

Evolutionary trade-offs at two time-scales: competition versus persistence

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The evolution of many natural systems is complicated due to dynamics at a mixture of time-scales. This is especially true when there is a trade-off between large reproductive rates and long-term persistence; such behaviour is frequently observed in disease models. In this paper, a simple partial differential equation model is formulated which describes the evolutionary dynamics of two disease strains in a metapopulation: one strain is a better short-term competitor; the other has greater persistence. By considering the behaviour of means and higher-order moments, analytical expressions for the evolutionary behaviour are produced in the case when the two strains are phenotypically close.

Keywords: disease evolution; metapopulation; moment closure

1. INTRODUCTION

Many populations and models of population dynamics display boom–bust cycles (Nicholson & Bailey 1935; Grenfell *et al.* 1992; Bowers *et al.* 1993; Ranta *et al.* 1997; Lindstrom *et al.* 1997; Blarer & Doebeli 1999; Blasius *et al.* 1999); frequently the amplitude of such cycles increases with the reproductive rate. The most simple model that displays this behaviour is the logistic map $x_{t+1} = rx_t(1 - x_t)$ (May 1976). In the chaotic regime we find that,

$$\max(x_t) = \frac{r}{4} \quad \text{and} \quad \min(x_t) = \frac{r^2}{16}(4 - r),$$

so the minimum clearly decreases with r ; hence, in a stochastic framework, populations with large r should be doomed to rapid extinction. A similar pattern can be found for the more realistic disease models (figure 1) where the frequency of local extinctions increases for large transmission rates. However, organisms with high reproductive rates have a clear short-term evolutionary advantage.

In this paper, equations are developed for metapopulations where the trade-off between short-term reproduction and long-term persistence can be considered in more detail. Without loss of generality, and mainly to keep the language simple, this paper concentrates exclusively on the evolutionary dynamics of diseases, an area of research that is becoming increasingly popular (Levin *et al.* 1999; Wilkinson 1999), and has important public health considerations (Brown & Richman 1997; Baquero & Blazquez 1997; Hastings & Mackinnon 1998).

The short-term dynamics of many diseases can be accurately captured by deterministic or stochastic models of the susceptible–infectious–recovered (SIR)-type (Anderson & May 1992; Grenfell 1992; Bolker 1993; Keeling 1997). However, when these models are used as a basis for the long-term evolutionary dynamics of the system, they fail to reproduce the observed results. The standard epidemiological models predict that a disease should evolve to have maximal transmissibility and long infectious periods. Many diseases of public health interest do not match these criteria and hence some form of

trade-off is required to limit evolution in the models. A large number of researchers have proposed a physiological trade-off between transmissibility and virulence (Levin & Pimentel 1981; Anderson & May 1982; May & Anderson 1990; Read & Schrag 1991; Bonhoeffer & Nowak 1994; May & Nowak 1995; Herre 1995), although until recently there has been little supporting evidence (Messenger *et al.* 1999). In this paper the trade-off used, between fast transmission and persistence, is dynamically generated and is therefore likely to be highly generic.

To understand the long-term evolutionary dynamics, consider the behaviour of two competing strains of pathogen, P_0 and P_1 , spread across an infinite set of coupled populations (a metapopulation). Using the classic Levins approach (Levins 1969), each population can be classified into two distinct forms, uninfected populations which are a proportion U of the total, and infected populations, P . The infected populations are further subdivided, such that $P(x)$ is the ‘density’ of populations where the ratio of strain 1 to the total amount of pathogen is x (hence $0 \leq x \leq 1$). More precisely,

$$\text{prob}(a < x < b) = \int_a^b P(x) dx.$$

After calculating the short-term dynamics within a single patch, a partial differential equation (PDE) is formulated which captures the generic behaviour of P . This is augmented by the use of moment closure analysis to find an evolutionarily stable strategy (ESS) (Rand *et al.* 1994) for the disease.

2. SHORT-TERM BEHAVIOUR

Let us suppose that pathogen 1 replicates faster than pathogen 0, but is more prone to extinction. Figure 1 shows how the persistence time for an epidemic is affected by the contact rate β ; we note that persistence is maximized close to (but less than) the observed contact rate. For a single population, we expect x , the ratio of disease 1 to the total amount of infection, to obey

$$\frac{dx}{dt} = \alpha x(1 - x),$$

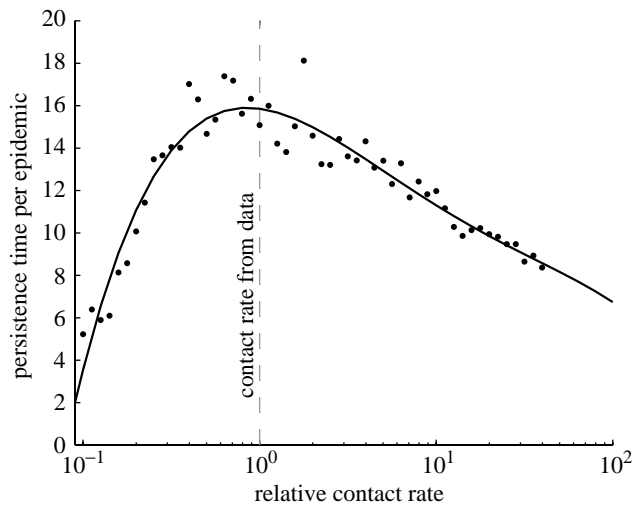


Figure 1. Results from a stochastic age-structured model for measles (Keeling & Grenfell 1997) with a population of 5000. A similar pattern is also observed for the standard SIR model (Anderson & May 1992) with stochastic updating. The horizontal axis shows the value of the contact parameter (β) relative to that of the standard model which has been parameterized to fit the observed case reports from England and Wales. The vertical axis gives the average length of an epidemic in weeks from a simulation of 100 years, and therefore gives a measure of the persistence. The line is a quartic fit to the data.

where $\alpha > 0$ measures the extent to which disease 0 is transmitted faster than disease 1. Using an SIR-type model (Anderson & May 1992), the dynamics of two pathogen strains competing in a population is given by

$$\begin{aligned} \frac{dS}{dt} &= B - \beta_0 SP_0 - \beta_1 SP_1, \\ \frac{dP_0}{dt} &= \beta_0 SP_0 - g_0 P_0, \\ \frac{dP_1}{dt} &= \beta_1 SP_1 - g_1 P_1. \end{aligned}$$

Here S is the number of susceptibles, B is the birth rate, β is the contact rate and g^{-1} is the infectious period; for mathematical convenience it has been assumed that the average age of infection is low, so that all deaths occur within the recovered class. This model implicitly assumes cross-immunity between the two strains, such that they compete for the same limited resource (susceptibles). The behaviour of x is determined by the relative growth rates of the two strains, so that

$$\begin{aligned} \frac{dx}{dt} &= \frac{d}{dt} \left(\frac{P_1}{P_0 + P_1} \right) \\ &= (\beta_1 S - g_1) \frac{P_1}{P_0 + P_1} - (\beta_1 S - g_1) \frac{P_1^2}{(P_0 + P_1)^2} \\ &\quad - (\beta_0 S - g_0) \frac{P_0 P_1}{(P_0 + P_1)^2} \\ &= (\beta_1 S + g_0 - \beta_0 S - g_1)x(1 - x), \end{aligned}$$

and

$$\alpha = (\beta_1 S + g_0 - \beta_0 S - g_1). \tag{1}$$

Hence, there exists an explicit form for α in terms of the underlying epidemiological parameters, and in a single population there is dominance by the strain with the largest $\beta S - g$, which equates to the disease with the largest R_0 being most successful. Note that in a general ecological model, α could also be a function of x , which would make the following analysis far more difficult, although the principles would remain the same.

3. METAPOPOPULATION EQUATIONS

Metapopulations have been widely used in ecology (Gilpin & Hanski 1991; Hanski & Gilpin 1997; Grenfell & Harwood 1997) because they provide a simple and robust means of incorporating space into models of population dynamics. Metapopulations assume global coupling because they do not associate a particular spatial location with each sub-habitat; hence spatial correlations cannot develop. Metapopulations are therefore particularly useful when one is solely interested in maintaining diversity between populations. In the original formulation by Levins (1969) each sub-habitat was considered to be either empty or occupied; more recently researchers have also been interested in the population level within each habitat. The equations formulated in this paper possess elements of both approaches, assuming that the number of pathogens within an infected population has reached some equilibrium, but modelling the ratio of pathogens explicitly.

It should be realized that in many situations it is difficult, if not impossible, to identify the absolute number of individuals that constitutes one subpopulation. For many disease models each subpopulation is often taken to represent a single community (Grenfell & Harwood 1997), but in other evolutionary situations the size of a subpopulation is less well defined. Although in this work the size of a subpopulation does not enter directly into the equations, many of the parameters used are expected to depend on the exact metapopulation structure.

Let the extinction rate of a population be a linear combination of the extinction rates for the two strains present: the extinction rate of populations with a strain ratio of $x(P(x))$ is therefore taken as $d + Dx$ (where d is the extinction rate of strain 0 and $d + D$ is the extinction rate of strain 1). Because it is generally most useful to consider competition between two phenotypically close strains of the disease, it can be assumed that D is small and therefore this linear approximation is valid.

To simplify notation let us define the following global parameters:

$$\begin{aligned} L &= \int_0^1 xP(x)dx, \\ M &= \int_0^1 P(x)dx = 1 - U, \\ X &= \frac{L}{M}. \end{aligned}$$

Let μ be the rate at which infection is released from a subpopulation, allowing it to recolonize uninfected sites. Therefore the equation for the proportion of uninfected sites, U , is

$$\begin{aligned} \frac{dU}{dt} &= - \text{colonization} + \text{extinction}, \\ &= - \mu U \int_0^1 P(x) dx + \int_0^1 (d + Dx)P(x) dx, \\ &= - \mu UM + dM + DL = (d + DX - \mu U)M. \end{aligned} \quad (2)$$

Hence either both diseases die out ($d + DX > \mu$), or there exists a globally attracting fixed point [$U^* = (d + DX) / \mu$].

In a similar manner, the rate of change of the infected populations can be expressed as a PDE by considering the effects of four distinct processes

$$\begin{aligned} \frac{\partial P(x)}{\partial t} &= \text{colonization and extinctions} \\ &\quad + \text{competition between viruses} \\ &\quad + \text{dispersal of viruses} + \text{stochasticity.} \end{aligned}$$

These four elements will be considered separately.

(a) Colonization and extinctions

New infected populations are formed from colonization of uninfected sites at rate $\mu UP(x)$, and this is assumed to give rise to a population with strain ratio x . (An alternative formulation, where only one strain of pathogen colonizes an uninfected site is considered in §6.) The disease dies out in infected populations at a rate $d + Dx$. These two processes add the following terms to the PDE:

$$(\mu U - d - Dx)P(x).$$

Only the parameter D causes a change in the global population composition: the effect of a larger extinction rate ($D > 0$) is to cause the populations to move towards smaller x -values.

(b) Direct competition between pathogens

Within every infected population, strain 1 is continually displacing strain 0, as shown for a single population in isolation (equation (1)). The rate of change is therefore

$$-\alpha \frac{\partial}{\partial x} [x(1 - x)P(x)].$$

The competition between the two strains leads to a movement of populations towards larger x -values.

(c) Dispersal of pathogens

It has already been assumed that infected populations are throwing out pathogens (at a rate μ and in the ratio $1 - x$). Besides colonizing uninfected sites, these pathogens can also settle on already infected sites, changing the local ratio. If a small number of pathogens, $p \ll 1$, from a site of type y land on a site of type x , then this site is transformed to type

$$\frac{x + py}{1 + p} \approx x + p(y - x).$$

Given that pathogens are thrown out at a rate μ , then the addition this component makes to the PDE is loss of $P(x)$ + gain of $P(x)$ from $P(z)$, i.e.

$$\begin{aligned} &-\frac{\mu}{p} \int_0^1 P(y) dy P(x) + \frac{\mu}{p} \int_0^1 \int_0^1 \delta(x - z - p(y - z)) \\ &\times P(y)P(z) dy (1 + p) dz. \end{aligned}$$

Integrating the last term with respect to z , and then Taylor expanding about x leads to

$$\begin{aligned} \mu MP(x) + \mu[Mx - L] \frac{\partial P(x)}{\partial x} &= \mu \frac{\partial}{\partial x} [(Mx - L)P(x)] \\ &= \mu M \frac{\partial}{\partial x} [(x - X)P(x)]. \end{aligned}$$

This component of the PDE will act to concentrate the distribution of populations around the average value X , but will not affect the value of X .

(d) Stochasticity

The final component of the PDE is the effect due to stochasticity in the underlying dynamics. This can be approximated by diffusion with a scaling parameter Q ,

$$Q \frac{\partial^2}{\partial x^2} [x(1 - x)P(x)].$$

This component will act to spread the distribution of populations over a wider range of x . The form within the square brackets is because the amount of change to the ratio x is assumed to be proportional to the densities of both strains; hence there is no diffusion outside the range $0 < x < 1$.

(e) The full equations

Putting the above four components together we arrive at

$$\begin{aligned} \frac{\partial P(x)}{\partial t} &= (\mu U - d - Dx)P(x) + \frac{\partial}{\partial x} [(\mu M(x - X) \\ &\quad - \alpha x(1 - x))P(x)] + Q \frac{\partial^2}{\partial x^2} [x(1 - x)P(x)], \end{aligned}$$

$$P(0) = P(1) = 0. \quad (3)$$

The boundary conditions mean that there are no populations that contain just a single strain; if this condition is satisfied initially then it should hold for all time, although care will be needed when using numerical routines. Because the above second-order PDE also contains integrals (contained within the terms X and U), there is little or no chance of finding a general analytical solution: in §4 we will therefore resort to numerical techniques.

4. DYNAMICS

Figure 2 shows the evolutionary dynamics of the PDE (3) for three sets of parameters with different fixed point distributions. For graph (a), when the difference in extinction rates is largest, the slower more persistent strain (P_0) wins. In graph (b), when D is smaller, the advantage is with the faster reproducing strain. Finally, graph (c) shows the more rare occurrence where the two strains coexist. To try to understand (and hopefully predict) this behaviour, we shall examine the dynamics of X , the global ratio of strain 1 to the total amount of disease.

When $D = \alpha = 0$ and the two strains are phenotypically identical, then there should be no change in X from its initial value with the populations tending to a

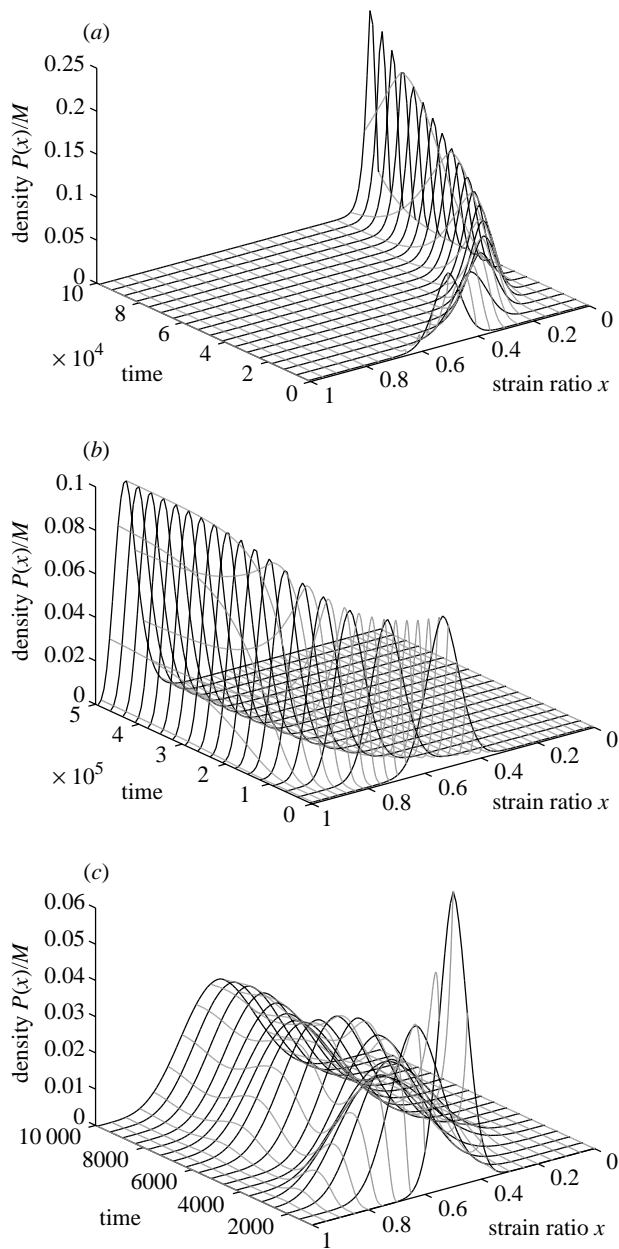


Figure 2. The relative dynamics of the two disease strains can be seen by studying the relative densities of population types $P(x)/M$. Throughout the simulations, $\mu = 2 \times 10^{-2}$, $d = 10^{-2}$ and $Q = 10^{-4}$, while the competition parameters D and α are varied to obtain different scenarios. Graph (a) shows convergence to $X = 0$; this fixed point is globally attracting ($\alpha = 10^{-4}$ and $D = 10^{-2}$, giving $\zeta_0 \approx 10^{-2}$). Graph (b) shows far slower convergence to $X = 1$; again this fixed point is globally attracting ($\alpha = 10^{-4}$ and $D = 5 \times 10^{-3}$, giving $\zeta_0 \approx 2 \times 10^{-2}$). Graph (c) shows the stability of a distribution with intermediate $X = \hat{X}$ such that the two strains coexist ($\alpha = 1 \times 10^{-3}$ and $\zeta_0 = 6.25 \times 10^{-2}$, giving $D \approx 1.5 \times 10^{-2}$).

Gaussian-like distribution about the average value X . Consider how X changes when both D and α are positive and hence there is a trade-off between short-term competitive advantage and long-term persistence. From the definition of X and equation (3),

$$\frac{dX}{dt} = \frac{1}{M} \int_0^1 x \frac{\partial P(x)}{\partial t} dx + \frac{X}{M} \frac{dU}{dt}. \tag{4}$$

This equation for X is found to contain the second-order moment of the pathogen distribution; hence for convenience we define

$$M(X^2 + \sigma^2) = \int_0^1 x^2 P(x) dx.$$

Using the fact that $M = 1 - U$, together with equations (2)–(4), we find that the dynamics of X are governed by

$$\frac{dX}{dt} = \alpha X - D\sigma^2 - \alpha(X^2 + \sigma^2). \tag{5}$$

It is clear that the value of σ^2 , and hence the distribution of the strains, is very important for the long-term disease dynamics. When the two strains occupy distinct sites ($\sigma^2 = X - X^2$), the level of strain 0 will always increase; conversely when all habitats contain the same ratio of pathogens ($\sigma^2 = 0$), the level of strain 1 increases. This would imply that greater stochasticity Q will favour the more persistent (and less reproductive) disease strain.

From equation (5), using standard dynamical systems techniques, the fixed points of X and their stability can be calculated. Because σ^2 is constrained to lie between 0 and $X - X^2$, we shall set $\sigma^2 = zX(1 - X)$ where z is between zero and unity. Using this new form for σ^2 , equation (5) becomes

$$\frac{dX}{dt} = X(1 - X)[\alpha - (\alpha + D)z(X)].$$

Thus the dynamics of X are controlled by the value of $z(X)$ with respect to a threshold value $\zeta_0 = \alpha/(\alpha + D)$.

- (i) $X = 0$ is a stable fixed point if and only if $z(0) > \zeta_0$.
- (ii) $X = 1$ is a stable fixed point if and only if $z(1) < \zeta_0$.
- (iii) X^* is a stable fixed point if and only if $z(X^*) = \zeta_0$ and $(dz/dX)|_{X^*} > 0$.

However, there exists one final complication to predicting the long-term dynamics. Suppose that X^* is an attracting fixed point of equation (5) as defined above, but that $\mu < d + DX^*$; i.e. at the fixed point extinctions occur at a faster rate than colonizations, so the disease dies out. In this case we observe evolution to a critical ratio $\hat{X} = (\mu - d)/D$ where the disease persists at very low densities: this can be compared with the evolution to a critical transmissibility observed by Rand *et al.* (1995) for a cellular automaton model. Figure 3 gives a simple pictorial representation of the long-term dynamics of the two strains as $z(X)$ varies about ζ_0 —it is doubtful whether such multiple stable states would be observed for any ecological example.

These results explain the observed long-term behaviour of the PDE in figure 2. In graph (a) $z > \zeta_0$ for all X ; hence strain 1 dies out irrespective of the initial conditions. In graph (b) the situation is reversed and strain 0 always dies out. For graph (c), we again find that $z < \zeta_0$ for all X ; however, above $\hat{X} = 2/3$ the pathogen fails to persist and so we see evolution to this critical ratio.

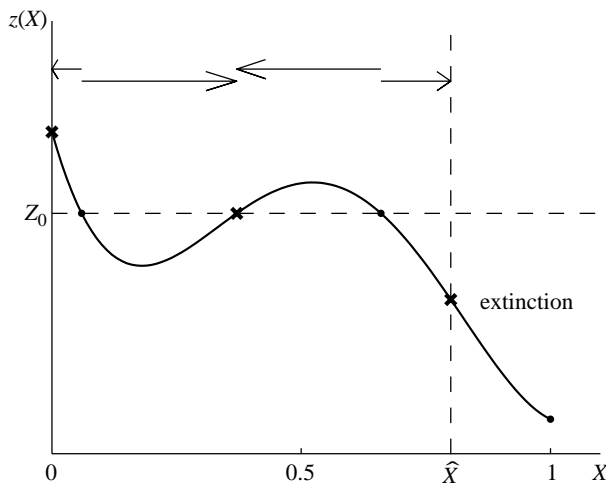


Figure 3. A graphical representation showing how the long-term competition between the two strains is governed by the value of $z(X)$ relative to the threshold Z_0 . The dots show unstable fixed points, the crosses are attracting fixed points, values above \hat{X} are doomed to extinction, and the arrows show the direction of long-term dynamics.

5. MOMENT APPROXIMATION FOR PHENOTYPICALLY CLOSE STRAINS

In a similar manner to the formulation of an equation for the mean X , by considering the time evolution of the second-order moment we can find a differential equation for the behaviour of σ^2 . This will, of course, contain other higher-order moments which will need to be approximated if we are to close the system—the moment closure technique (Renshaw 1991; Isham 1995; Keeling 1999). However, by assuming α and D are small, the contribution of these higher-order moments is negligible and the form for σ^2 is greatly simplified,

$$\frac{d\sigma^2}{dt} = -2(M\mu + Q)\sigma^2 + 2Q(X - X^2).$$

Hence we find

$$z \approx \frac{Q}{Q + M\mu} = \frac{Q}{Q + \mu - d}. \tag{6}$$

This formula for z has been compared to results from simulations of the PDE, which again show the surprising fact that when D and α are small there is little or no change to z as the value of X alters. Figure 4 shows the values of z calculated from numerical solution of the PDE (3): these are in precise agreement with equation (6). If the differences between competing strains of disease is small, because z does not depend on X , coexistence of the strains will never be observed; either $X = 0$ or $X = 1$ will be globally attracting. This form for z predicts that the strain with the higher R_0 , strain 1, will dominate if and only if

$$\frac{Q}{Q + \mu - d} < \frac{\alpha}{\alpha + D}. \tag{7}$$

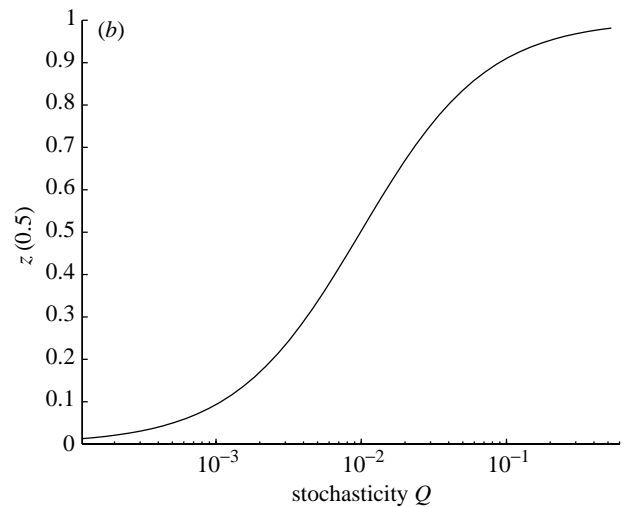
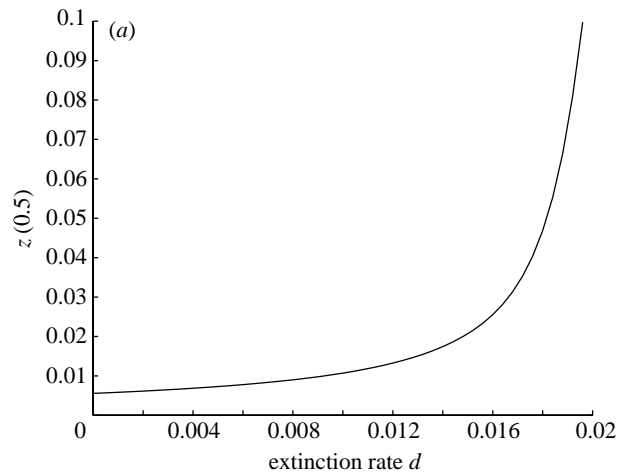


Figure 4. The changes in the second moment parameter z calculated from the PDE; z displays little variation with X . Graph (a) shows how z changes with d ; D and α are assumed to be negligible, $X = 0.5$, $\mu = 0.02$, $Q = 10^{-4}$. For values of d greater than μ ($= 0.02$) the disease fails to persist as the rate of extinction is always greater than the rate of colonization. Fixing $d = 0.01$, graph (b) shows how z changes with the stochasticity Q (again $X = 0.5$, $\mu = 0.02$ and D and α are negligible).

(a) Evolution

So far only the competition between two disease strains has been considered; however, this can be used to infer the evolutionary dynamics. If mutations are a very rare occurrence, then in general we will only ever observe competition between two strains, the wild-type and the mutant. Hence our above theory can predict which of these will dominate and therefore the direction of evolution. When the two competing strains are phenotypically close, we would expect α and therefore d to increase until

$$\frac{Q}{Q + \mu - d} = \frac{\alpha}{\alpha + D}, \tag{8}$$

so that the wild-type is an ESS and cannot be invaded. In this situation, the system will never evolve to the critical point where $\mu = d$.

The moment closure model can now be used to predict the evolution of the contact parameter β . For simplicity, it

is assumed that Q and μ are independent of β and that any two strains differ in their contact rate by a small amount $\delta\beta$. From equation (1) we find that

$$\alpha = \delta\beta S = \delta\beta \frac{g}{\beta},$$

(assuming S is at equilibrium). So long as $d(\beta) < \mu$, one strain of the disease should always remain in the metapopulation. If the persistence of the strains increases with β , ($d' = \partial d / \partial \beta \leq 0$), as is the case for small β in figure 1, then evolution will obviously favour the faster reproducing, and more persistent, pathogen. It is only when $d' > 0$ that a trade-off between persistence and short-term competition occurs. From equation (7) we predict that there should be evolution towards higher β as long as

$$\frac{Q}{Q + \mu - d(\beta)} < \frac{\delta\beta g}{\delta\beta g + \beta[d(\beta + \delta\beta) - d(\beta)]},$$

that is,

$$\frac{Q\beta}{g} d' + d < \mu \quad \text{as } \delta\beta \rightarrow 0.$$

Therefore the local evolutionarily stable contact parameter β^* is such that

$$\beta^* = \frac{[\mu - d(\beta^*)]g}{Qd'(\beta^*)}. \quad (9)$$

Using the quartic fit to the data shown in figure 1, the value of β^* relative to the observed contact rate can be calculated for a range of coupling rates, μ , and stochasticity levels, Q (figure 5). It is clear that when the stochasticity is high and the coupling low, the ESS is close to the contact rate β_0 that maximizes persistence ($d'(\beta_0) = 0$); in contrast, when the stochasticity is low and the coupling high, the ESS is close to $\hat{\beta}$, the threshold contact rate which corresponds to the limit of disease extinction ($d(\hat{\beta}) = \mu$). In these two extreme situations, analytical approximations for β^* can be found.

When μ is small and Q large,

$$\beta^* \approx \beta_0 + \frac{(\mu - d)g}{Q\hat{\beta}d''},$$

where d and d'' are calculated at β_0 . In the converse situation, the ESS is given by

$$\beta^* \approx \hat{\beta} \left(1 - \frac{Q}{gd' + Q\hat{\beta}d''} \right),$$

where d' and d'' are calculated at $\hat{\beta}$.

6. DISCUSSION

Simple evolutionary models of diseases and more complex organisms predict there should be continual evolution towards large reproductive rates. In this way organisms evolve to be the best competitor in their local environment. To prevent this run-away evolution, either physiological limitations or trade-offs are required. For diseases, it is often postulated that there is a trade-off between transmission rates and virulence (Anderson & May 1982; Bonhoeffer & Nowak 1994; Messenger *et al.* 1999).

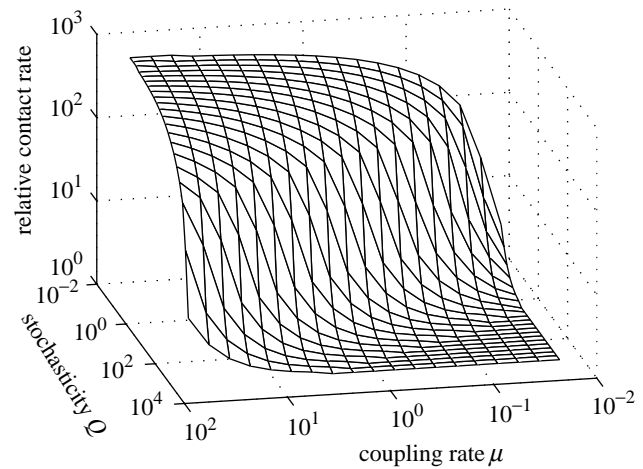


Figure 5. Using the persistence times from the age-structured model of measles (shown in figure 1), the evolutionarily stable contact rate β^* that satisfies equation (9) can be found. For extreme values of coupling or stochasticity, β^* asymptotes to either the contact rate associated with maximum persistence or the contact rate associated with the extinction threshold. ($g=1/13$ was taken as a reasonable approximation to the measles exposed and infectious periods.)

This paper presents a novel approach, that the very dynamics themselves could provide a trade-off (between reproductive rate and persistence) that limits the evolution. Although the precise relationship between transmission rates and persistence cannot be obtained from observations, it is to be hoped that the results from stochastic models (parameterized from case reports) should give an accurate local prediction. This dynamically generated trade-off can also be applied to higher organisms, whereas trade-offs between transmissibility and virulence have no direct analogue.

This trade-off works over two different time-scales. High reproductive rates offer a short-term gain, whereas greater persistence is only of long-term benefit. This trade-off has no effect on a single deterministic population; it relies on the variability between subpopulations. This variability could come from a variety of sources. In this paper a diffusion approximation was used to model the stochasticity within each subpopulation—this allowed a set of closed moment equations to be formulated. If the dispersal parameter μ is small, a realistic alternative is to assume that a pure strain of pathogen (either $x = 0$ or $x = 1$) colonizes each uninfected population—again this is another form of stochasticity. Preliminary investigations show that the precise means of introducing the variability is unimportant, and the same basic phenomenon will hold in any stochastic multi-habitat population.

Focusing attention on the disease scenario considered here in some detail, it is interesting to ask what are the evolutionary consequences of recent social changes. As communities become larger and transport easier, there should be an overall decrease in Q and d , an increase in μ , and also an increase in $\hat{\beta}$. All of these changes should push diseases towards an increase in the transmission rate; this has important public health implications.

Notice that while β^* has been shown to be locally an attracting ESS, it is not necessarily true that it will be a

global ESS. That is, while local strategies (phenotypically close strains) cannot invade, it is possible that a new strain with very different behaviour could replace β^* . Therefore, to be able to fully predict the evolution of a disease, we have to be able to predict the entire set of possible mutations and be able to map these genotypes onto the macro-scale parameters of interest.

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As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.

