The Population Biology of Multispecies Helminth Infection

Thesis submitted to the University of London for the degree of Doctor of Philosophy in the Faculty of Science

by

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Abstract

Vertebrate hosts are frequently infected with multiple helminth species. There is a body of experimental evidence to suggest that infection with one parasite species can have either an antagonistic or synergistic effect on another species; such interactions may occur through parasite establishment, survival and fecundity. The extent to which such interactions are involved in the organization of helminth communities is largely unknown.

Mathematical models based on Markov processes are used to explore two themes: 1) The effect of interspecific interactions on the joint distribution of helminth parasites in a population of hosts, and 2) conditions under which interacting species can coexist. To explore the former, models are formulated that describe the process by which helminths of two species are acquired and lost in a cohort of ageing hosts. In these models, the interspecific interaction occurs at the point of parasite establishment within the host such that the rate of establishment depends on the current worm burdens of the two species. The results are used to highlight some of the difficulties associated with inferring interspecific interactions from ecological data.

The relationship between competition and species coexistence is investigated using models of the long-term dynamics of interacting species. Models are developed in which there is a free-living larval stage whose population size is dependent on the size of the adult worm population. The models are analyzed using 'hybrid' and 'moment-closure' approximations; the former involves replacing stochastic components of the model with deterministic approximations, and the latter assumes a functional relationship between higher and lower order moments based on a specified distribution.

The Lotka-Volterra model of competition is derived for the case where hosts are equally exposed to parasites of the same species. Coexistence of two competing species is promoted by heterogeneous host exposure to each parasite species, provided that the rates of exposure to the two parasite species are not perfectly, positively correlated, and provided that the degree of heterogeneity in host exposure is similar for both species. In addition, it is shown that the conditions required for coexistence are the same regardless of whether competition occurs at the point of parasite establishment within the host or via parasite fecundity. These results are discussed within the context of helminth community ecology.

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Glossary

Abiotic factors Non-living factors that affect ecosystems, e.g. rainfall, sunlight; cf. biotic which refers to living.

Antibodies Glycoproteins produced by B-cells that bind to antigens on foreign particles. Antibodies provide the immune system with a way of recognizing invading pathogens. There are five classes of antibodies (also known as immunoglobulins): IgA IgD IgE IgG IgM each of which has different properties. For example, IgE binds to mast cells.

Antigens Molecules, usually on the surface of pathogens, to which antibodies bind.

Antibody-dependent cellular cytotoxicity (ADCC) The process by which antibody-coated cells are destroyed by cells of the immune system such as macrophages.

B-cells Cells that produce antibodies

Convex age intensity profile The unimodality often observed when mean worm burden is plotted as a function of age, i.e. mean worm burden rises in young age groups, reaches a peak and then declines to an equilibrium level at older ages. This definition does *not* correspond to the definition of a convex function in mathematics.

Cospeciation The simultaneous speciation of two or more species, e.g. a host and its parasite species.

Covariance The covariance of random variables X and Y is

$$\mathrm{Cov}(X, Y) = E[(X - \mathrm{E}[X])(Y - \mathrm{E}[Y])]$$

where E stands for expectation.

Cytokines Chemicals produced by cells of the immune system to communicate with one another.

Determinant For a 2×2 matrix

$$\mathbf{A} = \begin{pmatrix} a & b \\ c & d \end{pmatrix},$$

the determinant of $\mathbf{A}$ is $\text{Det}(\mathbf{A}) = ad - bc$. For an $n \times n$ matrix, $\mathbf{A}$, the determinant can be computed using the following property of determinants

$$\text{Det}(\mathbf{A}) = a_{i1}C_{i1} - a_{i2}C_{i2} + a_{i3}C_{i3} - \ldots a_{in}C_{in}$$

where a_{ij} is the jth element of row i in $\mathbf{A}$, and C_{ij} is the determinant of the 'submatrix' obtained by deleting row i and colum j from $\mathbf{A}$.

Eigenvalue The eigenvalues (λ) of a matrix $\mathbf{A}$ satisfy

$$\mathbf{Av} = \lambda\mathbf{v}$$

where $\mathbf{v}$ is a vector known as an eigenvector. They are found by solving $\text{Det}(\mathbf{A} - \lambda\mathbf{I})$ where $\mathbf{I}$ is matrix of 1's on the diagonal and zeros elsewhere. Eigenvalues are used to determine the stability of equilibrium points.

Eigenvector See eigenvalue

Equilibrium $\mathbf{x}^*$ is an equilibrium point for a system of differential equations $\frac{d\mathbf{x}}{dt}$ if $\frac{d\mathbf{x}^*}{dt} = \mathbf{0}$.

Expectation For a random variable X that takes on values $1, .., n$ the expectation, or mean, of X is $\text{E}[X] = \sum_{x=1}^{n} x\text{P}(X = x)$. When X is a continuous random variable $\text{E}[X] = \int_{-\infty}^{+\infty} xf(x)dx$ where $f(x)$ is the density function associated with X.

Interactive site segregation The phenomenon whereby the location of one parasite species within the host is determined by the presence/absence of another species. See also selective site segregation.

Jacobian matrix For the system of differential equations

$$\begin{pmatrix} dx_1/dt \\ \vdots \\ dx_n/dt \end{pmatrix} = \begin{pmatrix} f_1(x_1, \ldots, x_n) \\ \vdots \\ f_n(x_1, \ldots, x_n) \end{pmatrix}$$

the Jacobian matrix is given by

$$\begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}$$

In the analysis of non-linear differential equations, the eigenvalues of the Jacobian evaluated at an equilibrium, $\mathbf{x}^*$, can be used to determine properties of $\mathbf{x}^*$, e.g. whether it is stable/unstable.

K-selection The opposite of r-selection, i.e. the selection for low fecundity and high offspring survival that is predicted to occur in an environment where resources are limited.

Laplace transform The Laplace transform of a function $f(t)$ is $F(s) = \int_0^\infty e^{-st} f(t) dt$. It is a useful tool for solving certain differential equations.

Markov Process A stochastic process, $X(t)$, is a Markov process if the probability of transition from current state, i, to a future state, j, depends only on the current state and not on previous states. Formally,

$$\mathrm{P}(X(t+s) = j | X(t) = i, X(u) = x(u)) = \mathrm{P}(X(t+s) = j | X(t) = i)$$

where $s > 0$ and $0 < u < t$.

Mast cells Inflammatory cells that bind IgE and secrete histamine.

Phylogeny A tree representing the evolutionary relationships between species

Poisson distribution Arises when counting the number of occurrences of an event (e.g. infection) in an interval of time. If a random variable, X, follows a Poisson distribution with mean λ, then the probability of x events is $\mathrm{P}(X = x) = e^{-\lambda}\lambda^x / x!$.

r-selection In an environment where resources are plentiful individuals that are able to rapidly exploit their environment are selected for. This corresponds to selection for high rates of fecundity, at the expense of high rates of offspring survival. When resources are scarce, low fecundity and high rates of survival are selected for (K-selection). This hypothesis was originally proposed by MacArthur & Wilson (1967), r and K refer, respectively, to the parameters for intrinsic growth rate and carrying capacity in the logistic equation of population growth.

Selective site segregation The non-random distribution of present-day parasite species within hosts arising from historic interspecific competition.

Stationary point See equilibrium point.

T-cells Have a receptor (the T-cell receptor) that binds to antigen when presented on an MHC molecule. Certain T-cells are involved in the regulation of the immune response through cytokine signalling (T-helper cells and Treg cells) others destroy invading pathogens (cytotoxic T-cells).

Trace The trace of an $n \times n$ matrix, $\mathbf{A}$, corresponds to the sum of the diagonal components, $\mathrm{Tr}(\mathbf{A}) = \sum_{i=1}^{n} = a_{ii}$.

Trophic levels Levels within the food chain.

Variance The variance of a random variable X is $\mathrm{Var}[X]=\mathrm{E}[X^2]-\mathrm{E}[X]^2$, where E stands for expectation.

Chapter 1

Overview

The study of helminth communities has a relatively long history. The first substantial body of work has been attributed to the Russian scientist V. A. Dogiel (Esch *et al.*, 1990), and certainly since the 1960s considerable data have been collected on the composition of helminth communities. The subject is now sufficiently well developed to have its own concepts and terminology, set apart from those of general community ecology.

Helminth communities are unusual in that the component species tend to occupy a single trophic level: predator-prey interactions between helminth species are extremely rare. Nonetheless despite the absence of predator-prey interactions there is a reasonable body of experimental evidence to suggest that there are other interactions between helminth species arising through competition for limited resources or indirectly mediated through the host's immune system.

The experimental evidence supporting interspecific interaction has not been followed up with conclusive field data. Yet it is both of theoretical and practical benefit, in terms of human and animal health, to identify interactions between helminth species in natural settings.

Currently data on the distribution of worm burden is often interpreted intuitively in terms of interspecific interaction. By exploring the effects of interactions between helminth species on the distribution of worm burden, this thesis aims to inform intuitive interpretations of data. In particular, the thesis identifies difficulties associated with attributing positive correlations between species to synergistic interactions and negative correlations with antagonistic interactions, as is commonly done.

As well as examining the distribution of worm burden, the question of species coexistence is addressed. Competitive exclusion of one species by another is to be expected when two species share the same limiting resource. This applies equally to helminth species. Further, antagonistic interspecific interactions mediated through

the host's immune system may also lead to competitive exclusion. Explaining how interacting helminth species are able to coexist is key to understanding helminth diversity. Yet, surprisingly, this question has received little attention.

Chapter 2 begins by introducing the subject of helminth community ecology. This chapter is fairly general and considers a number of models aimed at describing helminth community structure. Chapters 3 and 4 also function as review. Chapter 3 evaluates the evidence for interactions between helminth species, while Chapter 4 introduces mathematical models of helminth infection.

Chapters 5-8 form the original component of the thesis in which models of interspecific interaction are developed. Chapters 5 and 6 are derived from work in Bottomley *et al.* (2005), and chapters 7 and 8 from work in Bottomley *et al.* (2006).

A deterministic model for the accumulation of worm burden of two interacting species within a *single* host is introduced in Chapter 5. This model provides a basis for the stochastic model of Chapter 6 which explores the effects of synergistic and antagonistic interactions on the distribution of worm burden in different host age groups.

Chapter 7 presents a single species model in which the population size of infective larvae depends on the numbers adult worms in the host population. The model is extended in Chapter 8 to examine the effect of interspecific competition on the coexistence of species. Finally, Chapter 9 concludes with a discussion of the potential for future research in this area.

Chapter 2

The Structure of Helminth Communities

2.1 Introduction

The assemblage of species to be found in a particular environment can often be predicted from a knowledge of the species found in similar environments. It is in general difficult to determine when environments are similar or dissimilar; therefore ecologists often require that the species within an assemblage must interact, or at least share the same resources if they are to be considered a 'community' (e.g. Whittaker, 1975). For helminth species (see table 2.1), however, the situation is simpler since the environment can be clearly defined in terms of a host, or population of hosts. Communities of helminths are therefore often defined without reference to interspecific interactions, and simply in terms of the species present within a single host, or population of hosts.

Helminth communities can be thought of in terms of a hierarchy. At the lowest level of the hierarchy, the species found within an individual host form a community. At the next level up there is a community of helminths within a population of hosts of the same species. Finally, grouping together the communities from different host species, there is a community consisting of all helminths found in a particular ecosystem. These three levels of helminth community are known, respectively, as the *infracommunity*, the *component community*, and the *compound community* (Holmes & Price, 1986; Esch & Fernandez, 1993).

It is of interest to community ecologists to uncover the processes responsible for organizing communities. Here, and subsequently, the definition of community organization given by Hairston (1964) will be adopted: 'animal communities may be considered organized if any property of a natural assemblage of species can be

Phylum	Nematoda (Round Worms)		Platyhelminthes (Flat Worms)	
Class		Monogenea	Digenea	
Description	Nematodes are generally cylindrical in shape. They have a gut with both a mouth and anus. Most species are dioecious and exhibit sexual dimorphism, although some species are hermaphrodite. The basic nematode life-cycle involves six stages: adults, eggs and four larval stages. The larval stages resemble the adult, but lack a reproductive system. Depending on the species, transmission can be either direct or indirect.	Monogeneans are dorsoventrally flattened. Their gut lacks an anus. Unlike other platyhelminths they have a posterior attachment organ to secure them to their host. Typically they are ectoparasitic, living on the skin or gills of fish. Adult worms are hermaphrodite, and both cross- and self-fertilization are possible. Transmission between hosts is direct, but requires water.	Digenea are variable in shape and size ranging from 0.5mm to 100mm. They usually possess two oral suckers for host attachment and have an incomplete digestive system. With some exceptions (e.g. *Schistsoma sp.*), adult worms are hermaphrodite. Transmission involves at least one intermediate host. The first intermediate host is always a mollusc and often a gastropod.	Cestod trally f sist of a ment c of segn each o a hern ductive typical testina brates partial ents. usually one or hosts.
Examples	The Guinea worm (*Dracunculus medinensis*) is a human parasite primarily found in Africa. Adult females induce the formation of a blister. The blister bursts on contact with water, releasing larvae. The intermediate host, a copepod, ingests the larvae. Humans become infected by drinking water that contains infected copepods.	*Gyrodactylus salaris* has had a severe impact on Wild salmon (*Salmo salar*) populations in Norway since its introduction from the Baltic. Unusually the parasite species has no transmission stage, with females giving birth to live adults (Olstad *et al.*, 2006).	*Schistosoma sp.* infect approximately 200 million people worldwide (Mascie-Taylor & Karim, 2003). Chronic infection can lead to damage of the liver, lungs and intestine. The intermediate hosts are snails. *Schistosome* species have free-living aquatic stages that infect snails and humans.	*Ligula* sitizes The f hosts a taceans by fish swim u ing th predati definiti

Table 2.1: A description of the taxonomic groups to which helminth spec

predicted'. Which factors are involved in the organization of helminth communities depends on the level within the hierarchy of communities being considered. This is partly a consequence of the different time-scales over which the communities exist: infra-communities are short-lived while component and compound communities have longer life-spans. For infra-communities, host susceptibility, host age and parasite survival are, for example, important to community organization. In contrast, component and compound communities are organized by processes that occur on longer time-scales, such as colonization, extinction, host switching and cospeciation.

The work presented in the following chapters deals with interactions between species and their role in community organization. To introduce the subject, an overview of models used to describe and explain the organization of helminth communities is given.

2.2 Distribution of the number of species per host

The component community can, relatively simply, be described by the distribution of the number of species per host; often this is compared with the Poisson distribution. For example, the number of parasite species per host appears to be approximately Poisson for black bears and muskrats (Dobson, 1990).

Testing the null hypothesis of a Poisson distribution is in effect testing the hypothesis that the component community was formed by a simple stochastic process. The number of species per host will be approximately Poisson under the following conditions: 1) infections by different species occur independently from one another; 2) the number of possible infecting species is large, and 3) the probability of infection by any one species is small. If in addition the probability of infection is the same for all species, then the distribution will be binomial (N is the total number of species and p is the probability of infection with any given species). In this case, assumptions 2) and 3) amount to the Poisson approximation to the binomial distribution. However, this latter condition is not necessary for the distribution of the number of species to be Poisson; it is sufficient that conditions 1)-3) are upheld.

In many situations there will be fewer species and/ or some species will have high prevalences, i.e. assumptions 2) and 3) are not upheld. Under these circumstances, the distribution of parasites can be modelled by the distribution of a random variable $\sum_{i=1}^{n} I_i$ where I_i is a random variable indicating infection with species i ($i = 1, ..., n$) for which $\mathrm{P}(I_i = 1)$ is given by the prevalence of species i. Janovy *et al.* (1995) find that this model fits well with data sets of intestinal helminths within Wiscosin bats, and digeneans within snails (*Physa gyrina*).

The number of helminth species per host is a summary property of the joint distribution of worm burdens, for all helminth species, across the population of hosts. Thus while the data sets may appear consistent with very simple models according to this summary property, there may exist discrepancies between the models and data that are not evident from the distribution of the number of helminth species per host.

2.3 Nestedness

Nestedness is a concept that was originally proposed to explain patterns of species distribution in fragmented habitats. As with the distribution of the number of species per host, measures of nestedness are used to detect departures from a random assemblage of species, either within hosts or within a collection of component communities.

Consider a large habitat that becomes fragmented such that there exist a number of smaller habitats of varying sizes. These smaller habitats will support smaller population sizes and are therefore likely to contain only a subset of the species that existed in the original, unfragmented habitat. If there is an order in which extinctions occur such that vulnerable species exist only in large patches and resistant species are present in smaller patches, then a nested pattern is predicted: the species present in a patch will be a subset of the species in *any* larger patch. In reality there is unlikely to be an exact order for the extinction of species, thus Atmar & Patterson (1993) have proposed a measure for degree of nestedness where at one extreme communities are perfectly nested, and at the other extreme they are simply random samples from all available species.

The concept of nestedness has been appropriated by parasite community ecologists, and the extent to which infracommunities and component communities are nested has been determined in various field studies. To date, the exploration of nestedness has been restricted to fish species and their parasites. Most studies have focused on determining the nestedness of infracommunities (Norton *et al.*, 2004; Rohde *et al.*, 1998; Matějusovà *et al.*, 2000; Poulin & Valtonen, 2001, 2002; Vidal-Martinez & Poulin, 2003), although Simkova *et al.* (2001) have shown that component communities of roach (*Rutilus rutilus*) from different lakes are nested.

The identification of nestedness involves testing the null hypothesis that the communities are composed of species randomly selected from all available species. In general, infracommunities are not sufficiently nested to reject the null hypothesis. However, a large number of fish species has been examined and a nested pattern of

infracommunities has been identified in a significant number of these species.

In its original application to fragmented habitats, nestedness is explained in terms of ordering in the extinctions of different species. Nestedness of helminth infracommunities can most easily be explained in terms of an ordered colonization so that hosts are initially colonized by the most prevalent species when they are young, and then less prevalent species as they become older (Norton *et al.*, 2004). Assuming that this hypothesis is true, then the degree of nestedness should be greatest for host species where there is a strong correlation between species richness and host size (a proxy for host age); both Vidal-Martinez & Poulin (2003), and Poulin & Valtonen (2001) have found this to be the case.

The concept of nestedness suggests the concept of 'anti-nestedness': a collection of communities is anti-nested if species-poor communities are *less* likely to be subsets of species-rich communities than would be expected in a random assemblage of communities. Note that this is in contrast to nestedness where species-poor communities are *more* likely to be subsets of species rich communities than would be expected by chance. Data on the ectoparasite communities of 50 marine fish species examined by Rohde *et al.* (1998) was reanalyzed by Poulin & Guegan (2000). In addition to the 15 fish species for which parasite infracommunities were nested, Poulin & Guegan (2000) identified 15 fish species in which infracommunities were anti-nested. The causes of the anti-nestedness identified by the study are unclear, sampling infracommunities from a heterogeneous habitat may be one possibility. For example, consider a collection of infracommunities sampled across two habitats, one of which has a greater number of species than the other. Anti-nestedness will occur if the species in the species-poor habitat are different, i.e. not a subset of those in the species-rich habitat.

As with the distribution of the number of helminth species per host discussed in the previous section, nestedness is a summary measure of the joint distribution of parasite burden. The absence of nestedness should not be interpreted as an absence of organization within a helminth community. Interestingly, nestedness of some degree should be expected in *all* communities since young hosts are likely to be infected initially with the most prevalent species. It is therefore potentially more of a challenge to explain why nestedness is not more commonly observed.

2.4 Core and satellite species hypothesis

The core and satellite species hypothesis was originally proposed by Hanski (1982), based on a metapopulation model for a community of free-living species. Hanski

observed that the proportion, p, of patches occupied by a species was bimodally distributed under the assumptions of the metapopulation model, and termed species with high and low values of p as core and satellite species respectively. The original model has since been elaborated, and it appears that bimodality is a product of the rescue effect: the process whereby increased p leads to increased immigration which reduces the number of local extinctions (Hanski & Gyllenberg, 1993).

In his original paper, Hanski (1982) also observed that the abundance of a species at different sites was positively related to the proportion of sites where it was present. This is intuitively reasonable and Hanski provides many examples from field data. In the parasitological literature, this relationship between the proportion of sites occupied and abundance within sites is used as the basis for the definition of core and satellite parasite species; core species are regionally common and locally numerous, i.e. both prevalence and intensity of infection in a population of hosts are high, and satellite species have the opposite characteristics (Bush & Holmes, 1986b; Holmes & Price, 1986; Esch & Fernandez, 1993). Defining core and satellite species in this way seems reasonable given that infection prevalence and intensity are strongly positively related for helminth species. However, the definition used in the parasitological literature applies in the absence of the original hypothesis (i.e. that the distribution of p is bimodal). Thus Bush & Holmes (1986b), for example, identify 'core' and 'satellite' species in their analysis of the intestinal helminth species of the lesser scaup (*Athya affinis*) duck based on prevalence, even though the distribution of species' prevalence is not bimodal.

The relevance of the original core-satellite species hypothesis to parasite communities is still open to debate. Hanski & Gyllenberg (1993) cite data on the intestinal helminths of grebes (Podicipedidae) (Stock, 1985; Stock & Holmes, 1988) where p is clearly bimodal; while later studies have been unable to identify a bimodality in the distribution of p (Rohde *et al.*, 1995; Simkova *et al.*, 2002).

2.5 Island biogeography

The theory of island biogeography was developed over 40 years ago by MacArthur & Wilson (1963, 1967). Since then, various authors have suggested that ideas from the theory could be used to interpret patterns of species richness in helminth communities (e.g. Esch & Fernandez, 1993; Holmes & Price, 1986). The theory can be employed at different levels of the parasite community by defining the "island" and its corresponding area in different ways. The most direct comparisons with the original theory can be made by defining islands to be geographically separated

habitats, e.g. lakes, and area as either host population size or the area of the habitat. Alternatively it has been suggested that different host species act as islands with the geographic range of the host corresponding to island area (Dritschilo *et al.*, 1975). Finally, the individual host may itself be treated as the island. Kuris *et al.* (1980) have questioned the usefulness of this latter analogy for the following reasons: 1) these "islands" exist for a short period of time (the life-expectancy of the host) such that the number of parasite species may not reach an equilibrium; 2) host life-expectancy may depend on parasite burden; 3) when hosts are mobile, the distance between "islands" will vary; 4) adult helminths do not multiply within their hosts, population sizes are determined by immigration-death processes and may change dramatically over time. Despite suggestions that island biogeography might be useful in explaining structure in parasite communities, application of the theory has been limited, although a certain amount of progress has been made with species area curves, as is now discussed.

The relationship between the number of species, S, and the size of a geographical area, A is well described by $S = kA^z$ where k is a constant and the exponent, z, is typically in the range of 0.25 to 0.35 for island faunas (MacArthur & Wilson, 1967). The empirical relationship has been explained in terms of the distribution of species abundances. Preston (1962) argues that a power law species-area relationship with $z = 0.26$ is predicted by a lognormal species abundance curve. However, this simply involves replacing one empirical relationship with another. The species area curve is explained mechanistically either in terms of increased habitat heterogeneity, and therfore species richness with increasing area, or in terms of diminished extinction rate with increased area (Hanski & Gyllenberg, 1997). Metapopulation models have been successfully fitted to species-area data supporting the latter hypothesis (Hanski & Gilpin, 1997). The power law has also been derived by a self-similarity argument, in particular, by assuming that the proportion of species in an area, A, that are also found in half the area of A, is independent of A (Harte *et al.*, 1999).

Using data from Kennedy (1978) for the number of parasite species in brown trout (*Salmo trutta*) from different British lakes, the exponent for the species-area relationship is estimated to be $z = 0.45$ (Fig.2.1). Price & Clancy (1983) found an almost linear relationship, i.e. $z = 1$, between the number of parasites and host range in fish. And Dritschilo *et al.* (1975) found $z = 0.37$ for the number of mite species on cricetid rodents, again using host range as the measure for area. These z values are slightly in excess of z values reported for island faunas ($0.25 - 0.35$), and substantially in excess of z-values for continental areas ($0.15 - 0.17$)(MacArthur & Wilson, 1967). MacArthur & Wilson (1967) suggested that z is increased by

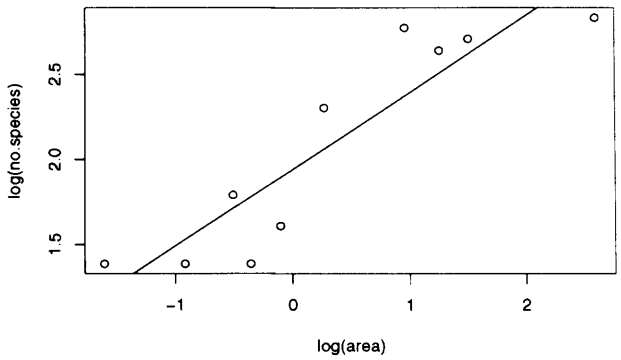


Figure 2.1: Log-log plot of number of parasite species of brown trout and lake area for 10 British lakes (Kennedy, 1978). The regression line is log(no.species)=1.94+0.45×area, which implies no.species is proportional to area$^{0.45}$.

reducing migration; thus the 'parasite' islands in these studies are more isolated than is typical for geographical islands.

2.6 Host-parasite cospeciation

Cospeciation occurs when allopatric host speciation (speciation due to geographic separation of populations) leads to geographically separate parasite populations and allopatric parasite speciation. Thus cospeciation, if it occurs, will affect the distribution of parasite species across host species, and therefore the structure of the compound community (Brooks, 1979).

The role of cospeciation in structuring parasite communities can be determined by examining the degree of congruence between host and parasite phylogenies. This may be done, for example, by treating the presence/absence of parasite species as binary characters (Brooks, 1988). By mapping these characters onto the phylogeny of host species, incongruences can be detected as cases where the parasite has 'evolved' on more than one occasion. Congruent host and parasite phylogenies implies cospeciation (Fahrenholz' rule). Incongruence between the phylogenies may arise through a number of different mechanisms such as host switching (a parasite species colonises another lineage), extinction, sympatric speciation (parasite speciation in the absence of host speciation), the absence of parasite speciation after host speciation.

When there is little incongruence between host and parasite phylogenies, then incongruences are usually easy to explain. On the other hand, when the extent of the incongruence is large, systematic methods are required. For example, the

program Treemap examines all possible switching events (and the accompanying sorting and duplication events) that are consistent with the observed parasite and host phylogenies; the program then chooses the scenario that maximizes the number of cospeciation events. For a review of this and other systematic methods (see Paterson & Banks, 2001).

Desdevises *et al.* (2002) examined the congruence between the phylogenies of fish in the family Sparidae (Teleosts) and their parasites of the genus *Lamellodiscus* (Monogenea). They used a number of different methods, e.g. TreeFitter, TreeMap, ParaFit, and observed that host-switching events were common. Based on this observation, they concluded that parasite-host associations, in this instance, are due more to ecological factors than co-evolutionary processes. Moreover they argue that host switching is to be expected among monogenean parasites since transmission is direct and the larval stages are highly motile.

In general, host switching appears to be prevalent in marine host-parasite systems (Hoberg & Klassen, 2002). However, there is no reason to assume *a priori* that this must be true. Indeed, in a study of the chondracanthid copepod parasites of teleost fish, Paterson & Poulin (1999) concluded that there were a significant number of cospeciation events, and that host-switching was rare. Interestingly, these copepods are transmitted directly and have a free-living larval stage, although the larvae are small and cannot move long distances which may explain why host switching is not more common.

In other host-parasite systems biological features of the system make host switching improbable; cospeciation is therefore the dominant process. For example, cospeciation has been observed between chewing lice of the genera *Geomydoecus* and *Thomomydoecus* and pocket gophers. It has been postulated that this is because the lifecycle of the lice is restricted to the fur of host, and different host species rarely interact (Hafner *et al.*, 1994).

2.7 Interspecific interactions

Ultimately population sizes must be regulated by negative density-dependent effects; otherwise exponential growth of populations would be unhindered; this applies to parasitic as well as free-living species. However, if abiotic factors periodically reduce population sizes such that they are substantially below their carrying capacity (equilibrium size) then density dependence will have a limited role to play. This is clearly true on the time-scale overwhich ecological processes take place, but it is also true on the timescale of evolutionary processes. MacArthur & Wilson (1967)

pointed out that in an environment where resources are plentiful, traits that lead to rapid exploitation (termed r-selection in the biological literature) will be selected, while for populations close to carrying capacity, selection will favour efficient use of resources (K-selection).

Given the existence of intraspecific competition, it seems reasonable to suppose that there will also be interspecific competition between ecologically similar species. The importance of interspecific competition in structuring parasite communities has been an area of considerable debate. While ecologists tend to focus on the role of competition, there is also evidence that the establishment of one helminth species in a host may further facilitate the establishment of members of that and other parasite species (see Chapter 3); clearly this will also have a role to play in structuring communities.

At the level of the infracommunity, workers have examined the spatial distribution of helminth species along the host gut. By examining different individual hosts, it is sometimes observed that the spatial distribution of one parasite species is altered by the presence of another species. This phenomenon is known as interactive site segregation and has been observed in both natural (e.g. Bush & Holmes, 1986a), and experimental (Holmes, 1961) systems. Intuitively one can imagine that if the niches of two competing helminth species overlap, then one or both species may alter their distribution when the two species co-occur to minimize interspecific competition. However, this phenomenon has not been formally modelled, and it seems likely that whether or not interactive site segregation occurs will depend on the details, e.g. the extent of overlap in the fundamental niches, the strength of intra- and interspecific competition, and the distribution of the resource(s) over which competition is taking place. It should not be assumed that competition between helminth species necessarily leads to interactive site segregation.

On an evolutionary timescale, competition may alter the fundamental niche of a species to reduce overlap with other species; in the parasitological literature this is referred to as selective site segregation (see above). More generally, selective site segregation is an example of character displacement, the character in question being the position occupied by the species along the intestine.

Selective site segregation (or character displacement) can be detected in helminth infracommunities by determining whether the distribution of parasites within the intestine is more uniform than expected by chance. The phenomenon has been observed in studies of the intestinal helminths of lesser scaup ducks (*Aythya affinis*) (Bush & Holmes, 1986a), and the European tortoise (*Testudo graeca*) (Schad, 1963).

As with interactive site segregation, the absence of selective site segregation

does not imply an absence of competition. Several quantitative population genetic models of character displacement have been proposed (Drossel & McKane, 1999; Slatkin, 1980; Bulmer, 1974; Doebeli, 1996) to elucidate the circumstances under which character displacement is possible. These models make the following biological assumptions (Slatkin, 1980):

- A quantitative character such as size is under genetic control, and the mean and variance of the character's distribution can be modified by natural selection.
- The extent to which an individual of either species can utilize a subset of resources that are in limited supply, depends on the measure of the character in the individual.
- The extent of the competition between two individuals of the same or different species, depends on the relative values of the character.
- Each species is limited by the same set of resources and individuals of each species utilize these resources in the same way.

In the model of Slatkin, the distribution of the character is assumed to be normal, but the mean and variance are allowed to evolve over time. Thus the distribution of parasites in the gut, for example, should follow the normal curve being centred at a particular position in the gut. The model allows the mean and variance of this distribution to change from generation to generation in response to selection. Slatkin proposed that displacement will only occur if either: 1) the variance of the character is sufficiently constrained, e.g. because the genetics of the character do not allow the variability of a character to exceed a certain value; or 2) resource utilization is different for the two species. In the example of helminths within the host's gut, resource utilization would be different for the two species if some aspect of the resource varied along the length of the intestine, and one species was *a priori* more adept at utilizing the resource towards the proximal end while the other species species was better suited to using the resource at the distal end. Clearly, character displacement is not an inevitability of sustained competition between species, and even if it does occur, there is no guarantee that it will be sufficiently large to be perceptible.

While competition between species need not result in selective site segregation, the existence of non-overlapping niches is not necessarily explained by competition. Rohde (1991,1994) has proposed that selective site segregation has evolved as a mechanism to increase mating success. In support of his hypothesis, Rohde observes that for ectoparasites of fish, niches are more restricted amongst adults than juveniles, and among sessile species compared with motile species.

2.8 Summary and concluding remarks

Many of the concepts of parasite community ecology are derived from metapopulation models and island biogeography. Although the concepts have to a certain extent been successfully applied to helminth communities, the usefulness of models that treat hosts as islands or patches is questionable.

Summary measures of the joint distribution of parasite burden such as nestedness and the distribution of number of parasite species per host, are often found to be consistent with very simple 'null' models for the construction of parasite assemblages. However, aspects of community organization are potentially being overlooked since these summary measures lack statistical power.

The effects of interspecific interactions on the spatial distribution of helminths within infracommunities have not been formerly modelled, but the results of more general models of character displacement suggest that selective site segregation need not occur when there is interspecific competition. Thus interspecific competition is potentially difficult to detect from the spatial distribution of helminths within the host.

Chapter 3

Mechanisms of Interspecific Interaction

3.1 Introduction

The strongest evidence for the existence of interactions between helminth parasite species comes from experimental systems. At the most basic level, experiments of coinfection reveal whether one species has a numerical effect on another species, i.e. whether there is a measurable impact on establishment, survival or fecundity (Poulin, 1998). Such work has a long history and has been undertaken in many animal models, (reviewed by Christensen *et al.*, 1987). More recently, work has focused on the helminth parasites of livestock (Helwigh *et al.*, 1999; Christensen *et al.*, 1997; Dobson & Barnes, 1995).

Although experiments using animal models provide evidence for the existence of interactions between helminth species, the results from such experiments should be interpreted cautiously since experiments never fully mimic the acquisition of larvae in a natural setting. Typically in animal models of helminth infection each species is administered to the host as a single, artificially large dose of infective larvae. Occasionally one species is administered as a trickle infection, i.e. through smaller repetitive doses (Helwigh *et al.*, 1999), though, with the exception of experiments conducted by Dobson & Barnes (1995), the two species are almost never both 'trickled' into the host. This is problematic since there is evidence to suggest that the immune system reacts differently to a single dose infection compared with a trickle infection (Bancroft *et al.*, 2001). Furthermore, this extends to the ability of the parasite to survive within the host. For example, *Nippostrongylus brasiliensis* when administered to hosts in a single large dose, leads to a strong host immune response and the infection is short-lived. On the other hand, the infection is chronic in young

rats if the parasite is acquired by trickle infection (Jenkins & Phillipson, 1971). Although it should be noted that later studies have been unable to replicate this latter result in adult rats (Jenkins, 1974).

With a better understanding of the immune system, investigators are now able to offer more elaborate mechanistic explanations for the outcome of coinfection experiments than was possible when many of the experiments reported by Christensen *et al.* (1987) were undertaken. For example, the immunology of interactions between helminth species in rodent models has been relatively recently reviewed by Behnke *et al.* (2001). However, non-immunologically-mediated interactions are also potentially significant and should not be neglected.

As with free-living species it is likely that parasites compete for limited resources. In the ecological literature competition for resources is termed exploitative competition, while indirect competition such as competition in parasites that is mediated through the host immune system is referred to as interference competition. To begin with, exploitative competition and non-immunologically-mediated mechanisms of interaction will be discussed. In general, immunologically-mediated competition is not exploitative, although this classification is not entirely clear-cut. For example, if there is local inflammation within the gut such that parasites cannot establish in close proximity to one another, then space may become a limiting resource for which parasites compete, although inflammation is itself immune-mediated. Nonetheless exploitative competition is not usually immune-mediated and is therefore discussed in conjunction with other non-immunological mechanisms of interaction.

3.2 Exploitative competition and non-immunologically mediated interactions

The identification of resources through which interspecific exploitative competition occurs is not straightforward. In Gausse's classic experiments of exploitative competition among free-living *Paramecium* species (Gausse, 1934), the experiments were carefully controlled to ensure that factors other than the supply of bacterial food source were not limiting the growth of the *Paramecium* populations. The problem of environmental control becomes even more acute when studying competition in species that are not free-living. Nonetheless, a very significant discovery was made by a number of parasitologists working in the 1920's and 1930's who showed that helminths often exhibit stunting when worm burdens are high (Woodland, 1924; Shorb, 1933; Hunninen, 1935; Chandler, 1939). Read (1951) termed this the 'crowding effect.' Although crowding was originally described as an intraspecific effect in

cestodes, it has since been shown also to operate interspecifically (Holmes, 1961, 1962) and in non-cestode species (e.g. Holmes, 1961, 1962; Fleming, 1988).

Read (1951) originally hypothesized that the crowding effect was due to competition for oxygen. Since then, it has been shown that the availability of oxygen does not affect the development of *Hymenolepis diminuta* (Roberts & Mong, 1969), and neither does the availability of vitamins in the host diet (Platzer & Roberts, 1969). On the other hand, carbohydrate appears to be a significant limiting resource (Mead & Roberts, 1972), and interference competition may also play a role in the crowding effect. For a full discussion of the potential mechanisms for parasite stunting see Roberts (2000).

The crowding effect is a manifestation of competition. It does not in itself represent a quantitative effect that will influence helminth population dynamics. However, crowding can be used as a marker for such effects. In particular, fecundity is typically positively correlated with the size of adult worms (e.g. Holmes, 1961; Jones & Tan, 1971; Stear & Bishop, 1999).

Exploitative competition is hard to demonstrate and yet likely to be a pervasive mechanism for interaction, while other rare forms of interaction are much easier to identify. Predator-prey interactions have been observed amongst digenean trematode species, where the larvae of large species tend to prey on those of smaller species within snail intermediate hosts (Kuris & Lafferty, 1994). Amongst schistosome species, interbreeding has been observed in natural settings (Cunin *et al.*, 2003), and experimentally (Tchuem Tchuenté, 1994) where it has also been shown that the hybrid miracidia have low-infectivity. Combining these observations, it is likely that fertility of one or more species is reduced where several schistosome species are coendemic.

3.3 Cross-reactivity

Antibody-antigen interactions are highly specific. However, occasionally the antibodies produced in response to one antigen will have a strong affinity for a different antigen; this usually occurs when two antigens have the same epitope, but may also occur when two antigens have very similar chemical properties (Kuby, 1997).

It is not only antibodies that exhibit cross-reactivity, T-cell receptors may also bind to more than one antigen (Regner, 2001). More generally, if the memory cell populations (which include both T-cells and B-cells) that respond to two different antigens are identified, the cells belonging to both populations constitute the cross-reactive response (Smith *et al.*, 1997). Although memory T-cells produced

in response to one parasite species (or strain) may be of importance in fighting a different species (or strain), most experimental evidence concentrates on the cross-reactivity of antibodies.

A strong line of evidence for cross-reactivity potentially leading to interspecific interaction, comes from experiments in which the host response to parasite antigen from one species provides protection against another parasite species. For example, Almeida *et al.* (2003) demonstrated that the *Schistosoma mansoni* derived recombinant antigen Sm14 can be used to vaccinate against *Fasciola hepatica* in both sheep and mice. Similarly, Rosas *et al.* (2002) have shown that the recombinant antigen Ts018 derived from *Taenia saginata* protects against *Taenia crassiceps* infection in mice. Interestingly, in this latter example, antibodies induced by the vaccine reacted to a 66kDa antigen fraction from both *T.crassiceps* and *T. saginata* antigens. In addition CD4+ and CD8+ T-cells proliferated in response to antigens from both species suggesting these cells play a role in the protective effect induced by the vaccine.

It is difficult to show directly that cross-reactivity leads to cross-protection, but it is usually assumed to be the mechanism of cross-protection when the two species involved are closely related, as is the case when two strains of the same species cross-protect against one another.

The filarial nematode species *Onchocerca volvulus* and *Onchocerca ochengi* are closely related and exhibit substantial protein homology (Hoch *et al.*, 1994). Cattle are the definitive host of *O. ochengi*, and humans are the definitive host of *O. volvulus*, but both species share the same vector, *Simulium damnosum s.l.*. In Cameroon, the prevalence of onchocerciasis in humans seems to be low where there is intensive cattle breeding (Wahl *et al.*, 1998) and it is thought that this may be due to human infection with *O. ochengi* larvae cross-protecting against *O. volvulus*. The production of specific antibodies to *O. ochengi* antigens was found to be very high in onchocerciasis patients with low microfilarial densities, suggesting that cross-reactivity of antibodies produced in response to *O. ochengi* provide protection against *O. volvulus* (Hoch *et al.*, 1994). Cross-protection between other filarial species has also been demonstrated experimentally (Geiger *et al.*, 1996). Again, because the species are closely related it is deemed likely that cross-protection is due to cross-reactivity.

Cross-reactivity does not necessarily result in interspecific interaction. Smith *et al.* (2001) found that proteases from *Haemonchus contortus* were not protective when given as a vaccine against *Teladorsagia circumcincta* in sheep, even though anti-sera specific to the *Haemonchus* proteases recognized some *Telador-*

sagia polypeptides.

It is also possible that cross-reactivity may facilitate rather than protect against parasite establishment as certain antibody isotypes can inhibit a protective immune response. IgG4, for example, is known to competitively inhibit IgE (Vercelli *et al.*, 1998). The interaction between *Trichinella spiralis* and *Heligmosomoides polygyrus* is potentially an example of cross-reactivity facilitating establishment. Antibodies to the two species cross-react and the establishment of *T.spiralis* is enhanced by the presence of *H. polygyrus* (Robinson *et al.*, 1997), although it should be noted that the interaction is not mutually synergistic as the inflammatory response to *T. spiralis* acts to expel *H. polygyrus* (Behnke *et al.*, 1992).

3.4 Th1/Th2

In the mid-1980's Mosmann *et al.* (1986) showed that T-helper (Th) cells in mice could be classified into one of two groups based on patterns of cytokine expression. In a Th1-type (type 1) response, the dominant population of T-helper cells secrete the cytokines interleukin-2 (IL-2) and interferon-γ (IFN-γ). These cytokines reinforce the Th1 status of T-helper cells and also activate cytotoxic T-cells and macrophages. Thus a type-1 response is generally associated with the activation of the cellular arm of the immune system. In a Th2-type response, the predominant cytokines are IL-4, IL-5, IL-10 and IL-13; these cytokines reinforce the Th2 nature of the T-helper cells, while the effector mechanisms they induce are associated with an antibody-mediated (humoral) response.

Evidence for the importance of the type 2 response in host immunity to helminths comes from mice that are unable to produce a Th2 response because IL-4 has been eliminated, either by knocking out the IL-4 gene or by producing antibodies against the IL-4 receptor. These mice are often unable to produce an effective response against helminths. For example, IL-4 knock-out mice become chronically infected with *Trichuris muris* (Bancroft *et al.*, 1998), as do resistant strains when the IL-4 receptor is blocked by antibodies (Else *et al.*, 1994).

In addition to the experimental evidence, epidemiological data on humans also supports the hypothesis that Th2 cytokines in general are associated with protection against intestinal helminths. In an *ex-vivo* study using blood from *Ascaris lumbricoides* infected individuals, Turner *et al.* (2003) found that levels of the cytokines Il-4, IL-9, IL-10 and IL-13 produced in response to *Ascaris lumbricoides* antigen were inversely related to the intensity of infection. Another Th2 cytokine, IL-5, has been found associated with resistance to reinfection with *Necator americanus*

(Quinnell *et al.*, 2004) and also with *T. trichiura*, but not *A. lumbricoides* (Jackson *et al.*, 2004).

There are difficulties with this simple paradigm of Th2 responses providing protection against helminth infection. Maizels & Yazdanbakhsh (2003) cite several anomalies. First, helminths do not always induce a type 2 response. For instance *T. muris* induces Th1 or Th2 depending on the strain of mouse, and the microfilarial stage of *Brugia malayi* consistently causes a Th1 response in mice. Secondly, even if a Th2 response is induced, it is not necessarily protective. In humans there is evidence that individuals who are putatively immune to onchocerciasis produce a Th1-dominated response to *Onchocerca volvulus*. And in general, the Th2 response is often associated with chronic helminth infection. Maizels *et al.* (2004) have recently suggested that this may be because the helminth parasites are able to down-regulate the Th2 effector mechanisms such as eosinophils and IL-5 without affecting the regulatory cytokines (IL-4 and IL-10) which give the Th2 'signature'.

Given that at least certain aspects of the type 2 response are protective, it seems reasonable that a Th2 response induced against one species may help protect against a second species. This is thought to be why strains of mice that produce a Th1 response, and are therefore susceptible to *Trichuris muris*, can be made resistant by infecting with a strong Th2-inducing parasite such as *Trichinella spiralis* (Hermanek *et al.*, 1994) or *Schistosoma mansoni* (Curry *et al.*, 1995). Citing the reinfection studies of Jackson *et al.* (2004), Bradley & Jackson (2004) have proposed that the Th2 cytokine IL-5 induced by *Ascaris lumbricoides* may hinder the establishment of *Trichuris trichiura* in humans. They speculate that the reverse interaction is unlikely since there is no association between the level of IL-5 and the rate of reinfection with *A. lumbricoides*.

It is surprising that more interspecific interactions mediated by the Th2 response have not been identified. This may be in part because the type 2 response is different for different parasites, and in particular, the effector mechanisms associated with protection are often species-specific (Maizels *et al.*, 2004). It may also be because the immune responses are often compartmentalized. For example, mice coinfected with the filarial parasite *Litomosoides sigmodontis* and the protozoan *Leishmania major*, exhibit a type 1 response to *L.major* in the popliteal lymph nodes and a type 2 response to *L. sigmodontis* in the thoracic lymph nodes (Maizels *et al.*, 2004).

3.5 Immunosuppression

In the previous section it was argued that in some situations, a type 2 response to one parasite species can act to diminish establishment or survival of another species. A similar argument can be made for a species that induces an immunosuppression. This seems, for example, to occur in coinfections involving *Heligmosomoides polygyrus (Nematospiroides dubius)*. Adult *H. polygyrus* worms suppress the mast cell response (Dehlawi *et al.*, 1987)) and induce the T-regulatory (Treg) phenotype in T-cells (Else, 2005) (discussed below). Potentially as a consequence of one or both of these immunomodulatory effects, infections with *Trichinella spiralis*, *Trichuris muris* and *Hymenolepis citelli* are prolonged by the presence of *H. polygyrus* (Behnke *et al.*, 1978; Jenkins & Behnke, 1977; Alghali *et al.*, 1985). Also, tapeworms recovered from mice coinfected with *H. polygyrus* and *Hymenolepis microstoma* are larger than those recovered from mice infected with *H. microstoma* alone (Courtney & Forrester, 1973). Again this may be a consequence of the immunomodulatory effects of *H. polygyrus*. The following is an overview of the mechanisms of immunosuppression.

A down-regulated immune response is often observed during chronic helminth infection in which T-cell proliferation and the production of inflammatory cytokines are reduced (Maizels & Yazdanbakhsh, 2003). It is thought that a population of T-cells known as T-regulatory (Treg) cells and their associated cytokines, primarily IL-10 and transcription growth factor β (TGF-β), may be responsible. Studies undertaken in onchocerciasis endemic areas show that peripheral blood Mononuclear Cells (PBMC) from individuals with generalized onchocerciasis (GEO) are hyporesponsive to *Onchocerca volvulus* antigen (i.e, show reduced proliferation) as compared to PBMC's from individuals who are putatively immune; and it is the PBMC's from GEO individuals that produce much higher levels of TGF-β and IL-10 (Doetze *et al.*, 2000). This pattern of high IL-10 levels and hyporesponsiveness in individuals with high worm burdens has also been documented for schistosomiasis (King *et al.*, 1996) and lymphatic filariasis (Mahanty *et al.*, 1996).

The connection between hyporesponsiveness and protection against helminth infection has been made experimentally for mice infected with the filarial parasite *Litomosoides sigmodontis*. In these experiments, clearance of *L. sigmodontis* is enhanced by neutralizing Treg cells using antibodies to the cell surface markers CD25 and GITR (Maizels *et al.*, 2004). There is potentially also a relationship between hyporesponsiveness observed in patients with onchocerciasis and enhanced parasite establishment. Duerr *et al.* (2003b) have shown that cross-sectional data on worm burden (Duerr *et al.*, 2003b) from W. Africa is consistent with a mathematical model of *O. volvulus* infection that treats parasite establishment as an increasing

function of host worm burden.

Helminths manipulate the immune system by secreting immunomodulatory compounds. Homologues of host-produced cytokines form an important class of immunomodulatory compounds. *Brugia malayi* produces two homologues of the cytokine TGF-β. Since TGF-β is an downregulatory cytokine that induces naive T-cells to adopt the T-regulatory phenotype, Maizels *et al.* (2004) have proposed that this may be the mechanism behind hyporesponsiveness in *B. malayi*. Another example is provided by *Trichiuris muris* which secretes an IFN-γ-like molecule that is able to bind to IFN-γ receptor, thereby establishing a non-protective type 1 response in mice (Grencis & Entwistle, 1997).

Helminths also secrete molecules that have a more targeted effect; often these molecules are proteases. By way of example, the digenean *Fasciola hepatica* secretes a cysteine protease which cleaves IgG antibodies (Berasain *et al.*, 2000); the dog hookworm, *Ancylostoma caninum*, secretes a glycoprotein that acts as a neutrophil inhibitory factor (Moyle *et al.*, 1994); and the rodent hookworm, *Nippostrongylus brasiliensis*, secretes acetylcholinesterase which is thought to inhibit peristalsis and decrease mucus production (Lee, 1996).

3.6 Specific vs non-specific effector mechanisms

Antibody and T-cell responses are typically specific to one species or even a particular strain within a species. Effector mechanisms that involve either antibodies or T-cells, e.g. cytotoxic T-cells, or antibody-dependent cellular cytotoxicity (ADCC), tend therefore to be species or strain specific, unless they exhibit cross-reactivity as discussed above. However, whilst some effector mechanisms are closely linked with antibody or T-cell receptors, many are non-specific, e.g. mucus production or enhancement of peristalsis. Such non-specific mechanisms have by definition the potential to act interspecifically if the timing of infections is right. For instance, a non-specific environmental change in the gut appears to be responsible for the premature expulsion of *Nippostrongylus brasiliensis* in mice in which *Trichinella spiralis* are established prior to expulsion and, conversely, for the premature expulsion of *T. spiralis* in which *Nippostrongylus brasiliensis* are established (Kennedy, 1980). Similarly, the non-specific inflammatory repsonse occuring during the the rejection phase of *T. spiralis* reduces rates of survival for *Hymenolepis diminuta* in both rats and mice (Christie *et al.*, 1979; Behnke *et al.*, 1977).

Non-specific effector mechanisms would seem to make interactions between species unavoidable. However, helminth species differ substantially in the niches they utilize

within the host and often immune responses are specific to the locality of the infection (Maizels *et al.*, 2004). Even when species occupy the same locality, the effector mechanisms to which parasites are susceptible may still be particular to each species. For example, mast cells are superfluous in infections of *Trichuris muris* (Betts & Else, 1999), but are critical in the elimination of *Trichinella spiralis* (Grencis *et al.*, 1993). The specificity of effector mechanisms has also been demonstrated in dual infections. In a coinfection of *N. brasiliensis* and *Strongyloides ratti* in athymic mice, the injection of IL-4 and subsequent induction of mastocytosis facilitates the expulsion of *S. ratti* but not *N. brasiliensis* (Nawa *et al.*, 1994).

3.7 Summary

There is a large literature on experiments undertaken in animal models where it is demonstrated that one species of helminth alters the survival or establishment of another species. The artificial nature of these experiments makes it difficult to infer that interactions between helminth species are frequent outside laboratory settings.

Broadly speaking, interactions can be classified according to whether or not they are immunologically-mediated, although in practice it is sometimes difficult to distinguish between the two. Exploitative competition is potentially the most significant form of non-immunologically-mediated interaction, and is implicated by the 'crowding effect'. The availability of carbohydrate has been identified as a limiting resource.

When parasite species are closely related, cross-reactivity of antibodies (or T-cells) may lead to interspecific interaction. On occasion, cross-reactivity can occur when species are not closely related, and it may be involved with synergistic as well as antagonistic interactions.

The Th2 type response is engendered by most helminth species and, through Th2-2-dependent effector mechanisms, may provide some protection against reinfection. It is therefore a potential cause of interspecific interaction. However, the compartmental nature of many immune responses and the variability of the type 2 response may make it of little significance.

Many helminth species are able to down-regulate the immune system. This is achieved by secreting homologues of host-produced cytokines to interfere the regulation of the immune response, or by secreting proteases to hinder particular effector mechanisms. It is likely that immunosuppression by one species will have wider effects on infection with other species.

Chapter 4

Mathematical Models of Helminth Infection

4.1 Introduction

Kostizin (1934) realized early on in the development of epidemic models that the standard SIR (Susceptible, Infected, Recovered) model framework was not generally applicable to host infection by helminth parasites. Helminth infection differs fundamentally from infection with bacteria, viruses and protozoa since hosts are classified not by being infected/uninfected, but rather by the number of worms that they harbour. Anderson & May (1991) have introduced a functional classification of parasites into micro- and macroparasites. Macroparasites, which includes helminths and arthropods, do not multiply within the host, they tend to be large, long-lived and unable to induce significant acquired immunity, thus reinfection is the norm for these parasites. On the other hand, microparasites, which includes most bacteria, viruses and protozoa, multiply within the host have short-life generation times and induce immunity to reinfection, often for the duration of the host's life.

Most models of macroparasite infection have been developed for species that parasitize humans. The first models were for schistosomiasis (Macdonald, 1965; Nåsell & Hirsch, 1972), but there are now numerous models covering most of the major human helminth infections (Anderson & May, 1985a; Chan *et al.*, 1994; Basáñez & Ricardez-Esquinca, 2001; Michael *et al.*, 2006). The economic impact of gastrointestinal nematodes of livestock (Tallis & Leyton, 1969; Cornell *et al.*, 2004) has also provided motivation, as has theoretical ecology. Here mathematical models have been used to explore the potential of helminths to regulate host population size (Crofton, 1971; May, 1977a; Anderson & May, 1978; May & Anderson, 1978).

In general, models of helminth infection have been developed with the aim of

achieving one of the following: 1) explaining age-specific patterns of host worm burden; 2) explaining the distribution of worm burden among hosts; 3) describing the long-term dynamics of host and parasite populations and 4) exploring the efficacy of possible control interventions. Both deterministic and stochastic models have been proposed to deal with these various problems.

To understand age-specific patterns, worm burdens can be modelled deterministically within a single host. Alternatively, mean worm burden within a population of hosts can be treated as a deterministic variable (Anderson & May, 1985b; Woolhouse, 1992b), although since the model is no longer individual-based, the interpretation of model parameters is less clear in this case. Stochastic models have the advantage of being individual-based, and also allowing population-level properties, such as mean and variance to be explored. In fact they provide the only means of analyzing the higher moments, such as variance, of the distribution of worm burden.

The long-term dynamics of interacting host-parasite populations are modelled by incorporating a 'feedback' mechanism so that larval population size depends on the size of the adult worm population. As yet, long-term dynamics have only successfully been explored using deterministic models (e.g. Anderson & May, 1978; Hadeler & Dietz, 1984; Kretzschmar, 1989; Pugliese *et al.*, 1998). Fully stochastic models that incorporate a feedback component are difficult to analyze. However, assuming that parasites do not affect host mortality, the long-term dynamics of the parasite population alone can be analyzed using models that combine both stochastic and deterministic elements (Nåsell & Hirsch, 1972; Nåsell, 1985). Models that are less formally defined but nonetheless incorporate stochastic elements have been explored through simulation to predict the outcome of control scenarios (Davies, 1993; Plaisier *et al.*, 1998).

No attempt will be made to give a comprehensive review of all models of helminth infection, but significant classes of model will be discussed. The order in which models are presented will mirror that of later chapters in as much as deterministic models of infection in a single host (either with a single or multiple parasite species) can be viewed as a prelude to stochastic models that deal with the distribution of worms in the host population.

4.2 Deterministic models of infection in the definitive host

The deterministic immigration-death model (Anderson & May, 1991) is a useful starting point for a discussion of mathematical models of helminth infection. It

describes the establishment and subsequent death of adult worms in a single host. Though simple, the model offers insights into the nature of age-intensity profiles of helminth infection.

Consider a host whose exposure to infective larvae is a function of age (a). Then the rate at which mature adult worms become established within a host, $\lambda(a)$, is also a function of age. Once inside the host, adult worms die at a constant percapita rate, μ_M. This leads to the following differential equation for the change in the mature worm population size, $M(a)$, in a host with increasing age

$$\frac{dM}{da} = \lambda(a) - \mu_M M. \tag{4.1}$$

Assuming that $M(0) = 0$, then the solution to Eqn 4.1 is

$$M(a) = \int_0^a \lambda(s) e^{-\mu_M(a-s)} ds. \tag{4.2}$$

In the special case where exposure is constant, $\lambda(a) = \lambda$, the solution to Eqn 4.1 is

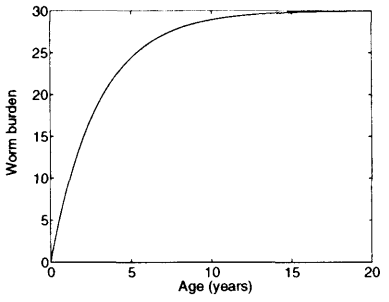
$$M(a) = \frac{\lambda}{\mu_M}(1 - e^{-\mu_M a}).$$

In this simple case, the adult worm burden increases monotonically with age, approaching the equilibrium value, $\frac{\lambda}{\mu_M}$ (Fig.4.1(a)). If exposure varies with age then the number of worms may no longer increase monotonically. For example, exposure may decrease with age. This could be modelled using $\lambda(a) = \lambda_0 e^{-\gamma a}$, then the solution to Eqn 4.1 with initial condition $M(0) = 0$ is

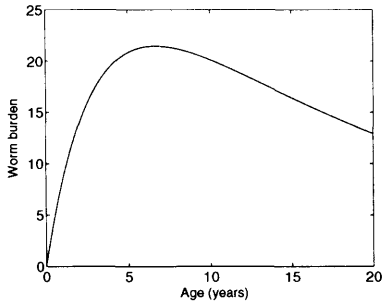
$$M(a) = \begin{cases} \frac{\lambda_0}{\mu_M - \gamma}(e^{-\gamma a} - e^{-\mu_M a}) & \gamma \neq \mu_M \\ \lambda_0 a e^{-\mu_M a} & \gamma = \mu_M \end{cases}. \tag{4.3}$$

Eqn 4.3 has a maximum, so the worm burden in this model has what is often referred to as a 'convex' age-intensity profile (Fig.4.1(b)). A decreasing rate of exposure with age is not the only possible mechanism for generating convex age-intensity profiles; the action of acquired immunity may also be significant in this respect. The following is a description of a model with acquired protective immunity proposed by Anderson & May (1985b).

Assuming that acquired immunity reduces the probability with which an adult worm becomes established in a host, (Anderson & May, 1985b) propose the following model for change in worm burden with host age



(a)



(b)

Figure 4.1: Age profiles of infection intensity. a) Host exposure is constant with age, $\lambda = 10$ year^{-1}. b) Exposure decreases with age, $\lambda(a) = \lambda_0 e^{-\gamma a}, \lambda_0 = 10$ year$^{-1}, \gamma = 1/20$ year^{-1}. In both a) and b) the per capita death rate of adult worms, μ_M, is $1/3$ year^{-1}.

$$\frac{dM}{da} = \lambda(1 - \epsilon I(a)) - \mu_M M. \tag{4.4}$$

Here λ is the rate of exposure, and the 'probability' of establishment is assumed to be linearly dependent on an immune variable, I; the strength of the dependence is determined by a positive parameter, ϵ. (Note that technically the model is only clearly defined for regions of parameter space where the quantity $1-\epsilon I(a)$ is positive.) As before, adult worms die at a rate μ_M.

If the rate at which immunity is acquired is proportional to the current worm burden (immunity is concomitant) and decays at a rate σ, then the rate of change in the immunity variable is

$$\frac{dI}{da} = M - \sigma I. \tag{4.5}$$

Using the initial conditions $I(0) = M(0) = 0$, Eqn 4.5 can be integrated to express immunity as a function of $M(a)$.

For, multiplying both sides by $e^{\sigma a}$, Eqn 4.5 becomes

$$\frac{d}{da} e^{\sigma a} I(a) = e^{\sigma a} M(a)$$

and integrating both sides gives

$$I(a) = \int_0^a e^{-\sigma(a-a')} M(a') da'. \tag{4.6}$$

Eqn 4.6 lends itself to another interpretation of the immunity variable. $I(a)$ may be thought of as the sum of past parasite loads, each parasite load being weighted by an exponentially decaying term according to how far in the past it occurred, so that distant parasite loads accrue less weight than loads that are closer in time to a; the parameter σ controls the extent to which past values are weighted.

This model can produce monotonic and convex age-intensity profiles (see Fig.1, in Anderson & May, 1985b). Convexity is possible since acquired immunity introduces a time lag into the system: the rate at which worms are acquired is dependent on past numbers of worms. Factors that make convexity more likely are: 1) long immune memory (small σ); 2) high transmission (large λ); 3) a long worm life expectancy (small μ_M). If the age intensity profile is convex, then the age at which peak intensity occurs is primarily a function of μ_M and ϵ.

An alternative model, where acquired immunity is a function of past exposure to infective larvae rather than adult worms, can be formulated by assuming that the number of larvae acquired by the host is proportional to exposure. Thus exposure

is a surrogate measure for the number of larvae and Eqn 4.5 is modified so that

$$\frac{dI}{da} = \lambda - \sigma I. \tag{4.7}$$

The results of this model are not qualitatively different from the first model (Woolhouse, 1992b), which is to be expected since past numbers of adult worms are dependent on past exposure to larvae.

A drawback to these deterministic models is that, technically, the results apply only to the worm burden within an individual host. Often, to facilitate comparisons with data, results are compared with data on mean worm burden in a population of hosts even though the comparison is not strictly correct. Part of the motivation for using stochastic models, as discussed in the following section, is that they can be used to determine mean worm burden over a population of hosts.

4.3 A stochastic model of infection in the definitive host

A simple model for the distribution of adult parasites in the definitive host will be presented. The model is based loosely on that of Tallis & Leyton (1969), though the complexities that are dealt with in their paper (clumped input of the infective stages and a non-constant hazard of death for adult worms) have been ignored.

If a host of age a acquires adult parasites singly and independently at a rate $\lambda(a)$, and there is no parasite death (a pure birth process), then the number, $N(a)$, of adult worms in a host of age a has a Poisson distribution with mean

$$\int_0^a \lambda(s)ds. \tag{4.8}$$

Without parasite death, the model is only useful over time-spans that are short relative to the parasite's life-expectancy; over longer time-spans, parasite death must be incorporated.

If there is worm death, then $N(a)$ represents the cumulative number of worms that have established themselves within the host by age a. The distribution of the number of *live* worms within the host at age a, $N_1(a)$, is obtained by computing the probability that an arbitrary worm of the $N(a)$ establishments is still alive in a host of age a. The age of the host at the point of establishment for this arbitrary worm has density $\frac{\lambda(s)}{\int_0^a \lambda(s)ds}$ on $(0, a)$. [In the special case where λ is constant this corresponds to a uniform distribution on $(0, a)$.] If a worm that infects a host at

age, s, survives until the host is of age a with probability $P(s,a)$, then the arbitrary worm is still alive at a with probability $p(a)$ where

$$p(a) = \int_0^a \frac{\lambda(s)}{\int_0^a \lambda(s)} P(s,a)ds.$$

Assuming that the lifetimes of worms are independent and conditional on there being $N(a) = n$ establishments, the distribution of live worms i.e. $N_1(a)|N(a) = n$ is binomial with parameters $n, p(a)$. It is then straightforward to show that $N_1(a)$ has a Poisson distribution with mean

$$\int_0^a \lambda(s)P(s,a)ds. \tag{4.9}$$

Intuitively, the mean number of worms in a host of age a that infected the host at age s is the product of the expected number of infections at s, $\lambda(s)ds$, and the probability of survival $P(s,a)$. Thus the mean number of worms at age a is the sum of $\lambda(s)P(s,a)$ over all ages up to a. In the special case where the hazard of death for the parasite is a constant, μ_M (i.e. survival times are exponentially distributed), $P(s,a) = e^{-\mu_M(a-s)}$ and the mean of the Poisson distribution is the same as the solution of the deterministic model (Eqn 4.2), i.e.

$$\mathrm{E}[N_1(a)] = \int_0^a \lambda(s)e^{-\mu_M(a-s)}ds.$$

The equivalence is not surprising since the deterministic model (Eqn 4.1) also effectively assumes a constant hazard of death.

4.4 Dispersion

The model of the previous section, predicts that worm burden should follow a Poisson distribution. The variance and mean of the Poisson distribution are the same. However, empirical studies have frequently shown that the variance in worm burden exceeds mean worm burden (Anderson & May, 1985a). One of the main uses of stochastic models has therefore been to identify processes that generate this overdispersion and modify its severity.

It is immediately apparent from the preceding model that heterogeneity in the rate at which worms are acquired over time and the distribution of parasite lifespan have no effect on the degree of dispersion under the simple assumptions of this model. This also seems to be the case for more complicated models that allow for host death (Herbert & Isham, 2000; Isham, 1995).

One of the simplifications of the basic model is that the rate of infection, $\lambda(a)$, is the same for all hosts. In reality hosts differ in their susceptibility to helminth infection due to behaviour, genetics and local environment. This variability can be modelled by treating the rate of infection, $\Lambda(a)$, as an age-dependent random variable (Tallis & Leyton, 1969; Isham, 1995; Herbert & Isham, 2000). The model described previously is then equivalent to conditioning on a particular rate of infection $\Lambda(a) = \lambda(a)$. Therefore the mean number of adult worms in a host of age a is computed as follows

$$\begin{aligned} \mathrm{E}[N_1(a)] &= \mathrm{E}[\mathrm{E}[N_1(a)|\Lambda(a)]] \\ &= \int_0^a \mathrm{E}[\Lambda(s)]P(s,a)ds. \end{aligned} \tag{4.10}$$

[where E[ ] is the expectation or mean, and | means 'conditional on'].

Similarly the variance is

$$\begin{aligned} \mathrm{Var}(N_1(a)) &= \mathrm{E}[\mathrm{Var}(N_1(a)|\Lambda(a))] + \mathrm{Var}[\mathrm{E}(N_1(a)|\Lambda(a))] \\ &= \int_0^a \mathrm{E}[\Lambda(s)]P(s,a)ds + \mathrm{Var}[\int_0^a \Lambda(s)P(s,a)ds], \end{aligned} \tag{4.11}$$

and the index of dispersion (variance:mean ratio) is therefore

$$\mathrm{I}(a) = 1 + \frac{\mathrm{Var}[\int_0^a \Lambda(s)P(s,a)ds]}{\int_0^a \mathrm{E}[\Lambda(s)]P(s,a)ds}. \tag{4.12}$$

Clearly the index of dispersion is greater than one. For the special case where Λ is not age-dependent, and parasite survival is exponentially distributed,

$$\mathrm{I}(a) = 1 + \frac{\mathrm{Var}[\Lambda]}{\mathrm{E}[\Lambda]}\frac{1}{\mu_M}(1 - e^{-\mu_M a}). \tag{4.13}$$

In this case it is apparent that the index of dispersion for worm burden increases with host age.

Overdispersion also arises when infective stages are acquired in clumps rather than singly as is assumed in the above model. In a model where parasite survival is exponentially distributed and the rate of helminth infection is constant across hosts, Isham (1995) shows that overdispersion will arise provided that there is a chance that more than one parasite is acquired in a single exposure. Moreover, dispersion is increased in this model by increasing the chance of getting a large number of worms in an infection instant. The formula given for the index of dispersion is

$$\mathrm{I}(a) = 1 + \frac{\mathrm{E}(C^2 - C)}{2\mathrm{E}(C)}(1 + e^{-\mu_M a}) \tag{4.14}$$

where C is a random variable representing the number of parasites acquired in an exposure. In contrast to Eqn 4.13 it can be seen here that dispersion decreases with increasing host age. Thus, from the simple models analyzed, it would appear that overdispersion *increases* with host age when caused by heterogeneity in parasite acquisition amongst hosts, and *decreases* with host age when caused by parasite clumping. Intuitively this is because differences between host worm burdens become exacerbated with age if there is heterogeneity among hosts, while differences become less significant with age if there is clumping as hosts acquire both small and large clumps over time.

The models considered so far have all assumed that worm burden has no effect on host survival. Assuming instead that the per capita host death rate, α, is proportional to worm burden then, in the absence of clumping and host heterogeneity, Herbert & Isham (2000) show that the number of adult worms is Poisson with mean

$$\int_0^a \lambda(s)P(s,a)e^{-\alpha(a-s)}ds. \tag{4.15}$$

The integrand is as it is in the model of section 4.3 (Eqn 4.9) except for the factor of $e^{-\alpha(a-s)}$; this corresponds to the probability that a parasite acquired at age s has not killed the host by time a.

Herbert & Isham (2000) further explore the effect of parasite-induced host death on dispersion. In their model, the rate of host death is assumed to be proportional to the parasite load and overdispersion is introduced through clumping. They find that the effect of parasite induced host mortality is to reduce the index of dispersion, although it cannot be reduced below unity; this is intuitive since it is the hosts with the most parasites that are being removed from the population.

4.5 Models of population dynamics

The models described thus far have considered worm burden either within a single host, or a cohort of hosts. Further, the models have implicitly assumed that the number of infective larvae in the environment is constant. However the size of the larval population clearly depends on the number of adult worms over the population of hosts. Therefore the models described so far effectively assume that the size of the adult worm population has reached an equilibrium level. To determine whether such an assumption is reasonable, and to understand what factors can influence

equilibrium parasite population sizes, models must allow larval population size to depend on the number of adult worms across the host population. The following deterministic model was originally proposed by (Anderson & May, 1978), and variants have been analyzed by many authors.

Let $n_i(t)$ represent the number of hosts carrying i worms at time t in an infinite population of hosts. Therefore $N(t) = \sum_{i=0}^{\infty} n_i(t)$ is the total number of hosts and $P(t) = \sum_{i=0}^{\infty} i n_i(t)$ is the total number of parasites. Also let $L(t)$ be the numbers of larvae at time t. Treating hosts with i worms as a subpopulation for each of $i = 0, 1, 2....$, an infinite set of differential equations can be derived to describe changes to these subpopulations as worms are acquired and lost from the subpopulations and hosts are born and die. The parameters are defined in table 4.1.

$$\begin{aligned}
\frac{dn_0}{dt} &= bN + \mu n_1 - (\alpha + \phi L)n_0 \\
\frac{dn_i}{dt} &= \phi L n_{i-1} + \mu(i+1)n_{i+1} - (\alpha + \delta i + \mu i + \phi L)n_i \\
\frac{dL}{dt} &= \epsilon P - \mu_L L - \phi N L.
\end{aligned} \tag{4.16}$$

Since $\frac{dN}{dt} = \sum_{i=0}^{\infty} \frac{dn_i}{dt}$ and $\frac{dP}{dt} = \sum_{i=0}^{\infty} i \frac{dn_i}{dt}$, in terms of N and P we have,

$$\begin{aligned}
\frac{dN}{dt} &= (b - \alpha)N - \delta P \\
\frac{dP}{dt} &= \phi L N - (\mu + \alpha)P - \delta \sum_{i=1}^{\infty} i^2 n_i \\
\frac{dL}{dt} &= \epsilon P - \mu_L L - \phi L N.
\end{aligned} \tag{4.17}$$

Assuming that worm burden does not affect host life expectancy so that $\delta = 0$ and also that host population size is constant ($b = \alpha$), then the system is linear, and can be written in matrix form as

$$\begin{pmatrix} \frac{dP}{dt} \\ \frac{dL}{dt} \end{pmatrix} = \begin{pmatrix} -(\alpha + \mu) & \phi N \\ \epsilon & -(\mu_L + \phi N) \end{pmatrix} \begin{pmatrix} P \\ L \end{pmatrix}. \tag{4.18}$$

There is a single equilibrium point ($P = 0, L = 0$) that is stable provided the matrix in Eqn 4.18 has a positive determinant. If the determinant is negative then $P \to \infty$ and $L \to \infty$. The determinant is positive provided that

$$\frac{\epsilon \phi N}{(\alpha + \mu)(\mu_L + \phi N)} < 1. \tag{4.19}$$

Parameter/Variable	*Definition*
n_i	Number of hosts with i worms
$N = \sum_{i=0}^{\infty} n_i$	Host population size
$P = \sum_{i=0}^{\infty} i n_i$	Worm population size
α	Host death rate in absence of infection
δ	Per worm increase in host death rate
b	Host birth rate
ϕ	Per larva rate of host infection
μ	Worm death rate
μ_L	Larval death rate
ϵ	Per worm rate of larval production

Table 4.1: Parameter definitions for model defined in Eqn 4.16

The quantity on the left hand side (LHS) of Eqn 4.19 is referred to as the basic reproduction number, R_0, and provides a criterion for the establishment of a helminth infection in a population of hosts. The basic reproduction number may also be defined biologically as the number of adult worms produced by an adult worm (assuming the worm is hermaphrodite) during its lifetime. It is easy to see that the two definitions are equivalent if one considers R_0 to be the product of two terms: 1) the number of infective larvae produced by each adult during its lifetime; 2) the probability that a larva survives to infect a host. Thus R_0 maybe written as

$$R_0 = \left(\frac{\epsilon}{(\alpha+\mu)}\right)\left(\frac{\phi N}{(\mu_L+\phi N)}\right) \tag{4.20}$$

which is equivalent to the definition of R_0 based on Eqn 4.19.

Complications arise arise if the worm species is dioecious (has two separate sexes). In this case the expression for R_0 will depend on the probability of mating which is determined by the distribution of parasites among hosts (May, 1977b).

Originally Anderson & May (1978) used the model defined by Eqn 4.17 to investigate the circumstances under which a helminth species is able to regulate host population size. In their analysis, Anderson & May (1978) express Eqn 4.17 in terms of mean worm burden $m(t) = \frac{P(t)}{N(t)}$ and assume that the relationship between between mean and variance is the same as it is in the negative binomial distribution, i.e. $\sigma^2(t) = m(t) + \frac{m(t)^2}{k}$, where k is an inverse measure of the degree of overdispersion. Under this assumption, Eqn 4.17 becomes

$$\begin{aligned}
\frac{dN}{dt} &= (b-\alpha)N - \delta mN \\
\frac{dm}{dt} &= \phi L - (\mu+\alpha+\delta)m - \frac{\delta}{k}m^2 \\
\frac{dL}{dt} &= \epsilon mN - \mu_L L - \phi LN. \qquad (4.21)
\end{aligned}$$

The endemic equilibrium for Eqn 4.21 exists only when k is sufficiently large relative to δ (see Anderson & May, 1978), i.e. as parasite induced host mortality increases, the level of aggregation must decrease ($k \to \infty$) for the equilibrium to remain stable. This is because as aggregation increases, the number of worms lost through host mortality must be reduced if the helminth is to regulate the host population. The model can be further extended to incorporate other regulatory processes such as parasite-induced reduction in host fecundity, and density dependence in the parasite population (Anderson & May, 1978; May & Anderson, 1978).

A difficulty with the model of Eqn 4.21 is that it implicitly assumes that the degree of overdispersion is constant over time and therefore independent of other parameters in the model. This assumption is not necessarily upheld since the degree of overdispersion is known to depend on, for example, the level of parasite-induced host mortality (Herbert & Isham, 2000). The problem can be overcome by analyzing the infinite set of differential equations of Eqn 4.16 (Hadeler & Dietz, 1984; Kretzschmar, 1989). Alternatively, Kretzschmar & Adler (1993) use the infinite system to derive equations for mean and variance:mean ratio of worm burden and then apply the negative binomial approximation to this system, thereby allowing aggregation to vary over time.

As the models mentioned above do not include aggregation-generating mechanisms such as host heterogeneity and parasite clumping, the level of aggregation in these models is necessarily much lower than is typically observed for distributions of worm burden (Shaw *et al.*, 1998). Pugliese *et al.* (1998) and Rosà & Pugliese (2002) address this problem by incorporating either parasite clumping or host heterogeneity into the model; they find that the stability of the endemic equilibrium is strongly dependent on which mechanism for generating overdispersion is used.

A further drawback to the model defined in Eqn 4.16 is that density-dependent mechanisms that operate within the host, e.g. acquired immunity, do not fit naturally within this framework. Subsequent chapters will focus on within-host density dependence. To accommodate within host mechanisms an individual-based modelling framework developed in Nåsell & Hirsch (1972) and Nåsell (1985) is intro-

Parameter/Variable	*Definition*
X_i	Worm burden of host i
I	Number of infected snails
ϕ_H	per infected snail rate of host infection by cercariae
μ_X	per capita worm death rate
Φ_S	Per host rate of snail infection by miracidia
μ_I	per capita death rate of infected snails

Table 4.2: Parameter definitions for the schistosomiasis model

duced. This framework combines both stochastic and deterministic elements.

4.6 Hybrid models

The following is a presentation of the hybrid model developed by Nåsell & Hirsch (1972) and Nåsell (1985) for schistosomiasis.

Consider a populations of N_H definitive hosts and N_S snails. Let X_i $i = 1, ...N_H$ be the worm burden in host i and I be the number of infected snails. A fully stochastic model is defined in terms of a $N_H + 1$ dimensional Markov of processes. The Markov property implies that rates of transition to other states depend only on the current state, not on past states. Thus the process can be specified in terms of the following transitions (parameter definitions given in table 4.2),

1. $X_i \rightarrow X_i + 1$ at rate $\phi_H I$
2. $X_i \rightarrow X_i - 1$ at rate $\mu_X X_i$
3. $I \rightarrow I + 1$ at rate $\Phi_S(N_S - I) \sum_{i=1}^{N_H} X_i$
4. $I \rightarrow I - 1$ at rate $\mu_I I$.

Analysis of the model is simplified by replacing I with m_I in the first transition and $\sum_{i=1}^{N_H} X_i$ with $N_H m_X$ in the third transition, where m_I and m_X represent the mean number of infected snails and mean worm burden respectively. If $X_i(0)$ $(i = 1, ..N_H)$ are independent and identically distributed (i.i.d.), then $X_i(t)$ will also be i.i.d. for $t > 0$, and m_I and m_X can be expressed in terms of a pair of differential equations which will now be derived.

Given (X_t, I_t), the expected change in worm burden over a small interval of time, δ, is

$$\mathrm{E}[X_{t+\delta} - X_t | X_t, I_t] = \phi_H m_I \delta - \mu_X X_t \delta \tag{4.22}$$

to first order in δ.

The unconditional mean is obtained by taking the expected value of both sides

$$\mathrm{E}[X_{t+\delta} - X_t] = \phi_H m_I \delta - \mu_X m_X \delta. \tag{4.23}$$

Then dividing by δ, and taking the limit as $\delta \to 0$ gives

$$\frac{dm_X}{dt} = \phi_H m_I - \mu_X m_X. \tag{4.24}$$

Similarly m_I can be expressed in terms of a differential equation

$$\frac{dm_I}{dt} = \phi_S N_H m_X (N_S - m_I) - \mu_I m_I. \tag{4.25}$$

Eqns 4.24 and 4.25 exhibit a threshold phenomenon in terms of the quantity

$$R_0 = \frac{\phi_H \phi_S N_S N_H}{\mu_X \mu_I}.$$

The equilibrium $m_X = m_I = 0$ is stable when $R_0 < 1$ and unstable when $R_0 > 1$. The model as defined is for a hermaphrodite species; Nåsell (1985) also explores an extension of this model for a parasite species with two sexes. For this system, there is either a single stable equilibrium at $m_X = m_I = 0$, or 3 equilibria: a stable zero equilibrium and a stable nonzero equilibrium separated by an unstable equilibrium. The unstable equilibrium is referred to as the transmission 'breakpoint' by Macdonald (1965) since $m_X \to 0$ if worm burden is reduced below this value. The transmission breakpoint arises because parasites cannot meet and mate below a certain density. Although for an overdispersed distribution the critical density, can be very small (May, 1977b).

Density dependence appears implicitly in these schistosomiasis models since the number of infected snails cannot exceed N_S. The models of Chapters 7 and 8 incorporate density dependence explicitly, by assuming that either the probability of parasite establishment or adult worm fecundity are functions of current worm burden. Furthermore, in contrast to the model presented here, the models of Chapters 7 and 8 will allow for death of the definitive host.

4.7 Summary

A range of mathematical models have been developed in the literature to describe various aspects of helminth population biology. Deterministic models have been used to explain age-dependent patterns of infection intensity and to model the regulation of host populations through parasite-induced host mortality. Properties of the distribution of worm burden have been elucidated through the use of stochastic models. In the following chapters, these various approaches will be drawn upon to address multispecies infection. To begin with, the worm burdens of two interacting species are modelled deterministically in a single host (Chapter 5). This model will form the basis of a stochastic model to explore the distribution of worm burden in a population of hosts (Chapter 6). Finally, a hybrid model will be developed to explore the long-term dynamics of a single species (Chapter 7), and two competing species (Chapter 8).

Chapter 5

Coinfection in a Single Host

5.1 Introduction

Before exploring the distribution of worm burden in a population of hosts, it is necessary to understand the dynamics of worm burden within a single host. Deterministic models for the worm burdens of two interacting species, in a single, ageing host will be formulated and analyzed here. The results of these models are helpful in understanding age-intensity patterns. Furthermore, the model itself will be used as the basis for a stochastic model (Chapter 6) which explores the distribution of worm burden in a cohort of ageing hosts.

The models developed here assume that the mode of interaction is through the density of adult, established worms affecting the rates of establishment of incoming, larval stages of their own (homologous) species or the other (heterologous) species. These interactions may arise as the result of direct effects (e.g. exploitation competition) or may be immunologically-mediated (Chapter 3), although the immune response is not modelled explicitly.

The terminology of Behnke *et al.* (2001) will be adopted and interactions categorized as antagonistic or synergistic. In addition, mutually antagonistic interactions are defined as those in which parasites of each species reduce the establishment of parasites of the other species. Thus, these interactions induce host-protection from heterologous infection. Mutually synergistic interactions are defined as those in which parasites of each species enhance the establishment of the other species. These interactions result in increased host susceptibility to heterologous infection.

5.2 Formulation of deterministic model (D)

A model for two interacting helminth species in a *single* ageing host, can be constructed by modifying the simple immigration-death framework (Tallis & Leyton, 1966; Anderson & May, 1991; Duerr *et al.*, 2003a).

The model includes larval (l_1, l_2) and adult (x_1, x_2) stages. At age $a = 0$, there are no larvae or adults of either species: $l_i(0) = x_i(0) = 0$ $(i = 1, 2)$. For $a > 0$, the rate of change with respect to host age a of the numbers of larvae and adults of each parasite species can be modelled as follows,

$$\begin{aligned}
\frac{dl_1}{da} &= \lambda_1 - \eta_1 e^{\gamma_{11}x_1 + \gamma_{21}x_2} l_1 - \sigma_1 l_1 \\
\frac{dx_1}{da} &= \sigma_1 l_1 - \mu_1 x_1 \\
\frac{dl_2}{da} &= \lambda_2 - \eta_2 e^{\gamma_{22}x_2 + \gamma_{12}x_1} l_2 - \sigma_2 l_2 \\
\frac{dx_1}{da} &= \sigma_2 l_2 - \mu_2 x_2. \qquad (5.1)
\end{aligned}$$

In this model, λ_i represents the net rate at which larval stages of species i $(i = 1, 2)$ invade the host. Incoming larvae either die or become established and reach the adult stage. Larvae of species i become adults at a per capita rate σ_i, and in the absence of any adult worms (of either species) die with a per capita death rate η_i. When adult worms are present, η_i is modulated by a factor of $e^{\gamma_{ji}}$ for each adult worm of species j $(j = 1, 2)$. Thus adult worms of species j increase the larval death rate of species i if $\gamma_{ji} > 0$ and decrease it if $\gamma_{ji} < 0$. Note that the modulation is due to homologous adult worms when $j = i$ and heterologous adult worms when $j \neq i$. The per capita death rate, μ_i, of adult worms of species i is unaffected by the worm burden of either species (it is density-independent). The notation, definition and units of the parameters for this model are summarized in Table 5.1.

The model can be simplified by making the assumption that the larval stage in each species is short-lived, relative to the adult lifespan $(\sigma_i \gg \mu_i \; i = 1, 2)$. Under this assumption, the dynamics of adult worm numbers are well described by a model in which larval numbers are at equilibrium, i.e. $\frac{dl_1}{da} = \frac{dl_2}{da} = 0$ (for a formal justification of this procedure based on Korzuhin's theorem, see Klonowski, 1983); Eqn 5.1 then becomes

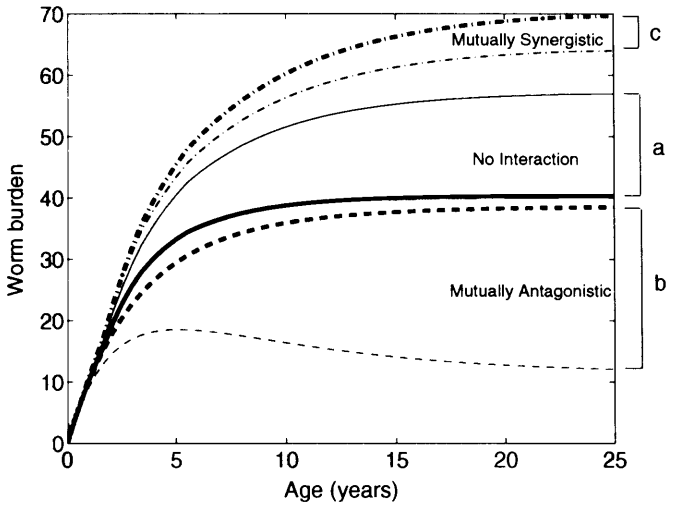


Figure 5.1: Solutions to the deterministic model (D) giving worm burden as a function of host age. Three scenarios are illustrated: a) no interaction ($\gamma_{21} = \gamma_{12} = 0$); b) mutually antagonistic interaction ($\gamma_{21} = 0.01, \gamma_{12} = 0.07$), and c) mutually synergistic interaction ($\gamma_{21} = -0.01, \gamma_{12} = -0.005$). For each scenario, the thick line represents species 1 and the thin line species 2. Other parameter values: $\lambda_i = 1.5$ month^{-1}, $\sigma_i = 1$ month^{-1}, $\mu_i = 1/72$ month^{-1}, $\eta_i = 0.5$ month^{-1} $(i = 1, 2)$, $\gamma_{11} = 0.03$, $\gamma_{22} = 0.01$.

$$\begin{aligned} \frac{dx_1}{da} &= \frac{\sigma_1 \lambda_1}{\sigma_1 + \eta_1 e^{\gamma_{11} x_1 + \gamma_{21} x_2}} - \mu_1 x_1 \\ \frac{dx_2}{da} &= \frac{\sigma_2 \lambda_2}{\sigma_2 + \eta_2 e^{\gamma_{22} x_2 + \gamma_{12} x_1}} - \mu_2 x_2. \end{aligned} \tag{5.2}$$

The model will be referred to as D (for *deterministic*). The differential equations in the system of Eqn 5.2 can be solved numerically to give numbers of worms of species 1 and species 2 as functions of host age. It is worth stressing that $x_i(a)$ has been defined as the species i worm burden in a *single* host. Alternatively, $x_i(a)$ may be viewed as the mean worm burden of species i in an ageing cohort of hosts (Woolhouse, 1992b). This interpretation is advantageous in that it allows comparisons to be made with data from a population of hosts. However, the interpretation of the inter- and intraspecific interaction parameters (the γ coefficients) is now less obvious since the model is no longer individual-based.

For mutually antagonistic interactions, simulations frequently show that the intensity of infection of one of the species is convex, i.e. it peaks, while that of the other species increases monotonically to approach an equilibrium. This is illustrated by the bottom two curves (the dashed lines) in Fig.5.1. Since processes explaining 'convex' age-infection patterns are of interest in parasitology (Chapter 4), we explore

Parameter/variable	*Definition*	*Units*
l_i	Number of worms of species i	no units
x_i	Number of adult worms of species i	no units
λ_i	Rate at which host acquires species i larvae	larvae month^{-1}
σ_i	Maturation rate of species i larvae	month^{-1}
η_i	Per capita death rate of species i larvae	month^{-1}
μ_i	Per capita death rate of species i adults	month^{-1}
$e^{\gamma_{ij}}$	Factor by which each adult worm of species i ($i,j = 1,2$) modifies species j larval mortality	no units

Table 5.1: Parameter definitions for the deterministic model (model D).

this phenomenon further in the next chapter.

5.3 Number and stability of equilibria

An important feature of the dynamical system specified by Eqn 5.2 is that trajectories $(x_1(a), x_2(a))$ are contained within the region $0 < x_1 < \frac{\lambda_1}{\mu_1}, 0 < x_2 < \frac{\lambda_2}{\mu_2}$ (provided that they start in this region). This follows from the fact that $dx_1/da < 0$ for all values of x_2 whenever $x_1 > \lambda_1/\mu_1$, and $dx_2/da < 0$ for all values of x_1 whenever $x_2 > \lambda_2/\mu_2$. The property of boundedness can be used in conjunction with properties of the Jacobian matrix to deduce the number and type of equilibria that occur when intra- and interspecific terms are antagonistic ($\gamma_{ji} > 0$, $i,j = 1,2$).

The Jacobian matrix, J, is obtained by differentiating $(dx_1/da, dx_2/da)$ with respect to x_1 and x_2.

$$J = \begin{pmatrix} \frac{-\lambda_1\sigma_1\gamma_{11}\eta_1 e^{\gamma_{11}x_1+\gamma_{21}x_2}}{\left(\sigma_1+\eta_1 e^{\gamma_{11}x_1+\gamma_{21}x_2}\right)^2} - \mu_1 & \frac{-\lambda_1\sigma_1\gamma_{21}\eta_1 e^{\gamma_{11}x_1+\gamma_{21}x_2}}{\left(\sigma_1+\eta_1 e^{\gamma_{11}x_1+\gamma_{21}x_2}\right)^2} \\ \frac{-\lambda_2\sigma_2\gamma_{12}\eta_2 e^{\gamma_{22}x_2+\gamma_{12}x_1}}{\left(\sigma_2+\eta_2 e^{\gamma_{22}x_2+\gamma_{12}x_1}\right)^2} & \frac{-\lambda_2\sigma_2\gamma_{22}\eta_2 e^{\gamma_{22}x_2+\gamma_{12}x_1}}{\left(\sigma_2+\eta_2 e^{\gamma_{22}x_2+\gamma_{12}x_1}\right)^2} - \mu_2 \end{pmatrix}.$$

The eigenvalues of J evaluated at an equilibrium point determine the behaviour of trajectories close to the equilibrium. Let J_{ik} $(i = 1,2; k = 1,2)$ be the element of J in the i^{th} row and k^{th} column; then the eigenvalues of J can be expressed as $\frac{1}{2}(\mathrm{Tr}(J) \pm \sqrt{\mathrm{Tr}^2(J) - 4\mathrm{Det}(J)})$ where $\mathrm{Tr}J = J_{11} + J_{22}$ and $\mathrm{Det}(J) = J_{11}J_{22} - J_{21}J_{12}$.

Intra- and interspecific effects are antagonistic when $\gamma_{ji} > 0$ $(j,i = 1,2)$. Under this condition, it is immediately apparent that $\mathrm{Tr}J < 0$. Furthermore, $4\mathrm{Det}J < \mathrm{Tr}^2J$, since $\mathrm{Tr}^2J = (J_{11} + J_{22})^2 \geq 4J_{11}J_{22} > 4\mathrm{Det}(J)$ for all values of (x_1, x_2).

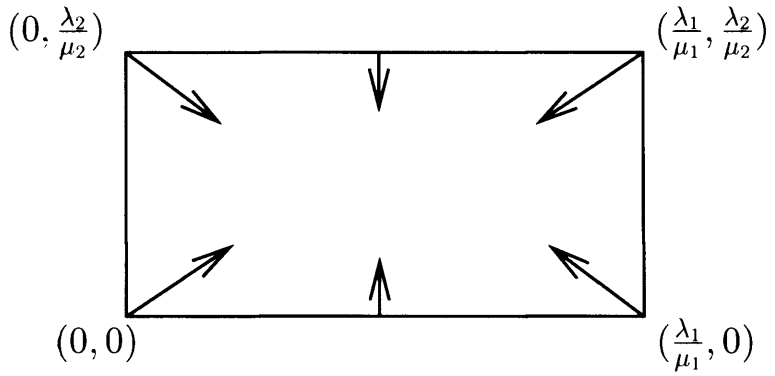


Figure 5.2: The index of the curve, C, is $+1$: Moving around the curve, C, defined by the lines $x_1 = 0, x_2 = 0, x_1 = \frac{\lambda_1}{\mu_1}, x_2 = \frac{\lambda_2}{\mu_2}$ in a counterclockwise direction, the vector field $(\frac{dx_1}{da}, \frac{dx_2}{da})$ rotates 360^o in the counterclockwise direction therefore C has index $+1$.

Imposing the further restriction on the intra- and interspecific terms that $\gamma_{11}\gamma_{22} > \gamma_{12}\gamma_{21}$ guarantees that $\mathrm{Det}J > 0$ for all values of (x_1, x_2). Therefore all eigenvalues of J are real and negative if intra- and interspecific effects are antagonistic, and the product of the intraspecific terms is less than the product of the interspecific terms. When the eigenvalues associated with an equilibrium are real and negative, then the equilibrium is a stable node. In the vicinity of a stable node a trajectory will approach the equilibrium point without oscillation (Strogatz, 1994).

Information on the number of equilibria can be obtained through the use of indices. The index of a simple, closed curve in the vector field defined by $(\frac{dx_1}{da}, \frac{dx_2}{da})$ is the net number of counter-clockwise revolutions made by the vector field as a point (x_1, x_2) moves around the curve (Strogatz, 1994). Consider the closed curve, C, formed by the lines $x_1 = 0, x_2 = 0, x_1 = \frac{\lambda_1}{\mu_1}, x_2 = \frac{\lambda_2}{\mu_2}$. Moving around C, the vector field rotates 360 degrees in the anticlockwise direction, thus the index of C is $+1$ (Fig.5.2). This is informative since the index of C is the sum of the indices of all the equilibrium points contained within it. The index of an equilibrium point is determined by what type of equilibrium it is; saddle points (both eigenvalues real, but with opposite signs) have an index of -1 while all other types of equilibria have an index of $+1$.

It has been shown that all equilibria are stable nodes when intra- and interspecific effects are antagonistic ($\gamma_{ji} > 0$ $j, i = 1, 2$), and the interaction between species is greater than within ($\gamma_{11}\gamma_{22} > \gamma_{12}\gamma_{21}$). Based on the fact that the index of C is $+1$ it is therefore possible to conclude that under this condition there can be only one equilibrium since otherwise the index of C would have to be greater than $+1$.

Conversely, when $\gamma_{11}\gamma_{22} < \gamma_{12}\gamma_{21}$ (and $\gamma_{ji} > 0$) then there may be more than

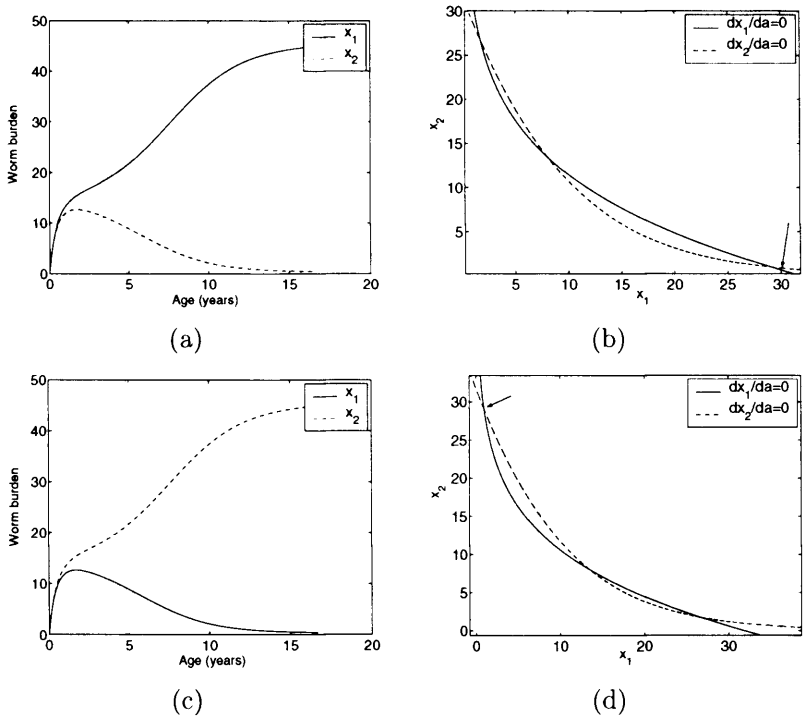


Figure 5.3: When intra- and interspecific effects are antagonistic, and the interaction between species is greater than within species, there may be three equilibria: two stable nodes and one saddle point. a) Age-intensity profiles. b) A phase portrait where the arrow indicates the stable equilibrium that is approached. The parameter values for a) and b) are: $\gamma_{11} = \gamma_{22} = 0.01, \gamma_{21} = 0.12, \gamma_{12} = 0.13, \eta_1 = \eta_2 = 1$ month$^{-1}, \sigma_1 = \sigma_2 = 1$ month$^{-1}, \lambda_1 = \lambda_2 = 6$ month$^{-1}, \mu_1 = \mu_2 = 0.05$ month^{-1}. Figures c) and d) are produced with identical parameter values except that $\gamma_{21} = 0.13$ and $\gamma_{12} = 0.12$. This minor change in parameter values results in a trajectory that approaches the other equilibrium.

one equilibrium. Since the index of C is $+1$, the number of equilibria must be odd. Moreover if there are $2n+1$ equilibria, then n of these are saddle points. For the remaining $n+1$ equilibria $\mathrm{Det}J > 0$ otherwise they would also be saddle points, and $4\mathrm{Det}J < \mathrm{Tr}^2 J$ because $\gamma_{ji} > 0$. These $n+1$ equilibria are therefore stable nodes.

Numerical work shows that when $\gamma_{ji} > 0$ $(j,i = 1,2)$ and $\gamma_{11}\gamma_{22} < \gamma_{12}\gamma_{21}$, then there are frequently three equilibria. In this situation the (unstable) saddle point is a mixture of the two species while in each of the stable nodes one species dominates the other (Fig.5.3). The situation is inherently unstable in the sense that the parameter values that give rise to two very different trajectories may be quite similar. Biologically this implies that when interspecific antagonistic effects are much stronger than intraspecific antagonistic effects, one might find the paradoxical situation of similar hosts in similar environments with very different worm burdens of the two species. This result is a prelude to results that will be derived in the following chapter, where it will be shown than the size of interspecific effects *relative* to intraspecific effects is critical in determining the distribution of worm burden in host population.

5.4 Linear model

The non-linear model of the previous section may be approximated by a linear one. By making this approximation, expressions for the worm burdens of each species as functions of host age can be derived.

For species 1 define $z_1 = \gamma_{11}x_1 + \gamma_{21}x_2$; then a Taylor expansion of the immigration rate for species 1 in terms of z_1 gives

$$\begin{aligned}
\frac{\sigma_1\lambda_1}{\sigma_1+\eta_1 e^{z_1}} &= \frac{\sigma_1\lambda_1}{\sigma_1+\eta_1} - \frac{\sigma_1\lambda_1\eta_1}{(\sigma_1+\eta_1)^2}z_1 + o(z_1) \\
&= \frac{\sigma_1\lambda_1}{\sigma_1+\eta_1}\left(1 - \frac{\eta_1}{\eta_1+\sigma_1}z_1\right) + o(z_1) \\
&= \lambda_1(1-q_1)(1-q_1z_1) + o(z_1)
\end{aligned}$$

where $1-q_1 = \frac{\sigma_1}{\eta_1+\sigma_1}$ is the probability of a species 1 larva surviving to become an adult worm in the absence of density-dependent effects.

Similarly, for species 2

$$\frac{\sigma_2\lambda_2}{\sigma_2+\eta_2 e^{z_2}} = \lambda_2(1-q_2)(1-q_2z_2) + o(z_2)$$

where $z_2 = \gamma_{22}x_2 + \gamma_{12}x_1$ and $q_2 = \frac{\eta_2}{\eta_2+\sigma_2}$.

Provided that $z_1 \ll 1$ and $z_2 \ll 1$ the non-linear model maybe approximated by

the following linear model

$$\frac{dx_1}{da} = \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}x_1 - \tilde{\gamma}_{21}x_2) - \mu_1 x_1 \tag{5.3}$$

$$\frac{dx_2}{da} = \tilde{\lambda}_2(1 - \tilde{\gamma}_{22}x_2 - \tilde{\gamma}_{12}x_1) - \mu_2 x_2 \tag{5.4}$$

where $\tilde{\lambda}_i = (1 - q_i)\lambda_i$ and $\tilde{\gamma}_{ij} = q_i\gamma_{ij}$.

Solution to the linear model (L) Using the initial conditions $x_1(0) = x_2(0) = 0$ it is possible to obtain an analytic solution to the pair of differential equations using Laplace transforms. By integrating Eqn 5.4, and substituting into Eqn 5.3, the 2-dimensional system is reduced to a 1-dimensional integro-differential equation, the solution of which is the number of worms of species 1 at host age a.

$$\frac{dx_1}{da} = \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}x_1 - \tilde{\gamma}_{21}x_2) - \mu_1 x_1 \tag{5.5}$$

$$x_2 = \tilde{\lambda}_2 \int_0^a e^{-\beta_2(a-u)}(1 - \tilde{\gamma}_{12}x_1(u))du \tag{5.6}$$

where $\beta_2 = \tilde{\lambda}_2\tilde{\gamma}_{22} + \mu_2$.

This integro-differential equation may be solved by taking the Laplace transform of both sides. The Laplace transform of the function $x_1(a)$ is $x_1^*(s) = \int_0^\infty e^{-sa}x_1(a)da$. On the LHS of Eqn 5.5, the Laplace transform of $x_1'(a)$ is $sx_1^*(s) - x_1(0) = sx_1^*(s)$. On the RHS of Eqn 5.5, the Laplace transform of 1 is $1/s$; and the Laplace transform of the convolution, $x_2(a)$, given in Eqn 5.6 is $(1/s - \tilde{\gamma}_{21}x_1^*)/(s + \beta_2)$ (the product of the Laplace transforms of the 2 functions in the convolution, namely $(1/s - \tilde{\gamma}_{21}x_1^*)$ and $1/(s + \beta_2)$). The Laplace transform is a linear operator, therefore taking the Laplace transform of both sides yields,

$$sx_1^* = \tilde{\lambda}_1\left(\frac{1}{s} - \tilde{\gamma}_{11}x_1^* - \tilde{\lambda}_2\tilde{\gamma}_{21}\frac{\frac{1}{s} - \tilde{\gamma}_{12}x_1^*}{s + \beta_2}\right) - \mu_1 x_1^*.$$

Thus the Laplace transform of $x_1(a)$ is

$$x_1^*(s) = \frac{\tilde{\lambda}_1}{s}\frac{(s + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)}{(s + \beta_1)(s + \beta_2) - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12}} \tag{5.7}$$

where $\beta_1 = \tilde{\lambda}_1\tilde{\gamma}_{11} + \mu_1$.

Using partial fractions, Eqn 5.7 can be rewritten as

$$x_1^*(s) = \frac{A_1}{s} + \frac{B_1}{s-\alpha_1} + \frac{C_1}{s-\alpha_2} \tag{5.8}$$

where α_1, α_2 are the two roots of $(s+\beta_1)(s+\beta_2) - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12} = 0$. Thus $\alpha_1 = \frac{1}{2}\left(-(\beta_1+\beta_2)+\tau\right)$ and $\alpha_2 = \frac{1}{2}\left(-(\beta_1+\beta_2)-\tau\right)$ where $\tau = \sqrt{(\beta_1-\beta_2)^2 + 4\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12}}$ and the coefficients A_1, B_1, C_1 have the following values

$$\begin{aligned} A_1 &= \frac{\tilde{\lambda}_1(\beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)}{\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}} \\ B_1 &= \frac{\tilde{\lambda}_1(\alpha_1 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)}{\alpha_1\tau} \\ C_1 &= \frac{-\tilde{\lambda}_1(\alpha_2 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)}{\alpha_2\tau}. \end{aligned}$$

To find $x_1(a)$, the inverse Laplace transform is applied to Eqn 5.8,

$$\begin{aligned} x_1(a) &= A_1 + B_1 e^{\alpha_1 a} + C_1 e^{\alpha_2 a} \\ &= A_1 + \frac{\tilde{\lambda}_1}{\tau}\left(\frac{\alpha_1 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2}{\alpha_1} e^{\alpha_1 a} - \frac{\alpha_2 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2}{\alpha_2} e^{\alpha_2 a}\right). \end{aligned} \tag{5.9}$$

Even if τ is not real valued, $x_1(a)$ is still real valued. When the imaginary component of *tau* is nonzero ($Im(\tau) \neq 0$), a more useful formulation of $x_1(a)$ can be obtained by using an alternative partial fraction expansion of the Laplace transform of $x_1(a)$

$$\begin{aligned} x_1^*(s) &= \frac{\tilde{\lambda}_1}{s}\frac{(s+\beta_2-\tilde{\gamma}_{21}\tilde{\lambda}_2)}{(s+\beta_1)(s+\beta_2) - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12}} \\ &= \frac{D_1}{s} + \frac{E_1 s + F_1}{s^2 + (\beta_1+\beta_2)s + \beta_1\beta_2\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}} \\ &= \frac{D_1}{s} + \frac{E_1(s + \frac{F_1}{E_1})}{(s+\frac{(\beta_1+\beta_2)}{2})^2 - \frac{(\beta_1-\beta_2)^2}{4} - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}} \end{aligned} \tag{5.10}$$

where $D_1 = A_1, E_1 = -A_1, F_1 = \tilde{\lambda}_1 - A_1(\beta_1+\beta_2)$. The inverse Laplace transform of Eqn 5.10 is

$$x_1(a) = D_1 + E_1\left[e^{-\frac{(\beta_1+\beta_2)}{2}a}\left(\cos\xi a + \frac{\frac{F_1}{E_1} - \frac{(\beta_1+\beta_2)}{2}}{\xi}\sin\xi a\right)\right] \tag{5.11}$$

where $\xi = \frac{1}{2}\sqrt{-(\beta_1-\beta_2)^2 - 4\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}}$.

From the symmetry of the system of ODE's (Eqn 5.3 and Eqn 5.4), it is easy to see that the number of worms of species 2 at host age a is

$$x_2(a) = A_2 + \frac{\tilde{\lambda}_2}{\tau}\left(\frac{\alpha_1 + \beta_1 - \tilde{\xi}_{12}\tilde{\lambda}_1}{\alpha_1}e^{\alpha_1 a} - \frac{\alpha_2 + \beta_1 - \tilde{\xi}_{12}\tilde{\lambda}_1}{\alpha_2}e^{\alpha_2 a}\right) \tag{5.12}$$

where $A_2 = \frac{\tilde{\lambda}_2(\beta_1 - \tilde{\gamma}_{12}\tilde{\lambda}_1)}{\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}}$ or if $Im(\tau) \neq 0$,

$$x_2(a) = D_2 + E_2\left[e^{-\frac{(\beta_1+\beta_2)}{2}a}\left(\cos\xi a + \frac{\frac{F_2}{E_2} - \frac{(\beta_1+\beta_2)}{2}}{\xi}\sin\xi a\right)\right] \tag{5.13}$$

where $D_2 = A_2, E_2 = -A_2, F_2 = \tilde{\lambda}_2 - A_2(\beta_1 + \beta_2)$.

The solutions for $x_1(a)$ and $x_2(a)$ imply that both species will approach stable equilibria, $(x_1 = A_1, x_2 = A_2)$, provided that the real components of α_1 and α_2 are negative, or equivalently, provided that $\beta_1 + \beta_2 > 0$ and $\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} > 0$. If these conditions are not met then $x_1(a) \to \pm\infty, x_2(a) \to \pm\infty$. This will occur, for instance, when intra- and interspecific terms are positive and the interspecific terms are much greater than intraspecific terms, or alternatively, when the intraspecific terms ($\tilde{\gamma}_{11}$ and $\tilde{\gamma}_{22}$) are negative, (i.e., immunosuppressive) and sufficiently large in magnitude. Clearly under these circumstances, the linear model is inadequate.

5.5 A criterion for convexity

Despite producing unrealistic behaviour in certain parameter ranges, the fact that the linear model has an analytic solution offers insights into the sorts of age profiles of infection intensity that can be produced, and the conditions that produce them. For instance, the age-intensity profiles for both species will exhibit damped oscillations when τ has a nonzero imaginary component $Im(\tau \neq 0)$, which only occurs when the interspecific terms ($\tilde{\gamma}_{12}, \tilde{\gamma}_{21}$) have different signs.

An important result obtained from numerical simulation of the non-linear model is that when intra- and interspecific effects are antagonistic ($\gamma_{ji} > 0$, $i, j = 1, 2$), it is often observed that the age-intensity profile for one species is convex (see chapter 4), while the other is monotonic. The solution to the linear model allows a condition to be derived for the existence of convex age-profiles of infection.

If intra- and interspecific effects are antagonistic then $Im(\tau) = 0$, and the solution is given by Eqn 5.9 and Eqn 5.12 with real values of α_1 and α_2. By differentiating $x_1(a)$ (Eqn 5.9) and setting to zero, it can be seen that $x_1(a)$ has at most

one stationary point. Furthermore, when this stationary point exists it must be a maximum since $x_1(a)$ is initially an increasing function of age. The age at which the maximum occurs is denoted a_{1max} where

$$a_{1max} = \frac{1}{\tau}\log\left(\frac{\alpha_2 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2}{\alpha_1 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2}\right). \tag{5.14}$$

Thus a criterion for the existence of the maximum and therefore convexity in species 1 is that

$$\frac{\alpha_2 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2}{\alpha_1 + \beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2} > 0,$$

or alternatively that

$$\frac{\beta_2 - \beta_1 - \tau - 2\tilde{\gamma}_{21}\tilde{\lambda}_2}{\beta_2 - \beta_1 + \tau - 2\tilde{\gamma}_{21}\tilde{\lambda}_2} > 0.$$

Since intra- and interspecific effects are antagonistic, the numerator must always be negative, therefore the requirement for a maximum is that the denominator also be negative i.e. $\beta_2 - \beta_1 + \tau - 2\tilde{\gamma}_{21}\tilde{\lambda}_2 < 0$; this condition can be simplified:

$$\begin{aligned}
\beta_2 - \beta_1 + \tau - 2\tilde{\gamma}_{21}\tilde{\lambda}_2 &< 0 \\
\Rightarrow \beta_2 - \beta_1 + \sqrt{(\beta_2 - \beta_1)^2 + 4\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}} - 2\tilde{\gamma}_{21}\tilde{\lambda}_2 &< 0 \\
\Rightarrow (\beta_2 - \beta_1)^2 + 4\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} &< \left(2\tilde{\gamma}_{21}\tilde{\lambda}_2 - (\beta_2 - \beta_1)\right)^2 \\
\Rightarrow \beta_2 - \beta_1 &< \tilde{\gamma}_{21}\tilde{\lambda}_2 - \tilde{\gamma}_{12}\tilde{\lambda}_1.
\end{aligned} \tag{5.15}$$

By symmetry, the condition for the existence of a maximum in species 2 is

$$\begin{aligned}
\beta_1 - \beta_2 &< \tilde{\gamma}_{12}\tilde{\lambda}_1 - \tilde{\gamma}_{21}\tilde{\lambda}_2 \\
\Rightarrow \beta_2 - \beta_1 &> \tilde{\gamma}_{21}\tilde{\lambda}_2 - \tilde{\gamma}_{12}\tilde{\lambda}_1.
\end{aligned} \tag{5.16}$$

From the inequalities given in Eqn 5.15 and Eqn 5.16, it is apparent that whilst one of the two species must be convex, they cannot both be convex. The inequalities will determine which of the two species is convex, but they give no information as to the degree of convexity. This is most easily obtained by examining the solution for particular sets of parameter values. Figure 5.4 illustrates how quite substantial convexity may arise in one of the parasite species as a result of: 1) mutually antagonistic interspecific effects and differences in immunological parameters between the two species and 2) mutually antagonistic interspecific effects and differences in

life-expectancies of the two parasite species.

While there is often a lack of age-specific data on the distribution of worm burdens in non-human hosts, in humans such age-specific data are frequently available. Convexity is a common feature of these data (e.g. *Schistosoma*, *Ascaris*, *Trichuris* parasites in humans). Based on mathematical models (Anderson and May, 1985b; Woolhouse, 1992b; Woolhouse *et al.* 1994) two explanations for this phenomenon have been proposed: 1) host exposure or susceptibility decreases with age; 2) hosts build up protective acquired-immunity to the helminths. Whilst these proposals are undoubtedly the most likely explanations for 'convex' age-intensity patterns, it is tempting to speculate that in some situations convexity may be the result of mutually antagonistic interactions between two species. The analysis of the linearized version of model D demonstrates that a mutually antagonistic interaction must always result in one of the two species having a convex age-intensity pattern. However, two features (both illustrated in Fig.5.4) of the age-intensity pattern suggest that such an interpretation of an observed age-intensity profile should be employed with caution. First, even though in theory one of the two species must have a convex age-intensity profile when there is a mutually antagonistic interspecific interaction, the degree of convexity maybe negligible and therefore practically irrelevant. Secondly, it would appear that often the peak worm burden occurs at younger ages in the model than is observed in data sets of human helminth infection (Anderson and May, 1985a).

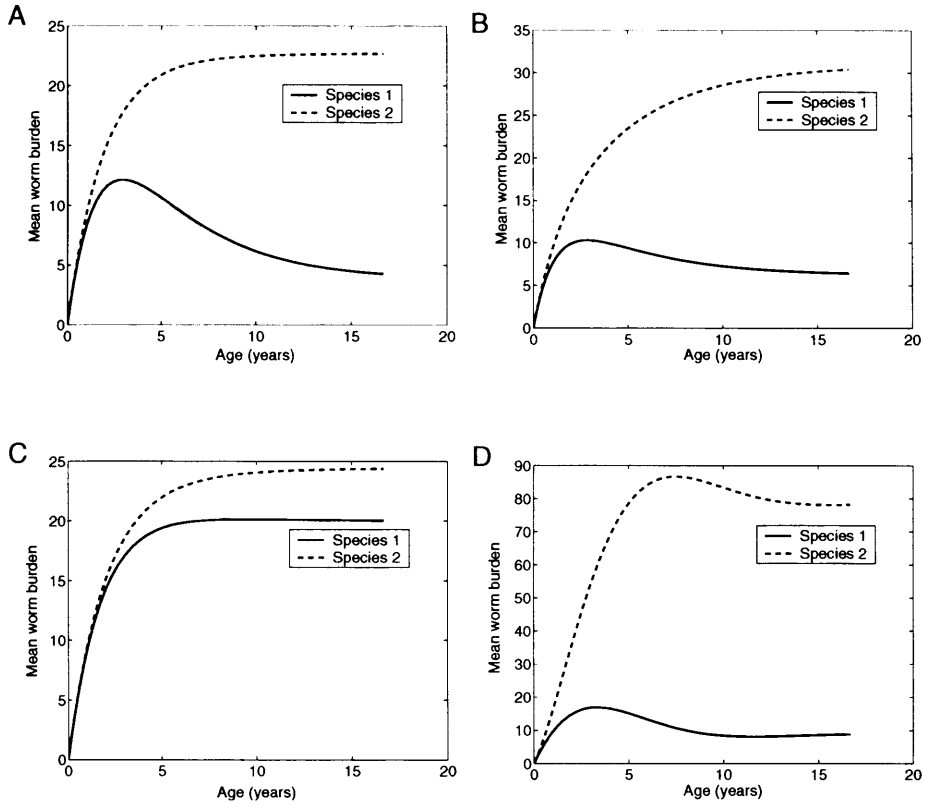


Figure 5.4: Worm burden as a function of host age (from Eqns 5.9 and 5.12). In A) - C) intra- and interspecific interactions are antagonistic, and one of the two species has a convex age-intensity profile. A) Worm burden as a function of age peaks in species 1 and increases monotonically in species 2 due to differences in the intra and inter-specific terms. Parameter values: $\tilde{\lambda}_1 = \tilde{\lambda}_2 = 1$ month^{-1}, $\mu_1 = \mu_2 = 1/72$ month^{-1}, $\tilde{\gamma}_{11} = 0.01, \tilde{\gamma}_{22} = 0.03, \tilde{\gamma}_{21} = 0.04, \tilde{\gamma}_{12} = 0.001$. B) When all the interaction parameters are equal, then the species with the shorter life-expectancy (species 1) will exhibit the peak. Parameter values $\tilde{\lambda}_1 = \tilde{\lambda}_2 = 1$ month^{-1}, $\mu_1 = 1/24$ month^{-1}, $\mu_2 = 1/120$ month^{-1}, $\tilde{\gamma}_{11} = \tilde{\gamma}_{22} = \tilde{\gamma}_{21} = \tilde{\gamma}_{12} = 0.02$. C) The peak maybe imperceptible so that both species appear to increase monotonically. Parameter values: $\tilde{\lambda}_1 = \tilde{\lambda}_2 = 1$ month^{-1}, $\mu_1 = \mu_2 = 1/36$ month^{-1}, $\tilde{\gamma}_{22} = \tilde{\gamma}_{12} = \tilde{\gamma}_{21} = 0.01, \tilde{\gamma}_{11} = 0.005$. D) The interspecific terms have opposite signs and age-intensity curves for *both* species are convex. Parameter values: $\tilde{\lambda}_1 = \tilde{\lambda}_2 = 1$ month^{-1}, $\mu_1 = \mu_2 = 1/72$ month^{-1}, $\tilde{\gamma}_{11} = \tilde{\gamma}_{22} = \tilde{\gamma}_{21} = 0.01, \tilde{\gamma}_{12} = -0.1$.

5.6 Summary

A non-linear model of the dynamics of worm burden in a single ageing host is derived. The number and type of equilibria are analyzed when intra- and interspecific effects act antagonistically. To further facilitate analysis a linearized version of the model is derived. From the linearized model, expressions for species 1 and species 2 worm burdens as functions of host age are obtained. Further, it is shown that if there is a mutually antagonistic interaction between two species then the age-intensity for one of the two species will be convex and the other monotonically increasing towards an equilibrium. These results are discussed in light of the current hypotheses proposed to explain convexity in age-profiles of helminth infection.

Chapter 6

Coinfection in a Cohort of Hosts

6.1 Introduction

Worm burdens in individual hosts are often small. For any given host, the dynamics of worm burden are therefore ostensibly governed by chance. For this reason, when comparisons are made between models and ecological data it is useful to consider properties of the distribution of parasites among hosts, e.g. mean and variance. Stochastic models that explore how processes such as heterogeneity in exposure, parasite clumping, parasite-induced host death and host acquired immunity, influence the distribution of a *single* parasite species among hosts are reasonably well understood (see Chapter 4 for a review of these models). However, there appear to be no models that examine the joint distribution of several interacting parasite species, despite evidence from experimental and field studies to support the existence of interspecific interactions (see Chapter 3), and the ubiquity of multispecies coinfection (Petney & Ross, 1998).

In the previous chapter, differential equations were employed to model changes in worm burden for two interacting helminth species within a single, ageing host. Here these equations will be used to define the transition rates of a bivariate Markov process. Realizations of this process mimic patterns of worm burden in individual hosts, and moments of the process, e.g. mean, variance and covariance, resemble the empirical moments for a large population of hosts.

The Markov process is used to examine the effects of different types of interaction on mean worm burden and aggregation for each parasite species, and the correlation between these species. The joint distribution arising from the Markov process is a function of age. Since ecological data on animal hosts are often not age-specific, the effects of combining measures of parasite aggregation and association across host age-classes are also explored.

Parameter	*Definition*	*Units*
λ_i	Rate at which host acquires species i larvae	larvae month^{-1}
σ_i	Maturation rate of species i larvae	month^{-1}
η_i	Per capita death rate of species i larvae	month^{-1}
μ_i	Per capita death rate of species i adults	month^{-1}
$e^{\gamma_{ij}}$	Factor by which each adult worm of species i ($i = 1, 2; j = 1, 2$) modifies species j larval mortality	no units

Table 6.1: Parameter definitions for model S.

6.2 Non-linear model (S)

Consider possible changes of state for a host of age a, with X_{1a} worms of species 1 and X_{2a} worms of species 2, during a small time period of length δ. By making δ arbitrarily small, the changes of state are limited to: 1) a worm of species i is acquired; 2) a worm of species i dies. The stochastic model is specified by the rates of transition from one state to another. Formally, a Markov model is assumed for the bivariate process $\{X_{ia}; a \geq 0\}$ with initial conditions $\mathrm{P}(X_i(0) = 0) = 1$. The transition rates for this process are based on model D of the previous chapter. Specifically, the possible transitions for species 1 and the corresponding rates are as follows,

$$(X_{1a}, X_{2a}) \rightarrow (X_{1a} + 1, X_{2a}) \text{ at rate } b_1(X_{1a}, X_{2a})$$

where $b_1(x_1, x_2) = \sigma_1\lambda_1/(\sigma_1 + \eta_1 e^{\gamma_{11}x_1 + \gamma_{21}x_2})$; and

$$(X_{1a}, X_{2a}) \rightarrow (X_{1a} - 1, X_{2a}) \text{ at rate } d_1(X_{1a}, X_{2a})$$

where $d_1(x_1, x_2) = \mu_1 x_1$.

Similar rates can be defined for species 2, i.e. for the transitions $(X_{1a}, X_{2a}) \rightarrow (X_{1a}, X_{2a} + 1)$ and $(X_{1a}, X_{2a}) \rightarrow (X_{1a}, X_{2a} - 1)$. This model will be referred to as model S (for stochastic). The parameter definitions are as for model D of the previous chapter, and are repeated here for convenience in Table 6.1.

Model S is analyzed by simulating species 1 and species 2 worm burdens in a number of ageing hosts using two properties of Markov processes. First, given that a host has x_1 species 1 worms and x_2 species 2 worms, the amount of time for which a host is in state (x_1, x_2) is determined by sampling from an exponential distribution

with rate $b_1 + b_2 + d_1 + d_2$ (note that the arguments of b_1, etc. have been dropped for notational convenience). Secondly, on leaving state (x_1, x_2), the host enters state (x_1+1, x_2) with probability $\frac{b_1}{b_1+b_2+d_1+d_2}$, state (x_1-1, x_2) with probability $\frac{d_1}{b_1+b_2+d_1+d_2}$, etc. This can be simulated by generating a uniform random number, U, in $[0, 1]$. If $U < \frac{b_1}{b_1+b_2+d_1+d_2}$, the host enters state $(x_1 + 1, x_2)$, if $\frac{b_1}{b_1+b_2+d_1+d_2} \leq U < \frac{b_1+d_1}{b_1+b_2+d_1+d_2}$ it enters $(x_1 - 1, x_2)$ and so on.

The non-linearity of the functions b_1 and b_2 makes analysis of model S difficult. A model, L, is therefore defined in the following section where the functions b_1 and b_2 are replaced by linear approximations.

6.3 Linear model (L)

Provided that $\gamma_{11}x_1 + \gamma_{21}x_2 \ll 1$ and $\gamma_{22}x_2 + \gamma_{12}x_1 \ll 1$, the functions $b_i(x_1, x_2)$ $(i = 1, 2)$ may be approximated by the first terms of Taylor series expansions (see Chapter 5). The resulting approximations are linearly dependent on x_1 and x_2,

$$\begin{aligned} b_1(x_1, x_2) &\approx \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}x_1 - \tilde{\gamma}_{21}x_2) \\ b_2(x_1, x_2) &\approx \tilde{\lambda}_2(1 - \tilde{\gamma}_{22}x_2 - \tilde{\gamma}_{12}x_1) \end{aligned} \tag{6.1}$$

where $\tilde{\lambda}_i = \lambda_i(\frac{\sigma_i}{\sigma_i+\eta_i})$, $\tilde{\gamma_{ji}} = \gamma_{ji}(\frac{\eta_i}{\sigma_i+\eta_i})$ $(i, j = 1, 2)$. These new 'composite' parameters can be thought of as follows: $\tilde{\lambda}_i$ represents the rate of parasite establishment of species i in the absence of adult worms, and $\tilde{\gamma}_{ji}$ $(i, j = 1, 2)$ represents the extent to which each adult worm of species j affects the rate of establishment of species i. The effect is homologous (intraspecific) for $j = i$ and heterologous (interspecific) for $j \neq i$.

Using this linearization, we define a linear stochastic model (L). In this model, the rates at which adult worms are acquired are given by the linearized form of $b_1(x_1, x_2)$ and $b_2(x_1, x_2)$ provided that these functions are non-negative. For those values of x_1 and x_2 where the functions are negative, the rates are set to zero. Again, let the random variables X_{ia} represent the numbers of worms of species i $(i = 1, 2)$ in a host of age a. Model L is a bivariate Markov process $\{X_{ia}; a \geq 0\}$ with initial condition $\mathrm{P}(X_{i0} = 0) = 1$ and transition rates:

$$\begin{aligned} (X_{1a}, X_{2a}) &\rightarrow (X_{1a} + 1, X_{2a}) \text{ at rate } \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}x_1 - \tilde{\gamma}_{21}x_2)^+ \\ (X_{1a}, X_{2a}) &\rightarrow (X_{1a} - 1, X_{2a}) \text{ at rate } \mu_1 X_{1a}. \end{aligned}$$

where the notation z^+ implies $z^+ = z$ if $z > 0$ and 0 otherwise. The rates for

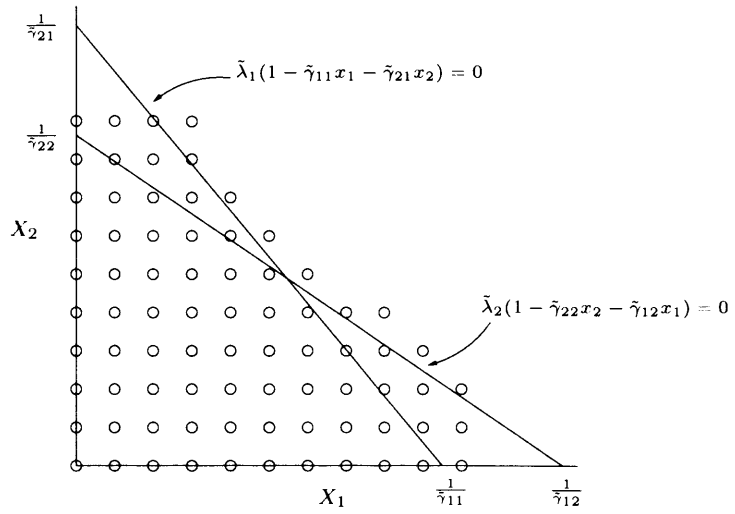


Figure 6.1: State space for model L; the circles represent the possible states. In the figure, $\gamma_{11} > \gamma_{21} > 0$ and $\gamma_{22} > \gamma_{12} > 0$, but similar diagrams may be constructed for different relationships between the intra- and interspecific interaction parameters.

species 2 transitions $(X_{1a}, X_{2a}) \rightarrow (X_{1a}, X_{2a}+1)$ and $(X_{1a}, X_{2a}) \rightarrow (X_{1a}, X_{2a}-1)$ are similarly defined.

The Markov process L has a finite state space illustrated in Fig.6.1. Furthermore all states inter-communicate (it is possible to reach any state from any other state in a finite number of transitions). Given these two properties, it follows that the process will approach an equilibrium distribution, as $a \rightarrow \infty$ (Cox & Miller, 1965, p.183).

Further analysis of L is undertaken by deriving a set of differential equations, whose solutions is used to approximate the first and second moments.

6.4 An approximation to first and second moments of model L

Assuming that $\mathrm{P}(\tilde{\gamma}_{ii}X_{ia} + \tilde{\gamma}_{ji}X_{ja} > 1) \ll 1$ for all a $(i = 1,2; j \neq i)$, a set of differential equations to approximate the first two moments of model L can be derived as follows:

After a small time period of length δ, the expected change in the number of worms of species 1, given X_{1a} and X_{2a} is

$$\mathrm{E}[X_{1a+\delta} - X_{1a} | X_{1a}, X_{2a}] = \tilde{b}_1(X_{1a}, X_{2a})\delta - d_1(X_{1a}, X_{2a})\delta + o(\delta).$$

The unconditional mean is obtained by taking the expected value of both sides,

$$\mathrm{E}[X_{1a+\delta} - X_{1a}] = \mathrm{E}[\tilde{b}_1(X_{1a}, X_{2a})\delta - d_1(X_{1a}, X_{2a})\delta + o(\delta)].$$

Dividing by δ and taking the limit $\delta \longrightarrow 0$ gives the differential equation

$$\begin{aligned}
\frac{d}{da}\mathrm{E}[X_{1a}] &= \mathrm{E}[\tilde{b}_1(X_{1a}, X_{2a}) - d_1(X_{1a}, X_{2a})] \\
&= \sum_{(x_1,x_2)} \Big(\tilde{b}_1(x_1, x_2) - d_1(x_1, x_2)\Big)\, p_a(x_1, x_2) \\
&= \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}\mathrm{E}[X_{1a}] - \tilde{\gamma}_{21}\mathrm{E}[X_{2a}]) - \mu_1\mathrm{E}[X_{1a}] - \Sigma_1
\end{aligned}$$

where $p_a(x_1, x_2) := P(X_{1a} = x_1, X_{2a} = x_2)$,

$$\Sigma_1 = \sum \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}x_1 - \tilde{\gamma}_{21}x_2)p_a(x_1, x_2),$$

and the summation for Σ_1 is over the set $\{(x_1, x_2) : \tilde{\gamma}_{11}x_1 + \tilde{\gamma}_{21}x_2 > 1\}$.

Similarly,

$$\frac{d}{da}\mathrm{E}[X_{2a}] = \tilde{\lambda}_2(1 - \tilde{\gamma}_{22}\mathrm{E}[X_{2a}] - \tilde{\gamma}_{12}\mathrm{E}[X_{1a}]) - \mu_2\mathrm{E}[X_{2a}] - \Sigma_2$$

where Σ_2 is equivalently defined. Therefore if $p_a(x_1, x_2)$ is negligible in the sets over which the summation in Σ_1 and Σ_2 takes place, then $\mathrm{E}[X_{1a}]$ and $\mathrm{E}[X_{2a}]$ can be approximated by the solution to the following pair of differential equations

$$\frac{d}{da}\mathrm{E}[X_{1a}] = \tilde{\lambda}_1(1 - \tilde{\gamma}_{11}\mathrm{E}[X_{1a}] - \tilde{\gamma}_{21}\mathrm{E}[X_{2a}]) - \mu_1\mathrm{E}[X_{1a}] \tag{6.2}$$

$$\frac{d}{da}\mathrm{E}[X_{2a}] = \tilde{\lambda}_2(1 - \tilde{\gamma}_{22}\mathrm{E}[X_{2a}] - \tilde{\gamma}_{12}\mathrm{E}[X_{1a}]) - \mu_2\mathrm{E}[X_{2a}]. \tag{6.3}$$

Under the same assumptions, and given $\mathrm{E}[X_{1a}]$ and $\mathrm{E}[X_{2a}]$, the derivatives of the second moments are approximated by the following set of differential equations

$$\begin{aligned}
\frac{d}{da}\mathrm{E}[X_{1a}^2] = {} & 2\tilde{\lambda}_1\left(\mathrm{E}[X_{1a}] - \tilde{\gamma}_{11}\mathrm{E}[X_{1a}^2] - \tilde{\gamma}_{21}\mathrm{E}[X_{1a}X_{2a}]\right) \\
& + 2\mu_1\left(\mathrm{E}[X_{1a}] - \mathrm{E}[X_{1a}^2]\right) + \frac{d\mathrm{E}[X_{1a}]}{da}
\end{aligned} \tag{6.4}$$

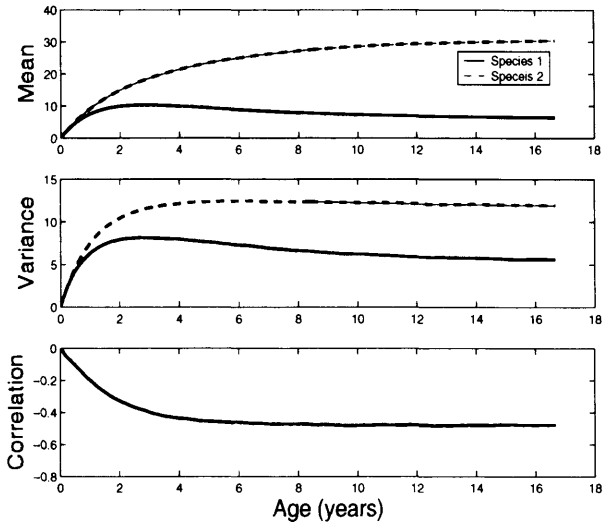


Figure 6.2: Means, variances and correlations obtained through simulation of model L (100,000 realizations), and using the set of differential equations that approximate the moments of L. Parameter values as in Fig.5.4B of Chapter 5.

$$\frac{d}{da}\mathrm{E}[X_{2a}^2] = 2\tilde{\lambda}_2\left(\mathrm{E}[X_{2a}] - \tilde{\gamma}_{22}\mathrm{E}[X_{2a}^2] - \tilde{\gamma}_{12}\mathrm{E}[X_{1a}X_{2a}]\right) + 2\mu_2\left(\mathrm{E}[X_{2a}] - \mathrm{E}[X_{2a}^2]\right) + \frac{d\mathrm{E}[X_{2a}]}{da} \tag{6.5}$$

$$\frac{d}{da}\mathrm{E}[X_{1a}X_{2a}] = \tilde{\lambda}_1\mathrm{E}[X_{2a}] - \tilde{\gamma}_{21}\tilde{\lambda}_1\mathrm{E}[X_{2a}^2] + \tilde{\lambda}_2\mathrm{E}[X_{1a}] - \tilde{\gamma}_{12}\tilde{\lambda}_2\mathrm{E}[X_{1a}^2] - (\beta_1 + \beta_2)\mathrm{E}[X_{1a}X_{2a}]. \tag{6.6}$$

where $\beta_i = \tilde{\lambda}_i\tilde{\gamma}_{ii} + \mu_i$ $i = 1, 2$.

The approximation is known to be good if $\mathrm{P}(\tilde{\gamma}_{ii}X_{ia} + \tilde{\gamma}_{ji}X_{ja} > 1) \ll 1$ $(i = 1, 2; j \neq i)$ for all host ages, a. Unfortunately, the parameter values under which this probability is small are unknown. However, to be consistent with a small probability, the equilibrium solution of Eqns 6.2-6.6 should satisfy $\tilde{\gamma}_{ii}\mathrm{E}[X_i]_e + \tilde{\gamma}_{ji}\mathrm{E}[X_j]_e < 1$ $(i = 1, 2; j \neq i)$ (e is used to denoted equilibrium value). In practice, it seems that the solution to Eqns 6.2-6.6 approximate the first two moments of model L well when this condition is met (Fig.6.2).

6.5 Properties of ODEs approximating model L

Existence and stability of the equilibrium Eqns 6.2-6.6 can be written in matrix form as

$$\frac{d}{da}\mathbf{x} = A\mathbf{x} + \mathbf{b} \tag{6.7}$$

where

$$\mathbf{x} = (\ \mathrm{E}[X_1], \mathrm{E}[X_2], \mathrm{E}[X_1^2], \mathrm{E}[X_2^2], \mathrm{E}[X_1X_2])\ )'$$
$$\mathbf{b} = (\ \tilde{\lambda}_1, \tilde{\lambda}_2, \tilde{\lambda}_1, \tilde{\lambda}_2, 0\ )'$$

$$A = \begin{pmatrix} -\beta_1 & -\tilde{\lambda}_1\tilde{\gamma}_{21} & 0 & 0 & 0 \\ -\tilde{\lambda}_2\tilde{\gamma}_{12} & -\beta_2 & 0 & 0 & 0 \\ 2(\tilde{\lambda}_1+\mu_1)-\beta_1 & -\tilde{\lambda}_1\tilde{\gamma}_{21} & -2\beta_1 & 0 & -2\tilde{\lambda}_1\tilde{\gamma}_{21} \\ -\tilde{\lambda}_2\tilde{\gamma}_{12} & 2(\tilde{\lambda}_2+\mu_2)-\beta_2 & 0 & -2\beta_2 & -2\tilde{\lambda}_2\tilde{\gamma}_{12} \\ \tilde{\lambda}_2 & \tilde{\lambda}_1 & -\tilde{\lambda}_2\tilde{\gamma}_{12} & -\tilde{\lambda}_1\tilde{\gamma}_{21} & -(\beta_1+\beta_2) \end{pmatrix}.$$

At equilibrium $\frac{d}{da}\mathbf{x} = 0$, and provided that $\mathrm{Det}A \neq 0$ there is a single solution to Eqn 6.7

$$\mathbf{x} = -A^{-1}\mathbf{b}. \tag{6.8}$$

$\mathrm{Det}A$ can be computed by expanding on the first row

$$\mathrm{Det}A = \beta_1\beta_2\mathrm{Det}C - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12}\mathrm{Det}C$$

where

$$C = \begin{pmatrix} -2\beta_1 & 0 & -2\tilde{\lambda}_1\tilde{\gamma}_{21} \\ 0 & -2\beta_2 & -2\tilde{\lambda}_2\tilde{\gamma}_{12} \\ -\tilde{\lambda}_2\tilde{\gamma}_{12} & -\tilde{\lambda}_1\tilde{\gamma}_{21} & -(\beta_1+\beta_2) \end{pmatrix}$$

and

$$\mathrm{Det}C = 4(\beta_1+\beta_2)(\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} - \beta_1\beta_2).$$

Therefore,

$$\mathrm{Det}A = -4(\beta_1+\beta_2)\left(\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}\right)^2.$$

Clearly $\mathrm{Det}A \neq 0$ provided that $\beta_1 + \beta_2 \neq 0$ and $(\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} - \beta_1\beta_2) \neq 0$. To

determine the stability of the equilibrium, it is necessary to compute the eigenvalues of A. The eigenvalues of A are the roots of the polynomial $\mathrm{Det}(A - xI)$ where I is the identity matrix.

$$\begin{aligned}\mathrm{Det}(A - xI) &= (\beta_1 + x)(\beta_2 + x)\mathrm{Det}(C - xI) - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}\mathrm{Det}(C - xI) \\ &= \mathrm{Det}(C - xI)\left((\beta_1 + x)(\beta_2 + x) - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21}\right)\end{aligned}$$

where $\mathrm{Det}(C - xI) = (\beta_1 + \beta_2 + x)\left(4\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} - (2\beta_1 + x)(2\beta_2 + x)\right)$.

The 5 eigenvalues of A are therefore:

$$-(\beta_1 + \beta_2) \quad \frac{-(\beta_1+\beta_2)\pm\tau}{2} \quad -(\beta_1 + \beta_2) \pm \tau$$

where $\tau = \sqrt{(\beta_1 - \beta_2)^2 + 4\tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12}}$.

The eigenvalues are all negative provided that

$$(\beta_1 + \beta_2) > 0 \text{ and } \beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} > 0. \tag{6.9}$$

Under these conditions, the ODE's 6.2-6.6 approach an equilibrium as $a \to \infty$. As has already been discussed, the Markov process defined by L approaches an equilibrium as $a \to \infty$. These conditions therefore provide a necessary but not sufficient condition for the ODE's 6.2-6.6 to reasonably approximate the first two moments of L.

Mean worm burden Eqn 6.2 and Eqn 6.3 are identical in form to the linear differential equations of Chapter 5 that describe change in worm burden in a single ageing host. Thus the dynamics of mean worm burden in the stochastic model L are approximately equivalent to the dynamics of worm burden in the linearized version of the deterministic model D. Specifically, solving Eqn 6.2 and Eqn 6.3 as in Chapter 5, mean worm burden as a function of host age is approximately given by

$$\mathrm{E}[X_{ia}] = \mathrm{E}[X_i]_e + \frac{\tilde{\lambda}_i}{\tau}\left(\frac{\alpha_1 + \beta_j - \tilde{\gamma}_{ji}\tilde{\lambda}_j}{\alpha_1}e^{\alpha_1 a} - \frac{\alpha_2 + \beta_j - \tilde{\gamma}_{ji}\tilde{\lambda}_j}{\alpha_2}e^{\alpha_2 a}\right) \tag{6.10}$$

where $i, j = 1, 2$ $i \neq j$, $\alpha_{1,2} = \frac{1}{2}\left(-(\beta_1 + \beta_2) \pm \tau\right)$ and $\mathrm{E}[X_i]_e = \frac{\tilde{\lambda}_i(\beta_j - \tilde{\gamma}_{ji}\tilde{\lambda}_j)}{\beta_i\beta_j - \tilde{\lambda}_i\tilde{\lambda}_j\tilde{\gamma}_{ij}\tilde{\gamma}_{ji}}$ is the mean species i worm burden at equilibrium.

At equilibrium (where $\beta_1 + \beta_2 > 0$ and $\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{12}\tilde{\gamma}_{21} > 0$), the mean worm burdens, $\mathrm{E}[X_i]_e$, are nonnegative if, and only if,

$$(\beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2) > 0 \text{ and } (\beta_1 - \tilde{\gamma}_{12}\tilde{\lambda}_1) > 0. \tag{6.11}$$

Worm burden cannot be negative in model L. Thus Eqn 6.11 should hold for a reasonable approximation. Provided $\mu_1, \mu_2 > 0$, both the conditions in Eqn 6.9 and Eqn 6.11 are satisfied when

$$\gamma_{11} \geq |\gamma_{12}| \text{ and } \gamma_{22} \geq |\gamma_{21}|. \tag{6.12}$$

Hence Eqn 6.12 is a sufficient condition for the approximation of the first two moments (Eqns 6.2-6.6) to approach a stable equilibrium where mean worm burden is positive for both species. In the subsequent analysis of the approximate equilibrium covariance and index of dispersion, it will be assumed that Eqn 6.12 holds.

Equilibrium covariance At equilibrium Eqns 6.2-6.6 reduce to

$$0 = \tilde{\lambda}_1(\mathrm{E}[X_1]_e - \tilde{\gamma}_{11}\mathrm{E}[X_1^2]_e - \tilde{\gamma}_{21}\mathrm{E}[X_1X_2]_e) - \mu_1\mathrm{E}[X_1^2]_e + \mu_1\mathrm{E}[X_1]_e \tag{6.13}$$

$$0 = \tilde{\lambda}_2(\mathrm{E}[X_2]_e - \tilde{\gamma}_{22}\mathrm{E}[X_2^2]_e - \tilde{\gamma}_{12}\mathrm{E}[X_1X_2]_e) - \mu_2\mathrm{E}[X_2^2]_e + \mu_2\mathrm{E}[X_2]_e \tag{6.14}$$

$$0 = \tilde{\lambda}_1\mathrm{E}[X_2]_e + \tilde{\lambda}_2\mathrm{E}[X_1]_e - \tilde{\lambda}_1\tilde{\gamma}_{21}\mathrm{E}[X_2^2]_e - \tilde{\lambda}_2\tilde{\gamma}_{12}\mathrm{E}[X_1^2]_e - (\beta_1+\beta_2)\mathrm{E}[X_1X_2]_e \tag{6.15}$$

where $\mathrm{E}[\ .\ ]_e$ denotes expectation at equilibrium.

From Eqn 6.13 and Eqn 6.14, $\mathrm{E}[X_j^2]_e = \frac{1}{\beta_j}(\tilde{\lambda}_j\mathrm{E}[X_j]_e - \tilde{\lambda}_j\tilde{\gamma}_{ij}\mathrm{E}[X_1X_2]_e + \mu_j\mathrm{E}[X_j]_e)$. Substituting into Eqn 6.15,

$$\mathrm{E}[X_1X_2]_e\sum_{\mathcal{A}}\beta_i - \frac{\tilde{\lambda}_i\tilde{\lambda}_j\tilde{\gamma}_{ij}\tilde{\gamma}_{ji}}{\beta_j} = \sum_{\mathcal{A}}\tilde{\lambda}_i\mathrm{E}[X_j]_e - \frac{\tilde{\lambda}_i\tilde{\gamma}_{ji}}{\beta_j}(\tilde{\lambda}_j\mathrm{E}[X_j]_e + \mu_j\mathrm{E}[X_j]_e). \tag{6.16}$$

where $\mathcal{A}= \{(i,j) : i,j = 1,2\ j \neq i\}$. Multiplying both sides by $\beta_1\beta_2$,

$$\begin{aligned}&\mathrm{E}[X_1X_2]_e(\beta_1+\beta_2)(\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12})\\ &= \sum_{\mathcal{A}}\mathrm{E}[X_j]_e\left(\beta_1\beta_2\tilde{\lambda}_i - \beta_i\tilde{\lambda}_i\tilde{\gamma}_{ji}(\tilde{\lambda}_j+\mu_j)\right).\end{aligned} \tag{6.17}$$

Therefore,

$$\mathrm{E}[X_1X_2]_e = K\sum_{\mathcal{A}}\beta_i(\beta_i - \tilde{\gamma}_{ij}\tilde{\lambda}_i)(\beta_j - \tilde{\gamma}_{ji}(\tilde{\lambda}_j+\mu_j)) \tag{6.18}$$

where

$$K = \frac{\tilde{\lambda}_1\tilde{\lambda}_2}{(\beta_1+\beta_2)(\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12})^2}.$$

Subtracting $\mathrm{E}[X_1]_e\mathrm{E}[X_2]_e$ from Eqn 6.18 gives the covariance between X_1 and X_2 at equilibrium,

$$\begin{aligned}\mathrm{Cov}(X_1,X_2)_e &= K\sum_{\mathcal{A}}\beta_i(\beta_i - \tilde{\gamma}_{ij}\tilde{\lambda}_i)(\beta_j - \tilde{\gamma}_{ji}(\tilde{\lambda}_j+\mu_j))\\ &- K(\beta_1+\beta_2)(\beta_1 - \tilde{\gamma}_{12}\tilde{\lambda}_1)(\beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)\end{aligned}$$

which simplifies to

$$\mathrm{Cov}(X_1, X_2)_e = -K\left(\beta_1\tilde{\gamma}_{21}\mu_2(\beta_1 - \tilde{\gamma}_{12}\tilde{\lambda}_1) + \beta_2\tilde{\gamma}_{12}\mu_1(\beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)\right). \tag{6.19}$$

It is apparent from Eqn 6.19 that the covariance between the two species is negative if $\tilde{\gamma}_{21}$ and $\tilde{\gamma}_{12}$ are both positive, and positive if they are both negative (given that Eqn 6.12 holds). Thus mutually antagonistic interactions yield a negative correlation between worm burdens at equilibrium whereas mutually synergistic interactions give a positive equilibrium correlation.

Equilibrium index of dispersion Aggregation is a key feature of virtually all parasitic helminth distributions. Here, and subsequently, the example of Isham (1995), Fulford *et al.* (1992) and others will be followed and the variance : mean ratio (VMR) will be used as a quantitative measure of aggregation (aggregation $\Rightarrow$VMR > 1). When the variance is greater than the mean, the distribution is said to be overdispersed relative to the Poisson distribution; when it is less than the mean it is underdispersed. Mathematical models have been used to investigate the effects of various processes on the VMR, e.g. parasite-induced host mortality (Herbert and Isham, 2000); clumping of infective stages (Isham, 1995); heterogeneity in host susceptibility (Tallis and Leyton, 1969), and host immunity (Anderson and Gordon, 1982; Pacala and Dobson, 1988). However, to date, it appears that the impact of interspecific interactions on dispersion has not been examined. In fact it is an implicit assumption of most ecological models of competition between helminth species that interspecific interactions have no effect on the level of aggregation (Dobson, 1985; Roberts and Dobson, 1995; Gatto and De Leo, 1998).

Using the properties of the equilibrium covariance given above, it will be shown here that both mutually antagonistic and mutually synergistic interactions increase the equilibrium VMR relative to the case where there are no interspecific interactions.

From Eqn 6.4, the equilibrium VMR of species 1 can be written as

$$\frac{\mathrm{Var}[X_1]_e}{\mathrm{E}[X_1]_e} = \frac{1}{\beta_1}\left((\tilde{\lambda}_1 + \mu_1) - \tilde{\lambda}_1\tilde{\gamma}_{21}\frac{\mathrm{E}[X_1X_2]_e}{\mathrm{E}[X_1]_e}\right) - \mathrm{E}[X_1]_e. \tag{6.20}$$

In the absence of interaction, Eqn 6.20 simplifies to $\frac{\mu_1}{\beta_1}$. Therefore an interspecific interaction will increase the VMR if the following condition is met

$$\frac{1}{\beta_1}\left((\tilde{\lambda}_1 + \mu_1) - \tilde{\lambda}_1\tilde{\gamma}_{21}\frac{\mathrm{E}[X_1X_2]_e}{\mathrm{E}[X_1]_e}\right) - \mathrm{E}[X_1]_e > \frac{\mu_1}{\beta_1}. \tag{6.21}$$

This condition may be re-expressed as

$$\mathrm{E}[X_1]_e(\lambda_1 - \beta_1\mathrm{E}[X_1]_e - \lambda_1\gamma_{21}\mathrm{E}[X_2]_e) > \lambda_1\gamma_{21}\mathrm{Cov}[X_1, X_2]_e.$$

At equilibrium $d\mathrm{E}[X_1]/da = 0$, hence from Eqn 6.2, it can be seen that $\lambda_1 - \beta_1\mathrm{E}[X_1]_e - \lambda_1\gamma_{21}\mathrm{E}[X_2]_e = 0$. Interspecific interactions therefore increase VMR if

$$\gamma_{21}\mathrm{Cov}[X_1, X_2]_e < 0. \tag{6.22}$$

This condition is satisfied when the interspecific interaction is mutually antagonistic or mutually synergistic.

Now a condition for overdispersion in species 1 is derived. The equilibrium VMR for species 1 is greater than 1 if $\mathrm{Var}[X_1]_e > \mathrm{E}[X_1]_e$. This can be written in terms of the equilibrium values of the first two moments

$$\frac{1}{\beta_1}(\tilde{\lambda}_1\mathrm{E}[X_1]_e - \tilde{\lambda}_1\tilde{\gamma}_{21}\mathrm{E}[X_1X_2]_e + \mu_1\mathrm{E}[X_1]_e) - (\mathrm{E}[X_1]_e)^2 > \mathrm{E}[X_1]_e,$$

or, in terms of $\mathrm{Cov}[X_1, X_2]_e$,

$$\mathrm{E}[X_1]_e(\tilde{\lambda}_1 + \mu_1 - \beta_1 - \beta_1\mathrm{E}[X_1]_e - \tilde{\lambda}_1\tilde{\gamma}_{21}\mathrm{E}[X_2]_e) > \tilde{\lambda}_1\tilde{\gamma}_{21}\mathrm{Cov}[X_1X_2]_e. \tag{6.23}$$

Since $\tilde{\lambda}_1 - \beta_1\mathrm{E}[X_1]_e - \tilde{\lambda}_1\tilde{\gamma}_{21}\mathrm{E}[X_2]_e = 0$ at equilibrium, Eqn 6.23 becomes

$$\tilde{\gamma}_{21}\mathrm{Cov}[X_1, X_2]_e + \tilde{\gamma_{11}}\mathrm{E}[X_1]_e < 0. \tag{6.24}$$

Substituting in the equilibrium values for $\mathrm{E}[X_1]_e$ and $\mathrm{Cov}[X_1, X_2]_e$ gives the following condition

$$\begin{aligned}\tilde{\lambda_1}\Big\{&\tilde{\gamma}_{11}(\beta_2 - \tilde{\lambda_2}\tilde{\gamma_{21}})(\beta_1 + \beta_2)(\beta_1\beta_2 - \tilde{\lambda}_1\tilde{\lambda}_2\tilde{\gamma}_{21}\tilde{\gamma}_{12}) \\ &- \tilde{\lambda}_2\tilde{\gamma}_{21}\left(\beta_1\tilde{\gamma}_{21}\mu_2(\beta_1 - \tilde{\gamma}_{12}\tilde{\lambda}_1) + \beta_2\tilde{\gamma}_{12}\mu_1(\beta_2 - \tilde{\gamma}_{21}\tilde{\lambda}_2)\right)\Big\} < 0.\end{aligned} \tag{6.25}$$

It is immediately apparent that Eqn 6.25 is *not* satisfied when $\tilde{\gamma}_{12} < 0$ and $\tilde{\gamma}_{21} < 0$. Thus the equilibrium variance : mean ratio is *not* greater than unity for mutually synergistic interspecific interactions. By contrast the distribution may be overdispersed when the interspecific terms are positive. This can be seen, for example, by setting $\tilde{\gamma}_{11} = 0$, which implies $\tilde{\gamma}_{12} = 0$ since it is assumed that $\tilde{\gamma}_{11} \geq |\tilde{\gamma}_{12}|$.

However, it seems that equilibrium overdispersion is not possible when the inter-

specific effect acting on a species is smaller than the intraspecific effect ($0 \leq \tilde{\gamma}_{21} \leq \tilde{\gamma}_{11}$). This is demonstrated for the symmetric case (parameters for the two species are identical). Under these assumptions, Eqn 6.25 can be written as

$$\tilde{\gamma}_{11}(\beta_1^2 - \tilde{\lambda}_1^2\tilde{\gamma}_{21}^2) - \lambda_1\tilde{\gamma}_{21}^2\mu_1 < 0. \tag{6.26}$$

Eqn 6.26 does not hold when $0 \leq \tilde{\gamma}_{21} \leq \tilde{\gamma}_{11}$. Thus VMR ≤ 1 for symmetric mutually antagonistic interactions when $\tilde{\gamma}_{21} \leq \tilde{\gamma}_{11}$.

6.6 Simulation results for model S

The effects of interspecific interactions on dispersion and correlation have been investigated for model L for regions of parameter space where intraspecific terms are antagonistic and larger in magnitude than the interspecific terms, i.e where $\gamma_{ii} > |\gamma_{ij}|$ $(i, j = 1, 2; i \neq j)$. Here results from the simulation of model S are presented. These simulations examine regions of parameter space that were not explored in model L. In particular, model S is used to investigate the effect on dispersion and correlation of synergistic intraspecific terms ($\gamma_{ii} < 0$) $(i = 1, 2)$, and interspecific terms that are larger in magnitude than the intraspecific terms ($|\gamma_{ij}| > |\gamma_{ii}|$ $(i, j = 1, 2; i \neq j)$). Simulations of model S also cover part of the parameter space explored in model L; the results are consistent with those obtained for model L in these regions (see Table 6.2 and Fig.6.3).

The conclusions drawn from the linear model regarding equilibrium correlation and VMR were only dependent on the signs and relative magnitudes of the intra- and interspecific effects. It is therefore expected that the qualitative behaviour of equilibrium correlation and VMRs of model S are governed by the signs and relative magnitudes of the intra- and interspecific effects. Nonetheless parameter values are used for the simulations that are consistent with the life-cycles of a number of human and non-human helminth species; some examples are given in Table 6.3. For simplicity it is assumed that all parameters (demographic and interaction) are the same for both species.

A helminth life-expectancy, μ_i, of 20 months and a maturation time, σ_i, of 1 month are chosen. The larval life-expectancy in the absence of immunity, η_i, is taken to be 1 month. This implies that 50% of larvae become established as adult worms ($\frac{\sigma_i}{\sigma_i+\eta_i} = 0.5$) which is consistent with establishment in some experiments (Leathwick *et al.* 1999). The level of exposure ($\lambda_i = 5$ larvae per month) was chosen to give worm burdens in the region of 0-100 (Hall and Holland, 2000). The γ's range between 0 and 0.1, implying that each adult worm increases or decreases the death

Case	*Interaction Parameters* Intra-specific	Inter-specific	Relative magnitude	*Description*
a		$\gamma_{ji} > 0$	$\gamma_{ji} \leq \gamma_{ii}$	Intra- and interspecific interactions antagonistic, and intraspecific effects equal or larger than interspecific effects.
b		$\gamma_{ji} < 0$	$\lvert\gamma_{ji}\rvert \leq \gamma_{ii}$	Intraspecific interactions antagonistic, interspecific interactio Intraspecific effects equal or larger in magnitude than intersp
	$\gamma_{ii} > 0$			
c		$\gamma_{ji} > 0$	$\gamma_{ji} \gg \gamma_{ii}$	Intra- and interspecific interactions antagonistic, and interspecific effects much greater in magnitude than intraspe
d		$\gamma_{ji} < 0$	$\lvert\gamma_{ji}\rvert \gg \gamma_{ii}$	Intraspecific interactions antagonistic, interspecific interactio Interspecific effects much greater in magnitude than intraspe
e		$\gamma_{ji} > 0$	$\gamma_{ji} \leq \lvert\gamma_{ii}\rvert$	Intraspecific interaction synergistic, interspecific interactions Intraspecific effects equal or larger than interspecific effects.
f		$\gamma_{ji} < 0$	$\lvert\gamma_{ji}\rvert \leq \lvert\gamma_{ii}\rvert$	Intra- and interspecific interactions synergistic, and intraspecific effects equal or larger in magnitude than intersp
	$\gamma_{ii} < 0$			
g		$\gamma_{ji} > 0$	$\gamma_{ji} \gg \lvert\gamma_{ii}\rvert$	Intraspecific interactions synergistic, interspecific interaction Interspecific effects much greater in magnitude than intraspe
h		$\gamma_{ji} < 0$	$\lvert\gamma_{ji}\rvert \gg \lvert\gamma_{ii}\rvert$	Intra- and interspecific interactions synergistic, and interspecific effects much greater in magnitude than intraspe

Table 6.2: Equilibrium index of dispersion (variance to mean ratio, VMR) for each helminth spec between species at equilibrium for stochastic model S. Correlations that approach zero at equ negative at younger ages are denoted by ≈ 0(+ve) and ≈ 0(-ve) respectively. Results are based o are identical for both species.

Parasite species	*Life expectancy (years)*	*Length of maturation (days)*
Ascaris lumbricoides	$1-2$[1]	$50-80$[1]
Trichuris trichiura	$1-2$[1]	$50-84$[1]
Schistosoma japonicum	2[2]	$25-30$[1]
Haemonchus contortus	>2[3]	$21-25$[4]

Table 6.3: Some examples of helminth demographic parameter values. [1] Tables 15.2 and 15.3 of Anderson and May (1991), [2] Table 5.1 of Esch and Fernandez (1993), [3] Gems (2000).

rate of incoming larvae by an amount between 0 and 10%.

The findings are summarized in Table 6.2. For the simulations undertaken, equilibrium was reached after about 5 years (or roughly two parasite life-times). In general, it can be seen that the magnitude of the interspecific terms (γ_{ji}) *relative* to the size of the intraspecific terms (γ_{ii}) and the signs of intra- and interspecific terms are critical in determining the equilibrium index of dispersion and the sign of the equilibrium correlation.

Dispersion From the analysis of the linear model, it was shown that the equilibrium distribution is not overdispersed when the interspecific effect acting on a species is *smaller* in magnitude than the intraspecific effect. In contrast, from the simulation of model S, overdispersion can occur if the relative magnitudes of the inter- and intraspecific terms are reversed so that interspecific terms are positive and *larger* in magnitude than the intraspecific terms. This is true both when $\gamma_{ii} > 0$ (Fig.6.3A) and when $\gamma_{ii} < 0$ (Fig.6.4A).

For the situation in which interspecific effects are much larger than intraspecific effects ($\gamma_{ji} \gg |\gamma_{ii}|$), each species has a bimodal equilibrium distribution in which hosts have either no (or very few) worms or very many (Fig.6.5). The joint distribution of the two species reveals that under these conditions those hosts with no (or very few) worms of one species tend to have a large number of worms of the other species. The bimodal marginal distribution of each species can be interpreted in light of this: hosts tend to have either a high or a very low worm burden of one species at equilibrium, depending on the abundance of the *other* species.

Such distributions are likely to be rare since both interspecific terms must be

much larger than the intraspecific terms. Nonetheless, occasionally such distributions have been identified and interspecific interaction suggested as an explanation. For example, Kennedy (1975) tentatively explains the observation that *Haematoloechus* sp. and *Rhabdias bufonis* seldom occur together in lungs of frogs in this way. A more plausible scenario for the generation of aggregation by interspecific interaction is that one species, species 1 say, has both a large interspecific effect as well as intraspecific effect, while the species it interacts with, species 2, has smaller intra- and interspecific effects. If the difference is sufficiently large then species 1 will cause the equilibrium distribution of species 2 to be overdispersed.

When interactions are mutually synergistic they have less impact on dispersion than they do when they are mutually antagonistic. From Fig.6.3A and Fig.6.4A, it appears that the index of dispersion is bounded by one, no matter how large a mutually synergistic interaction becomes and irrespective of whether each species regulates ($\gamma_{ii} > 0$) or enhances ($\gamma_{ii} < 0$) itself.

Correlation In keeping with the results of the linearized model, in all age classes mutually antagonistic interspecific terms yield negative correlations (cases (a) and (c) in Table 6.2), and mutually synergistic interspecific interactions yield positive correlations (Fig.6.3B). However, for mutually synergistic interactions that are large in magnitude relative to the intraspecific terms ($\gamma_{ji} < 0, |\gamma_{ji}| \gg \gamma_{ii} > 0$) the correlation peaks in the younger age classes, and then approaches zero at equilibrium.

Although this is an interesting result, it seems unlikely that a helminth species would operate to decrease its own rate of establishment ($\gamma_{ii} > 0$) whilst facilitating the establishment of the larvae of another species ($\gamma_{ji} < 0$). It is more plausible that a helminth species facilitates the establishment of larvae of its own species and as a *byproduct* also enhances the establishment of another species. This situation ($\gamma_{ii} < 0$) is explored in Fig.6.4B where it is apparent that the equilibrium correlation is close to zero for both small and large mutually synergistic interactions. Interestingly, the equilibrium correlation is also close to zero for small mutually antagonistic interactions ($0 < \gamma_{ji} < |\gamma_{ii}|$).

These results suggest that inspection of the equilibrium correlation is not a good predictor for the existence of an interaction between helminth species when adult worms of each species facilitate the establishment of their own species. Furthermore, even when intraspecific interactions are antagonistic, the equilibrium correlation may still be zero for a mutually synergistic interaction if the interspecific terms are greater in magnitude than the intraspecific terms.

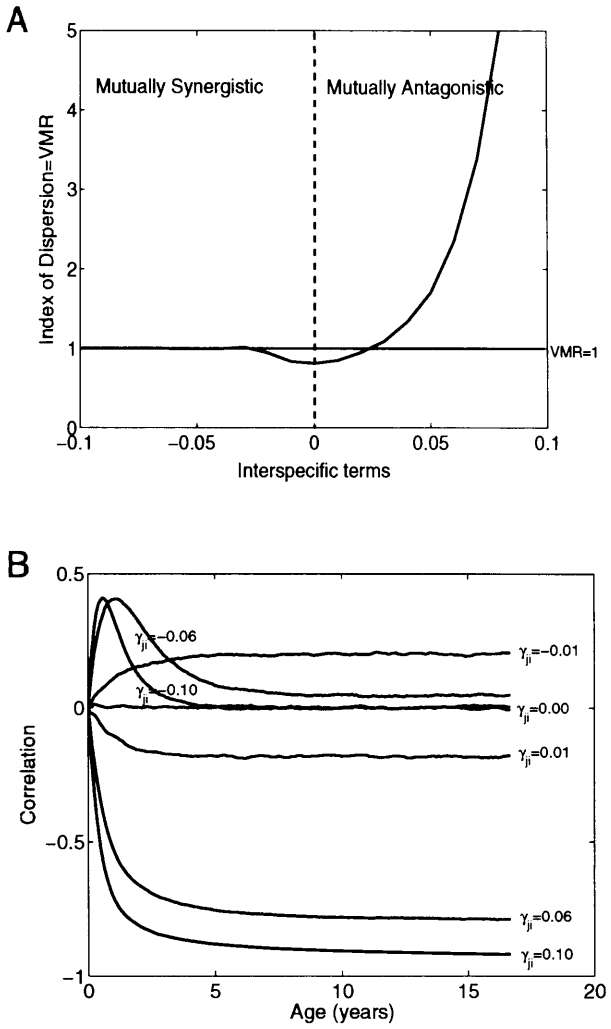


Figure 6.3: Equilibrium dispersion index, and correlation as a function of host age from 100,000 realizations of model S, when the intraspecific terms are antagonistic ($\gamma_{ii} > 0$ $i = 1, 2$). A) Equilibrium dispersion index (VMR) for different strengths of interspecific interaction (γ_{ji}). B) Correlation between species 1 and 2 as a function of host age. Parameter values are: $\lambda_i = 5$ month^{-1}, $\sigma_i = 1$ month^{-1}, $\mu_i = 0.05$ month^{-1}, $\eta_i = 1$ month^{-1}, $\gamma_{ii} = 0.01$ $i = 1, 2$.

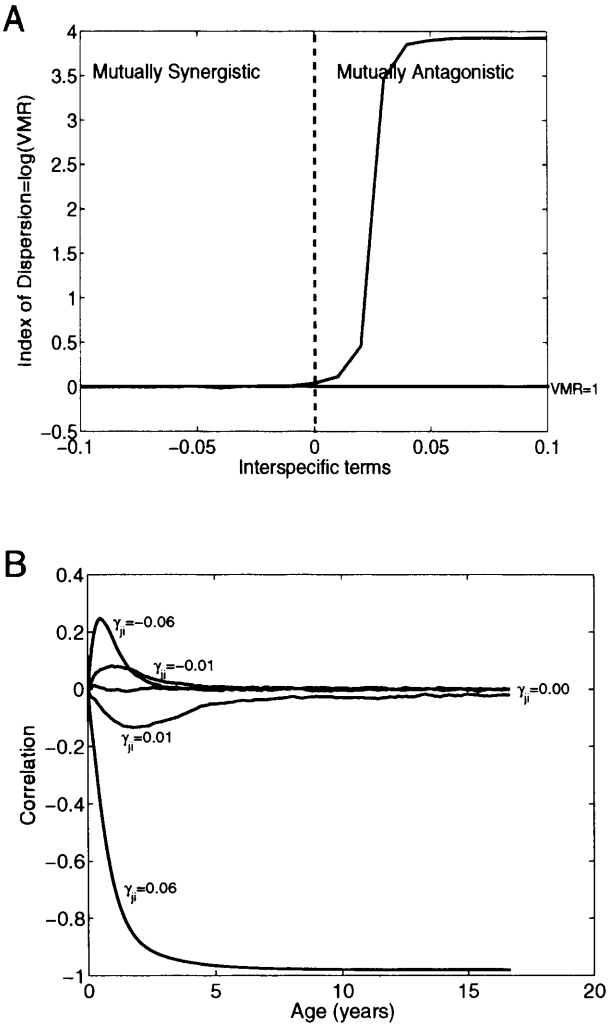


Figure 6.4: Equilibrium dispersion index, and correlation as a function of host age from 100,000 realizations of model S, when the intraspecific effects are synergistic ($\gamma_{ii} < 0$ $i = 1, 2$). A) Equilibrium dispersion index=log(VMR) for varying γ_{ji}. B) Correlation between the worm burdens of species 1 and 2 as a function of host age. Parameter values: $\gamma_{ii} = -0.05$ $i = 1, 2$, others as in Fig.6.3.

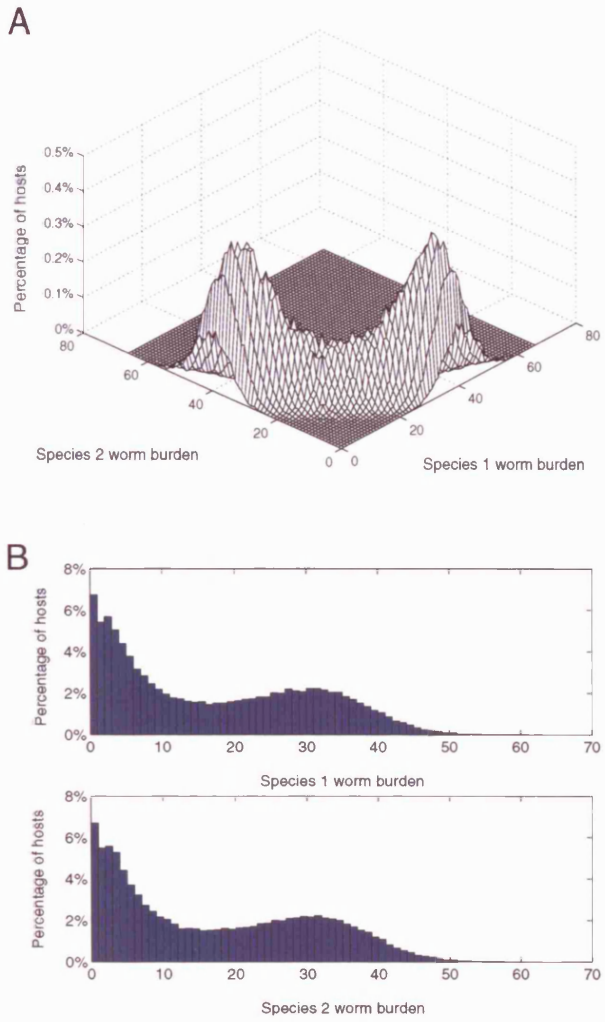


Figure 6.5: The A) joint equilibrium distribution, and B) single species distributions of species 1 and species 2 worm burdens (100,000 realizations of model S) for a mutually antagonistic interaction in which the interspecific effects are much stronger than the antagonistic intraspecific effects ($\gamma_{ji} \gg \gamma_{ii} > 0$). Hosts tend to have a large worm burden for one species and a very small or zero worm burden for the other species. Parameter values: $\lambda_i = 5$ month^{-1}, $\sigma_i = \eta_i = 1$ month^{-1}, $\mu_i = 0.05$ month^{-1}, $\gamma_{ii} = 0.01$, $\gamma_{ji} = 0.1$, $i = 1, 2$; $j \neq i$.

6.7 Incorporating heterogeneity (model S_{RE})

Model S can be modified by treating the rates of exposure as a pair of correlated random variables (Λ_1, Λ_2); this model will be referred to as S_{RE} (where RE stands for random exposure). This adds biological realism because: 1) there is heterogeneity among hosts in their exposures/susceptibility to the infective stages which can be modelled by the variability of Λ_1 and Λ_2; 2) pairs of helminth species with similar biologies often share similar routes of transmission implying a positive correlation between the rates of exposure (e.g., soil-transmitted helminths such as *Ascaris* and *Trichuris*); and 3) susceptibility to one species may be linked with susceptibility to many species through, for example, genetic predisposition (Quinnell, 2003). Although Λ_1, Λ_2 will be referred to as 'exposure' random variables, they may incorporate heterogeneity and correlation due to susceptibility because, for the purposes of this model, exposure and susceptibility are essentially indistinguishable.

The random exposure model, S_{RE}, is analyzed by simulation. For each realization, the rates of exposure (λ_1, λ_2) are sampled from a bivariate normal distribution, truncated so that $\lambda_1 > 0, \lambda_2 > 0$. The bivariate normal distribution is used because it provides a straightforward way of introducing correlation between the exposure rates (one of the parameters of the bivariate normal is the correlation coefficient); while truncation is necessary to ensure non-negative exposure rates. The normal distribution is parameterized to have mean vector (ζ_1, ζ_2) and covariance matrix

$$\begin{pmatrix} \nu_1^2 & \rho\nu_1\nu_2 \\ \rho\nu_1\nu_2 & \nu_2^2 \end{pmatrix}$$

where ν_i^2 $(i = 1, 2)$ is the variance in exposure for species i and ρ is the correlation between exposures for the two worm species. In practice, the truncation is achieved by sampling from the full bivariate normal distribution and excluding samples where either $\lambda_1 < 0$ or $\lambda_2 < 0$. Results will be presented from simulations where $\zeta_i = 5, \nu_i = 2, \rho = 0.5$; $i = 1, 2$. The means, standard deviations and correlation for Λ_1 and Λ_2 can be computed by numerical integration. For the parameter values used, they are $5.049, 1.949$ and 0.485 respectively.

Dispersion The effects of both mutually antagonistic and synergistic interspecific interactions on the equilibrium index of dispersion differ qualitatively in models S (homogeneous exposure) and S_{RE} (random exposure). For mutually antagonistic interactions, the equilibrium VMR in model S_{RE} is crucially dependent on the size of the interaction. When the interspecific interaction is small $(0 < \gamma_{ji} \ll \gamma_{ii})$, the equilibrium VMR is smaller than it would be in the absence of interaction,

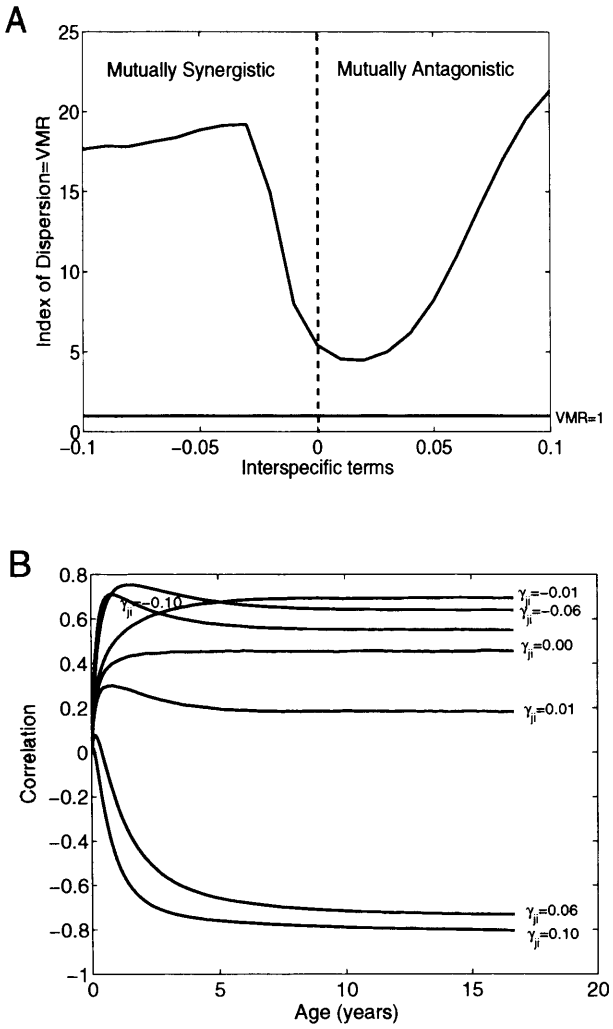


Figure 6.6: Index of dispersion at equilibrium and correlation as a function of host age from 100,000 realizations of model S_{RE}, where exposure to species 1 (Λ_1) and exposure to species 2 (Λ_2) are positively correlated random variables. A) Equilibrium dispersion index (VMR) for varying γ_{ji}. B) Correlation between the worm burdens of species 1 and 2 as a function of host age. The distribution of (Λ_1, Λ_2) has parameter values: $\zeta_i = 5, \nu_i = 2, \rho = 0.5$; $i = 1, 2$. All other parameters are as in Fig.6.3.

while for large mutually antagonistic interspecific interactions ($\gamma_{ji} \gg \gamma_{ii} > 0$), it is substantially greater (Fig.6.6A). This is in marked contrast to the results of model S described earlier, where mutually antagonistic interactions increase the equilibrium index of dispersion (as compared with the no interaction case) irrespective of their magnitude (Fig.6.3A).

This is of interest because it demonstrates that while it is often useful to explore different factors independently and assume that they combine linearly to determine the degree of aggregation (Anderson and Gordon, 1982), on occasion factors may combine in a non-linear way. A similar phenomenon has been shown to occur with parasite-induced host mortality (Herbert and Isham, 2000): when there is heterogeneity in host exposure/susceptibility, parasite-induced host mortality will reduce the VMR, but in the absence of this heterogeneity it has no effect.

In the homogeneous exposure model, S, mutually synergistic interactions increase the equilibrium index of dispersion when, in the absence of interaction, the distribution is underdispersed, but appear not to be able to induce overdispersion. However, in the random exposure model, S_{RE}, mutually synergistic interactions can greatly increase the extent to which equilibrium worm burdens are overdispersed.

Correlation If exposures to the two helminth species are positively correlated, worm burdens will also tend to be positively correlated. In Fig.6.6B it can be seen that for small mutually antagonistic interactions the correlation between exposures dominates and the equilibrium worm burdens are positively correlated, but when the interactions are large the correlation between exposures is countered by the strong interaction and the equilibrium correlation becomes negative.

6.8 Averaging across age classes

The results for the models presented have assumed knowledge of host age. That is to say, they describe the joint distribution of the two worm species for a given age. In contrast, in field studies of non-human parasites, host age is usually not determined explicitly, although surrogate measures are sometimes used (Morris, 1972; Lello *et al.*, 2004). When age is ignored, the distribution that is sampled and described is averaged across all age groups in the population. Here, the effect that this has on the index of dispersion and correlation will be discussed.

Consider model S in the absence of inter- and intraspecific effects. The worm burdens X_{1a} and X_{2a} for the two species at age a are then independent Poisson variables with means

$$\frac{\tilde{\lambda}_i}{\mu_i}(1 - e^{-\mu_i a}) \qquad i = 1, 2. \tag{6.27}$$

The mean worm burden across all ages can be computed by weighting the mean worm burden at age a by the probability of a host being in age class $(a, a + \delta)$ and summing over all age classes. For simplicity it is assumed that the distribution of ages in the host population is exponential with parameter μ_H; then the mean worm burden of species i in the population of hosts is

$$\frac{\tilde{\lambda}_i}{\mu_i + \mu_H}. \tag{6.28}$$

The variance in species i worm burden for the population of hosts is the sum of two components: the average variance within age classes and the variance of the mean between age classes. Specifically it is

$$\frac{\tilde{\lambda}_i}{\mu_i + \mu_H} + \frac{\tilde{\lambda}_i^2 \mu_H}{(2\mu_i + \mu_H)(\mu_i + \mu_H)^2} \tag{6.29}$$

where the first term corresponds to the 'within' component and the second to the 'between' component. From Eqn 6.28 and Eqn 6.29 it is apparent that the VMR is greater than unity. The covariance between the two species can similarly be decomposed into the weighted sum of the average covariance within age classes and the covariance of the mean worm burdens between age classes. For a given host age, the worm burdens of species 1 and species 2 are independent, thus within age classes the covariance is zero; between age classes it is given by

$$\frac{\tilde{\lambda}_1 \tilde{\lambda}_2 \mu_H}{(\mu_1 + \mu_2 + \mu_H)(\mu_1 + \mu_H)(\mu_2 + \mu_H)}. \tag{6.30}$$

The worm species will therefore be positively correlated when the host population is not stratified by age even in the absence of interaction. Furthermore, this positive correlation can be large. For example, using the parameter values of Fig.6.3 ($\tilde{\lambda}_i = 2.5$ month^{-1}, $\mu_i = 1/20$ month^{-1}; $i = 1, 2$) and setting $\mu_H = 1/48$ month^{-1}, gives a correlation of 0.86 (from Eqn 6.29 and Eqn 6.30).

6.9 Inferring interspecific interaction from ecological data

In the absence of extraneous factors, the correlations at equilibrium between species associated with different types of interaction are in agreement with intuition. Mu-

tually antagonistic interactions yield negative correlations; mutually synergistic interactions yield positive correlations, and when there is a mixed interaction (one interspecific term positive, the other negative) then the correlation can be positive or negative. Therefore if the correlation at equilibrium between two species is negative this implies that at least one of the interspecific terms is positive (antagonistic), and conversely if it is positive then one term must be negative (synergistic). This intuition has been used to identify potential interactions between species from matrices of correlations for data on intensity of infection (Hayward, Perera and Rohde, 1998; Byrne *et al.* 2003) or contingency tables for presence/absence data (Kuris and Lafferty, 1994; Jackson *et al.* 1998). Here some of the difficulties of inferring the existence of interactions will be discussed in light of the current models.

In the section on *Averaging Across Age Classes* it is shown that in the absence of interaction and correlation between exposures, the species will be positively correlated if correlation is measured in the population of hosts as a whole, i.e. across all age classes. Indeed this correlation may be very strong. Intuitively, the reason for this is that young hosts tend to have fewer worms of both species than older hosts. Unfortunately, many studies of helminth communities in non-human hosts are not age-specific. It is therefore not surprising that in many of these studies there are an excess of positive associations between species (Bush and Holmes, 1986b; Lotz and Font, 1994; Hayward *et al.* 1998). Recently, a number of studies have controlled for the effects of age statistically by fitting regression models that include age and then examining the correlation between species in the residuals from these models (Pion *et al.*, 2006; Behnke *et al.*, 2005; Faulkner *et al.*, 2005; Tchuem Tchuenté *et al.*, 2003). It is interesting that an analogous situation has been addressed in the context of immunity to a single parasite species. Here sampling across age groups similarly leads to positive associations between antibodies such as IgG and IgA and worm burden. This suggests that antibody-mediated immunity is ineffective at reducing worm burdens. However, these positive correlations are weakened or reversed after controlling for age (Woolhouse, 1992a).

An important feature of strong synergistic intra- and interspecific effects is that they frequently lead to an equilibrium correlation between species that approaches zero at large ages. Beyond a certain degree of strength, mutually synergistic interactions produce a zero equilibrium correlation between the two species. In general, this is not true of mutually antagonistic interactions. However, if intraspecific terms act synergistically there may also be zero correlation at large ages if the mutually antagonistic interaction between species is sufficiently weak relative to the synergistic intraspecific terms.

These effects occur because the rate at which worms become established has un upper bound. If either intra- or interspecific effects are sufficiently synergistic so that the worm burden for each species and thus the rates of establishment are maintained at an 'upper limit', then the rate of establishment for each species is effectively independent of worm numbers producing a zero correlation between species. This phenomenon will make it difficult to detect interactions in older age groups. In ecological studies, it is therefore important to sample the young hosts. Mutually synergistic interactions, for example, will be manifest in younger age classes as a positive correlation between species even though the correlation may disappear in older age classes.

The identification of interspecific interactions is complicated by heterogeneity in host exposure (or susceptibility) if there is correlation between the exposure rates for the two species as in model S_{RE} (Kuris and Lafferty, 1994). This heterogeneity may be due to: 1) differences between hosts due to factors such as host sex (Behnke *et al.* 2005; Wilson *et al.* 2002), host genetics (Quinnell, 2003) and host behaviour (Wong, Bundy and Golden, 1988); 2) the spatial distribution of infective stages; 3) the distribution of infective stages amongst any intermediate hosts. To a certain extent, these complexities can be eliminated; either by controlling statistically for the effect of area, sex, etc. (Haukisalmi and Henttonen, 1998; Behnke *et al.* 2005), or by sampling appropriately. On other occasions, stratification alone will not deal with the problem, as in the case when two helminth species share an intermediate host. In this situation, it might be worthwhile exploring how correlation changes with host age. Model S_{RE} suggests that there is often a decline in correlation in older age groups for a mutually antagonistic interaction; such a decline does not occur when there is no interaction.

The models analyzed in this chapter have been restricted to two interacting species. In reality, many species of parasite may occupy a single host. Under these circumstances, the interpretation of correlations between species becomes even more complicated because interspecific interactions can cause associations between species that do not interact (Moore and Simberloff, 1990; Haukisalmi and Henttonen, 1998). For example, a mutually antagonistic interaction between species 1 and species 2; and between species 2 and species 3 will result in a positive correlation between species 1 and species 3 in the absence of any interaction between these latter species. Species 2 is in effect a 'confounding factor' of the relationship between species 1 and species 3. One way of dealing with this is to use partial correlations (Kleinbaum *et al.* 1998); this provides the correlation between species 1 and species 3 having controlled for species 2. Such an approach has been used by Thomas (1964) to

explore associations between helminth species in brown trout. However, it assumes that the joint distribution of the numbers of each parasite species is multivariate normal, which may often not be a reasonable assumption to make.

6.10 Summary

A non-linear stochastic model, S, of worm burden for two interacting species in a cohort of ageing hosts is defined; the model is based on the deterministic single host model of Chapter 5. An analytically tractable linear model, L, and an extension of S that incorporates heterogeneous exposure, model S_{RE}, are also defined. These three models are used to explore changes in the joint distribution of worm burden for the two species that occur within an ageing cohort of hosts. In particular, mean worm burden, variance : mean ratio (VMR) and correlation between worm burdens are examined.

In Chapter 5 it was shown that interspecific interactions often lead to convex age intensity profiles of worm burden in individual hosts. Since the dynamics of mean worm burden in model L approximate the dynamics of worm burden in the linearized version of the deterministic model D, convex age-intensity patterns can also be expected in data on mean worm burden when helminth species interact.

The Markov processes defined in model L approaches an equilibrium distribution. Simulation suggests that models S and S_{RE} also approach equilibrium distributions for the range of parameter values examined. The equilibrium distributions are used to approximate the distribution of worm burden in older hosts. Both the VMR and the correlation between species are explored at equilibrium.

The VMR is used as a measure of aggregation. At equilibrium, the marginal distribution of worm burden for a species becomes increasingly aggregated (VMR> 1) when the interspecific effect acting on the species exceeds the intraspecific effect.

In the absence of correlated exposures, the sign of the correlation between species at equilibrium is in agreement with intuition: mutually synergistic (antagonistic) interactions lead to positive (negative) correlations. However, strong synergistic inter- or intraspecific effects can result in correlations that tend to zero at large ages, suggesting that synergistic interactions are hard to detect in older age groups. Correlation between the rates of exposure (model S_{RE}) to the two species translates into correlation between worm burdens, and may therefore mask the effect of interspecific interactions on correlation.

It is often not possible to identify host age when collecting data on worm burden of non-human hosts. Averaging correlation across age groups, as is done implicitly

when there is no stratification by host age, can lead to strong positive correlations between species.

Chapter 7

Single Species Models of Helminth Population Dynamics

7.1 Introduction

To model the long-term dynamics of helminth populations, it is necessary to allow the size of the larval population to depend on the number of adult worms in the host population. This creates a feed-back loop, that makes the analysis of stochastic models difficult. One method of simplification involves incorporating deterministic elements into stochastic models (Nåsell & Hirsch, 1972; Nåsell, 1985). These 'hybrid' models can be viewed as approximations to fully stochastic models (see Chapter 4).

Here the techniques developed by Nåsell & Hirsch (1972) and Nåsell (1985) will be used to examine the effect of heterogenous rates of host exposure on the dynamics of mean worm burden. Host heterogeneity has previously only crudely been incorporated in deterministic models, by assuming that hosts fall into a fixed number of exposure classes (usually two) (Anderson & May, 1985b; Pugliese, 2000; Rosà & Pugliese, 2002). The stochastic models used here allow host exposure to vary continuously. Furthermore, the models will form the basis of the models used in the following chapter to explore competition between helminth species.

7.2 A model for density-dependent establishment

The following is a description of a fully stochastic model for a single, directly-transmitted, helminth parasite species in a population of n hosts. In this model, the population of larvae with the potential to infect hosts is of size L, and there are X_i adult worms within host i, where L and X_i are random variables. Infective larvae are produced by the population of adult worms at a rate, $\epsilon \sum_{i=1}^{n} X_i$. Thus the

parameter ϵ represents the product of the rate of egg production and the probability that an egg develops into a larva with the potential to infect a host. Larvae are lost from the larval population either through larval death, at a per capita rate μ_L, or through host infection and subsequent maturation to the adult stage. Host i comes into contact with infective larvae at a rate, $\Phi_i L$, therefore larvae are lost through infection at rate $\sum_{i=1}^{n} \Phi_i L$. It is assumed that density dependence acts on the rate at which worms become established in a host, so that a larva infecting host i survives to become established as an adult worm with probability $(1 - \gamma X_i)^+$. Thus the current worm burden, X_i, of host i affects the establishment of incoming larvae, and the parameter γ measures the severity of density-dependent establishment. The notation z^+ is introduced because $(1 - \gamma X_i)$ can become negative if $\frac{1}{\gamma}$ is not an integer; it should be interpreted as $z^+ = z$ if $z > 0$ and $z^+ = 0$ otherwise. The number of adult worms in host i decreases by one when a worm dies and becomes zero when the host dies. The per capita rate at which worms and hosts die are, respectively, μ_X and α. It is assumed that the rate of host death, α, is independent of worm burden and that each time a host dies it is immediately replaced by an uninfected host. One might imagine, for example, a host population limited by the number of available territories: as soon as a territory becomes available it is filled by a young, uninfected host. This assumption ensures that the host population size is maintained at size n.

The model is defined in terms of the following $n+1$ dimensional Markov process for larval population in the environment, and adult worm burdens within each of the hosts. Parameter definitions are given in Table 7.1.

1. $L \rightarrow L + 1$ at rate $\epsilon \sum_{i=1}^{n} X_i$
2. $L \rightarrow L - 1$ at rate $(\mu_L + \sum_{i=1}^{n} \Phi_i) L$
3. $X_i \rightarrow X_i + 1$ at rate $L\Phi_i(1 - \gamma X_i)^+$
4. $X_i \rightarrow X_i - 1$ at rate $\mu_X X_i$
5. $X_i \rightarrow 0$ at rate α.

To begin with it is assumed that each host has the same per larva rate of contact, ϕ, with the population of infective larvae so that $\Phi_i = \phi$ for all i. To facilitate analysis, the random variable L is replaced by its mean, m_L, in the third transition rate defined above. The model is no longer fully stochastic; such 'hybrid models' of helminth infection have been proposed by Nåsell & Hirsch (1972) and Nåsell (1985). As a result of this simplification, and assuming that $X_i(0)$ are independent and identically distributed (i.i.d.), then $X_i(t)$ are i.i.d. for all t.

Parameter	*Definition*	*Units*
Φ_i	per infective larva rate of parasite exposure for host i	month^{-1}
γ	per worm reduction in probability of establishment	dimensionless
μ_X	per capita death rate of adult worms	month^{-1}
μ_L	per capita death rate of larvae	month^{-1}
α	per capita death rate of hosts	month^{-1}
ϵ	per worm infective larva production rate	month^{-1}

Table 7.1: Parameter definitions for the single species model with density-dependent establishment

7.3 Homogeneous exposure

When exposure is constant, it is straightforward to derive differential equations for the mean larval population size $m_L(t)$, mean host worm burden, $m_X(t)$, and the variance in worm burden, $\sigma_X^2(t)$; the derivations follow.

Let host i ($i = 1, ..., n$) have a worm burden $X_i(t)$ at time t, and a rate ϕ of contact with infective larvae. Let $L(t)$ be the size of the larval population at time t. Then given $(L(t), X_i(t))$, the expected change in the number of infective larvae over a small time interval of length δ is

$$\mathrm{E}[L(t+\delta) - L(t)|L(t), X_i(t)] = \epsilon \sum_i^n X_i \delta - (\mu_L + n\phi)L(t)\delta. \tag{7.1}$$

to first order in δ.

Taking the expectation with respect to $(L(t), X(t))$ (the subscript i has been dropped since the $X_i(t)$ are i.i.d. random variables), dividing through by δ and taking the limit as $\delta \to 0$ gives

$$\frac{dm_L}{dt} = n\epsilon m_X - (\mu_L + \phi n)m_L. \tag{7.2}$$

Recall that m_L has been substituted for L in the rate for the $X \to X + 1$ transition, then applying the above procedure to X_t gives the following expression

$$\frac{dm_X}{dt} = m_L\phi(1 - \gamma m_X) - (\mu_X + \alpha)m_X. \tag{7.3}$$

Strictly speaking, $\frac{1}{\gamma}$ must be an integer for Eqn 7.3 to hold. This is because $(1 - \gamma X)$ might otherwise be negative. However, Eqn 7.3 appears to work well as an approximation, even when $\frac{1}{\gamma}$ is not integer-valued.

It can also be shown that the variance, σ_X^2, satisfies

$$\frac{d\sigma_X^2}{dt} = m_L\phi\left\{1-\gamma(2\sigma_X^2+m_X)\right\}+\mu_X m_X+\alpha m_X^2-(2\mu_X+\alpha)\sigma_X^2. \tag{7.4}$$

Technically, m_X and σ_X^2 represent limiting values of the mean and variance as the host population size tends to infinity. In practice, they describe the dynamics in finite populations well, provided that these are of a reasonable size (in Chapter 8, n=100 hosts are successfully used in simulations). The quantity $m_L(t)$ is the average larval population size at time t ignoring stochastic noise. Imagining infinitely many realizations of the same process, i.e. infinitely many identical populations, $m_L(t)$, is the average larval population over all these realizations. Alternatively, when the distribution of larval population size is at equilibrium, m_L may be viewed as the long-term average larval population size.

Dynamics of mean worm burden Assuming that larval dynamics occur on a faster time-scale than those of adult worms so that $(\mu_L + n\phi) \gg (\mu_X + \alpha)$, and consequently setting $\frac{dm_L}{dt} = 0$ (for a formal justification of this procedure based on Korzuhin's theorem, see Klonowski, 1983), the dynamics of the mean worm burden can be expressed in terms of the following differential equation

$$\frac{dm_X}{dt} = \epsilon' m_X(1-\gamma m_X)-(\mu_X+\alpha)m_X \tag{7.5}$$

where $\epsilon' = \frac{\epsilon\phi n}{\mu_L+\phi n}$ is the product of the rate, ϵ, at which an adult worm produces transmission stages and the probability, $\frac{\phi n}{\mu_L+\phi n}$, with which a larva survives to infect a host.

Eqn 7.5 can be understood in terms of the basic reproductive number, $R_0 = \frac{\epsilon'}{(\mu_X+\alpha)}$. When $R_0 < 1$ the helminth species is unable to establish itself in the host population since the fixed point $m_X = 0$ is stable. When $R_0 > 1$, $m_X = 0$ is unstable and mean worm burden increases approaching an equilibrium where $m_X = \frac{1}{\gamma}(1-R_0^{-1})$.

Since the model is stochastic, there is a significant chance of extinction soon after parasites are introduced into the host population. For the purposes of the analysis given above, parasite 'establishment' refers to the tendency of the mean worm burden to increase from a zero value. Taking this approach, even if extinction occurs after one particular introduction, future introductions will eventually lead to the establishment of a parasite population when $R_0 > 1$.

Overdispersion At the non-zero equilibrium, $\frac{\sigma_X^2}{m_X}$, the variance : mean ratio of worm burden satisfies

$$\frac{\sigma_X^2}{m_X} = \frac{2\mu_X + \alpha + \frac{\alpha}{\gamma}(1 - \frac{\mu_X + \alpha}{\epsilon'})}{2\epsilon' - \alpha}. \tag{7.6}$$

When $\alpha = 0$ (which approximates the case where host death rate is much smaller than all other rates), the variance : mean ratio simplifies substantially to R_0^{-1}. Hence, if $R_0 > 1$ then $\frac{\sigma_X^2}{m_X} < 1$ which implies that, for this simple model, worm burden is distributed more evenly across hosts than if worms were assigned to hosts at random (which would lead to a Poisson distribution). However, empirical data show that the distribution of worm burden is almost always aggregated (Anderson & May, 1985a; Shaw *et al.*, 1998) so that worm burden is *less* evenly distributed amongst hosts than in the Poisson distribution; realistic models must therefore incorporate mechanisms for generating aggregation (Anderson & Gordon, 1982). One such mechanism is heterogeneity in host exposure, and a model incorporating heterogeneity in host exposure is developed in the next section.

7.4 Heterogenous exposure

It is well established that heterogeneous exposure is significant to the population dynamics of helminth infection. In host-parasite systems in which there is parasite-induced host death, heterogeneity has either indirectly (Anderson & May, 1978) or directly (Rosà & Pugliese, 2002) been shown to stabilize the equilibrium at which both host and parasite coexist. The stabilizing effect of heterogeneity contrasts with the destabilizing effects of parasite-induced reduction in host fecundity, and time delays introduced as a consequence of the maturation process in larval stages (May & Anderson, 1978).

Heterogeneity is incorporated into deterministic models either through the level of aggregation in worm burden (as measured by the parameter k in the negative binomial distribution) (Anderson & May, 1978; May & Anderson, 1978), or explicitly by assuming that hosts fall into different categories (usually just two) of susceptibility to infection (Anderson & May, 1985b; Pugliese, 2000; Rosà & Pugliese, 2002). We now extend the stochastic model described in the previous section to allow for heterogeneity in host exposure. It is mathematically convenient to do this by allowing each host to have a random rate of contact with infective larvae, Φ_i, where the Φ_i $i = 1, .., n$ are independent and identically distributed (i.i.d.) each with mean m_Φ and variance σ_Φ^2. A set of differential equations describing the dynamics of the mo-

ments of the process can be derived, as was done for the case of constant exposure. However, in order to do so, it is necessary to use several additional approximations. The derivations of the differential equations, and the approximations used are now described.

Given $(L(t), X_i(t), \Phi_i)$, the expected change in the number of infective larvae during a small interval of time of length δ is

$$\mathrm{E}[L(t+\delta) - L(t)|L(t), X_i(t), \Phi_i] = \epsilon \sum_i^n X_i \delta - (\mu_L + \sum_i^n \Phi_i) L(t) \delta. \tag{7.7}$$

to first order in δ.

To deal with the dependence between Φ and L, $\sum_i^n \Phi_i$ is approximated by $m_\Phi n$. It is then straightforward to obtain a differential equation for m_L, by dividing by δ and taking the limit as $\delta \to 0$

$$\frac{dm_L}{dt} = n\epsilon m_X - (\mu_L + m_\Phi n) m_L. \tag{7.8}$$

With random Φ, the equation for m_X is

$$\frac{dm_X}{dt} = m_L(m_\Phi - \gamma \mathrm{E}[\Phi X]) - (\mu_X + \alpha) m_X. \tag{7.9}$$

Thus $\mathrm{E}[\Phi X]$ must be determined. The differential equation for $\mathrm{E}[\Phi X]$ is a function of $\mathrm{E}[\Phi^2 X]$:

$$\frac{d\mathrm{E}[\Phi X]}{dt} = m_L(\mathrm{E}[\Phi^2] - \gamma \mathrm{E}[\Phi^2 X]) - (\mu_X + \alpha) m_X. \tag{7.10}$$

In general, to determine $\mathrm{E}[\Phi^n X]$, $\mathrm{E}[\Phi^{n+1} X]$ must be known leading to an infinite set of differential equations. However, the system of differential equations can be closed by expressing $\mathrm{E}[\Phi^2 X]$ in terms of lower moments. One way to do this is based on the bivariate normal distribution, in which case, $\mathrm{E}[\Phi^2 X] = 2\mathrm{E}[\Phi]\mathrm{E}[\Phi X] + \mathrm{E}[\Phi^2]\mathrm{E}[X] - 2\mathrm{E}[\Phi]^2\mathrm{E}[X]$. In terms of the covariance, $\sigma_{\Phi X}$, Eqn 7.9 and Eqn 7.10 become

$$\frac{dm_X}{dt} = m_L(m_\Phi - \gamma(\sigma_{\Phi X} + m_\Phi m_X)) - (\mu_X + \alpha) m_X \tag{7.11}$$

$$\frac{d\sigma_{\Phi X}}{dt} = m_L(\sigma_\Phi^2 - \gamma(\sigma_{\Phi X} m_\Phi + \sigma_\Phi^2 m_X)) - (\mu_X + \alpha)\sigma_{\Phi X}. \tag{7.12}$$

An expression for the variance in worm burden can be derived along the same lines. The second moment of worm burden satisfies the following differential equa-

tion

$$\frac{d\mathrm{E}[X^2]}{dt} = m_L\left\{2\mathrm{E}[\Phi X] - 2\gamma\mathrm{E}[\Phi X^2] + m_\Phi - \gamma\mathrm{E}[\Phi X]\right\} + \mu_X m_X - (2\mu_X + \alpha)\mathrm{E}[X^2].$$

Using the bivariate normal moment closure approximation

$$\mathrm{E}[\Phi X^2] = 2\mathrm{E}[X]\mathrm{E}[\Phi X] + \mathrm{E}[X^2]\mathrm{E}[\Phi] - 2\mathrm{E}[X]^2\mathrm{E}[\Phi]$$

and writing the above equation in terms of variances and covariances gives

$$\begin{aligned}\frac{d\sigma_X^2}{dt} &= m_L\left\{2\sigma_{\Phi X} + m_\Phi - \gamma(2\sigma_{\Phi X}m_X + 2\sigma_X^2 m_\Phi + \sigma_{\Phi X} + m_\Phi m_X)\right\} \\ &+ \mu_X m_X + \alpha m_X^2 - (2\mu_X + \alpha)\sigma_X^2. \end{aligned} \tag{7.13}$$

For the approximation to be effective, it is sufficient that the relationships between higher and lower order moments are similar to those of the bivariate normal distribution; it is not necessary for the joint distribution of $(\Phi, X(t))$ to be bivariate normal. Indeed, since Φ and $X(t)$ are non-negative, their exact distribution cannot be bivariate normal, although it may be a good approximation if their means are sufficiently large relative to their standard deviations.

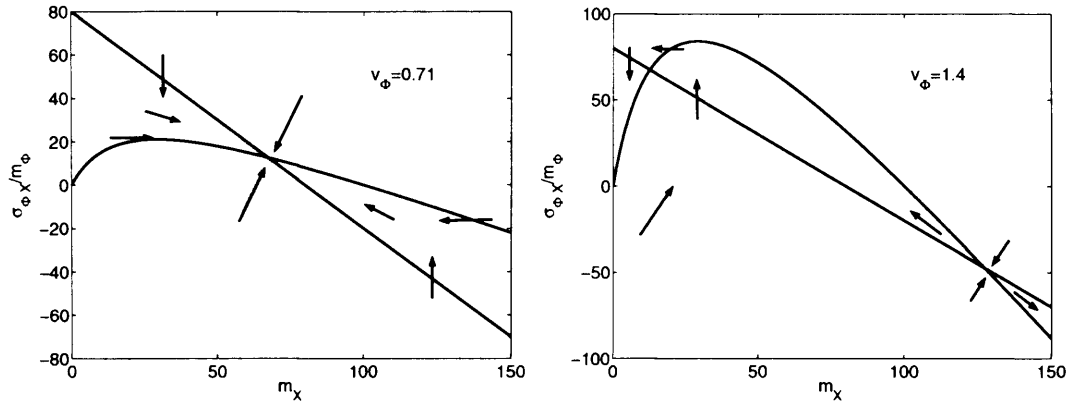
A greater degree of accuracy may be obtained by basing approximations on other joint distributions (Chan & Isham, 1998), or using higher moments. However, at this stage we restrict ourselves to the first two moments and use the bivariate normal moment closure to demonstrate analytically tractable results.

Dynamics of mean worm burden By setting $\frac{dm_L}{dt} = 0$, and making the change of variables $\tau = \epsilon' t$ and $\tilde{\sigma}_{\Phi X} = m_\Phi^{-1}\sigma_{\Phi X}$, Eqn 7.11 and Eqn 7.12 can be written as

$$\begin{aligned}\frac{dm_X}{d\tau} &= m_X(1 - \gamma(\tilde{\sigma}_{\Phi X} + m_X)) - R_0^{-1}m_X \\ \frac{d\tilde{\sigma}_{\Phi X}}{d\tau} &= m_X(v_\Phi^2 - \gamma(\tilde{\sigma}_{\Phi X} + v_\Phi^2 m_X)) - R_0^{-1}\tilde{\sigma}_{\Phi X} \end{aligned} \tag{7.14}$$

where $v_\Phi = \frac{\sigma_\Phi}{m_\Phi}$ is the coefficient of variation for the rate of exposure.

Again the dynamics are determined by the value of R_0. When $R_0 < 1$ the helminth species cannot establish itself in the host population, while when $R_0 > 1$ it tends to a non-zero equilibrium distribution. From Eqn 7.14 it can be seen that there are in fact two nonzero fixed points, however, only one of these is stable; this



(a) (b)

Figure 7.1: Phase portraits of mean worm burden, m_X, and the covariance between exposure and worm burden, $\sigma_{\Phi X}$, scaled by mean exposure, m_Φ. One of two scenarios is possible, depending on the level of heterogeneity in host exposure as measured by v_Φ. In a) $v_\Phi < 1$ and m_X is nonnegative at the single fixed point. In b) $v_\Phi > 1$ and m_X is positive at both fixed points, but only one of the fixed points is stable. The two scenarios are illustrated using parameter values $R_0 = 5$ and $\gamma = 0.01$ per worm.

is demonstrated in the phase plane analysis of Fig.7.1. At the stable non-zero fixed point,

$$m_X = \begin{cases} \frac{1}{2\gamma(v_\Phi^2-1)}\left(v_\Phi^2 - 1 + 2R_0^{-1} - \sqrt{(v_\Phi^2-1)^2 + 4v_\Phi^2 R_0^{-2}}\right) & v_\Phi \neq 1 \\ \frac{1}{2\gamma}(1 - R_0^{-1}) & v_\Phi = 1. \end{cases} \tag{7.15}$$

Thus, it can be seen that the equilibrium mean worm burden is dependent on the strength of density-dependence, γ, the degree of heterogeneity, v_Φ, and the basic reproductive number, R_0. This result is analogous to that of the deterministic models where mean worm burden is a function of γ, R_0 and the level of aggregation in the distribution of worm burden as measured by the overdispersion parameter, k, of the negative binomial distribution (Anderson & May, 1985a; Churcher *et al.*, 2005).

The equilibrium mean worm burden decreases as heterogeneity in exposure, σ_Φ, increases. A maximum mean worm burden of $m_X = \frac{1}{\gamma}(1 - R_0^{-1})$ is reached at $\sigma_\Phi = 0$; mean worm burden approaches zero as $\sigma_\Phi \to \infty$. Intuitively this can be explained as follows. With increasing heterogeneity there are more individuals with very high and very low rates of exposure. However, since no host can harbour more than $\frac{1}{\gamma}$ adult worms, those individuals with very high rates of exposure do not have correspondingly high worm burdens. On the other hand, hosts with rates of

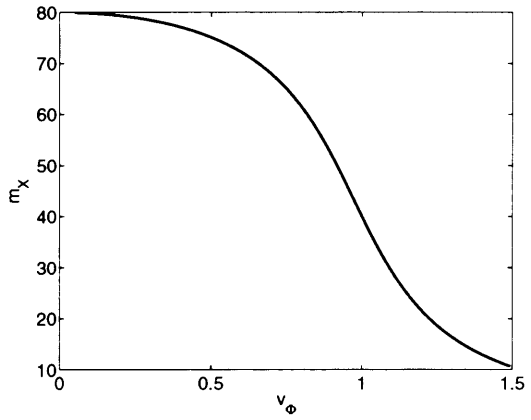


Figure 7.2: Mean worm burden at equilibrium as a function of heterogeneity in host exposure, $v_\Phi = \frac{\sigma_\Phi}{m_\Phi}$. Other parameters: $R_0 = 5, \gamma = 0.01$ per worm

exposure close to zero will have very low worm burdens. Thus mean worm burden decreases as heterogeneity increases (Fig.7.2).

The negative relationship between heterogeneity and mean worm burden can be demonstrated formally by showing that m_X is a decreasing function of v_Φ at the stable equilibrium. Differentiating m_X at the stable equilibrium with respect to v_Φ gives

$$\frac{dm_X}{dv_\Phi} = \frac{2v_\Phi}{2\gamma(v_\Phi^2-1)^2}\left(\sqrt{A} - (v_\Phi^2-1)\frac{v_\Phi^2 - 1 + 2R_0^{-2}}{\sqrt{A}} - 2R_0^{-1}\right)$$

where $A = (v_\Phi^2-1)^2 + 4v_\Phi^2 R_0^{-2}$.

Furthermore, it can be seen from the following that $\frac{dm_X}{dv_\Phi} < 0$ on $[0,\infty)$ when $R_0 > 1$:

$$\begin{aligned}
& & \frac{dm_X}{dv_\Phi} &< 0 \\
\Leftrightarrow & & \sqrt{A} - (v_\Phi^2-1)\tfrac{v_\Phi^2-1+2R_0^{-2}}{\sqrt{A}} - 2R_0^{-1} &< 0 \\
\Leftrightarrow & A - (v_\Phi^2-1)(v_\Phi^2-1+2R_0^{-2}) - 2R_0^{-1}\sqrt{A} &< 0 \\
\Leftrightarrow & 2v_\Phi^2 R_0^{-1} - (v_\Phi^2-1)R_0^{-1} - \sqrt{A} &< 0 \\
\Leftrightarrow & (v_\Phi^2+1)^2 R_0^{-2} &< (v_\Phi^2-1)^2 + 4v_\Phi^2 R_0^{-2} \\
\Leftrightarrow & R_0 &> 1.
\end{aligned}$$

Overdispersion As in other models (Pacala & Dobson, 1988; Isham, 1995), the variance : mean ratio, $\frac{\sigma_X^2}{m_X}$, can be shown to be an increasing function of the heterogeneity in host exposure. For heterogeneous exposure, the equilibrium variance to mean ratio is

$$\frac{\sigma_X^2}{m_X} = \frac{\epsilon'\tilde{\sigma}_{\Phi X}(2 - 2\gamma m_X - \gamma) + \epsilon'(1 - \gamma m_X) + \mu_X + \alpha m_X}{2\mu_X + \alpha + 2\gamma\epsilon' m_X}. \tag{7.16}$$

Recall that at the non-zero equilibrium $\tilde{\sigma}_{\Phi X} = \frac{1}{\gamma}(1 - R_0^{-1}) - m_X$. Therefore in terms of m_X, Eqn 7.16 becomes

$$\begin{aligned}\frac{\sigma_X^2}{m_X} &= \frac{\epsilon'\left(\frac{1}{\gamma}(1 - R_0^{-1}) - m_X\right)(2 - 2\gamma m_X - \gamma) + \epsilon'(1 - \gamma m_X) + \mu_X + \alpha m_X}{2\mu_X + \alpha + 2\gamma\epsilon' m_X} \\ &= \frac{2\epsilon'\gamma m_X^2 + (2\mu_X + 3\alpha - 4\epsilon')m_X + \frac{\epsilon'}{\gamma}(1 - R_0^{-1})(2 - \gamma) + \epsilon' + \mu_X}{2\mu_X + \alpha + 2\gamma\epsilon' m_X}. \end{aligned} \tag{7.17}$$

The numerator of Eqn 7.17 is a convex quadratic in m_X with a minimum at $L = \frac{4\epsilon' - 2\mu_X - 3\alpha}{4\gamma\epsilon'}$. Let $\hat{m}_X = \frac{1}{\gamma}(1 - R_0^{-1})$ be the maximum possible value of m_X (attained when there is no heterogeneity in exposure). The numerator is positive at $\hat{m}_X$, and is a decreasing function of m_X on the interval $(0, \hat{m}_X)$, since $L > \hat{m}_X$. Hence the numerator is a positive, decreasing function on $(0, \hat{m}_X)$. The denominator is clearly a positive increasing function on $(0, \hat{m}_X)$. Thus $\frac{\sigma^2}{m_X}$ is a decreasing function of m_X on $(0, \hat{m}_X)$. Since m_X is a decreasing function of v_Φ, the variance to mean ratio must be an *increasing* function of v_Φ.

This suggests that a comparison between the distributions of helminths of different communities will reveal a negative relationship between variance : mean ratio and mean worm burden. Indeed, such a negative relationship has been observed for *Onchocerca volvulus* (Basáñez *et al.*, 2002). However, this argument assumes that there is no relationship between m_Φ and σ_Φ. If, for example, an increase in m_Φ is accompanied by an increase in σ_Φ, then this will affect the nature of the relationship between m_X and $\frac{\sigma_X^2}{m_X}$.

At equilibrium, $\tilde{\sigma}_{\Phi X} = \frac{\sigma_{\Phi X}}{m_\Phi} = \frac{1}{\gamma}(1 - R_0^{-1}) - m_X$. Thus the covariance (and therefore correlation) between worm burden and susceptibility is positive since the equilibrium mean worm burden cannot exceed $\frac{1}{\gamma}(1 - R_0^{-1})$. This is important in terms of anthelminthic control. At any given time, targeting individuals with the highest worm burdens for continued treatment will ensure that those most susceptible and therefore responsible for greatest transmission in the future will be treated. The extent to which this is true depends on the magnitude of the correlation between susceptibility and worm burden which will vary for different parameter combinations; this will be the subject of further investigation.

7.5 Density-dependent fecundity

In the model presented above it is assumed that density dependence affects parasite establishment. Alternatively, density dependence may impact the rate of egg production. Parasite stunting and low rates of egg production in hosts with high worm burdens were originally observed in cestodes (Read, 1951). This 'crowding effect' has also been observed in non-cestode species (e.g. Fleming, 1988; Stear & Bishop, 1999) and has been shown to be attributable to both intra- and interspecific competition (Holmes, 1961, 1962).

Density dependent fecundity can be modelled using the framework previously described by making the rate of increase of the larval population a function of the within-host worm burden. Thus, larval $L \rightarrow L+1$ transitions occur at rate $\epsilon \sum_{i=1}^{n} X_i(1-\gamma(X_i-1))^+$. Observe that γ now represents the effect of each established worm on the per capita rate of egg production. Notice also that $\gamma(X_i-1)$ is used rather than γX_i because there is no density-dependent effect on egg production when only one adult worm is present. For simplicity, density-dependent establishment is neglected so that the rate of $X_i \rightarrow X_i+1$ transitions is $L\Phi_i$. Otherwise transition rates are as in the model for density-dependent establishment. Specifically,

1. $L \rightarrow L+1$ at rate $\epsilon \sum_{i=1}^{n} X_i(1-\gamma(X_{1i}-1))^+$
2. $L \rightarrow L-1$ at rate $(\mu_L + \sum_{i=1}^{n} \Phi_i)L$
3. $X_i \rightarrow X_i+1$ at rate $L\Phi_i$
4. $X_i \rightarrow X_i-1$ at rate μX_i
5. $X_i \rightarrow 0$ at rate α

where Φ_i are i.i.d. random variables. As with the model for density-dependent establishment, to facilitate analysis L is replaced by m_L in the third transition rate, and $m_\Phi n$ replaces $\sum_{i=1}^{n} \Phi_i$. If in addition the condition

$$\sum_{\{x:x>1+\frac{1}{\gamma}\}} |x(1-\gamma(x-1))\mathrm{P}(X_t=x)| \ll 1$$

holds, then closed set of differential equations for the first and second moments may

be derived

$$\begin{aligned}
\frac{dm_L}{dt} &= n\epsilon\left((1+\gamma)m_X - \gamma(\sigma_X^2 + m_X^2)\right) - (\mu_L + m_\Phi n)m_L \\
\frac{dm_X}{dt} &\; m_L m_\Phi - (\mu_X + \alpha)m_X)m_X \\
\frac{d\sigma_X^2}{dt} &= m_L m_\Phi + \mu_X m_X + 2m_L\sigma_{\Phi X} - (2\mu_X + \alpha)\sigma_X^2 + \alpha m_X^2 \\
\frac{d\sigma_{\Phi X}}{dt} &= m_L\sigma_\Phi^2 - (\mu_X + \alpha)\sigma_{\Phi X}.
\end{aligned} \tag{7.18}$$

The accuracy of the approximation is only good when host death, α, is small relative to other rates. Intuitively this is because net egg output per host is maximized at intermediate levels of worm burden, and intermediate levels will be attained with higher probability when old, heavily parasitized hosts are frequently replaced by unifected hosts, i.e. when the rate of host death is high. Subsequently, it will be assumed that the host death rate is small relative to other rates so that $\alpha = 0$.

When exposure is constant ($\Phi = \phi$) the covariance terms are zero. Furthermore if $\frac{dm_L}{dt} = 0$ then Eqn 7.18 becomes

$$\begin{aligned}
\frac{dm_X}{dt} &= \epsilon'\left((1+\gamma)m_X - \gamma(\sigma_X^2 + m_X^2)\right) - \mu_X m_X \\
\frac{d\sigma_X^2}{dt} &= \epsilon'\left((1+\gamma)m_X - \gamma(\sigma_X^2 + m_X^2)\right) + \mu_X m_X - 2\mu_X\sigma_X^2.
\end{aligned} \tag{7.19}$$

where $\epsilon' = \frac{\phi n}{\mu_L + \phi n}\epsilon$.

If $m_X(0) = \sigma_X^2(0)$ then $m_X(t) = \sigma_X^2(t)$ for all t. In fact it is apparent from the transition rates, having replaced L by m_L in the third rate, that the distribution of adult worms is given by a non-homogeneous immigration-death process with immigration rate $m_L\phi$ and death rate $\mu_X X$, and is therefore Poisson provided that the initial distribution is Poisson (Nåsell, 1985). Therefore

$$\frac{dm_X}{dt} = m_X\epsilon'(1 - \gamma m_X) - \mu_X m_X.$$

This is identical to the expression for $\frac{dm_X}{dt}$ in the establishment model (Eqn 7.5) with $\alpha = 0$. The dynamics of mean worm burden is therefore the same regardless of whether density dependence acts through parasite establishment or fecundity.

7.6 Summary

Singles species, stochastic models are developed in which the size of the larval population depends on the number of adult worms in the host population. The models are used to explore long-term dynamics of mean worm burden in a population of hosts when density-dependence occurs either at the point of establishment of larvae within hosts or during egg production by adult worms.

The establishment of helminth infection in a population of hosts is determined by R_0 (the basic reproductive number): a helminth species is only able to survive within a host population when $R_0 > 1$. For $R_0 > 1$ mean worm burden in a population of hosts approaches an equilibrium value. When hosts vary in their exposure to infective larvae, the mean worm burden is a decreasing function of the level of heterogeneity. This result suggests a negative relationship between mean worm burden and the variance : mean ratio, although in practice the nature of the dependency will also be determined by the relationship between mean and variance in exposure.

The dynamics of mean worm burden are the same irrespective of whether density dependence occurs through parasite establishment or fecundity. Thus these results apply under both models.

Chapter 8

Interspecific Competition

8.1 Introduction

The existence of interspecific interactions is becoming increasingly well documented in helminth parasites of mammalian hosts (see chapter 3). Although the overall importance of interspecific interactions in shaping helminth communities has been questioned (Kennedy, 1975), it is likely that both exploitation competition (individuals interact negatively on one another indirectly through a limiting resource), and interference competition (individuals have a direct negative effect on other individuals) play a role in structuring some parasite communities (Roberts, 2000). Simberloff (1990) discusses four possible mechanisms for within-host competition: 1) competition for space (exploitation); 2) competition for nutrients (exploitation); 3) local inflammation of the gut (interference); 4) cross-reactivity to specific immune responses (interference). In addition to these within-host mechanisms, if parasite infection increases host mortality, then exploitation competition occurs as the host itself becomes the limiting resource.

Each of the above-mentioned mechanisms of within-host competition may affect one or more parameters in the life-cycle of the parasite. Parameters that might be impacted by competition are: 1) the rate at which adult worms establish in the host; 2) the death rate of adult worms; 3) the death rate of the host; 4) the rate of egg production by the parasite. To date, mathematical modelling of competition between helminth species has focused on parasite-induced host mortality (Dobson, 1985; Roberts & Dobson, 1995; Gatto & De Leo, 1998; Pugliese, 2000); the effects of competition on life-history parameters of the worms themselves seem not to have been investigated. In this chapter, Markov processes are used to explore the population dynamics of two competing species, where competition occurs either at the point of establishment or during egg production by the adult worm.

The models proposed here are extensions of the models of the previous chapter; like those models they incorporate heterogeneous host exposure. It is currently unclear how heterogeneity influences the coexistence of helminth species. Macroparasite models that include aggregation phenomenologically suggest that aggregation, and therefore by implication the mechanisms such as heterogeneity that generate aggregation, act to promote coexistence. On the other hand, by incorporating aggregation-generating mechanisms explicitly, Pugliese (2000) has shown that coexistence is not necessarily promoted.

The model proposed by Pugliese (2000) assumes that the mode of interaction between helminth species is via parasite-induced host mortality, whereas the models presented here assume that competition takes place within hosts either at the point of parasite establishment or via parasite fecundity. Furthermore, the heterogenous rates of host exposure are not assumed to be perfectly positively correlated as they are in Pugliese (2000).

8.2 A model for two species interacting via density-dependent establishment

The single species models of the previous chapter can be extended to include a competitive interaction with a second species. In the following model, competition may be for limited resources (e.g. space, nutrients) or it may be indirectly-mediated through the host immune system. Competition occurs at the point of establishment within the host: the probability with which a larva of either species becomes established is dependent on the number of adult worms of the heterologous species already residing within the host (as well as the number of adult worms of its own species). Host i now has $X_{1i}(t)$ adult worms of species 1 and $X_{2i}(t)$ worms of species 2 at time t. The numbers of species 1 and species 2 larvae are, respectively, $L_1(t)$ and $L_2(t)$. Transition rates for species 1 adult worm burdens in each host, and numbers of larvae are as follows (transitions for species 2 are similar):

1. $L_1 \rightarrow L_1 + 1$ at rate $\epsilon_1 \sum_{i=1}^{n} X_{1i}$
2. $L_1 \rightarrow L_1 - 1$ at rate $(\mu_{L_1} + \sum_{i=1}^{n} \Phi_{1i}) L_1$
3. $X_{1i} \rightarrow X_{1i} + 1$ at rate $L_1 \Phi_{1i} (1 - \gamma_{11} X_{1i} - \gamma_{21} X_{2i})^+$
4. $X_{1i} \rightarrow X_{1i} - 1$ at rate $\mu_{X_1} X_{1i}$
5. $X_{1i} \rightarrow 0$ at rate α.

The parameter γ_{jk} $j,k = 1,2$ represents the effect of species j worms on the probability of establishment of species k. Other parameters are defined as in Chapter 7. The notation z^+ (which implies $z^+ = z$ when $z > 0$ and 0 otherwise) is used as the quantity $(1 - \gamma_{11}X_{1i} - \gamma_{21}X_{2i})$ could become negative and so the transition rate for $X_{1i} \rightarrow X_{1i}+1$ is set to zero whenever this occurs. As in the single species models, analysis is facilitated by replacing L_1 with m_{L_1} in the third transition rate above, and when Φ_1 is random, replacing $\sum_{i=1}^{n} \Phi_{1i}$ with $m_{\Phi_1} n$ in the second transition rate. The pairs of random variables $(X_{1i}(t), X_{2i}(t))$ $i = 1,..n$ are then i.i.d. for all t (provided they are i.i.d. at $t = 0$).

Taking larval exposure to each species to be the same for all hosts, so that $\Phi_{1i} = \phi_1$ and $\Phi_{2i} = \phi_2$ for $i = 1,..,n$, and setting $\frac{dm_{L_1}}{dt} = \frac{dm_{L_2}}{dt} = 0$, the mean worm burdens can be approximated by quantities satisfying the pair of differential equations,

$$\begin{aligned} \frac{dm_{X_1}}{dt} &= m_{X_1}\epsilon_1'(1 - \gamma_{11}m_{X_1} - \gamma_{21}m_{X_2}) - (\mu_{X_1} + \alpha)m_{X_1} \\ \frac{dm_{X_2}}{dt} &= m_{X_2}\epsilon_2'(1 - \gamma_{22}m_{X_2} - \gamma_{12}m_{X_1}) - (\mu_{X_2} + \alpha)m_{X_2} \end{aligned} \tag{8.1}$$

where $\epsilon_i' = \frac{\epsilon_i \phi_i n}{\mu_{L_i} + n\phi_i}$ $i = 1,2$ is the product of the rate at which potentially infective larvae are produced by an adult worm, and the probability a larva survives to infect a host.

The solution to these differential equations only approximates the mean worm burdens for the two species because $(1 - \gamma_{11}X_1 - \gamma_{21}X_2)$ (and the equivalent species 2 expression) is potentially negative. More specifically, the approximation given in Eqn 8.1 is good if the following two quantities are small in magnitude

$$\sum (1 - \gamma_{jj}x_j - \gamma_{kj}x_k)p_t(x_1, x_2) \quad (j,k = 1,2; j \neq k)$$

where $p_t(x_1, x_2)$ =P$(X_{1t} = x_1, X_{2t} = x_2)$ and the summations are over the sets $\{(x_1, x_2) : 1 - \gamma_{jj}x_j - \gamma_{kj}x_k < 0\}$.

The solution to the differential equations is compared with mean worm burden obtained by simulating the model. Parameters were chosen, for the comparison, to be consistent with estimates for helminth species (e.g. see Table 6.3 and Tables 15.2-15.4 Anderson & May, 1991), where such estimates are available. In Fig.8.2a,b it can be seen that the approximation works very well for the parameters used.

The two ODE's in Eqn 8.1 are identical in form (though the interpretation of the model parameters is different) to the Lotka-Volterra model used to explore the effects

of competition on the coexistence of free-living species (e.g. Maynard-Smith, 1974). The behaviour of the system is determined by the basic reproductive numbers for the two species and the inter- and intra-specific interaction parameters. For $m_{X_k}(t)$ $k = 1, 2$ to increase, it is necessary that

$$R_{0k} > 1 \quad k = 1, 2$$

where $R_{0k} = \frac{\epsilon'_k}{\mu_{X_k} + \alpha}$ is the reproductive number for species k.

When both reproductive numbers exceed unity, and worms of both species are present initially, it is straightforward to show, by phase-plane analysis, that the system approaches either a single species equilibrium where one species has excluded the other, or a mixed equilibrium where both species coexist (Maynard-Smith, 1974). The next section explores a special case in relation to the competitive exclusion principle.

Competitive exclusion principle It is useful for conceptual purposes to distinguish two different types of interspecific competition, namely exploitative competition and interference competition (Schoener, 1983). Exploitative competition occurs when both species utilize the same limiting resource. Once a unit of resource has been consumed by one species, it is no longer available for consumption by the other species. In cestode species, for example, it appears that the carbohydrate intake of the host is frequently a limiting resource (Roberts, 2000).

The alternative, interference competition, encompasses a wide variety of mechanisms that cause one species to have a negative impact on the other, and that are not resource-mediated, e.g. territoriality, excretion of toxins, overgrowth in plants. A pertinent example for helminths is any negative effect that the host immune response elicited by one parasite species has on the establishment, survival or fecundity of another parasite species.

As defined, the model does not distinguish between the two classes of interaction. However, whilst there are no restrictions on the intra- and interspecific terms for interference competition, when competition is exploitative and the probability of establishment is determined by the availability of a single resource, then $\gamma_{11} = \gamma_{12}$ and $\gamma_{22} = \gamma_{21}$. To see this, recall that the term $(1 - \gamma_{11}X_1 - \gamma_{21}X_2)^+$, (and the equivalent term for species 2) represents the probability of establishment in a host where X_1 worms of species 1 and X_2 worms of species 2 are present. If the probability of establishment in both species is determined by the availability of a single resource, then the probability of establishment, for both species, is reduced by the same amount for each worm of species 1 present, and therefore we must have

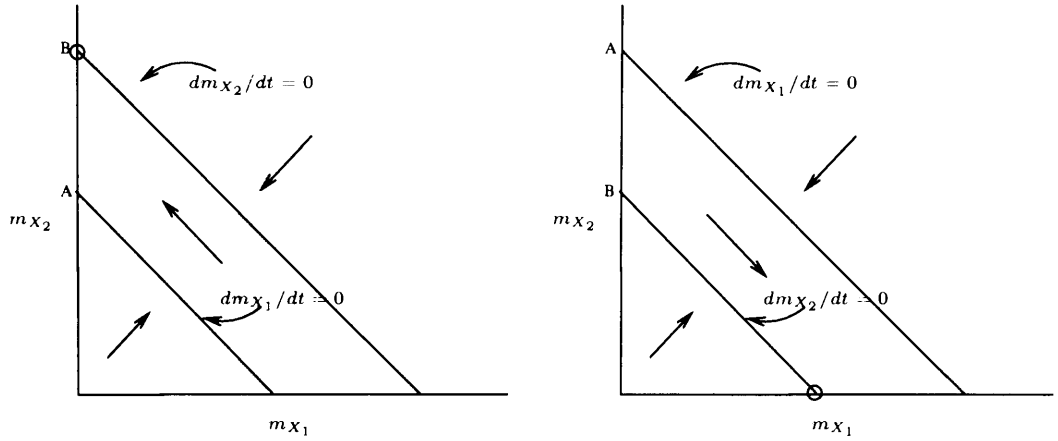


Figure 8.1: Phase plane analysis for two species competing for a single resource ($\gamma_{11} = \gamma_{12}$ and $\gamma_{22} = \gamma_{21}$). The circle represents the stable equilibrium in each figure, and A=$\frac{1}{\gamma_{22}}(1 - R_{01}^{-1})$, $B = \frac{1}{\gamma_{22}}(1 - R_{02}^{-1})$ are, respectively, the values of the isoclines $\frac{dm_{X_1}}{dt} = 0$ and $\frac{dm_{X_2}}{dt} = 0$ at $m_{X_1} = 0$. a) When $R_{01} > R_{02}$ then $A < B$ and species 1 excludes species 2. b) When $R_{02} > R_{01}$ species 2 excludes species 1.

$\gamma_{11} = \gamma_{12}$. Similarly each worm of species 2 has the same effect on the probability of establishment of species 1 and species 2, and therefore $\gamma_{22} = \gamma_{21}$.

Under this restriction, phase plane analysis reveals that the two non-zero isoclines are parallel lines; the mixed equilibrium can therefore not exist. The species with the higher R_0 'wins', excluding the species with the lower R_0 (Fig 8.1b). This result is equivalent to that obtained for free-living species by Volterra (Armstrong & McGehee, 1980). As with the result for free-living species, it implies the competitive exclusion principle which states that two species cannot occupy the same ecological niche (Hardin, 1960).

8.3 Heterogeneous exposure

Heterogeneity in exposure can be modelled by reverting to the case of a correlated pair of random variables, (Φ_1, Φ_2), as in the original description of the model in the previous section. The same simplifying assumptions are made as in the model with homogeneous exposure. In addition, it is assumed that the expectation of products of three random variables can be expressed in terms of lower order moments as would be the case if they followed a multivariate normal distribution, i.e.

$$\mathrm{E}[W_1W_2W_3] = \mathrm{E}[W_1]\mathrm{E}[W_2W_3]+\mathrm{E}[W_2]\mathrm{E}[W_1W_3]+\mathrm{E}[W_3]\mathrm{E}[W_1W_2]-2\mathrm{E}[W_1]\mathrm{E}[W_2]\mathrm{E}[W_3].$$

This moment closure assumption is similar to that used for the single species model with heterogeneous exposure.

Setting $\frac{dm_{L_1}}{dt} = \frac{dm_{L_2}}{dt} = 0$, the following set of differential equations can be derived (the notation $\mathrm{E}(Z) = m_Z$, $\mathrm{var}(Z) = \sigma_Z^2$, $\mathrm{cov}(Y, Z) = \sigma_{YZ}$ is used as for the single species model)

$$\frac{dm_{X_1}}{dt} = \epsilon_1' m_{X_1}\left(1 - \gamma_{11}(\frac{\sigma_{\Phi_1 X_1}}{m_{\Phi_1}} + m_{X_1}) - \gamma_{21}(\frac{\sigma_{\Phi_1 X_2}}{m_{\Phi_1}} + m_{X_2})\right) - \mu'_{X_1} m_{X_1} \tag{8.2}$$

$$\frac{d\sigma_{\Phi_1 X_1}}{dt} = \epsilon_1' m_{X_1}\sigma^2_{\Phi_1}\left(m_{\Phi}^{-1} - \gamma_{11}(\frac{\sigma_{\Phi_1 X_1}}{\sigma^2_{\Phi_1}} + \frac{m_{X_1}}{m_{\Phi_1}}) - \gamma_{21}(\frac{\sigma_{\Phi_1 X_2}}{\sigma^2_{\Phi_1}} + \frac{m_{X_2}}{m_{\Phi_1}})\right) - \mu'_{X_1}\sigma_{\Phi_1 X_1} \tag{8.3}$$

$$\frac{d\sigma_{\Phi_1 X_2}}{dt} = \epsilon_2' m_{X_2}\sigma_{\Phi_1\Phi_2}\left(m_{\Phi_2}^{-1} - \gamma_{22}(\frac{\sigma_{\Phi_1 X_2}}{\sigma_{\Phi_1\Phi_2}} + \frac{m_{X_2}}{m_{\Phi_2}}) - \gamma_{12}(\frac{\sigma_{\Phi_1 X_1}}{\sigma_{\Phi_1\Phi_2}} + \frac{m_{X_1}}{m_{\Phi_2}})\right) - \mu'_{X_2}\sigma_{\Phi_1 X_2} \tag{8.4}$$

where $\mu'_{X_k} = \mu_{X_k} + \alpha$ $(k = 1, 2)$.

Similarly, differential equations may be derived for $m_{X_2}, \sigma_{\Phi_2 X_2}$ and $\sigma_{\Phi_2 X_1}$, to give a closed set of differential equations.

Coexistence The criterion that will be adopted for the coexistence of two species is that of mutual invadability: two species coexist when each species can invade an equilibrium where only the other species is present (Hutson & Schmitt, 1992). Introduction of a small quantity of worms of the invading species will perturb the means and covariances by a small amount. To determine whether invasion is likely to be successful we therefore perform stability analyses for the equilibria where only species 1 or only species 2 is present; we denote these equilibria by e_1 and e_2 respectively. Our criterion for coexistence will be that both e_1 and e_2 must be

unstable, i.e. each species is susceptible to invasion by the other species.

The Jacobian matrix, J, corresponding to the system of differential equations for two competing species with random exposure (Eqns 8.2-8.4 and the corresponding differential equations for species 2) is

$$\begin{pmatrix}
A_1 - \mu'_{X_1} & -\frac{\epsilon'_1}{m_{\Phi_1}}\gamma_{11}m_{X_1} & -\frac{\epsilon'_1}{m_{\Phi_1}}\gamma_{21}m_{X_1} & -\epsilon'_1\gamma_{21}m_{X_1} & 0 & 0 \\
C_1 & -\epsilon'_1\gamma_{11}m_{X_1} - \mu'_{X_1} & -\epsilon'_1\gamma_{21}m_{X_1} & -\epsilon'_1\frac{\sigma^2_{\Phi_1}}{m_{\Phi_1}}\gamma_{21}m_{X_1} & 0 & 0 \\
-\epsilon'_2\frac{\sigma_{\Phi_1\Phi_2}}{m_{\Phi_2}}\gamma_{12}m_{X_2} & -\epsilon'_2\gamma_{12}m_{X_2} & -\epsilon'_2\gamma_{22}m_{X_2} - \mu'_{X_2} & B_1 & 0 & 0 \\
-\epsilon'_2\gamma_{12}m_{X_2} & 0 & 0 & A_2 - \mu'_{X_2} & -\frac{\epsilon'_2}{m_{\Phi_2}}\gamma_{22}m_{X_2} & -\frac{\epsilon'_2}{m_{\Phi_2}}\gamma_{12}m_{X_2} \\
-\epsilon'_2\frac{\sigma^2_{\Phi_2}}{m_{\Phi_2}}\gamma_{12}m_{X_2} & 0 & 0 & C_2 & -\epsilon'_2\gamma_{22}m_{X_2} - \mu'_{X_2} & -\epsilon'_2\gamma_{12}m_{X_2} \\
B_2 & 0 & 0 & -\epsilon'_1\frac{\sigma_{\Phi_1\Phi_2}}{m_{\Phi_1}}\gamma_{21}m_{X_1} & -\epsilon'_1\gamma_{21}m_{X_1} & -\epsilon'_1\gamma_{11}m_{X_1} - \mu'_{X_1}
\end{pmatrix}$$

where

$$\begin{aligned}
A_1 &= \epsilon'_1\left(1 - \gamma_{11}(\frac{\sigma_{\Phi_1X_1}}{m_{\Phi_1}} + 2m_{X_1}) - \gamma_{21}(\frac{\sigma_{\Phi_1X_2}}{m_{\Phi_1}} + m_{X_2})\right) \\
B_1 &= \epsilon'_2\left(\frac{\sigma_{\Phi_1\Phi_2}}{m_{\Phi_2}} - \gamma_{22}(\sigma_{\Phi_1X_2} + 2\frac{\sigma_{\Phi_1\Phi_2}}{m_{\Phi_2}}m_{X_2}) - \gamma_{12}(\sigma_{\Phi_1X_1} + \frac{\sigma_{\Phi_1\Phi_2}}{m_{\Phi_2}}m_{X_1})\right) \\
C_1 &= \epsilon'_1\left(\frac{\sigma^2_{\Phi_1}}{m_{\Phi_1}} - \gamma_{11}(\sigma_{\Phi_1X_1} + 2\frac{\sigma^2_{\Phi_1}}{m_{\Phi_1}}m_{X_1}) - \gamma_{21}(\sigma_{\Phi_1X_2} + \frac{\sigma^2_{\Phi_1}}{m_{\Phi_1}}m_{X_2})\right) \\
\mu'_{X_k} &= \mu_{X_k} + \alpha \qquad k = 1, 2,
\end{aligned}$$

and A_2, B_2, C_2 are the species 2 counterparts to A_1, B_1, C_1. At e_2 (the equilibrium where species 2 is present and species 1 is absent),

$$\begin{aligned}
&\mathrm{Det}(J|_{e2} - \lambda I) \\
&= (\mu'_{X_1} + \lambda)^2(\mu_{X_1} - A_1|_{e2} + \lambda)(\epsilon'_2\gamma_{22}m_{X_2} + \mu'_{X_2} + \lambda) \\
&\times \left((\mu'_{X_2} - A_2|_{e2} + \lambda)(\epsilon'_2\gamma_{22}m_{X_2} + \mu'_{X_2} + \lambda) + C_2|_{e2}\frac{\epsilon'_2}{m_{\Phi_2}}\gamma_{22}m_{X_2}\right) \qquad (8.5)
\end{aligned}$$

where

$$\begin{aligned}
A_1|_{e2} &= \epsilon'_1\left(1 - \gamma_{21}(\frac{\sigma_{\Phi_1X_2}}{m_{\Phi_1}} + m_{X_2})\right) \\
A_2|_{e2} &= \epsilon'_2\left(1 - \gamma_{22}(\frac{\sigma_{\Phi_2X_2}}{m_{\Phi_2}} + 2m_{X_2})\right) \\
C_2|_{e2} &= \epsilon'_2\left(\frac{\sigma^2_{\Phi_2}}{m_{\Phi_2}} - \gamma_{22}(\sigma_{\Phi_2X_2} + 2\frac{\sigma^2_{\Phi_2}}{m_{\Phi_2}}m_{X_2})\right)
\end{aligned}$$

and $m_{X_2}, \sigma_{\Phi_1X_2}, \sigma_{\Phi_2X_2}$ take on the values that they have at the equilibrium, e_2. The

notation $|_{e_2}$ is used to emphasize that J, A_1, A_2 and C_2 are being evaluated at at the equilibrium e_2.

The roots $\lambda = -(\epsilon_2'\gamma_{22}m_{X_2} + \mu_{X_2}')$ and $\lambda = -\mu_{X_1}'$ are both negative. The stability of the equilibrium, e_2, is therefore determined by a third order polynomial in λ. Using the Routh-Hurwitz criterion for a third order polynomial (May, 1973), e_2 is stable if the following conditions are met

$$\mu_{X_1} - A_1|_{e2} > 0 \tag{8.6}$$

$$\mu_{X_2}' - A_2|_{e2} + \epsilon_2'\gamma_{22}m_{X_2} + \mu_{X_2}' > 0 \tag{8.7}$$

$$(\mu_{X_2}' - A_2|_{e2})(\epsilon_2'\gamma_{22}m_{X_2} + \mu_{X_2}') + C_2|_{e2}\frac{\epsilon_2'}{m_{\Phi_2}}\gamma_{22}m_{X_2} > 0. \tag{8.8}$$

At e_2, from the species 2 equivalent of Eqn 8.2, $\sigma_{\Phi_2 X_2}$ can be written in terms of m_{X_2} as

$$\frac{\sigma_{\Phi_2 X_2}}{m_{\Phi_2}} = \frac{1}{\gamma_{22}}(1 - R_{02}^{-1}) - m_{X_2}.$$

Using this relationship, $\mu_{X_2}' - A_2|_{e2} = \epsilon_2'\gamma_{22}m_{X_2} > 0$ and so condition Eqn 8.7 is satisfied.

Rewriting Eqn 8.8,

$$\mu_{X_2}'(\mu_{X_2}' - A_2|_{e2}) + \epsilon_2'\gamma_{22}m_{X_2}(\frac{C_2|_{e2}}{m_{\Phi_2}} + \mu_{X_2}' - A_2|_{e2}) > 0.$$

For Eqn 8.8 to hold, it is sufficient to show that $\frac{C_2|_{e2}}{m_{\Phi_2}} + \mu_{X_2}' - A_2|_{e2} > 0$. Rewriting this condition,

$$R_{02}^{-1} + (v_{\Phi_2}^2 - 1)(1 - 2\gamma_{22}m_{X_2}) > 0 \tag{8.9}$$

where $v_{\Phi_2} = \frac{\sigma_{\Phi_2}}{m_{\Phi_2}}$.

Recall from the single species model that m_{X_2} is a decreasing function of v_{Φ_2} and that at $v_{\Phi_2} = 1$, $m_{X_2} = \frac{1}{2\gamma_{22}}(1 - R_{02}^{-1})$. Eqn 8.9 holds as a result of this (and hence so does Eqn 8.8) because when $v_{\Phi_2}^2 > 1$

$$m_{X_2} < \frac{1}{2\gamma_{22}}(1 - R_{02}^{-1}) \Rightarrow (1 - 2\gamma_{22}m_{X_2}) > R_{02}^{-1}$$

and when $v_{\Phi_2}^2 < 1$

$$m_{X_2} > \frac{1}{2\gamma_{22}}(1 - R_{02}^{-1}) \Rightarrow (1 - 2\gamma_{22}m_{X_2}) < R_{02}^{-1}.$$

The stability of e_2 is therefore determined by Eqn 8.6. From this condition and a similar condition for the stability of e_1, it follows that the two species can coexist if and only if

$$R_1 > 1 \quad \text{and} \quad R_2 > 1 \tag{8.10}$$

where

$$R_1 = R_{01}\left(1 - \gamma_{21}\left(\frac{\sigma_{\Phi_1 X_2}}{m_{\Phi_1}} + m_{X_2}\right)\right)\Bigg|_{e_2} \tag{8.11}$$

$$R_2 = R_{02}\left(1 - \gamma_{12}\left(\frac{\sigma_{\Phi_2 X_1}}{m_{\Phi_2}} + m_{X_1}\right)\right)\Bigg|_{e_1}. \tag{8.12}$$

R_1 and R_2 are, respectively, the effective reproductive numbers of species 1 at e_2 and species 2 at e_1. That is to say, $R_1(R_2)$ is the number of adult worms produced by an invading parasite of species 1(2) during its lifetime, at the equilibrium where only species 2(1) is present. Each effective reproductive number is the product of the basic reproductive number and a term representing the probability of establishment. It can be seen that this probability depends not only on the average worm burden of the resident species, but also on the covariance between the worm burden of the resident species and the host's susceptibility to the invading species. This is intuitively reasonable since the probability of establishment for the invading species will be small if hosts that are more susceptible than average to the invading species have large worm burdens of the resident species; conversely the probability will be large if these hosts have few worms of the resident species.

The criteria for coexistence, formally derived above via stability analysis can also be derived intuitively as follows. Consider perturbing e_2 by introducing a small number of worms of species 1. Species 1 will invade if, after a small time increment, there is an increase in m_{X_1}, i.e. if $\frac{dm_{X_1}}{dt} > 0$. Since the number of worms of species 1 introduced is small, the quantities m_{X_1} and $\sigma_{\Phi_1 X_1}$ are small relative to m_{X_2}. From Eqn 8.2 the rate, r_1, of increase in m_{X_1} is therefore given by

$$r_1 = \epsilon_1'\left(1 - \gamma_{21}\left(\frac{\sigma_{\Phi_1 X_2}}{m_{\Phi_1}} + m_{X_2}\right)\right) - \mu_{X_1}'\Bigg|_{e_2}.$$

The rate r_1 determines the stability of e_2: the equilibrium is stable when $r_1 < 0$ and unstable when $r_1 > 0$. An equivalent rate, r_2, determines the stability of e_1. The two species will coexist if $r_1 > 0$ and $r_2 > 0$, which is equivalent to the condition that $R_1 > 1$ and $R_2 > 1$ given above.

At e_2, $\sigma_{\Phi_1 X_2}|_{e_2}$ can be written in terms of $m_{X_2}|_{e_2}$ since

$$\sigma_{\Phi_1 X_2}|_{e_2} = \frac{\sigma_{\Phi_1\Phi_2}}{\sigma^2_{\Phi_2}}\sigma_{\Phi_2 X_2}|_{e_2} = \frac{\rho\sigma_{\Phi_1}}{v_{\Phi_2}}(\hat{m}_{X_2} - m_{X_2}|_{e_2}),$$

where $\hat{m}_{X_2} = \frac{1}{\gamma_{22}}(1 - R_{02}^{-1})$ is the maximum possible value of the equilibrium mean worm burden for species 2, attained when $v_{\Phi_2} = 0$, and $\rho = \frac{\sigma_{\Phi_1\Phi_2}}{\sigma_{\Phi_1}\sigma_{\Phi_2}}$ is the correlation between susceptibility to species 1 and susceptibility to species 2. Similarly, $\sigma_{\Phi_2 X_1}|_{e_1} = \frac{\rho\sigma_{\Phi_2}}{v_{\Phi_1}}(\hat{m}_{X_1} - m_{X_1}|_{e_1})$, where $\hat{m}_{X_1} = \frac{1}{\gamma_{11}}(1 - R_{01}^{-1})$. Thus the effective reproductive numbers can be written as

$$R_1 = R_{01}\left(1 - \gamma_{21}\left(\rho\frac{v_{\Phi_1}}{v_{\Phi_2}}(\hat{m}_{X_2} - m_{X_2}|_{e_2}) + m_{X_2}|_{e_2}\right)\right) \tag{8.13}$$

$$R_2 = R_{02}\left(1 - \gamma_{12}\left(\rho\frac{v_{\Phi_2}}{v_{\Phi_1}}(\hat{m}_{X_1} - m_{X_1}|_{e_1}) + m_{X_1}|_{e_1}\right)\right). \tag{8.14}$$

At, e_2, the equilibrium where species 2 alone is present, the species 2 mean worm burden, $m_{X_2}|_{e_2}$, is independent of the correlation, ρ, between host susceptibility to species 1 and host susceptibility to species 2. From Eqn 8.13, the effective reproductive number for species 1 at e_2, is therefore a decreasing function of ρ. Similarly, R_2 is also a decreasing function of ρ. Thus, as one might expect intuitively, coexistence is promoted by decreasing the correlation between exposure rates.

When heterogeneity, as measured by the coefficient of variation for host exposure, is the same for both species, i.e. $v_{\Phi_1} = v_{\Phi_2} = v_\Phi$, then the effective reproductive numbers R_1 and R_2 are increasing functions of v_Φ for $\rho < 1$. This result follows from the results of the single species model which imply that at e_1, m_{X_1} is a decreasing function of v_Φ, as is m_{X_2} at e_2. Consequently, coexistence is facilitated by increasing the heterogeneity in host exposure to both parasite species, v_Φ, provided that $\rho \neq 1$.

Heterogeneity in host exposure is most likely to facilitate coexistence when hosts have similar degrees of heterogeneity in their exposure to both species. When $\rho > 0$, it can be seen from Eqn 8.13 and Eqn 8.14, that it is hard for a species for which host heterogeneity in exposure is relatively high to invade a population where host heterogeneity to the already established parasite species is relatively low. For example, if species 1 is invading a host population where species 2 is already established, and $v_{\Phi_1} >> v_{\Phi_2}$, then the effective reproductive number for species 1 (Eqn 8.13) will be small because $\frac{v_{\Phi_1}}{v_{\Phi_2}} >> 1$. Coexistence therefore becomes increasingly hard the more the degree of heterogeneity in host exposure differs between the parasite species.

These results are illustrated in Fig.8.2 through the results of model simulations as well as by numerical solution of the set of differential equations that approximate

the moments (Eqns 8.2-8.4). For the simulations (Fig.8.2c,d), 100 realizations were obtained from each of two independent gamma distributions representing rates of host exposure to the the two species. Dependence was introduced (Fig.8.2d) by splitting the 100 realizations for each species into quartiles and pairing values at random from each quartile of species 1 with the corresponding quartile of species 2. Results from the simulation were compared with the approximation using the means, variances and correlation of the two sets of realizations as the values for m_{Φ_k}, $\sigma^2_{\Phi_k}$ $(k = 1, 2)$ and ρ, respectively. The results of the simulation suggest that the approximation is qualitatively reasonable for the parameters used, although it tends to underestimate mean worm burden.

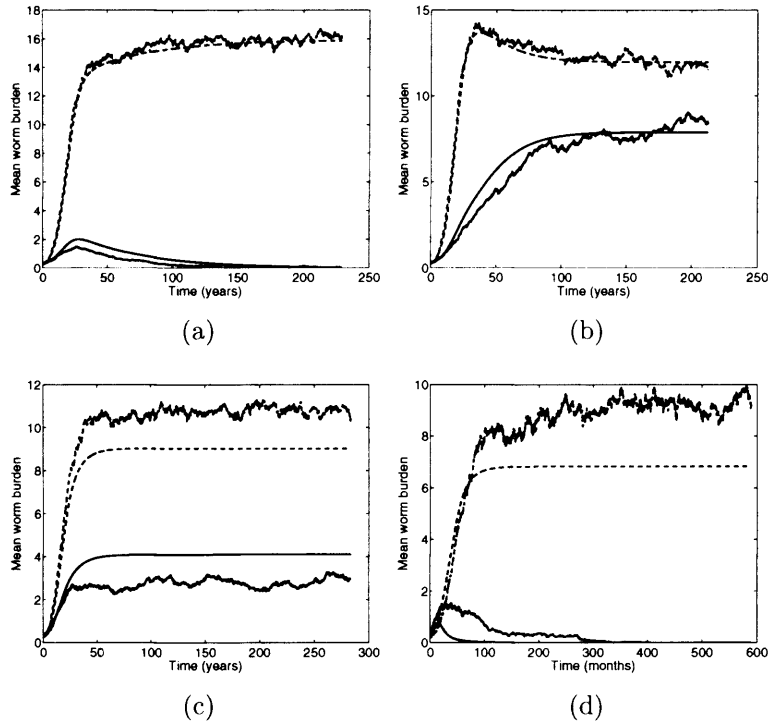


Figure 8.2: Coexistence and competitive exclusion for density-dependent parasite *establishment.* Mean worm burden as a function of time obtained by simulating from the Markov process defined in the text; results for the corresponding approximation using Eqns 8.2-8.4 are also given. Species 1 and species 2 mean worm burdens are given by the dashed and solid lines respectively (for both simulation and approximation). For a) - c) $R_{01} > R_{02}$, and hence species 1 has a competitive advantage. a) Competitive exclusion of species 2 by species 1 when all hosts have the same rate of exposure to parasites ($\phi_1 = \phi_2 = 0.001$). b) Coexistence when host exposure is homogeneous ($\phi_1 = \phi_2 = 0.001$) due to weak interspecific terms ($\gamma_{12} = \gamma_{21} = 0.025$). c) Coexistence when rates of exposure to species 1 and species 2 are heterogeneous, imperfectly correlated and the degree of heterogeneity is approximately the same for both parasite species. Means, variances and correlation for the rates of exposure to species 1 and species 2 are: $m_{\Phi_1} = 0.0010, v_{\Phi_1} = 0.82, m_{\Phi_2} = 0.0012, v_{\Phi_2} = 1.0, \rho = 0.07$. d) Competitive exclusion when R_0 is the same for both species ($\epsilon_1 = \epsilon_2 = 10$) and rates of exposure are positively correlated and differ substantially between the two species. Means, variances and correlation for the rates of exposure to species 1 and species 2 are: $m_{\Phi_1} = 0.0009, v_{\Phi_1} = 1.0, m_{\Phi_2} = 0.0012, v_{\Phi_2} = 3.3, \rho = 0.51$. Parameter values (unless otherwise indicated): $n = 100, \epsilon_1 = 15, \epsilon_2 = 10, \mu_{X_j} = 0.05, \mu_{L_j} = 5, \alpha = 0.01, \gamma_{jk} = 0.05$ $j, k = 1, 2$.

8.4 Density-dependent fecundity

As in Chapter 7, density-dependent fecundity can be modelled by allowing the rate of larval production to depend on host worm burdens. The transition rates for species 1 in the model of density-dependent fecundity are as follows (species 2 rates are equivalently defined):

1. $L_1 \rightarrow L_1 + 1$ at rate $\epsilon_1 \sum_{i=1}^{n} X_{1i}(1 - \gamma_{11}(X_{1i} - 1) - \gamma_{21}X_{2i})^+$
2. $L_1 \rightarrow L_1 - 1$ at rate $(\mu_{L_1} + \sum_{i=1}^{n} \Phi_{1i})L_1$
3. $X_{1i} \rightarrow X_{1i} + 1$ at rate $L_1\Phi_{1i}$
4. $X_{1i} \rightarrow X_{1i} - 1$ at rate $\mu_1 X_{1i}$
5. $X_{1i} \rightarrow 0$ at rate α

where (Φ_{1i}, Φ_{2i}) are i.i.d. pairs of random variables.

As with the model for density-dependent establishment, to facilitate analysis L_1 is replaced by m_{L_1} in the third transition rate, and $m_{\Phi_1} n$ replaces $\sum_{i=1}^{n} \Phi_{1i}$. A closed set of differential equations for the first and second moments may be derived by assuming

$$\sum x_1(1 - \gamma_{11}(x_1 - 1) - \gamma_{21}x_2)p_t(x_1, x_2) \ll 1,$$

where $p_t(x_1, x_2)$ =P$(X_{1t} = x_1, X_{2t} = x_2)$ and the summation is over the set (x_1, x_2) : $1 - \gamma_{11}(x_1 - 1) - \gamma_{21}x_2 < 0$.

$$\begin{aligned}
\frac{dm_{L_1}}{dt} &= n\epsilon_1 \left((1 + \gamma_{11})m_{X_1} - \gamma_{11}(\sigma^2_{X_1} + m^2_{X_1}) - \gamma_{21}(\sigma_{X_1X_2} + m_{X_1}m_{X_2})\right) - (\mu_{L_1} + m_{\Phi_1}n)m_{L_1} \\
\frac{dm_{X_1}}{dt} &= m_{L_1}m_{\Phi_1} - (\mu_{X_1} + \alpha)m_{X_1} \\
\frac{d\sigma^2_{X_1}}{dt} &= m_{L_1}m_{\Phi_1} + \mu_{X_1}m_{X_1} + 2m_{L_1}\sigma_{X_1\Phi_1} - (2\mu_{X_1} + \alpha)\sigma^2_{X_1} + \alpha m^2_{X_1} \\
\frac{d\sigma_{\Phi_1X_1}}{dt} &= m_{L_1}\sigma^2_{\Phi_1} - (\mu_{X_1} + \alpha)\sigma_{\Phi_1X_1} \\
\frac{d\sigma_{\Phi_2X_1}}{dt} &= m_{L_1}\sigma_{\Phi_1\Phi_2} - (\mu_{X_1} + \alpha)\sigma_{\Phi_2X_1} \\
\frac{d\sigma_{X_1X_2}}{dt} &= m_{L_1}\sigma_{\Phi_1X_2} + m_{L_2}\sigma_{\Phi_2X_1} + \alpha m_{X_1}m_{X_2} - (\mu_{X_1} + \mu_{X_2} + \alpha)\sigma_{X_1X_2}.
\end{aligned} \tag{8.15}$$

When exposure is constant $(\Phi_i = \phi_i)$ $i = 1, 2$ the covariance terms are zero. Furthermore setting $\frac{dm_{L_i}}{dt} = 0$, and $\alpha = 0$, Eqn 8.15 becomes

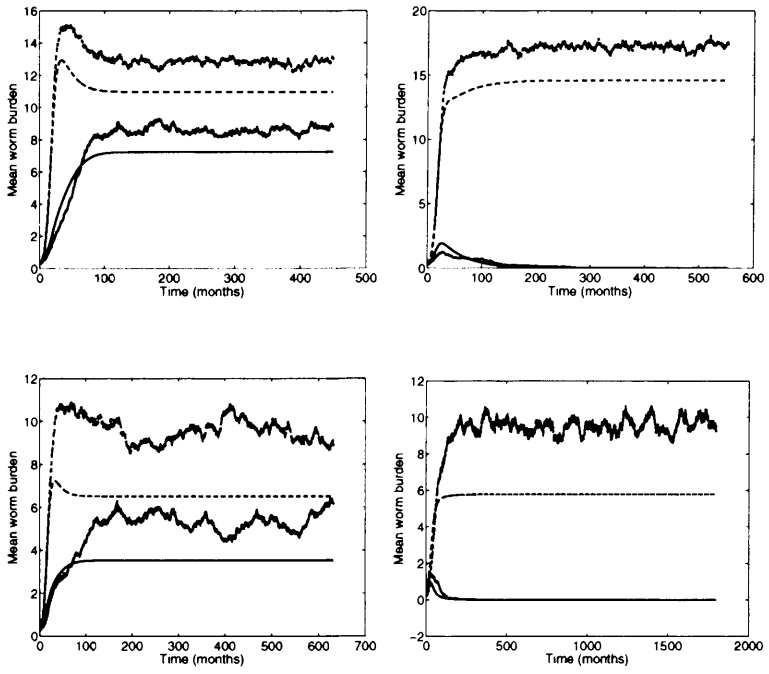


Figure 8.3: Coexistence and competitive exclusion for density-dependent parasite *fecundity*. The different scenarios and parameter values are as in Fig.8.2.

$$\begin{aligned}
\frac{dm_{X_1}}{dt} &= n\epsilon_1' \left((1+\gamma_{11})m_{X_1} - \gamma_{11}(\sigma^2_{X_1} + m^2_{X_1}) - \gamma_{21} m_{X_1} m_{X_2}\right) - \mu_{X_1} m_{X_1} \\
\frac{d\sigma^2_{X_1}}{dt} &= n\epsilon_1' \left((1+\gamma_{11})m_{X_1} - \gamma_{11}(\sigma^2_{X_1} + m^2_{X_1}) - \gamma_{21} m_{X_1} m_{X_2}\right) + \mu_{X_1} m_{X_1} - 2\mu_{X_1}\sigma^2_{X_1}.
\end{aligned} \tag{8.16}$$

If $m_{X_i}(0) = \sigma^2_{X_i}(0)$ then it follows from Eqn 8.16 and the species 2 equivalent that $m_{X_i}(t) = \sigma^2_{X_i}(t)$ $(i = 1, 2)$ for all t. Hence the mean level of worm burden for species 1 and species 2 satisfy the pair of differential equations in Eqn 8.1 implying that the dynamics of mean worm burden are not affected by the mechanism of competition. For heterogeneous exposure, the model is analyzed by simulation. As with the model for density-dependent establishment, coexistence is promoted by heterogeneity provided that the degree of heterogeneity is similar for the two species and the rates of exposure are not perfectly correlated. It can be seen in Fig.8.3 (as in Fig.8.2) that the approximation tends to underestimate mean worm burden, and is only qualitatively reasonable.

8.5 Competition, coexistence and the structure of communities of helminth species

Competition between species is responsible for structure at each level of helminth community organization, be it in terms of a functional or numerical response (Poulin, 1998) at the level of the individual host, the distribution of worm burdens in a component community, or the distribution of helminth species in a compound community. In this chapter, competition has been examined in terms of the coexistence of helminth species in host populations; the focus of the following discussion is therefore on the structuring of the component and compound communities by interspecific competition.

The models developed here for homogeneous host exposure, suggest that competitive exclusion will occur if the probability of establishment or fecundity for both parasite species is determined by a single, limiting resource. This is because under such circumstances, the effect that each species has on the establishment (or fecundity) of members of its own species is the same as the effect it has on the establishment of the heterologous species. In the situation where interspecific effects between two species are weaker than intraspecific effects, the species with the higher basic reproductive value (R_0) may still drive its competitor to extinction if the difference between the reproductive values of the two species is sufficiently great. In particular, competitive exclusion is most likely to occur in communities where reproductive values are close to unity, and parasite densities are correspondingly low. This result is of significance because component communities are often classified according to the interactive-isolationist continuum based on parasite population densities (Poulin & Luque, 2003). At the interactive end of the continuum are component communities where parasite population densities are high. Because the potential for interaction is high in such communities, it is argued that competition maybe a significant structuring force. Conversely, competition is thought to play a minimal role in isolationist component communities where parasite densities are low. The concept was originally proposed by Holmes & Price (1986) at the level of the infra-community. At this level it is intuitively reasonable that competitive interactions will only become important in determining the spatial distribution of parasite species within the host, e.g. in the intestine, if parasite densities are sufficiently high. However, as we have shown, competitive exclusion may be more likely in component communities where parasites occur at low density. One can imagine that the component communities of different localities may vary in the composition of their parasite species as a result of small shifts in competitive advantage. Thus

it may be that the variability in the combinations of species that parasitize eels in different localities (Kennedy, 2001) is, in part, the result of shifting competitive advantage, since parasite densities are small and competitive interspecific effects have been demonstrated (Bates & Kennedy, 1990, 1991).

A potentially significant factor in determining when species will coexist is the distribution of worm burdens amongst hosts, or for non-parasitic species, the distribution of individuals amongst patches. It has been argued that independent aggregation of species promotes their coexistence (Shorrocks *et al.*, 1979; Atkinson & Shorrocks, 1981). The hypothesis considers a species utilizing a temporary resource that is patchily distributed, such as *Drosophila* species laying eggs on fruit. Atkinson & Shorrocks (1981) simulate a model where each species lays eggs in the patches independently of the other according to a negative binomial distribution. Competition is then assumed to take place between the fly larval stages. In this model, coexistence is promoted by increasing aggregation in the distribution of eggs amongst patches.

Similar conclusions have been drawn from models of competition between helminths species, where the mechanism of competition is parasite-induced host mortality (Dobson, 1985; Roberts & Dobson, 1995; Gatto & De Leo, 1998). Again helminths occur in patches (hosts) and typically follow an overdispersed distribution among hosts. In these models, it is assumed that the relationship between the mean and variance of worm burden is the same as the relationship between mean variance in the negative binomial distribution with a constant degree of overdispersion. The covariance between worm burdens of different species is assumed to be zero (Gatto & De Leo, 1998) or a function of mean worm burden (Dobson, 1985; Roberts & Dobson, 1995).

However, in the case of competition between helminth species, such results are harder to interpret since the level of aggregation is itself dependent on the degree of parasite-induced host mortality (Anderson & Gordon, 1982; Herbert & Isham, 2000). Similarly, it is likely that the dependence (and therefore covariance) between worm burdens of the two species is determined by the severity of parasite-induced host mortality.

Pugliese (2000) has incorporated causes of aggregation, namely host heterogeneity in exposure and clumping of infective stages, into a multispecies model where competition is through parasite-induced host mortality. He finds that including these causes does not in itself promote coexistence. However, for heterogeneity in host exposure, Pugliese considers only the case where each host is equally susceptible to both species. Here this assumption has been relaxed so that the correlation

between host exposures to the two species, ρ, is not necessarily +1. By doing so it is apparent that coexistence can be promoted by heterogeneity in host exposure when $\rho < 1$ and the extent of the heterogeneity is similar for both species. However, heterogeneity in host exposure may reduce the likelihood of coexistence if $\rho > 0$ and there is a substantial difference in the level of heterogeneity for the two species. These results hold when competition occurs through either density-dependent establishment or fecundity. The case where competition acts through parasite-induced host mortality has not been examined, but it maybe possible to extend these results to cover this case.

For clarity, two examples are given of scenarios that will promote the coexistence of competing species. First, consider the case where heterogeneity among hosts is a result of differences in immune status between hosts. This may be due to host genetics as well as environmental determinants such as nutrition and exposure to other parasite species. The many determinants of immune status are likely to affect susceptibility to the two species differently, thus while host susceptibility to one parasite species may be positively correlated with susceptibility to a different species, the correlation is unlikely to be close to unity. For the second example, consider two species, each of which preferentially parasitizes a different host type, e.g. young *vs* old hosts. In this case, hosts will differ in their exposure to each species depending on the variable used by the parasite to identify preference, e.g. host age. Furthermore, in this example exposures to the two species will be negatively correlated: those hosts that have greater exposure to one species are less likely to be exposed to the other species. This negative correlation will greatly enhance the likelihood of coexistence.

These ideas can be extended to competing strains within a single species. The second scenario, favouring coexistence, seems particularly relevant. One can imagine different strains becoming adapted to different host types. Evidence for the existence of genotype-dependent life-history traits is limited. Nonetheless the hypothesis has been tested in *Strongyloides ratti* (Paterson & Viney, 2003) using genetically homogenous lines. Differences were observed in the number of worms present in rats 23 days post-infection for different genetic lines, reflecting differences in establishment and/or survivorship. Clearly these differences require explanation in terms of other differences that might exist between the lines. Otherwise one would predict that in a natural setting the genotype with the greatest rate of establishment (and therefore greatest R_0) should out-compete the other genotypes. Paterson & Viney (2003) explained this finding in terms of a trade-off between survivorship and fecundity. An alternative explanation is that the different genotypes parasitize different

host types so that the heterogeneity allows coexistence even if the R_0 values differ.

Understanding how competing species are able to coexist has been a long-standing question in ecology. Here it has been shown that the coexistence of helminth species is promoted by heterogeneity under a range of circumstances. In particular, heterogeneity promotes coexistence when the correlation between exposure rates is imperfect and the degree of heterogeneity in host exposure to the competing species is not too dissimilar.

8.6 Summary

The models of Chapter 7 are extended to explore competition between two helminth species. Under the assumption of homogeneous host exposure, the Lotka-Volterra model is derived thus demonstrating that two helminth species cannot coexist on a single limiting resource. Heterogeneity in host exposure promotes coexistence provided that the rates of exposure to the two species are not perfectly correlated, and, if they are positively correlated, provided that the degree of heterogeneity in host exposure is similar for the two competing helminth species. These results are robust to the mechanism of competition.

Chapter 9

Discussion

9.1 Models in helminth community ecology

Although the community ecology of parasites has received reasonable attention, and ecological theory is often tested on parasites, there are few models that deal specifically with the ecology of helminth species. Broad comparisons have been made with metapopulation models, models from island biogeography and epidemiological models (Bascompte & Rodriguez-Trelles, 1998; Nee, 1994). In parasite community ecology, concepts such as nestedness (Atmar & Patterson, 1993) and 'core' and 'satellite' species (Hanski, 1982) are derived from metapopulation models. However, results from these models should be cautiously applied to helminth communities since there are fundamental differences between helminth infracommunities and islands or patches. Perhaps the most important is that helminths do not multiply directly within their host (although there are some species where auto-infection is common such as *Enterobius* and *Strongyloides*); thus population size is dependent on the age of the host and the rate of parasite establishment. In contrast, in metapopulation models it is assumed that once colonized, a population will achieve its equilibrium size so that it is sufficient to treat patches as colonized or empty (Levins, 1969).

The existing models that specifically describe the population dynamics of multispecies helminth infection are limited to deterministic models that assume that the mode of interaction is through parasite-induced host mortality (Dobson, 1985; Roberts & Dobson, 1995; Gatto & De Leo, 1998; Pugliese, 2000). The lack of multispecies models is particularly surprising given that the development of single species models is considerably advanced. The negative impact of helminth infection on the health of humans and livestock has provided motivation for the development of a range of models for parasites of different life-histories.

9.2 Extending single species models

Apart from the model of Chapter 5 that considers a single host, all other models are stochastic. The models developed seem to be the first application of stochastic modelling to multispecies helminth infection, and as such allow features of interspecific interactions to be explored that are not amenable to analysis through deterministic models. The model of Chapter 6 provides the first exposition of the effect of interspecific interactions on the distribution of worm burden in a host population. Similarly the stochastic model of Chapter 8 is a first attempt at examining the impact of within host interspecific competition on the coexistence of parasite species.

One of the advantages of using stochastic models rather than deterministic models is that heterogeneity in the susceptibility of hosts to infection can be incorporated into models with relative ease. Heterogeneity in susceptibility is known to be important for the dynamics of microparasites as very susceptible individuals are rapidly infected at the beginning of an epidemic, so that the remaining population is less susceptible (Veliov, 2005). In models of macroparasite infection, heterogeneity has been identified as an important mechanism for generating an overdispersed distribution of worm burden (Anderson & May, 1985a), and deterministic models have shown that the degree of overdispersion can affect the long-term dynamics of mean worm burden in a population of hosts (Anderson & May, 1978). The effect of incorporating heterogeneity directly into models of macroparasite population dynamics has received limited attention (Rosà & Pugliese, 2002). In this thesis, the effects of heterogeneity have been examined in the context of single and multispecies models.

While all the stochastic models explored have been fully stochastic at the point of definition, to analyze the models, both hybrid techniques and moment closure assumptions have been used. There is considerable scope for improvement of these approximations, particularly with regard to the moment closure approximations. In Chapters 7 and 8 the moment closure approximations assumed that third order moments could be expressed in terms of lower order moments according to a functional forms based on the multivariate normal distribution. Alternatively, the 'closure' could use higher order moments; expressing fourth order moments, say, in terms of lower order moments. Alternative functional forms based on other multivariate distributions would also be possible (Chan & Isham, 1998).

9.3 Directions for future work

This thesis proposes models of interspecific interaction among helminth species. The behaviour of the models is examined to determine what effects interactions

may have on the distribution of worm burden and the coexistence of species. To a certain extent such exploration sheds light on the interpretation of data with regard to the existence of interspecific interaction. For instance, the models of Chapter 6 highlight the inadequacy of examining pairwise associations between species to identify interspecific interaction. However, if further progress is to be made, these models or similar ones should be fitted to data. The following is a brief sketch of methods that might be used to do this. Methods are proposed for dealing with both the cross-sectional data that is frequently collected on humans (e.g., Booth *et al.*, 1998; Bundy *et al.*, 1988), and data from non-human hosts that is usually not age-specific (e.g., Behnke *et al.*, 2005; Lotz & Font, 1994; Bush & Holmes, 1986b).

Approximating the distribution of worm burden To fit models to data using maximum likelihood, the distribution of worm burden according to the model must be known. Unfortunately, for the models of Chapter 6, it was not possible to determine the distributions analytically. However, for the linear model, it was at least possible to derive approximations to the first two moments. One approach to fitting the linear model would therefore be to solve the differential equations for the approximations to the first two moments and assume a bivariate normal distribution. This approach is not ideal. Firstly, the moments are only well approximated for a parameter range that will exclude most synergistic interactions; and secondly, the bivariate normal distribution may not be appropriate if the distribution arising from the model is markedly different from the bivariate normal. To address this latter problem other distributions could be fitted. Unfortunately when multivariate distributions other than the multivariate normal are used it is difficult to allow sufficient flexibility in the covariance. For example, Chan & Isham (1998) have used a multivariate distribution based on the negative binomial, but the covariance for this distribution is constrained to be non-negative.

Empirical likelihood As an alternative to specifying a form for the distribution of worm burden to obtain a likelihood, the distribution can be approximated through model simulation. This method of obtaining an empirical likelihood has been adopted by Riley *et al.* (2003) and Duerr *et al.* (2003b), although Duerr does not simulate a fully stochastic model.

Consider observing cross-sectional data $\{(x_1, a_1), ..., (x_n, a_n)\}$ from a random sample of a host population; where $x_i = (x_{1i}, x_{2i})$ is the species 1 and species 2 worm burden in the ith host and a_i is host age. Given host ages, the x_i may be viewed as independent realizations of the non-linear model of Chapter 6 (with heterogeneity) with a certain parameter vector $\theta = (\tilde{\gamma}_{ji}, \mu_{X_i}, \zeta_i, \nu_i, \rho;\ i, j = 1, 2)$. Thus

for given host ages and parameter vector, θ, the distribution of worm burden can be approximated by simulating from the model. The log likelihood of the data is

$$\sum_{i=1}^{n} \log \mathrm{p}(x_i|\theta, a_i) + \log \mathrm{p}(a_i)$$

where $\mathrm{p}(x_i|\theta, a_i)$ is the probability given θ that a host of age a_i has a worm burden x_i, while $\mathrm{p}(a_i)$ is the probability a host survives to age a_i (treating age as a discrete variable).

To obtain a maximum likelihood estimate of the parameter vector, θ, it is sufficient to maximize $\sum_{i=1}^{n} \log \mathrm{p}(x_i|\theta, a_i)$ with respect to θ since the distribution of host age, $p(a)$, is independent of θ. The quantity $\sum_{i=1}^{n} \log \mathrm{p}(x_i|\theta, a_i)$ can be estimated by fixing a value of θ and simulating the distribution of worm burdens at each of the ages a_i. The maximum likelihood estimate is then given by the θ, from a grid of θ values, that maximizes this quantity.

Frequently host age is unknown. Under such circumstances, empirical likelihood can still be used if host ages come from a known distribution $\mathrm{p}(a|\lambda)$ with parameter vector λ. Then the maximum likelihood estimate is obtained by integrating out host age and maximizing

$$\sum_{i=1}^{n} \log \mathrm{p}(x_i|\theta, \lambda)$$

with respect to (θ, λ). In practice, the distribution $\mathrm{p}(x|\theta, \lambda)$ can be simulated for given (θ, λ) by simulating a host age, and then using the model to simulate worm burden at this age.

A drawback to the empirical likelihood approach is that the level of computation may be prohibitive. For a model of filariasis, Riley *et al.* (2003) found that the number of simulations required to ensure a non-zero likelihood was too large for empirical likelihood to be a feasible method of fitting the model to data. Instead, Riley *et al.* (2003) fitted the model using fewer simulations to estimate the distribution function $F(x|\theta, a)$, and minimizing a goodness of fit statistic comparing the estimate of $F(x|\theta, a)$ with the empirical distribution function. Alternatively, the number of simulations could be reduced by smoothing the simulation-derived density function to ensure that there are no zero densities. However, this approach has, as yet, not been tried and it may not be computationally feasible.

Presence/absence data Models can be simplified by considering only the presence/absence of species. Let X be a vector of random variables where X_i, $i = 1, ..., n$,

denotes the presence/absence of species i in a random host. There are only 2^n possible states since $X_i = 0$ or $X_i = 1$. A simple model for the transitions between the states can be specified assuming that: 1) hosts become infected by species i at a rate $\phi_i \mathrm{P}(X_i = 1)$ (i.e. at a rate proportional to to the prevalence of infection) and remain infected throughout their lifetime; 2) hosts die at a constant rate, α, and are replaced by uninfected hosts. The equilibrium distribution can be determined for this model and used to fit the model to data.

The model, as specified, assumes infections with different species occur independently of one another. Thus the model should be viewed as a 'null model' to test for associations between species. It is possible to define models where the rate of infection for a particular species depends on the presence/absence of other species. However, if too many dependencies are introduced into the model, then parameters become unidentifiable.

As it stands, the null model is quite crude, in particular it takes no account of varying host susceptibility. One way of incorporating variable host susceptibility would be to assume that a fraction q of hosts have an increased susceptibility to parasite infection such that the rate of infection with any parasite species is increased by a factor κ. The distribution of presence/absence for the n parasite species, $\mathrm{p}(x|, \phi_i, \alpha, \kappa)$, can be expressed as a mixture of: (i) the distribution that arises given that the random host is of low susceptibility, $s = 0$, and (ii) the distribution given the host is of high susceptibility, $s = 1$, i.e.

$$\mathrm{p}(x|, \phi_i, \alpha, \kappa) = \mathrm{p}(x|s = 1, \phi_i, \kappa, \alpha)q + \mathrm{p}(x|s = 0, \phi_i, \alpha)(1 - q)$$

The expectation-maximization (EM) algorithm has been developed for maximizing likelihood when there are mixtures of distributions, and it may be useful to apply it in this context.

The advantage of using null models such as the ones proposed here over those described in Chapter 2 is that they attempt to model the process of infection and are able to eliminate associations driven by host age and general susceptibility to parasites. Although, by using only presence/absence information, and not incoporating host age explicitly, the models may be too crude to detect weak interactions. Departures from the null model can be identified using a goodness of fit statistic, and should be interpreted in terms of ecological associations between species such as a shared intermediate host or interspecific interaction.

9.4 Concluding remarks

Helminth communities are often described in the terminology of Holmes & Price (1986) as either interactive or isolationist. The terminology is based on the premise that interactions between species are of significance to parasite community structure when parasite densities are high and niches overlap. Thus communities with high parasite densities in which the niches of different species overlap are 'interactive', while communities with low densities and segregated niches are non-interactive. Unfortunately this terminology gives the impression that interactions have been identified in 'interactive' communities. Furthermore it suggests that interactions are unimportant in structuring communities where parasite densities are low. In reality, far less is known about either the existence or the role of interspecific interactions than these definitions would suggest. This thesis has addressed the latter issue; using mathematical models to provide a framework within which to explore the effect of interspecific interactions on the distribution of worm burden and coexistence of species.

The work presented here has confirmed some of the previously used intuitive results regarding the distribution of worm burden, and also produced some less intuitive results and potential avenues for new research. For instance, in contrast to the intuition of Holmes & Price (1986), it has been shown in Chapter 8 that competitive exclusion is more likely in communities where parasite densities are low. Identifying the role of competitive exclusion in determining the composition of low-density parasite communities appears to be an area of research that has thus far been overlooked.

The models developed have not yet been explicitly fitted to data. While this may be a useful undertaking, it should not be seen as a panacea to the problem of identifying interspecific interactions in natural settings. Models are only likely to be useful in situations where the natural history of the helminth species, and heterogeneities in host exposure are reasonably well understood. Moreover, models of interactions between two parasite species should only be applied when there are no confounding effects of interactions with parasite species other than the ones under investigation. Ideally mathematical models should be used when a putative mechanism for interaction has already been identified through experimental studies. Hopefully, developments in immunology will make this scenario increasingly commonplace.

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