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Modeling Effects of T Cell Exhaustion on the Dynamics of Chronic Viral Infection

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Abstract. During chronic viral infection, sustained antigen stimulation leads to exhaustion of virus-specific $CD8^+$ T cells, characterized by elevated expression of inhibitory receptors and progressive functional impairment, including loss of cytokine production, reduced cytotoxicity, and diminished proliferative capacity. In this paper, to investigate how T cell exhaustion influences viral persistence, we developed a within-host mathematical model integrating viral infection dynamics with adaptive immune responses. The model demonstrates three non-trivial equilibria: infection-free equilibrium (S_1), uncontrolled-infection state (S_2), and immune-controlled equilibrium (S_3). Through dynamical systems analysis, we established the local stability of all states (S_1-S_3) and prove global stability for both S_1 (complete viral clearance) and S_2 (chronic infection). Notably, the system exhibits Hopf bifurcations at S_2 and S_3, with distinct critical thresholds governing oscillatory dynamics. Numerical simulations reveal that successful immune-mediated control of viral load and infected cell levels requires maintenance of low $CD8^+$ T cell exhaustion rates.

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Key words: Viral infection dynamics, T cell exhaustion, stability analysis, Hopf bifurcation.

1 Introduction

The T-cell response plays a central role in the adaptive immune-mediated clearance of pathogen-infected cells. During acute infection, antigen-specific naive $CD8^+$ T cells undergo activation, clonal expansion, and effector differentiation following antigen recognition and costimulatory signaling [12]. While most effector cells are eliminated via apoptosis after pathogen clearance, a small subset persists to form the memory $CD8^+$ T cell compartment [13,14]. To ensure proper immune termination and maintain self-tolerance,

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inhibitory receptors/immune checkpoint molecules are transiently upregulated on activated effector T cells during the resolution phase [30]. Following antigen clearance, expression of these regulatory molecules gradually returns to baseline levels in memory T cells. This tightly regulated process represents a critical self-limiting mechanism of adaptive immunity, balancing effective pathogen clearance with prevention of excessive immune activation.

In chronic infections, however, persistent antigen exposure of $CD8^+$ T cells to high levels of antigen drives T cells into a severe T-cell dysfunctional state called exhaustion [2, 11, 26, 36], first identified in murine lymphocytic choriomeningitis virus (LCMV) models and later observed in human chronic viral infections (e.g. human imunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV)). Exhausted T cells (T_{ex}) exhibit progressive functional decline [9, 26], marked by: (i) impaired cytotoxicity, reduced cytokine production (e.g. IL-2, IFN-γ), and limited proliferative capacity; and (ii) upregulated co-inhibitory receptors (such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and mucin domain containing-3 (TIM-3), lymphocyte activation gene 3 (LAG-3)), which further suppress T-cell function. This exhausted T cell compartment is developmentally distinct from conventional effector T cells and comprises heterogeneous subsets [4, 9, 39]: stem-like $CD8^+T_{ex}$ precursors/progenitors, effector-like transitory $CD8^+T_{ex}$, and terminally dysfunctional $CD8^+T_{ex}$. The stem-like $CD8^+$ T_{ex} precursors/progenitors exhibit proliferative potential but low inhibitory receptor expression, while effector-like transitory $CD8^+$ T_{ex} has high proliferative potential and transient cytotoxicity. In contrast, terminally dysfunctional $CD8^+T_{ex}$ cells exhibit multiple irreversible functional impairments, including restricted proliferative capacity, diminished cytotoxic activity, and elevated expression of multiple co-inhibitory receptors [29]. While stem-like $CD8^+T_{ex}$ sustain immune responses, terminal subsets are shown to dominate in high-antigen environments, perpetuating immune evasion [40].

Mathematical models have been extensively used to explore within-host chronic viral infection dynamics and the corresponding immune response and treatment strategies, including HIV [5, 10, 17, 18, 27, 31, 32, 37, 38, 41], HBV and HCV [7, 34, 43]. The basic model [5, 27] employs a three-compartment ODE framework (uninfected target cells, infected cells, and free virions) to comprehensively represent a within-host viral infection dynamics, The model's dynamical behavior is primarily governed by the basic reproduction number [18]. The basic model has been extended to incorporate: latent reservoirs [10, 43], cell-to-cell transmission [17, 19, 32], adaptive immune regulation [8, 35, 37, 38, 41], antiviral drug interventions [7, 31, 34], coupling of within-host and between-host dynamics [1]. These models have provided key insights for HIV, HBV/HCV, and other chronic infections.

Through analysis of HIV-immune system interactions during natural infection and under various treatment regimens, Wodarz and Nowak [41] demonstrated that sustained viral control depends critically on robust cytotoxic T lymphocyte (CTL) memory responses. Their mathematical modeling revealed that specific treatment schedule interruptions