Multiple endemic equilibria for a multipatch Ross-Macdonald model with fast migrations

Pierre AUGER[1] — Gauthier SALLET[1,3]
Maurice TCHUENTÉ[1,2] — Berge TSANOU[2,3,4]

[1] IRD UMMISCO, 43 Avenue Henri Varagnat 92400, Bondy Cedex, France,
Pierre.Auger@bondy.ird.fr
[2] University of Yaounde I, UMI 209 UMMISCO, Faculty of Sciences, P.O. Box 812 Yaounde, Cameroon,
Maurice.Tchuente@ens-lyon.fr
[3] INRIA-MASAIE Grand-Est, LMAM-CNRS UMR 7122, Metz-France,
sallet@loria@.fr
[4] University of Dschang, Faculty of Sciences, P.O. Box 67, Dschang-Cameroon,
LIRIMA-GRIMCAPE Yaounde Camreoun, Corresponding author
bergetsanou@yahoo.fr

RÉSUMÉ. Nous étudions l'extension du modèle classique de Ross-Macdonald aux environnements hétérogènes formés de plusieurs zones géographiques. Nous supposons que les hôtes humains migrent entre les zones et que les moustiques ne migrent pas. Le cas particulier où le taux migration ne dépend pas du statut épidémiologique a été complètement étudié dans [1]. Ici, nous nous intéressons au cas où le taux migration varie selon le staut épidémiologique. En supposant que le phénomène de migration est plus rapide que le phénomène épidémiologique, nous nous servons de la méthode d'aggrégation de variables (voir [7]) pour réduire le modèle. Nous donnons une formule pour le taux de reproduction de base $\mathcal{R}_0$, et montrons par des simulations numériques que lorsque $\mathcal{R}_0 < 1$ l'équilibre sans maladie (DFE) est globalement stable. Nous montrons aussi que pour $\mathcal{R}_0 > 1$, le modèle admet plusieurs équilibres endémiques.

ABSTRACT. We study the extension of the classical Ross-Macdonald model which describes the dynamics of malaria, to heterogeneous environments composed of several geographics zones. We assume that the hosts migrate between zones while mosquitoes do not. The particular case where the rate of migration does not depend on the epidemiological status was completely studied in [1]. Here we are interested in the case where the migration rates vary with the epidemiological compartments. Assuming that migrations are fast compared to the speed of the epidemiological phenomenon, we use the aggregation method (see [7]) to reduce the model and give an explicit formula for the basic reproduction ratio $\mathcal{R}_0$. We show using numerical simulations that if $\mathcal{R}_0 < 1$, then the disease free equilibrium (DFE), is globally stable. When $\mathcal{R}_0 > 1$, we show that the model has multiple endemic equilibria.

MOTS-CLÉS : Modèle de metapopulation, Ross-Macdonald, dynamique, migration rapide, taux de reproduction de base, équilibres endémiques.

KEYWORDS : Metapopulation models, Ross-Macdonald, dynamics, fast migration, basic reproduction ratio, endemic equilibria.

1. Introduction

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes.
According to a recent World Malaria Report (see [6]), there were around 243 millions cases of malaria in 2008 worldwide. The vast majority of cases (85 %) were in the African Region. Malaria accounted for an estimated 863 000 deaths in 2008, of which (89 percent) were in the African Region. Malaria is preventable and curable. Therefore, there is a strong need to understand the key factors in the transmission of malaria in order to formulate effective prevention and control strategies for this disease. Among the key factors in the transmission is the spatial or geographic heterogeneities that can be modeled using an approach based on the metapopulation concept. Here, the space is considered discrete and one considers sparsely populated geographic zones, corresponding to locations such as villages where groups of human population are located (see [1]-[2]), with migrations between zones. Within a zone or patch, the human population is subdivided into compartments corresponding to different epidemiological status. In this paper, we use the formulation that considers local infections within patches, with migrations of humans (hosts) between patches (see [1]).
Classically, the basic reproduction ratio $\mathcal{R}_0$, is defined as the number of new infections produced by a typical infective individual introduced in a susceptible population (see [5], [4], [3]). Unlike the classical model introduced by Ross and Macdonald, that has a unique stable disease free equilibrium when $\mathcal{R}_0 \leq 1$ and a unique endemic equilibrium when $\mathcal{R}_0 > 1$, the model presented here exhibits a different behavior. Indeed, we show that if the migration process is faster than the epidemic phenomenon, and the migration rates of susceptible humans are different from those of infective hosts, then there can be multiple equilibria for $\mathcal{R}_0 > 1$.
The remaining of this paper is organized as follows : the general multipatch
Ross-Macdonald model is presented in section 2 ; assuming fast migrations, the aggregated method is used to obtain a reduced model in section 3 ; the formula for $\mathcal{R}_0$ is presented in section 4 and the existence of endemic equilibria is shown in section 5.

2. Model formulation

2.1. Notations

We start with the extension of the Ross-Macdonald model in [1] , in a particular case where the mosquitoes are present in all patches and the rate of migration of susceptible hosts are different from those of infectives. We use the following notations and definitions :

n : the total number of geographic zones (patches), numbered from 1 to n
H_i, V_i : the total host and mosquitoes populations of patch i, respectively,
H, V : the total host (susceptibles and infectives) and mosquitoes populations respectively,
$S_{h,i}$, $I_{h,i}$: the susceptible and infective host populations patch i, respectively,
S_{oh}, I_{oh} : the total susceptible host and infective host populations respectively,
$I_{v,i}$: the infectious mosquitoes population of patch i,
a_i : the man biting rate of mosquitoes in patch i,
$b_{1,i}$: the proportion of infectious bites on hosts that produce a patent infection in patch i,
$b_{2,i}$: the proportion of bites by susceptible mosquitoes on infectious hosts that produce an infection in patch i,
$\gamma_{h,i}$: the per capita rate of host recovery from infection in patch i,
$\mu_{v,i}$: the per capita rate of mosquito mortality in patch i,
$m^s_{i,j}$: the migration rate of susceptible hosts form patch j to patch i,
$m^I_{i,j}$: the migration rate of infectious hosts form patch j to patch i,

2.2. Hypothesis

We assume that the migration phenomenon is faster than the epidemiological process. This means that there are two time scales : a first one τ for the migration process and the second one t for the epidemiological process. Thus, $t = \varepsilon\,\tau$, where ε is a very small positive number. For instance if $\varepsilon = 0.01$, then for a migration time $\tau = 100$, the epidemiological time is $t = 1$. As in classical Ross-Macdonald model, we neglect the natural morbidity rate $\mu_{h,i}$ of (hosts) and the recovery rates $\gamma_{v,i}$ of mosquitoes for $i = 1, ..., n$.

2.3. The complete model

The differentiation with respect to the migration process time scale τ leads to the following system of equations :

$$\dot{S}_{h,i} = \sum_{j\neq i}^{n} m^s_{i,j}\, S_{h,j} - S_{h,i} \sum_{j\neq i}^{n} m^s_{j,i} - \varepsilon\, b_{1,i}\, a_i\, I_{v,i}\, \frac{S_{h,i}}{H_i} + \varepsilon\, \gamma_{h,i}\, I_{h,i} \tag{1}$$

$$\dot{I}_{h,i} = \sum_{j\neq i}^{n} m^I_{i,j}\, I_{h,j} - I_{h,i} \sum_{j\neq i}^{n} m^I_{j,i} + \varepsilon\, b_{1,i}\, a_i\, I_{v,i}\, \frac{S_{h,i}}{H_i} - \varepsilon\, \gamma_{h,i}\, I_{h,i} \tag{2}$$

$$\dot{I}_{v,i} = \varepsilon\, b_{2,i}\, a_i\, (V_i - I_{v,i})\, \frac{I_{h,i}}{H_i} - \varepsilon\, \mu_{v,i}\, I_{v,i} \tag{3}$$

2.4. Remarks

It's worth noting if $m^s_{i,j} = m^I_{i,j} = m_{i,j}$ for all i, j, (i.e the migration rates do not depend on the epidemiological status of hosts), then one can sum equations (1) and (2) to obtain the single equation
$\dot{H}_{h,i} = \sum_{j\neq i}^{n} m_{i,j}\, H_{h,j} - H_{h,i} \sum_{j\neq i}^{n} m_{j,i}$ that governs the evolution of the total host population in the different patches, then study the coupling of that equation with equations (2) and (3). This particular case was solved in [1]. Hereafter, we assume that the rates of migration depend on the epidemiological status of the host (i.e, there exist i, j such that $m^s_{i,j} \neq m^I_{i,j}$).

3. Reduction of the model

Thanks to the existence of two times scales, a fast one for migration and a slow one for the epidemiological process, we can apply the "aggregation method" and proceed in two steps as follows :
Step 1 : neglect terms of order of ε in the complete system, and find the stable equilibria for the fast system.
Step 2 : substitute the fast equilibrium into the equations of the initial model (see [7]) in order to obtain the reduced equivalent model. This aggregated model is much simpler and can be used to compute the basic reproduction number of the system.

3.1. Analysis of the fast system : ($\varepsilon = 0$)

3.1.1. Fast equilibria and their stability

Let $\varepsilon = 0$, $S_h = (S_{h,1}, S_{h,2}, ..., S_{h,n})$ $I_h = (I_{h,1}, I_{h,2}, ..., I_{h,n})$ We define the matrices M^s and M^I describing the movements of susceptible hosts and infected hosts respectively as follows :
$M^s(i,j) = m^s_{i,j},\ M^s(i,i) = -\sum_{j=1,j\neq i}^{n} m^s_{j,i}$; $M^I(i,j) = m^I_{i,j},\ M^I(i,i) = -\sum_{j=1,j\neq i}^{n} m^I_{j,i}$
With theses notations $(1-2)$ becomes

$$\dot{S}_h = M^s\, S_h \tag{4}$$

$$\dot{I}_h = M^I\, I_h \tag{5}$$

Assume as in [1] that the matrices M^s and M^I are irreducible. Following the proof in [1], since these matrices are positive, it's easy to show that there exists a unique equilibrium for the susceptible hosts (see (4)) and a unique equilibrium for the infected hosts (see (5)) each of which is asymptotically stable. In order to obtain these equilibria, first observe that for $\varepsilon = 0$, then the total susceptible host S_{oh} and the total infective host I_{oh} are constant since $\sum_{i=1}^{n} \dot{S}_{h,i} = \sum_{i=1}^{n} \dot{I}_{h,i} = 0$, in other words the total susceptible hosts and the total infected hosts are both constant such that $H = S_{oh} + I_{oh}$ is also a constant. Therefore, if we denote by $\overline{S_h}$ and $\overline{I_h}$ the aforementioned fast equilibria, then by [1] there exist positive vectors W^s and W^I such that : $\overline{S_h} = S_{oh}\, W^s, \quad \overline{I_h} = I_{oh}\, W^I$; Moreover $W^s = (d_1, d_2, \ldots, d_n),\ W^I = (c_1, c_2, \ldots, c_n)\,,\ \sum_{i=1}^{n} d_i = \sum_{i=1}^{n} c_i = 1$; where d_i, c_i are positve real numbers depending on $M^s_{i,j}$ and $M^I_{i,j}$ respectively.

3.2. Aggregated model : Reduced system

Here we substitute the fast equilibria $\overline{S_{h,i}} = S_{oh}\, d_i$ and $\overline{I_{h,i}} = I_{oh}\, c_i$ into the initial system and sum over the host population to get the model governing the evolution of the total host population and the evolution of the mosquitoes populations in each patch.
For the sake of simplicity, let's denote : $\sum_{i=1}^{n} S_{h,i} = S_{oh},\ \sum_{i=1}^{n} I_{h,i} = I_{oh},\ \gamma_i = \gamma_{h,i},\ \mu_i = \mu_{v,i}$
According to the above remark, the total host population
$H = \sum_{i=1}^{n} S_{h,i} + \sum_{i=1}^{n} I_{h,i} = \sum_{i=1}^{n} \overline{S_{h,i}} + \sum_{i=1}^{n} \overline{I_{h,i}} = S_{oh} + I_{oh}$ is constant. We have $S_{oh} = H - I_{oh}$.
Let us normalize the host variables by setting :

$$x = \frac{I_{oh}}{H}\ , y_i = \frac{I_{v,i}}{V_i}\ , m_i = \frac{V_i}{H}\ , \beta_{1,i} = b_{1,i}\, a_i\ , \beta_{2,i} = b_{2,i}\, a_i\ , \gamma = \sum_{i=1}^{n} \gamma_i\, c_i$$

System (1-2-3) becomes

$$\dot{x} = \sum_{i=1}^{n} \beta_{1,i}\, m_i\, d_i\, y_i\, \frac{(1-x)}{c_i\, x + d_i\, (1-x)} - \gamma\, x \tag{6}$$

$$\dot{y}_i = \beta_{2,i}\, c_i\, x\, \frac{(1-y_i)}{c_i\, x + d_i\, (1-x)} - \mu_i\, y_i \qquad \forall i = 1, ..., n \tag{7}$$

Hereafter, we shall focus our analysis on system (6-7) which is our equivalent aggregated system. Observe at first that this system is mathematically well posed in the biological feasible domain $\mathcal{K} = \{(x, y_i) | x \in [0; 1]; y_i \in [0; 1]; \forall i = 1, ..., n\}$, which is a subset of $[0; 1]^{n+1}$. This is easily checked since its vector field point inward on the faces of $\mathcal{K}$.

Proposition 1 *: System (6-7) is cooperative and strongly monotone in $\mathcal{K}$.*

The proof of this proposition is straightforward. One just needs to check that the jacobian matrix associated with system (6-7) is a Metzler and irreducible matrix in $\mathcal{K}$.

4. The basic reproduction ratio $\mathcal{R}_0$

The basic reproduction ratio $\mathcal{R}_0$ is given by the following theorem.

Theorem 1 *: The basic reproduction ratio $\mathcal{R}_0$ is given by the following expression :*

$$\mathcal{R}_0^2 = \sum_{i=1}^{n} \frac{\beta_{1,i}\, \beta_{2,i}\, m_i\, c_i}{\gamma\, \mu_i\, d_i}$$

Proof : Following the method presented in [4], we classify the $(n+1)$ compartments into two classes : infected and uninfected, and we consider

$$\mathcal{F} = (\sum_{i=1}^{n} \beta_{1,i}\, m_i\, d_i\, y_i\, \frac{(1-x)}{c_i\, x + d_i\,(1-x)};\ \beta_{2,1}\, c_1\, x\, \frac{(1-y_1)}{c_1\, x + d_1\,(1-x)};$$

$$\beta_{2,2}\, c_2\, x\, \frac{(1-y_2)}{c_2\, x + d_2\,(1-x)};\ \cdots;\ \beta_{2,n}\, c_n\, x\, \frac{(1-y_n)}{c_n\, x + d_n\,(1-x)})^T$$

Here, $\mathcal{F}$ is a $(n+1)\times 1$ vector and represents the input rate of new infections in the entire population (see [4]). Furthermore, we define

$$\mathcal{V} = (\gamma\, x; \mu_1\, y_1; \mu_2\, y_2; \cdots; \mu_n\, y_n)^T$$

Here, $\mathcal{V}$ is $(n+1)\times 1$ vector and represents the net decreasing rate of infected classes due to migrations (movements), recovery, and death inside the population (see [4]).
We define $X = (x, y_1, y_2, ..., y_n)$, $F = \mathcal{D}_X\, \mathcal{F}(0;0)$, and $V = \mathcal{D}_X\, \mathcal{V}(0;0)$. According to ([5], [4]) the matrix FV^{-1} is called the *next generation matrix*, its greatest eigenvalue is the basic reproduction ratio for system (6-7), i.e $\mathcal{R}_0 = \rho(FV^{-1})$, with

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\beta_{1,1}\, m_1}{\mu_1} & \cdots & \frac{\beta_{1,n}\, m_n}{\mu_n} \\ \frac{\beta_{2,1}\, c_1}{\gamma\, d_1} & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\beta_{2,n}\, c_n}{\gamma\, d_n} & 0 & \cdots & 0 \end{bmatrix},$$

which is a rank 2 and irreducible matrix, it has 2 opposite real eigenvalues. Furthermore,

$$\det(FV^{-1} - \lambda\, I_{n+1}) = \lambda^{n-1} \left(\lambda^2 - \sum_{i=1}^{n} \frac{\beta_{1,i}\, \beta_{2,i}\, m_i\, c_i}{\gamma\, \mu_i\, d_i}\right).$$

Hence $\mathcal{R}_0$ is the only positive eigenvalue of FV^{-1} and,

$$\mathcal{R}_0^2 = \sum_{i=1}^{n} \frac{\beta_{1,i}\, \beta_{2,i}\, m_i\, c_i}{\gamma\, \mu_i\, d_i}$$

With this explicit formulae of $\mathcal{R}_0$, we can point out some remarkable particular cases

Case 1 : If $n = 1$, $\mathcal{R}_0$ is exactly the reproduction number the classical Ross-Macdonald model.
Case 2 : Assume the migration rates are independent of the epidemiological status and that the epidemiological parameters are the same for all patches. It follows that $d_i = c_i$ and $\beta_{1,i} = \beta_1,\ \beta_{2,i} = \beta_2,\ \mu_i = \mu,\ \gamma_i = \gamma^*$. Therefore $\mathcal{R}_0^2 = \frac{\beta_1\, \beta_2}{\gamma^*\, \mu}\, \frac{V}{H}$ where $V = \sum_{i=1}^{n} V_i$ is the overall vector (mosquito) population. Once again, as in the first case, the formulae for $\mathcal{R}_0$ looks like that of the classical one patch Ross-Macdonald model if the quantity $m = \frac{V}{H}$ stands for the total vector density.

5. Existence of endemic equilibria

5.1. Existence of at least one endemic equilibrium : General case

We use the intermediate value theorem to prove the existence of at least one EE.

Theorem 2 *: If $\mathcal{R}_0 > 1$, then there exist at least one endemic equilibrium for system* $(6-7)$

Proof : It's easy to check (after some substitutions) that $(\bar{x}, \bar{y}_i) \gg 0$ is an endemic equilibrium of system $(6-7)$ if and only if the following equations are satisfied :

$$\bar{y}_i = \frac{\beta_{2,i}\, c_i\, \bar{x}}{\beta_{2,i}\, c_i\, \bar{x} + \mu_i[c_i\, \bar{x} + d_i\, (1-\bar{x})]} \tag{8}$$

$$F(\bar{x}) = \frac{Q(\bar{x})}{\gamma + \bar{x}\, Q(\bar{x})} = 1 \tag{9}$$

where

$$Q(\bar{x}) = \sum_{i=1}^{n} \frac{\beta_{1,i}\, \beta_{2,i}\, mi\, c_i\, d_i}{[c_i\, \bar{x} + d_i\, (1-\bar{x})]\, [\beta_{2,i}\, c_i\, \bar{x} + \mu_i\, [c_i\, \bar{x} + d_i\, (1-\bar{x})]]}$$

If the function $F(\bar{x})$ denotes the right side of (9), and $G(\bar{x}) = F(\bar{x}) - 1$, then
$G(0) = \mathcal{R}_o^2 - 1 > 0$ and $\lim_{\bar{x}\to+\infty} G(\bar{x}) = -1 < 0$, if $\mathcal{R}_o^2 > 1$. Thus, using the intermediate value theorem on $G(\bar{x})$, we conclude that there exist at least one solution $\bar{x} > 0$ for equation (9), therefore, replacing $\bar{x}$ in equation (8), we have $\bar{y}_i > 0$, and the theorem is proven.

5.2. Existence of multiple equilibria : Case of 2 patches (n=2)

Let's us call the *total force of infection* of the infected host population, the quantity

$$\lambda_h = \sum_{i=1}^{n} \beta_{1,i}\, m_i\, d_i\, \frac{y_i}{c_i\, x + d_i\, (1-x)}$$

then, the existence of endemic solutions problem reduces to the seeking of solutions of : $H(\lambda_h) = 1$, where

$$H(\lambda_h) = (\gamma + \lambda_h) \sum_{i=1}^{n} \frac{\beta_{1,i}\, \beta_{2,i}\, m_i\, c_i\, d_i}{[c_i\, \lambda_h + \gamma\, d_i]\, [\mu_i\, d_i\, \gamma + \lambda_h\, (\mu_i\, c_i + \beta_{2,i}\, c_i)]} = 1 \tag{10}$$

When $n = 2$, we set : $A_i = \beta_{1,i}\, \beta_{2,i}\, m_i\, c_i\, d_i$; $B_i = \mu_i\, c_i + \beta_{2,i}\, c_i$; $K_i = \mu_i\, d_i\, c_i + d_i\, B_i$
and equation (10) is equivalent to the following polynomial equation

$$A\, \lambda_h^4 + B\, \lambda_h^3 + C\, \lambda_h^2 + D\, \lambda_h + E = 0 \tag{11}$$

where

$A = c_1\, c_2\, B_1\, B_2 > 0$; $B = \gamma\, (c_1\, B_1\, K_2 + c_2\, d_2\, B_1) - A_1\, c_2\, B_2 - A_2\, c_1\, B_1$

$C = \gamma^2\, \left(\mu_1\, d_1^2\, c_2\, B_2 + \mu_2\, d_2^2\, c_1\, B_1 + K_1\, K_2\right) - \gamma\, [A_1\, (K_2 + c_2\, B_2) + A_2\, (K_1 + c_1\, B_1)]$

$D = \gamma^3\, \left(\mu_1\, d_1^2\, K_2 + \mu_2\, d_2^2\, K_1\right) - \gamma^2\, \left[A_1\, \left(K_2 + \mu_2\, d_2^2\right) + A_2\, \left(K_1 + \mu_1\, d_1^2\right)\right]$

$E = \gamma^3\, \left(\gamma\, \mu_1 \mu_2\, d_1^2\, d_2^2 - A_1\, \mu_2\, d_2^2 - A_2\, \mu_1\, d_1^2\right) = \gamma^4\, \mu_1 \mu_2\, d_1^2\, d_2^2\, \left(1 - \mathcal{R}_0^2\right)$

It can be easily seen that $A > 0$ (since all the model parameters are non-negative). Further, $E > 0$ whenever $\mathcal{R}_0^2 < 1$ ($\mathcal{R}_0 < 1$). Thus, the number of possible positive real roots of (11) depends on the signs of $B,\ C,\ D$. This can be analyzed using the Descartes Rules of Signs of the polynomial : $P(z) = A\,z^4 + B\,z^3 + C\,z^2 + D\,z + E$ given by (11) (with $z = \lambda_h$). The various possibilities for the positive roots of $P(z)$ are displayed in the following table . Moreover this table inspired the next theorem :

Cases	A	B	C	D	E	$\mathcal{R}_0$	Nb of sign changes	Nb of + roots
1	+	+	+	+	-	$\mathcal{R}_0 > 1$	1	1
2	+	-	-	-	-	$\mathcal{R}_0 > 1$	1	1
3	+	+	-	-	-	$\mathcal{R}_0 > 1$	1	1
4	+	+	+	-	-	$\mathcal{R}_0 > 1$	1	1
5	+	-	+	-	-	$\mathcal{R}_0 > 1$	3	1,3
6	+	-	-	+	-	$\mathcal{R}_0 > 1$	3	1,3
7	+	+	-	+	-	$\mathcal{R}_0 > 1$	3	1,3
8	+	-	+	+	-	$\mathcal{R}_0 > 1$	3	1,3

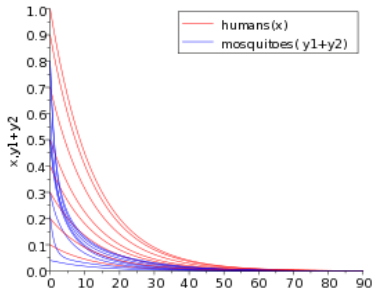
Theorem 3 *: The aggregated model (6-7) always has endemic equilibria if $\mathcal{R}_0 > 1$ and*
(i) has a unique endemic equilibrium if $\mathcal{R}_0 > 1$ and cases 1 to 4 are satisfied ;
(ii) could have more than one endemic equilibrium if $\mathcal{R}_0 > 1$ and cases 5 to 8 are satisfied

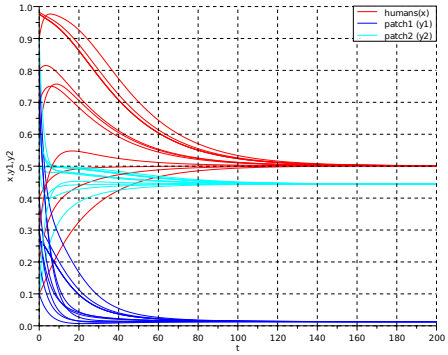
5.3. Numerical simulations and Discussions

Figure 1 illustrate the global stability of the DFE, when parameters are : $\beta_{1,1} = 0.1,\ \beta_{1,2} = 0.15,\ \beta_{2,1} = 0.08,\ \beta_{2,2} = 0.09,\ m_1 = 0.01,\ m_2 = 0.02,\ c_1 = 0.01,\ c_2 = 0.99,\ d_1 = 0.7,\ d_2 = 0.3,\ \mu_1 = 0.2,\ \mu_2 = 0.8,\ \gamma_1 = 0.16,\ \gamma_2 = 0.08$ and $\mathcal{R}_0 = 0.0138548 < 1$

We choose the time unit as a day, and consider parameters which are nearest relevant to plasmodium falciparum malaria and anopheles gambiae. We choose the migration rates $m_{1,2}^S, m_{2,1}^S, m_{1,2}^I, m_{2,1}^I$ such that
$c_1 = 0.01, c_2 = 0.99; d_1 = 0.75; d_2 = 0.25$; and other parameters to be :
$\beta_{11} = 0.15; \beta_{12} = 0.18; \beta_{21} = 0.12; \beta_{22} = 0.2; m_1 = 0.3; m_2 = 0.4; \mu_1 = 0.2 = \mu_2; \gamma_1 = 0.01; \gamma_2 = 0.02$. With this set of parameters, we fall in case 5 of the above table , where there are 3 sign changes but one endemic equilibrium : namely $\lambda_h = 0.0142304$ corresponding to ($\bar{x} = 0.4169421, \bar{y}_1 = 0.0093562, \bar{y}_2 = 0.424965$) and $\mathcal{R}_0 = 14.345729$, whereas the following set of parameters : $\beta_{11} = 0.27; \beta_{12} = 0.25; \beta_{21} = 0.2; \beta_{22} = 0.25; m_1 = 0.3; m_2 = 0.4; c_1 = 0.01$; $c_2 = 0.99; d_1 = 0.75; d_2 = 0.25; \mu_1 = 0.2; \mu_2 = 0.25; \gamma_1 = 0.01; \gamma_2 = 0.02$ remains in case 5 of table1 with 3 endemic equilibria. Namely : $\lambda_{h_1} = 0.0202847$; $\lambda_{h_2} = 0.8535569; \lambda_{h_3} = 1.1767786$ corresponding to $EE_1 = (\bar{x}_1 = 0.5047866, \bar{y}_{11} = 0.0132314, \bar{y}_{21} = 0.4448921)$; $EE_2 = (\bar{x}_2 = 0.9772170, \bar{y}_{12} = 0.2667687, \bar{y}_{22} = 0.4985325)$ and $EE_3 = (\bar{x}_3 = 0.9833706, \bar{y}_{13} = 0.3059701, \bar{y}_{23} = 0.4989347)$ respectively, with $\mathcal{R}_0 = 19.953769$ and $EE_1 \ll EE_2 \ll EE_3$. Linearizing the model around these equilibria shows that the eigenvalue of the jacobian matrices of the model taken at EE_1 and EE_3 are all real and negative , whereas the jacobian matrix taken atEE_2 have a positive eigenvalue. Therefore EE_1 and EE_3 are locally stable and EE_2 is unstable. Moreover, one can notice that EE_1 is effectively in the interior of $\mathcal{K}$, and EE_2, EE_3 are approximately on the face of the boundary of $\mathcal{K}$ defined by $x = 1$. Therefore, simulations in the case of multiple equilibria, show that the solutions will converge to the interior endemic equilibrium. This remark is pertinent according to figure 2 . Interchanging d_1 and c_1 in this last simulation, and keeping the other parameters unchanged, we fall in case 3 of the above table , where there is only one sign change with one endemic equilibrium. Recall, here $\mathcal{R}_0 = 488.0202$ and $\lambda_h = 0.0334814$. So the change in migration rates can deeply influence the dynamic behavior of the model. For instance the number of endemic equilibria can move from 3 to 1 and vice-versa according to migration rates changes.
Figure 1 conjecture the global stability of the DFE and therefore rule out the possibility of having other endemic

equilibria than the DFE when $\mathcal{R}_0 < 1$. We did not succeed in proven this analytically but we think that the theory of "convergence almost everywhere" of M. W. Hirsch will be applied conveniently in this case since the model is monotone.





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