Vector-borne disease outbreak control via instant vector releases

Jesús Bellver Arnau
Thesis advisors: L. Almeida (LJLL) & Y. Privat (IRMA)
Joint work with C. Rebelo (Universidade de Lisboa)

PGMO days
EDF's Lab, Palaiseau

November 29th, 2022

This program has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754362.

Aedes mosquitoes: A public health problem

- *Aedes* mosquitoes transmit: Dengue fever, Zika, Chikungunya, Yellow fever, West Nile fever...

Aedes mosquitoes: A public health problem

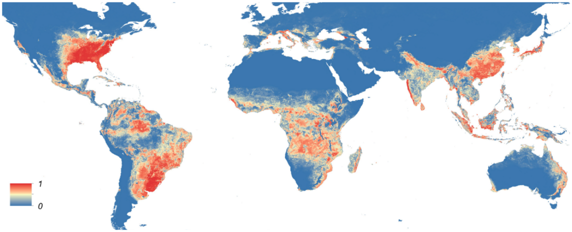
- *Aedes* mosquitoes transmit: Dengue fever, Zika, Chikungunya, Yellow fever, West Nile fever...
- Up to 400 million infections every year and 3.9 billion people at risk in 129 countries for Dengue alone.

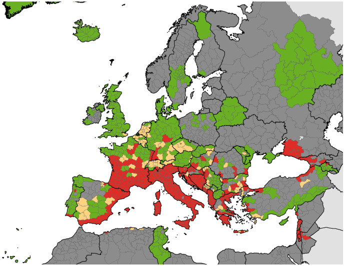
Aedes mosquitoes: A public health problem

- *Aedes* mosquitoes transmit: Dengue fever, Zika, Chikungunya, Yellow fever, West Nile fever...
- Up to 400 million infections every year and 3.9 billion people at risk in 129 countries for Dengue alone.
- No efficient vaccine, nor antiviral drugs.

Aedes mosquitoes: A public health problem

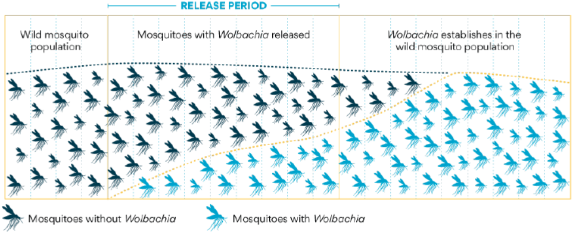
- *Aedes* mosquitoes transmit: Dengue fever, Zika, Chikungunya, Yellow fever, West Nile fever...
- Up to 400 million infections every year and 3.9 billion people at risk in 129 countries for Dengue alone.
- No efficient vaccine, nor antiviral drugs.
- Expansion of vector's habitat (trade, global warming, reduction of predator populations ...)





How to fight it? Two methods

- *Wolbachia* method
  - Reduction of the vector capacity.
  - Cytoplasmic incompatibility.
  - *Wolbachia* vertical transmission.
  - Population replacement.

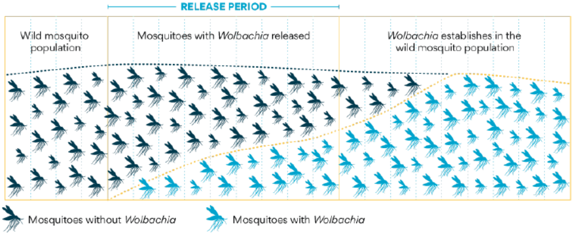


Source: http://www.eliminatedengue.com/our-research/Wolbachia

♀\♂	Infecté	Sain
Infecté	I	I
Sain	×	S

How to fight it? Two methods

- *Wolbachia* method
  - Reduction of the vector capacity.
  - Cytoplasmic incompatibility.
  - *Wolbachia* vertical transmission.
  - Population replacement.



Source: http://www.eliminatedengue.com/our-research/Wolbachia

♀\♂	Infecté	Sain
Infecté	I	I
Sain	$\times$	S

- Sterile insect technique
  - Population suppression.
  - Recurrent intervention

The model

$$\begin{aligned} S'_H &= b_H H - \frac{\beta_M}{H} I_M S_H - b_H S_H \\ E'_H &= \frac{\beta_M}{H} I_M S_H - \gamma_H E_H - b_H E_H \\ I'_H &= \gamma_H E_H - \sigma_H I_H - b_H I_H \end{aligned}$$

$$M' = b_M M \left(1 - \frac{M}{K}\right) - d_M M$$

The model

$$
\begin{aligned}
S_H' &= b_H H - \frac{\beta_M}{H} I_M S_H - b_H S_H \\
E_H' &= \frac{\beta_M}{H} I_M S_H - \gamma_H E_H - b_H E_H \\
I_H' &= \gamma_H E_H - \sigma_H I_H - b_H I_H
\end{aligned}
$$

$$
\begin{aligned}
S_M' &= b_M M \left(1 - \frac{M}{K}\right) - \frac{\beta_M}{H} S_M I_H - d_M S_M \\
E_M' &= \frac{\beta_M}{H} S_M I_H - \gamma_M E_M - d_M E_M \\
I_M' &= \gamma_M E_M - d_M I_M
\end{aligned}
$$

The model

$$
\begin{aligned}
S_H' &= b_H H - \frac{\beta_M}{H} I_M S_H - b_H S_H \\
E_H' &= \frac{\beta_M}{H} I_M S_H - \gamma_H E_H - b_H E_H \\
I_H' &= \gamma_H E_H - \sigma_H I_H - b_H I_H
\end{aligned}
$$

$$
\begin{aligned}
S_M' &= b_M M \left(1 - \frac{M}{K}\right) - \frac{\beta_M}{H} S_M I_H - d_M S_M \\
E_M' &= \frac{\beta_M}{H} S_M I_H - \gamma_M E_M - d_M E_M \\
I_M' &= \gamma_M E_M - d_M I_M
\end{aligned}
$$

Impulsive control: $u(t) = \sum_{i=1}^{n} c_i \delta(t - t_i)$ **Constraint:** $\sum_{i=1}^{n} c_i = C$

The model

$$
\begin{aligned}
S_H' &= b_H H - \frac{\beta_M}{H} I_M S_H - b_H S_H \\
E_H' &= \frac{\beta_M}{H} I_M S_H - \gamma_H E_H - b_H E_H \\
I_H' &= \gamma_H E_H - \sigma_H I_H - b_H I_H
\end{aligned}
$$

$$
\begin{aligned}
S_M' &= b_M M \left(1 - \frac{M}{K}\right) - \frac{\beta_M}{H} S_M I_H - d_M S_M \\
E_M' &= \frac{\beta_M}{H} S_M I_H - \gamma_M E_M - d_M E_M \\
I_M' &= \gamma_M E_M - d_M I_M
\end{aligned}
$$

Impulsive control: $u(t) = \sum_{i=1}^{n} c_i \delta(t - t_i)$ **Constraint:** $\sum_{i=1}^{n} c_i = C$

Goal: Minimise $J(u)$ during an outbreak

$$J(u) := \int_0^T I_H(t)dt$$

Use of Wolbachia

We add the mosquitoes with Wolbachia:

$$
\begin{aligned}
S_H' &= b_H H - \frac{\beta_M}{H} I_M S_H - \frac{\beta_{WH}}{H} I_W S_H - b_H S_H \\
E_H' &= \frac{\beta_M}{H} I_M S_H + \frac{\beta_{WH}}{H} - \gamma_H E_H - b_H E_H \\
I_H' &= \gamma_H E_H - \sigma I_H - b_H I_H
\end{aligned}
$$

$$
\begin{aligned}
S_M' &= b_M M \left(1 - \frac{M+W}{K}\right) \left(1 - s_h \frac{W}{M+W}\right) - \frac{\beta_M}{H} S_M I_H - d_M S_M \\
E_M' &= \frac{\beta_M}{H} S_M I_H - \gamma_M E_M - d_M E_M \\
I_M' &= \gamma_M E_M - d_M I_M
\end{aligned}
$$

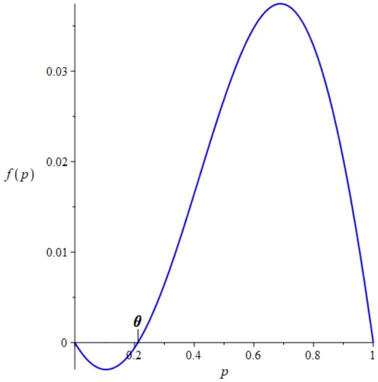
$$
\begin{aligned}
S_W' &= b_W W \left(1 - \frac{M+W}{K}\right) - \frac{\beta_{HW}}{H} S_W I_H - d_W S_W + u \\
E_W' &= \frac{\beta_{HW}}{H} S_W I_H - \gamma_W E_W - d_W E_W \\
I_W' &= \gamma_W E_W - d_W I_W
\end{aligned}
$$

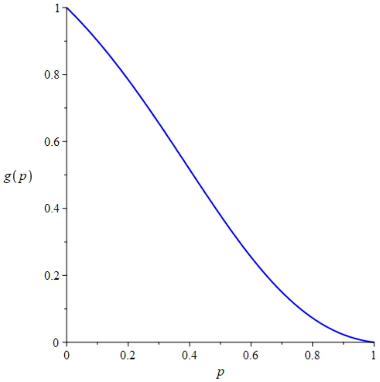
Problem Reduction [Almeida, Privat, Strugarek, Vauchelet (2019)]

We define $p := \frac{W}{M+W}$, the proportion of Wolbachia infected mosquitoes in the population.

We assume a high birth rate $b_N = b_N^0/\epsilon$, $b_W = b_W^0/\epsilon$. In the limit, $\epsilon \to 0$, p obeys the equation:

$$p' = f(p) + ug(p)$$





Problem reduction

1) Assuming a high birth rate we obtain $M = K(1-p)$ and $W = Kp$.

2) Since $S_M = K(1-p) - E_M - I_M$ and $S_W = Kp - E_W - I_W$ eliminate two equations from the system.

$$
\begin{aligned}
S'_H &= b_H H - \frac{\beta_M}{H} I_M S_H - \frac{\beta_{WH}}{H} I_W S_H - b_H S_H \\
E'_H &= \frac{\beta_M}{H} I_M S_H + \frac{\beta_{WH}}{H} I_W S_H - \gamma_H E_H - b_H E_H \\
I'_H &= \gamma_H E_H - \sigma_H I_H - b_H I_H \\
\\
E'_M &= \frac{\beta_M}{H} \left(K(1-p) - E_M - I_M\right) I_H - \gamma_M E_M - d_M E_M \\
I'_M &= \gamma_M E_M - d_M I_M \\
\\
E'_W &= \frac{\beta_{HW}}{H} \left(Kp - E_W - I_W\right) I_H - \gamma_W E_W - d_W E_W \\
I'_W &= \gamma_W E_W - d_W I_W \\
\\
p' &= f(p) + u g(p)
\end{aligned}
$$

Instant releases

$u(t) = \sum_{i=1}^n c_i \delta(t - t_i) = \lim\limits_{\varepsilon \to 0} \sum_{i=1}^n \frac{c_i}{\varepsilon} \mathbb{1}_{[t_i, t_i+\varepsilon]}$

$$p'(t) = f(p(t)) + g(p(t)) \sum_{i=1}^{n} \frac{c_i}{\varepsilon} \mathbb{1}_{[t_i, t_i+\varepsilon]}.$$

Instant releases

$u(t) = \sum_{i=1}^{n} c_i \delta(t - t_i) = \lim_{\varepsilon \to 0} \sum_{i=1}^{n} \frac{c_i}{\varepsilon} \mathbb{1}_{[t_i, t_i + \varepsilon]}$

$$p'(t) = f(p(t)) + g(p(t)) \sum_{i=1}^{n} \frac{c_i}{\varepsilon} \mathbb{1}_{[t_i, t_i + \varepsilon]}.$$

In the limit

$$\begin{cases} p' & = & f(p), \quad t \in [t_i, t_{i+1}], \quad i = 0, \dots, n \\ p(t_i^+) & = & G^{-1}(G(p(t_i^-)) + c_i), \quad i = 1, \dots, n \end{cases}$$

Where $G(p) := \int_0^p \frac{dq}{g(q)}$

Numerics

We compute the derivative of the criterion with respect to each t_i and c_i.

We implemented a gradient descent for the times the Uzawa Algorithm with an augmented Lagrangian for the costs

$$J(u,\lambda) = \int_0^T I_H(t)dt + \lambda\left(\sum_{i=1}^n c_i - C\right) + \frac{\rho}{2}\left(\sum_{i=1}^n c_i - C\right)^2$$

The solution is a saddle point of $J(u,\lambda)$

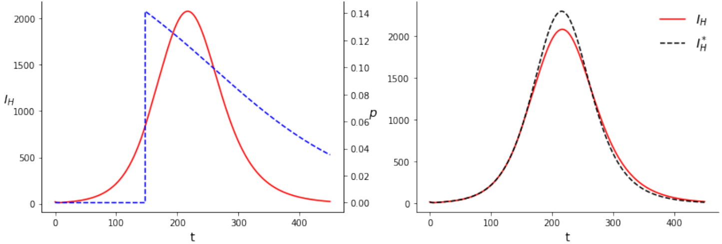
Minimization w.r.t. u**:** $\mathbf{c}_{k+1} = \mathbf{c}_k - \epsilon\left(\nabla_c J(u_k) + \lambda_k + \rho\left(\sum_{i=1}^n c_i - C\right)\right)$

Maximization w.r.t. λ**:** $\lambda_{k+1} = \max\left(\lambda_k + \rho\left(\sum_{i=1}^n c_i - C\right), 0\right)$

Results: *Wolbachia*

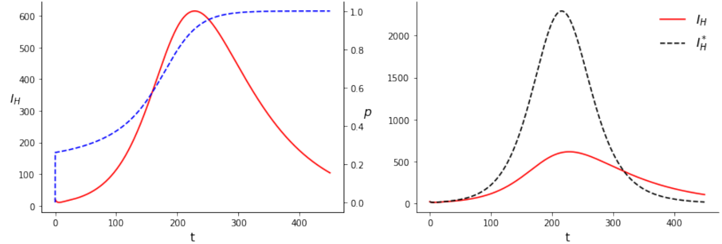
- $C < G(\theta)$: release before the outbreak reaches its peak.
- $C > G(\theta)$: Release at $t = 0$.

$\mathbf{C = 10000}$
Reduction:
2.1%



$\mathbf{C = 20000}$
Reduction:
56.2%

$\mathbf{G(\theta) \approx 14850}$



Use of Sterile mosquitoes

$$
\begin{aligned}
S_H' &= b_H H - \frac{\beta_M}{H} I_M S_H - b_H S_H \\
E_H' &= \frac{\beta_M}{H} I_M S_H - \gamma_H E_H - b_H E_H \\
I_H' &= \gamma_H E_H - \sigma_H I_H - b_H I_H
\end{aligned}
$$

$$
\begin{aligned}
S_M' &= b_M M \left(1 - \frac{M}{K}\right) \qquad - \frac{\beta_M}{H} S_M I_H - d_M S_M \\
E_M' &= \frac{\beta_M}{H} S_M I_H - \gamma_M E_M - d_M E_M \\
I_M' &= \gamma_M E_M - d_M I_M
\end{aligned}
$$

Use of Sterile mosquitoes

$$
\begin{aligned}
S_H' &= b_H H - \frac{\beta_M}{H} I_M S_H - b_H S_H \\
E_H' &= \frac{\beta_M}{H} I_M S_H - \gamma_H E_H - b_H E_H \\
I_H' &= \gamma_H E_H - \sigma_H I_H - b_H I_H \\
\\
S_M' &= b_M M \left(1 - \frac{M}{K}\right) \frac{M}{M + s_c M_S} - \frac{\beta_M}{H} S_M I_H - d_M S_M \\
E_M' &= \frac{\beta_M}{H} S_M I_H - \gamma_M E_M - d_M E_M \\
I_M' &= \gamma_M E_M - d_M I_M \\
\\
M_S' &= u - d_S M_S
\end{aligned}
$$

Instant Releases

Considering again instant releases the equation for the sterile mosquitoes becomes:

$$\begin{cases} M_S' & = & -d_S M_S, \quad t \in [t_i, t_{i+1}], \quad i = 0, \dots, n \\ M_S(t_i^+) & = & M_S(t_i^-) + c_i, \quad i = 1, \dots, n \end{cases}$$

Instant Releases

Considering again instant releases the equation for the sterile mosquitoes becomes:

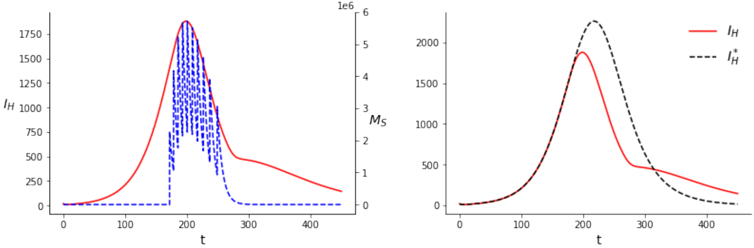
$$\begin{cases} M_S' & = & -d_S M_S, \quad t \in [t_i, t_{i+1}], \quad i = 0, \dots, n \\ M_S(t_i^+) & = & M_S(t_i^-) + c_i, \quad i = 1, \dots, n \end{cases}$$

We can solve this equation explicitly, finding

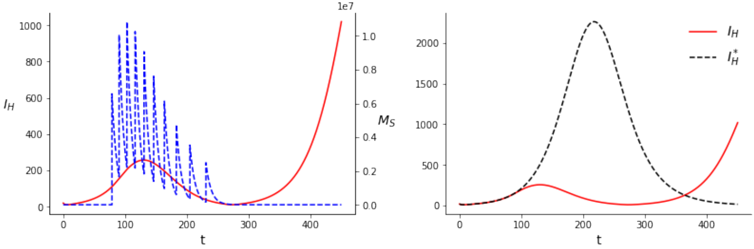
$$M_S(t) = \sum_{j=1}^{i} c_j e^{-d_S(t-t_j)}, \quad t \in [t_i, t_{i+1}], \quad i = 0, \dots, n$$

Results: 10 releases

$\mathbf{C = 3 \cdot 10^7}$
Reduction: 14.7%

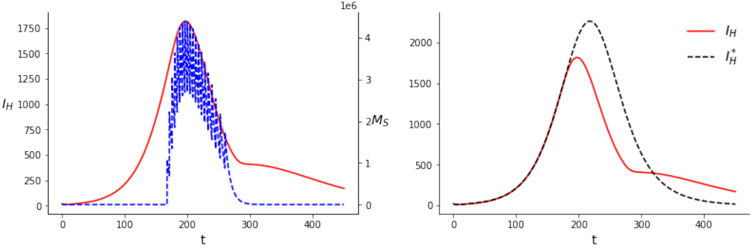


$\mathbf{C = 6 \cdot 10^7}$
Reduction: 75.1%

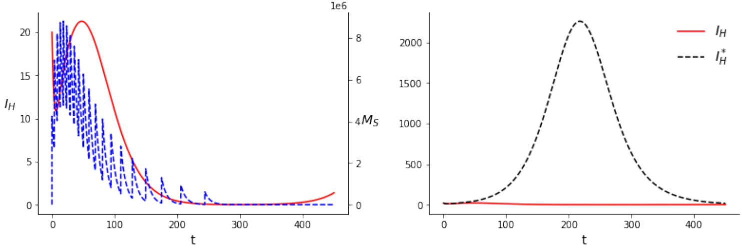


Results: 20 releases

$\mathbf{C = 3 \cdot 10^7}$
Reduction:
16.9%



$\mathbf{C = 6 \cdot 10^7}$
Reduction:
99.3%



Conclusions

Conclusions

- Wolbachia:
    - Optimal strategy: One single release
    - If we have enough mosquitoes to trigger a population replacement: release as soon as possible.
    - If we don't have enough: release before the peak of the outbreak.

Conclusions

- Wolbachia:
  - Optimal strategy: One single release
  - If we have enough mosquitoes to trigger a population replacement: release as soon as possible.
  - If we don't have enough: release before the peak of the outbreak.
- Sterile mosquito:
  - Strategy and results depend highly on the number of releases at first.
  - After ~ 20 releases almost no improvement.
  - With few mosquitoes: spaced releases around the peak.
  - With a lot of mosquitoes: spaced releases from the begginning.

Conclusions

- Wolbachia:
  - Optimal strategy: One single release
  - If we have enough mosquitoes to trigger a population replacement: release as soon as possible.
  - If we don't have enough: release before the peak of the outbreak.
- Sterile mosquito:
  - Strategy and results depend highly on the number of releases at first.
  - After ~ 20 releases almost no improvement.
  - With few mosquitoes: spaced releases around the peak.
  - With a lot of mosquitoes: spaced releases from the begginning.

Thank you for your attention