REVIEW ARTICLE

Optimal control strategies for a class of vector borne diseases, exemplified by a toy model for malaria

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Abstract—**This paper contains a unified review of a set of previous papers by the same authors concerning the mathematical modelling and control of malaria epidemics. The presentation moves from a conceptual mathematical model of malaria transmission in an homogeneous population. Among the key epidemiological features of this model, two-age-classes (child and adult) and asymptomatic carriers have been included. As possible control measures, the extra mortality of mosquitoes due to the use of long-lasting treated mosquito nets (LLINs) and Indoor Residual Spraying (IRS) have been included. By taking advantage of the natural double time scale of the parasite and the human populations, it has been possible to provide interesting threshold results. In particular, key parameters have been identified such that below a threshold level, built on these parameters, the epidemic tends to extinction, while above another threshold level it tends to a nontrivial endemic state. The above model has motivated further analysis when a spatial structure of the relevant populations is added. Inspired by the above, additional model reductions have been introduced, which make the resulting reaction-diffusion system mathematically affordable. Only the dynamics of the infected mosquitoes and of the infected humans has been included, so that a two-component reaction-diffusion system is finally**

taken. **The spread of the disease is controlled by three actions (controls) implemented in a subdomain of the habitat: killing mosquitoes, treating the infected humans and reducing the contact rate mosquitoes-humans. To start with, the problem of the eradicability of the disease is considered, while the cost of the controls is ignored. We prove that it is possible to decrease exponentially both the human and the vector infective population everywhere in the relevant habitat by acting only in a suitable subdomain. Later the regional control problem of reducing the total cost of the damages produced by the disease, of the controls and of the intervention in a certain subdomain is treated for the finite time horizon case. In order to take the logistic structure of the habitat into account the level set method is used as a key ingredient for describing the subregion of intervention. Here this subregion has been better characterized by both area and perimeter. The authors wish to stress that the target of this paper mainly is to attract the attention of the public health authorities towards an effective and affordable practice of implementation of possible control strategies.**

Keywords-**malaria; nonlinear ODE models; qualitative analysis; reaction-diffusion system; zero-stabilization; regional control; optimal control; epidemic systems;**

I. INTRODUCTION

"Mathematical Models are lies
that make us reach the truth".
(Paraphrased from Picasso)

Human malaria is caused by one or a combination of four species of plasmodia: *Plasmodium falciparum, P. vivax, P. malariae*, and *P. ovale*. The parasites are transmitted through the bite of infected female mosquitoes of the genus Anopheles. Mosquitoes can become infected by feeding on the blood of infected people, and the parasites then undergo another phase of reproduction in the infected mosquitoes.

According to [https://data.unicef.org/topic/child-health/malaria/], "Prevention has been mainly carried out by the use of bed nets. Sleeping under insecticide-treated mosquito nets (ITNs) on a regular basis is one of the most effective ways to prevent malaria transmission

and reduce malaria related deaths. Since 2000, production, procurement and delivery of ITNs, particularly Long Lasting Insecticide Treated Nets (LLINs) have accelerated, resulting in increased household ownership and use. ... Household ownership of ITNs/LLINs is uneven across countries in the region, with an average coverage of 66 per cent in sub-Saharan Africa ranging from less than 30 per cent to approximately 90 per cent but most countries have made considerable progress in the past decade. The proportion of sub-Saharan African households with at least one ITN increased to 67 per cent in 2016, thus, a third of households where ITNs are the main method of vector control did not have access to a net. Additionally, only 42 per cent of households had sufficient ITNs for all household members which is drastically short of the universal access of 100 per cent to this preventive measure."

This shows the relevance of studies as the ones proposed in this paper, concerning the identification of regions where universal access might be implemented, with respect to areas where this is not affordable because of various restrictions due to financial and logistic affordability.

The earliest attempt to provide a quantitative understanding of the dynamics of malaria transmission was that of Ross [41]. Ross' models consisted of a few differential equations to describe changes in densities of susceptible and infected people, and susceptible and infected mosquitoes. Macdonald [34], [35] extended Ross' basic model, analyzed several factors contributing to malaria transmission, and concluded that "the least influence is the size of the mosquito population, upon which the traditional attack has always been made".

The work of Macdonald had a very beneficial impact on the collection, analysis, and interpretation of epidemic data on malaria infection [36] and guided the enormous global malaria-eradication campaign of his era.

The classical Ross-Macdonald model has inspired many contributions considering a variety of additional epidemiological features of the contagion [12], [26] (see also [13], [20], [22], [23], [27],

[31], [42], [44]).

A realistic mathematical model for an epidemic malaria system would require, at least for the human population, splitting the population with respect to stages of the disease, e. g. susceptibles, infectives, immunes, and alike; age structure, spatial structure, and alike. Even though we may suppose that indeed such a model is realistic, it might exhibit a complexity that make it hard for a sound mathematical analysis, and its validation as far as fitting real data is concerned. Expected uncertainty in the parameters would add additional complexity, so that the design of sound control strategies appears to be unaffordable.

Reduction of complexity has then become a key issue, though one must take into account that reduction has not to lead to meaningless models with respect to real epidemic systems (a great interpretation of this concept has been offered by Picasso http://www.dailyartmagazine. com/pablo-picassos-bulls-road-simplicity/).

This paper is meant to present a unified review of a set of previous papers by the same authors, the crucial issue being the implementation of optimal control strategies solely on an optimally chosen subregion of the habitat.

In order to include specific issues of malaria epidemic, we have started by considering a spatially homogeneous population with two age groups (children and adults) for the human population, and two classes of human individuals with respect to symptoms (asymptomatic and symptomatic) [39], [15]. In [39] the role of uncertainty in data was analyzed with respect to optimal control strategies. But the mathematical analysis of the full model was far from satisfactory, due to its intrinsic nontrivial structure.

In [15], by taking advantage of the natural double time scale of the parasite and the human populations, the authors have been able to obtain a significant model reduction and then to provide interesting threshold results. In particular, there it is shown that key parameters can be identified such that below a threshold level the epidemic tends to extinction, while above another threshold level it tends to a nontrivial endemic state.

In [8], [10] a spatial structure has been taken into account, but no age structure.

Though the above mentioned simplifications lead *de facto* to a toy model, we have been using it as the basis for implementing sound realistic control strategies, inspired by the outcomes of the results in [39], [15]. The implementation of control strategies on an optimally chosen subregion of the habitat is a crucial addition of our proposal.

Although we have tried to make clear the assumptions underlying our model, it has not been validated yet, by comparison with experimental data. Therefore it has to be cautioned that it is far from being the last word on a real malaria epidemic. However it is hoped that our model, with additional features that make it more realistic, when combined with efficient numerical methods, might provide the foundations for designing optimal control strategies by public health authorities.

We wish to clarify that the reference to malaria does not exclude possible applications to other vector borne diseases, with relevant modifications that may take into account their specific epidemiological issues.

For optimal control problems related to population dynamics we refer to the monographs [2], [3], [33], and references therein.

A control problem of malaria for a space independent model may be found in [1].

For basic results and methods in shape optimization we refer to [25], [30], [40], [46].

It can be just mentioned that the models presented here might be extended to other vector borne diseases, though this would require taking into account specific features of other diseases.

This paper is organized as follows. In Section II a spatially homogeneous population with two age groups (children and adults) for the human population, and two classes of human individuals with respect to symptoms (asymptomatic and symptomatic). By taking advantage of the double scale structure of the model, a reduced epidemic model is obtained, for which a qualitative analysis is carried out so to obtain a key threshold theorem.

Attention is paid to the behaviour of the total human population. In Section III the modelling, analysis and possible control strategies of the epidemic system with spatial structure has been reported. In particular a theorem is reported concerning the eventual eradicability of the disease, guaranteed by the proposed control strategies. In Section IV optimal regional control problems are discussed, including possible control strategies, and the optimal choice of the region of intervention. Different from previous papers, here the region of intervention has been characterized by both its area and perimeter.

II. A COMPARTMENTAL MODEL WITH TWO AGE GROUPS

The model developed in this paper combines two sub-models, the vectorial dynamics and the human host dynamics. Similar to Ross-MacDonald model [34], [32], once it is assumed that the vector population is comprised of only female Anopheles mosquitoes, they are categorized into

S_v : uninfected (susceptible) mosquitoes, and

I_v : infected mosquitoes.

Therefore the total mosquito population is

$$N_v = S_v + I_v.$$

The total human population N_h has been divided into six classes:

X : susceptible children ,

Y : susceptible adults,

X_1 : asymptomatic infected children,

X_2 :symptomatic infected children,

Y_1 : asymptomatic infected adults,

Y_2 : symptomatic infected adults (Y_2).

Hence,

$$N_h = X + X_1 + X_2 + Y + Y_1 + Y_2.$$

The parameters of the model are:

η_h: Per capita birth rate of humans.

η_v: Per capita birth rate of mosquitoes.

λ_h: Transmission rate from infected mosquitoes to susceptible humans.

λ_v: Transmission rate from infected humans to susceptible mosquitoes.

a: Mosquito biting rate.

b: Probability of transmission of infection from an infectious mosquito to a susceptible human.

c: Probability of transmission of infection from an infectious human to a susceptible mosquitoes.

f_x: Proportion of symptomatic infection in children.

f_y: Proportion of symptomatic infection in adults.

ν_x: Child natural recovery rate from asymptomatic infection.

ν_y: Adult natural recovery rate from asymptomatic infection.

r_x: Child natural recovery rate from symptomatic infection.

r_y: Adult natural recovery rate from symptomatic infection.

ϕ: Modification parameter for recovery rate from symptomatic infection.

g: Human maturity rate.

μ_v: Mosquito natural mortality rate.

μ_h: Human natural mortality rate.

δ_y: Disease induced mortality rate in adults.

δ_x: Disease induced mortality rate in children.

In the mathematical model we have denoted by λ_h the infection rate, due to the infective humans, acting on each susceptible mosquito, while by λ_v we have denoted the infection rate, due to the infective mosquitoes, acting on each susceptible human individual.

We will adopt here the infection rates as in the classical Ross-McDonald model [34] so that

$$
\begin{aligned}
\lambda_h \;=\; & \text{probability per unit time} \\
& \text{that a susceptible human is infected} \\
& \text{due a bite by an infective mosquito} \\
=\; & \text{relative abundance of mosquitoes} \\
& \text{with respect to the human population} \\
\times\; & \text{probability per unit time a human} \\
& \text{is bitten by a mosquito} \\
\times\; & prob\{\text{the biting mosquito is infective}| \\
& \text{a mosquito has bitten a human}\} \\
\times\; & prob\{\text{a susceptible human is infected}| \\
& \text{he has been bitten by an infective} \\
& textnormal mosquito\} \\
=\; & \frac{N_v}{N_h} a \frac{I_v}{N_v} b.
\end{aligned}
$$

Similarly,

$$
\begin{aligned}
\lambda_v \;=\; & \text{probability per unit time} \\
& \text{that a susceptible mosquito is infected} \\
& \text{due to a bite to an infective human} \\
=\; & \text{probability per unit time a mosquito} \\
& \text{bites a human} \\
\times\; & prob\{\text{the bitten human is infective}| \\
& \text{a mosquito has bitten a human}\} \\
\times\; & prob\{\text{a susceptible mosquito is infected}| \\
& \text{he has bitten an infective human}\} \\
=\; & a \frac{I_h}{N_h} c.
\end{aligned}
$$

where $I_h = X_1 + X_2 + Y_1 + Y_2$.

It is assumed that the individuals in the adult subpopulation have acquired an immunity and hence they are able to clear fast the infections ($r_y > r_x$), may have prolonged period of asymptomatic *P. falciparum* infection ($1/\nu_y > 1/\nu_x$) and suffers less disease induced mortality ($\delta_x > \delta_y$) compared to children.

An extra death rate α_v of the total mosquitoes population has been included, which may take into account the additional mortality due to the use of LLINs and the Indoor Residual Spraying (IRS) of mosquitoes. As in the force of infection of humans by mosquitoes, we have made the choice that this extra death rate of mosquitoes depends itself upon the relative abundance of mosquitoes with respect to the total human population. This modification takes into account the epidemiological issues of the Ross-McDonald model.

In this framework it is more convenient to deal with fractional quantities by scaling each subpopulation with the total population at any time t as

$$
x(t) = \frac{X(t)}{N_h(t)}, \; y(t) = \frac{Y(t)}{N_h(t)}, \; \cdots, \; i_v(t) = \frac{I_v(t)}{N_v(t)}.
$$

In this way, if we set

$$
m(t) := \frac{N_v(t)}{N_h(t)},
$$

the infection rates become

$$
\begin{aligned}
\lambda_h(t) &= bam(t)i_v(t), \\
\lambda_v(t) &= aci_h(t).
\end{aligned}
$$

The compartmental mathematical model for malaria transmission is then represented by the system (1) of non-linear ordinary differential equations, where

$$
x \;=\; 1 - (x_1 + x_2 + y + y_1 + y_2).
$$

$$
\begin{aligned}
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= (1 - f_x)bami_v x + (1 - \phi)r_x x_2 - (g + \nu_x)x_1 - \eta_h x_1 + x_1(\delta_x x_2 + \delta_y y_2), \\
\frac{\mathrm{d}x_2}{\mathrm{d}t} &= f_x bami_v x - (g + r_x + \delta_x)x_2 - \eta_h x_2 + \delta_x x_2^2 + \delta_y x_2 y_2, \\
\frac{\mathrm{d}y}{\mathrm{d}t} &= gx + \nu_y y_1 + \phi r_y y_2 - bami_v y - \eta_h y + y(\delta_x x_2 + \delta_y y_2), \\
\frac{\mathrm{d}y_1}{\mathrm{d}t} &= (1 - f_y)bami_v y + (1 - \phi)r_y y_2 + gx_1 - \nu_y y_1 - \eta_h y_1 + y_1(\delta_x x_2 + \delta_y y_2), \qquad (1) \\
\frac{\mathrm{d}y_2}{\mathrm{d}t} &= f_y bami_v y + gx_2 - (r_y + \delta_y)y_2 - \eta_h y_2 + \delta_x x_2 y_2 + \delta_y y_2^2, \\
\frac{\mathrm{d}i_v}{\mathrm{d}t} &= \lambda_v - (\lambda_v + \eta_v)i_v, \\
s_v &= 1 - i_v
\end{aligned}
$$

System (1) is complemented by the two equations for the total human and mosquito populations

$$
\frac{\mathrm{d}N_h}{\mathrm{d}t} = (\eta_h - \mu_h - \delta_x x_2 - \delta_y y_2)N_h, \qquad (2)
$$

$$
\frac{\mathrm{d}N_v}{\mathrm{d}t} = (\eta_v - \mu_v - \alpha_v m)N_v. \qquad (3)
$$

It is not difficult to show that System (1) is well posed, i.e., given suitable initial conditions, it admits a unique solution. Moreover if the initial conditions are such that $x(0), x_1(0), x_2(0), y(0), y_1, y_2(0) \geq 0$, with $x(0) + x_1(0) + x_2(0) + y(0) + y_1(0) + y_2(0) = 1$, and $s_v(0), i_v(0) \geq 0$, with $s_v(0) + i_v(0) = 1$, then the same holds at any later time $t > 0$.

We may then continue our analysis by referring only to the lower dimensional vector $\underline{x}_h := (x_1, x_2, y, y_1, y_2)^T \in \pi := \{\underline{x}_h \in \mathbb{R}_+^5 | x_1 + x_2 + y + y_1 + y_2 \in [0, 1]\}$, for the human population, and $i_v \in [0, 1]$ for the mosquito population.

The total fraction of human susceptibles is

$$
s_h = x + y. \qquad (4)
$$

If we introduce the vector of all fractions of infective humans

$$
\underline{i}_h := (x_1, x_2, y_1, y_2)^T, \qquad (5)
$$

the total fraction of human infectives is given by

$$
i_h = x_1 + x_2 + y_1 + y_2, \qquad (6)
$$

so that

$$
s_h + i_h = 1. \qquad (7)
$$

For the mosquito population we have just

$$
s_v + i_v = 1. \qquad (8)
$$

Our analysis may be concentrated on the time behaviour of the functions $i_h(t)$, and $i_v(t)$ describing the fractions of total infective human population, and the fraction of infective mosquito population, respectively.

A. The time scales

According to the parameter values reported in [39], we can see that the natural birth rate η_h for the human population is of the order 10^{-5}days^{-1}, much lower to the natural birth rate η_v for the mosquito population which is of the order 10^{-2}days^{-1}, so that their ratio $\varepsilon := \dfrac{\eta_h}{\eta_v} \ll 1$, say $\varepsilon \sim 10^{-3}$.

It is then meaningful the introduction of two adimensional time scales as follows

$$
\tau_h := \eta_h t, \qquad \tau_v := \eta_v t.
$$

The relationship between these two time scales is

$$
\tau_h = \varepsilon \tau_v,
$$

so that τ_v, the natural time scale of the mosquito population results to be the *fast* time scale, while

τ_h, the natural time scale of the human population, is the *slow* time scale.

By taking into account all the above, we can obtain the time evolution of the functions $i_h(t)$, and $i_v(t)$ with respect to these time scales.

Let

$$\Omega_h := \{ \underline{i}_h \in \mathbb{R}_+^4 | \ x_1 + x_2 + y_1 + y_2 \in [0,1] \} \quad (9)$$

and

$$\Omega_v := [0,1]. \quad (10)$$

Introduce the function

$$f : \Omega_h \times \Omega_v \to \mathbb{R}, \quad (11)$$

such that, for $(\underline{i}_h, i_v) \in \Omega_h \times \Omega_v$,

$$f(\underline{i}_h, i_v) := \frac{1}{\eta_h}[F(i_h, i_v) - R(\underline{i}_h)], \quad (12)$$

with

$$F(i_h, i_v) := bami_v(1 - i_h) - \eta_h i_h, \quad (13)$$

and

$$R(\underline{i}_h) := (1 - i_h)(\delta_x x_2 + \delta_y y_2) \\ + (\nu_x x_1 + \nu_y y_1) + \phi(r_x x_2 + r_y y_2). \ (14)$$

Because of (1), the time evolution of i_h is then given by

$$\frac{di_h}{d\tau_h} = f(\underline{i}_h, i_v), \quad (15)$$

coupled with

$$\frac{di_v}{d\tau_v} = g(i_h, i_v), \quad (16)$$

where

$$g(i_h, i_v) := \frac{1}{\eta_v}[aci_h - (\eta_v + aci_h)i_v]. \quad (17)$$

B. *Qualitative analysis of the mathematical model*

At first we may provide some information about the time behaviour of $m = \frac{N_v}{N_h}$. It can be shown that, at the fast time scale

$$\lim_{\tau_v \to +\infty} \frac{N_v(\tau_v)}{N_h(\tau_v)} = m^*, \quad (18)$$

for

$$m^* := \frac{\eta_v - \mu_v}{\alpha_v} = \frac{\sigma_v}{\alpha_v}, \quad (19)$$

if we denote

$$\sigma_v := \eta_v - \mu_v > 0. \quad (20)$$

As a consequence, we may then assume, at the "slow" time scale τ_h,

$$m(\tau_h) := \frac{N_v(\tau_h)}{N_h(\tau_h)} \equiv m^*. \quad (21)$$

1) The slow time scale: With respect to the same slow time scale τ_h, equations (15) and (16) can be rewritten as follows

$$\frac{di_h}{d\tau_h} = f(\underline{i}_h, i_v), \quad \underline{i}_h(0) \in \Omega_h; \quad (22)$$

$$\varepsilon \frac{di_v}{d\tau_h} = g(i_h, i_v), \quad i_v(0) \in \Omega_v. \quad (23)$$

2) The fast time scale: Viceversa, at the fast time scale the above equations become

$$\frac{di_h}{d\tau_v} = \varepsilon f(\underline{i}_h, i_v) \quad (24)$$

$$\frac{di_v}{d\tau_v} = g(i_h, i_v), \quad (25)$$

under the same initial conditions.

Due to the fact that $\varepsilon \simeq 0$, at this scale i_h can be considered constant, so that Equation (25) admits the equilibrium

$$i_v^* \equiv \varphi(i_h) := \frac{aci_h}{\eta_v + aci_h}, \text{ for any } i_h \in [0,1]. \quad (26)$$

Notice that, for any $i_h \in [0,1]$, $\varphi(i_h)$ is the only solution of

$$g(i_h, i_v) = 0$$

in $[0, 1]$.

By the usual Lyapunov methods, the following proposition has been proven in [15].

Proposition II.1. *For any choice of $i_h \in [0, 1]$, the point $i_v^* = \varphi(i_h)$ is a globally asymptotically stable equilibrium solution for Equation (25).*

It is though interesting to directly evaluate the rate of convergence to the equilibrium $i_v^* = \varphi(i_h)$ of Equation (25).

If we take

$$z_v(\tau_v) := i_v(\tau_v) - i_v^*, \qquad (27)$$

its evolution equation is

$$\frac{dz_v}{d\tau_v} = -K(i_h)z_v, \qquad (28)$$

subject to

$$z_v(0) = i_v(0) - i_v^*. \qquad (29)$$

Here

$$K(i_h) := \frac{\eta_v + aci_h}{\eta_v} \geq 1. \qquad (30)$$

As a consequence, the solution of (28)-(29) is such that

$$z_v(\tau_v) = z_v(0)\exp(-K(i_h)\tau_v) \leq z_v(0)\exp(-\tau_v), \qquad (31)$$

i.e.

$$|i_v(\tau_v) - i_v^*| \leq |i_v(0) - i_v^*|\exp(-\tau_v). \qquad (32)$$

Equation (32) shows that an upper estimate of the convergence rate can be made, independent of i_h. Furthermore, since $|i_v(0) - i_v^*| \leq 1$, at the slow time scale τ_h this will be seen as

$$|i_v(\tau_h) - i_v^*| \leq \exp(-\tau_h/\varepsilon). \qquad (33)$$

which tends to zero extremely fast; indeed for $\varepsilon \simeq 10^{-3}$, and $\tau_h = 10^{-1}$, $\exp(-\tau_h/\varepsilon) \simeq \exp(-100) \simeq 0$.

C. Qualitative analysis at the slow time scale

Proposition II.1, and the fast convergence of $i_v(\tau_h)$ to $i_v^* = \varphi(i_h)$ at the slow time scale justify, by Tikhonov Theorem (see e.g.[14]), the direct substitution of i_v by i_v^* in Equation (22). In addition, the above analysis allows us to assume that the ratio $m(\tau_h) := \frac{N_v(\tau_h)}{N_h(\tau_h)}$ has reached its asymptotic value $m^* = \frac{\sigma_v}{\alpha_v}$, so that

$$\frac{di_h}{d\tau_h} = \widetilde{f}(\underline{i}_h), \quad \underline{i}_h(0) \in \Omega_h, \qquad (34)$$

where

$$\widetilde{f}(\underline{i}_h) := \frac{1}{\eta_h}[\widetilde{F}(i_h)) - R(\underline{i}_h)] \qquad (35)$$

with

$$\widetilde{F}(i_h) = \frac{-i_h^2\alpha + i_h\beta}{\eta_v + aci_h}. \qquad (36)$$

Here

$$\alpha = ba^2cm^* + ac\eta_h, \qquad (37)$$

and

$$\beta = ba^2cm^* - \eta_h\eta_v. \qquad (38)$$

$R(\underline{i}_h)$ is taken from (14). Due to the structure of (14), Equation (34) has always to be considered coupled with System (1) with (2) and (3), which makes its qualitative analysis rather complicated. A way to reduce such complexity is given below.

We may observe that the function $\widetilde{f}$ can be minorized by the function

$$f^\ell(i_h) := \frac{1}{\eta_h}[\widetilde{F}(i_h)) - \overline{K}i_h], \qquad (39)$$

since

$$R(\underline{i}_h) \leq \overline{R}(\underline{i}_h) := \overline{K}i_h, \quad i_h = \|\underline{i}_h\|_1 \in [0, 1],$$

for

$$\overline{K} := \max\{\delta_x + \phi r_y, \nu_x\} > 0. \qquad (40)$$

On the other hand the function $\widetilde{f}$ can be majorized by the function

$$f^u(i_h) := \frac{1}{\eta_h}[\widetilde{F}(i_h)) - \underline{K}i_h], \qquad (41)$$

since

$$R(\underline{i}_h) \geq \underline{R}(\underline{i}_h) := \underline{K}i_h, \quad i_h = \|\underline{i}_h\|_1 \in [0, 1],$$

for

$$\underline{K} := \min\{\nu_y, \phi r_x\} > 0. \qquad (42)$$

We have denoted by $\|\underline{i}_h\|_1 = x_1 + x_2 + y_1 + y_2$.

For the qualitative analysis it is then more convenient to study the minorant equation

$$\frac{\mathrm{d}i_h^\ell}{\mathrm{d}\tau_h} = f^\ell(i_h^\ell), \qquad (43)$$

together with the majorant equation

$$\frac{\mathrm{d}i_h^u}{\mathrm{d}\tau_h} = f^u(i_h^u). \qquad (44)$$

They are such that

$$f^\ell(i_h) \le f(i_h) \le f^u(i_h). \qquad (45)$$

These equations are now decoupled from System (1).

If we denote by $i_h(\tau_h; \underline{i}_h(0))$ the solution of Equation (34) (coupled with System (1)-(3)), subject to the inital condition $\underline{i}_h(0)$; by $i_h^\ell(\tau_h; i_h(0))$ the solution of (43), subject to the initial condition $i_h(0) = \|\underline{i}_h(0)\|_1$; and by $i_h^u(\tau_h; i_h(0))$ the solution of (44), subject to the initial condition $i_h(0) = \|\underline{i}_h(0)\|_1$, then, by classical comparison theorems we may claim that for any $\tau_h \ge 0$,

$$i_h^\ell(\tau_h; i_h(0)) \le i_h(\tau_h; \underline{i}_h(0)) \le i_h^u(\tau_h; i_h(0)).$$

Then we have proved that, for any $i_h(0) \in (0, 1]$:

$$\lim_{\tau_h \to +\infty} \left[i_h^\ell(\tau_h; i_h(0)), i_h^u(\tau_h; i_h(0)) \right] = \left[\widehat{i_h^\ell}, \widehat{i_h^u} \right]$$

where $\left[\widehat{i_h^\ell}, \widehat{i_h^u} \right]$ is the "attractor interval" for the total fraction $i_h(\tau_h; i_h(0))$ of human infectives.

D. The main threshold theorem

By using the majorant equation, in [15] the authors have been able to show the following extinction theorem.

Theorem II.2. *If*

$$\frac{\alpha_v}{a^2} \ge bc \frac{\eta_v - \mu_v}{\eta_v(\eta_h + \underline{K})} \qquad (46)$$

then the attractor interval $\left[\widehat{i_h^\ell}, \widehat{i_h^u} \right]$ collapses to $\{0\}$ and for all i.c. $i_h(0) \in (0, 1]$ we have:

$$\lim_{\tau_h \to +\infty} i_h(\tau_h; i_h(0)) = 0. \qquad (47)$$

Since all parameters, but α_v and a, are specific of the relevant populations, as expected we might control the malaria eradication acting on α_v, the killing rate of mosquitoes by the use of LLIN's and IRS, and on a, the mosquito biting rate, by the use of LLIN's, and any other device/policy of contact reduction between mosquitoes and humans.

We have to point out that Theorem II.2 offers only a sufficient condition for the eventual eradication of the epidemic.

By the minorant equation it has been also possible to find a sufficient condition for the existence of a globally attractive endemic interval for the human infectives i_h.

E. About the total human population

In the previous paragraphs we have reported a threshold theorem for the possible extinction of the malaria epidemic. An important issue is the persistence of the total human population, otherwise fractions may loose any epidemiological meaning.

As a first step, let us rewrite Equation (2) at the slow time scale

$$\frac{\mathrm{d}N_h}{\mathrm{d}\tau_h}(\tau_h) = \frac{\sigma_h - (\delta_x x_2(\tau_h) + \delta_y y_2(\tau_h))}{\eta_h} N_h(\tau_h), \qquad (48)$$

for $\tau_h \ge 0$, subject to an initial condition

$$N_h(0) = N_{h0} > 0.$$

As above, we have denoted by $\sigma_h := \eta_h - \mu_h$, that we assume to be strictly positive.

In the sequel of this section we will write τ instead of τ_h.

A minorant equation for (48) can be obtained as follows.

If we denote by

$$\overline{\delta} := \max\{\delta_x, \delta_y\}, \qquad (49)$$

and by $i_h(\tau; i_{h0})$ the total fraction of human infectives, solution of Equation (34) (with (1)-(3)),

subject to an initial condition $\underline{i}_h(0) \in \Omega_h$, it is not difficult to realize that the following equation for a function $N^\ell(\tau)$, $\tau \geq 0$,

$$\frac{\mathrm{d}N^\ell}{\mathrm{d}\tau}(\tau) = \frac{\overline{\delta}}{\eta_h}\left[\frac{\sigma_h}{\overline{\delta}} - i_h(\tau; i_{h0})\right]N^\ell(\tau), \quad (50)$$

subject to the initial condition $N^\ell(0) = N_{h0} > 0$, is a minorant equation of (48)

Hence, for any $\tau \geq 0$, the following inequality holds

$$N_h(\tau) \geq N^\ell(\tau), \quad (51)$$

where

$$N^\ell(\tau) := N_{h0}\exp\left\{\frac{\overline{\delta}}{\eta_h}\left[\frac{\sigma_h}{\overline{\delta}}\tau - \int_0^\tau i_h(u; i_{h0})du\right]\right\}.$$

A sufficient condition for the "persistence in time" of the total human population $N_h(\tau)$, i.e. a sufficient condition which let us exclude that

$$N_h(\tau) \downarrow 0^+, \quad \text{as} \quad \tau \to +\infty \quad (52)$$

is (see [15])

$$\sigma_h > \overline{\delta}\widehat{i}_h^u, \quad (53)$$

where $\widehat{i}_h^u$ is the upper extreme of the "attractor interval".

Since in Theorem II.3 it occurs that $\widehat{i}_h^\ell = \widehat{i}_h^u = 0$ then we may claim that

Theorem II.3. *Under the assumptions of Theorem II.2 a sufficient condition for the persistence in time of N_h is*

$$\sigma_h > 0. \quad (54)$$

Unfortunately we have not been able to show that N_h is upper bounded, so that it might eventually explode to $+\infty$, though not in a finite time.

Theorem II.2 suggests relevant control strategies for more detailed and realistic mathematical models. Next sections are devoted to the case of spatially structured models; eradication theorems will be shown, and an optimal control problem will be analyzed.

III. A SPATIALLY STRUCTURED MODEL

We now report about the modelling, analysis and possible control strategies of a malaria epidemic system with spatial structure, as from [8], [10]. About the modelling let us anticipate that, in order to keep the model affordable for the mathematical analysis further reductions have been introduced, still (we hope) in the spirit of Picasso. Indeed we have analyzed realistic control strategies, inspired by the above outcomes taken from [39], [15].

By considering a spatially structured system, we will refer to an habitat $\Omega \subset \mathbb{R}^2$ (a nonempty bounded domain with a sufficiently smooth boundary $\partial\Omega$). The two populations of humans and mosquitoes will be described in terms of their spatial densities. Specifically, we will consider a population of infected mosquitoes with spatial density $u_1(x, t)$ at a spatial location $x \in \overline{\Omega}$ and a time $t \geq 0$; while $u_2(x, t)$ will denote the spatial distribution of the human infective population.

For our model reduction we have assumed that the spatial density $C(x)$ of the total human population has been taken essentially constant in time, independent of removals by possible acquired immunity, isolation, or death, so that $C(x) - u_2(x, t)$ provides the spatial distribution of susceptible humans, at a spatial location $x \in \overline{\Omega}$ and a time $t \geq 0$. Further it has been assumed that the total susceptible mosquito population is so large that it can be considered time and space independent.

As far as the "local incidence" for humans, at point $x \in \overline{\Omega}$, and time $t \geq 0$, it is taken of the form

$$\begin{aligned}(i.r.)_H(x, t) &= g(x, u_1(x, t), u_2(x, t)) \\ &= (C(x) - u_2(x, t))h\left(\frac{u_1(x, t)}{C(x)}\right),\end{aligned}$$

depending upon the local densities of both populations via a suitable functional response h that will be better described later.

Here we have taken into account that, in accordance with the Ross-McDonald model [34] the function h, describing the force of infection of humans by mosquitoes, depends upon the relative

concentration of the total mosquito population with respect to the total human population, because of the specific biting habits of humans by mosquitoes.

On the other hand, we have here extended the (linear) response of the Ross-McDonald model, by using a possibly nonlinear functional response $h(\frac{u_1(x,t)}{C(x)})$. This choice may allow possible saturation effects, $\sigma-$type responses, etc. (see [19], [17]). For example behavioral changes can be taken into account; for a very large density of the infective population the force of infection represented by $h(\frac{u_1(x,t)}{C(x)})$ may tend to reduce itself because of reduction of open exposure of the human population. This aspect had been already proposed in [19], which has motivated a large recent literature (see [28], and references therein).

As pointed out in [36], seasonality of the aggressivity to humans by the mosquito population might also be considered in the functional response h; this has been a topic of the authors research programme in [18], [17], and [6].

As far as the "local incidence" for mosquitoes, at point $x \in \overline{\Omega}$, and time $t \geq 0$, as in previous models [16], we assume that it is due to contagious bites to human infectives at any point $x' \in \Omega$ of the habitat, within a spatial neighborhood of x represented by a suitable probability kernel $k(x, x')$, depending on the specific structure of the local ecosystem (see also [43]); as a trivial simplification one may assume $k(x, \cdot)$ as a Gaussian density centered at x; hence the "local incidence" for mosquitoes, at point $x \in \Omega$, and time $t \geq 0$, is taken as

$$(i.r.)_M(x,t) = \int_\Omega k(x, x')u_2(x', t)dx'.$$

As proposed in [13], we have included spatial diffusion of the infective mosquito population (with constant diffusion coefficient to avoid purely technical complications), but we assume that the human population does not diffuse. More refined models may include some kind of mobility of the human population, due to migration mechanisms;

but this would require further nontrivial complicacies, that we leave to further investigations.

Finally, we have denoted by $\eta(x)u_1(x,t)$ the (possibly space dependent) natural decay of the infected mosquito population, while $a_{22}u_2(x,t)$ denotes the removal of the human infective population (by acquired immunity, isolation or death).

All the above leads to the following over simplified model for the spatial spread of malaria epidemics, in which we have ignored various additional features, such as the possible differentiation of the mosquito population, etc. (see e.g. [31])

$$\begin{cases} \partial_t u_1(x,t) = d\Delta u_1(x, t) - \eta(x)u_1(x, t) \\ \qquad + \int_\Omega k(x, x')u_2(x', t)dx' \\ \partial_t u_2(x,t) = -a_{22}u_2(x,t) + g(x, u_1(x,t), u_2(x,t)) \end{cases}$$

in $\Omega \times (0, +\infty)$, where $\eta(x)$ is the natural decay rate of the infected mosquitoes at $x \in \Omega$ (it is negative), $a_{22} > 0$, $d > 0$ are constants.

The reader may recognize that the above system, apart from its spatial structure, corresponds to System (22)-(23), under additional simplifications.

A. Regional Control Strategies

The public health concern consists of providing methods for the eradication of the disease in the relevant population, as fast as possible. On the other hand, very often the entire domain Ω, of interest for the epidemic, is unknown, or difficult to reach for the implementation of suitable environmental sanitation programmes. This has led the authors to suggest that implementation of such programmes might be done only in a given subregion $\omega \subset \Omega$, conveniently chosen so to lead to an effective eradication of the epidemic in the whole habitat Ω ("Think globally, act locally", as in [4], [5], [6], [7]). This practice may have an enormous importance in real cases with respect to both financial and practical affordability. More recently, in [24], a patch control approach has been suggested, via the identification of zones with different disease burden.

We assume here homogeneous Neumann boundary condition, to mean complete isolation of the

habitat:

$$\partial_\nu u_1(x,t) = 0 \qquad \text{on } \partial\Omega \times (0,+\infty),$$

where ∂_ν denotes the normal derivative.

We also impose initial conditions

$$\begin{cases} u_1(x,0) = u_1^0(x) \\ u_2(x,0) = u_2^0(x) \end{cases}$$

in Ω, where u_1^0 and u_2^0 are the initial densities of the population of infective mosquitoes and of the human infected population, respectively.

Let $\omega \subset \Omega$ be a nonempty open subset; we denote by χ_ω the characteristic function of ω and use the convention

$$\chi_\omega(x)w(x) = 0, \qquad x \in \mathbb{R}^2 \setminus \overline{\omega},$$

even if function w is not defined on the whole set $\mathbb{R}^2 \setminus \overline{\omega}$.

Our goal is to study the controlled system

$$\begin{cases} \partial_t u_1(x,t) - d\Delta u_1(x,t) = \eta(x)u_1(x,t) \\ \qquad + \int_\Omega k(x,x')u_2(x',t)dx' \\ \qquad -\gamma_1(x,t)\chi_\omega(x)u_1(x,t), \qquad (55) \\ \partial_t u_2(x,t) = -(a_{22}+\gamma_2(x,t)\chi_\omega(x))u_2(x,t) \\ \qquad +(1-\gamma_3(x,t)\chi_\omega(x))g(x,u_1(x,t),u_2(x,t)), \end{cases}$$

for $(x,t) \in Q$, together with

$$\partial_\nu u_1(x,t) = 0, (x,t) \in \Sigma \qquad (56)$$

and

$$u_1(x,0) = u_1^0(x), \quad u_2(x,0) = u_2^0(x), x \in \Omega, \qquad (57)$$

where $Q = \Omega \times (0,+\infty)$, $\Sigma = \partial\Omega \times (0,+\infty)$.

The idea underlying the controls is the following:

$$\gamma_1(x,t)u_1(x,t)\chi_\omega(x)$$

represents the additional killing of mosquitoes by the combined action of a general insecticide spraying, and the use of treated nets in the subregion ω;

$$\gamma_2(x,t)u_2(x,t)\chi_\omega(x)$$

describes the treatment of the infected population in the subregion ω;

$$\gamma_3(x,t)\chi_\omega(x)$$

is the reduction of the contact rate mosquitoes-humans by means of treated nets.

As far as the epidemiological significance of the various control terms, let us consider at first the quantity $\gamma_1(x,t)$. This may be interpreted as a harvesting rate of infective mosquitoes, by the use of chemical-physical devices such as insecticides, and $\gamma_1(x,t)u_1(x,t)$ as the corresponding distroyed mosquitoes population at location $x \in \Omega$, and time $t > 0$.

The control $\gamma_2(x,t)$ represents the recovery rate due to the medical treatment at location $x \in \Omega$, and time $t > 0$; the corresponding cured population is $\gamma_2(x,t)u_2(x,t)$.

The control $\gamma_3(x,t)$ gives the additional segregation rate for the population of infective mosquitoes and for the human susceptible population at location $x \in \Omega$, and time $t > 0$, due to the use of the treated bed nets (see e.g. [45], [47], and references therein).

1) Wellposedness: We have been working under the following technical assumptions:

(H1) $\eta \in L^\infty(\Omega)$, $k \in L^\infty(\Omega \times \Omega)$, $k(x,x') \geq 0$ a.e. in $\Omega \times \Omega$,

$$\int_\Omega k(x,x')dx > 0 \qquad \text{a.e. } x' \in \Omega;$$

(H2) $C \in L^\infty(\Omega)$, $C(x) \geq \tau > 0$ a.e. in Ω, where τ is a positive constant;

(H3) $h : \mathbb{R} \to [0,+\infty)$, and $h|_{[0,+\infty)}$ is continuously differentiable and increasing,
$h(x) = 0$, for $x \in (-\infty, 0]$,
$h(x) \leq a_{21}x$, for any $x \in [0,+\infty)$,
where a_{21} is a positive constant;

(H4) u_1^0, $u_2^0 \in L^\infty(\Omega)$, $0 \leq u_1^0(x)$, $0 \leq u_2^0(x) \leq C(x)$ a.e. $x \in \Omega$.

Based on epidemiological considerations ([10]), the control functions $\gamma = (\gamma_1, \gamma_2, \gamma_3)$, introduced above, have been assumed to belong to

$$\mathcal{G} = \{\gamma = (\gamma_1, \gamma_2, \gamma_3) \in L^\infty(Q) \times L^\infty_{loc}(\overline{Q}) \times L^\infty(Q) :$$
$$0 \leq \gamma_1(x,t) < \Gamma_1, 0 \leq \gamma_2(x,t),$$
$$0 \leq \gamma_3(x,t) < \Gamma_3, \text{ a.e. } (x,t) \in Q\},$$

for suitable constants $\Gamma_1, \Gamma_3 > 0$.

Theorem III.1. *[Existence and Uniqueness] For any $\gamma \in \mathcal{G}$, Problem (55) has a unique (weak) solution (u_1^γ, u_2^γ). The solution satisfies*

$$0 \leq u_1^\gamma(x,t), \ 0 \leq u_2^\gamma(x,t) \leq C(x), \ a.e.(x,t) \in Q.$$

2) Eradicability:

Definition III.2. We say that the disease is *eradicable* if for any u_0^1 and u_0^2 satisfying Assumption (H4) there exists a $\gamma \in \mathcal{G}$ such that the solution (u_1^γ, u_2^γ) to the controlled system satisfies

$$\lim_{t \to +\infty} u_1^\gamma(\cdot, t) = \lim_{t \to +\infty} u_2^\gamma(\cdot, t) = 0$$

in $L^\infty(\Omega)$.

In [10] it has been shown that

Theorem III.3. *For any u_0^1, u_0^2 satisfying hypothesis (H4) and such that $u_0^1(x), u_0^2(x) > 0$ a.e. $x \in \Omega \setminus \overline{\omega}$, and for any $\gamma = (\gamma_1, \gamma_2, \gamma_3) \in \mathcal{G}$, the solution (u_1^γ, u_2^γ) satisfies*

$$u_1^\gamma(\cdot, t) \to 0$$

and

$$u_2^\gamma(\cdot, t) \to 0$$

in $L^\infty(\Omega)$ (as $t \to +\infty$) slower than or as slow as $\exp(-a_{22}t)$.

The above theorem provides information on the lower bound for the convergence to zero of the epidemic. Additional analysis based on the magnitude of the principal eigenvalue of an appropriate operator, provides information about an upper bound on the convergence.

For a given nonempty open subregion ω of Ω, such that $\Omega \setminus \overline{\omega} \neq \emptyset$, a given constant control $\gamma = (\gamma_1, \gamma_2, \gamma_3) \in \mathcal{G}$, and $\varepsilon \in (0, a_{22})$, consider the following eigenvalue problem

$$\begin{cases} -d\Delta\psi_1(x) - (a_{22} - \varepsilon)\psi_1(x) - \eta(x)\psi_1(x) \\ \quad - \int_\Omega k(x,x')\psi_2(x')dx' + \gamma_1\chi_\omega(x)\psi_1(x) \\ \quad = \lambda\psi_1(x), x \in \Omega \\ \\ \partial_\nu\psi_1(x) = 0, x \in \partial\Omega \\ \\ (\varepsilon + \gamma_2\chi_\omega(x))\psi_2(x) \\ \quad -(1 - \gamma_3\chi_\omega(x))a_{21}\psi_1(x) = 0, x \in \Omega, \end{cases}$$

By the Krein-Rutman Theorem, we may state that

Proposition III.4. *The principal eigenvalue $\lambda_{1\varepsilon}^\omega$ of the above problem is real, simple and admits at least an eigenvector (ψ_1, ψ_2) such that*

$$\psi_1(x) \geq \psi_1^0, \qquad \psi_2(x) \geq \psi_2^0, \quad a.e. \quad x \in \Omega,$$

for suitable positive constants ψ_1^0, ψ_2^0.

By usual comparison theorems, the following monotonicity properties can be obtained.

Proposition III.5. *For a given set of control parameters $\gamma \in \mathcal{G}$,*

(i) *The mapping $\varepsilon \in (0, a_{22}) \mapsto \lambda_{1\varepsilon}^\omega$ is continuous and strictly increasing.*

(ii) *The mapping $\omega \subset \Omega \mapsto \lambda_{1\varepsilon}^\omega$ is increasing, with respect to the ordering by inclusion.*

(iii) *If $\{\omega_n\}_{n \in \mathbf{N}^*}$ is an increasing sequence of open subsets of Ω such that $\cup_{n=1}^\infty \omega_n = \Omega$, then*

$$\lim_{n \to +\infty} \lambda_{1\varepsilon}^{\omega_n} = \lambda_{1\varepsilon}^\Omega.$$

So that we may finally state our main eradicability result, i.e. an exponential eradicability.

Theorem III.6. *If $\varepsilon \in (0, a_{22})$, $\gamma \in \mathcal{G}$, and $\omega \subset \Omega$ are such that the principal eigenvalue of the above problem is $\lambda_{1\varepsilon}^\omega > 0$, then*

$$\lim_{t \to +\infty} u_1^\gamma(\cdot, t) = \lim_{t \to +\infty} u_2^\gamma(\cdot, t) = 0,$$

in $L^\infty(\Omega)$ faster than or as fast as $\exp(-(a_{22} - \varepsilon)t)$.

The following remark guarantees that this theorem is indeed applicable.

Remark III.7. *If $\Gamma_1 > a_{22} + \|\eta\|_{L^\infty(\Omega)}$, then for $\varepsilon \in (0, a_{22})$ sufficiently small, γ_1 sufficiently close to Γ_1, γ_2 sufficiently large and ω sufficiently large, we have that $\lambda_{1\varepsilon}^\omega \geq 0$, and consequently the constant control $\gamma = (\gamma_1, \gamma_2, \gamma_3)$ (γ_3 is arbitrary but fixed in $[0, \Gamma_3)$) can make the epidemic exponentially eradicable.*

IV. OPTIMAL REGIONAL CONTROL OF THE EPIDEMIC

For an optimal control problem during a finite time interval of intervention $[0, T]$, we need to introduce a cost functional which takes into account all relevant costs concerning on one side the costs of intervention associated with the functions $(\gamma_1, \gamma_2, \gamma_3) \in \mathcal{G}$; on the other side they must be taken also into account the costs deriving from loss of work hours, hospitalization, and alike associated with the infected human population ($\ell(u_2)$), and the general costs associated with the specific choice of the subregion of intervention $\omega \subset \Omega$ (by assigning a suitable function $\alpha(x), \quad x \in \Omega$, the specific costs related to the logistic structure of the habitat can be taken into account) .

It should be then of the form

$$J(\gamma, \omega) = \int_0^T \int_\Omega \zeta_1(\gamma_1(x, t)) C(x) \chi_\omega(x) dx\, dt$$

$$+ \int_0^T \int_\Omega \zeta_2(\gamma_2(x,t) u_2(x,t)) \chi_\omega(x) dx dt$$

$$+ \int_0^T \int_\Omega \zeta_3(\gamma_3(x, t)) C(x) \chi_\omega(x) dx\, dt$$

$$+ \int_0^T \int_\Omega \ell(u_2(x, t)) dx\, dt$$

$$+ \int_\Omega \alpha(x) \chi_\omega(x) dx. \tag{58}$$

Based on suitable epidemiological considerations (see [10]), the following choices can be made for the specific cost functionals $\zeta_1, \zeta_2, \zeta_3$:

(H5) $\zeta_1 : [0, \Gamma_1) \to [0, +\infty)$ is a continuously differentiable function, bijective, strictly increasing;
$\zeta_3 : [0, \Gamma_3) \to [0, +\infty)$ is a continuously differentiable function, bijective, strictly increasing;

(H6) $\zeta_2 : [0, +\infty) \to (\Gamma_2, \tilde{\Gamma}_2]$ is a continuous differentiable function, bijective, and strictly decreasing.

A. Optimal Control for a Fixed Region of Intervention

At first let the subregion $\omega \subset \Omega$ be fixed, so that the cost functional $J(\gamma, \omega)$ is just a function

of γ, say $J(\gamma)$. We shall denote by

$$\begin{aligned}\mathcal{G}_T \ = \ &\{\gamma = (\gamma_1, \gamma_2, \gamma_3) \in L^\infty(Q_T)^3 : \\ &0 \le \gamma_1(x, t) < \Gamma_1, 0 \le \gamma_2(x, t), \\ &0 \le \gamma_3(x, t) < \Gamma_3 \text{ a.e. } (x, t) \in Q_T\},\end{aligned}$$

where $Q_T = \Omega \times (0, T)$.

Under the above assumptions the following theorem holds.

Theorem IV.1. *The optimal control problem*

$$Minimize_{\gamma \in \mathcal{G}_T} \ J(\gamma)$$

admits at least one solution $\gamma^* = (\gamma_1^*, \gamma_2^*, \gamma_3^*)$.

If we denote by $dJ(\gamma)$ the gradient of $J(\gamma)$, an optimal choice γ^* is such that

$$dJ(\gamma^*)(w) \ge 0,$$

for any w as in next proposition.

Proposition IV.2. *For any $\gamma \in \mathcal{G}_T$ and $w \in L^\infty(Q_T) \times L^\infty(Q_T) \times L^\infty(Q_T)$ such that $\gamma + \theta w \in \mathcal{G}_T$ for any $\theta > 0$ sufficiently small, we have that*

$$dJ(\gamma)(w) = \int_0^T \int_\Omega w_1(x, t) u_1^\gamma(x, t) q_1(x, t) \chi_\omega(x) dx dt$$

$$+ \int_0^T \int_\Omega w_1(x, t) C(x) \zeta_1'(\gamma_1(x, t)) \chi_\omega(x) dx dt$$

$$+ \int_0^T \int_\Omega w_2(x, t) \zeta_2'(\gamma_2(x, t) u_2^\gamma(x, t)) u_2^\gamma(x, t) \chi_\omega(x) dx dt$$

$$+ \int_0^T \int_\Omega w_2(x, t) u_2^\gamma(x, t) q_2(x, t) \chi_\omega(x) dx\, dt$$

$$+ \int_0^T \int_\Omega w_3(x, t) C(x) \zeta_3'(\gamma_3(x, t)) \chi_\omega(x) dx\, dt$$

$$+ \int_0^T \int_\Omega (w_3(x, t)(C(x) - u_2^\gamma(x, t))$$

$$\times h(\frac{u_1^\gamma(x, t)}{C(x)}) q_2(x, t) \chi_\omega(x)) dx\, dt,$$

where (q_1, q_2) is the solution to (59)

$$\begin{cases} \partial_t q_1(x,t) + d\Delta q_1(x,t) = -\eta(x)q_1(x,t) + \gamma_1(x,t)\chi_\omega(x)q_1(x,t) \\ \qquad\qquad -(1-\gamma_3(x,t)\chi_\omega(x))\dfrac{C(x)-u_2^\gamma(x,t)}{C(x)}h'\left(\dfrac{u_1^\gamma(x,t)}{C(x)}\right)q_2(x,t), \\ \partial_t q_2(x,t) = -\displaystyle\int_\Omega k(x',x)q_1(x',t)dx' + (a_{22}+\gamma_2(x,t)\chi_\omega(x))q_2(x,t) \\ +(1-\gamma_3(x,t)\chi_\omega(x))h\left(\dfrac{u_1^\gamma(x,t)}{C(x)}\right)q_2(x,t)+\tilde\zeta_2'(\gamma_2(x,t)u_2^\gamma(x,t))\gamma_2(x,t)\chi_\omega(x)+\ell'(u_2^\gamma(x,t)), \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{for} \quad (x,t) \in Q_T; \\ \partial_\nu q_1(x,t) = 0, \qquad (x,t) \in \Sigma_T; \\ q_1(x,T) = q_2(x,T) = 0, \qquad x \in \Omega. \end{cases} \tag{59}$$

Numerical results have been obtained by the gradient method, for suitable choices of all parameters (see [10]).

B. *Optimal Choice of the Region of Intervention*

The optimization with respect to both the control functions and the subregion of intervention by the gradient method, requires the evaluation of the directional derivative of the cost functional with respect to both the parameters $\gamma_1, \gamma_2, \gamma_3$, and the region ω.

A convenient way to handle the shape and position of ω is to use the level set method [40]. According to the implicit representation of subsets of Ω, we consider those subsets ω for which there exists a smooth function $\varphi : \overline\Omega \to \mathbb{R}$ such that

$$\omega = \{x \in \Omega; \ \varphi(x) > 0\}$$

and

$$\partial\omega = \{x \in \Omega; \ \varphi(x) = 0\}.$$

Hence, instead of investigating the total cost function J defined in the first section, we shall deal with (H denotes the usual Heaviside function)

$$\tilde{J}(\gamma,\varphi) = \int_0^T\!\!\int_\Omega \zeta_1(\gamma_1(x,t))C(x)H(\varphi(x))dxdt$$
$$+ \int_0^T\!\!\int_\Omega \zeta_2(\gamma_2(x,t)u_2(x,t))H(\varphi(x))dxdt$$

$$+ \int_0^T\!\!\int_\Omega \zeta_3(\gamma_3(x,t))C(x)H(\varphi(x))dxdt$$
$$+ \int_0^T\!\!\int_\Omega \ell(u_2(x,t))dxdt$$
$$+ \int_\Omega \alpha(x)H(\varphi(x))(x)dx. \tag{60}$$

where now $\gamma \in \mathcal{G}_T$, $\varphi : \overline\Omega \to \mathbb{R}$ is continuously differentiable, and (u_1, u_2) is the solution to

$$\begin{cases} \partial_t u_1(x,t) - d\Delta u_1(x,t) = -\eta(x)u_1(x,t) \\ \qquad + \displaystyle\int_\Omega k(x,x')u_2(x',t)dx' \\ \qquad -\gamma_1(x,t)H(\varphi(x))u_1(x,t), \\ \partial_t u_2(x,t) = -(a_{22}+\gamma_2(x,t)H(\varphi(x)))u_2(x,t) \\ +(1-\gamma_3(x,t)H(\varphi(x)))g(x,u_1(x,t),u_2(x,t)), \end{cases} \tag{61}$$

for $(x,t) \in Q_T$, subject to the boundary and initial conditions

$$\partial_\nu u_1(x,t) = 0, \qquad (x,t) \in \Sigma_T \tag{62}$$

$$u_1(x,0) = u_1^0(x), \ u_2(x,0) = u_2^0(x), \ x \in \Omega, \tag{63}$$

where $Q_T = \Omega \times (0,T)$, $\Sigma_T = \partial\Omega \times (0,T)$.

Actually H is usually replaced by its mollified version $H_\varepsilon(s) = \frac{1}{2}(1 + \frac{2}{\pi}\arctan\frac{s}{\varepsilon})$ ($\varepsilon > 0$ is a sufficiently small number).

It is possible to prove that [10]

Theorem IV.3. *For any $\gamma \in \mathcal{G}_T$ and $w \in L^\infty(Q_T) \times L^\infty(Q_T) \times L^\infty(Q_T)$ such that $\gamma + \theta w \in \mathcal{G}_T$ for any $\theta > 0$ sufficiently small, and for any smooth functions $\varphi, \psi : \overline{\Omega} \to \mathbb{R}$ we have that*

$$
\begin{aligned}
d\tilde{J}_\varepsilon(\gamma,\varphi)(w,\psi) = {}& \int_0^T \int_\Omega w_1(x,t) H_\varepsilon(\varphi(x)) u_1^{\gamma,\varphi}(x,t) q_1(x,t) dx\, dt \\
& + \int_0^T \int_\Omega w_1(x,t) C(x) \zeta_1'(\gamma_1(x,t)) H_\varepsilon(\varphi(x)) dx\, dt \\
& + \int_0^T \int_\Omega w_2(x,t) \zeta_2'(\gamma_2(x,t) u_2^{\gamma,\varphi}(x,t)) u_2^{\gamma,\varphi}(x,t) H_\varepsilon(\varphi(x)) dx\, dt \\
& + \int_0^T \int_\Omega w_2(x,t) u_2^{\gamma,\varphi}(x,t) q_2(x,t) H_\varepsilon(\varphi(x)) dx\, dt \\
& + \int_0^T \int_\Omega w_3(x,t) C(x) \zeta_3'(\gamma_3(x,t)) H_\varepsilon(\varphi(x)) dx\, dt \\
& + \int_0^T \int_\Omega w_3(x,t)(C(x) - u_2^{\gamma,\varphi}(x,t)) H_\varepsilon(\varphi(x)) h\left(\frac{u_1^{\gamma,\varphi}(x,t)}{C(x)}\right) q_2(x,t)] dx\, dt \\
& + \int_\Omega \psi(x)[\delta_\varepsilon(\varphi(x)) \Psi(x)] dx, \quad\quad\quad (64)
\end{aligned}
$$

where

$$
\delta_\varepsilon(x) = H_\varepsilon'(x) = \frac{1}{\pi} \frac{\varepsilon}{x^2 + \varepsilon^2},
$$

and $\Psi(x)$ is given by

$$
\begin{aligned}
\Psi(x) = \int_0^T \Big[& C(x) \zeta_1(\gamma_1(x,t)) + \zeta_2(\gamma_2(x,t) u_2^{\gamma,\varphi}(x,t)) + C(x) \zeta_3(\gamma_3(x,t)) + \alpha(x) + \gamma_1(x,t) u_1^{\gamma,\varphi}(x,t) q_1(x,t) \\
& + \gamma_2(x,t) u_2^{\gamma,\varphi}(x,t) q_2(x,t) + \gamma_3(x,t)(C(x) - u_2^{\gamma,\varphi}(x,t)) h\left(\frac{u_1^{\gamma,\varphi}(x,t)}{C(x)}\right) q_2(x,t) \Big] dt.
\end{aligned}
$$

Here $(u_1^{\gamma,\varphi}, u_2^{\gamma,\varphi})$ is the solution to (61), and (q_1, q_2) is the solution to

$$
\begin{cases}
\partial_t q_1(x,t) + d\Delta q_1(x,t) = -\eta(x) q_1(x,t) + \gamma_1(x,t) H_\varepsilon(\varphi(x)) q_1(x,t) \\
\qquad\qquad - (1 - \gamma_3(x,t) H_\varepsilon(\varphi(x)) \dfrac{C(x) - u_2^{\gamma,\varphi}(x,t)}{C(x)} h'(\dfrac{u_1^{\gamma,\varphi}(x,t)}{C(x)}) q_2(x,t), \\
\partial_t q_2(x,t) = - \displaystyle\int_\Omega k(x',x) q_1(x',t) dx' + (a_{22} + \gamma_2(x,t) H_\varepsilon(\varphi(x)) q_2(x,t) \\
+ (1 - \gamma_3(x,t) H_\varepsilon(\varphi(x))) h\left(\dfrac{u_1^{\gamma,\varphi}(x,t)}{C(x)}\right) q_2(x,t) + \tilde{\zeta}_2'(\gamma_2(x,t) u_2^{\gamma,\varphi}(x,t)) \gamma_2(x,t) H_\varepsilon(\varphi(x)) + \ell'(u_2^{\gamma,\varphi}(x,t)), \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{for} \quad (x,t) \in Q_T; \\
\partial_\nu q_1(x,t) = 0, \qquad (x,t) \in \Sigma_T; \\
q_1(x,T) = q_2(x,T) = 0, \qquad x \in \Omega.
\end{cases} \quad (65)
$$

Remark 1: We may notice that for a given $\gamma = (\gamma_1, \gamma_2, \gamma_3) \in \mathcal{G}_T$ the quantity

$$
\partial_s \varphi(x,s) = -\delta_\varepsilon(\varphi(x,s)) \Psi(x) \quad\quad\quad (66)
$$

for $x \in \Omega$, $s > 0$, where (u_1, u_2) is the solution of the state equation and (q_1, q_2) is the solution to the adjoint equation as above, in terms of the fictitious "time" variable s, gives the descent of the optimal search with respect to φ.

We may introduce additional costs due to shape of the subregion ω, by considering the perimeter of that region. As in [29] and [9], this would add the following term in the cost functional $\tilde{J}(\gamma, \varphi)$ (see (60))

$$\int_\Omega \beta(x)\delta(\varphi(x))\,|\nabla\varphi(x)|\,dx. \qquad (67)$$

As a consequence, in the gradient $d\tilde{J}_\varepsilon(\gamma, \varphi)(w, \psi)$ (see (64)) last term would then become

$$\int_\Omega \psi(x)[\delta_\varepsilon(\varphi(x))\hat{\Psi}(x)]dx$$
$$+ \int_{\partial\Omega} \psi(x)\frac{\delta_\varepsilon(\varphi(x))}{|\nabla\varphi(x)|}\partial_\nu\varphi(x)d\ell \qquad (68)$$

where now

$$\hat{\Psi}(x) = \int_0^T [C(x)\zeta_1(\gamma_1(x,t)) + \zeta_2(\gamma_2(x,t)u_2^{\gamma,\varphi}(x,t))$$
$$+ C(x)\zeta_3(\gamma_3(x,t)) + \gamma_1(x,t)u_1^{\gamma,\varphi}(x,t)q_1(x,t)$$
$$+ \gamma_2(x,t)u_2^{\gamma,\varphi}(x,t)q_2(x,t)$$
$$+ \gamma_3(x,t)(C(x) - u_2^{\gamma,\varphi}(x,t))h\left(\frac{u_1^{\gamma,\varphi}(x,t)}{C(x)}\right)q_2(x,t)$$
$$+ \alpha(x) - \beta(x)div\left(\frac{\nabla\varphi(x)}{|\nabla\varphi(x)|}\right)]dt.$$

Under these circumstances Equation (66) becomes

$$\partial_s\varphi(x,s) = -\delta_\varepsilon(\varphi(x,s))\hat{\Psi}(x),\ x \in \Omega, s > 0, \qquad (69)$$

subject to the boundary condition

$$\beta(x)\frac{\delta_\varepsilon(\varphi(x,s))}{|\nabla\varphi(x,s)|}\partial_\nu\varphi(x) = 0,\ x \in \partial\Omega, s > 0 \qquad (70)$$

(see [29] and [9]).

We may recognize that this is strictly related to the literature on image segmentation (see [38], [37], [21]).

V. CONCLUSIONS

- Based on the main ideas of relevant literature concerning epidemiological issues of malaria, we have proposed a mathematical model describing the dynamics of infected mosquitoes and humans in a spatially structured habitat.

- In order to reduce the number of infected mosquitoes and humans, we have taken into account three possible control measures to be implemented only in a suitable subdomain ω of the relevant global habitat.

- To start with, we have shown that if such a subdomain of intervention is sufficiently large and if the magnitude of the control efforts is sufficiently large, then eventual eradication of both infected populations is possible at an exponential rate.

- We have then analyzed the optimal control problem for the reduction of the infected human population (in a finite time interval) at a minimum cost.

- Further analysis for the identification of an optimal subdomain ω, together with optimal control efforts, has been left to future investigations.

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