PROPAGULE INTERACTIONS AND THE EVOLUTION OF VIRULENCE[1]

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Running title: Evolution of virulence

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Abstract

The evolution of parasite virulence is thought to involve a trade-off between parasite reproductive rate and the effect of increasing the number of propagules on host survivorship. Such a trade-off should lead to selection for an intermediate level of within-host reproduction (λ). Here I consider the effects of parasite propagule number on selection affecting λ when (i) the effect of each propagule is independent of propagule number, and (ii) when the effect of each propagule changes as a function of propagule number. Virulence evolves in these models as a correlated response to selection on λ. If each propagule has the same effect (s) as all previous propagule, the survivorship of infected hosts is reduced by more than 60% at equilibrium, independent of the value of s. If, instead, each propagule has a more negative effect on host survivorship than previous propagules, host survivorship at equilibrium is expected to increase as the effect becomes more pronounced. These results are directly parallel to results derived for population mean fitness at mutation-selection balance; and they suggest that high virulence should be associated with parasites for which the effect of adding propagules either remains constant or diminishes with propagule number.

Keywords. -- life-history evolution, mutation accumulation, parasites, population growth, R_0, trade-offs, virulence

… if the deleterious effect of the mutant genes is proportional to the square of their number, the load under random mating becomes roughly half as large as in the case of no epistasis. Kimura & Maruyama (1966)

Introduction

As the reproductive rate of a parasite increases, the number of propagules produced over time also increases. Host survivorship, however, is expected to decline with increasing rates of propagule production, leading to a trade-off between the rate of parasite reproduction and host survivorship. This trade-off between reproductive rate and host survivorship can lead to selection for intermediate rates of parasite reproduction, and it forms the conceptual core of recent theories for the evolution of parasite virulence (e.g., May & Anderson, 1990; Bull, 1994; Read, 1994; Ebert & Herre, 1996; Frank, 1996).

Convincing experimental evidence for a trade-off has recently been presented for rodent malaria. Parasite replication rates were significantly different among eight strains of the malaria (*Plasmodium chabaudi*), and the rate of replication was significantly and positively related to virulence (Mackinnon & Read, 1999). In addition, parasite replication rate was genetically based, and it was positively and significantly correlated with transmission to mosquitoes. Similarly, a positive genetic correlation has been found between spore production by a microsporidian and host mortality in *Daphnia* (Ebert, 1994). Hence, a critical assumption of models for the evolution of virulence has an empirical foundation (review in Ebert & Herre, 1996).

Although host survivorship is expected to decline with the number of parasite propagules produced by a single infection, it is not obvious how interactions among these propagules might affect the evolution of parasite virulence. For example, each propagule

might reduce host survivorship by the same proportion as previous propagules, or it might decrease host survivorship by a greater or lesser amount. If each propagule decreases host survivorship by the same proportion, then the effects of these propagules on host survivorship are independent. Conversely, if each additional propagule decreases host survivorship by an ever-increasing amount, then the propagules have a compounding effect. This particular kind of compounding effect may be expected, for example, whenever the gradual destruction of host tissue leads, at some point, to catastrophic loss of function in a key host organ. Finally, the effect of each propagule on host survivorship may diminish with propagule number.

While the differences between independent, compounding, and diminishing effects of propagules have not been widely considered in models of parasite virulence, the underlying concepts have a rich history in theoretical population genetics. Early models of mutational load solved for mean fitness in populations exposed to recurrent deleterious mutations, which either had independent or compounding effects. The basic result was that mean fitness of sexual populations is expected to be higher at mutation-selection balance when each subsequent mutation exhibits a more negative effect than previous mutations (King, 1966; Kimura & Maruyama, 1966, Crow, 1970; Crow & Kimura, 1979). The reason stems, in part, from the fact that each genetic death eliminates more mutations from the population if mutations interact in such a way (Muller, 1950). These early models lead to the construction of deterministic mutation models for the maintenance of sexual reproduction (Kondrashov, 1982, 1988; Charlesworth, 1990), which make sense because the reduction in mutational load

experienced by sexual populations does not carry over to asexual populations (Kimura & Maruyama, 1966, Crow, 1970).

Here I construct a life-history model that seeks to determine the equilibrium level of within-host reproduction by a single strain of parasite. I then determine the effect of this equilibrium value on host survivorship for different kinds of interactions among propagules. The results are similar to the models of mutational load in suggesting that host survivorship at equilibrium should be related to the degree and type of interactions among propagules.

Models

The standard equation governing the number of secondary infections, R_0, generated by a primary infection is

$$R_0 = \frac{B(v)N_h}{\delta + v + c(v)}, \tag{1}$$

where, $B(v)$ gives the rate of disease transmission; N_h is the number of susceptible hosts; δ is the rate of host mortality, independent of infection; $c(v)$ is the recovery rate of infected hosts; and v is the rate of parasite-induced host mortality (Anderson & May, 1981; May & Anderson, 1990; variable labels following Frank, 1996). Note that both the rate of disease transmission, $B(v)$, and the rate of recovery, $c(v)$ may be functions of parasite virulence, v. Although the equation is strictly valid only for endemic diseases at equilibrium (Lenski & May, 1994; Frank, 1996), recent theory suggests that evolution will tend to move host-parasite systems to either extinction or stable population dynamics (Lenski & May, 1994; Koella & Doebeli, 1999), unless transmission is achieved through long-lasting spores (Koella & Doebeli, 1999).

For the purpose of the present study, it is helpful to rewrite the eq. (1) as

$$R_0 \quad W = \frac{f(\lambda)}{\delta + v(\lambda) + c(\lambda)}, \tag{2}$$

where λ is the within-host rate of reproduction, and $f(1)$ gives the number of parasite propagules available for transmission at time t. Under this form of the model, R_0 is maximized by maximizing W. In what follows, I assume that (i) that a single parasite strain exists within an infected host; (ii) that transmission is strictly horizontal; (iii) that infected hosts either do not have an immune system, or cannot clear the infection (thus c(1) =0); and (iv) that the rate of host mortality in the absence of infection is unity (thus d = 1). Thus,

$$W = \frac{f(\lambda)}{1 + v(\lambda)}. \tag{3}$$

These assumptions could later be relaxed, but their effects have been treated previously (review in Frank, 1996).

If a parasite has time t for reproduction within its host, then the number of propagules available for horizontal transmission to the next host at time t, N_t, is:

$$N_t = N_0\lambda^t = f(1). \tag{4}$$

This expression gives the standard equation for density-independent population growth, where N_0 is the number of parasites at time 0. (See Ebert & Weisser, 1997 for a model including density-dependent effects.) After the growth period, the parasite becomes infective, and decreases host survivorship in proportion to N_t. The total time of infection, T, is derived as the integral of the probability of survivorship for infected hosts, where this probability is estimated as exp–[d + v(1) + c(1)] (Bremermann and Pickering, 1983). Under the present assumptions of d = 1 and c(1) = 0, the time of infection is estimated as:

$$T = \int_0^{\infty} e^{-(1+v(\lambda))t}\,dt = \frac{1}{1+v(\lambda)}\,. \tag{5}$$

Hence, by substitution from eqs. (4) and (5), the estimate for parasite fitness, eq. (3), can also be expressed as:

$$W = TN_t\,. \tag{6}$$

Of primary interest here is defining the function *T*, which depends on the parasite-induced rate of mortality for infected hosts [v(l)]. To define the function, I borrow from population genetic theory, developed to understand the effects of mutations on population mean fitness at mutation-selection balance (Kimura & Maruyama, 1966; Crow, 1970; Crow & Kimura, 1979; Kondrashov, 1982, 1988; Charlesworth, 1990). The borrow makes sense, because adding additional propagules is conceptually similar to adding additional mutations. Of particular interest in mutation theory is the difference between models where mutations act independently versus models in which mutations have epistatic effects. The same is true for the present paper, except that, instead of mutations, I am interested in the effects of interactions among propagules on host survivorship. In particular, I am interested in cases where a parasite propagule has the same effect as preceding propagules versus cases where a propagule has a more (or less) effect than previous propagules.

In what follows, I find the value of l that maximizes parasite mean fitness for different kinds of interactions among parasite propagules. Parasite virulence evolves as a correlated response of selection on l. The models assume that there is additive genetic variation in the parasite's reproductive rate (l), and that genetic constraints do not prevent its evolution. The models further assume that the variation does not affect the direction of selection in the vicinity of the equilibrium. The equilibrium solutions are seen as

attractors of local evolutionary dynamics, not as predictions for the existence of genetically monomorphic populations. In addition, the present models assume that the number of parasite propagules affects the survivorship of hosts, but not the rate of contact between infected hosts and susceptible hosts. This important assumption could later be relaxed. The structure of all three models follows Bremermann and Pickering (1983) in assuming that parasite-induced mortality begins after the parasite stops reproducing and becomes infective. The qualitative results of the present study, however, should be conservative with respect to this assumption.

Independent effects of propagules

When the effects of propagules are independent, the rate of parasite-induced host mortality can be expressed as:

$$T = \frac{1}{1 + v(\lambda)} = (1 - s)^{N_t}, \tag{7}$$

where s gives the effect of each propagule (Fig. 1). This expression for T is analogous to the equation for independent effects of mutations (Kimura & Maruyama, 1966; Crow, 1970; Haigh, 1978). The idea here is that each additional parasite propagule has the same effect on the period of infection as all previous propagules (The shape of the function for various values of s is given in Fig. 1). For an avirulent parasite (s = 0), virulence is equal to zero (v(1) = 0); and the time of infection is unity (T = 1). Thus the model is directly comparable to mutation models where mean fitness in the absence of mutation is also unity. By substitution, R_0 is proportional to:

$$W = N_t (1 - s)^{N_t}. \tag{8}$$

The change in parasite fitness with respect to small changes is λ is determined by taking the first partial derivative of W with respect to λ. Local maxima in fitness meet two criteria, specifically that the first derivative is equal to zero, and the second derivative is negative (Maynard Smith, 1982):

$$\frac{\partial f(\lambda)}{\partial \lambda} = 0 \text{ and } \frac{\partial^2 f(\lambda)}{\partial \lambda^2} < 0 . \tag{9}$$

The value for λ that meets both criteria is:

$$\hat{\lambda} = \left[-\frac{1}{N_0 \mathrm{Ln}[1-s]} \right]^{\frac{1}{t}} . \tag{10}$$

Note that $\hat{\lambda}$ decreases with increasing values of s.

The equilibrium value for N_t is found by solving eq. (4) for $\lambda = \hat{\lambda}$, which gives

$$\hat{N}_t = -\frac{1}{\mathrm{Ln}[1-s]} . \tag{11}$$

Similarly, the equilibrium value for virulence is found by solving eq. (7) for $N_t = \hat{N}_t$, which gives:

$$\hat{v}(\lambda) = (1-s)^{-\hat{N}_t} - 1 = \mathrm{e} - 1 . \tag{12}$$

Interestingly, virulence at equilibrium is independent of s, the effect of each propagule. Time of survivorship of infected hosts at equilibrium is also independent of s, and is calculated as:

$$\hat{T} = \frac{1}{1+\hat{v}} = \mathrm{e}^{-1} \tag{13}$$

Finally, since the survivorship time of hosts infected by avirulent parasites (or uninfected hosts) is equal to 1, the survivorship of hosts infected by virulent parasites relative to that of hosts infected by avirulent parasites is simply $\mathrm{e}^{-1} = 0.368$. Since infection is likely to

reduce host fecundity as well as host survivorship, this value would likely represent a minimum effect on host fitness, which is nonetheless quite high.

Interactions among propagules: the exponential quadratic function

When the effects of propagules are not independent, host survivorship can be expressed as:

$$T = \frac{1}{1+v(\lambda)} = e^{-(\alpha N_t + \beta N_t^2)}. \tag{14}$$

Here I borrowed the basic formulation for T from studies of mutational load by Kimura & Maruyama (1966), and the exponential form of the equation from Charlesworth (1990). In this formulation, a is the coefficient of the linear term, N_t. The coefficient for the quadratic term, b, controls the degree and type of interaction among propagules. If b is positive, each additional propagule increases virulence by a greater amount (Fig. 2); if the term is negative, each additional propagule decreases virulence by a lesser amount (Kimura & Maruyama, 1966). If b is zero, the effects of propagules are independent, and eq. (14) is the same as eq. (7), assuming small values of s (Crow, 1970). By substituting eq. (14) into eq. (6), R_0 becomes proportional to:

$$W = N_t e^{-(\alpha N_t + \beta N_t^2)}. \tag{15}$$

Provided $\beta \neq 0$, the value for λ that meets the conditions of eq. (9), and thereby attracts the local evolutionary dynamics, is:

$$\hat{\lambda} = \left[\frac{-\alpha + \sqrt{\alpha^2 + 8\beta}}{4N_0\beta} \right]^{1}. \tag{16}$$

N_t evaluated at $\hat{\lambda}$ is:

$$\hat{N}_t = \frac{-\alpha + \sqrt{\alpha^2 + 8\beta}}{4\beta}, \tag{17}$$

and virulence evaluated at $\hat{N}_t$ reduces to:

$$\hat{v}(\lambda) = e^{\left(-\alpha^2 + 4\beta + \alpha\sqrt{\alpha^2 + 8\beta}\right)/8\beta} - 1. \tag{18}$$

Thus, in contrast to the previous case, virulence at equilibrium is not constant, but rather decreases with increases in the degree of interaction among propagules (which increases with b). Similarly the survivorship of infected hosts at equilibrium is

$$\hat{T} = e^{\left(\alpha^2 - 4\beta - \alpha\sqrt{\alpha^2 + 8\beta}\right)/8\beta} \tag{19}$$

Note that for $\alpha = 0$, the period of infection reduces to $\hat{T} = 1/\sqrt{e} = 0.607$. Thus host survivorship time is much (1.65 times) greater at equilibrium when propagules have compounding effects than when the effects of propagules are independent ($\hat{T} = 1/e = 0.368$). A similar result is given by Bremermann and Pickering (1983).

For b = 0 (i.e., no interactions), l at equilibrium is

$$\hat{\lambda} = \left[\frac{1}{N_0\alpha}\right]^{1/t}. \tag{20}$$

The equilibrium time of survival for infected hosts at this value is $\hat{T} = e^{-1}$, which corroborates the result above [eq. (13)] for independent effects of propagules.

Interactions among propagules: Infection-mediated truncation in host survivorship

Alternatively, interactions among parasite propagules or mutations may cause host survivorship to go to zero at some threshold number (following King, 1966; Kimura & Maruyama, 1966; Crow, 1970; Kondrashov, 1982, 1988). When the effects of propagules are dependent on the number of propagules and host fitness is truncated at

some value, k, host survivorship time (T) can be expressed as (following Howard's [1994] study of mutation accumulation):

$$T = \frac{1}{1+v(\lambda)} = 1 - \left[\frac{N_t}{k}\right]^a, \tag{21}$$

where the exponent, a, controls the shape of the virulence function. For values of a less than one, the effect of each propagule diminishes with propagule number. In contrast, for values of a greater than one, the effect of each propagule increases with propagule number. For example as the exponent, a, goes to infinity, host survivorship becomes more threshold-like, going from one to zero as N_t approaches k. Finally, if a is equal to one, the effect of each propagule is constant at $1/k$ (Fig. 3). Substituting from eq. (21) into eq. (6), R_0 becomes proportional to:

$$W = N_t \left[1 - \left(\frac{N_t}{k}\right)^a\right]. \tag{22}$$

The value for λ that meets the conditions of (9) and thus gives the attractor of local evolutionary dynamics is:

$$\hat{\lambda} = \left[\frac{k}{N_0}\left(\frac{1}{1+a}\right)^{\frac{1}{a}}\right]^{\frac{1}{t}}. \tag{23}$$

The equilibrium value of N_t, evaluated at $\hat{\lambda}$ is

$$\hat{N}_t = k\left[\frac{1}{1+a}\right]^{\frac{1}{a}}; \tag{24}$$

and virulence of the parasite evaluated at $\hat{N}_t$ simplifies to:

$$\hat{v}(\lambda) = \frac{1}{a}. \tag{25}$$

Finally, the period of survivorship of infected hosts at equilibrium reduces to:

$$\hat{T} = \frac{a}{1+a}. \tag{26}$$

Hence, consistent with the exponential quadratic model, strong interactions among propagules should lead to high levels of host survivorship at equilibrium. For example, as *a* goes to infinity, the period of survivorship of infected hosts at equilibrium goes to unity, which is equal to the period of survivorship of uninfected hosts.

Discussion

The results of the present models are consistent with previous theory suggesting that parasite virulence should evolve to intermediate levels when there is a trade-off between within-host growth rate and host survivorship (e.g., Anderson & May, 1981; Levin & Pimentel, 1981; Bremermann & Pickering 1983; Anita et al. 1994; Bull, 1994; Read, 1994; Frank, 1996). The results also suggest that interactions among propagules can have dramatic effects on the evolution of parasite virulence. For example, interactions among the propagules produced by a single infection should lead to the evolution of low virulence when the effect of each propagule greatly increases (or compounds) as the number of propagules increase (Fig. 3). The basic result ("compounding leads to lower virulence") may sound counter-intuitive at first, but makes sense when one considers the cost imposed on host survivorship when parasites that exhibit such strong interactions also reproduce too quickly. The result is perhaps easiest to envision under threshold effects (i.e., large *a* in eq. 21), in which producing one propagule too many drives host survivorship from one to zero. Natural selection for a slightly slower growth rate would result in a dramatic increase in host survivorship at equilibrium. Although it seems

unlikely that the interaction among propagules would be this dramatic, the basic reasoning holds for lower levels of compounding effects.

In the construction of the present models, I borrowed from theory regarding the effects of mutation of host fitness, reasoning that adding parasite propagules is conceptually similar to adding mutations. The main difference between the mutational models and the virulence model presented here is that parasite virulence can evolve in response to host survivorship, while the genome-wide rate of deleterious mutations (U) is usually treated as a fixed parameter. In the present models, parasite virulence evolves as a correlated response to selection on the within-host rate of reproduction (λ). Standard techniques were used to find the equilibrium values of λ that maximizes parasite fitness. These equilibrium solutions are probably best regarded as attractors of local dynamics, given additive genetic variation for parasite reproductive rate.

If the effects of propagules are independent, the results suggest that $\hat{\lambda}$ should decrease with increasing values of s, but that host survivorship at $\hat{\lambda}$ should hold constant at e^{-1} (for d =1) independent of the value of s (Fig. 1). This finding is similar to results from mutation-accumulation models for population mean fitness. In these models of genetic load, mean fitness of large populations is expected to be e^{-U}, independent of the value of selection against individual mutations (Kimura & Maruyama, 1996; Crow, 1970, Haigh, 1978). Note that for $U = 1$, the results of the virulence model and the mutation accumulation model are identical. It would appear that, for this special case, the balance between mutation and selection occurs at the same point as the balance between the parasite's rate of within-host reproduction and the effects of this reproduction on host survivorship.

The results are more complex if the effects of propagules are not independent, but rather change as the number of propagules changes. I considered two cases for interactions among propagules. In both cases, parasite virulence at $\hat{\lambda}$ decreased with increasingly negative effects as the number of propagules increased (Figs. 2 and 3). In the truncation model, host survivorship approaches an asymptote of 1 as the value of *a* increases, where *a* gives the measure for interactions in this model. These results are also similar to population genetic models, which show that the mean fitness of sexual populations increases at mutation-selection balance as negative epistasis among mutations increases (e.g., Kimura & Maruyama, 1966; Crow, 1970, Crow & Kimura, 1979).

For the exponential quadratic model, host survivorship at equilibrium increases with increases in interactions among propagules, unless the coefficient (α) for linear coefficient is equal to zero. If the linear term is equal to zero, then the expected level of infected host survivorship is $e^{-0.5}$, independent of the value of the quadratic term, b. For non-zero values of the linear term, the survivorship of infected hosts appears to rapidly converge on $e^{-0.5}$ as the quadratic term is increased from zero. Hence even small degrees of negative interactions (b >1) lead to about a 1.6 fold increase in host survivorship [$e^{-0.5}/e^{-1} = 1.6$]. On the other hand, even slightly negative values of b should lead to high virulence ($< e^{-1}$) at equilibrium. This later result is again in parallel to results from mutation models, which show that population mean fitness should be very low under diminishing returns epistasis (Kimura & Maruyama, 1966).

One difference between the two formulations for interactions is that they have different qualitative effects on selection for $\hat{\lambda}$. In the exponential quadratic model, for

example, $\hat{\lambda}$ decreases with increases in the degree of interaction (increases in b), while in the truncation model, $\hat{\lambda}$ increases with the degree of interactions (increases in *a*). I think the reason for this result is simply that increasing the compounding effects of propagules pushes the host survivorship curve to the left in the exponential quadratic model, while increasing the effect pushes the survivorship curve to the right in the truncation model. Pushing the curve to the right selects for a higher growth rate in the parasite by virtue of increasing host survivorship.

Taken together, these results suggest that (all else equal) higher virulence should be found in parasites producing propagules that have independent effects on host survivorship, or parasites for which each additional propagule reduces survivorship by less than previous propagules. Such parasites would also be more likely, in general, to select for sex and high levels of recombination in their host populations (Howard & Lively, 1994, 1998; Peters & Lively, 1999), especially if the effects on host survivorship and host reproductive rate are positively correlated. Conversely, parasites that produce propagules that interact strongly should have lower effects on host survivorship at $\hat{\lambda}$, although they might still have dramatic effects on host fecundity, as for cases of parasitic castration. The qualitative prediction (that stronger interactions among propagules should lead to lower levels of virulence at equilibrium) could be tested by experimentally increasing the propagule loads for virulent and benign parasites. The models presented here suggest that relatively benign parasites should cause a more dramatic decrease in host survivorship as the number of parasites is experimentally increased.

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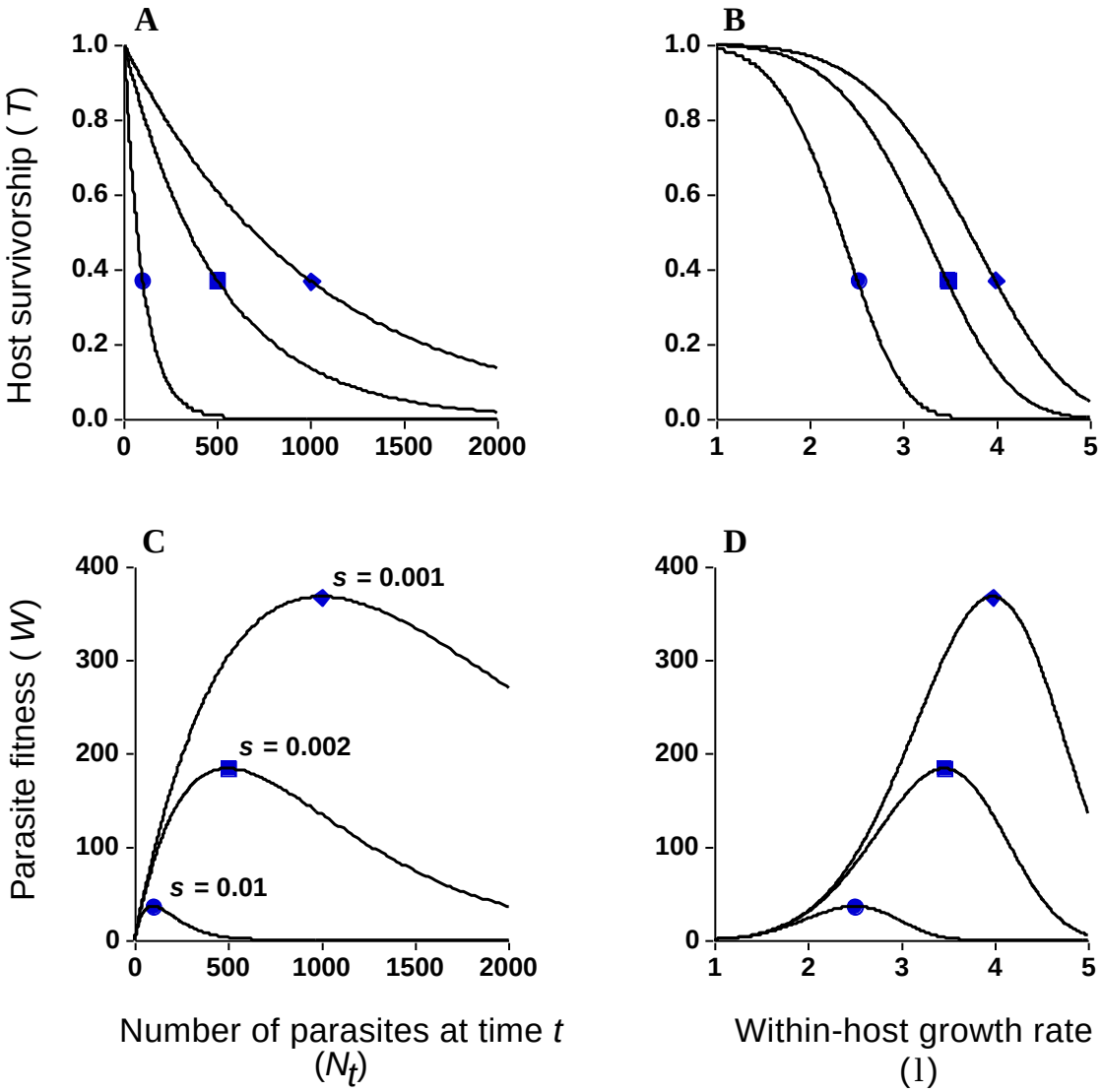

Fig. 1. Independent effects of parasite propagules, where the variable s gives the effect of each propagule. In all four panels, the values of s are as follows: lower curve, $s = 0.01$; middle curve, $s = 0.002$; and upper curve, $s = 0.001$. Symbols give the analytical solutions for the equilibrium values l (eq. 10) and N_t (eq. 11) as follows: circle: $s = 0.01$; square: $s = 0.002$; and diamond: $s = 0.001$. Note that these equilibrium values do not vary with the value of s. Curves in all four panels were drawn for $t = 5$, and $N_0 = 1$. *A*. The relationship between the survivorship of infected hosts and number of parasite propagules at time, $T = (1-s)^{N_t}$. *B*. The relationship between the survivorship of infected hosts and the parasite's growth rate, l. *C*. The relationship between parasite fitness and number of propagules at time t (from eq. 8). *D*. The relationship between parasite fitness and l.

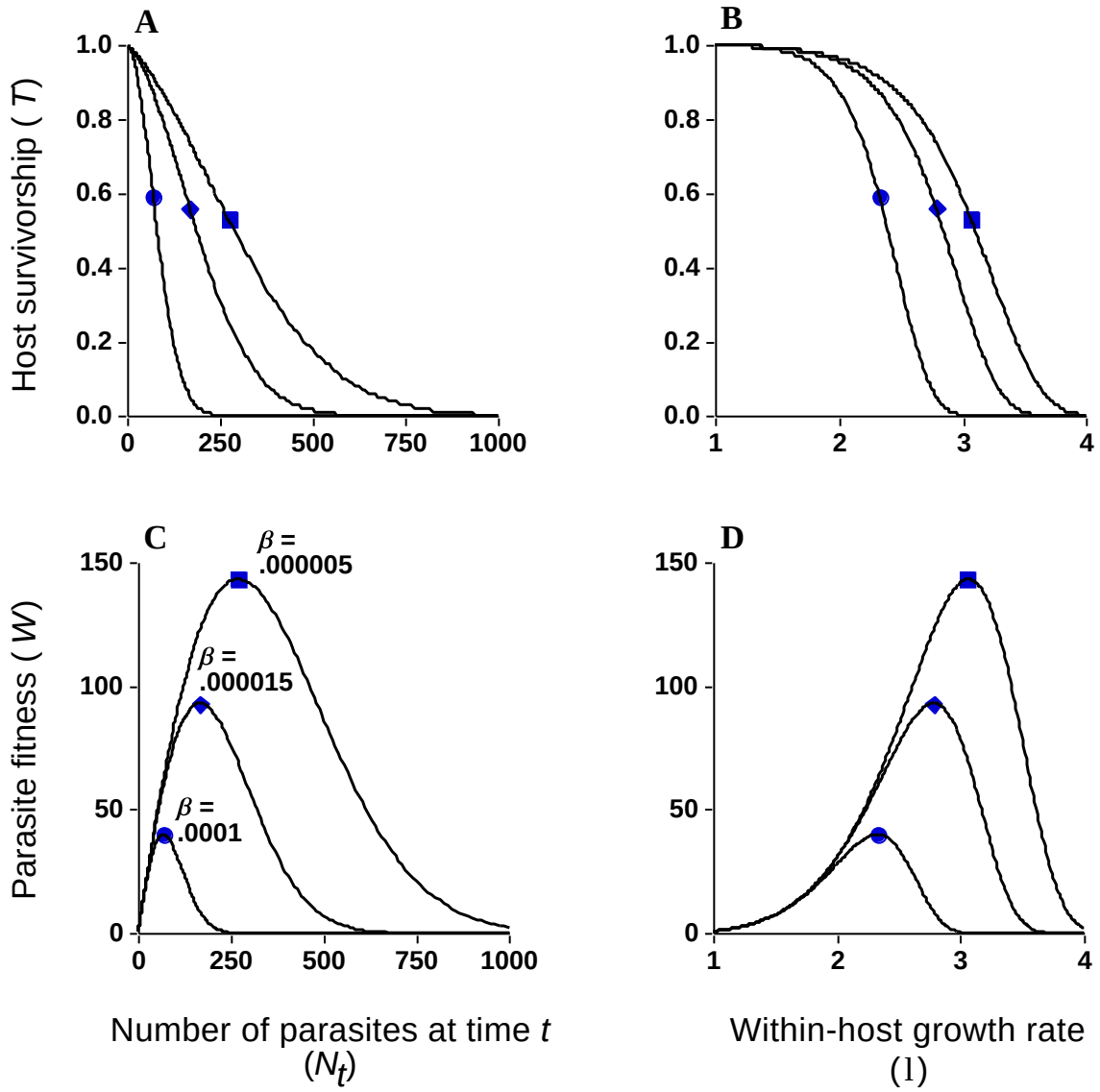

Fig. 2. Compounding effects of parasite propagules using the exponential quadratic function, where b gives the coefficient to the quadratic term (eq. 14). In all four graphs the values of b are as follows: lower curve, b = 0.0001; middle curve, b = 0.000015; and upper curve, b = 0.000005. Symbols give the analytical solutions for the equilibrium values of l (eq. 16) and N_t (eq. 17) as follows: circle: b = 0.0001; square: b = 0.000015; and diamond: b = 0.000015. Note that the equilibrium values increase with increasing values of synergism among propagules. Curves in all figures drawn for t = 5, a = 0.001, and N_0 = 1. *A*. The relationship between host survivorship and number of parasite propagules at time t (derived from eq. 14). *B*. The relationship between host survivorship and l. *C*. The relationship between parasite fitness and number of propagules at time t (from eq. 15). *D*. The relationship between parasite fitness and l. Lively, Fig. 2

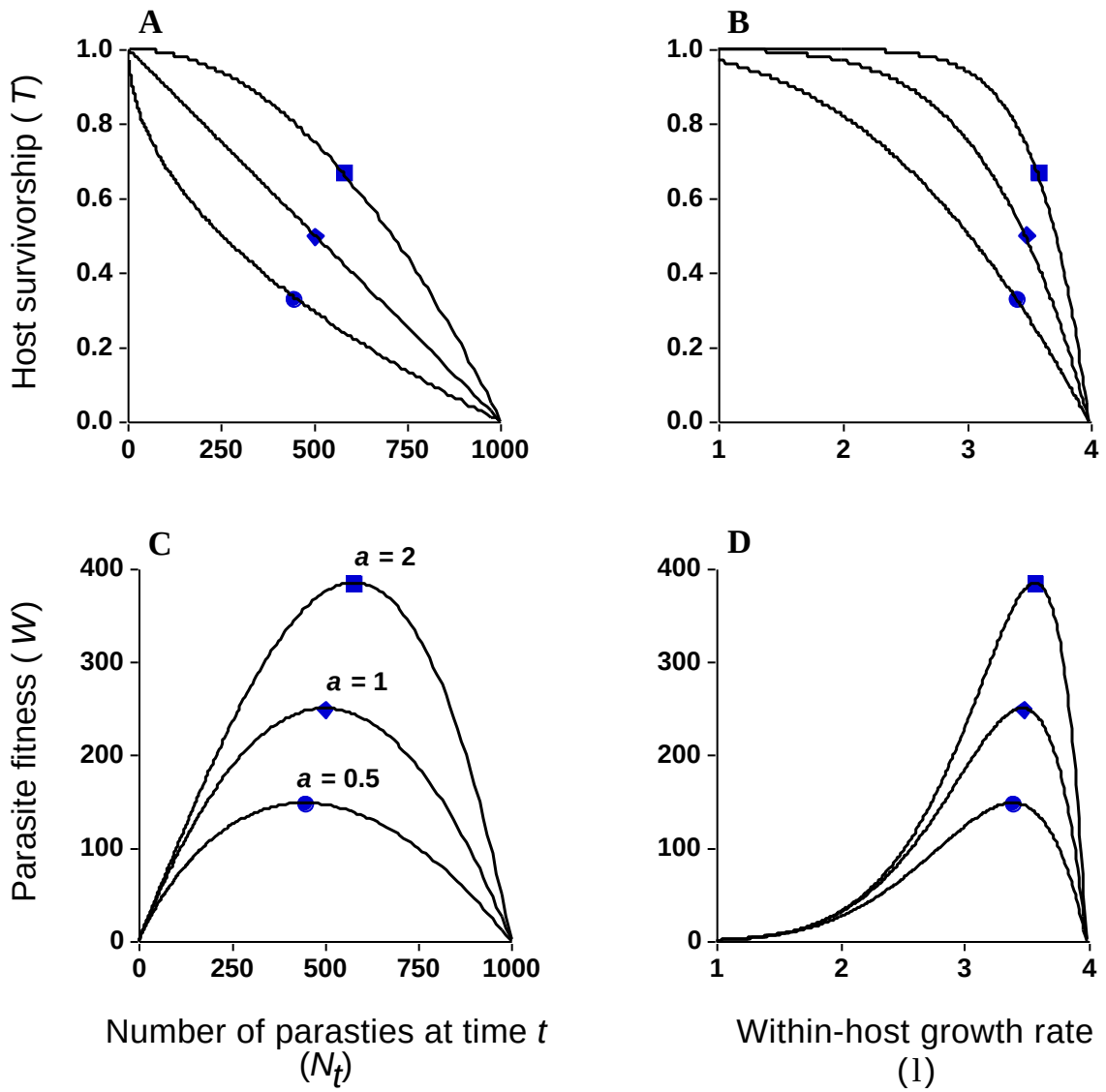

Fig. 3. Effects of parasite propagules using the truncation function, where the variable a gives the strength of interaction among propagules (eq. 15). In all four panels the values of a are as follows: lower curve, $a = 0.5$; middle curve, $a = 1$; and upper curve, $a = 2$. Symbols give the analytical solutions for the equilibrium values of l and N_t as follows: circle: $a = 0.5$; square: $a = 1$; and diamond: $a = 2$. Note that the equilibrium values increase with increasing values of synergism among propagules. Curves in all figures drawn for $t = 5$, $k = 1000$, and $N_0 = 1$. *A*. The relationship between host survivorship and number of propagules at time t (derived from eq. 21). *B*. The relationship between host survivorship and l (derived from eq. 21). *C*. The relationship between parasite fitness and number of propagules at time t (eq. 22). *D*. The relationship between parasite fitness and l (derived from eq. 22).