NOLTA'07

Competition among viruses at the within- and between-host scales

Daniel Coombs[†], Colleen L. Ball[†] and Michael A. Gilchrist[‡]

†Department of Mathematics and Institute of Applied Mathematics, University of British Columbia,
1984 Mathematics Road, Vancouver, BC V6T 1Z2 Canada
‡Department of Ecology & Evolutionary Biology, 569 Dabney Hall, University of Tennessee
Knoxville, TN 37996-1610 USA
Email: coombs@math.ubc.ca, ball_colleen@hotmail.com, mikeg@utk.edu

Abstract—Many infectious pathogens, and in particular viruses, have an extremely high rate of mutation. This can lead to rapid evolution driven by selection pressures operating at the within- and between- host levels, as strains compete for resources within their host while also competing to effectively transmit to new hosts. In the case of chronic viral infections, such as those caused by HIV or hepatitis C, substantial viral evolution may take place within a single infected individual. The fitness of a pathogen has been studied at the epidemic scale and at the within-host level, but linking the two levels of selection pressure has yet to be satisfactorily resolved. We modify a simple model describing the within-host dynamics of HIV infection by including N different pathogen strains and allowing these strains to mutate. Within the host we observe different strategies for pathogen success during different stages of infection. We embed the within-host model into a simple epidemic model first analytically, resulting in a largest-eigenvalue problem for a particular integral operator, and into a Monte Carlo simulation. We show that co-existence of strains is possible and we explore the factors leading to pathogen success.

1. Introduction

Within an infected host, viruses compete for host resources while simultaneously competing for transmission to a new host. The possibility of natural selection at these two scales raises the possibility of conflicts between selection pressures acting at the two scales [1] and raises the question of how such conflicting selection pressures can be resolved [2, 3].

The simplest statement of parasite fitness derived from epidemiological considerations alone is

$$R \sim \frac{\beta}{\delta + \alpha + \gamma}, \qquad (1)$$

where β, δ, α and γ are rates of transmission, uninfected host mortality, virulence and recovery from infection. Clearly, virulence is detrimental to pathogen fitness and this raises the question of why pathogens kill or harm their hosts. Early work in this area explored explicit trade-offs between virulence and transmission [4–6], which can be criticised because the relationship between virulence and transmission is based on plausible arguments, but not on
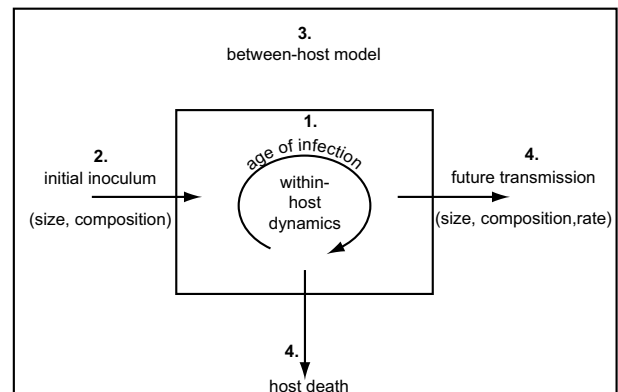

Figure 1: Elements of our model procedure

the detailed biology of the host-parasite interaction. Ideally, one should derive the transmission-virulence relationship from basic between- and within-host processes, rather than imposing a particular linkage. A useful framework for considering these questions is one of nested models where a within-host model of parasite population dynamics is linked to a population-level model for between-host infection dynamics e. g. [7–12] Such a framework allows one to explicitly link the between-host model to the behaviour of the within-host model. An alternative hypothesis is that of short-sighted evolution, in which a pathogen evolves to maximize its fitness within a host at the expense of its spread through a population of hosts [13]. Evidence for within-host evolution exists e. g. for HIV [14].

Our approach to pathogen evolution is based on dynamic models at the within- and between- host levels, along with the linkage between these models (representing transmission). We present semi-analytic results for competition between two strains and numerical simulations of scenarios with more strains. Our results are shown for particular models, but our procedure is adaptable to a wide range of situations.

2. Modeling

Within-host model   We will use a modified HIV dynamics model [15]: (i) we assume a trade-off between viral production rate p and infected cell death rate μ by taking

$\mu = \mu(p)$ to be an increasing, concave-up function [16, 17]; (ii) multiple strains of virus, different only in their production rates compete within the host; (iii) we introduce a small mutation rate ϵ between viral strains. The complete model is expressed as a system of $2N + 1$ equations:

$$\frac{dT}{dt} = \lambda - dT - kT \sum_{j=1}^{M} V_j$$

$$\frac{dT_i^*}{dt} = k(1 - \epsilon)TV_i - \mu(p_i)T_i^* + \frac{\epsilon kT}{M} \sum_{j=1}^{M} V_j \quad (2)$$

$$\frac{dV_i}{dt} = p_i T_i^* - cV_i \qquad i = 1..M$$

This model is described in more detail in [18]. The appropriate measure of within-host viral fitness for strain i is

$$\rho_i = \frac{N_i k_i (1 - \epsilon)\lambda}{c_i d} \tag{3}$$

In the absence of mutation, fitter viruses competitively exclude weaker viruses. Further, there is a single optimal production rate p^* that maximizes ρ [16]. The uninfected steady state exists at $T = \lambda/d, T_i = 0, V_i = 0$ for all i and there is a single infected steady state with all viruses present: the p^* virus present in significant numbers, while its weaker competitors are present at $O(\epsilon)$ only [18]. However, in this work, transients are important. Elsewhere we show that a range of viruses with $p > p^*$ dominate the p^* virus during the early dynamics [18] before eventually being overtaken. This is significant since the host is probably still alive and transmitting at this point so such viruses can be transmitted.

We can summarize the dynamic possibilities for a scenario where the optimal within-host strain p^* competes with a second strain of production rate p_2: (1) if $p_2 < p^*$ then the density of the within-host optimal strain, p^*, always exceeds that of the p_2-strain; (2) if $p^* < p_2 < p^\dagger$ then the p_2 strain is initially dominant, with the peak of the initial virus spike increasing with p_2. The time for the p^* strain to overtake the p_2 strain decreases with p_2. (3) there is a range $(p^\dagger < p_2 < p_{\max})$ of p_2-values within which the p_2 strain could establish an infection if it were alone in the host, but in the presence of the optimal within-host competitor, its density always decreases.

Between-host model We now propose an SI model incorporating the within-host dynamics and consider, for simplicity, only two viral strains. We focus on the initial inoculum that infects a previously susceptible host, defining $0 \leq x_0 \leq 1$ as the fraction of viruses of strain 1 in the infecting inoculum.

$$\dot{S} = b - \delta S - S \int_0^\infty \int_0^1 \int_0^1 \beta(a, x_0, x_0')I(t, a, x_0')dx_0 dx_0' da \quad (4)$$

$$\frac{\partial I(t, a, x_0)}{\partial t} + \frac{\partial I(t, a, x_0)}{\partial a} = -(\delta + \alpha(a, x_0)) I(t, a, x_0) \quad (5)$$

$$I(t, 0, x_0) = S \int_0^\infty \int_0^1 \beta(a, x_0, x_0')I(t, a, x_0')dx_0' da. \quad (6)$$

$I(t, a, x_0)$ represents the density of infected individuals that were infected by an inoculum x_0 at time $t - a$. Susceptibles are born at rate b and die at rate δ. Infection occurs by random mixing and at rate $\beta(a, x_0, x_0')$, producing infecteds that die from natural mortality and addition mortality due to infection, at rate $\alpha(a, x_0)$. By defining the survivorship probability $\sigma(a, x_0)$ and integrating, we can obtain a simplified system (abbreviating):

$$\sigma(a, x_0) = \exp\left(-\delta a - \int_0^a \alpha(z, x_0)dz\right) \quad (7)$$

$$\dot{S} = b - \delta S - S \int_0^\infty \int_0^1 \int_0^1 \beta(.)I(t - a, 0, x_0')\sigma(.)dx_0 dx_0' da \quad (8)$$

$$I(t, 0, x_0) = S \int_0^\infty \int_0^1 \beta(.)I(t - a, 0, x_0')\sigma(.)dx_0' da. \quad (9)$$

Now defining the transmission kernel

$$\Phi(x_0, x_0') = \int_0^\infty \beta(a, x_0, x_0')\sigma(a, x_0')da \quad (10)$$

we can construct the next generation operator K:

$$K[i(x_0)] = \int_0^1 \Phi(x_0, x_0')i(x_0')dx_0'. \quad (11)$$

R_0 is then $S_0 = b/\delta$ times the largest eigenvalue of the next generation operator, i.e. the largest solution Λ of the eigenvalue equation $K[i(x_0)] = \Lambda i(x_0)$. R_0 represents the maximum rate of initial increase of infecteds over all possible structures of the initial infected population. [19].

We write the steady state distribution of infected individuals of age 0 as $I(t, 0, x_0) = \hat{i}(x_0)$ and that of susceptibles as $\hat{s}$. Upon substitution of $\hat{i}(x_0)$ into (8-9), we find

$$\frac{1}{\hat{s}}\hat{i}(x_0) = \int_0^1 \Phi(x_0, x_0')\hat{i}(x_0')dx_0' = K[\hat{i}(x_0)] \quad (12)$$

$$\hat{s} = \frac{b}{\delta + \int_0^1 K[\hat{i}(x_0)]dx_0} \quad (13)$$

Therefore any given equilibrium density of new infections $\hat{i}(x_0)$ is an eigenfunction of K with eigenvalue $1/\hat{s}$.

We write such an equilibrium $\hat{i}(x_0) = zf_j(x_0)$ where $f_j(x_0)$ is the jth eigenfunction of K with corresponding eigenvalue Λ_j. Dropping the j subscript, we find that, $\frac{1}{\hat{s}}zf(x_0) = z\Lambda f(x_0)$. Using (13), we find that the eigenvalue corresponding to this equilibrium is

$$\Lambda = \left(\delta + \Lambda z \int_0^1 i(x_0)dx_0\right)\Big/ b \quad (14)$$

with

$$z = (\Lambda b - \delta)\Big/\left(\Lambda \int_0^1 i(x_0)dx_0\right). \quad (15)$$

For an endemic equilibrium to exist, the dominant eigenvalue Λ must be greater than δ/b. Equivalently, $R_0 > 1$.

The operator K acts on a function $i(x_0)$ defined on $0 \leq x_0 \leq 1$. Take an arbitrary distribution of infected individuals structured by initial condition, $\phi_0(x)$, and operate on

it repeatedly with K. The simplest possibility is that, irrespective of $\phi_0(x_0)$, all possible strain-mixes are eventually found in the population. That is, for every strain-mix y, there is a generation n such that $\phi_n(y) = K^n[\phi_0(x_0)](y) > 0$. Such an operator is the analogue of an irreducible, positive matrix. In this case, it can be shown that there is a single dominant eigenvalue (R_0) and it is the only eigenvalue with a non-negative eigenfunction, indicating that there is only one stable distribution of strain mixes $\hat{i}(x_0)$. If K is not ergodic, we can find isolated collections of initial infection states and then the final distribution of infected individuals over x_0 depends on $\phi_0(x_0)$.

Initial inoculum   We assume that the inoculum size is a fixed small density, but the proportions of the viral strains in the inoculum reflect that of the transmitting host at the moment of transmission. Specifically, we define the strain mix at time 0 to be $x_0 = V_1/(V_1 + V_2)$ and write the initial conditions $(T, T_1^*, T_2^*, V_1, V_2) = (\lambda/d, 0, 0, \xi x_0, \xi(1 - x_0))$. where ξ is the initial virion concentration introduced by one inoculum. While different x_0 values lead to different trajectories in the $V_1 - V_2$ phase plane, all trajectories lead to the final state where the superior within-host competitor, strain 1, has essentially excluded strain 2.

Between-host model linkage functions   At the between-host level we will use the SI model described above with the simple functions $\beta = \beta V$ and $\alpha = a_1\delta(T_0 - T)$ where $T_0 = \lambda/d$.

3. Simulation

We numerically solve the within-host model for a range of initial conditions, for a period of time long enough that the host will have died by the end of the period with high probability. We store the dynamic variable T and V_i for equally spaced time-steps through the simulation. We then introduce a single newly-infected individual into the population. We the run a stochastic simulation of the epidemic. Each infected is considered at each time step and the probability of infecting a susceptible host is calculated using the function β (described above). β changes with the host viral load and so the infectivity changes as the infection progresses in each host. Newly infected individuals are introduced (with appropriate initial conditions) according to the infectivities that are calculated (a Poisson process is assumed). At each time step, new susceptibles are introduced, and some die (with constant rates) and infecteds die (and are removed) according to their death rates α (dynamic variable depending on their level of target cells, T).

In figure 2 we plot simulation results from 2-strain simulations where the p^* strain competes with a single different strain, p_2. We plot the steady-state fraction of transmissions of the p^* strain and compare with results obtained using the model described above.
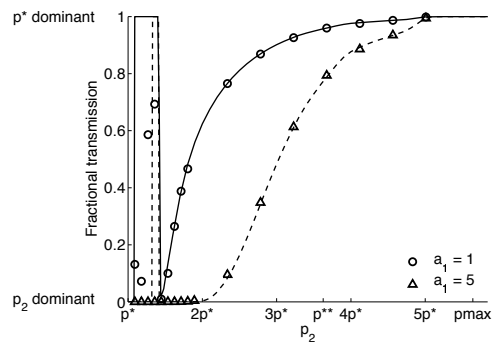

Figure 2: Two-strain competition results

In figure 3 we show the results of a simulation performed using five strains, with production rates evenly spaced between p^* and p^{**}, over varying levels of virulence. When pathogen virulence is low, production rates closer to the within-host optimum are favoured. As pathogen virulence increases, strains with faster production rates become more prevalent. This indicates that when virulence is high, the main selection pressure comes from the need to transmit, rather than within-host optimization. Although we generally observe co-existence of multiple strains in the population, the p^* strain is scarcely present at higher virulence, and the p^{**} strain is scarcely present for lower virulence.

If we also calculate the total number of each strain present in the population, we find the proportions are almost the same. This means that the lower producing strains infect a high proportion of hosts but transmit relatively rarely. The higher-producing strains operate conversely. This is because, in a single host, the higher producing strains are always replaced by lower-producing strains over time (due to mutation).

4. Discussion

We have shown that coexistence of multiple strains is possible under the above assumptions, but typically there is a dominant strain. In general, we found that the most successful strains have an intermediate production rate that is nonetheless higher than the within-host optimum rate p^*. Our simulations show that as virulence decreases, the within-host optimal strain is more favoured in this model. Drug treatment effectively increases the host lifetime, and so might give an advantage to such strains (assuming, of course, that the within-host model maintains).

Given the great diversity of host-parasite systems, it is clear that no single model will explain every aspect of the all host-parasite interactions. However, we hope that the general method presented here can be used to incorporate detailed cell-level biology into our understanding of the evolution of parasite virulence, appropriately evaluating the importance of selection pressure at multiple levels.
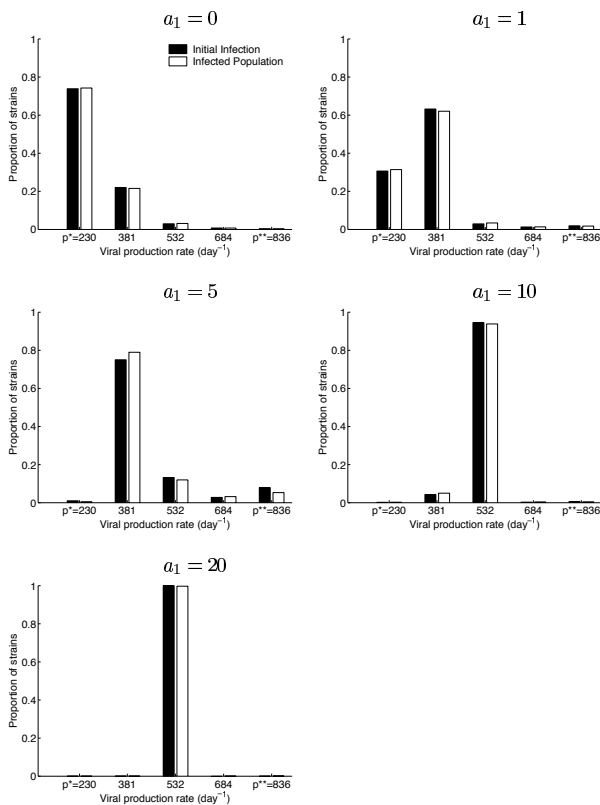
Figure 3: Five-strain competition results

Acknowledgments

References

[1] Gilchrist, M. A., and D. Coombs. 2006. Evolution of virulence: interdependence, constraints and selection using nested models. *Theor. Pop. Biol.* 69:145–153.

[2] Boldin, B., and O. DIekmann. in press. Superinfections can induce evolutionarily stable coexistence of pathogens. *J. Math. Biol.* .

[3] Coombs, D., M. A. Gilchrist, and C. L. Ball. 2007. Evaluating the importance of within- and between-host selection pressures on the evolution of chronic pathogens. *submitted.* .

[4] Anderson, R., and R. May. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. *Proc. Roy. Soc. Lond. Ser. B. Biol. Sci.* 219:281–313.

[5] Frank, S. A. 1992. A kin selection model for the evolution of virulence. *Proc. Roy. Soc. Lond. B.* 25:195–197.

[6] Lenski, R. E., and R. M. May. 1994. The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. *J. theor. Biol.* 169:253 –265.

[7] Sasaki, A., and Y. Iwasa. 1990. Optimal growth schedule of pathogens within a host: switching between lytic and latent cycles. *Theor. Pop. Biol.* 39:201–239.

[8] Antia, R., B. R. Levin, and R. M. May. 1994. Within-host population dynamics and the evolution and maintenance of parasite virulence. *Am. Nat.* 144:457–472.

[9] Gilchrist, M. A., and A. Sasaki. 2002. Modeling host-parasite coevolution: a nested approach based on mechanistic models. *J. theor. Biol.* 218:289–308.

[10] Andre, J. B., J. B. Ferdy, and B. Godelle. 2003. Within-host parasite dynamics, emerging trade-off, and evolution of virulence with immune system. *Evolution.* 57:1489–1497.

[11] Andre, J. B., and S. Gandon. 2006. Vaccination, within-host dynamics and virulence evolution. *Evolution.* 60:13–23.

[12] Alizon, S., and M. van Baalen. 2005. Emergence of a convex trade-off between transmission and virulence. *Am. Nat.* 165:E155–E167.

[13] Levin, B. R., and J. J. Bull. 1996. Short-sighted evolution and the virulence of pathogenic microorganisms. *Trends Microbiol.* 2:308–315.

[14] Arien, K. K., R. M. Troyer, Y. Gali, R. L. Colebunders, E. J. Arts, and G. Vanham. 2005. Replicative fitness of historical and recent HIV-1 isolates suggests HIV-1 attenuation over time. *AIDS.* 19:1555–1564.

[15] Perelson, A. S., and P. W. Nelson. 1999. Mathematical models of HIV-1 dynamics in vivo. *SIAM Review.* 41:3–44.

[16] Coombs, D., M. A. Gilchrist, J. Percus, and A. S. Perelson. 2003. Optimal viral production. *Bull. Math. Biol.* 65:1003–1023.

[17] Gilchrist, M. A., D. Coombs, and A. S. Perelson. 2004. Optimizing within host viral fitness: Infected cell lifespan and virion production rate. *J. Theor. Bio.* 229:281–288.

[18] Ball, C. L., M. A. Gilchrist, and D. Coombs. 2007. Modeling within-host evolution of HIV: Mutation, competition and strain replacement. *in press, Bull. Math. Biol.* .

[19] Diekmann, O., and J. A. P. Heesterbeek. 2000. Mathematical epidemiology of infectious diseases, 1st Ed. Wiley, Chichester.