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Discrete-Event Simulation Models of *Plasmodium falciparum* Malaria

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Abstract

We develop discrete-event simulation models using a single “timeline” variable to represent the *Plasmodium falciparum* lifecycle in individual hosts and vectors within interacting host and vector populations. Where they are comparable our conclusions regarding the relative importance of vector mortality and the durations of host immunity and parasite development are congruent with those of classic differential-equation models of malaria, epidemiology. However, our results also imply that in regions with intense perennial transmission, the influence of mosquito mortality on malaria prevalence in humans may be rivaled by that of the duration of host infectivity.

Keywords

Epidemiology; infectious disease; malaria; population biology; prevalence; transmission; vector

1. Introduction

The proximate cause of malaria in a human is the presence of *Plasmodium* parasites, which may appear after an infective bite by an *Anopheles* mosquito. The probability that parasites are transmitted from a mosquito to a human in any given interaction necessarily depends on the probability that parasites were transmitted from a human to that mosquito in some previous human-mosquito interaction, which in turn depends on earlier links in the chain of transmission, and thus on densities of infectious and susceptible humans and mosquitoes, on innate and acquired host immunity, strains and species of parasite and vector, sea and environmental factors, and so forth. That is, human malaria is characterized by hierarchies of dynamic processes, occurring on diverse time scales within and between heterogeneous populations.

Here we develop models of malaria epidemiology by depicting the biology of parasite development in individual humans and mosquitoes, and the corresponding interactions between humans and mosquitoes. We distinguish each host and vector unit by its state within a characteristic repertoire of states, we define a set of probabilistic interactions that may effect state transitions in interacting units, i.e., parasite transmission, and we simulate multiple interactions among multiple entities. This scheme requires no special computing resources, but it provides realistic sampling processes by representing large, finite populations of individuals, and allows relatively realistic degrees of complexity in population-level dynamics to emerge from simple, transparent representations of individual-level malaria infections.

Such discrete-event models complement the differential-equation “compartment” models that have made such enormous contributions to our understanding of malaria transmission [1,2,3, 4]. The most influential of these models, Macdonald’s refinement [5,6] of the Ross archetype [7], focused a global malaria-eradication campaign on reducing adult mosquito survivorship [8]. Though this campaign succeeded brilliantly in many temperate and subtropical regions, it

often failed elsewhere, particularly in regions with intense perennial transmission. Macdonald published posthumously [6] that “a powerful tool for the design of eradication and control programs, and for the analysis of difficulties in them, could be produced by the extension of dynamic studies using computer techniques.” Our objectives here are to introduce a basic discrete-event simulation model, compare its results in conditions of intense perennial transmission to those of differential-equation models, and investigate circumstances in which the utility of such abstractions as average individuals and infinite populations might be challenged.

2. Design

Plasmodium infection of a human begins with a small inoculum of sporozoites from the salivary glands of a blood-feeding female *Anopheles* mosquito. The sporozoites penetrate liver cells, and in hepatic schizogony transform and multiply to produce thousands of free merozoites. Each of these merozoites invades a red blood cell, completes another round of multiplication (in erythrocytic schizogony), then bursts the cell, releasing 8 to 32 more merozoites to invade more red blood cells. This asexual blood cycle may be repeated many times, in the course of which some invading merozoites may instead develop into the sexual, non-replicating transmissible stages known as gametocytes. If viable gametocytes of each sex are taken up by a feeding *Anopheles*, fertilization may produce the zygotes from which infective sporozoites arise within the mosquito, in sporogony.

Our discrete-event models identify the potential states of an individual host or vector with the sequential phases of a *P. falciparum* malaria infection in each such that a single variable that tracks an individual’s progress along an infection timeline also sketches the life cycle of the parasite. Because the fundamental question for two-party interactions is whether one participant is infectious and the other susceptible with respect to a parasite, the state of each host and vector thereby represents the presence or absence of a parasite life cycle stage appropriate for infectivity or susceptibility. Unit interactions simply mimic host-vector contact — i.e., the mosquito taking a blood meal—and each corresponding potential state transition the potential transmission of a parasite between host and vector. Actual transmission of a parasite in any given host-vector interaction may involve chance as well as additional biological factors; our representations here include a host immune component and a vector mortality function. Figure 1 is a schematic of the basic model.

Infection timelines express the dynamic individual-level states that lead to the compartments of traditional population-level models; their single-valued state representations allow compact, efficient data structures that permit representations of very large interacting populations. Simple binning can translate the individual state descriptions into familiar population-level classes such as “infected” and “infectious,” and allows ready calculation of prevalence and other epidemiological measures.

The full infection timeline in our malaria models corresponds to the “incubation interval” in Macdonald’s model [5], i.e., “the complete period from the occurrence of infective gametocytes in one case to the development of infective gametocytes in the secondary cases derived from it,” comprising “the period of extrinsic development of the parasite in the mosquito; the pre-patent period, or incubation period as it is normally known, in man; and any interval between the patency of asexual parasites and the development of fully infective gametocytes.” Our malaria models represent this full interval, and the parasite life cycle, as a circuit from position “0” on the host timeline through position “0” on the vector timeline and back to the host “0,” by way of two blood meals (see Figure 1).

Three of the five temporal parameters of our basic model correspond directly to those in Macdonald's:

1. Vector Delay (DV) is the length of the interval between infection (gametocyte ingestion) and the onset of infectivity (sporozoite migration) in a vector, i.e., Macdonald's "period of extrinsic development," above;
2. Host Delay (DH) is the length of the interval between infection (sporozoite inoculation) and the onset of infectivity (gametocyte maturation) in a host, i.e., Macdonald's "pre-patent period" and subsequent "interval," above;
3. Vector Survivorship (VS) is the daily probability of a mosquito's survival, i.e., synonymous with Macdonald's expression [5] for the "probability of survival through one day."

The two remaining temporal parameters do not correspond directly to any parameters in Macdonald's model:

4. Host Window (WN) is the duration of a host's infectivity to vectors, from the first to the final presence of infective gametocytes. This factor was addressed by Macdonald at most indirectly, in terms of recovery rates and infective proportions; WN is closely analogous to the "loss rate" α_1 in the Dietz et al. extension of Macdonald's model [9].
5. Host Immunity (IM) defines a host's susceptibility to re-infection through the daily decay of a blocking immunity. This was addressed at most indirectly in Macdonald's model; IM closely resembles the "loss rate" γ in the Aron and May extension [10].

3. Implementation

Populations of hosts and vectors are represented by arrays that contain the state of each constituent host or vector with respect to its stage of infection, with these states represented on the corresponding infection timeline by the variables h and v , respectively. Thus a value $0 < h < DH$ indicates that the host is infected but not yet infectious, $-WN < h \leq 0$ that the host is (infected and) infectious, and any other value of h that the host is not currently infected. For $h < -WN$, the host's immunity to re-infection is declining, as explained below. Similarly, $-DV < v < 0$ indicates a vector that is infected but not infectious, $v \leq -DV$ a vector that is (infected and) infectious, and any other value of v a vector that is not currently infected. The basic model does not encompass the possibility of mosquito immunity. At each successive day of a simulation run, all h and v values are decremented by 1, advancing them through the appropriate delay, window or decay periods.

Parasite transmission is represented as a single state-altering interaction between an individual host and an individual vector. At each time step the model selects a mosquito at random and a human at random for an interaction. An initial parameter, V_B , the total number of daily host-vector interactions, sets the number of times this random pair selection is repeated each day. Only two pairs of host-vector states permit interactions that may directly induce state transitions:

1. If the mosquito is infectious, then with a probability based on the immune state of the human, that human changes state and becomes infected, setting h to DH ;
2. If the human is infectious, then with some probability, taken to be 1 in the basic model, that mosquito changes state and becomes infected, setting v to 0.

In the other possible state combinations there are no transitions: superinfection of a human already infected with a given strain does not reset h , and superinfection of a mosquito already infected with a given strain does not reset v . Hence, in humans, superinfections with identical

strains affect neither immune responses nor gametocyte production, and in mosquitoes they simply accumulate, neither accelerating nor delaying the onset of infectiousness. This follows Macdonald's conventions, but an advantage of our modeling approach is that virtually any superinfection scheme can be implemented [11]. Host and vector populations are sampled with replacement, so multiple feedings by a single mosquito as well as multiple bites on a single human may occur within a single day; both phenomena occur in nature [12,13,14].

Any host not previously infected is considered wholly susceptible. The decay of immunity in a previously-infected host is represented by a changing probability of re-infection of that host when bitten by an infectious mosquito. During an infection, i.e., for h greater than $-WN$, this probability is considered 0, consistent with the absence of state change noted above; after an infection is cleared, i.e., when the host state reaches $-WN$, this probability exponentially, asymptotically approaches 1. For h less than $-WN$, we model the probability of infection as $1 - e^{IM(h+WN)}$; note that with h always more negative than $-WN$, the exponent is always negative. The immune half-life, $(\ln 2)/IM$, is the number of days required for this probability to reach 0.5. When an infectious mosquito is paired with any human, that human's probability of acquiring an infection is calculated, as above, and a uniform random number between 0 and 1 is compared with that probability. If the random number is less than the calculated probability, then the human becomes infected, setting the host state h to DH ; otherwise the host state remains unchanged.

At each time step for each vector, a uniform random number between 0 and 1 is compared with the probability of death, $(1-VS)$. If the random number is less than that probability, then the mosquito is removed from the population and replaced with a new mosquito, maintaining the vector population at constant size. The vector half-life, $(\ln 2)/(1-VS)$, is the number of days over which mortality reduces any given cohort of new mosquitoes by half.

The initial parameters N_H and N_V fix the host and vector population sizes, respectively. Initially no mosquitoes are infected, and an initial fraction of the host population is infected by setting each h to a random value between DH and 0. The initial state of each uninfected host is set to a large negative value, implying no initial immunity. We coded the models in C++ and ran them on an IBM-compatible PC under Windows 95.

4. Parameter Values and Initial Conditions

Figure 2 shows the typical pattern of damped oscillations in prevalence for the wide ranges of parameter values and initial conditions considered here. The results presented in this paper are from data collected every tenth day during the last 100 days of 365-day runs. Because varying the delay parameters in this context leads to phase differences with little effect on such prevalence data, we generally fixed $DH = 20$ and $DV = 10$, then examined the relative influence of the remaining temporal parameters on prevalence by systematically varying these parameter values within a large plausible subspace. We most closely examined parameter values over a range from 50% to 150% of a plausible mean value for each [1–10], such that the values of the host window (WN) ranged from 10 to 30 days, vector half-life from 5 to 15 days (i.e., VS from 0.954 to 0.861), and host immunity half-life from 50 to 150 days (i.e., IM from 0.014 to 0.005). For each $\langle VS, WN, IM \rangle$ point, we performed 100 replicate runs; standard deviations in prevalence about each of the mean $\langle VS, WN, IM \rangle$ points used in our analyses were <0.01 . We used Mathematica 2.0 (Wolfram Research, Champaign IL) to obtain best-fit planes to surfaces of 231 prevalence points for each pair-wise combination of parameters at five levels of the third parameter.

We generally set $N_V = 5000$ and $V_B = 2500$, in accord with the usual idealized two-day gonotrophic cycle for *Anopheles* (i.e., $N_V/V_B = 5000/2500$), and set $N_H = 500$ (i.e., $N_V/N_H = 10$), with 25% of the hosts and none of the vectors initially infected. Varying the proportion

(s) initially infected had little effect on prevalence data in this context, though as one would expect, the further the initially-infected proportion(s) from the bounds within which the later prevalences stabilize, the greater the range(s) of earlier oscillations. As discussed below, the results are also valid for a range of vector population sizes and interaction frequencies.

In the context of perennial single-strain transmission, the parameter ranges considered here lead to human prevalences of 50 % to 85%, a typical range in several tropical regions [15, 16]. Recent results with PCR-based detection methods [17,18] indicate that these high prevalences are even more common than had been assumed based on surveys using conventional microscopy. Our results show that, as expected under such conditions, prevalence in humans increases as mosquito survivorship increases (as in Macdonald's model), and prevalence in vectors increases as either the period of host infectivity or the rate of host immune decay increases.

5. Results—Vector Population Size

It has long been recognized that the differing degrees of anthropophily among *Anopheles* species convolve with relationships between mosquito lifespans, parasite development cycles and other factors such that at any given moment a relatively small fraction of a mosquito population actually contributes to the transmission of malaria in a human population [19,20]. Our models not only manifest similar behavior, but do so in a manner that allows quantification and scaling of the vector population required to maintain several key epidemiologic characteristics of infection in a given human population. All else being equal, maintaining a constant prevalence of infection in humans and a constant number of infectious mosquito bites per human per day requires a total number of mosquito bites per day, V_B , that scales less than linearly with the total mosquito population size, N_V . That is, some of the effects of enormous populations of vectors may be modeled without fully representing each constituent, such that it may be possible to consider “effective” vector population sizes in epidemiological as well as population-genetic terms.

Figure 3 plots prevalence isoclines for two extremes of mosquito survivorship, showing the joint values of V_B and N_V equivalent to a population of 5,000 mosquitoes feeding only on the given human population, with an idealized blood meal cycle (N_V/V_B) of two days. That is, in terms of the prevalence of infection in humans and the number of infectious mosquito bites per human per day in this context, 5,000 is the “effective” mosquito population size of each of these $\langle N_V, V_B \rangle$ combinations. The six $\langle N_V, V_B \rangle$ points shown for each parameter set closely follow an exponential (power-law) function, $V_B = aN_V^b$. Equivalently, for a given human population size and number of daily mosquito bites, the scaling formula $N_V = (V_B/a)^{1/b}$ approximates all population sizes of mosquitoes synonymous in key epidemiological terms with a given population size of mosquitoes biting only humans; other population sizes imply zoophylaxis [21] or different gonotrophic cycles. We estimated values for the constants a and b using Systat 4.0 (Systat Inc., Evanston, IL), and found that maintaining constant “effective” vector population sizes requires that the total number of daily host-vector interactions increase by less than the square root of the total vector population size.

6. Results—Prevalence in Humans

Figure 4 shows the overall prevalence of infection in humans as a function of mosquito survivorship, the duration of human infectivity (host window) and the duration of human immunity to reinfection. Each response surface shows 231 prevalence points, each of which is an average of 100 simulation runs, resulting in a standard deviation of 0.01 or less. We have shown the best-fit planes not to suggest the existence of any underlying linear process, but simply to allow comparisons among the average effects of each parameter. The average effects

on the overall prevalence of infection in humans of variations in vector mortality and variations in the duration of host infectivity are of similar magnitude, while the duration of host immunity is less influential.

7. Comparisons with Differential-Equation Models

Figure 5 illustrates the dynamics of classic differential-equation and differential-delay-equation “compartment” models analogous to the discrete-event model; the models we have constructed are described in detail in the Appendix, as is Macdonald’s model. Parameter values for Figure 5 were calculated such that the prevalence curves are as closely comparable as possible to those shown in Figure 2 (see Appendix).

The obvious differences are in the three rates of decay of oscillation. Given the parameter values and initial conditions of Figure 5, the classic differential-equation and differential-delay-equation models settle at equilibria within four and 10 to 12 months, respectively, with an overall human prevalence of 75%. Continuing out 10 years with the parameter values used in Figure 2, an average over 25 runs shows overall human prevalence still oscillating slightly (within 1%) around an overall human prevalence of 82%.

In the discrete-event model, immunity is considered a continuous process of change in the probability that a previously exposed individual will block an infection when bitten by an infectious mosquito, i.e., the parameter IM represents the rate of decay of immune resistance to reinfection in an individual human. This operational view thereby incorporates the existence of partial immunity to reinfection, an aspect of epidemiology difficult to represent in terms of the discrete step transitions and flow rates of aggregate population-level models [2,3,4,9,10]. That is, if adjacent discrete compartments are “totally immune” and “totally susceptible,” and some quantity or proportion is lost from one to the other over each interval of time, conventional differential-equation models represent this loss as a rate of population flow between the two distinct states rather than as a process of decay within each individual in a population.

These two views of immunity cannot be reconciled, but the models that embody them can be compared by finding particular parameter values that relate an average duration of immunity in an aggregate in the simulation model in its stationary state, to an equilibrium flow rate in the differential-equation models. To do so requires the resolution of the full “age” distribution of intervals since infection over all “immune” individuals in the simulation, relative to each individual’s probability of becoming infected (see Appendix). The dynamics of the three systems away from such fixed points of comparison may differ dramatically.

8. Discussion

There are many useful approaches to modeling human malaria, and many differences among models constructed for different purposes, but some forms that are analogous are not equivalent: analogous classic differential-equation and differential-delay-equation models have different properties, and each has properties very different from those of the discrete-event models developed here, including different dynamics leading to the same equilibrium.

Among the factors in malaria epidemiology most difficult to represent in compartment models is the immunity of individuals. In the discrete-event simulation models, complex population-level dynamics emerge from a simple representation of individual-level malaria infections. Accordingly, we can readily represent probabilities that a human becomes infected if bitten by an infectious mosquito, even if those probabilities depend on that host’s prior infection history and waning immunity to reinfection. We can represent the decay of immunity within an individual to one “strain,” even if that decay depends on the interval since that individual cleared another “strain,” and so forth. The decay of immunity within an individual may have

a very complex relation to the decay of the immune component of a population, and in fact the time scales involved at the individual and the population levels may differ by orders of magnitude.

Any individual character that changes based on calculations with respect to that individual can be represented by aggregates in *a priori* population-level models only if the aggregates either incorporate individual histories or make broad assumptions about their distribution. Therefore, if individuals in a population differ with respect to some character, and the behavior of the population critically depends upon these differences, models such as those developed here may provide a better approach. Discrete-event simulation models are thus worthy partners of differential-equation models of malaria epidemiology in the many situations in which their representations can more closely approximate the underlying biological processes and mechanisms.

Discrete-event models are often criticized because they provide no closed-form analytic solutions. Obviously we believe that in the appropriate context some advantages of discrete-event models are compensatory. One such advantage is the intrinsic occurrence of heterogeneous mixing [22,23]: interactions may occur between rare variants rather than only between aggregates or averages within a given distribution. Recent mathematical and empirical studies that examine variously-defined subdivisions of parasite, host and vector populations [24–32] suggest that the diversity and abundance of phenotypes and genotypes involved in malaria may have profound implications for vaccine, drug and other intervention strategies.

The models presented here have many other shortcomings. We consistently treat human populations as static, and we largely ignore mosquito population dynamics. There is not a certainty but some probability that a mosquito biting an infectious human becomes infected, and this probability should be represented by something other than an ad hoc tuning parameter. Our operational view of immunity incorporates the existence of partial immunities to reinfection, but it fails to encompass the possibility that immune responses may act to limit parasite densities upon reinfection. So little is known about human malaria immunology that the shortest immune half-life we consider may be too long, or the longest too short. We have not yet examined the many possibilities of immunologically cross-reactive or potentially recombinant strains of parasite.

Nonetheless, our results are strikingly congruent with those of the differential-equation models developed and tested during the past century, and the few seemingly anomalous results at this level of analysis concern factors our predecessors were unable to address in similar terms. Certainly the unsuspected importance of the duration of host infectivity merits some attention with respect to planned vaccine-based interventions, at least in regions with intense perennial transmission. Our preliminary results with a seasonal-transmission extension of the model suggest that vector mortality is in fact the dominant influence on prevalence in humans in short seasons, but that the influence of host window grows to near-parity with longer, ultimately perennial transmission seasons. The influence of host immunity appears to rise more rapidly with season length than that of either vector mortality or host window, but still falls short of parity in the perennial-transmission case.

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Appendix. Comparisons with Differential-Equation Models

We developed two related forms of a differential-equation “compartment” model parallel to the discrete-event simulation model. The first, more traditional form is given by the equations:

$$\begin{aligned}
 dS/dt &= qR - hFS, \\
 dM/dt &= hFS - kM, \\
 dG/dt &= kM - pG, \\
 dR/dt &= pG - qR, \\
 dU/dt &= b - hGU - dU, \\
 dL/dt &= hGU - cL - dL, \text{ and} \\
 dF/dt &= cL - dF,
 \end{aligned}$$

where the dynamic variables S, M, G and R denote the proportions of susceptible, infected, infectious and immune humans, and U, L and F the proportions of susceptible, infected and infectious vectors, respectively. The parameters h, b and d represent daily rates of vector biting, natality and mortality, respectively; b/d gives the ratio of vectors to hosts (N_V/N_H). Flow rates between human compartments are represented by the parameters q, from immune to susceptible, k, from infected to infectious, and p, from infectious to immune; c represents the

flow rate between the infected and infectious mosquito compartments. The equilibrium values for this model are:

$$\begin{aligned} S^* &= dp(c+d)(d+hG^*)/(bch^2), \\ M^* &= pG^*/k, \\ G^* &= kq[bch^2 - d^2(c+d)^2] / \{h[bch(kp+kq+pq)+dkpq(c+d)^2]\}, \\ R^* &= pG^*/q, \\ U^* &= b/(d+hG^*), \\ L^* &= bhG^*/[(c+d)(d+hG^*)], \text{ and} \\ F^* &= bchG^*/[d(c+d)(d+hG^*)]. \end{aligned}$$

The central problem in relating the population flow rates between compartments in the differential-equation models to the individual half-lives in each state in discrete-event models is that population transition rates in the latter depend upon infection histories, i.e., the “age” distribution of individual times since infection. It is possible to compare the models by equating average residence times in the “immune” state at an equilibrium, but their dynamics remain completely different.

Consider a “cohort” in the discrete-event model, i.e., all hosts infected on a single day, and let $M = M(t)$ represent the fraction of that cohort still immune at time t , such that $-dM/dt$ is the fraction losing immunity in dt , or, equivalently, is the probability density of the transition from the immune to the successor state. Then the average length of immunity is $\int_0^\infty t(-dM/dt)dt$, with the time integral taken from 0 to infinity.

The probability of an individual being infected on day t is $(1-e^{-qt})$, where $q = IM$, hence the number of cohort members being infected and thus moving from the immune to the successor state on day t is $M(1-e^{-qt})$. That is, M decays as $dM/dt = -M(1-e^{-qt})$, where q is the rate of decay of the probability of becoming infected once in the immune state (i.e., once the infection has been cleared). This cannot be substituted directly into the formula for the average length of immunity because this derivative includes the function $M(t)$ itself. Therefore it is necessary to solve for $M(t)$ first. By separation of variables:

$$\begin{aligned} dM/M &= -(1 - e^{-qt})dt, \text{ and} \\ \ln(M) &= -(t + e^{-qt})/q \end{aligned}$$

By substituting the initial condition $M(0) = 1$, $M = [e^{1/q}]/\exp[t + (e^{-qt}/q)]$ is the fraction of the cohort still immune, where $\exp(x)$ is synonymous with e^x , and hence:

$$\int_0^\infty t(-dM/dt)dt = \int_0^\infty t(1 - e^{-qt})e^{1/q} / \exp[t + (e^{-qt}/q)] dt$$

is the average time in the immune state.

Now let q_s represent this $q (= IM)$, the rate of decay of immunity to reinfection in an individual, in the discrete-event model, and let q_c represent the flow rate q in the differential-equation model. Because in differential-equation models the immunity of any immune entity decays exponentially (i.e., if $G = 0$, $dR/dt = -q_c R$), the average time in the immune state in the discrete-event model, q_s , calculated by the integral above, is $(\ln 2)/q_c$.

For example, to generate Figure 5 we evaluated the integral with $q_s = IM = 0.01$ (an individual host immunity half-life of 70 days in the discrete-event model), which yields an average time in the immune state of 12.55 days. Thus $q_c = \ln(2)/12.55 = 0.055$. To further illustrate the differences between an individual-level and a population-level time scale, note that a population average residence time of 70 days in the differential-equation models (i.e., $q_c = 0.01$) corresponds to a discrete-event-model immune half-life of 2,166 days.

Of course q_s and q_c can be equated in this manner only when the distribution of the individuals in the immune state over the times since they entered that state is uniform, which will usually be the case near an equilibrium (i.e., with hosts entering and leaving each state at a constant daily rate). As this is not likely to be true elsewhere, even with identical equilibria one would expect different system dynamics away from that point.

In this classic differential-equation model, translating the delays, DV and DH, and the host window of infectivity, WN, poses the problem of approximating a deterministic step function by a flow rate in an exponential decay process. As above, assuming the system at equilibrium, we set $p = k = (\ln 2)/WN = (\ln 2)/DH$, and $c = (\ln 2)/DV$. With respect to vector mortality, because we assume that each mosquito has the same probability of dying each day we do not need to know the distribution, and we take this directly as the aggregate, exponential decay, i.e., $d = (1 - VS)$.

The second, differential-delay form replaces each of the parameters k , p and c with an explicit time lag corresponding to the host delay, the host window and the vector delay parameters in our simulation model, respectively, such that:

$$\begin{aligned} dS/dt &= qR - hFS, \\ dM/dt &= hFS - [hFS]_{t-k} \\ dG/dt &= [hFS]_{t-k} - [hFS]_{t-(k+p)} \\ dR/dt &= [hFS]_{t-(k+p)} - qR, \\ dU/dt &= b - hGU - dU, \\ dL/dt &= hGU - [1 - e^{-cd}][hGU]_{t-c} - dL, \text{ and} \\ dF/dt &= [1 - e^{-cd}][hGU]_{t-c} - dF, \end{aligned}$$

where the dynamic variables and other parameters are as above.

Here the system is underdetermined, i.e., no equilibrium can be calculated, and its dynamics depend on the initial conditions.

We obtained numerical approximations to solutions (Figure 5) by translating each of the models into a BASIC program, typically setting 25% of the hosts and none of the vectors initially infected, as in the discrete-event simulation model.

Macdonald's model [2–6] can be expressed by the equations:

$$\begin{aligned} dX/dt &= abmY - X(abmY + r), \text{ and} \\ dY/dt &= aX - Y(aX - \ln p), \end{aligned}$$

where the dynamic variable X represents, according to Macdonald, “the proportion of people affected,” the dynamic variable Y its (implicit) counterpart in the vector population, and the parameters as follows, also quoted from Macdonald:

m	the anopheline density in relation to man,
a	the average number of men bitten by one mosquito in one day,
b	the proportion of those anophelines with sporozoites in their glands which are actually infective,
p	the probability of a mosquito surviving through one whole day, and
r	the proportion of affected people, who have received one infective inoculum only, who revert to the unaffected state in one day.

The crucial aspects of Macdonald's model are summarized in his formula for Z_0 , the “basic reproduction rate” of malaria:

$$Z_0 = -(ma^2b)p^n / [r(\ln p)] = (b/r)C,$$

where the parameter n represents “the time taken for completion of the extrinsic cycle,” and $C = -(ma^2b)p^n / (\ln p)$ summarizes the “vectorial capacity” of malaria [5,50–52].

Macdonald derived Z_0 as an estimate of the average number of secondary cases arising in a very large population of completely susceptible humans following the introduction of a single primary case, and $Z_0 = 1$ as the transmission threshold, i.e., the value above which cases propagate and below which they recede. This formula for Z_0 holds that the influence of vector survivorship, p , is greater than that of a or n , which are in turn greater than that of b , m , or r , and hence that vector survivorship is the single most important element in the basic reproduction rate of malaria. Macdonald's "affected" proportions do not distinguish between infected and infectious states, but his conclusion with respect to host infectivity was that [5]: "Transmission can be altered by reduction of the mean period of infectivity of a case of malaria. The influence is, however, relatively small; the reproduction rate varies directly with the mean duration of infectivity, very great changes in which would be necessary to reduce the high rates common in Africa and some other places below the critical level."

In terms of our model the "basic reproduction rate" is:

$$Z_0 = -k [V_B^2 / (N_H N_V)] [VS^{DV} / \ln(VS)] = kC$$

where "k" represents an equivalent to the ratio b/r (see below).

Our parameters VS and D_V correspond directly to Macdonald's "p" and "n," and the ratios of our initial parameters N_V/N_H and V_B/N_V translate his "m" and "a," respectively (substituting "bites" for "men bitten"), such that for our model " ma^2 " = $V_B^2 / (N_H N_V)$. Macdonald's "b" is a measure of incidence (e.g. by its role in expressions for "inoculation rate" and "force of infection"), and "r" the reciprocal of the average duration of the "affected" state. Macdonald [5] wrote that "in nature the value of the reproduction rate is greatly influenced by immunity altering the values of r and b ," and in our model these proportions actually do vary dynamically with distributions of host immune states and infection histories, in a convolved, partly stochastic manner.

Therefore it is difficult to interpret "b" and "r" in terms of our model, particularly in terms of our parameters WN and IM . However, the C values considered here range from 3.7 to 29.2, in accord with field estimates [33–38, but see 39–40], so if we consider $1/(DH+WN)$ roughly equivalent to r , then k ranges from 30b to 50b. Even if we consider the b-equivalent values in our model as ranging from 0.1 to 1 (k values from 3 to 50), field estimates span the resulting range of Z_0 values.

Figure 1.

A schematic of the basic malaria model. The inner loop (white letters on black) represents the *Plasmodium falciparum* life cycle in a female *Anopheles* mosquito (top) and a human (bottom), linked by the transmission of the parasite through mosquito bloodmeals on humans (vertical). The horizontal axes above the inner loop represent the model timeline (with corresponding parameters) and survivorship in the vector, while those below similarly represent the timeline and decay of immunity in the host.

Figure 2.

An example of the time course of the overall malaria prevalence (solid line) and of the prevalence of infectious stages (dashed line) in a human population, demonstrating damped oscillations. The levels and rates at which prevalences stabilize depend on parameter values in the model. These curves represent the average of 25 runs, using the parameter values $D_V = 10$, $D_H = 20$, $VS = 0.95$, $IM = 0.01$, and $WN = 20$, and the initial conditions $N_H = 500$, $N_V = 5000$, and $V_B = 2500$.

Figure 3.

An illustration of an “effective” mosquito population size (see text), with the parameter values $N_H = 500$, $D_V = 10$, $D_H = 20$, $WN = 15$, $IM = 0.01$, and $VS = 0.95$ or 0.86 . For each level of the parameter N_V , a point represents that value of V_B required to maintain the overall prevalence of infection in humans and the number of infectious vector bites per day constant at the levels obtained with $N_V = 5000$ and a two-day blood meal cycle, $V_B = 2500$. For $VS = 0.95$ and 0.86 , respectively, the overall prevalence in humans remains constant at 71% and 52%, and the average number of infectious mosquito bites per day at 1,008 and 167 (i.e., 2.02 and 0.33 per human per day). Our regressions estimate that for $VS = 0.95$ (solid line), $V_B = 336N_V^{0.237}$, and for $VS = 0.86$ (dashed line), $V_B = 103N_V^{0.367}$ (see text). Note the different spans of the vertical and horizontal scales: the number of bites per day, V_B , increases only two- to three-fold with a 20-fold increase in the mosquito population, N_V .

Figure 4.

Plots of overall malaria prevalence in a human population, with parameter values $D_V = 10$ and $D_H = 20$, and initial conditions $N_H = 500$, $N_V = 5000$ and $V_B = 2500$. Values of the remaining temporal parameters range from 50% to 150% of a plausible mean value for each: the vector half-life from 5 to 15 days, host window from 10 to 30 days, and host immunity half-life from 50 to 150 days. In the comparisons of vector half-life and host window, only the two endpoints of the host immunity half-life range are shown, as parts A (50 days) and B (150 days). The best-fit planes (see text) describe these prevalences as: (A) $0.630 + [0.006/(1-VS)] + 0.005WN$, and (B) $0.464 + [0.008/(1-VS)] + 0.007WN$. In the comparisons of vector half-life and host immunity half-life, only the two endpoints of the host window range are shown, as parts C (10 days) and D (30 days). The best-fit planes describe these prevalences as: (C) $0.654 + [0.009/(1-VS)] - 0.0007/IM$, and (D) $0.791 + [0.006/(1-VS)] - 0.0004/IM$.

Figure 5.

An example of the time course of the overall malaria prevalence (solid lines) and the prevalence of infectious stages (dashed lines) in a human population, in (A) classic differential-equation and (B) differential-delay-equation “compartment” models analogous to the discrete-event model (see the text and Appendix). The curves represent average prevalences over 25 runs, with parameter values $k = p = [(\ln 2)/20] = 0.035$, $c = [(\ln 2)/10] = 0.069$, $h = 0.5$ (a two-day gonotrophic cycle), $q = 0.055$ (see text and Appendix), $b = 0.5$ (see below) and $d = [1 - VS] = 0.05$, and initial conditions $S(0) = 0.75$, $M(0) = 0.25$, $G(0) = R(0) = L(0) = F(0) = 0$ and $U(0) = b/d = 10$ (a mosquito:human ratio of 10:1). For the differential-delay model, three rate parameters are replaced by explicit time lags: $k = p = 20$ and $c = 10$.