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INTRODUCTION

Introduction to modeling viral infections and immunity

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Infectious agents, such as HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), malaria, and influenza remain significant public health threats, with ~41 million people chronically infected by HIV, ~331 million infected by HBV, ~148 million infected by HCV, and ~351 million cases of malaria, according to the Global Burden of Disease 2013 study.[1] In addition, threats of new influenza pandemics or emerging viruses, such as Ebola and Zika, have created alarm in the United States and in many parts of the world. Despite intensive research efforts by public and private institutions, there are still no vaccines for HIV, HCV, malaria, Ebola, Zika, and many other pathogens. Even though there has been enormous progress with antiviral therapies for chronic infections, we are still unable to cure HIV and HBV, and life-long treatment is needed.

Nevertheless, the knowledge gained in the last two decades about the epidemiology, pathobiology, and molecular details of many of these infections has been impressive. One of the fundamental discoveries (or perhaps, realizations) is that crucial aspects of within-host pathogen biology and immunity against pathogens depend on the dynamics of the interplay among the agents involved. The simple conceptual model that microbes and the immune cells that fight them enter the body or in the case of immune cells are generated from precursors, replicate, and are lost—due to a myriad of complex mechanisms—has been a powerful driving force in our understanding of infections. This framework allows us to analyze at different levels of detail the life cycle of the cells and microbes involved in any given infection process (Figure 1).

While mathematical modeling of viral infections and immunity has a long history, the application of the idea of quantifying the within-host dynamics of the pathogen made a major impact in clinical practice with the publication of two seminal papers in 1995[2,3] using modeling to show that HIV infection was a very dynamic process, in which virus was rapidly replicating and being cleared within infected individuals. Before this realization, HIV was thought by many to be a "dormant" virus similar to other lentiviruses, because of the observation that HIV infection took close to a decade to lead to AIDS and during most of this period plasma HIV levels hardly changed. The realization of fast (and error prone) HIV replication indicated that drug resistance was inevitable, if just one or two drugs were used for which the virus could become resistant with one- or two-point mutations. This lead to the conclusion that combination therapy with at least three drugs was needed. Modeling of HIV and then of other pathogens elucidated various aspects of the dynamics, such as the lifespan of infected cells, efficacy of drug treatment, modes of action of treatment, dynamics of different populations of infected cells, etc. These insights spanned the range of helping to understand basic pathogen biology to influencing clinical decisions. For example, in the case of HCV infection, modeling showed how one could estimate the in vivo effectiveness of new antivirals with clinical trials that lasted days rather than the previous standard of 48 weeks.[4] This ushered in the clinical evaluation of scores of new candidate agents eventually leading to the current highly successful interferon-free combination therapies with direct acting antivirals (DAAs) that are curing almost all treated patients.

Over the years since these early breakthroughs, modeling has taken a prominent place in infectious disease research, as well as immunology.[5-8] There is now a large community of researchers, both in academia and industry, working at the interface of quantitative virology, immunology, therapeutics and medicine. The purpose of this volume is to review research in these areas, to better understand the nature of the challenges that treating and curing infections bring, and to foster new therapeutic progress. We aimed for this volume to cover a broad range of topics exemplifying the impact that modeling has had in multiple fields, from molecular aspects of T-cell activation to phylodynamics of viral infections. However, we could not cover every topic, and for the most part, the extremely active field of systems immunology, using "big data sets" was not included in the present volume.[5] Our choice was to emphasize mechanistic models of viral infection and immunology. Our objective is to promote an interdisciplinary assessment of the state-of-the-art, the future of the field and to explore how best to navigate roadblocks and hurdles to fully realize the potential of modeling of infections for improving human health.

Given the recent history of the field, it is appropriate that this volume opens with a modern review of the impact of viral dynamics

This article introduces a series of reviews covering the topic of Modeling Viral Infection and Immunity appearing in Volume 285 of *Immunological Reviews*.

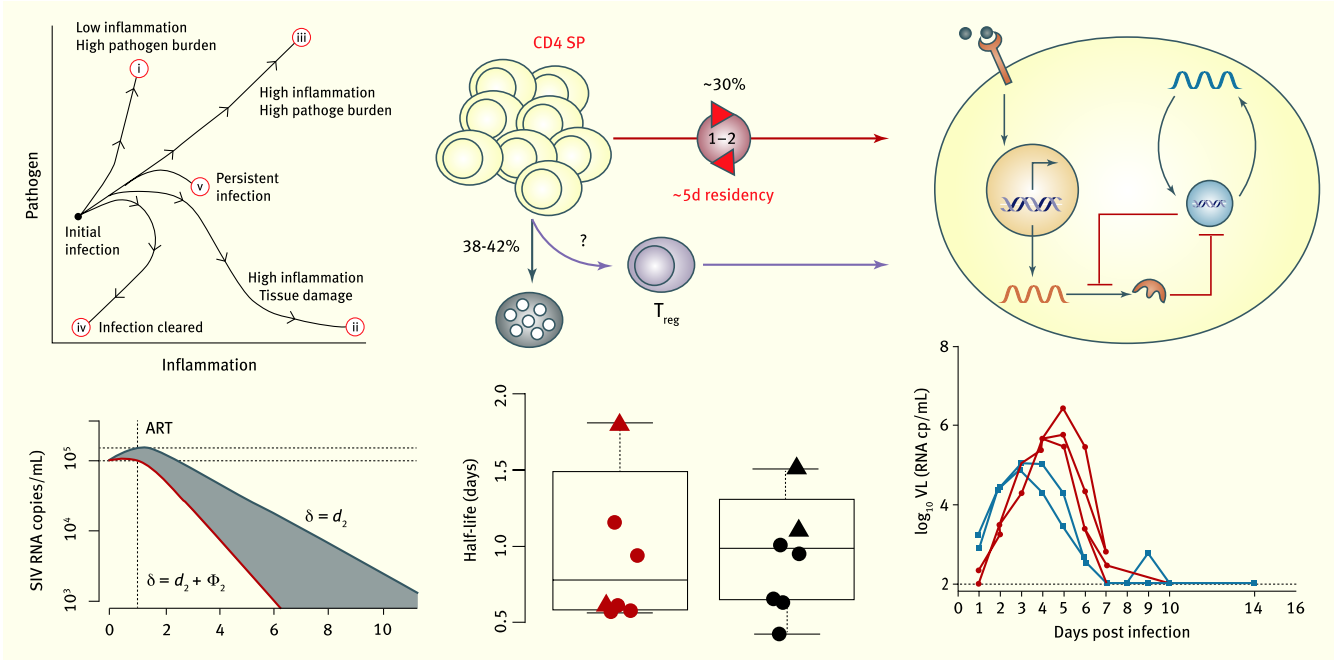

FIGURE 1 Dynamical models can be powerful tools to understand infectious diseases, immune response, and outcomes of infection. Developing models of the dynamics of cell populations or subcellular compartments interacting with pathogens, computing the target cell, pathogen, and immune system kinetics under different possible scenarios, and estimating model parameters leads to predictions about the course of the disease and clinical outcome. In this volume, there are multiple examples of the state-of-the-art in applying these principles to multiple important problems in infectious diseases and immunity. The panels in this figure highlight some of the models and results discussed later in this volume

models in the treatment of HIV, including discussion of antiretroviral treatment, and also more recent modeling analyses of latency reactivation agents.[9] At the same time, one of the greatest challenges in the HIV field is understanding the effector immune mechanisms, why they fail, what are the correlates of immunity. and how to model immune effects. One aspect of this is the subject of the second review, where experiments depleting $CD8^+$ cells in the simian immunodeficiency (SIV)—macaque model are discussed.[10] These have led to substantial controversy on the interpretation of the ensuing viral dynamics, which depend to a large extent on the use of mathematical models with different assumptions. Next, these general ideas from HIV are applied to two other important viruses, HBV and HCV, with a contrasting recent history. Chronic HBV is still mostly an incurable disease, and the review by Ciupe discusses models of acute infection, the virus-host characteristics responsible for transition to chronic disease, and the use of optimal control ideas to design drug therapy regimes.[11] On the other hand, the clinical care of HCV has seen an enormous transformation, where DAAs are able to cure a large fraction of infected patients with treatments that typically last 12 weeks or less. Although these have been very successful, there may be scope for improving protocols and Raja et al[12] discuss the role of interferon in HCV treatment with DAAs. Here, it is clear that understanding the ongoing innate immune response may be critical to designing better treatment protocols. The theme of understanding the type I interferon response is continued in the review by Talemi & Höfer[13], where the tug of war between the antiviral interferon response and virus replication is described at the single cell level. At this level, the response is very heterogeneous and typically only 10%-30% of cells in a population uniformly infected by virus express interferon-β. The same preoccupation with understanding immune mechanisms is clear in the review by Best & Perelson[14] on Zika virus infection, where identifying and understanding the key mechanisms of both innate and adaptive immune control should provide the foundation for the development of effective vaccines and antiviral therapy. Zika is an emerging disease and it is associated with significant risk of morbidity especially for pregnant women and newborns. By adapting existing mathematical models of within-host infection to this acute virus, it is hoped that it will be possible to understand key aspects of the viral life cycle, to predict antiviral efficacy, and to define correlates of immunity and pathogenesis.

Another important acute infection that modelers have studied in detail is influenza, which can generate both seasonal (relatively mild) epidemics and (potentially devastating) pandemics. Smith reviews[15] recent advances in modeling influenza, with the important twist of considering coinfections with other microorganisms, especially bacterial coinfections, which are thought to be one of the main causes of mortality in influenza infection. Because mice represent a reasonable small-animal model for this infection, influenza studies and experiments can be designed with modeling in mind. This review discusses utilizing model-driven experimental design, which can represent a paradigm for other infectious diseases.[15] An important aspect of influenza is that the infection is usually localized in the lungs and Smith

shows how the virus spreads through the lungs as a function of time during infection in mice and raises the issue of to what extent the infection is target cell vs innate response limited. More generally, taking into account the spatial localization and potential production and spread of virus within tissues, both by cell-to-cell infection and by cell free virus, is becoming an important area of research (eg,[16]). The next review deals with one such viral infection: herpes simplex virus 2 (HSV-2).[17] In this case, it is not just the viral dynamics that are modeled, but also viral containment by tissue resident $CD8^+$ memory (TRM) T cells. The review by Schiffer et al describes the use of mathematical models to correlate large spatial gradients in TRM density with the heterogeneity of observed shedding within a single person. They also describe how models have been leveraged for clinical trial simulation, as well as his future plans "to model the interactions of multiple cellular subtypes within mucosa, predict the mechanism of action of therapeutic vaccines, and describe the dynamics of three-dimensional infection environment during the natural evolution of an HSV-2 lesion"[17]. A more abstract approach to spatial localization of infection and to develop a method to ascertain anatomical colonization pathways is presented in the review by Bons & Regoes[18], which discusses phylodynamic methods to infer not just migration of virus, but also other dynamics characteristics of within-host viral expansion.

The two reviews that follow deal with *Mycobacterium tuberculosis* (Mtb) and malaria. These are two very good examples of how the ideas of viral dynamics may be applied to pathogens that are potentially more complex in their life cycles, and (as in these cases) that have thwarted our efforts to control them for millennia. Cicchese et al[19] adopt the very interesting perspective that one mechanism that allows long-term control of persistent Mtb infection without an overly deleterious immune response is for the immune system to balance pro- and anti-inflammatory cells and signals. Because this balance is dynamic, involving continuous feedback, they argue that mathematical modeling is the right framework to understand this infection and its control by the immune system. Khoury et al[20] review work done to date on within host modeling of the blood stage of *Plasmodium* spp. infection. The approach they discuss, centered on understanding the complex dynamics of the malaria life cycle and the effect of different drugs at different stages, is more reminiscent of "traditional viral dynamics models" particularly those that are age-structured. It is extremely interesting to see how adaptation of those ideas to a new pathogen, with the necessary modifications to account for the more complex life cycle, is already bearing novel insights into malaria biology.

The second part of this volume is dedicated to mathematical models of the immune system, with a particular focus on T-cell biology. This is an area of large expansion with many groups and pioneering studies in the last two decades or so. This in itself is very interesting, because many of the earlier quantitative models in immunology were dedicated to B-cell biology, antibody specificity and affinity maturation.[21-26] The work reviewed in this second part spans the scales from modeling the quantitative aspects of T-cell receptor (TCR) activation, focusing on the molecular mechanisms that underpin the exquisite sensitivity of this receptor[27]; to a global theory of T-cell (and B-cell) fate decision. The TCR defines the cell specificity and a clonotype is the set of cells with the same specificity. There has been a long-standing interest in understanding how the diversity of clonotypes is maintained, which hinges on knowledge of how many clonotypes actually exist. This is a very difficult, nearly impossible, question to answer experimentally and mathematical models are essential to analyze this issue. Such models and interpreting experimental results in this area are the topics of the review by Lythe & Molina-Paris.[28] They review statistical and heuristic models of diversity in the T-cell repertoire, but this is followed by a review of more mechanistic models of the biology of naive T cells from birth to maturity.[29] These models have been developed by integrating modeling and experiments to discover a better picture of the life history of T cells, in an exemplar long-standing collaboration among the authors of that review. A crucial component of understanding T-cell life histories is to have a good estimate of the turnover rates of different subsets of cells. The review by Borghans et al[30] address this issue not only for T cells, but also for many other leukocytes, based on state-of-the-art experimental techniques (using deuterium as a label of newly formed DNA in replicating cells) and modeling. This provides perhaps one of the best examples of experiments that only make sense in the context of modeling. In fact, simple observation or description of experimental results are very difficult to interpret, and adequate modeling and understanding of the assumptions involved are crucial for reaching any conclusions from the data. The final review by Hodgkin[31] proposes a unifying concept for cell fate decisions, such as division, death or differentiation, based on independent functional components within the cell subject to stochastic variation, and influenced by cellular calculus integrating signals reaching the cell. In support of this concept, the author reviews a sizable body of work of very quantitative experiments measuring cell division, cell integration of multiple signals and mathematical models that provide unifying insights into these multiple processes.

The various authors of the reviews in this issue tended to emphasize biology and biological implications of mathematical modeling in the various systems. We also asked them to include some details of the mathematical approaches used. Thus, one can see that although simple ordinary differential equations are the tool of choice in most cases, many other mathematical techniques are important in modeling pathogens and immune response. These include the gamut from stochastic models and equations[28] to agent-based models,[19] including partial differential equations,[27] and probabilistic models.[31]

Altogether, this volume represents a unique opportunity for researchers in a variety of allied fields to learn about the state-of-the-art in modeling viral infections and immunity. At the same time, one can already see emerging future directions in these fields. More complex biological processes, including pathogens with complicated life cycles, interactions of both the innate and adaptive immune system with pathogens and the effects of coinfections are all areas of great research interest and where modeling has only scratched the surface.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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