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Competition and coexistence in host-parasite systems: the myxomatosis case

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Abstract Co-circulation of several strains of parasites has been observed in many host-parasite systems. However, simple epidemiological models cannot sustain this coexistence. In this work we study the coexistence of viral strains in the myxomatosis case. Myxomatosis, a highly lethal disease of the European rabbit, has been used in Australia and Europe as a biological control of rabbit populations. A few years after its introduction, the original highly virulent strains were almost completely replaced by field strains covering a wide range of virulence. Here, we study several mechanisms that may explain the field observations. First we considered spatial heterogeneity. The establishment of any strain over regions occupied by host populations may delay the spread of any superior competitive virus strain, producing global coexistence in the long term. On the other hand, sub-populations with different resistance levels in epidemiological contact, as observed in the field, can maintain several different virus strains co-circulating. The second class of mechanism introduces diversity among hosts of a local population sharing a territory. We considered different classes of host resistance to myxomatosis: belonging to a resistance class is a random fact. Host age-dependent resistance is also especially considered. These types of population heterogeneity can sustain local coexistence for many years, although exclusion takes place for long enough periods. The concurrent action of both types of mechanisms could explain why the diversity of virus strains is sustained, and the local coexistence. Finally, we briefly discuss the influence of host genetic dynamics in the coevolution of the system.

Keywords Co-evolution · Epizootic · Mathematical model · Population dynamics · Rabbit · Virulence

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Introduction

Competition and predation, including parasitism, are ecological processes that play a fundamental role in the dynamics, evolution, and regulation of the populations. Competition among species is usually modelled with systems of differential equations of the form (see, for example, Murray 1989),

$$\frac{dN_i}{dt} = N_i F_i(N_1, N_2, \ldots), \quad \text{for } i = 1, 2 \ldots \tag{1}$$

where N_i is the number or density of the ith species, or the number of patches occupied by one or several individuals or unoccupied. The inhibitory effect that each species exerts on the others is incorporated through the function F_i. Usually, resources are considered implicitly but not as dynamical variables. However, in the case of host-parasite systems, the different parasite populations compete among them for the susceptible host population, which is a dynamical variable of the system. On the other hand, different host populations compete for survival. We use the competition concept in a broad sense, for us "...competition is said to occur when species reciprocally inhibit each other's population growth" (Law and Watkinson1989). In several cases in this work, competition for resources by the hosts is disregarded on the assumption that the host population is kept far below the environmental carrying capacity by the disease. Coexistence is the other face of competition. The *competitive*

exclusion principle stands that if two or more species compete for the same limited resources, only one will survive. Therefore coexistence of competing populations requires partitioning of resources, existence of refuges, specialism or generalism of some competitors, etc., that is, some kind of heterogeneity. It is well known that a variable environment, in space or time, may support coexistence of competing species although exclusion takes place in an completely homogeneous environment (see, for example, Chesson1986). Moreover an homogeneous environment with a patchy distribution of the populations may preclude exclusion of inferior competitors (see, for example, Levins and Culver 1971; Tilman1994; Hanski and Gilpin1997; Ohsawa et al. 2004).

In this work, we study some aspects of competitive exclusion and coexistence in the framework of host-parasite systems. The knowledge of its dynamics have important implications in determining strategies of resource management, and biological and disease control among others. Fundamentally, we are interested in the coexistence of different parasite strains in competition.

The models presented in this work were developed for the *myxoma* virus—European rabbit system but the mechanisms proposed are quite general, and can be translated easily to other host-parasite systems. However, we chose to work on a concrete example to avoid the temptation of twiddling with parameter values arbitrarily.

Myxomatosis is a viral disease of the European rabbit *Oryctolagus cuniculus* vectorized by fleas (*Spyllopsylus cuniculi*) and mosquitoes (*Anopheles annulipes*, *Culex annulirostris*). Myxoma viruses causes a mild disease in their original host, the South American rabbit *Sylvilagus brasilensis*. The disease was introduced in around the 1950s as a biological control agent of European rabbit populations in Australia and Europe. Since then, the evolution of the rabbit population and the virus strains have been monitored. The system myxoma-*Oryctolagus cuniculus* is a rare case in which the co-evolution of a host-parasite system has been followed since its beginning.

The initial effect of myxomatosis was dramatic. The disease killed almost every rabbit that became infected and the population levels decreased enormously. A few years later, the original strain was rare and several strains of intermediate virulence were predominant (Hudson and Mansi 1955; Ross and Sanders 1987). This permitted the increase of the mean genetic resistance of the rabbit populations and, as a result of co-evolution, the predominant strains have become more virulent (Fenner1983; Ross and Sander 1987). Myxomatosis is the classical example where a parasite does not evolve towards lower virulence in the long term. By 1980, Lloyd estimated that the Britain population was at about 20% of the pre-myxomatosis levels (Lloyd 1981). In some regions of Australia, post-myxomatosis rabbit populations are between 1 and 10% of the pre-myxomatosis numbers (Fenner and Ross 1994).

The virus strains are classified in six groups: I, II, IIIA, IIIB, IV and V, from higher to lower virulence. Why are the intermediate virulence strains competitively dominant? Myxomatosis is mechanically transmitted by mosquitoes and fleas. The disease produces lesions where the vectors feed (Fenner 1983). On the one hand, rabbits infected with the more virulent strains die so quickly that the probability of transmission to vectors is low. On the other hand, the less virulent strains, associated with longer survival times, produce a low virus titer in the rabbits' skin, and then the probability of vector infection is low again. Therefore, only intermediate virulence strains have an adequate survival time and produce high virus titer (Mead-Briggs and Vaughan 1975).

Although each host population has a dominant strain associated, depending on the level of the host resistance, at any time during the co-evolution process, there are other coexisting strains, more and less virulent, i.e., the less fit strains are not totally excluded. The main aim of this work is to provide plausible explanations for this coexistence.

Levin and Pimentel (1981) proposed a model that allows coexistence of two viral strains. In their model, hosts are divided into the categories empty, infected with an nonvirulent strain, and infected with two strains (non-virulent and virulent). This 'superinfection' mechanism was generalized by Nowak and May (1994) to allow for the local coexistence of several related strains, but the assumptions are not fulfilled by the myxoma-*Oryctolagus* system. Multiple infection is rare in the field due to the low probability of a second infection taking place (Dwyer et al. 1990).

Dwyer et al. (1990) developed a detailed, age-structured model without allowing for multiple infection. This model does not result in coexistence. The dominant strain is in grade IV and excludes the others. As possible explanations of the observed coexistence, they suggested the mechanism proposed by Levin and Pimentel (1981) as well as other possibilities such as genetic diversity, regional coexistence and high viral mutation rates.

In this work, we study these possibilities and propose other plausible mechanisms. In the next section we present the basic model and some basic results. It is shown that a completely homogeneous model cannot sustain co-circulation of strains. Then we discuss the case of spatially separated populations. First, we consider a homogeneous population that spreads over a region. We show that the occupation of a territory by any strain delays or precludes the spread of other strains. Next, we consider the case in which the geographically separated populations present different genetic resistance. In this context, we consider the simplest case, in which there are only two homogeneous subpopulations. In each subpopulation a different virus strain is dominant. When both populations are in epidemiological contact, local coexistence of the two strains occurs. Also, we consider the effects on parasite coexistence of the intrinsic heterogeneity of any real population. We study the effects on parasite coexistence of the differences in the resistance of individuals associated to: circumstantial factors such as immune

response state; genetic diversity; age, etc. Finally, we discuss the possible influence of factors omitted in the models, the limitations of the results, and perspectives for further research.

Basic epidemiological model and some basic results

We considered an *SIR* model for the transmission of an infectious disease in a homogeneous host population (see, for example, Anderson and May 1979). Let S be the density of the susceptible host population, i.e., those individuals capable of contracting the disease. The density of infected population with the jth parasite strain have density I_j. These are the classes responsible for disease transmission.

As usual, we assume total cross-immunity, i.e., a host that has recovered from infection with any strain is immune to infection with any other strain. Therefore, in one class of immune individuals (with density R) we collect all the hosts that have recovered from any infection. Total cross-immunity has been demonstrated in experiments (Marshall and Fenner 1958). Other evidence of cross-immunity include the use of low-virulence strains as vaccines for myxomatosis (Parer et al. 1985; Barcena et al. 2000). Therefore, the total population is $N=S+I+R$. We consider a density-dependent per capita birth rate (Myers 1960; Rödel et al. 2004), $a(1-N/K)$ with parameters K and a constant. We also take into account the host natural mortality rates (b), recovery (c), disease-induced mortality (d), and infection coefficient (β) constant. We further assume homogeneous mixing (an infectious individual can transmit the disease with the same probability to any other susceptible host). Although myxomatosis is a vectorized disease, we do not consider vector populations as dynamic system variables. Mosquito populations are independent of rabbit populations, and the availability of vectors is taken into account in the parameter β. The case of fleas is different (see Seymour 1992). The dependence of β on the virulence of the virus strains is quite similar for mosquitoes and fleas (Dwyer et al. 1990). Also, we consider that immune and infective individuals have susceptible offspring. With these hypotheses, we arrive to the following basic deterministic model for an homogeneous host population and n parasite strains,

$$\frac{dS}{dt} = aN\left(1-\frac{N}{K}\right) - bS - S\sum_{i}^{n}\beta_i I_i, \tag{2}$$

$$\frac{dI_j}{dt} = S\beta_j I_j - (b+c_j+d_j)I_j, \quad 1 \le j \le n \tag{3}$$

$$\frac{dR}{dt} = \sum_{i}^{n} c_i I_i - bR. \tag{4}$$

Model development in this work is derived from this basic model.

As expected, this basic model does not possess an endemic equilibrium with more than one competing strain coexisting. If the parameter values are such that $\beta_i/(b+c_i+d_i) \sim \beta_j/(b+c_j+d_j)$, where one of the strains is a superior competitor, the exclusion of the other may develop during a long period of time. The above system has two types of equilibria: the free infection equilibrium and the endemic equilibrium with only one virus strain

$$S_0 = \frac{\gamma}{\beta}, \quad I_0 = \frac{1}{(1+b/c)}\left[\frac{(a-b)}{a}K - S\right], \quad R_0 = \frac{cI_0}{b},$$

where we have dropped subscripts for simplicity and the total removal rate was denoted as $\gamma \equiv (b+c+d)$. Existence of this endemic equilibrium requires $R_0 \equiv \frac{(a-b)}{a}\frac{\beta K}{\gamma} > 1$. R_0 is the basic reproductive number for this model. The solutions of the system (2, 3, 4) present damped oscillations towards the equilibrium (but see Aparicio and Solari 2001b). The oscillation period depends on the parameter values. For the cases considered in this work it is around 1.5 years. Considering that this biological rhythm is very close to the seasonal rhythm, we expect an important influence of the latter on the behavior of the epizootic.

Based on the fact that intermediate virulence strains are prevalent in the wild, Massad (1987) suggested a non-linear relationship between the infection rate (β) and the mean survival time ($T=d^{-1}$),

$$\beta_i = a_1 \operatorname{sech}^2(a_2 d_i + a_3), \tag{5}$$

where $a_2 = 42.788$ day^{-1} and $a_3 = -1.875$. The coefficient a_1 determines the maximum value of β which is reached for $T = 22.8$ days. In our case, it is a fitting parameter. We set its value in order that at the endemic equilibrium the total population per unit of area is 20% of the carrying capacity [$C = K(1-b/a)$] from the model (2, 3, 4). Therefore, for strains with virulence close to the maximum, we may approximate the per capita birth rate by a, i.e., we can neglect the density-dependence of the birthrate. Furthermore, since the infective period is very short, we can neglect the contribution of the infective population to the demography. We will use the empirical relation (5) for each host-virus association. For each set of parameters that characterize virus strains in their relationship to the hosts, there is one competitively dominant strain. Development of a parasite strain in a host population requires that if there is a small number of infectives I_{0i} with the strain i, then $dI_{0i}/dt > 0$, i.e., $S > (b+c_i+d_i)/\beta_i$. Therefore, the density of susceptible hosts must be larger than the threshold value

$$S_{th} = \frac{\gamma_i}{\beta_i}, \tag{6}$$

and populations with susceptible host density below the threshold value cannot sustain the development of any strain. The strain that produces the minimum equilibrium value for the density of susceptible hosts cannot be invaded by any other strain (Anderson and May 1982). This means that the absolute superior competitor at

local level is the strain for which the basic reproductive number is maximum.

Interaction between spatially separated populations

In this section, we explore some consequences of spatiality in the dynamics of the system. Space plays an essential role in the outcome of competing species (Levins and Culver 1971; Slatkin1974; for recent reviews see Tilman1994; Hanski and Gilpin1997), with sometimes unexpected consequences (see, for example, Nee and May 1992, 1997). A fruitful way of considering spatiality is the metapopulation approach (see, for example, Hanski and Gilpin 1997). In this framework, two competing species may coexist in a patchy world, although exclusion takes place at a local level (within the patch), coexistence may take place if the (locally) inferior competitor has some advantage such as higher mobility or lower local extinction rate (see, for example, Nee and May 1992, 1997; Tilman 1994). This is not the case for myxomatosis. Rabbits live in groups sharing and defending a territory. If we consider each of these host colonies as habitable patches by parasite populations, and all of the hosts have the same degree of resistance, the local superior competitive parasite strain has the highest spread and the lowest extinction rates. On the other hand, the environment is heterogeneous: rabbits from different locations may have different mean resistance (Parer et al. 1994; Ross and Sanders 1984) and this fact may sustain coexistence. Although the models developed are spatially explicit (in the sense that we consider interconnected spatial arrangements) we do not use explicit space variables.

Geographical spread of an homogeneous population

The European wild rabbit is a gregarious species that forms stable breeding groups (see, for example, Cowan 1987a, 1987b). Group size varies from two to more than 20 individuals and the composition is, roughly, two females to each male (Cowan 1987a). During the reproductive season this number increases because of the newborns. The average production of weaned offspring per female per season is around 20 (Cowan 1987b). Each breeding group share a warren and defends its territory. Usually, several warrens are clustered. We call such an aggregation of warrens a colony. The assumption of homogeneous mixing approximately holds for colonies. In the following, we considered a homogeneous rabbit population spread over a region, i.e., an arrangement of colonies. The probability that an infectious individual from one colony infects a susceptible one from a neighboring colony is lower than the probability of infection within a colony. Therefore, the infection rate between neighboring colonies is σ times the intra-colony one with $\sigma < 1$. We assign a null probability of contact among individuals of non-neighboring colonies. A general situation is to take a bi-dimensional arrangement in which each colony is in contact with its neighboring colonies. However, we considered a linear arrangement in which each colony has only two neighbors. The motivation is two-fold. First, in many places the rabbit population spreads along rivers or creeks (Brereton 1953; Bonino and Amaya 1985; Bonino and Gader 1987) and, second, in the framework of continuous deterministic models the solutions of one-dimensional and bi-dimensional models share many qualitative features while the one-dimensional model is more accessible from a computational point of view. We consider the case of only two virus strains and N host colonies labelled by subscripts $1 \leq j \leq N$. For $j \neq 1, N$ we have

$$\frac{dS_j}{dt} = a\left(1 - \frac{N_j}{K}\right)N_j - bS_j - S_j\{\beta_1 I_{1j} + \beta_2 I_{2j} + \sigma[\beta_1(I_{1j-1} + I_{1j+1}) + \beta_2(I_{2j-1} + I_{2j+1})]\} \quad (7)$$

$$\frac{dI_{1j}}{dt} = S_j\beta_1\left[I_{1j} + \sigma(I_{1j-1} + I_{1j+1})\right] - (b + c_1 + d_1)I_{1j} \quad (8)$$

$$\frac{dI_{2j}}{dt} = S_j\beta_2[I_{2j} + \sigma(I_{2j-1} + I_{2j+1})] - (b + c_2 + d_2)I_{2j} \quad (9)$$

$$\frac{dR_j}{dt} = c_1 I_{1j} + c_2 I_{2j} - bR_j. \quad (10)$$

For $j = 1, N$ the equations are the same but these colonies have only one neighbor. In the model (7, 8, 9, 10), the dynamics within a colony is governed by the homogeneous two-strain model (2, 3, 4) plus the contribution of the infected hosts from the neighboring colonies. The linking allows the spread of the disease from colony to colony. The model (7, 8, 9, 10) is a finite-difference version of the usual reaction-diffusion models.

The model (7, 8, 9, 10) can be used to study the influence of the parameters and initial conditions on the spread of the disease. Disease transmission from colony $j-1$ to colony j depends on the number of susceptible hosts in colony j, the number of infected hosts in colony $j-1$, β and σ. The spreading velocity increases when such values increase (if the others remain constant).

We considered colonies with carrying capacity $C = 50$ each (then $\beta \sim 2$ for the dominant strain). Taking the distance between neighboring colonies as 100 m, $\sigma = 0.1$, and 30% of immune individuals in the rabbit population, the speed of spreading obtained is about 500 m per month, and is of the order of the observed spread in Great Britain (Ross and Tittensor 1986b). In the case of Australia, where the main vector is the mosquito, the speed of the spread of myxomatosis reported was around 5 km/day for the initial outbreaks (Brereton 1953). This speed is incompatible with realistic values of the infection rate and the hypothesis of infections to next-neighbor warrens, and suggests that interactions with further-away neighbors have to be considered for the Australian case. Another point of view is that for

mosquitoes transmission the homogeneous mixing approximation is valid over larger areas, and therefore all magnitudes must be re-scaled. Mobility of mosquitoes is surprisingly high, with an average daily flight range in the order of 5 km (Fenner and Ross 1994).

A stochastic realization of the model (7, 8, 9, 10) has the requirements of a classical metapopulation (see, for example, Hanski and Simberloff 1997). Colonies with susceptible rabbits are habitable patches, colonies without rabbits or with a fully immune population are uninhabitable patches. Patches can be colonized by one or more parasite strain and extinction may take place. However, in our case the competitively superior strain dominates the local dynamics and possesses higher colonization and spread rates than the others. Therefore, we do not expect long term coexistence, as found in the Nee et al. model (Nee et al. 1997, and references cited therein). Nevertheless, such situations can favor coexistence. The establishment of any virus strain over a region with rabbit populations reduces the number of susceptible hosts available for infection. A competitively superior virus strain can spread over the region because the susceptible host population is still above its threshold value (6). However, the speed of the spread is lower than the one obtained on a region free of myxomatosis. Numerical solutions show that the establishment of non-dominant strains in a region can delay exclusion by the dominant strain for a long time. We have considered 100 colonies with 50 individuals each when free of myxomatosis. Thus a colony occupies an area of around 100 m^2, and then the arrangement represents an extension in the order of 10 km. Initially, we consider the whole region to be infected by a non-dominant strain. An epizootic with the dominant strain begins at the border of the array. Exclusion in each colony proceeds rapidly but in the whole region there is coexistence for some time: the non-dominant strain is totally excluded only after about 20 years.

Genetic diversity of two spatially separated populations

Since the introduction of myxomatosis for the control of European rabbit populations, an increase in hereditary resistance has been observed (Marshall and Fenner 1958; Ross and Sanders 1977, 1984; Ross 1982; Fenner 1983; Parer et al. 1994).

Development of rabbit resistance to myxomatosis occurred earlier in Australia than in Britain (Ross and Sanders 1984). In Australia, after a few epizootics the wild rabbit population presented lower mortality and longer survival time of infected rabbits than the domestic controls. In Britain the situation was different. The first symptom of an increase in resistance was the increase in the survival time without a significant decline in mortality (Vaughan and Vaughan 1968; Ross and Sanders 1977). Several years later, the situation evolved into the Australian pattern. Mimicking these observations, we propose two different sets of recovery rate values for the rabbit resistance description. The first one presents an appreciable increase in survival time with little increase in the recovery rate (set A). The second one shows an appreciable increase in both survival time and recovery rate (set B). Almost every case of increase in resistance observed in the wild is between these extremes. For simplicity, we consider only two classes of resistant rabbits: one is as resistant to myxomatosis as unselected domestic controls; the other has an increased resistance of '20%' and the corresponding recovery rates belonging to set A or to set B (see Appendix for parameter values). The parameter values used in the simulations are listed in Tables 1 and 2.

For unselected rabbits, the dominant strain is in the grade IIIB but for 20% more resistant rabbits the dominant strain is grade IIIA using set A as well as set B recovery rate values. In this way, the parameter variations reflect the change in the dominant strain, as rabbit resistance increases, as observed in the field.

If two populations with different degrees of resistance do not interact, there is coexistence in an obvious way. Since the dominant strain is different in each population, we have a global coexistence. In several places, distance between populations is relatively small and the migration of the hosts or vectors can break the isolation. We consider a host population with two subpopulations in epidemiological contact. Each subpopulation is homogeneous and possesses a different level of resistance. We consider only the dominant strains of each population, which maintains them far below the carrying capacity. We also neglect the contribution of the infected class to population growth. This simplified hypothesis will be used in the rest of the models. We further assume that the hypothesis of homogeneous mixing holds and that the infection rate between subpopulations is much smaller than the contact rate inside each subpopulation. With these assumptions, the resulting model is

$$\frac{dS_1}{dt} = (a-b)S_1 + aR_1 - S_1(\beta_{11}I_{11} + \beta_{12}I_{12} + \sigma\beta_{21}I_{21} + \sigma\beta_{22}I_{22}), \quad (11)$$

$$\frac{dI_{11}}{dt} = S_1(\beta_{11}I_{11} + \sigma\beta_{21}I_{21}) - (b + c_{11} + d_{11})I_{11}, \quad (12)$$

$$\frac{dI_{12}}{dt} = S_1(\beta_{12}I_{12} + \sigma\beta_{22}I_{22}) - (b + c_{12} + d_{12})I_{12}, \quad (13)$$

Table 1 Parameter values for laboratory rabbits

	Strain					
	I	II	IIIA	IIIB	IV	V
k(%)	0.5	3	7.5	20	40	77.5
T(days)	11	15	20	26	40	118
d	33.2	24.3	18.25	14.04	9.12	3.09
c	0.17	0.75	1.48	3.5	6.08	10.65
β	0.1352	0.8615	1.8436	1.8805	1.0988	0.3505

k survival rate (%), T mean survival time. All of the rates are $year^{-1}$

Table 2 Parameter values for rabbits 20% more resistant, using criteria A and B for the recovery rates assignment (c_A and c_B)

	Strain					
	I	II	IIIA	IIIB	IV	V
k(%)	0.6	3.6	9	24	48	93
T(days)	13.2	18	24	31.2	48	141.6
d	27.27	20	15	11.54	7.5	2.54
β	0.4549	1.5550	1.9630	1.5515	0.8521	0.3133
c_A (set A)	0.11645	0.747	1.483	3.64	6.92	33.77
c_B (set B)	6.98	5.77	5.26	6.49	8.12	11.58

The β values were chosen in such a way that, in the endemic equilibrium of a IIIB strain, the total number of a domestic rabbit population is about 10 individuals, i.e., roughly the population for 1 ha under the assumption of homogeneous mixing. All of are the rates are year $^{-1}$

$$\frac{dR_1}{dt} = c_{11}I_{11} + c_{12}I_{12} - bR_1, \tag{14}$$

$$\frac{dS_2}{dt} = (a-b)S_2 + aR_2 - S_2(\beta_{21}I_{21} + \beta_{22}I_{22} + \sigma\beta_{11}I_{11} + \sigma\beta_{12}I_{12}), \tag{15}$$

$$\frac{dI_{21}}{dt} = S_2(\beta_{21}I_{21} + \sigma\beta_{11}I_{11}) - (b + c_{21} + d_{21})I_{21}, \tag{16}$$

$$\frac{dI_{22}}{dt} = S_2(\beta_{22}I_{22} + \sigma\beta_{12}I_{12}) - (b + c_{22} + d_{22})I_{22}, \tag{17}$$

$$\frac{dR_2}{dt} = c_{21}I_{21} + c_{22}I_{22} - bR_2, \tag{18}$$

where the first subscript indicates the subpopulation to which the hosts belong and the second subscript which strain is infecting the host. The system presents several equilibria: the free infection equilibrium, which is unstable; and the endemic equilibria with only one strain or both. A numerical exploration shows that the stability depends on parameter σ which determines the degree of isolation between host subpopulations.

When the two subpopulations are in close epidemiological contact ($\sigma \sim 1$) but do not co-habit the same region, the only stable equilibrium is the one in which the less resistant class of rabbits becomes extinct and the more virulent strain excludes the less virulent one. In this case, each host population does not compete for resources, since the subpopulations do not share the same territory. However, there is competition between them because the presence of the more resistant rabbit population results in the extinction of the other. For $\sigma = 0.41$ this equilibrium, as well as any equilibrium in which a class of rabbits or virus strain is excluded, is unstable. The only stable equilibrium is the one in which the two strains coexist locally.

Populations with different levels of mean resistance to myxomatosis have been observed in Britain (Ross and Sanders 1984) and Australia (Parer et al. 1994). The degree of isolation can be important and is mainly determined by the distances involved relative to the mobility of vectors. The solutions of the system (11, 12, 13, 14, 15, 16, 17, 18) for $\sigma = 0.001$ and strains IIIA and IIIB show that in each subpopulation the corresponding dominant strains almost exclude the others, which represent 7 and 0.7% of the total of infected hosts. Thus, for small coupling this mechanism sustains coexistence, but with the non-dominant strains at very low levels. However, epidemiological contact between the subpopulations may be strong. For example, populations on different sides of a creek may have different resistance levels but they are in close epidemiological contact.

Recent data from Australasia (Parer et al. 1994) suggest that field strains of different virulence (ranked by survival time rather than survival rate) are linked with the level of resistance of the host populations at each location. When the wild strains are classified by survival time, as usual, they range from grade III to grade II (although when classified by survival rate they range from grade II to grade I). These data suggest that strain diversity is sustained by the myxomatosis-resistance diversity of the subpopulations of wild rabbits.

The population described by Parer et al. (1994) have four subpopulations at distances ranging from 200 to 700 km and are connected by the Murray-Darling river system. As rabbit colonies are established along the waterway, myxomatosis is transmitted very efficiently (Brereton 1953). The maximum resistance difference among subpopulations is slightly above 30%, a value which is enough to sustain strains in the range III–II. Therefore, each subpopulation can be thought of as reservoir of strains with different virulence, and can originate outbreaks along the river system of the kind considered in our simulations.

Heterogeneity of the local host populations

Patchy environments may sustain coexistence of very similar competing species (Slatkin 1974) or, in general, species with adequate relationships between colonization and extinction rates, among other traits (Tilman 1994). However, under the assumption of a homogeneous rabbit population, as in model (2, 3, 4), exclusion of any inferior competitive virus strain proceeds so fast (one epizootic) at a local level that there is no similar inhibitory effect between related strains to what Slatkin (1974) assumes. However, local populations are not homogeneous: resistance varies from host to host and may change over time for each of them. This local-population host-heterogeneity may achieve similar competitiveness for some of the strains that some parasite strains are very similar competing species, and then may favor coexistence as metapopulations. For parasites, a heterogeneous (local) host population is a heterogeneous environment, since different parasite strains dominate each resistance class of hosts. This host heterogeneity may be thought of as partitioning of resources. However, in this case, any susceptible host is available to any parasite strain. Also, a time of varying host population is a time of varying environment for the

parasite population, and such variation may favor coexistence of competing strains (Chesson 1986).

Essential parameters in metapopulation modeling, such as colonization, dispersal or extinction rates, are difficult to obtain (see, for example, Ims and Yoccoz 1997; Harrison and Taylor 1997) and models for local populations may be useful in such parameter estimations.

Random heterogeneity

In the previous section we have considered each population to be homogeneous. However, there is an important difference, in terms of resistance to myxomatosis, among its members. Experimental observations of survival time present a considerable dispersion of the data (see, for example, Parer et al. 1994). Moreover, some rabbits do not die, but recover and become immune. The differences in the response of individuals to the infection might correspond to a diversity of causes such as genetic diversity, age, level of response of the immune hosts, etc.

For simplicity, we divided the population into only two classes, with different degrees of resistance to myxomatosis. Belonging to a class is a random fact and is not inherited. Therefore, we assume that there is the same probability of a newborn belonging to each class. The model resulting from these hypothesis reads

$$\frac{dS_1}{dt} = \frac{a}{2}(S_1 + S_2 + R_1 + R_2) - bS_1 - S_1(\beta_{11}I_{11} + \beta_{12}I_{12} + \beta_{21}I_{22} + \beta_{22}I_{22}), \tag{19}$$

$$\frac{dI_{11}}{dt} = S_1(\beta_{11}I_{11} + \beta_{21}I_{21}) - (b + c_{11} + d_{11})I_{11}, \tag{20}$$

$$\frac{dI_{12}}{dt} = S_1(\beta_{12}I_{12} + \beta_{22}I_{22}) - (b + c_{12} + d_{12})I_{12}, \tag{21}$$

$$\frac{dR_1}{dt} = c_{11}I_{11} + c_{12}I_{12} - bR_1, \tag{22}$$

$$\frac{dS_2}{dt} = \frac{a}{2}(S_1 + S_2 + R_1 + R_2) - bS_2 - S_2(\beta_{21}I_{21} + \beta_{22}I_{22} + \beta_{11}I_{11} + \beta_{12}I_{12}), \tag{23}$$

$$\frac{dI_{21}}{dt} = S_2(\beta_{21}I_{21} + \beta_{11}I_{11}) - (b + c_{21} + d_{21})I_{21}, \tag{24}$$

$$\frac{dI_{22}}{dt} = S_2(\beta_{22}I_{22} + \beta_{12}I_{12}) - (b + c_{22} + d_{22})I_{22}, \tag{25}$$

$$\frac{dR_2}{dt} = c_{21}I_{21} + c_{22}I_{22} - bR_2. \tag{26}$$

This system has three equilibria: the origin which is unstable; and two endemic equilibria each with only one strain. The susceptible one-strain equilibrium values are $S_{1j} = S_{2j} \equiv S_{0j} = \gamma_{1j}\gamma_{2j}/(\beta_{1j}\gamma_{2j} + \beta_{2j}\gamma_{1j}) > 1$ ($j = 1, 2$, and $\gamma_{ij} \equiv b + c_{ij} + d_{ij}$), and the invasibility condition is $R_{0j} \equiv S_{0i}\left(\beta_{1j}/\gamma_{1j} + \beta_{2j}/\gamma_{2j}\right) > 1 (i \neq j, i, j = 1, 2)$. That is, the jth strain may invade a host population infected with the other strain (and exclude it) only for $R_{0j} > 1$. For the parameter set A, the strain IIIA quickly invades a host population infected by the strain IIIB. For the parameter set B, the strain IIIB invades an infected host population with strain IIIA, but in this case the two strains are competitively almost identical, and therefore invasion takes a very long time. This is an unexpected result, because in the latter case the host population has more resistance than the previous case. This fact may explain, in part, the bias towards higher virulence of the Britain prevalent strains in respect to the Australian ones. As we said above, myxomatosis resistance developed earlier in Australia than in Britain. The first symptom of developing resistance in British rabbits was an increase in the survival time without significant changes in recovery rates, as in set A, which favors the establishment of highly virulent strains like IIIA. A progressive increase in the recovery rates could favor a less virulent strain (like IIIB) becoming dominant. However, exclusion of the other strain may take a very long time. In our simulations we have considered small rabbit populations of about 1,000 individuals under the assumption of homogeneous mixing, which overestimates the time to exclusion. We changed recovery rate values from those of set A to those of set B for some time T between 1 and 5 years. The higher virulence strain is competitively superior only for a short period of time, but this is enough to further maintain the dominant (lower virulence) strain at lower numbers for a very long time.

In Fig. 1a we show the case when $T = 1$ year, and coexistence for more than the 50 years of the two strains, at very similar numbers, is observed. If $T = 5$ years, the lower virulence strain, which is almost always competitively superior, is maintained at very low numbers during the 50 year simulation period. In both cases, strain IIIA is a superior competitor only for a very short period (between some months and about 2 years). Incorporation of the observed heterogeneous response to the disease was enough to produce long-term coexistence. In both cases, mean resistance to myxomatosis of each class of rabbits was kept constant over time. However, in Britain as well as in Australia resistance to myxomatosis has been continuously increasing with time, a fact that has a significant effect on the resulting dynamics favoring the establishment of higher virulence strains. It is likely that the difference between vectors, among others factors, plays a role in determining the different patterns between the British and Australian cases, but dynamical effects, as discussed here, should be taken into account.

Age as a source of heterogeneity

Resistance of an individual rabbit changes with age (Parer et al. 1994; Fenner and Marshall 1954). This fact may provide a mechanism for coexistence. To test this hypothesis we developed an age-structured model in

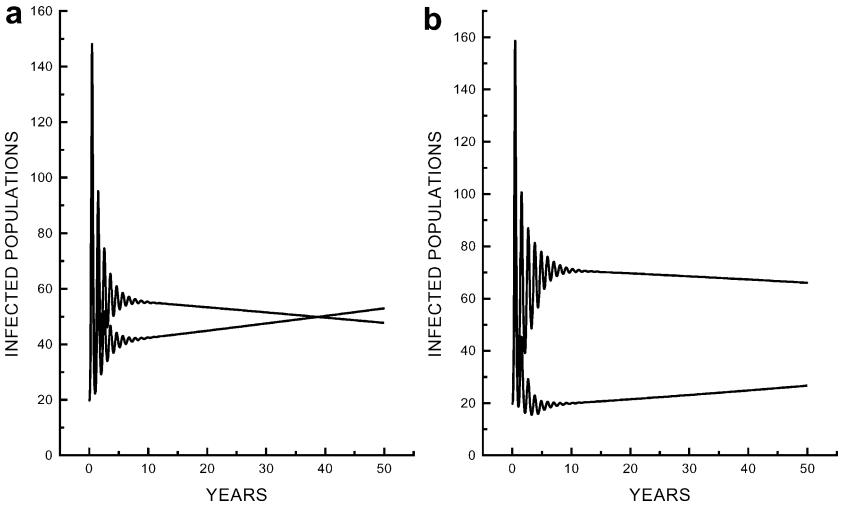

Fig. 1a, b Solutions to the model (7). The recovery rate was changed linearly with time from the values of set A to those of set B in a period T. **a** $T=1$ year. Coexistence in similar numbers is achieved for more than 50 years. **b** $T=5$ years. Strain IIIB is the absolutely superior competitor for about 48 years, however this time is not enough to take over the region. In both cases we have considered a small rabbit population with homogeneous mixing which favors exclusion. In both cases the total population size was less than 1,000

which the only population heterogeneity was host age. We assumed homogeneous mixing over a large enough area since, in this manner, all age classes can be in appreciable numbers.

Rabbits reach maturity between 4 and 6 months of age. We take the maturity age (adulthood) to be 150 days. All the adults have been included in a unique class. Infected individuals become infectious about 1 week after contracting the illness, but this aspect is not incorporated in the model. This delay has been reduced to 2 days to simplify the model (why this choice simplifies the model will soon become apparent).

Juveniles are divided into 2-day age classes and the step time was also set at 2 days. We assume that rabbits are born susceptible, thus disregarding inherited immunity. The first age class with infected members is the 2-day class and the first class with recovered and immune individuals is the 4-day age class. The transfer diagram is as follows

$$
\begin{array}{ccccc}
\mathrm{S}(0) & & & & \\
\downarrow & \searrow & & & \\
\mathrm{S}(1) & & \mathrm{I}(1) & & \\
\downarrow & \searrow & \downarrow & \searrow & \\
\mathrm{S}(2) & & \mathrm{I}(2) & & \mathrm{R}(2) \\
\vdots & & \vdots & & \vdots \\
\vdots & & \vdots & & \vdots \\
\mathrm{S}(N-1) & & \mathrm{I}(N-1) & & \mathrm{R}(N-1) \\
\downarrow & \searrow & \downarrow & \searrow & \downarrow \\
\mathrm{S}(N) & \rightarrow & \mathrm{I}(N) & \rightarrow & \mathrm{R}(N)
\end{array}
$$

where indices between parentheses label age classes. Adults belong to class N ($=75$ in this case). We make mortality rates and recovery rates age-dependent but not time-dependent. The birth rate is strongly seasonal and the beginning of the reproductive season depends on the climate of the region. We take the percentage of the population that is pregnant from New Zealand (Flux 1965), and from these data we estimate the mean number of newborns in 2 days. The values obtained are listed in Table 3. Data from several places show the same pattern: of course, for the northern hemisphere, months must be shifted in 6 months approximately.

We have not taken into account the density dependence of the birth rate (Myers 1960; Rödel et al. 2004) because we assume that the disease maintains the population numbers at low levels.

The choice of initial conditions for the simulation deserves some discussion. In particular, we must choose an age profile because simulations that are run with different initial age profiles present considerable differences (see Fig. 2a).

Because of the seasonal dependence of the birthrate, a stable age profile is never reached. To obtain possible profiles we developed a myxomatosis-free model in which mortality rates include emigration. Adults defend their territory and younger juveniles cannot leave the protection of the family: migration affects only older juveniles. To simulate this effect we add a density-dependent migration term for juveniles between 1 month of age and adulthood in the form

$$b(S_T) = \frac{(b/2)(1-b/2)e^{rS_T}}{1-(b/2)+(b/2)(e^{rS_T}-1)}$$

where S_T is the total number of rabbits and r is a parameter controlling age of emigration pressure. For low rabbit densities, the migration terms approach to $b/2$,

Table 3 Mean monthly birth rate of rabbits from New Zealand (adapted from Flux 1965)

Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
0.04	0.026	0.026	0.013	0.00	0.053	0.073	0.12	0.12	0.12	0.093	0.066

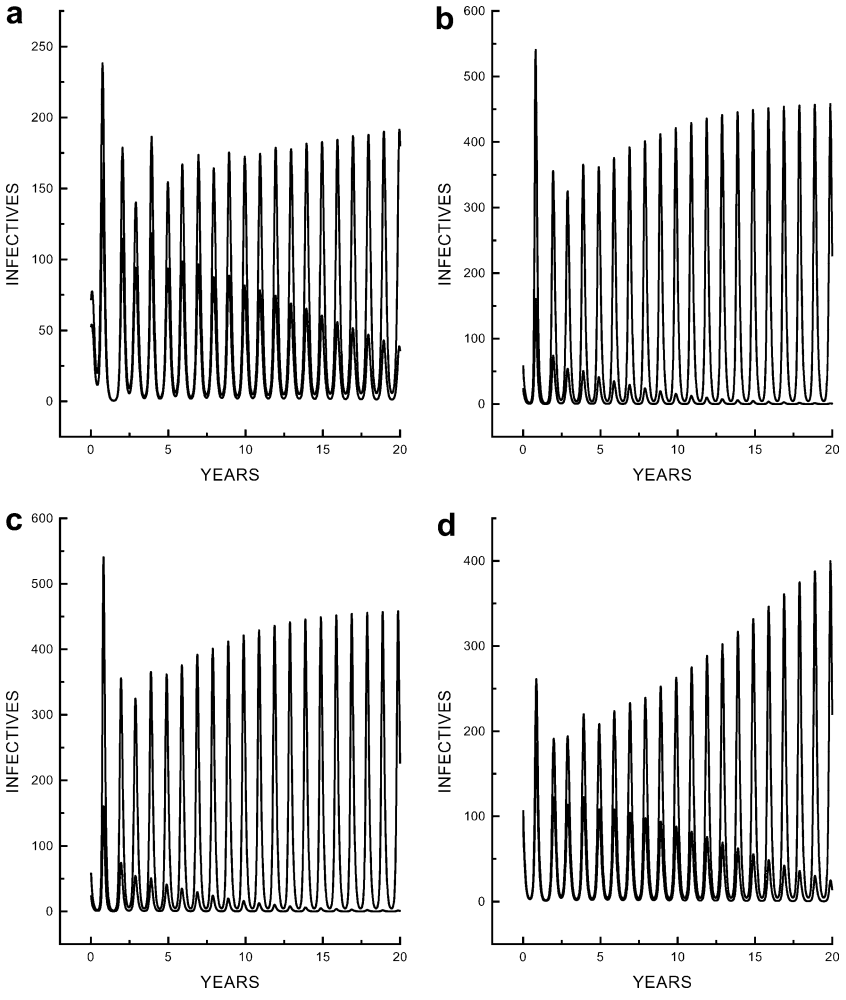

Fig. 2a–d Solutions to the age-structured model for different initial conditions. They show delayed and fast exclusion, depending on the initial age profiles. Birthrates are those estimated in New Zealand (Flux 1965). One individual infected with strain IIIA and one infected with strain IIIB (dominant) were introduced in different seasons: March (**a**), June (beginning of the reproductive season) (**b**), September (**c**) and December (**d**). Set A was used for recovery rate values. The first epidemic outbreak is not shown

while for large densities they are close to $1-b/2$. The model is

$$S(0) = a(t)S(N), \tag{27}$$

$$S(j) = S(j-1)(1-b) \quad \text{for } 0<j<15, \tag{28}$$

$$S(j) = S(j-1)\left[1-\frac{b}{2}-b(S_T)\right] \quad \text{for } 15<j<N, \tag{29}$$

$$S(N) = S(N)(1-b) + S(N-1)(1-b). \tag{30}$$

Adults have offspring at a rate $a(t)$ which changes month by month as in Table 3. The number of hosts in age class j is the number from class $j-1$, less the number of rabbits that die or emigrate. With model (27, 28, 29, 30) we can generate age profiles beginning with some adults and iterating enough time. After the transitory phase, the profiles change only with season. At the beginning of the reproductive season (June in our case) there is a large number of adults and few juveniles. Six months later the situation is the opposite.

We can now introduce the dynamics associated with the disease. The survival rate varies strongly with host age as shown in Table 4 (adapted from Parer et al. 1994).

Table 4 Age dependence of survival rates. Modified from Parer et al. (1994)

Age (days)	35	70	105	140	175
1-CM (%)	19	29	35	40	43

For simplicity we considered only two classes of rabbits: young; and older than 105 days. The latter group was assigned a 20% increase in resistance to myxomatosis. We took constant natural mortality and recovery rates, while disease-induced rates are age dependent. According to the transfer diagram, we see that the classes of newborns, 2- and 4-day-old offspring, and adults are special cases. The following model takes into account these hypotheses and, despite its number of equations, it is conceptually simple.

$$S(0) = a(t)[S(N) + R(N)] \tag{31}$$

$$S(1) = S(0)(1-b-\beta_{11}I_{1J}-\beta_{21}I_{1A}-\beta_{12}I_{2J}-\beta_{22}I_{2A}) \tag{32}$$

$$I_1(1) = S(0)(\beta_{11}I_{1J}+\beta_{21}I_{1A}), \tag{33}$$

$$I_2(1) = S(0)(\beta_{12}I_{2J}+\beta_{22}I_{2A}), \tag{34}$$

$$S(2) = S(1)(1 - b - \beta_{11}I_{1J} - \beta_{21}I_{1A} - \beta_{12}I_{2J} - \beta_{22}I_{2A}) \tag{35}$$

$$I_1(2) = S(1)(\beta_{11}I_{1J} + \beta_{21}I_{1A}) + (1 - b - c_{11} - d_{11})I_1(1), \tag{36}$$

$$I_2(2) = S(1)(\beta_{12}I_{2J} + \beta_{22}I_{2A}) + (1 - b - c_{12} - d_{12})I_2(1), \tag{37}$$

$$R(2) = c_{11}I_1(1) + c_{12}I_2(1), \tag{38}$$

$$S(j) = S(j-1)(1 - b - \beta_{11}I_{1J} - \beta_{21}I_{1A} - \beta_{22}I_{2J} - \beta_{22}I_{2A}), \tag{39}$$

$$I_1(j) = S(j-1)(\beta_{11}I_{1J} - \beta_{21}I_{1A}) + (1 - b - c_{11} - d_{11})I_1(j-1), \tag{40}$$

$$I_2(j) = S(j-1)(\beta_{12}I_{2J} + \beta_{22}I_{2A}) + (1 - b - c_{12} - d_{12})I_2(j-1), \tag{41}$$

$$R(j) = R(j-1)(1 - b) + c_{11}I_1(j-1) + c_{12}I_2(j-1), \tag{42}$$

$$\begin{aligned} S(N) \;=& S(N-1)(1-b-\beta_{11}I_{1J}-\beta_{21}I_{1A}-\beta_{12}I_{2J}-\beta_{22}I_{2A}) \\ &+S(N)(1-b-\beta_{11}I_{1J}-\beta_{21}I_{1A}-\beta_{12}I_{2J}-\beta_{22}I_{2A}), \end{aligned} \tag{43}$$

$$\begin{aligned} I_1(N) =& S(N-1)(\beta_{11}I_{1J}+\beta_{21}I_{1A}+(1-b-c_{11}-d_{11})I_1(N-1) \\ &+S(N)(\beta_{11}+\beta_{21}I_{1A})+(1-b-c_{11}-d_{11})I_1(N), \end{aligned} \tag{44}$$

$$\begin{aligned} I_2(N) =& S(N-1)(\beta_{12}I_{2J}+\beta_{22}I_{2A})(1-b-c_{12}-d_{12})I_2(N-1) \\ &+S(N)(\beta_{12}+\beta_{22}I_{2A})+(1-b-c_{12}-d_{12})I_2(N), \end{aligned} \tag{45}$$

$$\begin{aligned} R(N) \;=& R(N-1)(1-b) + c_{11}I_1(N-1) + c_{12}I_2(N-1) \\ &+R(N)(1-b) + c_{11}I_1(N) + c_{12}I_2(N), \end{aligned} \tag{46}$$

where $I_{1J} \equiv \sum_{j=0}^{53} I_1(j)$, $I_{2J} \equiv \sum_{j=0}^{53} I_2(j)$, $I_{1A} \equiv \sum_{j=54}^{N} I_1(j)$, and $I_{2A} \equiv \sum_{j=54}^{N} I_2(j)$. It is important to note that newborns belong to the lowest resistance class, and only adults can reproduce. The resulting dynamics are highly sensitive to the parameter values, especially to the recovery rates. If recovery rates are low and similar (set A), we find coexistence for long times for some initial age profiles as shown in Fig. 2a. Actually there is exclusion at infinite time, but for more than 10 years the exclusion process cannot be noticed. The age profile of the population at the beginning of the disease greatly determines the proportion of infected rabbits in the near future, as shown in Fig. 2. When the birth rate is taken to be constant [$a = \sum a(t)/12$] exclusion proceeds faster. In this way, seasonality of the birthrate plays a fundamental role in the development of coexistence.

If we use set B for recovery rates, the dominant strain for the older group is excluded after a few epizootics independently of the initial age profiles. The reason is that the recovery rates of the more resistant individuals are large enough, and produce a larger percentage of immune rabbits in the adult population, than in the previous case. The susceptible population is composed of young individuals (non-resistant) and the strain favored by this population competitively excludes the other.

Sire transmission provides a degree of immunity until approximately 2 months of age (Parer et al. 1995). At this age, the individuals belong to the more resistant class and, therefore, results might change. This transmitted immunity has not been incorporated in the present model.

Discussion

The aim of this section is to discuss the possible influence of those aspects omitted previously. The results presented have been obtained in all cases using deterministic models. We believe this is a reasonable starting point, and a good guide for the development of stochastic models as well as metapopulation models. The stochastic effects are expected to be important for some aspects of the dynamics. For example, after a disease outbreak the density of infected individuals is very low and extinction can take place. This feature modifies the dynamics strongly. For low populations of infected individuals, the dynamics will be dominated by the non-deterministic effects (Aparicio and Solari 2001a). When populations of individuals infected with a given strain become extinct, the future of the disease will be dominated by stochastic factors which in some cases may favor inferior competitors just by chance. In some simulations this circumstance was introduced by hand. After an epizootic we introduced a small number of host infected with the less competitive strain in a heterogeneous local host population. This procedure is enough to achieve coexistence in similar proportions of rabbits infected with both strains during the three or four epizootics that followed. Nevertheless, in many places myxomatosis is present at all times (Ross and Tittensor 1986a), and deterministic models are a good and simple description.

Another important point is the parameter determination, mainly the transmission rate (β) because its value has a strong influence on determining the dominant strain. For each level of resistance of the host population, β approximately varies with parasite strain as in (5). It is important to note that this expression was obtained relating the survival time to the percentage of infected fleas present in the individual, without considering the strain. In the original work (Mead-Briggs and Vaughan 1975), we can see that the correlation between survival time and infecting strain is strong, but the relationship of these characteristics to the strain of the

virus presents important fluctuations. On average, an intermediate virulence strain, which kills rabbits in an intermediate time, is the most efficiently transmitted. However, in many cases the dominant strain, in the latter sense, is less efficiently transmitted than other strains for some individuals. This means that the infection rate is strongly stochastic. In the models presented, it always takes its maximum value for the same strain for each homogeneous population. Incorporation of stochasticity in parameter values can reflect the fact that each individual is different to the others and, then, its responses will be different. Moreover, an individual may have different responses at different times. Studies performed with the stochastic counterpart of the deterministic models presented show that the main trends of the deterministic results are followed. The only possible exception to this rule, a situation that deserves further study, is the fluctuation of the infection rate, β, with respect to the viral strain.

Another aspect omitted from this work was system co-evolution. We have developed a genetic-epidemiological model for the simple case of a diploid host with random mating (Aparicio et al., unpublished). The main result shows that although host genotype composition varies smoothly and (relatively) slowly, the arising of the new competitive dominant strain and extinction of the earlier dominant strain is abrupt. The time elapsed since the introduction of myxomatosis to the change in the dominant strain depends on the host genotype composition before myxomatosis and may be a few years or some decades. Therefore, successive different dominant virus strains in local host populations could have arisen at different times in different regions, depending on the genetic pool of such populations before myxomatosis.

Finally, we think that the influence of the virus population dynamics within the host may play a very important role if the strains are mixtures. The immune system response and the survival time, among others factors, can modify the composition of the virus population transmitted with respect to the one received. In this way the appearance and coexistence of several strains could be explained by the interaction between the host and the parasite populations. We have not considered this mechanism since there is no evidence of it reported. The standard classification of myxoma strains can neither rule-out or confirm such possibility.

Conclusions

We have explored different scenarios for the coexistence of competing parasite strains using myxomatosis as an example. The general proposed mechanism can be extended, with suitable changes, to other host-parasite systems. However, work on a concrete example is a good test for the plausibility of the results. It is known that partial cross-immunity (Castillo-Chavez et al. 1988, 1989), no cross-immunity (Castillo-Chavez and Feng 1997) or superinfection (Levin and Pimentel 1981; Nowak and May 1994) can lead to coexistence of competing parasite strains, but this is not the case for myxomatosis, where there is total cross-immunity and multiple infection is unlikely. On the other hand, a classical metapopulation approach requires knowledge of unknown population parameters such as colonization and extinction rates.

We have developed new models for general and known ecological mechanisms, but no plausible coexistence mechanism will work in any real system. In contrast to other systems, the description of totally homogeneous models cannot sustain coexistence. Therefore, we must consider different causes of heterogeneity that can be grouped in two classes: those that involve spatiality for the host populations; and those that consider heterogeneity of local host populations.

The models developed for spatially separated populations are robust. When the populations are homogeneous the essential feature that delays the exclusion is the occupation of the territory by a weak strain. Inclusions of more viral strains or more classes of hosts will not affect the main results. In the case of subpopulations with different degrees of resistance, the situation is similar. In each host subpopulation a different dominant strain is preponderant but the epidemiological contact among host subpopulations ensures local co-circulation. The degree of isolation will strongly depend on the mobility of vectors and will be different for fleas and mosquitoes. The field studies in the Murray-Darling river system (Parer et al. 1994), give some experimental support to this possibility. The incorporation of stochasticity as well as aspects of virus population dynamics might favor the coexistence. These approaches are related to the metapopulation ones where local host populations are habitable or uninhabitable patches for the virus populations.

The heterogeneity provided by classes that consider heterogeneity of local host populations does not result, in the long term, in co-circulation of different viral strains but can delay exclusion for a moderately long time ($\sim$20 years or more). The models developed for this local population may help in the estimation of the parameters related to a classical metapopulation approach. The heterogeneity by random facts of local host populations is a kind of 'spatially heterogeneous environment' for the parasite populations. The age-structured model is simpler than that produced by Dwyer et al. (1990) and leads to very similar results. Age-dependence of the rabbit's resistance (age-heterogeneity), combined with seasonal dependence, is able to delay exclusion for many years. It is an example of the diversity being sustained by a time-varying environment (Chesson 1994). At this point we want to remark that this kind of ''non-equilibrium'' coexistence cannot be disregarded, in spite of the fact that in the equilibrium only one strain survives. The real system is not at equilibrium because parameters change continuously due to the course of the coevolution process. Myxomatosis history is less than 50 years old, and the outcome of the coevolution process depends on the

evolutive changes in both hosts and parasites, and is open-ended.

In summary, we have developed a simple general framework for the study of the dynamics of the myxoma-*Oryctolagus* system that is useful for a general view of the problem, including control, which may be improved in several directions depending on the particular necessities. In the course of our research we had to rely on rough estimations and "reasonable" hypotheses for determining the various coefficients in the models. Higher discrimination in the collection of the field data, including response of wild hosts to all (or several) strains, age dependence, field location of the different strains collected, and existence (or not) of virus reservoirs, will permit further discrimination among the possible scenarios.

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Appendix

Parameter estimation

Birth rates

The different birth rates used in this work have been estimated from the observed pregnant percentages (Flux 1965). These results depend on the region but all are similar and seasonal. We adopted the curve for New Zealand, obtaining from this data the mean percentage of females pregnant for each month. Assuming that the ratio male-female is one to one we can calculate the daily birth rates. The results (scaled by a factor of two) are shown in Table 3.

For aggregated models like (2, 3, 4) we used a constant birth rate. The birth-rate value was adopted with the criteria that the Malthusian population growth of the aggregated model should match the growth in the age-structured model. A value of three year^{-1} provides an excellent match between both model solutions.

Mortality rates

Natural mortality (from causes other than myxomatosis) it is not as strongly seasonal as the birth rate but is age-dependent (Myers 1970; Wheeler and King 1985). The 'natural' mortality decreases with age. It is higher for juveniles than for subadults, and still smaller for adults. The solutions shown in this work were obtained using constant mortality rates, although we have considered age-dependent mortality rates in some cases not reported here. Usually, the death rate is obtained by means of capture-recapture methods and a lower limit of 0.004 day^{-1} = 1.5 year^{-1}(Wheeler and King 1985) was estimated.

Recovery rate and myxomatosis-induced mortality

Disease-induced mortality is estimated as the inverse of the mean survival time for the infected individuals that die (T). For myxomatosis, the disease-induced death rate (d) is usually called virulence (but see Parer et al. 1994).

The recovery rates were obtained from the percentage of mortality caused by each myxoma strain. If the survival for a strain is k (and initially there are I_0 infected individuals) the number of recovered individuals at time t is given by

$$R(t=\infty) = cI_0 \int_0^\infty e^{-(c+d)t} dt = \frac{kI_0}{100}$$

it follows that

$$c = \frac{kd}{100-k}. \tag{47}$$

From the experimental values k and $T = d^{-1}$, we estimated the values of c using (47).

Development of disease resistance and its characterization

We say that a rabbit is 20% more resistant that an unselected domestic rabbit if its survival time is 20% longer for each strain. Naturally this assumption does not always hold, but in many cases is close to the observations (Ross and Sanders 1984; Parer et al. 1994).

We also need to set the case mortalities for the resistant class. We presented two criteria. The first one is to consider a 20% increase in the survival rate ($k = 1-CM$) (*criterion A*). The second one is to consider a case mortality ($CM = 1-k$) decline of 20% (*criterion B*).

In some cases the observations are better fitted with one or the other set of parameters, but in general the experimental values are between these extremes. Finally, as each strain is associated with a survival time, we can obtain the infection rates using (5). For the parameter values considered in this work, the dominant strain in a domestic rabbit population is grade IIIB while in a 20% more resistant rabbit population the dominant strain is IIIA using any of the above mentioned criteria.

Criterion A provides a small variation between old and new recovery rates. This corresponds well with the observations made a few years after the introduction of myxomatosis in Britain (Vaughan and Vaughan 1968). On the other hand, *Criterion B* leads to an appreciable increase in the recovery rates. This resembles the changes observed after the first outbreaks in Australia, and are close to the present observed values. The parameter values used in the simulations are listed in Tables 1 and 2.

Infection rate

There are no direct measurements of the infection rate. It depends on season, age, kind and availability of vectors, disease resistance of host, virus strain, density, and spread of the host population, among other factors.

European rabbits are a sociable species and form reproductive groups. Each group shares a warren and before the reproductive season its size is about seven individuals but this number increases with the newborns. Within a warren, the homogeneous mixing assumption is a good approximation and we can take an infection rate independent of warren size. The same holds if there are some warrens very close to each other. The probability of an infected rabbit from one warren infecting a susceptible from another warren is much smaller than the probability of intra-warren infection.

Pre-myxomatosis densities in some rabbit-populated areas were about 50–80 rabbits per ha (Bonino and Amaya 1985), and as high as 200 rabbits per ha in others (Williams et al. 1995). We considered that the post-myxomatosis numbers are around 20% of their original values, hence we set the value of β such that for the dominant strain endemic-equilibrium of the model (2, 3, 4) the total population is 20% of the carrying capacity (approximately 10 rabbits per ha in our simulations). For domestic rabbits and strain IIIB, this value is 1.8805 year^{-1}. Simulations performed with a two-dimensional arrangement of N warrens indicate that the intra-warren value of β_i scales with the number of warrens considered, if the solution is going to agree roughly with the solutions of the homogeneous model (2, 3, 4) with infection rate β_h, this is $N\beta_h = \beta_i$, with N the number of warrens. Numerical solutions show that after two epizootics both solutions are quite similar.

Stability analysis of the equilibria in (11–26) and (19–26)

We consider the one strain equilibrium of system (11–26)

$$S^0_{1j} = \frac{\gamma_{1j} I^0_{1j}}{\beta_{1j} I^0_{1j} + \sigma\beta_{2j} I^0_{2j}},\ S^0_{2j} = \frac{\gamma_{j2} I^0_{2j}}{\beta_{2j} I^0_{2j} + \sigma\beta_{1j} I^0_{1j}},$$
$$I^0_{2j} = \frac{(a-b)[(\gamma_{j2}/\sigma A_{2j}) - (\gamma_{1j}/A_{1j})]}{\beta_{2j}(\sigma - \sigma^{-1})},$$
$$I^0_{1j} = -\frac{\gamma_{1j}(a-b) + A_{1j}\beta_{2j} I^0_{2j}}{A_{1j}\beta_{1j}},$$
$$R^0_{1j} = (c_{1j}/b) I^0_{1j},\ R^0_{2j} = (c_{2j}/b) I^0_{2j},$$

where $\gamma_{ij} = b + c_{ij} + d_{ij}$ and $A_{ij} = (a/b)c_{ij} - \gamma_{ij}$.

The linearization of the system around the equilibrium point leads to the matrix

$$\begin{bmatrix}
a-b-\sum\beta I & \beta_{11}S^0_{1j} & \beta_{j2}S^0_{1j} & a \\
\beta_{11}I^0_{11} + \sigma\beta_{21}I^0_{21} & \beta_{11}S^0_{1j} - \gamma_{11} & 0 & 0 \\
\beta_{11}I^0_{11} + \beta_{21}I^0_{21} & 0 & \beta_{12}S^0_{1j} - \gamma_{12} & 0 \\
0 & c_{11} & c_{12} & -b \\
0 & \sigma\beta_{11}S^0_{2j} & -\sigma\beta_{12}S^0_{2j} & 0 \\
0 & \sigma\beta_{11}S^0_{2j} & 0 & 0 \\
0 & 0 & \sigma\beta_{12}S^0_{2} & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}$$

$$\begin{bmatrix}
0 & -\sigma\beta_{21}S^0_{1j} & -\sigma\beta_{22}S^0_{1j} & 0 \\
0 & \beta_{21}S_0 & 0 & 0 \\
0 & 0 & \sigma\beta_{22}S^0_{1j} & 0 \\
0 & 0 & 0 & 0 \\
a-b-\sum & 0 & -\beta_{22}S^0_{2j} & a \\
\beta_{21}I^0_{21} + \sigma\beta_{11}I^0_{11} & \beta_{21}S^0_{2j} - \gamma_{21} & 0 & 0 \\
\beta_{22}I^0_{22} + \sigma\beta_{12}I^0_{12} & 0 & \beta_{22}S^0_{2} - \gamma_{22} & 0 \\
0 & c_{21} & c_{22} & -b
\end{bmatrix}$$

where $\sum\beta I \equiv \beta_{1j}I^0_{11} + \beta_{21}I^0_{21} + \sigma(\beta_{21}I^0_{21} + \beta_{22}I^0_{22})]$.

We consider the stability of these equilibria for different values of σ. For $\sigma = 1$ the only stable equilibrium is the one in which the IIIA strain excludes the IIIB strain. For $\sigma = 0.41$ this equilibrium becomes unstable.

A similar situation holds in the case of system (19–26). Now, the one-strain equilibrium is

$$S^0_{1j} = S^0_{2j} \equiv S^0$$

and

$$\gamma_{1j} I^0_{1j} = \gamma_{2j} I^0_{2j},\ \ S^0 = \frac{\gamma_{1j} I_{1j}}{\beta_{1j} I^0_{1j} + \beta_{2j} I^0_{2j}},$$
$$I^0_{1j} = \frac{(a-b)\gamma_{1j}}{\left(\beta_{1j} + \beta_{2j}\frac{\gamma_{1j}}{\gamma_{2j}}\right)\left[\gamma_{1j} - \left(c_{1j} + c_{2j}\frac{\gamma_{1j}}{\gamma_{2j}}\right)\frac{a}{2b}\right]},$$
$$I^0_{2j} = \frac{\gamma_{1j}}{\gamma_{2j}} I^0_{1j}, R^0_1 = \frac{c_{11}}{b} I^0_{11},\ \ R^0_2 = \frac{c_{21}}{b} I^0_{21}.$$

The matrix of the linearization reads:

$$\begin{bmatrix}
\frac{a}{2}-b-\sum & \beta_{12}S^0_j & \beta_{21}S^0_j & \frac{a}{2} \\
\sum & \beta_{11}S^0_j - \gamma_{11} & 0 & 0 \\
0 & 0 & \beta_{12}S^0_j - \gamma_{12} & 0 \\
0 & c_{11} & c_{12} & -b \\
\frac{a}{2} & -\beta_{11}S^0_j & -\beta_{12}S^0_j & \frac{a}{2} \\
0 & \beta_{11}S^0_j & 0 & 0 \\
0 & 0 & \beta_{12}S^0_j & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}$$

$$\begin{bmatrix}
\frac{a}{2} & -\beta_{21}S^0_j & \beta_{22}S^0_j & \frac{a}{2} \\
0 & \beta_{21}S^0_j & 0 & 0 \\
0 & 0 & \beta_{22}S^0_j & 0 \\
0 & 0 & 0 & 0 \\
\frac{a}{2}-b-\sum\beta I & -\beta_{21}S^0_j & -\beta_{22}S^0_j & \frac{a}{2} \\
\sum\beta I & \beta_{21}S^0_j - \gamma_{21} & 0 & 0 \\
0 & 0 & \beta_{22}S^0_j - \gamma_{22} & 0 \\
0 & c_{21} & c_{22} & -b
\end{bmatrix}$$

with $\sum\beta I \equiv [\beta_{1j}I^0_{11} + \beta_{21}I^0_{21} + \beta_{21}I^0_{21} + \beta_{22}I^0_{22}]$.

If we assume that we have domestic classes and 20% more resistant classes, then the equilibrium with only strain IIIB is stable for set B and unstable for set A, while for the equilibrium with strain IIIA we have the opposite situation.

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