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Infectious diseases

# *In silico* modeling in infectious disease

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**Infectious disease has witnessed the emergence of mathematical modeling a tool of synthesizing data of growing complexity now available to clinicians and basic scientists alike. The purpose of this review is to introduce mathematical tools commonly used to model infectious disease. We will illustrate the use of equation-based, agent-based or statistical modeling approaches to a variety of examples pertaining to acute inflammation, bacterial dynamics, viral dynamics, and signaling pathways, focusing of host-pathogen interactions rather than population models. We will discuss the strengths and weaknesses of these approaches and offer future perspectives for this rapidly evolving field.**

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## Introduction

The increasing use of mathematics and computational tools in medicine is inevitable. Improvements in the quantity and quality of data streams, from genomic to administrative in nature, have resulted from the introduction of new measurement, data gathering and data storage techniques. Physiological complexity constitutes a formidable challenge to a coherent and meaningful interpretation of these data. Clearly, the development of tools to assimilate and interpret data is just as critical as the data itself to the knowledge discovery process in this new, data-rich ear [1].

The advantage of mathematical modeling of disease lies in the fact that such models not only shed insight as to how a complex process works, which could be very difficult to infer an understanding of each component of this process, but also

predict what may follow as time evolves or as the characteristics of particular system components are modified. This approach is particularly helpful where these predictions are not already obvious to clinical or biological researchers, or where particular outcomes are expected, but the mechanisms leading to these outcomes cannot be directly intuited. According to how much a priori information of the system to be modeled is available, mathematical models are classified into black box (data-driven or data-supported) and white box (knowledge-driven) models. Practically all systems we wish to model are both knowledge-driven and data-supported and therefore somewhere between black and white box models, so that this general construct is only used as a guiding approach.

## Types of models

### Black, white and grey box models
A black box model represents a system for which there is no a priori information available or assumed. Such models are characterized in terms of their input and output characteristics. The construction of black box models requires estimation of functional forms of associations between variables and the parameters in those functions. If prior knowledge of factors (inputs) driving outcome (output) and sufficient data exist, one could build up a set of functions that robustly describe the relationship between input and output. Several statistical models take advantage of such knowledge [2]. But since in the case of black box models there is usually no or less

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a priori information available one would try to use functions as general as possible to describe the given system. The main drawback of black box models lies in the fact that the mapping between input and output remains largely unexplained, that is, hidden in the black box. Calculation of such maps are often computationally intensive. An often cited example of a black box model is an artificial neural networks (ANN). Neural networks are non-linear statistical data modeling tools useful to learn complex relationships between inputs and outputs, classify patterns in data, or predict time series [3,4]. An artificial neural network involves a network of simple processing elements which can exhibit global behavior, determined by the connections between the processing elements and element parameters. It is a trainable model designed to solve complex problems from a set of examples and generalize the acquired knowledge to solve unforeseen problems, that is it is a self-adaptive system. ANNs are applicable to situations where the complexity of the data or task makes the design of a function inferred by observations by hand impractical. For instance, ANNs are used to model different aspects of biological neural systems, and have been used successfully for prognostication in critical illness where it may present advantages over traditional statistical models, especially when data is sparse [5–7].
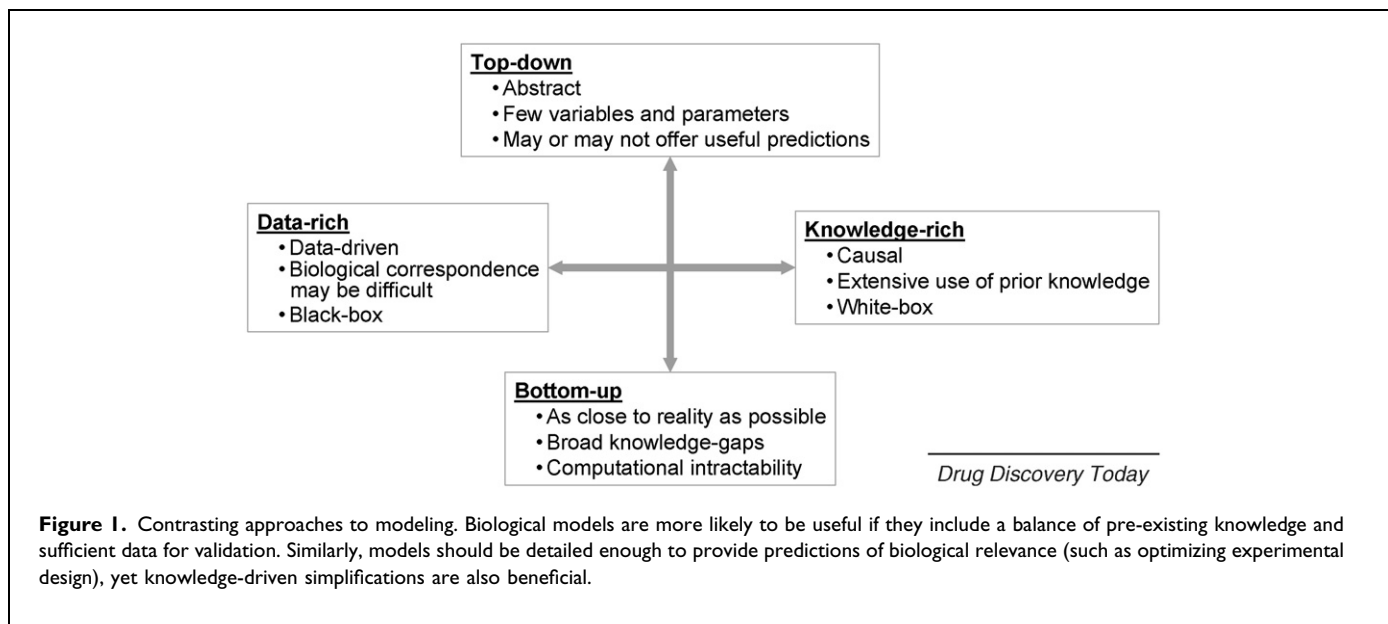
A white box model (often also called clear box or glass box model) is a knowledge driven system where all necessary information needed to build the functions describing the relationships between variables is given. White box models are usually considered easier, because the functional relations between the variables are given. In that sense, the processes driving the evolution of the system are modeled explicitly and those explicit relations, expressed in the model as rules or equations, embody prior knowledge of causality. Typical white box models are (1) differential equation-based models, like ordinary differential equations (ODEs), partial differential equations (PDEs), stochastic ODEs and PDEs, and (2) agent-based models (ABM). Both platforms are used extensively to model infectious phenomena. No data are actually needed to build such models.

Differential equations, as a modeling approach, have enormous appeal. They (1) provide an intuitive means to translate mechanistic concepts into a mathematical framework, (2) can be analyzed using a large body of existing techniques, (3) can be numerically simulated easily and inexpensively on a desktop computer, (4) provide *both* qualitative and quantitative predictions, and (5) allow for the systematic incorporation of higher levels of complexity and uncertainty. Equation-based models usually depend on a large number of parameters that quantify biological interaction, and that specifying these parameters is a difficult task. However, these parameters are explicit. Therefore, knowledge gaps are readily identified, unlike alternative modeling approaches. Further,

the speed of computation of differential equation-based models allows for massive experimentation with parameters that may not be determined experimentally, leading to the development of hypotheses on the roles of individual parameters, reflecting the presence and relative importance of biological processes or interactions that can drive subsequent experimental investigations.

In some cases, biological systems may be so fragmented that the use of differential equations may be impractical. In such situations, agent-based models (ABM) certainly represent a more practical simulation platform than PDEs [8,9]. ABMs focus on the rules and mechanisms of behavior of the individual components of a system. The components of a system are classified into types of agents by virtue of shared mechanisms that have been identified experimentally. The mechanisms are expressed as a series of ('if-then') rules. Tang *et al.* [10], for instance, developed an agent-based model of the dynamics of rolling, activation and adhesion of individual leukocytes *in vitro*. Other models relevant to infectious disease have been applied to the progression of infection and the ensuing immune host response [8,11], the dissemination of infection in a limited environment [12], in a city, where health care service points, schools, restaurants and churches all represent privileged areas of disease transmission, would be difficult to simulate with equation-based models [13], or even country-wide [9]. Although intuitive and often the best modeling approach, ABMs are difficult to calibrate with experimental data, there are no tools to analyze their expected behavior, or the impact of varying model assumptions, without actually performing the simulations and such simulations are computationally intensive for medium to large size models.

Grey box models are a mixture of knowledge driven and data supported systems. Many statistical models fall into this category, where the choice of predictors is based in large part on prior knowledge. Most of the assumptions underlying large-scale models of infectious disease spread of the type susceptible-infected-recovered (SIR) rely on epidemiological or microbiological observations. Yet, formal validation of those models, or of their ABM counterparts, that would be refined estimation of model parameters from prospective epidemiological data, remains problematic. As a consequence, predictions from such models must be carefully evaluated. Knowledge-based models of host–pathogen that have been fit to experimental data and provided quantitative predictions are typical examples of grey box models of relevance. Clermont *et al.* [14], Vodovotz *et al.* [15] and Chow *et al.* [16], for instance developed equation-based models of the acute inflammatory response (AIR) based on the kinetics of well-accepted constituents of the AIR and on experimental data. Such models might prove very useful in rational drug design, in patient selection for a given intervention, or in

**Figure 1.** Contrasting approaches to modeling. Biological models are more likely to be useful if they include a balance of pre-existing knowledge and sufficient data for validation. Similarly, models should be detailed enough to provide predictions of biological relevance (such as optimizing experimental design), yet knowledge-driven simplifications are also beneficial.

optimizing intervention strategies that could serve as basis for clinical trial design [17,18].

### Top-down and bottom-up models

Top-down models abstract a complex system into high-level biological functions and quantities to simplify the description and prediction of its dynamics. In the physical world, such models have been enormously successful in describing the behavior of large collection of interacting objects, such as molecules in a gas where pressure, volume and temperature emerge as useful observables. Although significant insight and non-intuitive predictions may result from such models of biological systems [19,20], insufficiently detailed biological models may be impossible to validate and should be perceived as mostly exploratory in nature. Bottom-up models on the other hand, attempt to maximize granularity, and thus for example will reconstruct an entire cell from detailed and hierarchical models of its subcomponents [21], or data-mine extremely large datasets to extract patterns and associations. Such models may suffer from severe knowledge-gaps or suggest incorrect biological inference from data-discovery exercises, when no prior interpretative filter is offered to such computationally intensive tools. Therefore, just as important as the modeling exercise itself, high priority should be placed on the development of methods that reconcile top-down and bottom-up models [22], and guide optimal use of data to refine knowledge-rich models, or appropriate use of existing knowledge to inform data-mining algorithms (Fig. 1).

### *In silico* disease models

In this section we will focus on a selection of mathematical models of diseases. We chose relevant examples out of the field of acute inflammation, bacterial dynamics, viral dynamics and signaling pathways.

### Acute inflammation

An [23] has produced an abstracted ABM of acute inflammation centered on cell-cell interaction, much like the ODE models discussed above [14–16]. The model focuses on the interactions that occur at the interface between endothelial cells and blood-borne inflammatory cells and mediators. The model was designed to respond to insults that stimulate both infection and noninfectious tissue injury such as trauma. The premise is based on the idea that similar pathways and actions are responsible for the propagation of inflammation once the process has been initiated. The ODE models and the ABM focus on slightly different mechanisms occurring in different anatomic regions and they predict similar results both in individuals and in simulated clinical trials [24].

### Models of bacterial dynamics

Models of diverse degree of sophistication have been constructed to simulate bacterial dynamics, such as growth under various nutritional and chemical conditions [25–27], chemotactic response [28,29] and interaction with host immunity [30–32]. Such models have both theoretical interest and practical applications. For example, elucidating the determinants of bacterial size, total bacterial biomass and nutrient requirements are primarily theoretical [33–35]. Yet, the impact of physical factors on such variables are of particular relevance to the food industry [36,37]. Clinically relevant models of bacterial dynamics relating to peritoneal dialysis [38], pulmonary infections [30], and particularly of antibiotic treatment and bacterial resistance [39–42] have appeared in the past several years.

Surprisingly however, it remains difficult to document simple parameters for most models of bacterial dynamics. For example, there are very few reports documenting the dynamics of total bacterial load in the course of an infection

in an animal model, total number of active phagocytes and their maximal phagocytic capacity, or compartmentalization dynamics of infections. Thus, realistic models of *in vivo* infections are correspondingly difficult to design and calibrate to empirical observations.

### Models of viral dynamics within a host

Baccam *et al.* [43] utilized a series of mathematical models of increasing complexity, which incorporate target cell limitation and the innate interferon response, to examine influenza A virus kinetics in the upper respiratory tracts of experimentally infected adults. These author show that these models can be applied to improve the understanding of influenza A virus infection and estimated that during an upper respiratory tract infection, influenza virus initially spreads rapidly with one cell, on average, infecting ~20 others. The model suggests that, as target cells are consumed and by the time of the virus peak at days 2 to 3, the vast majority of the initial target cells have been destroyed. Thus, influenza A infection could be self-limiting providing the ensuing inflammatory response in not excessive. Hancioglu *et al.* published a more complex model of Influenza A [44], expanding from prior work by Bocharov [45] and others [46], providing a biological basis for population variability in severity and course of infection. The purpose of such models is to provide a biological basis for parameters, such as symptom duration, severity of illness and infectivity, generally assumed in population simulations. Such biological models also have the potential to test the usefulness of alternative host-centered intervention strategies. For example, simple target cell-limited (infection spread in a host is limited by the number of residual healthy cells that can be infected) models of hepatitis C virus infection have been used to estimate the antiviral efficacy of interferon [47] and the effects of ribavirin [48].

### Human immunodeficiency virus

Several groups of investigators modeled the Human Immunodeficiency Virus (HIV)-host dynamics as reviewed by Wodarz and Nowak [20], who by themselves use a basic model of virus infection and replication to study HIV dynamics and to measure crucial parameters that lead to a new understanding of the disease process [49]. Simulation studies have shown that (1) HIV is continuously replicating with a high turn-over rate during the asymptomatic phase of the infection, which enables the virus to evolve at a fast rate [50,51], and (2) successful therapy can suppress virus below detection limit but complete virus eradication is not possible under normal circumstances because of long-lived latently infected cells [52,53]. Relatively simple models describe the effect of antigenic escape on disease progression, and are examples of the general principle that virus evolution can drive disease progression and the destruction of the immune system [54–56]. A large number of experimental studies [56]

have demonstrated the enormous potential of the virus to escape from any kind of selective pressure exerted by CTL responses, antibody responses or drug treatment. Thus, it is predicted that the viral population in any one patient will evolve away from control by the immune system (or drug treatment) toward faster reproduction and broader cell tropism. In addition to its clinical appeal, a mathematical model of Wodarz *et al.* [57] suggested that structured therapy interruptions (STI) for HIV can boost immunity against HIV, especially when performed relatively early after infection [58–60]. Such predictions have not been supported by ensuing clinical trials of STI, suggesting that further models should improve biological fidelity [46,61]. The predictions of such models have not been directly tested [62].

### Model parameters and spread of disease

As mentioned earlier, one of the main challenges in mathematical modeling is the estimation of model parameters. Since not all model parameters have a physiological meaning, they need to be estimated numerically, which yields a given uncertainty in these parameter values. Tools such as sensitivity analysis, identifiability analysis, and bifurcation analysis give us the opportunity to understand how model outcome and model parameters are correlated, how sensitive a system is with respect to certain parameters and how big the uncertainty in the model outcome yielded by the uncertainties in the parameter values is [63,78].

Chowell *et al.* [64] and Sanchez *et al.* [65] used uncertainty and sensitivity analysis to asses the role input parameters play on the basic productive rate ($R_o$) of the severe acute respiratory syndrome (SARS) and tuberculosis, respectively. Control of the SARS outbreak was based on rapid diagnosis coupled with effective patient isolation. Mathematically spoken control of an outbreak relies partly on identifying what disease parameters are likely to lead to a reduction in $R_o$. Therefore, these authors and others [66] perform uncertainty and sensitivity analysis to identify key parameters in outbreak control.

### Signaling pathways

Activation of pathways leading to NFκB upregulation play a key role in the initiation of an immune response to infectious products. The activation dynamics of the transcription factor NFκB exhibit damped oscillatory behavior when cells are stimulated by tumor necrosis factor-a (TNFα) but stable behavior when stimulated by lipopolysaccharide (LPS). LPS binding to Toll-like receptor 4 (TLR4) causes activation of NFκB that requires two downstream pathways, each of which when isolated exhibits damped oscillatory behavior. Computational modeling of the two TLR-4 dependent signaling pathways [67] suggests that one pathway requires a time delay to establish early antiphase activation of NFκB by the two pathways. The MyD88-independent pathway required Inferon regulatory factor 3-dependent expression of TNFα to

activate NFκB, and the time required for TNFα synthesis established the delay.

Mathematical models describing the dynamics of NFκB in T-lymphocytes have been developed by Carlotti *et al.* [68] and Hoffman *et al.* [69] The first model describes the association and dissociation of NFκB and IκB and their translocation into the nucleus both in the associated and dissociated forms. This model demonstrates that NFκB is localized in the cytoplasm at rest because of its association with IκB and the export of NFκB from the nucleus. The second model demonstrates that the temporal control was because of coordinated degradation and resynthesis of IκB and that IκB provides a strong negative feedback that can turn off the NFκB response. The hope of such models is two-fold: (1) to probe mechanisms of action such as the relative importance of competing pathways under a variety of circumstances [70] and (2) the identification of key intracellular targets for prospective immunomodulatory interventions.

## Multi-scale models of disease

Multi-scale models are key to understanding the function of complex organs based on their genetic and cellular composition. In essence, a multi-scale model comprises several components hierarchically organized, where the behavior of a higher-level component is explained by the joint dynamics of lower-level components [71–73]. The different components which must be taken into account in the modeling process range from genetic information through cells and tissue to the behavior of whole organs, organisms, and whenever relevant societal behaviors [73,74]. We presented above a compelling argument for the inclusion of multi-scale methodology in simulations of disease spread and containment. The identification of key drivers of disease spread may only be identified from host-centered models. Such drivers include $R_o$ and $\theta$, but also the presence of a combination of host factors characteristic of superspreading capability [75,76], or of pre-existing immune function conveying vulnerability or resistance to an infectious agent. Of note, a model need only be as complicated as the level of insight sought, or the target of a proposed investigation or manipulation.

Complex systems and Systems Biology are emerging fields that aim at systems-level understanding of biological systems. The highly mathematical and statistical aspect of those modeling efforts were pioneered by engineers, physicians, chemists and mathematicians, a growing proportion of which now focusing on biological applications. New organizations such as the International Society for Systems Biology (http://www.issb.org/) and the Society of Complexity in Acute Illness (http://www.scai-med.org/) [77], have been founded to bring together researchers from those quantitative fields with biological and clinical scientists to discuss complex systems approaches in modeling different diseases with the goal of understanding and solving the core challenges impeding the development of robust methods of knowledge discovery in the high-throughput era, and translating this knowledge into improving clinical outcomes.

## Conclusion

Modeling infectious disease is a rich and growing field. Traditionally focused on models of infection spread and containment, increasingly sophisticated models are leveraging the newly available rich clinical, physiological, molecular and genetic data steams. Progress will result from the concerted actions of highly interactive inter-disciplinary teams, where knowledge discovery will itself be model guided [1].

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