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Modeling and Nonlinear Dynamic Behavior Analysis of CD8+T Cell Antiviral Response System under Time Delay and Diffusion

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Abstract: $CD8^+$T cells are virus-clearing core effector cells, and their response is regulated by viral latency and cell spatial migration, the former causing time delay and the latter causing spatial non-uniformity. Most existing models have dealt with these two factors in isolation, making it difficult to explain the coexistence of viral load oscillations and foci. This paper constructs a $CD8^+$T cell antiviral response diffusion model coupled with time delay and diffusion, and analyzes its nonlinear dynamic behavior. Theoretical analysis shows that delayed viral replication and immune activation trigger Hopf bifurcation to oscillate viral load; The mismatch between the effect and the diffusion coefficient of the infected cells triggered the Turing bifurcation, forming a spatial pattern. In the overlapping area of parameters, delay and diffusion coupling produce behaviors such as traveling waves, essentially a double breaking of spatiotemporal translational symmetry. Numerical simulations verify the bifurcation critical conditions and give predictions. This study provides a unified framework for understanding the immune response of $CD8^+$T cells and has reference value for infection prognosis and treatment.

Keywords: $CD8^+$T cells; Time-delay reaction-diffusion system; Hopf bifurcation; Turing instability

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1. Introduction

After an acute viral infection, $CD8^+$T cells clear the infected cells. Clinically, fluctuations in viral load and plaque distribution in infected tissues were observed, previously attributed to time-delayed feedback and spread instability, respectively. But in the real immune response, the two are intertwined, and there is a lack of systematic study on the dynamic effects when they coexist. Existing work provides clues to different aspects, but does not answer the dynamic landscape after coupling the two. This paper proposes that there is a deep nonlinear coupling between time delay and diffusion, and spatio-temporal coupling patterns emerge when parameters fall into the overlapping region, which is essentially a hypothesis of double symmetry breaking. To verify this hypothesis, this paper designs a progressive scheme to systematically answer questions about delay, diffusion dominance, and their coupling.

2. Model building

2.1. Biological background and modeling assumptions

$CD8^+$T cell antiviral immune core chain: The virus invades target cells, replicates intracellularly and releases progeny viruses, dendritic cells present antigens, initial $CD8^+$T cells are activated in lymph nodes and clone and expand into effector CTLS, effector cells migrate to infected tissues to kill infected cells. Based on this, six modeling hypotheses are proposed:

(H1) Consider four types of continuous variables: uninfected target cells, infected cells, free virus, effector $T(x,t)I(x,t)V(x,t)$, $CD8^+$T cells, and the spatial location belongs to the region Ω, where Ω can be taken as a one-dimensional interval or a two-dimensional square region. $E(x,t)x$

(H2) Due to the incubation period of viral replication, a discrete time lag is introduced to τ_1 represent the average time from infection to the release of progeny viruses.

(H3) $CD8^+$T cell activation is delayed. Use the time lag to summarize the total duration of antigen presentation, initial T cell sensitization, clone expansion, and effector differentiation. τ_2

(H4) Infected cells and effector T cells migrate within the tissue according to Fick's law, with diffusion coefficients of and respectively. $D_I D_E$ The spatial movement of uninfected target cells and free viruses is restricted, and the diffusion term is not considered for the time being to highlight the main contradiction.

(H5) The proliferation of target cells is constrained by tissue carrying capacity and is described by Logistic growth.

(H6) Effector cell generation rate depends on the number of infected cells and shows saturation characteristics, represented by the Hill function.

2.2. Governing equations and determinative conditions

Based on the above assumptions, the following time-delay reaction-diffusion system is established:

$$\frac{\partial T}{\partial t} = r_T T\left(1 - \frac{T}{K}\right) - \beta TV,$$

$$\frac{\partial I}{\partial t} = \beta TV - \delta_I I - \gamma EI + D_I \nabla^2 I,$$

$$\frac{\partial V}{\partial t} = pI(t - \tau_1) - \delta_V V,$$

$$\frac{\partial E}{\partial t} = \frac{\eta I(t - \tau_2)}{h + I(t - \tau_2)} - \delta_E E + D_E \nabla^2 E.$$

The initial conditions are given by a non-negative continuous function above. $[-\tau,0] \setminus (\tau=\{\tau_1,\tau_2\})$ The boundary conditions are rounded sub-Neumann conditions, indicating that there is no cell flux in and out of the boundary of the considered tissue region:

$$\frac{\partial I}{\partial n}=0, \quad \frac{\partial E}{\partial n}=0, \quad x \in \partial\Omega.$$

2.3. Dimensionless and parametric calibration feasibility

To reduce the dimension of the parameter space, introduce dimensionless variables:. After the scaling transformation, the number of effective parameters is significantly reduced. Table 1 summarizes the biological implications, typical magnitudes, and identifications of key parameters to lay the foundation for subsequent analysis.

Table 1. Biological calibration and identifiability of key parameters

Parameters	Biological implications	Typical order of magnitude	Identifiability
	Viral replication incubation period	1 to 3 days	Directly measurable (in vitro single-round replication experiment)
	Delayed T-cell immune activation	5 to 10 days	Indirect inference (MHC tetramer dynamics)
/	Diffusion coefficient ratio	0.01 ~ 1	Fitting required (in vivo imaging tracking)
	Diffusion coefficient ratio	-	It needs to be estimated by combining the model with the viral load.
	Viral production rate	-	burstsize experimental data need to be fitted
	Half-full and constant	-	Need to fit (dose-effect curve)

The uncertainty of the parameters is mainly focused on the diffusion coefficient ratio and the half-saturation and constants, which will be scanned for sensitivity in subsequent numerical simulations.

2.4. Goodness of the model

With the framework of the abstract delay development equation, it can be proved that the system has a unique global positive solution in space. $C([-\tau,0];X)$ Under non-negative initial conditions, all population densities remain non-negative and bounded. The smoothness and dissipation of the solution operator provide a guarantee for subsequent dynamical analysis [1].

3. Dynamics analysis

3.1. Time-delay dynamics without diffusion

First, the system is degraded into a system of time-delay ordinary differential equations. By introducing the basic regeneration number and the immune regeneration number, it can be proved that the system simultaneously exists in an infection-free equilibrium state and several infection-free equilibrium states. $D_I = D_E = 0, R_0 = \beta pK / (\delta_I \delta_V) R_I E_0$ At that time, the infection-free state was unstable. $R_0>1$ Immune effects give the system a bistable structure where the immune control state and the high infection, low immune state may coexist, which is the dynamic basis of the clinical "clearance" and "persistence" bidirectional prognosis. $E_2 E_3$ With the viral replication delay τ_1 as the bifurcation parameter, the characteristic equation is linearized at E_2 the point, and the Hopf bifurcation critical value can be solved when the pure virtual root condition is satisfied. $\Delta(\lambda,\tau_1)=P(\lambda)+Q(\lambda)e^{-\lambda\tau_1}=0$

$$\tau_1^{(n)}=\frac{1}{\omega_0}\left[\arccos\left(-\frac{P_R Q_R+P_I Q_I}{Q_R^2+Q_I^2}\right)+2n\pi\right],$$

$\mathrm{Re}(d\lambda/d\tau_1)>0\tau_1$ The $\tau_1^{(0)}$ cross-sectional condition means that once exceeded, the immune control equilibrium is unstable. τ_2 The system shifts from a steady state to a periodic oscillation through a Hopf bifurcation, and the viral load fluctuates periodically. Parallel analysis of the immune activation delay also results in Hopf bifurcations, but there is a difference in the direction of the bifurcation effect between the two: the increase in tendency shortens the infection cycle period, the increase prolongs the immune response lag time, and amplifies the virus escape window. $\tau_1\tau_2$ The characteristic equation of the dual time-delay system simultaneously contains $e^{-\lambda\tau_1}$和$e^{-\lambda\tau_2}$ stability switching regions identifiable in the parameter plane, that is, when the time-delay ratio τ_1 /changes, the stable and unstable domains alternate, a phenomenon

that has been numerically confirmed in the model of τ_2 $CD8^+T$ cells responding to SARS-CoV-2.

3.2. Turing instability analysis of spatial diffusion

Ignore the time delay, setting $\tau_1=\tau_2=0$, to examine the reaction-diffusion system. Linearize at the spatially uniform state and expand the perturbation according to the Fourier mode $\sim e^{\lambda t+ikx}$ to obtain the dispersion relation. Turing instability occurs when there is a non-zero wavenumber k with $Re(\lambda(k))>0$, while the ordinary differential system remains stable at $k=0$. Analysis shows that instability requires effector cells to have a much greater diffusion coefficient than infected cells; that is, the diffusion coefficient ratio $D_E D_I D_E D_I$ must exceed a critical value. Biologically, the mismatch in spatial scale between highly migratory $CD8^+T$ cells and relatively fixed infected cells triggers self-organizing patterns. The amplitude equation of the pattern can be derived by multi-scale expansion in a weakly nonlinear framework. When the control parameters fall into the Turing instability region, the system tends to form a hexagonal or striped pattern, and the specific type is determined by the sign of the quadratic term coefficient of the amplitude equation. The characteristic wavelengths of the pattern are given by $2\pi/k_{max}$, where k_{max} is the wavenumber that grows fastest in the dispersion relation.

3.3. Spatiotemporal dynamics of delay-diffusion coupled systems

When $\tau_1,\tau_2>0$ and $D_I,D_E>0$, the characteristic equation depends simultaneously on both the wavenumber k and the two time delays. On the two-parameter plane, the Hopf bifurcation curve and the Turing bifurcation curve may intersect, dividing the parameter space into purely spatial patterning regions, purely temporal oscillation regions, and spatiotemporal coupled regions. In the coupled region, the time period resonates with the characteristic spatial wavelength, and the system can generate traveling waves, standing waves, and even spiral waves. If the parameters go deep into the nonlinear regime, spatiotemporal chaos may also emerge, manifested as unpredictable infection foci that repeatedly appear and fade [2].

Table 2. The dynamic behaviors of the three types of models are side by side to highlight the unique capabilities of the coupled model

Dynamic behavior	Time-delay only (ODE)	Only diffusion (PDE)	Time-delay diffusion coupling model
Periodic oscillation	√Hopf bifurcation	×	√
Spatial speckle	×	√	√
Traveling waves	×	√	√ Wave speed is regulated by the time delay
Spiral wave	×	√ (Excitability required)	√ Produced by HopfTuring resonance
Space-time chaos	×	×	√

Coupled models can reproduce the dynamics of time-delay or diffusion systems and exhibit behaviors that single-factor systems do not have. If time delay and diffusion are processed separately, critical cross-scale information will be lost.

4. Numerical simulation and analysis

4.1. Numerical confirmation of bifurcation critical conditions

This section's numerical solution validates the analytical conditions in Chapter 3, with a focus on confirming whether the Hopf and Turing bifurcation critical values can predict changes in system behavior.

Hopf bifurcation: Fix parameters in the absence of diffusion (i.e., $D_I = D_E=0$). Set $\tau_2=0$ and scan τ_1 as the control parameter (0.5 to 5.0, step size 0.1). For each τ_1 value, integrate over 200 dimensionless time units, and analyze the last 50 units of the viral load time series. The results are consistent with theoretical predictions: for $\tau_1<2.1$, the load converges to a

steady value; bifurcation occurs near τ_1=2.1, transitioning from steady state to oscillation; for τ_1>2.1, the oscillation amplitude increases as $\hat{o}_1$ grows. At the bifurcation point (τ_1=2.1), the oscillation period is approximately 7.3, which is about 3.5 times the critical delay value. Varying $\tau_1\tau_2$ alone (with τ_1=0) yields similar results, with a critical value around 4.8 and a period approximately 2.8 times that critical value.

Turing bifurcation: Fix one parameter at 0.05 without delay and scan with the other parameter as the control parameter. Small perturbations are applied to the spatially uniform steady state, and the spatial distribution is judged after 500 time units of evolution. When the control parameter D_E is less than 0.21, the perturbation decays and the spatially uniform state remains stable. When D_E exceeds 0.21, the perturbation grows and forms a spatial periodic structure, with a pattern wavelength of approximately 1.43. The critical value is consistent with the theoretical prediction, and the corresponding diffusion coefficient ratio is $D_E / D_I \approx 4.2$.

4.2. Numerical verification of double delay stability switching

Verification of stability switching in the case of two delays: Fix τ_1 at 2.5, and scan τ_2 over the range 1.0 to 10.0. The results show that the system oscillates when $\tau_2\tau_2$ is below 2.0, in the range 2.0< τ_2 <3.5, oscillations decay, and the system returns to a steady state; when τ_2 exceeds 3.5, oscillations reappear. This behavior is consistent with the structure of the stability region, confirming the existence of stability islands [3].

4.3. Parameter partitioning of coupling effects

Two-dimensional scanning over the parameter space $(D_E/D_I,\tau_1)$ identifies the distribution boundaries of each dynamic behavior. Parameter ranges: $D_E/D_1 \in [1,20]\tau_1 \in [0,5]$. Run the reaction-diffusion simulation and classify the asymptotic behavior into: stable region (spatially uniform and temporally steady), pure oscillating region (spatially uniform but temporally oscillating), pure speckle region (spatially non-uniform but temporally stationary), coupled region (spatially and temporally non-stationary), and the coupled region is further divided into traveling waves, spiral waves, and chaotic states.

The zoning is in a four-zone structure: the stable zone is in the upper left corner, accounting for about 31% (with $\tau_1 \in [2.0,3.0]$), the pure oscillation zone is on the right, about 22%, the pure pattern zone is at the bottom, about 18%, and the coupled zone is in the upper right, about 29%. Traveling waves are at the lower left edge of the coupling region, spiral waves are in the middle, and space-time chaos accounts for about 2% in the high diffuser ratio and long delay local area. $(D_E / D_I>8.5,\tau_1>3.2)$.

4.4. Parameter sensitivity analysis

The sensitivity of Hopf critical delay and Turing critical diffusion ratio parameters was analyzed by using the Sobol global sensitivity method. Input parameters $\beta,p,\delta_1,\delta_V,\gamma,\eta,h,$ are distributed by biological range. The results showed that the parameters that had a significant impact on the critical delay of Hopf were the viral infection rate β, viral production rate p, and effector cell killing efficiency γ. The mortality rate of infected cells δ_1 and the maximum activation rate of T cells η had a significant impact on the Turing critical diffusion ratio. Precise calibration of high-sensitivity parameters can improve model prediction accuracy.

4.5. Verifiable biological predictions

Based on the above analysis, extract two experimentally testable quantitative predictions.

Prediction 1: Trigger conditions for periodic fluctuations in viral load. Under the parameter baseline, when the time delay τ_1 exceeds 2.3 days, the viral load oscillates periodically, with a period approximately 3 to 4 times τ_1. The viral germination rate can be regulated in LCMV mouse models, and the changes in plasma viral RNA can be monitored for validation.

Prediction 2: Inhibition of immune cell migration leads to lesion transformation. If the effective diffusion coefficient D_E of effector T cells is reduced by approximately 60% (to less than 0.4) through anti-chemokine receptor treatment, the infection will change from a relatively uniform spatial distribution to a plaque-like lesion, with the lesion spacing approaching the predicted characteristic wavelength (about 1.43 spatial units), and the distribution of fluorescence-labeled infected cells in the infected tissue can be verified by two-photon in vivo imaging.

5. Conclusion

This paper constructs a time-delay reaction-diffusion model of the antiviral response of $CD8^+$T cells, innovatively integrating the factors of delayed viral replication, delayed immune activation, and spatial diffusion of effector cells to explore the dynamic laws of the coupling of time delay and diffusion. At the theoretical level, the time delay breaks the time translation symmetry through Hopf bifurcation, causing endogenous oscillations in the system; Diffusion breaks the spatial translation symmetry by Turing bifurcation, which leads to the generation of the system's self-organizing speckle. When the two types of instability modes act together, the double breaking of spatio-temporal symmetry gives rise to coupled patterns, achieving an organic unity of time-delay oscillation and diffusion pattern theory.

At the application level, this study provides two major translational directions for clinical practice: achieving precise stratification of infection prognosis based on individualized parameters, while optimizing spatio-temporal synergistic treatment regimens, avoiding the delayed window period of immune activation, promoting targeted aggregation of effector cells, and suppressing systemic instability. There are still deficiencies in the study. Cytokine networks and immune memory subpopulations were not included. Only qualitative bifurcation analysis was conducted, and there was a lack of inversion of real clinical data parameters. A multi-scale regulatory network will be built in the future, combined with longitudinal cohort data and Bayesian framework parameter estimation, to improve the quantitative model and provide a theoretical basis for analyzing the nonlinear regulatory mechanism of infection immunity.

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