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EVOLUTION OF VIRULENCE IN A HETEROGENEOUS HOST POPULATION

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Abstract.—There is a large body of theoretical studies that investigate factors that affect the evolution of virulence, that is parasite-induced host mortality. In these studies the host population is assumed to be genetically homogeneous. However, many parasites have a broad range of host types they infect, and trade-offs between the parasite virulence in different host types may exist. The aim of this paper is to study the effect of host heterogeneity on the evolution of parasite virulence. By analyzing a simple model that describes the replication of different parasite strains in a population of two different host types, we determine the optimal level of virulence in both host types and find the conditions under which strains that specialize in one host type dominate the parasite population. Furthermore, we show that intrahost evolution of the parasite during an infection may lead to stable polymorphisms and could introduce evolutionary branching in the parasite population.

Key words.—Evolution of virulence, genetic trade-offs, host heterogeneity, host-parasite coevolution, intrahost evolution, serial passage.

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The relationship between a parasite and its host is a story of benefits and harms. The parasite benefits from the host by living in and on it and by using host resources to reproduce. The parasite's benefit gives rise to the host's harm: The life span of the host is usually shortened by infection, and important fitness traits of the host, such as fecundity, are often negatively affected by the parasite (Ewald 1994). However, by reducing the life span or the fitness of its host, the parasite may inflict harm upon itself. The question emerges: What evolutionary forces determine the level of harm inflicted on the host? In this paper, we focus on the evolution of parasite virulence, here defined as parasite-induced host mortality.

If virulence were an independent trait, natural selection should favor parasites with low virulence. A parasite that does not kill its host has more time to exploit it and to be transmitted, thus increasing its own fitness. Therefore, in the long run the parasite should evolve to be avirulent. Nevertheless, there are many examples of intermediately or highly virulent host-parasite systems with a long coevolutionary history (Fenner and Ratcliffe 1965; Herre 1993). To account for virulent host-parasite interactions, trade-offs between virulence and other parasite traits such as infectivity, transmissibility, or reproduction rate were postulated (Anderson and May 1979, 1981, 1982, 1991; May and Anderson 1979, 1983, 1990; Levin and Pimentel 1981; Bremermann and Pickering 1983; Ewald 1983; Knolle 1989; Frank 1992; Antia et al. 1994). Furthermore, it was argued that in systems in which the parasite can super- or coinfect hosts or in which the parasites frequently generate new mutant strains within a host, a parasite strain with high virulence may have a competitive advantage over less virulent strains within the host (Hamilton 1972; Bremermann and Pickering 1983; Knolle 1989; Sasaki and Iwasa 1991). In models that take into consideration this competition between different mutants within a single host in addition to the competition for transmission between hosts, one finds the persistence of parasite mutants that are highly virulent and in some cases too virulent to survive on their own (Bonhoeffer and Nowak 1994; Nowak and May 1994; May and Nowak 1995; van Baalen and Sabelis 1995).

The genetic or phenotypic composition of the host population also influences the dynamics of a host-parasite system (Jaenike 1978, 1996; Hamilton 1980; Lively 1987; Lipsitch et al. 1995; Ebert and Hamilton 1996). Many theoretical studies investigate the interaction of parasites with a heterogeneous host population, concentrating mainly on the stability of such systems (Cramer and May 1972; Murdoch and Oaten 1975; Roughgarden and Feldman 1975; Comins and Hassel 1976; Fujii 1977; Hassel 1979; Dobson 1990; Jones et al. 1994). Frank analyzed the coevolution of polymorphic host-pathogen systems using models in which parasite virulence and host resistance are closely linked (Frank 1991, 1994).

In the present paper, we focus on the evolution of parasite virulence in a genetically heterogeneous host population. We investigate a model that describes many parasite strains in a population of two different hosts. The parasite strains differ with regard to their reproduction rate and their virulences in the two hosts, and we assume trade-offs between the parasite virulences. To our knowledge, there are no studies investigating the evolution of virulence in a genetically heterogeneous host population as a consequence of such trade-offs.

In the following two sections, we introduce our model and give equilibrium solutions. Then we address two main questions: (1) What determines whether generalist or specialist strains evolve? and (2) How does host heterogeneity influence the evolution of parasite virulence? In the last part of the paper, we extend our model to include within-host evolution of the parasite. There are many studies reporting changes in parasite virulence as a consequence of within-host evolution during an infection (Bull 1994; Ewald 1994; Ebert and Hamilton 1996; Lipsitch and Moxon 1997; Ebert 1998, 1999). We incorporate these findings, to study their effect on the

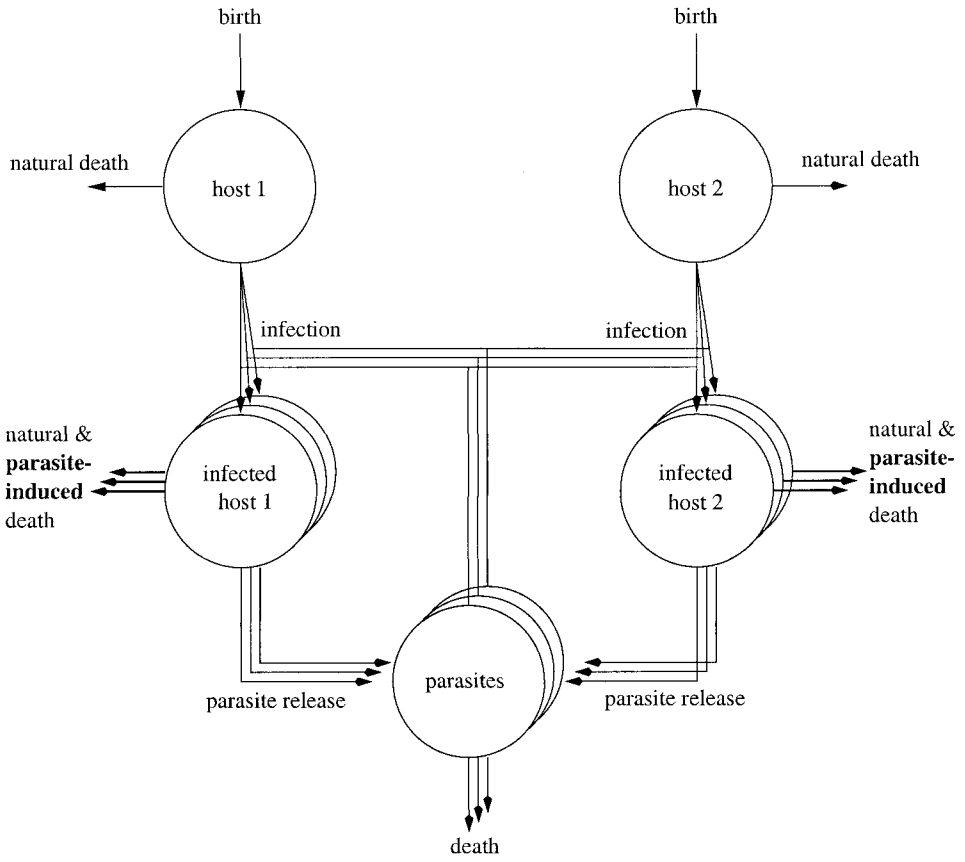

FIG. 1. Diagrammatic representation of the model in equations (1–5). The arrows correspond to processes, which we incorporated into the model. Multiple layers of circles for parasites and infected hosts indicate that there are many parasite strains that can infect the hosts, giving rise to different classes of infected hosts. The parasite-induced death rate, that is the *virulence*, is shown in boldface because it is the focus of the present study.

evolution of parasite virulence in a heterogeneous population. In simulations of the model, we find stable polymorphisms in the parasite population, some of which could introduce evolutionary branching of the parasite population.

MODEL

At first we consider a model where two types of hosts can be infected by n parasite strains. The densities of uninfected hosts of type 1 and type 2 are denoted by x_1 and x_2. The densities of hosts infected by parasite strain i are denoted by y_{1i} and y_{2i}, respectively. The densities of free parasites are described by the variable v_i. Uninfected hosts are produced at constant rates, λ_1 and λ_2 and die at rates dx_1 or dx_2. (In the absence of parasites, the equilibrium ratio of the two host types is given by λ_1/λ_2.) By infection they turn into infected hosts, y_{1i} and y_{2i}, at the rates, $\beta x_1 v_i$ and $\beta x_2 v_i$, respectively. For simplicity we assume equal infection rates, β. We discuss the implications of this assumption further below. The death rates of infected hosts of type 1 and type 2 are given by $(a_{1i} + d)y_{1i}$ and $(a_{2i} + d)y_{2i}$, respectively. Here the parameters, a_{1i} and a_{2i}, represent the virulences, that is the contribution of parasite strain i to the mortality in the respective host type. Furthermore, we assume that hosts, y_{1i} and y_{2i}, which are infected by strain i, release parasites of strain i at rates $c_{1i}y_{1i}$ and $c_{2i}y_{2i}$, and that free parasites die at a rate uv_i. These assumptions lead to the following set of differential equations:

$$\dot{x}_1 = \lambda_1 - dx_1 - \beta x_1 v, \tag{1}$$

$$\dot{x}_2 = \lambda_2 - dx_2 - \beta x_2 v, \tag{2}$$

$$\dot{y}_{1i} = \beta x_1 v_i - (a_{1i} + d)y_{1i}, \tag{3}$$

$$\dot{y}_{2i} = \beta x_2 v_i - (a_{2i} + d)y_{2i}, \quad \text{and} \tag{4}$$

$$\dot{v}_i = c_{1i}y_{1i} + c_{2i}y_{2i} - uv_i. \tag{5}$$

Here $v = \sum_{i=1}^{n} v_i$ denotes the total population size of free parasites. Figure 1 presents our model diagrammatically.

There is good experimental evidence for a positive correlation between the reproduction rate and virulence for many parasites (Muskett et al. 1985; Bull et al. 1991; Bull and Molineux 1992; Ni and Kemp 1992; Ebert and Mangin 1997). Thus, we assume for the following that the reproduction rate of parasites is proportional to their virulences, that is $c_{1i} = p \times a_{1i}$ and $c_{2i} = p \times a_{2i}$, where p is a constant of proportionality.

Another important asumption is a trade-off between the virulences a_{1i} and a_{2i}, which the parasite attains in the different hosts. The higher the virulence of a particular parasite strain is in one host type, the lower it be in the other host. As trade-offs we could, for example, assume $a_{1i} + a_{2i} =$

const or $a_{1i}a_{2i} = const$. As will be shown below the particular form of these trade-offs plays an important role in the evolution of virulence.

This model is designed to study parasite evolution in a genetically heterogeneous host population. We restrict our analysis to two host types only and intentionally exclude the possibility that new host types can invade. In the above model the host types can change in abundance, but none of them can ever become extinct. Furthermore, the model disregards parasite competition within the host as a consequence of super- or coinfection or parasite mutation during the infection of a host. Here we first study the effect of host heterogeneity on parasite virulence in isolation. Later we add further layers of complexity.

Solutions

At equilibrium, the following condition must hold for all parasite strains:

$$v_i^* g_i(v^*) = 0. \tag{6}$$

Here v_i^* denotes the equilibrium abundance of parasite strain i, and v^* denotes the total equilibrium abundance of parasites, $v^* = \Sigma_i v_i^*$. The function $g_i(v^*)$ represents the growth rate of strain i at equilibrium and is given by:

$$g_i(v^*) = u[R_i d/(d + \beta v^*) - 1], \tag{7}$$

where

$$R_i = \frac{\beta}{ud}\left[\frac{\lambda_1 c_{1i}}{(a_{1i} + d)} + \frac{\lambda_2 c_{2i}}{(a_{2i} + d)}\right]. \tag{8}$$

Equation (6) excludes the possibility that two or more parasite strains coexist. At equilibrium, either the abundance of a parasite strain, v_i^*, or its growth rate, $g_i(v^*)$, equals zero. In the generic case, the growth rate cannot be zero for more than one parasite strain. Thus, at equilibrium only one strain will survive; all other strains will become extinct. The outcome of competition is solely determined by R_i and the winning strain is the one with maximal R_i. For future purposes we label this strain with the index k.

R_i has a clear intuitive interpretation. It can be rewritten as

$$R_i = R_i^{host1} + R_i^{host2}, \tag{8a}$$

where

$$R_i^{host1} = \frac{\lambda_1 \beta c_{1i}}{d(a_{1i} + d)u} \quad \text{and} \tag{9}$$

$$R_i^{host2} = \frac{\lambda_2 \beta c_{2i}}{d(a_{2i} + d)u} \tag{10}$$

represent the basic reproductive rates of parasite strain i in host 1 and host 2, respectively. The notion of the basic reproductive rate stems from epidemiology (Anderson and May 1991) and denotes the number of secondary parasites that arise after one parasite has been placed into an environment consisting exclusively of susceptible hosts. An intuition for the basic reproductive rate in host 1, R_i^{host1}, can be obtained by noting that $1/d$ is the equilibrium density of uninfected, susceptible hosts in the absence of parasites and β is the probability that a parasite infects a susceptible host on encounter. The average life span of a host of type 1 infected by strain i is $1/(a_{1i} + d)$. During their lifetime, infected hosts will release a total of $c_{1i}/(a_{1i} + d)$ parasites. These, in turn, have an average life span of $1/u$. Thus, R_i^{host1} is the number of secondary parasite of strain i arising from a single parasite in host population 1. R_i^{host2} can be interpreted analogously. R_i is simply the sum of the numbers of secondary infected hosts of types 1 and 2. Therefore, we will refer to R_i as the basic reproductive rate of parasite strain i in the heterogeneous host population consisting of hosts 1 and 2.

It is interesting that only one parasite can persist at equilibrium, although there are two different host types. Even if we relax the assumption, that every parasite strain infects the hosts at the same rate, β, and take infection rates that are randomly distributed around some average value (that may differ for the two host types), we do not observe coexistence of parasite strains in our simulations. Thus, the fact that only one parasite strain persists is not a consequence of our assumption of a uniform infection rate β. We only found two strains coexisting, when we assumed a positive correlation between the infection rate of a parasite strain and its virulence. An intuitive explanation for these findings is that, when infection rates are independent of the virulence, the resident parasite strain reduces the abundance of both host types by equal amounts. Even those hosts are infected, in which the resident parasite strain does not perform very well, that is in which its virulence and therefore also its reproductive capacity is low. Thus, the resident parasite reduces the resource for a potential invader. However, if we assume a positive correlation between the infection rate, β and the virulence of a parasite strain, the resident parasite strain reduces mainly the abundance of the hosts, in which it performs well. In this case, there may be enough other hosts left that can serve as resources for the invasion of another parasite strain, which performs well in these other hosts.

Specialism or Generalism?

A key assumption in our model is that the parasite virulences in the two host types are traded off against each other. A parasite replicating in a heterogeneous host population, consisting of these two host types, may evolve to specialize for one of the two host types at the cost of losing its specialization for the other type. Therefore, the next question that we investigate is whether the fittest strain attains intermediate levels of virulence in both hosts or is very virulent in one host, but harmless in the other. We call the former generalist strains and the latter specialist strains. What determines whether the parasite evolves specialist or generalist strategies? (Note that this notion of specialism relates to the virulence of a strain, which corresponds to its reproductive capacity and thus to the performance of the parasite in a certain host. In many studies of specialization, however, the notion of specialism relates to the preference of a parasite strain for a particular host, which in our model would be measured by the infectivity parameter β.)

We approach this problem graphically by plotting the isoclines of the basic reproductive rate as a function of a_1 and

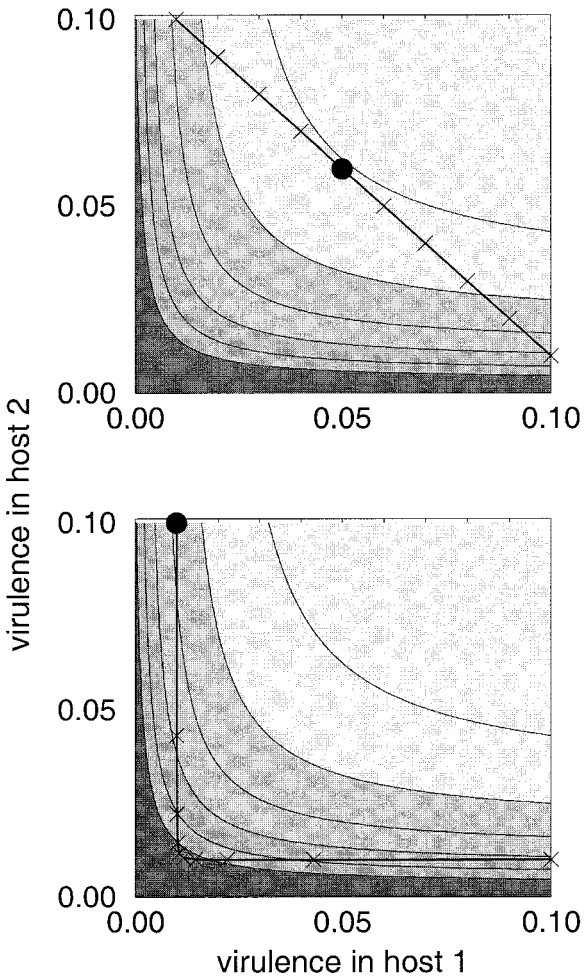

FIG. 2. Evolutionary end points of the dynamics (marked with big dots) for different trade-offs between the virulences a_1 and a_2. Here we assumed a linear relation between the parasite's reproduction rate and its virulence, $c_{1i} = p \times a_{1i}$ and $c_{2i} = p \times a_{2i}$. For a linear trade-off a generalist strain (strain 5) evolves (top graph), for a hyperbolic trade-off a specialist strain (strain 1) wins the game (bottom graph). (As parameters we chose $\lambda_1 = 2.9$, $\lambda_2 = 3.1$, $d = 0.01$, $\beta = 0.0005$, $u = 0.1$ and p.)

a_2 and the trade-off between a_1 and a_2. The maximum of the basic reproductive rate on the trade-off line yields the virulences of the surviving strain in both hosts.

Figure 2 shows examples for dynamics that select for specialist or generalist strains depending on the trade-off between the virulences a_1 and a_2. We find that a specialist strain evolves if the trade-off line is more convex than the isoclines of the basic reproductive rate. For trade-offs that are less convex than the isoclines of the basic reproductive rate, we observe evolution toward generalism. The shape of the trade-off line contains information about how similar the hosts appear to the parasite. The hyperbolic trade-off suggests that the parasite loses its specialization to one host before it can specialize to the other. In the case of a linear trade-off, the switch from one host to the other is smoother. The convexity of the trade-off line apparently corresponds to the cost that the parasite has to pay for a host switch. Thus, our model predicts the evolution of specialist strains if the switch from one host to the other is connected with a high cost for the parasite.

An analytical solution can be obtained by determining the extrema of the basic reproductive rate, R, under the boundary conditions given as the trade-offs (see Appendix 1). We also investigated a model in which we assume that the parasites reproduce at constant rates, that is $c_{1i} = c_{2i} = c$. Because this case does not seem to be as relevant as the present one, we have deferred its discussion to Appendix 2. A comment on the relation between our approach to the specialism-generalism problem and Levins's ''Theory of Fitness in a Heterogeneous Environment'' (Levins 1962, 1963) can be found in Appendix 3.

HETEROGENEITY AND VIRULENCE

In this section, we investigate how natural selection will affect parasite virulence and under which circumstances host heterogeneity influences virulence evolution.

Because we have assumed that the reproduction rate of the parasite is proportional to its virulence, the basic reproductive rates, R_i^{host1} and R_i^{host2}, are increasing functions of parasite virulence. Thus, our model predicts an escalation of parasite virulence in a homogeneous host population—in concordance with the observation, which has emerged from serial passage experiments (Ebert 1998, 1999).

If there is no trade-off between the virulences, which the parasite attains in the different host types, then also in a heterogeneous environment, the virulences would increase without bounds. As we have seen already, in the presence of trade-offs, host heterogeneity may prevent virulence from escalating. In the preceding section, we determined which trade-offs between the virulences in the different host types lead to the evolution of generalist strains. On the basis of these trade-offs, host heterogeneity leads to intermediate levels of virulence in both host types. For trade-offs, which result in the evolution of specialist strains, a heterogeneous environment cannot keep virulence at intermediate levels in both host types simultaneously. In these cases, parasite virulence escalates in one of the host types. Thus, the influence of host heterogeneity on the evolution of parasite virulence depends sensitively on the virulence-trade-offs.

We have seen that in our model selection operates to maximize the basic reproductive rate, R, of the parasite, and not to maximize the virulence in any of the host types. Whether virulence escalates or evolves to intermediate levels depends on the nature of the trade-off between the parasite virulences in the two hosts. Note that maximizing the basic reproductive rate is not generally equivalent to maximizing the average virulence, defined as

$$\bar{a} := a_{1k} f_{1k} + a_{2k} f_{2k}, \tag{11}$$

where $f_{1k} = y_{1k}^*/(y_{1k}^* + y_{2k}^*)$ and $f_{2k} = y_{2k}^*/(y_{1k}^* + y_{2k}^*)$ are the equilibrium fractions of hosts infected with strain i of types 1 or 2, respectively. However, the average virulence is often a good correlate of parasite fitness. Solving equations (1–5) for the equilibrium frequencies of infected hosts, y_{1k}^* and y_{2k}^*, and substituting the result into equation (11), we obtain for the average virulence:

$$\bar{a} := \frac{(\lambda_1 + \lambda_2)a_{1k}a_{2k} + (\lambda_1 a_{1k} + \lambda_2 a_{2k})d}{\lambda_1 a_{2k} + \lambda_2 a_{1k} + (\lambda_1 + \lambda_2)d}. \quad (12)$$

Writing $\bar{a}$ in terms of the basic reproductive rate, R,

$$\bar{a} = \frac{R_k d}{\beta u[p\lambda_1/(a_{1k} + d) + p\lambda_2/(a_{2k} + d)]}, \quad (13)$$

we see that the average virulence tends to be high for the fittest parasite.

As in earlier models, which described the evolution of virulence in a homogeneous host population (Anderson and May 1979, 1981, 1982, 1991; May and Anderson 1979, 1983, 1990; Levin and Pimentel 1981; Bremermann and Pickering 1983; Ewald 1983; Knolle 1989; Frank 1992; Antia et al. 1994), the outcome of competition is determined by the basic reproductive rate. In these models, trade-offs were assumed between the virulence and other traits of the parasite, such as infectivity or transmissibility.

For parasites that replicate in a heterogeneous host population, trade-offs between the virulences in the two hosts may exist. In our model, these trade-offs play the role that the trade-offs between the parasite virulence and infectivity played in models with homogeneous host populations. The maximum of the basic reproductive rate determines the levels of virulences that the fittest strain attains in both hosts. Thus, host heterogeneity in itself is sufficient to explain the evolution toward intermediate (i.e., nonextreme) levels of virulence in a particular host type.

Model with Parasite Evolution

The model that we investigated in the previous sections does not consider intrahost parasite evolution. In this section, we will take into consideration the possibility that the parasite undergoes evolutionary changes in virulence during the infection of a host.

Experimental evidence for such changes comes from the observation that when parasites are serially transmitted from one host to another host of the same type, this is often accompanied by an increase of its virulence in that host type and a decrease of virulence, or attenuation, in hosts of different types (Ebert 1998, 1999).

To study the consequences of these observations, we expand our model by assuming that infected hosts of a particular type release parasites, with increased virulence in this host type and decreased virulence in the other host type. Moreover, because increases in virulence often go hand in hand with increases of the parasite's growth rate (Muskett et al. 1985; Bull et al. 1991; Bull and Molineux 1992; Ni and Kemp 1992; Ebert and Mangin 1997; Ebert 1998, 1999), we again assume that the parasite reproduction rate is linearly dependent on the virulences, $c_{1i} = p \times a_{1i}$ and $c_{2i} = p \times a_{2i}$. Formally, the change in virulence after passage can be implemented into the model as follows: We assume a negative relation between the virulences in the two hosts (i.e., a_2 is decreasing as a_1 is increasing). Next, without loss of generality, we order the parasites such that the virulences fulfill $a_{11} < a_{12} < \ldots < a_{1n}$. This implies the reversed order of virulences in host 2, that is $a_{21} > a_{22} > \ldots > a_{2n}$. Finally, we change the rates at which parasite of strain i are released in equation (5) to $c_{1i}y_{1,i-1}$ and $c_{2i}y_{2,i+1}$. (This actually reflects the observation that virulence increases in one host type while it decreases in the other. Parasites of strain i are assumed to be released by hosts infected with the more virulent strain—which is strain $i - 1$ in host 1 and strain $i + 1$ in host 2. By passage through either host, parasite virulence increases: $a_{1i} > a_{1,i-1}$, $a_{2i} > a_{2,i+1}$.)

The model with parasite evolution is given by equations (1–4) and the following equation for free parasites:

$$\dot{v}_i = c_{1i}y_{1,i-1} + c_{2i}y_{2,i+1} - uv_i. \quad (14)$$

The equilibria of the model with evolution can be given for $n = 3$ strains only. For more strains we did not derive analytical solutions. Nevertheless, from the structure of equation (14) we can conclude that all strains are present in the nontrivial equilibrium simultaneously. (If a particular strain i is present in the equilibrium, it gives rise to parasites of strain $i + 1$ and $i - 1$, which themselves give rise to parasites of strains $i + 2$, i and $i - 2$, etc.). Thus, we expect stable polymorphisms to evolve (see Fig. 3).

The observed parasite distributions can be classified into two categories. The first category consists of distributions that peak in the middle. In these cases, the parasite strains that attain intermediate levels of virulence in both host, that is generalist strains, dominate the parasite population. We call these distributions generalist distributions. The second category consists of distributions peaking at the edges, that is in these cases specialist strains dominate the parasite population. Therefore, we call these distributions specialist distributions.

Numerical simulations suggest that the conditions for the evolution of generalism and of specialism are equivalent to the conditions that we have derived for the model without parasite evolution. For a linear trade-off between the virulences a_1 and a_2, we observe a generalist distribution, whereas for a hyperbolic trade-off, specialist distribution evolves (see Fig. 3). The specialist distributions could introduce evolutionary branching of the parasite population.

Discussion

We have analyzed models for the evolution of virulence in a genetically heterogeneous host population. Our models describe the interaction between many parasite strains—differing in their virulences and their reproduction rates—and two host types. The difference of the two host types is reflected in their distinct birth rates, λ_1 and λ_2, and in the different levels of the virulence and reproduction rate that a parasite strain attains in both hosts. We assumed that the rate with which an infected host releases parasites is linearly dependent on the parasite virulence in this host. We excluded the possibility of super- or coinfection of hosts, but in the section Model with Parasite Evolution we considered that parasites evolve when passing through a host. Our model is based on insights that have emerged from serial passage experiments. Therefore, it applies to a wide variety of host-parasite systems. The common characteristics of such systems are the existence of more than one host type and a multistrained structure of the parasite population.

Investigating the model without parasite evolution, we

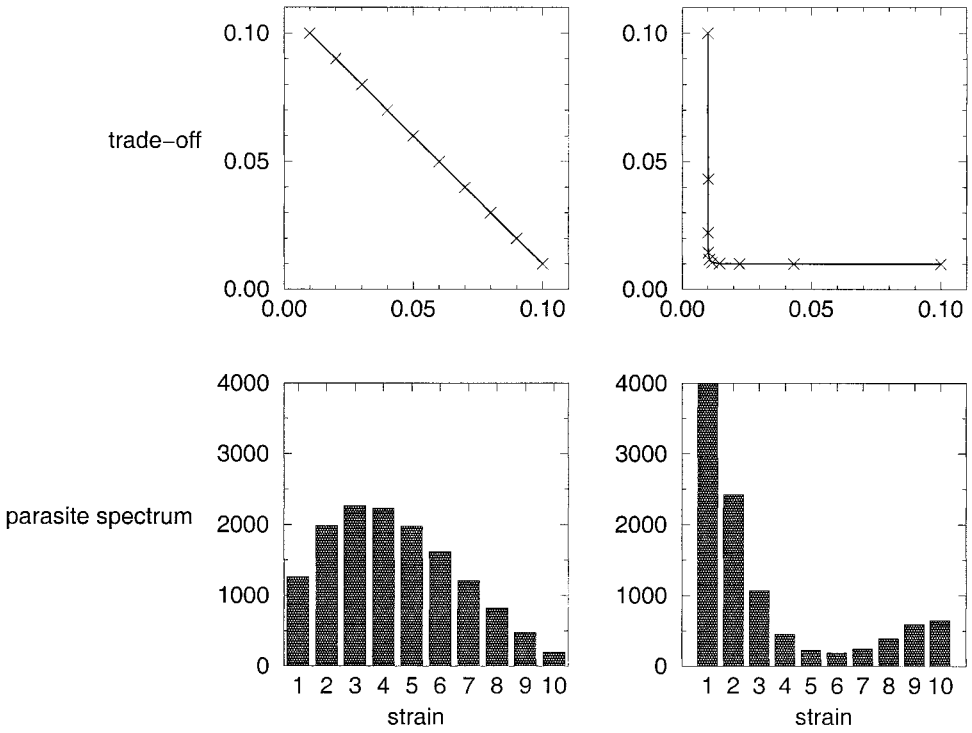

FIG. 3. Including within-host evolution into our model, we observe stable parasite polymorphisms. For a linear trade-off we observe a parasite spectrum peaking at strain 3, a generalist strain, slightly more virulent in host 2. For a hyperbolic trade-off we get a parasite distribution with a high peak at strain 1 and a low peak at strain 10; the high peak corresponds to the specialist strain with maximum virulence in host 2. That the distributions are skewed to the left indicates the parasite's preference for host 2, which is due to a higher proportion of type 2 hosts in the host population, $\lambda_2 > \lambda_1$. These results are in concordance with the simulations performed on the model without mutation, shown in Figure 2. The distribution on the bottom left represents a state of the system that could introduce parasite speciation. (The parameters were chosen as in Fig. 2.)

could determine the trade-offs between the virulences in the two hosts for which the system evolves toward specialism or generalism. The system evolves toward specialism for virulence trade-offs that are more convex than the isoclines of the basic reproductive rate. The degree of convexity of the virulence trade-off corresponds to the cost that the parasite has to pay for switching from one host to the other. Our model, therefore, implies that parasites specialize on a particular host type if the cost for a host switch is high.

Furthermore, we found that host heterogeneity may be an important determinant for the evolution of virulence. The influence of heterogeneity depends on the nature of the trade-off between the parasite virulences in the different host types. For trade-offs, that result in the evolution of a generalist parasite strain, host heterogeneity prevents virulence from escalating. In our model, the trade-offs between the parasite virulences in the two host types replace the trade-offs between parasite virulence and the infectivity that were introduced in earlier models to explain why the parasite attains intermediate levels of virulence (Anderson and May 1979, 1981, 1982, 1991; May and Anderson 1979, 1983, 1990; Levin and Pimentel 1981; Bremermann and Pickering 1983; Ewald 1983; Knolle 1989; Frank 1992; Antia et al. 1994). We do not have to evoke the existence of any other trade-off. Host heterogeneity itself is sufficient to explain the evolution of intermediate parasite virulences.

In the second model we assumed that the parasites evolve within the hosts. Unlike in the model without parasite evolution, we find that all parasite strains persist in the equilibrium, that is we observe stable polymorphisms in the parasite population. The observed parasite distributions can be classified as specialist or generalist distributions, depending on whether the most abundant strain is a specialist or a generalist. The conditions for specialism that we derived for the model without evolution also apply to the parasite distributions of the model with mutation: Trade-offs of sufficient convexity give rise to specialist distributions. Thus, the analysis of the simple model is useful to guide our intuition even in situations that go in their complexity beyond the first, simple model.

Stable polymorphisms are common to all models that assume some kind of within-host dynamics, such as models that allow super- or coinfection of hosts or models that consider mutating parasites (Nowak et al. 1991; Bonhoeffer and Nowak 1994; May and Nowak 1994, 1995; Nowak and May 1994; Nowak and Bangham 1996; Regoes et al. 1998). The parasite polymorphisms that were observed in the above-mentioned models fall into the category of generalist distributions. However, the specialist distributions that we observe in our model are to our knowledge novel and could introduce evolutionary branching in the parasite population.

A possible extension of the present investigation would be to consider more than two host types. In this case we would have to introduce more categories than just generalists and

specialists. (How would one classify a parasite strain that attains high virulence in host 1, low virulence in host 2, and intermediate levels of virulence in host 3 and host 4?) We would like to point out that whether the system evolves toward specialism or toward generalism can be asked in systems with a heterogeneous host population only and thus represents the most intriguing question in our models. The analysis regarding specialism or generalism has bearings on all infections in which more than one potential host is present and in which the parasite is variable enough to provide a spectrum of differing strains.

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Appendix 1

Solving for the Extrema of R on the Trade-off Line

To determine the extrema of the basic reproductive rate

$$R(a_1, a_2) = \frac{\beta}{ud}\left[\frac{\lambda_1 c_1}{(a_1 + d)} + \frac{\lambda_2 c_2}{(a_2 + d)}\right] \tag{A1}$$

on the trade-off line given by $\tau(a_1, a_2) = 0$, $a_1, a_2 > 0$, we have to solve the equations:

$$\partial_1 F(a_1^0, a_2^0, \sigma) = 0, \tag{A2}$$

$$\partial_2 F(a_1^0, a_2^0, \sigma) = 0, \quad \text{and} \tag{A3}$$

$$\partial_3 F(a_1^0, a_2^0, \sigma) = 0, \tag{A4}$$

where $F(a_1, a_2, \sigma) = R(a_1, a_2) + \sigma\,\tau(a_1, a_2)$. Whether the extremum is a maximum or a minimum has to be determined separately.

If the solution (a_1^0, a_2^0, σ) is a maximum, the surviving strain is a generalist. If the solution (a_1^0, a_2^0, σ) is a minimum, R attains its maximum on one of the edges of the trade-off line and the surviving strain is a specialist.

As an example, we take parasite reproduction rates that depend linearly on the parasite virulences, $c_1 = p \times a_1$ and $c_2 = p \times a_2$, as in the main body of the paper, and a linear trade-off, $\tau(a_1, a_2) = a_1 + a_2 - const = 0$, $0 < a_1, a_2 < const$. Equations (A4) is equivalent to the trade-off equation, and can be solved in this simple case: $a_2 = \text{constant} - a_1$.

By substituting this into equation (A3) and equating to equation (A2), we get for the coordinates of the extremum:

$$a_1^0 = \frac{const\sqrt{\lambda_1} + d(\sqrt{\lambda_1} - \sqrt{\lambda_2})}{\sqrt{\lambda_1} + \sqrt{\lambda_2}} \quad \text{and} \tag{A5}$$

$$a_2^0 = \frac{const\sqrt{\lambda_2} + d(\sqrt{\lambda_2} - \sqrt{\lambda_1})}{\sqrt{\lambda_1} + \sqrt{\lambda_2}}. \tag{A6}$$

For sufficiently large trade-off constants, $const > d$ and comparable birth rates, $\lambda_1 \approx \lambda_2$, the solution (a_1^0, a_2^0) lies in the first quadrant and is a maximum, that is the surviving strain is a generalist (cf. Fig. 2). The power of the abstract formalism presented here becomes apparent if we deal with more complicated trade-offs.

Appendix 2

Model with Constant Parasite Reproduction Rate

In the main body of the paper we concentrate on a model in which the parasites differ in their virulences as well as their reproduction rates. The reproduction rates are assumed to be linearly dependent on the virulences. In this appendix, we analyze a model in which the parasites differ only with respect to their virulences in the two hosts and assume the reproduction rates to be constant, $c_{ij} = c$, that is independent of the virulences. Whereas in the model of the main part of this paper the parasite evolves toward high levels of virulence in both hosts, we observe the reversed trend here. If the reproduction rates are constant, then it is not advantageous for the parasite to maintain high levels of virulence. The reversed trend in parasite evolution results in a reversal of the predictions.

Specialism or generalism?—We observe an evolution for specialism for trade-offs between the virulences that are less convex than the isoclines of the basic reproductive rate, such as a linear trade-off. For a hyperbolic trade-off, the parasite population evolves toward generalism. These results imply that in a model with constant parasite reproduction rates, the parasite specializes on a particular host type if the cost, which the parasite has to pay to adapt to the other host, is relatively low.

Heterogeneity and virulence.—In the present case of constant reproduction rates, parasite virulence tends to vanish in a homogeneous environment. Does host heterogeneity prevent the parasite virulence from vanishing in the course of evolution? The answer depends on the nature of the trade-off between the virulences in the two host types: For hyperbolic trade-offs, parasite virulence remains at intermediate levels. For linear trade-offs, parasite virulence vanishes in one of the host types. Thus, also in the case of a constant reproduction rate, host heterogeneity is an important factor for the evolution of virulence. As in the case, in which the reproduction rate of the parasite is proportional to its virulence, the appropriate measure of parasite fitness is the basic reproductive rate. However, the *average virulence*, as defined above, can serve as an approximate indicator of parasite fitness. For the fittest parasite, the average virulence $\bar{a}$ tends to be low, as can be seen from the inverse relation between $\bar{a}$ and R:

$$\bar{a} = \frac{\beta cu[\lambda_1 a_{1k}/(a_{1k} + d) + \lambda_2 a_{2k}/(a_{2k} + d)]}{R_k d}. \tag{A7}$$

Appendix 3

Relation to Levins's Theory of Fitness

We would like to comment on the relation between our approach to the specialism-generalism problem and Levins's ''Theory of Fitness in a Heterogeneous Environment'' (Levins 1962, 1963). Levins investigated fitness trade-offs that favor specialism and considered the cases of simultaneous as well as sequential habitat use. He plotted the isoclines of what he called the ''adaptive function,'' a measure for the species' fitness in the heterogeneous environment. For the case of simultaneous habitat use these isoclines were linear, and if one assumed that the species used both habitats sequentially, the isoclines were convex as the isoclines of the parasite's basic reproductive rate in Figure 2.

Our method of solving the system graphically is equivalent to Levins's approach. However, the resemblance of Figure 2 and Levins's plots of the adaptive function for the case of sequential habitat use is deceptive, because the axes of Levins's plots measure the *fitness* components of a species in a homogeneous environment, which would correspond to the *basic reproductive rate* in our model, whereas the axes of Figure 2 measure the *virulence* of the parasite in the respective host type. If we plotted the basic reproductive rate of the parasite in the heterogeneous host population as a function of the basic reproductive rates of the parasite in a homogeneous population, consisting only of host 1 or host 2, respectively, we would obtain linear isocline in concordance with Levins's theory.