Between-host evolution of mutation-rate and within-host evolution of virulence.

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It has been recently realized that parasite virulence (the harm caused by parasites to their hosts) can be an adaptive trait. Selection for a particular level of virulence can happen either at at the level of between-host tradeoffs or as a result of short-sighted within-host competition. This paper describes some simulations which study the effect that modifier genes for changes in mutation rate have on suppressing this short-sighted development of virulence, and investigates the interaction between this and a simplified model of immune clearance.

1 Introduction.

In recent years a challenge [1, 2] has been mounted to the "conventional wisdom" that parasites will evolve to a mutualistic relationship with their hosts, where the parasite causes no harm to the host. This theory is intuitively appealing, as harm to the host is in the long run detrimental to the parasite, but such a simple explanation rests on group-selectionist arguments. A closer analysis suggests that intermediate levels of *virulence* (the harm caused by a parasite to its host)

are an active adaptation, not just an accidental artifact. This idea has been supported both theoretically [3, 4, 5] and to a lesser degree in real biological systems (e.g. the phage experiments described in [6]).

There are two evolutionary scenarios which could give rise to non-minimal virulence in parasite-host coevolution. The first is between-host selection, where there is a tradeoff between harm caused by the host and some advantage such as increased transmissibility. An easy to understand example [1] is the water-borne bacterium *vibrio cholerae* which causes cholera. One virulent symptom of cholera, often fatal, is severe diarrhea, leading to dehydration. However in an environment with poor sanitation this results in infection of the drinking water, leading to increased transmissibility. As long as the rate of new infections caused by this transmission route remains higher than the disadvantages caused by host morbidity/debility, the virulent form will continue to spread.

The second evolutionary force acting to promote virulence is *short-sighted within-host* selection [5]. Once a host has been infected new mutant strains will emerge, and competition for resources within the host may lead to virulent strains emerging [5, 4]. This competition can lead to strains which are less good for long-term transmission of the host—hence the use of the term *short-sighted*. A simple example [3] is where a strain emerges which uses host resources at a rate faster than the current strain, yet at the expense of killing the host faster. If this strain and the milder strain were to circulate freely in the population without mutation, then the milder strain would dominate However because of the mutability the virulent strain continues to be produced by local mutation events.

There are other mechanisms for within-host evolution of virulence. One possibility [5] is within-host niche expansion—a parasite normally lives in some part of the host without causing harm, but a runaway (possibly mutant) variant finds a way into another tissue of the host, where it causes harm. Again the virulent effects are maintained by the harmless "trojan horses" circulating in the population. Another possibility [7] is that the diversity created by within-host competition overwhelms the immune system.

It is also well known [8, 9] that mutation rates can be controlled by

modifier genes. These can either be specific modifiers of particular loci, or modifiers which alters the mutation error-checking mechanism thus changing the mutation-rate of the entire genome. It has been suggested [10, 11] that these mechanisms can be adaptive, for example a parasite may benefit by presenting a diverse range of variants to the immune system [12, 7], or if the environment is fluctuating the production of fitted variants in different environments may dominate the production of deleterious mutants [13, 14].

In this paper we investigate the hypothesis that natural selection acting at the between-host level on mutation rates will work to lower those mutation rates at loci where increased mutation rates lead to higher probabilities of virulence being increased.

2 A simple model.

We know that virulence can evolve by within-host mutation, and we know that selection can act to influence mutation rates. To what extent will between-host selection choose to alter parasite mutation rates to reduce the chance of a short-sighted mutant appearing? We use an individual-based model [15] of a freely-mixing host population with parasites of varying degrees of virulence being transmitted between them. This individual-based model allows a simulation of a complex heterogeneous population. However it is difficult to read off broad qualitative predictions in the same way that is possible with mass-action models, and (as pointed out in [10]) these models are sensitive to parameter choice and implementation details. Our ongoing work includes analysing this same problem from an analytic, mass-action or pairwise-approximation perspective.

2.1 Details of the model.

We represent the population by a set of hosts, each of which is able to harbour one parasite strain. Parasite strains are defined by two genes. The first of these is *virulence* and defines the rate at which resources within the host are used, hence it is a measure both of how

likely the host is to die of the infection, and of how likely that parasite is to take over from existing parasites within the host. The second gene is *mutation*, which measures the probability per unit time that a mutant strain of the *virulence* gene will arise and be able to take over the host. This mutation rate itself is subject to occasional mutation, with a probability of 0.1/timestep of changing by ± 0.05.

We make several important assumptions here. The first is that there is no cross-reactive immunity (where the presence of one parasite prevents invasion by another). The second is that there is no structure to the host population, meaning that there are no internal heterogeneties in the host population and that the contact between hosts is random with equal probability of contact between any two hosts.

Here is the simulation algorithm. A timestep is roughly the time taken between a superior mutant strain arising within a host and it taking over that host.

Create a homogeneous, uninfected population.
Introduce parasites with various mutation rates into the population.
LOOP (until population at equilibrium) :
Calculate some random transmissions to new hosts.
Remove some hosts with a probability dependent on their parasite's *virulence* gene.
Replace those hosts with new hosts.
Carry out mutations with a probability dependent on the parasite's *mutation* gene.
Carry out a low level mutation of some of the *mutation* genes.
End LOOP

2.2 Results and Discussion.

The averaged results of the simulation over 20 runs are illustrated in figure 1. This illustrates the evolution of mean *virulence* and *mutation* probabilities with time. This was for a population of 500 hosts with an initial population of 20 infectees, where the initial virulence was 0.0 for all parasites, and the initial mutation rate chosen randomly and uniformly within the range $[0.0, 0.005]$. Transmission rate was

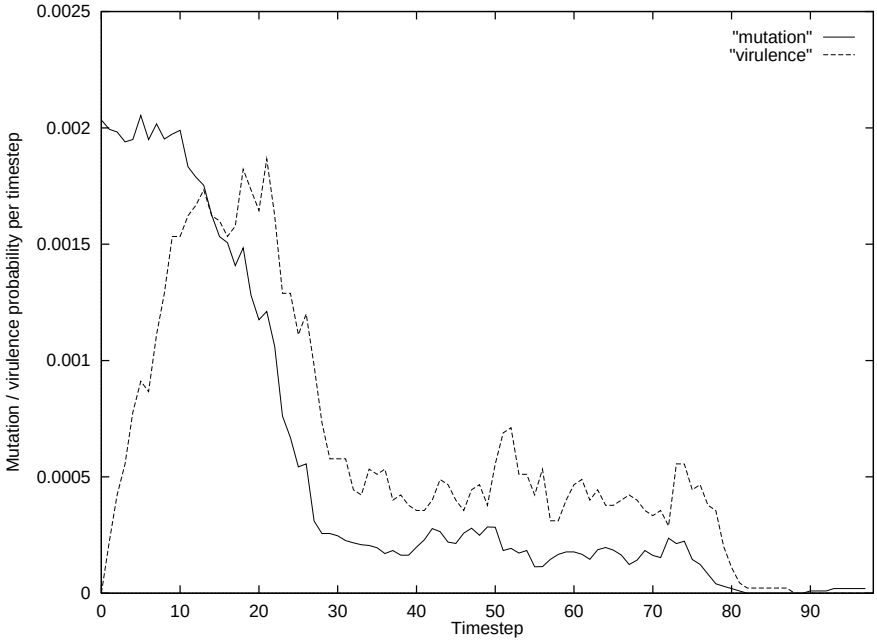

Figure 1: Evolution of average mutation and virulence rates with time.

0.1 timestep regardless of virulence, as this is an attempt to capture the within-host dynamics without between-host tradeoffs (the coevolutionary dynamics would be an interesting area for future study).

As would be expected there is an initial, exponential rate of take-over by parasites mutating into more virulent forms. However after about 20 timesteps these effects are tempered by host death, and eventually only the lower-mutating parasites remain by around timestep 40. After this there is a gradual drift within the the population, eventually reducing virulence to zero. This provides us with a "null model" on which to build other features.

3 A model with clearance.

There will of course be other pressures acting on the mutation rate of the parasites [13]. Some of these will support the reduced mutation rate, particularly the generation of deleterious mutants ("mutation load"). However in a dynamic environment there is an opposing force ("substitution load") which is the advantage to be gained by evolutionary flexibility in a changing environment.

In a parasite-host system where the host has an immune system, there

is evolutionary pressure towards maintaining diversity as (in general) more mutable forms will stand more chance of hitting upon variants which can escape the immune system. We adapt the above model to contain a simple model of clearance.

3.1 Details of the model.

We construct the model as before, however we assume that hosts are able to clear the parasites. Mutation is a force which works against this immune clearance, by presenting different images to the immune system, thus preventing the immune system learning the shape of the parasites [12]. Therefore we assume that the clearance rate is reduced when *mutation* is high

$$total\_clearance = clearance\_rate - clearance\_coefficient \times mutation\_rate$$

where *total_clearance* is the probability that the host will clear the parasite per timestep, and *clearance_rate* is the base probability that the host will clear the parasite given that there is no mutation within the parasite population. The *clearance_coefficient* measures the strength of the hosts immune system to cope with differing levels of parasite diversity—if *clearance_coefficient* is low, then the host is resistant to a wide range of strains, whereas if it is high then mutant parasites can easily evade the immune system. This could also be thought of as a measure of the diversity of parasites presented to the immune system. Clearly this is a vastly simplified model, and it would be interesting to model the acquisition of immune resistance through repeated infection.

3.2 Results and Discussion.

Figure 2 illustrates a typical run from the model when there is no clearance. Parameter values in this run are $transmission\_rate = 0.2$ and $clearance\_rate = clearance\_coefficient = 0.0$.

Figure 3 illustrates a typical run when there is a broad immune response where the capacity of the immune system to clear parasites

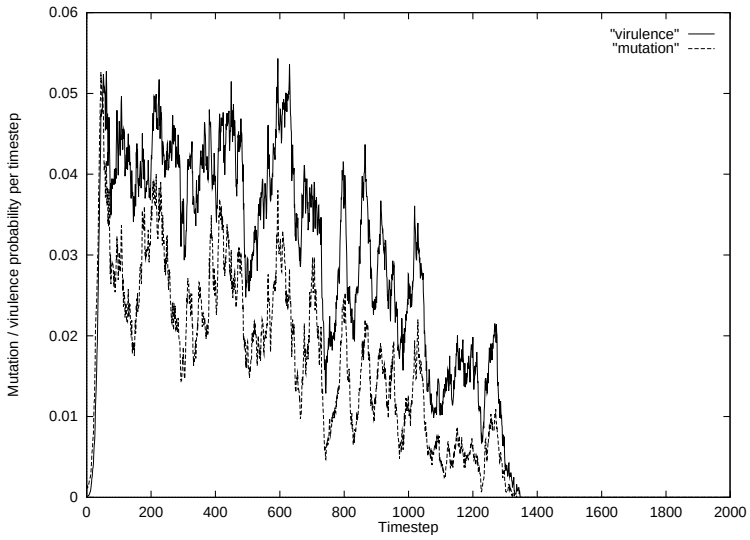

Figure 2: A typical run with no parasite clearance.

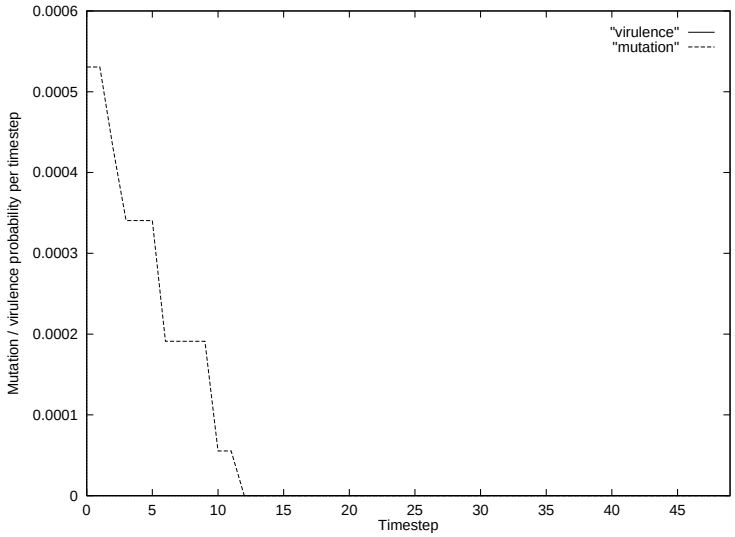

Figure 3: A typical run with parasite clearance and no escape mutants.

dominates the ability of the parasite to create mutants that can evade the immune system. The parameters here are $transmission\_rate = 0.2$, $clearance\_rate = 0.2$ and $clearance\_coefficient = 0.0$. In this case all the parasites are cleared within a few timesteps.

The final run (figure 4) illustrates the case where parasites with a higher mutation rate are able to create variants which evade the immune system.The parameters here are $transmission\_rate = 0.2$, $clearance\_rate = 0.2$ and $clearance\_coefficient = 2.0$.

Clearly there is a tradeoff for the parasite here, between increased mutation rate, allowing it to evade the immune system, yet running into

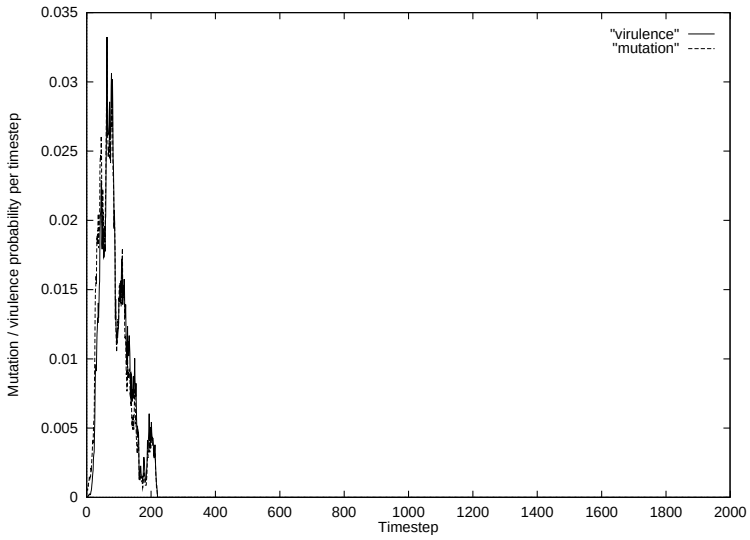

Figure 4: A typical run with parasite clearance dependent upon mutation rate.

the danger of increasing the probability of creating virulent variants from time to time. It would be interesting to find the optimal mutation rate in this circumstance, a problem made more complicated if we consider that this is coevolving with a host capable of changing the amount of resource invested in clearance according to levels of parasite danger [16].

4 Conclusions and ongoing work.

This has been a simple analysis of a complex problem, and several variations and enhancements suggest themselves. A more realistic host population would have various social structures, and an attempt to incorporate these structures (modelled, for example, by the methods described in [17]) into a model of virulence evolution would be an interesting future study. Another factor which is worthy of further study is kin selection within the parasite population [18].

There is also interest in combining these models with more accurate models of host response. Modelling the long-term evolution of hosts in response to parasite invasions is an important area in ecology, with implications for important questions such as the evolution of sex [19]. A more immediate and tractable problem is modelling the immune response in a more realistic way.

It is unlikely that appropriate modifiers will exist in all cases. In this case we can calculate conditions on the (ecological and epidemiological) parameters such that short-sighted evolution will persist in a population. In the simplest case the number of new infections caused by a less virulent parasite before mutation must on average be greater than the number caused by the more virulent parasite in the time between mutation and host death.

An aspect for further thought and investigation is the effect of "metaevolutionary" processes (what has been called "Darwinian genomics") in this system. What pressures will cause appropriate mutation-modifiers to arise? How will evolution shape mutability at different parts of the genome to make best use of localized mutations (see the examples and theories discussed in [12])?

One possible application of these ideas is to use mutation rates could as a gauge to ascertain whether within-host virulence evolution is present in a population. It may prove easier to measure the mutation rates of pathogens (see the *E. Coli* experiments described in [9]) than to measure their virulences directly. By combining the existing work on optimal rates of evolution in dynamic environments (e.g. [10, 9, 11]) with theories of optimal mutation rates for within-host virulence we may be able to give broad quantitative predictions for the correlation between virulence and mutation rates.

Another area for future exploration would be to look at the application of these ideas to genetic algorithms. There has been work [20, 21] on optimizing the mutation rates for genetic algorithms, and the trade-offs outlined above suggest a possible way of modifying mutation and crossover rates in a genetic algorithm. By encoding possible solutions to a problem on parasites with differing mutation and crossover rates, we can select for optimal solutions to the problem at the within-host level, whilst selecting for optimal mutation and crossover rates at the between-host level.

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