

Article

Effects of Diffusion and Delays on the Dynamics of an HIV Infection Model

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Abstract

This paper investigates the effects of diffusion and two time delays on the dynamics of an HIV infection model in one-dimensional domain. The Galerkin method is employed to derived theoretical equations. A condition is established for identifying exact Hopf bifurcation points, followed by an in-depth discussion on stability analysis maps. Bifurcation maps are constructed to illustrate the system dynamics under three distinct delay scenarios, highlighting the stable and unstable areas. When the delay parameter $\tau_i > 0$, there are two distinct stability areas, whereas in the absence of delay, only one stable region exists. The findings indicate that the time delays and the diffusion rate significantly influence the stability regions of the system. Bifurcation maps are presented to illustrate selected examples of 3D periodic oscillations to validate all theoretical outputs shown in this paper.

Keywords: HIV infection model; Hopf bifurcation; delayed immune response; stability; bifurcation; reaction-diffusion equation; periodic solutions

MSC: 37Gxx; 35B10; 35B32; 35B35; 35K57; 35Q92; 37G15; 35B05; 62P10

1. Preliminaries and Introduction

A variety of biological and epidemic models have been extensively studied over the last few decades, the models being expressed in ordinary and partial differential equations (ODEs and PDEs) and applied to various scenarios including population dynamics, illnesses and infectious diseases [1–3]. In particular, modeling has proven essential for understanding the population dynamics of viral load in vivo, which can significantly enhance our understanding of disease and inform the development of various drug therapy strategies [4,5].

Among the many diseases of concern, we focus here on acquired immune deficiency syndrome (AIDS), an incurable, chronic infectious disease caused by the human immunodeficiency virus (HIV). The classical model of viral infection includes the interaction between three variables: the density of healthy target cells, infected cells, free virus particles, and cytotoxic T lymphocytes (CTL) [6,7]. HIV dynamics within a host can generally be classified into three stages [4,5]: First, following infection, there is a dramatic decrease in healthy cells $CD4^+T$, and the viral load peaks sharply during the acute stage. The body then enters a prolonged asymptomatic phase, characterized by a gradual increase in viral load while the immune system remains functional. In the third stage, the virus disrupts the immune system, leading to various opportunistic infections that eventually prove terminal. To better



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understand the disease and develop effective drug treatments, we consider the basic model for the population dynamics of viral infection with CTL response as in [8,9]:

$$\begin{aligned}\dot{u}_1(t) &= \lambda - \alpha_4 u_1 - \beta u_1 u_2, \\ \dot{u}_2(t) &= \beta u_1 u_2 - \alpha_1 u_2 - p u_2 u_3, \\ \dot{u}_3(t) &= f(u_1, u_2, u_3) - \alpha_2 u_3.\end{aligned}\quad (1)$$

The biological meanings of all quantities in model (1) are as explained in Table 1. Furthermore, $f(u_1, u_2, u_3)$ covers three dynamical cases. The first of these cases, when $f(u_1, u_2, u_3) = \alpha_3 u_2$, occurs when CTLs are generated solely by the stimulation from infected cell levels. In the second case, $f(u_1, u_2, u_3) = \alpha_3 u_2 u_3$, CTLs result from the interaction between infected cells and their own population. In the final case, when $f(u_1, u_2, u_3) = \alpha_3 u_1 u_2 u_3$, the activation and proliferation of CTLs rely on the levels of all three cell types mentioned above. These three cases of viral dynamics with CTL immune response have been proposed by various researchers, and have been expressed as both ODE and delay differential equation (DDE) systems. For example, refs. [1,10] demonstrate that free viruses replicate more quickly than virus-infected cells, allowing for a quasi-steady state in which free virus production is balanced with the quantity of infected cells. Ref. [11] presented the stability of a class of systems for an in vivo virus considering the CTL immune response. Moreover, viral reproduction has been analyzed while accounting for their reliance on host cells' cellular machinery for synthesizing the viral genome and other components [12]. Also, ref. [13] highlighted a fundamental system in the population dynamics of viral infections involving CTLs, showing that CTLs are crucial in preventing and modulating infections. Essential elements of a typical immune response to a virus encompass T cells, antibodies, cytokines, and natural killer cells, which target virus-infected cells and bolster the host's immune response. Ref. [14] established the global stability of the virus dynamics system with the Beddington–DeAngelis infection rate, illustrating the CTL immune response through the construction of Lyapunov functions.

Table 1. Nomenclature.

Parameter	Description
u_1	the number healthy target cells (susceptible host cells)
u_2	the number of virus-infected cells
u_3	the number of cytotoxic T lymphocytes (CTLs)
τ_1	the latency associated with cell-to-cell infection
τ_2	the latency in CTL activation triggered by infected cells
λ	the reproduction rate of healthy cells
β	the virus's rate of cell infection and multiplication
d	the diffusion coefficient of the three cell populations
α_1	the mortality rate of infected cells
α_2	the decay rate of the specific CTL
α_3	The activation and proliferation coefficient of CTL cells
α_4	the death rate of healthy host cells
p	probability of CTLs fighting against infection

HIV infection systems including delays have been considered in various studies. The presence of time delays in immune response is especially significant, as these delays can markedly influence the dynamics, potentially leading to instability and Hopf bifurcations, see [2,7,15–18] and references therein. Recently, ref. [7] investigated the stability and bifurcation behavior of an HIV infection model incorporating time delays. They focused on determining conditions under which the model's equilibria were stable or undergo

Hopf bifurcations, leading to periodic oscillations. They also noted that intracellular delay does not impact the stability of the equilibrium when immunity is present. However, delays in the immune response can lead to instability of this equilibrium through a Hopf bifurcation. In another study, ref. [2] studied the impact of time delay on the dynamics of a viral infection model for immune impairment analyzed through bifurcation and stability analysis. The authors found that, while immune impairment rates did not affect the stability of the ODE system, they did significantly affect the DDE system. The effects of delayed immune responses from infected cells and CTLs in a 2D model were examined in [17], whereas refs. [9] and [15] investigated the influences of time delays on immune responses in both 3D and 4D systems, respectively.

2. The Model

In this work, we study the system outlined in (1), mainly considering the case in which all three cell populations affect the dynamics, i.e., $f(u_1, u_2, u_3) = \alpha_3 u_1 u_2 u_3$. Furthermore, we concentrate on integrating two time delays— τ_1 and τ_2 —with a diffusion rate d to the three cell populations. Introducing these time delays and diffusion coefficients produces significant effects, including the emergence of spatial oscillations. In addition, these delays can shift the system's solutions from a stable state to an unstable one, and produce points of instability and bifurcation [19–21].

From a biological perspective, the delay τ_1 represents the intracellular latency period associated with cell-to-cell viral infection. This delay accounts for the time required for a target cell to become productively infected after exposure to the virus, including intracellular processes such as viral entry, replication, and the production of new infectious particles. The delay τ_2 denotes the activation lag of cytotoxic T lymphocytes (CTLs) induced by infected cells. Biologically, this reflects the time needed for antigen recognition, immune signaling, clonal expansion, and differentiation of CTLs before an effective immune response can be mounted against infected cells [5,7]. Consequently, τ_1 characterizes the progression of viral infection within host cells, whereas τ_2 describes the response time of the adaptive immune system. Since both processes are inherently time-dependent, incorporating these delays provides a more realistic description of virus-immune interactions and enables the model to capture complex dynamical behaviors observed in biological systems. This nonlinear, diffusive, viral infection model system, incorporating two delays and boundary conditions, is expressed as:

$$\begin{aligned} u_1(t) &= d\Delta u_1 + \lambda - \alpha_4 u_1(t) - \beta u_1(t)u_2(t), \\ u_2(t) &= d\Delta u_2 + \beta u_1(t - \tau_1)u_2(t - \tau_1) - \alpha_1 u_2(t) - p u_2(t)u_3(t), \\ u_3(t) &= d\Delta u_3 + \alpha_3 u_1(t)u_2(t - \tau_2)u_3(t) - \alpha_2 u_3(t), \\ u_1 &= u_2 = u_3 = 0, \quad \text{with } x = \mp 1 \quad \text{and } t = 0, \\ u_i &= u_{is} \quad \text{at } i = 1, 2, 3, \quad \text{and } -\tau_1, -\tau_2 < t \leq 0. \end{aligned} \quad (2)$$

Here, d represents the diffusion coefficient for the three concentrations and all of the rates τ_1 , τ_2 , λ , β , d and α_i are positive and carry the biological meanings in Table 1. The domain of this system is open, with a zero-flux boundary condition applied at the center of domain. Consequently, the model exhibits symmetrical behavior at $x = 0$. The domain is connected to a reservoir via a permeable boundary at $x = \pm 1$, where the concentrations of u_1 , u_2 and u_3 remain constant at the reactor's permeable boundary. The parameter $u_{1s} > 0$, $u_{2s} > 0$ and $u_{3s} > 0$ are used for analysis, representing the populations u_1 , u_2 and u_3 when the time interval is $t \in (-\tau_1, 0)$ and $t \in (-\tau_2, 0)$.

Diffusion dynamics of an HIV infection model with delay have been considered before; these have important implications for understanding biological interpretation phenom-

ena. For instance, ref. [5] analyzed one-dimensional a viral infection model, focusing on the effects of diffusion and time delay. The author employed the Galerkin method and constructed bifurcation maps which show distinct stable and unstable areas. They complemented their analytical investigation with numerical simulations. Ref. [3] illustrated a refined mathematical model of HIV infection dynamics, incorporating several key improvements. The enhancements include the introduction of distributed delay kernels to account for the variability in viral invasion and replication times, a nonlinear incidence function to model virus infections more realistically, and a nonlinear removal rate function for infected cells. These factors were found to simultaneously decrease virus transmission while enhancing protection in vivo. Ref. [22] discussed the nonlinear diffusion of a viral infection model incorporating a delayed immune response. Bifurcation and stability analysis revealed that a zero-delay scenario led to stability, while non-zero delays resulted in Hopf points. Numerical examples support and illustrate these theoretical results. Ref. [20] presented a semi-analytical investigation of a viral infection model with time delay, illustrating steady-state results and constructing bifurcation maps. The influence of delay and diffusion rates was illustrated, particularly that the critical values at the Hopf bifurcation point rose with increased growth and reproduction rates, while the death rate of free viruses declined.

The previous research related to model (2) makes clear that there is a gap in understanding the effects of diffusion when the system involves two delay rates: most existing research has focused on delay differential equations (DDEs) [2,7,15–18], or on reaction–diffusion models without delays. Although some research has tackled the theoretical aspects of PDE models with a single delay [3,5,22], none have comprehensively investigated the overall impact of introducing two delays and diffusion rates on stability. Consequently, this work aims to contribute by analyzing the effects of incorporating two time delays along with diffusion rates, with a particular emphasis on Hopf bifurcation points, bifurcation maps, and stability regions. This study has several goals:

1. To examine how the three types of delay terms influence stability and Hopf bifurcation regions, facilitating an understanding of their interaction with other free rates in the system.
2. To find an analytical framework for the delay ODEs using the Galerkin approach.
3. To determine a theoretical equation for the presence of exact Hopf points.
4. To create bifurcation graphs and 3-D maps for validating the theoretical outcomes.
5. To explore how these outputs connect to biological interpretation as well as the potential advantages of their practical implementation.

In summary, this paper will focus on investigating the comprehensive effects of diffusion, growth, and two delays rates on stability and Hopf bifurcation as derived from delay partial differential equations (DPDEs). The paper is organized as follows: Section 2 shows the mathematical formulations with their Dirichlet boundary conditions and motivations. Section 3 explores the methodology used to establish the theoretical framework, including the conditions for identifying Hopf points. In Section 4, we examine three distinct delay scenarios and their effects on the stability analysis maps. Finally, in Section 5, bifurcation diagrams are constructed both theoretically and numerically, illustrating the impacts of diffusion and delay rates on stability.

3. Methodology and Theoretical Framework

3.1. Analytical Framework

Analytical solutions for nonlinear PDEs system with time delays can be quite challenging to obtain, and some systems have proven especially difficult to solve, or even to address at all. In this work, we concentrate on a reliable analytical methodology that has been extensively discussed and explained for application to various systems. This approach, the

Galerkin analytical method [23], can be employed to analyze PDE models and derive an associated ODE system. One significant advantage of the Galerkin method is its flexibility in selecting basis functions; a variety of basis functions can be utilized. Overall, this technique serves as a powerful numerical simulation scheme for approximating outputs to both differential and integral equations.

The Galerkin method has been effectively applied to significant real-world problems. For instance, Nicholson's blowfly equation, various classes of delay logistic equations, the Belousov–Zhabotinsky system, limited-food systems, the advection competition model, viral infection models, competition and cooperation models, business cycle models, neural network models, the Lotka–Volterra predator–prey system, and Gray and Scott's system, etc, for more details, see [5,20,21,24–26] and references therein. Generally, all outputs derived by this method present excellent agreement with corresponding numerical results. Hence, this method is effective and reliable, and can be applied to the HIV model considered in this work.

The first step in developing the DDE system from the initial model as in (2) begins by considering the following equations:

$$\begin{aligned} u_{i(x,t)} &= u_{i1}(x, t) \cos c_1 + u_{i2}(x, t) \cos c_2 \text{ where } i = 1, 2, 3. \\ u_{j\tau_1} &= u_j(x, t - \tau_1) = u_{j1}(t - \tau_1) \cos c_1 + u_{j2}(t - \tau_1) \cos c_2, \\ u_{j\tau_2} &= u_j(x, t - \tau_2) = u_{j1}(t - \tau_2) \cos c_1 + u_{j2}(t - \tau_2) \cos c_2, \\ \text{where } c_1 &= \frac{1}{2}\pi x \text{ and } c_2 = \frac{3}{2}\pi x \text{ and } j = 1, 2. \end{aligned} \quad (3)$$

The trial functions are designed to ensure adherence to the boundary conditions as specified in (2). The free parameters of the trial functions are determined by computing the corresponding spatial averages in the DPDE system. To derive the reduced system of DDEs, each equation in model (2) is projected onto the corresponding trial functions, $\cos c_1$ and $\cos c_2$. This weighting transforms the original DPDE system into a finite-dimensional system of DDEs. As a result, a system of six DDEs is obtained, which is referred to as the “theoretical two-term system”, and is given by

$$\begin{aligned} Z_1 &= \frac{du_{11}}{dt} = -\frac{\pi^2}{4} du_{11} - \alpha_4 u_{11} - \frac{8\beta}{3\pi} u_{11} u_{21} - \frac{8\beta}{15\pi} u_{11} u_{22} - \frac{8\beta}{15\pi} u_{12} u_{21} - \frac{72\beta}{35\pi} u_{12} u_{22} + \frac{8\lambda}{\pi}, \\ Z_2 &= \frac{du_{21}}{dt} = -\frac{\pi^2}{4} du_{21} - \frac{8p}{3\pi} u_{21} u_{31} - \frac{8p}{15\pi} u_{21} u_{32} - \frac{8p}{15\pi} u_{22} u_{31} - \frac{72p}{35\pi} u_{22} u_{32} + \frac{8\beta}{3\pi} u_{11\tau_1} u_{21\tau_1} \\ &\quad + \frac{8\beta}{15\pi} u_{11\tau_1} u_{22\tau_1} + \frac{8\beta}{15\pi} u_{12\tau_1} u_{21\tau_1} + \frac{72\beta}{35\pi} u_{12\tau_1} u_{22\tau_1} - \alpha_1 u_{21}, \\ Z_3 &= \frac{du_{31}}{dt} = -\frac{\pi^2}{4} du_{31} + \frac{3\alpha_3}{4} u_{11} u_{31} u_{21\tau_2} + \frac{\alpha_3}{4} u_{11} u_{31} u_{22\tau_2} + \frac{\alpha_3}{4} u_{11} u_{32} u_{21\tau_2} + \frac{\alpha_3}{2} u_{11} u_{32} u_{22\tau_2} \\ &\quad + \frac{\alpha_3}{4} u_{12} u_{31} u_{21\tau_2} + \frac{\alpha_3}{2} u_{12} u_{31} u_{22\tau_2} + \frac{\alpha_3}{2} u_{12} u_{32} u_{21\tau_2} - \alpha_2 u_{31}, \\ Z_4 &= \frac{du_{12}}{dt} = -\frac{9\pi^2}{4} du_{12} - \alpha_4 u_{12} - \frac{8\beta}{15\pi} u_{11} u_{21} - \frac{72\beta}{35\pi} u_{11} u_{22} - \frac{72\beta}{35\pi} u_{12} u_{21} + \frac{8\beta}{9\pi} u_{12} u_{22} - \frac{4\lambda}{3\pi}, \\ Z_5 &= \frac{du_{22}}{dt} = -\frac{9\pi^2}{4} du_{22} - \frac{8p}{15\pi} u_{21} u_{31} - \frac{72p}{35\pi} u_{21} u_{32} - \frac{72p}{35\pi} u_{22} u_{32} + \frac{8p}{9\pi} u_{22} u_{32} + \frac{8\beta}{15\pi} u_{11\tau_1} u_{21\tau_1} \\ &\quad + \frac{72\beta}{35\pi} u_{11\tau_1} u_{22\tau_1} + \frac{72\beta}{35\pi} u_{12\tau_1} u_{21\tau_1} - \frac{8\beta}{9\pi} u_{12\tau_1} u_{22\tau_1} - \alpha_1 u_{22}, \\ Z_6 &= \frac{du_{32}}{dt} = -\frac{9\pi^2}{4} du_{32} + \frac{\alpha_3}{4} u_{11} u_{31} u_{21\tau_2} + \frac{\alpha_3}{2} u_{11} u_{31} u_{22\tau_2} + \frac{\alpha_3}{2} u_{11} u_{32} u_{21\tau_2} + \frac{\alpha_3}{2} u_{12} u_{31} u_{21\tau_2} \\ &\quad + \frac{3\beta}{4\pi} u_{12} u_{32} u_{22\tau_2} - \alpha_2 u_{32}, \\ u_{11\tau_1} &= u_{11}(x, t - \tau_1) \text{ \& } u_{12\tau_1} = u_{12}(x, t - \tau_1) \text{ \& } u_{21\tau_1} = u_{21}(x, t - \tau_1), \\ u_{22\tau_1} &= u_{22}(x, t - \tau_1) \text{ and } i = 1, 2. \end{aligned} \quad (4)$$

The series expansion in system (3) is truncated to create two-term trial function equations. This truncation is justified, as the two-term approximation offers a valid and practical representation of the solutions. Moreover, a one-term trial equation can be formulated by defining $u_{i2} = u_{i2\tau_i} = 0$ in Z_1, Z_2 and Z_3 in system (4). This simplification eliminates the

contribution of the second term in the trial expansion; however, even with this reduction, the one-term trial function still yields reliable results.

3.2. Dynamical Theoretical Formulations

We now describe how the Galerkin method is applied to develop a theoretical framework for analyzing stability and Hopf bifurcation. The Hopf bifurcation point marks the system's transition from a stable equilibrium to an unstable state, resulting in the emergence of periodic limit cycle oscillations. At this transition, the eigenvalues of the linearized system intersect the imaginary axis, leading to a pair of complex conjugate eigenvalues with non-zero imaginary components; for more details, see [27–29]. To analytically determine the Hopf bifurcation points for system (4), we utilize a Taylor series expansion around the steady state and consider a condition that facilitates the examination of these bifurcation points as follows:

$$\begin{aligned} u_{1i} &= u_{1is} + \epsilon \Delta_1 e^{-\phi t}, & u_{2i} &= u_{2is} + \epsilon \Delta_2 e^{-\phi t}, & u_{3i} &= u_{3is} + \epsilon \Delta_3 e^{-\phi t}, \\ u_{1i\tau_1} &= u_{1is} + \epsilon \Delta_i e^{-\phi t} e^{\phi \tau_1}, & u_{2i\tau_1} &= u_{2is} + \epsilon \Delta_i e^{-\phi t} e^{\phi \tau_1}, \\ u_{2i\tau_2} &= u_{1is} + \epsilon \Delta_i e^{-\phi t} e^{\phi \tau_2}, & \text{where } i &= 1, 2 \text{ and } \epsilon \ll 1. \end{aligned} \quad (5)$$

We then substitute all of the functions in (5) into the system (4). Next, we linearize the system around the steady-state point [25,26]. The associated Jacobian matrix $J(\phi)$ is detailed in Appendix A. The Jacobian's eigenvalues ϕ provide the growth of small perturbations in the model. From these, the characteristic polynomial equation is defined via letting $\phi = i\omega$, where rate i is represented by the imaginary unit and ϕ is oscillation frequency ω . The characteristic polynomial equation is then divided into its real $\Re$ and imaginary $\Im$ parts. Thus, the Hopf bifurcation point is identified by considering the following condition:

$$Z_i = \Re = \Im = 0, \text{ where } i = 1, 2, \dots, 6. \quad (6)$$

Our numerical solutions of the delay ODE system (4) are obtained using fourth-order Runge–Kutta approximations [30,31]. For the numerical solution of the delay PDE system (2), we employ a Crank–Nicolson finite difference scheme. Both methods are well-regarded for their accuracy and stability with both delay and non-delay equations. In the numerical simulations, spatial and temporal discretizations are set to $\Delta x = 0.005$ and $\Delta t = 0.001$. Also, the rates $u_{1is} = u_{2is} = 1$ are selected as initial positive values for all numerical investigations conducted in this study. Simulations were conducted in Maple [32].

4. Stability Analysis Hopf Bifurcation

This part employs time lag as both a bifurcation and control rate to evaluate stability. Three distinct delay scenarios instances are analyzed: a single delay $\tau_1 = \tau_2 = \tau \neq 0$, two different delays $\tau_1 \neq \tau_2$, and no delay $\tau_1 = \tau_2 = 0$. Bifurcation graphs are created to demonstrate the effect in each scenarios of the time delay on all free parameters within the system, especially on the infection rate β , the reproduction rate λ and diffusion coefficient parameter d . In each map, the theoretical outputs from the delay ODEs (4) are contrasted with the numerical PDE model (1), and the stability regions of the Hopf bifurcation are identified and plotted. Throughout this part, the following rates are fixed: $\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = 1$ and $p = 1$.

4.1. One Delay ($\tau_1 = \tau_2 = \tau > 0$)

Figure 1 depicts various regions for the reproduction rate λ and infection rate β as they relate to the time delay τ . In these plots, black markers denote numerical simulations

of the PDE, whereas the red solid lines represent the analytical solutions from the two-term DDEs. The other parameters are $d = 0.1$ and $\beta = 1$ for Figure 1a, and $\lambda = 5$ for Figure 1b. In Figure 1a, the unstable (US) region lies above the stable (ST) area, separated by an asymptotically decreasing curve. Considering the delay as a main bifurcation rate, it is observed that, when increasing the time lag τ , the rate of the Hopf bifurcation of the reproduction parameter (λ) steadily decrease. In contrast, the stable area for Figure 1b surrounds the stable region on three sides so that there are two Hopf points for viral infection parameter β for any given delay, whereas there was only one Hopf point for growth rate λ . In both graphs, the analytical solutions from the DDE model closely agree, within 2%, with the numerical solutions from the PDE.

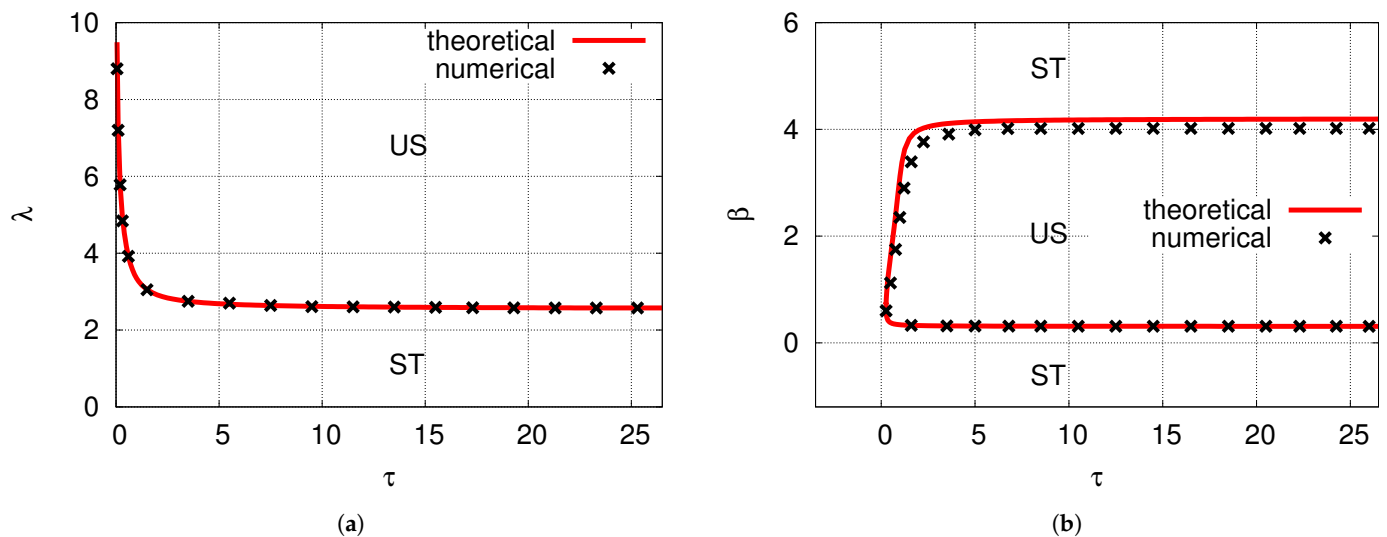


Figure 1. Bifurcation phase in τ - λ and τ - β maps, The other parameters are $d = 0.1$, $\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = p = 1$ and $\beta = 1$ for Figure (a) while, in Figure (b), $\lambda = 5$.

Figure 2a,b display the Hopf bifurcation regions in τ - d space for four generation rates λ (with $\beta = 1$) and four infection rates β (with $\lambda = 5$), respectively. Both figures show solutions separating the unstable bifurcation area on the left, and the stable zone on the right side. It is evident that, as diffusion d increases, the delay time τ also rises. Notably, for any fixed delay τ , the diffusion d increases while the generation parameter λ rises as well as the Hopf bifurcation lines are displaced to the right. Conversely, the infection rate β decreases as diffusion d increases for fixed τ , and the Hopf bifurcation lines of the rate of infection β shift from right to left. This can be interpreted as meaning that higher rates of generation and infection promote stability in the system. Furthermore, the stability region expands at increased values of both λ in both phase planes, suggesting that increased generation rate also contributes to greater stability. These observations partially aligns with findings reported in previous studies [5,22].

Figure 3a,b explore the Hopf bifurcation areas in the λ - β map with different examples for both diffusion and time lag. The other rates applied here are $\tau = 1$ for Figure 3a, and $d = 0.1$ for Figure 3b. Both maps show analytic solutions of the two-term model. In each case, the unstable zone is on the right of each curve, and a stable zone to the left. Moreover, with increases in reproduction rate λ , the Hopf bifurcation points of the infection value shift to the left and then increase with elevated values of the reproduction rate λ . In Figure 3a, the generation value λ increases with the diffusion value d . Meanwhile, Figure 3b indicates at every fixed value of the infection parameter (β), the reproduction value λ decreases with the time lag increases. Furthermore, at any set generation parameter, there are two Hopf points corresponding to the β value.

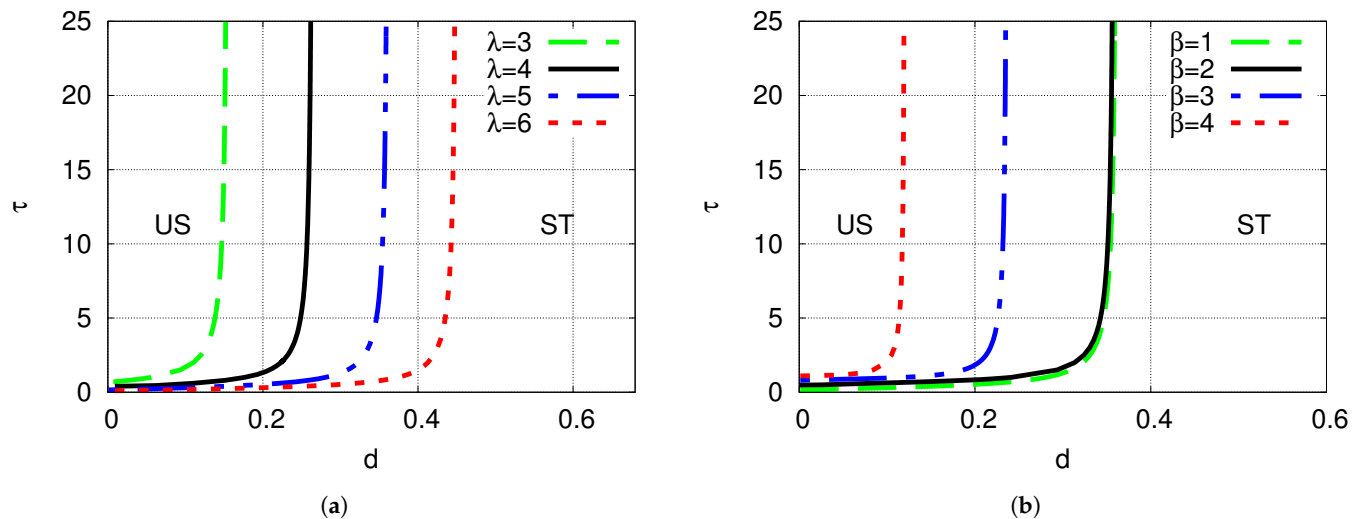


Figure 2. Bifurcation graphs for d - τ maps featuring values for rates λ (a) and β (b).

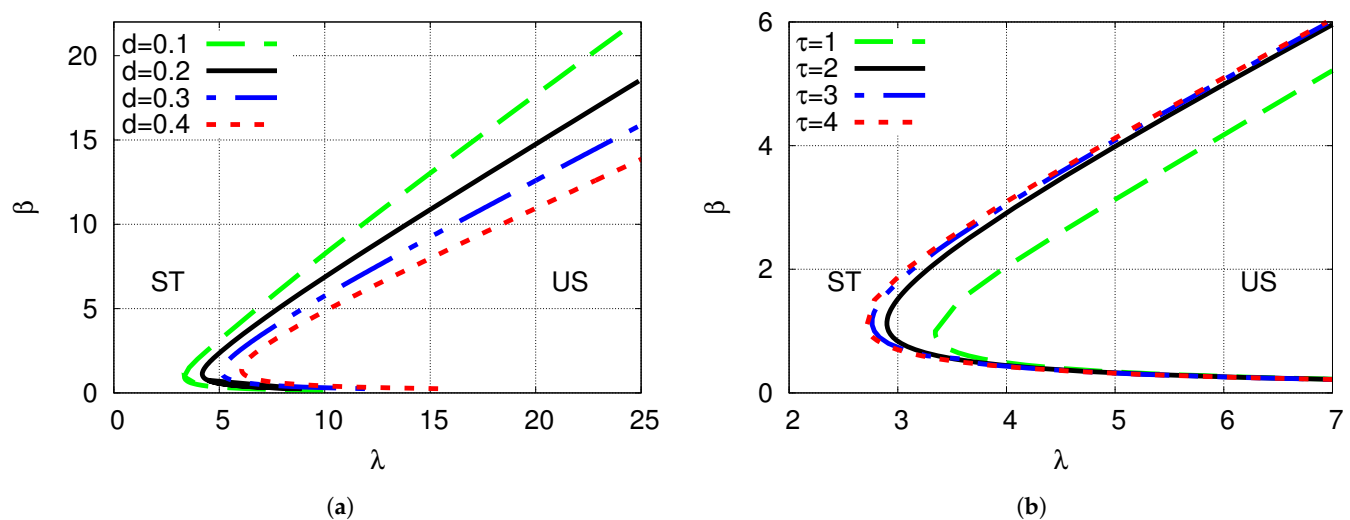


Figure 3. Bifurcation graphs in the λ - β plane for different values of: (a) the time delay τ ; and (b) the diffusion coefficient d .

As with the previous scenario considered above, it can be inferred that, for any fixed generation parameter, raising the viral infection value increases the mortality rate α_1 of infected cells. Conversely, β diminishes as the activation parameter α_3 increases.

Figure 4a,b display two phase planes illustrating the diffusion rate d versus rates of λ (generation value) and β (infection parameter). The solutions use $\tau = 1$ and $\beta = 1$ for Figure 4a and $\lambda = 5$ for Figure 4b. The Hopf bifurcation points form a curve which divides the graph till two regions: stable above, and unstable below. Clearly, as diffusion value (d) increases, the Hopf points for the growth parameter λ also increase. Further, it was observed that as the diffusion value d grows, the Hopf bifurcation points for the infection value β rise to point: $(d, \beta) \approx (0.289, 1.197)$, beyond which the Hopf of the infection value β decline until the case where $d = 0$ (no diffusion), at which point they approach $(\beta, d) \approx (0.203, 0)$. In addition, there are two Hopf points for the infection parameter β at any fixed diffusion rate (d); however, there is only one Hopf bifurcation point for the generation value λ . This result confirms what was found from Figure 1. The diffusion rates d substantially influence solutions, showing a strong correspondence between the theoretical predictions and the numerical simulations, with a relative discrepancy of less than 3% across the entire domain of d .

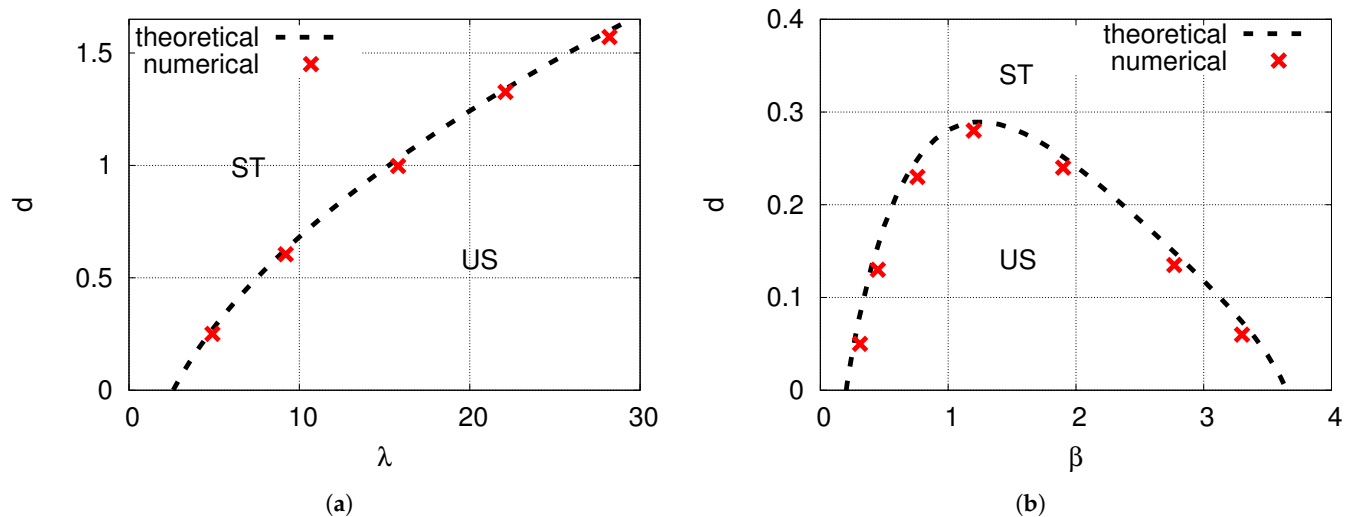


Figure 4. Bifurcation maps in the parameter planes: (a) λ - d ; and (b) β - d .

Figure 5 presents four graphs analyzing stability in terms of the delay τ against various parameters: the infected-cell mortality rate α_1 , the CTL decay rate α_2 , the activation rate α_3 , and the healthy cell death rate α_4 . Each graph displays the two-term results from the DDE system, with $\lambda = 5$, $\beta = 1$, $d = 0.1$ and $\tau = 1$. In each map the unstable and stable regions are distinctly separated. As τ rises, the Hopf points for the activation parameter α_3 gradually decrease, whereas the Hopf points for α_1 , α_2 , and α_4 all increase. With larger delays, all of α_1 , α_2 , α_3 and α_4 exhibit limited influence, resulting in stabilization of the model.

Figure 6a illustrates the Hopf bifurcations in the $\lambda - \beta$ space for two scenarios regarding the diffusion coefficient: the first scenario represents the case without diffusion term (denoted by black curve), and the second scenario includes the diffusion effect (red dashed line), with $\tau = 1$. As in Figure 3a, increasing the reproduction rate λ , the Hopf bifurcation points of infection rate β fall and then rise again. Moreover, the behaviors between the two cases differ markedly at high values of λ when β is substantial. Figure 6b,c present the λ - ω and β - ω planes for both cases with and without diffusion. Here, it is evident that the oscillation frequency ω is unsteady as the generation value (λ) and infection parameter β is increased. It can be seen that ω is stable for the non-diffusion case but unstable and changeable for the diffusion case. This further underscores the significance of the diffusion coefficient in the model.

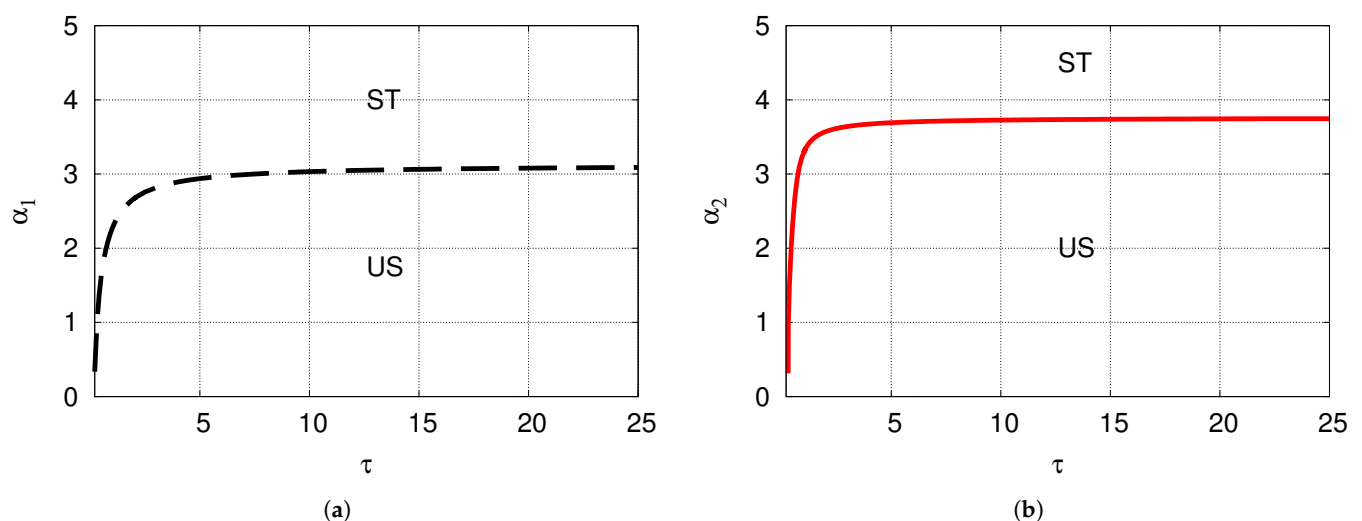


Figure 5. Cont.

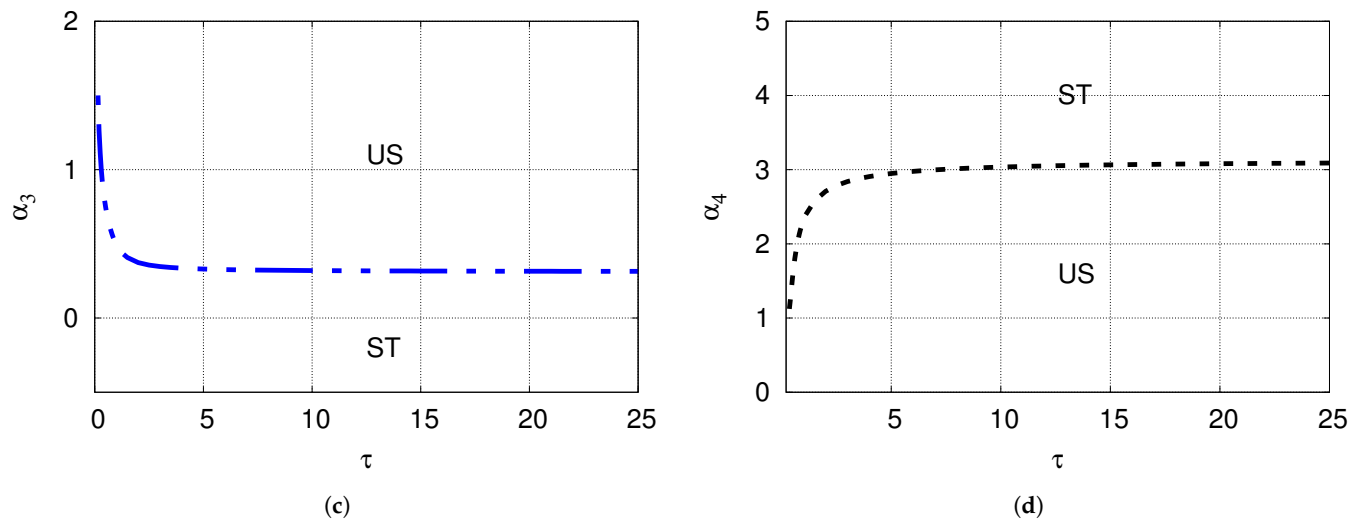


Figure 5. Bifurcation diagrams for delay time τ with four different parameters of: (a) α_1 ; (b) α_2 ; (c) α_3 ; and (d) α_4 .

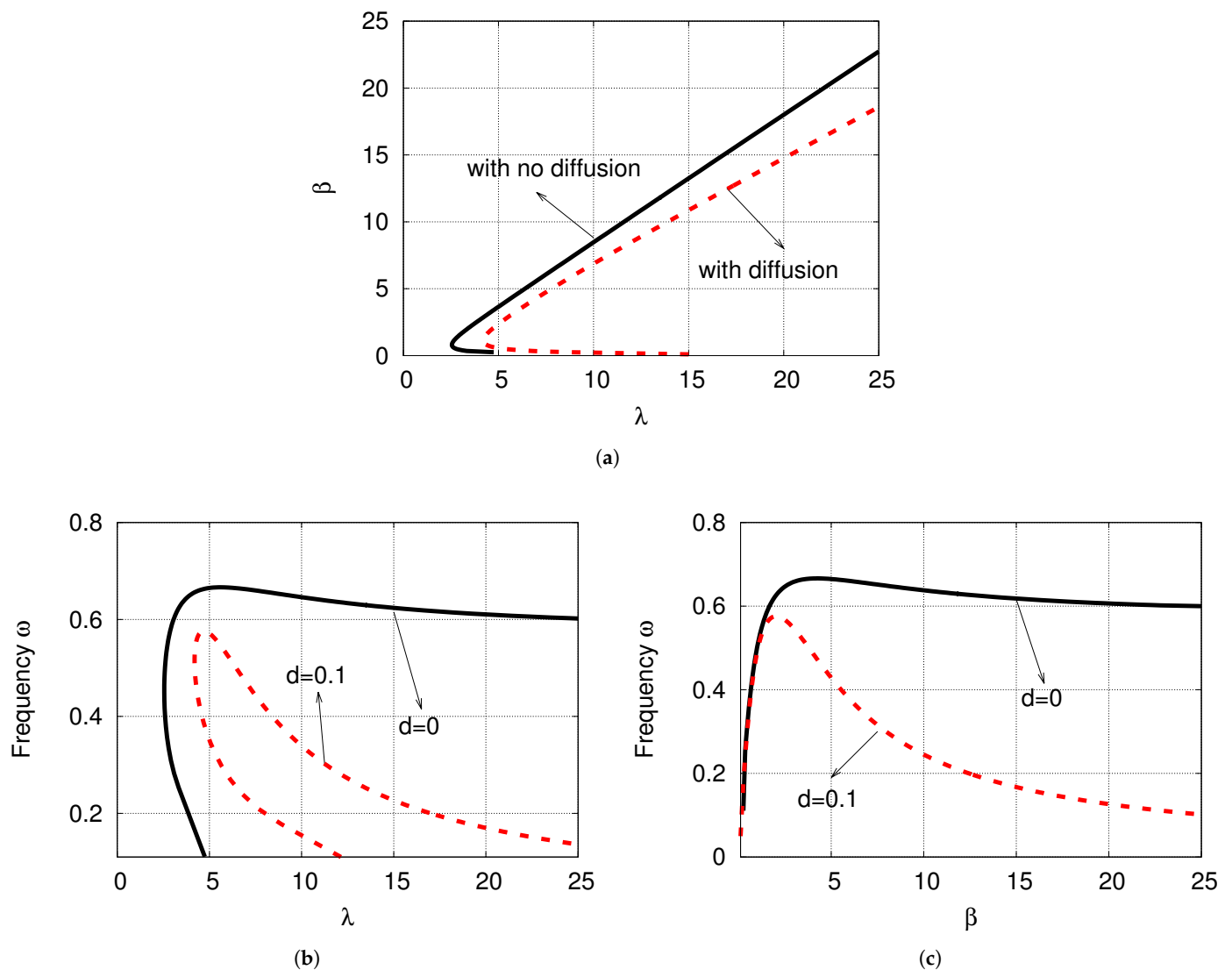


Figure 6. Bifurcation maps in λ - β (a), λ - ω (b) and β - ω (c). Two cases are shown: $d = 0$ and $d = 0.1$.

In conclusion, given any particular delay, all of the system parameters can significantly affect the stability region and Hopf points rates for cell generation, infection, and the other free rates.

Overall, in all of the figures in this part, the theoretical results from the DDE model closely align with the numerical PDE solutions, differing by less than 3%. Furthermore, the observed behavior of τ is qualitatively consistent with findings from previous studies [5,25,33].

4.2. Two Distinct Delays ($0 < \tau_1, \tau_2$)

Figure 7 display the Hopf bifurcation region in the $\tau_1 - \tau_2$ parameter space. Each graph is derived from an analytical system and features four examples of the reproduction parameters of λ and β . The fixed parameters here are $d = 0.1$ and $\beta = 1$ for Figure 7a, whereas in Figure 7b $\lambda = 5$. Both graphs illustrate an unstable area up each line and a stable area down it. Moreover, as the latency τ_1 of cell-to-cell infection increases, Hopf points occur at higher values of the time lag τ_2 for CTL activation induced by infected cells. In addition, an increase in the reproduction rates λ and β raises the Hopf curve, enlarging the stable area.

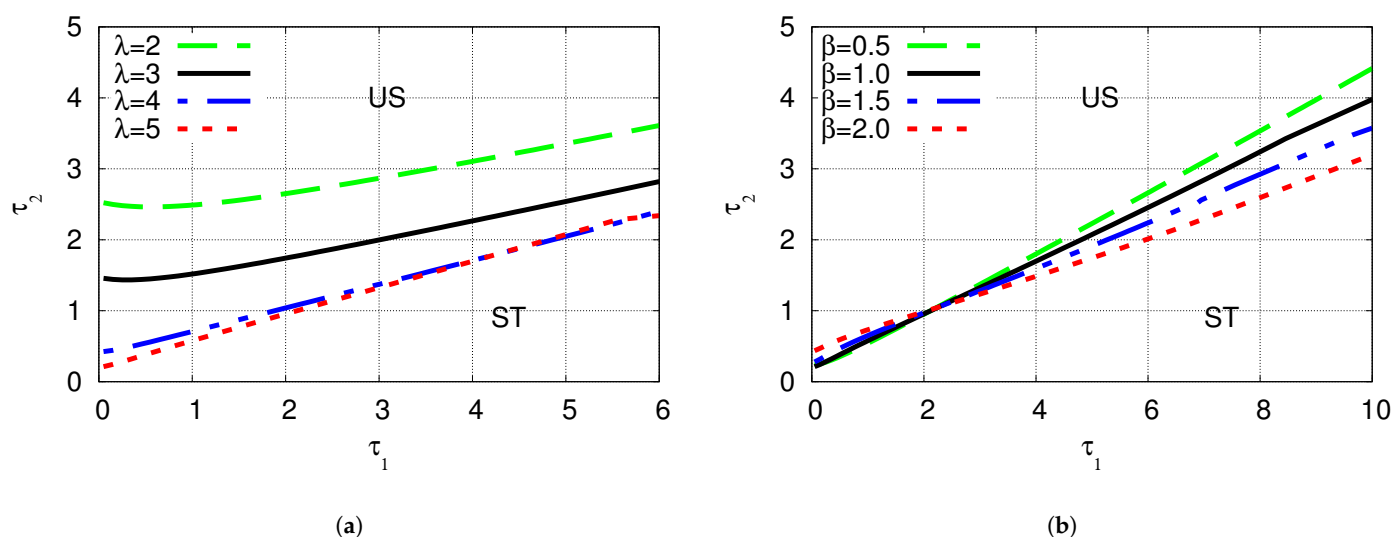


Figure 7. (a,b) Bifurcation diagrams in $\tau_1 - \tau_2$ map, with various rates λ, β .

Figure 8a,b illustrate the Hopf bifurcations of τ_1 —the latency of cell-to-cell infection—against the reproduction rate λ and the infection rate β , respectively. Each graph is derived from an analytical system of DDEs and numerical solution of DPDEs. The fixed parameters are $d = 0.1$ and $\beta = 1$ for Figure 8a, while in Figure 8b $\lambda = 5$. Two separate stability regions are seen: the unstable area above, and the stable zone is found below. The Hopf points for λ and β increase as the time delay τ_1 grows; then these values rise vertically. Beyond this point, τ_1 loses its influence over both the reproduction and the infection rates. Note that the behavior and impact of the time delay value in the activation of CTLs τ_2 is quite similar to that of τ_1 for λ and β .

Figure 9 shows the Hopf bifurcation zone of the $\tau_1 - \tau_2$ diagram, each showcasing distinct examples of (a) d , (b) α_1 , (c) α_3 , and (d) α_4 . The other parameters are $\beta = 1$, $\lambda = 5$, and $d = 0.1$. As above in Figure 7, each plot shows clear separation of one stable region from one unstable region, and increasing the time delay τ_1 (the intracellular latency) results in the Hopf points occurring at steadily increasing values of the CTL activation latency τ_2 . These figures also explore the impact of the delay rates τ_2 : at any τ_1 , the Hopf point for the diffusion parameter d , α_1 , (rate of infected cells die) and α_4 , (the death rate) increase as τ_2 increases. However, the Hopf points for the activation parameter α_3 go down as shown in Figure 9c.

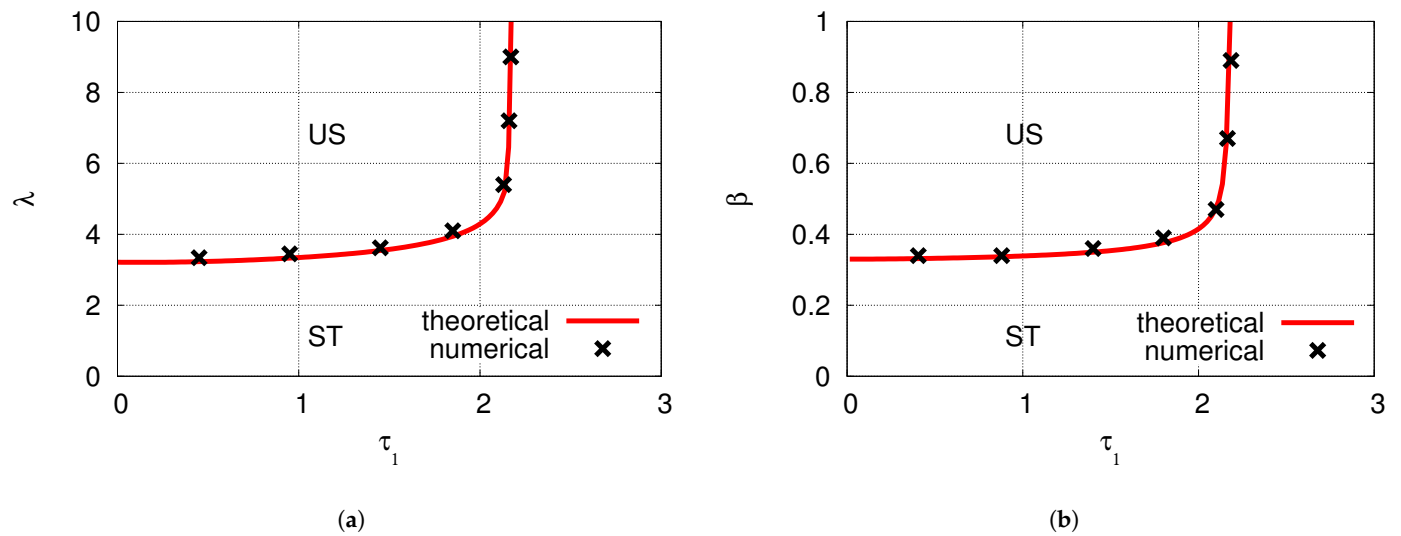


Figure 8. (a,b) Bifurcation maps of τ_1 against λ and β .

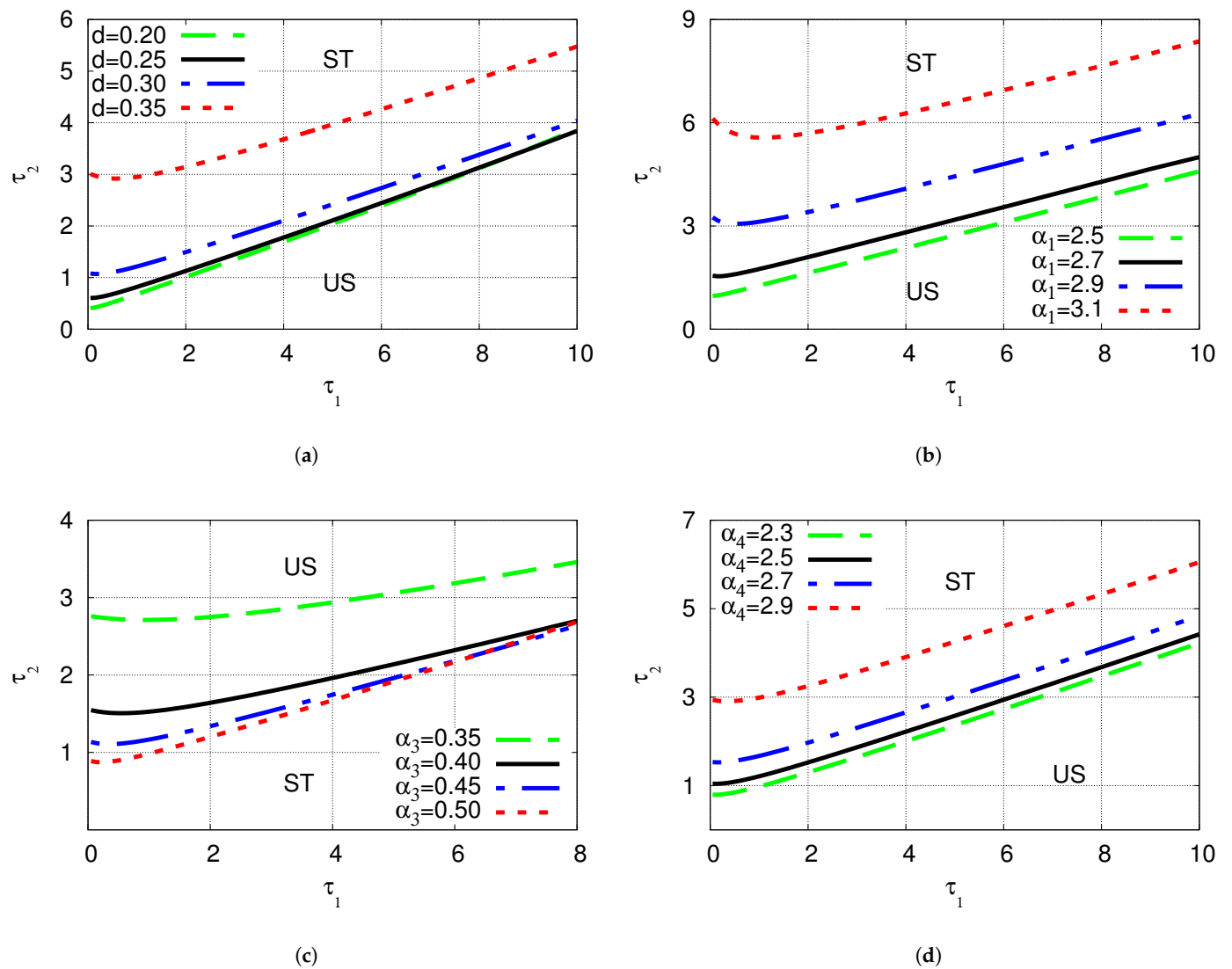


Figure 9. Hopf bifurcation curves in the τ_1 - τ_2 plane with various rates of: (a) d ; (b) α_1 ; (c) α_3 ; and (d) α_4 .

Figure 10a,b display bifurcation maps of the $\lambda - \beta$. Each graph is derived from an analytical system of ODEs and includes four examples of τ_1 and τ_2 , with diffusion rate $d = 0.1$. It can be seen that the solutions with two delays are similar to those with only one delay as in Figure 3b. Clearly, at any set point of the infection value β in Figure 10a, the time delay τ_1 increase as the reproduction rate λ is rised. Whereas in Figure 10b, the time lag τ_2 in CTL activation grows as the reproduction rate λ decrease. It is evident that increasing τ_1 shifts the Hopf bifurcation boundary to the left. Conversely, in Figure 10b, the Hopf bifurcation boundary shifts right as τ_2 increases.

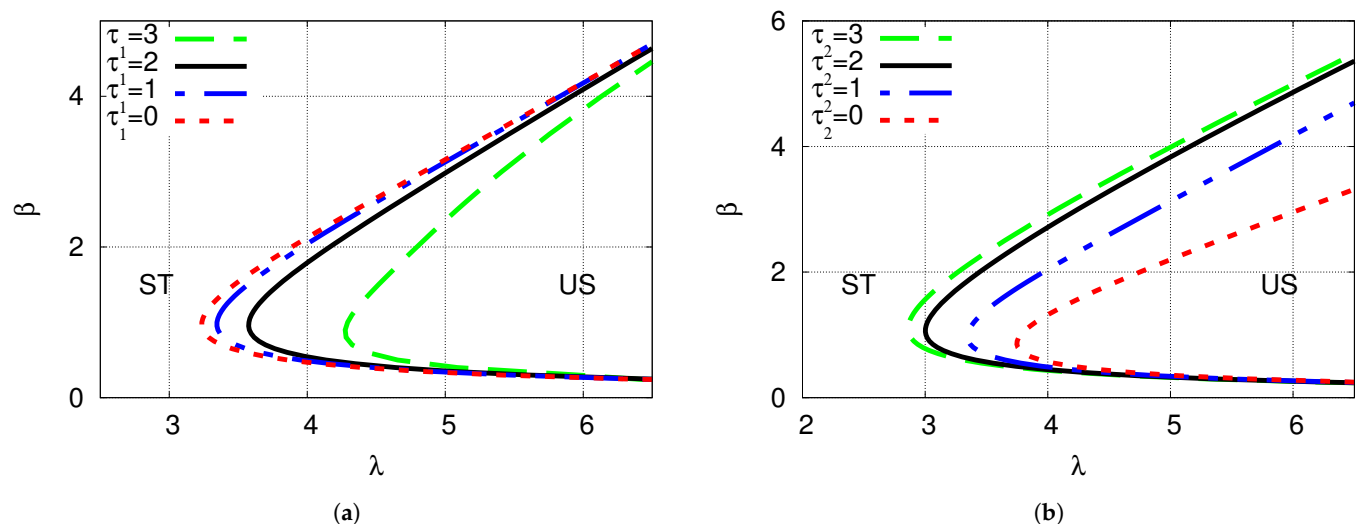


Figure 10. Bifurcation graphs for $\lambda - \beta$ with various examples of τ_1 and τ_2 . Two examples are shown: $\tau_2 = 1$ (a) and $\tau_1 = 1$ (b).

Figure 11 display the Hopf bifurcation diagram in the $\tau_1 - \tau_2$ map (graph a) and the $\tau_1 - \omega$ plane (graph b) and $\tau_2 - \omega$ plane (graph c). Two cases are considered: with diffusion (black solid curve) and without (red dashed line); in both cases $\lambda = 5$ and $\beta = 1$. In Figure 11a, it is evident that the delay τ_1 increases as τ_2 increases. In the $\tau_1 - \omega$ and $\tau_2 - \omega$ planes, the oscillation frequency ω decreases with increases in either delays, and exhibits stable behavior regardless of diffusion. This underscores the importance of the diffusion rate, indicating that it can greatly impact upon the model's bifurcation boundaries.

In summary, the delay to CTL activation by triggered cells and the intracellular latency of cell-to-cell infection output have important implications for all other free parameters in the system such as the mortality rate of infected cells, the CTL decay rate, the activation and proliferation rates, reproduction rate, and infection rate.

4.3. Non-Delay Case ($\tau_1 = \tau_2 = 0$)

This part establishes the steady-state properties for the three cell populations: u_1 (healthy host cells), u_2 (virus-infected cells), and u_3 (CTLs). The analysis employs both analytic results and PDE simulations with no delay effect. It is important to note that no Hopf point is discovered at the no-delay situation $\tau_1 = \tau_2 = 0$, indicating that all solutions without delay are stable [5,22]. To determine the steady-state outcome, we first set all delays to zero in the ODE (4) and DPDE Equation (2); for more details, see [21]. The analytic steady-state solution can be found by solving for Z_i as in (4). In this case, we have four cases of non-negative, steady-state equilibrium points:

- (i) the steady-state results at the origin point $S_1 = (u_1, u_2, u_3) = (0, 0, 0)$, always present,
- (ii) the axial steady-state point $S_2 = (u_1, u_2, u_3) = \left(\frac{16\lambda}{\pi(d\pi^2 + 4\alpha_4)}, 0, 0 \right)$ exists only if $\lambda > 0$,

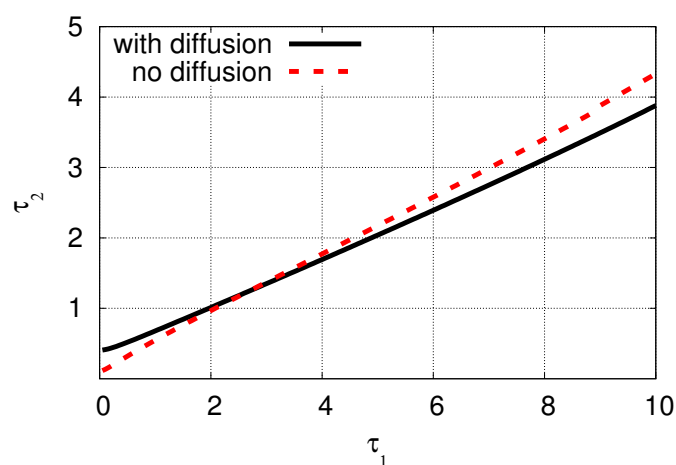
(iii) the axial steady-state point at

$S_3 = (u_1, u_2, u_3) = \left(\frac{3\pi(d\pi^2 + 4\alpha_1)}{32\beta}, -\frac{3\pi^6 d^2 + 12\pi^4 \alpha_1 d + 12\pi^4 d \alpha_4 + 48\pi^2 \alpha_1 \alpha_4 - 512\beta\lambda}{32\pi\beta(\pi^2 d + 4\alpha_1)}, 0 \right)$ exists only if $\lambda, \beta > 0$,

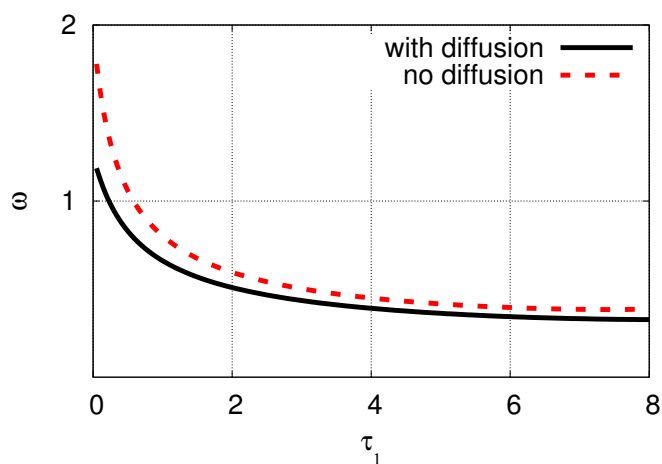
(iv) the positive steady-state point $S_4 = (u_1, u_2, u_3)$ which exists at

$$\begin{aligned} u_1 &= -\frac{16(2d\pi^2\beta + 8\alpha_2\beta - 9\alpha_3\lambda)}{9\alpha_3\pi(\pi^2 d + 4\alpha_4)}, \\ u_2 &= \frac{-3\pi(\pi^4 d^2 + 4d\pi^2\alpha_2 + 4d\pi^2\alpha_4 + 16\alpha_2\alpha_4)}{16(2d\pi^2\beta + 8\alpha_2\beta - 9\alpha_3\lambda)}, \\ u_3 &= -\frac{\alpha_3(27\pi^6 d^2 + 108d\pi^4\alpha_1 + 108d\pi^4\alpha_4 + 432\pi^2\alpha_1\alpha_4 - 4608\beta\lambda) + \beta^2(1024d\pi^2 + 4096\alpha_2)}{288(\alpha_3\pi p(d\pi^2 + 4d\alpha_4))}. \end{aligned}$$

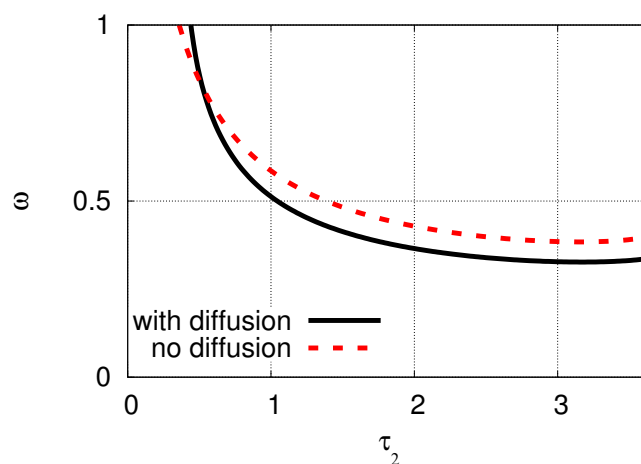
Note that the diffusion-case behaviors are qualitatively similar to the non-diffusion case [9,14].



(a)



(b)



(c)

Figure 11. Bifurcation graphs in the τ_1 - τ_2 plane (a), τ_1 - ω (b) and τ_2 - ω (c). Two cases are shown: $d = 0$ and $d = 0.1$.

Figure 12 illustrates the behavior of steady-state outputs for the populations u_1 (healthy host cells), u_2 (infected cells), and u_3 (CTLs) against the reproduction rate λ with $d = 0.1$ and $\beta = 1$. The analytic ODE results are represented by the red line, while the numerical PDE solution is shown by the black dotted curve. The steady-state lines are determined

by allowing both delay lags to approach zero ($\tau_1, \tau_2 \rightarrow 0$) in the ODE system (4), as in [5,25]. Each graph displays a single line representing the steady-state outcomes for each species concentration, demonstrating that as the reproduction parameter raises, the number of susceptible host cells u_1 and the number of CTLs u_3 grow to maximum values of $(u_1, u_3) \approx (17,692, 16.457)$ by the end of the selected interval at $\lambda = 20$. However, the figure clearly shows that, as the reproduction rate λ increases, the number of virus infected cells u_2 falls to attain a minimum at a significant value of λ . These findings indicate near-perfect consensus among the analytical DDE and DPDE simulation results, as evidenced by close agreement to about 1%. When there is no delay term present, a Hopf bifurcation does not occur. As a result, all three concentrations in the models exhibit asymptotically stable outcomes; these findings are consistent with those previously examined in [5,25,34].

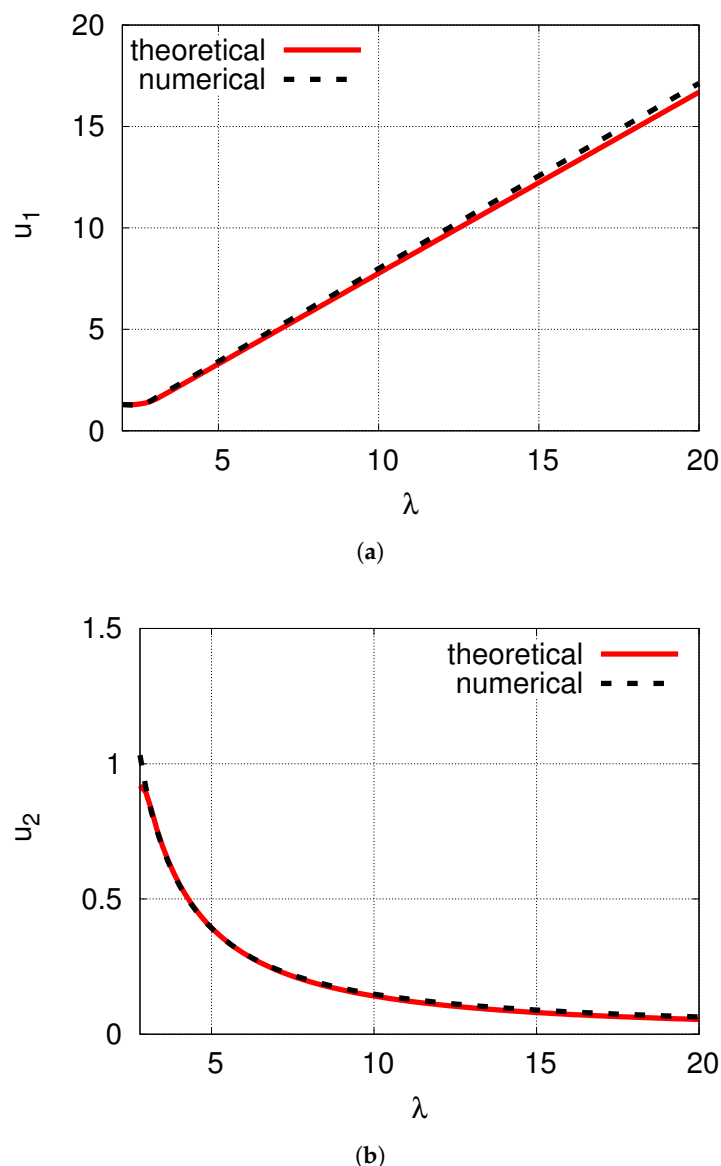


Figure 12. Cont.

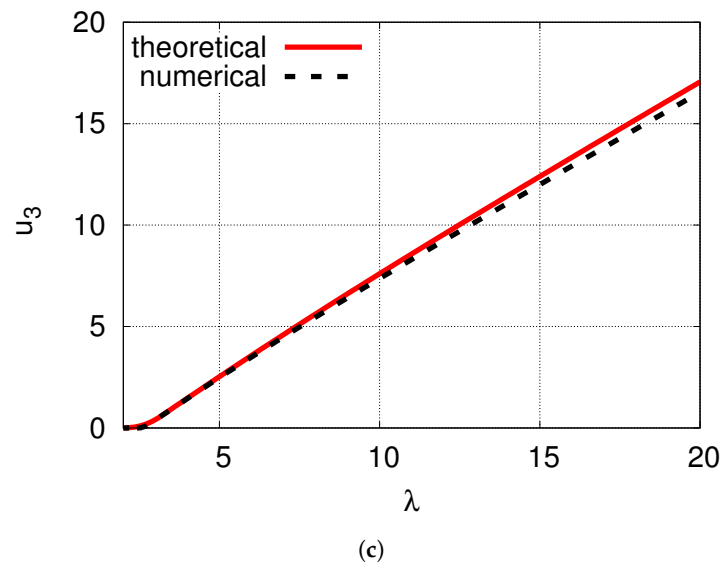
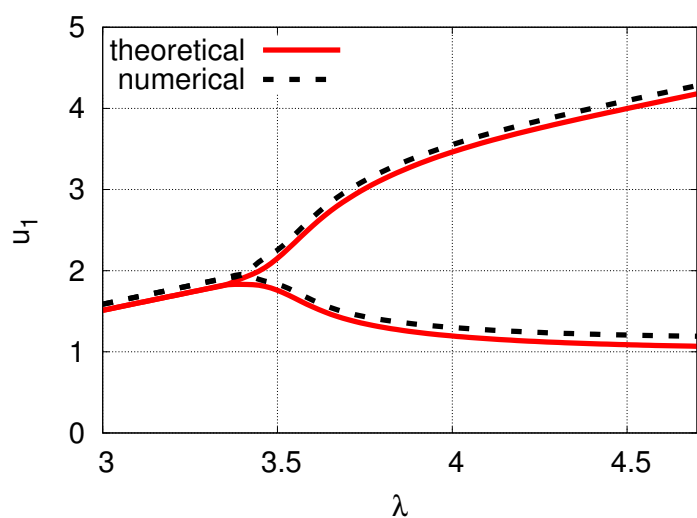


Figure 12. Steady-state population densities as functions of the growth rate λ : (a) u_1 ; (b) u_2 ; and (c) u_3 .

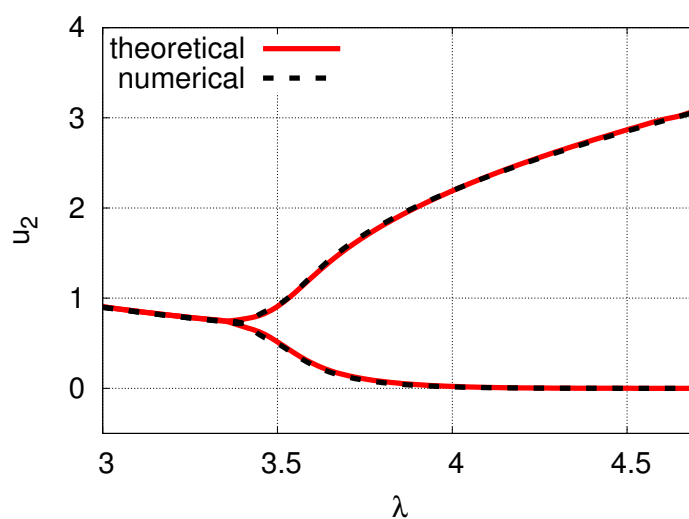
5. Bifurcation Diagrams and 3-D Phase-Plane Maps

Bifurcation diagrams are a standard and common method for examining the behavior of nonlinear dynamical models. This graphical representation visualizes how the steady states of a system change as parameters are varied, revealing critical transitions. For systems that exhibit complex periodic behavior, including potentially chaotic dynamics, phase-plane maps serve as essential tools, providing a visual representation of the trajectories of the system's state variables, and thereby enabling deeper insights into stability analysis and limit cycles [35]. Such investigation not only enhances our understanding of the underlying mechanisms driving these dynamics but also validates the theoretical approach as a reliable tool for studying complex delay PDE models. In this section, we select the reproduction rate λ and the infection rate β as the main parameters, fixing $\tau_1 = \tau_2 = p = \alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = 1$ for all examples in this section.

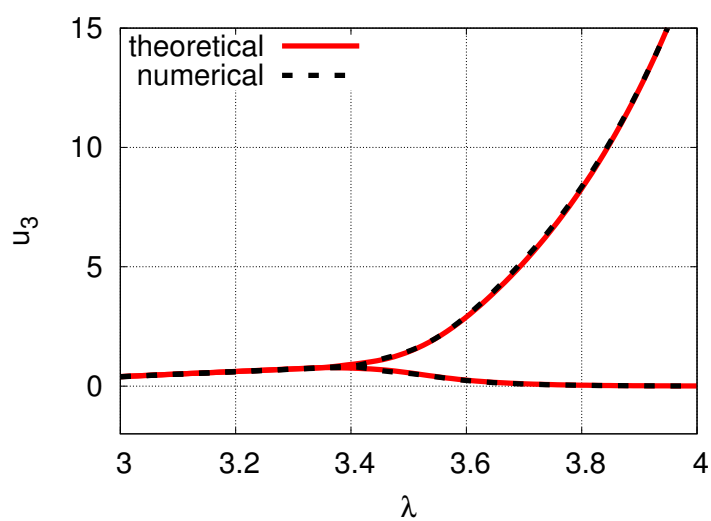
Figures 13 and 14 present bifurcation diagrams for the healthy target cell population u_1 , the number of virus-infected cells u_2 , and the number of CTLs u_3 versus λ as well as β rates. Both analytical solutions as well as DPDE simulations are presented, illustrating the significance of time delays in the model, which can lead to both stable and unstable steady-state behaviors. Each figure depicting periodic results features a supercritical Hopf point for each cell population. In Figure 13, there is a single Hopf point for every population. The Hopf point at the delay PDE model is approximately $\lambda_c \simeq 3.420$, while, for the theoretical outputs, $\lambda_c \simeq 3.397$. Beyond this point, a supercritical Hopf bifurcation appears, leading to the emergence of periodic limit cycles. Figure 14 reveals two Hopf points of the infection value β_c at each population. The theoretical solution becomes unstable within the range $0.554 < \beta_c < 2.345$. The numerical solution of the delay PDE system produces oscillating outputs for $0.568 < \beta_c < 2.357$. This graph displays a range with two bifurcation points at the value β (infection parameter), verifying the results presented in Figure 1b as well as Figure 4b. In the region where the generation value λ rises above λ_c , the peak limit cycle grows, whereas the minimum limit cycle diminishes. Furthermore, as the infection rate β rises, the maximum oscillation increases for both u_1 (healthy target cells) and u_3 (CTLs) until reaching $\beta = 1.120$, while the maximum oscillation point for u_2 (the number of infected cells) arrives at $\beta = 1.586$. Beyond these maxima, the curves decrease to a second Hopf point at $\beta_c \simeq 2.35$, after which the solutions become stable. The analytical predictions from the two-term model align with the numerical results from the PDE system with delays within less than 1%.



(a)



(b)



(c)

Figure 13. Bifurcation maps of the population densities with respect to the growth rate λ : (a) u_1 ; (b) u_2 ; and (c) u_3 , with $\beta = 1$ and $d = 0.1$.

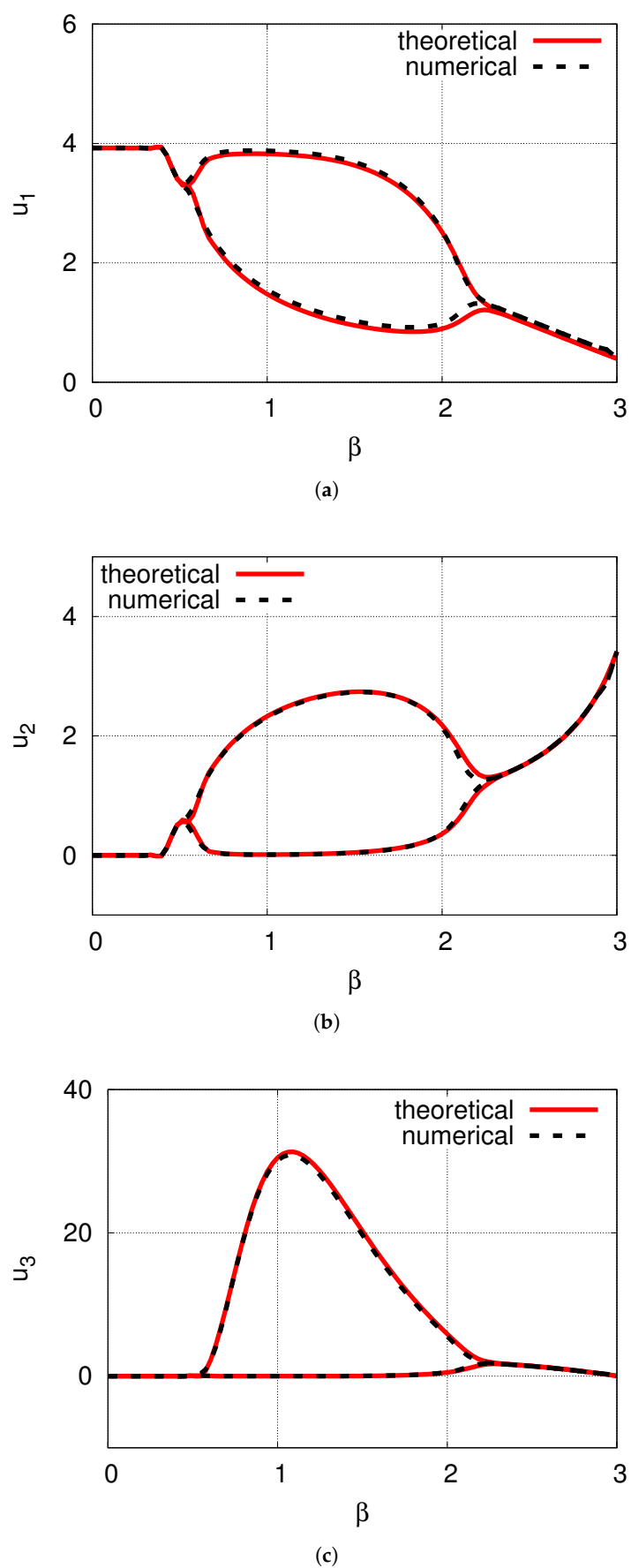


Figure 14. Bifurcation diagrams of the population densities with respect to β : (a) u_1 ; (b) u_2 ; and (c) u_3 , with $\lambda = 5$ and $d = 0.2$.

Figure 15a displays the evolutions of populations u_1 (susceptible host cells), u_2 (infected cells), and u_3 (cytotoxic T lymphocytes) over a long time t . This figure illustrates that, with $\beta = 2.5 < \beta_c$, the system is in the stable region in Figure 14. The solution eventually converges to a stable steady state at approximately $u_1(0, t) = 1.036$, $u_2(0, t) = 1.568$ and $u_3(0, t) = 1.380$ after a transient periodic oscillation. The analytical and numerical solutions agree closely, to within 1.5% at time $t = 100$. Figure 15b shows a 3D phase portrait map for u_1 , u_2 and u_3 . The rates in this example are the same as in Figure 15a, but with $\beta = 2.5$ (in the oscillation region in Figure 14). This phase portrait provides insights into the system's trajectory as it evolves. The cycle period is calculated to be 5.628 via the analytical DDEs and 5.685 via the numerical scheme, agreeing within 1%.

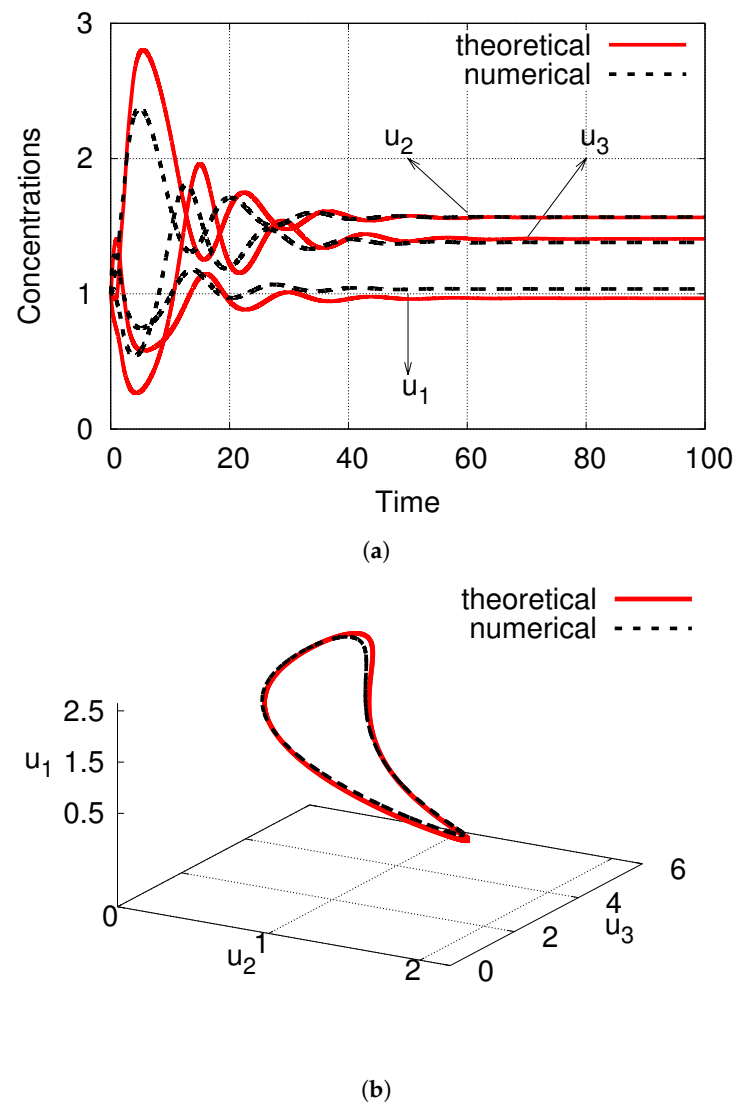


Figure 15. (a) Populations u_1 , u_2 and u_3 versus time, showing analytical and numerical DPDE solutions at $\beta = 2.5$ with other parameters are $\lambda = 5$ and $d = 0.2$. (b) 3D phase portrait for the three populations with $\beta = 2$.

Figure 16 illustrates a 3D phase-space graph for the three populations u_1 , u_2 and u_3 system, examining the effects of six different rates: λ , β , d , α_1 , α_3 and α_4 . This figure provides valuable insights into how the system's behavior changes as these rates are varied. In Figure 16a,e, increasing the reproduction rate λ and the activation rate α_3 leads to moderate rises in the oscillation amplitudes. On the contrary, Figure 16b–d,f demonstrate a different trend: as the infection rate β , the diffusion coefficient d , the infected cell death

rate α_1 and the healthy cell death rate α_4 increase, the oscillation amplitudes consistently decrease. Moreover, over time, the oscillations appear to diminish, and the system tends to move toward a stable region as these rates increase. The illustrated solutions validate the findings presented in the stability and Hopf bifurcation maps section. It is important to note that the cases analyzed here are specifically taken from beyond the Hopf bifurcation point, and also that these graphs illuminate and reinforce the findings derived in Section 4.

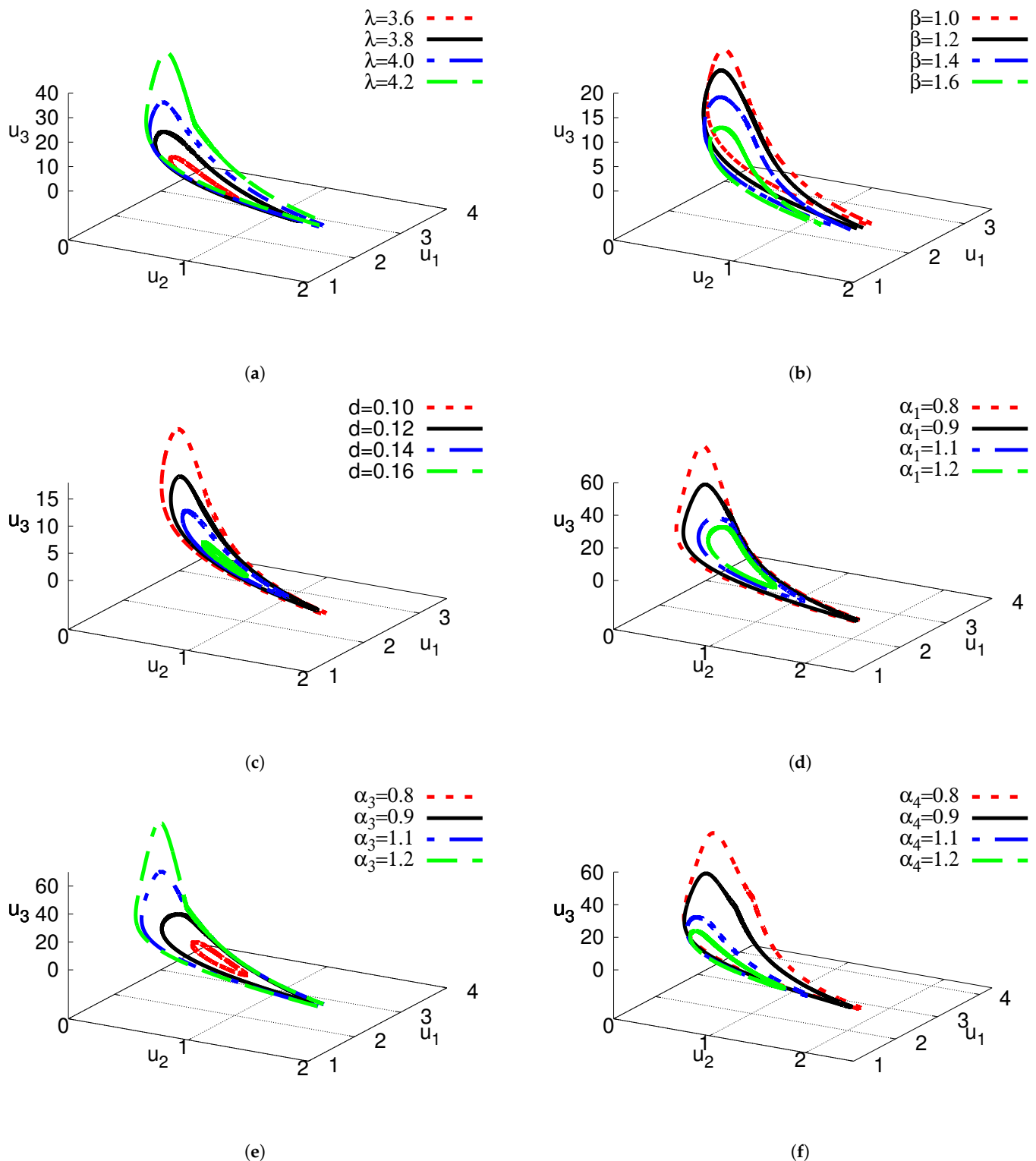


Figure 16. 3D phase portraits of the three cell populations at various rates of: (a) λ ; (b) β ; (c) d ; (d) α_1 ; (e) α_3 ; and (f) α_4 . The control parameter values are $\beta = 1$, $d = 0.1$, and $\lambda = 4$.

It is worth noting that several other biological population delay systems, for example, Nicholson's blowflies equation, the Schnakenberg model [25,33], and immune model [15,17], all demonstrate period doubling and chaotic behavior, phenomena that are not found and observed in this work.

6. Conclusions and Outlook

This research examined the impacts of both diffusion and delays on an HIV infection model. The stability and Hopf bifurcations were investigated using the Galerkin technique. Time lags and diffusion rates were identified as bifurcation controls to define the model's stability analysis behavior as well as assess the influence of these and to all free rates within the model. It was discovered that, when the delays are greater than zero, there are two distinct stability regions, while when both delays are zero, only one stability region exists, with no Hopf point to explore, resulting in a stable outcome. Comprehensive diagrammatic analyses were developed for the three different delay scenarios configurations, revealing their connections to other parameters in the system. We also explained and found benefits of choosing between one or two delays in the model: when applying two different delays, the Hopf points corresponding to the lag in CTL activation increase as the delay in intracellular infection increases. Further, the Hopf bifurcation points for virus infection were increased with elevations in the reproduction rate. It was also found that, as the delay increases, the Hopf point values for the reproduction rate steadily decrease, whilst the diffusion parameter increases and the Hopf points for the activation rate gradually decrease. However, when the Hopf points for the decay value of the specific CTL, the decay value of the specific CTL and the death value increase.

We also explained and found benefits of choosing between one or two delays in the model: when applying two different delays, the Hopf points corresponding to the lag in CTL activation increase as the delay in intracellular infection increases. Further, the Hopf bifurcation points for virus infection were increased with elevations in the reproduction rate. It was also found that, as the delay increases, the Hopf point values for the reproduction rate steadily decrease, whilst the diffusion parameter increases and the Hopf points for the activation rate gradually decrease. However, when the Hopf points for the decay value of the specific CTL, the decay value of the specific CTL and the death rate increase.

In addition, bifurcation planes and 3D maps were generated to illustrate the dependencies of periodic orbits through several examples. Numerical simulations confirmed the main findings, validating that the system exhibits a Hopf bifurcation. Solutions were carried through over long time periods to further illustrate these dynamics. This visual representation enhances the understanding of how delays influence the stability and oscillatory behavior of the system, providing valuable insights into the interplay between various parameters. In a forthcoming study, we plan to apply the same methodology to this model, incorporating two different delays and adding a feedback term as described in [24,26].

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Conflicts of Interest: The author declares no conflicts of interest.

Appendix A. Jacobian Matrix $J_\phi(u_{11}, u_{21}, u_{31}, u_{12}, u_{22}, u_{32})$

$$J_\phi = \begin{bmatrix} \frac{\partial Z_1}{\partial u_{11}} - \phi & \frac{\partial Z_1}{\partial u_{21}} & \frac{\partial Z_1}{\partial u_{31}} & \frac{\partial Z_1}{\partial u_{12}} & \frac{\partial Z_1}{\partial u_{22}} & \frac{\partial Z_1}{\partial u_{32}} \\ \frac{\partial Z_2}{\partial u_{11}} & \frac{\partial Z_2}{\partial u_{21}} - \phi & \frac{\partial Z_2}{\partial u_{31}} & \frac{\partial Z_2}{\partial u_{12}} & \frac{\partial Z_2}{\partial u_{22}} & \frac{\partial Z_2}{\partial u_{32}} \\ \frac{\partial Z_3}{\partial u_{11}} & \frac{\partial Z_3}{\partial u_{21}} & \frac{\partial Z_3}{\partial u_{31}} - \phi & \frac{\partial Z_3}{\partial u_{12}} & \frac{\partial Z_3}{\partial u_{22}} & \frac{\partial Z_3}{\partial u_{32}} \\ \frac{\partial Z_4}{\partial u_{11}} & \frac{\partial Z_4}{\partial u_{21}} & \frac{\partial Z_4}{\partial u_{31}} & \frac{\partial Z_4}{\partial u_{12}} - \phi & \frac{\partial Z_4}{\partial u_{22}} & \frac{\partial Z_4}{\partial u_{32}} \\ \frac{\partial Z_5}{\partial u_{11}} & \frac{\partial Z_5}{\partial u_{21}} & \frac{\partial Z_5}{\partial u_{31}} & \frac{\partial Z_5}{\partial u_{12}} & \frac{\partial Z_5}{\partial u_{22}} - \phi & \frac{\partial Z_5}{\partial u_{32}} \\ \frac{\partial Z_6}{\partial u_{11}} & \frac{\partial Z_6}{\partial u_{21}} & \frac{\partial Z_6}{\partial u_{31}} & \frac{\partial Z_6}{\partial u_{12}} & \frac{\partial Z_6}{\partial u_{22}} & \frac{\partial Z_6}{\partial u_{32}} - \phi \\ \frac{\partial u_{11}}{\partial u_{11}} & \frac{\partial u_{21}}{\partial u_{21}} & \frac{\partial u_{31}}{\partial u_{31}} & \frac{\partial u_{12}}{\partial u_{12}} & \frac{\partial u_{22}}{\partial u_{22}} & \frac{\partial u_{32}}{\partial u_{32}} \end{bmatrix} \quad (A1)$$

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