

Viral Blips May Not Need a Trigger: How Transient Viremia Can Arise in Deterministic In-Host Models*

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Abstract. Recurrent infection is characterized by short episodes of high viral reproduction, separated by long periods of relative quiescence. This recurrent pattern is observed in many persistent infections, including the “viral blips” observed during chronic infection with the human immunodeficiency virus (HIV). Although in-host models which incorporate forcing functions or stochastic elements have been shown to display viral blips, simple deterministic models also exhibit this phenomenon. We describe an analytical study of a 4-dimensional HIV antioxidant-therapy model which exhibits viral blips, showing that an increasing, saturating infectivity function contributes to the recurrent behavior of the model. Using dynamical systems theory, we hypothesize four conditions for the existence of viral blips in a deterministic in-host infection model. In particular, we explain how the blips are generated, which is not due to homoclinic bifurcation since no homoclinic orbits exist. These conditions allow us to develop very simple (2- and 3-dimensional) infection models which produce viral blips, and we determine the complete parameter range for the 3-dimensional model in which blips are possible, using stability analysis. We also use these conditions to demonstrate that low-dimensional in-host models with linear or constant infectivity functions cannot generate viral blips. Finally, we demonstrate that a 5-dimensional immunological model satisfies the conditions and exhibits recurrent infection even with constant infectivity; thus, an increasing, saturating infectivity function is not necessary if the model is sufficiently complex.

Key words. recurrent infection, HIV viral blips, bifurcation theory, dynamical system

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1. Introduction. Mathematical models have a rich history in the investigation of infectious disease and have proven foundational to our understanding of epidemiological dynamics and control [2]. Over the last several decades, mathematical ideas regarding the transmission of infectious agents between hosts have been extended to develop models of infection within a single infected individual [29]. These *within-host* models typically track the populations of pathogens and relevant cellular populations,

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such as the cells which may be infected by the pathogen, infected cells, and possibly the host's immune response to the infectious agent.

Although current work in the field addresses a wide range of pathogens and diseases, the most well developed area of within-host modeling concerns the dynamics of viral infections. Viruses are infectious **intracellular parasites**; they can reproduce only inside the living cells of host organisms, and must spread from host to host for continued existence. In animals, viruses tend to exhibit either an acute or a persistent mode of infection to ensure this continuity [41]. An acute viral infection is characterized by a relatively short period of symptoms and resolution within days or weeks. In these cases the host immune response usually clears the infection, and a memory immune response can then prevent the same virus from infecting the same host. Pathogens such as the influenza virus and the rhinovirus typically cause acute viral infections. In contrast, persistent infections [3] establish long-lasting infections in which the virus is not fully eliminated but remains in infected cells. Persistent infections involve both silent and productive infection stages without rapid killing or excessive damage to infected cells. Latent infection is a type of persistent infection.

In latent infection, no clinical signs or detectable infectious cells can be observed during the silent or quiescent stage of low-level viral replication. However, the virus has not been completely cleared, and recurrent episodes of rapid viral production and release can periodically punctuate relatively long periods in the silent stage. These episodes of recurrent infection are a clinical phenomenon observed in many latent infections [27].

Recurrent infection can also occur in the context of drug treatment for persistent infections. The human immunodeficiency virus (HIV), for instance, is now treated by highly active antiretroviral therapy (HAART). When the concentration of HIV viral particles in the blood, called *viremia*, is measured in individuals beginning HAART treatment, it decays rapidly at first and then follows a slower second stage of decay. For individuals on long-term HAART, viremia can typically be held below the limit of detection for months or years [5, 9], that is, HIV is undetectable in the blood using standard techniques. Nonetheless, supersensitive assays are able to detect low levels of virus in the blood during this stage [9, 32, 31]. Moreover, these long periods of relative quiescence are sometimes interrupted by unexplained intermittent episodes of high viremia, termed viral blips [36, 35]. Although these blips have been the focus of much recent research [13, 18, 15, 6], their etiology is still not well understood [18, 35].

To set the stage for a review of mathematical models of viral blips, we quickly review some of the main features of HIV infection. HIV infects specific cells of the immune system, in particular the $CD4^+$ T cells. Once infected, a $CD4^+$ T cell may be either *productively infected*, meaning that the cell actively produces new HIV viral particles, or may enter a quiescent long-lived stage called *latently infected*. Productively infected cells are vulnerable to attack by other arms of the immune system, such as the $CD8^+$ or *cytotoxic* T cells, but latently infected cells are essentially invisible to the immune system and present the main difficulty in clearing the disease. Because $CD4^+$ T cells themselves are an important component of the immune response, these quiescent cells can be woken up, or *activated*, in response to challenges to the immune system. For example, the presence of foreign particles called *antigens* can induce latently infected cells to enter the productively infected stage and begin to produce new HIV viral particles.

To date, many possible explanations for viral blips during HIV infection have been explored mathematically. An early model of the long-term pathogenesis of HIV [12] incorporates the activation of T cells in response to antigens, as suggested

by [10]. In [12], both HIV and non-HIV antigen exposure are considered in a coupled deterministic-stochastic model. The probability of antigenic exposure evolves continuously in time, and Poisson distributed exposure events are generated, by simulation, at the appropriate probabilities. This approach captures a number of features of long-term HIV dynamics, including episodic bursts of viral replication. Further work [11] considers the number of distinct antigens which activate the $CD4^+$ T cell pool as a random variable, coupled to an ODE model. Stochastic changes to this number drive fluctuations in the basic reproductive number and viral load. This model is also able to capture the episodic burst-like nature of HIV viral replication during long-term infection.

More recent models are based on the recurrent activation of latently infected T cells, a class of infected cells described above. By introducing antigen concentration as an explicit variable, Jones and Perelson [23] developed a system of ODEs that exhibits viral blips. The model describes the proliferation and contraction of the $CD8^+$ T cell population and exhibits low viral loads under HAART, as expected. Secondary infection by non-HIV pathogens, modeled as an initial concentration of antigen, activates the immune system and is shown by numerical simulation to elicit a transient viral blip. The same authors further showed that occasional infections by other pathogens can generate viral blips by the activation of uninfected cells or latently infected cells, predicting that blip amplitude and viral load will be related by a power law [24].

In further work, by considering the asymmetric division of latently infected cells, Rong and Perelson [35] developed a 4-dimensional ODE model based on the basic model of latent cell activation [33]. This new model not only generates viral blips, but also maintains a stable latent reservoir in patients on HAART. In this model, latently infected cells can divide to produce latently infected daughter cells, or differentiate into activated, productively infected cells, depending on antigen concentrations. In a further 5-dimensional ODE model [36], these two types of daughter cells were distinguished as dependent variables, and a contraction phase was added to the activated daughter cells. Numerical simulation showed that both cases gave rise to viral blips and a stable latent reservoir, which were generated from the activated and the latently infected daughter cells, respectively. In both papers [35, 36], the antigenic stimulation of latently infected cells was modeled as an “on-off” forcing function, and viral blips were initiated during brief pulses in which this activation function was “on.”

Most recently, a stochastic model developed by Conway and Coombs [6] presented another possible treatment of latent cell activation. In this model [6], the authors derived the probability generating function for a multitype branching process describing the populations of productively and latently infected cells and free virus. A numerical approach was then used to estimate the probability distribution for viral load, which was used to predict blip amplitudes and frequencies; blip durations were studied by simulation. The authors were able to conclude that with effective drug treatment and perfect adherence to drug therapy, viral blips *cannot* be explained by stochastic activation of latently infected cells, and other factors such as transient secondary infections, or imperfect adherence, must be involved.

In order to elicit transient episodes of high viral replication, all of the models described above incorporate either transient immune stimulation, for example, as a forcing function, or stochastic components which act as “triggers” preceding the generation of each viral blip. Thus something exogenous to the within-host infection—for example, a secondary infection which transiently activates the immune response—is necessary to produce the patterns observed in recurrent infection. It should be noted

that, clinically, viral blips in HIV typically have varying magnitudes, frequencies, and durations, and thus stochastic models offer a natural approach to describing this phenomenon. We note, however, that the analysis of fully deterministic models can offer insights into the global behavior of the system that are difficult to assess in more complex models. Moreover, nonlinear deterministic systems can indeed display varying amplitudes and frequencies of motion merely by using a time-varying parameter in the system; these are in fact key characteristics of nonlinear systems.

Thus, given our familiarity with previous stochastic or forcing function approaches, we were mathematically intrigued when two recent studies demonstrated that quite simple deterministic systems can exhibit viral blips. Based on the close relation between recurrent infection and antibody immunodeficiency, Yao, Hertel, and Wahl [42] investigated a 5-dimensional ODE model which included antibody concentrations as an explicit variable, and exhibited transient periods of high viral replication. By numerical simulation at specific, meaningful parameter values, the authors explored factors affecting the intervals between recurrent episodes and their severity. Later, an even simpler 4-dimensional antioxidant model [40] was explored for HIV and was similarly used to simulate viral blips with appropriate parameter values. These examples indicated that deterministic systems can produce blips as part of the natural, rich behavior of the nonlinear system. However, for both of these deterministic models, numerical simulation was used to delineate behavior and explore parameter space; the mathematical underpinnings which gave rise to recurrent infection, or viral blips, remained unexplained.

In this paper, we take advantage of dynamical systems theory to reinvestigate deterministic in-host infection models that exhibit viral blips. By examining the bifurcation behavior in parameter spaces close to the region where blips occur, we propose an understanding of the features of the dynamical system which underlie this complex model behavior.

We then propose four conditions which, when satisfied, guarantee that an in-host infection model will exhibit long periods of quiescence, punctuated by brief periods of rapid replication: viral blips. Based on these conditions, we develop very simple 2- and 3-dimensional models that produce blips and apply stability criteria to determine parameter ranges which may yield this phenomenon. Moreover, for the 2-dimensional model, we apply Poincaré–Bendixson theory to prove the existence of the blips. We also pay particular attention to how viral blips are generated; contrary to the expectation that viral blips may arise through homoclinic bifurcation, we show that no homoclinic orbits can exist in the 4-dimensional, 3-dimensional, and 2-dimensional models developed in this paper. Most of the models discussed share a similar infectivity function, describing the rate at which new infected cells are created. In a final section, we examine a related 5-dimensional immunological model and demonstrate that viral blips are possible in this system even when infectivity is constant. The main conclusion of our work is that exogenous, stochastic triggers are not necessary for the generation of viral blips; patterns of recurrent infection can instead naturally arise as part of the rich behavior of the underlying nonlinear system.

The rest of the paper is organized as follows. In section 2, the previously proposed 4-dimensional HIV antioxidant model is reinvestigated analytically. Based on the insights of our bifurcation analysis, conditions for generating viral blips are proposed. In section 3, we use these conditions to propose a simpler 3-dimensional in-host infection model, and parameter ranges which will exhibit blips in the simpler model are determined. In section 4, we develop a 2-dimensional model, characterized by an increasing and saturating infectivity function, which can also generate viral blips. In

section 5, we demonstrate that a 5-dimensional immunological model [42] can exhibit viral blips with constant infectivity. In the final section, we discuss the implications of our results and demonstrate that blips of varying amplitude and frequency can be recovered in our models with deterministic but time-dependent parameter values.

2. A 4-Dimensional Model Which Exhibits Viral Blips. In this section, we reconsider a 4-dimensional HIV antioxidant-supplementation therapy model which was developed and studied numerically in [40]. This model novelly introduces reactive oxygen species (ROS) and antioxidants to an in-host model of HIV infection. In uninfected individuals, ROS play a positive physiological role at moderate levels [17, 25, 8, 21, 19] but are harmful at high levels [40].

HIV infection may lead to chronic and acute inflammatory diseases, which may cause high levels of ROS [26] as well as lowered antioxidant levels; this phenomenon has been observed clinically and experimentally [26, 16, 22, 37, 39]. In addition, high levels of ROS may cause damage to $CD4^+$ T cells, impair the immune response to HIV [38], and exacerbate infected cell apoptosis, releasing more HIV virions. Thus, infected cells produce high levels of ROS, which in turn increase the viral production by infected cells. To control this cycle, antioxidant supplementation (vitamin therapy) has been suggested as a potential complement to HIV therapy [16, 14], with the aim of counteracting and reducing ROS concentrations [17].

The equations of the 4-dimensional model are described by [40]

$$(2.1) \quad \begin{aligned} \dot{x} &= \lambda_x - d_x x - (1 - \epsilon)\beta(r)xy, \\ \dot{y} &= (1 - \epsilon)\beta(r)xy - d_y y, \\ \dot{r} &= \lambda_r + ky - mar - d_r r, \\ \dot{a} &= \lambda_a + \alpha - par - d_a a, \end{aligned}$$

where a dot indicates the derivative with respect to time t ; x , y , r , and a represent, respectively, the population densities of the uninfected $CD4^+$ T cells, infected $CD4^+$ T cells, ROS, and antioxidants. The constant λ_x denotes the production rate of $CD4^+$ T cells, and $d_x x$ is the death rate. Uninfected cells become infected at rate $(1 - \epsilon)\beta(r)xy$, where ϵ is the effectiveness of drug therapy, and d_y is the per-capita death rate of infected $CD4^+$ T cells. ROS are generated naturally at rate λ_r and by the infected cells at rate ky ; the ROS decay at rate $d_r r$ and are eliminated by interaction with antioxidants at rate mar . Antioxidants are introduced into the model through natural dietary intake at a constant rate λ_a and through antioxidant supplementation at rate α , which is treated as a bifurcation parameter. Antioxidants are eliminated from the system by natural decay at rate $d_a a$ and by reacting with the ROS at rate par , where p is much smaller than m .

An important novel feature of this model is that the infectivity $\beta(r)$ is a positive, increasing, and saturating function of r (ROS),

$$(2.2) \quad \beta(r) = b_0 + \frac{r(b_{\max} - b_0)}{r + r_{\text{half}}},$$

where b_0 represents the infection rate in the ROS-absent case, while b_{\max} denotes the maximum infection rate, and r_{half} is the ROS concentration at half maximum. It is obvious that $\beta(r) > 0$, and it is also assumed that $0 < \epsilon < 1$. Therefore, all the parameters in (2.1) and (2.2) are positive. The experimental values used for studying model (2.1) are given in Table 2.1. Importantly, these parameters were chosen with careful reference to clinical studies, such that the predicted equilibrium densities are

Table 2.1 *Parameter values used in model (2.1) [40].*

| Parameter | Value |
|-------------------|--|
| λ_x | 60.76 cells $\mu\text{L}^{-1} \text{ day}^{-1}$ |
| d_x | 0.0570 day^{-1} |
| d_y | 1.0 day^{-1} |
| λ_a | 2.74×10^{13} molecules $\mu\text{L}^{-1} \text{ day}^{-1}$ |
| d_a | 0.0347 day^{-1} |
| ε | $\frac{1}{3}$ |
| b_0 | 2.11×10^{-4} cell $^{-1} \mu\text{L} \text{ day}^{-1}$ |
| b_{\max} | 0.00621 cell $^{-1} \mu\text{L} \text{ day}^{-1}$ |
| r_{half} | 3.57×10^{13} molecules μL^{-1} |
| d_r | 1.66×10^7 day^{-1} |
| λ_r | 1.86×10^{21} molecules $\mu\text{L}^{-1} \text{ day}^{-1}$ |
| k | 1.49×10^{19} molecules cell $^{-1} \text{ day}^{-1}$ |
| m | 1.27×10^{-6} molecule $^{-1} \mu\text{L} \text{ day}^{-1}$ |
| p | 5.04×10^{-14} molecule $^{-1} \mu\text{L} \text{ day}^{-1}$ |

clinically reasonable. Also note that the densities of antioxidants and ROS are of order 10^{13} per μL , while cell densities are of order 10^2 or 10^3 per μL .

In [40], this model was explored numerically to assess the potential of antioxidant therapy as a complement to HIV drug therapy. In that study, regions of oscillatory behavior, reminiscent of viral blips, were observed. In the following subsections we perform a thorough equilibrium and stability analysis of the model in order to shed further light on the factors underlying these rich behaviors.

2.1. Well-Posedness of the Solutions of System (2.1).

By defining

$$\Gamma = \{(x, y, a, r) \in R^4 \mid 0 \leq x \leq \frac{\lambda_x}{d_x}, 0 \leq x+y \leq \frac{\lambda_x}{d}, 0 \leq r \leq \frac{\lambda_r + k\lambda_x/\tilde{d}}{d_r}, 0 \leq a \leq \frac{\lambda_a + \alpha}{d_a}\},$$

we can show that Γ is a positively invariant set and attracts all nonnegative solutions of (2.1), by using the method of variation of constants and differential inequality. The details of the proof can be found in [46].

2.2. Equilibrium Solutions of (2.1) and Their Stability. To find the equilibrium solutions of (2.1), simply setting $\dot{x} = \dot{y} = \dot{r} = \dot{a} = 0$ yields two solutions, the uninfected equilibrium solution E_0 and the infected equilibrium solution E_1 , given, respectively, by

$$(2.3) \quad E_0 : (x_{e0}, y_{e0}, r_{e0}, a_{e0}) = \left(\frac{\lambda_x}{d_x}, 0, r_{e0}, \frac{\lambda_r - d_r r_{e0}}{m r_{e0}} \right),$$

where r_{e0} is determined by the equation

$$(2.4) \quad F_0(r, \alpha) \equiv \alpha + \lambda_a + \frac{1}{m} \left(p d_r r - \frac{d_a \lambda_r}{r} \right) + \frac{d_a d_r - p \lambda_r}{m} = 0$$

and

$$(2.5) \quad E_1 : (x_{e1}, y_{e1}, r_{e1}, a_{e1}), \quad x_{e1} = \frac{d_y}{(1-\epsilon)\beta(r_{e1})},$$

$$y_{e1} = \frac{\lambda_x - d_x x_{e1}}{(1-\epsilon)\beta(r_{e1})x_{e1}}, \quad a_{e1} = \frac{\lambda_a + \alpha}{d_a + p r_{e1}},$$

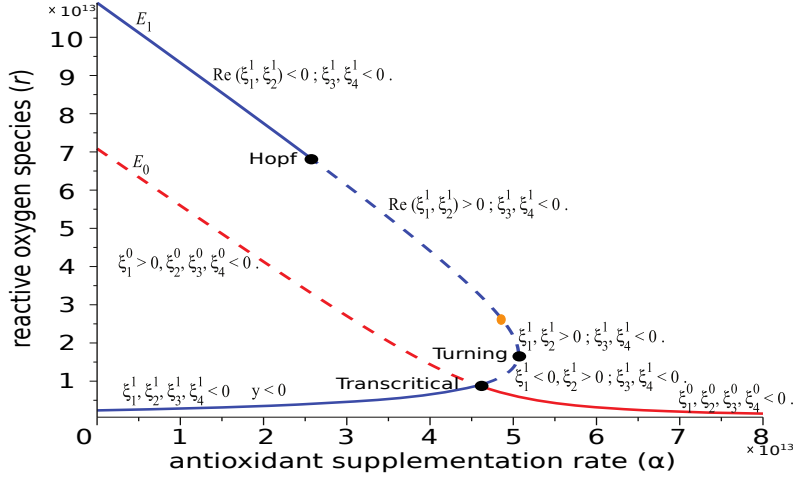


Fig. 2.1 Bifurcation diagram for the 4-dimensional HIV antioxidant-therapy model (2.1) projected on the r - α plane, restricted to the first quadrant, with the red and blue lines denoting E_0 and E_1 , and the dashed and solid lines indicating unstable and stable, respectively.

where r_{e1} is a function in the system parameters, particularly α (see the function F_1 in 2.8)). Both E_0 and E_1 are expressed in terms of r (r_{e0} or r_{e1}) for convenience.

We first consider the uninfected equilibrium E_0 . The solution of r_{e0} is determined by (2.4), which is a quadratic equation in r . To simplify the analysis, we use r to express the parameter α since (2.4) is linear in α , and α is treated as a bifurcation parameter. Thus, solving $F_0(r, \alpha) = 0$ for α , we obtain

$$(2.6) \quad \alpha_0(r_{e0}) = -\lambda_a - \frac{1}{m} \left(p d_r r_{e0} - \frac{d_a \lambda_r}{r_{e0}} \right) - \frac{d_a d_r - p \lambda_r}{m}.$$

To find the stability of the equilibrium solution E_0 , we first evaluate the Jacobian of system (2.1) at E_0 to get $J_0(r_{e0})$, where (2.6) has been used, and then we use $\det(\xi I - J_0)$ to obtain the fourth-degree characteristic polynomial given by $P_0(\xi, r_{e0}) = (\xi + d_x)[\xi^2 + (p r_{e0} + d_a + \frac{\lambda_r}{r_{e0}})\xi + (\frac{d_a \lambda_r}{r_{e0}} + p d_r r_{e0})](\xi + P_{0r})$, where

$$(2.7) \quad P_{0r} = d_y - \frac{(1 - \epsilon)\lambda_x(b_0 r_{\text{half}} + r_{e0} b_{\text{max}})}{d_x(r_{e0} + r_{\text{half}})}.$$

$P_0(\xi, r_{e0})$ contains three factors: the first is a linear polynomial of ξ , the second is a quadratic polynomial of ξ , and both are stable polynomials (i.e., their roots (eigenvalues) have negative real part); thus the stability of E_0 depends only on the third factor, a linear polynomial of ξ . Therefore, when $P_{0r} > 0$ ($P_{0r} < 0$), the equilibrium solution E_0 is asymptotically stable (unstable).

The bifurcation diagram for system (2.4) is shown in Figure 2.1, where only the part in the first quadrant is depicted. The graph for the equation $F_0(r, \alpha) = 0$ given in (2.4) is shown as the red line in Figure 2.1, which clearly shows a hyperbola. It is seen from this red line that the relation (2.4) also defines a single-valued function r in α . More precisely, it can be shown that the biologically meaningful solutions must be located on the first quadrant and above, including the red line, since E_0 has the component $y_{e0} = 0$.

Next, consider the infected equilibrium solution E_1 . The solution of r_{e1} can be similarly obtained by solving for r from the equation

$$(2.8) \quad F_1(r, \alpha) = \lambda_r + \frac{k\lambda_x}{d_y} - \frac{kd_x(r + r_{\text{half}})}{(1 - \epsilon)(b_0 r_{\text{half}} + b_{\text{max}} r)} - \frac{mr(\lambda_a + \alpha)}{pr + d_a} - d_r r = 0,$$

which is again a linear function of α , and we can use r_{e1} to express α as

$$(2.9) \quad \alpha_1(r_{e1}) = -\lambda_a + \frac{\lambda_r(pr_{e1} + d_a)}{mr_{e1}} + \frac{k\lambda_x(pr_{e1} + d_a)}{mr_{e1}d_y} - \frac{kd_x(r_{e1} + r_{\text{half}})(pr_{e1} + d_a)}{mr_{e1}(1 - \epsilon)(b_0 r_{\text{half}} + b_{\text{max}} r_{e1})} - \frac{(pr_{e1} + d_a)d_r}{m}.$$

The graph of the equations $F_0(r, \alpha) = 0$ given in (2.4) and $F_1(r, \alpha) = 0$ given in (2.8) is shown in Figure 2.1. To find the stability of E_1 , in a similar way, we evaluate the Jacobian of (2.1) at E_1 to obtain the fourth-degree characteristic polynomial, $P_1(\xi, r_{e1}) = \xi^4 + a_1(r_{e1})\xi^3 + a_2(r_{e1})\xi^2 + a_3(r_{e1})\xi + a_4(r_{e1})$, where the lengthy expressions for the coefficients a_1 through a_4 are omitted here for brevity.

2.3. Bifurcation Analysis. To understand the conditions underlying oscillatory behavior and viral blips in this model, we now consider possible bifurcations which may occur from the equilibrium solutions E_0 and E_1 .

2.3.1. Transcritical Bifurcation. First, for the uninfected equilibrium E_0 , it follows from $P_0(\xi, r_{e0})$ and (2.7) that in general E_0 is stable for $P_{0r} > 0$, and the only possible singularity occurs at the critical point, determined by $P_{0r} = 0$ (see (2.7)). At this point, one eigenvalue of the characteristic polynomial becomes zero (and the other three eigenvalues still have negative real part), leading to a static bifurcation, and E_0 becomes unstable. More precisely, when the parameter values in Table 2.1 are used, the two equilibrium solutions E_0 and E_1 intersect and exchange their stability at the point $(r_t, \alpha_t) \approx (8.89 \times 10^{12}, 4.58 \times 10^{13})$, indicating that a *transcritical bifurcation* occurs at this critical point (see Figure 2.1). Here, the subscript “t” stands for transcritical bifurcation. The value of α_t is obtained by substituting r_t into either $\alpha_0(r_t)$ in (2.6) or $\alpha_1(r_t)$ in (2.9). In fact, $\alpha_0(r_t) = \alpha_1(r_t)$.

As discussed above, biologically meaningful solutions should be above or on the uninfected equilibrium solution E_0 (the red line shown in Figure 2.1), since solutions below the red line contain the component $y < 0$. The above discussion indicates that the uninfected equilibrium E_0 is asymptotically stable (unstable) when $r < r_t$ ($r > r_t$) or $\alpha > \alpha_t$ ($\alpha < \alpha_t$) (see Figure 2.1), leading to the conclusion that no Hopf bifurcation exists on E_0 .

It should also be noted from Figure 2.1 that, besides a transcritical bifurcation point, E_1 has a *saddle-node* bifurcation which occurs at the so-called *turning point*. To determine this turning point, using (2.9) and $\frac{d\alpha_1(r)}{dr} = 0$ yields $(r_s, \alpha_s) \approx (1.72 \times 10^{13}, 5.06 \times 10^{13})$, where the subscript “s” denotes saddle-node bifurcation, and $\alpha_s = \alpha_1(r_s)$ by using (2.9). Note that this bifurcation does not change the stability of E_1 since the characteristic polynomial $P_1(\xi, r_{e1})$ still has an eigenvalue with positive real part when r_{e1} (or α) is varied along E_1 to pass through the turning point (see Figure 2.1), where a saddle-node bifurcation occurs. This can be seen more clearly by examining the local dynamics close to the turning point on the center manifold; interested readers can find this detailed analysis in [46].

2.3.2. Hopf Bifurcation and Limit Cycles. To find any possible Hopf bifurcation which may occur from the infected equilibrium E_1 , we first need to determine the critical points at which Hopf bifurcation occurs. The necessary and sufficient conditions for general n -dimensional systems to have a Hopf bifurcation are obtained in [44]. When the parameter values in Table 2.1 are used, the critical values are given by $(r_H, \alpha_H) \approx (6.72 \times 10^{13}, 2.64 \times 10^{13})$.

To find the approximate solutions of the limit cycles and to determine their stability, we apply normal form theory to the model associated with this singularity. First, we apply a transformation $(x, y, r, a)^T = (x_{e1}, y_{e1}, r_{e1}, a_{e1})^T + T_H(x_1, x_2, x_3, x_4)^T$, where $(x_{e1}, y_{e1}, r_{e1}, a_{e1})$ is the infected equilibrium solution E_1 and T_H is a constant, nonsingular matrix. We obtain a transformed system of (2.1), which we omit due to its lengthy expression. Then, applying the formulas of the normal form given in [45], we obtain

$$(2.10) \quad \dot{\rho} = \rho(v_0\mu + v_1\rho^2 + \dots), \quad \dot{\theta} = \omega_c + t_0\mu + t_1\rho^2 + \dots,$$

where $\mu = \alpha - \alpha_H$, and ρ and θ denote the amplitude and phase of motion, respectively; ω_c comes from the pure imaginary eigenvalues $\pm i\omega_c$ at the Hopf critical point. Then the first equation of (2.10) can be used to approximate the amplitude of bifurcating limit cycles and to determine their stability. The second equation of (2.10) can determine the frequency of periodic motion. The coefficient v_1 , usually called the first-order focus value, plays an important role in determining the stability of limit cycles. When $v_1 < 0$ ($v_1 > 0$, respectively), the Hopf bifurcation is called supercritical (subcritical) and the bifurcating limit cycles are stable (unstable). For the transformed system of (2.1) at the Hopf critical point, we obtain $v_0 \approx 3.15 \times 10^{-15}$ and $t_0 \approx 3.33 \times 10^{-15}$. Further, we apply the Maple program [43] to the transformed system to obtain $v_1 \approx -4.18 \times 10^{-7}$ and $t_1 \approx -3.38 \times 10^{-6}$. Thus, the normal form up to third order is given by

$$(2.11) \quad \begin{aligned} \dot{\rho} &\approx \rho(3.15 \times 10^{-15}\mu - 4.18 \times 10^{-7}\rho^2 + \dots), \\ \dot{\theta} &\approx 0.308 + 3.33 \times 10^{-15}\mu - 3.38 \times 10^{-6}\rho^2 + \dots. \end{aligned}$$

Now, setting $\dot{\rho} = 0$ results in two solutions: $\rho = 0$, which represents the infected equilibrium solution E_1 , and $\rho \approx 8.68 \times 10^{-5} \sqrt{\mu}$ ($\mu > 0$), which is an approximation of the amplitude of bifurcating limit cycles. Since $v_1 < 0$, this is a supercritical Hopf bifurcation, and bifurcating limit cycles are stable. For example, choosing $\mu = 10^{12}$, we obtain the amplitude approximation of the limit cycle as $\rho \approx 86.8$, and the frequency of the limit cycle approximately as $\omega \approx 0.283$, slightly less than $\omega_c \approx 0.308$. The phase portrait of the simulated limit cycle, projected on the x - y plane, is shown in Figure 2.2(d). It can be seen from Figures 2.2(a) and (d) that the analytical prediction from the normal form, $\rho \approx 86.8$, agrees well with the simulated result.

The above analysis based on normal form theory is for local dynamical behavior; that is, the limit cycles must be near the Hopf critical point (r_H, α_H) . It can be seen from Figure 2.1 that values of α taken from the interval $\alpha \in (\alpha_H, \alpha_t)$ lead to unstable equilibrium solutions (since both E_0 and E_1 are unstable for this interval). However, due to the solutions being nonnegative and bounded, we expect that there should exist certain persistent motions such as oscillating solutions for the values of α taken from this interval, and the amplitudes of these oscillations can be large. For example, for $\alpha = 3.50 \times 10^{13}$, the phase portrait of the simulated solution, projected on the x - y plane, is shown in Figure 2.2(e), corresponding to the oscillations in time

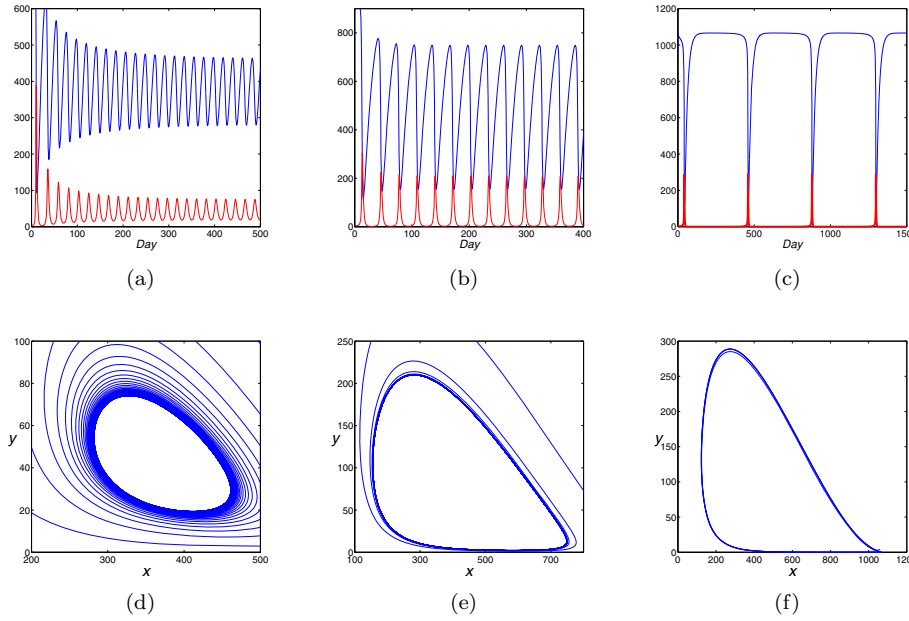


Fig. 2.2 Simulated limit cycles of system (2.1) for the parameter values taken from Table 2.1, with the time course of x (blue) and y (red) on the top row and the corresponding phase portraits projected on the x - y plane on the bottom row. For (a) and (d) $\alpha = 2.74 \times 10^{13}$, for (b) and (e) $\alpha = 3.50 \times 10^{13}$, and for (c) and (f) $\alpha = 4.55 \times 10^{13}$.

shown in Figure 2.2(b), which have much greater amplitude than the oscillations in Figure 2.2(a).

Now, we take a particular value of α from the interval $\alpha \in (\alpha_H, \alpha_t)$, which is close to α_t , to simulate the system. For example, taking $\alpha = 4.55 \times 10^{13} < \alpha_t \approx 4.58 \times 10^{13}$, we obtain the phase portrait of the simulated oscillating solution, projected on the x - y plane, shown in Figure 2.2(f), with the corresponding time history of x and y shown in Figure 2.2(c). This clearly shows viral blips.

Next, we will discuss what conditions are needed for creating the phenomenon of viral blips.

2.4. Conditions for Generating Viral Blips. In the previous subsection, we carefully analyzed the occurrence of viral blips in a 4-dimensional HIV model (2.1). System (2.1) is an example of an *in-host infection model*, an ODE system describing the dynamics of infection within a single infected individual. In-host infection models, based on classical susceptible-infected-recovered (SIR) models in epidemiology [1], typically include populations of uninfected target cells, infected target cells, and the infection dynamics between the two classes [29]. More complex models also include populations of free virus, latently infected cells, and various relevant components of the immune response, depending on the infection under study. Although there are many exceptional cases, in-host models typically admit an uninfected equilibrium and at least one infected equilibrium, analogous to the disease-free and endemic equilibria of an SIR model.

Since in-host infection models share many similar features, much of our understanding regarding the behavior of system (2.1) can be generalized to other models.

Based on insights obtained in analyzing system (2.1), we propose in the following hypothesis four conditions for an in-host infection model to generate viral blips.

Hypothesis 1. The following conditions are needed for an in-host infection model to generate viral blips:

- (i) there exist at least two equilibrium solutions;
- (ii) there exists a transcritical bifurcation at an intersection of the two equilibrium solutions;
- (iii) there is a Hopf bifurcation which occurs from one of the equilibrium solutions; and
- (iv) large oscillations (or, more generally, global, persistent motions) can occur near the transcritical critical point.

The reasons for conditions (i) and (ii) are simple because when a parameter that reflects infection severity is chosen as a bifurcation parameter, an in-host infection model typically starts at the uninfected equilibrium and then bifurcates to the infected equilibrium as the parameter is increased. Thus, these two equilibrium solutions must exchange their stability, yielding a transcritical bifurcation. For the 4-dimensional model considered in the previous subsection, the uninfected equilibrium E_0 and the infected equilibrium E_1 intersect at the critical point (α_t, r_t) , where they exchange their stability. In fact, E_0 is stable (unstable) for $\alpha > \alpha_t$ ($\alpha < \alpha_t$), while the lower branch of E_1 is stable (unstable) for $\alpha < \alpha_t$ ($\alpha > \alpha_t$), as shown in Figure 2.1.

Condition (iii), the existence of a Hopf bifurcation, is necessary to obtain oscillations. It can be seen from Figure 2.1 that limit cycles bifurcate from E_1 at the Hopf critical point (α_H, r_H) , and they become larger if $\mu = \alpha - \alpha_H > 0$ increases.

The reasoning behind condition (iv) is not so obvious. Large oscillations (or global, persistent motions) are necessary, near the transcritical point, for viral blips to emerge. As shown in Figure 2.1, both E_0 and E_1 are unstable for $\alpha \in (\alpha_H, \alpha_t)$ (though a part of the lower branch of E_1 is stable, it is biologically meaningless since $y < 0$). Thus, there exist large oscillations near the transcritical critical point α_t . Moreover, it is noted from Figure 2.1 that at the left side of the transcritical point α_t , the eigenvalues evaluated at E_0 are all real, containing one positive eigenvalue ($\xi_1^0 > 0$) and three negative eigenvalues ($\xi_i^0 < 0, i = 2, 3, 4$). In other words, any point on the uninfected equilibrium E_0 for $\alpha < \alpha_t$ is a saddle point. Since ξ_1^0 crosses zero at the critical point $\alpha = \alpha_t$, it is very small near the transcritical point for $\alpha < \alpha_t$. On the other hand, the infected equilibrium E_1 is an unstable focus-type point since the eigenvalues at E_1 contain a complex conjugate pair with positive real part and two negative real eigenvalues (see Figure 2.1). Now, we need to answer two questions: (1) Where does the large periodic solution (limit cycle) come from? (2) Why does the periodic solution contain a region of very fast motion and a region of very slow motion?

To answer the first question, see from Figure 2.2(f) that since there exists a saddle point outside the stable limit cycle and the stable limit cycle encloses an unstable singular point, there may exist an unstable *homoclinic* orbit which passes through the saddle point and encloses the stable limit cycle. The possible homoclinic orbit and the limit cycle can be thought of as being embedded in a 2-dimensional submanifold. However, this possibility can be ruled out as follows: Suppose there exists a homoclinic orbit embedded in a 2-dimensional submanifold. Then this homoclinic orbit must start from E_0 (the saddle point) and return to the same point. First note that all the eigenvalues at this saddle point are real (see Figure 2.1), and one of them is $-d_x$. It can be shown that the eigenvector associated with this eigenvalue is $(1, 0, 0, 0)$, i.e., in the direction of the x -axis. Now consider the line in the 4-dimensional space, through the two points $(x, y, r, a) = (0, 0, r_{e0}, a_{e0})$ and $(x, y, r, a) = (x_{e0}, 0, r_{e0}, a_{e0})$, and call

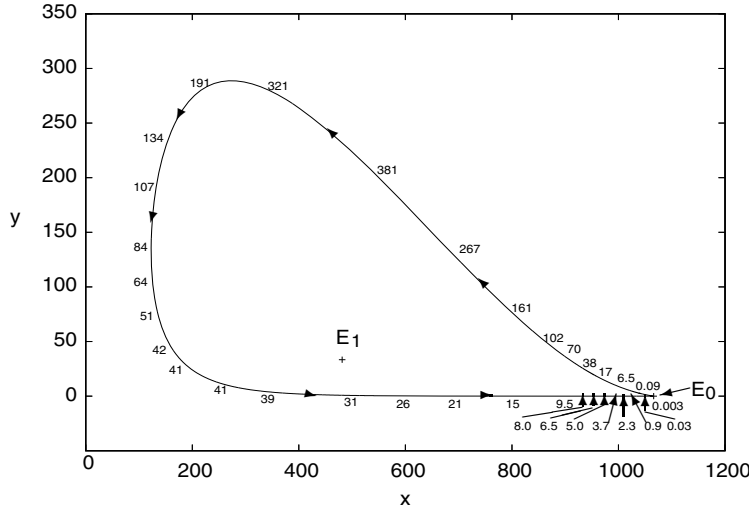


Fig. 2.3 *Simulated blips projected on the x - y plane. Labels along the solution curve reflect the relative speed of the trajectory at each point.*

the line segment between the two points S^* . It is easy to see that this line passes through the equilibrium solution (the saddle point) E_0 and is in the direction of the eigenvector $(1, 0, 0, 0)$. Moreover, it can be shown by using (2.1) that this line itself is actually a solution trajectory of the system (an invariant manifold of the system). This implies that if a homoclinic orbit passing through the saddle point E_0 exists, it must return to the saddle point E_0 along S^* . In other words, S^* must be a part of the homoclinic orbit. But this is impossible because S^* does not contain singular points for $x \in [0, x_{e0})$ and thus no other possible trajectories can connect this particular trajectory S^* due to the uniqueness of solutions. This will be seen more clearly later when we discuss the 2-dimensional model in section 4.

To answer the second question and make the answer more clear, we consider a value of $\alpha < \alpha_t$, but near the critical point $\alpha = \alpha_t$ (e.g., $\alpha = 4.55 \times 10^{13}$, as shown in Figures 2.2(c) and (f)). For simplicity, we consider the projection of the solution trajectory for this case on the x - y plane, as depicted in Figure 2.3, where the two equilibrium points E_0 and E_1 are shown. Due to $0 < \xi_1^0 \ll 1$, it is expected that the trajectory moves very slowly near the saddle point E_0 , while it moves rapidly when it is away from this point. In fact, we have shown in Figure 2.3 the speed of the trajectory along the solution curve (limit cycle). It can be seen from this figure that the speed indeed varies from very small (near the saddle point), on the order of 3×10^{-3} , to very large (away from the saddle point), on the order of 3×10^2 . Thus, the small part in the phase portrait with very slow speed actually takes a longer time, while the large part in the phase portrait with very fast speed takes much less time, as shown in the time history (see Figure 2.2(c)). This fast-slow motion yields the blips phenomenon, with slow changes corresponding to the near-flat section in the time history, and rapid changes occurring during the viral blips, as shown in Figures 2.2(c) and (f). In other words, the trajectory spends relatively long periods in regions of state space which lie very close to the uninfected equilibrium and then transiently visits regions of state space which are close to the infected equilibrium.

3. A Simple 3-Dimensional In-Host Infection Model Producing Blips. Having established the conditions in Hypothesis 1 for generating viral blips, we are ready to turn to some basic questions such as the following: What types of in-host infection models can generate blips, and what is the minimum dimension of such models?

3.1. Generalizing ROS to Other Physical Variables. In model (2.1), the variable r represents ROS, which are produced naturally in the body. In HIV infection, extra ROS are generated by infected cells, and these in turn directly accelerate HIV progression [30, 37]. Therefore, infectivity β is an increasing and saturating function of ROS concentrations. However, we note that the form of the infection term is not specific to HIV or to ROS, and models of a similar form could in fact apply to other infections. To generalize the physical meaning of the variable r , we can, for example, let r denote any damage caused by the infection to, for example, the humoral immune response, the infected organs, or the infected individual aspecifically. The model assumes that “damage” increases with the extent of the infection at rate ky and is repaired or cleared at rate $d_r r$. This yields the 3-dimensional system

$$(3.1) \quad \dot{x} = \lambda_x - d_x x - \beta(r)xy, \quad \dot{y} = \beta(r)xy - d_y y, \quad \dot{r} = ky - d_r r.$$

To achieve an infection term similar to that in model (2.1), we further assume that accrued damage makes target cells more vulnerable to infection, that is, accrued damage increases the infection rate. We thus take $\beta(r)$ to be an increasing, saturating function of r .

In the original model (2.1), r represents ROS, for example, H_2O_2 , whose production and decay rates are both extremely fast. For the more general model (3.1), we would like to assess whether viral blips are still possible at more moderate production and repair rates, k and d_r . For ROS the decay rate $d_r = 1.66 \times 10^7 \text{ day}^{-1}$ implies a half life of only 4ms. We decreased d_r by several orders of magnitude and found that, in particular, at $d_r = 1.0 \times 10^3 \text{ day}^{-1}$, a half life of 60s, viral blips are still possible. For this value of d_r , we can take $k = 1.49 \times 10^{15} \text{ molecules cell}^{-1} \text{ day}^{-1}$. Note that λ_x has been set to zero in (3.1) to make the model more general.

For simplicity, let $a = b_{\max} - b_0$, $b = b_0$, and $c = r_{\text{half}}$. Then the function $\beta(r)$ is rewritten as $\beta(r) = b + \frac{ar}{r+c}$, and a , b , and c are treated as bifurcation parameters. Parameter values λ_x , d_x , d_y , k , d_r , b_0 , b_{\max} , and r_{half} are given in Table 2.1. For practically meaningful solutions, the values of the bifurcation parameters will be chosen close to the values in Table 2.1.

To analyze (3.1), we can follow the same procedure used in the previous section and treat b as a bifurcation parameter. First, it is easy to prove the well-posedness of system (3.1). Next, we get the infection-free equilibrium $E_0 : (x_{e0}, y_{e0}, r_{e0}) = (\frac{\lambda_x}{d_x}, 0, 0)$ and the infected equilibrium $E_1 := (x_{e1}, y_{e1}, r_{e1})$, where $x_{e1} = \frac{d_y(r_{e1}+c)}{(a+b)r_{e1}+bc}$, $y_{e1} = \frac{1}{d_y}(\lambda_x - d_x x_{e1})$, and r_{e1} is determined by $F_1(r, c) = d_r d_y(a+b)r^2 + [d_y(d_r bc + k d_x) - k \lambda_x(a+b)]r + kc(d_x d_y - b \lambda_x) = 0$. Again, it is easy to show that E_0 and E_1 intersect at the transcritical bifurcation point $(b_t, r_t) \approx (9.38 \times 10^{-4}, 0)$. On the infected equilibrium E_1 , there is a saddle-node bifurcation point (turning point) $(b_s, r_s) \approx (-1.49 \times 10^{-3}, 4.18 \times 10^{13})$ and a Hopf bifurcation point $(b_H, r_H) \approx (6.56 \times 10^{-4}, 7.24 \times 10^{13})$.

The bifurcation diagram and simulated results are shown in Figure 3.1. All the conditions (i)–(iv) in Hypothesis 1 are satisfied. Blips do appear since the Hopf critical point is close to the transcritical point. However, because E_1 is not globally stable, depending on the initial conditions, the oscillation may converge to the stable equilibrium E_1 (see Figure 3.1(b)) or converge to a limit cycle with large amplitude

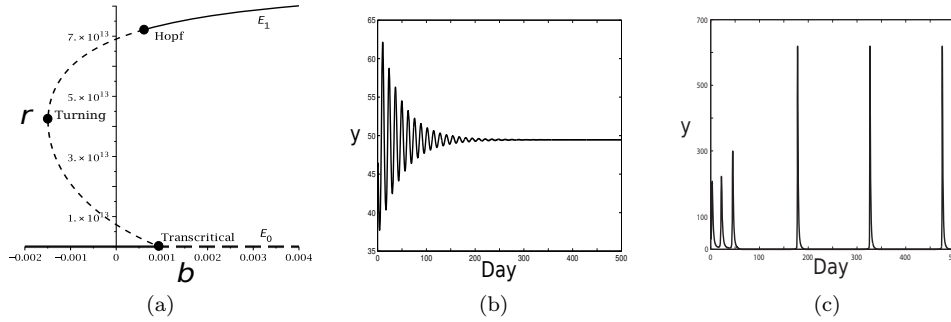


Fig. 3.1 Dynamics and bifurcation of system (3.1) for $d_r = 1.0 \times 10^3$, $k = 1.49 \times 10^{15}$: (a) bifurcation diagram projected on the b - r plane; (b) simulated time history $y(t)$ converging to E_1 for $b = 0.001$ with the initial condition $(x, y, r) = (178, 46, 73)$ close to E_1 ; and (c) simulated time history $y(t)$ converging to a stable limit cycle (blips) for $b = 0.001$ with the initial condition $(x, y, r) = (1005, 3, 3)$ close to E_0 .

(blips), as shown in Figure 3.1(c). Convergence to a smaller, regular oscillation due to the Hopf bifurcation is also possible (not shown in Figure 3.1). Similarly, following the discussion in the previous section for the 4-dimensional model, we can show that the existence of the blips (limit cycle) is not due to homoclinic bifurcation. In fact, no homoclinic orbits can exist.

3.2. Identifying the Region of Parameter Space Exhibiting Viral Blips. Having found viral blip behavior in the simple 3-dimensional infection model (3.1), we are now further interested in identifying the region of parameter space in which viral blips may occur. This is particularly useful in applications since, in reality, all parameters are roughly measured. Thus, we need to study the robustness of the phenomenon to variations in the system parameters. If blips appear only for a very small region in the parameter space, then the results are not practically useful. The main idea of identifying the region where blips may occur is to study the instability of the solutions of the system. Once the unstable region is identified, blips can be found by using the other conditions in Hypothesis 1. In order to simplify the analysis, we first introduce state variable scaling and parameter rescaling into system (3.1).

3.2.1. State Variable Scaling and Parameter Rescaling. Introducing the scaling $x = c_1 X$, $y = c_2 Y$, $r = c_3 R$, $t = c_4 \tau$, where $c_1 = \frac{\lambda_x}{d_y}$, $c_2 = \frac{\lambda_y}{d_y}$, $c_3 = \frac{\lambda_x k}{10^{12} d_y^2}$, $c_4 = \frac{1}{d_y}$, to (3.1) and letting $A = \frac{a \lambda_x}{d_y^2}$, $B = \frac{b \lambda_x}{d_y^2}$, $C = \frac{c d_y^2}{\lambda_x k}$, $D_x = \frac{d_x}{d_y}$, $D_r = \frac{d_r}{d_y}$ yields the scaled system

$$(3.2) \quad \frac{dX}{d\tau} = 1 - D_x X - \left(B + \frac{AR}{R+C} \right) XY, \quad \frac{dY}{d\tau} = \left(B + \frac{AR}{R+C} \right) XY - Y, \quad \frac{dR}{d\tau} = Y - D_r R,$$

which will be used in the following analysis, with the scaled parameter values given by

$$(3.3) \quad A = 0.364, \quad C = 3.94 \times 10^{-4}, \quad D_x = 0.057, \quad D_r = 1000$$

and with B treated as a bifurcation parameter.

3.2.2. Equilibrium Solutions and Their Stability. The bifurcation patterns of the scaled system (3.2) are the same as those of system (3.1). Two equilibrium

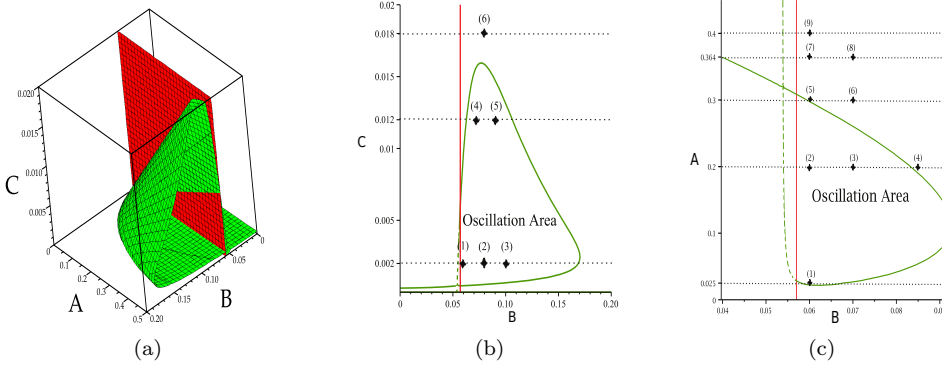


Fig. 3.2 (a) Graph of $\Delta_2 = 0$ in the A - B - C parameter space, identifying the region yielding oscillations; (b) cross section of panel (a), where $A = 0.364$; and (c) cross section of panel (a), where $C = 3.94 \times 10^{-4}$.

solutions are $E_0 : (X_{e0}, Y_{e0}, R_{e0}) = (\frac{1}{D_x}, 0, 0)$ and $E_1 : (X_{e1}, Y_{e1}, R_{e1})$, where $X_{e1} = \frac{R_{e1} + C}{(A+B)R_{e1} + BC}$, $Y_{e1} = D_r R_{e1}$, and R_{e1} is determined from the equation $F_3(R) = D_r(A+B)R^2 + [D_r + BC + D_x - (A+B)]R + (D_r - B)C = 0$.

The characteristic polynomial for E_0 is $P_0(\xi) = (\xi + D_x)(\xi + D_r)(\xi - \frac{B}{D_x})$. It is easy to show that E_0 and E_1 exchange stability at the transcritical bifurcation point $B = D_x$. The characteristic polynomial for E_1 is $P_1(\xi, r_{e1}) = \xi^3 + a_1(r_{e1})\xi^2 + a_2(r_{e1})\xi + a_3(r_{e1})$, and the Hopf critical point is determined by $\Delta_2 = a_1(r_{e1})a_2(r_{e1}) - a_3(r_{e1}) = 0$. We fix parameters D_r and D_x and choose A , B , and C as bifurcation parameters. Then we want to find the parameter region where blips may occur. First, a Hopf bifurcation is necessary, requiring the condition $\Delta_2(A, B, C) = 0$. The graph of $\Delta_2(A, B, C) = 0$ is plotted in the 3-dimensional A - B - C parameter space, as shown in Figure 3.2(a), where the green hypersurface defines a set of points which are Hopf critical points; the region bounded by the green surface is unstable for E_1 , leading to oscillations. Thus blips may occur within this region and near the boundary as well, depending on the relative position of the Hopf critical point with respect to the transcritical point.

In the following, we fix either parameter A or parameter C to enable the analysis and obtain 2-dimensional graphs, which illustrate more clearly the bifurcations necessary for blips.

3.2.3. Parameter A Fixed. Fix $A = 0.364$, which cuts the surface in Figure 3.2(a) to yield curves, as shown in Figure 3.2(b). The transcritical bifurcation occurs at $B = 0.057$, which is denoted by a red line in Figure 3.2(b). A Hopf bifurcation occurs on the green curve, and the region bounded by the green and red curves indicates where oscillations can happen. It should be noted that the above results are based on local dynamical analysis; thus blips may also appear outside this bounded region but close to the green curve.

We take three typical values of C (as the three dotted lines shown in Figure 3.2(b)), and we obtain the Hopf critical points as follows:

$$\begin{aligned}
 (3.4) \quad C = 0.002 : \quad & (B_H, R_H) \approx (1.69 \times 10^{-1}, 7.90 \times 10^{-4}), \\
 C = 0.012 : \quad & (B_{H_1}, R_{H_1}) \approx (6.27 \times 10^{-2}, 1.53 \times 10^{-4}), \\
 C = 0.012 : \quad & (B_{H_2}, R_{H_2}) \approx (1.06 \times 10^{-1}, 5.31 \times 10^{-4}), \\
 C = 0.018 : \quad & \text{No Hopf critical point.}
 \end{aligned}$$

The bifurcation diagrams corresponding to the three lines $C = 0.002$, $C = 0.012$, and $C = 0.018$ are shown in the top three graphs in Figure 3.3. Six simulated results are also presented in this figure, corresponding to the six points marked on the three dotted lines in Figure 3.2(b). It can be seen that the values taken from the points (1)–(4) generate blips, point (5) leads to a regular oscillation, while point (6) gives a simple stable equilibrium solution, as expected. For this case when parameter A is fixed, no blips have been found for the values outside the region bounded by the red and green curves. It should be noted in the top middle figure of Figure 3.3 that there are two Hopf bifurcation points on the equilibrium E_1 . One of them is supercritical, while the other is subcritical, but the two families of the limit cycles bifurcating from these two critical points are both stable, since the stability change is reversed at the two points. In fact, the three eigenvalues along the unstable part of E_1 between the two Hopf bifurcation points contain one negative eigenvalue and a pair of complex conjugates with positive real part. On the two stable parts, the real part of the complex conjugate eigenvalues changes sign to become negative. As the parameter C increases from 0.002 to 0.018, the two Hopf bifurcation points merge to a single point on E_1 (corresponding to the turning point on the green curve (see Figure 3.2(b)), at which the horizontal line is tangent to the green curve); the corresponding eigenvalues contain a negative eigenvalue and a purely imaginary pair. This indeed characterizes a degenerate Hopf bifurcation (see, e.g., [45]) different from the Hopf bifurcation defined by (2.10). A similar discussion applies to the other two Hopf bifurcation points shown in the top left panel in Figure 3.4.

3.2.4. Parameter C Fixed. Now we fix parameter $C = 3.94 \times 10^{-4}$, which results in curves in the A - B plane by cutting the surface in Figure 3.2(a), as shown in Figure 3.2(c). The transcritical point is kept the same: $B = 0.057$. We choose three typical values of A and find the Hopf bifurcation points as follows:

$$(3.5) \quad \begin{aligned} A = 0.025 : \quad & (B_{H_1}, R_{H_1}) \approx (5.82 \times 10^{-2}, 9.84 \times 10^{-5}), \\ A = 0.025 : \quad & (B_{H_2}, R_{H_2}) \approx (6.75 \times 10^{-2}, 2.65 \times 10^{-4}), \\ A = 0.200 : \quad & (B_H, R_H) \approx (8.32 \times 10^{-2}, 7.33 \times 10^{-4}), \\ A = 0.364 : \quad & (B_H, R_H) \approx (3.99 \times 10^{-2}, 7.99 \times 10^{-4}). \end{aligned}$$

The bifurcation diagrams corresponding to the three lines $A = 0.025$, $A = 0.200$, and $A = 0.364$ are shown in the top three graphs in Figure 3.4. Nine simulated results are also presented in this figure, corresponding to the nine points marked on the five dotted lines in Figure 3.2(c). It is observed from these graphs that among the nine chosen parameter values, seven cases exhibit blips (see the points (2)–(7) and (9) in Figure 3.2(c) with the corresponding simulated results shown in Figure 3.4). It is noted that some of these points are not even close to the red line, nor are they in the region bounded by the red and green curves, suggesting that a simple 3-dimensional HIV model can generate rich blips.

3.3. A 3-Dimensional Immunological Model. In this subsection, we briefly consider an immunological model [29] and apply Hypothesis 1 to show that the model can have blips. For simplicity, the original 4-dimensional model [4] is reduced (by a quasi-steady-state assumption on the virus particles) to a 3-dimensional model, described by

$$(3.6) \quad \dot{x} = \lambda - dx - \beta(y)xy, \quad \dot{y} = \beta(y)xy - ay - pyz, \quad \dot{z} = cyz - bz,$$

where x , y , and z represent the densities of the uninfected cells, infected cells, and cytotoxic T lymphocytes (CTLs), respectively. The system (3.6) with constant $\beta(y)$

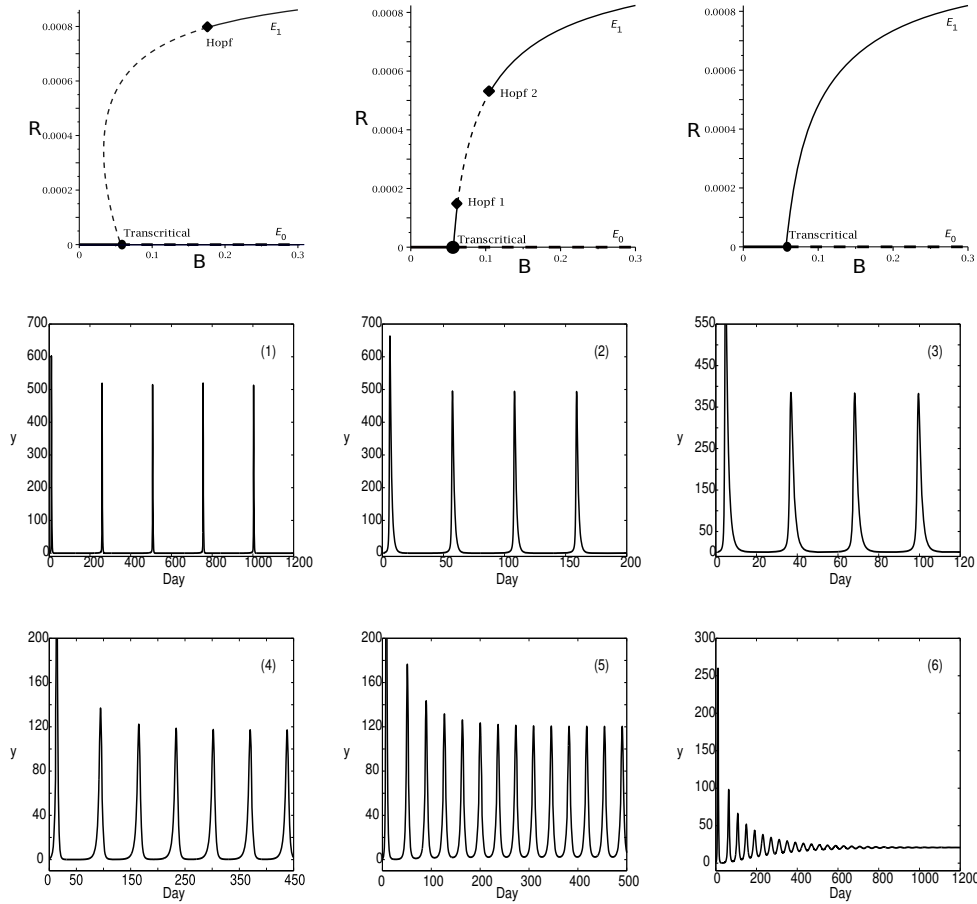


Fig. 3.3 Bifurcation diagrams corresponding to $C = 0.002, 0.012$, and 0.018 , respectively, and numerical simulation results for the parameter values $(B, C) = (0.06, 0.002)^{(1)}$, $(0.08, 0.002)^{(2)}$, $(0.10, 0.002)^{(3)}$, $(0.07, 0.012)^{(4)}$, $(0.09, 0.012)^{(5)}$, $(0.08, 0.018)^{(6)}$.

is well known [7, 28] and does not exhibit blips. In order to generate viral blips, here we choose $\beta(y) = n + \frac{my}{y+k}$, where n and m are minimum and maximum infectivity, and k represents the density of infected cells when the infectivity takes its median value. Since the analysis is similar to previous models, we omit the details and give only the results as follows. The system (3.6) has three equilibrium solutions: the infection-free equilibrium, E_0 , the infected equilibrium with CTL, E_1 , and the infected equilibrium without CTL, E_2 . There are two transcritical bifurcation points. One, named “Transcritical 1” in Figure 3.5(a), is at the intersection of E_0 and E_2 : $(n_{t1}, y_{t1}) \approx (0.005, 0)$, at which E_0 and E_2 exchange their stability. The second occurs at the intersection of E_1 and E_2 : $(n_{t2}, y_{t2}) \approx (-0.01, 0.5)$, called “Transcritical 2” in Figure 3.5(a). However, note that they only exchange their stability if restricted to a 1-dimensional manifold, and both are unstable in the whole space since one of the eigenvalues stays positive when crossing this transcritical point. E_1 becomes stable until n is increased to cross a Hopf critical point (called “Hopf 1” in Figure 3.5(a)): $(n_{1H}, y_{1H}) \approx (0.206, 0.5)$. Another Hopf bifurcation point (called “Hopf 2” in Figure 3.5(a)) happens on E_2 at $(n_{2H}, y_{2H}) \approx (0.0213, 1.81)$. It should be noted that

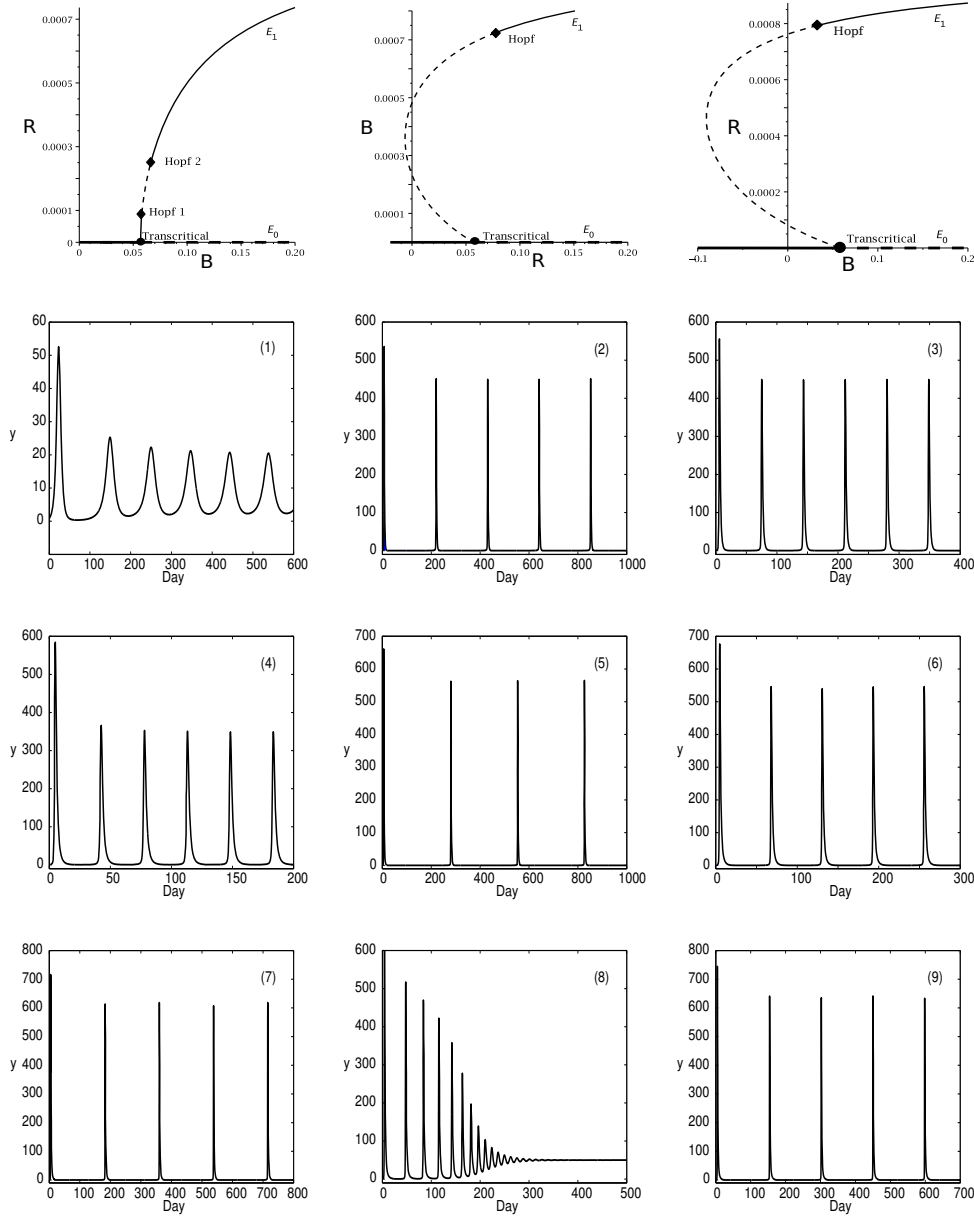


Fig. 3.4 Bifurcation diagrams corresponding to $A = 0.025, 0.200, 0.364$ and numerical simulation results for the parameter values $(A, B) = (0.025, 0.060)^{(1)}, (0.200, 0.060)^{(2)}, (0.200, 0.070)^{(3)}, (0.200, 0.085)^{(4)}, (0.300, 0.059)^{(5)}, (0.300, 0.070)^{(6)}, (0.364, 0.060)^{(7)}, (0.364, 0.070)^{(8)}, (0.400, 0.060)^{(9)}$.

this Hopf bifurcation occurs from a 2-dimensional manifold that is orthogonal to a 1-dimensional unstable manifold. That's why the E_2 stays unstable when the parameter is varied to pass through this Hopf critical point. The limit cycles bifurcating from "Hopf 1" are stable, while those from "Hopf 2" are unstable, leading to large oscillating motions when the values of n are chosen near the two singular points "transcritical

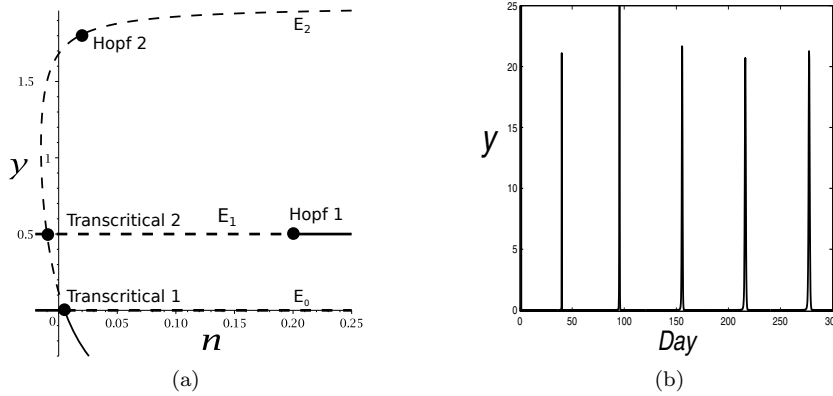


Fig. 3.5 (a) Bifurcation diagram of system (3.6), showing the equilibrium solutions E_0 , E_1 , and E_2 with dashed and solid lines denoting unstable and stable, respectively. (b) Simulated viral blips in system (3.6) for $n = 0.04$. Other parameter values used here are $\lambda = k = p = 1$, $d = 0.01$, $m = b = 0.05$, $a = 0.5$, $c = 0.1$.

1” and “Hopf 2.” The above results show that all four conditions in Hypothesis 1 are satisfied, and blips indeed appear. The simulated blips for $n = 0.04$ are depicted in Figure 3.5(b).

4. A 2-Dimensional In-Host Infection Model. For the generalized 3-dimensional model discussed in section 3, we assume that r is some form of damage to the host or to the host immune system that increases with the extent of the infection, that is, in proportion to the infected cell density. Here, we further assume that there is a quasi-steady state (as used in (3.1)) between the damage r and the infected cell y . Thus, the 3-dimensional HIV model can be further reduced to a 2-dimensional model, given by

$$(4.1) \quad \dot{x} = \lambda_x - d_x x - \beta(y)xy, \quad \dot{y} = \beta(y)xy - d_y y.$$

Note that system (4.1) is now in the form of an in-host infection model, which includes only uninfected and infected target cell populations and the most basic “birth” and death rates. However, we now think of the infectivity $\beta(y)$ as a possible function of y ; other parameters have the same meaning as in (3.6). We will show that this simplified 2-dimensional infection model may also be able to generate blips.

4.1. A 2-Dimensional In-Host Model with Constant and Linear Infection Rates. First, we consider the case when the infection rate, $\beta(y)$, is simply a constant function; that is, $\beta(y) = \beta$. Taking β itself as a bifurcation parameter, it is easy to show that there exist two equilibrium solutions and a transcritical bifurcation point, but no Hopf bifurcation exists. This violates Hypothesis 1, and therefore no blips can appear in this case.

Next, suppose the infection rate $\beta(y)$ is a linear function of the infected cell density, y , that is, $\beta(y) = b + ay$, where the parameters a and b represent the same constants as before and a is treated as a bifurcation parameter. In this case, we have two equilibrium solutions E_0 and E_1 . But E_0 is always stable for all values of a though there exists a Hopf bifurcation on E_1 . Therefore, no transcritical bifurcation point exists for this case, which violates Hypothesis 1, implying that blips are not possible when $\beta(y)$ is a linear function.

4.2. A 2-Dimensional In-Host Model with Saturating Infection Rate. Motivated by our previous results for the 3- and 4-dimensional models, we next assume that infectivity is an increasing saturating function of the infected cell density y , namely, $\beta(y) = b + \frac{ay}{y+c}$. For our numerical work, we take the same values of a and b as used in section 3.1, while c is taken to be $c = 50$, obtained by numerical simulation based on the experimental data given in [40]. Other parameter values are as described for model (3.1).

4.2.1. Scaling. For convenience in the following analysis, we first simplify system (4.1) by the following scaling to reduce the number of parameters. Let $x = e_1 X$, $y = e_2 Y$, $t = e_3 \tau$, where $e_1 = \frac{\lambda_x}{d_y}$, $e_2 = \frac{\lambda_x}{d_y}$, $e_3 = \frac{1}{d_y}$, and set $A = \frac{a\lambda_x}{d_y^2}$, $B = \frac{\lambda_x b}{d_y^2}$, $C = \frac{cd_y}{\lambda_x}$, $D = \frac{d_x}{d_y}$. Then the rescaled system is given by

$$(4.2) \quad \frac{dX}{d\tau} = 1 - DX - \left(B + \frac{AY}{Y+C} \right) XY, \quad \frac{dY}{d\tau} = \left(B + \frac{AY}{Y+C} \right) XY - Y,$$

with B treated as a bifurcation parameter. Taking the parameter values from [29], we have the scaled parameter values $A = 0.364$, $C = 0.823$, and $D = 0.057$ for system (4.2).

4.2.2. Equilibrium Solutions and Their Stability. By setting $\dot{X} = \dot{Y} = 0$ in (4.2), we get two biologically meaningful equilibrium solutions, the uninfected equilibrium solution $E_0 : (X_0, Y_0) = (\frac{1}{D}, 0)$ and the infected equilibrium solution $E_1 = (X_1, Y_1)$, where $X_1 = \frac{Y_1 + C}{(A+B)Y_1 + BC}$ and Y_1 is determined by the equation $F_1 = (A+B)Y^2 + (D+BC-A-B)Y + (D-B)C = 0$. This indicates that condition (i) in Hypothesis 1 is satisfied. Similarly, it is easy to find that E_0 is stable (unstable) if $B < D$ ($B > D$).

4.2.3. Bifurcation Analysis. By using the characteristic polynomials at E_0 and E_1 , we can show that a transcritical bifurcation occurs at the critical point, $(Y_t, B_t) = (0, 0.057)$, which satisfies condition (ii) in Hypothesis 1. E_0 and E_1 intersect at this critical point and exchange their stability. Further, a Hopf bifurcation happens at the critical point $(B_H, Y_H) \approx (0.121, 0.811)$. E_1 is stable (unstable) on the right (left) side of the Hopf bifurcation point. Therefore, condition (iii) in Hypothesis 1 holds for this case. If we take a value of B near B_t on the side where both E_0 and E_1 are unstable, then condition (iv) in Hypothesis 1 is also satisfied and so blips occur. The bifurcation diagram is shown in Figure 4.1(a), and the simulated viral blips for $B = 0.060$ are depicted in Figure 4.1(b).

For this 2-dimensional model, we study the blips phenomenon more carefully and rigorously show the existence of the blips. To achieve this, we plot the phase portrait, corresponding to the time history in Figure 4.1(b), as shown in Figure 4.2(a), where E_0 is a saddle point, with eigenvalues $0.0526, -0.057$, and E_1 is an unstable focus, with eigenvalues $0.0766 \pm 0.3865i$. Comparing Figure 4.2(a) with Figure 2.3 indeed shows that the qualitative behavior of the system does not change after the model reduction from four dimensions to two dimensions, with only the value of y increased in the 2-dimensional model. Note that we do not show the speed of the trajectory in Figure 4.2(a) since it is similar to that in Figure 2.3.

Now we want to show that no homoclinic orbits can exist for this model. First, it is easy to find that the two eigenvalues at the saddle point E_0 are $\xi_1 = -D$ and $\xi_2 = \frac{B}{D} - 1$ (> 0 for $B > D$), and their corresponding eigenvectors are $v_1 = (1, 0)$ and $v_2 = (1, \frac{D}{B}(1 - D) - 1)$, respectively. It should be noted that for convenience (x, y) are used in Figure 4.2(a), while (X, Y) are used in Figure 4.2(b); their relation

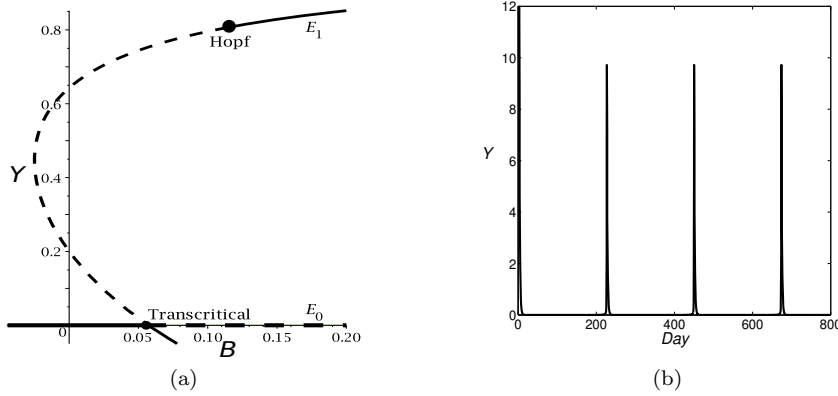


Fig. 4.1 (a) Bifurcation diagram projected on the B - Y plane, with the thick and thin lines denoting E_0 and E_1 , respectively, and dotted and solid lines indicating unstable and stable, respectively. (b) Simulated time history of $y(t)$ for $B = 0.060$.

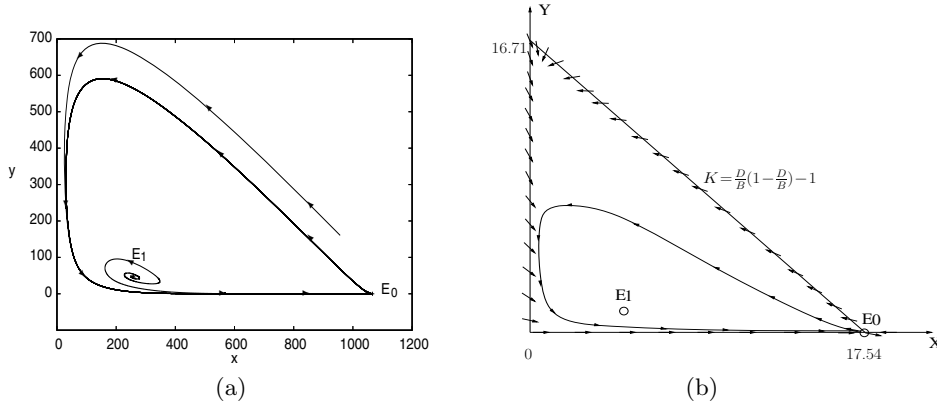


Fig. 4.2 (a) Simulated phase portrait of the blips (see Figure 4.1(b) for the time history). (b) Construction of the trapping region of the blips (limit cycle).

is given by $(x, y) = (60.76X, 60.76Y)$. The first eigenvector v_1 is in the direction of the X -axis. Thus, if a homoclinic orbit exists, it must leave the saddle point E_0 along the direction of v_2 and return to the point along v_1 . Further, we can use (4.2) to show that the X -axis is actually a solution trajectory of this system. Thus, if a homoclinic orbit passing through the saddle point E_0 exists, it must contain the part of the X -axis from $X = 0$ to $X = \frac{1}{D}$. However, this is impossible because this part of the X -axis for $X \in [0, \frac{1}{D})$ does not contain singular points and so no other trajectories can connect the X -axis for $X \in [0, \frac{1}{D})$ due to the uniqueness of solutions. Therefore, no homoclinic orbits can exist and thus the stable limit cycle (blips) is not due to homoclinic bifurcation.

Next, we apply Poincaré-Bendixson theory to prove the existence of the limit cycle. Since E_1 is an unstable focus point, we can construct an annulus to form a trapping region, with the inner closed boundary, a circle with small enough radius, enclosing the focus point E_1 , and the outer boundary, a right triangle as shown in Figure 4.2(b), consisting of the X -axis, the Y -axis, and the hypotenuse $Y = K(X - \frac{1}{D})$,

where $K = \frac{D}{B}(1 - \frac{D}{B}) - 1$ is the slope of the hypotenuse. It is obvious that all solution trajectories inside the inner boundary move toward the trapping region, since E_1 is an unstable focus. For the outer boundary, first note that the slope of the hypotenuse is less than that of the eigenvector v_2 , i.e., the hypotenuse stands more vertically than v_2 . As has been shown above, the X -axis is a trajectory of the system. For the Y -axis, it is easy to see that for $Y > 0$, $\frac{dX}{d\tau} = 1$, $\frac{dY}{d\tau} = -Y < 0$, implying that trajectories cross the Y -axis in the left to right, downward direction (see Figure 4.2(b)). For the hypotenuse $Y = K(X - \frac{1}{D})$, $X \in [0, \frac{1}{D})$, we can use the equation of the hypotenuse and the differential equations in (4.2) to show that all trajectories cross the hypotenuse in the direction toward the trapping region, as shown in Figure 4.2(b). Therefore, by applying Poincaré–Bendixson theory, we know that there exists at least one closed orbit (limit cycle) within this trapping region. The numerical simulation shows that only one closed orbit (limit cycle) exists within this trapping region. It is noted that for the given parameter values $B = 0.06$, $D = 0.057$, the two eigenvalues at the saddle point E_0 are -0.06 and 0.053 , associated with the eigenvectors $v_1 = (1, 0)$ (in the X -axis direction) and $v_2 = (1, -0.104)$, respectively (see Figure 4.2(b)). This is why the trajectory moves very slowly around the corner of the saddle point E_0 , while it moves very quickly when it is away from this corner. For example, at the point $(X, Y) = (6.641, 9.574)$ the eigenvalues are $-1.020 \pm 1.625i$, so the convergence rate at this point to that of the point near the saddle point E_0 is about $\frac{1.02}{0.05} \approx 20$, showing that the trajectory moves through this point much faster than the points near the saddle point E_0 .

Summarizing the results of this section, we conclude that the simple 2-dimensional in-host model is sufficiently complex to exhibit viral blips, provided the infectivity function is an increasing, saturating function of infected cell density. However, for this model, the range of parameter space in which blips occur is relatively restricted, compared with the 3-dimensional model, which is established in the previous section.

An interesting question naturally arises: Does there exist a more general function $\beta(y)$ such that the existence of blips depends upon the general properties of the function like its maximal values and/or its derivatives? In fact, it has been found that by choosing the parameter c large enough in the function β , a threshold is reached beyond which the Hopf bifurcation and hence also the viral blips disappear.

5. Recurrency in a 5-Dimensional Model. So far, we have considered 2-, 3-, and 4-dimensional in-host infection models with increasing, saturating, infectivity functions and have shown that all these models exhibit blips. Moreover, it has been shown for the 2-dimensional model (and can be shown for the 3- and 4-dimensional models, though omitted here) that replacing the infectivity function with a constant or linear function of y will cause blips to disappear. However, in this section we will show that higher-dimensional systems may have blips even with a constant infectivity function.

We consider a previously proposed 5-dimensional immunological model in which recurrent phenomena or viral blips have been observed via numerical simulation [42]. The model describes antibody concentrations and CTLs explicitly and is described as follows:

$$\begin{aligned}
 (5.1a) \quad & \dot{x} = \lambda - dx - \beta xv, \\
 (5.1b) \quad & \dot{y} = \beta xv - ay - pyz, \\
 (5.1c) \quad & \dot{z} = cyz - bz + hy, \\
 (5.1d) \quad & \dot{u} = \xi z - \eta u - kuv, \\
 (5.1e) \quad & \dot{v} = ey - kuv - \gamma xv - qv.
 \end{aligned}$$

Here x , y , z , u , and v are, respectively, the population densities of uninfected target cells, infected target cells, CTLs, antibodies, and virions. The parameters λ and

Table 5.1 *Parameter values used in model (5.1) [42].*

| Parameter | Value |
|-----------|--|
| λ | 10^4 cells μL^{-1} day $^{-1}$ |
| d | 0.100 day $^{-1}$ |
| β | 1.25×10^{-5} virion $^{-1}$ μL day $^{-1}$ |
| p | 10^{-4} cells $^{-1}$ μL day $^{-1}$ |
| c | 10^{-4} cells $^{-1}$ μL day $^{-1}$ |
| b | 0.200 day $^{-1}$ |
| h | $[0, 10^{-4}]$ day $^{-1}$ |
| ξ | 10.0 molecules cell $^{-1}$ day $^{-1}$ |
| η | 0.040 day $^{-1}$ |
| k | 2.50×10^{-5} particle $^{-1}$ μL day $^{-1}$ |
| e | 2.50 virions cell $^{-1}$ day $^{-1}$ |
| γ | 5.00×10^{-5} cell $^{-1}$ μL day $^{-1}$ |

dx represent the uninfected cells' constant growth rate and death rate, respectively. Target cells are infected by the virus at rate βxv . The infected cells die at rate ay , being killed by CTLs at rate pyz . It is assumed that CTLs proliferate at rate cyz and decrease with the natural death rate bz . Equation (5.1d) describes the antibody growth rate, ξz , which is proportional to the number of CTLs, the natural death rate of antibody, ηu , and the binding rate of one antibody with one antigen, kuv . In (5.1e), viruses are released from infected cells at rate ey and are bound by antibody, absorbed by uninfected cells, or cleared at rates kuv , γxv , and qv , respectively. The term hy corresponds to the CTL differentiated from memory T cells [42] and should be expressed as $h_M y z_M$, where z_M is the population density of virus-specific memory T cells, which produce activated CTLs with rate $h_M y$. In [42], z_M is assumed to be a constant, and so we have $h = h_M z_M$. We will consider two cases: $h = 0$ and $h \neq 0$; $h = 0$ is due to the absence of memory T cells (that is, $z_M = 0$) during the primary effector stage. We will show the relation between the two cases. For simplicity, without loss of the properties of antibodies, we assume $q = 0$ according to [42]. Other experimental parameter values used for studying model (5.1) are given in Table 5.1.

5.1. Well-Posedness of Model (5.1). Due to physical reasons, negative values of the state variables of system (5.1) are not allowed. Only nonnegative initial conditions are considered, and the solutions of (5.1) must be nonnegative. The parameters in (5.1) are all positive, again for biological reasons. Expressing the solutions of system (5.1) by variation of constants yields

$$(5.2a) \quad x(t) = x(0) \exp \left[- \int_0^t (d + \beta v(s)) ds \right] + \lambda \int_0^t \exp \left[- \int_s^t (d + \beta v(w)) dw \right] ds,$$

$$(5.2b) \quad y(t) = y(0) \exp \left[- \int_0^t (a + pz(s)) ds \right] + \beta \int_0^t x(s) v(s) \exp \left[- \int_s^t (a + pz(w)) dw \right] ds,$$

$$(5.2c) \quad z(t) = z(0) \exp \left[\int_0^t (cy(s) - b) ds \right] + h \int_0^t y(s) \exp \left[\int_s^t (cy(w) - b) dw \right] ds,$$

$$(5.2d) \quad u(t) = u(0) \exp \left[- \int_0^t (\eta + kv(s)) ds \right] + \xi \int_0^t z(s) \exp \left[- \int_s^t (\eta + kv(w)) dw \right] ds,$$

$$(5.2e) \quad v(t) = v(0) \exp \left[- \int_0^t (ku(s) + \gamma x(s) + q) ds \right] + e \int_0^t y(s) \exp \left[- \int_s^t (ku(w) + \gamma x(w) + q) dw \right] ds.$$

First, we have the following result: When the initial conditions are taken to be positive, the solutions of system (5.1) remain positive for $t > 0$. Moreover, they are bounded. This can be shown as follows: By the initial condition $x(0) > 0$, it is easy to see from (5.2a) that $x(t) > 0 \forall t > 0$. Next, we show that $y(t) > 0 \forall t > 0$ by contradiction. Suppose, otherwise, that $y(t) < 0$ for some interval $t \in (t_1, t_2)$, $t_1 > 0$. Since $y(0) > 0$, without loss of generality, we may assume t_1 is the first time that y crosses zero, i.e., $y(t) > 0 \forall t \in [0, t_1)$, $y(t_1) = 0$, and $y(t) < 0 \forall t \in (t_1, t_2)$. Thus, from (5.2e) we have $v(t_1) > 0$ due to $v(0) > 0$. On the other hand, it is seen from (5.2b) that $v(t)$ must cross zero to become negative at some $t < t_1$, since $y(t) < 0 \forall t \in (t_1, t_2)$. However, it follows from (5.2e) that

$$v(t) > 0 \quad \forall t \in [0, t_1],$$

leading to a contradiction. Hence $y(t) > 0 \forall t > 0$, and it then follows from (5.2c) and (5.2e) that $z(t) > 0$ and $v(t) > 0 \forall t > 0$. Finally, by the positivity of $z(t)$, (5.2d) gives $u(t) > 0 \forall t > 0$.

It remains to prove that positive solutions of system (5.1) are all bounded. First, consider (5.1a), which yields $\dot{x} \leq \lambda - dx$. Given that the exponential functions have negative exponents, we show that $x(t)$ for $t > 0$ is bounded since as $t \rightarrow +\infty$,

$$x(t) \leq \exp\left(-\int_0^t d ds\right) [x(0) + \lambda \int_0^t \exp\left(\int_0^s d du\right) ds] = x(0)e^{-dt} + \frac{\lambda}{d}(1 - e^{-dt}) \leq \frac{\lambda}{d}.$$

Thus, denote $x_{\max} = \lim_{t \rightarrow +\infty} \sup x(t) = \frac{\lambda}{d}$. It is easy to see that $x_{\min} > 0$. Next, we add (5.1a) and (5.1b) together to obtain $\dot{x} + \dot{y} = \lambda - dx - ay - pyz \leq \lambda - \min(d, a)(x + y)$. Using the same boundedness argument for $x(t)$, we get $x(t) + y(t) \leq \frac{\lambda}{\min(d, a)}$ as $t \rightarrow +\infty$, and thus $y_{\max} = \lim_{t \rightarrow +\infty} \sup y(t) \leq \frac{\lambda}{\min(d, a)}$. Now consider (5.1e), yielding $\dot{v} \leq ey_{\max} - (\gamma x_{\min} + q)v$. Similarly, using the same boundedness argument as for $x(t)$, we have $\lim_{t \rightarrow +\infty} v(t) \leq \frac{ey_{\max}}{r x_{\min} + q}$. To prove boundedness of $z(t) \forall t > 0$, we use proof by contradiction. Assume $z(t)$ is unbounded, i.e., $\lim_{t \rightarrow +\infty} z(t) \rightarrow +\infty$. Due to positivity of x, y, z , and v and boundedness of x, y , and v , it follows from (5.1b) that $\dot{y} < 0$ for $z > z^*$ or for $t > t^* > 0$ (z^* and t^* are finite), which implies $\lim_{t \rightarrow +\infty} y(t) \rightarrow 0$. Then from (5.1c) we have $\dot{z} = (cy - b)z + hy$, so for sufficiently large t , $cy - b < 0$, and so \dot{z} becomes negative (for some $z > z^*$), implying that z cannot increase unboundedly, which is a contradiction. Thus, we denote $z_{\max} = \max\{z(t), t \geq 0\}$. Finally, from (5.1d), we have $\dot{u} \leq \xi z_{\max} - \eta u$, which yields $u(t) \leq \frac{\xi z_{\max}}{\eta}$ as $t \rightarrow +\infty$. Hence, we have shown that the solutions of system (5.1) are positive and bounded.

If the initial conditions have some zero elements, it is easy to see from (5.2) that solutions are nonnegative. Hence, system (5.1) is proved to be a well-posed biological model, with nonnegative and bounded solutions.

5.2. Equilibrium Solutions and Their Stability. The following results are obtained based on the assumption $q = 0$ [42]. The equilibrium solutions of (5.1) are obtained by simply setting the vector field of (5.1) to zero. There are two equilibrium solutions, the infection-free equilibrium $E_0 : (x_{e0}, y_{e0}, z_{e0}, u_{e0}, v_{e0}) = (\frac{\lambda}{d}, 0, 0, 0, 0)$ and the infected equilibrium $E_1 : (x_{e1}, y_{e1}, z_{e1}, u_{e1}, v_{e1})$, where $v_{e1} = \frac{\lambda - dx_{e1}}{\beta x_{e1}}$, $z_{e1} = \frac{u_{e1}(\eta + kv_{e1})}{\xi}$, and $y_{e1} = \frac{v_{e1}(ku_{e1} + \gamma x_{e1})}{e}$. From the bifurcation analysis, with the parameter values in Table 5.1 (with $h = 10^{-4}$), we obtain a transcritical point $(x_t, a_t) = (0.625, 1.00 \times 10^5)$ at which E_0 and E_1 exchange their stability, which actually holds for both cases $h \neq 0$ and $h = 0$. We also find a Hopf bifurcation point

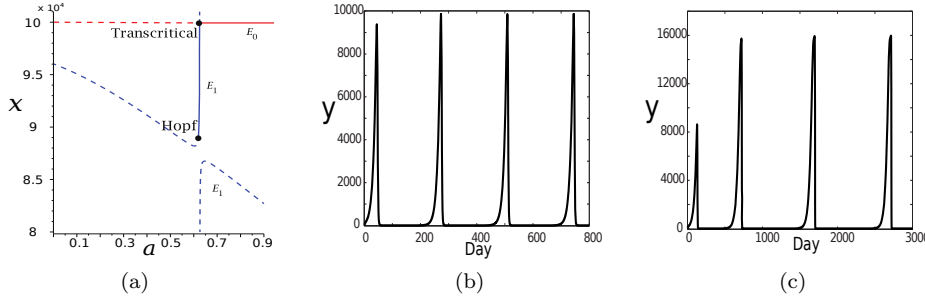


Fig. 5.1 Bifurcation diagram and simulated viral blips for system (5.1) with the parameter values taken from Table 5.1 when $a = 0.500$: (a) Bifurcation diagram for $h = 10^{-4}$, with the red and blue lines denoting E_0 and E_1 , respectively, and the dotted and solid lines indicating unstable and stable, respectively (the lower branch of E_1 is biologically meaningless, due to negative values in the solution); (b) simulated time history of $y(t)$ for $h = 10^{-4}$; and (c) simulated time history of $y(t)$ for $h = 0$.

$(x_H, a_H) \approx (8.85 \times 10^4, 0.617)$. Note that the Hopf bifurcation point is above the turning point $(x_{\text{Turning}}, a_{\text{Turning}}) \approx (8.82 \times 10^4, 0.604)$ in the upper branch of E_1 (see Figure 5.1).

The above results show that the case $h \neq 0$ satisfies all four conditions in Hypothesis 1 to generate recurrent infection, and indeed recurrence occurs for $a \in (0, a^*)$, where $a^* < a_H$. Moreover, a^* should not be too close to a_H ; otherwise the period of limit cycles bifurcating from the Hopf critical point (x_H, a_H) is relatively small. The bifurcation diagram, shown in Figure 5.1(a), indicates that the Hopf critical point a_H is located on the left side of $a = a_t$, where E_0 is unstable. A simulated time course exhibiting recurrent infection is depicted in Figure 5.1(b).

5.3. Bifurcation Analysis for $h \rightarrow 0^+$. Now we consider the special case, $h = 0$. It is easy to observe from (5.1c) that the solutions of system (5.1) are discontinuous at $h = 0$. Therefore, to have continuity, we should regard the special case $h = 0$ as the limiting case $h \rightarrow 0^+$. When $h = 0$, the seemingly vertical line in the bifurcation diagram for $h = 0$ disappears, clearly showing the discontinuity of E_1 at $h = 0$. This causes difficulty in bifurcation analysis. However, if we treat the case $h = 0$ as the limiting case $h \rightarrow 0^+$, the solution E_1 continuously depends on h , and the bifurcation diagram becomes smooth. Therefore, we can still use our theory to explain the occurrence of blips for the case $h = 0$, as shown in Figure 5.1(c).

Similarly, we may conclude that the occurrence of the blips (for both cases $h \neq 0$ and $h = 0$) are not due to homoclinic bifurcation since we can show that no homoclinic orbits exist in system (5.1).

6. Conclusion and Discussion. In this paper, the problem of recurrent infection (viral blips) in in-host infection models is studied via the qualitative analysis of dynamical systems. A 4-dimensional HIV antioxidant-therapy model [40], which produces viral blips, is investigated in detail using bifurcation theory. A hypothesis consisting of four conditions for the emergence of viral blips is proposed. These conditions describe two equilibrium solutions which intersect at a transcritical bifurcation point, with a Hopf bifurcation which originates from the equilibrium solution. Under these conditions, blips appear for values of the bifurcation parameter near the transcritical point, where equilibrium solutions are unstable. We also discuss how the blips

are generated and find that they are not due to homoclinic bifurcation since we have shown that no homoclinic orbits exist in all the models considered in this paper.

Guided by the proposed hypothesis, we propose several simpler in-host infection models that can also generate viral blips. We develop a 3-dimensional in-host model with an increasing, saturating infection rate similar to the HIV antioxidant-therapy model and show that all four conditions in the hypothesis are satisfied, leading to blips. Further, stability and bifurcation analysis determine all possible regions in parameter space where blips may occur. We then investigate an even simpler 2-dimensional in-host model. This very simple model can also exhibit blips, as long as the infection rate is an increasing, saturating function of infected cell density. We also apply the hypothesis to study a standard HIV model with CTL response [29] and find blips by using an increasing, saturating infection rate function.

Overall, our results suggest that simple ODE models of in-host infection dynamics are sufficient to describe transient periods of high viral replication, separated by long periods of quiescence. Rather than needing an exogenous trigger such as stochastic stimulation of the immune system, the natural dynamics of such systems may be sufficiently rich, in many cases, to exhibit viral blips. One key to obtaining this rich behavior is to propose an infection rate which increases, but saturates, with the extent of the infection. This is a natural assumption if the infection itself (high density of infected target cells) makes the host more vulnerable to further infection. Such an assumption is certainly natural for HIV, where the primary target cells are T lymphocytes.

All the simulated oscillating motions and blips presented in this paper show constant amplitudes and frequencies. This is because all parameter values are fixed in the simulations. We note, however, that nonlinear, deterministic systems can indeed generate oscillations with varying amplitudes and phases, called “amplitude modulation” and “frequency modulation,” due to nonlinearity. This can be seen from (2.11), where both amplitude and phase are functions of the parameter μ . Since in reality parameters are not constant, time-varying parameters can be seen as analogous to the variation due to random perturbations in stochastic models. Although deterministic models with fixed parameter values cannot generate varying amplitude and phase, deterministic models can generate such variation if the system is nonlinear and some parameters vary with time. For example, Figure 6.1 shows the result of changing the fixed α used in Figure 2.2(c) to a time-varying deterministic function, clearly demonstrating that a deterministic model can generate blips of varying magnitude, frequency, and duration.

We note that, mathematically, a system of delay differential equations (DDEs) could also generate oscillatory behaviors similar to viral blips. However, in this case, the inherent delay would need to be of the same order as the interval between blips, that is, on the order of several months. Since it is difficult to suggest a physiological or immunological process that would impose a delay of this magnitude, it seems unlikely that DDEs are the most natural approach for modeling viral blips.

While we are able to show that linear or constant infection rates do not lead to blips in the 2-, 3-, or 4-dimensional models we have studied, further study of a 5-dimensional immunological model reveals that a system with a constant infection rate can also generate blips. This suggests that the use of an increasing, saturating infection rate function is not necessary but is effective in low-dimensional models. The results presented here provide a useful tool for the mathematical study of viral blips or other examples of recurrent infection. The conditions in our hypothesis may also be used or generalized to study recurrent phenomena in other physical systems.

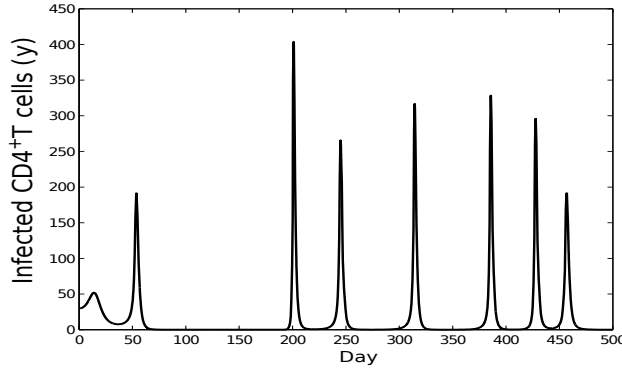


Fig. 6.1 Simulated viral blips of system (2.1) with varying amplitude and frequency when using a time-varying function $\alpha(t) = \alpha_T + [-0.31 + 0.3e^{-3 \cos(t/50)} \cos(t/100)] \times 10^{13}$, where $\alpha_T = 4.58 \times 10^{13}$ is the transcritical bifurcation value.

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