Method for Identifying Spatial Reservoirs of Malaria Infection and Control Strategies

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***Abstract*—Managing spatial reservoirs of malaria infection plays a crucial role in effective disease control. In this paper, a reservoir of infection refers to one or more interconnected subpopulations that sustain the epidemic at the level of the metapopulation to which applying a (linear) control strategy suffices to eradicate the disease in the whole system. We propose a numerical method to explain the steps for identifying reservoirs of malaria infection within n connected regions with the explicit movement of human population from the previous theoretical results in order to design an efficient computational tool. Furthermore, we determine the minimal percentage (critical vaccination fraction) of susceptible individuals in the reservoirs that should be protected to eliminate malaria. The costs and cost-effectiveness of malaria control interventions were analysed considering two strategies of control. (i) protecting the minimal fraction of susceptible individual; (ii) protecting any fraction greater than the minimal fraction. Cost-effectiveness analysis shows that the less cost and more effective strategy is to vaccinate (or protect) the minimal fraction of susceptible human in the reservoir of infection to halt outbreak. A numerical example provides insight into the efficiency of this approach.**

***Index Terms*—Control, Optimization, Metapopulation, Basic reproductive number, cost-effectiveness analysis.**

I. Introduction

Malaria is a mosquito-borne infections disease caused by protozoa of the genus plasmodium (parasite). It is estimated that about 1.5–3 million of people, mostly children, die of malaria every year [29]. Malaria control requires an integrated approach, including prevention and prompt treatment [30].

The parasites are transmitted indirectly from human to human by the bite of infected female mosquitoes of the genus Anopheles. There is some natural acquired partial immunity to the pathogen in humans developed after many years of repeated infections [4], [8], [16], [24].

Models have already been proposed to provide an explicit framework for understanding malaria transmission dynamics in human population for over 100 years [6], [10], [20], [22] and references there in. Human movement has rarely been taken into account in models. Recently, it was shown that the role of human movement plays a signif cant role on disease reemergence and persistence [2], [5], [23]. There are two standard approaches to study the spatial dynamics of vector borne disease such as malaria: partial differential equations [19], [31], [32], [33] and meta-population models [3], [18], [31]. More precisely, in [3], a metapopulation malaria model was proposed using SI and SIRS models for the vectors and hosts, respectively. The mobility of human population has been proved to have a signif cant impact on the epidemic behavior. For example, the impact of the movement of human population on malaria transmission in different realistic situations: from rural into urban areas and colonization of heretofore unused territories was performed. Using type reproduction numbers approach developed in [14], [26], the authors identify the reservoirs of infection and evaluate the effect of control measures. We point out that the reservoirs of infection remain variously and loosely def ned in the literature [12], [13], [27], [28]. In this paper, a reservoir of infection is a subpopulation to which applying a (linear) control strategy suff ces to eradicate the disease in the whole system [3], [14], [26]. A reservoir may comprise multiple connected subpopulation of human and/or mosquitoes. Thus to reduce or eliminate malaria over time, a control should be applied simultaneously in the different reservoirs of infection, but the minimal fraction of susceptible individuals of each reservoir to be protected is not specif ed, thus a control like that should be cost a great deal of money. Therefore arise the following question, what minimal fraction of each group of the reservoir should be protected to eliminate malaria? This minimal fraction can be interpreted as the critical vaccination fraction (fraction of population to vaccinate to halt outbreak).

The main purpose of this paper is threefold: (i) to explain the steps for identifying reservoirs of malaria infection from the theoretical results derived in [3] in order to design an eff cient computational tool; (ii) determine the minimal percentage of susceptible individuals in the reservoir namely, those that should be protected to eliminate the malaria over time in the whole of the region; (iii) analysis the cost and cost-effectiveness when controlling infection within the reservoir from the minimal percentage of susceptible individuals to protect. Cost-effectiveness analysis is very important because it compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money [1], [25]. This informs decision-makers who have to determine where to allocate limited healthcare resources.

II. Description of model formulation

In this section we give a summary of the model as already discussed in [3] before to extend it. The space was split into n geographical regions. For each geographical unity i, $i = 1, \dots, n$, human population was divided into three subclasses: susceptible $S_{H,i}(t)$, infectious $I_{H,i}(t)$ and semi-immune $R_{H,i}(t)$. Total size of the human population $H_i(t) = S_{H,i}(t) + I_{H,i}(t) + R_{H,i}(t)$ and the mosquito population into two subclasses: susceptible $S_{V,i}(t)$ and infectious $I_{V,i}(t)$. Total mosquito population $V_i(t) = S_{V,i}(t) + I_{V,i}(t)$. Table III summarizes the model parameters as well as their biological interpretation and Table I summarizes the state variables.

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TABLE I
THE STATE VARIABLES

State variables for humans
$S_{H,i}(t)$: susceptible class
$I_{H,i}(t)$: infectious class
$R_{H,i}(t)$: semi-immune class
$H_i(t)$: total size of the human population
$\Phi_{H,i}$ force of infection from mosquitoes to humans
State variables for mosquitoes
$S_{V,i}(t)$: susceptible class
$I_{V,i}(t)$: infectious class
$V_i(t)$: total mosquito population
$\Phi_{V,i}$: force of infection from humans to mosquitoes

Humans were assumed move from patch to patch but the movement of mosquitoes was neglected, so humans were assumed do not change their epidemiological status during travel. The model was read as follows: for each $i = 1, \ldots, n$,

$$\begin{aligned} \frac{dS_{H,i}}{dt} &= \Lambda_{H,i} + \beta_{H,i}R_{H,i} + \rho_{H,i}I_{H,i} - \mu_{H,i}S_{H,i} \\ &\quad - \Phi_{H,i}S_{H,i} + \sum_{j=1}^{n} m_{ij}^{S} S_{H,j} - \sum_{j=1}^{n} m_{ji}^{S} S_{H,i}, \\ \frac{dI_{H,i}}{dt} &= \Phi_{H,i}S_{H,i} - \epsilon_{H,i}I_{H,i} + \sum_{j=1}^{n} m_{ij}^{I} I_{H,j} \\ &\quad - \sum_{j=1}^{n} m_{ji}^{I} I_{H,i}, \\ \frac{dR_{H,i}}{dt} &= \alpha_{H,i}I_{H,i} - \delta_{H,i}R_{H,i} + \sum_{j=1}^{n} m_{ij}^{R} R_{H,j} \\ &\quad - \sum_{j=1}^{n} m_{ji}^{R} R_{H,i}, \\ \frac{dS_{V,i}}{dt} &= \Lambda_{V,i} - \mu_{V,i}S_{V,i} - \Phi_{V,i}S_{V,i}, \\ \frac{dI_{V,i}}{dt} &= \Phi_{V,i}S_{V,i} - \mu_{V,i}I_{V,i} \end{aligned} \tag{1}$$

with initial conditions $S_{H,i}(0), S_{V,i}(0) > 0$, $I_{H,i}(0), R_{H,i}(0), I_{V,i}(0) \geq 0$, $\epsilon_{H,i} = \alpha_{H,i} + \gamma_{H,i} + \rho_{H,i} + \mu_{H,i}$, $\delta_{H,i} = \beta_{H,i} + \mu_{H,i}$. In the above formulation, m_{ij}^{π}, $\pi = S, I, R$, denote the constant rate of travel of humans from patch j to patch i, for all $i, j = 1, \ldots, n$, $i \neq j$. $M^{\pi} = [m_{ij}^{\pi}]$, $\pi = S, I, R$, is the travel rate matrices. The matrices $M^{\pi}, \pi = S, R$, was assumed to be irreducible and $m_{ii}^{\pi} = 0$, for $\pi = S, I, R$ and $i = 1, \ldots, n$. In this paper, we use the force of infection derived in [6] as follows:

$$\Phi_{H,i} = \frac{a_{V,i}a_{H,i}V_i}{a_{V,i}V_i + a_{H,i}H_i}\sigma_{V_iH_i}\frac{I_{V,i}}{V_i}, \tag{2a}$$

$$\Phi_{V,i} = \frac{a_{V,i}a_{H,i}H_i}{a_{V,i}V_i + a_{H,i}H_i}\left(\sigma_{H_iV_i}\frac{I_{H,i}}{H_i} + \widehat{\sigma}_{H_iV_i}\frac{R_{H,i}}{H_i}\right). \tag{2b}$$

A. Disease free state

An equilibrium solution of system (1) at which there is no disease in any of the patches is called a disease-free equilibrium. The local stability of this point is governed by the basic reproduction number denoted by $\mathcal{R}_0$. This latter is the expected number of secondary cases produced by a typical infective individual introduced into a completely susceptible population, in the absence of any control measure [7]. Next generation approach was used to derive $\mathcal{R}_0$ (see [9]). When $\mathcal{R}_0 < 1$ the infection will die out in the long run. But if $\mathcal{R}_0 > 1$ the infection will be able to spread in a population. It was shown that when disease induce mortality is large, a backward bifurcation may occur at $\mathcal{R}_0 = 1$, that to say, reduce $\mathcal{R}_0$ below 1 is not always sufficient to eliminate malaria.

B. Reservoir of infection

In this paper, a subgroup of patches is said to be a reservoir of infection when only targeting a control strategy which linearly reduce the number of susceptible is sufficient to eliminate the malaria in the whole of the patches. Define by $J_h = \{H_1, H_2 \ldots, H_n\}$ the set of humans population, it was shown that a control only targeted on human population was possible to eliminate malaria. In this paper we focus on a control type targeted only to the human population. A new next generation operator M_{J_h} was defined by

$$M_{J_h} = [\mathcal{R}_{H_iH_j}]_{1 \leq i,j \leq n}, \tag{3}$$

where $\mathcal{R}_{H_iH_j}$ can be interpreted as the expected number of secondary infected humans in patch j that would arise from a single infected human case in patch i, in a situation where all the patches contain a completely susceptible population. Moreover we have

$$\rho(M_{J_h}) < 1 \Leftrightarrow \mathcal{R}_0 < 1 \tag{4}$$

where $\rho(A)$ is the spectral radius of a matrix A (see [3] for details).

C. Sufficient condition for a patch to be a reservoir of infection

In [3], it was shown that if there exists some patch ℓ in the subset $\{1, 2, \ldots, n\}$ such that $\mathcal{R}_{H_\ell H_\ell} \geq 1$, then patch ℓ is an infection reservoir. In this case, we need to target simultaneously a control to the whole of susceptible population of the reservoir to eliminate malaria over time.

III. Minimal and efficient control

From results obtained in [3], arise the following **question**: *What minimal fraction of each group of the reservoir should be protected to eliminate malaria?*

Let J_{res} be the set of reservoirs of infection. From section II-C, we have

$$J_{res} = \{\ell \in \{1, 2, \ldots, n\} : \mathcal{R}_{H_\ell H_\ell} \geq 1\} \tag{5}$$

In the sequel, denotes by p the number of patches reservoirs, it is clear that $p = \text{cardinal}(J_{res})$ so that $(n - p)$ represents the number of un-reservoirs patches while n is the number of patches.

From [14], one can define a new next generation matrix as follows:

$$M_{J_{res}} = E_{J_h}^{T} M_{J_h} \left[I_n - (I_n - P_{J_h})M_{J_h}\right]^{-1} E_{J_h}, \tag{6}$$

where E_{J_h} and P_{J_h} are, respectively, $n \times p$ and $n \times n$ projection matrices satisfying $(E_{J_h})_{jj} = (P_{J_h})_{jj} = 1$ for $j \in J_{res}$ and $(E_{J_h})_{jj} = (P_{J_h})_{jj} = 0$ otherwise. $M_{J_{res}}$ is a $p \times p$ matrix satisfying $\rho(M_{J_{res}}) < 1 \Leftrightarrow \mathcal{R}_0 < 1$. In the sequel, we set

$$M_{J_{res}} = [M_{ij}]_{1 \leq i,j \leq p}. \tag{7}$$

The entries of $M_{J_{res}}$ are similar in concept to the entries of M_{J_h}.

A. Formulation of the objective function

Let $S^*_{H_\ell}$ be the number of susceptible individuals within each patch ℓ at the disease free equilibrium, $\ell = 1, \ldots, p$. this number is obtained from Theorem (10) in [3].

Let f_ℓ denotes the fraction of these susceptible that should be protected in patch ℓ. Then, $S^*_{H_\ell} f_\ell$ (resp. $S^*_{H_\ell}(1 - f_\ell)$) represents the number of protected (resp. not protected) individuals at the disease-free state in the patch ℓ, $\ell = 1, \ldots, p$.

The fraction of susceptible in the whole population is denoted by $F = (f_1, f_2, \ldots, f_p)$ and those who will not need to be protected is denoted by $\overline{F} = (1-f_1, 1-f_2, \ldots, 1-f_p)$.

From now, one can define a new next generation matrix with variable F denoted by $M_{J_{res}}(F)$:

$$M_{J_{res}}(F) =$$
$$\begin{bmatrix} (1-f_1)M_{11} & (1-f_2)M_{12} & \cdots & (1-f_p)M_{1p} \\ (1-f_1)M_{21} & (1-f_2)M_{22} & \cdots & (1-f_p)M_{2p} \\ \vdots & \vdots & \vdots & \vdots \\ (1-f_1)M_{p1} & (1-f_2)M_{p2} & \cdots & (1-f_p)M_{pp} \end{bmatrix}$$

Note that when $F = 0$ then $M_{J_{res}}(F) = M_{J_{res}}$.

To determine the minimal fractions of susceptible individuals, we set

$$\rho(M_{J_{res}}(F)) = 1 \Leftrightarrow \rho(M_{J_{res}}) = 1 \Leftrightarrow \mathcal{R}_0 = 1. \tag{8}$$

Now, one can formulate the objective function to minimized as follows:

$$\min_{0 \leq F \leq 1} \mathcal{J}(F) = \sum_{\ell=1}^{p} S^*_{H_\ell} f_\ell, \tag{9a}$$

$$\text{subject to the constraint } \rho(M_{J_{res}}(F)) = 1 \tag{9b}$$

Existence of an unique solution of Eqs (9 can be easily derived by a similar argument as in [15].

A powerful tool for numerical solving of Eqs (9) is the method of Lagrange multipliers [17]. In the sequel we denote by $F^* = (f_1^*, \ldots, f_p^*)^T$ the solution of Eq (9).

B. Dynamics of system (1) with control over time

We recall that the minimal control is obtained by solving Eqs. (9). To test its effect on the dynamic of the system (1), we define a new force of infection, $\widehat{\Phi_{H,i}}(t)$, with the value of the minimal control as follows:

$$\widehat{\Phi_{H,i}}(t) = \begin{cases} (1 - f_i^*)\Phi_{H,i}(t) \text{ if } & i \in J_{res} \\ \Phi_{H,i}(t) & \text{otherwise.} \end{cases} \tag{10}$$

for all $i = 1, \ldots, n$. In the above equation, $\Phi_{H,i}(t)$ represents the initial force of infection defined in Eq. (2), J_{res} represents the set of reservoirs of infection defined by Eq (5), the control is only introduced within the reservoir of infection.

C. Analysis of Optimal control

We point out that the minimal control derived in the previous section is not an optimal control. The minimal control does not depend on the time, it is constant over time. An optimal control can be considered when we would like to apply a prevention depending of the time with a given final time T for disease eradication as well as budget constraint, this type of control was already investigated in [35]. In that case an optimal control problem can be formulated in the set of the identified reservoirs $\{1, \ldots, p\} \subset \{1, \ldots, n\}$ with the following objective (cost) functional:

$$\begin{aligned} J(f) = & \sum_{i=1}^{p} \int_0^T \left(I_{H,i}(t) + R_{H,i}(t) + \frac{a_i}{2} f_i^2(t) \right) dt \\ & - \sum_{i=1}^{p} C_i S_{H,i}(T) \end{aligned} \tag{11}$$

where $f = (f_1, f_2, \ldots, f_p)$. $I_{H,i}$ and $R_{H,i}$ represent the number of infectious and semi-immune in patch i respectively, p is the number of reservoirs patches, $(n - p)$ represents the number of unreservoirs patches while n is the number of patches. The term $\frac{a_i}{2} f_i^2(t)$ is the cost of prevention with $a_i > 0$ are the weight factor in the cost of control. $C_i S_{H,i}(T)$ is the fitness of the susceptible at the end of the process as a result of the prevention efforts implements for the patch $i = 1, \ldots, p$. Using a similar argument as in [35] and under suitable condition one can prove the existence of an optimal control.

D. Methodology for numerical implementation

Here, we present the steps for numerical implementation.
Step 1: Compute principal next generator matrix K from [3, Theorem 3].
Step 2: Compute next generator matrix extracted $\tilde{K}$ from [3, Corollary 1].
Step 3: Compute M_{J_h} from in [3, Eq. (17)].
Step 4: Compute $M_{J_{res}}$ from Eq. (6).
Step 5: Solving Eq. (9) to find minimal control.
Step 6: Solving Eqs. (1) using the minimal control obtained in step 5 to represent the dynamic of malaria model.

IV. Costs and cost-effectiveness of malaria control for two strategies

Cost-effectiveness analysis compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money [1], [25]. This informs decision-makers who have to determine where to allocate limited healthcare resources. It is performed in this section to assess the effectiveness of a control targeted on the minimal fraction obtained in previous section considering two strategies of control over a reference period $T - T_I$, where T_I is the initial time for which the control is introduced and T the final time.

Strategy 1 : Protecting the minimal fraction of susceptible individuals to eliminate malaria in the reservoir of infection over the period $T - T_I$.

Strategy 2 : Protection of any fraction of susceptible individuals greater than the minimal fraction for eradicate malaria at the same over the period $T - T_I$.

To achieve this purpose for our above strategies, we need to compare the differences between the cost and health outcome. This is done by calculating the incremental cost effectiveness ratio (ICER) defined as follows:

$$ICER = \frac{C^* - C}{HE^* - HE} \tag{12}$$

where HE^* (resp. HE) denotes the health effect of strategy 1 (resp. strategy 2) and C^* (resp. C) denotes the present value (at time $t = 1$) of costs for the whole project of strategy 1 (resp. strategy 2). A similar method is used in [21].

A. Method to calculate costs C (resp. C^*) for strategy 2 (resp. strategy 1)

Let c_ℓ^t denotes financial cost of protecting one individual for one unit of time t (here one month) in patch ℓ. Because $f_l S_{H_l}^*$ is the number of individuals to be protect in patch ℓ then $c_\ell^t f_\ell S_{H_\ell}^*$ is the total required financial cost to protect all individuals in patch $\ell = 1, \ldots, p$. It follows that the total cost allowed to strategy 2 (resp. strategy 1) is given by

$$C^t = \sum_{l=1}^{p} c_l^t f_l S_{H_l}^*, \quad \text{and} \quad C^{*t} = \sum_{l=1}^{p} c_l^t f_l^* S_{H_l}^* \quad t = 1, \ldots, T$$

When cost effectiveness ratios are reported with discounting of future costs and benefits due to the longer-term implementation time, if we denote by r s the social discount rate, we have

$$C^* := \sum_{t=1}^{T} \frac{C^{*t}}{(1+r)^{t-1}}$$

and

$$C := \sum_{t=1}^{T} \frac{C^t}{(1+r)^{t-1}},$$

B. Method to calculate health effect of strategy 1 HE (resp. of strategy 2 HE^*)

$$HE = \frac{1}{T - T_I} \int_{T_I}^{T} \sum_{l=1}^{p} S_{H_l}^{f}(t)dt$$

and

$$HE^* = \frac{1}{T - T_I} \int_{T_I}^{T} \sum_{l=1}^{p} S_{H_l}^{f^*}(t)dt,$$

where $S_{H_l}^{f}(t)$ denote the number of susceptible at time t when $\widehat{\Phi_{H,i}}(t) = \Phi_{H,i}$ and $S_{H_l}^{f^*}(t)$ denote the number of susceptible at time t when $\widehat{\Phi_{H,i}}(t) = (1 - f_i^*)\Phi_{H,i}$.

V. Simulation Experiments

A. Parameters values

To test the method, we have assumed that the travel rates of humans depend on the distance between cities. We set

$$M^S = M^I = M^R = \frac{10^{-3}}{n-1} \cdot [|i - j|], \ 2 \leq i, j \leq n; \tag{13}$$

the maximum number of mosquito bites a human can receive per unit time, a_H and the number of time one mosquito would bite humans per unit time a_V are shown in Table II. The rest of parameters values of model are shown in Table III.

TABLE II

The minimal fraction F^* and the maximal fraction F depending of the parameters values of a_H and a_V.

City	1	2	3	4	5	6	7
a_H	1.6	2	2.5	1.5	2.1	2.3	1.2
a_V	0.6	0.65	0.35	0.4	0.3	0.5	0.2
F^*	0	0.6	0.80	0	0.63	0.70	0
F	0	1	1	0	1	1	0
City	8	9	10	11	12	13	14
a_H	1.9	1.7	2.4	1.6	2	2.5	1.5
a_V	0.55	0.8	0.45	0.6	0.65	0.35	0.4
F^*	0.48	0	0.70	0	0.51	0.72	0
F	1	0	1	0	1	1	0
City	15	16	17	18	19	20	
a_H	2.1	2.3	1.2	1.9	1.7	2.4	
a_V	0.3	0.5	0.2	0.55	0.8	0.45	
F^*	0.56	0.65	0	0	0	0.71	
F	1	1	0	0	0	1	

TABLE III

Baseline values found in the literature [3], [10], [6], [34]. We have assumed that the parameters are identical in all the patches excepted $a_{H,i}$ that varies from a patch to another and the rate of travel m_{ij}^{π} that depends on the distance between patches.

Symbol	Description	Values
$\Lambda_{H,i}$:	recruitment into the susceptible class	0.4
$\alpha_{H,i}$:	rate of progression from the infectious to the semi-immune class	0.0035
$\rho_{H,i}$:	rate of recovery from being infectious	0.035
$\beta_{H,i}$:	rate of recovery from being semi-immune	5.5×10^{-4}
$\gamma_{H,i}$:	disease induced death rate	9×10^{-5}
$\mu_{H,i}$:	natural death rate	5×10^{-4}
$\Lambda_{V,i}$:	recruitment into the susceptible class	500
$\mu_{V,i}$:	natural death rate	0.04
$\sigma_{H_iV_i}$:	probability of transmission from an infectious human to a susceptible mosquito	0.48.
$\widehat{\sigma}_{H_iV_i}$:	probability of transmission from a semi-immune human to a susceptible mosquito	0.048
$\sigma_{V_iH_i}$:	probability of transmission from an infectious mosquito to a susceptible human	0.022
$a_{H,i}$:	maximum number of mosquito bites a human can receive per unit time	Table II
$a_{V,i}$:	number of times one mosquito would bite humans per unit time	Table II
M^{π}:	$\pi = S, I, R$ rate of travel of humans from patch j to patch i	Eq. (13)

B. Results and Discussion

The computation provides the basic reproductive number value: $\mathcal{R}_0 = 1.3239$. That to say, without control, one has malaria that persists in the human population.

1) Reservoir of infection: Numerical implementation of the method shown in Appendix allowed to identify the set of reservoirs shown on Table II and Figure 1. Cities number 2,3,5,6,8,10,12,13,15,16 and 20 represent the reservoirs of infection based on the value of the minimal fraction $F^* := (f_1^*, \ldots, f_{20}^*)$. Indeed, one considers that a city ℓ is a reservoir when $f_\ell^* \neq 0$.

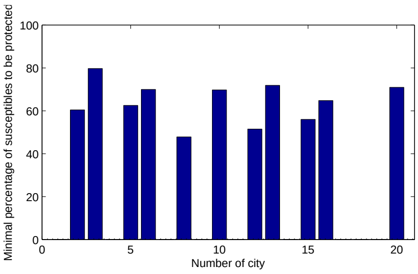
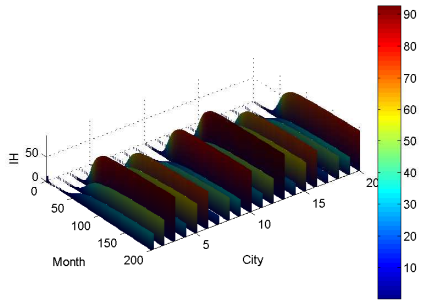
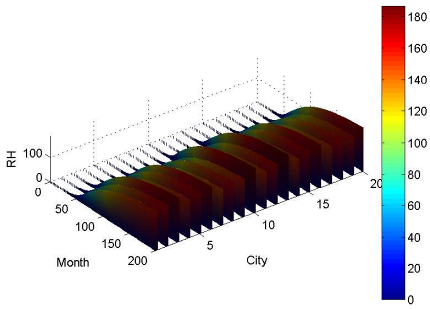


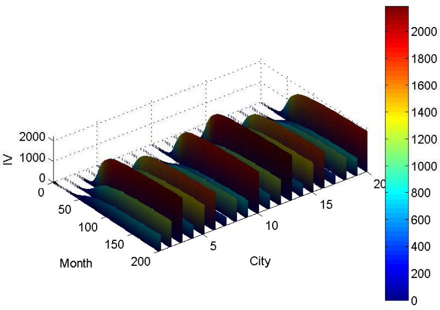
Fig. 1. This figure shows the cities which represent reservoirs of infection when we use the data in Table III and the algorithm presented in this paper. Cities number 2,3,5,6,8,10,12,13,15,16 and 20 represent the reservoirs of infection while cities 1,4,7,9,11,14,17,18,19 are not. Moreover this figure provides the minimal percentage (i.e. $100F^*$, where $F^* := (f_1^*, \ldots, f_{20}^*)$ is shown on Table (II)) of human within each reservoir that should be protected to eliminate malaria in the whole of the population (human and mosquitoes).



[(a)]



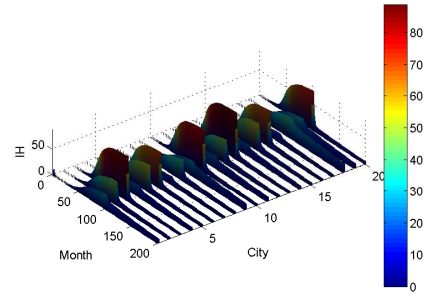
[(b)]



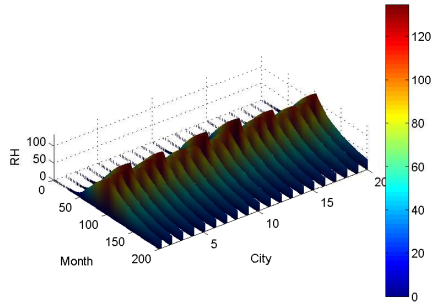
[(c)]

Fig. 2. Simulation of the evolution over month of the density of human in infectious class $(I_{H,i})$ and semi-immune class $(R_{H,i})$, as well as the density of infectious mosquitoes $(I_{V,i})$ for 20 cities when we have no control measures. Initial condition: $S_{H,i}(0) = 500, i = 1, \ldots, 20$, $I_{H,1}(0) = 10$, and $I_{H,i}(0) = 0$, i=2,..., 20; $R_{H,i}(0) = 0, i = 1, \ldots, 20$; $S_{V,i}(0) = 100, i = 1, \ldots, 20$; $I_{V,i}(0) = 0, i = 1, \ldots, 20$.

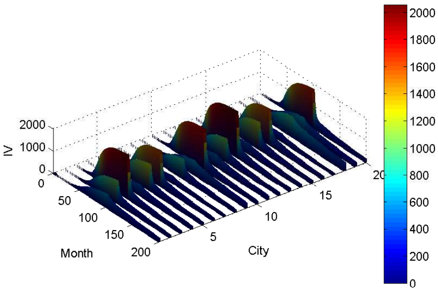
2) Dynamics of system (1) with/ or without minimal control: Figure 2 show the endemicity of malaria without control. Indeed, Although others cities are not reservoirs of infection, they are supported by the mobility of infectious and semi-immune human coming from the reservoirs patches. This process gives rise an endemic disease in the 20 cities. When we introduce the minimal percentage to control malaria after 100 months post-infection, one can see on Figure 3 the reduction overtime of the disease.



[(a)]



[(b)]



[(c)]

Fig. 3. Simulation of the evolution over month of the density of human in infectious class $(I_{H,i})$ and semi-immune class $(R_{H,i})$, as well as the density of infectious mosquitoes $(I_{V,i})$ for 20 cities when the minimal percentage of susceptible human shown in Table II are protected 100 months post-infection. Initial condition: $S_{H,i}(0) = 500, i = 1, \ldots, 20$, $I_{H,1}(0) = 10$, and $I_{H,i}(0) = 0$, i=2,..., 20; $R_{H,i}(0) = 0, i = 1, \ldots, 20$; $S_{V,i}(0) = 100, i = 1, \ldots, 20$; $I_{V,i}(0) = 0, i = 1, \ldots, 20$.

3) Cost-infectiveness results: Numerical cost-effectiveness analysis was performed by setting $T_I = 100$ months and $T = 200$ months.

Strategy	number of susceptibles	Total cost
Strategy 1	7801,2	56422
Strategy 2	7812,3	88000

$$ICER(1) = \frac{56422}{7801,2} = 7,2325$$

and

$$ICER(2) = \frac{88000 - 56422}{7812,3 - 7801,2} = 2844,8649$$

The comparison between ICER(1) and ICER(2) shows a cost saving of 7,2325 for strategy 1 over strategy 2. The

ICER for strategy 1 indicates the strategy 2 is "strongly dominated". Strategy 2 is then more costly and less effective than strategy 1. With this result, we therefore conclude that strategy 1 is the less cost and most effective.

VI. Conclusion

In this article, we have extended the model derived in [3] to give a numerical method to explain the steps for identifying reservoirs of malaria infection within n connected regions with the explicit movement of human population. This method is intended to design an efficient computational tool.

In the one hand, we have shown how to determine the minimal percentage of susceptible individuals in the reservoirs that should be protected to eliminate malaria over time in the whole population. The minimal percentage quantifies the degree of malaria risk in the reservoirs areas. It is regulated by the mobility flux of human population between patches. Thus for the public health decision makers, when datasets on human migration flux, demographic and epidemic are known, this method can aid to estimate the minimal percentage of susceptible individuals to be protected. We have explained that the minimal percentage is not necessarily an optimal control but allows to reduce the cost of intervention. It is constant over time. An optimal control can be considered when we would like to apply a preventative depending of the time with a given final time T for disease eradication as well as a budget constraint. In that case we have shown how to formulate such a problem.

In the second hand, the costs and cost-effectiveness of malaria control interventions is performed considering two strategies of control: (i) protecting the minimal fraction of susceptible individual; (ii) protecting any fraction greater than the minimal fraction. Cost-effectiveness analysis shows that the less cost and more effective strategy is to protect the minimal fraction of susceptible individual in the reservoir of infection. Biologically relevant parameters have been estimated and used to fulfill numerical simulations of the model. These simulations was implemented through an example using Matlab (www.matlab.org). Simulation of the evolution over month of the density of human in infectious class $(I_{H,i})$ and semi-immune class $(R_{H,i})$, as well as the density of infectious mosquitoes $(I_{V,i})$ for 20 cities was shown on Figure 2-3. Together with the both Figures and the Cost-infectiveness results, we argue that Strategy (ii) is then more costly and less effective than strategy (i). With this result, we therefore conclude that strategy (i) is the less cost and most effective, namely the minimal fraction of population to vaccinate (or protect) to halt outbreak is efficient.

Our study will be useful for spatial vaccination programs in which optimization methods are needed to minimize the costs. Moreover thanks to this study, when the datasets on human migration flux, demographic and epidemic are known, one can estimate the minimal percentage of susceptible individuals to be protected. The method developed in this paper may be allow to the implementation of a software for monitoring spatio-temporal variations in malaria epidemic risk.

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