Mathematical modeling of the spread of Wolbachia for Dengue control

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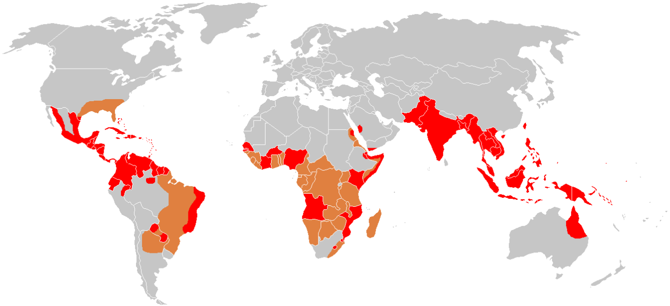
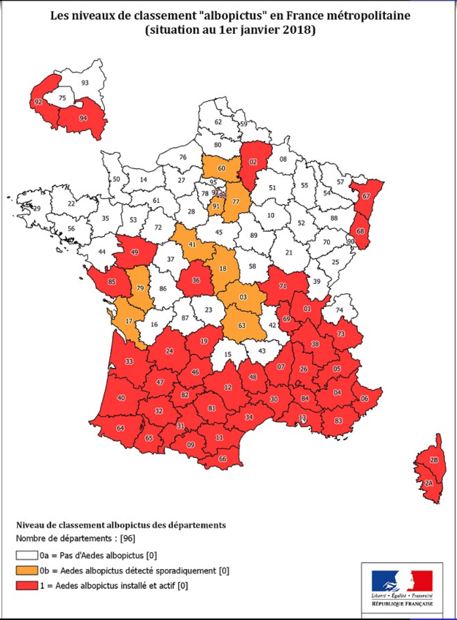
Outline

Some fact about Dengue fever

- Dengue is a tropical vector-borne disease. Infect >100M, kills 20k annually. 4 different serotypes. No efficient vaccine.
- Mosquitoes *Aedes Aegypti* and *Aedes Albopictus* are the main vector (but also for Chikugunya, and Zika).





Source : Ministère des Solidarités et de la Santé

Fight against arboviruses

In absence of vaccine or curative treatment, acting on the population of mosquitoes *Aedes* is essentially the only feasible control method.

- Mechanical remove of breeding sites.
  Difficult to implement to have good efficiency.
- Application of insecticides.
  Increase of moquito resistance.
  Negative impact on the environment.
- Sterile insect techniques : release of sterilized (or incompatible) males.
- Population replacement strategies

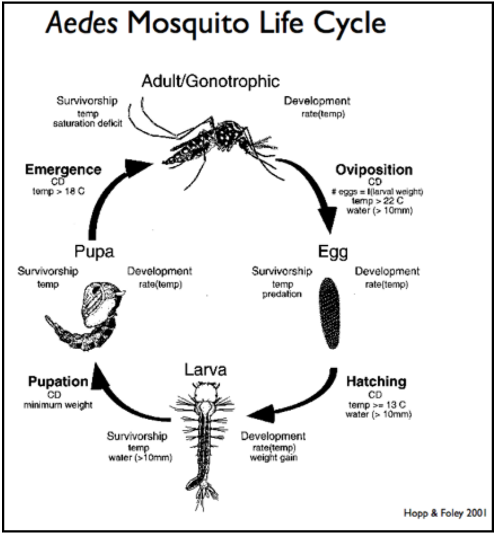
The two latter techniques have been studied by the HCB (Haut Conseil des Biotechnologies) in June 2017.

Main vector : *Aedes* mosquitoes

Some fact about *Aedes* mosquitoes, considered as the most dangerous species of mosquitoes for human :

- There are more than 100 species of *Aedes* among them the major arbovirus vectors are *Aedes aegypti* (tropical region) and *Aedes alpopictus* (more resistants to low temperature).
- Its life cycle is divided into two phases : aquatic (egg, larva,pupa) and aerial (adult).
- Female lays 40-80 eggs by oviposition. Several oviposition per female during her life.
- Only females suck bloods, preferentially from humans, to maturate their eggs.
- Adults can fly and their dispersal is estimated less than 1km during its life.

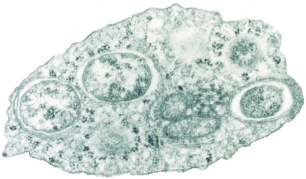
Aedes mosquitoes



Aquatic phase :
egg (few days to several months)
larvae (3 days to several weeks)
pupa (1-3 days)
Adult phase ($\sim$ 1 month)

Wolbachia

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



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Infected	I	I
Sound	×	S

Method under study

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

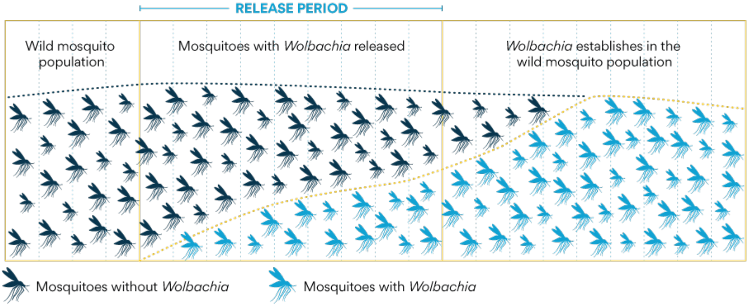

Figure taken from the *eliminate dengue* program
`http://www.eliminatedengue.com/program`

Method under study

We are dealing with a population replacement problem.

Questions

- Is it possible to guarantee the spatial spread of the Wolbachia infected population thanks to local releases of mosquitoes ? How ?
- What is the influence of spatial heterogeneities ?

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) ;
- K : carrying capacity ;

Model

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

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

Mathematical model : equilibria

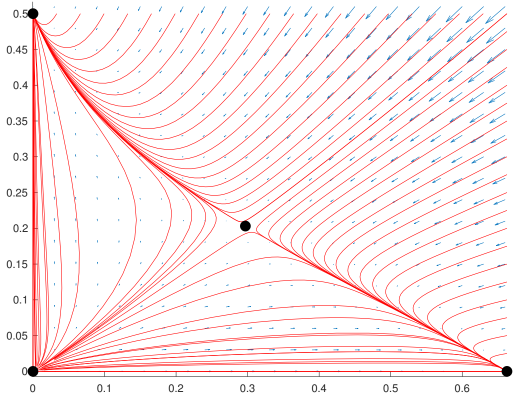

Figure – Phase portrait representing the equilibria and their stability for the dynamical system without spatial diffusion

Large fertility asymptotics

To further reduce this model, we assume that the birth rate is high and introduce the parameter ϵ such that $F_u = \frac{F_u^0}{\epsilon}$,

$$\begin{cases} \partial_t n_i - \Delta n_i & = (1 - s_f)\frac{F_u^0}{\epsilon} n_i \left(1 - \frac{n_i + n_u}{K}\right) - \delta d_u n_i, \\ \partial_t n_u - \Delta n_u & = \frac{F_u^0}{\epsilon} n_u \left(1 - s_h \frac{n_i}{n_i + n_u}\right)\left(1 - \frac{n_i + n_u}{K}\right) - d_u n_u. \end{cases}$$

We are interested in the limit $\epsilon \to 0$.

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We are interested in the limit $\epsilon \to 0$.
We first observe that

$$n_i + n_u = K + O(\epsilon).$$

Large fertility asymptotics

In order to perform the asymptotics study, we introduce

$$n = \frac{1}{\epsilon}\left(1 - \frac{n_i + n_u}{K}\right), \qquad p = \frac{n_i}{n_i + n_u} \text{ (fraction of infected).}$$

After straightforward computations, we find

$$\begin{cases} \partial_t n - \Delta n = -\frac{1-\epsilon n}{\epsilon}\left(F_u^0 n(s_h p^2 - (s_f + s_h)p + 1) - d_u((\delta - 1)p + 1)\right), \\ \partial_t p - \Delta p + \frac{2\epsilon}{1-\epsilon n}\nabla p \cdot \nabla n = p(1-p)\left(F_u^0 n(s_h p - s_f) + (1-\delta)d_u\right). \end{cases}$$

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

$$n \to n_0 = \frac{d_u((\delta - 1)p_0 + 1)}{F_u^0(s_h {p_0}^2 - (s_f + s_h)p_0 + 1)}.$$

Reduction of the model

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

$$\partial_t p_0 - \Delta p_0 = \delta d_u s_h \frac{p_0(1-p_0)(p_0-\theta)}{F_u^0(s_h {p_0}^2 - (s_f+s_h)p_0 + 1)}, \quad \theta = \frac{s_f+\delta-1}{\delta s_h}.$$

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 celebrated model 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

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

$$f(p_0) = \frac{\delta d_u s_h}{F_u^0} \frac{p_0(1-p_0)(p_0-\theta)}{s_h p_0^2 - (s_f + s_h)p_0 + 1}, \qquad \theta = \frac{s_f + \delta - 1}{\delta s_h}.$$

Steps for the proof[2] :

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

2. M. Strugarek, N. V., *Reduction to a single closed equation for 2 by 2 reaction-diffusion systems of Lotka-Volterra type, SIAM J. Appl. Math.* (2016)

Generality for bistable reaction-diffusion equation

General **bistable** equation for p

$$\partial_t p - \partial_{xx} p = f(p),$$

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

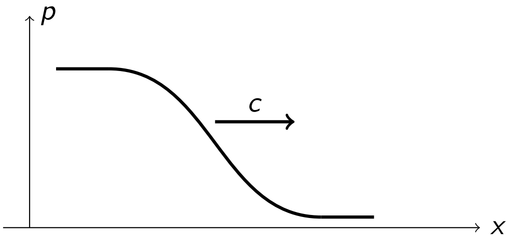
- Can an invasion of the steady state $p = 1$ (Wolbachia infected) occurs ?
- If an invasion can occur, how to guarantee it with releases of Wolbachia infected mosquitos ?

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 $\widetilde{p}' < 0$.



Generality for bistable reaction-diffusion equation

Considering the reaction-diffusion equation

$$\partial_t p - \partial_{xx} p = f(p),$$

and looking for a particular solution under the form $p(t,x) = \widetilde{p}(x-ct)$, we get

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

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

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

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

Generality for bistable reaction-diffusion equation

Consequence

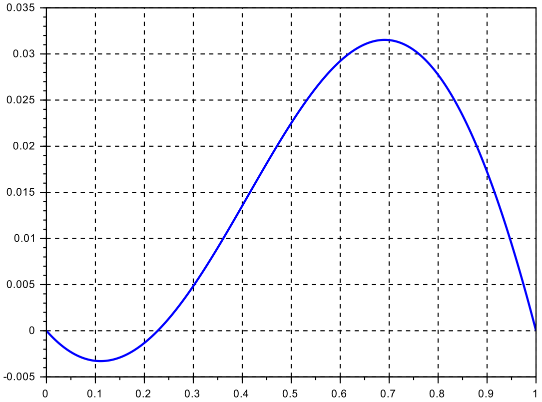
$$c > 0 \quad \text{if and only if} \quad \int_0^1 f(\xi)d\xi > 0.$$

In other words, we can have invasion of the state 1 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.

Generality for bistable reaction-diffusion equation

Possible shape for f :



Generality for bistable reaction-diffusion equation

Existence of traveling waves

There exists a decreasing traveling wave with $c > 0$ for the reduced model for Wolbachia, $\partial_t p - \partial_{xx} p = f(p)$, f bistable as above.

Idea : phase-space method [3]

We look for $c \in \mathbb{R}$ and a decreasing function $\tilde{p}$ to the following differential system thanks to a shooting method :

$$\begin{cases} -c\widetilde{p}' - \widetilde{p}'' = f(\widetilde{p}), \\ \widetilde{p}(-\infty) = 1, \quad \widetilde{p}(+\infty) = 0. \end{cases}$$

3. H. Berestycki, B. Nicolaenko, B. Scheurer, SIAM J. Math. Anal. 1985.

Critical propagule

Critical propagule

How to spatially introduce *Wolbachia*-infected mosquitoes to guarantee invasion ? How to initiate a wave ?

Critical propagule

Critical propagule

How to spatially introduce *Wolbachia*-infected mosquitoes to guarantee invasion ? How to initiate a wave ?

Answer

There exists a family of functions $(v_\alpha)_\alpha$, 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.

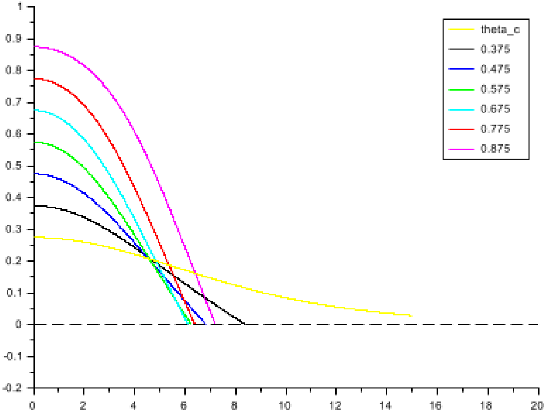
Critical propagule

References :

- A. Zlatos. *Sharp transition between extinction and propagation of reaction*. J. Amer. Math. Soc., 2006.
- P. Polacik. *Threshold solutions and sharp transitions for nonautonomous parabolic equations on* $\mathbb{R}^N$. Archive for Rational Mechanics and Analysis, 2011.
- Y. Du, H. Matano, *Convergence and sharp thresholds for propagation in nonlinear diffusion problems*. J. Eur. Math. Soc., 2010.
- C. Muratov, X. Zhong, *Threshold phenomena for symmetric-decreasing radial solutions of reaction-diffusion equations*, Discrete Contin. Dyn. Syst., 2017.

Critical bubble in one dimension

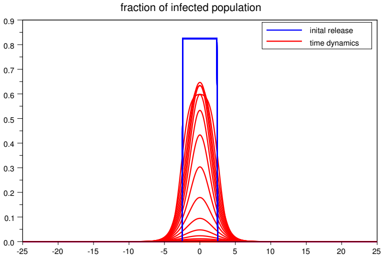
Family of initial data (u_α) above which invasion occurs (one dimension, to symmetrize with respect to zero) :



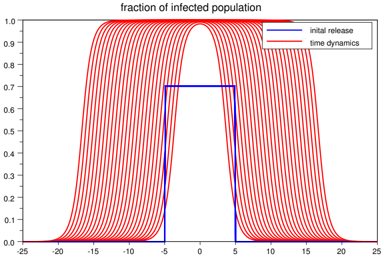
Numerical results in one dimension

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

Extinction



Invasion

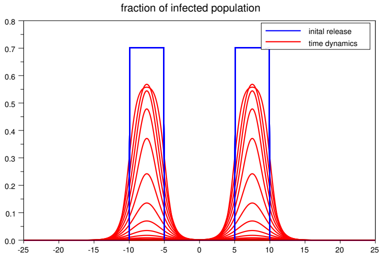


Spatial distribution is important.

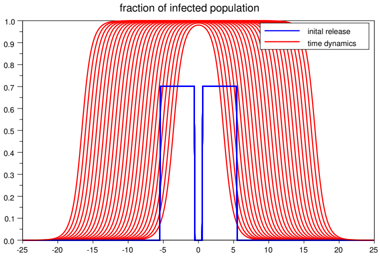
Numerical results in one dimension

Other examples to emphasize the importance of the spatial distribution :

Extinction



Invasion



Multiple releases : movie

Uncertainty quantification of the releases

Using the same idea, with radial symmetry, we may prove that such result holds also in higher dimension [4].

Consequence

Let Ω be a bounded domain containing the support of one bubble. Let us assume that we perform some random point releases in Ω. Then, the probability of success of invasion tends to 1 as the number of releases goes to $+\infty$.

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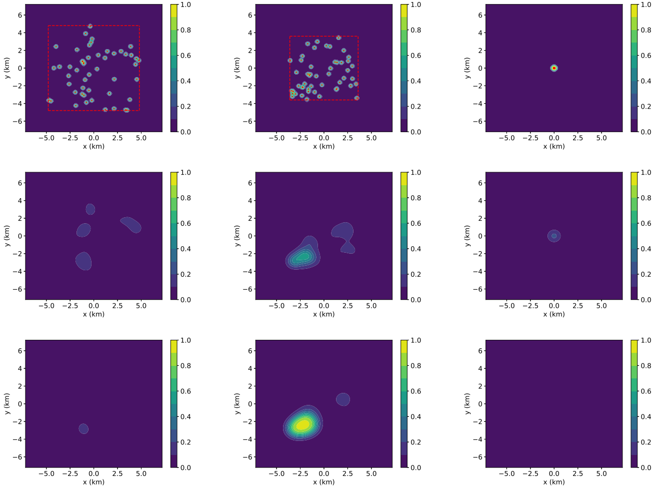
4. M. Strugarek, N. V., J. Zubelli, *Quantifying the survival uncertainty of Wolbachia-infected mosquitoes in a spatial model*, Math. Biosci. Eng.

Uncertainty quantification of the releases



Initial time

after 25 days

after 50 days

Active control

Let us consider the problem of active control with a function u (which may depend on p : feedback control)

$$\partial_t p - \Delta p = f(p) + u\mathbf{1}_{[0,T]\times\Omega}, \qquad p(t=0) = 0.$$

Due to the existence of this bubble, it is easy to prove[5]

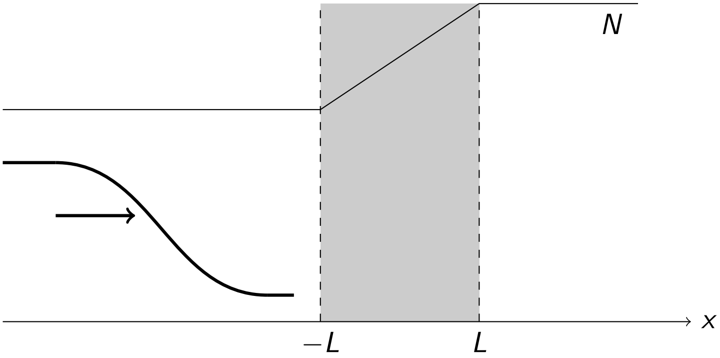
Theorem

There exist a time $T > 0$, a bounded open set $\Omega \subset \mathbb{R}^d$ and an active control $u = g(p)$ such that the solution p to the above equation converges to 1 as t goes to $+\infty$, locally uniformly on $\mathbb{R}^d$.

5. P.A. Bliman, N. V., *Establishing traveling wave in bistable reaction-diffusion system by feedback*, IEEE Control Systems Letter, 2017.

Blocking waves

The environment is heterogeneous. Can strong variations in the total density of mosquitoes N stop the propagation ?



Blocking waves

In order to take into account the spatial variation in the total density of mosquitos, denoted N, the following equation has been introduced [6]

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

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 $[-L, L]$,

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

6. The term $\partial_x(\log N)$ is usually called the *gene flow*.

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 [7]

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

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

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

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

7. G. Nadin, M. Strugarek, N. V., *Hindrances to bistable front propagation : application to Wolbachia invasion*, J. Math. Biol. 76 (2018), no 6, 1489-1533.

Blocking waves

Proposition

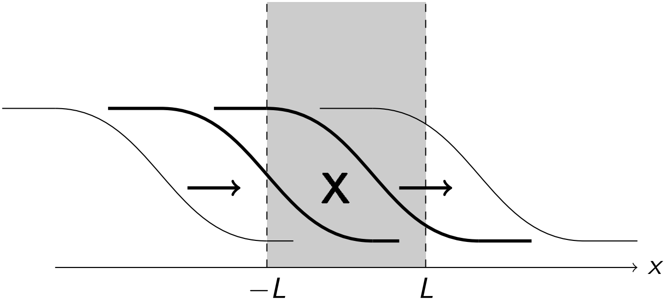
Let $C > 0$ and $L > 0$. We have the following characterisation of $(C, L)-$barrier :

1. Any $(C, L)-$barrier is decreasing.
2. Il $L > L_*(C)$, then there exists at least two $(C, L)-$barriers and they are totally ordered. Then we can define a maximal and a minimal $(C, L)-$barrier.
3. The maximal $(C, L)-$barrier is unstable from above and the minimal $(C, L)-$barrier is stable from below.

Blocking waves

We can draw the following consequences, if $L > L_*(C)$:

- The front cannot cross the minimal $(C, L)-$barrier if it is initially below it.
- The extra cost we have to pay to cross the obstacle is to create a profile above the maximal $(C, L)-$barrier.



Blocking waves

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- T.J. Lewis and J.P. Keener, *Wave-block in excitable media due to regions of depressed excitability*, SIAM Journal on Applied Mathematics, 2000.
- G. Chapuisat and R. Joly, *Asymptotic profiles for a traveling front solution of a biological equation*, Math. Mod. Methods Appl. Sci., 2011.
- H. Berestycki, N. Rodriguez, L. Ryzhik, *Traveling wave solutions in a reaction-diffusion model for criminal activity*, SIAM MMS, 2013.

Blocking waves : numerical examples

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

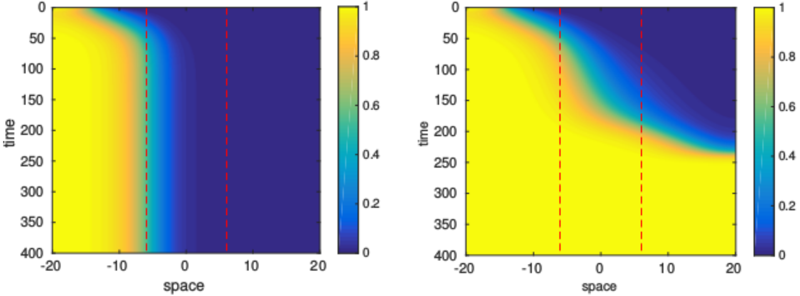

Figure – Left : Blocking with $L = 6$ and $C = 0.5$; Right : Propagation with $L = 6$ and $C = 0.2$.

Blocking waves : numerical examples

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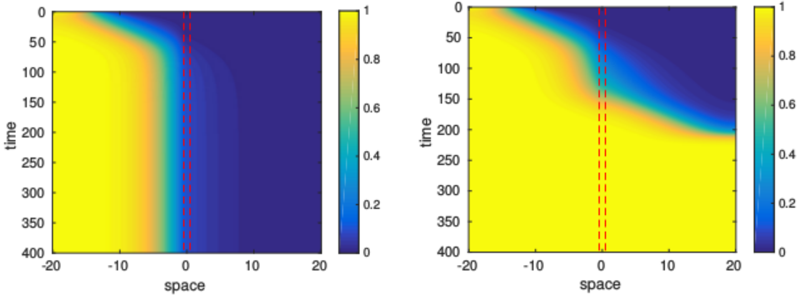

Figure – Left : Blocking with $L = 0.5$ and $C = 2$; Right : Propagation with $L = 0.5$ and $C = 1$.

Conclusion and perspectives

Answering to the questions raised in the introduction :

- The success of the spatial propagation of the Wolbachia-infected population depends strongly on the position of the releases, which must be done in a sufficiently large area with a sufficient amount of mosquitoes.
- Spatial heterogeneities in the environment may block the propagation.

Conclusion and perspectives

Some perspectives :

Critical propagule. Study for the system of two populations.

Blocking. What is the delay ?

Invasion. Comparison of numerical results with what is really observed ?
Optimization of the releases (ongoing work in collaboration with Martin Strugarek, Yannick Privat and Luis Almeida).

Mosquito life cycle. Towards a better understanding of the mosquito life cycle to model the mosquito dynamics.

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Thank you for your attention.