Ecological Monographs, 60(4), 1990, pp. 423–447

A SIMULATION MODEL OF THE POPULATION DYNAMICS AND EVOLUTION OF MYXOMATOSIS[1]

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Abstract. Myxoma virus was released into Australia to control the introduced European rabbit, *Oryctolagus cuniculus.* Within a few years after introduction, the virulence of the virus had declined to an intermediate level, while the resistance of field rabbits had increased sharply. In the nearly 40 yr since the disease was introduced, host resistance has continued to increase, while viral virulence has only recently begun to show signs of counter-increases in some areas. The two questions of interest are thus: Is this system in a coevolutionary arms race (Dawkins and Krebs 1979); that is, will both host and pathogen continue to evolve antagonistically? Will the virus continue to control the rabbit in the future?

We present a simulation model based loosely on previous host–pathogen models (Anderson and May 1979), but with detailed accounting of the virus titer in infected hosts, and using realistic estimates of the demographic parameters of the rabbit, including age structure and seasonally varying reproduction.

For a single virulence grade, by varying the non-disease (or "natural") mortality of the rabbit, the age at first reproduction of the rabbit, and the virulence grade of the virus, we explored the parameter range for which the rabbit population is controlled. For the most prevalent grades of the virus, grades IIIB and IV, the virus can control the rabbit for most realistic values of natural mortality and age at first reproduction. However, control is dependent on both natural mortality and virus virulence. Since natural mortality varies both geographically and seasonally, the usefulness of the virus may vary geographically and seasonally, and management policies must be sensitive to this variation.

When competing against several virus strains that together encompass the complete range of virulence seen in the field, a strain of grade IV virulence competitively excludes strains of all other grades. This competitively dominant grade is close to the most prevalent virulence grades seen in the field. We discuss possible mechanisms of coexistence, including local competitive exclusion with global persistence, variability in host resistance, high mutation rates, and trade-offs between within-host and between-host competitive ability.

By examining the effects of flea transmission efficiency, we are able to show that, contrary to commonly held belief, whatever effect fleas have upon the outcome of selection on virulence cannot be due to differences in transmission efficiency between fleas and mosquitoes.

Finally, by including host resistance, we improve our prediction of the most prevalent grade of virulence. We conclude that control of the rabbit by the virus is likely for the near future, but that until we understand the genetics of resistance in the rabbit and the relationship between resistance and virulence for different grades of virulence, we cannot make a useful prediction of the long-term state of this system.

Key words: biological control; coevolution; disease transmission; epizootiology; myxomatosis; Oryctolagus cuniculus; *population dynamics; simulation model; virulence.*

INTRODUCTION

The introduction of myxoma virus to control the European rabbit, *Oryctolagus cuniculus,* represents one of the great successes of biological control. The virus, which causes the often fatal disease myxomatosis, was successfully introduced in the early 1950s into Australia, England, and France, and in each case resulted in huge reductions in the rabbit population. Within a few years, the virulence of the virus declined, and the resistance of the rabbit increased, as a result of simultaneous evolutionary changes in both host and pathogen. Because the mechanism of natural selection that

[1] Manuscript received 27 February 1989; revised 4 January 1990; accepted 5 January 1990; final version received 12 February 1990.

caused these changes is reasonably well understood, and because the changes in both virus and rabbit occurred on a time scale of at most a decade, the myxoma–*Oryctolagus* association is a textbook example of host–parasite coevolution.

Although the myxoma–*Oryctolagus* system has been intensively studied, it is not yet clear whether a balance will be reached between host resistance and viral virulence, or whether the system will continue to evolve. The issue is whether this coevolutionary system is an "arms race" (Dawkins and Krebs 1979), in which each species is perpetually evolving new adaptations to counter the defenses of the other, or whether it will tend to some kind of equilibrium (Levin and Lenski 1985). The practical question for the myxoma–*Oryctolagus* system is whether viral virulence can evolve rapidly enough to allow the virus to continue to be an effective control agent, or whether rabbit resistance will finally outstrip viral virulence.

In this paper, we present the results of simulations of a set of models of the myxoma–*Oryctolagus* system. Our ultimate goal in modelling this system is to predict how both the virus and the rabbit will evolve, and especially whether the virus will continue to be useful in rabbit control. Our more immediate goal, however, is to illustrate the usefulness of the mathematical theory of epidemiology in studying epizootics of animal diseases. Great strides have been made in adapting the theory of human infectious diseases to animal diseases, notably by Anderson and May (1979). In the present paper, we use this theory to provide some guidance for the management of rabbits in Australia.

The paper is in five sections. In the first, we present a brief history of the rabbit–myxoma interaction in Australia and Europe, focusing on recent developments that have received little attention in the ecological literature. By so doing, we summarize the wealth of data that are relevant to our modelling efforts. In the second section, we review some of the relevant mathematical background used in our modelling approach. For example, previous models have presented mechanisms by which selection can favor myxoma strains of intermediate or reduced virulence (Levin and Pimentel 1981, Anderson and May 1982). As we show in the third section, however, the data available on this system allow us to build into our model a mechanism that is more biologically intuitive. First of all, we incorporate differences in infectiousness as a function of time since infection; although this is a fundamental feature of insect-vectored diseases such as myxomatosis, it rarely is included in mathematical models. Second, we include vector efficiency, as the myxoma virus can be transmitted by several species of insect that are believed to have very different impacts on rabbit populations. Lastly, we make a first step towards building a coevolutionary model of the system. To do this, we tie the epidemiological parameters of the virus together by finding expressions relating each to the mortality rate of infected rabbits. This enables us to view each virus strain as a variant on a basic theme, paving the way for a coevolutionary model of the system.

In order to make the model useful for management, we build a realistic and detailed model of the population dynamics of the rabbit, one that is based closely on field data. The distinguishing characteristic of our model is thus the combination of a biologically accurate description of the interaction between host and virus with realistic host population dynamics, at the cost of analytic tractability.

In the fourth section, we show that these innovations allow us to (1) make a quantitatively accurate prediction of the outcome of selection upon viral virulence, (2) explore the relationship between virulence and control, as well as the relationship between different methods of control, and (3) make a preliminary prediction of the outcome of coevolution in this system. In the final section, we discuss the implications of these results, concentrating especially on the data that are needed to improve our prediction of the outcome of coevolution in the model, and on general approaches to building coevolutionary models of host–pathogen systems.

As a caveat, we note that even though our model is more detailed than previous models, there are certain things that we are not able to do. We do not attempt to make yearly predictions of the size of the rabbit population in a particular area, nor can we make year-to-year predictions of the success of different management options. Instead, by developing a better understanding of the most important influences on rabbit population dynamics, we hope to point the way to improved control strategies. Second, we do not attempt to predict quantitatively the time course of the evolution of either the virus or the rabbit, as the data are not detailed enough to allow this. Although we could have done this by using conventional population or quantitative genetic models of the genetic structure of the rabbit population, we felt that the limitations on knowledge of the genetics of the relevant traits argued for a phenotypically based model. As a result, we simply predict the outcome of evolution, and only consider the time course of evolution qualitatively.

What we are, and are not, able to do with the model is dependent on the model's structure. To some extent we constrained our model to include only parameters that could be estimated from available data. Nevertheless, we have more confidence in the values of some parameters than others. For example, the published data are inadequate for predicting the outcome of coevolution between virus and host. However, our attempt to make this prediction allows us to illustrate how to go about building an ecologically meaningful model of the coevolution of host and pathogen, and to make clear what data are needed before one can build a truly useful coevolutionary model. This is true in general for our model-building efforts. We present a number of useful simulation results, and where the model's results are obviously unrealistic, our modelling

TABLE 1. Virulence of field isolates of myxoma virus in Australia. Data show percentage of all field samples falling into each virulence grade (Fenner 1983).

	Virulence grade					
	I	II	III	IV	V	
Mean rabbit survival time (days)	<13	14–16	17–28	29–50	>50	
Case mortality* (%)	>99	95–99	70–95	50–70	<50	
			% of samples in grade			No. of samples
1950–1951	100					
1952–1955	13.3	20.0	53.3	13.3	0	60
1955–1958	0.7	5.3	54.6	24.1	15.5	432
1959–1963	1.7	11.1	60.6	21.8	4.7	449
1964–1966	0.7	0.3	63.7	34.0	1.3	306
1967–1969	0	0	62.4	35.8	1.7	229
1970–1974	0.6	4.6	74.1	20.7	0	174
1975–1981	1.9	3.3	67.0	27.8	0	212

* Mortality of rabbits infected with the virus.

approach nevertheless illustrates widely useful techniques.

History of the myxoma—Oryctolagus cuniculus *association in Australia*

Myxomatosis originated in the South American jungle rabbit, *Sylvilagus brasiliensis,* in which it is a mild disease that rarely kills its host (Fenner and Ratcliffe 1965). However, when it infects the European rabbit *Oryctolagus cuniculus,* myxomatosis usually is fatal (Fenner and Ratcliffe 1965).

Myxoma virus, the causative agent of myxomatosis, was introduced into Australia in order to control the introduced species *O. cuniculus,* which had become a serious pest of sheep and cattle grazing lands. The disease began to spread rapidly in 1950–1951, and was successful at controlling *O. cuniculus* populations throughout much of Australia; although quantitative data are scarce, at some sites rabbit populations were reduced by >90% (Fenner and Ratcliffe 1965, Fenner and Myers 1978).

At the same time that the disease was reducing the rabbit population of Australia, both virus and host were undergoing evolutionary changes. In the year that the disease was introduced into Australia, the fraction of infected rabbits that died was in excess of 99%. Within a year, however, this fraction, termed the "case mortality," was as low as 90%, and in successive years it declined further (Fenner and Ratcliffe 1965).

Fenner and his co-workers measured the genetic changes in the rabbit and the virus independently by carefully establishing baseline genetic strains for both rabbit and virus. Both virus virulence and rabbit resistance were measured in terms of the case mortality of a group of rabbits that had been injected with the virus. The virulence of field samples of the virus was measured in terms of the case mortality each strain produced in groups of rabbits from an unselected, domestic laboratory strain of *O. cuniculus.* The resistance of rabbits from different field populations was measured in terms of their case mortality when injected with one strain of the virus, a particular field isolate labeled KM13 (Fenner and Ratcliffe 1965).

In order to keep track of the decline in virus virulence, Fenner and his colleagues classified field samples of the virus into categories that they termed grades (see Table 1). The most virulent strains, those killing >99% of infected laboratory rabbits, were placed in grade I, while the least virulent strains, those killing <50% of infected laboratory rabbits, were placed in grade V, with the intermediate strains falling in grades II, III, and IV. Table 1 shows the decline in virulence of the virus as a reduced percentage of grades I and II, and an increased percentage of grades III and IV. The strain used to introduce the disease was in grade I; however, as early as 1952, most field isolates of the virus were in grades III and IV (Fenner and Ratcliffe 1965).

Fig. 1, from Marshall and Douglas (1961), shows the increase in the resistance of rabbits from the field, measured as a decline in the case mortality of rabbits in-

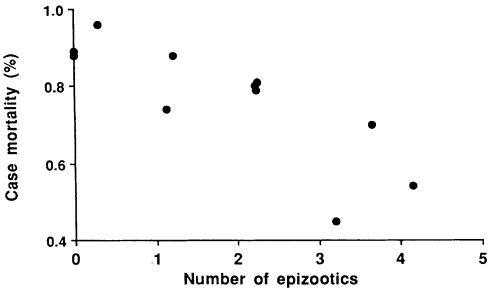

FIG. 1. Decline in case mortality (mortality of infected animals) of field-collected non-immune rabbits over time. Vertical axis represents the case mortality (%) of a group of rabbits challenged with a grade III strain of the virus. Horizontal axis represents the number of epizootics that the source population had experienced, weighted by the proportion immune after each epizootic (from Marshall and Fenner 1957).

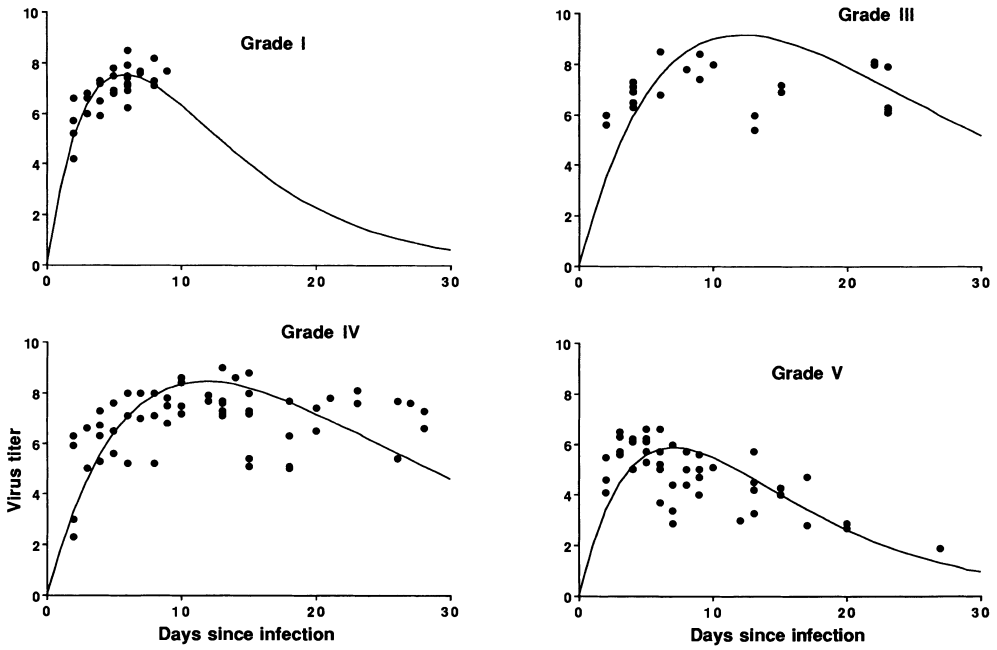

FIG. 2. Virus titer vs. time since infection for four different virus strains. Points represent data from Fenner et al. (1956). Solid lines represent best fit to Ricker curve, $v = k_1te^{-k_2t}$ where v is virus titer (concentration of virus particles in skin of an infected rabbit), t is time since infection, and k_1 and k_2 are constants (units of virus titer in $\log_{10}$ rabbit infectious doses; Fenner et al. 1956). Curves were fit using linear regression following log transformation, $\ln(v/t) = \ln(k_1) - k_2t$. The virus strains and the fit of a Ricker curve to each set of points are as follows (see Fenner et al. 1956): (a) Grade I—Standard lab strain (SLS) ($r^2 = 0.918$, $n = 35$); (b) Grade III—KM13 ($r^2 = 0.911$, $n = 48$); (c) Grade IV—Uriarra III ($r^2 = 0.884$, $n = 24$); (d) Grade V—Neuromyxoma ($r^2 = 0.913$, $n = 62$).

jected with the KM13 strain, as a function of the number of not-quite-annual epizootics that the population had experienced. The average case mortality of rabbits injected with this strain declined from nearly 90% after the first epizootic, in 1950–1951, to <30% after about seven epizootics, 8 yr later.

The increased genetic resistance of the rabbit was due to the disease-induced mortality of genetically susceptible rabbits, while the decline in the frequency of the more virulent strains of the virus depended more specifically upon the interaction between the virulence of the virus and its transmissibility by the vector. When myxomatosis was introduced into Australia, the main vectors of the disease were a few species of mosquito, notably *Anopheles annulipes* (Fenner and Ratcliffe 1965). As Fenner et al. (1956) demonstrated in the laboratory, the virus strains of high virulence, the grade I and II strains, kill their hosts so quickly that the probability that they will be transmitted is low. On the other hand, since the virus is transmitted mechanically on the mouthparts of the mosquito, virus strains of lower virulence, notably the grade V strains, produce such small numbers of virus particles in the skin of their hosts that the mosquito vector is unlikely to pick up an infectious dose from rabbits infected with these strains. The most successful strains are thus of intermediate virulence, as has been observed in the field.

In Fig. 2, we have plotted data from Fenner et al. (1956) showing virus titer, which is a measure of the concentration of virus particles in the skin of an infected rabbit, as a function of the time since the rabbit was infected. As can be seen in Fig. 2a, the grade I strain of the virus produces a very rapid increase in virus titer, but kills its host soon after the virus titer has reached a high level. Fig. 2d shows that the least virulent grade V strain produces a low virus titer that rapidly falls away. In contrast, the grade III and IV strains (Fig. 2b and c) produce a high virus titer and allow their host to survive for a relatively long time.

Field experiments later confirmed the competitive superiority of strains of intermediate virulence. When a grade I strain was introduced into a field population, it was outcompeted by an indigenous grade III strain, and infected a relatively small number of rabbits (Fenner et al. 1957).

This interpretation of the coevolution between myxoma virus and *O. cuniculus* suggests that ultimately viral virulence will increase as the resistance of the

TABLE 2. Virulence of field isolates of myxoma virus in the Mallee region vs. the rest of Victoria. Data show percentage of all field samples falling into each virulence grade (Fenner 1983).

	Virulence grade					No. of samples
	I	II	III	IV	V	
			Mallee			
1959–1963	0	4.3	57.1	34.3	4.3	70
1964–1966	2.0	0	64.7	31.3	2.0	51
1967–1969	0	0	68.1	31.9	0	31
1970–1974	1.0	6.9	77.5	14.7	14.7	102
1975–1980	13.3*	7.6	60.0	19.0	0	105
1984–1985	0	23.0	69.2	7.6	0	13
			Victoria less Mallee			
1959–1963	2.1	12.4	61.2	19.5	4.7	379
1964–1966	0.4	0.4	63.5	34.5	1.2	255
1967–1969	0	0	61.6	36.4	2.0	198
1970–1974	0	1.4	69.4	29.2	0	72
1975–1980	0	4.3	50.0	45.6	0	46
1984–1985	0	14.2	80.0	4.7	0	21

* High frequency of grade I strains partly due to intentional release of these strains.

rabbit increases, at least if one assumes that the effect of increased host resistance within a rabbit is such that each strain essentially becomes less virulent. As can be seen in Table 1, preliminary evidence indicates that this may be happening, as the proportions of grade I and II strains isolated from the field have increased since 1970 in Australia. More recent data, up to 1984–1985, have confirmed this trend for grade II, and also suggest that grade IV may be declining while grade III is increasing (Table 2; J. R. Backholer, *personal communication*).

However, there are three caveats that complicate this simple explanation of the myxoma–*Oryctolagus* system. First of all the rabbit flea, *Spilopsyllus cuniculi,* an alternative vector of the disease, was introduced into parts of Australia in the late 1960s and early 1970s (Williams and Parer 1972, King and Wheeler 1985). At first it was thought that fleas would only move from a rabbit when the rabbit was dead, so that fleas would favor the seleciton of virulent strains of the virus, but fleas were subsequently shown to be quite mobile (Williams and Parer 1972). Nevertheless, in rabbit populations in which *Spilopsyllus* is the most important vector of the disease, there is more severe disease-induced mortality among young rabbits than in populations in which the mosquito is the more important vector (Cooke 1983). Although the flea has been shown to be somewhat less efficient at transmitting the virus than is the mosquito (Mead-Briggs and Vaughan 1975), it is not obvious how this would affect the outcome of evolution in the virus. It is possible, however, that the increase in virulence of the virus in the field is due to the replacement of the mosquito vector by the flea. In fact, in Britain, where the virus is vectored mainly by fleas, the predominant strains of the virus are considerably more virulent (Cooke 1983).

The second caveat is that Sobey and Conolly (1986) report evidence indicating that some of the observed resistance of rabbits in the field may be nongenetic. They show that offspring of parents from lines that had never been exposed to the disease had higher resistance to the disease if their parent doe had been mated up to 7 mo earlier with a buck that had recovered from the disease. This indicates that there is some kind of virus resistance factor in the semen of resistant bucks. The effect seems to be somewhat strain-specific, in that bucks that have recovered from a particular strain confer upon the doe's later offspring higher resistance to that strain than they do to other strains.

Finally, the rabbit's capability to evolve resistance to the virus may be limited. In selection experiments carried out between 1968 and 1974, Sobey and Connolly (1986) were unable to produce much increase in the resistance of laboratory rabbits. Although there is no complementary evidence from the field, it is possible that the resistance of field populations already has ceased, or eventually will cease, to increase.

History of the myxoma–Oryctolagus cuniculus *association in Europe*

Myxomatosis was introduced into France in June of 1952, whence it was carried to Great Britain in 1953. In both France and Great Britain, the disease caused heavy mortality; by 1955, 90% of the wild *Oryctolagus* in Great Britain are believed to have died of the disease (Ross 1982). In both Great Britain and France the virulence of the virus decreased, but with different outcomes. In France, levels of virulence are lower than in Australia, with grade IV achieving dominance by 1968 (Table 3; to our knowledge, no data on the distribution of virulence in France have been published since then). In contrast, in Great Britain, levels of virulence have been dramatically higher, as grade II strains have remained relatively high, with grade III strains being dominant after the initial decline in virulence from grade I (Ross 1982, and Table 3). As mentioned earlier, virulence may be higher in Great Britain because the flea *S. cuniculi* is essentially the only vector.

TABLE 3. Virulence of field isolates of myxoma virus in Europe. Data show percentage of all field samples falling into each virulence grade (Fenner 1983).

	Virulence grade					No. of samples
	I	II	III	IV	V	
			Great Britain			
1953	100					
1962	4.1	17.6	63.6	14.0	0.9	222
1975	1.6	24.2	64.9	9.4	0	125
1974–1980	0	25.0	70.4	4.5	0	449
			France			
1953	100					
1962	2.8	19.3	34.6	20.8	13.5	
1968	2.0	4.1	35.1	58.8	4.3	

TABLE 4. Increase in resistance of *Oryctolagus* in Great Britain, as indicated by the case mortality (*CM*) of groups of rabbits challenged with a particular virulence grade of myxoma virus (Fenner 1983, after Ross 1982).

Location	Year	Grade of test virus	*CM* (%)	No. tested
Norfolk	1966	III	90	41
	1967	III	94	34
	1968	III	86	71
	1969	III	84	74
	1970	III	59	27
	1974	III	13	15
	1974	I	100	11
	1975	I	100	11
	1976	III	21	63
Wiltshire	1978	III	45	71
	1979	II	45	53
	1980	I	56	44

As was the case in Australia, the resistance of rabbits in Great Britain increased dramatically after the disease was introduced. By 1976, the case mortality of wild rabbits infected with a grade III strain had declined from 90–95% to 21% (Ross 1982, and Table 4). This dramatic increase in resistance may also help to explain the higher virulence of the virus in Great Britain.

Introduction to the problem

After two decades of declining viral virulence, Australian field workers began to question whether myxoma was still controlling rabbit populations. Parer (1977) suggested that predators, including introduced feral cats and foxes, play a more important role than the virus in keeping the rabbit in check. More recent tests of this idea have suggested that, to the contrary, the virus remains the major control agent. In particular, when an avirulent strain of the virus was used to inoculate rabbit populations in New South Wales, these populations increased by a factor of 8–12 within only 4 yr (Parer et al. 1985). The multiplication of these experimental populations when immunized with an avirulent strain suggests that the virus is still the major regulator of rabbit populations (Parer et al. 1985). Comprehensive field surveys have confirmed that myxomatosis is an important source of mortality in rabbit populations in many parts of Australia (Gilbert et al. 1987).

The question nevertheless remains of whether the virus will continue to control the rabbit in the future. Because of the complexity of the interaction between virus and host, we have approached this question through modelling. This approach is necessitated by the difficulty and expense of field studies, as well as by the interest of Australian field workers in the future dynamics of this system (J. R. Backholer, *personal communication*).

PREVIOUS MODELS

The myxoma–*Oryctolagus* system has been the focus of much theoretical attention (Lewontin 1965), but the first mathematical model of the system was not published until 1981. Levin and Pimentel (1981) built on the framework of Anderson and May (1979), who had modified the structure of Kermack and McKendrick (1927) to develop a general theoretical approach to epizootics.

The basic epidemiological model presented by Anderson and May (1979) has the form

$$\frac{dS}{dt} = r(S + I + R) - \beta IS - mS \tag{1}$$

$$\frac{dI}{dt} = \beta SI - (\alpha + m + v)I \tag{2}$$

$$\frac{dR}{dt} = vI - mS \tag{3}$$

In this model, the host population is divided into three categories: susceptibles S, infecteds I, and a recovered-and-immune class, R. These divisions ignore age and deme structure, but allow for convenient mathematical analysis (Anderson and May 1979). The three densities (S, I, and R) are measured either as number of individuals or as number of individuals per unit area. In this paper, we use the latter convention.

Births, deaths, and recoveries are assumed to occur at certain characteristic rates. Here, susceptible and recovered-and-immune individuals have the same per capita death rate m (b in the notation of Anderson and May 1979), but infecteds die at the higher per capita rate $\alpha + m$. Infecteds recover from the disease at the per capita rate v. The per capita birth rate is simply r. Finally, infections occur according to βSI, so that the rate of spread of the disease increases with the density of both susceptibles and infecteds (Anderson and May 1979). The function βSI is known in the epidemiological literature as the incidence function, while βI is the force of infection. Although more complicated forms have been considered (Liu et al. 1987), the bilinear form given above is the most common and provides a logical starting point.

This model does not allow for more than one strain of the pathogen, in our case the myxoma virus. However, it does represent the basics of the myxoma–*Oryctolagus* system, in that rabbits that recover from the virus are immune to reinfection.

Anderson and May's (1979) model is an extension of a model presented by Kermack and McKendrick (1927). Kermack and McKendrick (1927) make the realistic assumption that the infectiousness of an infected individual depends on how long that individual has had the disease, but this assumption leads to an analytically intractable model. Kermack and McKendrick (1927) therefore limit their analysis to a sim-

pler model in which infectiousness is independent of time since infection. However, for both of Kermack and McKendrick's models, the only changes occurring in the host population are due to the effects of the disease. While this may be appropriate for many epidemic diseases of humans, in which births and non-disease deaths occur much less frequently than do deaths or immunizations due to disease, it is not appropriate for a disease like myxomatosis in which births and non-disease deaths occur nearly as frequently as do disease-induced deaths and immunizations.

The dynamics of both Anderson and May's (1979) model, and, in slightly different form, Kermack and McKendrick's (1927) model, depend upon the quantity

$$R_0 = \frac{\beta S}{\alpha + m + v}, \tag{4}$$

which is the number of secondary infections that result from a single primary infection. When S is such that $R_0 > 1$, the number of infected individuals will increase; conversely, when S is such that $R_0 < 1$, the number of infected individuals will decrease.

Anderson and May's model can be used to predict the outcome of competition among viral strains by considering the success of a rare strain invading a rabbit population in which a second strain is dominant. In the early stages of invasion, the value of S will be roughly constant. At this quasi-equilibrium, $R_0 = 1$ for the common strain, so S may be calculated from Eq. 4. The strain that maintains the lowest equilibrium value of S will be the competitive dominant, as this S will be such that $R_0 < 1$ for all other strains. Then, by Eq. 4, the competitive dominant will have the highest value of $\frac{\beta}{\alpha + m + v}$, which is thus an evolutionary stable strategy (ESS) for this model (Anderson and May 1982).

Anderson and May (1982) use data from Fenner and Ratcliffe's (1965) definition of the grades of myxoma virus in Eq. 4 to find the ESS for the virus in the following way. Under the assumption of constant mortality, α can be computed as the inverse of survival time, and v can be calculated from the relationship between α, v, and case mortality (CM). Since in the laboratory any individual that becomes infected either recovers or dies from the disease,

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

This can be solved for v, to yield

$$v = \alpha\left(\frac{1}{CM} - 1\right).$$

Anderson and May (1982) calculate values for α and v for each grade, and then fit a curve to v as a function of α. By assuming that β is constant and is the same for each strain, they obtain $\frac{\beta}{\alpha + m + v}$ as a function of α, where α is taken to be a measure of virulence. Since the resulting curve has a distinct peak, there is a value of α that maximizes the ratio. This value lies between the α's for grades IV and V. Although this predicts a lower virulence than the most prevalent grades observed in the field, it is an excellent first approximation, especially since the effects of variation in transmissibility among strains and the evolution of host resistance are not considered.

Massad (1987) modifies Anderson and May's (1982) calculation of R_0 by dropping the assumption that β is constant for all strains. He uses data on the percentage of fleas that transmit different strains of the virus from infected to healthy rabbits (Mead-Briggs and Vaughan 1975) as a measure of β, and uses nonlinear regression to find this β as a function of α. By recalculating R_0 as a function of α, with both β and v now functions of α, Massad (1987) is able to make the more accurate prediction that the optimal grade of the virus will be roughly in grade III.

The first application to myxoma of Anderson and May's (1979) approach was made by Levin and Pimentel (1981), who explain the evolution of virulence in terms of interdemic selection, in the sense that each infected rabbit is a virus deme. Unlike Anderson and May (1982) and Massad (1987), they do not attempt to explain the actual level of virulence in the field; however, they are able to demonstrate stable coexistence of strains by allowing individuals to become infected with both strains. For a particular range of parameter values, the more virulent strain ultimately outcompetes the less virulent strain within the rabbit, if a rabbit is infected with both strains. On the other hand, the less virulent strain has a compensatory advantage, in that it has a longer survival time in singly infected individuals. One problem with Levin and Pimentel's model is that doubly infected individuals are rarely observed in unmanipulated field populations (F. Fenner, *personal communication*), although they have been observed in a field experiment (Parer et al. 1985). Moreover, although this is not critical to their conclusions, Levin and Pimentel do not allow infected rabbits to recover and thus become immune (but see Levin 1983).

The model that we describe here includes both disease-induced immunity and multiple virus strains. In contrast to Levin and Pimentel's (1981) model, however, there is no allowance for doubly infected rabbits.

Description of the Basic Model

Overview of the model

The model that we present here is a hybrid of the models of Anderson and May (1979) and Kermack and

McKendrick (1927) in that, as do Anderson and May (1979), we allow for births and non-disease deaths; but as do Kermack and McKendrick (1927), we allow infectiousness to depend on how long infected individuals have had the disease. Unlike Kermack and McKendrick (1927), however, we are able to use a computer to get around the analytic intractability of the resulting model.

Although our detailed model requires extensive simulations, it nonetheless has several advantages over the earlier models that we have described. First of all, we can utilize the wealth of quantitative laboratory and field data on this system to determine if the available data are sufficient to explain quantitatively the distribution of virulence and the importance of the virus in the field. To do this we use laboratory data on the interaction between virus and host to predict the distribution of virulence in the field. The data we use to make this prediction are thus independent of the data that we use to test the model. Moreover, we use observations of the behavior of the virus within individuals to predict the outcome of selection upon the virus population (Hassell and May 1985). As we shall demonstrate, this allows us to make a fairly accurate prediction of mean virulence.

Second, by using a detailed model of both the epidemiology of the disease and the life history of the rabbit, we hope to link the theoretical question of the determinants of the distribution of virulence in the field with the practical problem of the usefulness of the virus as an agent for the control of the rabbit.

We present the model in two sections. In the first, we describe a model of the epidemiology of the disease; in the second, we include the population dynamics of the rabbit. Because the structural detail of our model strongly depends on the quality of the existing data, model development and parameter estimation are not presented separately.

Epizootiology

In this section, we modify Eqs. 1–3 to incorporate more detail about the epidemiology of the disease; detailed demographic information regarding the host is suppressed until later sections. Because our intent is to use the model for computer explorations, we replace Eqs. 1–3 by an equivalent discrete version that can incorporate day-to-day changes in disease dynamics.

Following Anderson and May (1979) we divide the rabbit population into susceptible, infected, and recovered-and-immune classes. We allow for multiple strains of the virus by subdividing the infected class according to the strain infecting each group.

We assume that an *O. cuniculus* that has recovered from infection with a particular strain subsequently is immune to reinfection with any strain, not just that from which it recovered. Cross-immunity in this fashion has been demonstrated in the laboratory by Marshall and Fenner (1957). Also, as mentioned above, we assume that an infected rabbit cannot be infected by two different strains at the same time.

In order to include multiple strains of the virus, we distinguish among virus strains on the basis of three characteristics of the disease, following Fenner et al. (1956) and Fenner and Woodroofe (1965). First, each strain in the model has a case mortality (CM) and a survival time (T) that are determined from its virulence grade (see Table 1). In the model, the values of CM and T for each grade are in the middle of the range of values for the grade so that, for example, the grade II strain has a CM of 97% and a survival time of 15 d.

We also allow for differences among virus strains in terms of infectiousness, following Fenner et al. (1956). To do this, we could simply assign a different transmission constant, β, to each strain, but there is no way to do this that is not arbitrary. Instead, we explicitly include the growth of the virus population in an individual rabbit by using the data in Fig. 2 to describe the process. We fit these data for each of the four strains to both a parabolic curve and a two-parameter family of negative binomial distributions, the so-called "Ricker" functions,

$$v = k_1 t e^{-k_2 t}.$$

To fit the Ricker equation, we used linear regression to fit the following transformed version,

$$\ln(v/t) = \ln(k_1) - k_2 t$$

(see Fig. 2). For each strain the fit was much better for the Ricker curve (r^2 between 0.88 and 0.91, vs. r^2 between 0.14 and 0.50). We thus use the Ricker curve throughout as a phenomenological description of the temporal dynamics of the virus population within the rabbit. Each strain thus has associated with it two parameters, k_1 and k_2, that describe the shape of this curve for that strain.

The Ricker curve has the biologically reasonable property that it rises more or less linearly and decays exponentially. k_1 can be interpreted as the slope of the initial (linear) rise in virus titer, while k_2 is the reciprocal of the time at which the virus titer reaches its maximum value. Alternatively, k_2 can be interpreted as the rate of decay of virus titer. Thus, for example, grade V has relatively high values of both k_1 and k_2 so that the virus concentration in rabbits infected with this strain rises and declines rapidly.

We used analysis of covariance (ANCOVA) to test whether the regressions used to fit the Ricker curves are statistically distinguishable (Table 5). This analysis indicated that the values of the parameter k_2 (the slope of the transformed data) do not differ significantly among strains ($P = .78$), but the four strains do differ with respect to k_1 (the intercept of the transformed data). Further analysis using a planned comparisons test indicated that the four strains could be split into two groups based on the values of the parameter k_1 (Table 5). That is, the grade I and III strains are not

TABLE 5. Parameter values for linear regression on transformed Ricker curve ($\ln[v/t] = \ln k_1 - k_2 t$, where v is virus titer and t is time since infection) with results of ANCOVA.

Virus virulence grade	k_1*	k_2
I	3.53[a]	−0.1721
III	2.06[a]	−0.0827
IV	1.94[b]	−0.0845
V	2.27[b]	−0.1424
Results of ANCOVA	df = 3, 109 $F = 27.292$ $P < .0001$	df = 1, 109 $F = 0.107$ $P = .744$

* a and b indicate not significantly different by post-hoc contrast, a at $P = .957$, b at $P = .857$. All other contrasts of k_1 values significant at $P < .0001$.

significantly different, nor are the grade IV and V strains, but *either* I *or* III is significantly different from *either* IV *or* V.

The results of these analyses indicate that the virus grades differ only in k_1, the initial rate of rise in titer. Nevertheless, we decided to retain the distinctive k_1 and k_2 values of each grade, for several reasons. First of all, our intent is to use the best-fitting data to examine the consequences of variable infection rates for viral evolution and rabbit population dynamics, rather than to test whether the virus strains are significantly different. Nonsignificant differences may have more to do with the effect of small sample size on the fit of the virus growth curve model than with whether the titer of different strains is truly different over time. In particular, the nonsignificant differences in k_2 are probably due to sparse data for time periods long after infection, especially for the grade I strain. Similarly, the lack of significance for the difference between the k_1's of the grade I and III strains is probably due to the lack of data for the grade III strain.

Our approach has the additional advantage that we describe the virus titer curve for each strain by modifying a single basic curve. Although we may be able to achieve a better fit using a different curve for each strain, using the same curve allows us to view each strain as a variation on some basic plan. This allows a far more intelligible approach to modelling coevolution than would an ad hoc approach.

Fenner et al. (1956: Table 12) also present data demonstrating how virus titer affects the efficiency of disease transmission by the mosquito vector. We used a linear regression model that accurately predicts the probability of transmission as a function of virus titer ($r^2 = 0.97$). Although the rabbit flea *S. cuniculi* recently has become a more important vector than the mosquito *A. annulipes* (Cooke 1983, King et al. 1985), we have chosen to use data on mosquito transmission for several reasons. First of all, grade III and IV strains became the most abundant strains in the field in Australia within only a few years after the introduction of the disease, and have maintained this position until recently, when grade IV strains have begun to decline. Thus, in order to explain the original changes in the distribution of virulence, it is important to focus on the original vector, the mosquito.

Secondly, the relationship between efficiency of transmission and titer for the flea is also linear (Vaughan 1981, $r^2 = 0.98$). Although the slope and intercept of the resulting line are different than those for mosquitoes, the relationship is still linear, and we will show that any differences in transmission efficiency between the vectors have negligible effects (see *Discussion*).

In summary, we use Fenner et al.'s (1956) data on within-host virus dynamics to scale the transmission constant, β, for each strain or virulence grade. Of course, the rate of spread of myxomatosis in the field depends on many factors, especially the availability of vectors. Although the model framework allows exploration of the effects of variation in vector availability, in the interests of simplicity and in the absence of any quantitative data on vector populations, we ignore the population dynamics of vectors. Instead we adjust the maximum value of β in the model so that epizootics in the model last $\approx$8 wk, which is as long as they last in the field (Williams and Parer 1972, Parer et al. 1985). A value of $\beta = 8 \times 10^{-4}$ (in units of per individual per day) produces epizootics that last $\approx$8 wk. β is thus a fitted parameter, the only one in the model.

Using Fenner et al.'s (1956) data gives us four virus growth curves, one for each of grades I, III, IV, and V. This poses two problems. The first is that we do not have parameter values for grade II. The second and more serious problem is that, to include the effects of continuously changing host resistance, we need a continuous distribution of virulence. We have generated such a continuous distribution by considering the interrelationships of the parameters we have defined: case mortality *CM*, survival time *T*, and the two virus concentration parameters k_1 and k_2. We have used these

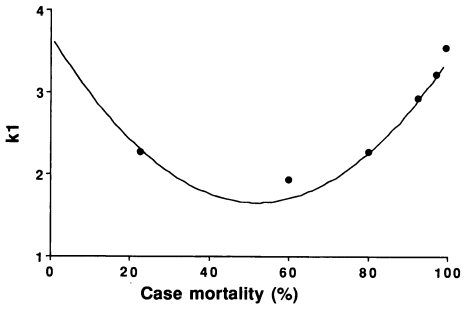

FIG. 3. Virus growth parameter k_1 (from equation $v = k_1 t e^{-k_2 t}$ in Fig. 2) plotted against case mortality of virus (mortality of infected rabbits). Points represent k_1 for each virus grade, and solid line represents parabolic regression ($r^2 = 0.894$, $n = 4$) according to $k_1 = 3.68 - 0.078c + 0.00075c^2$, where c is case mortality (%).

FIG. 4. As in Fig. 3, but for parameter k_2. Solid line represents parabolic regression ($r^2 = 0.891$, $n = 4$) according to $k_2 = -0.265 + 0.0066c - 0.000056c^2$, where again c is case mortality in percent.

four parameters to describe the virulence of the virus, or in other words the severity of the disease it causes.

In practical terms, since we know the case mortality (CM) associated with each virus grade for which we have k_1 and k_2, we simply can perform a nonlinear regression of k_1 and k_2 on CM (Figs. 3 and 4). Similarly, following Anderson and May (1982), we can find T as a function of CM (Fig. 5). Once we have done this, we can consider a virus grade of any level of virulence, not just grades I–V. For example, Fenner and Woodroofe (1965) split grade III into grades IIIA and IIIB, in order to resolve more finely the virulence of field grades of the virus. Since we know the values of CM (and T for that matter) for these two grades, we can find values of k_1 and k_2 for each grade and include them in the model. In short, we do not know the mechanism underlying the relationship between virulence and each parameter, but through curve-fitting we can describe the relationship phenomenologically.

The values of CM, T, k_1, and k_2 for each grade in the model are summarized in Table 6.

For now, we retain Anderson and May's (1979) assumptions that per capita birth and non-disease mortality are constant and thus not density dependent. With the additional assumption that infected individuals do not reproduce, the disease processes that we have just described can be written as

$$S(t+1) = \{(S(t) + r[S(t) + R(t)]\}(1 - m) \cdot \left[1 - \sum_{i=1}^{n} \phi(i, t)\right] \quad (5)$$

$$I(i, 0, t+1) = S(t)\phi(i, t)(1 - m) \quad \text{for } i = 1, \ldots, n; \quad (6)$$

$$I(i, \tau + 1, t + 1) = I(i, \tau, t)(1 - m) \quad \text{for } i = 1, \ldots, n; \tau = 0, \ldots, T_i - 1 \quad (7)$$

$$R(t+1) = R(t)(1 - m) + \sum_{i=1}^{n} [1 - CM(i)]I(i, T_i, t), \quad (8)$$

where t is measured in days and the force of infection $\phi(i, t)$, measured as new infections per susceptible animal, is

$$\phi(i, t) = \sum_{\tau=0}^{T_i - 1} \beta(i, \tau)I(i, \tau, t).$$

As before, S, I, and R refer to susceptible, infected, and recovered-and-immune. $S(t + 1)$ refers to the density of susceptible rabbits at time $t + 1$, $R(t + 1)$ is the density of recovered-and-immune rabbits at time $t + 1$, and similarly for $S(t)$ and $R(t)$. The infected population $I(i, \tau + 1, t + 1)$ is indexed according to infecting strain i, time since infection $\tau + 1$, and time $t + 1$, and $I(i, r, t)$ is defined similarly. n is the number of virus strains present. m is the probability of mortality from non-disease causes, and as described above, $\beta(i, \tau)$ is the probability of infection per susceptible per infective per day. Note that the dimensionless quantity $\alpha/(\alpha + \nu)$ is replaced by $CM(i)$ as the case mortality for the disease, and $1/(\alpha + \nu)$ is replaced by T_i as the average time of infection. Furthermore, survival time in the infectious class is no longer exponential; instead, removals occur after a fixed delay T_i. Obviously, rabbits infected on the same day do not all die at the same time; but since we lack data on actual distributions of survival times, we have opted for the simplest assumption commensurate with the available data.

As can be seen from these equations, susceptibles in the model are exposed to infection from a mixture of infecteds that vary in terms of both the infecting strain and the time since infection. Once a group of susceptibles is infected with a particular strain, their time

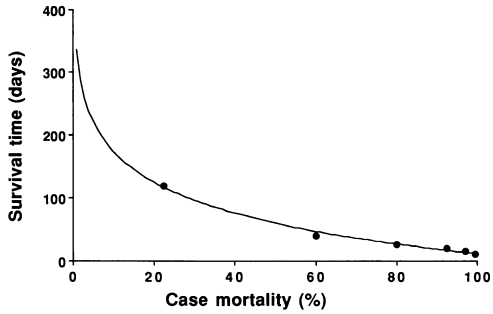

FIG. 5. Mean survival time vs. case mortality (mortality of infected rabbits) for virus virulence grades as defined by Fenner and Woodroofe (1965). Solid line represents linear regression of survival time on log-transformed case mortality ($r^2 = 0.98$, $n = 5$), $T = 334.7 - 70.3 \ln(c)$, where T is survival time in days and c is case mortality as percent.

TABLE 6. Epidemiological parameters of the model for each grade of the virus. CM = case mortality (%), T = survival time (d), and k_1 and k_2 are parameters in the equation $v = k_1 t e^{k_2 t}$, where v = virus titer.

	Viral virulence grade					
	I	II	IIIA	IIIB	IV	V
CM	99.5	97	92.5	80	60	22.5
T	11	15	20	26	40	118
k_1	3.533	3.215	2.923	2.272	1.94	2.265
k_2	−0.1721	−0.1524	−0.1343	−0.0960	−0.0845	−0.1424

course of infectiousness is determined by the transmission function, $\beta(i, \tau)$. For rabbits infected with strain i that have had the disease for T_i time units, a fraction $CM(i)$ die, and a fraction $[1 - CM(i)]$ recover to join the recovered-and-immune class, R.

Note that the state variables S, I, and R are expressed in terms of densities, rather than in terms of absolute numbers. That is, we are not keeping track of each rabbit, but rather classes of rabbits. Thus, $I(i, \tau, t)$ is the density of rabbits at time t that have been infected with strain i for τ days.

Rabbit population dynamics

In our model, the non-disease aspects of the rabbit's population dynamics loosely follow Anderson and May's (1979) model, in that we do not explicitly include any nonlinear effects of predators or resource depletion. As do Anderson and May (1979), we assume that per capita reproduction and per capita natural mortality are independent of rabbit density. It is of course not difficult to incorporate density dependence in order to put a ceiling on population size, and we have done so in simulations not reported here. However, to avoid confusion in our interpretations of the capability of the disease to control the rabbit, we do not treat explicit density dependence here. In fact, there is no evidence to suggest that rabbits in the field are regulated in a density-dependent manner in the absence of the disease (Gilbert et al. 1987), although such regulation would be inevitable at high enough densities. Unlike Anderson and May (1979), we allow reproduction to vary with the season, as the scarcity of susceptible rabbits between breeding seasons is believed to have a significant effect upon the ability of the virus to maintain itself in the field (Fenner and Ratcliffe 1965).

As rabbit reproduction is strongly seasonal, with a strong peak in the spring and a lesser peak in the fall (Gilbert et al. 1987), we have used seasonal data on reproductive output from two sites in Queensland (Texas and Dunroy stations, see Marshall et al. 1957). These data, for six (Dunroy) and seven (Texas) months of the year, are in terms of the percentage of the population that is pregnant; we extrapolated for the remaining months. Marshall et al. (1957) also provide figures for the average litter size at each site.

In the model, to find the number of rabbits born on a particular day, we simply multiply the percentage of the population that is pregnant times the female population size to get the number of pregnant rabbits. To find the number of rabbits actually born, we multiply the number of pregnant rabbits by the average litter size. Finally, since the value of the percentage of the population that is pregnant represents an entire month, we divide by the number of days in the month to find the number born on that day.

We assume that the sex ratio is 1:1, so that half of the rabbit population is female. Field data indicate that this is approximately correct (Myers and Poole 1962, Parer 1977). Kittens born to infected rabbits usually die (Parer 1977), so we assume that only susceptible and recovered-and-immune rabbits can reproduce.

Juvenile *O. cuniculus* take from 3–5 mo to reach reproductive maturity (Parer 1977, Gilbert and Myers 1981, Gilbert et al. 1987). In order to incorporate this time lag, we include age structure for juvenile rabbits. That is, we index the rabbit population according to day of birth up until the age of first reproduction, at which point each newly reproductive age group is simply added to the adult class. As a result, only juveniles are divided into age classes.

In the model, we assume that the daily number of rabbits dying from natural mortality is a fixed fraction of the population. We also assume that this mortality is not age-specific. This is an oversimplification, as juveniles are more likely to die from predation or starvation than are adults (Parer 1977, Wheeler and King 1985), but it is unavoidable in the absence of better data.

For both natural mortality and age at first reproduction, we consider a wide range of parameter values. We thus postpone a consideration of realistic estimates for these parameters until the next section, in which we consider the output of the model.

Finally, in the interests of simplicity, we assume that rabbits are not born immune or infected.

Model equations

When the above assumptions relating to rabbit demography are introduced into Eqs. 5–8, the full equations are as follows.

Juvenile Population Dynamics (for $a = 0, \ldots, A - 2$)

$$S(0, t + 1) = r(t)[S(A, t) + R(A, t)] \quad (9)$$

$$S(a + 1, t + 1) = (1 - m)S(a, t)\left[1 - \sum_{i=1}^{n} \phi(i, t)\right] \quad (10)$$

$$I(i, 0, 0, t + 1) = 0 \quad (11)$$

$$I(i, 0, a + 1, t + 1) = (1 - m)S(a, t)\phi(i, t), \qquad \text{for } i = 1, \ldots, n \quad (12)$$

$$I(i, \tau + 1, a + 1, t + 1) = (1 - m)I(i, \tau, a, t), \qquad \text{for } i = 1, \ldots, n; \tau = 0, \ldots, T_i - 1 \quad (13)$$

$$R(0, t + 1) = 0 \quad (14)$$

$$R(a + 1, t + 1) = (1 - m)R(a, t) + (1 - m) \sum_{i=1}^{n} [1 - CM(i)] \cdot I(i, T_i, a, t). \quad (15)$$

Adult Population Dynamics

$$S(A, t + 1) = (1 - m)[S(A, t) + S(A - 1, t)] \cdot \left[1 - \sum_{i=1}^{n} \phi(i, t)\right] \quad (16)$$

$$I(i, 0, A, t + 1) = (1 - m)[S(A, t) + S(A - 1, t)]\phi(i, t), \qquad \text{for } i = 1, \ldots, n \quad (17)$$

$$I(i, \tau + 1, A, t + 1) = (1 - m)[I(i, \tau, A, t) + I(i, \tau, A - 1, t)], \qquad \text{for } i = 1, \ldots, n; \tau = 1, \ldots, T_i - 1 \quad (18)$$

$$R(A, t + 1) = (1 - m)[R(A, t) + R(A - 1, t)] + (1 - m) \sum_{i=1}^{n} [1 - CM(i)][I(i, T_i, A, t) + I(i, T_i, A - 1, t)]. \quad (19)$$

Here the force of infection, $\phi(i, t)$ is

$$\phi(i, t) \equiv \sum_{\tau=0}^{T_i-1} \sum_{a=0}^{A} \beta(i, \tau)I(i, \tau, a, t).$$

The population is still split into the classes S, I, and R, but now these classes are indexed according to both age, a, and time, t. In addition, the infected population is still indexed according to strain i and time since infection, τ. As a result, instead of one equation for each of S, I, and R we now have an equation for S, I, and R for each age class. In order to make clear the motivation behind the model equations, here we describe each equation.

Juveniles.—We begin with newborns. Eq. 9 says that the number of newborn susceptibles is equal to a seasonally varying birthrate $r(t)$ times the number of adult suceptibles at time t, $S(A, t)$, plus the number of adult recovered-and-immunes, $R(A, t)$.

Eq. 10 says that the number of susceptibles of age $a + 1$ at time $t + 1$ is equal to the number of susceptibles in the preceding age class at time t times the fraction that escaped both death due to natural mortality $(1 - m)$ and infection with any of the n strains, $[1 - \sum_{i=1}^{n} \phi(i, t)]$.

Eq. 11 says that rabbits cannot be born infected, so that the number of individuals infected with strain i in the 0th age class and 0 d since infection at time $t + 1$ is zero.

Eq. 12 says that the number of new infections with strain i in individuals of age $a + 1$ at time $t + 1$ is equal to the number of susceptibles in the preceding age times the fraction that survived death due to natural causes, times the fraction that became infected with strain i at time t.

Eq. 13 says that at time $t + 1$ the number of juveniles of age $a + 1$ that have been infected with strain i for $\tau + 1$ time units at time $t + 1$ is equal to the number of juveniles at time t of age a who have been infected with strain i for τ time units, times the fraction that survived death due to natural causes, $(1 - m)$.

Eq. 14 says that rabbits cannot be born immune, so that the number of immune rabbits in the 0th age class at time $t + 1$ is zero.

Finally, Eq. 15 says that the number of recovered-and-immune of age $a + 1$ at time $t + 1$ is equal to the number of recovered-and-immune of age a at time t times the fraction that did not die of natural causes, $(1 - m)$, plus the number of infecteds of all n strains of age a at time t that have reached the mean survival time T_i associated with strain i, $I(i, T_i, a, t)$, times the fraction that survived the disease $[1 - CM(i)]$ times the fraction that did not die of natural causes, $(1 - m)$.

Adults.—The equations for adults, Eqs. 16–19, are the same as the equations for the juveniles, except that adults do not change age classes. Thus for adult susceptibles, we have Eq. 16, in which the number of adult susceptibles at $t + 1$, $S(A, t + 1)$ equals the number of adult susceptibles at t, $S(A, t)$, plus the number of pre-adults at t, $S(A - 1, t)$, times the fraction that survived natural mortality, $(1 - m)$, times the fraction that did not become infected with strain i, $[1 - \sum_{i=1}^{n} \phi(i, t)]$.

Simulation Results

Eqs. 9–10 describe the iterative steps in the model. By setting all but one strain to zero, we can investigate the dynamics of isolated strains, as a first step towards

understanding the model. In particular, we shall study the dependence of disease dynamics upon natural mortality. This allows exploration of the sensitivity of the model to parameter variations and consideration of interregional geographic variation in dynamics. Furthermore, by varying natural mortality, which includes all sources of mortality not due to the virus, we can use such analyses to explore the interplay between the disease and other methods of control.

Single-strain dynamics

In a single computer run of the model, Eqs. 9–10 are iterated with a time step of 1 d for a period of 40 yr. At the beginning of a run, the population density of susceptibles is set at 250, evenly divided among age classes, and the number of recovered-and-immunes is set to zero. To start an epizootic of the disease, we introduce a number of infected individuals equal to 1% of the susceptible population. Although we chose these starting conditions for reasons of simplicity, it matters little what conditions we choose. Simulations with widely varying starting conditions, not shown here in the interest of brevity, show essentially the same dynamics after an initial transitory phase.

At the beginning of each run, we specify:

1) a reproductive data set (Texas or Dunroy),
2) a natural mortality,
3) an age at first reproduction (age of adulthood).

For all of the simulations shown here, we use only the reproductive schedules from Texas station (see *Description of the basic model*); results with data sets from other sites were very similar. Moreover, the values for percent pregnant and kittens per doe are comparable across a variety of sites (Wheeler and King 1985, Gilbert et al. 1987).

The results of a set of simulations for grade IV and IIIB strains are shown in Fig. 6. After an initial transitory phase, the rabbit population settles into a pattern of fluctuation that is driven both by the forcing imposed by the seasonal reproductive rate and by the host–pathogen dynamics. The initial fluctuations are dependent on the starting conditions of the model, in terms of both total numbers of rabbits and the age structure of the rabbit population; yet for pre-myxomatosis Australia, we have no information on either. Because of this, for the model with only a single strain, we show here only years 20 through 40. Our aim is to demonstrate the range of dynamical behavior that can occur for rabbit populations driven by the disease.

These results show that both the ability of a particular virus strain to control the rabbit population and the period of the cycles in the rabbit population are determined by the level of natural mortality and the age of first reproduction of the rabbits. Characteristically, we see behavior ranging through unbounded growth, stable equilibrium, and a series of period-doubling bifurcations, possibly eventually giving way to chaotic behavior. For example, consider the dynamics associated with grade IIIB when the age of first reproduction is set at 120 d, but natural mortality is varied from 0.004 to 0.0085 daily per capita deaths (Fig. 6). For natural mortality of <0.004, the virus is unable to control the rabbit population, which increases exponentially. When natural mortality is increased to 0.004, the disease controls the rabbit population; for a natural mortality of 0.005, the population eventually enters a cycle with a period of 2 yr. For natural mortality of 0.007, the rabbit population is controlled by the disease, but is now in a cycle of a very long period, or may be fluctuating aperiodically. For natural mortality of 0.0085, the virus fades out of the population, and then the rabbit population slowly goes extinct, as the non-disease death rate exceeds the birth rate. Fig. 6 shows a similar sequence for strain IV. The interplay between intrinsic periodicity and the forcing period due to seasonality is mathematically fascinating, but is beyond the scope of the present paper. Here we simply note that relatively small changes in either the virulence of the virus or natural mortality can lead to very different population dynamics. In particular, as the value of natural mortality is increased for a particular strain and age at first reproduction, the period of the oscillation in the rabbit population increases.

The minimum value of natural mortality for which the virus ceases to be able to control the rabbit depends on the virulence of the virus, and tends to decrease as the age of first reproduction increases. In Fig. 7, we show how this value depends on natural mortality and age of first reproduction for each grade of the virus. The solid line on the right indicates values of natural mortality and age of first reproduction for which the rabbit population cannot maintain itself, and for which of course the virus goes extinct. The lines connected by +'s represent the lowest value of natural mortality for which each virus grade is able to control the rabbit, and below which the virus is no longer able to control the rabbit. For values of natural mortality above this minimum, and below the value at which the rabbit population cannot maintain itself, the rabbit population is stable, in the sense that it neither increases without bound nor decreases asymptotically to zero. Within these bounds, it may fluctuate. As can be seen in Fig. 7, the lower limit decreases as the virulence of the virus grade increases. Thus, for the intermediate grade IV this lower limit ranges from 0.004 to 0.006, whereas for the highly virulent grade I this lower limit is essentially zero. One way of interpreting Fig. 7 is that the range of natural mortalities for which a virus strain can control the rabbit population increases with the virulence of the virus. In other words, virus grades that kill a higher percentage of the rabbits they infect will provide more certain control, which is hardly a surprising result. It is also not surprising that the value of natural mortality at which each grade ceases to be able to control the rabbit should decrease slightly as age at

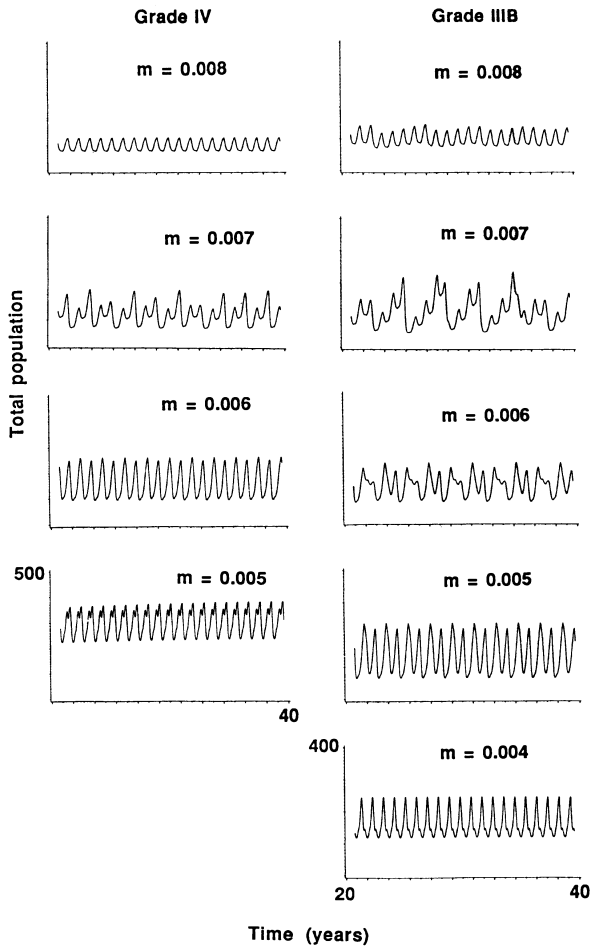

FIG. 6. Model output using grade IV and IIIB strains of the virus. Each graph represents total population of rabbits from 20 to 40 yr, to show population trajectory after dissipation of transients due to starting conditions. In all cases, age at first reproduction is 120 d. m indicates value of natural mortality (day^{-1}). For $m > 0.008$, both the virus and the rabbit go extinct. For grade IV, for $m < 0.005$ the rabbit population increases exponentially, while the corresponding value for grade IIIB is $m < 0.004$.

first reproduction increases. This is because as age at first reproduction increases, the growth rate of the rabbit population decreases, making control more likely.

The increase in the period of the cycles in the rabbit population with increasing values of natural mortality is less obvious. The extremely long cycles for some combinations of age of first reproduction and natural mortality suggest that for the right values of these parameters, chaos may ensue (May 1976).

Competition between virus strains

In order to see whether the model accurately mimics the distribution of grades seen in the field, we ran the model including all six grades of the virus. In Fig. 8, we show a series of simulations for steadily increasing values of natural mortality, similar to the series described above for grade IIIB, except that now we show only the number of rabbits that are infected with each grade. We began the model with all the grades present in equal proportions; after a single generation, only grades IIIB and IV remain, regardless of the level of natural mortality. Eventually, grade IV competitively excludes grade IIIB, but it takes from 4 to 10 generations, depending on the value of natural mortality. Grade IV is thus the competitively superior grade of the six grades in our model. Of course, we note that

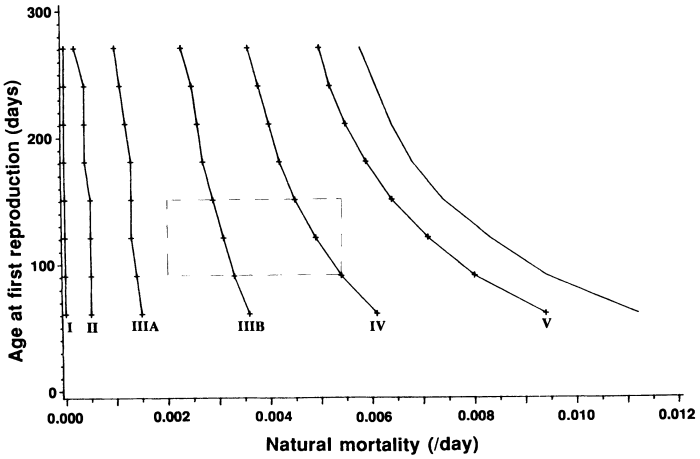

FIG. 7. The regions of stability of the model with respect to natural mortality and age of first reproduction. The solid line on the right marks the boundary of stability for all virulence grades of the virus. For values of natural mortality and age of first reproduction greater than values on this line, the rabbit population goes extinct regardless of which grade of the virus is present. For values of natural mortality and age of first reproduction lower than the values on this line, the stability of the model depends upon the virus grade that is present. The lower limit of values of the two parameters, below which the rabbit population increases exponentially, is represented for each grade by the lines connected by +'s, and each line is labeled with its appropriate grade. The dashed rectangle represents the area of parameter space corresponding to the range of values for age of first reproduction and adult natural mortality reported in the literature (see *Application of the model to field data: control of the rabbit*).

for the model we assume that rabbit resistance has not evolved, but rather is that of pre-myxoma animals.

Unfortunately, our model is complex enough that it is hard to understand why grade IV is favored over, say, IIIB. In general, analysis of competition between viral grades is complicated by the oscillatory dynamics demonstrated in the previous section; moreover, no formal theory exists for such situations. However, it is helpful to look at the outcome of evolution if we assume that the susceptible and infected populations are at equilibrium. To simplify matters further, we consider only the basic model, Eqs. 5–8, that does not include age structure or detailed rabbit population dynamics. Our justification for this approach is that, as we shall see, the simplified model at equilibrium adequately describes the outcome of viral competition in the more complicated model.

In a manner similar to that of Anderson and May (1982), as described earlier, we consider an established strain, and ask whether a rare invader can increase. We assume that the resident strain, call it grade k, is at equilibrium, so that

$$I(k, \tau, t) = \hat{I}(k, \tau) = \hat{I}(k, 0)(1 - m)^{\tau} \qquad (20)$$

for all τ and t; when we substitute Eq. 20 into Eq. 6, $S(t) = \hat{S}$ is given by

$$\hat{S} = 1/\left[\sum_{\tau=0}^{T_k-1} \beta(k, \tau)(1 - m)^{\tau+1}\right]. \qquad (21)$$

By analogy with a stable age distribution (Pielou 1977), a rare invader (call it grade j) will attain a stable time-since-infection (τ) distribution, in which each class grows by a factor λ each generation. Setting

$$I(j, \tau, t + \tau) = I(j, \tau, t)\lambda^{\tau} \qquad (22)$$

and

$$I(j, 0, t + 1) = I(j, 0, t)\lambda \qquad (23)$$

in Eq. 6 (where the condition for invasion is that $\lambda > 1$), we obtain

$$I(j, 0, t) = (1 - m)\hat{S}\sum_{\tau=0}^{T_k-1} \beta(j, \tau)I(j, \tau, t + \tau)\lambda^{-(\tau+1)}. \qquad (24)$$

From Eq. 7,

$$I(j, \tau, t + \tau) = I(j, 0, t)(1 - m)^{\tau} \qquad (25)$$

so,

$$1 = \hat{S}\left[\sum_{\tau=0}^{T_j-1} \beta(j, \tau)\lambda^{-(\tau+1)}(1 - m)^{(\tau+1)}\right]. \qquad (26)$$

Since the term in brackets is a decreasing function of λ, the condition for grade j to invade (i.e., for $\lambda > 1$) is,

$$1 < \hat{S}\left[\sum_{\tau=0}^{T_j-1} \beta(j, \tau)(1 - m)^{(\tau+1)}\right]. \qquad (27)$$

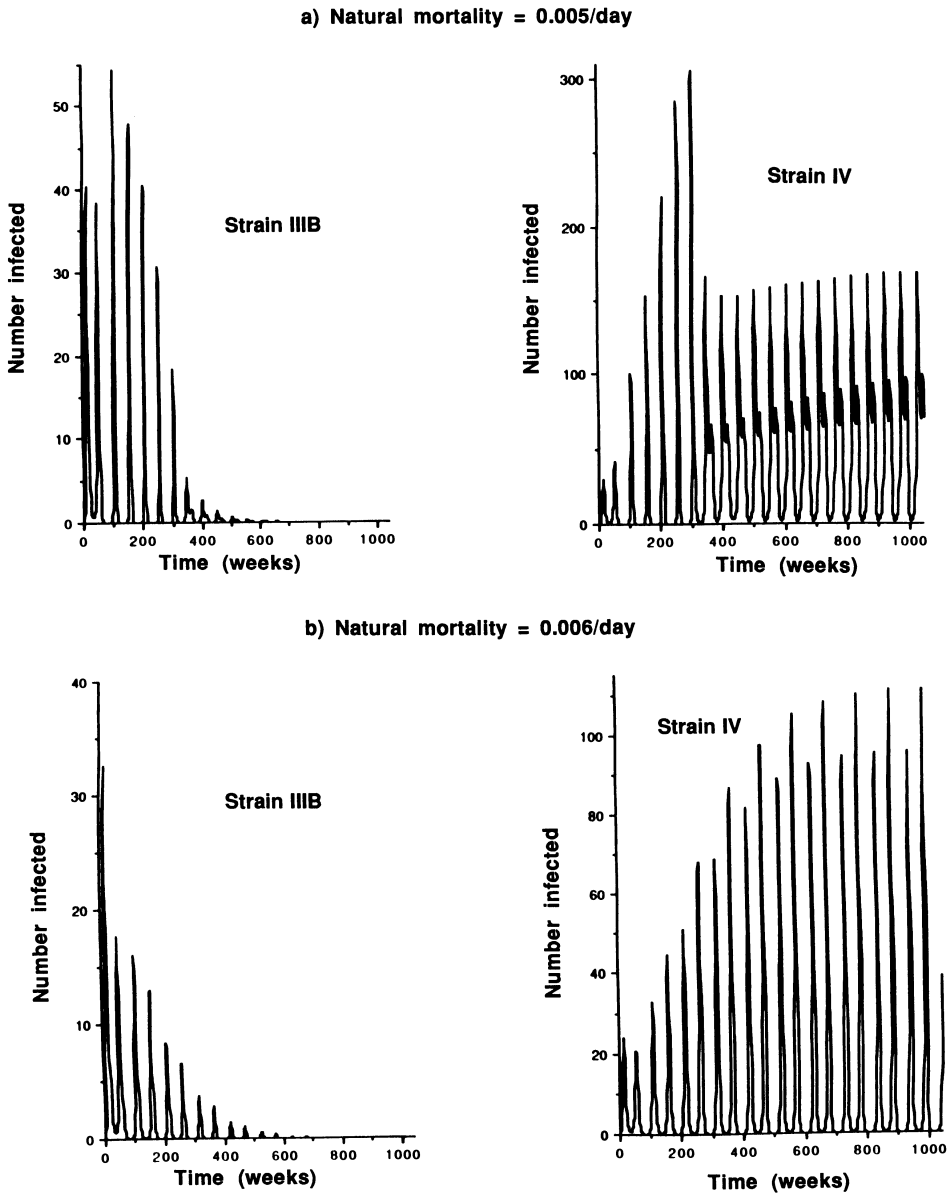

FIG. 8. Outcome of competition among virus strains of different virulence. Strains of virulence grades I, II, IIIA, and V are eliminated in the first generation, so we show only grades IIIB and IV. Ordinate is total number of rabbits infected, abscissa is time in weeks.

Together with Eq. 21, this in turn implies that the invasion condition is

$$\sum_{\tau=0}^{T_j-1} \beta(j, \tau)(1 - m)^\tau > \sum_{\tau=0}^{T_k-1} \beta(k, \tau)(1 - m)^\tau. \quad (28)$$

(Note that both sides have been divided by $[1 - m]$.) In other words, grade j will only increase if the value of $\sum_{\tau=0}^{T_j-1} \beta(j, \tau)(1 - m)^\tau$ is higher than the corresponding value for grade k. The competitively dominant strain will thus be the one that maximizes this expression. It

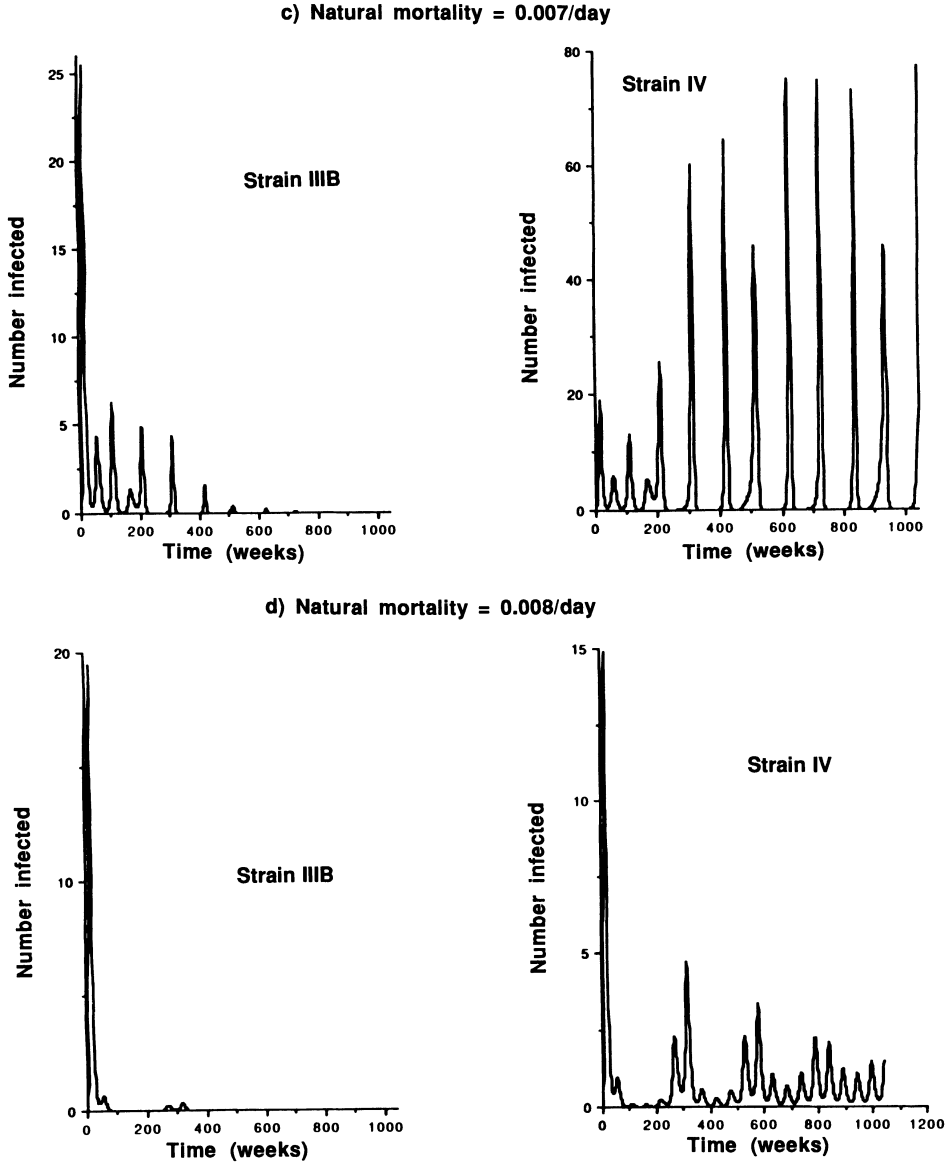

FIG. 8. Continued.

is not clear how to modify this condition in the fluctuating environment embodied by the full model, but it is useful for predicting the outcome of viral competition in the full model. That is, we look for the grade that maximizes $\sum_{\tau=0}^{T_i-1} \beta(i, \tau)(1 - m)^\tau$. Since m is small, $(1 - m)$ is close to 1, and $(1 - m)^\tau$ is very close to 1, so that m can be ignored, which is equivalent to ignoring non-disease deaths during the infectious period. We thus seek to maximize $\sum_{\tau=0}^{T_i-1} \beta(i, \tau)$, while recognizing that a slight correction is needed for $m > 0$.

As we explained earlier, $\beta(i, \tau)$ incorporates the virus titer growth curve as well as the transmission efficiency of the vector. That is,

$$\beta(i, \tau) = p[v_i(\tau)], \tag{29}$$

where v is the virus titer within a rabbit, so that

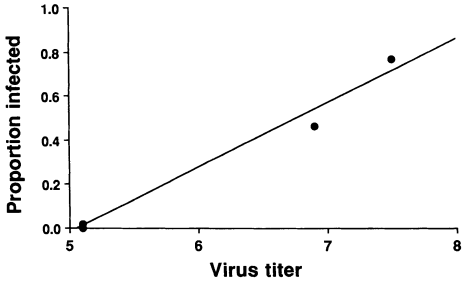

FIG. 9. The proportion of rabbits that become infected by a mosquito that had fed on an infected rabbit vs. the virus titer in the infected rabbit. Points are from Fenner et al. (1956). Solid line represents a linear regression ($r^2 = 0.97$, $n = 4$), $p = -1.48 + 0.293v$, where p is the proportion of healthy rabbits that become infected, and v is virus titer.

$$v_i = k_1(i)\tau e^{-k_2(i)\tau}. \tag{30}$$

p is the probability that a mosquito will transmit the disease from an infected rabbit with a virus titer of v_i to a healthy rabbit, so that

$$p = 0.293v_i - 1.48$$

(see Fig. 9). The sum of β between 0 and $T_i - 1$, the survival time of the infected rabbit, is thus similar to the value of R_0 computed by Massad (1987) (see *Previous work*).

The resulting value of $\sum_{\tau=0}^{T_i-1} \beta(i, \tau)$ (which we abbreviate as $\Sigma\ \beta$) for each grade (Table 7) accurately predicts both the outcome of competition and the sequence of extinctions. That is, the strain with the largest value of $\Sigma\ \beta$ (grade IV strain) eventually excludes all of the other strains, which in turn are eliminated in order of increasing value of $\Sigma\ \beta$: V, I, II, IIIA, and IIIB.

Moreover, since we have each of the parameters in Eq. 29 as a function of case mortality (*CM*), it is possible to find the case mortality of the optimal grade. Although we cannot find a closed-form expression for the maximum of Eq. 29, $\Sigma\ \beta$ is a reasonably smooth function, so we can easily calculate a rough value for its optimum. $\Sigma\ \beta$ is plotted in Fig. 10, and its maximum is at a case mortality of $\approx$65%, which is roughly a grade IV strain.

We again point out that these calculations are presented for laboratory rabbits that have not undergone selection for resistance to the disease. In the field, we might expect that such selection would lead to higher virulence. In order to test this, we need to allow for increased host resistance in our analysis, which also will allow us to look at the coevolution of host and pathogen.

Incorporating host resistance

One of our goals in modelling the myxoma–*Oryctolagus* system is to predict the efficacy of the virus in the future. In order to do this, we need to include the evolution of rabbit resistance in the model. Since the parameters of the virus in the model (T, k_1, k_2), as well as those of the resistance of *Oryctolagus* in the field, are defined in terms of case mortality, we can include the effects of host resistance by assuming that the rabbits in the model have the same level of resistance as rabbits in the field. We have already defined the parameters of the virus in terms of a common currency. That is, by finding the survival time (T), the virus titer parameters (k_1 and k_2) in terms of the case mortality (*CM*) we have effectively defined the virulence of each grade in terms of its case mortality. The next steps are (1) to define the effect of increasing rabbit resistance upon the case mortality of different grades, and (2) to model the genetics of heritability of disease resistance. In light of the difficulties inherent even in defining the effect of increasing resistance upon virulence, we make some extremely simplistic assumptions about rabbit genetics and concentrate on the consequences of one particular definition of the effect of increasing resistance. Before detailing our assumptions, however, we first note that our motivation is not simply to predict the ultimate outcome of coevolution in the system, but to make clear what information is necessary before one can make a truly meaningful prediction.

First of all, we assume that all *Oryctolagus* in the model are equally resistant. Although this is obviously unrealistic, it is a reasonable first step. Also, we assume that the virus tracks the evolution of the rabbit essentially instantaneously, so that we do not need to keep track of the dynamics of the evolution of the virus, only the outcome of viral competition. This is an especially problematic assumption, as not only do the field data indicate that recent changes in virulence have been gradual (Table 1, Table 2), but our own simulations show that competition between strains occurs on the same time scale as the evolution of the rabbit.

Finally, and most importantly, we need some way of interpreting how changes in rabbit resistance affect the interaction between the virus and the rabbit within an individual rabbit. Resistance is measured as the

TABLE 7. The transmission function $\sum_{\tau=0}^{T_i-1} \beta(i, \tau)$ (where τ is time since infection, i is virus virulence grade, and T_i is the grade-specific survival time) for each grade of virus in the model with either mosquitoes or fleas as vector. This function is abbreviated as $\Sigma\ \beta$.

		$\Sigma\ \beta$	
Grade	*CM* (%)	Mosquitoes	Fleas
I	99.5	4.8	3.4
II	97	6.2	4.5
IIIA	92.5	8.0	5.7
IIIB	80	14.9	9.5
IV	60	15.4	10.3
V	22.5	1.2	2.0

decline in the case mortality caused by a certain virus strain, and we have already defined the other epidemiological parameters of the model in terms of case mortality. Because of this, for the particular virus strain used to measure the resistance of field rabbits, we assume that increasing resistance is equivalent to a reduction in virulence. That is, each strain is assumed to be in a grade of lower virulence when infecting a resistant rabbit than when infecting a rabbit without resistance.

The real difficulty is that the available data are inadequate for making strong predictions. Typical data only give the case mortality of resistant rabbits for a strain or strains in a single grade, whereas we need this information for all the grades. The most obvious solution is to assume that all the grades are affected in the same way by a given increase in rabbit resistance. There are several ways to interpret this, but we will limit ourselves to two, which we label "additive" and "proportional." By "additive," we mean that if a grade I strain, which in unselected rabbits has a case mortality of 99%, has a case mortality of, say, 84% in resistant rabbits, then the case mortalities of strains in all other grades are similarly decreased by 15%. For example, the case mortality of the grade IV strain would decrease from 60 to 45%. By "proportional," we mean that if a grade I strain again has a case mortality of 84% in resistant rabbits, which is about 0.85 times its original value, then the case mortality of strains in all the other grades would similarly be multiplied by 0.85. The case mortality of grade IV would now drop from 60 to 51%.

Both the assumption of equivalent effects across grades (by either interpretation), and the assumption that an increase in resistance is equivalent to a decrease in virulence, are made in the absence of adequate data. Proceeding further may thus seem ill advised, especially as we are making a host of other assumptions about the genetic structure of the rabbit population. The point is that when the statement is made that virulence may increase in response to an increase in rabbit resistance (Fenner and Ratcliffe 1965, Anderson and May 1982, Ross 1982, Fenner 1983), some version of the above assumptions is being used, sometimes unwittingly. We are simply making the assumptions explicit. The take-home message is that for us to be able to say anything quantitative about the effects of increasing host resistance upon the control of the rabbit, the relationship between increasing resistance and virulence must be understood.

By using these assumptions, we can use actual field data on variations in resistance among rabbit populations to explore the consequences of increased resistance among field rabbits. For instance, Fenner (1983) gives the case mortality of field rabbits from Gippsland challenged with a grade I strain as ≈82% (average of SLS and Glenfield strains), while the case mortality of

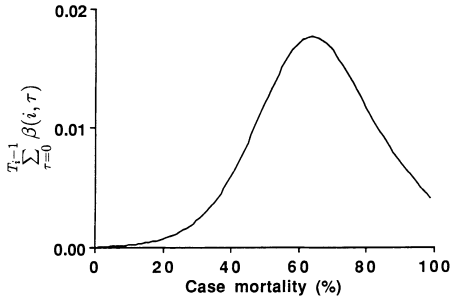

FIG. 10. The transmission function $\Sigma\,\beta$ vs. case mortality (mortality of infected rabbits) for myxomatosis transmitted by mosquitoes.

field rabbits from the Mallee is ≈76% (average of SLS and Glenfield strains; Table 8). The additive changes in the case mortality of grade I are thus ≈17% in Gippsland and about 23% in the Mallee, while the corresponding proportional changes in the case mortality of grade I are ≈0.83 in Gippsland and ≈0.77 in the Mallee.

Since in our previous analysis of the model we predicted that the competitively dominant strain in unselected rabbits will have a case mortality of ≈65%, we can use either the additive or proportional changes in the case mortality of grade I to predict what the competitively dominant strain should be in Gippsland and the Mallee. Based on an additive change, we predict that the competitively dominant strain in Gippsland would have a case mortality of 65 + 17 = 82%, while the competitively dominant strain in the Mallee would have a case mortality of 65 + 23 = 88%. Based on proportional changes, we predict that the competitively dominant strain in Gippsland would have a case mortality of 65 ÷ 0.83 = 78%, while the competitively dominant strain in the Mallee would have a case mortality of 65 ÷ 0.77 = 84%. In short, for both areas and for either method, we predict that the competitively dominant strain should be in grade III.

By allowing for the increase in resistance of field rabbits, our prediction of the competitively dominant grade changes from IV to III, which is closer to the observed field data for both Gippsland and the Mallee (Table 2). We also correctly predict a higher level of virulence in the Mallee, although of course the model predicts only a single, competitively superior strain rather than a distribution of virulence.

Our use of the model in this way indicates that the error in our initial prediction of virulence levels in Australia may be due to the effects of increasing host resistance leading to compensating increases in virulence. Moreover, we further predict that future increases in virulence should be great enough that the virus will continue to control the rabbit for the foreseeable

future. In particular, the case mortality (*CM*) of rabbits infected with a grade I strain would have to drop well below 60% before the virus would cease to be able to control the rabbit. In the past 30 yr, the case mortality of Australian rabbits infected with a grade I strain has not dropped any lower than 76%; therefore, using the assumptions we have made above, we would very tentatively guess that the virus will continue to be useful for as long as another 15–20 yr, *assuming resistance continues to evolve at the same rate.*

In Great Britain, the case mortality of field rabbits infected with a grade III strain dropped from ≈90% in 1966 to ≈33% in 1976, compared to a case mortality of 83% in unselected rabbits (Table 4). This corresponds to an additive change of 50% and a proportional change of ≈40%. This of course points out a problem with our method, in that we would predict for these cases that a competitively dominant strain would have a case mortality in excess of 100%. However, although grade II strains have been at consistently higher frequencies in Great Britain than in Australia, grade I has been at very low frequencies since shortly after the introduction of the virus, whereas grade III has predominated.

Allowing for the increased resistance of rabbits in Great Britain thus results in a prediction of a competitively dominant strain that is far more virulent than the dominant strain observed in the field. If the values reported for the case mortality of field rabbits in Great Britain are reliable, then our error may be due to our assumption that the decline in case mortality of field rabbits relative to unselected rabbits is the same for all strains. Indeed there is evidence from Great Britain (Ross 1982) that this assumption is incorrect. For example, a grade III strain caused only 13% mortality in field rabbits in 1974 as compared to a case mortality of 70–95% in unselected rabbits, yet a grade I strain in the same rabbits still caused nearly 100% mortality.

Application of the Model to Field Data

The output of the model compares favorably with field data with respect to both the control of the rabbit and the evolution of virulence. We document this in the sections that follow.

Control of the rabbit

Gilbert et al. (1987) review estimates of age-specific mortality from studies of rabbit populations in five different areas of Australia. Although these estimates include mortality due to both the disease and natural causes, for all of the studies reviewed, almost all the disease-induced mortality occurs among juvenile *Oryctolagus.* If we assume that the non-disease mortality of both juveniles and adults in the model is equivalent to the field values for the natural mortality of adults alone, then we can examine the behavior of the model for the values of natural mortality of adults given by Gilbert et al. (1987). Since non-disease mortality (due to drowning, starvation, predation, etc.) is in general considerably higher for juveniles than for adults, this will give us a conservative estimate of the range of non-disease mortality for which the virus can control the rabbit.

The values of non-disease mortality in Gilbert et al. (1987) range from 83 to 45%, which corresponds to daily mortality of ≈0.005 to 0.002 deaths per capita per day. Estimates of age of first reproduction of *Oryctolagus* range from 3 to 5 mo (90–150 d) (Parer 1977, Gilbert and Myers 1981, Gilbert et al. 1987).

These ranges for the values of natural mortality and age of first reproduction provide us with a way of considering the behavior of the model under realistic conditions (Fig. 7). For natural mortalities above 0.008, the model predicts that the rabbit population will go extinct even without the virus. In the model, grade I is capable of controlling the rabbit for natural mortalities all the way down to 0. However, for a given age at first reproduction, the range of natural mortalities for which the rabbit is controlled grows progressively narrower as the grade of virulence decreases. Nevertheless, for the grades of the virus that are most abundant in the field, grades III and IV, and for realistic values of age at first reproduction, the model predicts that the disease will be capable of controlling the rabbit population for natural mortalities between ≈0.003 and 0.008 (see Fig. 7), corresponding to yearly mortalities of 67–96%. Moreover, as we are using only adult mortality, this is a very conservative estimate.

The model thus predicts that the virus will be able to control the rabbit for most of the range of the values of natural mortality observed in the field, and so is in accord with Parer et al.'s (1985) result that the virus plays an important role in regulating *Oryctolagus* populations. Nevertheless, for the prevalent strains of the virus in the field, the model indicates that background sources of mortality must be at a high enough level for the rabbit population to be controlled. That is, *the most prevalent strains of the virus in the field cannot control the rabbit by themselves.* Although this relationship between control and different sources of mortality is not a new result in the theoretical literature (Anderson and May 1979), to our knowledge it has not been recognized by field workers.

The qualitative predictions of our simulations agree with a continuous time model presented by Andreasen (1988) that is based on the model we have presented. It differs in that he assumes that transmission depends on age rather than time since infection, and that survival time is exponentially distributed rather than fixed. For Andreasen's model, as in our model, the minimum non-disease mortality rate at which the disease can control the rabbit increases with decreasing case mortality, so that the range of natural mortalities where the rabbit is maintained at a moderate population density decreases with decreasing case mortality.

The dependence of control on non-disease sources of mortality has important implications for the management of the rabbit. First of all, it is possible that for some natural levels of non-disease mortality, the rabbit may not be controlled by the disease. In such situations, the model indicates that supplemental programs, such as burrow destruction (Cooke and Hunt 1987) or poisoning or gassing of rabbits (Oliver et al. 1982), may act together with the disease to control the rabbit, even though neither mortality agent is sufficient when acting alone.

Secondly, since levels of non-disease mortality may vary among years and different geographical areas, the efficacy of the disease as a control agent may also vary yearly or geographically. As a result, management policies must be sensitive to yearly variation or geographical differences in non-disease mortality. Differences in the ability of the virus to control the rabbit have been observed among geographical areas in Australia, but are usually attributed to geographical variations in the abundance of disease vectors (J. R. Backholer, *personal communication*). Although such variability is certainly a sufficient explanation, the results of our model indicate that variability in the background levels of non-disease mortality is undoubtedly important, and may also provide a sufficient explanation.

The extremely long cycles in the rabbit population that occur for some values of natural mortality may be due to the somewhat arbitrary time delay between infection and death in infected rabbits (Andreasen 1988). However, since chaos has been shown to occur even in extremely simple difference equation models of disease (May 1985), it seems likely that long cycles or more complex trajectories are inherent in such dynamics, so that we might realistically expect such behavior in the field. The implication of this is that in some areas of Australia rabbit populations may fluctuate unpredictably, which could complicate long-term management plans.

The evolution of virulence and the coexistence of viral strains

Like Anderson and May's (1982) model, our model predicts that a single strain of the virus, in our case a grade IV strain, will prevail. This predominant strain is slightly more attenuated than the grade IIIB strain which is observed to be most prevalent in the field. The prediction of the model is thus roughly in accord with the data from the field. Moreover, the differences in parameter values between IIIB and and IV are so slight that in the simulations the grade IIIB strain takes a long time to go extinct. Furthermore, as we have already pointed out, inclusion of host evolution is likely to shift this result towards IIIB.

This result leads to two possible interpretations of the observed coexistence of virus strains in the field. First of all, it may be that the differences among virus grades are small enough, and the dynamics of the system are slow enough, that the less common strains in the field are only excluded competitively over a period of many decades. This interpretation is supported by our simulations, although of course other mechanisms could be operating as well.

Alternatively, it may be that the measurement errors in assigning viruses to different grades, due to the variability in host response, are large enough that the apparent coexistence of strains in the field is due to the misassignment of strains to grades. The small amount of spread in the data makes this possibility seem unlikely, but only a re-analysis of the original data on abundance of strains could unambiguously address this possibility.

These two interpretations are based on the assumption that coexistence in the field is essentially an artifact, either because the system has not yet reached equilibrium, or because the breakdown of the viruses into grades is misleading. If neither of these possibilities holds true, we must search for a mechanism of coexistence. Moreover, the fact that strains of different virulence have been collected from the same sample site (J. R. Backholer, *personal communication*) indicates that long-term coexistence is at least a possibility.

At present, there is no evidence that might explain how strains of the virus coexist in the field. In fact, experiments carried out by Fenner et al. (1957) and Parer et al. (1985) indicate that continued coexistence is not likely at a local level. Fenner et al. (1957) initiated an epizootic in a rabbit population near Lake Urana, New South Wales, with a grade I strain, only to have the grade I strain displaced by an unidentified local strain of intermediate virulence. Parer et al. (1985), as we have already described, performed a similar experiment by introducing both an attenuated strain (grade V) and a highly virulent strain (grade I) into the same population of rabbits at Lake Urana, every year between 1978 and 1982. In spite of the fact that the introduced strains had a large initial advantage over the local field strain, the field strain appeared every year, and in the final year, the field strain was nearly as abundant as the introduced strains (Parer et al. 1985).

In short, the results of these experiments indicate that long-term coexistence is not likely at a local level, although the data do not cover a long enough period of time to make this a firm conclusion. Another intriguing possibility that has been long overlooked is that secondary infections are more common than is usually believed. Parer et al. (1985) mention that some of the infected rabbits in the experiments they performed were infected with both strains. This indicates that the mechanism proposed by Levin and Pimentel (1981) may be correct; that is, the more virulent grade I, II, and IIIA strains may maintain themselves in the system by outcompeting the less virulent strains within individual rabbits. For example, if a rabbit is infected with, say, both grade IIIA and IV strains, the grade IIIA strain may reach a higher titer before the grade

TABLE 8. Increase in resistance of *Oryctolagus* in Australia, as indicated by the case mortality of groups of rabbits challenged with a particular test strain of myxoma virus (Fenner 1983).

	Virus strain	
	SLS	Glenfield
Gippsland		
1961–1966	94	98
1967–1971	90	99
1972–1975	85	98
1976–1981	79	95
Mallee		
1961–1966	68	98
1967–1971	66	94
1972–1975	67	96
1976–1981	60	91

IV strain, be transmitted to another rabbit, and then kill the rabbit before the grade IV strain is itself transmitted. At present, the data in support of this mechanism are too sketchy to be conclusive. Moreover, the existing observations are from artificial experiments, and what is needed are observations of epidemics in natural populations, to see if several strains are present at once.

If coexistence really is not possible at a local level, then we are forced to search for coexistence of strains over larger areas. One obvious possibility is that genetic differences in resistance among different areas of Australia are great enough to allow for differences in the associated virus strains. This possibility has empirical support because, as mentioned above, rabbit populations in different areas of Victoria do indeed have different levels of genetic resistance (Table 8), and these areas also have different levels of associated virulence (Edmonds in Fenner 1983). Even without such geographical differences, it is clear from the theoretical literature that patchiness within even homogeneous environments can lead to coexistence, or at least delay competitive exclusion (Levin 1974, Slatkin 1974). The deme structure of rabbit populations in Australia may provide the requisite patchiness.

A possibility that has received little attention is that the persistence of marginal strains, those of very high or low virulence, is due to high mutation rates (M. Slatkin, *personal communication*). That is, considering how rapidly mutant strains appeared in the field, and how short the generation time of the virus is, it is possible that the genetic diversity of the virus is maintained simply by mutation of intermediate strains to higher or lower virulence.

Finally, it may be that the interplay between the evolution of resistance and the evolution of virulence is such that the diversity of both is maintained mutually.

The effect of the rabbit flea, S. cuniculi, *on the evolution of virulence*

One reason why our results differ from those of Massad (1987) could be that the transmission probabilities that he used were based on experiments with fleas (Mead-Briggs and Vaughan 1975) rather than mosquitoes. The difference is still interesting for several reasons. First, both mosquitoes and fleas were transferred by hand, so that differences in movement rates between the vectors could not have caused the differences in transmission efficiencies that were observed in the laboratory. These differences presumably were due to morphological differences between the mouthparts of fleas and mosquitoes.

Second, when we repeat our ESS calculation of the competitively dominant strain using data from fleas for the relationship between transmission efficiency and titer (Vaughan 1981), we reach the same prediction. For fleas, as for mosquitoes, this relationship is linear ($r^2 = 0.98$; $n = 4$), but the slope and the y intercept of the regression line are different from those for mosquitoes. Specifically, for fleas, the slope of this line is smaller (0.121 vs. 0.293), as is the absolute value of the y intercept (-0.496 vs. -1.48). The biological meaning of these differences is that fleas are less efficient at transmitting at high titers, but are more efficient at transmitting at low titers. Nonetheless, the competitively superior virus strain still has a case mortality in the vicinity of 65% (grade IV), and the ranking of the six virus grades in the model is unchanged (Table 7), although the shape of the $\Sigma\,\beta$ curve changes slightly (Fig. 11).

We thus suggest that the difference between Massad's (1987) result and our present result is due either to differences in the way the data were originally collected or to lack of resolution in the original data. That is, the difference may be due simply to noise in the original data, rather than to the effect of differences in transmission efficiency between fleas and mosquitoes. This

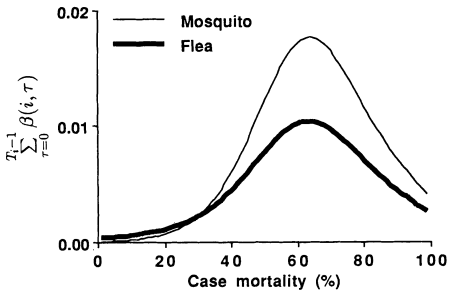

FIG. 11. The transmission function $\Sigma\,\beta$ vs. case mortality (mortality of infected rabbits) for myxomatosis transmitted by fleas (▬) compared with mosquitoes (——).

seems especially likely since the absolute difference between the two results is small.

This has the implication that differences between mosquito-vectored and flea-vectored rabbit–virus associations can only be due to differences in the behavior or population dynamics of fleas vs. mosquitoes. In other words, we suggest that *the lower transmission efficiency of fleas at high virus titers cannot explain the higher virulence of field strains in Great Britain (Ross 1982), nor can it explain the higher mortality of rabbits in flea-vectored epizootics in Australia (Rendel 1971, Cooke 1983).*

In fact, any explanation for an increase in virulence, whether between Great Britain and Australia, or in Australia between 1967 and 1985, that invokes differences between fleas and mosquitoes as vectors *must* explain how fleas favor more virulent strains to a greater degree than do mosquitoes. No explanation that has been offered to date, including the reduced efficiency of fleas as vectors (Ross 1982) or an increase in case mortality due to a change in the seasonal timing of epizootics (Cooke 1983), satisfies this criterion.

Coevolution of rabbit and virus

Our conclusion that strains of intermediate virulence should continue to control the rabbit for the near future contrasts sharply with Rendel's (1971) conclusion that only grade I strains should now be capable of controlling the rabbit. Although field data indicate that grade III strains are still capable of controlling the rabbit (Parer et al. 1985), Rendel's (1971) analysis is nonetheless interesting because he explicitly takes into account the heritability of resistance in the rabbit, a facet of the interaction ignored by us and other theoreticians. We believe that a profitable future direction for modelling myxomatosis will be to combine the epidemiological approach that we have adopted in the present paper with Rendel's (1971) quantitative genetics approach.

To a large extent, our conclusion of continued control is built into our approach to the problem. This is because our assumption that the effect of increasing host resistance is the same for all virus grades means that an increase in host resistance only changes which grade is competitively dominant. If, on the other hand, an increase in host resistance allows rabbits to combat more virulent strains preferentially, then the virus might no longer be able to control the rabbit population. Of course, the reverse is also true, in that if an increase in host resistance has less effect on the more virulent strains than on the less virulent strains, the virus will more easily be able to control the rabbit population. This assumption is critical to our interpretation of the future dynamics of the myxoma–*Oryctolagus* system.

The very long-term dynamics of the system are even harder to anticipate than which grade can control rabbit populations. Even if the virus does continuously track increasing host resistance, eventually the competitively dominant strains may all be of a level of virulence that is even greater than grade I. The question then becomes, is there enough variance in the virulence of the virus for hypervirulent strains to become abundant? Fenner (1983) presents evidence that there may be a large amount of variance within grade I, as two grade I strains (SLS and Glenfield) that produce similar case mortalities in unselected rabbits produced very dissimilar case mortalities in highly resistant rabbits (Table 8). In particular, the Glenfield strain had a high case mortality even in the resistant rabbits, whereas the SLS strain produced a relatively low case mortality in the resistant rabbits. Viruses that are now all called grade I may thus be lumped together only because the severity of their effects upon unselected rabbits makes them hard to distinguish. If this is the case, it could mean that there is more variability in virulence among field strains of the virus than is immediately apparent.

Conclusion

In summary, it appears that the myxoma virus will continue to be an effective biological control agent of *O. cuniculus* in Australia for the near future. Predicting whether this will be true over the long term requires greater knowledge of the genetic structure of the populations of both virus and rabbit. Specifically, to make a truly useful prediction as to the outcome of coevolution between myxoma and *Oryctolagus,* the following questions must be answered.

1) How are virus strains in different grades affected by increases in host resistance?

2) What are the mechanisms of viral coexistence at the local level?

3) What are the levels of variability of genetic resistance within and between rabbit populations?

4) What is the extent of migration of either rabbits or viruses between rabbit populations?

Ultimately, as Fenner and Ratcliffe (1965) suggest, the virus and the rabbit may reach a coevolutionary equilibrium similar to that observed in the interaction between myxoma virus and its original host, *S. brasiliensis,* in which the disease is rarely fatal, yet is easily transmitted. One of the most helpful aspects of this system is that it seems to be evolving so fast that tests of a model's predictions may be made within the lifetime of those making the prediction.

Acknowledgments

Joy Bergelson, Dan Doak, Joel Kingsolver, Peter Kareiva, Bill Morris, and Tim Wootton made extensive comments on earlier versions of the manuscript. Two anonymous reviewers also made useful suggestions. Viggo Andreasen made many helpful suggestions on the development of the model. Joy Bergelson devoted many hours to helping G. Dwyer with the ANCOVA. Sara Hiebert helped with some of the figures. G.

Dwyer was supported by grants from the Cornell University Undergraduate Honors Thesis Research Fund, N.S.F. grant DMS-8406472 and McIntire-Stennis grant NYC-183568 to S. A. Levin, and an N.S.F. Graduate Fellowship. S. A. Levin was supported by NSF grant DMS-8406472 and McIntire-Stennis grant NYC-183568.

This publication is ERC-199 of the Ecosystems Research Center (ERC), Cornell University, and was supported in part by the U.S. Environmental Protection Agency Cooperative Agreement CR812685. The work and conclusions published herein represent the views of the authors, and do not necessarily represent the opinions, policies, or recommendations of the Environmental Protection Agency.

This research was conducted using the Cornell National Supercomputer Facility, a resource of the Center for Theory and Simulation in Science and Engineering (Cornell Theory Center), which receives major funding from the National Science Foundation and IBM Corporation, with additional support from New York State and members of the Corporate Research Institute.

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