Discrete versus continuous-time models of malaria infections

Level 2 module in "Modelling course in population and evolutionary biology"

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1 Introduction

Models of population dynamics can be formulated as differential equations in continuous time or difference equations in discrete time. Continuous-time models treat organisms as continuously reproducing, whereas in discrete models organisms reproduce at defined intervals. Continuous-time models are typically used when organisms have overlapping generations and discrete models when generations are distinct, with all individuals present at one time being the offspring of individuals present at a previous time. Models of the within-host dynamics of infectious diseases, including malaria, are usually expressed in continuous-time. However, as you will see in the next section, malaria parasites reproduce at a fixed age and have non-overlapping generations, suggesting that a discrete model would be more appropriate.

In this module you will investigate the consequences of modelling malaria infections in continuous rather than discrete time when the production of transmission stages is included. You will see that when we are interested in how the production of transmission stages affects the parasite dynamics and hence how malaria parasites can optimise their transmission, the results from the two types of models can be different. By the end of this module, you should have learnt that continuous and discrete models can produce contrasting results and lead to different

conclusions and therefore that it is important to chose the most biologically appropriate type for a given system.

1.1 Malaria life cycle

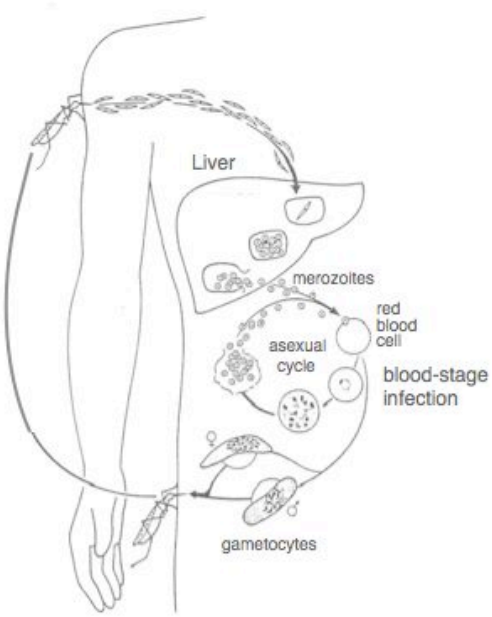

Figure 1: Life cycle of malaria infection

Malaria infections begin with a bite from an infectious mosquito (Figure 1). Injected parasites quickly travel to the liver, where they divide for several days, then release many thousands of free parasites, called merozoites, into the blood. This begins the blood stage of infection, which is the part of infection described by the models in this module. During this time, infections can be monitored by taking blood samples and counting parasites under a microscope. Merozoites enter red blood cells and grow. They can develop in one of two ways, as asexuals, which go on to produce merozoites, or sexually, as gametocytes. Asexuals[a] rupture and release merozoites after a fixed time (the cycle period). Cycles of replication occur throughout the infection. Parasites usually tightly synchronise their development so that merozoite release occurs at regular intervals (Figure 2). This simultaneous release of large numbers of merozoites causes

[a]Note that in this context we use this term to refer to infected blood cells that are going to produce merozoites.

the periodic fevers that are characteristic of malaria infections.

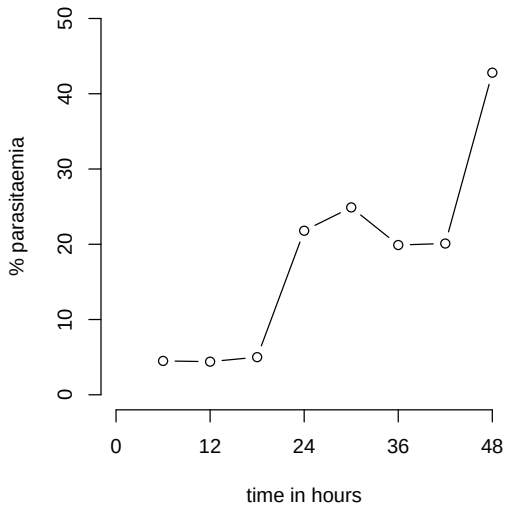

Figure 2: Data from a mouse malaria infection, showing that parasite numbers increase at discrete times. Data from Caillard et al. (1992).

Gametocytes are the sexual form of the parasite that is essential for transmission. Once taken up by mosquitoes, gametocytes transform into gametes and male and female gametes combine to produce zygotes, which leads to the mosquito becoming infectious to new hosts. Gametocytes do not replicate inside the host. They therefore represent a diversion of resources away from parasite growth within the host and towards transmission between hosts. This presents a classical trade-off between growth and reproduction, which has been the motivation for using malaria models to determine the optimal level of investment that parasites should make into gametocyte production.

2 Modelling malaria infections

2.1 A continuous-time model of malaria infection

A simple model for malaria infections is:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = rm(1-g)A - rA \qquad t < 8 \tag{1a}$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = rm(1-g)A - (r+k)A \qquad t \geq 8 \tag{1b}$$

$$\frac{\mathrm{d}G}{\mathrm{d}t} = rmgA - lG\ , \tag{2}$$

where A and G denote the number of asexuals and gametocytes, respectively; r is the rate at which asexuals burst cells to produce new parasites, m is the number of parasites produced by each asexual, g is the fraction of parasites that become gametocytes (gametocyte investment), k is the rate at which asexuals are killed by immunity, and l is the death rate of gametocytes. In this model immunity is represented very simply by an increased death rate of asexuals starting on day 8 of infection. Note that this model assumes that all merozoites instantaneously infect red blood cells. It ignores any effect of red blood cell dynamics, which are included in some malaria models. However, it is arguable whether red blood cell dynamics significantly affect parasite dynamics, except in severe anaemia when the basic models are likely to be inappropriate.

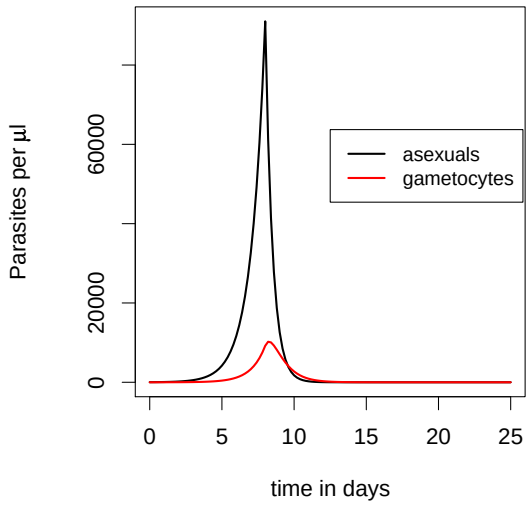

Figure 3: Plot of dynamics of continuous model when gametocyte investment is 0.15. Asexual densities are in black and gametocyte densities are in red.

The dynamics can be calculated for a series of times by numerical integration of the equations using the `R` function `lsoda()`, for which you must supply values of the asexual and gametocyte densities at the first time point. `lsoda` is found in the `R` library `odesolve` (which can be downloaded from the CRAN website under packages). Once the library is installed on your computer it must be loaded (once per `R` session) using the command `library(odesolve)`. `R` hint: The function `lsoda()` overshoots its target and then back interpolates. This means that it can produce negative values, which of course are biologically nonsensical. A simple method for dealing with this is to calculate the results and then set any results less than 1 to 0. This can be achieved easily by using the appropriate comparison to generate an index vector. E.g. `v[v<1]<-0` sets all elements of vector (or array) `v` that are below 1 to 0.

The continuous model defined by Equations 1-2 has been implemented in the file `start_malaria.r` that you can download from the course webpage. The parameter values given are close to those for infections by the malaria species *Plasmodium chabaudi*, which is an

important model system for studying malaria. Use the `R` script to calculate and plot the dynamics of infection for a gametocyte investment (fraction of parasites that become gametocytes) $g = 0.15$. The graph should look like Figure 3. Explore the effect of each parameter by running simulations with different parameter values.

2.2 A discrete model of malaria infection

The equivalent discrete model is:

$$A[t] = m(1-g)A[t-1] \qquad tc \leq 8 \tag{3a}$$

$$A[t] = m(1-g)A[t-1]e^{-kc} \qquad tc > 8 \tag{3b}$$

$$G[t] = mgA[t-1] + G[t-1]e^{-lc} \qquad tc \leq 8 \tag{4a}$$

$$G[t] = mgA[t-1]e^{-kc} + G[t-1]e^{-lc} \qquad tc > 8 \tag{4b}$$

Here $A[t]$ is the number of asexuals and $G[t]$ is the number of gametocytes after t cycle periods; c is the length of a cycle period. This formulation assumes that the onset of immunity coincides with the end of one cycle period and beginning of the next. The survivals of asexuals and gametocytes between time steps have been chosen so that they are the integral of a continuous process occurring at a fixed rate ($x[0]e^{-\lambda t}$ is the integral of $dx/dt = -\lambda x$). Asexuals present at time $t-1$ that survive for one cycle period produce m new parasites that are present at time t. A fraction g of these parasites become gametocytes and some gametocytes remain from previous replication cycles.

Implement this model. Instead of numerical integration, you can calculate parasite numbers at the next time step (cycle) directly by Equations 3-4. Hint: be careful to update G first and A second (why is this important?). For the parameters shared between the continuous and the discrete model (m, g, k, l) use the same values as before. Set a fixed value for the cycle length $c = 1$, and try to find the value of r in the continuous model for which you obtain maximum equivalence (i.e. similar behaviour) between the two models. Try different measures of equivalence: e.g. best fit between asexual or gametocyte numbers, at the end of cycle periods or averaged over the entire simulation. Besides trial and error, can you think of a way to calculate the optimal value(s) of r with formula(e)? What happens if you change one of the fixed parameters? Does it affect the maximum equivalence value of r? Is it the same for all parameters and for all equivalence measures? Conclude: is it possible to create equivalence between the discrete and the continuous model?

3 Exercises

3.1 Basic exercises

Eb1. In the discrete model and in the real biological system, asexuals live for one cycle period. In the continuous model, asexuals die with a given probability (rate) at any time point,

which implies that the lifespan of "individuals" varies, and has a mean of 1/rate of death (equivalent to $1/r$ in the model). Why is then the value for r ensuring maximum equivalence with the discrete model (as obtained above) not equal to 1/cycle period? To help answer this, write a function that also calculates parasite numbers within cycle periods for the discrete model. Asexual and gametocyte numbers should decay exponentially within periods and increase only at integer multiples of the cycle period. (Hint: the modulo operator %% gives the remainder of a division and can be used to determine which time points are multiples of the cycle period; to ensure this works correctly you need to generate the time points as a sequence starting from 0). Compare the dynamics within a cycle period of the continuous-time and discrete model.

Eb2. The parasite dynamics can be summarised by X, asexual multiplication per cycle period and P, relative gametocyte production per cycle period. The equations for X and P are:

$$X[t] = A[t]/A[t-1] \tag{5}$$

$$P[t] = \frac{G[t] - e^{-lc}G[t-1]}{A[t-1]}\ , \tag{6}$$

where t is time in cycle periods. Calculate X and P for the continuous and discrete model for $g = 0.15$. How do X and P change over time? How do they compare for the two models? Does immunity alter X and P by the same factor in the two models?

Write functions to calculate X and P in the two models for values of g from 0 to 1 in steps of 0.01 (note that in order to get smooth curves you will need to rewrite the functions for the models so that parasite densities are not treated as zero when they fall below 1). Plot the results for X before the onset of immunity and P both before and after the onset of immunity. For what value of g do X and P differ most between the two models? (`R` hint: you can apply arithmetic operations to corresponding elements in lists by using the operation on the vectors).

Eb3. One measure of transmission from malaria infections is the sum of gametocyte densities over time. Write a function to calculate the sum of gametocyte densities after each cycle period across the range of g. Plot the results for the continuous and discrete models. How does transmission from the two models compare? What level of gametocyte investment is predicted to maximise transmission for each model? Is this optimal gametocyte investment the same for the two models?

3.2 Advanced/additional exercises

Ea1. The problems with the continuous-time model stem from the considerable variability in the time when asexuals replicate in the model. It has been suggested that this variability could be reduced by splitting asexuals between several compartments, through which they

move in turn. Such a model can be represented by:

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = \frac{1}{nc}\left(m(1-g)A_n - A_1\right) \qquad t < 8 \tag{7a}$$

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = \frac{1}{nc}\left(m(1-g)A_n - A_1\right) - kA_1 \qquad t \geq 8 \tag{7b}$$

$$\frac{\mathrm{d}A_i}{\mathrm{d}t} = \frac{1}{nc}\left(A_{i-1} - A_i\right) \qquad t < 8 \tag{8a}$$

$$\frac{\mathrm{d}A_i}{\mathrm{d}t} = \frac{1}{nc}\left(A_{i-1} - A_i\right) - kA_i \qquad t \geq 8 \tag{8b}$$

$$\frac{\mathrm{d}G}{\mathrm{d}t} = \frac{1}{nc}mgA_n - lG\ , \tag{9}$$

where A_i is the number of asexuals in compartment i and n is the number of asexual compartments. Asexuals move from each compartment at rate $1/nc$ and replicate when they leave the last compartment. Note that in this model the sum of the rates does equal 1/cycle period. Write an `R` function that defines this model for different n. Hint: the most efficient way to do this is with a matrix equation $dx = M\%*\%x$, where x is a vector of variables $(A_1, \ldots, A_n, G)$, M is an $(n+1) \times (n+1)$ matrix of the form:

$$\frac{1}{nc}\begin{pmatrix} -1 & 0 & 0 & \ldots & m(1-g) & 0 \\ 1 & -1 & 0 & \ldots & 0 & 0 \\ 0 & 1 & -1 & \ldots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \ldots & -1 & 0 \\ 0 & 0 & 0 & 0 & mg & -l \end{pmatrix}$$

and $\%*\%$ is the function for standard matrix multiplication in `R`. You will, of course, have to modify the matrix at the onset of immunity. Run the model for different values of n (you can choose how to specify starting values). How do the dynamics compare to the one-compartment continuous model and to the discrete model? What happens as n increases? How does transmission and optimal gametocyte investment compare to the previous models?

Ea2. So far we have used a very simple constant death rate to represent immunity. This could be easily added to the discrete model (despite being a continuous function) as a survival term, because the effect over one cycle could be easily determined by basic integration. Most malaria models instead explicitly incorporate a population of immune cells whose dynamics are tied to the parasite dynamics and it would be interesting to see how this affects the outcomes of the models. However it is not obvious how such functions can be translated into a discrete model. One possibility is to use continuous equations for the dynamics within a cycle period, with discrete parasite replication occurring between periods. Within a period the dynamics are calculated by numerical integration, then parasite replication occurs and the resultant numbers of parasite and immune cells are used as initial values for a second round of integration. This technique is called piecewise integration. Using this approach, try to add more complicated immune functions to the

models and see how this affects their comparative dynamics. A starting possibility is to use the discrete equations 3a and 4a until the onset of immunity (day 8), and then switch to continuous dynamics within cycles:

$$\frac{\mathrm{d}A}{\mathrm{d}t} = -cIA \tag{11}$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = sA - qI \tag{12}$$
$$\frac{\mathrm{d}G}{\mathrm{d}t} = -lG\ , \tag{13}$$

with discrete parasite replication occuring at the end of each cycle (i.e. when $t\%\%c = 0$):

$$A' = m(1-g)A \tag{14}$$
$$G' = G + mgA\ , \tag{15}$$

then substituting $A' \to A$ and $G' \to G$.

Here immune cells, I, increase in proportion to the number of asexuals at a rate sA, die at a fixed rate qI, and kill asexuals at a rate proportional to the product of their densities, cIA (killing occurs on contact, assuming mass-action). Gametocytes have the same dynamics as before, and parasite replication occurs instantaneously at the end of each cycle period. Try starting with s=1.5, c=0.01 and q=0.01, but feel free to explore how the values of these parameters affect the dynamics.

Other immune representations that you could try are: 1) immune cells increase at a rate proportional to the product of the densities of immune cells and asexuals (sAI), i.e. the production of new cells depends on the current number of cells; 2) immune cells increase at rate that is a saturating function of the number of asexuals ($\rho AI/(A+\phi)$); 3) immune cells are regulated by negative feedback (die at a rate proportional to their density squared, $-bI^2$). You can freely combine 3) with all three possibilities for the input of immune cells, and you are also encouraged to try further variations to the scheme.

Ea3. We have considered fixed investment into gametocytes, but in vitro studies show that malaria parasites can alter their level of gametocyte investment in response to a range of factors. Try incorporating a changing level of gametocyte investment into the models. You might start by assuming a step function, with 0 investment up to time t_g and then fixed investment afterwards. How do the courses of infection in the continuous-time and discrete model compare with this variable investment? What is the effect of changing t_g, the point at which gametocyte investment begins? Find the level of investment, g, that maximises transmission for a given t_g. How does this compare for the different models? Can you see what value of t_g maximises transmission? Does such a pattern of investment make biological sense?

In *P. chabaudi* infections, gametocyte investment seems to be low during the increasing phase of infection then rapidly increase to a peak of about 10% around day 10 of infection before decreasing again. Write g as a function of time so that it follows this pattern (for example it is 0 below a certain t_g, increases linearly at rate r_g to time $t_g + \tau$ and then

decreases linearly at the same rate). (Hint: you can write a function $g(t, t_g, r_g)$ to calculate g at any time point, and call this function from within the model). How does the course of infection compare for the different models under this pattern of investment? What is the effect on transmission compared to constant gametocyte investment? You could also look at what happens if gametocyte investment increases in proportion to the asexual density or to the density of immune cells.

Ea4. In the comparison of the discrete and continuous-time models, you had to find parameter values to maximize equivalence between the two models. This can be done numerically by linear optimization. Look up the `R` function `nlm()` and try to find the optimal parameters by this method[b].

[b] You may refer to the reader of the module "Within-host HIV dynamics: estimation of parameters" for further help.