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Population Biology

Periodic and chaotic host–parasite interactions in human malaria

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ABSTRACT **It has been recognized since ancient times that malaria fever is highly periodic but the mechanism has been poorly understood. Malaria fever is related to the parasite growth cycle in erythrocytes. After a fixed period of replication, a mature parasite (schizont) causes the infected erythrocyte to rupture, releasing progeny that quickly invade other erythrocytes. Simultaneous rupture of a large number of schizonts stimulates a host fever response. Febrile temperatures are damaging to *Plasmodium falciparum*, particularly in the second half of its 48-hr replicative cycle. Using a mathematical model, we show that these interactions naturally tend to generate periodic fever. The model predicts chaotic parasite population dynamics at high multiplication rates, consistent with the classical observation that *P. falciparum* causes less regular fever than other species of parasite.**

Human malaria parasites, in the asexual erythrocytic stage of infection, demonstrate an exponential growth phase that terminates shortly after the onset of periodic fever, as shown in Fig. 1 (1). The periodic nature of the fever is attributable to three factors. First, malaria parasites undergo repeated cycles of replication in host erythrocytes: schizont rupture occurs at the end of each cycle and is associated with fever (1, 3). Second, the duration of each cycle (i.e., the parasite generation time) is essentially constant, being 48 hr for *Plasmodium falciparum, Plasmodium vivax*, and *Plasmodium ovale*, and 72 hr for *Plasmodium malariae*. Finally, the parasites have an intriguing tendency to replicate in synchrony with each other *in vivo*, so that each generation of schizonts ruptures more or less simultaneously, causing periodic paroxysms of fever. However, parasites do not generally grow in synchrony *in vitro*, and the cause of synchronization *in vivo* is unclear.

Febrile temperatures inhibit the development of *P. falciparum* in erythrocytes *in vitro*, with maximal effect in the second half of the replicative cycle (4). Moreover, periodic elevations of temperature can synchronize parasite growth *in vitro*, raising the possibility that fever itself might promote parasite synchronization *in vivo* (4, 5). We describe a mathematical model that generalizes these observations (using fever as an example) to show that synchronization could be generated by any host response with the following features: (*i*) it should be promptly triggered by schizont rupture, with a large number of schizonts causing a greater response than a small number; (*ii*) it should inhibit parasite growth, with maximal effect on the later stages of the growth cycle.

Let x_t be the number of young parasites (0–24 hr postinvasion) on day t and let y_t be the number of old parasites (24–48 hr postinvasion). Then

$$y_{t+1} = d_1 x_t f(x_t)$$

$$x_{t+1} = r d_2 y_t g(x_t). \qquad [1]$$

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r represents the number of newly infected erythrocytes that arise from a single rupturing schizont. d_1 and d_2, respectively, denote the probabilities that a parasite survives the first and second half of its life cycle in the absence of fever. The functions $f(x_t)$ and $g(x_t)$ represent the fraction of young and old parasites, respectively, that survive the damaging effect of the fever. $f(x_t)$ and $g(x_t)$ are decreasing functions, representing a negative feedback, because large numbers of newly infected erythrocytes are associated with high levels of fever, which are survived by a small fraction of parasites. We choose $f(x_t) > g(x_t)$ because of the evidence that fever is more harmful to older parasites (4).

This simple difference equation has interesting dynamical properties (Fig. 2). Initially, the parasite population replicates asynchronously, with a multiplication rate $R = r d_1 d_2$ every 2 days. When parasite density increases beyond a certain level, significant fever occurs. This exerts a negative feedback force, terminating exponential growth and causing parasite density to oscillate. The asymmetry of the feedback mechanism $[f(x_t) > g(x_t)]$ drives the system into synchronization—i.e., one day there are mainly young parasites ($x_t >> y_t$) and the next day there are mainly old parasites ($y_{t+1} >> x_{t+1}$) so that fever occurs on alternate days. In a synchronous population, when $f(x_t)$ falls below R^{-1}, parasite density will start to oscillate around an equilibrium value.

Having illustrated the general properties of the interaction, we consider two specific features: in natural infection, fever can recur daily as well as on alternate days (Fig. 1); and *in vitro* observations indicate that parasites demonstrate a minor degree of heterogeneity in cycle duration. These effects can be understood by breaking down the parasite population into four (rather than two) stages of development and by allowing a small proportion of parasites to progress more slowly than the others from one stage of development to the next (Fig. 3). The parasite population can now be observed to cluster either in one major cohort (with fever on alternate days) or in two cohorts replicating directly out of phase (with daily fever) and to fluctuate between these two states as classically described (1).

In a state of complete synchronization, Eq. **1** reduces to

$$x_{t+2} = R x_t f(x_t). \qquad [2]$$

One-dimensional mappings of this kind have been investigated by several authors (6–8). As a generic property—i.e., rather independent of the specific form of $f(x_t)$—the dynamical behavior becomes chaotic as the multiplication rate, R, increases. It is classically observed that *P. falciparum* infection is generally less synchronous, and associated with less regular fever, than other forms of human malaria (1). This can be explained by chaotic dynamics resulting from the high multiplication rate of this species of parasite (Figs. 1–3).

Since the parasite generation time is an exact multiple of 24 hr, host circadian rhythms, by modulating the fever response, could influence at what time of day schizont rupture is most likely to occur. There is experimental evidence that diurnal temperature cycles have such an effect in simian and avian malaria (9, 10).

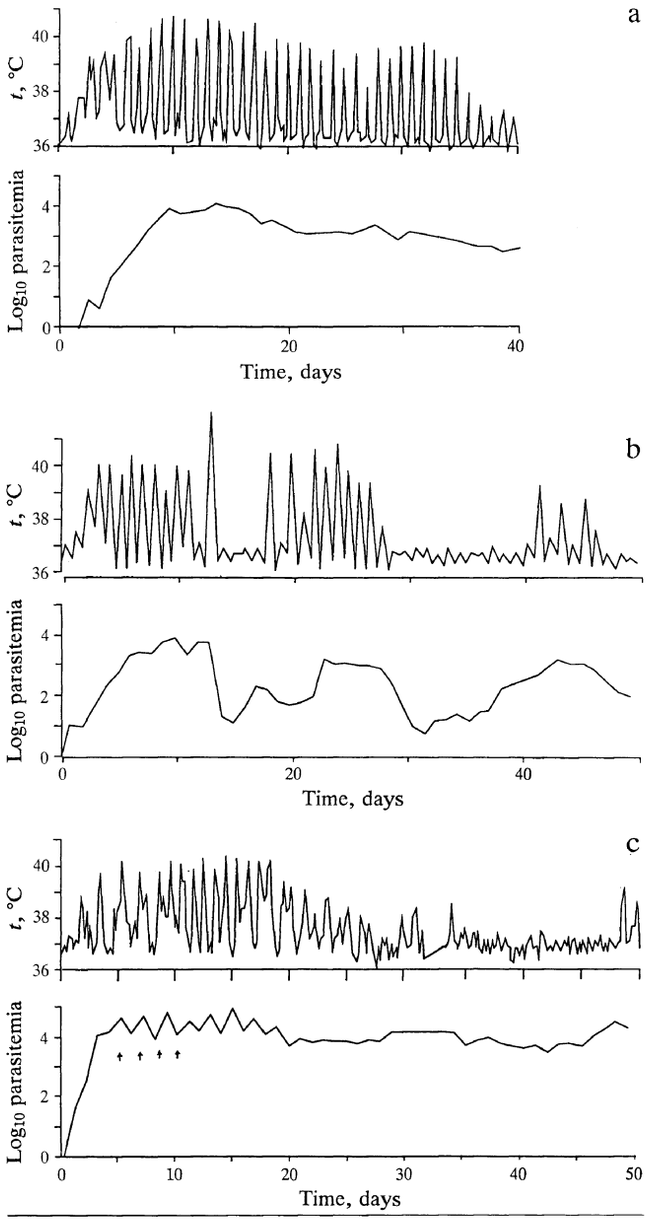

FIG. 1. Malaria infections in nonimmune subjects. (*a*) *P. vivax*. (*b*) *P. vivax*. (*c*) *P. falciparum*. Infection was artificially induced as treatment for neurosyphilis: data are from ref. 1. Log_{10} parasitemia refers to parasite density per μl of blood: the limit of detection is 1–10 per μl. Day 0 refers approximately to the first detection of parasites (after inoculation several days previously); prior to this, fever did not occur. Subcurative doses of cinchona alkaloids were given to attenuate the *P. falciparum* infection (indicated by arrows). An absolute constraint on the parasite multiplication rate is set by the maximum number of daughter parasites per schizont (32 for *P. falciparum*, 24 for *P. vivax*, 16 for *P. ovale*, and 12 for *P. malariae*) and their invasion capacity (*P. falciparum* infects erythrocytes of all ages whereas *P. vivax* and *P. ovale* primarily infect reticulocytes, and *P. malariae* infects older erythrocytes). Clinical observations documenting the initial exponential growth rate, such as shown here, indicate that the *in vivo* multiplication rate in nonimmune individuals can be in the region of 20 for *P. falciparum* and is considerably <10 for other species of parasite (1). After the initial exponential growth phase, parasitemia stabilizes and subsequently tends to decline slowly although relapses are common (b and c). The pattern of decline may relate to the acquisition of specific antiparasitic immunity and other growth-limiting factors [such as erythrocyte availability (2)], which are beyond the scope of this paper but might be represented in the present model by shifts in the parameters r and d. Note the abrupt drop in parasitemia following an episode of extremely high fever in *b*.

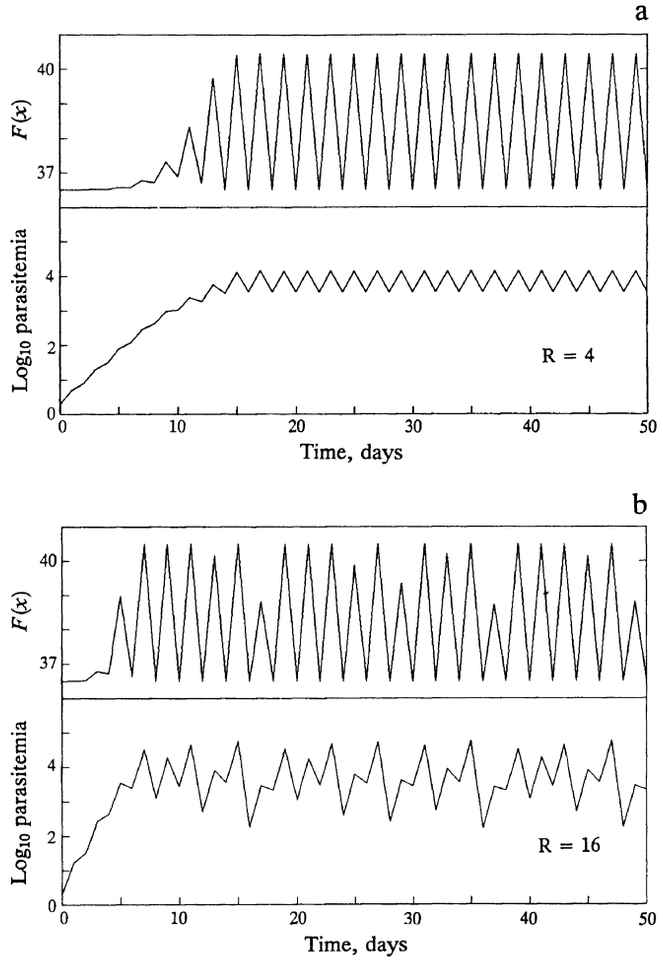

FIG. 2. Dynamics of Eq. **1** for different parasite multiplication rates. In this example, we choose $f(x) = e^{-px}$ and $g(x) = e^{-sx}$—i.e., the probability of a parasite surviving the fever response is an exponential function of the number of young parasites arising from the rupturing schizonts that induce the fever. We make $s > p$ because of the greater inhibitory effect of fever on older parasites. Parasitemia refers to total parasite density $(x_t + y_t)$. The fever response is not explicitly quantitated in our model but for illustration we show an exponential function of the number of young parasites present that varies in the range of human body temperature $F(x) = 36.5 + 4(1 - e^{-0.0003x})$. (*a*) Regular oscillations for $R = r = 4$. (*b*) Chaotic oscillations for $R = r = 16$. In both *a* and *b*, $d_1 = d_2 = 1$; $p = 0.00001$; $s = 0.001$. At time $t = 0$, $x = y = 1$. In the state of complete synchronization, the number of young parasites (present on every second day) oscillates around the equilibrium value $p^{-1} \log R$—i.e., the equilibrium density increases as a logarithmic function of the reproductive rate and as a hyperbolic function of the parameter p, which quantifies the effect of fever on young parasites. The above example is illustrative: note that similar dynamical features can be observed for other choices of $f(x)$ and $g(x)$, as will be discussed in more mathematical detail elsewhere (unpublished data).

This analysis demonstrates that a simple form of host defense can promote synchronization and periodic phenomena while tending to equilibrate parasite population density. We use fever as an example but other host defense mechanisms may reinforce the effect. Rupturing schizonts cause fever by stimulating macrophages and other cells to release pyrogenic cytokines including tumor necrosis factor (11): tumor necrosis factor can also induce cell-mediated parasite killing by free oxygen radicals (12) and is associated with other circulating antiparasitic factors that are maximal at the peak of the fever (13). A critical feature of these mechanisms is their short response time, in contrast to antibody generation, which is slow in relation to the generation time of the parasite and therefore could not generate the sort of periodic effects described here (see Fig. 3 legend).

We note that the high multiplication rates of *P. falciparum* in nonimmune individuals could lead to large chaotic bursts

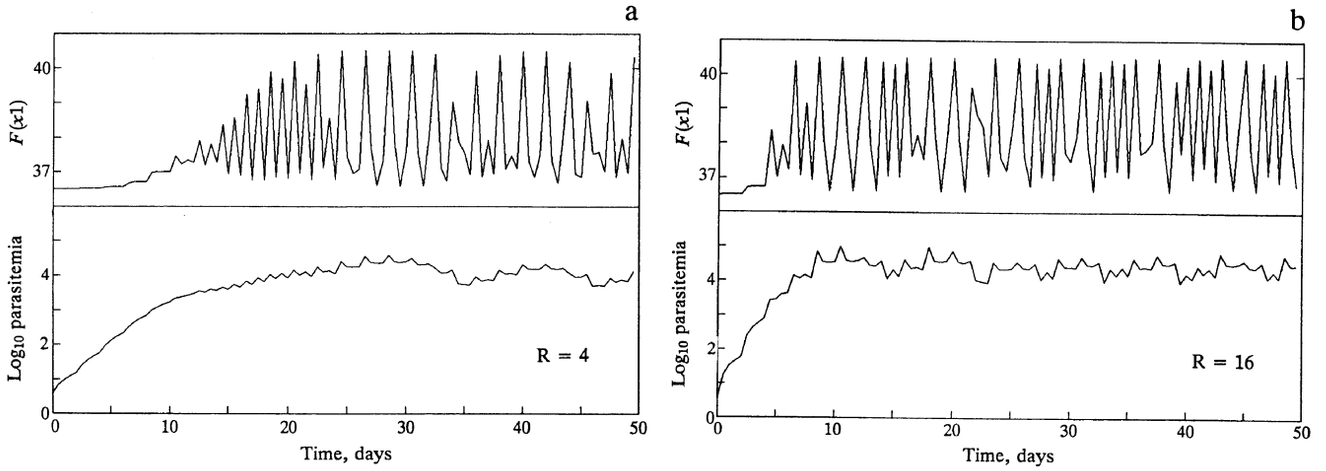

FIG. 3. Parasite population dynamics following two simple modifications to the model. (*i*) Time interval for analysis has been shortened to 0.5 day, such that the parasite population is now divided into four stages of development: $x1$ (0–12 hr postinvasion), $x2$ (12–24 hr postinvasion), $x3$ (24–36 hr postinvasion), $x4$ (36–48 hr postinvasion). (*ii*) To introduce heterogeneity into cycle duration, we suppose that at each transition a small fraction of otherwise viable parasites, h, fail to go through to the next stage of development. By analogy to Eq. **1**, $x1_{t+0.5} = (1 - h)rd_4x4_tf_4(x1_t) + hd_1x1_tf_1(x1_t)$; $x2_{t+0.5} = (1 - h)d_1x1_tf_1(x1_t) + hd_2x2_tf_2(x1_t)$; $x3_{t+0.5} = (1 - h)d_2x2_tf_2(x1_t) + hd_3x3_tf_3(x1_t)$; $x4_{t+0.5} = (1 - h)d_3x3_tf_3(x1_t) + hd_4x4_tf_4(x1_t)$. As in Fig. 2 we choose $f_n(x1) = e^{-s}n^{x1}$. The greater effect of fever on older parasites is represented by $s_1 < s_2 < s_3 < s_4$. The fever response is illustrated by $F(x1) = 36.5 + 4(1 - e^{-0.0003x1})$, as explained in Fig. 2. (*a*) $R = r = 4$, showing periods of daily fever fluctuating with periods of fever every 2 days. (*b*) $R = r = 16$, showing chaotic oscillations in the parasite population and in the fever response. In both *a* and *b*, $d_1 = d_2 = d_3 = d_4 = 1$; $s_1 = 0.00001$; $s_2 = 0.00002$; $s_3 = 0.0001$; $s_4 = 0.001$; $h = 0.05$. At time $t = 0$, $x1 = x2 = x3 = x4 = 1$. For simplicity we treat d and r as constants, but in fact they will tend to decrease gradually as specific immunity is acquired (over weeks or months) and when $R = rd_1d_2d_3d_4$ falls below 1, the population will go into steady decline. Superimposed on the effects described here, slower oscillations may arise as a result of antigenic variation and limited erythrocyte availability (2).

of schizont rupture that might contribute, for example through massive tumor necrosis factor release (11, 12, 14), to a fatal outcome.

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