

Aging and Adaptation in Infectious Diseases II

April 30-May 2, 2019

Post-meeting Summary by Organizers

The group made progress toward four different areas:

Innate/Adaptive collaboration: The innate and adaptive components of the immune system do not age independently. We have now developed a mathematical model that couples these two complementary responses, and have demonstrated a mechanism by which the progression of immunosenescence in the adaptive response leads to aging in the inflammatory response. We began analysis of the innate-adaptive interface of this coupled immune model by studying cytomegalovirus infection, a persistent infection that interacts with both components of the immune system. Advances and discussions during the meeting included: improvements to the model equations; visualization of the history of system states in phase plane, for comparison to experimental data and potential warning signs of failure (death); consideration of the ('shape space') structure of antigenic variation in an ensemble of pathogens; and possible extensions to the epidemiological level (for a population of hosts).

Imprinting of acquired immune memory: consequences for maps of antigenic variation : Many pathogens consist of multiple strains that are perceived differently by the immune system. This variation can be represented concisely in "antigenic maps", where distances between strains can be used to quickly estimate immunity to a new strain in hosts previously infected with another. However, the data and mathematical tools used to construct antigenic maps have so far ignored that hosts with different infection histories often perceive pathogens differently. For example, on exposure to a new strain of influenza, the immune system prefers to deploy memory responses that target familiar parts of the virus, instead of generating *de novo* responses that target unfamiliar antigenic structures. Thus, across a series of lifetime exposures, immune memory can become hyper-focused on the few parts of the virus that have not changed since childhood. And because influenza evolves antigenically over time, individuals born during different eras can develop immune repertoires that become focused on different parts of a given virus. Existing antigenic maps do not take this sort of historical contingency into account, and therefore fail to reflect population structure in how different birth cohorts perceive specific antigenic mutations. So far, at least two examples have been documented in which existing antigenic maps perceived a novel strain as similar to previously circulating ones when in fact mutations in the new strain caused antigenic escape (and unusually large numbers of cases) within some birth cohorts whose immune memory had failed. So far, cohort-specific immune escape has only been identified *post-hoc*, in response to outbreaks that have caused unusual age-specific impacts. By developing new theory, we aim to pave the way toward new antigenic mapping methods, with the eventual goal of predicting cohort-specific antigenic escape before it happens, and guiding preemptive vaccine updates. We are developing a simple model to compare a simulated virus's "true" antigenic phenotype (based on viral structure, represented in shape space), with its "perceived" antigenic phenotype (a function of antigenic structure and host immune history). We will compare our new, history-dependent antigenic models with history-naïve models to ask, how often and how egregiously maps that do or do not consider immune history disagree. We will ask whether immune memory follows specific paths toward failure

(antigenic escape), and whether specific paths to failure are particularly likely to remain undetected in history-naive antigenic maps.

Allometrically scaled immune responses. Body size scaling has a significant history at SFI; we have been using insights from these approaches to develop simple models for the immune systems of vertebrates that might be used from mice (the standard lab model), through sheep, humans, cows and horses to elephants. (We will most certainly take some digressions into bats and sea birds). Our approach combines the development of simplified very general models of an immune system, with literature surveys that examine how different components of the immune system function in hosts with different body sizes. Some key questions we are addressing are: (1) How does the trade off between Type I, cellular, and Type II acquired Immunity change for hosts with different life expectancy? If you only live for a short time, why should you develop any form of acquired immunological memory? Why not treat everything as a chronic infection? An alternate way to ask this question is to examine how the component cells of the immune system change in size in hosts with different body sizes. Are T-cells and B-cells always the same size or do they increase in size in larger bodied hosts as these individual components need to live longer to conserve memory? Or do longer lived hosts simply produce more of them?

Endemism and eco-evolutionary dynamics of pathogens with extensive antigenic diversity: We are motivated here by malaria and other important infectious diseases of humans and animals that achieve endemism in regions of high transmission, and are characterized by high prevalence with a large fraction of asymptomatic, but still infectious, individuals of all ages. Immunity built from repeated exposure as hosts age remains only partial and protects against severe disease but not infection. These pathogens rely on extreme antigenic variation typically encoded by multigene families to evade the immune system. Extreme antigenic variation underlies the extensive reservoir of transmission present across the host population, which makes *Plasmodium falciparum* and other similar pathogens so resilient to intervention/elimination efforts in endemic regions. In work that predates the SFI meetings, we have been developing theory for the eco-evolutionary dynamics of *P. falciparum* from the perspective of one important multigene family (known as var) encoding the major antigen of the blood stage of infection. At SFI, we have discussed analytical and computational results on a new threshold in transmission intensity whose crossing sharply modifies the ability of the pathogen to sustain antigenic diversity. At this second meeting, we specifically formulated a novel epidemiological model (as a system of partial differential equations) that considers host age and pathogen genetic diversity in synthetic form. This formulation is intended as an abstraction of the epidemiology in the high-dimensional agent-based model of malaria and var genes. It goes beyond extensions of the known SIR (Susceptible-Infected-Recovered) models that represent partial immunity but do not account for pathogen diversity. Initial bifurcation results show the possibility of a threshold response to parameter changes. We are addressing whether the PDE model can capture major features of the more complex agent-based one. This work involved Andre de Roos who was visiting SFI at the time of the meeting.