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STOCHASTIC MODELS OF HOST–MACROPARASITE INTERACTION

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The interactions between macroparasites and their hosts, in terms of parasite-induced acquired immunity and additional mortality of the host, are of considerable interest and importance. In this paper, a simple nonlinear stochastic model for the parasite load within a single host over the lifetime of the host is investigated. By concentrating on a model incorporating only parasite-induced excess host mortality, exact algebraic results are possible, which provide insight into the effects of this interaction mechanism. A method of approximating the moments of parasite load is explored under a range of parametric assumptions. Extensions of the model to allow for heterogeneity between hosts and to incorporate various types of acquired immunity within the host are discussed briefly.

1. Introduction. Modeling the immuno-epidemiology of infection is a problem of considerable current interest and importance; see, for example, the papers and their cited references in the volumes edited by Grenfell and Dobson (1995) and Isham and Medley (1995), on infectious diseases in, respectively, wildlife and humans, that resulted from the recent *Epidemic Models* program at the Isaac Newton Institute in Cambridge.

In this paper, we shall consider macroparasitic infections. For such infections, both the severity of symptoms of disease in the host and the degree to which the host passes on the infection to others depends not only on whether or not the host is infected, but on the actual level of infection as measured by the parasite load. There is a substantial literature on modeling macroparasitic infections, mostly using a deterministic approach, although often allowing for variation over the population; see Hadeler (1984), Kretzschmar (1989) for some specific examples as well as the general survey of Anderson and May (1991). Few papers take a stochastic view, and the present paper has its antecedents in the work of Tallis and Leyton (1966, 1969), although in those papers there is no attempt to model the interaction between the parasites and their hosts.

In a recent paper, Grenfell, Dietz and Roberts (1995) developed a stochastic model that incorporates host–parasite interactions, for a host population infected by macroparasites such as helminths. The key problem is to investi-

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gate how the host develops immunity to the parasite as a result of infection, and the consequent effect that this has on the demography of both host and parasite populations. Specifically, the model considers the parasite burden as a function of the age of the host, allowing for the effect of parasite-induced host mortality and acquired immunity. It is assumed that the effect of acquired immunity is to increase the mortality of the parasites, but other effects such as reduced fertility of the parasite or resistance of the host to reinfection are also possible and of interest.

In this model, the state of a host at age a (conditionally upon survival to that age) is a triple of variables $\{I(a), L(a), M(a)\}$, where I represents the host's immunity level and reflects the host's experience of past infections, and L and M are, respectively, the numbers of parasite larvae and mature parasites infecting the host. It is assumed that parasite larvae are acquired by the hosts at time points modeled by a Poisson process (in principle the rate could be age-dependent) and that at each such time point a random number, C, of larvae are ingested. Of particular interest is the way in which the variability of the input process of infections, and most especially of C, is transformed into the variability of the state of the host as a function of age. While I is a conceptual construct of the model, empirical data on L and M are available and can be compared with theoretical predictions. Often biologists assume that such data follow a negative binomial distribution, which provides an acceptable fit; see, for example, Anderson and May (1978), Pacala and Dobson (1988) and Wilson (1994) and the recent review given by Shaw (1994).

Grenfell, Dietz and Roberts (1995) derive differential equations for the joint probability generating function of $I(a)$, $L(a)$ and $M(a)$ conditionally upon the host reaching age a, and for the first- and second-order moments of these variables. The nonlinearity of the model means that the latter equations involve higher-order moments and cannot therefore be solved as they stand. The authors look at approximate solutions, obtained by assuming that the variables have a multivariate normal distribution [Whittle (1957)] so that their higher moments can all be expressed as appropriate functions of their mean vector and covariance matrix. The appropriateness of this type of approximation will be discussed in Section 4; intuitively it is plausible when large parasite burdens have become established.

In the special case of this model when the parasites have no effect on their host, either by inducing an increased host mortality rate or by stimulating an immune reaction, the effect of which is to increase the death rate of the parasites in the host, the model is linear. This means that the equations for the moments of the variables can be solved without the need for approximation, and in this case Grenfell, Dietz and Roberts (1995) deduce some simple relations between the coefficient of variation of C and those for L and M.

It is highly desirable to obtain corresponding relations in the more complicated nonlinear model, and Grenfell, Dietz and Roberts (1995) have used numerical simulations of the model to show that in some cases of practical interest, the parameter values are such that the relations for the linear case

are approximately valid. It is also important to know how well the normal approximations work in the nonlinear case. For these reasons, in this paper, the properties of an even simpler model will be investigated.

In this simpler model, no attempt will be made to incorporate the effects of acquired immunity or to distinguish between the mature and larval stages of the parasite. This means that the state of the host at age a can be taken to be a single variable $M(a)$ representing the number of parasites infesting the host. The model is still nonlinear because the parasites increase the mortality of their host. However, the model is substantially simpler to analyze and, in particular, the distribution of $M(a)$ can be derived analytically, allowing both its dependence on the distribution of C and the adequacy of the normal approximation to be explored under a range of parametric assumptions.

The formal definition of this model is given and its properties are derived in Section 2 of this paper. In Section 3, we consider the results in more detail for some particular special cases of the input distribution for the number C of parasites ingested per encounter, while in Section 4 some approximations to the first- and second-order moments of the process are examined. In both these sections, some numerical comparisons are made for illustration. Some extensions of the model to allow for heterogeneity between hosts are considered in Section 5 and further generalizations to allow for the incorporation of various sorts of immune reaction are discussed briefly in Section 6.

2. The Model.

2.1. *Definition.* We consider the following model for the parasite load $M(a)$ of a particular host that has survived to age a, as a function of a. We assume that at birth the host is free of parasites [i.e., $M(0) = 0$ a.s.] and over its lifetime is exposed to parasites at times that form a nonhomogeneous Poisson process of rate $\phi(a)$. At an exposure instant, the host acquires a random number C of parasites, independently from one exposure to another. Let C have probability generating function $h(z) = \sum_{c=0}^{\infty} h_c z^c$. While we could, without loss of generality, take $h_0 = 0$, we shall not do so here because we shall later assume some standard forms for the distribution of C and it is convenient not to have to condition on $C > 0$ there. We make no attempt to incorporate parasite reproduction in the model and, for simplicity, assume implicitly that the population of parasites in the environment of the host is at a constant level. However the case considered does cover a scenario in which not all the acquired parasites become established in the host, as long as the establishment mechanism acts independently between parasites (see Section 5.2).

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 parasite present. Let parasites within the host die off independently at rate μ_M per parasite. Thus, for a host that has survived to age a, with

$M(a) = m$, the possible transitions are:

1. to $m + c$ at rate $\phi(a)h_c$ for $c = 1, 2, \ldots$;
2. to $m - 1$ at rate $\mu_M m$;
3. that the host dies, at rate $\mu_H(a) + \alpha m$.

2.2. *Model equations.* Let $p_m(a) :=$ P(host survives to age a and $M(a) = m$). Then for $m \geq 0$,

$$\begin{aligned}\frac{dp_m(a)}{da} &= -\{\mu_H(a) + \alpha m + (1 - h_0)\phi(a) + \mu_M m\}p_m(a) \\ &\quad + \mu_M(m+1)p_{m+1}(a) + \phi(a)\sum_{c=1}^{m} p_{m-c}(a)h_c,\end{aligned} \tag{2.1}$$

and the generating function $P(a; z) := \sum_{m=0}^{\infty} p_m(a)z^m$ satisfies the differential equation

$$\begin{aligned}\frac{\partial P(a;z)}{\partial a} &= -\{\mu_H(a) - \phi(a)[h(z) - 1]\}P(a;z) \\ &\quad -\{(a + \mu_M)z - \mu_M\}\frac{\partial P(a;z)}{\partial z}.\end{aligned} \tag{2.2}$$

It follows that $S(a) := P(a; 1) =$ P(host survives to age a) satisfies

$$\frac{dS(a)}{da} = -\mu_H(a)S(a) - \alpha m_M(a)S(a), \tag{2.3}$$

where $m_M(a) := \mathrm{E}\{M(a)\}$. We emphasize that $M(a)$ is the parasite load conditionally upon the survival of the host to age a.

Then the probability generating function $Q(a; z) := P(a; z)/S(a)$ of $M(a)$ is the solution of

$$\begin{aligned}\frac{\partial Q(a;z)}{\partial a} &= \{\phi(a)[h(z) - 1] + \alpha m_M(a)\}Q(a;z) \\ &\quad -\{(\alpha + \mu_M)z - \mu_M\}\frac{\partial Q(a;z)}{\partial z}.\end{aligned} \tag{2.4}$$

For the rest of this paper, we shall assume that the rate of exposure of the host to parasites is not age-dependent, that is, that $\phi(a) \equiv \phi$, a constant. In this case, it is straightforward to solve (2.4) by standard methods, using the boundary conditions $Q(a; z) \equiv 1$ when $a = 0$ or $z = 1$, to obtain the explicit solution

$$Q(a;z) = \exp\left\{\left[\int_{\theta(a;1)}^{1} + \int_{z}^{\theta(a;z)}\right]\frac{\phi[1 - h(u)]\,du}{(\mu_M + \alpha)u - \mu_M}\right\}, \tag{2.5}$$

where

$$\theta(a;z) := \{\mu_M + [(\alpha + \mu_M)z - \mu_M]\exp(-(\alpha + \mu_M)a)\}/(\alpha + \mu_M).$$

Note that this distribution does not depend upon the function μ_H since we are conditioning on the survival of the host.

The properties of the distribution of $M(a)$ can now be found as required. In principle, it is possible to expand $Q(a; z)$ in a power series in z to determine explicitly the probability distribution of $M(a)$. In practice, this does not give rise to nice expressions in general and this option will not be considered further. However, the first few moments of the distribution are easy to write down and, in particular,

$$\mathrm{E}(M(a)) = \phi\{1 - h(\theta(a;1))\}/\alpha, \tag{2.6}$$

$$\begin{aligned}\mathrm{var}(M(a)) = \{&\phi h'(1) - \mu_M \mathrm{E}(M(a)) \\ &- \phi h'(\theta(a;1))\exp(-(\alpha + \mu_M)a)\}/\alpha\end{aligned} \tag{2.7}$$

and hence the index of dispersion, $\mathrm{I}_M(a)$, for $M(a)$ is given by

$$\begin{aligned}\mathrm{I}_M(a) &:= \frac{\mathrm{var}(M(a))}{\mathrm{E}(M(a))} \\ &= \frac{h'(1) - h'(\theta(a;1))\exp(-(\alpha + \mu_M)a)}{1 - h(\theta(a;1))} - \frac{\mu_M}{\alpha},\end{aligned} \tag{2.8}$$

where $h'(1)$ is just the mean $\mathrm{E}(C)$. Note that equations (2.6)–(2.8) are given on the assumption $\alpha \neq 0$; results for the case $\alpha = 0$ will be given separately in Section 3.1.

The probability that a host of age a has never been infected is $\exp\{-\phi(1 - h_0)a\}$, the probability that a host of age a is infected is simply $1 - Q(a;0)$, while the probability, $S(a)$, that the host survives to that age can be expressed as

$$S(a) = \exp\left\{-\int_0^a \mu_H(u)\,du\right\}\exp\left\{-\alpha\int_0^a \mathrm{E}(M(u))\,du\right\},$$

where the first term of the product represents the probability of the host's survival in the absence of parasite-induced effects, while the second term is the chance of escaping parasite-induced mortality.

To determine the prevalence of infection in the population it is necessary to weight the probability, $1 - Q(a;0)$, that an individual of age a is infected, by the probability that an arbitrarily chosen member of the population is of age a. Thus the prevalence of infection is given by

$$\int_0^\infty [1 - Q(a;0)]S(a)\,da \Big/ \int_0^\infty S(a)\,da.$$

If we let $a \to \infty$, then the distribution of $M(a)$ approaches an equilibrium; since a only appears in the distribution of $M(a)$ via the expression $\exp\{-(\alpha + \mu_M)a\}$, it is clear that this exponential decay governs the rate of convergence. Remember that $M(a)$ is the number of parasites *conditionally upon surviving to age a*. In fact, as we shall see in some numerical illustrations later, in many cases the equilibrium values will be achieved fairly quickly

relative to a typical host lifetime, and therefore these values are of substantial interest. The behavior of the function $\theta(a;1)$ is crucial: As a increases, this function decreases from $\theta(0;1) = 1$ to $\theta(\infty;1) = \mu_M/(\mu_M + \alpha)$, so that if $\alpha \ll \mu_M$ it is nearly constant. We have, as $a \to \infty$,

$$\theta(a;z) \to \frac{\mu_M}{(\alpha + \mu_M)},$$

$$Q(a;z) \to \exp\left\{\int_z^1 \frac{\phi[h(\mu_M/(\alpha+\mu_M)) - h(u)]\,du}{(\alpha+\mu_M)u - \mu_M}\right\}, \tag{2.9}$$

$$\mathrm{E}(M(a)) \to \frac{\phi}{\alpha}\left\{1 - h\left(\frac{\mu_M}{\alpha+\mu_M}\right)\right\}, \tag{2.10}$$

$$\mathrm{var}(M(a)) \to \frac{\phi h'(1)}{\alpha} - \frac{\mu_M \phi}{\alpha^2}\left\{1 - h\left(\frac{\mu_M}{\alpha+\mu_M}\right)\right\}, \tag{2.11}$$

$$\mathrm{I}_M(a) \to \frac{h'(1)}{1 - h(\mu_M/(\alpha+\mu_M))} - \frac{\mu_M}{\alpha}.$$

Note that the limiting generating function in (2.9) is the generating function of the limiting stochastic process, so that there is no ambiguity as to the interpretation of these results.

3. Special cases.

3.1. *No parasite-induced mortality*: $\alpha = 0$. As a basis for comparison, it is useful to consider first the special case when $\alpha = 0$, although our main interest is in the impact on the system of parasite-induced mortality ($\alpha > 0$). In this case, there is no interaction between the parasites (once ingested) and their host, and the model is linear; see Tallis and Leyton (1969). Equation (2.5) simplifies to

$$Q(a;z) = \exp\left\{-\int_z^{\theta(a;z)} \frac{\phi[1 - h(u)]\,du}{\mu_M(1-u)}\right\},$$

where $\theta(a;z) = 1 - (1-z)\exp(-\mu_M a)$ and $\theta(a;1) \equiv 1$. Then

$$\mathrm{E}(M(a)) = \phi h'(1)\{1 - \exp(-\mu_M a)\}/\mu_M$$

and

$$\mathrm{var}(M(a)) = \mathrm{E}(M(a)) + \phi h''(1)\{1 - \exp(-2\mu_M a)\}/(2\mu_M),$$

and, since $h'(1) = \mathrm{E}(C)$ and $h''(1) = \mathrm{E}(C^2 - C)$,

$$\mathrm{I}_M(a) = 1 + \frac{\mathrm{E}(C^2 - C)}{2\mathrm{E}(C)}(1 + \exp(-\mu_M a)).$$

Thus $M(a)$ is overdispersed for all ages a, as long as $\mathrm{P}(C \le 1) < 1$, that is, if there is a chance of acquiring more than one parasite in a single exposure. In fact, it is easy to use expansions to show that this also applies for $a \neq 0$ as long as α/μ_M is sufficiently small. If we write I_C for the index of dispersion of

C, we see that, as $a \to \infty$,

$$I_M(a) \to \tfrac{1}{2}\{1 + E(C) + I_C\}.$$

3.2. *Constant C.* We consider only the simplest case, when, at each exposure instant, a single parasite is ingested by the host. Then $C = 1$ a.s. and $h(z) \equiv z$. In this case the general results simplify very substantially and we find that $M(a)$ has a Poisson distribution with mean

$$\phi(1 - \exp(-(\mu_M + \alpha)a))/(\mu_M + \alpha).$$

This process is perhaps more familiar as a modification of an M/M/∞ queue in which the system has a random lifetime, conditionally upon the survival of that system.

3.3. *Negative binomial C.* Suppose that C has a negative binomial distribution with an integer index, $k \geq 1$, and parameter p, $0 < p < 1$; that is,

$$P(C = r) = \binom{k + r - 1}{r} p^k (1 - p)^r \quad \text{for } r = 0, 1, \ldots,$$

so that $h(z) = p^k/\{1 - (1 - p)z\}^k$. It is convenient to reparameterize this distribution in terms of k and the mean $m_C = E(C) = k(1 - p)/p$, and we note that the index of dispersion of this distribution can then be expressed as $I_C = 1 + m_C/k$. By using a partial fraction expansion of the integrand in (2.5), and integrating term by term, it can be shown that

$$\begin{aligned} Q(a; z) = \exp\{&f(k + m_C(1 - \theta(a; 1))) - f(k) \\ &+ f(k + m_C(1 - z)) - f(k + m_C(1 - \theta(a; z)))\} \\ &\times \psi^{-(\rho_1/\rho_0)^{k-1} k^k \phi/(\rho_0 m_C)}, \end{aligned} \tag{3.1}$$

where

$$\psi = \left[1 + \frac{\rho_1 m_C (1 - z)\exp(-\rho_1 m_C a)}{k\rho_1 + \alpha(1 - \exp(-\rho_1 m_C a))}\right]^{-1},$$

$$f(w) = \frac{\phi k^k}{m_C \rho_0 w^{k-1}} \sum_{j=1}^{k-1} \frac{1}{k - j} \left(\frac{\rho_1 w}{\rho_0}\right)^{j-1}$$

and $\rho_1 = (\alpha + \mu_M)/m_C$, $\rho_0 = \rho_1(k + m_C) - \mu_M$.

In equilibrium, that is, as $a \to \infty$, $\theta(a; z) \to \mu_M/(\alpha + \mu_M)$ for all values of z, and therefore (3.1) simplifies to

$$\begin{aligned} Q(a; z) \to \exp\{&f(k + m_C(1 - z)) - f(k)\} \\ &\times (1 + m_C(1 - z)/k)^{-(\rho_1/\rho_0)^{k-1} k^k \phi/(\rho_0 m_C)}. \end{aligned} \tag{3.2}$$

Thus we see that $M(\infty)$ can be regarded as a sum of k independent variables $Y_1 + \cdots + Y_{k-1} + X$, where the probability generating function of Y_i is

$$\exp\left\{\frac{\phi k^k \{(k + (1 - z)m_C)^{i-k} - k^{i-k}\}}{(\mu_M + \alpha)(k - i)} \left[\frac{\mu_M + \alpha}{(\mu_M + \alpha)k + \alpha m_C}\right]^i\right\}$$

and X has a negative binomial distribution with mean

$$\frac{\phi m_C}{(\alpha + \mu_M)k}\left[\frac{(\mu_M + \alpha)k}{(\mu_M + \alpha)k + \alpha m_C}\right]^k$$

and index $k\mathrm{E}(X)/m_C$. Note that the index of dispersion for X is $1 + \mathrm{E}(C)/k$.

In the special case when $k = 1$ so that the parasite input, C, has a geometric distribution with mean m_C, the equilibrium distribution of parasite load is negative binomial with mean

$$\mathrm{E}(M(\infty)) = \frac{\phi m_C}{\mu_M + \alpha + \alpha m_C}$$

and index $\nu := \mathrm{E}(M(\infty))/m_C$, so that $\mathrm{I}_M(\infty) = 1 + m_C = \mathrm{I}_C$. Thus, in this very special case, the index of dispersion of the input C is invariant under the transformation to the output M of the process. Note also that, in this limiting case, the probability that a host is free of parasites is $(1 + m_C)^{-\nu}$.

3.4. *Poisson C.* Another important special case, when C has a Poisson distribution, could be obtained by considering the above negative binomial case in the limit as $k \to \infty$. Clearly taking this limit requires care and the resulting expressions are not particularly simple. The alternative is to return to the general solutions obtained in Section 2.2 and substitute the Poisson probability generating function $h(z) = \exp(-(1 - z)m_C)$, thus deriving solutions expressed in terms of the exponential integral function $\mathrm{Ei}(w)$ (which has derivative $w^{-1}e^w$). For example, in equilibrium, the probability generating function $Q(\infty, z)$, of the parasite load $M(\infty)$, is given by

$$\begin{aligned}\ln Q(\infty; z) = {} & \frac{-\phi}{\alpha + \mu_M}\exp\left\{\frac{-\alpha m_C}{(\alpha + \mu_M)}\right\} \\ & \times\left\{\mathrm{Ei}\left(\frac{\alpha m_C}{\alpha + \mu_M}\right) - \mathrm{Ei}\left(\frac{(\alpha + \mu_M)m_C z - \mu_M m_C}{\alpha + \mu_M}\right)\right. \\ & \left. + \ln\left|\frac{(\alpha + \mu_M)z - \mu_M}{\alpha}\right|\right\}\end{aligned} \tag{3.3}$$

Of course the moment expressions are much simpler, as can be seen, for example, by making the substitution for the function h directly in (2.10) and (2.11).

3.5. *Some numerical results.* Perhaps the simplest way to make some comparisons of the effect of the distribution of the parasite input, C, on the behavior of the parasite load, $M(a)$, as a function of age, is to show some numerical results. We shall assume that C has a negative binomial distribution and consider three cases: (1) the limiting Poisson case, where the index $k \to \infty$, (2) the geometric case, where $k = 1$, and (3) the case $k = 0.5$, to represent the situation when $k < 1$.

In Figures 1–3 the means and indices of dispersion of $M(a)$ as functions of age are plotted for several sets of parameter values. For the sake of example,

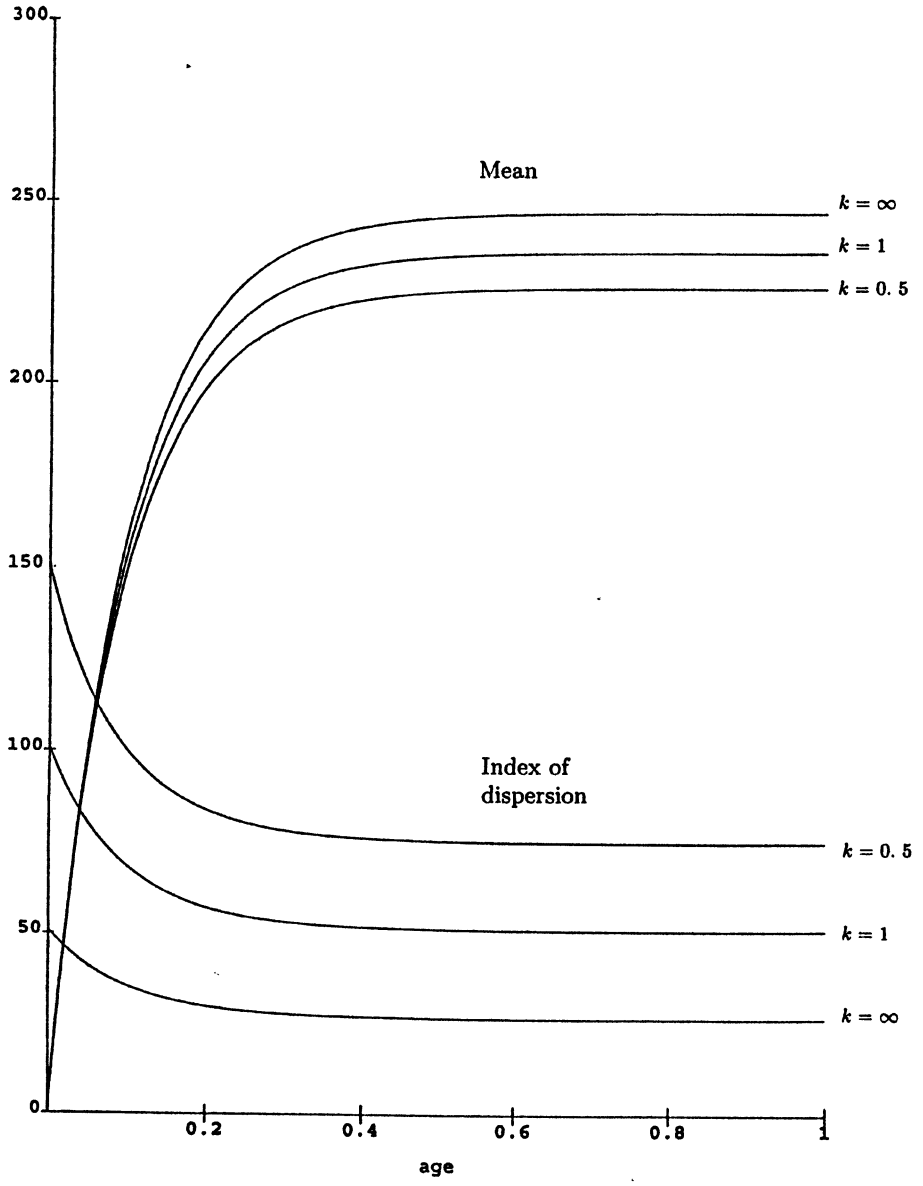

FIG. 1. *Exact mean and index of dispersion for the Poisson distribution* ($k = \infty$), *the geometric distribution* ($k = 1$) *and the negative binomial distribution* ($k = 0.5$) *using parameter values* $\phi = 52$, $\alpha = 0.02$, $\mu_M = 10$ *and* $m_C = 50$.

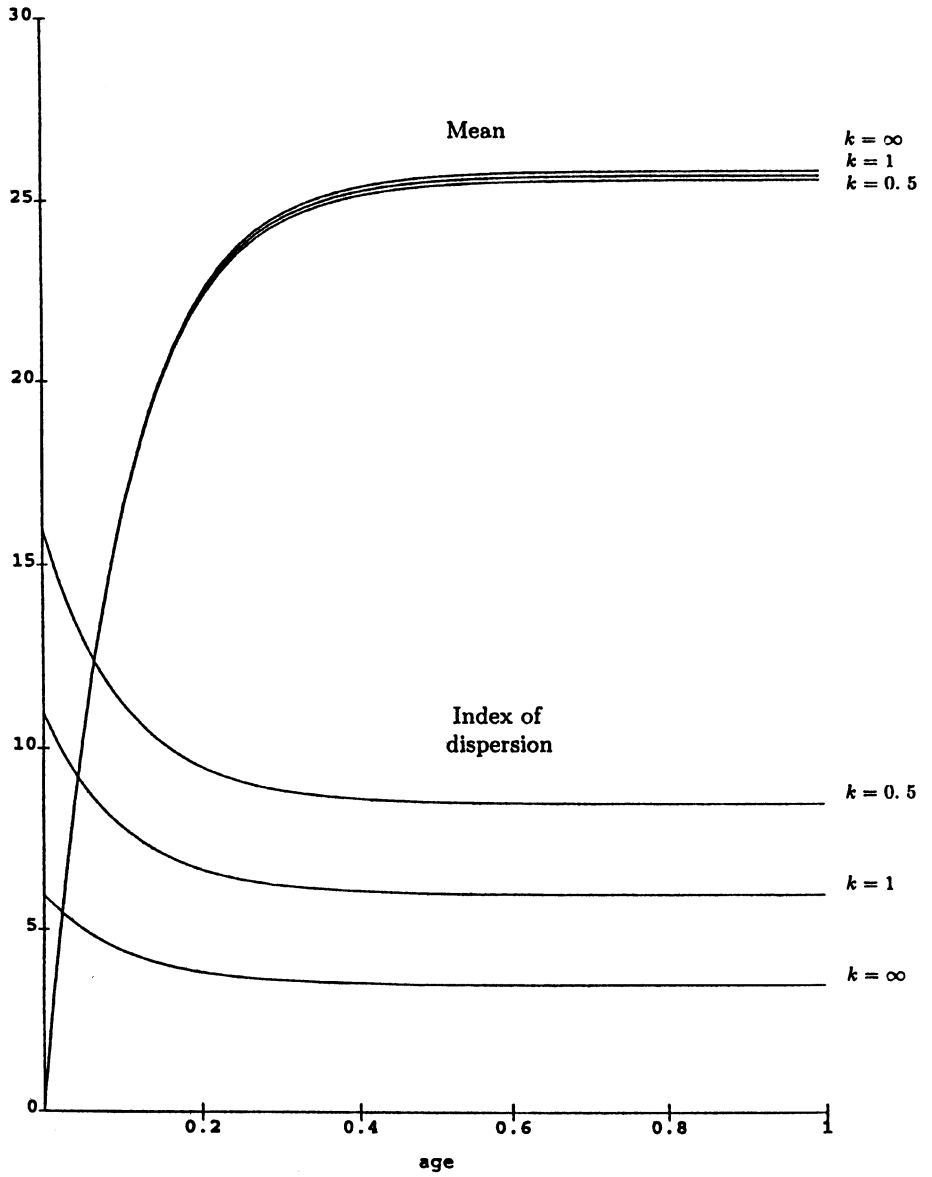

FIG. 2. *Exact mean and index of dispersion for the Poisson distribution* ($k = \infty$), *the geometric distribution* ($k = 1$) *and the negative binomial distribution* ($k = 0.5$) *using parameter values* $\phi = 52$, $\alpha = 0.02$, $\mu_M = 10$ *and* $m_C = 5$.

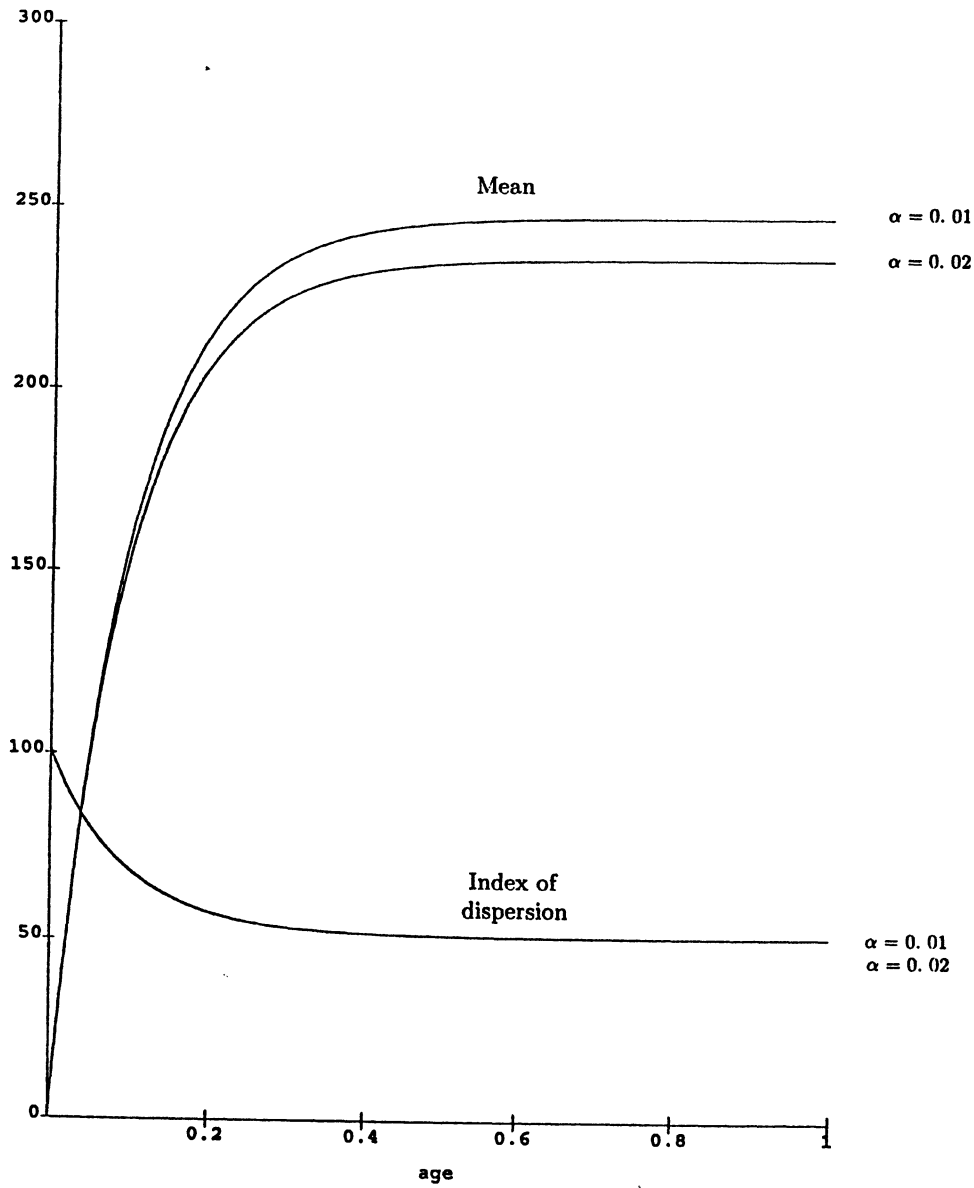

FIG. 3. *Exact mean and index of dispersion for the negative binomial distribution* ($k = 0.5$) *using parameter values* $\phi = 52$, $\alpha = 0.01$, $\mu_M = 10$, $m_C = 50$ *and* $\phi = 52$, $\alpha = 0.02$, $\mu_M = 10$, $m_C = 50$. *The function with* $\alpha = 0.01$ *is the upper curve of each pair.*

we imagine time to be measured in years and have kept the parasite death rate, μ_M, fixed at a biologically plausible value of 10, and varied the values of the other parameters, ϕ, α and m_C; see Grenfell, Dietz and Roberts (1995) with regard to the choice of these numerical values.

We see (e.g., Figures 1 and 2) that for such cases the system rapidly approaches equilibrium over just a few parasite lifetimes. The mean of $M(a)$ decreases gradually with k, so that the curve for geometric input lies slightly below that for Poisson input, while that for $k = 0.5$ is a little lower again. In contrast, the index of the dispersion increases substantially as k decreases, reflecting the greater variability of the input distribution (the index of dispersion of C is $1 + m_C/k$).

The mean and variance of $M(a)$ are both proportional to ϕ, so that making a change in ϕ simply rescales the curves for the mean, while leaving those for the index of dispersion unchanged. The effect of changing m_C is less straightforward algebraically, but by comparing Figures 1 and 2 we see that the overwhelming effect (at least at these parameter values) is a corresponding rescaling of both the mean and the index by the same factor (10 for these figures). The effect of changing α is again complicated algebraically, but, for the sorts of parameter values considered here, there is little effect on the mean of $M(a)$, while the variance increases slightly when α is decreased. Of the three values of k considered, these effects are most pronounced when $k = 0.5$ and this case is illustrated in Figure 3.

It is perhaps worth noting that various approximating expansions to these exact results are possible, perhaps the most obvious being when $\alpha \ll \mu_M$, as in these numerical calculations. For example, if in the limiting mean given in (2.10), the generating function h is expanded about the point 1, we find that

$$\mathrm{E}(M(a)) \simeq \frac{\phi m_C}{\mu_M}\left\{1 - \frac{\alpha m_C}{2\mu_M}\left(1 + \frac{1}{k}\right)\right\},$$

confirming the limiting spacing between the mean curves shown in Figures 1 and 2, and the remarks of the previous paragraph. Similar results apply for the index of dispersion curves.

4. Approximations.

4.1. *Theoretical results.* It can easily be deduced from (2.4) that the mean, $m_M(a)$, and variance, $\sigma_M^2(a)$, of $M(a)$ satisfy the following differential equations:

$$\frac{dm_M(a)}{da} = \phi h'(1) - \alpha\sigma_M^2(a) - \mu_M m_M(a), \tag{4.1}$$

$$\begin{aligned}\frac{d\sigma_M^2(a)}{da} &= \phi\{h''(1) + h'(1)\} + \mu_M m_M(a) - 2\mu_M\sigma_M^2(a) \\ &\quad + \alpha\left\{3m_M(a)\sigma_M^2(a) + m_M^3(a) - \mathrm{E}\left(M(a)^3\right)\right\},\end{aligned} \tag{4.2}$$

where, as usual, $h'(1) = m_C = \mathrm{E}(C)$ and $h''(1) = \mathrm{E}(C(C-1))$. If $M(a)$ has a normal distribution, then the term multiplying α in (4.2) is identically zero for all a, since the third-order moment is expressible in terms of the mean and variance, and therefore the pair of equations can be solved to determine $m_M(a)$ and $\sigma_M^2(a)$. The *normal approximation to the moments* is obtained by *setting* this term in (4.2) to zero and solving

$$\frac{d\sigma_M^2(a)}{da} = \phi\{h''(1) + h'(1)\} + \mu_M m_M(a) - 2\mu_M \sigma_M^2(a) \tag{4.3}$$

in conjunction with (4.1). The explicit form of the solution of these equations is given in the Appendix.

An extremely widely used method of approximating a stochastic population process is to use a deterministic model. This entails ignoring all random variation in the process and treating integer-valued variables as continuous. For the present model, the deterministic approximation to the mean is obtained by setting $\sigma_M^2(a) = 0$ in (4.1), which then has solution

$$m_M(a) = \phi m_C(1 - \exp(-\mu_M a))/\mu_M .$$

The normal approximation improves upon this by using the correct differential equation (4.1) for the mean, although its solution is not exact because it is used in conjunction with an approximating equation (4.3) for the variance.

Any theoretical justification for using the normal *distribution* as an approximation to the true distribution, for processes of this sort, would have to be an asymptotic one, based on an assumption that the parameters of the model are such that a host surviving sufficiently long will acquire a large parasite load which can be approximated by a continuous variable, and that the host does survive long enough to escape the constraint of the boundary (whereby the host is parasite-free at birth). The method of normal approximation was first proposed by Whittle (1957), and was rigorously explored in a series of papers by Kurtz (1970, 1971, 1981), who proved conditions under which a general class of Markov jump processes converge to Gaussian processes. For an application of the technique of normal approximation as a means of getting approximate moments in the context of particular epidemic models, and especially in relation to the AIDS epidemic, see Isham (1991, 1993). Further work would be needed to extend Kurtz's results to processes of the sort being considered in this paper.

It is emphasized that there is no suggestion in this paper that $M(a)$ is, even approximately, normally distributed. However, it is possible for the approximate *moments* obtained by solving the differential equations for the normal approximation, to be good even in cases where the normal *distribution* is a wholly inappropriate approximation to the true distribution. For example, if $\alpha = 0$, the model for parasite load is linear and the normal approximation equations are exact in the sense that their solution gives the exact mean and variance of $M(a)$. This does not mean that $M(a)$ is normally distributed. The parasite load is a nonnegative integer-valued random variable and has initial value $M(0) = 0$, so that a normal approximation to its

distribution can never be justified for small a, although it may be reasonable when a is relatively large and $\phi m_C \gg \mu_M$. In general, for $\alpha \neq 0$ the validity of the approximation to the moments will depend entirely on the relative size of the term set to zero in (4.2). In the next section, numerical examples will be given to show that (for $\alpha \neq 0$) the method of normal approximation does give surprisingly good approximations to the mean and variance of $M(a)$, even close to the boundary, when $M(a)$ is zero or very small.

The practical justification for using approximate moments obtained by solving normal approximation equations like (4.1) and (4.3) is a pragmatic one: that such sets of simultaneous differential equations are very easy to solve (at least numerically) in many cases where exact moments are algebraically intractable and have to be obtained by simulation. Of course, ease of calculation by itself is not a sufficient reason for their use and it is necessary to ascertain how good these approximate moments are, in cases where an asymptotic justification cannot apply. One nice feature of the model formulated in this paper is that exact results are available, and therefore it presents an opportunity to compare exact and approximate moments in a variety of situations. This will be discussed further in the numerical comparisons of the next section.

Note that, if required, approximations could be obtained by assuming other two parameter distributions for $M(a)$, by substituting the appropriate form for $\mathrm{E}(M(a)^3)$ in (4.2); the negative binomial distribution is an obvious possibility and details for this will be given in a forthcoming paper, which will explore the adequacy of the distributional approximation as well as that of the first and second moments.

4.2. *Numerical comparisons.* As in Section 3.5, it is simplest to concentrate on some particular special cases, and again we shall assume that C has a negative binomial distribution with three particular values for the index k: $k \to \infty$ (Poisson), $k = 1$ (geometric) and $k = 0.5$. As before, we imagine time to be measured in years and have kept the parasite death rate, μ_M, fixed at the value of 10 while varying the values of the other parameters, ϕ, α and m_C.

We shall access the approximations directly in terms of the mean and standard deviation of the distribution of parasite load, rather than using the index of dispersion derived from these. In Figure 4, we compare the exact means and standard deviations for the same set of parameter values as used in Figure 1, with the normal approximation to these moments and with the deterministic approximation to the mean.

We see that deterministic approximation overestimates the true mean, the approximation being best when $k = \infty$, and getting worse as k decreases. The normal approximations come much closer to the true means, although the effect is to overcorrect the deterministic curves so that the approximate means slightly underestimate the exact means. On the other hand, the normal approximations to the standard deviations overestimate the true values. Again the approximations are best when $k = \infty$, so that C has a Poisson distribution, and become more pronounced as k decreases and the

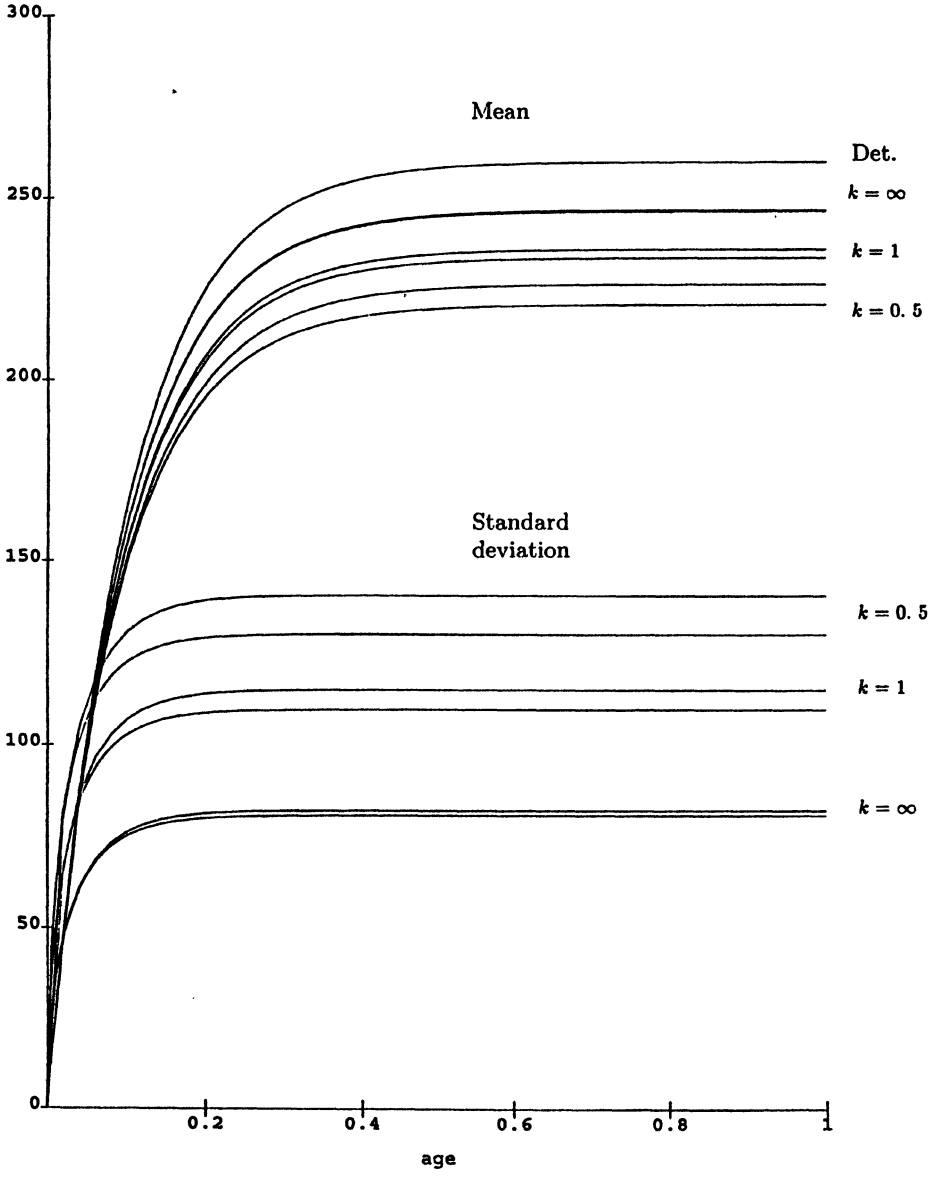

FIG. 4. *Exact and approximate mean and standard deviation for the Poisson distribution* ($k = \infty$), *the geometric distribution* ($k = 1$) *and the negative binomial distribution* ($k = 0.5$) *using parameter values* $\phi = 52$, $\alpha = 0.02$, $\mu_M = 10$ *and* $m_C = 50$, *with deterministic and normal approximations. The normal approximations to the means lie below the true curves. The normal approximations to the standard deviations lie above the true curves. The deterministic approximation to the means lies above the true curves.*

distribution of C becomes increasingly overdispersed. Thus, while the normal approximations are probably good enough for most purposes when $k \geq 1$, it may be necessary to exercise more care when $k < 1$ and the variability of C is relatively large.

In this connection, it is useful to return to (4.1) and (4.2) and consider briefly their exact solution in the limiting case when $\alpha \to \infty$. Denote the limiting mean, variance and third moment about the mean, by m, σ^2 and s, respectively, and the corresponding moments for the normal approximation by m_0 and σ_0^2 (and 0). Then it is straightforward to show that

$$m = m_0 + \frac{\alpha^2 s}{\mu_M(\alpha + 2\mu_M)} \quad \text{and} \quad \sigma^2 = \sigma_0^2 - \frac{\alpha s}{\alpha + 2\mu_M},$$

so that if the limiting distribution of $M(a)$ has a positive skewness ($s > 0$), then the normal approximation will underestimate the limiting mean and overestimate the limiting variance. While it is not immediately obvious, generally, that the limiting distribution does have $s > 0$, it is straightforward to show by expansion that this is the case when, as in the numerical examples, $\alpha \ll \mu_M$. We also note that, as mentioned in the Introduction, the negative binomial distribution, which is often suggested by comparison with empirical data as providing a good fit to the distribution of parasite load, has positive skewness.

Our original motivation for looking at the normal approximations to the moments of the stochastic process was an asymptotic one. Except soon after the birth of the host, the parasite load for the parameter values used for Figure 4 is reasonably large and one might therefore expect the approximations to be close to the true values. However, it is interesting to note that the approximations do well even at small ages. To investigate this further, we repeat the same comparisons with a different set of parameter values, for which the equilibrium parasite load is only a little over 2. The results are shown in Figure 5, from which the same qualitative conclusions can be drawn as from Figure 4. It is important to repeat that in such cases, the normal *distribution* will *not* be a good approximation to the distribution of parasite load.

5. Extensions for host heterogeneity.

5.1. *Random* ϕ. Probably the most tractable way of modeling between-host variability is to suppose that the rate at which hosts encounter parasites varies from one host to another, that is, to allow the parameter ϕ for each host to be an independent observation on a random variable Φ. Within a particular host, all the results are as already derived, although they must now be interpreted as properties of the conditional distribution of the parasite load $M(a)$ given $\Phi = \phi$.

Suppose that Φ has moment generating function $G_\Phi(s) := \mathrm{E}(e^{s\Phi})$ with index of dispersion I_Φ. Then it follows immediately from (2.5), (2.6) and (2.7)

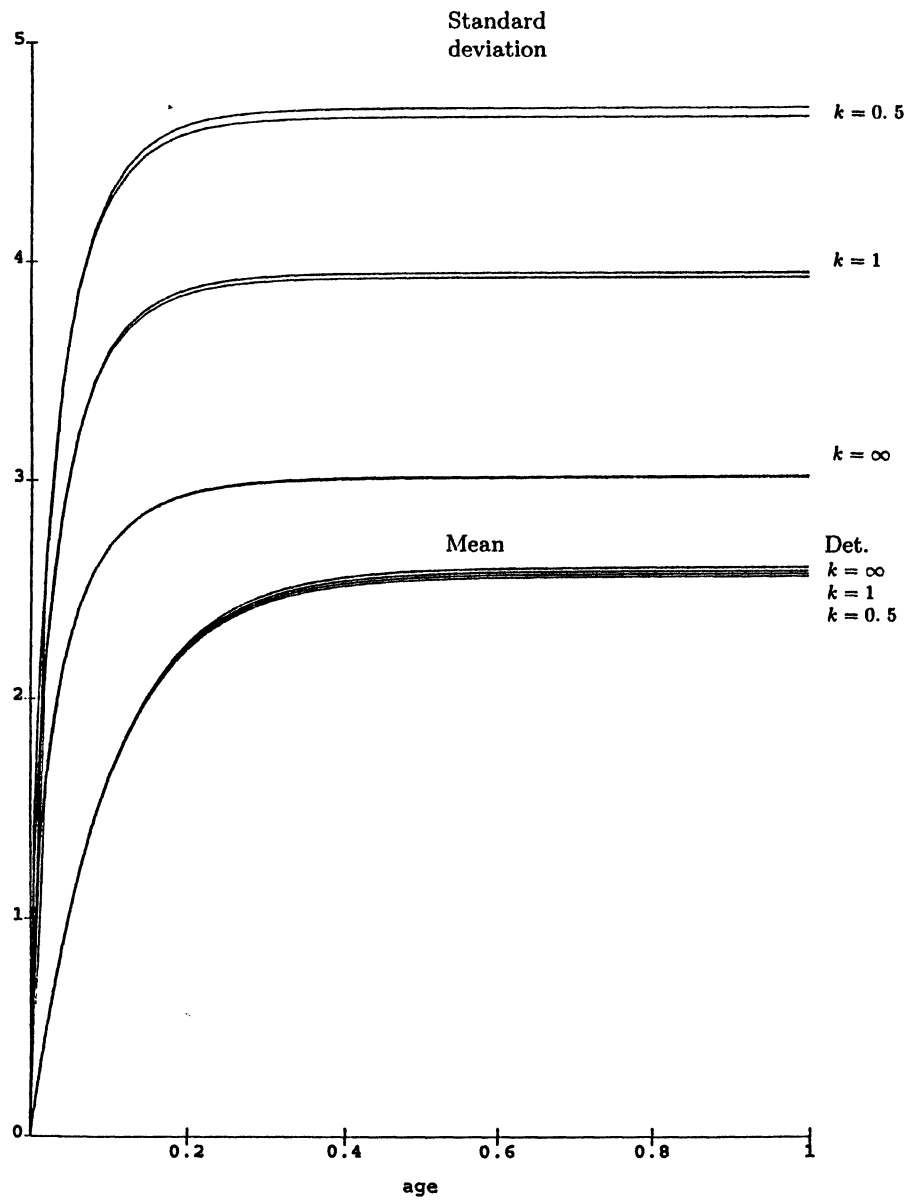

FIG. 5. *Exact and approximate mean and standard deviation for the Poisson distribution* ($k = \infty$), *the geometric distribution* ($k = 1$) *and the negative binomial distribution* ($k = 0.5$) *using parameter values* $\phi = 5.2$, $\alpha = 0.02$, $\mu_M = 10$ *and* $m_C = 5$, *with deterministic and normal approximations. The normal approximations to the means lie below the true curves. The normal approximations to the standard deviations lie above the true curves. The deterministic approximation to the means lies above the true curves.*

that, unconditionally, $M(a)$ has probability generating function

$$G_\Phi\left(\left[\int_{\theta(a;1)}^{1} + \int_{z}^{\theta(a;z)}\right]\frac{[1-h(u)]\,du}{(\mu_M+\alpha)u-\mu_M}\right),$$

with mean and index of dispersion given by

$$\begin{aligned} \mathrm{E}(M(a)) &= \mathrm{E}(\Phi)\{1-h(\theta(a;1))\}/\alpha, \\ \mathrm{I}_M(a) &= \mathrm{I}_{M|\Phi}(a) + \mathrm{I}_\Phi\{1-h(\theta(a;1))\}/\alpha, \end{aligned} \tag{5.1}$$

where the first term on the right-hand side of (5.1) is the corresponding index for a single host (i.e., for fixed $\Phi = \phi$) given in (2.8), which is independent of ϕ. The effect of allowing for between-host variability is thus that the population index of dispersion is increased over that for a single host by an amount that can be expressed as

$$\mathrm{E}(M(a))\mathrm{var}(\Phi)/[\mathrm{E}(\Phi)]^2.$$

5.2. *Alternative randomizations.* An alternative strategy would be to allow the parameter α, which represents the effect of a single parasite on the rate of mortality of the host, to vary randomly over the population. It is clear from the way that α enters into the expressions for properties of $M(a)$ for a single host, derived in Section 2.2, that while it is perfectly possible, such randomization does not lead to algebraically simple and easily interpretable results.

Another possible scenario is the following. Suppose that the number of parasites initially picked up by the host in a single encounter is a random variable K, and that each parasite independently survives and becomes established in the host with a probability π, where π varies from one host to another as a random variable Π. Then for a particular host, given $K = k$, the number C of surviving parasites per encounter has a binomial distribution with index k and π. Unconditionally, if K has probability generating function h_K, then the corresponding function for C is given by $h_C(z) = h_K(1 - \pi + \pi z)$. The previous expressions for the properties of $M(a)$ for a single host can now be modified by substituting this form for h_C and then randomizing with respect to π to obtain population values. The resulting expressions for these properties are straightforward although a little unwieldy. In the special (and not especially interesting) case when $\alpha = 0$, for example, we find

$$\begin{aligned} \mathrm{E}(M(a)) &= \phi\mathrm{E}(\Pi)\mathrm{E}(K)(1-\exp(-\mu_M a))/\mu_M, \\ \mathrm{I}_M(a) &= 1 + \{\phi\mathrm{I}_\Pi\mathrm{E}(K)/\mu_M + (\mathrm{I}_\Pi + \mathrm{E}(\Pi))(\mathrm{I}_K + \mathrm{E}(K) - 1)/2\} \\ &\quad \times(1-\exp(-\mu_M a)), \end{aligned}$$

where I_Π and I_K are the indices of dispersion for Π and K, respectively.

6. Discussion. The model discussed above allows for interaction between the host and parasite populations only through the additional mortality that the parasites present induce in their host. We now consider very briefly how various sorts of immune reactions might be incorporated.

Perhaps the simplest possibility is to suppose that, rather than being a constant μ_M, the rate at which a parasite dies is increased by the presence of other parasites within the host. Such an effect could also result from competition between parasites. It is straightforward to extend the methods of this paper to a more general model in which, given $M(a) = m$, the parasite death rate has the form $\mu_M + \kappa(m - 1)$. The factor $m - 1$ is chosen in preference to m for mathematical convenience and without any loss of generality. In this case, there does not appear to be a simple closed form for the probability generating function of $M(a)$, as there is when $\kappa = 0$, but properties can still be obtained by expansions, numerical solutions and other approximations as appropriate.

In this modification of the basic model, the immune reaction to the parasite load is envisaged as a simple sort of density dependence, but it is of more interest to model host immunity as a stochastic variable. Thus, we might replace the univariate model by a bivariate one, in which the host's immunity is represented by a nonnegative, integer-valued stochastic process $I(a)$ at age a. For example, a natural assumption is that the immunity level increases at a rate proportional to the current parasite load $M(a)$, and decays at a rate proportional to $I(a)$, so that $\{I(a)\}$ is a particular birth and linear death process. We can now use the immunity variable to increase the parasite death rate from μ_M *to* $\mu_M + \beta I$, so incorporating an additional form of nonlinearity into the model. Host death depends on parasite load as before. The effects of both of these modifications will be described in more detail in a forthcoming paper.

This latter modification of the basic model can be extended further by allowing parasites to exist in two forms within the host: as larvae and as mature parasites. Such a model has already been investigated (mostly numerically) by Grenfell, Dietz and Roberts (1995) as described in Section 1 of this paper. In their model, Grenfell, Dietz and Roberts assume that, at an encounter, the C parasites ingested are in larval form, and each parasite independently remains in this stage for an exponentially distributed time before either dying (at a rate that depends on the immunity level) or maturing. The stochastic immunity process is a birth and linear death process where the birth rate depends on the current total number of larvae present in the host.

In all of this we have only considered the evolution of a parasite population within a single host. A challenge for the future must be the question of how such stochastic models can be embedded within a suitable model for the dynamics of the host population; see, for example, Anderson and May (1978), who demonstrate the regulation of a host population by a macroparasite, using a *deterministic* model in which the parasite load is assumed to have a negative binomial distribution over the population, where the mean of this distribution is age-dependent, but where the shape is assumed to be fixed.

APPENDIX

The explicit solution to (4.1) and (4.3), for the normal approximation to the moments of the distribution of the parasite load $M(a)$, is as follows:

$$\begin{aligned} m_M(a) &= A - (A/2 + \beta B)\exp(-(3\mu_M - \beta)a/2) \\ &\quad -(A/2 - \beta B)\exp(-(3\mu_M + \beta)a/2), \\ \sigma_M^2(a) &= C - (C/2 + \beta D)\exp(-(3\mu_M - \beta)a/2) \\ &\quad -(C/2 - \beta D)\exp(-(3\mu_M + \beta)a/2), \end{aligned}$$

where

$$\begin{aligned} \beta &= \sqrt{\mu_M(\mu_M - 4\alpha)}, \\ A &= \phi\{2\mu_M m_C - \alpha(m_C^2 + v_C)\}/\{\mu_M(\alpha + 2\mu_M)\}, \\ B &= \phi\{2(\mu_M - \alpha)m_C - 3\alpha(m_C^2 + v_C)\}/\{2\mu_M(\alpha + 2\mu_M)(\mu_M - 4\alpha)\}, \\ C &= \phi(m_C + m_C^2 + v_C)/(\alpha + 2\mu_M), \\ D &= \phi\{3\mu_M m_C - (2\alpha + \mu_M)(m_C^2 + v_C)\}/\{2\mu_M(\alpha + 2\mu_M)(\mu_M - 4\alpha)\}. \end{aligned}$$

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