Spatial epidemic network models with viral dynamics

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A mathematical model is presented for the spread of viral diseases within human or other populations in which both the dynamics of viral growth within individuals and the interactions between individuals are taken into account. We thus bridge the classical macroscopic approach to the growth and population dynamics of disease at the microscopic level. Each member, i, of the population of n individuals is represented by a vector function of time whose components are antibody numbers $a_i(t)$, and the virion level $v_i(t)$. These quantities evolve according to $2n$ differential equations, which are coupled via a transmission matrix **B** with elements β_{ij}, $i,j=1,...,n$, such that $\beta_{ij}v_i$ is the expected rate of transmission of infectious particles from individual i to individual j. We study nearest-neighbor interaction and transmission which declines exponentially with distance between the individuals. Results are shown to be related to those of classical macroscopic (SIR) models. We find threshold effects in the occurrence of epidemics as the parameters of the viral and antibody dynamics change. The distribution of the final size of an epidemic is estimated, for various initial patterns of infection, at various values of the parameter which describes the mobility of the population. We also determine the final size in the cases of extreme clustering and dispersion of infected individuals. [S1063-651X(98)11902-5]

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INTRODUCTION

There has been much interest recently in coupled dynamical systems representing networks of connected elements with and without noise [1]. In this article we consider such a system in which the prime focus is the growth and spread of virus particles within a population of susceptible hosts. We first consider a simple deterministic model, which nevertheless incorporates the stochastic nature of transmission. The advantage of the present approach is that one can analyze the spread of disease in terms of empirically determined parameters that describe the microscopic dynamics of the underlying viral organisms and a quantitative knowledge of demographic factors. The importance of such an approach has been emphasized recently by the World Health Organization in its endeavors to manage the threat of many emerging (HIV, ebola) and resurgent (tuberculosis, malaria, cholera) diseases.

The mathematical study of the spread of diseases has a rapidly growing literature: see [2] for an early comprehensive treatment and [3,4] for some more recent developments in quantitative theories for the growth and spread of disease and methods for data analysis. Many recent studies of the spread of particular diseases have used classical or semiclassical models [5]. Others have considered stochastic aspects, usually leading to random processes of the Markov chain or branching process type [6]. A discrete state-space spatial model with either the random arrival of new susceptibles or their delayed arrival and with nearest-neighbor interaction was employed in [7] and in [8] a stochastic network epidemic model with imposed threshold conditions was introduced.

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DESCRIPTION OF THE MODEL

The immune response to viral infection involves a complicated set of reactions that depends on the nature of the virus and the immunological response properties of the infected individual. A simplified dynamical system is obtained by supposing that there are two principal variables of interest; the antibody population and the viral population. These may represent different quantities in various conditions such as densities in plasma, total numbers, or numbers in specific body organs or tissues. However, we gather antibody particles into one dynamical variable and invading disease-causing particles into another dynamical variable. A similar procedure has been adopted in recent modeling studies including those on HIV [9] with three or more basic variables.

Network equations

We consider a population of n individuals. At time t, let $a_i(t)$ be the antibody response in the i-th individual and $v_i(t)$ be the viral charge in that individual where $i=1,2,...,n$. In accordance with experimental evidence on viral charge and immune response [10] a pair of basic equations representing the antibody and viral populations have been given [3]. In a network of connected individuals we have the following system of coupled equations:

$$\frac{da_i}{dt}=\lambda_i-\mu_i a_i+\epsilon_i a_i v_i, \tag{1}$$

$$\frac{dv_i}{dt}=r_i v_i-\gamma_i a_i v_i+F\left[\sum_{j\neq i}^{n}\beta_{ji}v_j\right]. \tag{2}$$

Here the parameters for individual i are as follows: λ_i is the rate of production and/or transport of antibodies, μ_i is the death rate of antibodies, ϵ_i is rate of production of antibodies induced by a unit viral population, r_i is the intrinsic growth rate of viral population, and γ_i is the rate of destruction of viruses by a unit antibody population. The function F is a possibly nonlinear function that describes the rate of growth of the viral population due to external sources of the virus,

namely, the remaining $n-1$ members of the population. However, F may also depend on additional variables as we explain below.

The form of the transmission term $T_i(t)=\Sigma_{j\neq i}^{n}\beta_{ji}v_j$ is justified by supposing that invading particles that arrived at an earlier time have been removed. Thus the effective quantity of virions, with the power to infect, arriving at individual i from other members of the population in the time interval $(t-\delta t,t)$ is

$$T_i^*(t,\delta t)=\int_{t-\delta t}^{t}\sum_{j\neq i}^{n}\beta_{ji}v_j(s)ds.$$

If δt is small, this may be approximated by

$$T_i^*\approx\delta t\sum_{j\neq i}^{n}\beta_{ji}v_j(s)=T_i(t)\,\delta t.$$

Individual solutions

Without interaction terms the system defined by $da/dt=\lambda-\mu a+\epsilon av$, $dv/dt=rv-\gamma av$ has critical points at $P_1=(\lambda/\mu,0)$ and $P_2=r/\gamma,(\mu-\gamma\lambda/r)/\epsilon$. Analysis [11] shows that either P_1 is an asymptotically stable node and P_2 is at unphysical values or P_1 is an unstable saddle point and P_2 is an asymptotically stable node or spiral point. We avoid recurrent outbreaks and make the time course of the responses in each infected individual the same. We assume for simplicity in the numerical examples that all five parameters ϵ, λ, μ, r, and γ are the same for each individual even though it is clear that in real populations these parameters will have probability distributions. There are three situations in which outbreaks may be nonrecurrent. Firstly, if P_1 is asymptotically stable and P_2 is unphysical, secondly, if P_1 is unstable and P_2 is an asymptotically node, and thirdly, if P_1 and P_2 coincide. We have chosen the latter because it obtains from setting the period, given approximately by (see [3]) $T\approx 2\pi(r\mu-\lambda\gamma)^{-1/2}$, to infinity, and there is no possibility of multiple outbreaks.

The elements β_{ji} of the *transmission matrix* **B**, representing the strength of transmission from j to i may depend on spatial factors; these elements are multiplied by the viral population in the transmitting individual. We assume that *while transmission occurs* from individual j to individual i, $\beta_{ji}v_j$ is the *expected number of viruses transmitted per unit time* from j to i. We therefore retain a stochastic approach but use approximate expected values. Thus whenever an individual is a host to a viral population, there is always a chance that viruses may be transmitted from that individual to others and in particular to others who do not yet carry the virus—in contrast with the classical notion of a discontinuous *infectious period*. Note that Eq. (2) incorporates the *loss* of viruses by a transmitting individual into the term r_iv_i. In order to describe the macroscopic state of the population, we introduce the total viral population, $V(t)=\Sigma_{i=1}^{n}v_i(t)$, and its average across the population $\bar{V}(t)=V(t)/n$. Similarly one may define an average antibody level, $A(t)$.

SOLUTIONS FOR THE NETWORK MODEL

Since Eq. (2) has solutions that may become unbounded if the immune response is switched off we have modified the growth term for the viral population to give rise to saturation at level $k_i<\infty$:

$$\frac{dv_i}{dt}=r_iv_i\left(1-\frac{v_i}{k_i}\right)-\gamma_ia_iv_i+F\left[\sum_{j\neq i}^{n}\beta_{ji}v_j\right]. \tag{3}$$

However, we assume that $k_i=k$ for all members of the population. We consider two kinds of transmission matrices. In the first transmission is restricted only to an individual's *nearest neighbor* so that

$$\beta_{ij}=\beta(\delta_{i,j+1}+\delta_{i,j-1}). \tag{4}$$

Here, δ_{ij} is Kronecker's delta; that is, it is unity if $i=j$ and zero otherwise. The constant β is non-negative and determines the overall strength of transmission. Secondly, we have considered the case of transmission, which declines *exponentially* with distance so that

$$\beta_{ij}=\beta(1-\delta_{ij})e^{-\alpha|i-j|}, \tag{5}$$

where α is another positive constant. Small α leads to widespread influence, whereas large α is associated with principally local spread. Populations in which there is great mobility and frequent interactions will have a small value of α. In empirical terms, we define $e^{-\alpha|i-j|}$ suitably normalized as the *probability per unit time that individual i interacts with individual j*, or as the expected number of interactions per unit time between these individuals. If $\alpha=0$, the transmission is uniform with $\beta_{ij}=\beta(1-\delta_{ij})$, which is equivalent to homogeneous mixing as in many classical models.

Standard parameters and initial conditions

We chose the following set of parameter values as standard, guided in part by [3] and the condition $r=\lambda\gamma/\mu$: $\epsilon=0.01$, $k=50$, $\lambda=0.5$, $\mu=0.05$, $r=1$, $\gamma=0.1$. In the system of equations without interaction, if $v(t)$ is any positive value for some $t_0\geq 0$, then the pair $[a(t),v(t)]$ commences on an orbit from $[a(t_0),v(t_0)]$, which ends up at the equilibrium point P, which is (10,0) with the standard set of parameters. We chose a threshold value v_{c_1} of v so that if for individual i, not yet afflicted with the disease, the total number of virions received per unit time first exceeded v_{c_1} at time t_i, then the value of v_i at that instant jumped to $v_i(t_i)=v_0$. Let the set of all individuals be $N=\{1,2,...,n\}$ and let the set of initially $(t=0)$ infected individuals be $N_0\subseteq N$. If $i\in N_0$, then $v_i(0)=v_0$. If $i\in N_0$, then $v_i(0)=0$ and let $t_i=\inf\{t|\Sigma_{j\neq i}^{n}\beta_{ji}v_j(t)\geq v_{c_1}\}$. Then

$$\frac{dv_i}{dt}=\begin{cases}0, & 0\leq t<t_i,\\ rv_i\left(1-\dfrac{v_i}{k}\right)-\gamma a_iv_i, & t>t_i.\end{cases} \tag{6}$$

This means that here F is replaced by $F(x,t_i)=v_0\delta(x-v_{c_1})\delta(t-t_i)$, where t_i is the time at which T_i reaches v_{c_1}. The results do not depend critically on the choices of either

the threshold parameters or the initial values of the dynamical variables. Alternatively a suitable nonlinear function can be used as the source term of the virions, which is negative at small viral numbers. A cubic, which has found widespread application in nonlinear threshold models in physics and neurobiology, is one such function so that in the absence of external sources

$$\frac{dv}{dt}=g(a,v)=rv\left(1-\frac{v}{k}\right)(v-\theta)-\gamma av, \tag{7}$$

where $0<\theta<k$. Using an equation such as this as a starting point for a network model makes the dynamical system very similar to those used in neuronal network modeling as signaled in [8]. For the corresponding antibody equations we employ a similar condition. Thus, if $i\in N_0$, then $a_i(0)=0$ and da_i/dt remains at zero until that particular time t_i when $v_i(t)$ first reaches the critical value v_{c_1}. Thus all orbits of diseased individuals commence at the point $(0,v_0)$. Note that because of this procedure, which we have introduced in order to make the (a,v) orbits the same for each infected individual, Eq. (1) does not apply until $t=t_i$.

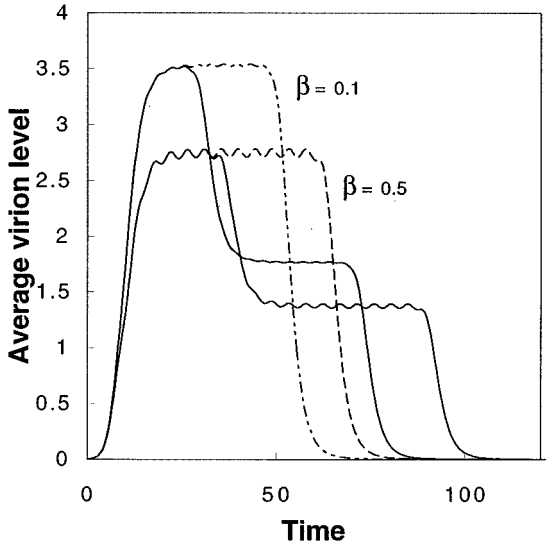

FIG. 1. Average virion level, for $\beta=0.1$ and $\beta=0.05$, with $n=25$ individuals when there is one initially infected individual who is situated either at the center (dot-dashed curves) or at $i=6$ (solid curves). Based on a quantitative study of influenza virus, units of time can be taken as approximately 5 h and for viral numbers, 10^{11} per ml of infected tissue—see text and [13].

Relation to *SIR* models

In classical models the population is divided into groups such as S for susceptibles, I for infectives, and R for removed—see [2]. Sometimes a further distinction is made between those individuals who are infected but not infectious, giving group E as well. In the present model the diseased individuals have a continuum of states. However, a further critical value v_{c_2} of v can be introduced such that the ith individual is classified as in each of the groups S, I, or R according to the following criteria. Before time t_i the individual is in group S; between the time t_i and the time t_i' when v_i falls to v_{c_2} the individual is in group I; then, after the level drops below v_{c_2} the individual is classed as type R.

1. Nearest-neighbor interactions

We first illustrate the application of the model to a small population with nearest-neighbor interaction. With $n=25$ we considered the simplest situation in which there is only one infected at $t=0$. The critical viral influx rate was set at $v_{c_1}=0.1$ and the standard orbit had $v_0=0.05$. Figure 1 shows the time course of the average virion level V when individual $i=6$ or the center individual $i=13$ is the first to carry the disease when the transmission parameter $\beta=0.1$ and for $\beta=0.05$. In Fig. 1 we have indicated possible units for viral and antibody densities based on approximate figures for influenza type A virus [12,13]. However, these and other units in subsequent figures are not precisely defined—magnitudes of responses depend on the amount and nature of infected tissue.

2. Exponentially decreasing transmission

In all the following results we assume a transmission matrix whose coefficients are an exponentially decreasing function of distance. If there is just one initially infected individual then the threshold condition is that if $\beta<v_{c_1}e^{\alpha}/v_{\max}$ there can be no spread.

Stochastic initial configuration and dependence on mobility

Suppose a fraction ρ of the population is initially infected. We choose the positions of ρn initially infected individuals according to a discrete uniform distribution on $N=\{1,2,...,n\}$ and call ρ the initial rate of infection. That is, we generate ρn (or the greatest integer contained therein) independent random variables on N. Because there is a chance of repeats, especially if n is small and/or ρ is large, we keep generating until ρn distinct sites have been obtained.

It is then of interest to see how the spread of disease depends, for fixed β, on changes in the mobility parameter α and on the initial configuration. With an initial rate of infection of $\rho=0.1$ we solved the network equations. We first illustrate the large difference in behavior of solutions obtained with a relatively small change in the value of α. Figures 2(a) and 2(b) show three-dimensional plots for the course of the disease for two values of α, 0.75 and 0.8. In both cases the same (randomly chosen) initial distribution of $N_0=\{4,7,15,23,57,60,78,91,99,100\}$ for $n=101$. Note that there are about 2×10^{13} different initial configurations. In Fig. 2(a) there is insufficient mobility with $\alpha=0.8$ for the disease to spread to more than a few of the initially uninfected individuals. If there are two infecteds close enough, they may start minor local spread as occurs around individuals 57 and 60, for example. However, some individuals contribute not at all to the spread of disease through lack of cooperative effects. On the other hand, a small increase in mobility with $\alpha=0.7$ shows, in Fig. 2(b), how the entire population is ultimately infected even though the initial configuration is the same. Clearly between these two values of α

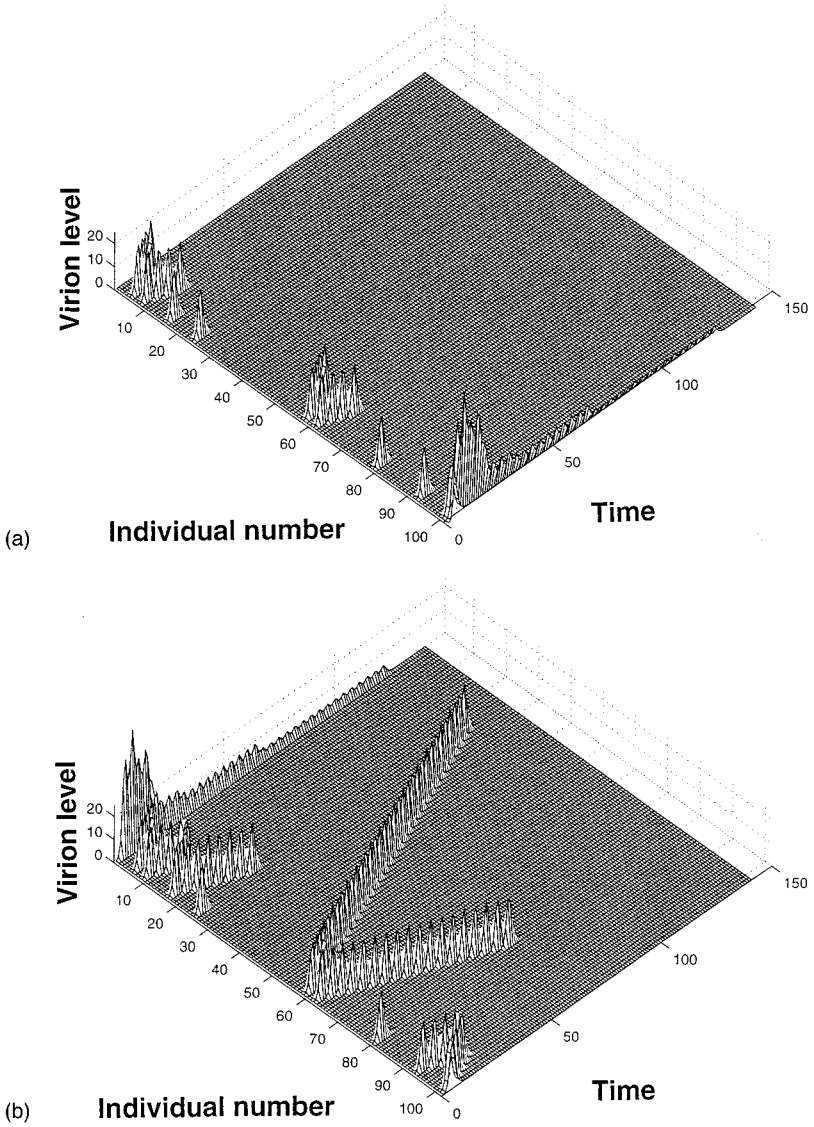

FIG. 2. (a),(b) Graphical representation of the virion levels across the population. Units as in Fig. 1. Random initial configuration but the same in both (a) and (b). In (a) the population is less mobile ($\alpha=0.8$) than in (b) ($\alpha=0.7$).

there is a critical value α_c, depending on the other parameters, but particularly on the initial configuration, below which there is spread to the entire population and above which there is only local spread.

Results with a stochastic initial condition were converted to the classical S,I,R variables. An example is shown in Fig. 3 for $n=500$, an infection rate $\rho=0.1$ and $\alpha=0.75$. The forms of these trajectories depend strongly on the parameters of the antibody-virus dynamical equations and have characteristic shapes for particular infectious particles for a given initial configuration.

Prevalence and final size

We describe some results for the effects of changing the parameters of the virion-antibody population dynamical system. Let $P_I(t)$, the *induced prevalence* at time t, be the ratio of the number of new cases to the total susceptible population at $t=0$. Thus if $n_I(t)$ denotes the number of individuals who are infected at t, then $P_I(t)=[n_I(t)-n_I(0)]/[n-n_I(0)]$. Clearly $P_I(0)=0$ and $0\leqslant P_I(t)\leqslant 1$ for all $t>0$.

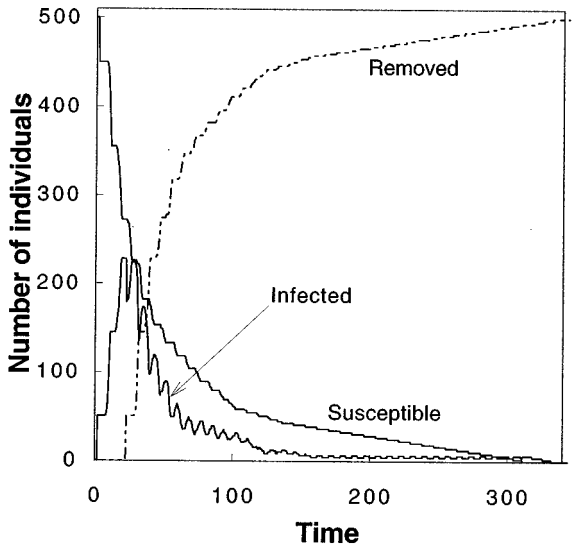

FIG. 3. S,I,R variables vs time for exponentially decreasing transmission, a stochastic initial condition, and $n=500$. Time in units of 5 h.

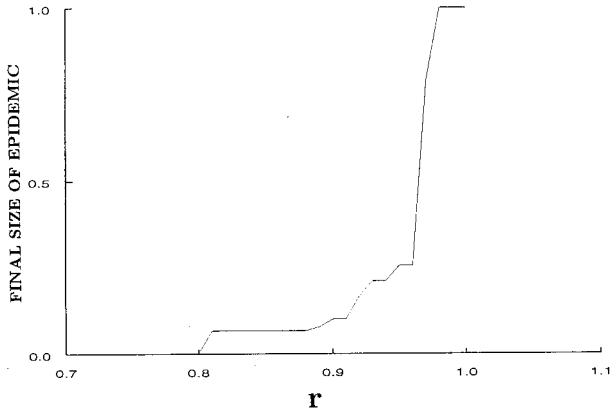

FIG. 4. The dependence of the final size P_F (dimensionless quantity between 0 and 1) of the epidemic on the microscopic variable r, whose units may be taken as $(5\,\mathrm{h})^{-1}$.

The quantity $P_I(t)$ is a measure of the degree of penetration of the susceptible population. Furthermore, we define the *final size of the epidemic* as $P_F = P_I(\infty)$, the total fraction of the initially uninfected population to whom the disease is transmitted.

Dependence on virion intrinsic growth rate

In Fig. 4 we show the variation in P_F as r changes for a stochastic initial condition in a population of 100 individuals. There is zero spread until the value $r = 0.8$, a slowly increasing final penetration of the epidemic until the value $r = 0.96$ is attained, followed by an abrupt increase to the maximum value of $P_F = 1$. Thus the final size depends very nonlinearly on the intrinsic growth rate of the virion population. A small change in virion growth rate, for example, by changing environmental conditions or drug therapy, can have a dramatic effect on the degree to which the population is invaded by a disease. We also investigated the effects of changing the antibody production rate λ. Results for the dependence of the epidemic's final size on λ also shown a sharp threshold. Thus a small change in this parameter, which reflects the tone of the immune system, may also have a drastic effect on the spread of disease throughout the population.

3. Changes in initial distribution

With parameters in the standard set we first randomly generated 50 different initial configurations, with $n = 100$ and a 10% initial rate of infection and determined the final size of the epidemic as a function of the parameter α. In Fig. 5 are shown plots of P_F versus α for the 50 different initial configurations. In addition, at each value of α we determined the sample mean and sample 95% confidence intervals of P_F. These are also marked on Fig. 5. Examination of the various curves shows very sensitive behavior with respect to variations in the configuration of the initially infected and the envelope about the mean formed by the indicated confidence intervals is very large relative to the mean.

We sought to delimit the extreme functional forms of the final size of the epidemic as α varied. To this end we have, for parameters in the standard set, put the initial infection

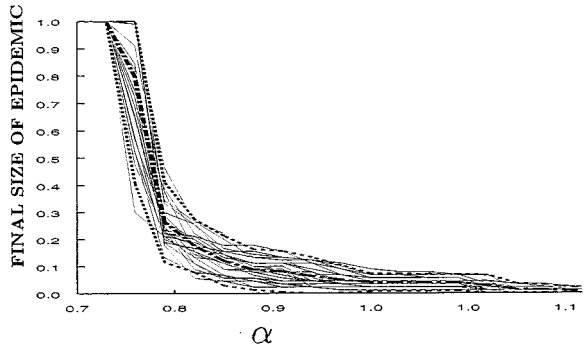

FIG. 5. Final size is plotted against the parameter α (dimensionless or per unit distance between individuals) for 50 different, randomly generated initial configurations. The estimated mean and 95% confidence intervals are shown.

rate at 0.1 and used a population of $n = 110$ for specific initial conditions defined as follows: Edge: $N_0 = \{1,2,...,10\}$; middle: $N_0 = \{51,52,...,60\}$; and uniform: $N_0 = \{6,17,28,...,94,105\}$. In Fig. 6(a) are shown the variations

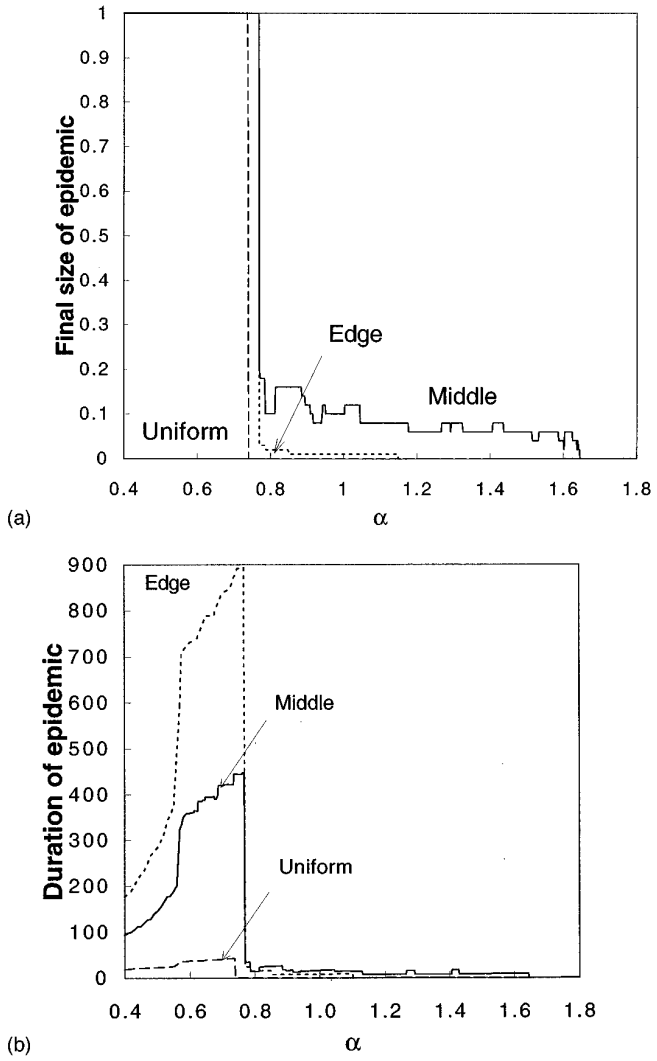

FIG. 6. (a). Final size P_F (dimensionless) plotted against the parameter α (dimensionless or per unit distance between individuals) for the three extreme cases of initial distribution described in the text. (b) Total duration of epidemic vs α.

in final epidemic size, P_F as a function of α, for the three ''extreme'' initial configurations. When the initially infected individuals are most dispersed (uniform case) the epidemic is practically ''all or none'' with a sharp threshold at a critical value of the mobility $\alpha \approx 0.75$. A larger value of v_{c_1} gave quite different results, indicative of the delicate interplay between the dynamical properties of viral growth within an individual on the one hand and the mobility of individuals in the population at large. If a disease is harder to establish within an individual (higher viral threshold) then spread will be negligible unless the population is extremely mobile (α small). Similarly, a virus that readily establishes itself within individuals will pervade an entire population even if the individuals in the population at large interact very little amongst themselves.

When the initially infected individuals occur in one region at the *edge*, the threshold effect with respect to variations in α is blunted or smoothed out, as can be seen in Fig. 6(a). There are now chances for partial epidemics (i.e., with $P_F \ll 1$) for values of α between 0.77 and 1.15. However, when α is significantly greater than the value at which the epidemic is total ($P_F = 1$), the spread is very limited and the epidemic is still practically an ''all or none'' phenomenon. In distinction to this, when the initially infected individuals are all in the central region, case ''middle,'' there is a much less well defined threshold effect as α varies. The final size of the epidemic is practically independent of the mobility, for $1.6 < \alpha < 1.8$.

Duration of the epidemic

For the same configurations of initially infected individuals as described in the preceding section, we have also found the duration of the epidemic, defined as the time interval between the arrival of the first individuals infected and the time after which there are no new cases of the disease. Figure 6(b) shows the duration versus α. For the dispersed initial infected group if there is an epidemic it is fast and total. For the clustered case ''edge'' there is a rapid rise in the duration of the epidemic as α increases through the small values of this parameter where the final size is $P_F = 1$. Thus there may be a very rapid total epidemic or one that takes a very long time, but is still nevertheless of total penetration. Similar effects, but to a lesser extent, occur for the other clustered initial condition ''middle.'' We have also found that there are epidemics of the same duration which may be of radically different sizes, even for the same initial condition.

DISCUSSION

The spread of disease involves the interplay of two classes of important dynamical processes. One is the mechanism of transmission, which may be through direct social processes or via secondary agents such as in the case of malaria. The other component is the evolution of the invading bacteria or virus within individuals. Classical epidemic modeling has usually been concerned with the population-dynamical and demographical processes. On the other hand there have been many recent studies of the dynamics of viral growth within individuals, with special emphasis on HIV. We have attempted here to combine these two components in a single framework so that it is possible to examine the effects of parameters at the microscopic level on the spread of disease within a population. We have found that there are threshold effects in many parameters at both the microscopic level, such as r and λ, and at the demographic level, such as α and β. It will be of interest to examine the effects of vaccination on such threshold effects and such studies may be useful in the formulation of public health policy. Equally important will be the analysis of stochastic effects when parameters are near their threshold values to assess the probabilities of occurrence of noise-induced epidemics analogous to noise-induced activity in neurons and neural networks [11,12]. We will consider recurrent diseases, which may occur when the condition for an infinite period is relaxed, in a future article. We conclude by pointing out that more realistic features of population dynamics can be included in easily solved models such as the following in two space dimensions.

(i) Discrete model with noise. Instead of employing only one position index in the discrete model used in the above numerical results it is useful to put the individuals at the points of a grid or lattice. Labeling the lattice points (i,j), with $i = 1,2,...,m$; $j = 1,2,...,n$, we may put, using the simplest form for the intrinsic viral growth rate,

$$\frac{da_{ij}}{dt} = \lambda_{ij} - \mu_{ij} a_{ij} + \epsilon_{ij} a_{ij} v_{ij}, \tag{8}$$

$$\frac{dv_{ij}}{dt} = r_{ij} v_{ij} - \gamma_{ij} a_{ij} v_{ij} + F\left[\sum_{k_1}^{m} \sum_{k_2}^{n} \beta_{k_1 k_2, ij} v_{k_1 k_2} \right] + \sigma_{ij} \frac{dW_{ij}}{dt}. \tag{9}$$

Here the W_{ij} are mn independent standard Wiener processes and summation is over the $mn-1$ points $\neq (i,j)$; the σ_{ij} are measures of the noise amplitudes.

(ii) Continuous approximation. If the population density is large one may turn to a continuous approximation in two space dimensions. We let $a(x,y,t)$ and $v(x,y,t)$ be the antibody and virion densities in a two-dimensional region. Then the two equations

$$\frac{\partial a}{\partial t} = \lambda - \mu a + \epsilon a v, \tag{10}$$

$$\frac{\partial v}{\partial t} = g(a,v) + F\left[\int_{x_1}^{x_2} \int_{y_1}^{y_2} \beta(w,z,y,x) v(w,z,t) dw dz \right]$$

may be used to describe the evolution of the viral population in the chosen region. We plan to report on these and other extensions of the basic model in future articles.

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