# Evolution of viral strain structure through host immune response

Bas Dutilh and Paulien Hogeweg
Theoretical Biology and Bioinformatics
Utrecht University, The Netherlands

August 6, 1999

Recently, it was shown that host immune responses can form a strong selective pressure on the antigenic strain structure of pathogen populations. In an ODE model described by Gupta et al. [1], the evolutionary dynamics of infective agents (each viral strain is defined as a specific combination of several alleles at a number of epitopes) can lead to discrete strain structures, called discordant sets. Discordant sets consist of viruses which have no antigens in common, and together fill up the complete antigen space with their genotypes. These sets of infective agents inhibit the spreading of related pathogens in a host population, by making the hosts resistant to all antigens in the world.

We further examine potential emergent strain structures due to host immune responses, in a spatially explicit model including a population of immunologically reactive hosts. The hosts, which are individually implemented in a cellular automata machine, can each carry their own virus, and are each resistant to a specific combination of antigens. Thus, we are able to study many different assumptions on immune systems in one simple model. In the present study, for example, we assume that when a host is infected with several viruses, it can collect resistances against all their antigens. Upon encounter of a newly attacking infection, a host's immunity is proportional to the amount of the infectious agent's antigens it has gathered resistance to.

Surprisingly, we discovered that spatial pattern formation in the cellular automata machine is necessary for generation of discordant strain structure such as found in the ODE model of Gupta et al. [1]. In the case of a mean field approximation (randomly reshuffling the cellular automata every time step), agglomerative clustering techniques reveal strain structure in larger sets of viruses. There is a clear selection for minimisation of the encountered immunities, and for each virus, this is optimised in a set with symmetric and minimum amounts of antigenic overlaps. Though these conditions are satisfied in any collection of discordant sets (including the complete viral population) the co-fluctuating sets never contain discordants. The observed strain structures allow for larger virus populations, causing more infections during the lifetime of a host than an equal number of viruses organised in discordant sets would.

We conclude that host immune response can structure viral populations into discrete sets, which are not invadable by new mutants. Moreover, we see that spatial pattern formation, which leads to discordant sets of viruses, protects the hosts and reduces the numbers of viruses that survive.

[1] Sunetra Gupta, Neil Ferguson & Roy Anderson; Chaos, Persistence, and Evolution of Strain Structure in Antigenically Diverse Infectious Agents, *Science*, 280: 912-915, 1998.