Different levels of host-pathogen interactions and consequences for the pathogen life history evolution

by

Sourya Shrestha

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Doctoral Committee:

Assistant Professor Aaron A. King, Co-Chair
Professor Ottar N. Bjønstad, Co-Chair, Pennsylvania State University
Professor James S. Koopman
Professor Robert Krasny

Dedicated to Ma and Ba.

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CHAPTER I

Introduction

This dissertation, in general, will deal with questions relating to evolution of pathogens associated with infectious diseases. Impact of infectious diseases, despite advances in sciences and public health, can not be overstated — the sheer number of human lives lost (even today they are estimated to be responsible for more than half of human deaths in sub-Saharan Africa (Lopez et al., 2006)), the debilitating effect they have in our ability to carry out everyday activities and consequently the socio-economic health of communities, the threat they pose to wildlife and plants, and simply the overall burden to our society. Most of the pathogens are microparasite, that include viruses (such as influenza or HIV), bacteria (such as *Bordetella pertussis* that causes whooping cough and *Bacillus anthracis* that causes anthrax), protozoa (such as *Trypanosoma* species that cause sleeping sickness and *Plasmodium* species that cause malaria), and pathogenic fungi (such as *Candida* species that cause thrush and *Tinea pedis* that causes Athlete's foot). They typically have short generation time relative to their hosts and undergo many generations in the course of a single infection, allowing for rapid evolution as a consequence of evolutionary pressures. In this regard, the questions regarding pathogen evolution are central to the study of infectious diseases.

1.1 The role of host in infectious disease pathogens

In a host-parasite system, particularly in the context of pathogens that cause infectious disease, the incidence and the abundance of the disease inducing pathogen, as well as the epidemiological characteristics of the disease is expected to be dependent on the interactions between the host and the pathogen. Typically, a pathogen has to enter a host and proliferate inside of a host, and manage to transmit it's progeny to other hosts in the population either before the pathogen is cleared or before the host is killed. Furthermore, the pathogen has to be able to persist in the host population by traveling between the hosts. Density of the host, movement patterns and transmission mechanisms will affect pathogen's ability to maintain circulation. Hence, from an evolutionary standpoint, the pathogen's survival hinges on the interactions it has with the host. Questions regarding the evolution of the pathogen are inextricably linked to understanding these host-pathogen interactions.

These host-pathogen interactions, then can be, very generally thought to be at two different levels — (i) between the pathogen and a single host, as the pathogen infects a host and multiplies within it; and (ii) between the pathogen and the host population, as the pathogen transmits between hosts and circulates in the host population. Within a host, the pathogen is likely to encounter resistance from the immune system of the host. The host's immune system has an arsenal of responses, which vary not only in the way they tackle the invading pathogen but also in their specificity. The adaptive/acquired immune response that is specific to the pathogen is activated by the pathogen's presence and selected for their success at clearing these pathogens, and consequently, is likely to depend on the pathogen density itself. The pathogen load within a host, the host's propensity to shed pathogen, and conse-

quently the pathogen's ability to transmit to other hosts is likely to be influenced by the description of the interaction between the pathogen and part of the host's immune response.

The nature of disease spread is such that the infection process in a host is not independent of infection processes in other hosts. In fact, the propensity of a susceptible host of getting infected, or the force of infection acting on a susceptible host, is at the most basic level, dependent on both the characteristics of the disease and the level of infection that is prevalent in the host population. So a fundamentally different type interaction – between the pathogen and the host viewed as a population, arises. In this regard, the consequences for a pathogen's fitness depends on a different set of questions. Can an infection proliferate across the host population, and what are its competitive advantage against other strains that have different traits? Can the infection persist in the population? And how will the structure of the host population or meta-population affect the answer to the above questions?

1.2 Dissertation outline

In this dissertation, I attempt to explore the role of host in pathogen evolution, particularly with a view that the interactions the pathogen has with the host are different at different levels. The focus will be to on formulating models of various types to address key features of these interactions with respect to the central question of pathogen evolution. Although the chapters are intended to be stand-alone papers, the progression of the thesis will somewhat mirror the path of my own exploration.

Chapter II, titled "Integration of within-host and between-host dynamics and the Invasion-persistence trade-off" will focus on exploring the role of the host both at the within-host level and at the population level in the maintenance of acute

and rapidly transmitting pathogens. A slightly modified version of this chapter is published in the April 2009 edition of *The American Naturalist* (King et al., 2009). As a second author, my contributions to this paper were (i) assisting the first author in the formulation of the model, (ii) numerical implementation of the model, and (iii) partial writing of sections on the model and results. Here, we build a modeling framework that (i) captures the within-host dynamics of a pathogen infection; and (ii) scales it up to population level that allows us to make inferences about the epidemic dynamics and consequently the risks and fitness associated with such a pathogen. The nature of the within-host interactions between pathogen and the host immune system, in conjunction with dose response curves (the relationship between transmission and pathogen load) play crucial roles in understanding (i) the evolutionary constraints pathogens face; and (ii) population level fitnesses for the pathogen. Furthermore, pathogen evolution under such constraint is likely to push pathogens where population level extinction risks become relevant. This can result in a trade-off for pathogens — increasing its invasion fitness can result in higher population level extinction risks. We show that depending on the size of the host population and the shape of the dose response curve, we can observe contrasting results — pathogen evolution driving to the edge of its own extinction, as well as robust persistence of acute pathogen.

Chapter III will extend this model to include (i) structure on the host population, (ii) stochasticity in birth, death and transmission processes, and (iii) explicit competition between strains of pathogen for susceptible hosts. We construct an individual-based model to implement epidemic and evolutionary dynamics. The host population is structured into smaller equally sized and globally connected patches. Epidemic dynamics occur within a patch, but hosts can migrate between patches.

Multiple strains are allowed to circulate in a population, and their diversity is maintained through a mutation process. Strains compete for susceptibles, and are selected depending on their success in recruiting susceptibles. Evolutionary trajectories and stable strain distributions are constructed for host populations that differ in patch sizes and number of patches. Results show significant role of the host structure and local extinction dynamics on the optimal pathogen life-history traits. Evolutionarily stable pathogen traits depend on the structure of the host population, both the size of the local patch and the number of such patches. Host-pathogen interactions at different levels seem to provide conflicting evolutionary signals, and pathogens optimize their trait to suit the balance of the evolutionary forces in the host population.

Chapter IV will focus on understanding the role of the local extinction dynamics for a pathogen's life history evolution. We attempt to understand the dynamics of conflicting evolutionary signals originating at different levels for pathogen, a result from the earlier section. We construct models for (i) epidemic dynamics of acute pathogens that are prone to local extinction but circulate in a host meta-population via rescue effects, and (ii) competition between pathogen strains within a patch for susceptibles. By observing competition between strains for susceptibles in a patch and consequently their ability to colonize patches in the meta-population, we extrapolate evolutionary outcomes in the host meta-population. Results show that evolutionarily stable or optimal pathogen traits can depend on the structure of the meta-population, particularly the size of the local host communities, and host migration rates, among others. The framework of the model is abstract but analytical — allowing us to extract the functional relationship between several key meta-population parameters and pathogen's optimal traits. The work will also shed some light on the nature of the conflicting evolutionary forces, and how they op-

erate in shaping pathogen evolution. The final two chapters are currently under preparation to be submitted to peer-reviewed journals.

CHAPTER II

Integration of within-host and between-host dynamics and the Invasion-persistence Trade-off

2.1 Introduction

The dominant theory pertaining to the pathogen's life history evolution focuses on the trade-off between pathogen's virulence and its transmission. The premise of this "transmission-virulence" trade-off theory (Anderson and May, 1991; Ewald, 1993; Frank, 1996; Lenski and May, 1994; Bull, 1994) relies on the implied but conceivable nature of the relationship between the pathogen's transmission potential within an infected host and its virulence. A pathogen that seeks to increase the rate of transmission from a host to another, would spread more rapidly in the host population, and consequently have fitness advantage over its less transmissive counterpart. But increasing the transmission can have costs associated with it. The pathogen, for example, might have to induce symptoms, or proliferate to large number in the host to facilitate transmission, both of which can threaten the host's life. Under the framework of this trade-off, pathogens are expected to find an intermediate optimal in-host multiplication rate, and associated exploitation rate that is also intermediate (May and Anderson, 1983b). This theory has also garnered important empirical support (Fenner, 1983; Messenger et al., 1999).

A host of work has gone into understanding the mechanistic basis for the na-

ture of relationship between transmission and virulence, as well as the evolutionary consequences for pathogen (Sasaki and Iwasa, 1991; Antia et al., 1994; Antia and Lipsitch, 1997; Gilchrist and Sasaki, 2002; Gilchrist and Coombs, 2006; André et al., 2003; Day and Proulx, 2004; Alizon and van Baalen, 2005). But for rapidly transmitting pathogens that cause acute disease that are not necessarily virulent, the ability to maintain circulation in the host population can be an equally important component of its fitness. The epidemics of acute and immunizing infections tend to go through cycles. Typically, infection rapidly spreads through the susceptible population. Each infected host then recovers from the infection, but acquires immunity in the process. This depletion of susceptibles results in deep trough in the aftermath of an epidemic peak. Furthermore, these fluctuations can be accentuated by seasonal forces. In host communities that are relatively small, in particular, smaller than the critical community size (Bartlett, 1956a; Keeling, 1997), such pathogens are vulnerable to local extinction. Consequently, a new trade-off can arise at the population level, between the pathogen's transmission rate and its ability to persist in the population. This "invasion-persistence" trade-off (Grenfell, 2001) mediates a balance between a strain's infectious period and its transmission rate. Acute pathogen strains that cause highly transmissive infections will have an evolutionary advantage over less acute counterparts by being able to spread more rapidly over the host population. However, over a longer term, the epidemics of these infections also face greater extinction risk compared to less acute strains that cause longer lasting infections. Hence the short-term invasion advantage comes at a cost of diminished longer term persistence.

Grenfell (2001), using a simple SIR framework, showed that among pathogens that have identical basic reproductive number (R_0), the ones that are more transmissive

are also likely to more be vulnerable to extinction. We take a more mechanistic approach. We construct a within-host model that relates pathogen life history to epidemic patterns, allowing us to draw on its fitness as well the extinction risks. As a result, not only can we predict direction of pathogen life history evolution, but also explore the role of the invasion-persistence trade-off in the evolutionary process.

2.1.1 Story of *Bordetellae*

This part of the study is also loosely motivated by the different life-history strategies observed in different species of *Bordetellae*. The *Bordetellae* pathogens are gram-negative bacteria that infect the respiratory tracts of a wide range of mammalian hosts. The species *B. bronchiseptica* is common in a variety of mammals both wild and domesticated, with the notable exception of humans. Its congener, *B. pertussis*, on the other hand, is an exclusive parasite of humans. Mira et al. (2006), analyzing DNA sequence similarity between these two species, found dramatic genomic changes in the case of *B. pertussis*, suggesting that *B. pertussis* went through intense transformations at around the time of the Neolithic revolution. In particular, the genome of *B. pertussis* is substantially smaller than that of *B. bronchiseptica* mostly due to loss of numerous multigenic regions, some that are implicated in the interaction of the pathogen with its host's immune system. Most notable is the loss, in *B. pertussis* of the gene coding for O-antigen assembly. The O-antigen is known to inhibit the alternative-complement-mediated phagocytosis of the pathogen. *B. pertussis* also has lost the type-III secretion system machinery, which is used by *B. bronchiseptica* to inhibit phagocytosis by inducing mortality of polymorphonuclear leukocytes. In contrast, the gene encoding pertussis toxin (PTX) is apparently only expressed in *B. pertussis*. PTX is known to delay the recruitment of neutrophils that play a key role in pathogen clearance (Kirimanjeswara et al., 2005). These

genetic modifications translate, via modified interactions with host immunity, into differences in pathology and course of infection.

B. bronchiseptica and *B. pertussis* differ significantly in pathology and course of infection. Symptoms of *B. bronchiseptica* are relatively mild, and typically tend to persist for the lifetime of the host in the nasal cavity (Kirimanjeswara et al., 2003). *B. pertussis* infections, on the other hand, are quite acute, causing severe coughing (which can progress to spasmodic coughing, i.e., whooping cough, in children), but are systemically cleared within a month or two at most.

The phenomenon of an acute infectious agent (*B. pertussis*) evolving from an ancestor (*B. bronchiseptica*) producing persistent infection is repeated in the case of *B. parapertussis*. The symptoms and course of infection of the *B. parapertussis* is markedly similar to that of *B. pertussis*. Intriguingly, these two human specialists arose from distinct ancestors. This suggests that a new niche, absent before the neolithic, opened up for *Bordetella* as human pathogens; the potential for such a new niche, however, is far from clear. In particular, it remains to be seen what advantage *B. pertussis* might have achieved to compensate for the significantly reduced duration of infection it has suffered. Bjørnstad and Harvill (2005) hypothesized that invasion-persistence trade-off may be of consequences in the evolution of the acutely infecting *B. pertussis* and *B. parapertussis* from their chronic *B. bronchiseptica*-like ancestors.

2.1.2 Modeling Approach

Our approach will to be construct a modeling framework that allows us to evaluate population level extinction risk of pathogens that exhibit a variety of infection profile. The infection profile is generated by constructing a within-host model that captures the essential dynamics of interactions between the pathogen and the host immune response. The within-host model is combined with transmission and between-host

models to extrapolate epidemic curves. This allows us to study consequences of pathogen life-history strategies on invasion and persistence at the population level. The main insights are as follows: (i) pathogen evolution under the constraints derived from the mechanistic within-host dynamics can lead to traits in pathogen where the invasion-persistence trade-off can be important for pathogen life history evolution (ii) the shape of the dose-response curve (relating pathogen load in a host to its transmission rate) is a key determinant of the outcome of pathogen evolution, and (iii) only in host populations above a critical threshold is a robust persistence of acute pathogens possible.

2.2 Modeling

We begin by setting up a within-host model that captures the transient interaction of the pathogen with the host's immune system. The model is chosen to be parsimonious as well as flexible enough to describe both acute and persistent infections. The dynamics at the within-host level is then scaled up to the between-host level via a dose-response function. Finally, we use the between-host model to compute epidemic curves in the host population. This allows us to explore the population level epidemic patterns of the pathogen traits expressed at the within-host level. In particular, it enables us to make inferences about the fitness the pathogen, and determine which features of the within-host model lead to emergent trade-offs. The three parts of the model are described in the following subsections – (i) subsection 2.2.1 describes the within-host models of pathogen-host immune response dynamics; (ii) subsection 2.2.2 describes the dose-response functions that determine how transmission rates depend on within-host pathogen load; and (iii) subsection 2.2.3 describes the between-host epidemic model.

2.2.1 Within-host models

The commonly used standard SIR-type models assume a constant level of infectiousness in an infected host and an exponentially distributed infectious period. We approach the within-host level with a few specific things in mind. We aim to build a more mechanistic model that captures basic features of within-host growth an clearance of pathogen, that qualitatively resembles the infections of *Bordetallae*. We also aim to formulate the model in terms of biologically meaningful parameters that are subject to evolutionary pressures.

A slightly modified version of the model of Pilyugin and Antia (2000) suits this purpose. The authors proposed a simple model for the in-host interaction of pathogen with the host's specific immunity. In this model, the parasite grows exponentially at the rate r, but is killed upon encounter with immune cells. The kill rate of the immune response is k. Immune cells are produced at a baseline rate α and have mean lifetime $1/d$. Immune cells proliferate at a rate proportional to the current rate of killing: the constant of proportionality is γ. Our model is slightly simpler than that of Pilyugin and Antia (2000) in that we assume handling time associated with pathogen-immune cell interactions is negligible. Our results are not sensitive to the model details: inclusion of more realism such as, for example, handling time in the immune response (which results in a maximum rate of immune response) or a programmed immune response (which entails an overshoot following pathogen clearance (Kaech and Ahmed, 2001)), does not change our conclusions. The model consists of a pair of differential equations for pathogen load P and specific immune

response X,

$$\begin{aligned} \frac{dP}{da} &= r\,P - k\,X\,P \\ \frac{dX}{da} &= \alpha - d\,X + \gamma\,k\,X\,P. \end{aligned} \tag{2.1}$$

We integrate the differential equations from initial condition $P = 1$, $X = 0$. The model possesses only two dynamical regimes. When $d/k < \alpha/r$, there is a stable equilibrium at $P = 0$, $X = \alpha/d$. When $d/k > \alpha/r$, the parasite load exhibits damped oscillations to a nonzero equilibrium, $P = \frac{1}{\gamma}\,(d/k - \alpha/r)$, $X = r/k$. En route to this equilibrium, however, the pathogen load falls to extremely low values. In particular, for all parameters we have examined, P falls to less than its initial value of 1, indicating pathogen clearance. Moreover, this equilibrium must be interpreted as a pitched battle between pathogen and immune system, an outcome not found in the class of infections with which we are concerned. Accordingly, we assume the infection has been cleared once P returns to its initial level. We denote this age of infection at which the clearance occurs by a_c. In both regimes, therefore, the infection is ultimately cleared, but its duration and severity, i.e., the cumulative parasite load generated, depends on the parameters.

2.2.2 Transmission models

The within-host dynamics determine the parasite load $P(a)$ and immune response at different infection ages. To integrate these dynamics into the between-host model, we assume a relationship between parasite load and transmission. In particular, we will assume that the instantaneous transmission rate, β, is a function of age of infection and parasite load. We explore three families of transmission function:

(i) *Linear β.* The almost invariable assumption in the literature is that between-host transmission rate is simply proportional to within-host parasite load: $\beta(a) =$

$q_1\,P(a)$.

(ii) *Delayed β.* Because transmission may depend upon the expression of symptoms (e.g., coughing) which typically manifest not immediately upon infection but only after some time has passed, we consider a delayed-onset model of transmission. In this model, $\beta(a) = q_2\,P(a)/(1+\exp(-s\,(a-a^*)))$: transmission is negligible until a certain time, after which it becomes proportional to parasite load.

(iii) *Saturating β.* It is unlikely that the transmission rate is linearly dependent on parasite load at very high values of the latter. In particular, the probability of a contact resulting in infection saturates at high innoculum sizes. To investigate the effects of this saturation effect, we consider a nonlinear coupling of transmission to parasite load: $\beta(a) = q_3\,(1-\exp(-P(a)/P^*))$.

2.2.3 Between-host Model

At a between-host level, we model the age-specific spread of disease using the McKendrick-von Foerster equations. To derive these equations, let $\int_{a_1}^{a_2} i(t,a)\,\mathrm{d}a$ denote the fraction of the host population at time t consisting of individuals who were infected between times $t-a_2$ and $t-a_1$. Conservation of individuals implies that

$$\frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = -\mu(a)\,i, \qquad i(t,0) = \lambda(t)\,(1+\epsilon\,\sin 2\pi t)\,S(t), \tag{2.2}$$

where $\mu(a)$ is age-specific mortality, $\lambda(t)$ is the force of infection, the sinusoidal factor models seasonality in transmission, and $S(t)$ is the fraction of the host population susceptible to infection at time t. Transmission is assumed to be frequency dependent

so that the force of infection is

$$\lambda(t) = \int_0^{a_c} \beta(a)\, i(t,a)\, \mathrm{d}a = \int_0^{a_c} \beta(a)\, \ell(a)\, i(t-a,0)\, \mathrm{d}a. \tag{2.3}$$

Here, $\ell(a) = \exp\left(-\int_0^a \mu(a')\, \mathrm{d}a'\right)$ denotes the probability that an individual infected a time units ago has not yet died. For the remainder of the paper, we will assume that infections are nonlethal; this amounts to assuming a constant death rate: $\ell(a) = e^{-\mu a}$.

To complete the system of equations, we need an equation for the susceptible fraction $S(t)$. We assume that the susceptible pool is replenished by births and that the total host population size remains constant in time. We therefore assume that $S(t)$ obeys

$$\frac{dS}{dt} = \mu\,(1-S) - \lambda(t)\,(1+\epsilon\,\sin 2\pi t)\,S. \tag{2.4}$$

The all-important basic reproductive ratio is given by

$$R_0 = \int_0^{a_c} \beta(a)\, \ell(a)\, \mathrm{d}a.$$

Equations (2.2–2.4) can be solved numerically to predict the population-level dynamical consequences of a particular set of assumptions at the within-host level. For all simulations, we assumed that 1% of the host population was initially infected.

2.2.4 Numerical methods

The within-host pathogen load borne by a host is determined by the within-host models Eq. 2.1. One can numerically integrate these ordinary differential equations to obtain the trajectory of the pathogen load, $P(a)$. Having computed $P(a)$, each of the transmission models translates this into between-host transmission rate $\beta(a)$ and basic reproductive ratio R_0. With $\beta(a)$ in hand, one can integrate Eqs. 2.2–2.4 to obtain the epidemic curves. We used a simple backward Euler scheme for this purpose.

Table 2.1: Model parameters and value(s).

Symbol	Parameter	Value
	Within-host model:	
r	parasite growth rate	5–130
k	kill rate of the immune response	3.5
α	baseline production rate of immune response	1
d	death rate of immune response	0.5
γ	immune response recruitment rate	$.5 - 1.5 \times 10^{-4}$
	Transmission models:	
q_1	transmissibility factor, linear model	10^{-3}
q_2	transmissibility factor, delayed model	1.5×10^{-3}
q_3	transmissibility factor, saturating model	10^{-3}
a^*	delay constant	0.1
P^*	saturation constant	5×10^5
	Between-host model:	
μ	host mortality rate	0.02
ϵ	seasonality amplitude	0–1

2.2.5 Quantifying extinction risk

Other things being equal, immunising pathogens that give rise to more violent epidemic fluctuations are less likely to persist over the long term. This is because extinction risk is greatest immediately following an outbreak, when the fraction of infected hosts,

$$H(t) = \int_0^{a_c} i(t,a)\,\mathrm{d}a,$$

is at a minimum and therefore the expected number of transmission events is so small that the probability of failure of transmission becomes appreciable.

Even when $R_0 > 1$, i.e., the endemic equilibrium is, deterministically speaking, stable, stochastic extinction may occur. Extinction is most likely in the deep trough immediately following a novel pathogen's introduction. If the pathogen survives this trough, extinction risk decreases with time as H approaches equilibrium via damped oscillations. Seasonal variation in transmission, however, results in sustained oscillations. In seasonal environments therefore, each outbreak is associated with elevated risk of extinction. In both cases, the depth of the trough following an

outbreak gives an indication of the magnitude of this risk. In order to determine how extinction risk depends on model parameters, we examined the depth of predicted troughs in two scenarios: (1) a virgin epidemic in a nonseasonal environment and (2) recurrent epidemics in a seasonal environment. Specifically, we defined H^* to be the minimum value of H in each scenario: higher values of H^* correspond to lower extinction risk.

What is the connection between H^* and the critical community size (Bartlett, 1956a, 1957, 1960a; Keeling and Grenfell, 1997)? A definitive answer to this question would require a fully stochastic treatment, with concomitant loss of analytical tractability. However, for a standard, nonseasonal SIR model with demographic stochasticity, Nåsell (2005) was able to derive an approximate formula for the critical community size, N_{crit}:

$$N_{\text{crit}} \approx \frac{2\pi R_0}{\log 2}\left(\frac{\mu+\gamma}{\mu\,(R_0-1)}\right)^{3/2}, \tag{2.5}$$

where μ is the host birth rate and γ is the recovery rate. For the purposes of comparison, we calculate H^* for the standard nonseasonal SIR model

$$\begin{aligned} \frac{dS}{dt} &= \mu\,(1-S) - \beta\,S\,I \\ \frac{dI}{dt} &= \beta\,S\,I - \gamma\,I - \mu\,I \\ \frac{dR}{dt} &= \gamma\,I - \mu\,R \end{aligned} \tag{2.6}$$

Here, β is the contact rate; $1/\gamma$, the infectious period. As in (2.4), μ is the birthrate (=death rate) of the host population. Fig. 2.1 shows the results of a comparison of H^* for this model with Nåsell's approximate N_{crit}. The results show that these quantities give essentially the same qualitative picture.

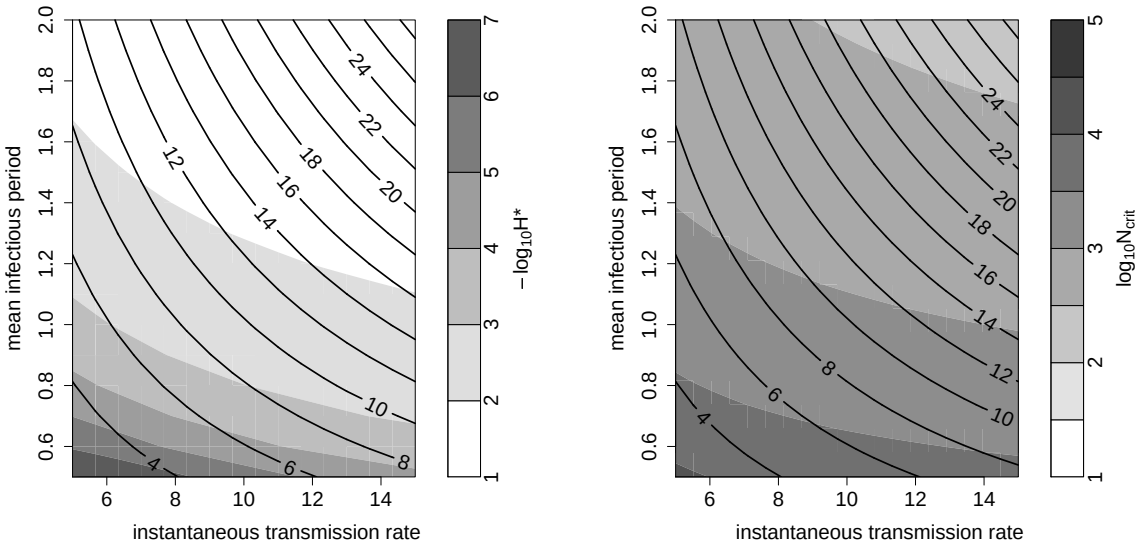

Figure 2.1: [Left] Surfaces of H^* (grey scale) and R_0 (solid lines) under the standard SIR model (A.1). Darker area correspond to higher H^* and higher extinction risk. Increasing the transmission rate and/or increasing the infectious period increases both the pathogen fitness and its ability to persist in the population. [Right] Surfaces of the Critical community size (grey scale) using Nåsell's approximation and R_0 (solid lines). Qualitatively, $-\log_{10} H^*$ and $\log_{10} N_{\text{crit}}$ depend similarly on the transmission rate and the infectious period.

2.3 Results

In this section, we derive and compare the population-level consequences of the various assumptions outlined above on within-host pathogen dynamics and transmission. We focus on the pathogen's evolution, holding the host fixed. Given perfect cross immunity among strains of pathogens, the pathogen strategy with the highest R_0 will be the evolutionary stable strategy. The landscape of R_0, therefore, tells us the likely direction of pathogen evolution. However, not all regions of this landscape are accessible. For a given host population size, certain parameter combinations will with high probability lead to stochastic fadeout, i.e., local extinction of the pathogen. These regions of parameter space are therefore effectively inaccessible to the pathogen. We use the quantity H^*, described above, to circumscribe the accessible region of parameter space.

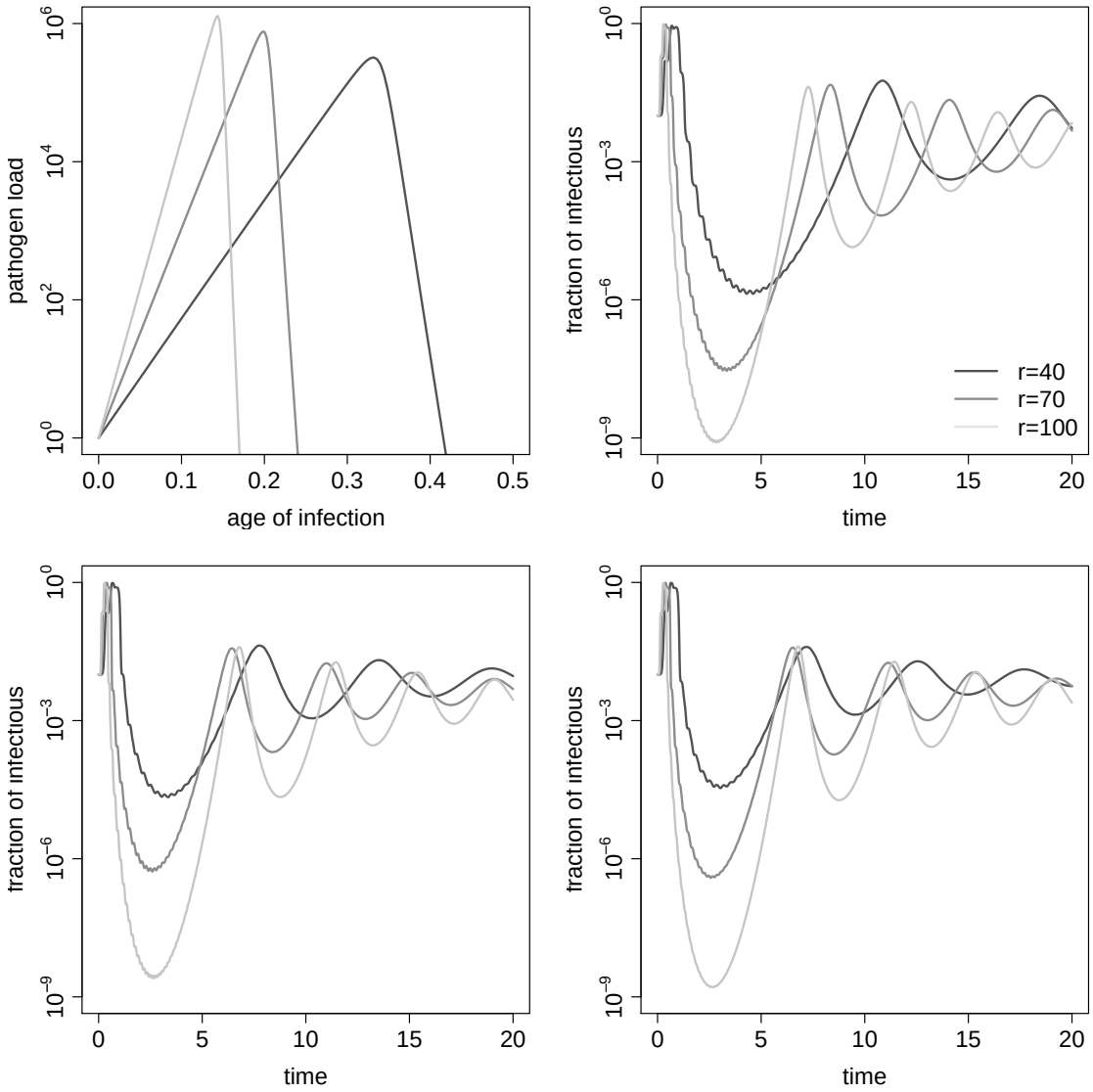

Figure 2.2: Samples of within-host dynamics and population level epidemics. [Top-Left] Within-host pathogen dynamics for three different r values. Also shown are the corresponding nonseasonal epidemic curves for the [Top-Right] linear transmission model, [Bottom-Left] delayed transmission model, [Bottom-Right] saturating transmission model. Parameters, α, d, and k are set to the values shown in the table; $\gamma = 10^{-4}$ and $\epsilon = 0$. In general, increasing r first increases, then decreases H^*. Increasing acuteness, therefore, eventually leads to elevated risk of stochastic extinction.

Fig. 2.2[Top-Left] shows the within-host pathogen dynamics. A key parameter of this model is the parasite growth rate, r. Higher values of r lead to more acute infections, which stimulate stronger immune response and are therefore cleared more rapidly. Fig. 2.2[Top-Right, Bottom-Left & Bottom-Right] show the corresponding population-level dynamics under the three transmission models. In all models, increasing r eventually results in deeper post-epidemic troughs (lower H^*).

By varying r and another parameter (in this case γ), we can build up surfaces showing pathogen fitness (R_0) and relative stochastic fadeout risk (H^*). Figs. 2.3[Left] shows the contours of R_0 and H^* under the three transmission models. Under the linear transmission model, shown in fig. 2.3[Top-Left], R_0 increases as we move towards the bottom right corner, where the parasite growth rate, r, is largest and the immune-cell recruitment rate, γ, smallest. This is to be expected, since a pathogen that can reproduce rapidly and/or retard immune response will do well. Under this model, more acute infections generate sharper immune responses, the infectious period will decrease as r increases. Nevertheless, the cumulative pathogen load produced over the course of an infection increases with r, so that the net effect is an increase in R_0. It follows that, under the assumptions of this model, a pathogen maximizing R_0 will evolve ever more acute infections.

Limits to the tendency toward acute infection arise at the level of the host population. From Fig. 2.3[Top-Left], we see that, for a given host population size, the accessible region is bounded above by some H^* contour. Thus a pathogen evolving to maximize R_0 will increase its growth rate to the maximum value compatible with the host population size. This suggests that the pathogen should evolve to the brink of its own local extinction. Similar results have been suggested previously by Sasaki and Iwasa (1991) under similar framework and by Rand et al. (1995) in a spatially

explicit, individual-based model. Moreover, as host population increases, the accessible region expands and allows the evolution of more acute infection. Thus a trade-off between invasion and persistence emerges.

To see this, consider a scenario in which γ is fixed at 10^{-4}, and the pathogen can control r. Let us suppose that the host population is of a size such that it supports, say, $-\log_{10} H^* > 6$. In such a scenario, the pathogen will evolve to the highest r consistent with $-\log_{10} H^* > 6$, which is $r \approx 40$ (Fig. 2.3[Top-Right]). This optimum strategy lies on the boundary of the accessible region. Should the host population increase, the accessible region will grow, since $-\log_{10} H^*$ is positively related to the critical community size. If the host population grows so as to support $-\log_{10} H^* > 8$. The pathogen is now free to increase r to about 80: it should evolve to generate a more acute infection. Again, however, the pathogen is predicted to evolve to the brink of its own local extinction.

In figure 2.3[Middle], we show the analogous results based on the delayed transmission model. Here, contours of H^* are similar to those in Fig. 2.3[Top], but the contours of R_0 are very different. The R_0 contours bend down at right end (higher r), an indication that for a given γ, R_0 is maximized at an intermediate value of r. As before, a pathogen maximizing R_0 will evolve to the largest r consistent with H^* associated with a given population size. For example, if the population allowed for $-\log_{10} H^* > 4$, the optimal r compatible is ≈ 30. Again, this point lies on the boundary of the accessible region. The optimal r continues to be on the boundary of the accessible region determined by contours of H^* until $-\log_{10} H^* > 6$. Should the host population increase to support, say, $-\log_{10} H^* > 8$, the optimal r is no longer to be found on the boundary of the accessible region, but in its interior. The pathogen should increase r only to this point, where $-\log_{10} H^* \approx 6$, and $r \approx 70$,

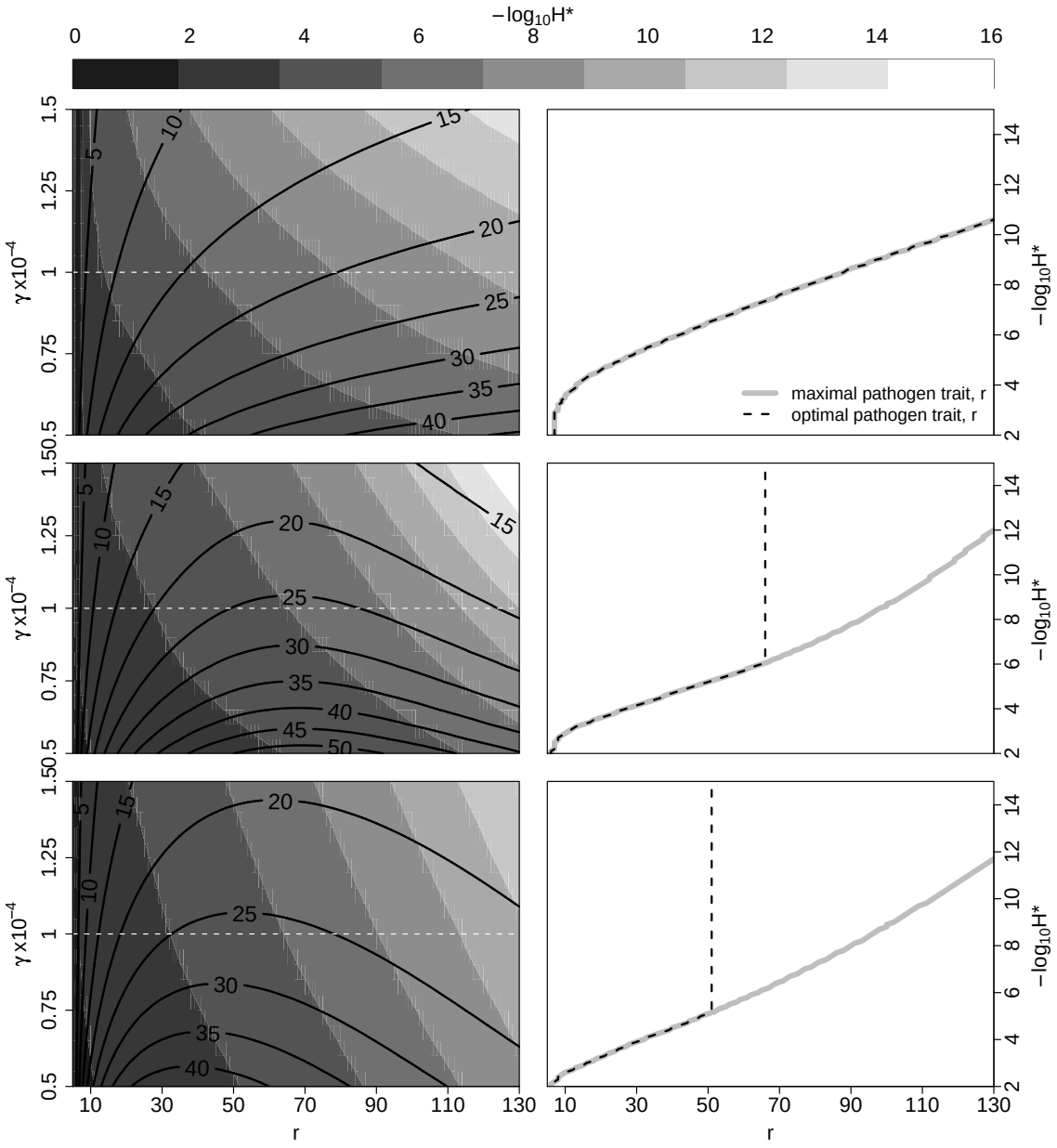

Figure 2.3: Surfaces of H^* and R_0 under different transmission models. The left panel shows the surfaces of R_0 (black lines) and H^* (in grey scale) under the Pilyugin-Antia model with linear [Top], delayed [Middle] and saturating [Bottom] transmission models, respectively. The right panel plots optimal and maximal r against $-\log_{10} H^*$ under the linear [Top], delayed [Middle] and saturating [Bottom] transmission models, respectively. Immune cell proliferation rate, γ, is fixed at 10^{-4} for the figures in the right panel. As host population size increases, H^* decreases (and $-\log H^*$ increases). Maximal r compatible with a given host population size and the optimal r, the one that maximizes pathogen fitness, are shown in solid and dashed lines, respectively. Under the linear transmission model [Top], the optimal r coincides with the maximal r, where as under the delayed and saturation transmission models [Middle and Bottom], it cease to coincide after the population has reached a certain level.

even though r of up to 90 is feasible. Further increases in the host population size will not change r.

The same effect is observed under the saturating-transmission model (Fig. 2.3[Bottom]). Here, increases in pathogen load beyond a certain point no longer lead to increases in transmission intensity. These diminishing returns, combined with decreasing infectious period, reduce the fitness of extremely acute pathogens. In this respect, the case is similar to that of the delayed model, under which the peak in pathogen load passes before the symptoms that facilitate transmission set in. Under both of the more realistic models, greater acuteness leads to increased transmission only up to a point; beyond that point, the reduction in infectious period associated with increased acuteness erodes R_0.

To summarize, we find that, for each of the transmission models considered, increased host population size favors the evolution of more acute infections. An additional effect arises when transmission is not simply proportional to pathogen load: infections of a pathogen with intermediate acuteness may then be favored. Put another way, under realistic models of transmission, when the host population size is sufficiently large, the population-level dynamics cease to constrain the acuteness of infection. Under these conditions only within-host mechanisms impose constraints.

The situation contrasts with that obtained using the more phenomenological SIR model. Fig. 2.1 shows that H^* increases (and critical community size decreases) as R_0 increases. Under this simple model, then, no trade-off arises. In the SIR model, the within-host dynamics is primarily ignored, and the infectiousness of an individual is assumed to be constant throughout the course of an infection. The emergent trade-off only becomes evident when a sufficiently realistic description of within-host dynamics, in particular, the relationship between infectious period and

infection intensity, is taken into account.

In a nonseasonal environment, the greatest barrier to establishment faced by the pathogen occurs in the trough immediately following the virgin epidemic. In a seasonal environment, however, outbreaks will recur, with elevated risk of extinction associated with each one. We can use H^* to quantify this long-term extinction risk. For this purpose, we define H^* to be the minimum of H on the dynamical attractor. Fig. 2.4 shows that the conclusions from the virgin epidemic hold in seasonal environments as well. The contours of H^* show a similar pattern under all transmission models: in more seasonal environments, troughs are deeper and extinction more likely. As in the case of nonseasonal framework, under the linear transmission model, R_0 increases with r, and pathogens maximizing R_0 should evolve to the edge of their own extinction. When the transmission is delayed until the onset of symptoms or is saturating with pathogen load, the maximum R_0 is attained at an intermediate value of r, indicating that pathogens only evolve to this intermediate r whereby avoiding the edge of extinction.

2.4 Conclusions

Infectious diseases have historically been and continue to be among the most important public health concerns worldwide not only because of the high burden of mortality and morbidity but also because of ensuing socio-economic consequences. Among several important questions pertaining to infectious disease, are questions of pathogen evolution. Vaccination programs and drug development strategies as well as changing host ecology mean changing terrain for pathogen and their survival. Pathogens, with considerably shorter generation, are primed to use evolution towards their own ends. Here, we have attempted to understand the evolutionary terrain for

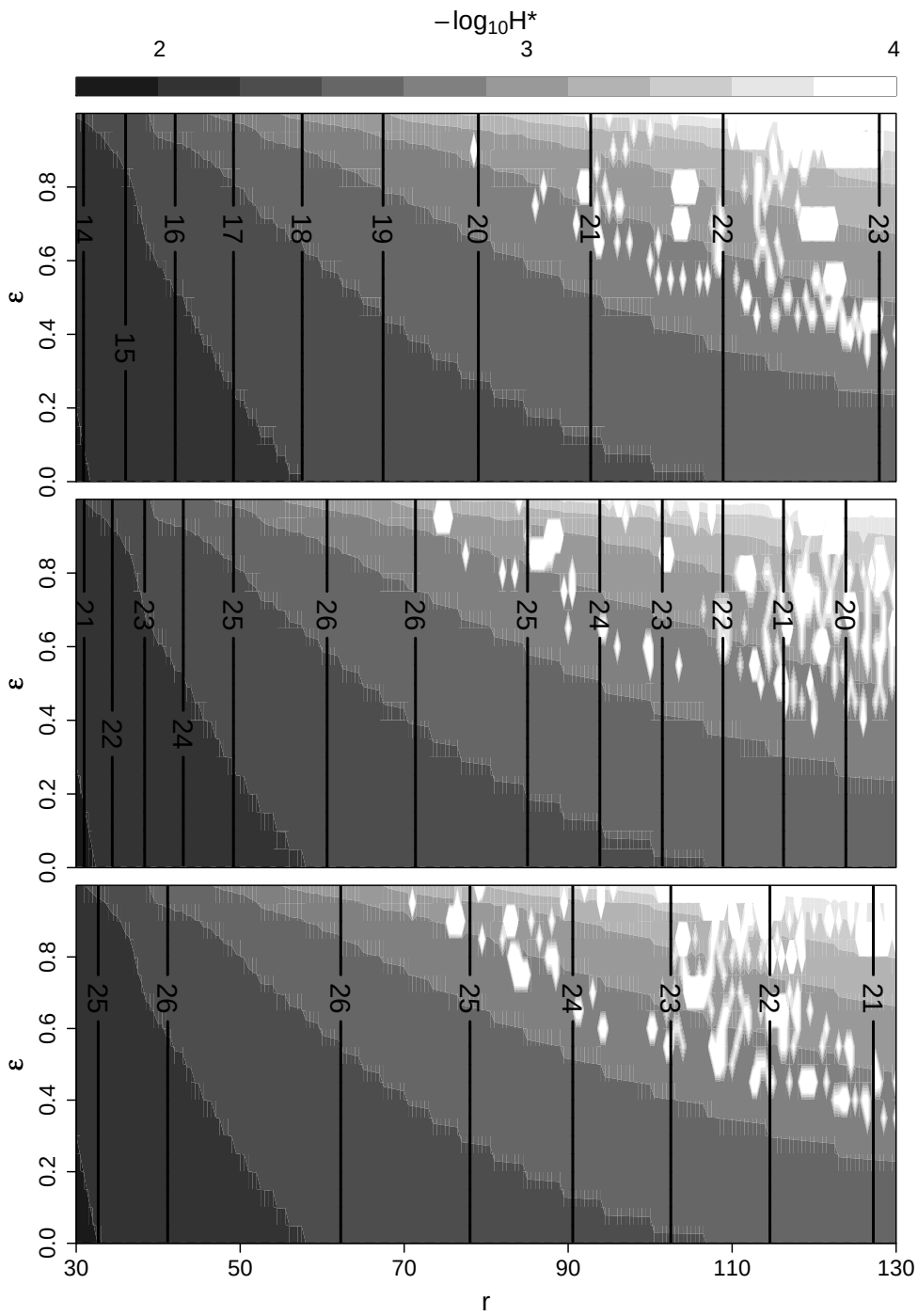

Figure 2.4: Surfaces of H^* and R_0 with seasonality. Effect of seasonality on H^* (the colored surfaces plot $-\log H^*$) in the epidemics for the Pilyugin-Antia model with linear (a), delayed (b), and saturating (c) transmission models. R_0 surfaces (black lines) are independent of the amplitude of the seasonal forcing, ϵ, but they continue to increase with r for linear-transmission model, as opposed to reaching a maximum at an intermediate value of r for delayed and saturating transmission models. The rugged landscape for large r and large ϵ reflect complex dynamics (including multiannual attractors coexisting with annual ones). H can be extremely low during some of these cyclical fluctuations.

acute and rapidly transmitting pathogens that do not necessarily exhibit virulent characteristics. We formulate models of within-host infection dynamics and then scale these models up to derive their between-host dynamical consequences and evolutionary implications. An important insight is that the optimal life-history may also depend on the *size* of the local host population through an emergent colonization-persistence trade-off. In particular, evolution will tend to favour increasing acuteness to push immunizing pathogens toward the edge of their own extinction. Only in host populations above a threshold size is robust persistence of these acute pathogens possible. Similar observations have been made by Sasaki and Iwasa (1991); Rand et al. (1995).

Several others have pondered on similar questions along the lines of the invasion-persistence trade-off. Levin and Pimentel (1981) postulated that extinction dynamics in virulent pathogen can allow for stable selection of avirulent pathogens based on reduced host survival. Keeling (2000) examined the mathematical underpinnings of the invasion-persistence trade-off in a meta-population context. He showed that, in competition between a highly transmissible but extinction-prone strain and a strain that is less prone to extinction but is also less transmissible, evolution may favor either strain, depending on their relative within-patch competitive ability, relative patch-level extinction rate, as well as the degree of stochasticity (itself related to patch size). Here, we examine the dependence of these parameters on more basic parameters that govern pathogen life history, as well as the coupling of the within-host pathogen dynamics to between-host transmission. We find that the shape of the dose response curve (the transmission model) is crucial in determining how and when the invasion-persistence trade-off sets in. Under the linear transmission model, so favoured in the literature, the constraint is active at every population size. The

pathogen's growth rate, r, and consequently R_0, can increase monotonically with population size. Under the more realistic models, the effects of the trade-off may be less clear cut when selection acts both within and between hosts. This highlights two critical points. First, at large population sizes, selection at the within-host level is more important than that between hosts. Second, in small populations, selection at both levels combines—potentially in a non-additive way—to shape the evolutionary landscape.

This result has been derived in the context of a well-mixed population, i.e., mass-action kinetics. How might more realistic assumptions regarding host population structure change our conclusions? The simplest approach here is to consider a host population with two levels of mixing, i.e., a meta-population. Preliminary simulations of a stochastic meta-population model show that subdivision of a population into local patches always effectively increases the critical community size. This effect is modest until the degree of connectivity among patches becomes quite small; for very small connectivities, the effective critical community size grows rapidly as connectivity decreases. The effect of meta-population structure, then, at least within this simple one-strain model, appears to be entirely quantitative: the qualitative picture remains as we have described. Interesting spatial effects may arise in models with explicit competition among strains. We develop an individual based model, that includes meta-population structure and explicit competition amongst pathogen strains to fully explore these effects in chapter III).

We have focused on the case of a completely avirulent, that is, nonlethal, family of pathogens. As we have shown, under realistic transmission functions, when the population size is sufficiently large, the invasion-persistence trade-off is not enforced. In such a regime, then, one expects that, other things being equal, virulence is one

factor that will influence pathogen evolution. When the host-population is small, however, the evolutionary forces acting on a virulent pathogen will depend on the intricate constraints among transmission, infectious period, and virulence—constraints imposed, again, by the interaction of the pathogen with the host's immune system.

While theoretical models of pathogen evolution abound, empirical support is available only in a relatively small number of case-studies. This may in part be because conspicuous shifts in life-history optima will only happen in the face of rapid changes in host population structure (or invasion into a new host, as in the case *myxomatosis* in European rabbits; Fenner 1983). The dawn of the Neolithic era some 10000 yr ago offers an interesting 'historical experiment' of relevance. The Neolithic revolution was marked by numerous changes in human community structure and agricultural practice. In particular, sizes and densities of human settlements increased massively as hunter-gatherers adopted more sedentary agrarian lifestyles and human population growth rates stabilized at 0.1% per year (Eshed et al., 2004). In an intriguing recent review, Mira et al. (2006) argue that the evidence for dramatic changes in the genomes of human-associated bacteria represents the signature of rapid evolution in the face of the altered host community structure. Our theoretical exploration is motivated by the independent emergence of two epidemic strains of *Bordetella* (*B. pertussis* and *B.parapertussis*) that cause acute whooping cough and whooping cough-like illness in humans. The ancestor of these, *B. bronchiseptica* cause more-or-less chronic, nonlethal infection in a wide range of non-human mammals (Bjørnstad and Harvill, 2005). Interestingly, Mira et al. (2006) uses genomic analysis of *B. bronchiseptica* vs *B. pertussis* as a key exhibit; full genome sequences was recently published for all three species (Parkhill et al., 2003). Mira et al. (2006) argue that intense genomic changes—reduction in size, loss of genes coding for functions related

to free-living metabolism, etc.—can be dated to around the time of the Neolithic revolution. We speculate that this may be an instance where invasion-persistence trade-off shaped life history evolution in these pathogens. The acute strains that currently circulate are the evolutionary response to the radically larger population sizes of human host — the larger host populations having served as fertile grounds for pathogens to evolve their life history to become more acute.

CHAPTER III

Host population induces conflicting pressures on pathogen life history evolution

3.1 Introduction

In a host-parasite system, particularly in the context of pathogens that cause infectious disease, the incidence and the abundance of the disease inducing pathogen, and the epidemiological characteristics of the disease is expected to be dependent on the interactions between the host and the pathogen. Typically, a pathogen has to enter a host and proliferate inside of a host, and manage to transmit its progeny to other hosts in the population either before the pathogen is cleared or before the host is killed. Furthermore, the pathogen has to be able to persist in the host population by traveling between the hosts. Hence, from an evolutionary standpoint, the pathogen's survival hinges on the interactions it has with the host.

These host-pathogen interactions can be, very generally at two different levels – (i) between the pathogen and a single host, as the pathogen infects a host and multiplies within it; and (ii) between the pathogen and the host population, as the pathogen transmits between hosts and circulates in the host population. Within a host, the pathogen is likely to encounter resistance from the immune system of the host. The host's immune system has an arsenal of responses, which vary not only in the way they tackle the invading pathogen but also in their specificity. The adaptive/acquired

immune response that is specific to the pathogen is activated by the pathogen's presence and selected for their success at clearing these pathogens, and consequently, is likely to depend on the pathogen density itself. The pathogen load within a host, the host's propensity to shed pathogen, and consequently the pathogen's ability to transmit to other hosts is likely to be influenced by the description of the interaction between the pathogen and part of the host's immune response.

At a larger scale, the pathogen has to circulate in a host population, by successfully transmitting between hosts. The host population can vary in size, and the way it is structured, and this makeup of the host population itself can affect pathogen's ability to sustain in the population and its abundance. Extinction of the pathogen as a result of the size of the host population is one well known effect. Bartlett's seminal work on measles showed that observed gaps in the patterns of recurrent epidemics in smaller towns in England in the pre-vaccination era could be explained by accounting for the risk of extinction due to pure demographic stochasticity. (Bartlett, 1956b, 1957, 1960b) These fade-out events are a direct result of depletion of susceptibles, especially pertinent to acute and immunizing diseases such as measles. The chance of a fade-out event for a particular disease epidemic relates directly to the size of the host population; smaller the size, likelier it is that the susceptibles deplete and result in a fade-out. Furthermore, should the size of the local host population be below a critical threshold, the critical community size, the disease will not persist in such a population, even when its invasive fitness given by the reproductive number, R_0 is above the critical threshold of 1.

This has prompted consideration of possible consequences for evolution of pathogen life history. A possible trade-off, between a pathogen's invasive fitness and its ability to persist in the population, has been postulated by Grenfell (2001). Given two

pathogen of identical invasive fitness, i.e. equal R_0, one that is more acute that drives the susceptible pool to lower levels is likely to be disadvantaged when the host population size is relatively small (closer to critical community size). We have shown in chapter 2 that this invasion-persistence trade-off can indeed be relevant for evolution of pathogen life history. If one were to consider a fitness landscape for a pathogen, the direction in which pathogen's invasive fitness, R_0 increases can very well be in the direction in which its extinction risk grows, when one considers the within-host mechanisms that are biologically plausible.

These insights for trade-offs and potential evolutionary consequences though overlooks the rescue effect that host migration between host communities might bring. Indeed, when one considers a host population in a larger meta-population, with hosts migrating between these communities, there are significant effects pertaining to the disease extinction. Epidemics on the brink of extinction, or even already extinct at the local community level, can be rescued when there are simultaneous but possibly asynchronous epidemics occurring in a nearby community. It is then relevant to consider, if the meta-population effects quell the local community level extinction risks.

Models that consider host population with structure and relate to or directly examine the evolutionary consequences have varied both in their approach and their insights. A common approach has been to place hosts in a two-dimensional space, and weight their frequency of contacts according to the physical distance between hosts in the space. When contacts are limited to hosts in their local neighborhood, Boots and Sasaki (1999) have observed "self shading" behavior, where virulent pathogens quickly deplete susceptible hosts in its local neighborhood, diminishing its chances of spreading. The authors also find that increase in the frequency of global contacts

allows these virulent pathogens to escape extinction, and hence a selection of more virulent pathogens. In a similar model, but allowing for waning of immunity, van Ballegooijen and Boerlijst (2004) observe various spatial patterns ranging from localized disease outbreaks to epidemics spreading in waves through the space. Simulations that explored the evolutionary dynamics showed evolution towards pathogen traits that maximized outbreak frequency (the number of times a host becomes infected), instead of R_0. In the absence of any physiological trade-off at the within-host level, the authors argue that the pathogen evolution can be constrained by this emergent trade-off at the population level. These results suggest that adding structure in the host population can bring about further meta-population level patterns that might affect the disease epidemiology and consequently muddles the notion of pathogen fitness. It is also unclear whether these results do hinge on the particular description of the space and or on the asynchronous behavior that is normally associated with the meta-population dynamics. Nor is it helpful pinning down the underlying dynamics at work, and predicting what the fitness landscape for the pathogen looks like and how it might change with the description of the host structure.

In a more deliberate effort to capture the consequences of extinction risks on pathogen evolution, Keeling (2000) explores a model that scales the between host interactions to meta-population level. A competition between two strains, a fitter (higher R_0) but extinction prone one and a relatively less fit but also less extinction prone one, he finds, can result in domination of either strain or a coexistence between them. He points out that the coupling between patches and the stochasticity in the meta-population as primary factors that determine the evolutionarily stable strategies. The within-patch competition is modeled to operate at a separate time scale, and the strain composition is assumed to tilt towards the one with larger R_0

over time. The extinction risk for a pathogen is assumed to linearly scale with R_0. In contrast, we build an individual based model, where both the competition within a patch for susceptibles, and the local extinction dynamics are handled explicitly. The details of the model are described in section 3.2.

In this paper, our goal is to understand the evolution of pathogen traits in structured host populations. Our approach will be to begin with a parsimonious model that describes the underlying within-host and transmission mechanisms. This provides a mechanistic basis for a relationship between transmission rates and length of infection for a pathogen. We observe the evolution of pathogens constrained by this relationship in a model that allows for explicit competition between pathogen strains. While the evolutionarily stable strategy (ESS) is the one that maximizes between host transmission, i.e. one with the highest R_0, for homogeneously mixing population, we will show that adding structure in the host population will change these ESS. In particular, structure in the population can result in an emergent patch level dynamics — extinction and colonization at the patch level, and consequently allow for patch level selection. As a result evolutionary pressures are acting at two levels, modulated by competition for hosts at the between-host level and by colonization-extinction dynamics at the between-patch level. Furthermore, a pathogen's fitnesses at two levels, corresponding to the abilities to compete for hosts and to colonize patches, do not correlate. In fact, we show that pathogens that maximize their between-host transmission necessarily forgo their ability to transmit and exist at the patch level. The effect of these conflicting evolutionary forces can allow for a range of evolutionary trajectory depending on the magnitudes of each of the forces, which in turn depends on the host structure. In particular, patchiness in the host population rewards pathogen that are less acute but persistent.

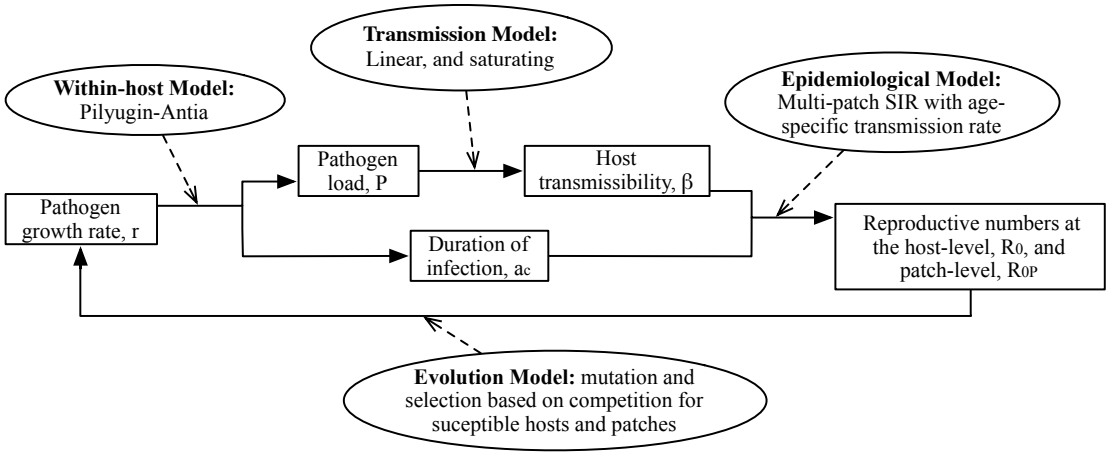

Figure 3.1: A flow chart to illustrate the schematics of the model. We consider the evolutionary forces on a specific pathogen trait, r, which is its within-host proliferation rate. The within-host model relates this trait to calculate the pathogen load, P, and the duration of the infection, a_c. The transmission model translates the pathogen load to the host transmission potential, β. The epidemiological model then generates the epidemics of pathogen with the prescribed transmission rate and infectious period. Pathogens are selected based on the relative abundance in the host meta-population.

3.2 Models

The general approach we take is to systematically model the effect of variation in pathogen traits and more generally their life history strategies firstly on the characteristics of the infection, primarily the intensity and the duration of the infection within a host, and then consequently on epidemic patterns in a host population. These epidemic patterns themselves are likely to vary depending on the way the host population is structured, particularly the risk that they face of extinction and their the role of the "rescue effect" in maintaining in the host. The variation in pathogen's ability to sustain in the host population in turn is modeled to affect the selection of the pathogen traits, thereby completing the feedback loop. We begin by modeling dynamics at the within-host level, and then scale them up to between-host and population levels. At the within-host level, we seek to capture the basic mechanisms of pathogen growth and its interaction with the immune system with

relative parsimony. Yet, the model needs to be flexible enough to allow for a range of different types of infections. The model we use enables us to first, identify biologically significant parameters, and second, observe the effects on them when they are subject to evolutionary pressures. Transmission functions that describe the pathogen shedding rates for hosts at different stages of their infection, translate these within-host dynamics to between-host level. The deterministic models for within-host and transmission dynamics are detailed in the subsection 3.2.1. We have previously used McKendrick-von Foerster equations to explore the dynamics unfold at the population level (also see the Appendix B.1).

Here, we implement an individual based model to the study of disease spread and extinction patterns in structured host population. This choice is motivated by several factors. First, stochasticity, both in host demographic processes and transmission dynamics, are intrinsic in extinction or fade-out events that we aim to focus on. In an individual based framework, demographic and transmission processes easily and perhaps more naturally translate into stochastic processes. Second, we consider host populations that are structured. Later in this section, we will describe in detail the way in which we structure the host population. But regardless of the structure, by individually tracking every single host, we can easily add this additional attribute of the host in the model. Finally, perhaps the most important motivation is to be able implement explicit competition between pathogen strains and capture the evolutionary dynamics more comprehensively. This is important because we expect the evolutionary process to depend on two fundamentally different dynamics; (i) the invasion dynamics which deals with the ability of pathogen strains to compete for susceptibles, and (ii) persistence, which relates to their ability to circulate in the meta-population by avoiding extinction. The standard pairwise strain invasion

analysis can run into potentially tricky questions. Such questions can involve directly comparing fitness given by the two criteria. For example, if strain A has slightly higher R_0 than strain B, but is also slightly more likely to go extinct, what are the evolutionary consequences? This framework, in contrast, allows us to directly implement the strain competition, and the evolutionary consequences can directly emerge. It also allows for circulation of multiple strains, and multiple invasion and re-invasion dynamics are naturally incorporated. This method also provides not only the final evolutionary optima, but also the trajectories, which can be more insightful. The individual-based model is fully described in subsection 3.2.2.

3.2.1 Models of within-host and transmission dynamics

We use a fairly generic description of the pathogen-host immune system interactions to model the within-host dynamics. The model is a slight modification of a model proposed by Pilyugin and Antia (2000). Here, the course of infection is modeled in the most basic terms: the parasite load, P, as a function of the age of infection, a, defined as the time elapsed since innoculation. Pathogens are modeled to grow exponentially at the rate r, but are killed at the rate k upon encounters with host immune response, X. The successful killing of the pathogen proliferates the growth of the immune response at the rate γ. α and d are background growth and death rates for these immune cells.

$$\begin{aligned} \frac{dP}{da} &= r\,P - k\,X\,P \\ \frac{dX}{da} &= \alpha - d\,X + \gamma\,k\,X\,P \end{aligned} \tag{3.1}$$

This system of differential equations is initiated with a single pathogen in the absence of the specific immune cells signifying start of an infection, i.e $P = 1, X = 0$. There are two dynamical regimes in this system with stable equilibria at (i) $P =$

$0, X = \alpha/d$ when $d/k < \alpha/r$, and (ii) $P = \frac{1}{\gamma}(d/k - \alpha/r), X = r/k$ when $d/k > \alpha/r$. En route to the second non-zero equilibrium, however, the parasite load, P exhibits damped oscillations falling to extremely low values. We interpret this as pathogen clearance, as P falls below the critical pathogen load of initial dose, 1 before it reaches the equilibrium. Consequently, in both regimes, the host is infectious until age a_c when the pathogen load returns to the initial dose. The pathogen growth rate parameter r plays a key role in shaping the infection - low r results in less acute and more persistent infection, whereas, high r results in more acute and less persistent infection. (Also see fig. 3.2) Additionally, the pathogen growth rate is likely to be most sensitive to evolutionary pressures faced by pathogens. For these reasons, we take r to be the parameter indicative of the evolutionary dynamics.

The pathogen load an infectious host is carrying affects the host's shedding rate at different stages of infection and consequently its contribution to the force of infection. The simplest, a linear model, assumes a proportional increase in the shedding rate as pathogen load increases. However, in a biologically more realistic scenario the shedding rate is likely to saturate with pathogen load. Transmission mechanisms involved, for example coughing in *Bordetellae*, is likely to act as a bottleneck in saturating the expulsion of pathogen propagules. This saturating model and the linear model are described by the equations below:

Linear	Saturating
$\beta(P(a)) = q_l\, P(a)$	$\beta(P(a)) = q_s\,(1 - \exp(-P(a)/P^*))$

Here, $\beta(a)$ is the transmission rate of an infectious host that was infected a time units ago.

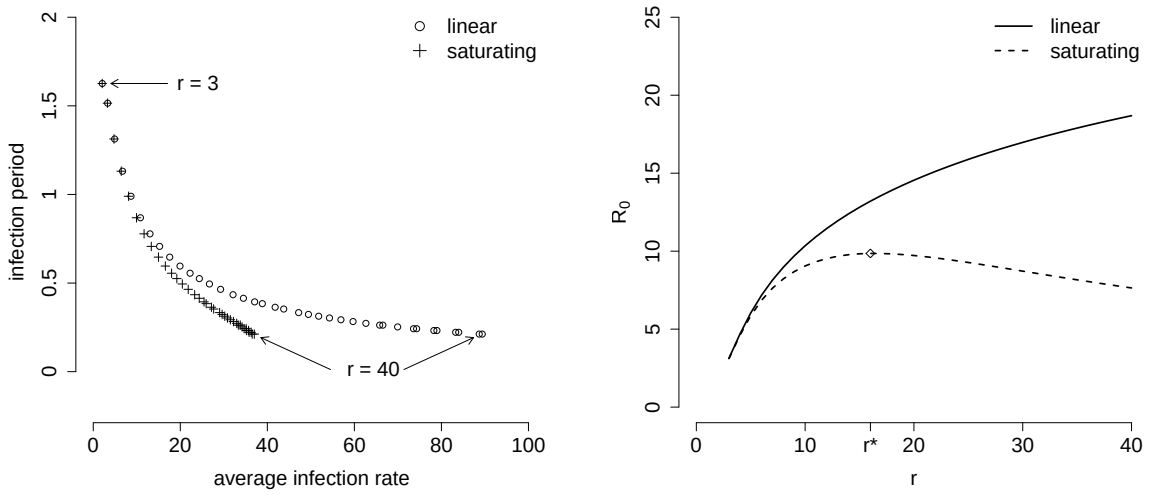

Figure 3.2: Transmission rates, duration of infection and R_0 as a result of within-host and transmission dynamics. [Left] Dose response generated by within-host and transmission models vary with r. Here, we observe the length of infection (on the vertical axis) and average infection rate (on the horizontal axis). The figure shows the trace of paths, for both linear and saturating transmission models, when parameter r increases from 3 to 40. The infections tend to become more acute and less persistent in both cases, but the infection rates saturate for the saturating transmission model. [Right] Consequently, R_0 also varies with r. For linear model, R_0 keeps increasing with r, whereas for saturating model, it reaches a maximum at $r = r^*$.

3.2.2 Model for population structure and evolutionary dynamics

Models incorporating structure in the population have taken many different directions, primarily depending on the particular heterogeneity that is relevant to the disease epidemics at hand. Some are explicit in space, where host contacts are confined in a neighborhood of its location, sometimes also allowing some random global contacts outside of the neighborhood. (Boots and Sasaki, 2000; van Ballegooijen and Boerlijst, 2004) Others focus on the network of contact structure, which might take certain forms depending on social or other factors. Since our interest lies in exploring extinction events, a more appropriate choice is a simple globally-connected meta-population model, where we partition the host population into smaller patches, similar to Hanski's "patch" model (Hanski and Gilpin, 1991) or Ball's "household" model (Ball et al., 1997). The host population comprises of N_P patches of size n. Hosts mix homogeneously within a patch and transmission event also occur only within a patch, but hosts can migrate between patches.

An individual host inhabits in one of the total N_P patches, and can be in one of the three states, susceptible (S), infected (I) or recovered (R). An infected host can be further characterized by the pathogen strain it is carrying. Multiple infections are disallowed, and the cross-immunity between the strains is assumed to be perfect. The course of infection in an infected host depends on the pathogen strain r. In particular, the pathogen load a host is carrying at age of infection a, $P(a)$ follows a deterministic course given by the within-host model given by Eq. (3.1) where the parameter r corresponds to the pathogen strain it is carrying. The host recovers once the infection is cleared — the clearance criterion is that the pathogen load to returns to the initial level. The infection imparts life-long immunity, so the recovered hosts do not enter the infection cycle again.

The transmission occurs only within a patch, and it is assumed to be frequency dependent. In a patch, each infected host contributes to the total force of infection in the patch. If a host carries a pathogen load $P(a)$, then $\beta(P(a))$ is the contribution to the total force of infection. $\beta(P(a))$ depends on the transmission model and age of infection but does not vary between strains. Since there are multiple strains in circulation, we calculate strain specific force of infection for all circulating pathogens. The strain specific force of infection for a strain r in a patch j is:

$$\lambda_{r,j} = \frac{1}{n_j} \sum_{\text{all hosts in patch j infected with r}} \beta(P(a)),$$

where, n_j is the size of the patch j. The total force of infection is the sum of all strain-specific forces of infection, i.e. $\lambda_j = \sum_r \lambda_{r,j}$. So a susceptible host in patch j faces a total force of infection λ_j, and the probability it will become infected in a small time step Δt is $1 - e^{-\lambda_j \Delta t}$. Furthermore, the probability that this new infected will carry strain r is proportional to the contribution of λ_r to λ. Hence the strains compete for susceptibles within a patch through the force of infection they generate in the patch.

The birth and death rates of the host are held equal at a constant rate μ, so the average population size remains constant. The probability that a host dies in time Δt is $1 - e^{-\mu \Delta t}$, and the number of total births is distributed binomially (binom($n = \sum_j n_j, p = 1 - e^{-\mu \Delta t}$)). The new born susceptibles are equally likely to land in any of the patches, since the patches are assumed to be of equal size n. The hosts also migrate between patches at a given migration rate m, so the number of hosts that migrate in time step Δt is distributed binomially (binom($n = \sum_j n_j, p = 1 - e^{-m \Delta t}$)). These migrating hosts are equally likely to land in any of the patches, so any two patches are equally connected.

The evolutionary process is fueled by the competition between strains, and the

diversity of the strains is maintained by a mutation process. During each transmission event, a strain r is likely to mutate with probability m. Mutation event is drawing a new strain s from a normal distribution with mean r and a fixed standard deviation σ.

Each run is initialized by infecting 1% of population by a single strain drawn from uniform distribution between $r = 3$ and $r = 10$. A single run is assumed to have led to pathogen extinction when there are no infecteds left. Evolutionary trajectory is constructed by finding the average r (weighted by the number of hosts each strain is present in) at each time t. 1000 runs were simulated for each set of parameters. The evolutionary trajectory of the strain distribution is the distribution of average r in these 1000 runs. For each simulation (of 1000 runs for a set of parameters) considered, with the exception of one simulation corresponding to single patch with linear transmission (discussed in subsection 3.3.1), the strain distribution converges to an apparently stable distribution. The time taken by the simulations to converge, though, can vary. The steady-state distributions are generated by excluding the transient period. 1000 more runs reinitialized, according to the state of runs at the end of the transient period, and progressed for 2000 more time units to derive the steady-state strain distributions. Time step Δt was taken to be 0.01.

3.2.3 Fitness measure, R_0

If we take the number of patches, $N_P = 1$, and disallow mutation, i.e. set $\chi = 0$, the model reduces to a stochastic version of the model we discussed in Chapter 2. The details are also described in appendix B.1. In such a setting, for a given pathogen with growth rate r, we can deterministically calculate the net reproductive number,

$$R_0 = \int_0^{a_c} \beta(a)\, \exp(-\mu\, a)\, \mathrm{d}a.$$

Table 3.1: Parameters for the meta-population model.

Symbol	Parameter	Value
	Within-host model:	
r	parasite growth rate	3–60
k	kill rate of the immune response	3.5
α	baseline production rate of immune response	1.0
d	death rate of immune response	0.5
γ	immune response recruitment rate	0.1
	Transmission models:	
q_l	transmissibility factor, linear model	1.0
q_s	transmissibility factor, saturating model	100.0
P^*	saturation constant	-0.01
	Population model:	
N_P	number of patches	1–200
n	size of the patch	20–2000
m	migration rate	0.1
μ	host mortality rate	0.1
χ	mutation rate (probability per transmission event)	0.01
σ	mutation size (standard deviation)	0.35

Fig. 3.2(Right) shows the R_0 for a range of pathogens for both transmission models. R_0 increases monotonically with r for a linear transmission model — the more acute the pathogen, the better they fare in between-host transmission. In contrast, R_0 reaches a maximum at an intermediate r for a saturating transmission model, a consequence of diminishing returns for increasing pathogen load as the pathogen shedding rate saturates.

3.3 Results

3.3.1 Single patch model and evolution to the edge of extinction

In a single patch model, hosts mix homogeneously within the population. Diversity of pathogen strains are maintained through mutation events, and the strains that circulate at any point in time are competing against each other for susceptible hosts. We observe the evolution of the pathogen strains over time. The strain distribution is expected to change over time, and eventually converging to values representing evolutionarily stable pathogen strategy, when they exist. For linear transmission model,

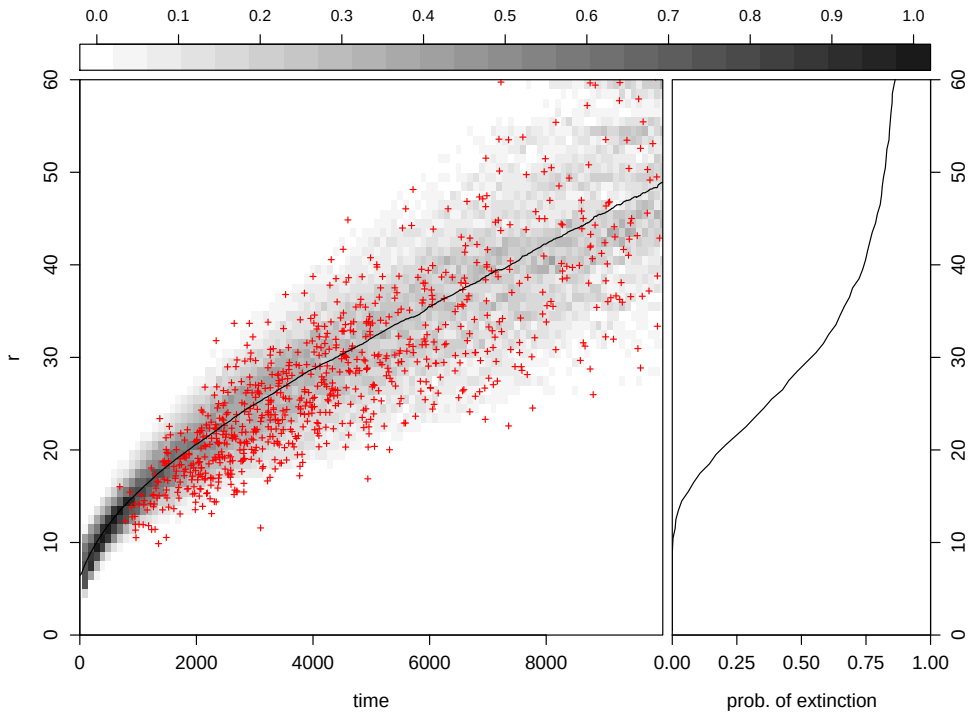

Figure 3.3: The evolution to the edge of extinction. Simulation results for a single patch model (initialized with 2000 hosts) with a linear transmission showing pathogen evolution over time. We construct the pathogen distribution at a given time, $r(t)$, by observing the average r of the pathogen present at that time, t, in each of the 1000 simulations. In the left panel, shades of grey shows the pathogen densities, and the solid line plots the average of the distribution $r(t)$. The evolutionary trajectory shows pathogen evolution towards higher acuteness corresponding to higher r. Consequently, they also become more prone to extinction events, shown by the red cross marks. Probability of extinction (proportion of simulations that result in extinction) increases as r grows, as shown in the right panel. In the absence of external constraints, a linear transmission model in a single patch population shows the pathogen evolving to the edge of their own extinction.

this distribution continues to change in the direction of higher r, corresponding to shorter and more acute infections as shown in Fig. 3.3. This is to be expected, since the net reproductive number, R_0 increases with r (Fig. 3.2[Right]). As the pathogens continually increase r, they become more acute. Acute infections burn through the pool of susceptibles quickly, hence risking stochastic fadeout. The direction of evolution leads the pathogen to the brink of their own extinction. This is in agreement with our results in Chapter 2.

Under the saturating transmission model, R_0 is maximized for intermediate r. Diminishing returns sets in for the pathogen increasing their pathogen load beyond this r. Consequently, pathogens evolve to this optimal value, which is evolutionarily stable as long as the population is large enough to sustain such a pathogen. Fig. 3.3.1[Left] shows that the strain distribution settles around $r = 16$. This coincides with r^*, the r that maximizes R_0 (Fig. 3.3.1[Right]).

3.3.2 Population structure and approximation of the emergent patch dynamics

To explore the role of population structure, we subdivide the host population into smaller patches (N_P patches of size n). We find that the evolutionarily stable pathogen strain varies widely depending on the structure of the host population. We focus on the effect of two meta-population parameters, (i) the size of the patch, n, and (ii) the number of patches, N_P.

Under the saturation transmission model, with $N_P = 1$ and $n = 2000$, we already showed (Fig. 3.3.1) that the steady state distribution of the pathogen strain was centered around a mean of $r = 16$, the strain that maximizes R_0. Increasing n in this case will only reduce the frequency of extinction, but not change the steady state distribution. Decreasing n will increase the frequency of extinction, and if it is small enough the steady state distribution might not be reached. For meta-

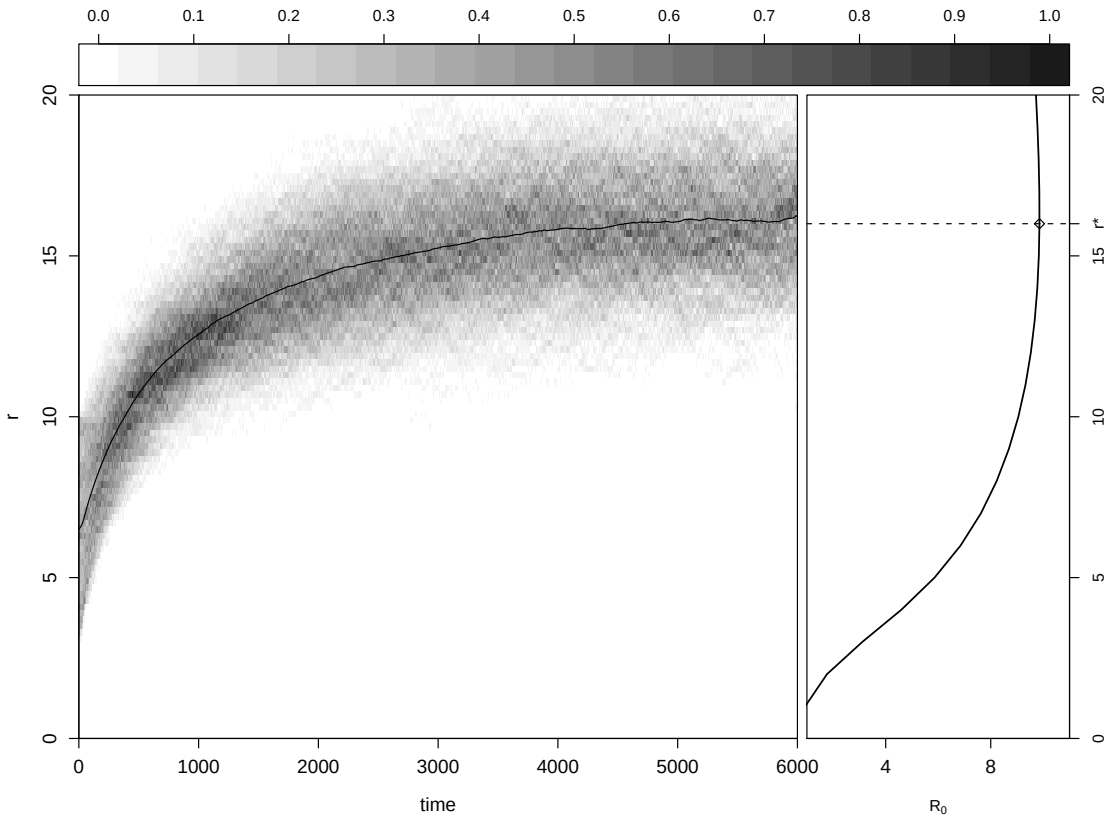

Figure 3.4: Evolutionary trajectory. Simulation results for a single patch model (initialized with 2000 hosts) with a saturating transmission model. Pathogens evolve to a evolutionarily stable r, this is equal to the r that maximizes the net reproductive number R_0. Note that R_0 for a linear transmission model increases monotonically with r without a maximum.

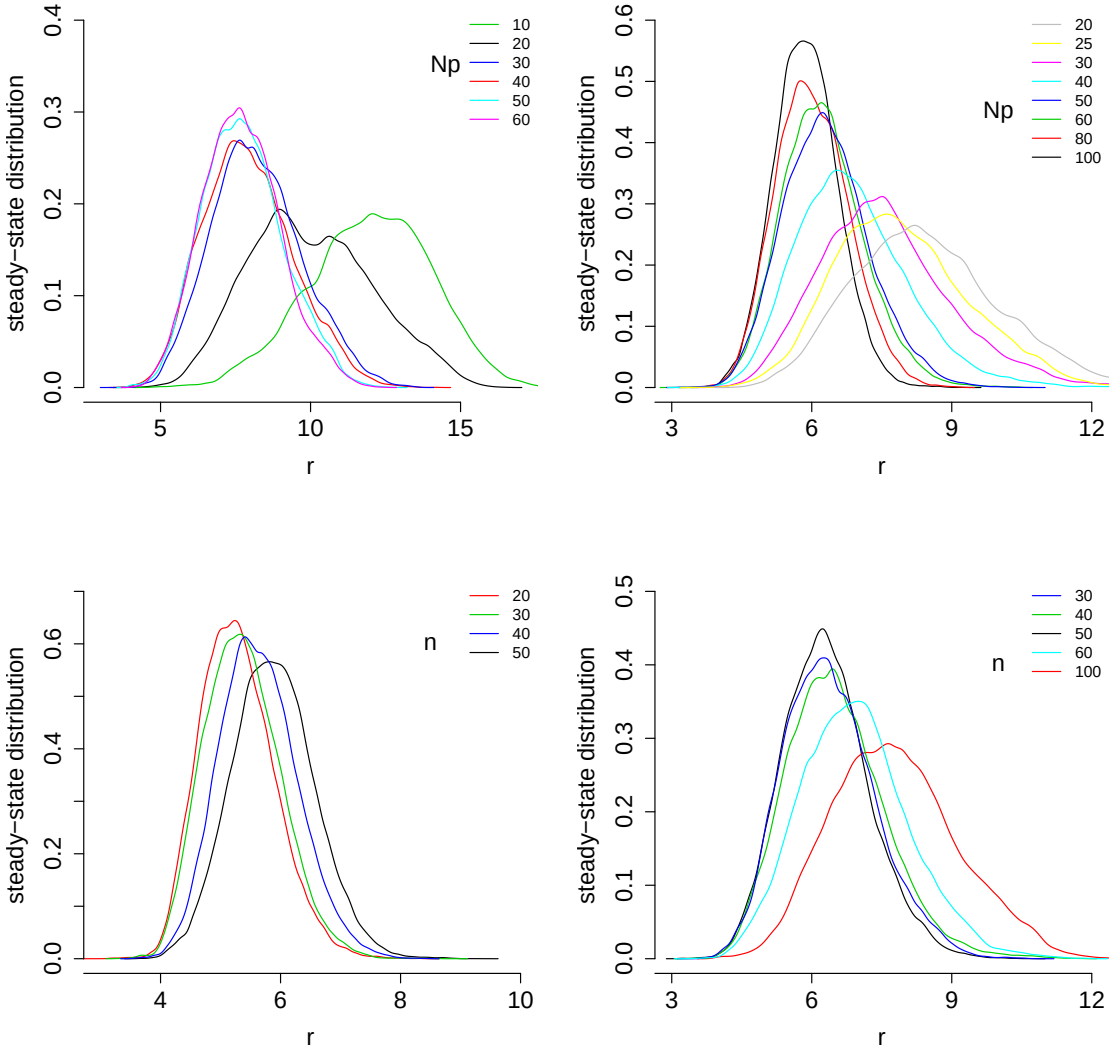

Figure 3.5: Steady state strain distributions. [Top-Left] For n fixed at 100, and changing N_P. [Top-Right] For n fixed at 50, and changing N_P. [Bottom-Left] For N_p fixed at 100, and changing n. [Bottom-Right] For N_p fixed at 50, and changing n.

populations with N_P larger than 1, the evolutionarily stable strains were always below $r = 16$. But in general, increasing the size of the patch selected for more acute pathogens. Fig. 3.5 [Bottom-Left] shows the steady state strain distributions, when N_p is fixed at 100, and n is varied between 20 to 50. Distributions moves move slightly to the right as n increases. Results are more pronounced for $N_p = 50$ and n is taken up to 100. (Fig. 3.5 [Bottom-Right]) Increasing n results in two things. First, the frequency of the local extinction are reduced allowing for selection of more acute pathogens. Second, even in the case where local extinctions are prevalent, the number for transmission events within a patch in increased. This should also favor more acute pathogen since they have higher R_0 (up to $r = 16$).

The effect of changing N_p was less intuitive. Meta-populations with many small patches appeared to favor pathogen significantly less acute than the one that maximized R_0. In fact, increasing the total population size by adding more patches tended to select for less acute pathogen. In Fig. 3.5 [Top-Left], we plot the strain distributions at the respective steady states for meta-populations with number of patches, N_p varying between 10 and 60, and patch size fixed at $n = 100$. The transmission model is taken to be saturating. Simulations with N_P smaller than 10 result in global extinction, and N_P greater than 60 is infeasible due to the size of the computation. But in the range of N_p considered, the steady state strain distributions move and accumulate to the left towards lower r as N_P increases from 10 to 60. Similar behavior can also be seen for $n = 50$ in Fig. 3.5 [Top-Right].

While it is not completely obvious why there are significantly different ESS, especially with lower acuteness, in patchier populations, it is still quite clear that the original measure of pathogen fitness, R_0 is not sufficient in including the effect of population level dynamics. In a population model, where there are large number of

small patches, it is more worthwhile to think of the dynamics at the patch level. Consider an infected patch, a patch that has infected hosts. When an infected host from this patch moves to a susceptible patch, a patch that has susceptible hosts, it turns into an infected patch. The infected patch goes through an epidemic, and the hosts recover, turning the patch to a recover patch. This recovered patch, through birth and migration replenishes susceptibles hosts and turns into a susceptible patch again, and the cycle continues. The following set of equations provide an approximation to the patch dynamics:

$$
\begin{aligned}
\frac{dS_P}{dt} &= f(\mu)\, R_P - \bar{\iota}\, m\, n\, S_P\, \frac{I_P}{N_P} \\
\frac{dI_P}{dt} &= \bar{\iota}\, m\, n\, S_P\, \frac{I_P}{N_P} - \frac{1}{\bar{\delta}}\, I_P \\
\frac{dR_P}{dt} &= \frac{1}{\bar{\delta}}\, I_P - f(\mu)\, R_P
\end{aligned}
\tag{3.2}
$$

where, S_P, I_P, R_P and N_P are number of susceptible, infected, recovered and total patches respectively; μ is the host birth rate; n is the per patch population; m is the between patch migration rate; $\bar{\iota}$ is the average proportion of infected hosts in an infected patch; and $\bar{\delta}$ is the average duration on an epidemic. Susceptible patches become infected when infected hosts move from an infected patch to a susceptible patch. The rate at which that will happen will depend on the between-patch migration rate, σ, the average number of infected host in an infected patch, given by the product of $\bar{\iota}$ and n, and the probability such patches interact (in exchange of hosts), which is given by the product of S_P and I_P/N_P. An epidemic in a patch will last $\bar{\delta}$ on average, at which point the patch becomes recovered. The recovered patch themselves turn susceptible, the rate $f(\mu)$ is a function of the host birth rate, μ.

One can also draw comparison with the general Levins model (Levins, 1969),

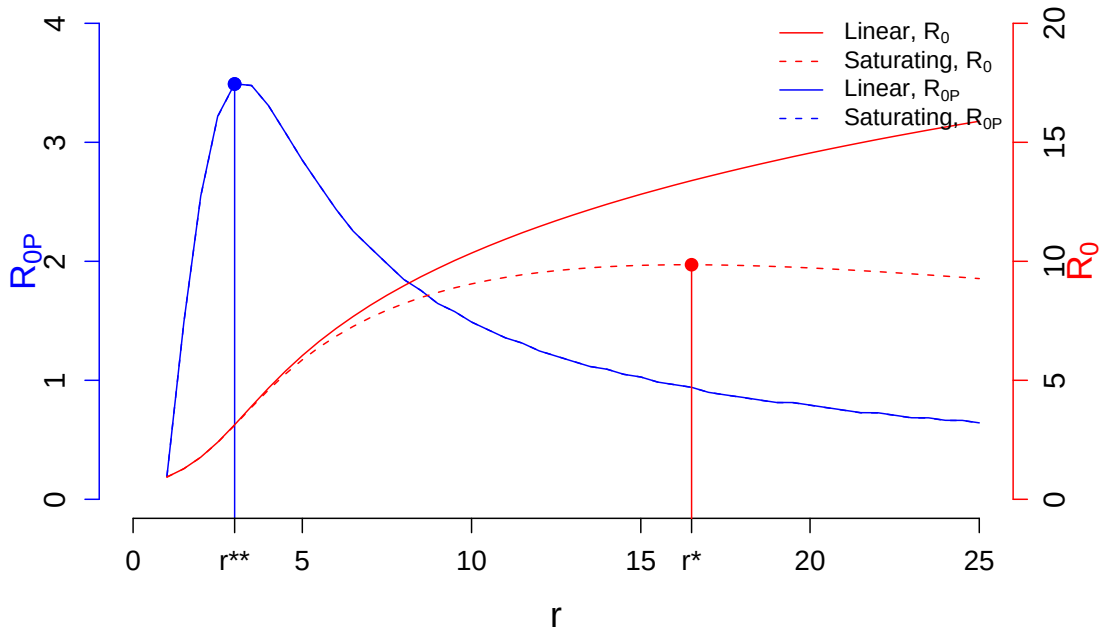

Figure 3.6: R_0 and R_{0P} have different optima for saturating transmission model. R_0 is maximized at $r = r^*$, whereas R_{0P} is maximized for $r = r^{**}$. Here, R_{0P} is calculated with patch size, $n = 30$, and migration rate, $m = 0.1$.

described by the following equation:

$$\frac{dp}{dt} = c\,p\,(1-p) - e\,p \tag{3.3}$$

where, p is the fraction of occupied patches, and c and e are colonization and patch level extinction rates respectively. The appropriate analogy would be to think of the patches being occupied by pathogens carried by hosts. In comparison, $\bar{\iota}\,m\,n$ is the colonization rate, and $\frac{1}{\bar{\delta}}$ is the patch level extinction rate. The key distinction between the Levins model, and our patch dynamics model is that patches in our model do not become susceptible immediately after the pathogen becomes extinct in a patch. Since the hosts remain immune to the pathogen once they recover, the patches consisting of recovered hosts, remain in recovered class, not available for the pathogens to occupy. The recovered patches turn into susceptible ones once the old recovered hosts are replaced by new susceptible hosts through births and deaths. This formulation is also closely related to the model proposed by Keeling et al. (2004) — ours neglects dispersal events (migration of infected hosts from and to infected patches) for simplicity.

In our formulation, the average number of new infected patches resulting from a single infected patch, the patch-level R_0,

$$R_{0P} = \bar{\iota}\,\bar{\delta}\,m\,n.$$

Quantities $\bar{\iota}$ and $\bar{\delta}$ can be approximated both deterministically and stochastically. The resulting R_{0P} are shown Fig. B.2 of appendix B.2.

3.3.3 Evolutionary consequences of selections at different levels

The key issue here is that the fitness measures, R_0 and R_{0P} can have different optima, as seen in Fig. 3.6. Pathogen evolution in a less patchy population is governed

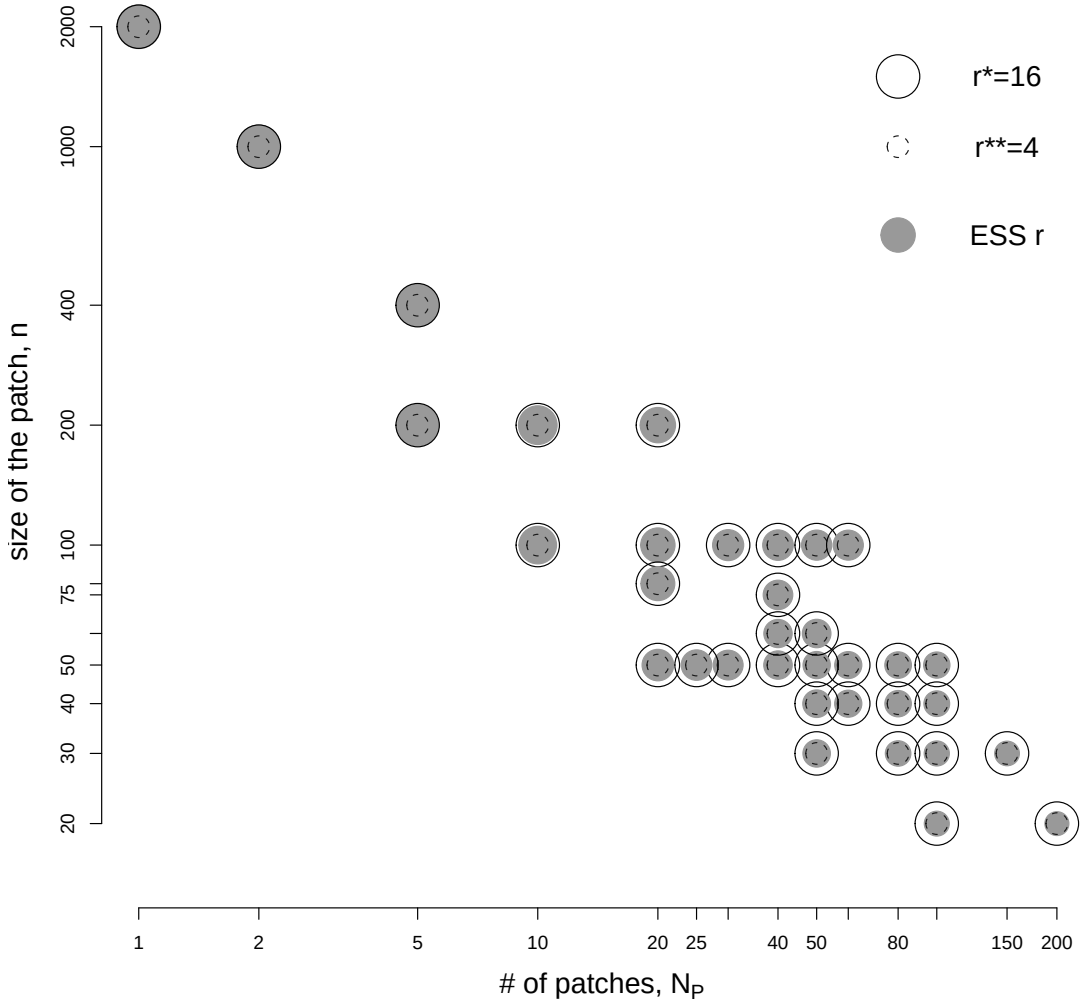

Figure 3.7: Evolutionarily Stable Strategies (ESS). Here, $r^* \approx 16$ maximizes R_0, and $r^{**} \approx 4$ maximizes R_*. Depending on the population structure, ESS r varies between r^* and r^{**}. Specifically, ESS r is closer to r^*, when there are small number of large patches, and to r^{**} when there are large number of small patches.

by a single population dynamics, and the fitness in such such a case is given by R_0. Pathogens find that ESS $r = r_{\max}$ that maximizes R_0. In a patchy population, however, the pathogen evolution is governed by patch dynamics. The fitness measure in this scenario is given by R_{0P}, and pathogens find ESS $r = r^{**}$ that maximizes this fitness. When we explore a range of populations, as shown in Fig. 3.7, we see that the ESS r varies from r^* to r^{**} as we make the population patchier. This suggests that a pathogen in a given population will face evolutionary pressures functioning at two different levels. A pathogen that is more successful at spreading within a patch is also more likely to burn through the susceptibles quickly and go extinct much more rapidly within the patch. Consequently, there is a shorter window for the pathogen to colonize a new patch. In contrast, a pathogen that causes a more persistent infection, is able to also persist longer in a patch and hence favored to be able to move to a susceptible patch and avoid extinction. But it is inferior in its ability to spread within a patch. The exact structure of the population is going to determine the optimum growth rate for the pathogen, and a balance of selection pressures at two levels.

This also highlights the fact that increase in the host population does not have a single effect on the pathogen evolution. If the increase in the population constitutes increase in patch sizes, within-patch selection pressure is increased, favoring more acute pathogen. On the other hand, if one were to increase the number of patches, this increases availability of susceptible patches, and hence favor pathogens that are successful at colonizing patches — the persistent ones.

3.4 Discussion

In this chapter we have taken a "bottom-up" approach; beginning with a model for pathogen and host immune system interaction at the within-host level and explored the full dynamics of disease epidemics unfold in structured host populations. We focus on the pathogen evolution modeled via explicit competition between pathogen strains for susceptible hosts. We find that structure in the population plays a critical role in determining the trajectory of pathogen evolution. While in a large well-mixed population, pathogens evolve to a stable strategy corresponding to optimal pathogen traits depending on their between-host fitness, i.e., the one maximizing R_0, the evolutionarily stable strategies diverge from this optima as the population becomes patchier. In populations with large number of small patches, emergent patch level dynamics governs the pathogen evolution. Consequently, the pathogens more equipped to out-survive its competitors within a patch, the one maximizing R_{0P} is evolutionarily stable.

The role of host population structure in pathogen evolution has been pointed out by a number of authors. Ball et al. (1997) derive a threshold quantity for pathogen invasion in the context of several meta-population models. Their metric for the average number of new infected patches resulting from a single infected patch, R_*(Ball et al., 1997; Ball and Neal, 2002) simplifies to R_{0P} for structurally similar "household" model. The effectiveness of R_* over R_0 in predicting the disease invasion threshold has also been pointed out by Cross et al. (2005, 2006) in host population grouped into spatially distributed patches. The authors suggest that in a patchy population chronic infections benefit from having more time for between-patch transmissions, yet for the selection of pathogen to be effective at this scale there should be signifi-

cant patch level extinction risks. We have shown that host population structure, in particular the size and the number of patches, plays an important role in allowing for extinction and colonization dynamics to unfold at the patch level.

Large scale meta-population patterns, and their role in shaping pathogen traits have also been observed in spatially explicit models, such as "self shading" behavior reported by Boots and Sasaki (1999) and pathogen evolution towards maximizing outbreak frequency instead of R_0 in van Ballegooijen and Boerlijst (2004)'s model. Models in developed in this framework, though, present a difficult challenge of quantifying evolutionary forces active at a larger scale. In the absence of such a measure, the predictions of evolutionarily stable strategies will lack theoretical basis. We have also shown that the shift in the evolutionary pressure in structured population is not completely a function of space. The bottleneck that structure in the host population provides, whether it is explicitly defined in space or not, still can potentially shape the pathogen evolution.

The behavior of evolution of pathogen towards a self-destructive end is an interesting yet a challenging result to interpret. As we have discussed in our previous work, when (i) transmission is modeled to increase linearly with pathogen load, and (ii) the hosts mix homogeneously in a single population, we observe pathogen evolution towards the brink of their own extinction. While both of these modeling assumptions are simplistic and have various shortcomings, it is not obvious initially that this should also create a self-destructive evolutionary trajectory. Acute and rapidly transmitting pathogens are known to be vulnerable to stochastic extinction. Similar phenomena has also been observed previously by Rand et al. (1995), albeit in a spatial individual-based model framework. One interpretation of this result is that modeling transmission to grow linearly with the pathogen load is flawed. There are

likely to be bottlenecks in transmission mechanism that would not allow for such a linear relationship. Additionally, the host biology might now allow for an unbounded growth of parasites, given resource limitation. (Levin and Pimentel, 1981)

Here we have specifically explored pathogens that are avirulent. The course of the infection and the clearance were modeled using a within-host model. Literature on evolution of pathogen virulence have primarily focused on the physiological trade-off between transmission and virulence (Anderson and May, 1991; Frank, 1996), including the role of within-host dynamics in such trade-off (Antia et al., 1994; Gilchrist and Coombs, 2006; André et al., 2003; Alizon and van Baalen, 2005). But the invasion-persistence trade-off can be of consequence for virulent pathogens as well. First, virulence factors will affect the course of infection in a host, depending how the virulence itself is modeled. A common approach is to let virulence increase with pathogen load, in which case, pathogens that increase their acuteness beyond a certain level will face diminishing returns due to increasing death risk it poses to the host. This will result in pathogens with intermediate growth rate and virulence to maximize R_0, similar to the saturating transmission model. Pathogens should evolve to such optimal virulence in a single patch setting provided the size of the patch is large enough. But in a meta-population context, where the local patches are small enough to pose extinction risk to the pathogen, rescue effect will play a significant role, in the same way it does for avirulent pathogens. Faced with evolutionary pressure arising at the meta-population level, virulent pathogen can evolve to low acuteness and virulence in such meta-populations.

We have managed to show evolutionary pressures acting different levels can be in conflict. While there is a clear domination of between-host selection for large patches, and between-patch selection for large number of small patches, it remains

a challenge to resolve this conflict for anything in between. How might the balance of evolutionary pressures change as the population is changing in structure? Our simulations suggest that as patch size increases, so does the frequency of between-host transmission. This in turn increases the force of selection acting at this scale favoring more acute pathogens. But once pathogens are acute enough so that local extinctions are frequent, the role of rescue effect becomes more critical. Interestingly the pathogens that survive from the rescue effect tend to be the ones that are more persistent. These more persistent pathogens are better colonizer, since they produce larger epidemics, primarily due to their ability to persist longer in the host. So if there are large number of patches that are open for colonization, this increases the frequency of colonization events and selection at the patch level. To address this issue in detail, one will need to work on a modeling framework that accounts for dynamics and evolution at both levels. In chapter IV, we take a modeling approach towards this end. By exploring epidemic dynamics in a meta-population, and competition dynamics within a patch, we further show the role of meta-population parameters in determining the balance of competition and colonization events, which then affect the evolutionarily stable traits.

Finally, we will return to *Bordetellae* infections, the original motivation for this project. The independent emergence of two acute strains of *Bordetellae*, *B. pertussis* and *B. parapertusis* in humans from relatively less acute but persistent *B. bronchiseptica*, only common in mammals raised the question of the role of host structure in their divergent evolutionary paths (Bjørnstad and Harvill, 2005). In our previous work, we laid the framework that illustrates the functioning of "invasion persistence" trade-off within a single well mixed population. Here, in a meta-population context, the extinction dynamics coupled with colonization, allows for selection of different

pathogen traits depending on the population structure. A strain circulating in an animal host is likely to evolve persistent characteristics due to the inherently patchy structure. A well mixed human population can provide fertile grounds for pathogen to forgo traits of persistence and maximize fitness by proliferating rapidly within a host and then transmit rapidly across the population.

CHAPTER IV

Epidemic and evolutionary dynamics in meta-populations

4.1 Introduction

The epidemic dynamics of acute, rapidly transmitting infections that impart long lasting immunity typically exhibit strong cyclical behavior — high and steep epidemic peaks followed by deep troughs. Empirical data for the well studied measles dynamics in the pre-vaccination era in the UK provides a classic example (Grenfell and Harwood, 1997; Bolker and Grenfell, 1995). There can be a number of reasons for this periodicity, such as the seasonal trends in factors that affect transmission or more complex interaction between stochasticity and spatial aspect of the disease transmission, but the basis of it can be understood in terms of the basic processes inherent in such epidemic dynamics — the infection and the recovery processes. Initially, the infection rapidly spreads through the population that primarily constitutes of susceptibles. The infected hosts soon recover from the infection and in the process gain immunity. As a result the epidemic process slows down considerably due to lack of susceptibles. If birth and migration rates (the processes that replenish the susceptibles) are relatively low, the depletion of susceptibles can result in an abrupt end to what would otherwise be a continuation of cyclical epidemic patterns. This fade out, or local extinction behavior has been documented and well studied for

measles (Bartlett, 1956a, 1957; Keeling and Grenfell, 1997), and is also of relevance to whooping cough.

What are the implications of such extinction dynamics for evolution of pathogen life history? Chapter II of this thesis explored this question in the context of a single homogeneously mixing host population. The key insight was that mechanistic within-host dynamics can lead to selection of pathogens that are not only more acute but also more extinction prone. Given the size of the host population, acute and highly transmissive strains generally spread across a host population faster than milder but more persistent ones, but they risk of going extinct in the population. This invasion-persistence trade-off (Grenfell, 2001) can result in evolution of intermediate acuteness in strains, depending on the size of the host population as well as the nature of the transmission.

In smaller host populations, particularly if they are below the critical community size (Bartlett, 1956a, 1957; Keeling and Grenfell, 1997; Nåsell, 2005), epidemic patterns of such infections that are prone to local extinction can be episodic (Grenfell and Harwood, 1997; Bjørnstad and Grenfell, 2008). Epidemics deplete the susceptibles in the local community driving the pathogen to local extinction, only to be reignited later by a pathogen existing elsewhere in the host meta-population via the rescue-effect (Earn et al., 1998; Grenfell, 2001). To truly assess the evolutionary consequences of these local extinction risk, one would have to account for rescue-effects that emerge at the meta-population level. It is then relevant to ask how the invasion-persistence trade-off manifests in a meta-population context.

In this regard there are two major insights that serve as motivation for the modeling choices in this chapter. The first insight comes from work by Keeling (2000). The author models competition between two strains, characterized by their difference in

R_0 and local extinction risk, in a meta-population with infinitely many patches. By explicitly separating the time scales of within-patch and between-patch interactions, and exploring the evolution of distribution of the mixture of the two strains, he finds that coupling of the patches and the stochasticity in the model are key factors in determining the evolutionarily stable strains. In particular, high patch coupling and/or low stochasticity favors a more acute strain, and the converse scenario favors a more persistent strain. The simulation based study of patchy host population in chapter III provides additional insights on the evolutionary forces at play in a meta-population with frequent local extinctions. Pathogen are selected not only based on their R_0 (how well they perform within a patch of hosts), but also based on how well they colonize patches. Our results show that there is an inherent conflict of evolutionary pressures, one that arises at the patch level to maximize between host transmission, and one at the meta-population level that maximizes the between-patch circulation. Hence the optimal pathogen characteristics are contingent upon the host-population structure, patch size and migration rate.

The goal of this chapter is to understand the evolutionary implications for pathogens that face extinction risk in their local host community, but benefit from the rescue effects that emerge due to the meta-population dynamics. In contrast to Keeling (2000), we consider a host meta-population where the local patches are well below the critical community size. Local epidemics always end with local extinction of the pathogen, but the size and the duration of the epidemics, as well as the interval between two epidemics, inter-epidemic period (or the fade-out length) are modeled to vary with the host demographic rates, the structure of the meta-population and with the strain traits. Meta-population models for disease in this regard (Grenfell and Harwood, 1997; Keeling et al., 2004) have built on ecological meta-population

models (Levins and Culver, 1971; Hanski and Gilpin, 1991). We adapt a slight variant of the widely used Levins-type model (Levins and Culver, 1971). In section 4.2, we describe the meta-population model and the disease dynamics in this setting.

In order to be able to ask questions regarding pathogen evolution, we will need to integrate models of competition between pathogen strains within the meta-population framework. We present two models, one that examines the invasion dynamics in the standard way, and an alternative model for pathogen competition. These are described in section 4.3. We extend these models of competition to find evolutionarily stable or optimal pathogen traits, and examine the effect of change in population structure on these traits.

Finally, we examine the effects of the host structure and demographics on pathogen evolution. To do this, we adapt this general framework in the context of simplified SIR model, as described in section 4.4. We find that the structure of the meta-population, the migration rate of hosts and the size of the patch will influence the invasion dynamics and the competition among strains for susceptibles within a local patch and globally in the meta-population. Evolutionarily stable, and optimal pathogen traits change as these meta-populations change in structure. In particular, meta-population with higher migration rates favor more transmissive strains. As the host interactions become more localized, strains that are less transmissive but more persistent are selected. The model for pathogen competition illustrates how pathogen's ability to compete for susceptibles within a patch, and its ability to colonize patches can favor different pathogen traits, resulting in conflicting evolutionary pressures that arise at two levels. The optimal strain finds a balance of different traits, and this balance is dependent on the structure of the meta-population.

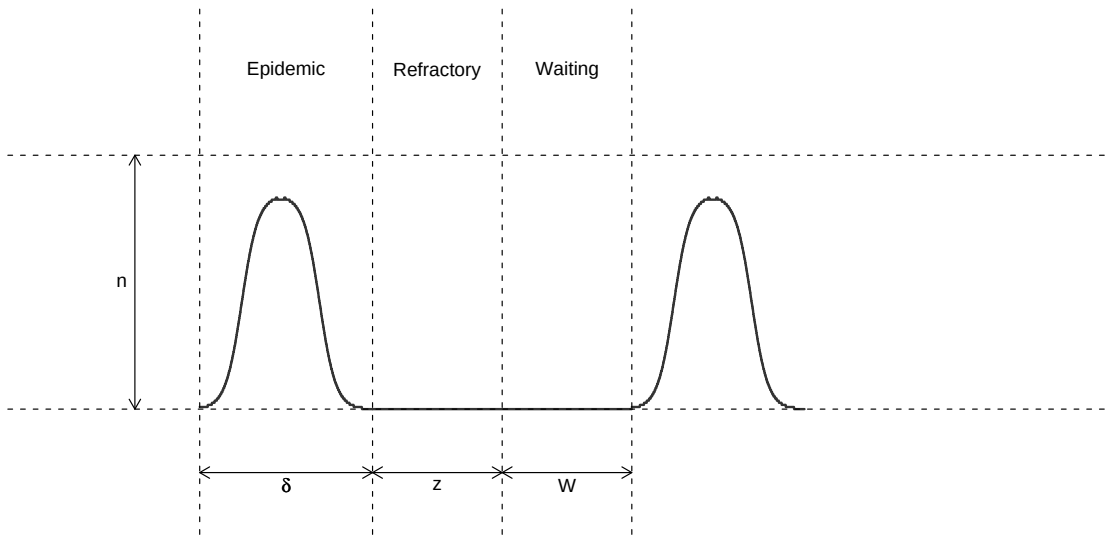

Figure 4.1: The Epidemic dynamics in a patch within the meta-population. The patch is in an epidemic phase when there are infectious hosts in the patch. This phase lasts for duration δ. All of the infectious hosts eventually recover, and the patch enters a refractory phase, which lasts for duration z. Once the patch is replenished with susceptibles, it is "susceptible" to new epidemics. It enters a waiting phase which lasts for duration W.

4.2 Meta-population Model

We consider a host meta-population that is a collection of infinitely many small and equally sized patches (local host communities), each of size n. This in similar to Levins-type meta-population model (Levins and Culver, 1971), except we do not explicitly keep track of the number of the patches. All of the host's interactions are restricted to hosts within its own patch, but the patches interact with each other through movement of individual hosts. We assume that this host migration rate, m, is constant throughout the meta-population. An individual host that is moving out of a patch is equally likely to land in any patch.

Now, consider that there is an infection prevalent in the meta-population. Each patch is going through different phases of epidemic dynamics. The epidemic dynamics we consider are caricatures of episodic epidemics observed in a meta-population

of small local communities where the disease goes locally extinct after an epidemic. The epidemic starts with a single infected host, and spreads through the population in the patch. The infection lasts for a certain duration in each infected host, and eventually each one of them recovers. This epidemic phase lasts for a duration of Δ. Once the epidemic phase is over, the patch remains in a refractory phase, where the recovered hosts one-by-one become susceptible to the infection. If the infection is fully immunizing, this phase will last until there are enough new born susceptibles in the patch. If the immunity from the infection wanes, this phase will also depend on the duration of immunity. Let us assume that this phase lasts for duration Z. Once sufficiently many of these hosts are susceptible, we will assume that it will enter a waiting phase. The patch is susceptible to new epidemic, and is waiting for an infected host (from a different patch) to migrate into the patch and start an epidemic. We will assume that this waiting time W is a random variable distributed exponentially with parameter λ, i.e, $W \sim \exp(\lambda)$. Once the epidemic starts, the patch cycles through all the phases.

The final size of an epidemic and its duration in a stochastic setting will have variability. Typically, these distributions tend to be bimodal — the epidemic either fizzles before taking off, or it takes off and follows a fairly deterministic course. With this in mind, we simplify the epidemic process by considering only these two extremes. The epidemic either takes off with probability ϵ, in which case they will last for a fixed duration $\Delta = \delta$, otherwise, we assume that there is no epidemic. The length of epidemic, δ, though, depends both on the patch size, n, and on the characteristics of the infection, the later of the two is expected to have direct evolutionary consequences. So, we focus on the variability of the epidemic durations (and sizes) arising from difference in pathogen traits. We approximate δ for different

patch sizes and pathogen strains using a simplified SIR model in subsection 4.4.2. The refractory period is assumed to fixed at $Z = z$, and is taken to be independent of pathogen strain — we revisit the implication of this assumption in the conclusion of this chapter.

As long as $\lambda > 0$, a patch moves through a chain of phases, epidemic(P_E), refractory(P_R) and waiting(P_W), with waiting times Δ, Z, and W, in each phase respectively. This process can be thought of a Markov chain in continuous time and with finite states P_E, P_R, and P_W. The probability that the patch will be in given a state in near future will only depend on which state it is now, regardless of where it has been in the past. Furthermore, since it always possible for a patch in any phase to get to any other phase, this is an irreducible chain that will attain a stationary state. In this stationary state, the probability of the patch being in any particular phase is the average waiting time in that phase as a fraction of sum of average waiting times in all phases. Hence,

$$\mathbb{P}(P_E) = \frac{\mathbb{E}(\Delta)}{S} = \frac{\delta}{S}; \qquad \mathbb{P}(P_R) = \frac{\mathbb{E}(Z)}{S} = \frac{z}{S}; \text{and} \qquad \mathbb{P}(P_W) = \frac{\mathbb{E}(W)}{S} = \frac{\frac{1}{\lambda}}{S},$$

where $S = \delta + z + \frac{1}{\lambda}$. We will call λ to be the force of epidemic, since the waiting time for a susceptible patch to start the epidemic is dictated by this parameter. If this force of epidemic is high, the patch is likely to cycle through more quickly, and if it is low, the patch is likely to be waiting phase for longer.

We imagine that what we observe in a single patch is representative of any other patch. In particular, we assume the epidemic dynamics in a given patch is independent of what is happening in another patch, i.e. epidemics between patches are asynchronous. One scenario under which this assumption will fail is if the migration rate is very high, or if there are too few patches. In such a scenario the dynamics of the patches will likely synchronize, and hence the force of epidemic is likely

to fluctuate in time with epidemic dynamics (Bjørnstad et al., 1999; Bjørnstad and Bolker, 2000). A careful thought should be given to understand the conditions for synchronization of patch dynamics, but will be beyond the scope of this endeavor. Our model operates under the assumptions that there are infinitely many patches and the migration rate is small enough such that patch level epidemic dynamics are asynchronous. Under these assumptions, the force of epidemic prevalent in the meta-population, λ, should be constant during the stationary state of this patch dynamics. This force of epidemic, though, should be in fact be generated by the epidemic dynamics of the patches themselves. This will give a self-consistency requirement for λ. In particular, if m is the migration rate of individual hosts, ϵ is the probability that a single migrant sparks an epidemic, and A_e is the area under the epidemic curve, then,

$$\lambda = \overbrace{m}^{\substack{\text{migration}\\ \text{rate}}} \cdot \overbrace{\epsilon}^{\substack{\text{prob. epidemic}\\ \text{is sparked}}} \cdot \overbrace{\frac{\delta}{\delta + z + \frac{1}{\lambda}}}^{\mathbb{P}(P_E)} \cdot \overbrace{\frac{A_e}{\delta}}^{\substack{\text{avg. height}\\ \text{of epidemic}}} = \frac{m\,\epsilon\,A_e}{\delta + z + \frac{1}{\lambda}}. \tag{4.1}$$

And, by satisfying this self consistency condition, we get $\lambda = \dfrac{m\,\epsilon\,A_e - 1}{\delta + z}$.

Since $\lambda > 0$, we must have $m\,\epsilon\,A_e > 1$. Ecologically this makes sense – the patch level epidemic dynamics (cycling through the three phases) can only persist if m, ϵ and A_e are large enough such that on average an epidemic can result in another epidemic at some other patch. This general framework is adapted in the context of simplified SIR model in subsection 4.4.2.

4.3 Models of pathogen competition and invasion dynamics

Given the disease dynamics in the meta-population model we introduced, we are interested in understanding the nature of competition between pathogen strains, and ultimately what evolutionarily optimal pathogen traits are likely to be. In this

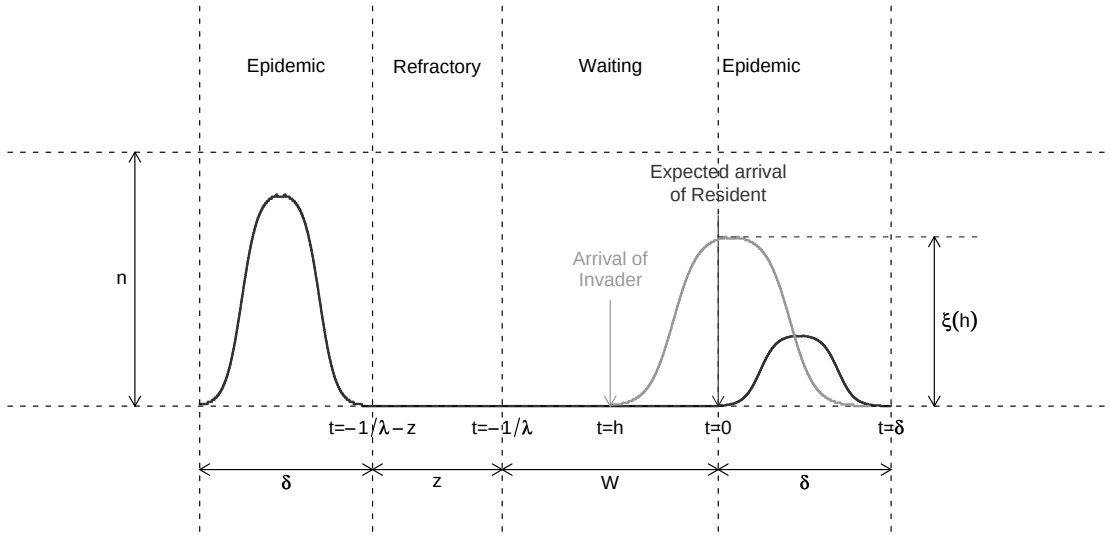

Figure 4.2: Invasion dynamics in the patch model. The expected arrival of the resident is time $t = 0$. The invader arrives at time $t = h$. Depending on h, it recruits/infects $\xi(h)$ susceptibles.

section, we will introduce two different approaches to this. In subsection 4.3.1, we develop a model of invasion dynamics. The meta-population is considered to be in a steady state with a resident strain, and we ask whether an invading strain introduced in a patch will be able to generate a force of epidemic that will result in successful colonization of new patches. In subsection 4.3.2, we will introduce a different model for competition. Here we consider a fragmented meta-population, where two different strains are simultaneously present, but in different habitats. We ask which of the two strains is more likely to capture a new susceptible patch.

4.3.1 Model for invasion dynamics

Consider a meta-population, that is characterized by {patch size, n; migration rate of individual hosts between patches, m; and host demographics that results in refractory period of length z}. Typical setting for invasion analysis is to assume that the meta-population is inhabited by a resident strain, R, and the epidemic dynamics

has reached a steady state. From the steady state distribution, it is possible to infer the probability of this patch being in a given phase – epidemic, refractory or waiting (and the average duration of each phase).

Suppose that a pathogen of an invader strain I is introduced into this meta-population. The success of this pathogen is determined by (i) its ability to recruit susceptibles within patch; and (ii) its ability then to generate epidemics at other patches. Within a patch, the competition between the two strains is for susceptibles and is likely to depend on a variety of factors: the strain characteristics, the size of the patch, but also on the timing of the arrival of each strain. We know that the average duration of waiting period in the meta-population is $1/\lambda$, λ being the force of epidemic in the meta-population. Let $t = 0$, be the time when the resident strain starts the epidemic, which lasts for δ. The resident would have waited for $1/\lambda$ from the end of the refractory period, which lasted for z. Hence, an epidemic cycle can be taken to be from $t = -z - 1/\lambda$ to $t = \delta$, for the total duration of $z + 1/\lambda + \delta$. The invader I is equally likely to have arrived at any time during the epidemic cycle. So the arrival time of I, H is uniformly distributed in the interval $[-z - 1/\lambda, \delta]$. So, the probability that arrival of the invader strain occurs at time $t < h$, or the cumulative distribution function of invader arrival times is:

$$F_h = \mathbb{P}(H < h) = \frac{h + z + 1/\lambda}{z + 1/\lambda + \delta}, \tag{4.2}$$

$$\text{and the respective density function, } f_h = \frac{1}{z + 1/\lambda + \delta}.$$

Let us now suppose that $\xi_I(h)$ is the number of susceptibles infected by strain I if it arrives at time h. Then, the average number of susceptibles captured by this invader during the course of the epidemic is:

$$\omega = f_h \int_{-\frac{1}{\lambda}}^{\delta} \xi_I(h) \mathrm{d}h. \tag{4.3}$$

Note that the integral only starts from $-1/\lambda$ since there is no chance of sparking an epidemic when the patch is in refractory period.

Ultimately, we are interested in whether this invader that was introduced into the patch will be able to sustain in the meta-population by being able to spark an epidemic in a new patch. A host that has been infected by this new strain has to migrate while it is infectious and successfully spark an epidemic. Hence, the number of new patches this invader will capture will be (or the number of new epidemic sparked):

$$\zeta(I, R) = m\,\epsilon\,\omega\,\frac{1}{\gamma_I}, \tag{4.4}$$

where, m is the migration rate, ϵ is the probability that this single migrant will successfully start an epidemic, and $1/\gamma_I$ is the duration of the infection caused by this new strain. Apart from being a function of the traits of two strains, ζ is also dependent on the host demographics rates, and the meta-population parameters. Also note that since the epidemic dynamics is in a steady state for the resident strain – an epidemic of the resident strain on average produces exactly one new epidemic. This implies that if $\zeta(I, R) > 1$, then the invader I can successfully invade into the meta-population currently inhabited by R.

4.3.2 Model for strain competition

Here, we introduce a slightly different model of strain competition. Let us consider a scenario where two strains X and Y both simultaneously exist in the meta-population. It is unclear what the dynamics of disease is likely to be in such a meta-population, since the epidemic dynamics of each of the strains could possibly be interacting with each other. Regardless, we will assume here that both of the strains have reached their respective steady states. Hence, the force of epidemic that

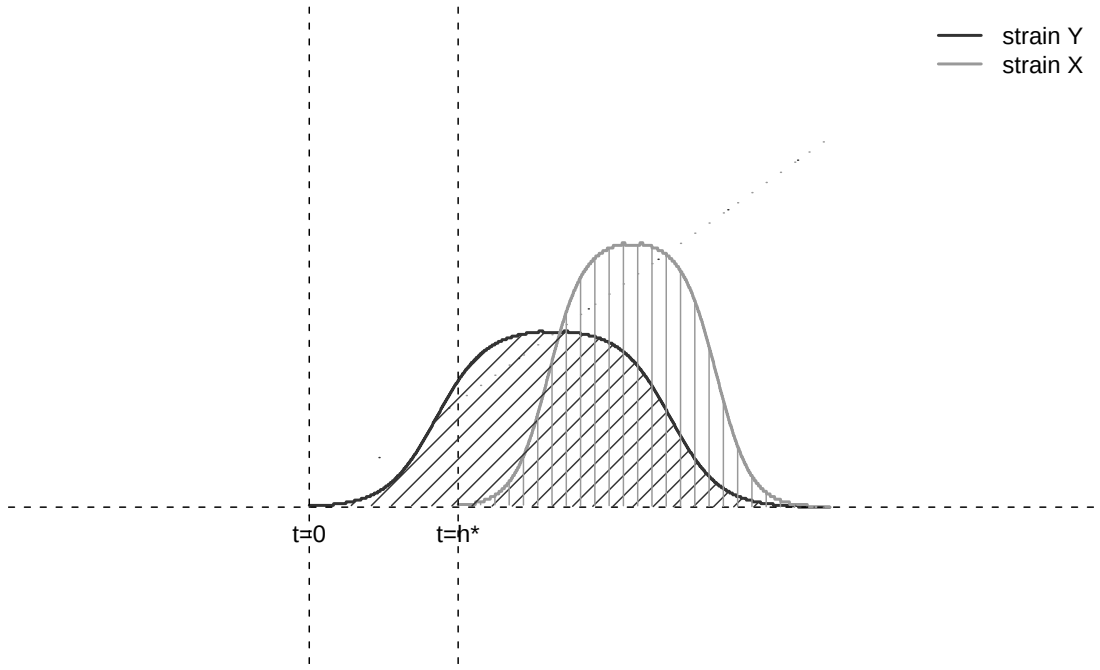

Figure 4.3: If strain X enters the patch h^* after Y, then the infected-time generated by X (the shaded area underneath epidemic curve for strain X) is equal to that generated by Y (the shaded area underneath epidemic curve for strain Y). If X arrives before h^*, then it will generate larger infected-time, and take over the patch. Otherwise, Y will keep the patch.

each strain generates is given by λ_X and λ_Y, respectively.

Suppose that a patch has just recently become susceptible, and we are interested in knowing which one of the two strains is more likely to take this patch. The number of susceptibles X and Y will recruit, as discussed previous section, will depend on their infection characteristics, the size of the patch, and the timing of their arrival. Here, the waiting time for arrival of both of the strains are exponentially distributed with rate given by their respective forces of epidemic. So, the waiting time for arrival of X, $W_X \sim \exp(\lambda_X)$, and the waiting time for arrival of Y, $W_Y \sim \exp(\lambda_Y)$.

Let us suppose that X arrives h time units after Y, and consequently X captures $\xi_X(h)$ susceptibles, and Y captures $\xi_Y(h)$ susceptibles. Let us further suppose that the average duration of infections of X and Y are $1/\gamma_X$ and $1/\gamma_Y$, respectively. The product of the number of infecteds with a strain and the average duration of the infection, infected-time, is $\frac{\xi_X(h)}{\gamma_X}$ for X and $\frac{\xi_Y(h)}{\gamma_Y}$ for Y. Further, let us suppose that there is a unique $h^*(X,Y)$, such that $\frac{\xi_X(h)}{\gamma_X} = \frac{\xi_Y(h)}{\gamma_Y}$, i.e. they both generate equal infected-time.(See Fig. 4.3 for illustration) Note that if strain X needs to arrive $h^*(X,Y)$ after Y for both to generate equal infected-time, then equivalently, Y need to arrive $h^*(X,Y)$ before X. So, $h^*(Y,X) = -h^*(X,Y)$. Now, if X arrives earlier than $h^*(X,Y)$ time units before Y does then X will generate larger infected-time. In such a case, we will say that X will take over the patch, otherwise Y will. The probability that this will happen, $\mathbb{P}(W_X < W_Y + h^*)$, is:

$$\begin{aligned}
\mathbb{P}(W_X < W_Y + h^*) &= \int_0^\infty \mathbb{P}(W_X < w_Y + h^* | W_Y = w_Y)\, \mathbb{P}(W_Y = w_Y) \mathrm{d}w_Y \\
&= \int_0^\infty (1 - e^{-(w_Y + h^*)\,\lambda_X})\, \lambda_Y\, e^{-w_Y\,\lambda_Y} \mathrm{d}w_Y \qquad (4.5) \\
&= \frac{\lambda_X + \lambda_Y\,(1 - e^{-h^*\,\lambda_X})}{\lambda_X + \lambda_Y}.
\end{aligned}$$

We will denote this criterion,

$$\mathcal{C}(X,Y) = \frac{\lambda_X + \lambda_Y\,(1 - e^{-h^*\,\lambda_X})}{\lambda_X + \lambda_Y}.$$

If both strains are identical to each other ($X = Y$), they can only generate equal infected-times, if they both arrive at the same time. Hence, $h^*(X,Y) = 0$. Similarly, their forces of epidemic are identical, i.e. $\lambda_X = \lambda_Y$. So, $\mathcal{C}(X,Y) = 1/2$. As expected, X and Y are equally likely to take the patch.

We will use the edge of the above criterion, $\mathcal{C}(X,Y) = \frac{1}{2}$, to derive the following condition:

$$-h^*(X,Y) = \frac{1}{\lambda_X}\,\log\frac{\lambda_X + \lambda_Y}{2\,\lambda_Y}. \tag{4.6}$$

Consider a pair of strains $X \neq Y$ that satisfy this condition. It is not clear a priori that for any strain Y, there will necessarily be a strain X satisfying this condition. But regardless, if we expect it to be fulfilled, this condition, interestingly relates the fitnesses at two levels. If strain X has a time advantage of $h^*(X,Y)$ over Y while competing for susceptibles within a patch, Y must compensate by generating additional force of epidemic at the meta-population level by the quantity given by the right hand side of the above equation. Conversely, if $h^*(X,Y) > 0$, then the above condition can only be satisfied if $\lambda_X < \lambda_Y$. So, this condition is only applicable if the fitnesses at the two levels are acting in the opposite directions. We shall see in subsequent section that such a scenario is indeed plausible.

4.3.3 Evolutionary stability and optimality condition

We have described two different models for comparing pathogen in a pairwise manner. The model of invasion dynamics gave us a criterion for determining whether an invader strain can successfully invade a meta-population inhabited by a resident

strain. This model is amenable to the standard evolutionary stability analysis. The standard notion of evolutionary stability relies on examining whether a new trait introduced in a small proportion in a population with a resident trait, will fare better than the resident trait. If no new traits can do better, then the existent trait is evolutionarily stable (Hofbauer and Sigmund, 1998). We will adapt this idea in this context and call a strain R to be evolutionarily stable if:

$$\zeta(I, R) < \zeta(R, R) \text{ for all } I \neq R. \tag{4.7}$$

Recall that $\zeta(I, R)$ is number of epidemics sparked by strain I on average, when introduced into a meta-population with already resident strain, R. So the above condition is equivalent to saying that a strain R is evolutionarily stable if it produces on average the largest number of epidemics (compared to any other strains) when introduced in the meta-population of itself.

The model of competition examined a different scenario. Here the pathogen are assumed to be at their respective steady states, and competing for a susceptible patch. If the criterion $\mathcal{C}(X, Y) > \frac{1}{2}$ is satisfied then strain X will out-compete Y at recruiting a new patch. We can extend this idea by asking which strain is optimal at competing for patches. We begin with the condition given by equation (4.6). Let us consider a competition between strain s and a slightly variant strain $s + \Delta s$. Then, $-h^*(s, s + \Delta s)$ is the time advantage the variant $s + \Delta s$ will have over s, since $-h^*(s, s + \Delta s) = h^*(s + \Delta s, s)$. Consequently, $s + \Delta s$ will face a reduction in its force of epidemic $\lambda_{s+\Delta s}$. And, for $s + \Delta s$ to be as likely as s to take the patch, $\frac{1}{\lambda_{s+\Delta s}} \log \frac{\lambda_s + \lambda_{s+\Delta s}}{2\lambda_s}$ should be equal to the time advantage, $-h^*(s, s + \Delta s)$. Then for a strain $s = s_{OPT}$ that is locally optimal, the marginal gain in terms of the time advantage should be negated by the marginal loss in the force of infection, such that it there is no change in the its ability to compete for a patch. Dividing both sides

by Δs and taking the limit as $\Delta s \to 0$, we arrive to the following condition:

$$\lim_{\Delta s \to 0} -\frac{h^*(s, s+\Delta s)}{\Delta s} = \lim_{\Delta s \to 0} \frac{\frac{1}{\lambda_{s+\Delta s}} \log \frac{\lambda_s + \lambda_{s+\Delta s}}{2\lambda_s}}{\Delta s}. \tag{4.8}$$

We will call strain s_{OPT}, evolutionarily optimal, and is different from evolutionarily stable strain described earlier. Implicit in the construction of the above condition is an assumption that a strain and its close variant have similar traits. So in particular, the surfaces of $h*$ and λ are required to be continuous and differentiable.

4.4 Evolutionary dynamics in a SIR setting

The framework we have developed in the previous sections is fairly general, and purposely so. We have not made any assumptions regarding the details of the epidemic process. The meta-population model only requires that the patch epidemic is ignited by an infected migrant, and always ends after a certain duration. Similarly, the competition model assumes that for a pair of strains, we can characterize the within-patch fitness differential in terms of h^* – the time advantage the one strain has over the other. Given an epidemic process, we can compare the epidemic size of each strains when both compete for susceptibles in the same patch, and consequently find the advantage in terms of time, one has over the other. In this section, we will apply the model we developed for patches where the epidemic process follows the standard SIR dynamics. SIR dynamics are relatively simple, they are well studied and have been successfully used for several disease models. This makes it a suitable beginning point for exploring the evolutionary dynamics.

A standard SIR model tracks hosts in different compartments depending on their infection status. Susceptibles (S) become infected (I) at a rate proportional to the rate at which they mix. Each infected recovers from the infection, the average duration of the infection being L. These hosts are then tracked in the recovered (R)

compartment. To simplify the ensuing dynamics, we will make a few assumptions. The first one is to ignore host birth and death processes while looking at the patch epidemic. There are a few reasons for this. First, in a deterministic setting, SIR epidemic with birth and death produce periodic dynamics, and the epidemics can reach to very small numbers, but never end. So the notion of size and the duration of the epidemic has to rely on arbitrary cut-off. Second, we imagine the infection and recovery processes to be relatively faster than the demographic turnover rates. So, in relatively small patches in particular, the duration and the size of the epidemic might not be drastically affected by these demographic rates. Third, from a view point of the pathogen competition and evolution the host demographic rates are exogenous, something they have no bearing over. So the effect of the demographic rates can be observed by adjusting relevant parameters, after the evolutionary conditions have been derived.

The second assumption is to assume that infection and recovery processes can be separated. If the patches are relatively small and the infections spread fairly quickly – basically infecting all of the hosts, before the recovery process sets in, then separating the two processes will give a fair approximation of the epidemic. As a result, the problem simplifies enormously allowing for analytical results – something we are striving for. We will discuss the shortcomings, possible repercussions of some of these assumptions in the conclusion section.

In subsection 4.4.1, we describe how competition for susceptibles within a patch unfolds for two competing strains. This will include derivations of quantities $\xi(h)$, and h^* that were used to describe invasion and competition dynamics. The parameters for the meta-population model are estimated in subsection 4.4.2. And finally, we discuss evolutionarily stable and optimal strain characteristics in subsection 4.4.3.

4.4.1 Within-patch competition

Competition between strains in SI setting

Consider a virgin epidemic of a resident pathogen strain at a patch. Suppose that a virgin epidemic with a resident pathogen with transmission rate β is in progress at a patch with size $n+1$. At time, h an invasive strain migrates into the patch. We begin with a simple scenario where only transmission event are allowed. Recovery process is introduced later on. We will divide the epidemic into two phases – the first phase with only the resident strain, and the second phase with both strains. We begin by examining the epidemic in the first phase. If S is the number of susceptibles and I_r is the number of infecteds due to the resident strains, the equation below describes this scenario.

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta\, S\, I_r. \tag{4.9}$$

Since, $I_r = n + 1 - S$, and by letting $\tau = \beta\, t$ in (4.9), we get,

$$\frac{\mathrm{d}S}{\mathrm{d}\tau} = -S\, I_r = S\,(n + 1 - S), \tag{4.10}$$

with the initial condition $S(0) = n$, and $I_r(0) = 1$. The solution to (4.10) is $S(\tau) = \dfrac{n\,(n+1)}{n + e^{(n+1)\,\tau}}$. Consequently, the number of susceptibles recruited by the resident strain, $I_r(\tau) = n + 1 - S(\tau)$. (Bailey, 1964)

The second phase of the epidemic succeeds the first phase. It begins with introduction of a single infected host by a new invasive strain. The invasive strain is characterized by a different transmission rate, which we'll suppose to be $k\,\beta$. The number of susceptibles at the onset of this phase is equal to the susceptibles remaining at the end of the first phase. Similarly, the number of infected by the resident strain initially is equal to the number of hosts recruited by the resident strains by the end of the first phase. If we denote the number of infected hosts by this invasive

strain by I_i, and let the time it takes for the first phase to end be h, then this new system with both the resident and the invading strains will be as follows:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}\tau} &= -S\,I_r - k\,S\,I_i \\ \frac{\mathrm{d}I_r}{\mathrm{d}\tau} &= S\,I_r \\ \frac{\mathrm{d}I_i}{\mathrm{d}\tau} &= k\,S\,I_i, \end{aligned} \tag{4.11}$$

$$\text{with initial condition, } \{S_0 = S(h), I_0 = I_r(h), I_i = 1\}.$$

The set of equations (4.11) does not yield a solution directly, but it can be further simplified to get some useful results. First, we can equate I_i in terms of I_r.

$$\text{Since, } \frac{\mathrm{d}I_i}{\mathrm{d}I_r} = k\,\frac{I_i}{I_r}, \qquad I_i = c\,I_r^k, \text{ where } c = I_0^{-k}.$$

Furthermore, $S = n + 2 - I_r - I_i$, so we get,

$$\frac{\mathrm{d}I_r}{\mathrm{d}\tau} = I_r\,S = I_r\,(n + 2 - I_r - I_i) = I_r\,(n + 2 - I_r - \frac{I_r^k}{I_0^k}), \tag{4.12}$$

$$\text{where, } I_0 = I_r(h) = n + 1 - \frac{n\,(n+1)}{n + e^{(n+1)\,h}}.$$

Derivation of $\xi(h)$

Since transmission is the only process in this system, we expect the system to settle to the point where there are no susceptibles remaining. The population is divided between the hosts recruited by the resident strain and the hosts recruited by the invading strain. Let ξ_r and ξ_i be the number of susceptibles recruited by resident R, and invader, I, respectively. At such a fixed point, we expect $\frac{\mathrm{d}I_r}{\mathrm{d}\tau} = 0$. Hence,

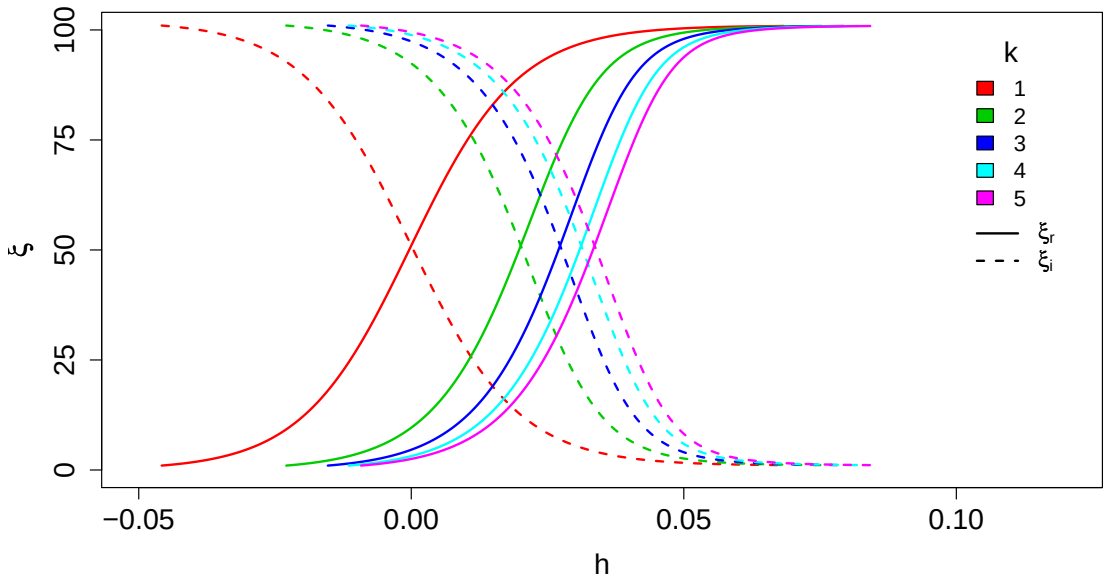

Figure 4.4: Illustration of ξ. In the vertical axis, we plot the number of susceptibles recruited by resident, ξ_r (in solid lines), and the number of susceptibles recruited by invader, ξ_i (in dashed lines), when the invader arrives h (in the horizontal axis) units after the resident. Colors distinguish the different types of invaders, where $k = \beta_i/\beta_r$. $n = 100$, and $\beta_r = 1$. The number of susceptibles recruited by the invader in given patch (with size n), depends on its relative transmission rate, k, and its arrival time compared to the resident, h.

from equation (4.12), we have:

$$n + 2 - I_r - \frac{I_r^k}{I_0^k} = 0, \qquad \text{where, } I_0 = n + 1 - \frac{n\,(n+1)}{n + e^{(n+1)\,h}}.$$

(4.13) $I_r = \xi_r$, and $I_i = n + 2 - I_r = \xi_i$ when the system has settled.

$$\text{So, } h(\xi_r) = \frac{1}{\beta}\left[\frac{1}{n+1}\,\log\frac{n\,\xi_r\,(n+2-\xi_r)^{\frac{-1}{k}}}{(n+1) - \xi_r\,(n+2-\xi_r)^{\frac{-1}{k}}}\right].$$

Note that in the original parametrization of time, we had scaled time by setting $\tau = t\,\beta$. Hence, there is an extra factor of $\frac{1}{\beta}$ in the calculation of h. So, if the resident, R were to recruit ξ_r susceptibles, and invader I were to recruit the remaining $n+2-\xi_r$ susceptibles by the end of the epidemic, then, the arrival time of the invader, h, is given by the above equation. Furthermore, h is a monotonic function in the interval $\xi_r \in [1, n+1]$. So the inverse of this function, $h^{-1}(\xi_r)$ exist, although it is not possible to write in a closed form for all k. This inverse function will give the number of susceptibles captured by R, i.e. $\xi_r(h) = h^{-1}(\xi_r)$. Consequently, the number of susceptibles recruited by invader arriving h time units after the resident, $\xi_i(h)$, is given by the equation below:

(4.14) $$\xi_i(h) = n + 2 - h^{-1}.$$

Fig. 4.4 shows ξ curves for a range of different invaders. As expected, an invader captures more susceptibles the earlier it arrives (smaller h), leaving less for the resident. So, ξ_i is large for small h and decreases as h increases, and the trend is opposite for ξ_r. The ξ-curves shift to the right as k increases: the more transmissive strains can arrive later and still manage to recruit bulk of the susceptibles.

Derivation of h^*

Recall from section 4.3.2 that we defined h^* in a context of a competition between two strains X and Y. Suppose that strain X arrives h time units after Y, and they

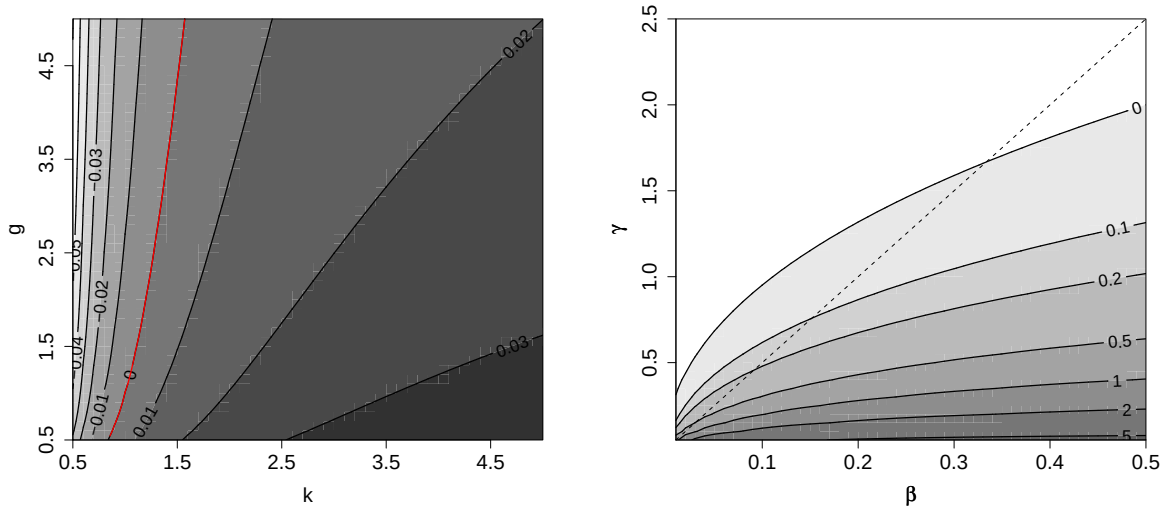

Figure 4.5: Surfaces of h^* and λ. [Left] Surface of h^* as k and g varies. Here, we take $n = 99$, and $\beta = 1$. So, for example point (2,2) gives $h^*(k = 2, g = 2)$ – the time advantage for a strain whose infection is twice as transmissive and last half as long. [Right] Surfaces of λ (force of epidemic) for a range of β and γ. Parameters: $\{n = 100, m = 0.1, z = 10\}$. $\lambda < 0$ in the unshaded region – the meta-population epidemic dynamics cannot persist in this region. In the feasible region, as expected, λ increases as β increases and γ decreases in general. The dotted line is R_0-invariant (β/γ is constant).

each recruit $\xi_X(h)$ and $\xi_Y(h)$ susceptibles, respectively. If the infections of X and Y on average last $1/\gamma_X$ and $1/\gamma_Y$ time units, respectively, then the infected-time generated by each is $\frac{\xi_X(h)}{\gamma_X}$ and $\frac{\xi_Y(h)}{\gamma_Y}$, respectively. Then, $h = h^*(X, Y)$ is that unique arrival time of X with respect to Y, such that $\frac{\xi_X(h)}{\gamma_X} = \frac{\xi_Y(h)}{\gamma_Y}$, i.e. they both generate equal infected-time.

Let $g = \frac{\gamma_X}{\gamma_Y}$. Then at $h = h^*$, $\xi_Y = \frac{n+2}{1+g}$, and consequently, $\xi_X = n + 2 - \xi_Y = n + 2 - \frac{n+2}{1+g}$. Substituting these in equation (4.13), we get the equation for h^*.

$$h^*(k, g) = \frac{1}{\beta}\left[\frac{1}{n+1}\log\frac{n\left(\frac{n+2}{1+g}\right)\left(n+2-\frac{n+2}{1+g}\right)^{\frac{-1}{k}}}{n+1-\left(\frac{n+2}{1+g}\right)\left(n+2-\frac{n+2}{1+g}\right)^{\frac{-1}{k}}}\right]. \tag{4.15}$$

Note, that we have parametrized h^* in terms of $k = \frac{\beta_X}{\beta_Y}$ and $g = \frac{\gamma_X}{\gamma_Y}$, with $\beta = \beta_Y$. Fig. 4.5[Left] shows the plot of h^* for a range of k and g.

4.4.2 Parameters of the meta-population

Here we estimate size and duration of the epidemic in an SIR setting with the assumptions we laid out earlier. In a SIR model, with no recovery, the expected waiting time for jth infection $\mathbb{E}(t_j) = \dfrac{1}{\beta\, j\,(n-j+1)}$. And, the total expected waiting time is the sum of expected waiting times of each infections, $\dfrac{1}{\beta}\displaystyle\sum_{j=1}^{n} \dfrac{1}{j\,(n-j+1)}$. (See Appendix C.2) The duration of infection is L ($L = 1/\gamma$ if γ is the recovery rate). The epidemic ends when the very last infected recovers, so the duration of the epidemic is the time it takes for the nth host to get infected and additional L to recover. Hence, the average duration of epidemic, δ, for a pathogen characterized by transmission rate β, and recovery rate γ, in a patch of size n is given by the equation below.

$$\delta = \frac{1}{\beta}\sum_{j=1}^{n} \frac{1}{j\,(n-j+1)} + L.$$

The area under this epidemic curve, is simply $n\,L$, since everyone gets infected and each was infectious for period L.

$$\text{So, } A_e = n\,L.$$

The average refractory period, z is going to depend on birth and death processes, loss of immunity if relevant, and possibly also on the size of the patch. (See Appendix C.2) We assume the evolution of the host to be fixed, so the birth and death rates of the host are treated exogenously in the model of pathogen evolution. The loss of immunity can certainly be an evolutionarily sensitive parameter. For now, we ignore evolution along this direction, and fix the refractory period.

Parameter ϵ is the probability that a single migrant sparks an epidemic. We take $\epsilon = \frac{\beta}{\beta+\gamma}$ – this is the probability that transmission occurs before recovery. Fig. 4.5[Right] shows the plot of λ for a range of β and γ.

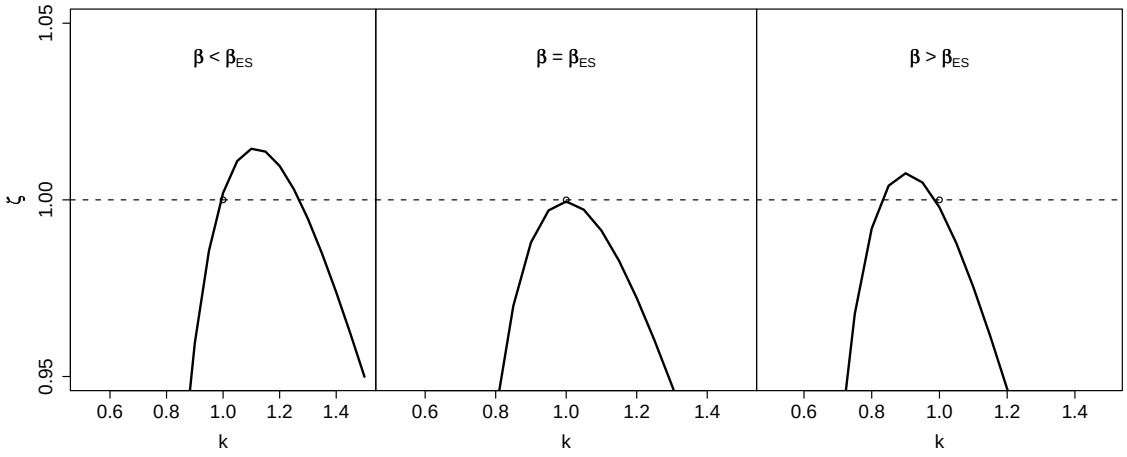

Figure 4.6: Evolutionarily stable pathogen strains. Using the model for invasion dynamics, one can find the evolutionarily stable strain. With the evolutionary constraint $\gamma = \theta\,\beta$, strains can be compared in a linear manner. $k = \beta_i/\beta_r$, so $k = 1.5$ implies an invader that is one and a half time more transmissive. If the strain is less than evolutionarily stable ($\beta < \beta_{ES}$), the strains with larger β will be able to invade it. Similarly, if the strain is more than evolutionarily stable($\beta > \beta_{ES}$), the strains with smaller β will be able to invade it. Evolutionarily stable strain β_{ES} produces the largest ζ when introduced into the meta-population of itself.

4.4.3 Evolutionary stability and optimal strains

The framework we have built allows us to compare strains in a pairwise manner. For the invasion model, as described in subsection 4.3.3, we can exhaustively compare strains to find the evolutionarily stable strain. This is computationally expensive, and results are hard to interpret. Instead we look for evolutionarily stable strain among a specified group of strains. Suppose the strains evolve along the line $\gamma = \theta\,\beta$. This is equivalent to looking at evolution of strains that have the same R_0. Note that $R_0 = n\,\frac{\beta}{\gamma} = \frac{n}{\theta}$ in our setting.

Under a given evolutionary constraint, θ, we will seek for an evolutionarily stable strain, by examining the invasion dynamics between a strain and its close variant. If we let $\beta_i = k\,\beta_r$, and $k = 1$ being the resident, then $\gamma_i = k\,\gamma_r = k\,\theta\,\beta_r$. Then $\zeta(1, k)$ for k around 1, gives the ability of a close variant to invade a meta-population of the currently resident strain. If $\zeta(1, 1) < \zeta(1, k)$ for $k > 1$, then strains that are more

transmissive (and also less persistent) are fitter, and if $\zeta(1,1) < \zeta(1,k)$ for $k < 1$ then the trend is reversed. And for the evolutionarily stable strain with transmission rate β_{ES}, $\zeta(1,k) < \zeta(1,1)$ for all $k \neq 1$. Figure 4.6 illustrates this process of finding this evolutionarily stable strain.

For the competition model, with the same constraint, $\gamma = \theta\,\beta$, we are able to find the optimal strain traits, without having to rely on the exhaustive search. Consider two slightly different strains characterized completely by the difference in β, say, β and $\beta + \Delta\beta$. With this constraint, the force of epidemic will be a function of β. (Also see appendix C.4)

$$\lambda(\beta) = \frac{m\,n - (1+\theta)\,\theta\,\beta}{(1+\theta)\,(1+q\,\theta + z\,\theta\,\beta)}, \qquad \text{where,}$$
$$q = \sum_{j=1}^{n} \frac{1}{j\,(n-j+1)}. \tag{4.16}$$

The condition given by equation (4.8), can be adapted for this scenario.

$$\lim_{\Delta\beta\to 0} -\frac{h^*(n, k = g = \frac{\beta+\Delta\beta}{\beta})}{\Delta\beta} = \lim_{\Delta\beta\to 0} \frac{\frac{1}{\lambda(\beta+\Delta\beta)} \log \frac{\lambda(\beta)+\lambda(\beta+\Delta\beta)}{2\lambda(\beta)}}{\Delta\beta}. \tag{4.17}$$

We find the limits of both sides of the equation (4.17) separately. The details of the calculations are included in appendix C.5. On the right hand side, we find that,

$$\lim_{\Delta\beta\to 0} \frac{\frac{1}{\lambda(\beta+\Delta\beta)} \log \frac{\lambda(\beta)+\lambda(\beta+\Delta\beta)}{2\lambda(\beta)}}{\Delta\beta} = \frac{\mathrm{d}\lambda}{\mathrm{d}\beta} \frac{1}{2\lambda^2}.$$

On the left hand side, we find that,

$$\lim_{\Delta\beta\to 0} -\frac{h^*(n,k,g)}{\Delta\beta} = -\frac{\log \frac{n+2}{2} - 1}{\beta^2\,n}.$$

Equating both the sides, we find,

$$-\frac{\log \frac{n+2}{2} - 1}{\beta^2\,n} = \frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\,\frac{1}{2\,\lambda^2}. \tag{4.18}$$

By substituting both λ and $\frac{\mathrm{d}\lambda}{\mathrm{d}\beta}$ with their equivalents in terms of β, this results in a quadratic equation for β.

$$
\begin{aligned}
& A\beta^2 + B\beta + C = 0, \qquad \text{where,} \\
& A = (1+\theta)^2\theta^2 - \frac{n\,\theta(1+\theta)\left[(1+\theta)(1+q\,\theta) + z\,m\,n\right]}{2\left[\log\frac{n+2}{2} - 1\right]}, \\
& B = -2\,m\,n\,\theta\,(1+\theta), \text{ and} \\
& C = m^2\,n^2.
\end{aligned}
\tag{4.19}
$$

The positive solution to this quadratic equation gives the evolutionarily optimal strain.

$$
\begin{aligned}
\beta_{OPT} &= \frac{-B - \sqrt{B^2 - 4AC}}{2A} = \frac{mn}{1+\sqrt{Q}}, \\
\text{where, } Q &= \frac{n\left[(1+\theta)(1+q\theta) + zmn\right]}{\theta(1+\theta)2\left[\log\frac{n+2}{2} - 1\right]}.
\end{aligned}
\tag{4.20}
$$

Details of derivation, and the conditions for existence are given in appendix C.6.

4.5 Discussion on the results

4.5.1 Comparison of two models

We explored the dynamics of pathogen strain competition in a host meta-population. We described two different models of pathogen competition. The first model is akin to the standard invasion dynamics analysis and is described in subsection 4.3.1. It examined the ability of pathogen strain to invade the meta-population currently occupied by a different strain. Quantities used for the analysis are calculated in subsection 4.4.1, in the context of a simplified SIR model. In subsection 4.4.3, we extended this model to derive the notion of evolutionary stability. The second model, described in subsection 4.3.2, focused on competition between already established strains for an empty patch. This model is also used in the context of a simplified SIR model by calculating appropriate quantities as described in subsection 4.4.1. Optimality con-

ditions for this model, described in subsection 4.4.3, are derived analytically. This avoids having to exhaustively compare strains to find the optima.

Pathogen strain that are evolutionarily stable under the invasion criterion tend to be more persistent than the strain that are optimal in competing for open patch when there both in equilibrium condition. This can be seen in the the figures 4.7,4.8, and 4.9. The evolutionarily stable strains β_{ES} (shown in left panels) have smaller transmission rates compared to optimal ones, β_{ES} (shown in right panels). More persistent strains generally produce larger force of epidemic in the meta-population, and hence are more difficult to be invaded. But their competition to take a patch favors more transmissive strains. Changing migration rate, the size of the patch, and the length of refractory period, have qualitatively similar effect on both evolutionarily stable and optimal strains.

4.5.2 Conflicting evolutionary pressures

By simplifying the within-patch epidemic dynamics, in particular by separating the infection and recovery processes and neglecting the role of host demographics, we were able to attain an analytical expression h^*, given by equation (4.15), that quantified pathogen's competitive fitness at recruiting susceptibles within patch. Fig. 4.5[Left] shows h^* as k and g varies. As k increases, so does the h^* – as expected, a more transmissive strain has more time to come in and invade. As g increases, h^* decreases – shorter lasting strains have less time to invade. Given that R_0 in this case is proportional to $\frac{\beta}{\gamma}$, a diagonal line $g = k$ is R_0-invariant. Interestingly, h^* is not invariant along this line. On the line $g = k$, $h^* < 0$ for $k < 1$, and $h^* > 0$ for $k > 1$. This suggests that among the strains that have the same R_0, a more transmissive one will have a larger window of time to come in and invade.

At the meta-population level, we are able to calculate the force of epidemic gener-

ated by a pathogen strain λ. Figure 4.5[Right] plots the surfaces of λ. An interesting feature to note is that this force of epidemic changes along the R_0-invariant line. Two strains with the same R_0 can have different patch level epidemic dynamics, and consequently different contribution to the force of epidemic. In particular, among the strains that have equal R_0, the one that prolongs the epidemic produces larger λ.

This points to how the dynamics at two levels can result in conflicting evolutionary pressures for the pathogen. While more transmissive strains are favored when pathogens are competing for susceptibles within a patch, the meta-population dynamics governed by patch colonization are better suited for strains that prolong the epidemic by prolonging the infection. The model for strain competition developed in subsection 4.3.2 provides a framework where these two forces can be seen to be interacting.

4.5.3 Effect of migration rate and size of the patch

In Fig. 4.7, we explore the effect of migration rate, m, on both evolutionarily stable traits, and evolutionarily optimal traits. Both, evolutionarily stable traits, β_{ES} (Fig. 4.7[Left]), and evolutionarily optimal traits β_{OPT}(Fig. 4.7[Right]), move further along the evolutionary constraint $\gamma = \theta\beta$, when migration rate is increased. Meta-population with higher host migration rate favors more transmissive strains. Ecologically, increasing migration rate, increases the force of epidemic in the meta-population. The patches are likely to wait shorter for an epidemic to start, and hence a migrating pathogen is more likely to land where an epidemic is already in progress. Pathogens that are more transmissive are more likely to out-compete already present strains, and are favored in such a scenario.

The size of the patch n, also affects the evolutionarily stable (β_{ES}) and evolution-

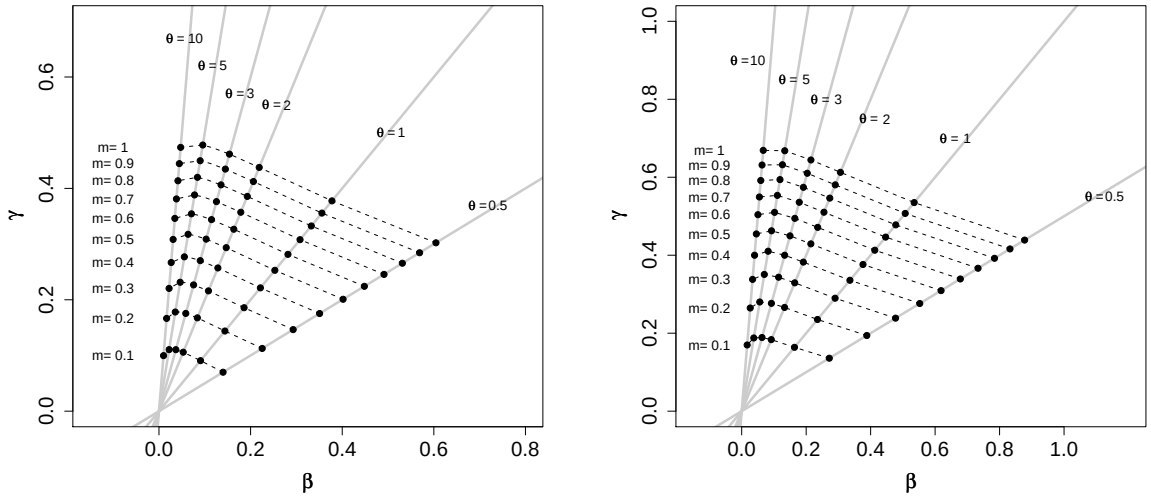

Figure 4.7: Evolutionarily stable and optimal strains as migration rate changes. Change in evolutionarily stable/optimal β along the evolutionary constraint $\gamma = \theta\beta$, as migration rate m changes. Patch size is fixed at $n = 100$, and the refractory phase is fixed at $z = 10$. [Left] Dots are evolutionarily stable strains, β_{ES}, using invasion model. [Right] Dots are evolutionarily optimal strains, β_{OPT}, using competition model.

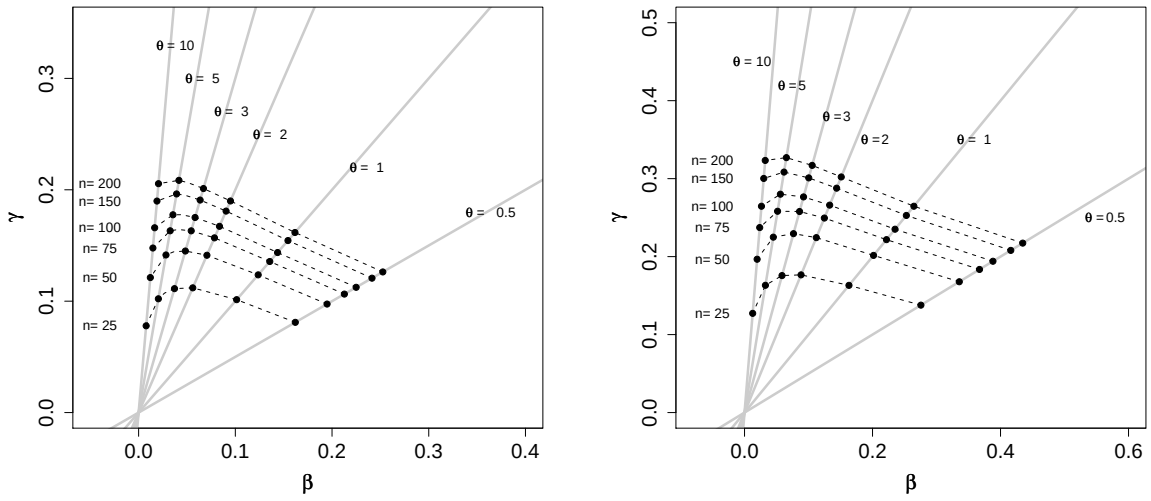

Figure 4.8: Evolutionarily stable and optimal strains as patch size changes. Change in evolutionarily stable/optimal β along the evolutionary constraint $\gamma = \theta\beta$, as patch size n changes. Migration rate is fixed at $m = 0.2$, and the refractory phase is fixed at $z = 10$. [Left] Dots are evolutionarily stable strains, β_{ES}, using invasion model. [Right] Dots are evolutionarily optimal strains, β_{OPT}, using competition model.

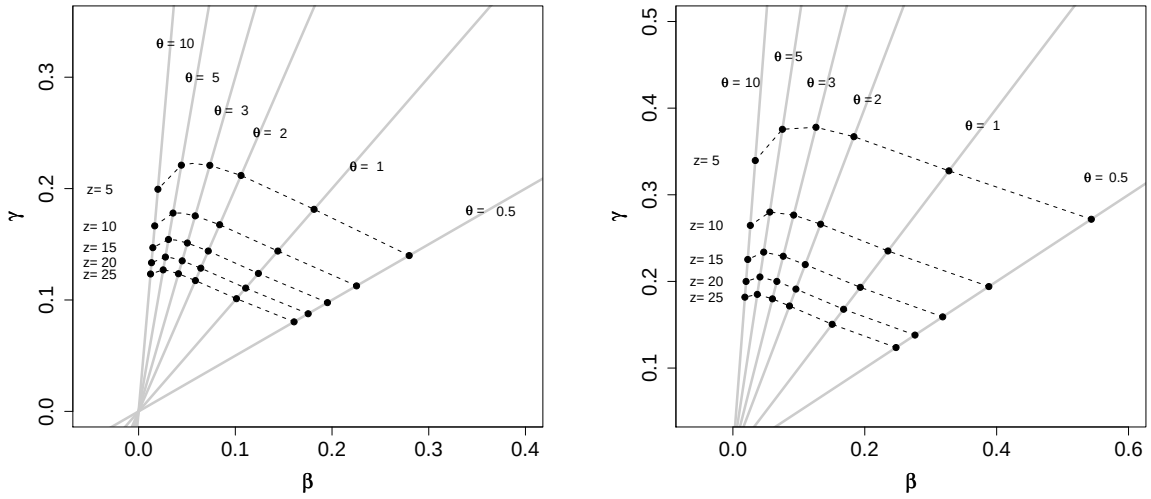

Figure 4.9: Evolutionarily stable and optimal strains as refractory period changes. Change in evolutionarily stable/optimal β along the evolutionary constraint $\gamma = \theta\beta$, as the refractory period z changes. Migration rate is fixed at $m = 0.2$, and the patch size is fixed at $n = 100$. [Left] Dots are evolutionarily stable strains, β_{ES}, using invasion model. [Right] Dots are evolutionarily optimal strains, β_{OPT}, using competition model.

arily optimal (β_{OPT}) traits. As seen in Fig. 4.8, increasing n shifts the locations of β_{ES} (Fig. 4.8[Left]), and β_{OPT}(Fig. 4.8[Right]), to the right and up. Increasing the size of the patch increases the number of migrating hosts, the way we have it in our model. Hence the force of epidemic increases with n for the same reason as when the migration rate increases. And this leads to a more favorable condition for more transmissive strain.

4.5.4 Effect of refractory period

In our model, we have taken refractory period to be exogenous to the strain evolution model. This period is likely to depend mostly on the host mortality rates if the infection results in a life-long immunity. Hosts that have longer life-span, and hence smaller mortality rates will result in longer refractory periods. Increasing the refractory period z, shifts the evolutionarily stable, β_{ES} (Fig. 4.9[Left]) and evolutionarily optimal β_{OPT}(Fig. 4.9[Right]) traits to the left and down. Other things

being equal, a longer refractory phase means that the patches are less likely to be in epidemic phase, and hence the force of epidemic in the meta-population is smaller. This in turn prolongs the waiting phase. Hence a migrant is more likely to land in a susceptible patch in the waiting phase. This favors pathogen that are less transmissive.

4.6 Conclusions

Epidemic dynamics in meta-populations or host populations with structure or heterogeneity are known to exhibit several interesting but equally complex and confounding features. Extinction events, for one, are inherently stochastic phenomena, and when the size of the local communities (patches) are on the order of the critical community size, one is likely to observe variability in the extinction events. Keeling (2000) examines the evolutionary consequences for pathogens with varying local extinction risks in a meta-population context. He finds that the intensity of the patch coupling, as well as the stochasticity in the meta-population can affect the evolutionarily stable strategies (ESS), with ESS ranging from ones that represent pathogen strains that are persistent, to highly transmissive ones that are close to local extinction. Here we have taken a different approach — letting patches go extinct but allowing the time between epidemics to vary depending on the overall force of epidemic in the meta-population. The force of epidemic, λ, is related to, among other things, the migration rate, m, size of the epidemic, A_e, and the nature of the infection. We find that changing the force of epidemic, either by changing the host migration rate or the size of the patch, will affect the likelihood of finding the patch in a given state; susceptible to an epidemic, refractory or in an epidemic phase. Bjørnstad and Grenfell (2008) develop a more comprehensive hazard model to derive

distributions of inter-epidemic period (which is analogous to the sum of the refractory and waiting period in our model). The shape of these distributions and the effect of various components such as the migration rate and host demographics are qualitively similar to what we observe in our model. Consequently, meta-populations with higher prevalence of epidemics will mean that pathogens are more likely to be competing for susceptibles. In contrast, meta-populations with longer lag between different episodes of epidemics, will find pathogen more frequently entering susceptible patches available for them to colonize. Given that pathogen strains are competing for susceptibles in a patch and for susceptible patches themselves, the force of epidemic determines the composition of different levels of competitions the pathogen strains face. Are they more likely to be competing for susceptibles within a patch, or for empty susceptibles patches — this is a key element in determining the appropriate fitness for pathogen.

Another key insight is that that a pathogen's ability to compete for susceptibles and its ability to colonize patches in general can be at conflict. In small patches where pathogens compete for susceptibles hosts, the pathogen that spreads faster is able to recruit more susceptibles and hence favored. But pathogen's ability to compete for patches is mostly governed by duration of the epidemic, which tends to be larger when the infections are longer lasting. This feature is accentuated in our framework where we have simplified the SIR model by separating the time scales of infection and recovery. In particular, we assume that everyone in the patch becomes infected before they recover. This simplification facilitates understanding the competition between strains within a patch. In particular, quantities $\xi(h)$ and h^* become more readily available. Extending this to a complete SIR model, at least until now is only numerically possible, and computing this numerically is computationally expensive.

However, estimates obtained by separating the two processes are still very close to the quantity we derived from the complete SIR model, albeit for only a handful of parameters. As expected, the simplified model is closer to the complete SIR model where recovery process is relatively slower compared to the infection process. This is discussed in greater detail in appendix C.3.

The results can also be interpreted in a scenario where the strains do not completely exhaust the susceptibles. If the size of the epidemic is $\tilde{n}$, i.e. $\tilde{n}$ of the n in the patch get infected over the course of the epidemic, then the force of epidemic will be scaled down by the same factor. Consequently, the average waiting period will be longer and the refractory period shorter. Now, if epidemic sizes for both the competing strains are equal, then the strains will compete for these $\tilde{n}$ available susceptibles in the same manner as we model. Note that the size of the epidemic is dependent on R_0. The size of the epidemic in an density dependent SIR model with no host demographics is given by the following relation (Brauer, 2008; Kermack and McKendrick, 1927):

$$\log n - \log S_\infty = R_0 \left[1 - \frac{S_\infty}{n}\right],$$

where S_∞ is the number of susceptibles that escape the infection — so $\tilde{n} = n - S_\infty$. So competition between two strains with equal R_0, which is what we have considered, can be handled in the same manner, by scaling the force of epidemic by a factor of $\frac{\tilde{n}}{n}$. A more accurate measure might also consider the change in the length of the refractory period, which will be slightly shorter but equal for both strains. So the qualitative results we have offered should hold.

We have also assumed that the refractory period to be constant among pathogen strains. For infections that impart life long immunity, and with the assumption that every single host in the patch becomes infected in an epidemic, this refractory period

is going to depend on the host birth rate and the size of the patch, both of which are independent of pathogen strain parameters. But more realistically, infection characteristics can affect the length of the refractory period. For example, if we allow the size of the epidemic to vary depending on the strain, then the time for the patch to replenish enough susceptibles to come out of the refractory period can change. But if the size of the epidemic itself is dependent on R_0, then by the same argument as in the above paragraph, the results should qualitatively hold.

Our choice to only consider evolution among pathogens that have identical reproductive number, R_0, can perhaps be understood in light of the above two scenarios we discussed. Some of the assumptions we have made to simplify the model, limits us to make more general predictions. A possible future direction then is to expand this model so that it can be flexible enough to ask questions for pathogens that face evolutionary constraints that are biologically motivated, increasing the scope of the work. Yet, it should be pointed out that by focusing on pathogens that are otherwise indistinguishable in terms of their fitness (same R_0), we have argued that the dynamics of meta-population epidemics provides an additional dimension in which pathogen fitness can vary.

A number of researchers have explored questions relating to pathogen evolution in spatially explicit host population (Boots and Sasaki, 1999, 2000; Boots et al., 2004; van Ballegooijen and Boerlijst, 2004). The works report emergent spatial patterns, such as epidemic waves (van Ballegooijen and Boerlijst, 2004), and "self-shading" behaviour (Boots and Sasaki, 2000) can affect pathogen fitness, and as a consequence act as mechanisms that drive pathogen evolution. In the light that epidemic patterns of spatially explicit meta-population, especially in conjunction with stochasticity, can exhibit degrees of synchronous behaviour (Grenfell and Bolker, 1998; Rohani

et al., 1999; Keeling et al., 2004), it is not far fetched to imagine that these patterns will affect pathogen evolution. In that respect, we have taken a different course by considering spatially implicit meta-population that in particular diminishes emergent spatial patterns such as synchrony. By disentangling effects of synchrony, we suggest that different evolutionary pressures can arise at different levels regardless of the space. In patchy host populations, where extinctions are frequent, we are likely to observe dynamics at both levels in action.

APPENDICES

APPENDIX A

Chapter II: Integration of within-host and between-host dynamics and the Invasion-persistence Trade-off

A.1 Standard compartmental models and the classical Transmission-Virulence trade-off

Consider a simple scenario, where the hosts are grouped into compartment based on their epidemiological status – compartment S if they are susceptible to the infection, compartment I if they are infected (and infectious), and compartment R if they have recovered from the infection, and consequently immune to further infection. Hosts in each compartment are indistinguishable from one another, and they move from one compartment to another with rates associated with the underlying biological/epidemiological processes. The susceptibles are replenished via birth, and the per-capita birth rate is taken to be b. Death removes hosts from each compartment, and the background mortality rate is μ. Infected hosts face an additional disease-related mortality, the rate per unit time is ν. A susceptible host becomes infected upon successful transmission of the infection; this transmission rate is β. Infected hosts recover from the infection at the rate γ. The following set of ordinary differential equations describe this deterministic system.

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= b\,(S+I+R) - \beta\,S\,I - \mu\,I \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta\,S\,I - (\mu+\nu+\gamma)\,I \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma\,I - \mu\,R \end{aligned} \tag{A.1}$$

In this framework, the fitness of the pathogen associated with the infection is the net reproductive number, R_0. This is the number of secondary infections originating from a single infected in a disease-free host population. (This number derived in this deterministic framework is the average compared to a stochastic counterpart.)

$$R_0 = \frac{\beta\,N}{\mu+\gamma+\nu}. \tag{A.2}$$

Other things being equal, a pathogen with higher R_0 is the fitter — it is able to invade host population infected with a lesser strain and is also able to resist colonization by other strains (Anderson and May, 1991). R_0 is directly proportional to the transmission rate β, and inversely proportional to disease-related mortality rate ν. Hence, R_0 is maximized by increasing β and decreasing ν. So completely benign and extremely transmissive pathogen are the fittest from this perspective. The transmission-virulence trade-off is then based on the implied relationship between transmission and virulence. This trade-off theory predicts that a virulent pathogen may kill its host so fast, or stimulate such a strong immune response, that it may have little time to transmit to a secondary host (May and Anderson, 1983a). A more commensalistic pathogen, by contrast, may have so low a within-host multiplication rate that it fails to shed sufficiently many propagules to successfully engender infection in recipient hosts. This can lead to an intermediate optimal host-exploitation rate with associated intermediate infectious period and degree of acuteness.

APPENDIX B

Chapter III: Host population induces conflicting pressures on pathogen life history evolution

B.1 McKendrick-von Foerster equations

We consider the spread of a disease in a well mixed homogeneous population, where the transmission rate of a single host during an infection is varying, specified by the mechanistic model described earlier by equations 2.1. The transmission rate of a host infected a units of time ago is $\beta(a)$. Let $\int_{a_1}^{a_2} i(t,a)\,\mathrm{d}a$ be the fraction of host at time t infected between times $t-a_1$ and $t-a_2$. Then, the fraction of infected host at time t that have progressed a units into their infection follows:

$$\frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = -\mu(a)\, i, \qquad i(t,0) = \lambda(t)\, S(t), \tag{B.1}$$

where $\mu(a)$ is age-specific mortality, $\lambda(t)$ is the force of infection, and $S(t)$ is the fraction of the host population susceptible to infection at time t. The force of infection is

$$\lambda(t) = \int_0^{a_c} \beta(a)\, i(t,a)\,\mathrm{d}a = \int_0^{a_c} \beta(a)\, \ell(a)\, i(t-a,0)\,\mathrm{d}a. \tag{B.2}$$

Here, a_c is the time when the infection is cleared in the host, and $\ell(a) = \exp\left(-\int_0^a \mu(a')\,\mathrm{d}a'\right)$ denotes the probability that an individual infected a time units ago has not yet died. We will assume that infections are nonlethal; this amounts to assuming a constant

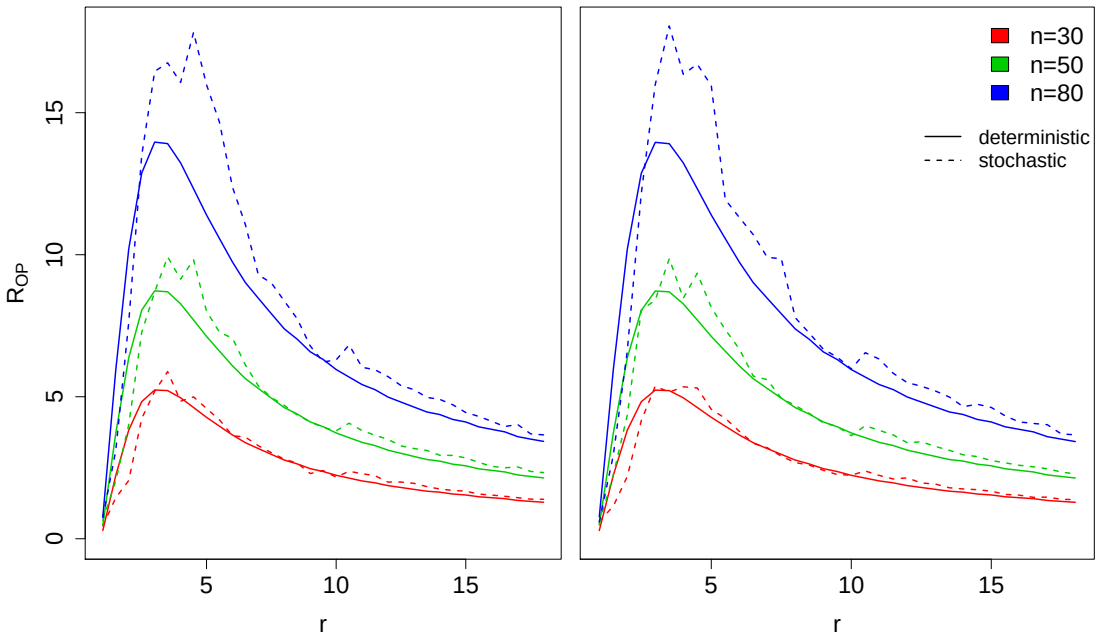

Figure B.1: Estimates of R_{0P} for linear [Left] and saturating [Right] models, using both deterministic and stochastic frameworks. The stochastic curve is the average over 100 simulations. The curves are similar both models, and they attain a maximum for $r \approx 4$.

death rate: $\ell(a) = e^{-\mu a}$. We assume that the total host population remains constant, and the fraction of susceptible, $S(t)$ obeys

$$\frac{dS}{dt} = \mu\,(1 - S) - \lambda(t)\,S. \tag{B.3}$$

B.2 Approximation of epidemic sizes

For small enough patches, we consider the extinction of the pathogen in the patch when the fraction of infected hosts,

$$H(t) = \int_0^{a_c} i(t, a)\,\mathrm{d}a,$$

reaches the minimum. We define the average duration of the epidemic $\bar{\delta}$ to be this duration. Similarly, the average fraction of infected,

$$\bar{\iota} = \frac{1}{\bar{\delta}} \int_0^{\bar{\delta}} H(t)\,\mathrm{d}t.$$

The patch-level net reproductive number, $R_{0P} = \bar{\iota}\,\bar{\delta}\,m\,n$. We can also stochastically estimate R_{0P}. Shown in Fig. B.2 are the estimates of R_{0P} using both the deterministic and stochastic frameworks for patch sizes $n = 30$, 50, and 80. The curves show that they attain a maximum for $r \approx 4$.

APPENDIX C

Chapter IV: Epidemic and evolutionary dynamics in meta-populations

C.1 More on invasion model

It is of interest to know what $\zeta(R,R)$ will be. Since the resident is in steady state, a resident epidemic will on average generate exactly one epidemic. Hence, intuitively one would expect $\zeta(R,R)=1$. We carry out the calculation in the SIR setting to see if and when this is true.

$$\zeta(R,R) = m\,\epsilon\,\omega\,\frac{1}{\gamma_R}\,f_h\int_{-\frac{1}{\lambda}}^{\delta}\xi(h)\,\mathrm{d}h = \frac{\lambda}{n}\left[\int_{-\frac{1}{\lambda}}^{-\delta}\xi(h)\mathrm{d}h + \int_{-\delta}^{\delta}\xi(h)\mathrm{d}h\right]. \tag{C.1}$$

Note that (i) $\xi(h)=n$, when, $h<-\delta$, so $\displaystyle\int_{-\frac{1}{\lambda}}^{-\delta}\xi(h)\mathrm{d}h = n\left(\frac{1}{\lambda}-\delta\right)$.

And, (ii) $\xi(h)$ is symmetric about $\{h=0,\xi=n/2\}$, so $\displaystyle\int_{-\delta}^{\delta}\xi(h)\mathrm{d}h = 2\delta\,\frac{n}{2}$.

$$\text{Hence, } \zeta(R,R) = \frac{\lambda}{n}\left[n\left(\frac{1}{\lambda}-\delta\right)+2\delta\,\frac{n}{2}\right] = 1. \tag{C.2}$$

Here, we have assumed that $1/\lambda > \delta$, to subdivide the integral. If this condition does hold then $\zeta(R,R)=1$. But if λ is large then $\zeta(R,R)$ is not necessarily 1. One should note though that we can refine this condition, since $\xi(h)$ in general becomes 0 much earlier that $h=\delta$. So, we can subdivide the integral at this earlier point, which is more likely to be smaller that the average waiting time, $1/\lambda$.

C.2 On waiting time of k of n arrivals

Consider, there are n individuals, and you are interested in the waiting time for k of such arrivals. The arrival of each individual is independent of the others, and exponentially distributed with parameter λ. The waiting time for jth arrival, t_j is also distributed exponentially, but weighted by the number of individuals waiting, i.e. $f_{t_j} = \lambda\,(n-j+1)\,e^{\lambda\,(n-j+1)\,t_j}$. The total waiting time is the sum of each arrival times, $\sum_{j=1}^{k} t_j$. The expected waiting time for jth arrival $\mathbb{E}(t_j) = \dfrac{1}{\lambda\,(n-j+1)}$. And, the total expected waiting time is the sum of expected waiting times of each arrivals, $\dfrac{1}{\lambda}\displaystyle\sum_{j=1}^{k}\frac{1}{n-j+1}$.

This same idea can be employed to look at the progression of an epidemic process. We turn to the simple SIR epidemic, with only infection and no recovery or demographic processes. Consider an epidemic at a state where there are j infecteds and $n-j+1$ susceptibles. The force of infection on each individual susceptible is $\beta\,j\,(n-j+1)$. So the waiting time for $(j+1)$th infection, $f_{t_j} = \beta\,j\,(n-j+1)\,e^{\beta\,j\,(n-j+1)\,t_j}$. The expected waiting time for this $(j+1)$th infection is $\dfrac{1}{\beta\,j\,(n-j+1)}$, and the expected waiting time for the entire population to become infected is $\dfrac{1}{\beta}\displaystyle\sum_{j=1}^{n}\frac{1}{j\,(n-j+1)}$ (Bailey, 1963, 1964).

C.3 Comparing with SIR simulation

The simplification, we made on the SIR model, allowed us to derive ξ (the number of susceptibles captured by the invader and the resident) as a function of h (the difference in their arrival). It is then of interest, to compare then to ξs generated by simulating a complete SIR model. Fig. C.1 compares ξ_i in the two setting. As expected, the simplification we made to the SIR model, is more accurate when the

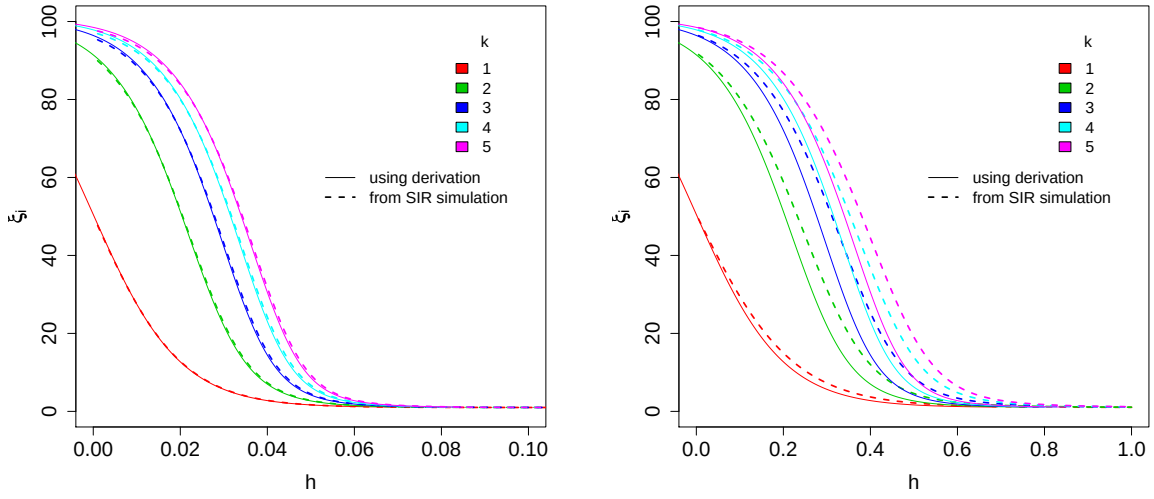

Figure C.1: Plots of ξ_i for different ks. [Left] for $\beta_r = 1$ and [Right] for $\beta_r = 0.1$. The solid lines are calculated using equation (4.14), and the dashed lines are estimated by simulating a standard SIR model. Here, $n = 100$, and $\gamma_r = 1$. The derivation is closer to the complete SIR dynamics when the transmission rates are higher.

transmission rates are higher.

C.4 SIR meta-population

With SIR-type epidemic dynamics, the force of epidemic, $\lambda = \dfrac{m\epsilon\, A_e - 1}{\delta + z}$, where, $A_e = \frac{n}{\gamma}$, $\delta = \frac{q}{\beta} + \frac{1}{\gamma}$ with, $q = \displaystyle\sum_{j=1}^{n} \frac{1}{j\,(n-j+1)}$, and $\epsilon = \frac{\beta}{\beta+\gamma}$. So, $\lambda = \dfrac{\frac{m\beta\, n}{\gamma(\beta+\gamma)} - 1}{\frac{q}{\beta} + \frac{1}{\gamma} + z}$, and with the constraint, $\gamma = \theta\beta$, we get

$$\lambda = \frac{m\, n - (1+\theta)\,\theta\,\beta}{(1+\theta)\,(1 + q\,\theta + z\,\theta\,\beta)}.$$

We can also find how λ changes with β; and in fact,

$$\frac{\mathrm{d}\lambda}{\mathrm{d}\beta} = \frac{-\theta\,\left[(1+\theta)\,(1+q\,\theta) + z\,m\,n\right]}{(1+\theta)\,(1 + q\,\theta + z\,\theta\,\beta)^2}.$$

C.5 Limits and evolutionary optimum

Consider two slightly different strains, characterized by their difference in transmission rates β and $\beta + \Delta\beta$. The forces of epidemic they will generate in the

meta-population will then be $\lambda(\beta)$ and $\lambda(\beta+\Delta\beta)$, respectively. But, $\lambda(\beta+\Delta\beta) = \lambda + \frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\Delta\beta$. The condition for finding the evolutionary optimum is:

$$\lim_{\Delta\beta\to 0} -\frac{h^*(n,k=g=\frac{\beta+\Delta\beta}{\beta})}{\Delta\beta} = \lim_{\Delta\beta\to 0} \frac{\frac{1}{\lambda(\beta+\Delta\beta)}\log\frac{\lambda(\beta)+\lambda(\beta+\Delta\beta)}{2\lambda(\beta)}}{\Delta\beta}.$$

First, consider the right hand side of this equation, which we will denote by ϕ.

$$\begin{aligned}\phi &= \frac{1}{\lambda(\beta+\Delta\beta)}\log\frac{\lambda(\beta)+\lambda(\beta+\Delta\beta)}{2\lambda(\beta)} \\ &= \frac{1}{\lambda+\frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\Delta\beta}\log\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\frac{1}{2\lambda}\Delta\beta+1\right)\end{aligned}$$

Since, the Taylor expansion of $\log(bx+1)$, around 0, is $bx - \frac{b^2x^2}{2} + \frac{b^3x^3}{3} + \ldots$

$$\phi = \left[\frac{1}{\lambda+\frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\Delta\beta}\right]\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\frac{1}{2\lambda}\Delta\beta - \frac{1}{2}\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\frac{1}{2\lambda}\Delta\beta\right]^2 + \ldots\right]$$

And, $\lim_{\Delta\beta\to 0}\frac{\phi}{\Delta\beta} = \frac{\mathrm{d}\lambda}{\mathrm{d}\beta}\frac{1}{2\lambda^2} = \hat{\phi}$.

On the left hand side of the equation, in the calculation of h^*, $k = g = \frac{\beta+\Delta\beta}{\beta} = 1+\frac{\Delta\beta}{\beta}$. And, $\Delta\beta = \beta(k-1)$. So,

$$\lim_{\Delta\beta\to 0} -\frac{h^*(n,k,g)}{\Delta\beta} = -\frac{1}{\beta}\lim_{k\downarrow 1}\frac{h^*}{k-1}.$$

Now, let $\hat{h^*} = \lim_{k\downarrow 1}\frac{h^*}{k-1}$.

$$\hat{h^*} = \lim_{k\downarrow 1}\frac{h^*}{k-1} = \lim_{k\downarrow 1}\frac{f(k)}{g(k)} \text{ where,}$$

$$f(k) = \frac{1}{\beta}\left[\frac{1}{n+1}\log\frac{n\left(\frac{n+2}{1+k}\right)\left(n+2-\frac{n+2}{1+k}\right)^{\frac{-1}{k}}}{n+1-\left(\frac{n+2}{1+k}\right)\left(n+2-\frac{n+2}{1+k}\right)^{\frac{-1}{k}}}\right], \text{ and}$$

$$g(k) = k-1.$$

Now, since, $\lim_{k\downarrow 1} f(k) = \lim_{k\downarrow 1} g(k) = 0$, and $\lim_{k\downarrow 1}\frac{f'(k)}{g'(k)}$ exists, we use l'Hopital's rule to find the limit. So, $\lim_{k\downarrow 1}\frac{f(k)}{g(k)} = \lim_{k\downarrow 1}\frac{f'(k)}{g'(k)}$. Clearly, $g'(k) = 1$, and it turns out that $f'(k) = \frac{\mathrm{d}h^*}{\mathrm{d}k}$ can be calculated, and is equal to

$$\frac{1}{\beta}\left[\frac{-\frac{1}{k+1}+\frac{\log u}{k^2}-\frac{n+2}{u\,k\,(k+1)^2}}{n+1-w\,u^{\frac{-1}{k}}}\right],$$

where, $u = n + 2 - \frac{n+2}{k+1}$, and $w = \frac{n+2}{k+1}$. So, $\lim_{k\downarrow 1} \frac{f'(k)}{g'(k)} = \lim_{k\downarrow 1} f'(k) = \frac{\log \frac{n+2}{2} - 1}{\beta\, n}$. Hence, $\hat{h^*} = \frac{\log \frac{n+2}{2} - 1}{\beta\, n}$. And,

$$\lim_{\Delta\beta\to 0} -\frac{h^*(n,k,g)}{\Delta\beta} = -\frac{1}{\beta} \lim_{k\downarrow 1} \frac{h^*}{k-1} = -\frac{\log \frac{n+2}{2} - 1}{\beta^2\, n}.$$

C.6 More on evolutionarily optimal strains

The quadratic equation for optimal $\beta = \beta_{OPT}$ is $A\beta^2 + B\beta + C = 0$, where,

$$A = (1+\theta)^2\theta^2 - \frac{n\,\theta(1+\theta)\left[(1+\theta)(1+q\,\theta) + z\,m\,n\right]}{2\left[\log \frac{n+2}{2} - 1\right]},$$

$$B = -2\,m\,n\,\theta\,(1+\theta), \text{ and}$$

$$C = m^2\,n^2.$$

The discriminant, $B^2 - 4AC = \frac{4m^2n^3\theta(1+\theta)\left[(1+\theta)(1+q\theta) + zmn\right]}{2\left[\log \frac{n+2}{2} - 1\right]}$ is greater than 0 as long as $n > 2(e-1)$. Hence the roots are guaranteed to be real. The two roots of the quadratic equation are:

$$\frac{-B \pm \sqrt{B^2 - 4AC}}{2A} = \frac{-2m\,n\theta\,(1+\theta)\left[1 \pm \sqrt{Q}\right]}{-2(1+\theta)\theta\,[Q-1]} = \frac{mn}{1 \pm \sqrt{Q}}$$

$$\text{where, } Q = \frac{n\left[(1+\theta)(1+q\theta) + zmn\right]}{\theta(1+\theta)2\left[\log \frac{n+2}{2} - 1\right]}$$

Root $\frac{mn}{1+\sqrt{Q}}$ is always positive as long as $n > 2(e-1)$, and root $\frac{mn}{1-\sqrt{Q}}$ will be negative as long as $Q > 1$ or $n\,\left[(1+\theta)(1+q\,\theta) + z\,m\,n\right] > 2\left[\log \frac{n+2}{2} - 1\right]\,(1+\theta)\theta$. Numerically, these are well within the range of biologically realistic parameters we will consider. Hence, given the population size n, migration rate m, duration of refractory phase z, and the evolutionary constraint $\gamma = \theta\beta$, $\beta_{OPT} = \frac{-B - \sqrt{B^2 - 4AC}}{2A} = \frac{mn}{1+\sqrt{Q}}$, is the evolutionary optimum.

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