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Advancing therapies for viral infections using mechanistic computational models of the dynamic interplay between the virus and host immune response

Veronika I Zarnitsyna[1], Juliano Ferrari Gianlupi[2,3], Amit Hagar[4], TJ Sego[2,3] and James A Glazier[2,3]

The COVID-19 pandemic has highlighted a need for improved frameworks for drug discovery, repurposing, clinical trial design and therapy optimization and personalization. Mechanistic computational models can play an important role in developing these frameworks. We discuss how mechanistic models, which consider viral entry, replication in target cells, viral spread in the body, immune response, and the complex factors involved in tissue and organ damage and recovery, can clarify the mechanisms of humoral and cellular immune responses to the virus, viral distribution and replication in tissues, the origins of pathogenesis and patient-to-patient heterogeneity in responses. These models are already improving our understanding of the mechanisms of action of antivirals and immune modulators. We discuss how closer collaboration between the experimentalists, clinicians and modelers could result in more predictive models which may guide therapies for viral infections, improving survival and leading to faster and more complete recovery.

Addresses
[1] Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA, USA

[2] Department of Intelligent Systems Engineering, Indiana University, Bloomington, IN, USA
[3] Biocomplexity Institute, Indiana University, Bloomington, IN, USA
[4] Department of History and Philosophy of Science, Indiana University, Bloomington, IN, USA

Corresponding author: Glazier, James A (jaglazier@gmail.com)

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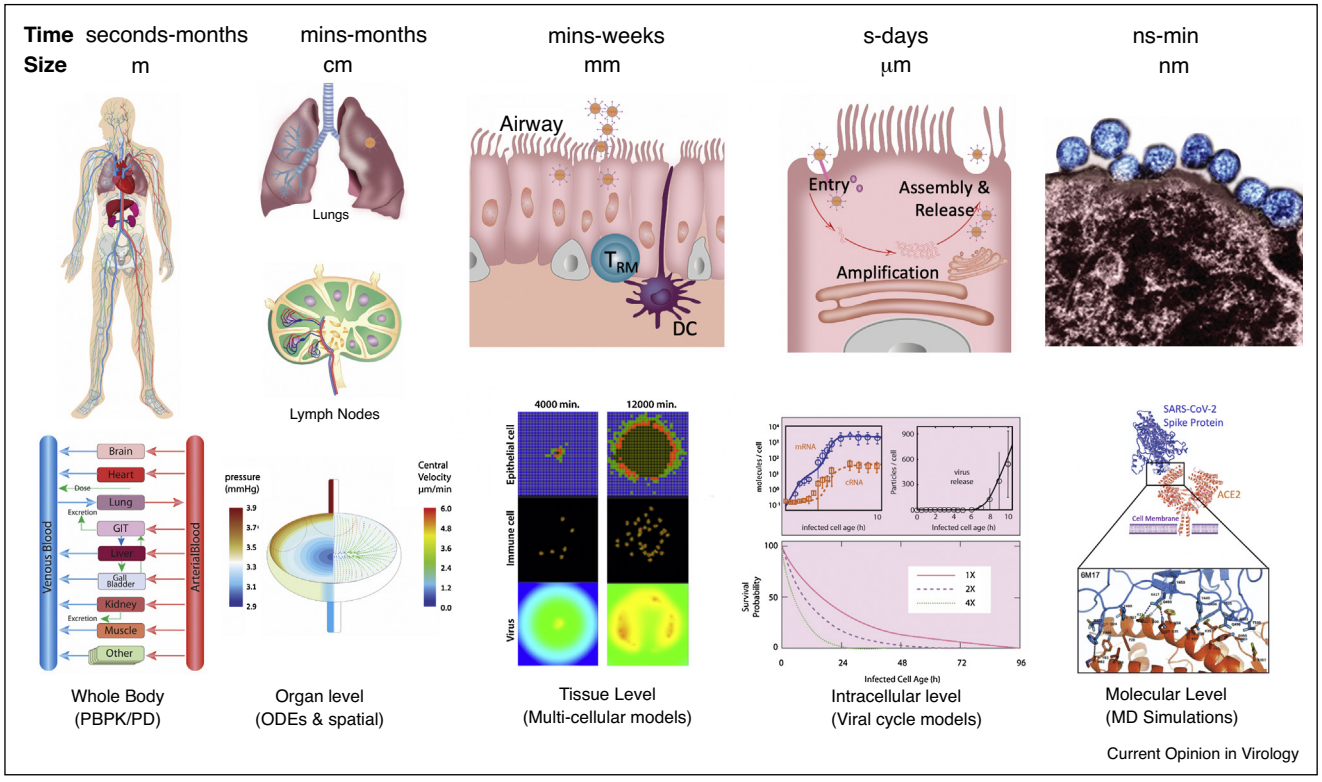
Introduction

Therapies for viral infection can function in many ways. For example, small molecules or antibodies can directly interfere with viral life cycle, drugs can promote interferon-induced or other types of antiviral resistance in target cells, drugs can stimulate cellular responses for more effective elimination of virus-infected cells, and drugs can reduce the severity of symptoms resulting from infection or hyper-immune response [1,2]. The development of therapies that minimize the duration and severity of illness may require multiple approaches to treatment at different phases of infection. Patient-to-patient variability may mean that the choice of drugs, and their dosing and timing all need to be personalized.

Traditionally, the standard pipeline of drug-therapy development progresses from a serendipitous guess of drug candidates, through *in vitro* and *in vivo* drug testing, to clinical trials in humans, and post-clinical optimization, with a dramatic drop in the probability of success at each phase [1]. Data-based methodologies like bioinformatics and Machine Learning have been able to augment serendipity with extrapolation and structural similarity metrics for lead identification [3] but have not yet allowed the design of optimized therapies. Two types of mechanistic computer models which explicitly simulate biological components, interactions and dynamics are commonly used in drug development and therapy optimization: molecular dynamics (MD) simulations of limited numbers of individual molecules allow docking calculations which are widely used in lead identification [4,5], and models of drug absorption, transport, metabolism and elimination allow dosage optimization [6]. However, these molecular-scale and whole-body-scale models generally neglect the spatio-temporal complexity of the dynamic multicellular immune response, the movement of virus within the body, and the ways in which both virus and immune response can lead to either pathological outcomes or recovery.

Available blood-based clinical measurements of viral load, cytokine or immune-cell profiles and imaging-based measurements of regions and types of damage provide snapshots of viral infection in individuals, which when aggregated, allow us to characterize typical patterns of infection progression. However, these measurements are usually too limited in frequency and detail to predict individual immune responses in a way that allows optimized personalized treatments. Our inability to predict the immune response and immune-viral interactions in individuals, means that we still have very limited mechanistic understanding of why some individuals have mild

Figure 1



Spatiotemporal scales in virus infection dynamics.
Top row shows schematics of biological systems at different scales. Bottom row shows sample model representations and outputs for the scales shown in the top row. From left to right: (1) top: Schematic of a whole body, bottom: PBPK model of drug absorption, distribution, metabolism, and excretion, (2) top: Lung and Lymph node, bottom: model of flow, transport and response in a lymph node (adapted from Ref. [16]), (3) top: Infection and immune response in a lung epithelial tissue, bottom: multi-cellular simulation of virus, target cells and immune cells in a patch of lung epithelium [17•]. (4) top: Viral life cycle inside a host cell, bottom: multiscale model of influenza A virus infection (adapted from Ref. [18]), (5) top: Middle East Respiratory Syndrome virus particles (blue) binding to a VERO E6 cell (adapted from Ref. [19]), bottom: molecular dynamics model of ACE2 - SARS-CoV-2 S protein docking (adapted from Ref. [13]).

symptoms, while others develop severe disease in response to the same virus, or why recovery is complete in some individuals and long-term consequences like post-polio syndrome or long-COVID occur in others [7,8]. Consequently, at present, we usually cannot accurately predict how a particular patient will respond to treatment with an antiviral drug or immune modulators, whether for new viruses introduced by a pandemic, or endemic circulating viruses such as seasonal influenza.

Mechanistic models are most useful when we lack intuitive understanding of the significance of experimental observations and the causal processes that underlie them. The complex web of interactions between virus, cytokines and immune cells both at the site of infection and in the lymph nodes is a classic example of how multiple feedback cycles can lead initially similar situations to evolve in very different temporal and spatial patterns and result in different clinical outcomes. In the immune system, cytokine levels, immune-cell profiles and damage patterns can change in complex ways in space and time, making prediction from qualitative models nearly impossible.

The complexity of viral infection and immune response has led to the development of *mechanistic computational models*, differing in their mathematical and computational representation of components, interactions, levels of spatial detail and the time scales they consider. A *conceptual mechanistic model* is a phenomenological description of the dynamics of a biological system. In the case of a model of infection, it is based on *biologically motivated hypotheses* identifying the key physical components of viral infection and immune response, how their interactions lead to infection dynamics and what key measurable variables best describe these components and interactions. To make this model quantitative and dynamic, requires hypotheses for the specific mathematical forms governing

the changes of the variables describing these components. To build a *mechanistic computational model*, we also need to decide how to translate the dynamic mechanistic model into a computer simulation, for example, by deciding if we will represent individual virions or viral concentrations, or whether changes happen continuously in time or as stochastic events. For an interesting discussion of the process of constructing a complex model of immunological cross-talk see Ref. [9].

This short piece cannot cover the many existing relevant models comprehensively. For a more comprehensive review see Refs. [10••,11]. Here we describe successful models of gradually increasing complexity, and end by discussing some promising areas of research and development that would benefit from more intensive collaboration between experimentalists and modelers.

How understanding viral kinetics and immune response can assist development of antiviral therapies

The COVID-19 crisis has revealed significant gaps in our understanding of within-host viral kinetics and immune response, which impede the discovery of new therapies, and the optimization and personalization of existing therapies. *Mechanistic computational models* are uniquely positioned to bridge these gaps.

The dynamics of interaction between a virus, host cells and the immune response are complex, involving multiple spatial and temporal scales (Figure 1). Infection starts from viral transport to the site of initial infection, evasion of host defenses and infection of target cells. As infection progresses, both virus dissemination and immune response progressively involve more components and can spread to different tissues and organs.

At the smallest scale, MD simulations rely on information on the dynamic properties of macromolecules and can provide information about details of virus recognition not accessible using crystallography. For example, flexibility of the viral peptide presented by the major histocompatibility complex (MHC) may play an important role in the recognition of the peptide by a T cell, leading in some cases to 'conformational frustration' [12]. Molecular-docking simulations of affinity between SARS-CoV-2 spike and ACE2 in different species [13] were able to identify the most useful animal models of human infection. At the largest whole-body scale, physiologically based pharmacokinetic (PBPK) modeling is a well-developed framework that models drug absorption, distribution, metabolism, and excretion (ADME) and may help to optimize drug treatment in the case of emergent viruses. For example, a PBPK model was used to scale the optimal dosing of *remdesivir* from adults to pediatric patients with COVID-19 [14].

Proper understanding of the immune response to a viral infection requires modeling at multiple scales simultaneously. Picking the correct level of detail for each scale requires us to decide which elements are critical to the behaviors of the system [15]. Often, we need to represent the intermediate scales with the most detail. For example, a weather forecasting model of hurricane trajectory and strength might include a detailed submodel of the winds in the hurricane, and less detailed submodels representing heat flow in the ocean beneath and weather patterns across the globe, which provide boundary conditions for the detailed hurricane submodel. Multi-level models of factories, traffic in cities and agent-based models in epidemiology also often represent the intermediate-scale components in the most detail. To understand and control the interaction between a virus and the immune system, we need models that cover intermediate scales between molecules and the whole body. We will focus on models at these intermediate scales, including population-dynamics models, models of viral life cycle, multi-cellular models and their integration into multi-scale models.

The challenge of understanding the immune response in HIV infection has shaped the field of mathematical modeling in immunology. A target-cell-limited model initially proposed to understand the dynamics of HIV infection [20,21] established a framework for within-host modeling that later was extended in multiple ways and applied to different viral infections. The simple target-cell-limited model has three variables: uninfected susceptible target cells, infected virus-producing cells, and the viral load. Fitting this model to the viral-load data allowed estimation of the rate of production of virions by infected cells and the life-spans of infected target cells and virus particles [20]. These early models provided the groundwork for later development of greatly improved HIV therapies.

Interferons (IFNs) are the frontline defenders of the innate immune system, both interfering with infection of host cells and reducing viral replication inside infected cells. Recent models have explored the importance of innate immune response feedback pathways in determining the outcome of disease in individuals [22•,23]. The target-cell-limited modeling framework has been extended to analyze the effect of interferon-α therapy in treatment of Hepatitis C virus (HCV) infection [24] and to evaluate the relative importance of the two modes of IFN action (reducing production of virions by infected cells and reducing *de novo* rates of cell infection) [24]. The model allowed estimation of the otherwise unobservable death rate of infected cells, and showed that its variation correlated closely with the variability in patient outcomes, with higher cell death rates during the first two weeks of IFN therapy predicting eventual cure, with virus undetectable by polymerase chain reaction after 3 months.

Results of this kind can help personalize the optimal duration of therapies.

The failure of the simple target-cell-limited model to explain observed primary HIV dynamics in an infected host suggested a role for cytotoxic T lymphocytes (CTLs) and cytokine suppression of viral replication in controlling the viral load after the initial acute viral-load peak [25]. Models including the adaptive immune response have provided insights with significant therapeutic value. For example, a model of effector-cell response and exhaustion explained the 'post-treatment control' of HIV viral load observed in some HIV patients [26], and suggested that boosting effector-cell response through therapeutic vaccination [27] before termination of antiretroviral treatment might increase the chances of post-treatment control of viral load. A recent extension of the model [26] explored four different mechanisms behind post-treatment control of Simian immunodeficiency virus (SIV) in macaques and showed that the primary mechanism differs between individuals, an important step towards using modeling to personalize treatment [28••]. The target-cell-limited modeling framework was adapted to model viral-load dynamics under antiviral treatment and to explore three different mechanisms of action [29•] and to compare within-host SARS-CoV-2, MERS-CoV, and SARS-CoV dynamics. The model predicted a shorter time from symptom onset to viral-load peak for SARS-CoV-2 infection compared to MERS-CoV and SARS-CoV, suggesting that controlling SARS-CoV-2 infection using antivirals would be more difficult.

The cost and toxicity of direct-acting antiviral (DAA) therapy led to models optimizing the length of the therapy. Dahari *et al.* [30] demonstrated that viral-kinetic models applied to early viral-kinetic data under drug treatment can predict the duration of DAA therapy needed to achieve cure in patients infected with HCV (a virus able to cause a persistent infection in humans), and thus personalize the treatment. Interestingly, the model predicted that the one patient who relapsed under standard 12-week DDA therapy would have benefitted from an additional week of sofosbuvir + ledipasvir. Goyal *et al.* [31] extended these models [30,32] by assuming that HCV RNA in serum includes both infectious and non-infectious virus, explaining the ability of ultrashort DAA therapy to cure some individuals. Baral *et al.* [33] explored the hypothesis that the viral decline induced by DAAs during chronic HCV treatment reversed the exhaustion of CTLs, which then cleared the infection after treatment. Estimating the parameters defining the CTL response for individual patients allowed the model to predict the necessary duration of DAA therapy for each patient and thus personalize the treatment.

In age-structured models, the rate of production of viral particles and the death rate of infected cells depend on how long a cell has been infected [34]. All viruses share steps in their replication: attachment to a target cell in a host, release of viral genetic material into the host cell, replication using host-cell machinery, assembly of new viral particles and release of viral particles from the infected cell. Mechanistic models can determine which of these steps should be blocked for the fastest and most effective treatments. For example, models can explore how multiplicity of infection affects viral replication rate [35]. Model simulations can also predict the effects of drug-based perturbations when viral-replication pathways contain both positive and negative feedback. Age-structured models with detailed submodels of the viral life cycle allow systematic exploration of new drug targets [32,18]. A multi-scale model of influenza A virus infection [18] combined an intracellular model of the synthesis of new viral particles with an extracellular model of virus spread to new host cells to explore how drugs affecting different stages of the viral life cycle might affect the dynamics of viral titer. The model allowed ranking of the effectiveness in decreasing viral titer of potential antivirals targeting different stages of the viral life-cycle, including viral entry, nuclear trafficking, viral RNA and protein synthesis and viral particle assembly and release.

Often simulations show that changes in particular model parameters change model dynamics in ways that could correlate with improved clinical outcomes. Drugs that control these parameters become promising drug candidates. In both *in vivo* and clinical trials, the savings in time, labor and cost can be substantial. In Ref. [36•], exhaustive combinatorial sensitivity analysis for all pairwise parameter changes in a model of the SARS-CoV-2 viral life cycle predicted that drugs targeting viral genome replication (like *remdesivir*) and protein synthesis would result in the most effective reduction of viral titer.

In cases where we have a highly effective antiviral, we might expect that the optimal treatment strategy would be to treat as soon as possible after infection or diagnosis. Delaying antiviral therapy carries a risk of tissue damage from the virus and immune response. However, early antiviral treatment might prevent triggering of the adaptive immune response and hence the development of long-term protective immunity. A model by Stromberg *et al.* [37] explored this trade-off and suggested a limited time window after infection during which antiviral therapy could limit disease symptoms without inhibiting development of long-term immunity, thus ensuring that those infected receive the benefits of vaccination with reduced risk from the disease.

While the within-host models described above model mean levels of virus and immune components clinically measurable in the blood, patterns of infection and immune response are spatially localized within an infected individual. In respiratory disease, lesions are usually highly localized and develop in different places

at different times, even within a single individual [38]. In the models discussed above (PBPK, ODE-population models) in each compartment, each cell senses the same level of, for example, cytokines. In cellular automaton (CA) and agent-based models (ABM), cells are discrete and occupy explicit volumes in space, and chemicals are expressed as concentration fields. CA and ABMs can explore the effects of spatial heterogeneity on the progression of infection, immune response and therapy [17•,39], and improve estimates of parameters and their typical ranges of variation for the non-spatial models we described above.

Figure 1 shows a tissue-scale agent based multicellular simulation of COVID infection and immune response ('tissue level', bottom row). This simulation represents the dynamic evolution of a small (typically 1 mm × 1 mm) patch of host tissue, the extracellular viral and cytokine concentrations, and various immune-cell types and their functions [17•,39]. Individual host cells contain independent models of viral entry, replication, and release. Models of this type can explore the effects of stochasticity at the subcellular, cell and patch level in determining local outcomes and the effects of viral spread, interferon, antiviral and immune modulators. These models are often coupled to pharmacodynamic (PD) and PBPK models of therapeutics and to models of lymph-node response to allow more detailed understanding of heterogeneity in patient response and treatment optimization [17•,36•]. They can also be coupled to larger-scale spatial models of transport within and between organs, as has been done for bacterial infections like tuberculosis [40•], or generated from calibrated non-spatial models, as has been done for influenza infections [41,42].

Computational fluid dynamic (CFD) flow models consider transport at the level of entire organs. Immune response is orchestrated by chemokines and depends on leukocyte migration in infected tissues and lymph nodes (LNs). The models of Jafarnejad *et al.* [16,43] showed how lymph flow (Figure 1, 'whole organ level'), fluid exchange with blood vessels, chemokine binding, and cell response determine immunosurveillance and response in LNs. Such understanding may allow development of improved immunomodulatory therapies and clarify the way in which innate and adaptive immune responses coordinate after vaccination, allowing the design of improved adjuvants and vaccines. CFD models have also been valuable in determining the distribution of aerosol-delivered drugs in the lungs [44,45] and the localization of infectious virus after inhalation and in estimating the infectivity of individuals with lung infections during different activities [46].

Mathematical approaches can help us prioritize experiments to improve understanding of immune response. Classical numerical sensitivity analysis identifies conditions where the model predicts that small changes of parameters or different hypothesized model structures will lead to different quantitative or qualitative outcomes. When these parameters are ones which can be manipulated in experiments, the model can be used to design maximally discriminatory experiments to test hypotheses, optimizing experimental time, cost and effort.

While the models mentioned above vary in scope and methodology, they can all be useful in optimizing windows for time, dosage, and personalization of treatment (see recent work on patient heterogeneity in SARS-CoV-2 pathogenesis [47]). When modelers collaborate with experimentalists to develop therapy-design models which predict the effects of experimentally changeable biological parameters, the models become a powerful tool to reduce the cost, time and effort of antiviral drug discovery.

Conclusion

Mechanistic computational models can help us to understand the heterogeneous outcomes of infection in different individuals, distinguish between mechanistic hypotheses, extrapolate from *in vitro* and animal experiments to humans and infer parameters that would be difficult to measure directly in experiments, using synthetic data sets. Using computational models, we can design *Virtual Clinical Trials* [48] to test the efficacy of complex combination therapies, where the number of possible combinations is challenging to test in animal or human trials. The models can suggest previously overlooked vulnerabilities of viruses (including repurposing drugs developed in other contexts). Simulations can help identify the most informative experiments to test hypotheses and improve the design of clinical trials [49]. Often, the process of building a self-contained, meaningful model will reveal critical missing information, whether in the form of pathways, relationships between stimuli and outcomes, parameters, or inter-individual variability. Indeed, model building is brutally effective at revealing what we don't know.

Mechanistic computational models are not an alternative to bioinformatics and Omics data-driven statistical models. On the contrary, combining these approaches along with the modeler's intuition and knowledge will usually work better than any approach alone. New data emerge almost daily from modern Omics studies, and as the sample size increases, information connecting an individual's characteristics (age, sex, pre-existing conditions, level of prior immunity, etc.) with disease-course outcomes will provide correlative data that can help to develop mechanistic models. Integrating machine learning with mechanistic multiscale modeling could be especially beneficial [50].

A new generation of mathematical models may help us solve some of the key puzzles in immune response, such as the determinants of the duration and amplitude of T-cell and B-cell memory, the onset and severity of septic responses, and viral evolution and escape from immune

control. Models could help us understand how to handle coinfections, where you might need separate therapies for each virus and specific approaches to deal with viral-immune-viral interactions, like giving an IFN booster after IAV infection to reduce the pathogenic effects of secondary respiratory viral infections.

While the promise of *mechanistic computational models* to improve the development and use of antiviral therapies is strong, their successful creation and implementation will require more than the current over-the-fence approach which separates modelers from therapy developers and clinicians. Currently, we face a bootstrapping problem. Contemporary models are not always sufficiently predictive to be useful to therapy developers, so the motivation to do experiments specifically to enable modeling is limited. However, current experiments often measure end points with limited time-series data, which limits our ability to build and validate models. We can't infer dynamics from even a limitless number of single-time-point snapshots if they are done in different individuals. Building useful dynamic models requires expensive and demanding experiments which measure key metrics (viral load, cytokine levels, fraction of infected cells) frequently in individual samples, animals or patients. Similarly, if modelers design models without considering the needs and priorities of therapy developers from the beginning, they are likely to deliver models which solve the 'wrong' problems. To build experimentally and clinically useful models, modelers need experimentalists to be clear about what they can practically measure and manipulate. Ultimately, effective model building requires team effort at all stages from exploratory research to therapeutic application.

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Conflict of interest statement

JAG is the owner/operator of Virtual Tissues for Health, LLC, which develops applications of multiscale tissue models in medical applications and is a shareholder in Gilead Life Sciences.

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