

Interaction between viral population dynamics and demography in the spread of disease

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Summary – Spatial epidemic network models which include the population dynamics of a viral or other invading particle are considered. In a simplified approach, for a host population of size n , there are $2n$ coupled first order differential equations for the host effector and viral populations. The connectivity matrix is taken as exponential and the population distributed geographically either on a line or plane. Threshold effects, which may be related to a transcritical bifurcation in the dynamical system for one individual, are found with respect to many parameters. In the deterministic case, a sharp threshold is found for the variation in epidemic size with contact rate, with initial density of infected individuals and for parameters controlling within-host viral dynamics and immune response. With a stochastic spatial distribution of initially infected individuals one may find the distribution of the final size of the epidemic. When there is additive white Gaussian noise, a broad-based stochastic resonance is observed as the noise parameter varies in nonlinear models for viral growth.

viral dynamics / spatial model / spread of disease / stochastic resonance

Introduction

The mathematical study of the spread of diseases has a rapidly growing literature: see [1] for an early comprehensive treatment and [2, 3] for some more recent developments in quantitative theories for the growth and spread of disease and methods for data analysis. Many recent studies have used classical or semi-classical models [4]. Others have considered spatial aspects within a classical framework [5]. A discrete state-space spatial model with either the random arrival of new susceptibles or their delayed arrival and with nearest neighbor interaction has been employed [6] and stochastic models [7] were used to examine the relationship between population size. *Figure 1* shows an example of data, which can be downloaded in graphical or numerical form, obtained from the Sentinelles network (see the web address <http://www.b3e.jussieu.fr>).

It is apparent that the speed and pattern of viral spread throughout a host population depends inter-alia on two classes of dynamical processes:

1) transmission from host to host, which may involve 'vectors' and 2) growth and spread of the viral population within hosts. The first set of processes is called demographic, whereas the second is a property of the invading particle-immune system dynamics within individuals.

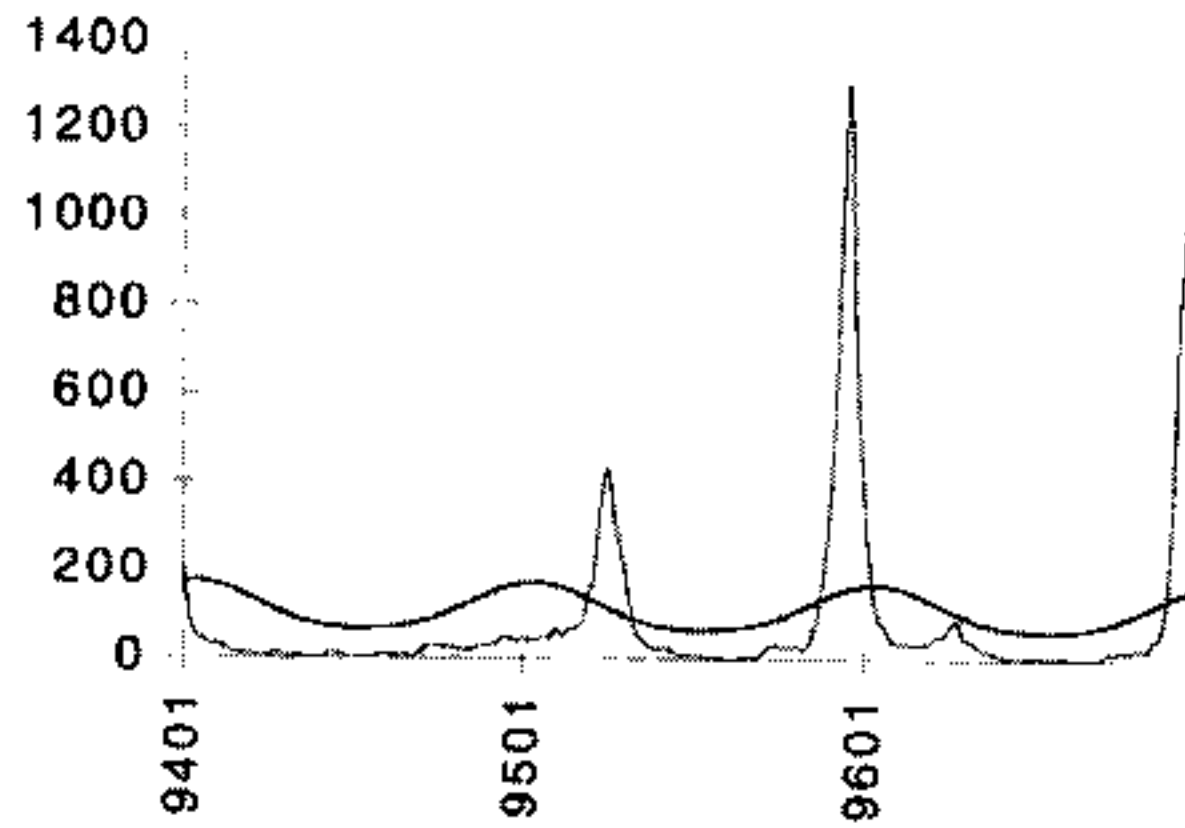


Figure 1. Showing the frequency of weekly new cases of influenza-like illness in France for the period 1994–1997, with peaks in the winter. (Data courtesy of Réseau Sentinelles, operated by Inserm U444 in Paris).

In most analyses, as for example in S, I, R or related models, emphasis is placed on the host population. We shift the main emphasis to the viral (or other disease-causing particle) population and study its overall dynamics so that in a sense the host population is playing a more or less secondary role. We will summarize here some of our recent work with a new class of such dynamical spatial models [8, 9].

Deterministic model and threshold effects

We consider a population of n individuals. At time t , let $a_i(t)$ be the effector population in the i -th individual and $v_i(t)$ be the viral charge in that individual where $i = 1, 2, \dots, n$. In accordance with experimental evidence on viral charge and immune response, in a network of connected individuals we have the following system of coupled equations,

$$\frac{da_i}{dt} = \lambda_i - \mu_i a_i + \varepsilon_i a_i v_i \quad (1)$$

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

Here the parameters for individual i are: λ_i = rate of production/transport of effectors, μ_i = their death rate, ε_i = rate of production of effectors induced by a unit viral population, r_i = intrinsic growth rate of viral population, and γ_i = rate of destruction of viruses by a unit effector population. The function F is a possibly nonlinear function which 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. We assume that transmission declines ‘exponentially’ with distance so that

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

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. We chose the following set of parameter values as standard: $\varepsilon = 0.01$, $k = 50$, $\lambda = 0.5$, $\mu = 0.05$, $r = 1$, $\gamma = 0.1$.

Individual solutions

A considerable part of the network behavior is explained by a consideration of the corresponding system for one individual,

$$\frac{da}{dt} = \lambda - \mu a + \varepsilon a v \quad (3)$$

$$\frac{dv}{dt} = r v - \gamma a v \quad (4)$$

which has been analyzed in detail elsewhere [10]. There are two critical points, $P_1 = (\lambda/\mu, 0)$ and $P_2 = (r/\gamma, (\mu r - \lambda\gamma)/(\varepsilon r))$. If $\lambda\gamma > \mu r$, the point P_2 occurs at negative v and is hence not at a biologically relevant value. There is then just one meaningful critical point P_1 on the a -axis and this is an asymptotically stable node. Thus, no matter where solutions start in the non-negative quadrant, they end up at P_1 with zero virions and with $a(\infty) = \lambda/\mu$ effectors. On the other hand, when $\lambda\gamma < \mu r$, there is an unstable saddle point on the a -axis at P_1 together with an equilibrium point P_2 in the positive quadrant, which is either an asymptotically stable node or an asymptotically stable spiral point. Then, whenever the initial value $v(0)$ is positive, regardless of whether $a(0)$ is positive or zero, the system ends up at P_2 . Therefore, in such cases it is impossible to end up with zero virions; an equilibrium is reached with r/γ effectors and $(\mu r - \lambda\gamma)/\varepsilon r$ virions. If λ is relatively small, the solutions undergo damped oscillations on their approach to P_2 ; if λ is large enough, solutions show no oscillatory behavior and proceed directly to P_2 . At the critical value $\lambda\gamma = r\mu$ where there is a change of stability of P_1 and P_2 , the two critical points coincide, both being located at $(\lambda/\mu, 0)$ with P_2 emerging as the asymptotically stable steady state for $\lambda/\mu < r/\gamma$. Thus, there is a 'transcritical bifurcation', with P_2 emerging as λ/μ decreases below r/γ . This transcritical bifurcation plays a key role in understanding some of the threshold effects. An example of this is seen in *Figure 2* (for a population

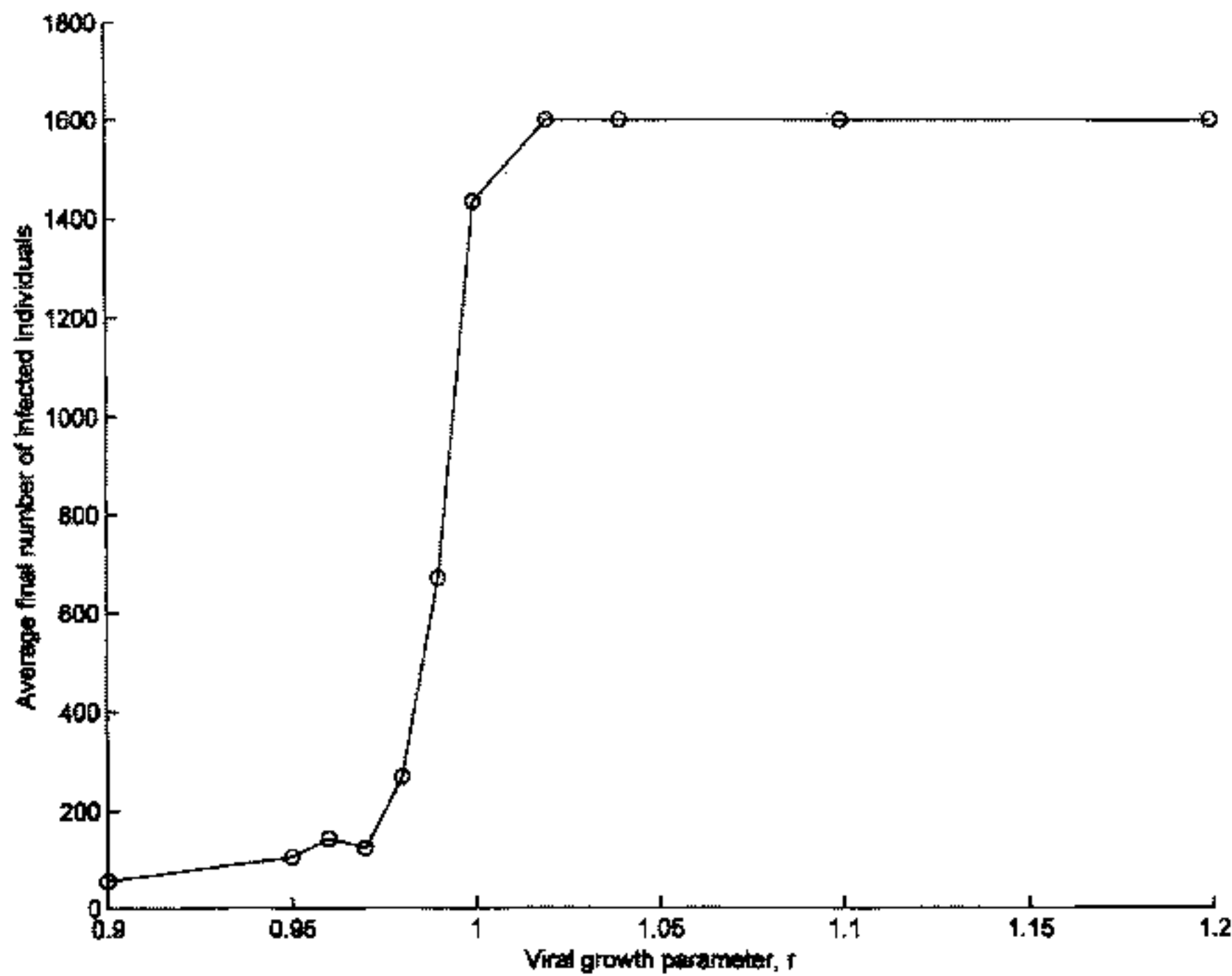


Figure 2. Plot of numerical results for a two-dimensional deterministic network model of viral spread, showing the dependence of the number of infected individuals on the viral growth rate parameter.

in the plane) where we show the variation in the average final number of infected individuals versus the viral intrinsic growth rate parameter r .

It can be seen that at values smaller than the critical value r_c , the point near where there is a transcritical bifurcation, the disease penetrates the population to a very small degree. When $r \approx r_c$, there is an explosive increase in the number of hosts infected and this quickly saturates at the entire population when $r > r_c$. Similar effects are found for other parameters, indicating that there is a very fine margin in both viral and immune system properties which separates a highly successful penetration by a virus from a successful defence by the hosts.

Stochastic model

We may also examine stochastic effects on the dynamical process of viral growth and the transmission of virions among population members. Noise, even of a small amplitude, is found to accelerate the spread of the virus and to synchronize the development of disease across the population. We use capitals to denote random variables. The equation describing the evolution of the effector population within the i -th individual is

$$\frac{dA_i}{dt} = \lambda_i - \mu_i A_i + \varepsilon_i A_i V_i \quad (5)$$

and for the corresponding viral densities we have

$$\frac{dV_i}{dt} = r_i V_i \left(1 - \frac{V_i}{k_i} \right) - \gamma_i A_i V_i + F \left[\sum_{j \neq i} \beta_{ji} V_j \right] + \sigma_i w_i \quad (6)$$

We have inserted additive white noise terms, with variance parameter σ_i^2 in each viral equation as a first approximation to a study of stochastic effects. The latter may result from random variations in the processes of viral growth within individuals, or random environmental effects. Here $w_i = dW_i/dt$, $i = 1, 2, \dots$ are white noises, the $\{W_i\}$ being assumed to be n independent standard Wiener processes.

We first examined the effects of noise on the responses of the viral-immune system in a single individual. For the range of noise parameters considered, it is found that increasing the amplitude of the noise tends to decrease the maximum mean virion level and slightly accelerates its attainment. Two different spatial dynamical models have been employed to ascertain the effects of environmental stochasticity on viral spread. In the first model transmission is unrestricted and there is no threshold within individuals. This model has the advantage that it can be analyzed using a Fokker-Planck approach [9]. The noise is found to both synchronize and uniformize the trajectories of the viral levels across the population of infected individuals and thus to promote the epidemic spread of the virus. Quantitative measures of the speed of spread and overall amplitude of the epidemic may be defined as functions of the noise and virulence parameters. The mean amplitude increases steadily without threshold effects for a fixed value of the virulence as the noise amplitude σ is increased, and there is no evidence of a stochastic resonance. However, the speed of transmission, both with respect to its mean and variance, undergo rapid increases as σ changes by relatively small amounts. In the second more realistic model there is a threshold for infection and an upper limit to the transmission rate. There may be no spread of infection at all in the absence of noise. With an increasing noise level and a low threshold, the mean maximum virion level grows quickly and shows a broad-based stochastic

resonance effect. When the threshold within individuals is increased, the mean population virion level increases only slowly as σ increases, until a critical value is reached at which the mean infection level suddenly increases. Similar results are obtained when the parameters of the model are also randomized across the population.

Discussion

A complete quantitative study of epidemics involves demographic components, which reflect properties of the host population and components which describe the dynamics of the invading organisms which are usually either virus particles or bacteria. Most previous studies have omitted the second of these components, as in the family of S, I, R or SEIR models. It is also necessary to include spatial distributions of hosts, which may be done via partial differential equations of the diffusion type, or as integro-differential equations or in a discrete framework as employed in this article. We have considered here a cartesian system of hosts whose viral populations interact with one another via contact and transmission. The properties of the dynamical system describing the viral-effector system are very influential in determining the magnitude and time course of outbreaks of disease, and for this reason we have included a brief analysis of the virus-effector system in a single individual. Most relevant is the occurrence of a transcritical bifurcation, which gives rise to threshold effects as effector and viral parameters change. In particular, we have determined the temporal evolution of the population virion level and the distribution of the total numbers of infected individuals as parameters vary on either side of the bifurcation. We have also examined these quantities as certain demographic parameters, such as contact rate, mobility, and the number of initially infected individuals change. In a recent article (Tuckwell, Toubiana and Vibert, unpublished, 2000) we have examined how immunization rate affects the final size of the epidemic. We have found that the greatest benefit is obtained when the immunization rate increases to 20%, with diminishing returns for further increases. In future articles we hope to explore in more detail geometric and stochastic effects in two and three space dimensions.

References

- 1 Bailey NTJ. The mathematical theory of infectious diseases and its applications. London: Griffin; 1975.
- 2 Anderson RM and May R M. Infectious diseases of humans. Oxford: Oxford University Press; Oxford, 1991.
- 3 Mollison D, ed. Epidemic models. Cambridge : Cambridge University Press; 1995.
- 4 Li MY, Graef JR, Wang L and Karsai J. Global dynamics of an SEIR model with varying population size. *Math Biosci* 1999 ; 160 : 191-213.
- 5 Lloyd AL and May RM. Spatial heterogeneity in epidemic models. *J Theor Biol* 1996 ; 179 : 1-11.
- 6 Johansen A. A simple model of recurrent epidemics. *J Theor Biol* 1996 ; 178 : 45-51.
- 7 Keeling MJ and Grenfell BT. Disease extinction and community size. *Science* 1997 ; 275 : 65-67.
- 8 Tuckwell HC, Toubiana L and Vibert J-F. Spatial epidemic network models with viral dynamics. *Phys Rev E* 1998 ; 57 : 2163-9.
- 9 Tuckwell HC, Toubiana L and Vibert J-F. Enhancement of epidemic spread by noise and stochastic resonance in spatial network models with viral dynamics. *Phys Rev E* 2000 ; 61 : 5611-9.
- 10 Tuckwell HC and Wan FYM. Nature of equilibria and effects of drug treatments in some viral population dynamical models. *IMAJ Math Biol Med* 2000 (in press).