

Models for the in-host dynamics of malaria revisited: errors in some basic models lead to large over-estimates of growth rates

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SUMMARY

The mathematical model of the in-host dynamics for malaria parasites of Anderson, R. M., May, R. M. & Gupta, S. (1989), *Parasitology* **99** (Suppl.) S59–S79, and subsequently used by other authors, contains an error. This leads to very substantial over-estimates in parasite growth rates. A corrected form of the model is presented in this paper.

Key words: mathematical models, *Plasmodium*, malaria, deterministic models.

THE MODEL

As our knowledge of the biology of malaria parasites has increased, there has been parallel interest in trying to understand the quantitative processes which regulate parasite growth in its host. This has resulted in several papers over the past decade modelling the interaction of parasites and their hosts. These include 4 studies of the effect of red cell destruction and specific immunity on the regulation of parasite levels (Anderson, May & Gupta, 1989; Hellriegel, 1992; Gravenor, McLean & Kwiatkowski, 1995; Hetzel & Anderson, 1996). All 4 papers are based on the parasite growth model proposed by Anderson *et al.* (1989). In its simplest state, in the absence of immunity, the model uses 3 linked differential equations to describe changing levels of uninfected and infected red blood cells and free merozoites. These equations are

$$dx/dt = A - \mu x - \beta xs \quad (1)$$

$$dy/dt = \beta xs - \alpha y \quad (2)$$

$$ds/dt = \alpha y - \delta s - \beta xs, \quad (3)$$

where x , y and s are the concentrations of uninfected cells, infected cells and free merozoites, respectively (cells/ml); A the rate at which new red cells are formed (cells/ml/day); μ , α and δ are the death rates of uninfected red cells, infected red cells and merozoites, respectively (/day); β is the rate constant describing the rate at which merozoites invade red cells (/cell/ml/day) and r the number of merozoites released/rupturing schizont.

In this model, it is assumed that all red cell destruction in addition to the normal removal of old red cells, is due only to the rupture of infected cells.

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The life of an infected red cell is assumed to follow an exponential decay, with an average span equal to the parasite growth cycle (i.e. 48 h for *Plasmodium falciparum*) so $1/\alpha$ = parasite cycle time.

This assumption of an exponential decay in the infected red cell, and of smooth exponential growth in the increase in the free merozoites and infected red cells contrasts with the essentially discontinuous process which occurs in nature. Infected red cells have a fixed life-time and for each subset of the parasite population, the number of infected cells increases essentially instantaneously every 48 h for *P. falciparum*. This difference between the model and the actual process leads to the anomalous growth rates detailed below.

Although it seems intuitively obvious that the rate at which merozoites are being released (the αy term in Equation 3) should be the number of merozoites times the rupture rate of schizonts, further reflection will indicate that there is a significant problem in this term. To readily appreciate this, let us consider an even simpler model than the one proposed above. Under initial conditions, the number of red cells will be nearly constant, and experimental work shows that under these conditions nearly all merozoites invade (Gravenor *et al.* 1995; Cheng *et al.* 1997) and there is an exponential increase in parasitaemia (i.e. $y_t = y_0 e^{kt}$). Under these conditions, the temptation is to say that the growth rate (k) is αr or 8/day for *P. falciparum* (cycle time of 2 days and 16 merozoites/schizont). Even for a discontinuous model, this is clearly not correct. An increase of 8 in 1 day would give an increase of $8 \times 8 = 64$ over 2 days. If exponential models are being considered as above, then the growth constant should be $\alpha \ln(r)$ or 1.3863/day not the 8/day calculated from αr . The calculated growth over 2 days using values of 1.3863 and 8 is 16 and 8.89 million, respectively, or

approximately a 0.55 million-fold error when the latter is used.

A similar but more complicated problem arises with the model defined by Equations 1–3. An idea of the magnitude of the error can be obtained by numerically solving these equations under boundary conditions. Specifically, where $x \gg y$, $\beta x \gg \delta$ and β sufficiently large so that merozoites released will rapidly invade, the concentration of infected cells should grow exponentially, reaching r times the initial concentration over a period of $1/\alpha$. Again, these are conditions which could approximate the early stages of an infection. However, with $r = 16$ and $\alpha = 0.5$, appropriate for *P. falciparum*, then the model predicts that the concentration of infected cells increases by approximately 2.8 million-fold over 2 days, not the expected 16-fold increase. Clearly, there is an error in Equations 1–3 which leads to very large errors in the parasite growth rates.

A more appropriate form of the equations can be derived by again considering the boundary conditions approximating initial growth. Rewriting Equation 3 to substitute an unknown growth constant, k , for r gives

$$ds/dt = \alpha ky - \delta s - \beta sk. \quad (3a)$$

Combining this with Equation 2, again assuming $x \gg y$ and $\beta x \gg \delta$, gives

$$dy/dt = (k-1)\alpha y - ds/dt. \quad (4)$$

Integration of this equation gives

$$y_t = y_o e^{(k-1)\alpha t} + s_o - s_t. \quad (5)$$

If we examine the situation where the free concentration of merozoites is small compared to the number of infected cells (β sufficiently large), $s_o - s_t$ will be negligible compared to y_t . After 1 parasite growth cycle ($t = 1/\alpha$), $y_t = y_o = ry_o$. I.e. under conditions where all merozoites can invade, the increase in the concentration of infected cells over 1 growth cycle is equal to the number of merozoites released/schizont. Substituting these values into Equation 5 gives $r = e^{(k-1)}$. Hence, $k = \ln(r) + 1$ and Equation 3 becomes

$$ds/dt = \alpha(\ln(r) + 1)y - \delta s - \beta xs. \quad (3b)$$

Numerical simulation of parasite growth using Equations 1, 2 and 3b gives the expected values (i.e. growth over a period of $1/\alpha$ is $\leq r$).

Left uncorrected, the use of Equation 3 in work based on the original model may lead to substantial errors in the dynamics of the processes these models describe. Substitution of Equation 3b in order to get the correct growth rates in these models may still have a significant impact on the results and conclusion of papers using this model. Until re-examined, the conclusions in such papers need to be treated with caution.

Although it offers a mathematical solution to the problem of incorrect growth rates, the $\ln(r) + 1$ term

in Equation 3b has no biological counterpart in a qualitative model of parasite growth. For example, it is not the number of parasites released/schizont, only the theoretical rate constant required to get correct growth kinetics. While there may be situations in modelling where such solutions offer computational convenience, the penalty is the loss of direct biological relevance.

In the accompanying note, Gravenor & Lloyd (1998) offer an elegant solution to this problem. By splitting the parasite population into enough small compartments one can accurately model discontinuous parasite growth using a series of differential equations.

An alternative strategy is not to describe the process as a series of differential equations relying on rate constants, but to directly describe such processes as a series of recursion equations. These describe the population at discrete times in terms of the multiplication factors which occur between different stages and the probability of surviving from one time point to the next and the size of the population at a previous time. This technique leads to computationally efficient, deterministic and stochastic simulations of population dynamics. It can also lead to simple analytical solutions for equilibrium situations. This approach has been used for examining the transmission dynamics of malaria in immune host populations (Saul, 1996) and for calculating vectorial capacity of mosquito populations (Saul, Graves & Kay, 1990).

In the latter case, calculation of vectorial capacity assuming that mosquitoes feed on a cyclic basis, rather than the biologically inappropriate assumption that mosquitoes feed at a constant rate as used by Macdonald (1957), actually leads to a simpler equation for vectorial capacity and also gives a higher estimate of vectorial capacity than the equation derived by Garrett-Jones (1974) based on Macdonald's model.

This re-evaluation of the Anderson model was prompted by the author's reviews of unpublished work in which the original equations were adopted without detecting the problem. The use of this model in at least 4 published, peer-reviewed papers by highly competent researchers shows how much care is needed in this type of modelling. Deterministic modelling based on sets of linked differential equations is a powerful tool for understanding the biological processes as demonstrated by Anderson (1982). However, the simple conversion of essentially discontinuous, probability-driven events to continuous rates sometimes leads to equations which do not necessarily reflect the underlying process. *Cavaet emptor!*

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