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Validated Models of Immune Response to Virus Infection

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Abstract

Viruses are a main cause of disease worldwide and many are without effective therapeutics or vaccines. A lack of understanding about how host responses work to control viral spread is one factor limiting effective management. How different immune components regulate infection dynamics is beginning to be better understood with the help of mathematical models. These models have been key in discriminating between hypotheses and in identifying rates of virus growth and clearance, dynamical control by different host factors and antivirals, and synergistic interactions during multi-pathogen infections. A recent focus in evaluating model predictions in the laboratory and clinic has illuminate the accuracy of models for a variety of viruses and highlighted the critical nature of theoretical approaches in virology. Here, I discuss recent model-driven exploration of host-pathogen interactions that have illustrated the importance of model validation in establishing the model's predictive capability and in defining new biology.

Introduction

A wide range of viruses infect humans to cause significant health and economic burdens [1]. Some viruses (e.g., human immunodeficiency virus (HIV), hepatitis C virus (HCV), Epstein Barr virus (EBV)) result in chronic infections while other viruses (e.g., rhinovirus (RV), respiratory syncytial virus (RSV), and influenza A or B viruses (IAV or IBV)) result in acute infections. Viral infections range in severity from asymptomatic to lethal and have varying disease etiologies (e.g., pneumonia, meningitis, or cirrhosis). In addition, many viruses can predispose a host to becoming coinfected with other pathogens and, thus, modifying the dynamics [2,3], or have a role in cancer, autoimmune diseases, and Alzheimer's disease (e.g., EBV, Human Papilloma virus (HPV), or Herpes simplex virus (HSV)) [4–6]. These complications broaden the health and economic impact of viruses. With few vaccines and antiviral therapies approved for use, management of viral-associated diseases is challenging. Even in instances where preventative or therapeutic options are available, inducing protective immunity may not be guaranteed (e.g., as with IAV vaccine [7]) and there may be reduced, time-dependent efficacy in single- or multi-pathogen infections [8]. A lack of understanding about how host responses control viral spread, how different viral factors

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antagonize these responses, and how these relate to disease outcome has hindered effective development of new preventative and therapeutic measures.

In recent years, advances in multiparameter flow cytometry, high-throughput technologies, and robust imaging techniques have produced an abundance of quantitative data and illuminated the need for new theoretical approaches that can unravel complex biological interactions. In addition, the emergence of new data on multi-pathogen infections (reviewed in [9]), important viral-induced pathologies (e.g., by Zika virus (ZV) [10,11], Ebola virus (EV) [12], or BK virus (BKV) [13]) and better data on virus-induced autoimmunity (e.g., by EBV [4]) has opened the door for novel investigative designs. For over 20 years, mathematical models have been developed to assess infection kinetics during acute or chronic viral infection to better understand virus replication, elucidate mechanisms of viral persistence and control by host immune responses, disentangle pathogen-pathogen interplay, and evaluate the clinical potential of different antiviral therapies [cite]. These models have been calibrated to data and used to perform *in silico* experiments and generate novel hypotheses [cite]. Moreover, integrated laboratories and improved collaborative efforts have resulted in innovative model-driven experiments being employed and in new biology being defined. These studies, some of which are highlighted here, have advanced the field and opened new research directions.

Overview of Modeling Virus Infection Dynamics

Numerous mathematical approaches have been employed to evaluate host immune responses, including ordinary differential equation (ODE) models and spatially-resolved agent-based models (ABM). The most used model is the standard viral dynamics model (Figure 1), which was introduced over 20 years ago (reviewed in [14,15]). The model has since been successfully applied to study a variety of virus infections, including HIV [16], HCV[17], IAV [9], West Nile virus (WNV) [18], Dengue virus (DENV) [19], Adenovirus (ADV) [20], RSV [21], yellow fever virus (YFV) [22], ZV [23], BKV [24,25], and HPV [26,27], among others. These viruses range from acute to chronic and have varied sites of infection (e.g., lung versus liver) and pathologies (e.g., pneumonia versus cirrhosis). Interestingly, viral kinetics across these systems are relatively similar. That is, virus increases exponentially, reaches a peak, and declines exponentially in a monophasic, biphasic, or triphasic manner until clearance (acute) or until a steady state (chronic) is achieved (Figure 1).

Models vary in complexity and assess host responses either through individual parameter values involved in virus clearance (c) and infected cell clearance (δ) or through inclusion of specific equations for various immune components (Figure 1). However, the generation and efficacy of various cellular (e.g., macrophages, T cells, or B cells) and soluble (e.g., type I interferons (IFNs) or antibodies (Abs)) host immune factors responsible for controlling viral spread have also been assessed mathematically (Figure 1). In addition, some models have examined how spatial heterogeneity and cell-to-cell viral spread influences viral kinetics [26,28–32]. The use of different functional forms, such as saturating or time-dependent functions [20,33–35], can achieve more complex dynamics than those in Figure 1 while simultaneously retaining model simplicity. Approximating the biology in this way

maximizes the predictive capability, particularly when quantitative data is limited and the model cannot be effectively parameterized/calibrated (i.e., fit to data). Verifying a model's predictions with targeted experiments or clinical studies is referred to as "model validation". Note that this is distinct from verifying a model's formulation (i.e., different equation structures may be possible), which is often not possible due to the use of approximations, and from fitting a model to data (termed "model calibration").

Validating Viral Dynamics and Immune Response Models

A recent increase in experimental validation of model predictions has led to important biological insight, improvements in model development and interpretation, and exciting progress in the field. This progress manifested through close collaborations between theoreticians and experimentalists (e.g., as in [24,36–39]), through theoreticians acquiring training in experimental biology (e.g., as in [40,41]), and through experimentalists or clinicians acquiring training in mathematical modeling (e.g., as in [28]). Novel data with measurements on frequent time scales and new research directions arose as a result. Improving mathematical models and emphasizing their predictive capabilities is particularly important given the complexity in host-pathogen responses, which are nonlinear and vary across time scales, and the focus on generating large data sets (e.g., 'omics').

Ideally, models are calibrated to a data set, used to perform *in silico* experiments and make predictions about the underlying biology, and, if possible, used to design confirmatory experiments (Figure 2) (reviewed in [9]). Examining the likelihood of different pre-defined hypotheses and matching the model output to quantitative or qualitative data helps select the hypothesis most consistent with the data. This type of hypothesis rejecting is informative and critical to effective modeling [42], but experimental validation of the selected hypothesis remains necessary. Note that validation experiments are distinct from confirming a model fit with a secondary data set (e.g., viral load dynamics from an infection with a different strain). Instead, experiments that are designed specifically to investigate a model-derived hypothesis/prediction are required. These are termed "model-driven experiments".

One study that utilized the model-testing/hypothesis rejecting approach discovered interesting new results about vaccine efficacy and epitope masking by antibodies in shaping the humoral response to IAV (Figure 2) [36,43]. The same type of model testing and discrimination resulted in important information on BKV infection [24], which causes kidney disease and transplantation failure in kidney transplant recipients. In that study, 9 different hypotheses were examined and the model that agreed best with the data predicted that BKV clearance could only be obtained when immunity to non-structural proteins improved infected cell death (Figure 2) [24]. Another example was in a study that investigated post-treatment control of HIV. Analysis of a model discovered that the killing rate by $CD8^+$ T cells was the determining factor in whether a patient would control viral growth after therapy [44]. Importantly, in some of these examples, the models were not fit to data due to technical limitations in acquiring appropriate data. In these cases, qualitative data was compared to the model behavior and predicted outcome. Obtaining sufficient data from humans to validate these findings would be cumbersome, but the results are compelling and provocative.

Novel hypotheses primed for experimental or clinical investigation have been generated within several modeling studies. The most iconic example of a validated model occurred during original development and application of the standard viral kinetic model to HIV [37,38,45]. In those studies, the models predicted that HIV was a fast replicating virus, which was not previously known because infected individuals maintain constant viremia. Subsequent data, however, verified the hypothesis. Novel inference can also arise from models that require terms without a predetermined understanding in order to fit a data set. In these situations, designing and carrying out experiments that test the resulting prediction(s) are imperative. Model-driven experiments have defined new biological dynamics, assisted interpretation of the model, substantiated parameter estimates, and indicated portions of the model that were accurate and those that were inaccurate (discussed further below).

One example of this tandem model-experiment investigative design was for IAV-bacterial coinfection (Figure 2). The model identified a viral-induced defect in bacterial clearance as the dominant mechanism facilitating bacterial invasion during influenza and a bacterial-induced enhancement of virus production [40]. At least six distinct experimental studies directly investigated these two model's findings [41,46–50]. Three of these validation studies [41,46,47] led to the identification that IAV depletes alveolar macrophages (aMΦs) in BALB/cJ mice [46] or renders them dysfunctional in C57BL/6 mice [47]. The model's estimate of the degree of these decreases was also deemed accurate (i.e., a parameter value was validated). In addition, the magnitude corresponded to the rate of bacterial growth and determined whether bacteria will establish during the virus infection [40,41]. The model [40] and two additional validation studies [48,49] also determined that bacteria enhance virus replication by inhibiting IFN stimulated genes [48] and/or by bacterial neuraminidases cleaving viral NA [49]. Interestingly, the data generated from a subset of these validation experiments indicated inaccuracies in one of the functional forms used in the model. A saturating function was used to describe the aMΦ inhibition because the data used to parameterize the model (viral loads) did not allow for more complex functions or equations [40]. However, the kinetics of these cells were more dynamic [46]. Nevertheless, as the experimental studies emphasized, accurate predictions were still possible. Moreover, these studies broke dogmas regarding issues with parameter estimation (e.g., identifiability) (reviewed in [9]). That is, model parameters are often correlated or cannot be uniquely defined (i.e., they are uniformly distributed). Although these need to be noted, this collection of studies nicely showed that they do not inhibit accurate parameter estimates or accurate model predictions (reviewed in [9]).

Similar model-driven experiments were undertaken to assess spatial spread and immune correlates during HSV infection (Figure 2). Here, the model predicted that infected individuals continuously release HSV at a slow rate [51], that the density of tissue-resident T cells (T_{rm}) correlates to the peak viral load and number of infected cells [52], that resurgence of virus occurs when new regions are seeded by neighboring ulcers producing copious amounts of virus [53], and that T_{rm}s cluster at the infection site [28]. Spatial biopsies from infected individuals confirmed the localized distribution of T_{rm}s and their maintenance during chronic infection [28].

The accuracy of a multi-scale model of HCV infection, which connected the intracellular and extracellular dynamics, was also recently verified. The model suggested that there were two distinct mechanisms of the antiviral daclatasvir: blocking of viral RNA synthesis and of virion assembly/secretion (Figure 2) [39]. The model-derived *in vitro* experiment agreed with the finding [39]. The study's use of the multi-scale model further yielded a more accurate estimate of HCV's half-life [39]. Another example utilizing model-driven experiments was in a study of DENV infection [19]. The model predicted that a 2'-O-methylation deficient virus had a reduced rate of virus production that was mediated by an increased rate of autocrine IFN activation (Figure 2). A suite of experiments verified these predictions in addition to several parameter estimates [19].

These are merely a few studies that have highlighted the critical nature of mathematical models and corresponding validation studies to define host-pathogen mechanisms during virus infection. Collectively, they demonstrate that multiple experiments are often necessary to confirm a single model prediction. This is because models contain a significant amount of insight that cannot be captured within a single experiment. These examples further illustrate that approximating the underlying biology, rather than attempting to detail every host and pathogen component, leads to meaningful and accurate results. Although the use of approximations is well accepted and highly favored in the modeling community, it is often a critique of biologists. A common misconception is that excluding certain immunological components from a model is indicative of a model's inaccuracy. Unfortunately, this view has hampered potential collaborations and scientific advancement. It has, however, led to integrated laboratories with dually trained investigators being established. As more studies like those described here are completed and model predictions validated, this skepticism should be naturally abrogated.

Concluding Remarks and Future Directions

Kinetic models yield substantial insight about the rates of virus production and clearance, the complex host-pathogen interactions that govern the viral infection, and the formation of protective immunity for a variety of viruses (reviewed in [9,54–59], among others, and herein). In addition, an understanding of how direct cell-to-cell viral spread and spatial heterogeneity influences the disease course is beginning to be understood for viruses like HSV, HIV, HCV, HBV, and HPV [26,28–32]. How population kinetics correlate to tissue-level measurements is also increasing for IAV [9]. For these questions, modeling is essential to depict the infection and elucidate potential regulatory dynamics because it can be difficult to measure viral spread with precision. Samples, such as tissue biopsies from humans or animals, are ideal for this type of study, but these can be challenging to obtain. However, the strategies outlined for some viruses, such as HSV and IAV, should prove useful for other virus infections. In addition, models such as these should aid future studies on RSV infection, which can spread by cell-to-cell contact and has only begun to be assessed with mathematical models [21].

Two major benefits of mathematical analyses are that they link correlation with causation and can be used to perform *in silico* experiments. Robust experimental designs can then be directly derived. Although experimental systems do not currently exist for all viruses, the

methodology being established in areas like those discussed here will undoubtedly be valuable once new methods are available. Exploiting an iterative theory-experiment design will continue to be integral in effectively defining the conditions that give rise to different biological phenomena and in finding new strategies to combat virus infections and the suite of diseases that ensue as a result of the infection.

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Highlights

- Kinetic models of host-pathogen interactions identify important regulatory mechanisms
- *In silico* experiments are rapid, insightful, and aid hypothesis discrimination
- Model-driven experimental studies significantly improve biological insight
- Experimentally validating kinetic models maximizes their predictive capabilities

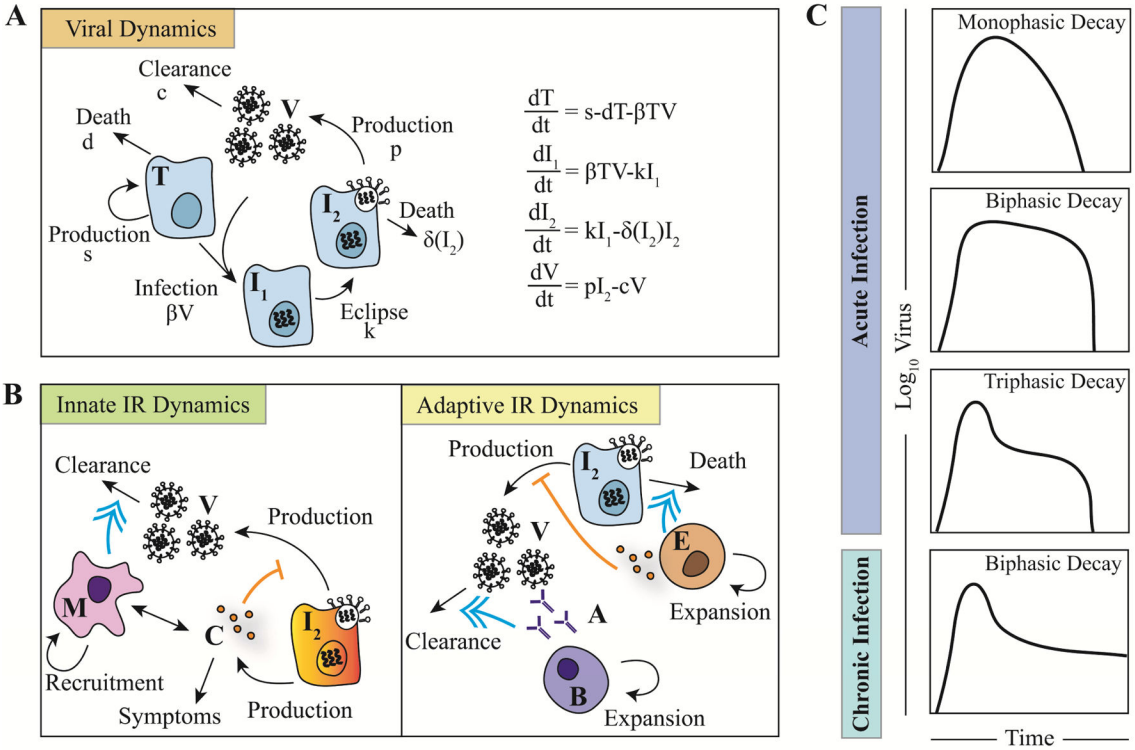

Figure 1. Summary of Viral Dynamics and Immune Response Models.

(A) Schematic and equations of the standard viral kinetic model [14,15,60]. In this model, target cells (T) are supplied at rate s cells/day, die at rate d per day, and are infected by virus (V) at rate βV cells per day. Once cells are infected, they undergo an eclipse phase where virus is not yet being produced (I_1). These cells transition at rate k per day to an infectious state (I_2), where virus is produced at rate p virus/cell/day. Infected cells are cleared at rate $\delta(I_2)$ per day and virus is cleared at rate c per day. **(B)** Schematics of innate and adaptive immune response (IR) dynamics. Innate response models have examined the production of cytokines (C) from infected cells and immune cells (e.g., macrophages, M), the effect of cytokines in producing symptoms and inhibiting virus production, and the role of immune cells can in the clearance of infected cells (not shown) and free virus. Adaptive response models have assessed the expansion of T cells (E), their role in infected cell clearance and cytokine production, the expansion of B cells (B), antibody (A) production, and antibody-mediated virus clearance. **(C)** Various viral load dynamics observed in acute and chronic infections. Viral dynamics models can produce monophasic or biphasic decay kinetics while IR models are needed to replicate triphasic decay kinetics.

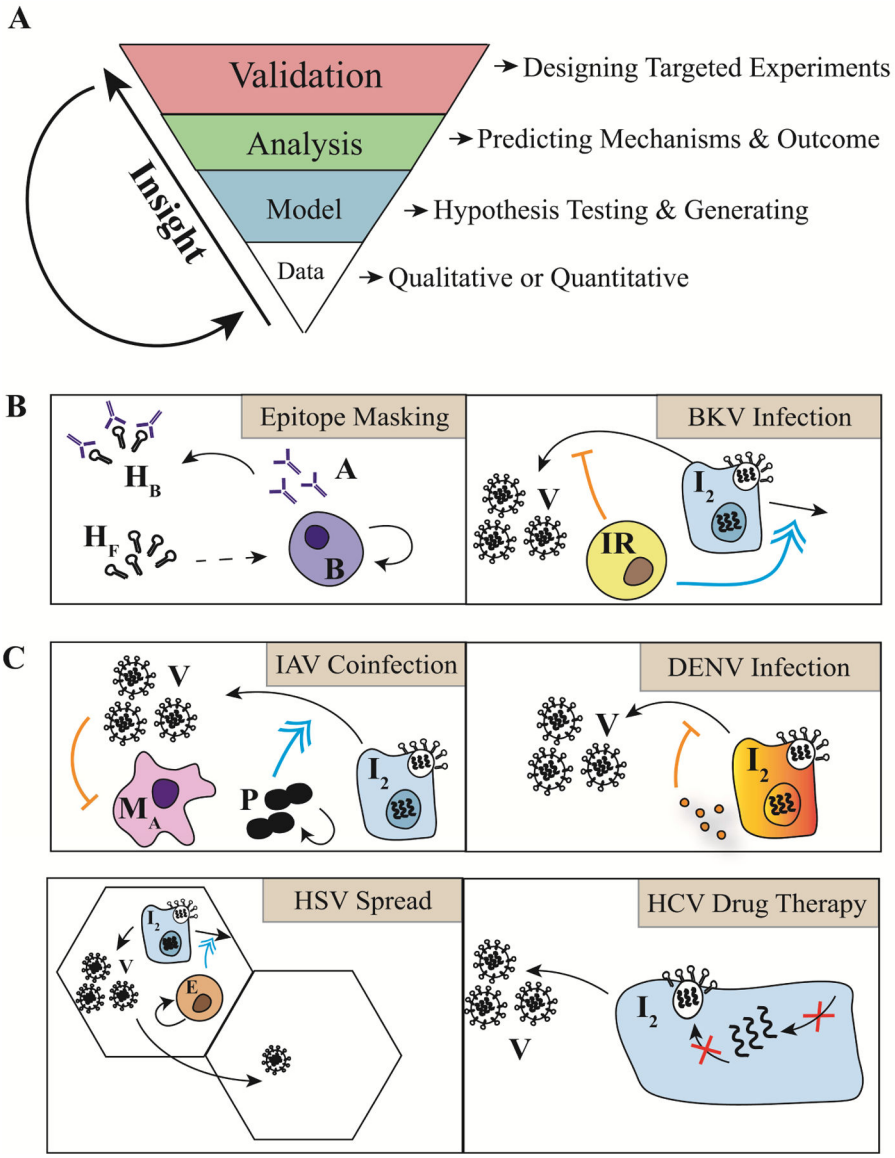

Figure 2. Model Validation Schematic and Examples.

(A) Validating kinetic models begins with quantitative or qualitative data that is used to calibrate the model. Models can be used to test or generate hypotheses, predict mechanisms and outcome, and design confirmatory experiments. Insight into the underlying biology increases if validation can be achieved. **(B)** Model schematics of epitope masking in IAV infection [36] and BKV infection [24]. Each of these examples used a set of models and clinical data to discriminate between various hypotheses. **(C)** Model schematics of IAV coinfection with bacteria [40], HSV infection and spread [28], HCV drug therapy [39], and DENV infection [19]. Each of these examples evaluated multiple hypotheses and validated the model predictions with *in vivo* or *in vitro* experiments.