Sociality, Sterility, and Poverty; Host-Pathogen Coevolution, with Implications for Human Ecology

by

Matthew H. Bonds

(Under the direction of Pejman Rohani)

Abstract

Disease ecology constitutes a frontier of human ecology that is primed for integrated research between the natural and social sciences. Here, I present a framework for such integration. Relying on game theory and optimization theory - techniques found in both the economics and evolutionary biology literatures - I first develop a theory of the coevolution of social behavior and infectious diseases for non-human social organisms, where I find that increases in pathogen virulence can surprisingly result in greater sociality. I then develop a model of pathogen-induced sterility that is integrated into the general evolution of virulence framework, and explains a well-known but poorly understood phenomenon: pathogen-induced gigantism. The model predicts that sterility could cause the host to invest more resources into maintenance versus reproduction. Under certain circumstances, the pathogen could therefore evolve to manipulate the host via castration, causing gigantism. Finally, I develop a formal ecological model of global health and economic development, where I find that fertility may play an even larger role in the persistence of poverty and disease than previously thought.

Index words: ESS,CoESS, Evolution of Virulence, Pathogen Manipulation, Sociality, Infectious Disease, Poverty Trap

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Dedication

This is dedicated to Adam, Meredith, Mom, and Gran'anne.

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Chapter 1

Introduction

"In October 1838, fifteen months after I had begun my systematic inquiry, I happened to read for amusement Malthus on Population, and being prepared to appreciate the struggle for existence which everywhere goes on, from long-continued observation of the habits of animals and plants, it at once struck me that under these circumstances favourable variations would tend to be preserved, and unfavourable ones to be destroyed. The result would be the formation of a new species."
Charles Darwin (1887)

"The enterprise within the social sciences best poised to bridge the gap to the natural sciences, the one that most resembles them in style and self-confidence, is economics."
E.O. Wilson (1998)

1.1 The need for integrated ecological and economic research

Among other things, human beings have been very successful reproducers. The world human population has grown from approximately ten million, before the agricultural revolution ten thousand years ago, to over six billion today, having added nearly four billion people in the last fifty years alone (Diamond, 1997). Such intense population growth seems *almost* natural. After all, the tendency to more-than-reproduce oneself is universally observed throughout the living world. Without "positive checks" such as "famine" and "disease" or perhaps "moral restraint", populations of any organism will experience exponential growth. This basic principle was laid out by the political economist Rev. Thomas Robert Malthus in his

landmark, "Essay on the Principle of Population," (Malthus, 1798), and constituted a key insight for Charles Darwin's explanation for the origin of species via evolution by natural selection (Darwin, 1879), which remains the primary over-arching paradigm in ecology today. Darwin's logic was relatively straightforward. A constant population level requires that the average individual produces exactly one reproductive offspring in its lifetime. However, in reality, individuals of all species tend to reproduce many more times than once, with each offspring often slightly different from the rest. Because most natural populations are *not* growing exponentially, the vast majority of organisms in the world must be dying prematurely. An ultimate consequence of all of this reproduction, variation, and death is evolution and diversity. And, like all of the other organisms that are part of the life-death evolutionary process, humans also tend to more-than-reproduce themselves... and we survive better.

That the key paradigmatic theory of the natural sciences - evolution by natural selection - relies on principles first developed in the social sciences should be of no surprise. As humans, we are, after all, the most studied animals on earth. Since Darwin's theory was first presented, intellectual parallels between ecology and economics have remained, yet genuine synthesis is almost totally absent. This is a problem - the differences between humans and other organisms is more than just an intellectual curiosity. Our "unnatural" population growth has been sustained by a reliance on biotic and abiotic resources that, in many cases, is not sustainable and is permanently altering ancient physical, geologic, and ecological processes. Just feeding the U.S. population, for example, has resulted in the removal of thousands of years of accumulated topsoil (Soil Conservation Service, 1994). Some of it has eroded into waterways, every major one of which has been dammed in order to fuel our activities (Graf, 1999). Energy that has not been removed from water has mostly been extracted from finite reserves of solar energy that were fossilized hundreds of millions of years ago. Their sudden large-scale production is heating global water temperatures and changing the earth's climate (IPCC, 2001). But even endowments of natural resources collected over millions of years have not been sufficient to sustain our population. International economic markets have facilitated

the transfer of goods, services, and raw materials across the globe, and, along with them, provided transportation routes for invasive species including infectious diseases (Taylor and Irwin, 2004; Daszak et al., 2000). Habitats have been destroyed and fragmented. And we now may be experiencing the seventh major extinction event to have occurred on earth (Crowley and North, 1988; Novacek and Cleland, 2001). Solving such ecological problems cannot ultimately be disentangled from the systematic economic forces that create them.

The irony is that while there are many shared intellectual parallels and corresponding analytical techniques shared between ecology and economics, these approaches are especially divergent where the subject-matter seems to overlap the most - in understanding human interactions with the environment. There are two disparate academic literatures that specifically attempt to address the relationships between economics and the environment: 1) environmental economics; and 2) ecological economics. Environmental economics is part of the neoclassical economics tradition that dates back to Adam Smith. It tends to treat the environment as a resource that provides goods and services that people value much like other commodities that are traded in the marketplace, with the exception that environmental services are often not easily traded. The fact that such services, like clean air, are "external" to typical market transactions poses a problem for true economic efficiency. The challenge for economic policy is then usually framed in terms of "internalizing" the externalities of private decision-making. An obvious example would be to charge pollution taxes on goods that pollute, such as on the consumption or production of fossil fuels (Tietenber, 2003).

I consider environmental economics principles, like economics principles in general, to be perfectly consistent with sound long-term environmental policy. But the problem with the environmental economics literature is that it is almost entirely composed of economists. They tend not to be formally trained in the complexity of ecological processes. What are the true externalities of various market transactions? The environmental consequences (that is, the third-party effects) are often complex, nonlinear, and may even feedback on eco-

nomic activity. Economists have been slow to "internalize" such processes into the academic literature.

Ecological economists, having been suspicious of the neoclassical economics approach to environmental management, have recently established a paradigm of their own under the general rubric of "sustainability" and "steady-state" economics (Costanza, 1989; Costanza and Daly, 1992). It is a field started largely by ecologists and "sustainability" itself is often posed as the objective. But what are we trying to sustain? The answer from ecological economists would be environmental services. But neoclassical economists view natural and environmental resources as simply components of human welfare, like all other goods and services. Sustaining clean air as an end in itself, would be no more sensible than sustaining access to automobiles - both give people pleasure, though in different ways.

I think the problem with such disparate approaches to environmental management, is that the intellectual cultures associated with them are not easily reconcilable, and productive cross-fertilization becomes very difficult. As a result, environmental economists continue to address the welfare issues associated with the environment, while ecological economists focus on the complex environmental consequences of economic activity, and we remain surprisingly devoid of productive treatments of welfare economics that incorporate the complex environmental consequences of economic decisions.

Arguably, the most noble attempts at productive integration have been efforts to assess the "economic value" of ecological services across the globe (Costanza et al.; Daily et al., 2000). But those attempts are also quite intellectually unsatisfying in that they fail to capture the important and interesting elements and potential contributions of their respective fields. However, their value, in my opinion, is not the actual assessed value of ecosystems - though, conceptually, that is important - it is the prospect of getting economists and ecologists just talking the same language, as base as that language may be. Given the complexity of global economic and ecological activity, and the maturity of the corresponding academic disciplines, productive interdisciplinary work is simply difficult. And we need to start somewhere.

Even *within* the respective disciplines, there lack general theories that integrate small-scale "micro" behavior into general large-scale "macro" processes; macroeconomic theory is disjointed from microeconomic theory just as ecosystem ecology is disjointed from theories of population and evolutionary ecology. If theories cannot be integrated within disciplines, what hope is there for productive cross-disciplinary scientific progress? What would a truly integrated economic-ecological theory even look like?

Fortunately, in terms of analytical approaches, intellectual culture and language, some fields in ecology such as behavioral, population, and evolutionary ecology, do have much in common with economics. After all, "as Goethe expressed it, 'in order to spend on one side, nature is forced to economise on the other side'" Darwin (1879). The earliest formal conscious use of economics principles in ecology relied on optimization theory, with MaCarthur and Pianka's theory of optimal patch selection (MacArthur and Pianka, 1966), which marked a wave of research in foraging theory (Schoener, 1971; Pulliam, 1975; Charnov, 1976; Pyke et al., 1977; Belovsky, 1984). At about the same time, game theory, which was originally developed by mathematicians (von Neumann and Morgenstern, 1944; Nash, 1950a,b, 1951) but fairly quickly picked up by economists, was being applied to the analysis of animal behavior by ecologists (Maynard Smith, 1974, 1982; Maynard Smith and Price, 1973; Pulliam et al., 1977; Caraco et al., 1980). Unfortunately, the arenas in which ecologists and economists share such analytical techniques, the subject matter itself (i.e. human vs animal behavior) and perhaps the underlying objectives (to understand patterns of economic welfare vs. conservation) are divergent.

What has yet to be done in a meaningful way is the integration of common principles in ecology and economics - such as optimization theory, game theory, and modeling of nonlinear dynamics - applied to problems of interest to *both* economists and ecologists. As a result, genuinely fruitful collaborations have been lacking.

1.2 Infectious Diseases as Frontier of Human Ecology

The relationship between human economic activity and ecological processes is not always as complex as the effect of, for example, fossil fuel production on ecosystem processes through climate change, and it now seems surprising that economists and ecologists have struggled to find genuine common ground. After all, the most critical determinants of human survival and economic welfare throughout history and in much of the world today are other biological agents: infectious diseases (World Health Organization, 2004). These are *natural* enemies, behaving according to ecological principles, which claim most of the human lives in the developing world and as much as two-thirds of those in sub-Saharan Africa. Such diseases have been with us throughout human history, have directed human evolution (Motulsky, 1960; Ewald, 1994; Curtis, 2001; Carter and Mendis, 2002), and have played formative roles in the development of modern civilizations (McNeill, 1976; Diamond, 1997). More recently, infectious diseases have been implicated in conspiring with economic forces to form "poverty-traps", making them potentially responsible for the persistence of extreme poverty experienced by one-sixth of the world today, and thus continue to constitute major factors of economic growth (Gallup and Sachs, 2001b; Sachs and Malaney, 2002; Sachs et al., 2004).

1.3 Objectives

This dissertation has been written with a specific intellectual objective: to contribute to a foundation for integrated work between the natural and social sciences - specifically, between ecology and economics - ultimately for the purposes of a better understanding of how humans relate to each other in the context of the natural world. In that sense, the underlying theme is human ecology. However, only the final substantive chapter (Chapter 4) explicitly addresses this theme. The primary reason for this is simple: I didn't know exactly where to begin. Because that chapter is perhaps the first piece of its kind to explicitly incorporate economic development into a formal disease ecology framework, I did not have a theoretical frame-

work to rely on. Instead, I began by seeking analogues of human behavior in the natural world that could possibly help me think more clearly about how to frame an integrated economic-ecological study of infectious disease of humans. Chapters 2 and 3 do not mention humans, and do not attempt to offer insights into how we relate to each other or the natural world. Instead, what they strive to offer are novel frameworks for understanding interspecific relationships of the general kind that dominate much of human activity: host-pathogen interactions. And each framework itself relies on techniques that have been explored in parallel between both the evolutionary ecology and the economics communities: game theory and optimization theory. So while Chapters 2 and 3 do not address human activity, they do address processes that other organisms share with humans - specifically, strategic "economic behavior" - and therefore, despite their focus on non-human host-pathogen interactions, they could be of interest to some economists.

1.4 Chapter 2: Coevolution of Sociality and Infectious Diseases

Human beings are social organisms. In the simplest terms, this is because the "benefits" of social behavior in terms of survival and reproduction, have outweighed the costs in terms of mortality over the course of our evolutionary history. One of the primary costs of social behavior is the transmission of infectious diseases (Alexander, 1974; Brown and Brown, 1986; Pulliam and Caraco, 1984; Lee, 1994; Møller et al., 2001). An obvious example of benefits and costs from social behavior would be those associated with sexual contact, whose benefits potentially include sexual pleasure and reproduction, among other things, and the costs are the risk of transmitting harmful venereal diseases, such as HIV/AIDS.

Economists and ecologists alike have explicitly considered such benefits and costs of sexual behavior (Philipson and Posner, 1993; Ahituv et al., 1996a; Boots and Knell, 2002; Kokko et al., 2002), but have slightly different approaches to modeling such behavior. The issue is what constitutes a "decision function"? Economists tend to rely on "utility functions" that represent the relationship between choice variables and individual welfare. If individuals are

rational, then they choose the combination of choice variables that maximizes their welfare - that is, they optimize the decision function. This is actually an *assumption* that underlies much of micro-economic modeling. But what exactly does a real utility function look like? When people make decisions, what do they really optimize?

It is my opinion that ecologists tend to be on safer scientific grounds when modeling animal behavior, which is known to be heritable. And so, instead of relying on the assumption of "rational" agents making optimal decisions, ecologists can rely on natural selection to do it for them. After all, not all behavior has the same probability of being passed on to the next generation - only those behaviors that increase the probability of survival and reproduction. The analogue of the economist's "utility function" is therefore a "fitness function", but instead of simply assuming that such an objective function exists, and with certain properties, it can often be *derived* from first principles. It is in the derivation of the fitness function that the evolutionary biology literature has made some nice intellectual strides.

As mentioned above, optimization theory and game theory were first applied to the analysis of animal behavior in the 1960s and 1970s (MacArthur and Pianka, 1966; Schoener, 1971; Pulliam, 1975; Maynard Smith, 1974, 1982; Maynard Smith and Price, 1973; Pulliam et al., 1977). John Maynard Smith introduced the concept of an "evolutionarily stable strategy" (ESS) as a strategy that, if adopted by a resident population, could not be invaded by any other strategy. An ESS is a kind of Nash noncooperative equilibrium (Nash, 1951). For heuristic purposes, the original ESS literature simply assigned payoffs to different strategies (Maynard Smith, 1982). More recently, the infectious disease literature has shown how these payoffs can be derived from models of population dynamics (van Baalen, 1998). Consider the growth rate of phenotypic strain, x_i, as a function of all other strains in the population, $dx_i/dt = f_i(x_j)$, where j represents other strains in the population. The strain with the maximum positive growth rate when the population is at equilibrium is evolutionarily stable. This conveniently turns out to be the strain that maximizes the number of offspring in its

lifetime, which is a well-known relationship in population ecology: the basic reproductive ratio, commonly referred to as R_0.

These derivations, their analysis, and their implications for the evolution of social behavior in non-humans in the context of infectious diseases is the central focus of Chapter 2, "Higher Disease Prevalence Can Induce Greater Sociality; a Game Theoretic Coevolutionary Model," published in 2005 in the journal *Evolution* (Bonds et al., 2005). I focused explicitly on non-human social behavior because, from a modeler's perspective, the analysis was simpler and could rely on a more scientifically sound theoretical tradition. After all, the relevant time-scale for this analysis is evolutionary, and I could therefore invoke evolutionary stability as a necessary condition for an "optimal" behavior, with the metric for costs and benefits being in terms of effects on fitness - specifically, in this case, survival. I could then solve for the evolutionarily stable host and pathogen strategies simultaneously to determine an evolutionary endpoint. Modeling human social behavior would have only seemed relevant over short decision-making timescales (e.g., in the midst of an epidemic). I therefore could not assume that the pathogen dynamics equilibrated - which is a necessary condition for the calculation of evolutionary stability - and would not have been able to consider a coevolutionary outcome. As a first step towards developing theories of human ecology in the context of infectious diseases, I therefore focused on a simpler process in non-human social organisms.

As the title suggests, we found an interesting and counter-intuitive result that as the probability of infection per contact rises because of greater disease prevalence, the evolutionarily stable (ES) level of contact may also rise. This is because, past a threshold level of disease prevalence, the benefits of contact in terms of lower death rate (assumed to be because of, for example, lower predation), eventually outweigh the benefits of disease-avoidance. At the extreme, this becomes rather obvious. For example, if the disease prevalence is 100% because of high transmission, then there are no advantages to avoidance - infection becomes inevitable - while there remain fitness advantages to social contact. To confirm the robustness of these

results, I also considered the coevolution of the pathogen, which also maximizes its basic reproductive ratio, R_0, and found a novel twist. Not only can increases in disease prevalence select for greater ES contact, but greater contact can select for lower disease virulence. This is counter to a growing conventional wisdom that high contact, through greater transmission opportunities, selects for increased disease virulence (Ewald, 1994).

Given the substantial literature on the evolution of social behavior, and the presumed negative influence that would result from disease pressure, these results are interesting in and of themselves, and there is little reason to muddle them with applications to human ecology. But there is an analogue to human behavior which is of some interest and could be important. The increased sociality resulting from higher disease prevalence is analogous to "fatalism", and begs the question: when disease avoidance seems to become sufficiently difficult in cases where prevalence is super high, such as HIV/AIDS in the gay male community in San Francisco or in many parts of Africa, does risky sexual behavior increase (Ahituv et al., 1996b)? If so, the implications for long-term effects for the epidemic are important.

1.5 Chapter 3: Host Life-History Strategy Explains Pathogen Induced Sterility

The theory that I present of sterilizing pathogens (Chapter 3) (Bonds, 2006) was originally meant to be a direct extension of the piece on the evolution of sociality (Chapter 2) (Bonds et al., 2005), but with a focus on sexually transmitted diseases (STDs). Given that HIV/AIDS has become the most threatening infectious disease on the planet, and that sexually transmitted diseases are common in the natural world, it seemed that a coevolutionary model of sexual behavior and STDs was warranted. And I liked the prospect of a simple extension. However, I quickly discovered that a *general* model was unrealistic. As STDs go, HIV/AIDS is an enigma. Most STDs (other than HIV/AIDS) are not deadly. This actually represents a quandary for theory on the evolution of virulence, which tends to rely on the assumption that pathogens face a trade-off between transmission and virulence, almost always defined

as disease-induced mortality (Bremmermann and Pickering, 1983; Ewald, 1994; Frank, 1996; Day, 2001; Bonds et al., 2005). If the pathogen does not kill its host - what then would be the fitness cost to the pathogen of infection and transmission? It turns out that many sexually transmitted diseases are partially or totally sterilizing. The small literature that has addressed evolution of sterilizing pathogens, all assume that the benefit of sterilizing the host is to increase transmission (Obrebski, 1975; Jaenike, 1996; O'Keefe and Antonovics, 2002). While never modeled explicitly, this is implicitly assumed to be because the pathogen can either directly or indirectly redirect host reproductive resource towards its own reproduction - i.e., transmission. But sterilization, from the pathogen's perspective is not a cost - it does not itself lower pathogen fitness, the way death does. The assumption therefore implies that complete sterilization is evolutionarily stable (in economists parlance, this would be a "corner solution"), which is what the meager theoretical literature finds (Obrebski, 1975; Jaenike, 1996; O'Keefe and Antonovics, 2002). Why then do we often observe only partial sterility? What is even more confusing is that infection by some sterilizing pathogens is known to actually result in increased host size - known as gigantism - a phenomenon not easily integrated into the general evolution of virulence literature, which assumes that pathogens steal host resources. There has been little progress on theories of the evolution of sterilizing pathogens and none of the existing theories could be integrated into the broader evolution of virulence literature.

So, what began as an attempt to develop a simple theory on the evolution of sexually transmitted diseases turned into a desire to formally treat the *other* kinds of fitness costs experienced from infection - decreased reproduction. I also wanted to advance the general evolution of virulence framework by not having to assume static behavior over the course of the host's lifetime. Chapter 2 assumes that an individual inherits some level of social contact and remains that way its whole life, even after infection. In reality, many organisms are known to change their behavior after infection, which has, on some occasions, been hypothesized to be the consequence of pathogen manipulation (Milinski, 1985; McAllister

and Roitberg, 1988). This presented another theoretical challenge for understanding host-pathogen relations. How could we even model pathogen manipulation? What would be the constraints? Is the pathogen simply a puppeteer? To my knowledge, there are no formal theories of pathogen manipulation.

This paper therefore presents a new framework altogether. Its chief novelty is that it makes no *a priori* assumptions about whether the pathogen draws host resources from reproduction or longevity, but that such resources are used by the host for both purposes. The consequence of infection therefore emerges from relative changes in the evolutionarily stable allocations of host resources for reproduction versus longevity, after infection.

Given that the "decision" to invest in reproduction versus longevity amounts to a fairly straightforward optimization problem, the model in Chapter 3 is partly borrowed from the economics literature. As is typical in economics, I assume that the allocation of (host) resources is based on the maximization of some function (in this case, a fitness function), subject to a resource constraint. The host can invest these resources in either reproduction or longevity, with the general form of the fitness function (in absence of the disease) being: $\omega = a r_b^{\alpha} r_m^{\gamma}$, with r_b representing investment in reproduction and r_m representing the investment in maintenance. This function is actually the basic reproductive ratio of the host, and is something I derived from a population growth model (equation (2)), but it turns out to have the identical form as the classical Cobb-Douglas utility function used so frequently in the economics literature. I very much like this general form, and am surprised it had not been developed previously given the substantial literature on the assumed trade-off between reproduction and survival that dates back at least as far as Lack's theory of optimal clutch size (Lack, 1947) and was formalized in r- and K-selection theories presented by MacArthur and Wilson (MacArthur and Wilson, 1967; Pianka, 1970). The evolutionarily stable strategy of the host is therefore the combination of pre- and post-infection allocations of resources towards reproduction and maintenance that maximizes its fitness - its lifetime reproductive success.

I find some quite interesting results. First, the ES pre-infection investment in reproduction is always greater than the post-infection investment. This is due to two forces that I term (1) the budget effect, and (2) the allocation effect. The budget effect simply refers to the loss of total resources after infection to the pathogen. The allocation effect refers to the relative reallocation of host resources due to infection. The investment in reproduction falls because (1) the host has fewer total resources, and (2) because it compensates for its future loss of resources before infection. This is because when the host invests in survival before infection, a portion of that investment is stolen by the pathogen, but when it invests in reproduction, it is not. After infection, however, the pathogen depletes resources from both causes. The host therefore compensates for its future loss of resources by investing more in reproduction before infection. Indeed, such pre-infection fecundity compensation eventually becomes sufficiently high, that pre-infection investment in maintenance is reduced to its post-infection levels, despite the loss of total host resources after infection. In other words, sterility may simply be a host life-history strategy in the context of a resource-depleting pathogen. I also find that, if the pathogen explicitly lowers the return on reproductive investments - i.e., through castration - it can induce the host to redirect more resources towards maintenance. Thus, through castration, the pathogen could potentially manipulate the hosts self-interest, causing gigantism. This paper is currently in press in *The American Naturalist* (Bonds, 2006)

1.6 Chapter 4: An Ecological Framework for Global Health and Economic Development

Finally, after becoming familiar with the current natural science literature on pathogen evolution, and then contributing to that literature (Bonds et al., 2005; Bonds, 2006), my goal was to more effectively revisit the original motivation for this dissertation: to integrate principles in ecology and economics for the purposes of understanding human ecology - with host-pathogen interactions as a case study.

From Bonds et al. (2005) and others, we know that host social behavior can influence the evolution of virulence. Are there ways in which *human* behavior, both recently and over the course of history, have systematically influenced the evolution of pathogen virulence? This is a potentially important question, given the rapid rates of pathogen evolution and the emergence of novel infectious diseases, such as HIV/AIDS, SARS, West Nile virus, as well as the emergence of anti-drug-resistant strains of endemic infectious diseases, such as malaria and tuberculosis. We now know, after all, that the flip-side of this equation is true: infectious diseases have systematically affected human activity. This is true over evolutionary as well as historical time (McNeill, 1976; Diamond, 1997; Motulsky, 1960; Ewald, 1994; Curtis, 2001; Carter and Mendis, 2002), and remains true today (Nokes et al., 1992; Holding and Snow, 2001; Fernando et al., 2006; Ezeamama et al., 2005; Sachs and Malaney, 2002; Sachs et al., 2004).

The most significant impact of infectious diseases is on the developing world. This effect is both direct, such as through morbidity and mortality, as well as indirect through the effects on child-learning and economic growth. It is this latter effect that would naturally attract the most attention of social scientists and is primed for collaborative work. But, while I originally set out to consider the evolutionary consequences of certain forms of human activity, such as changes in disease exposure due to economic development, it became obvious that we actually do not yet even have a formal *ecological* framework for exploring the relationship between economic development and the ecology of infectious diseases. As mentioned above, such a framework is a necessary precursor for evolutionary models.

As in Bonds et al. (2005) (Chapter 2), Chapter 4 focuses on the effect of host behavior on pathogen transmission. But in this case, the behavior is explicitly determined by economic factors - specifically, per capita income. The question we ask is: how do changes in income systematically affect the ecology of infectious disease (specifically, we consider a general model for childhood diseases) through changes in the transmission, and how does that, in turn, affect per capita income and therefore economic development.

The premises of this model are quite simple and well-established in the respective ecology, epidemiology, and economics literatures. A primary determinant of exposure to infectious diseases (i.e., of the transmission rate) is household income. This is because protection from pathogens - something humans do naturally and systematically - requires economic resources in the form of housing conditions, clothing, basic sanitation, water quality, etc. However, it is believed that a key component of per capita income in the developing world is health, arising from both the need to perform physical labor, as well as for the acquisition of training and skills during childhood. Thus, lower income results in greater disease transmission, and greater disease transmission results in lower income. Such a positive feedback has been hypothesized to form a poverty trap (Gallup and Sachs, 2001b; Sachs et al., 2004), but no formal ecological framework has been developed.

We present such a framework here that is unique in its simultaneous treatment of economic and ecological feedbacks not present in other efforts of integration (Daily et al., 2000; Costanza and Daly, 1992), and have some interesting conclusions along with some possible implications for public policy. We find that, after accounting for an income effect, reducing fertility may result in significantly lower disease prevalence over the long (economic) term than would a standard S-I-R epidemiological model predict, and might even be an effective strategy for eradicating some infectious diseases. Such a solution would make Malthus proud.

Chapter 2

Higher Disease Prevalence Can Induce Greater Sociality; a Game Theoretic Coevolutionary Model

2.1 Introduction

It is well known that infectious diseases constitute a substantial source of morbidity and mortality in natural populations, and are, perhaps, especially common among social organisms. Indeed, many communicable diseases are thought to require a minimum level of host interaction - e.g. mating, gregariousness, or population density - to avoid extinction. There is also growing evidence that animals have evolved behavioral responses to mitigate the risks of infection, such as lowering their contact (Hart, 1990; Loehle, 1995; Møller et al., 2001; Moore, 2002; Altizer et al., 2003). For example, in 1976, Freeland presented his hypothesis that, "individual primates increase their fitness by patterning their behavior and social interaction so that they minimize the probability of acquiring new pathogens and minimize the pathogenicity of diseases they already harbor." It is therefore reasonable to suspect that diseases represent a selective force - specifically, a cost - on the evolution of social systems (Alexander, 1974; Brown and Brown, 1986; Pulliam and Caraco, 1984; Lee, 1994; Møller et al., 2001). Indeed, it has been suggested that infectious diseases may actually determine *upper* limits of host group size and contact levels (Freeland, 1976, 1979; Moore, 2002). But while theories on the evolution of sociality abound, formalizations of the role of infectious diseases are lacking. Here, we present a theory of the evolution of host sociality in response to infectious diseases. We then augment this theory with the evolution of virulence and present coevolutionarily stable strategies of host sociality.

We find that, for systems where the benefits of social behavior are expressed in the form of lower mortality rates - such as decreased predation - pathogens become *less* virulent at high contact rates. This is in direct contrast to leading theories on pathogen evolution that have posited that greater transmission opportunities should either result in higher pathogen virulence (Ewald, 1994; Massad, 1996), or have no long-term effect on pathogen evolution (Frank, 1996; Lipsitch and Nowak, 1995; Lipsitch, 1997; Day, 2002; Bull, 1994). Moreover, we find that increases in disease prevalence can ultimately induce *greater* host sociality.

2.2 The Evolution of Social Contact in the Context of Infectious Diseases

The theoretical literature on the evolution of host contact in response to infectious diseases has mostly focused on sexually transmitted diseases, where such contacts are discrete and their benefits (reproduction) and costs (risk of sterilization or death through contracted disease) are explicit (Freeland, 1976; Møller et al., 1993; Sheldon, 1993; Antonovics and Thrall, 1994; Thrall and Antonovics, 1997; Boots and Knell, 2002; Kokko et al., 2002). However, there has been significant theoretical exploration of the benefits of sociality generally, which often focuses on non-reproductive life-history traits such as greater survival from decreased predation (Pulliam et al., 1977; Caraco et al., 1980; Szekely et al., 1991). For example, many social species of birds have been documented to benefit from "early warning" of predators (Caraco et al., 1980; Pulliam, 1973; Hoogland and Sherman, 1976; Lazarus, 1979; Whitfield, 2003; Beauchamp, 2004). These same benefits have been hypothesized for many other social animals, from prairie dogs (Hoogland, 1979) to squirrel monkeys (Boinski et al., 2003). Other advantages of grouping include enhanced defense, such as through mobbing of predators (Hoogland and Sherman, 1976), and "selfish herding" (Hamilton, 1971), where neighboring group members serve as alternative targets for predation. Of course, sociality is not without costs, and there has been much speculation on what factors limit social evolution. The most obvious candidate is intragroup competition for resources (Freeland, 1976; Pulliam and Caraco, 1984; Lee, 1994), but there are also costs associated with predation. For

example, larger group sizes may be more conspicuous to predators, leading to higher rates of attack per group member, in addition to possible greater attack efficiency that results from the prey density (Krebs, 1971; Andersson and Wicklund, 1978; Pulliam and Caraco, 1984). Another proposed limiting factor of sociality - and the one that constitutes the focus of this analysis - is the spread of infectious diseases (Freeland, 1976; Brown and Brown, 1986; Pulliam and Caraco, 1984; Møller et al., 2001; Moore, 2002; Lee, 1994). Here we present a theory on the evolutionary relationship between non-reproductive social behavior and horizontally transmitted infectious diseases.

2.3 Model

We consider the evolution of social behavior of a homogeneous host population that reproduces asexually. Specifically, we imagine social behavior such as grouping, which confers both fitness benefits (early warning) and costs (group conspicuousness) in the form of individual survival. We assume that the relationship between survival and contact obeys a trade-off, so that, in the absence of the disease, the host's contact rate or group size will evolve to some finite optimum, K.

The system is described by a traditional S-I (susceptible-infected) model, in which we explicitly define the role of contact on host mortality and disease transmission, with each phenotype i corresponding to a rate of contact, C_i. The population dynamics of phenotype i can be described by the following differential equations:

$$\frac{dS_i}{dt} = (a - hN)(N_i) - \left(d + p(K - C_i)^2 + \frac{\beta_i(C_i)I}{N}\right) S_i, \quad (1)$$

$$\frac{dI_i}{dt} = \frac{\beta_i(C_i)I}{N} S_i - (d + p(K - C_i)^2 + v) I_i. \quad (2)$$

The state variables, S_i and I_i, represent the number of susceptible and infected individuals of phenotype i. The density-dependent reproductive rate is $a - hN$, with $N = S + I$, $S = \sum_i S_i$, and $I = \sum_i I_i$. The parameter a represents the maximum per capita birth rate (as

N approaches 0), and h represents the decrease in the birth rate that results from density dependence (e.g. through competition of resources). The death rate depends on the infection status of the host in addition to the contact rate. The death rate of susceptibles is the quadratic function, $d + p(K - C_i)^2$, which, in the absence of the disease, can be minimized by a contact rate of $C_i = K$. The "cost" of deviating away from the disease-free optimum, K, is partially determined by the parameter, p (i.e., if $p = 0$, then there are no advantages to sociality, and as p rises away from 0, the cost of "avoidance" rises). The pathogen is virulent, with infected individuals dying at the same rate as the susceptibles plus the rate of virulence, v. We assume that the hosts mix randomly, so that an individual's contact frequency can be viewed as the product of its own "contact effort", E_i, and the average contact effort of the population, E_a, so that $C_i = E_i E_a$. The transmission rate is equal to the probability of infection per contact, ρ, times the contact frequency: $\beta_i(C_i) = \rho E_i E_a$.

Because the benefits (survival) and costs (disease transmission) of contact are determined not only by the contact effort of the individual, but also by that of the rest of the population, the optimal contact effort, $\hat{E}$, can be considered the solution to an evolutionary game. The first step to solving this game is to maximize a fitness function (equation (3)) with respect to E_i. The fitness function equals the number of offspring in the lifetime of the host, which can be treated as a Markov process with three events: birth, infection, and death. The fitness function is therefore:

$$\begin{aligned} \omega_i \quad \propto \quad & \frac{1}{d + p(K - E_i E_a)^2 + \rho E_i E_a \frac{I}{N}} + \\ & \frac{\rho E_i E_a \frac{I}{N}}{(d + p(K - E_i E_a)^2 + \rho E_i E_a \frac{I}{N})} \frac{1}{(d + p(K - E_i E_a)^2 + v)} \end{aligned} \tag{3}$$

The first term, $1/(d + p(K - E_i E_a)^2 + \rho E_i E_a I/N)$, equals the time spent susceptible, $\rho E_i E_a (I/N)/(d + p(K - E_i E_a)^2 + \rho E_i E_a I/N)$ is the likelihood of reaching the infectious class (as opposed to dying), and $1/(d + p(K - E_i E_a)^2 + v)$ represents the time spent infected.

In order to obtain an expression for the optimal contact rate, we first define $\hat{E}_i = f_1(I/N, E_a)$ as the value of the contact effort, E_i, that maximizes equation (3). Because

this game is symmetric (i.e. the "rules" are identical for all "players"), at the optimum, the contact efforts are equal to the Nash equilibrium level, $E_i = \hat{E}_i$ for all i. Therefore, to find the optimal contact effort, we set E_a equal to $\hat{E}_i$, generating $\hat{E} = f_2(I/N)$. The optimal contact rate is therefore, $\hat{C} = \hat{E}^2$. Figure 2.1 shows that, when the average contact effort equals $\hat{E}$, the fitness for any invading phenotype, $E_i \neq \hat{E}$, is less than that conferred from $\hat{E}$.

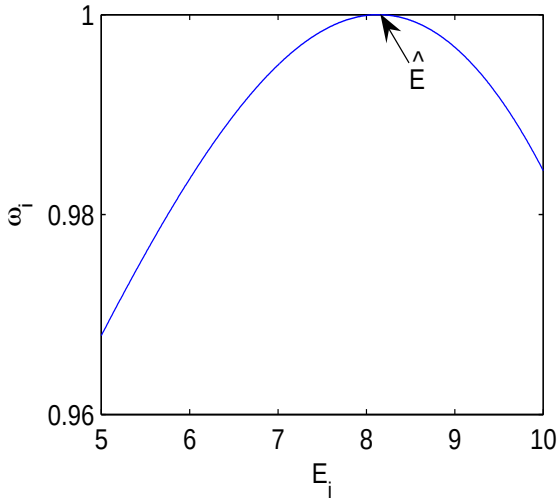

Figure 2.1: The fitness of individual i, ω_i, defined as its lifetime reproductive success, is presented for values of invading contact efforts, E_i, when the population adopts the contact effort, $\hat{E}$. Some of the parameter values used ($v, I/N$, and ρ) are determined dynamically as state variables in the coevolutionary model in Section 2.5. These results therefore complement those presented in Figures 2.5 and 2.6; $v = 0.4, I/N = 0.7, p = 0.00005, K = 81, \rho = 0.03, d = 0.15$.

The Optimal Contact Responds to Disease Prevalence

To understand the evolutionary response of host sociality to changes in disease prevalence, we present the optimal contact rates and disease prevalence over a range of background mortality and transmission probability parameters (Figure 2.2). To maintain consistency with the evolution of virulence literature as well as the developments in Section 2.5, we specify the transmission probability, ρ, as a function of pathogen virulence: $\rho(v) = gv/(v+\xi)$, with g representing the maximum probability of transmission as v approaches infinity, and ξ determining the "rate" at which that limit is arrived as virulence increases.

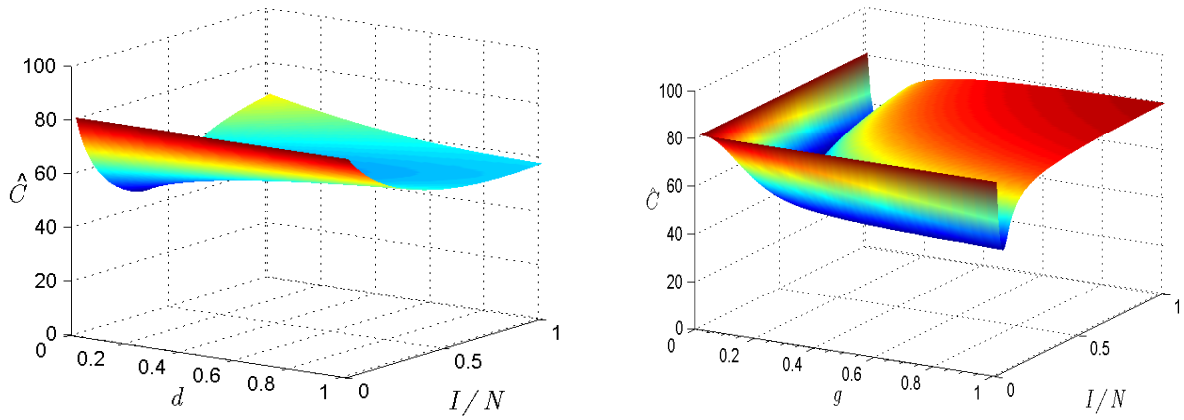

Figure 2.2: a) The optimal contact rate is presented over a range of exogenously determined rates of mortality and disease prevalence; $K = 81, \rho = gv/(v+\xi), g = 0.1, v = 0.5, \xi = 1, p = 0.00005$ (the value for p corresponds to more than a 50% increase in the host mortality rate when the contact rate is reduced by 50%). b) The optimal contact rate is presented over a range of exogenously determined transmission probabilities and disease prevalence; $d = 0.15, K = 81; \rho = gv/(v+\xi), v = 0.5, \xi = 1, p = 0.00005$.

As expected, we find that, as disease prevalence rises away from zero, the optimal contact rate falls from its disease-free optimum, K. What is more surprising however, is that, after some threshold level of prevalence, the optimal contact rate rises for a large range of d and g values (this phenomenon was also observed with an alternative mortality function; see Supplementary Material available online). This is because, when the disease prevalence is high, the benefits of disease avoidance, in terms of decreased likelihood of acquiring the disease, are negated by the survival advantages conferred from higher contact rates. This is directly analogous to the finding by van Baalen (1998) that the optimal host investment in an immune response (which, similar to disease avoidance, is assumed to have negative effects on host survival) is a nonmonotonic function of the force of infection. Specifically, optimal immune investment is highest at intermediate probabilities of infection, and is lowest at high and low probabilities. It is important to be mindful that in our system we are assuming there remain benefits of contact even after infection. So, the benefits of lowering contact come in

the form of a delayed timing of infection, where the cost of lowering contact is suffered throughout the course of the host's life. This is why, at high transmission probabilities, the optimal contact rates start rising with respect to disease prevalence. As van Baalen (1998) writes, the host makes, "the best of a bad job." This is also why, as the pathogen becomes increasingly pathogenic, and the benefits of contact after infection fall (because the host dies sooner), the relationship between contact and disease prevalence becomes monotonic (Figure 2.3).

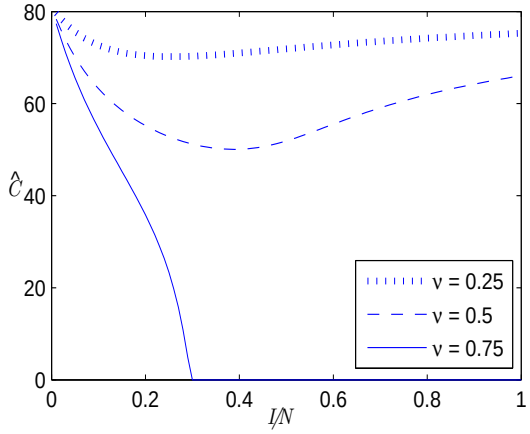

Figure 2.3: The optimal contact rate is presented over a range of exogenously determined rates of disease prevalence, with different values of pathogen virulence. At relatively low levels of virulence, the ES contact rate responds nonmonotonically to disease prevalence. At high levels of virulence, the ES contact rate responds negatively to disease prevalence; $p = 0.00005, K = 81, \rho = gv/(v+\xi), g = 0.1, \xi = 1; d = 0.15$.

The important point to draw from the figures above is that there is no *a priori* reason to expect host sociality to generally decrease with increases in disease prevalence. Indeed, while the contact rate never rises above its disease-free optimum, K, the ability of the disease to induce contact rates below K is weakest when the prevalence is both low and high. As a result, when the prevalence increases above some threshold level, so too may the optimal contact rate.

2.4 Evolutionarily Stable Contact and Disease Prevalence Respond to Each Other

The analysis in Section 2.3 is important for a partial understanding of the interactions between host evolution in response to communicable diseases but it is nevertheless superficial in that it unrealistically treats disease prevalence as exogenous. In reality, host contact is not only a function of the pathogen prevalence, but the prevalence is also a function of host contact. Solving for the fitness-maximizing contact rate and equilibrium disease prevalence simultaneously results in the evolutionarily stable (ES) contact rate, $C^* = f_3(I^*/N^*)$ (note that we use the "hat" (^) notation to denote the optimal value when prevalence is not in equilibrium with contact, and the "star" (*) notation to denote the ES value when prevalence is in equilibrium with contact). In Figure 2.4, we present corresponding values of C^* and I^*/N^* over a range of background mortality and transmission probabilities.

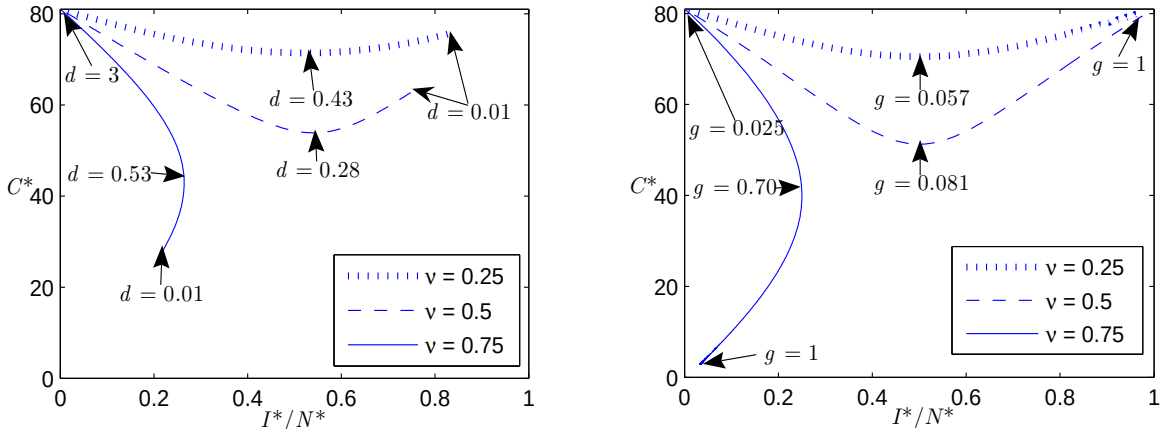

Figure 2.4: a) ES contact and the corresponding equilibrium disease prevalence are presented for different values of virulence, v, over a range of background mortality rates; $d \in [0.01, 3]; K = 81, p = 0.00005, \rho = gv/(v+\xi), g = 0.1, \xi = 1$. b) ES contact and the corresponding equilibrium disease prevalence are presented for different values of virulence, v, over a range of transmission probabilities; $g \in [0.025, 1]; K = 81, p = 0.00005, d = 0.15, \rho = gv/(v+\xi), \xi = 1$.

From Figure 2.4, we see a discernible trend in the general relationship between equilibrium disease prevalence and ES host contact rates. Both high rates of host mortality (Figure 2.4a) and low probabilities of disease transmission (Figure 2.4b) cause pathogen prevalence

to be low (or even zero), selecting for contact rates near the disease-free optimum of K. In essence, we can view being infectious for a short time (due to high mortality) and being poorly transmissive per unit of time (due to low transmission probabilities) as epidemiologically analogous, with both limiting the spread of the disease. At all nonzero rates of pathogen virulence, contact rates fall from their disease-free optimum as disease prevalence rises in response to decreases in background mortality or increases in disease transmission probabilities. Whether contact rates continue to fall as the parameters shift depends on the virulence of the disease. At relatively low rates of pathogen virulence, contact rates eventually begin to rise as prevalence rises. This is expected because we know from Figure 2.2 that contact rates will rise at high rates of disease prevalence when virulence is low. But when the pathogen threatens a relatively quick death (with high virulence), infection poses a more powerful deterrent to contact (Figure 2.2), and the relationship between contact and the parameters d or g become monotonic.

2.5 Coevolution of Host Sociality and Infectious Disease

We have shown that ES host contact rates may be nonmonotonic functions of disease parameters for organisms whose survival depends on sociality. However, just as the analysis in Section 2.2 is partial in the sense that it treats disease prevalence as exogenous to host contact, the analysis in Section 2.3 is only partial in that it treats pathogen virulence as exogenous. The question we now pose is: in what way will the host influence the evolution of the pathogen? And if the host is evolving in response to the pathogen, and the pathogen evolves in response to the host, what general properties of this coevolutionary system can we predict? In other words, how does host sociality *coevolve* with infectious diseases?

Ewald (1994) hypothesized that higher host contact rates select for more virulent strains of pathogens. This is because, he argued, there is a positive relationship between pathogen virulence and transmission, and high levels of host contact offer transmission opportunities

for the pathogen, increasing the benefits of being transmissive while lowering the costs of virulence. However, because most evolutionary models of simple disease-host systems predict that pathogens maximize their basic reproductive ratio, R_0 (Bremmermann and Thieme, 1989; Frank, 1996), host behavior that influences birth rates and transmission rates multiplicatively will not have any influence on pathogen evolution at the population equilibrium (Lipsitch and Nowak, 1995; Lipsitch, 1997; Day, 2001; Bull, 1994). For example, a typical R_0 for an S-I equation is $R_0 = \beta(C, v)/(d + v)$, where $\beta(C, v) = \rho(v)C$, and $\rho(v) = gv/(v + \xi)$. The evolutionarily stable rate of virulence is, $v^* = \sqrt{\xi d}$, which is a simple positive function of the host's death rate. The reasoning is that, by shortening the time allotment for transmission, high host death rates select for high transmission rates and their corresponding level of virulence. Alternatively, long-lived hosts favor lower pathogen virulence and lower transmission rates. And because the evolution of virulence literature has generally assumed host contact to be independent of host survival, it is considered to not influence long-run pathogen evolution.

However, we emphasize here that the reason for contact among social organisms is precisely *because* it confers greater fitness, which may often be due to lower death rates. Therefore we predict host contact rates to have a long-run influence on the evolution of virulence. In our model, R_0 is:

$$R_0 = \frac{C\rho(v)}{d + p(K - C)^2 + v}, \tag{4}$$

where $\rho(v) = gv/(v + \xi)$. The evolutionarily stable virulence is then:

$$v^* = \sqrt{\xi(d + p(K - C)^2)}. \tag{5}$$

Our prediction is therefore exactly opposite of the ideas put forth by Ewald (1994). Starting from the disease-free optimum, K, any decrease in C will result in a higher host death rate and greater virulence. Alternatively, any increase in host contact rates from some preexisting equilibrium of C that is necessarily less than K would result in longer life expectancy and lower virulence. Perhaps more importantly, because pathogen evolution is a function of host

sociality, and host sociality is a function of virulence, the appropriate approach to considering this relationship is by calculating *coevolutionarily* stable strategies (van Baalen, 1998; Restif et al., 2001; Gandon et al., 2002b; Restif and Koella, 2003).

Now we can solve both evolutionarily stable strategies simultaneously to determine the coevolutionarily stable (CoES) contact rate, $C^{**} = f_4(\rho(v^*), v^*)$, and virulence, $v^{**} = f_5(C^*)$, (note that we use the "star " (*) notation to denote the ES value, and the "double-star" (**) notation to denote the CoES value). In Figure 2.5 we can see that a coevolutionary equilibrium is located at the intersection of the host contact curve (or "reaction function") and the pathogen virulence curve. Notice that pathogen virulence *falls* as contact rises, counter to the hypothesis by Ewald (1994). It is also not surprising to see that, as virulence rises, the ES contact rate falls, which can also be seen in Figures 2.3 and 2.4. We verified these results in Figure 2.5 by stochastically simulating coevolution from an initial population of pathogens and hosts with a wide range and even distribution of virulence and contact rates respectively (Figure 2.6). The mean values converge on C^{**} and v^{**} as the distribution of these phenotypes narrows over time. For a more detailed explanation of the simulation, see Appendix.

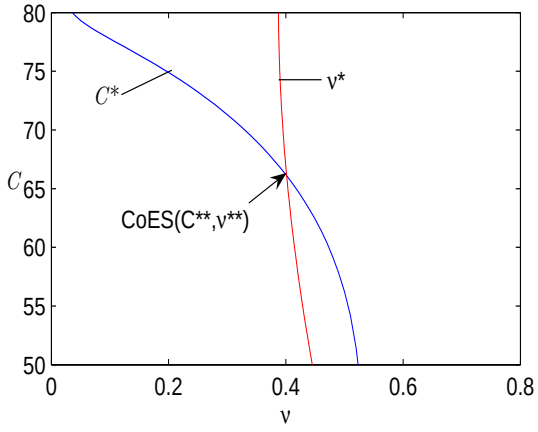

Figure 2.5: The coevolutionary equilibrium is where the contact and virulence curves intersect. Notice that the optimal virulence falls as contact rises; $d = 0.15, \xi = 1, K = 81, p = 0.00005, g = 0.1$.

Coevolutionarily stable rates of contact are presented with their corresponding pathogen prevalences over a range of parameter values in Figure 2.7. The important feature is that

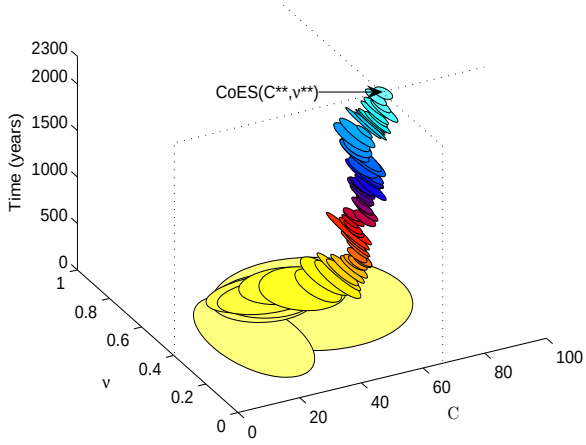

Figure 2.6: Contact and virulence coevolve in a stochastic simulation. The coordinates of the center of each disk represent the average contact and virulence at each time period, which is incremented in units of 25 years. The distance between the top and bottom of the disk along the v and C gradients represent the standard deviation of the virulence and contact rates respectively. The dotted lines represent the analytically predicted values of the CoES equilibrium; $d = 0.15, \xi = 1, K = 81, p = 0.00005, g = 0.1$. For a more detailed explanation of the simulation, see Appendix C.

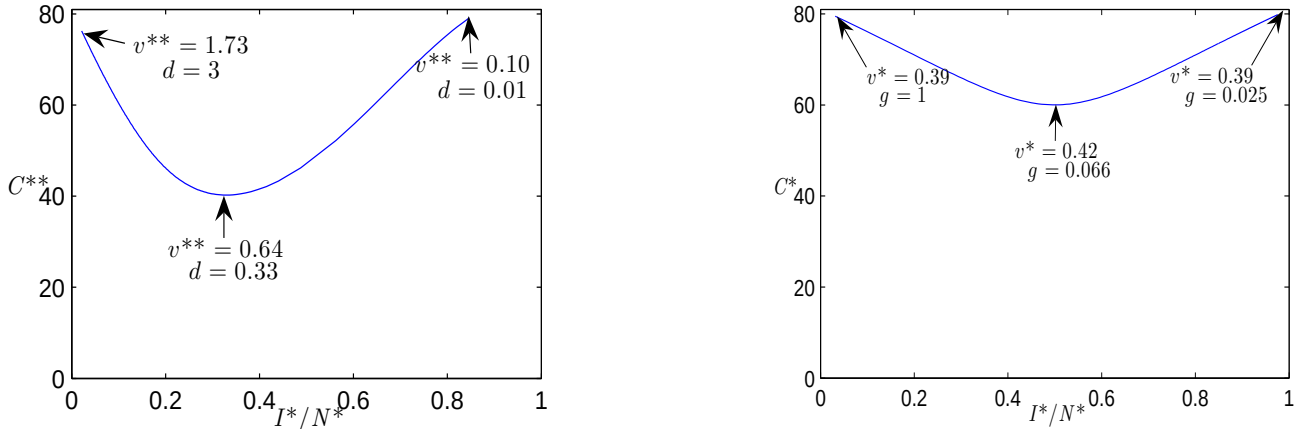

Figure 2.7: a) The coevolutionary relationship between contact and disease prevalence is U-shaped across background mortality rates; $d \in [0.01, 3], \xi = 1, K = 81, p = 0.00005, g = 0.1$. b) The coevolutionary relationship between contact and disease prevalence is U-shaped across a range of transmission probabilities; $g \in [0.025, 1], d = 0.15, \xi = 1, K = 81$.

the relationship between host contact and pathogen prevalence is nonmonotonic, and indeed we see contact rates with maximum values at low and *high* values of pathogen prevalence. While the ultimate reasons for this are complex, there are partial relationships that play an important role: 1) high levels of disease prevalence negate the value of avoidance, selecting for contact rates near the disease-free optimum; and 2) high contact rates induce *lower* pathogen virulence, increasing the life expectancy of infected individuals and feeding back to higher disease prevalence.

It is also worth noting that the range of virulence values observed between the two figures varies substantially from $v = 0.1$ to $v = 1.75$ (Figure 2.7a), to $v = 0.38$ to $v = 0.42$ (Figure 2.7b). This can be understood by considering the strategy of the pathogens (equation 5), which is a function of background mortality, d, but is not a function of the transmission probability parameter, g. Therefore, when we change the value of g, we alter the strategy of the host, but not that of the pathogen. This corresponds to a *different* contact curve, so that the coevolutionarily stable strategies move *along* the virulence curve - which, in this case, has a relatively narrow range. However, when we alter the value of d, *both* strategies change, corresponding to new curves for both players in this coevolutionary game, resulting in a broader suite of values for virulence. Another consequence of d influencing the strategies of both players (instead of only one) is that we find a nonmonotonic relationship between the ES rates of contact and virulence over different d values (Figure 2.8). In other words, the *coevolutionary* outcome suggests a parameter range where contact and virulence are indeed positively related, which is not the case for our model in which only the pathogen evolves. Alternatively, plotting changes in g values would simply reproduce the monotonic virulence curve in Figure 2.5 because the pathogen strategy is not a direct function of g.

2.6 Discussion

There are two separate literatures on the relationship between host contact or sociality and disease prevalence. On the one hand, it is suggested that, because higher contact will

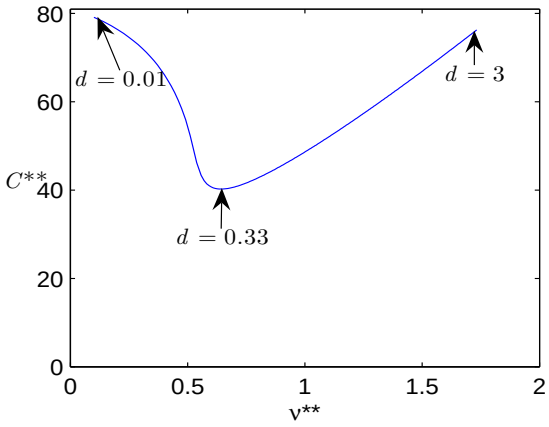

Figure 2.8: The CoES values of contact and prevalence are nonmonotonic over a range of background mortality rates; $d \in [0.01, 3], \xi = 1, K = 81, p = 0.00005, g = 0.1$.

induce greater disease transmission, we can expect a positive correlation between contact and prevalence (Anderson and May, 1979; Møller et al., 1993; Arneberg et al., 1998; Ezenwa, 2003). On the other hand, Freeland (1976, 1979), Hart (1988a, 1990), Loehle (1995), Moore (2002), and others have argued that the host may respond to higher prevalence with lower contact. These seemingly conflicting positions need to be addressed by noting, first, that the two variables - contact and prevalence - are determined simultaneously for systems in which diseases represent a cost to sociality. Moreover, systematic evolutionary responses from the pathogen must also be accounted for. Because of the complexity of this system, it is helpful to first consider the different processes in isolation in order to understand their interactions.

We present a model that differs from the standard S-I framework in two ways: host contact rates are assumed to determine both the rates of disease transmission and host mortality - as is expected to be the case for many social species. Specifically, we assume that, in the absence of the pathogen, the host would evolve to some finite optimal value of contact, and that the impacts on host survival that result from deviations from this optimum can be

represented by a quadratic function (though an alternative functional form produces similar results, see Supplementary Material available online).

We show that, as generally hypothesized, exogenously increasing disease prevalence from initial low values results in a decrease in the evolutionarily stable rate of contact (Figure 2.2). However, for a large range of the parameter space, the optimal contact rate increases as prevalence rises past a threshold level. In other words, though the disease never causes sociality to rise above the disease-free optimum, higher disease prevalence can actually *induce* greater sociality. This result is similar to that of van Baalen (1998), who finds that the optimal investment in immunity rises and then falls as infection probabilities rise. The reason for both of these results is that the costs of the host's response to the disease, in terms of higher mortality, eventually overwhelm the benefits of those responses when infection is sufficiently difficult to evade. In our model, this means that the host would then evolve greater sociality at high levels of disease prevalence. An exception to this relationship is when the pathogen is sufficiently virulent to eliminate the value of contact after infection (Figure 2.3). In this case, the optimal contact will fall monotonically as prevalence rises.

It is these partial phenomena that explain the more complex interplay between equilibrium levels of disease prevalence and host contact, which is depicted in Figure 2.4. We alter the equilibrium disease prevalence through changes in background mortality (Figure 2.4a) and the transmission probability (Figure 2.4b). In both cases, we observe the U-shaped relationship between contact rates and prevalence for relatively low levels of pathogen virulence. At high virulence the relationship is backward bending - that is, contact rates continue to fall as the parameters shift, but the equilibrium disease prevalence also falls with it. In all cases, the relationship is nonmonotonic.

Finally, we consider pathogen evolution. We show that lower contact increases pathogen virulence, counter to Ewald's (1994) hypothesis. This is because, as contact rates fall from the disease-free optimum, so does host survival, lowering the benefits for the pathogen of preserving the host, and increasing the advantages of being transmissive. As we alter various

parameter values, we continue to find a U-shaped relationship between the CoES level of host sociality and the equilibrium disease prevalence (Figure 2.7). We also find a U-shaped relationship between the CoES level of host sociality and pathogen virulence (Figure 2.8).

How well does this model stack up against the evidence? While we are unaware of any studies that have tracked all three variables - contact rates, disease prevalence, and virulence - simultaneously, there a number of studies that have considered both disease prevalence and host group size (which is assumed to be highly correlated with contact rates), with a positive relationship often being observed (Davies et al., 1991; Côté and Poulin, 1995; Dobson and Meagher, 1996; Arneberg et al., 1998; Ezenwa, 2003). Such a positive relationship would always be predicted in cases where evolutionary forces were expected to be irrelevant. This would be the case if variations in group size merely represented stochastic variations around an evolutionary equilibrium, and not genetic heterogeneity due to localized differences in selection pressures such as background mortality.

However, if the variation in group size can be attributed to evolutionary forces operating under different ecological conditions then there are some statistical issues that would complicate the analysis. A necessary condition for making statistical inference from simple linear regression analyses is that the "regressor" (or "independent variable") is "independent" of the "regressand" (or "dependent variable"). However, in cases where host demographics can be attributed to genetic variation responding to selection pressure from diseases, both variables - group size and disease prevalence - are *dependent* on each other. In other words, such analyses suffer from an "endogeneity bias". This is in addition to an "omitted variable bias", with the relevant omitted variable being pathogen virulence. Unfortunately, the system we are describing is *nonlinear* and our expected relationship between these variables is not even monotonic. Therefore, we have no *a priori* expectation of the direction (up or down) of such biases; it depends on the parameter values that generate the different equilibrium outcomes for these subpopulations. It is not surprising therefore that Ezenwa (2003), for example, found no significant correlation between group size and disease prevalence for 4 out of 6

populations of African bovids she studied. One might also wonder how many unpublished studies found no significant correlations.

In contrast to the studies that find a positive relationship between group size and disease prevalence, the absence of studies that find a negative general correlation is conspicuous. This is especially surprising given the mounting evidence that animals change their behavior in response to risks of infection. Such behaviors include avoidance of infected conspecifics - observed, for example, experimentally in mice (Edwards, 1988) and guppies (Kennedy et al., 1987) - as well as individual preference for parasite-free habitats, such as nesting sites (Emlen, 1986; Christe et al., 1994), and grazing space (Hart, 1988b). If diseases constitute strong enough selection pressure to alter animal behavior temporarily, why have we not seen evidence of more substantial evolutionary influences on social structure such as grouping? One possible answer is simply that we would expect both positive *and* negative relationships, something that *cannot* be distilled from simple regression analyses. Those that have found positive relationships may be capturing population ecological forces that are expected to be positive in the absence of evolutionary responses.

Because of all of the important interacting factors between host contact rates, pathogen prevalence, and virulence, it would appear that the proper first step to confirming a theory such as this is in the laboratory, where the relevant parameter values can be systematically altered and the analysis can be conducted on data with high resolution.

In their classic paper, Brown and Brown (1986) suggest that, "without compensating benefits of coloniality, the cost of ectoparasitism would quickly select for solitary nesting in Cliff Swallows." Similarly, Møller et al. (2001) argue that "if the cost of parasitism is greater in colonial species than in solitary ones, there should be selection for early fledging within species since nestlings thereby could evade their parasites." This logic is common. Counter-intuitively, our analysis indicates that increased prevalence of infectious diseases can actually induce greater sociality.

Chapter 3

Host Life History Strategy Explains Pathogen-Induced Sterility

3.1 Introduction

Host fitness can be decomposed into two essential components: reproduction and longevity. Theory on the effect of pathogens on the latter has received much attention in the last several decades, and indeed has largely come to define virulence (Bremmermann and Pickering, 1983; Frank, 1996; Day, 2001; Bonds et al., 2005), but the ability for pathogens to decrease host reproduction has received only minimal theoretical treatment (Obrebski, 1975; Forbes, 1993; Perrin and Christe, 1996; Jaenike, 1996; O'Keefe and Antonovics, 2002). In reality, virulence can, and often does, manifest itself in the reduction of host fecundity without significantly altering host mortality.

Pathogen-induced fecundity-reduction has been found in a wide range of taxa (Baudoin, 1975; Kuris, 1974; Hurd, 2001), and is perhaps especially common in invertebrate systems such as crustaceans (Ebert et al., 2004) and molluscs (Sorenson and Minchella, 2001). Though some have considered such fecundity-effects to be simply an incidental consequence of infection (Polak, 1996; Sousa, 1983), general explanations tend to focus on whether it is an explicit evolutionary strategy of the host (McClelland and Bourns, 1969; Moret and Schmid-Hempel, 2000; Hurd, 2001), or of the pathogen (Rothschild and Clay, 1952; Baudoin, 1975; Ebert et al., 2004). In the case of the former, the host is thought to mount a defense against the disease, which involves the redirection of host resources away from reproduction and towards survival (van Baalen, 1998; Day and Burns, 2003).

Alternatively, lost host fecundity has been thought to be due to the general loss of host resources to the pathogen for its own transmission (Salt, 1927; Reinhard, 1956), or the outcome of the pathogen selectively targeting host reproductive resources in order to minimize the negative effect of infection on host survival, which is also the pathogen's (Summerfelt and Warner, 1970; Cheng et al., 1973). This latter scenario has been formalized by Jaenike (1996) and O'Keefe and Antonovics (2002), who assume a negative relationship between host and pathogen reproduction, and therefore find that the optimal pathogen strategy would be complete sterilization, which is relatively rare in nature. In contrast, Gandon et al. (2002a) considered the possibility that investments in both reproduction and survival evolve in response to parasitism, and found that, if virulence is in the form of greater host mortality, pathogens should induce the host to increase reproductive effort upon infection. How can these results be reconciled?

At first glance, the dearth of theory on pathogen-induced fecundity-reduction would seem to be easily remedied and integrated into the general evolution of virulence literature. After all, the principles on which this literature currently relies - that disease transmission depends on host resources, often causing death - would seem to also explain loss of fecundity. That is, because host reproduction also requires resources, we should naturally conclude that it would be compromised by infection. Indeed, this common need for scarce resources is the basis of the long-standing principle of life-history theory that organisms face a trade-off between reproduction and longevity (Stearns, 1992). However, in reality, the effect of parasites on host reproductivity can be even more complex and interesting. For example, sterilized hosts have been known to actually become larger or live longer after infection (Baudoin, 1975; Moore, 2002; Ebert et al., 2004), betraying the simple loss of host resources as a general explanation. Clearly, parasitism sometimes influences the allocation of those resources. But how?

I present a general model of the evolution of pathogen-induced changes in host fecundity, which integrates into the evolution of virulence literature by assuming that virulence is the

result of the pathogen's need for host resources for its own transmission. Importantly, I do not assume that the pathogen explicitly targets either host reproductive resources or maintenance resources. Rather, I assume that the host can direct its resources to either objective, and thus its resources are used for both host reproduction and survival. Sterility is then treated as the result of two driving forces: 1) the loss of total host resources that are directed to the pathogen for its own transmission; and 2) the loss of resources for host reproduction due to their reallocation towards maintenance after infection.

I find that, assuming plasticity in the allocation of host resources, a pathogen which necessarily steals some of those resources for its own transmission, will always induce the host to invest a greater proportion of its total resources towards reproduction before infection compared to after infection. This is because the benefits of investing in reproduction of an uninfected host are enjoyed solely by that host, whereas the investments in longevity are partly stolen by the pathogen. Moreover, such pre-infection "fecundity compensation" may be sufficiently high that it reduces pre-infection investment in survival to its post-infection levels, despite the loss of total available resources after infection. In other words, the relative affect of a pathogen on host reproduction and survival may be determined by the host life-history strategy.

However, the special case of pathogen-induced gigantism can only be explained in this context by the direct interference of the host reproductive system - i.e., castration - inducing the infected host to decrease its reproductive effort in order to increase its investment in maintenance. Thus, the pathogen manipulates the host's self-interest for its own survival.

3.2 Model

To analyze the evolution of pathogen-induced changes in host fecundity, I determine evolutionarily stable (ES) allocations of host resources toward reproduction and maintenance before and after infection. The evolutionarily stable strategies (ESSs) are derived from a classic S-I (susceptible-infected) population framework. This model framework does not

allow for host recovery, and therefore it would not apply to acute disease systems where the pathogens are cleared rapidly, but would apply to many parasite systems such as that of *Daphnia magna* infected with the sterilizing bacterium *Pasteuria ramosa*, (Ebert et al., 2004). The expected effects of host recovery on the ES resource allocations is considered in the Discussion.

Consider the following S-I equation:

$$\frac{d\ddot{S}}{dt} = (b_S\ddot{S} + b_I\ddot{I})\left(\frac{K-\ddot{N}}{K}\right) - d_S\ddot{S} - \lambda\ddot{S} \quad (1)$$

$$\frac{d\ddot{I}}{dt} = \lambda\ddot{S} - d_I\ddot{I}. \quad (2)$$

A scale-free model can be derived by dividing equations (1) and (2) by the carrying capacity, K, and setting $S = \ddot{S}/K, I = \ddot{I}/K$, and $N = \ddot{N}/K$, which results in equations (3) and (4):

$$\frac{dS}{dt} = (b_S S + b_I I)(1-N) - d_S S - \lambda S \quad (3)$$

$$\frac{dI}{dt} = \lambda S - d_I I. \quad (4)$$

The parameters b and d represent birth and death rates respectively. Notice that they are allowed to change after infection, with the S and I subscripts indicating the rates for susceptible and infected individuals respectively. The variable N represents the total population, which is the number of susceptibles, S, plus the number of infecteds, I, scaled by the carrying capacity. The parameter, λ, is the force of infection.

The specific model used above is very similar to that used by O'Keefe and Antonovics (2002), and Gandon et al. (2002a). The important difference between their models is that the former assume that, for the purposes of transmission, the pathogen must directly reduce host reproduction and the latter assume that the pathogen must reduce host survival. These assumptions are very important because they are what drive O'Keefe and Antonovics (2002) to conclude that complete sterilization is the optimal pathogen strategy, where Gandon et al. (2002a) determine that host reproduction should actually rise after infection. I do not make any assumptions about which host life-history properties are compromised by

pathogen virulence, but instead assume reproduction and survival both rely on a fundamental resource, r, that is limited per time period, and which the pathogen also marshals for its own transmission.

Host fecundity can be decomposed into two basic phenomena: 1) reproductive effort, which I define as the investment of resources into reproduction; and 2) reproductive efficiency, defined as the number of offspring produced per unit of reproductive effort. Reduction of host reproductive effort upon infection has been further reduced to two mechanisms: 1) loss of host resources to the pathogen for its own transmission; and 2) reallocation of host resources away from reproduction and towards survival. Such a trade-off between reproduction and survival is accounted for in this model by the assumption that the fundamental resource, r, has a fixed value per time period of $\bar{r}$. The general functions for the birth and death rates for the susceptible individuals are $b_S = ar_{b,S}^{\alpha}$ and $d_S = gr_{m,S}^{-\gamma}$ respectively, with $r_{b,S}$ and $r_{m,S}$, representing the respective investments in reproduction and maintenance for susceptible individuals. The parameters a, α, g, and γ determine the efficiency by which the host converts its resources to reproduction and survival. The allocation of host resources towards reproduction and survival are therefore in direct competition with each other as well as with the pathogen, so that $\bar{r}_S = r_{b,S} + r_{m,S}$ and $\bar{r}_I = r_{b,I} + r_{m,I} = \bar{r}_S - r_v$, where $r_{b,I}$ and $r_{m,I}$ are the amount of the infected host resources invested in reproduction and maintenance respectively, and r_v is the amount of host resources stolen by the pathogen. For an illustration of the relationship between $\bar{r}_I, \bar{r}_S$, and r_v, see Figure 3.1. To allow for the loss

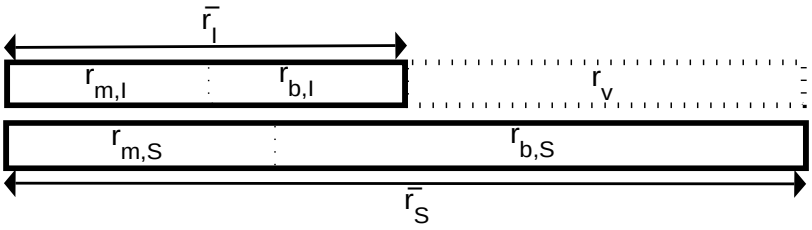

Figure 3.1: The resource budget of the infected host, $\bar{r}_I$, is equal to the pre-infection resource budget, $\bar{r}_S$, less the resources stolen by the pathogen, r_v.

of host reproductive efficiency, such as would result from pathogen-induced castration, the

birth function for infected individuals is $b_I = \rho a r_{b,I}^{\epsilon\alpha}$, with $\rho \in [0,1]$ and $\epsilon \in [0,1]$ representing sterility parameters that are controlled by the pathogen. The difference between the effects of ϵ and ρ on host reproductive efficiency are discussed in a later section and are depicted in Figure 3.8. The death function for infected individuals is $d_I = g r_{m,I}^{-\gamma}$.

Thus the pathogen has two avenues by which it can reduce host fecundity: indirectly, through stealing resources from the host, represented by an increase in r_v; or directly, by "castrating" the host, which corresponds to a decrease in ρ or ϵ.

3.3 Pathogen-Induced Sterility as Host Life-History Strategy

Because the allocation of resources into reproduction and maintenance have fitness consequences for the host, natural selection would favor such allocations that maximize the host's lifetime reproductive success when the population is in equilibrium. The question addressed in this section is: how would we expect parasitism to influence the change in the optimal allocation of host resources? What is $r_{b,S}^* - r_{b,I}^*$, and $r_{m,S}^* - r_{m,I}^*$? To answer this, we must first determine the host's fitness, ω, measured as its lifetime reproductive success:

$$\omega = \frac{b_S(1-N)}{d_S+\lambda} + \frac{\lambda}{(d_S+\lambda)}\frac{b_I(1-N)}{(d_I)} \tag{5}$$

$$= \frac{a r_{b,S}^{\alpha}(1-N)}{g r_{m,S}^{-\gamma}+\lambda} + \frac{\lambda}{(g r_{m,S}^{-\gamma}+\lambda)}\frac{\rho a r_{b,I}^{\epsilon\alpha}(1-N)}{(g r_{m,I}^{-\gamma})}. \tag{6}$$

The first term, $b_S(1-N)/(d_S+\lambda)$, represents the number of offspring the individual has while uninfected. The term, $\lambda/(d_S+\lambda)$, represents the probability of infection as opposed to death. And the final term, $b_I(1-N)/(d_I)$, refers to the number of offspring an individual has while infected. For a more detailed treatment of the evolutionary stability of this general fitness function see van Baalen (1998) or Gandon et al. (2002a).

There are two sets of ES allocations of host resources: before infection, $r_{b,S}^*$ and $r_{m,S}^*$; and after infection, $r_{b,I}^*$ and $r_{m,I}^*$. While the ES allocation before infection depends on the behavior after infection, the optimal behavior after infection is independent of the pre-infection allocation.

Table 1	
Variable	**Definition**
$\ddot{S}$	number of susceptible individuals
$\ddot{I}$	number of infected individuals
$\ddot{N} = \ddot{S} + \ddot{I}$	total population
K	carrying capacity: the maximum sustainable population in the absence of the di
$S = \ddot{S}/K$	number of susceptible individuals adjusted by the carrying capacity
$I = \ddot{I}/K$	number of infected individuals adjusted by the carrying capacity
$N = \ddot{N}/K$	total population adjusted by the carrying capacity
$b_S = ar_{b,S}^{\alpha}$	birth rate of susceptibles
$b_I = \rho a r_{b,I}^{\epsilon\alpha}$	birth rate of infecteds
$d_S = g r_{m,S}^{-\gamma}$	death rate of susceptibles
$d_I = g r_{m,I}^{-\gamma}$	death rate of infecteds
$r_{b,S}$	reproductive effort of susceptibles
$r_{b,I}$	reproductive effort of infecteds
$r_{m,S}$	investment in maintenance of susceptibles
$r_{m,I}$	investment in maintenance of infecteds
$r_v = \bar{r}_S - \bar{r}_I$	amount of host resources lost to the pathogen
$\bar{r}_S = r_{b,S} + r_{m,S}$	total resources available for reproduction and survival for susceptibles
$\bar{r}_I = r_{b,I} + r_{m,I}$	total resources available for reproduction and survival for infecteds
$\rho \in [0, 1]$	pathogen sterility parameter
$\epsilon \in [0, 1]$	pathogen sterility parameter
λ	force of infection: the rate at which susceptibles become infected

Thus, we can find the post-infection strategy by reducing equation (6) into an "infected fitness" function, equal to the number of offspring while the host is infected,

$$\omega_I = \frac{\rho r_{b,I}^{\epsilon\alpha}}{g r_{m,I}^{-\gamma}} \propto r_{b,I}^{\epsilon\alpha} r_{m,I}^{\gamma}, \tag{7}$$

and maximizing it with respect to $r_{b,I}$ and $r_{m,I}$, subject to the budget constraint, $\bar{r}_I = r_{b,I} + r_{m,I}$. Figure 3.2 is a graphic representation of how the ES allocation of host resources are determined given the budget constraint.

The optimal post-infection allocations are:

$$r^*_{b,I} = \frac{\bar{r}_I}{1 + \gamma/\epsilon\alpha} \tag{8}$$

$$r^*_{m,I} = \frac{\bar{r}_I}{1 + \epsilon\alpha/\gamma}. \tag{9}$$

For simplicity, I begin this analysis with a parsimonious assumption that the pathogen has no direct effect on host reproductive efficiency, but does deplete host resources (i.e., $\epsilon = 1$, and $r_v > 0$). In this case, we see from equations (8) and (9) that the post-infection investments in reproduction and maintenance are determined entirely by the resource budget, $\bar{r}_I$, and the efficiency parameters, α and γ, which determine the curvature of the "returns" (in terms of reproduction and maintenance) to those investments. If, for example, we assume that host reproduction and life expectancy are directly proportional to the investments in each (i.e., $\alpha = \gamma = 1$), then the host simply splits those investments evenly between the two objectives (Figure 3.2).

Now, to determine the change in the use of host resources we must compare $r^*_{b,I}$ and $r^*_{m,I}$ with the allocations before infection, which are found by inserting equations (8) and (9) into the fitness function (6) and maximizing with respect to $r_{b,S}$ and $r_{m,S}$, subject to the resource constraint, $\bar{r}_S = r_{b,S} + r_{m,S}$.

Figure 3.3 illustrates the effect of parasitism on investments in fecundity and maintenance. The change in investments of host resources can be attributed to two separate mechanisms. 1) The budget effect (BE) refers to the change in investments in reproduction and survival that result from the loss of resources to the pathogen. 2) The reallocation effect (RE) refers to the change of investments that results from the strategic reallocation of resources in response

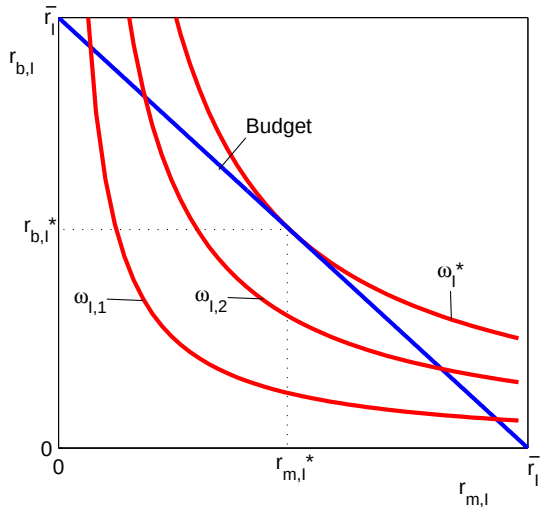

Figure 3.2: The fitness curves, $\omega_{I,1} < \omega_{I,2} < \omega_I^*$, represent all combinations of resources required to maintain a given level of fitness while infected. The budget line represents the amount of resources that are available to the host; any allocation of resources under the budget line is therefore feasible. The ES allocation of host resources, $r_{b,I}^*$ and $r_{m,I}^*$, is therefore the allocation associated with the highest fitness curve within the budget constraint, which is where the budget line and the fitness curve, ω_I^*, are tangent; $\epsilon = 1, \alpha = 1, \gamma = 1, g = 10, a = 1, \bar{r}_S = 100, r_v = 50, \omega_1 = 0.25\omega_I^*, \omega_2 = 0.6\omega_I^*$.

to parasitism:

$$\textit{Change in Reproductive Effort} = BE_b + RE_b \tag{10}$$

$$r_{b,S}^* - r_{b,I}^* = [r_{b,H}^* - r_{b,I}^*] + [r_{b,S}^* - r_{b,H}^*], \tag{11}$$

where $r_{b,H}^*$ refers to the optimal reproductive effort if the host is never parasitized;

$$\textit{Change in Investments in Maintenance} = BE_m + RE_m \tag{12}$$

$$r_{m,S}^* - r_{m,I}^* = [r_{m,H}^* - r_{m,I}^*] + [r_{m,S}^* - r_{m,H}^*], \tag{13}$$

where $r_{m,H}^*$ refers to the optimal investment in maintenance if the host is never parasitized.

To understand the impact of a resource-depleting pathogen on host reproductivity, Figure 3.4 presents the optimal pre- and post-infection allocation of host resources, $\hat{r}_{b,S}$, $\hat{r}_{m,S}$, $\hat{r}_{b,I}$ and $\hat{r}_{m,I}$. Note that, for heuristic purposes, these values were not calculated at the demographic

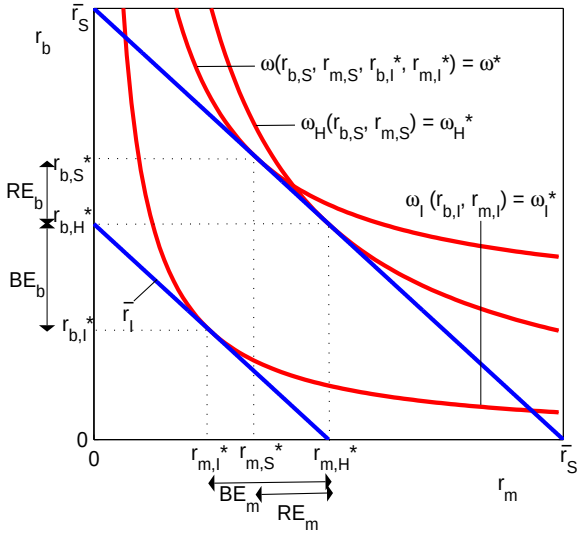

Figure 3.3: The curve, $\omega(r_{b,S}, r_{m,S}, r^*_{m,S}, r^*_{m,I})$, represents all combinations of resource allocations when uninfected that result in a level of fitness that is equal to the maximum attainable fitness given the resource constraints and the post-infection strategy, $\omega^*(r^*_{b,S}, r^*_{m,S}, r^*_{b,I}, r^*_{m,I})$. The curve, $\omega_I(r_{b,I}, r_{m,I})$, represents all combinations of resource allocations of an infected individual that results in an "infected fitness" equal to the maximum number of offspring an infected individual can have given its resource constraint, $\omega^*_I(r^*_{b,I}, r^*_{m,I})$. The curve, ω_H, represents all combinations of resource allocations that result in a level of fitness that is equal to the maximum attainable fitness if the host is never infected, $\omega_H = \omega^*_H$. The change in fecundity and survival can be explained as a combination of two factors: a budget effect (BE), and a reallocation effect (RE). The budget effect refers to the change in fecundity that results purely from the loss of host resources upon infection: $BE_b = r^*_{b,H} - r^*_{b,I}, BE_m = r^*_{m,H} - r^*_{m,I}$. The reallocation effect is the additional change that results from reallocating resources towards maintenance after infection: $RE_b = r^*_{b,S} - r^*_{b,H}, RE_m = r^*_{m,S} - r^*_{m,H}; \epsilon = 1, \alpha = 1, \gamma = 1, g = 10, a = 1, \bar{r}_S = 100, \bar{r}_I = \bar{r}_S - \bar{r}_v, r_v = 50$.

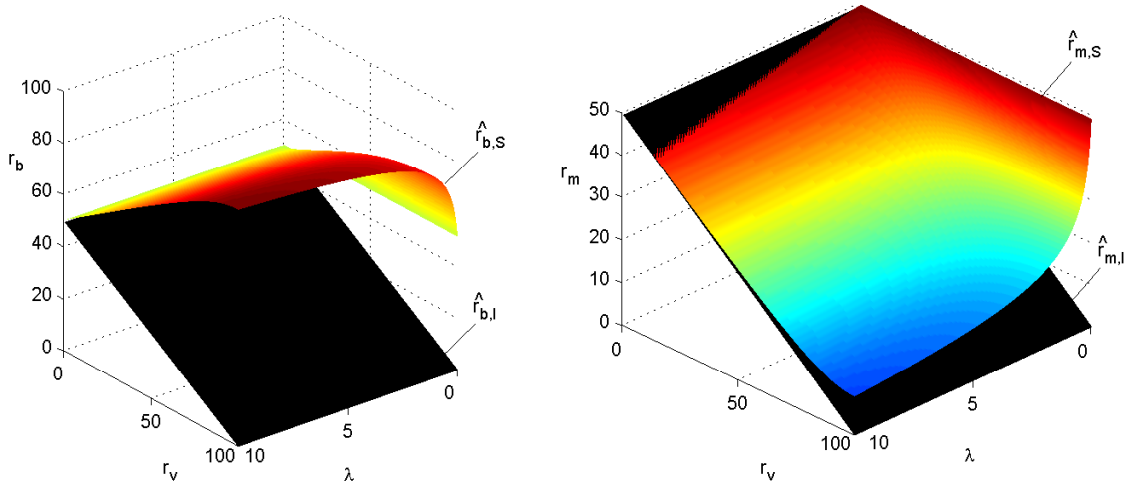

Figure 3.4: a) As the force of infection, λ, and pathogen virulence, r_v, rise, so does the difference between the optimal pre- and post-infection fecundity, $\hat{r}_{b,S}$ and $\hat{r}_{b,I}$. b) As pre-infection reproductive effort rises from greater force of infection, the pre-infection investment in maintenance, $\hat{r}_{m,S}$, approaches the post-infection investment, $\hat{r}_{m,I}$, lowering the apparent mortality effect of the pathogen; $a = 5, g = 10, \alpha = 1, \gamma = 1, h = 1, \bar{r}_S = 100$.

equilibrium, and are therefore "optimal" but not necessarily "evolutionarily stable" (the ES allocations are presented in Figure 3.5). They are treated *as if* pathogen virulence and the force of infection are independent exogenous forces. Figure 3.4 shows that the loss of host fecundity can be explained by the rate at which a host is infected, λ, and the rate at which the host loses resources upon infection, r_v. When the pathogen depletes no resources from the host (i.e., it is avirulent), there is no change in host fecundity after infection (Figure 3.4a). But as both virulence and the force of infection rise, so does the difference between pre- and post-infection reproductive effort. This is because the urgency of reproduction increases relative to survival as a host loses its future resources. After all, when the host invests in survival, a portion of that investment is stolen by the pathogen, but when it invests in reproduction, it is not. After infection, however, the pathogen depletes resources from both causes. The host therefore compensates for its future loss of resources by investing more in reproduction before

infection. Indeed, such pre-infection fecundity compensation eventually becomes sufficiently high (Figure 3.4a), that pre-infection investment in maintenance is reduced to its post-infection levels, despite the loss of total host resources after infection (Figure 3.4b). In other words, for systems in which there is a high probability of infection (due to high disease prevalence or high transmission rate) or a significant loss of resources upon infection (due to high virulence), pathogens may often be effectively sterilizing, while appearing to have minimal impact on host mortality. This is true for all positive values of α and γ and is entirely based on the host life-history strategy.

The results in Figure 3.4 represent optimal host behavior over a range of values of pathogen virulence and force of infection, which are treated independently. However, if transmission is modeled as either frequency- or density-dependent ($\lambda = \beta I/N$, or $\lambda = \beta I$, where β is the rate of transmission), pathogen virulence would feedback on the force of infection because higher virulence would result in greater host death rate, which lowers the equilibrium disease prevalence, but would also increase the rate of disease transmission, which raises the equilibrium disease prevalence. As a result, one might expect the relationship between the ES pre-infection reproductive effort and pathogen virulence to be nonmonotonic. This is illustrated in Figure 3.5, where the effect of the pathogen on the pre-infection reproductive effort becomes zero when virulence is very high because the high mortality rates reduce the equilibrium disease prevalence, and therefore the force of infection, to zero. However, note that the change in reproductive effort after infection is always negative.

3.4 Coevolution of Pathogen Virulence

From Figure 3.4 we know that the burden of the pathogen in terms of the force of infection and virulence are what determine the difference between pre- and post-infection reproductive effort. However, from Figure 3.5 we can see that pathogen virulence feeds back on the force of infection, $\lambda = \beta I$, suggesting that, in nature, we would expect to find a nonmonotonic

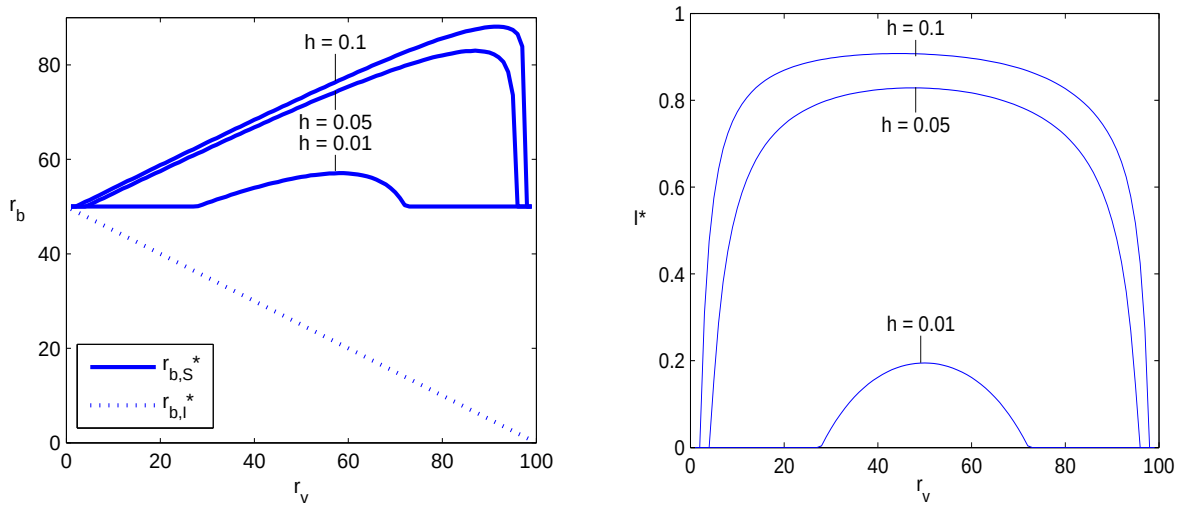

Figure 3.5: a) Assuming frequency dependent transmission, $\lambda = \beta I$, the ES pre-infection reproductive effort, $r^*_{b,S}$, responds nonmonotonically to pathogen virulence, r_v. This is because, the "optimal" pre-infection reproductive effort responds monotonically to independent increases in virulence and the force of infection (Figure 3.4a), but b) the relationship between virulence and the force of infection is nonmonotonic because of the effect of virulence on the equilibrium disease prevalence; $g = 10, \alpha = 1, \gamma = 1; \bar{r} = 100, \lambda = \beta I, \beta = h r_v^{\delta}, \delta = 1$.

relationship between disease virulence, disease prevalence, and pathogen-induced fecundity-reduction. But the analysis above ignores pathogen evolution which we would expect to have predictable consequences on this feedback between disease prevalence and virulence, given that the pathogen would be expected to evolve to maximize its basic reproductive ratio, which would maximize the equilibrium disease prevalence.

Consider the pathogen's basic reproductive ratio, R_0:

$$R_0 = \frac{\beta}{d_I} \propto r_v^{\delta} r_{m,I}^{*\gamma} = \left(\frac{\gamma}{\epsilon\alpha + \gamma}\right)^{\gamma} r_v^{\delta} (\bar{r} - r_v)^{\gamma}. \tag{14}$$

Notice that the pathogen's fitness function incorporates the ES behavior of the host, r^*_m, because that behavior constitutes the regime in which the pathogen evolves. Thus, the pathogen's ESS is also coevolutionarily stable (CoES).

Because this section is only concerned with pathogen virulence, not direct castration, on host reproductive behavior, I continue to assume here that ϵ is fixed at 1, which reduces the fitness function (14) of the pathogen to:

$$R_0 \propto r_v^{\delta}(\bar{r}_S - r_v)^{\gamma}. \tag{15}$$

From equation (15), we can see that the CoES virulence would be influenced by only two parameters in this system: δ, which affects the rate of conversion of host resources to pathogen transmission; and γ, which affects the rate of conversion of host resources to pathogen (and host) survival. Both of these parameters also influence the equilibrium prevalence of the disease. For a clearer understanding of how δ and γ influence pathogen transmission and survival, see Figure 3.6.

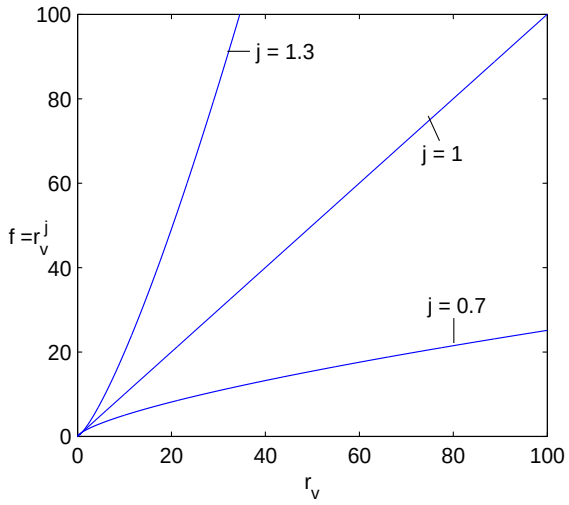

Figure 3.6: The pathogen transmission term, $\beta = hr_v^{\delta}$, and the host life-expectancy, $r_{m,I}^{\gamma}/g$ have the general functional form, $f \propto r_v^j$. The parameter j (i.e., δ and γ) determines the rate at which additional investments of host resources influence transmission and survival. If j is greater than 1, then the benefits to the pathogen of investing in transmission or survival rise with each additional unit of investment. If j is equal to 1, then each additional unit of investment confers the same marginal benefits. And if j is less than one, then the benefits of investing in transmission or survival fall with each additional unit of investment.

Figure 3.7 presents the effect of changes in δ and γ on the CoES levels of pathogen-induced changes in host reproductive effort. In all cases, the relationship between the CoES loss of fecundity and the corresponding risk factors, virulence and force of infection, is monotonic.

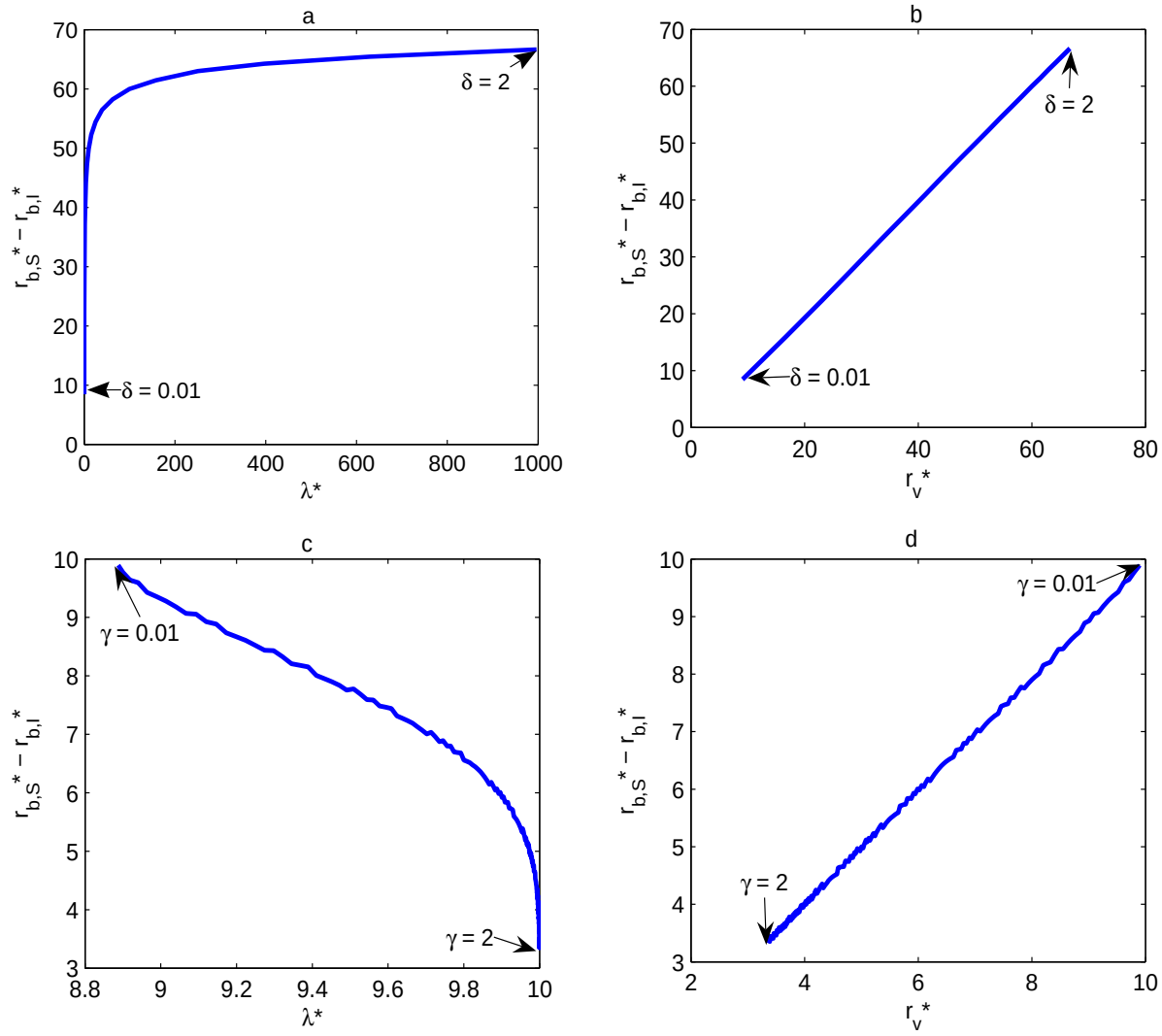

Figure 3.7: The CoES change in fecundity, $r^*_{b,S} - r^*_{b,I}$, is presented with its corresponding CoES virulence, r^*_v, and the equilibrium force of infection, $\lambda^* = \beta(r^*_v)I^*$, over a range of δ and γ values; $\rho = 1, a = 1, \epsilon = 1, \alpha = 1, g = 1, \bar{r}_S = 100, h = 0.1$; a) and b) $\gamma = 1$; c) and d) $\delta = 1$.

Figures 3.7a and 3.7b depict the effect of δ on the relationship between the equilibrium force of infection, $\lambda^* = \beta(r_v^*)I^*$, and the CoES change in fecundity, $r_{b,S}^* - r_{b,I}^*$, and between the CoES virulence, r_v^*, and the CoES change in fecundity. Low δ implies not only a relatively low transmission efficiency per unit of resources taken from the host, but if δ is less than one, this efficiency diminishes with increasing investments (see Figure 3.6). As δ rises, transmission efficiency rises, and the pathogen, which maximizes the number of infected individuals in its lifetime, evolves towards higher virulence which necessarily corresponds to both a higher transmission rate and higher equilibrium force of infection. Thus, over δ space, the relationships between the equilibrium force of infection and CoES loss of fecundity, and between the CoES virulence and the CoES loss of host fecundity, are both positive and monotonic.

Figures 3.7c and 3.7d depict the effect of γ on the relationship between the equilibrium force of infection and the CoES change in fecundity, and between the CoES virulence and the CoES change in fecundity. Low γ implies that each additional unit of host resources invested in maintenance not only results in relatively low increases in life-expectancy, but these increases actually diminish with each additional unit of investment if γ is less than one. As γ rises, maintenance efficiency rises, increasing the benefits of preserving the host relative to transmission, and decreasing the CoES level of virulence. The greatest reduction in host fecundity occurs when γ is low, which corresponds to a high virulence, but a low force of infection. Thus, over γ space, the CoES virulence and force of infection are negatively correlated, allowing for a monotonically decreasing relationship between the force of infection and CoES pathogen-induced fecundity reduction.

From the analysis so far, there are two important conclusions. First, all combinations of the force of infection and pathogen virulence result in reduced host fecundity after infection (Figure 3.4). The direct effect of the force of infection and virulence on host fecundity-reduction is always positive. However, because pathogen virulence interacts nonmonotonically with the force of infection, the indirect effects of pathogen virulence make it impossible

to make an a priori prediction on how the force of infection would correlate with pathogen-induced fecundity reduction in the natural world. However, in all cases, I find a positive and monotonic relationship between the CoES level of virulence and pathogen-induced fecundity reduction.

However, the simple role of pathogen virulence never reduces pre-infection maintenance to below the post-infection levels, and therefore cannot explain gigantism.

3.5 Pathogen Manipulates Host Life-History Strategy, Causing Gigantism

The section above shows that a simple host life-history strategy can explain pathogen-induced fecundity reduction, but cannot explain gigantism. That analysis assumes that the pathogen harms the host through the loss of host resources, an assumption which describes a wide variety of host-pathogen relationships, such as that of the fruit fly, *Drosophila nigrospiracula*, and its parasitic mite, *Macrocheles subbadius* (Polak, 1996), or the mosquito, *Aedes aegypti*, and the filarial nematode, *Brugia pahangi* (Javadian and Macdonald, 1974). However, the explicit destruction of host reproductive tissue, known as parasitic castration, has also been shown in a large range host-pathogen systems, and is often associated with host gigantism (Arnott et al., 2000; Krist, 2001; Ebert et al., 2004).

No formal theory has previously been developed to explain the evolution of parasite-induced gigantism, but the conceptual arguments emphasize the benefits to the pathogen. Indeed, the prospect of a host strategically evolving towards complete castration has been considered by some to be untenable. After all, completely sterile individuals do not reproduce, eliminating a mechanism for the heritability of such a strategy: "Consequently, adaptation can only be on the side of the parasite" (Rothschild and Clay, 1952). The proposed benefit for the pathogen is that the inability for host reproduction results in more resources available for pathogen survival and transmission. But it is important to emphasize here that this reasoning implicitly assumes that decreased reproductive efficiency somehow translates to decreased reproductive effort. What drives this relationship? In search for such a mechanism,

this section considers the optimal host response to a parasite's direct interference of the host's reproductive system.

Remember from the birth function, $b_I = \rho a r_{b,I}^{\epsilon\alpha}$, that host castration is represented by the fecundity parameters, ρ and ϵ, taking on values of less than 1. However, notice from equations (8) and (9) that ρ has no influence on the optimal allocation of host resources, and therefore its manipulation would confer no strategic benefit to the pathogen. Intuitively, this may be surprising, as we might expect that a decrease in the marginal benefits of investing in reproduction to result in a decrease in reproductive effort. But from the infected fitness function, $\omega_I \propto \rho a r_{b,I}^{\epsilon\alpha} r_{m,I}^{\gamma}/g$, we can see that decreasing the marginal benefits of reproduction by, for example, halving ρ, and decreasing the marginal benefits of survival by doubling g, are evolutionarily equivalent. Though the mechanism is different, the effect on host fitness remains the same; both parameters are simply scalars of the fitness function and therefore, while influencing the fitness of the host, they do not alter the trade-off between investments in survival and reproduction. This is an especially important point because a simple proportional decrease in reproductive efficiency (i.e., a decrease in ρ) would be the most intuitive kind of interference of the host reproductive system. For a better understanding of the difference between the sterility parameters, ρ and ϵ, see Figure 3.8.

On the other hand, the value of the parameter that influences the curvature of the returns to reproductive effort, ϵ, does influence the optimal allocation of host resources. If the pathogen castrates the host by lowering ϵ, then this would result in a strategic decrease in host reproductive effort, and a corresponding increase in the investment towards maintenance (Figure 3.9).

From equation 15, we can see that the evolutionarily stable ϵ for the pathogen is,

$$\epsilon^* = 0, \tag{16}$$

implying that complete castration, if done properly (i.e., not through reduction of ρ), is an optimal pathogen strategy. To understand the meaning of ϵ, consider a case where pre-infection reproductivity is proportional to reproductive effort (i.e., $\alpha = 1$). An ϵ of less

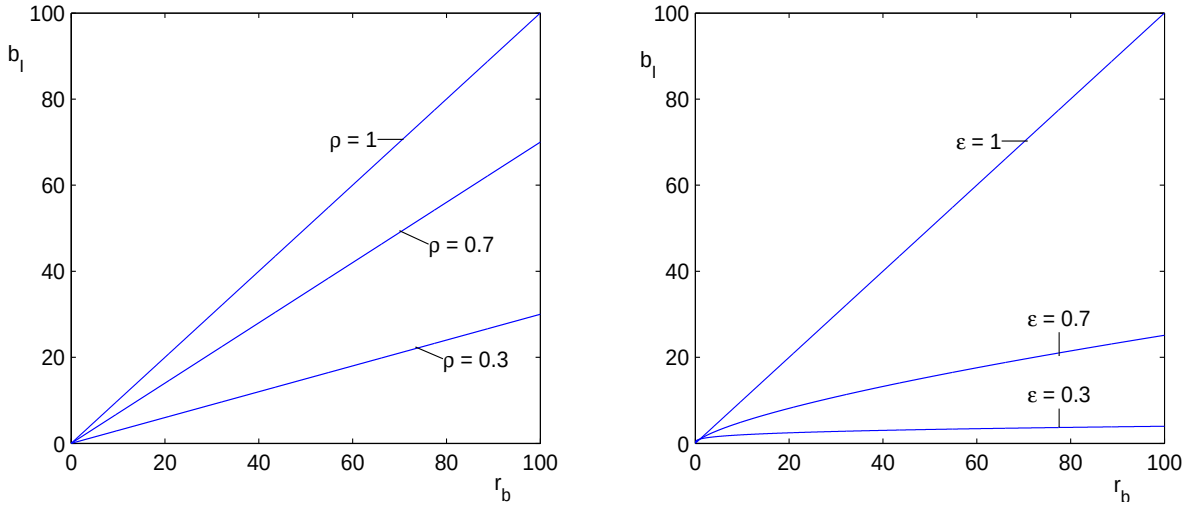

Figure 3.8: The infected host birth function, $b_I = \rho a r_{b,I}^{\epsilon\alpha}$, allows for the pathogen to interfere with host reproductive efficiency through the sterility parameters, ρ and ϵ. a) A decrease in ρ results in a proportional decrease in reproductive efficiency, but does not alter the curvature of the birth function; $a = 1, \alpha = 1, \epsilon = 1$. b) The parameter, ϵ, influences the curvature of the birth function. If ϵ falls below one, the per-unit reproductive efficiency of the host diminishes as the reproductive effort rises; $a = 1, \alpha = 1, \rho = 1$.

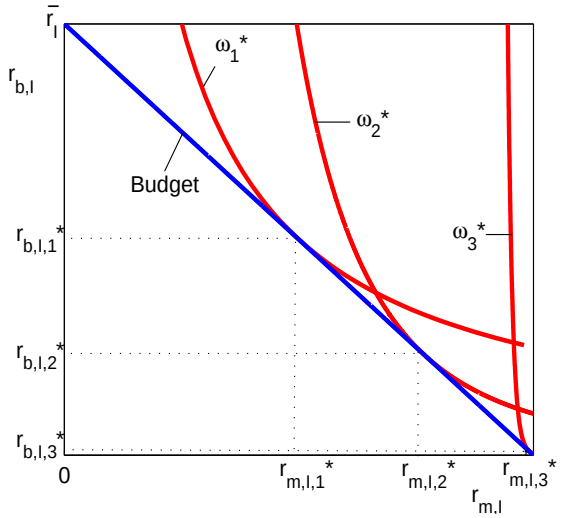

Figure 3.9: As the pathogen castrates the host by reducing ϵ, the host invests more in survival; ω_1^*, ω_2^*, and ω_3^* correspond to the maximum host fitness when $\epsilon = 1, 0.3$, and 0.01 respectively; $h = 1, g = 100, \bar{r}_S = 100, \alpha = 1, \gamma = 1$.

than one implies that, as post-infection reproductive effort rises, the output per unit of effort would fall. This diminishing returns to reproductive effort - or increasing costs of reproduction - induces the host to reallocate resources towards maintenance (Figure 3.9). What is especially interesting is that this act of manipulation is "passive", as opposed to direct, in that it relies on the host's optimal response, which is not even heritable at the limit, but is heritable up until the limit. Moreover, such direct castration can increase host investment in maintenance beyond the pre-infection levels despite the loss of total resources after infection. Thus, direct castration in the form of lowering ϵ could cause host gigantism (Figure 3.10) via the manipulation of the host's self-interest. A biological mechanism for this specific form of castration is presented in the Discussion.

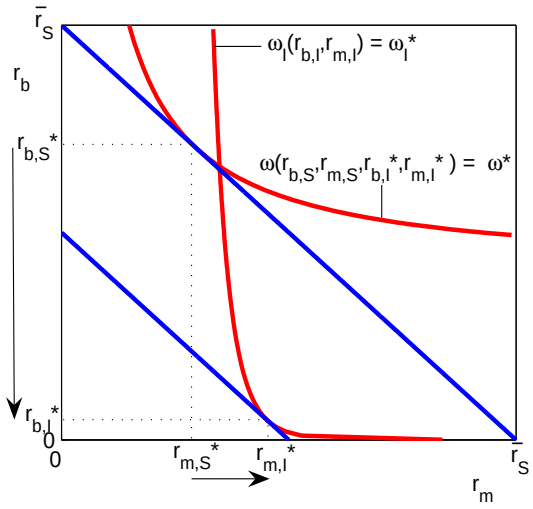

Figure 3.10: The curve, $\omega(r_{b,S}, r_{m,S}, r^*_{m,S}, r^*_{m,I})$, represents all combinations of resource allocations when uninfected that result in a level of fitness that is equal to the maximum attainable fitness given the resource constraints and the post-infection strategy, $\omega^*(r^*_{b,S}, r^*_{m,S}, r^*_{b,I}, r^*_{m,I})$. The curve, $\omega_I(r_{b,I}, r_{m,I})$, represents all combinations of resource allocations of an infected individual that results in an "infected fitness" equal to the maximum number of offspring an infected individual can have given its resource constraint, $\omega^*_I(r^*_{b,I}, r^*_{m,I})$. Despite a loss of total resources to the pathogen after infection, the optimal host investment in maintenance may actually rise in response to castration; $h = 1, g = 100, \bar{r}_S = 100, \alpha = 1, \gamma = 1; \epsilon = 0.1$.

3.6 Discussion

There is a great deal of evidence that pathogens often cause host fecundity to fall, with proposed explanations spanning the full range of evolutionary possibilities: loss of fecundity could be a host strategy (Hurd, 2001), a pathogen strategy (Baudoin, 1975; Ebert et al., 2004), a coevolutionary outcome, or none of the above - it could be an incidental outcome of depleted host nutrients (Polak, 1996).

The explanations for the evolution of pathogen-induced fecundity reduction rely on a common principal: the trade-off between host longevity and reproduction. The simplest theories merely assume that pathogen transmission is a negative function of host reproduction, and therefore the pathogen evolves to become completely sterilizing (Jaenike, 1996; O'Keefe and Antonovics, 2002). These theories treat sterilization as if it is a separate kind of virulence from that of pathogen-induced mortality, requiring new assumptions and new models that are not integrated into the general evolution of virulence framework. Alternatively, assuming the host can recover, lost fecundity has been considered a possible indirect consequence of the host mounting costly defenses against pathogens that directly target host survival (van Baalen, 1998; Day and Burns, 2003).

Here, I show that explaining lost host fecundity does not require that the pathogen targets host reproductive resources, nor must it be a consequence of host defense. Rather, it is an implication of general theories of virulence, where the pathogen is assumed to require host resources for its own transmission. Such resources, in this model, are used both for host survival and reproduction, but are constrained by a total resource budget.

There is a simple but powerful implication of this trade-off in the context of a resource-depleting pathogen: if the host can freely transfer its resources between reproduction and survival, then it should always be expected to reduce its fecundity after infection, not merely because of a loss of total resources for the host, but also because the threat of infection causes the host to allocate pre-infection resources to greater reproduction, with pre-infection maintenance being correspondingly lower. This is because such pathogens always steal host

investments in survival but cannot steal pre-infection investments in reproduction. After infection, on the other hand, the pathogen steals resources from both causes. As presented in Figure 3.4, the strongest sterilizing effect is expected when the threat of the disease is very high, such as at high pathogen prevalence or virulence. Consistent with this theory, Krist (2001) found a positive correlation between average size-adjusted reproductivity of eight populations of uninfected freshwater snails, *Elimia livescens*, and the prevalence of sterilizing trematodes. My result is in contrast to Gandon et al.'s (2002) findings, that the host should increase reproduction after infection. The key difference between my model and that of Gandon et al. (2002a), is that they assume that pathogen virulence directly affects host mortality, while I assume that the pathogen takes host resources, whose relative allocation between reproduction and survival is determined by the host.

There is a wrinkle to this theory that can explain another commonly observed phenomenon in the field: early-infection fecundity compensation (Thornhill, 1986; Polak and Starmer, 1998). In cases where there is both sufficient plasticity in the use of host resources, as well as enough time between the initial infection and the maximum parasite burden, the host would not necessarily need to completely anticipate the infection, but could wait until it is infected before redirecting resources into reproduction. In this case, reproductivity would be expected to quickly rise before dropping off when the parasite burden is high. This was found, for example, in *Daphnia magna* that invested in early reproduction when exposed to the parasitic microsporidian, *Glugoides intestinalis* (Chadwick and Little, 2005).

The analysis presented here would suggest host strategic behavior as a parsimonious explanation for pathogen-induced sterility. Whether the host compensates before infection or immediately after infection would be determined by the time after initial infection that it takes the pathogen to become a burden on host resources relative to the time (and cost) required to redirect host resources to reproduction. However, such a simple model does not explain gigantism.

It is often postulated that castration "frees" host resources that would have been otherwise relegated to reproduction, which explains gigantism as either an incidental consequence of a parasite targeting host reproductive resources (Sousa, 1983), or a strategy of the pathogen (Baudoin, 1975; Ebert et al., 2004). What has not previously been demonstrated is a specific mechanism for converting lost host reproductive efficiency to lower reproductive effort, and therefore greater maintenance. After all, a completely sterilized host benefits from neither. Indeed, by facilitating the prosperity of the costly parasite, castrated hosts are harmed by self-preservation in that their kin are necessarily worse off, if only marginally, while they are not better off. A more specific mechanism for the redirection of host resources is therefore warranted. I present a model that relies on a few simple assumptions: 1) host and pathogen vie for limited host resources, 2) such resources can be used either for host reproduction or maintenance, and 3) the host does not recover. In a laboratory system of *Daphnia magna* infected with the bacterium *Pasteuria ramosa*, Ebert et al. (2004) presents the most careful study to date of parasitic castration and confirms that these assumptions hold true for their system.

An interesting and obvious extension of this model would be to allow for host recovery, which is often found in host-macroparasite systems, where the host outlives the parasite. While the results presented here cannot be directly applied to such systems which are inherently more complex, the principles on which these results rely are applicable. Specifically, even with recovery, parasite-induced loss of host resources puts inherent selective pressure on reproduction before the host loses such resources - i.e., before infection. Presumably, the prospect of recovery would put additional pressure on surviving until the pathogen is cleared, after which the host would again invest disproportionately in reproduction before its future loss of resources is stolen again by another infection.

Despite previous, and highly intuitive, suggestions that parasitic castration cannot be a host strategy because such a strategy is not heritable, the analysis presented here suggests that it is heritable - indeed evolutionarily stable - up until (but not at) the limit, where

reproductive effort is zero. This is only true for a specific castrating effect: the pathogen must force the reproductive efficiency of the host to fall as reproductive effort rises. Such a mechanism would be possible where pathogen abundance is based on the consumption of host reproductive resources, such as is common of trematode infections of molluscs (Wilson and Denison, 1980; Hurd, 2001), and if one of two forces were working for the pathogen: 1) an Allee effect; or 2) a Type II functional response. In either case, as pathogen abundance rises in response to increased host investment in reproduction, pathogen consumption of those resources would rise at an increasing rate, either because of increased consumption efficiency (Type II functional response), or increased aggregate growth efficiency (Allee effect). Both mechanisms would clearly reduce the incentive of the host to invest in reproduction. Whether such a mechanism is truly at work is unknown because it has not been previously searched for. Such a test would constitute valuable future experimental work. This coevolutionary dynamic could potentially result in complete castration. Thus, castration and gigantism would actually be the product of host-pathogen coevolution, where the pathogen manipulates the host's self-interest.

Chapter 4

Reducing Fertility More Effective than Vaccinating for Improving Global Health and Economic Development; A Simple Ecological Framework

4.1 Introduction

More than one sixth of the world lives in extreme poverty, defined as subsisting on less than one dollar (US) per day (UN Millenium Project, 2005). Such a paucity of economic resources limits not only access to the goods and services important for quality of life, but limits access to the goods and services necessary to maintain life itself. In the developing world, most lives are claimed by infectious diseases, which account for as much as two-thirds of all deaths in sub-Saharan Africa (World Health Organization, 2004). Such a negative effect of poverty on public health is well-established in the epidemiology literature and is becoming increasingly familiar to the public at large (World Health Organization, 1998, 2001; Farmer, 2001; Lee, 1994). But there has also been growing attention to the effect of health on poverty (Gallup and Sachs, 2001b; Sachs and Malaney, 2002; Sachs, 2005). This positive feedback between poverty and disease-induced morbidity and mortality on the one hand, and between economic growth and public health on the other, has become a keystone issue within the global development community (World Health Organization, 2002; von Schirnding, 2002) and constitutes the conceptual foundation for what has been termed a disease-induced poverty trap (Sachs et al., 2004). It is also the theoretical foundation for the UN Millennium Project, whose goal is to reduce the number of people suffering from extreme poverty by half by the year 2015 (UN Millenium Project, 2005). While such an initiative is framed in policy terms, there are very important broader scientific principles that both underly and emerge from it: the most critical determinants of human survival and economic welfare in many parts of

the world are *ecological*. That is, it is our *natural* enemies - more specifically, our interaction with them - that are partly responsible for the persistence of poverty, illness, and death that have been experienced throughout human history (McNeill, 1976; Diamond, 1997).

The explanation for this ecological relationship between health and economics is straightforward. Economic development requires human resources - specifically, "human capital" - and therefore relies on biological processes in the form of physical labor and cognition, which are often compromised by infection (Glewwe, 2002; Nokes et al., 1992; Holding and Snow, 2001; Fernando et al., 2006; Ezeamama et al., 2005). So, while humans serve as resources for each other through economic activity, we also provide direct biological resources to infectious diseases for the purposes of their survival and transmission (Anderson and May, 1992; Frank, 1996). And therefore an understanding of global development over the short and long term requires a broader scientific understanding of the forces - biological and economic - that vie for human resources. While some theories of poverty traps have been developed in the economics literature (Azariadis, 1996; Bloom et al., 2003; Sachs et al., 2004), such models have not yet formally incorporated the ecology of infectious diseases. Here we present a simple ecological framework for understanding the interaction between economic growth and the prevalence of infectious diseases. We focus on the role of two important variables that are simultaneously mediated by economic and biological factors: 1) the disease transmission rate; and 2) the host rate of reproduction. We find that reductions in the birth rate - which is typically considered analogous to vaccination - has significantly greater long-term benefits than would a standard epidemiological model predict, and could be a surprisingly effective mechanism for eradicating endemic, and very costly, infectious diseases in the developing world.

Throughout their history, humans have faced a relentless battle with infectious diseases, which have even constituted a selective force on human evolution (Motulsky, 1960; Ewald, 1994; Curtis, 2001; Carter and Mendis, 2002). It is therefore not surprising that, like many other animals, people of all societies play active roles in directly lowering transmission oppor-

tunities for diseases through various measures such as the employment of basic sanitation, protocols of social and sexual behavior, shoes and clothing, bednets, glass and screen windows, etc... (Hart, 1990; Gangestad and Buss, 1992; Loehle, 1995; Tsagkamilis, 1999). Thus, the disease transmission rate is determined by a combination of host and pathogen factors (Bonds et al., 2005). But humans also indirectly facilitate the success of infectious diseases through the basic biological function of reproduction (McLean and Anderson, 1988a,b; Earn et al., 2000). Because of high disease transmissibility, coupled with the acquisition of host immunity, many of the most important diseases of the world such as malaria, measles, and parasitic worms, have low mean ages of infection. The host population would therefore have the potential to eradicate some infectious diseases if not for the continual injection of immunologically naive, susceptible children. But children do not merely serve as new hosts for the pathogens. They also serve as new conduits for transmission. As a result, the birth of a child in the poorest parts of the world represents not only a new infection opportunity for a disease, but also an increase in the probability of infection for the rest of the susceptible host population.

What makes these two behavioral epidemiological drivers - reproduction and transmission - so interesting and important is that they are, in the long run, dependent on each other through a process mediated by economic activity. After all, while transmission interventions can serve to preserve human resources for human purposes, resulting in greater health and economic welfare, the interventions themselves often *require* economic resources. The availability of such resources per child naturally depends on the number of children per household - i.e., the rate of reproduction. Moreover, the number of offspring also influences the rate of transmission between the individuals within the household (Reves, 1985; Aaby, 1992).

The model we present here strives to capture the essential elements of this long-term feedback between disease and income. The most dangerous diseases in Africa are those that are thought to have the most significant impact on mortality rates and childhood learning, and therefore ultimately on labor productivity, which are diseases that mostly afflict children.

We therefore represent this disease system with a classic childhood disease S-I-R model, in which individuals are born susceptible, become infected, and then acquire lifelong immunity.

4.2 Classic S-I-R Epidemiological Model

The ecological dynamics of childhood diseases have been successfully modeled by compartmentalizing the host population according to their disease status - susceptible, infected, and recovered (Anderson and May, 1992; Grenfell and Dobson, 1995). The general model is:

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

where S, I, and R represent proportions of susceptible, infected, and recovered individuals respectively. The parameters, α, μ, and γ are the respective rates of birth, natural death, and recovery. The transmission rate is β. The parameter, ν, is the additional death rate caused by disease, and p is the proportion of individuals vaccinated at birth. The variable definitions can be found in Table 1.

The corresponding equilibrium disease prevalence is:

$$I^* = \frac{\alpha(1-\rho)}{\mu + v + \gamma} - \frac{\mu}{\beta}. \tag{2}$$

Such a simple framework can lead to useful policy prescriptions. For example, it predicts that "herd immunity" - the required proportion of the population to be vaccinated to eradicate an infectious disease - can be acquired by vaccinating only a proportion of the population equal to ρ^c (Anderson and May, 1979; Keeling and Rohani, 2006):

$$p^c = 1 - \frac{1}{R_0}\frac{\mu}{\alpha}, \tag{3}$$

where R_0 is the basic reproductive ratio of the pathogen:

$$R_0 = \frac{\beta}{\mu + \nu + \gamma}, \tag{4}$$

and represents the number of secondary infections that would result from a single infected individual in a totally susceptible population.

Table 1	
Variable	**Definition**
S	proportion of susceptible individuals
I	proportion of infected individuals
R	proportion of recovered individuals
α	per capita birth rate
ρ	proportion of population vaccinated at birth
μ	natural death rate
γ	rate of recovery
ν	virulence
β	transmission rate
$r(LE)$	investment in protection
ϕ	half-saturation constant of protection from disease
c	cost of protection measures
$\bar{\beta}$	maximum transmission rate in the absence of protection
LE	Life expectancy

4.3 Income Effect Creates Feedback Between Disease Prevalence and the Transmission Rate

It is obvious that human behavior influences the transmission rate, β, and therefore R_0, of diseases that require direct social or sexual contact, such as measles, tuberculosis, and HIV/AIDS. But even for vector-borne diseases such as malaria, lymphatic filariasis, and dengue fever, host-to-host proximity matters because the geographic range of the mosquito vectors is limited, which is known to result in disease-clustering at fine spatial scales such as at the individual household level (Gamage-Mendis et al., 1991; Ghebreyesus et al., 2000;

Harrington et al., 2005; Carter et al., 2000). Such indirect host contact can even extend beyond animal-vectors, through what Ewald (1994) termed "cultural vectors", for pathogens with free-living stages in the environment, as occurs with dysentery, cholera, and hookworm, which are transmitted through fecal routes.

What all of the diseases mentioned above have in common is that they are found disproportionately among the poor, who often lack the economic resources to prevent such disease transmission. Sanitation measures such as proper hygiene, fecal waste management, and the filtration of drinking water are all examples of economically-determined human actions that lower transmission rates. But there are also more subtle influences. Poor housing conditions, such as mud walls (which allow infected mosquitoes to rest), thatched roofs, exposed sleeping conditions, and crowding are known to increase the probability of malaria infection (Gamage-Mendis et al., 1991). Lack of footwear exposes children to ground-dwelling parasitic worms. And limited access to prophylactics increases the transmission of sexually-transmitted diseases such as HIV/AIDS.

But while the transmission rate is a function of household income, the average income is itself ultimately a function of the ecology of infectious diseases. This is due to both 1) a direct effect of health on labor productivity, and more importantly, 2) an indirect effect on labor productivity through the effect of childhood health on the acquisition of "human capital" - the training and education of the workforce. Diseases such as malaria and parasitic worms, among others, are known to directly interfere with childhood learning processes, and therefore ultimately undermine long-term economic success (Nokes et al., 1992; Holding and Snow, 2001; Fernando et al., 2006; Ezeamama et al., 2005).

The epidemiological literature almost always assumes the transmission rate is determined by exogenous (i.e., fixed) parameters, which seems reasonable over short time periods. However, over the relevant economic time (i.e., inter-generational time), the transmission rate is determined by this feedback between economics and disease ecology, and is thus endogenous to the system (Nokes et al., 1992; Holding and Snow, 2001; Fernando et al., 2006; Ezea-

mama et al., 2005). To account for the role of human behavior on the transmission rate, we introduce the following transmission function:

$$\beta = \frac{\bar{\beta}\phi}{r(M) + \phi}, \tag{5}$$

where $\bar{\beta}$ represents the baseline transmission rate, which would include environmental factors outside the influence of human behavior. The variable, r, is the average level of protection from disease invested per child (e.g., bednets, sanitation, etc...,), and ϕ is the half-saturation constant associated with the effectiveness of those protection measures. It is important to emphasize here that the average level of protection, r, is ultimately determined by per capita income, M. Specifically, we assume that each household allocates a fixed portion, z, of its income to protection measures from diseases. Dividing this allocation by the cost of protection, c, and the birth rate, α, yields the average level of protection per child, r:

$$r(M) = \frac{zM}{c\alpha}, \tag{6}$$

There are many ways in which per capita income, M, could be modeled. For the sake of simplicity, we assume here that per capita income is proportional to the life expectancy, which is our index of childhood health:[1] $r(LE) = zLE/(c\alpha)$. Note that this framework can be easily extended to incorporate different functional relationships between health and income. [2] Based on the S-I-R model, the life expectancy is the weighted average of the life expectancy of unvaccinated (u) and vaccinated (p) individuals:

$$LE = LE_u(1 - p) + LE_p p, \tag{7}$$

where p represents the proportion of the population that is vaccinated. The life expectancy of vaccinated individuals, LE_p, is equal to the natural life expectancy,

$$LE_p = 1/\mu, \tag{8}$$

[1]Note that the life expectancy term, presented in equation (9) only varies according to properties of the (childhood) disease and therefore is a monotonic function of the average health of children.

[2]This assumption does not imply a linear correlation between life-expectancy and income throughout the world, because other economically important factors also vary across national boundaries.

and the life expectancy of unvaccinated individuals is a Markov process with four states: birth, infection, recovery, and death,

$$LE_u = \frac{1}{\mu + \beta I} + \frac{\beta I}{(\mu + \beta I)} \frac{1}{(\mu + \nu + \gamma)} + \frac{\beta I}{(\mu + \beta I)} \frac{\gamma}{(\mu + \nu + \gamma)} \frac{1}{\mu}. \tag{9}$$

The first term,$1/(\mu+\beta I)$, represents average time spent in the susceptible class. Unvaccinated individuals then move to the infected class with probability $\beta I/(\mu + \beta I)$, and stay in that class for an average time of $1/(\mu + \nu + \gamma)$. The average time spent recovered is equal to the "natural" life expectancy, $1/\mu$, times the probability of making it to the recovered class, which is the joint probability of becoming infected, $\beta I/(\mu + \beta I)$, and of recovering, $\gamma/(\mu + \nu + \gamma)$.

From equations, (5), (6), and (9), we can solve for the average level of protection from disease as a function of disease prevalence, $r^*(I)$ (see Appendix D). However, note that from equations (2) and (5), we know that the equilibrium disease prevalence is itself determined by the average level of protection:

$$I^*(r) = \frac{\alpha(1-\rho)}{\mu + v + \gamma} - \frac{\mu(r+\phi)}{\bar{\beta}\phi}. \tag{10}$$

This interaction between $I^*(r)$ and $r^*(I)$ is illustrated in Appendix D. The long-term equilibrium disease prevalence, $I^{**} = I^*(r^*)$, and average protection from disease, $r^{**} = r^*(I^*)$ are therefore determined simultaneously. Because the solutions for I^{**} and r^{**} are unwieldy, we do not present them here, but they are discussed in more detail below.

Understanding that the transmission rate and the disease prevalence are determined simultaneously over long epidemiological/economic time periods is necessary for a better understanding of the relationship between economic development and global health, and therefore of the long-term consequences of sustained policy interventions. For example, from equation (2), we see that the classic (short-term) S-I-R model predicts that a proportional change in the birth rate, α, has the same effect on the equilibrium disease prevalence as vaccinating an equivalent proportion of the host population. However, over the long-term, such a change in the birth rate would not merely change the direct flow of susceptibles in the population. It also changes the transmission rate, because the lower birth rate would

necessarily result in lower within-household transmission opportunities, as well as more economic resources available per child (illustrated in Appendix D). The long-term benefits of lowering the birth rate are therefore always greater than what would be expected from the short-term epidemiological models.

The basic reproductive ratio for the present (long-term) model is:

$$R_0^{**} = \frac{\bar{\beta}\phi}{(\mu + \nu + \gamma)(r^{**} + \phi)}. \tag{11}$$

And therefore the required proportion of the population to be vaccinated to eradicate an infectious disease is:

$$p^{c*} = 1 - \frac{\mu}{\alpha R_0^{**}} \tag{12}$$

In Figure 4.1, we illustrate the effect of changes in the birth rate and the proportion vaccinated on the equilibrium disease prevalence and the corresponding life expectancy in the classic S-I-R model with no income effect, and the present model with an income effect. Notice that Figures 4.1a and 4.1c are identical. This is because the short-term effect of vaccination is identical to that of lowering the birth rate: both immediately remove susceptibles from the population. However, over the longer term, lowering the birth rate does not only directly lower the disease prevalence via reduction of the susceptible pool, it also indirectly increases per capita income via greater average health. The greater income, combined with the smaller households, results in greater per capita protection from disease and a lower transmission rate. In other words, the long-term effect of lowering the birth rate is to necessarily also lower the transmission rate, which combines to have a significant impact on the equilibrium disease prevalence. This qualitative result is robust over the full range of possible parameter values.

The corresponding effects on the life expectancy from changes in the birth rate and the proportion vaccinated are presented in Figure 4.2. Although changes in the birth rate and the proportion vaccinated have the same effect on the equilibrium disease prevalence in the short-term model with the income effect, the corresponding effect on life-expectancy differs.

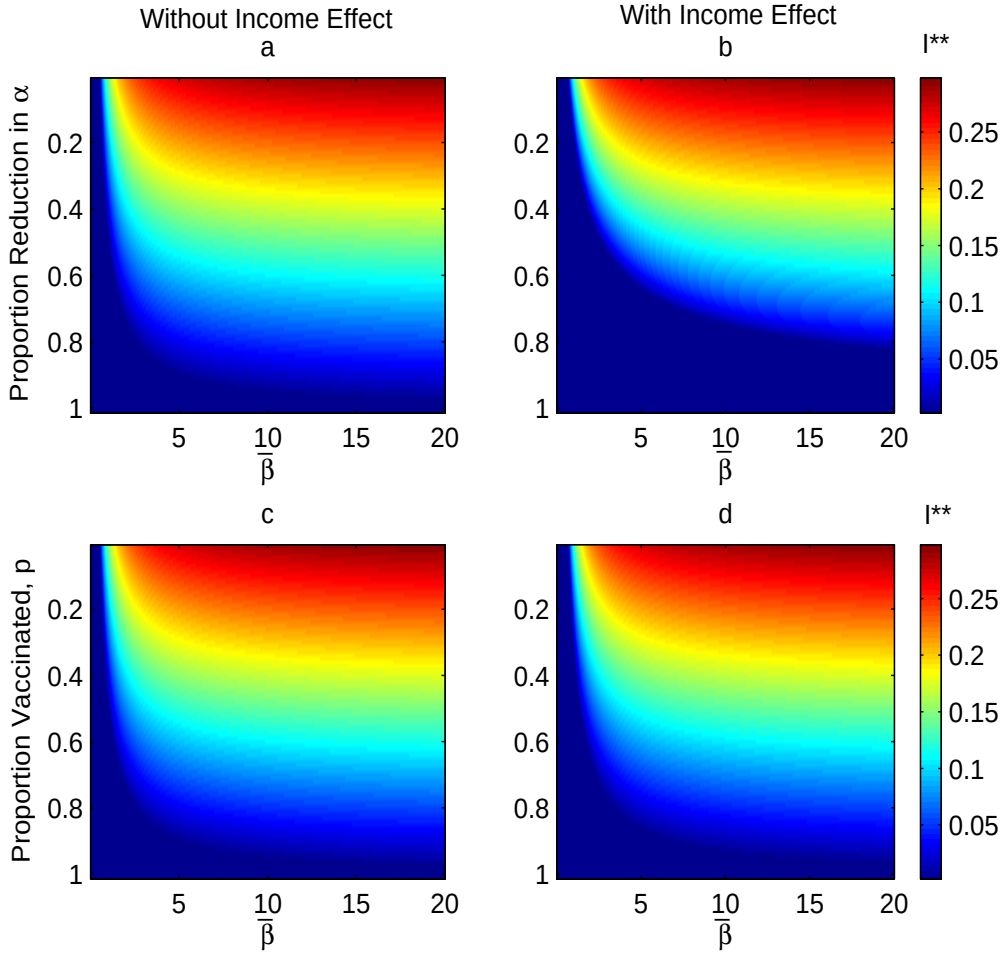

Figure 4.1: Disease prevalence as a result of changes in the reproduction and transmission (a and b) and changes in proportion vaccinated and transmission (c and d). The color-bar indicates the equilibrium disease prevalence. We assume that the initial birth rate is $\alpha = 0.05$, which is approximately equal to the average birth rate in sub-Saharan Africa. Figures a and c represent how changes to the respective birth rate and the proportion vaccinated affect the equilibrium disease prevalence without an income effect, and they are therefore identical. Figures b and d represent how changes to the respective birth rate and the proportion vaccinated affect the equilibrium disease prevalence, accounting for an income effect. Notice that, with an income effect, changes in the birth rate are always more significant than either the original model or the effect of vaccination. $\mu = 0.015, \gamma = 0.1, c = 10, \phi = 10, \nu = 0.05, z = 1, \alpha(0) = 0.05; a)$ and $c)\beta = 0.5$

This is because the effect of vaccines on the life expectancy for unvaccinated individuals is the same as lowering the birth rate, but the average lifespan includes both unvaccinated and vaccinated individuals, the latter of whom enjoy the natural life expectancy.

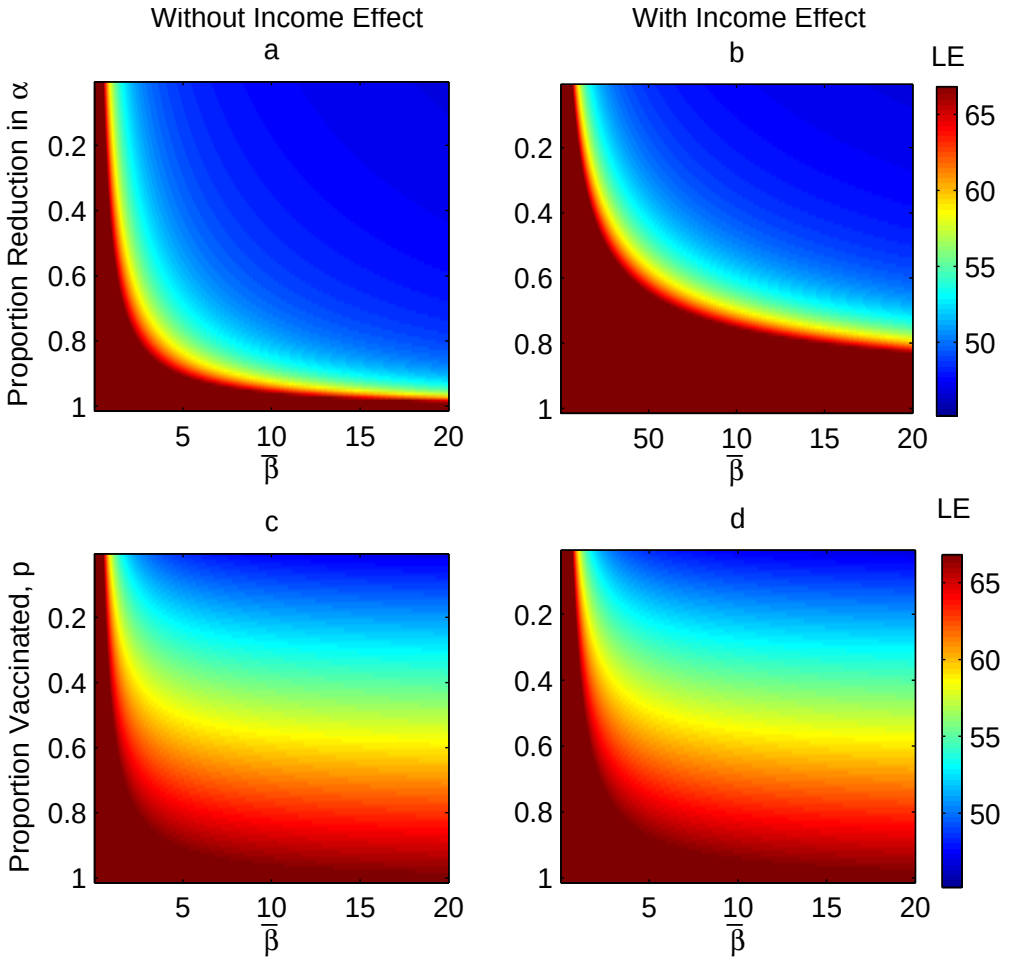

Figure 4.2: Life expectancy as a result of changes in reproduction and transmission (a and b) and changes in proportion vaccinated and transmission (c and d). The color-bar indicates the equilibrium life expectancy. We assume that the initial birth rate is $\alpha = 0.05$, which is approximately equal to the average birth rate in sub-Saharan Africa. $\mu = 0.015, \gamma = 0.1, c = 10, \phi = 10, \nu = 0.05; \alpha(0) = 0.05; a)$ and $c)\beta = 0.5$

The potentially dramatic benefits of lowering the birth rate on the life expectancy are perhaps more clear in the cross-section of Figures 4.2a and 4.2b, presented in Figure 4.3a. By reducing the birth rate by 60% with the help of the smaller household and greater resources per child, the disease becomes eradicated, and the life-expectancy increases by over 35%. The same reduction in fertility in the conventional S-I-R model, would correspond to a

mere 5% increase in the life expectancy. Such a large reduction in fertility, along with the corresponding effect on life expectancy might, at first glance, seem unreasonable. However, such a change in the birth rate would correspond to the difference between sub-Saharan Africa, where infectious diseases are ubiquitous and poverty prevails, and Western Europe and the U.S. where the same diseases that were once responsible for the lives of so many children - malaria, measles, parasitic worms - have been mostly or totally eliminated.

From equations (3) and (12), we see that for any given birth rate, α, there is a corresponding critical vaccination threshold, p^{c*}, that would result in the eradication of the disease. The flip-side of this relationship is that, for any given level of vaccine, there is some maximum birth rate, α^c, that can result in eradication:

$$\alpha^c = \frac{\mu}{R_0(1-p)}. \tag{13}$$

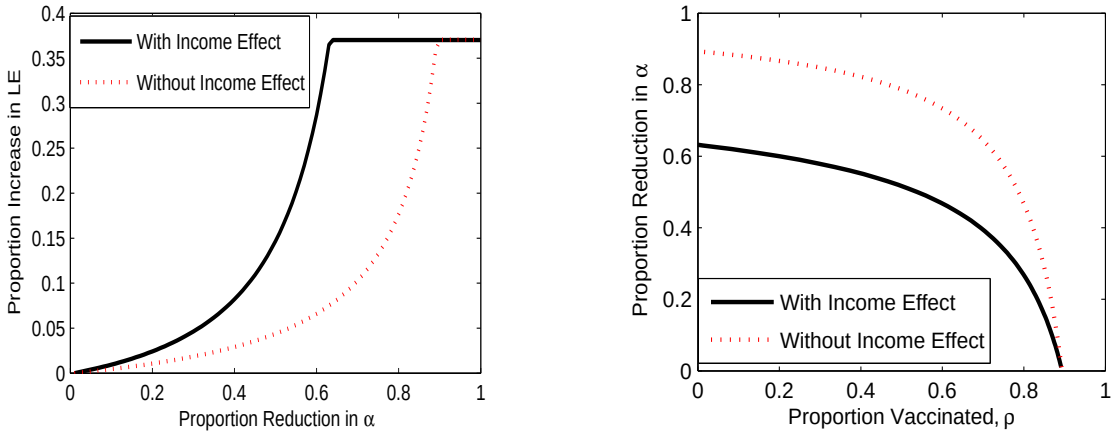

Figure 4.3: a) Proportional increase in the life expectancy that results from a proportional decrease in the birth rate. b) The area above the curves represents the combination of birth rate reduction and the proportion vaccinated that will result in eradication of the disease $\mu = 0.015, \gamma = 0.1, c = 10, \phi = 10, \nu = 0.05, z = 1, \bar{\beta} = 5; \alpha(0) = 0.05; b) p = 97$.

In Figure 4.3b, all combinations of vaccination and birth rate reduction necessary to eradicate a disease are presented for both the old S-I-R model with no income effect and the present model with an income effect. As mentioned above, in the classic model, reductions in fertility and vaccination are considered epidemiologically equivalent, which is why the corresponding eradication curve in Figure 4.3b is symmetric along the diagonal axis.

However, the new model, which accounts for an economic effect, predicts that a reduction in fertility may be significantly more effective than a vaccine. It also illustrates that a sustained vaccination policy would be more likely to eradicate a disease if done in conjunction with decreased reproduction.

4.4 Discussion

The biggest killers of human beings in the developing world are infectious diseases. Substantial progress has been made in understanding the ecology and evolution of such diseases, which have appropriately relied on the principles of predator-prey relationships (Lotka, 1925; Volterra, 1926; Anderson and May, 1979, 1992). Important policy implications have emerged. For example, we have learned that disease eradication does not necessarily require vaccination of an entire population. Rather, "herd immunity" can be acquired by vaccinating only a proportion of the population (equation (3)). And while much analysis has successfully focused on child diseases (Grenfell et al., 2001; Rohani and Grenfell, 1999; Rohani et al., 2003), these efforts have focused on dynamics in developed countries, where the populations are relatively stable and the mortality effect of the diseases are near zero. As a result, the death and birth rates can be reasonably treated as equal, and the critical vaccination coverage, ρ^*, is therefore simply equal to $1 - 1/R_0$. The key factors for these systems are therefore the transmission rate and the rate of recovery, which are almost always considered to be exogenous parameters.

Infectious diseases, however, continue to be most significant in developing countries, which experience relatively rapid population growth. The effect of this influx of children on the persistence and dynamics of childhood diseases, as well as on the critical vaccination coverage, is reasonably well-established (McLean and Anderson, 1988a; Broutin et al., 2005). But it is now warranted to turn this framework on its head: can fertility reduction be an integral element of a disease eradication campaign? From the old S-I-R framework, the return of such a strategy seems minimal (equation (3), Figure 4.3). However, we are now coming to realize

that the success of many infectious diseases is not merely due to the static biology of their transmission. Instead, there is a very important insidious effect where such biology arrives at a crossroads with economics. It is during youth, when immunity is naive and susceptibility is high, that children must acquire the training and skills necessary for economic success later in life. In addition to the naive immunity, the diseases can therefore enjoy indirect advantages of targeting children by debilitating their human hosts when they are young, which ultimately, through poverty, undermines their ability to protect their own children from the assault of the same infectious agents. Over the longer term, the basic reproductive ratio, R_0, is therefore determined simultaneously by both the biology of disease transmission and the economics of host vulnerability. This feedback has been hypothesized to drive a poverty-trap which could be defined in this case as an unstable equilibrium level of protection, r^{**}, and disease prevalence, I^{**}. Our simple framework, with per capita income scaled to the life-expectancy, captures the essential elements of such a feedback, but does not generate the kind of unstable equilibria that would characterize a disease-induced poverty trap. Still, it does provide important qualitative predictions. For example, the simultaneous indirect effect on the transmission rate that would result from a reduction in fertility can substantially reduce disease prevalence over the long-term and could potentially result in the eradication of some infectious diseases. It is important to emphasize here that our model considers only a single "representative" childhood disease. This model is likely to understate the true benefits of reduced fertility because the effect of reducing the birth rate is to reduce the flow of susceptibles for *all* diseases, which is the equivalent of a vaccine for all infectious diseases at the same time.

However, as with vaccines, there is subtle economic behavior that may be a critical barrier to lowering the disease prevalence. The benefits of vaccinating a child are not isolated to that individual but, by lowering disease transmission, increase the welfare of all susceptible people in the community. As a result, voluntary eradication of a disease may be very difficult because, as vaccination coverage rises, the disease prevalence will fall sufficiently low that

the individual benefits of vaccinating eventually fall below the perceived costs (e.g., pain, inconvenience, risks of side-effects, etc.) (Geoffard and Philipson, 1997). Such group-vs-self-interest in vaccine coverage has been characterized as a "prisoner's dilemma" (Bauch et al., 2003; Bauch and Earn, 2004). The same subtle conflict of interest between individuals and their communities would also be applicable to the decision-process of reproduction. The costs of having children are not just borne to the individual household, but to other susceptible individuals because of the corresponding higher rate of disease transmission. Economists would therefore expect a greater birth rate than would be "optimal" for the community.

Underlying the intense and broad upsurge of interest in global health and economic development are important questions. Why do people from some parts of the world enjoy continued exponential economic growth, while others, such as those in sub-Saharan Africa, suffer from the kind of extreme poverty their ancestors did thousands of years ago? While some very important explanations have come forth that explicitly link economic development to disease ecology (Diamond, 1997; Sachs, 2005), we continue to lack formal integrated theories. Fortunately, the structure of economic and ecological modeling is primed for such integration. Our simple framework here presents an example of such integration, and hopefully constitutes more than an epidemiological model of poverty, but a step towards more general integrated theories of ecology and economics.

Chapter 5

Concluding Remarks and Future Research

"If we knew what we were doing it wouldn't be called research, would it." - Albert Einstein

The ultimate objective of my research has been to help lay a better foundation for integrated work between the natural and social sciences - specifically between economics and ecology. I believe what has been lacking is a decent framework for such integration; a major "bottle-neck", in my opinion, is the lack of new ideas based on both sound ecological *and* economic principles. I have made a case for why disease ecology constitutes an incredibly under-explored frontier of human ecology, primed for integrated research between both disciplines. But, as mentioned in the introduction, I did not originally know where exactly to begin. Because of their common vision with economics of a kind of "rational order" associated with a notion of "efficiency", and therefore with shared techniques such as optimization theory and game theory, evolutionary and behavioral dimensions of host-pathogen interactions seemed to be a good place to start.

5.1 What has Been Accomplished

Accordingly, Chapter 2 (Bonds et al., 2005) explores a natural analogue to the feedback between human behavior and infectious diseases: the coevolution of sociality and infectious diseases in non-humans. This has the advantage of being considered over evolutionary timescales, and we can therefore invoke principles of evolutionary stability to get an idea of how social behavior may be influenced by infectious diseases in the natural world. The most significant result here - that higher disease prevalence can induce greater sociality - has

some value without having been tested. We formally explored a hypothesis that had grown into a conventional wisdom - that increased disease burden should result in lower sociality (Freeland, 1976; Brown and Brown, 1986; Møller et al., 1993) - and determined that there is no *a priori* reason to think so. The theory is sufficiently coherent and simple that it could be tested in the laboratory if one wished to do so. Ultimately, the purpose of that exploration was personal - to help me organize my thoughts and understanding of how to model host behavior in the context of infectious diseases while accounting for the potential evolutionary reactions of the disease itself. But I wanted to do so while making a small contribution to the literature that stood on its own. Its biggest weakness is the treatment of the evolution of virulence - assumed to be determined by a nonlinear trade-off between transmission and disease-induced mortality. While such an assumed trade-off has quite a bit of theoretical justification (Frank, 1996; Bremmermann and Thieme, 1989; Bremmermann and Pickering, 1983; Frank, 1992; Day, 2002; Ewald, 1994; Day, 2001; Day and Proulx, 2004), the evidence of this trade-off is mixed and general models of the evolution of virulence remain controversial. However, the key findings on the evolution of social behavior do not rely on the treatment of pathogen evolution, rather they are simply *robust* to it.

In some respects, I think Chapter 3 (Bonds, 2006) is the best short-term scientific contribution out of this dissertation. To me, it has all of the trademarks of a good theory. It develops a novel framework that coherently integrates two otherwise disparate literatures - pathogen-induced mortality vs. sterility - while potentially answering some broad, as well as narrowly defined, empirical questions that have been circulating for some time: 1) why do pathogens often sterilize their hosts, and 2) why do some hosts become larger after infection. The assumptions that I relied on: 1) that both host and pathogens vie for host resources; 2) that such resources are used for both reproduction and longevity; and 3) that the host does not recover from infection; were all confirmed experimentally by Ebert et al. (2004) in a well-studied laboratory system of *Daphnia magna* that experiences gigantism when infected with the bacterium *Pasteuria ramosa*. In the end, we are left with a somewhat new theoretical

framework that is based on scientifically established premises and that explains otherwise poorly understood patterns observed in nature. It also has some economic anthropomorphic appeal. The pathogen actually manipulates the host by changing its incentives: castration induces the host to invest more resources into maintenance versus reproduction, thereby increasing the survival of the pathogen. But despite the value that I ascribe to further integrating economic and ecological frameworks, this, again, was not in a way that would be of interest to both economists and ecologists.

Superficially, Chapter 4 (Bonds et al., 2006) is the simplest and perhaps least creative contribution from this dissertation. But as a point of departure for developing integrated theories of economic development and infectious disease ecology, I also think it will ultimately prove to be the most important - both socially and scientifically. Many people are dying from natural enemies in the form of infectious diseases in accordance with well-known ecological processes. In addition to mortality, diseases have many sublethal effects. In particular, they reduce the productivity of the workforce, directly through laborer illness, as well as indirectly through impacts on the educational development of children, thereby affecting long-term economic processes. It would seem quite difficult to disentangle the economics and ecological feedbacks that are accountable for the persistence of poverty and disease throughout much of the world. Thus, an integrated framework is necessary. Chapter 4 presents such a framework.

By explicitly linking disease exposure to income, which is, in turn, determined by the prevalence of the infectious diseases, we shed light on some of the dominant forces that determine patterns of global health and economic development over the long-term. We find that, by providing a constant source of susceptible individuals for disease transmission, high birth rates constitute a greater barrier to improving public health and economic development than any existing model has suggested. With the combined effect on per capita income, lowering the birth rate in developing countries to levels comparable to those in the western world, could potentially be sufficient to eradicate some infectious diseases. Combined with the effect of population pressures on resource availability and environmental quality, this

finding has particular appeal: in this case, what is good for the environment is good for public health, and for economic development. Darwin, Malthus, and Adam Smith would all be pleased.

5.2 Where to Go From Here

To me, Chapter 4 represents the first major step towards my ultimate objectives, but it is clearly just the beginning. The feedback between disease ecology and economic development has been suggested to form a poverty trap (Sachs et al., 2004; Gallup and Sachs, 2001b). I have a couple of potentially important extensions of Chapter 4 that I plan to pursue in the immediate future. One of them is presented below.

5.2.1 Feedback Between Malaria Evolution and Economic Development

While we have had much success in modeling the ecological dynamics of infectious diseases (Anderson and May, 1992; Grenfell and Dobson, 1995; Keeling and Rohani, 2006), our understanding of disease evolution has been slower to develop. However, our understanding of malaria evolution from laboratory experiments marks a very important area of progress (Mackinnon and Read, 2004b). The most common malaria species in Africa, *Plasmodium falciparum*, is one of the world's leading killers, claiming the lives of as many as 2 million people annually, and harming an estimated 100 to 500 million sub-lethally. *P. falciparum* is ancient (Volkman et al., 2001), and remains dominant in the oldest inhabited parts of the world - sub-Saharan Africa - where it continues to claim the lives of the poorest. Indeed, it is this general relationship, that wide-scale extreme poverty is found almost where malaria is endemic, that has led some to conclude that malaria is a driving force behind poverty (Gallup and Sachs, 2001a; Sachs and Malaney, 2002; Sachs, 2005). But it is also these parts of the world where malaria is the most virulent. Indeed, 90% of all malaria deaths are in Africa. This explicit feedback between poverty and malaria virulence has yet to be explored theoretically or empirically.

I plan to develop a theory of how a malaria-driven poverty trap could rely on malaria evolution. The basis of such a theory is that exposure to disease vectors not only causes poverty, but also causes malaria to evolve greater virulence. The poverty trap is illustrated below. The model relies on three premises: 1) virulence and prevalence of malaria are causes of poverty; 2) poverty increases exposure to malaria vectors; and 3) greater exposure increases malaria transmission and virulence. Premises 1) and 2) are straightforward extensions of the treatment in Chapter 4. There are two justifications for premise 3). The first is well established on theoretical grounds, and the second is more novel.

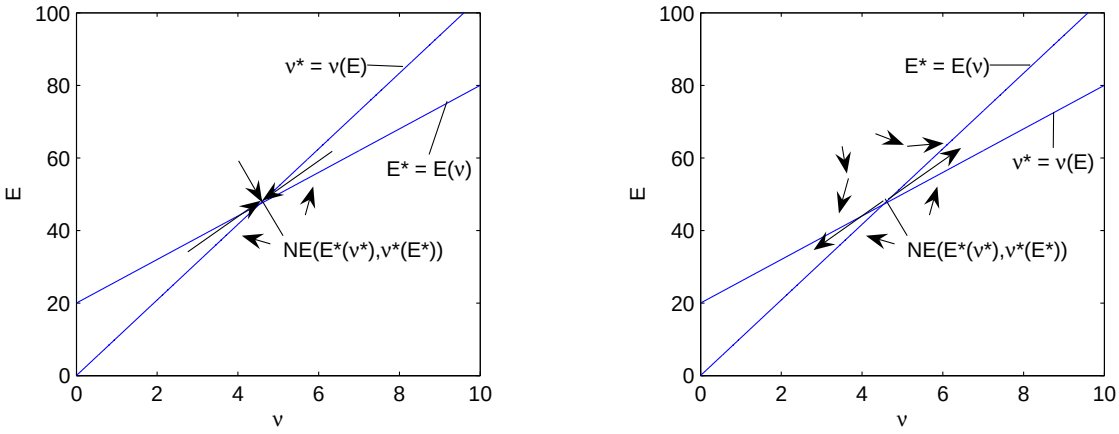

Figure 5.1: As virulence rises, the decrease in labor productivity, and therefore in wealth, causes an increase in disease exposure, $E^*(\nu)$. Moreover, as disease exposure increases, so does the average investment in immunity, causing an increase in pathogen virulence, $\nu^*(E)$. The intersection of these two functions is a Nash Equilibrium (NE). Whether there is a disease-driven poverty trap depends on whether the NE is stable or unstable. a) The NE is stable: no "trap". b) The NE is unstable, implying a a poverty trap. The initial conditions therefore matter. If the society starts off with some combination of relatively high disease exposure and pathogen virulence, the system will evolve towards ever-increasing poverty and disease. If the society starts off with relatively low exposure and low disease virulence, it enjoy ever-increasing economic growth and public health.

Greater exposure to disease tends to increase the number of different strains that infect an individual at one time (Ewald, 1994; Read and Taylor, 2001). Such within-host competition favors strains with the fastest rate of replication, which is also the fastest rate of host exploitation, and is therefore the most virulent (Hamilton, 1971; Bremmermann and Pickering, 1983; van Baalen and Sabelis, 1995; Frank, 1996). Thus we have a disease version of the "tragedy of the commons" (Hardin, 1968), where individual competition over a

common resource leads to over-exploitation. The classic example of "the tragedy" is competitive fishermen in a fishery; conservation for the purposes of future harvesting becomes necessarily undermined if the future beneficiary of such conservation is a competitor. This kind of dynamic has been formalized more generally, and has also been characterized as a "prisoner's dilemma," with the outcome known as a Nash noncooperative equilibrium. In the case of multiply-infected hosts, the host represents the common resource. The strains, which, in isolation, would therefore have an "incentive" to preserve the host, end up destroying it quicker. Such theories are well-developed and have been attributed to general disease relationships. However, the evidence in natural disease-host systems is limited.

As an important exception, animal models of *Plasmodium chapaudi*, a strain that shares many similarities with *P. falciparum*, have shown evidence of competition between strains. Indeed, a review by Read and Taylor (2001) finds that all *in vivo* experiments of competition between malaria strains finds some amount of within-host competition. The best and most recent finding is by de Roode et al. (2005), who find that the winner of necessarily competitive interactions between genetically diverse malarial infections within a host is also the most virulent strain. If this basic relationship holds true for *P. falciparum*, the implications for a disease-driven poverty trap are significant.

Gandon et al. (2001) presented a novel theory that vaccines, which are inherently imperfect, select for more "intrinsically virulent" strains of malaria. The reason is because vaccines reduce the cost to the pathogen of being virulent, in terms of shorter infectious period due to clearance or death, without equally reducing the benefits of virulence in the form greater transmission. This idea remains controversial, but one implication is significant: the acquisition of host immunity (which is analogous to vaccines), which is driven by exposure, results in more intrinsically virulent pathogens, killing the hosts who are immunological naive. In other words, an arms race between the host immune system and malaria virulence may be the primary cause of malaria-induced child mortality. This arms race has been shown exper-

imentally in the *P. chapaudi* model (Mackinnon and Read, 2004a), and would be driven by disease exposure for humans.

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Appendix A

Stochastic Simulation of Coevolving Contact and Virulence

The system is simulated using the Gillespie algorithm (Gillespie, 1977), with birth, death, and transmission events occurring stochastically in accordance with the probabilities that correspond to the deterministic equations (1) and (2). Initially, we assign 600 host phenotypes with contact efforts that are evenly distributed between 0 and 10. We also assign 400 pathogen phenotypes with rates of virulence that are evenly distributed between 0 and 1. For 99% of birth events, the offspring inherits the contact effort of its parent. For 1% of the birth events, the contact effort mutates within -1 and 1 units from its parent's contact effort, with a uniform probability for all values within that range. For 99% of transmission events, the newly infected individual contracts a pathogen which is equally virulent to the individual that infected it. For 1% of the transmission events, the pathogen virulence mutates within -0.2 and 0.2 units, with a uniform probability for all values within that range. For a detailed account of the conversion of a deterministic model into a stochastic simulation using the Gillespie algorithm, see Wearing et al. (2004).

Appendix B

The Optimal Contact Rate as a Function of Pathogen Prevalence with Alternative Fitness Function

Figures 2 and 3 were generated from the fitness function in equation (3), with a quadratic mortality rate, $d + p(K - C_i)^2$. This rate has a minimum at $C_i = K$, and implies a finite optimal contact rate for all levels of pathogen virulence and prevalence (including 0 or 1). To confirm the generality of our basic results, we also considered the following mortality rate: $d + \pi/C_i$. This alternative mortality rate asymptotically approaches the limit, d, as the contact rate approaches infinity. As a result, the optimal contact rate approaches infinity as the disease prevalence approaches 0 or 1. More importantly, however, is that this relationship is similar to that derived from the quadratic mortality function in that it is nonmonotonic. Compare Figures 2 and 3 with Figures B.1 and B.2 below.

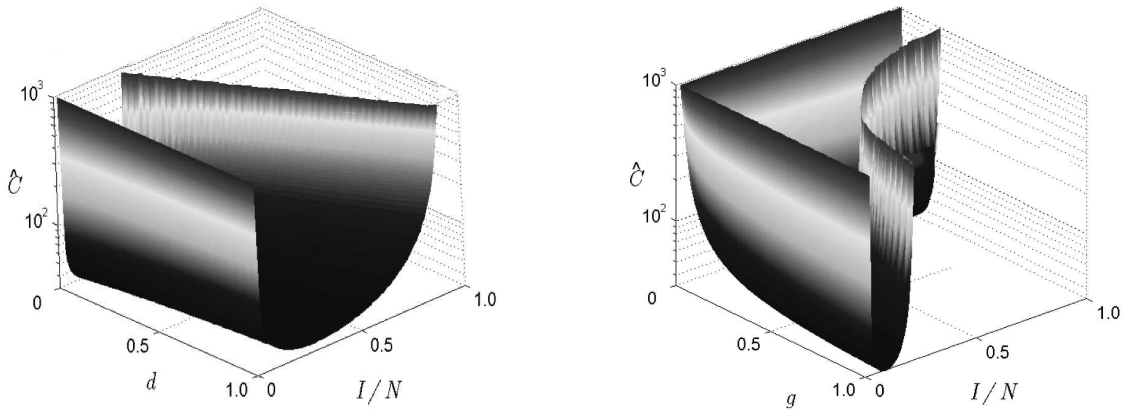

Figure B.1: a) The optimal contact rate is presented over a range of exogenously determined rates of mortality and disease prevalence, with $\hat{C}$ approaching infinity as prevalence approaches 0 or 1; $d \in [0,1], I/N \in [0,1], \pi = 5, \rho = gv/(v+\xi), g = 0.1, v = 0.5, \xi = 1$. b) The optimal contact rate is presented over a range of exogenously determined transmission probabilities and disease prevalence, with C approaching infinity as prevalence approaches 0 and 1; $g \in [0,1], I/N \in [0,1], d = 0.15, K = 81; \rho = gv/(v+\xi), v = 0.5, \xi = 1, p = 0.00005$.

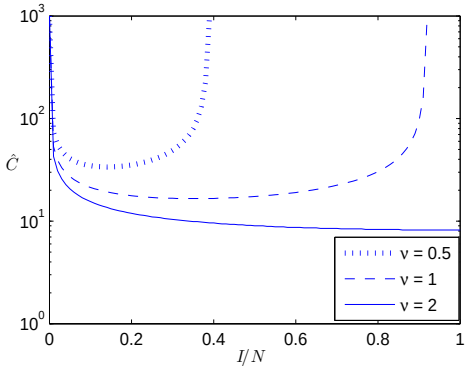

Figure B.2: The optimal contact rate is presented over a range of exogenously determined rates of disease prevalence, with different values of pathogen virulence. At relatively low levels of virulence, the ES contact rate responds nonmonotonically to disease prevalence. At high levels of virulence, the ES contact rate responds negatively to disease prevalence; $v \in [0,1], I/N \in [0,1], \pi = 5, \rho = gv/(v+\xi), g = 0.1, \xi = 1; d = 0.15$.

Appendix C

Solution to the Equilibrium levels of Protection and Disease Prevalence

$$r^*(I) = \frac{-\left(\mu\phi + \bar{\beta}\phi I - \frac{\delta}{c\alpha}\right) + \sqrt{\left(\mu\phi + \bar{\beta}\phi I - \frac{\delta}{c\alpha}\right)^2 + \frac{4\mu\delta}{c\alpha}\left(\phi + \frac{(1-\rho)\bar{\beta}\phi I(1+\gamma/\mu)}{\mu+\nu+\gamma} + \frac{\bar{\beta}\phi I\rho}{\mu}\right)}}{2\mu}. \quad (1)$$

$$p^3\mu^2 + p^2(2(\mu^2\phi + \mu\bar{\beta}\phi I) - \delta/ck) + p[(\mu\phi + \bar{\beta}\phi I)^2 - 2\delta(\phi + \bar{\beta}\phi IW)/(ck)] - \delta(\phi + \bar{\beta}\phi IW)^2/(ck) = 0 \quad (2)$$

,

where $W = \Omega - r\Omega + r/\mu$.

Let,

$$A = \bar{\beta}\phi W \quad (3)$$

$$B = (p+\phi)(1+W\mu) - \frac{k(1-r)\bar{\beta}\phi}{\mu+v+\gamma} \quad (4)$$

$$C = \mu(p+\phi)\left(\frac{(p+\phi)}{\bar{\beta}\phi} - \frac{k(1-r)}{\mu+v+\gamma)}\right) \quad (5)$$

$$I^{**} = \frac{-B + \sqrt{B^2 - 4AC}}{2A} \quad (6)$$

Appendix D

Illustration of Feedback Between Protection and Disease Prevalence

From Figure D.1, we can see how the average rate of protection, $r^*(I)$, the corresponding transmission rate, $\beta^*(I)$, and the equilibrium disease prevalence, $I^*(r)$, feedback on each other. The long run equilibrium prevalence, I^{**}, the level of protection, r^{**}, and rate of transmission, β^{**}, are found where the $I^*(r)$ and $r^*(I)$ curves intersect, and where the $I^*(\beta)$ and $\beta^*(I)$ curves intersect respectively:

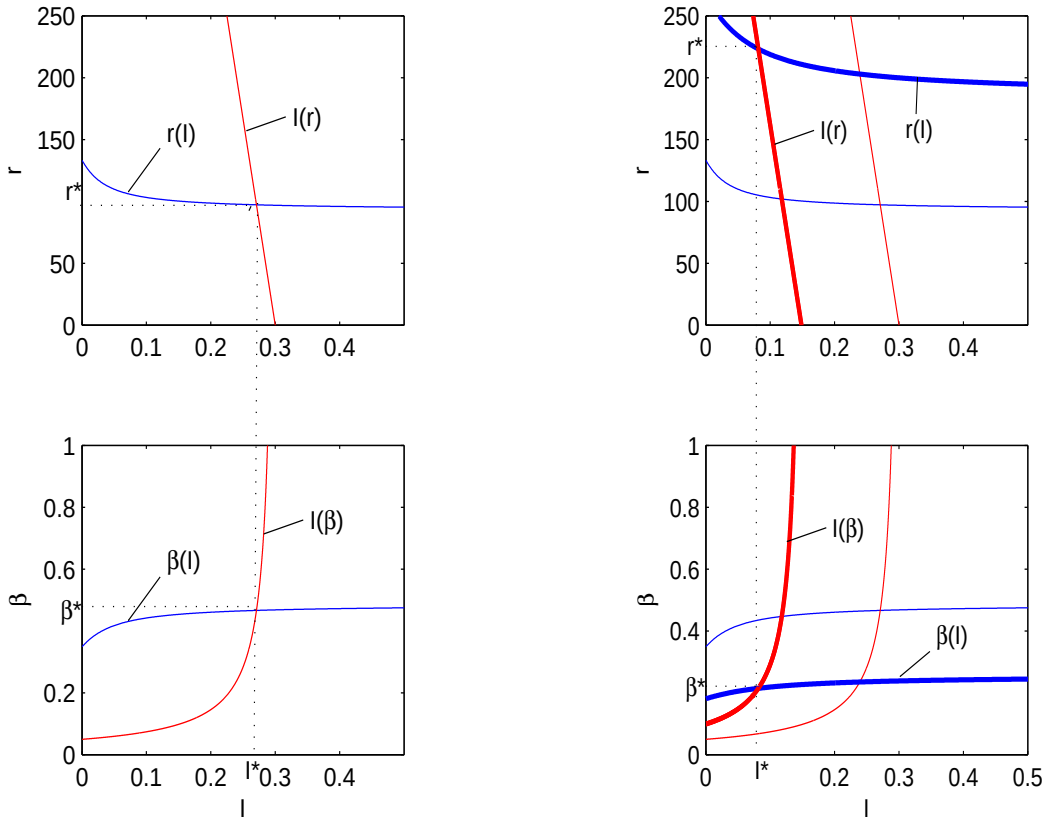

Figure D.1: The transmission rate is determined by both host and pathogen behavior, the interaction of which therefore determines the long term equilibrium disease prevalence. a) As the disease prevalence, I, rises, the per capita investment in protection, $r^*(I)$, falls due to an income effect. However, as the investment in protection rises, the equilibrium disease prevalence, $I^*(r)$, also falls. These two forces determine the long-term equilibrium prevalence, I^{**}, which can be found at the intersection of the $I^*(r)$ and $r^*(I)$ curves. b) The effect of a decrease in the birth is more significant in the long run because of the income effect. This is illustrated by a leftward shift of the $I^*(r)$ curve *and* an upward shift of the $r^*(I)$ curve. c) The investment in protection corresponds to a transmission rate, $\beta^*(I) = \bar{\beta}\phi/(r^*(I)+\phi)$, which rises when the disease prevalence rises due to an income effect. And as the transmission rate rises, the disease prevalence, $I^*(\beta)$ falls. These forces equilibrate at the intersection of $I^*(\beta)$ and $\beta^*(I)$ curves. d) The effect of a decrease in the birth rate is more significant in the long run because of the income effect. This is illustrated by a leftward shift of the $I^*(\beta)$ curve *and* a downward shift of the $\beta^*(I)$ curve. $\mu = 0.015, \nu = 0.05, \gamma = 0.1, c = 10, \bar{\beta} = 5, \phi = 10$. a) and c) $\alpha = 0.05$; b) and d) $\alpha = .025$.