



## Population Dynamics and the Evolution of Virulence in Epidemiological Models with Discrete Host Generations

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Chaos is the likely outcome of the interaction between a parasite and a host with discrete generations, if the parasite's virulence is high and if transmission from one generation to the next is held constant. We studied two alternative routes of transmission—vertical transmission from infecteds to their offspring, and transmission via long-lasting spores produced in those individuals that were killed by the infection—to investigate the influence of the transmission route on the system's evolution and population dynamics. The major results are: (1) vertical transmission often leads to low virulence, thus confirming most epidemiological models. However, if hosts can become super-infected, the evolutionary dynamics of virulence can have several equilibrium points, including 100% disease-induced mortality; (2) when parasites are transmitted with long-lasting spores, the evolutionary dynamics of virulence can become unstable, leading to the repeated bifurcation of two sub-populations with high and low virulence or to punctuated equilibria with sudden changes in the average level of virulence; (3) in general, the evolution of virulence moves the system to an area where the population dynamics are stable. When evolution leads to chaos, the system most often becomes extinct. Only for a restricted parameter space in the system where transmission from one generation to the next is via long-lasting spores do the dynamics become chaotic without extinction of the system.

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### Introduction

Why are parasites virulent? Up to about a decade ago, it was widely believed that parasite–host systems should evolve towards commensalism, because parasites would ensure their reproductive success by minimizing their impact on host survival. The most influential ideas leading to the

demise of this “conventional wisdom” (Anderson & May, 1982; Bremermann & Pickering, 1983; Ewald, 1994; Levin & Pimentel, 1981) are based on mathematical models proposed by Anderson & May (e.g. Anderson & May, 1981). These models describe the dynamics of parasite transmission in a host population and lead to the basic reproductive number as a pivotal parameter of parasite transmission. In the most simple models, where host reproduction is continuous and parasites are transmitted directly

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from one host to another, the basic reproductive number is

$$R_0 = \frac{\beta N}{\alpha + \mu + \nu}$$

where  $\beta$  is the rate parameter for disease transmission,  $N$  is the number of susceptible hosts,  $\alpha$  is the rate of parasite-induced mortality,  $\mu$  is the rate of parasite-independent mortality and  $\nu$  is the rate of recovery of infected hosts (Anderson & May, 1981). The basic reproductive number illustrates the mechanisms by which selection operates. Selection in the parasite population will favor a high  $R_0$ , which can be achieved with a high rate of transmission,  $\beta$ , or with low rates of parasite-induced mortality,  $\alpha$ , or recovery,  $\nu$ . If  $\beta$ ,  $\alpha$  and  $\nu$  are independent parameters, selection for high  $R_0$  will result in the evolution of highly transmissible, benign parasites, an outcome in line with the conventional wisdom noted above. However, if the parameters that determine  $R_0$  are associated with one another, various evolutionary endpoints are possible, including a move towards virulence or a move towards avirulence. For example, if  $\beta$  increased more than linearly with  $\alpha$ , selection would favor parasites that kill every infected host.

This approach has been modified in recent years to include trade-offs between horizontal and vertical transmission (Lipsitch *et al.*, 1995), the concept of an evolutionarily stable strategy (i.e. the conditions under which a mutant with a different level of virulence cannot invade a population dominated by a resident parasite) (van Baalen & Sabelis, 1995) or spatial heterogeneity in contact and infection rates (Claessen & de Roos, 1995). Such extensions, however, did not change the general conclusions regarding the evolution of virulence.

The predictions generated by these models have led to the wide-spread belief that virulence is the result of selection increasing the parasite's reproductive number, and that if a parasite's virulence is to be maintained, it must be associated with other aspects of its life-cycle, e.g. rate of transmission or recovery rate. Only recently have other mechanisms leading to the maintenance of virulence been suggested. One such mechanism is that virulence could infer a

growth advantage within the host and be selected despite a disadvantage at the level of transmission among hosts (Levin & Bull, 1994). A similar suggestion is that genes coding for virulence might be advantageous in aspects that are not necessarily related to transmission (Levin & Svanborg-Eden, 1991). These suggestions seek to explain the maintenance of virulence through selection acting on different levels—transmission among hosts vs. growth within hosts—, whereby they assume that selection within hosts is the stronger force.

The idea that virulence is formed by selection acting at several levels is also important in epidemiological models where hosts have discrete generations. Parasites then transmit within individual cohorts of hosts, but must also transmit to the next host generation. The selection pressures affecting these two levels—within cohort and among cohorts—need not be the same, so that the level of virulence eventually reached will be a balance of processes within and among cohorts.

A mathematical model of parasite dynamics in hosts with discrete generations was described by May (1985). May showed that changing the assumptions about host reproduction from continuous generations, as assumed in models following Anderson & May (1981), to discrete generations could change the host's population dynamics from having a stable equilibrium to being chaotic. Similar conclusions were found in other models where the host-pathogen interaction was seasonal (Briggs & Godfray, 1996; Hochberg *et al.*, 1990). Evolutionary questions, however, remain largely unanswered. Will virulence follow the evolutionary predictions made on the basis of models with continuous host reproduction? Will the evolution of virulence bring with it stable or chaotic dynamics? Will the evolutionary pattern of virulence follow the chaotic population dynamics or will virulence settle to a stable pattern even when dynamics are chaotic?

In this paper, we will begin to answer these questions. We will first review May's original model, go on to investigate the dynamics of the host and parasite populations with different assumptions about transmission among generations, and finally consider the evolution of

virulence and its implications for the population dynamics. We emphasize here that we do not intend to explore the full range of parameter space on the behavior of our models, but that we vary selected parameters to demonstrate possible dynamic and evolutionary outcomes of epidemiology in discrete time. Similarly, we chose to investigate May's (1985) model in more detail not as the best predictor of parasite transmission in discrete generations, but to focus on possible consequences of changing critical assumptions in the epidemiological models most commonly used to describe the evolution of parasite virulence.

### Dynamics

#### THE BASIC MODEL

A model describing the dynamics of parasites in a host with discrete, non-overlapping generations was proposed by May & Anderson (1983a) and further investigated by May (1985). While other models describe similar situations (Briggs & Godfray, 1996; Hochberg *et al.*, 1990), this one has the advantage that its results are to some extent analytically tractable. The epidemiological dynamics of the cohort are described by

$$\begin{aligned}\frac{dX}{dt} &= -\beta XY \\ \frac{dY}{dt} &= \beta XY - (\alpha + \nu)Y \\ \frac{dZ}{dt} &= \nu Y\end{aligned}\quad (1)$$

where  $X$  denotes the number of susceptible hosts,  $Y$  the number of infecteds, and  $Z$  the number of recovered and immune hosts. The model assumes that  $N$  hosts are initially born into a cohort, of which a fraction  $f$  are born infected, and that the dynamics within a cohort reach their equilibrium before the individuals within the cohort reproduce. In other words, the model assumes that the epidemic—given that the cohort size exceeds the threshold density of the parasite—sweeps through a generation and reaches its final state where all individuals are

either susceptible or immune. At equilibrium the densities of each category can be calculated as

$$\begin{aligned}X_\infty &= N(1 - I) \\ Y_\infty &= 0 \\ Z_\infty &= N \frac{\nu}{\alpha + \nu} I\end{aligned}\quad (2)$$

where  $I$ , the proportion of individuals infected, is given by

$$I = 1 - (1 - f)e^{-RI}\quad (3)$$

and  $R$ , the basic reproductive number of the parasite within the cohort, is given by

$$R = \frac{\beta N}{\alpha + \nu}\quad (4)$$

In the next generation the number of offspring born to susceptible and recovered individuals will be

$$N' = \lambda N(1 - sI)\quad (5)$$

where  $\lambda$  is the reproductive rate of susceptibles and

$$s = \frac{\alpha}{\alpha + \nu}$$

is the disease-induced mortality.

The dynamics resulting from these equations were investigated by May (1985) under the assumption that all infected individuals die ( $s = 1$ ). In this case, the dynamics are chaotic at any growth rate  $\lambda$  [Fig. 1(a)]. May also noted that, if a few individuals survive their infection, the dynamics can be stabilized, and he calculated the parasite-induced mortality leading to stable dynamics. The dynamics for values of virulence lying between this limit and 100% mortality were not investigated. If, for example, disease-induced mortality is decreased to allow one out of 1000 infected individuals to survive their infection, i.e.  $s = 0.999$ , the dynamics are reduced to a two-cycle for a large range of growth rates [Fig. 1(b)]. If mortality is decreased further to  $s = 0.99$ , the dynamics remain chaotic only for small growth rates, are reduced to two- and 2<sup>n</sup>-cycles at higher growth rates, and finally become stable at very rapid growth [Fig. 1(c)]. If  $s$  is reduced to 0.95, the dynamics have a two-cycle at intermediate growth rates and are

otherwise stable [Fig. 1(d)]. As shown by May, when

$$\lambda > \frac{1}{1-s}$$

[In Fig. 1(d):  $\lambda > 20$ ] the host population can no longer be controlled by the parasite, but grows exponentially at a rate less than the intrinsic growth rate  $\lambda$ .

TRANSMISSION AMONG GENERATIONS

The model described assumes that infected individuals die out within each generation. Therefore, infection among generations requires repeated inoculation from an external source. This external inoculation is emphasised in the simulations described here (Fig. 1) and in May's paper by the choice of the parameter  $f \equiv 0$ , i.e. by the assumption that there is no

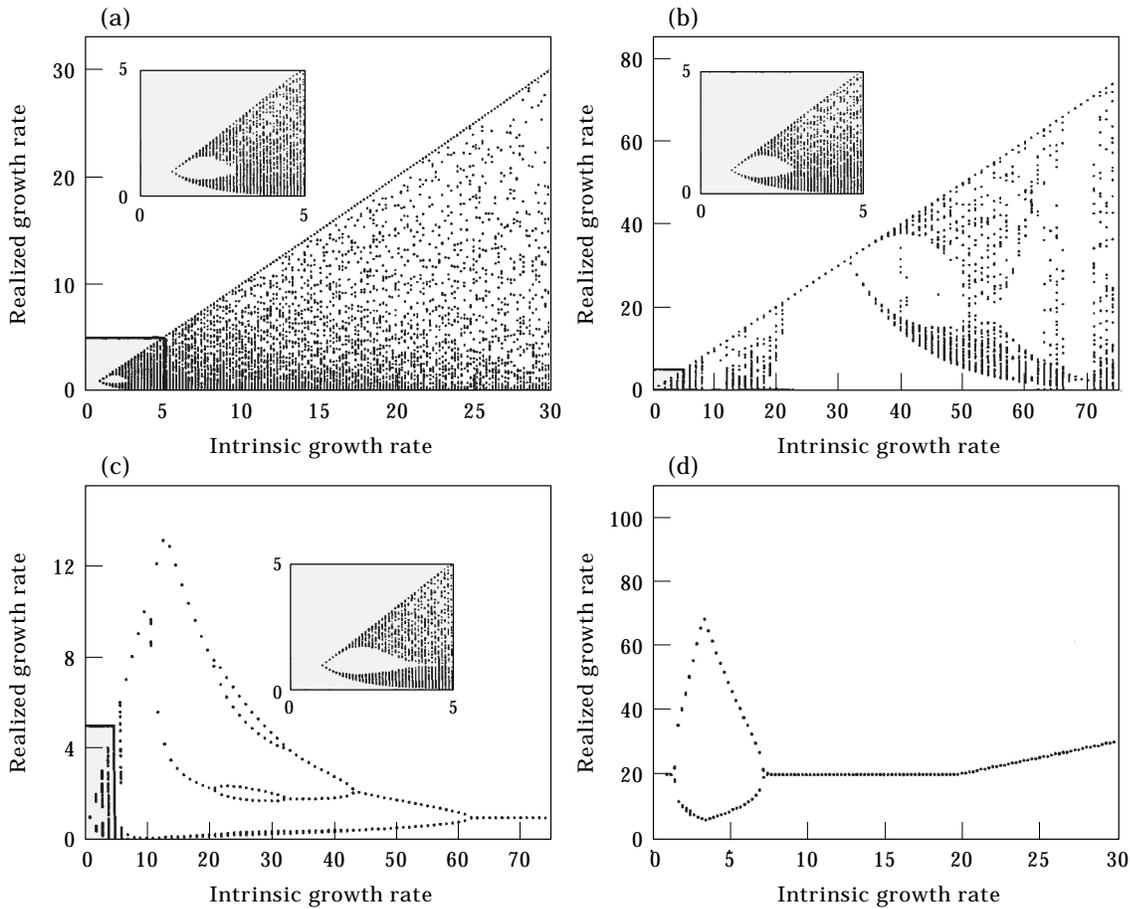


FIG. 1. Phase-plots for the population dynamics with constant transmission from one generation to the next. The phase-plots show the realized growth rates,  $\lambda(1 - sI)$  [eqn (5)], as a function of the intrinsic growth rate,  $\lambda$ . The realized growth rates are generated by iterating eqns (2)–(5) for 500 generations after an initial of 250 generations to eliminate the edge effects. In each panel, the transmission rate  $\beta$  and the recovery rate are given implicitly by the threshold density

$$N_T = \frac{\alpha + v}{\beta} = 100$$

and the disease-induced mortality

$$s = \frac{\alpha}{\alpha + v}.$$

The proportion,  $f$ , of initially infected individuals is assumed to be 0. The disease-induced mortalities are (a)  $s = 1$ , (b)  $s = 0.999$ , (c)  $s = 0.99$ , and (d)  $s = 0.95$ . In panels (a)–(c), the insets show a reduced range of growth rates to emphasize the details.

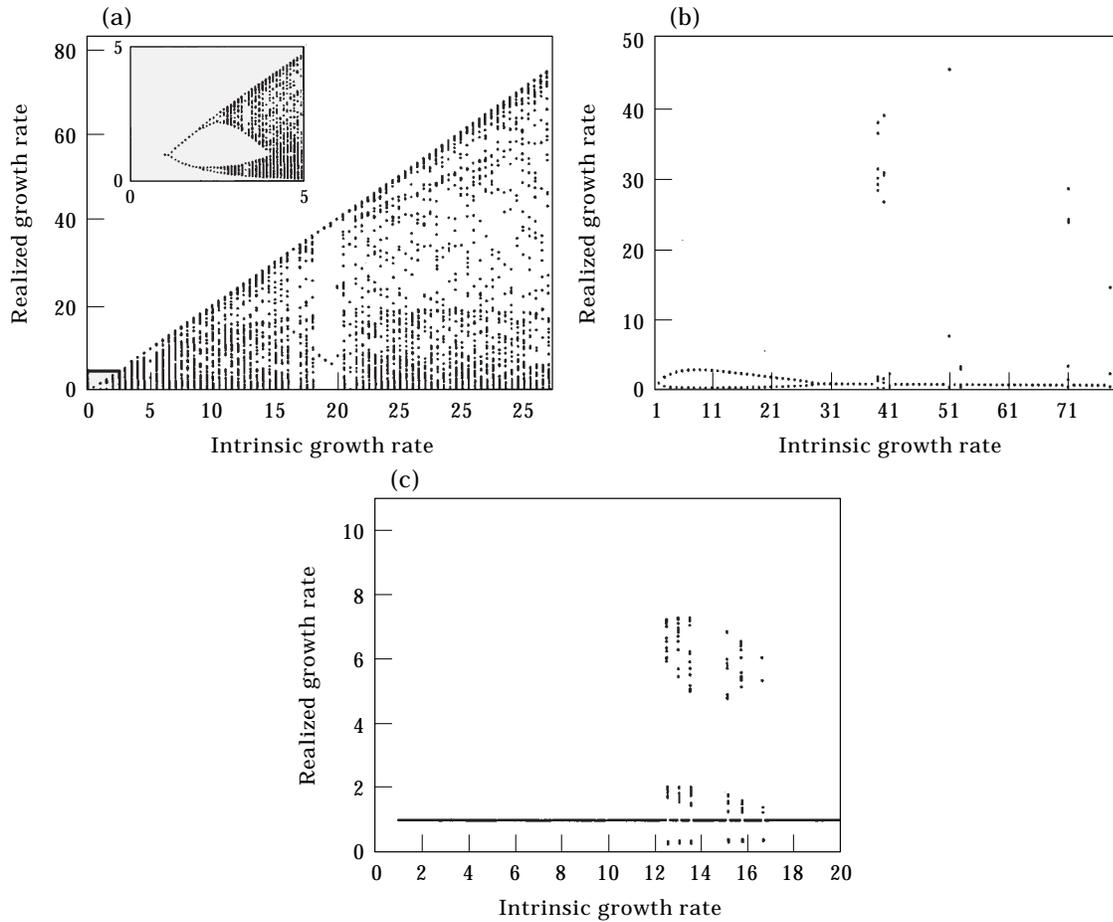


FIG. 2. Phase-plots for the population dynamics with vertical transmission from one generation to the next [eqns (2)–(6)]. Vertical transmission is achieved by assuming that the individuals surviving the infection pass the parasite on to the next generation via infected offspring. Parameters are as given in Fig. 1, except for the disease-induced mortalities, which are (a)  $s = 0.999$ , (b)  $s = 0.99$ , and (c)  $s = 0.98$ .

direct transmission from one generation to the next. The simulations thus implicitly assume either that parasites are slowly released from a reservoir or that the host and parasite populations are structured in a way that allows an influx of parasites into the system.

Here we model two ways in which a parasite can be transmitted to a future generation within the same population: with vertical transmission from infected mothers to their offspring and with transmission with long-lasting spores.

(i) *Vertical transmission*

We assume that the individuals that have recovered from infection, while having cleared the parasites capable of horizontal transmission within a cohort, remain infected with a stage of the parasite that can be transmitted to their

offspring. Vertical infection thus occurs through recovered individuals. With the additional assumption that recovered hosts are as fecund as susceptible ones (i.e. that there is no cost of infection in terms of fertility), the proportion,  $f$ , of offspring that are infected is calculated as

$$f = \frac{Z_\infty}{X_\infty + Z_\infty} \tag{6}$$

Parasite transmission within a cohort is described by eqns (1)–(4), and the population dynamics of the host are described by eqn (5).

Inserting eqn (6) into eqn (3) leads to the dynamics shown in Fig. 2. When parasites are invariably lethal, there is obviously no vertical transmission from recovered individuals to their offspring, so that the parasite goes extinct within a single generation. At slightly lower virulence

( $s = 0.999$ ), the dynamics are chaotic at almost all growth rates [Fig. 2(a)]. When the parasite-induced mortality decreases to 99%, the chaos is reduced to a two-cycle at intermediate growth rates and to stability at very low and at high growth rates [Fig. 2(b)], and when the parasite-induced mortality decreases to 98%, the dynamics become stable for almost all growth rates [Fig. 2(c)]. At both lower levels of virulence, the dynamics are chaotic at a few individual growth rates, despite the overall pattern of stability. Thus, compared with May's original equations, vertical transmission tends to stabilize the dynamics at all but very high levels of virulence.

(ii) *Transmission with long-lasting spores*

To model transmission with long-lasting spores, we assume that they are harbored in dead infected individuals and are transmitted by contact between dead individuals and uninfected ones. We further assume that these parasites are as infective to the host as parasites transmitted horizontally within a cohort, and that they are lost due to mortality (or that they lose their infectivity) at a constant rate  $\mu_s$ . With these assumptions, the dynamics within a cohort [eqns (1)] can be rewritten as

$$\begin{aligned} \frac{dX}{dt} &= -\beta X(Y + S_0 e^{-\mu_s t}) \\ \frac{dY}{dt} &= \beta X(Y + S_0 e^{-\mu_s t}) \\ \frac{dZ}{dt} &= \nu Y \end{aligned} \tag{7}$$

where  $S_0$  is the initial number of dead individuals harboring long-lasting spores in the cohort. This can be written as the number of individuals,  $\tilde{Y}$ , that died during the course of the epidemic within the previous generation:

$$S_0 = \tilde{Y} = N - X_\infty - Z_\infty = N \frac{\alpha}{\alpha + \nu} I \tag{8}$$

The equilibrium of these equations is

$$I = 1 - (1 - f)e^{-\beta \tilde{S} e^{-Rt}} \tag{9}$$

where

$$\tilde{S} = \frac{S_0}{\mu_s}$$

is the integral of the number of long-lasting spores throughout the duration of the cohort.

These equations lead to the dynamics shown in Fig. 3. At  $s = 1$ , the dynamics are chaotic at all growth rates but a restricted range of intermediate values [Fig. 3(a)]. At  $s = 0.999$  the dynamics are reduced to two- and  $2^n$ -cycles over a large range of growth rates, but remain chaotic at very low or very high growth rates. In contrast to May's original equations [Fig. 1(b)] the maximal realized growth rate never reaches the intrinsic growth rate. At  $s = 0.99$  [Fig. 3(c)], the dynamics are similar to May's equations [Fig. 1(c)]. At  $s = 0.95$  [Fig. 3(d)] the dynamics are stable at high growth rates as in May's equations [Fig. 1(d)], but at intermediate growth rates the two-cycle of May's equations is changed to chaos. The temporal pattern of the dynamics is considerably different from the chaos observed with May's equations (Fig. 4). While May's equations yield dynamics that most often alternate between a high and a low density [Fig. 4(a)], transmission with long-lasting spores yields dynamics that behave more like a periodical cycle with a variable amplitude and with most of the period spent at a very low density [Fig. 4(b)].

**Evolution of Virulence**

WITHIN COHORT

Within a cohort, selection pressure will change during the course of the epidemic, and a general term describing the evolutionary dynamics of virulence within a cohort is difficult to find. However, remember that the model assumes an epidemic sweeping through the cohort and reaching its equilibrium during each generation. Thus, the evolutionary pressure will eventually be governed by the equilibrium values of the epidemic, in particular the equilibrium number of susceptibles. We can therefore follow the methods described by van Baalen & Sabelis (1995) to find the evolutionarily stable virulence reached by the end of the epidemic; this ESS is given by the virulence that maximises the reproductive number  $R$  given by eqn (4), where  $N$  is replaced by the number of susceptibles remaining in the cohort after the epidemic. The

evolutionary outcome is determined by the relationship between the rate of transmission,  $\beta$ , and virulence,  $\alpha$ . Frank (1996) gives a detailed review about possible associations between these two parameters, and of the biological factors that could affect them. As an example, let transmission be related to virulence with the equation  $\beta = k\alpha^n$  (we later refer to the parameter  $n$  as the strength of the association between transmission and virulence). If  $n < 1$ , i.e. if transmission increases less than linearly with virulence, the reproductive number  $R$  is maximized, if virulence reaches the level

$$\alpha = \frac{n}{1 - n}v$$

(or rewritten as  $s = n$ ); if transmission increases at least linearly with virulence, i.e.  $n \geq 1$ , ever-increasing virulence ( $s = 1$ ) is favored.

VERTICAL TRANSMISSION

If a parasite is transmitted vertically, a measure of a clone's success among generations is the number of individuals recovered from infection (and thus able to have infected offspring). As given by eqn (2), this number is

$$w_i = N \frac{v}{\alpha + v} I \tag{10}$$

Maximizing this requires large transmission  $\beta$  (so that many individuals become infected) and small virulence  $\alpha$  (so that many recover). When

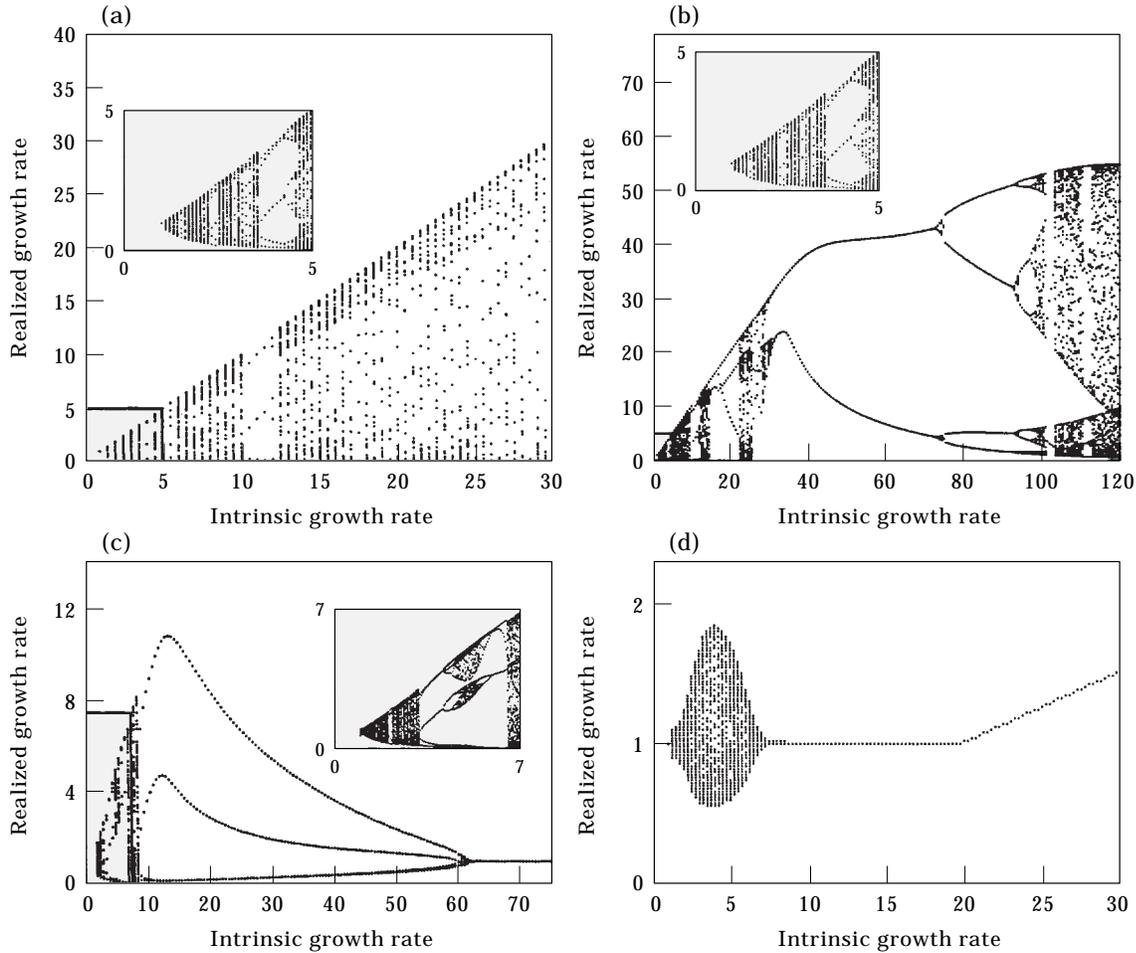


FIG. 3. Phase-plots for the population dynamics with transmission from one generation to the next via long-lasting spores [eqns (7)–(9)]. This transmission is generated by assuming that the individuals killed by the parasite produce spores that infect susceptible new-borns at the beginning of the next generation. Parameters are as given in Fig. 1, except for the disease-induced mortalities, which are (a)  $s = 1$ , (b)  $s = 0.999$ , (c)  $s = 0.99$ , and (d)  $s = 0.95$ .

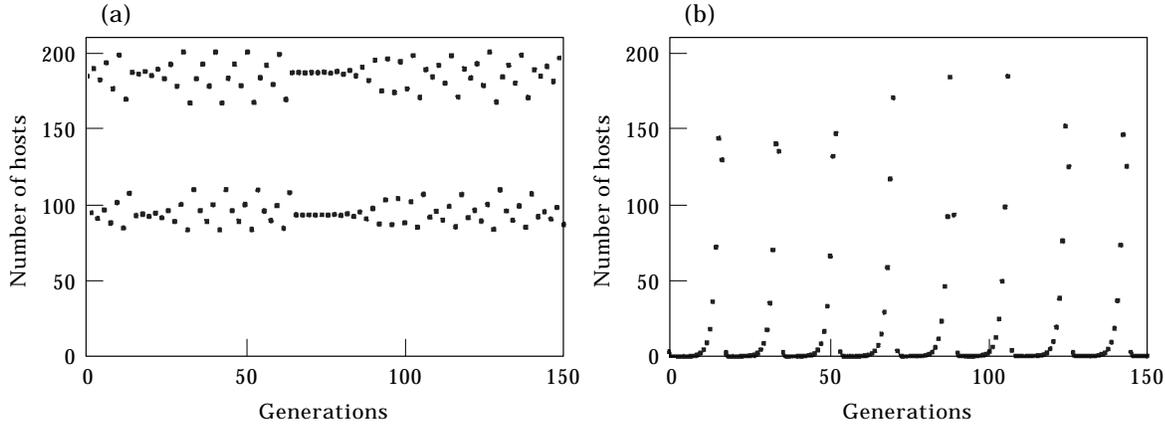


FIG. 4. Comparison of temporal pattern of the dynamics for systems with constant transmission among generations and for systems with transmission via long-lasting spores. In each panel disease-induced mortality is  $s = 0.995$  and the threshold density is

$$N_T = \frac{\alpha + v}{\beta} = 100.$$

(a) Constant transmission, (b) long-lasting spores.

the two parameters are associated, this number remains maximal at zero virulence. (Although the proportion of individuals infected,  $I$ , is maximal at intermediate virulence, the product

$$\frac{v}{\alpha + v} I$$

decreases with increasing virulence, and the product is highest at zero virulence.) Therefore, even when selection favors increasing virulence within a cohort (by maximizing  $R$ ), vertical transmission among cohorts constrains the parasite to be benign. We confirmed this result with numerical simulations of eqns (1)–(6), slightly changed to allow for competition among several parasite genotypes.

However, eqns (1) and thus this result hold only when there is no super-infection, i.e. when infected individuals cannot be super-infected by a different parasite. To find the optimal virulence in a situation allowing super-infection, we changed the equations governing the dynamics within a cohort to allow competition of two parasites for their hosts. With the indices 1 denoting parasite type 1, 2 denoting type 2 and 12 denoting super-infection, the equations can be

written as

$$\begin{aligned} \frac{dX}{dt} &= -X[\beta_1(Y_1 + Y_{12}) + \beta_2(Y_2 + Y_{12})] \\ \frac{dY_1}{dt} &= \beta_1 X(Y_1 + Y_{12}) - \beta_2 Y_1(Y_2 + Y_{12}) - (\alpha_1 + v)Y_1 \\ \frac{dZ_1}{dt} &= vY_1 \\ \frac{dY_2}{dt} &= \beta_2 X(Y_2 + Y_{12}) - \beta_1 Y_2(Y_1 + Y_{12}) - (\alpha_2 + v)Y_2 \\ \frac{dZ_2}{dt} &= vY_2 \\ \frac{dY_{12}}{dt} &= \beta_1 Y_2(Y_1 + Y_{12}) + \beta_2 Y_1(Y_2 + Y_{12}) - (\alpha_{12} + v)Y_{12} \\ \frac{dZ_{12}}{dt} &= vY_{12} \end{aligned} \tag{11}$$

These equations assume that the recovery rate,  $v$ , is the same for both parasites and that the rate parameter of transmission,  $\beta_i$ , depends only on the type of the parasite being transmitted, but not on whether the host becoming infected

already harbors the other parasite type (i.e. the infectivity of a given parasite does not depend on the other strains present). Super-infected individuals pass on their parasites to susceptibles and infecteds individually (i.e. a susceptible individual cannot develop a super-infection from a single contact with a super-infected individual), and they recover by losing both parasites simultaneously. For the following results we assumed that the parasites' virulence in the super-infected hosts,  $\alpha_{12}$ , is the sum of the two virulences. These assumptions are, of course, arbitrary, and determine the quantitative details of our results; however changing the assumptions, for example, by letting  $\alpha_{12}$  be any value larger than the lower value of the two parasites did not change the conclusions qualitatively.

As we could not find the equilibrium of these equations analytically, we integrated them numerically until the density of both types of infected individuals was less than  $10^{-4}$ , i.e. until

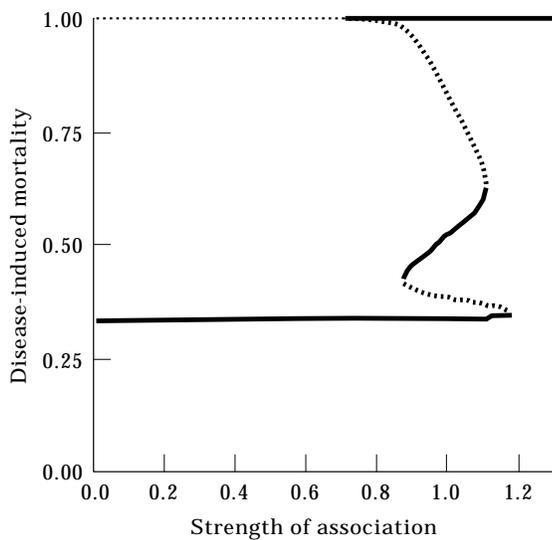


FIG. 5. Equilibrium levels of disease-induced mortality,

$$s = \frac{\alpha}{\alpha + v},$$

for the system with vertical transmission among generations. The  $x$ -axis shows the exponent,  $n$ , of the association between transmission and virulence; the  $y$ -axis shows the level of virulence that leads to a local maximum (—) or local minimum fitness (.....). Where there is more than one equilibrium value, the highest level is globally maximal. The parameters used to simulate eqns (11) are  $\lambda = 2$ ,  $\beta = 0.01$ ,  $\alpha^n$ ,  $v = 0.1$ .

the dynamics within the cohort were close to their equilibrium. We then used the resulting densities of susceptible and recovered individuals to calculate the host's reproduction and the transmission of each parasite type to the next generation. We repeated this procedure for as many generations as required to recognize which parasite was favored by selection. We found the evolutionary optimum in two ways. First, after the result of competition between two parasites was determined, we replaced the inferior competitor with a parasite whose virulence was randomly chosen from a Gaussian distribution with the superior competitor's virulence as the mean and 10% of this value as the standard deviation. We repeated this process until the virulence reached a stable value, i.e. a parasite could not be replaced by one with slightly lower or higher virulence. Second, we approximated the slope of the fitness function with respect to  $\alpha$  by letting two parasites with slightly different virulences compete and varied  $\alpha$  until the slope was approximately 0. With this procedure we were able to find the virulence at local and global maxima and minima of fitness.

When virulence and transmission are not associated, the pattern of evolution of simple infections is the same as in the case with no super-infection: benign parasites evolve. However, when transmission is associated to virulence with the relationship  $\beta = b\alpha^n$ , where  $n > 0$ , super-infection is associated with increased virulence (Fig. 5), as is generally expected (Bremermann & Pickering, 1983). However, the pattern is much more complex than that predicted by the processes within a population, with up to three local maxima. The fitness maximum with the lowest value of the virulence, which appears when  $n$  is below a threshold value (in the simulations shown in Fig 5:  $n < 1.177$ ), is just above the lowest level of virulence that can control the host's density. The virulence at this evolutionary steady state remains almost constant as  $n$  varies. A second fitness maximum, i.e. a second evolutionary steady state for the virulence, appears at intermediate values of  $n$  (in Fig. 5:  $0.85 < n < 1.177$ ). While both fitness maxima are locally stable for the evolutionary dynamics of virulence, parasites with a virulence

corresponding to the higher maximum outcompete those at the lower local maximum. The third fitness maximum, which appears for high  $n$  (in Fig. 5:  $n > 0.7$ ), is at infinite virulence. Thus, the parasites will evolve themselves to extinction if the parasites enter the region of attraction of this third evolutionary equilibrium. Moreover, this equilibrium is the global fitness maximum. As its region of attraction is very small for low  $n$ , while the regions of attraction for intermediate and infinite virulence increase with increasing  $n$ , extinction as a consequence of the evolutionary dynamics of virulence becomes more likely as  $n$  increases. When  $n$  passes the threshold (in Fig. 5:  $n > 1.177$ ), evolution of infinite virulence is the only possible outcome.

#### HORIZONTAL TRANSMISSION

As preliminary investigations showed that the evolutionary dynamics can become complex and can allow more than one parasite clone to exist, we modified eqns (7) to allow several parasites to compete. Thus the equations of the infection dynamics within a cohort become

$$\begin{aligned} \frac{dX}{dt} &= -X \sum_i \beta_i (Y_i + S_{i,0} e^{-\mu}) \\ \frac{dY_i}{dt} &= \beta_i (Y_i + S_{i,0} e^{-\mu}) X - (\alpha_i + \nu) Y_i \\ \frac{dZ_i}{dt} &= \nu Y_i \end{aligned} \quad (12)$$

where the subscript  $i$  denotes the parasite genotype and  $S_{i,0}$  is calculated as the integral of  $\alpha_i Y_i$  in the outcome of the previous generation. The equations assume no super-infection. As super-infection has almost no effect on the main qualitative predictions of the simulations, we do not present the corresponding equations or the results.

To determine the evolutionary dynamics, we integrated these equations for 12 parasite genotypes (a compromise between sufficient genotypes and computer time and space) up to their equilibrium and thus determined the outcome of competition among parasites within each cohort. Parasites with less than 1%

frequency were replaced by a novel genotype. The virulence of this parasite was a random number selected from a Gaussian distribution with the mean given by the virulence of a parasite selected randomly (but weighted by the phenotype frequencies) from the distribution of parasites in the cohort and with a standard deviation of 10% of the mean. We repeated this process over as many generations as was necessary to determine the evolutionary outcome.

Because the mode of transmission from one cohort to the next requires killing of infected individuals, virulence never decreases to 0. Even when there is no association between virulence and potential of transmission within a cohort, virulence can evolve to a level where about 50% of the infected individuals are killed. The evolutionary dynamics can be divided into four categories, depending on the value of  $n$  (Fig. 6). At low values of  $n$  virulence evolves to a stable level. This level increases as  $n$  increases, until virulence reaches a level that codes for chaotic dynamics. The complex dynamics do not allow a stable equilibrium, but lead to a branching of virulence [Fig. 7(a)], so that one sub-population keeps on increasing virulence while the other one evolves towards lower virulence. The divergence increases until the highly virulent parasites deplete the host cohort before the parasites with low virulence and low transmission can infect enough hosts to ensure their transmission success. The lower virulence then becomes unstable and the corresponding sub-population disappears. The higher virulence then returns towards the branching point, where the divergence process is repeated. As  $n$  increases more, the amount of divergence between the sub-populations decreases [Fig. 7(c)] until an evolutionarily stable equilibrium containing several levels of virulence is reached [Fig. 7(e)]. At higher values of  $n$  the stability is again broken. The parasite can maintain an apparently stable state of virulence for a long period, whereupon it switches to a different quasi-stable state during a burst of high or low virulence within a very short time period [Fig. 7(g)]. Finally, as  $n$  increases to even higher values, the virulence during these bursts can reach such high levels that the host and parasite go extinct [Fig. 7(i)].

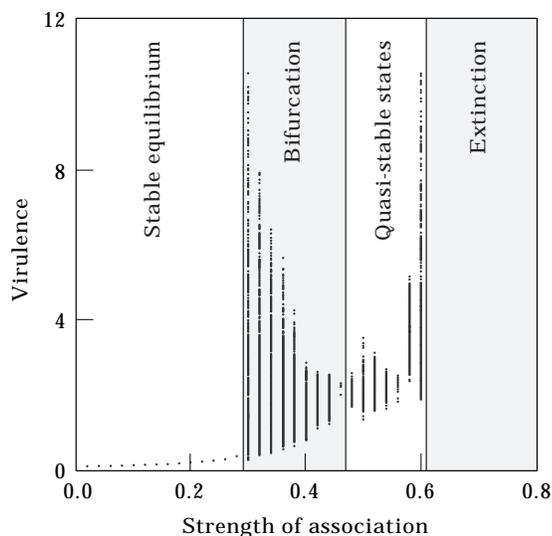


FIG. 6. Levels of virulence for the system where transmission among generations relies on long-lasting spores. The  $x$ -axis shows the exponent,  $n$ , of the association between transmission and virulence; the  $y$ -axis shows the values of virulence that appear within 100 000 generations of simulating eqns (12) with 12 genotypes. The system was first allowed to evolve for 50 000 generations to eliminate edge-effects. Depending on this parameter, the system evolves to a stable value of virulence [see also Fig. 7(e)], to a branching pattern [Fig. 7(a,c)], to punctuated equilibria [Fig. 7(g)] or to extinction [Fig. 7(i)]. The parameters used to simulate eqns (12) are  $\lambda = 2$ ,  $\beta = 0.01\alpha^n$ ,  $\nu = 0.1$ .

### Discussion

The results of the models can be looked at from three viewpoints, (1) the stability of the population dynamics, (2) the evolution of virulence, and (3) the evolution of stable population dynamics.

*Population dynamics:* the model described by May (1985) leads to chaos at any growth rate, if all infected individuals die. If, however, only few infected individuals are allowed to survive, the dynamics can be changed dramatically. If, for example one out of 1000 infected individuals survives their infection, the dynamics are reduced to a two-cycle for a large range of growth rates. If survival is increased further to 1% of the infected individuals, the dynamics remain chaotic only for small growth rates, are reduced to two- and  $2^n$ -cycles at higher growth rates, and finally become stable at very rapid growth. If survival is increased to 5% of the infected individuals, the dynamics are never chaotic, have a two-cycle at intermediate growth rates and are otherwise stable.

The extensions to the model proposed here—extensions involving transmission of the parasite among generations—change the quality of the dynamics. When transmission among generations is vertical, dynamics are generally stabilized. However, when virulence is extremely high, the dynamics are chaotic over a wider range of growth rates than in May's model. In further contrast to May's model, the dynamics at low to intermediate growth rates follow a more "normal" bifurcation pattern: as growth rate increases, the dynamics move from stability through a two-cycle, a four-cycle, etc. to chaos.

When parasites are transmitted among generations with long-lived spores, the dynamics are chaotic under similar conditions as under May's model. However, the temporal pattern is changed qualitatively. While May's equations yield dynamics that tend to alternate between a high and a low density, cross-generation transmission with long-lasting spores yields dynamics that behave more like a periodical cycle with a variable amplitude. During most of this cycle, the parasite has no effect on the hosts and the host grows exponentially. When the parasite can spread, it kills most of the hosts, so that the population crashes to a very low density within very few generations.

That small changes in the description of the dynamics lead to qualitative changes in the dynamics is not new. Doebeli & Koella (1994) and Ruxton (1995), for example, introduced sexual reproduction—and thus population genetics—into population dynamics models that often lead to chaos (one of the models discussed by Doebeli & Koella was May's host-parasite model) and found that the complexity of the dynamics was often reduced from chaos to stability or periodic cycles. Similarly, Allen *et al.* (1993) and Ruxton (1994) showed that population structure with small rates of migration among sub-populations could increase the dynamic stability. In other models of host-parasite interactions in seasonal environments the dynamic behavior ranged from stable point equilibria to chaos, depending on the transmission rate among seasons (Briggs & Godfray, 1996; Hochberg *et al.*, 1990).

*Evolution of virulence:* epidemiological models have led to three predictions about the evolution

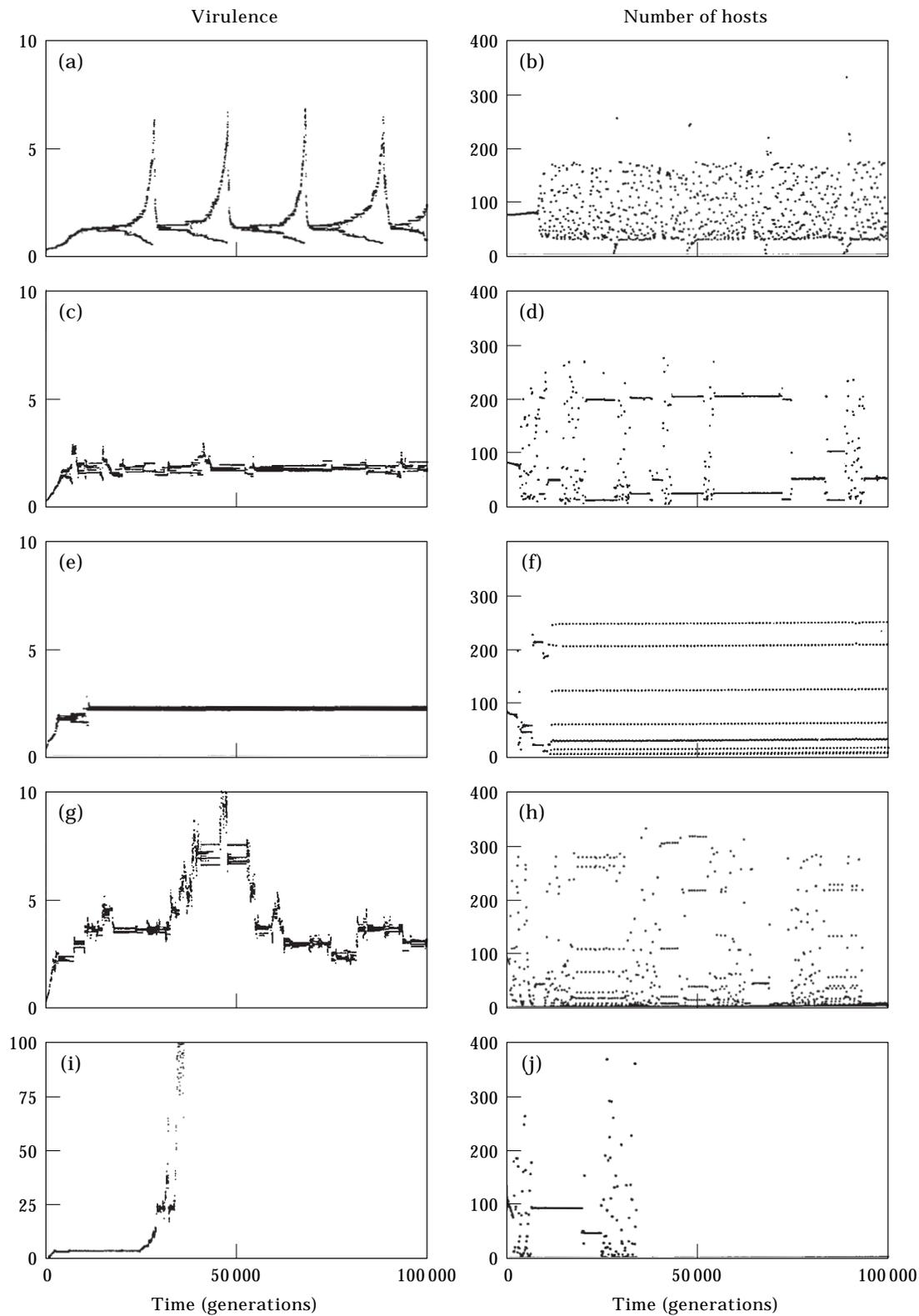


FIG. 7. Evolutionary dynamics of virulence (left-hand side) and density (right-hand side) in the system where transmission among generations relies on long-lasting spores. The parameters used to simulate eqns (12) are  $\lambda = 2$ ,  $\beta = 0.01\alpha^n$ ,  $v = 0.1$ . (a), (b) branching pattern with  $n = 0.34$ ; (c), (d) branching pattern with  $n = 0.44$ ; (e), (f) stable equilibrium with  $n = 0.46$ ; (g), (h) punctuated equilibria with  $n = 0.6$ ; (i), (j) extinction with  $n = 0.64$ . Note the different scale in (i).

of virulence to dominate the current literature: that the optimal level of virulence will increase as the association between transmission potential and virulence becomes stronger (Anderson & May, 1982; Ewald, 1994), that super-infection can favor higher virulence (Bremermann & Pickering, 1983; Frank, 1992; Nowak & May, 1994) and that vertical transmission will favor low virulence (Agnew & Koella, 1997; Bull *et al.*, 1991; Herre, 1993), unless an association between the potential of horizontal and vertical transmission maintains a high level of virulence (Lipsitch *et al.*, 1995). These predictions appear to hold true in systems where the host reproduces continuously, the systems for which most theories have been established (Bull *et al.*, 1991; Read & Schrag, 1991). However, the results shown here suggest that they may break down in other systems [but see Herre (1993) for a test in discrete generations].

Consider first the case where the parasite transmits vertically from one cohort to the next. When there is no association between virulence and transmissibility within a cohort, our model conforms with previous predictions: the parasite should evolve to avirulence. However, when super-infection is possible and when there is an association between the two parameters, the results become more complex. There is an evolutionary steady state at the level of virulence that just maintains the population density. This optimum is almost independent of the strength of the association (i.e. the exponent in the relationship  $\beta = b\alpha^n$ ). As the strength increases, however, a second fitness optimum with intermediate virulence and a third optimum at infinite virulence appear. As the strength of the association increases more, the region of attraction of the intermediate virulence decreases until, when the association is strong enough, only the one optimum at infinite virulence remains. Thus, under many conditions the parasite can evolve to low, intermediate or infinite virulence. Which level will be reached depends on the virulence the system has started out with. Furthermore, as virulence evolves towards infinity, the parasite will evolve itself and the host to extinction. Thus, with only slightly different parameters, the system moves from a relatively low level of virulence to self-extinction,

reminiscent to the situation in asymmetric competition (Matsuda & Abrams, 1994). These patterns can be contrasted with those found by Lipsitch *et al.* (1995), investigating the evolution of virulence for parasites that transmit vertically among continuous generations of hosts. In their model, high (and stable) virulence of a parasite with vertical transmission was found only with an explicit association between the potential of horizontal and vertical transmission.

When long-lasting spores transmit to the next generation, virulence is maintained at an intermediate level, even when there is no association between virulence and transmission within a cohort. The reason for this is clear: if virulence is low, the number of infecteds is high, but only very few of these die to transmit the parasite to the next generation. On the other hand, if virulence is high, individuals die before they can transmit the parasite, so that the number of infecteds and thus transmission to the next generation is low. This explanation makes clear that, though there is no association between virulence and transmission within a cohort, the evolution is driven by an association between virulence and transmission at a higher level: from one generation to the next. Rather than being intrinsic to the parasite's life cycle, the association is imposed on the system through particularities of the epidemiology.

If virulence is associated with transmission within a cohort, virulence can evolve to a level where the population dynamics become complicated, which in turn leads to complicated evolutionary dynamics for the virulence. This increases the dimensionality of the system, allowing several parasite types to coexist. Depending on the strength of the association between transmission and virulence, the evolutionary dynamics of virulence can then have branching patterns where two sub-populations evolve diverging virulence until one of the sub-populations goes extinct, it can exhibit evolutionary quasi-stability reminiscent of punctuated equilibria where the virulence is maintained at the same level for many generations before it switches to a different level within only a few generations, or it can be unstable such that high levels of virulence evolve which lead to the extinction of host and parasite. Such

complicated evolutionary dynamics are a consequence of complex ecological dynamics, which are on the one hand determined by phenotypic properties of the parasites, and on the other hand themselves determine the selective pressure on virulence. The results of Fig. 7 show that the interaction between ecological and evolutionary dynamics can lead to interesting and unexpected evolutionary scenarios, in which sudden changes and repeating patterns occur without any change in the external environment. Complex evolutionary dynamics in a host–parasite system have also been observed by Nowak & May (1994), modelling the evolution of virulence in a system where three parasite genotypes can superinfect their hosts. The results contribute to the growing body of work emphasizing the general importance of such eco-evolutionary scenarios, which tend to occur in systems in which the ecological dynamics are influenced by a trait whose evolution is in turn determined by the ecological dynamics (e.g. Doebeli & Ruxton, 1997; Geritz *et al.*, 1998; Hochberg & Holt, 1995; Holt & McPeck, 1996).

In summary, the conclusions from continuous models about the evolution of virulence can be misleading for systems where the hosts have discrete generations. In particular, the prediction that virulence should evolve to a level determined by the association between virulence and transmission potential no longer holds. This difference arises, because in the presented models, in contrast to continuous models, selection operates at two levels: within and among cohorts. Furthermore, the results show that details of the parasite's life cycle are crucial in determining its virulence, as also emphasized by Ebert & Herre (1996).

*Evolution and population dynamics:* allowing the virulence to evolve often leads to values of virulence that give rise to stable population dynamics. This reflects the pattern seen in other studies: evolution of the parameters coding for population dynamics in a competition system (Doebeli & Koella, 1995) and evolution of the degree of density-dependence in an age-structured model of population growth (Ebenman *et al.*, 1996) generally lead to stability. Whether evolution towards stability is the usual pattern remains to be seen; at least in one model

evolution moves towards chaos (Ferrière & Gatto, 1993).

When virulence evolves to a level that gives rise to chaos, two general patterns are possible. First, if the association between virulence and transmission within a cohort is strong enough, virulence will evolve to such high levels that the host and parasite go extinct. Therefore, group selection will tend to favor stability. Second, the chaotic population dynamics can give rise to chaotic evolutionary dynamics (see above). This, however, is found only for a restricted parameter space. Furthermore, when the association between virulence and transmission is allowed to evolve, the system evolves to stability (simulations not shown). Thus, in general, the trend towards stability dominates.

The evolution towards stability will have implications for other evolutionary trends. For example it is often claimed that sexual reproduction is maintained because of the coevolutionary dynamics in host–parasite systems. The reason for the maintenance of sex lies in the cycles intrinsic to some host–parasite dynamics when virulence is high (e.g. Bell & Maynard Smith, 1987; Hamilton, 1980). Thus, if virulence generally evolves to values yielding stable dynamics, it becomes much less likely that the coevolutionary dynamics of the host and parasite are responsible for the maintenance of sex (see also May & Anderson, 1983b). Note that this does not imply that parasites have no influence on their hosts' sexuality. In fact, Koella (1993), discussing patterns of recombination among 200 plant species, suggested and Keeling & Rand (1995) showed formally that parasites could maintain sex in their hosts in a spatially heterogeneous system without the need of coevolutionary cycles.

In conclusion, moving the host's population from continuous reproduction to reproduction in discrete generations leads to qualitative changes not only in the system's population dynamics (May, 1985), but also in the evolutionary dynamics of virulence. Details of the parasite's epidemiology influence qualitatively the evolutionary pressure on virulence, so that predictions about virulence cannot be made without a detailed understanding of the parasite's life cycle (Ebert & Herre, 1996). These

differences in virulence feed back onto the population dynamics: while some life cycles lead to chaos, sometimes associated with extinction of the system, most life cycles favor stable population dynamics.

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