Outbreaks of Hantavirus induced by seasonality

C. Escudero†, J. Buceta‡, F. J. de la Rubia†, and Katja Lindenberg‡

†Departamento de Física Fundamental,
Universidad Nacional de Educación a Distancia,
C/ Senda del Rey 9, 28040 Madrid, Spain
‡Department of Chemistry and Biochemistry,
and Institute for Nonlinear Science,
University of California San Diego,
9500 Gilman Dr., La Jolla, CA 92093-0340, USA

Abstract

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.

PACS numbers: 87.19.Xx, 87.23.Cc, 05.45.-a
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, 2, 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 in 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 fifty percent, 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 made to understand the population dynamics of deer mice 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]. Multi-year 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 have 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 duration of seasons becomes shorter than the relaxation time of the population, the disease spreads.

The paper is organized as follows. In Sec. II we briefly review the model for mouse populations introduced in [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 is given in Sec. IV. Finally, in Sec V we summarize the main conclusions and propose some directions for future work.

II. THE MODEL

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

\[
\frac{dM_S}{dt} = bM - cM_S - \frac{M_SM}{K} - aM_SM_I, \\
\frac{dM_I}{dt} = -cM_I - \frac{M_SM}{K} + aM_SM_I,
\]

(1a) (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 coefficient \( a \). 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 equations (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 \( M_I < 0 \).
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 $K_c = 20$.

for any value of the parameters. The other two equilibria are

$$M_S = K(b - c) \quad M_I = 0,$$

(2)

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

(3)

The stability of the equilibrium points (2) and (3) depends on the value of the carrying capacity. If $K < K_c = \frac{1}{a} \left( \frac{b}{b - c} \right)$ then (2) is stable and (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. As soon as $K$ 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).
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 the alternation between dry and rainy seasons. We will therefore assume alternation in time of 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 \( T/2 \). Again, this particular alternation pattern is not essential for the mechanism. Other schemes of season alternation, e.g. different duration of the seasons or random switching between seasons, do not qualitatively change the phenomenology.

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

\[
\rho(t) = \rho_+ + \rho_- \mu(t),
\]

(4)

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

\[
\mu(t) = \begin{cases} 
1 & : 0 < t < \frac{T}{2} \\
-1 & : \frac{T}{2} < t < T 
\end{cases}
\]

Let us now suppose the following conditions for the sets \( \{\rho_i\} \) according to seasonality:

\[
a_1 < a_2, \quad b_1 < b_2, \quad c_1 < c_2, \quad K_1 > K_2,
\]

(5)

where 1 stands for the rainy season and 2 for the dry one. The biological motivation for these conditions is the following. The dry season provides less resources for the colony than the rainy season \( (K_2 < K_1) \), and as a consequence the death rate is higher \( (c_2 > c_1) \), and the transmission rate is also larger since fights for the available resources are expected to increase \( (a_2 > a_1) \). However, notice that we consider the birth rate to be larger during the dry season \( (b_2 > b_1) \). There are two reasons for this. First is the assumption that the colony makes an attempt to maintain its population. Second is an implementation of the maturation process in the model: baby mice do not contribute to the propagation of the disease [1], and, therefore, even if births were actually more numerous during the rainy season, the
FIG. 2: \((K_1, K_2)\)-region of disease propagation due to seasonal alternation. The values of the other relevant parameters are given in Eqs. (6) and (7). Every value of \(K_1\) or \(K_2\) within the 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 when alternation of seasons is sufficiently fast.

The contribution of this fact to the propagation of the infection will only be important in the next (dry) season, when mice have matured and are ready to fight. It will be shown later that these assumptions lead to a situation with high population during the rainy season and low population during the dry one, in agreement with the available data [1, 2].

Moreover, we assume that \(K_1 < \min(K_{c1}, K_{c2})\), i.e., the resources are 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.

The equilibrium populations of the susceptible and infected mice are determined by the set 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, \(t_e = T/2\). 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., \( t_i = \min[t_r(i \rightarrow j)] \).

“Fast” or “slow” seasonal alternation then refers to the comparison between these two time scales. If \( t_e \gg t_i \) 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, \( t_e \ll t_i \), seasonal changes occur too fast, the relaxation process is interrupted, and no equilibrium can be reached from season to season. Then note that 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 \( K_{c+} = \frac{b_+}{a_+(b_+-c_+)} \). 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:

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

and the infection propagates.

General conditions leading to this behavior can be posed, but the expressions are rather cumbersome. We prefer, for the sake of simplicity, to show a particular typical case. We use the following values for the parameters:

\[
a_1 = \frac{1}{4}, \quad b_1 = 1, \quad c_1 = \frac{1}{3}, \quad (6)
\]

\[
a_2 = 4, \quad b_2 = \frac{73}{72}, \quad c_2 = 1, \quad (7)
\]

that lead to \( K_{c1} = 6 \) and \( K_{c2} = 73/4 \) respectively. 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:

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

These conditions lead to the points \( (K_1, K_2) \) that fulfill the seasonal requirements given by Eq. (5), 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. Notice in particular that the point \((K_1 = 4, K_2 = 1)\) lies inside the region and that \(K_i < K_{ci}\). In the next section we illustrate the seasonality-induced propagation of the disease for this particular point.

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 are short enough. Now we establish the meaning of “short enough” quantitatively. Since \(K_{c+}\) is strictly smaller than the effective value of the carrying capacity, there should be 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.

In order to obtain the value of the critical period we need to solve the system of equations (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:

\[
M_I(t, I_0, S_0; \{\rho\}) = \frac{I_0 \Omega(t)}{S^{aK-1} + aI_0 \int_0^t \Omega(\tau)d\tau}, \quad (8a)
\]

\[
M_S(t, I_0, S_0; \{\rho\}) = \frac{SM_0e^{\frac{t}{K} - 1}}{(\Omega(t)e^{ct})^{\frac{1}{aK-1}}} - \frac{I_0 \Omega(t)}{S^{aK-1} + aI_0 \int_0^t \Omega(\tau)d\tau}, \quad (8b)
\]

where \(I_0\) and \(S_0\) are the initial conditions for \(M_I\) and \(M_S\) respectively, and the following definitions have been introduced,

\[
\Omega(t) = e^{-ct} \left(M_0 \left(e^{\frac{t}{K}} - 1\right) + S\right)^{\frac{1}{aK-1}},
\]

\[S = K(b - c), \quad M_0 = I_0 + S_0.\]

Because the external forcing due to the alternation of seasons is periodic, Floquet theory ensures the existence of a periodic solution. The values of \(I_0\) and \(S_0\) compatible with the non-equilibrium 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,

\[
M_I \left(\frac{T}{2}, M_I \left(\frac{T}{2}, I_0, S_0; \{\rho_1\}\right)\right) = I_0, \quad M_S \left(\frac{T}{2}, I_0, S_0; \{\rho_1\}\right) = S_0, \quad (9a)
\]

\[
M_I \left(\frac{T}{2}, M_I \left(\frac{T}{2}, I_0, S_0; \{\rho_1\}\right)\right) = I_0, \quad M_S \left(\frac{T}{2}, I_0, S_0; \{\rho_1\}\right) = S_0. \quad (9b)
\]
FIG. 3: Population of susceptible (top) and infected (bottom) mice versus the period of the seasons. The dashed and continuous lines indicate the populations at the end of the rainy and dry seasons respectively. The critical period for which the virus begins to spread due to seasonality is $T_c \simeq 12$. 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 rainy and dry seasons respectively.

In order to close the system in the non-equilibrium steady state $M_I (t, T; \{\rho_{1,2}\})$ and $M_S (t, T; \{\rho_{1,2}\})$, the values of $I_0$ and $S_0$ that solve that system of equations (9a) and (9b) must be then re-introduced in Eqs. (8a) and (8b). The critical period is then the largest value of $T$ satisfying the condition

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

We illustrate the procedure with the example mentioned above where the parameters are given by Eqs. (6) and (7), and with $K_1 = 4$ and $K_2 = 1$. The results are shown in Figs. 3 and 4. 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 the susceptible and infected mice at the end of each season are given. As seen in that figure, the value of the critical period is $T_c \simeq 12$. 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 $M_I > 0$. Notice that in the limit $T \to 0$ the
V. 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 duration of the seasons is longer than the relaxation time, no propagation of Hantavirus occurs. On the other hand, if the relaxation process is interrupted by a fast seasonal alternation, the disease spreads. We have analyzed the general conditions for which the phenomenon occurs. Moreover, we have illustrated the mechanism with a particular example that can be solved exactly.

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 or of noisy contributions to the dynamics. Finally, we stress that the general idea underlying the mechanism is model-insensitive and can therefore be extended to other systems where seasonality plays a relevant role. Work along these directions is in progress.

Acknowledgments

The authors gratefully acknowledge fruitful comments from and discussions with V. M. Kenkre during the elaboration of this work. C. Escudero is grateful to the Department of Chemistry and Biochemistry of the University of California, San Diego for its hospitality. This work has been partially supported by the National Science Foundation under grant PHY-9970699, by the Ministerio de Educación y Cultura (Spain) through grants No. AP2001-2598 and EX2001-02880680, and by the Ministerio de Ciencia y Tecnología (Spain), Project No. BFM2001-0291.

[1] J. N. Mills, T. L. Yales, T. G. Ksiazek, C. J. Peters and J. E. Childs, Emerg. Infect. Dis. 5, 95 (1999). D. M. Engelthaler, D. G. Mosley, J. E. Cheek, C. E. Levy, K. K. Komatsu, P.
Ettestad, T. Davis, D. T. Tanda, L. Miller, J. W. Frampton, R. Porter and R. T. Bryan, ibid. 5, 87 (1999). J. N. Mills, T. G. Ksiazek, C. J. Peters and J. E. Childs, ibid. 5, 135 (1999).
A. J. Kuenzi, M. L. Morrison, D. E. Swann, P. C. Hardy and G. T. Downard, ibid. 5, 113 (1999). K. D. Abbott, T. G. Ksiazek and J. N. Mills, ibid. 5, 102 (1999). C. H. Calisher, W. Sweeney, J. N. Mills and B. J. Beaty, ibid. 5, 126 (1999).
[2] B. Hjelle and G. E. Glass, J. Infect. Dis. 181, 1569 (2000).
[3] J. W. Hooper, T. Larsen, D. M. Custer and C. S. Schmaljohm, Virology 289, 6 (2001).
[4] J. F. Selgrade and J. H. Roberds, Physica D 158, 69 (2001).
[5] A. A. King and W. M. Schaffer, J. Math. Biol. 39, 439 (1999).
[6] W. M. Schaffer, B. S. Pederson, B. K. Moore, O. Skarpaas, A.A. King and T. V. Bronnikova, Chaos, Solitons and Fractals 12, 251 (2001).
[7] M. Lima, N. C. Stenseth and F. M. Jaksic, Ecology Letters 5, 273 (2002).
[8] S. Gubbins and C. A. Gilligan, J. Theor. Biol. 188, 241 (1997).
[9] G. Abramson and V. M. Kenkre, Phys. Rev. E 66, 011912 (2002).
[10] R. D. Astumian and P. Hänggi, Physics Today 54, 33 (2002).
[11] J. Buceta and K. Lindenberg, Phys. Rev. E 66, 046202 (2002).
[12] C. W. Gardiner, *Handbook of Stochastic Methods* (Springer, Berlin, 1996).
[13] V. W. Kenkre, *Memory Formalism, Nonlinear Techniques, and Kinetic Equation Approaches*, in *Modern Challenges in Statistical Mechanics: Patterns, Noise, and the Interplay of Nonlinearity and Complexity*, AIP Conference Proceedings 658, 2003.