

Simulating Limited Diversity in Evolution of Influenza

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Abstract

In many cases, analyses on infectious diseases focus on how the epidemic arises, spreads, and whether diminishes or gets fixated among host populations under particular conditions, without taking the evolutionary perspective into account. With some infectious diseases, however, the pathogens themselves evolve comparatively rapidly during the time course, so that the co-evolutionary dynamics among hosts and pathogens should be considered at the same time. In this paper, we focus on influenza and propose a bilayered, multi-agent-based simulation that combines an epidemic model and a viral evolution model. The latter model includes genomic segments of the viruses whose evolutionary paths are guided by two selective pressures; one originates from the viral-host immune interaction and the other originates from intra-genomic constraints within the virus. By including such a micro-level representation in the model, we show mechanisms that generate the limited diversity of viruses, which is a fundamental yet unexplained temporal characteristic observed in the evolution of influenza. The full version of this work has already been published in (Sasaki, 2013).

Introduction: Limited Diversity

While influenza is a quite common infectious disease, the pattern of its global circulation and evolutionary dynamics still pose many questions to be answered (Nelson and Holmes, 2007). *Limited diversity* observed in the viral evolution of influenza is the one that has not been fully investigated. Influenza viruses have single-stranded RNA, which lacks an error correction mechanism and thus results in the high mutation rate of the genome. Thus, while continual changes accumulate in the viruses as time passes, there is always a chance for a new genetic lineage to diverge, which could theoretically result in ever-increasing explosive diversity. However, in reality, the diversity of the existing viruses is relatively limited to a certain extent at the population level and at any particular point in time. On one hand, this evolutionary behavior is in practice an important matter to be considered when we make effective plans and take medical action for minimizing the negative impact of infectious diseases, while on the other hand, it purely engages our inquisitive minds and makes us think about what causes the emergence of limited diversity in influenza viruses.

For example, Ferguson et al. (2003) discussed the role of short-lived non-specific cross-immunity as a possible mechanism that limits viral diversity. However, the biological mechanisms or evidence that actually support it have not necessarily been fully shown. By adding a more precise micro-level representation of viral evolution to the model, we propose another mechanism that also generates the limited diversity with more natural explanation than the previous work.

Methods: Model

We propose a bilayered multi-agent-based model that consists of an epidemic circulation layer and a viral evolution layer. As in typical epidemic simulations, each member of the host population is individually represented as a virtual agent (Eubank et al., 2004; Parker, 2007; Epstein, 2009). The viruses, also represented as agents, are replicated and circulated among the hosts with their genomes evolving.

Reflecting the fact that the genome of the real influenza virus is composed of eight distinct but possibly interrelated segments, we represent our pseudo virus as a composite of multiple strings instead of treating it as just a monolithic component like most of the previous studies have done. In our model, for simplification we just consider two strings. The first, string g , determines the epitope recognized by the immune systems of the hosts, and the other, string r , does not directly interact with the immune systems but mutually regulates the evolution of g and of itself.

The key and unique point of our model is that the evolution of viruses is driven and/or regulated by two distinct selective pressures (Fig. 1). On one side, string g is subjected to repulsive pressure because immune systems prevent hosts from being infected repeatedly by viruses with the same genomic configuration. Thus, p_1 , a component of viral fitness derived from the repulsive pressure, can be represented as a monotonic increasing (possibly sigmoidal) function of d_i , the distance between the binary pattern of g and the binary pattern of those held in immune memory. On the other side, however, g is subjected to attractive pressure because of intra-genomic constraints. Even though the viral genome

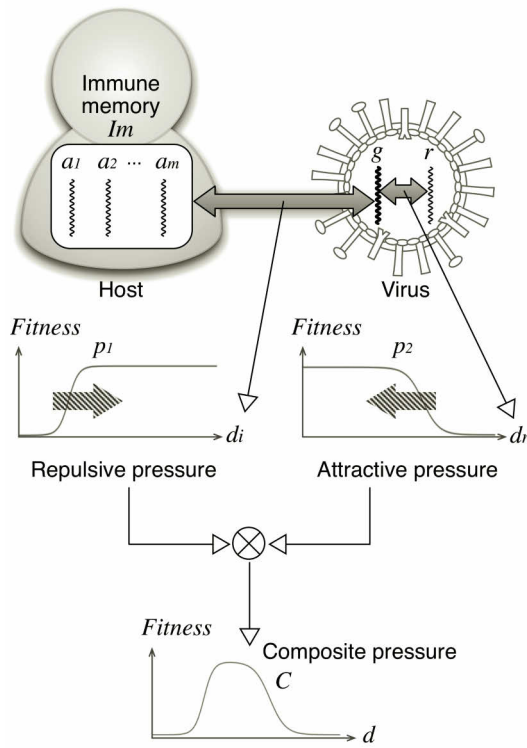


Figure 1: Micro-model of viral evolution

is separated into several segments, none of these segments can evolve totally independently from the others but a certain degree of consistency among them must be held to keep viral functions effective (Rambaut et al., 2008). Thus, p_2 , another component of viral fitness derived from the attractive pressure, can be represented as a monotonic decreasing function of d_r , the distance between the epitope segment g and regulatory segment r .

As a result of these two selective pressures working in opposite directions, the shape of the composite pressure $C = p_1 \times p_2$ becomes bell-shaped. The curve indicates the existence of a *window of diversity* that determines a certain advantageous range for viruses to thrive, i.e., “*Move a certain distance from here but not too far.*”

The details of our model have already been described in (Sasaki, 2013).

Experimental Results

We conducted experiments with the model described in the previous section to investigate its dynamical behavior. Figure 2 shows the changes in diversity, which were simply measured as the number of distinct types of viruses co-circulating in the world in each time step. The dashed line shows that when the viruses evolved under only the selective pressure of immune interaction, the diversity of the viral population grew rapidly and explosively as the steps of the simulation proceeded. In contrast, the solid line shows

that when the viral evolution was under combined selective pressure from both immunity and intra-genomic constraints, the diversity did not grow explosively but saturated at a certain limit, which in this case was around 50, even in the later steps. The result indicates that our hypothetical mixture of two counter-directed selective pressures could be a possible factor to drive the evolutionary changes but at the same time limit its diversity.

Reproducing limited diversity with the simulation model is not our ultimate objective, but it is an inevitable challenge that needs to be tackled to explore the entire spectrum of temporal evolutionary behavior of the systems.

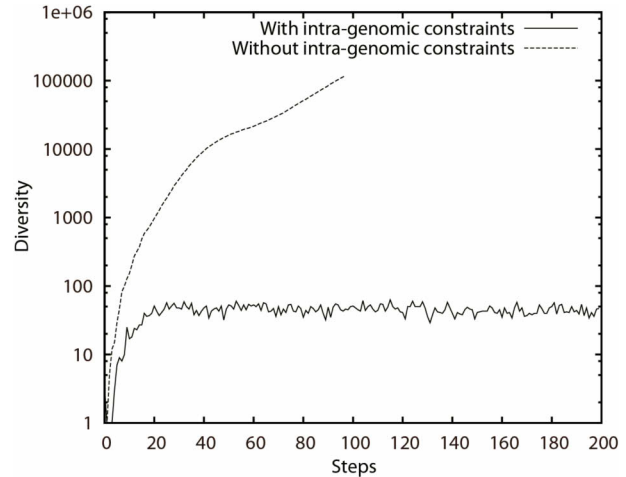


Figure 2: Experimental results

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