Chaotic Modeling and Simulation (CMSIM) 3: 259–268, 2018

A simple mathematical model for HIV infection with delayed immune response

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Abstract. In this paper, we propose a mathematical model for the human immunodeficiency virus infection that includes a delay between the antigenic stimulation and the generation of cytotoxic T cells. The model provides good insights on the dynamics of HIV when the time delay is varied. More work is needed in order to better understand the role of the immune response delay in HIV infection.

1 Introduction

Cytotoxic T cells (CTL) play an important role in the control of viral infections. Some results show that the level of viral load is determined by the efficacy of CTL and that the degree of the response to viruses may influence the outcome of the disease. Nevertheless, there are viruses able to escape the host immune responses and establish persistent infections. HIV is one of those virus. In the acute (first) phase of HIV infection, the CTL response to HIV is mostly linked with the viral set-point, influencing the rate of HIV disease progression. In the chronic phase of the infection, CTL response is associated with the partial containment of HIV replication [1]. More than two million people are newly infected with HIV annually, therefore, understanding the principles involved in HIV clearance and persistence, and the mechanisms of long-term immunological response, is of great importance to develop vaccines or better treatments against HIV [9].

Throughout the years, mathematical models have contributed to a better understanding of the mechanisms behind the immune response against HIV. Some of these models include time delays, namely the time needed for infected cells to produce new virus, and the delay in the stimulation of the immune response. In 2006, Ciupe *et al.* [2] model the dynamics of the primary HIV infection and the beginning of the latency phase, considering a delay in the CTL response. This delay leads to the appearance of periodic solutions, through a

Received: 22 March 2017 / Accepted: 14 March 2018

ISSN 2241-0503

Hopf bifurcation. These oscillations describe the rapid rotation between viral strains and the CTL response, needed to control the infection. Huanga et al. [6] present a model for HIV infection with treatment and delayed immune response. They conclude that the higher the delay, the higher the amount of virus and infected T cells in the body and the frequency of oscillations. In 2016, Prakast et al. [10] study a model for macrophages infection by HIV that includes CTL. The authors conclude that the inclusion of the delay may destabilize the solutions of the model. This could help devise new treatment options.

Bearing these ideas in mind, we propose a model for HIV infection that includes a delay in the immune response. We describe the model, compute the reproduction number, and discuss the results of the simulations of the model for distinct values of the delay.

2 The Model

The CD4$^+$ T cells are produced at a rate s and die at a rate μ_T. They are infected by HIV at a rate k_1. A fraction, η, of infected CD4$^+$ T cells becomes latently infected. The latently infected CD4$^+$ T cells become productively infected at a rate a_L and die at a rate μ_L. The infected CD4$^+$ T cells, $I(t)$, die at a rate δ and are killed by CTL at a rate k_2. The viruses are produced by the infected CD4$^+$ T cells at a rate p and are cleared at a rate c. The CTLs are produced by uninfected and infected CD4$^+$ T cells at a rate k_4 and die at a rate δ_C. In this model we consider a delay, τ, between the antigenic stimulation and the generation of CTL. The non-linear delay system describing the dynamics of the model is given by:

$$\begin{aligned}
\dot{T}(t) &= s - \mu_T T(t) - k_1 V(t) T(t) \\
\dot{L}(t) &= k_1 \eta V(t) T(t) - a_L L(t) - \mu_L L(t) \\
\dot{I}(t) &= k_1 (1-\eta) V(t) T(t) + a_L L(t) - \delta I(t) - k_2 I(t) Z(t) \\
\dot{V}(t) &= p I(t) - c V(t) \\
\dot{Z}(t) &= k_4 T(t-\tau) I(t-\tau) Z(t-\tau) - \delta_C Z(t)
\end{aligned} \tag{1}$$

3 Positivity and boundedness

Let $X = C([-\tau, 0], \mathbb{R})$ be the Banach space of continuous mapping from $[-\tau, 0]$ to $\mathbb{R}$ equipped with the sup-norm. The initial conditions for system (1) are given as follow:

$$\begin{array}{lllll}
T(\theta) \geq 0, & L(\theta) \geq 0, & I(\theta) \geq 0, & V(\theta) \geq 0, & Z(\theta) \geq 0, \theta \in [-\tau, 0] \\
T(0) > 0, & L(0) > 0, & I(0) > 0, & V(0) > 0, & Z(0) > 0
\end{array} \tag{2}$$

From [5,7], we know that there is a unique solution $(T(t), L(t), I(t), V(t), Z(t))$ to system (1) with initial conditions (2). Let $(T(t), L(t), I(t), V(t), Z(t))$ be such solution. The following lemma is useful for discussing the positivity and boundedness.

Lemma 1. *For any solution $(T(t), L(t), I(t), V(t), Z(t))$ of (1) satisfying conditions (2), we have that* $\limsup_{t\to\infty} T(t) \leq \frac{s}{\mu_T}$

Proof. Let $t_1 > 0$ such that $T(t_1) > \frac{s}{\mu_T}$ and $\dot{T}(t_1) > 0$, then we have:

$$\dot{T}(t_1) = s - \mu_T T(t_1) - k_1 V(t_1) T(t_1) \leq -k_1 V(t_1) T(t_1) \leq 0 \tag{3}$$

We considered $T(t_1) > \frac{s}{\mu_T}$ which is a contradiction to $\dot{T}(t_1) > 0$. So, the conclusion of Lemma 1 holds.

Theorem 1. *Let $(T(t), L(t), I(t), V(t), Z(t))$ be the solution of system (1) satisfying conditions (2). Then $T(t)$, $L(t)$, $I(t)$, $V(t)$ and $Z(t)$ are positive and there exists an $M > 0$, such that $T(t) < M$, $L(t) < M$, $I(t) < M$, $V(t) < M$ and $Z(t) < M$ holds after sufficiently large time t.*

Proof. From (1), we have

$$\begin{aligned}
T(t) &= T(0)e^{-\int_0^t (\mu_T + k_1 V(\epsilon))d\epsilon} + \int_0^t s e^{-\int_\nu^t (\mu_T + k_1 V(\epsilon))d\epsilon} d\nu \\
L(t) &= L(0)e^{-(a_L+\mu_L)t} + \int_0^t k_1 \eta V(\nu) T(\nu) e^{-(a_L+\mu_L)(t-\nu)} d\nu \\
I(t) &= I(0)e^{-\int_0^t (\delta + k_2 Z(\epsilon))d\epsilon} + \int_0^t k_1 (1-\eta) V(\nu) T(\nu) e^{-\int_\nu^t (\delta + k_2 Z(\epsilon))d\epsilon} d\nu \\
V(t) &= V(0)e^{-ct} + \int_0^t p I(\nu) e^{-c(t-\nu)} d\nu \\
Z(t) &= Z(0)e^{-\delta_C t} + \int_0^t k_4 T(\nu-\tau) I(\nu-\tau) Z(\nu-\tau) e^{\delta_C t} d\nu
\end{aligned} \tag{4}$$

It is easy to see that $T(t)$ is positive on the existence interval. Then, we prove that $I(t)$ is positive. In fact, let $t_1 > 0$ be the first time such that $I(t_1) = 0$. By the fourth equation of system (1), we obtain $V(t_1) = V(0)e^{-ct_1} + \int_0^{t_1} pI(\nu)e^{-c(t-\nu)}d\nu > 0$. On the other hand, from the third equation of (1), we have $\dot{I}(t_1) = k_1(1-\eta)V(t_1)T(t_1) > 0$. This means that $I(t) < 0$ for $t \in (t_1 - \xi, t_1)$, where ξ is an arbitrarily small positive constant, which leads to a contradiction. It follows that $I(t) > 0$ and $V(t) > 0$. By a similar argument and from the second and fifth equations of (1), it is easy to show that $L(t)$ and $Z(t)$ are positive on the existence interval.
Next, we sketch the arguments for ultimate boundedness of the solution of system (1). Let

$$N(t) = T(t) + L(t) + I(t) + V(t) + Z(t) \tag{5}$$

By Lemma 1 and the positivity of solutions of system (1), we have

$$\begin{aligned}\dot{N}(t) &= s - \mu_T T(t) - \mu_L L(t) - \delta I(t) - k_2 I(t) Z(t) + pI(t) - cV(t) \\ &\quad + k_4 T(t-\tau) I(t-\tau) Z(t-\tau) - \delta_C Z(t) \\ &\leq s - \mu_T T(t) - \mu_L L(t) - \delta I(t) - cV(t) - \delta_C Z(t) \\ &< s - qN\end{aligned} \tag{6}$$

Therefore, $N < \frac{s}{\mu_T} + \xi$ for all large t, where ξ is an arbitrarily small positive constant. Thus, $T(t)$, $L(t)$, $I(t)$, $V(t)$ and $Z(t)$ are ultimately bounded by some positive constant M. This completes the proof of Theorem 1.

4 Stability analysis

We calculate the equilibrium points of the model (1):

- Disease-Free Equilibrium: $P_0 = \left(\frac{s}{\mu_T}, 0, 0, 0, 0\right)$
- Endemic but CTL-absent Equilibrium:

$$P_1 = \Big(\tfrac{\delta(a_L+\mu_L)c}{k_1 p(a_L+(1-\eta)\mu_L)}, \tfrac{\eta[sk_1 p(a_L+(1-\eta)\mu_L)-\mu_T\delta(a_L+\mu_L)c]}{k_1(a_L+\mu_L)p(a_L+(1-\eta)\mu_L)}, \tfrac{sk_1 p(a_L+(1-\eta)\mu_L)-\mu_T\delta(a_L+\mu_L)c}{k_1\delta(a_L+\mu_L)p}, \tfrac{sk_1 p(a_L+(1-\eta)\mu_L)-\mu_T\delta(a_L+\mu_L)c}{k_1\delta(a_L+\mu_L)c}, 0\Big)$$

- Endemic Equilibrium:

$$P_2 = \Big(\tfrac{sck_4-k_1p\delta_C}{\mu_T ck_4}, \tfrac{k_1\eta p\delta_C}{(a_L+\mu_L)ck_4}, \tfrac{\delta_C\mu_T c}{sck_4-k_1p\delta_C}, \tfrac{p\delta_C\mu_T}{sck_4-k_1p\delta_C}, \tfrac{1}{k_2}\left[\tfrac{k_1p(a_L+(1-\eta)\mu_L)(sck_4-k_1p\delta_C)}{\mu_T(a_L+\mu_L)k_4c^2} - \delta\right]\Big)$$

Using the notation in [3] on system (1), matrices for the new infection terms, F, and the other terms, V, are computed to be:

$$F = \begin{pmatrix} 0 & 0 & \frac{sk_1\eta}{\mu_T} \\ 0 & 0 & \frac{sk_1(1-\eta)}{\mu_T} \\ 0 & 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} a_L+\mu_L & 0 & 0 \\ -a_L & \delta & 0 \\ 0 & -p & c \end{pmatrix}$$

The associative basic reproduction number, R_0, is computed to be:

$$R_0 = \rho(FV^{-1}) = \frac{sk_1 p(a_L+(1-\eta)\mu_L)}{\mu_T\delta c(a_L+\mu_L)} \tag{7}$$

where ρ indicates the spectral radius of FV^{-1}. By Theorem 2 [3], we obtain the following lemma.

Lemma 2. *The disease-free equilibrium P_0 is locally asymptotically stable for any time delay $\tau \geq 0$ if $R_0 < 1$ and these point is unstable if $R_0 > 1$.*

Lemma 3. *The equilibrium point P_1 is locally asymptotically stable for any time delay $\tau \geq 0$ if $R_0 > 1$ and $R_1 < 1$, where $R_1 = R_0 - \frac{\delta_C k_1^2 p^2 (a_L + (1-\eta)\mu_L)}{k_4 \mu_T \delta (a_L + \mu_L) c^2}$*

5 Numerical Results

We simulate the model (1). The parameters used in the simulations are given in Table 1 and the initial conditions are set to $T(0) = 10^6\ ml^{-1}$, $L(0) = I(0) = 0\ ml^{-1}$, $V(0) = 10^2\ ml^{-1}$, $Z(0) = 333 \times 10^3\ ml^{-1}$.

Table 1. Parameters used in the numerical simulations of model (1)

Parameter	Values	Units	Reference
s	10^4	$\text{ml}^{-1}\ \text{day}^{-1}$	[8]
μ_T	0.01	day^{-1}	[8]
k_1	2.4×10^{-8}	ml day^{-1}	[8]
η	0.03		[4]
a_L	0.1	day^{-1}	[8]
μ_L	4×10^{-3}	day^{-1}	[8]
δ	1	day^{-1}	[8]
k_2	4.5×10^{-7}	ml day^{-1}	[4]
p	2000	day^{-1}	[8]
c	23	day^{-1}	[8]
k_4	3.3×10^{-7}	ml day^{-1}	[4]
δ_C	0.015	day^{-1}	[4]
τ	1	day	

In Figure 1, we plot the dynamics of the variables of the model (1). Tthe model approaches asymptotically the stable disease free equilibrium, P_0. The corresponding reproduction numbers are $R_0 = R_1 = 0.83 < 0$.
In Figure 2, we depict the stable endemic but CTL-absent equilibrium, P_1. The corresponding reproduction numbers are $R_0 = 1.01 > 1$ e $R_1 = 0.99 < 0$.
In Figure 3, we plot the stable endemic equilibrium, P_2. The corresponding reproduction numbers are $R_0 = R_1 = 2.08 > 1$.
In Figures 4-5, we plot the dynamics of the variables of the model (1) for different values of the delay τ. We observe as τ is increased the appearance of periodic oscillations, characterized by a sharper amount of viruses and infected T cells. Moreover, the frequency of the oscillations also increase with τ [6].

6 Conclusions

We propose a simple model for the dynamics of HIV infection with a delay between the antigenic stimulation and the generation of CTL. Numerical simulations of the model show three distinct equilibria: the stable disease-free

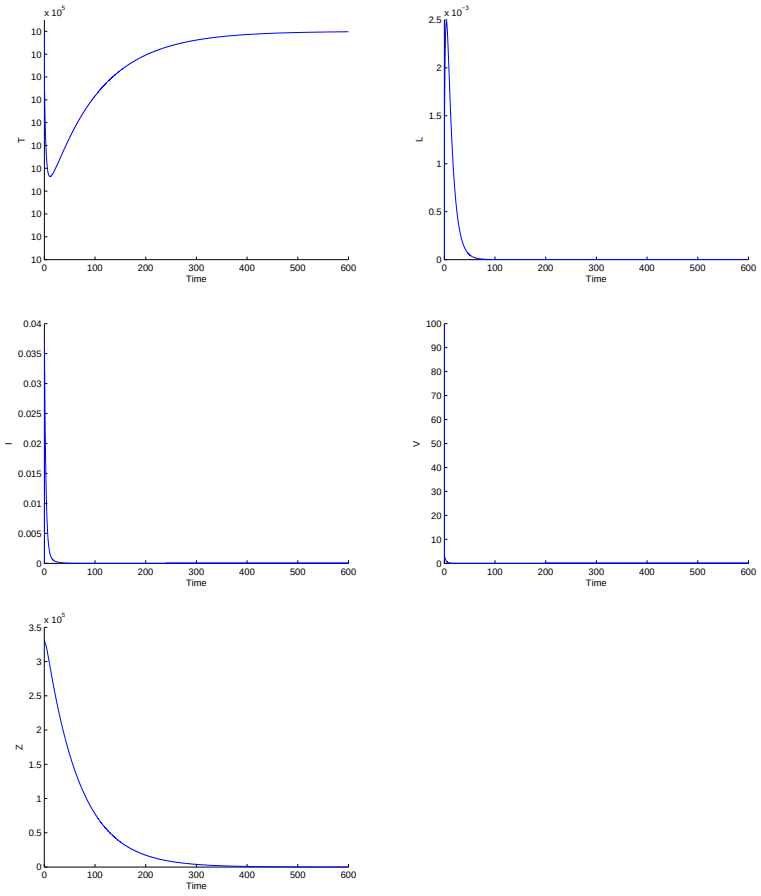

Fig. 1. Dynamics of the variables of the system (1) for parameter values in Table 1, except $k_1 = 9.5 \times 10^{-9}$ and initial conditions given in the text.

equilibrium, the stable endemic but CTL-absent equilibrium, and the stable endemic equilibrium. Moreover, as the delay is increased, it is observed the generation of periodic oscillations in the model. These oscillations describe viral blips, seen in HIV patients, and the necessary CTL response to control the infection. More work is needed in order to better understand the role of the delay in this type of model.

7 Acknowledgments

Authors wish to thank the Polytechnic of Porto, through the PAPRE Programa de Apoio à Publicação em Revistas Científicas de Elevada Qualidade for financial support. The authors were partially funded by the European Regional Development Fund through the program COMPETE and by the Portuguese Government through the FCT - Fundação para a Ciência e a Tecnologia un-

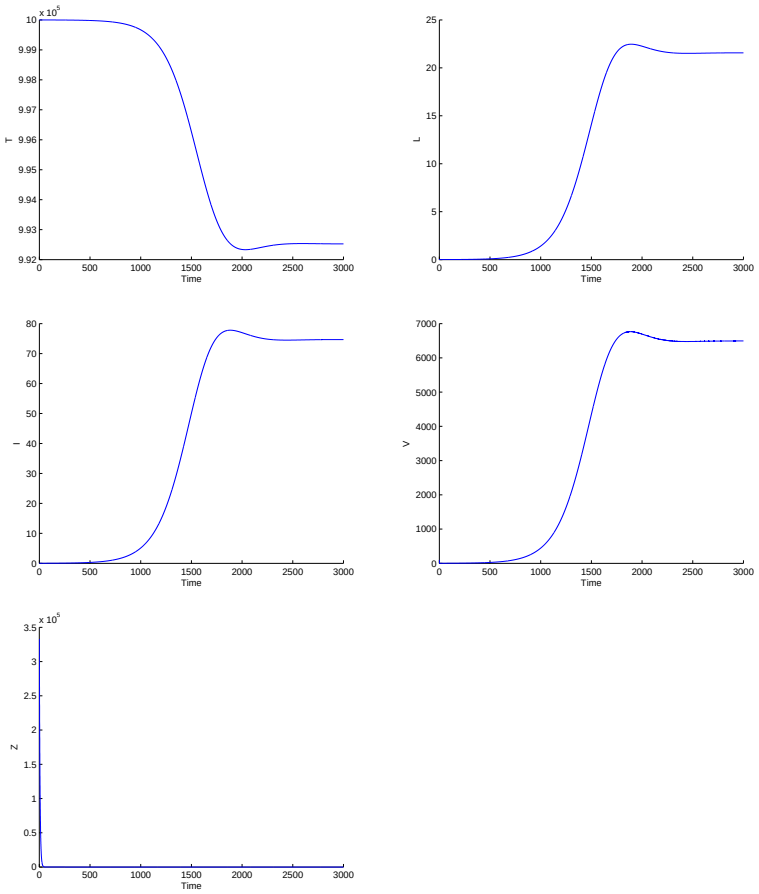

Fig. 2. Dynamics of the variables of the system (1) for parameter values in Table 1, except $k_1 = 1.16 \times 10^{-8}$, $k_4 = 10^{-9}$ and $\delta_C = 0.15$, and initial conditions given in the text.

der the project PEst-C/MAT/UI0144/2013. The research of AC was partially supported by a FCT grant with reference SFRH/BD/96816/2013.

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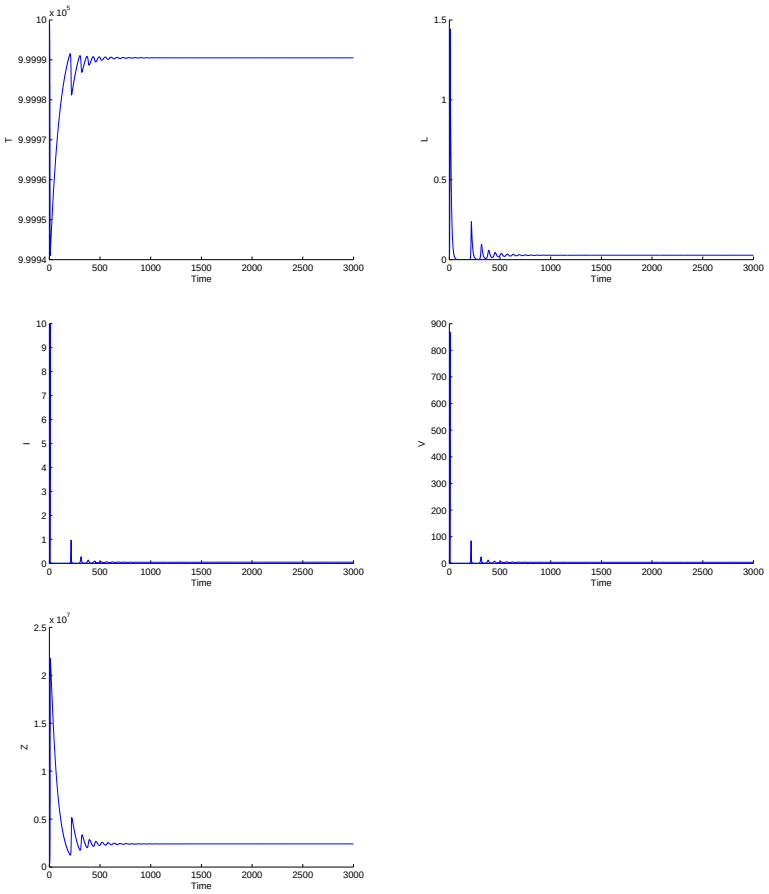

Fig. 3. Dynamics of the variables of the system (1) for parameter values in Table 1 and initial conditions given in the text.

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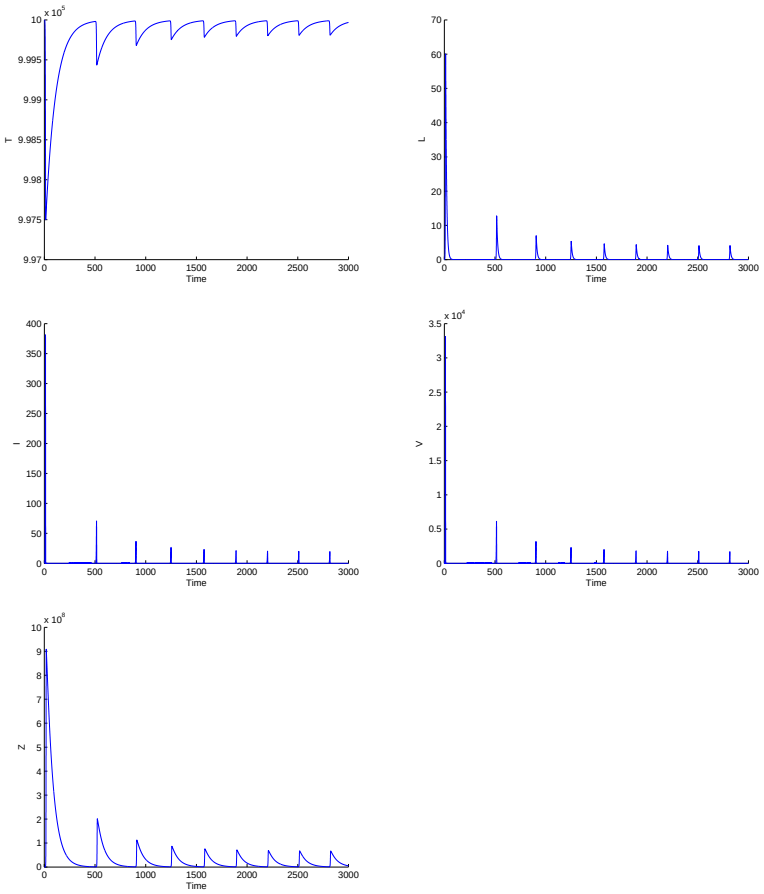

Fig. 4. Dynamics of the variables of the system (1) for parameter values in Table 1, except $\tau = 5$ and initial conditions given in the text.

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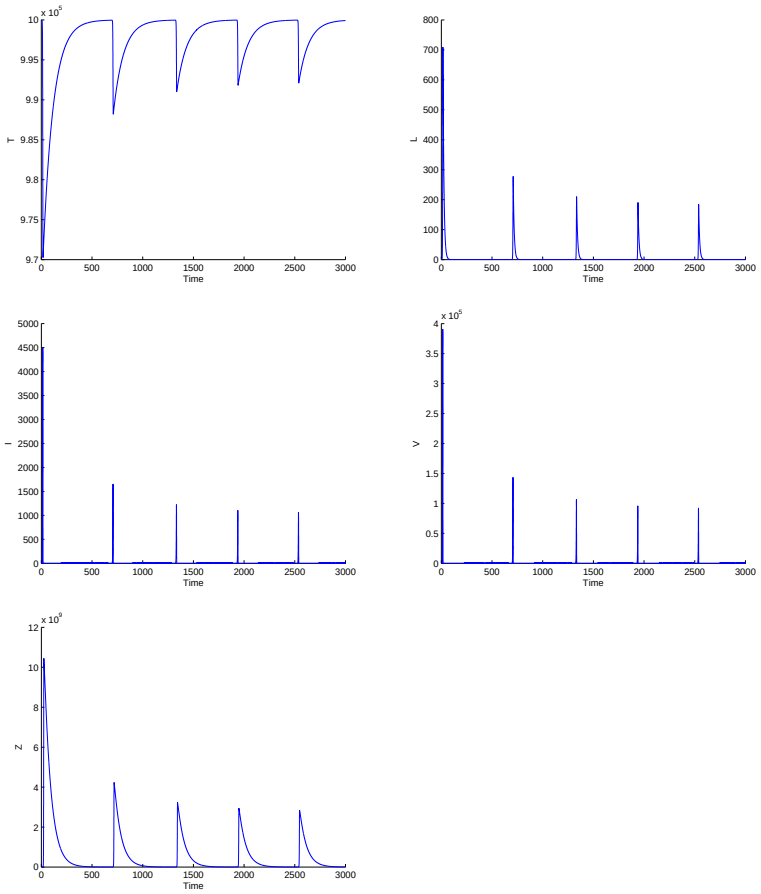

Fig. 5. Dynamics of the variables of the system (1) for parameter values in Table 1, except $\tau = 8$ and initial conditions given in the text.