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Dynamical Analysis of Virulence Evolution in Multistrain Infection Model within Hosts

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Abstract Understanding the evolutionary patterns of viral virulence characteristics from a microscopic perspective is crucial for effectively combating viral mutations. This paper investigates the dynamics of virulence trait development within healthy cells following pathogen invasion using adaptive dynamics, building on a viral dynamics model that accounts for multiple infectious strains within hosts. Ignoring viral evolution, stability analysis of equilibria reveals the competitive exclusion principle. When viral virulence evolves, we assume that the infection rate of healthy cells and the mortality rate of infected cells are functions of virulence. We establish global stability conditions for the system and examine the evolutionary trajectory of viral virulence using adaptive dynamics. Our results indicate that mutant viruses can cause trait substitution. The evolutionary singular strategy is identified as a continuously stable strategy without producing evolutionary branching. Furthermore, we consider the influence of certain parameters in the system on the evolution of singular strategies.

Keywords Viral infection model, adaptive dynamics, evolutionary singular strategy, stability analysis

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1. Introduction

Over the past few decades, extensive research has been conducted on the evolution of virulence using a theoretical framework grounded in the principles of natural selection. This framework not only explains the varying levels of virulence observed in host-parasite interactions but also offers opportunities for effectively managing virulence to control disease spread. Furthermore, this evolutionary perspective elucidates the extent to which infectious agents contribute to the development of chronic illnesses and identifies diseases that can be prevented or treated through disease-control strategies such as vaccines and antibiotics.

The majority of recent theories that endeavor to elucidate the evolutionary mechanisms of parasites posit an association between virulence and transmission, commonly referred to as the "virulence-transmission trade-off" [2]. However, this

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concept has been met with significant controversy. To gain a comprehensive understanding of the ongoing debates in this field, it is crucial to recognize that the evolution of virulence had been studied extensively prior to the formulation of the trade-off hypothesis.

The presence of strain-specific virulence and the ability to convert one strain into another were highlighted in the attenuation of the anthrax bacillus. Then, evolutionary theories emerged to elucidate the mechanisms driving parasite virulence. Subsequently, research into viral strain virulence gained momentum. In nature, the interactions between hosts and pathogens are ubiquitous, leading hosts to develop a variety of defense mechanisms in response to pathogenic challenges [4,6–8,10,11,32,38,41]. In addition, during viral infection, the dynamics within the host can be analyzed using mathematical models [25]. Taking the human immunodeficiency virus (HIV) as an example, its unique intra-host dynamics distinguish it from other viral infections. One key feature is HIV's high degree of genetic variability, which results from its rapid replication and mutation rates. This genetic diversity poses significant challenges for both the immune system and antiviral therapies in completely eradicating the virus. Understanding these intra-host dynamics is crucial for developing effective treatment strategies, as the genetic diversity of HIV complicates efforts to find a cure for the infection.

What factors contribute to the variability in disease progression? Several key factors have been identified, including the virus's reproductive capacity, the immune system's proliferative ability, and the accelerated degradation of $CD4^+T$ cells caused by HIV [1, 3, 14, 17, 23, 24, 40]. Since the early 1990s, the predominant explanations for HIV's evasion of the immune response and subsequent immune system failure have centered on its evolutionary capabilities [9, 26, 27, 35, 36]. While all viruses can undergo evolutionary changes, HIV is recognized as the most rapidly evolving organism, generating multiple novel variants daily within a single host [18, 24, 33, 39]. This rapid evolution and extensive viral diversity can be attributed to several virus-specific factors. These include an exceptionally rapid reproduction cycle, producing approximately $10^{10} \sim 10^{12}$ new virions per patient per day [37], and an exceedingly high mutation rate of about 3×10^5 mutations per nucleotide base per replication cycle.

The extremely rapid rate of evolution has led to the emergence of drug-resistant strains [12] and significantly hindered the development of an efficacious vaccine [9]. The gradual increase in viral load during the asymptomatic stage can be attributed to evolutionary processes, where organisms adapt to enhance their fitness, particularly in terms of viral reproductive capacity [22]. As a result, the viral load increases proportionally with improvements in its reproductive potential.

There has been a significant increase in the application of mathematical models to investigate viral evolution at both population and within-host levels. This advancement has been facilitated by integrating within-host viral dynamics with between-host transmission dynamics. Most researchers have incorporated within-host models into epidemiological frameworks by introducing transmission rates that depend on viral load or disease-induced mortality [13, 16, 21, 42]. Additionally, it is commonly assumed that higher viral loads within hosts lead to increased parasite virulence, which in turn correlates with elevated transmission rates between hosts. Recently, Liu et al. [30] proposed a model that couples the evolutionary dynamics of viral virulence with the kinetics of transmission. A two-way coupling is achieved through the modeling method to study the influence of viral virulence evolution