Outbreaks of Hantavirus induced by seasonality

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Using a model for rodent population dynamics, we study outbreaks of Hantavirus infection induced by the alternation of seasons. Neither season by itself satisfies the environmental requirements for propagation of the disease. This result can be explained in terms of the seasonal interruption of the relaxation process of the mouse population toward equilibrium, and may shed light on the reported connection between climate variations and outbreaks of the disease.

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I. INTRODUCTION

Hantaviruses are rodent-borne zoonotic agents that may cause diseases in humans such as hemorrhagic fever with renal syndrome and Hantavirus pulmonary syndrome [1–3]. Hantaviruses have been identified at an increasing rate in recent years, and as of now about thirty different ones have been discovered throughout the world. One of these, the Sin Nombre virus, was not isolated until 1993 after an outbreak in the Four Corners region of the USA [1,2]. The host of this particularly dangerous virus is the deer mouse, *Peromyscus maniculatus*, the most numerous mammal in North America. The virus produces a chronic infection in the mouse population, but it is not lethal to them. It is believed that transmission in the rodent population is horizontal and due to fights, and that the subsequent infection of humans, where the mortality rate can be as high as 50%, is produced by their contact with the excreta of infected mice. Moreover, so far there is no vaccine or effective drug to prevent or treat the Hantavirus pulmonary syndrome. Therefore, a major effort has been launched to understand the population dynamics of deer mouse colonies in order to design effective prevention policies [1].

It has been noted that environmental conditions are directly connected to outbreaks of Hanta [2]. For instance, the 1993 and 1998 outbreaks occurring in the Four Corners Region have been associated with the so-called El Niño southern oscillation [2]. Related to this and other such observations, the effects of seasonality in ecological systems have been a subject of recent interest [4,5]. Multiyear oscillations of mammal populations [6], prey-predator seasonal dynamics [7], and persistence of parasites in plants between seasons [8] are examples that illustrate the importance of seasonality in population dynamics.

Recently, Abramson and Kenkre proposed a phenomenological model for mice population that successfully reproduces some features of Hantavirus propagation [9]. In particular that model explores the relation between resources in the medium, carrying capacity, and the spread of the infection in the rodent colony. Herein we study the effects of seasonality in that model. Our motivation is not only to provide more realism to the model, but also to investigate the counterintuitive effects that dynamic alternation may cause in a biological system. Brownian motors [10] and switching-induced morphogenesis [11] are examples that show that alternation in time of ''uninteresting'' dynamics may produce ''interesting'' outcomes. Along these lines, we will show that alternation of seasons, neither of which by itself fulfills the environmental requirements on the carrying capacity for spreading of the infection, may produce an outbreak of the disease. The mechanism driving this behavior is the interruption of the relaxation process that equilibrates the mouse population from season to season: if the relaxation time of the population becomes longer than the duration of seasons, the disease spreads.

The paper is organized as follows. In Sec. II we briefly review the model for mouse populations introduced in Ref. [9]. In Sec. III we explain how seasonality is introduced in that model and analyze the conditions for Hanta outbreaks to take place due to the alternation of seasons. The exact solution of the model and a particular example that illustrates the phenomenology are given in Sec. IV. The stability of our solutions is discussed in Sec. V. Finally, in Sec. VI, we summarize the main conclusions and propose some directions for future work.

II. THE MODEL

The model introduced in Ref. [9] for the temporal evolution of a population of mice subjected to the Hantavirus infection reads

$$\frac{dM_S}{dt} = bM - cM_S - \frac{M_S M}{K} - aM_S M_I, \tag{1a}$$

$$\frac{dM_I}{dt} = -cM_I - \frac{M_I M}{K} + aM_S M_I, \tag{1b}$$

where M_S and M_I are the population densities of susceptible and infected mice, respectively, $M = M_S + M_I$ is the total population of mice, and a, b, c, and K are positive constants. The terms on the right-hand sides of Eqs. (1a) and (1b) take into account the following processes: births with rate constant b, depletion by death with rate constant c, competition for the resources in the medium characterized by the carrying capacity K, and transmission of the infection with rate coef-

ficient a. Note that competition is less important when the carrying capacity is larger. The competition is assumed to be proportional to the probability of an encounter between a mouse of the population of interest (M_S or M_I) and any other mouse (M). It is worth noting that infected pregnant mice produce Hanta antibodies that keep their fetus free from the infection; that is, *all* mice are born susceptible [1], as indicated by the absence of a birth term in Eq. (1b). Note also the absence of a recovery term in the model since, as mentioned earlier, mice become chronically infected by the virus.

The system of Eqs. (1a) and (1b) has four equilibrium points. Two of them are irrelevant for the analysis: the null state $M_I=M_S=0$, which is always unstable if $b>c$ (a condition that we will assume throughout this paper), and a meaningless state with $M_I<0$ for any value of the parameters. The other two equilibria are

$$M_S=K(b-c), \quad M_I=0, \tag{2}$$

$$M_S=\frac{b}{a}, \quad M_I=K(b-c)-\frac{b}{a}. \tag{3}$$

The stability of the equilibrium points Eqs. (2) and (3) depends on the value of the carrying capacity. If $K<K_c=b/a(b-c)$ then Eq. (2) is stable and Eq. (3) unstable. If $K>K_c$ it is the other way around. That is, when the available resources, K, are below the critical value, K_c, the infection does not propagate in the colony, the whole population of mice grows healthy, and its size increases proportionally with those resources. If K surpasses K_c the virus spreads in the colony, the susceptible mouse population saturates, and the fraction of infected mice becomes larger as K increases (see Fig. 1).

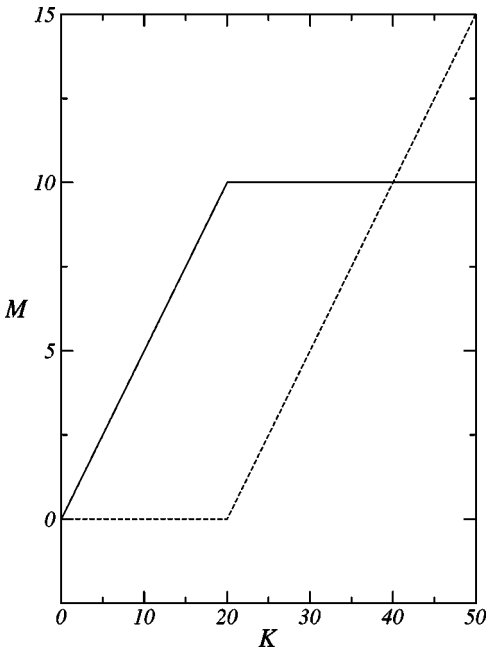

FIG. 1. Stable equilibrium population of susceptible (solid line) and infected (dashed line) mice as a function of the resources present in the medium, K. The values of the parameters are the same as those used in Ref. [9]: $a=0.1$, $b=1$, and $c=0.5$. The value of the critical carrying capacity is $K_c=20$.

III. SEASONAL ALTERNATION

The Four Corners Region, where an important number of cases of Hantavirus pulmonary syndrome have occurred, has a desert climate. The largest climate variations within this region come from periods of rain and of drought. With some delay, rainy and dry episodes lead to seasons that we will call ''mild'' and ''harsh,'' and we will assume alternation in time between these two seasons. It is important to remark that a two-season assumption is not crucial, and that the analysis with four seasons is also straightforward within the formalism introduced herein. During each of the two seasons under consideration we assume there to be no climate variations, so that each season can be characterized by a set of time-independent parameters $\{\rho_i\}=\{a_i,b_i,c_i,1/K_i\}$, where $i=1,2$. We implement square-periodic season alternation where the duration of each season is $T/2$. In dimensioned units T is thus one year. Note that other alternation sequences, e.g., different durations of the seasons (even with more of them fitting within T), or even random switching between seasons, do not qualitatively change the phenomenology.

Any quantity $\rho(t)$ alternating in the way described above can be written as

$$\rho(t)=\rho_+ + \rho_- \mu(t), \tag{4}$$

where $\rho_\pm=\frac{1}{2}(\rho_1 \pm \rho_2)$ and $\mu(t)$ is a periodic square wave

$$\mu(t)=\begin{cases} 1 & : \quad 0<t<\dfrac{T}{2} \\ -1 & : \quad \dfrac{T}{2}<t<T. \end{cases} \tag{5}$$

There are unfortunately very few experimental data available for the model parameters, which we thus choose to be consistent with data when possible but otherwise select on the basis of reasonable qualitative arguments. We thus suppose the following conditions for the sets $\{\rho_i\}$ according to seasonality:

$$a_1<a_2, \quad b_1<b_2, \quad c_1<c_2, \quad K_1>K_2, \tag{6}$$

where 1 stands for the mild season and 2 for the harsh one. The biological motivation for these inequalities is the following. The harsh season provides less resources for the colony than the mild season ($K_2<K_1$), and as a consequence the death rate is higher ($c_2>c_1$). The transmission rate is also larger ($a_2>a_1$) under the assumption that fights for the available resources increase in harsh times.

While these inequalities for K, c, and a are intuitively straightforward, our assumption that the birth rate is larger during the harsh season ($b_2>b_1$) (albeit by a very small amount, cf. below) requires further argumentation. One might interpret the parameter b not as a simple birth rate but rather as the rate at which new mice able to propagate the

disease become part of the population (only adult mice seem to fight). Due to the period of maturation, the parameter b would then reflect the birth rate but at an earlier time [1]. A better way to deal with this time shift might be to introduce an explicit delay in the equations of evolution, but this would render the model far more complex than warranted in view of other simplifying assumptions that have been made. Equivalently, we might want to subdivide T more finely. As mentioned earlier, at least in the adiabatic limit this would not affect the qualitative outcome. It will be shown later that our simplified assumption leads to a situation with highest population toward the end of the mild season and lowest population toward the end of the harsh one, in agreement with the available data [1,2]. We do note that given the other parameter inequalities, the assumption $b_1<b_2$ is necessary for the model to lead to the effect that we wish to illustrate herein. If the assumption turns out to be invalid, then the mechanism that we propose would require the reversal of another inequality, which could perhaps also be argued on biological grounds. For example, one might find that fighting among mice is driven mainly by mating competition, which would lead to $a_1>a_2$. These facts can, of course, only be ascertained one way or another through experimental data, which is unfortunately not available at this point. We do note that the magnitude of the reversal assumed in our model can be very small; in our later application we take b_2 to be only 1.4% greater than b_1.

Our critical assumption is that $(K_1,K_2)<\min(K_{c1},K_{c2})$, i.e., that the resources are *at all times* (during *both* seasons) *below* the minimum critical threshold that triggers the propagation of the disease. We will show that nevertheless it is possible for the infection to spread. This is the main point of our work.

The equilibrium populations of the susceptible and infected mice are determined by the sets of values $\{\rho_i\}$. When switching from season to season, the populations evolve trying to reach a new equilibrium. Therefore, the dynamics is driven by the competition between two characteristic times. On the one hand there is an *external* time scale determined by the seasonal forcing, $t_{ext}=T/2$. On the other hand, the relaxation toward equilibrium after a switching of seasons involves a relaxation time. The latter measures the time required for the mouse colony to relax to the equilibrium state associated with $\{\rho_j\}$ after having been driven during the previous season by the conditions $\{\rho_i\}$, that is, $t_r(i\rightarrow j)$ where $i,j=1,2$. The *internal* time scale is defined as the fastest relaxation process, i.e., $t_{int}=\min[t_r(i\rightarrow j)]$. ''Fast'' or ''slow'' seasonal alternation then refers to the comparison between these two time scales. If $t_{ext}\gg t_{int}$ the mouse population has enough time to accommodate to the new conditions from season to season and relax to equilibrium. Moreover, since we have imposed the condition that the resources at any time of the year are below the critical thresholds K_{ci}, there will be no infected mice. In the other limit, $t_{ext}\ll t_i$, seasonal changes occur too fast, the relaxation process is interrupted, and no equilibrium can be reached from season to season. In this case an adiabatic elimination can be implemented [12], and $\mu(t)$ in Eq. (4) can be replaced by its average value, $\langle\mu(t)\rangle=0$. Therefore, in the limit of fast season alternation the system is driven by the set of averaged values $\{\rho_+\}=\{a_+,b_+,c_+,(1/K)_+\}$, and the critical carrying capacity is given by $K_{c+}=b_+/a_+(b_+-c_+)$. As a consequence, it is possible to find regions of parameters where K_{c+} is smaller than the *effective* value of the carrying capacity associated with the averaged values,

$$\left[\left(\frac{1}{K}\right)_+\right]^{-1}=\left[\frac{1}{2}\left(\frac{1}{K_1}+\frac{1}{K_2}\right)\right]^{-1}=\frac{2K_1K_2}{K_1+K_2}, \tag{7}$$

and the infection propagates.

General conditions leading to these behaviors are given later in Sec. V, but the expressions are rather cumbersome. Instead, here we choose a particular set of parameters to illustrate these points:

$$a_1=\frac{1}{4},\quad b_1=1,\quad c_1=\frac{1}{3}, \tag{8}$$

$$a_2=4,\quad b_2=\frac{73}{72},\quad c_2=1. \tag{9}$$

These parameter choices lead to $K_{c1}=6$ and $K_{c2}=73/4$, respectively. Some important observations about these particular parameter choices are in order. For the a_i there seem to be no experimental data, so these choices (subject to the inequality $a_2>a_1$) are rather arbitrary. The death rates c_i are separately not based on data (unavailable), but are consistent with the average reported lifetimes of 18 months. The seasonal difference in the maturation rates is very small ($\sim 1\%$) but, as noted earlier, the inequality $b_2>b_1$ is necessary for the model. Again, we could not find specific data for these values. We do note that the chosen values lead to a net rate of increase $(b-c)$ that is larger in the mild season, $b_1-c_1\gg b_2-c_2$, in agreement with observations [1].

The dynamics are completely determined once the value of the carrying capacity during each season is specified. According to the previous discussion, these parameters can be chosen such that the following conditions hold:

$$[(1/K)_+]^{-1}>K_{c+},\quad K_1>K_2,\quad K_1<\min(K_{c1},K_{c2}).$$

These conditions lead to the points (K_1,K_2) that fulfill the seasonal requirements given by Eq. (6), so that slow alternation of seasons leads to infection-free states while fast alternation leads to Hanta outbreaks. This region is plotted in Fig. 2 for two values of the period T. In some of our calculations we have chosen the particular point $(K_1=4,K_2=1)$ for our illustrations. This point satisfies the conditions $K_i<K_{ci}$ and lies inside the epidemic region in both cases in the figure. In the following section we illustrate the seasonality-induced propagation of the disease for this particular point.

It is important to clarify a matter of terminology used above and subsequently. When we refer to ''fast'' or ''slow'' alternation, or to ''short'' and ''long'' seasons, we do not really mean that T varies. T is to be thought of as one year. Instead, we are talking about variations in the values of the relaxation time t_{int}, determined by model parameter choices, relative to the fixed value of the seasonal duration t_{ext}

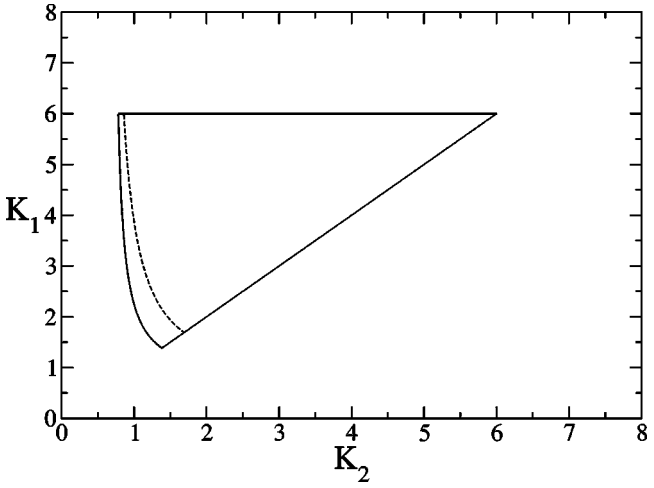

FIG. 2. (K_1,K_2) regions of disease propagation due to seasonal alternation. The values of the other relevant parameters are given in Eqs. (8) and (9). The straight lines are common to all values of the period T. The solid curve is for an extremely short period, $T\to 0$, and the dashed curve is for $T=11$. Every value of K_1 or K_2 within either enclosed area by itself does *not* satisfy the required environmental conditions that support spreading of the virus in the mice colony. Yet, those same points lead to outbreaks of Hanta upon seasonal alternation.

$=T/2$. The terminology is thus simply a matter of analytic convenience because it is simpler to speak in terms of varying the single parameter T for a fixed set of system parameters than it is to do the converse. The qualitative information conveyed either way is of course the same.

IV. THE CRITICAL PERIOD

So far we have determined that outbreaks of Hanta induced entirely by seasonal changes can occur if the duration of the seasons is short enough relative to t_{int}. Now we establish the meaning of ''short enough'' quantitatively. Since K_{c+} is strictly smaller than the effective value of the carrying capacity, we assume that there is a finite value of T_c such that for any $T<T_c$ the population of infected mice is greater than zero, but for periods above this critical period the infected population goes to zero. A more rigorous argument for the existence of T_c that does not rely on any of the assumptions made in this section is given in Sec. V. Here, in order to obtain the value of the critical period we solve the system of Eqs. (1a) and (1b). In spite of its nonlinearities the system can be solved analytically by means of a reciprocal transformation [13] and the following exact solution is obtained:

$$M_I(t,M_{I,0},M_{S,0};\{\rho\})=\frac{M_{I,0}\Omega(t)}{(Kg)^{aK-1}+aM_{I,0}\int_0^t\Omega(\tau)d\tau}, \tag{10a}$$

$$M_S(t,M_{I,0},M_{S,0};\{\rho\})=\frac{KgM_0e^{gt}}{(\Omega(t)e^{ct})^{\frac{1}{aK-1}}}-\frac{M_{I,0}\Omega(t)}{(Kg)^{aK-1}+aM_{I,0}\int_0^t\Omega(\tau)d\tau}, \tag{10b}$$

where $M_{I,0}$ and $M_{S,0}$ are the initial conditions for M_I and M_S, respectively, and the following definitions have been introduced:

$$\Omega(t)=e^{-ct}(M_0(e^{gt}-1)+Kg)^{aK-1},$$

$$g=(b-c),\quad M_0=M_{I,0}+M_{S,0}.$$

Because the external forcing due to the alternation of seasons is periodic, we search for a periodic solution. The values of $M_{I,0}$ and $M_{S,0}$ compatible with the nonequilibrium periodic solution can be obtained by evolving the system during the first half of a period under dynamics 1 and the second half under dynamics 2, and forcing periodicity on the solutions after a whole period of evolution, that is,

$$M_I\left(\frac{T}{2},M_I\left(\frac{T}{2},M_{I,0},M_{S,0};\{\rho_1\}\right),M_S\left(\frac{T}{2},M_{I,0},M_{S,0};\{\rho_1\}\right);\{\rho_2\}\right)=M_{I,0}, \tag{11a}$$

$$M_S\left(\frac{T}{2},M_I\left(\frac{T}{2},M_{I,0},M_{S,0};\{\rho_1\}\right),M_S\left(\frac{T}{2},M_{I,0},M_{S,0};\{\rho_1\}\right);\{\rho_2\}\right)=M_{S,0}. \tag{11b}$$

In order to close the system in the nonequilibrium stationary state $M_I(t,T;\{\rho_{1,2}\})$ and $M_S(t,T;\{\rho_{1,2}\})$, the values of $M_{I,0}$ and $M_{S,0}$ that solve the system of Eqs. (11a) and (11b) must be reintroduced in Eqs. (10a) and (10b). As we will show in Sec. V, the solution is not unique, but only one pair is nonnegative and stable, and this is the solution at issue here. The critical period is then the largest value of T satisfying the condition

$$M_I(t,T;\{\rho_{1,2}\})>0 \tag{12}$$

(the solution $M_I=0$ becomes unstable, see Sec. V).

We illustrate the procedure with the example mentioned above where the parameters are given by Eqs. (8) and (9), and with $K_1=4$ and $K_2=1$. The results are shown in Figs. 3–5. The values of M_I and M_S as a function of the period of the seasons are depicted in Fig. 3, where the populations of

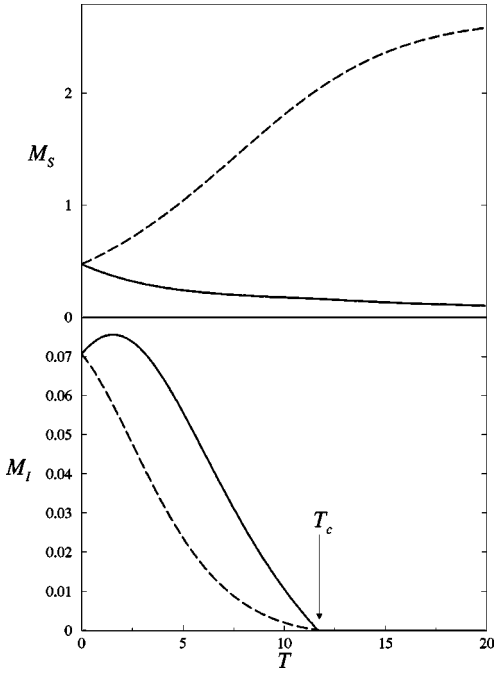

FIG. 3. Population of susceptible (top) and infected (bottom) mice vs the period of the seasons. The dashed and continuous lines indicate the populations at the end of the mild and harsh seasons, respectively. The critical period for which the virus begins to spread due to seasonality is $T_c \simeq 11.67$. The values of the relevant parameters are $a_1 = 1/4$, $b_1 = 1$, $c_1 = 1/3$, $K_1 = 4$, and $a_2 = 4$, $b_2 = 73/72$, $c_2 = 1$, $K_2 = 1$ for the mild and harsh seasons, respectively.

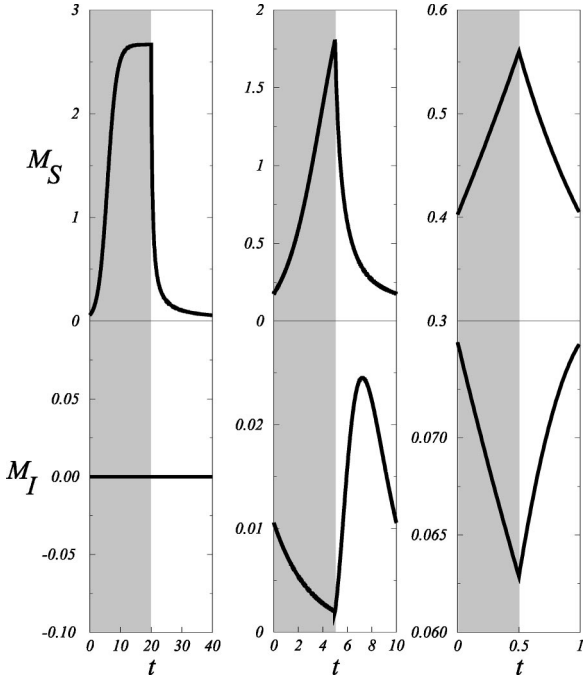

FIG. 4. Population of susceptible (top) and infected (bottom) mice vs time for a period of evolution. The values of the relevant parameters are the same as those used in Fig. 3. The critical period is $T_c \simeq 11.67$. Left panel: Results for a very long period ($T = 40$). Right panel: short period ($T = 1$). Central panel: Results for a near-critical period ($T = 10$). In all cases the first semiperiod (shadowed region) corresponds to the mild season and the second to the harsh one.

the susceptible and infected mice at the end of each season are given. As seen in that figure, the value of the critical period for these particular values of the K_i is $T_c \simeq 11.67$ (see Sec. V for a more detailed calculation of this value). Note that if the alternation is slow, $T > T_c$, all mice grow healthy. On the other hand, if the alternation is faster than the relaxation time required by the colony to accommodate its population from season to season, $T < T_c$, the virus spreads and $M_I > 0$. Our specific sample system with $T = 1$ (a ''special'' value in that it can be thought of as one year) lies well below this critical value, in the ''fast'' alternation region. Note that in the limit $T \to 0$ the dynamics is driven by $\{\rho_+\}$ and the populations of susceptible and infected mice are given by Eq. (3) with $a = a_+$, $b = b_+$, $c = c_+$, and $1/K = (1/K)_+$. We emphasize that the carrying capacity is below its critical threshold at any time.

In Fig. 4 we plot, for different period lengths, the solutions $M_I(t,T;\{\rho_{1,2}\})$ and $M_S(t,T;\{\rho_{1,2}\})$ as a function of time through one period of evolution. The first semiperiod corresponds to the mild season and the second to the harsh season. When seasons last long (left panel), there are no infected mice and the susceptible population simply oscillates between the two equilibrium states given by Eq. (2). For sufficiently short seasons (right panel), there is propagation of the disease and the values of M_I and M_S fluctuate around the equilibrium points determined by Eq. (3) and the set of parameters $\{\rho_+\}$. Finally, when the period of the seasons is near, but below, the critical period (central panel), the infected population is small and the population M_I oscillates in a more pronounced manner. The associated graphs showing susceptible vs infected mice through one period are shown in Fig. 5. Note that $T = 1$ indeed leads to a spread of the disease. An explicit feature of the actual data that our model as shown in Fig. 4 captures is the observation that the infected and healthy mice population maxima are out of phase, and that the maximum of the infected population occurs within (near the end of) the harsh season [1]. This may serve as an *a posteriori* indication that, in the absence of experimental data to the contrary, our assumptions about the values of the parameters may be biologically relevant.

V. STABILITY OF SOLUTIONS

In order to complete our analysis we need to ascertain the stability of our solutions, which requires an analysis that goes beyond simply finding the solutions. For this purpose, it is convenient to work with the variables $M = M_S + M_I$ and M_I. Addition of Eqs. (11a) and (11b) with Eqs. (10a) and (10b) then yields the relation that determines the fixed point of the Poincaré map for the total number of mice [14],

$$M(T;M_0) = M_0, \tag{13}$$

which yields two solutions. One is the uninteresting null solution

$$M_{0,1} = 0, \tag{14}$$

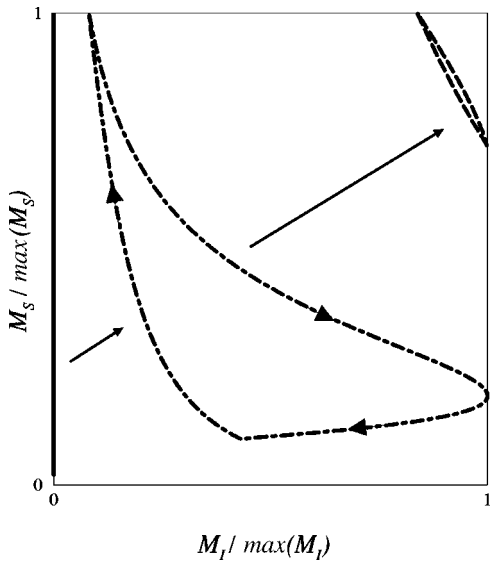

FIG. 5. Population of susceptible mice vs infected mice (both normalized to their respective maxima) for a period of evolution. The values of the relevant parameters are the same as those used in Figs. 3 and 4. For a very long period ($T=40$) there are no infected mice, and the susceptible mouse population oscillates up and down the vertical axis, indicated by a bold solid line. Strictly speaking, the solid line should be drawn on the right axis since $\lim_{M_I\to 0} M_I/\max(M_I)\to 1$. However, we have placed it on the left axis to emphasize the actual value $M_0\to 0$. For a near-critical period ($T=10$) the populations undergo a cyclic variation as indicated by the dash-dotted curve. This cyclic variation becomes narrower with decreasing period, e.g., the dashed curve for $T=1$. As $T\to 0$ the cycle reduces to a single point corresponding to the values given in Eq. (3) with the average parameters.

and the other is

$$M_{0,2}=\frac{(b_1-c_1)K_1}{1+\dfrac{(e^{(c_2-b_2)T/2}-1)[(b_1-c_1)K_1-(b_2-c_2)K_2]}{(b_2-c_2)(e^{(c_1+c_2-b_1-b_2)T/2}-1)K_2}}. \tag{15}$$

Linearization of the Poincaré map about these solutions, $M_i=M_{0,i}+\delta M_i$, leads to

$$M(T;M_1)=e^{-(c_1+c_2-b_1-b_2)T/2}\delta M_1+o(\delta M_1^2) \tag{16}$$

and

$$M(T,M_2)=M_{0,2}+e^{(c_1+c_2-b_1-b_2)T/2}\delta M_2+o(\delta M_2^2). \tag{17}$$

Thus the null solution is unstable and the closed orbit stable for all finite periods provided $b_1+b_2>c_1+c_2$, i.e., provided the death rate does not overwhelm the birth/maturation rate. In our explicit examples we have implemented this condition.

With this condition on the parameters, we can now use the stable solution for $M(t)$ and substitute it in the equation for $M_I(t)$, which can now be written as the set of equations

$$\frac{dM_I}{dt}=-\left[c-\left(a-\frac{1}{K}\right)M(\theta)\right]M_I-aM_I^2, \tag{18a}$$

$$\frac{d\theta}{dt}=1. \tag{18b}$$

Our goal is to establish the conditions that lead to the stability of a solution involving a finite positive number of infected mice. While it might be desirable to find all the solutions of Eqs. (18a) and (18b) and establish their stability as we did for M, this is analytically intractable and not necessary. It is sufficient (as it would have been for M) to establish the stability properties of the null solution $M_I=0$; if this solution is *unstable*, there will be an epidemic. We therefore only need to consider the system of equations linearized about the null solution, which leads to the reduced problem

$$\frac{dM_I}{dt}=-\left[c-\left(a-\frac{1}{K}\right)M(t)\right]M_I. \tag{19}$$

This equation can again be solved exactly and thus again allows construction of a Poincaré map. We obtain

$$\begin{aligned}M_I(T/2;M_{I,0})=&e^{-(b_1-a_1b_1K_1+a_1c_1K_1)T/2}\\&\times[(b_1-c_1)K_1]^{(1-a_1K_1)}\\&\times[e^{(c_1-b_1)T/2}(b_1K_1-c_1K_1-M_0)\\&+M_0]^{a_1K_1-1}M_{I,0},\end{aligned} \tag{20a}$$

$$\begin{aligned}M_I(T;M_{I,0})=&e^{-(b_2-a_2b_2K_2+a_2c_2K_2)T/2}\\&\times[(b_2-c_2)K_2]^{(1-a_2K_2)}\\&\times[e^{(c_2-b_2)T/2}(b_2K_2-c_2K_2-M_0')\\&+M_0']^{a_2K_2-1}M_I(T/2;M_{I,0}),\end{aligned} \tag{20b}$$

where $M_{I,0}$ is, as before, the initial condition for the infected mice, and M_0 and M_0' in the second equation are shorthand notations, respectively for $M(T;M_0)$ and $M(T/2;M_0)$ for the stable orbit. We can find the fixed points of the Poincaré map by solving for the fixed point,

$$M_I(T,M_{I,0})=M_{I,0}. \tag{21}$$

This equation has the unique solution

$$M_{I,0}=0, \tag{22}$$

as expected. A small deviation of the Poincaré map around this null solution (no further linearization is necessary since the map itself is linear) leads to

$$m\equiv\frac{M_I(T,M_{I,0})}{M_{I,0}}=A_1\times\left(\frac{A_2}{A_3}\right)^{a_2K_2}\times\left(\frac{A_4}{A_5}\right)^{a_1K_1}. \tag{23}$$

Here

$$A_1\equiv e^{-(b_1+b_2-a_1g_1K_1-a_2g_2K_2)T/2}(g_1K_1)^{-a_1K_1}(g_2K_2)^{-a_2K_2}, \tag{24}$$

$$A_2 \equiv g_2 K_2 [g_1 (e^{-g_2 T/2} - 1) K_1 + g_2 e^{-g_2 T/2} (e^{-g_1 T/2} - 1) K_2], \tag{25}$$

$$A_3 \equiv g_2 (e^{-g_1 T/2} - 1) K_2 + g_1 e^{-g_1 T/2} (e^{-g_2 T/2} - 1) K_1 . \tag{26}$$

$$A_4 \equiv g_1 K_1 [g_2 (e^{-g_1 T/2} - 1) K_2 + g_1 e^{-g_1 T/2} (e^{-g_2 T/2} - 1) K_1], \tag{27}$$

$$A_5 \equiv g_1 (e^{-g_2 T/2} - 1) K_1 + g_2 e^{-g_2 T/2} (e^{-g_1 T/2} - 1) K_2, \tag{28}$$

and

$$g_i \equiv (b_i - c_i). \tag{29}$$

If $m > 1$, *the null solution is unstable*. Note that the system of Eqs. (18a) and (18b) can be written as $d(M_I, \theta)/dt = f[(M_I, \theta)]$, where $f[(M_I, \theta)]$ is piecewise continuously differentiable, with discontinuities only in the variable θ at the integer and half-integer multiples of T. Therefore, between the discontinuities of $f[(M_I, \theta)]$, the solution of the differential equation exists, is unique, and is smooth. Since we take the final point of every semiperiod as the initial condition for the next one, we can claim existence and uniqueness of the solution for all values of t, as well as continuity for every t. This implies that if $M_I > 0$, it will remain positive for all times. Since the system has the unique fixed point $M_I = 0$, our nonzero initial condition will not encounter any steady state. Furthermore, $M_I < M$, and since M is bounded (as we established, it performs a stable closed orbit), M_I is bounded. We can thus conclude that for $m > 1$, M_I must perform a closed orbit in a region of the phase space with $0 < M_I < M$ for all time.

We have therefore established $m > 1$ as the general condition for an outbreak to occur in our seasonal environment. This condition is entirely general, i.e., it holds *for all possible values of the model parameters and for all possible values of the period*. We can thus easily establish whether or not a given set of parameters will lead to an epidemic. For the particular values of the parameters a_i, b_i, c_i that we have chosen for our illustrations in the previous sections, we find that seasonality-induced outbreak for $K_1 = 4$, $K_2 = 1$ occurs only in the open interval $0 < T < T_c$, with $T_c \simeq 11.67$ (cf. Fig. 2).

It is interesting to ascertain the behavior of the system in the limit $T \to 0$, since we discussed this behavior earlier as an adiabatic elimination limit [cf. Eq. (7)]. For this case we can expand m in a McLaurin series in the period and retain only the first order:

$$m = 1 - \frac{[(b_1 + b_2) K_1 + (b_1 b_2 - (a_1 + a_2)(b_1 + b_2 - c_1 - c_2) K_1) K_2]}{2(K_1 + K_2)} T + o(T^2). \tag{30}$$

In this case $m > 1$ if and only if

$$K_1 > - \frac{(b_1 + b_2) K_2}{b_1 + b_2 - (a_1 + a_2)(b_1 + b_2 - c_1 - c_2) K_2}, \tag{31}$$

which is exactly the condition obtained with an adiabatic elimination.

Finally, we stress that the condition $m > 1$ can be used to calculate the conditions for the outbreak to occur for any combination of parameters, not only those we have chosen to focus on in this paper and that lead to $0 < T < T_c$ with $T_c \simeq 11.67$. In particular, it is interesting to note that for the particular values of the a's, b's and c's used in our illustration, when the period exceeds the value $T \simeq 242.73$ there are no values of K_1, K_2 that lead to an outbreak, i.e., the enclosed region illustrated in Fig. 2 shrinks away completely.

VI. CONCLUSIONS

By introducing seasonality in a paradigmatic model for Hantavirus propagation in mice colonies, we have shown that the alternation of seasons may cause outbreaks of the disease. The striking feature of that behavior lays in the fact that neither season satisfies the conditions for the infection to spread in terms of the availability of resources. The mechanism responsible for the phenomenon is the competition between two time scales: an external one, the duration of a season, and an internal one, the relaxation time for the mouse colony to equilibrate its population from season to season. We have shown that if the relaxation time were shorter than the duration of the seasons, no propagation of Hantavirus would occur. On the other hand, if the relaxation process is interrupted by the seasonal alternation, the disease spreads. We have analyzed the general conditions for which the phenomenon occurs, and established the stability of the solutions that characterize an outbreak. Moreover, we have illustrated the mechanism with a particular example based on physically reasonable parameter choices consistent with data where available.

This work may help to clarify the reported relation between climate and propagation of Hanta in mice populations. However, to elucidate whether the proposed phenomenon actually takes place in nature we depend on data that unfortunately are not available in the literature. One can envision further modifications of the model that may improve its features, such as, for example, the inclusion of spatial dependence [9,13], of explicit delay effects, or of noisy contributions to the dynamics. Finally, we stress that the general idea underlying the mechanism may be extended to other systems where seasonality plays a relevant role. Work along these directions is in progress.

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