Mathematical modeling of the spread of Wolbachia for Dengue control

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Collaboration with FioCruz

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Introduction : PDE model for population dynamics

Let us denote $n(t,x)$ the density of a species at time t, position $x \in \mathbb{R}^d$. We assume that the species move randomly according to Brownian motions. We denote by $B(t,x)$ and $D(t,x)$ respectively the birth and death rate. The system governing the dynamics of the population n reads

$$\partial_t n(t,x) \underbrace{-A(x)\,\Delta n(t,x)}_{\text{Brownian motion}} = \underbrace{B(t,x)n(t,x) - D(t,x)n(t,x)}_{\text{birth and death}}.$$

The quantity $A(x) > 0$ is the diffusion coefficient.

Outline

1. Introduction : the case of *Wolbachia*
2. Mathematical modeling
3. Spatial spread of Wolbachia
4. Blocking waves

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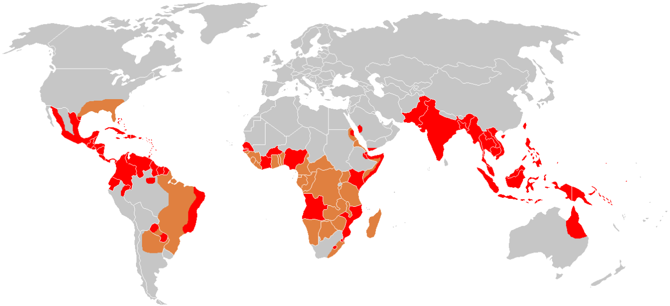
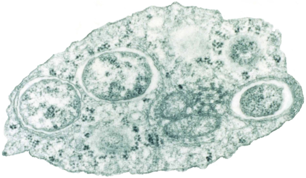
Some fact about Dengue fever

- Dengue is a tropical vector-borne disease. Infect 50M, kills 20k annually. 4 different serotypes. No efficient vaccine.
- Mosquitoes *Aedes Aegypti* (urban) and *Aedes Albopictus* are the main vector (but also for Chikugunya, and Zika).



Wolbachia

- Endo-symbiotic bacteria found in most arthropod species.
- Causes cytoplasmic incompatibility (CI) and blocks transmission of some viruses (Dengue, Chikungunya, Zika) by *Aedes* mosquitoes.
- Several side-effects on its host (enhances/reduces fecundity, reduces lifespan, ...).



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Infected	I	I
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The situation

Method under study

Releasing *Wolbachia*-infected mosquitoes to replace the existing population.

Will they establish and invade, or disappear ?

1. Introduction : the case of *Wolbachia*
2. **Mathematical modeling**
3. Spatial spread of Wolbachia
4. Blocking waves

Mathematical model

We introduce the following quantities :

- n_i : density of Wolbachia-infected mosquitoes ;
- n_u : density of uninfected mosquitoes ;
- $d_u, d_i = \delta d_u$: death rate, $\delta > 1$;
- $F_u, F_i = (1 - s_f)F_u$: fecondity ;
- s_h : cytoplasmic incompatibility parameter (fraction of uninfected females' eggs fertilized by infected males which will not hatch) ;
- σ : resource parameter ;

Model

$$\begin{cases} \partial_t n_i - \Delta n_i & = (1 - s_f)F_u n_i\big(1 - \sigma(n_i + n_u)\big) - \delta d_u n_i, \\ \partial_t n_u - \Delta n_u & = F_u n_u\big(1 - s_h \frac{n_i}{n_i + n_u}\big)\big(1 - \sigma(n_i + n_u)\big) - d_u n_u, \end{cases}$$

Mathematical model : equilibria

We first consider the steady states (equilibria) for the associated ODE model, with no diffusion.

Steady states

As soon as $s_f + \delta - 1 < \delta s_h$, there are four distinct nonnegative equilibria :

- *Wolbachia* invasion $(n_{iW}^*, n_{uW}^*) := (\frac{1}{\sigma} - \frac{d_u}{F_u}\frac{\delta}{1-s_f}, 0)$ is stable ;
- *Wolbachia* extinction $(n_{iE}^*, n_{uE}^*) := (0, \frac{1}{\sigma} - \frac{d_u}{F_u})$ is stable ;
- co-existence steady state $(n_{iC}^*, n_{uC}^*) :=$ $\left((\frac{1}{\sigma} - \frac{d_u}{F_u}\frac{\delta}{1-s_f})\frac{\delta-(1-s_f)}{\delta s_h}, (\frac{1}{\sigma} - \frac{d_u}{F_u}\frac{\delta}{1-s_f})\frac{\delta(s_h-1)+(1-s_f)}{\delta s_h}\right)$ is unstable ;
- extinction $(0, 0)$ is unstable.

Mathematical model : equilibria

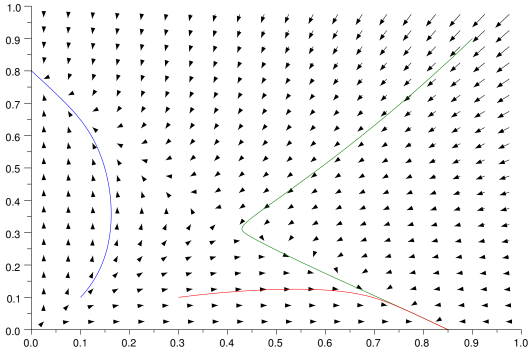

Figure: Phase portrait representing the stability of the equilibria for the dynamical system without spatial diffusion

Large population asymptotics

To further reduce this model, we introduce the parameter ϵ to characterize the high fertility and competition that result in a carrying capacity of order $\frac{1}{\epsilon}$,

$$\begin{cases} \partial_t n_i - \Delta n_i &= (1-s_f) F_u n_i \big(\frac{1}{\epsilon} - \sigma(n_i+n_u)\big) - \delta d_u n_i, \\ \partial_t n_u - \Delta n_u &= F_u n_u (1 - s_h \frac{n_i}{n_i+n_u}) \big(\frac{1}{\epsilon} - \sigma(n_i+n_u)\big) - d_u n_u. \end{cases}$$

We are interested in the limit $\epsilon \to 0$ (large population asymptotics).

Large population asymptotics

In order to perform the asymptotics study, we introduce

$$n = n_i + n_u \text{ (total population)}, \qquad p = \frac{n_i}{n_i + n_u} \text{ (fraction of infected)}.$$

After straightforward computations, we find

$$\begin{cases} \partial_t n - \Delta n = (n - \frac{1}{\epsilon})(\sigma F_u n(s_h p^2 - (s_f + s_h)p + 1) - d_u((\delta - 1)p + 1)), \\ \partial_t p - \Delta p + \frac{2\epsilon}{1-\epsilon n} \nabla p \cdot \nabla n = p(1-p)(\sigma F_u n(s_h p - s_f) + (1-\delta)d_u). \end{cases}$$

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Formally, when $\epsilon \to 0$, we deduce from the first equation that

$$n \to n_0 = \frac{d_u((\delta - 1)p_0 + 1)}{\sigma F_u(s_h {p_0}^2 - (s_f + s_h)p_0 + 1)};$$

Reduction of the model

Injecting this expression into the second equation, we obtain after letting $\epsilon \to 0$,

$$\partial_t p_0 - \Delta p_0 = \delta d_u s_h \frac{p_0(1-p_0)(p_0-\theta)}{\sigma F_u(s_h {p_0}^2 - (s_f+s_h)p_0 + 1)}, \quad \theta = \frac{s_f+\delta-1}{\delta s_h}.$$

Notice that for $\delta \geq 1$ and $s_f < s_h$, we have $\theta \in (0,1)$ and the denominator never vanishes on $(0,1)$.

This is the model recently proposed by *Barton & Turelli*[1]

1. *Spatial Waves of Advance with Bistable Dynamics : Cytoplasmic and Genetic Analogues of Allee Effects*, The American Naturalist, 2011

Reduction of the model

Theorem

Assuming 'well-prepared' initial data, then when $\epsilon \to 0$, we have $p := \frac{n_i}{n_i+n_u} \to p_0$ strongly in $L^2_{loc}(\mathbb{R}^+; L^2(\mathbb{R}^d))$, weakly in $L^2_{loc}(\mathbb{R}^+; H^1(\mathbb{R}^d))$ where p_0 is the unique solution to

$$\partial_t p_0 - \Delta p_0 = f(p_0),$$

$$f(p_0) = \delta d_u s_h \frac{p_0(1-p_0)(p_0-\theta)}{s_h p_0^2 - (s_f+s_h)p_0 + 1}, \qquad \theta = \frac{s_f+\delta-1}{\delta s_h}.$$

Steps for the proof :

- Uniform estimate of n and p and their gradient in L^2 ;
- Relative strong compactness thanks to a 'Aubin-Lions' Lemma ;
- Passing to the limit.

1 Introduction : the case of *Wolbachia*

2 Mathematical modeling

3 **Spatial spread of Wolbachia**

4 Blocking waves

Generality for bistable reaction-diffusion equation

General **bistable** equation for p

$$\partial_t p - \Delta p = f(p),$$

where f is bistable, i.e. $f(0) = 0$, $f(\theta) = 0$ and $f(1) = 0$, $f < 0$ on $(0, \theta)$ $f > 0$ on $(\theta, 1)$.

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We have two stable steady states : 0 and 1

Question

- Can an invasion of the steady state $p = 1$ (Wolbachia infected) occur ? What will be the speed of invasion ?
- If an invasion can occur, how to guarantee it with releases of Wolbachia infected mosquitos ?

Generality for bistable reaction-diffusion equation

To answer to the first question, we study traveling waves.

Traveling waves

Particular solution in translation with a constant velocity c :
$p(t,x) = \widetilde{p}(x - ct)$, with $\widetilde{p}(-\infty) = 1$, $\widetilde{p}(+\infty) = 0$ and $\widetilde{p}' < 0$.

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$$-c\widetilde{p}' - \widetilde{p}'' = f(\widetilde{p}).$$

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Multiplying by $\widetilde{p}'$ and integrating we get :

$$c\int_{\mathbb{R}} (\widetilde{p}'(x))^2 dx = -\int_{\mathbb{R}} f(\widetilde{p}(x))\widetilde{p}'(x)dx = \int_0^1 f(\xi)d\xi.$$

Generality for bistable reaction-diffusion equation

Consequence

$$c > 0 \quad \text{if and only if} \quad \int_0^1 f(\xi)d\xi > 0.$$

In other words, we can have invasion of the state 1 if and only if $\int_0^1 f(\xi)d\xi > 0$.

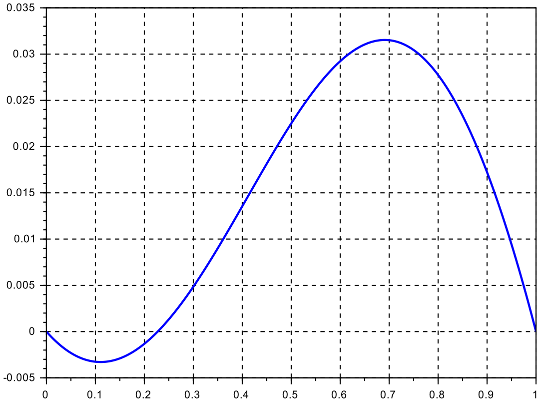
Fortunately, with the numerical data taken from literature, we have $\int_0^1 f(\xi)d\xi > 0$ for the above model for Wolbachia.

Traveling waves

There exists a traveling wave with $c > 0$ for the reduced model for Wolbachia.

Generality for bistable reaction-diffusion equation

Possible shape for f :



Critical propagule

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Answer

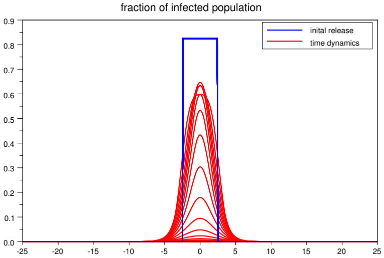
There exists a family of function $(v_\alpha)_\alpha$, compactly supported, radially symmetric and decreasing, such that if there exists a time $\tau > 0$, for which we have $p(\tau) \geq v_\alpha$, then $p(t) \to 1$ uniformly on every compact as $t \to +\infty$. We call them α-bubbles.

Consequence. Let Ω be a bounded domain containing the support of one bubble. Then, the probability of success of invasiveness tends to 1 as the number of releases goes to $+\infty$.

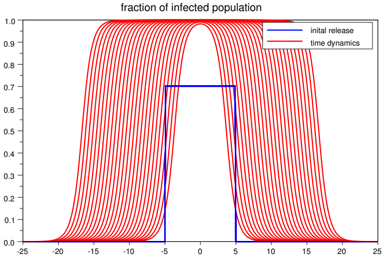
Numerical results in one dimension

With the same amount of mosquitoes, we consider two different initial repartitions :

Extinction



Invasion

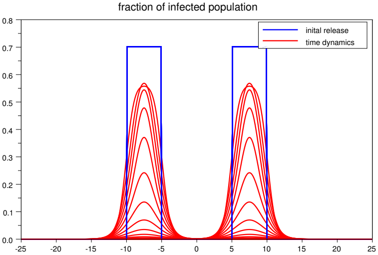


Spatial distribution is important.

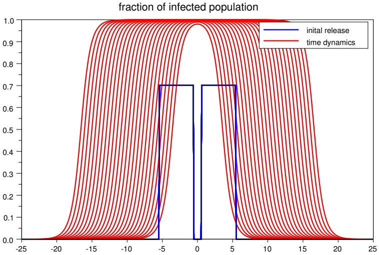
Numerical results in one dimension

Other examples to emphasize the importance of the spatial distribution :

Extinction



Invasion



Multiple releases : movie

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Blocking waves

The environment is not heterogeneous. In order to take into account the spatial variation in the total density of mosquitos, denoted N, the following equation has been introduced

$$\partial_t p - \partial_{xx} p - 2\partial_x(\log N)\partial_x p = f(p),$$

f is bistable (i.e. $f(0) = f(\theta) = f(1) = 0$, $f < 0$ on $(0,\theta)$, $f > 0$ on $(\theta, 1)$), and $\int_0^1 f(x)dx > 0$.

For the sake of simplicity, we assume that we have exponential variation of the density in a domain $[-L, L]$,

$$\partial_x \log(N) = \begin{cases} \frac{C}{2}, & \text{on } [-L, L]; \\ 0, & \text{on } \mathbb{R} \setminus [-L, L]. \end{cases}$$

Blocking waves

Existence of a stationary wave boils down to existence for

$$\begin{aligned} & -p'' - Cp' = f(p), && \text{on } [-L, L], \\ & -p'' = f(p), && \text{on } \mathbb{R} \setminus [-L, L], \\ & p(-\infty) = 1, p(+\infty) = 0, p > 0. && \end{aligned}$$

For C and L given, we call (C, L)-barrier a solution to this system.

Blocking waves

Assume that there exists a (C, L)-barrier, denoted p_B. Then any solution to

$$\partial_t p - \partial_{xx} p - 2\partial_x(\log N)\partial_x p = f(p),$$

with initial data such that $p^{ini} \leq p_B$, has stopped propagation, i.e. $\forall\, t \geq 0, p(t) \leq p_B$.

Blocking waves

We recall that, for bistable equation, there exists a unique traveling wave solution $(\tilde{p}, c^*)$ solution to

$$-\tilde{p}'' - c^*\tilde{p}' = f(\tilde{p}), \qquad \text{on } \mathbb{R},$$
$$\tilde{p}(-\infty) = 1, \quad \tilde{p}(+\infty) = 0.$$

Moreover, since we have assumed $\int_0^1 f(x)dx > 0$, we have $c^* > 0$.
This is the particular case $L = \infty$ in our blocking wave problem.
It seems then natural to have $C \geq c^*$.

Blocking waves

More precisely, we have the following result

Theorem

Let $C > 0$ and $L > 0$. For $C > c^*$, there exists $L_*(C) > 0$ such that there exists a (C, L)-barrier if and only if $L \geq L_*(C)$. Moreover, $C \mapsto L_*(C)$ is decreasing and

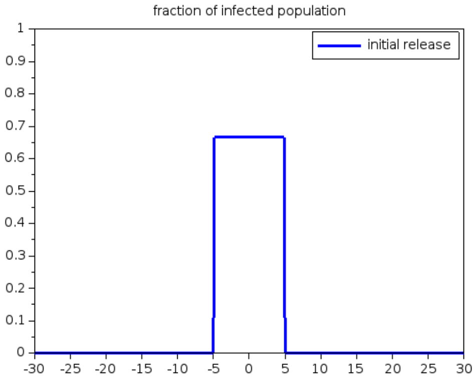
$$\lim_{C \to c^*} L_*(C) = +\infty,$$

$$L_*(C) \sim \frac{1}{4C} \log\left(1 - \frac{F(1)}{F(\theta)}\right), \text{ when } C \to +\infty,$$

where $F(x) = \int_0^x f(z)dz$ (thus $F(1) > 0$ and $F(\theta) < 0$).

Blocking waves : numerical example

In the following example, we consider the previous model for Wolbachia invasion and consider that $C = 0.07$ on the domain $[-20, -10]$.



Conclusion and perspectives

Critical propagule. Study in higher dimension.

Invasion. Comparison of numerical results with what is really observed ? Active control on the release protocol.

Environment. How do spatial-heterogeneity in parameters interfere ?

Mosquito life cycle. Towards a better understanding of the mosquito life cycle to model the mosquito dynamics. Influence of larvae on hatching ?

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Thank you for your attention !