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In-host modeling

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ABSTRACT

Understanding the mechanisms governing host-pathogen kinetics is important and can guide human interventions. In-host mathematical models, together with biological data, have been used in this endeavor. In this review, we present basic models used to describe acute and chronic pathogenic infections. We highlight the power of model predictions, the role of drug therapy, and advantage of considering the dynamics of immune responses. We also present the limitations of these models due in part to the trade-off between the complexity of the model and their predictive power, and the challenges a modeler faces in determining the appropriate formulation for a given problem.

1. Introduction

Mathematical models of in-host pathogen kinetics have improved our understanding of the mechanistic interactions that govern chronic infections with pathogens such as HIV (Arinaminpathy, Metcalf, & Grenfell, 2014, pp. 81–96; Ciupe, de Bivort, Bortz, & Nelson, 2006; Frascoli, Wang, Sahai, & Heffernan, 2013; Heffernan & Wahl, 2005; Heffernan & Wahl, 2006; Ho, Neumann, Perelson, Chen, Leonard, & Markowitz, 1995; Nowak and May, 2001; Perelson & Nelson, 1999; Perelson & Ribeiro, 2013; Perelson, Neumann, Markowitz, Leonard, & Ho, 1996; Schwartz, Biggs, Bailes, Ferolito, & Vaidya, 2016; Smith & Wahl, 2004; Stafford et al., 2000; Wang, Zhou, Wu, & Heffernan, 2009; Wei et al., 1995), hepatitis B (Ciupe, Ribeiro, Nelson, Dusheiko, & Perelson, 2007, Ciupe, Ribeiro, Nelson, & Perelson, 2007; Dahari, Shudo, Ribeiro, & Perelson, 2009; Lewin et al., 2001; Nowak and May 2001; Nowak et al., 1996; Qesmi, Wu, Wu, & Heffernan, 2010; Qesmi, ElSaadany, Heffernan, & Wu, 2011; Ribeiro, Germanidis et al., 2010; Tsiang, Rooney, Toole, & Gibbs, 1999; Whalley et al., 2001; Wodarz, 2005, Wodarz, 2014), hepatitis C (Canini and Perelson, 2014; Dahari, Guedj, Perelson, & Layden, 2011; Guedj, Rong, Dahari, & Perelson, 2010; Herrmann, Neumann, Schmidt, & Zeuzem, 2000; Neumann et al., 1998a, Neumann et al., 1998b, 2000; Qesmi et al., 2010; Qesmi et al., 2011; Reluga, Dahari, & Perelson, 2009; Rong et al., 2013; Snoeck et al., 2010; Wodarz, 2005), tuberculosis (Du, Wu, & Heffernan, 2017; Gammack, Doering, & Kirschner, 2004; Gong, Linderman, & Kirschner, 2015; Guirado & Schlesinger, 2013; Linderman and Kirschner, 2015; Marino & Kirschner, 2004; Wigginton & Kirschner, 2001); as well as acute infections such as influenza (Arinaminpathy et al., 2014, pp. 81–96; Baccam, Beauchemin, Macken, Hayden, & Perelson, 2006; Beauchemin and Handel, 2011; Beauchemin et al., 2008; Cao et al., 2015; Dobrovolny, Reddy, Kamal, Rayner, & Beauchemin, 2013; Hadjichrysanthou et al., 2016; Handel, Longini, & Antia, 2010; Murillo, Murillo, & Perelson, 2013; Pawelek et al., 2012; Price et al., 2015; Smith et al., 2013), dengue (Ben-Shachar & Koelle, 2015; Clapham, Tricou, Nguyen, Simmons, & Ferguson, 2014; Nikin-Beers & Ciupe, 2015, 2016), and malaria (Childs

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& Buckee, 2015; De Leenheer & Pilyugin, 2008; Simpson, Zaloumis, DeLivera, Price, & McCaw, 2014). Analytical investigation of these models has helped quantify the in-host basic reproduction numbers (R_0), which estimate the number of secondary infections that arise from one infected cell over the course of its life-span at the beginning of infection when cells susceptible to infection are not depleted. Numerical investigation and data fitting of in-host models have also helped uncover important biological parameters, including the pathogen and infected cell half-lives and the daily pathogen production. Most importantly, such models have been used to estimate the efficacy of different drug therapies, the strength of the immune responses (innate and/or adaptive immune responses), and to ultimately make predictions of disease outcome.

In this paper, we provide a review of in-host mathematical models. We present model variations of chronic and acute infections, changes observed through the incorporation of different components of the immune response and drug therapy, and the role of the data in validating the theoretical results. We conclude with a discussion on the trade-off between model complexity and its power to inform outcomes.

2. Basic model of pathogen dynamics

Depending on the pathogen being studied, the basic model of pathogen dynamics must include certain characteristics that are 'basic' to the disease dynamics in-host. These include, for example, the cells that the pathogen infects, the existence of the pathogen in the host (i.e. in what areas of the body pathogen particles may reside in), the time-scale of the infection of the host (i.e. long-lived and persistent (chronic) or short-lived (acute) infections) and the life-cycle of the pathogen (which includes all of the different methods by which the pathogen can produce progeny). Taking these points into consideration, one would thus expect that the basic model of infection with different pathogen types (i.e., virus, bacteria, parasite) would vary. It is interesting to note, however, that the format of the basic model for each type is very similar and may differ in very few respects. In this section we outline the basic models of pathogen dynamics that encapsulate the aforementioned 'basic' characteristics of infection in-host. These models are termed 'target cell-limitation' models because they do not explicitly incorporate the effects of the immune responses, and the pathogen decay from the peak infection is due to infection and depletion of the majority of target cells. We begin with the most famous and widely used basic model, the basic model of chronic virus infections.

2.1. Chronic virus infections

First used to model HIV in-host viral kinetics (Ho et al., 1995; Perelson et al., 1993, 1996), the basic model describing the interaction between uninfected target cells T, infected cells I, and the virus V, is presented in the diagram from Fig. 1 and governed by the following system of differential equations:

$$\begin{aligned} \frac{dT}{dt} &= s - dT - \beta TV, \\ \frac{dI}{dt} &= \beta TV - \delta I, \\ \frac{dV}{dt} &= pI - cV\,. \end{aligned} \tag{1}$$

Briefly, uninfected target cells are produced by the body at a constant rate (s), and have a natural death rate d where $1/d$ is the expected lifetime of an uninfected target cell. Uninfected target cells T can be infected by virus particles V at rate β, producing infected target cells I. It is assumed that infected target cells have a death rate $\delta \geq d$, depending on the pathogen being considered. Finally, infected target cells produce virus particles V at rate p and these are either degraded or cleared by the immune system at rate c.

Analysis of Eq. (1) shows that there are two different equilibria, a disease free equilibrium (E_0), and one where the patient is chronically infected (E_1). The disease free and infected equilibria are given by:

$$E_0 = \left(\frac{s}{d}, 0, 0\right),$$

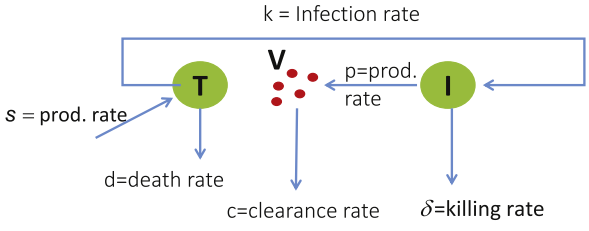

Fig. 1. Model diagram for Eq. (1).