A kin selection model for the evolution of virulence

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SUMMARY

The costs and benefits of parasite virulence are analysed in an evolutionarily stable strategy (ESS) model. Increased host mortality caused by disease (virulence) reduces a parasite's fitness by damaging its food supply. The fitness costs of high virulence may be offset by the benefits of increased transmission or ability to withstand the host's defences. It has been suggested that multiple infections lead to higher virulence because of competition among parasite strains within a host. A quantitative prediction is given for the ESS virulence rate as a function of the coefficient of relatedness among co-infecting strains. The prediction depends on the quantitative relation between the costs of virulence and the benefits of transmission or avoidance of host defences. The particular mechanisms by which parasites can increase their transmission or avoid host defences also have a key role in the evolution of virulence when there are multiple infections.

Parasites face a tradeoff between damaging their hosts (virulence), which destroys their food supply, and the benefits of rapid growth and transmission. Levin & Pimental (1981) showed that intermediate levels of virulence are often favoured when the advantages of high transmission rate are offset by the costs of high virulence. Similarly, Anderson & May (1982, 1991; May & Anderson 1983) showed that a tradeoff between virulence and the host's ability to purge itself of infection (recovery rate) can favour the evolution of intermediate levels of virulence. Finally, Bremermann & Pickering (1983) and Knolle (1989) have shown that competition among parasites within a host can favour the evolution of increased virulence. In this case the group of co-infecting parasites may gain by sparing the host, but competition among parasites within the group favours high transmission and greater virulence.

I present a simple model for the evolution of virulence. This model is useful in two ways. First, specific quantitative predictions are given for the relation between the genetic variability among co-infecting strains and the evolution of virulence. This is important because genetic variability, rather than the number of co-infecting strains (Bremermann & Pickering 1983; Knolle 1989), determines how virulence evolves. In addition, genetic variability of parasites within a host is easier to measure than the number of co-infecting strains.

The second contribution of this model is that it focuses attention on the mechanisms by which a parasite increases its transmission or avoids the host's defences. For example, if the mechanism of transmission is a sneeze, and all parasites within a host gain equally from an increased rate of sneezing, then relatedness among co-infecting strains does not influence the evolution of virulence. This point will be made more precisely later.

Anderson & May (1981, 1982) have shown that qualitative aspects of host–parasite co-evolution can be derived from analysis of the basic reproductive rate of a parasite (see also Dietz 1975, 1976; Yorke *et al.* 1979). For a standard set of dynamic equations that link the numbers of susceptible, infected, and recovered and immune hosts according to demographic properties of the parasite, the basic reproductive rate of the parasite is

$$R = \beta(\alpha)\, N/[d+\alpha+v(\alpha)], \tag{1}$$

where d is the host's disease-free mortality rate, α is the disease-induced mortality rate (virulence), $v(\alpha)$ is the rate at which hosts recover from disease and become immune to further infection, $\beta(\alpha)$ is the transmission rate of disease upon contact between infected and susceptible hosts, and N is the total population size of the host.

Now suppose that parasites differ in their virulence, $\alpha_g = \alpha + \delta g$, where g is the additive genotypic value of a parasite and δ is the effect of genotypic value on virulence. The virulence caused by a mixed infection of different parasite strains within a single host is $\alpha_{g'} = \alpha + \delta g'$, where g' is the average genotypic value of the group of co-infecting parasites. Thus the basic reproductive rate of a parasite with genotypic value g is

$$R_g = \beta(\alpha_g)\, N/[d+\alpha_{g'}+v(\alpha_g)], \tag{2}$$

where virulence, $\alpha_{g'}$, is determined by the aggregate genotype of the mixed infection. Transmission, $\beta(\alpha_g)$, and the rate at which the host purges itself of infection by genotype g, $v(\alpha_g)$, are here assumed to be properties of the individual parasite's genotype. Alternatively, transmission or recovery may be properties of the aggregate genotype of the infection: this will be considered below. In any case, the basic reproductive rate of a group of parasites infecting a single host is

$$R_{g'} = \beta(\alpha_{g'})\, N/[d+\alpha_{g'}+v(\alpha_{g'})]. \tag{3}$$

The Price equation is the most powerful method for analysing selection when there is genetic substructuring

in populations (Price 1970, 1972; Hamilton 1970, 1975; Grafen 1985; Taylor 1988; Queller 1992). The particular techniques that I use are based on the evolutionarily stable strategy (ESS) method (Maynard Smith & Price 1973; Maynard Smith 1982). Application of the Price equation to ESS problems is explained in Frank (1986, 1987). The Price equation can be written as

$$\bar{R}\Delta\bar{g} = \mathrm{Cov}_{g'}(R_{g'}, g') + \mathrm{E}_{g'}[\mathrm{Cov}_{g\cdot g'}(R_g, g)],$$

where $\bar{R}$ and $\bar{g}$ are, respectively, population averages for basic reproductive rate (fitness) and genotypic value, $\mathrm{Cov}_{g'}$ and $\mathrm{E}_{g'}$ are the covariance and expectation over hosts each of which is infected by parasite mixtures with average genotypic values g', and $\mathrm{Cov}_{g\cdot g'}$ is the covariance over genotype g when group genotype g' is held constant.

The ESS virulence rate, α^*, is obtained by solving

$$\left.\frac{\partial\bar{R}\Delta\bar{g}}{\partial\delta}\right|_{\delta=0} = 0,$$

which yields

$$\frac{\partial\beta(\alpha)}{\partial\alpha}(d+\alpha^*+v(\alpha^*)) - \beta(\alpha^*)\left(r+\frac{\partial v(\alpha)}{\partial\alpha}\right) = 0, \qquad (4)$$

where the partial derivatives are evaluated at $\alpha = \alpha^*$, and

$$r = \mathrm{Cov}(g', g)/\mathrm{Cov}(g, g)$$

is the regression coefficient of relatedness from kin selection theory, which is the slope of group genotypic value, g', on individual genotypic value, g (Hamilton 1972; Queller 1992).

Specific functional forms are useful for analysing equation (4):

$$\beta(\alpha) = b\alpha^k,$$
$$v(\alpha) = \gamma/\alpha^m.$$

Here transmission, β, increases with virulence, imposing a tradeoff between a parasite's survival and transmission. Host recovery, v, decreases with virulence, imposing a tradeoff for the parasite between length of stay within a living host and loss of the host through death from disease.

If the only tradeoff is between transmission and virulence, $m = 0$, then

$$\alpha^* = k(d+\gamma)/(r-k) \quad r > k$$
$$\to\infty \qquad\qquad r \leqslant k, \qquad (5)$$

which is a generalization of the formula given by Bremermann & Pickering (1983) for single-strain infections in which $r = 1$. Equation (5) shows the quantitative relationships among relatedness of co-infecting strains, r, the rate of change in transmission with virulence, k, and the expected patterns of virulence evolution, α^* (figure 1).

Note in equation (5) that virulence is favoured to be as large as possible when $r < k$. This result is a generalization of Anderson & May's (1982) comment that large virulence is favoured when transmission increases at a greater than linear rate with increasing virulence, $k > 1$, for the special case of one strain per infection, $r = 1$. If n co-infecting strains are unrelated and equally abundant in the inoculum, then $r = 1/n$, and virulence is favoured to be as large as possible for $k > 1/n$. This supports Bremermann & Pickering's (1983) and Knolle's (1989) conclusion that virulence is expected to be large for mixed infections.

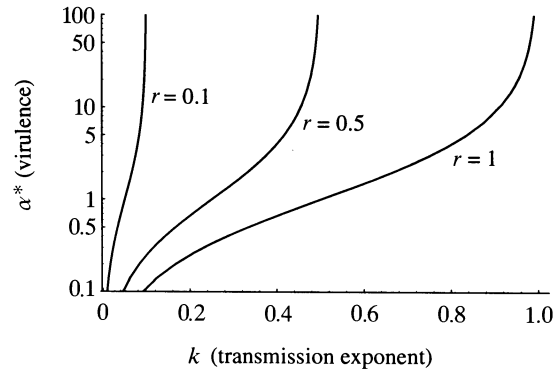

Figure 1. Predicted level of virulence as a function of relatedness, r, and the exponent k in the relation between transmission and virulence, $\beta(\alpha) = b\alpha^k$. The figure is based on equation (5) with $d+\gamma = 1$.

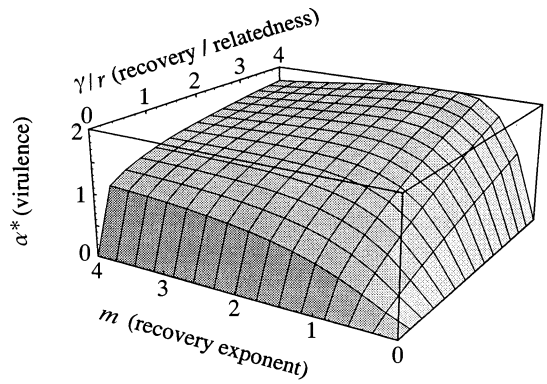

Figure 2. Predicted level of virulence based on the tradeoff between virulence and recovery rate given by $v(\alpha) = \gamma/\alpha^m$. The figure is based on equation (6).

These results for the tradeoff between transmission and virulence depend on the assumption that transmission is a property of each genotype in a mixed infection rather than of the aggregate genotype. If, however, transmission increased with the number of lesions formed, and each genotype gained equally from each lesion, then transmission would be a property of the aggregate. The term $\beta(\alpha_g)$ would be replaced by $\beta(\alpha_{g'})$ in equation (2) and, following through, the solution would be obtained by setting $r = 1$ in equation (5). In this case there would be no conflict among parasite strains within a host, and the evolution of virulence would be independent of the relatedness among co-infecting strains.

If the only tradeoff is between recovery rate and virulence, $k = 0$, then

$$\alpha^* = (\gamma m/r)^{1/(m+1)}. \qquad (6)$$

This tradeoff has a strongly stabilizing effect on virulence (figure 2), as noted by Anderson & May (1982, 1991). As in the previous case, this result depends on benefits accruing separately to each strain.

If, however, the host immune response acts indiscriminately against the different strains, then the host recovery term depends on the aggregate genotype. In this case the term $v(\alpha_g)$ would be replaced by $v(\alpha_{g'})$ in equation (2) and, following through, the solution would be obtained by setting $r = 1$ in equation (6). As in the transmission case, dependence only on the aggregate genotype removes the conflict among strains and reduces the predicted level of virulence in multiple infections.

In these models it has been assumed that the relatedness, r, among co-infecting strains is the same for all hosts. If r varies, and parasites are not able to detect any correlates for the value of r within their hosts, then the results would depend on some sort of averaging of r among hosts.

Alternatively, if parasites can obtain some information about the number of infections within their host, then they are expected to adjust their virulence level to the local value of r in accord with the general predictions of the models given above. This type of conditional behaviour in response to variable levels of relatedness within hosts is well understood for the sex ratios of parasitic wasps (Werren 1980; Frank 1985; Herre 1985; Orzack *et al.* 1991). Whether infectious parasites adjust their virulence in response to multiple infection is not known at present. The wide range of virulence among malarial strains, and recent discussions about co-infection and population structure for this disease (Read *et al.* 1992), suggest that malaria may be a good system in which to pursue the relation between relatedness and virulence (Bremermann & Pickering 1983).

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