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Age- and bite-structured models for vector-borne diseases

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ABSTRACT

The biology and behaviour of biting insects is a vitally important aspect in the spread of vector-borne diseases. This paper aims to determine, through the use of mathematical models, what effect incorporating vector senescence and realistic feeding patterns has on disease. A novel model is developed to enable the effects of age- and bite-structure to be examined in detail. This original PDE framework extends previous age-structured models into a further dimension to give a new insight into the role of vector biting and its interaction with vector mortality and spread of disease. Through the PDE model, the roles of the vector death and bite rates are examined in a way which is impossible under the traditional ODE formulation. It is demonstrated that incorporating more realistic functions for vector biting and mortality in a model may give rise to different dynamics than those seen under a more simple ODE formulation. The numerical results indicate that the efficacy of control methods that increase vector mortality may not be as great as predicted under a standard host–vector model, whereas other controls including treatment of humans may be more effective than previously thought.

1. Introduction

The role of biting insects is of the utmost importance in the transmission dynamics of vector-borne diseases; without them many diseases simply could not spread. Vector biology such as longevity and biting rate has long been known to determine not only the persistence of such diseases but also to affect the size and speed of epidemics and the equilibrium prevalence of endemics. Indeed, in the early mathematical models of malaria, Ross indicates that vector death rate and bite rate are important with both featuring in his threshold theorem for malaria (Ross, 1916).

The Ross–Macdonald ordinary differential equation (ODE) model (Macdonald, 1957; Ross, 1911) and its many variations dominate the literature in vector-borne disease modelling. However, key assumptions regarding insect behaviour and biology are often disregarded or overlooked. Taking a basic model of vector-borne disease, one can use a mechanistic approach driven by observation of the biology of transmission and introduce more of the inherent complexity. It is important that this is introduced in such a way that the direct effects of the new elements can be ascertained. Here, the biology and corresponding behaviour of the vector is scrutinised.

It will be assumed that the basic underlying vector-borne disease model takes the form:

$$\text{Hosts}\quad\begin{cases}\dfrac{dS_H}{dt} &= b_H N_H - d_H S_H + \gamma_H I_H - \lambda_H S_H\\ \dfrac{dE_H}{dt} &= -d_H E_H - \sigma_H E_H + \lambda_H S_H\\ \dfrac{dI_H}{dt} &= -(d_H + D_H) I_H + \sigma_H E_H - \gamma_H I_H\end{cases}$$

$$\text{Vectors}\quad\begin{cases}\dfrac{dS_V}{dt} &= b_V N_V - \lambda_V S_V - d_V S_V\\ \dfrac{dE_V}{dt} &= \lambda_V S_V - \sigma_V E_V - d_V E_V\\ \dfrac{dI_V}{dt} &= \sigma_V E_V - d_V I_V\end{cases} \tag{1.1}$$

where $\lambda_i = \alpha p_i I_j/(N_H + m)$ is the force of infection of species j on species i ($j \neq i$). This term is a standard "criss-cross" transmission term associated with purely disassortative mixing. It arises through a vector biting at a rate α, picking a single host from all other hosts (N_H) and other animals (m) and the probability of transmission from infected host/vector to susceptible vector/host being successful (p_V/p_H). Other parameter notation is given in Table 1.

This susceptible-exposed-infected (SEI) host–vector model has recovery (at a rate γ_H) for hosts, but not vectors and additionally

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Table 1
Parameters for the SEI Ross–Macdonald model (1.1).

Parameters and variables	Description
b_H	Per capita host birth rate
d_H	Host death rate
λ_H	Force of infection upon host
γ_H	Host recovery rate
σ_H	Inverse of host latent period
D_H	Disease-induced host death rate
p_H	Probability of host becoming infected from a single infected bite
b_V	Per capita vector birth rate
d_V	Vector death rate
λ_V	Force of infection upon vector
σ_V	Inverse of vector latent period
α	Average bite rate
p_V	Probability of vector becoming infected from a single bite on an infected host
m	Number of other animals available for blood feeding (assuming no feeding preference between hosts) or number of other animals scaled by the vector's relative preference of these animals over the primary hosts (see Rock et al., in press for more details on vector preference).

Table 2
New parameters for the age and bite-structured model (other parameters remain the same as the standard ODE model (1.1).)

Parameters and variables	Description	Note
t	Chronological time	
τ	Time since last bite (TSLB)	
a	Age of vector	Since biting maturity
$\alpha(\tau)$	Per capita bite rate	$\alpha(\tau)=\beta r(\tau)$
β	Maximum per capita bite rate	Constant
$r(\tau)$	"Desire to bite" probability that a vector will take a blood-meal if it finds a host	
δ	Kronecker delta	$\delta(x)=\begin{cases}1 & \text{if } x=0\\ 0 & \text{otherwise}\end{cases}$

disease-induced mortality (D_H) for hosts. Next a more complex model is derived from (1.1), however the following methodology could be applied to almost any ODE vector model.

2. Methodology

2.1. Age structure (vector senescence)

The *age* at which a vector becomes infectious affects the number of secondary infections that can result from this one individual. If infection occurs near the start of the vector's life, it will inflict a higher number of bites (Styer et al., 2007; Bailey, 1982). This notion is that on average the vector which is infected at a low age will spend longer infectious than its counterpart which was infected nearer to the end of its life; more bites occur (on average) whilst it is infected and consequently it spreads disease more to the host population. The relationship between vector survivorship and its important effects on both vectorial capacity and the basic reproductive ratio was first discussed by Macdonald in the 1950s (Macdonald, 1956, 1952, 1961), however it was not until much later that different type of distributions for vector mortality were used rather than simply altering the fixed daily survivorship.

Traditional ODE models such as the Ross–Macdonald model, make use of the simple Markovian formulation by assuming that the (instantaneous) death rate is constant regardless of age; this leads to exponentially distributed life expectancies. In some cases this may be a reasonable and/or justifiable assumption, however more recent work on vectors such as the mosquito (Styer et al., 2007; Bellan, 2010) and tsetse (Hargrove et al., 2011) indicate that not modelling realistic death rates may lead to inaccuracies when estimating the transmission and prevalence of vector-borne disease. This certainly warrants further investigation and is cited as one of the most overlooked aspects of vector-borne disease modelling; Styer et al. (2007) and Bellan (2010) emphasise the importance of vector senescence as part of the modelling procedure.

Others have also attempted to resolve this neglected insight into vector-borne disease modelling by means of *Lumped-Age Classes* whereby the vector population is partitioned into classes in which parameters (in particular the death rate) are assumed to be constant (Hancock and Godfray, 2007). This method is commonly found in single population age-structured models; instead of modelling ageing by some rate of loss and gain between classes, the technique utilises a delay differential equation (DDE) framework where individuals effectively spend fixed times in each stage. DDEs are general more complex to work with than ODEs, particularly during numerical simulation.

A natural way to introduce age structure within the vector population is via a partial differential equation (PDE) type model in a similar manner to creating an age structure in single species disease models (described by various authors Keeling and Rohani, 2008; Murray, 2002; Britton, 2003), whereby a more realistic death rate which is a function of age is chosen.

Imposing a PDE-type age structure on the SEI host–vector model necessitates:

- Dependence of both chronological time and age for vectors (but not for hosts, although hosts could be treated similarly):

$$S_H(t), E_H(t), I_H(t), S_V(a,t), E_V(a,t), I_V(a,t)$$

- Forced births for vectors (births must occur at age zero, $a=0$):

$$b_V\delta(a)$$

- Age dependent deaths for vectors:

$$-d_V(a)$$

- Inclusion of the ageing process for vectors:

$$-\frac{\partial N_V}{\partial a}$$

- A new infection term within the host population (the infection term for the vector population remains unchanged and it is assumed that infectiousness does not vary with age hence the probability of transmission is independent of age):

$$\lambda_H = \alpha p_H \frac{1}{(N_H+m)}\int_0^\infty I_V(u,t)\,\mathrm{d}u$$

2.2. Bite structure (vector feeding behaviour)

Age structure in vector-borne disease models is not in itself new, although vector-borne age-structured models predominantly focus on age in the host population rather than the vector (Geisse et al., 2012; Hethcote and Thieme, 1985). However, not only is vector ageing important but the feeding patterns of the vector also play a vital role in disease transmission. After a vector has reached biting maturity it will start to "desire" a blood-meal; as time passes the vector becomes more and more likely to feed given the opportunity.

Once sated from feeding the vector is unlikely to feed again for some time, during which the desire to bite will rise once again until the feeding cycle repeats. To deal with the mechanics of biting the model may be further adapted, in a comparable way to adding age structure, however with the additional property of resetting "*time since last bite*" (TSLB) after the vector has fed.

$$\text{Hosts} \quad \begin{cases} \dfrac{dS_H}{dt} = b_H N_H - d_H S_H + \gamma_H I_H - p_H \dfrac{S_H}{(N_H+m)} \displaystyle\int_0^\infty \int_0^u \alpha(q) I_V(u,q,t)\,dq\,du \\ \dfrac{dE_H}{dt} = -d_H E_H - \sigma_H E_H + p_H \dfrac{S_H}{(N_H+m)} \displaystyle\int_0^\infty \int_0^u \alpha(q) I_V(u,q,t)\,dq\,du \\ \dfrac{dI_H}{dt} = -(d_H + D_H) I_H + \sigma_H E_H - \gamma_H I_H \end{cases}$$

$$\text{Vectors} \quad \begin{cases} \dfrac{\partial S_V}{\partial t} = \delta(\tau)\delta(a) b_V \displaystyle\int_0^\infty \int_0^u N_V(u,q,t)\,dq\,du + \delta(\tau)\left[1 - p_V \dfrac{I_H}{(N_H+m)}\right] \int_0^a \alpha(q) S_V(a,q,t)\,dq - d_V(a) S_V - \alpha(\tau) S_V - \dfrac{\partial S_V}{\partial a} - \dfrac{\partial S_V}{\partial \tau} \\ \dfrac{\partial E_V}{\partial t} = \delta(\tau) \displaystyle\int_0^a \alpha(q) \left[p_V \dfrac{I_H}{(N_H+m)} S_V(a,q,t) + E_V(a,q,t)\right] dq - d_V(a) E_V - \alpha(\tau) E_V - \sigma_V E_V - \dfrac{\partial E_V}{\partial a} - \dfrac{\partial E_V}{\partial \tau} \\ \dfrac{\partial I_V}{\partial t} = \delta(\tau) \displaystyle\int_0^a \alpha(q) I_V(a,q,t)\,dq - d_V(a) I_V - \alpha(\tau) I_V + \sigma_V E_V - \dfrac{\partial I_V}{\partial a} - \dfrac{\partial I_V}{\partial \tau} \end{cases} \tag{2.1}$$

In addition to the age structure, TSLB structure gives further additions to the PDE model:

- Dependence on age (a) and TSLB (τ) as well as chronological time (t), for vectors (but not for hosts):

  $S_H(t), E_H(t), I_H(t), S_V(a,\tau,t), E_V(a,\tau,t), I_V(a,\tau,t)$

- Forced births for vectors. Births must occur at age zero and TSLB zero ($a=0, \tau=0$):

  $b_V \delta(a)\delta(\tau)$

- TSLB-dependent biting rate:

  $-\alpha(\tau)$

  and so vectors are upon biting vectors are transferred into the same age but $\tau=0$ TSLB category (i.e. a non-infective bite moves $S_V(a,\tau,t)$ to $S_V(a,0,t)$). In general vectors will either remain susceptible and so move to $S_V(a,0,t)$ with probability $1-(p_V I_H)/(N_H+m)$ or become exposed and enter $E_V(a,0,t)$ in a similar manner to the Ross–Macdonald model. Vectors that are already exposed or infectious do not change infection status through biting, only TSLB category.
- Inclusion of the "not biting" process for vectors:

  $$-\frac{\partial N_V}{\partial \tau}$$

- A slight change to the host infection term:

  $$\lambda_H = p_H \frac{1}{(N_H+m)} \int_0^\infty \int_0^u \alpha(q) I_V(u,q,t)\,dq\,du$$

  noting that vectors cannot have gone longer without biting than their age ($\tau \le a$). Here the function $\alpha(\tau)$ appears along with the infected vectors under the integral as now the biting rate is dependent not only on the total number of vectors of all ages, but also the respective biting rates of all the individual vectors from those that have just fed (TSLB equals zero) to those that have never fed (TSLB equals age).

2.3. Novel model

A new system (2.1) can be derived using the concepts of age-dependence and bite rate structure. For notational ease, S_H, E_H and I_H will be written as such despite being functions of time (t). Likewise S_V, E_V and I_V are functions of age, TSLB, and time (a, τ, t) (see Table 2):

In order to generate solutions from this system of PDEs a range of analytical and numerical methods are outlined. First the system is considered in the disease-free case which allows analytical solutions to be obtained. With the addition of disease the system becomes unsolvable using these techniques, however the stationary disease-free solutions yield plausible initial conditions from which to initialise numerical simulations. Suitable methods for solving PDEs are outlined and discussed before results can finally be generated and conclusions drawn.

It is noted that the Ross–Macdonald model (1.1) is the limiting case of the new system (2.1) where the death rate and bite rate are of independent of age and TSLB respectively.

3. Disease-free solutions

In the absence of disease, the underlying dynamics (births, deaths and biting) of the vector population do not change. Therefore by solving the PDE for the vector population for I_H, $I_V=0$ the age and bite rate structured distribution of the vector population can be found.

3.1. Age-structured PDEs

First, the age structure alone is considered: this can be solved using the McKendrick approach to age structure (Britton, 2003).

A Lexis diagram (Fig. 1) is a useful way to visualise the vector population. Each line represents an individual ageing with time. Births are denoted with circles and occur at the rate $b_V N_V(t)$ (the per capita birth rate multiplied by the total population size at time t). Deaths are modelled according to the relevant distribution, $d_V(a)$, and are shown as crosses. The number of vectors aged a will be denoted by $v(a,t)$ or simply v in the following.

The corresponding equations for this age-structured PDE are:

$$\begin{aligned} &\frac{\partial v}{\partial a} + \frac{\partial v}{\partial t} = -d_V(a) v \\ &v(0,t) = b_V(t) \int_0^\infty v(a,t)\,da \end{aligned} \tag{3.1}$$

with the boundary condition giving the influx of new vectors into the population at age zero.

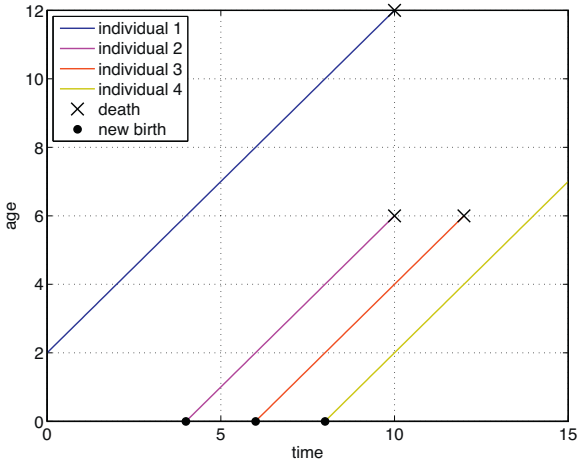

Fig. 1. 2D Lexis diagram for age-structured populations. Individuals are represented by lines passing through time and age at the same rate. Here one individuals is alive at time zero and births of others, which are denoted by circles, occur at times 4, 6 and 8. Deaths are marked by crosses; a single individual is alive at time 15.

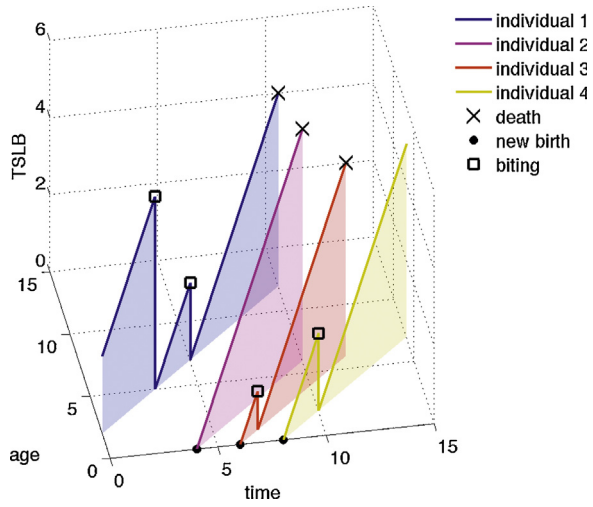

Fig. 2. 3D Lexis diagram for age- and bite-structured populations. These individuals are identical to those in Fig. 1, as would be seen by a top-down view, however the lines now pass through 3 dimensions. Here individuals travel through time, age and TSLB with the same rate and births and deaths occur as before. Additionally, biting events occur and are denoted by a square. Upon biting an individual moves directly back onto the zero TSLB plane leading to the saw-tooth pattern seen.

It can been seen from the Lexis diagram that characteristics of this PDE are given by $a = t + c$ where c is constant. Using the method of characteristics this system can be solved and it is seen that $v_0(a) = A\exp(-\int_0^a d_V(u)\,\mathrm{d}u)$ is a stationary distribution (S.1 gives more details).

To find A, it is necessary to select the function, $d_V(a)$; biologically motivated choices are described and used in the Section 5.1.

3.2. Age and bite-structured PDEs

Returning to the main age- and bite-structured PDE model of the form:

$$\begin{aligned}
&\frac{\partial v}{\partial a} + \frac{\partial v}{\partial \tau} + \frac{\partial v}{\partial t} = -(d_V(a) + \alpha(\tau))v \\
&v(0,0,t) = b_V \int_0^\infty \int_0^a v(a,\tau,t)\,\mathrm{d}\tau\,\mathrm{d}a \\
&v(a,0,t) = \int_0^{a-\tau} v(a,q,t)\alpha(q)\,\mathrm{d}q \quad \text{for} \quad a \neq 0
\end{aligned} \tag{3.2}$$

adds one further dimension to the problem. The previous two-dimensional Lexis diagram is now extended into this third dimension, as can be seen in Fig. 2. Here it is demonstrated how individuals move through time, age and TSLB classes with the same rate, however when a bite occurs (at a total rate of $-\alpha(\tau)v$), there is a discontinuity in the graph unlike that of the 2D version. To handle this discontinuity mathematically, it is easier to formulate equations for the resetting of the bite class as a new individual entering at the boundary $\tau = 0$ while the biting vector exits the population.

The method of characteristics may be utilised again, this time to yield a general solution of:

$$v(a,\tau,t) = v_0(a-t,\tau-t)\exp\left(-\int_{a-t}^{a} d_V(u)\,\mathrm{d}u - \int_{\tau-t}^{\tau} \alpha(q)\,\mathrm{d}q\right) \tag{3.3}$$

where v_0 is the initial distribution of vectors across ages and TSLBs (further details and computation are given in S.2).

To find a stationary solution, the boundary conditions are used. If

$$v_0(a,\tau) := B(a-\tau)\exp\left(-\int_{a-\tau}^{a} d_V(u)\,\mathrm{d}u - \int_0^{\tau} \alpha(q)\,\mathrm{d}q\right) \tag{3.4}$$

in the domain $0 \le \tau \le a, a \ge 0$ where the function B is defined by the non-local boundary conditions of either births (in the case $a = \tau$) or by biting (otherwise):

$$B(a-\tau) = \begin{cases} \displaystyle\int_0^{a-\tau} v(a,q,t)\alpha(q)\,\mathrm{d}q & \text{if} \quad a > \tau \quad \text{bites} \\ \displaystyle b_V \int_0^\infty \int_0^a v(a,\tau,t)\,\mathrm{d}\tau\,\mathrm{d}a & \text{if} \quad a = \tau \quad \text{births} \end{cases} \tag{3.5}$$

then this v_0 (given by (3.4) and (3.5)) is a stationary distribution defined implicitly.

To clarify, the total influx of births into a population enter at $(a, \tau) = (0, 0)$. Births here are assumed to arise from each vector producing offspring at a rate b_V.

Once born (or more accurately, upon reaching biting maturation) the vector will age and move through TSLB classes until it either dies or bites; before either of these events occur the individual is classified such that $a = \tau$. Upon dying or biting, individuals move off the characteristic line $a = \tau$ and so the number of vectors decays according to the functional forms of the death and bite rates.

Deceased vectors are removed from the total population, however upon biting a vector is assigned zero TSLB; this can be visualised mathematically as a new individual entering the population on the boundary $(a, \tau) = (a, 0)$. The newly fed individuals at age a are all the individuals which were previously also age a but of any TSLB.

4. Numerical methods

The above work enabled disease-free analytic solutions of the vector PDE to be obtained, however introducing the additional vector and host classes to capture disease spread necessitates numerical schemes to be utilised. This section outlines one such method before the results are given in Section 5.

There are many numerical methods to solve PDEs, however in this case the *method of lines* (MOL) is a sensible choice for this type of first order 3D PDE with non-local boundary conditions. The MOL first requires (2.1) to be *semi-discretised* (discretised in all dimensions except time). Next these new ODEs, which correspond to vertices on a grid, are solved using standard numerical methods and finally the solutions at these points are interpolated between

Table 3
Additional parameters for numerical analysis of the age- and bite-structured vector model.

Parameters	Description	Note
h	Step-size	This is the width of the grid in both age and TSLB directions
A	Maximum life expectancy	
T	Maximum TSLB	
N_1	Number of age intervals	$N_1 = \frac{A}{h}$
M	Number of age grid points	$M = N_1 + 1$
N_2	Number of TSLB intervals	$N_2 = \frac{T}{h}$
Q	Number of TSLB grid points	$Q = N_2 + 1$

to generate a surface. The MOL is a common technique in other disciplines such as physics and may be used here instead of other approaches (such as partitioning the vector population into age and TSLB classes). It is chosen here as it is known that there are preferred directions in this system corresponding with the characteristics of the PDE. The MOL, which are used in conjunction with finite differences, are standard choices for many numerical analyses of PDEs (Ekolin, 1991; Dehghan, 2003).

A uniform 2D grid is taken where the maximum age is A, maximum TSLB is T and the spacing between lines in each direction (age and TSLB) is set to h_1 and h_2 respectively. Across this grid the PDEs can be discretised by computing finite differences.

Under this method $N_V(a, \tau)$ is the number of individual vectors of the specific age a and TSLB τ. By interpolating between grid points in the MOL a quasi-smooth surface representing the solution may be projected above the domain.

From here onwards it will be assumed that $h_1 = h_2 = h$; this allows for faster calculation during simulation due to simpler formulation. To find the number of vectors between *any* two ages and TSLBs the volume below the surface must be calculated. Due to interpolation is it possible to generate an reasonable approximation for this number of individuals even if the ages and TSLBs do not correspond to grid lines.

There are two types of grid point to consider: the boundary $\tau = 0$ where new bites or births occur and all other points in the domain. Each type is computed differently. Points not on the $\tau = 0$ boundary can be calculated be using the technique of *finite differences* (see S.3); at these points there is an influx of ageing and non-biting vectors and an outflux of deaths and biting. On the boundary, new bites and births are calculated from the integral equations (3.5) using the *composite trapezoidal rule*. This system has non-local Dirichlet boundary conditions along $\tau = 0$ and so, whilst it is necessary to compute them at every time step using the composite trapezoidal rule, the derivative at $u(a, 0, t)$ does not have to be computed.

The vector population will be represented by three (M-by-Q) matrices, S_V, E_V and I_V (see Table 3). It will be assumed that biting instantaneously moves an individual to the $\tau = 0$ category but to the same age category (i.e. $S_V(a, \tau) \mapsto S_V(a, 0)$). Biting may lead to a change in disease status (i.e. a susceptible individual becomes exposed) however biting does not affect movements from exposed to infectious classes. These happen instantaneously at the rate σ_V which is independent of TSLB, as is biologically representative. This means the continuous disease-dynamics of the system are maintained.

Table 4
The four cases of death and bite rates under consideration.

	(i)	(ii)
(a)	Age and bite structure has no effect. This is the standard Ross–Macdonald model (1.1)	Age-structured population only
(b)	Bite-structured population only	Full age- and bite-structured vector population

As the step-size, h, tends to zero and A and T become large, the discretised system of ODEs converges to PDE system (2.1). Ideally values of h, A and T can be found such that the MOL approximates projected epidemic outcomes well but that M and Q are not so large that simulation duration becomes infeasible.

In order to compensate for the loss of the tail of the distribution caused by using maximum age, A, and maximum TSLB, T, scaling is used during simulation so that the volume under the projected surface restricted by these bounds is the total vector population size required.

5. Results

The ODEs generated by the MOL were solved through time with MATLAB's ode45 to simulate the dynamics of an epidemic. Simulations have been performed for the four different cases given in Table 4 to compare the effects of age and/or bite structure upon disease dynamics of vector-borne disease.

5.1. Choosing a mortality function

In order to be able to include realistic life expectancies, the precise form of the vector death rate as a function of age, $d_V(a)$ must be chosen carefully. The Ross–Macdonald model (1.1) gives the vector death rate as:

$$d_V(a) = d_1 \qquad \text{(Case (i))}$$

where d_1 is constant; this gives rise to exponentially distributed life expectancies. To improve upon this original rate, age-dependent mortality is chosen such that the death rate increases with age to incorporate the concept of senescence. Crude supposition may lead to the simplest case that is age-dependent, where $d_V(a) = d_2 a$, however data for senescence in female, blood-fed mosquitoes (Styer et al., 2007) suggests that life expectancies might be assumed to be logistically distributed and so the death rate may given in the form:

$$d_V(a) = d_3 \frac{1}{1 + e^{d_4(-a+d_5)}} \qquad \text{(Case (ii))}$$

In this case d_3 corresponds with the maximum value of the function, d_4 controls the steepness and d_5, where the "switching" behaviour occurs. Case (ii) has already been parameterised using experimental data available for the mosquito *Aedes aegypti* in laboratory conditions (Styer et al., 2007). Unfortunately the parameterisation found in the study is deemed to be unrepresentative for these purposes as laboratory bred mosquitoes have a higher mean life expectancy than those found in the wild, however Styer et al. (2007) did develop a model and generated a variety of parameterisations for other life expectancies.

The logistic model is assumed to still be a good fit for mortality patterns of blood-feeding vectors and the new parameterisation used later for simulation will reflect the approximate shape of the hazard obtained in this study. Styer et al. did not give parameterisations for 14 day life expectancies, so these cannot be used

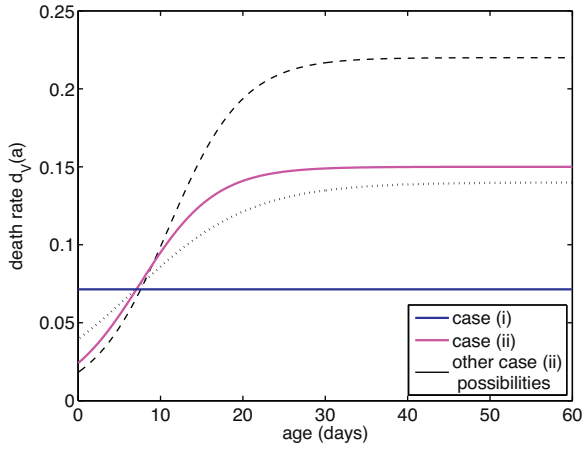

Fig. 3. Examples of the types of possible death rate which all give a mean 14 day life expectancy. For case (i), $d_1 = 1/14$ and for case (ii), $d_3 = 0.15$, $d_4 = 0.22$ and $d_5 = 7.51$. Some other possible parameter combinations for case (ii) are shown by: dotted (with $d_3 = 0.14$, $d_4 = 0.14$ and $d_5 = 6.69$) and dashed (with $d_3 = 0.22$, $d_4 = 0.22$ and $d_5 = 10.9$).

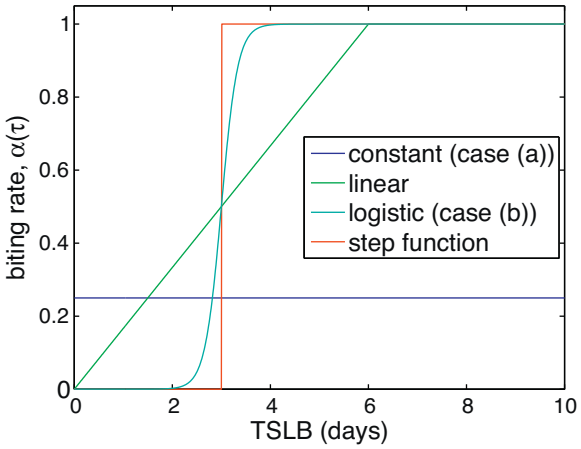

Fig. 4. Examples of different biting functions all with the same mean time to bite (4 days) including (Hargrove and Williams, 1995) feeding/non-feeding pattern represented by a step function; this is a limiting case of the logistic case.

directly. Some of the different shaped functions which have a mean life expectancy of 14 days are shown in Fig. 3.

These mortality functions are the instantaneous death rates at a given age, a. Amongst the literature (Parham and Michael, 2010; Styer et al., 2007; Bellan, 2010) and in survival analysis these functions may be also referred to as *mortality hazards* or *hazard rates*. Mortality with age may differ across species and so it is important to emphasise that the function given here for the vector death rate may not be appropriate for other vectors, subspecies or environments. The PDE model developed here is able to cope with a generic death rate, assumed in general to be age-dependent.

In order to compare and contrast between different mortality rate formulations in simulation (i.e. cases (i) and (ii)), the mean survival time is kept constant at 14 days (Chitnis et al., 2008).

5.2. Choosing a bite rate function

Little information is available for the derivation of the bite rate function, $\alpha(\tau)$. Unlike vector mortality, which can be estimated in a variety of ways, studies have concluded (at best) an approximation of the mean time between blood-meals for mosquitoes and conducted somewhat inconclusive cost-benefit analyses of possible feeding patterns of tsetse (Hargrove and Williams, 1995).

It is conjectured that the bite rate, $\alpha(\tau)$ may be decomposed into 2 elements:

1. β, a rate parameter that determines that maximum rate at which a vector may obtain blood-meals or encounter hosts. This term assumes that the vector can always find a suitable host for biting or alternatively it could be presumed that the probability of finding a suitable host is absorbed into this rate.
2. $r(\tau)$, the probability that the vector will take a blood-meal if it encounters a host given that it last took a blood-meal (or matured) τ days ago

In the absence of information, the simplest case is to take a constant bite rate:

$$r(\tau) = r_a \qquad \text{(Case (a))}$$

leading to exponentially distributed times between feeding. However by considering the biological imperative, a vector will be unlikely to bite again immediately after taking one blood-meal and the desire to bite should increase until saturation (defined here as the probability of a vector biting being one, should the vector find a suitable host). Therefore it will be assumed that there may be various types of suitable candidates for the bite rate including logistically distributed time between bites:

$$r(\tau) = \frac{1}{1 + e^{r_c(-\tau + r_d)}} \qquad \text{(Case (b))}$$

Other functions have been posed, such as a fixed period of non-feeding following a blood-meal (Hargrove and Williams, 1995), however, for now these other formulations will be put aside both for ease of implementation (it is harder to formulate the PDE model with non-continuous biting functions such as this Heaviside step function) and as there is no compelling evidence to suggest such functions give a more realistic representation of vector feeding behaviour. Some of the potential feeding rates are shown in Fig. 4. The logistic case (case (b)) is particularly apt as it may approximate either a linear function or a Heaviside step function by a simple change in parameter choice.

The waiting times until a bite occurs can be considered to be independent random variables governed by the probability function, $r(\tau)$, and the rate parameter, β, which will remain consistent throughout any changes made to $r(\tau)$. $r(\tau)$ is constructed in such a way that the mean time to bite is the same in both cases (a) and (b).

The parameters used in the simulation have been based on "typical" values from the literature for a human-mosquito population with endemic malaria (see Table 5), however it is noted that estimates for almost all parameters vary greatly according to vector species, location and disease strain (Chitnis et al., 2008 outline many of these variations). The initial conditions are important; simulations with disease are started from an equilibrium distribution of vectors across age and TSLB classes in the susceptible population. Disease is introduced via infected individuals in the host population only, so that disease enters the vector population in a "natural" way (i.e. upon vectors feeding). This avoids the problem of needing to know where infection lies in the vector population.

5.3. Effect of age and bite structure

The MOL was used to simulate epidemics in both host and vector populations. As an example of the type of impact age and bite structure can have, parameter values which are representative for "typical" endemic malaria were used and are given in Table 5. Four simulations, cases (ia), (iia), (ib) and (iib) as described in Table 4, were run for this set of parameters in order to compare the resultant effect on the epidemic in: the host population; the distribution of

Table 5
Parameters used in the PDE model simulation. All parameter values were taken from mid-range estimates for malaria from the literature (see Chitnis et al., 2008) unless specified otherwise. Cases (i), (ii), (a) and (b) are described in Table 4.

Parameters	Description	Value
N_H	Population size of hosts, non-reservoir hosts, and vectors respectively	1000[a]
m		500[a]
N_V		5000[a]
α_0	Average vector feeding rate	0.25 days^{-1}
β	Maximum vector feeding rate	0.5 days^{-1}[b]
r_a	Parameter in case (a)	0.25[b]
r_c	Parameter in case (b)	6[b]
r_d	Parameter in case (b)	3[b]
b_H, d_H	Per capita birth/death rate of hosts	0.02 yr^{-1}
b_V	Per capita birth rate of vectors	0.0714 days^{-1}
d_V	Average vector "natural" death rate	0.0714 days^{-1}
d_1	Parameter in case (i)	0.0714 days^{-1}[c]
d_3	Parameter in case (ii)	0.15[c]
d_4	Parameter in case (ii)	0.22[c]
d_5	Parameter in case (ii)	7.51[c]
σ_H	Incubation rate of infection in hosts and vectors respectively	0.1 days^{-1}
σ_V		0.1 days^{-1}
γ_H	Recovery rate of hosts 1 and 2 and vectors respectively	0.002 days^{-1}
γ_V		0
D_H	Disease-induced mortality rate in hosts	0 yr^{-1}
p_H	Probability of transmission from vectors to hosts	0.022
p_V	Probability of transmission from host to vector	0.31
A	Maximum age	60 days
T	Maximum TSLB	60 days
h	Age and TSLB step-size	0.167 days

[a] These values were selected for this simulation based on a "village" of 1000 people and a human/mosquito population ratio of 1:5 (as given for areas with lower malarial prevalence by Chitnis et al. (2008)).
[b] This estimated feeding pattern retains a mean time to bite of 4 days.
[c] Computed to retain an average life expectancy $1/d_V$.

infected vectors across ages; and TSLBs and the prevalence in both host and vector populations.

The distribution of the vector population across ages and TSLBs is dependent on the vector death rate, d_V, and bite rate, α; this can be represented graphically using a contour plot. In each simulation the distribution of the vector population changed according to the death and bite functions used, however the total vector population size was kept constant ($N_V = 5000$). The vector population size is colour-coded on a log-scale for the four cases under examination in Fig. 5. Under the assumption of logistically distributed time

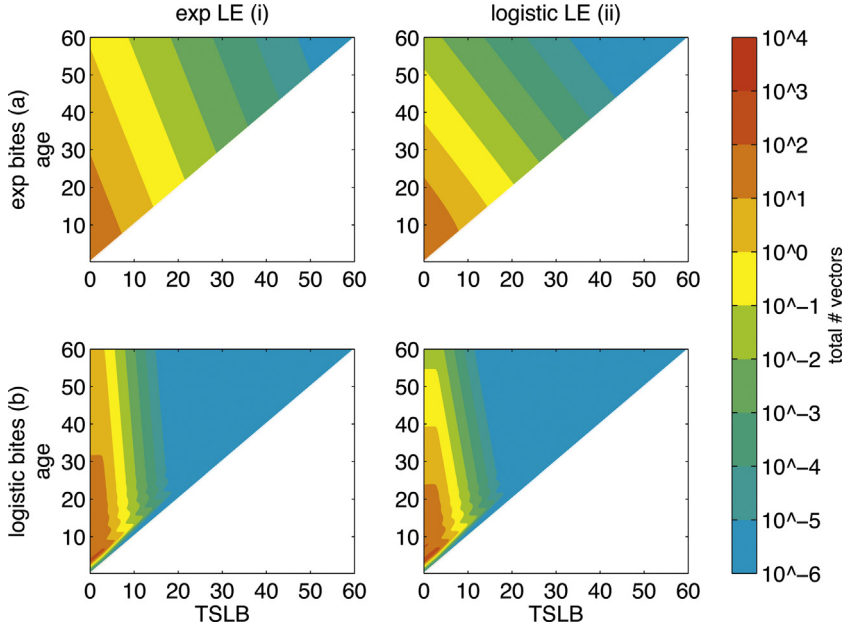

Fig. 5. Contour plot of age and TSLB distribution of all vectors in the four cases under the disease-free model. The left-hand plots are for simulations in case (i); exponentially distributed life expectancy (LE) with constant per capita death rate. The right-hand side shows cases (ii); logistically distributed LE. Likewise the top graphs show simulations with exponentially distributed time between bites with TSLB-independent bite rate; this is case (a). Finally the bottom graphs show case (b) with logistic time between bites. Parameter values are taken from Table 5 with the total vector population size kept constant between cases.

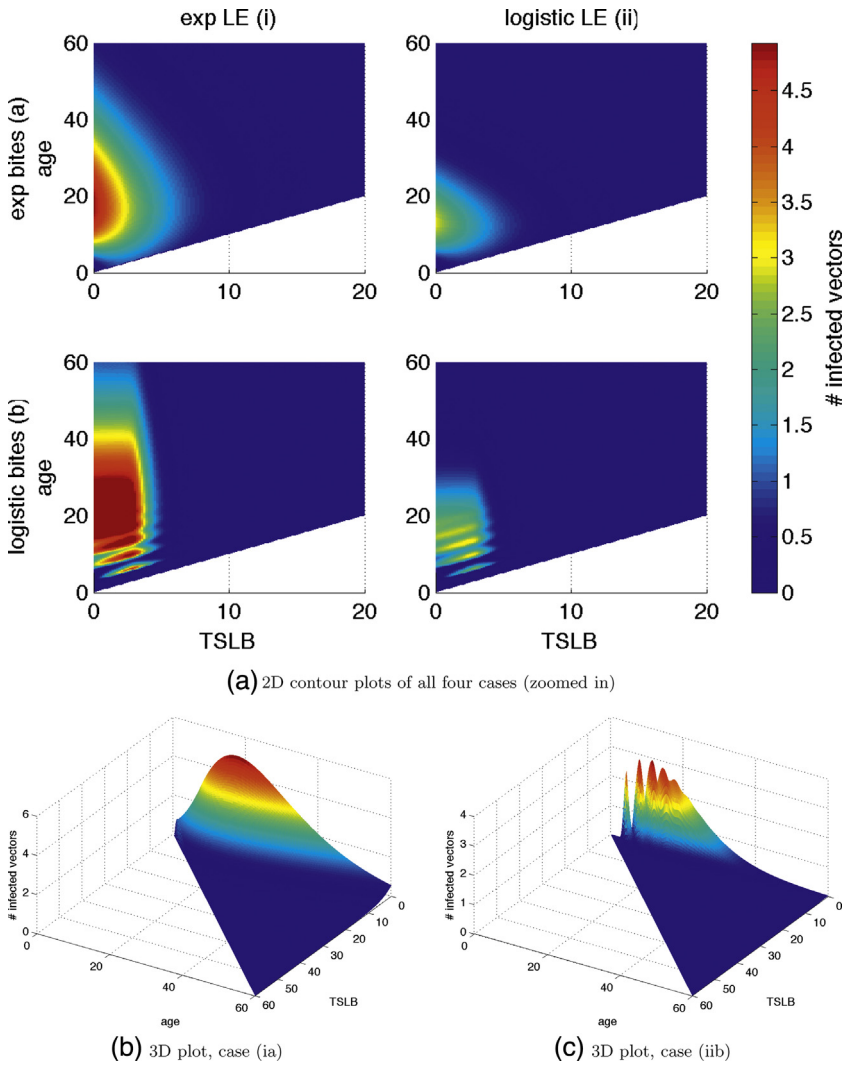

Fig. 6. Endemic disease distribution in the vector population. Parameter values are taken from Table 5 with simulations run for 4000 days. (a) The 2D representation of the distribution of infected vectors in all four cases, zoomed in to show only vectors with TSLB less than 20 days. (b) and (c) The same information as 3D plots of the age and TSLB-independent case (ia) and the age- and TSLB-dependent case (iib) respectively.

between bites (case (b)), the population is shifted greatly towards lower TSLBs. Logistically distributed life expectancies (case (ii)) reduce the tail end of the distribution.

Fig. 6 demonstrates the effect of age and bite structure upon the distribution of infection in the vector population. It is seen that for exponentially distributed life expectancy (case (i)), there is a distinct "tail" into the older ages, which is not present under the logistic distribution (case (ii)). Likewise, in case (b) the majority of the infected population has a lower TSLB than in the case (a), the TSLB-independent case. Age structure not only significantly reduces the numbers of older vectors but there is less total infection in case (ii) than in case (i). The impact of bite structure on the distribution of vectors is particularly striking; in the logistic case (case (b)), distinct bands of infection are seen corresponding to vectors which fed and ages around 4 and 8. For older vectors these effects smear out.

The dynamics of host infection may also differ substantially between different cases (see Fig. 7). Introducing an age-dependent death rate leads to large reductions in prevalence in both the host and vector populations (see Table 6), whereas the effect of a TSLB-dependant bite rate are more complex; the TSLB-dependent biting here causes more infection when life expectancy is exponentially distributed but less in the logistic case (again in both hosts and vectors). The results are highly stratified by age-dependence, whereas TSLB-dependent effects are noticeable but less dramatic.

Table 6
The total percent prevalence at equilibrium in both host and vectors for the four cases of the PDE model using parameters from Table 5.

	(i)		(ii)	
	Host	Vector	Host	Vector
(a)	53.4	13.0	29.2	4.8
(b)	57.0	15.2	26.2	4.3

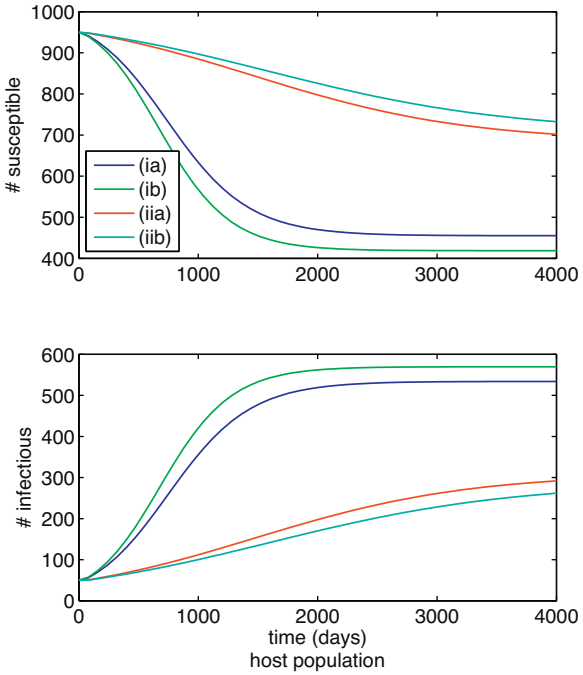

Fig. 7. Dynamics of disease prevalence in the host population under the four cases. Parameter values are taken from Table 5.

6. Conclusions

The effects of age and bite structure in vector populations can lead to non-negligible changes in disease prevalence in both host and vector populations. Results show it is possible to generate significant differences in host infection levels in each of the four cases. This demonstrates that it is quite possible for the distributions of the vector bite and death rates to play a key role in disease transmission to the host population, as has been discussed in the literature for vector senescence (Styer et al., 2007; Bellan, 2010).

It is concluded that age structure plays a large role in disease prevalence in both vectors and humans with age-dependant mortality being linked with lower levels of infection. Simulations using other choices of death function (not shown here) indicate that this result holds for a range of plausible age-dependent functions. This finding echos previous conclusions that effect of vector senescence in disease transmission is of great importance.

Another key result of these simulations is the distribution of infection within the vector population due to feeding patterns. The prevalence in the vector population may be similar between cases (a) and (b), however, the distribution of infection in the vectors is still significantly different. In case (b), where the bite rate was taken to be TSLB-dependent, noticeable bands in vector infection numbers were produced at low age and TSLB. This result is a remnant of the biting process; whilst there are several processes (including latency period distribution and deaths) governing the appearance and location of the bands, they arises through the overlapping of the biting poisson process of many individuals. For other choices of biting function with the same mean time between bites, this effect is also observed (results not shown here) although as the variance increases it becomes less apparent.

This shift in distribution poses questions about the efficacy of mosquito controls such as shortening vector life expectancy via controls using *Wolbachia*. *Wolbachia* is a maternally inherited bacterium which can reduce the life expectancy of mosquitoes including those which carry malaria and dengue (Iturbe-Ormaetxe et al., 2011) as well as other disease vectors such as the tsetse (Medlock et al., 2013). It is thought to have good potential as a form of vector-borne disease biocontrol. Under the ODE model this may eliminate some of the "infection tail" seen for older ages, however under age-dependent mortality, the majority of vector infection occurs in younger individuals.

There is an interesting relationship between bite structure and disease prevalence which changes dependent upon age structure. For exponential vector life expectancies, imposing logistic feeding patterns yields a higher prevalence (in both hosts and vectors), whereas in the age-dependent case, the same feeding patterns give lower prevalence. Bite structure is strongly linked to age structure. By considering the extreme case where vectors bite exactly every 4 days and survive exactly 7 days, it is seen that there would be no possibility for transmission as vectors must bite once to acquire infection and a second time to transmit. At the other end of the spectrum, with a constant biting function ($\alpha = 0.25$) and the same 7 day survival, it is more than possible to have sustained disease spread provided that transmission probabilities were sufficiently high.

Finally the simulations show that under this malaria-like parameterisation the effects of age structure in the vector population overshadow those of bite structure in terms of prevalence, however vector feeding has distinct ramifications for distributions of infected vectors which should not be disregarded, especially when modelling control strategies.

7. Discussion

The PDE model introduced provides an extension of current the ODE models such as (1.1) and it emphasises the importance of incorporating vector ageing within models. Whilst not explicitly demonstrated, reducing vector life expectancy may not eliminate much of the infection in the vector population. Obviously, the manner in which the distribution is changed will affect how much infection is removed from the vector population and, consequently, the host population.

Further work using this model could examine the effects of altering various other parameters which can be physically changed in order to explore the efficacy of different types of control. In particular controls which impact upon age-structure (mass-spraying), bite-structure (bed nets) or both (insecticide-treated bed nets) could be examined with a new perspective using this novel methodology.

This new model structure may also enable more detailed study of vector species such as the tsetse (*Glossina*) for which feeding is intrinsically linked to survival; tsetse must blood-fed or else they will starve. Here there is a clear relationship with starvation and TSLB which it has not been possible to model mechanistically before.

In the simulations performed here, the age-dependent death rate (case ii) was extrapolated from data pertaining to laboratory-bred mosquitoes. It would be expected that wild vector populations may have slightly different shaped-distributions from laboratory-bred ones and the same is true between different species as well; this may have an impact on the results. The biting function was constructed from the limited information available in the literature about the feeding frequency of vectors. Gaining a better understanding of the shape of the distribution resulting from this biological process would lead to greater confidence in the results generated by the model.

Here a simple SEI host–vector model was used as a base model upon which an age- and bite-structured model was constructed in order to easily examine the effects of age and bite structure on disease dynamics. In reality, a SEIR or other similar type of disease progression model is more likely to be suitable. This will vary by disease.

Whilst introducing age-structure in the vector population via a PDE model is unusual it has been done before (Adler, 1976). It is, however, more common to see age-structured host populations in host–vector models. If a model includes a death-dependent mortality function without a similar TSLB bite-rate it is possible that disease prevalence may be under-estimated. The introduction of TSLB-structure here is believed to be novel for an epidemiological model and reveals that lower prevalences are seen in both the host and vector populations with no bite structure than with.

It is computationally expensive to perform the simulations required to solve this PDE system and so it is necessary to assess whether the advantages of the extra information gained outweigh the disadvantage of increased computation time. The obvious advantages of the more simple models are transparency, mathematical tractability and computational cheapness. Integrating more of the known biology through this PDE model does indicate that simple models may not capture important complexities caused by vector senescence and biting patterns; in particular the relative efficacy of control measures.

There is certainly much to be said for retaining enough simplicity to really elucidate the effect of each parameter on a model and keep mathematical tractability. However, if key features of the inherent biological system are missing, it is hard to perceive whether these models really perform satisfactorily in predicting disease dynamics. In all mathematical modelling, there is a balancing act between exceedingly complex, "realistic" models, which may be esoteric and difficult to analyse, and simple models, which may miss key factors contributing to disease transmission.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2015.02.006.

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