Mathematical analysis for a multiscale model describes hepatitis C virus infection dynamics

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Mathematical analysis for a multiscale model describes hepatitis C virus infection dynamics

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Preface

I here consider mainly mathematical analysis for a multiscale model of hepatitis C virus, which express both inter- and intra- dynamics. Such models describing multiple scales of dynamics called as multiscale model. Multiscale model is a useful tool for more detailed data analysis and makes sense in biology, virology, medical science and life science. Note that the results I show here are not limited only the dynamics model for hepatitis C virus, because it does not demand essentially that the dynamics is for only hepatitis C. I summarize the contents of two chapters as follows.

Chapter 1: A PDE multiscale model of hepatitis C virus infection can be transformed to a system of ODEs.

The popular antiviral treatment for hepatitis C virus (HCV) is called Direct-acting antivirals (DAAs). DAA realizes high effective and high clinical performance by targeting HCV's intracellular viral replication. Now the HCV treatments generally adopt combination of two or three DAAs with different action mechanisms, but optimal treatment regimen has not established. To accurately quantify the antiviral effect of these DAA treatments and optimize multi-drug combinations, it is necessary to install multiscale mathematical model describes the intracellular viral replication processes corresponding to some of the different action mechanisms. Previous multiscale models of HCV treatment have been formulated by partial differential equations (PDEs). However, parameters estimation of clinical datasets requires comprehensive numerical PDE computations that are time consuming and often converge poorly. Here I show transformation the standard PDE multiscale model of HCV infection to mathematically identical ordinary differential equations (ODEs) without any assumptions. This derived ODE model brings us higher performance for analysis clinical data to estimate parameters. I also give confirmation of consistency between the transformed ODE model and the original PDE model about numerical solutions. This relationship called "model aggregation

problem" is a fundamental important topic in theoretical biology. In particular, as the parameter estimation of ODEs is already established, the derived ODE model avoid the time-consuming computations and is available for further data analysis.

Chapter 2: Mathematical Analysis of a Transformed ODE from a PDE Multiscale Model of Hepatitis C Virus Infection.

In Chapter 1, I derived a mathematically identical ODE model from original PDE model, which helps to get over the hardships of the PDE model for clinical data analysis. In mathematical model analysis, researching about the equilibriums is the most basically and important. In this chapter I show additional mathematical analysis for the ODEs. Here, I formulate the basic reproduction number and give conditions for global stability of all possible steady states of the ODE model by constructing Lyapunov function.

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Chapter 1

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

The study in this chapter, done in collaboration with Dr. Shinji Nakaoka, Dr. Yusuke Asai, Dr. Koichi Watashi, and Dr. Shingo Iwami, was published in Journal of Theoretical Biology in 2018

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 [1-5]. 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 [6], 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 [5, 7-10].

The quite great treatment for HCV, direct-acting antivirals (DAAs) with different antiviral mechanisms, have dramatically improved the sustained virological response (SVR) rate of the infected host. Targeting intracellular viral replication, the DAAs and current standard multi-drug treatments, based on DAAs (e.g., sofosbuvir and ledipasvir), succeeded to enhance the SVR from approximately 50% in classical HCV treatment (combined interferon-α and ribavirin) [11] to 95% or higher [12]. 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 ordinary differential equations (ODEs) [1, 2, 4, 5, 13]. However, ODE can describe only the intercellular dynamics of viral infection or a single-scaled dynamics, 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 inseparably compressed antiviral effect as a composite parameter.

To more precisely describe and quantify the different antiviral effects of anti-HCV drug(s), multiscale model has been introduced by several researchers [14-17]. By describing the intracellular

viral replication processes with various parameters in mathematical models, they capture the different antiviral effectiveness corresponding to the action mechanisms of drugs. Viral replication dynamics starts and works only in virus-infected cells; that is, they depend on the time since the cell has been infected (here called the infection age). To describe both of 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 [14, 16, 17]. The original PDE model of the multi-drug HCV treatment, with its mathematically strong but biologically reasonable assumptions [14, 16], provides approximate solutions to the clinical data fitting. However, I propose a different approach with another way avoids the costly numerical computations. This approach I adopted is called "model aggregation" which has been well established in theoretical biology [18-20]. I also discuss how my approach can improve data analysis with mathematical model in virology.

Results

The well-parameterized basic model of viral dynamics including the antiviral effect is described by the following ODEs [2, 3]:

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

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. In quantitative data analyses of viral infection, the above model is often recast as simple ODEs [2, 4, 13, 21]. However, these models don't look 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 formulation 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, defining the effect to which drugs inhibit viral production. This composite parameter ε cannot be divided into individual antiviral effects by conventional data fittings.

A multiscale model for HCV infection formulated by PDEs

To describe more precisely the different antiviral effects on various part of viral lifecycle, multiscale model should be introduced. Several such models have been proposed and investigated for data analysis [14-17]. I here introduce a multiscale model formulated by PDEs for analyzing clinical data under multi-drug HCV treatment [14]:

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

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

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

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

with the following initial and boundary conditions:

$$i(t,0) = \beta T(t)V(t), \qquad i(0,a) = i_0(a), \qquad R(t,0) = \zeta, \qquad R(0,a) = R_0(a).$$

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 [22]. 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 [14], ζ was fixed to 1.

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:

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

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

From Eqs. (2)–(3), we have

$$\frac{\partial i(t,a)}{\partial t} = -\frac{\partial i(t,a)}{\partial a} - \delta i(t,a),$$

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

Eq. (5) is evaluated as follows:

$$\frac{dI(t)}{dt} = \int_0^\infty \frac{\partial i(t,a)}{\partial t}da = \int_0^\infty \left\{-\frac{\partial i(t,a)}{\partial a} - \delta i(t,a)\right\}da = -[i(t,a)]_0^\infty - \delta I(t).$$

The density of cells converges to 0 as $a \to \infty$, that is, $\lim_{a\to\infty} i(t,a) = 0$. Moreover, as $i(t,0) = \beta T(t)V(t)$, we obtain the following differential equation for $I(t)$:

$$\frac{dI(t)}{dt} = \beta T(t)V(t) - \delta I(t).$$

Similarly, Eq. (6) is calculated as follows:

$$\begin{aligned}
\frac{dP(t)}{dt} &= \int_0^\infty \frac{\partial\big(R(t,a)i(t,a)\big)}{\partial t} da \\
&= \int_0^\infty \left\{ \frac{\partial R(t,a)}{\partial t} \cdot i(t,a) + R(t,a) \cdot \frac{\partial i(t,a)}{\partial t} \right\} da \\
&= \int_0^\infty \left\{ \left(-\frac{\partial R(t,a)}{\partial a} + \alpha - (\mu+\rho)R(t,a) \right) i(t,a) + R(t,a) \left(-\frac{\partial i(t,a)}{\partial a} - \delta i(t,a) \right) \right\} da \\
&= \int_0^\infty \left\{ -\left(\frac{\partial R(t,a)}{\partial a} \cdot i(t,a) + R(t,a) \cdot \frac{\partial i(t,a)}{\partial a} \right) + \alpha i(t,a) - (\mu+\rho+\delta)R(t,a)i(t,a) \right\} da \\
&= -\int_0^\infty \frac{\partial R(t,a)i(t,a)}{\partial a} da + \alpha \int_0^\infty i(t,a) da - (\mu+\rho+\delta) \int_0^\infty R(t,a)i(t,a) da \\
&= -[R(t,a)i(t,a)]_0^\infty + \alpha I(t) - (\mu+\rho+\delta)P(t).
\end{aligned}$$

As $\lim_{a\to\infty} i(t,a) = 0$ and $\lim_{a\to\infty} R(t,a) = \alpha/(\mu+\rho)$, we have $\lim_{a\to\infty} R(t,a)i(t,a) = 0$ and $R(t,0)i(t,0) = \zeta\beta T(t)V(t)$. Therefore, the following differential equation is obtained:

$$\frac{dP(t)}{dt} = \zeta\beta T(t)V(t) + \alpha I(t) - (\mu+\rho+\delta)P(t).$$

Note that Eq. (4) can be rewritten as a simple linear equation:

$$\frac{dV(t)}{dt} = \rho P(t) - cV(t).$$

Taken together, the multiscale PDE model is transformed into the equivalent system of ODEs:

$$\frac{dT(t)}{dt} = s - dT(t) - \beta T(t)V(t), \tag{7}$$

$$\frac{dI(t)}{dt} = \beta T(t)V(t) - \delta I(t), \tag{8}$$

$$\frac{dP(t)}{dt} = \zeta\beta T(t)V(t) + \alpha I(t) - (\mu+\rho+\delta)P(t), \tag{9}$$

$$\frac{dV(t)}{dt} = \rho P(t) - cV(t). \tag{10}$$

Note that the original PDE model and the transformed ODE model (i.e., Eqs. (7)–(10)) are mathematically identical because no specific assumptions are imposed on my formulations (see **Fig. 1-1** for numerical

comparisons).

Numerical simulations under multi-drug HCV treatments

The multiscale model distinguishes the different antiviral effects of multi-drug HCV treatments. I thus defined the reduced viral RNA production rate (i.e., $\tilde{\alpha} = (1 - \varepsilon_\alpha)\alpha$) and exportation rate (i.e., $\tilde{\rho} = (1 - \varepsilon_\rho)\rho$), and the enhanced viral degradation rate (i.e., $\tilde{\mu} = \kappa\mu$), where $0 < \varepsilon_\alpha, \varepsilon_\rho < 1$ and $1 < \kappa$ are the corresponding antiviral effects in the HCV lifecycle [14, 16]. Under multi-drug HCV treatments, I replaced the parameters α, ρ and κ with $\tilde{\alpha}$, $\tilde{\rho}$ and $\tilde{\mu}$ in both the original PDE model (Eqs. (1)–(4)) and my transformed ODE model (Eqs. (7)–(10)). I also assumed that treatment is initiated at time $t = 0$, and defined $i_0(a)$ and $R_0(a)$ as the baseline values of the infected cell number and intracellular viral RNA (i.e., steady state distributions), respectively [16]. For simplicity, I fixed the parameters in this numerical simulations. The parameter values, which were estimated from clinical datasets in [14], are summarized in **Table 1-1**.

[14] and [16] assumed that no *de novo* infection occurs after the treatment initiation, that is, $i(t, a) = 0$ for $a < t$. They considered that current multi-drug HCV treatments are quite potent and generally achieve high antiviral effects [9, 14, 23, 24]. This assumption removes the nonlinear term $\beta T(t)V(t)$ from the boundary conditions of the PDE model. $V(t)$ then simplifies to the following approximation for robust parameter estimation from the viral load data:

$$V(t) = V_0 \left\{ e^{-ct} + \frac{\tilde{\rho} c \delta (\rho + \mu + \delta)}{\rho(\alpha + \delta)} \left[\frac{\tilde{\alpha}}{\delta(\delta - c)(\tilde{\rho} + \tilde{\mu})} \left(e^{-ct} - e^{-\delta t} \right) + \frac{1}{\tilde{\rho} + \tilde{\mu} + \delta - c} \left(\frac{\rho(\alpha + \delta)}{\delta \rho (\rho + \mu + \delta)} - \frac{\tilde{\alpha}}{\delta(\tilde{\rho} + \tilde{\mu})} \right) \left(e^{-ct} - e^{-(\tilde{\rho} + \tilde{\mu} + \delta)t} \right) \right] \right\}. \quad (11)$$

Discussion

One of major problem in modeling study is how we make a simple model. Mathematical models including many variables and parameters with different time scales seem to be required to explain complex biological phenomena [18-20]. Without an essential loss of information demanded on data analysis, reduction of a detailed

structured model to a simple model is a fundamental important in modern biology, which is called model aggregation. This is because the aggregated model is simpler and easier to handle both analytically and numerically than the original one. Hence my model aggregation introduced here helps us to analyze clinical and experimental data as discussed below:

I transformed the multiscale PDE model of HCV infection (Eqs. (1)–(4)) into an ODE model (Eqs. (7)–(10)). Without any assumptions, the ODE model and the original PDE model are mathematically identical. Such ODE models are quite useful, especially for estimating parameters from clinical datasets by comprehensive numerical computations, because numerical simulations of PDEs often converge poorly and are generally time consuming. These problems are especially severe on small age grids Δ_a (see Appendix). For example, when $a_{max} = 100$ and $\Delta_a = 0.1$, the i and R distributions are divided into 1001 compartments, so the fully discretized system becomes a 2004-dimensional system of ODEs. This means that 2004 ODEs must be evaluated at each time step, requiring 4380.0 seconds per simulation up to 5 days post-treatment initiation by an implicit Euler scheme with step size 0.1. My approach evaluates just four ODEs (Eqs. (7)–(10)) in 725.6 seconds (all simulations were run in R version 3.2.1 on a Windows 10 OS with an Intel(R) Core(TM) i5 CPU, 1.70 GHz, 4.0 GB RAM). Therefore, my transformed ODE model considerably reduces the numerical costs. Note that when the intracellular viral-replication dynamics are formulated by linear differential equation(s), any multiscale PDE model can be similarly transformed into an ODE system. In this chapter, I transformed the multiscale model of [14] as an illustrative example, but the approach is quite general.

Several numerical methods for parameter estimation in ODEs are now well developed. PDEs can be simulated by software such as FREEFEM++, which is rather user-unfriendly [25], but ODEs can be solved by a variety of numerical computation tools that support diverse types of analyses. For example, Stan is a popular and versatile language for Bayesian modeling and computation, which currently supports parameter estimation of ODEs. Stan can be implemented through a dedicated package [26] in the statistical software R [27]. Nonlinear mixed-effect modeling of ODEs is also widely implemented in the R package nlmeODE [28]. Hence, my simple transformation approach from PDEs to ODE systems will become broadly available for further data analysis.

As described in Fig.1, my transformed ODE model numerically agrees with that of the original PDE model, which is independent of antiviral effects, but the approximate solution diverges from the complete solutions under a low antiviral effect. This implies that the antiviral effects in difficult-to-treat HCV patients are underestimated. Although current DAAs effectively treat HCV infections, the treatment failure rates of DAAs are increased in HCVs carrying resistant-associated substitutions, especially substitutions in the NS5A region of the HCV genome [29]. My transformed ODE models are advantageous, as they accurately quantify the antiviral effect from clinical datasets, although all parameters in Eqs. (7)–(10) must be estimated. This approach is particularly useful for analyzing the data of in vitro cell-culture experiments, because we can now obtain frequent samples of several kinetic variables in a simpler environment than in vivo infection [30]. Indeed, these mathematical models can be fully parameterized on modern in vitro data, and the virus infection kinetics can be robustly quantified [30-37].

In conclusion, the parameters in ODEs can be estimated by several well-developed numerical methods. Therefore, my transformed ODE model and its modified version avoid time-consuming computations and are appropriate and suitable for data analysis

Abbreviations

HCV: Hepatitis C Virus; ODE: Ordinary Differential Equation; PDE: Partial Differential Equation

Figure and Table

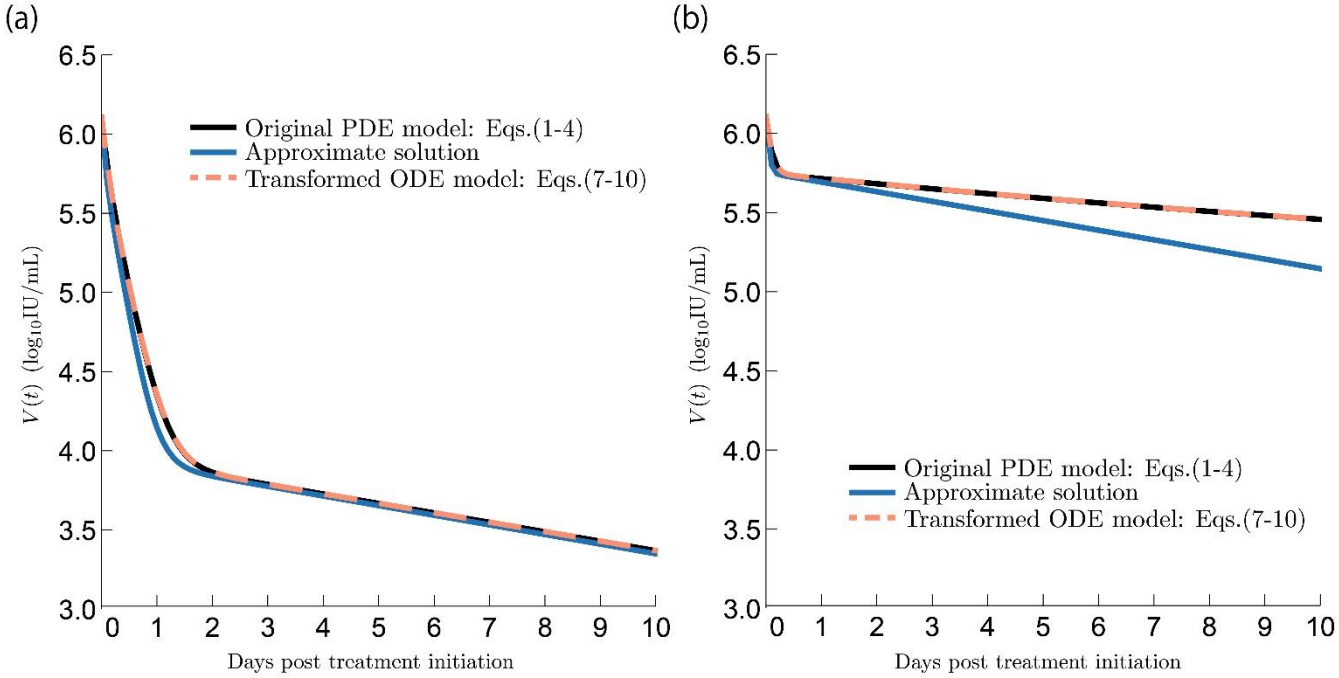

Figure 1-1 | Comparison of numerical simulations. Results of three models. the original PDE model (Eqs. (1)–(4), black lines) my transformed ODE model (Eqs. (7)–(10), orange lines) and the approximate solution (Eq. (11), blue lines) under anti-HCV drug therapy with (a) a high antiviral effect and (b) a low antiviral effect. The model parameters are listed in **Table 1-1**.

Table 1-1. Fixed parameter values in the numerical simulations

Parameter name	**Parameters**	**Unit**	**values**
Supply of target cells	s	$\text{cells/ml} \cdot \text{day}^{-1}$	1.30×10^{5}
Infection rate	β	$\text{day}^{-1} \cdot \text{virion/ml}^{-1}$	5.00×10^{-8}
Death rate of target cells	d	day^{-1}	0.01
Death rate of infected cells	δ	day^{-1}	0.14
Viral clearance rate	c	day^{-1}	22.3
Production rate of viral RNA	α	day^{-1}	40.0
Degradation rate of viral RNA	μ	day^{-1}	1.00
Exportation rate of viral RNA	ρ	day^{-1}	8.18
Antiviral effect on viral RNA production	ε_{α}	day^{-1}	0.99 and 0.50 in **Fig.1(a)** and **(b)**
Antiviral effect on viral RNA degradation	κ	day^{-1}	1.00
Antiviral effect on viral RNA exportation	ε_{ρ}	day^{-1}	0.56

Appendix

The original PDE model (Eqs. (1)–(4)), proposed by Guedj J et al. and published in Proc. Natl. Acad. Sci. USA 2013;110(10): 3991–6, is a coupled system of PDEs and ODEs. Here we derived a system of ODEs by discretizing the i and R compartments with respect to age as follows.

I first prepared the equidistant age interval $0 = a_0 < a_1 < \cdots < a_N = a_{max}$, where the age grid Δ_a satisfies $\Delta_a = a_j - a_{j-1}$ for $j = 1, \ldots, N$, and a_{max} is the maximum infection age of the infected cells $i(t,a)$, i.e. $i(t, a > a_{max}) = 0$. The Taylor expansion of $i(t,a)$ about a is given by

$$i(t, a + \Delta_a) = i(t,a) + \Delta_a \frac{\partial}{\partial a} i(t,a) + O\left({\Delta_a}^2\right),$$

where $O\left({\Delta_a}^2\right)$ is the ${\Delta_a}^2$-order remainder term. Thus we get

$$\frac{\partial}{\partial a} i(t,a) = \frac{1}{\Delta_a}\left(i(t, a + \Delta_a) - i(t,a)\right) - O(\Delta_a).$$

Now, let $I_j(t) = i\left(t, a = a_j\right)$, i.e., let the number of cells at age $a = a_j$. By discarding the remainder term $O(\Delta_a)$ and substituting $i\left(t, a_j\right)$ with $I_j(t)$, we obtain the following discretized ODE:

$$\frac{dI_j}{dt} = -\delta I_j(t) - \frac{1}{\Delta_a}\Big(I_j(t) - I_{j-1}(t)\Big),$$

where $j = 1, \ldots, N$. The boundary condition is given by $i(0,t) = \beta T(t) V(t)$ and the corresponding boundary term becomes $I_0(t) = \beta T(t) V(t)$.

Similarly, Eq. (2) is discretized as follows:

$$\frac{dR_j}{dt} = \alpha - (\mu + \rho) R_j(t) - \frac{1}{\Delta_a}\Big(R_j(t) - R_{j-1}(t)\Big),$$

where $R_j(t) = R\left(t, a = a_j\right)$ for $j = 1, \ldots, N$. Before the treatment, R is time-independent, i.e., $\frac{\partial}{\partial t} R(t,a) = 0$. This time-independent R, denoted by R^*, is given by the following ODE:

$$\frac{dR^*}{da}(a) = \alpha - (\mu + \rho) R^*(a).$$

The analytical solution to this expression can be used as the initial distribution of $R_j(0)$ for $j = 1, \ldots, N$ with $R_0(0) = \zeta$.

On the other hand, $i(t,a)$ and $R(t,a)$ in Eq. (4) can be substituted by $I_j(t)$ and $R_j(t)$ respectively as follows. Dividing the integration in Eq. (4) into intervals, we obtain

$$\begin{aligned}\frac{dV}{dt} &= \rho\sum_{j=0}^{\infty}\int_{j\Delta_a}^{(j+1)\Delta_a} R(t,a)i(t,a)da - cV(t)\\ &= \rho\lim_{|\Delta_a|\to 0}\sum_{j=0}^{\infty} R\big(t,a_j\big)i\big(t,a_j\big)\Delta_a - cV(t)\\ &= \rho\lim_{|\Delta_a|\to 0}\sum_{j=0}^{\infty} R_j(t)I_j(t)\Delta_a - cV(t).\end{aligned}$$

Thus, the coupled ODE and PDE system (Eqs. (1)–(4)) is transformed into the following system of discretized ODEs:

$$\begin{aligned}\frac{dT}{dt} &= s - \beta T(t)V(t) - dT(t),\\ \frac{dI_j}{dt} &= -\delta I_j(t) - \frac{1}{\Delta_a}\Big(I_j(t) - I_{j-1}(t)\Big),\\ \frac{dR_j}{dt} &= \alpha - (\mu+\rho)R_j(t) - \frac{1}{\Delta_a}\Big(R_j(t) - R_{j-1}(t)\Big),\\ \frac{dV}{dt} &= \rho\lim_{|\Delta_a|\to 0}\sum_{j=0}^{\infty} R\big(a_j\big)I_j(t)\Delta_a - cV(t),\end{aligned}$$

for $j = 1, \dots, N$. The boundary terms $I_0(t)$ and $R_0(t)$ are given by $\beta T(t)V(t)$ and ζ, respectively, and the initial conditions $I_j(t)$ and $R_j(t)$ by $i_0\big(a_j, 0\big)$ and $R^*\big(a_j\big)$, respectively. In the numerical simulation (**Fig. 1-1**), I assumed that the i and R compartments reach steady states with respect to time before the treatment starts, meaning that only age-dependent derivatives remain in the system. The corresponding ODEs of the i and R compartments can be analytically solved, and the initial distributions of I_j and R_j for $j = 1, \dots, N$ in the original PDE model are given by $I_j(0) = \beta V_0 T_0 \exp(-\delta a_j)$ and $R_j(0) = \exp\big(-(\mu+\rho)a_j\big)\Big(\zeta - \frac{\alpha}{\mu+\rho}\Big) + \frac{\alpha}{\mu+\rho}$, respectively. Depending on the action mechanism of the drugs, the antiviral effect changes the corresponding parameters (e.g., $(1-\varepsilon_\alpha)\alpha$) from those of the model that do not take account to the antiviral effect.

Chapter 2

Mathematical Analysis of a Transformed ODE from a PDE Multiscale Model of Hepatitis C Virus Infection

The study in this chapter, done in collaboration with Dr. Toshikazu Kuniya, Dr. Shinji Nakaoka, Dr. Yusuke Asai, Dr. Koichi Watashi, and Dr. Shingo Iwami, was accepted in Bulletin of Mathematical Biology in 2019

Introduction

Stability analysis is one of the most fundamental and important approaches for understanding the dynamic behavior of mathematical models and has been performed for every type of mathematical model in all areas[38-45]. Age-structured models referred to as “multiscale model” have been widely used to study the within-host dynamics of infections by several viruses [15, 46-48], especially for analyzing hepatitis C virus (HCV) clinical datasets under multidrug treatments [14, 16, 48]. Age-structured models are generally formulated by partial differential equations (PDEs), so they are considerably more difficult to analyze mathematically and numerically. However, since the multiscale models can describe both intercellular and intracellular viral infection dynamics including the intracellular viral replication processes corresponding to the action mechanisms, it is necessary to accurately quantify antiviral effects (i.e., estimating parameters) from clinical datasets under multidrug treatments [49, 50], .

For example, Guedj et al. developed an age-structured multiscale model of HCV infection considering the intracellular HCV replication/degradation by PDEs. The original PDE model of a potent multidrug HCV treatment, with its mathematically strong but biologically reasonable assumptions, provided approximate solutions to the clinical data fitting, and their approximation successfully estimated several important parameters in a previous study [14]. On the other hand, when multidrug treatments are relatively impotent, it has been reported that their approximation could not accurately trace numerical PDE solutions, and therefore might underestimate the antiviral effects [50]. Thus, in addition to the derivation of approximate solutions [14, 16], to robustly perform parameter estimation based on direct numerical solutions of PDEs, several advanced numerical methods that overcome the property of stiffness of the differential equation have been developed [48, 49, 51, 52]. Furthermore, in my recent report [50], to improve achievement of the numerical solution of the multiscale model, I proposed “model aggregation” [19, 20], and derived mathematically identical ordinary differential equations (ODEs) from the original PDE model [14, 16]. Since the parameters of ODEs could be estimated by already established methods

including “R,” “Mathematica,” and “Matlab,” my transformed ODE model and its modified version avoid the time-consuming computations and are broadly available for data analysis.

Thanks to the identical ODE derivation from the original PDE model, mathematical analysis for the multiscale model might be markedly accelerated. In fact, compared with numerical analysis of multiscale models, mathematical analysis of multiscale models described by PDEs has not been well achieved. This is because comprehensive stability analysis for PDE is mathematically difficult and often limited to local asymptotically stable (LAS) [17]. Here, taking advantage of standard approaches for mathematical analysis of ODE, I analyzed the transformed ODE model and determined the mathematical structure of the original PDE model. The goal of this paper is to improve a mathematical analysis reported previously [17]. I derived the basic reproduction numbers of the transformed ODE, and discussed their biological meanings. Furthermore, I provided the global stability of all possible steady states of the transformed ODE.

Results

The following multiscale model formulated by PDEs describing the intracellular HCV lifecycle has been proposed and applied for analyzing clinical data under multidrug HCV treatment [14, 16]:

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

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

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

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

with the following initial and boundary conditions:

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

and

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

Here, the variable $T(t)$ is the number of (uninfected) target cells, while $V(t)$ denotes the number of viruses. In addition, the variable $i(t,a)$ represents the age distribution of 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 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 the progeny viruses are cleared at rate c. 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 be secreted from an infected cell as viral particles at rate ρ. Note that the entry virus-derived RNA starts to replicate from ζ copies in a newly infected cell. In this model, all parameters are defined as non-negative values.

In my recent report [50], I proposed "model aggregation" [19, 20] which transforms the above PDE multiscale model of HCV infection [i.e., Eqs. (1–4)] into the following mathematically identical ODEs:

$$\frac{dT(t)}{dt} = s - dT(t) - \beta T(t)V(t), \tag{7}$$

$$\frac{dI(t)}{dt} = \beta T(t)V(t) - \delta I(t), \tag{8}$$

$$\frac{dP(t)}{dt} = \zeta\beta T(t)V(t) + \alpha I(t) - (\mu + \rho + \delta)P(t), \tag{9}$$

$$\frac{dV(t)}{dt} = \rho P(t) - cV(t). \tag{10}$$

Here, the total number of infected cells and the total amount of intracellular viral RNA pooled in all infected cells are defined as $I(t) = \int_0^\infty i(t,a)da$ and $P(t) = \int_0^\infty R(t,a)i(t,a)da$, respectively, with the initial distributions $I(0) = \int_0^\infty i_0(a)da$ and $P(0) = \int_0^\infty R_0(a)i_0(a)da$. The derivation from the original PDE [i.e., Eqs. (1–4)] to the transformed ODE model [i.e., Eqs. (7–10)] is detailed elsewhere [50].

Basic reproduction number of transformed ODE

I first derived an important index to quantify "potential for viral infection," that is, the basic reproduction number [3, 30], R_0. Since the basic reproduction number is defined as the expected total number of cells newly infected from one typical infected cell during its lifetime at the beginning of infection, I assumed $T(0) = T_0 = s/d$. Therefore, the ODE model [i.e., Eqs. (7–10)] is written as the following linearized version:

$$\begin{aligned}
\frac{dI(t)}{dt} &= \beta T_0 V(t) - \delta I(t), \\
\frac{dP(t)}{dt} &= \zeta\beta T_0 V(t) + \alpha I(t) - (\mu + \rho + \delta)P(t), \\
\frac{dV(t)}{dt} &= \rho P(t) - cV(t).
\end{aligned}$$

Let $b(t)$ be the number of infected cells newly produced in the linear phase:

$$b(t) := \beta T_0 V(t).$$

Applying the variation of constants formula, we have:

$$\begin{aligned}
I(t) &= I(0)\exp(-\delta t) + \int_0^t \exp\big(-\delta(t-s)\big)\, b(s)ds\,, \\
P(t) &= P(0)\exp(-(\rho+\mu+\delta)t) + \int_0^t \exp\big(-(\rho+\mu+\delta)(t-s)\big)\big(\zeta b(s) + \alpha I(s)\big)\, ds\,, \\
V(t) &= V(0)\exp(-ct) + \int_0^t \exp\big(-c(t-s)\big)\, \rho P(s)ds\,.
\end{aligned}$$

with initial values of $I(0) = 1$, $P(0) = \zeta$, and $V(0) = 0$. This leads to

$$\begin{aligned}
I(t) &= \exp(-\delta t) + \int_0^t \exp\big(-\delta(t-s)\big)\, b(s)ds\,, \\
P(t) &= \zeta\exp(-(\rho+\mu+\delta)t) + \int_0^t \exp\big(-(\rho+\mu+\delta)(t-s)\big)\big(\zeta b(s) + \alpha I(s)\big)\, ds\,, \\
V(t) &= \int_0^t \exp\big(-c(t-s)\big)\, \rho P(s)ds.
\end{aligned}$$

Inserting $P(t)$ and $I(t)$ into $V(t)$, we have:

$$V(t) = \int_0^t \exp\big(-c(t-s)\big)\,\rho\Big\{\zeta \exp(-(\rho+\mu+\delta)s) + \int_0^s \exp\big(-(\rho+\mu+\delta)(s-r)\big)\Big(\zeta b(r) + \alpha \exp(-\delta r) + \alpha \int_0^r \exp\big(-\delta(r-u)\big)\, b(u)du\Big)dr\Big\}ds.$$

Exchanging the order of integrals, we can arrive at the following renewal equation:

$$b(t) = \Psi(t) + \int_0^t \Psi(s) b(t-s) ds,$$

where $\Psi(t)$ is given by:

$$\Psi(t) := \psi_1(t) + \psi_2(t).$$

Here, $\psi_1(t)$ and $\psi_2(t)$ are given by:

$$\psi_1(t) = \int_0^t \zeta\rho\beta T_0 \exp(-cr) \exp\big(-(\mu+\rho+\delta)(t-r)\big)\, dr\,,$$
$$\psi_2(t) = \int_0^t \int_0^r \alpha\rho\,\beta T_0 \exp(-cu) \exp\big(-(\mu+\rho+\delta)(r-u)\big) \exp\big(-\delta(t-r)\big)\, du\, dr\,.$$

From the general theory of the basic reproduction number [53], R_0 for the reproduction of infected cells is given by:

$$\begin{aligned} R_0 &= \int_0^\infty \Psi(t)dt = \int_0^\infty \big(\psi_1(t) + \psi_2(t)\big)dt \\ &= \frac{\beta\rho T_0 \zeta}{c(\mu+\rho+\delta)} + \frac{\beta\rho\alpha T_0}{c\delta(\mu+\rho+\delta)} \\ &= R_v + R_r \end{aligned}$$

Interestingly, R_0 is divided by the two renewal processes, R_v and R_r, denoting the reproduction number for infected cells mediated by the viral RNA brought by the entered virion (entry virus-derived RNA, ζ) and the newly replicated intracellular viral RNA (replicated viral RNA), respectively (**Fig. 2-1**). Here the basic reproduction number explains the average number of newly infected cells based on the dynamics of the total amount of intracellular viral RNA, which corresponds to $P(t)$ [i.e., Eq. (9)] in the transformed ODE model, instead of the dynamics of the individual amount of intracellular viral RNA in

the original PDE model [50]. Note that the lifecycles of both extracellular viral and total intracellular viral RNA are explicitly considered in my ODE model, and the viruses are formulated from the viral RNAs.

Existence of steady states of transformed ODE

As has been well investigated for many ODE models, the basic reproduction number might determine the threshold phenomena behind mathematical models, especially for the existence of steady states and their stability. Here, I calculated the steady states of the transformed ODE model [i.e., Eqs. (7–10)]. There are two steady states, that is, $E_0 = (T_0, 0, 0, 0)$, the virus-free equilibrium, and $E_+ = (T_+, I_+, P_+, V_+)$, the virus-infection equilibrium, which are satisfied with the following equations:

$$0 = s - dT_+ - \beta T_+ V_+, 0 = \beta T_+ V_+ - \delta I_+, 0 = \zeta\beta T_+ V_+ + \alpha I_+ - (\mu + \rho + \delta)P_+,$$

$$0 = \rho P_+ - cV_+,$$

where

$$T_+ = \frac{c\delta(\mu + \rho + \delta)}{\beta\rho(\alpha + \zeta\delta)}, I_+ = \frac{s}{\delta}\left(1 - \frac{1}{R_0}\right), P_+ = \frac{cd}{\beta\rho}(R_0 - 1), V_+ = \frac{d}{\beta}(R_0 - 1).$$

Note that E_0 always exists in $\mathbb{R}^4_+$ (i.e., $E_0 \in \mathbb{R}^4_+$) where $\mathbb{R}^4_+ = \{(T, I, P, V)^\intercal \in \mathbb{R}^4 : T \geq 0, I \geq 0, P \geq 0, V \geq 0\}$. On the other hand, E_+ exists in $\mathbb{R}^4_+$ (i.e., $E_+ \in \mathrm{int}\mathbb{R}^4_+$) if and only if $R_0 \geq 1$, where $\mathrm{int}\mathbb{R}^4_+ = \{(T, I, P, V)^\intercal \in \mathbb{R}^4 : T > 0, I > 0, P > 0, V > 0\}$.

Stability of steady states of transformed ODE

Although comprehensive stability analysis for PDE is usually mathematically difficult and often limited to local asymptotically stable (LAS) [17], exploiting standard approaches for mathematical analysis on the ODE model, I next showed the global stability of the steady states of transformed ODE [i.e., Eqs. (7-10)].

Let us consider the following Lyapunov function:

$$L_0\big(T(t), I(t), P(t), V(t)\big) \coloneqq \left(\zeta + \frac{\alpha}{\delta}\right) T_0 g\left(\frac{T(t)}{T_0}\right) + \frac{\alpha}{\delta} I(t) + P(t) + \frac{\mu + \rho + \delta}{\rho} V(t),$$

where $g(x) \coloneqq x - 1 - \log x$ is defined for $x > 0$. Note that $g(x) \geq 0$ for $x > 0$ and $g(x) = 0$ at $x = 1$, implying that the Lyapunov function, $L_0(t)$, is always non-negative in $\mathbb{R}^4_+$, but equal to 0 at E_0. It is also clear that:

$$\frac{d}{dt}\left(x_* g\left(\frac{x(t)}{x_*}\right)\right) = \frac{d}{dt}\left(x(t) - x_* - x_* \log\frac{x(t)}{x_*}\right) = \frac{dx(t)}{dt} - \frac{x_*}{x(t)} \cdot \frac{dx(t)}{dt} = \left(1 - \frac{x_*}{x(t)}\right)\frac{dx(t)}{dt}$$

for any constant x_*. In addition, we have:

$$\begin{aligned}
\frac{d}{dt}\left(\left(\zeta + \frac{\alpha}{\delta}\right) T_0 g\left(\frac{T(t)}{T_0}\right)\right) &= \left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_0}{T(t)}\right)\left(s - dT(t) - \beta T(t)V(t)\right) \\
&= \left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_0}{T(t)}\right)\left(dT_0\left(1 - \frac{T(t)}{T_0}\right) - \beta T(t)V(t)\right) \\
&= \left(\zeta + \frac{\alpha}{\delta}\right)\left\{dT_0\left(2 - \frac{T_0}{T(t)} - \frac{T(t)}{T_0}\right) - \beta T(t)V(t)\left(1 - \frac{T_0}{T(t)}\right)\right\}.
\end{aligned}$$

Then, the following relation can be derived:

$$\begin{aligned}
\frac{dL_0(t)}{dt} &= \left(\zeta + \frac{\alpha}{\delta}\right) dT_0\left(2 - \frac{T_0}{T(t)} - \frac{T(t)}{T_0}\right) - \left(\zeta + \frac{\alpha}{\delta}\right)\beta T(t)V(t)\left(1 - \frac{T_0}{T(t)}\right) + \frac{\alpha}{\delta}\left(\beta T(t)V(t) - \delta I(t)\right) \\
&\quad + \left(\zeta\beta T(t)V(t) + \alpha I(t) - (\mu + \rho + \delta)P(t)\right) + \frac{\mu + \rho + \delta}{\rho}\left(\rho P(t) - cV(t)\right) \\
&= \left(\zeta + \frac{\alpha}{\delta}\right) dT_0\left(-g\left(\frac{T_0}{T(t)}\right) - g\left(\frac{T(t)}{T_0}\right)\right) + \left\{\left(\zeta + \frac{\alpha}{\delta}\right)\beta T_0 - \frac{c(\mu + \rho + \delta)}{\rho}\right\} V(t) \\
&= \left(\zeta + \frac{\alpha}{\delta}\right) dT_0\left(-g\left(\frac{T_0}{T(t)}\right) - g\left(\frac{T(t)}{T_0}\right)\right) + \frac{c(\mu + \rho + \delta)(R_0 - 1)V(t)}{\rho}.
\end{aligned}$$

Therefore, I concluded that $dL_0(t)/dt \leq 0$ if $R_0 \leq 1$. In particular we can see that $dL_0(t)/dt = 0$ only if $T(t) = T_0$. Substituting $T(t) = T_0$ into both sides of Eq. (7), I have $0 = -\beta T_0 V(t)$, and hence $V(t) = 0$. If $V(t) = 0$, then $P(t) = 0$ follows from Eq. (10), and thus $I(t) = 0$ follows from Eq. (9). Consequently, I derived that $dL_0(t)/dt = 0$ only if the solution is in virus-free equilibrium, E_0. Hence, by applying Lyapunov–LaSalle's invariance principle, all of the trajectories of the transformed ODE [i.e., Eqs. (7–10)] converge to E_0, that is, E_0 is globally asymptotically stable (i.e., GAS) if $R_0 \leq 1$.

Next, I defined the following Lyapunov function:

$$L_+\big(T(t), I(t), P(t), V(t)\big)$$

$$:= \left(\zeta + \frac{\alpha}{\delta}\right) T_+ g\left(\frac{T(t)}{T_+}\right) + \frac{\alpha}{\delta} I_+ g\left(\frac{I(t)}{I_+}\right) + P_+ g\left(\frac{P(t)}{P_+}\right) + \frac{\mu + \rho + \delta}{\rho} V_+ g\left(\frac{V(t)}{V_+}\right).$$

We have:

$$\frac{dL_+(t)}{dt} = \left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_+}{T(t)}\right)\frac{dT(t)}{dt} + \frac{\alpha}{\delta}\left(1 - \frac{I_+}{I(t)}\right)\frac{dI(t)}{dt} + \left(1 - \frac{P_+}{P(t)}\right)\frac{dP(t)}{dt}$$

$$+ \frac{\mu + \rho + \delta}{\rho}\left(1 - \frac{V_+}{V(t)}\right)\frac{dV(t)}{dt}.$$

The first term could be evaluated as follows:

$$\left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_+}{T(t)}\right)\frac{dT(t)}{dt} = \left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_+}{T(t)}\right)\big(s - dT(t) - \beta T(t)V(t)\big)$$

$$= \left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_+}{T(t)}\right)\big(dT_+ + \beta T_+ V_+ - dT(t) - \beta T(t)V(t)\big)$$

$$= \left(\zeta + \frac{\alpha}{\delta}\right)\left(1 - \frac{T_+}{T(t)}\right)\left\{dT_+\left(1 - \frac{T(t)}{T_+}\right) + \beta T_+ V_+\left(1 - \frac{T(t)V(t)}{T_+V_+}\right)\right\}$$

$$= \left(\zeta + \frac{\alpha}{\delta}\right)\left\{dT_+\left(1 - \frac{T_+}{T(t)}\right)\left(1 - \frac{T(t)}{T_+}\right) + \beta T_+ V_+\left(1 - \frac{T_+}{T(t)}\right)\left(1 - \frac{T(t)V(t)}{T_+V_+}\right)\right\}$$

$$= \left(\zeta + \frac{\alpha}{\delta}\right)\left\{dT_+\left(2 - \frac{T_+}{T(t)} - \frac{T(t)}{T_+}\right) + \beta T_+ V_+\left(1 - \frac{T_+}{T(t)} - \frac{T(t)V(t)}{T_+V_+} + \frac{V(t)}{V_+}\right)\right\}$$

$$\leq \left(\zeta + \frac{\alpha}{\delta}\right)\beta T_+ V_+\left(1 - \frac{T_+}{T(t)} - \frac{T(t)V(t)}{T_+V_+} + \frac{V(t)}{V_+}\right)$$

$$= \left(\zeta + \frac{\alpha}{\delta}\right)\beta T_+ V_+\left[-g\left(\frac{T_+}{T(t)}\right) - g\left(\frac{T(t)V(t)}{T_+V_+}\right) + g\left(\frac{V(t)}{V_+}\right)\right].$$

In addition, the second, third, and fourth terms are rewritten as follows:

$$\frac{\alpha}{\delta}\left(1-\frac{I_+}{I(t)}\right)\frac{dI(t)}{dt}=\frac{\alpha}{\delta}\left(1-\frac{I_+}{I(t)}\right)\left(\beta T(t)V(t)-\delta I(t)\right)-=\frac{\alpha}{\delta}\left(1-\frac{I_+}{I(t)}\right)\left(\beta T(t)V(t)-\delta I_+\cdot\frac{I(t)}{I_+}\right)$$

$$=\frac{\alpha}{\delta}\left(1-\frac{I_+}{I(t)}\right)\left(\beta T(t)V(t)-\beta T_+V_+\frac{I(t)}{I_+}\right)=\frac{\alpha}{\delta}\beta T_+V_+\left(1-\frac{I_+}{I(t)}\right)\left(\frac{T(t)V(t)}{T_+V_+}-\frac{I(t)}{I_+}\right)$$

$$=\frac{\alpha}{\delta}\beta T_+V_+\left(\frac{T(t)V(t)}{T_+V_+}-\frac{I(t)}{I_+}-\frac{T(t)I_+V(t)}{T_+I(t)V_+}+1\right)$$

$$=\frac{\alpha}{\delta}\beta T_+V_+\left[g\left(\frac{T(t)V(t)}{T_+V_+}\right)-g\left(\frac{I(t)}{I_+}\right)-g\left(\frac{T(t)I_+V(t)}{T_+I(t)V_+}\right)\right],$$

and

$$\left(1-\frac{P_+}{P(t)}\right)\frac{dP(t)}{dt}=\left(1-\frac{P_+}{P(t)}\right)\left(\zeta\beta T(t)V(t)+\alpha I(t)-(\mu+\rho+\delta)P(t)\right)$$

$$=\left(1-\frac{P_+}{P(t)}\right)\left(\zeta\beta T(t)V(t)+\alpha I(t)-(\mu+\rho+\delta)P_+\cdot\frac{P(t)}{P_+}\right)$$

$$=\left(1-\frac{P_+}{P(t)}\right)\left(\zeta\beta T(t)V(t)+\alpha I(t)-(\zeta\beta T_+V_++\alpha I_+)\frac{P(t)}{P_+}\right)$$

$$=\left(1-\frac{P_+}{P(t)}\right)\left(\zeta\beta T(t)V(t)+\frac{\alpha}{\delta}\delta I_+\frac{I(t)}{I_+}-\zeta\beta T_+V_+\frac{P(t)}{P_+}-\frac{\alpha}{\delta}\delta I_+\frac{P(t)}{P_+}\right)$$

$$=\left(1-\frac{P_+}{P(t)}\right)\left(\zeta\beta T(t)V(t)+\frac{\alpha}{\delta}\beta T_+V_+\frac{I(t)}{I_+}-\zeta\beta T_+V_+\frac{P(t)}{P_+}-\frac{\alpha}{\delta}\beta T_+V_+\frac{P(t)}{P_+}\right)$$

$$=\left(1-\frac{P_+}{P(t)}\right)\left\{\zeta\beta T_+V_+\left(\frac{T(t)V(t)}{T_+V_+}-\frac{P(t)}{P_+}\right)+\frac{\alpha}{\delta}\beta T_+V_+\left(\frac{I(t)}{I_+}-\frac{P(t)}{P_+}\right)\right\}$$

$$=\zeta\beta T_+V_+\left(\frac{T(t)V(t)}{T_+V_+}-\frac{P(t)}{P_+}-\frac{T(t)P_+V(t)}{T_+P(t)V_+}+1\right)$$

$$+\frac{\alpha}{\delta}\beta T_+V_+\left(\frac{I(t)}{I_+}-\frac{P(t)}{P_+}-\frac{I(t)P_+}{I_+P(t)}+1\right)$$

$$=\zeta\beta T_+V_+\left[g\left(\frac{T(t)V(t)}{T_+V_+}\right)-g\left(\frac{P(t)}{P_+}\right)-g\left(\frac{T(t)P_+V(t)}{T_+P(t)V_+}\right)\right]$$

$$+\frac{\alpha}{\delta}\beta T_+V_+\left[g\left(\frac{I(t)}{I_+}\right)-g\left(\frac{P(t)}{P_+}\right)-g\left(\frac{I(t)P_+}{I_+P(t)}\right)\right],$$

and

$$\frac{\mu+\rho+\delta}{\rho}\left(1-\frac{V_+}{V(t)}\right)\frac{dV(t)}{dt}=\frac{\mu+\rho+\delta}{\rho}\left(1-\frac{V_+}{V(t)}\right)\left(\rho P(t)-cV(t)\right)$$

$$=\frac{\mu+\rho+\delta}{\rho}\left(1-\frac{V_+}{V(t)}\right)\left(\frac{\rho}{\mu+\rho+\delta}\frac{P(t)}{P_+}(\mu+\rho+\delta)P_+-\frac{V(t)}{V_+}cV_+\right)$$

$$=\frac{\mu+\rho+\delta}{\rho}\left(1-\frac{V_+}{V(t)}\right)\left(\frac{\rho}{\mu+\rho+\delta}\frac{P(t)}{P_+}(\mu+\rho+\delta)P_+-\frac{V(t)}{V_+}\rho P_+\right)$$

$$=\frac{\mu+\rho+\delta}{\rho}\left(1-\frac{V_+}{V(t)}\right)\left(\frac{\rho}{\mu+\rho+\delta}\frac{P(t)}{P_+}(\mu+\rho+\delta)P_+\right.$$

$$\left.-\frac{V(t)}{V_+}\frac{\rho}{\mu+\rho+\delta}(\mu+\rho+\delta)P_+\right)$$

$$=\frac{\mu+\rho+\delta}{\rho}\frac{\rho}{\mu+\rho+\delta}(\mu+\rho+\delta)P_+\left(1-\frac{V_+}{V(t)}\right)\left(\frac{P(t)}{P_+}-\frac{V(t)}{V_+}\right)$$

$$=(\zeta\beta T_+V_++\alpha I_+)\left(1-\frac{V_+}{V(t)}\right)\left(\frac{P(t)}{P_+}-\frac{V(t)}{V_+}\right)$$

$$=\left(\zeta\beta T_+V_++\frac{\alpha}{\delta}\delta I_+\right)\left(1-\frac{V_+}{V(t)}\right)\left(\frac{P(t)}{P_+}-\frac{V(t)}{V_+}\right)$$

$$=\left(\zeta\beta T_+V_++\frac{\alpha}{\delta}\beta T_+V_+\right)\left(1-\frac{V_+}{V(t)}\right)\left(\frac{P(t)}{P_+}-\frac{V(t)}{V_+}\right)$$

$$=\left(\zeta\beta T_+V_++\frac{\alpha}{\delta}\beta T_+V_+\right)\left(\frac{P(t)}{P_+}-\frac{V(t)}{V_+}-\frac{P(t)V_+}{P_+V(t)}+1\right)$$

$$=\left(\zeta\beta T_+V_++\frac{\alpha}{\delta}\beta T_+V_+\right)\left[g\left(\frac{P(t)}{P_+}\right)-g\left(\frac{V(t)}{V_+}\right)-g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$=\zeta\beta T_+V_+\left[g\left(\frac{P(t)}{P_+}\right)-g\left(\frac{V(t)}{V_+}\right)-g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$+\frac{\alpha}{\delta}\beta T_+V_+\left[g\left(\frac{P(t)}{P_+}\right)-g\left(\frac{V(t)}{V_+}\right)-g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right],$$

respectively. Taken together the four rewritten terms, we get evaluation as follows:

$$\frac{dL_+(t)}{dt} \le \left(\zeta + \frac{\alpha}{\delta}\right)\beta T_+ V_+ \left[-g\left(\frac{T_+}{T(t)}\right) - g\left(\frac{T(t)V(t)}{T_+V_+}\right) + g\left(\frac{V(t)}{V_+}\right)\right]$$

$$+ \frac{\alpha}{\delta}\beta T_+ V_+ \left[g\left(\frac{T(t)V(t)}{T_+V_+}\right) - g\left(\frac{I(t)}{I_+}\right) - g\left(\frac{T(t)I_+V(t)}{T_+I(t)V_+}\right)\right]$$

$$+ \zeta\beta T_+ V_+ \left[g\left(\frac{T(t)V(t)}{T_+V_+}\right) - g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{T(t)P_+V(t)}{T_+P(t)V_+}\right)\right]$$

$$+ \frac{\alpha}{\delta}\beta T_+ V_+ \left[g\left(\frac{I(t)}{I_+}\right) - g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{I(t)P_+}{I_+P(t)}\right)\right]$$

$$+ \zeta\beta T_+ V_+ \left[g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{V(t)}{V_+}\right) - g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$+ \frac{\alpha}{\delta}\beta T_+ V_+ \left[g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{V(t)}{V_+}\right) - g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$= \zeta\beta T_+ V_+ \left[-g\left(\frac{T_+}{T(t)}\right) - g\left(\frac{T(t)V(t)}{T_+V_+}\right) + g\left(\frac{V(t)}{V_+}\right) + g\left(\frac{T(t)V(t)}{T_+V_+}\right) - g\left(\frac{P(t)}{P_+}\right)\right.$$

$$\left. - g\left(\frac{T(t)P_+V(t)}{T_+P(t)V_+}\right) + g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{V(t)}{V_+}\right) - g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$+ \frac{\alpha}{\delta}\beta T_+ V_+ \left[-g\left(\frac{T_+}{T(t)}\right) - g\left(\frac{T(t)V(t)}{T_+V_+}\right) + g\left(\frac{V(t)}{V_+}\right) + g\left(\frac{T(t)V(t)}{T_+V_+}\right) - g\left(\frac{I(t)}{I_+}\right)\right.$$

$$\left. - g\left(\frac{T(t)I_+V(t)}{T_+I(t)V_+}\right) + g\left(\frac{I(t)}{I_+}\right) - g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{I(t)P_+}{I_+P(t)}\right) + g\left(\frac{P(t)}{P_+}\right) - g\left(\frac{V(t)}{V_+}\right)\right.$$

$$\left. - g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$= \zeta\beta T_+ V_+ \left[-g\left(\frac{T_+}{T(t)}\right) - g\left(\frac{T(t)P_+V(t)}{T_+P(t)V_+}\right) - g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right]$$

$$+ \frac{\alpha}{\delta}\beta T_+ V_+ \left[-g\left(\frac{T_+}{T(t)}\right) - g\left(\frac{T(t)I_+V(t)}{T_+I(t)V_+}\right) - g\left(\frac{I(t)P_+}{I_+P(t)}\right) - g\left(\frac{P(t)V_+}{P_+V(t)}\right)\right] \le 0.$$

As per this derivation, $dL_+(t)/dt = 0$ holds only if $T(t) = T_+$. Substituting $T(t) = T_+$ into both sides of Eq. (7), we have $0 = s - dT_+ - \beta T_+ V(t)$. Since the virus-infection equilibrium, E_+, is unique, this equality implies $V(t) = V_+$. Then, substituting $V(t) = V_+$ into both sides of Eq. (10), we

have $P(t) = P_+$. By substituting $T(t) = T_+$, $V(t) = V_+$, and $P(t) = P_+$ into Eq. (9), we have $I(t) = I_+$. Consequently, we can revealed that $dL_+(t)/dt = 0$ only if the solution is in E_+. Hence, by Lyapunov–LaSalle's invariance principle, We can concluded that E_+ is GAS in $\text{int}\mathbb{R}^4_+$ whenever it exists (i.e., $R_0 > 1$)..

Discussion

The first mathematical model of viral dynamics formulated by a linear equation was applied to the analysis of clinical datasets of cases under human immunodeficiency virus type I (HIV-1) monotherapy [1, 54]. Then, the basic model of viral dynamics and its revised versions as described by ODEs were well parameterized for infections by several viruses using datasets for HIV-1, HCV, Ebola virus, and influenza virus [2, 4-6, 21, 55-57]. In contrast, an age-structured PDE model of viral dynamics was first studied for HIV-1 infection [47]. This model was extended to consider the effect of antiviral therapies [42]. Stability analysis for age-structured PDE models is generally rather difficult, especially for, analysis for the virus-infection equilibria, were restricted to LAS [17]. To show GAS of the virus-infection equilibrium of age-structured PDE systems, we not only have to construct a suitable Lyapunov function, but also have to show the existence of a compact persistent attractor in which such a Lyapunov function is well defined. This usually requires some long proofs and calculations on the necessary mathematical arguments, including the relative compactness (asymptotic smoothness) of the solution orbit, the existence of a compact attractor that consists of total trajectories, and the uniform persistence of the system [40, 58]. For example, by constructing suitable Lyapunov functions, GAS of the virus-infection equilibrium was investigated [43]. However, in that previous study [43], analysis of the relative compactness of the solution orbit was omitted, and it was completed for a more general model with a nonlinear infection rate [44]. These processes make the global stability analysis for age-structured PDE models difficult, and some methods of reducing such a PDE system to an ODE system are often more valid [50].

In my recent report [50], I transformed the original PDE model of HCV infection [Eqs. (1–4)] into an ODE model [Eqs. (7–10)]. Without any assumptions, the ODE model and the original PDE model are mathematically identical. In the work (Guedj et al. 2013), they solved approximately the PDE model about the compartment of concentration of virus [i.e., $V(t)$ in Eq. (4)]. The solution includes fewer parameters than the PDE model, this means that it enables us to easily estimate other parameters with smaller datasets. While this is merit of the approximation, it does not accept any other data but the concentration of virus. And more, even if we can get enough dataset to estimate parameters with very high accuracy, the approximation remains some error depends on the effectiveness of antiviral treatments. In contrast, compared with the approximate solution, my ODE model includes full of parameters and requires some rich dataset for parameter estimation. However, the ODE model can accept any other data, so we can answer the request by giving additional data from in vitro experiment for example time series of the amount of virus RNA [i.e., $R(a)$ in Eq. (3)]. Note that my transformed ODE describes the total amount of intracellular viral RNA dynamics [i.e., $P(t)$ in Eq. (9)], while the original PDE model describes the individual amount of intracellular viral RNA dynamics [i.e., $R(t)$ in Eq. (3)]. In this paper, I derived the basic reproduction number, R_0, from the ODE model. The basic reproduction number explains the average number of newly infected cells produced from any one infected cell based on the dynamics of the total amount of intracellular viral RNA (**Fig. 2-1**), which provides the threshold of the mathematical structure of the ODE system. In addition, exploiting standard approaches for mathematical analysis on the ODE model, I proved GAS of the steady states of the transformed ODE: E_0 always exists in $\mathbb{R}_+^4$ and GAS if $R_0 \leq 1$, and E_+ is GAS in int$\mathbb{R}_+^4$ if $R_0 > 1$. Thus, I showed that the dynamic behavior of the multiscale model is determined by R_0.

Although we have a limitation that there are more parameters in the transformed ODE model compared with approximate solutions [14, 16], in addition to these mathematical advantages, the ODE model makes a significant contribution work effectively in “data-rich cases” like in vitro experimental data analysis previously [30]. For example, once we could estimate all parameters in the transformed

ODE model, since the ODE model includes all parameters in the original PDE model, we could reconstruct the virus infection dynamics including “age information” which cannot be obtained by conventional experimental approach. These novel insights for the age-structured multiscale model provide us further understanding for several viral infections including HCV infection.

Abbreviations

HCV: Hepatitis C Virus; ODE: Ordinary Differential Equation; PDE: Partial Differential Equation, LAS: Local Asymptotically stable, GAS: Global Asymptotically stable

Figure

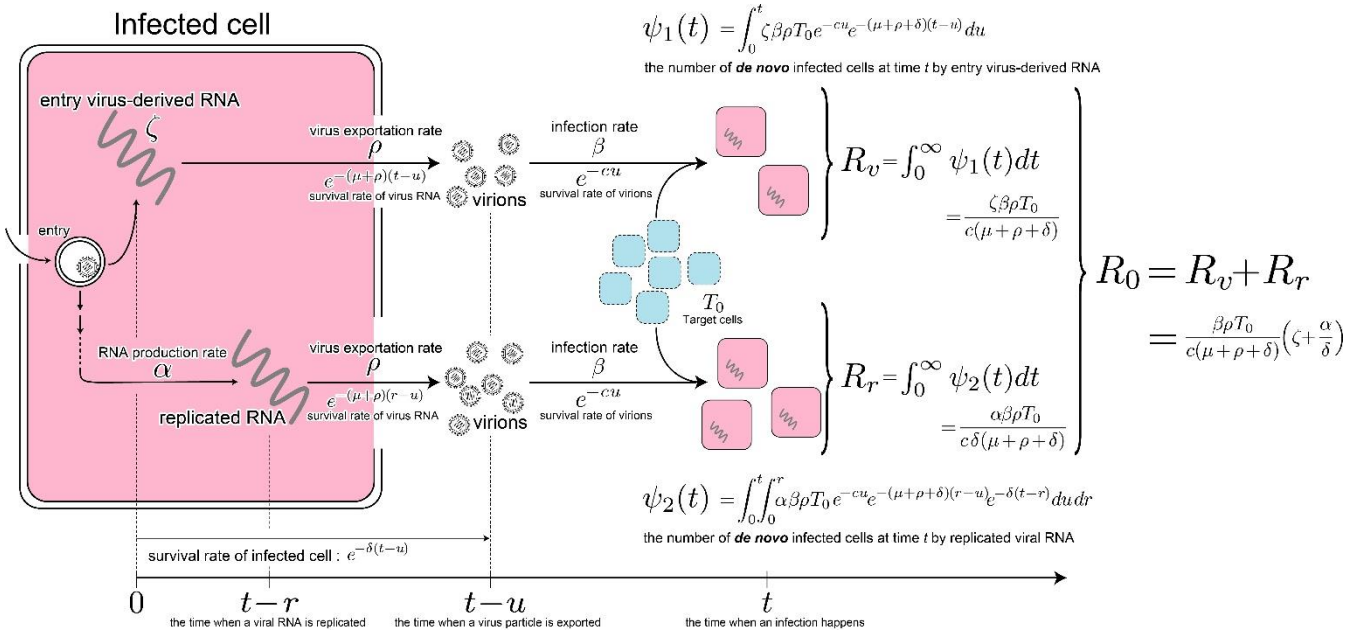

Figure 2-1 | Biological interpretation of basic reproduction number. Instead of the dynamics of the individual amount of intracellular viral RNA in the original PDE model, the dynamics of the total amount of intracellular viral RNA is described in the transformed ODE model, and the viruses are formulated from the viral RNAs. The basic reproduction number, R_0, derived from the ODE model is divided by the two renewal processes: R_v is the reproduction number for infected cells mediated by the viral RNA brought by the entered virion (entry virus-derived RNA, ζ) and R_r is the newly replicated intracellular viral RNA (replicated viral RNA).

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