Modelling patterns of parasite aggregation in natural populations: trichostrongylid nematode–ruminant interactions as a case study

B. T. GRENFELL[1], K. WILSON[1], V. S. ISHAM[2], H. E. G. BOYD[1] *and* K. DIETZ[3]

[1] *Department of Zoology, University of Cambridge, Downing Street, Cambridge CB2 3EJ, UK*
[2] *Department of Statistical Science, University College London, Gower Street, London WC1E 6BT, UK*
[3] *Department of Medical Biometry, University of Tübingen, 72070 Tübingen, Westbahnhofstr. 55, Germany*

SUMMARY

The characteristically aggregated frequency distribution of macroparasites in their hosts is a key feature of host–parasite population biology. We begin with a brief review of the theoretical literature concerning parasite aggregation. Though this work has illustrated much about both the sources and impact of parasite aggregation, there is still no definitive analysis of both these aspects.We then go on to illustrate the use of one approach to this problem – the construction of Moment Closure Equations (MCEs), which can be used to represent both the mean and second moments (variances and covariances) of the distribution of different parasite stages and phenomenological measures of host immunity. We apply these models to one of the best documented interactions involving free-living animal hosts – the interaction between trichostrongylid nematodes and ruminants. The analysis compares patterns of variability in experimental infections of *Teladorsagia circumcincta* in sheep with the equivalent wildlife situation – the epidemiology of *T. circumcincta* in a feral population of Soay sheep on St Kilda, Outer Hebrides. We focus on the relationship between mean parasite load and aggregation (inversely measured by the negative binomial parameter, k) for cohorts of hosts. The analysis and empirical data indicate that k tracks the increase and subsequent decline in the mean burden with host age. We discuss this result in terms of the degree of heterogeneity in the impact of host immunity or parasite-induced mortality required to shorten the tail of the parasite distribution (and therefore increase k) in older animals. The model is also used to analyse the relationship between estimated worm and egg counts (since only the latter are often available for wildlife hosts). Finally, we use these results to review directions for future work on the nature and impact of parasite aggregation.

Key words: Wildlife diseases, parasite, aggregation, *Teladorsagia circumcincta*, sheep, St Kilda, model, negative binomial distribution, moment closure equations, egg counts, immunity.

INTRODUCTION

Macroparasite abundance is measured ultimately by the statistical distribution of parasites between hosts. Parasites are characteristically aggregated in their hosts and, as reviewed by Shaw & Dobson (1995, this volume), this pattern can generally be described empirically by the negative binomial distribution. Theoretical models have shown that the observed patchiness in parasite abundance can have important consequences for host–parasite population dynamics (Anderson & May, 1978*a*, *b*; Roberts, Smith & Grenfell, 1995). However, current models cannot capture both the origins of parasite aggregation and its ecological impact (Grenfell, Dietz & Roberts, 1995).

In this paper, we use models and analyses of epidemiological data to explain the generation of macroparasite aggregation patterns in natural host populations. The main case study explores the epidemiology of gastrointestinal nematode parasites in wild ruminant populations, where there is a mass of comparative data from domestic ruminants (Coyne & Smith, 1994). We focus in particular on patterns of parasitism in an especially well-documented feral population of Soay sheep on the island group of St Kilda (Gulland, 1992; Gulland & Fox, 1992). In this system (as in many wildlife and human helminth infections) only counts of reproductive stages (in the St Kilda system, via faecal egg counts) are available. We therefore also use the models to assess how variability spreads through the parasite life-cycle, from infective larvae, through adult worms, to egg production.

The rest of the introduction gives a brief review of previous models for parasite aggregation. We then introduce a new model and review observed patterns of parasitism in domestic sheep on St Kilda. A combination of models and data is then used to interpret general patterns of parasite aggregation.

Modelling parasite aggregation

Previous studies can be divided into 3 broad categories.

Ecological consequences of parasite aggregation. These have been explored mainly by using the negative binomial distribution as a phenomenological model. The resulting formulations have been

highly successful in exploring the potential impact of parasites on the stability of natural populations (Crofton, 1971; Anderson & May, 1978*a*, *b*, 1991; Dietz, 1982; Grenfell, 1988, 1992; Hudson & Dobson, 1995). The crucial issue here is the balance between parasite-induced mortality, and reproductive limitations due to parasitism (which act, respectively, to stabilize and destabilize host dynamics (Anderson & May, 1978*a*, *b*; Roberts *et al.* 1995)). Essentially, increasing parasite aggregation enhances the stabilizing effects of parasite-induced host mortality (Anderson & May, 1978*a*, *b*).

Causes of parasite aggregation. The above strategy does not focus on the mechanisms generating observed aggregation patterns. The second approach attacks this problem using explicit stochastic models of the demographic processes which generate parasite distributions (Hadeler & Dietz, 1983; Kretzschmar, 1989; Kretzschmar & Adler, 1993). The general age- and time-specific case is too intractable to generate biologically useful results relevant to parasite dynamics (Grenfell *et al.* 1995). However, simulation of special cases (Anderson & Gordon, 1982; Anderson & Medley, 1985*a*), and analytical approximations (Adler & Kretzschmar, 1992; Kretzschmar & Adler, 1993), can yield useful insights.

Interpreting observed aggregation patterns. One of the most successful approaches here has been to analyse the change in aggregation that accompanies observed patterns of parasite intensity with host age (Anderson & Gordon, 1982; Anderson & Medley, 1985*b*; Pacala & Dobson, 1988; Grenfell *et al.* 1990; Anderson & May, 1991; Grenfell *et al.* 1995). The main application of theory has been to interpret changes in parasite aggregation in cross-sectional age-structured data, though the approach is also applicable to longitudinal parasite data from cohorts of hosts (Grenfell *et al.* 1995). In essence, if aggregation (inversely measured by the negative binomial parameter, k) decreases with host age, this is evidence of a density-dependent effect, such as acquired immunity or parasite-induced host mortality (Pacala & Dobson, 1988).

This work parallels an extensive development of *immuno-epidemiological* theory (Anderson & Medley, 1985*b*; Quinnell & Keymer, 1990; Woolhouse, 1992), which examines the impact of acquired immunity to helminth infections on age-prevalence and intensity patterns. Most of the development of this theory has been based on the negative binomial assumption; however, recent work has emphasized the stochastic implications of immunity (Woolhouse, 1992; Grenfell *et al.* 1995; Isham, 1995).

Synthesising these approaches would involve producing a tractable model for host–macroparasite dynamics which allows for both the origins and effects of aggregation. This is a difficult technical problem (Grenfell *et al.* 1995). Though refinements to non age-structured models can generate useful insights (Adler & Kretzschmar, 1992; Kretzschmar & Adler, 1993), ideally we need to record parasite dynamics though host age as well as time. The resulting models should also track the development of mean parasite burdens, as well as the second moments (variances and covariances) of the distribution of different parasite stages, which determine their level of aggregation. However, the inclusion of second and higher moments in models involving nonlinearities, such as host immunity or parasite-induced host mortality, requires us to achieve *moment closure* (Isham, 1995). Specifically, we have to allow for the fact that equations for the second moments have terms involving third moments, and so on for the higher moments.

These effects can be modelled by using normal approximations for the third and higher moments (Whittle, 1957; Kurtz, 1971; Isham, 1991; Grenfell *et al.* 1995) – see the Appendix for more details. In principle, the resulting Moment Closure Equations (MCEs) could be used to represent the full parasite life-cycle in age-structured host populations. However, their behaviour is potentially very complex and, first, we need to establish how observed transmission patterns in natural host populations generate the observed age-distribution of aggregation, in both adult parasite and egg counts.

This is the aim of the present paper, which focuses on two issues.

(a) *How do age-specific parasite burden and degree of aggregation co-vary?* Previous work has focused on looking for decreases in aggregation (indicated by an increase in the fitted negative binomial parameter, k) with increasing host age (Anderson & Gordon, 1982; Pacala & Dobson, 1988; Roberts *et al.* 1995). This shortening of the upper tail of the parasite distribution in older hosts provides evidence for density-dependent effects, such as parasite-induced host mortality or host immunity (Anderson & May, 1991; Roberts *et al.* 1995). Recently, Grenfell *et al.* (1995) used a MCE to show that, in homogeneous host populations, the fitted value of k for the parasite load tends to track the mean parasite load in the host population, which plateaus or declines with host age. By contrast, host heterogeneities, especially differences in immunocompetence or host survival in the face of parasitism, can cause k to increase in old individuals, whilst the mean declines or remains constant (Anderson & Gordon, 1982). Here, we examine how the models relate to data on the aggregation of parasites in cohorts of hosts, in experimental or natural infections.

(b) *Are egg counts reliable indicators of these epidemiological patterns?* There is an extensive literature in this area (Smith, 1995), examining the use and abuse of egg counts as an index of parasitism.

Here, we use models to examine the relationship between variability in worm and egg counts and the effects of the latter of immunological limitations on parasite egg production.

DATA SETS AND MODELS

Epidemiological data

General reviews of the epidemiology of trichostrongyid nematode–ruminant interactions are given by Grenfell, Smith & Anderson (1987*a*, *b*) and Coyne & Smith (1994). We focus on the interaction between sheep and the trichostrongylid nematode *Teladorsagia circumincta* – the main parasite species on St Kilda (Gulland, 1992; Gulland & Fox, 1992). The analysis of parasite variability is based on two data sets.

Experimental infections. These are a rich source of data on the infection dynamics of *T. circumcincta* and other gastrointestinal parasites of ruminants (Michel, 1970; Grenfell *et al.* 1987*a*, *b*; Hong, Michel & Lancaster, 1987; Smith & Galligan, 1988; Coyne & Smith, 1994). The main division is between experimental infections on a single occasion and trickle infections, which simulate better the conditions of infection in the field. Here, we concentrate on a detailed series of trickle infection experiments, performed by Hong *et al.* (1987) and previously modelled by Smith (1989). The design involved worm counts from replicated serial sacrifice of groups infected at 3 different daily levels (250, 500 and 1000 infective larvae per day), with parallel egg counts. The replication of counts (4 at each time point) allows us to estimate crudely the change in parasite aggregation, in addition to mean burdens.

Naturally-regulated hosts : St Kilda parasite counts. St Kilda is a small group of islands west of the Outer Hebrides in north-west Scotland. Soay sheep have occupied the archipelago for at least 2000 years and the study population has lived on Hirta, the largest of the islands, since 1932. The sheep are entirely unmanaged and have no regular predators or competitors. However, they do harbour a significant parasite community, which has been implicated in the severe population 'crashes' that occur every 3–4 years (Grenfell *et al.* 1992; Gulland, 1992; Gulland & Fox, 1992). The helminth parasites of the sheep have been intensively monitored since August 1988 (Gulland, 1992; Gulland & Fox, 1992). This entails both the regular collection of fresh faecal samples from ear-tagged sheep for the estimation of faecal egg counts and an assessment of the adult worm burdens of sheep dying naturally during population crashes.

For comparative purposes, we also analyse data on the aggregation pattern of egg counts from field infections of domestic sheep, presented by Stear *et al.* (1995).

The model

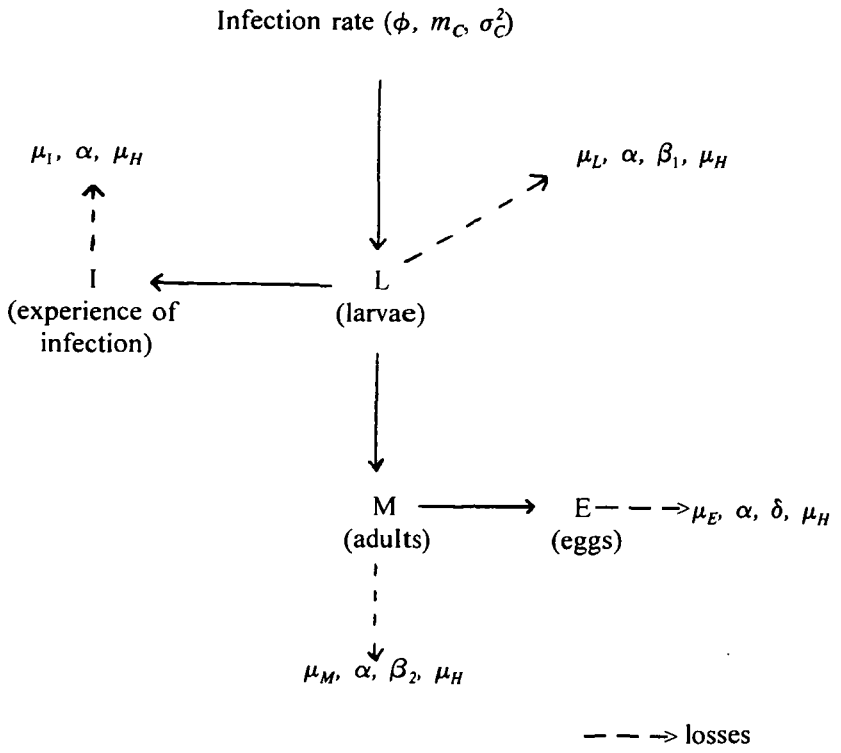
Coyne & Smith (1994) give a general review of models for trichostrongylid parasites of ruminants. These formulations follow the standard pattern for directly transmitted macroparasites (Anderson & May, 1991). Hosts ingest infective larvae, which pass through larval stages in the gut mucosa, then emerge and develop into adults. Adult female worms produce eggs, which are voided in the host faeces, then develop into infective larvae on the pasture, completing the cycle. Early in the infection of young animals, the infection dynamics are approximately linear (Grenfell *et al.* 1987*b*), though immunity subsequently develops with the host's accumulated experience of larval intake. Immunity can limit any combination of larval establishment, adult parasite survival, or parasite reproductive rate, depending on the species of parasite (Coyne & Smith, 1994); immunity to *T. circumcincta* acts on all these processes (Smith & Galligan, 1988).

Previous models have generally been framed in terms of the dynamics of mean parasite burden (Coyne & Smith, 1994). Here, we adapt a general MCE for the immuno-epidemiology of these parasites, proposed by Grenfell *et al.* (1995). This allows us to track the degree of parasite aggregation as a function of host age, as well as of the mean burden. Full details of the model are given in the Appendix. The main features of the model are as follows (see Fig. 1 for a flow diagram and definitions of parameters).

(*i*) *Variability in infection rate* is modelled explicitly by using a compound Poisson process. Thus we assume that, for any individual host, encounters with parasite transmission stages occur in an inhomogeneous Poisson process (i.e. the rate, $\phi(a)$, depends on the age a of the individual host). During an encounter, the number of parasites input, C, is a random variable with mean m_C and variance σ_C^2. By taking $m_C = 1$ and $\sigma_C^2 = 0$, this model for the infection process reduces to an ordinary (inhomogeneous) Poisson process. The model tracks infection variability through larval (L), adult (M) and egg (E) parasite stages. Additional variability due to differences between hosts can then be modelled by replicating the model equations with varying parameters (see below). The constant background *per capita* death rates of larvae and adults are denoted by μ_L and μ_M per unit time respectively. Larvae develop into adults at rate γ.

(*ii*) *Parasite reproduction and the calculation of egg counts*: adult parasites are assumed to reproduce at an average rate λ per unit time (we ignore sex in this first version of the model). We wish to model egg counts per gram of faeces, rather than total egg

(a)



(b) DEFINITION

Loss rates:

$1/\mu_I$	Duration of immunological memory
$1/\mu_L$	Life expectancy of larvae in the host
$1/\mu_M$	Life expectancy of adult worms
$1/\mu_E$	'Loss rate' of eggs from faeces (see text)
$1/\mu_H$	Life expectancy of hosts without parasites
α	Additional death rate of hosts induced by 1 adult parasite
β_1	Additional death rate of larvae due to 1 unit of infection experience
β_2	Additional death rate of adult parasites due to 1 unit of infection experience
δ	Additional loss rate of eggs due to 1 unit of infection experience

Infection and development rates:

φ(a)	Encounter rate with infective larvae constant with age
m_C, σ_C^2	Mean and variance of larvae ingested per encounter
γ	Development rate larvae
ν	Rate of increase of immunity level due to larvae
λ	Egg production rate per adult parasite

Fig. 1. (a) Schematic diagram of the model infection process. (b) Definitions of model parameters.

production. In principle, this would involve integrating the net egg production rate over a short time interval, corresponding to the production of 1 g of faeces. However, we can model this more simply by assuming that the 'loss rate' of eggs, μ_E, reflects the expulsion of eggs from faeces, as well as their death rate in the absence of immunity. Soay sheep produce on the order of 1 kg of faeces per day (K. Wilson, unpublished data), so that a gram of faeces will be expelled on a much shorter timescale (0·001 days on average) than other processes in the model. The 'loss rate' of eggs, μ_E, is therefore dominated by the expulsion of eggs in faeces (which is much larger than any of the other loss rates). Given this assumption (i.e. that $\mu_E \approx 1000$/day), we can use E as a crude index of eggs available to be counted per gram of faeces.

(*iii*) *Nonlinear effects: immunity and parasite-induced host mortality*: immunity is assumed to accumulate with the host's previous experience of

larval intake (Coyne & Smith, 1994). We make the simplest assumption, mathematically, that previous experience of infection accumulates with the larval burden (L) at rate ν, and decays at rate μ_I (so that $1/\mu_I$ is the average 'memory' of previous infection (Grenfell *et al.* 1995)). Since the simulations described below consider infection in young animals, we take $\mu_I = 0$ (i.e. no fading of immune memory; (Smith & Galligan, 1988)). Previous experience of infection (I) is assumed to increase the mortality of larvae by a rate $\beta_1 I$ and the mortality of adults by $\beta_2 I$, where β_1 and β_2 are parameters. Immune regulation of egg production is controlled by a third parameter, δ: egg production is reduced at rate δI. Parasite-induced host mortality is taken to be proportional to the adult burden, with rate parameter α per adult worm. Host mortality then, of course, kills both larvae and adults. Hosts die in the absence of parasites at rate μ_H (which we take to be zero in most of the simulations presented below).

(*iv*) *Parasite variables.* The model tracks parasite abundance and average immunological experience as a function of host age (a), in terms of the first moment (mean). Means are denoted by $m_A(a)$, where $A = I, L, M, E$ for the respective variables. The variability of the system is represented by the second moments, for example $\sigma_L^2(a)$ is the variance of larval counts and $\sigma_{ME}(a)$ is the covariance of adult burden and egg counts.

The Appendix derives a set of ordinary differential equations to describe the dynamics of these variables as a function of host age. We then assess parasite aggregation by the moment estimate of the negative binomial parameter, k. For example, k for adult parasites is given by $k_M(a) = m_M(a)^2/(\sigma_M^2(a) - m_M(a))$. Though the underlying distribution will not, in general, be exactly negative binomial, $k_M(a)$ gives us a basis for comparison of the model with measures of parasite aggregation from field data. The covariances also allow us to assess correlations between parasite variables, as described below.

RESULTS AND DISCUSSION

Experimental infections

Mean worm and egg counts. Figs. 2 and 3 show the observed temporal pattern of worm and egg counts respectively from the trickle infection experiments reported by Hong *et al.* (1987). We use the MCE approach to examine the relationship between mean adult worm and egg counts and the corresponding levels of parasite aggregation. The first step is to fit the model to the observed mean worm and egg counts.

Mean patterns of parasitism. Fig. 2 displays a least squares fit of the model to total worm count for the 3 infection levels, estimating the larval and adult

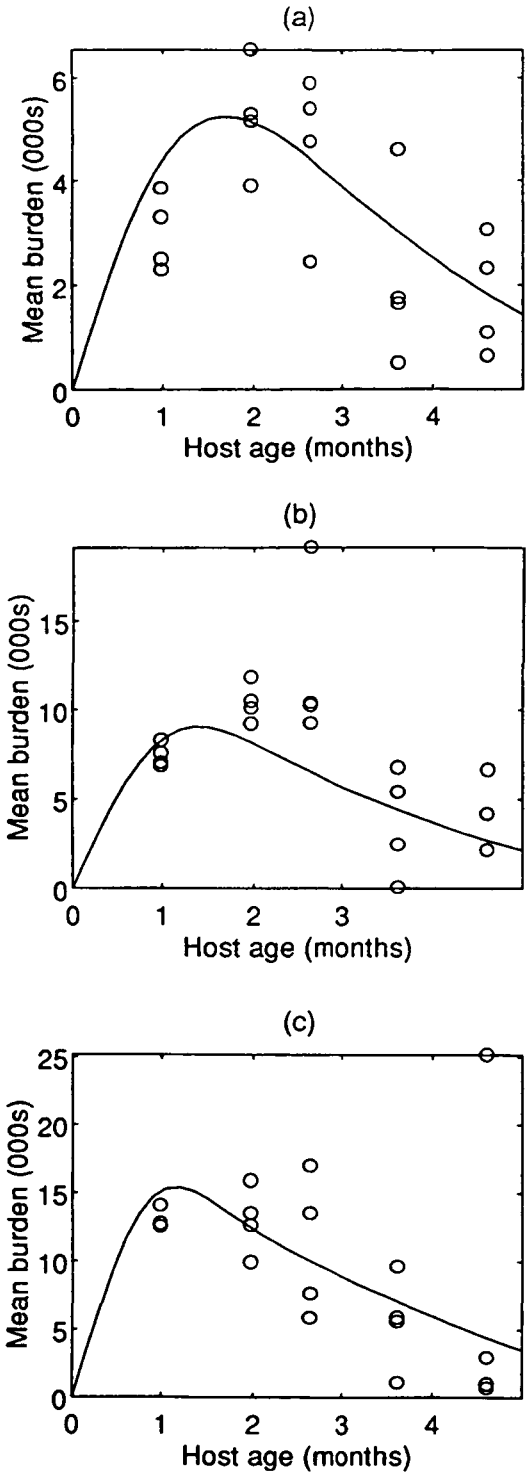


Fig. 2. Total worm burden in lambs infected daily with (a) 250, (b) 500 and (c) 1000 infective larvae of *T. circumcincta* (Hong *et al.* 1987). Symbols are observed burdens and the curves are from numerical simulation of the model described in the text. The model was fitted to the observed counts by nonlinear least squares, estimating the immunity parameters: $\beta_1 = 0{\cdot}15$ (95% limits 0·132, 0·17); $\beta_2 = 0{\cdot}045$ (95% limits 0·032, 0·06). Other parameters of the model were taken from Smith & Galligan (1988), as follows (rates are all per day): $\nu = 1$, $\mu_M = 0{\cdot}02$, $\gamma = 0{\cdot}1$, $\alpha = 0$, $\phi = 1$. Following Smith & Galligan (1988), we assume that 75% of larvae succeed in establishing in the abomasum.

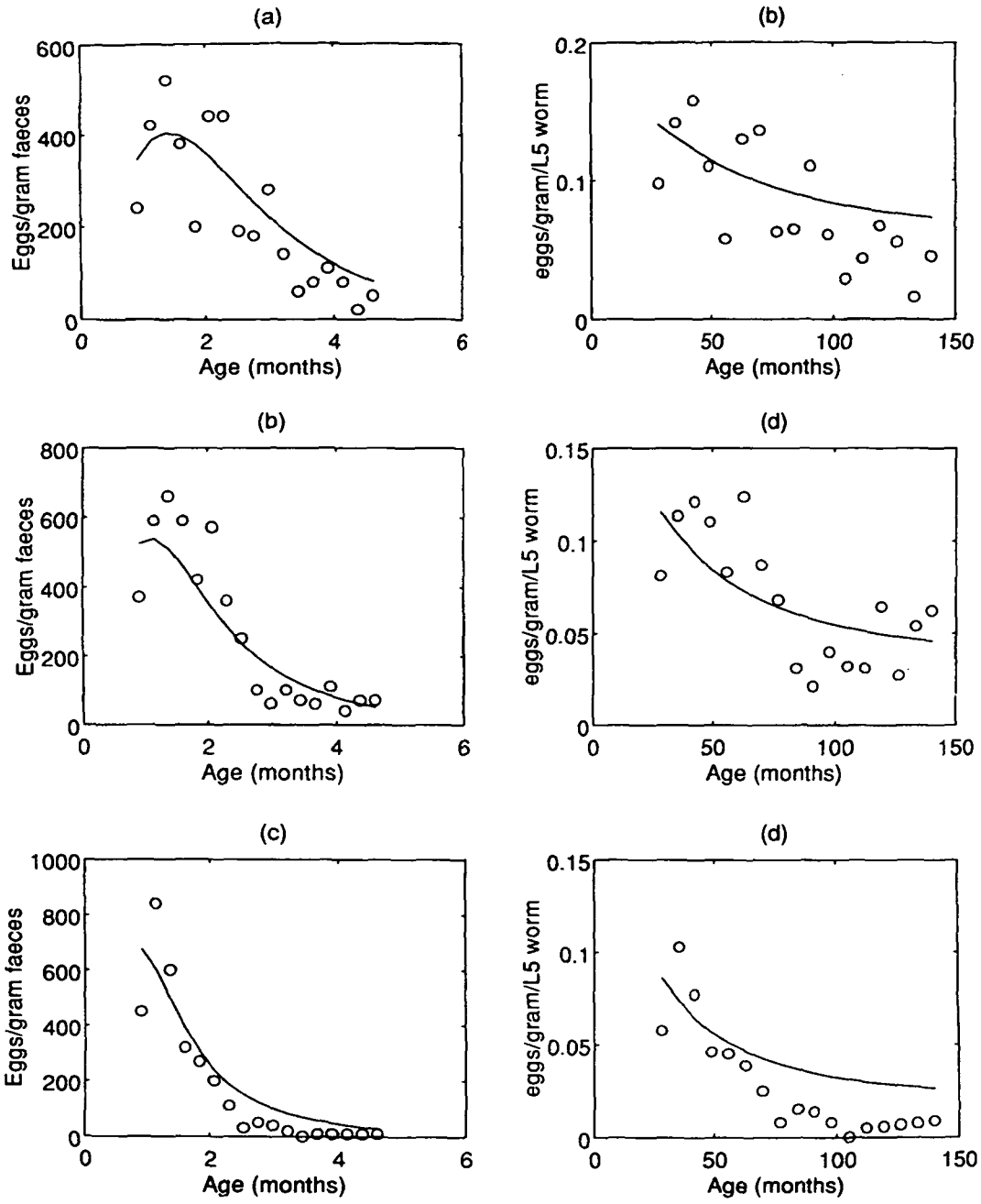


Fig. 3. Egg counts from the same experiment as Fig. 2 (Hong *et al.* 1987). (a)–(c) total eggs per gram faeces; (d)–(f) eggs per gram faeces per adult worm. Curves show a least squares fit of the model, as described in the text, estimating the parasite reproductive parameters: $\lambda = 179{\cdot}5$/day (95% limits 161, 196·2), $\delta = 2{\cdot}97$/day (95% limits 2·53, 3·46). Other model parameters are as in Fig. 2.

immunity parameters, β_1 and β_2 (other model parameters were taken from Smith (1989) – see legend to Fig. 3). The dose of infective larvae in this class of infection experiments is generally found to be approximately Poisson-distributed (Anderson & Michel, 1977). We allow for this by assuming a daily infection rate (ϕ) and setting the dose per encounter, C, to unity (i.e. $m_C = 1$; $\sigma_C^2 = 0$). We also assume a homogeneous host population, so that model parameters do not vary between hosts.

Like similar deterministic formulations (Smith, 1989), the MCE approach captures the dynamics of mean burden relatively well – burdens rise initially, then decline as larval and adult immunity increase the loss rate of parasites. In order to represent the equivalent observed pattern of egg counts, we also need to estimate the reproductive immunity parameter, δ. Fig. 3 shows the resulting least squares fit between observed and expected egg counts. Though the model captures the overall decline in egg counts (Fig. 3a–c), it tends to underestimate the decline in egg counts in older hosts. This implies that there may be a more nonlinear increase in limitations on egg production than indicated by δ in our simple

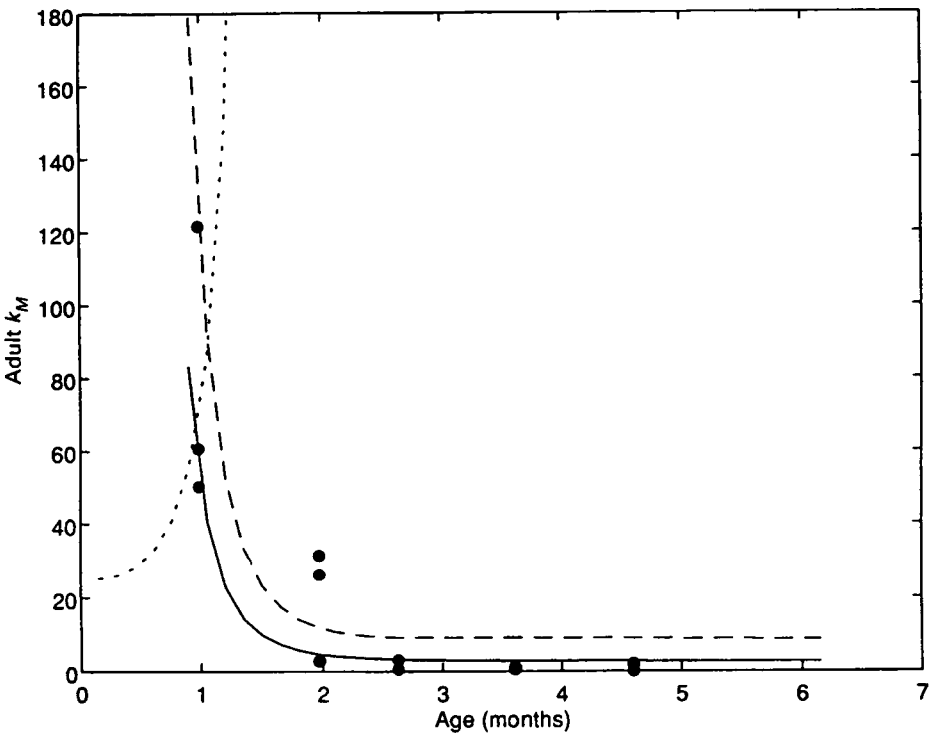


Fig. 4. Estimated negative binomial parameter, k_M, for adult counts from Hong *et al.* (1987) (circles). The curves show various model fits, as described in the text (other parameters as in Fig. 2). Dotted line, 2 groups with a 50% difference in the infection parameter (ϕ). Solid line, 2 groups with 25% difference in the immunity parameter, β_2; dashed line, 10% difference in β_2.

model. The observed decline in worm reproductive rate probably reflects the stunting of worms in later cohorts during the infections (Coyne & Smith, 1994).

Patterns of variability in worm counts. We can assess the observed degree of aggregation in worm burden, using the replication of counts at each time point. The observed burdens show a progressive increase in aggregation with time, illustrated by a plot of the moment estimate of k_M for adult worms (Fig. 4). Early in the infections, the k_M values for all infection levels are high (> 40, indicating consistency with a Poisson distribution); k_M then declines sharply (and in a similar manner for the 3 infection levels).

By contrast, the homogeneous model with $C = 1$ generates a distribution for worm burden that is approximately Poisson – the variance is almost equal to the mean and the moment estimate of k_M is uniformly high and much greater than that observed after host age 2 months. This result is not surprising, since Poisson input tends to generate a Poisson distribution of burden in this broad class of parasite model (Pacala & Dobson, 1988; Isham, 1995).

The relatively high aggregation of the observed counts indicates that the model is missing a significant source of heterogeneity. Since models and data are both consistent with a Poisson distribution for the early infections, it seems likely that the extra variation is due to heterogeneity between hosts, rather than greater heterogeneity in the infection process. Differences between hosts could be some combination of:

(*a*) *Linear effects*, for example density-independent variations in establishment of infection between hosts (Smith, 1989). To test this extreme with the model, we assumed that half the hosts had a 50% higher infection rate, ϕ, and calculated k_M from the weighted variance of the two groups (again assuming that $C = 1$). Fig. 4 shows the results. The model k_M value is relatively low at the start of the infection, reflecting the heterogeneity in infection rate. It then increases rapidly, as a greater level of immunity in the higher infection group causes the two sets of worm burdens to converge. This is the *opposite* of the observed aggregation pattern.

(*b*) *Nonlinear effects*, in particular, differences in immunocompetence between hosts. To investigate this, we assumed that the two groups of hosts were identical, except that the adult immunity level, β_2, was higher in one group. Fig. 4 shows the effects of 10 and 25% differences in β_2. Both generate patterns qualitatively similar to the observations – a high initial k_M which declines sharply with time. At the start of the infection immunity levels in the model are low, so that the two groups of hosts are very similar and the adult k_M reflects a Poisson distribution. Increasing immunity then affects one group more than the other, causing the two populations to diverge and increasing the level of aggregation.

Overall, the results in Fig. 4 are consistent with

the impact of immunological heterogeneity on levels of parasite aggregation. This conclusion is supported by observed clinical and parasitological heterogeneities in some sheep during the experiment (Hong *et al.* 1987).

Egg count variability. Surprisingly, simulated egg counts have the *same* degree of aggregation (as measured by k_E) as worm counts. The effect can be explored by considering the asymptotic equilibrium of the model, in the absence of immunity and parasite-induced host mortality ($\nu = \alpha = 0$; see Appendix and Grenfell *et al.* (1995)). For this special case, we can write (assuming that the egg loss rate μ_E is much larger than other parasite loss rates)

$$m_E = \lambda m_M/\mu_E, \quad \sigma_E^2 = m_E + m_E\sigma_{ME}/m_M.$$

It follows (see Appendix) that $\sigma_E^2 \approx (m_E/m_M)^2\,\sigma_M^2$ and therefore that the coefficient of variation of E, CV_E obeys:

$$\mathrm{CV}_E^2 = \sigma_E^2/\mu_E{}^2 \approx \sigma_M^2/\mu_M^2 = \mathrm{CV}_M^2.$$

In other words, the coefficient of variation (and therefore also k, since $k \approx 1/\mathrm{CV}^2$ when the mean is large) is similar for adult worms and egg counts – how much variability this represents then depends on the size of the mean burden. These results ignore the relative sampling efficiency for eggs and worms – allowing for this, we would expect observed egg counts to be more variable than worms counts. However, they do indicate (as we observed for the St Kilda system) that the coefficient of variation (and therefore estimated k) for worm and egg counts should be of roughly the same magnitude.

Relationship between worm and egg counts: Apart from assessing levels of variability, the model also allows us to calculate the correlation between parasitological variables. In terms of analysing field data, the most important of these is the relationship between worm and egg counts. Fig. 5 analyses the expected correlation of worm and egg counts from the trickle infection model and, in particular, the effects of immunity against egg production. Fig. 5a shows the fitted mean egg count curve for the highest infection level, compared to the curve without reproductive limitations on the parasites (i.e. $\delta = 0$). The equivalent correlation coefficients between worm and egg counts are shown in Fig. 5b. For $\delta = 0$, the correlation essentially tracks the mean egg and worm counts, increasing and then declining over the period of the experiment. This happens because, at low mean egg and worm counts, the variances are relatively higher than the covariance, which lowers the correlation. When parasite reproductive limitation ($\delta > 0$) is superimposed on this, the same qualitative picture holds. However, as the degree of host immunity increases, this reduces the correlation disproportionately as compared to $\delta = 0$ – in other words, host immunity acts to reduce the correlation between egg and worm counts. These results are based on a Poisson infection process ($C = 1$). Further simulations (for example, the dashed line, documented further in Fig. 4) show that aggregated infection rates ($C > 1$) *increase* the correlation between worm and egg counts, as compared to the Poisson case. Essentially this happens because, in the aggregated input case, pulses of high infection

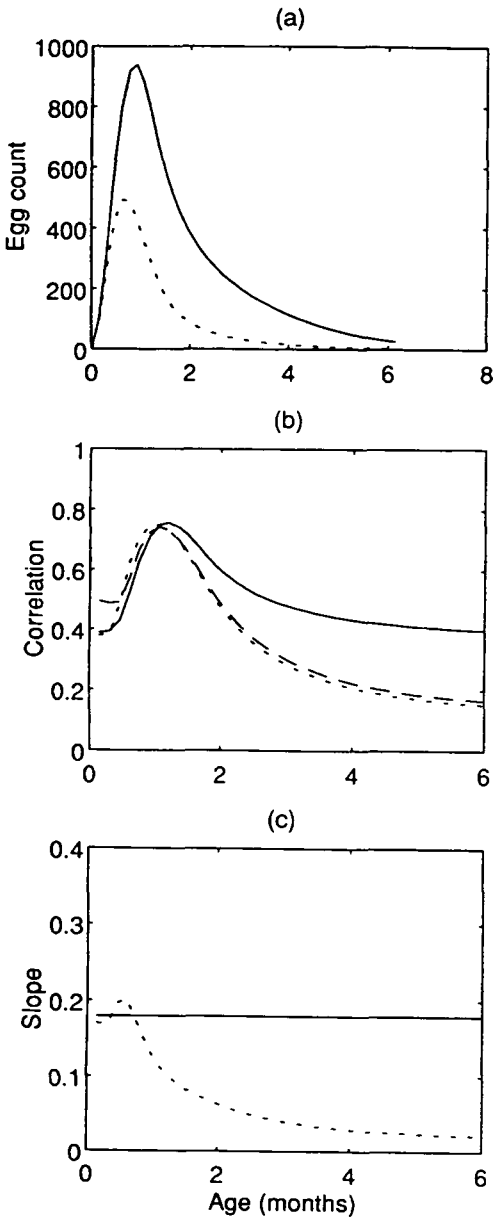


Fig. 5. Relationship between worm and egg counts from the model described in Fig. 2. (a) Egg counts as a function of host age: solid line, no immunological limitations on parasite reproduction ($\delta = 0$); dotted line, $\delta = 2{\cdot}97$. (b) Correlation between worm and egg counts as a function of host age; line styles as above – the dashed line is from a simulation identical to the dotted line, except that the infection rate (C) is aggregated, with $m_C = 1$, $\sigma_C^2 = 5$. (c) Regression coefficient of egg counts against worm counts, for the cases in (a).

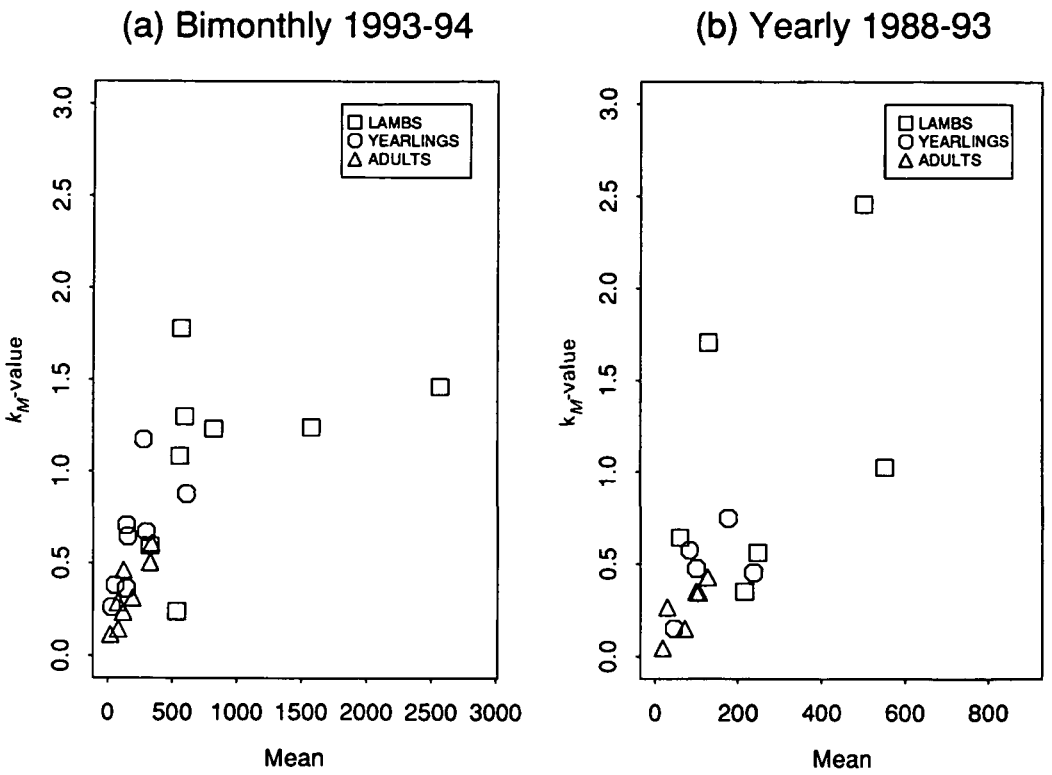


Fig. 6. Relationship between mean and degree of aggregation in faecal strongyle egg count and aggregation in female Soay sheep on St Kilda, as measured by the moment estimate of the index k of the negative binomial distribution. Different symbols refer to different age-classes, see key. (a) approximately bimonthly egg counts made between August 1993 and June 1994, when 'lambs' were 4–13 months old, 'yearlings' 16–25 months old and 'adults' at least 28 months old; (b) yearly egg counts made each August between 1988 and 1993, when 'lambs' were approximately 4 months old, 'yearlings' 16 months old and 'adults' at least 28 months old.

rate in some individuals will be passed through the parasite life-cycle from larvae, through adults to eggs.

Finally, Fig. 5c shows the estimated regression coefficient between worms and egg counts. As expected, this is constant for $\delta = 0$. By contrast, immunity causes the slope to decrease after an early transient over the infection, as the effective per capita reproductive rate of worms decreases.

Field infections

The overall epidemiological pattern of trichostrongylid infections in St Kilda sheep is similar to that in mainland hill sheep (Gulland, 1992; Gulland & Fox, 1992). Egg counts peak in the summer in lambs and at times of stress or immunosuppression in older animals. A subsequent paper will consider models of these patterns – here we examine the relationship between the mean and degree of aggregation of egg counts. Fig. 6 illustrates the relationship between k_E and the mean for faecal egg counts for female Soay sheep on St Kilda at 2 temporal scales: 8 monthly or bimonthly counts made between August 1993 and June 1994 and 7 yearly counts made in August each year between 1988 and 1994. Regardless of whether one looks at

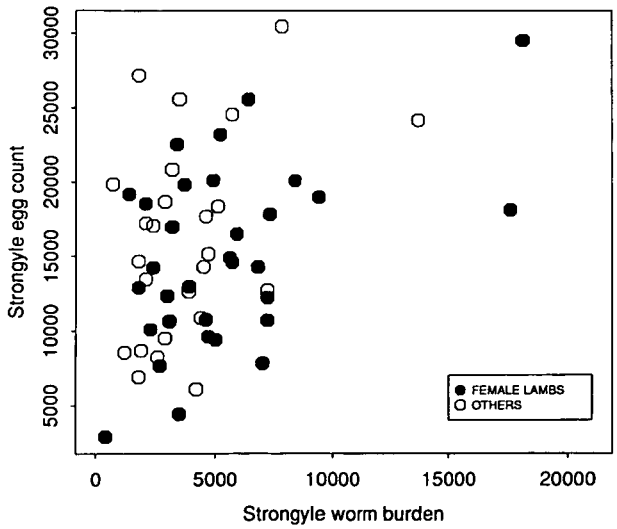


Fig. 7. Relationship between strongyle worm burden and faecal egg counts in 75 sheep that died during the population crash of 1991/2. Closed symbols refer to female lambs ($n = 32$) and open symbols to the other age–sex classes. Faecal egg counts are the last counts made before the death of the sheep (mean number of days before death $\pm$ S.D. = 16·6 $\pm$ 14·3). Pearson's correlations: all sheep, $r = 0{\cdot}425$ ($p < 0{\cdot}002$); female lambs, $r = 0{\cdot}629$ ($p < 0{\cdot}0003$).

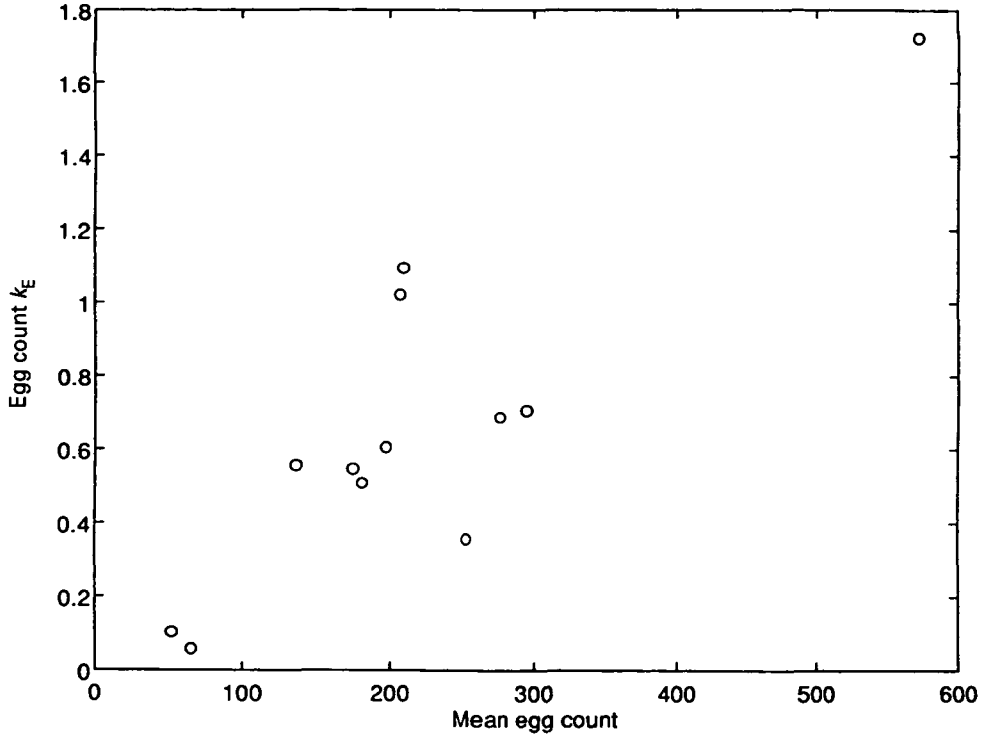


Fig. 8. Relationship between moment estimate of k_E and mean for egg counts of *T. circumcincta*, reported by Stear *et al.* (1995).

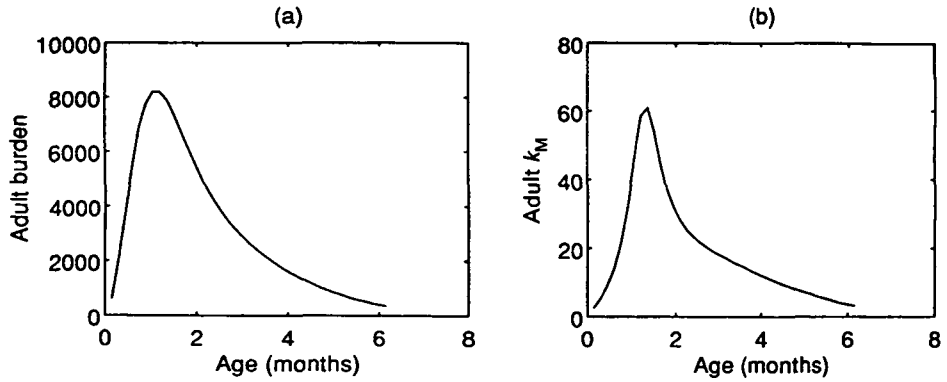


Fig. 9. Simulated (a) worm burden and (b) faecal egg count as a function of host age. The model is as in Fig. 2, except that the infection process has an aggregated distribution ($\phi = 500$/day, $m_C = 500$, $\sigma_C^2 = m_C + m_C^2$).

variation within or between years (Fig. 6a, b, respectively), k_E tracks the mean egg count. Although there is some evidence for k_E plateauing at high mean egg counts (Fig. 6a), this is far from clear.

On St Kilda, the strongyle worm burdens of sheep dying naturally during the 1991/2 crash were positively correlated with their last faecal egg count before death (Fig. 7). For all sheep combined the correlation coefficient was 0·425 ($n = 75$, $p < 0{\cdot}002$) and for female lambs (the most numerous class of animals for which we have data) it was 0·629 ($n = 38$, $p < 0{\cdot}01$), though there are other complexities in the within the range of worm–egg correlations shown in Fig. 5.

For comparison, Fig. 8 shows the relationship between egg count mean and the moment estimate of k_E for *T. circumcincta* infections in domestic sheep (Stear *et al.* 1995). Again k_E roughly tracks the mean (Pearson correlation between mean and k, $r = 0{\cdot}846$, $p < 0{\cdot}01$), though there are other complexities in the detailed pattern (Stear *et al.* 1995). Stear *et al.* (1995) measured the dynamics of aggregation using egg counts. It would be interesting for further field studies to measure the temporal dynamics of *worm burden* aggregation, as well as the correlation between worm and egg counts.

Model interpretation of field patterns

By contrast with experimental infections, where we

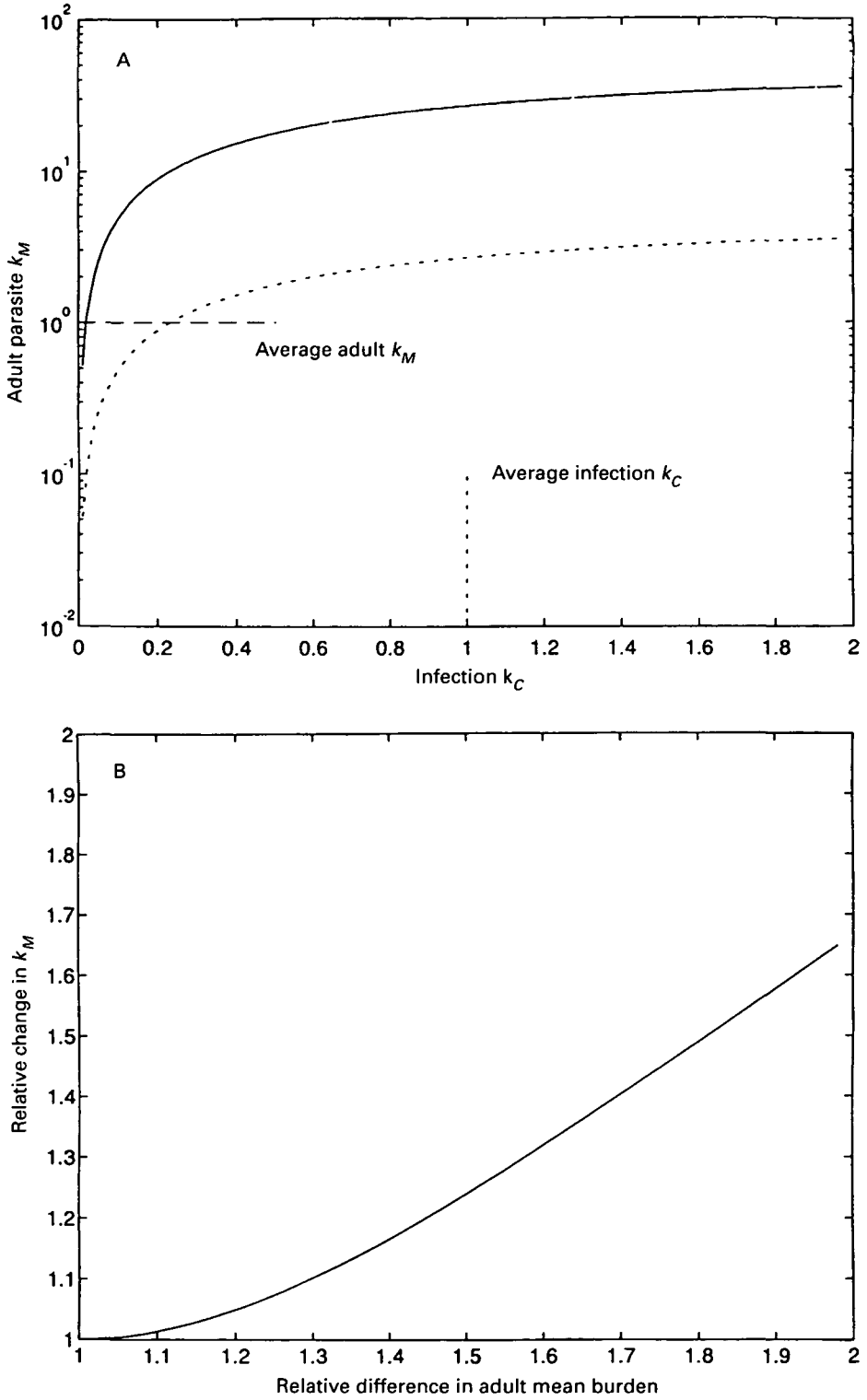


Fig. 10. (a) Asymptotic relationship ($a \to \infty$) between moment estimates of negative binomial index k_M for adults and for the infection process k_C, as defined in the text (see also (Grenfell *et al.* 1995)). Parameters are as in Fig. 2, the encounter rate (ϕ) is adjusted to give mean adult worm burdens of 1000 (dotted curve, $\phi = 20$) and 10000 (solid curve, $\phi = 200$). The horizontal and vertical lines show the average levels of aggregation observed on St Kilda: vertical (dotted) line – average k_C; horizontal (dashed) line – average k_M from post-morten worm counts) for St K. (b) Estimated change in overall index k_M when one of 2 initial populations dies of parasitism. Population 1 has mean burden 10000 worms and $k_M = 5$, while population 2 has the same k_M and a variable (larger) mean than population 1. the curve shows the increase in overall k_M (calculated from the weighted mean and variance of the 2 populations) when population 2 dies from parasitism, as a function of the difference between the means of the 2 populations.

can assume a Poisson process for the infections, the infection rate in the field is likely to be highly variable (Pacala & Dobson, 1988). For example, field surveys on St Kilda indicate that pasture counts of infective larvae are aggregated, with a moment estimate of k_L of around unity. Following Grenfell *et al.* (1995), we can include this in the model by allowing C to be variable and defining $k_C \equiv m_C^2/(\sigma_C^2 - m_C)$. Fig. 9 shows the simulated dynamics of mean adult parasite worm counts, and k_M for adult parasites, assuming that $k_C = 1$. As with the empirical picture, the mean tracks k_M.

However, one significant discrepancy with the field results is that k_M in the models is much higher (and therefore the variability is lower) than that observed (compare Figs 6, 7 and 9). Fig. 10a explores this further by plotting the asymptotic relationship between the index k_C for the infection process, and the index k_M for the adult parasites – see Grenfell *et al.* (1995) for more details. To achieve the observed level of variability for both worms and eggs ($k \approx 1$, for the St Kilda counts), requires an input variability of $k_C \approx 0{\cdot}2$. In fact, as shown in Fig. 10a, the observed variability of pasture counts of infective larvae corresponds to an infection input value for k_C of around 1.

This implies that we need to allow for other sources of variability. The obvious culprit here is heterogeneity in the response of the host to infection, as explored in Fig. 4. Such between-host heterogeneities are also likely to be primarily responsible for situations when k_M does not track the mean burden (Anderson & Gordon, 1982; Grenfell *et al.* 1995). This is most important when the mean burden plateaus or declines in older hosts, whereas k_M increases, due to parasite-induced host mortality or immunity. In fact, even though there is strong evidence for parasite-induced host mortality during population crashes on St Kilda (Gulland, 1992; Gulland & Fox, 1992), k_M still tracks the mean over these periods. This occurs even though egg counts in survivors of a crash are significantly lower than those of future victims for a considerable period before the crash. Fig. 10b explores this effect, calculating the overall weighted k_M of two groups of hosts with different mean counts, then simulating a crash by eliminating the group with the higher mean. Fig. 10b shows the resultant increase in k_M as a function of the initial difference between means. In general, a relatively large difference in mean counts is required to produce a significant increase in k_M after the crash (for example, in the figure, a 50% difference in mean produces a 20% increase in k_M). Since the observed difference in mean egg counts is only about 20%, we may therefore not be able to register any increase in k_M resulting from the crash. The increase in egg counts due to immunosuppression even of hosts that survive the crash will also complicate this picture.

CONCLUSION

In this paper, we have used analyses of published data, and epidemiological models, to examine the relationship between the mean and degree of aggregation of parasite load in trichostrongylid infections of experimental and wild sheep. The analysis focused on the simplest case – patterns of parasite aggregation in cohorts of hosts. However, even in this simple epidemiological scenario, the Moment Closure approach illustrates that nonlinearities, such as immunity and parasite-induced host mortality, can generate potentially complex interactions between the variance and covariances of parasite load and immunity.

In principle, this approach can be extended to produce an age-structured model of the full dynamics. However, modelling the dynamics of the free-living stages, as well as allowing for immunological and other differences between hosts, would produce a very complex formulation. Nevertheless, we consider this a useful approach (compared to studies based on stochastic simulation alone), because analytical results can be derived from special cases of the MCE model.

As illustrated above, this analytical approach can be used to generate simple, testable predictions about the origins and properties of parasite aggregation. We highlight two particular results. First, the model allows us to trace patterns of variability through the parasite life cycle. This leads to the surprising result that (ignoring differential sampling variance), we might expect similar coefficients of variation (and therefore k values) for adult worm and faecal egg counts. Though the result was derived from a simplified linear model, ignoring immunity and parasite-induced host mortality, it appears from simulations to be robust when these nonlinear effects are included. Essentially, the approximate invariance of the coefficient of variation derives from the fact that, over short time periods, the number of eggs generated is the sum of $M(a)$ Poisson variables, where $M(a)$ is the current worm burden. Clearly we need to examine the evidence for this effect in other host–parasite relationships. For example, the available evidence from the cat model for lymphatic filariasis indicates that k for adult worms and microfilariae are of similar size (Michael *et al.*, unpublished).

The second benefit of the analytical approach is that we can use the *covariance* structure of the model to examine relationships between variables. Potentially, this is particularly useful in human immuno-epidemiological work, where the models can be used to analyse observed correlations between immunological and parasitological variables.

Finally, in terms of future quantitative 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 infection simultaneously. Modelling prevalence as well as intensity would provide another variable for comparison with field data. It would also reflect both the persistence of the parasite population and the effects of host immunity on it, much more accurately than tracking parasite intensity alone. Again, this is technically a difficult task, though preliminary work indicates that approximations based on the negative binomial distribution show promise.

ACKNOWLEDGEMENTS

This research was supported by NERC (H.E.G.B., B.G., K.W.) and the Isaac Newton Institute for Mathematical Sciences, Cambridge (K.D., B.G., V.S.I.).

APPENDIX

Model definition

In this paper, we are considering a single host that is born at time $t = 0$, so that time and host age are synonymous. We assume that the host is exposed to a particular species of parasite at time instants modelled by a point process, and that at each such instant a random number of larvae is ingested. The state of the host at age a (conditionally upon the survival of the host to that age) is defined to be quadruple of variables $\{I(a), L(a), M(a), E(a)\}$ where $I(a)$ is a non-negative integer-valued variable representing the host's immunity level and reflects the host's experience of past infections of the parasite, and $L(a)$ and $M(a)$ are respectively the numbers of parasite larvae and mature parasites infecting the host. The variable $E(a)$ denotes the egg-load associated with the host.

We assume that at birth the host is free of parasites (i.e. $M(0) = 0$) and over its lifetime is exposed to parasite larvae at times that form a nonhomogeneous Poisson process of rate $\phi(a)$. At an exposure instant, the host acquires a random number C of larvae, independently from one exposure to another. Let C have probability generating function $h(z) := \Sigma_{c=0}^{\infty} h_c z^c$. Without loss of generality we could take $h_0 = 0$, but we shall not do so here because we shall often want to assume a standard form for the distribution of C and it is convenient not to have to condition on $C > 0$. In this version of the model, we make no attempt to model the dynamics of the host population.

Let each of the larvae, independently of the rest of the parasites, mature at a rate γ. Assume that the immunity variable increases by one unit at a rate, νL, proportional to the current larval load and decreases linearly, at rate $\mu_I I$. Assume that the larval and mature parasites within the host die off independently at rates $\mu_L + \beta_1 I$ and $\mu_M + \beta_2 I$ per parasite, respectively, where these death rates are affected by the current immunity level. Each mature parasite generates eggs at rate λ, and each egg, independently of the rest, dies at a rate $\mu_E + \delta I$ depending on the current immunity level. Let $\mu_H(a)$ be the death rate of a host at age a in the absence of any parasite burden and assume that this rate is increased by an amount α for each mature parasite present.

Additional independencies are assumed as appropriate between the components of the model, so that $\{I(a), L(a), M(a), E(a)\}$ is a Markov process. Thus, finally, for a host that has survived to age a, with $I(a) = i$, $L(a) = l$, $M(a) = m$, $E(a) = e$, the possible transitions are:

to $i, l+c, m, e$ at rate $\phi(a) h_c$ for $c = 1, 2, \ldots$,
to $i+1, l, m, e$ at rate νl,
to $i-1, l, m, e$ at rate $\mu_I i$,
to $i, l-1, m+1, e$ at rate γl,
to $i, l-1, m, e$ at rate $(\mu_L + \beta_1 i) l$,
to $i, l, m-1, e$ at rate $(\mu_M + \beta_2 i) m$,
to $i, l, m, e+1$ at rate λm,
to $i, l, m, e-1$ at rate $(\mu_E + \delta i) e$,
that the host dies, at rate $\mu_H(a) + \alpha m$.

Note that, in a *stochastic* model, the interpretation of a transition *rate* is that, for example, if the system is in state $\{i\,l\,m\,e\}$ at time a then the *probability* that, during the time increment $(a, a+da)$ there is a transition to state $\{i\,l+c\,m\,e\}$, is $\phi(a) h_c da + o(da)$.

Model equations

Let $p_{i\,l\,m\,e}(a) := \mathrm{P}$ (host survives to age a and $I(a) = i$, $L(a) = l$, $M(a) = m$, $E(a) = e$). To obtain a differential equation for $p_{i\,l\,m\,e}(a)$, we need to express the probability $p_{i\,l\,m\,e}(a+da)$ for the state of the system at time $a+da$ in terms of the probabilities the various states $\{i'\,l'\,m'\,e'\}$ say) that *could* have been occupied at time a, together with the probabilities of the necessary transitions from $\{i'\,l'\,m'\,e'\}$ to $\{i\,l\,m\,e\}$, for a small time-increment $(a, a+da)$: that is,

$$p_{i\,l\,m\,e}(a+da) = \sum_{\{i'\,l'\,m'\,e'\}} p_{i'\,l'\,m'\,e'}(a) \times \mathrm{P}(\{i'\,l'\,m'\,e'\} \to \{i\,l\,m\,e\}).$$

From above, the possible transition are

from $i, l-c, m, e$ at rate $\phi(a) h_c$ for $c = 1, 2, \ldots$,
from $i-1, l, m, e$ at rate νl,
from $i+1, l, m, e$ at rate $\mu_I(i+1)$,

from i, $l+1$, $m-1$, e at rate $\gamma(l+1)$,
from i, $l+1$, m, e at rate $(\mu_L+\beta_1 i)(l+1)$,
from i, l, $m+1$, e at rate $(\mu_M+\beta_2 i)(m+1)$,
from i, l, m, $e-1$ at rate λm,
from i, l, m, $e+1$ at rate $(\mu_E+\delta i)(e+1)$,

where, now, there is no chance of host death in $(a, a+da)$ since the host survives to age $a+da$. We must also include the possibility that, at time a, the host is already in state $\{i\,l\,m\,e\}$ and no transition out of this state occur in $(a, a+da)$. The probability of this event is

$$(1-\{\mu_H(a)+\alpha m+(1-h_0)\phi(a)+\nu l+\mu_I i+\gamma l+\mu_L l+\beta_1 il+\mu_M m+\beta_2 im+\lambda m+\mu_E e+\delta ie\}\,da+o(da))\,p_{i\,l\,m\,e}(a).$$

Thus, combining the above expressions, we can obtain an expansion for

$$\{p_{i\,l\,m\,e}(a+da)-p_{i\,l\,m\,e}(a)\}/da$$

in terms of the probabilities for the state of system at time a. Taking the limit as $da\to 0$ we find that, for i, l, m, $e \geqslant 0$,

$$\begin{aligned}\frac{dp_{i\,l\,m\,e}(a)}{da} &= -\{\mu_H(a)+\alpha m+(1-h_0)\phi(a)+\nu l+\mu_I i+\gamma l+\mu_L l\\ &\quad+\beta_1 il+\mu_M m+\beta_2 im+\lambda m+\mu_E e+\delta ie\}\,p_{i\,l\,m\,e}(a)\\ &\quad+\phi(a)\sum_{c=1}^{i} p_{i\,l-c\,m\,e}(a)\,h_c+\nu l p_{i-1\,l\,m\,e}(a)+\mu_I(i+1)\,p_{i+1\,l\,m\,e}(a)\\ &\quad+\gamma(l+1)\,p_{i\,l+1\,m-1\,e}(a)+(\mu_L+\beta_1 i)(l+1)\,p_{i\,l+1\,m\,e}(a)\\ &\quad+(\mu_M+\beta_2 i)(m+1)\,p_{i\,l\,m+1\,e}(a)+\lambda m p_{i\,l\,m\,e-1}(a)\\ &\quad+(\mu_E+\delta i)(e+1)\,p_{i\,l\,m\,e+1}(a)\end{aligned} \tag{1}$$

and the generating function

$$P(a;x,y,z,w) := \sum_{i=0}^{\infty}\sum_{l=0}^{\infty}\sum_{m=0}^{\infty}\sum_{e=0}^{\infty} p_{i\,l\,m\,e}(a)\,x^i y^l z^m w^e$$

satisfies the differential equation

$$\begin{aligned}\frac{\partial P(a;x,y,z,w)}{\partial a} &= -\{\mu_H(a)-\phi(a)[h(y)-1]\}\,P(a;x,y,z,w)+\mu_I(1-x)\frac{\partial P(a;x,y,z,w)}{\partial x}\\ &\quad-\{\nu(1-x)\,y-\mu_L(1-y)+\gamma(y-z)\}\frac{\partial P(a;x,y,z,w)}{\partial y}\\ &\quad-\{(\alpha+\mu_M)\,z-\mu_M+\lambda z(1-w)\}\frac{\partial P(a;x,y,z,w)}{\partial z}\\ &\quad+\mu_E(1-w)\frac{\partial P(a;x,y,z,w)}{\partial w}+\delta x(1-w)\frac{\partial^2 P(a;x,y,z,w)}{\partial x\partial w}\\ &\quad+\beta_1 x(1-y)\frac{\partial^2 P(a;x,y,z,w)}{\partial x\partial y}+\beta_2 x(1-z)\frac{\partial^2 P(a;x,y,z,w)}{\partial x\partial z}.\end{aligned} \tag{2}$$

It follows that $S(a) := P(a;1,1,1,1) = \mathrm{P}$ (host survives to age a) satisfies

$$\frac{dS(a)}{da} = -\{\mu_H(a)+\alpha m_M(a)\}\,S(a), \tag{3}$$

where $m_M(a) := E\{M(a)\}$ and it is emphasized that $M(a)$ is the parasite load *conditionally* upon the survival of the host to age a.

Then the joint probability generating function $Q(a;x,y,z,w) := P(a;x,y,z,w)/S(a)$ of $I(a)$, $L(a)$, $M(a)$, and $E(a)$ is the solution of

$$\begin{aligned}\frac{\partial Q(a;x,y,z,w)}{\partial a} &= \{\phi(a)[h(y)-1]+\alpha m_M\}\,Q(a;x,y,z,w)+\mu_I(1-x)\frac{\partial Q(a;x,y,z,w)}{\partial x}\\ &\quad-\{\nu(1-x)\,y-\mu_L(1-y)+\gamma(y-z)\}\frac{\partial Q(a;x,y,z,w)}{\partial y}\\ &\quad-\{(\alpha+\mu_M)\,z-\mu_M+\lambda z(1-w)\}\frac{\partial Q(a;x,y,z,w)}{\partial z}\\ &\quad+\mu_E(1-w)\frac{\partial Q(a;x,y,z,w)}{\partial w}+\delta x(1-w)\frac{\partial^2 Q(a;x,y,z,w)}{\partial x\partial w}\\ &\quad+\beta_1 x(1-y)\frac{\partial^2 Q(a;x,y,z,w)}{\partial x\partial y}+\beta_2 x(1-z)\frac{\partial^2 Q(a;x,y,z,w)}{\partial x\partial z}.\end{aligned} \tag{4}$$

Moments

One can deduce corresponding differential equations for the moments of $I(a)$, $L(a)$, $M(a)$ and $E(a)$, by differentiating (4) appropriately and setting $x = y = z = w = 1$. We use the notation $m_I(a) := E(I(a))$, $\sigma_{IL}(a) := \mathrm{cov}\,(I(a), L(a))$, $\sigma_I^2(a) := \sigma_{II}(a) = \mathrm{var}\,(I(a))$, etc. Then differentiating (4) separately with respect to x, y, z and w gives the following equations:

$$\begin{aligned}
dm_I(a)/da &= -\mu_I m_I(a) + \nu m_L(a) - \alpha\sigma_{IM}(a)\\
dm_L(a)/da &= \phi(a)\, m_C - (\mu_L + \gamma)\, m_L(a) - \beta_1(\sigma_{IL}(a) + m_I(a)\, m_L(a)) - \alpha\sigma_{LM}(a)\\
dm_M(a)/da &= -\mu_M m_M(a) + \gamma m_L(a) - \alpha\sigma_M^2(a) - \beta_2(\sigma_{IM}(a) + m_I(a)\, m_M(a))\\
dm_E(a)/da &= \lambda m_M(a) - \mu_E m_E(a) - \alpha\sigma_{ME}(a) - \delta(\sigma_{IE}(a) + m_I(a)\, m_E(a)),
\end{aligned} \tag{5}$$

where $m_C = E(C) = h'(1)$.

Note that the nonlinearity of the system means that these equations involve second moments of the variables.

We can now derive a set of similar equations with the derivatives of the second moments on the left-hand sides. For example, differentiating (4) with respect to both x and y gives an expression for $\partial E(I(a)\, L(a))/\partial a$. This can be combined with the earlier equations to give a differential equation for $\sigma_{IL}(a)$, as

$$\frac{\partial\sigma_{IL}(a)}{\partial a} = \frac{\partial E(I(a)\, L(a))}{\partial a} - m_I(a)\frac{\partial m_L(a)}{\partial a} - m_L(a)\frac{\partial m_I(a)}{\partial a}.$$

Again, the nonlinearity of the system means that there will be terms involving third moments on the right-hand sides of these equations, so that we do not obtain a closed system of equations for solution. To obtain *exact* moments of the variables it is necessary to solve equation (4). However, one method of obtaining *approximate* results is to assume that the joint distribution of the 4 variables is multivariate normal, so that their third moments can be expressed in terms of their means and second moments. In particular, if general variables X, Y, Z (which need not be distinct) have a multivariate normal distribution then, in an obvious notation,

$$E(XYZ) = m_X\sigma_{XY} + m_Y\sigma_{ZX} + m_Z\sigma_{XY} + m_X m_Y m_Z. \tag{6}$$

By this device we obtain a closed set of equations (given in (7), together with (5)) that can be solved to give approximate results for the means, variances and covariances of the variables.

$$\begin{aligned}
d\sigma_I^2(a)/da = {} & \mu_I\{m_I(a) - 2\sigma_I^2(a)\} + \nu\{m_L(a) + 2\sigma_{IL}(a)\}\\
d\sigma_L^2(a)/da = {} & \phi(\sigma_C^2 + m_C^2) + (\mu_L + \gamma)\{m_L(a) - 2\sigma_L^2(a)\}\\
& + \beta_1\{\sigma_{IL}(a) + m_I(a)\, m_L(a) - 2m_I(a)\,\sigma_L^2(a) - 2m_L(a)\,\sigma_{IL}(a)\}\\
d\sigma_M^2(a)/da = {} & \mu_M\{m_M(a) - 2\sigma_M^2(a)\} + \gamma\{m_L(a) + 2\sigma_{LM}(a)\}\\
& + \beta_2\{\sigma_{IM}(a) + m_I(a)\, m_M(a) - 2m_I(a)\,\sigma_M^2(a) - 2m_M(a)\,\sigma_{IM}(a)\}\\
d\sigma_E^2(a)/da = {} & \mu_E\{m_E(a) - 2\sigma_E^2(a)\} + \lambda\{m_M(a) + 2\sigma_{ME}(a)\}\\
& + \delta\{m_I(a)\, m_E(a) + \sigma_{IE}(a) - 2m_E(a)\,\sigma_{IE}(a) - 2m_I(a)\,\sigma_E^2(a)\}\\
d\sigma_{IL}(a)/da = {} & -(\mu_I + \mu_L + \gamma)\,\sigma_{IL}(a) - \beta_1\{m_I(a)\,\sigma_{IL}(a) + m_L(a)\,\sigma_I^2(a)\} + \nu\sigma_L^2(a)\\
d\sigma_{IM}(a)/da = {} & -(\mu_I + \mu_M)\,\sigma_{IM}(a) - \beta_2\{m_I(a)\,\sigma_{IM}(a) + m_M(a)\,\sigma_I^2(a)\}\\
& + \nu\sigma_{LM}(a) + \gamma\sigma_{IL}(a)\\
d\sigma_{LM}(a)/da = {} & -(\mu_L + \mu_M + \gamma)\,\sigma_{LM}(a) - \beta_1\{m_I(a)\,\sigma_{LM}(a) + m_L(a)\,\sigma_{IM}(a)\}\\
& - \beta_2\{m_I(a)\,\sigma_{LM}(a) + m_M(a)\,\sigma_{IL}(a)\} - \gamma\{m_L(a) - \sigma_L^2(a)\}\\
d\sigma_{IE}(a)/da = {} & -(\mu_I + \mu_E)\,\sigma_{IE}(a) - \delta\{m_I(a)\,\sigma_{IE}(a) + m_E(a)\,\sigma_I^2(a)\}\\
& + \nu\sigma_{LE}(a) + \lambda\sigma_{IM}(a)\\
d\sigma_{LE}(a)/da = {} & -(\mu_L + \mu_E + \gamma)\,\sigma_{LE}(a) - \beta_1\{m_L(a)\,\sigma_{IE}(a) + m_I(a)\,\sigma_{LE}(a)\}\\
& - \delta\{m_E(a)\,\sigma_{IL}(a) + m_I(a)\,\sigma_{LE}(a)\} + \lambda\sigma_{LM}(a)\\
d\sigma_{ME}(a)/da = {} & -(\mu_M + \mu_E)\,\sigma_{ME}(a) - \beta_2\{m_M(a)\,\sigma_{IE}(a) + m_I(a)\,\sigma_{ME}(a)\}\\
& - \delta\{m_E(a)\,\sigma_{IM}(a) + m_I\,\sigma_{ME}(a)\} + \lambda\sigma_M^2(a) + \gamma\sigma_{LE}(a),
\end{aligned} \tag{7}$$

where $\sigma_C^2 := \mathrm{var}\,(C) = h''(a) + h'(1) - (h'(1))^2$. In fact, in order to derive these equations there is no need to assume the multivariate normality of the variables $I(a)$, $L(a)$, $M(a)$ and $E(a)$, but only that their third moments satisfy (6).

Isham (1995) discusses this method (termed *normal approximation*) of obtaining approximations for the moments of stochastic processes, in the context of a simpler host–macroparasite model in which there is a single random variable representing parasite load, and there is no attempt to model immunity, larval burden or associated egg count. For this model, exact solutions are obtainable. It is found that the exact mean parasite load, as a function of time (age), is generally well approximated by the mean of the normal approximation, which is a substantial improvement over the deterministic solution. In addition, the normal approximation provides reasonably good estimates of the variability of the process.

The equations for the deterministic approximation to our model are the simplified version of (5) in which all second moments (of the form $\sigma_{ij}(a)$) are identically zero. The normal approximation improves upon this by using the correct differential equations (5) for the means, although their solution is not exact because it is used in conjunction with approximating equations (7) for the variances and covariances.

It is important to emphasize that the variables $I(a)$, $L(a)$, $M(a)$ and $E(a)$ need not be, even approximately, normally distributed. In Isham (1995) it is shown that it is quite possible for the approximate *moments*, obtained by the method of normal approximation, to be good even in cases where the normal *distribution* is a wholly inappropriate approximation to the true distribution.

If required, approximations can be obtained by assuming other forms for the joint distribution of the variables, and using the corresponding forms for the third moments in place of (6). It has often been observed empirically (Anderson & May, 1978*a*; Pacala & Dobson, 1988; Shaw, 1994; Wilson, 1994) that the distribution of parasite load is close to negative

binomial, and therefore an approximation based on this distribution is explored, in a forthcoming paper, for the univariate model of Isham (1995). There, it will be demonstrated that the negative binomial approximation provides a further improvement over the normal approximation, and the paper will discuss the adequacy of the *distributional* approximation as well as that of the first and second moments. Ideally, we would explore here a multivariate negative binomial approximation to the joint distribution of $I(a)$, $L(a)$, $M(a)$ and $E(a)$. 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.

In the specification of this model, the variable E represents eggs 'associated with' the host. However, the choice of appropriate parameter value depends very much on exactly what is meant by this. In particular, if $E(a)$ represents the 'within host' egg-burden, then the parameter μ_E must include both the genuine 'death' of eggs and the effect of frequent voiding in faeces. The latter will dominate μ_E, which will be much greater than the other rates involved in the process. Thus it is reasonable to assume that the process $E(a)$ is in equilibrium and that its moments (m_E, σ_E^2) are independent of time.

Numerical work also indicates that, to a good approx, we can set $d\sigma_{LE}/da$ and $d\sigma_{ME}(a)/da$ to zero if μ_E is large. In practice, therefore, we have used (5) and (7) to calculate the moments of I, L and M (not involving E) numerically (Grenfell *et al.* 1995). We then calculated moments involving E (m_E, σ_E^2, etc) as functions of the variables by setting the rate equations for the E moments to zero.

Asymptotic approximations

We assume that there is no immunity $\nu = \alpha = 0$ and that age, $a \to \infty$.
In this case (and assuming that μ_E is much greater than other loss rates),

$$\sigma_E^2 = m_E + m_E\sigma_{ME}/m_M \approx (m_E/m_M)^2[\sigma_M^2 + m_M + \gamma\sigma_{LM}/\mu_E]$$

so that $CV_E^2 \approx CV_M^2$ as long as $m_M + \gamma\sigma_{LM}/\mu_E \ll \sigma_M^2$. This can be shown to be true as long as $\mu_E \gg \gamma$, μ_M and γ are of roughly equal magnitude and the mean adult burden, $\mu_M \gg 1$. All these requirements are satisfied for trichostrongylid–ruminant interactions so that, as confirmed by further numerical simulations, $CV_E^2 \approx CV_M^2$.

REFERENCES

ADLER, F. R. & KRETZSCHMAR, M. (1992). Aggregation and stability in parasite–host models. *Parasitology* **104**, 199–205.

ANDERSON, R. M. & GORDON, D. (1982). Processes influencing the distribution of parasite numbers within host populations with special emphasis on parasite-induced host mortalities. *Parsitology* **85**, 373–8.

ANDERSON, R. M. & MAY, R. M. (1978*a*). Regulation and stability of host–parasite population interactions. I. Regulatory processes. *Journal of Animal Ecology* **47**, 219–47.

ANDERSON, R. M. & MAY, R. M. (1978*b*). Regulation and stability of host–parasite population interactions. II. Destabilising processes. *Journal of Animal Ecology* **47**, 248–67.

ANDERSON, R. M. & MAY, R. M. (1991). *Infectious Diseases of Humans : Dynamics and Control*. Oxford: O.U.P.

ANDERSON, R. M. & MEDLEY, G. F. (1985*a*). Community control of helminth infections of man by mass and selective chemotherapy. *Parasitology* **90**, 629–60.

ANDERSON, R. M. & MEDLEY, G. F. (1985*b*). Community control of helminth infections of mass and selective chemotherapy. *Parasitology* **90**, 629–60.

ANDERSON, R. M. & MICHEL, J. (1977). Density-dependent survival in populations of *Ostertagia ostertagi*. *International Journal for Parasitology* **7**, 321–9.

COYNE, M. & SMITH, G. (1994). Trichostrongylid parasites of domestic ruminants. In *Parasitic and Infectious Diseases : Epidemiology and Ecology* (ed. Scott, M. & Smith, G.). San Diego: Academic Press.

CROFTON, H. (1971). A quantative approach to parasitism. *Parasitology* **62**, 179–93.

DIETZ, K. (1982). Overall population patterns in the transmission cycle of infectious agents. In *Population Biology of Infectious Diseases* (ed. Anderson, R. & May, R.). Berlin: Springer.

GRENFELL, B. T. (1988). Gastrointestinal nematode parasites and the stability and productivity of intensive ruminant grazing systems. *Philosophical Transactions of the Royal Society of London Series B – Biological Sciences* **321**, 541–63.

GRENFELL, B. T. (1992). Parasitism and the dynamics of ungulate grazing systems. *American Naturalist* **139**, 907–29.

GRENFELL, B. T., DAS, P., RAJAGOPALAN, P. & BUNDY, D. (1990). Frequency distribution of lymphatic filariasis microfilariae in human populations: population processes and statistical estimation. *Parasitology* **101**, 417–27.

GRENFELL, B. T., DIETZ, K. & ROBERTS, M. (1995). Modelling the immuno-epidemiology of macroparasites in wildlife host populations. In *Ecology of Infectious Diseases in Natural Populations* (ed. Grenfell, B. T. & Dobson, A.). Cambridge. C.U.P.

GRENFELL, B. T., PRICE, O., ALBON, S. & CLUTTON-BROCK, T. (1992). Overcompensation and population cycles in an ungulate. *Nature* **355**, 245–8.

GRENFELL, B. T., SMITH, G. & ANDERSON, R. (1987*a*). A mathematical model of the population biology of *Ostertagia ostertagi* in calves and yearlings. *Parasitology* **95**, 389–406.

GRENFELL, B. T., SMITH, G. & ANDERSON, R. (1987*b*). The regulation of *Ostertagia ostertagi* populations in calves: the effect of past and current experience of infection on proportional establishment and parasite survival. *Parasitology* **95**, 363–72.

GULLAND, F. (1992). The role of nematode parasites in Soay sheep (*Ovis aries* L.) mortality during a population crash. *Parasitology* **105**, 493–503.

GULLAND, F. & FOX, M. (1992). Epidemiology of nematode infections in Soay sheep (*Ovis aries* L.) on St Kilda. *Parasitology* **105**, 485–92.

HADELER, K. & DIETZ, K. (1983). Nonlinear hyperbolic partial differential equations for the dynamics of parasite populations. *Computing and Mathematics with Applications* **3**, 415–30.

HONG, C., MICHEL, J. & LANCASTER, M. (1987). Observations on the dynamics of worm burdens in lambs infected daily with *Ostertagia circumcincta*. *International Journal for Parasitology* **17**, 951–6.

HUDON, P. & DOBSON, A. (1995). Macroparasites: observed patterns. In *Ecology of Infectious Diseases in Natural Populations* (ed. Grenfell, B. & Dobson, A.). Cambridge: C.U.P.

ISHAM, V. (1991). Assessing the variability of stochastic epidemics. *Mathematical Biosciences* **107**, 209–24.

ISHAM, V. (1993). Stochastic models for epidemics with special reference to AIDS. *Annals of Applied Probability* **3**, 1–27.

ISHAM, V. (1995). Stochastic models of host–macroparsite interaction. *Annals of Applied Probability* **5**, (In Press).

KRETZCHMAR, M. (1989). Persistent solutions in a model for parasitic infections. *Journal of Mathematical Biology* **27**, 549–73.

KRETZSCHMAR, M. & ADLER, F. (1993). Aggregated distributions in models for patchy populations. *Theoretical Population Biology* **43**, 1–30.

KURTZ, T. (1971). Limit theorems for sequences of jump Markov processes approximating ordinary differential processes. *Journal of Applied Probability* **8**, 344–56.

MICHEL, J. (1970). The regulation of populations of *Ostertagia ostertagi* in calves. *Parasitology* **61**, 435–47.

PACALA, S. & DOBSON, A. (1988). The relation between the number of parasites/host and host age: population dynamic causes and maximum likelihood estimation. *Parasitology* **96**, 197–210.

QUINNELL, R. & KEYMER, A. (1990). Acquired immunity and epidemiology. In *Parasites: Immunity and Pathology: the Consequences of Parasitic Infections in Mammals* (ed. Behnke, J.). London: Taylor & Francis.

ROBERTS, M., SMITH, G. & GRENFELL, B. (1995). Mathematical models for macroparasites of wildlife. In *Ecology of Infectious Diseases in Natural Populations* (ed. Grenfell, B. & Dobson, A.). Cambridge: C.U.P.

SHAW, D. (1994). Distributions of Macroparasites in Naturally-fluctuating Host Populations. PhD thesis, University of Cambridge.

SMITH, G. (1989). Population biology of the parasitic phase of *Ostertagia circumcincta*. *International Journal for Parasitology* **19**, 385–93.

SMITH, G. (1995). Macroparasite group report. In *Ecology of Infectious Diseases in Natural Populations* (ed. Grenfell, B. & Dobson, A.). Cambridge: C.U.P.

SMITH, G. & GALLIGAN, D. (1988). Mathematical models of the population biology of *Ostertagia ostertagi* and *Teladorsagia circumcincta* and the economic evaluation of control strategies. *Veterinary Parasitology* **27**, 73–83.

STEAR, M., BAIRDEN, K., DUNCAN, J., GETTINBY, G., MCKELLAR, Q., MURRAY, M. & WALLACE, D. (1995). The distribution of fecal nematode egg counts in Scottish blackface lambs following natural, predominantly *Ostertagia circumcincta* infection. *Parasitology* **110**, 573–81.

WHITTLE, P. (1957). On the use of the normal approximation in the treatment of stochastic processes. *Journal of the Royal Statistical Society* **B19**, 268–81.

WILSON, K. (1994). Analysis of worm and egg counts from the 1992 crash. Technical report, Department of Zoology, University of Cambridge.

WOOLHOUSE, M. (1992). A theoretical framework for the immunoepidemiology of helminth infection. *Parasite Immunology* **14**, 563–78.