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Coinfection and the evolution of parasite virulence

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SUMMARY

Analyses of the selection pressures acting on parasite virulence are made more complicated when individual hosts can simultaneously harbour many different strains or genotypes of a parasite. Here we explore the evolutionary dynamics of host–parasite associations in which individual hosts can be coinfecting with many different parasite strains. (We take coinfection to mean that each strain transmits at a rate unaffected by the presence of others in the same host.) This study thus represents the opposite extreme to our earlier work on superinfection in which there is a dominance hierarchy such that only the most virulent strain present in a host is transmitted. For highly diverse populations of parasite strains, we find that such coinfection leads to selection for strains whose virulence-levels lie in a relatively narrow band close to the maximum consistent with the parasite's basic reproductive ratio, R_0 , exceeding unity.

1. INTRODUCTION

Recently, many papers have been published on the subject of the evolution of parasite virulence (with parasite defined broadly to include viruses, bacteria, and protozoans along with the conventional helminth and arthropod parasites: see May & Anderson 1990; Anderson & May 1991; Nowak 1991; Frank 1992; Antia *et al.* 1993; Ewald 1993; Yamamura 1993; Bonhoeffer & Nowak 1994; Levin & Bull 1994; Rand *et al.* 1994; Lipsitch *et al.* 1995*a, b*; empirical studies include Bull *et al.* 1991, 1992; Herre 1993; Ebert 1994; for review articles we refer to Bull 1995; Herre *et al.* 1995). On the theoretical side, one of the most complicated issues is understanding how parasite diversity within individual hosts alters the selective forces determining virulence. Essentially, parasites compete and evolve at two different levels: within a host and between hosts.

We recently studied the evolution of virulence in mathematical models where already-infected hosts can be 'superinfected' by other parasites (May & Nowak 1994; Nowak & May 1994). There we assumed a competitive hierarchy among the different parasite strains such that a more virulent parasite can infect and 'take over' a host that is already infected by a less virulent strain; multiply-infected hosts transmit only the most virulent of the strains they harbour. Here we analyse the opposite extreme of this scenario. We assume that individual hosts can be 'coinfecting' by a large number of different parasites and that there is no competition among different parasites in the same host; each strain produces transmission stages, and thence new infections, at a rate that is unaffected by the presence of any other strains coinfecting its hosts. We thus use the term 'coinfection' to indicate a stable coexistence of different parasites (or strains) in the same host. Hence, the coinfection model describes

situations where a host species is infected with strains of a given parasite species, or with a number of different parasite species.

This study of coinfection and our earlier studies of superinfection represent the two opposite extremes in situations where hosts experience multiple infection with many different strains of a parasite. By studying these two extremes, we hope to 'bracket' the more general range of possible situations.

Both these simplified extremes are amenable to analytical understanding. Eventually our aim is to combine the full scenario of multiple infections in a single host with the selection dynamics for evolution within and among hosts. Such studies will mostly rely on computer simulations, and therefore we regard it as important to understand the simple cases first.

In what follows, we first define a simple model for the dynamics of a host–parasite association with coinfection. We then present numerical studies of this system, along with supporting analytic understanding, for the case where all strains have the same transmission rate. Next we extend the numerical studies and supporting analytic approximations to the more general case where more virulent strains have higher transmission rates. We conclude by comparing these results with our earlier studies of superinfection and discuss the implications for evolutionary trends in parasite virulence.

2. A BASIC MODEL FOR COINFECTION

A simple model for coinfection is the following:

$$dy_i/dt = y_i[\beta_i(1 - y_i) - u - \bar{v}_i], \quad \text{with } i = 1, \dots, n. \quad (1)$$

There are n strains of parasite. The total population size of hosts is assumed to be held constant by other ecological factors, and may be normalized to unity. The fraction of hosts infected by strain i is given by y_i .

Several parasites can be present in the same host and so the sum over all y_i will in general exceed the fraction of all hosts that are infected. The infectivity (transmission rate) of strain i is denoted by β_i . Strain i can infect any host which is not already infected by strain i . The infectivity of a strain is unaffected by the presence of other strains in the same host, which indeed represents our definition of 'coinfection'. Thus $\beta_i y_i(1-y_i)$ is the rate at which new infections with strain i occur.

There is a natural death rate, u , and a disease induced death rate, \bar{v}_i , which denotes the average death rates of hosts infected by strain i . Given that hosts may simultaneously harbour several parasite strains, we assume that the death rate of an infected host is determined by the most virulent strain present. In a single infection, strain i has virulence v_i . We label the strains such that $v_i < v_{i+1}$ for all i ; thus 1 is the least virulent and n the most virulent strain.

We define P_i as the probability that a host is not infected with a strain more virulent than i . That is,

$$P_i = \prod_{j=i+1}^n (1-y_j). \quad (2)$$

Note that $P_n = 1$ and $P_i = (1-y_{i+1})P_{i+1}$. The fraction of hosts that are uninfected is given by $P_0 = \prod_{j=1}^n (1-y_j)$. The average virulence of strain i is now given by

$$\bar{v}_i = v_i P_i + \sum_{j=i+1}^n v_j y_j P_j. \quad (3)$$

Note that $y_j P_j$ is the probability that j is the most virulent strain found in a host. Clearly $P_i + \sum_{j=i+1}^n y_j P_j = 1$ for all values of i .

The coinfection model is completely defined by equations (1–3). The equilibrium of equation (1) is given in a recursive way:

$$\begin{aligned} y_n &= 1 - (\bar{v}_n + u)/\beta_n, \\ y_{n-1} &= 1 - (\bar{v}_{n-1} + u)/\beta_{n-1}, \\ &\vdots \\ y_1 &= 1 - (\bar{v}_1 + u)/\beta_1. \end{aligned} \quad (4)$$

Note that \bar{v}_n is simply v_n (which is intuitively obvious, and also follows from equation (3)).

Our aim is to solve this recursion and to get expressions for the average level of virulence, and for the relative abundances of the various strains, as a function of parasite diversity, n .

The average virulence of the parasite population is given by

$$\bar{v} = \sum_{i=1}^n v_i y_i P_i / (1 - P_0). \quad (5)$$

Using equation (3) for $i = 1$, we can rewrite equation (5) as

$$\bar{v}(1 - P_0) = \bar{v}_1 - v_1 P_0. \quad (6)$$

Using equation (3) for \bar{v}_{i+1} and \bar{v}_i , we can also see that

$$\bar{v}_{i+1} - \bar{v}_i = P_i(v_{i+1} - v_i). \quad (7)$$

Summing both sides of equation (7) from i to $n-1$, and rearranging, we get

$$\bar{v}_i = v_n \left(1 - \sum_{j=i}^{n-1} P_j \Delta v_j \right), \quad (8)$$

with $\Delta v_j = (v_{j+1} - v_j)/v_n$. From equations (6) and (8) we get

$$\bar{v}(1 - P_0) = v_n \left(1 - \sum_{j=1}^{n-1} P_j \Delta v_j \right) - v_1 P_0. \quad (9)$$

It is reasonable to assume that P_0 becomes small for large n (this will be proved below). Hence a good approximation is

$$\bar{v} \approx v_n \left(1 - \sum_{j=1}^{n-1} P_j \Delta v_j \right). \quad (10)$$

We now proceed to obtain analytic approximations for the average virulence, \bar{v} , and for the relative abundances of the various strains, y_i (and thence for P_i), as a function of the number of strains originally present, n , and other relevant variables. We do this first for the case where β_i is the same for all i and second for the more general case where β_i increases with increasing v_i . These analytic results provide insight into our numerical explorations of the dynamics of the basic model (1)–(3), as summarized below.

3. STRAIN-INDEPENDENT TRANSMISSION RATE, $\beta_i = \text{const}$

We assume we are given the virulence values, v_i . All strains have the same transmission rate, β . We now seek expressions for y_i and P_i in terms of the given v_i . Thence, via equation (10), we can calculate \bar{v} .

Returning to equation (4), we see that the equation for y_n puts a limit on v_n , the most virulent strain: $y_n \geq 0$ implies $v_n \leq v_+ = \beta - u$. This upper limit to the virulence spectrum corresponds to the limit $R_0 = \beta/(v_i + u) \rightarrow 1$.

More generally, from equation (4) with $\beta_i = \beta$, we get a relation between y_i and \bar{v}_i :

$$y_{i+1} - y_i = -(\bar{v}_{i+1} - \bar{v}_i)/\beta. \quad (11)$$

Substituting from equation (7) in the right hand side of equation (11), we obtain a relation among y_i , P_i and v_i :

$$y_{i+1} - y_i = -P_i(v_{i+1} - v_i)/\beta. \quad (12)$$

In the continuous limit, which will represent a good approximation as the spacing between adjacent strains along the virulence axis becomes small, equation (12) becomes

$$[dy(v)/dv] = -P(v)/\beta. \quad (13)$$

We need a further relation between y_i and P_i (or $y(v)$ and $P(v)$) to close this system. Such a relation is supplied by the definition of P_i , equation (2), which can be rewritten

$$\ln P_i = \sum_{j=i+1}^n \ln(1 - y_j). \quad (14)$$

If the individual abundances, y_i , are small (as they will be seen to be for $n \gg 1$, below), we may approximate equation (14) by

$$\ln P_i \simeq - \sum_{j=i+1}^n y_j. \quad (15)$$

In the continuous limit, this gives

$$\ln P(v) \simeq - \frac{n}{\Delta} \int_v^{v_+} y(v') dv'. \quad (16)$$

Here we have used the facts that: (i) $v_n \simeq v_+ (= \beta - u)$; (ii) there are n strains in the virulence interval of width $\Delta \equiv v_+ - v_-$ (where $v_+ = \beta - u$ is the most virulent possible persisting strain, and $v_- = 0$ the least virulent one), so that there are on average $(n/\Delta) dv$ strains in an interval of width dv . Notice that here, where $v_- = 0$, we have $\Delta = v_+$; we preserve the notational distinction between Δ and v_+ , however, because in the more general case when β_i varies with v_i (as in the next section) $v_- \neq 0$ and $\Delta < v_+$.

We now proceed to get a relation between $P(v)$ and v , from equations (13) and (16), in the continuous limit. Expressions for \bar{v} and for $y(v)$ follow easily.

It is convenient to introduce $Z(v) \equiv \ln P(v)$. Differentiating both sides of equation (16) twice with respect to v , we get

$$d^2 Z/dv^2 = (n/\Delta) [dy(v)/dv]. \quad (17)$$

Substituting from equation (13) on the right hand side, and using $d^2 f/dx^2 = 1/2(df/dx)^2$, we arrive at

$$d[dZ/dv]^2/dZ = -(2n/\beta\Delta) e^Z. \quad (18)$$

Integrating from v to the maximum value v_+ , and noting that $Z(v_+) = \ln P_n = 0$ and $dZ(v_+)/dv = (n/\Delta) y(v_+) = 0$, we get

$$(dZ/dv)^2 = (2n/\beta\Delta) (1 - e^Z). \quad (19)$$

Re-expressing equation (19) in terms of $P(v)$ rather than $Z(v)$, we arrive at

$$(1/P)(dP/dv) = (2n/\beta\Delta)^{1/2} (1 - P)^{1/2}. \quad (20)$$

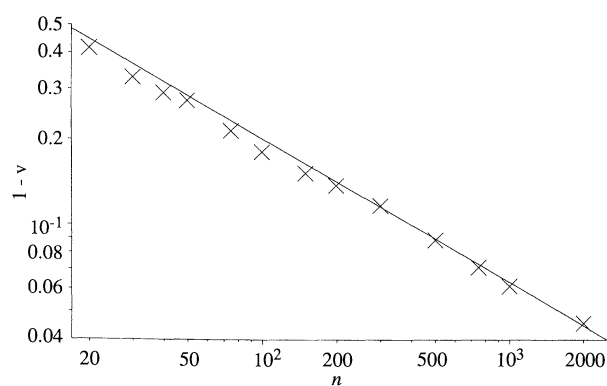


Figure 1. The average level of virulence versus the number of different parasite strains in the population for the coinfection model given by equations (1-3). The individual parasite strains have randomly assigned levels of virulence ranging from 0 to 1. All parasite strains have the same transmission rate, $\beta = 2$. The natural death rate is $u = 1$. For different numbers of strains, n , the equilibrium population structure is computed according to equation (4). The figure shows that for large n there is excellent agreement between the numerical calculations (the points, x) and the theoretical curve, given by equation (23).

We now return to equation (10) for \bar{v} , and express it in the continuous limit:

$$\bar{v} \simeq v_+ \left[1 - \int_{v_-}^{v_+} P(v') dv' / v_+ \right]. \quad (21)$$

Substituting directly from equation (20) for $P dv$, we get

$$\bar{v} \simeq v_+ \left[1 - (\beta\Delta/2nv_+^2)^{1/2} \int_0^1 (1-P)^{-1/2} dP \right]. \quad (22)$$

Performing the integration, and recalling that $\Delta = v_+ = \beta - u$, we get

$$\bar{v} \simeq v_+ [1 - c/\sqrt{n}], \quad (23)$$

with $c = [2\beta/(\beta - u)]^{1/2}$.

This result, equation (23), agrees well with the extensive numerical simulations summarized in figure 1, especially as n becomes very large.

Returning to equation (20), we may integrate from $v = v$ to $v = v_+ (= \beta - u)$, to get

$$\int_P^1 [dP/P(1-P)^{1/2}] = (2n/\beta\Delta)^{1/2} \int_v^{v_+} dv' \equiv \theta. \quad (24)$$

Here we have defined

$$\theta = (2nv_+^2/\beta\Delta)^{1/2} (1 - v/v_+), \quad (25a)$$

or, equivalently,

$$\theta = (2nv_+^2/\beta\Delta)^{1/2} (1 - i/n), \quad (25b)$$

where i is the index 'counting' the n persisting strains, from least ($v_- = 0$) to most ($v_n = v_+ = \beta - u$) virulent. Integrating the left hand side of equation (24) gives

$$\ln \{ [1 + (1 - P)^{1/2}] / [1 - (1 - P)^{1/2}] \} = \theta. \quad (26)$$

And thence, after some manipulation,

$$P(v) = [\cosh(\theta/2)]^{-2}. \quad (27)$$

Equation (27) describes the behaviour of $P(v)$, or equivalently P_i , as we move down the virulence spectrum, away from values of v close to v_{\max} (i.e. values of i close to n). $P(v)$ will remain close to unity so long as θ is small, which is to say $(v_+ - v)/v_+ \approx \leq n^{-1/2}$, or $1 - (i/n) \approx \leq n^{-1/2}$. This corresponds to a narrow band of strains with virulence-values close to v_+ , representing a fraction of order $n^{-1/2}$ of all strains, or a total of order $n^{1/2}$ of the n persisting strains. For strains with v -values below this narrow band, the probability that they are the most virulent in a given host becomes very small; $P(v) \simeq 4e^{-\theta}$, with $\theta \gg 1$ for v -values not close to v_+ , for $n \gg 1$. In particular,

$$P_0 \simeq 4 \exp[-\{2n(\beta - u)/\beta\}^{1/2}]. \quad (27a)$$

This, incidentally, justifies our earlier approximation that $P_0 \ll 1$ for $n \gg 1$.

These insights translate into a corresponding understanding for the patterns of relative abundance of the various strains, $y(v)$. Equation (16) gives us $y(v) = (\Delta/n) d(\ln P)/dv$, or, using equation (25), $y(v) = [-(2\Delta/n\beta)^{1/2} d(\ln P)/d\theta]$. Thence equation (27) gives

$$y(v) = (2\Delta/n\beta)^{1/2} \tanh(\theta/2). \quad (28)$$

Unless we are very close to v_+ , $y \simeq [2(\beta - u)/n\beta]^{1/2}$. Within a narrow band of v -values close to v_+ ($v_+ - v \approx \leq v_+/n^{1/2}$), we have θ small, and $y(v)$ falls from $(2\Delta/n\beta)^{1/2}$

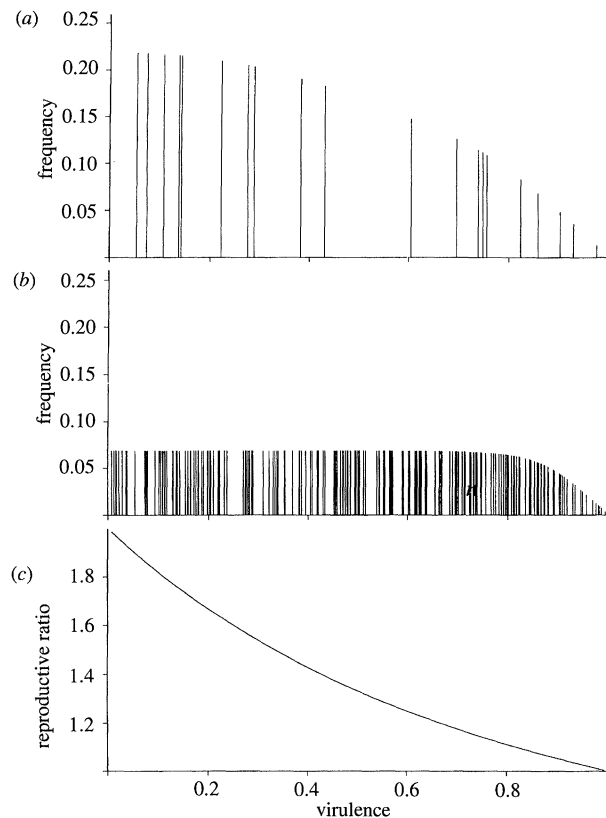


Figure 2. Equilibrium distributions of the coinfection model as specified by equations (1–3). The individual parasite strains have randomly assigned levels of virulence ranging from 0 to 1. All parasite strains have the same transmission rate, $\beta = 2$. The natural death rate is $u = 1$. (a) $n = 20$ strains of parasite. The figure shows the frequency of hosts, y_i , infected by parasite strain i , which has virulence v_i . The most virulent strain is the least abundant, but all strains survive (as long as their virulence is smaller than 1). We obtain an average virulence, as defined by equation (5), of $\bar{v} = 0.5856$ and a fraction of uninfected hosts of $P_0 = 0.0397$. The frequency of hosts infected by the least virulent parasite is $y_1 = 0.2178$. The analytic approximations of equations (23), (27), and (28) give $\bar{v} \approx 0.55$, $P_0 \approx 0.04$, and $y_1 \approx 0.22$, respectively. (b) $n = 200$ strains of parasite. We obtain an average virulence of $\bar{v} = 0.8631$, a fraction of uninfected hosts of $P_0 = 2.08 \times 10^{-6}$, and for the least virulent parasite $y_1 = 0.0684$. Here the corresponding analytic approximations are $\bar{v} \approx 0.86$, $P_0 \approx 2.9 \times 10^{-6}$, and $y_1 \approx 0.071$. (c) The basic reproductive ratio, R_0 , as a function of virulence.

to zero at $v = v_+$. This is illustrated by the numerical results presented in figure 2. Notice that $y(v)$ is small, of order $n^{-\frac{1}{2}}$, for all v , which justifies the approximation made in equation (15) for $n \gg 1$.

4. TRANSMISSION RATE INCREASING WITH VIRULENCE

We now turn to the more general case where the transmission rate for strain i is not constant, but increases with increasing virulence, v_i .

Specifically, we assume a functional relation between $\beta(v)$ and v of the form

$$\beta(v) = \beta v / (\gamma + v). \quad (29)$$

Here β is a constant. The results of the previous section are recovered as the limit $\gamma \rightarrow 0$. From equation (1) or

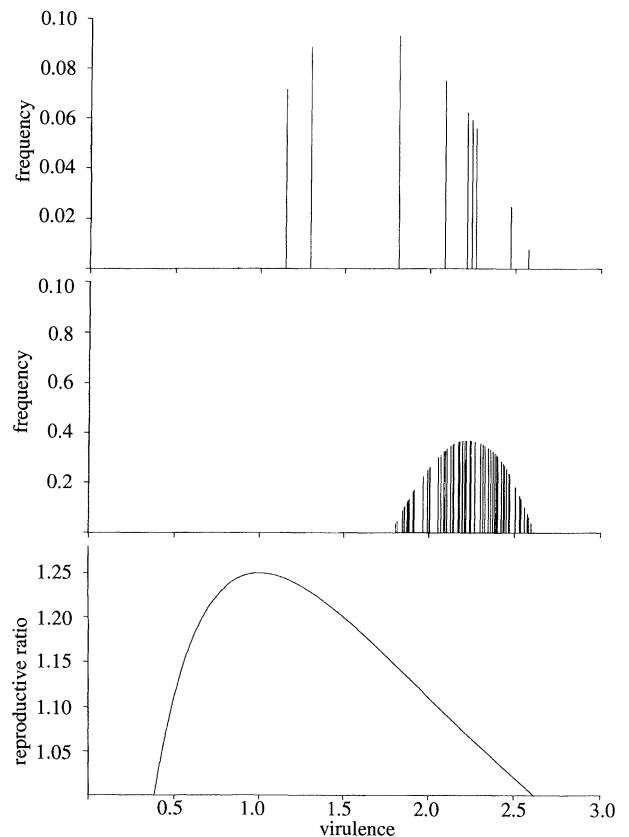


Figure 3. Equilibrium distribution of the coinfection model with a trade-off between transmission rate β_i and virulence v_i . We chose $\beta_i = 5v_i/(1+v_i)$. This gives a one humped curve for the basic reproductive rate as a function of virulence. The natural death rate is $u = 1$. The parasites have levels of virulence uniformly distributed between 0 and 3. We observe that all parasite strains persist with a level of virulence above a certain minimum v_{\min} and the maximum level of virulence that corresponds to $R_0 = 1$, i.e. $v_+ = (3 + \sqrt{5})/2$. (a) $n = 20$ parasite strains. We obtain an average virulence of $\bar{v} = 1.9246$ and a fraction of uninfected hosts of $P_0 = 0.5716$. (b) $n = 200$ parasite strains. We obtain an average virulence of $\bar{v} = 2.3039$ and a fraction of uninfected hosts of $P_0 = 0.1952$. The persisting strains occupy a band of virulence-values of width $\delta v = 0.87$; the roughly approximate equation (39) gives $\delta v \approx 0.86$ (note that here we should put $\Delta = 3$ for $n = 200$). (c) The basic reproductive rate, R_0 , as a function of virulence. **3**

equation (4) we can see that the basic reproductive ratio for strain i , $R_{0,i}$, is now

$$R_{0,i} = \beta v / [(\gamma + v)(u + v)]. \quad (30)$$

R_0 is thus maximized by the strain with virulence $v_m = (\gamma u)^{\frac{1}{2}}$, and is $R_{0,\max} = \beta / (u^{\frac{1}{2}} + \gamma^{\frac{1}{2}})^2$. The minimum and maximum virulence-values for strains that have the potential to maintain themselves within the host population, v_- and v_+ respectively, are given by setting $R_{0,i} = 1$:

$$v_{\pm} = \{\beta - u - \gamma \pm [(\beta - u - \gamma)^2 - 4u\gamma]^{\frac{1}{2}}\} / 2. \quad (31)$$

This relation between R_0 and v is illustrated in figure 3 (and for the limit $\gamma \rightarrow 0$, $\beta_i = \text{constant}$, in figure 2).

The derivations of equation (10) for \bar{v} , and of the corresponding equation (21) in the continuous limit, are both independent of whether β_i is constant or not; they therefore remain true. Likewise, equation (15) or

equation (16) (which relate $P(v)$ and $y(v)$) do not involve β_i , and so remain valid. The difficulties caused by a non-constant β_i (or $\beta(v)$) arise in the steps which in the previous section took us from equation (11) to equations (12) and (13). As we shall now see, once $\beta(v)$ varies with v the second relation between $P(v)$ and $y(v)$ is substantially more complicated than the simple $dy/dv = -P/\beta$ of equation (13).

Specifically, equation (4) leads not to equation (11), but to the more general relation

$$y_{i+1} - y_i = -[(\bar{v}_{i+1} + u)/\beta_{i+1} - (\bar{v}_i + u)/\beta_i]. \quad (32)$$

Equation (7), connecting $(\bar{v}_{i+1} - \bar{v}_i)$ and $(v_{i+1} - v_i)$, is however unaffected by β_i , and remains valid. Using equation (7) in equation (32), we have

$$y_{i+1} - y_i = [-(v_{i+1} - v_i)P_i/\beta_i] + [(\bar{v}_{i+1} + u)(\beta_{i+1} - \beta_i)/(\beta_i\beta_{i+1})]. \quad (33)$$

When $n \gg 1$, we can take the continuous limit to get

$$dy(v)/dv = [1/\beta(v)][-P(v) + \{1 - y(v)\}d\beta(v)/dv]. \quad (34)$$

Here we have used equation (4) to rewrite $(\bar{v} + u)\beta$ as $(1 - y)$. Finally, we recognize that the abundance of any one strain is small when $n \gg 1$ ($y \sim n^{-\frac{1}{2}}$), so that

$$dy/dv \simeq [P(v)/\beta(v)] + \{d[\ln \beta(v)]/dv\}. \quad (35)$$

This equation (35) represents the generalization of equation (13) to the situation where β_i is not constant. Substituting for $P(v)$ from equation (16), we can alternatively write equation (15) as a relation between $y(v)$ and v :

$$dy/dv = -\left\{\exp\left[-(n/\Delta) \int_v^{v_+} y(v') (dv')\right]/\beta(v)\right\} + \{d[\ln \beta(v)]/dv\}. \quad (36)$$

Figure 3 shows numerical studies of the dynamics of equation (1) when $\beta(v)$ increases with v according to equation (29). We could compare these simulations with numerical integrations of equation (36). It is, however, more illuminating to think about how the additional term in equation (35), compared with equation (13), leads to the qualitative differences between the strain-abundance patterns, $y(v)$, of figure 3 and those of figure 2.

If $\beta(v)$ is set constant in equation (36), the second term on the right hand side of equation drops out, and we recover exactly the results of the previous section. This leads to equation (28) for $y(v)$: as illustrated in figure 2, $y(v_+) = 0$, and $y(v)$ increases as v decreases below v_+ , saturating to the value $y_{\max} \simeq (2\Delta/n\beta)^{\frac{1}{2}}$ once v is sufficiently far below v_+ (i.e. once $\theta \ll 1$, with θ defined by equation (25)). The modifying effect of a non-constant $\beta(v)$ can be seen by integrating equation (36) from v to v_+ :

$$y(v) = \int_v^{v_+} [e^{-\phi} dv/\beta(v)] - \ln[\beta(v_+)/\beta(v)]. \quad (37)$$

Here ϕ is the exponent in the first term on the right hand side in equation (36). The effect of the $\ln(\beta_+/\beta)$

term is to diminish $y(v)$ below the value it would have if β were constant; this diminution becomes progressively more marked as $\beta(v)$ falls further and further below $\beta(v_+)$. For large n (when $y_{\max} \sim n^{-\frac{1}{2}}$), this $\ln(\beta_+/\beta)$ term on the right hand side in equation (37) will eventually drive $y(v)$ to zero at some v -value above v_- . Hence, for $n \gg 1$, we get the band of v -values lying just below v_+ , which are seen in figure 3 and which contrast with figure 2.

A crude approximation to the width of this band, δv , can be obtained for $n \gg 1$ by assuming that $y(v)$ roughly saturates to the constant- β value of equation (28), and then decreases to zero as the effects of the $\ln(\beta_+/\beta)$ term become increasingly important. On this basis, we have

$$\ln[\beta(v_+)/\beta(v_+ - \delta v)] \simeq [2\Delta/n\beta(v_+)]^{\frac{1}{2}}. \quad (38)$$

Expanding the left hand side under the assumption that $\delta v/v_+ \sim n^{-\frac{1}{2}}$, and using equation (29) for $\beta(v)$, we arrive at

$$\delta v \simeq [v_+(v_+ + \gamma)/\gamma] [2\Delta/n(v_+ + u)]^{\frac{1}{2}}. \quad (39)$$

Here v_+ and v_- are defined by equation (31), $\Delta = v_+ - v_-$, and we have used the relation $\beta(v_+) = v_+ + u$. This approximation gives an intuitive feeling for the numerical results of figure 3, and shows that in the limit $n \gg 1$ only a relatively narrow band of strains persist (a fraction of order $n^{-\frac{1}{2}}$, or a total of order $n^{\frac{1}{2}}$, of the original set of n strains with v -values such that $R_0 > 1$).

This crude approximation also provides a rough estimate of P_0 , the fraction of uninfected hosts, for systems of this kind with $n \gg 1$. For such a system, equation (16) gives

$$\ln P_0 \simeq \left\{- (n/\Delta) \int_{v_+ - \delta v}^{v_+} [y(v') dv']\right\}. \quad (40)$$

Following the very rough approximation outlined above, we can now write:

$$y(v) \simeq (2\Delta/n\beta_+)^{\frac{1}{2}} \tanh(\theta/2) - \ln[\beta(v_+)/\beta(v)] \quad (41)$$

in equation (40), to arrive (after considerable manipulation) at:

$$P_0 \simeq e^{\nu} \cosh^{-2}(\nu), \quad (42)$$

with $\nu = [v_+(v_+ + \gamma)/(v_+ + u)\gamma]$. This fraction is roughly independent of n in the limit $n \gg 1$. As n increases, the width of the band of surviving strains scales as $n^{\frac{1}{2}}$, with the abundance of each strain scaling roughly as $n^{-\frac{1}{2}}$; hence the overall probability for a host to escape infection tends to some n -independent constant. Contrast this to the constant- β case of the previous section, where all n strains coexist, so that P_0 scales as $\exp(-cn^{\frac{1}{2}})$ in the limit of large n (see equation (27a)).

5. DISCUSSION

Suppose we are dealing with a situation where more and more strains appear, by mutation, as time goes on. From the preceding analysis, we would expect the persisting strains to be confined to an ever narrower band of v -values, of width $\sim n^{-\frac{1}{2}}$, just below the critical value, v_+ , for which $R_0(v_+) = 1$ (except in the special

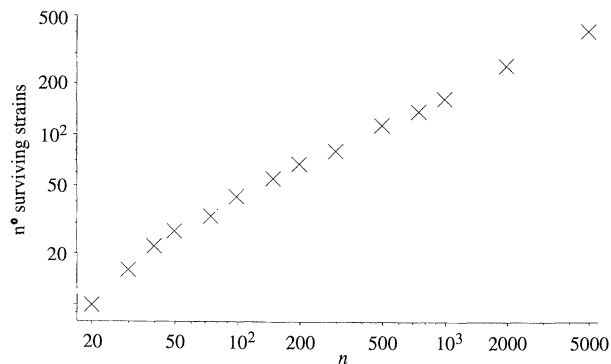


Figure 4. The number of surviving strains, s , versus the total number of strains which have been generated by mutation, n ($n = \lambda T$, where λ is the mutation rate, and T the elapsed time), for the coinfection model assuming a trade-off between virulence and transmission rate. As for figure 3 we have $\beta_i = 5v_i/(1+v_i)$; the natural death rate is $u = 1$.

case when all strains have the same transmission rate, and consequently all persist; see figure 2). The total number of strains, however, increases as $n^{1/2}$ as n increases. If new mutations appear at a roughly constant rate, λ , we have $n = \lambda T$ after time T , and consequently the total number of persisting strains is expected to increase with T as

$$N(T) \sim T^{1/2}. \quad (43)$$

This analytic expectation is confirmed by the numerical studies illustrated in figure 4.

These findings provide an interesting contrast with our earlier studies of 'superinfection' models. For superinfection, we assumed a rigorous dominance hierarchy, so that only the most virulent strain in a given host was transmitted. As explained earlier (Nowak & May 1994; May & Nowak 1994), this resulted in effective 'limits to similarity' among strains, which emerged from the dynamics of the model (see also Tilman *et al.* 1994), and which meant that many new mutants could not establish themselves; if they did, they tended to displace existing strains. Consequently, the superinfection models showed the total number or diversity of strains rising only slowly with time (i.e. with number of mutants): $N_{\text{superinfection}} \sim \ln T$. On the other hand, these same limits to similarity resulted in a wide range of virulence-values persisting in the system. By contrast, the present coinfection models have no limits to similarity, and surviving strains are packed ever closer as time goes on (see figure 4). These coinfecting strains are, however, constrained to lie in a very narrow band of virulence-values, close to the maximum consistent with persistence ($R_0 \rightarrow 1$). This effectively represents competitive exclusion of most strains; less virulent strains cannot realize their potentially superior R_0 -values, because hosts are killed by more virulent strains which have higher transmission rates, although lower R_0 -values.

Our simple models for superinfection (transmission only by the most virulent strain within a host) and for coinfection (all strains transmit, albeit at different rates, independent of other strains present in the host) represent extremes that are likely to bracket the reality

of polymorphic parasites. In both cases, we find the anticipated tendency towards the predominance of strains which are significantly more virulent than those which maximize parasite reproductive success in singly infected hosts. The numbers and virulence range of persisting strains, however, depend on the details: coinfection tends to favour a larger number of coexisting strains, but more closely grouped around a maximum virulence level, than does superinfection. There are suggestive parallels with notions of 'scramble' (coinfection) and 'contest' (superinfection) in ecological theory (Begon *et al.* 1986).

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