

Virulence evolution in fragmented populations

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Goal

To study how virulence evolution is altered by the fragmentation of an infectious disease's host population.

Background and motivation

Epidemiological models focus on infection dynamics without considering evolution of the infectious agent. However, since the generation times of infectious agents are often much shorter than the generation times of their hosts, infectious agents often evolve on timescales considerably shorter than a host generation. This means that the evolution of an infectious agent can be important in studying disease dynamics, giving rise to the field of evolutionary epidemiology (Ewald & de Leo 2002; Restif 2009).

Virulence is typically measured by the extent to which the infectious agent reduces the fitness of its host (Alizon *et al.* 2009; Galvani 2003). Virulence evolution is often governed by a trade-off between an infectious agent's needs for achieving a high rate of transmission between hosts while keeping them alive to prolong such transmission. Classical models for the evolution of virulence therefore assume a trade-off between transmission rate and virulence, with elevated virulence implying higher transmission rate (Galvani 2003). Since directly transmitted diseases are dependent on the movement of their hosts for transmission, it is assumed that the transmission rate decreases for high virulence, reflecting the immobilizing effect the infectious agent has on the host (Ewald & de Leo 2002).

Models for the evolution of virulence also often assume that the host population is well-mixed, so that all pairs of hosts experience equal encounter rates (Read & Keeling 2003). However, many natural host populations are spatially structured. An important form of spatial structure is described by metapopulations: populations of hosts that are internally well-mixed inhabit different patches that are loosely connected to each other, enabling some exchange of hosts between the populations. Typical examples are groups of villages for human diseases or groups of farms for livestock diseases. To describe the epidemiological dynamics of directly transmitted diseases in metapopulations, it is crucial to consider the movement of hosts between patches. This is especially important if the size of populations is so small that the disease cannot persist in a patch in the absence of such movement. In that case, the recurrent spread of the infectious agent into patches with susceptible individuals is critical for the disease to persist in the metapopulation (Hanski 1999).

In this project, we will model a metapopulation in which an infectious disease spreads within and between populations. We consider a directly transmitted infectious disease, which only spreads through the movement of its hosts. Modeling the movement of hosts between patches allows us to investigate the possible immobilizing effect of the infectious agent on the host: hosts infected by agents with higher virulence may stay longer in a patch before moving to another. Similarly, higher virulence may

reduce the number of patches that hosts pass through during a movement step, and increase the mortality they suffer during movement.

In models of disease evolution, virulence often affects the disease's transmission rate, the host's recovery rate, or the host's mortality rate (Alizon *et al.* 2009; Galvani 2003). We will extend these earlier studies, by investigating the staying duration, movement distance, and movement mortality of hosts as functions of virulence. We expect that, depending on these dependences, costs and benefits of virulence balance at different levels of virulence. This will allow us to predict how a disease's impact on host mobility alters its severity.

Research questions

We will study how virulence evolution depends on the impact of virulence on the demography, epidemiology, and movement of hosts in a metapopulation. Specific questions that will be addressed are as follows:

- How is virulence evolution affected by the impact of virulence on the average duration a host stays in a patch, on the average number of patches it traverses during movement, and on the average probability of dying it experiences during such movement?
- How are these effects altered by the impacts of virulence on the death rate and recovery rate of hosts, and on the transmission rate among hosts?
- How does a metapopulation's connectivity structure influence virulence evolution?

Methods and work plan

The model we will examine is stochastic and continuous in time and describes the spread and virulence evolution of an infectious disease in a metapopulation of hosts. Hosts can move between the metapopulation's patches, and these movements are modeled explicitly. In each patch, an SI_vS -type dynamics occurs, with each host being either susceptible (S) or infected (I) by a strain with virulence v . Infected hosts are infectious. While a host is infected by one strain of the infectious agent, it cannot be infected by a different strain (i.e., super-infection and co-infection are precluded). The disease is transmitted directly, which makes the movement of hosts among metapopulation patches a key factor for its spread and persistence.

The populations in each patch are well-mixed and change through the following events: birth, death, infection, recovery, and movement to and from another patch. We assume a maximum population size of K for each patch; beyond this maximum size, there is no birth or immigration. When hosts emigrate from a patch, they enter the disperser pool. Since mortality during movement is an important factor regulating the evolution of virulence (Ewald & de Leo 2002), we consider how the disease's virulence alters the survival probability of hosts in the disperser pool. Individuals trying to leave the disperser pool can only enter patches in which the total number of hosts is smaller than K .

The equations describing this model extend the traditional differential equations for the number or density of susceptible and infected hosts in a single population. In our model, the state of the metapopulation is described by the fractions $p_{s,i}$ of popula-

tions with precisely s susceptible and i infected hosts. Following Metz & Gyllenberg (2001), the equations for the dynamics of $p_{s,i}$ are combined with equations for the dispersal of susceptible and infected hosts. We denote the birth rate by b , the death rate by μ , the disease-induced mortality by α , the transmission rate by β , the recovery rate by γ , the emigration rate by m_{out} , and the immigration rate by m_{in} . The latter two rates may differ between susceptible and infected hosts. The metapopulation dynamics are then given by

$$\begin{aligned} \frac{d}{dt} p_{0,0} &= -p_{0,0}[m_{\text{in},S}D_S + m_{\text{in},I}D_I] + p_{0,1}[\mu + \alpha + m_{\text{out},S}] + p_{1,0}[\mu + m_{\text{out},S}], \\ \frac{d}{dt} p_{s,i} &= -p_{s,i}[b(s+i) + \mu(s+i) + \alpha i + \gamma i + \beta \frac{si}{s+i} + m_{\text{in},S}D_S + m_{\text{in},I}D_I + m_{\text{out},S}s + m_{\text{out},I}i] \\ &\quad + p_{s+1,i}[\mu(s+1) + m_{\text{out},S}(s+1)] + p_{s,i+1}[\mu(i+1) + \alpha(i+1) + m_{\text{out},I}(i+1)] \\ &\quad + p_{s+1,i-1}\beta \frac{(s+1)(i-1)}{s+i} + p_{s-1,i+1}\gamma(i+1) + p_{s-1,i}[m_{\text{in},S}D_S + b(s-1+i)] + p_{s,i-1}m_{\text{in},I}D_I. \end{aligned}$$

The fraction of susceptible and infected hosts in the disperser pool, D_S and D_I , respectively, change according to

$$\begin{aligned} \frac{d}{dt} D_S &= m_{\text{out},S} \sum_{s,i=1}^{s+i \leq K} p_{s,i}s - m_{\text{in},S}D_S \sum_{s,i=1}^{s+i < K} p_{s,i} - \mu_{D,S}D_S, \\ \frac{d}{dt} D_I &= m_{\text{out},I} \sum_{s,i=1}^{s+i \leq K} p_{s,i}i - m_{\text{in},I}D_I \sum_{s,i=1}^{s+i < K} p_{s,i} - \mu_{D,I}D_I, \end{aligned}$$

where $\mu_{D,S}$ and $\mu_{D,I}$ denote a susceptible or infected host's death rate during movement. Since the maximum population size in a patch is K , the fraction of patches with more than K hosts equals zero ($p_{s,i} = 0$ for $s+i > K$). Obviously, negative population sizes are also not feasible ($p_{s,i} = 0$ for $s, i < 0$).

Variations in virulence are introduced by allowing the infectious agent to mutate within an infected host. Such a mutation will be expressed when an infected host infects a susceptible host. Simple functions will be used to describe the effects of virulence. For example, for the transmission rate we will use the function $f(v) = \sigma v / (1 + \sigma v)$, while for the duration of stay we will use the function $f(v) = m / (1 + \sigma v)$, where σ specifies the function's sensitivity to variations in virulence and m specifies the function's maximum.

In order to get some feeling for this model, it will first be studied semi-analytically in the case that (i) the number of patches is large, (ii) the mutation probability is small, and (iii) all patches are equivalent and equally connected. The invasion fitness defined by Metz & Gyllenberg (2001) will be used to derive the fitness of virulence mutants. This invasion fitness, the equivalent of the basic reproduction number R_0 for single populations, measures the expected number of mutants leaving the disperser pool for each mutant entering it (Parvinen et al. 2008). First, the equilibrium of the metapopulation model will be determined numerically for a monomorphic resident population infected by a disease with virulence v . Then, the invasion fitness of a mu-

tant infectious agent with virulence v' will be calculated. Based on this invasion fitness, the course and outcome of virulence evolution can be predicted.

After these semi-analytical studies, the model will be programmed in C++ in order to study the effects of relaxing the simplifying assumptions (i) to (iii). In particular variations in connectivity structure are considered important for virulence evolution (Alizon *et al.* 2009; Read & Keeling 2003). The Gillespie algorithm (Gillespie 1976) will be used to determine the schedule of events, resulting in exponentially distributed waiting times between events and in events being chosen according to their relative probabilistic rates. We will examine situations in which host movement is restricted to nearest neighbors on a square grid with periodic boundaries, before allowing movement over longer distances and/or on other connectivity structures.

If time permits, we will include the possibility of recovery with permanent immunity. This requires the consideration of recovered-and-immune hosts and studying the epidemiological and evolutionary aspects of the resultant SI_vR -dynamics.

Relevance and link to EEP's research plan

Contributing to EEP's research project on *Adaptive Dynamics Theory*, this project combines evolutionary biology with epidemiology and ecological realism. It is fundamental in the sense that it broadens our knowledge of virulence evolution in metapopulations.

Expected output and publications

This research is intended for co-authored publication in an international scientific journal and will be part of my PhD thesis.

References

- Alizon S, Hurford A, Mideo N & van Baalen M (2009). Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future. *Journal of Evolutionary Biology* 22: 245-259
- Ewald P & de Leo G (2002). Alternative transmission modes and the evolution of virulence. pp. 10-25 in: *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management* (eds U. Dieckmann, J.A.J. Metz, M.W. Sabelis & K. Sigmund), Cambridge University Press
- Galvani AP (2003). Epidemiology meets evolutionary ecology. *Trends in Ecology and Evolution* 18: 132-139
- Gillespie DT (1976). A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of Computational Physics* 22: 403-434
- Hanski I (1999). *Metapopulation Ecology*. Oxford University Press
- Metz JAJ & Gyllenberg M (2001). How should we define fitness in structured metapopulation models? Including an application to the calculation of evolutionarily stable dispersal strategies. *Proceedings of the Royal Society B: Biological Sciences* 268: 499-508
- Parvinen K & Metz JAJ (2008). A novel fitness proxy in structured locally finite metapopulations with diploid genetics, with an application to dispersal evolution. *Theoretical Population Biology* 73: 517-529
- Read JM & Keeling MJ (2003). Disease evolution on networks: the role of contact structure. *Proceedings of the Royal Society B: Biological Sciences* 270: 699-708
- Restif O (2009). Evolutionary epidemiology 20 years on: challenges and prospects. *Infection Genetics and Evolution* 9: 108-123