Construction of a Kinetic Model for CD8 T Cell Response to Viral Infection under the Combined Effects of Time Delay and Reaction-Diffusion

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Abstract: There is an inherent time delay in the CD8T cell response itself, and viral spread leads to spatially heterogeneous characteristics of infection. Currently, there is a lack of in-depth research on the combined effect of these two factors. This study constructs a partial functional differential equation model that combines the CTL amplification delay and the viral spread process, which not only demonstrates the forward boundability of the model solution but also clearly defines the basic reproduction number of the virus and immunity. Using the analysis method of characteristic equations, the study obtained the critical conditions for Turing instability in the pure diffusion scenario and the criteria for Hopf branching in the pure delay scenario respectively. In the delay-diffusion two-parameter plane, the study further identified the specific regions of the Turing-Hopf double instability. The numerical simulation results show that the system has multiple behavioral patterns such as uniform steady state, time-period oscillation, and spatiotemporal chaos. This result also reveals that the infection outcome is non-monotonic regulated by the ratio of delay length to diffusion rate. The model framework provides a new approach to understanding the spatiotemporal complexity of CTL antiviral immunity, and also has theoretical implications for optimizing relevant intervention strategies.

***Keywords*:** Time delay; Reaction-diffusion; CD8T cells; Turing instability; Hopf branch

1. Introduction

In order for CD8T cells to kill target cells, they typically need to go through a series of processes including activation, proliferation, and differentiation into effector cells, a process that causes a fixed delay of about several days in the immune response. At the same time, the spread of viral particles in the interstitial Spaces often gives the infection a very significant spatial pattern. Most of the existing mathematical models have examined time-delay or diffusion alone - time-delay models can induce periodic oscillations and bistable phenomena of viral load. However, in the actual infection process, these two factors are actually coexisting and coupled with each other. Studies that integrate time-delay and reaction-diffusion into the framework of partial functional differential equations to explore their co-instability and pattern formation are still scarce [1].

When hysteresis and diffusion coexist, the linearized characteristic equation transforms from a polynomial to a transcendental equation, and Turing instability and Hopf bifurcation may converge in the parameter space, thereby forming codimensional -2 bifurcation, which may trigger complex dynamical behaviors such as space-time chaos [2]. From a biological perspective, this phenomenon corresponds to the spatiotemporal mismatch between effector cells and infection foci caused by the delay of CTL response, as well as the spatial symmetry breaking caused by the differences in the diffusion rates of each component. For this purpose, this study constructs a mathematical model that includes CTL amplification delays and viral diffusion, and explores the following three core issues: (1) constructing a well-defined model while analyzing the forward bounsibility of the model solution; (2) The critical conditions that cause instability in the system when the delay and diffusion exist alone or together are given respectively; (3) Reveal the specific form of the spatio-temporal pattern and the regulation of parameters in the case of Turing-Hopf double instability. The core objective of this study is to deepen the theoretical understanding of immune spatiotemporal dynamics.

2. Mathematical Models

(1) Compartments and assumptions.

Consider four dynamic components of the local region of the host tissue: healthy target cells, infected cells, free viruses, and CD8T effector cells. *TIVC* The basic assumptions are:

(H1) The target cells were replenished at a constant rate, and the natural mortality rate was. sd_T The virus infects the target cells according to a bilinear law. βTV

(H2) Infected cells die via programmed cell death (d_I) and are killed by cytotoxic T lymphocytes (CTLs) through γIC

-mediated cytotoxicity.

(H3) Infected cells produce viruses at rate p, and the viruses are cleared at rate d_V.

(H4) CTL generation depends on the density of infected cells at the time. $t-\tau$ Because the activation, proliferation, and differentiation of initial T cells take time, the process produces a fixed lag >0. ôThe generation rate takes the HollingII type saturation form: $kI(t-\tau)/[1+\eta I(t-\tau)]$ The natural mortality rate of CTL is d_C.

(H5) Target cells and CTL do not spread much, and infected cells do not migrate actively. D_V Free viruses can spread freely in the interstitial Spaces with a diffusion coefficient >0. This is because the virus is much smaller than the cell, and Brownian motion and tissue fluid convection make the diffusion significant.

(H6) Take one dimension of the spatial region $\equiv \Omega = [0, L]$ with the boundary being the zero-flux Neumann condition to describe the reflection at the tissue interface [3].

(2) Governing equations.

The above setting leads to the following time-delay reaction-diffusion system:

$$\frac{\partial T}{\partial t} = s - d_T T - \beta TV,$$

$$\frac{\partial I}{\partial t} = \beta TV - d_I I - \gamma IC,$$

$$\frac{\partial V}{\partial t} = D_V \frac{\partial^2 V}{\partial x^2} + pI - d_V V,$$

$$\frac{\partial C}{\partial t} = -d_C C + \frac{kI(t-\tau)}{1+\eta I(t-\tau)}, \quad x \in \Omega, t > 0,$$

Boundary conditions, initial values are non-negative continuously bounded above. $\partial V / \partial x = 0 and x = 0, L, [-\tau, 0] \times \Omega$

(3) Parameters and dimensionless.

Table 1 lists the meanings of the main parameters. D_V To simplify the analysis, the independent quantities to be discussed can be condensed into two control quantities, virus spread coefficient and CTL response delay, by scaling, and the remaining coefficients are combined into a dimensionless combination. τ The specific scaling process is omitted.

(4) Fitness.

Since only the viral component in the equation contains the diffusion term, the target cell, infected cell, and CTL equations are all reaction terms without spatial derivatives, the system can be embedded in the framework. $C([-\tau, 0]; H^1(\Omega))$ By using the abstract development equation and the delayed generalization of the Lumer-Phillips theorem, it can be proved that there exists uniqueness. The positivity is guaranteed by the comparison principle: the right end of the target cell equation is when, blocking the negative crossing; $T = 0 s > 0$ The virus equation satisfies the extremum principle; $I \geq 0$ The delay term in CTL equations is non-negative at times. All solutions remain non-negative and bounded.

3. Qualitative Analysis

(1) ODE Reference States.

When = 0 and τ = 0, the model degenerates into a spatially homogeneous ordinary differential system [4]. Its equilibrium points fall into three categories:

(E_1) infection-free equilibrium points $E_0 = (s/d_T, 0, 0, 0)$;

(E_2) The equilibrium point for no immune infection:: $E_1 = (T^*, I^*, V^*, 0)$;

(E_3) Fully immunologically activated state: $E_2 = \left(\overline{T}, \overline{I}, \overline{V}, \overline{C}\right)$

Define the basic reproduction number of the virus. $R_0 = \frac{s}{d_T} \frac{\beta p}{d_I d_V}$ Asymptotically stable when <1, the virus is cleared; $R_0 E_0 R_0$>1 establishes the infection. Introduce the basic number of immune reproductions as a threshold for whether CTL

can be activated at the site. $R_1E_1R_0$>1 and the system's direction; $R_1 < 1E_1R_1 > 1$ Then CTL fully amplifies and the system tends. E_2

(2) Diffusion-driven Turing instability.

Set τ=0 to examine the effect of virus diffusion on the positive equilibrium state. E_2 In linearization, perturbation take, wavenumber. $E_2(\delta T, \delta I, \delta V, \delta C)^\top e^{\lambda t + iqx} q \geq 0$ Only the virus equation introduces additional terms, and the characteristic equation is transformed into a cubic polynomial: $-D_V q^2 \lambda$

$$\lambda^3 + a_2(q^2)\lambda^2 + a_1(q^2)\lambda + a_0(q^2) = 0$$

Uniform state requirements for ODE stability. $a_0(0)$>0 The Turing instability criterion is reduced to the existence such that. q>0$a_0(q^2)$<0 The critical diffusion coefficient can be solved from the negative value condition of the quadratic form written. $a_0(q^2)q^2D_V^c$ At that time, the system was unstable in a certain wavenumber interval and spontaneously formed a stationary spatial pattern. $D_V > D_V^c$ The mechanism is that the virus locally produced by the infected cells constitutes an "activator", while the rapid outward spread of the virus acts as a long-range "suppressor". Just as in the classical Turing mechanism, when the repressor spreads much faster than the activator, the homogeneous state breaks down.

(3) Time-delay-driven Hopf branching.

Let DV =0, analyzing the role of the time delay τ. D_V =0 At this point, the characteristic equation contains transcendental functions:

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0$$

By separating the real and imaginary parts and eliminating the trigonometric function, we get the algebraic equation of about. $\lambda = i\omega(\omega > 0)\omega^2$ If positive roots exist, then the critical delay sequence is ω_0.

$$\tau_k = \frac{1}{\omega_0}[\arccos\Phi(\omega_0) + 2k\pi], \quad k = 0,1,\ldots$$

When the cross-sectional condition is met, it stabilizes downward, and after τ passes τ0, it becomes unstable and gives birth to periodic solutions. $d\,\mathrm{Re}(\lambda)/d\tau|_{\tau_0} > 0\tau < \tau_0 E_2$ Biologically, a slow CTL response leads to a "chase oscillation" : the infection rises first and then kills, the killing signal weakens, the number of CTLS drops, the infection reignites, and so on.

(4) Turing Hopf joint instability.

While preserving the time delay and diffusion, the characteristic equation is linearized at point E_2 as follows:

$$P(\lambda; q^2) + Q(\lambda; q^2)e^{-\lambda\tau} = 0$$

In the two-parameter space, the system may exhibit three types of instability: (i) pure Hopf instability if and τ are over the critical value; $(D_V, \tau)q = 0$. (ii) Pure Turing instability when τ=0 and exceeds the critical value; D_V. (iii) Turing-Hopf combined instability, where the Hopf branch curve and the Turing branch curve intersect in the parameter plane and simultaneously excite oscillations and spatial instability at the same wavenumber. Near this region, the central manifold is codimensional 2, and the amplitude equation evolves into a GinzburgLandau type coupling system, which can describe the competition and switching between uniform oscillations, stationary patterns, oscillatory patterns, and even space-time chaos.

4. Numerical Simulation

A finite difference discrete space is used, and the delay term is processed in fixed time steps. $R_0 > 1$ Take the dimensionless space interval length 100, the number of meshes 200, and the time step 0.01. The reference parameters are based on acute influenza virus-like infections and are dimensionless to ensure the existence of positive homeostasis. $R_1 > 1E_2$

(1) Baseline: No delay, no spread.

After the transient, the system rapidly falls into a uniform steady state, with all components spatially straight and without time oscillations. E_2 Corresponding to the ideal situation of successful immune control of infection.

(2) Pure time lag effect.

Let, gradually increase τ. $D_V = 0$ Beyond the Hopf threshold, points in space vibrate synchronously, and the phase diagram shows a stable limit loop. The number of viruses and CTLS fluctuates, with a constant period. This is a pure time oscillation, with no structure in space. This pattern corresponds to periodic fluctuations in viral load observed in some chronic infections.

(3) Pure diffusion effect.

Set τ=0 and increase to above. $D_V D_V^c$ The uniform state is abandoned, and a spatial stationary pattern emerges. High-value and low-value regions of the virus are interlaced; CTL density was also higher at virus-rich sites, consistent with the chemotactic infiltration of T cells observed in experiments. Once the pattern was established, it did not change over time.

(4) Synergy Effect.

To further examine the coupling effect between time delay and diffusion, we conduct numerical scans on the parameter plane. $\tau - D_V$ Based on the instability mechanism, four dynamical behavior patterns can be roughly distinguished.

If both the delay and diffusion are at low levels and the corresponding branches are not triggered, the system eventually returns to a uniform positive state. E_2 Once only the delay crosses the critical point and the diffusion is weak, the space remains uniform but oscillates synchronously everywhere, showing periodic fluctuations. Conversely, only when the virus diffusion intensity exceeds the threshold and the response is delayed can the uniform state no longer be maintained, and a stationary spatial structure spontaneously emerges - the distribution of the virus and effector cells forms a stationary pattern of high and low.

The situation where both hysteresis and diffusion exceed their respective thresholds simultaneously. Time oscillations are entangled with spatial patterns, the pattern morphology is constantly reorganized, the rhythm at different positions is out of sync, and the system behavior tends to be spatio-temporal chaos. In this state, regular periodic features fade away and are replaced by disordered patterns of patches constantly generating and drifting. A moderate spread helps confine the infection to a local area, while an overly long response delay, once superimposed to strengthen the spread, may cause the body to lose effective control of the virus in both spatiotemporal dimensions.

(5) Biological implications.

The simulation gives three insights: First, the CTL response delay determines whether the infection recurs periodically. A short delay is conducive to virus clearance, while a long delay is prone to oscillation. Second, the rate of virus spread changes the spatial pattern of infection. A moderate limit is conducive to local clearance, while enhanced spread and weakened tissue barrier will break this pattern. Third, minor parameter perturbations in the joint instability zone can alter the spatiotemporal fate of infection. This indicates that the effect of one-dimensional intervention is difficult to predict, and intervention plans need to be formulated by taking into account the temporal and spatial dimensions of infection.

5. Conclusions

In this study, a partial functional differential equation model with CTL amplification delay and virus spread was constructed to systematically analyze the combined dynamic effects of the two factors. The study demonstrated that the system solution is forward bounded, characterizing the conditions of infection establishment and immune activation through the threshold of the number of reproductions. When only spreading, the Turing instability of the system produces a spatial stationary pattern; When there is only time delay, the Hopf branch is triggered to produce uniform time oscillations. In the delay-diffusion two-parameter plane, the two instability curves intersect to form the Turing-Hopf joint instability region, and their nonlinear coupling leads to the oscillation pattern and even spacetime chaos. According to the show, the ratio of delay length to diffusion rate for infection outcome regulation is non-monotonic: moderate diffusion can limit the range of infection, while too long delay and too high diffusion rate can disrupt immune control. The model provides a theoretical tool for interpreting the spatiotemporal complexity of the immune response, and in the future, details such as CTL chemotactic migration can be incorporated to derive the bifurcation norm for obtaining the global dynamic response, providing a theoretical basis for the design of infection intervention strategies.

Acknowledgments

Project Category: Provincial Project — the Special Basic Cooperative Research Programs of Yunnan Provincial Undergraduate Universities' Association (Project No.:202301BA070001-089).

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