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学位(専攻分野)　博士(理学)

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学 位 論 文 題 目　Antagonistic population dynamics of viruses and host immunity

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博士論文の要旨

氏　　名：熊田隆一

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.

（別紙１ Separate Sheet 1）

Results of the doctoral thesis defense

博士論文審査結果

Name in Full
氏 名　熊田　隆一

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

The applicant, Mr. Ryuichi Kumata, has theoretically studied antagonistic interactions between hosts and viruses from evolutionary perspectives. His doctoral thesis consists of four chapters, based on two distinct studies of virus evolution.

In Chapter 1, the applicant discusses the importance of studying antagonistic interactions between hosts and viruses and how it can contribute to effective disease control measures. He points out that viruses have acquired a variety of strategies to counter adaptive immunity, which plays a pivotal role in protecting hosts from viral infection. The applicant discusses immune escape and immunosuppression as two counterstrategies that viruses adopt.

In Chapter 2, the applicant theoretically studies the impact of immunocompromised hosts on the speed of antigenic escape of viruses. The basic model assumes that there are two types of hosts, normal and immunocompromised ones and that the recovery rate of immunocompromised hosts is slower than normal ones due to weak immune competency. A diffusion model is employed to explain viral antigenic escape from host immunity, and the applicant found an analytic formula for the speed of the traveling wave in an antigenic space. This formula represents how fast antigenic escape occurs as a function of the proportion of immunocompromised hosts in the population. A practically important result the applicant found is that the presence of even a small proportion of immunocompromised hosts can significantly increase the speed of antigenic escape, suggesting that the protection of immunocompromised hosts should be prioritized to suppress the antigenic evolution of viruses. The applicant studies several extensions of the model as well, including the effect of cross-immunity and the other heterogeneity in epidemiological parameters. This research provides a novel theoretical contribution to our understanding of immune escape and guides us on how to control evolving viruses. The committee has confirmed that the content of this chapter has already been published in the Proceedings of the Royal Society B and that the applicant is the first author.

In Chapter 3, the applicant investigates the effects of spatial structure on the epidemiological dynamics of host bacteria and phages. This chapter discusses the antagonistic interaction between host bacteria that have a CRISPR immune system and phages that have Acr gene that suppresses CRISPR immunity. One of the central questions is how spatial structure favors or disfavors Acr-phages. A key factor involved

in this question is that even if these phages fail to directly lyse a CRISPR-immune host, they can turn the host into an immunosuppressed host that is readily exploited by spatially adjacent Acr-phages. Through computer simulations and a pair-approximation analysis of the dual-lattice model, the applicant has found that the presence of spatial structure has multiple effects, both positive and negative, that it generally favors the invasion of strong but not weak Acr-phages in the system, and that it narrows the parameter window of bistability. These predictions agree with experimental results. This research deepens our understanding of the interplay between host-virus interactions and spatial structure and provides valuable insights into arms-race evolution between hosts and parasites.

Chapter 4 concludes this thesis. The applicant summarizes findings in previous chapters and stresses the need for in-depth studies of viral evolution and epidemiological dynamics. It is pointed out that host heterogeneity and spatial structure are two keys in this thesis.

In summary, this doctoral thesis has several novel findings on antagonistic evolution between hosts and viruses, and the members of the committee unanimously agree that it has excellent academic value. For those reasons, the committee hereby finds that this doctoral thesis is worthy of a doctoral degree in science.