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7

Contact Networks and the Evolution of Virulence

Minus van Baalen

7.1 Introduction

Virulence management can be defined as that set of policies that not only aims to minimize the short-term impact of parasites on their host population (e.g., incidence, mortality, and morbidity), but also to account for the longer-term consequences of the evolutionary responses of these parasites, for example by adopting measures that select for less virulent strains.

An important question pertaining to the scope of virulence management concerns the effect of contact structures in the host population. For successful transmission many parasites require close contact between the host they are infecting and new susceptible hosts. Consequently, the network of social contact in their host population is of paramount importance. It has already become clear that differently structured networks lead to different types of epidemiology (Keeling 1999). For example, a sparsely connected host population is more difficult to invade than a densely connected host population. But to what extent will the contact structure of their host population affect the evolution of the parasites, in particular of their virulence? Can we change the selective pressures on the parasites by modifying these contact structures? Claessen and de Roos (1995) and Rand *et al.* (1995) carried out computer simulations of evolving parasites in spatially structured host populations and concluded that less virulent (hypovirulent) parasites are favored with respect to well-mixed systems. Clearly, parasite evolution does depend on host population structure. Qualitative insight into the pertinent aspects of population structure, in the form of social networks, is still lacking, however (Wallinga *et al.* 1999).

Networks of social contacts may vary in a number of ways. First, the number of social contacts per host may vary (across the host population and in time). The relevance of whether a parasite's host interacts with a large or small number of other hosts is not immediately obvious, as explained below. Second, the overall structure of the social network may vary. Consider the contact structures depicted in Figures 7.1a and 7.1b. In both networks every host is connected to three other hosts, but in one the overall structure is laid out in a regular fashion (Figure 7.1a) whereas in the other it is completely random (Figure 7.1b). Watts and Strogatz (1998) and Keeling (1999) showed that such variations in network structure may have far-reaching consequences for, among other things, epidemiology. For example, a parasite can expand more rapidly in a random contact network than in a regular network, as suggested by the shaded nodes in Figures 7.1a and 7.1b. But

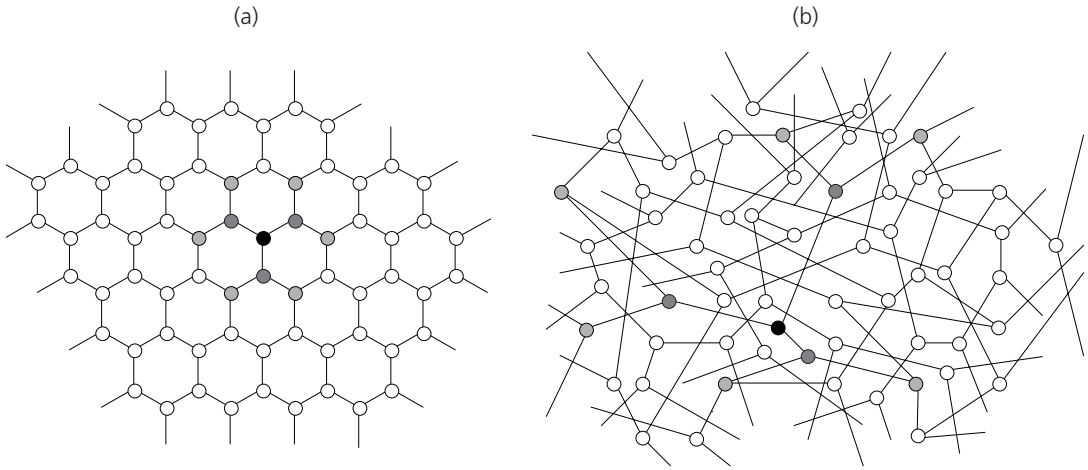


Figure 7.1 A regular network (a) and a random network (b). Both have a neighborhood size of three. In each structure, a focal host is indicated (black) with its neighbors up to two links away (dark and light gray).

how is parasite evolution determined by the number of contacts and the structure of the network? What are (if any) the evolutionary consequences of changes in a network structure?

It is not easy to find answers to these kinds of questions. In fact, a simple evolutionary analysis predicts *no* relationship between the number of contacts per host and the evolution of virulence. The reasoning is as follows. Whether a given mutant will increase (and hence invade a resident parasite population) is determined by its basic reproduction ratio R_0, that is, by the number of new infections produced by a host infected with the mutant parasite. In the simplest host–parasite models, this is given by the well-known expression

$$R_0 = \frac{\beta_{\text{mut}} S^*}{d + \alpha_{\text{mut}}} , \tag{7.1}$$

where β_{mut} is the mutant's transmissibility, $S^* = S$ is the encounter rate with susceptible hosts (whose density S^* is set by the resident parasite), d the background host mortality rate, and α_{mut} the mutant's virulence (disease-induced mortality rate, Boxes 2.1 and 2.2; Anderson and May 1982; Bremermann and Pickering 1983; Lenski and May 1994; Van Baalen and Sabelis 1995a). [Note that this definition of R_0 is slightly different from the standard epidemiologic definition, in which it represents the number of secondary cases produced by a single infected individual in an entirely susceptible population. In an evolutionary setting, as in this chapter, the relevant fitness measure is the number of descendants of a *mutant* parasite introduced into a population in which a resident parasite is at equilibrium. See Box 5.1 and Mylius and Diekmann (1995) for a further discussion of the relationship between these R_0 concepts.]

A mutant parasite maximizes its fitness (i.e., its R_0) under all conditions if it strikes the optimal balance of infectivity and host longevity (as it cannot influence

the density of susceptible hosts). Such optimal exploitation on a per-host basis depends only on the relationship between per-contact transmissibility (β) and disease-induced mortality (α). Since the optimum does not depend on population-level quantities, how many susceptible hosts there are, or how many of these an infected host will meet, is irrelevant (see Box 5.1 for more details). As a consequence, no change in the hosts' environment induces an evolutionary response in the parasite population. This implies that virulence management should focus on individual hosts and their current infections (for example, choosing among different medical treatments). Policies affecting the host–parasite interaction on a larger scale (vaccination, sanitary measures) may have desirable consequences on the epidemiological time scale, but may leave unchanged selection pressures on the parasites: lowering the density of infected hosts does not necessarily affect the optimal balance.

A number of observations suggest that parasite evolution *does* depend on such factors. Ewald (1993, 1994a, 1994b) discusses several examples in which the introduction of measures to hamper transmission is followed by a reduction in evolutionarily stable strategy (ESS) virulence. His explanation is that when transmission is more difficult the parasites are forced to deal more carefully with their host. For example, this explains the reduction in virulence of certain pathogenic bacteria infecting newborns in maternal wards after the introduction of measures to improve hygiene. Conversely, when transmission becomes "easier", more virulent strains have the advantage; this explains the emergence of more virulent parasites in response to the turmoil associated with war (e.g., the 1918 influenza pandemic), or to increased rates of global movement and partner change [as for the human immunodeficiency virus (HIV)].

As discussed, the standard "R_0-argument" cannot explain such evolutionary changes. However, since the argument is based on a number of simplifying assumptions, certain aspects of host–parasite relationships are not taken into account. For example, the standard argument assumes that hosts are exploited by single clones of parasites only. If this assumption is relaxed, then *within*-host competition among the parasites may drive an eco-evolutionary feedback (Van Baalen and Sabelis 1995a; Eshel 1977; Nowak and May 1994) that can explain Ewald's observations at least partially (Van Baalen and Sabelis 1995b; see Box 7.1). In this chapter, it is shown that Ewald's observations can also be explained if another assumption is relaxed, namely that of a "well-mixed" host population. The importance of this result is that contact structure becomes an essential aspect in explaining virulence.

Paraphrasing Tolstoy, it can be said that all well-mixed populations resemble one another, but that every structured population is structured in its own way. For example, host and parasite populations may be subdivided into discrete subpopulations, either because their habitat is patchy, or because the host forms different social groups that do not mix [see Anderson and May (1991) for a number of examples]. A common modeling approach for such cases assumes that subpopulations are well-mixed, while between subpopulations hosts and parasites disperse

Box 7.1 Models of virulence evolution accounting for within-host competition

Whenever multiple infections occur, a within-host conflict arises between the parasites. This conflict shifts the balance of virulence evolution toward the short-term advantage of faster host exploitation and away from host preservation. Multiple infection therefore favors increased virulence (Bremermann and Pickering 1983; Frank 1992a; Van Baalen and Sabelis 1995a).

If multiple infection is a factor determining the evolution of virulence, there will also be a feedback via epidemiology: the number of strains sharing a given host depends on the risk of infection, and this risk depends, in turn, on the strategies in the resident parasite population (Eshel 1977; Van Baalen and Sabelis 1995a; Van Baalen and Sabelis 1995b). Evolution will then depend on the small-scale interactions within hosts as well as on the large-scale interactions at the population level.

One of the earliest attempts to understand the evolutionary consequences of within-host competition is based on the assumption that more virulent parasites quickly replace less virulent clones. This process, called "superinfection," results in intermediate levels of virulence (Levin and Pimentel 1981) and increased levels of parasite polymorphism (Nowak and May 1994).

A problem with superinfection models is that the assumptions become highly artificial when applied to strains that differ very little in virulence: increasing virulence a tiny bit entails a huge fitness benefit since in these models the ancestral strain is assumed to be ousted immediately. Biologically, it is much more likely that strains that differ very little coexist within a host for a certain time. "Coinfection" models therefore make no assumptions about within-host competitive exclusion. However, unless alternative special assumptions are made, these models are more difficult to analyze, because the bookkeeping is more complex (hosts with one, two, three, etc., infections need to be tracked separately). Van Baalen and Sabelis (1995a) showed that, if the number of coinfections is limited to two, increased virulence results, but no polymorphism develops. Mosquera and Adler (1998) combined superinfection and coinfection models into a single framework. For more details on these models, see Chapters 9 and 10.

Another approach is to ignore the discrete character of infection events and focus instead on average relatedness among the parasites. This type of modeling, pioneered by Frank (1992a, 1994b, 1996c; see Box 11.1), allows analytic insight into the effects of within-host competition, but it is difficult to incorporate epidemiology into such models. Using this approach, Gandon (1998) argued that propagule survival affects the evolution of virulence through changes in average relatedness among the parasites (see also Chapter 11). Analysis of coinfection models suggests that within-host competition may include a component that favors *reduced* virulence, that is, parasites trade-in their capacity for within-host growth for an increased competitiveness (Chao *et al.* 2000).

Yet another approach ignores multiple infection altogether and focuses on the within-host diversity generated by mutations during within-host replication (Nowak *et al.* 1990; Nowak and May 1992). Such models are geared to take the immune system process into account, but are difficult to link to epidemiological models.

Notice that since within-host competition depends on multiple infection, the evolution of virulence depends on many epidemiological details that can be interfered with, thus greatly enhancing the scope for virulence management (Van Baalen and Sabelis 1995b).

Table 7.1 Events in a two-strain SIR model.

Event		Rate
Infection	$IS \rightarrow II$	β_I
	$JS \rightarrow JJ$	β_J
Recovery	$I \rightarrow R$	θ_I
	$J \rightarrow R$	θ_J
Loss of immunity	$R \rightarrow S$	ρ

"Mirror image" pair events always have the same rate.

much more slowly. Often, however, such a structure exists even when boundaries between subpopulations are less clear, or do not exist at all. Human populations, for example, tend to be highly structured, even when clear boundaries are absent. Such systems are much harder to analyze.

Populations without an imposed large-scale spatial structure, but with local dispersal, are called "viscous" (Hamilton 1964) or "mobility limited" (de Roos *et al.* 1991) populations. Such populations are much more "grainy" than well-mixed populations: instead of all members experiencing the same environment, individuals interact with their own local neighborhood, which consists of a finite number of other individuals, each of which may be infected or not.

This type of model is often studied by means of computer simulation of the so-called "probabilistic cellular automata" (PCA). In such simulations the state of a lattice of sites (a network of hosts, as is the case here) is changed by the occurrence of local events (birth, death, infection, and so on) that are governed by simple and local rules. Usually, the sites are arranged so as to form a regular, square lattice, in which every individual either interacts with its four or eight closest neighbors. This is, of course, a natural assumption if the system studied (plants, for example) inhabits a two-dimensional world. However, in many systems, in particular when interactions are determined by social relations rather than purely by geographical distance, other arrangements may be more appropriate (Keeling *et al.* 1997; Keeling 1999; Keeling 2000).

Spatial host–parasite dynamics have been studied for some time using the PCA approach (Satō *et al.* 1994; Rand *et al.* 1995; Rhodes and Anderson 1996; Jeltsch *et al.* 1997). More recently, the so-called pair dynamics (or correlation dynamics) approach has proved useful in explaining phenomena observed in these studies (Satō *et al.* 1994; Keeling *et al.* 1997; Boots and Sasaki 1999; Keeling 2000). This is a mathematical technique to analyze spatially extended systems (Matsuda *et al.* 1992; Satō *et al.* 1994; Van Baalen and Rand 1998; Van Baalen 2000; Iwasa 2000; Satō and Iwasa 2000). For example, a correlation dynamics model accurately predicted temporal patterns observed in childhood diseases in terms of contact structures (Keeling *et al.* 1997; Keeling 1999; Keeling 2000). Here, this technique is used to explore how social structure of the host population might affect the evolution of parasites, in terms of neighborhood size (the number of hosts a given host interacts with) and a parameter that describes the structure of the network.

Insight into the factors that determine selection pressures on parasites is vital for the development of virulence management strategies. If the shape of contact networks influences the evolution of virulence, then we know that virulence reflects not only small-scale (within-host) processes, but also larger-scale processes (comprising groups of hosts). Such knowledge may suggest ways to favor less virulent parasites by modifying the structure of contact networks or by changing the way parasites can spread through these.

7.2 Epidemics on Contact Networks

Hosts are assumed to form a fixed social network, in which every host is in contact with n other hosts, which here is called the host's interaction neighborhood. Any host is either susceptible S, infected with one of the two parasite strains I and J, or recovered and immune to infection by both parasite strains R. The events that change the state of the network are listed in Table 7.1. All these changes are stochastic; the associated rates are the probability per unit time for these events to occur. The model thus defines a PCA with asynchronous updating.

Assuming a fixed network means that there is no host dynamics in the model. This may be a reasonable assumption in many cases, but it renders the concept of "virulence" problematic. Usually, virulence is defined as the increase in host mortality [factor α in Equation (7.1)] or, more generally, as the reduction in host fitness. In the present model there is no host mortality, and thus no proper "virulence." For simplicity, it is assumed that there exists a trade-off between parasite virulence and clearance rate θ: the more infectious ("virulent") a parasite, the quicker it is eradicated by the host's immune system. The underlying idea is that such parasites are more detrimental to their hosts, which therefore put more effort into counteracting them. Of course, other relationships can be envisaged as well. For example, there could be a relationship between the parasite's host-exploitation strategy ("virulence") and the duration of the ensuing period of immunity. This yields a similar but more complex model (as different classes of immune hosts need to be tracked). A full analysis of the evolution of virulence requires that host dynamics be taken into account as well, but this is beyond the scope of this chapter.

Note that in Table 7.1 transmission events are characterized in terms of the per-contact transmission rate $\tilde{\beta}$. If this is fixed, the total transmission rate will be proportional to the number of contacts per host (i.e., to neighborhood size). Here, however, we are more interested in the consequences of the structure of the contact network than in the consequences of the absolute number of contacts. Therefore, it is assumed that per-contact transmission rates are inversely proportional to neighborhood size n,

$$\tilde{\beta}_x = \frac{\beta_x}{n} , \tag{7.2}$$

with $x = I$ or J. Consequently, the total infectivity β_x of an infected host is constant, but spread out over more hosts if neighborhood size increases (i.e., the

per-contact transmission efficiency $\tilde{\beta}_x$ decreases, but this is counterbalanced by the larger number of contacts).

At the lowest level the model is thus defined exclusively in terms of local and discrete events. The question now is how the model behaves at a larger scale, that is, how the numbers of host in the various states change over time in the network.

7.3 Mean-field Dynamics

Before analyzing the viscous system, it is insightful to consider the equivalent nonstructured ("mean-field") model. This tells us what to expect in the standard case of no social structure, that is, when every host can potentially infect every other. The mean-field model is therefore obtained by letting the neighborhood size n go to infinity: every infected host can potentially infect every susceptible host. This yields

$$[S]' = -\beta_I[S][I] - \beta_J[S][J] + \rho[R] \,, \tag{7.3a}$$

$$[I]' = \beta_I[S][I] - \theta_I[I] \,, \tag{7.3b}$$

$$[J]' = \beta_J[S][J] - \theta_J[J] \,, \tag{7.3c}$$

$$[R]' = \theta_I[I] + \theta_J[J] - \rho[R] \,, \tag{7.3d}$$

where $[S]$, $[I]$, $[J]$, and $[R]$ are the densities of susceptible, infected, and recovered hosts, respectively. The total density of hosts does not change, and is scaled to one. This set of equations is a very basic model that has been studied extensively (Anderson and May 1991; see Boxes 2.1, 2.2, and 9.1). The main difference to the usual formulation is that host mortality is not included; normally, it is assumed that when a host dies, it is replaced instantaneously by a susceptible host, but this presupposes extremely tight control of the host population. In the present model, there is essentially no host population dynamics: from the viewpoint of the parasites, the host population (and its social structure) is "frozen" in time.

If one of the parasite strains (say strain J) is rare, the other strain (strain I) settles at a stable equilibrium ($[S]^*$, $[I]^*$, $[R]^*$). Parasite strain J is able to invade this equilibrium if $[J]'$ is positive when $[J]$ is small, which is the case if

$$\beta_J[S]^* - \theta_J > 0 \,. \tag{7.4}$$

The invasion condition can also be expressed in terms of the mutant's basic reproduction ratio $R_0(J)$,

$$R_0(J) = \frac{\beta_J[S]^*}{\theta_J} > 1 \,, \tag{7.5}$$

which gives the number of secondary infections caused by a host infected with the mutant J in a population infected by the resident parasite I. Since in a well-mixed population the mutant does not influence the density of susceptible hosts it

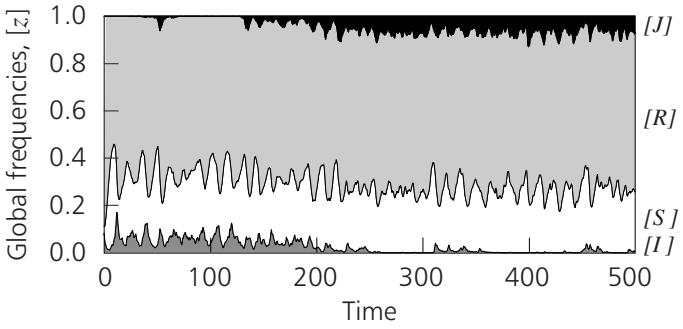


Figure 7.2 Simulations of the dynamics across a network. The hypovirulent strain J (black area) of parasites can invade and replace the strain adapted for well-mixed host populations I (dark gray shade; white, susceptible hosts; light gray shade, immune hosts). A total of 3 600 hosts are arranged in a triangular lattice (with periodic boundary conditions), in which every host is connected to its six nearest neighbors (i.e., $n = 6$). Parameters: $\beta_I = 30$, $\theta_I = 1$, $\beta_J = 25$, $\theta_J = 0.9$, $\rho = 0.1$. In addition to the events listed in Table 7.1, a small mutation rate is included: a fraction (0.001) of the infection events produces a host infected with the other type. The simulation was started with only parasite I present, close to the equilibrium for well-mixed populations.

encounters ($[S]^*$ is set by the resident), its evolutionary success is entirely determined by its "per-host transmission factor" β_J/θ_J, that is, by infectivity times the mean duration of the infective period.

Since equilibrium conditions imply

$$[S]^* = \frac{\theta_I}{\beta_I} , \tag{7.6}$$

it can be concluded that the strategy with the largest per-host transmission factor β/θ is the ESS. Note that this maximum is independent of the density of susceptible hosts (the role of the per-host transmission factor is explained in more detail in Box 5.1; see also Bremermann and Pickering 1983; Lenski and May 1994; Van Baalen and Sabelis 1995a).

7.4 Across-network Dynamics

In a well-mixed population, all that matters to a parasite is to maximize the per-host transmission factor by striking the optimum balance of intensity and duration of infectiousness. In a structured host population, however, the situation is different. A first indication is provided by the simulation presented in Figure 7.2, which shows a parasite with a per-host transmission rate almost 8% lower than the strain that maximizes per-host transmission (the ESS in well-mixed populations can invade and replace the latter). Hence, compared to well-mixed populations, spreading through contact networks favors reduced virulence. Our task is now to determine why this is the case and to determine ESS levels of virulence in contact networks.

The change in selection pressure on virulence turns out to be tightly coupled to the distribution of susceptible, infected, and immune hosts across the contact

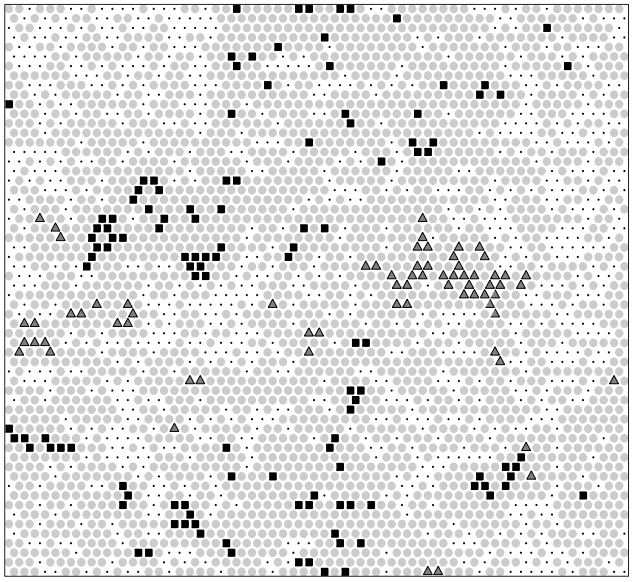


Figure 7.3 Clusters of the hypovirulent strain J (squares) competing with the strain adapted for well-mixed populations I (triangles) on a triangular lattice ($n = 6$). Susceptible hosts are represented by small points, immune hosts by gray circles. The snapshot is taken at $t = 200$ from the simulation presented in Figure 7.2.

network. Figure 7.3 is a snapshot of the network when the mutant of Figure 7.2 is invading. As can be seen, the parasites' distributions are far from homogeneous. Though there are no clear boundaries separating patches, patches of infected hosts tend to be surrounded by regions of immune hosts. This, of course, blocks the parasites' transmission into regions with many susceptible hosts. The distribution is highly dynamic. Patches of immune hosts lose their immunity and at some point in time a parasite breaks through and infects the hosts. The peaks in the time series (Figure 7.2) represent such episodes of parasites bursting into patches of susceptible hosts.

Since it is able to invade, mutant J is somehow better adapted to spread through the network. The snapshot presented in Figure 7.3 contains a clue about what may be happening. If we calculate the global densities in the network as well as the local densities that surround the two strains of parasites (results are shown in Figure 7.4), we observe that a host infected with a hypovirulent parasite J has on average more susceptible hosts in its immediate neighborhood than does the more virulent strain I (about twice as many). Reducing virulence therefore seems to allow the hypovirulent strain to exploit the fact that immune hosts lose their immunity after a while. Strain I cannot easily profit from this because the strains tend to be segregated across the network. Figure 7.4 shows that parasites of strain J have fewer parasites of strain I in their neighborhood and vice versa.

It can be shown (Matsuda *et al.* 1992; Van Baalen and Rand 1998; Van Baalen 2000; Dieckmann and Law 2000) that local densities equilibrate faster than global densities. In particular, a mutant parasite strain that is globally rare experiences a characteristic environment that includes related mutants, because an invading mutant tends to form clusters if infection is local. The characteristics of such

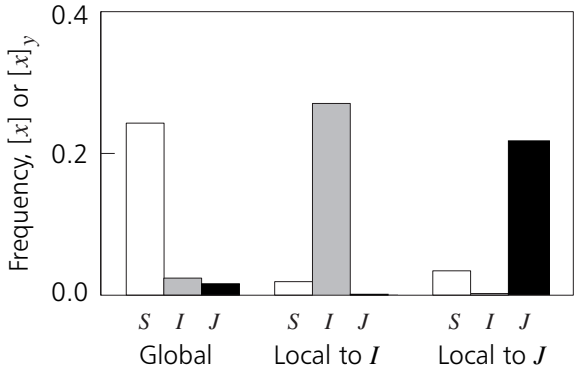


Figure 7.4 Global and local densities of susceptible and infected hosts and of parasites. The local densities experienced by parasites I and J correspond to the distribution shown in Figure 7.3.

clusters, viewed as more or less coherent units, determine the invasion success (Van Baalen and Rand 1998).

Thus, to understand the epidemiology and evolution in contact networks, we have to account for the heterogeneous distributions of the parasites. This is particularly important when considering the fate of (globally) rare mutants. One way to study evolutionary outcomes is to run simulations in which many strains of parasites compete over a range of aspects like neighborhood size and the geometrical structure of the contact network. An initial disadvantage of such an approach is that it is very computationally intensive (the single simulation shown in Figure 7.2 took several hours on a desktop computer). More importantly, even though the network is fairly large (3 600 hosts), the resultant dynamics are characterized by much demographic stochasticity. In particular, this is a major drawback if the aim is to study evolution, as numerous invasions have to be "tried" before one can decide that a certain mutant is likely to invade (Claessen and de Roos 1995). And even after numerous simulations, it may still be very difficult to gain insight into exactly which aspects of the interaction are important, as the simulations have to be repeated for many different combinations of parameters. It is here that the correlation dynamics approach can lead to greater insight.

7.5 Pair Dynamics

The differential Equations (7.3a) to (7.3d) keep track of the densities of susceptible, infected, and immune hosts. Such densities are nothing more than the probabilities that a randomly picked host is in a given state. In a similar fashion, we can define the densities of *pairs* (or "doublets") of neighboring hosts: these represent the probability that a pair of connected hosts is in a given combination of states (for example, one susceptible and the other infected). As for the "singlets," differential equations can be derived for the changes in the densities of doublets. This gives rise to an increased number of differential equations (one for every combination of states). These differential equations are rather complex because they keep track of all possible transitions that create and destroy pairs. For comparison: the only

singlet "events" are $S \to I$, $I \to R$, and $R \to S$; the set of pair events is much larger: $SS \to IS$, $IS \to RS$, $SS \to RS$, $SR \to IR$, etc. The full set of equations taking into account all pair events is given in Box 7.2.

The major advantage of knowing pair densities is that local densities (the quantities shown in Figure 7.4) can be calculated directly. A local density of x experienced by y is simply the conditional probability that a given neighbor of a site in state y will be in state x, and is given by

$$[x]_y = \frac{[xy]}{[y]} , \tag{7.7}$$

where $[xy]$ is the density of xy pairs of hosts (x, $y = S$, I, R) and $[y]$ is the density of y-state hosts.

From the pair equations (given in Box 7.2) it follows that the global dynamics of both parasite strains are given by

$$[I]' = (\beta_I [S]_I - \theta_I)\,[I] , \tag{7.8a}$$

$$[J]' = (\beta_J [S]_J - \theta_J)\,[J] . \tag{7.8b}$$

Rewriting in terms of reproduction ratios, the condition for invasion of strain J is

$$R_0(J) = \frac{\beta_J [S]_J}{\theta_J} > 1 . \tag{7.9}$$

The important aspect is that the expected rate of increase of parasite strain J does not depend on the global density of susceptible hosts $[S]$, but on their local density $[S]_J$. A hypovirulent strain can then invade if it can offset its less efficient host-use (indicated by its reduced per-host transmission ratio β_J/θ_J) by surrounding itself with a higher density of susceptible hosts $[S]_J$. Hypovirulent parasites can then be said to exploit their local host population more prudently. Such prudent exploitation cannot evolve in well-mixed systems, in which both strains exploit the same global population of susceptible hosts. In viscous systems, however, both strains are segregated to a certain extent (see Figures 7.3 and 7.4), which makes it difficult for more virulent strains to profit from the increased density of susceptible hosts that surrounds the hypovirulent parasites.

The local density of susceptible hosts rises if the parasites shorten the immune period (at a cost of reduced infectivity). The parasites "wait," as it were, for immune hosts to become available again. If they are too "impatient" they surround themselves quickly by immune hosts, and so their spread is blocked. Their problem is that increasing the density of susceptible hosts may be exploited by competing parasite strains; they must not give away too much if there are too many of these in their neighborhood. It is therefore the clustering of the parasites in the network that favors the reduced virulence. In this system, reduced virulence is essentially an altruistic trait, disadvantageous for the parasite itself but of benefit to the parasites in their environment. In viscous populations these neighboring parasites tend to be related; hence the evolution of reduced virulence is an example of kin selection (Hamilton 1964; Maynard Smith 1964). Any parasite unit (a

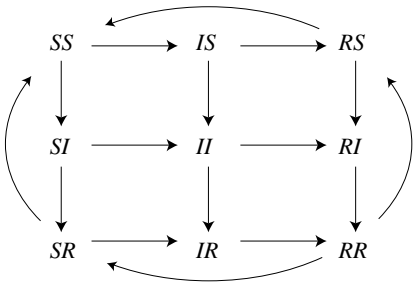
Box 7.2 Pair approximation for incompletely mixed host populations

Since the pioneering work of Kermack and McKendrick (1927) the standard framework for epidemiological models is based on the assumption that the host population is well-mixed. That is, every host is equally likely to meet (and transmit any infection to) every other host in the population. This is obviously not true in many cases, and mathematical techniques have been developed to deal with the epidemiological consequences of spatial and/or social structures. One of these techniques is the correlation dynamics or pair approximation approach.

This method is based on three ingredients:

- The network that represents space or social structure (such as shown in Figure 7.1);
- The set of states that any site may be in (here, the susceptible state S, the infected states I and J, and the recovered state R);
- The set of rules for how sites may change state (listed in Table 7.1).

The simplest correlation dynamics equations keep track of the states of neighboring pairs of hosts on the lattice (Matsuda *et al.* 1992). If $[xy]$ denotes the proportion of pairs in states x and y, either the x or the y site can change through one of the events listed in Table 7.1. Notice that both individuals in such a pair also form pairs with other individuals for which events may occur. For the model summarized in Table 7.1, the differential equations for the resident SIR system therefore have to take into account all the transitions shown below.



In deriving the differential equations for the changes in densities of pairs, use is made of the fact that the densities in the network of symmetrical pairs (for example, the densities of SI and IS pairs) are identical.

The resultant differential equations are:

$$
\begin{aligned}
[SS]' &= 2\rho[RS] - 2\beta_I(1-n^{-1})[I]_{SS}[SS]\,,\\
[SI]' &= \beta_I(1-n^{-1})[I]_{SS}[SS] - \{\beta_I(n^{-1}+(1-n^{-1})[I]_{SI}) + \nu_I\}[SI]\\
&\quad + \rho[RI]\,,\\
[SR]' &= \theta_I[SI] - \{\beta_I(1-n^{-1})[I]_{SR} + \rho\}[SR] + \rho[RR]\,,\\
[II]' &= 2\beta_I(n^{-1}+(1-n^{-1})[I]_{SI})[SI] - 2\theta_I[II]\,,\\
[IR]' &= \beta_I(1-n^{-1})[I]_{SR}[SR] - [\rho+\theta_I][IR] + \theta_I[II]\,,\\
[RR]' &= 2\theta_I[IR] - 2\rho[RR]\,.
\end{aligned}
$$

continued

Box 7.2 *continued*

$[x]_{yz}$ denotes the proportion of sites neighboring yz pairs that are in state x, i.e., $[x]_{yz} = [xyz]/[yz]$. The equations involving J are analogous to those involving I. Van Baalen (2000) explains in detail how these differential equations are derived from the set of transitions. Keeling *et al.* (1997) have analyzed a more complex version of this model.

Since $[x] = [xS] + [xI] + [xJ] + [xR]$, the dynamics of singlets follows from that of pairs,

$$[x]' = [xS]' + [xI]' + [xJ]' + [xR]' .$$

This results in Equations (7.8), but only if every host has the same number of contacts. If the number of contacts varies, differential equations that describe singlet dynamics have to be derived separately (Morris 1997; Van Baalen 2000).

The set of equations that describe pair dynamics is exact but it is not yet closed. The problem is that some of the equations depend on quantities of the type $[x]_{yz}$, which depend on the densities of xyz-triplets in the network. Van Baalen (2000) showed that the local density $[x]_{yz}$ can be approximated by

$$[x]_{yz} = [x]_y\{(1-e) + eC_{xz}\}\tau_{xyz} ,$$

where e is the proportion of triplets that are in a closed triangular configuration and $C_{xz} = [xz]/([x][z])$ is the correlation between neighboring sites in state x and z (see also Keeling 1999). The remaining problem is to find correction factors τ_{xyz} that preserve the consistency of the system. One cannot simply assume that all $\tau_{xyz} = 1$ because then the $[x]_{yz}$ will not, as they must, add up to 1 when summed over all x. There are several alternative choices for the τ_{xyz} that preserve consistency but it is as yet unknown which one leads to the best approximation. The assumption adopted here is

$$\tau_{xyz} = 1 \quad \text{if} \quad x \neq z ,$$

and τ_{xyz} is chosen such that

$$[z]_{yz} = 1 - \sum_{x \neq z} [x]_{yz} .$$

This is the simplest choice and has been demonstrated to work quite well in other cases (see Van Baalen 2000).

clone infecting a given host) does best by optimizing its per-host transmission ratio. Reducing virulence therefore does not benefit the individual itself, but rather the cluster of related individuals to which it belongs (Van Baalen and Rand 1998).

7.6 Implications of Network Structure

Let us now start to vary the structure of the contact network. Consider first the consequences of a finite neighborhood *per se*. Figure 7.5a shows that the hypovirulent parasite can only invade and replace strain I if the neighborhood size is fairly

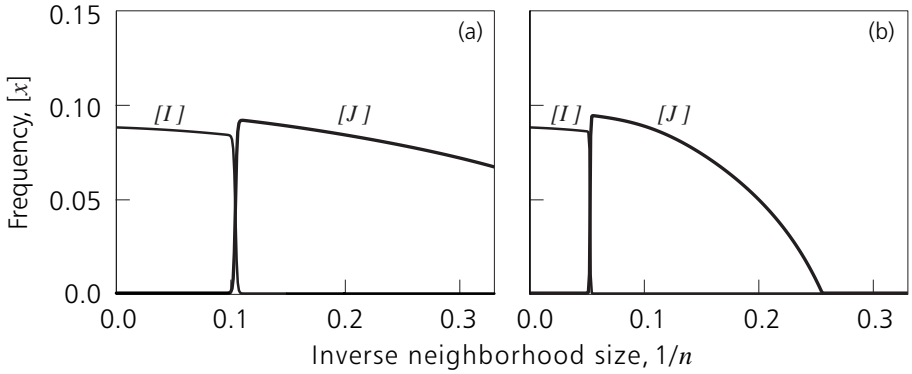


Figure 7.5 Equilibrium densities of strain I (adapted to well-mixed populations) and hypovirulent strain J for different neighborhood sizes n in (a) random and (b) regular ($e = 2/5$) contact networks.

small (i.e., if $1/n$ is larger than a threshold value). This is no surprise because if n becomes large the system approaches a well-mixed system to which strain I is adapted (as it maximizes the per-host transmission factor).

Working out the effects over all the network structure is more complicated. For this we need a parameter that describes whether the network is regular (as in Figure 7.1a), random (as in Figure 7.1b), or in between. Such a parameter emerges from a close consideration of the assumptions that underlie the pair equations (Van Baalen 2000).

The differential equations for singlets depend on the densities of pairs (for example, $[I]'$ depends on the density of SI pairs). In a similar fashion, the differential equations for the pairs may depend on triplet densities. More precisely, the differential equation for a given pair may depend on local densities of the form

$$[x]_{yz} = \frac{[xyz]}{[yz]} \, . \tag{7.10}$$

In effect, it is necessary to approximate $[x]_{yz}$ in terms of pairs. In technical terms, a "closure assumption" must be made. The simplest possible approximation is the "pair approximation" given by

$$[x]_{yz} \approx [x]_y \, , \tag{7.11}$$

which assumes that the probability of finding a neighbor of y in state x is independent of the fact that one of y's other neighbors is in state z (Matsuda *et al.* 1992).

Pair approximation is only one of the many possible ways to "close" the set of differential equations (see Van Baalen 2000; Dieckmann and Law 2000; Bolker *et al.* 2000), and consideration of the network structure becomes important in choosing a way to "close" the equations. The pair approximation can be shown to represent best random contact networks, such as depicted in Figure 7.1b. In more regular networks, however, a pair of neighbors share part of their neighborhood. For example, in the triangular lattice depicted in Figure 7.3, a pair always has two common neighbors.

For such triangular lattices we can use the fact that $2/5$ of all randomly picked triplets will be triangular (i.e., with a connection between the far ends). In Box 7.2 an expression is given for the conditional probability $[x]_{yz}$ that takes into account the correlation between x and y's z-neighbor based on the assumption that a proportion e of triplets are triangles.

This approximation allows the consequences of different degrees of network regularity to be assessed: $e = 0$ for random lattices, $e = 2/5$ for triangular lattices, and semi-regular networks have intermediate e values. In more everyday terms, e is a measure of the likelihood that a relation of one neighbor is also a relation of the other: if e is large, the friends of my friend are probably also my friends, whereas if e is zero, my friend and I have no common acquaintances. By varying e we can investigate some of the consequences of changes in overall social structure while keeping the number of contacts per host constant.

Figure 7.5b shows that for regular networks (with a fixed proportion $e = 2/5$ of triangles) the hypovirulent strain J can invade and replace strain I at a larger neighborhood size than for random networks. This suggests that regularity favors reduced virulence. Conversely, disruption of a social network from regular to random benefits the more virulent parasites.

Note that for the regular network, even the hypovirulent strain cannot maintain itself at low neighborhood sizes (approximately $n > 4$; see also Satō *et al.* 1994). It may be possible that strains with even lower virulence are able to maintain themselves. The information gained by letting only two strains compete is thus limited. More strains must be considered, but this poses some problems. Which strains are possible? Which of these will natural selection weed out? Does the parasite population become monomorphic? How will the ensemble of strains respond to changes in their host population? These and related question are the domain of adaptive dynamics models (Dieckmann and Law 1996; Metz *et al.* 1996a; Geritz *et al.* 1997). The focus here is on potential evolutionary endpoints only, at which the resident population comprises a single strain of parasites.

7.7 Evolutionary Stability

When considering a multitude of parasite strains, we have to specify a constraint that links all possible transmissibilities β to a recovery rate θ. Ideally, this constraint should be derived from a submodel of how the parasites interact with their host's immune system, but this is quite an ambitious undertaking. Here, we analyze the example

$$\theta(\beta) = \theta_0 + c\beta^2 \,, \tag{7.12}$$

which assumes that the recovery rate increases more than linearly with the parasite's infectivity. The idea behind the monotonic shape of this relationship is again that more transmissible parasites are likely to be more detrimental to their hosts, which will consequently put more effort into combatting them. Notice that we have to assume that the relationship between θ and β is nonlinear with a coefficient c,

for otherwise there is no intermediate level of virulence that optimizes per-host exploitation (see the figure in Box 5.1). Equation (7.12) then is the simplest choice.

Maximization of the per-host transmission factor $\beta/\theta(\beta)$ gives the ESS virulence β^* in a well-mixed system,

$$\beta^* = \sqrt{\theta_0/c}\,. \tag{7.13}$$

The question now is how the ESS changes when the host population is not well-mixed, but socially structured. Whether or not a mutant J will invade a given resident population is, in general, determined by its invasion fitness, denoted by f_J and defined as its expected rate of increase when globally rare (Metz *et al.* 1992; Rand *et al.* 1994). For the socially structured SIR model, f_J cannot be calculated analytically, but for the present purpose a numerical analysis is sufficient.

The dynamics of the resident parasite I can be simply established by numerically integrating the differential equations for $[SS]$, $[SI]$, $[SR]$, $[IR]$, and $[RR]$. In a well-mixed model, the system always results in a stable endemic equilibrium; the same is true for the network-structured model (in fact, the analysis would be much more difficult if the resident parasite gave rise to cycles or chaotic dynamics). From the values of the pair densities we can infer the mean density of a resident parasite and the degree of clustering that it causes.

Subsequently, we can numerically calculate the selection pressure from the dynamics of a globally rare mutant parasite strain J with a strategy close to that of the resident (i.e., $\beta_J = \beta_I + \Delta\beta$, with $\Delta\beta \ll \beta_I$). The mutant dynamics are described by four more differential equations (we need differential equations for $[SJ]$, $[JJ]$, $[RJ]$, and $[IJ]$, which are derived as outlined in Box 7.2). When the mutant is rare, its effect on the resident system can be ignored and the pair densities $[SS]$, $[SI]$, $[SR]$, $[IR]$, and $[RR]$ remain at their equilibrium values. From the mutant dynamics, the mutant's invasion fitness can be calculated and from this, in turn, the selection pressure, which is proportional to $(f_J - f_I)/\Delta\beta$. By continually adjusting the resident strategy β_I in the direction indicated by the selection pressure until the selection pressure becomes zero, the evolutionary endpoint is eventually found numerically. (The method ensures that the point thus found is convergence stable. As only one mutant is tested at a time, it does not identify branching points, at which the parasite strains diverge because of disruption selection; see Metz *et al.* 1996a; Geritz *et al.* 1997.) Notice, however, that for this particular model such divergence is unlikely; the construction of the model means that the point found by the procedure used here will always be an ESS, that is, correspond to a fitness maximum.

Figure 7.6 shows the results of an extensive parameter survey relating ESS infectiousness β^* to the network parameters. It confirms that, in general, a reduction of the hosts' neighborhood size is followed by a reduction in ESS virulence. The same is true if the regularity of the network (the proportion e of triangular connections) increases. Note, however, that Figure 7.6 predicts that if e is large (many triangles) *and* n is low (few connections), ESS virulence may *increase* again; however, these are very extreme cases and it may actually be impossible to construct

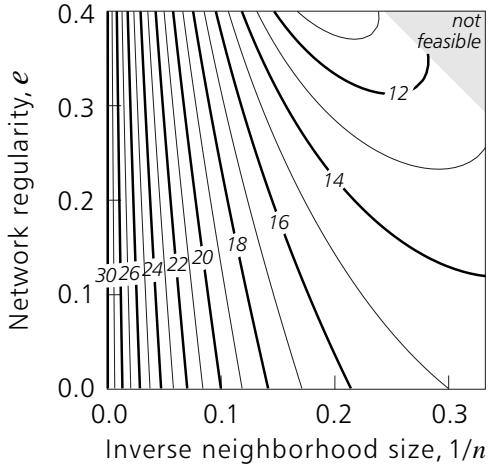


Figure 7.6 ESS transmissibility β^* [under the constraint $\theta(\beta) = \theta_0 + c\beta^2$], as a function of neighborhood size n and network regularity e. Parameters: $\theta_0 = 1/2$, $c = 1/1800$ (this parameter combination implies that $\beta^* = 30$ in a well-mixed host population), and $\rho = 0.1$. For combinations of small n and high e_{xyz} (gray area) the parasites always become extinct and hence an ESS is not feasible.

networks with such a combination of parameters. In most of the parameter region the pattern is remarkably clear: departures from well-mixedness favor reduced virulence.

7.8 Discussion

In socially structured host populations, less virulent parasites are favored compared to well-mixed host populations. To understand why one must focus on how a cluster of related parasites can expand through the social network. Clusters of virulent parasites tend to overexploit their local host population, which blocks their spread, whereas clusters of hypovirulent parasites exploit their hosts more prudently and can more easily expand. The effect is quite sensitive to the structure of contacts in the host population. The greater the neighborhood size of the hosts (the number of hosts a given host interacts with), the more the system approaches the dynamics of a well-mixed system, which benefits the more virulent strains. Figure 7.6 suggests that the same holds true when the network becomes more irregular.

Thus relatedness among parasites, whether it occurs *within* hosts (see Box 7.1) or *between* hosts, tends to favor reduced virulence. Anything that disrupts the pattern of relatedness among the parasites will favor increased virulence. It is shown here that increasing contact number or network randomness favors increased virulence; Boots and Sasaki (1999) showed that the same holds when infection is increasingly long-range as opposed to local. The same result can be expected for increases in host mobility, background host demographic rates, partner change (for sexually transmitted diseases), etc., since all these processes tend to disrupt patterns of relatedness.

An important aspect that remains to be studied is the relationship between the hosts' (physical) density and its contact structure. Neighborhood sizes may increase if host density increases, but also they might not. For example, in human populations one might suppose that the number of (sufficiently intense) social contacts would be almost independent of population density. Edmunds *et al.* (1997) recently carried out a survey to assess the number of contacts that are (presumably) suitable for the transmission of respiratory diseases. They found that the number of such contacts was remarkably constant across period of the week and age; subjects talked on average to about 30 persons per day (with the exception of Sundays). It would be very interesting to carry out similar surveys in different areas with different population densities, while also trying to assess network structure. The expectation is that the number of contacts will appear to be roughly the same, but that different densities will lead to different degrees of structure in the contact network. In rural communities an individual's contacts are also very likely to know each other, which is not necessarily the case in high-density areas (i.e., cities). If increasing (physical) density thus renders the contact structure less regular, we can expect parasites to evolve an increased virulence in response.

The model studied in this chapter is not very satisfactory as a model for the evolution of HIV: the assumption that every host has exactly n concurrent sexual relationships is rather extreme. (Contact network models for the spread of HIV are more complicated than those studied here and include processes like partnership formation and breakup, etc.; see Kretzschmar 1996; Kretzschmar and Morris 1996; Morris and Kretzschmar 1997.) Nonetheless, assuming that HIV infecting social networks exhibits similar relatedness patterns can give some insight into how HIV is likely to respond to changes in population structure. In particular, it is predicted that more virulent strains of HIV will emerge when the contact network becomes less regular. That is, evolutionary responses will ensue even if individual behavior does not change (the number of sexual partners remains constant and so forth).

The analysis, as reported in this chapter, confirms Ewald's hypothesis to a certain extent. That is, more "sparse" and more regular connection networks favor less virulent parasites. However, it should be realized that kin selection is at the heart of this phenomenon. The explanation is not that reduced virulence results because "the" parasite has to be more careful with "its" host, but rather that it allows a cluster of related parasites to exploit the local supply of hosts more efficiently. Changes in the pattern of relatedness thus entail an evolutionary response that results in a change in virulence.

Insight into the evolutionary consequences of contact structure is necessary to develop adequate "virulence management" strategies. In the first place, we need to know when (and how) social structure must be taken into account. Furthermore, such an insight might suggest opportunities to change the selection pressure acting on parasites. Of course, possible modifications to the contact network structure are limited and, in human populations, often plainly unethical. However, in some

cases we are able to influence some social structures, such as classrooms in schools etc. (Keeling *et al.* 1997).

Changing contact patterns may lie behind the phenomenon of many "emerging diseases" (Morse 1993). For example, McNeill (1976) hypothesized that syphilis emerged in the Middle Ages when the parasite that causes a leprosy-like disease called yaws changed its transmission strategy in response to altered patterns of social interaction. This particular hypothesis is, of course, difficult to test; nonetheless it underscores that social behavior may affect parasite evolution and hence should be part and parcel of virulence management.

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