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# Superinfection and the evolution of parasite virulence

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## SUMMARY

Earlier ideas that parasites evolve toward becoming harmless to their hosts have, in recent years, given way to more analytic studies, focused on the ‘basic reproductive rate’,  $R_0$ , of individual parasites. In general, the biology of the parasite life cycle will lead to constraining relations between virulence (parasite-associated host death or reduction in fertility) and transmissibility: the maximum  $R_0$  may then be attained by virulence being high, or low, or at some intermediate level, depending on the details of the constraining relations.

Such studies have not generally included superinfection (where an already-infected host is infected by another parasite). Here we propose a general, but simple, model of superinfection, which is amenable to analytical treatment. In such models selection does not simply act to maximize  $R_0$ ; superinfection leads to selection for higher levels of virulence, highly polymorphic parasite populations and very complicated dynamics. We calculate the equilibrium distribution of parasite strains and the maximum level of virulence that can be maintained by superinfection. We also note the equivalence between our ‘superinfection model’ and recent approaches to the study of the meta-population dynamics of multi-species interactions.

## 1. INTRODUCTION

The ‘conventional wisdom’ that successful parasites have to become benign is not based on exact evolutionary thinking. Rather than minimizing virulence, selection will work to increase a parasite’s reproductive rate. If the rate of transmission is linked to virulence (which we define as increased mortality due to infection), then selection may in some circumstances lead to intermediate levels of virulence, or even to ever-increasing virulence (May & Anderson 1979, 1983, 1990; Anderson & May 1991).

A much-cited example of evolution towards reduced virulence is the Australian myxomatosis-rabbit system (Fenner & Ratcliffe 1965; but see Anderson & May 1982, 1991). A more recent example is the observation that long-standing primate lentivirus associations are apathogenic (simian immunodeficiency virus and african green monkeys may have been coevolving for millions of years), whereas the human immunodeficiency virus causes disease in humans. However, there are also cases where long-standing host–parasite systems have not evolved to become harmless. An elegant and illuminating example is Herre’s (1993) study of nematodes of fig wasps; these nematodes have a clearly detrimental effect on their wasp host, despite the observation that fig wasps preserved in 20 million-year-old amber have already been infected by nematodes.

Several mathematical models have been developed to explore theoretical aspects of the evolution of virulence (May & Anderson 1979, 1983, 1990; Anderson & May 1981, 1982; Levin & Pimentel 1981; Levin 1982; Seger 1988; Seger & Hamilton 1988;

Knolle 1989; Frank 1992; Lenski & May 1993; Antia *et al.* 1994). Bremermann & Thieme (1989) have established a ‘competitive exclusion’ principle, which states that only the strain with maximum basic reproductive rate can survive under quite general conditions.

In general these models exclude the possibility of superinfection, whereby an already infected host can be infected by another parasite strain. There are some interesting exceptions. Levin & Pimentel (1981) and Levin (1983*a, b*) have analysed two-strain models with superinfection, where the more virulent strain can take over a host infected by the less virulent strain. They found conditions for coexistence between the two strains. Their model is in fact a two-strain version of a more general approach we are going to present here. Bremermann & Pickering (1983) have looked at competition between parasite strains within a host, and concluded that selection will always favour the most virulent strain. Frank (1992) has analysed a model for the evolutionarily stable level of virulence if there is a trade-off between virulence and infectivity, and if infection occurs with an ensemble of related parasite strains.

These models do not generally include vertical infection (i.e. the transmission of parasites from infected parent to offspring). Clearly the mode of transmission is very important for the evolution of virulence (May & Anderson 1979; Anderson & May 1981; Stewart & Levin 1984; Levin & Lenski 1985; Bull & Molineux 1991, 1992; Ewald 1993; Herre 1993; Read & Harvey 1993). Vertically transmitted parasites should be less virulent. There are some mathematical models for vertical transmission. Stewart & Levin (1984) discuss

different conditions for the evolution and maintainance of temperate and virulent phages in a model where phage reproduction can occur via infection of new cells or (vertically) via cell division. Nowak (1991) showed that vertical transmission can lead to complicated selective dynamics even for very simple models. Here selection need not optimize  $R_0$ . Yamamura (1993) analyses a host-parasite coevolution model, where vertical transmission leads to a reduction of parasite virulence. We refer also to Anderson & May (1991) and Busenberg & Cooke (1993) for more general surveys of epidemiological models for disease with vertical transmission.

The present paper is about parasite evolution (with 'parasite' defined broadly to include viruses, bacteria, protozoans, helminth and arthropod parasites). We assume that the host does not evolve (at least on timescales of interest to parasite evolution). We explore the selective forces acting on the parasite population. We break new ground by considering the evolutionary dynamics of a heterogeneous population of many different parasite strains (with many different degrees of virulence) and including superinfection. In our approach 'superinfection' means that a more virulent parasite can infect and 'take over' a host that is already infected by a less virulent parasite strain. Thus we equate virulence with a competitive advantage for the intra-host dynamics. We also do not consider the possibility that a particular host is infected by (and infectious for) more than one parasite strain at any given time. We propose to call this later situation 'coinfection' as opposed to superinfection.

We will show that superinfection shifts the average level of virulence above what would be optimal for the parasite population as a whole (here 'optimal' is used in the sense of maximum basic reproductive rate of the parasite). Superinfection also generates and maintains polymorphisms. We find complicated equilibrium distributions for the frequency of different parasite strains within a certain well-defined range of virulence. Under some circumstances we also find complicated oscillations (heteroclinic cycles).

Our intention here is to study the effect of superinfection on the evolution of virulence and we therefore neglect vertical transmission; we plan to study vertical transmission and a combination of superinfection and vertical transmission in a later paper.

## 2. THE BASIC MODEL WITHOUT SUPERINFECTION

The basic epidemiological dynamics of a host-parasite interaction can be described by the following ordinary differential equation (Kermack & McKendrick 1933; Bailey 1975; Anderson & May 1979, 1991)

$$\begin{aligned} dx/dt &= k - ux - \beta xy, \\ dy/dt &= y(\beta x - u - v). \end{aligned} \quad (1)$$

Uninfected and infected hosts are denoted by  $x$  and  $y$ , respectively. In the absence of the parasite, the host population is regulated by a simple immigration-death process, with  $k$  specifying the constant immigration

rate of uninfected hosts and  $u$  their natural death rate (this represents a simple, if somewhat artificial, way of attaining a stable host population in the absence of infection). Infected hosts transmit the parasite to uninfected hosts at the rate  $\beta xy$ , where  $\beta$  is the rate constant characterising the parasite's infectivity. Infected hosts die at an increased rate,  $u + v$ . The parameter,  $v$ , defines the virulence of the infection.

The basic reproductive rate of the parasite is defined as the number of new infections caused by a single infected host if introduced in a population of uninfected hosts (Anderson & May 1979, 1991, see also Diekmann *et al.* 1990). For equation (1) this is

$$R_0 = [\beta/(u+v)](k/u). \quad (2)$$

If  $R_0$  is larger than one, then the parasite will spread in an initially uninfected population, and damped oscillations will lead to the stable equilibrium

$$x^* = (u+v)/\beta, \quad y^* = [\beta k - u(u+v)]/\beta(u+v). \quad (3)$$

To understand parasite evolution we have to study the epidemiological dynamics of two parasite strains competing for the same host. Obviously a rigorous analysis requires the full apparatus of population genetics; our analysis in terms of 'strains' corresponds to a phenotypic or haploid model of evolution, and gives a feeling for the essentials. From equation (1) we obtain (see also May & Anderson 1983; Bremermann & Thieme 1989)

$$\begin{aligned} dx/dt &= k - ux - x(\beta_1 y_1 + \beta_2 y_2), \\ dy_1/dt &= y_1(\beta_1 x - u - v_1), \\ dy_2/dt &= y_2(\beta_2 x - u - v_2). \end{aligned} \quad (4)$$

The two parasite strains differ in their infectivity,  $\beta_1$  and  $\beta_2$ , and their degree of virulence,  $v_1$  and  $v_2$ . From equation (4) we see that coexistence between the two parasites is not possible. For a generic choice of parameters there is no interior equilibrium. If both parasite strains have  $R_0 > 1$ , we find that strain 2 always outcompetes strain 1 if

$$\beta_2/(u+v_2) > \beta_1/(u+v_1). \quad (5)$$

This is exactly the condition that the transversal eigenvalue  $\lambda_2 = \partial y_2 / \partial y_2$  at the equilibrium  $E_1(x^*, y_1^*, y_2 = 0)$  is positive while the transversal eigenvalue  $\lambda_1 = \partial y_1 / \partial y_1$  at the equilibrium  $E_2(x^*, y_1 = 0, y_2^*)$  is negative; that is 2 can invade 1, but 1 cannot invade 2. Equilibrium  $E_2$  is globally stable. This means that (i) strain 2 can spread in a population that consists only of uninfected hosts and hosts infected with strain 1, and (ii) that strain 1 will eventually be eliminated from the population.

Condition (5) also implies that the strain with higher basic reproductive rate will win. Thus evolution will tend to maximize  $R_0$ . If there is no relation between infectivity and virulence, then the evolutionary dynamics will increase  $\beta$  and reduce  $v$ . Such an implausibly constraint-free situation represents the 'conventional wisdom', whereby infectious diseases will evolve to become less virulent.

In general, however, we expect some relationship between  $v$  and  $\beta$ ; usually the harm done to hosts ( $v$ ) is

associated with producing transmission stages ( $\beta$ ). For certain functional relations between  $v$  and  $\beta$  there is an evolutionary stable degree of virulence, corresponding to the maximum value of  $R_0$ . Other situations allow evolution towards the extreme values of very high or low virulences. The detailed dynamics depends on the shape of  $\beta$  as a function of  $v$ . It is interesting to note that along some trajectories where virulence increases, parasite evolution can lead to lower and lower parasite population sizes (in terms of total number of infected hosts).

### 3. A MODEL FOR SUPERINFECTION

In this section we expand the basic model to allow for superinfection. We will consider a heterogeneous parasite population with a range of different virulences, and assume that more virulent strains can outcompete less virulent strains on the level of intra-host competition. For simplicity we assume that the infection of

a single host is always dominated by a single parasite strain. Thus in our framework superinfection means that a more virulent strain takes over a host infected by a less virulent strain. This can be described by the following system of differential equations:

$$\begin{aligned} \frac{dx}{dt} &= k - ux - x \sum_{i=1}^n \beta_i y_i, \\ \frac{dy_i}{dt} &= y_i (\beta_i x - u - v_i + s \beta_i \sum_{j=1}^{i-1} y_j - s \sum_{j=i+1}^n \beta_j y_j) \end{aligned} \tag{6}$$

$i = 1, \dots, n.$

Here  $v_i$  denotes the virulence of strain  $i$ , and we assume that  $v_1 < v_2 < \dots < v_n$ . Thus a more virulent strain can superinfect a host already infected with a less virulent strain. The parameter,  $s$ , describes the rate at which superinfection occurs relative to infection of uninfected hosts. If either the host or the parasite have evolved mechanisms to make superinfection more difficult, then  $s$  would be smaller than one. (In this context, the superinfection parameter  $s$  can also be interpreted as the effect of cross-reactive immunity among different parasite strains. Gupta & Anderson (1994) have developed a model for the transmission dynamics of malaria with a number of different strains and including cross-reactive immunity.) If already-infected hosts are more susceptible to acquiring a second infection (with another strain), then  $s > 1$ , i.e. superinfection occurs at increased rates.

For the numerical simulations (in figures 1 and 2) we assume a specific relation between virulence and infectivity,  $\beta_i = av_i/(c + v_i)$ . For low virulence, infectivity increases linearly with virulence; for high virulence the infectivity saturates. For the basic reproductive rate this means that, for strain  $i$ :

$$R_{0,i} = akv_i/u(c + v_i)(u + v_i). \tag{7}$$

The optimal virulence, which maximizes  $R_0$ , is given by  $v_{opt} = \sqrt{cu}$ . Figures 1 and 2 show the equilibrium population structure of the parasite for various values of  $s$  between 0 and 2. For both simulations we have assumed  $k = 1, u = 1$  and  $\beta_i = 8v_i/(1 + v_i)$ . For figure 1 we simulated  $n = 50$  strains of parasites with virulences regularly spaced between 0 and 5. Hence  $v_1 = 0.1, v_2 = 0.2$  up to  $v_{50} = 5$ . For this choice of parameters the strain with  $v_{10} = 1$  has the largest  $R_0$ . We find that this strain is indeed selected in the absence of superinfection,  $s = 0$ . If superinfection is possible ( $s > 0$ ), then there is selection of an ensemble of strains with a range of virulences between two boundaries  $v_{min}$  and  $v_{max}$ , with  $v_{min} > v_{opt}$ .

Thus superinfection has two important effects: (i) it shifts parasite virulence to higher levels, beyond the level that would maximize the parasite reproductive rate; and (ii) it leads to a coexistence between a number of different parasite strains with a range of virulences. Note the funny ups and downs in the equilibrium densities of strains. Often we find that exactly every second strain becomes extinct or is only present at very low frequencies.

For figure 2 we have  $n = 100$  strains of parasite with randomly chosen virulences within the interval (0, 5).

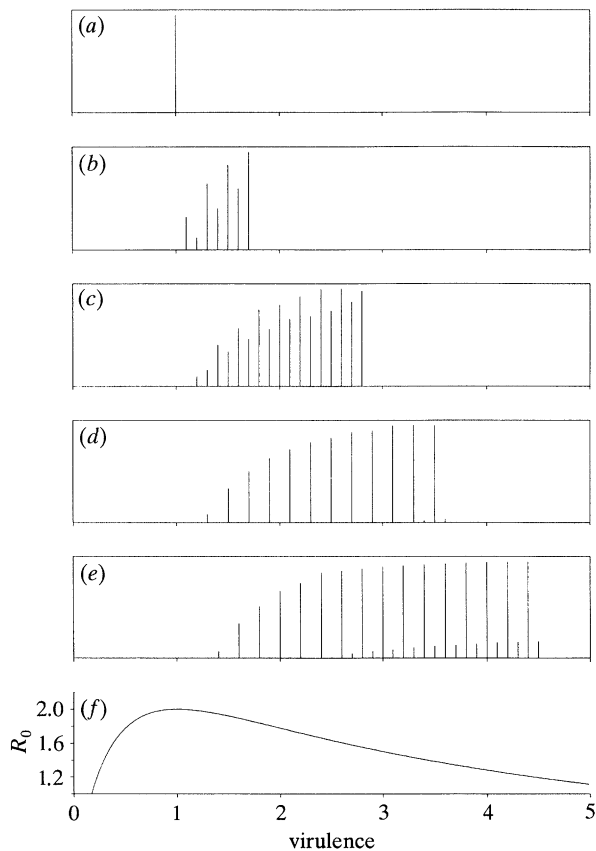


Figure 1. The equilibrium distribution of parasite strains with different virulences. The simulation is performed according to equation (6) with  $k = 1, u = 1, n = 50, \beta_i = 8v_i/(1 + v_i)$ . (a)  $s = 0$ ; (b)  $s = 0.1$ ; (c)  $s = 0.5$ ; (d)  $s = 1$ ; (e)  $s = 2$ ; (f) effect of virulence on  $R_0$ . The individual  $v_i$  are regularly spaced between 0 and 5. Thus  $v_1 = 0.1, v_2 = 0.2, \dots, v_{50} = 5$ . In the absence of superinfection ( $s = 0$ ) the strain with maximum basic reproductive rate,  $R_0$ , is selected. With superinfection ( $s > 0$ ) we find coexistence of many different strains with different virulences,  $v_i$ , within a range  $v_{min}$  and  $v_{max}$ , but the strain with the largest  $R_0$  is not selected; superinfection does not maximise parasite reproduction. For increasing  $s$ , the values of  $v_{min}$  and  $v_{max}$  also increase. The  $x$ -axis denotes virulence, the  $y$ -axis indicate equilibrium frequencies (always scaled to the same largest value).

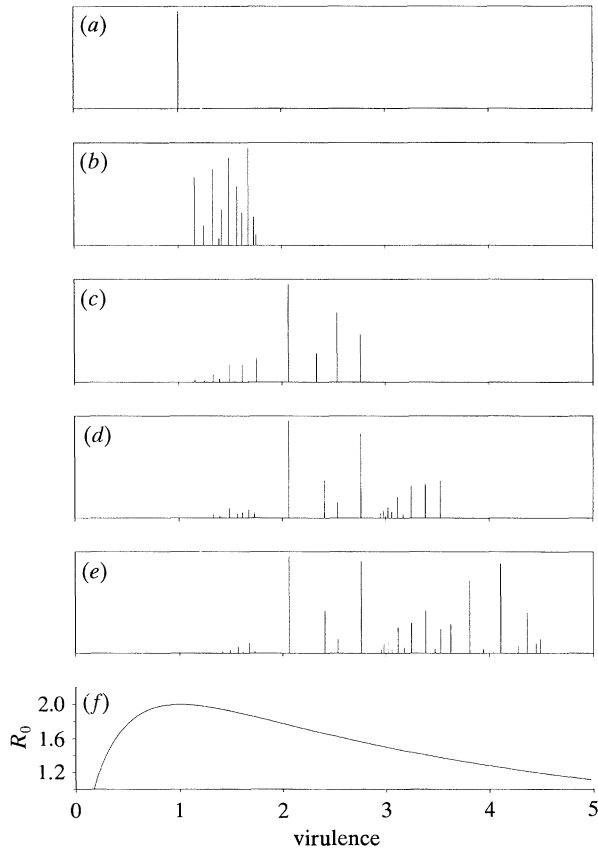


Figure 2. As for figure 1, except  $n = 100$  strains have been randomly distributed over the virulence interval  $(0, 5)$ . Again we find complex equilibrium distributions, with strains surviving if their virulence is within a well defined range. Again superinfection increases the average level of virulence. (a)  $s = 0$ ; (b)  $s = 0.1$ ; (c)  $s = 0.5$ ; (d)  $s = 1$ ; (e)  $s = 2$ ; (f) effect of virulence on  $R_0$ .

We find qualitatively similar results. Without superinfection,  $s = 0$ , the strain with the largest  $R_0$  will be selected and all others become extinct. For  $s > 0$  we find irregular equilibrium distributions between the same values  $v_{\min}$  and  $v_{\max}$  as in the simulation with regularly spaced virulence. Strains have a higher equilibrium frequency if the strains with slightly larger virulences have low frequencies. Conversely below a strain with very high frequency, strains are extinct or at very low frequencies. What determines such an equilibrium? Can we understand such complex equilibrium structures?

#### 4. AN ANALYTICAL MODEL FOR SUPERINFECTION

In this section we derive an analytical understanding of the complexities introduced by superinfection. Without losing the essential features of the model we will simplify equation (6) to

$$\begin{aligned} \frac{dx}{dt} &= uy + \sum_{i=1}^n v_i y_i - x \sum_{i=1}^n \beta_i y_i, \\ \frac{dy_i}{dt} &= y_i [\beta_i x - v_i - u + s(\beta_i \sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^n \beta_j y_j)] \end{aligned} \quad (8)$$

$$i = 1, \dots, n.$$

The total number of infected hosts is given by  $y = \sum_{i=1}^n y_i$ . We assume that immigration of uninfected hosts exactly balances the death of uninfected or infected hosts,  $k = ux + uy + \sum v_i y_i$ . Without loss of generality we can then set  $x + y = 1$ . This leads to the system of  $n$  equations (with  $\sum_{i=1}^n y_i \leq 1$ )

$$\frac{dy_i}{dt} = y_i [\beta_i (1 - y) - u - v_i + s(\beta_i \sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^n \beta_j y_j)] \quad i = 1, \dots, n. \quad (9)$$

This is a Lotka-Volterra system of equations

$$\frac{dy_i}{dt} = y_i (R_i + \sum_{j=1}^n A_{ij} y_j) \quad i = 1, \dots, n, \quad (10)$$

with  $R_i = \beta_i - v_i - u$  and the matrix given by

$$A = - \begin{pmatrix} \beta_1 & \beta_1 + s\beta_2 & \beta_1 + s\beta_3 & \cdots & \beta_1 + s\beta_n \\ \beta_2(1-s) & \beta_2 & \beta_2 + s\beta_3 & \cdots & \beta_2 + s\beta_n \\ \beta_3(1-s) & \beta_3(1-s) & \beta_3 & \cdots & \beta_3 + s\beta_n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \beta_n(1-s) & \beta_n(1-s) & \beta_n(1-s) & \cdots & \beta_n \end{pmatrix}. \quad (11)$$

For an analytic understanding, we take the limit  $c \rightarrow \infty$  in our expression for  $\beta_i = av_i/(c + v_i)$ . All parasite strains then have the same infectivity,  $\beta$ , and differ only in their degree of virulence,  $v_i$ . We obtain

$$\frac{dy_i}{dt} = y_i \beta \left[ 1 - y - \frac{v_i + u}{\beta} + s \left( \sum_{j=1}^{i-1} y_j - \sum_{j=i+1}^n y_j \right) \right] \quad i = 1, \dots, n. \quad (12)$$

This is a Lotka-Volterra system with  $R_i = \beta - v_i - u$  and

$$A = -\beta \begin{pmatrix} 1 & 1+s & 1+s & \cdots & 1+s \\ 1-s & 1 & 1+s & \cdots & 1+s \\ 1-s & 1-s & 1 & \cdots & 1+s \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1-s & 1-s & 1-s & \cdots & 1 \end{pmatrix}. \quad (13)$$

Because  $A + A^t$  (where  $A^t$  is the transposed matrix of  $A$ ) is, up to the multiplicative factor  $-\beta$ , the  $n \times n$  matrix whose entries are all equal to 1, it follows that it is negative definite (although not strictly so). A simple variant of the proof in chapter 21.3 of Hofbauer & Sigmund (1988) shows that (12) has only one globally stable fixed point, i.e. one equilibrium which attracts all orbits from the interior of the positive orthant. If this equilibrium lies on a face of the positive orthant, then it also attracts all orbits from the interior of the face.

Equation (12) can be rewritten in the following way

$$dy_i/dt = y_i \beta [f_i - sy_i], \quad (14)$$

with

$$f_i = 1 - \frac{v_i + u}{\beta} - (1-s)y - 2s \sum_{j=i+1}^n y_j. \quad (15)$$

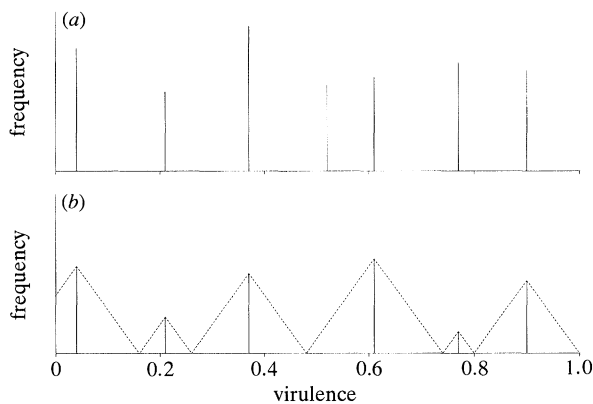


Figure 3. For  $s = 1$  there is a simple geometric method to construct the equilibrium configuration (using triangles or circles). (a) Starting configuration; (b) equilibrium configuration. Suppose there are  $n$  strains, given by their virulences  $v_1, \dots, v_n$  all between 0 and 1. Consider virulence on the  $x$ -axis versus frequency on the  $y$ -axis. Start by drawing vertical lines at  $v_1, v_2, \dots, v_n$ . Draw a  $45^\circ$  line running up to the left from  $v = 1$ ; the intersection with the vertical line at  $v_n$  determines  $y_n$ . This corresponds to  $y_n = 1 - v_n$ . Now mirror the constructed triangle at the axis given by the vertical line at  $v_n$ . The intersection of the downward pointing  $45^\circ$  line with the baseline determines the point  $v = 1 - 2y_n$ . Now there are two possibilities: (i) either  $v_{n-1} < v$ , in which case draw a new  $45^\circ$  line upwards to the left from  $v$ ; the intersection with the vertical line at  $v_{n-1}$  gives  $y_{n-1}$ ; this corresponds to  $y_{n-1} = v_n - v_{n-1} - (1 - v_n)$ ; or (ii)  $v_{n-1} > v$ , in which case the strain  $n-1$  will not be present at equilibrium and the construction method proceeds directly with strain  $v_{n-2}$ ; and so on. Figure 3 is self-explaining. In the figure we chose seven strains with arbitrary virulences. Six of these strains are present at equilibrium.

All possible equilibrium points of equation (14) are given by the following relations:

$$\begin{aligned} y_1 &= 0 \quad \text{or} \quad y_1 = f_1/s, \\ y_2 &= 0 \quad \text{or} \quad y_2 = f_2/s, \\ &\vdots \\ y_n &= 0 \quad \text{or} \quad y_n = f_n/s. \end{aligned} \quad (16)$$

Note that each  $f_i$  only depends on the total sum  $y$  and all  $y_j$  with  $j > i$ . Supposing we know  $y$ , then we can construct a specific equilibrium point in a recursive 'top-down' way:

$$\begin{aligned} y_n &= \max\{0, f_n/s\}, \\ y_{n-1} &= \max\{0, f_{n-1}/s\}, \\ y_{n-2} &= \max\{0, f_{n-2}/s\}, \\ &\vdots \\ y_1 &= \max\{0, f_1/s\}. \end{aligned} \quad (17)$$

The notation  $\max\{.,.\}$  simply denotes the larger of the two numbers. This equilibrium point is 'saturated' (this means that all transversal eigenvalues are negative): for perturbations about any one of the points where  $y_i \rightarrow 0$  (say,  $y_k = \delta_k$ , where  $\delta_k$  represent a small perturbation), we have from a linearization of equation (14) that  $d\delta_k/dt = \beta f_k \delta_k$ ; but  $f_k < 0$  (otherwise we would have  $y_k \rightarrow f_k/s > 0$ ), and hence saturation. As noted above, following Hofbauer & Sigmund (1988,

chapter 21.3), we know that (i) any saturated equilibrium of (12) has to be stable, and (ii) there is a unique globally stable equilibrium. Therefore this unique and globally stable equilibrium is given by equation (17).

We can also rewrite equation (12) to obtain

$$dy_i/dt = y_i \beta [g_i + sy_i], \quad (18)$$

with

$$g_i = 1 - \frac{v_i + u}{\beta} - (1 + s)y + 2s \sum_{j=1}^{i-1} y_j. \quad (19)$$

If we again assume to know  $y$  we can use equation (18) to construct a specific equilibrium point now in a recursive 'bottom-up' way.

$$\begin{aligned} y_1 &= \max\{0, -g_1/s\}, \\ y_2 &= \max\{0, -g_2/s\}, \\ y_3 &= \max\{0, -g_3/s\}, \\ &\vdots \\ y_n &= \max\{0, -g_n/s\}. \end{aligned} \quad (20)$$

Confirming Hofbauer & Sigmund's (1988) general result, a specific analysis shows this equilibrium to be unstable. As above,  $d\delta_k/dt = \beta g_k \delta_k$  for small perturbation about  $y_k = 0$ , but now  $g_k > 0$  (otherwise we would have  $y_k = -g_k/s > 0$  at equilibrium), and hence this solution is not stable. An extension of this argument to solutions constructed by moving upwards and downwards from an intermediate value of  $v_i$  show explicitly that only the 'top-down' approach leads to a stable equilibrium.

(a) The case  $s = 1$

The important special case  $s = 1$  offers a quick solution, because  $y$  drops out of equations (17). The unique stable equilibrium distribution is then given recursively in the following way:

$$\begin{aligned} y_n &= \max\left\{0, 1 - \frac{v_n + u}{\beta}\right\}, \\ y_{n-1} &= \max\left\{0, 1 - \frac{v_{n-1} + u}{\beta} - 2y_n\right\}, \\ y_{n-2} &= \max\left\{0, 1 - \frac{v_{n-2} + u}{\beta} - 2(y_n + y_{n-1})\right\}, \\ &\vdots \\ y_1 &= \max\left\{0, 1 - \frac{v_1 + u}{\beta} - 2(y_n + y_{n-1} + \dots + y_2)\right\}. \end{aligned} \quad (21)$$

This fixed point is saturated because for each parasite strain  $i$  with equilibrium frequency  $y_i = 0$  we obtain  $\partial \dot{y}_i / \partial y_i < 0$  for a generic choice of parameters, i.e. all the transversal eigenvalues evaluated at this fixed point are negative. Hence this fixed point is stable and it is the only stable fixed point in the system (Hofbauer & Sigmund, 1988).

Equation (21) corresponds to a very simple and illuminating geometric method for constructing the equilibrium (see figure 3).

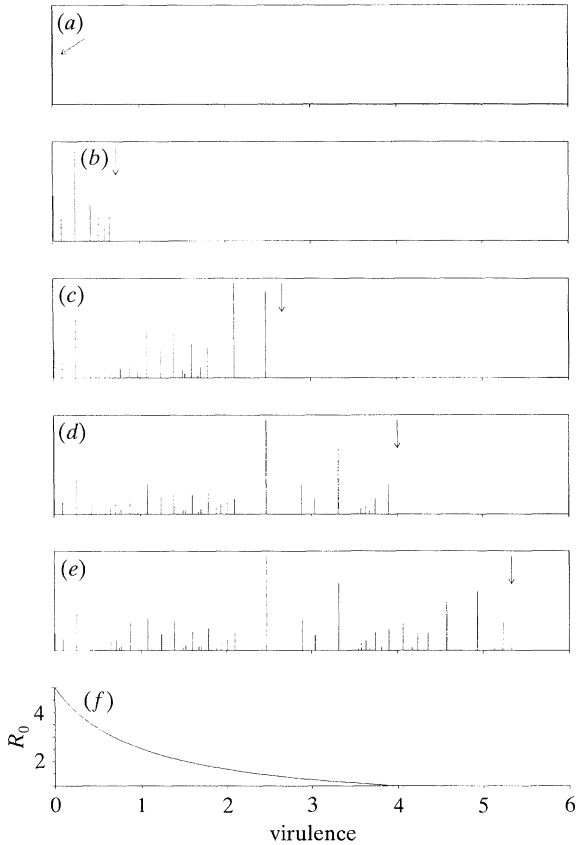


Figure 4. Equilibrium distribution of strains, for the simplified model with constant infectivity,  $\beta$ . The simulation is performed according to equation (12) with  $\beta = 5$ ,  $u = 1$  and  $n = 100$  strains of parasite with randomly distributed levels of virulence within the interval  $(0, 6)$ . (a)  $s = 0$ , (b)  $s = 0.1$ ; (c)  $s = 0.5$ ; (d)  $s = 1$ ; (e)  $s = 2$ ; (f) effect of virulence on  $R_0$ . Arrows indicate  $v_{\max}$ . For  $s = 0$  the strain with lowest  $s$  (and hence largest  $R_0$ ) is selected. For  $s > 1$  we find complex equilibrium structures. The arrows indicate the theoretically predicted largest levels of virulence,  $v_{\max} = 2s(\beta - u)/(1 + s)$ . Note that for  $s = 2$  strains with  $R_0 < 1$  are maintained in the population.

(b) *The case for general  $s (> 0)$*

Let us consider an equilibrium distribution with  $y_i > 0$  for  $i = 1, \dots, n$ ; i.e. we count only those strains which are present at equilibrium. From equations (15) and (16) we get

$$y_i = B_i - 2 \sum_{j=i+1}^n y_j, \quad (22)$$

with  $B_i = [1 - (v_i + u)/\beta - (1 - s)y]/s$ . We obtain

$$\begin{aligned} y_n &= B_n, \\ y_{n-1} &= -2B_n + B_{n-1}, \\ y_{n-2} &= 2B_n - 2B_{n-1} + B_{n-2}. \end{aligned} \quad (23)$$

For even  $n$  we obtain  $y = B_1 - B_2 + B_3 - \dots - B_n = (v_n - v_{n-1} + \dots - v_1)/\beta_s$ . For odd  $n$  we obtain  $y = B_1 - B_2 + B_3 - \dots + B_n$  and hence  $y = (\beta - u - v_n + v_{n-1} - \dots - v_1)/\beta$ . At first sight the expressions for odd and even  $n$  look quite different. We want to calculate  $v_{\max}$ , the maximum level of virulence present in an equilibrium distribution for a given  $s$ . Assuming equal spacing (on average), i.e.  $v_k = kv_1$ ,

leads to  $y = v_n/2\beta s$  for  $n$  even and to  $y = 1 - (u/\beta) - (v_n/2\beta)$  for  $n$  odd. (For  $n$  odd we have used the approximation  $n-1 \approx n$ .) From  $y_n \geq 0$  we derive in both cases

$$v_{\max} = 2s(\beta - u)/(1 + s). \quad (24)$$

This is the maximum level of virulence that can be maintained in an equilibrium distribution. For  $s = 0$  this is simply  $v_{\max} = 0$ , i.e. the strain with the lowest virulence, which for our choice of parameters is also the strain with the highest basic reproductive rate. For  $s > 1$  strains can be maintained with virulences above  $\beta - u$ . These are strains that are by themselves unable to invade an uninfected host population, because their basic reproductive rate is smaller than one.

Finally resolving the even- and oddities we insert  $v_{\max}$  for  $v_n$  into the two different expressions for  $y$  and find in both cases

$$y = (\beta - u)/\beta(1 + s). \quad (25)$$

This is the equilibrium frequency of infected hosts. The more superinfection the fewer infected hosts!

Figure 4 shows equilibrium distributions for 100 parasite strains with randomly chosen levels of virulence, for various values of the superinfection parameter,  $s$ . The arrows indicate the theoretically predicted largest levels of virulence, as given by equation (24). The analytic methods seem to work very well.

## 5. DYNAMICAL COMPLEXITIES

Let us now return to the model with different strains having different infectivities,  $\beta_i$ , as given by equation (9). Here the solutions need not converge to a stable equilibrium. Equation (9) can lead to very complex dynamics.

For two strains of parasite ( $n = 2$ ) we may find coexistence (i.e. a stable equilibrium between the two strains) or a bistable situation where either one or the other strain wins depending on the initial conditions. An interesting situation can occur if  $s > 1$ , and strain 1 has a virulence too high to sustain itself in a population of uninfected hosts ( $R_0 < 1$ ), whereas strain 2 has a lower virulence but an  $R_0 > 1$ . As  $s > 1$ , infected hosts are more susceptible to superinfection, and thus the presence of strain 2 can effectively shift the reproductive rate of strain 1 above one. Superinfection can stabilize parasite strains with extremely high levels of virulence.

For three or more strains of parasite we may observe oscillations with increasing amplitude and period, tending towards a heteroclinic cycle (figure 5). Imagine three parasite strains, each of which by itself is capable of establishing an equilibrium between uninfected and infected hosts (i.e. all have  $R_0 > 1$ ). The system where these three strains occur simultaneously has three boundary equilibria, where always two strains have frequency 0 and the population consists of uninfected hosts and hosts infected by the third strain only. There is also one unstable interior equilibrium with all three strains present. The system converges toward the boundary equilibria and cycles from the first one to the

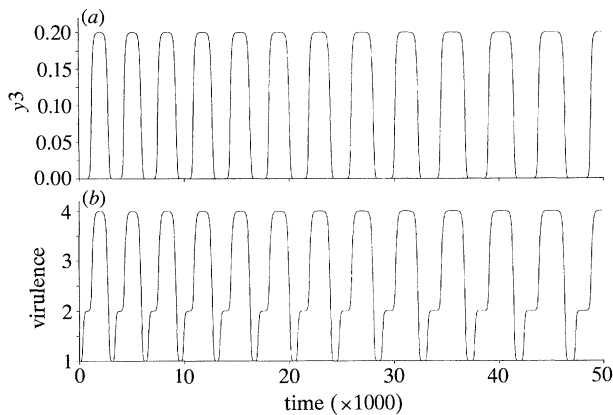


Figure 5. A simulation of equation (9) with  $n = 3$  strains with  $\beta_1 = 2$ ,  $\beta_2 = 3$ ,  $b_3 = 5$ ,  $v_1 = 1.07$ ,  $v_2 = 2.05$ ,  $v_3 = 4.04$ ,  $u = 0$  and  $s = 0.5$ . The figure shows oscillations with increasing period and amplitude towards a heteroclinic cycle. (a) Population size of hosts infected with strain 3; (b) average virulence of the parasite population,  $\bar{v} = \sum v_i y_i / \sum y_i$ , versus time.

second to the third and back to the first. The period of such cycles gets larger and larger. There will be long times where the infection is just dominated by one parasite strain (and hence only one level of virulence) and then suddenly another strain takes over. Such a dynamics can, for example, explain sudden upheavals of pathogens with dramatically altered levels of virulence. If we wait long enough one of the parasite strains may become extinct by some fluctuations when its frequency is low. Then one of the two remaining strains will outcompete the other. (Heteroclinic cycles in Lotka-Volterra systems have been described, for example, by May & Leonard (1975), Hofbauer & Sigmund (1988), Nowak & Sigmund (1989) or Nowak (1990).)

For small values of  $s$  all elements of matrix (11) will be negative. Such a Lotka-Volterra system is called ‘competitive’, and all trajectories will converge to an  $n-1$  dimensional subspace, which reduces the dynamical complexities (Hirsch 1988). This implies that for  $n = 2$  there are no damped oscillations, and for  $n = 3$  one can exclude chaos.

## 6. EVOLUTIONARY DYNAMICS

Imagine that mutation is continually generating new strains with altered levels of virulence. Selection is then acting on the different strains according to the dynamics described in the previous sections. The virulences are constrained to a range between  $v_{\min}$  and  $v_{\max}$ , but there will be an ever changing parasite population. There will always be new strains capable of invading the polymorphic population. Some of the old strains may then become extinct, and many strains will have altered frequencies. If this evolutionary dynamics is iterated for a very long time, then one can define a distribution function  $y(v)$ , which describes the long-term equilibrium frequencies of strains as a function of their virulence,  $v$ . Figure 6 shows a computer simulation of such an evolutionary process.

The distribution of virulences can best be studied by a differential equation that uses a continuous virulence

parameter,  $v$ . The continuous version of equation (12) is

$$dy(v)/dt = \beta y(v) F(v), \quad (26)$$

with

$$\begin{aligned} F(v) &= 1 - \bar{y} - \frac{v+u}{\beta} + s \int_0^v y(z) dz - s \int_v^\infty y(z) dz \\ &= 1 - (1+s)\bar{y} - \frac{v+u}{\beta} + 2s \int_0^v y(z) dz. \end{aligned} \quad (27)$$

Here  $y(v) dv$  is the total density of parasite strains with virulences between  $v$  and  $v+dv$ ;  $y(v)$  is the product of the average abundance of each strain around  $v$ , times the number of such strains. The total parasite population is denoted by  $\bar{y} = \int_0^\infty y(z) dz$ . An equilibrium solution can be found by putting  $F(v) = 0$  for all values of  $v$  within 0 and  $v_{\max}$ . We define  $v_{\max}$  as the smallest level of virulence such that  $y(v) = 0$  for all  $v > v_{\max}$ . From  $F(0) = 0$  we obtain for the total parasite population

$$\bar{y} = (\beta - u) / \beta(1 + s). \quad (28)$$

From  $F(v_{\max}) = 0$  and equation (28) we obtain

$$v_{\max} = 2s(\beta - u) / (1 + s). \quad (29)$$

Of course, these are the same expressions for  $\bar{y}$  and  $v_{\max}$  as in the discrete case, but here the derivation is much simpler and more elegant. We also get a very simple expression for the distribution function by combining equations (27) and (28). This leads to

$$\int_0^v y(z) dz = v/2\beta s \quad (30)$$

and hence by differentiation (assuming continuity)

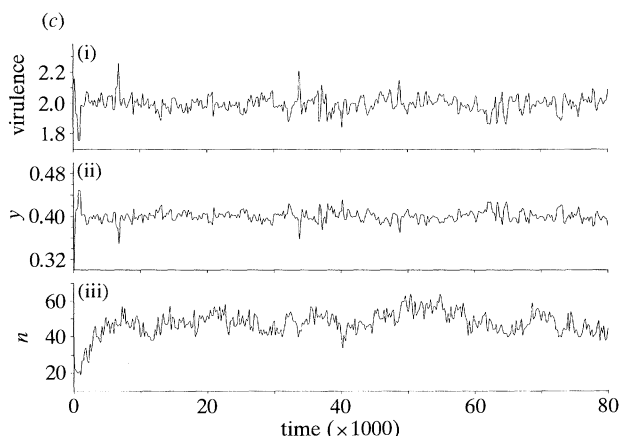
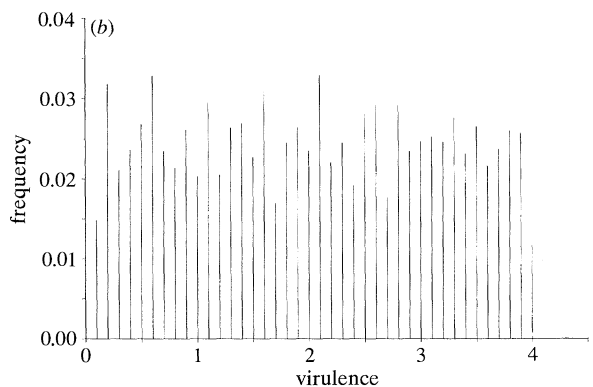
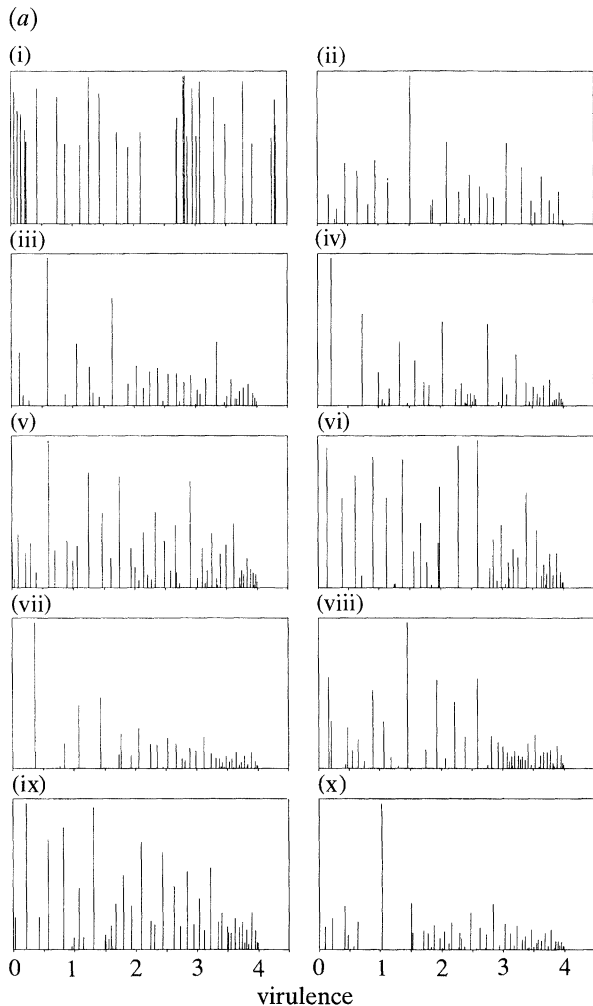
$$y(v) = 1/2\beta s. \quad (31)$$

Thus we obtain a uniform distribution over the interval  $[0, v_{\max}]$ , i.e.  $y(v) = 1/2\beta s$  for  $0 \leq v \leq 2s(\beta - u)/(1 + s)$  and  $y(v) = 0$  otherwise.

For this continuous solution we do not have a fully rigorous proof of stability and uniqueness. But note that, in this section, we are considering an evolutionary version of our model, where mutation is continuously generating new parasite strains and therefore fills any potential gaps along the virulence-level spectrum. Intuitively – and also in our extensive computer simulations – it seems clear that the solution given by equations (29) and (31) is globally stable for the mutation-selection process.

This section lends itself to further investigations. Among the interesting questions are: How many strains of parasite are there on average? What are the equilibrium distributions of density and abundance of strains along the interval  $[v_{\min}, v_{\max}]$ ? Answers to these questions lead to an approximate analysis which suggests the above equilibrium, given by equations (29) and (31), is indeed stable and unique. The questions also have relevance in a more general, ecological context of the meta-population dynamics of competing species. They are answered in a separate paper (May & Nowak 1994).

For constant  $\beta$  (i.e. in the limit  $c \rightarrow 0$  in  $\beta(v) = av/(c+v)$ ), we can also solve the continuous version of



the related equation (6) and obtain for the equilibrium the explicitly parameterized expressions

$$y(v) = 1/2s\beta \quad \text{for } 0 \leq v \leq v_{\max}, \tag{32}$$

$$v_{\max} = 2s\beta\bar{y}, \tag{33}$$

$$\bar{y} = \frac{-u(1+s) + \sqrt{u^2(1+s)^2 + 4s(k\beta - u^2)}}{2s\beta}. \tag{34}$$

### 7. CONCLUSIONS

For mathematical convenience we have assumed that individual infections are always dominated by single parasite strains. Thus ‘superinfection’ in our context means that a new parasite strain takes over a host already infected by another parasite strain. The new strain must have a competitive advantage for the intra-host selection dynamics. We assumed that virulent strains have an intra-host competitive advantage over less virulent strains. However, less virulent strains may have a better reproductive rate in the population (they allow the host to live longer, on average), so that they have an inter-host advantage. Essentially the tradeoff between intra- and inter-host selection maintains our polymorphisms. We propose the following conclusions:

1. Superinfection leads to an increase of the average level of virulence above what would be optimal for the parasite population. The intuitive reason for this is that superinfection leads to intra-host competition among strains, resulting in increased levels of virulence and reduction in overall transmission rates.
2. Superinfection does not maximise the basic reproductive rate. The strain with highest  $R_0$  may even become extinct.
3. Superinfection leads to a polymorphism of parasite strains with many different levels of virulence within a well defined range.
4. Superinfection can maintain strains with very high levels of virulence (even strains that are so virulent that they themselves could not persist alone in an otherwise uninfected host population).

Figure 6. An evolutionary simulation of a heterogeneous parasite population with superinfection. The dynamics of selection are defined by equation (12) with the same parameters as figure 4 and  $s = 1$ . We start with  $n = 30$  randomly chosen strains. Every 10 time steps (on average) a new parasite strain is generated with a virulence taken from a uniform distribution on the interval (0, 5). Figure 6a shows the population structure at different time points. (i)  $t = 0$ ; (ii)  $t = 2000$ ; (iii)  $t = 4000$ ; (iv)  $t = 6000$ ; (v)  $t = 8000$ ; (vi)  $t = 10000$ ; (vii)  $t = 12000$ ; (viii)  $t = 14000$ ; (ix)  $t = 16000$ ; (x)  $t = 18000$ . There is an ever changing structure of the virulence polymorphism. There are always new strains capable of invading the population. An evolutionarily stable population does not exist. Figure 6b shows the long-term equilibrium distribution of parasite virulence. For this we sampled the parasite population structure at 1000 time points between  $t = 0$  and  $t = 1000000$ . As expected, we find an excellent approximation to a uniform distribution. Figure 6c shows: (i) the average virulence, defined as  $\bar{v} = \sum v_i y_i / \sum y_i$ ; (ii) the total number of infected hosts,  $y = \sum y_i$ ; and (iii) the number of parasite strains,  $n$  as a function of time (an analytic explanation of these and allied results will be provided elsewhere: May & Nowak 1994).

5. Superinfection can lead to very complicated dynamics, such as heteroclinic cycles, with sudden and dramatic changes in the average level of virulence.

6. The higher the rate of superinfection the smaller the number of infected hosts ( $y$  decreases with  $s$ ).

7. There is a formal similarity between the models developed in this paper and various approaches to the dynamics of metapopulations (Nee & May 1992), where a 'host' is equivalent to a patch or a habitat and superinfection is 'taking over' of a patch by another individual. The superinfection model can also be applied to this more general context.

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