Epidemic Models, Spatial

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If we are to gain proper understanding of the dispersal and control of diseases such as malaria, rabies, and **AIDS**, then we have to recognize that they develop within a truly spatial framework. The common assumption that individuals mix homogeneously over the whole region available to them stems mainly from mathematical convenience (*see* **Random Mixing**); in real life, we have to accept that both individuals and disease often develop within separate subregions. Classic examples of such spatial catastrophes include: 25 million deaths in fourteenth century Europe from Black Death out of a population of 100 million; the Aztecs lost half their population of 3.5 million from smallpox; around 20 million died in the world influenza pandemic in 1919; whilst millions of people are believed to be currently affected by HIV/AIDS. A particularly interesting case is the spread of one of the world's greatest cholera pandemics, the El Tor strain. It was first identified outside Mecca in 1905, and was later recognized in the 1930s as being endemic in the Celebes. Little was heard of it until 1961, when it suddenly exploded out of the Celebes, reaching India in 1964, and advancing into central Africa, Russia, and Europe by the early 1970s. The total burden of misery and suffering that results from such disease is clearly immense, and any understanding that modeling techniques can bring to alleviate this terrible state of affairs *has* to invoke spatial transmission properties.

Disease is spread through two different mechanisms. First, infected individuals may *migrate* to a different location, thereby infecting susceptibles at this new site. Migration patterns can be truly local (spread of HIV in "shooting galleries"), mid-range (sexual transmission between neighboring cities), or global (spread of human disease through intercontinental travel). Second, the disease itself may spread through *cross-infection*, either locally (between neighboring trees) or globally (aerosol dispersal of plant disease). Some situations may involve both mechanisms, such as the UK outbreaks of foot-and-mouth disease. Hengeveld's account [6] of documented invasion scenarios contains many varied examples, including cholera in North America, stripe rust in wheat, the expansion of cattle egret in North and South America, and rabies in Central Europe.

If migration or cross-infection is highly localized, then infectives/infection may *diffuse* over a continuous region. In contrast, if it results in substantive changes in location, then we either have a *spatial jump* process (plants infected by windblown spores), or a *stepping-stone* process if infection can only occur at specific sites (influenza epidemics in Icelandic coastal settlements).

Given that many populations develop within reasonably well-defined subregions, the stepping-stone approach is a sensible one to consider first. We envisage the process as being spatially distributed amongst n sites, with migration and/or cross-infection being allowed between them. This may involve nearest neighbors, all sites with a common transmission rate, or all sites but with the transmission rate changing with intersite distance (called the *contact distribution*). Such migration scenarios were first posed by Kimura [8] in a genetics context, but substantive theoretical development really began following Bailey's simple birth–death–migration process [1]. In this model, the population develops on an infinite set of colonies (thereby avoiding edge-effect problems), all individuals undergo a simple birth–death process with rates λ and μ, respectively (*see* **Stochastic Processes**), and individuals in colony i can migrate at rate ν_1, ν_2 to the two nearest neighbors $i+1$, $i-1$. For the equivalent general epidemic process, with $X_i(t)$ susceptibles and $Y_i(t)$ infectives in colony i at time t, the infective population at i increases at rate $\beta X_i(t)Y_i(t)$. In the opening stages, $\beta X_i(t) \simeq \beta X_i(0) = \lambda$ (say), so there the two processes are roughly equivalent. Unfortunately, even Bailey's process teeters on the edge of mathematical tractability, so the prospects for making substantial theoretical progress with more complicated spatial epidemic processes are remote. Replacing migration with cross-infection (at rate α_1, α_2) makes this situation even worse, since the infective population birth rate changes to $X_i(t)[\beta Y_i(t) + \alpha_1 Y_{i-1}(t) + \alpha_2 Y_{i+1}(t)]$.

Consider, for example, the recent (nonspatial) upsurge of interest in modeling the population dynamics of the AIDS epidemic. Much of the mathematical development is deterministic (*see* **Epidemic Models, Deterministic**), though this does facilitate the allowance of many sources of change [7]. One surprisingly tractable nonlinear model is that of Ball & O'Neill [2], and to place this within a spatial nearest-neighbor setting, let $x_i(t)$, $y_i(t)$, and $z_i(t)$ denote the

number of susceptible, HIV-infected, and removed (i.e. full-blown AIDS or dead) individuals at site i. Then allowing for the migration of infectives gives rise to the deterministic representation

$$\begin{aligned}\frac{dx_i}{dt} &= \frac{-\beta x_i y_i}{x_i + y_i},\\ \frac{dy_i}{dt} &= \frac{\beta x_i y_i}{x_i + y_i} - (\nu_1 + \nu_2)y_i + \nu_1 y_{i-1} + \nu_2 y_{i+1},\\ \frac{dz_i}{dt} &= \gamma y_i. \end{aligned} \tag{1}$$

This situation is in marked contrast with the spatial general epidemic model with cross-infection, with

$$\begin{aligned}\frac{dx_i}{dt} &= -x_i[\beta y_i + \alpha_1 y_{i-1} + \alpha_2 y_{i+1}],\\ \frac{dy_i}{dt} &= x_i[\beta y_i + \alpha_1 y_{i-1} + \alpha_2 y_{i+1}] - \gamma y_i,\\ \frac{dz_i}{dt} &= \gamma y_i. \end{aligned} \tag{2}$$

Such equations are easily modified to enable general migration at rate ν_{ij} from site i to site j, and cross-infection at rate α_{ij} between infectives in site i and susceptibles at site j. Exact solution is usually not possible, though approximate results may be obtained using careful linearization procedures: for numerical solutions use MATLAB, and so on. Often, we are interested in qualitative, rather than quantitative, behavior, and visual inspection of graphical output over a range of parameter settings is usually sufficient to highlight the most important aspects of the process.

Although the propagation of an epidemic through towns or villages is easily visualized in terms of a stepping-stone process, for disease dispersal in animals or plants, a diffusion model may be more appropriate. Near the wavefront itself, the number of susceptibles may be assumed to be fairly constant, and so there the process reduces to a simple birth–death process amenable to Skellam's diffusion approach [21]. On describing the infective density at position (u, v) by **Brownian motion** with zero drift and displacement variances $\mathrm{var}[u(1)] = \mathrm{var}[v(1)] = D^2$, we have the polar normal probability density function (pdf) (*see* **Bivariate Normal Distribution**)

$$\phi(r, \theta; t) = (2\pi D^2 t)^{-1} r \exp\left[\frac{-r^2}{2D^2 t}\right]. \tag{3}$$

Since there is no drift, this pdf spreads out in ever-expanding circles, and for an infective population of final size N, the radial velocity $R(t)/t$ is $D\{[2\ln(N)]/t\}^{1/2}$, which decreases as $t^{-1/2}$. For a long timescale, say, several decades, which is the case for fox rabies in Europe and the El Tor cholera strain, we might assume exponential growth at rate ψ, whence N is replaced by $N\exp(\psi t)$ and the velocity now remains constant at $D\{[2\psi\ln(N)]\}^{1/2}$. The combination of population growth and diffusion is essential if spatial expansion is not to fade out.

The diffusion approach involves a poor Taylor series expansion, and so the two scenarios can give rise to substantially different results. For example, with Bailey's birth–death process, the wavefront velocities (for $\lambda > \mu$) are the solutions to the equation [13]

$$\begin{aligned}\nu_1 + \nu_2 + \mu - \lambda &= (c^2 + 4\nu_1\nu_2)^{1/2}\\ &\quad - c\ln\left\{\frac{[c + (c^2 + 4\nu_1\nu_2)^{1/2}]}{(2\nu_1)}\right\}, \end{aligned} \tag{4}$$

while the equivalent diffusion velocities take the much simpler form

$$c_{\mathrm{diff}} = (\nu_1 - \nu_2) \pm \{2(\lambda - \mu)(\nu_1 + \nu_2)\}^{1/2}. \tag{5}$$

These two results are compatible only if $\lambda - \mu \ll \nu_1 + \nu_2$.

Mollison [9] argues strongly that when considering the velocity of spread, one should lean heavily towards using basic linear deterministic models, claiming that their assumptions are relatively transparent, they are easy to analyze, yet they generally give the same velocity as more complex linear stochastic and nonlinear deterministic models. Their relative simplicity allows more freedom to choose a biologically/epidemiologically realistic model, and hence, greatly facilitates examination of the dependence of conclusions on model components. Note, however, that such linear models provide only an upper bound for the velocity of more realistic stochastic nonlinear models. Further, both deterministic and stochastic linear models are usually completely unsuitable for modeling complex features such as the transition to endemicity and endemic patterns. Nonlinear deterministic models may provide useful information regarding the transition to endemicity but they are usually wholly inadequate for fluctuations about an endemic state.

Many useful conclusions from models for spatial spread are sensitive to the assumptions made in formulating and fitting them, and incorporating realistic epidemiological parameters will make exact theoretical analysis impossible to achieve. Such parameters can be framed in terms of the following concepts. The *basic reproductive ratio* R_0 is the mean number of contacts made by an infective, and this plays a crucial role in determining whether an epidemic outbreak can occur (*see* **Reproduction Number**); the *carrying capacity* K, which enters via R_0, denotes the maximum population density. The time T of a typical infection relative to that of its parent infective is called the *generation gap*, and its relative location in space X, the *dispersal distance*; whilst the distribution of T itself is called the *reproduction kernel* and that of X, the *dispersal* or *contact* distribution. The *wavefront velocity* c can then be expressed as a function of $R_0\beta(x, t)$, where $\beta(x, t)$ is a probability kernel describing the joint distribution of X and T; see [9] for details.

Note that when determining *population size*, linearization is a highly suspect technique, since different nonlinear models can have the same linearization (e.g. epidemics with (i) removals and (ii) recovery); though it is strongly conjectured that nonlinear differential equations for population spread will always have the same *velocity* as their linear approximation.

Given that substantial behavioral differences can occur between deterministic and stochastic analyses of the same process, ideally, a deterministic approach should always be performed in parallel with a stochastic analysis. Unfortunately, even the simplest stochastic spatial scenario of a two-site birth–death–migration process produces intractable mathematics. Some degree of success is possible using approximation techniques, such as regarding $\{x_i(t), y_i(t), z_i(t)\}$ as a **multivariate normal distribution** with **moments** obtained from the cumulant equations by replacing third- and higher-order cumulants by zero. Though a far more powerful way of using such moment closure is to evaluate cumulants up to the third- or fourth-order, and then use these in the multivariate saddlepoint approximation, thereby determining a much more realistic approximating probability density function [17]. Any awkward algebraic manipulation may be easily overcome through the use of a **computer algebra** package, whilst direct numerical computation of the original population probability equations presents another option.

The problem with probability "solutions" is that they usually convey information only on population values at a fixed time t. What we really require is the full history of process development. **Simulation** provides the answer, for given the rapidly expanding nature of affordable computer power, moments and probabilities may be obtained using standard **Monte Carlo** procedures. Detailed examples of how to construct simulation code for space–time stochastic models are contained in [14], and these are easily modified to cope with any spatial epidemic construction. No matter how complicated, a process can always be described as a series of events $E_1, E_2, \ldots$ occurring at times $t_1, t_2, \ldots$. First, detail all possible infection, removal, migration, and cross-infection changes. Then, in essence:

1. evaluate the corresponding rates $r_1, r_2, \ldots$ and put $R = r_1 + r_2 + \cdots$;
2. generate two **uniform** U(0,1) random variables U_1 and U_2;
3. select the jth event if $r_1 + \cdots + r_{j-1} \leq U_1 R < r_1 + \cdots + r_j$;
4. evaluate the interevent time $s = -\ln(U_2)/R$;
5. update population sizes and time $t \to t + s$, and return to 1.

Figure 1 shows two simulations of a two-colony Ball & O'Neill process under both migration and cross-infection regimes. At time $t = 0$ there are 100 susceptibles in each colony, with one infective in colony 1 and none in colony 2. For illustration, only one-way spatial rates are used, namely, from colony 1 to 2. Thus, an epidemic in colony 2 has to be kick-started from colony 1 before all the infectives there have been removed. Whilst the deterministic and stochastic developments for cross-infection are broadly comparable, under migration, substantial time-shift differences occur between them, especially in colony 2. Though rough agreement between stochastic and deterministic realizations will usually occur, the problem is one of consistency. Unlike cross-infection, with migration, total colony sizes are not fixed, so individual sites may pass through their threshold population values and thereby undergo considerable behavioral change.

Such differences can become even more marked when the system comprises three or more sites, and susceptibles may both migrate and give birth. For with appropriate parameter values, susceptibles can move ahead of epidemic flare-ups and grow to

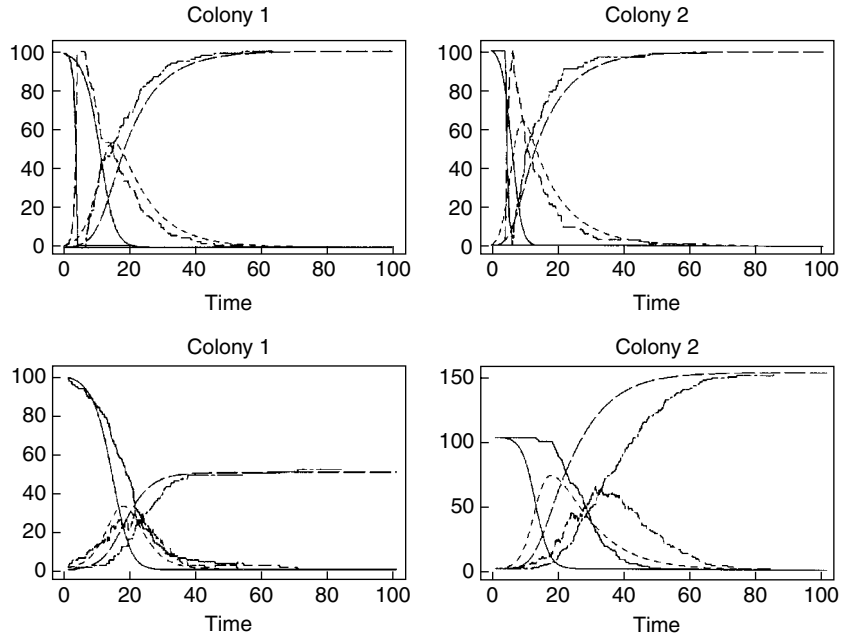

Figure 1 Deterministic (smooth) and stochastic (rough) realizations of a two-colony Ball & O'Neill model under cross-infection (upper) and migration (lower) showing the number of susceptibles (————), infectives (- - - - -) and removals (— — — —): parameter values are $\beta = 0.5$, $\gamma = 0.1$, $\nu_1 = 0.1$, $\nu_2 = 0$, $\alpha_1 = 0.01$, $\alpha_2 = 0$ (produced by Ian Hirsch)

above the local threshold population value before either a migrating infective or cross-infection starts a fresh epidemic outbreak (*see* **Epidemic Thresholds**). Persistence occurs through a *stochastic dynamic*: it is precisely the ability of susceptibles to be constantly on the move recolonizing empty sites, and infectives to pursue them, that keeps the whole process alive. In such situations, we have to rely on simulating individual stochastic realizations. For even if exact probability expressions could be constructed, they would tell us little, being an average over all possible realizations. Moreover, if the behavioral variability between realizations is considerable, then even using a basic deterministic approach can be risky, especially when it relates to epidemic control (*see* **Epidemic Models, Control**). Mollison [9] provides a striking example of this, in which he challenges Murray et al.'s deterministic study [12] of how fox rabies might invade a new country: they predict a roughly circular expanding wave of advance, followed after a quiet phase of about seven years by another wave originating from the same starting point. First, European evidence suggests that after a short while, the rabies invasion could break back across the devastated territory immediately behind it and induce an epidemic equilibrium there. Second, the later wave is an artifact of modeling population size as continuous, rather than discrete. For the model has fox density declining not to zero, but to 10^{-18} of a fox per square kilometer, and this "atto-fox" restarts the epidemic wave as soon as the susceptible population has grown sufficiently large. Though such numerical nonsense may be easily eliminated by replacing any population size below a given cut-off value by zero, the discrepancies between the overall predictions and reality are a serious cause for concern, and highlight the danger in using deterministic models at very low levels of infection prevalence.

The mathematics surrounding spatial stochastic processes is notoriously difficult, and where deterministic solutions can be of considerable help is in determining *qualitative* behavior when there exists an underlying endemic equilibrium level $\{X^*, Y^*\}$ of susceptibles and infectives. In a brilliant pioneering paper, Turing [23] developed elegant deterministic solutions that predict the types of behavior likely to

be encountered when N colonies lie on a ring. In general, let $f(X_i, Y_i)$ and $g(X_i, Y_i)$ denote the rates of change at colony i in susceptibles, $X_i(t)$, and infectives, $Y_i(t)$, respectively. Then if susceptibles and infectives migrate to neighboring sites at rates μ and ν,

$$\frac{dX_i}{dt} = f(X_i, Y_i) + \mu(X_{i+1} - 2X_i + X_{i-1}),$$
$$\frac{dY_i}{dt} = g(X_i, Y_i) + \nu(Y_{i+1} - 2Y_i + Y_{i-1}). \quad (6)$$

On considering local departures from equilibrium by writing $X_i(t) = X^* + x_i(t)$ and $Y_i(t) = Y^* + y_i(t)$, the functions f and g may be approximated by linear forms in x_i and y_i [14, 16]. The resulting equations are amenable to Laplace transform solution, whilst adding white noise (*see* **Noise and White Noise**) to the linearized deterministic equations allows the construction of second-order moments and **spectra** [15]. Cross-infection may be treated similarly. Turing's aim was to examine whether it is feasible to generate *spatially* stable waves, and his idea is simple but profound. For, if in the absence of diffusion, X_i and Y_i tend to a *linearly stable* uniform state, then under certain conditions, spatially inhomogeneous patterns can evolve through *diffusion-driven instability*. Since diffusion is usually considered to be a stabilizing process, care is clearly needed when "guessing" how nonspatial models will behave when they are placed in a spatial environment. Furthermore, the behavior of nonlinear stochastic models can change radically with dimension, as even the number of local sites affected by the migration or cross-infection contact distribution increases markedly as the dimension increases.

Whilst so far we have considered population *numbers* of infected, susceptible, immune, recovered, and so on individuals, for processes that develop over a grid, it is worthwhile highlighting the close link with *percolation processes*. For a wealth of asymptotic theory has been developed (see references in [5]), which can be carried across directly to epidemic scenarios. Here, the information is essentially qualitative, rather than quantitative, with each site being in (say) one of three states, namely, immune, healthy, or infected. Note the close interpretation here with models for "forest fires", which have the equivalent states burned, live, and on fire. Typically, an infected individual emits germs according to a **Poisson process**, which then move to one of the four nearest neighbors chosen at random. If a germ goes to a healthy site, then that site becomes infected and immediately starts to emit more germs, staying infected for a random time with known distribution function until it recovers and is immune to further infection. Questions of interest revolve around the set of sites that will ever become infected if initially the origin is infected and all other sites are healthy. Though this structure lends itself to substantial mathematical analysis, to study time-dependent behavior, we have to revert to using simulation. The advantage of this latter approach is that there is no need to make unrealistic assumptions in order to achieve mathematical tractability, and that with a little practice, computer codes can be developed extremely quickly. A prime example relates to the 2001 UK foot-and-mouth epidemic, whose aftermath left heated discussion over the control policies employed. A simple QBASIC program with good screen graphics output can be developed almost instantaneously to show (for example) an array of farms where each site is either healthy, infected, burned, or culled [18]. Everyday, each healthy site next to an infected site becomes infected itself with probability q; healthy sites neighboring an infected site are culled with probability p; whilst infected sites are burned (i.e. become removed) with probability r. Simulation experiments quickly reveal not only threshold values of p and r for fixed q, above which the disease soon stops but below which the infection keeps on advancing, but also the existence of "creep" in which slow advance relentlessly continues in spite of the process appearing to be under control. This latter behavior was observed for real in parts of the United Kingdom. Had such qualitative features been known at the start of the outbreak, far better control strategies could have been developed, especially since the position, size, and network connections of all farms are held on GIS (geographic information system) **databases**, thereby enabling this simple grid-based simulation exercise to be extended to the UK itself through the development of a more refined space–time structure.

Although the spread of infectives/infection through local migration/contact is commonplace, propagation will often occur between nonnearest colonies. Provided the colonies lie on a regular grid, such as a Turing ring, spatial measures of autocorrelation and frequency may be obtained by using **time-series** techniques [19]. However, sites will often not be regularly spaced: for example, cities, towns, and villages

connected by air, road, and rail; and we need to use weighted measures based upon local population size, area of location, extent of links with other areas, and so on. [4]. We therefore have a space–time bivariate marked point process $\{(X_{u,v}, Y_{u,v}); (u, v) \in R\}$ with association between the locations (u, v) in a region R, local epidemic reactions at each location, and spatial epidemic migration/infection between different locations. The study of such complexity is still in its infancy (see [20] for a single-"species" discussion), and stochastic modeling has to proceed through simulation. Appropriate measures of spatial correlation that are applicable to both marks (X, Y) and points (u, v) can be found in Stoyan and Stoyan's excellent overview [22].

For the purpose of illustration, we have concentrated on purely spatially homogeneous scenarios. However, recent interest in AIDS has stimulated much progress in diverse areas of epidemic modeling, particularly with regard to the treatment of heterogeneity, both between individuals and in mixing of subgroups of the population. The study of epidemics is an exciting, active, and rapidly expanding field, and the review papers of Mollison et al. [11] and Bolker et al. [3] provide excellent starting points for investigating the dynamics of diseases in human, animal, marine, and plant populations. Key theoretical issues are addressed in [10]. Moreover, improved computer technology has led to the availability of better databases and computationally intensive methods in the analysis of data: it has also allowed the simulation of more detailed and realistic models. We can therefore now tackle major challenges to our understanding of spatial epidemics, including the effects of: heterogeneity due to differences between both individuals and mixing; the dependence of persistence on chaotic behavior and spatial patchiness (*see* **Chaos Theory**); nonstationarity due to weather, demographic variables, and evolution; varying migration and cross-infection scenarios; and boundary edge-effects.

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(*See also* **Epidemic Models, Stochastic**; **Infectious Disease Models**; **Migration Processes**)

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