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► **To cite this version:**

Xinyue Fan, Claude-Michel Brauner. Hopf bifurcation in a HIV model with a quadratic logistic growth term. 2010. hal-00537467v1

HAL Id: hal-00537467

<https://hal.science/hal-00537467v1>

Preprint submitted on 18 Nov 2010 (v1), last revised 25 May 2012 (v2)

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HOPF BIFURCATION IN A HIV MODEL WITH A QUADRATIC LOGISTIC GROWTH TERM ^{*}

XINYUE FAN [†] AND CLAUDE-MICHEL BRAUNER [‡]

Abstract. We consider a model of disease dynamics in the modeling of Human Immunodeficiency Virus (HIV). This model consists of three ODEs for the concentrations of the target T cells, the infected cells and the virus particles. There are two bifurcation parameters, N , the total number of virions produced by one infected cell, and r , the logistic parameter which controls the growth rate. This paper focuses on the stability of the uninfected and infected steady state. We identify two domains, \mathcal{U} and \mathcal{S} , where the uninfected equilibrium is respectively asymptotically stable and unstable. The infected equilibrium is asymptotically stable in \mathcal{S} , except in a region \mathcal{P} where we prove its instability. Hopf bifurcations occur at the interface. Numerical results are presented.

Key words. Stability, Hopf bifurcation, HIV modeling

subject classifications. 34D20, 92C37

1. Introduction

The major target of Human Immunodeficiency Virus (HIV) infection is a class of lymphocytes, or white blood cells, known as $CD4^+$ T cells. As a consequence, the immune response of the host to opportunistic infections is progressively compromised, leading to Acquired Immunodeficiency Syndrome (AIDS). T cells, like other lymphocytes, are produced in the bone marrow. Immature cells migrate to the thymus, where they undergo further differentiation and maturation into immunocompetent T cells (see [9]).

The reason for the fall in the T cell count is unknown, as are the processes by which infection may affect the source of new T cells, or the homeostatic processes which control the number of T cells in the human body. Over the past decade, a number of models, both stochastic and deterministic, have been developed to describe the immune system and its interaction with HIV. A substantial number of nonlinear systems have been suggested by Perelson et al. (see the survey [10]) to model the complex dynamics of HIV-host interaction.

In this article we consider the following model of viral dynamics with a logistic term. It focuses on $CD4^+$ T cells and includes three variables. Let T and I denote the respective concentrations of uninfected and infected $CD4^+$ T cells. The concentration of free virus particles, or virions, is V . For the sake of simplicity, we call V the virus in the paper. The model reads see ([10, p. 10]):

$$\frac{dT}{dt} = \alpha - \mu_T T + rT \left(1 - \frac{T}{T_{max}}\right) - \gamma VT, \quad (1.1)$$

$$\frac{dI}{dt} = \gamma VT - \mu_I I, \quad (1.2)$$

$$\frac{dV}{dt} = N\mu_I I - \mu_V V, \quad (1.3)$$

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where α is the rate of supply of immunocompetent T cells from precursors in the thymus. T cells, like all cells in the body, have a finite lifetime. Here μ_T is the natural death rate of CD4⁺ T cells, the term γVT models the rate at which free virus infects a CD4⁺ T cell. The infected cells die at a rate μ_I and produce free virus during their life-time at a rate N . In addition, μ_V is the death rate of the virus.

We assume that the growth of T cells is governed by a quadratic *logistic* equation (see [9]). In (1.1), r is the average specific T-cell growth rate obtained in the absence of population limitation. It depends on the average degree of antigen or idiotypic network stimulation of T-cell proliferation. The term $1 - T/T_{max}$ shuts off T-cell growth as the population level T_{max} is approached from below.

In the absence of virus, the T cells population has a steady state value:

$$T_0 = \frac{(r - \mu_T) + \sqrt{(\mu_T - r)^2 + \frac{4r\alpha}{T_{max}}}}{2r} T_{max}.$$

Note that the quantity $r - \mu_T$, the net T-cell proliferation rate, needs not to be positive, see [9, p. 86].

We set $X(t) = (T(t), I(t), V(t))$ and write System (1.1)-(1.3) as the Cauchy problem:

$$\frac{dX}{dt}(t) = F(X(t)), \quad X(0) = X_0, \quad (1.4)$$

where X_0 corresponds to non-negative initial conditions.

It is easily seen that System (1.4) has two possible nonnegative equilibria:

(i) the uninfected steady state $X_u = (T_u, I_u, V_u)$:

$$T_u = T_0 = \frac{(r - \mu_T) + \sqrt{(\mu_T - r)^2 + \frac{4r\alpha}{T_{max}}}}{2r} T_{max}, \quad I_u = 0, \quad V_u = 0, \quad (1.5)$$

which corresponds to a positive equilibrium in case of no infection;

(ii) the infected steady state $X_i = (T_i, I_i, V_i)$:

$$\begin{aligned} T_i &= \frac{\mu_V}{\gamma N}, \quad I_i = \frac{\alpha}{\mu_I} - \frac{\mu_T \mu_V}{N \gamma \mu_I} + \frac{r \mu_V}{N \gamma \mu_I} \left(1 - \frac{\mu_V}{N \gamma T_{max}} \right), \\ V_i &= \frac{\alpha N}{\mu_V} - \frac{\mu_T}{\gamma} + \frac{r}{\gamma} \left(1 - \frac{\mu_V}{N \gamma T_{max}} \right). \end{aligned} \quad (1.6)$$

The infected steady state or ‘‘seropositivity steady state’’ corresponds to a positive equilibrium in case of infection.

De Leenheer and Smith (see [2]) considered a general system of three ODEs which generalizes System (1.1)-(1.3), as well as a model by Nowak and May [8]. Their bifurcation parameter is the basic reproduction ratio for the model, which reads with our notations:

$$R_0 = \frac{\gamma N T_0}{\mu_V}. \quad (1.7)$$

However, the basic reproduction number R_0 defined by (1.7) depends on the logistic parameter r , whereas its critical value is equal to unity for all r . Therefore, it is appropriate to take another quantity as bifurcation parameter, such as N (see [9]). In this paper, we consider $N > 0$ and $r \geq 0$ as independent bifurcation parameters.

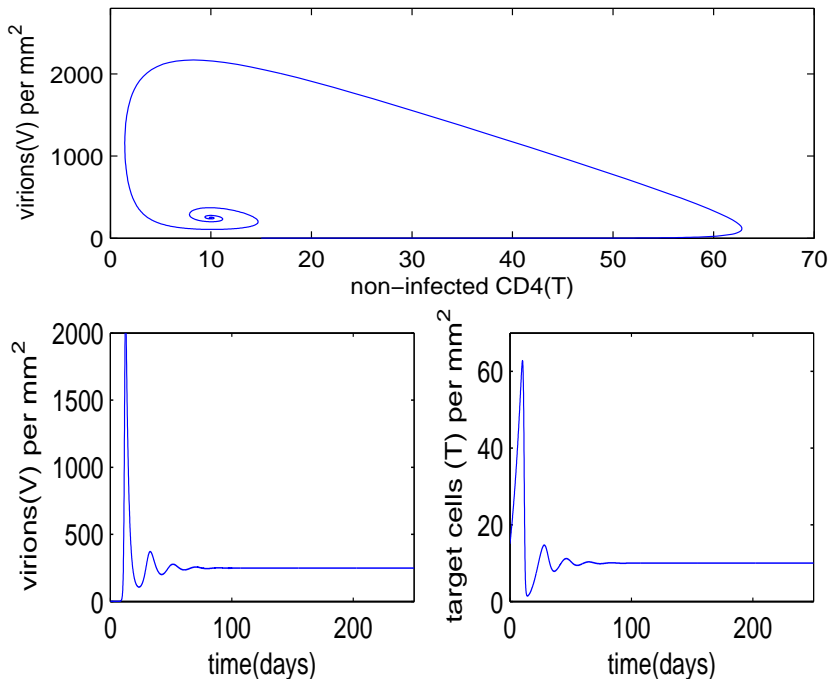


FIG. 1.1. Typical profiles of virus vs. target cells in the phase plane (front), virus (left) and target cells (right) in the case of infection, corresponding to domain \mathcal{I} where the infected equilibrium is stable. Here $N=1000$, $r=0.2$. The other quantities have the values: $T_{max}=1500$, $\alpha=1.5$, $\gamma=0.001$, $\mu_T=0.1$, $\mu_I=0.5$, $\mu_V=10$, as in the figures hereafter except Fig. 2.3.

Another important quantity is T_{max} , which mathematically plays the role of a large perturbation parameter. The quantities $\mu_T, \mu_I, \mu_V, \alpha$ and γ will be fixed numbers.

We first determine two domains, \mathcal{U} and \mathcal{I} , in the first quarter plane. It is easy to see that the uninfected equilibrium is asymptotically stable in \mathcal{U} and unstable in \mathcal{I} . The positive infected equilibrium exists in \mathcal{I} only. We prove in Section 2 that it is asymptotically stable, except in a subdomain \mathcal{P} of \mathcal{I} . The region \mathcal{P} is explicitly delimited by two curves $r_1(N)$ and $r_2(N)$ which meet at $N=N_2$. We use the Routh-Hurwitz criterion which ensures that the eigenvalues of the Jacobian matrix have negative real part if and only if the corresponding Hurwitz determinants are positive.

In Section 3, we prove that the infected equilibrium X_i is unstable in the interior of the region \mathcal{P} . Furthermore, Hopf bifurcations occur at the boundary of \mathcal{P} at fixed N . We use a criterion of Liu (see [5]) and Orlando's formula which establishes a simple relation between the Hurwitz determinant D_2 and the sums of pairs of eigenvalues.

Numerical computations show oscillations in the region \mathcal{P} . However, the biological meaning of these oscillations remains unclear, see [9, p. 108]). We refer to [2] for the existence of an orbitally asymptotically stable periodic orbit.

REMARK 1.1. It is possible to replace (1.1) by

$$\dot{T} = \alpha - \mu_T T + rT \left(1 - \frac{T+I}{T_{max}}\right) - \gamma VT, \quad (1.8)$$

see [10, 1]. However, the proportion of infected cells is very small, on the order of 10^{-4} to 10^{-5} of T cells, therefore this correction in the logistic proliferation term may be ignored (see [10, p. 10]). Wang and Li (see [11]) studied the global dynamics of System (1.8)(1.2)(1.3).

2. Stability

2.1. Equilibria

The notations are those of Section 1. More precisely, we state:

- (i) $N > 0$ and $r \geq 0$ are bifurcation parameters;
- (ii) the quantities $\mu_T, \mu_I, \mu_V, \alpha$ and γ , which are positive numbers, are fixed throughout the paper;
- (iii) T_{max} is a large perturbation parameter. Hereafter “ T_{max} large enough” means with respect to any combination of $\mu_T, \mu_I, \mu_V, \alpha$ and γ . It was already assumed in [9, p. 85] that

$$T_{max} > \frac{\alpha}{\mu_T}. \quad (2.1)$$

We consider the possible nonnegative equilibria of System (1.1)-(1.3) given by Formulae (1.5) and (1.6). Taking N as a bifurcation parameter at fixed $r \geq 0$, it is not difficult to compute the critical value at which $V_u = V_i = 0$:

$$N_{crit}(r) = \frac{\mu_V \left((\mu_T - r) + \sqrt{(\mu_T - r)^2 + \frac{4\alpha r}{T_{max}}} \right)}{2\alpha\gamma} = \frac{\mu_V}{\gamma T_0}.$$

At $r = 0$, $N_{crit}(0) = \frac{\mu_T \mu_V}{\alpha\gamma}$, and, as $r \rightarrow +\infty$,

$$N_{crit}(r) \rightarrow N_{crit}(+\infty) = \frac{\mu_V}{\gamma T_{max}}.$$

Note that $N_{crit}(0)$ does not depend on T_{max} , whereas $N_{crit}(+\infty)$ is small for large T_{max} . We compute the derivative of N_{crit} with respect to r :

$$\dot{N}_{crit}(r) = \frac{\mu_V}{2\alpha\gamma} \left(\frac{-(\mu_T - r) + \frac{2\alpha}{T_{max}}}{\sqrt{(\mu_T - r)^2 + \frac{4\alpha r}{T_{max}}}} - 1 \right).$$

LEMMA 2.1. *We assume that (2.1) holds. Then, for $r \geq 0$, the mapping $r \mapsto N_{crit}(r)$ is decreasing and convex.*

Proof. Obviously, $\dot{N}_{crit}(r)$ is positive,

$$\dot{N}_{crit}(0) = \frac{\mu_V}{\alpha\gamma\mu_T} \left(\frac{\alpha}{T_{max}} - \mu_T \right) < 0,$$

and $\dot{N}_{crit}(r) \rightarrow 0$ as $r \rightarrow +\infty$, therefore $\dot{N}_{crit}(r) < 0$ for any $r > 0$. \square

Therefore we can define two domains of the quarter plane $N > 0, r \geq 0$: first (\mathcal{I}) for infected, which lies strictly above the graph of mapping $r \mapsto N_{crit}(r)$, second (\mathcal{U}) for uninfected, which lies below the graph.

Under the condition (2.1), the curve $r \mapsto N_{crit}(r)$ is one-to-one from $[0, +\infty)$ onto $(N_{crit}(+\infty), N_{crit}(0)]$, as in Figure 2.1. In such a case, the role of parameters N and r can be exchanged and one can define a critical value $r_{crit}(N)$ for each $N_{crit}(+\infty) < N \leq N_{crit}(0)$,

$$r_{crit}(N) = \frac{\mu_T \mu_V - \gamma \alpha N}{\mu_V \left(1 - \frac{\mu_V}{N \gamma T_{max}}\right)}. \quad (2.2)$$

By convention, $r_{crit}(N) = 0$ whenever $N > N_{crit}(0)$.

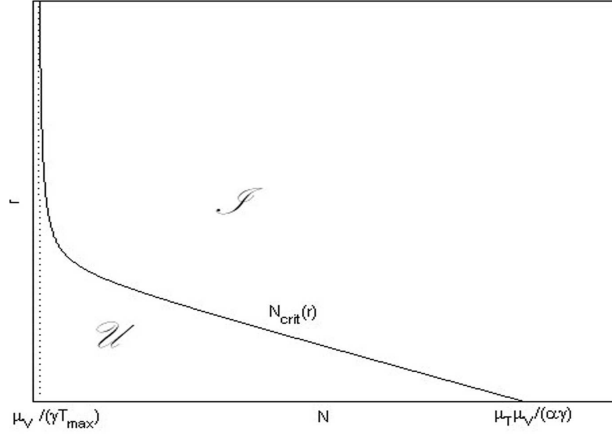


FIG. 2.1. Profile of the curve $r \mapsto N_{crit}(r)$ which defines the two domains \mathcal{U} and \mathcal{S} . With the values of Fig. 1, N decreases from $\mu_T \mu_V / \alpha \gamma = 666.67$ to $\mu_V / \gamma T_{max} = 6.67$.

LEMMA 2.2. (i) In the domain (\mathcal{U}), the uninfected steady state $X_u = (T_u, I_u, V_u)$ is the only nonnegative equilibrium. In the domain (\mathcal{S}), there are two nonnegative equilibria, X_u and the infected steady state $X_i = (T_i, I_i, V_i)$.

(ii) It always holds $0 < T_u < T_{max}$ and, in (\mathcal{S}), $0 < T_i < T_{max}$.

Proof. It remains only to prove (ii). Thanks to (2.1), on the one hand

$$\begin{aligned} T_u &= \frac{(r - \mu_T) + \sqrt{(\mu_T - r)^2 + \frac{4r\alpha}{T_{max}}}}{2r} T_{max} \\ &< \frac{(r - \mu_T) + \sqrt{(\mu_T - r)^2 + 4\mu_T r}}{2r} T_{max} = T_{max}. \end{aligned}$$

On the other hand, $T_i = \mu_V / (\gamma N) < T_{max}$ whenever $N > N_{crit}(r) = \mu_V / (\gamma T_{max})$. \square

The study of the stability of the uninfected solution is easy, however we include it for the convenience of the reader.

PROPOSITION 2.1. (i) In the domain (\mathcal{U}), the uninfected steady state is asymptotically stable. (ii) In the domain (\mathcal{S}), the uninfected steady state is unstable.

Proof. Let $r \geq 0$ be fixed. We compute explicitly the eigenvalues of the Jacobian

matrix

$$J(X_u) = \begin{pmatrix} r - \mu_T - \frac{2rT_u}{T_{max}} & 0 & -\gamma T_u \\ 0 & -\mu_I & \gamma T_u \\ 0 & N\mu_I & -\mu_V \end{pmatrix}.$$

They are all real:

$$\begin{aligned} \lambda_1 &= -\sqrt{(-r + \mu_T)^2 + 4\frac{r\alpha}{T_{max}}} < 0, \\ \lambda_2 &= -\frac{1}{2} \left((\mu_I + \mu_V) + \sqrt{(\mu_I + \mu_V)^2 - 4(\mu_I\mu_V - N\gamma\mu_I T_u)} \right) < 0, \\ \lambda_3 &= \frac{1}{2} \left(-(\mu_I + \mu_V) + \sqrt{(\mu_I + \mu_V)^2 - 4\mu_I\mu_V \left(1 - \frac{N}{N_{crit}(r)} \right)} \right). \end{aligned}$$

It is clear that $\lambda_3 < 0$ for $N < N_{crit}(r)$, therefore the three eigenvalues are negative. As long there is no eigenvalue on the imaginary axis, it is standard that linear stability yields nonlinear stability for a system of the form (1.4), therefore we will not elaborate this point. \square

The issue of the stability of the infected solution is obviously more complicated. For $(N, r) \in \mathcal{S}$, we consider the Jacobian matrix:

$$J(X_i) = \begin{pmatrix} r - \mu_T - \frac{2rT_i}{T_{max}} - \gamma V_i & 0 & -\gamma T_i \\ \gamma V_i & -\mu_I & \gamma T_i \\ 0 & N\mu_I & -\mu_V \end{pmatrix}. \quad (2.3)$$

The spectrum of $J(X_i)$ is given by the roots (three real roots or one real and two complex conjugates) of the following characteristic equation:

$$\lambda^3 + d_1\lambda^2 + d_2\lambda + d_3 = 0 \quad (2.4)$$

where the coefficients (functions of N and r) read:

$$\begin{aligned} d_1 &= \mu_I + \mu_V + \frac{\gamma\alpha N}{\mu_V} + \frac{r\mu_V}{\gamma T_{max}N}, \\ d_2 &= \frac{\gamma N\alpha\mu_I}{\mu_V} + \gamma\alpha N + \frac{r\mu_I\mu_V}{\gamma T_{max}N} + \frac{r\mu_V^2}{\gamma T_{max}N}, \\ d_3 &= \left(\mu_I\mu_V - \frac{\mu_V^2\mu_I}{\gamma T_{max}N} \right) r + \gamma N\alpha\mu_I - \mu_V\mu_I\mu_T. \end{aligned}$$

2.2. Study of the characteristic equation (2.4)

We recall that the Routh-Hurwitz criterion gives necessary and sufficient conditions for all the roots of a real polynomial to have negative real parts (see, e.g., [3, Chap. XV, 6]). Therefore it provides a stability analysis only by examining the coefficients of the characteristic polynomial, without computing the eigenvalues. In the case of (2.4) where $d_0 = 1$, the roots have negative real part if and only if the corresponding Hurwitz determinants are positive:

$$D_1 = d_1 > 0, \quad D_2 = d_1d_2 - d_3 > 0, \quad D_3 = d_3D_2 > 0.$$

In other words, the roots of (2.4) have negative real part if and only if

$$d_1 > 0, \quad d_3 > 0, \quad D_2 = d_1 d_2 - d_3 > 0. \quad (2.5)$$

Obviously, $d_1 > 0$. We compute $d_3 = 0$, which is equivalent to

$$\alpha \gamma N^2 + (r \mu_V - \mu_V \mu_T) N - \frac{r \mu_V^2}{\gamma T_{max}} = 0,$$

whose positive solution is $N_{crit}(r)$. Therefore $d_3 > 0$ for $N > N_{crit}(r)$, i.e., whenever $(N, r) \in \mathcal{S}$.

Next, we compute the leading determinant

$$D_2 = d_1 d_2 - d_3 = \frac{1}{\mu_V^2 (T_{max})^2 \gamma^2 N^2} (Ar^2 + Br + C), \quad (2.6)$$

which obviously has the sign of $Ar^2 + Br + C$. The coefficients reads:

$$\begin{aligned} A &= \mu_V^5 + \mu_V^4 \mu_I, \\ B &= -N \gamma T_{max} \mu_V^2 (N \gamma \mu_I \mu_V T_{max} - 2 \gamma \alpha N \mu_V - 2 N \gamma \mu_I \alpha \\ &\quad - \mu_V^3 - 3 \mu_V^2 \mu_I - \mu_I^2 \mu_V), \\ C &= N^2 \gamma^2 (T_{max})^2 (N \gamma \mu_V^3 \alpha + N \gamma \mu_I \alpha \mu_V^2 + N \gamma \mu_I^2 \mu_V \alpha + \gamma^2 N^2 \alpha^2 \mu_V \\ &\quad + \gamma^2 N^2 \alpha^2 \mu_I + \mu_V^3 \mu_I \mu_T). \end{aligned}$$

Note that $A > 0$ is fixed, B and C depend on N . While $C > 0$, $B(N)$ vanishes at

$$N_0 = \frac{\mu_V (3 \mu_I \mu_V + \mu_I^2 + \mu_V^2)}{\gamma (\mu_I \mu_V T_{max} - 2 \mu_V \alpha - 2 \mu_I \alpha)}. \quad (2.7)$$

Since T_{max} is large with respect to the other data, N_0 is positive but small:

$$N_{crit}(+\infty) = \frac{\mu_V}{\gamma T_{max}} < N_0 < N_{crit}(0).$$

Therefore, for $N_{crit}(+\infty) \leq N < N_0$, we have $B > 0$, and $B < 0$ for $N > N_0$.

To determine the sign of the second order polynomial $Ar^2 + Br + C$, we compute the discriminant

$$\Delta(N) = B^2 - 4AC = N^2 \gamma^2 (T_{max})^2 \mu_V^5 (aN^2 + bN + c),$$

which in turn is of the sign of $aN^2 + bN + c$.

The coefficient a, b and c reads:

$$\begin{aligned} a &= \gamma^2 T_{max} \mu_I (-4 \mu_I \alpha + \mu_I T_{max} \mu_V - 4 \mu_V \alpha), \\ b &= -2 \gamma \mu_I \mu_V (T_{max} \mu_I^2 + 3 \mu_I T_{max} \mu_V - 4 \mu_I \alpha + \mu_V^2 T_{max} - 4 \mu_V \alpha), \\ c &= \mu_V (\mu_V^4 + 6 \mu_V^3 \mu_I + 11 \mu_V^2 \mu_I^2 - 4 \mu_V^2 \mu_I \mu_T + 6 \mu_V \mu_I^3 - 4 \mu_I^2 \mu_V \mu_T + \mu_I^4). \end{aligned}$$

For T_{max} large enough, $a > 0$ and $b < 0$. However, the sign of c , which does not contain T_{max} , depends on the data.

Next we compute:

$$\begin{aligned}\delta &= b^2 - 4ac \\ &= 16\gamma^2\mu_I(\mu_I + \mu_V)\mu_V(T_{max}\alpha\mu_I^4 + 4T_{max}\alpha\mu_V\mu_I^3 + 5\mu_I^2\mu_V^2T_{max}\alpha \\ &\quad + \mu_I^2\mu_V^2(T_{max})^2\mu_T + 4\mu_I^2\mu_V\alpha^2 - 4\mu_I^2\mu_VT_{max}\alpha\mu_T + 4\mu_I\mu_V^3T_{max}\alpha \\ &\quad + 4\mu_I\mu_V^2\alpha^2 - 4\mu_I T_{max}\alpha\mu_V^2\mu_T + \mu_V^4\alpha T_{max}).\end{aligned}$$

For large T_{max} , δ has the sign of the coefficient of $(T_{max})^2$, hence $\delta > 0$.

The roots of $\Delta = 0$, namely those of $aN^2 + bN + c = 0$, are $N_1 < N_2$:

$$N_1 = \frac{-b - \sqrt{\delta}}{2a}, \quad N_2 = \frac{-b + \sqrt{\delta}}{2a}. \quad (2.8)$$

It is clear that $N_2 > 0$, while N_1 has the sign of c . However, N_1 plays a role only if larger than $N_{crit}(+\infty)$. We also remark that N_2 is small for large T_{max} , therefore $N_2 < N_{crit}(0)$.

It is useful to determine the position of N_0 , see (2.7), with respect to N_1 and N_2 :

LEMMA 2.3. *We have $N_1 < N_0 < N_2 < N_{crit}(0)$.*

Proof. Since $B(N_0) = 0$, $\Delta(N_0) = -4AC < 0$, hence $aN_0^2 + bN_0 + c < 0$. \square

Now we are in position to begin our discussion following the position of N .

Case 1. The first case corresponds to $N_1 < N < N_2$. In such a case, $aN^2 + bN + c < 0$, hence $\Delta(N) < 0$. Obviously, $Ar^2 + Br + C$ has the sign of A which is positive.

Case 2. The second case corresponds to $N < N_1$ or $N > N_2$.

(i) If $N < N_1$, then, by Lemma 2.3, $B > 0$. Hence, $Ar^2 + Br + C > 0$ for any $r \geq 0$ since $A, B, C > 0$. It thus follows that $D_2 > 0$.

(ii) If $N > N_2$, then, by Lemma 2.3, $B < 0$. Since $\Delta > 0$, the equation $Ar^2 + Br + C = 0$ admits the two real and positive solutions

$$r_1(N) = \frac{-B - \sqrt{\Delta}}{2A}, \quad r_2(N) = \frac{-B + \sqrt{\Delta}}{2A}. \quad (2.9)$$

Consequently, the Hurwitz determinant D_2 is positive for $r_{crit}(N) \leq r < r_1(N)$ and $r > r_2(N)$, it vanishes at $r = r_1(N)$ and $r = r_2(N)$, it is negative for $r_1(N) < r < r_2(N)$.

Case 3. The third case corresponds to $N = N_1$ or $N = N_2$. In such a case, $\Delta = 0$ and the polynomial $Ar^2 + Br + C$ has the double root $r = -B/2A$. However, this solution makes sense only if $B < 0$, namely $N > N_0$. Then by Lemma 2.3, we discard the case $N = N_1$. Therefore at $N = N_2$, D_2 is positive except at $r(N_2) = -B/2A$ where it vanishes.

REMARK 2.2. *It is important to see that $r_{crit}(N) < r_1(N)$ whenever $N \geq N_2$ (see (2.2)). For $N_2 \leq N \leq N_{crit}(0)$, if $r_{crit}(N) = r_1(N)$, then we would have simultaneously $d_3 = 0$ and $D_2 = 0$ which is impossible since d_1 and d_2 are always positive. When $N > N_{crit}(0)$, $r_{crit}(N) = 0$ by convention and $r_1(N) > 0$.*

We are now in position to define the subdomain \mathcal{P} of \mathcal{I} by

$$\mathcal{P} = \{(N, r), N \geq N_2, \quad r_1(N) \leq r \leq r_2(N)\}, \quad (2.10)$$

with

$$N_2 = \frac{-b + \sqrt{\delta}}{2a}, \quad r_1(N) = \frac{-B - \sqrt{\Delta}}{2A}, \quad r_2(N) = \frac{-B + \sqrt{\Delta}}{2A},$$

and at $N = N_2$, $r_1 = r_2 = -B/2A$.

We have seen that, in the domain \mathcal{I} , d_1 and d_3 are positive, and $d_1 d_2 - d_3$ is positive except in \mathcal{P} . More precisely, $d_1 d_2 - d_3$ is negative for $N > N_2$, $r_1(N) < r < r_2(N)$ and $d_1 d_2 - d_3$ vanishes at $r = r_1(N)$ and $r = r_2(N)$.

The following theorem is a consequence of the above discussion and the Routh-Hurwitz criterion.

THEOREM 2.4. *We assume T_{max} large enough. Then the infected equilibrium $X_i = (T_i, I_i, V_i)$ is asymptotically stable for $(N, r) \in \mathcal{I} \setminus \mathcal{P}$.*

However, we can not infer from Theorem 2.4 that the infected equilibrium X_i is unstable in \mathcal{P} or its interior. This issue will be addressed in Section 3.2.

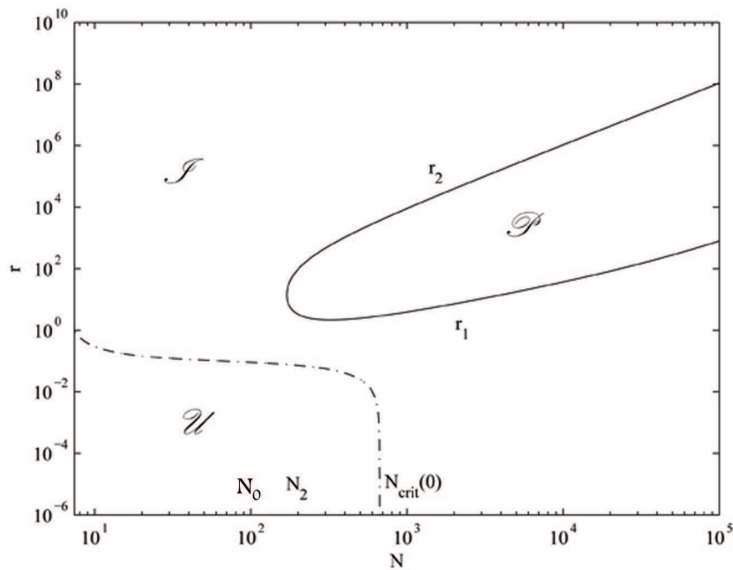


FIG. 2.2. Full portrait of the domains \mathcal{I} , \mathcal{U} and \mathcal{P} in the (N, r) quarter plan in logarithmic scales. Numerical values are as in Figure 1. Here $N_0 = 154.35$, $N_2 = 169.81$, $N_{crit}(0) = 666.67$, $r_{crit}(N_2) = 0.08$, $r_1(N_2) = r_2(N_2) = 14.03$.

2.3. Asymptotics

It is interesting to consider the asymptotical case when $T_{max} \rightarrow +\infty$. First, we

compute explicitly N_2 from Formula (2.8):

$$N_2 = \frac{1}{\gamma T_{max} \mu_I (-4\mu_I \alpha + \mu_I T_{max} \mu_V - 4\mu_V \alpha)} \left\{ \mu_V T_{max} \mu_I^3 + 3\mu_I^2 \mu_V^2 T_{max} - 4\mu_I^2 \mu_V \alpha \right. \\ \left. + \mu_I \mu_V^3 T_{max} - 4\mu_I \mu_V^2 \alpha + 2 \left\{ (\mu_V + \mu_I) \mu_I \mu_V (\alpha T_{max} \mu_I^4 + 4\mu_V T_{max} \alpha \mu_I^3) \right. \right. \\ \left. \left. + 5\mu_I^2 \mu_V^2 T_{max} \alpha + 4\mu_I^2 \mu_V \alpha^2 - 4\mu_I^2 T_{max} \mu_V \alpha \mu_T + \mu_I^2 (T_{max})^2 \mu_V^2 \mu_T \right. \right. \\ \left. \left. + 4\mu_I \mu_V^3 T_{max} \alpha + 4\mu_I \mu_V^2 \alpha^2 - 4\mu_I T_{max} \mu_V^2 \alpha \mu_T + \mu_V^4 T_{max} \alpha \right\}^{\frac{1}{2}} \right\}.$$

Therefore, for large T_{max} ,

$$N_2 = \frac{\mu_I^2 + \mu_V^2 + 3\mu_I \mu_V + 2\sqrt{\mu_V \mu_I \mu_T (\mu_I + \mu_V)}}{\gamma \mu_I} (T_{max})^{-1} + \text{L.O.T.} \quad (2.11)$$

Next, we compute, for $N_2 \leq N \leq N_{crit}(0)$,

$$r_1(N) - r_{crit}(N) =$$

$$\frac{\gamma}{2\mu_V^4 (\mu_V + \mu_I) (\gamma N T_{max} - \mu_V)} \left\{ \mu_I \mu_V^3 \gamma^2 N^3 (T_{max})^3 - 2\mu_V^2 \mu_I \gamma^2 \alpha N^3 (T_{max})^2 \right. \\ \left. - N^2 \mu_V^5 \gamma (T_{max})^2 - 2\mu_V^3 \gamma^2 \alpha N^3 (T_{max})^2 - \mu_I^2 N^2 \mu_V^3 \gamma (T_{max})^2 - 4N^2 \mu_V^4 \mu_I \gamma (T_{max})^2 \right. \\ \left. + 4\mu_V^3 \mu_I \gamma \alpha N^2 T_{max} + 4\mu_V^4 \gamma \alpha N^2 T_{max} + N \mu_V^6 T_{max} + 3N \mu_V^5 \mu_I T_{max} \right. \\ \left. + \mu_I^2 N \mu_V^4 T_{max} - \left\{ N^2 T_{max}^2 \mu_V^5 (\mu_V^5 + 6\mu_V^4 \mu_I - 2\mu_V^3 \gamma N \mu_I T_{max}) \right. \right. \\ \left. \left. + 11\mu_V^3 \mu_I^2 - 4\mu_V^3 \mu_I \mu_T + 8\mu_V^2 \gamma N \mu_I \alpha - 6\mu_V^2 \gamma N \mu_I^2 T_{max} - 4\mu_V^2 \mu_I^2 \mu_T \right. \right. \\ \left. \left. + 6\mu_V^2 \mu_I^3 + \mu_V \gamma^2 N^2 \mu_I^2 (T_{max})^2 - 4\mu_V \gamma^2 N^2 \alpha \mu_I T_{max} + 8\mu_V \gamma N \mu_I^2 \alpha \right. \right. \\ \left. \left. - 2\mu_V \gamma N \mu_I^3 T_{max} + \mu_V \mu_I^4 - 4\gamma^2 N^2 \mu_I^2 \alpha T_{max} \right\}^{\frac{1}{2}} N \gamma T_{max} - 2\mu_V^5 N \mu_T T_{max} \right. \\ \left. - 2\mu_V^4 N \mu_T \mu_I T_{max} + \left\{ N^2 (T_{max})^2 \mu_V^5 (\mu_V^5 + 6\mu_V^4 \mu_I - 2\mu_V^3 \gamma N \mu_I T_{max}) \right. \right. \\ \left. \left. + 11\mu_V^3 \mu_I^2 - 4\mu_V^3 \mu_I \mu_T + 8\mu_V^2 \gamma N \mu_I \alpha - 6\mu_V^2 \gamma N \mu_I^2 T_{max} - 4\mu_V^2 \mu_I^2 \mu_T \right. \right. \\ \left. \left. + 6\mu_V^2 \mu_I^3 + \mu_V \gamma^2 N^2 \mu_I^2 (T_{max})^2 - 4\mu_V \gamma^2 N^2 \alpha \mu_I T_{max} + 8\mu_V \gamma N \mu_I^2 \alpha \right. \right. \\ \left. \left. - 2\mu_V \gamma N \mu_I^3 T_{max} + \mu_V \mu_I^4 - 4\gamma^2 N^2 \mu_I^2 \alpha T_{max} \right\}^{\frac{1}{2}} \mu_V \right\}$$

that we take at $N = N_2$. As $T_{max} \rightarrow +\infty$, it comes out that the quantity $r_1(N_2) - r_{crit}(N_2)$ has a finite limit $\ell > 0$:

$$\ell = \frac{1}{(\mu_V^2 + 2\mu_I \mu_V + \mu_I^2 + 2\sqrt{\mu_I \mu_V \mu_T (\mu_I + \mu_V)}) \mu_I \mu_V} \left\{ \left\{ \mu_I \mu_V \mu_T \right. \right. \\ \left. \left. + \mu_I \sqrt{\mu_I \mu_V \mu_T (\mu_I + \mu_V)} + \mu_V \sqrt{\mu_I \mu_V \mu_T (\mu_I + \mu_V)} \right\} \left\{ \mu_V^2 + 3\mu_I \mu_V + \mu_I^2 \right. \right. \\ \left. \left. + 2\sqrt{\mu_I \mu_V \mu_T (\mu_I + \mu_V)} \right\} \right\}.$$

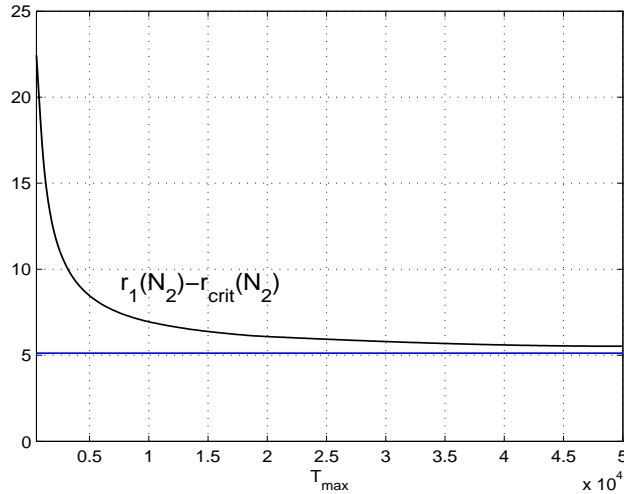


FIG. 2.3. $r_1(N_2) - r_{crit}(N_2)$ is computed vs. T_{max} . The limiting value is $\ell = 5.12$. For the usual value $T_{max} = 1500.0$, we have $r_1(N_2) - r_{crit}(N_2) = 13.95$.

3. Hopf bifurcation and instability

While the Routh-Hurwitz criterion ensures asymptotic stability, clearly instability does not hold automatically when the criterion is not satisfied. Additional information is needed. In this section we will prove that the infected steady state is unstable in the interior of the region \mathcal{S} and Hopf bifurcation occurs at the boundary on a vertical line.

3.1. Parametrization of the eigenvalues

Let us fix $N > N_2$. We may simply write r_1 (resp. r_2) for $r_1(N)$ (resp. $r_2(N)$). We consider the family of infected equilibria $X_i(r)$, smoothly parameterized by the logistic parameter $r \geq r_{crit} = r_{crit}(N)$.

The Jacobian matrix (2.3) reads

$$J(X_i(r)) = \begin{pmatrix} r - \mu_T - \frac{2rT_i}{T_{max}} - \gamma V_i(r) & 0 & -\gamma T_i \\ \gamma V_i(r) & -\mu_I & \gamma T_i \\ 0 & N\mu_I & -\mu_V \end{pmatrix},$$

where

$$V_i(r) = \frac{\alpha N}{\mu_V} - \frac{\mu_T}{\gamma} + \frac{r}{\gamma} \left(1 - \frac{\mu_V}{N\gamma T_{max}} \right),$$

and the associated characteristic equation (2.4) is:

$$\lambda^3 + d_1(r)\lambda^2 + d_2(r)\lambda + d_3(r) = 0.$$

We recall that $d_3 > 0$ in \mathcal{S} , hence $d_3(r) > 0$ for $r > r_{crit}$. Let us denote by $\lambda_i(r)$, $i = 1, 3$, the three eigenvalues. At fixed r , one of the eigenvalues is real whereas the others are either real or complex conjugate. The mappings $r \mapsto \lambda_i(r)$ are continuous, and smooth except at exceptional points where two of the λ_i 's coincide as in Figure 3.1 (see [4, Chap. II, 1]).

We also have the notations, according to Subsection 2.4:

$$D_1(r) = d_1(r), \quad D_2(r) = d_1(r)d_2(r) - d_3(r). \quad (3.1)$$

The relation between the Hurwitz determinant $D_2(r)$ and the sums of pairs of λ_i 's is given by Orlando's formula (see [3, Chap. XV, 7]):

$$D_2(r) = -(\lambda_1(r) + \lambda_2(r))(\lambda_2(r) + \lambda_3(r))(\lambda_1(r) + \lambda_3(r)). \quad (3.2)$$

From the results of Section 2 and Theorem 2.4, we know that the equilibria $X_i(r)$ are asymptotically stable whenever $r_{crit} < r < r_1$ or $r > r_2$. Stability may be lost when either $d_3(r) = 0$ or $D_2(r) = 0$. The former case corresponds to $r = r_{crit}$ where, say, $\lambda_1 = 0$ and

$$\lambda_{2,3} = \frac{1}{2} \left(-d_1 \pm \sqrt{d_1^2 - 4d_2} \right) < 0,$$

(see Figure 3.1). The latter case occurs at $r = r_1$ where a pair of purely imaginary complex roots exists, as we are going to see. Before we observe:

LEMMA 3.1. *At least one of the eigenvalues is negative whenever $r > r_{crit}$.*

Proof. For $r_{crit} < r < r_1$, all the eigenvalues are negative or have negative real part. If a real eigenvalue crosses the origin at some value $r \geq r_1$, then d_3 vanishes, which contradicts $d_3(r) > 0$ for $r > r_{crit}$. \square

As a consequence, only a pair of complex conjugate eigenvalues may cross the imaginary axis.

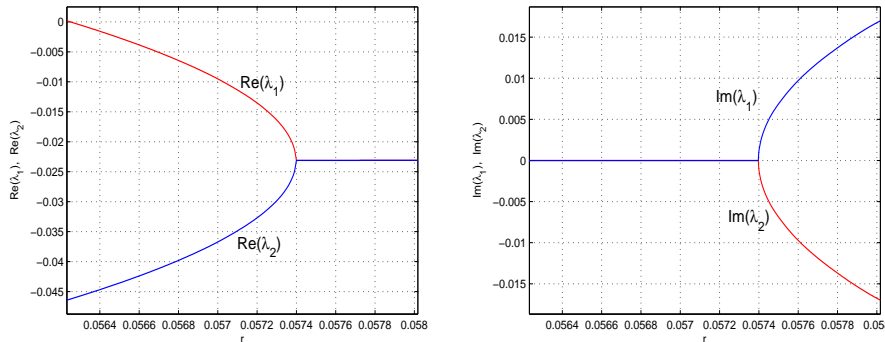


FIG. 3.1. Real part (left) and imaginary part (right) of eigenvalues λ_1 and λ_2 as a function of the bifurcation parameter r at fixed $N = 300$. The graphic starts at $r_{crit} = 0.05625$, $\lambda_1 = \lambda_2$ at $r = 0.05734$. The real eigenvalue $\lambda_3 < -10$ is not pictured.

3.2. Hopf bifurcation

Let examine the values $r = r_1$ and $r = r_2$. According to Lemma 3.1 one of the eigenvalues is negative, say λ_3 . Since $D_2(r_j) = 0$, $j = 1, 2$, it follows from Orlando's formula (3.2) that $\lambda_1(r_j) + \lambda_2(r_j) = 0$. More precisely, there is a simple Hopf bifurcation:

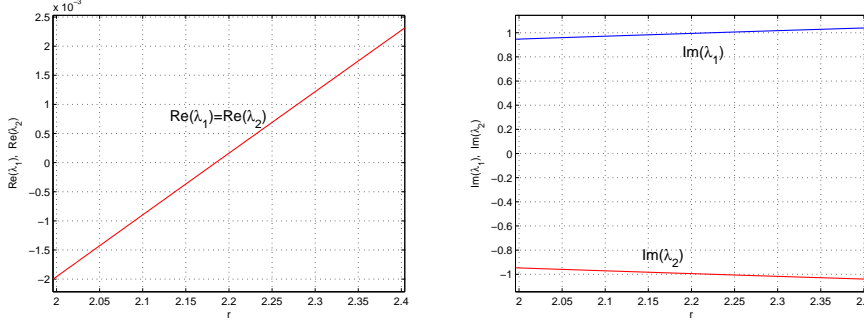


FIG. 3.2. Real part (left) and imaginary part (right) of eigenvalues λ_1 and λ_2 as a function of the bifurcation parameter r at fixed $N=300$. They cross the imaginary axis at $r_1=2.1846$.

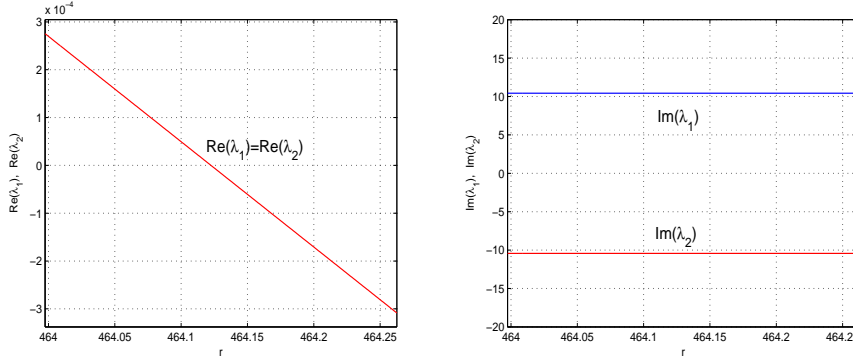


FIG. 3.3. For larger r , real part (left) and imaginary part (right) of eigenvalues λ_1 and λ_2 as a function of the bifurcation parameter r at fixed $N=300$. They cross the imaginary axis at $r_2=464.1225$.

THEOREM 3.2. (i) At $r=r_j, j=1,2$, the eigenvalues $\lambda_1(r_j)$ and $\lambda_2(r_j)$ are purely imaginary and conjugate;
(ii) in a neighborhood of r_j , $\lambda_2(r) = \overline{\lambda_1(r)}$, the mapping $r \mapsto \lambda_1(r)$ is smooth and $(d/dr)\text{Re}(\lambda_1)(r_j) \neq 0, j=1,2$;
(iii) the third eigenvalue $\lambda_3(r_j)$ is real and negative.

Proof. We apply a criterion of Liu (see [5, 6], [7]). It remains to prove that $dD_2/dr(r_j) \neq 0$.

Let us solve $dD_2/dr(r_j)=0$ which is easy: it follows from (2.6) that $2Ar_j + B=0, j=1,2$, hence $r_1=r_2$ which happens only at $N=N_2$. Since $N > N_2$, we reach a contradiction and it holds $dD_2/dr(r_j) \neq 0$. \square

3.3. Instability

We are now in position to complete the analysis begun in Theorem 2.4.

THEOREM 3.3. The infected equilibrium $X_i = (T_i, I_i, V_i)$ is unstable for $(N, r) \in \overset{\circ}{\mathcal{P}}$, the interior of \mathcal{P} .

Proof. Let $N > N_2$ be fixed and $r \in (r_1(N), r_2(N))$. We have $D_2(r) < 0$. Again, according to Lemma 3.1, $\lambda_3 < 0$. Hence, by the reciprocal of Ruth-Hurwitz criterion, one of the eigenvalues $\lambda_k, k=1,2$ has a non-negative real part. If $\text{Re}(\lambda_k)$ is positive,

instability is proved. Therefore, assume $\text{Re}(\lambda_k)=0$. Clearly $\lambda_k \neq 0$ since $d_3 > 0$. Hence, $\lambda_1(r)$ and $\lambda_2(r)$ should be purely imaginary and conjugate eigenvalues and $\lambda_1(r)+\lambda_2(r)=0$. Then, by Orlando's formula (3.2), $D_2(r)=0$ and we reach a contradiction. More precisely, we have that $\lambda_3(r) < 0$ and $\lambda_1(r)$ and $\lambda_2(r)$ have positive real part. \square

3.4. Numerical results

In order to show the infected steady state stability numerically, we can fix $N = 300$, start from the value $r_{crit} = 0.05625$, increase the logistical parameter r monotonically until a critical condition is reached such that any further change would result in instability, other parameters can be found in Fig. 1. We present the graphs of numerical solution of the system (1.1)-(1.3) and the trajectory of the solution in the T - V phase plane, see Figures 3.4 to 3.8. Initial data are $T_0 = T_u$, $I_0 = 0.0$, $V_0 = 0.0185$. Some figures assure that this solution approaches the limit cycle in the instability subdomain \mathcal{P} .

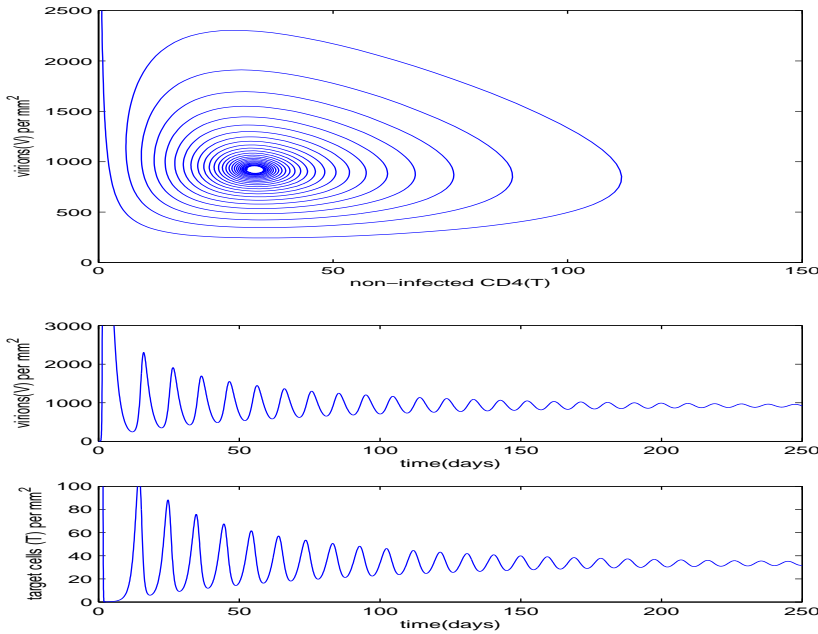


FIG. 3.4. Numerical solution of System (1.1)-(1.3) in the domain \mathcal{S} . Parameter values are $N = 300$ and $r_{crit} = 0.05625 < r = 1.0 < r_1 = 2.1846$. The infected equilibrium is stable.

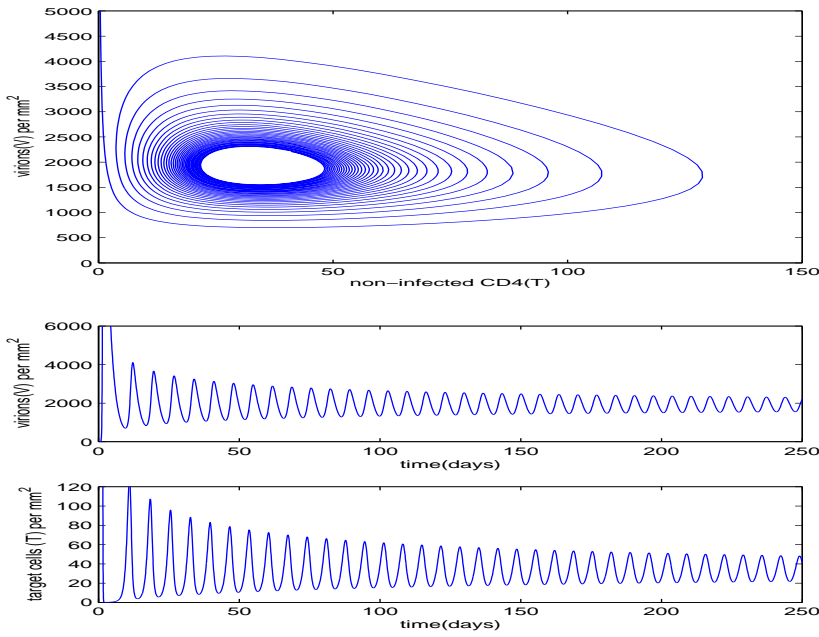


FIG. 3.5. Numerical solution of System (1.1)-(1.3) in the domain \mathcal{S} . Parameter values are $N = 300$ and $r = 2.0 < r_1 = 2.1846$. The infected equilibrium is stable.

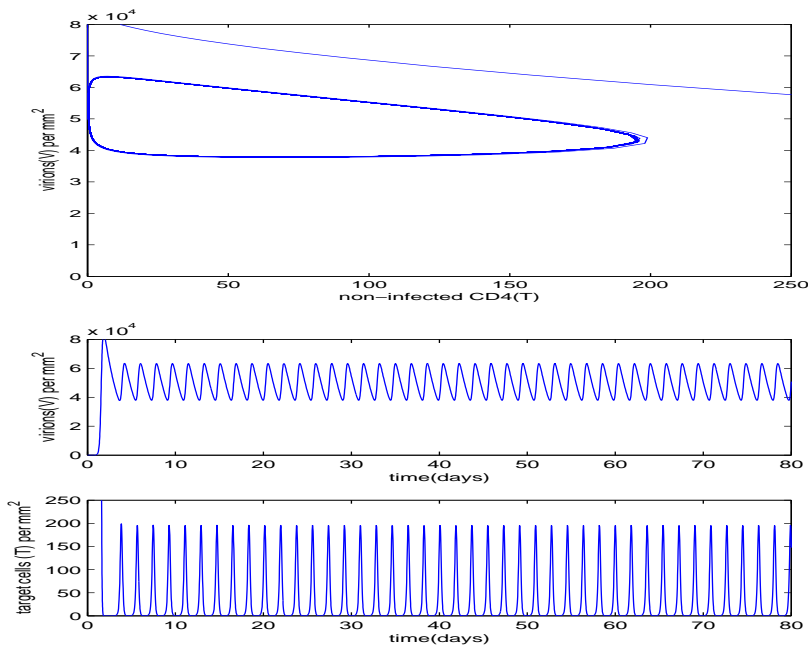


FIG. 3.6. Numerical solution of System (1.1)-(1.3) in \mathcal{P} . Parameter values are $N = 300$ and $r_1 < r = 50.0 < r_2$. The infected equilibrium is unstable, a periodic orbit is observed.

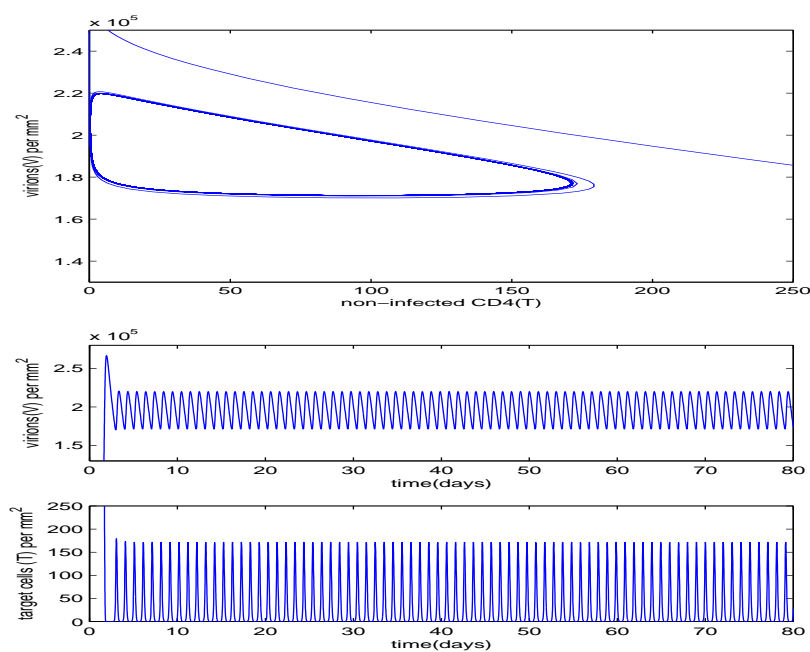


FIG. 3.7. Numerical solution of System (1.1)-(1.3) in \mathcal{P} . Parameter values are $N=300$ and $r=200.0 < r_2=464.1225$. The infected equilibrium is unstable, a periodic orbit is observed.

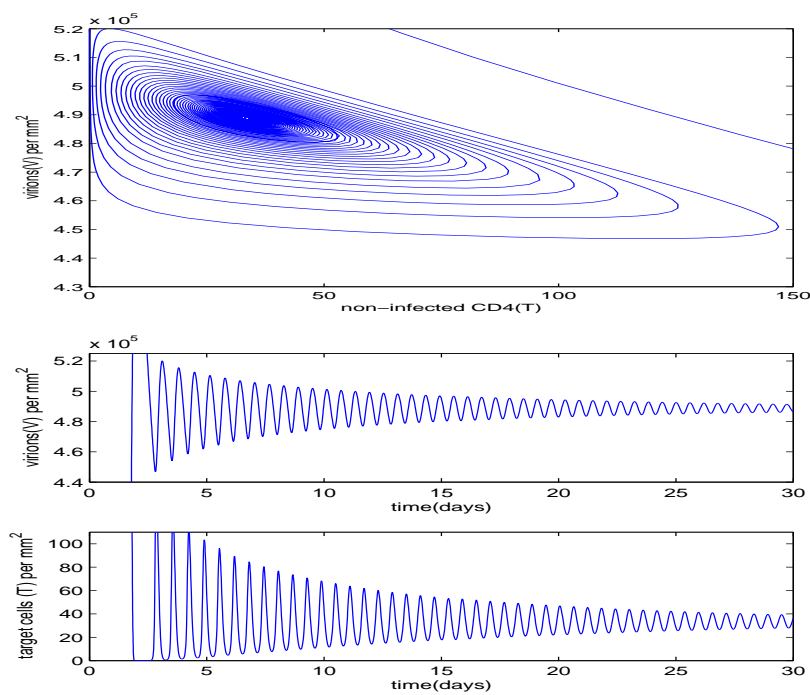


FIG. 3.8. Numerical solution of System (1.1)-(1.3) in \mathcal{I} . Parameter values are $N=300$ and $r=500.0 > r_2=464.1225$. The infected equilibrium is again stable.

Acknowledgement. We gratefully thank Luca Lorenzi for his comments.

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