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The role of host population heterogeneity in the evolution of virulence

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I examine here the effects of host heterogeneity in the growth of immune response on the evolution and co-evolution of virulence. The analysis is based on an extension of the 'nested model' by Gilchrist and Sasaki [*Modeling host-parasite coevolution*, J. Theor. Biol. 218 (2002), pp. 289–308]; the criteria for host and parasite evolution, in the paradigm of adaptive dynamics, for that model are derived in generality. Host heterogeneity is assumed to be fixed at birth according to a lognormal distribution or to the presence of two discrete types. In both cases, it is found that host heterogeneity determines a dramatic decrease in pathogen virulence, since pathogens will tune to the 'weakest' hosts. Finally, the difference in modelling assumptions is clarified why different results are present in the literature.

Keywords: evolution of virulence; host heterogeneity; host–pathogen coevolution; pathogen-immune dynamics

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1. Introduction

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The evolution of virulence is at the centre of very extensive theoretical investigations, with also practical consequences and experimental tests [10]. Within a very extensive literature on the subject, only few papers have considered the effect of heterogeneity in host population, with contrasting results [13,14,17,29].

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I analyse here this problem in the framework of 'nested models' where the between-host transmission model is coupled with a (simplified) model of host immune response [2,15,16,21]; precisely, I assume that individuals differ in the rate of immune response, so that the host population will consist of a mixture of individuals more or less able to cope with a pathogen infection. This idea is applied to the model proposed by Gilchrist and Sasaki [16], slightly modified as for host demography; this modification allows for a clear presentation of the assumptions used in the invasion analysis.

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The model is presented in Section 2 and its evolutionary analysis in Section 3, where I look specifically at the evolution of disease-induced mortality; the criterion for host evolution, studied by Gilchrist and Sasaki [16] only in the limiting case of negligible natural mortality, is

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extended to arbitrary natural mortality. In the following section, the model is extended allowing for heterogeneous hosts; the focus of the analysis is on the effect of heterogeneity on the evolution of disease-induced mortality. In Section 5, I compare the results obtained on the effect of heterogeneity with those obtained by different authors and suggest possible extensions to make the model more realistic.

2. Nested model

In the 'nested models' framework, there is a model for within-host pathogen dynamics that is then coupled to a between-host transmission model.

2.1. Within-host model

The analysis here is based on the model proposed by Gilchrist and Sasaki [16], in which within-host immune response is described in a very simple way. Precisely, the within-host state is described through the pathogen load P and the host's level of specific immunity B. The variable B may represent some precise quantity, such as the density of specific B-cells, or a more generic index related to the different types of immune cells specific for that pathogen agent.

The model has the structure of a predator–prey model, with pathogens (the prey) replicating at, in the absence of immune response, rate r and being killed by the immune system at rate c on encounter, while the immune cells proliferate proportionally (with a proportionality constant a) to the pathogen load:

$$\frac{dP}{d\vartheta} = rP - cBP,$$

$$\frac{dB}{d\vartheta} = aBP, \tag{1}$$

where ϑ represents the time since infection of the individual host.

The initial conditions (at the time of infection) $P(0) = P_0$ and $B(0) = B_0$ are assumed to be identical for all individuals that get infected. Note that by appropriate rescaling of variables, it would be possible to set $P_0 = B_0 = 1$ (and $c = 1$) as in [16]. I choose to avoid this, so that one could consider evolutionary dynamics of different parameters.

From an analysis of the phase plane of Equation (1), one easily sees that, as long as the initial conditions satisfy $r > cB_0$, pathogen level $P(\vartheta)$ initially increases to a maximum and then declines to 0, while $B(\vartheta)$ increases to an asymptotic level (depending on initial conditions) B_∞. From the similarity of Equation (1) to the classical SIR epidemic models, Gilchrist and Sasaki [16] found that the asymptotic value B_∞ can be obtained as the unique root in $(B_0, +\infty)$ of

$$c(B_\infty - B_0) = r \log\left(\frac{B_\infty}{B_0}\right) + aP_0. \tag{2}$$

Note that recovery is not explicitly modelled in this system; however, when an individual reaches a B level close to B_∞, it is effectively immune to further infections and its pathogen load is effectively 0.

Other simple models for within-host pathogen–immune interactions have been considered [24,28,33] with potentially different behaviours that may be realistic in many cases. For the purpose of this analysis, system (1) describes adequately the dynamics of an acute infection that is eventually cleared by the immune system. This is therefore the kind of infection dynamics that is considered in this paper.

2.2. *Between-hosts transmission*

As for between-hosts transmission, the basic idea is to assume that the force of infection of an infected host is proportional to its pathogen load, i.e. equal to $\beta_0 P$. The constant β_0 will be related to the probability that an infecting particle reaches a host compartment from which it can be released outside (saliva, skin, ..., depending on transmission features) and can then reach another host.

The other 'macroscopic' feature that will depend on internal state is the death rate of infected hosts. The assumption used by Gilchrist and Sasaki [16] is that, beyond a natural mortality level d, infected hosts will die, proportionally to rP, because of direct ill effects caused by pathogen growth and, proportionally to aBP, because of resource strains caused by immune system growth. Hence, the death rate of infected individuals will be

$$d + \alpha(B, P) := d + k_1 r P + k_2 a B P. \tag{3}$$

Note that Ganusov *et al.* [14] made a very different assumption about pathogen-induced deaths.

In order to insert these assumptions into a proper mathematical framework, one could introduce a density function $i(t, B, P)$ of infected hosts with immune level B and pathogen load P and derive a partial differential equation (to be intended in a weak sense) for it. Alternatively, as in [16], one can describe infected hosts only in terms of their infection age ϑ, since Equations (1) together with initial conditions $B(0) = B_0$ and $P(0) = P_0$ yield unique expressions $B(\vartheta)$ and $P(\vartheta)$, albeit impossible to compute explicitly; then a partial differential equation in t and ϑ can be derived.

Following the approach by Diekmann *et al.* [11], I prefer to write the equations in terms of 'birth' (in this context meaning infection) rates and kernels, since this framework allows for generalizations without too many technical problems. In this case, the state at birth is unique (all infected individuals start with the same initial conditions), and within-host dynamics after infection is not influenced by the rest of the population. Then it is possible to compute the probability of surviving to infection age ϑ as

$$\exp\left\{\int_0^\vartheta [d + \alpha(B(\tau), P(\tau))]\,d\tau\right\} = e^{-d\vartheta}\pi(\vartheta) \tag{4}$$

with (check Equation (21) of [16])

$$\pi(\vartheta) = \exp\left\{-\int_0^\vartheta [k_1 r P(\tau) + k_2 a B(\tau) P(\tau)]\,d\tau\right\} = \left(\frac{B(\vartheta)}{B_0}\right)^{-k_1 r/a} e^{-k_2(B(\vartheta)-B_0)}. \tag{5}$$

Then the density of infectives of infection age ϑ at time t will be given by

$$i(t, \theta) = \varphi(t - \vartheta)\,e^{-d\vartheta}\pi(\vartheta), \tag{6}$$

where $\varphi(t)$ is the instantaneous rate of new infections at time t ('birth' rate).

$\varphi(t)$ will be the product of susceptibles $S(t)$ times the force of infection; this latter is given by the integral (over all infection ages ϑ) of $\beta_0 P(\vartheta)$ times the density of infectives of age ϑ $i(t, \theta)$, i.e.

$$\varphi(t) = S(t)\int_0^\infty \beta_0 P(\vartheta)\,e^{-d\vartheta}\pi(\vartheta)\varphi(t - \vartheta)\,d\vartheta. \tag{7}$$

The total population size is

$$N(t) = S(t) + \int_0^\infty i(t, \theta)\,d\vartheta = S(t) + \int_0^\infty e^{-d\vartheta}\pi(\vartheta)\varphi(t - \vartheta)\,d\vartheta. \tag{8}$$

The dynamics must be completed by an equation for susceptibles $S(t)$. This will be a balance between fertility (it is assumed that new hosts are born susceptibles both from susceptible and

infected individuals), mortality d and infection rate $\varphi(t)$. We then obtain

$$S'(t) = b(N(t))N(t) - dS(t) - \varphi(t). \tag{9}$$

Following Bremermann and Thieme [6], I assume that fertility is a decreasing function $b(N)$ of total population size $N(t)$ such that $b(0) > d$ and there exists a carrying capacity K such that $b(K) = d$. An extreme assumption would be $b(N) = \Lambda/N$, so that $K = \Lambda/d$.

If $b(N) = \Lambda/N$, system (7)–(9) is in the class of systems studied by Thieme and Castillo-Chavez [32] in their study of models for HIV/AIDS. Following their analysis with a generic function $b(N)$, it can be seen that a key quantity in determining the behaviour of the system is

$$R_0 = K \int_0^\infty \beta_0 P(\vartheta) \, e^{-d\vartheta} \pi(\vartheta) \, d\vartheta. \tag{10}$$

The quantity R_0 can be easily interpreted as the expected number of hosts infected by a newly infected host over its lifetime, if the susceptible population is kept at the disease-free equilibrium K.

If $R_0 \leq 1$, the only equilibrium is $(S, \varphi) = (\Lambda/d, 0)$, which is globally asymptotically stable; if $R_0 > 1$, $(\Lambda/d, 0)$ is unstable and there exists a unique endemic equilibrium (S^*, φ^*) (Appendix 1).

Although a general proof of stability is missing, I will take for granted that, if $R_0 > 1$, the endemic equilibrium (S^*, φ^*) is the global attractor of the solutions of (7)–(9).

3. Pathogen and host evolution

3.1. *Pathogen evolution*

Bremermann and Thieme [6] proved, within the context of SIR ODE models, that in the competition between several pathogen strains with complete cross-immunity, only the strain with the highest value of R_0 survives. The same result was proved (through invasion analysis) by Anderson and May [1] and has been widely used.

In the paradigm of adaptive dynamics (small and rare mutations) [20], this property leads to the evolution of the pathogen strain with the highest feasible value of R_0.

Gilchrist and Sasaki [16] employ the same criterion, without giving a proof since they considered it to be standard through invasion analysis. For the sake of completeness, in Appendix 2, I present a proof of the maximization of R_0 for the current model, as long as it is true that (S^*, φ^*) is the global attractor of the solutions of Equations (7)–(9).

If it is assumed [16] that pathogen replication rate r is free to evolve, evolution will lead to reaching a maximum of R_0 as a function of r. To see how R_0 defined in Equation (10) will depend on r, one uses Equation (5) and, with a change of variables, arrives at

$$\begin{aligned}
R_0 &= \beta_0 K \int_0^\infty P(\vartheta) \, e^{-d\vartheta} \pi(\vartheta) \, d\vartheta \\
&= \beta_0 K \int_0^\infty P(\vartheta) \, e^{-d\vartheta} \left(\frac{B(\vartheta)}{B_0} \right)^{-k_1 r/a} e^{-k_2(B(\vartheta) - B_0)} \, d\vartheta \\
&= \frac{\beta_0 K}{a B_0} \int_{B_0}^{B_\infty} e^{-dB^{-1}(u)} \left(\frac{u}{B_0} \right)^{-k_1 r/a - 1} e^{-k_2(u - B_0)} \, du.
\end{aligned} \tag{11}$$

This is Equation (26) of [16], except that there $d = 0$ is used, assuming that d is much smaller than other parameters.

Looking just at the direct dependence of Equation (11) on r, it may seem that R_0 is a decreasing function of r. However, also B_∞ is an increasing function of r, and since for any t $B(t)$ is an increasing function of r, $B^{-1}(u)$ is a decreasing function of r.

Therefore, R_0 is affected by r in opposite directions, and it is not easy to understand analytically the overall effect. By numerical computations, R_0 has always been found a function with a single maximum; when a or k_1 is very large, it is possible to prove that $\mathrm{d}R_0/\mathrm{d}r|_{r=0} < 0$, so that the maximum is at $r = 0$. Using parameter values that give rise to epidemic dynamics that appear more realistic, R_0 is a bell-shaped function with an intermediate maximum (Figure 1).

How can pathogen virulence corresponding to a given r be defined? In the context of evolutionary epidemiology, virulence is generally synonymous to deaths induced by infection.

The probability of surviving the infection, neglecting natural deaths, is

$$\pi(\infty) = \left(\frac{B_\infty}{B_0}\right)^{-k_1 r/a} e^{-k_2(B_\infty - B_0)}. \tag{12}$$

$1 - \pi(\infty)$ is the case–fatality ratio and can be considered as a simple measure of virulence. It is apparent that $\pi(\infty)$ is a decreasing function of r; in Figure 1, it can be seen that it decreases sharply around the maximum of R_0. Note that from the figure it appears that survival increases with r for small values of r; this is an artefact, due to the fact that in that figure survival is actually computed as total survival (also from natural deaths) up to the end of infection and that infections are much longer with small r.

A slightly different definition of virulence, which keeps into account natural death rate, is given in [27]. Using that definition, the apparent decrease in virulence with increasing r for small r is avoided.

3.2. *Host evolution*

Gilchrist and Sasaki [16] analysed the evolution of a, the parameter measuring the speed of immune response growth. Considering the limiting case when the natural death rate d goes to 0, they prove, by invasion analysis, that evolution will tend to maximize $\pi(\infty)$, the probability of surviving the infection.
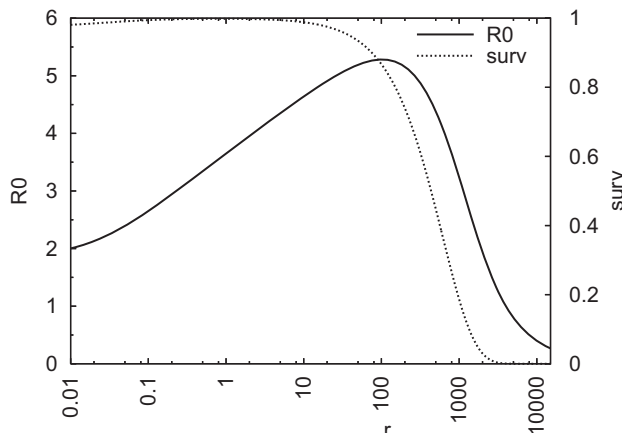

Figure 1. The values of the reproductive ratio R_0, from Equation (11), and host survival to the end of the infection, for different values of r. The scale for R_0 is on the left and that for survival on the right. Parameter values are $a = 1$, $c = 1$, $P_0 = 0.1$, $B_0 = 10^{-3}$, $d = 10^{-4}$, $k_1 = 10^{-4}$, $k_2 = 10^{-6}$ and $\bar{\beta}K = 0.4$.

In Appendix 3, I extend the analysis to an arbitrary mortality rate d, showing that, in the paradigm of adaptive dynamics, evolution will tend to the maximum of expected life of a newly infected individual, defined as

$$L = \int_0^{+\infty} e^{-d\vartheta} \pi(\vartheta) \, d\vartheta = \int_0^{+\infty} e^{-d\vartheta} \left(\frac{B(\vartheta)}{B_0} \right)^{-k_1 r/a} e^{-k_2(B(\vartheta)-B_0)} \, d\vartheta. \tag{13}$$

This principle is probably well known, but I could not find a precise reference in the literature.

It is then necessary to analyse L as a function of a, and it is not difficult to show that, analogously to $\pi(\infty)$ in [16], it will generally have a maximum at an intermediate value of a.

In fact, as long as $k_2 > 0$, $\lim_{a\to\infty} L = 0$, since, for each $\vartheta > 0$, $\lim_{a\to\infty} B(\vartheta) = +\infty$, while for each $a > 0$, $(B(\vartheta)/B_0)^{-k_1 r/a} < 1$.

On the other hand, a direct computation of the solution of Equation (1) for $a = 0$ [16], and of the corresponding variational equations, shows that $dL/da|_{a=0}$ is proportional to

$$\int_0^\infty e^{-d\vartheta - (k_1 r P_0/(r - cB_0))(e^{(r-cB_0)\vartheta} - 1)}$$

$$\times \left(\frac{k_1 r c P_0}{2(r - cB_0)^2} (e^{2(r-cB_0)\vartheta} - 1 - 2(r - cB_0)\vartheta e^{(r-cB_0)\vartheta}) - k_2(e^{(r-cB_0)\vartheta} - 1) \right) d\vartheta. \tag{14}$$

If Equation (14) is negative (which is true for small r), then L has a maximum at $a = 0$. Otherwise, it will have an intermediate maximum, which numerically appears to be always unique (Figure 2).

Note from Figure 2 that, while the qualitative dependence of L and $\pi(\infty)$ on a is similar, there is some quantitative difference, with the maximum of L being reached at quite lower values of a than the maximum of $\pi(\infty)$.

3.3. *Host–pathogen coevolution*

Gilchrist and Sasaki [16] have analysed in detail the co-evolution of r (controlled by pathogens) and a (controlled by hosts) using the canonical equations [7–9] with pathogen fitness proportional to the gradient of R_0 and host fitness proportional to the gradient of L. The isoclines of the system are given by the curves $r^*(a)$ (the value of r that maximizes R_0 for a given value of a) and $a^*(r)$ (the value of a that maximizes L for a given value of r). The direction of the vector field depends on the relative rates and size of mutations in host and parasites.
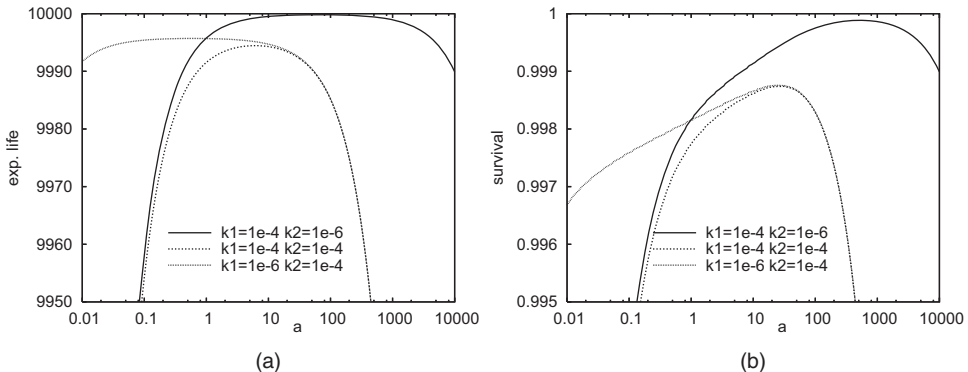

Figure 2. (a) The values of an infected individual expected life (13) L against a and (b) the values of the probability of survival (12) *vs. a*; for three different couples (see legend) of values of k_1 and k_2. Other parameter values are $r = 0.5$, $c = 1$, $P_0 = 10^{-1}$, $B_0 = 10^{-3}$, $d = 10^{-4}$ and $\bar{\beta} K = 40$.

301   In principle, co-evolutionary dynamics might depend on the relative speed of evolution in
302 host and parasites, although it is well possible that there is convergence to the co-evolutionary
303 equilibrium (intersection of the two isoclines) for any mutation structure [19]. As a simplified
304 case, a reasonable assumption is that the time scale of pathogen evolution is faster than that of
305 hosts; hence, in the limiting case, pathogens first evolve to $r^*(a)$ with a fixed; on the slower time
306 scale, a will evolve in the direction of $a^*(r)$, but r will immediately change, so that, on the slow
307 time scale, evolution will take place on the curve $r^*(a)$.
308   The shape of the two functions $r^*(a)$ and $a^*(r)$ is crucial in determining co-evolutionary
309 dynamics. As observed by Gilchrist and Sasaki [16], the function $a^*(r)$ is equal to 0 for r very
310 small (check Equation (14)) and then is an increasing function, following the intuition that the
311 more aggressive the pathogens are, the faster is the immune response to mount. On the other hand,
312 the function $r^*(a)$ is increasing for small a and then, after a long plateau, decreases, being equal
313 to 0 for very large a.
314   If k_1 is very large, it is possible that the intersection of the two isoclines occurs in the region where
315 $r^*(a)$ is decreasing. This corresponds to a co-evolutionary equilibrium with very small values of
316 r [16, Figure 7], even lower than cB_0, so that the pathogen level does not grow during an infection
317 beyond the initial inoculum P_0. This does not appear a realistic picture of actual infections;
318 moreover, in such cases, the model is lacking because it neglects the decrease in the within-host–
319 pathogen level due to transmitting an inoculum in the course of an infection (such a decrease is
320 not very relevant if P_0 is much lower than the pathogen level in the course of an infection).
321   For these reasons, in the rest of the manuscript, I restrict the consideration to low or moderate
322 values of k_1; in such cases, I always found that the two curves two curves $r^*(a)$ and $a^*(r)$ intersect
323 in the region where $r^*(a)$ is still increasing (Figure 3(a)). In such a case, necessarily evolution will
324 lead towards the unique intersection (a^{**}, r^{**}) of the two curves, independently of the structure
325 of host and pathogen mutations.
326   When this occurs, along most of the co-evolutionary path, host (and pathogen) fitnesses actually
327 decrease, at least in the limiting case of faster pathogen evolution. An example of this can be seen
328 in Figure 3(b) where the functions $L(a, r^*(a))$ and $R_0(a, r^*(a))$ are shown for each value of a.
329   In Appendix 4, I prove that if $r^*(a)$ is increasing for a close to the co-evolutionary attractor a^{**},
330 then $L(a, r^*(a))$ is a decreasing function of a over the same range. As long as a increases over
331 evolutionary time (the alternative would occur if the situation would be one of a host population
332 with too strong initial immune response), this implies that expected lifetime L will eventually
333 decrease over the course of evolution, i.e. virulence will increase.

(a)   (b)

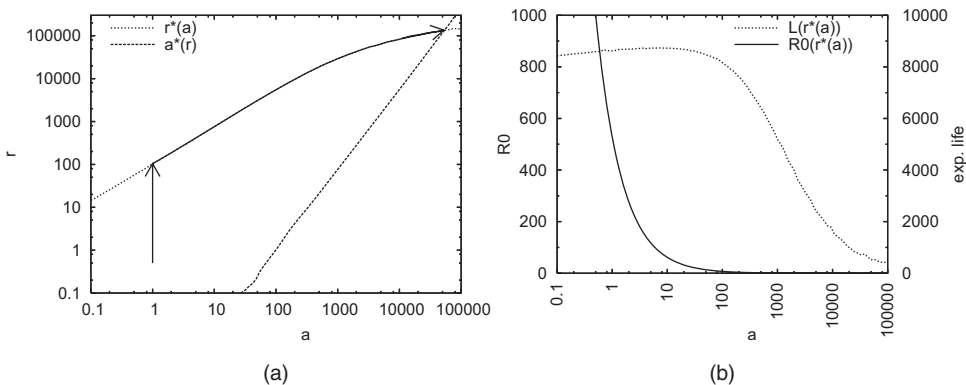Figure 3.   (a) The curves $r^*(a)$ and $a^*(r)$. Evolution will increase r when (a, r) is below $r^*(a)$ and will decrease it when above; analogously, a will increase when (a, r) is to the left of $a^*(r)$, decrease it when to the right. The bold line shows an evolutionary trajectory in the limiting case of separate time scale for the evolution of a and r. (b) The values of L and R_0 at $(a, r^*(a))$. Parameter values are $c = 1$, $P_0 = 10^{-1}$, $B_0 = 10^{-3}$, $d = 10^{-4}$, $\bar{\beta}K = 40$, $k_1 = 10^{-4}$ and $k_2 = 10^{-6}$.

4. Heterogeneous host population

The previous results can be described as implying that host–parasite co-evolution will bring, through an arms race, towards rather pathogenic infections. One aspect, among many other ones, that has not been considered in the analysis is host heterogeneity. This is the subject of this section through the analysis of a simple model, definitely not realistic or exhaustive, but capable of bringing qualitative conclusion about the issue.

4.1. *Parasite evolution*

Assume hosts are born with a fixed distribution $p(a)$ in the values of a. The resulting model can be written (in a slightly imprecise notation) as

$$S'_a(t) = p(a)b(N)N - (d + \lambda(t))S_a(t) \tag{15}$$

$$\varphi_a(t) = S_a(t)\lambda(t) \tag{16}$$

$$\lambda(t) = \iint_0^\infty \beta_0 P_a(\vartheta)\,e^{-d\vartheta}\pi_a(\vartheta)\varphi_a(t - \vartheta)\,d\vartheta\,dp(a), \tag{17}$$

where $P_a(\vartheta)$ and $\pi_a(\vartheta)$ are found from Equations (1) and (5), stressing their dependence on the value of a.

In writing model (15), it is implicitly assumed that the value of a affects the host's properties, if and after it is infected, but does not influence its birth or death rates, nor the probability of getting infected. Furthermore, there is random mixing, precisely no correlation between the value of a of a newly infected individual and that of its infector.

Finally, the fact that individuals are always born with the same distribution $p(a)$ means that a is not genetically transmitted. It may be thought as something like nutritional status, or social rank, except that it does not vary in time, but is fixed at birth.

The advantage of such a simplified model is that it is immediate to obtain an evolutionary principle. If the parameter r is evolving among pathogens, the uninvadable r will maximize

$$\int R_0(r, a)\,dp(a). \tag{18}$$

I have studied numerically, comparing them with the case where a is a constant, two possible cases: that of a lognormally distributed a and the one (whose results are easier to understand intuitively) where a has only two possible values.

In Figure 4, I show the values of R_0 *vs.* pathogen's replication rate r under the assumption of a lognormally distributed with different variances. Computations are made integrating an approximation of Equation (11) using the Gauss–Hermite method, as implemented in [26].

The feature most apparent in Figure 4 is the large increase in R_0 with increasing variance, for all but the largest values of r. Moreover, with increasing variance, the maximum of R_0 is reached at much smaller values of r. Finally, looking at the effect of variance on host survival, it can be seen (the bars on the graph should help) that, while at most fixed levels of r host survival decreases with increasing r, host survival at the value of r that maximizes R_0 increases with increasing variance.

In order to better understand the mechanism why the optimal r decreases with increasing variance, I consider the case where hosts are divided into two groups, differing in their immune
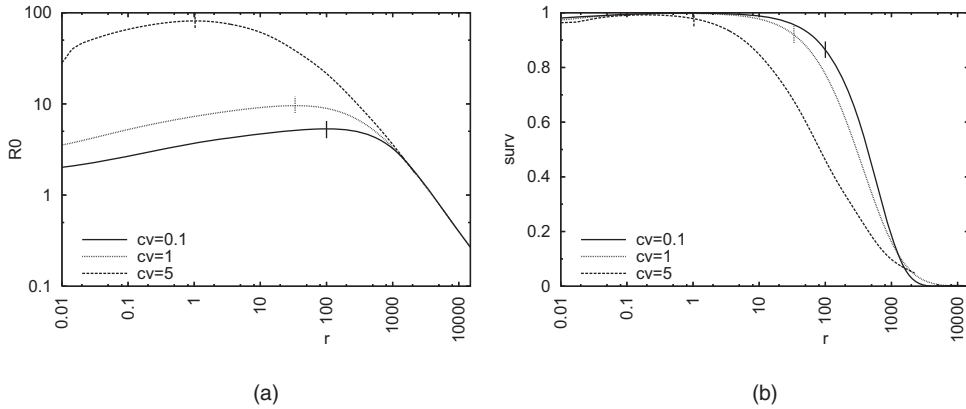
(a)   (b)

Figure 4.   (a) The values of the reproductive ratio R_0 (Equation (18)) against r. (b) Host survival to the end of the infection against r. a follows a lognormal distribution with mean 1 and different coefficients of variation (corresponding in this case to standard deviations) shown in the legend. The bars are at the values of r that maximize R_0 for each coefficient of variation. Parameter values are $c = 1$, $P_0 = 0.1$, $B_0 = 10^{-3}$, $d = 10^{-4}$, $k_1 = 10^{-4}$, $k_2 = 10^{-6}$ and $\bar{\beta}K = 0.4$.

response. Precisely, I choose

$$p(a) = p_1 \delta_{a_1}(a) + (1 - p_1)\delta_{a_2}(a) \tag{19}$$

with $p_1 = 10\%$ and a_1 fixed equal to 1 and study how the parasite optimal replication rate r depends on a_2, the value of a for the majority of the population.

Observing Figure 5(a), it can be noted that, while the optimal r is close to $r^*(a_2)$ (compare Figure 3) for $a_2 < a_1$ and also for a_2 slightly larger than a_1, increasing a_2 further causes the optimal r to decrease towards $r^*(a_1)$. In words, when a_2 is much larger than a_1, pathogen replication rate evolves towards the value best suited to a_1, although immune response is equal to a_1 only in a minority of hosts (10% in the example).

The reason for this can be seen graphically in Figure 5(b), where R_0 as a function of r is shown for $a = 1$ and $a = 20$. The loss for being suboptimal with hosts of $a = 1$ is much larger than with hosts of $a = 20$. Even if the losses are weighed by the proportion of hosts, still R_0 is largest with r close to 100.

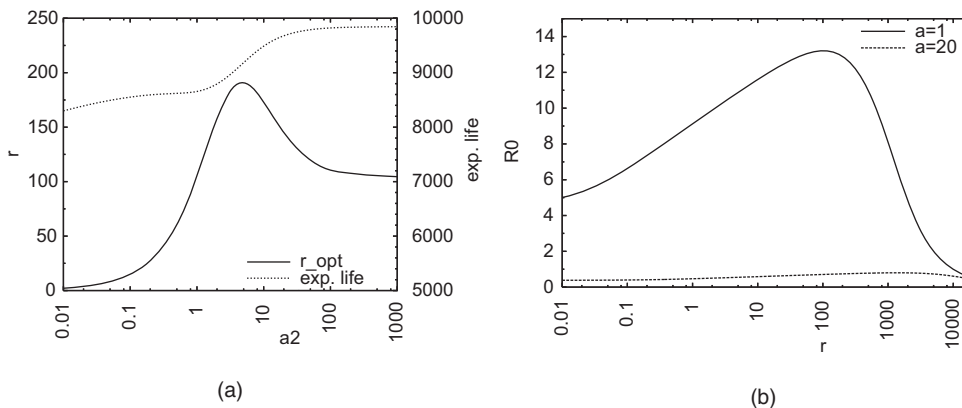

(a)   (b)

Figure 5.   (a) The value of r that maximizes R_0, given by Equation (18), and the corresponding host survival, for different values of a_2 (Equation (19)), $p_1 = 0.1$ and $a_1 = 1$. (b) R_0 as a function of r for $a = 1$ and $a = 20$. Common parameter values are $c = 1$, $P_0 = 0.1$, $B_0 = 10^{-3}$, $d = 10^{-4}$, $k_1 = 10^{-4}$, $k_2 = 10^{-6}$ and $\bar{\beta}K = 0.4$.

The result of the decrease in the optimal r with a is that the host survival computed at $(a_2, r^*(a_2))$ increases with a_2, contrary to what was found in Figure 3(b).

4.2. Host–parasite coevolution

In the previous subsection, it was assumed that state-at-birth of hosts were independent of the current population structure. If a were transmitted from mother to daughter, host population would tend to become monomorphic at the value of a maximizing L: heterogeneity would be lost.

I now study a model for host evolution, constrained to maintain the environmentally induced heterogeneity considered in the previous subsection. Specifically, I have considered two submodels corresponding to the cases examined in Figures 4 and 5.

In the first submodel, a is assumed to be lognormal, i.e. $\log(a) \sim N(\mu, \sigma^2)$: μ is assumed to be subject to selection and mutation, while σ is related to μ by the relation

$$\sigma = k(\mu - \mu_m). \tag{20}$$

In other words, each offspring of a mother with trait μ (or mutant with trait μ) will have a value of a from the corresponding lognormal distribution.

Relation (20) (that makes sense only for $\mu > \mu_m$) means that the standard deviation grows linearly with the mean, a scaling relation (sometimes known as Taylor's law [31]) widely applied in ecology [18] and recently also in cell biology [4].

Moreover, the idea that a may be small because of young age, low nutrition or similar reasons, entails that the evolution of μ must anyway allow for an almost constant quota of offsprings with low a, which implies that σ must increase with a. Some resulting distributions of $\log(a)$ are shown in Figure 6(a).

Using relation (20), I computed numerically for each μ the value of r ($r^*(\mu)$) maximizing Equation (18) and, for each r, the value of μ ($\mu^*(r)$) that maximizes

$$\int L(r, a)\, dp_\mu(a), \tag{21}$$

where p_μ represented the log-normal distribution parametrized from μ through Equation (20).

(a)   (b)
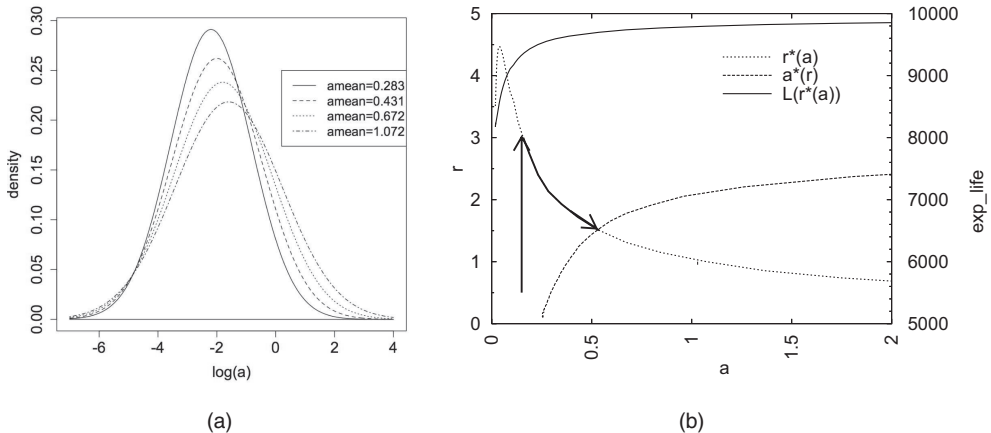
Figure 6.   (a) The density curves of a (in logarithmic scale) for different values of μ and relation (20). (b) The curves $r^*(\bar{a})$ and $\bar{a}^*(r)$ similar to Figure 3 but using the densities for a shown in (a). The bold line shows an evolutionary trajectory in the limiting case of separate time scale for the evolution of a and r. The solid line represents the average host survival after infection at the values $(\bar{a}, r^*(\bar{a}))$. Parameter values are the same as in Figure 3 plus $k = 0.7613$ and $\mu_m = -4$.

501   The results are shown in Figure 6(b) where, for ease of comparison with Figure 3, the distri-
502   butions are parametrized through $\bar{a} = e^{\mu + \sigma^2/2}$ instead of μ. It can be seen that $r^*(\bar{a})$ is initially
503   increasing but eventually decreasing with $\bar{a}$, as in Figure 5(a). Consequently, at least in the lim-
504   iting case (sketched in the figure) of time-scale separation, life expectancy (and host survival)
505   increases along the course of evolution (check Appendix 4), contrary to the case of homogeneous
506   host population but exactly as in Figure 5(a).
507   From the shape of the two curves, it is not possible to infer the evolutionary dynamics without
508   assumptions on the relative mutation rates. Indeed, just by looking at Figure 6(b), co-evolutionary
509   cycles cannot be excluded. In the limiting case where pathogen evolution is infinitely faster than
510   that of hosts, evolution proceeds vertically and then along the curve $r^*(\bar{a})$ obviously implying
511   convergence to the co-evolutionary steady state. By continuity, the same will be true whenever
512   pathogen evolution is much faster than hosts, a quite reasonable assumption.
513   The second submodel is based on the distribution (19) for a. Precisely, it is assumed that p_1
514   and a_1 are fixed, while a_2 can evolve. The resulting curve $r^*(a_2)$ is shown in Figure 5(a); the
515   curve $a_2^*(r)$ has a shape similar to those in Figure 3 or Figure 6(b), giving rise to an evolutionary
516   dynamics qualitatively similar to Figure 6(b).

5.   Discussion

The current manuscript is based on the model and methods proposed by Gilchrist and Sasaki [16].
I show that, for parameter values giving rise to realistic infection patterns, virulence evolution
and co-evolution in that model will tend to produce relatively high fatality rates after infection
and that inevitably these will eventually increase through co-evolution.
    The model has been extended allowing for host heterogeneity in immune response arising from
environmental causes. Admittedly, heterogeneity is modelled in a rather primitive way, since
immune response is taken as fixed at birth according to a given distribution. However, this allows
to perform computations rather quickly, and thus to obtain a first approximation of the effect of
this heterogeneity on virulence evolution.
    Just a limited amount of host heterogeneity causes a striking change in optimal parasite strategy:
the level of virulence selected for in pathogen drops dramatically (compare Figures 3 and 6).
    Using anthropomorphic language, we could say that 'optimal' pathogens tune their replication
rates to the weakest hosts, since these can allow for a long and persisting infection with ample
opportunities for pathogens' propagation; this is a selected strategy, even if it entails that the
pathogens get immediately cleared from most hosts with a better immune response. On the other
hand, more aggressive pathogens can resist (for some time, since eventual pathogen clearance
is certain in the within-host model) immune response of stronger hosts and obtain some pay-off
from these infections, but at the cost of killing immediately weaker hosts, therefore losing the
much higher pay-off they could provide.
    Indeed, many human viral infections, from cytomegalovirus to Epstein–Barr or rotavirus, are
quite widespread (as can be seen through serological tests) but create noticeable symptoms, often
in the form of mild but prolonged infections, only in a small minority of cases. The present
results show that this could actually be the outcome of pathogen evolution; clearly, a wide col-
lection of data with a quantification of heterogeneity in immune response in different contexts
would be necessary, before making any connection with the conclusion of this model, or of more
realistic ones.
    In principle, optimal pathogens could adjust their replication rate to the host they have infected.
A plastic strategy in which parasites achieve information about hosts' immune response and tune
their replication rate accordingly does not seem feasible for acute transient infections and is not

included in the current model focused on such infections. For pathogens with long infections, an adjustment in strategy depending on time since infection and environmental cues could instead be likely and has been analysed in [30].

As discussed above, several aspects of the model are not realistic: the within-host model, while capturing the basic behaviour of rapid infections, has the disadvantage of always ending with complete clearance of pathogens and persistence of high level of immunity. Several other qualitative models of pathogen–immune dynamics have been introduced in recent years that can yield different outcomes from persisting infections at low pathogen densities, to cycles, to bistable behaviours in which initial conditions can lead either to pathogen clearance or persistence.

It is not difficult changing within-host system (1) to a different one, although they will not share some features of the former that allow for some analytical computations. The real complication is that, if hosts' immunity is allowed to decrease, then reinfections have to be allowed to obtain a biologically consistent model, and this leads to much more complicated epidemiological models that, to my knowledge, nobody has analysed.

The infection process could also be modelled differently; instead of assuming that the force of infection is a linear function of pathogen load, it could be assumed that inoculum size and probability of transmission depend nonlinearly on the pathogen load. Such a model (definitely more complex) would probably avoid the phenomenon that, for high values of pathogen cost k_1, the optimal pathogen strategy [16] is not to replicate at all ($r = 0$).

Genetic and non-genetic heterogeneities could exist also in B_0, the immune level in naïve hosts. Non-genetic heterogeneities in B_0 would increase host diversity and presumably enhance the effects already seen from heterogeneities on a. As for genetic heterogeneities, it can be conceived that a trade-off exists between B_0 and fertility or mortality rates [22], so that, as remarked by Gilchrist and Sasaki [16], a potential cost of immune response is borne by all hosts, not only by those that get infected. Such an analysis would open new issues, outside the scope of the present manuscript.

As remarked above, a gross simplification in modelling host heterogeneity is that the parameter a, the speed of immune build-up, has been assumed to have been fixed at birth. More realistically, it will change during a host's life for predictable (young *vs.* adults) or unpredictable (starvation, stress,…) reasons. Models allowing for such changes are inevitably more complex, and optimal strategies cannot be computed by maximizing a specific quantity. I believe that the results obtained here (see, for instance, Figure 5(b) that shows $R_0(r)$ for different values of a) can be used to build models that allow for host changes in immune response, without the need for a detailed model of within-host immune–pathogen dynamics. On the whole, it seems likely that, if the dependence of $R_0(r)$ on a is similar to that in Figure 5(b), there will be a strong selection for pathogen suitable to hosts with low a, whether a is a constant property or a dynamic variable of individual hosts.

How does this result compare with the previous literature? The conclusion that host heterogeneity should cause a decrease in pathogen virulence had already been reached by Ebert and Hamilton [12] using verbal arguments and by Regoes *et al.* [29] using a model with two host types. On the other hand, Ganusov and Antia [13] and Ganusov *et al.* [14] reached the opposite conclusion, analysing a model somewhat similar to the one considered here. The main difference of their model lies in how host mortality occurs, which instead of being continuously dependent on replication rates of pathogen and immune system as here and in [16] is a threshold phenomenon occurring as soon as pathogen density increases or host resources decrease below a given level. Hosts are heterogeneous in the lethal level, not in any parameter affecting within-host pathogen–immune dynamics, and pathogen virulence increases with heterogeneity. Indeed, in their model, optimal virulence is 0 when the host population is homogeneous, because of the threshold mortality; hence, this kind of heterogeneity seems tied more to model details than to biological processes.

601 Fundamentally, the reason of the opposite conclusion is that, in the present model, hosts that,
602 if optimally exploited, would yield the highest returns to a pathogen are the 'weak' ones, those
603 that would be most easily killed. Hence, adapted pathogens will avoid killing those, even if the
604 cost is being immediately cleared when infecting a 'strong' host. On the other hand, in [13],
605 hosts that would yield the highest returns are those with the highest lethal dose; hence, adapted
606 pathogens will be tuned to optimal exploitation of these, at the cost of killing hosts with lower
607 lethal dose and lower returns. Different biological systems may be closer to one or the other
608 situation, although I believe that the model presented here is much closer to reasonable biological
609 mechanisms.

610 The effect of host heterogeneity on pathogen evolution has been analysed also by Kao [17] in
611 terms of 'exploitation of heterogeneity', without reaching precise conclusions about virulence.
612 His model concerns heterogeneity in contact rates or probability of being infected. In the present
613 model, instead, all individuals have the same probability of being infected; heterogeneity in
614 immune response affects only the course of the infection or disease.

615 As often recognized [5], between-host transmission and within-host competition could exert
616 selection pressures in different directions on the pathogen replication rate. This issue is not
617 explored here, mainly for the sake of simplicity: co-occurrence of genetically different pathogens
618 within a host could be due to within-host mutations, to reinfections or to genetically mixed
619 infections. The first two cases have little relevance in the present model focused on short, acute
620 infections with steep rise of immune response, while examining the last case would require a
621 more complex model than what analysed here.

622 In conclusion, the present analysis upholds the original suggestion by Ebert and Hamilton that
623 stochastic heterogeneity should decrease pathogen virulence. The decreased virulence is mediated
624 through reduced replication rate, a phenomenon suggested also in [3]. It is also clarified why an
625 opposite conclusion was reached in [13,14]. Heterogeneity is assumed here in rates of immune
626 response. It seems possible that heterogeneity in contact rates [17] or other aspects of infection
627 dynamics [13] could instead cause an increase in virulence, but the effects shown here seem very
628 strong.

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631 ## Acknowledgements

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Appendix 1. Endemic equilibrium of system (7)–(9)

Setting $\varphi(t) \equiv \varphi^*$ in Equation (7), one immediately obtains $R_0(S^*/K) = 1$. This is a usual property [25], meaning that at the endemic equilibrium, each newly infected host infects on average exactly one susceptible. Setting the right-hand side of Equation (9) equal to 0, one obtains

$$\varphi^* = N^* b(N^*) - \frac{\mathrm{d} K}{R_0} \tag{A1}$$

while from Equation (8)

$$N^* = \frac{K}{R_0} + \varphi^* L, \tag{A2}$$

where L is the expected life of a newly infected individual, as in Equation (13).

Comparing Equations (A1) with (A2), one finally obtains an equation that determines N^*, i.e.

$$R_0 N^* \left(\frac{1}{L} - b(N^*) \right) = K \left(\frac{1}{L} - d \right). \tag{A3}$$

The left-hand side of Equation (A3) is an increasing function of N^*; hence, there exists a (unique) solution in $(0, K)$ if and only if $R_0 > 1$, as stated in the text.

The stability of the endemic equilibrium depends on the location of the roots of the characteristic equations. For the case $b(N) = \Lambda/N$, Thieme and Castillo-Chavez [32] list several conditions that ensure the asymptotic stability of (S^*, φ^*), but give also a counter-example [23]. It seems likely that the properties of the function $P(\vartheta)$ that has a unique peak yield the stability of (S^*, φ^*), but this may depend also on the function $b(N)$.

Appendix 2. Proof of the maximization of R_0

Assuming that (S^*, φ^*) is the global attractor of the solutions of Equations (7)–(9) when $R_0 > 1$, it is very easy to find the condition under which a second pathogen strain, with complete cross-immunity, can invade a host population already co-existing with one pathogen strain.

Following the techniques of adaptive dynamics [20], it suffices writing the linearized equation for the dynamics of the second strain at the attractor (S^*, φ^*). Modifying Equation (7), one immediately obtains

$$\varphi_2(t) = S^* \int_0^\infty \beta_0 P_2(\vartheta)\, e^{-d\vartheta} \pi_2(\vartheta) \varphi_2(t-\vartheta)\, d\vartheta, \tag{A4}$$

where the subscript 2 refers to the equations for hosts infected with pathogen 2, which may differ in the parameters r, a and/or c.

Equation (A4) is a linear convolution Volterra integral equation. It is well known that the growth rate of the solutions can be obtained through the Laplace transform of the kernel. Formally, one sets $\varphi_2(t) = Ce^{\lambda t}$ in Equation (A4) and sees that this is a solution if and only if

$$S^* \int_0^\infty \beta_0 P_2(\vartheta)\, e^{-d\vartheta} \pi_2(\vartheta)\, e^{-\lambda\vartheta}\, d\vartheta = 1. \tag{A5}$$

Standard methods show that Equation (A5) has a solution λ with $\Re\lambda > 0$ if and only if

$$S^* \int_0^\infty \beta_0 P_2(\vartheta)\, e^{-d\vartheta} \pi_2(\vartheta)\, d\vartheta > 1. \tag{A6}$$

Remembering that $R_0^1 S^* = 1$, where R_0^1 refers to expression (10) with the parameters of the first strain, and defining analogously R_0^2, it is immediate to see that condition (A6) can be written as $R_0^2/R_0^1 > 1$.

Hence, invasion can be successful if and only if $R_0^2 > R_0^1$.

Appendix 3. Criterion for host invasion

Again, one can use the methods of adaptive dynamics to understand which type will outcompete the other. Let $S_2(t)$ the density of susceptible hosts of type 2 and $\varphi_2(t)$ the rate at which they become infected, $S_1(t)$ and $\varphi_1(t)$ the corresponding quantities for resident hosts of type 1. The equations for $S_2(t)$ and $\varphi_2(t)$ are:

$$S_2'(t) = N_2(t)b(N_1(t) + N_2(t)) - dS_2(t) - \varphi_2(t)$$

$$\varphi_2(t) = S_2(t)\left(\int_0^\infty \beta_0 P_1(\vartheta)\, e^{-d\vartheta}\pi_1(\vartheta)\varphi_1(t-\vartheta)\, d\vartheta + \int_0^\infty \beta_0 P_2(\vartheta)e^{-d\vartheta}\pi_2(\vartheta)\varphi_2(t-\vartheta)\, d\vartheta\right). \tag{A7}$$

$P_i(\cdot)$ and $\pi_i(\cdot)$ refer to the solutions of Equation (1) with the parameters of hosts i.

Linearizing these equations at the endemic equilibrium (S^*, φ^*) for the resident hosts, one obtains:

$$S_2'(t) = N_2(t)b(N^*) - dS_2(t) - \varphi_2(t)$$

$$\varphi_2(t) = S_2(t)\left(\int_0^\infty \beta_0 P_1(\vartheta)\, e^{-d\vartheta}\pi_1(\vartheta)\varphi^*\, d\vartheta\right) = S_2(t)R_0^1\frac{\varphi^*}{K}. \tag{A8}$$

From $\varphi_2(t) = S_2(t)R_0^1\varphi^*/K$, one obtains

$$N_2(t) = S_2(t) + \int_0^\infty \varphi_2(t-\vartheta)\pi_2(\vartheta)\, e^{-d\vartheta}\, d\vartheta = S_2(t) + \frac{R_0^1\varphi^*}{K}\int_0^\infty S_2(t-\vartheta)\pi_2(\vartheta)\, e^{-d\vartheta}\, d\vartheta.$$

Using these in Equation (A8a), and trying $S_2(t) = ce^{\lambda t}$, one obtains

$$\lambda - b(N^*)\frac{R_0^1\varphi^*}{K}\hat{\pi}_2(d+\lambda) = b(N^*) - d - \frac{R_0^1\varphi^*}{K}, \tag{A9}$$

where $\hat{\pi}_2(\cdot)$ denotes the Laplace transform of π_2. Remember that the expected life of infected individuals of type i, L_i, is equal to $\hat{\pi}_i(d)$.

Applying first Equation (A1) and then Equation (A2) to the right-hand side of Equation (A9), it follows

$$b(N^*) - d - \frac{R_0^1 \varphi^*}{K} = b(N^*)\left(1 - \frac{R_0^1 N^*}{K}\right) = -b(N^*)\frac{R_0^1 \varphi^*}{K}L_1.$$

Then, defining $G(\lambda)$ as its left-hand side, Equation (A9) can be rewritten as

$$G(\lambda) := \lambda - b(N^*)\frac{R_0^1 \varphi^*}{K}\hat{\pi}_2(d + \lambda) = -b(N^*)\frac{R_0^1 \varphi^*}{K}L_1. \tag{A10}$$

Looking initially at $\lambda \in \mathbb{R}$, it can be seen that $G(\cdot)$ is an increasing function growing to infinity; hence, there exists a real positive solution of Equation (A10) if and only if $G(0) < -b(N^*)(R_0^1 \varphi^*/K)L_1$, i.e. if $L_2 = \hat{\pi}_2(d) > L_1$.

Assume there are no real positive solutions (hence, $L_2 \leq L_1$) and look for complex solutions $\lambda = x + iy$ with $x \geq 0$ and $y > 0$ of Equation (A10). This can be written as

$$\lambda - A\hat{q}(\lambda) + B = 0$$

with

$$B = b(N^*)\frac{R_0^1 \varphi^*}{K}L_1, \quad q(\vartheta) = \frac{e^{-d\vartheta}\pi_2(\vartheta)}{L_2}, \quad A = b(N^*)\frac{R_0^1 \varphi^*}{K}L_2,$$

so that $\hat{q}(0) = 1$ and the condition $L_1 \geq L_2$ becomes $A \leq B$.

Setting the real part of Equation (A10) equal to 0 implies

$$x = -B + A\Re(\hat{q}(x + iy)) \leq -B + A|\hat{q}(x + iy)| < -B + A\hat{q}(0) \leq 0$$

against the claim $x \geq 0$.

Hence, the condition under which hosts of type 2 invade a resident population is that the expected life L_2 of an infected 2-host is greater than L_1, that of an infected resident.

Finally, consider the limiting case of $d \to 0$. One obtains

$$\lim_{d \to 0^+} dL_i = \lim_{d \to 0^+} d\int_0^\infty e^{-d\vartheta}\pi_i(\vartheta)\,d\vartheta = \lim_{d \to 0^+} \int_0^\infty e^{-u}\pi_i\left(\frac{u}{d}\right)\,du = \pi_i(\infty).$$

Hence, the condition $L_1 > L_2$ becomes, as d goes to 0, $\pi_1(\infty) > \pi_2(\infty)$, recovering the criterion used by Gilchrist and Sasaki [16].

Appendix 4. Decrease in host fitness near the co-evolutionary equilibrium

I show here that, if $r^*(a)$ is increasing at a^{**}, the derivative of $L(a, r^*(a))$ is negative at a^{**}.

To prove this, note (it can be easily seen) that

$$\frac{\partial}{\partial r}L(a, r) < 0, \quad \frac{\partial}{\partial a}R_0(a, r) < 0, \tag{A11}$$

while, by definition,

$$\frac{\partial}{\partial r}R_0(a, r^*(a)) = 0 \quad \frac{\partial}{\partial a}L(a^*(r), r) = 0. \tag{A12}$$

Now

$$\frac{d}{da}L(a, r^*(a)) = \frac{\partial L}{\partial a}(a, r^*(a)) + \frac{\partial L}{\partial r}(a, (r^*(a))(r^*)'(a). \tag{A13}$$

As $a^{**} = a^*(r^{**})$ so that $(\partial L/\partial a)(a^{**}, r^{**}) = 0$, Equation (A13) computed in a^{**} is negative, since $(r^*)'(a) > 0$. By continuity, the same will hold for a close to a^{**}, proving the claim.

Analogously, if $r^*(a)$ were increasing at a^{**}, the opposite conclusion would be reached.

It is very easy showing that $R_0(a, r^*(a))$ is decreasing too. In fact,

$$\frac{d}{da}R_0(a, r^*(a)) = \frac{\partial R_0}{\partial a}(a, r^*(a)) + \frac{\partial R_0}{\partial r}(a, r^*(a))(r^*)'(a) = \frac{\partial R_0}{\partial a}(a, r^*(a)) < 0. \tag{A14}$$

Note that these properties come out of the relations (A11), which may intuitively be accepted as generally valid, beyond the specific model considered here.