MATHEMATICAL MODELING OF REFUGIA IN THE SPREAD OF THE HANTAVIRUS

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We describe a mathematical model we have recently developed to address some features of the interaction of deer mice infected with Hantavirus in terms of simple differential equations involving the mice population. As one of the consequences of our calculations we provide a possible mathematical answer to the question of what may be responsible for the observed "refugia" in the North American Southwest. Specifically, we show how environmental factors could lead to the extinction of the infection in localized areas and its persistence in other localized areas from which, under favorable conditions it can spread again.

INTRODUCTION

We have recently developed a mathematical framework to address a few observed features in the spread of the Hantavirus. Here we describe the essential starting point and conclusions of that framework. Hantaviruses, which are infectious and harmful to humans, are carried by rodents throughout the whole world. Thus, Sin Nombre Virus was responsible for a Hantavirus Pulmonary Syndrome (HPS) that, in an outbreak in 1993, struck with a mortality of 50% in the Four Corners region of the North American Southwest [1-3]. Sin Nombre Virus is primarily carried by the deer mouse, *Peromyscus maniculatus*. Since that outbreak of 1993, when the virus was first isolated and described, immense effort has been devoted to the understanding of the virus reservoir, its temporal and spatial dynamics, and its relation to the human population.

Our model [4] incorporates some basic ecological and epidemiological features of the mice. Two characteristic observations regarding the disease correspond to natural consequences of a bifurcation phenomenon in the solutions of our model. Both features are related to the role of the environment on the dynamics and persistence of the infection. One is that the infection can completely disappear from a population of mice when environmental conditions are inadequate, reappearing sporadically or when conditions change [3, 5, 6]. The other is that there is "focality" of the infection in "reservoir" populations [3, 5-7]. A spatial segregation is observed between regions where the mice population is free of infection and regions where the infection persists. As environmental changes occur, these "refugia"[*] of the reservoir expand or contract, carrying the virus to other places.

BASIC MODEL OF MOUSE POPULATION

Our model [4] addresses only the mouse population, since there are no feedback effects of the human population: mice bite humans but humans do not (normally) bite mice. Consider the mouse population composed of two classes, susceptible and infected, represented by M_S and M_I respectively [8]. The temporal evolution of M_S and M_I contains two basic ingredients: the contagion of the infection, that

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[*] Terry L. Yates, personal communication (2001).

converts susceptible into infected, and a population dynamics independent of the infection. The equations describing the model are:

$$\frac{dM_S}{dt} = bM - cM_S - \frac{M_S M}{K} - aM_S M_I,$$

$$\frac{dM_I}{dt} = -cM_I - \frac{M_I M}{K} + aM_S M_I,$$

(1)

where $M(t) = M_S(t) + M_I(t)$ is the total population. Each of the terms of Eq. (1) is supported by a biological motivation, as follows.

To describe population growth, bM represents births of mice. Given that infected mice are made, not born, and that all mice are born susceptible, bM mice are born at a rate proportional to the total density: all mice contribute equally to the procreation [3]. To describe deaths, $-cM_{S,I}$ represent deaths for natural reasons, at a rate proportional to the corresponding density. To include effects of competition for shared resources, the terms $-M_{S,I}M/K$ represent a limitation process in the population growth. Each one of these competition terms is proportional to the probability of an encounter of a pair formed by one mouse of the corresponding class, susceptible or infected, and one mouse of any class. The reason for this is that every mouse, either susceptible or infected, has to compete with the whole population. The "carrying capacity" K, in this process, characterizes in a simplified way the capacity of the medium to maintain a population of mice. Higher values of carrying capacity represent higher availability of water, food, shelter and other resources that mice can use to thrive [9]. Finally, to model the primary process, infection, we take $aM_S M_I$ to represent the number of susceptible mice that get infected, due to an encounter with an infected (and consequently infectious) mouse. This rate a could generally depend on the density of mice, for example due to an increased frequency of fight when the density is too high and the population feels overcrowded [5]. However, we will assume it to be constant for the sake of simplicity. The fact that the infection is chronic, infected mice do not die of it, and infected mice do not lose their infectiousness probably for their whole life [3, 5-7], supports this description.

The sum of the two equations of (1) provides an equation for the whole population of logistic form:

$$\frac{dM}{dt} = (b-c)M\left(1 - \frac{M}{(b-c)K}\right).$$

(2)

Logistic growth has been observed in laboratory populations of *Peromyscus* [10]; it is a well established metaphor of the dynamics of a self limiting population and has been studied in a variety of contexts [9, 11-13].

Four parameters characterize the system (1): a, b, c and K. We shall consider a, b and c fixed, and analyze the dynamics as K varies. We choose K as a control parameter of the dynamics, because it is the one that best represents the influence of the environment. One could imagine a situation in which external perturbations are reproducibly introduced in K through the control of water and vegetation.

The system (1) has four equilibria. Two of them are irrelevant to the present analysis (the null state, which is always unstable, and a state with $M_I < 0$ for any parameters). The other two equilibria interchange their stability character at a critical value of the carrying capacity:

$$K_c = \frac{1}{a}\left(\frac{b}{b-c}\right).$$

(3)

When $K < K_c$, the stable equilibrium has $M_I = 0$ and $M_S > 0$. When $K > K_c$, the stable equilibrium has both $M_I > 0$ and $M_S > 0$. As a result of this bifurcation the prevalence of the infection can be correlated, through K, with the diversity of habitats and other ecological conditions. A scarcity of resources, for example, is accompanied by a lower number of infected mice [3, 7, 14]. Moreover, for values of K below the threshold K_c the number of infected animals is effectively zero, as has been observed in the field [3, 5, 6]. That is, if temporarily the ecological conditions at a place in the landscape become very adverse (a drought, for example) the infection can drop to zero. Similarly, when conditions improve (perhaps greatly, due to rare climatic events such as El Niño, which preceded the outbreak of HPS in 1993 in the Southwest [15]) the infection reappears.
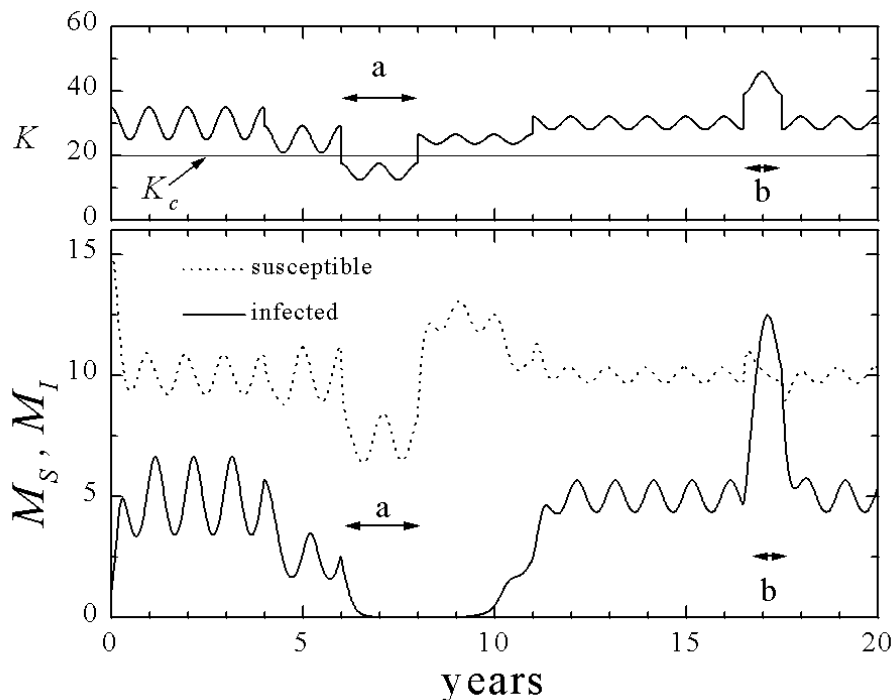

FIG. 1: Top: A (fictitious, albeit realistic) time dependent carrying capacity. Bottom: Temporal evolution of the population of mice. Model parameters are: $a = 0.1$, $b = 1$, $c = 0.5$.

Figure 1 displays a simulation of such events. A time-dependent carrying capacity has been assumed, shown in Fig. 1 (top). The corresponding values of the susceptible and infected mice populations are shown in Fig. 1 (bottom). Yearly seasonal variation is represented by a sinusoidal behavior of the carrying capacity. We display a period of 20 years, during which the carrying capacity oscillates around a value, sometimes above K_c (shown as a horizontal line), sometimes below it. Discontinuities in the carrying capacity, some of which are present in Fig. 1 (top), do not necessarily occur in nature. They appear here because we keep the modeling of K at an elementary level, to illustrate the main features of the system. The period marked "a" in Fig. 1 (from years 6 to 8) is characterized by values of K below K_c, corresponding to strongly adverse environmental conditions. During such "bad years" the infection level drops to zero, even while the population of healthy mice, reduced, subsists. A return to "normal" carrying capacities after year 8 produces a very slow recovery of the infected population, which attains again appreciable values after year 11, delayed with respect to the recovery of susceptible mice. An extraordinary event on year 17 is marked as "b" in Fig. 1. Note the corresponding increase in the carrying capacity (top), perhaps following an event such as El Niño the year before. These improved

environmental conditions are followed by an immediate (if moderate) increase in the population of susceptible mice (bottom, dotted line), and by a slightly delayed outbreak of infection (bottom, full line). An event such as this would appreciably increase the risk for the human population to become infected.

SPATIALLY EXTENDED PHENOMENA

We now analyze the effects of spatial extension in the model. The range of distribution of the deer mice comprises diverse landscapes and habitats, and this affects local populations in an inhomogeneous way. To include this we allow M_S, M_I and K to become functions of a space variable x. Mice of the genus *Peromyscus* are known to tend to hold a home range during their adult life, occasionally shifting it to nearby locations if there are vacant ones [16, 17]. Therefore, an adequate model mechanism of transport for the mice is diffusion. Because juvenile animals are the most mobile [5] and the infection affects mainly adult males [2], we take generally different diffusion coefficients for susceptible and infected mice. Thus, the spatial extension of the model gives

$$\frac{\partial M_S(x,t)}{\partial t} = bM - cM_S - \frac{M_S M}{K(x)} - aM_S M_I + D_S \nabla^2 M_S,$$

$$\frac{\partial M_I(x,t)}{\partial t} = -cM_I - \frac{M_I M}{K(x)} + aM_S M_I + D_I \nabla^2 M_I, \tag{4}$$

where we are specifically taking into account a spatial dependence of the carrying capacity, $K(x)$, and D_S and D_I are the diffusion coefficients of susceptible and infected mice respectively.

Analytical determination of the solutions of the system (4) appears impossible for an arbitrary function $K(x)$. Some general results can be obtained for uniform carrying capacity. For example, it can be shown that an unstable homogeneous steady states develops a homogeneous perturbations that takes the system to the stable state [4]. The most interesting scenarios, however, correspond to non-homogeneous carrying capacities, and are explored in the following section.

REFUGIA

Real nature situations can be characterized by a spatially varying K, following the diversity of the landscape. We analyze two of these situations, employing for the purpose a numerical procedure applied to Eqs. (4). The first is a 1-dimensional case whereas the second is 2-dimensional. We show the former because the profile displayed by the stationary solutions of the populations is readily accessible, and the latter to provide a more realistic picture of the consequences of the bifurcation.

A simple 1-dimensional landscape consists of a spot of high carrying capacity ($K > K_c$) in the middle of a bigger region of low carrying capacity ($K < K_c$). A typical situation is in Fig. 2, where vertical lines represent the boundaries between the three zones. Equations (4) are solved with an arbitrary initial condition of the populations, and after a transient a steady state is reached in which the infected population is concentrated at the spot of higher K, that constitutes a "refugium." A "leak" of infection is seen outside the high-K region, due to the diffusion. Far from this, the mouse population remains effectively not infected.
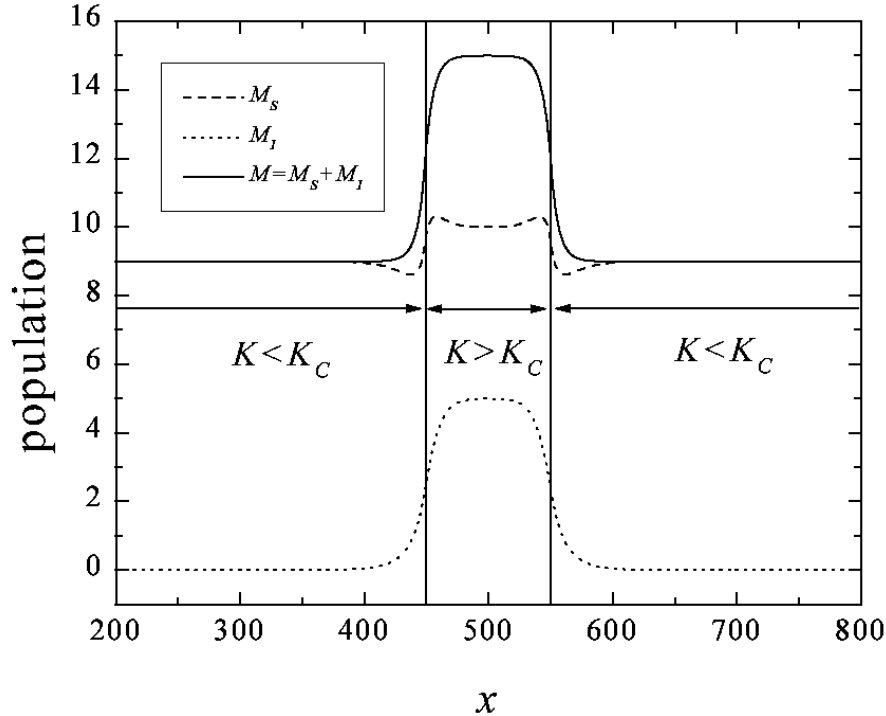
FIG. 2: A refugium in 1D. Model parameters as in Fig. 1, $D = 20$, $K = 1.5K_c$ in the refugium, $K = 0.9K_c$ outside of it.

The steady state of a 2-dimensional realization of the system (4), performed on a square grid which simulates a hypothetical habitat by assigning different values to K_{ij}, the carrying capacity at each site, is displayed in Fig. 3. The landscape is based on satellite images of northern Patagonia, and comprises a region of about 10km on each side, including a river and a diversity of vegetations (Fig. 3, top, left). The carrying capacity has been supposed higher on the more densely covered places, mainly along the river (Fig. 3, top, right). The density plots in Fig. 3 (bottom) show the population of mice in a scale of grays, where pure black corresponds to zero population. Higher population are shown as progressively lighter shades of gray. The peaks of the distributions are shown as pure white to enhance their contrast with neighboring sites. The non-infected population occupies the whole landscape, with a non-homogeneous density. Moreover, as expected from the results of the homogeneous model, for small and moderate values of the diffusion coefficient, the infected population survives in a patchy pattern, only in the regions of high carrying capacity, becoming extinct in the rest. These "islands" of infection become reservoirs of the virus [7] or refugia[*], and are the places of highest risk for human exposure and contagion of the virus. It is also from these refugia that the disease would spread (blurring the patchiness, as observed in [3, 14]) when environmental conditions change.

These features predicted by our admittedly qualitative model are precisely what is observed in the field. We observe also that the steady state distribution of neither infected nor susceptible mice reproduces exactly the distribution of the carrying capacity. This is so because there is interaction of diffusion with the nonlinear terms. Notice in the 1-dimensional representation shown in Fig. 2 that, although the carrying capacity follows a step distribution, the mice populations are not steps. Both M_S and M_I have diffusive "leaking," the former exhibiting a dip as one moves out of the region of large capacity. Similarly, in the 2-

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dimensional case shown in Fig. 3, we see that the peaks of the populations represented by pure white appear at different places for the susceptible and infected. They do not occupy the entire "river" region or follow precisely the peaks of the distribution of the carrying capacity.
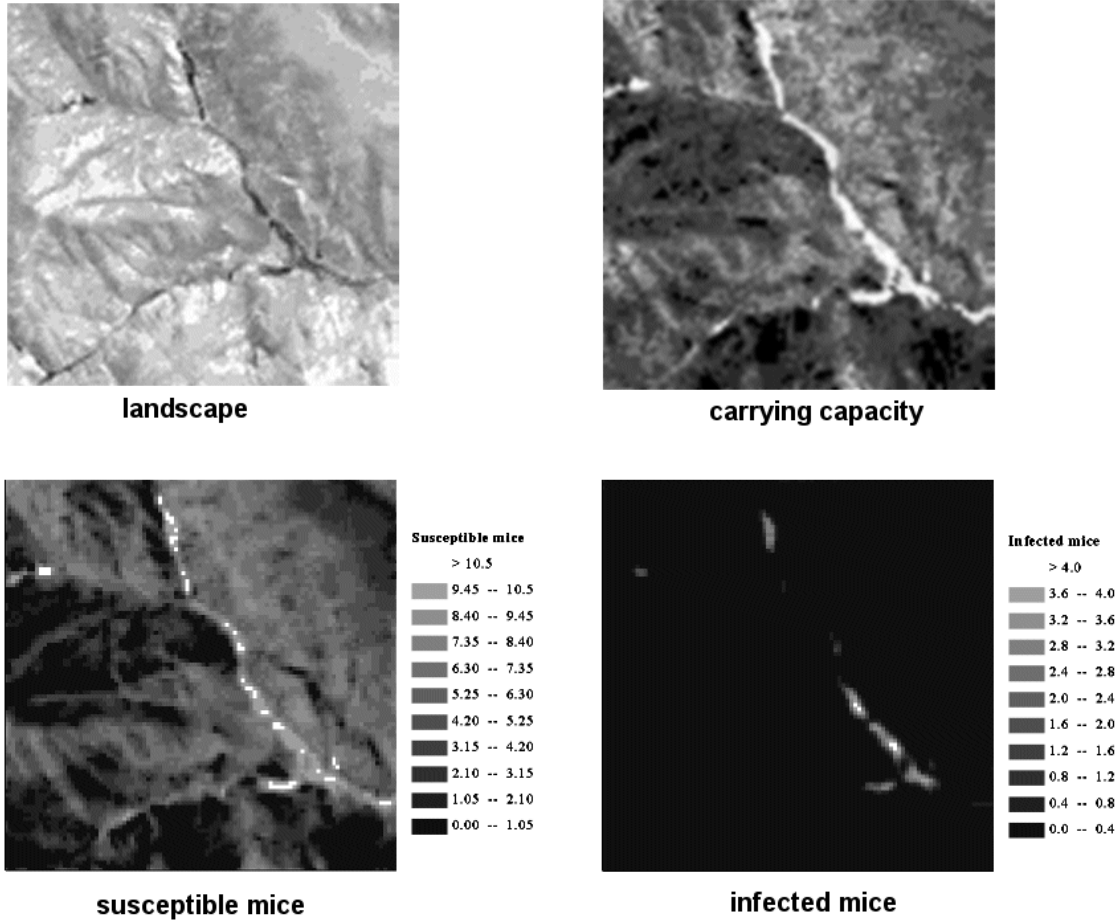

FIG. 3: Refugia in 2D. Model parameters as in Fig. 2, $D_S = D_I = 1$.

CONCLUDING REMARKS

Our study so far has reproduced, through mathematical considerations applied to a simple model [4], temporal patterns in the evolution of the population of infected mice, as well as refugia: emergence of spatial features in the landscape of infection. Extensions we are involved in at the moment address traveling waves, which depict the spread of fronts of infection moving out from the refugia in favorable periods, and a variety of other issues such as non-diffusive motion of the mice and stochastic disturbances in the environment.

ACKNOWLEDGMENTS

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