Final chapters are dedicated to defining the host response to hepatitis C virus infection and therapy, to drug target and biomarker identification, and to new computational approaches, including data-driven modeling. By assembling a diverse spectrum of perspectives and expertise, it is hoped that the information provided here will serve as a catalyst for additional innovative approaches that will continue to drive the field forward and that will ultimately transform how we view, treat, and protect against infectious disease.

Seattle, Washington, July 2012

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