学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Population genetics of variants in infectious diseases and its application to the prediction of variant replacement
（感染症における変異株の集団遺伝学と変異株の置き換わりの予測）

Genotypes of circulating viruses change over time by natural selection acting on their phenotypes. These phenotypes include antigenicity, transmissibility, and pathogenicity of viruses. A variant of a virus is defined as a group of the viruses belonging to closely related genotypes that have similar phenotypes. This dissertation constructs population genetics models describing the natural selection of variants of viruses and investigates the predictability of variant replacements in future using observed data.

In Chapter 1, the fixation and extinction of variants of H1N1 influenza viruses were investigated. The selective advantage of variants having an amino acid substitution on the hemagglutinin (HA) protein was modeled by linear combinations of patient age distributions and the involvement on antigenic sites. Based on Kimura's formula of fixation probability under advantageous selection, coefficients were estimated using sequence data of H1N1 influenza viruses circulating from 2009 to 2020. Cross validation tests showed that the fixation and extinction of variants having a new amino acid on HA could be predicted with a sensitivity of 0.78, specificity of 0.86, and precision of 0.83 once the relative frequency of the amino acid exceeded 0.11. Estimated parameters showed that the fixation probability increased when variants having a new amino acid could infect patients in higher age groups better than those having the old amino acid. This result suggested that variants of H1N1 influenza viruses tend to be selected in the adult population and that patient ages of variants are useful for predicting fixation and extinction of variants of H1N1 influenza viruses.

In Chapter 2, the replacement from the Alpha variant to the Delta variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in England was investigated. The variant replacement was modeled using the relative reproduction number, which is the ratio between the reproduction number of a variant and that of another variant. Using nucleotide sequences collected from 18 March to 4 July 2021 in England, the relative reproduction number of Delta with respect to Alpha was estimated to be 1.88 (95% confidence interval: 1.85–1.91). Retrospective prediction tests using partial data showed that the relative

reproduction number and future trajectory of replacement could be accurately predicted once the relative frequency of Delta reached 0.15, which was observed one month before Delta reached a relative frequency of 0.90. Public health policymakers would have had one month to prepare control measures for the predicted increase in viral transmissibility.