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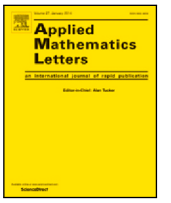

Global dynamics of a multiscale model for hepatitis C virus infection ☆

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ABSTRACT

Hepatitis C virus (HCV) can establish infection via two distinct modes: virus-to-cell infection and cell-to-cell transmission. These infections prompt the activation of two types of adaptive immune responses: the cytotoxic T lymphocyte response and the antibody response. In this paper, we study HCV dynamics by developing a multiscale model that incorporates both modes of infection as well as the two types of immune responses. We derive both the basic reproduction number of virus and four immune reproduction numbers for the model. We identify five equilibria, the existence of which depends on the values of basic reproduction number of virus and the immune reproduction numbers. We also establish the global asymptotic stability of the equilibria by employing Lyapunov functions, which further underscores the profound impact of the aforementioned reproduction numbers on the model's overall stability.

1. Introduction

Hepatitis C is a condition characterized by liver inflammation due to the presence of the hepatitis C virus (HCV). This virus can lead to both acute and chronic hepatitis, with outcomes ranging from mild illness to severe, lifelong conditions including liver cirrhosis and cancer. According to the World Health Organization (WHO), in 2019 alone, approximately 290,000 people succumbed to hepatitis C, primarily due to complications such as cirrhosis and hepatocellular carcinoma. Currently, there exists no effective vaccine against hepatitis C. The virus is prevalent globally, with an estimated 58 million individuals living with chronic HCV infection. Each year witnesses around 1.5 million new infections, and there are roughly 3.2 million adolescents and children affected by chronic hepatitis C. The Eastern Mediterranean and the European regions bear the highest burden of this disease, with approximately 12 million chronically infected in each region [1].

Mathematical modeling plays a crucial role in studying the transmission of infectious diseases, including HCV infection [2–6]. It enables us to comprehend the dynamics of infection and offers novel theoretical strategies for disease prevention and treatment. In the work by Rong et al. [7], a multiscale HCV model was developed, encompassing both intracellular viral RNA replication within

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infected cells and extracellular viral infection of cells, formulated as follows:

$$\begin{cases} \dfrac{dT(t)}{dt} = \Lambda - \beta T(t)V(t) - \sigma T(t), \\ \dfrac{\partial}{\partial t}I(a,t) + \dfrac{\partial}{\partial a}I(a,t) = -\delta(a)I(a,t), \\ I(0,t) = \beta T(t)V(t),\ I(a,0) = I_0(a), \\ \dfrac{\partial}{\partial t}R(a,t) + \dfrac{\partial}{\partial a}R(a,t) = \alpha(a) - (\rho(a)+\mu(a))R(a,t), \\ R(0,t) = 1,\ R(a,0) = R_0(a), \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty \rho(a)R(a,t)I(a,t)da - cV(t), \end{cases} \tag{1.1}$$

where, the variable $T(t)$ represents the number of uninfected hepatocytes at time t, while $V(t)$ denotes the number of free viruses at the same time point. Additionally, $I(t,a)$ and $R(t,a)$ represent the number of infected cells and intracellular viral RNA within an infected cell at time t with age of infection a, respectively. The production rate of uninfected hepatocytes is assumed to be Λ, while they become infected by viruses at a rate of β and experience mortality at a rate of σ. Parameters $\alpha(a)$, $\rho(a)$, and $\mu(a)$ correspond to intracellular viral RNA production, degradation, and assembly/secretion, respectively, and all of these parameters can depend on age. Infected cells undergo cell death at a rate of $\delta(a)$. Viruses are cleared at a rate of c.

Using the method of model aggregation and treating $\alpha(a)$, $\rho(a)$, $\mu(a)$ and $\delta(a)$ as constants, Kitagawa *et al.* [8] showed that the combined ODE and PDE model (1.1) can be transformed into the following equivalent ODE model, which is easier for mathematical analysis and data fitting.

$$\begin{cases} \dfrac{dT(t)}{dt} = \Lambda - \beta T(t)V(t) - \sigma T(t), \\ \dfrac{dN(t)}{dt} = \beta T(t)V(t) - \delta N(t), \\ \dfrac{dH(t)}{dt} = \beta T(t)V(t) + \alpha N(t) - (\mu+\rho+\delta)H(t), \\ \dfrac{dV(t)}{dt} = \rho H(t) - cV(t). \end{cases} \tag{1.2}$$

The total number of infected cells and the cumulative amount of viral RNA within these cells are denoted as $N(t) = \int_0^\infty I(a,t)da$ and $H(t) = \int_0^\infty R(a,t)I(a,t)da$, respectively. The other parameters have the same biological meaning as described in model (1.1). Kitagawa et al. [9] also used numerical simulations to verify the consistency between (1.2) and (1.1).

Infection with HCV can occur not only through direct cell-free infection but also through the transfer from infected cells to neighboring uninfected cells via the formation of a virological synapse [10]. Direct cell-to-cell transfer is faster and more efficient than cell-free infection, because it obviates rate-limiting early steps in the virus life cycle, such as virion attachment [10]. Understanding the kinetics of viral infection progression in the presence of immune responses is also crucial. After viruses enter the human body, antibodies are stimulated by antigens and released from B cells to neutralize viral particles [5]. In addition to the antibody immune response, Cytotoxic T Lymphocyte (CTL) immune response is also critical. CTLs play an important role in defending against viral infections by targeting and attacking infected cells [11]. In this paper, we will develop a multiscale model, based on (1.2), by considering both cell-free infection and cell-to-cell transmission, as well as the two types of adaptive immune responses. The model is given by the following differential equation system

$$\begin{cases} \dfrac{dT(t)}{dt} = \Lambda - \sigma T(t) - \beta T(t)V(t) - kT(t)N(t), \\ \dfrac{dN(t)}{dt} = \beta T(t)V(t) + kT(t)N(t) - \delta N(t) - \gamma Z(t)N(t), \\ \dfrac{dH(t)}{dt} = \beta T(t)V(t) + kT(t)N(t) + \alpha N(t) - (\mu+\rho+\delta)H(t), \\ \dfrac{dV(t)}{dt} = \rho H(t) - cV(t) - qV(t)W(t), \\ \dfrac{dZ(t)}{dt} = uN(t)Z(t) - bZ(t), \\ \dfrac{dW(t)}{dt} = gV(t)W(t) - hW(t), \end{cases} \tag{1.3}$$

with initial condition $(T(0), N(0), H(0), V(0), Z(0), W(0)) \in \mathbb{R}^6_+$. In the model, the variable $Z(t)$ represents the quantity of CTL cells at time t. The CTL cells are stimulated by the infection to increase at a rate of u and decrease at a rate of b. The parameter γ represents the rate at which infected cells are killed by the CTL response. The variable $W(t)$ represents the level of antibodies at time t. Antibodies are generated at rate of g due to the infection and decay at a rate of h, where q represents the rate at which virus particles are neutralized by the antibodies. The parameter k is used to describe the cell-to-cell transmission.

2. Preliminary results

There exists a unique infection-free equilibrium $E_0 = (T_0, 0, 0, 0, 0, 0)$ for model (1.3), where $T_0 = \Lambda/\sigma$. The basic reproduction number of virus of model (1.3) is obtained by the next-generation matrix approach. We define matrices $\mathbb{F}$ and $\mathbb{V}$ as

$$\mathbb{F} = \begin{pmatrix} kT_0 & 0 & \beta T_0 \\ kT_0 & 0 & \beta T_0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad \mathbb{V} = \begin{pmatrix} \delta & 0 & 0 \\ -\alpha & \mu+\rho+\delta & 0 \\ 0 & -\rho & c \end{pmatrix},$$

which yield

$$\mathbb{F}\mathbb{V}^{-1} = \begin{pmatrix} \frac{kT_0}{\delta} + \frac{\alpha\rho\beta T_0}{\delta c(\mu+\rho+\delta)} & \frac{\rho\beta T_0}{c(\mu+\rho+\delta)} & \frac{\beta T_0}{c} \\ \frac{kT_0}{\delta} + \frac{\alpha\rho\beta T_0}{\delta c(\mu+\rho+\delta)} & \frac{\rho\beta T_0}{c(\mu+\rho+\delta)} & \frac{\beta T_0}{c} \\ 0 & 0 & 0 \end{pmatrix}.$$

By calculating the spectral radius of the matrix $\mathbb{F}\mathbb{V}^{-1}$, we derive the basic reproduction number of virus R_0 as follows

$$R_0 = \rho(\mathbb{F}\mathbb{V}^{-1}) = \frac{kT_0}{\delta} + \frac{\rho\beta(\alpha+\delta)T_0}{c\delta(\mu+\rho+\delta)}.$$

R_0 represents the number of virions (or infected cells) released by one virion (or one infected cell) in its lifespan in a fully susceptible environment for a within-host virus dynamic model [12]. To study the existence of all the equilibria, we also define the following four threshold parameters

$$R_{0W} = \frac{g\Lambda\rho(\alpha+\delta)}{hc\delta(\mu+\rho+\delta)}\left(1-\frac{1}{R_0}\right), \qquad R_{0Z} = \frac{\Lambda u}{b\delta}\left(1-\frac{1}{R_0}\right),$$
$$R_{1W} = \frac{gb\rho\alpha(gu\sigma+hu\beta+kbg)+gu\rho\Lambda(hu\beta+kbg)}{uhc(\mu+\rho+\delta)(gu\sigma+hu\beta+kbg)},$$
$$R_{1Z} = \frac{u\Lambda(hu\beta+kbg)}{\delta b(gu\sigma+hu\beta+kbg)},$$

where R_{0W} is the reproduction number for the antibody immune response, representing the average number of activated antibodies per successful virus infection without the CTL immune response. Similarly, R_{0Z} is the reproduction number for the CTL immune response, representing the average number of activated CTL immune cells per successful virus infection without the antibody response. R_{1W} and R_{1Z} are the competitive reproduction numbers for the antibody and CTL immune responses, respectively. R_{1W} represents the average number of antibodies activated by virus when the body establishes the CTL immune response during successful infection, while R_{1Z} represents the average number of CTL immune cells activated by infected cells when the body establishes the antibody immune response during successful infection.

Besides the infection-free equilibrium point E_0, in order to obtain the other equilibria of model (1.3), we let all the derivatives be zero and obtain the following four scenarios.

(i). When $Z, W = 0$ and $T, N, H, V \neq 0$, we can get the immune-free equilibrium

$$E_1 = (T_1, N_1, H_1, V_1, 0, 0) = \left(\frac{T_0}{R_0}, \frac{\Lambda}{\delta}\left(1-\frac{1}{R_0}\right), \frac{\Lambda(\delta+\alpha)}{\delta(\mu+\rho+\delta)}\left(1-\frac{1}{R_0}\right), \frac{\Lambda\rho(\delta+\alpha)}{c\delta(\mu+\rho+\delta)}\left(1-\frac{1}{R_0}\right), 0, 0\right).$$

Thus, model (1.3) has a unique immune-free equilibrium E_1 if and only if $R_0 > 1$.

(ii). When $Z = 0$ and $T, N, H, V, W \neq 0$, the infection equilibrium with only antibody response $E_2 = (T_2, N_2, H_2, V_2, 0, W_2)$ satisfies

$$T_2 = \frac{\delta(c+qW_2)(\mu+\rho+\delta)}{\rho\beta(\alpha+\delta)+k(c+qW_2)(\mu+\rho+\delta)}, \quad N_2 = \frac{h(c+qW_2)(\mu+\rho+\delta)}{g\rho(\alpha+\delta)}, \quad H_2 = \frac{h(c+qW_2)}{g\rho}, \quad V_2 = \frac{h}{g},$$

where W_2 is a positive root of $F_1(W)$ with

$$\begin{aligned} F_1(W) =& hk\delta q^2(\mu+\rho+\delta)^2W^2 + q(\mu+\rho+\delta)[2chk\delta(\mu+\rho+\delta)+\rho(g\delta\sigma+h\delta\beta-gk\Lambda)(\alpha+\delta)]W \\ &- ch\delta(\mu+\rho+\delta)[ck(\mu+\rho+\delta)+\rho\beta(\alpha+\delta)](R_{0W}-1). \end{aligned}$$

Note that $F_1(0) = -ch\delta(\mu+\rho+\delta)[ck(\mu+\rho+\delta)+\rho\beta(\alpha+\delta)](R_{0W}-1)$. By the Existence Theorem of Roots, $F_1(W) = 0$ has a unique positive root if and only if $R_{0W} > 1$.

(iii). When $W = 0$ and $T, N, H, V, Z \neq 0$, the infection equilibrium with only CTL response $E_3 = (T_3, N_3, H_3, V_3, Z_3, 0)$ satisfies

$$T_3 = \frac{c(\delta+\gamma Z_3)(\mu+\rho+\delta)}{\rho\beta(\alpha+\delta+\gamma Z_3)+ck(\mu+\rho+\delta)}, \quad N_3 = \frac{b}{u}, \quad H_3 = \frac{b(\alpha+\delta+\gamma Z_3)}{u(\mu+\rho+\delta)}, \quad V_3 = \frac{b\rho(\alpha+\delta+\gamma Z_3)}{cu(\mu+\rho+\delta)},$$

where Z_3 is a positive root of $F_2(Z)$ with

$$\begin{aligned} F_2(Z) =& b\rho\beta\gamma^2Z^2 + [c(\mu+\rho+\delta)(u\sigma+bk)+b\rho\beta(\alpha+2\delta)-u\rho\beta\Lambda]\gamma Z \\ &- b\delta[ck(\mu+\rho+\delta)+\rho\beta(\alpha+\delta)](R_{0Z}-1). \end{aligned}$$

Because $F_2(0) = -b\delta[ck(\mu+\rho+\delta)+\rho\beta(\alpha+\delta)](R_{0Z}-1)$, we know that $F_2(Z) = 0$ has a unique positive root if and only if $R_{0Z} > 1$.

(iv). When $T, N, H, V, Z, W \neq 0$, we can get the infection equilibrium with both CTL and antibody responses $E_4 = (T_4, N_4, H_4, V_4, Z_4, W_4)$ that satisfies

$$\begin{aligned}
T_4 &= \frac{(c+qW_4)(\delta+\gamma Z_4)(\mu+\rho+\delta)}{\rho\beta(\alpha+\delta+\gamma Z_4)+k(c+qW_4)(\mu+\rho+\delta)},\ N_4 = \frac{b}{u},\\
H_4 &= \frac{b(\alpha+\delta+\gamma Z_4)}{u(\mu+\rho+\delta)},\ V_4 = \frac{h}{g},\\
Z_4 &= \frac{\delta}{\gamma}\left[\frac{u\Lambda(hu\beta+kbg)}{\delta b(gu\sigma+hu\beta+kbg)}-1\right] = \frac{\delta}{\gamma}(R_{1Z}-1),\\
W_4 &= \frac{c}{q}\left[\frac{gb\rho\alpha(gu\sigma+hu\beta+kbg)+gu\rho\Lambda(hu\beta+kbg)}{uhc(\mu+\rho+\delta)(gu\sigma+hu\beta+kbg)}-1\right] = \frac{c}{q}(R_{1W}-1),
\end{aligned}$$

which means that model (1.3) has the infection equilibrium with CTL and antibody response $E_4 = (T_4, N_4, H_4, V_4, Z_4, W_4)$ when $R_{1Z} > 1$ and $R_{1W} > 1$.

The conditions for the existence of these equilibria of model (1.3) are summarized in the following result.

Proposition 2.1.

(i) If $R_0 < 1$, model (1.3) has a unique infection-free equilibrium E_0.
(ii) If $R_0 > 1$, besides E_0, model (1.3) has a unique immune-free equilibrium $E_1 = (T_1, N_1, H_1, V_1, 0, 0)$.
(iii) If $R_{0W} > 1$, besides E_0 and E_1, model (1.3) has a unique infection equilibrium with only antibody response $E_2 = (T_2, N_2, H_2, V_2, 0, W_2)$.
(iv) If $R_{0Z} > 1$, besides E_0 and E_1, model (1.3) has a unique infection equilibrium with only CTL response $E_3 = (T_3, N_3, H_3, V_3, Z_3, 0)$.
(v) If $R_{1Z} > 1$ and $R_{1W} > 1$, besides E_0, E_1, E_2 and E_3, model (1.3) has an infection equilibrium with both CTL and antibody responses $E_4 = (T_4, N_4, H_4, V_4, Z_4, W_4)$.

3. Global stability

To prove the global stability using the Lyapunov function, we employ the Volterra-type function $g(x) = x - 1 - \ln x$, which satisfies $g(x) \geq 0$ for $x > 0$ and $g(x) = 0$ if and only if $x = 1$ [13].

Theorem 3.1. *If $R_0 \leq 1$, then the infection-free equilibrium E_0 of model (1.3) is globally asymptotically stable.*

Proof. We define a Lyapunov function $L_0(t)$

$$\begin{aligned}
L_0(t) = {} & T_0 g\left(\frac{T(t)}{T_0}\right) + \left(1-\frac{\beta\rho T_0}{c(\mu+\rho+\delta)}\right)N(t) + \frac{\beta\rho T_0}{c(\mu+\rho+\delta)}H(t)\\
& + \frac{\beta T_0}{c}V(t) + \left(\frac{\gamma}{u}-\frac{\gamma\beta\rho T_0}{cu(\mu+\rho+\delta)}\right)Z(t) + \frac{q\beta T_0}{cg}W(t).
\end{aligned} \tag{3.1}$$

When $R_0 = \frac{kT_0}{\delta} + \frac{\rho\beta(\alpha+\delta)T_0}{c\delta(\mu+\rho+\delta)} \leq 1$, we have $\frac{\rho\beta T_0}{c(\mu+\rho+\delta)} < 1$. Using $T_0 = \Lambda/\sigma$ and calculating the derivative of $L_0(t)$ along the solution of (1.3), we get

$$\begin{aligned}
\frac{dL_0(t)}{dt} = {} & \left(1-\frac{T_0}{T(t)}\right)(\Lambda - \sigma T(t) - \beta T(t)V(t) - kT(t)N(t))\\
& + \left(1-\frac{\beta\rho T_0}{c(\mu+\rho+\delta)}\right)(\beta T(t)V(t) + kT(t)N(t) - \delta N(t) - \gamma Z(t)N(t))\\
& + \frac{\beta\rho T_0}{c(\mu+\rho+\delta)}(\beta T(t)V(t) + kT(t)N(t) + \alpha N(t) - (\mu+\rho+\delta)H(t))\\
& + \frac{\beta T_0}{c}(\rho H(t) - cV(t) - qV(t)W(t))\\
& + \left(\frac{\gamma}{u}-\frac{\gamma\beta\rho T_0}{cu(\mu+\rho+\delta)}\right)(uN(t)Z(t) - bZ(t)) + \frac{q\beta T_0}{cg}(gV(t)W(t) - hW(t))\\
= {} & \Lambda\left(2-\frac{T_0}{T(t)}-\frac{T(t)}{T_0}\right) + \left(kT_0 + \frac{\alpha\rho\beta T_0}{c(\mu+\rho+\delta)} - \delta + \frac{\rho\beta\delta T_0}{c(\mu+\rho+\delta)}\right)N(t)\\
& + \left(\frac{\beta\rho T_0}{c(\mu+\rho+\delta)}-1\right)\frac{\gamma b}{u}Z(t) - \frac{hq\beta T_0}{cg}W(t)\\
= {} & \Lambda\left(2-\frac{T_0}{T(t)}-\frac{T(t)}{T_0}\right) - (1-R_0)\delta N(t) - \left(1-\frac{\beta\rho T_0}{c(\mu+\rho+\delta)}\right)\frac{\gamma b}{u}Z(t) - \frac{hq\beta T_0}{cg}W(t).
\end{aligned}$$

Clearly, if $R_0 \leq 1$, then $\frac{dL_0(t)}{dt} \leq 0$ and $\frac{dL_0(t)}{dt} = 0$ if and only if $T(t) = T_0$, $N(t) = 0$, $Z(t) = 0$ and $W(t) = 0$. It is easy to verify that the largest invariant of $\{\frac{dL_0(t)}{dt} = 0\}$ is the singleton $\{E_0\}$. Therefore, by LaSalle's Invariance Principle, the infection-free equilibrium E_0 is globally asymptotically stable when $R_0 \leq 1$. Biologically, in this scenario, the virus is predicted to be cleared.

Theorem 3.2. *If $R_0 > 1, R_{0W} < 1$ and $R_{0Z} < 1$, then the immune-free equilibrium E_1 of model (1.3) is globally asymptotically stable.*

Theorem 3.3. *If $R_{0W} > 1 > R_{1Z}$, then the infection equilibrium E_2 with only antibody response of model (1.3) is globally asymptotically stable.*

Theorem 3.4. *If $R_{0Z} > 1 > R_{1W}$, then the infection equilibrium E_3 with only CTL response of model (1.3) is globally asymptotically stable.*

Theorem 3.5. *If $R_{1W} > 1$ and $R_{1Z} > 1$, then the infection equilibrium E_4 with CTL and antibody response of model (1.3) is globally asymptotically stable.*

The proofs of Theorems 3.2 to 3.5 are given in the online supplementary material.

4. Conclusion

In this paper, we developed a comprehensive multiscale model for HCV infection by incorporating both virus-to-cell and cell-to-cell transmission modes, as well as CTL and antibody immune responses. The model was shown to generate very rich dynamics, which may provide insights into HCV infection and control.

We have identified key threshold parameters, including the basic reproduction number of virus (R_0) and various immune response reproduction numbers, shedding light on distinct infection outcomes. When $R_0 \leq 1$, the infection-free equilibrium (E_0) demonstrates global asymptotic stability, indicating successful viral clearance. Conversely, $R_0 > 1$ leads to chronic infection. Conditions characterized by $R_0 > 1$, $R_{0W} < 1$, and $R_{0Z} < 1$ result in the global asymptotic stability of the immune-free equilibrium (E_1), signifying unsuccessful establishment of both CTL and antibody immune responses.

Our model further illustrates diverse outcomes under varying immune response scenarios. For instance, when $R_{0W} > 1 > R_{1Z}$, the infection equilibrium (E_2) with only antibody response achieves global asymptotic stability, indicating successful activation of the antibody response in the absence of CTL response. Conversely, when $R_{0Z} > 1 > R_{1W}$, the infection equilibrium (E_3) with only CTL response attains global asymptotic stability, reflecting activated CTL immune response without concurrent activation of the antibodies.

The last scenario where $R_{1W} > 1$ and $R_{1Z} > 1$ leads to the global asymptotic stability of the infection equilibrium (E_4), signifying sustained infection along with activation of both CTL and antibody immune responses. This robust immune response results in a substantial reduction in infected cells, intracellular viral RNA, and free virus. Our findings also underscore the efficiency of direct cell-to-cell transmission in addition to virus-to-cell transmission.

Our modeling results provide valuable insights into the dynamics of HCV infection. They underscore the critical role of both modes of transmission and the immune responses in shaping the course of infection. The model highlights the impact of immune responses on reducing viral load and controlling infection. These findings enhance our understanding of HCV infection dynamics and also hold implications for the development of effective therapeutic strategies against this widespread and impactful virus.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.aml.2023.108904.

References

[1] The World Health Organization, Hepatitis C. Key Facts, https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.
[2] X. Wang, S. Tang, X. Song, et al., Mathematical analysis of an HIV latent infection model including both virus-to-cell infection and cell-to-cell transmission, J. Biol. Dyn. 11 (sup2) (2017) 455–483.
[3] S. Pan, S.P. Chakrabarty, Threshold dynamics of HCV model with cell-to-cell transmission and a non-cytolytic cure in the presence of humoral immunity, Commun. Nonlinear Sci. Numer. Simul. 61 (2018) 180–197.
[4] A. Meskaf, Y. Tabit, K. Allali, Global analysis of a HCV model with CTL, antibody responses and therapy, Appl. Math. Sci. 9 (81) (2015) 3997–4008.
[5] D. Wodarz, Mathematical models of immune effector responses to viral infections: Virus control versus the development of pathology, J. Comput. Appl. Math. 184 (1) (2005) 301–319.
[6] H.A. Elkaranshawy, H.M. Ezzat, N.N. Ibrahim, Lyapunov function and global asymptotic stability for a new multiscale viral dynamics model incorporating the immune system response: Implemented upon HCV, PLoS One 16 (10) (2021) e0257975.
[7] L. Rong, A.S. Perelson, Mathematical analysis of multiscale models for Hepatitis C virus dynamics under therapy with direct-acting antiviral agents, Math. Biosci. 245 (1) (2013) 22–30.
[8] K. Kitagawa, S. Nakaoka, Y. Asai, et al., A PDE multiscale model of Hepatitis C virus infection can be transformed to a system of ODEs, J. Theoret. Biol. 448 (2018) 80–85.
[9] K. Kitagawa, T. Kuniya, S. Nakaoka, et al., Mathematical analysis of a transformed ODE from a PDE multiscale model of Hepatitis C virus infection, Bull. Math. Biol. 81 (2019) 1427–1441.
[10] J.M. Timpe, Z. Stamataki, A. Jennings, et al., Hepatitis C virus cell–cell transmission in hepatoma cells in the presence of neutralizing antibodies, Hepatology 47 (1) (2008) 17–24.
[11] M.A. Nowak, C.R.M. Bangham, Population dynamics of immune responses to persistent viruses, Science 272 (5258) (1996) 74–79.
[12] X. Wang, L. Rong, HIV low viral load persistence under treatment: Insights from a model of cell-to-cell viral transmission, Appl. Math. Lett. 94 (2019) 44–51.
[13] X. Wang, Q. Ge, Y. Chen, Threshold dynamics of an HIV infection model with two distinct cell subsets, Appl. Math. Lett. 103 (2020) 106242.