The Evolution of Virulence in RNA Viruses under a Competition–Colonization Trade-Off

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Abstract RNA viruses exist in large intra-host populations which display great genotypic and phenotypic diversity. We analyze a model of viral competition between two viruses infecting a constantly replenished cell pool. We assume a trade-off between the ability of the virus to colonize new cells (cell killing rate or virulence) and its local competitiveness (replicative success within coinfected cells). We characterize the conditions that allow for viral spread by means of the basic reproductive number and show that a local coexistence equilibrium exists, which is asymptotically stable. At this equilibrium, the less virulent competitor has a reproductive advantage over the more virulent colonizer reflected by a larger equilibrium population size of the competitor. The equilibria at which one virus outcompetes the other one are unstable, i.e., a second virus is always able to permanently invade. We generalize the two-virus model to multiple viral strains, each displaying a different virulence. To account for the large phenotypic diversity in viral populations, we consider a continuous spectrum of virulences and present a continuum limit of this multiple viral strains model that describes the time evolution of an initial continuous distribution of virulence without mutations. We provide a proof of the existence of solutions of the model equations, analytically assess the properties of stationary solutions, and present numerical approximations of solutions for different initial distributions. Our simulations suggest that initial continuous distributions of virulence evolve toward a distribution that is extremely skewed in favor of competitors. At equilibrium, only the least virulent part of the population survives. The discrepancy of this finding in the continuum limit with the two-virus model is attributed to the skewed equilibrium subpopulation sizes and to the transition to a continuum. Consequently, in viral quasispecies with high
virulence diversity, the model predicts collective virulence attenuation. This result may contribute to understanding virulence attenuation, which has been reported in several experimental studies.

**Keywords** SIR models of viral infection · Competition–colonization dynamics · RNA virus · Evolution of virulence · Attenuation of virulence

1 Introduction

RNA viruses are fast evolving pathogens that can adapt to continuously changing environments. Due to their error-prone replication, large population size, and high turnover, RNA virus populations exist as quasispecies (Eigen et al. 1988; Holland et al. 1992; Domingo and Holland 1997). The viral mutant spectrum consists of many genetic variants which give rise to diverse phenotypes. This phenotypic diversity is reflected in different traits, including the rate of killing host cells, which is referred to as virulence herein.

The concept of virulence has been used in various areas of the life sciences with different meanings. In evolutionary biology, the virulence of a pathogen is defined as the fitness costs to the host that are induced by the pathogen. In epidemiology, the term usually means the pathogen-induced host mortality. In clinical settings, virulence often refers to the severity of disease symptoms induced by a pathogen. In this article, we consider intra-host virus dynamics and use the term virulence to denote the cell killing rate of a virus infecting tissue. Thus, we apply the epidemiological meaning of virulence to the intra-host viral microepidemics. This definition is related to the macroscopic or inter-host concept of virulence, because, in general, the cell killing rate of a virus affects the course of infection and the mortality of the host.

The evolution of virulence has been studied using experimental and theoretical approaches in a variety of host-pathogen systems and under diverse conditions or assumptions. In the past few decades, the “conventional wisdom” that well-adapted pathogens are avirulent has been replaced by the stricter evolutionary reasoning that successful pathogens exploit their hosts to maximize their number of offspring (Anderson and May 1982; Ewald 1983). In fact, the basic epidemiological model of infection predicts that pathogens will evolve to maximize their basic reproductive number (Nowak 2006). Depending on the specific way how infectivity and virulence are linked in this model, the relationship between pathogens and their hosts can range from commensalism to high pathogenicity (Bremermann and Thieme 1989).

Because pathogens are exposed to different environmental conditions during their life cycle, they face different types of selective pressure, and adaptation is typically controlled by various phenotypic traits that are not independent. In order to investigate the constraints of adaptability and their impact on the evolution of virulence, several adaptive trade-off theories have been proposed (Bull 1994; Frank 1996). These models assume finite resources and make an economic argument by trading off two or more pathogen traits. For example, the trade-off between rapid pathogen reproduction (virulence) and longer transmission time due to longer life time of the host is often considered (Bremermann and Thieme 1989; Bonhoeffer et al. 1996; Cooper et al. 2002). The virulence-transmission trade-off can