博士論文の要約

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論文題目：Antagonistic population dynamics of viruses and host immunity

Viruses, the ubiquitous agents of infectious disease, challenge all life forms and impact global ecosystems. They depend on host cells to reproduce, often causing disease and, in severe cases, host death. Their replication and transmission can lead to widespread epidemics affecting human health and agriculture, with recent events like COVID-19 illustrating their devastating potential. Organisms counter viruses with adaptive immune systems that exhibit a highly specific defensive response. Adaptive immunity not only rapidly eliminates viruses from the body, but also confers an immune memory against viruses that once infected, so that a population with an increased number of hosts with an immune memory suppresses viral epidemics (population immunity effect). Viruses also have countermeasures to host adaptive immunity. Viruses counter immunity by altering the antigenic sites recognized

by the host immune system (immune escape) or suppressing immunity (immunosuppression). My dissertation focuses on the antagonistic relationship between viruses and host immunity and conducts two topics on the coupled dynamics of host immunity and viral epidemic dynamics: immune escape in heterogeneous host populations and the emergence of immunosuppressive viruses in spatially structured host populations.

In Chapter 2, I theoretically studied the dynamics of viral infections that repeatedly escape immunity through antigenic mutations. Repeated emergence of VOCs (Variants of Concerns) due to immune escape of SARS-CoV-2 is a major threat to humanity today. The rate of antigenic evolution in the host population needs to be examined to predict and control the emergence of new mutants. As a driver of the antigenicity evolution of SARS-CoV-2, the presence of immunocompromised patients has been suggested due to their long persistent infections accompanied by impaired immune function. However, it is unclear whether immunocompromised hosts, who constitute only a small fraction of the population, have a disproportionally large

impact on antigenic evolution. By constructing an evolutionary epidemiological model that takes into account both the pathogen variants differing in antigenicity and host heterogeneity in recovery rates, I examined how the rate of antigenic evolution is affected by the presence, and the fraction, of immunocompromised hosts. The rate of antigenic change in the heterogeneous host populations was derived analytically. I found that the rate of antigenic change would be significantly accelerated even if only a small number of immunocompromised patients were present. The findings emphasize that protecting immunocompromised individuals is crucial not just for their personal health but also plays a pivotal role in mitigating the progression of viral evolution on a broader public health scale. Furthermore, our model allows us to examine the optimal intervention strategy to slow down viral antigenic escape. In the case of targeted intervention, where the degree of intervention varies between host classes, we derived the optimal intervention strategy that most effectively suppresses the rate of antigenic evolution.

In Chapter 3, I theoretically studied the effect of spatial structure on the epidemiological dynamics of immunosuppressive phages that have anti-CRISPR (Acr) genes to counter the CRISPR immunity of bacteria. Although Acr is a potent suppressor of CRISPR immunity, the prevalence of Acr gene in phages is sparse compared to the prevalence of the CRISPR system in host bacteria, and the ecological conditions favoring Acr are unclear. I hypothesize that the cooperative nature of Acr phages may work more in favor of Acr due to spatial viscosity. To investigate this hypothesis, I constructed the spatially explicit epidemiological dynamics of Acr phages assuming that both hosts and phages reside in lattice-structured populations (dual lattice model). Using pair approximation, a technique to keep track of the spatial correlation in ecological dynamics, I analytically examined the effect of spatial structure on Acr phage epidemiological dynamics and found that spatial viscosity favors Acr phages by increasing the local accessibility of Acr phages to immunosuppressive hosts produced by Acr. By contrast, when the effect of Acr is weak and the duration of the immunodeficient state is short, spatial structure works rather to discourage Acr phages. These analytical results provide

theoretical insights into the experimentally observed complex effects of local spatial structure on the spread of Acr phages by giving a simple ecological condition that favors and disfavors the Acr gene.