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# Evolution of pathogens towards low $R_0$ in heterogeneous populations

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**Abstract**

Maximization of the basic reproduction ratio or $R_0$ is widely believed to drive the emergence of novel pathogens. The presence of exploitable heterogeneities in a population, such as high variance in the number of potentially infectious contacts, increases $R_0$ and thus pathogens that can exploit heterogeneities in the contact structure have an advantage over those that do not. However, exploitation of heterogeneities results in a more rapid depletion of the potentially susceptible neighbourhood for an infected host. Here a simple model of pathogen evolution in a heterogeneous environment is developed and placed in the context of HIV transmission. In this model, it is shown that pathogens may evolve towards lower $R_0$, even if this results in pathogen extinction. For sufficiently high transmissibility, two locally stable strategies exist for an evolving pathogen, one that exploits heterogeneities and results in higher $R_0$, and one that does not, and results in lower $R_0$. While the low $R_0$ strategy is never evolutionarily stable, invading strains with higher $R_0$ will also converge to the low $R_0$ strategy if not sufficiently different from the resident strain. Heterogenous transmission is increasingly recognized as fundamental to epidemiological dynamics and the evolution of pathogens; here, it is shown that the ability to exploit heterogeneity is a strategy that can itself evolve.


*Keywords:* Evolution; Pathogen; Heterogeneous contact; HIV

## 1. Introduction

Theoretical epidemiology is underpinned by the concept of a invasion threshold associated with the basic reproduction ratio or $R_0$. For $R_0>1$, a pathogen will be successful, in the sense that the introduction of a single infected individual into a wholly susceptible population will on average result in at least one other infected individual (Anderson and May 1991; Diekmann et al., 1990). Heterogeneities in the available host population that increase the susceptibility and transmissibility (probability of transmission per potentially infectious contact or $\tau$) associated with a host subpopulation confer advantages to pathogens that can exploit them, and for a given average transmissibility, results in higher $R_0$ (Yorke et al., 1978). In the case of sexually transmitted diseases (STD's) for example, highly active and therefore highly connected individuals are both more exposed and cause more infections, and they can play a crucial role in disease spread and persistence (Anderson and May, 1991; Hethcote et al., 1982). In theory, disease can persist even for vanishingly small $\tau$, so long as the variance in the number of contacts per individual is sufficiently high (Albert et al. 2000). Thus exploitation of heterogeneities has been suggested as a route by which new pathogens can emerge (May et al. 2001). As the "adaptive model" of evolution is typically driven by maximization of $R_0$ (Anderson and May, 1982), this also implies that, at least initially, a pathogen able to exploit heterogeneities in the host population will always be favoured over one that does not.

However, a strategy that relies on heterogeneity has disadvantages; the high-risk individuals are infected first, and thus while $R_0$ is higher, the average number of individuals infected by a single infectious individual at a given time in an epidemic (the reproduction rate $R(t)$) declines more quickly if heterogeneities are exploited than if they are not (Barthelemy et al., 2004; Kiss et al., 2006a). This can result in a lower final epidemic size compared to a strategy with the same $\tau$, but which does not exploit heterogeneities (Kiss et al., 2006b; May and Lloyd, 2001). Since an evolving pathogen will only be able to exploit $R(t)$

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and not $R_0$ (Anderson and May, 1982), this suggests that maximization of $R_0$ does not necessarily predict the direction of evolution. Here a simple, deterministic model of a population with heterogeneous contacts is developed, showing that evolution towards low $R_0$ may occur, possibly resulting in pathogen extinction even if the starting value of $R_0$ would predict successful pathogen invasion. In this model, stable states only exist if the pathogen either fully exploits available heterogeneities or does not exploit them at all (i.e. the strain has the same potential to infect all individuals). The final state depends on both the demographic structure and the initial conditions. Implications for epidemic diseases are briefly considered, establishing a plausible mechanism for evolution to low $R_0$ where disease persistence is maintained by a metapopulation structure. While the high-$R_0$ strategy is an evolutionarily stable one (ESS), the low-$R_0$ strategy is not, though invading strains insufficiently differentiated from the prevailing strain are predicted to "converge" towards it.

## 2. Model description—evolution in diseases with *SIRS* or *SIS* dynamics

Heterogeneity in the number of potentially infectious connections is considered, though the model would apply to any form of heterogeneity that equally affects both susceptibility and transmissibility. Consider a population of which a fixed number $N_x$ individuals are highly connected, with the average number of connections scaled by a factor $\sigma$ above the low risk population $N_y$, individuals of which are poorly connected. The epidemiology is described by a susceptible–infected–removed–susceptible (*SIRS*) system for each of the subpopulations $N_x$ and $N_y$, with states , $S_x$, $S_y$, $I_x$, $I_y$, $R_x$, $R_y$ referring to the states of the subpopulations. Infected individuals either recover and eventually become susceptible again or equivalently are removed and replaced by susceptible individuals in such a way that $N_x$ and $N_y$ are constant. In a population with heterogeneities in the contact structure, each individual in $N_y$ has $\kappa$ potentially infectious contacts or links, and each individual in $N_x$ has $\sigma>1$ more links than individuals in $N_y$. Then the expected value of the number of connections per individual over the whole population is

$$\langle\kappa\rangle=\kappa_{av}=\frac{N_x\kappa\sigma+N_y\kappa}{N_x+N_y}. \tag{1}$$

Assume that the pathogen can exploit this heterogeneity in the contact structure to a variable degree, ranging from full, or a "high-$R_0$ strategy", to no exploitation, a "low-$R_0$ strategy". Let $z$ be the extent to which the low-$R_0$ strategy is adopted, so that at $z=1$, all individuals potentially infect a number of others given by $\kappa_{av}$ in Eq. (1). Therefore *(1-z)* is the proportion of transmission that exploits heterogeneities in the population. Shifts in the net strategy of the pathogen population are governed by the relative proportion of new infections that occur according to each of the two extreme strategies, at a rate determined by a parameter $\mu$. The "direction" of evolution is determined by the relative numbers of new infections resulting from each route; in order to retain biologically sensible dynamics, a multiplier of $z(1\text{-}z)$ forces $\mathrm{d}z/\mathrm{d}t$ to be zero at $z=0$ and 1. Let the mortality of the infected individuals be $\delta$ and that of removed individuals be $\varepsilon$ and recall that the probability of transmission per connection is $\tau$. Then the model system can be described by a set of differential equations:

$$\begin{aligned}
&\frac{\mathrm{d}I_x}{\mathrm{d}t}=F_1(I_x,I_y)+F_2(I_x,I_y)-\delta I_x,\\
&\frac{\mathrm{d}I_y}{\mathrm{d}t}=G_1(I_x,I_y)+G_2(I_x,I_y)-\delta I_y,\\
&\frac{\mathrm{d}R_x}{\mathrm{d}t}=\delta I_x-\varepsilon R_x,\\
&\frac{\mathrm{d}R_y}{\mathrm{d}t}=\delta I_y-\varepsilon R_y,\\
&\frac{\mathrm{d}z}{\mathrm{d}t}=\mu\tau z(1-z)\big(F_2(I_x,I_y)+G_2(I_x,I_y)\\
&\qquad+F_1(I_x,I_y)-G_1(I_x,I_y)\big),\\
&F_1(I_x,I_y)=(1-z)\tau(\kappa\sigma I_x+\kappa I_y)\frac{\kappa\sigma(N_x-I_x)}{N_x\kappa\sigma+N_y\kappa},\\
&F_2(I_x,I_y)=z\tau\kappa_{av}(I_x+I_y)\left(\frac{N_x-I_x}{N}\right),\\
&G_1(I_x,I_y)=(1-z)\tau(\kappa\sigma I_x+\kappa I_y)\frac{\kappa(N_y-I_y)}{N_x\kappa\sigma+N_y\kappa},\\
&G_2(I_x,I_y)=z\tau\kappa_{av}(I_x+I_y)\left(\frac{N_y-I_y}{N}\right),\\
&N_j=S_j+I_j\quad j=x,y\quad(\text{const}),\\
&0\leqslant z\leqslant 1,\\
&\sigma>1.
\end{aligned}$$

Taking proportions of populations $x=I_x/N_x$, $y=I_y/N_y$, $r_x=R_x/N_x$, $r_y=R_y/N_y$, $f=N_x/N$, letting $\tau\kappa_y/\delta=\gamma$ and $\eta=\varepsilon/\delta$ and assuming dimensionless time (equivalently, setting the removal rate of infected individuals $\delta=1$), the model can be expressed as

$$\frac{\mathrm{d}x}{\mathrm{d}t}=\gamma\left((1-z)(\sigma x+y)\frac{\sigma(f-x-r_x)}{f\sigma+1-f}+z(f\sigma+1-f)(x+y)(f-x-r_x)\right)-x \tag{2a}$$

$$\frac{\mathrm{d}r_x}{\mathrm{d}t}=x-\eta r_x, \tag{2b}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t}=\gamma\left((1-z)(\sigma x+y)\frac{1-f-y-r_y}{f\sigma+1-f}+z(f\sigma+1-f)(x+y)(1-f-y-r_y)\right)-y, \tag{2c}$$

$$\frac{\mathrm{d}r_y}{\mathrm{d}t}=y-\eta r_y, \tag{2d}$$