Stochastic Processes for Parasite Dynamics

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by

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"Faced with the achievements of Darwin, one cannot claim that mathematics are needed for successful theoretical work in biology. But they certainly make it easier."

John Maynard Smith (1989)

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Abstract

The thesis addresses various problems arising in parasite population dynamics through the use of mathematical techniques, and in particular of stochastic processes.

Parasite diseases generally fall into two categories, those in which a host has a small number of disease classifications, such as susceptible, infected and immune, and those in which the severity of the infection is an important property of the disease. It is the latter type that is addressed in this thesis. Parasite-host interactions are studied via simple nonlinear stochastic processes describing the dynamics of parasites within hosts. In particular, the effect of parasite-induced host mortality and acquired immunity on the distribution of parasite numbers in hosts is considered. Moment closure techniques for approximating nonlinear stochastic processes are investigated for the models, including an assumption based on a new multivariate negative binomial distribution. Approximate results are compared with exact results where obtainable, and results from stochastic simulations elsewhere.

Various stochastic models are proposed for the study of between-host parasite dynamics in a population of immortal hosts. Their solutions and properties are evaluated through the use of systems of differential equations, which lead to varying results according to the host population size and the assumptions made concerning the method of parasite transmission. It is suggested that the structure of a disease transmission process, often implicitly ignored in the modelling process, may have a greater effect on the parasite distributions than currently thought.

Throughout the thesis examples of diseases in humans and wildlife are given to illustrate the motivation behind the mathematical models and the discussions.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Thesis Overview

This thesis addresses and discusses various problems arising in parasite population dynamics through the use of mathematical techniques, and in particular of stochastic processes. The structure of the thesis is as follows. In the following section we introduce the biological aspects of parasitology that are relevant to the studies of the thesis. We then introduce some of the roles mathematics has to play in analysing populations in Section 1.3, and in Section 1.4 we review some of the relevant mathematically-based work in the area.

In Chapter 2, some basic techniques for the analysis of stochastic population processes that will be used in the thesis are outlined. The techniques are illustrated with a simple example.

Chapter 3 begins with a further discussion of mathematical models in various areas of parasite dynamics, and then the subject of parasite-induced excess host mortality is investigated with a particular model. Approximation techniques applicable to this, and other parasite dynamic models, are investigated in this chapter, and further in Chapter 4.

In Chapter 4, the problem of including acquired immunity into parasite-host

models is discussed, and further suggestions for both models and analysis of approximation techniques are considered.

Chapter 5 compares the effects of a number of different transmission mechanisms on the distribution of parasites among hosts. Again, discussion of other work relevant to the area is included.

Finally, in Chapter 6 we outline some areas where the work of this thesis may be extended and where further research would be relevant and interesting.

1.2 Aspects of Parasitology

In this section we outline some of the biological aspects relevant to the modelling and discussions of this thesis. We do not attempt to cover any aspect of parasitology extensively, but merely try to give a flavour of the biology that motivates the ideas presented.

Parasites have been credited with representing more than half the living species of animals and plants (Price, 1980). However, there is no universal definition of a parasite. Anderson and May (1978) require a parasite to utilize its host as a habitat, have nutritional dependence on and cause 'harm' to its hosts. Esch and Fernandéz (1993) give the 'classical' definition of parasitism as

> ... an intimate relationship between two organsims in which one lives on, off, and at the expense of the other,

though they point out that the major problem of this definition is that '...harm is a relative term.' A discussion of definitions and different historical approaches to the study of parasites is given by Cheng (1969), and in Price (1980, Chapter 1).

For the purpose of studying the dynamics, effects and properties of parasites from a modelling perspective, as we shall mostly be doing, the strict definition is not too important. Parasites are closely associated with disease and this in itself makes their study important. However, even if there is no firm evidence of parasites

directly afflicting a host species this does not mean their study is not of interest from an ecological point of view. As Price (1980, Preface) writes, "Parasites affect the life and death of practically every other living organism."

For the purpose of modelling, parasites can be split roughly into two different categories. The first contains those in which the most important factor is simply whether the host does or does not have the infection, and the second involves parasites for which it is important to model the severity of the infection. Mathematically, the former category can usually be sensibly modelled using compartmental models, the latter must also include a more detailed account of the dynamics of the parasite population. The difference can be thought of as being in the choice of unit of study, the host or the parasite.

The terms microparasite and macroparasite have become widely used for the two categories (Anderson and May, 1979). Roughly speaking, viruses, bacteria, funghi and protazoa can be thought of as microparasites, and are associated with compartmental models. Macroparasites can be thought of relating to metazoa (multi-cellular organisms) including helminths and, for modelling purposes some arthropods such as ticks and lice. It is on models for macroparasites that we shall concentrate in this thesis. The numbers of humans infected with macroparasites are enormous, for example it is estimated that one quarter of the world's population is affected by intestinal helminths (Bundy and Cooper, 1989).

The main differences betwen microparasites and macroparasites are as follows. Microparasites are typically much smaller and reproduce directly, and usually at a very fast rate inside the host. Macroparasites do not generally reproduce *directly* inside the host, but have complicated life cycles, involving many stages inside and outside the host, and often vector hosts and free living stages. They are physically much larger than microparasites, as the name suggests, and usually have longer generation lifetimes. The acquired immunity stimulated in the host by microparasites often provides long term protection, whereas specific immunity to macroparasites is usually short term (Anderson and May, 1979). As hosts do not usually develop

full immunity after infection by macroparasites, these infections tend to be more persistent and endemic in a host population. Microparasites are often associated with epidemics in the host population, though they too can be endemic.

The essential features of a parasitic relationship between two organisms were drawn out in one of the earliest pieces of work on quantitative ecological parasitology by Crofton (1971b) as

1) The parasite is physiologically dependent on the host;
2) The infection process tends to produce an overdispersed distribution of parasites within the host population;
3) The parasite kills heavily infected hosts;
4) The parasite species has a higher reproductive potential than the host species.

This second property can also be known as contagion, clumping or clustering, but is most frequently described in present ecological literature as aggregation of parasites.

Aggregation is one of the most important aspects of macroparasite epidemiology and ecology. It has effects on both the host and parasite populations. Anderson and May (1991, page 10) describe it by saying that '...sometimes 20% of the hosts can harbour 80% of the parasites'. As the morbidity or mortality of a disease is often related to the parasite level of the host, the aggregation can cause the hosts with high parasite levels to suffer the effects of disease that would otherwise be quite mild if the parasites were spread evenly among the hosts. This has implications for the application of chemotherapy treatment to reduce disease. Many macroparasites reproduce sexually inside the definitive host and so sexual mating chances inside the host are increased by aggregation. On the negative side for the parasites, the sum of intra-host density-dependent constraints in the whole parasite population will be larger than if parasites were distributed uniformly over a host population.

The cause of aggregation has been subject to much debate but with no con-

clusive answer. The distinction often made (see for example Esch and Fernandéz (1993, Chapter 4) or Poulin (1998, Chapter 6)) is that hosts can gain unusually high parasite burdens either due to chance effects or by being more predisposed to parasitism. Host predisposition could occur through heterogeneities in host behaviour (affecting their chance of becoming infected) or in host immunity and resistance levels, often genetic (Wassom, Dick, Arnason, Strickland, and Grundmann, 1986; Lively and Apanius, 1995). Even if predisposition is established in a host-parasite relationship in the field, it is often difficult to separate out the immune and behavioural differences (Chan and Isham, 1998). In chapters 3 and 5 we study and discuss further some possible causes of aggregation.

The role this clustering of parasites plays in regulating the host population has itself been the subject of study (Anderson and May, 1978). As well as increasing the morbidity of heavily infected hosts, parasite infections can be considered to cause mortality, either directly or, more frequently, through indirect mechanisms (Hudson and Dobson, 1995). These may include reducing the host nutritional levels and thereby increasing susceptibilities to predators and further infection (see Booth, Clayton, and Block (1993), Slater and Keymer (1986) and Slater and Keymer (1988) for examples of this), or reducing the host's ability to obtain food (Saumier, Rau, and Bird, 1994). In any case, mortality rates have often been shown to be related to parasite burden, and this has an effect on the parasite host population stucture (Scott and Anderson (1984), Boray (1969) and Hudson and Dobson (1995) provide examples). This is related to the third of Crofton's aspects of parasitism. Aspects of this area are discussed in Chapter 3, where specifically the effect of parasite-induced excess host mortality on the distribution of parasites in a host population is studied.

In general, a parasite can enter a host through direct means, (by penetrating the host's skin) or indirectly, for example by encysting (protecting itself in a shell inside a vector host until the vector is eaten) or by more direct ingestion by the definitive host from the environment. Endoparasites live within their hosts, while

ectoparasite is the term given to parasites that live on the exterior of the host and are usually not entirely dependent on their hosts for survival. Studies in this thesis will relate to endoparasites, but some models may be applicable to ectoparasites as well.

1.2.1 Parasite Life Cycles

A helminth is a term used for parasitic worms that usually covers the phylum *Platyhelminthes, Nematoda* and *Acanthocephalanes*, or flatworms, roundworms and spiny-headed worms respectivley. We briefly describe some of the important properties and examples of each, and give more detailed descriptions of life cycles of three particular parasites. This is with the aim of illustrating the variety of complicated life cycles macroparasites can have, and to give an indication of the potential difficulties that arise when attempting to transfer information about a life cycle into a model. We will refer to the examples given here throughout the thesis. See Lyons (1978), Despommier and Karapelou (1987) and LaPage (1963) for more details, on which much of the following is based.

The classes of flatworms that are endoparasitic are *Cestoida* (tapeworms) and *Trematoda* (flukes). Endoparasitic flukes are usually in the subclass *Digenea.* They are mostly found in the gut of a vertebrate host. Male and female reproductive organs are both found on adults, except in the family *Schistosomatoidea.* Two of the most common human fluke diseases are Schistosomiasis (estimated to afflict 200 million people worldwide (WHO, 1993)), and the human liver fluke, *Clonorchis Sinensis* which infects through encysts in fish. The life cycle of *Schistosoma mansoni*, one of the three main species that cause Schistosomiasis, starts when the *cercariae* stage of the worm penetrates the human host's skin from freshwater. They then migrate to the liver, mature in about forty days and then mate. The female produces around 300 eggs per day, about half of which reach the intestine and are passed out of the host with faeces. If the eggs reach water, *miracidium*

hatch from the eggs, penetrate into snails and release around two hundred thousand *cercariae* each, 15-75 days later. The *cercariae* swim to the water surface and remain infectious to hosts for around one day.

Tapeworms (*Cestoida*) usually live in the intestine of veterbrates. Adult worms contain both male and female reproductive organs. Definitive hosts are infected by ingesting either an infected intermediate host or its faeces.

Nematodes (roundworms) tend to have less complicated life cycles than flatworms, and the sexes are always separate. There are always four larval stages, termed L1-L4. Nematode parasites that live in animal intestines have direct life cycles, and examples include Hookworm (a disease caused by *Necator americanus* and *Ancyclostoma duodenale* and estimated to effect several hundred million people (Bundy and Cooper, 1989)) and many parasites of livestock. The lifecycle of the *Teladorsagia circuminta* nematode which infects sheep is as follows. Each female in the host lays around 10^5 eggs per day, some of which pass out through host faeces onto the pasture, and hatch in around 15 hours. Once L3 larvae have developed, they climb up grass blades to become more easily ingested by grazing sheep. Once ingested, they take 3-4 weeks to become mature and able to reproduce sexually.

Filarial nematodes are usually transmitted by mosquitoes and flies, and are responsible for causing filariasis, a complex of diseases including onchoceriasis (or river blindness) and elephantiasis, that are widesperad in warm climates (an estiamted prevalence of 300 million (Wakelin and Blackwell, 1988)). Elephantiasis is caused by *Wuchereria Bancrofti*, the life cycle of which is as follows. When an infected mosquito bites a human host, L3 larvae enter the blood stream and migrate to the lymphatic nodes where they develop to sexual maturation in approximately one year. Females produce larvae known as microfilarie which can live for about $1\frac{1}{2}$ years in the blood stream. The microfilarie are found in peripheral blood at periodic time intervals, corresponding to the times when the appropriate vector mosquitoes feed on the host most frequently. Once microfilarie have been taken up by a biting mosquito they become infectious within two weeks, and so the life cycle

is completed.

The third phyla of parasitic helminths are spiny-headed worms (*Acanthocephalanes*) which usually live in the gut of birds and fish and often have indirect life cycles.

1.2.2 Immunity to Parasites

As previously mentioned, acquired immunity to macroparasites is not usually long term. In Chapter 4 we discuss and compare models for the immune response, some previously proposed and some new. The area of immuno-epidemiology, the study of the role of the immune system on a disease at the population level is a relatively new, but growing area. It is, however, a difficult area in which to apply mathematical modelling as knowledge of the details of the dynamics, biological workings and effects of the immune system is still incomplete. The immune system of vertebrate hosts is extremely complicated. and it is difficult to identify the roles and effects of cells involved, and still harder to quantify these effects. The details and workings of an immune response are very particular to the host-parasite interaction concerned but here we give an extremely rough outline that is necessarily a huge oversimplification.

There are many difficulties when measuring an immune response to a parasite infection, not least the question of which antigen or antibody should be measured (Woolhouse, 1995). An antigen is the material released by the parasite, often proteins, that is recognised as 'foreign' by the host so that an antibody reaction is produced. Due to its relative complexity, a macroparasite is likely to release a wider range of antigens upon entering the host than a microparasite. For this reason details of all the immune responses to macroparasites are harder to understand fully. Additionally, there may be more than one type of macroparasite in the host, each stimulating a different immune response.

The immune system involves a large number of different cell types interacting

and stimulating reactions against the invading body. The defence is either through direct attacks by antibodies, by cytotoxic T cells killing infected host cells or by macrophages killing intracellular parasites. The whole process involves an enormous amount of feedback, signalling and self-regulation that itself is the subject of a growing amount of mathematical modelling. Often the mature parasites are capable of evading the hosts' immune defences, so that the immune response may only cause pathological effects to the host itself. In helminth infections, it is the larval worms that are often killed directly by antibodies before they are able to mature. In some host-parasite relationships the cost to the host of mounting an immune response high enough to completely expel the macroparasite may be too great when considered as a trade off against the harm of the parasite. The complexity of the response may also partly explain why host immunity is rarely life long.

Detailed knowledge of immune responses to helminths is still limited, if growing. For this reason, the approach taken towards modelling the immune system in Chapter 4 is to simplify the process greatly and consider the effects of possible mechanisms on the parasite population, rather than details of cell interactions. Further details are given in Chapter 4. For a more detailed account of the biological workings of the immune response to helminths, see for example Stites, Terr, and Parslow (1994, Chapter 50), Roitt, Brostoff, and Male (1996, Chapter 18) or Wakelin and Blackwell (1988).

1.3 Mathematics and Population Biology

Mathematics does not rest as easily with biology as it does with physics, astronomy or even chemistry. These disciplines have made advances hand in hand with mathematics for centuries, whereas it is relatively recently that a wide theory involving the synthesis of mathematics and biology has developed. The main reason for this is of course the scarcity of robust, general laws in biology that can be expressed mathematically. As J. Maynard Smith (Maynard Smith, 1968, page 2), a long time

proponent of the use of mathematics in biology, says

> We rarely know enough about the laws governing the components of biological systems to be able to write down the appropriate equation with any confidence in the first place.

Ultimately, perhaps this can be viewed as a consequence of a biological system itself consisting of many physical and chemical systems ongoing within, for every tiny biological action.

Historically, the biological sciences appeared to lag behind the physical sciences until the last hundred years or so. When the great advances of the seventeenth century were being made in quantitative studies of mathematics, physics and astronomy (or natural philosophy as it was known then), the view of Descartes of the body as a mechanical device, and more generally his idea of universality encompassing biology, was widely accepted. William Harvey (1578-1637) is often cited as providing some of the first work in quantitative biology (see for example Asimov (1965)), following his publication in 1628 that showed that blood must circulate the body (Harvey, 1628). However, many other attempts at applying the advances in quantitative and mechanistic thinking proved unsuccessful due to the lack of biological knowledge.

John Graunt's (1620-1674) famous study of disease in London, and the invention of the life table using the London Bills of Mortality (Graunt, 1662) are some of the earliest examples of analysis of population data. Thomas Malthus' seminal essay on populations (Malthus, 1798; Boulding, 1959) suggesting that they tend to grow geometrically (exponentially) included one of the earliest mathematical models of populations. It led to the term 'Malthusian parameter' used by Fisher (1930) for the intrinsic natural growth rate; that is, the growth rate of a population in the absence of changes in birth and death rates due to resource or other constraints. Even earlier than Malthus, Euler (1767) used mathematical techniques to study human population growth (see Keyfitz and Keyfitz (1970) for an English transla-

tion). P.F Verhulst first proposed a mathematical model that included constraints on the exponential growth of the Malthus model, known as Verhulst's Logistic Curve (Verhlust, 1838). Other important pioneering work included models with age structure and the renewal integral equation by Lotka (1907) and Sharpe and Lotka (1911). The following work of Lotka (1924), Volterra (1926) and Volterra (1931), including the well known predator-prey equations, provided the foundations for much of the further mathematical modelling of populations that has developed this century (see Scudo and Ziegler (1978) for some English translations of this work). The area has now grown to be a vast field, both in the range of biological populations modelled and the mathematical techniques used. On a historical note, perhaps the first published use of mathematics in the study of populations in biology in Western Science was Fibonacci's series, in Leonardo of Pisa's (c 1170-1250) *Liber Abaci*, published in 1202 (Young, 1998). The series was given as an answer to the problem

> How many pairs of rabbits can be produced from a single pair in a given year if every month each pair begets a new pair, which from the second month on becomes productive ?

and is now known to be relevant for patterns of petals and leaves in plants.

In general it could be argued that just as the physical sciences have traditionally stimulated advances in mathematics, biological sciences have also contributed to a large number of advances in mathematics this century, particularly in the area of probability and statistics. Bienaymé (1845) and, independently, Galton and Watson (Galton, 1873; Watson, 1873; Galton and Watson, 1874) studied populations probabilistically and laid the foundations for branching process theory. A large amount of early work in stochastic processes was applied to problems on population growth (see for example Kendall (1949)). Perhaps the first widespread and most successful application of mathematics to biology has been in the field of population genetics, Mendel's laws of inheritance providing a relatively rigorous basis

for establishing the mathematical foundations.

Generally, the use of probability and statistics is important in biology due to the inherent differences between 'similar' organisms. The applications of stochastic processes to the biological, and especially population, sciences has therefore been a flourishing field. The choice between stochastic and deterministic models should depend largely on the motivation behind the modelling, and often both have a role to play. Mathematical and statistical models can be used for a wide range of purposes. It may not be especially productive to attempt a general discussion on the merits of different approaches to modelling here, but it is worth understanding the benefits that can be gained.

Models can be used for purely predictive purposes, for description of processes and for gaining understanding of the mechanisms of a process under study. Often purely predictive models have no relationship to the actual (physical or otherwise) mechanisms involved. This may be because the processes are not of interest, or are too complicated to be modelled directly. None of the models presented in this thesis are of this type. However, the use of stochastic mechanisms themselves may be considered as a way of subsuming the workings of a large amount of highly detailed mechanisms into a probabilistic description. As mentioned earlier, this is especially relevant in the biological sciences as the intricate details of so many processes are too complicated to model explicitly.

Descriptive models generally provide information about the relationship between different variables, whilst mechanistic models start from assumptions about the actual physical process involved and study the consequences. Of course there is a large amount of overlap in model types. There exists a spectrum of approaches within mechanistic models ranging from detailed models aiming at a high level of realism, to more general models aimed at providing a framework for discussion of the processes being modelled. May (1973) has called the two approaches (respectively) tactical and strategic models. As they contain specific details, the benefits of the tactical models are perhaps more obvious, whilst on the benefit of the stategic

models May (1973) writes 'such (strategic) framework can serve a useful purpose in indicating key areas or relevant questions for field and laboratory (study), or simply in sharpening discussion of contentious issues.' Further, he writes, 'tactical and strategic approaches mutually reinforce, each providing new insights for the other.' In this thesis, the models of chapters 3 and 4 lie somewhere in between the two approaches, whilst as they stand the models of Chapter 5 are very much of the strategic nature.

For excellent overviews on the use of mathematical techniques in population biology see Renshaw (1991) and Nisbet and Gurney (1982). In the following section we concentrate on mathematical models of infectious diseases.

1.4 Population Dynamics of Infectious Diseases

The first recorded instance of mathematics being used to study the dynamics of a disease was by Daniel Bernouilli in 1760 (Bernoulli, 1760), but it was not until the early part of this century that the area really progressed. This is in part due to a greater knowledge of the biological workings of diseases. The understanding of biology was such that it was not until the mid eighteenth century that the idea of spontaneous generation of micro-organisms was completely dispelled by Louis Pasteur. The advances around this time in microbiology paved the way for a better understanding of infectious diseases.

Hamer (1906) was the first to propose the idea of an epidemic developing according to mathematical rules involving susceptibles and infectives using a compartmental model. Ross (1911) and Kermack and McKendrick (1927) (reprinted in Kermack and McKendrick (1991)) developed these ideas into deterministic continuous time models for malaria and general epidemics respectively, and the foundations of a growing body of literature in epidemic theory developed. Early probabilitic work on epidemics included McKendrick (1926), who introduced a stochastic compartmental model, and the chain binomial models of Reed and Frost (Abbey, 1952)

and Greenwood (1931). The number of papers on mathematical studies of infectious disease has grown enormously since these early works, and reviews have been provided by Bailey (1975), Anderson and May (1991); see also the collections Anderson and May (1982b), Isham and Medley (1995), Mollison (1995) and Grenfell and Dobson (1995).

The early works on epidemics described above are relevant to microparasites. Kostitzin (1934) was perhaps the first to study mathematical models that directly considered disease severity in terms of parasite numbers in hosts (see Scudo and Ziegler (1978, pages 369-408) for an English translation). He considered an infinite system of differential equations representing numbers of hosts in particular infection states. Despite the huge number of people affected by macroparasite infections, it was not until much later, in the nineteen sixties, that mathematical modelling in this area was taken further.

Hairston (1962), Hairston (1965) and MacDonald (1965) provided early deterministic attempts to model schistosome parasites, whilst Tallis and Leyton (1966), Tallis and Leyton (1969) and Leyton (1968) used stochastic models for within host dynamics of nematode parasite infections in sheep. The papers of MacDonald (1965) and Leyton (1968) were amongst the first to include sexual mating of parasites in modelling terms. Initially, schistosome parasite modelling received the majority of the attention in macroparasite modelling, which included deterministic work (May, 1977; Cohen, 1977; Goddard, 1978), and hybrids of stochastic and deterministic models (Nåsell and Hirsch, 1973; Nåsell, 1985; Lewis, 1975).

A more ecological approach to helminth modelling with the interaction of the host and parasite populations being the focus, was initiated by Crofton (1971b), Crofton (1971a) and pursued by Anderson (1974), Anderson and May (1978) and May and Anderson (1978).

Both the models tailored towards specific parasite host relationships and more general host parasite models have received a growing amount of attention since the nineteen eighties. See Anderson and May (1985), Anderson and May (1991),

Roberts (1995) and Roberts, Smith, and Grenfell (1995) for reviews. Here we give a brief selection of recent work in this area, – more detailed outlines of some macroparasite models will be given in Section 3.1.

Much of the work in macroparasite modelling has concentrated on models that are essentially deterministic although some allowance for the variability of parasite load between hosts may be made. One way of doing this is to make assumptions about the statistical distribution of parasites in the host population that remains fixed in time. Essentially this reduces the dimension of the dynamical system to a manageable level. See Crofton (1971a), Anderson and May (1978) and May and Anderson (1978) for early work using this method. The technique has been used for the study of a large number of ecological effects involving parasitic diseases, often with the purpose of assessing whether particular host parasite effects are stabilising or destabilising for the host population. Diekmann and Kretzschmar (1991) provide a more general model based on the assumptions of Anderson and May (1978), and Kretzschmar (1993), Adler and Kretzschmar (1992) and Kretzschmar and Adler (1993) analysed these assumptions further and suggested extensions to the method. White, Grenfell, Hendry, Lejeune, and Murray (1997) and White and Grenfell (1997) have used the technique to consider seasonality of host birth rates. Roberts and Dobson (1995) have looked at the dynamics of more than one type of parasite in a host population. Also see Damaggio and Pugliese (1996) and Pugliese, Rosa, and Damaggio (1998) for further work in this area.

The collections Scott and Smith (1994) and Grenfell and Dobson (1995) provide a good source of work on a wide number of problems in parasite dynamics. See also Roberts and Heesterbeek (1995) and Heesterbeek and Roberts (1995)

The work of Hadeler and Dietz (1983) provides a neat solution using generating functions to the problem of keeping parasite numbers discrete whilst anlaysing host parasite population dynamics. Hyperbolic partial differential equations were solved for a model that included age structure of the host population. See also Hadeler (1984) in this area, as well as extensions of this work by Kretzschmar (1989b) and

Kretzschmar (1989a).

Anderson and Gordon (1982) looked at different processes affecting the dispersion of parasite loads, with emphasis on the effect of parasite-induced host mortality. They summarised some stochastic immigration-death processes, as well as providing some Monte Carlo simulations. See also Pacala and Dobson (1988) for studies of parasite distributions on host populations.

There are few stochastic models for macroparasites, especially when taken in comparison with the microparasite literature. The interesting work of Barbour and Kafetzaki (1993) uses a stochastic model to investigate possible causes of aggregation for a closed populations of identical, immortal hosts. The model contains an assumption concerning the hosts's immune mechanism that leads to interesting threshold phenonema that are looked at in Barbour, Heesterbeek, and Luchsinger (1996). Recently, but without including parasite-host interactions, Quinnell, Grafen, and Woolhouse (1995) have proposed a discrete-time stochastic model in which they investigate the effects of predisposition (of hosts to infection) on parasite aggregation by assuming that the numbers of parasites picked up by a particular host in separate time periods are dependent random variables. Grenfell, Dietz, and Roberts (1995a) extended within-host stochastic models to include immune effects and parasite induced host mortality analytically, and work by Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) and Isham (1995) follows on from this. Many of the studies in chapters 3 and 4 of this thesis have developed from the ideas of these three papers.

Chapter 2

Stochastic Population Processes

2.1 Probability Equations

The stochastic processes used in this thesis will represent population processes. They are all discrete and positively valued, and in continuous time. Some basic theory is presented in this chapter with emphasis on those techniques used later on. Markov processes are mostly used, though possible extensions to Semi-Markov processes are indicated, and in places analysed. The advantage of Markov processes is that they are relatively tractible mathematically, whilst still providing qualitative information about the process under study.

In this section we describe a method for writing down a partial differential equation for a probability generating function of a discrete valued Markov process that is based on the forward equations of the Chapman-Kolmogorov property. As we use discrete valued processes, we work mostly with probability generating functions, though the results given apply more generally to characteristic functions.

Assume the joint probability generating function for an N variable, continuous time Markov process, $\boldsymbol{X}(t)$, exists and is written $P(\boldsymbol{s};t) := \mathrm{E}\left(\boldsymbol{s}^{\boldsymbol{X}(t)}\right)$, where $\boldsymbol{s}^{\boldsymbol{X}(t)} = \prod_{i=1}^{N} s_i^{X_i(t)}$. Its partial derivative can be written in the form

$$\frac{\partial P}{\partial t} = \lim_{\delta t \to 0} \frac{\mathrm{E}\left(\left(\boldsymbol{s}^{\boldsymbol{\Delta X}(t)} - 1\right)\boldsymbol{s}^{\boldsymbol{X}(t)}\right)}{\delta t} \tag{2.1}$$

where $\boldsymbol{\Delta X}(t) = \boldsymbol{X}(t+\delta t) - \boldsymbol{X}(t)$. If the Markov process is specified such that the limit

$$K(\boldsymbol{s};\boldsymbol{X};t) := \lim_{\delta t \to 0} \frac{1}{\delta t}\left(\mathrm{E}(\boldsymbol{s}^{\boldsymbol{\Delta X}(t)} \mid \boldsymbol{X}(t)) - 1\right) \tag{2.2}$$

exists, and $\left(\mathrm{E}(\boldsymbol{s}^{\boldsymbol{\Delta X}(t)} \mid \boldsymbol{X}(t)) - 1\right)/\delta t$ is bounded above and below for finite δt, we can interchange the expectation and limit and write (2.1) as

$$\frac{\partial P}{\partial t} = \mathrm{E}\left(K\left(\boldsymbol{s};\boldsymbol{X}(t);t\right)\boldsymbol{s}^{\boldsymbol{X}(t)}\right). \tag{2.3}$$

Consider more specifically an N variable integer valued Markov process that has a set of possible transitions, $\mathcal{C} = \mathbb{Z}^N \backslash \mathbf{0}$, with transition probabilities of the form

$$P(\boldsymbol{\Delta X}(t) = \boldsymbol{c} \mid \boldsymbol{X}(t) = \boldsymbol{x}) = f_{\boldsymbol{c}}(\boldsymbol{x})\delta t + o(\delta t)$$

for all $\boldsymbol{c} \in \mathcal{C}$, so that

$$P(\boldsymbol{\Delta X}(t) = \mathbf{0} \mid \boldsymbol{X}(t) = \boldsymbol{x}) = 1 - \sum_{\boldsymbol{c}\in\mathcal{C}} f_{\boldsymbol{c}}(\boldsymbol{x})\delta t + o(\delta t),$$

where $f_{\boldsymbol{c}}(\boldsymbol{x})$ is assumed to be a multinomial in the components of $\boldsymbol{x}$ for each $\boldsymbol{c}$. We can write K as

$$\begin{aligned} K(\boldsymbol{s};\boldsymbol{x};t) &= \lim_{\delta t \to 0} \frac{1}{\delta t}\left(\sum_{\mathbf{c}\in\mathcal{C}} \boldsymbol{s}^{\mathbf{c}}\left(f_{\mathbf{c}}(\boldsymbol{x})\delta t + o(\delta t)\right) - \sum_{\mathbf{c}\in\mathcal{C}} f_{\mathbf{c}}(\boldsymbol{x})\delta t + o(\delta t)\right) \\ &= \sum_{\mathbf{c}\in\mathcal{C}} f_{\mathbf{c}}(\boldsymbol{x})\left(\boldsymbol{s}^{\mathbf{c}} - 1\right) \end{aligned} \tag{2.4}$$

and hence (2.3) can be written as

$$\frac{\partial P}{\partial t} = \mathrm{E}\left(K\left(\boldsymbol{s};\boldsymbol{s}\frac{\partial}{\partial \boldsymbol{s}};t\right)\left(\boldsymbol{s}^{\boldsymbol{X}(t)}\right)\right)$$

where K is now a partial differential operator and $\boldsymbol{s}\frac{\partial}{\partial \boldsymbol{s}}$ has i^{th} component $s_i\frac{\partial}{\partial s_i}$ for $i = 1, ..., N$. As $K\left(\boldsymbol{s};\boldsymbol{s}\frac{\partial}{\partial \boldsymbol{s}};t\right)\left(\boldsymbol{s}^{\boldsymbol{X}(t)}\right)$ is infinitely differentiable for $|\boldsymbol{s}| \leq 1$ we can interchange the expectation and differential operator and write

$$\frac{\partial P}{\partial t} = K\left(\boldsymbol{s};\boldsymbol{s}\frac{\partial}{\partial \boldsymbol{s}};t\right)\left(P(\boldsymbol{s};t)\right) \tag{2.5}$$

which provides a partial differential equation for the probability generating function of $\boldsymbol{X}(t)$. Whittle (1957, page 269) has referred to (2.5) as the *Bartlett relation*, but Bartlett himself (Bartlett, 1949) credits Palm (1943) as being the first to publish this result. Bailey (1964, page 70) refers to this as the *'Random variable' technique*, (possibly because it uses $\boldsymbol{\Delta X}(t)$ as a random variable), but we shall call it the *Palm relation*, or the forward equation for the probability generating function.

2.2 Moment Equations

Though this section is concerned with moments of a stochastic process, we first post a brief warning about relying too heavily on them. Some processes may have realisations that rarely look anything like their means. The obvious example for population processes is a population that relies on self perpetuation so that there is a chance of extinction. In such cases the mean of the process may fall well below the mean conditional on the survival of the population. Fade out in epidemics (in which a disease in a closed population may become extinct) is one of many examples of this (see Bailey (1975)). The observation of a population will sometimes occur only if the population has survived, and so care should naturally be taken in interpreting these sorts of results. In addition, if a distribution is typically non-Gaussian then only considering say the first two moments may leave out a lot of important information.

The result (2.5) given in Section 2.1 enables us to find a partial differential equation for the probability or moment generating function of many Markov population processes. If this can be solved then moments are easily obtainable from either generating function. It is also possible to derive ordinary differential equations for any order moment without directly solving the Palm relation (2.5) by differentiating and setting the arguments to 1 or equivalently equating coefficients of powers of the argument. This is of interest if the partial differential equation is not easily solved, or if only the moments of the process are required and so there is no need

to find the full generating function.

It is often the case that if the Palm relation (2.5) is not directly solvable then the ordinary differential equations for the moments derived from it are also not easily solvable. Markov processes in which the transition probabilities are nonlinear in the variables, called nonlinear processes, often fall into this category. The benefit of deriving the ordinary differential equations for the moments comes from being able to interpret more readily any solutions obtained via approximation techniques, numerical or otherwise. When numerical approximation techniques are applied to the partial differential equation for the generating function, results are at best difficult to utilise.

Any differential equation for a moment of a nonlinear process will involve terms of higher order moments so a solution cannot be found as no system of moments will ever be closed. Various methods of approximating nonlinear processes will be discussed in the next section.

There is a slightly quicker method of deriving moment ordinary differential equations that does not involve the use of generating functions. It is essentially similar in that it utilises the forward equation for the process. We use an example to illustrate this.

Consider an immigration-death process. If the death rate of each individual is constant regardless of the number of individuals present, then we have linear death. Suppose, however, that the death rate of each individual increases when there are more individuals present, due to density dependent constraints such as competition for resources. It may be that the individual death rate is proportional to the total number of individuals present, and we then have a density dependent immigration-death process. In this case deaths occur in the population during $(t, t+\delta t)$ with probability $\mu M(t)^2 \delta t + o(\delta t)$, where $M(t)$ is the population total at time t. The

two possible transitions we are considering are, from $M(t)$ to

$$\begin{array}{ll} M(t)+1 & \text{at rate } \lambda \\ M(t)-1 & \text{at rate } \mu\, M(t)^2 \end{array}$$

by which we mean that, conditional on $M(t)$, $M(t+\delta t)$ can take the values

$$\begin{array}{rll} M(t)+1 & \text{with probability} & \lambda\delta t + o(\delta t) \\ M(t)-1 & \text{with probability} & \mu(M(t))^2\delta t + o(\delta t) \\ M(t) & \text{with probability} & 1-\lambda\delta t - \mu(M(t))^2\delta t + o(\delta t) \\ M(t)+c & \text{with probability} & o(\delta t) \qquad\qquad \text{for } c \in \mathbb{N}\backslash\{-1,0,1\}. \end{array}$$

Using the notation of Section 2.1,

$$\begin{aligned} f_1(x) &= \lambda \\ f_{-1}(x) &= \mu x^2 \end{aligned}$$

so that the Palm relation (2.5) for the probability generating function $P(x;t) := \mathrm{E}\left(s^{M(t)}\right)$ is

$$\frac{\partial P}{\partial t} = (1-s)\left(\mu s \frac{\partial^2 P}{\partial s^2} + \mu \frac{\partial P}{ds} - \lambda P\right). \tag{2.6}$$

As mentioned above, succesive differentiation of (2.6) with evaluation at $s=1$ will give an ordinary differential equation for the moments, as will expansion and evaluation of coefficients. Alternatively, these differential equations can be formed from the specification of the process itself as follows. Using the transition probabilities above, we can write

$$\begin{aligned} \mathrm{E}(M(t+\delta t)\,|M(t)) = \quad & (M(t)+1)\,(\lambda\delta t + o(\delta t)) + \\ & (M(t)-1)\left(\mu M(t)^2\delta t + o(\delta t)\right) + \\ & M(t)\left(1-(\lambda+\mu M(t)^2)\delta t + o(\delta t)\right) + \\ & \sum_{c\in\mathbb{N}/\{-1,0,1\}} (M(t)+c)\, o(\delta t) \end{aligned}$$

and

$$\begin{aligned}\mathrm{E}(M(t+\delta t)^2|M(t)) = \quad & (M(t)+1)^2\left(\lambda\delta t + o(\delta t)\right) + \\ & (M(t)-1)^2\left(\mu M(t)^2\delta t + o(\delta t)\right) + \\ & M(t)^2\left(1-(\lambda+\mu M(t)^2)\delta t + o(\delta t)\right) + \\ & \sum_{c\in\mathbb{N}/\{-1,0,1\}} (M(t)+c)^2 o(\delta t).\end{aligned}$$

Rearranging and dividing both sides by δt gives

$$\frac{1}{\delta t}\left(\mathrm{E}(M(t+\delta t)|M(t)) - M(t)\right) = \lambda - \mu(M(t))^2 + \frac{o(\delta t)}{\delta t}$$

and

$$\frac{1}{\delta t}\left(\mathrm{E}(M(t+\delta t)^2|M(t)) - M(t)^2\right) = \lambda + 2\lambda M(t) + \mu M(t) - 2\mu(M(t))^3 + \frac{o(\delta t)}{\delta t}$$

where upon we remove the conditioning and take limits as $\delta t \to 0$ to obtain

$$\begin{aligned}\frac{d\mathrm{E}(M(t))}{dt} &= \lim_{\delta t\to 0}\left\{\mathrm{E}\left(\frac{1}{\delta t}\left(\mathrm{E}(M(t+\delta t) - M(t)|M(t))\right)\right)\right\} \\ &= \lambda - \mu\mathrm{E}(M(t)^2) \qquad (2.7)\end{aligned}$$

and

$$\begin{aligned}\frac{d\mathrm{E}(M(t)^2)}{\delta t} &= \lim_{\delta t\to 0}\left\{\mathrm{E}\left(\frac{1}{\delta t}\left(\mathrm{E}(M(t+\delta t)^2 - M(t)^2|M(t))\right)\right)\right\} \\ &= \lambda + 2\lambda\mathrm{E}(M(t)) + \mu\mathrm{E}(M(t)^2) - 2\mu\mathrm{E}(M(t)^3). \qquad (2.8)\end{aligned}$$

This is not a closed system as each equation contains terms of higher order moments. Equation (2.8) includes $\mathrm{E}(M(t)^3)$ - including the differential of $\mathrm{E}(M(t)^3)$ would add the term $\mathrm{E}(M(t)^4)$ and so on. As already noted, this will be the case in general for processes with nonlinear transition probabilities.

The degree of the nonlinearity of the transition probabilities will affect how many higher order terms are in each equation. If the transition probabilities for variable M involve k variables multiplied together, the ordinary differential equation for a moment of M will contain moments of order $k-1$ higher. For example,

if there are transition probabilities which are products of *three* of the variables of the process, (in a univariate case proportional to $M(t)^3$), then each differential equation of the n^{th} order moment will contain terms of the $n+2$ $^{\text{th}}$ order . This can be seen from studying the form of (2.5).

2.3 Approximation Methods

2.3.1 Moment Approximations

Various approximations can be made in order to close the system of differential equations for the moments of the process. One is to assume a relationship between some of the moments of different orders. This involves taking the equations for the moments we are interested in and writing all higher order terms in those equations in terms of the variables concerned. The crudest of these approximations is to make the deterministic assumption that $\mathrm{E}(M^2) = \mathrm{E}(M)^2$ so that the system of means is closed. This is equivalent to assuming that there is no variance in the process.

A slightly more sophisticated, but sometimes more ad-hoc, method is to use fixed relationships between higher order moments that are determined from a specified random variable. (The deterministic approximation uses the constant random variable). There may be some reason or practical justification as to why a particular distribution is used, or the method may be used in a pragmatic, heuristic way.

For example, often the normal distribution is used to provide the assumptions about the moment relationships. An early discussion of this approximation technique was given by Whittle (1957). Some of the early uses of the method include Moyal (1949), see also Chandrasekhar (1943). Whittle himself, referring to the equivalent assumption of Chandrasekhar (1955) that the variates have cumulants which vanish for order greater than the third, says "the justification for this assumption is not clear, but results yielded by treatments of this type appear to agree

relatively well with both intuition and experiment." This was of course before the days when extensive simulations were routinely possible.

There is a class of population processes (called density dependent population processes in Kurtz (1981)) that converge weakly to Gaussian processes in the limit of the initial population size, shown in Kurtz (1970) and Kurtz (1971). See Kurtz (1981) and Ethier and Kurtz (1986) for more details. For large populations, this provides some justification for the moment assumptions based on the normal distribution, and in some cases accurate results (see Isham (1991)). The processes considered in this thesis are not of this type.

The univariate normal distribution is defined by two parameters, and so the system of equations involving the first and second moments can be closed in a unique way. The univariate normal distribution yields the relationship

$$\mathrm{E}(X^3) = 3\mathrm{E}(X)\mathrm{E}(X^2) - 2(\mathrm{E}(X))^3. \tag{2.9}$$

If the moment relationships are derived by assuming simply that the univariate random variable is symmetric, then setting the skewness to zero gives the same relationship. Thus in the univariate normal approximation case the assumption used to derive the moment relationship can be weakened to assuming symmetry about the mean.

If a distribution other than the normal is more likely to resemble the population distribution then using its moment relationships may give more accurate results. For example, if the population is highly skewed and takes only positive integer values (as most population processes will), a negative binomial distribution may sometimes be more appropriate. This distribution is relevant to some of the biological processes studied later, and is frequently used in ecological models to fit field data. We investigate the accuracy of using this alternative distribution for various models in Section 2.4 and in Chapter 3. There are many ways of parameterising the negative binomial distribution; in the univariate case we will use parameters

such that $Y \sim \text{NegBin}(p, k)$ if Y has probability generating function

$$P_Y(z) = \left(\frac{p}{1-(1-p)z}\right)^k \tag{2.10}$$

for real $k > 0$ and $0 < p < 1$.

From (2.10) we have that $\text{E}(Y) = k(1-p)/p$, $\text{Var}(Y) = k(1-p)/p^2$ and the relationship

$$\text{E}(Y^3) = \text{E}(Y)^2 + \text{E}(Y^2)\left(2\text{E}(Y^2)/\text{E}(Y) - \text{E}(Y) - 1\right) \tag{2.11}$$

can be derived.

We can see that this will present a problem if we wish the mean to have value zero at any point. In practice, positive integer valued population processes will not have mean zero unless the population is zero with probability 1. The only practical situation of interest where this may be the case is the initial state of a population. Ways of getting around this, such as setting the initial mean to a very small value should be used carefully, though in many models it is unlikely that the moment equations will be sensitive to initial conditions. The problem arises from the fact that a constant value of zero cannot be obtained from the negative binomial distribution, unlike the normal distribution. However, given the approximate nature of the method, ways around the problem used carefully should not affect the results greatly.

As with the normal distribution, the negative binomial distribution has two parameters and so (2.9) and (2.11) will provide a unique method of substitution for systems with first and second order moments. If a third order moment is required, or included as an attempt provide more accuracy to the first two equations, then a univariate three parameter distribution is needed. The negative binomial can be extended to a three parameter version by considering the number of trials until k runs of r successes occur, often called a negative binomial distribution of order r. We do not use this in the thesis, but setting $r = 1$ gives the negative binomial distribution so any process whose moments follow the negative binomial moments

relationship closely are likely to be at least as closely approximated using this distribution.

If we have more than one variable in our stochastic process, we need to assume the moment relationships derived from a multivariate distribution. In order that there is a unique way of closing the system there should be the same number of parameters as there are moments we are interested in. For example, if the first and second order moments are kept in the system then an n variable system will provide $\frac{1}{2}n(n+3)$ equations, (n 1^{st} order and $\sum_{i=1}^{n} i = \frac{1}{2}n(n+1)$ 2^{nd} order moments) and so any multivariate distribution used will need to have $\frac{1}{2}n(n+3)$ parameters to provide a unique closure.

A multivariate normal distribution has this required number of parameters. For example, if $n = 3$ there are three means and six elements of the symmetric variance matrix (giving the nine parameters needed) and the third order moments have the form

$$\begin{aligned} E(W_1W_2W_3) &= E(W_1)E(W_2W_3) + E(W_2)E(W_3W_1) + E(W_3)E(W_2W_1) - \\ &\quad 2E(W_3)E(W_1)E(W_2), \end{aligned}$$

with the others following by symmetry of W_1, W_2 and W_3. Possible choices for a multivariate negative binomial distribution are discussed in Section 3.6.

While there are situations in which there is a good justification for using these types of approximations (Kurtz, 1971; Ethier and Kurtz, 1986; Isham, 1991), often the only 'justification' is a pragmatic one. Of course, in these cases, great care needs to be taken in their use and interpretation. In analysis of models of parasite dynamics Grenfell, Dietz, and Roberts (1995a) and Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) have used the approximations without any real theoretical justification. Isham (1995) provides exact results for simple cases of the models of Grenfell, Dietz, and Roberts (1995a) that show some success for the approximations. More discussion of these approximation techniques is given in chapters 3 and 4. Clearly care, and more research, is needed in this area, particularly as these

so called 'moment closure' approximations appear to be attracting great interest in the study of parasite dynamics, as well as in other biological fields (Chan and Isham, 1998; Michael, Grenfell, Isham, Denham, and Bundy, 1998).

In this thesis we provide further studies and insight into the use of these methods, particularly in the area of parasite dynamics. The models studied are often simple enough that stochastic (or Monte Carlo) simulations can be run to check the accuracy of the approximations in relevant parameter areas where exact theoretical results are not available. We investigate the performance of the approximations for models proposed in this thesis and by others.

2.3.2 Deterministic Rate Approximations

In addition to the uncertainty of their accuracy, moment closure approximations do not provide information about the probability distributions of variables, or individual probabilities of events. A further form of approximation is described here that does provide this information, though admittedly in a fairly crude way.

The idea underlying this section is as follows. If the probability of a transition is nonlinear, being a product of several variables (not necessarily distinct), then it can be approximated by the product of just one of these variables, and the means of each of the others, so that we then have an approximating, linear process. This will be equivalent to using the deterministic value for some of the variables in the transition probabilities.

As an example we return to the density dependent immigration-death process. Suppose we reformulate the problem, and let the per capita death rate be $\mu m(t)$ for some function $m(t)$, and keep the immigration rate at λ. The partial differential equation for the probability generating function $P(s;t) := \mathrm{E}\left(s^{M(t)}\right)$ is then

$$\frac{\partial P}{\partial t} = (1-s)\left(\mu m(t)\frac{\partial P}{\partial s} - \lambda P\right), \tag{2.12}$$

with $P(x;0) = 1$, the solution of which is

$$P(s;t) = \exp\left\{\lambda(s-1)\int_0^t e^{-\kappa(t,u)}\,du\right\} \tag{2.13}$$

where $\kappa(u,t) = \mu\int_u^t m(s)ds$. This is simply a time inhomogeneous linear immigration-death process. If we now let $m(t) = \mathrm{E}(M(t))$ then we obtain an approximation to the original density dependent process described above. We call this a *deterministic rate approximation.*

For stochastic population processes of the type considered in this chapter it will often be possible to find the probability generating function by using one or more approximations of this type, even if it is not in a closed form. It will be given in terms of at least one of the means of the process, for which a differential equation can be found by differentiating the probability generating function. If a closed solution is not obtainable for the mean, then any equation for any properties obtained from the probability generating function in terms $m(t)$ can be solved in conjunction with this differential equation (numerically if required). In multivariate models, or models with rates that depend on powers of the variable greater than one, there is more than one way of making this approximation. Notice that this approximating method will give the same means as an analogous deterministic model. From (2.13) we can see that in the particular example given the population follows a Poisson distribution. This is a consequence of it in effect being modelled as simply an immigration-death process.

We can approximate a large number of complicated nonlinear stochastic population processes this way. It often amounts to simply considering the variables as nonhomogeneous birth, death, immigration or emmigration processes, whatever is required, and then writing down ordinary differential equations for the rates (usually involving the means). This gives the advantage of adding simplicity to the relationship between variables in stochastic systems, or adding some stochasticity to deterministic systems whose means have already been modelled. However, often the process will not yield much information about the original nonlinear *stochastic*

process modelled. In the nonlinear density dependent immigration-death process example above, the deterministic rate approximation simply amounts to using a deterministic model, with a Poisson distribution imposed about the mean. This will happen with any process that involves only death and immigration (in the sense that the level of a particular variable does not increase at a rate proportional to that variable itself, i.e. there is no birth), as nonhomogeneous immigration linear death processes produce Poisson population levels. A large amount of the dependence structure between the variables will always be lost, and we only use this approximation as a comparison to other methods of obtaining probabilities not otherwise obtainable.

Nåsell has used hybrid approximations in which he replaces some processes by their expectations in population models for schistosomiasis (Nåsell, 1985). This was justified by the large numbers relating to the variable (number of infective vector hosts) involved. Parthasarathy and Kumar (1991) is another example of this type of assumption being used to produce a stochastic model with means following a logistic growth curve, though in fact the stochastic process studied is just a linear birth-death process with the inhomogeneous death rate adjusted to obtain the desired means. We use and assess this method in Section 4.2 to estimate individual probabilities of a nonlinear stochastic population process.

2.4 A Density Dependent Immigration-Death Process as an Illustration

As an illustration of the methods outlined in this chapter we consider some of the different approximations to the density dependent immigration-death process introduced in Section 2.2. For notational convenience we write $m(t)$ for the mean, $\mathrm{E}(M(t))$, and $s(t)$ for the second moment, $\mathrm{E}(M(t)^2)$. We assume that the process is initially zero, i.e. $\mathrm{M}(0) = 0$ with probability 1. Therefore the following differential

equations should be solved with the boundary conditions $m(0) = 0, s(0) = 0$. The deterministic approximation of equations (2.7) and (2.8) gives

$$\begin{aligned} \dot{m} &= \lambda - \mu m^2 \\ s &= m^2. \end{aligned}$$

The symmetric or normal approximation assumption that $\mathrm{E}(M(t)^3) = 3sm - 2m^3$ reduces (2.7) and (2.8) to

$$\dot{m} = \lambda - \mu s \tag{2.14}$$

$$\dot{s} = \lambda + 2\lambda m + \mu s - 6\mu m s + 4\mu m^3 \tag{2.15}$$

and the negative binomial moments approximation assumption that $\mathrm{E}(M(t)^3) = m^2 + s(2s/m - m - 1)$ reduces (2.7) and (2.8) to

$$\dot{m} = \lambda - \mu s \tag{2.16}$$

$$\dot{s} = \lambda + 2\lambda m + \mu s + 2\mu \left(sm + s - m^2 - 2\frac{s^2}{m} \right) \tag{2.17}$$

which were solved numerically with the boundary conditions $m(0) = 10^{-10}, s(0) = 10^{-20}$ to avoid the singularity at $m = 0$. Tables 2.1 and 2.2 show the results for the mean and variance of various approximations of the density dependent process for parameter values $\lambda = 16$ and $\mu = 1$.

In these tables, and throughout the thesis, simulations are conducted for Markov processes by the standard technique of generating exponential distributions for the time-lengths between events, and then deciding which event occurs by reading from a uniform distribution. Estimates of properties of interest are then generated from a large number of runs. Approximate confidence intervals may be calculated using asymptotic results concerning convergence to normal distributions for the sampling distributions of the estimates (see Bickel and Doksum (1977, Chapter 4) for more details). The simulation estimates given in this thesis have distributions that are normal in the limit of the number of runs performed, and so rough 95% confidence

intervals can be taken as plus or minus two standard errors of the estimate. In the results given in this section 6×10^4 runs were conducted. The values given in brackets after the estimate are twice the estimated standard error of the estimate. Note that for this simple process, approximate equilibrium results can be found numerically via analytical results for the equilibrium distribution using time reversibility of the process.

Table 2.1: Simulated and Approximated Mean of Density Dependent Immigration-Death Process

Time	Simulation (2 s.e.)	Deterministic	Normal	Negative Binomial
0.1	1.46 (0.01)	1.52	1.45	1.45
0.2	2.48 (0.01)	2.66	2.46	2.48
0.5	3.58 (0.01)	3.86	3.55	3.57
1.0	3.73 (0.01)	4.00	3.72	3.72

Table 2.2: Simulated and Approximated Variance of Density Dependent Immigration-Death Process

Time	Simulation (2 s.e.)	Deterministic Rate	Normal	Negative Binomial
0.1	1.34 (0.01)	1.52	1.45	1.33
0.2	1.91 (0.01)	2.66	2.14	1.92
0.5	2.02 (0.01)	3.86	2.19	2.11
1.0	2.00 (0.01)	4.00	2.16	2.11

We see that both the normal and negative binomial approximations evaluate the mean extremely well (Table 2.1), with the negative binomial approximation providing a slight improvement over the normal. However, it is in the evaluation of

the variance of the process (Table 2.2) that the negative binomial noticeably outperforms the normal. The deterministic approximation significantly over-estimates the value of the mean, whilst the deterministic rate approximation is of little use for estimating the variance.

The mean levels in this example are not high, and yet the 'moment closure' approximations still work well. It is worth noting, however, that the normal approximations do not always provide sensible solutions. Consider the phase portraits Figure 2.1 and Figure 2.2 on page 42 for the system obtained from the normal approximations ((2.14) and (2.15)). The solid lines are the isoclines upon which $\dot{m}$ and $\dot{s}$ are zero, and so from Figure 2.1 in which $\lambda/\mu = 1.5$ we can see there is no equilibrium for which both m and s are positive. Notice that the isocline for $\dot{m} = 0$ is just the vertical line $s = \lambda/\mu$. For $\lambda = 1.5, \mu = 1$ the simulated equilibrium mean is 0.93, the negative binomial approximation gives a value of 0.92, whilst the normal approximation becomes negative. The threshold at which there are no longer any positive equilibrium values for the mean under the normal approximation comes when $\lambda/\mu < 27/16 = 1.6875$. For λ/μ above this value (Figure 2.2) there are two positive equilibrium values. The one arrived at from the initial point of $m = s = 0$ is the higher of the two m values and is stable, which can be seen from the direction arrows indicating whether m and s are increasing or decreasing.

The deterministic approximation of course does not have this problem of giving negative means. The negative binomial approximation is shown to be of greater practical use than the normal approximation in this model. Intuitively this can be considered as being a consequence of its discrete, positive valued properties.

The linear death case provides a Poisson distribution for population numbers, and hence an index of dispersion, defined as $\mathrm{I}(M) := \mathrm{var}(M)/\mathrm{E}(M)$, of 1. Notice from the simulated results that the index of dispersion of the process is less than 1, and hence reduced from the linear death case. We conjecture that this will be the case for all parameter values of this process, and is a result of the density dependence. The per capita death rate in realisations with unusually large values

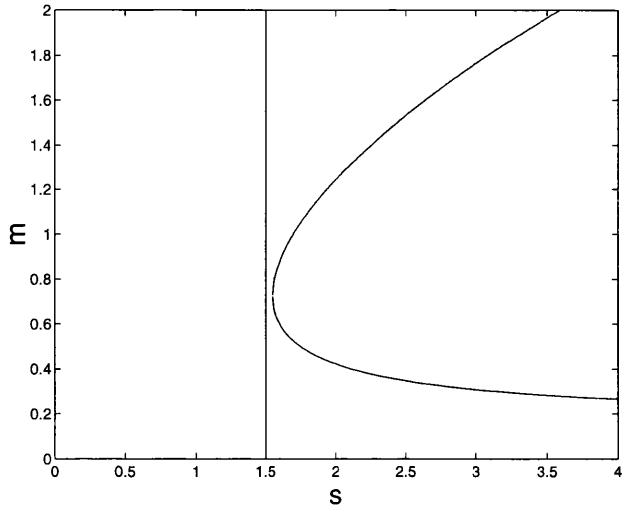

Figure 2.1: Phase Portrait for $m := \mathrm{E}(M(t))$ and $s := \mathrm{E}(M(t)^2)$ with $\lambda/\mu = 1.5$

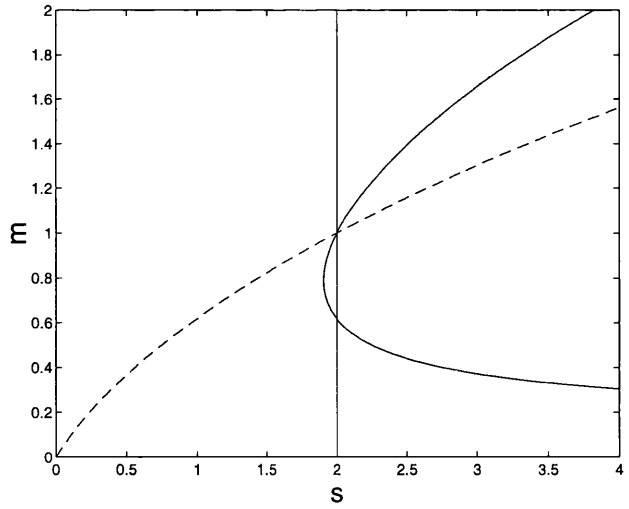

Figure 2.2: Phase Portrait for $m := \mathrm{E}(M(t))$ and $s := \mathrm{E}(M(t)^2)$ with $\lambda/\mu = 2$

will increase, and this will act to reduce the variation of the process with respect to its mean. The approximations capture this phenomena for the parameters given in Tables 2.1 and 2.2, but, as we have seen above, the normal approximation can give misleading results for low population numbers. In Figure 2.2 the dashed line indicates where I(M) is 1, so that we see for $27/16 < \lambda/\mu < 2$ the approximations wrongly predict overdispersion at equilibrium (I(M) > 1), whilst at $\lambda/\mu = 2$, in Figure 2.4 we see that I(M) at equilibrium will be estimated as one. For $\lambda/\mu > 2$, I(M) will be correctly estimated as less than one at equilibrium.

To illustrate this with a numerical example, when $\lambda = 1.7$ and $\mu = 1$, so that λ/μ is just above the threshold discussed above of $27/16$, the normal approximation equilibrium index of dispersion is 1.36 whilst the simulated value is 0.67, and the negative binomial provides 0.71. Again the negative binomial approximation is shown to be a more useful approximation method than the normal, but clearly care must be taken when using either. When used for more complicated nonlinear stochastic processes, any conclusions drawn from moment closure approximation without theoretical justification should be checked with stochastic (Monte Carlo) simulations. In this simple model, the fact that the normal approximations seem to work better at equilibrium for larger λ/μ corresponds to both the parameter governing the nonlinearity (μ) being smaller, and the rate of parasites entering the host being larger, two effects that both seem likely to improve the approximations.

Whilst we do not provide any theoretical justification for the negative binomial approximation, it does appear useful for processes of the immigration-death form often used in this thesis and elsewhere for studies of parasite dynamics. We investigate further the suitability of moments closure approximations in the models of parasite dynamics in chapters 3 and 4.

Chapter 3

Host Parasite Interactions

3.1 Introduction

One of the most important common feature of macroparasites is their high level of aggregation amongst the host population. Important early work in Crofton (1971b) and Crofton (1971a) highlighted this, and there have been numerous studies of host parasite relationships revealing highly aggregated parasite numbers (see Shaw and Dobson (1995), Hudson and Dobson (1995) and Anderson and May (1991, Chapter 15) for examples and further references). Essentially, parasite aggregation means that a large proportion of the parasite population is harboured by a small number of hosts so that the frequency distribution of parasites per host is highly overdispersed (see Poulin (1998) for further discussion).

The interactions between host and parasite dynamics are highly complicated and models so far have tended to concentrate on particular aspects of the relationship in order to make the analysis tractable. As a result, capturing both the cause and effect of aggregated parasite distributions has eluded theoreticians, and studies usually focus on one or the other. The importance of the variability in parasite numbers across hosts means that including statistical or stochastic effects at some level is necessary to help investigate the issues of interest.

As we have discussed in Section 1.2 distributional models rather than compartmental models are necessary for the study of macroparasite infections. In theory, the models could be purely deterministic, so that all random chance events are excluded, and still model the frequency distribution of parasites across the host population. Two methods of achieving this immediately spring to mind. The first is to model variables $P_i(\boldsymbol{t})$ say, (where $\boldsymbol{t}$ could incorporate the time and/or host age or type) for the number of hosts harbouring i parasites (for $i \in \mathbb{Z}$). The second is to model the parasite load in each individual, say j^{th}, host, $H_j(t)$. Both could of course be extended to include stages of parasite development and parasite stages that are free living or harboured in vector hosts, along with many other complications.

In practice, however, it is difficult to gain much information directly from the first method as it yields an infinite number of differential equations. It is usually used as a starting point for further simplification via statistical assumptions about the parasite frequency distribution, see Crofton (1971b), Crofton (1971a), Anderson and May (1978), Kretzschmar and Adler (1993) and Pugliese, Rosa, and Damaggio (1998) for examples. It has the advantage of modelling parasite loads as discrete values and of incorporating host death more easily than the second method, which uses discrete and fixed values for the number of hosts but continuous values for parasite numbers. The property of discrete parasite loads is sometimes mistakenly used to identify such models as stochastic even though there is no random element involved. This property has added importance when modelling macroparasites that reproduce sexually inside the definitive host, as successful mating between male and females is not always guaranteed at low parasite levels (May, 1977; Leyton, 1968; Gabriel, Hanisch, and Hirsch, 1989).

The second method (modelling the load in host j as $H_j(t)$) will produce a finite system of differential equations for finite host populations, and is useful for modelling aggregation due to host heterogeneities. In a deterministic framework that does not allow for demographic stochasticity or random effects, this method

can *only* obtain aggregation across all hosts if the host population is modelled as heterogeneous. However, the dynamics of the host population are difficult to incorporate in this framework.

In general, purely deterministic models with no statistical or stochastic additions that attempt to include parasite load distributions will be restrictive in the information they provide. A technique introduced in Crofton (1971b) and extended in Anderson and May (1978) to simplify the problem uses statistical assumptions about the parasite distribution to reduce an infinite system of differential equations to a lower dimensional system (often just two or three variables). Anderson and May (1978) used this approach to investigate stabilizing and destabilising parasite related effects on the host population; for example they concluded that overdispersed frequency distributions result in parasite-induced host mortality being a stabilising factor that regulates the host population. This has become a generally accepted idea but the statistical assumptions made can often implicitly impose properties on the model. In the example of Anderson and May (1978) given above, Kretzschmar and Adler (1993) point out that choosing any distribution for the parasite frequency with an index of dispersion that is an increasing function of the mean in the Anderson and May (1978) model necessarily makes parasite-induced host mortality a stabilising factor. This approach has its use in allowing complicated nonlinear effects in parasite dynamics to be investigated. However, aggregation is always considered as an external, and crucially a static factor. This clearly limits the understanding that can be gained into aggregation in particular, and parasite dynamics in general. Hence, as an alternative method of study, stochastic processes have an important role to play in the area of parasite dynamics.

The first macroparasite models to use stochastic processes were Tallis and Leyton (1966) and Tallis and Leyton (1969) which considered within-host parasite dynamics, primarily aimed at modelling experiments of trickle infections of nematode parasites given to sheep. These, and other stochastic (and deterministic) *within*-host parasite dynamics models are usually variants of an immigration-death

process (Anderson and May, 1991). Stochastic models of between host parasite dynamics are rare. The exceptions are the works of Barbour (Barbour and Kafetzaki, 1993; Barbour, Heesterbeek, and Luchsinger, 1996) who models parasites in a population of immortal hosts. Nåsell and Hirsch (1973) use hybrid approximations so the models are part stochastic, part deterministic. The assumption is that the vector host population is large enough so that a deterministic approximation is appropriate, whilst the within-host parasite populations are modelled using stochastic processes (see Nåsell (1985) for a summary and further references).

A summary of some within-host models, and the effect of various factors such as parasite-induced host mortality and density dependent constraints on parasite distributions, is given in Anderson and Gordon (1982). One of the points the authors highlight is that within-host density dependent effects reduce dispersion, an example of which we saw in the density dependent immigration-death process discussed in Chapter 2. Interestingly, they also state that

> ... the prime cause of overdispersion in the distribution of parasite numbers within a host population will be stochastic factors in the environment, as opposed to a demographic nature

which they conclude from the fact that

> ... the underlying pattern of variability in parasite abundance between hosts, generated by stochastic factors of a demographic nature, will be Poisson in form where the variance to mean ratio is approximately equal to unity.

The explanation given for this is that the basic immigration-death process (an $M/M/\infty$ queue) provides a Poisson distribution, (remember there is no direct internal reproduction i.e. no 'birth' in the process). The environmental factors they refer to are host heterogeneities in exposure, suceptibilities and defense capabilities modelled by making parameters such as the immigration rate random variables across the host population.

Their conclusion is a slightly naive generalisation for two reasons. Firstly, it *is* possible to have overdispersed distributions in within-host models without making the parameters random variables. The most obvious example being an $M/M/\infty$ queue with batch arrivals, corresponding to parasites entering the host in clusters rather than one at at time. The second reason is that the immigration rate may well depend on the parasite levels in other hosts, themselves subject to demographic stochastic effects, and hence it will not necessarily be deterministic in form, even in each host. Both these effects create more dependence between parasites than the simple $M/M/\infty$ queue model that provides Poisson distributions. The first of these points is discussed in this chapter (specifically, see Section 3.3.5), whilst the second is addressed in Chapter 5.

The Anderson and Gordon (1982) paper used Monte Carlo simulations to show that parasite induced host mortality (in which hosts with higher parasite burdens are more likely to die) reduces dispersion of the parasite distribution, (though see Section 3.3.6 for an exception to this). A more complicated nonlinear stochastic model for within-host dynamics incorporating acquired host immunity as well as parasite-induced host mortality was studied in Grenfell, Dietz, and Roberts (1995a). This provides a framework for incorporating these two effects stochastically and though exact results were not obtained, it was an advance in the recognition of the role stochastic models have to play in the area. Moment closure approximations, as described in Section 2.3.1, were used to analyse the models. In common with many other within-host parasite dynamic models focusing on the evolution of parasite loads, the underlying assumption of this model is that the age distribution of parasites within hosts is in equilibrium with respect to time. This essentially means that the input of parasites into the host is independent of any parasite levels.

In this and the following chapter we extend and expand the ideas presented in Grenfell, Dietz, and Roberts (1995a). The present chapter mostly focuses on parasite-induced host mortality, whilst acquired immunity is the main focus of Chapter 4. We also discuss the use of moment closure approximations for these

kind of systems.

Isham (1995) solved a simpler version of the Grenfell, Dietz, and Roberts (1995a) model where the only nonlinearity was the parasite-induced host mortality increasing at a rate linearly proportional to the parasite load. Isham investigated the relationship between load distribution and input distribution when this parasite-induced host mortality is added, following on from results given in Grenfell, Dietz, and Roberts (1995a) for the purely linear model (obtainable through simple queueing theory). As exact results for the moments conditional on host survival are obtainable, Isham was able to asses the moment closure approximation used in Grenfell, Dietz, and Roberts (1995a) for this particular nonlinearity. The results are fairly impressive, though the parameter governing the nonlinearity is small relative to all others. See Section 3.7 for further discussion of these.

In Section 3.2 we extend the Isham (1995) model to include parasite larvae, mature parasites and parasite offspring, and we relax some assumptions made, including exponential parasite lifetimes. In addition, we investigate important properties such as disease control and parasite load at host death in Section 3.3. The model is extended further to describe how host morbidity can be incorporated in Section 3.4. Sections 3.5 - 3.8, are concerned with assessing the moment closure technique for this multivariate conditional system, and include an alternative moment assumption derived from a multivariate negative binomial distribution (Section 3.6) and incorporation of random parameters into the approximation (Section 3.8).

3.2 A Model of the Dynamics of Killing Parasites

The model presented here is designed to study within-host parasite dynamics, with emphasis on the effect of parasite-induced excess host mortality. We consider hosts as coming under attack from parasites and hence hosts that harbour higher parasite loads have increased death rates. Although we model the parasites as being able to "kill" their hosts, they do not necessarily have to cause host mortality directly.

They can be considered as simply weakening the host, making it more vulnerable to predators, or more susceptible to other diseases. In this way the parasites simply increase the host's overall death rate, but we do not consider whether this is by direct and indirect methods.

The main assumption made concerning parasite-induced host mortality is that the death rate of a host increases linearly with its parasite burden. There is evidence for this in some parasite-host relationships (Anderson and May, 1991; Hudson and Dobson, 1995). Generally, if parasites have a large effect on the death rate of hosts, this will adversely effect their own productivity. Once a host dies, the parasites no longer have a livelihood, and so with parasite-induced host mortality, average parasite burdens in surviving hosts can intuitively be expected to be lower than for identical, non-killing parasites. There are many other issues concerning the effect of parasite-induced host mortality, in particular how it affects the full distribution of parasite loads, that are discussed in Section 3.3.

3.2.1 Model Definition

We consider a particular host that is born, free of parasites, at time $t = 0$ and is exposed to parasite larvae at times of a non-homogeneous Poisson process of rate $\phi(t)$. At an exposure instant, the host acquires a random number C of larvae, independently from one exposure to another, where C has probability generating function $h(z) = \sum_{c=0}^{\infty} h_c z^c$. Once in the host, each parasite evolves independently of all others. A particular larva remains in the larval stage for a random time, T_L that has probability density function f_L. At the end of this period, the larva either matures, with probability $\sigma(T_L)$, or dies. The mature parasite has a random lifetime as an adult, T_M, that is independent of T_L and has density f_M, at the end of which the parasite dies. During this adult stage, the parasite gives birth to clumps of offspring in a non-homogeneous Poisson process of rate $\rho(a)$ where a is the age of the parasite since maturation. At each birth a random number, D,

of offspring are produced, independently between births, where D has probability generating function $k(z) = \sum_{d=0}^{\infty} k_d z^d$. The offspring have independent lifetimes, T_N, with density f_N, that do not depend on the age of the parent at birth or any other variables of the process.

At time t, we are interested in the following three variables: $L(t)$, the number of parasite larvae in the host; $M(t)$, the number of mature parasites in the host; $N(t)$, the number of parasite offspring still alive at t that have been generated during $(0, t]$ by adult parasites infecting the host. We assume that the host has a natural death rate $\mu_H(t)$ at time (and age) t in the absence of any parasite burden and that this rate is increased by an amount α_l for each larva and α_m for each adult parasite with which it is currently infected. In practice, it will usually be the case that only one of α_l and α_m is non-zero, for example $\alpha_l = 0$ in the model of (Grenfell, Dietz, and Roberts, 1995a). However an alternative interpretation of this model with non-zero α_l, could be to regard the 'maturation' of a parasite as representing a change in a parasite's virulence during its lifetime in the host. There is no problem including an α_N corresponding to an offspring effect if this is appropriate, but we shall not do so here. Properties of the variables $L(t), M(t), N(t)$ will be needed, *conditionally* upon the survival of the host to age t for comparison with observed data.

As long as the three lifetime variables (T_L, T_M, T_N) are all exponentially distributed, and $\sigma(\cdot)$ and $\rho(\cdot)$ are constant, the trivariate process $\{L(t), M(t), N(t)\}$ is a Markov process and its properties can be investigated by appropriate use of forward equations, in the way followed by Isham (1995), who investigated the special case when $\phi(\cdot)$ is constant and $\sigma(T_L) \equiv 0$ *a.s.*. Here we shall consider the more general model with arbitrary lifetime distributions, and follow the alternative approach previously suggested by F.G.Ball (1995, private communication).

3.2.2 Model Equations

It is convenient to suppose that the process by which the host acquires larvae continues indefinitely (even after the death of the host) and let $Z(t)$ be an indicator variable which takes the value 1 if the host is alive at t and 0 otherwise. (Note the difference from the notation used in Isham (1995) where $M(t)$ represents the parasite level *conditional on host survival*).

Since the excess instantaneous death rate of the host over and above the rate of natural mortality depends upon the current numbers of larvae and mature parasites, it is clear that the distribution of $Z(t)$ depends on the aggregated variables $A(t) = \int_0^t L(u)du$, the accumulated lifetimes of all larvae within the host from birth up to time t, and $B(t) = \int_0^t M(u)du$, the corresponding total for mature parasites.

We start by finding the joint generating function of the five variables $\{L(t), M(t), N(t), A(t), B(t)\}$. We condition first upon the number K of infection instants that have occurred up to time t, and given $K = k$, the arbitrarily labelled times $\mathbf{T} = \{T_1, \ldots, T_k\}$ of these events and the corresponding clump sizes $\mathbf{C} = \{C_1, \ldots, C_k\}$. By assumption, K has a Poisson distribution with mean $\Phi(t) := \int_0^t \phi(u)du$ and the T_i are independently distributed with density $\phi(\cdot)/\Phi(t)$ over $(0, t]$. It follows immediately that

$$\begin{aligned} G(x, y, z, s_1, s_2; t) &:= \mathrm{E}\left(x^{L(t)} y^{M(t)} z^{N(t)} e^{-s_1 A(t)} e^{-s_2 B(t)}\right) \\ &= \mathrm{E}_{K,\mathbf{T},\mathbf{C}}\left\{\prod_{i=1}^{K}\left[\mathrm{E}\left(x^{L_{ij}} y^{M_{ij}} z^{N_{ij}} e^{-s_1 A_{ij}} e^{-s_2 B_{ij}} | T_i\right)\right]^{C_i}\right\} \quad (3.1) \end{aligned}$$

where $\{L_{ij}, M_{ij}, N_{ij}, A_{ij}, B_{ij}\}$ are the contributions to $\{L(t), M(t), N(t), A(t), B(t)\}$ resulting from the jth parasite in the ith clump, $j = 1, \ldots, C_i$ and $i = 1, \ldots, K$, and the dependence of these variables on t is not made explicit. Thus if we define

$$g(x, y, z, s_1, s_2; w) := \mathrm{E}\left(x^{L_{ij}} y^{M_{ij}} z^{N_{ij}} e^{-s_1 A_{ij}} e^{-s_2 B_{ij}} | T_i = t - w\right),$$

it follows that

$$G(x, y, z, s_1, s_2; t) = \exp\left\{-\int_0^t \phi(t - w)[1 - h(g(x, y, z, s_1, s_2; w))]dw\right\}. \quad (3.2)$$

To find $g(x, y, z, s_1, s_2; w;)$ we focus first on all of the offspring of a particular parasite (the jth member of the ith clump of parasites encountered by the host, say) where we assume that this parasite is one that matures, rather than dying at the end of the larval stage, and that it does so at time $t-\tau, \tau < t$. We are interested in the number $N_{i,j}$ of these offspring that are still alive at time t and define the variable $\Xi_{i,j}$ to be the smaller of τ and the 'age' (*i.e.* the time after maturity) of the mature parasite at death. With probability $\mathcal{F}_M(\tau)$, $\Xi_{i,j} = \tau$, while for $0 < \xi < \tau$, $\Xi_{i,j}$ has probability density $f_M(\xi)$, where $\mathcal{F}_M(u) = \mathrm{P}(T_M > u)$.

Given $\Xi_{i,j} = \xi$, the offspring are generated over the interval $u \in (t-\tau, t-\tau+\xi)$ in clumps that occur in a Poisson process of rate $\rho(u-t+\tau)$; the number of these clumps has a Poisson distribution with mean $\int_0^\xi \rho(u)du$, and they are, conditionally, independently located with density $\rho(u-t+\tau)/\int_0^\xi \rho(u)du$. An offspring born at u has a probability $\mathcal{F}_N(t-u)$ of being alive at t, independently of all other offspring in both the same and distinct clumps.

Putting all these results together, it is straightforward to deduce that, for the jth member of the ith clump of parasites encountered by the host, conditionally upon that parasite maturing at $t-\tau$ and having $\Xi_{i,j} = \xi$, the number, $N_{i,j}$, of offspring still alive at t has probability generating function

$$\eta(z; \xi, \tau) := \mathrm{E}(z^{N_{i,j}} | \xi, \tau) = \exp\left\{ -\int_0^\xi \left[1 - k\left(1 - (1-z)\mathcal{F}_N(\tau - v)\right)\right] \rho(v)dv \right\}$$

(using the substitution $v = u - t + \tau$).

Now consider the possible histories of the jth member of the clump of larvae ingested at $T_i = t_i$ over the interval $(t_i, t]$, and the corresponding values of the five variables $L_{ij}, M_{ij}, N_{ij}, A_{ij}$ and B_{ij}. There are a number of mutually exclusive possibilities

- the larva is still alive at t, so that $L_{ij} = 1, M_{ij} = 0, N_{ij} = 0, A_{ij} = t - t_i$ and $B_{ij} = 0$; — with probability $\mathcal{F}_L(t - t_i)$;
- the larva dies at some time $t_i + v \in (t_i, t]$, so that $L_{ij} = 0, M_{ij} = 0, N_{ij} =$

$0, A_{ij} = v$ and $B_{ij} = 0$; — with probability density $f_L(v)\{1 - \sigma(v)\}$;

- the larva matures at some time $t_i + v \in (t_i, t]$ and dies at $t_i + v + \xi$, for some $\xi \in (0, t - t_i - v)$, so that $L_{ij} = 0, M_{ij} = 0, N_{ij}$ is a random variable with probability generating function $\eta(z; \xi, t - t_i - v)$, $A_{ij} = v$ and $B_{ij} = \xi$; — with probability density $f_L(v) f_M(\xi)\sigma(v)$;

- the larva matures at some time $t_i + v \in (t_i, t]$ and is still alive at t so that $L_{ij} = 0, M_{ij} = 1, N_{ij}$ is a random variable with probability generating function $\eta(z; t - t_i - v, t - t_i - v)$, $A_{ij} = v$ and $B_{ij} = t - t_i - v$; — with probability density $f_L(v)\mathcal{F}_M(t - t_i - v)\sigma(v)$.

Combining these cases, we find that

$$\begin{aligned} g(x, y, z, s_1, s_2; w) &:= \mathrm{E}\left(x^{L_{ij}} y^{M_{ij}} z^{N_{ij}} e^{-s_1 A_{ij}} e^{-s_2 B_{ij}} | T_i = t - w\right) = \\ & xe^{-s_1 w}\mathcal{F}_L(w) + \int_0^w e^{-s_1 v} f_L(v)\{1 - \sigma(v)\}dv + \\ & \int_0^w e^{-s_1 v} f_L(v)\sigma(v) \int_0^{w-v} e^{-s_2 \xi}\eta(z; \xi, w - v) f_M(\xi) d\xi dv + \\ & \int_0^w y e^{-s_1 v} f_L(v)\sigma(v) e^{-s_2(w-v)}\eta(z; w - v, w - v)\mathcal{F}_M(w - v)dv. \end{aligned} \tag{3.3}$$

Now let

$$P(x, y, z; t) := \mathrm{E}(x^{L(t)} y^{M(t)} z^{N(t)} Z(t))$$

and

$$Q(x, y, z; t) := \mathrm{E}(x^{L(t)} y^{M(t)} z^{N(t)} | Z(t) = 1).$$

It is clear that

$$\mathrm{P}(Z(t) = 1 | A(t), B(t)) \;=\; \exp\left\{-\left(\alpha_l A(t) + \alpha_m B(t) + \int_0^t \mu_H(u)du\right)\right\} \tag{3.4}$$

and therefore that

$$P(x, y, z; t) \;=\; G(x, y, z, \alpha_l, \alpha_m; t) \exp\left\{-\int_0^t \mu_H(u)du\right\}. \tag{3.5}$$

Thus $\mathrm{P}(Z(t)=1) = P(1,1,1;t)$ and

$$\begin{aligned} & Q(x,y,z;t) \\ & \quad = P(x,y,z;t)/P(1,1,1;t) \\ & \quad = G(x,y,z,\alpha_l,\alpha_m;t)/G(1,1,1,\alpha_l,\alpha_m;t) \\ & \quad = \exp\left\{-\int_0^t \phi(t-u)[h(g(1,1,1,\alpha_l,\alpha_m;u)) - h(g(x,y,z,\alpha_l,\alpha_m;u))]du\right\} \end{aligned} \quad (3.6)$$

Due to the conditioning on host survival the natural host death rate $\mu_H(t)$ plays no part in this final result.

3.3 Results and Ecological Implications

3.3.1 Moments

We denote by $L_c(t), M_c(t)$ and $N_c(t)$ respectively the larval, mature and offspring numbers *conditional upon the survival of the host to time* t, so that $Q(x,y,z;t)$ is the joint probability generating function of these variables.

Many interesting properties of this process can be derived from the joint probability generating function (3.6), and we give a few here to provide some illustrations of the mechanisms of the process. The first two moments of $M_c(t)$ are

$$\mathrm{E}(M_c(t)) = \int_0^t \phi(t-w)h'(\tilde{g}(w))\tilde{g}_y(w)dw \quad (3.7)$$

$$\mathrm{var}(M_c(t)) = \int_0^t \phi(t-w)h''(\tilde{g}(w))(\tilde{g}_y(w))^2 dw + \mathrm{E}(M_c(t)) \quad (3.8)$$

where

$$\tilde{g}(w) := g(1,1,1,\alpha_l,\alpha_m;w) = e^{-\alpha_l w}\mathcal{F}_L(w) + \int_0^w e^{-\alpha_l u} f_L(u)\left[1-\sigma(u)+\sigma(u)\{e^{-\alpha_m(w-u)}\mathcal{F}_M(w-u) + \int_0^{w-u} e^{-\alpha_m v} f_M(v)dv\}\right] du$$

and

$$\tilde{g}_y(w) := \left.\frac{\partial g(x,y,z,\alpha_l,\alpha_m;w)}{\partial y}\right|_{x=y=z=1} = e^{-\alpha_m w}\int_0^w e^{(\alpha_m-\alpha_l)u}\sigma(u)f_L(u)\mathcal{F}_M(w-u)du.$$

The covariance between $L_c(t)$ and $M_c(t)$ is

$$\text{cov}(L_c(t), M_c(t)) = \int_0^t \phi(t-w)\, h''(\tilde{g}(w))\, \mathcal{F}_L(w)\, e^{-\alpha_l w}\, \tilde{g}_y(w)\, dw, \quad (3.9)$$

and further second order moments are provided in Appendix A. Notice that $\tilde{g}(w)$ and $\tilde{g}_y(w)$ are both decreasing in α_l and α_m and hence any differential of $h(x)$ evaluated at $x = \tilde{g}(w)$ is non-increasing in α_l and α_m. From this we can see that $\text{E}(M_c(t)), \text{var}(M_c(t))$ and $\text{Cov}(L_c(t), M_c(t))$ are all decreasing in α_l and α_m, and indeed this is the case for all the means, variances and covariances of the process.

Note that the indices of dispersion of $L_c(t), M_c(t)$ and $N_c(t)$ and the correlations between any of these do not depend upon the rate of exposure to parasite clumps, $\phi(\cdot)$, if this rate is constant. In addition, from (3.7) and (3.8) we can see that $\text{I}(M_c(t)) := \text{var}(M_c(t))/\text{E}(M_c(t)) \geq 1$ so that the parasite-induced host mortality can never generate underdispersion, contrary to the results presented in Anderson and Gordon (1982). See Section 3.3.5 for more details.

If $\alpha_l = \alpha_m = 0$ we have $\tilde{g}(w) = 1$ and these results reduce to those obtainable from queueing theory models; see Section 3.5. It is intuitively obvious, and can be seen by noticing that $g(x, y, 1, \alpha_l, \alpha_m; w)$ does not depend upon the survivor function of the offspring lifetime, that the joint distribution of numbers of larvae and mature parasites is not affected by the offspring. Also, when $\alpha_m = 0$ (i.e. only the larvae affect the host's death), $g(x, 1, 1, \alpha_l, 0; w)$ does not depend upon the survivor function for mature parasites either, and hence nor does the marginal distribution of the number of larvae. This is to be expected, as the only way the properties of the offspring or mature parasites can affect larval distribution is through their influence on host mortality. Some simplification occurs when either α_l or α_m is zero. For example, if $\phi(\cdot)$ is constant and $\alpha_l = 0$ then

$$\text{E}(M_c(t)) = \frac{\phi}{\alpha_m}(h(\tilde{g}(t)) - 1).$$

Some probabilities of empirically observable events are simply expressed in terms of the generating function $Q(x, y, z; t)$. In particular, the probability that a

live host is free of all parasites (larvae, adults and offspring) is given by $Q(0,0,0;t)$, while the probability that the host is free of both larvae and mature parasites is $Q(0,0,1;t)$. The probability distribution of the number of offspring associated with the host at time t has probability generating function $Q(1,1,z;t)$, while that of the number of offspring at time t, associated with a host that is parasite-free (both larvae and adults) at t is $Q(0,0,z;t)/Q(0,0,1;t) = P(0,0,z;t)/P(0,0,1;t)$.

In some macroparasitic infections the offspring may be the only variable easily observable, so the distribution of the mature and larval loads given the offspring number is of interest. In theory this can be obtained from the joint probability generating function, but in practice the individual probabilities are generally difficult to obtain. However, the distribution of $M_c(t)$ and $L_c(t)$ given that $N_c(t)$ is zero is easily expressed in terms of the function Q. We have $P(N_c(t) = 0) = Q(1,1,0;t)$, and so the joint probability generating function of $M_c(t)$ and $L_c(t)$ given $N_c(t) = 0$ is $Q(x,y,0;t)/Q(1,1,0;t) = P(x,y,0;t)/P(1,1,0;t)$. For example, $P(M_c(t) = 0|N_c(t) = 0) = P(1,0,0;t)/P(1,1,0;t)$, which is the probability that a host is truly free of infection if it has no parasite offspring.

3.3.2 Host Survival

The probability that the host survives to time t is

$$S(t) := P(1,1,1;t) \;=\; \exp\left\{\int_0^t \phi(t-w)(h(\tilde{g}(w))-1)\,dw\right\}\exp\left\{-\int_0^t \mu_H(w)\,dw\right\}$$

If $\phi(t)$ is constant, this can be written as

$$S(t) \;=\; \exp\left\{-\int_0^t \mu_H(w)dw\right\}\exp\left\{-\int_0^t \alpha_l \mathrm{E}(L_c(w))dw\right\}\exp\left\{-\int_0^t \alpha_m \mathrm{E}(M_c(w))dw\right\} \tag{3.10}$$

so that the survival of the host can be expressed in terms of just the *expectations* of the parasite loads given survival (and of course the host's natural death rate).

Figures 3.1 and 3.2 on pages 58 and 59 plot the survival probability of the host for different input distributions. The parameter values not stated are $\mathcal{F}_L(x) =$

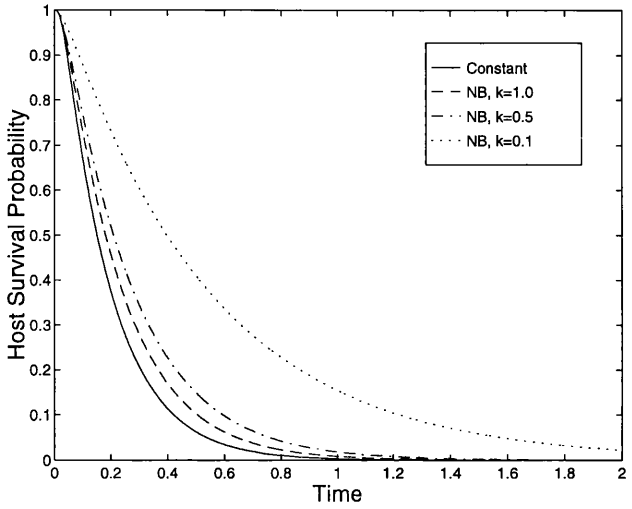

Figure 3.1: Host Survival Probability with $\phi = 6$ and $m_c = 50$ for Various Distributions of C

$e^{-(\mu_l+\gamma_l)x}, \sigma(x) = \gamma_l/(\mu_l + \gamma_l)$ and $\mathcal{F}_M(x) = e^{-\mu_m x}$, with $\mu_l = 20, \gamma_l = 30, \mu_m = 10$ and $\alpha_l = 0, \alpha_m = 0.2$. The figures show that the overdispersion of the random variable, C, has a noticeable effect on the survival function of the host when the mean of C is high relative to the encounter rate, $\phi(\cdot)$. In that case, hosts with unusually large parasite loads will be subject to high death rates; it follows that the effect is more marked the larger the impact of the parasites on host death, i.e. when α_l and α_m are high. The effect C has on the host survival probabilities comes directly from the effect C has on $\mathrm{E}(M_c(t))$ (see result 3.10). Higher aggregation of C will decrease the effect of parasite-induced host mortality on the mean of the parasite load means conditional on host survival, $\mathrm{E}(M_c(t))$.

The probability that the host is dead by time t is $1 - S(t)$ (for $t \geq 0$), so that we can easily obtain the probability density function, f_D, of the time of host death; in particular when $\phi(\cdot)$ is constant,

$$\begin{aligned} f_D(t) = \frac{d}{dt}(1 - S(t)) &= S(t)[\alpha_l \mathrm{E}(L_c(t)) + \alpha_m \mathrm{E}(M_c(t)) + \mu_H(t)] \\ &= S(t)\left[\phi(1 - h(\tilde{g}(t)) + \mu_H(t)\right] \qquad (t \geq 0). \quad (3.11) \end{aligned}$$

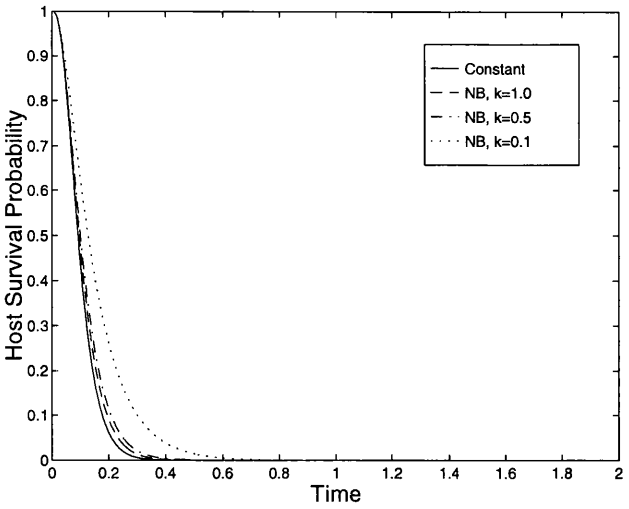

Figure 3.2: Host Survival Probability with $\phi = 60$ and $m_c = 5$ for Various Distributions of C

Often the only data obtainable on parasite numbers are from dead hosts, so that the distribution of the parasite load at the time of death of the host is of interest. If the age of a host upon death is known, then it is useful to compare the load of hosts upon death with that of surviving hosts of a similar age. For the remainder of this section we assume that $S(t) < 1$ for $t > 0$, i.e. that there is a non-zero probability of host death. Suppose that the host dies at time t and let $L_{d(t)}$, $M_{d(t)}$ and $N_{d(t)}$ be the number of larvae, mature parasites and offspring present at this time, i.e. $P(M_{d(t)} = m) \equiv \lim_{\delta t \to 0} P(M(t) = m | Z(t + \delta t) = 0, Z(t) = 1)$. The joint

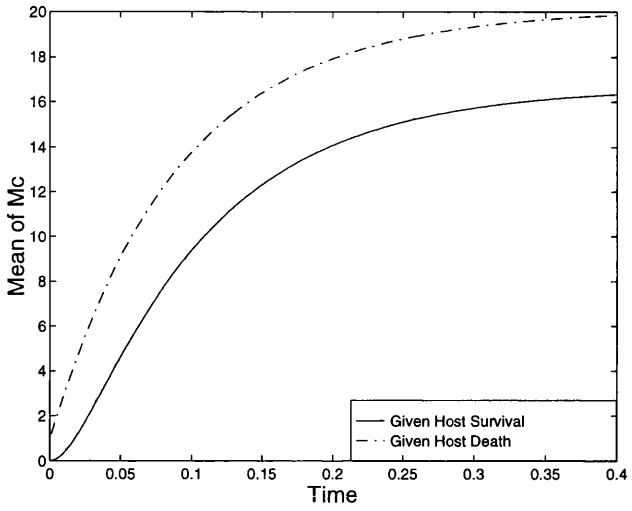

Figure 3.3: Mean Parasite Loads at Host Death and in Surviving Hosts; $\phi = 60, m_c = 5, \alpha_m = 0.2$

probability generating function for $L_{d(t)}, M_{d(t)}$ and $N_{d(t)}$ is then

$$
\begin{aligned}
&\Psi(x,y,z;t) \\
&\quad := \mathrm{E}(x^{L_{d(t)}}\, y^{M_{d(t)}}\, z^{N_{d(t)}}) \\
&\quad = \lim_{\delta t \to 0} \sum_{l,m,n \geq 0} x^l y^m z^n P(L(t)=l, M(t)=m, N(t)=n | Z(t)=1, Z(t+\delta t)=0) \\
&\quad = \lim_{\delta t \to 0} \sum_{l,m,n \geq 0} \Bigg\{ x^l y^m z^n P(Z(t+\delta t)=0 | Z(t)=1, L(t)=l, M(t)=m, N(t)=n) \times \\
&\qquad\qquad \frac{P(L(t)=l, M(t)=m, N(t)=n | Z(t)=1)}{P(Z(t+\delta t)=0 | Z(t)=1)} \Bigg\} \\
&\quad = \frac{S(t)}{f_D(t)} \left\{ \alpha_l x \frac{\partial Q(x,y,z;t)}{\partial x} + \alpha_m y \frac{\partial Q(x,y,z;t)}{\partial y} + \mu_H(t) Q(x,y,z;t) \right\}.
\end{aligned}
$$

The moments of $L_{d(t)}, M_{d(t)}$ and $N_{d(t)}$ can be easily found, for example

$$
\mathrm{E}(M_{d(t)}) = \frac{S(t)}{f_D(t)} \left\{ \alpha_l \mathrm{E}(L_c(t) M_c(t)) + \alpha_m \mathrm{E}(M_c(t)^2) + \mu_H(t) \mathrm{E}(M_c(t)) \right\}.
$$

In the special case when $\alpha_l = 0$ and $\mu_H(t) \approx 0$, i.e. when larvae do not affect host death and the host's natural death rate is insignificant compared with the effect of mature parasites, we have $\mathrm{E}(M_{d(t)}) \approx \mathrm{E}(M_c(t)) + \mathrm{I}(M_c(t))$, where $\mathrm{I}(\cdot)$ indicates

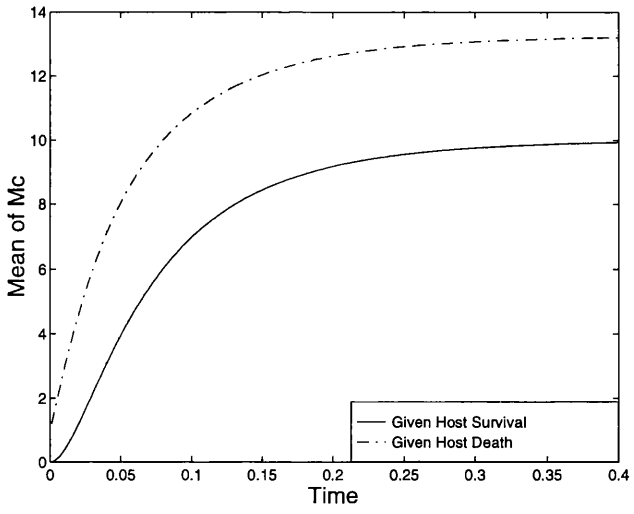

Figure 3.4: Mean Parasite Loads at Host Death and in Surviving Hosts; $\phi = 60, m_c = 5, \alpha_m = 2.0$

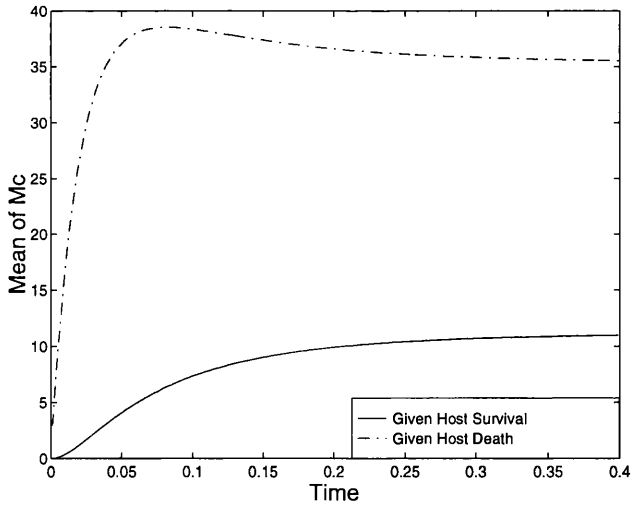

Figure 3.5: Mean Parasite Loads at Host Death and in Surviving Hosts; $\phi = 6, m_c = 50, \alpha_m = 0.2$

index of dispersion, so that the difference between the expected loads of surviving hosts and those that have just died is simply the index of dispersion of the load of the surviving hosts. For this case, Figures 3.3, 3.4 and 3.5 on pages 60 and 61 show the expectation of the mature parasite load at host death as a function of time, together with the expectation of the mature parasite load for surviving hosts with the same exposure time. Parameter values not stated are as in Figures 3.1 and 3.2. The difference between the two means is larger in relative terms when C is greater relative to $\phi(\cdot)$, i.e. for higher input variability (compare Figure 3.4 with Figure 3.5), and as expected this is more marked for higher α_m (compare Figure 3.3 with Figure 3.4).

These results illustrate that the high variability of the parasite numbers causes the effect of parasite-induced host mortality to be greater.

Results for the larval load at death can be found in the same way, as can higher order moments of $M_{d(t)}$, e.g.

$$\mathrm{E}(M_{d(t)}^2) = \frac{\alpha_l \mathrm{E}(L_c(t)M_c(t)^2) + \alpha_m \mathrm{E}(M_c(t)^3) + \mu_H(t)\mathrm{E}(M_c(t)^2)}{\alpha_l \mathrm{E}(L_c(t)) + \alpha_m \mathrm{E}(M_c(t)) + \mu_H(t)}.$$

If the age of a host is not known upon death, for example if a host is found to be dead in the wild, then the parasite loads at death can be used; let these be L_d, M_d, N_d. Their joint generating function is simply

$$\begin{aligned}\mathrm{E}(x^{L_d}y^{M_d}z^{N_d}) &= \int_0^\infty \Psi(x,y,z;t) f_D(t)dt \\ &= \int_0^\infty S(t)\left\{\alpha_l x \frac{\partial Q(x,y,z;t)}{\partial x} + \alpha_m y \frac{\partial Q(x,y,z;t)}{\partial y} + \mu_H(t)Q(x,y,z;t)\right\}dt.\end{aligned}$$

Thus the expectation of the number of mature parasites at death can be expressed as

$$\mathrm{E}(M_d) = \int_0^\infty S(t)\left\{\alpha_l \mathrm{E}(L(t)M(t)) + \alpha_m \mathrm{E}(M(t)^2) + \mu_H(t)\mathrm{E}(M(t))\right\}dt$$

and further moments can be expressed similarly.

3.3.3 Disease Control

If the transmission of the parasite to the host is stopped, for example by controlling the parasite vector outside the host or by moving the host to an uninfected area, then it is of interest to see how long it is before the host becomes parasite free (or dies). Suppose transmission is at a constant level until it ceases at time θ, i.e. $\phi(t) \equiv \phi$ for $0 \leq t \leq \theta$; $\phi(t) \equiv 0$ for $t > \theta$, then from (3.6), the joint probability generating function for $L_c(t), M_c(t), N_c(t)$ for $t \geq \theta$, is

$$Q(x,y,z;t) = \exp\left\{-\phi\int_{t-\theta}^{t}[h(g(1,1,1,\alpha_l,\alpha_m;u)) - h(g(x,y,z,\alpha_l,\alpha_m;u))]du\right\} \quad (3.12)$$

Given a host is alive at time θ, the probability that it is still alive at $t \geq \theta$ is simply $S(t)/S(\theta)$, where S is as given in Section 3.2. Thus if the host is alive when transmission is stopped at time θ, the probability the host survives further to time $\theta + \beta$ is simply

$$\exp\left\{\left(\int_{\beta}^{\theta+\beta} - \int_{0}^{\theta}\right)(\phi(h(\tilde{g}(w)) - 1)\, dw)\right\} \exp\left\{-\int_{\theta}^{\theta+\beta}\mu_H(w)\, dw\right\}. \quad (3.13)$$

As $S(t) \times Q(0,0,0;t)$ is the probability the host is parasite free *and* alive, $S(t)\{1 - Q(0,0,0;t)\}$ is the probability that a host is alive and contains parasites and so can pass on the infection. Figures 3.6, 3.7 and 3.8 on pages 64 and 65 show $1 - S(t)\{1 - Q(0,0,0;t)\}$, with $\phi(t) = 0$ for $t > 10$, which allows enough time for the parasite level to be at its quasi-stationary level before control is started. This gives an idea of how long transmission control needs to be maintained. Three different lifetime distributions for the mature and larval parasites are used with means fixed at the values in Figures 3.3 - 3.5, but with shape parameters varying as indicated in the figures. Other parameters not given are as in Figures 3.3 - 3.5. The different tail lengths of the mature parasite lifetime distributions affect the time for which control needs to be maintained. With higher parasite-induced host mortality, the curves approach 1 faster, because of the extra chance that the host dies and is unable to transmit infection further (compare Figure 3.6 with Figure 3.7).

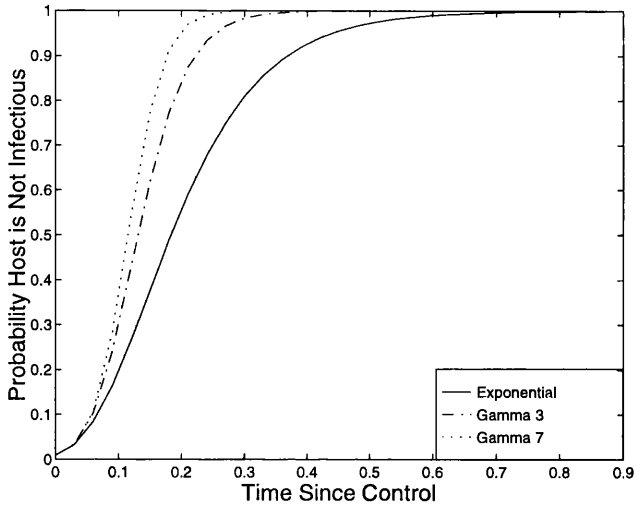

Figure 3.6: Probability Host is Not Infectious; $\phi = 6, m_c = 50, \alpha_m = 2$

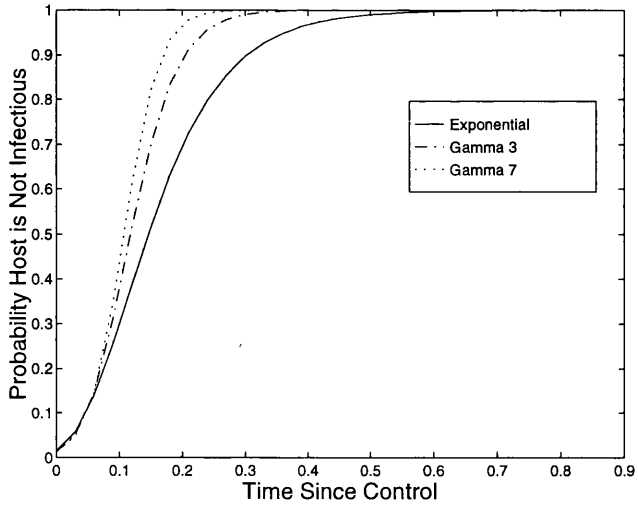

Figure 3.7: Probability Host is Not Infectious; $\phi = 6, m_c = 50, \alpha_m = 0.2$

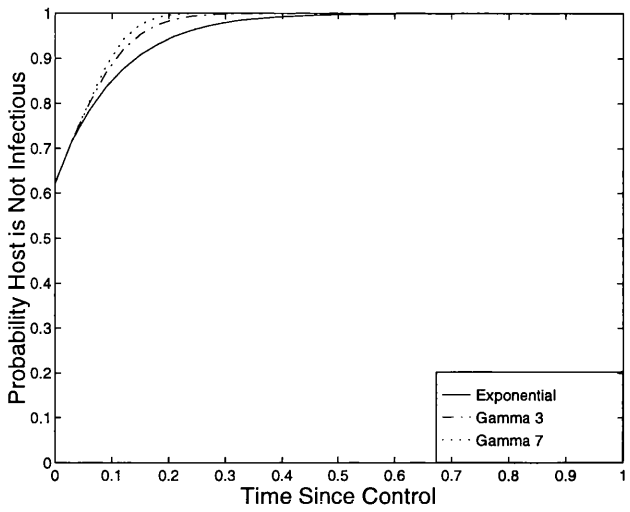

Figure 3.8: Probability Host is Not Infectious; $\phi = 60, m_c = 5, \alpha_m = 0.2$

As this effect increases, the choice of lifetime distribution becomes less important. With more parasite inputs events i.e. greater ϕ, the chance of the host being parasite free is less, even though the mean load levels may be similar (Figure 3.8). This emphasises the difficulty in relating prevalence data to actual parasite load levels in host populations.

3.3.4 Variable Input

So far we have considered a single host, or equivalently a population consisting of a cohort of identical hosts. However, for many infections there may be substantial heterogeneity between hosts. A simple way of incorporating such heterogeneity into the model is to allow the function $\phi(\cdot)$ to be a random function, $\Phi(\cdot)$. This additional random variation could represent differences between hosts in their exposure to infection (see Isham (1995) and Chapter 5 for brief discussions of other models for between host hetereogenity). Suppose we assume that the exposure rate Φ is a constant ϕ for a particular host, but varies randomly between hosts. Writing $\epsilon_{1L}(t) = \int_0^t h'(\tilde{g}(w))e^{-\alpha_l w}\mathcal{F}_L(w)\,dw$ and $\epsilon_{2L}(t) = \int_0^t h''(\tilde{g}(w))e^{-2\alpha_l w}(\mathcal{F}_L(w))^2\,dw$, it

is straightforward to show from the results in Appendix A that

$$\begin{aligned} \mathrm{E}[L_c(t)] &= \epsilon_{1L}(t)\mathrm{E}[\Phi] \\ \mathrm{Var}[L_c(t)] &= \epsilon_{1L}(t)^2\mathrm{Var}[\Phi] + (\epsilon_{1L}(t) + \epsilon_{2L}(t))\mathrm{E}[\Phi] \end{aligned}$$

so that the index of dispersion of $L_c(t)$ can be expressed as

$$I_L := \frac{\mathrm{Var}(L_c)}{\mathrm{E}(L_c)} = \frac{\epsilon_{1L}(t) + \epsilon_{2L}(t)}{\epsilon_{1L}(t)} + \epsilon_{1L}(t)\mathrm{I}_\Phi$$

where $\mathrm{I}_\Phi = \mathrm{Var}(\Phi)/\mathrm{E}(\Phi)$. The first term is the within-host index of dispersion (independent of Φ) obtained from the compound Poisson input, whilst the second term represents the contribution of the between-host variation (also see Isham (1995)), so this decomposition allows comparison of the relative sizes of the contributions from the two source of variation. Similar results are obtainable for $M_c(t)$ and $N_c(t)$.

Writing $\epsilon_{3L}(t) = \int_0^t h''(\tilde{g}(w))\ \mathcal{F}_L(w)e^{-\alpha_l w}\tilde{g}_y(w)dw$, and
$\epsilon_{1M}(t) = \int_0^t h'(\tilde{g}(w))\tilde{g}_y(w)dw$ we also have (from (3.9)),

$$\mathrm{Cov}(L_c, M_c) = \epsilon_{3L}\mathrm{E}(\Phi) + \epsilon_{1L}\epsilon_{1M}\mathrm{Var}(\Phi).$$

If we define the index of co-dispersion of L and M, $\mathrm{I}_{L,M}$, as $\frac{\mathrm{Cov}(L_c,M_c)}{\sqrt{E(L_c)E(M_c)}}$, then we have

$$\mathrm{I}_{L,M} := \frac{\mathrm{Cov}(L_c, M_c)}{\sqrt{E(L_c)E(M_c)}} = \frac{\epsilon_3(t)}{\sqrt{\epsilon_{1L}(t)\epsilon_{1M}(t)}} + \sqrt{\epsilon_{1L}(t)\epsilon_{1M}(t)}\mathrm{I}_\Phi,$$

again giving a contribution from within individual hosts together with a between hosts term. We have similar results for $\mathrm{I}_{L,N}$, and $\mathrm{I}_{M,N}$.

3.3.5 No Parasite Induced Mortality

If there is no parasite-induced host mortality, i.e. $\alpha_l = \alpha_m = 0$, then there is no interaction between parasites and host and the process is linear (Tallis and Leyton, 1966; Tallis and Leyton, 1969), and is simply an M/M/∞ queue with batch arrivals. It is useful to consider this simple case as a means of comparison for results with parasite-induced host mortality. We have $\tilde{g}(w) \equiv 1$, and the i^{th} moment of the

process only depends on the moments of C, the clump size distribution, up to order i (see (3.6), (3.7), (3.8), (3.9) and Appendix A). It is the non-linear effect of the parasite-induced host mortality that causes the full distribution of the input clump size, C, to affect even the first moment of the parasite loads. In general, a similar result holds for the effect of the distribution of offspring clump size, D, on the offspring number $N_c(t)$. However, in this model we have not included any effect of offspring on host death (i.e. $\alpha_N = 0$ throughout), so when looking at moments of $N_c(t)$ only the equivalent moments of D need to be specified.

Consider the special case when all lifetimes are exponentially distributed and $\rho(\cdot)$ and $\sigma(\cdot)$ are constant, so that the model is Markov, with larvae, adult and offspring parasite lifetimes having parameters $\mu_l + \gamma_l, \mu_m, \mu_N$ respectively, and with $\sigma(u) = \lambda/(\lambda + \mu_l)$, and further assume that $\phi(t)$ is constant. Then it is straightforward to perform the integrals in equations (3.7), (3.8), (3.9) and Appendix A to obtain explicit expressions for the second-order moments. For simplicity, we state here only the limiting (quasi-stationary) moments as $t \to \infty$ which can be expressed in terms of input and output rates to each of the three stages;

$$\begin{aligned}
\mathrm{E}(L_c(t)) &\to \frac{\phi \mathrm{E}(C)}{\mu_l + \gamma_l} \\
\mathrm{E}(M_c(t)) &\to \frac{\gamma_l}{\mu_m} \frac{\phi \mathrm{E}(C)}{(\gamma_l + \mu_l)} \\
\mathrm{E}(N_c(t)) &\to \frac{\rho \mathrm{E}(D)}{\mu_N} \frac{\gamma_l}{\mu_m} \frac{\phi\ \mathrm{E}(C)}{(\gamma_l + \mu_l)} \\
\mathrm{I}(L_c(t)) &\to 1 + \frac{1}{2}(\mathrm{I}(C) + \mathrm{E}(C) - 1) \\
\mathrm{I}(M_c(t)) &\to 1 + \frac{1}{2} \frac{\gamma_l}{\gamma_l + \mu_l + \mu_m} (\mathrm{I}(C) + \mathrm{E}(C) - 1).
\end{aligned} \tag{3.14}$$

The dispersion of the mature parasite load is always less than that of the larval load. As $\mathrm{I}(C) + \mathrm{E}(C) \geq 1$, we can see again that none of the loads can be underdispersed (i.e. the index of dispersion of L_c and M_c are at least 1.) Furthermore, they are only equal to 1 when $\mathrm{E}(C^2) = \mathrm{E}(C)$, i.e. when $C = 1$ a.s. (see Section 3.6). Notice that to produce this parasite load overdispersion C itself does not have to be overdispersed

- there merely needs to be some probability of C taking values greater than 1.

Of course, when $\alpha_l = \alpha_m = 0$ the model is linear and these moments can be obtained directly from the set of ordinary differential equations for these properties, without any need to find the full solution for the probability generating function $Q(x, y, z; t)$ first.

In their analysis of the same (linear) model with larval and mature parasites, Grenfell, Dietz, and Roberts (1995a, p371) give the index of dispersions at equilibrium in 3.14, though the values for $\mathrm{I}(M)$ and the "negative binomial parameter" $k_M := (\mathrm{E}(M))^2/(\mathrm{Var}(M) - \mathrm{E}(M))$ appear to have been misprinted. They plot this k statistic for M against the k statistic for the input distribution C. This is done for fixed values of $\mathrm{E}(C)$ so that $\mathrm{Var}(C) = \mathrm{E}(C)(\mathrm{E}(C) + k_C)/k_C$. The plot is given for various levels of ϕ, the encounter rate, and hence for various levels of $\mathrm{E}(M) = \phi\mathrm{E}(C)/\mu_m$. The results show that as ϕ increases, the value of k_M increases, and hence the aggregation in M decreases. This is due to the swamping of the clustering effect of C by the higher rate of encounters, making ingestion levels more uniform across realisations of the process.

In the paper (page 372), the authors infer from this that the aggregation of M decreases as the mean of M increases, because, "the asymptotic values of I for L and M are independent of the means". This is of course only true for fixed mean of C, as in fact the equilibrium values of $\mathrm{I}(L)$ and $\mathrm{I}(M)$ are only independent of ϕ, μ_l, γ and μ_m (see (3.14)). When fixing $\mathrm{E}(C)$, they do then become independent of $\mathrm{E}(M)$ and $\mathrm{E}(L)$. However, since the mean parasite burden can be increased by increasing either ϕ *or* $\mathrm{E}(C)$, their conclusions should not be taken in general. Higher parasite levels in the hosts could produce more eggs per release of faeces, therefore higher larva concentration on the pasture, and hence higher levels for $\mathrm{E}(C)$. Presumably their fixed level of $\mathrm{E}(C)$ was used because of field data and the conclusions were based on the assumption that ϕ is more likely to vary than $\mathrm{E}(C)$ in the particular case investigated. Similar arguments are used in Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) when the model is fitted to data.

For a system of this type, the important biological question is to establish whether increased parasite burdens are due to higher contact rates (ϕ) or higher clump sizes (C). This then directly affects the level of dependence between parasites entering a host, which is the cause of overdispersion in this linear system.

3.3.6 Pure Poisson intake: $C \equiv 1$

If $C \equiv 1$ then exactly one larva is picked up at each encounter and so the input is Poisson. This affords considerable simplification of the model because then there is then no dependence between the life histories of distinct parasites. We have $h(x) \equiv x$ and it follows from (3.3) and (3.6) that $L_c(t)$ has a Poisson distribution, independent of $M_c(t)$ and $N_c(t)$, with mean

$$\int_0^t \phi(t-w)e^{-\alpha_l w}\mathcal{F}_L(w)dw \tag{3.15}$$

while the marginal distribution of $M_c(t)$ is Poisson with mean

$$\int_0^t \phi(t-w)\int_0^w e^{-\alpha_m(w-v)}e^{-\alpha_l v}\sigma(v)f_L(v)\mathcal{F}_M(w-v)dvdw. \tag{3.16}$$

Thus the distribution of $L_c(t)$ is not only independent of $M_c(t)$ and $N_c(t)$ but is also unaffected by any parameters or distributions relating to mature parasites or their offspring. This is true even when the mature parasite load has an effect on the host's survival ($\alpha_m \neq 0$), and holds only in this special case of Poisson input when the host picks up just one larval parasite at a time.

The mean in (3.15) has a direct interpretation as a sum of contributions from all larvae picked up over $(0,t]$. A larva picked up at $t-w$ (at rate $\phi(t-w)$) must survive until t (probability $\mathcal{F}_L(w)$) and not kill off the host (probability $e^{-\alpha_l w}$).

A similar argument applies to the mean of $M_c(t)$ in (3.16). However, this mean depends on the arrival rate into this second stage, which itself depends on the part of the model relating to larval parasites. Thus we still expect to see the larval lifetime distribution and α_l affecting the distribution of $M_c(t)$. A larva is picked up

at time $t-w$ at rate $\phi(t-w)$ when the host is alive, matures at rate $f_L(v)\sigma(v)$ after a lifetime v, and must have not killed the host before it matures (probability $e^{-\alpha_l v}$). Then the resulting mature parasite must have survived to time t (with probability $\mathcal{F}_M(w-v)$) and not have killed the host (probability $e^{-\alpha_m(w-v)}$).

Of course in this model $M_c(t)$ and $N_c(t)$ are not independent as the offspring are directly produced by the mature parasites.

The results here mean that if the model does not allow for larval parasites to be picked up in clumps (giving a cause of overdispersion in the absence of parasite-induced host mortality), then within a cohort of identical hosts, neither the larval nor mature parasite loads are underdispersed, (nor are they overdispersed), despite the regulatory effect of parasite-induced host mortality. This is in contrast to the intuitive idea put forward and demonstrated by Monte Carlo simulation in Anderson and Gordon (1982), in which it is stated that with Poisson immigration into the host, the variation to mean ratio of the parasite load will be decreased by parasite-induced host mortality. It is clear from the results of this section that it is only when there is a natural overdispersion of the parasite load in the absence of parasite-induced host mortality (generated in this model by the clumped input), that this parasite-induced host mortality will reduce the dispersion.

With the additional assumptions of the Markov model with constant ϕ, described in Section 3.3.5, the means of $L_c(t)$ and $M_c(t)$, given in (3.15) and (3.16), simplify to

$$\begin{aligned} \mathrm{E}(L_c(t)) &= \phi\frac{1-e^{-(\mu_l+\alpha_l+\gamma_l)t}}{\alpha_l+\mu_l+\gamma_l} \\ \mathrm{E}(M_c(t)) &= \frac{\phi\gamma_l}{\mu_m+\alpha_m-\gamma_l-\mu_l-\alpha_l}\left[\frac{1-e^{(\mu_l+\alpha_l+\gamma_l)t}}{\mu_l+\alpha_l+\gamma_l}-\frac{1-e^{(\mu_m+\alpha_m)t}}{\mu_m+\alpha_m}\right] \end{aligned}$$

and we can see that in this case the effect on $L_c(t)$ and $M_c(t)$ of allowing parasite-induced mortality is simply equivalent to an increase in the parasite death rates from μ_l to $\mu_l+\alpha_l$, and from μ_m to $\mu_m+\alpha_m$.

3.4 Disease Progression

In the previous model of Section 3.2 the host is in one of two states, either alive or dead. The method of model analysis proposed by Ball (private communication) can be extended to allow the host to move through different stages of disease before death occurs. In many macroparasitic diseases the host may move through different stages of morbidity before death occurs. In some human macroparasitic diseases, such as filariasis, the stages of morbidity are more important than death itself, which can be quite rare.

Consider the host as being in one of $m+2$ states, representing disease free, m disease states and death. Let Z_t be the variable denoting the state of the host, so that Z_t takes values in $0, 1, ..., m, m+1$, with state 0 denoting no disease, and state $m+1$ being an absorbing state representing host death.

The host increases its disease state at a rate proportional to its parasite load. Parasites evolve in the same way as described in Section 3.2, so that the model is similar, with just the addition of extra disease states before death. The host may also die from natural causes at any time, and so Z_t may jump to state $m+1$ at an additional rate of $\mu_H(t)$ from any state.

The general model is as follows. Let $\nu_r(t; L(t), M(t))$ be the rate of transfer of Z_t from state r to state $r+1$ as a result of the parasite load (so that $\nu_r(t; L(t), M(t))$ is defined conditionally on the parasite loads in the host at t, i.e. $\nu_r(t; L(t), M(t)) = P(Z_{t+\delta t} = Z_t + 1 \mid L_t, M_t)$ for $r = 0, 1, ..., m$). Ideally we would include a recovery rate, ρ_r say, so that Z_t can move from disease state r to $r-1$, and also we would have $\nu_r(t; L(t), M(t))$ depending on r in some way. However we wish to incorporate the evolution of the parasite loads $L(t)$ and $M(t)$ into the solution by removing the conditioning on them, and it appears that the only solution for which this is tractable is when $\rho_r = 0$ and also $\nu_r(t; L(t), M(t)) = \nu(L(t), M(t)) = \alpha_l L(t) + \alpha_m M(t)$ for all r. This means there is one way disease progression with no recovery, and the effect of an individual parasite on disease progression remains constant

throughout all disease states. This is neccesary because otherwise the contribution each parasite makes to the total history *in each disease stage* needs to be calculated, and hence a track of when each transition between stages occurs is needed. With the same linear function $(\alpha_l L(t) + \alpha_m M(t))$ for the disease progression rate across the disease states, only each parasite's contribution to the history *across all stages* needs be tracked, as given $\nu(L(t), M(t))$, the disease progression is moving in a Markovian type way.

We consider the formation of the relevant probability generating function for this simple, irreversible disease progression in which, given fixed parasite levels, the rate of progression through the disease states is constant.

Consider Z_t as a general non-homogeneous immigration process. This means, conditional on $L(t)$ and $M(t)$ and hence on $\nu(L(t), M(t))$, Z_t simply moves from state n to state $n+1$ at rate $\nu(L(t), M(t))$, for $0 \leq n \leq m$, but can still jump from any state to state $m+1$ at rate $\mu_H(t)$. There is no recovery, i.e. Z_t can only increase until it is absorbed in state $m+1$ (host death). If $\mathrm{P}(Z_t = r)$ is written as $p_r(t)$, then the forward differential difference equations conditional on the parasite loads $L(t)$ and $M(t)$, and therefore conditional on $\nu(t) = \alpha_l L(t) + \alpha_m M(t)$, are

$$\begin{aligned}
\frac{dp_0(t)}{dt} &= -(\nu(t) + \mu_H(t))p_0(t) \\
\frac{dp_r(t)}{dt} &= \nu(t)p_{r-1}(t) - (\nu(t) + \mu_H(t))p_r(t) \quad m \geq r \geq 1 \\
\frac{dp_{m+1}(t)}{dt} &= \nu(t)p_m(t) + \mu_H(t)\sum_{j=0}^{m} p_j(t)
\end{aligned}$$

with initial conditions $p_i(0) = 0$ for $i \neq 0, p_0(0) = 1$. The solution of these give the probability the host is in a particular disease state r, $(0 \leq r \leq m)$, as

$$\theta(\nu(\cdot); r; t) := \mathrm{P}(Z_t = r \mid v(\cdot)) = p_r(t) = \frac{e^{-\int_0^t (\nu(u)+\mu_H(u))du} \left(\int_0^t \nu(u)du\right)^r}{r!} \quad (3.17)$$

and the probability the host is dead can be found using

$$\mathrm{P}(Z_t = m+1) = 1 - \sum_{j=0}^{m} \mathrm{P}(Z_t = j).$$

As $\nu(u) = \alpha_l L(u) + \alpha_m M(u)$, the working required to solve this model and investigate the interrelations between disease stage and the distribution of parasites in the host follows similar lines as that in Section 3.2.2. We consider the generating function

$$\begin{aligned} P_r(x,y,z;t) &:= \sum_{l,m,n\geq 0} x^l y^m z^n \mathrm{P}(M=m, L=l, N=n, Z_t=r) \\ &= \mathrm{E}(x^L y^M z^N \theta(\alpha_l L + \alpha_m M; r; t)) \end{aligned}$$

and for notational convenience we define

$$G_r(x,y,z;t) := \frac{1}{r!}\mathrm{E}\left(x^{L(t)} y^{M(t)} z^{N(t)} e^{-(\alpha_l A(t)+\alpha_m B(t))}(\alpha_l A(t) + \alpha_m B(t))^r\right)$$

and

$$\begin{aligned} &g_r(x,y,z;w) := \mathrm{E}\left(x^{L_{ij}} y^{M_{ij}} z^{N_{ij}} \theta(\alpha_l A_{ij} + \alpha_m B_{ij}; r; w) | T_i = t - w\right) = \\ &\frac{1}{r!}\left\{ x e^{-\alpha_l w}(\alpha_l w)^r \mathcal{F}_L(w) + \int_0^w (e^{-\alpha_l v})(\alpha_l v)^r f_L(v)\{1-\sigma(v)\}dv + \right. \\ &\int_0^w f_L(v)\sigma(v) \int_0^{w-v} e^{-(\alpha_l v + \alpha_m \xi)}(\alpha_l v + \alpha_m \xi)^r \eta(z;\xi, w-v) f_M(\xi) d\xi dv + \\ &\left. \int_0^w y f_L(v)\sigma(v) e^{-(\alpha_l v + \alpha_m (w-v))}(\alpha_l v + \alpha_m (w-v))^r \eta(z; w-v, w-v)\mathcal{F}_M(w-v)dv \right\}, \end{aligned} \tag{3.18}$$

analogous to the definitions in Section 3.2.2. By the same argument as in that section we have

$$G_r(x,y,z;t) = \exp\left\{-\int_0^t \phi(t-w)[1-h(g_r(x,y,z;t))]dw\right\}.$$

By (3.17) we find that

$$P_r(x,y,z;t) = G_r(x,y,z;t)\exp\{-\int_0^t \mu_H(u)du\}$$

so that the probability generating function of the parasite loads, conditional on the host being in disease state r, is

$$Q_r(x,y,z;t) := \mathrm{E}(x^L y^M z^N | Z_t = r) = P_r(x,y,z;t)/P_r(1,1,1;t).$$

Unconditionally, the probability the host is in state r is $P_r(1,1,1;t)$.

The survival probability of the host is $S(t) = \sum_{i=0}^m P_i(1,1,1;t)$.

3.5 Moment Closure Approximations

Although relatively simple, the model in Section 3.2 incorporating parasite induced host mortality has the nice property that exact results are obtainable despite its nonlinearity. We can use this to investigate how closely the moment closure approximation technique for nonlinearities described in Section 2.2 matches the exact results. Grenfell, Dietz, and Roberts (1995a) and Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) have used these moment closure approximations to evaluate models of nematodes in ruminants. The additional non-linearity of an immune response was also included, but we have left its discussion to Chapter 4.

We consider only the Markov version of the above model, and investigate the moments of the process conditional on host survival. We cannot write down the moment equations for the conditional process directly from the specification of the model in the usual immediate way as this would involve conditioning on different events on either side of the forward equations, i.e. conditioning upon host survival at different times.

We can, however, proceed in the usual way if we consider $Z(t)$, the indicator of host survival, as another variable in the process, and initially ignore the conditioning. To illustrate this, consider just the single variable Markov version of the above model, i.e. consider only mature parasites, $M(t)$. We can write the Markov transitions for the model as being from $M(t), Z(t)$ to

$$\begin{array}{lll} M+c \quad Z & \text{at rate } \phi(t)h_c & \text{for } c=0,1,... \\ M-1 \quad Z & \text{at rate } \mu M & \\ M \quad Z-1 & \text{at rate } (\alpha M+\mu_H(t))\, Z & \end{array}$$

with the important initial condition that $Z(0)=1$, together with $M(0)=0$. When considering just the conditional process, we could of course write the parasite death transitions rate as μMZ instead of μM without altering the model, as we are not interested in the process after host death.

The nonlinearity of the process can be seen in the transition rate for Z, which is αMZ. On considering up to second order moments, we obtain five ordinary differential equations. Any of the usual assumptions discussed in Section 2.2 that are made about the bivariate distribution of $M(t)$ and $Z(t)$ would be unlikely to be appropriate as Z is simply an indicator variable.

The system can be reduced to two variables when we realise that $\mathrm{E}(Z^2) = \mathrm{E}(Z)$ and that the moments of $\mathrm{E}(M)$ and $\mathrm{E}(M^2)$ will be self contained and have no influence on the conditional process. The differential equation for $\mathrm{E}(M^2Z)$ needs to be added to obtain second order conditional properties. Using the result $\mathrm{E}(M^rZ) = \mathrm{E}(Z)\mathrm{E}(M_c^r)$ for r an integer, and the solution to the equation for $\mathrm{E}(Z(t)) \equiv S(t)$,

$$\frac{d\mathrm{E}(Z(t))}{dt} = -\alpha\mathrm{E}(M(t)Z(t)) - \mu_H(t)\mathrm{E}(Z(t)), \quad \text{with} \quad \mathrm{E}(Z(0)) = 1$$

which gives

$$S(t) = \exp\left\{-\int_0^t (\alpha_m \mathrm{E}(M_c(w)) + \mu_H(w))\, dw\right\},$$

we can write a set of differential equations purely in terms of the conditional moments. These will involve higher order moments and will not be closed, hence moment closure techniques can be used on the system. The results of using this method are given in Section 3.7.

By following the algebra above it can be seen that if any process without parasite induced host mortality has moments equations

$$\mathrm{E}(\dot{\boldsymbol{Y}}) = g(\mathrm{E}(\boldsymbol{Y}))$$

(where $\boldsymbol{Y}$ a vector of the variables of interest, $(M(t), M(t)^2)'$ in the example above) then the moments of the conditional process, $\mathrm{E}(\boldsymbol{Y}_c)$ follow the differential equations

$$\mathrm{E}(\dot{\boldsymbol{Y}}_c) = g(\mathrm{E}(\boldsymbol{Y}_c)) - \mathrm{cov}(\boldsymbol{Y}_c, h(\boldsymbol{Y}_c))$$

where generally $\mathrm{cov}(\boldsymbol{A}, \boldsymbol{B})$ is a vector with i^{th} term $\mathrm{cov}(A_i, B_i)$ and $h(\boldsymbol{Y})$ is the excess death rate of the host as a function of the variables $\boldsymbol{Y}$. In the above model $h(\boldsymbol{Y}) = \alpha M(t)$ so $h(\boldsymbol{Y}_c) = \alpha M_c(t)$.

An alternative but essentially equivalent method of deriving these conditional moments equations for the Markov model, used by Grenfell, Dietz, and Roberts (1995a), Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) and Isham (1995), is via the partial differential equation for the probability generating function of the conditional process. A general form that enables this differential equation for Markov models of this type to be immediately written down can be easily found by a slight modification of the Palm result (2.5) of Section 2.1. We outline this in the following Section, 3.5.1.

3.5.1 Derivation of Forward Moment Equations

We derive a general form for the partial differential equation of the probability generating function for Markov models with this additional feature concerning host death. The rate of host death depends on the state of the parasite population, and we are interested in not only time until host death, but results conditional on host survival (Grenfell, Dietz, and Roberts, 1995a).

The general set up we consider is a continuous time Markov process, $\boldsymbol{W}_t$ with state space $\mathbb{N}^N \times \{0,1\}$. Let $\boldsymbol{W}_t{}' = (\boldsymbol{X}_t' \; Z_t)$, where $\boldsymbol{X}_t \in \mathbb{N}^N$ and $Z_t \in \{0,1\}$. The interpretation of this is that Z_t indicates whether the host is alive or dead, and $\boldsymbol{X}_t$ represents the internal state of the host in some way, usually referring to the parasite population and the host's immune defences. We call $\boldsymbol{X}_t$ the internal process and Z_t the indicator process. The set of states $\{\boldsymbol{W}_t : Z_t = 0\} \in \mathbb{N}^N \times \{0\}$ are absorbing as they correspond to host death.

As in Section 2.1, we define the transition probabilities for the internal process as

$$f_{\mathbf{c}}(\boldsymbol{x})\delta t + o(\delta t) = P(\Delta \boldsymbol{X}_t = \mathbf{c} \mid \boldsymbol{X}_t = \boldsymbol{x}) \quad \text{for } \boldsymbol{c} \in \mathcal{C}$$

and in addition we define the transition rate for the indicator process as

$$f_d(\boldsymbol{x})\delta t + o(\delta t) = P(Z_{t+\delta t} = 0 \mid \boldsymbol{X}_t = \boldsymbol{x}, Z_t = 1)$$

where $f_d(\boldsymbol{x})$ is the death rate of the host, a function of the state of the internal process. For example, in the univariate case of the Markov version of the model of Section 3.2, (Isham, 1995) we have $f_i(x) = h_i\phi$, $f_{-1}(x) = \mu x$ and $f_d(x) = \alpha x$.

We consider the generating function,

$$P(\boldsymbol{s};t) := \sum_{\boldsymbol{x}\in\mathbb{N}^N} \boldsymbol{s}^{\boldsymbol{x}} P(\boldsymbol{X}_t = \boldsymbol{x}, Z_t = 1)$$

which is not a probability generating function because the probabilities $P(\boldsymbol{X}_t = \boldsymbol{x}, Z_t = 1)$ do not form a full probability distribution over $\boldsymbol{x} \in \mathbb{N}^N$. We use the convention that generally $\boldsymbol{s}^{\boldsymbol{x}} := \prod_{i=1}^N s_i^{x_i}$. If we define

$$K_c(\boldsymbol{s};\boldsymbol{x}_1;t) :=$$
$$\lim_{\delta t\to 0} \frac{1}{\delta t}\left(\sum_{\boldsymbol{x}_2\in\mathbb{N}^N} s^{(\boldsymbol{x}_2-\boldsymbol{x}_1)} P(\boldsymbol{X}_{t+\delta t} = \boldsymbol{x}_2, Z_{t+\delta t} = 1 \mid \boldsymbol{X}_t = \boldsymbol{x}_1, Z_t = 1) - 1 \right)$$

we find that

$$K_c(\boldsymbol{s};\mathbf{x};t) \;=\; \sum_{\mathbf{c}\in\mathcal{C}} (\boldsymbol{s}^{\mathbf{c}} - 1) f_{\mathbf{c}}(\boldsymbol{x}) - f_d(\boldsymbol{x}). \tag{3.19}$$

Compare K_c with the definition (2.4) of K, given in Section 2.1. Note that the c subscript in K_c refers to the conditioning on the host survival and not the jumps of the process.

Following along the lines of Section 2.1, we find that

$$\frac{\partial P}{\partial t} \;=\; K_c\left(\boldsymbol{s};\frac{\partial}{\partial \boldsymbol{s}};t\right)(P(\boldsymbol{s};t)). \tag{3.20}$$

We assume that initially $Z(0) = 1$. We have that $P(Z_t = 1) = \sum_{\boldsymbol{x}\in\mathbb{N}^N} P(\boldsymbol{X}_t = \boldsymbol{x}, Z_t = 1) = P(\mathbf{1}, t)$. If we define $Q(\boldsymbol{s};t) = P(\boldsymbol{s};t)/P(\mathbf{1};t)$ then

$$\begin{aligned} Q &= \sum_{\boldsymbol{x}\in\mathbb{N}^N} \boldsymbol{s}^{\boldsymbol{x}} P(\boldsymbol{X}_t = \boldsymbol{x}, Z_t = 1)/P(Z_t = 1) \\ &= \sum_{\boldsymbol{x}\in\mathbb{N}^N} P(\boldsymbol{X}_t = \boldsymbol{x} \mid Z_t = 1)\boldsymbol{s}^{\boldsymbol{x}} \end{aligned}$$

and $Q(\boldsymbol{s};t)$ is the probability generating function of $\boldsymbol{X}_t$, *conditional on* $Z_t = 1$, i.e. the probability generating function for the internal process conditional on host survival. The partial differential equation for $Q(\boldsymbol{s};t)$ is then

$$\frac{\partial Q(\boldsymbol{s};t)}{\partial t} = \frac{1}{P(\mathbf{1};t)}\left\{\frac{\partial P(\boldsymbol{s};t)}{\partial t} - Q(\boldsymbol{s};t)\frac{\partial P(\mathbf{1};t)}{\partial t}\right\}. \tag{3.21}$$

Whereas equation (3.20) may be solved for some simple processes of this type, for example the process described in Section 3.2, equation (3.21) is not explicit for Q. However, by differentiating with respect to the appropriate arguments the differential equations for the moments of the internal process conditional on host survival can be found, as in Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) and Isham (1995).

3.6 The Multivariate Negative Binomial Distribution

In the appendix of Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) the use of normal approximations is discussed, and an approximation based on moment relationships of a negative binomial distribution proposed, on the grounds that it often describes parasite loads closely. For the simple univariate model described in Isham (1995), Isham (private communication) has shown that the univariate negative binomial approximation can perform better than the normal approximation. Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) stated

> Ideally, we would explore here a multivariate negative binomial apprroximation to the joint distribution of I (immunity), L, M and E (written as N here). What is needed is a suitably broad class of joint distributions with negative binomial marginals and arbitrary covariances, but we have not yet found a satisfactory candidate for this.

We discuss possible choices for moments relationships in multivariate systems based on the negative binomial distribution in this section.

There are many ways of describing a multivariate distribution which has marginal negative binomial distributions. A common form is the negative multinomial distribution. An n variable negative multinomial distribution can be thought of as the number of outcomes of each of n types, before the k^{th} occurence of outcome 0, say, occurs, in a sequence of independent trials in which outcome i occurs with probability p_i $(i = 1, ..., n)$ and outcome 0 occurs with probability $p_0 = 1 - \sum_{i=1}^{n} p_i$. This gives the probability generating function as the negative multinomal expansion

$$p_0 \left(1 - \sum_{i=1}^{n} p_i z_i\right)^{-k}$$

with $k > 0$ and $0 < p_i < 1$ for all i. The joint probability mass function is

$$P(x_1, ...x_n) = \begin{pmatrix} k + \sum_{i=1}^{n} x_i - 1 \\ x_1, x_2, ..., x_n, k - 1 \end{pmatrix} {p_0}^k \prod_{i=1}^{n} p_i^{x_i}$$

where

$$\begin{pmatrix} k + \sum_{i=1}^{n} x_i - 1 \\ x_1, x_2, ..., x_n, k - 1 \end{pmatrix} = \frac{\Gamma\left(k + \sum_{i=1}^{n}\right)}{\Gamma(k) \prod_{i=1}^{n} x!}.$$

A different way of formulating the univariate negative binomial distribution, first derived by Greenwood and Yule (1920), is as a mixture of the Poisson and Gamma distributions. This can also be used to derive the negative multinomial distribution by mixing n independent Poisson distributions means $\lambda_i \Theta$ for $i = 1, ..., n$, with $\Theta \sim \Gamma(\alpha, k)$.

Consider the multivariate Poisson distribution i.e. one derived, for example in the two variable case, by letting

$$Y_1 = X_1 + X_{12}, \quad Y_2 = X_2 + X_{12}$$

where X_1, X_2 and X_{12} are independent Poissons. All multivariate distributions that have each marginal distribution as sums of independent Poissons have probability

generating function of the form

$$\exp\left\{xs\sum_{i=1}^{n}A_iz_i+\sum\sum_{1\leq i<j\leq k}A_{ij}(z_iz_j-1)+...+A_{12...n}(z_1z_2...z_n-1)\right\}$$

(see Johnson, Kotz, and Balakrishnan (1997)). On multiplying the means by Θ and then letting $\Theta\sim\Gamma(\alpha,k)$, the resultant distribution has probability generating function of the form

$$\left(1-\sum_{i=1}^{n}p_iz_i-\sum_{i<j}p_{ij}z_iz_j-...-p_{12...n}z_1z_2...z_n\right)^{-k}. \tag{3.22}$$

The scale parameter of the gamma distribution, α, is superfluous as it simply rescales the original Poisson means, so that this distribution, referred to by Patil and Joshi (1968) as the multivariate negative binomial distribution, provides 2^n parameters, 2^{n-1} from the multivariate Poisson distribution plus the k parameter. The negative multinomial distribution is a special case of this distribution.

We give a brief but interesting example comparing the two distributions described. Diggle and Milne (1983) considered certain types of point processes that might produce negative binomial distribution in 2-D space. When a mixed sample process is produced by taking a univariate negative binomial distribution, and conditional on its value scattering that number of points randomly on a region in space, then the number of points in n subregions follows the n variate negative binomial distribution described above. In particular, if the subregions are disjoint, then this simplifies to an n variable negative multinomial distribution.

If the systew of differential equations that we wish to evaluate has n stochastic variables and includes moments up to order r, then there will be

$$\sum_{i=1}^{r}\begin{pmatrix}n+i-1\\ i\end{pmatrix}$$

equations, where $\begin{pmatrix}n+i-1\\ i\end{pmatrix}$ is the number of unordered ways of choosing r items from a set of n distinct items, with replacement, i.e. the number of moments

of order r in an n variable system. The negative multinomial distribution has $n+1$ parameters and so is not particularly useful for our purposes here as for $n > 1$ and $r > 1$ there will never be sufficient parameters.

For $r = 2$ and $n \leq 3$ there are less parameters in the multivariate negative binomial distribution than the $\frac{1}{2}n(n+3)$ required for the system, and for $r = 3$ and $n \leq 6$ there are less than the $\frac{1}{6}n(6+(n+1)(n+5))$ required. Hence using this multivariate negative binomial distribution will rarely provide sufficient parameters, and even if it did, it wouldn't provide the *exact* number, so some would have to be set to zero to give the correct number, and it is not immediately clear how best to do this.

Instead we derive a different distribution that has the correct number of parameters when $r = 2$, for all values of n. It still has a negative binomial marginal distribution, and we still utilise a form of Poisson and Gamma mixing. The genesis is as follows.

Define X_{ij} for $i = 1, ..., n, j = 0, i+1, .., n$ as independent standardised gamma distributions with parameters $\theta_{ij} > 0$, i.e.

$$f_{X_{ij}}(x) = (\Gamma(\theta_{ij}))^{-1} x^{\theta_{ij}-1} e^{-x} \quad \text{and} \quad H_{X_{ij}}(s) := \mathrm{E}(e^{sX_{ij}}) = (1-s)^{-\theta_{ij}}.$$

Then let

$$Y_i = X_{i0} + \sum_{k=1}^{i-1} X_{ki} + \sum_{k=i+1}^{n} X_{ik}, \qquad i = 1, ..., n$$

and finally, independently for each i given the Y_i, let

$$W_i \sim \text{Poisson}(\lambda_i Y_i) \qquad \lambda_i > 0.$$

The joint probability generating function for the W_is is

$$\mathrm{E}\left(\prod_{i=1}^{n} s_i^{W_i}\right) = \prod_{i=1}^{n} (1+\lambda_i(1-s_i))^{-\theta_{i0}} \prod_{j=i+1}^{n} (1+\lambda_i(1-s_i)+\lambda_j(1-s_j))^{-\theta_{ij}}$$

and marginally each has probability generating function

$$\mathrm{E}(s_i^{W_i}) = (1-\lambda_i(s_i-1))^{-\left(\theta_{i0}+\sum_{j=1}^{i-1}\theta_{ji}+\sum_{k=i+1}^{n}\theta_{ik}\right)}$$

and therefore has a negative binomial distribution with parameters $k = \theta_{i0} + \sum_{j=1}^{i-1} \theta_{ji} + \sum_{k=i+1}^{n} \theta_{ik}$ and $p = \frac{1}{1+\lambda_i}$. For example, if $r = 2$ and $n = 3$, a case we will need later on, then the third order moments expressed in terms of the first and second order moments are

$$\begin{aligned} \mathrm{E}(W_i^3) &= m_i^2 + m_{ii}(2m_{ii}/m_i - m_i - 1) \\ \mathrm{E}(W_i^2 W_j) &= m_i m_j - m_{ii} m_j + m_{ij}(2m_{ii}/m_i - 1) \\ \mathrm{E}(W_1 W_2 W_3) &= m_{12} m_3 + m_{13} m_2 + m_{23} m_1 - 2m_1 m_2 m_3 \end{aligned}$$

for $i \neq j$, where we have written $m_i := \mathrm{E}(W_i)$, $m_{ij} := \mathrm{E}(W_i W_j)$; $i, j = 1, 2, 3$, for notational convenience. Note that this last result is the same as the corresponding result for the relationship derived from the normal distribution. For $r = 2$ this distribution will always provide the correct number of parameters, as the p_i parameters can be thought of as providing the same number as the means of the process, and θ_{ij}s can be thought of as providing parameters to account for the second order moments.

Unfortunately, this is a fairly restrictive distribution as it necessarily requires that all variables are positively correlated. A more general distribution is still ideally required. However, we can apply this distribution to approximate the model of Section 3.2 as we would expect all correlations to be positive.

On a general note, notice that the derivation cannot be extended further by use of the multivariate Poisson distribution in the way the negative multinomial could, as the marginals would then become the sum of negative binomials *with different p values*, and hence would no longer be negative binomial.

3.7 Evaluation of Approximation Techniques

Numerical solutions to the integrals of Section 3.3.1 and Appendix A will provide exact results for the moments of this model, and we use these to evaluate the normal and negative binomial approximations for the Markov case of the model

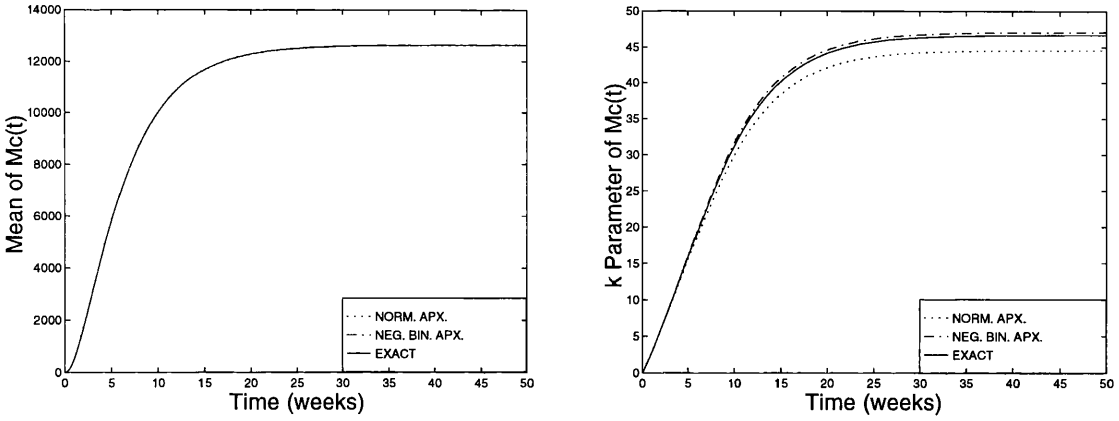

Figure 3.9: Mean and k Parameter of $M_c(t)$ with $\phi = 7, m_c = 500, \alpha_m = 2 \times 10^{-5}$

of Section 3.2. We investigate the model with only $L(t)$ and $M(t)$ included for simplicity, but this still enables us to evaluate the performance of the multivariate approximation techniques discussed in the last two sections. The Markov model requires exponential parasite lifetimes so that $f_L(x) = (\mu_l + \gamma_l)e^{-(\mu_l+\gamma_l)x}$, $\mathcal{F}_L(x) = e^{-(\mu_l+\gamma_l)x}$, $\sigma(u) = \gamma_l/(\gamma_l+\mu_l)$, $f_M(x) = \mu_m e^{-\mu_m x}$ and $\mathcal{F}_M(x) = e^{-\mu_m x}$, and additionally we assume that ϕ is constant throughout this section. The boundary conditions used to avoid singularities in all the multi-variate negative binomial approximations were $\mathrm{E}(M_c(0)) = \mathrm{E}(L_c(0)) = 10^{-10}$ and $\mathrm{E}(M_c(0)^2) = \mathrm{E}(L_c(0)^2) = 10^{-20}$.

Figure 3.9 uses the parameters of Grenfell, Dietz, and Roberts (1995a, Fig. 6), which are, with time measured in weeks, $\mu_l = 1/7.5, \gamma_l = 0.4, \mu_m = 0.2, \phi = 7, \alpha_l = 0, \alpha_m = 2 \times 10^{-5}, C \sim \text{Neg Bin}(k = 1, \text{mean} = 500)$. We see that both methods provide almost perfect estimates for the mean of $M(t)$, and fairly good estimates for $k_{M(t)}$, the k parameter of the negative binomial distribution, where $k_M = (\mathrm{E}(M))^2/(\mathrm{Var}(M) - \mathrm{E}(M))$. The parameter governing the nonlinearity in the model is small ($\alpha_m = 0.00002$), and we see that the figures using the normal approximation in Grenfell, Dietz, and Roberts (1995a) are fairly accurate. It is noticeable, however, that the negative binomial approximation provides better estimates for the k parameter than the normal approximation.

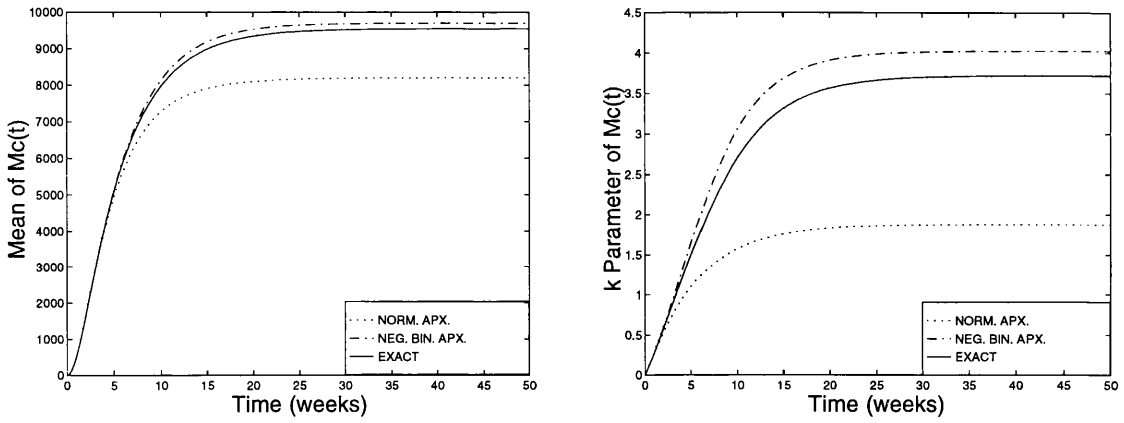

Figure 3.10: Mean and k Parameter of $M_c(t)$ with $\phi = 0.7, m_c = 5000, \alpha_m = 2 \times 10^{-5}$

Increasing the extent to which the parasites enter the host in clumps, and hence the dependence between parasites in the host, reduces the accuracy of the approximations. This can be seen from Figure 3.10, in which the average input rate of parasites and all other parameters are as in Figure 3.9, except that the mean clump size is increased so that $C \sim \text{Neg Bin}(k = 1, \text{mean} = 5000), \phi = 0.7$. Both approximations perform less well, but the negative binomial approximation is shown to be more robust to these changes, both for estimates of the mean and the k parameter of $M(t)$. Notice that the exact mean decreases with increasing C as a result of the parasite induced mortality interacting with the more aggregated input. This is the phenomenon seen in Section 3.3.2.

As α_m is increased, the approximations also become less accurate. This corresponds to the nonlinearity in the model increasing, and so is perhaps not a suprising result. For example, in Figure 3.11 (page 85) α_m is increased thirty-fold from its value in Figure 3.9, so that $\alpha_m = 0.0006$ and we see that the normal approximation provides negative means, the problem we found in normal approximations to the density dependent process in Section 2.4. Higher values of α_m give still worse normal approximations for the mean, and in Figure 3.11 the variance of $M(t)$ also

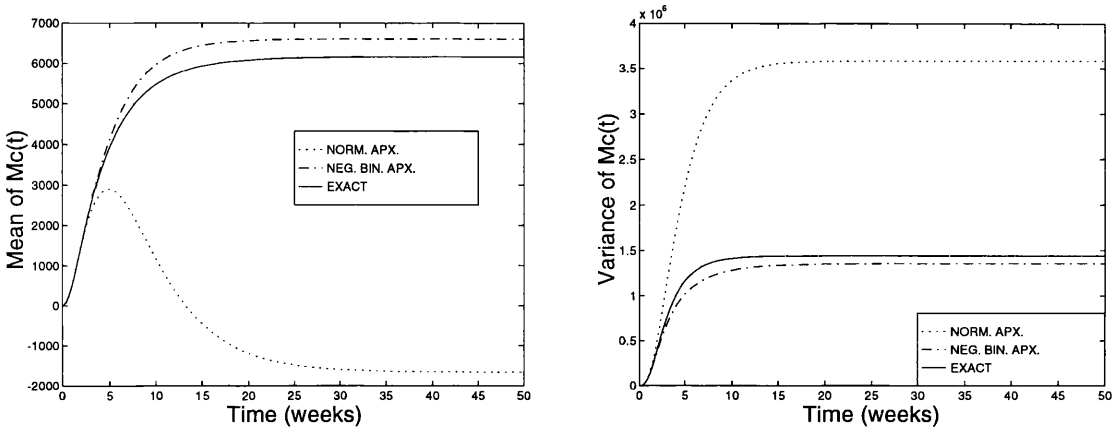

Figure 3.11: Mean and Variance of $M_c(t)$ with $\phi = 7, m_c = 500, \alpha_m = 0.0006$

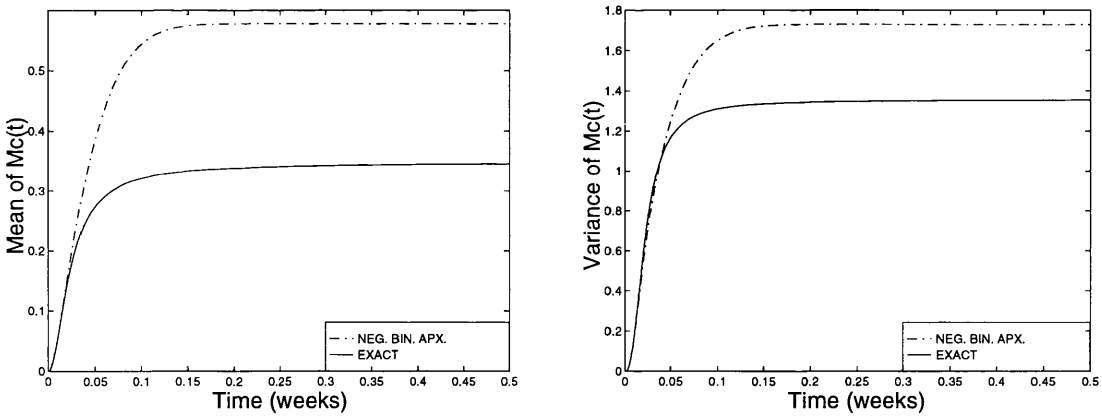

Figure 3.12: Mean and Variance of $M_c(t)$ with $\phi = 7, m_c = 500, \alpha_m = 20$

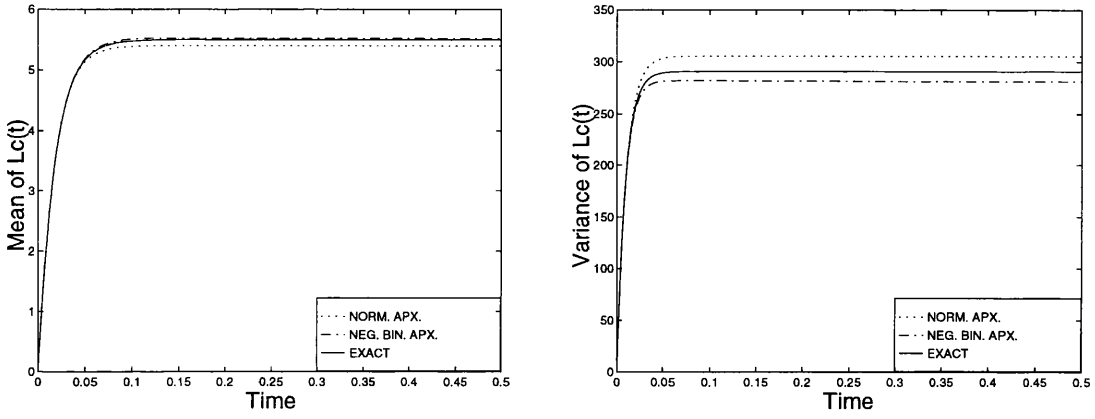

Figure 3.13: Mean and Variance of $L_c(t)$

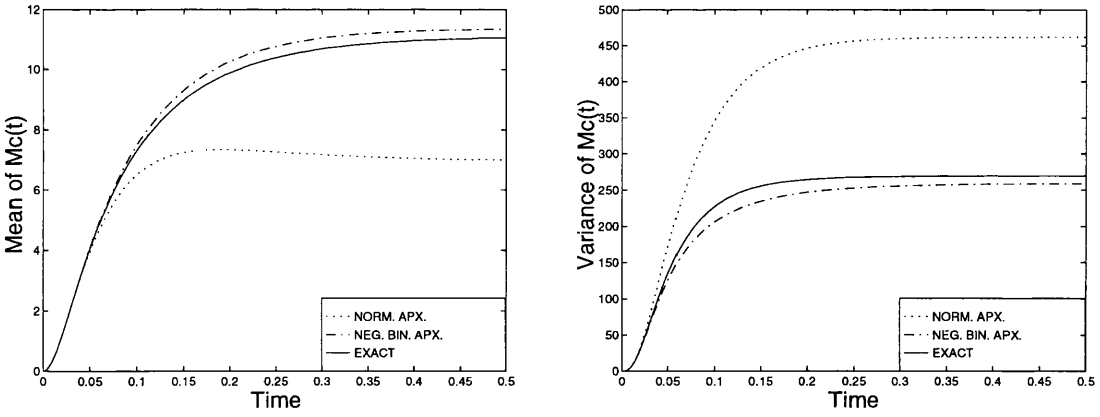

Figure 3.14: Mean and Variance of $M_c(t)$

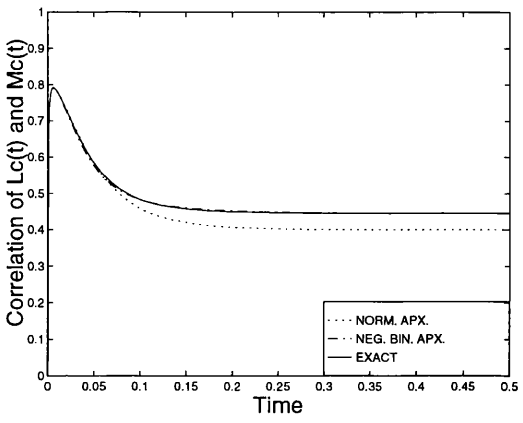

Figure 3.15: Correlation of $L_c(t)$ and $M_c(t)$

gives bad predictions. The negative binomial approximations still performs well at these higher values of α_m, but it is noticeable that they are not as accurate as in Figure 3.9. When α_m is increased still further to the implausible value of $\alpha_m = 20$, the negative binomial approximation still provides estimates in the right area, and does not appear to suffer the problem of giving negative means that the normal approximation suffers (see Figure 3.12, page 85). Notice that at such high values of α_m the moments are conditional on events with very small probabilities (host survival) and so are not especially useful for interpretation purposes. They do, however, indicate the success of the negative binomial approximation in models with high levels of nonlinearity.

Figures 3.13 - 3.15 on pages 86 - 87 use parameters $\mu_l = 20, \gamma_l = 30, \mu_m = 10, \phi = 6, \alpha_l = 0, \alpha_m = 0.2, C \sim \text{Neg Bin}(k = 1, \text{mean} = 50)$, chosen only to illustrate the approximation techniques for all the moments at lower parasite levels. They show that the approximations will capture the moments of $L(t)$ with much more success than those of $M(t)$. This can be thought of as a consequence of the approximating moment equations for $M(t)$ involving more estimated moments, as the equations involve moments of $L(t)$ as well as those of $M(t)$. Thus any

inaccuracies in the moments of $L(t)$ will carry over into the estimates of those of $M(t)$. As a consequence of this we would expect approximations of moments of $N(t)$ to be still less accurate.

Again Figures 3.13 - 3.15 show that the negative binomial approximation provides significantly better results than the normal approximation. However, the normal approximations do not have the restriction of always providing positive correlations, and so there is still a need to find a more flexible version of the multivariate negative binomial distribution. The normal approximations are investigated further in sections 4.2 and 4.3 with respect to a more complicated nonlinearity aimed at modelling the immune response of the host.

3.8 Random Environmental Parameters

In this section we explain how to adapt the moment closure equations to incorporate the situation in which a parameter of the system is considered as being drawn randomly from a population of parameters. This method can be applied to a general discrete valued stochastic population process of the type discussed in Section 2.1, but should not be confused with populations evolving in a random environment in which the parameters vary stochastically over time. If our "random" parameters are varying over time, each parameter in the population of parameters is varying *deterministically* over time. Effectively we are considering the moment properties and equations described above and in Section 2.2 as being conditional on the parameter concerned. We have already seen an example of this in Section 3.3.4. Processes of this type are important in parasite dynamics because of the inherent differences between hosts, and the potential effects this has on the distribution of parasites amongst the host population.

Specifically, suppose we have a system conditional on a vector of parameters, $\boldsymbol{\theta}$. Consider the moments we are interested in expressed in a vector $\boldsymbol{X}(t)$, with the higher order moments that we do not want as the vector $\boldsymbol{Y}(t)$. The random

parameters are given by $\boldsymbol{\theta}$, and the fixed parameters by $\boldsymbol{\eta}$. Write $\boldsymbol{X}_c(t;\boldsymbol{\theta})$ and $\boldsymbol{Y}_c(t;\boldsymbol{\theta})$ for the moments *conditional on* $\boldsymbol{\theta}$. Suppose we have the moment ordinary differential equations

$$\dot{\boldsymbol{X}}_c(t) = \tilde{g}(\boldsymbol{X}_c(t), \boldsymbol{Y}_c(t); \boldsymbol{\theta}, \boldsymbol{\eta}). \tag{3.23}$$

Assuming some relationship between the *conditional* moments, i.e. $\boldsymbol{Y}_c(t,\boldsymbol{\theta}) = f(\boldsymbol{X}_c(t,\boldsymbol{\theta}))$, we can write these as

$$\dot{\boldsymbol{X}}_c(t) = g(\boldsymbol{X}_c(t); \boldsymbol{\theta}, \boldsymbol{\eta}). \tag{3.24}$$

The marginal probability distribution of $\boldsymbol{\theta}$ will be specified in the model and is given as $f_{\boldsymbol{\theta}}(\boldsymbol{u})$ say, for the range $\boldsymbol{u} \in \mathcal{E}$. The unconditional moments, $\boldsymbol{X}$, are then simply

$$\boldsymbol{X}(t) = \int_{\mathcal{E}} f_{\boldsymbol{\theta}}(\boldsymbol{u})\boldsymbol{X}_c(t;\boldsymbol{u}))d\boldsymbol{u} \tag{3.25}$$

where $\boldsymbol{X}_c(t;\boldsymbol{u})$ is the moments conditional on $\boldsymbol{\theta} = \boldsymbol{u}$. If (3.24) can be solved explicitly then the problem reduces to one of numerically solving the integral of (3.25), otherwise (3.24) and (3.25) need to be solved numerically in unison. This enables us to calculate unconditional moments.

It may be more reasonable to assume an approximating relationship between *unconditional* moments, so that we have some relationship $\boldsymbol{Y}(t) = A(\boldsymbol{X}(t))$. This causes some complications. The equations that require solving are then (3.23) with

$$A\left(\int_{\mathcal{E}} f_{\boldsymbol{\theta}}(\boldsymbol{u})\boldsymbol{X}_c(t,\boldsymbol{u})d\boldsymbol{u}\right) = A(\boldsymbol{X}(t)) \quad = \quad \boldsymbol{Y}(t) = \int_{\mathcal{E}} f_{\boldsymbol{\theta}}(\boldsymbol{u})\boldsymbol{Y}_c(t,\boldsymbol{u})d\boldsymbol{u}. \tag{3.26}$$

If (3.23) can be expressed in the form

$$\boldsymbol{Y}_c = \varpi(\dot{\boldsymbol{X}}_c; \boldsymbol{X}_c; \boldsymbol{\theta}, \boldsymbol{\eta})$$

then we have

$$A(\boldsymbol{X}) = \int_{\mathcal{E}} f_{\boldsymbol{\theta}}(\boldsymbol{\theta})\varpi(\dot{\boldsymbol{X}}_c; \boldsymbol{X}_c; \boldsymbol{\theta}, \boldsymbol{\eta})d\boldsymbol{\theta}.$$

If further we can write

$$\varpi(\dot{\boldsymbol{X}}_c; \boldsymbol{X}_c; \boldsymbol{\theta}, \boldsymbol{\eta}) = \varpi_1(\boldsymbol{\theta}, \xi) + \varpi_2(\dot{\boldsymbol{X}}_c; \boldsymbol{X}_c; \boldsymbol{\eta})$$

then this yields

$$A(\boldsymbol{X}) = \mathrm{E}(\varpi_1(\boldsymbol{\theta})) + \varpi_2(\dot{\boldsymbol{X}}; \boldsymbol{X}; \boldsymbol{\eta})$$

which may be solved.

The first of these two requirements, i.e. writing (3.23) in the form $\boldsymbol{Y}_c = \varpi(\dot{\boldsymbol{X}}_c, \boldsymbol{X}, \boldsymbol{\theta}, \boldsymbol{\eta})$, will be possible if $\boldsymbol{Y}_c$ may be separated from $\dot{\boldsymbol{X}}_c$ and $\boldsymbol{X}_c$ in (3.23). This will certainly be possible if the transition probabilities are simply nonlinear multinomials in the variables, which is often likely to be the case. However the second requirement of separating this further into

$$\boldsymbol{Y} = \varpi_1(\dot{\boldsymbol{X}}_c, \boldsymbol{X}, \boldsymbol{\eta}) + \varpi_2(\boldsymbol{\theta}, \boldsymbol{\eta})$$

is less likely to be possible as it requires the environmental parameters to have no interaction with any of the variables in the transition probabilities. When thinking in terms of parasite-host dynamics this means that the "random" parameters are external environmental parameters, rather than "internal parameters" directly affecting individual parasites such as parasite death rates. (For example, the former applied when we varyed the infection rate, ϕ, in Section 3.3.4).

Chan and Isham (1998) have used these types of random environmental parameters in analysis of a schistosomiasis model, and solved the moment equations by assuming a moment relationship for the joint distribution between the variables and the parameters. The method outlined in this section would enable more natural assumptions that only concern relationships between the moments of the variables to be made in this, and other similar cases. In Section 4.5 we discuss a further application in which this method would be useful.

Chapter 4

Acquired Immunity

4.1 Introduction

The immune response to a macroparasite is highly complicated and knowledge of its specific dynamics, particularly in wild host populations, is not always clear. However, its importance in affecting a parasite-host relationship at the population level is now well established (Anderson and May, 1991). A host's immune response to a particular parasite, and in turn the parasites's defences against the response, will have co-evolved throughout the host-parasite relationship as both host and parasite adapt to selection pressures. The particular mechanisms involved for each relationship will vary enormously and so any model trying to capture the general aspects of the immune system is always going to suffer from a lack of biological detail and often accuracy. However, in this chapter we restrict our attention to a small number of aspects of modelling the acquired immune system, and discuss the possible effects of various general immune mechanisms on properties of the parasite population, such as parasite aggregation, age intensity curves and parasite prevalence. The approach is aimed at gaining insight into how host immune systems can affect parasite distributions at the host population level. We discuss and analyse further the immunological aspects of the model introduced by Grenfell,

Dietz, and Roberts (1995a), and propose and investigate two more models aimed at capturing particular aspects of immune mechanisms that operate in macroparasitic infections. For a brief introduction to the biology of the acquired immune response to macroparasites we refer back to Section 1.2.

Due to the difficulties of specifying the dynamics of the complex interactions between helper cells, regulation cells, antigens and other cells involved in the immune mechanism, we take the approach of considering only one variable to represent a host's specific immune capability against a specific parasite. This enables us to study the effect of general immune processes without becoming involved in analysing systems with large numbers of variables that are often difficult to gain insight from. However, see Austin and Anderson (1996) for more detailed deterministic modelling of macroparasite immune systems, and Burroughs and Rand (1998), Schweitzer, Swinton, and Anderson (1993) and Anderson and May (1991), and references contained therein, for models for microparasites.

The main assumption that is commonly used in modelling the acquired immune system (almost implicit in its name) is that host acquired immunity is related to the individual host's past experience of the infection. This could be in a number of forms, such as total time burden of mature worms, exposure to infection, larval challenge or total offspring seen. We study two mechanisms, exposure to infection in sections 4.3 and 4.4, and exposure to parasite burden in Section 4.2.

The immune response can have an effect on parasite survival, establishment or fecundity (ability to produce offspring). In some situations it can also have pathological effects on the host, but we do not investigate these. The two effects we specifically consider are on the parasite death rate (sections 4.2 and 4.3) and establishment (Section 4.4).

We discuss the use of the normal approximations in the study of immune responses and parasite dynamics, as proposed in Grenfell, Dietz, and Roberts (1995a), and assess its performance in that model (Section 4.2) and a further model proposed here (Section 4.3). The discussions are also relevant for other nonlinear

effects that may be incorporated into parasite dynamic models. Heterogeneities in host immune responses are often given as explanations for aggregated parasite levels (Anderson and May, 1991), and the incorporation of this into the models is briefly discussed in Section 4.5.

4.2 Immune Response Stimulated by Larval Burden

Grenfell, Dietz, and Roberts (1995a) introduced a stochastic model for studying the impact of immunity on within host macroparasite dynamics, focusing particularly on directly transmitted gastrointestinal nematode parasites of ungulates. Whereas the earlier stochastic models of Tallis and Leyton (1966) and Tallis and Leyton (1969) included 'antigenic information' in their models, this had no feedback to the parasite population. The model of Grenfell, Dietz, and Roberts (1995a) has direct interaction between an acquired immune variable and parasite level variables, as well as including parasite induced host mortality, as discussed in Chapter 3. We focus only on the immunological aspect of the model in this section.

As discussed in Section 3.1, the underlying assumption of the Grenfell, Dietz, and Roberts (1995a) model is that the age distribution of parasites within hosts is in equilibrium with respect to time, so that input of parasites into the host is independent of any parasite levels. In this section we describe the other main features of the model and add some further discussion, in particular assessing the suitability of the normal approximation used in the paper.

The authors state that

> The general consensus is that host immunity in ungulate gut nematode interactions accumulates with the accretion of new infections, (Grenfell, Smith, and Anderson, 1987a; Grenfell, Smith, and Anderson, 1987b). In principle, this could be modelled in terms of a specific point in the

establishment of larvae (for example, the entry of L3 larva) or the average larval burden. For mathematical simplicity we use average larval density.

In fact they used actual larva numbers, not averages, so that the transitions of the model, ignoring parasite induced host mortality ($\alpha_l = \alpha_m = 0$), were from $L(t), M(t), I(t)$ to

$L+c$	M	I	at rate	ϕh_c	for $c = 0, 1, ...$	(parasite ingestion)
$L-1$	$M+1$	I	at rate	$\gamma_l L$		(larval maturation)
L	M	$I+1$	at rate	νL		(immunity increase)
$L-1$	M	I	at rate	$(\mu_l + \beta I)L$		(larval death)
L	$M-1$	I	at rate	$\mu_m M$		(mature worm death)
L	M	$I-1$	at rate	$\mu_i I$		(immunity decrease)

with the experience of infection, $I(t)$, acting to increase the larval death rate. We consider the other situation described above (in which the experience of infection (acquired immunity) increases with the establishment of larvae) in Section 4.3. We have used the argument t instead of a, but this should still be considered as host age, or time from exposure to an infected area. During this chapter we shall refer to this Grenfell, Dietz, and Roberts (1995a) model as model 1. A system of nine ordinary differential equations was written down by Grenfell, Dietz, and Roberts (1995a) for moments up to order two, and normal approximations were used to obtain their numerical solution. Note that the term simulation is used in their paper to mean numerical solution of these normal approximations, rather than Monte Carlo simulations of the actual stochastic process.

The approximate solutions are able to generate the peak and following decline in the parasite load versus age graphs that are often observed in the field, as in Anderson and May (1985). The paper also considered between-host heterogeneities in immune ability, and their effect on parasite aggregation, which we discuss briefly

in Section 4.5.

The only other point made in (Grenfell, Dietz, and Roberts, 1995a) concerned the impact of homogeneous host immunity and was that, for high levels of immunity (β) the correlation between M and I becomes negative. This is due to the feedback effect of I increasing the death rate of larval parasites and so decreasing the rate of formation of mature parasites.

In a follow up paper, (Grenfell, Wilson, Isham, Boyd, and Dietz, 1995b) it is stated that

> ... we consider (moment closure) a useful approach compared to studies based on stochastic simulation alone because analytical results can be derived from special cases of the Moment Closure Equation (MCE) model.

Often the special cases they refer to that provide easily workable analytical results seem to be the linear simplifications, as is the case with the results given in Grenfell, Dietz, and Roberts (1995a) and Grenfell, Wilson, Isham, Boyd, and Dietz (1995b). In these cases, of course, neither moment closure or simulations are needed. However, results are much quicker to evaluate than through Monte Carlo simulation, and are easier to fit to data. Additionally, some insight into the mechanisms modelled may be possible using the moment closure equations even for the nonlinear system.

4.2.1 Use of the Normal Approximations

The multivariate negative binomial approximations for the moments, described in Section 3.6, are not considered in this chapter due to the possibility of obtaining negative correlations in this system. It is possible that they still provide sensible approximations in some areas of the parameter space, but we do not investigate this here.

The moment closure equations with normal approximations used in Grenfell, Dietz, and Roberts (1995a), and analysed further in this section, are given in Appendix B. Unfortunately, even using normal approximations for this model and considering only the steady state solutions, we obtain a quartic in the value of $\mathrm{E}(LI)$ at equilibrium, with most other steady state moments in terms of this, and transient solutions are even harder to analyse. It is difficult to gain insight from these equations. However, in the context of the process and approximations under discussion, it is interesting to consider the following model, with transitions from $L(t)$ to

$$\begin{array}{llll} L+c & \text{at rate} & \phi h_c & \text{for } c = 0, 1, ... \\ L-1 & \text{at rate} & DL & \end{array}$$

where D is an unspecified, positively valued stochastic process that is not necessarily independent of L. For example, in the case of simple linear death D would be just μ_l, and in the density dependent process described in Chapter 2, D would be $\mu_l L$. In the immunity model above D is $\mu_l + \beta I$. We consider h_c to be the probability that the clump random variable C takes the value c, as in previous models.

The first two moments of $L(t)$, with $L(0) = 0$ with probability 1, satisfy

$$\begin{aligned} \frac{d\mathrm{E}(L(t))}{dt} &= \lambda - \mathrm{E}(D(t)L(t)) \\ \frac{d\mathrm{E}(L(t)^2)}{dt} &= d + 2\lambda\mathrm{E}(L(t)) + \mathrm{E}(D(t)L(t)) - 2\mathrm{E}(D(t)L(t)^2) \end{aligned}$$

where $\lambda = \phi\mathrm{E}(C) = \phi\sum_{c=0}^{\infty} h_c c$, $d = \phi\mathrm{E}(C^2) = \phi\sum_{c=0}^{\infty} h_c c^2$ and $\mathrm{E}(L(0)) = \mathrm{E}(L(0)^2) = 0$. Assuming a steady state solution exists, we have at equilibrium

$$\begin{aligned} \tilde{\mathrm{E}}(LD) &= \lambda \\ \tilde{\mathrm{E}}(DL^2) &= \frac{1}{2}(\lambda + d) + \lambda\tilde{\mathrm{E}}(L) \end{aligned}$$

where $\tilde{\mathrm{E}}(\cdot)$ indicates the equilibrium expectation. If the normal approximations are introduced to this system, by assuming higher order moments of D and L follow

the relationships of those of a bivariate normal distribution, we are assuming

$$\mathrm{E}(DL^2) = 2\mathrm{E}(L)\mathrm{E}(DL) - 2\mathrm{E}(D)(\mathrm{E}(L)^2) + \mathrm{E}(D)\mathrm{E}(L^2)$$

and hence obtain at equilibrium

$$\tilde{\mathrm{E}}_a(L^2)\tilde{\mathrm{E}}_a(D) = 2(\tilde{\mathrm{E}}_a(L))^2\tilde{\mathrm{E}}_a(D) - \lambda\tilde{\mathrm{E}}_a(L) + \frac{1}{2}(\lambda + d)$$

where the subscript a indicates a value under the normal approximation. Notice that this moment relationship assumes the appropriateness of moment approximations from a multivariate normal for L and D, and is equivalent to the normal approximation used by Grenfell, Dietz, and Roberts (1995a). Writing r for the covariance between L and D so that $\tilde{r}_a = \tilde{\mathrm{E}}_a(DL) - \tilde{\mathrm{E}}_a(D)\tilde{\mathrm{E}}_a(L)$, we obtain $\tilde{\mathrm{E}}_a(D) = (\lambda - \tilde{r}_a)/\tilde{\mathrm{E}}_a(L)$ and hence

$$\tilde{\mathrm{I}}_a(L) := \tilde{\mathrm{E}}_a(L^2)/\tilde{\mathrm{E}}_a(L) - \tilde{\mathrm{E}}_a(L) = \frac{\tilde{r}_a}{\tilde{r}_a - \lambda}\tilde{\mathrm{E}}_a(L) + \frac{d+\lambda}{2(\lambda - \tilde{r}_a)}$$

for the approximating index of dispersion of L at equilibrium. Under the linear death model of Section 3.3.5 (i.e. $\beta = 0$ in Grenfell, Dietz, and Roberts (1995a) or $D = \mu_l$ here) we obtain

$$\begin{aligned} \tilde{\mathrm{I}}_a(L) = \tilde{\mathrm{I}}(L) &= \frac{d+\lambda}{2\lambda} \\ &= \frac{1}{2}(\mathrm{I}(C) + \mathrm{E}(C) + 1) := \tilde{\mathrm{I}}_{\mathrm{O}}, \end{aligned} \tag{4.1}$$

as previously given in Section 3.3.5 (or by putting $D = \mu_l$, hence $\tilde{r} = 0$), where $\mathrm{I}(C)$ and $\mathrm{E}(C)$ are respectively the index of dispersion and mean of the clump distribution, C. To evaluate the effect of the nonlinear death rate of D on the index of dispersion, we consider whether $\tilde{\mathrm{I}}_a(L)$ increases or decreases from this null value, $\tilde{\mathrm{I}}_{\mathrm{O}}$.

By considering $\tilde{\mathrm{I}}_a(L) - \tilde{\mathrm{I}}_{\mathrm{O}}$ we find that, at equilibrium, the approximating process has a decreased index of dispersion if and only if

$$\frac{\tilde{r}_a}{\tilde{r}_a - \lambda}(\tilde{\mathrm{E}}_a(L) - \tilde{\mathrm{I}}_{\mathrm{O}}) < 0$$

with the inequality reversed for an increase, and set to equality for no change. Using the fact that $\tilde{\mathrm{E}}_a(LD) = \lambda$ so that we can assume $\tilde{r}_a \leq \lambda$ (provided all approximating processes have positive means - something that is not guaranteed as we saw in Section 2.4, but clearly the approximation would be immediately thrown out if this was not the case), $\tilde{\mathrm{I}}_a(L)$ is increased or decreased from $\tilde{\mathrm{I}}_{\mathrm{O}}$ according to the following scenarios;

(1) When $\tilde{\mathrm{E}}_a(L) > \tilde{\mathrm{I}}_{\mathrm{O}}$, we have $\tilde{\mathrm{I}}_a(L)$ increased when $\tilde{r}_a < 0$
decreased when $\tilde{r}_a > 0$

(2) When $\tilde{\mathrm{E}}_a(L) < \tilde{\mathrm{I}}_{\mathrm{O}}$, we have $\tilde{\mathrm{I}}_a(L)$ decreased when $\tilde{r}_a < 0$
increased when $\tilde{r}_a > 0$.

Result (1) above, given by the approximations, is perhaps what we might expect for the exact moments. When there is a negative correlation between L and D, realisations with higher levels of L have lower per capita death rates due to lower levels of D, and hence still higher levels of larvae are encouraged. This leads to an increase in the variance of the process relative to the mean when correlations are negative. The reverse effect is expected with positive correlation, so that the overall dispersion is decreased in this case.

Result (2), however, is perhaps a little more suprising as it seems to indicate the opposite effect to the situation described above. If we expect that the index of dispersion will decrease when the nonlinearity is added and the true stochastic correlation is positive, then result (2) indicates that the normal approximation either provides misleading information about the sign of the correlation (through $\tilde{r}_a$), or about the qualitative change in $\tilde{\mathrm{I}}(L)$. Either way, as result (2) occurs when $\tilde{\mathrm{E}}_a(L) < \tilde{\mathrm{I}}_{\mathrm{O}}$, this may give evidence of the approximation breaking down at low levels of $\tilde{\mathrm{E}}_a(L)$ and high levels of intrinsic (linear) dispersion. We saw an example of this in Section 2.4 (the density dependent immigration death process in which $D = \mu_l L$). In that model, for the parameters $\lambda = 1.7, \mu = 1$, $\tilde{\mathrm{E}}_a(L) < \tilde{\mathrm{I}}_{\mathrm{O}}$ was satisfied, and so the approximations predicted an increase in the index of dispersion,

whilst the simulations showed a decrease.

It appears that some *qualitative* results break down in the normal approximations for immigration death models when $\tilde{\mathrm{E}}_a(L) < \tilde{\mathrm{I}}_0$. The kind of models under discussion here (density dependent and immunity models) will have $\tilde{\mathrm{E}}(L)$ decreasing as we move from the linear to nonlinear case. Therefore if the linear equilibrium mean $\tilde{\mathrm{E}}(L)_0$ satisfies $\tilde{\mathrm{E}}(L)_0 < \tilde{\mathrm{I}}_0$, we are likely to have $\tilde{\mathrm{E}}(L)_a < \tilde{\mathrm{I}}_0$. In terms of the Grenfell, Dietz, and Roberts (1995a) model parameters, $\tilde{\mathrm{E}}(L)_0 < \tilde{\mathrm{I}}_0$ requires

$$\frac{1}{k_C} + \frac{2}{\mathrm{E}(C)} \quad > \quad \frac{2\phi}{\mu_l + \gamma_l} - 1 \tag{4.2}$$

if C follows a negative binomial distribution with $k_C := (\mathrm{E}(C))^2 / (\mathrm{var}(C) - \mathrm{E}(C))$ as the k parameter.

Whilst this is by no means a rigorous result, it does give a rough indication of the kind of area of the parameter space that may give unreliable estimates for $\tilde{\mathrm{I}}_a(L)$. For example, it shows that in general, the smaller k_C is, i.e. the higher the aggregation of the input distribution, the less reliable the normal approximation. This corresponds to the intuitevely appealing idea that the normal approximation is more likely to break down for highly aggregated processes, as there is more dependence between the parasites. By this we mean the indicator functions for whether or not each particle in the host is alive have high correlations (see Ball and Donnelly (1988) for further discussions on this topic). Similarly, higher ϕ relative to $\mu_l + \gamma_l$ may make the approximations more reliable, a result similar to that found in Section 2.4. This means that there are likely to be both more parasites present and also a lower proportion of those present will have been ingested in the same clump.

Grenfell, Dietz, and Roberts (1995a) report an estimated field value of $k_C = 1$, obtained from examining infected pasture. This gives $\mathrm{I}(C) = 1 + \mathrm{E}(C)$, and hence we have $\tilde{\mathrm{E}}(L)_0 < \tilde{\mathrm{I}}_0$, indicating that we should mistrust the approximations if

$$\frac{\phi}{\mu_l + \gamma_l} < 1 + \frac{1}{\mathrm{E}(C)},$$

when C takes a negative binomial distribution. However, this condition does not hold for the parameters assumed in Grenfell, Dietz, and Roberts (1995a). For the parameters used in their paper the larval numbers are high because the size of each ingestion is large ($\mathrm{E}(C) = 500$). This means that stochastic simulations are extremely lengthy to run and very variable between simulations, so that many runs are required to obtain accurate equilibrium moment estimates.

Instead, we consider some properties of the process at equilibrium under different parameter assumptions in Tables 4.1, 4.2 and 4.3, for which simulations are less time consuming to run. This provides the opportunity to assess some qualitative aspects of the model and how the approximations perform. In the simulation results given throughout this chapter, twice the estimated standard error is given in brackets after each simulation estimate, as in Chapter 2. These standard erors are calculated from the results given in Bickel and Doksum (1977, Chapter 4) and in Stuart and Ord (1994, Chapter 10). The time at which the equilibrium results should be taken was decided by the ad hoc method of running each simulation long enough so that the property of interest had settled down to a roughly constant value, and then taking the result at double this time. This method is admittedly rough, but as the processes studied in this chapter are all versions of immigration-death processes, it is likely that equilibrium is obtained in a fairly straightforward manner i.e. without the process getting trapped in a quasi-equilibrium before reaching the true equilibrium. The parameters not stated in Tables 4.1, 4.2 and 4.3 are $\mu_l + \gamma_l = 5, \mu_i = 4, \nu = 2$, and C follows a negative binomial distribution with $k_C = 1$ and mean as given in the tables. For notational convenience we write m_c for the expectation of C.

The parameter values chosen and the results given in the tables illustrate the point made earlier concerning the change in equilibrium index of dispersion from the linear to the nonlinear model. In all three simulated processes, the nonlinearity of the immune mechanism causes a drop in $\tilde{\mathrm{I}}(L)$ from the linear model. However, all three (normal) approximating correlations are positive, and so according to the

Table 4.1: Immunity Model 1 Equilibrium Results with $\phi = 5, m_c = 5$

	$\beta = 0$	$\beta = 1$		
		Simulation (2 s.e.)	Normal Apx	Deterministic
$\tilde{\mathrm{E}}(L)$	5.00	3.35 (0.04)	3.31	3.66
$\tilde{\mathrm{I}}(L)$	6.00	5.36 (0.15)	6.36	n/a
$\tilde{k}_L$	1	0.72 (0.07)	0.62	n/a
$\tilde{\mathrm{cor}}(L, I)$	0.50	0.31 (0.01)	0.37	n/a

Table 4.2: Immunity Model 1 Equilibrium Results with $\phi = 20, m_c = 5$

	$\beta = 0$	$\beta = 1$		
		Simulation (2 s.e.)	Normal Apx	Deterministic
$\tilde{\mathrm{E}}(L)$	20.00	9.80 (0.08)	9.76	10.00
$\tilde{\mathrm{I}}(L)$	6.00	5.55 (0.12)	5.86	n/a
$\tilde{k}_L$	4	2.15 (0.24)	2.00	n/a
$\tilde{\mathrm{cor}}(L, I)$	0.50	0.17 (0.00)	0.18	n/a

above result the normal approximation will give a decrease (increase) in the index of dispersion when immunity is added to the model if $\tilde{\mathrm{E}}_a(L) > (<)\tilde{\mathrm{I}}_0$. The results from Tables 4.1 - 4.3 do indeed follow this rule, and hence, as can be seen from the simulations, the normal approximations in Tables 4.1 and 4.3 provide misleading qualitative results, by giving increases in the index of dispersion when immunity is added to the model. In these cases the ratio $\phi/(\mu_l + \gamma_l)$ is relatively low (compare with the result (4.2)).

When considering only the mean of the process in Table 4.1 (in which $\phi = 5, m_c = 5$) we find the equilibrium mean is approximated well, whereas in Table 4.3 (in which $\phi = 5, m_c = 20$) the approximations do not do so well, despite the

Table 4.3: Immunity Model 1 Equilibrium Results with $\phi = 5, m_c = 20$

	$\beta = 0$	$\beta = 1$		
		Simulation (2 s.e.)	Normal Apx	Deterministic
$\tilde{\mathrm{E}}(L)$	20.00	8.98 (0.08)	8.48	10.00
$\tilde{\mathrm{I}}(L)$	21.00	19.59 (0.64)	24.47	n/a
$\tilde{k}_L$	1	0.48 (0.06)	0.36	n/a
$\tilde{\mathrm{cor}}(L, I)$	0.61	0.32 (0.01)	0.39	n/a

process having a higher equilibrium mean. This is because with $\phi = 5, \mathrm{E}(C) = 20$ (Table 4.3) a higher proportion of parasites enter the host in large clumps. Overall, the normal approximations do well at capturing the equilibrium means in Tables 4.1 - 4.3 despite their small size, and improve significantly on the deterministic results. However, as we show below, the approximations do not estimate the means successfully over the whole parameter space.

Consider now the transient behaviour of the model. Figures 4a and 5a in Grenfell, Dietz, and Roberts (1995a) show that the normal approximation of the mean of $L(t)$ rises and then gradually declines to an equilibrium. However, a different behaviour is possible in other parts of the parameter space. When the immunity (and hence nonlinearity) has a large enough effect (β and ν large enough) and an aggregated C dominates the parasite input sufficiently, the normal approximation mean can decline after its peak before rising again to its equilbrium (see Figure 4.1 on page 103). Parameter values used in Figures 4.1 and 4.2 are $\beta = 2, \mu_l + \gamma_l = 5, \mu_i = 4, \nu = 2$ and $\phi = 5$, and C follows a negative binomial distribution with $k_C = 1$. The simulated mean value (after 1.2×10^5 runs) shows that this predicted phenomenon is misleading, and in this case the deterministic result provides a far better qualitative approximation. As is often the case in population models, the deterministic approximation overestimates the true stochastic

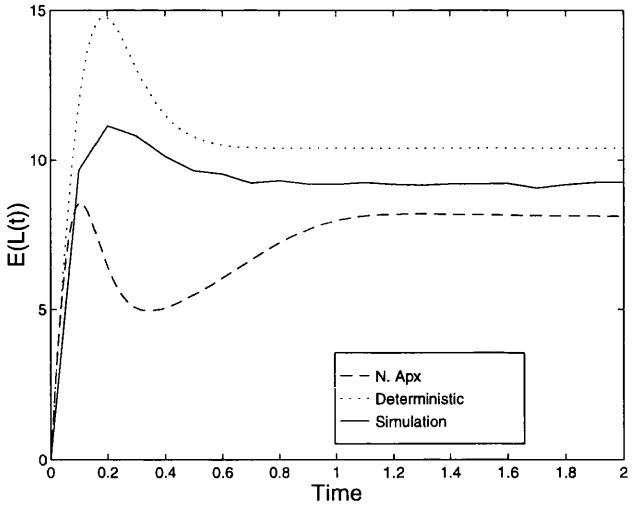

Figure 4.1: Mean of $L(t)$ for Immunity Model 1 with $m_c = 32$

mean, but unlike the normal approximation the graph does provide the right shape in this case. A small increase in the mean of C from $\mathrm{E}(C) = 32$ to $\mathrm{E}(C) = 35$ (increasing the dependence between parasites in the host) produces results for the normal approximation that would obviously be discarded (Figure 4.2) due to the negative means.

To summarise, we see that the normal approximation is most effective when the mean of the input process $\lambda = \phi m_c$ is dominated by ϕ so that there is little dependence between the parasites in the host. It is perhaps worth a reminder that we are not considering the possible normality of the distribution of L, only the suitability of the moment relationships derived from the normal distribution.

4.2.2 Further Model Analysis

In assessing the effect of the immune mechanism on the aggregation of L we need to compare nonlinear cases with linear versions that have equal means. For example, looking at Table 4.1 again we see that when comparing the *simulated* cases of $\beta = 0$ and $\beta = 1$, with all other parameters kept constant, both $\tilde{\mathrm{I}}(L)$ and $\tilde{k}_L$ are lower for the nonlinear model, providing apparently conflicting information about the effect

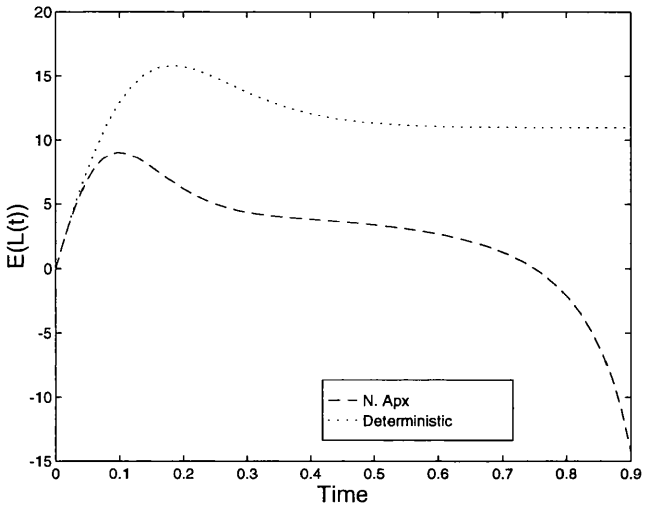

Figure 4.2: Mean of $L(t)$ for Immunity Model 1 with $m_c = 35$

of the immunity on the aggregation of larvae. However, in general both the index of dispersion and the k parameter depend on the mean, which itself drops when immunity is added, so this comparison is not especially revealing on this issue.

We choose parameters for a linear model that provide the same value of $\mathrm{E}(L)$ at equilibrium as the simulated nonlinear models in Tables 4.1 - 4.3. There is more than one way of choosing these parameters. We shall assume that the only variation is in the larval death rate (so ϕ and C are fixed), so that we are comparing two processes with equal equilibrium means, one of which has only linear larval death whilst the other additionally has larval death from immunity. For the linear model, $\mathrm{I}(L)$ at equilibrium is only dependent on C, and so will not depend on $\mu_l + \gamma_l$ (see Section 3.3.5). Thus Tables 4.1 - 4.3 are sufficient to show that $\tilde{\mathrm{I}}(L)$ is reduced when immunity is added, for the parameters shown. Table 4.4 shows the results for k_L at equilibrium for the linear process with $\mu_l + \gamma_l$ adjusted so that the equilibrium means are equal to those of the simulated nonlinear process in Tables 4.1 - 4.3. These simulated values are used for the $\beta = 1$ case. We see that $\tilde{k}_L$ is in fact increased when the immune mechanism is added. This, and the result concerning $\tilde{\mathrm{I}}(L)$, correspond to the intuitive idea that a homogeneous immune mechanism will

tend to reduce aggregation of parasites.

Table 4.4: Immunity Model 1 Equilibrium Results for k_L, with $\mu_l + \gamma_l$ adjusted

	$\phi = 5, m_c = 5$		$\phi = 20, m_c = 5$		$\phi = 5, m_c = 20$	
	$\beta = 0$	$\beta = 1$	$\beta = 0$	$\beta = 1$	$\beta = 0$	$\beta = 1$
$\tilde{\mathrm{E}}(L)$	3.32	3.32	9.80	9.80	8.98	8.98
$\tilde{k}_L$	0.66	0.72	1.96	2.15	0.45	0.48
$\tilde{\mathrm{I}}(L)$	6.00	5.36	6.00	5.55	21.00	19.59
$\mu_l + \gamma_l$	7.53	5.00	10.20	5.00	11.14	5.00

We have only concentrated on the effect of immunity on the larval population so far in this section. There is still much room for work studying the structure of this model, in particular in relation to how the nonlinear effects carry through to the distribution of the mature parasite population. We mention briefly here one result in relation to the mature parasite load.

If we consider the variable for mature parasites, the moment equations obtained from the model transition rates are

$$\begin{aligned}
\frac{d\mathrm{E}(M(t))}{dt} &= \gamma \mathrm{E}(L(t)) - \mu_m \mathrm{E}(M(t)) \\
\frac{d\mathrm{E}(M(t)^2)}{dt} &= 2\gamma \mathrm{E}(L(t)M(t)) + \gamma \mathrm{E}(L(t)) - 2\mu_m \mathrm{E}(M(t)^2) + \mu_m \mathrm{E}(M(t)).
\end{aligned}$$

At equilibrium we have

$$\tilde{\mathrm{I}}(M) = 1 + \frac{\gamma_l}{\mu_m} \frac{\tilde{\mathrm{cov}}(L, M)}{\tilde{\mathrm{E}}(M)} \quad \text{and} \quad \tilde{\mathrm{E}}(M) = \frac{\gamma_l}{\mu_m} \tilde{\mathrm{E}}(L)$$

from which we note that M is overdispersed at equilibrium if $\tilde{\mathrm{cov}}(L, M) > 0$ and underdispersed if $\tilde{\mathrm{cov}}(L, M) < 0$, where these are now the moments of the moments of the *true* stochastic variables at equilibrium, not the approximating ones. From an intuitive sense we would expect higher β to result in lower correlation between L and M, and we can see this occuring in the approximations of Grenfell, Dietz, and

Roberts (1995a, Figures 4c and 5c). However, it seems unlikely that this correlation could become negative and hence cause underdispersion, as the immigration rate into the mature parasites compartment depends entirely on the level of L.

4.2.3 Assessing Disease Prevalence

'Moment closure' techniques for examining the nonlinear immigration type models we are discussing have the disadvantage of not producing any results for individual probabilities, in addition to the uncertainty of their accuracy for moments. This means that results for prevalence of infection (i.e. $1 - P(M(t) = 0)$) for example are not immediate. These are often results that are measured in the field. To quote Grenfell, Wilson, Isham, Boyd, and Dietz (1995b)

> ...in terms of future qualitative epidemiological work on macroparasite infections of wildlife hosts, we suggest that the next priority is to develop models which track both the prevalence and intensity of infections simultaneously... (which) would provide another variable for comparison with field data."

To this end, we consider the deterministic rate approximation (as described in Section 2.3.2) to the process under discussion. We consider only larval parasites for simplicity, though of course the method can be extended, and to ease notation we take $\gamma_l = 0$. The approximation leads to the set of differential equations for the means

$$\begin{aligned} \frac{dL}{dt} &= \lambda - \mu_l L - \beta LI \\ \frac{dI}{dt} &= \nu L - \mu_I I \end{aligned} \tag{4.3}$$

with $L(0) = 0$ and $I(0) = 0$. Again we have written $\lambda = \phi \mathrm{E}(C)$. There exists one (stable) equilibrium solution to this system,

$$\begin{aligned} L^* &= \frac{1 + \sqrt{1 + 4\nu\rho\epsilon}}{2\epsilon} \\ I^* &= \frac{\nu L^*}{\mu_I} \end{aligned}$$

where we have writen $\epsilon = \lambda/\mu_l$ and $\rho = \beta/\mu_i$. Our transitions for the deterministic rate approximating process are now from $L(t), I(t)$ to

$$\begin{array}{lll} L + c \quad I & \text{at rate } \phi h_c & c = 0, 1, 2, \ldots \\ L - 1 \quad I & \text{at rate } d(t)L & \\ L \quad I + 1 & \text{at rate } \nu L & \\ L \quad I - 1 & \text{at rate } \mu_I I & \end{array}$$

where the per capita death rate of the larval parasites is inhomogeneous in time and is simply $d(t) = \mu_l + \beta \mathrm{E}(I(t))$. Here, $\mathrm{E}(I(t))$ simply corresponds to the deterministic $I(t)$ of (4.3) as this (approximating) system is a linear one. The marginal distribution of $L(t)$ is independent of $I(t)$, (of course this is one of the weaknesses of this method) and is simply a batch arrival immigration and time inhomogeneous death rate process (call this a BIID process). If $P_d(x, z; t) := \mathrm{E}(x^{L_t} z^{I_t})$ is the joint probability generating function for this deterministic rate approximation process, the marginal probability generating function for $L(t)$ is

$$P_d(x, 1; t) = \exp\left\{\phi \int_0^t \left(h(1 + (x-1)e^{-\kappa(t,u)}) - 1\right) du\right\}$$

where $\kappa(t, u) = \int_u^t d(s)ds = \mu_m(t-u) + \gamma \int_u^t \mathrm{E}(I(s))ds$ which can be calculated from $I(t)$ in (4.3).

The only real benefit of considering the deterministic rate approximation is that we are able to obtain approximations for $P(L(t) = 0)$ to accompany the deterministic means. This is

$$\mathrm{P}(L(t) = 0) = P_d(0, 1; t) = \exp\left\{\phi \int_0^t \left(h(1 - e^{-\kappa(t,u)}) - 1\right) du\right\}. \tag{4.4}$$

The only other option open to a deterministic modeller wishing to estimate $P(L(t) = 0)$ would be to assume a distributional form for $L(t)$. For example, the Poisson distribution would give an approximation $e^{-L(t)}$, whilst the negative binomial distribution with specified k values would give $(k/(k+L(t)))^k$. With moment closure equations encompassing second order moments for the fully stochastic model, the k parameter would not have to be specified for the negative binomial distribution. We call this approach the general negative binomial approximation (general NB), though it should be noted that it uses mean and variances taken from the normal approximation, and so has two approximating stages to it. Note that we have not considered the multivariate negative binomial approximations for the moments in this chapter due to the possibility of negative correlations in the process.

Notice that this assumption of a distributional form is in effect what the deterministic rate approximation does. We have essentially assumed the distribution that arises from a batch arrival immigration and time inhomogeneous death rate (BIID) process. For a given path of the mean of $L(t)$, we need only specify ϕ and the distribution of C to obtain the prevalence. The form of the time inhomogeneous death rate is then implicit. The distribution arising from this approximating BIID process is still not that of the original stochastic process modelled, but is an alternative to the negative binomial and Poisson approximations.

In Tables 4.5 and 4.6 we compare some of these approximating methods with the simulated value for $1-P(L(t) = 0)$ at equilibrium. The parameters of Grenfell, Dietz, and Roberts (1995a) yield almost 100% prevalence of the disease, so in Table 4.5 we consider parameters as in Table 4.1 for various values of β, i.e. $\mu_l = 5, \mu_i = 4, \nu = 2, \phi = 5$ and C follows a negative binomial distribution with $k_C = 1$ and $m_c = 5$. In Table 4.6 we consider the same parameters, except with pure Poisson input so that $C \equiv 1$ and $\phi = 25$. The number of runs used for each simulation was 5×10^4, and all standard errors are zero to two decimal places.

Table 4.5: Approximations of the Prevalence in Immunity Model 1, with $\phi = 5, m_c = 5$

β	$\tilde{\mathrm{E}}(L)_d$	Poisson	NB. k=1	General NB.	Det. Rate	Simulation (2 s.e.)
0.1	4.77	0.99	0.83	0.81	0.82	0.82 (0.00)
1.0	3.66	0.97	0.78	0.68	0.73	0.73 (0.00)
2.0	3.09	0.95	0.75	0.60	0.67	0.67 (0.00)

Table 4.6: Approximations of the Prevalence in Immunity Model 1, with $\phi = 25, C \equiv 1$

β	$\tilde{\mathrm{E}}(L)_d$	Poisson	NB. k=1	General NB.	Det. Rate	Simulation (2 s.e.)
0.1	4.77	0.99	0.83	0.99	0.99	0.99 (0.00)
1.0	3.66	0.97	0.78	0.97	0.97	0.98 (0.00)
2.0	3.09	0.95	0.75	0.95	0.95	0.95 (0.00)

The ad-hoc methods of using Poisson and Negative Binomial with fixed k value to derive $P(L(t) = 0)$ are not robust to changes in the input process. Whereas the Poisson approximation gives reasonably good estimates for prevalence when the input process is itself Poisson (Table 4.6), the fixed negative binomial approximation performs badly as it assumes an inappropriate level of dispersion. When the input process is compounded with a variable clump size distribution the estimates are dramatically wrong for the Poisson distribution (Table 4.5), but much better for the fixed negative binomial approximation. Both process give equivalent results for the two cases as they are only based upon the deterministic means, which are the same for each case.

The two methods that use more parameters (general negative binomial and deterministic rate) are more flexible and not suprisingly give much better results. It is noticeable, however, that for the parameters used, the deterministic rate approximation achieves more accuracy than the general negative binomial, and in fact achieves near perfect accuracy to two decimal places. This implies that for these parameters, the distribution given by a BIID process provides a better estimate of the probability of zero for the true distribution of the nonlinear process than simply using a negative binomial distribution. The general negative binomial approximation performs badly when β is higher and the input distribution is aggregated (see Table 4.5). For future work, further comparisons of these two approximation methods would be interesting.

4.3 Immune Response Stimulated by Parasite Challenge

In this section we propose and investigate a model similar to the one discussed in the previous section, but with the difference that the experience of infection increases with the ingestion of larvae, as opposed to increasing at a rate proportional to the larval load. We envisage this as representing the triggering of the immune system when larvae pass through a specific stage of its cycle. As before, the immunity level undergoes constant per capita decay, and the larval per capita death rate is proportional to the immune level. Thus we have the transitions from $L(t), I(t)$ to

$$\begin{array}{cccc} L+c & I+c & \text{at rate } \phi h_c & \text{for } c = 0, 1, ... \\ L-1 & I & \text{at rate } (\mu_l + \beta I)L & \\ L & I-1 & \text{at rate } \mu_i I & \end{array}$$

so that the immune level jumps up at the entrance of a larva into the host. We will only consider larval stages of the parasite, and so subsume the larva maturation

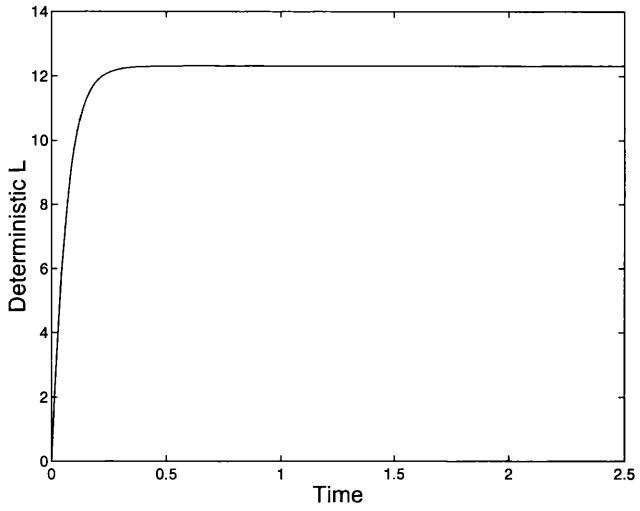

Figure 4.3: Deterministic $L(t)$ for Immunity Model 2 with $\beta = 1, \mu_i = 20$

rate γ_l into the death rate μ_l. The model can of course be extended to incorporate other stages, including mature parasites. In this chapter we shall call this immunity model 2.

This process yields simpler moment equations than the last because the evolution of $I(t)$ does not directly depend on $L(t)$. We can solve for the whole marginal distribution of $I(t)$ directly, as it is itself just an $M/M/\infty$ queue with batch arrivals, but this is not particularly useful in isolation as it is the affect of the immunity on the parasite load we are interested in.

A deterministic equivalent of this model is

$$\begin{aligned} \frac{dL}{dt} &= \lambda - \mu_l L - \beta L I \\ \frac{dI}{dt} &= \lambda - \mu_i I \end{aligned}$$

with $L(0) = 0$ and $I(0) = 0$, which has solution

$$\begin{aligned} I(t) &= \frac{\lambda}{\mu_i}\left(1 - e^{-\mu_i t}\right) \\ L(t) &= \lambda \int_0^t \exp\left\{ \frac{\mu_m \mu_i + \beta\lambda}{\mu_i}(w - t) + \frac{\lambda\beta(e^{-\mu_i w} - e^{-\mu_i t})}{\mu_i^2} \right\} dw. \end{aligned}$$

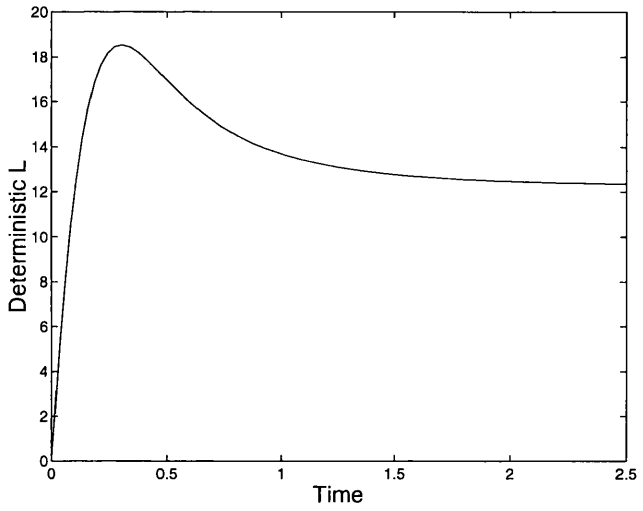

Figure 4.4: Deterministic $L(t)$ for Immunity Model 2 with $\beta = 0.1, \mu_i = 2$

Again we have written $\lambda = \phi \mathrm{E}(C)$. Some paths of this are shown in Figures 4.3 and 4.4 using $\lambda = 160$ and $\mu_l = 5$. As in immunity model 1, the larval load can either rise directly to an equilibrium level (Figure 4.3) or peak and then fall to an equilibrium (Figure 4.4). This deterministic version of model 2 shows similar behaviour to that of immunity model 1.

In equilibrium, we have the stable solution

$$\begin{aligned} L^* &= \frac{\epsilon}{1+\epsilon\rho} \\ I^* &= \rho \end{aligned} \tag{4.5}$$

where we have written $\epsilon = \phi m_c/\mu_l$ and $\rho = \beta/\mu_i$. The deterministic rate approximation results in $L(t)$ simply becoming an inhomogenous immigration death process, with death rate $\mu_l + \frac{\phi m_c}{\mu_i}(1 - e^{-\mu_i t})$. We lose the dependence between $L(t)$ and $I(t)$ which we expect to keep a check on those realistions with unusually high uptakes of parasites. We do not consider this further, but as in the previous section it could be used to obtain prevalence estimates.

We next analyse the linear case of this model to investigate the correlations between L and I that the process generate without immunity effecting the larval

death rate. If $P_2(t;x,z)$ is defined as the joint probability generating function for the nonlinear version of immunity model 2, the Palm relation gives

$$\begin{aligned}\frac{\partial P_2(t;x,z)}{\partial t} &= (h(xz)-1)P_2 + (\mu_l(1-x))\frac{\partial P_2}{\partial x} \\ &\quad +\mu_i(1-z)\frac{\partial P_2}{\partial z} + \beta z(1-x)\frac{\partial^2 P_2}{\partial x \partial z}.\end{aligned}$$

Setting $\beta = 0$ for the linear case gives the solution

$$\begin{aligned}&P_2(t;x,z) = \\ &\exp\left\{\phi\int_0^t h\left(e^{-(\mu_l+\mu_i)(t-w)}(x-1)(z-1) + e^{-\mu_l(t-w)}(x-1) + e^{-\mu_i(t-w)}(z-1) + 1\right)dw \right. \\ &\qquad \left. - \phi t\right\}.\end{aligned}$$

With pure Poisson input, i.e. $C \equiv 1, h(x) = x$, this gives a bivariate Poisson distribution. Generally, we have

$$\begin{aligned}\mathrm{cov}(L(t),I(t)) &= \frac{\phi \mathrm{E}(C^2)}{\mu_l+\mu_i}(1-e^{-(\mu_l+\mu_i)t}) \\ \mathrm{var}(L(t)) &= \frac{\phi}{\mu_l}\left(\frac{h''(1)}{2}(1-e^{-2\mu_l t}) + h'(1)(1-e^{-\mu_l t})\right)\end{aligned}$$

with $\mathrm{var}(I(t))$ given in a similar fashion, so that at equilibrium the correlation is

$$\frac{2\sqrt{\mu_l\mu_i}}{\mu_l+\mu_i}\frac{\mathrm{I}(C)+\mathrm{E}(C)}{\mathrm{I}(C)+\mathrm{E}(C)+1}$$

which is independent of the encounter rate, ϕ. As a function of μ_i, the correlation will in general be at a maximum when μ_i is equal to μ_l. If $C \equiv 1$ then the correlation will be $\sqrt{\mu_l\mu_i}/(\mu_l+\mu_i)$, and this has a maximum of $1/2$. Generally we see that the equilibrium correlation increases with $\mathrm{var}(C)$. The joint probability generating function for the linear case of immunity model 1 can be obtained by making the appropriate parameter choice in the model of Section 3.2. We compare the equilibrium correlations generated by the two models under discussion in Table 4.7 by setting $\nu = \mu_l$ so that the equilibrium means are the same for both models. We set $\mu_l = 5$, so the equilibrium means are $\tilde{\mathrm{E}}(L) = 20$ and $\tilde{\mathrm{E}}(I) = 5$ and in the first two cases C follows a negative binomial distribution with k_C.

Table 4.7: Correlations for Linear Immunity Models 1 and 2 ($\mu_l = 5$)

	$m_c = 20$			$m_c = 5$		
	$\phi = 5$			$\phi = 20$		
Model	$\mu_i = 1$	$\mu_i = 5$	$\mu_i = 20$	$\mu_i = 1$	$\mu_i = 5$	$\mu_i = 20$
One	0.397	0.676	0.804	0.373	0.612	0.667
Two	0.820	0.976	0.781	0.873	0.917	0.733

	$C \equiv 1$		
	$\phi = 100$		
Model	$\mu_i = 1$	$\mu_i = 5$	$\mu_i = 20$
One	0.275	0.408	0.365
Two	0.447	0.500	0.400

We can see that of the two linear processes immunity model 2, in which the immunity increases directly as larvae enter the system, tends to generate more correlation between the immunity and the larval level. This is not universal across the parameter space, however. As the larval and immunity death rates move apart the correlation will always reduce in immunity model 2, but, depending on the level of input aggregation, may increase for immunity model 1, so that for some parameters model 1 will have a higher correlation level than model 2. In both models, higher input aggregation generates higher correlation.

The differential equations for the moments of the stochastic immunity model 2

are

$$\begin{aligned}
\frac{d\mathrm{E}(L)}{dt} &= \phi\mathrm{E}(C) - \mu_l\mathrm{E}(L) - \beta\mathrm{E}(IL) \\
\frac{d\mathrm{E}(I)}{dt} &= \phi\mathrm{E}(C) - \mu_i\mathrm{E}(I) \\
\frac{d\mathrm{E}(L^2)}{dt} &= \phi\mathrm{E}(C^2) + (2\phi\mathrm{E}(C) + \mu_l)\mathrm{E}(L) - 2\mu_l\mathrm{E}(L^2) - 2\beta\mathrm{E}(L^2I) + \beta\mathrm{E}(LI) \\
\frac{d\mathrm{E}(I^2)}{dt} &= \phi\mathrm{E}(C^2) + (2\phi\mathrm{E}(C) + \mu_i)\mathrm{E}(I) - 2\mu_i\mathrm{E}(I^2) \\
\frac{d\mathrm{E}(IL)}{dt} &= \phi\mathrm{E}(C^2) + \phi\mathrm{E}(C)(\mathrm{E}(I) + \mathrm{E}(L)) - (\mu_i + \mu_l)\mathrm{E}(IL) - \beta\mathrm{E}(I^2L). \quad (4.6)
\end{aligned}$$

Explicit dependence on t has been dropped for notational convenience. In this system the two equations for $\mathrm{E}(I)$ and $\mathrm{E}(I^2)$ are self contained so we are able to make more progress than in the previous section. If we introduce the normal approximation results,

$$\mathrm{E}(IL^2) = 2\mathrm{E}_a(L)\mathrm{E}_a(IL) - 2\mathrm{E}_a(I)(\mathrm{E}_a(L))^2 + \mathrm{E}_a(L^2)\mathrm{E}_a(I)$$

and

$$\mathrm{E}(I^2L) = 2\mathrm{E}_a(I)\mathrm{E}_a(IL) - 2\mathrm{E}_a(L)(\mathrm{E}_a(I))^2 + \mathrm{E}_a(I^2)\mathrm{E}_a(L),$$

then, writing $\mathrm{E}_a(\cdot)$ for expectation under the normal approximations, equations (4.6) become

$$\begin{aligned}
\frac{d\mathrm{E}_a(L)}{dt} &= \phi\mathrm{E}(C) - \mu_l\mathrm{E}_a(L) - \beta\mathrm{E}_a(IL) \\
\frac{d\mathrm{E}_a(I)}{dt} &= \phi\mathrm{E}(C) - \mu_i\mathrm{E}_a(I) \\
\frac{d\mathrm{E}_a(L^2)}{dt} &= \phi\mathrm{E}(C^2) + (2\phi\mathrm{E}(C) + \mu_l)\mathrm{E}_a(L) - 2\mu_l\mathrm{E}_a(L^2) + \beta\mathrm{E}_a(LI) - \\
&\quad 2\beta(2\mathrm{E}_a(L)\mathrm{E}_a(IL) - 2\mathrm{E}_a(I)(\mathrm{E}_a(L))^2 + \mathrm{E}_a(L^2)\mathrm{E}_a(I)) \\
\frac{d\mathrm{E}_a(I^2)}{dt} &= \phi\mathrm{E}(C^2) + (2\phi\mathrm{E}(C) + \mu_i)\mathrm{E}_a(I) - 2\mu_i\mathrm{E}_a(I^2) \\
\frac{d\mathrm{E}_a(IL)}{dt} &= \phi\mathrm{E}(C^2) + \phi\mathrm{E}(C)(\mathrm{E}_a(I) + \mathrm{E}_a(L)) - (\mu_i + \mu_l)\mathrm{E}_a(IL) - \\
&\quad \beta(2\mathrm{E}_a(I)\mathrm{E}_a(IL) - 2\mathrm{E}_a(L)(\mathrm{E}_a(I))^2 + \mathrm{E}_a(I^2)\mathrm{E}_a(L)). \quad (4.7)
\end{aligned}$$

The steady state solutions are now obtainable in closed form after some algebraic manipulations. We could, in theory, investigate the effect of this immune response

on the approximate dispersion, correlation and other properties at equilibrium by investigating the full parameter space for these solutions, but in practice the results are too complicated to provide any general conclusions. However, from equations (4.7) we can write

$$\tilde{\text{var}}(L)_a = (\tilde{\text{E}}_a(L))^2 - \frac{\epsilon}{1+\epsilon\rho}\tilde{\text{E}}_a(L) + \frac{d+\lambda}{2(\mu_l+\rho\lambda)}$$

where again $\tilde{\text{E}}(\cdot)$ and $\tilde{\text{var}}(\cdot)$ indicate expectations and variance at equilibrium, $d = \phi\text{E}(C^2)$, $\lambda = \phi\text{E}(C)$, $\rho = \beta/\mu_i$ and $\epsilon = \lambda/\mu_l$. The approximating index of dispersion can now be written

$$\tilde{\text{I}}_a(L) = \tilde{\text{E}}_a(L) - \tilde{L}_{det} + \tilde{\text{I}}_0\frac{\tilde{L}_{det}}{\tilde{\text{E}}_a(L)}$$

where $\tilde{\text{I}}_0$ is the eqilibrium index of dispersion of L for the linear model, as described in Section 4.1, and $\tilde{L}_{det} = \epsilon/(1+\rho\epsilon)$ is the deterministic equilibrium mean of the process as given in (4.5). We can also find from equations (4.7) that

$$\tilde{\text{cov}}_a(L, I) = \lambda/\beta - \tilde{\text{E}}_a(L)(\mu_l/\beta + \tilde{\text{E}}(I))$$

which is greater than zero if

$$\tilde{\text{E}}_a(L) < \frac{\lambda}{\mu_l + \beta\tilde{\text{E}}(I)} = \tilde{L}_{det}.$$

(Remember that $\text{E}_a(I) = \text{E}(I)$). Hence we find that $\tilde{\text{cov}}_a(L, I) > 0$ if $\tilde{\text{E}}_a(L) < \tilde{L}_{det}$, i.e. if the normal approximation mean is less than the deterministic approximation mean. This, together with the results of the last section mean the approximating equilibrium index of dispersion is reduced from the linear model if $\tilde{\text{E}}_a(L)$ lies between $\tilde{\text{I}}_0$ and $\tilde{L}_{det}$, and increased otherwise.

Tables 4.8 - 4.10 show simulated, deterministic and normal approximation values for moments at the equilibrium of model 2 for various sets of parameter values. The remaining parameter is fixed as $\mu_l = 5$, and C is taken as a negative binomial distribution with $k_C = 1$.

Table 4.8: Immunity Model 2 Equilibrium Results with $\phi = 5, m_c = 5$

	$\beta = 0$		$\beta = 1, \mu_i = 20$		$\beta = 0.1, \mu_i = 2$		
	$\mu_i = 20$	$\mu_i = 2$	Sim. (2se)	N. Apx.	Sim. (2se)	N. Apx.	Det.
E(L)	5.00	5.00	2.88 (0.04)	2.44	3.59 (0.06)	3.52	4.00
I(L)	6.00	6.00	3.66 (0.10)	8.29	5.27 (0.16)	6.34	n/a
k_L	1.00	1.00	1.08 (0.11)	0.33	0.84 (0.12)	0.66	n/a
cor(L, I)	0.73	0.83	0.79 (0.01)	0.80	0.70 (0.01)	0.74	n/a

Table 4.9: Immunity Model 2 Equilibrium Results with $\phi = 20, m_c = 5$

	$\beta = 0$		$\beta = 1, \mu_i = 20$		$\beta = 0.1, \mu_i = 2$		
	$\mu_i = 20$	$\mu_i = 2$	Sim. (2se)	N. Apx.	Sim. (2se)	N. Apx.	Det.
E(L)	20.00	20.00	7.87 (0.07)	7.04	9.40 (0.08)	9.32	10.00
I(L)	6.00	6.00	3.20 (0.08)	5.56	5.18 (0.12)	5.76	n/a
k_L	4.00	4.00	3.58 (0.65)	1.54	2.25 (0.40)	1.96	n/a
cor(L, I)	0.73	0.83	0.78 (0.00)	0.87	0.51 (0.01)	0.54	n/a

In Table 4.8, for both sets of values of β and μ_i, $\tilde{E}_a(L)$ does not lie between $\tilde{I}_0 = 6$ and $L_{det} = 4$, hence the normal approximations incorrectly estimate $\tilde{I}(L)$ as increasing when immunity is added.

It is difficult to make direct numerical comparisons between model 1 and model 2 due to their different structures. However, in Tables 4.8 - 4.10 we have kept ϕ, C and μ_l as in Tables 4.1 - 4.3 so that the linear cases of the two processes are equivalent, and kept $\rho = \beta/\mu_i$ constant at 0.05 for each of the cases shown. In Tables 4.8 and 4.9 we see that the normal approximation for the means does not reach the accuracy of that for immunity model 1 (Tables 4.1 and 4.2) for either pair of values

Table 4.10: Immunity Model 2 Equilibrium Results with $\phi = 5, m_c = 20$

	$\beta = 0$		$\beta = 1, \mu_i = 20$	$\beta = 0.1, \mu_i = 2$	
	$\mu_i = 20$	$\mu_i = 2$	Sim. (2 s.e.)	Sim. (2 s.e.)	Deterministic
E(L)	20.00	20.00	10.34 (0.11)	8.23 (0.14)	10.00
I(L)	21.00	21.00	11.42 (0.31)	16.66 (0.60)	n/a
k_L	1.00	1.00	0.99 (0.19)	0.51 (0.62)	n/a
cor(L, I)	0.78	0.88	0.65 (0.01)	0.53 (0.01)	n/a

of $\{\beta, \mu_i\}$, but not suprisingly the lower the value of β (the parameter governing the only nonlinear transition) the better the normal approximation performs.

The parameters in Table 4.10 result in the normal approximation producing means that become negative so the approximation is completely inappropriate. The moments of immunity model 2 may be harder to capture using the normal approximation when C is dominating ϕ, due to the clumped input affecting immune levels as well as the larval levels.

Notice from Tables 4.8 - 4.10 that the correlation between I and L can either be reduced or increased when immunity is added to the model. This is in contrast to model 1 in which the correlation always decreased for the parameter space considered (see Tables 4.1 - 4.3).

4.4 Immunity Preventing Parasite Establishment

In the model investigated in this section we again view the acquired immune response as being suddenly triggered. However, unlike the model of Section 4.3 we consider it as having just two states, on or off. We assume that when the immunity is on, it has the strong effect of successfully killing all larval entering the host, so that none can become established.

This is similar to the assumption made by Roberts (1997) in his deterministic model in which the immune response is an indicator variable that can be considered as 'shutting the gate' on incoming larva when switched on. The motivation comes from modelling nematodes in farmed sheep. As sheep are moved to different pastures at the end of each season we may only be interested in one season of parasite dynamics, so we can consider the immunity as only increasing. For this reason, the parasite level is observed as rising and then declining as the new lambs establish immunity, and there is insufficient time for the immunity loss to play a part.

The model described here is a first step towards a stochastic model for the complete parasite dynamics of this farmed system. In completing the parasite life cycle loop, Roberts (1997) makes the assumption that at the start of each season the level of eggs on the pasture (giving the rate of uptake of larvae) is related to the egg output at the close of the last season. A new flock of lambs is introduced each year that are naive and so have no initial immune level.

The case we describe below is a model for just a single 'typical' host acquiring parasites from eggs already on the pasture.

The host acquires single parasites according to a Poisson process. We do not allow for parasite clumping in the input process. The experience of infection (or immunity level) is modelled as a random variable I_t that increases with each ingested larva, and its effect on parasite level of the host is such that, once $I_t > r$ any larval challenge to the host is unsuccessful (i.e. the immune response is switched on). Once again parasites have exponential lifetimes (though this is not neccessary for analysis of the model) so that the possible transitions are from L, I to

$$L+1 \quad I+1 \quad \text{at rate } \phi \qquad \text{for } I < r \tag{4.8}$$

$$L-1 \quad I \qquad \text{at rate } \mu L \tag{4.9}$$

The system is simply an $M/M/\infty$ queue in which only the first r arrivals contribute. Eventually the host will become parasite free permanently, though in practice this may well be beyond the one season time limit we are interested in. We refer to this

model as immunity model 3.

A possible deterministic version of this model is as follows. The immunity level, I_t grows without decay so that $\dot{I}_t = \phi$ and hence $I_t = \phi t$. It reaches the threshold value, r at time r/ϕ, which is when parasites can no longer enter the host. The parasite level, L_t initially undergoes immigration and death so that $\dot{L} = \phi - \mu L_t$ until the threshold time. After time r/ϕ, the parasite population suffers only death, i.e. $\dot{L}_t = -\mu L_t$. This gives the solution for L_t as

$$L_t = \begin{cases} \frac{\phi(1-e^{-\mu t})}{\mu} & \text{for } 0 < t < r/\phi \\ \frac{\phi}{\mu} e^{-\mu t}(e^{\mu r/\phi} - 1) & \text{for } t \geq r/\phi. \end{cases}$$

We now proceed to derive the probability generating function for the parasite load L_t under the assumptions of the stochastic model. In the stochastic model the immunity switches on at the time of the r^{th} arrival, T_r say. This random time is simply the sum of r exponential distributions, with parameter ϕ, and so has a gamma distribution,

$$T_r \sim \Gamma(r, \phi).$$

Its mean is of course the deterministic result for the threshold time, r/ϕ. Its probability density, $f_{T_r}(x)$, is $\phi^r x^{r-1} e^{-\phi x}/\Gamma(r)$ and the cumulative distribution function is $F_{T_r}(x) = \int_0^x f_{T_r}(u)du$.

Let X_t be the number of arrivals into the host, regardless of whether they become established or not. By standard queueing results, (see for example Karlin and Taylor (1975)) $X_t \sim$Poisson(ϕt). We have,

$$\begin{aligned} \mathrm{P}(X_t = x | T_r > t) &= \mathrm{P}(X_t = x | X_t < r) \\ &= \frac{\mathrm{P}(X_t = x, X_t < r)}{\mathrm{P}(X_t < r)} \\ &= \begin{cases} \frac{(\phi t)^x}{x! \sum_{i=0}^{r-1} \frac{(\phi t)^i}{i!}} & \text{for } x < r \\ 0 & \text{otherwise} \end{cases} \end{aligned}$$

so that

$$G_{X_t|X_t<r}(u) := \mathrm{E}(u^{X_t}|X_t < r) = \frac{\sum_{j=0}^{r-1}(\phi t u)^j/j!}{\sum_{i=0}^{r-1}(\phi t)^i/i!}.$$

Given the number of parasites arriving in $(0,t]$, the times of arrival are independently, uniformly distributed on $(0,t]$, and so have probability density functions $f(x) = 1/t$ for $x \in (0,t]$, and 0 otherwise. In addition, a parasite ingested at time τ has probability $e^{-\mu(t-\tau)}$ of still being alive at t. Combining these results, we find that given $T_r > t$, a randomly chosen parasite arriving in $[0,t]$ has probability $\theta(t)$ of being alive at t, where

$$\theta(t) = \int_0^t e^{-\mu(t-\tau)} \frac{1}{t} d\tau = \frac{1 - e^{-\mu t}}{\mu t}$$

Therefore, given that x parasites have arrived in $(0,t]$, the number alive at t has binomial distibution with a probability generating function of z of $(1+(z-1)\theta(t))^x$. We then have

$$\begin{aligned}
H_1(s;t) &:= \mathrm{E}(s^{L_t} | T_r > t) \\
&= \mathrm{E}(\mathrm{E}(s^{L_t} | T_r > t, X_t)) \\
&= \mathrm{E}((1 + (s-1)\theta(t))^{X_t} \mid T_r > t) \\
&= G_{X_t | X_t \leq r}(1 + (s-1)\theta(t)) \\
&= \frac{\sum_{j=0}^{r-1} (\phi t (1 + \theta_t (s-1))^j / j!}{\sum_{i=0}^{r-1} (\phi t)^i / i!}.
\end{aligned}$$

The derivation of $\mathrm{E}(s^{L_t} | T_r \leq t)$ follows similar lines, but note that we are no longer interested in the total number of arrivals, X_t. This is because we are conditioning on the fact that $X_t \geq r$, and so we are not interested in any arrivals after the first r as they do not become established. We have

$$H_2(s;t;T_r) := \mathrm{E}(s^{L_t} | T_r : T_r \leq t) = (1 + (s-1)\psi(t,T_r))^{r-1}(1 + (s-1)e^{-\mu(t-T_r)})$$

where $e^{-\mu(t-T_r)}$ is the probability the r^{th} parasite to arrive (at time T_r) survives to time t, and $\psi(t,T_r)$ is the probability a randomly chosen parasite of the first $r-1$ to arrive survives to time t, conditional on T_r.

Conditional on T_r, we know there are $r-1$ arrivals in $(0,T_r)$, so the arrival

times are independent and uniform on $(0, T_r)$. Therefore we find that

$$\begin{aligned}\psi(t, T_r) &= \int_0^{T_r} \frac{e^{-\mu(t-\tau)}}{T_r} d\tau \\ &= \frac{e^{-\mu t}}{\mu T_r}(e^{\mu T_r} - 1) \\ &= \theta(T_r) e^{\mu(t-T_r)}.\end{aligned}$$

Removing the conditioning on T_r we now obtain

$$P(s;t) := \mathrm{E}(s^{L_t}) \tag{4.10}$$

$$= H_1(s;t)(1 - F_{T_r}(t)) + \int_0^t H_2(s;t;x) f_{T_r}(x) dx, \tag{4.11}$$

the probability generating function for the parasite load at time t.

4.4.1 Properties

The mean of L_t is

$$\begin{aligned}\mathrm{E}(L_t) &= (1 - F_{T_r}(t)) \left.\frac{\partial H_1(s;t)}{\partial s}\right|_{s=1} + \int_0^t \left.\frac{\partial H_2(s;t;x)}{\partial s}\right|_{s=1} f_{T_r}(x) dx \\ &= \phi t \theta(t)(1 - F_{T_r}(t)) \frac{\sum_{j=0}^{r-2} (\phi t)^j / j!}{\sum_{i=0}^{r-1} (\phi t)^i / i!} + e^{-\mu t} \int_0^t e^{\mu x}((r-1)\theta(x) + 1) f_{T_r}(x) dx\end{aligned}$$

where f_{T_r} and F_{T_r} are the probability distribution function and cumulative distribution function of the $\Gamma(\phi, r)$ distribution, as given above.

Similarly, we also have

$$\mathrm{E}(L_t^2) - \mathrm{E}(L_t) = (1 - F_{T_r}(t)) \left.\frac{\partial^2 H_1}{\partial s^2}\right|_{s=1} + \int_0^t \left.\frac{\partial^2 H_2}{\partial s^2}\right|_{s=1} f_{T_r}(x) dx \tag{4.12}$$

$$= (\phi t)^2 \theta(t)^2 (1 - F_{T_r}(t)) \frac{\sum_{j=0}^{r-3} \phi^j / j!}{\sum_{i=0}^{r-1} \phi^i / i!} + \tag{4.13}$$

$$e^{-2\mu t}(r-1) \int_0^t \theta(x) e^{2\mu x}(2 + (r-2)\theta(x)) f_{T_r}(x) dx.$$

We show some plots of the means and index of dispersion compared with the deterministic model in Figures 4.5 and 4.6 on page 123. We see that as the mean approaches its peak the variance starts to decline so that the process becomes

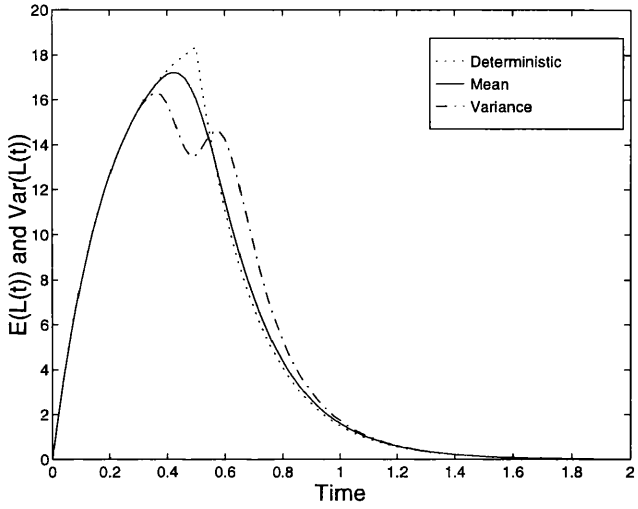

Figure 4.5: Mean and Variance of $L(t)$ for Immunity Model 3

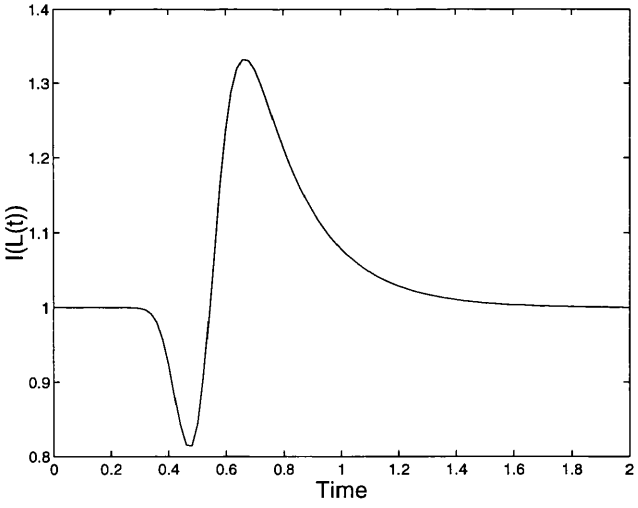

Figure 4.6: Index of Dispersion for Immunity Model 3

underdispersed. During the mean's descent, the variance starts to increase again so the process becomes overdispersed (Figure 4.5).

An explanation for this is as follows. Close to the time of the peak of the mean, the realisations with parasite levels above the mean will be more likely to have reached the threshold level of the number of parasites ingested (r), and so will have started a decline of parasites numbers in the absence of further immigration. This will bring the parasite number back down towards the mean level of all realisations, and so reduce the variance. Similarly, just after the time at which the mean reaches its peak, those realisations that have not yet reached the threshold will be closer to the mean than they would be without the immune mechanism. After most realisations have reached the immunity threshold, the variance increases because there is now a large discrepancy between those realisations that have undergone pure death for a while, and those that have only just reached the threshold. If r is increased the mean curve will be flatter.

Of course without the immune mechanism ($r = \infty$) the index of dispersion would be a constant value of one. Figure 4.6 shows its decline and then increase, followed by a slow decline back down to one as parasite levels decline towards zero. This corresponds to the changes in the variance discussed above.

This model does not involve any loss of in immunity, and is designed to consider short term effects of the immunity in farmed animals. However, it does indicate that immunity that affects the parasite establishment can cause an initial decline in dispersion, followed by an increase once parasite levels start to drop. This is in contrast to the immune processes discussed in Sections 4.2 and 4.3 which affect the larval death rate rather than establishment. Those models did not appear to be able to increase dispersion levels.

The probability the host is parasite free is $P(0;t)$ and the probability the host has never acquired any parasites is $e^{-\phi t}$. If a host is observed to be parasite free, it may be of interest to find the probability that it has acquired full immunity

assuming this model. This will be

$$P(T_r < t \mid L_t = 0) \;=\; P(L_t = 0 \mid T_r < t)\frac{P(T_r < t)}{P(L_t = 0)}.$$

The expressions $P(T_r < t)$ and $P(L_t = 0)$ can be obtained from the results given above, and $P(L_t = 0 \mid T_r < t)$ can be expressed as $= (\epsilon(t, T_r))^{r-1}(1 - e^{-\mu(t-T_r)})$, where $\epsilon(t, T_r)$ is the probability a parasite chosen at random from the first $r - 1$ has died by t,

$$\begin{aligned}\epsilon(t, T_r) &= \int_0^{T_r} \frac{1}{T_r}(1 - e^{-\mu(t-\tau)})d\tau \\ &= 1 + \frac{e^{-\mu t}}{\mu T_r}(1 - e^{\mu T_r}).\end{aligned}$$

Thus we have

$$P(T_r < t \mid L_t = 0) \;=\; F_{T_r}(t)\int_0^t \epsilon(t, x)^{r-1}(1 - e^{\mu(t-x)})f_{T_r}(x)dx \;/P(L_t = 0).$$

There is no reason why this model cannot be extended to include general parasite lifetimes, clumped parasite input (so long as the immunity still rises with each encounter, rather than each parasite entering) and parasite maturation and egg production. The analysis would proceed along similar lines.

4.5 Variable Immune Response

As previously mentioned, in many parasite-host systems a variation in host's immune capabilities is often given as a cause for high levels of parasite aggregation. Wassom, Dick, Arnason, Strickland, and Grundmann (1986) showed that in a species of mice the immune response that expels a parasitic tapeworm is genetically determined and argued that in the absence of all other ecological variables, host genetics contributes to parasite overdispersion. However, Munger, Karasov, and Chang (1989) subsequently found that in a very similar system, when mice infected in the laboratory were introduced into the field, prevalence rose dramatically. They argued that mice immune systems alone could not account for the level

of prevalence observed in the wild, and hence host differences in parasite expulsion could not play a large role in causing overdispersion.

The extent to which host genetics and variable acquired immune reponses *are* the cause of parasite overdispersion is still the subject of debate. In modelling terms, it can be clearly demonstrated that they *can* cause the aggregated effects observed (Grenfell, Dietz, and Roberts, 1995a; Grenfell, Wilson, Isham, Boyd, and Dietz, 1995b).

Grenfell, Wilson, Isham, Boyd, and Dietz (1995b) use two levels of immune response (β) to generate the extra aggregation not accounted for by estimated variability in the input distribution. A certain proportion of the host population is allocated to each level. This makes the approximate moments equations very easy to adapt, but in some cases such a model may not give a gradual enough variation between hosts' immune capabilities.

We point out here that the methods outlined in Section 3.8 on random parameters can be used to allocate a random variable to the level of immunity (β) throughout the host population, rather than simply splitting it up into two levels. This could also be used for any other parameter of the model that might be considered to vary across hosts such as parasite ingestion rate (ϕ), as in Section 3.3.4, or parasite death rate μ_l.

Chapter 5

Parasite Dynamics in a Static Host Population

5.1 Introduction

In the study of parasite dynamics, areas such as parasite regulation of a host population or the evolution of parasite virulence require the inclusion of host births and deaths into any model or hypothesis formulated. The host population needs to be considered as a dynamic process, as this is relevant to the questions being studied. However, there is considerable interest in studying parasite populations where these questions are less important, and other properties such as the spread, distribution and persistence of the parasite are relevant. There are many human diseases where host mortality is a small factor on the evolution of disease as compared with host immunity, susceptibility and other factors.

In this chapter we discuss some models that simply describe a parasite population reproducing on a fixed number of hosts that are immortal. In particular we study possible causes of parasite aggregation.

Often parasite aggregation is simply ascribed to host heterogeneities, whether they be heterogeneities in infection rates, behavioural patterns, immunities or oth-

ers (Anderson and May, 1991; Esch and Fernandéz, 1993). However in this chapter we explore the possibility that a large amount of aggregation may simply be caused by biological processes, for example the nature of the parasite life cycle could be identical for all hosts and yet parasites could be overdispersed amongst the hosts due to chance effects in the transmission of parasites.

Barbour and Kafetzaki (1993) have shown that with a simple immune mechanism, equal in all hosts, the probabilistic nature of a model incorporating the full cycle of transmission can itself cause aggregation. In this chapter we go a step further back. Without considering anything other than linear parasite birth and death, we focus on how the transmission mechanism itself can cause aggregation. We do not consider any density dependent or other regulatory effects on the parasite population which will act to reduce the growth of aggregation, and hence we are able to isolate and compare the natural tendencies of different biological transmission mechanisms to cause aggregation. Additionally, this allows more detailed consideration of possible working hypothesises used for the disease transmission mechanisms, something that is often missing in macroparasite modelling at the host population level. In particular, we suggest that the process of transmission itself can have a large effect on the level of aggregation due simply to demographic stochasticity.

The models considered are not meant to be a true representation of endemic parasite populations. In fact, in these initial, simple models we have exponential growth for the mean of the parasite distribution which is clearly not realistic. Instead they are designed for consideration of the growth of dispersion whilst the mean itself is growing, and hence to provide possible explanations for how aggregation could arise in an expanding parasite population. The extension of the models to incorporate density dependence is discussed, but not analysed here.

We model the evolution of parasite loads of the definitive hosts in a spreading parasite population. The unit we are modelling is taken to be the mature stage of the parasite within the definitive host. The main assumption made is that any

intake of parasites that a host receives comes directly from another infected host in the population. This is a vast simplifying assumption. In practice, an infection will occur after each parasite has been through a complicated life cycle, part of which is outside the host. As a result the dynamics of any vector host population or of free living parasite stages will affect the progression of the disease in the definitive host, something we do not investigate here.

Essentially, the assumption means that any individual host's ingestion of parasites at a particular time point can only involve offspring from parasites from one other host. There is no mixing of parasite offspring in the phase outside the host, though mixing within the host is not precluded. Thus we are assuming infecting hosts leave parasite offspring in the environment or in vector hosts, which are then picked up by receiving hosts, independently from parasite offspring of other infective hosts. This assumption and some alternatives to it are discussed further in Section 5.5.

The other main assumption in these types of models is that the time delay between parasites reproducing in one host and an infection occuring in the next is ignored. This time delay will include the development of parasites through their life cycle into mature parasites, including time spent as free living stages in some parasitic diseases, for example during arrested development of the L2 stage of some nematode parasites (Esch and Fernandéz, 1993, Chapter 5). This time delay will be relatively small in some diseases and is often ignored for modelling purposes, but in a fluctuating parasite population it may be important, particlarly where issues such as persistence are concerned, as some parasites can survive for long periods in the environment.

One possible scenario for parasite transmission is that there is complete mixing of offspring from different parasites within a host when an infectious contact occurs, so that each parasite within the infecting host contributes offspring to the receiving host *at exactly the same time.* As this accentuates any variation in the infecting host from the population mean, it is a source of variability in parasite loads. We

refer to this mechanism as parasite proliferation dependence.

The other extreme is when offspring from each parasite are transmitted separately from other parasites' offspring. This case (no parasite proliferation dependence at all) is perhaps less common biologically, but we model it in Section 5.2 for comparative purposes, and discuss how it might arise.

The other mechanism we investigate explicitly is that offspring will be transferred in clumps, i.e. more than one offspring from any individual parasite may enter the receiving host upon a single infection contact. This is something that is implicitly ignored in most deterministic models (see however Damaggio and Pugliese (1996)). There are some infections where the chance of a larva becoming established is so small that it is very rare that more than one parasite will result from any one infection contact e.g. schistosomiasis, but for many parasitic infections it is an important feature e.g. nematode infections in sheep.

In this chapter we consider how these two mechanisms (parasite proliferation dependence and clustered reproduction) exaggerate demographic stochasticity to affect the dispersion of the parasites.

5.2 A Branching Model

As a reference point for later work we start with an extremely simple model. Essentially the only variability in it comes from demographic stochasticity, and so we can see the extent to which this effect alone causes overdispersion. The main assumption is that parasites infect a host one at a time, and independently of each other. Taking schistosomiasis as an example, if we assume that after leaving the snail vector host, free living *cercarie* spread sufficiently in the water before entering a human host so that they become independent of each other (admittedly a big assumption), then, together with various other assumptions concerning the density of the vector host population and parasite reproductive density dependence within vector hosts (all of which can be considered as general transmission regulatory ef-

fects), the transmission of the disease can be roughly described by the model of this section. We acknowledge, though, that these are big assumptions, so the prime motivation for using this model is to use as a comparison with later models.

We have N identical, immortal hosts mixing homogenously and we model the parasite load in each. Parasites give rise to parasites in another randomly selected host, one at a time, at a constant rate, but independently of other parasites inside their host. This is making the assumption that a host only picks up one parasite at a time, and that the total rate at which a host's parasites generate further parasites is proportional to the host's parasite load. Each infection is equally likely to occur in each host, so that self infection is possible.

The per capita death rate of the parasites is μ and the parasite burden of the host population is given by $\boldsymbol{M}(t) = (M_1(t), ..., M_N(t))$.

The result of these assumptions is that all parasites behave independently, and in fact we have an N-type Markov branching process and in particular an N dimensional linear birth and death process. Infections occur according to a Poisson process, rate $\phi \sum_{i=1}^{N} M_i(t)$ i.e. with a rate proportional to the total number of parasites in the population.

The possible changes in the state of the system are, from $M_i(t)$ to

$$\begin{array}{lll} M_i + 1 & \text{at rate} & \dfrac{\phi}{N} \displaystyle\sum_{j=1}^{N} M_j \\ M_i - 1 & \text{at rate} & \mu M_i \end{array} \tag{5.1}$$

for $i = 1, ..., N$.

5.2.1 Model Analysis

Let

$$P(\boldsymbol{x}; t) = \mathrm{E}\left(\prod_{i=1}^{N} x_i^{M_i(t)} \right)$$

be the joint probability generating function of the $M_i(t)$s. From result (2.5) in Section 2.1, we have

$$\frac{\partial P}{\partial t} = \sum_{k=1}^{N} \frac{\partial P}{\partial x_k} \left(\mu(1 - x_k) + \frac{\phi}{N} \sum_{i=1}^{N} x_k(x_i - 1) \right). \tag{5.2}$$

The general boundary condition is $P(\mathbf{1}; t) = 1$ together with

$$P(\boldsymbol{x}; 0) = g(x_1, ...x_N) \tag{5.3}$$

where $g(\boldsymbol{x})$ is some arbitrary joint probability generating function. The auxiliary equations for the characteristics of (5.2) are

$$\frac{dx_k}{dt} = -\left(\mu(1 - x_k) + \frac{\phi}{N} \sum_{i=1}^{N} x_k(x_i - 1) \right) \quad \text{for } k = 1, ..., N. \tag{5.4}$$

Summing over k, we obtain an equation in terms of $\sigma := \sum_{i=1}^{N} x_i$,

$$\frac{d\sigma}{dt} = -N\mu + (\mu + \phi)\sigma - \frac{\phi}{N}\sigma^2. \tag{5.5}$$

The solution of this is

$$A = e^{-(\phi - \mu)t} \frac{N\mu - \phi\sigma}{\phi(N - \sigma)} \tag{5.6}$$

for $\phi \neq \mu$, where A is a constant of integration. Using this in the form

$$\sigma = \frac{N}{\phi} \left(\frac{\mu - \phi A e^{(\phi - \mu)t}}{1 - A e^{(\phi - \mu)t}} \right)$$

we can write $N - 1$ of the N equations of (5.4) as

$$\frac{dx_k}{dt} = -\mu + \mu x_k \left(\frac{A e^{(\phi - \mu)t} - \phi/\mu}{A e^{(\phi - \mu)t} - 1} \right)$$

for $k = 1, ..., N - 1$. These each solve to give

$$C_i = A e^{-\mu t}(x_i - 1) - e^{-\phi t}(x_i - \frac{\mu}{\phi}) \quad \text{for } i = 1, ..., N - 1 \tag{5.7}$$

for constants of integration C_i, so that a solution to all N of equations (5.4) can be written as

$$x_i = \frac{A e^{-\mu t} - \frac{\mu}{\phi} e^{-\phi t} + C_i}{A e^{-\mu t} - e^{-\phi t}} \quad \text{for } i = 1, ..., N - 1, \tag{5.8}$$

$$\begin{aligned} x_N &= \sigma - \sum_{i=1}^{N-1} x_i \\ &= \frac{A e^{-\mu t} - \frac{\mu}{\phi} e^{-\phi t} - \sum_{j=1}^{N-1} C_j}{A e^{-\mu t} - e^{-\phi t}}. \end{aligned} \tag{5.9}$$

The general solution of (5.2) is

$$P(\mathbf{x};t) = \Psi(C_1, ..., C_{N-1}, A) \tag{5.10}$$

for an arbitrary function Ψ. We use the boundary condition (5.3) and equations (5.8) and (5.9) evaluated at $t = 0$ to find that

$$\Psi(q_1, ..., q_{N-1}, b) = g\left(\left(\frac{b + q_1 - \frac{\mu}{\phi}}{b-1}\right), ..., \left(\frac{b + q_{N-1} - \frac{\mu}{\phi}}{b-1}\right), \left(\frac{b - \sum_{j=1}^{N-1} q_j - \frac{\mu}{\phi}}{b-1}\right)\right)$$

so that, substituting the constants from (5.6) and (5.7) into this we have

$$P(\mathbf{x};t) \;=\; g(y_1, .., y_N)$$

where

$$y_i = \frac{\left(\mu(e^{-\phi t} - 1) + \phi(e^{-(\phi-\mu)t} - e^{-\phi t})\right)\sum_{j=1}^{N} x_j - N\left(\mu(e^{-(\phi-\mu)t} - 1) + e^{-\phi t}(\mu - \phi)x_i\right)}{\phi(e^{-(\phi-\mu)t} - 1)\sum_{j=1}^{N} x_j + N(\phi - \mu e^{-(\phi-\mu)t})}.$$

With the particular set of initial conditions $P(\boldsymbol{x};0) = \prod_{j=1}^{N} a_j^{x_j}$ corresponding to fixed initial levels for each M_i, Adke (1964) has arrived at this result by using a slightly different route to solving (5.2), and incorporating immigration into the process. The application there was a study of the change in numbers of various genotypes in a population, extending work done by Mode (1962). Note the different parameterisation; ϕ was written in the form λN so the assumption used is analogous in our application to hosts mixing in a fixed area, so that the infection rate increases with host population size. We have chosen infections to occur at a rate $(\phi/N)\sum_i M_i(t)$ rather than $\phi\sum_i M_i(t)$ so that hosts come into contact with potential infections at a constant rate, regardless of the host population size. The hosts can be considered as having a fixed density, which is analogous to a mass action assumption rather than pseudo mass action. For further discussion on this subject see De Jong, Diekmann, and Heesterbeek (1995).

Of course, with $N = 1$, the process reduces to a classical birth and death process (Kendall, 1948), and results simplify correspondingly.

5.2.2 Model Results

We consider some of the many results that may be derived from the joint probability generating function to illustrate some properties of the parasite population. Qualitative results are given under the assumption that $\phi > \mu$ so that the mean of the parasite population is growing.

The marginal probability generating function for the number of parasites in an arbitrary host, $M_i(t)$, is

$$R_i(x_i;t) \;:=\; P(1,...,x_i,...,1;t)$$

and the mean of $M_i(t)$ is

$$\mathrm{E}(M_i(t)) \;=\; \bar{a}e^{(\phi-\mu)t} + (\bar{a}_i - \bar{a})e^{-\mu t} \tag{5.11}$$

where $\bar{a}_i = \mathrm{E}(M_i(0))$ and $\bar{a} = (1/N)\sum_{j=1}^{N}\mathrm{E}(M_j(0))$ are respectively the initial mean of host i and the average initial mean over the whole host population . The second term in (5.11) represents the decay of the host's mean parasite level from above or below the population mean, so that if host i starts with the average number of parasites in the population, then its mean follows the usual exponential growth $\bar{a}e^{(\phi-\mu)t}$. An uninfected host (i say, with $\bar{a}_i = 0$) placed into an infected environment will have mean $\tilde{a}(e^{(\phi-\mu)t} - e^{\mu t})$ where $\tilde{a} = (1/(N-1))\sum_{j\neq i}\mathrm{E}(M_j(t))$ is the mean in the population excluding host i.

For other results we need to be more specific about the initial conditions. We first assume the boundary conditions

$$P(\boldsymbol{x};0) \;= g(x_1,...,x_N) = \;\prod_{i=1}^{N} e^{\bar{a}_i(x_i-1)} \tag{5.12}$$

so that initially host parasite levels follow independent Poisson distributions with $\bar{a}_i$ the mean of host i. A consequence of this is that all M_i have an initial index of dispersion of one so there is no initial overdispersion. The marginal probability generating function for an arbitrary $M_i(t)$ is then

$$R_i(x_i;t) \;=\; \exp\left\{u_i\bar{a}_i + v_i\sum_{j\neq i}\bar{a}_j\right\} \tag{5.13}$$

where $v_i = y_j - 1$ and $u_i = y_i - 1$, both evaluated at $x_k = 1 \; \forall \; k \neq i$, and where $j \neq i$, so that

$$\begin{aligned} v_i &= \frac{(x_i - 1)(\phi - \mu)(1 - e^{-\phi t})}{\phi(x_i - 1)(e^{-(\phi-\mu)t} - 1) + N(\phi - \mu)e^{-(\phi-\mu)t}} \\ u_i &= \frac{(x_i - 1)(\phi - \mu)(1 + (N-1)e^{-\phi t})}{\phi(x_i - 1)(e^{-(\phi-\mu)t} - 1) + N(\phi - \mu)e^{-(\phi-\mu)t}}. \end{aligned}$$

If $\bar{a}_i = \bar{a}$ we find that the variance is

$$\mathrm{Var}(M_i(t)) = \frac{\bar{a}}{N(\phi - \mu)} \left((2\phi + N(\phi - \mu))e^{(\phi-\mu)t} + 2\phi e^{2(\phi-\mu)t} \right) \quad (5.14)$$

so that the index of dispersion is

$$\begin{aligned} \mathrm{I}(M_i(t)) &:= \mathrm{Var}(M_i(t))/\mathrm{E}(M_i(t)) & (5.15) \\ &= 1 + \frac{2\phi}{N(\phi - \mu)}(1 + e^{(\phi-\mu)t}). & (5.16) \end{aligned}$$

Notice that this result is invariant to the initial mean mean, $\bar{a}$. This index of dispersion is always greater than 1 for $t > 0$, so the parasite level will always be overdispersed. We see that the overdispersion grows at the same rate as the mean, $\phi - \mu$. The larger the host population size, the less the parasites are overdispersed as any large deviations from the mean will feed back on themselves more noticeably in smaller populations, the extreme case being just one host reinfecting itself. In the limit, for finite t,

$$\lim_{N \to \infty} \mathrm{I}(M_i(t)) = 1,$$

i.e. the limiting case as the host population size increases provides no overdispersion at all.

If we consider just the marginal probability generating function of $M_i(t)$, given in (5.13), and take the limit as $N \to \infty$ whilst keeping the average initial mean in all other hosts ($\tilde{a}$) fixed (so we write $\sum_{k \neq i} a_k = (N-1)\tilde{a}$), we find

$$\lim_{N \to \infty} R_i(x; t) = \exp\left\{ (x - 1) \left(\bar{a}e^{(\phi-\mu)t} + (a_i - \bar{a})e^{-\mu t} \right) \right\} \quad (5.17)$$

where $\bar{a}$ and $\tilde{a}$ are now equivalent due to the infinite host population size. By the continuity theorem we see that $M_i(t)$ tends to a Poisson distribution with mean

given by (5.11). This result is a consequence of $M_i(t)$ being made up from those initial parasites in host i that have survived to t, together with a contribution from the superposition of an infinite number of independent marked point processes. To see this, consider the contributions made by all ancestors of the initial parasites in each host to the parasite load of the arbitrary host i (at an arbitrary time). By the branching property, these processes will all be independent of each other, and can be considered as independent marked point process, with the marks representing types of events, namely parasite deaths and births into each host. Thus we can view the parasite load in an arbitrary host as the superposition of independent marked point process, the number of processes tending to infinity as $N \to \infty$.

If we consider the limit of $R_i(x;t)$ as $N \to \infty$ in the separate case where the initial conditions are

$$P(\boldsymbol{x};0) = \prod_{j=1}^{N} a_j^{x_j} \tag{5.18}$$

corresponding to host j having a fixed level of initial parasites, a_j, then we obtain

$$\lim_{N\to\infty} R_i(x;t) \;=\; \exp\left\{(x-1)\tilde{a}(e^{(\phi-\mu)t} - e^{-\mu t})\right\}\left(xe^{-\mu t} + 1 - e^{-\mu t}\right)^{a_i} \tag{5.19}$$

so that the marginal distribution becomes the sum of a Poisson and a binomial distribution. Whereas with initial Poisson distributions (5.12) the number of surviving initial parasites in host i follows a Poisson distribution that is thinned by parasite deaths (providing another Poisson distribution), with fixed initial levels the decay of parasites in host i provides a binomial distribution with each initial parasite having probability $e^{-\mu t}$ of surviving.

The mean of the Poisson part in (5.19), also present in (5.17), comes from the exponential growth term, $\bar{a}e^{(\phi-\mu)t}$ together with the decay in the immigration of offspring from initial parasites in the other hosts, $\bar{a}e^{-\mu t}$. The initial parasites in host i effectively never contribute any parasites back into the host due to the infinite host population size.

If we take $a_i = 0$ in initial conditions (5.18) so that we consider a host initially parasite free but placed into an infected population, the variance is

$$\mathrm{Var}(M_i(t)) = \frac{\sum_{j\neq i} a_j\,(e^{\phi t}-1)}{e^{2\mu t}N(\mu-\phi)}\left(e^{\mu t}(N(\mu-\phi)+2\phi)) - e^{\phi t}(\phi+\mu)+\mu-\phi\right)$$

so that the index of dispersion is

$$\mathrm{I}(M_i(t)) = 1+\frac{1}{N(\phi-\mu)}\left((\phi+\mu)e^{(\phi-\mu)t}+(\phi-\mu)e^{-\mu t}-2\phi\right) \qquad (5.20)$$

which again does not involve the initial parasite levels of the other hosts. This is of course only defined for $t > 0$ as the initial mean is zero, however the limit as $t \to 0$ from above is 1. Again the parasite level will always be overdispersed, and for finite t, $\lim_{N\to\infty} \mathrm{I}(M_i(t)) = 1$, which of course follows from $M_i(t)$ being purely Poisson (5.19 with no binomial part as $a_i = 0$).

If all hosts start with an identical number of parasites, a, we have $a_i = \tilde{a} = a$ and then the variance of $M_i(t)$ is

$$\mathrm{Var}(M_i(t)) = \frac{a}{N}\left(\frac{\phi+\mu}{\phi-\mu}e^{2(\phi-\mu)t}+\left(N-\frac{2\phi}{\phi-\mu}\right)e^{(\phi-\mu)t}-(N-1)e^{-2\mu t}\right) \qquad (5.21)$$

and the index of dispersion is

$$\mathrm{I}(M_i(t)) = 1+\frac{1}{N(\phi-\mu)}\left((\phi+\mu)e^{(\phi-\mu)t}-(N-1)(\phi-\mu)e^{-(\phi+\mu)t}-2\phi\right) \qquad (5.22)$$

which again does not involve the initial parasite levels. We have $\lim_{N\to\infty} \mathrm{I}(M_i(t)) = 1 - e^{-(\phi-\mu)t}$ so that in time the dispersion tends towards 1 from below. This initial underdispersion is simply a consequence of the initial variance being set at 0 in (5.18), whilst the initial mean is nonzero. Notice that this result is (5.20) with $e^{-(\phi+\mu)t}$ subtracted. This difference decays to zero with time as it is the change in index of dispersion from adding the nonzero number of parasites to host i at $t = 0$ (by setting $M_i(0) = a$).

The coefficient of variation,

$$\mathrm{CV}(M_i(t)) := \sqrt{\mathrm{Var}(M_i(t))}/\mathrm{E}(M_i(t)) = \sqrt{\mathrm{I}(M_i(t))/\mathrm{E}(M_i(t))}$$

may be considered as a more useful measure of variation in the population as it is dimensionless, but it is not as easily used by ecologists to determine the extent of overdispersion in a parasite population. However if the coefficient of variation is greater than or equal to one, we know that the index of dispersion is an increasing function in the mean. Using (5.22), we find

$$(\mathrm{CV}(M_i(t)))^2 = e^{(\mu-\phi)t} + \frac{1}{N(\phi-\mu)}\left((\phi+\mu) - (N-1)(\phi-\mu)e^{-\phi t} - 2\phi e^{(\mu-\phi)t}\right).$$

If $\phi > \mu$ (so the mean is growing) all exponents in this expression are non positive so that the coefficient of variation does not grow indefinitely, unlike the index of dispersion, and is in fact likely to decay.

In reality, there will be many factors preventing the indefinite growth of the mean of the parasite loads that this model provides. This model is useful, however, as it shows us that even with homogenous mixing in identical hosts, and parasites entering hosts one at a time, the index of dispersion grows at the same rate as the mean, $\phi - \mu$. The conclusion we can draw from this model is that this type of demographic stochasticity alone can cause overdispersion in a parasite population, with the degree of overdispersion growing at the same rate as the mean. The effect, however can be ignored in large host populations.

We do not study the prevalence and extinction probabilities of this model as it is designed to compare the growth of dispersion under certain transmission mechanisms and does not claim to represent the true transmission process. The models discussed in the following sections do not allow prevalence and extinction to be easily calculated so no comparison is possible. However a comparison of extinction probabilities will be made when heterogeneous host susceptibilities are added to this model in Section 5.4.2.

5.2.3 Branching Model with Clustered Reproduction

The model considered above was a multitype Markov branching process with all offspring distributions identically one. We now briefly consider the moments of this

branching model with a general offspring distribution C, where C has probability generating function $= h(x) := \mathrm{E}(x^C) = \sum_{c=0}^{\infty} h_c x^c$ and mean and variance $\mathrm{E}(C) = \theta$ and $\mathrm{Var}(C) = \sigma^2$. We term this clustered parasite reproduction as in general a parasite produces more than one offspring at any infection point. The transitions are from $\boldsymbol{M}(t)$ to

$$\begin{aligned} M_i + c \quad & \text{at rate} \quad \frac{\phi}{N} h_c \sum_{j=1}^{N} M_j \quad \text{for } c = 0, 1, ... \\ M_i - 1 \quad & \text{at rate} \quad \mu M_i \end{aligned} \tag{5.23}$$

for $i = 1, ..., N$. The moment equations satisfy

$$\frac{d\mathrm{E}(M_i(t))}{dt} = \frac{\phi\theta}{N} \sum_{j=1}^{N} \mathrm{E}(M_j(t)) - \mu \mathrm{E}(M_i(t)) \tag{5.24}$$

$$\begin{aligned} \frac{d\mathrm{E}(M_i(t)^2)}{dt} = {} & \mu \mathrm{E}(M_i(t)) - 2\mu \mathrm{E}(M_i(t)^2) + \frac{\phi(\sigma^2 + \theta^2))}{N} \sum_{j=1}^{N} \mathrm{E}(M_j(t)) + \\ & \frac{2\phi\theta}{N} \sum_{j=1}^{N} \mathrm{E}(M_i(t) M_j(t)) \end{aligned} \tag{5.25}$$

$$\begin{aligned} \frac{d\mathrm{E}(M_i(t) M_j(t))}{dt} = {} & \frac{\phi\theta}{N} \sum_{k=1}^{N} \{\mathrm{E}(M_i(t) M_k(t)) + \mathrm{E}(M_j(t) M_k(t))\} - \\ & 2\mu \mathrm{E}(M_i(t) M_j(t)) \end{aligned} \tag{5.26}$$

for $i \neq j$. The initial conditions we use are $\mathrm{E}(M_i(0)) = a$, $\mathrm{E}(M_i^2(0)) = \beta$ for $i = 1, ..., N$ and $\mathrm{E}(M_i(0) M_j(0)) = \gamma$ for $i \neq j$. If the initial distributions are independent then $\gamma = a^2$. As we have made all the hosts' moments identical at $t = 0$ they will evolve identically and we can use symmetry in equations (5.27), (5.28) and (5.29), i.e. $\mathrm{E}(M_i(t) M_k(t)) = \mathrm{E}(M_i(t) M_j(t))$ for all $j, k \neq i$, $\mathrm{E}(M_i(t)^2) = \mathrm{E}(M_j(t)^2)$ and $\mathrm{E}(M_i(t)) = \mathrm{E}(M_j(t))$ for all $i, j, = 1, ..., N$. The moment equations then become

$$\frac{d\mathrm{E}(M_i(t))}{dt} = (\phi\theta - \mu)\mathrm{E}(M_i(t)) \tag{5.27}$$

$$\begin{aligned} \frac{d\mathrm{E}(M_i(t)^2)}{dt} = {} & (\mu + \phi(\sigma^2 + \theta^2))\mathrm{E}(M_i(t)) + \left(\frac{2\phi\theta}{N} - 2\mu\right) \mathrm{E}(M_i(t)^2) + \\ & 2\phi\theta \frac{N-1}{N} \mathrm{E}(M_i(t) M_j(t)) \end{aligned} \tag{5.28}$$

$$\frac{d\mathrm{E}(M_i(t) M_j(t))}{dt} = \frac{2\phi\theta}{N} \mathrm{E}(M_i(t)^2) + 2\left(\phi\theta \frac{N-1}{N} - \mu\right) \mathrm{E}(M_i(t) M_j(t)). \tag{5.29}$$

Using the notation $\lambda = \phi\theta$ and $\delta = \phi(\sigma^2 + \theta^2)$, the solutions are

$$\begin{aligned}
\mathrm{E}(M_i(t)) &= ae^{(\lambda-\mu)t} \\
\mathrm{E}(M_i(t)^2) &= \frac{a}{N}\frac{\delta+\mu}{\lambda+\mu}\left(\left(\frac{2\lambda}{\mu-\lambda}+N\right)e^{(\lambda-\mu)t} - (N-1)e^{-2\mu t}\right) + \\
&\quad \left(\frac{a(\delta+\mu)}{N(\lambda-\mu)} + \gamma + \frac{\beta-\gamma}{N}\right)e^{2(\lambda-\mu)t} + \frac{(1-N)(\gamma-\beta)}{N}e^{-2\mu t} \\
\mathrm{E}(M_i(t)M_j(t)) &= \frac{a}{N}\frac{\delta+\mu}{\lambda+\mu}\left(\frac{2\lambda}{\mu-\lambda}e^{(\lambda-\mu)t} + e^{-2\mu t}\right) + \\
&\quad \left(\frac{a}{N}\frac{\delta+\mu}{\lambda-\mu} + \gamma + \frac{\beta-\gamma}{N}\right)e^{2(\lambda-\mu)t} + \frac{\gamma-\beta}{N}e^{-2\mu t}
\end{aligned}$$

so that if the initial loads are independent Poisson variables, then $\beta = a(a+1)$, $\gamma = a^2$ and the index of dispersion is

$$\mathrm{I}(M_i(t)) = \frac{1}{N}\frac{\delta+\mu}{\lambda+\mu}\left(\frac{2\lambda}{\mu-\lambda}+N\right) + \frac{\delta+\lambda}{N(\lambda-\mu)}e^{(\lambda-\mu)t} - \frac{(N-1)}{N}\frac{\delta-\lambda}{\lambda+\mu}e^{-(\lambda+\mu)t}.$$

We then have

$$\lim_{N\to\infty} \mathrm{I}(M_i(t)) = 1 + \left(\frac{\phi(\sigma^2+\theta^2-\theta)}{\phi\theta+\mu}\right)(1-e^{-(\lambda+\mu)t})$$

so that the dispersion grows from 1 to a maximum level of $(\delta+\mu)/(\lambda+\mu)$ as $t \to \infty$. If clusters are identically of size one (i.e. $C \equiv 1$ *a.s.*) so that $\sigma = 0$ and $\theta = 1$, then $\delta = \lambda$ and of course we obtain the results of the simple branching model.

It is interesting to note that if $\beta = \gamma = a^2$ so that all hosts start with a fixed level of a parasites, then the variance is

$$\mathrm{Var}(M_i(t)) = \frac{a}{N}\frac{\delta+\mu}{\lambda+\mu}\left(\frac{\lambda+\mu}{\lambda-\mu}e^{2(\lambda-\mu)t} + \frac{N(\lambda-\mu)-2\lambda}{\lambda-\mu}e^{(\lambda-\mu)t} - (N-1)e^{-2\mu t}\right) \tag{5.30}$$

and hence (compare with (5.21)) incorporating parasite offspring clusters into the simple branching model whilst maintaning the same mean simply multiplies the variance, and hence the index of dispersion, by a factor of

$$\frac{\delta+\mu}{\lambda+\mu} = \frac{\phi(\sigma^2+\theta^2)+\mu}{\phi\theta+\mu}.$$

We see that the clustered reproduction together with demographic stochasticity is able to produce overdispersion even in large host populations. It does not increase the rate of growth of overdispersion but has what we shall term a scaling effect, so that in (infinitely) large host populations the index of dispersion reaches an equilibrium, despite an exponentially growing mean.

5.3 Parasite Proliferation Dependence

As discussed in the introduction to this chapter, we model the transmission process by considering the parasites ingested by a host at any one time as all being the offspring of parasites in only one other host. This way the number of parasites a receiving host gains at an infection point is related to the load of the giving host, but no other hosts.

In the branching model of the previous section each infection point resulted in just one parasite from the giving host transmitting offspring to the receiving host. In this section we assume every parasite in a host must pass on its offspring at times identical to those of all other parasites in the same host i.e. at infection points. This assumption can be considered as a form of mixing of offspring within the host and gives the parasite proliferation dependence introduced in Section 5.1. We still do not allow mixing of offspring from different hosts.

Essentially we consider the hosts with higher loads, not as transmitting more often, as is the case in simple model outlined above, but as transmitting larger numbers of parasites. We now have the transmission rates between hosts fixed (they depended on the giving host's load in the branching model), but the number of parasites transmitted depending on the giving host's load.

Contacts between hosts, or infection points as we alternatively call them, occur according to a Poisson process of rate $N\phi$, with giving and receiving hosts being equally likely to be any of the N hosts. (Again, a particular host could be both the giving and receiving host, so that self infection is possible). As a result each host

individually picks up infections at rate ϕ, and so receives a transmission of parasites from a *particular* host at rate ϕ/N. We write the probability that a host with i parasites transmits j parasites at an infection point as $F(i,j)$. The transitions are from $\boldsymbol{M}$(t) to

$$M_i + c \quad \text{at rate} \quad \frac{\phi}{N}\sum_{j=1}^{N} F(M_j, c) \quad \text{for } c = 0, 1, ... \tag{5.31}$$

$$M_i - 1 \quad \text{at rate} \quad \mu M_i \tag{5.32}$$

for $i = 1, ..., N$.

These assumptions made about the transmission of parasites are similar to those used by Barbour (Barbour and Kafetzaki, 1993; Barbour, Heesterbeek, and Luchsinger, 1996). The main difference is that Barbour's model does not allow currently infected hosts to acquire parasites, an assumption made to represent the host's immune system. Here we obtain explicit solutions for the moments of the parasite load in each host.

Let $f(i)$ be a random variable with probabilities $\mathrm{P}(f(i) = j) = F(i,j)$ so that upon each contact made, the number of parasites transmitted is $f(M_i(t))$ if $M_i(t)$ is the load of the giving host.

The moments of the process can be shown to follow the system of equations

$$\frac{d\mathrm{E}(M_i(t)}{dt} = \frac{\phi}{N}\sum_{j=1}^{N}\mathrm{E}(f(M_j(t)) - \mu\mathrm{E}(M_i(t)) \tag{5.33}$$

$$\begin{aligned}\frac{d\mathrm{E}(M_i(t)^2)}{dt} &= \mu\mathrm{E}(M_i(t)) - 2\mu\mathrm{E}(M_i(t)^2) + \\ &\quad 2\frac{\phi}{N}\sum_{j=1}^{N}\mathrm{E}(M_i f(M_j(t))) + \frac{\phi}{N}\sum_{j=1}^{N}\mathrm{E}((f(M_j(t)))^2)\end{aligned} \tag{5.34}$$

$$\begin{aligned}\frac{d\mathrm{E}(M_i(t)M_j(t))}{dt} &= -2\mu\mathrm{E}(M_i M_j(t)) + \frac{\phi}{N}\sum_{k=1}^{N}\mathrm{E}(M_j(t)f(M_k(t))) \\ &\quad + \frac{\phi}{N}\sum_{k=1}^{N}\mathrm{E}(M_i(t)f(M_k(t))).\end{aligned} \tag{5.35}$$

The initial conditions we use are $\mathrm{E}(M_i(0)) = a$, $\mathrm{E}(M_i^2(0)) = \beta$ for $i = 1, ..., N$ and $\mathrm{E}(M_i(0)M_j(0)) = \gamma$ for $i \neq j$, so that, as in Section 5.2.3, we are able to use

symmetry in equations (5.33), (5.34) and (5.35). These equations thus simplify to

$$\frac{d\mathrm{E}(M_i(t))}{dt} = \phi\mathrm{E}(f(M_i(t)) - \mu\mathrm{E}(M_i(t)) \tag{5.36}$$

$$\frac{d\mathrm{E}(M_i(t)^2)}{dt} = \mu\mathrm{E}(M_i(t)) - 2\mu\mathrm{E}(M_i(t)^2) + 2\frac{\phi}{N}\mathrm{E}(M_i(t)f(M_i(t))) + 2\phi\frac{N-1}{N}\mathrm{E}(M_i(t)f(M_j(t))) + \phi\mathrm{E}(f(M_i(t))^2) \tag{5.37}$$

$$\frac{d\mathrm{E}(M_i(t)M_j(t))}{dt} = -2\mu\mathrm{E}(M_i(t)M_j(t)) + 2\frac{\phi(N-1)}{N}\mathrm{E}(M_i(t)f(M_j(t))) + 2\frac{\phi}{N}\mathrm{E}(M_i(t)f(M_i(t))) \tag{5.38}$$

for arbitrary i and j, and where $i \neq j$.

The next simplifying assumption is to let

$$F(i,j) = \mathrm{P}(\sum_{k=1}^{i} A_k = j) \tag{5.39}$$

or, in other notation,

$$f(X) = \sum_{i=1}^{X} A_i,$$

where A_i are all i.i.d. copies of a random variable A. This essentially means that upon each contact the number of offspring transmitted by each parasite is independent of all other parasites and drawn from the random variable A. However, the parasites in a host still have to transmit to another host at identical times, so we do not have a branching process as in Section 5.2, in which there was no parasite proliferation dependence. This assumption about the independence of offspring levels from each parasite inside the giving host is also made in the Barbour model (Barbour and Kafetzaki, 1993).

It is likely that in reality there will be some saturation in the number of parasites that can be transmitted at one infection point, and $f(X)$ will be a complicated mapping from the random variable X to a further random variable. Even if $f(X)$ is assumed to be a constant conditional on the value of X, a nonlinear form would probably be desirable and so equations (5.36), (5.37) and (5.38) are not likely to be closed due to terms such as $\mathrm{E}(M_i(t)f(M_i(t)))$. Other methods of analysis (such as approximations) are then needed. We do not investigate these here.

Writing $\mathrm{E}(A) = \theta$ and $\mathrm{Var}(A) = \sigma^2$, we have

$$\begin{aligned}
\mathrm{E}(f(X)) &= \theta\mathrm{E}(X) \\
\mathrm{E}(f(X)^2) &= \theta^2\mathrm{E}(X^2) + \sigma^2\mathrm{E}(X) \\
\mathrm{E}(Xf(Y)) &= \theta\mathrm{E}(XY).
\end{aligned}$$

For notational ease we write $\lambda = \phi\theta$ as the average rate of reproduction of each parasite.

Equations (5.36), (5.37) and (5.38) become

$$\frac{d\mathrm{E}(M_i(t))}{dt} = (\lambda - \mu)\mathrm{E}(M_i(t)) \tag{5.40}$$

$$\begin{aligned}
\frac{d\mathrm{E}(M_i(t)^2)}{dt} &= (\mu + \phi\sigma^2)\mathrm{E}(M_i(t)) + \left(\frac{2\lambda}{N} + \lambda\theta - 2\mu\right)\mathrm{E}(M_i(t)^2) + \\
&\quad 2\lambda\frac{N-1}{N}\mathrm{E}(M_i(t)M_j(t))
\end{aligned} \tag{5.41}$$

$$\frac{d\mathrm{E}(M_i(t)M_j(t))}{dt} = \frac{2\lambda}{N}\mathrm{E}(M_i(t)^2) + 2\left(\lambda\frac{N-1}{N} - \mu\right)\mathrm{E}(M_i(t)M_j(t)). \tag{5.42}$$

The mean of the process behaves in the conventional exponential growth manner, but it is interesting to study how the index of dispersion grows.

Notice the similarity of this system to equations (5.27),(5.28) and (5.29) for the branching model with clusters (transitions given by (5.23)). The only change is the term in the differential of $\mathrm{E}(M_i(t)^2)$ which is $\lambda\theta\mathrm{E}(M_i(t))$ in the branching model (see 5.28) and becomes $\lambda\theta\mathrm{E}(M_i(t)^2)$ in (5.41). As $\mathrm{E}(M_i(t)^2) > \mathrm{E}(M_i(t))$ (for $t > 0$) we can immediately see that as the mean grows, the variance, and hence the index of dispersion, grows faster when parasite proliferation dependence is present.

If we write the linear system (5.40), (5.41) and (5.42) as

$$\dot{\mathbf{Y}} = A\mathbf{Y}$$

with

$$\mathbf{Y} = (\mathrm{E}(M_i(t)) \quad \mathrm{E}(M_i(t)^2) \quad \mathrm{E}(M_i(t)M_j(t)))'$$

then we have

$$A = \begin{pmatrix} \lambda - \mu & 0 & 0 \\ \mu + \phi\sigma^2 & 2(\lambda/N - \mu) + \lambda\theta & 2\lambda(N-1)/N \\ 0 & 2\lambda/N & 2(\lambda(N-1)/N - \mu) \end{pmatrix}$$

The eigenvalues of this matrix are

$$\begin{aligned} \alpha_1 &= \lambda - \mu \\ \alpha_2 &= \lambda + \lambda\theta/2 - 2\mu + \lambda\sqrt{1 + \theta(\theta/4 + 2/N - 1)} \\ \alpha_3 &= \lambda + \lambda\theta/2 - 2\mu - \lambda\sqrt{1 + \theta(\theta/4 + 2/N - 1)} \end{aligned} \tag{5.43}$$

and the solution of (5.40), (5.41) and (5.42) with the initial conditions is given by

$$\mathrm{E}(M(t)) = ae^{(\lambda-\mu)t} \tag{5.44}$$

$$\begin{aligned} \mathrm{E}(M(t)^2) = {} & k_2 e^{(\lambda-\mu)t} + \\ & \frac{1}{Q}\left(\frac{\beta - k_2}{2}(\lambda(\theta - 2 + 4/N) + Q) + 2\lambda(\gamma - k_1)(N-1)/N\right) e^{\alpha_2 t} - \\ & \frac{1}{Q}\left(\frac{\beta - k_2}{2}(\lambda(\theta - 2 + 4/N) - Q) + 2\lambda(\gamma - k_1)(N-1)/N\right) e^{\alpha_3 t} \end{aligned} \tag{5.45}$$

$$\begin{aligned} \mathrm{E}(M_i(t)M_j(t)) = {} & k_1 e^{(\lambda-\mu)t} + \\ & \frac{1}{Q}\left(\frac{\gamma - k_1}{2}(Q - \lambda(\theta - 2 + 4/N)) + 2\lambda(\beta - k_2)/N\right) e^{\alpha_2 t} + \\ & \frac{1}{Q}\left(\frac{\gamma - k_1}{2}(Q + \lambda(\theta - 2 + 4/N)) - 2\lambda(\beta - k_2)/N\right) e^{\alpha_3 t} \end{aligned}$$

where

$$\begin{aligned} Q &= 2\lambda\sqrt{1 + \theta(\theta/4 + 2/N - 1)} \\ k_1 &= \frac{2a\lambda(\mu + \phi\sigma^2)}{(N(\mu - \lambda) + 2\lambda)(\lambda + \mu - 2\lambda/N - \lambda\theta) - 4\lambda^2(N-1)/N} \\ k_2 &= k_1\left(1 + \frac{N(\mu - \lambda)}{2\lambda}\right). \end{aligned}$$

It is interesting to note that the variance of the offspring distribution for each parasite, σ^2, only affects the variability of the parasite load levels through the

coefficients of the exponentials, it does not come into the exponents themselves. This shows that it is more of a scaling factor than a growth parameter, and is less important than the structure of the transmission process to the growth of variability.

The index of dispersion of $M_i(t)$ is $\mathrm{I}(M_i(t)) = \mathrm{E}(M_i(t)^2)/\mathrm{E}(M_i(t)) - \mathrm{E}(M_i(t))$, so we can see that the dominant exponent in $\mathrm{I}(M_i(t))$ is $(\alpha_2 - \lambda + \mu)t = \xi t$ say. From (5.43) we have

$$\xi = \frac{1}{2}\lambda\left(\theta + \sqrt{(\theta-2)^2 + 8\theta/N}\right) - \mu. \tag{5.46}$$

The comparison with the branching model without clustered reproduction (transition probabilities given by (5.1)) can be made by setting $\theta = 1$ (and $\sigma^2 = 0$, though this makes no difference to ξ). This shows the effect of the dependence in parasite proliferation alone by taking out the effect of parasites reproducing more than one parasite at a time (clustered reproduction). If $\theta = 1$ then $\xi = \frac{1}{2}\phi\left(1 + \sqrt{1 + 8/N}\right) - \mu$. Comparing this with the corresponding value $\phi - \mu$ for the branching model of Section 5.2 (see (5.22)), we see that the model with proliferation dependence always has larger ξ by an amount $\frac{1}{2}\phi\left(\sqrt{1 + 8/N} - 1\right)$. This difference will be more marked for higher values of ϕ, (faster rate of infections points) but will decrease as N, the host population size, increases. In the limit as $N \to \infty$, the two models have equal values of ξ. (Note from (5.44) and (5.45) that the coefficient of $e^{\xi t}$ is always positive and tends to a constant as $N \to \infty$. If $\theta = 2$ then in the limit as $N \to \infty$, A has repeated eigenvalues, which we do not consider further.)

We can conclude that for large host populations, *and in the absence of parasite offspring clumps*, the effect of parasite proliferation dependence on the growth rate of the index of dispersion can be ignored.

We found in Section 5.2 that the effect of the parasites transmitting in clusters when there was no parasite proliferation dependence was to multiply the index of dispersion by a scaling factor that increased as both the mean and variance of the

cluster size increased. The effect remained in large host populations.

We now investigate the effect of the parasites transmitting in clusters *in the presence of parasite proliferation dependence* by considering two versions of the model described in this section. Let model C have parameters $\phi = \phi_c$ and $\theta = \theta_c$ as described above, so that $\lambda = \phi_c\theta_c$. Consider another model, model T, in which exactly one offspring is produced by each parasite in a host at infection times. Let $\phi = \lambda = \phi_c\theta_c$ and $\theta = 1$ for model T, so that both models provide the same mean levels. In words, parasites in model T transmit one parasite at frequent intervals, while in model C parasites transmit in larger clumps, but less often (assuming $\theta_c > 1$). We have

$$\begin{aligned} \xi_C &= \frac{1}{2}\lambda\left(\theta_c + \sqrt{(\theta_c - 2)^2 + 8\theta_c/N)}\right) - \mu \\ \xi_T &= \frac{1}{2}\lambda\left(1 + \sqrt{1 + 8/N}\right) - \mu. \end{aligned}$$

The difference between the dominant exponent of each model is

$$\Delta := \xi_C - \xi_T = \frac{1}{2}\phi_c\theta_c\left(\theta_c - 1 + \sqrt{\theta_c(\theta_c - 4 + 8/N) + 4} - \sqrt{1 + 8/N}\right)$$

which is strictly positive if $\theta_c > 1$. We have that Δ is a decreasing function in N so that the clustered parasite reproduction effect of increasing the growth rate of the index of dispersion (in the presence of parasite proliferation dependence) reduces as the population size increases.

If $\theta_c < 1$ then $\xi_T > \xi_C$ so that the model T has the larger dominant growth rate in dispersion. This is because θ_c is the mean of the distribution of offspring each parasite in a host produces at an infection time, and if θ_c is less than 1 we have the reverse of the situation described above, with model T resulting in more parasites transfered less often (as $\phi_T = \theta_c\phi_c < \phi_c$). Notice that Δ does not include μ.

We have the following results for large populations;

- If $0 < \theta_c < 1$ then $\Delta \in [\lambda(\theta - 1), 0)$ so that $\Delta \to 0$ from below as $N \to \infty$

- If $1 < \theta_c < 2$ then $\Delta \in [0, \lambda(\theta - 1))$ so that $\Delta \to 0$ from above as $N \to \infty$

- If $\theta_c > 2$ then $\Delta \in [\lambda(\theta - 1), \lambda(\theta - 2))$ so that $\Delta \to \phi_c \theta_c (\theta_c - 2)$ from above.

In summary, when comparing two models having equivalent parasite load means, one with parasite offspring clusters with mean θ, the other with a single offspring transmitted from each parasite (no clusters), the highest, dominant growth rate in dispersion, ξ, satisfies the following as host populations become large;

$0 < \theta_c < 1$	Model without offspring clusters (T) has higher ξ
	- the two models becoming equal as $N \to \infty$
$1 < \theta_c < 2$	Model with offspring clusters (C) has higher ξ
	- the two models becoming equal as $N \to \infty$
$\theta_c \geq 2$	Model with offspring clusters (C) has higher ξ
	- difference tends to $\phi_c \theta_c (\theta_c - 2)$ from above as $N \to \infty$.

We can conclude that for large populations, and when we already have parasite proliferation dependence, the effect of parasites producing more than one offspring at any infection point on the growth of the index of dispersion can be ignored if the mean of each offspring clump is less than two. However, for higher values of θ the effect could be quite significant, even in large populations.

As we have not included any larval parasitic stage in these models, the offspring from a parasite is only the number of *succesfully transmitting* parasites. Imagine the scenario in which mature parasites produce high numbers of offspring, but very

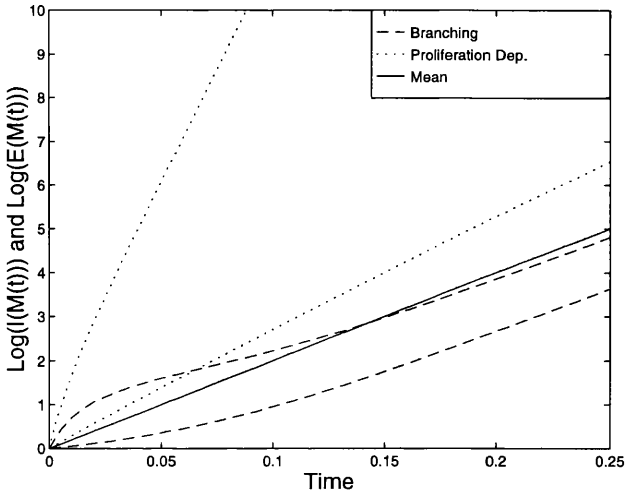

Figure 5.1: Log Index of Dispersion of $M(t)$ for Four Transmission Processes, $N = 10$

few become mature worms after entering the receiving host. In such cases it is quite possible to imagine having $\theta < 2$, but $\sigma > 1$. Notice that it is the transfer of offspring from each parasite *at identical times* that produces the higher growth rate of index of dispersion, not the variabilities in the number of offspring each parasite produces. The clump size could be a constant with no random variation ($\sigma = 0$) and we would obtain the same results concerning the growth of the rate of $I(M_i(t))$.

We can see that clustered reproduction has a greater effect when combined with parasite proliferation dependence. In the branching model it was merely a scaling type effect, whilst here it increases the growth rate of the overdipersion.

Figures 5.2 and 5.1 on the following page show a comparison of the log indices of dispersion of the load of an arbitrary host. Plots are given for the two transmission mechanisms, each with and without clustered reproduction, for populations of different sizes. For each of the two transmission mechanisms, the process with clustered reproduction is the higher of the two lines. All the plots tend to fixed slopes eventually, giving the dominant, underlying growth rate of the indices of dispersion.

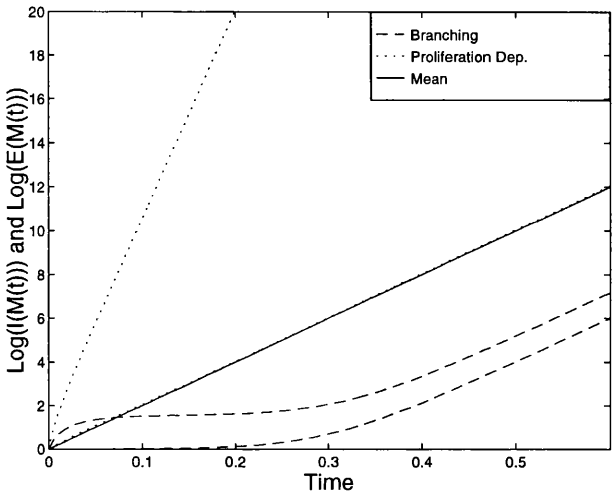

Figure 5.2: Log Index of Dispersion of $M(t)$ for Four Transmission Processes, $N = 1000$

The mean is included in the graphs for comparison, and the parameters used are $\phi = 5, \theta = 5, \sigma^2 = 3$ and $\mu = 5$ for the processes with clustered reproduction, and $\phi = 25, \mu = 5$ for those without.

Intitially in Figure 5.1 we see that the index of dispersion for the clustered reproduction branching model has faster growth than that for the model with parasite proliferation without clustered reproduction. However, the effect of parasite proliferation quickly becomes more important as the underlying growth rate for each model starts to dominate, and so the proliferation dependence model without clustered reproduction has higher index of dispersion growth. It is noticeable in both Figure 5.2 and Figure 5.1 how large the difference is between the growth of $\mathrm{I}(M(t))$ for the clustered, proliferation dependence model and the other three models. This underlines how the effect on $\mathrm{I}(M(t))$ of these two mechanisms together is in some sense greater than the sum of the two effects on their own.

In Figure 5.2 we see that the branching model with no clustered reproduction spends some time with index of dispersion around 1 (and hence $\log(\mathrm{I}(M(t)))$ at zero) due to the high host population level, but eventually the growth rate will

dominate, so the dispersion starts to increase exponentially. With a relatively small host population size of 10 in Figure 5.1 the proliferation dependence model without clusters has higher dispersion growth than the mean, whilst the clustered branching model has $\mathrm{I}(M(t))$ closely following the mean after sufficient time. With a larger host population size of 1000 in Figure 5.2, we see that the proliferation dependence model without clusters has dispersion growing identically with the mean (the line is partially hidden inder the mean plot), whilst the clustered branching model now has $\mathrm{I}(M(t))$ lower than the mean. This illustrates the results already presented algebraically in this chapter concering the reduction of the dispersion in larger host populations.

We briefly consider the coefficient of variation. The dominant exponent in the square of $\mathrm{CV}(M_i(t))$ is ϵt where

$$\epsilon = \frac{1}{2}\lambda\left(\theta - 2 + \sqrt{(\theta-2)^2 + 8\theta/N}\right).$$

For the branching model without clusters, this was zero. Again, to consider the effect of parasite proliferation dependence alone we let $\theta = 1$, giving $\epsilon = \frac{1}{2}\phi\left(\sqrt{1+8/N} - 1\right)$. We can see that parasite proliferation dependence is enough to make the coefficient of variation grow for values of N that are not too large. This rate of growth *of the square* of CV is always less than ϕ for $N > 1$ (equals ϕ when $N = 1$). We have that ϵ tends to the value of the branching model when $N \to \infty$ so that, as with the index of dispersion, for large populations, and in the absence of parasite offspring clumps, the parasite proliferation dependence does not affect the coefficient of variation.

It is interesting to note that ϵ does not involve μ, so that in relatively small host populations it is possible to have small growth in the mean ($\phi - \mu$ small) whilst having large growth in the coefficient of variation, purely as a result of parasite proliferation dependence. However, this will occur when ϕ is close to μ so that $\phi - \mu$ is small relative to $\sqrt{\phi}$. This will result in an increased chance of extinction, and so care must be taken in interpreting these results. When there is a high chance of

extinction, moments can be highly unrepresentative of actual realisations, and other properties such as distributions conditional on non extinction might be considered. Most of the results given in this section apply when the parasite population is flourishing and concern the effect of different factors on the aggregation when the population is growing.

As an addition to this work, it would be interesting to consider how the correlation between hosts is affected by the different transmission mechanisms. A summary of the results of this section is given in the conclusion to this chapter, Section 5.5

5.4 Host Heterogeneities

Heterogeneities are often cited as the source of high variability in parasite loads (Anderson and May, 1991; Wassom, Dick, Arnason, Strickland, and Grundmann, 1986). In this section we incorporate heterogeneities into the models of the previous two sections. Specifically we consider heterogeneities in host behaviour (Section 5.4.1), susceptibility (Section 5.4.2) and ability to expel parasites (Section 5.4.3), and look at the effect these will have on a selection of properties of the distribution of parasites among hosts.

5.4.1 Heterogeneities In Host Behaviour

Hosts may vary in their behavioural patterns, and so affect the transmission of parasites through the host population. For example, if the infection from the parasite life cycle outside host is via a river, as in schistosomiasis, the frequency of visiting the river will alter a host's ability both to pick up and to transmit infections. Similarly, dwelling location for humans may result in this type of heterogenous behaviour in mosquito transmitted diseases.

We represent these differences in the branching model of Section 5.2 by saying

that the rate at which a parasite in host i gives rise to a parasite in host j is assumed to be $\kappa_i k_j \phi/N$, and without loss of generality, $\sum_{i=1}^{N} k_i = \sum_{i=1}^{N} \kappa_i = N$. For the equivalent model used to study parasite proliferation dependence (5.3) we assume that this rate, $\kappa_i k_j \phi/N$, is the rate at which host i makes infectious contacts with host j.

We have an $N \times N$ mixing matrix for the contact between hosts with elements a_{ij} representing the relative contact rate from host i to host j, being $\kappa_i k_j$. In the branching model framework, the average infection rate for a parasite in a randomly chosen host at any time is thus kept the same as in our previous models, $\frac{1}{N}\sum_{i=1}^{N}\sum_{j=1}^{N} k_i \kappa_j \phi/N = \frac{\phi}{N^2}\left(\sum_{i=1}^{N} k_i\right)\left(\sum_{j=1}^{N} \kappa_j\right) = \phi$. This is also the average rate at which contacts between hosts occur in the equivalent model for parasite proliferation dependence.

The parameter κ_i represents a host's ability to transmit the disease, and k_i its ability to pick up an infection, relative to the rest of the population. If behavioural heterogeneities (as opposed to heterogeneities in host susceptibilities) are the only ones being considered, as in the two examples above, it would be expected that $\kappa_i = k_i$ for all i. Then the mixing matrix is symmetric and we have $a_{ij} = k_i k_j$.

With these heterogeneities the branching model considered in Section 5.2 has transitions from $M_i(t)$ to

$$\begin{array}{lll} M_i + 1 & \text{at rate} & \dfrac{\phi}{N} k_i \sum_{j=1}^{N} \kappa_j M_j \\ M_i - 1 & \text{at rate} & \mu M_i \end{array}$$

for $i = 1, ..., N$, so the equivalent to equation (5.2) for the probability generating function $P(\boldsymbol{x}; t) := \mathrm{E}\left(\prod_{i=1}^{N} x_i^{M_i(t)}\right)$ is

$$\frac{\partial P}{\partial t} = \sum_{j=1}^{N} \frac{\partial P}{\partial x_j}\left(\mu(1 - x_j) + \frac{\phi}{N}\kappa_j x_j \sum_{i=1}^{N} k_i (x_i - 1)\right) \tag{5.47}$$

and the auxiliary equations become

$$\frac{dx_j}{dt} = \mu(x_j - 1) + \frac{\kappa_j \phi}{N}\sum_{i=1}^{N} k_i (1 - x_i) \quad \text{for } j = 1, ..., N. \tag{5.48}$$

These appear difficult to solve in a useful form (see however the special case in the next section) and so we restrict ourselves to considering moments of this model.

The moment equations for this simple model with heterogeneous host behaviour are

$$\frac{d\mathrm{E}(M_i)}{dt} = \frac{\theta\phi}{N}k_i\sum_{j=1}^{N}\kappa_j\mathrm{E}(M_j) - \mu\mathrm{E}(M_i) \tag{5.49}$$

$$\frac{d\mathrm{E}(M_i^2)}{dt} = \frac{2\phi}{N}k_i\sum_{j=1}^{N}\kappa_j\mathrm{E}(M_iM_j) + \frac{\phi}{N}k_i\sum_{j=1}^{N}\mathrm{E}(M_j) + \mu\mathrm{E}(M_i) - 2\mu\mathrm{E}(M_i^2) \tag{5.50}$$

$$\frac{d\mathrm{E}(M_iM_j)}{dt} = \frac{\phi}{N}\left(k_i\sum_{r=1}^{N}\mathrm{E}(M_jM_r) + k_j\sum_{r=1}^{N}\kappa_r\mathrm{E}(M_iM_r)\right) - 2\mu\mathrm{E}(M_iM_j). \tag{5.51}$$

If we multiply equation (5.49) by κ_i, and then sum over i, we obtain an equation in terms of $C(t) := \sum_{i=1}^{N}\kappa_i\mathrm{E}(M_i(t))$. This is

$$\frac{dC(t)}{dt} = \left(\phi\frac{\sum_{i=1}^{N}\kappa_ik_i}{N} - \mu\right)C(t),$$

and with the initial conditions $C(0) = Na$ we obtain

$$\begin{aligned} C(t) &= aN\exp\left\{\left(\phi\frac{\sum_{i=1}^{N}\kappa_ik_i}{N} - \mu\right)t\right\} \\ &= aN\exp\left\{(\phi(1+V) - \mu)\,t\right\} \end{aligned}$$

where we have written

$$V = \frac{\sum_{i=1}^{N}\kappa_ik_i}{N} - 1. \tag{5.52}$$

We can think of V as being a measure of the covariance of the distribution of the k_i and κ_is across the population (V is equivalently $\frac{\sum_{i=1}^{N}\kappa_ik_i}{N} - \frac{\sum_{i=1}^{N}k_i}{N}\frac{\sum_{i=1}^{N}\kappa_i}{N}$). The solution of (5.49) with initial condition $\mathrm{E}(M_i(0)) = a$ for all i is then

$$\mathrm{E}(M_i(t)) = \frac{a}{1+V}\left(k_ie^{(\lambda(1+V)-\mu)t} + (1 - k_i + V)e^{-\mu t}\right) \tag{5.53}$$

Not surprisingly the host's ability to pick up infections, k_i, is in this expression directly, whilst the host's transmission ability (κ_i) is only involved as part of the

population expression V. If all k_is are equal so that hosts pick up infections at the same rate, then $V = 0$ so that all the means are identical and are the same value as in the homogeneous host model, despite any differences there may be in the hosts' transmission abilities, κ_is. In this situation the second order moments for this branching model, the clustered reproduction model and the parasite proliferation dependence model are solvable, though we do not provide solutions here. One biological explanation for this scenario of equal k_is but different κ_is is when hosts have varying abilities at limiting parasites' production of offspring within hosts, and hence the transmission of parasites varies among hosts, but the uptake of parasites does not.

For a host that has a contact rate that is the average of the whole population contact rate, we have $k_i = 1$. Using this value will also give us the mean of the parasite loads across the whole host population as

$$\mathrm{E}(M(t)) = \frac{a}{1+V}\left(e^{(\lambda(1+V)-\mu)t} + Ve^{-\mu t}\right).$$

If $V > 0$ then there is a positive covariance between hosts' relative transmission and uptake rates, and so the more heavily infected hosts transmit faster, and the overall mean is increased in comparison with the identical host models (5.44). When this covariance is negative the heterogenous model produces a lower overall mean for the reverse reason, though this scenario is less likely biologically.

If this system were modelled deterministically, with only these means being considered, some variability would still be obtained across the host population. Considering this variance of the means, we have

$$\begin{aligned}\mathrm{DVar}_i(\mathrm{E}(M_i(t))) &:= \frac{1}{N}\sum_{i=1}^{N}(\mathrm{E}(M_i(t)))^2 - \frac{1}{N^2}\left(\sum_{i=1}^{N}\mathrm{E}(M_i(t))\right)^2 \\ &= \frac{a^2}{(1+V)^2}\mathrm{Var}(K)\left(e^{(\lambda(1+V)-\mu)t} - e^{-\mu t}\right)^2 \qquad (5.54)\end{aligned}$$

where $\mathrm{Var}(K) := \frac{1}{N}\sum_{i=1}^{N} k_i^2 - \left(\frac{1}{N}\sum_{i=1}^{N} k_i\right)^2$ is the variance of the hosts' relative rates of contact with infection across the population. Notice that the variability

in the hosts' transmission abilities, the κ_is, enters to expression (5.54) through the covariance of the two types of heterogeneities, V. When $\kappa_i = k_i$ for all i,$\mathrm{Var}(K) = V$.

The fully stochastic variance of the $M_i(t)$s for this branching model is not so easily found as we no longer have the symmetry used in the previous section. The equations can of course be written as a linear system of $\frac{1}{2}N(N+1)$ equations and solved for specific values of k_is, but we shall not pursue this here. The same problem occurs in the parasite proliferation dependence model (which of course has the same means as described for the branching model). Thus it is hard to see the general effect of the combination of host heterogeneities and the structure of the transmission process on the variability of the process. A possible way to do this, not pursued here, is to consider two subpopulations with mixing at different rates within each and between subpopulations. This will lead to a system of seven linear differential equations for the first two moments of the process. It may, however, still be difficult to gain any insight from the solutions to these. This approach is used to consider the mean values in Section 5.4.3.

5.4.2 Heterogeneities in Host Susceptibilities

Consider the special case of the model of the previous section in which hosts behave identically in terms of their infectivity (so $\kappa_i = 1\ \forall i$), but their exposures are different, representing varying susceptibility to infection across the host population. For example this scenario is appropriate if some hosts have a better genetic disposition to the prevention of parasite establishment than others (Wassom, Dick, Arnason, Strickland, and Grundmann, 1986).

The joint probability generating function for the branching model with these host heterogeneities, $P(\boldsymbol{x};t)$, then satisfies

$$\frac{\partial P}{\partial t} = \sum_{j=1}^{N} \frac{\partial P}{\partial x_j} \left(\mu(1-x_j) + \frac{\phi}{N} x_j \sum_{i=1}^{N} k_i (x_i - 1) \right) \tag{5.55}$$

obtained by setting $\kappa_i = 1\ \forall i$ in (5.47). The auxiliary equations (5.48) reduce to

$$\frac{dx_j}{dt} = \mu(x_j - 1) + \frac{\phi}{N}\sum_{i=1}^{N} k_i(1 - x_i) \quad \text{for } j = 1, ..., N. \tag{5.56}$$

If we define $\sigma_H = \sum_{i=1}^{N} k_i x_i$ then the analysis proceeds along similar lines to that in Section 5.2. The constants of integration, $\tilde{A}, \tilde{C}_1, ..., \tilde{C}_N$ for the solutions of $\sigma_H, x_1, ..., x_{N-1}$ are the same as $A, C_1, ..., C_N$ (see (5.6) and (5.7)), but with σ_H replacing σ . We then have

$$\begin{aligned} x_N &= \frac{1}{k_N}\left(\sigma_H - \sum_{i=1}^{N-1} x_i\right) \\ &= \frac{\tilde{A}e^{-\mu t} - \frac{\mu}{\phi}e^{-\phi t} - \frac{1}{k_N}\sum_{j=1}^{N-1} k_j \tilde{C}_j}{\tilde{A}e^{-\mu t} - e^{-\phi t}} \end{aligned}$$

and hence using the general initial conditions

$$P(\boldsymbol{x}; 0) = g(x_1, ..., x_N)$$

we have

$$P(\boldsymbol{x}; t) = g(\tilde{y}_1, ..., \tilde{y}_N) \tag{5.57}$$

where

$$\tilde{y}_i = \left[\frac{\left(\mu(e^{-\phi t} - 1) + \phi(e^{-(\phi-\mu)t} - e^{-\phi t})\right)\sum_{j=1}^{N} k_j x_j - N\left(\mu(e^{-(\phi-\mu)t} - 1) + e^{-\phi t}(\mu - \phi)x_i\right)}{\phi(e^{-(\phi-\mu)t} - 1)\sum_{j=1}^{N} k_j x_j + N(\phi - \mu e^{-(\phi-\mu)t})}\right].$$

Shanbhag (1972) has derived a form for the time inhomogeneous version of this process by use of the backward equations, as an extension of the work of Mode (1962).

From this result we can see that if a host (i say) has an average susceptibility, (so $k_i = 1$), then its parasite load is not affected in any way by whether the other hosts in the population have identical or heterogeneous susceptibilities. Without heterogeneous transmission rates the effect of heterogeneous susceptibilities on the

parasite population is much weaker. This is because hosts with higher loads still transmit parasites at the same rate and hence the total being transmitted remains the same. The parasites are distributed amoung the hosts in a different way, but the distribution of the total population number ($\sum_{i=1}^{N} M_i(t)$) does not change. This can be seen algebraically by evaluating (5.57) at $x_i = x \ \forall i$ to obtain a probability generating funtion for the total parasite population, and noticing that the k_is do not appear in this expression.

As $\kappa_i = 1 \ \forall i$, $V = 0$ (i.e. there is zero covariance between κ_is and k_is), and so with initial conditions of $M_j(t) = a \ \forall j$, (5.53) gives

$$\mathrm{E}(M_i(t)) \ = \ a\left(k_i e^{(\phi-\mu)t} + (1-k_i)e^{-\mu t}\right)$$

which can be verified from (5.57) evaluated with $g(\boldsymbol{x}) = \prod_{j=1}^{N} x_j^a$. The average across the whole population is thus $ae^{(\phi-\mu)t}$, and so as a consequence of the point made above concerning total parasite numbers, there is no change from the homogeneous host result in Section 5.2.2 in which all hosts have identical susceptibilities.

If we look at the variability that a deterministic system would exhibit, we find equation (5.54) becomes

$$\mathrm{DVar}_i(\mathrm{E}(M_i(t))) \ = \ a^2\mathrm{Var}(K)\left(e^{(\phi-\mu)t} - e^{-\mu t}\right)^2$$

and so the deterministic result for the index of dispersion is

$$\mathrm{I}_{det}(M(t)) \ = \ a\mathrm{Var}(K)(e^{\phi t}-1)(1-e^{-\phi t})e^{-\mu t}.$$

If we change the initial conditions to $a_i = 0$ and $a_j = a$ for all $j \neq i$ so an uninfected host is introduced into an infected area, then the mean of $M_i(t)$ is

$$\mathrm{E}(M_i(t) \ = \ ak_i\frac{N-1}{N}e^{-\mu t}(e^{\phi t}-1)$$

(this is simply k_i times the value with homogeneous hosts) and the variance of $M_i(t)$, obtained from (5.57), is

$$\mathrm{Var}(M_i(t)) = \frac{ak_i(N-1)}{N^2}\frac{(e^{\phi t}-1)e^{-2\mu t}}{\mu-\phi}\left((\mu-\phi)(Ne^{\mu t}+k_i)+k_i(2\phi e^{\mu t}-(\phi+\mu)e^{-\phi t})\right).$$

The index of dispersion then becomes

$$\mathrm{I}(M_i(t)) \;=\; 1+\frac{k_i}{N(\phi-\mu)}\left((\phi-\mu)e^{-\mu t}+(\phi+\mu)e^{(\phi-\mu)t}-2\phi\right). \qquad (5.58)$$

Comparing this to the case with homogeneous susceptibilities and the same initial conditions, (5.20), we see that the amount by which $M_i(t)$ is overdispersed is simply multiplied by k_i. This means that the within host overdispersion of a host with below average susceptibilities (k values less than one) will be less than if all hosts had homogeneous susceptibilities. This is because the index of dispersion is related to the mean, which will also be reduced.

The probability generating functions (5.10) and (5.57) can be used to investigate how heterogeneous susceptibilies affect prevalence and extinction of the parasite population. For example, the extinction probability is given by evaluating $P(\boldsymbol{x};t)$ in (5.57) at $\boldsymbol{x}=\mathbf{0}$, and we find that the k_is all vanish and so heterogeneous susceptibilities alone do not affect extinction. This is a consequence of the total parasite population distribution being unchanged, as it is this population that must go to zero for extinction to occur.

5.4.3 Heterogeneities in Parasite Expulsion Abilities

In this section we consider heterogeneities in the hosts' abilities to expel parasites, which can be considered as a measure of their resistance to the parasites. We provide only a brief introduction to this scenario with the purpose of outlining a framework for the study of these heterogeneities in macroparasite infections.

We allow the parameter μ to vary across the hosts. If we let host i have internal parasite death rate μ_i then in general we will have separate ordinary differential equations for the moments for each host ($N(N+3)/2$ of them if second order moments are included) as we are not able to use any symmetry in host parasite levels. This is because the parameters μ_i act directly on the evolution of the parasites inside each host rather than simply being a scaling type parameter, as the k_i and κ_i were.

We restrict attention to the case where there are just two host death rates so the first n_1 of the hosts have internal parasite expulsion rates μ_1 and the remaining $n_2 = N - n_1$ have rate μ_2. The ordering is of course arbitrary. Then $M_i(t)$ has transitions to

$$\begin{array}{lll} M_i(t) + c & \text{at rate} & \phi/N \sum_{j=1}^{N} F(M_j(t), c) \quad \text{for } c = 0, 1, ... \\ M_i(t) - 1 & \text{at rate} & \mu_i M_i(t) \end{array}$$

for $i = 1, ..., N$, where $\mu_i = \mu_1$ if $i = 1, ..., n_1$ and $\mu_i = \mu_2$ if $i = n_1 + 1, ..., N$. The means satisfy

$$\begin{aligned} \frac{d\mathrm{E}(M_1(t))}{dt} &= (p\lambda - \mu_1)\mathrm{E}(M_1(t)) + q\lambda \mathrm{E}(M_2(t)) \\ \frac{d\mathrm{E}(M_2(t))}{dt} &= p\lambda \mathrm{E}(M_1(t)) + (q\lambda - \mu_2)\mathrm{E}(M_2(t)) \end{aligned} \tag{5.59}$$

where $p = n_1/N$ is the proportion of hosts in subpopulation 1, and $q = 1 - p = n_2/N$ is the proportion of hosts in subpopulation 2. There are five more equations to consider if we want the second order moments, giving a linear system of seven ordinary differential equations. We do not consider these further. The solution to (5.59) with the boundary conditions $\mathrm{E}(M_1(0)) = \mathrm{E}(M_2(0)) = a$ is

$$\begin{aligned} \mathrm{E}(M_1(t)) &= a\left(\frac{\lambda + \mu_2 - \mu_1 + \psi}{2\psi} e^{(\lambda - \mu_1 - \mu_2 + \psi)t/2} + \frac{\mu_1 - \mu_2 - \lambda + \psi}{2\psi} e^{(\lambda - \mu_1 - \mu_2 - \psi)t/2}\right) \\ \mathrm{E}(M_2(t)) &= a\left(\frac{\lambda + \mu_1 - \mu_2 + \psi}{2\psi} e^{(\lambda - \mu_1 - \mu_2 + \psi)t/2} + \frac{\mu_2 - \mu_1 - \lambda + \psi}{2\psi}) e^{(\lambda - \mu_1 - \mu_2 - \psi)t/2}\right) \end{aligned}$$

where

$$\psi = \sqrt{\lambda^2 + (\mu_2 - \mu_1)^2 - 2\lambda(p - q)(\mu_1 - \mu_2)}.$$

The average parasite level throughout the host population, $p\mathrm{E}(M_1(t)) + q\mathrm{E}(M_2(t))$, is

$$a\left(\frac{\psi + \lambda - \varpi}{2\psi} e^{(\lambda + \psi - (\mu_1 + \mu_2))t/2} + \frac{\psi - (\lambda - \varpi)}{2\psi} e^{(\lambda - \psi - (\mu_1 + \mu_2))t/2}\right)$$

where

$$\varpi = (p - q)(\mu_1 - \mu_2).$$

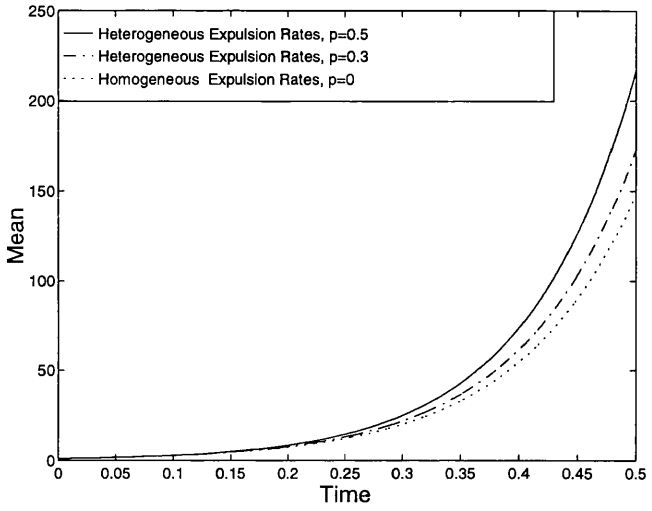

Figure 5.3: Mean Parasite Levels with Heterogeneous Host Parasite Expulsion Rates

If the two subpopulations are in equal proportions ($p = q = 1/2$) then $\varpi = 0$ and, assuming that the average expulsion rate is μ, we have $\mu_1 + \mu_2 = 2\mu$ so that the mean parasite level throughout the host population is now

$$a\left(\frac{\psi+\lambda}{2\psi}e^{(\lambda+\psi-2\mu)t/2} + \frac{\psi-\lambda}{2\psi}e^{(\lambda-\psi-2\mu)t/2}\right).$$

By considering μ as fixed, we see that this will be an increasing function in ψ, and hence in the size of the disparity between the two parasite death rates $(\mu_1 - \mu_2)^2$, if

$$\left(t - \frac{2\lambda}{\psi^2}\right)\left(e^{\psi t} - 1\right) + \frac{\lambda t}{\psi}\left(e^{\psi t} + 1\right) > 0$$

which is always true for

$$t \geq \frac{2\lambda}{\lambda^2 + (\mu_1 - \mu_2)^2}.$$

This means that after sufficient time, a host population with two equal subpopulations of hosts with differing parasite expulsion rates will certainly have larger mean than an equivalent homogeneous host population.

Figure 5.3 shows the mean parasite level across all hosts for fixed levels of $\lambda = 30, \mu = 20$ and $\mu_1 = 25$. The proportion of hosts with the higher than average

level of parasite expulsion rates is p, and is varied across the three plots. We see that the larger the proportion of hosts with high resistance, (p), the faster the mean increases. This will correspond to a bigger disparity between the levels of expulsion rates in the two host populations. Thus the case of homogeneous expulsion rates corresponds to the lowest possible growth of the mean. We conjecture that this will be the case for all parameters values. This is also the general situation with heterogeneous host behaviour in which there are heterogeneous contact rates, and the homogeneous case provides the smallest growth of the mean.

5.5 Conclusions

To summarise the results of this chapter, we have highlighted two possible mechanisms for the transmission process that, together with demographic stochasticity can cause the parasite population to become overdispersed even among identical, homogeneously mixing hosts.

Demographic stochasticity alone can cause the index of dispersion to grow at the same rate as the mean, though as the host population size becomes large the amount of the overdispersion tends to zero. The effect of individual parasites transmitting more than one offspring at a time acts to increase the overdispersion in a scaling way, so that as the host population size increases, overdispersion is still possible, but it will reach an equlibrium value in time.

The effect of parasites in a host transmitting their offspring simultaneously however causes the growth rate of the index of dispersion to increase. Further, the effect of offspring from individual parasites being transmitted simultaneously is magnified, so that it also increases the growth rate of the index of dispersion, though for large population sizes the mean of each clump size must be greater than two for this increase to remain.

The dominant growth rates in the index of dispersion, i.e. the highest exponents with positive coefficients under the transmission mechanisms discussed can

be summarised as follows;

		PARASITE PROLIFERATION DEPENDENCE	
		YES	NO
CLUSTERED REPRODUCTION	YES	$\frac{1}{2}\lambda\left(\theta+\sqrt{(\theta-2)^2+8\theta/N}\right)-\mu$	$\lambda-\mu$
	NO	$\frac{1}{2}\lambda\left(1+\sqrt{1+8/N}\right)-\mu$	$\lambda-\mu$

In the limit as the host population size $N \to \infty$ these become

		PARASITE PROLIFERATION DEPENDENCE	
		YES	NO
CLUSTERED REPRODUCTION	YES	$\theta > 2 : \lambda(\theta-1)-\mu$ $\theta < 2 : \lambda-\mu$	0
	NO	$\lambda-\mu$	0

The reason why we see the highest exponent with positive coefficient drop from $\lambda-\mu$ to zero as $N \to \infty$ is that the coefficient of the relevant exponent tends to zero. Thus, as described in Section 5.2, in the limit of N, the index of dispersion will not grow indefinitely in the absence of parasite proliferation dependence.

For a particular parasitic disease, information on the life cycle and transmission processes of the parasites can be evaluated to see which of the mechanisms discussed in this chapter are likely to be present, and hence an idea of the intrinsic aggregation

due to the biology of the parasite transmission process alone can be gained.

The two effects we have considered in this chapter (parasite proliferation dependence and clustered reproduction) are in fact very similar in concept. Clustered reproduction demands identical transmission time for clumps of offspring from individual parasites, whilst parasite proliferation dependence requires identical transmission times for offspring from parasites in the same host. Both mechanisms result in added dependence between parasites and hence higher variability in parasite loads.

Parasite proliferation dependence represents homogeneous mixing of offspring within a host, so that upon an infection point all parasites in the host transmit. The next level of offspring mixing, not investigated in the models of this chapter, is between hosts. Biologically this will occur during a phase of the parasites' lifecycle that is outside the definitive host. Free living larvae coming originally from different hosts may be picked up together by a receiving host, so that there may now be more than one giving host. For example if larvae are transmitted via host faeces spread in the environment, the mixing of faeces from different hosts will result in the mixing of offspring from different hosts at an infection point.

The general model for this transmission mechanism would have transitions from $\boldsymbol{M}(t)$ to

$$\begin{aligned} M_i(t) + \sum_{j=1}^{N} c_j \quad & \text{at rate} \quad \phi G(\boldsymbol{M}(t), \boldsymbol{c}) \quad \forall \boldsymbol{c} \in \mathbb{Z}^N \\ M_i(t) - 1 \quad & \text{at rate} \quad \mu M_i(t) \end{aligned}$$

for i=1,...,N. This means that at an infection point host j contributes c_j parasites (for $j = 1, ..., N$) with a probability that is some function G of the state of hosts, $\boldsymbol{M}(t)$, and the c_js.

A further assumption that could be made (analogous to assumption (5.39) made in Section 5.3 concerning independence of reproduction at the different mixing

levels) is to let

$$G(\boldsymbol{M}(t), \boldsymbol{c}) = \prod_{j=1}^{N} \tilde{G}(M_j(t), c_j,)$$

which is to assume that the number of offspring contributed by the parasites in host j at each infection point is independent of the number contributed by all other host and depends only on the load of host j, $M_j(t)$. This means that the total number of offspring acquired at an infection point is the sum of N random variables, each depending upon the load of one of the N hosts. The transition rate from $M_i(t)$ to $M_i(t) + c$ can then be written as

$$\phi \sum_{\boldsymbol{c}\ s.t.|\boldsymbol{c}|=c} \prod_{j=1}^{N} \tilde{G}(M_j(t), c_j)$$

where $\mid \boldsymbol{c} \mid = \sum_{j=1}^{N} c_j$

This models offspring mixing between hosts. For some biological systems we might expect the parasites ingested at an infection point to come from a small sample of hosts, rather than all hosts in the population. This could be achieved by making $\tilde{G}(M_j(t), 0)$ relatively close to one, so that the chance of a particular host contributing to any one infection point is low, or equivalently by making only k randomly drawn hosts contribute, where k will itself be independently drawn from a random variable at each infection point.

This further type of mixing assumption overcomes one of the main shortcomings of using the direct transmission assumption discussed in the introduction to this chapter. The other important process this assumption implicitly ignores is the time delay and survival of parasite stages outside the definitive hosts. An obvious way of including this would be to add one or more variables to the system to represent the number of parasites in stages outside the host. This will immediately require careful, detailed consideration of the transmission of parasites to and from these environmental stages, and in many cases it will not always be obvious how this should be modelled. A simple version of the branching model of Section 5.2 with an environmental stage might have variables $M_i(t), ..., M_N(t)$ as before, and an

additional variable $E(t)$ representing the number of parasites in the environment. The transitions might be from $\boldsymbol{M}(t), E(t)$ to

$$\begin{array}{rlll} \boldsymbol{M}+\boldsymbol{\epsilon}_i & E-1 \text{ at rate} & \phi_2 E(t) & \text{for } i=1,...,N \\ \boldsymbol{M}-\boldsymbol{\epsilon}_i & E \text{ at rate} & \mu M_i & \text{for } i=1,...,N \\ \boldsymbol{M} & E+1 \text{ at rate} & \phi_1 \sum_{j=1}^{N} M_j & \\ \boldsymbol{M} & E-1 \text{ at rate} & \mu_E E & \end{array}$$

where $\boldsymbol{\epsilon}_i$ is an N length vector of zeros with unity in the i^{th} position. This model is reasonably tractable to analysis and may give an idea of the effect of modelling the environmental stage explicitly.

Further ways of modelling the parasite transmission with an environmental variable include imagining $E(t)$ to represent the number of potential parasite 'clumps' in the environment, where each clump can release more than one offspring into a host when an infection contact is made. For example, this could represent the number of infective mosquitoes, or number of patches of infective faeces in the environment. As well as being able to include parasites entering a host in clusters rather than individually, the other main difference from the transitions outlined above is that the $E(t)$ variable would not drop when an infection event takes place, as the mosquito, for example, would remain in the environment, The transitions might be from $\boldsymbol{M}(t), E(t)$ to

$$\begin{array}{rlll} \boldsymbol{M}+c\boldsymbol{\epsilon}_i & E \text{ at rate} & \phi_2 h_c E(t) & \text{for } i=1,...,N \text{ and } c=0,1,... \\ \boldsymbol{M}-\boldsymbol{\epsilon}_i & E \text{ at rate} & \mu M_i & \text{for } i=1,...,N \\ \boldsymbol{M} & E+1 \text{ at rate} & \phi_1 \sum_{j=1}^{N} M_j & \\ \boldsymbol{M} & E-1 \text{ at rate} & \mu_E E & \end{array}$$

where as usual $h_c = \mathrm{P}(C = c)$, the number of offspring picked up by a host at each infection point. If this framework were used for more detailed models, the distribution of C would have to be specified from estimates of the amount of

parasite offspring a host picks up from an infective clump of grass, or an infective mosquito. This type of formulation is appropriate for parasites that have a large amount of asexual reproduction inside a vector host so that the infection to the definitive host involves large numbers of offspring being transmitted. Examples of this include filariasis.

It should be pointed out that that in most cases in this chapter the moments of parasite levels were given for individual hosts, and that the variability comes from different realisations of the stochastic process. These moments may not neccesarily be the same as the sampling moments that might be used from observations in the field. The general conclusions, however, are unlikely to be affected.

There may be some localised spatial effect in some biological systems so that hosts contributing to an infection point are more likely to be the neighbours of the receiving host. This would require us to lose the homogeneous mixing assumption that we have used throughout this chapter (with the exception of Sections 5.4.1 and 5.4.2) and of course would add extra variablility and aggregation into the process. The nice thing about most results and models of this chapter is that they do not rely on heterogeneous mixing to provide overdispersion of parasites but show how other mechanisms can contribute even in the presence of homogeneous mixing. Heterogeneous mixing is perhaps an 'obvious' cause of aggregation.

As an extension of this work it is important to see how the results of this chapter are affected by using more realistic, nonlinear effects for the transmission and survival of the parasites. Unfortunately this will quickly make the mathematics less tractable. Density dependent effects, immune mechanisms or other regulatory factors are likely to decrease the aggregation in the process, and work against the growth of dispersion that the transmission mechanisms provide. Considering the effects of various transmission mechanisms under linear growth does however provide an idea of their relative importance. One of the useful features of stochastically formulated models (such as those presented here) is that they force the modeller to think about the specific details of the mechanisms being modelled. Simplify-

ing assumptions will usually have to be made, but it is sometimes all too easy to write 'the rate of parasite transmission is ...' without considering the process of transmission in further detail.

Chapter 6

Discussion

6.1 Evolution of Parasite Virulence

In this section we briefly discuss how the model in Chapter 3 can be used for studies in the area of the evolution of parasite virulence. As parasites reduce their own transmission capabilities the more they kill their hosts, the initial assumption in this area is that parasites will naturally evolve to become more benign over time, through natural selection within the parasite species.

However, there are many well established parasite-host relationships in which this is not the case, and the parasite has remained highly virulent (see, for example, Schall (1990)). There has been much speculation on the reason for this, though the testing of ideas through experiment is particularly difficult in this area. Perhaps the simplest explanation, and one that is currently popular, comes from a hypotheses that can be roughly thought of as a conservation of biomass. It involves the assumption that parasites with higher virulence are able to transmit offspring at higher rates than those with lower virulence, as they use more nutrition from their hosts (Levin and Pimentel, 1981; Ewald, 1983). Thus there exists a trade off between virulence and transmissibility. This leads to leads to much discussion and hypothesis on the competition between parasites of different strains with differing

virulence, and on which level of virulence survives under natural selection in various host population structures (Novack and May, 1994; May, 1994; Lipsitch and Novak, 1995). Models by Anderson and May (1982a), May and Anderson (1983), Antia, Levin, and May (1994) give possible explanations for the evolution of strains with intermediate levels of virulence. Ebert and Herre (1996), Bull (1994) and Levin (1990) provide reviews of this area.

The majority of theoretical work on the evolution of parasite virulence has been in the study of microparasites. Some exceptions, however, are the studies of Herre (1993) and Herre (1995). He investigated the evolution of virulence of nematodes parasitising fig wasps. The fig wasps reproduced in fig fruits, each fruit containing a varied number of wasps. He showed that increased chances for horizontal transmission of parasites across host parents led to strains being more virulent than those transmitted from host parents to offspring. This was because the reproductive success of these parasites was less tied to that of the host. One of the aspects highlighted in the conclusion of Herre (1995) was that

> Thus far wasps and fig fruits have been characterized as either 'with' or 'without' nematodes. However, this simplification neglects the fact that the densities of nematodes vary among fig fruits and worm burdens vary among individuals.

Hence we see that in this host-macroparasite relationship the level of infection is again of importance to the issue under study. There are advantages for aggregated parasites that are discussed in Section 1.2 and Poulin (1998, Chapter 6), including increased mating probabilities for sexually reproducing parasites. In the remainder of this section we consider briefly how the model for killing parasites in Chapter 3 can be adapted to study the competition between different strains of parasites with different virulence levels, whilst also incorporating different levels of parasite aggregation. So far mathematical models for the evolution of parasite virulence do not seem to have included this effect.

For each parasite type we use a fitness measure of total parasite reproductive success for the duration of the host's lifetime. We represent this by the total time spent by all mature parasites in a host before it dies, times the reproductive rate of the mature parasites. Thus, for a one parasite type model, as we had in Chapter 3, we are interested in a measure of parasite fitness of $\rho\Omega$, where $\Omega := \int_0^\infty M(t)Z(t)dt$ and ρ is the reproductive rate of the mature parasites. Recall that $M(t)$ is the mature parasite load unconditional on survival of the host, and $Z(t)$ is an indicator that is 1 when the host is alive, and 0 once the host has died. We assume that only mature parasites kill the host, so that $\alpha_l = 0$ and we can concentrate on just one measure of parasite virulence, α_m.

We take $\mu_H = 0$ so that the host only dies as a result of its parasite burden, though results can be adapted to allow $\mu_H \neq 0$. We can see from the construction of the model that the Laplace transform of the density of Ω is

$$\begin{aligned} L_\Omega(s) &:= \mathrm{E}\left(e^{-s\Omega}\right) \\ &= \int_0^\infty \sum_{m\geq 0} \int_0^\infty e^{-sw} P(B(t) = w, M(t) = m, Z(t+\delta t) = 0, Z(t) = 1) dw\, dt \\ &= \int_0^\infty \sum_{m\geq 0} \int_0^\infty e^{-sw} \alpha_m m P(B(t) = w, M(t) = m, Z(t) = 1) dw\, dt \\ &= \int_0^\infty \alpha_m \mathrm{E}\left(M(t)e^{-sB(t)}Z(t)\right) dt \end{aligned}$$

where $B(t) := \int_0^t M(u)du$ as in Section 3.2.2. We can proceed by noting that

$$\begin{aligned} \mathrm{E}\left(M(t)e^{-sB(t)}Z(t)\right) &= \mathrm{E}\left(M(t)e^{-(\alpha_m+s)B(t)}\right) \\ &= \frac{\partial}{\partial y}\left(G(1, y, 1, 0, \alpha_m + s; t)\right)\Big|_{y=1} \end{aligned}$$

where G is given in Section 3.2.2. This provides a result for the Laplace transform of the density of Ω. In this simple, one parasite type case, this can be shown to provide an exponential disribution distribution with parameter α_m. This result can also be deduced from the way host death rate is defined in the model. Thus the expected total mature parasite load until host death is $1/\alpha_m$, or the reciprocal of

our measure of parasite virulence. If ρ is constant and independent of α_m then this leads to the obvious conclusion that it is optimal in this case for the parasite not to harm its host, i.e. for $\alpha_m = 0$. However, ρ, the reproductive rate of the mature parasites, will generally be modelled as being dependent on, and increasing in, the virulence α_m. Thus in the one parasite type case the solution for optimal parasite fitness will depend on the relationship chosen for ρ and α_m.

In this situation it is interesting to investigate competition between different parasites types, and, in particular this can be used to investigate which parasite properties are optimal under different conditions. For example, the variations that may be of interest include the level of clustering for each parasite input process, the degree of parasite virulences or the amount of correlation between different parasites entering a host in one infection point. Below we illustrate how to derive the initial results to investigate these effects for multiparasite models. Consider two types of parasites, with virulence α_1 and α_2 and variables $M_1(t)$ and $M_2(t)$ respectively for their mature parasite loads. Define $B_1(t) := \int_0^t M_1(t), \Omega_1 := \int_0^\infty M_1(t)Z(t)dt$ and $B_2(t)$ and Ω_2 similarly. We find that

$$\begin{aligned} L(s_1;s_2) &:= \mathrm{E}\left(e^{-s_1\Omega_1 - s_2\Omega_2}\right) \\ &= \int_0^\infty \Big[\alpha_1 \mathrm{E}\left(M_1(t)e^{-(s_1B_1(t)+s_2B_2(t))}Z(t)\right) + \\ &\qquad \alpha_2\,\mathrm{E}\left(M_2(t)e^{-(s_1B_1(t)+s_2B_2(t))}Z(t)\right)\Big]\,dt. \end{aligned}$$

If we define $G_2(x_1,x_2,\tau_1,\tau_2;t) := \mathrm{E}\left(x_1^{M_1(t)}x_2^{M_2(t)}e^{-\tau_1 B_1(t)}e^{-\tau_2 B_2(t)}\right)$ then

$$\begin{aligned} L(s_1;s_2) &= \int_0^\infty \Bigg[\alpha_1 \frac{\partial}{\partial x_1} G_2(x_1,x_2,s_1+\alpha_1,s_2+\alpha_2;t)\Big|_{x_1=x_2=1} + \\ &\qquad \alpha_2 \frac{\partial}{\partial x_2} G_2(x_1,x_2,s_1+\alpha_1,s_2+\alpha_2;t)\Big|_{x_1=x_2=1}\Bigg]\,dt. \end{aligned}$$

We can find $G_2(x_1,x_2,\tau_1,\tau_2;t)$, given specific assumptions about the host uptake of the different parasite types, by using the method described in Section 3.2.2. These assumptions could involve independent Poisson process of arrivals for the two types of parasites, or high levels of correlation between inputs of different parasite types.

In theory means and other properties of Ω_1 and Ω_2 can be found from this general function. Notice that $\mathrm{E}\left(M_1(t)e^{-(s_1B_1(t)+s_2B_2(t))}Z(t)\right) = \mathrm{E}\left(M_{1k}(t)\right) := \mathrm{E}(M_1(t) \mid Z_n(t) = 1)$ where $Z_n(t)$ is the indicator for host survival of an equivalent process with parasite virulence levels redefined as $\alpha_1 + s_1$ and $\alpha_2 + s_2$ instead of α_1 and α_2. The result of Section 3.5.1 provides equations for these conditional moments. This can be used to provide approximate results from moment closure equations when nonlinear effects such as host immunity are included.

The study of within host dynamics of competing parasites is further complicated by the action of the immune system. This may be extremely specific to the strain of parasite, or the presence of one type of parasite may in fact trigger the immune system against another type. Concommitant immunity, in which the mature parasites trigger immune response against any incoming larvae, may also be present in some infections. It would be interesting to study possible advantages for parasites entering hosts in clusters when concommitant immunity is present.

In general, models of this type may be used to provide hypotheses on the possible effects of aggregation in relation to parasite virulence and evolutionary success.

6.2 Conclusions

This thesis has proposed, analysed and discussed mathematical models, and in particular stochastic processes, that contribute to the study of parasite dynamics. The use of stochastic processes provides scope to include the intrinsic variabilities inherent in the physical processes involved in parasite dynamics. Discrete models are clearly desirable as parasite numbers within hosts are often low, and stochastic models are more suited to discrete state space models than are deterministic models.

Models for *between*-host parasite dynamic are useful for providing insight into the important processes that determine the spread and transmission of parasite infections. They are often able to provide initial hypotheses for causes and effects of properties that are observed in the field. In Chapter 5 we have presented some linear

stochastic models that provide a framework for studying stochastically parasite population dynamics on static host populations (see Barbour and Kafetzaki (1993) for earlier, similar formulations). Generally, these illustrate the importance of considering the details of the stochastic mechanisms when modelling populations, by showing a diverse range of results for extremely simple linear models that are identical deterministically. In terms of parasite dynamics, this shows how the specific details of parasite transmission mechanisms need careful consideration when models are formulated. The biological hypotheses that arises from these models is that the transmission mechanism of parasites may itself be able to generate a large amount of the parasite aggregation that is observed in hosts. This aggregation is often assumed to be caused primarily by host heterogeneities (Anderson and May, 1991). Of course, this is only a hypotheses, and the next step is to consider specific cases of parasite infections to test this. We have also begun to set up a framework in which host heterogeneities, and their dynamic effect on the parasite population, can be studied stochastically when the host population is static (Section 5.4).

The study of *within*-host parasite dynamics is important as it invariably provides the sexual stage of parasite reproduction. This is not only important for the full cycle of transmission, but issues such as the evolution of drug resistant strains of parasites are becoming increasingly important (Saul, 1995). Clearly the development of models that capture the within-host parasite dynamics effectively is essential before further complications can be included in models. Within-host models are more able to be tested experimentally than between-host models, as factors such as levels of parasite ingestion are easier to monitor and control.

In Chapter 3 we have studied a within-host parasite dynamics model that includes parasite-induced excess host mortality, although without modelling directly differnt sexes of parasites, which can be incorporated relatively easily if required. We have derived results that are observable in the field and hence important for model testing. The model was also shown to be able to provide some insight into areas such as the differences between parasite loads observed in dead hosts and

those in surviving hosts when parasite-induced mortality is present, and the interaction between parasite induced host mortality and types of statistical properties observed concerning parasite lifetimes and input distributions.

Including immune reponses in any parasite model is clearly fraught with difficulties. These not only include difficulties associated with proposing the workings of an immune mechanism, but also with estimating the rates of processes. This may often be harder than for those processes in which events are more easily observed, such as between host models and processes in which the immune response can be summarised more simply (as in many microparasite infections). The work presented in Chapter 4 provides two general contributions to this area. The first is in the investigation of the suitability of the moment approximations to models of this type. This helps the understanding of their use in any further models that may be developed in this area of immuno-epidemiology, and in parasite dynamics generally. There is much further work needed on this subject before this potentially powerful tool can be routinely used with confidence. There still appears to be insufficient theoretical investigation into the approximations applied to the sorts of processes under discussion. In addition, the possible uses of the multivariate negative binomial approximations outlined in sections 2.2, 3.6, and 3.7 need to be looked at further, though the univariate results presented in Section 2.4 are encouraging.

The second contribution made is towards the understanding of the general effect of various types of immune mechanisms on the within-host parasite distributions. This can be applied to particular results observed for parasite-host relationships, and may help both to propose and to rule out hypotheses concerning the immune system behind observed results, and even to give more insight into the immune mechanism at work. The studies in Chapter 4 are only an initial step towards this, and clearly there is a lot more work required both from the mathematical and more applied side of the subject.

Appendix A

Moments of the Model of the Dynamics of Killing Parasites

The second order moments not given in Section 3.3.1 for the conditional process of the parasite-induced host mortality model of Section 3.2 are as follows;

$$\begin{aligned}
\mathrm{E}(L_c(t)) &= \int_0^t \phi(t-w)h'(\tilde{g}(w))e^{-\alpha_L w}\mathcal{F}_L(w)\,dw \\
\mathrm{E}(N_c(t)) &= \int_0^t \phi(t-w)h'(\tilde{g}(w))\tilde{g}_z(w)\,dw \\
\mathrm{var}(L_c(t)) &= \int_0^t \phi(t-w)h''(\tilde{g}(w))e^{-2\alpha_L w}(\mathcal{F}_L(w))^2\,dw + \mathrm{E}(L_c(t)) \\
\mathrm{var}(N_c(t)) &= \int_0^t \phi(t-w)((h''(\tilde{g}(w))(\tilde{g}_z(w))^2 + h'(\tilde{g}(w))\tilde{g}_{zz}(w))\,dw + \mathrm{E}(N_c(t)) \\
\mathrm{cov}(M_c(t), N_c(t)) &= \int_0^t \phi(t-w)\left(h''(\tilde{g}(w))\tilde{g}_z(w)\tilde{g}_y(w) + h'(\tilde{g}(w))\tilde{g}_{yz}(w)\right)dw \\
\mathrm{cov}(L_c(t), N_c(t)) &= \int_0^t \phi(t-w)h''(\tilde{g}(w))\tilde{g}_z(w)e^{-\alpha_L w}\mathcal{F}_L(w)dw
\end{aligned}$$

where

$$\begin{aligned}
\tilde{g}(w) := g(1,1,1,\alpha_L,\alpha_M;w) = \quad & e^{-\alpha_L w}\mathcal{F}_L(w) \\
+ \int_0^w e^{-\alpha_L u} f_L(u)\left[1-\sigma(u)+\sigma(u)\{e^{-\alpha_M(w-u)}\mathcal{F}_M(w-u) + \int_0^{w-u} e^{-\alpha_M v} f_M(v)dv\}\right]\,du
\end{aligned}$$

$$\tilde{g}_y(w) := \left.\frac{\partial g(x,y,z,\alpha_L,\alpha_M;w)}{\partial z}\right|_{x=y=z=1} = e^{-\alpha_M w}\int_0^w e^{(\alpha_M-\alpha_L)u}\sigma(u)f_L(u)\mathcal{F}_M(w-u)du$$

$$\tilde{g}_z(w) := \left.\frac{\partial g(x,y,z,\alpha_L,\alpha_M;w)}{\partial z}\right|_{x=y=z=1} =$$

$$k'(1)\int_0^w e^{-\alpha_L u} f_L(u)\sigma(u)e^{-\alpha_M(w-u)}\mathcal{F}_M(w-u)\int_0^{w-u}\rho(\tau)(\mathcal{F}_N(w-u-\tau))d\tau\,du$$

$$+k'(1)\int_0^w e^{-\alpha_L u} f_L(u)\sigma(u)\int_0^{w-u} e^{-\alpha_M v} f_M(v)\int_0^v \rho(\tau)(\mathcal{F}_N(w-u-\tau))d\tau\,dv\,du,$$

$$\tilde{g}_{yz}(w) := \left.\frac{\partial^2 g(x,y,z,\alpha_L,\alpha_M;w)}{\partial y\partial z}\right|_{x=y=z=1} =$$

$$\int_0^w e^{-\alpha_L v} f_L(v)\sigma(v)e^{-\alpha_M(w-v)}\mathcal{F}_M(w-v)\int_0^{w-v} k'(1)\rho(\tau)\mathcal{F}_N(w-v-\tau)d\tau dv$$

and

$$\tilde{g}_{zz}(w) := \left.\frac{\partial^2 g(x,y,z,\alpha_L,\alpha_M;w)}{\partial z^2}\right|_{x=y=z=1} =$$

$$\int_0^w \Big\{ e^{-\alpha_L u} f_L(u)\sigma(u)e^{-\alpha_M(w-u)}\mathcal{F}_M(w-u)$$

$$\int_0^{w-u}\rho(\tau)\mathcal{F}_N(w-u-\tau)(k'(1)+k''(1)\mathcal{F}_N(w-u-\tau))d\tau\Big\}du$$

$$+\int_0^w \Big\{ e^{-\alpha_L u} f_L(u)(\sigma(u))\int_0^{w-u} e^{-\alpha_M v} f_M(v)$$

$$\int_0^v \rho(\tau)\mathcal{F}_N(w-u-\tau)(k'(1)+k''(1)\mathcal{F}_N(w-u-\tau))d\tau dv\Big\}\,du.$$

Appendix B

Moment Equations for Immunity Model 1

The moments for the stochastic model of Grenfell, Dietz, and Roberts (1995a), focusing only on immunity, as described in Section 4.2, are as follows.

$$\begin{aligned}
\frac{d\mathrm{E}(L(t))}{dt} &= \phi\mathrm{E}(C) - \mu_L\mathrm{E}(L) - \beta\mathrm{E}(IL) \\
\frac{d\mathrm{E}(I(t))}{dt} &= \nu\mathrm{E}(L) - \mu_I\mathrm{E}(I) \\
\frac{d\mathrm{E}(L^2)}{dt} &= \phi\mathrm{E}(C^2) + (2\phi\mathrm{E}(C) + \mu_L)\mathrm{E}(L) - 2\mu_L\mathrm{E}(L^2) - 2\beta\mathrm{E}(L^2I) + \beta\mathrm{E}(LI) \\
\frac{d\mathrm{E}(I^2)}{dt} &= 2\nu\mathrm{E}(IL) + \nu\mathrm{E}(L) + \mu_I\mathrm{E}(I) - 2\mu_I\mathrm{E}(I^2) \\
\frac{d\mathrm{E}(IL)}{dt} &= \phi\mathrm{E}(C)\mathrm{E}(I) + \nu\mathrm{E}(L^2) - (\mu_I + \mu_L)\mathrm{E}(IL) - \beta\mathrm{E}(I^2L).
\end{aligned}$$

With the use of the normal approximation,

$$\mathrm{E}(IL^2) = 2\mathrm{E}(L)\mathrm{E}(IL) - 2\mathrm{E}(I)(\mathrm{E}(L))^2 + \mathrm{E}(L^2)\mathrm{E}(I)$$

and

$$\mathrm{E}(I^2L) = 2\mathrm{E}(I)\mathrm{E}(IL) - 2\mathrm{E}(L)(\mathrm{E}(I))^2 + \mathrm{E}(I^2)\mathrm{E}(L),$$

this reduces to

$$
\begin{aligned}
\frac{d\mathrm{E}(L(t))}{dt} &= \phi\mathrm{E}(C) - \mu_L\mathrm{E}(L) - \beta\mathrm{E}(IL) \\
\frac{d\mathrm{E}(I(t))}{dt} &= \nu\mathrm{E}(L) - \mu_I\mathrm{E}(I) \\
\frac{d\mathrm{E}(L^2)}{dt} &= \phi\mathrm{E}(C^2) + (2\phi\mathrm{E}(C) + \mu_L)\mathrm{E}(L) - 2\mu_L\mathrm{E}(L^2) \\
&\quad -2\beta\left[2\mathrm{E}(L)\mathrm{E}(IL) - 2\mathrm{E}(I)(\mathrm{E}(L))^2 + \mathrm{E}(L^2)\mathrm{E}(I)\right] + \beta\mathrm{E}(LI) \\
\frac{d\mathrm{E}(I^2)}{dt} &= 2\nu\mathrm{E}(IL) + \nu\mathrm{E}(L) + \mu_I\mathrm{E}(I) - 2\mu_I\mathrm{E}(I^2) \\
\frac{d\mathrm{E}(IL)}{dt} &= \phi\mathrm{E}(C)\mathrm{E}(I) + \nu\mathrm{E}(L^2) - (\mu_I + \mu_L)\mathrm{E}(IL) \\
&\quad -\beta\left[2\mathrm{E}(I)\mathrm{E}(IL) - 2\mathrm{E}(L)(\mathrm{E}(I))^2 + \mathrm{E}(I^2)\mathrm{E}(L)\right].
\end{aligned}
$$

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