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A PDE multiscale model of hepatitis C virus infection can be transformed to a system of ODEs

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ABSTRACT

Direct-acting antivirals (DAAs) treat hepatitis C virus (HCV) by targeting its intracellular viral replication. DAAs are effective and deliver high clinical performance against HCV infection, but optimization of the DAA treatment regimen is ongoing. Different classes of DAAs are currently under development, and HCV treatments that combine two or three DAAs with different action mechanisms are being improved. To accurately quantify the antiviral effect of these DAA treatments and optimize multi-drug combinations, we must describe the intracellular viral replication processes corresponding to the action mechanisms by multiscale mathematical models. Previous multiscale models of HCV treatment have been formulated by partial differential equations (PDEs). However, estimating the parameters from clinical datasets requires comprehensive numerical PDE computations that are time consuming and often converge poorly. Here, we propose a user-friendly approach that transforms a standard PDE multiscale model of HCV infection (Guedj J et al., Proc. Natl. Acad. Sci. USA 2013; 110(10):3991–6) to mathematically identical ordinary differential equations (ODEs) without any assumptions. We also confirm consistency between the numerical solutions of our transformed ODE model and the original PDE model. This relationship between a detailed structured model and a simple model is called "model aggregation problem" and a fundamental important in theoretical biology. In particular, as the parameters of ODEs can be estimated by already established methods, our transformed ODE model and its modified version avoid the time-consuming computations and are broadly available for further data analysis.

1. Introduction

In several landmark papers, the turnover of human immunodeficiency virus type I (HIV-1) infection was determined *in vivo* from the declining viral load in patients after the start of antiviral therapy. Since then, mathematical modeling has evolved into an important tool in modern virology (Ho et al., 1995; Neumann et al., 1998; Nowak and May, 2000; Perelson et al., 1996; Perelson et al., 1997). For example, mathematical models of viral infection such as HIV-1, hepatitis B virus, hepatitis C virus (HCV) and cytomegalovirus have provided insights that cannot be directly obtained through experimental and clinical studies (Perelson, 2002), especially when quantifying the antiviral effects of drugs. Multiple drugs with different mode of actions enhance the antiviral activity and reduce the probability of emergent drug resistance. For this reason, the administration of multiple drugs is the standard strategy for antiviral treatments, provided that different classes of antiviral agents are available (Jilek et al., 2012; Koizumi et al., 2017; Lau et al., 2016; Ohashi et al., 2017; Perelson et al., 1997).

In anti-HCV treatments, direct-acting antivirals (DAAs) with different antiviral mechanisms have dramatically improved the sustained virological response (SVR) rate of the infected host. Current standard multi-drug treatments, based on DAAs targeting intracellular viral replication (e.g., sofosbuvir and ledipasvir), enhance the SVR from approximately 50% in classical HCV treatment (combined

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interferon-α and ribavirin) (Cheng et al., 2014) to 95% or higher (Pawlotsky, 2015). Multi-drug treatments dramatically improve the clinical outcome of HCV, and their antiviral effects can be accurately quantified by mathematical models, enabling further optimization. Conventionally, mathematical models of antiviral activity for quantitative data analysis are formulated by ordinal differential equations (ODEs) (Best et al., 2017; Ho et al., 1995; Neumann et al., 1998; Perelson et al., 1996; Perelson et al., 1997). However, ODE models describe only the intercellular dynamics of viral infection, and cannot reveal how the antiviral effects of drug(s) depend on the action mechanism(s) of the drug(s) when fitted to clinical (or experimental) data, unless each effect is reflected in a different model parameter. Instead, ODE methods estimate the mixed antiviral effect as a composite parameter.

To more precisely describe and quantify the different antiviral effects of anti-HCV drug(s), several researchers have proposed multiscale models (Guedj and Neumann, 2010; Guedj et al., 2013; Rong and Perelson, 2013; Rong et al., 2013). As these mathematical models deal with intracellular viral replication processes, they capture the different antiviral effects corresponding to the action mechanism(s) of drug(s) in the various parameters of the replication process. Viral replication dynamics begin only in virus-infected cells; that is, they depend on the time during which a cell has been infected (here called the *infection age*). To describe these intracellular and intercellular dynamics of virus infection, partial differential equations (PDEs) are required, which are time intensive and often poorly convergent in numerical procedures (Guedj et al., 2013; Rong and Perelson, 2013; Rong et al., 2013). The original PDE model of a potent multi-drug HCV treatment, with its mathematically strong but biologically reasonable assumptions (Guedj et al., 2013; Rong et al., 2013), provides approximate solutions to the clinical data fitting. However, we propose a different approach that avoids the costly numerical computations. Our approach is called "model aggregation" which has been well established in theoretical biology (Auger et al., 2000; Iwasa et al., 1987; Iwasa et al., 1989). We also discuss how our approach can improve mathematical model-oriented data analysis in virology.

2. Results

The well-parameterized basic model of viral dynamics including the antiviral effect is described by the following ODEs (Neumann et al., 1998; Nowak and May, 2000):

$$\frac{dT(t)}{dt} = s - dT(t) - \beta T(t)V(t),$$
$$\frac{dI(t)}{dt} = \beta T(t)V(t) - \delta I(t),$$
$$\frac{dV(t)}{dt} = (1-\varepsilon)pI(t) - cV(t).$$

The variables $T(t)$ and $I(t)$ are the numbers of (uninfected) target cells and infected cells, respectively, and $V(t)$ denotes the amount of viruses. The target cells are assumed to be supplied at rate s, infected by viruses at rate β, and naturally die at rate d. The infected cells die at rate δ and produce viruses at rate p, and the progeny viruses are cleared at rate c. By an antiviral treatment, the virus production rate p is decreased to $(1-\varepsilon)p$, where $0 \le \varepsilon \le 1$. In quantitative data analyses of viral infection, the above model is often recast as simple ODEs (Best et al., 2017; Martyushev et al., 2016; Neumann et al., 1998; Perelson et al., 1996). However, these models exclude the intracellular viral replication process (i.e., omit the multiscale properties between intracellular and intercellular viral infection). In particular, to separately quantify the antiviral effects of drug(s) on different viral replication processes, one needs explicit equation(s) describing the intracellular viral lifecycle. Otherwise, all antiviral effects of drug(s) on processes such as translation, processing, replication, assembly, transportation and release of viruses are embodied in a single parameter ε. This composite parameter ε cannot be divided into individual antiviral effects by conventional data fittings.

2.1. A multiscale model for HCV infection formulated by PDEs

The different antiviral effects on viral lifecycle are more precisely described by multiscale models. Several such models have been proposed and investigated for data analysis (Guedj and Neumann, 2010; Guedj et al., 2013; Rong and Perelson, 2013; Rong et al., 2013). We here introduce a multiscale model formulated by PDEs for analyzing clinical data under multi-drug HCV treatment (Guedj et al., 2013):

$$\frac{dT(t)}{dt} = s - dT(t) - \beta T(t)V(t), \tag{1}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) i(t,a) = -\delta i(t,a), \tag{2}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) R(t,a) = \alpha - (\mu+\rho)R(t,a), \tag{3}$$

$$\frac{dV(t)}{dt} = \rho \int_0^\infty R(t,a)i(t,a)da - cV(t), \tag{4}$$

with the following initial and boundary conditions:

$$T(0) = T_0,\ V(0) = V_0,\ i(0,a) = i_0(a),\ R(0,a) = R_0(a),$$

and

$$i(t,0) = \beta T(t)V(t),\ R(t,0) = \zeta.$$

Here, the variable $i(t, a)$ represents the age distribution of the infected cells (i.e., the density of cells with infection age a) at time t. Similarly $R(t, a)$ is the age and time distribution of intracellular viral RNA in a cell with infection age a. The definition of age-structured population model is referred to (Inaba, 2017). The initial value T_0 and V_0 are nonnegative. The parameters α and μ denote the production and degradation rates of the intracellular viral RNA, respectively. Viral RNA is assumed to assemble along with viral proteins and to secrete from an infected cell as virus particles at rate ρ (i.e. the exportation rate). Note that viral RNA starts to replicate from ζ copies in a newly infected cell. In Guedj et al. (2013), ζ was fixed to 1. In this model, all parameters defined as nonnegative values.

2.2. Multiscale model of HCV infection transformed by ODE

The total number of infected cells, denoted by $I(t)$, is calculated by integrating the age distribution over the infection age a; that is, $I(t) = \int_0^\infty i(t,a)da$.

Similarly, the total amount of intracellular viral RNA pooled in all infected cells is given by

$$P(t) = \int_0^\infty R(t,a)i(t,a)da.$$

The initial values can be calculated by integrating the initial distributions, $I(0) = \int_0^\infty i_0(a)da$ and $P(0) = \int_0^\infty R_0(a)i_0(a)da$. Differentiating $I(t)$ and $P(t)$ with respect to time t, we obtain the following differential equations:

$$\frac{dI(t)}{dt} = \int_0^\infty \frac{\partial}{\partial t} i(t,a)da, \tag{5}$$

$$\frac{dP(t)}{dt} = \int_0^\infty \frac{\partial}{\partial t}(R(t,a)i(t,a))da. \tag{6}$$