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Evolution of parasite virulence against qualitative or quantitative host resistance

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We analysed the effects of two different modes of host resistance on the evolution of parasite virulence. Hosts can either adopt an all-or-nothing qualitative response (i.e. resistant hosts cannot be infected) or a quantitative form of resistance (i.e. which reduces the within-host growth rate of the parasite). We show that the mode of host resistance greatly affects the evolutionary outcome. Specifically, a qualitative form of resistance reduces parasite virulence, while a quantitative form of resistance generally selects for higher virulence.

Keywords: virulence; resistance; herd immunity; kin selection

1. INTRODUCTION

The evolution of host resistance and the evolution of parasite virulence (i.e. the amount of damage a parasite causes to its host) have mostly been studied independently. For example, a major assumption in the majority of models on the evolution of parasite virulence is that all hosts are equally susceptible. Reciprocally, virulence is often used as a fixed parameter in studies on the evolution of host resistance. In this paper we analyse how different forms of resistance may affect the evolution of virulence.

We considered two forms of resistance. First, the host could adopt a qualitative form of resistance which would prevent any infection by the parasite (i.e. resistant hosts cannot be infected at all). For instance, plants were shown to have resistance genes which totally prevent infection by pathogens or insects (see Thompson & Burdon (1992), for a review). In humans and domestic animals, vaccination protects individual hosts against some strains or species of parasites (see Anderson & May 1991).

Second, a quantitative form of resistance can be used to limit the deleterious effects induced by the parasites. In this case all the hosts can be infected by the parasites but more resistant ones are harmed less. For example, the host immune response provides a way of fighting against parasites within the host. Resistant hosts are ones which allocate more of their resources to their immune system. As a consequence, resistant hosts are more efficient in expelling parasites (e.g. their recovery rate) (Van Baalen 1998) and/or decreasing the within-host growth rate of the parasites. Since the within-host growth rate is often correlated with the deleterious effects of parasites (Ebert 1998; Mackinnon & Read 1999) such resistance would directly affect the virulence of the parasite on the host. Note that, with this type of resistance, parasite virulence has to be defined with respect to a particular type of host (e.g. fully susceptible hosts).

These two types of resistance could be viewed as two lines of defence (Van Baalen 1998), though throughout this paper we assume that hosts may use only one of the two mechanisms. Using the elegant formalism developed by Frank (1994, 1996), we show that these two forms of resistance have very different effects on the evolution of parasite virulence. Qualitative resistance selects for lower parasite virulence while quantitative resistance selects for higher virulence. This result leads us to a discussion of the potential evolutionary outcomes of host–parasite coevolution between virulence and different forms of host resistance (i.e. when host resistance is coevolving with parasite virulence).

In the following, we first present the model used by Frank (1994, 1996) in order to study the evolution of virulence when all hosts are equally susceptible. We then use a modified version of this model to analyse the effects of the qualitative and quantitative forms of resistance on the evolutionarily stable parasite virulence.

2. THE EVOLUTION OF PARASITE VIRULENCE ON SUSCEPTIBLE HOSTS

Virulence is classically viewed as a pleiotropic (by-product) effect of the host exploitation strategy by the parasite. Such exploitation is necessary for the parasite (e.g. for reproduction) but it harms the host. However, since the fates of both the parasite and its host are intimately linked, extreme host exploitation strategies also harm the parasite. Indeed, parasite virulence decreases the life expectancy of infected hosts and, consequently, the chances of being transmitted to new hosts. There is a trade-off between transmission and within-host exploitation. This selects for intermediate levels of parasite virulence (Levin & Pimentel 1981; Anderson & May 1982; Bremermann & Pickering 1983; May & Anderson 1983). The problem becomes more complicated if multiple infections by different strains of the parasite occur. Within-host competition selects for higher host exploitation strategies and, consequently, for higher virulence. Frank (1994, 1996) developed an elegant formalism for studying the evolution of parasite virulence when multiple infections occur.

In this model we assume that there is an infinite number of hosts all infected by the same number of parasites (N). The population of infected hosts can be viewed

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as a metapopulation of parasites. Parasites have the following life cycle.

(i) Parasites compete within individual hosts and their level of competitivity is v.
(ii) Such within-host competition harms the host and reduces the productivity of the whole group of parasites which share the same host. The level of virulence (i.e. the deleterious effect on fully susceptible hosts) is also measured with parameter v.
(iii) Parasites produce an infinite number of propagules, a fraction (d) of which disperse out of the host and try to infect a new randomly chosen individual in the host population (i.e. the island model of migration). This implies that all susceptible hosts are infected. During the transmission phase dispersed parasites incur the cost of dispersal (c).
(iv) Adult parasites die.
(v) Hosts are infected by philopatric (derived from the last generation in the same host) and immigrant parasites (due to infections from other infected hosts).

The direct fitness of individual parasite i which shares an infected host with group j of parasites can be written in the following way:

$$w_{ij} = \frac{v_{ij}}{v_j}(1 - v_j), \tag{1}$$

where v_{ij} measures the level of competitivity of individual i in group j of parasites and v_j is the average level of competitivity of group j of parasites. This equation further assumes that competitivity (i.e. host exploitation strategy) has a negative pleiotropic effect on the host (i.e. virulence) and, as a consequence, on the productivity of the group of parasites which share the same infected host. In other words, the first term in the right-hand side of equation (1) formalizes the conflict between parasites within an individual host, while the second describes the trade-off between virulence and transmission. The evolutionarily stable parasite competitivity (or virulence) can be easily derived from this equation (see Appendix A) (Frank 1994, 1996):

$$v^* = 1 - R, \tag{2}$$

where R is the coefficient of relatedness among parasites within infected hosts. This result highlights the importance of kin selection in the evolution of virulence. When parasites competing within a host are unrelated, selfish strategies are selected for and virulence increases. This model is consistent with more complex formulations (May & Nowak 1994, 1995; Nowak & May 1994; Van Baalen & Sabelis 1995; Gandon 1998) which also predict an increase in the evolutionarily stable level of virulence with a higher probability of multiple infections.

In the following we analyse the evolution of virulence when hosts can develop one of two different mechanisms of resistance.

3. QUALITATIVE RESISTANCE

Let us now assume that a proportion α of the hosts are qualitatively resistant, i.e. cannot be infected by parasites.

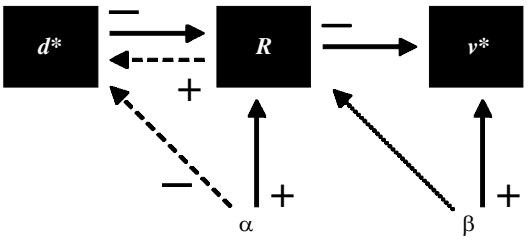

Figure 1. Schematic representation of the effects of qualitative (α) and quantitative (β) forms of resistance on the evolution of parasite virulence (v^*) and dispersal (d^*) strategies. Qualitative resistance only acts indirectly (via its effect on relatedness R) on the evolution of virulence while quantitative resistance acts directly. Quantitative resistance could in principle also act indirectly (dotted arrow) but our model does not take into account this effect. The sign by each arrow indicates the main effect of each factor. Dashed arrows represent the case where parasite dispersal is an evolving trait.

The direct fitness of the parasite is not affected by qualitative resistance. Indeed, qualitative resistance does not directly affect the within-host competition between parasites. This leads to the same evolutionarily stable level of virulence as when the population consisted only of susceptible individuals: $v^* = 1 - R$. However, the proportion of resistant hosts in the population reduces the probability of transmission of the parasite. Since transmission affects the relatedness among parasites within infected hosts, resistance acts indirectly on the evolution of virulence through its effect on the probability of multiple infections. In the following, we show how such indirect effects may affect the evolutionarily stable parasite virulence. Two different subcases will be considered depending on the ability of the parasite dispersal rate (i.e. transmission from one host to another) to evolve.

(a) *Dispersal as a fixed parameter*

We first assume that dispersal is a passive trait which does not evolve. In this situation qualitative resistance acts only through its effect on relatedness (see figure 1). If, for convenience, we further assume that parasites are haploid and asexual, the relatedness R can be derived from classical population genetics (see Appendix A, § (b)):

$$R = \frac{1}{\mathcal{N} - (\mathcal{N} - 1)(1 - m)^2}, \tag{3}$$

where m is the probability of immigration (i.e. the probability that a randomly chosen parasite has not been produced in this host; see Appendix A for an explicit expression of m).

At this stage of the derivation it is important to note that a qualitative form of resistance induces an extra cost of dispersal. Indeed, if there are many resistant hosts, a parasite has a very low probability of infecting a susceptible host. In the following, for the sake of simplicity, we assume that the only cost incurred during migration is due to qualitative resistance: $c = \alpha$. Replacing R in equation (2) by equation (3) we can derive the evolutionarily stable level of virulence as a function of $\mathcal{N}$, α and d. As shown in figure 2*a*, when α increases relatedness increases and, consequently, the evolutionarily stable virulence decreases.

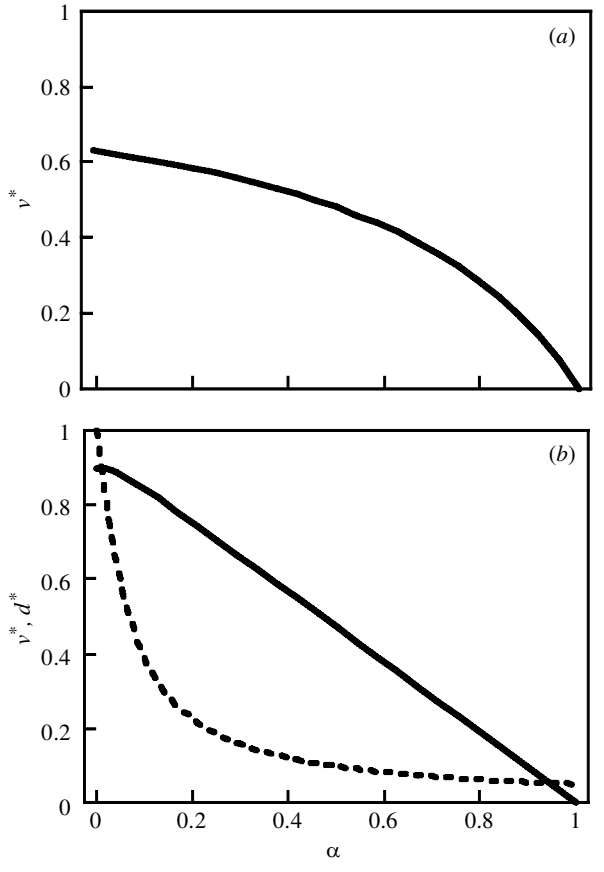

Figure 2. The effect of qualitative resistance (α) on the evolution of parasite virulence and dispersal. (*a*) The evolutionarily stable parasite virulence v^* plotted against qualitative resistance α for $N = 10$ and $d = 0.1$. (*b*) Parasite virulence and parasite dispersal coevolve. The evolutionarily stable virulence (v^*, continuous line) and dispersal (d^*, dashed line) strategies are plotted against qualitative resistance for $N = 10$.

(b) *Dispersal as an evolving trait*

In a second step we assume that the parasite dispersal rate is also evolving with parasite virulence. As shown by Frank (1986), the evolutionarily stable dispersal rate d^* depends on the cost of dispersal and on the intensity of kin competition within hosts:

$$d^* = \frac{R - c}{R - c^2}. \tag{4}$$

Combining equations (3) and (4) and substituting in $v^* = 1 - R$ leads to the evolutionarily stable level of virulence as a function of N and α. Figure 2*b* shows that the decrease in the optimal rate of virulence is more sensitive to the level of resistance when dispersal can evolve (see also Gandon 1998). This is due to an interesting feedback between resistance and the evolution of dispersal. An increase in α has a direct effect on relatedness but also an indirect one through a decrease in the evolutionarily stable dispersal rate. This enhances the increase in relatedness and, as a consequence, the decrease in evolutionarily stable virulence when α increases (compare figure 2*a*,*b*).

4. QUANTITATIVE RESISTANCE

We now assume that all the hosts have the same level of quantitative resistance, i.e. β. Therefore, parasite competitivity is reduced by a factor $(1 - \beta)$. Indeed, one can view quantitative resistance as the level of resources allocated to the immune system. A stronger immune response decreases the within-host growth rate of the parasite and, consequently, its competitive abilities. We assume that this form of resistance is not specific to particular parasitic strains, but rather that all parasites are equally affected. In this situation the direct fitness of an individual parasite has to be modified in the following way:

$$w_{ij} = \frac{v_{ij}}{v_j}(1 - (1 - \beta)v_j). \tag{5}$$

At the within-host level, the gain in fitness of individual parasite i from group j is still a function of v_{ij}/v_j because it is the relative gain in competitivity which matters. However, at the between-host level, the deleterious effect of the parasite will be decreased by a factor $(1 - \beta)$. This yields

$$v^* = \frac{1 - R}{1 - \beta}. \tag{6}$$

In other words, this form of host resistance acts directly on the evolution of virulence. The parasite evolves towards an increase in competitivity, which in turn results in an increase in virulence in order to compensate for the decrease in its growth rate due to host resistance. A similar argument was expounded by Fenner & Ratcliff (1965) and Fenner (1983) in their interpretation of the coevolution between the myxoma virus (the causative agent of myxomatosis) and the European rabbit *Oryctolagus cuniculus*. For example, Fenner (1983) wrote that '. . . one might expect increased genetic resistance to select for what in genetically unselected rabbits would be classed as more virulent strains of virus' (p. 269). Dwyer *et al.* (1990) summarized the argument behind this prediction in a very similar way as we have modelled it: '. . . ultimately viral virulence [i.e. on susceptible hosts] will increase as the resistance of the rabbit increases, at least if one assumes that the effect of increased host resistance within a rabbit is such that each strain essentially becomes less virulent [i.e. on resistant hosts]' (p. 426). We added the parts in brackets in the above citation to emphasize the need for a precise definition of virulence. Indeed, as pointed out by Fenner (1983), it is important to note that the evolutionarily stable virulence derived in equation (6) is measured on a fully susceptible host which is used as a referential (see point (ii) in the parasite's life cycle). At equilibrium, the deleterious effect induced by parasites on resistant hosts is

$$(1 - \beta)v^* = (1 - \beta)\frac{1 - R}{1 - \beta} = 1 - R. \tag{7}$$

Therefore, whatever the level of quantitative resistance, the parasite will evolve towards the same level of deleterious effect on its local host: $1 - R$. This can be seen as another illustration of the red queen metaphor: 'it takes all the running you can do to keep in the same place'.

The results of equations (6) and (7) have important implications for the detection of variability in the level of virulence induced by different strains (or populations) of parasites. Indeed, these results indicate that, if the deleterious effect of each strain is measured on the strain's local

hosts, then no variability will be detected. Such variability may be uncovered if infections are performed on non-local hosts. Interestingly, our definition of virulence was originally used by Fenner & Ratcliff (1965) in their study of the evolution of virulence of the myxoma virus in the rabbit. Because both the virus and host were undergoing evolutionary changes, Fenner & Ratcliff (1965) measured the virulence of field samples in terms of the case mortality induced in groups of rabbits from an unselected, laboratory strain of *Oryctolagus cuniculus* (i.e. the reference host population). These measures led Fenner & Ratcliff (1965) to classify virulence into five categories which they termed grades. This classification has proven to be very useful and has been largely adopted in subsequent studies on the evolution of virulence in Australia and in Europe.

5. DISCUSSION

Host–parasite interactions are characterized by different types of conflicts: first, an intraspecific conflict between parasites which share the same individual host and, second, when hosts are able to develop some resistance against their parasites, an interspecific conflict between hosts and parasites. Here, we incorporate both types of conflict into a single kin-selection model.

We found that the evolution of virulence is qualitatively affected by the mode of resistance (see figure 1). When resistance is qualitative we found that an increase in resistance decreases the evolutionarily stable virulence and this effect is even stronger when parasite dispersal coevolves with parasite virulence. A similar result was found by May & Nowak (1994) who used a structurally different model with superinfection and found that parasite virulence always decreases with a higher proportion of resistant hosts in the population. Contrary to qualitative resistance, an increase in quantitative resistance induces an increase in the evolutionarily stable virulence. This result is analogous to that obtained by Van Baalen (1998) who showed that a higher recovery rate (i.e. a special form of quantitative resistance) selects for higher parasite virulence (see also Frank 1994, 1996). Contrary to the present work, however, Van Baalen's (1998) model did not incorporate the effects of multiple infections. The qualitative agreement between our findings and those of the studies cited above indicates that these results are relatively insensitive to the details of the models.

The large difference in the outcomes of the two modes of resistance can be explained by the difference in their direct and indirect effects on the evolution of parasite virulence. First, only quantitative resistance directly affects the evolution of parasite virulence. Indeed, since qualitative resistance is an all-or-nothing response independent of the parasite's strategy, higher virulence does not allow the parasite to overcome qualitative resistance. In contrast, because higher virulence allows the parasite to avoid quantitative resistance at least partially, higher levels of quantitative resistance select for higher virulence.

Second, in the present model, only qualitative resistance indirectly affects the evolution of virulence. Indeed, increasing the number of resistant hosts decreases the risk of infection of susceptible hosts, a process known as 'herd immunity' (Anderson & May 1990). Our model highlights the evolutionary consequences of herd immunity. A higher proportion of resistant (or immune) hosts decreases the probability of multiple infections. Consequently, relatedness among parasites within infected hosts increases and virulence decreases. This suggests a double beneficial effect of herd immunity on hosts. First, a short-term advantage through a decrease in the risk of being infected. Second, a long-term advantage through a decrease in parasite virulence (Gandon & Michalakis 2000). It should also be noted that quantitative resistance may have indirect effects on the evolution of virulence as well (figure 1). Indeed, as soon as the quantitative resistance affects the parasite transmission rate, this mode of resistance should affect the force of infection (Frank 1998; Van Baalen 1998) and, consequently, the probability of multiple infection. However, this question would best be studied by an epidemiological model (Van Baalen & Sabelis 1995; Van Baalen 1998) which would model the force of infection explicitly.

(a) *Predictions and empirical evidence*

(i) *Qualitative resistance*

A possible prediction of the qualitative resistance model is that parasite populations issued from sites with a high frequency of resistant hosts should be less virulent than those parasite populations issued from sites with a low frequency of resistant hosts. This is a population property resulting from the two effects of herd immunity described above. It would be unwarranted to view this as an individual genotype property, equating high parasite infectivity with low host resistance, to predict that individual parasite genotypes able to infect many hosts should be more virulent than parasites of low infectivity. Indeed, the latter prediction would ignore the interactions between parasite genotypes on the evolution of virulence. We are unaware of any empirical study comparing parasite virulence in different host populations characterized by different levels of qualitative resistance. An alternative test of the effect of qualitative resistance would be to look at the evolution of the virulence of parasites which may have experienced strong selection pressures because of intensive vaccination campaigns. Indeed, since vaccination may confer qualitative resistance (at least for some time), according to our model, such vaccination campaigns may have selected for lower virulence.

(ii) *Quantitative resistance*

We expect virulence to increase when quantitative resistance increases. Again, the long-term study carried out on the coevolution between the myxoma virus and the rabbit *O. cuninculus* provides interesting information. It has been shown (see Dwyer *et al.* (1990), for a review) that, since 1970, the proportion of virulent strains (grades I and II in Fenner & Ratcliff's (1965) classification) isolated from the field in Australia has increased while low virulent strains (grade IV) have been declining. This could be due to the emergence of resistance in rabbit populations which could act as a selective pressure on the virus, tending to select for higher virulence grades of the virus. As pointed out by Anderson & May (1982), the above trend (evolution towards high virulence) is particularly apparent in Britain and Australia where the resistance of wild rabbits increased dramatically as compared to France. On a smaller spatial scale within the state of

Victoria (Australia), virus strains collected from the Mallee region in 1970–1974 were significantly more virulent than anywhere else in the state. In agreement with expectations, rabbits from the Mallee region had evolved resistance as early as 1966 while rabbits from other parts of Victoria showed no resistance at all (Ross 1982).

(b) *Host coevolution*

In this paper, we assumed host resistance to be fixed. In the first model there is a constant fraction of the population which is qualitatively resistant, while in the second model all hosts express the same level of quantitative resistance. The above evidence concerning the evolution of resistance of *O. cuninculus* against the myxoma virus suggests it might be particularly relevant to analyse the coevolution between host resistance and parasite virulence. Van Baalen (1998) obtained interesting results concerning the coevolution of parasite virulence and the host recovery rate. In particular he found that different evolutionary outcomes (coevolutionarily stable strategies, CoESSs) could be reached depending on the initial conditions. In the light of the present work it would be interesting to extend this analysis to (i) the case where multiple infections occur, and (ii) to a qualitative form of resistance.

Our results naturally lead to the question of the evolution of alternative forms of host resistance: under which conditions should hosts evolve qualitative versus quantitative resistance? Clearly, the evolutionary outcome will be highly dependent on (i) the short-term costs associated with each form of resistance, and (ii) on the long-term evolutionary consequences of each strategy through the evolution of parasite virulence. Note, however, that, since these two strategies are not mutually exclusive, it is very likely that the host will evolve both strategies at the same time. First, some form of qualitative resistance in order to try to prevent infection by the parasite and, second, some quantitative resistance against successful parasites. Indeed, plants develop both types of resistance against pathogens (e.g. Agrios 1997, pp. 122–124)

The main interest of this paper lies in the simple formalization of host–parasite interactions, allowing us to clarify the implications of different forms of host resistance on the evolution of parasite virulence. However, many aspects concerning the ecological feedback and epidemiology of such systems remain unclear (e.g. host coevolution and non-equilibrium dynamics). Future studies are needed to fill in these gaps.

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APPENDIX A

(a) *Derivation of evolutionarily stable parasite virulence*

Several kin selection models of parasite virulence have been developed by Frank (1994, 1996, 1998). In this appendix we detail the derivation of the evolutionarily stable parasite strategy in such models.

The direct fitness (w_{ij}) of an individual parasite depends on its own behaviour (v_{ij}) and on the average behaviour (v_j) of the other parasites which share the same infected host: $w_{ij} = w(v_{ij}, v_j)$. Different expressions of the direct fitness function are given in equations (1) and (5). The evolutionarily stable parasite strategy (v^*) can be derived from the direct fitness using the general approach developed by Taylor & Frank (1996).

Suppose that the behaviour of an individual is determined by its genotype and consider a monomorphic population with a constant genic value v^* at the behavioural locus (here we assume that the phenotype v^* is fully determined by the genic value). Select a random allele and mutate that allele and its identical-by-descent copies to a deviant value v. The condition for v^* to be evolutionarily stable is $\mathrm{d}w_{ij}/\mathrm{d}v|_{v=v^*} = 0$. Using the chain rule for the derivation of w yields

$$\frac{\mathrm{d}w_{ij}}{\mathrm{d}v} = \frac{\partial w_{ij}}{\partial v_{ij}}\frac{\mathrm{d}v_{ij}}{\mathrm{d}v} + \frac{\partial w_{ij}}{\partial v_j}\frac{\mathrm{d}v_j}{\mathrm{d}v}. \tag{A1}$$

Therefore, the condition for v^* to be evolutionarily stable becomes

$$\frac{\partial w_{ij}}{\partial v_{ij}} + \frac{\partial w_{ij}}{\partial v_j}R = 0, \tag{A2}$$

where $R = \mathrm{d}v_j/\mathrm{d}v_{ij}$ is the relatedness among parasites within the same infected host. This derivation yields the evolutionarily stable parasite virulence given in equations (2) and (6).

(b) *Derivation of relatedness*

Relatedness can be derived from classical identity by descent coefficients (Michod & Hamilton 1980; Taylor 1988; Taylor & Frank 1996). In our model, since parasites are assumed to be haploid and asexual, relatedness is simply equal to the probability of identity $\hat{f}$ between homologous genes in two parasites randomly chosen in the same infected host before parasite dispersal (before step (v) in the parasite's life cycle). This probability of identity at equilibrium (the hat indicates an equilibrium value) can be derived from the following recurrence equation:

$$f' = \frac{1}{N} + \frac{N-1}{N}(1-m)^2 f, \tag{A3}$$

where the prime indicates the value of f in the next generation and m is the parasite immigration rate: $m = (1-c)d/(1-cd)$. At equilibrium, this yields the value of $\hat{f} = R$ given in equation (3).

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