Optimal release of mosquitoes to control dengue transmission

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Dengue virus in numbers

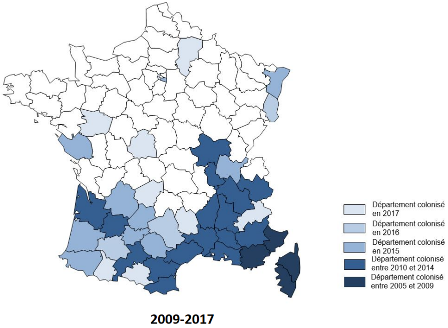
According to the World Health Organization:

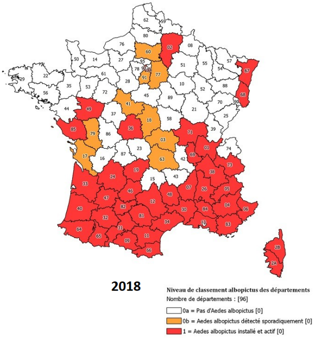
- 390 million of persons are infected by dengue per year,

- 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses.

As there exist no vaccine against dengue, effective control of the vector population is mandatory.

Aedes population in France





Controlling Aedes population

Up to now : pesticides $\rightarrow$ *Aedes* mosquitoes can develop resistance

Now : *wolbachia* bacteria $\rightarrow$ seems to work (tested in Rio and Australia)

Effect on mosquitoes population :
- No dengue transmission,
- Vertical transmission,
- Cytoplasmic incompatibility (CI) (no viable eggs when uninfected females mate to an infected males),
- Lifespan :

$$\text{Death rate of infected } (d_1) \; > \; \text{Death rate of uninfected}(d_2).$$

Research question

How to spatially release wolbachia infected mosquitoes to have an invasion in a given time?

The model

Equation (1)

For all $(x, t) \in \Omega\times]0, T]$

$$\begin{cases} \partial_t n_1 - \Delta n_1 = \frac{b_1^0}{\varepsilon} n_1(1 - \frac{n_1 + n_2}{K})(1 - \frac{n_2}{n_1 + n_2}) - d_1 n_1, \\ \partial_t n_2 - \Delta n_2 = \frac{b_2^0}{\varepsilon} n_2(1 - \frac{n_1 + n_2}{K}) - d_2 n_2 + u, \\ \partial_\nu n_1 = \partial_\nu n_2 = 0 \text{ on } \partial\Omega\times]0, T], \\ n_1(0, x) = n_1^0(x),\ n_2(0, x) = n_2^0(x) \text{ in } \Omega. \end{cases} \tag{1}$$

n_1 : uninfected mosquitoes,
n_2 : infected mosquitoes,
u : the control : number of infected mosquitoes released
$\frac{b_i^0}{\varepsilon}$: birth rate, d_i : death rate,
K : Carrying capacity.

Asymptotic model as $\varepsilon \to 0$

Defining

$$p(x,t) = \frac{n_2(x,t)}{n_1(x,t) + n_2(x,t)} = \textit{proportion of infected mosquitoes}$$

and letting $\varepsilon \to 0$, we find

Equation (2)

$$\begin{cases} \partial_t p - \Delta p = f(p) + ug(p), \text{ for } (x,t) \in \Omega \times]0,T] \\ \partial_\nu p = 0 \text{ on } \partial\Omega \times]0,T], \; p(0) = 0. \end{cases} \tag{2}$$

With

$$f(p) = p(1-p)\frac{b_2 d_1 - b_1 d_2 (1-p)}{b_1(1-p)^2 + b_2 p} \text{ and } g(p) = \frac{1}{K}\frac{b_1(1-p)^2}{b_1(1-p)^2 + b_2 p}.$$

The equation : $\partial_t p - \Delta p = f(p)$

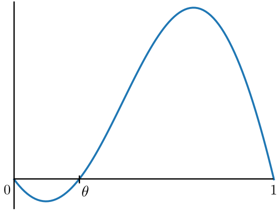


Figure: The bistable reaction term f

Proposition

$$p(0,x) = C < \theta \Rightarrow p(t) \underset{t \to +\infty}{\to} 0 \ \ (= \text{Extinction})$$

$$p(0,x) = C > \theta \Rightarrow p(t) \underset{t \to +\infty}{\to} 1 \ \ (= \text{Invasion})$$

The equation : $\partial_t p - \Delta p = f(p)$

Comparison Principle

Let p_- and p_+ be a subsolution and a supersolution of

$$\partial_t p - \Delta p = f(p) \text{ such that } p_-(0) \leq p_+(0)$$

then for all time $t > 0$

$$p_-(t) \leq p_+(t).$$

Many functions lead to invasion :

- Invasion whenever $p(0, x) = C_0 1_{B(0,r_0)}(x)$, for well-chosen values of $r_0 > 0$ and $C_0 > \theta$,
- Bubble functions.

Assumptions on the control

Equation (2)

$$\begin{cases} \partial_t p - \Delta p = f(p) + ug(p), \text{ for } (x,t) \in \Omega \times]0,T] \\ \partial_\nu p = 0 \text{ on } \partial\Omega \times]0,T], \; p(0) = 0. \end{cases} \quad (2)$$

The control u is taken such that:

- Maximum production capacity of infected mosquitoes :

$$\int_0^T \int_\Omega u(x,t)dx < C,$$

- Maximum release in one point :

$$0 \leq u(x,t) \leq m, \; \forall (x,t) \in \Omega \times [0,T].$$

Assumptions on the control

Assumption: The releases are "instantaneous":

$$u(x,t) = \sum_{i=0}^{N-1} \frac{u_i(x)}{\delta} 1_{[T_i, T_i+\delta)}(t) \text{ with } T_i = i \times \frac{T}{N}.$$

Letting $\delta \to 0$, we find

Equation (3)

$$\begin{cases} \partial_t p - \Delta p = f(p) \text{ in } \Omega \times]0,T], \\ \partial_\nu p = 0 \text{ on } \partial\Omega \times]0,T], \\ p(T_i^+) = G^{-1}(u_i + G(p(T_i^-)) \text{ for } i \in \{0,...,N-1\} \end{cases} \quad (3)$$

with $G(p) = \int_0^p \frac{1}{g(s)} ds$.

The Optimization Problem

The cost function is

$$J(u) = \int_\Omega (1 - p(x, T))^2 dx.$$

Proposition

There exists at least a function

$$\underline{u} \in \mathcal{V}_{T,C,M} = \left\{ u \in (L^\infty(\Omega))^N \mid 0 \leq u_i \leq m,\ \sum_{i=0}^{N-1} \int_\Omega u_i \leq C \right\}$$

such that

$$J(\underline{u}) = \min_{u \in \mathcal{D}} J(u).$$

Remark : We do not have any result about the uniqueness of the minimizer.

Single release problem

Goal

$$\min \left\{ \int_\Omega (1 - p(x, T))^2 dx \ : \ u \in \mathcal{V}_{T,C,M} \right\}$$

With p solution of

$$\begin{cases} \partial_t p - \Delta p = f(p) & \text{in } \Omega \times]0, T], \\ \partial_\nu p = 0 & \text{on } \partial\Omega \times]0, T], \\ p(x, 0) = G^{-1}(u(x)) & \text{in } \Omega \end{cases}$$

Constraint on u

$$\int_\Omega u(x) dx \leq C,$$

$$0 \leq u(x) \leq m.$$

Numerical Tools

We used *FreeFem++* since it has an interface with IPOPT.

- *FreeFem++* : Finite Element library for solving PDEs.
  - V_h finite element space, $(\varphi_i)_i$ basis :
    $p \approx p_h = \sum_i p_i \varphi_i, \quad u \approx u_h = \sum_i u_i \varphi_i$
- IPOPT : software library for large scale, non-linear, constrained optimization problems.
  - Cost function : $J_h(u_1, ..., u_n) = \int_\Omega (1 - p_h(T, x))^2 \, dx,$
  - Constraints : $0 \leq u_h(x) \leq m$ and
    $c_h(u_1, ..., u_n) = \int_\Omega u_h(x) \, dx \leq C,$
  - Gradient of cost function : $\nabla J_h = \left(\frac{\partial J_h}{\partial u_i} \right)_i$
  - Gradient of constraints : $\nabla c_h = \left(\frac{\partial c_h}{\partial u_i} \right)_i$

Gateaux-differential of cost

Proposition

Let $u \in \mathcal{V}_{T,C,M}$ and δu an admissible perturbation. The Gateaux-differential of J at u in direction δu is

$$\langle dJ(u), \delta u\rangle = \int_\Omega \delta u(x)(G^{-1})'(u(x))q(0,x)\,dx,$$

where q is the unique solution of the backward problem

$$\begin{cases} -\partial_t q(t,x) - \Delta q(t,x) - f'(p(t,x))q(t,x) = 0, \\ \partial_n q(t,x) = 0, \\ q(T,x) = p(T,x) - 1. \end{cases}$$

Approximation : $\delta u \approx \sum_i \delta u_i \varphi_i$

$$\langle dJ(u), \delta u\rangle \approx \sum_i \delta u_i \overbrace{\int_\Omega \varphi_i(x)(G^{-1})'(u(x))q(0,x)\,dx}^{\dfrac{\partial J_h}{\partial u_i}}$$

The heat equation

We first tested IPOPT with the heat equation:

$$\begin{cases} \partial_t p - \Delta p = 0 \text{ in } \Omega \times]0, T[, \\ \partial_\nu p = 0 \text{ on } \partial\Omega \times]0, T], \\ p(0) = u \text{ such that } \displaystyle\int_\Omega u \leq C = 1, \; 0 \leq u \leq m. \end{cases}$$

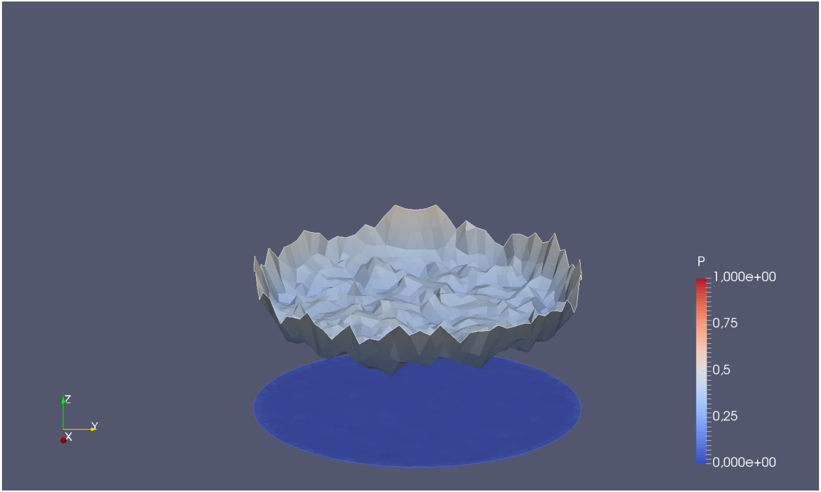
We found numerically the following theoretical result :

Proposition

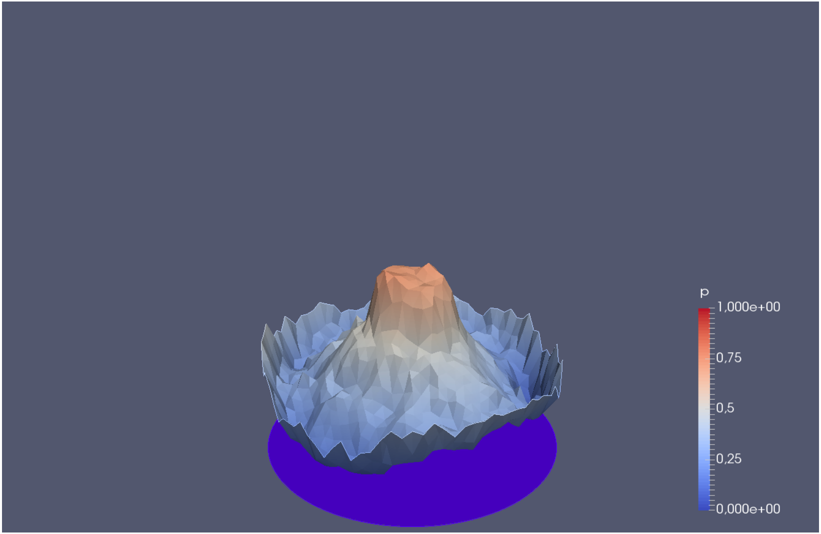
The constant $\underline{u} = \max(m, \frac{C}{|\Omega|})$ is the unique minimizer in $\mathcal{V}_{T,C,M}$ of

$$J(u) = \int_\Omega (1 - P(T))^2 dx.$$

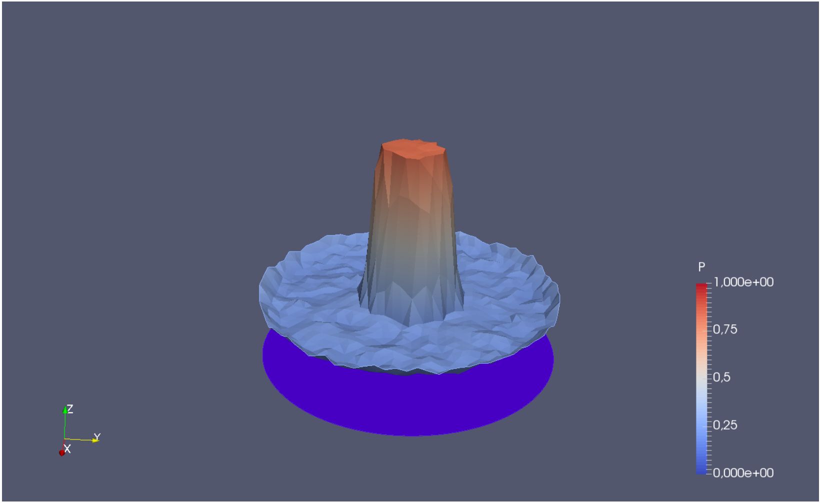
$C > G(\theta)$: Constant solution



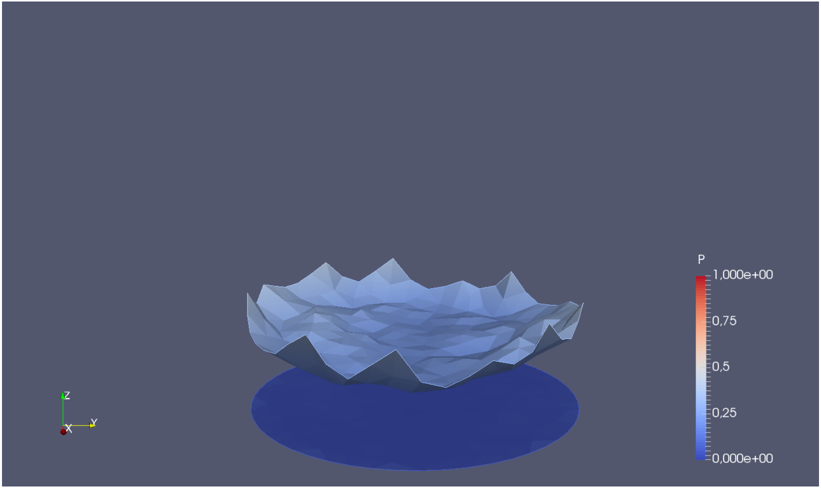
$C > G(\theta)$: "Bang-Bang" solution



$C > G(\theta)$: Greater Diffusion



$C \leq G(\theta)$: IPOPT Failure



Problem Encountered

- C too small $\rightarrow$ IPOPT does not succeed
- C close to $G(\theta)$ $\rightarrow$ partial success (high tolerance) and only with large final time
- IPOPT is dependent on the optimization parameters,
- IPOPT stops on local minimizers,
- Solutions are not feasible in practice.

Gaussian releases

New problem

Look for u on the form

$$u(x) = \sum_{k=0}^{K} m \; exp(\frac{\|x - x_k\|^2}{\sigma^2}),$$

with $x_k \in \Omega$ and m, σ such that $\int_\Omega u = C$.

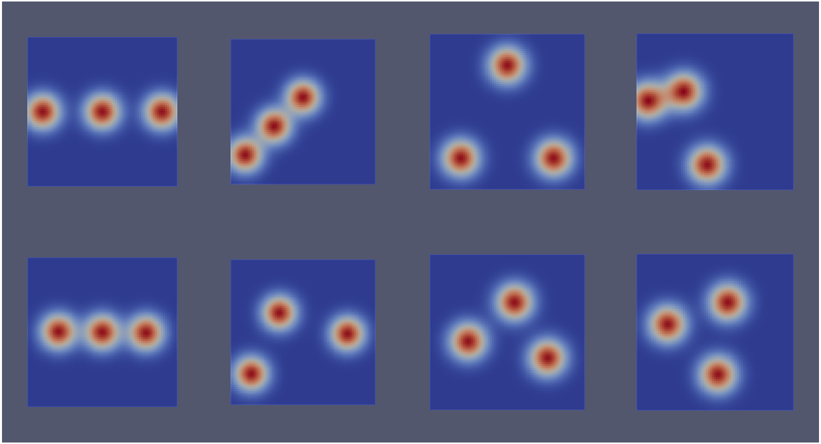
Goal : Look for the best position of the releases x_k.

Advantages :

- Finite dimensional system (with a "small" dimension),
- More close to the reality of the releases: each Gaussian represents a box of mosquitoes.

Dependence on initial guess

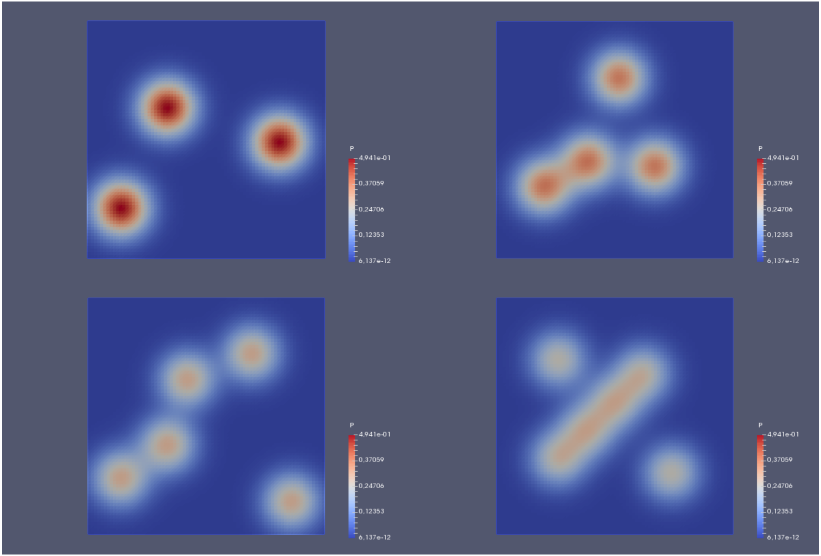
Initial Guess



IPOPT Solution

Problem of Gaussian release

- C small $\rightarrow$ extinction (even with $C > G(\theta)$),
- Strong dependence of the initial conditions,
- Small variance (σ) $\rightarrow$ Extinction.


P
4,941e-01
0,37059
0,24706
0,12353
6,137e-12

Perspectives

- Large number of releases of Gaussian (in space),
- Take into account the cytoplasmic incompatibility,
- Multiple releases in time,
- Change the boundary condition,
- Change the cost function J,
- Enter the PDE as a constraint,
- Better understanding of why IPOPT does not work.

Thank you for your attention !