Edgar Delgado-Eckert
Department of Biosystems Science and Engineering, ETH Zürich, Mattenstrasse 26, 4058 Basel, Switzerland.
e-mail: edgar.delgado-eckert@bsse.ethz.ch
Michael Shapiro
Pathology Department, Tufts University, 150 Harrison Ave., Boston, MA 02111, U.S.A.
e-mail: Michael.Shapiro@tufts.edu

A model of host response to a multi-stage pathogen

Pathogens that traverse different stages during their life cycle or during an infection process have been studied since the late nineteenth century. The most prominent genus is Plasmodium, causer of Malaria. Other important examples are Trypanosoma and the family of herpes viruses. Our focus is on the herpes virus Epstein-Barr (EBV), which is known to cycle through at least four different stages during infection within the human body. One remarkable characteristic of infections with many of such pathogens is *life-long persistent infection*.

The main goal of this work is to study the properties of the immune response to such a pathogen using mathematical modeling. In particular, we are interested in the existence and properties of steady-state behavior corresponding to life-long persistent infection. Our mathematical approach is based on standard ODE models of viral infection. For the postulated system of ODEs, we were able to characterize the equilibria in full generality regarding the number n of stages the pathogen cycles through. To establish the stability properties of the models' equilibria, we successfully applied techniques from modern control engineering.

If the pathogen is able to establish infection, (i.e., the basic reproductive number R_0 satisfies $R_0 > 1$), the model's parameters induce a partial order on the pathogen's stages. This binary relation $j \succ k$ is based on comparison of the rate at which stage j produces stage k with the rate at which stage k is lost to death and transformation into the next stage $k+1$. We say stage j *starves* stage k if immune regulation at stage j deprives stage k of sufficient population to support immune regulation. A stage k is called *starvable* if there is another stage j such that $j \succ k$. If no such j exists, k is called *unstarvable*. One of our main results is the fact that, generically, the system has a unique (local) asymptotically stable fixed point, namely, the one at which all unstarvable stages are regulated and all starvable stages are unregulated. In this sense, the immune regulation of unstarvable stages is sufficient to immunologically control the starvable stages. At steady state, immune regulation is only required against those stages that are produced with relatively higher yield.

This puts within reach a principled quantitative explanation of chronic infection with pathogens such as EBV, including the pattern of regulation (which is known to vary from person to person in the case of EBV), the sizes of the infected populations and the host response.

References

[1] E. Delgado-Eckert and M. Shapiro, *A model of host response to a multi-stage pathogen.* Journal of Mathematical Biology. 2010 Oct. 2. [Epub ahead of print]. DOI 10.1007/s11538-010-9596-2.