OF MICE AND VIRUSES

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SYNOPSIS

We review recent mathematical models of the epizootic of Hantavirus in mice population. The models are mainly based on field observations of *Peromyscus maniculatus* populations in New Mexico, which host Sin Nombre Virus. We explain the sporadic disappearance of the prevalence as a phase transition controlled by the environment. Refinements of the model allow to include the effect of non-host competitors, as well as to assess the validity of the diffusion transport.

SINOPSIS

En este trabajo presentamos una revisión de modelos matemáticos recientes del patrón de epizoótico de Hantavirus en poblaciones de ratones. Los modelos están basados principalmente en observaciones de campo de poblaciones de *Peromyscus maniculatus* en Nueva México, el cual es anfitrión del virus Sin Nombre. Explicamos la desaparición esporádica del predominio como una transición de fase controlada por el ambiente. Refinamientos del modelo permiten incluir el efecto de competidores no anfitriones, como también determinar la validez del transporte difusivo.

1. INTRODUCTION

In 1993 Sin Nombre Virus (Bunyaviridae: Hantavirus), the first Hantavirus to be discovered in the New World, was identified as the infectious agent causing an outbreak of Hantavirus Pulmonary Syndrome in the North American southwest. Its host and reservoir was identified, shortly afterwards, in the very common deer mouse (*Peromyscus maniculatus*). Since then, numerous new Hantaviruses have been discovered throughout the Americas, each one hosted by a single mouse species, and many of them responsible for severe human pathology[11]. An interdisciplinary effort has been devoted to understand the epizootic, with the ultimate goal of correctly assessing the human risk.

In recent years, a simple mathematical model of this epizootic has been proposed and analyzed by me and others [1, 2]. Of course, a complete mathematical description of the dynamics of the biological system, comprising the virus, the mice, the humans and the environment, is a daunting task. Our study attempted to extract a few major ingredients, based on observed ecological and epidemiological features of the mice population. As keystones for our analysis we chose two observed characteristics of the disease. Both arise from the fact that environmental conditions strongly affect the dynamics and persistence of the infection. One of them, a temporal characteristic, is the reported observation that the infection can completely disappear from a population of mice if environmental conditions are inadequate, only to reappear sporadically or when conditions change [6, 13, 16]. The other, a spatial characteristic, is that there are indications of "focality" of the infection in "reservoir" populations[13]; as environmental changes occur, these "refugia"[21] of the reservoir can expand or contract, carrying the infection to other places.

The model takes into account several peculiarities of the Hantavirus-rodent association, for example the fact that the infection does not produce any known disease in the mice, and consequently does not affect their death rate. The role of the spatio-temporal patterns of the environment on the prevalence of the infection, which has been found in field studies[21], has also been taken into account. In further developments, we have also analyzed the role of non-host competitors of the mice[17], and the validity of the transport mechanism of the population.

2. BASIC MODEL: ONE SPECIES, NO MOVEMENT

The basic model, consisting of a single mouse species, is an SI model in a mean field, or well mixed, approximation (thus disregarding any spatial effect). We also disregard the distinctions of sex and age, and consider the total population divided into two categories: susceptible and infected mice. The dynamics of the two subpopulations is:

$$\frac{dm_s}{dt} = bm - cm_s - \frac{m_s m}{K} - am_s m_i, \tag{1a}$$

$$\frac{dm_i}{dt} = -cm_i - \frac{m_i m}{K} - am_s m_i, \tag{1b}$$

where m_s and m_i are the populations (or densities) of susceptible and infected mice, respectively, and $m(t) = m_s(t) + m_i(t)$ is the total population of mice. The motivation for the terms in Eqs. (1) follows.

Births: bm represents births of mice, all of them born susceptible, at a rate proportional to the total density, since all mice contribute equally to the procreation[13].

Deaths: c represents the rate of depletion by death for natural reasons, proportional to the corresponding density. If necessary, separate rates c_s and c_i could be introduced for the susceptible and infected populations respectively.

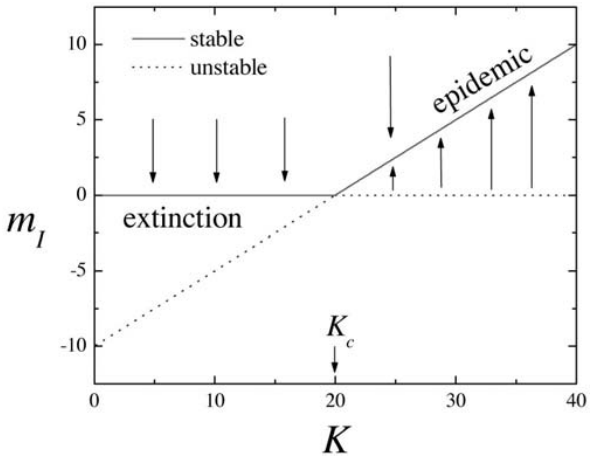

Figure 1. Bifurcation diagram of the basic model. The infected population is shown as a function of the carrying capacity K, which is used a control parameter. There is a transcritical bifurcation at a value $K_c = b/[s(b-c)]$.

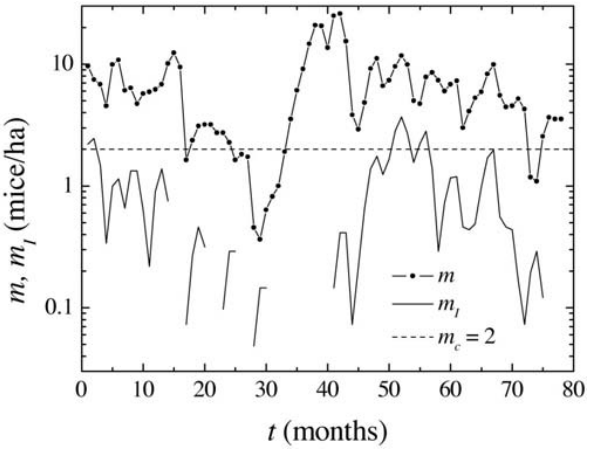

Figure 2. Mean density of *P. maniculatus* at two sites near Zuni, New Mexico [after [21], Fig. 7]. The rodent densities, in animals per hectare, are shown in log scale to emphasize the behavior at low densities. Shown: total population (line-dot), infected with SNV (line), critical density (dashed). The time axis counts months from December 1994.

Competition: $-m_{s,i}\, m/K$ represent a limitation process in the population growth, due to competition for shared resources. Each 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 (since every mouse, either susceptible or infected, has to compete with the whole population). K is a "carrying capacity," characterizing in a simplified way the capacity of the medium to maintain a population of mice. Higher values of carrying capacity represent a higher availability of water, food, shelter and other resources that mice can use to thrive[14].

Infection: $am_i m_s$ represents the number of susceptible mice that get infected, due to an encounter with an infected (and consequently infectious) mouse, at a rate a that we assume constant. More elaborate models could incorporate a density dependence on a, for example due to an increased frequency of fights, during which contagion occurs through bites, when the density is too high and the population feels overcrowded [6]. The infection is chronic, infected mice do not die of it, and infected mice do not lose there infectiousness probably for their whole life [10.13]. For these reasons, this single term adequately describes the infection dynamics of the two subpopulations.

This model is able to successfully explain several field observations as environmentally controlled phase transitions, thus providing an analytical support to biological hypotheses such as the trophic cascade discussed in [21]. Figure 1 shows that there is a critical value of the carrying capacity that separates two distinctive regimes: it the environmental parameter K is smaller than K_c, the stable equilibrium of m_i is zero and infection is driven to extinction. If $K>K_c$, infection may thrive. In an environmentally changing situation, the system is expected to undergo transitions from one state to the other. This corresponds to the documented sporadic disappearance of the infection, as shown in Figure 2. In this plot, the populations are displayed in a logarithmic scale to emphasize the dynamics for low density values. Total and infected densities are shown, as indicated in the legend. The dashed line represents the critical population able to sustain a positive prevalence of infection, as predicted by the model defined by Eqs. (1), by using approximate parameters obtained from

the time series (details of the calculation can be found in [3]. In this example, the prevalence of the infection is seen to decrease as soon as the population becomes subcritical, eventually recovering when it is supercritical again.

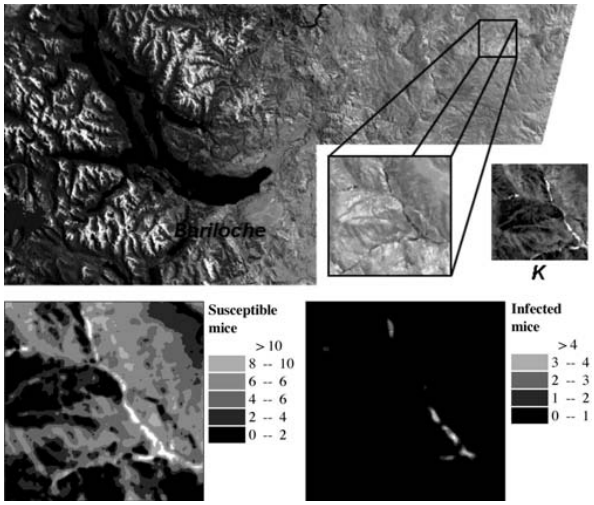

Figura 3. A simulated, albeit realistic, analysis of the formation of refugia of infection, based on the analysis of vegetation images in an inhomogeneous landscape. On the top, observe a satellite image of the northern Patagonian region, from the Andes to the steppe. A square outlines a region from which vegetation values have been converted to a simulated $K(\vec{x})$. The two bottom panels show the stationary population densities produced by model (2). It can be seen that the susceptible mice thrive over most of the landscape, while the infection remains confined to the refugia.

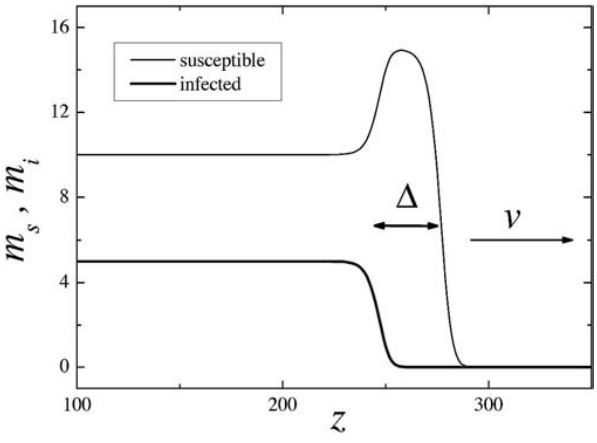

Figure 4. Front waves in the extended system, propagating from left to right.

3. SPATIALLY EXTENDED SYSTEM

The range of the deer mice is comprise a diverse landscape with a variety of habitats. The inhomogeneous way in which this spatial extent affects local populations can be included in a spatially extended version of the model, where m_s, m_i and K become functions of a space variable $\vec{x}$. Using a simple diffusion model for the transport mechanism of the population, we write the extended model:

$$\frac{\partial m_s}{\partial t} = bm - cm_s - \frac{m_s m}{K(\vec{x})} - am_s m_i + D\nabla^2 m_s, \qquad (2a)$$

$$\frac{\partial m_i}{\partial t} = -cm_i - \frac{m_i m}{K(\vec{x})} - am_s m_i + D\nabla^2 m_i. \qquad (2b)$$

The solution of the system (2), and even its stationary solution, may be impossible to find, analytically, for an arbitrary function $K(\vec{x})$. Interesting situations correspond to a $K(\vec{x})$ that mimics the available resources in the landscape, such as the plant cover. A simulation of this is shown in Figure 3, based on satellite images, and using arbitrary values of the parameters for the purpose of illustration of the formation of the "refugia."

4. WAVES OF INFECTION

How does infection spread form refugia? When the prevalence in a patch of landscape has dropped to zero, its eventual recovery, when environmental conditions change, necessarily involve the interaction with a region already infected. The system (2) can sustain nonlinear waves, of which some general properties can be found analytically in a homogeneous environment, in which K does not depend on $\vec{x}$. In such a case, as shown in [2], there can be invasion fronts consisting of a pair of waves, a leading one of susceptible mice, followed by a wave of infected ones. One such situation is illustrated in Figure 4. The speed of the susceptible front is the Fisher speed, $v_s = \sqrt{D(b-c)}$, while the infected front travels at $v_i = 2\sqrt{D[-b + aK(b-c)]}$.

The fact that the latter depends on a and K caused the existence of a new transition in the parameter K, a dynamical one this time. If $K<K_0=(2b-c)/[a(b-c)]$, then $v_i < v_s$ and the infected front progressively lags more and more behind the susceptible one. On the contrary, if $K>K_0$, then $v_i = v_s$ asymptotically, and the delay between the two fronts is a fixed value. This delay, shown as Δ in Figure 4, depends on K as well.

5. THE ROLE OF BIODIVERSITY

Other processes which limit the population size would play a similar role in the control of the infection. In real ecosystems mice share the environment with many others species, competing for limited resources with some, and being preyed on by others. We have made an initial step into the study of the effect of biodiversity on the prevalence of the infection by studying a model in which a non-host population competes with the host [17]. This is a common situation in Hantavirus-mice systems [18]. For the hosts, identified by the variable m, and the non-host "aliens," identified by z, the competition dynamics is the following:

$$\frac{dm_s}{dt} = bm - cm_s - \frac{m_s}{K}(m + qz) - am_s m_i, \qquad (3a)$$

$$\frac{dm_i}{dt} = -cm_i - \frac{m_i}{K}(m + qz) - am_s m_i, \qquad (3b)$$

$$\frac{dz}{dt} = -(\beta - \gamma)z - \frac{z}{\kappa}(z + \varepsilon m) - am_s m_i, \qquad (3c)$$

where, for the host species, b is the birth rate, c is the death rate, K is the carrying capacity in the absence of an alien population ($z = 0$), and q is the influence of the alien population; for the alien species, the analogous parameters are β, γ, κ and ε respectively.

The analysis of Eqs. (3) shows that competition reduces, in a specific way, the prevalence of the infection. Interestingly, this is in agreement with (and provides theoretical support to) a hypothesis that has been recently put to experimental test in populations of *Z. brevicauda*, the host of the Calabazo Hantavirus, in field studies in Panama [19]. Similarly, also in Panama, it has been proposed that the maintenance of competitive populations may serve to reduce the risk to human populations exposed to *O. fulvescens* infected with the Choclo Hantavirus [9]. The proposal which has been called a "moat" consists of an area surrounding human habitation maintaining a diversity of innocuous species, competing with the hosts of the Hantavirus. Our results are summarized in Figure 5 in the form of a phase diagram, which generalizes Figure 1 with the addition of the carrying capacity of the aliens, κ. It can be seen that a critical *6* drives the system to a noninfected state. It is interesting to observe that the "strength" of the competition with the alien population, q, is the same for both susceptible and infected hosts. Indeed, both subpopulations are reduced as a result of the competition, but the infected population suffers the consequences in a stronger manner, becoming extinct in a critical way (see [17] for a discussion of this effect).

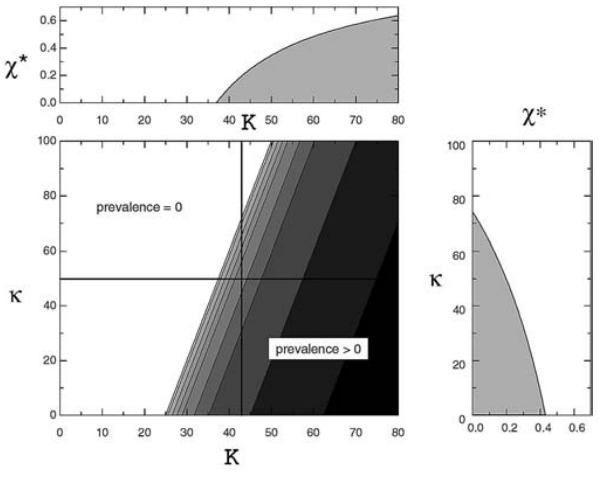

Figure 5. Phase diagram of the infection prevalence $\chi=m_i/m$, in the space defined by the host carrying capacity K and the alien carrying capacity κ. The contour plot shows the prevalence as shades of grey. The white region is the region of zero infection. The crossing lines indicate sections of the plot, shown in the upper and right side plots, where the prevalence is shown as a function of the relevant control parameter. The right panel represents the extinction of the infection controlled by the alien carrying capacity.

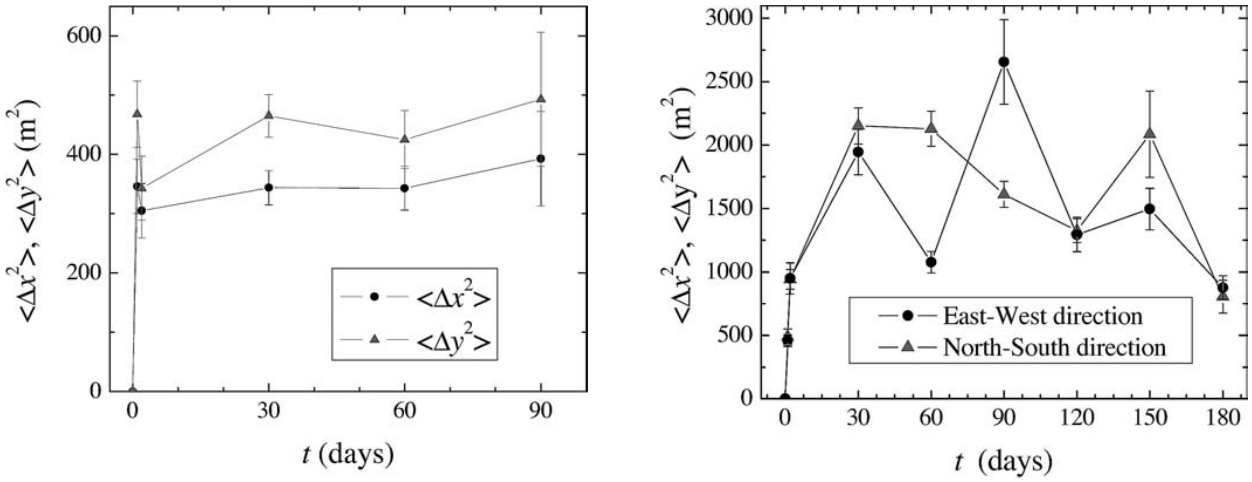

Figure 6. Mean square displacement as a function of time, from the two field works mentioned in the text (Panama, upper panel, and New Mexico, bottom).

6. MOUSE TRANSPORT

Many theoretical implications of the models presented in the previous sections have been, and are being, explored quite intensely. A major problem persists, nevertheless: the values of the parameters. Needless to say, the solution of this problem is crucial to the quantitative description of the spread of the epidemic. In a number of articles that rely heavily on six months of field work done in Panama [19] and over one decade in New Mexico [12] we have addressed this matter, in what regards the transport mechanism of mice [4, 7, 8]. Let us consider again Eqs. (2). There are several parameters in this equations, not all of them equally accessible to observation. On the one hand, the demographic parameters, b and c, are relatively easy to estimate from population data. On the other hand, the environmental parameter K can be obtained, at least in relative values, from satellite images or other remote sensing of the landscape. The contagion parameter a, unfortunately, has proven to be extremely difficult to measure, even in controlled experiments (which are particularly difficult because of the high levels of biosafety required). We chose to start with the diffusion coefficient D which, in principle, could be obtained from the data produced by the field work available, mentioned above. The task provided us, additionally, with an opportunity to assess the validity of the proposed diffusive transport, which sometimes is used for the lack of a better model, but which does not necessarily reflects the reality of the underlying animal phenomena (see the discussions in [15]).

From the field data we produced curves representing the mean square displacement of the mice as a function of time. These curves, shown in Figures 6, immediately indicate that, while the movement is initially diffusive, it saturates very fast to an asymptotic value, as if the animals were bound equilibrium positions, like the atoms in a crystal. This brings us back to the complexities of the underlying system: the objects we are describing do not move like free diffusive particles. They are mice, of diverse sexes, ages and correspondingly, behavior. And an unavoidable characteristic of adult mouse movement is the existence of a home range, where it passes the majority of its adult life. The saturation of the mean square displacement observed in Fig. 6 comes from the finite size of the home range. Unfortunately, the finitude of the capture grid used in the field work also contributes to the same saturation. Both effects need to be taken into consideration in the model. As a first

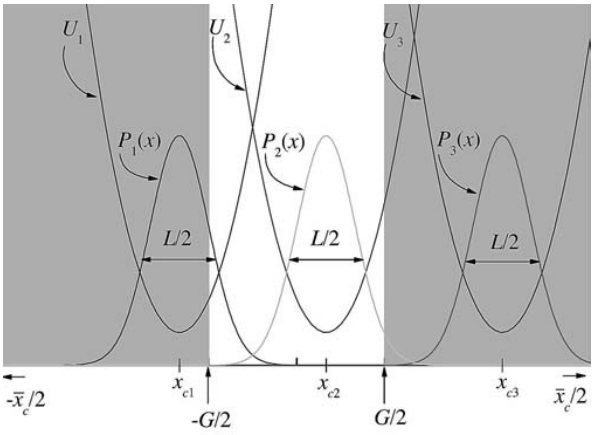

Figure 7. Illustration of the Fokker-Planck transport model. Three mice are shown, described by the probability density functions $P_i(x)$, each one living and diffusing within one of the potentials U_i. The central region, of width G, is the space accessible to observation, while the grey region is beyond reach of the capture grid.

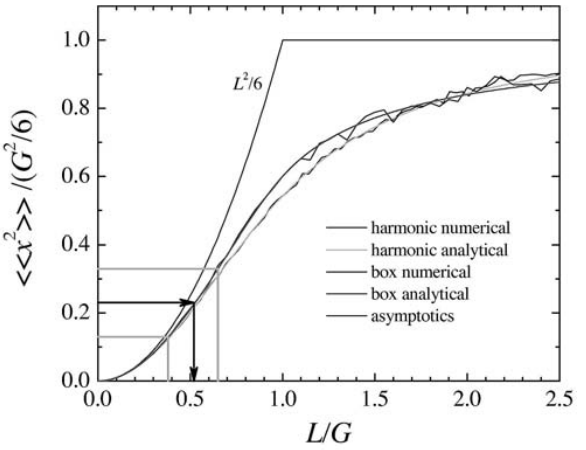

Figure 8. Stationary state of the mean square displacement, as a function of the ratio of the home range size to the grid size. Several possible potentials are shown. The arrows show the estimation of the home range size from the saturation values of the curves in Figure 6.

step, we have chosen a description in terms of a Fokker-Planck Equation, which is a diffusion equation in a constraining potential. Since the mice do not move as free diffusing particles, we choose to describe them as diffusing within a potential. An illustration of the idea is shown in Figure 7. Its mathematical formulation is:

$$\frac{\partial P(x,t)}{\partial t} = \frac{\partial}{\partial x}\left[\frac{dU(x)}{dx} P(x,t)\right] + D\nabla^2 P(x,t), \qquad (4)$$

Given a shape of the potential U (such as the parabolas used in Figure 7, it is possible to calculate the mean square displacement from Eq. (4), in some cases analytically. The diffusion coefficient follows from the short time behavior of the system. The long time behavior, on the other hand, gives information about the shape of U, or the home range size, and can be contrasted with the saturation value of observed displacements such as those shown in Figure 6. This is effectively, then, a method for calculating the (average) home range when no other observations (radio tracking, etc) are available. Figure 8 shows an example of such a calculation. Several curves are shown, corresponding to different chooses of the potential which give essentially the same results. The saturation of the mean square displacement from the New Mexico observation is shown as an arrow in the ordinate axis, from which the ratio between the home range length and the (known) grid length, is read in the abscissas.

7. CONCLUSIONS

We have shown that simple models of infection in the mouse population are able to capture the important effects controlled by the environment. As a result, several phenomena of the epizootic are observed, some in agreement with field observations, and other predicted: the extinction and spatial segregation of the infected population, the propagation of delayed infection fronts, the reduction of the prevalence by competition effect. We have also shown that relevant parameters of the system can be derived from limited data sets. Finally, even though mouse "transport" is more complex than diffusion, there is a certain possibility of analytical models of it to improve the analysis of the epizootic system. This, as well as other approaches, are currently under study.

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