REGIONAL CONTROL OF VECTOR BORNE DISEASES. MALARIA AS A WORKING EXAMPLE

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MOTIVATION

According to the WHO Malaria Report, 2017, " in 2016, there were an estimated 445 000 deaths from malaria globally, compared to 446 000 estimated deaths in 2015.
According to UNICEF
[https://data.unicef.org/topic/child-health/malaria/], " of these deaths about two thirds (290,000) were children under five years of age. This translates into a daily toll of nearly 800 children under age 5. Most of these deaths occurred in sub-Saharan Africa.
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A PUBLIC HEALTH PROBLEM

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. . .....
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."

OUR PROPOSAL: Regional Control

The public health concern consists of providing methods for the optimal control of the disease in the relevant population.

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 control programmes.

THINK GLOBALLY, ACT LOCALLY

This has led the author 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 control of the epidemic in the whole habitat Ω ("Think globally, act locally"). [Anita - Capasso, 2002 – 2012].

This practice may have an enormous importance in real cases with respect to both financial and practical affordability.

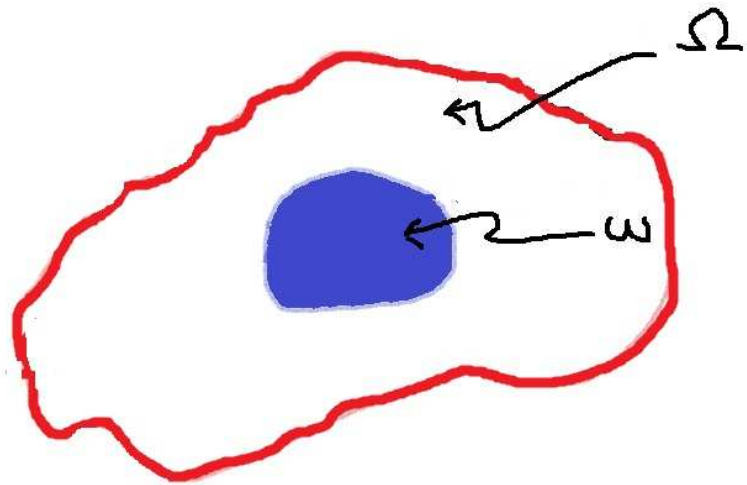

Figure: Think Globally, Act Locally.

A "TOY MODEL" for a Malaria System

As a working example, here we will consider an oversimplified model, concentrating on the problem of possible eradication and control of a vector borne epidemic, exemplified by malaria.

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,

$u_1(x,t)$ will denote the spatial density of the population of infected mosquitoes at a spatial location $x \in \overline{\Omega}$ and a time $t \geq 0$;

$u_2(x,t)$ will denote the spatial distribution of the human infective population.

A Spatially Structured Malaria Model

The spatial density $C(x)$ of the total human population will be assumed essentially constant in time, so that

$C(x) - u_2(x,t)$ will provide the spatial distribution of susceptible humans, at a spatial location $x \in \overline{\Omega}$ and a time $t \geq 0$.

We shall assume that the total susceptible mosquito population is so large that it can be considered time and space independent.

INCIDENCE RATE - HUMANS

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

$$(i.r.)_H(x,t) = g(x, u_1(x,t), u_2(x,t)) = (C(x) - u_2(x,t))h(\frac{u_1(x,t)}{C(x)}),$$

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, according to the Ross-Macdonald model [Macdonald, 1952], 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.

THE FUNCTIONAL RESPONSE

As proposed and discussed in [Capasso - Paveri-Fontana, 1979] for a cholera epidemic, and more in general in [Capasso - Serio, 1978], the functional response

$$h(\frac{u_1(x,t)}{C(x)})$$

is not necessarily linear; various epidemiological issues may suggest instead various nonlinear structures.

E. g., by taking into account Behavioral changes, which may include public health restrictions, 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 contact rates of the human population with respect to the disease vectors.

This idea has now driven a recent large literature (see [d'Onofrio–Manfredi, 2009], and references therein).

SEASONALITY

As pointed out in [Molineaux - Gramiccia, 1980], seasonality of the aggressivity to humans by the mosquito population might also be considered in the functional response h :

$$h(t, z) = p(t)g(z),$$

where g, the functional dependence of the incidence rate upon the vector , can be chosen as in the time homogeneous case

[Capasso – Maddalena, 1983; Capasso, 1993],
and [Anita – Capasso, 2010].

INCIDENCE RATE - MOSQUITOES

As far as the "local incidence" for mosquitoes, at point $x \in \overline{\Omega}$, and time $t \geq 0$, as in previous models [Capasso, 1984], 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 [Shcherbacheva et al, 2018]);
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

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

A Spatially Structured Malaria Model

As proposed in [Bacaer – Sokhna, 2005], we will include 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.

Mobility of the human population would be better modelled as migration or some nonlinear chemotactic mechanism, rather than pure diffusion (see e.g. [Barmak - Dorso - Otero, 2016] and references therein). On the other hand, from a mathematical point of view we may claim that, by including mobility for human population, similar results concerning the eradicability and the optimal control problems are expected.
We have left this issue to future investigations.

A Spatially Structured Malaria Model

Finally, from now on, we will denote by

$\eta(x)u_1(x,t)$ the (possibly space dependent) natural decay of the infected mosquito population, while

$a_{22}u_2(x,t)$ will denote the removal of the human infective population.

A Spatially Structured Malaria Model

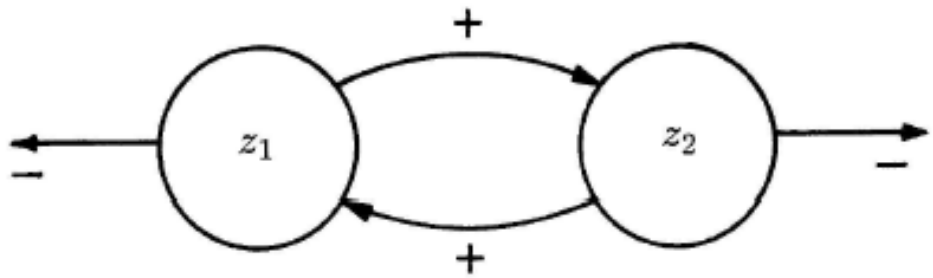

Figure: A COOPERATIVE SYSTEM:
z_1 denotes the infected mosquitoes; z_2 denotes the infected humans

$$\begin{cases} MOSQUITOES & = DIFFUSION - REMOVAL + INCIDENCE \\ HUMANS & = -REMOVAL + INCIDENCE \end{cases}$$

A Spatially Structured Malaria Model

All the above leads to the following over simplified model for the spatial spread of malaria epidemics, in which we have ignored additional ingredients, such as the possible acquired immunity of humans after exposure to the contagion, the possible differentiation of the mosquito population, etc. (see e.g. [Killeen et al, 2000])

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

in $\Omega \times (0,+\infty)$, subject to third type boundary conditions

$$\partial_\nu u_1(x,t) + \alpha_0 u_1(x,t) = 0 \qquad \text{on } \partial\Omega \times (0,+\infty),$$

where $\alpha_0 \geq 0$ is a constant and ∂_ν denotes the normal derivative.

The Controlled System - Regional Control

Given a subregion ω of the habitat Ω, the characteristic function

$$\chi_\omega(x)$$

allows to describe mathematically the local action of the relevant control measures.

The Controlled System

Our aim is to study the controlled system

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

subject to the boundary condition

$$\partial_\nu u_1(x,t) = 0, \qquad (x,t) \in \Sigma \tag{2}$$

and to the initial conditions

$$u_1(x,0) = u_1^0(x), \quad u_2(x,0) = u_2^0(x), \quad x \in \Omega, \tag{3}$$

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

The Controlled System

The idea underlying the controls is the following:

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

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

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

represents the recovery rate of infected humans due to medical treatment in the subregion ω;

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

represents the reduction of the contact rate mosquitoes-humans by means of treated nets in the subregion ω.

Based on epidemiological considerations, we assume that the control functions $\gamma := (\gamma_1, \gamma_2, \gamma_3) \in \mathcal{G}$, where

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

Well posedness

Under suitable assumptions existence and uniqueness of solutions (u_1^γ, u_2^γ) of the controlled system is guaranteed, for any choice of $\gamma \in \mathcal{G}$ such that

$$0 \leq u_1^\gamma(x,t), \quad 0 \leq u_2^\gamma(x,t) \leq C(x)$$

a.e. $(x,t) \in Q$.
They are weak solutions, belonging to $L^\infty(\Omega \times [0,T])$, satisfying the epidemic system a.e.

[Anita–Capasso–Dimitriu, 2018].

Eradicability

Definition

We say that the disease is *eradicable* if, for any nontrivial initial conditions u_0^1 and u_0^2, 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 $L^\infty(\Omega)$.

Exponential Decay

For a given $\varepsilon \in (0, a_{22})$, the following eigenvalue problem

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

by the Krein-Rutman Theorem admits a real, simple principal eigenvalue $\lambda^\omega_{1\varepsilon}$.

EXPONENTIAL DECAY

The following theorem holds.

ERADICABILITY

Theorem

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 $\exp(-(a_{22} - \varepsilon)t)$.

By comparison theorems, it is not difficult to show that $\lambda_{1\varepsilon}^{\omega}$ can be made as large as required, by acting on the controls γ's and on the size of the region of intervention ω.

AN OPTIMAL CONTROL PROBLEM

For an optimal control problem during the time interval of intervention $[0, T]$, we need to introduce a cost functional which takes into account all relevant costs concerning

a) the costs of intervention $\zeta_1, \zeta_2, \zeta_3$ depending upon $\gamma_1, \gamma_2, \gamma_3$ respectively;

b) the costs deriving from loss of work hours, hospitalization, and alike associated with the infected human population ($\ell(u_2)$);

c) the costs associated with the specific choice of the subregion of intervention $\omega \subset \Omega$;
for our scopes a planar set can be characterized by its area and perimeter, weighted by suitable logistic cost functions α and β which may take into account costs of transport of intervention devices, such as nets, pharmaceuticals, personnel, etc.

AN OPTIMAL CONTROL PROBLEM

It should be then of the form

$$
\begin{aligned}
J(\gamma,\omega) \quad = \quad & \int_0^T \int_\Omega \zeta_1(\gamma_1(x,t)) C(x) \chi_\omega(x) dx\, dt \\
& + \int_0^T \int_\Omega \zeta_2(\gamma_2(x,t) u_2(x,t)) \gamma_2(x,t) u_2(x,t) \chi_\omega(x) dx\, dt \\
& + \int_0^T \int_\Omega \zeta_3(\gamma_3(x,t)) C(x) \chi_\omega(x) dx\, dt \\
& + \int_0^T \int_\Omega \ell(u_2(x,t)) dx\ dt \\
& + \alpha \text{ Area}(\omega) + \beta \text{ Perimeter}(\omega). \qquad (4)
\end{aligned}
$$

AN OPTIMAL CONTROL PROBLEM

The optimal control problem proposed above clearly is an hard one, from both mathematical and computational points of view, since the space on which a search algorithm should act is a very high dimensional one.
A rigorous proof of the existence of a global optimum of the above cost functional is a very hard task.
But we may implement the usual search algorithm based on the gradient method, once we can evaluate the gradient of the relevant cost functional, with respect to both the γ's and the subregion ω.
Possible simplifications include neglecting space and time dependence of the controls γ, and splitting the problem into two parts, first by keeping fixed the subregion ω, and search for optimal γ's, and subsequently keep these as fixed and search for an optimal subregion ω.

The Level Set Method

From a computational point of view a convenient way to handle the shape and position of the subregion ω is the level set method (see Osher - Fedkiw (2003), and references therein). according to which there exists a smooth function $\varphi : \overline{\Omega} \to \mathbb{R}$ such that

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

Hence, instead of investigating the total cost function J defined above, we may deal with (take the γ's space independent)

$$\Phi(\gamma,\varphi) = \int_0^T \int_\Omega C(x)\zeta_1(\gamma_1(t))H(\varphi(x))dx\,dt$$
$$+ \int_0^T \int_\Omega \zeta_2(\gamma_2(t)u_2^{\gamma,\varphi}(x,t))\gamma_2(t)u_2^{\gamma,\varphi}(x,t)H(\varphi(x))dx\,dt$$
$$+ \int_0^T \int_\Omega C(x)\zeta_3(\gamma_3(t))H(\varphi(x))dx\,dt$$
$$+ \int_0^T \int_\Omega I(u_2^{\gamma,\varphi}(x,t))dx\;dt + \alpha\int_\Omega H(\varphi(x))dx$$
$$+\beta[\varepsilon\int_\Omega |\nabla H(\varphi(x))|^2\,dx + \frac{1}{\varepsilon}\int_\Omega (H(\varphi(x)))^2(1-H(\varphi(x)))^2dx],$$

where $\gamma \in \mathcal{G}_T$, and $\varphi : \overline{\Omega} \to \mathbb{R}$ is twice continuously differentiable, Here H is the Heaviside function. To describe the perimeter of the region ω we have taken into account the Modica -Mortola formula (1977) (ε is a sufficiently small parameter).

It is possible to prove that

THE GRADIENT METHOD

Theorem

For any $\gamma \in \mathcal{G}_T$ and $w \in L^\infty(0,T) \times L^\infty(0,T) \times L^\infty(0,T)$ 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

$$
\begin{aligned}
d\Phi(\gamma,\varphi)(w,\psi) &= \int_0^T w_1(t)\mathcal{F}_1(t)dt \\
&+ \int_0^T w_2(t)\mathcal{F}_2(t)dt + \int_0^T w_3(t)\mathcal{F}_3(t)dt \\
&+ \int_\Omega \psi(x)\mathcal{F}(x)H'(\varphi(x))dx \\
&+ \int_{\partial\Omega} \psi(x)\mathcal{G}(x)H'(\varphi(x))d\tilde{\sigma},
\end{aligned}
$$

where

THE GRADIENT METHOD

$$\mathcal{F}_1(t) = \int_\Omega H(\varphi(x))[u_1^{\gamma,\varphi}(x,t)q_1^{\gamma,\varphi}(x,t) + C(x)\zeta_1'(\gamma_1(t))]dx,$$

$$\begin{aligned}\mathcal{F}_2(t) = \quad & \int_\Omega H(\varphi(x))[u_2^{\gamma,\varphi}(x,t)q_2^{\gamma,\varphi}(x,t) \\ & + u_2^{\gamma,\varphi}(x,t)\tilde{\zeta}_2'(\gamma_2(t)u_2^{\gamma,\varphi}(x,t))]dx,\end{aligned}$$

$$\begin{aligned}\mathcal{F}_3(t) = \quad & \int_\Omega H(\varphi(x))[(C(x) - u_2^{\gamma,\varphi}(x,t))h(\frac{u_1^{\gamma,\varphi}(x,t)}{C(x)})q_2^{\gamma,\varphi}(x,t) \\ & + C(x)\zeta_3'(\gamma_3(t))]dx,\end{aligned}$$

THE GRADIENT METHOD

$$\begin{aligned}\mathcal{F}(x) = & \int_0^T [C(x)\zeta_1(\gamma_1(t)) + \tilde{\zeta}_2(\gamma_2(t)u_2^{\gamma,\varphi}(x,t)) + C(x)\zeta_3(\gamma_3(t)) \\ & +\gamma_1(t)u_1^{\gamma,\varphi}(x,t)q_1^{\gamma,\varphi}(x,t) + \gamma_2(t)u_2^{\gamma,\varphi}(x,t)q_2^{\gamma,\varphi}(x,t) \\ & +\gamma_3(t)(C(x) - u_2^{\gamma,\varphi}(x,t))h(\frac{u_1^{\gamma,\varphi}(x,t)}{C(x)})q_2^{\gamma,\varphi}(x,t) + \alpha]dt \\ & -2\beta\varepsilon\Delta[H(\varphi(x))] \\ & -\frac{\beta}{\varepsilon}[4(H(\varphi(x)))^3 - 6(H(\varphi(x)))^2 + 2H(\varphi(x))]\end{aligned}$$

and

$$\mathcal{G}(x) = \frac{2\beta}{\varepsilon}\partial_\nu(H(\varphi(x))).$$

THE GRADIENT METHOD

Here $(u_1^{\gamma,\varphi}, u_2^{\gamma,\varphi})$ is the solution of the controlled epidemic system, corresponding to the current choice of γ's and ϕ.

While $(q_1^{\gamma,\varphi}, q_2^{\gamma,\varphi})$ is the solution of the adjoint problem corresponding to the current choice of γ's and ϕ.

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.

CONCLUSIONS

- 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.
- Current numerical experiments are supporting the theory, with a significant everywhere reduction of both the infected mosquitoes and human populations, though acting only in a subregion of the whole habitat.

THANKS

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