Evolutionary dynamics of virulence

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1 Introduction

The evolution of virulence is a very active area of research (Ewald, 1994; Read, 1994; May and Nowak, 1994; Nowak and May, 1994; Lipsitch et al., 1995; Lipsitch and Nowak, 1995; van Baalen and Sabelis, 1995; Levin, 1996; Ebert and Herre, 1996; Frank, 1996; Stearns, 1999; Dieckmann et al., 2000); beyond the theoretical interest of the subject, this research area may provide advice in the design of therapy and vaccines (Bull, 1994; Dieckmann et al., 2000). Virulence may have different meanings (Bull, 1994); here I (like many of the cited authors) restrict myself to a precise definition: 'virulence' is the parasite-induced host mortality. The terms 'parasite' and 'pathogen' will be used here interchangablely, without referring to any specific life form.

A parasite may also decrease a host's fertility or well-being, but this, as long as this does not affect its transmissibility, does not make any harm to a parasite. On the other hand, a parasite that kills its host, kills also itself and prevents further transmission; from this observation, the view (named 'the common evolutionary wisdom' by Anderson and May (1982)) emerged that high virulence is maladaptive: parasites evolve to be relatively benign, since they have no interest in killing their host; parasites are virulent to a host only when their interaction has not been long enough for adaptation. Support for this view came from the devastating effects of some introduction of parasites into new hosts (*Myxoma*

virus, Dutch elm disease), although Ebert and Hamilton (1996) argue that these examples are rather the exception than the rule in the introduction of parasites.

In general, there is now good empirical evidence (Read, 1994) for virulence to persist in long-term parasite-host associations. Furthermore, in the case of the *Myxoma* virus in Australia, it is well documented that selection did not proceed all the way to leave only avirulent strains, but stabilized instead at an intermediate level of virulence (Fenner and Ratcliffe, 1965; Fenner, 1983)

It has been recently remarked (Poulin and Combes, 1999) that virulence is a property of a host-parasite interaction, and not simply of the parasite. From this point of view, it would be appropriate to study the evolution of virulence in a co-evolutionary setting, where host resistence is also considered. However, very few papers have analysed models for host-parasite coevolution (see, for instance, Andreasen and Christiansen (1993)), and most authors have restricted the analysis to the evolution of virulence in the pathogen, as I will also do here. A justification for this is that, usually, parasites have a much shorter generation time than their hosts. A time-scale argument lets us consider, as a first approximation, the case where only parasites can evolve.

A breakthrough in our understanding of the evolution of virulence occurred in the early 80's with the help of simple mathematical models, thanks to the seminal papers of Levin and Pimentel (1981), Anderson and May (1982), and Ewald (1983). Their main argument is based on the existence of a 'trade-off' between virulence and infectivity. This 'trade-off' might be mediated through the speed of replication: fast-replicating strains may harm their hosts but at the same time they will reach a high concentration in hosts' tissues and secretions; depending on the mode of transmission, they will then have a higher probability of being transmitted to another host than slowly replicating strains. Some empirical basis for this trade-off is discussed in (Ebert, 1998; Mackinnon and Read, 1999a). A trade-off funcion is explicitly built from the experimental data on *Myxoma* in Dwyer et al. (1990).

In this chapter I will follow a narrow route through the vast range of issues and models of virulence. Considering only the virulence–transmissibility trade-off, the main questions I will address will are the expected path of virulence evolution, and the possibility for several parasite strains to coexist at an evolutionarily stable state.

The analysis of this chapter will be mainly set in the framework of adaptive dynamics (Metz et al., 1996; Geritz et al., 1997) as presented in previous chapters. I will especially exploit 'pairwise invasibility plots' showing the sign of the invasion coefficients $s_x(y)$ where x and y represent the virulences of different parasite strains.

In Sections 2 and 3, I will examine the basic model of Anderson and May (1982), restating their results in this framework. In Section 4, I will investigate models with superinfections, where it is possible that a strain can infect also hosts that are already infected with another strain. In Section 5, I will describe a system in which polymorphic populations are modelled explicitly, in contrast to the approach of adaptive dynamics; I will restrict the analysis, however, to a system corresponding to the basic model of Anderson and May (1982). Finally in Section 6, some other approaches and open problems will be examined.

2 The basic epidemic model

The starting point in the adaptive dynamics approach is a model describing the interaction of different parasite types. This model will be a modification of a standard models for epidemics (Bailey, 1975; Hethcote, 1976) with a single type of parasites. To keep the models as simple as possible, while retaining the features necessary to discuss the evolution of virulence, I will discuss only SI models: hosts are born susceptible (S) to infection, then may become infected (I) and, if so, cannot recover (see Box 1 for more explanations on epidemic models). The model includes disease-related deaths, since the interest lies in the lethal effects caused

by the pathogen: thus host population size N will be a dynamic variable instead of a fixed constant.

The equations (its assumptions are presented in Box 1) are

$$\frac{dS}{dt} = b(N)N - \mu S - \beta SI \tag{1a}$$

$$\frac{dI}{dt} = \beta SI - \mu I - \alpha I \tag{1b}$$

where β is the contact rate (see Box 1), μ natural death rate, α parasite-induced death rate (= 'virulence') and $b(N)$ the birth rate, assumed to be density-dependent. In absence of the epidemic, the population size would converge to its carrying capacity K, which is found by solving the equation $b(K) = \mu$. The assumption of density-regulation through hosts' fertility is the same as in Bremermann and Thieme (1989) and differs from the simpler assumption of a constant birth rate b (Anderson and May, 1982) which entails exponential growth in absence of the epidemic.

The behaviour of equation (1) can be understood in terms of the 'basic reproductive ratio' R_0 of the parasite, representing the expected number of new infections caused by a single infected individual when the whole population is susceptible (see Box 2 for details). In our case, R_0 is given by

$$R_0 = \frac{\beta K}{\mu + \alpha}. \tag{2}$$

It is clear that, if each infective host infects, on average, less than one new host ($R_0 < 1$), the epidemic will fade out, since not enough new cases are produced. If, on the contrary, an infective host infects on average more than one other host ($R_0 > 1$), the epidemic will spread, at least as long as the number of susceptibles is large enough. For system (1), the epidemic will then settle at a globally attractive endemic equilibrium with a total host population $\bar{N}$ and a susceptible population $\bar{S}$. At the equilibrium each infective will on average infect one susceptible over its expected life time, so that

$$\frac{\beta \bar{S}}{\mu + \alpha} = 1. \tag{3}$$

Box 1. Epidemic models.

Epidemic models generally divide the host population into individuals that are currently infected and infectious (I), individuals that are not infected but are susceptible to the infection (S) and often individuals that are recovered from the disease and immune to further infection (R); the dynamics of the parasites is described simply as the dynamics of infected hosts. Within-host dynamics, in particular, are not modelled explicitly.

A lucid presentation of basic epidemic models is given, for instance in Hethcote (1989); here I just outline the main ideas. If the infection confers permanent immunity, the dynamics of the infection is $S \to I \to R$ (susceptible individuals become infected and then immune). Without immunity the dynamics of the infection is $S \to I \to S$ (susceptible individuals become infected and then susceptible again). A latency period after infection is often modelled by introducing the class of exposed (E), individuals that have been infected but are not yet infectious, obtaining a $S \to E \to I \to R$ dynamics.

New infections are assumed to occur because of encounters between infectious and susceptible individuals; assuming a mass-action law for encounters, the rate of new infections is βSI, where the constant β is called mixing rate. When population size N is variable, several authors (for instance de Jong et al. (1995)) argue that β will vary as well; they defend the view that, usually, the mixing rate will have the form $\beta = \frac{\lambda}{N}$ (they call this 'true mass-action law') where λ is the average number, assumed to be constant, of individuals contacted by one individual in unit time. I will use, instead, the assumption of constant β ('standard mass-action law'), mostly for consistency with previous analyses on virulence. Use of the 'true mass-action law' would change the algebraic details, but not the qualitative results in strain competition.

In the simple models discussed here, one needs also to consider rates of birth (all individuals are supposed to be born susceptible), of death, and of recovery.

Box 2. Computation of the basic reproductive ratio R_0.

The basic reproductive ratio R_0 is the average number of individuals infected by a single infective under some given and constant environmental conditions (often an equilibrium population with all susceptibles).

If the rate at which an infectious individual infects other individuals (the 'effective contact rate') does not depend on the time elapsed since infection, we can obtain R_0 simply from multiplying the 'effective contact rate' (β times the absolute number of susceptibles) with the expected time spent as infective.

In models (such as those consisting of ordinary differential equations) where future dynamics depends on present state only, and not on past history, the time spent in any state (for instance as an infective) will follow an exponential distribution; thus, the expected time spent as infective is simply the inverse of the exit rate from that state. If exits for different causes are possible (recovery, 'natural' death, parasite-induced death), their rates have to be added, yielding the total exit rate.

For instance in model (1), natural mortality rate μ and disease-related death rate α have to be added, giving an expected time as infected equal to $1/(\mu + \alpha)$. When examining whether a parasite is able to establish itself, we consider a completely susceptible population at carrying capacity K, thus obtaining (2).

When we discuss the success of the invasion of a parasite 2 in a population where parasite 1 is already established, the environment for parasite 2 is the population at the endemic equilibrium with parasite 1, so that the number of susceptibles is $\bar{S}_1$; the expected time as infective is as before $1/(\mu + \alpha_2)$, so that we obtain (6).

The invasion of an established epidemics by a 'new' parasite type can be studied by extending model (1) to allow for two different types of infected individuals I_1 and I_2. While other assumptions are possible (see Section 4), I assume here that an infected individual cannot be further infected. We thus obtain the following system of differential equations

$$\frac{dS}{dt} = b(N)N - \mu S - \beta_1 S I_1 - \beta_2 S I_2 \tag{4a}$$

$$\frac{dI_1}{dt} = \beta_1 S I_1 - \mu I_1 - \alpha_1 I_1 \tag{4b}$$

$$\frac{dI_2}{dt} = \beta_2 S I_2 - \mu I_2 - \alpha_2 I_2 \tag{4c}$$

with $N = S + I_1 + I_2$.

A complete analysis of (4) is presented by Bremermann and Thieme (1989) for n competing strains. Here I summarise the relevant results, with some intuitive explanations. It must be kept in mind that, while the present analysis relies on local stability analysis, the global picture is the same (Bremermann and Thieme, 1989), so that, in this case, consideration of pairwise invadibility provides all necessary information for predicting outcomes of competition between parasite strains.

The invasion fitness $s_x(y)$ can be computed linearizing (4) at the endemic equilibrium for only one strain; letting $s_1(2)$ denote the invasion coefficient of parasite 2 (with parameter values α_2, $\beta_2 \ldots$) into a population at equilibrium with parasite 1, we have

$$s_1(2) = \beta_2 \bar{S}_1 - (\mu + \alpha_2). \tag{5}$$

It is more transparent, however, to use a suitable reproductive ratio: specifically, let $R_0^1(2)$ be the expected number of new infections caused by a single individual infected with strain 2 when the host population is at its endemic equilibrium for strain 1. Strain 2 will invade into a population at equilibrium with strain 1 if $R_0^1(2) > 1$; it cannot do so if $R_0^1(2) < 1$. This is proved in a general setting, where

the definition of R_0 is more complex, by Diekmann et al. (1990); they also show that the condition on R_0 is equivalent to a condition on invasion fitness.

Following the computations outlined in Box 2, the invasion condition can be written as

$$R_0^1(2) = \frac{\beta_2 \bar{S}_1}{\mu + \alpha_2} > 1. \tag{6}$$

Note from (5) that, in this case, a very simple relation holds between $R_0^1(2)$ and $s_1(2)$: $s_1(2) = (\mu + \alpha_2)(R_0^1(2) - 1)$.

In order to compare different strains, it is convenient to define a 'per capita' reproductive ratio

$$R_i = \frac{\beta_i}{\mu + \alpha_i}. \tag{7}$$

Since we follow the 'standard mass-action law' (Box 1), the basic reproductive ratio of strain i when there are S susceptibles in the population is $R_i S$.

Now (6) reads $R_2 \bar{S}_1 > 1$, while (3) for $\bar{S}_1$ yields $R_1 \bar{S}_1 = 1$. Hence, the invasion of strain 2 will be successful if $R_2 > R_1$.

3 Optimal virulence

I now turn to the main topic of this chapter, the evolution of virulence, identifying, as discussed in the Introduction, virulence with parasite-induced death rate α. Several conclusions can be drawn from the fact that $s_2(1) > 0$ if and only if $R_2 > R_1$.

First of all, we see that, if $R_2 > R_1$, strain 2 can invade strain 1 but strain 1 cannot invade strain 2; thus mutual invasibility is impossible and coexistence may occur only as a transient or in the infinitely unlikely case where $R_1 = R_2$. Second, strain 1 cannot be invaded by any other parasite type if R_1 is larger than R_i for any other feasible strain i; in other words, an evolutionarily uninvadable state will be found at the state that maximises $\dfrac{\beta}{\mu + \alpha}$ among all feasible states.

It is clear from (7) that if two types differ only in their virulence, the less virulent type will have a larger R and will thus outcompete the other type. Therefore,

we would expect an evolutionary trend toward a decreased virulence, recovering the 'conventional wisdom'.

However, matters are different if one assumes, following Anderson and May (1982), a trade-off between contact rate β and virulence α: I will assume that a relation exists that gives the contact rate β as a function of virulence α (see a) and c) of Fig. 1). The existence of such a trade-off is a basic tenet of the current theory on the evolution of virulence, as discussed in the Introduction.

Since β is now envisaged as a function of α, and μ is independent of parasite strategy, the quantity R of (7) can be written as a function of virulence α

$$R(\alpha) = \frac{\beta(\alpha)}{\mu + \alpha}. \tag{8}$$

The invasibility condition $R_2 > R_1$ shows that an evolutionarily uninvadable state will be found at a maximum of the function $R(\alpha)$. This result is a consequence of the fact that, in this model, for a parasite the environment is one-dimensional: number of susceptibles S; hence, a maximisation principle holds (Chapter ??).

The qualitative conclusions depend on the shape of the function $\beta(\alpha)$: if it is a concave function (like in Fig. 1a), which seems likely because of the 'law of diminishing returns' (Lipsitch et al., 1995), there exists a single maximum of $R(\alpha)$. Simple arguments from one-dimensional adaptive dynamics show that, in this case, the value of α at which R is maximised is a final state for evolutionary dynamics (a 'continuously stable strategy' (Eshel, 1996)). Often, this strategy will correspond to an intermediate virulence (as shown in Fig. 1a)-b)), but it is also possible to have the maximum at $\alpha = 0$ ('avirulence').

If the function $\beta(\alpha)$ is convex, there are no maxima of the 'basic reproductive ratio' R, but often a single minimum; this, in the framework of adaptive dynamics, is an evolutionary repellor, i.e. a separating point for evolutionary trajectories: if the initial virulence α is lower than a threshold value, evolution will drive virulence to 0; if it is above, virulence will increase forever in the course of evolution. A more reasonable assumption is that $\beta(\alpha)$ is convex only within a certain range of

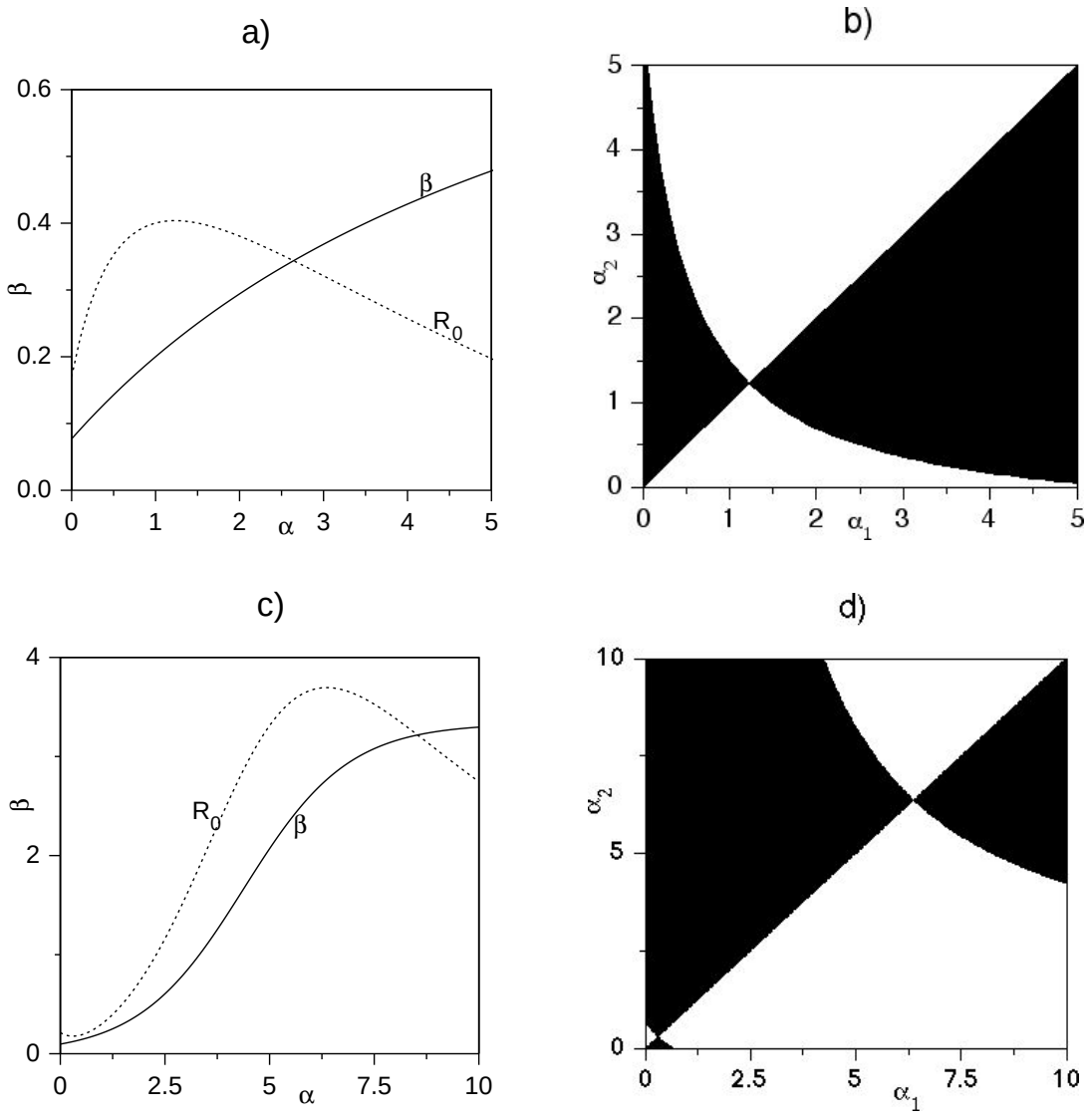

Figure 1: a) An example of a concave function: $\beta(\alpha) = \frac{C\alpha}{A+\alpha} + B$ and the corresponding $R(\alpha)$;
b) the 'invasibility plot' for the functions in a); α_2 can invade α_1 when (α_1, α_2) is in the black region;
c) an example of a concave–convex function: $\beta(\alpha) = \frac{1}{A+Be^{-C\alpha}}$, and the corresponding $R(\alpha)$; Parameter values are $A = 0.5,\ B = 10,\ C = 0.8$;
d) the 'invasibility plot' for the functions in c).

virulence, and concave beyond that (like in Fig. 1c). In this case, evolution could tend toward high or low virulence, depending on initial conditions.

4 Superinfection

It has been shown (Levin and Pimentel, 1981; Hochberg and Holt, 1990) that one mechanism leading to parasite coexistence is that of superinfection (see Box 3). Specifically, if the strain with lower R_0 is capable of superinfecting the other more often than vice versa, then coexistence may occur. The models are actually similar to models used for describing coexistence of plant species in patches of suitable habitat (Tilman, 1994).

In this section, I will perform, in the same spirit as in the previous sections, a mathematical analysis of the evolutionary dynamics of virulence when superinfection is possible. A very interesting analysis of the problem, mainly through numerical computation, is presented by Adler and Mosquera (1998), who consider coinfection, and superinfection as a limiting case of coinfection. I will present here some analytical results when possible, and show the similarities and differences, in assumptions and results, with Adler and Mosquera (1998). However, I will not discuss here coinfection models (see Box 3) because of their complexities. In fact, the state space of these models can be very large, since one should allow for hosts being infected with any combination of strains (a similar problem is tackled by Lin et al. (1999) in a model for influenza). To cope with these problem while maintaining the possibility of coinfection, some authors (van Baalen and Sabelis, 1995; Mosquera and Adler, 1998) do not allow further infections of doubly-infected hosts.

As in the previous section, we will consider several parasite strains differing in the value of virulence α, i. e. the disease-induced death rate. The density of infected individuals carrying strain α at time t is denoted by $i(t, \alpha)$. As before, we assume that the contact rate β depends on the virulence level according to

Box 3. Superinfection and coinfection.

The models of competition between different pathogen strains discussed in the previous sections assume that infection with one strain provides hosts with complete protection against infections by other strains.

Levin and Pimentel (1981) introduced the possibility of superinfections: a host infected with strain 1 may become infected by strain 2 upon contact with a host already infected with strain 2. It is further assumed that, in this case, the host will lose the previous infection with strain 1; thus, no host will be infected with more than one strain at the same time.

Following the same considerations as in Box 1, the rate at which such superinfections of strain 1 by strain 2 occur will be proportional to the product $I_1 I_2$ if I_i is the density of hosts infected with strain i. It is convenient to express the proportionality constant as the product of the contact rate β_2 with a scaling factor ρ_{21}. Thus the rate at which such superinfections of strain 1 by strain 2 occur is assumed to be $\beta_2 \rho_{21} I_1 I_2$. Conversely, superinfections of strain 2 by strain 1 occur at rate $\beta_1 \rho_{12} I_1 I_2$.

Generally, it is assumed that the constants ρ_{ij} are smaller or equal to 1: already infected individuals are not easier to infect than susceptible ones. This constant ρ_{ij} is called the *superinfection factor*.

This model of superinfection consists of several mechanisms at the level of the individual host: necessarily, a host already infected with strain 1 that is attacked by strain 2 will go through a period where both strains are present in its body. Superinfection models assume that this period is so short to be negligible and eventually only one strain will persist.

Coinfection models assume (more realistically) that hosts may be infected with more than one strain at the same time. A host already infected with strain 1 that is attacked by strain 2 will become a host infected with strains 1 and 2; afterwards, it may persist in this state or (because of competition between strains) revert to being infected with only one strain.

a given function $\beta(\alpha)$. Since also superinfections are now allowed, one needs a function relating virulence to superinfection rates. In the notation of Box 3, we need to know how the superinfection factor ρ_{ij} depends on the virulence of the infecting strain α_i and of the strain α_j that is being infected.

Nowak and May (1994) used the following assumption: if $\alpha_2 > \alpha_1$, then ρ_{21} is a positive constant; vice versa, if $\alpha_2 < \alpha_1$, then $\rho_{21} = 0$. A consequence of this assumption is that any resident strain can be invaded by any other strain with infinitesimally larger virulence; no strain will ever be evolutionarily stable, and no limit to similarity can be found, unless constraints on available strains are introduced (see also Kinzig, Levin and Pacala (1999)). These consequences may be regarded as being rather pathological.

Mosquera and Adler (1998) have considered in detail more general formulations for the superinfection law. Following their presentation, we assume that there exists a function $\rho(\alpha_2, \alpha_1)$ that gives the superinfection factor of a strain with virulence α_1 from a strain with virulence α_2. Hence, superinfections of a strain with virulence α_1 from a strain with virulence α_2 occur at rate $\beta(\alpha_2)\rho(\alpha_2, \alpha_1)i(t, \alpha_1)i(t, \alpha_2)$. The equation for $i(t, \alpha)$ is completed by assuming a death rate equal to μ (the natural death rate) plus α (the parasite-induced death rate), and by excluding other exits from the infected state. The equations when strains $\alpha_1, \ldots, \alpha_n$ are present are then, using the abbreviation $i_j(t) = i(t, \alpha_j)$,

$$\begin{aligned} \frac{d}{dt} i_j(t) = \beta(\alpha_j) i_j(t) \left(S(t) + \sum_{k \neq j} \rho(\alpha_j, \alpha_k) i_k(t) \right) \\ - i_j(t)(\mu + \alpha_j) - i_j(t) \sum_{k \neq j} \beta(\alpha_k) \rho(\alpha_k, \alpha_j) i_k(t) \qquad \text{for } j = 1, \ldots, n \end{aligned} \tag{9}$$

As before, we assume that $\beta(\alpha)$ is increasing with α (higher virulence allows for higher transmissibility). To simplify the analysis, we will assume that the 'per capita' reproductive ratio $R(\alpha)$, defined in (8), will have a single maximum (see Fig. 1a,b).

As for the function $\rho(\alpha_2, \alpha_1)$, for reasons discussed in Box 4, I will always assume that $\rho(\alpha_2, \alpha_1) = k(\alpha_2 - \alpha_1)$ with k an increasing function with values

ranging between 0 and 1. I will then consider the two following cases (illustrated in Fig. 2 through some examples) that do not exhaust all possible choices, but that should together cover most of the interesting results:

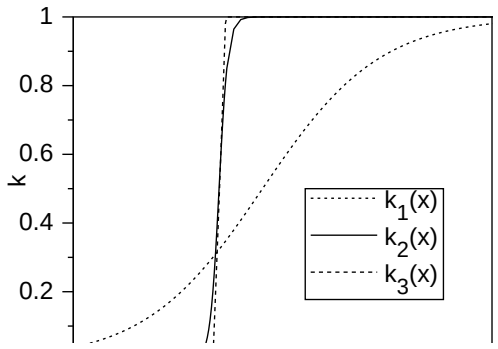

Figure 2: The functions k used in the numerical examples below. k_1 and k_2 are differentiable function, both of the form $k(x) = k_0/[k_0 + (1-k_0)e^{-Lx/(2k_0(1-k_0))}]$; $k_1(x)$ has $k_0 = 0.3$, $L = 1$; $k_2(x)$ has $k_0 = 0.2$, $L = 10$. $k_3(x)$ is not differentiable and is defined as follows: $k(x) = 0$ for $x \leq 0$; $k(x) = \min\{10x(1+x), 1\}$ for $x > 0$.

1. k is differentiable with $k(0) > 0$ and $k'(0) \geq 0$ (the differentiable case).

2. $k(t) = 0$ if $t \leq 0$; k is differentiable from the right in 0 and $k'_+(0) > 0$ (the non-differentiable case).

It is simpler to rewrite (9) using the notation

$$\delta(\alpha_2, \alpha_1) = \beta(\alpha_2)\rho(\alpha_2, \alpha_1) - \beta(\alpha_1)\rho(\alpha_1, \alpha_2) = \beta(\alpha_2)k(\alpha_2 - \alpha_1) - \beta(\alpha_1)k(\alpha_1 - \alpha_2). \tag{10}$$

Then (9) become

$$\frac{d}{dt}i_j(t) = i_j(t)\left(\beta(\alpha_j)S(t) + \sum_{k \neq j}\delta(\alpha_j, \alpha_k)i_k(t)(t) - \mu - \alpha_j\right) \qquad j = 1 \ldots n \tag{11}$$

The model is completed by an equation for the susceptibles. To simplify the mathematics, I assume exponential growth for the population in the absence of pathogens (contrary to the previous sections, where parasite-free growth was

Box 4. The function relating virulence to superinfection rate.

It seems likely that more virulent strains will have a faster replication rate, and thus will be better competitors within a host; thus, it is natural to assume that the superinfection factor $\rho(\alpha_2, \alpha_1)$ is an increasing function of α_2 and decreasing in α_1 (Mosquera and Adler, 1998).

A useful assumption is that the superinfection factor $\rho(\alpha_2, \alpha_1)$ depends only on the difference between the respective virulences, namely $\rho(\alpha_2, \alpha_1) = k(\alpha_2 - \alpha_1)$. This assumption is not necessary in the analysis, but has been used in all the numerical examples I have seen, and makes the results easier to state and understand.

Using this notation, Mosquera and Adler (1998) distinguish three classes of functions k, according to their regularity. A first class is that of discontinuous functions: the typical example is that of Nowak and May (1994): $k(t) = sH(t)$, where H is the Heaviside function: $H(t) = 1$ if $t > 0$, $H(t) = 0$ if $t < 0$. A second class is that of continuous but not differentiable functions. The third class is that of differentiable functions. They show that the evolutionary dynamics is rather different, according to the class of functions. Since, as discussed in the text, the model of Nowak and May with a discontinuous function yields paradoxical consequences, I will restrict the following considerations to the latter two cases.

Mosquera and Adler (1998) assume that always $k(t) = 0$ if $t \leq 0$. Although they give some reasonable justification for this condition, an alternative view holds that virulence affects the general trend of superinfections, but stochastic factors (host's health, timing and dosage of the inoculum, etc.) influence individual infections; hence it is possible (although perhaps unlikely) that a parasite infects a host already infected by a more virulent strain, i.e. $k(t)$ may be positive also for negative t, as has always be assumed in epidemic models with superinfections (Hochberg and Holt, 1990). This point is relevant, since if $k(t) = 0$ for $t \leq 0$, and the function k is differentiable, then $k'(0) = 0$. I will not make this assumption: hence, the differentiable case considered in the text differs from what used in Mosquera and Adler (1998).

assumed to be logistic). The equations for the susceptibles $S(t)$ are thus

$$\frac{d}{dt}S(t) = bN(t) - \mu S(t) - S(t)\sum_j \beta(\alpha_j) i_j(t). \tag{12}$$

with the total population $N(t) = S(t) + \sum_j i_j(t)$.

Under the assumptions of exponential growth of the host population and standard mass action law for infections (Box 1), any parasite strain alone can get established into the host population; moreover, it is possible that both hosts and parasites grow to infinity; the predictions of this model will be considered only for parameter values where this consequence does not occur.

Let us denote by $s_{\alpha_1}(\alpha_2)$ the rate of increase, when rare, of strain α_2 in a population at equilibrium with strain α_1. By looking at (11) with only two strains, denoted α_1 and α_2, we see that

$$s_{\alpha_1}(\alpha_2) = \beta(\alpha_2)\bar{S}_1 + \delta(\alpha_2, \alpha_1)\bar{i}_1 - \mu - \alpha_2 \tag{13}$$

where $\bar{S}_1$ and $\bar{i}_1$ represent the equilibrium levels of susceptibles and infectives when only strain α_1 is present in the population. Equation (3) can be rewritten as

$$\bar{S}_1 = \frac{\mu + \alpha_1}{\beta(\alpha_1)} = \frac{1}{R(\alpha_1)} \tag{14}$$

while (12) yields

$$\bar{i}_1 = \frac{(b-\mu)\bar{S}_1}{\mu + \alpha_1 - b} = \frac{b-\mu}{R(\alpha_1)(\mu + \alpha_1 - b)}. \tag{15}$$

Note that $\bar{i}_1$ in (15) is positive and thus is realistic only when $b - \mu < \alpha_1$. Otherwise, the population size will grow to infinity, as a consequence of exponential growth of hosts.

To determine the direction of virulence evolution, we need to compute $D(\alpha) = \frac{\partial}{\partial \alpha_2} s_\alpha(\alpha_2)|_{\alpha_2=\alpha}$. One finds

$$D(\alpha) = \left(\beta'(\alpha) + d_1(\alpha)\frac{b-\mu}{\mu + \alpha - b}\right)\frac{1}{R(\alpha)} - 1 \tag{16}$$

where $d_1(\alpha) = \dfrac{\partial}{\partial \alpha_2}\delta(\alpha_2, \alpha)|_{\alpha_2=\alpha}$. Note that $d_1(\alpha)$ exists even if k is not differentiable in 0. Specifically, we have

$$d_1(\alpha) = \begin{cases} \beta'(\alpha)k(0) + 2\beta(\alpha)k'(0) & \text{if } k \text{ is differentiable} \\ \\ \beta(\alpha)k'_+(0) & \text{if } k \text{ is non-differentiable.} \end{cases} \tag{17}$$

An evolutionarily singular state α^* satisfies $D(\alpha^*) = 0$, and thus, with some algebraic manipulations,

$$\frac{b-\mu}{\mu + \alpha^* - \beta} d_1(\alpha^*) + R'(\alpha^*)(\mu + \alpha^*) = 0. \tag{18}$$

From (18) one sees that necessarily $R'(\alpha^*) < 0$ so that α^* has to stay to the right of the maximum of the function $R(\alpha)$ (see Fig. 1). In agreement with intuitive expectations, the evolutionarily singular type in the presence of superinfections will thus be more virulent than the optimal type in the absence of superinfections.

A first question one may ask is whether an evolutionary singular state always exists and is unique. I could investigate this question only by choosing a specific form for the function $\beta(\alpha)$; here, I considered two possible functional forms, both in the class of concave functions for which the basic reproductive ratio has a unique maximum:

a) $\beta(\alpha) = C\alpha^a$ $(0 < a < 1)$ or

b) $\beta(\alpha) = C\frac{\alpha - \alpha_0}{\alpha}$.

The first class corresponds to a power law, a standard assumption in ecophysiology. The second class has been used (with $C = 1$ and $\alpha_0 = 1$)) by Mosquera and Adler (1998).

By computing (18) explicitly in the two cases and studying the behaviour of the functions involved in the equation, one obtains the following condition.

Let $L = 2k'(0)$ in the differentiable case; or $L = k'_+(0)$ in the non-differentiable case. If

$$(b-\mu)L < 1 - a \quad \text{in case a)} \qquad \text{or} \qquad (b-\mu)L < 1 \quad \text{in case b)} \tag{19}$$

there exists a unique singular state α^*. On the other hand, if (19) does not hold, $D(\alpha) > 0$ for all α; hence virulence will evolutionarily increase to infinity.

The conclusion when (19) does not hold appears paradoxical. Indeed, it is a consequence of the assumption of exponential growth of hosts: even infinitely virulent strains can maintain themselves in an exponentially growing populations; if $k'(0)$ is large enough, more virulent types have a large advantage at superinfections so that they can always invade a resident strain. Introducing density dependence in the model prevents both population size and virulence from increasing to infinity. It seems likely, but it is difficult to prove analytically, that a unique ESS will exist in this case as well (a numerical example that appears very similar to the cases without density dependence is shown in Fig. 3b). In all further computations I will then assume that (19) holds.

The techniques of Geritz et al. (1998) allow to classify the evolutionary dynamic properties of α^* according to the sign of the second derivatives of s at $\alpha_1 = \alpha_2 = \alpha^*$ (Chapter ??). However, if k is not differentiable in 0, the function s is not twice differentiable at α^*: derivatives from the right are different from derivatives from the left.

Analytical results are thus easier to obtain for the differentiable case. In this case, one can draw two conclusions. First, for any function $\beta(\alpha)$, $\frac{\partial^2 s(\alpha_1,\alpha_2)}{\partial \alpha_2^2}|_{\alpha_2=\alpha_1=\alpha^*} + \frac{\partial^2 s(\alpha_1,\alpha_2)}{\partial \alpha_1^2}|_{\alpha_1=\alpha_2=\alpha^*} > 0$ holds. According to Geritz et al. (1998), this property implies that there will exist pairs of mutually invasible strains on opposite sides of α^*. Dimorphisms thus arise naturally in this model. Second, for the two specific choices for $\beta(\alpha)$ introduced above, then $\frac{\partial^2 s(\alpha_1,\alpha_2)}{\partial \alpha_2^2}|_{\alpha_2=\alpha_1=\alpha^*} < 0$. This implies that α^* is always uninvadable, or evolutionarily stable (at least locally, i.e. from strains with virulence close to α^*). Therefore, at least under the assumptions considered, this superinfection model yields only transient dimorphisms shrinking towards a unique evolutionarily stable state.

We now construct some 'pairwise invasibility plots' by numerical computations. This is needed to establish global invasibility relations, since the previous

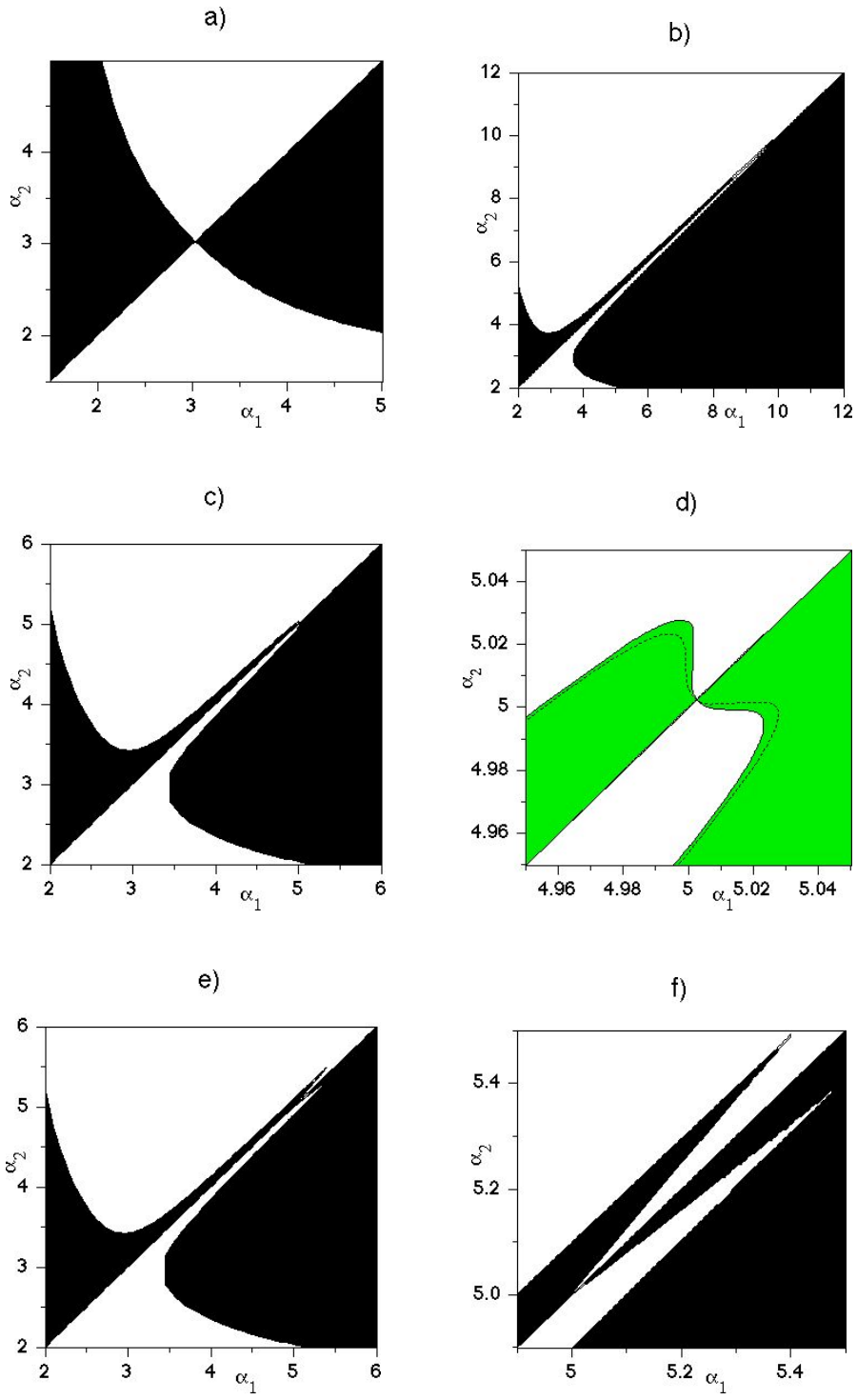

Figure 3: Some 'invasibility plots' for model (11) with $\beta(\alpha) = C\frac{\alpha-\alpha_0}{\alpha}$; α_2 can invade α_1 when (α_1, α_2) is in the black region. In a) $k(x) = k_1(x)$ of Fig. 2; in b), c) and d) (which is a detail of c)) $k(x) = k_2(x)$ of Fig. 2; In e) and f) (which is a detail of e)) $k(x) = k_3(x)$ of Fig. 2.
Common parameter values to all parts are $\alpha_0 = 1.2544$, and $C = 0.02$. In b) birth rate depends on density according to the law $b(N) = 1 - 2 \cdot 10^{-4}N$ and $\mu = 0.8$; in all the others $b = 1$ and $\mu = 0.95$.
In d) the dotted line is the reflected image of the boundary of the invasibility regions; when (α_1, α_2) lies between the dotted line and the invasibility boundaries, the states α_1 and α_2 are mutually invasible.

analytical considerations yield only local information. In Fig. 3 (a), c) and d), I present some examples with $\beta(\alpha) = C\frac{\alpha-\alpha_0}{\alpha}$ (the case $\beta(\alpha) = C\alpha^a$ gives very similar results). From all graphs it is evident that this superinfection model provides little room for polymorphisms. The plot in Fig. 3a is hardly distinguishable from that in Fig. 1. That in Fig. 3c is more complex, but still hardly allows for strain coexistence. This global picture seems not to follow any of the patterns established in (Geritz, Kisdi, Meszéna and Metz, 1998); moreover, it is not clear that the singular state is evolutionarily stable, as proved above. However, when one looks at a detail of the same picture (Fig. 3d), it appears that very close to the singular state the plot is equivalent to that of Fig. 3a, and that the singular state is indeed evolutionarily stable. Note however that this stability is only local, in the sense that mutants with a very similar virulence cannot invade, whereas mutants with a somewhat smaller virulence can invade: the pattern of evolutionary dynamics will then depend on the size of mutations. One also sees from Fig. 3d that the region of coexistence is not so small locally; it is theoretically possible that there exists a pair of coexisting strains that is uninvadable from any mutant; however, such a dimorphism would hardly be recognizable empirically, since the two strains would be very similar to each other.

The case when $k(x)$ is not differentiable is harder to approach analytically. For instance, one can see that

$$\lim_{\alpha_2\to\alpha^{*+}} \frac{\partial^2 s_{\alpha_1}(\alpha_2)}{\partial\alpha_2^2}|_{\alpha_1=\alpha^*} = \beta''(\alpha^*)\frac{\mu+\alpha^*}{\beta(\alpha^*)} + 2\beta'(\alpha^*)k'_+(0)\frac{b-\mu}{\alpha^*-b+\mu}\frac{\mu+\alpha^*}{\beta(\alpha^*)} + k''_+(0)\frac{b-\mu}{\alpha^*-b+\mu}\frac{\mu+\alpha^*}{\beta(\alpha^*)}(\mu+\alpha^*) \quad (20a)$$

$$\lim_{\alpha_2\to\alpha^{*-}} \frac{\partial^2 s_{\alpha_1}(\alpha_2)}{\partial\alpha_2^2}|_{\alpha_1=\alpha^*} = \beta''(\alpha^*)\frac{\mu+\alpha^*}{\beta(\alpha^*)} - k''_+(0)\frac{\mu+\alpha^*}{\beta(\alpha^*)}(\mu+\alpha^*) \quad (20b)$$

where $k'_+(0)$ and $k''_+(0)$ are the first and second right derivatives of k at 0. The singular state α^* will be (locally) uninvadable from the right when expression (20a) is negative, will be uninvadable from the left when expression (20b) is negative. It is thus possible that α^* will be invadible from the left and not from

the right, or vice versa, both from the right and from the left, or from neither direction. According to the choice of the function k, all these possibilities can be realised: from (20), one sees that an important factor is the sign of $k''_+(0)$; in contrast, the value of $k''(0)$ did not enter the formulae for $\frac{\partial^2 s(\alpha_1,\alpha_2)}{\partial \alpha_2^2}|_{\alpha_2=\alpha_1=\alpha^*}$ in the differential case.

An example of 'pairwise invasibility plot' is shown in part e) of Fig. 3. It can be seen that the plot becomes very complex, and locally (f) of Fig. 3) very different from that of part d), although the functions k_2 and k_3 are very close to each other (Fig. 2). Other (but still similar) non-differentiable functions give rise to 'pairwise invasibility plots' that are locally rather different. On the other hand, the global pictures are similar between each other, and also to that obtained for sharply bent but differentiable functions (c) of Fig. 3).

To summarise the results of this section, we stress that some conclusions seem to be robust to changing the details of the function k: there exists a unique singular state α^* for virulence, and this α^* is always larger than the optimal virulence without super-infections. Starting from low values of virulence, small mutations and selection will bring the virulence close to α^*. When α^* is much larger (because superinfections are likely) than the optimal virulence without superinfections, then mutants with virulence much smaller than α^* can invade. Thus, although in the strict adaptive dynamics framework (Metz et al., 1996), stable dimorphisms appear unlikely, coexisting strains may occur often if larger mutations are allowed. In these models, the environment for a parasite has several dimensions: number of susceptibles and number of individuals already infected by other strains; hence, coexistence of different strains is not unexpected.

On the other hand, the fine detail of evolutionary dynamics around α^* will depend on the exact shape of the function k, which is probably beyond any possibility of empirical investigation (see Fig. 2). Since the model itself is only an approximation of more complex processes, investigation on the exact dynamics close to the singular state α^* has mainly a mathematical interest.

5 Evolutionary dynamics when mutations are frequent

The approach of adaptive dynamics assumes that the successful invasion of favourable mutations is rare relatively to the selection process: therefore the resident population can always settle to its ecological equilibrium (or non-equilibrium attractor) before the next mutation comes in. However, at least for RNA-viruses, mutations may occur at the same time scale as epidemiological processes (Miralles et al., 2000), and the pathogen population can be better described as a "cloud" in the space of genotypes. It may be then worth studying the evolution of virulence in polymorphic resident populations.

Following the approach pioneered by Kimura (1965) in population genetics, we consider a one-dimensional continuous space for pathogen genotypes x; infected hosts are classified according to the value of the infecting genotype (we still keep the simplifying assumption that each host is infected by a single strain at any time), and the whole infected population at time t is thus characterized by a density distribution $i(x,t)$. Mutations of pathogen genotypes (say from x to y) occur randomly, and then they take over the host completely: basically, we assume that new mutations either go extinct quickly, or take over the host in which they occur; we can then restrict attention to mutations that succeed in taking over the host.

In the limit in which mutations are infinitesimally small, and occur infinitely often, mutations can be described by a diffusion operator (like Brownian motion is a limit of random walks). If mutations occur uniformly in genotypic space, their emergence is characterised by a single value γ, the mutation rate. The change in the distribution of viral genotypes due to mutation can then be described as

$$\frac{\partial i}{\partial t} = \gamma \frac{\partial^2 i}{\partial x^2}.$$

Virulence is assumed to be a function of the genotypic value, $\alpha = \alpha(x)$. We assume that $\alpha(x)$ is a monotonic function, and choose it increasing. Alternatively,

one could start from the phenotypic space of virulences α and allow for a non-uniform mutation rate. It is then possible to dilate and contract the virulence scale α obtaining an abstract space where mutations are uniform. Thus, the assumption of uniformity of mutations in the (somewhat fictitious) genotypic space is quite reasonable.

Changes in the composition of the host population other than those resulting from pathogen mutations will follow the epidemiological models discussed in the previous sections. We restrict ourselves to the simplest case discussed in Section 2, where it turned out that evolution brought virulence towards a level α^* that maximised R_0. We let μ be the natural death rate of hosts, and b, the birth rate, depend on population size N according to a decreasing function $b(N)$: the carrying capacity K will be the value at which $b(K) = \mu$. Finally, we assume a trade-off between transmission rate β and virulence α, namely $\beta = \varphi(\alpha)$; letting, as assumed above, $\alpha = \alpha(x)$ and thus $\beta = \varphi(\alpha(x)) = \beta(x)$, we obtain the following equations

$$\frac{dS}{dt} = b(N)N - \mu S - S\int_{-\infty}^{+\infty} \beta(y)i(y,t)\,dy \tag{21a}$$

$$\frac{\partial i(x,t)}{\partial t} = \gamma\frac{\partial^2 i}{\partial x^2} + S\beta(x)i(x,t) - (\mu + \alpha(x))i(x,t) \tag{21b}$$

with $I(t) = \int_{-\infty}^{+\infty} i(y,t)\,dy$ and $N(t) = S(t) + I(t)$. Boundary conditions need to be added to this system of equations. A natural condition is $\lim_{x\to\pm\infty} i(x,t) = 0$ (there are no pathogens infinitely away from the optimal type). Notice, however, that this condition poses some mathematical subtleties that we will ignore here.

The main analytical result obtained (Pugliese and Andreasen, in prep.) on system (21) concerns its stationary solutions: there exists exactly one positive stationary solution when a threshold condition (written in terms of the principal eigenvalue of a Sturm-Liouville problem is satisfied. At the stationary solution, the infectives are distributed in the genotypic space x as the principal eigenfunction of the same Sturm-Liouville problem. Numerical approximations are necessary to follow the evolution in time of the epidemics, as well as the stationary

distribution, an example of which is presented in Fig. 4.

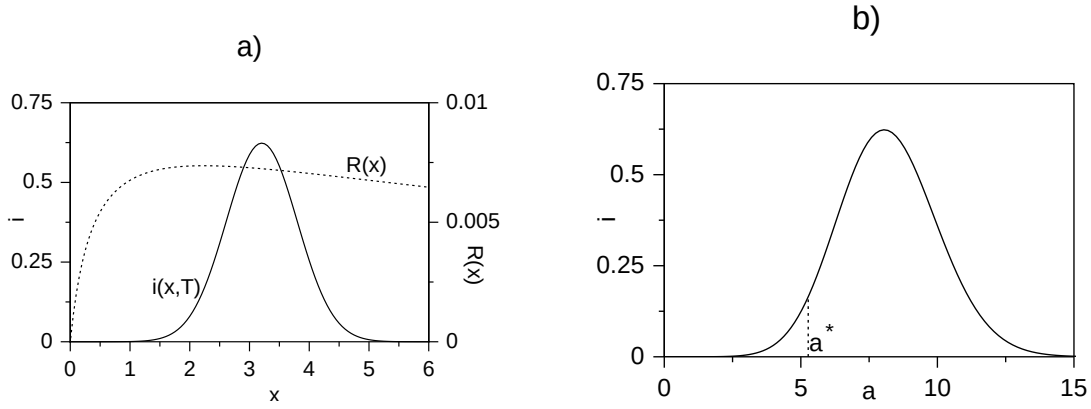

Figure 4: a) The numerical solution $i(x,T)$ of system (21)-(21) at time $T = 100$ together with the function $R(x)$. I used the functions $b(N) = 1 - N \cdot 10^{-4}$, $\mu = 0.8$, $\gamma = 0.01$, $\alpha(x) = 2x + 0.16x^2$, $\varphi(\alpha) = -0.125 + \sqrt{(0.125)^2 + 0.0025\alpha}$, so that $\beta(x) = 0.02x$. Initial values were $S(0) = 500$, $i(t,x)$ distributed according to a normal distribution (total mass equal to 1) of mean 2 and variance 0.2.
b) The same figure as in part a), except that virulence α is on the abscissa, showing also α^*.

It is then helpful to have a simpler system, passible of analytical investigation, which approximates (21)-(21). The variables of the approximating system will be the number of susceptibles $S(t)$ and the moments of order 0 to 2 of $i(x,t)$,

$$I(t) = \int_{-\infty}^{+\infty} i(x,t)\,dx \tag{22a}$$

$$M(t) = \frac{1}{I(t)} \int_{-\infty}^{+\infty} x i(x,t)\,dx \tag{22b}$$

$$V(t) = \frac{1}{I(t)} \int_{-\infty}^{+\infty} (x - M(t))^2 i(x,t)\,dx \tag{22c}$$

that represent, respectively, the total number of infective individuals, the mean value of virulence, and the variance of virulence, at time t.

To obtain a closed system in these variables, we basically follow the method of moments (Bolker and Pacala, 1997), with two main assumptions:

- $i(x,t)$ follows a normal distribution at any time t. This approximation is widespread in quantitative population genetics and other fields, and can be sometimes justified by a central limit theorem.

- $\alpha(x)$ and $\varphi(\alpha)$ can be approximated by a second-order Taylor expansion at $x = M(t)$.

By differentiating $I(t)$, $M(t)$, and $V(t)$, and then using these assumptions, one obtains:

$$\begin{aligned}
\frac{dS}{dt} &= b(N)N - \mu S - \left(\beta(M) + \frac{\beta''(M)}{2}V\right) SI && \text{(23a)}\\
\frac{dI}{dt} &= \left(\beta(M) + \frac{\beta''(M)}{2}V\right) SI - \left(\mu + \alpha(M) + \frac{\alpha''(M)}{2}V\right) I && \text{(23b)}\\
\frac{dM}{dt} &= \alpha'(M)\left(\varphi'(\alpha(M))S - 1\right) V && \text{(23c)}\\
\frac{dV}{dt} &= 2\gamma + \left(\beta''(M)S - \alpha''(M)\right) V^2. && \text{(23d)}
\end{aligned}$$

with $N = S + I$ and $\beta''(M) = \varphi''(\alpha(M))\left(\alpha'(M)\right)^2 + \varphi'(\alpha(M))\alpha''(M)$.

This system may still look rather complex, but a partial analysis is possible. First of all, by setting the right hand side of (23) equal to 0 and some algebra, one sees that, under reasonable assumptions, there exists a unique positive equilibrium if and only if a threshold condition (which is rather complex and unintuitive) is satisfied.

Some qualitative properties of such an equilibrium $(\bar{S}, \bar{I}, \bar{M}, \bar{V})$ can also be established, in comparison to the 'optimal' virulence α^* arising from adaptive dynamics. In order to do this, we follow the idea of Lenski and May (1994) of separating epidemic and evolutionary dynamics: if pathogens have a fixed virulence α; epidemic dynamics will bring the number of susceptibles to an equilibrium value $\bar{S}(\alpha)$, that we may consider (from the point of view of the pathogen) as unused resource. Vice versa, if the number of susceptibles were fixed to a number S, evolutionary dynamics would bring virulence to the level $\hat{\alpha}(S)$ ('optimal response') that has the highest growth rate. Bringing together the scales, the optimal virulence α^* has two properties: it is the optimal response to the resource it leaves, i.e. $\alpha^* = \hat{\alpha}(\bar{S}(\alpha^*))$; and it minimises the unused resource ($\bar{S}(\alpha^*) < \bar{S}(\alpha)$).

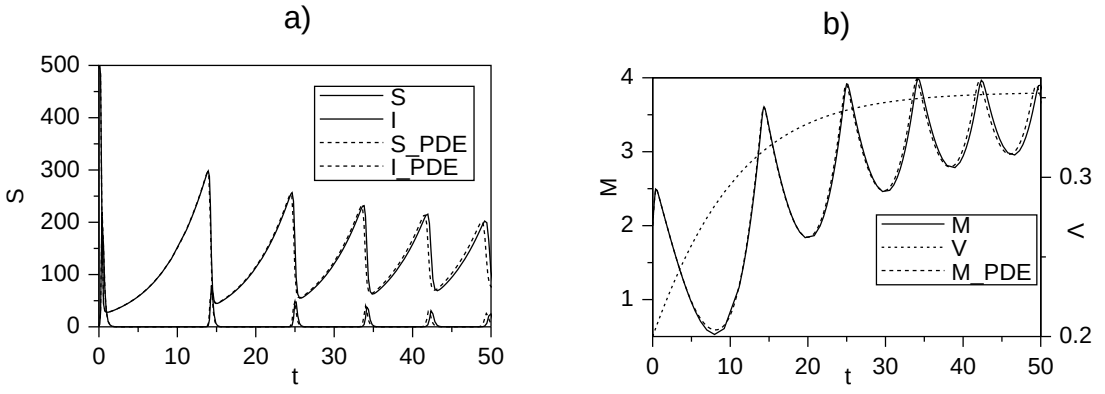

Figure 5: a) Values of the number of susceptibles (S) and the number of infectives (I) for the approximate system (23) compared with those (S_PDE and I_PDE) of the exact system (21)-(21). Everything as in Fig. 4; initial values for the approximate system are $S(0) = 500$, $I(0) = 1$, $M(0) = 2$, $V(0) = 0.2$.
b) Values of the mean virulence (M or M_PDE) and of the variance (V) for the same systems of part a). The values of V for the exact and approximate system are indistinguishable.

Letting x^* be the genotype that maximises R_0, so that $\alpha^* = \alpha(x^*)$, it can be proved that $\bar{S} > 1/R(x^*) = \bar{S}(\alpha^*)$; in words, the equilibrium number of susceptibles will always be higher, because of mutations, than the minimum level possible for a pure strain.

Moreover, it can be proved that $\bar{M} > x^*$, i.e. the mean virulence is higher than the 'optimal' virulence. A verbal explanation for this perhaps unexpected inequality starts from $\bar{S} > \bar{S}(\alpha^*)$; it can also be seen that the optimal response is increasing with the number of susceptibles, i.e. if $S > \bar{S}(\alpha^*)$, the evolutionary response is higher than the optimum ($\hat{\alpha}(S) > \alpha^*$). Because of frequent mutations, no monomorphic optimal response is possible; however, if the distributions are symmetrical, realised values of virulence are centred around those of the mean genotype $\alpha(\bar{M})$; thus, $\alpha(\bar{M})$ should be higher than α^*. Indeed, in the simplifying assumptions used to derive model (23) it is implicit that $i(x,t)$ is symmetrical and $R(x)$ not too asymmetrical.

Notice that in the exact model $R(x)$ may be very asymmetrical; then, if, for instance, $R(x)$ drops more quickly to the left of x^* than to its right (Fig. 4), it

is much more disadvantageous being brought by mutations to the left of x^*, and it is intuitively expectable that the centre $\bar{M}$ of the stationary distribution must be larger than α^*; vice versa, if $R(x)$ drops more quickly to the right of x^* than to the left, there is a selection for the centre $\bar{M}$ to move to the left of x^*. If the asymmetry is very strong, this factor may be more important than the previous argument, and it is possible that, in the exact model, at equilibrium $\alpha(M)$ is smaller than α^*.

How well does the approximate system approximate the original system? Although no analytical answer is available, it seems that the approximation is good, especially when the functions $\alpha(x)$ and $\beta(x)$ are close to second-order polynomial (see Fig. 5 where only a small difference in the period of oscillations appear). A more thorough investigation will be needed, in order to see the errors brought by the assumption of normality, and those by the use of second-order Taylor developments for β and α. More precise approximations could be used, if needed, for some special choices of β and α

From the study of the Jacobian of (23), one sees that, for most reasonable parameter values (including the ones used in Fig. 5), the equilibrium $(\bar{S}, \bar{I}, \bar{M}, \bar{V})$ is stable. It is possible, however, to choose parameter values that destabilize the equilibrium, opening the possibility for cyclic behaviour. However, since these values lie in the region where the assumptions used to derive the approximate model fail, it is not clear whether it is possible to obtain periodic solutions for the exact system (21).

On the other hand, convergence to the equilibrium level of virulence occurs usually through damped oscillations (Fig.5). Such a behaviour is impossible in one-dimensional adaptive dynamics, and is an interesting result of the polymorphic modelling approach.

6 Discussion

In this chapter I have considered the evolution of virulence assuming the existence of a fundamental trade-off between transmissibility and virulence. Using the adaptive dynamics framework (Geritz et al., 1998), the evolutionary dynamics in the simple model of Anderson and May (1982) is well understood: convergence to the strategy α that maximises $R(\alpha)$ (the 'per capita' reproductive ratio). Andreasen and Pugliese (1995) considered a variant of that model in which density-dependence acted on mortality instead of on fertility. Then, transient dimorphisms are possible; under the assumptions of adaptive dynamics, however, these contract towards the unique continuously stable strategy.

A complete analysis of the model with superinfection is still missing. Preliminary results suggest that, when the function k relating virulence to superinfection rates is differentiable, a unique continuously stable strategy for virulence α^* exists; in this model too, dimorphisms are only transients. However, the evolutionary dynamics may depend on the size of mutations, since α^* is only locally uninvadable. When the function k is not differentiable, evolutionary dynamics can be very complex.

This model for superinfection suffers, as most of the existing models, of a serious problems: the infected individuals are assumed to be infected with a single pathogen strain. If superinfection occurs, its instantaneously leads to a complete replacement of the original strain with the superinfecting strain. While this may be a viable approximation when strains differ considerably in their replication rate, the approximation becomes questionable when the virulence of competing strains is very similar. Yet such similar strains are considered when studying evolutionary stability. When concomitant infections are allowed, models become very complex and are difficult to handle (see, however, Nowak and May (1995) and van Baalen and Sabelis (1995)). It would seem promising to merge these epidemic models with models for intra-host competition among parasites.

Parasite competition would then occur at two levels, and it seems likely that stable coexistence of different parasite types may occur.

In Section 5, I analysed the model of Anderson and May (1982) assuming that mutations are frequent. The main difference is, of course, that then the evolutionary equilibrium is not a single state, but a frequency distribution of strains. The centre of this distribution is generally very close to the continuously stable strategy found through adaptive dynamics. There is, however, some differences in how the evolutionary equilibrium is approached. It would be interesting to use this approach in more complex cases, where there is not a single optimum for the basic reproductive ratio.

As stated at the beginning, the evolution of virulence is very actively studied, both experimentally (Ebert and Mangin, 1997; Ebert, 1998; Mackinnon and Read, 1999b; Koella and Agnew, 1999) and theoretically. Among the most important problems recently considered and not addressed here, I would mention the evolution of virulence in structured hosts, whether genetically (Regoes et al., 2000), or spatially (Haraguchi and Sasaki, 2000), in which multiple parasite types may be maintained; and the dynamics of host resistance and tolerance (Boots and Bowers, 1999; Roy and Kirchner, 2000). The latter problem, for which a full co-evolutionary treatment is needed, may have also implications for wide-ranging issues, such as the evolution of symbiosis, genomic conflicts and early evolution (Frank, 1996). I hope the present treatment may be a basis on which much more complex problems can be studied.

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