

Questions on Ewald (1996) Ch. 3

Perelson et al. (1996)

February 1, 2007

Evolution of Virulence/Benignness

1. McNeill states that a parasite is not capable of evolving to a benign equilibrium in the arthropod vector and the vertebrate host. But if such an equilibrium was reached would we even know about it?
2. Ewald points out consistently that the theory of evolution towards benignness is flawed, but it seems that this is what occurs with many diseases that infect mosquitoes. He mentions several minor affects that disease has on mosquitoes, but this is nothing compared to the disease that is caused in humans or other hosts. It seems that evolution toward benignness does occur in certain parasite-vector-host cycles.
3. An arms race between the rabbits and the myxomatosis virus? Given much higher replication rates, higher mutation rates, etc. I say that the virus wins hands down. If its evolutionary path were not toward benignness, why has it become so much more benign?

4. Why would a disease organism want to evolve toward benignness if it's successful as a deadly form? Has there ever been a documented case where a disease organism went extinct because it killed all of its suitable hosts?
5. Would McNeill's restricted adaptation hypothesis be false if a pathogen slowly kills the arthropod vector so it has enough time to spread the disease to the host before dying? If such a case existed how could McNeill's hypothesis be changed?
6. Paul Ewalds hypothesizes are based largely on examples of diseases spread by mosquitoes. Would they hold up if he included more examples of other arthropod vectors and diseases cycles?
7. In the third chapter of "Evolution of infectious disease" says that vectorborne pathogens of humans are more severe than non vectorborne pathogens. Which characteristics have evolved to produce this adaptation in viruses of humans?
8. "Vectorborne pathogens of humans are more severe than nonvectorborne pathogens." p 37. Why is this? Is this also the case for other mammals, reptiles, amphibians, etc. that are susceptible to both types of pathogens?

Disease Control

1. Both being vector borne diseases, what makes yellow fever amenable to control by vaccines or drugs while *P.falciparum* doesnot, in spite of decades of effort.
2. Given the fact that malaria has a superior ability to adapt to treatment and vaccines, as well as Ewald's (and other's) negative outlook on the potential for finding a long-term solution to malaria, is it worth continuing to try to find a solution?

3. Is it reasonable to assume that the incidence of malaria and many other vector borne diseases could be drastically reduced by developing or altering the landscape where the vectors breed (sort of like what has happened in the S.E. United States since European settlement)?
4. As evolution of viruses and bacteria can occur rapidly through mutations, acquisition of plasmids/exogenous DNA etc, how can we develop protocols for prevention that will not become obsolete before they are allowed in practice?
5. Genetic Control of Vectorborne Diseases: How do you create mosquito strains that can block the pathogens' ability to reach the saliva?
6. What is the best avenue to test the control of vectorborne diseases through genetic and evolutionary controls simultaneously?

Pathogen Biology

1. Why does the *Plasmodium falciparum* spread through the susceptible population more rapidly than the other human plasmodia?
2. How quickly is HIV evolving—I've heard in other situations that HIV drugs are effective in some individuals but not others. Is this a result of different strains of the virus or different host reactions to treatment?
3. Does the use of inhibitor protease for HIV have any effect in other proteins like p17, p24, gp120 or gp41?

4. According to the book - 'Evolution of infectious disease', the reproduction of rhinovirus within our noses is highly restricted. Is there any reason for this highly restricted reproduction?
5. Is there any reason why the newly produced HIV-1 virions become non-infectious after the administration of protease inhibitor?
6. Explain the causes for the loss of HIV-1 infected cells (i.e. viral cytopathicity, immune elimination, apoptosis).
7. "*P. malariae* can remain infectious for several decades." p 44. Is this infectious with/without symptoms or is it possible for symptoms to come and go?

Data Analysis

1. Although it might not be exactly ethical, it would seem that a lot could be learned by giving protease inhibitors to patients for a set time period and then withholding the drug for a set time to learn about the reverse kinetics.
2. In the HIV paper, it said that all their data came from 5 individuals. Is this number of samples adequate? Should the experiment be repeated? Which was the control that was used? How can we extrapolate this data to all humans infected with HIV, especially given that different people (possibly with genetically different types of HIV-1) react so differently to different drugs? (*Compiled from three different questions*)

Modeling

1. Can we use the concept of modeling to successfully predict the duration of time it would require to completely eradicate a vectorborne parasite and eliminate the risk of

resurgence of infection?

2. In Perelson's article he mentions that they assume complete inhibition by ritonavir, but could adjust the model for imperfect drugs, wouldn't a model that included a decaying/declining ability of the drug to inhibit over time be more accurate since we know that drugs lose their effectiveness over time?
3. How can the model we discussed in class be applied *in vitro* to all diseases, as most animals do not typically become immune to disease when exposed, and will re-enter the susceptible range once recovered?
4. Have the theoretical principles to "guide the development of treatment strategies" devised in the HIV article been applied successfully, (aka, did the mathematical model predictions hold true *in vitro*)?
5. The HIV paper talked about the direction of future research that will enable us to understand the dynamics of other viral compartments (e.g., decay rate of long-lived virus-producing populations, activation rate of cells causing infectious proviruses, etc.). This paper was published in 1996, where are we at today on this stuff?
6. Is it likely that due to human-kind's chronic, obtuse disregard for nature's ecological checks and balances, even the most testably predictive models might be rendered obsolete by the mutative and infectious capabilities of evolved pathogens? If so could a model be developed on a scale to predict just such a theory?

Other

1. What possible explanation can there be for the phenomenon in which a highly infectious vectorborne parasite suddenly disappears or becomes dormant for a prolonged period

of time and then suddenly resurfaces as a regional or an even broader flare-up?

2. For people who are intrigued by the conceptual basis for models, but confounded by the math, the symbols, ie. lost in a numerical quagmire, the literary, pictorial mind overwhelmed: Could a model be developed that appeals to "the other half of the brain"?
3. The research on *P. knowlesi* and syphilis described on p 40...how ethical was this study/treatment?