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A REACTION-DIFFUSION SYSTEM MODELING THE SPREAD OF RESISTANCE TO AN ANTIMALARIAL DRUG

Nicolas Bacaër

Institut de Recherche pour le Développement
32 avenue Henri Varagnat, 93143 Bondy Cedex, France

Cheikh Sokhna

Laboratoire de Paludologie, Institut de Recherche pour le Développement
B.P. 1386, Dakar, Sénégal

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Abstract. A mathematical model representing the diffusion of resistance to an antimalarial drug is developed. Resistance can spread only when the basic reproduction number of the resistant parasites is bigger than the basic reproduction number of the sensitive parasites (which depends on the fraction of infected people treated with the antimalarial drug). Based on a linearization study and on numerical simulations, an expression for the speed at which resistance spreads is conjectured. It depends on the ratio of the two basic reproduction numbers, on a coefficient representing the diffusion of mosquitoes, on the death rate of mosquitoes infected by resistant parasites, and on the recovery rate of nonimmune humans infected by resistant parasites.

1. **Introduction.** Malaria is a parasitic disease transmitted to humans by mosquito bites. Each year several hundred million malaria cases occur, causing around two million deaths. Death can be avoided by the use of antimalarial drugs, but their efficiency has been decreasing dramatically over the past few decades. Indeed, parasites with particular genes of resistance to a drug can survive the treatment. Because of this selective advantage and of the mobility of humans and mosquitoes, the genes can spread in populations over large areas. As an example, a map showing the spread of resistance to chloroquine (CQ), the most widely used antimalarial drug, from the beginning of the 1960s to the end of the 1980s in South America, Southeast Asia, and Africa appears in [1, p. 608]. The rise of resistance is responsible for a considerable increase in mortality [18]. In some areas with a high percentage of resistance to CQ, health workers have used alternative drugs such as sulphadoxine-pyrimethamine (SP), but again resistance to these drugs has emerged [4]. Presently, artemisinine derivatives, which are produced from a traditional Chinese plant, seem to be the most efficient antimalarial drugs left for the near future. For public-health authorities, finding money to replace the inefficient drugs with efficient (but more expensive) ones while trying to avoid or at least delay the appearance of resistance to these new drugs is a major concern.

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From a theoretical point of view, the introduction of new antimalarial drugs can be seen as an optimal control problem of a complex dynamical system (including humans, mosquitoes, sensitive parasites, and resistant parasites) with economic constraints (prices of drugs, budget for malaria control) and a control variable (the percentage of malaria cases treated with the new drug). Modeling these different ingredients may be helpful for people who advise public-health authorities of countries where malaria is endemic. Epidemiological models for drug-resistant malaria have already been developed in [2, 10], and the economic constraints were considered in [11]. But the models used in these papers either did not include space or only included it in the form of two disjointed areas related by migration [10].

This paper presents a model for the spread of resistance in spatially inhomogeneous populations but leaves economic aspects aside. The model begins with resistant parasites that have been introduced in an area by migrating humans but then considers the area as closed to migration and focuses on the diffusion of resistance due to the mobility of mosquitoes, which can explore a few square kilometers during their lifetime. Since most bites occur at night (the period of activity of anopheline female mosquitoes, the vector of malaria) and people generally sleep in the same place each night, the mobility of humans can be neglected in a first approximation. Of course, the spread of resistance involves many different phenomena. Some of them were included in the model, but others had to be omitted to keep the model mathematically tractable (e.g., the genetics related to the sexual reproduction of parasites [7] and the genetic variability in the human population [5]).

The model is a system of partial differential equations. The flight of the mosquitoes is supposed to be a Brownian motion so that a classical diffusion term appears in the equations governing the mosquito density. The model is nonlinear because of the "reaction" terms representing the transmission of the disease. Hence, the model belongs to the family of "reaction-diffusion systems." Such systems have attracted much attention in mathematical biology. Early work can be traced to Ronald A. Fisher [6], who was already focusing on the "wave of advance of advantageous genes." The topic developed greatly after this pioneering work, with more complex models, new areas of application (morphogenesis, the geographical spread of epidemics such as plague, and rabies [13]), and more sophisticated mathematical tools [15]. However, we are not aware of any work in which this kind of modeling has been used for the spread of resistance to antimalarial drugs, although a partial integro-differential system for the spread of malaria epidemics (*without* resistance) has been recently studied in [14].

The present system of reaction-diffusion equations exhibits traveling-wave solutions, which are supposed to mimic the geographical spread of resistance to an antimalarial drug (CQ, SP, or others). The main purpose of this paper is to give an expression for the speed of propagation v^*, an expression that can be used to study its dependency on the parameters of the model—some of which can be controlled by human decisions—particularly the fraction f of infected people treated with the antimalarial drug. The result gives a quantitative expression for the well-known qualitative property that v^* is an increasing function of f.

We hope that this expression will help develop some understanding for the more complex optimal control problem of finding the level of resistance above which cheap but partially inefficient drugs should be replaced with expensive but efficient ones—a question of more direct applicability and an active subject of dispute [3].

The plan of the article is as follows: Section 2 presents the model. The steady states, along with their stability, are studied in section 3. Linearizing the system, an expression that describes the speed of traveling waves representing the spread of resistance to antimalarial drugs, occurs in section 4. This expression is valid provided the "linear conjecture" holds [19, 12]. Numerical simulations tend to confirm that this conjecture holds for the present model; the results are discussed in section 5. From a mathematical point of view, the style is rather informal and closer to the one used in [13]. Future work will, one hopes, fill gaps in the proof.

2. **The model.** There are two independent variables: t (the time) and x (a one-dimensional space variable). The reduction to one dimension means that we are looking at the propagation of plane waves along one direction. The unknowns are

$S(t,x)$: proportion of nonimmune noninfected humans;
$I_1(t,x)$: proportion of nonimmune humans infected by sensitive parasites;
$I_2(t,x)$: proportion of nonimmune humans infected by resistant parasites;
$R(t,x)$: proportion of immune noninfected humans;
$J(t,x)$: proportion of immune infected humans;
$s(t,x)$: proportion of noninfected mosquitoes;
$i_1(t,x)$: proportion of mosquitoes infected by sensitive parasites;
$i_2(t,x)$: proportion of mosquitoes infected by resistant parasites.

The densities P, humans, and m, mosquitoes, are constants independent of t and x. The main parameter of the model is f, the fraction of the nonimmune infected humans treated with the antimalarial drug. Let us stress some of the simplifying assumptions underlying this compartmental model:

1. Immunity is either present or absent (instead of being a slowly varying process) and provides complete protection from malarial illness (instead of only partial protection).
2. Only those humans who are ill because of malaria (hence only nonimmune infected humans) take the antimalarial drug; this is of course a crude assumption since the nonspecific symptoms of malaria often lead humans living in endemic areas to take antimalarial drugs even when their illness is unrelated to malaria.
3. Infected humans and mosquitoes are infected either by sensitive parasites or by resistant parasites but not by both types at the same time.

One consequence of these assumptions is that it is unnecessary in the model to distinguish between immune humans infected by sensitive parasites and those infected by resistant parasites. Concerning the humans and their interactions with the parasites, set

c: rate at which nonimmune infected humans become immune;
e: rate at which immune noninfected humans lose their immunity;
b: rate at which nonimmune infected humans recover if they use no antimalarial drug or if they use the drug while infected by resistant parasites;
$\hat{b}$: rate at which nonimmune infected humans recover if they use the drug while infected by sensitive parasites ($\hat{b} > b$);
$\bar{b}$: rate at which immune infected humans recover ($\bar{b} > b$);
T_1 (resp. T_2): latent period before infectiousness of sensitive (resp. resistant) parasites in the human;
μ: death rate of humans;

ν: malaria-related death rate of nonimmune infected humans.

The average recovery rate of nonimmune humans infected by sensitive parasites is $(1-f)\,b + f\,\hat{b}$. Set

$$b_1 = (1-f)\,b + f\,\hat{b} + c + \mu + \nu\,, \quad b_2 = b + c + \mu + \nu.$$

Concerning the mosquitoes and their interactions with the parasites, set

d: diffusion of mosquitoes;
b'_1: death rate of mosquitoes infected by sensitive parasites;
b'_2: death rate of mosquitoes infected by resistant parasites;
T'_1 (resp. T'_2): latent period before infectiousness of sensitive (resp. resistant) parasites in the mosquito.

Concerning the interaction between humans and mosquitoes, set

k: biting rate on humans by a single mosquito (the number of bites per person per unit time is $k\,m/P$);
p (resp. $\bar{p}$): probability for a mosquito bite between an infectious mosquito and a nonimmune (resp. immune) noninfected human to lead to the infection of the human ($\bar{p} < p$);
p': probability for a mosquito bite between a noninfected mosquito and an infectious human to lead to the infection of the mosquito.

Set

$$\pi_1 = p\,\exp(-b'_1\,T'_1)\,, \quad \bar{\pi}_1 = \bar{p}\,\exp(-b'_1\,T'_1)\,, \quad \pi'_1 = p'\,\exp(-b_1\,T_1)\,,$$
$$\pi_2 = p\,\exp(-b'_2\,T'_2)\,, \quad \bar{\pi}_2 = \bar{p}\,\exp(-b'_2\,T'_2)\,, \quad \pi'_2 = p'\,\exp(-b_2\,T_2)\,.$$

These parameters have the following meaning:

π_1 (resp. π_2): probability for a mosquito bite between a mosquito infected by sensitive (resp. resistant) parasites and a *nonimmune* noninfected human to lead to the infection of the human;
$\bar{\pi}_1$ (resp. $\bar{\pi}_2$): probability for a mosquito bite between a mosquito infected by sensitive (resp. resistant) parasites and an *immune* noninfected human to lead to the infection of the human ($\bar{\pi}_1 < \pi_1$, $\bar{\pi}_2 < \pi_2$);
π'_1 (resp. π'_2): probability for a mosquito bite between a noninfected mosquito and a nonimmune human infected by sensitive (resp. resistant) parasites to lead to the infection of the mosquito.

Additionally, the simplifying assumption is made that immune infected humans cannot infect mosquitoes.

The model is sketched in Figure 1. It is of course very simplified, and many details of the transmission cycle have been omitted. In particular, the egg and larva periods of the mosquito life cycle have been omitted; instead, the eclosion of new adult mosquitoes compensates for the deaths so that the density m of adult mosquitoes is constant. However, the point here is to keep the model simple enough for it to be mathematically tractable. To simplify the notations, set

$$a_1 = k\,\pi_1\,\frac{m}{P}\,, \quad a'_1 = k\,\pi'_1\,, \quad \bar{a}_1 = k\,\bar{\pi}_1\,\frac{m}{P}\,,$$
$$a_2 = k\,\pi_2\,\frac{m}{P}\,, \quad a'_2 = k\,\pi'_2\,, \quad \bar{a}_2 = k\,\bar{\pi}_2\,\frac{m}{P}\,.$$

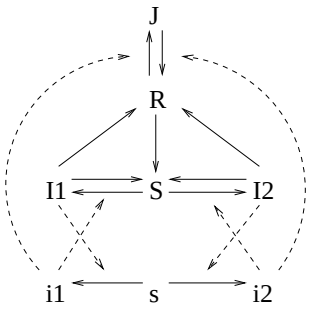

FIGURE 1. Compartments of the model, possible transitions (solid lines) and parasite transmission (dotted lines).

The mathematical formulation of the model is a system of partial differential equations with the humans on one side

$$\frac{\partial I_1}{\partial t} = a_1\, S\, i_1 - b_1\, I_1\,, \qquad \frac{\partial I_2}{\partial t} = a_2\, S\, i_2 - b_2\, I_2\,, \tag{1}$$

$$\frac{\partial R}{\partial t} = c\, I_1 + c\, I_2 - (e+\mu)\, R - \bar{a}_1\, R\, i_1 - \bar{a}_2\, R\, i_2 + \bar{b}\, J\,, \tag{2}$$

$$\frac{\partial J}{\partial t} = \bar{a}_1\, R\, i_1 + \bar{a}_2\, R\, i_2 - (\bar{b}+\mu)\, J \tag{3}$$

and the mosquitoes on the other

$$\frac{\partial i_1}{\partial t} = a_1'\, s\, I_1 - b_1'\, i_1 + d\, \frac{\partial^2 i_1}{\partial x^2}\,, \qquad \frac{\partial i_2}{\partial t} = a_2'\, s\, I_2 - b_2'\, i_2 + d\, \frac{\partial^2 i_2}{\partial x^2}\,. \tag{4}$$

Recall that $S = 1 - I_1 - I_2 - R - J$ and that $s = 1 - i_1 - i_2$.

3. **Steady states.** Let us first study the x-independent steady states of the system. First, there is the trivial steady state in which I_1, I_2, R, J, i_1, and i_2 equal 0, corresponding to the situation where malaria has been eradicated. Its stability depends on the signs of the eigenvalues of the matrix obtained by linearizing the system near $(0,0,0,0,0,0)$, which is (if we put the unknowns in the order $[i_1, I_1, R, J, i_2, I_2]$)

$$\begin{pmatrix} -b_1' & a_1' & 0 & 0 & 0 & 0 \\ a_1 & -b_1 & 0 & 0 & 0 & 0 \\ 0 & c & -(e+\mu) & \bar{b} & 0 & c \\ 0 & 0 & 0 & -(\bar{b}+\mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & -b_2' & a_2' \\ 0 & 0 & 0 & 0 & a_2 & -b_2 \end{pmatrix}.$$

The eigenvalues are $-(e+\mu)$, $-(\bar{b}+\mu)$, and the eigenvalues of the two submatrices are

$$\begin{pmatrix} -b_1' & a_1' \\ a_1 & -b_1 \end{pmatrix}, \quad \begin{pmatrix} -b_2' & a_2' \\ a_2 & -b_2 \end{pmatrix}.$$

Define the basic reproduction numbers of the sensitive and the resistant parasites by

$$\alpha_1 = \frac{a_1\, a_1'}{b_1\, b_1'}\,, \quad \alpha_2 = \frac{a_2\, a_2'}{b_2\, b_2'}.$$

The trivial steady state is stable (all the eigenvalues are negative) when $\alpha_1 < 1$ and $\alpha_2 < 1$, and it is unstable (at least one eigenvalue is positive) when $\alpha_1 > 1$ or $\alpha_2 > 1$.

When $\alpha_1 > 1$, another steady state exists. Set

$$\beta_1 = \frac{b'_1}{a'_1}\ ,\ \gamma_1 = \beta_1\,\frac{c}{e+\mu}\ ,\ \delta_1 = \gamma_1\,\frac{\bar a_1}{\bar b+\mu}\ ,\ \varepsilon_1 = \frac{\bar a_1}{\bar b+\mu}\,\frac{\mu}{e+\mu}.$$

It is defined by $i_1 = i_1^*$, $I_1 = I_1^*$, $R = R_1^*$, $J = J_1^*$, $i_2 = 0$, and $I_2 = 0$, where i_1^* is the positive root of

$$(\delta_1 + \varepsilon_1 + \beta_1\,\varepsilon_1)\,i_1^2 + \Big(1 + \beta_1 + \gamma_1 + \varepsilon_1\,\big(\frac{1}{\alpha_1} - 1\big)\Big)\,i_1 + \frac{1}{\alpha_1} - 1 = 0\,, \qquad (5)$$

and

$$I_1^* = \beta_1\,\frac{i_1^*}{1-i_1^*}\,, \qquad R_1^* = \frac{\gamma_1\,I_1^*}{\beta_1\,(1+\varepsilon_1\,i_1^*)}\,, \qquad J_1^* = \frac{\delta_1\,R_1^*\,i_1^*}{\gamma_1}\ . \qquad (6)$$

This steady state corresponds to the situation in which all the parasites are sensitive. Its stability depends on the signs of the eigenvalues of the matrix obtained by linearizing the system near $(i_1^*, I_1^*, R_1^*, J_1^*, 0, 0)$, which is

$$\begin{pmatrix}
-(b'_1 + a'_1\,I_1^*) & a'_1\,s_1^* & 0 & 0 & -a'_1\,I_1^* & 0 \\
a_1\,S_1^* & -(b_1 + a_1\,i_1^*) & -a_1\,i_1^* & -a_1\,i_1^* & 0 & -a_1\,i_1^* \\
-\bar a_1\,R_1^* & c & -(e+\mu+\bar a_1\,i_1^*) & \bar b & -\bar a_2\,R_1^* & c \\
\bar a_1\,R_1^* & 0 & \bar a_1\,i_1^* & -(\bar b+\mu) & \bar a_2\,R_1^* & 0 \\
0 & 0 & 0 & 0 & -b'_2 & a'_2\,s_1^* \\
0 & 0 & 0 & 0 & a_2\,S_1^* & -b_2
\end{pmatrix},$$

where for convenience we set $s_1^* = 1 - i_1^*$ and $S_1^* = 1 - I_1^* - J_1^* - R_1^*$. The eigenvalues of the 2×2 submatrix

$$\begin{pmatrix} -b'_2 & a'_2\,s_1^* \\ a_2\,S_1^* & -b_2 \end{pmatrix},$$

which are also eigenvalues of the full matrix, are

$$-\frac{1}{2}\,(b_2 + b'_2) \pm \frac{1}{2}\,\sqrt{(b_2+b'_2)^2 - 4\,[b_2\,b'_2 - a_2\,a'_2\,s_1^*\,S_1^*]}.$$

For this steady state, it is easily seen that $s_1^*\,S_1^* = \frac{b_1\,b'_1}{a_1\,a'_1}$. So if $\alpha_1 < \alpha_2$, one eigenvalue of the 2×2 submatrix is positive, and the steady state is unstable.

Similarly, when $\alpha_2 > 1$, there is another steady state, defined by $i_1 = 0$, $I_1 = 0$, $R = R_2^*$, $J = J_2^*$, $i_2 = i_2^*$, and $I_2 = I_2^*$. The formulas are the same as the previous ones, except that a'_1 should be replaced by a'_2, b'_1 by b'_2, and $\bar a_1$ by $\bar a_2$ (β_1, γ_1, δ_1, and ε_1 are replaced by β_2, γ_2, δ_2, and ε_2). This steady state corresponds to the situation in which all the parasites are resistant. The linearization of the system near this steady state shows that it is unstable when $\alpha_1 > \alpha_2$.

These results suggest that when $\alpha_1 > 1$ and $\alpha_2 > 1$, $(i_1^*, I_1^*, R_1^*, J_1^*, 0, 0)$ is stable if $\alpha_1 > \alpha_2$, and $(0, 0, R_2^*, J_2^*, i_2^*, I_2^*)$ is stable if $\alpha_2 > \alpha_1$.

Remark. In the simplified model where immunity is not taken into account ($c = 0$, $\bar a_1 = 0$), one obtains

$$i_1^* = \frac{1 - 1/\alpha_1}{1 + \beta_1}\,, \quad I_1^* = \frac{\alpha_1 - 1}{\alpha_1 + 1/\beta_1}\,.$$

These are formulas (14.5) and (14.6) in [1], where $1/\beta_1$ is called "Macdonald's stability index."

4. **Traveling waves.** When resistant parasites appear at some place, they will start spreading because of the selective pressure caused by the use of the drug. The purpose of this section is to compute the speed of propagation as a function of the parameters. We suppose that $\alpha_2 > \alpha_1 > 1$. The trivial steady state and the steady state $(i_1^*, I_1^*, R_1^*, J_1^*, 0, 0)$ are unstable, while the steady state $(0, 0, R_2^*, J_2^*, i_2^*, I_2^*)$ is stable. We focus on the evolution of a small perturbation (with compact support) of the x-independent unstable equilibrium $(i_1^*, I_1^*, R_1^*, J_1^*, 0, 0)$ so that $I_2(0, x) > 0$ (or $i_2(0, x) > 0$) for some x.

One can expect this small perturbation to spread over the whole domain in both directions. Looking at only one direction of propagation, the "wave of advance" is generally called a traveling wave. From a mathematical point of view, the system of partial differential equations (1)–(4) admits traveling-wave solutions if there exist nonnegative functions of one variable (still called I_1, I_2, R, J, i_1, and i_2 with an abuse in notation) and $v > 0$ (in the case where the wave travels toward the positive x) such that

$$\begin{array}{lll} I_1(x,t) = I_1(x - v\,t), & I_2(x,t) = I_2(x - v\,t), & R(x,t) = R(x - v\,t), \\ J(x,t) = J(x - v\,t), & i_1(x,t) = i_1(x - v\,t), & i_2(x,t) = i_2(x - v\,t), \end{array}$$

with the boundary conditions

$$\begin{array}{lll} I_1(z) \to 0, & I_2(z) \to I_2^*, & R(z) \to R_2^*, \\ J(z) \to J_2^*, & i_1(z) \to 0, & i_2(z) \to i_2^* \end{array}$$

as $z \to -\infty$ and the boundary conditions

$$\begin{array}{lll} I_1(z) \to I_1^*, & I_2(z) \to 0, & R(z) \to R_1^*, \\ J(z) \to J_1^*, & I_1(z) \to i_1^*, & i_2(z) \to 0 \end{array}$$

as $z \to +\infty$. Replacing these traveling-wave solutions in system (1)–(4), one gets

$$\begin{aligned} -v\,\frac{dI_1}{dz} &= a_1\,(1 - I_1 - I_2 - R - J)\,i_1 - b_1\,I_1, \\ -v\,\frac{dI_2}{dz} &= a_2\,(1 - I_1 - I_2 - R - J)\,i_2 - b_2\,I_2, \\ -v\,\frac{dR}{dz} &= c\,I_1 + c\,I_2 - (e + \mu)\,R - \bar{a}_1\,R\,i_1 - \bar{a}_2\,R\,i_2 + \bar{b}\,J, \\ -v\,\frac{dJ}{dz} &= \bar{a}_1\,R\,i_1 + \bar{a}_2\,R\,i_2 - (\bar{b} + \mu)\,J, \end{aligned}$$

and

$$\begin{aligned} -v\,\frac{di_1}{dz} &= a_1'\,(1 - i_1 - i_2)\,I_1 - b_1'\,i_1 + d\,\frac{d^2 i_1}{dz^2}, \\ -v\,\frac{di_2}{dz} &= a_2'\,(1 - i_1 - i_2)\,I_2 - b_2'\,i_2 + d\,\frac{d^2 i_2}{dz^2}. \end{aligned}$$

This system can be rewritten as a system of first-order ordinary differential equations by setting $j_1 = \frac{di_1}{dz}$ and $j_2 = \frac{di_2}{dz}$. Traveling-wave solutions correspond to nonnegative orbits of this new system, linking the steady state $[i_1 = i_1^*,\ j_1 = 0,\ I_1 = I_1^*,\ R = R_1^*,\ J = J_1^*,\ i_2 = 0,\ j_2 = 0,\ I_2 = 0]$ with the steady state $[i_1 = 0,\ j_1 = 0,\ I_1 = 0,\ R = R_2^*,\ J = J_2^*,\ i_2 = i_2^*,\ j_2 = 0,\ I_2 = I_2^*]$. Linearizing near the

latter, one gets the matrix

$$\begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{a_1' I_1^* + b_1'}{d} & \frac{-v}{d} & \frac{-a_1' s_1^*}{d} & 0 & 0 & \frac{a_1' I_1^*}{d} & 0 & 0 \\ \frac{-a_1 S_1^*}{v} & 0 & \frac{a_1 i_1^* + b_1}{v} & \frac{a_1 i_1^*}{v} & \frac{a_1 i_1^*}{v} & 0 & 0 & \frac{a_1 i_1^*}{v} \\ \frac{\bar{a}_1 R_1^*}{v} & 0 & \frac{-c}{v} & \frac{\bar{a}_1 i_1^* + e + \mu}{v} & \frac{-\bar{b}}{v} & \frac{\bar{a}_2 R_1^*}{v} & 0 & \frac{-c}{v} \\ \frac{-\bar{a}_1 R_1^*}{v} & 0 & 0 & \frac{-\bar{a}_1 i_1^*}{v} & \frac{\bar{b} + \mu}{v} & \frac{-\bar{a}_2 R_1^*}{v} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{b_2'}{d} & \frac{-v}{d} & \frac{-a_2' s_1^*}{d} \\ 0 & 0 & 0 & 0 & 0 & \frac{-a_2 S_1^*}{v} & 0 & \frac{b_2}{v} \end{pmatrix}.$$

For the orbits near this steady state to be positive, the eigenvalues of this matrix should all be real. Now consider the eigenvalues of the submatrix

$$\begin{pmatrix} 0 & 1 & 0 \\ \frac{b_2'}{d} & \frac{-v}{d} & \frac{-a_2' s_1^*}{d} \\ \frac{-a_2 S_1^*}{v} & 0 & \frac{b_2}{v} \end{pmatrix},$$

which are also eigenvalues of the full matrix. They are the roots of the polynomial equation $\chi(\lambda) = 0$, where

$$\chi(\lambda) = -\lambda^3 + \Big(\frac{b_2}{v} - \frac{v}{d}\Big)\lambda^2 + \frac{b_2 + b_2'}{d}\lambda + \frac{b_2\, b_2'}{v\, d}\Big(\frac{\alpha_2}{\alpha_1} - 1\Big).$$

PROPOSITION 1. *There exists a unique $v^* > 0$ such that the polynomial $\chi(\lambda)$ has a double root when $v = v^*$. Set*

$$y = \frac{b_2}{b_2'}, \quad z = \frac{\alpha_2}{\alpha_1} - 1.$$

The polynomial

$$\begin{aligned} F(X) = &\big[(1+y)^2 + 4\,y\,z\big]X^3 + 2\big[(1+y)^2\,(2+y) + 3\,(3+y)\,y\,z\big]X^2 \\ &+ y^2\,\big[(1+y)^2 - 6\,z\,(3+y) - 27\,z^2\big]X - 4\,y^4\,z \end{aligned}$$

has a unique positive root X^* and

$$v^* = \sqrt{b_2'\,d\,X^*}.$$

Proof. Set $\Lambda = \lambda - \frac{1}{3}\Big(\frac{b_2}{v} - \frac{v}{d}\Big)$. Then $\chi(\lambda) = -\chi_1(\Lambda)$, where $\chi_1(\Lambda)$ is of the form $\Lambda^3 + \mathcal{P}\,\Lambda + \mathcal{Q}$, with $\mathcal{P}$ and $\mathcal{Q}$ dependent on the parameters and on v. The polynomial $\chi_1(\Lambda)$ has a double root if and only if $4\mathcal{P}^3 + 27\mathcal{Q}^2 = 0$. Reordering this condition, one finds that it is equivalent to $F\Big(\frac{v^2}{b_2'\,d}\Big) = 0$. The proof that $F(X)$ indeed has a unique positive root is given in the appendix.

When $v < v^*$, the polynomial $\chi(\lambda)$ has complex eigenvalues, so the system cannot exhibit traveling waves. This situation, compared to previous studies on reaction-diffusion systems in which the minimum speed is the one actually selected by the system [13], suggests the following:

CONJECTURE 1. *The speed of traveling waves is v^*.*

Such a conjecture is generally called a "linear conjecture" for the reaction-diffusion system, since it has been obtained by linearizing the nonlinear system of partial differential equations near one steady state. Other studies [8] have demonstrated that for some models, such a conjecture holds only for a certain range of

parameter values. In [19], some sufficient conditions were given for the "linear conjecture" to hold for cooperative systems. In [12], these conditions were applied to a competition system that could be transformed through a change of unknowns into a cooperative system. Although the present competition model can also be transformed into a cooperative system as in [12], the sufficient conditions of [19] applied here become rather intractable.

Figure 2 shows the adimensional speed $v^*/\sqrt{b_2' d} = \sqrt{X^*}$ as a function of α_2/α_1 for different values of $y = b_2/b_2'$, found by solving numerically the third-order polynomial equation $F(X) = 0$ to get its unique positive root. Notice that $v^*/\sqrt{b_2' d}$ seems to be an increasing function of α_2/α_1. For $y \ll 1$, one obtains the approximate expression

$$X^* \underset{y\to 0}{\sim} \frac{-1 + 18\,z + 27\,z^2 + \sqrt{(-1 + 18\,z + 27\,z^2)^2 + 64\,z}}{8}\, y^2 .$$

The figure also shows the result of some numerical simulations of the nonlinear system of partial differential equations. Truncating the space to $-L < x < L$, starting from an initial condition in the form of a step function given by the stable equilibrium with resistant parasites for $x < -L/2$ and by the unstable equilibrium with sensitive parasites for $x > -L/2$, and waiting for the traveling wave to stabilize, the speed could be estimated numerically. The points in the figure correspond to $f = 30\%$, $f = 50\%$, $f = 70\%$, and $f = 100\%$. The other parameter values are the same as in section 5 (in particular, $y = 0.04$). To use the same grid with $L = 1,000$ km and $dx = 0.5$ km for the different simulations, the speed had to be estimated at different times when f varied (namely, after 50, 30, 20, and 15 years). For each case, the difference between the numerical speed and the speed from the conjecture was less than 1%. The details of the program (written for the software Scilab, www.scilab.org) can be found at www.bondy.ird.fr/∼bacaer/linearconjecture.sci.

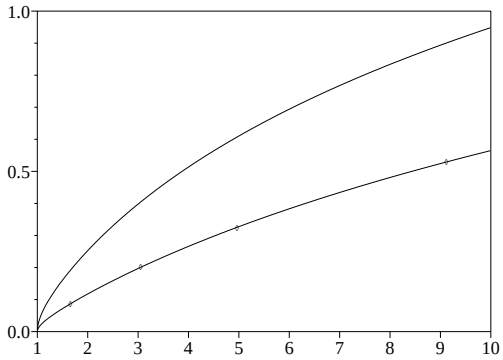

FIGURE 2. The adimensional speed $\sqrt{X^*} = v^*/\sqrt{b_2' d}$ as a function of α_2/α_1 for different values of $y = b_2/b_2'$, namely, $y = 0.04$ (below) and $y = 0.1$ (above). The points correspond to numerical simulations of the nonlinear system of partial differential equations.

Hence, these simulations tend to confirm the validity of the linear conjecture for the present model or at least for a certain range of paramater values including the ones used for the simulations.

5. **Discussion.** The main characteristics of the model are as follows:
   1. Resistance can spread only if the basic reproduction number α_2 of the resistant parasites is bigger than the basic reproduction number α_1 of the sensitive parasites.
   2. The ratio
   $$\frac{\alpha_2}{\alpha_1} = \frac{\exp(-b'_2\,T'_2)}{\exp(-b'_1\,T'_1)} \times \frac{\exp(-b_2\,T_2)}{\exp(-b_1\,T_1)} \times \frac{b_1\,b'_1}{b_2\,b'_2}$$
   is an increasing function of the fraction f of nonimmune infected humans who have access to the antimalarial drug, since $b_1 = b+c+\mu+\nu+f\,(\hat{b}-b)$. When $f = 0$, $\alpha_2/\alpha_1 < 1$ holds since parasites resistant to a drug are rare before the widespread use of that drug (the drug was designed for this reason). If $\alpha_2/\alpha_1 > 1$ for $f = 100\%$, then there is a threshold f^* such that resistance can spread only if $f > f^*$.
   3. The speed v^* at which resistance spreads depends on the ratio α_2/α_1, on the death rate b'_2 of mosquitoes infected by resistant parasites, on the recovery rate b_2 of nonimmune humans infected by resistant parasites, and on the diffusion coefficient of the mosquitoes. It is an increasing function of α_2/α_1.
   4. The speed v^* does not depend on the parameters concerning immune humans ($\bar{a}_1$, $\bar{a}_2$, e, and $\bar{b}$). This could be expected since no selective pressure is put on the parasites when they are hosted in immune humans.
   5. Finally, v^* does not depend on the intensity of transmission $k\,m/P$.

The qualitative result that resistance spreads faster in areas with better access to drugs is supported by fieldwork. In Senegal, for example, a country with a population of about ten million, one million malaria cases occur each year, causing 8,000 deaths. Resistance to CQ appeared in 1988 in Dakar, the capital city, and it has been increasing and spreading since then [16, 17]. In the study area of Mlomp, where an active control program promoting CQ had been conducted for many years ($f \simeq 100\%$), the emergence of resistance to CQ was particularly fast: no resistance in 1989, 10% in 1990, 51% in 1991, 71% in 1997. In the study area of Bandafassi in contrast, where no such program existed, emergence was much slower: first cases in 1993, 12% in 1994, 16% in 1995.

These data can serve as a comparison with our model. Some orders of magnitude for the parameters necessary to compute the speed v^* are shown in Table 1 (mortality has been neglected). Notice that infectiousness appears earlier ($T_2 < T_1$) in humans infected by resistant parasites, as suggested by the experimental results reviewed in [9]. For the parameters to accord with the fact that α_2/α_1 is less than 1 when $f = 0$, mosquitoes infected by resistant parasites must have a higher mortality ($b'_2 > b'_1$). The mortality of infected mosquitoes is also higher than the estimates for the mortality of uninfected mosquitoes ($\simeq 0.1$ day^{-1}) from [1]. The diffusion coefficient was estimated by the formula $d = L^2/t$, where $L \simeq 1$ km is the radius of the area a mosquito can explore during $t \simeq 1$ day.

With the estimates from Table 1, $y = b_2/b'_2 = 0.04$. If $f = 100\%$, then $\alpha_2/\alpha_1 \simeq 9.1$ and $v^* \simeq 86$ km/year. If $f = 30\%$ (an average estimate for Senegal [20]), then $\alpha_2/\alpha_1 \simeq 1.66$ and $v^* \simeq 14$ km/year. Hence, with these choices for the parameters, resistance spreads six times faster in an area with $f = 100\%$ than in an area

TABLE 1. Crude estimates for the parameters necessary to compute the speed v^*

Parameter	Symbol	Estimation
Mortality of i_1-mosquitoes	b'_1	0.12 day^{-1}
Mortality of i_2-mosquitoes	b'_2	0.2 day^{-1}
Recovery rate for nonimmunes	b	0.005 day^{-1}
Recovery rate with the drug	$\hat{b}$	0.1 day^{-1}
Rate of acquisition of immunity	c	0.003 day^{-1}
Latent period in mosquitoes	T'_1, T'_2	10 days
Latent period in I_1-humans	T_1	10 days
Latent period in I_2-humans	T_2	8 days
Mosquito diffusion	d	1 km^2/day

with $f = 30\%$. The threshold value f^* (corresponding to $\alpha_1 = \alpha_2$) above which resistance can spread is 17.6% (an estimate much more reasonable than the 89% found in [10, Fig. 3]).

Finally, it should be stressed that the model is intended to be only one step toward the development of more realistic spatial models of the diffusion of resistance to antimalarial drugs. Precise numerical values should be looked at without forgetting the numerous simplifying assumptions of the model, some of which may be relaxed in future work. Another direction not already mentioned would be to include spatial inhomogeneities between cities and countryside and temporal changes in the total human and mosquito population densities. For the mosquito density in particular, we did not consider seasonal variations, an important factor in Senegal, where mosquito density is highly related to rainfall.

Appendix. The fact that there is a unique positive root for $F(X)$ follows from elementary calculus, using that $y > 0$ and $z > 0$ (this last inequality is equivalent to $\alpha_2 > \alpha_1$). Indeed, let c_3, c_2, c_1, and c_0 be the coefficients of X^3, X^2, X, and 1 in $F(X)$. Notice that $c_3 > 0$, $c_2 > 0$, and $c_0 < 0$. The derivative $F'(X)$ is $3\,c_3\,X^2 + 2\,c_2\,X + c_1$. Simple inequalities can prove, using $y > 0$ and $z > 0$, that the discriminant of $F'(X)$, that is, $c_2^2 - 3\,c_1\,c_3$, is positive. Let X_1 and X_2 be the real roots of $F'(X)$. Then $X_1 + X_2 = -2\,c_2/(3\,c_3) < 0$ and $X_1\,X_2 = c_1/(3\,c_3)$.

If $c_1 \geq 0$, then $X_1\,X_2 \geq 0$; so, $X_1 < 0$ and $X_2 \leq 0$. In this case, $F(X)$ is monotone for $X > 0$ with $F(0) = c_0 < 0$, $F'(0) = c_1 \geq 0$, and $F(X) \to +\infty$ when $X \to +\infty$. Thus, there is a unique positive root of $F(X)$.

If $c_1 < 0$, then $X_1\,X_2 < 0$; so, $X_1 < 0$ and $X_2 > 0$. Hence $F'(X)$ changes its sign only once when $X > 0$. But $F(0) = c_0 < 0$, $F'(0) = c_1 < 0$, and $F(X) \to +\infty$ when $X \to +\infty$. So there is also a unique positive root of $F(X)$ in this case too.

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REFERENCES

[1] R. M. Anderson and R. M. May, INFECTIOUS DISEASES OF HUMANS: DYNAMICS AND CONTROL, Oxford University Press, Oxford, 1991.

[2] S. J. Aneke, MATHEMATICAL MODELLING OF DRUG RESISTANT MALARIA PARASITES AND VECTOR POPULATIONS, Math. Methods Appl. Sci. 25, no. 4 (2002), 335–46.

[3] A. Attaran, K. I. Barnes, C. Curtis, et al., WHO, the Global Fund, and Medical Malpractice in Malaria Treatment, Lancet 363, no. 9404 (2004), 237–40.
[4] P. B. Bloland, Drug Resistance in Malaria, WHO, Geneva, 2001.
[5] Z. Feng, D. L. Smith, F. E. McKenzie, and S. A. Levin, Coupling Ecology and Evolution: Malaria and the S-Gene across Time Scales, Math. Biosciences 189, no. 1 (2004), 1–19.
[6] R. A. Fisher, The Wave of Advance of Advantageous Genes, Ann. Eugenics 7 (1937), 355–69.
[7] I. M. Hastings, Modelling Parasite Drug Resistance: Lessons for Management and Control Strategies, Trop. Med. Intern. Health 6, no. 11 (2001), 883–90.
[8] Y. Hosono, The Minimal Speed of Traveling Fronts for a Diffusive Lotka-Volterra Competition Model, Bull. Math. Biol. 60, no. 3 (1998), 435–48.
[9] J. C. Koella, Costs and Benefits of Resistance against Antimalarial Drugs, Parasitology Today 14, no. 9 (1998), 360–64.
[10] J. C. Koella and R. Antia, Epidemiological Models for the Spread of Antimalarial Resistance, Malaria Journal 2 (2003), 3.
[11] R. Laxminarayan, ACT Now or Later: the Economics of Malaria Resistance, Resources for the Future, Washington DC, 2003.
[12] M. A. Lewis, B. Li, and H. F. Weinberger, Spreading Speed and Linear Determinacy for Two-Species Competition Models, J. Math. Biol. 45, no. 3 (2002), 219–33.
[13] J. D. Murray, Mathematical Biology, Springer-Verlag, New York, 1989.
[14] S. Ruan and D. Xiao, Stability of Steady States and Existence of Traveling Waves in a Vector Disease Model, Proc. Roy. Soc. Edinburgh (Section A) 134 (2004), 991–1011.
[15] J. Smoller, Shock Waves and Reaction Diffusion Equations, Springer-Verlag, New York, 1981.
[16] C. S. Sokhna, J.-F. Molez, P. Ndiaye, B. Sane, and J.-F. Trape, Tests in vivo de chimiosensibilité de Plasmodium Falciparum à la chloroquine au Sénégal: évolution de la résistance et estimation de l'efficacité thérapeutique, Bull. Soc. Path. Ex. 90 (1997), 83–89.
[17] J.-F. Trape, P. Agnamey, C. Enel, et al., Impact de l'introduction de l'association artesunate-amodiaquine sur l'évolution de la mortalité palustre en zone rurale au Sénégal, Médecine Tropicale 63 (2003), 301.
[18] J.-F. Trape, G. Pison, M.-P. Preziosi, et al., Impact of Chloroquine Resistance on Malaria Mortality, C. R. Acad. Sci. (Série III) 321, no. 8 (1998), 689–97.
[19] H. F. Weinberger, M. A. Lewis, and B. Li, Analysis of Linear Determinacy for Spread in Cooperative Models, J. Math. Biol. 45, no. 3 (2002), 183–218.
[20] WHO/UNICEF, The Africa Malaria Report 2003, WHO/UNICEF, 2003.

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E-mail address: bacaer@bondy.ird.fr
E-mail address: Cheikh.Sokhna@ird.sn