Mathematical modeling of control techniques for vector borne diseases and their epidemics

Nicolas Vauchelet
vauchelet@math.univ-paris13.fr

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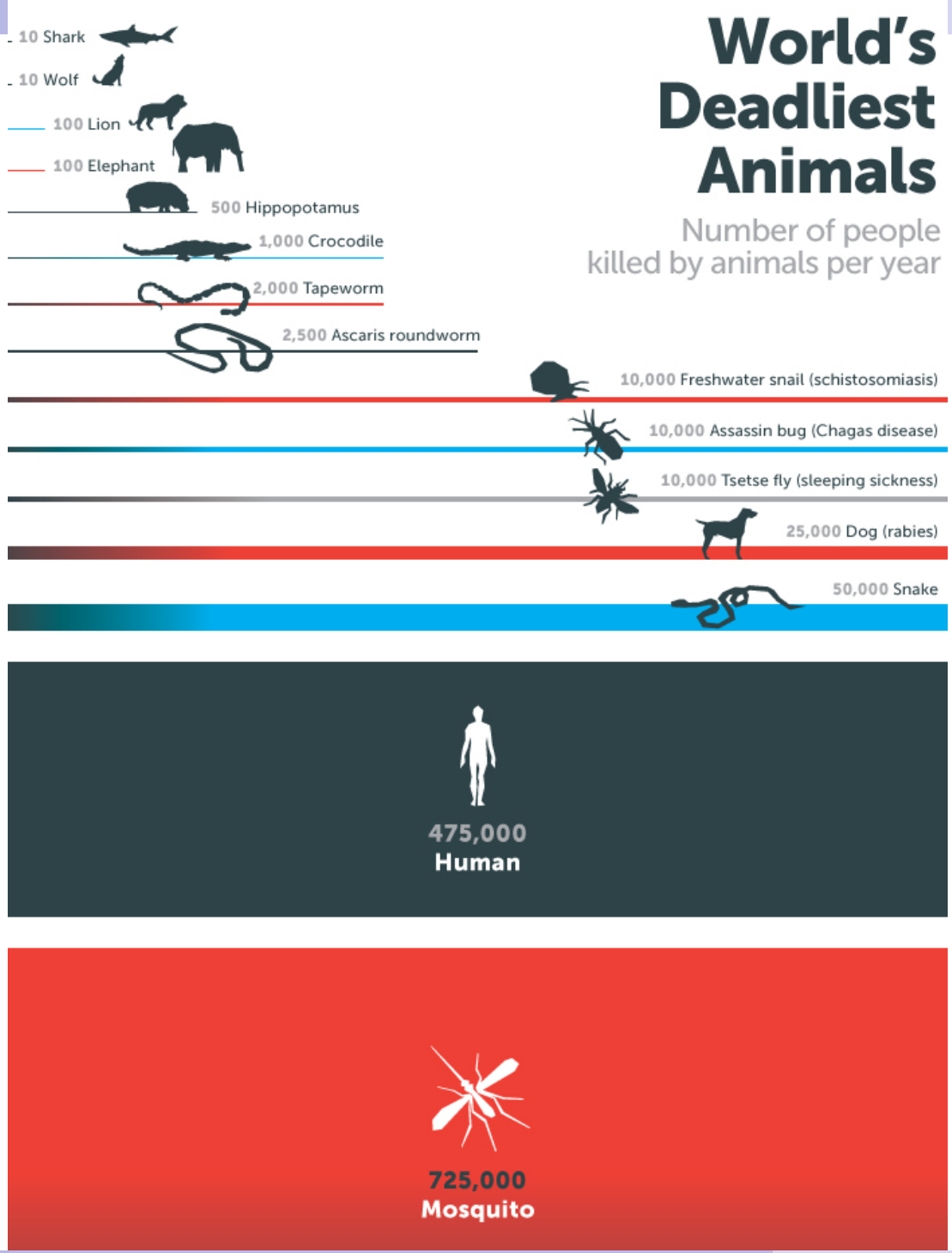


Picture taken from the Blog of Bill Gates

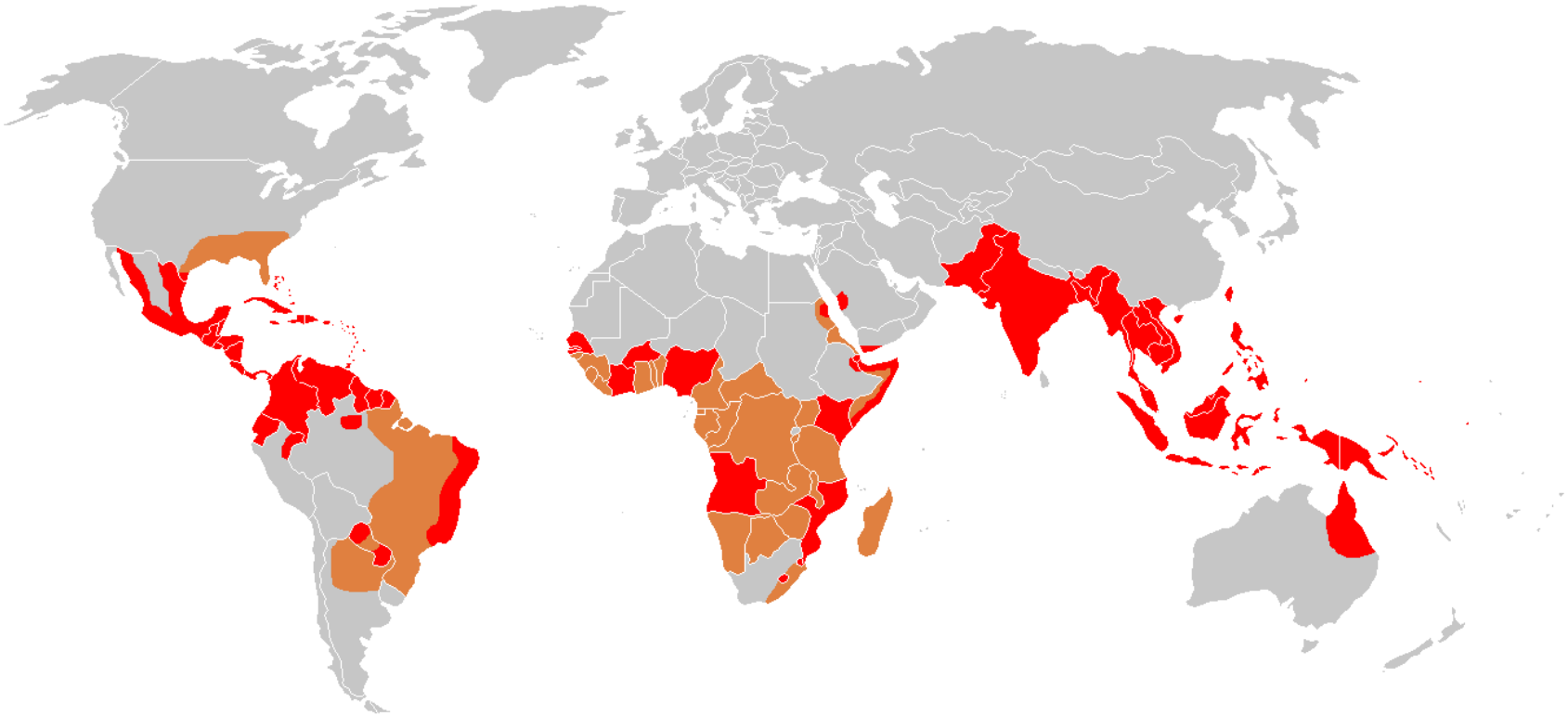
`https://www.gatesnotes.com/Health/Most-Lethal-Animal-Mosquito`

Introduction

- Because of the number of diseases that they carry, mosquitoes are considered as the most dangerous animal for human.
- There are more than 2500 species of mosquitoes and, apart from Antartica, mosquitoes are found in every region of the world. Most species are inoffensive to human but several of them are vectors for diseases :
  - *Aedes* mosquitoes (like *Aedes Aegypti* and *Aedes Albopictus*) are vectors for dengue fever, yellow fever, chikugunya, and zika.
  - *Anopheles* mosquitoes are the main vector of the transmission of *Plasmodium* parasites that causes malaria.
  - *Culex* mosquitoes are the main vector of west Nile virus.
  - Other mosquito-borne parasites include Myiasis, Filariasis, some Encephalitis, ...

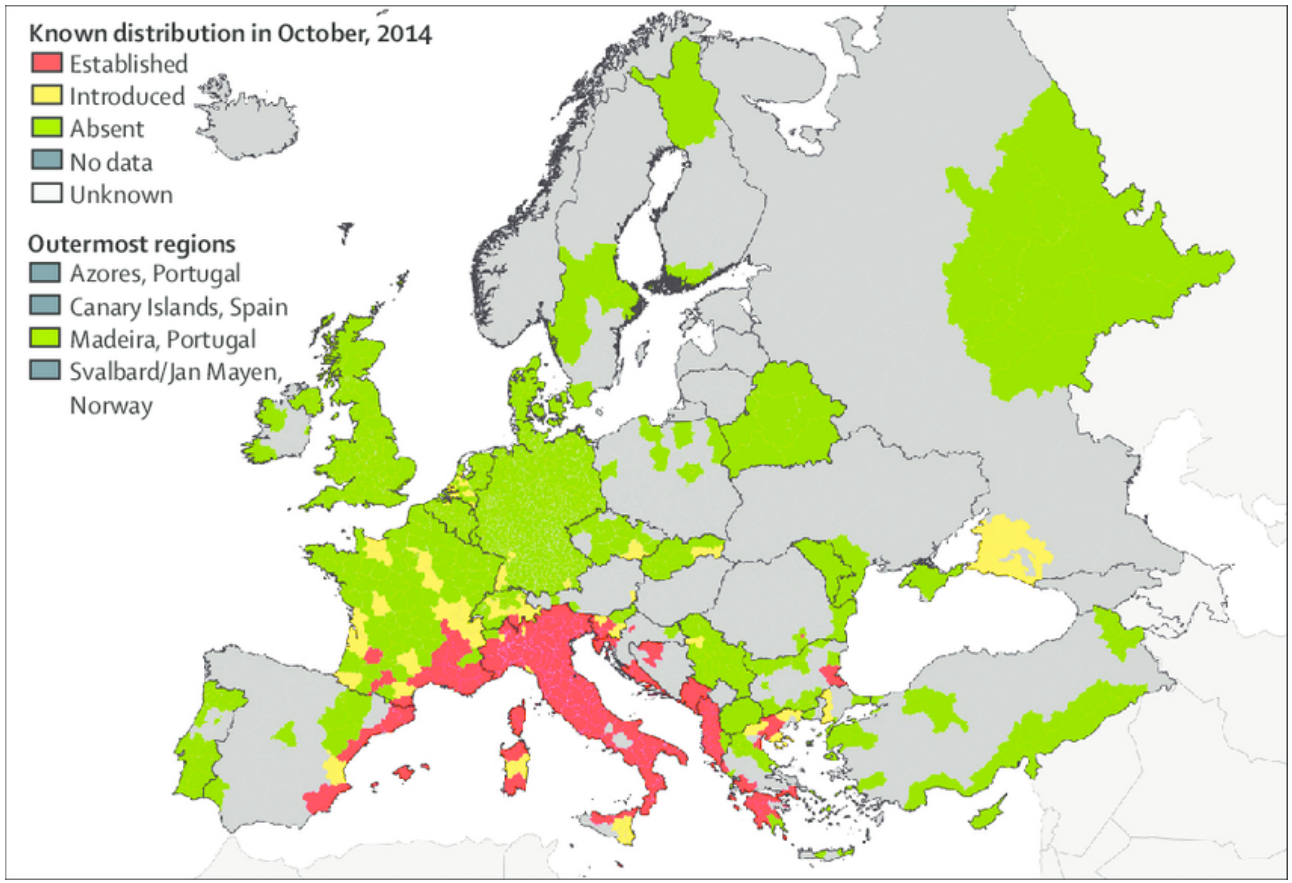
Aedes aegypti in the world

Mosquitoes *Aedes Aegypti* and *Aedes Albopictus* are the main vector (but also for Chikugunya, and Zika). *Aedes aegypti* mosquitoes are mainly present in tropical region of the world :



Aedes albopictus in Europe

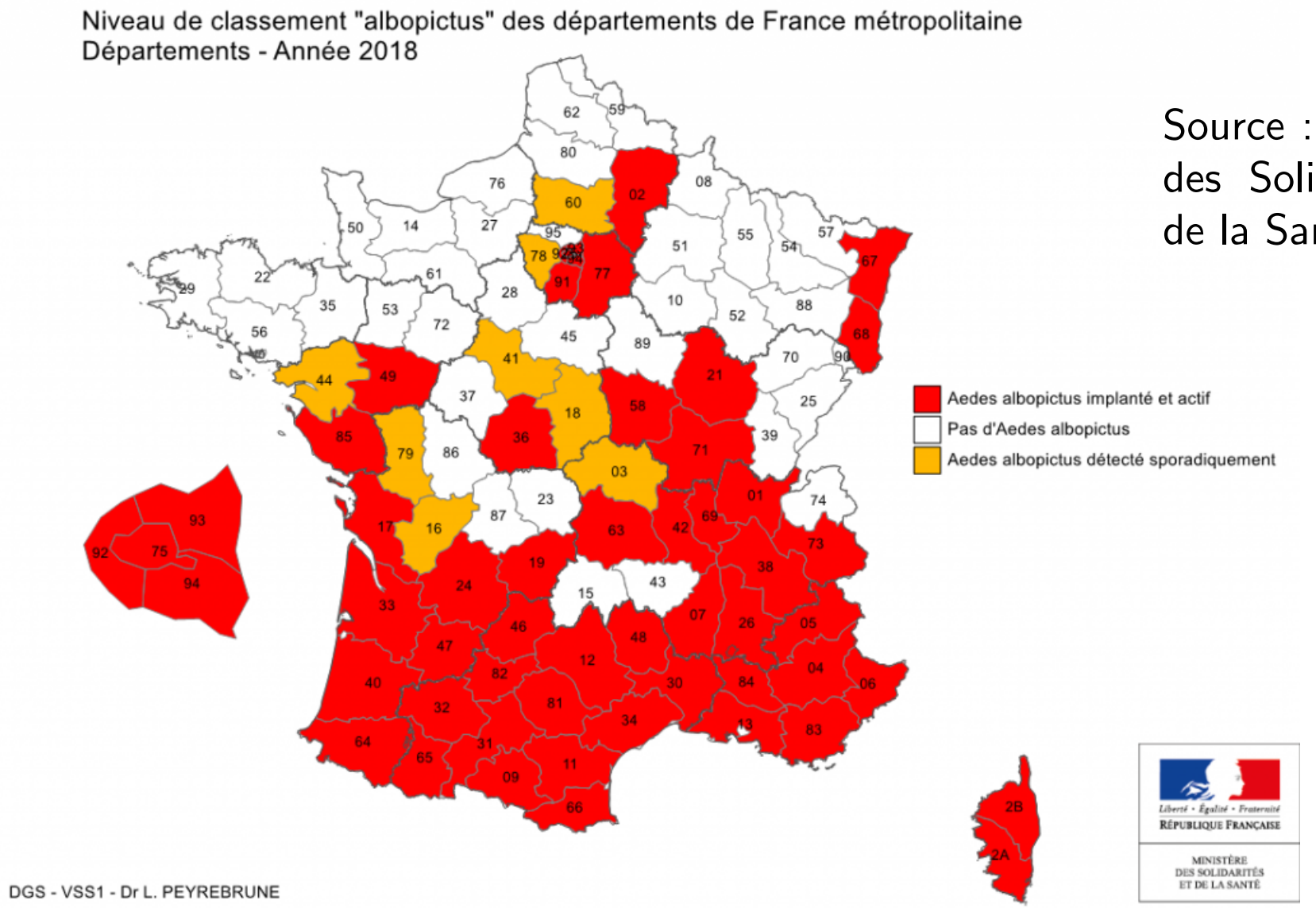
Aedes albopictus (usually called "tiger mosquitoes") is also present in more temperated region.



Distribution of *Aedes albopictus* in Europe in October 2014 [1].

1. source : European Center for Disease Prevention and Control (ECDC) and European Food Safety Authority (EFSA) VectorNet

Aedes albopictus in France



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.
The aim of these lectures is to present some mathematical questions related to the control of mosquitoes population.

- Mathematical modeling.
- Dynamical system to determine time dynamics.
- PDE of reaction-diffusion type to determine the spatio-temporal dynamics.
- Optimization tools.

Outline of lecture 1

1. Bio-ecology and monitoring of *Aedes* mosquitoes
   - Life cycle of mosquitoes
   - Data acquisition
   - Vector-borne diseases
   - Two vector control methods by releases
2. Mathematical modeling
   - Mosquitoes life cycle
   - Mathematical model for vector control strategies
   - Equilibria and stability
3. Optimization of the releases
   - Optimization of the releases for the *Sterile Insect technique*
   - Optimization of the releases for the *Wolbachia* strategy
   - Reduction of the problem
4. Mathematical epidemiology
   - Introduction
   - SIR model
   - Basic reproduction number R_0

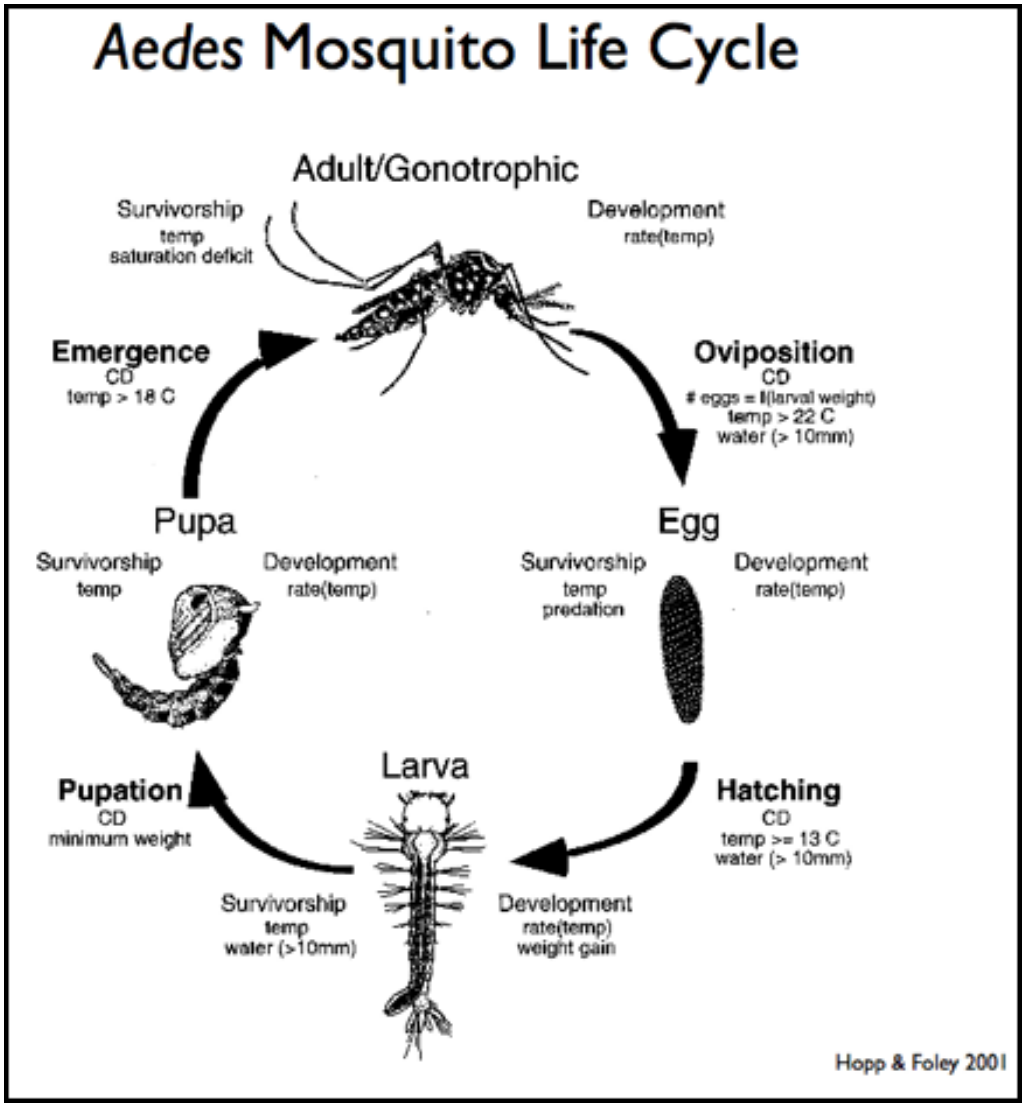
Outline of lecture 1

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)

Outline of lecture 1

Acquiring data on mosquito population is by no means an easy taks. Here is a list (non-exhaustive) of several techniques :

Trapping counts. Installing trap in the field and collecting regularly the captured individuals (it can be adults or eggs or preferentially adults females depending on the traps).
Easy and cheap but require a large workforce and may be biased since the mosquito population can adapt.

Laboratory data. Data acquired on a colony raised in the laboratory. Commonly used when a lab colony has been established.
Easy to get, but laboratory conditions can never be the same as in the field.

Genetic data among trapped individuals.
Provide important and valuable informations, but very expensive to collect.

Mark Release Recapture experiments. MRR experiments rely on the released of marked adults from the lab into the field with a trapping network around the release locations. It is used in particular to provide informations on the dispersal of mosquitoes.

Outline of lecture 1

Vectors and vector-borne diseases

Definitions

A vector is an arthropod which actively transmits an infectious agent.
A vector-borne disease is any infectious human disease whose agent (parasite, virus, bacterium) can be transmit by a vector.

According to World Health Organization [2] :

- Vector-borne diseases account for more than 17% of all infectious diseases, causing more than 700 000 deaths annually.
- More than 3.9 billion people in over 128 countries are at risk of contracting dengue, with 96 million cases estimated per year.
- Malaria causes more than 400 000 deaths every year globally, most of them children under 5 years of age.
- Other diseases such as Chagas disease, leishmaniasis and schistosomiasis affect hundreds of millions of people worldwide.
- Many of these diseases are preventable through informed protective measures.

Mosquito is the best known diseases vector. Others include ticks, flies, bugs, ...

2. see `https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases`.

Vector competence

The transmission of the virus from mosquito to human being is done through the saliva, during a bite. It is divided into three main steps

- The virus infects the vector during a blood meal.
- The virus multiplies in the vector and manages to reach the salivary glands
- The virus leaves the vector in its saliva.

definition

The time required to complete the three steps of arbovirus transmission is called the extrinsic incubation period.
The ability of a vector population to get infective for a given infectious agent is called vector competence. It can be quantified as the frequency of vector individuals which get infective after a blood meal on an infected vertebrate.

Vectorial capacity

definition

The vectorial capacity quantifies the ability of a vector population to transmit a given virus to human population. It is the daily rate at which future inoculations arise from a currently infective case.

Dye [3] gives the following formula for vectorial capacity

$$VC = \frac{ma^2 bp^{\tau_{EIP}}}{-\log(p)}.$$

where

- τ_{EIP} is the duration of the extrinsic incubation period ;
- a is the biting rate ;
- m is the relative abundance (number of active females per human) ;
- p is the daily survival rate of females ;
- $b \in [0,1]$ is the vector competence.

3. C. Dye, The analysis of parasite transmission by bloodsucking insects, 1992.

Vector control

Vector control methods are human interventions which aim at

- protect individuals from infectious bites ;
- prevent or reduce the circulation of vector-borne diseases.

Several strategies may be used to reduce the vectorial capacity (by reducing a and/or m and/or b) :

- environmental fight (remove breeding sites) ;
- mechanical fight (trapping) ;
- chemical fight (use of insecticide) ;
- biological fight (predator introduction or replacement strategy) ;
- genetic fight (RIDL, gene drive, sterile insect technique).

Outline of lecture 1

Sterile (or Incompatible) Insect Technique (SIT)

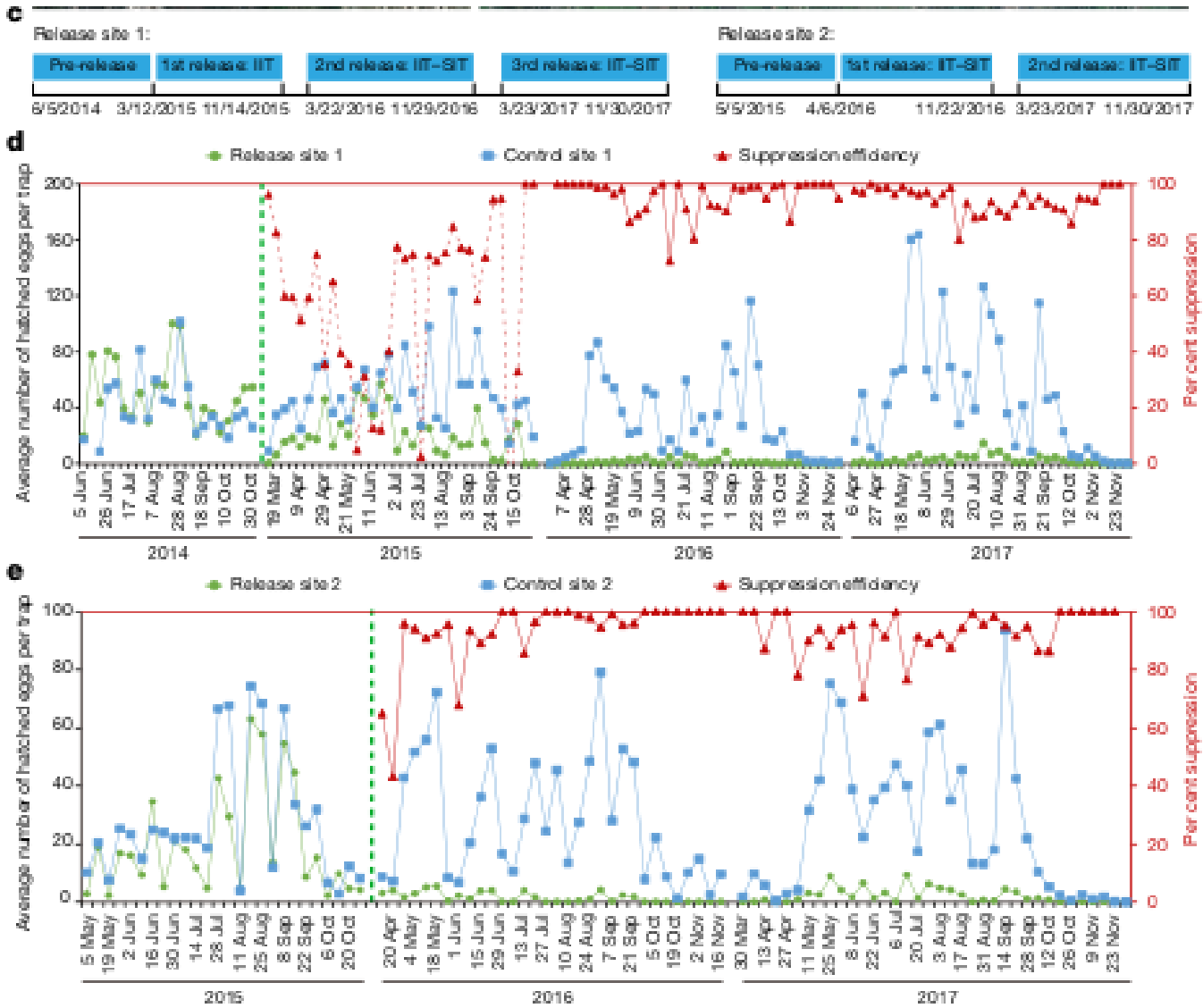
The sterile insect technique has been introduced in the '50 by Raymond C. Bushland and Edward F. Knipling. It has succesfully been used to eradicate the screw-worm fly in North and Central America.

Idea Massive release of sterilized males. These males will mate with females. The eggs resulting from these mating will not hatch, since the males are not fertile.

Objective To reduce the size of (or even eradicate) the population of *Aedes* mosquitoes.

This strategy is implemented and studied to eliminate mosquitoes in several countries.

A similar strategy is the so-called incompatible insect technique, consisting in releasing incompatible males (for instance males infected with the bacteria Wolbachia), since it has been observed that sterilized males are less competitive for reproduction.

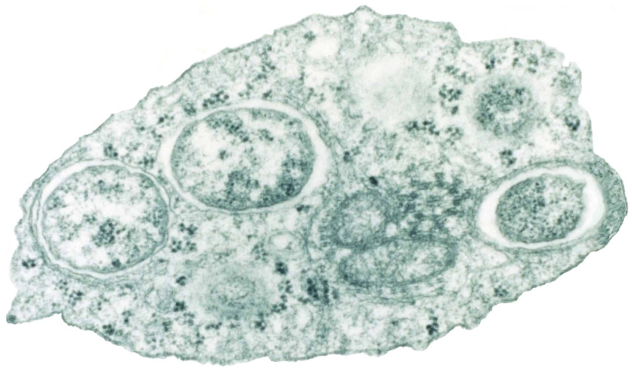


Example of experimental results conducted in 2015-2017 in two isolated riverine islands in Guangzhou, China [4].

4. Taken from X. Zheng et al, *Incompatible and sterile insect techniques combined eliminate mosquitoes*, Nature **572**, 2019.

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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The Wolbachia strategy

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

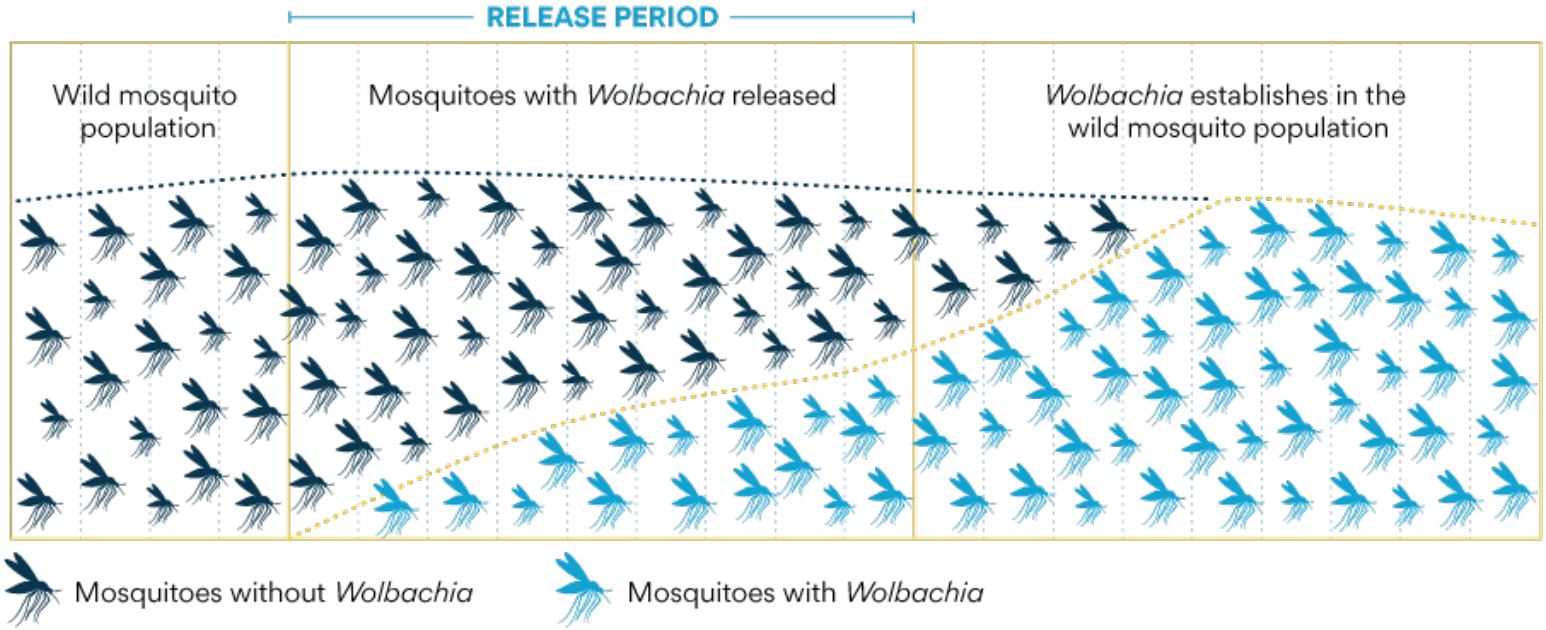
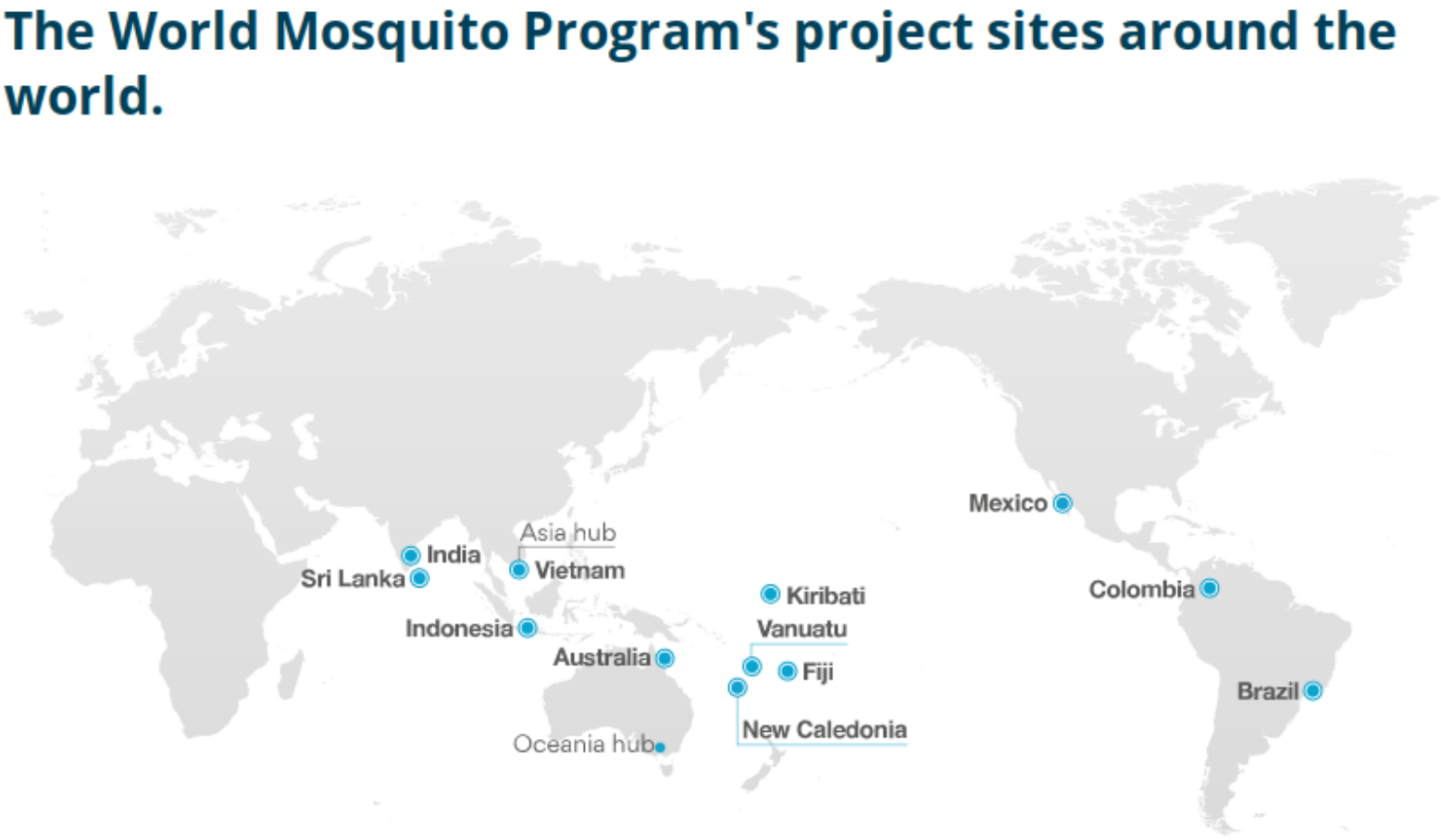
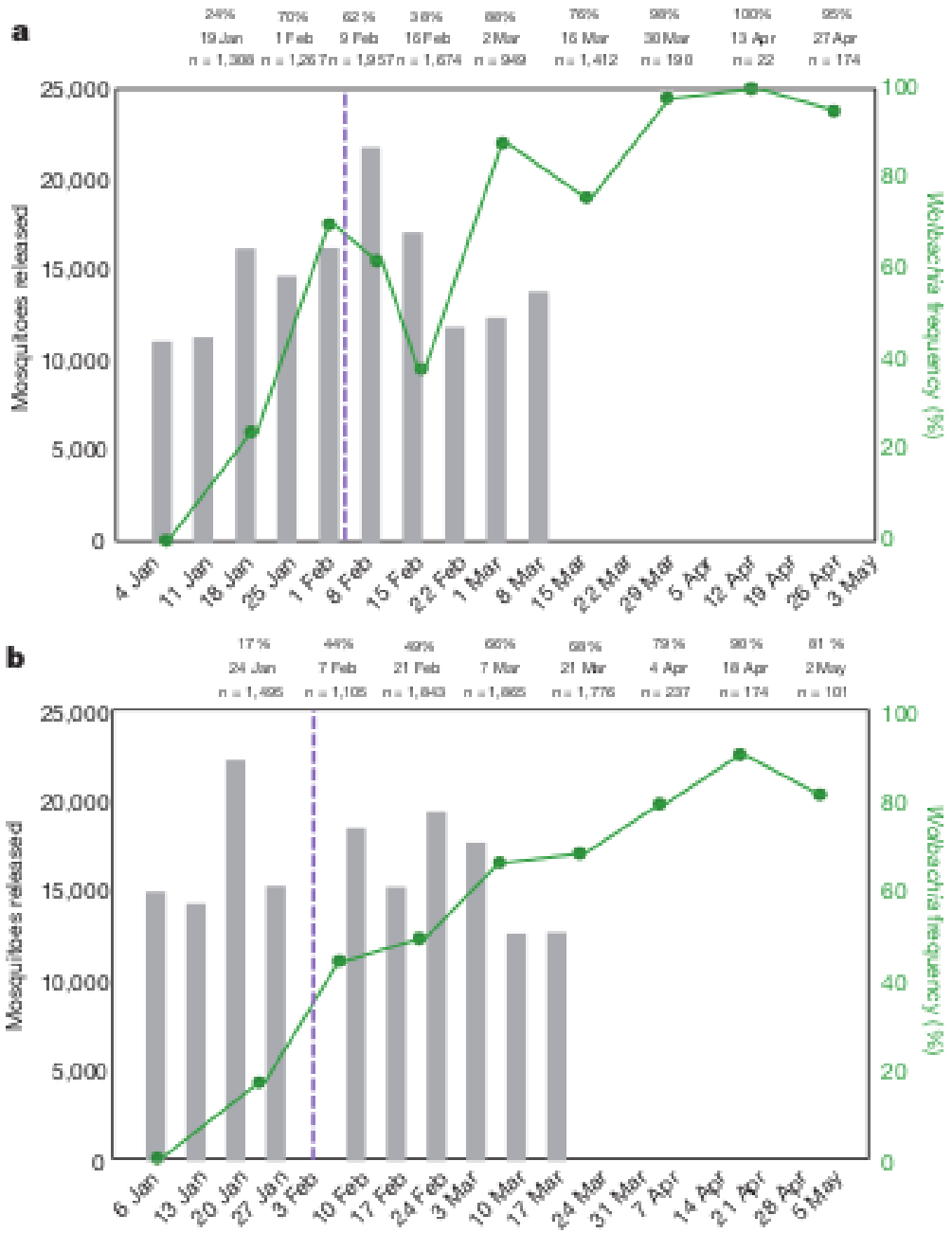


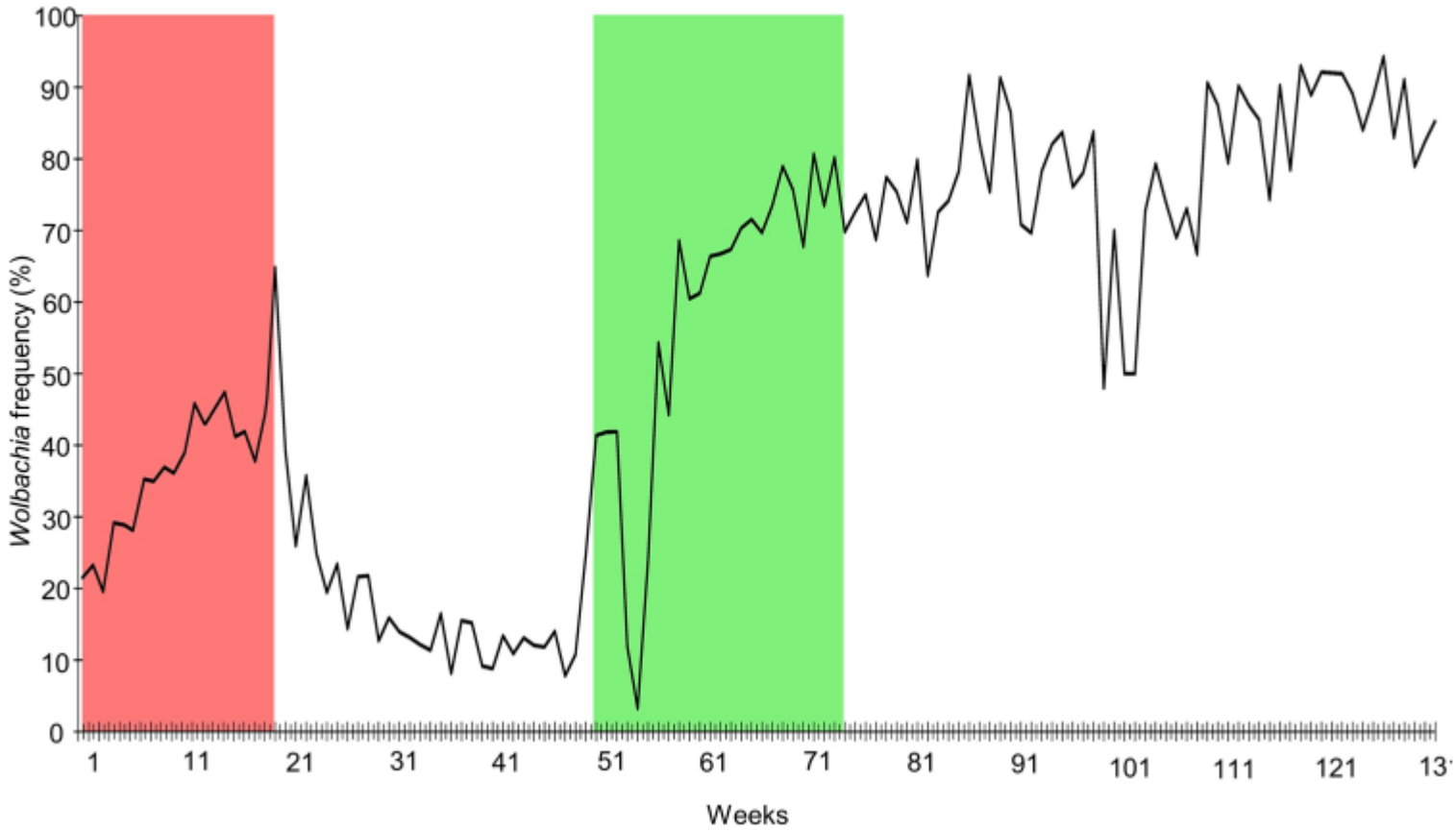
Figure taken from the *world mosquito program*
`http://www.eliminatedengue.com/program`

World mosquito program





Number of mosquitoes release, time of the releases and changes in infection frequencies over time in traps in two locations near the city of Cairn in north-eastern Australia.
(Dotted line = interruption due to a cyclone.)
Taken from [Hoffmann et al, *Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission*, Nature, 476, 2011.]



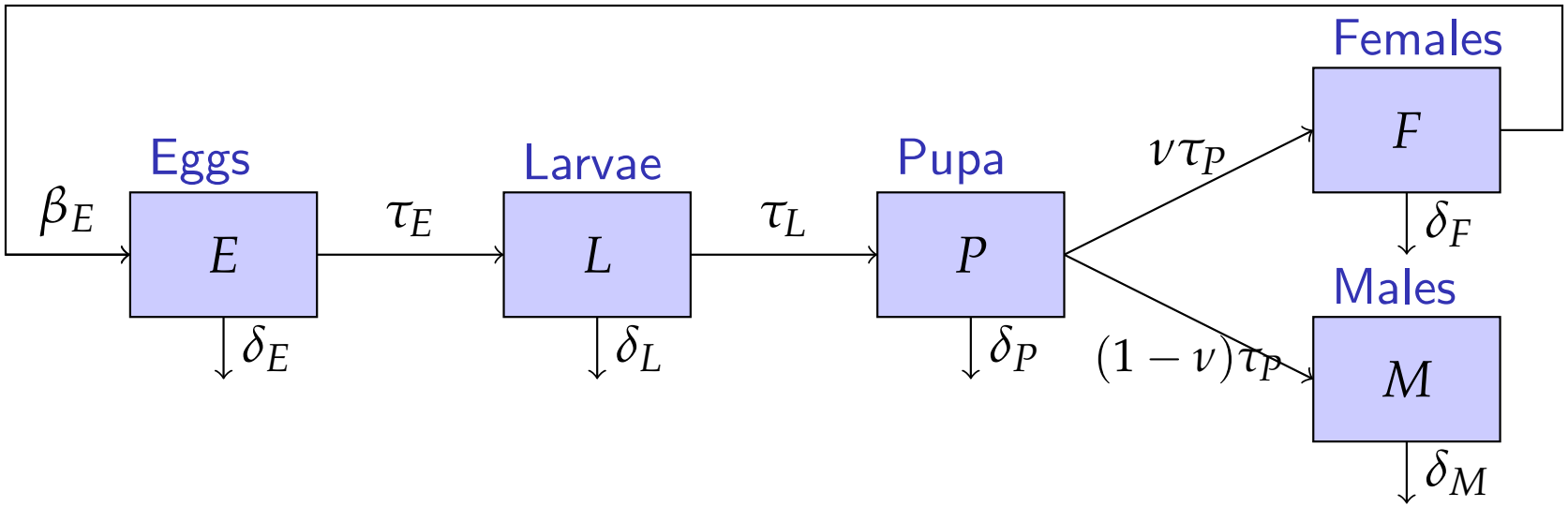
Frequency of Wolbachia-infected mosquitoes in the traps in Tubiacanga (Rio de Janeiro, Brazil). The colored zones correspond to the released period : Pink : release of a strain from the lab ; Green : release of a strain of mosquitoes crossed with wild mosquitoes.

Taken from [Azambuja Garcia et al, *Matching the genetics of released and local Aedes aegypti populations is critical to assure Wolbachia invasion*, PLoS Negl Trop Dis, 13, 2019.]

Outline of lecture 1

Mathematical model for mosquito life cycle

The life cycle for mosquitos may be schematized as follows :



- $\beta_E(M)$ birth rate (per female) ;
- τ_E, τ_L, τ_P transition rates ; ν sex ratio ;
- δ_E, δ_L, δ_P, δ_M, δ_F death rates.

Mosquito life cycle

$$\frac{d}{dt}E = \underbrace{\beta_E(M)F}_{\text{birth}} \underbrace{\left(1-\frac{E}{K}\right)}_{\text{competition intraspecific}} - \underbrace{\tau_E E}_{\text{transition to larvae}} - \underbrace{\delta_E E}_{\text{death}},$$

$$\frac{d}{dt}L = \tau_E E - \Big(\underbrace{cL}_{\text{competition}} + \underbrace{\tau_L}_{\text{transition}} + \underbrace{\delta_L}_{\text{death}} \Big) L,$$

$$\frac{d}{dt}P = \tau_L L - (\tau_P + \delta_P)P,$$

$$\frac{d}{dt}F = \nu\tau_P P - \delta_F F,$$

$$\frac{d}{dt}M = (1-\nu)\tau_P P - \delta_M M.$$

Mosquito life cycle

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$$\frac{d}{dt}P = \tau_L L - (\tau_P + \delta_P)P,$$

$$\frac{d}{dt}F = \nu\tau_P P - \delta_F F,$$

$$\frac{d}{dt}M = (1-\nu)\tau_P P - \delta_M M.$$

We first notice that if we assume that $\nu = \frac{1}{2}$ and $\delta_F = \delta_M$. Then, the equations for F and M are similar. Thus, if the initial data are the same, then for any time $F = M$.
From now on, we will consider $F = M$ and denote $A = F = M$.

Mathematical model for mosquitos life cycle

Then the system reduces to

$$\begin{aligned}
\frac{d}{dt}E &= \beta_E A\left(1-\frac{A}{K}\right) - \tau_E E - \delta_E E,\\
\frac{d}{dt}L &= \tau_E E - \left(cL + \tau_L + \delta_L\right)L,\\
\frac{d}{dt}P &= \tau_L L - (\tau_P + \delta_P)P,\\
\frac{d}{dt}A &= \frac{\tau_P}{2}P - \delta_F A.
\end{aligned}$$

Mathematical model : simplification

$$\frac{d}{dt}E = \beta_E A\left(1-\frac{A}{K}\right) - (\tau_E + \delta_E)E,$$

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Mathematical model : simplification

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\frac{d}{dt}L &= \tau_E E - (cL+\tau_L+\delta_L)L,\\
0 &= \tau_L L - (\tau_P+\delta_P)P,\\
\frac{d}{dt}A &= \frac{\tau_P}{2}P - \delta_A A.
\end{aligned}$$

Assumptions :

- Fast dynamics for pupa ;

Mathematical model : simplification

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Assumptions :

- Fast dynamics for pupa ;
- Intra-specific competition at larval stage neglected ($c \ll 1$) ;

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Assumptions :

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- Intra-specific competition at larval stage neglected ($c \ll 1$) ;
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Mathematical model : simplified model

Finally, a simplified model for the mosquito dynamics is given by

$$\frac{d}{dt}E = \beta_E A\left(1-\frac{A}{K}\right) - (\tau_E+\delta_E)E,$$
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where $\beta_A = \frac{\tau_p\tau_L\tau_E}{2(\tau_L+\delta_L)(\tau_P+\delta_P)}$.

Mathematical model : simplified model

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We will now model the Wolbachia strategy and the Sterile Insect Technique.

Assumption : Density of males = density of females.

Outline of lecture 1

Including Wolbachia

We first consider the Wolbachia strategy :

- We denote by a subscript i the infected population and by u the uninfected population.
- Assuming uniform repartition of the mosquitos population, the probability for a female to mate with an uninfected male is $\frac{A_u}{A_u+A_i}$, with an infected male is $\frac{A_i}{A_u+A_i}$.
- s_h : cytoplasmic incompatibility parameter (fraction of uninfected females' eggs fertilized by infected males which will not hatch).
- $1-s_f \in (0,1)$ fecundity reduction ; $\gamma > 1$ mortality increase.
- u is the release function of infected adults.

Mathematical model : Wolbachia strategy

Model for the *Wolbachia* technique

Then, we have everything at hand to write the mathematical model for the *Wolbachia* strategy. The dynamics for uninfected eggs E_u, uninfected adults A_u, *Wolbachia*-infected eggs E_i, *Wolbachia*-infected adults A_i is given by

$$\begin{aligned}
\frac{d}{dt}E_u &= \beta_E A_u \left(\frac{A_u}{A_u+A_i} + (1-s_h)\frac{A_i}{A_u+A_i}\right)\left(1-\frac{A_u+A_i}{K}\right) \\
&\quad - (\tau_E+\delta_E)E_u, \\
\frac{d}{dt}A_u &= \beta_A E_u - \delta_A A_u, \\
\frac{d}{dt}E_i &= (1-s_f)\beta_E A_i\left(1-\frac{A_u+A_i}{K}\right) - (\tau_E+\delta_E)E_i, \\
\frac{d}{dt}A_i &= \beta_A E_i - \gamma\delta_A A_i + u.
\end{aligned}$$

Mathematical model : Sterile Insect Technique

Then, we consider the Sterile Insect Technique,

- M_s denotes the density of sterilized males, with death rate δ_s ;
- u is a release function of sterilized males ;
- The probability to mate with a fertile mosquito is given by $\frac{A}{A+\gamma M_s}$, where γ is a parameter for the mating preference.

Model for the Sterile Insect Technique

The dynamics for eggs E, adults A, sterile males M_s is given by

$$\begin{aligned}
\frac{d}{dt}E &= \beta_E A\left(1-\frac{A}{K}\right)\frac{A}{A+\gamma M_s} - (\tau_E+\delta_E)E,\\
\frac{d}{dt}A &= \beta_A E - \delta_A A,\\
\frac{d}{dt}M_s &= u - \delta_s M_s.
\end{aligned}$$

Outline of lecture 1

Equilibrium

Let us consider a general *autonomous systems* for which we assume to have existence of a *global* solution on $[0, +\infty)$. We recall that existence and uniqueness theory is now well established under regularity assumptions on f.

Let $f : \mathbb{R}^d \to \mathbb{R}^d$, $f \in C^1(\mathbb{R}^d)$,

$$\begin{cases} y'(t) = f(y(t)), & t \in [0, +\infty), \\ y(0) = y_0 \in \mathbb{R}^d. \end{cases} \tag{C_0}$$

We call flow and we denote $\phi(t, y_0)$ a solution to this problem.

Equilibrium

For the above autonomous system, we introduce the following definitions :

Definitions

- An equilibrium is a stationnary solution, i.e. $\overline{y} \in \mathbb{R}^d$ such that $f(\overline{y}) = 0$.
- An equilibrium is stable if $\forall\, \varepsilon > 0$, $\exists\, \delta > 0$ such that $\forall\, y \in B(\overline{y}, \delta)$, $\phi(t, y) \in B(\overline{y}, \varepsilon)$.
- An equilibrium is asymptotically stable if it is stable and $\exists\, \eta > 0$ such that $\forall\, y \in B(\overline{y}, \eta), \|\phi(t, y) - \overline{y}\| \underset{t \to +\infty}{\to} 0$.
- An equilibrium is globally asymptotically stable (GAS) if it is stable and the above implication is true for all $\eta > 0$.
- An equilibrium is unstable if it is not stable.

Stability

For general system $y' = f(y)$. We use a Taylor expansion

$$\begin{aligned} f(y) &= f(\overline{y}) + Df(\overline{y}) \cdot (y - \overline{y}) + o(\|y - \overline{y}\|) \\ &= Df(\overline{y}) \cdot (y - \overline{y}) + o(\|y - \overline{y}\|). \end{aligned}$$

We deduce some stability results on the non-linear problem $y' = f(y)$ from a stability analysis on the linear problem $z' = Df(\overline{y})z$.
The flow for this linear system is $\phi(t, z_0) = e^{tDf(\overline{y})}z_0$. Then the long time behaviour of ϕ may be computed easily.

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Proposition (Lyapunov stability Theorem)

Let us consider the Cauchy problem (C_0), let $\overline{y}$ be an equilibrium $(f(\overline{y}) = 0$.
Denoting $(\lambda_1, \ldots, \lambda_k)$ $(k \leq d)$ the eigenvalues of $Df(\overline{y})$.
Then the equilibrium is (linearly) asymptotically stable if $\mathrm{Re}(\lambda) < 0$ for all eigenvalues $\lambda \in Sp(A)$.
The equilibrium is (linearly) unstable if there is at least one eigenvalue for which real part is positive.

Outline of lecture 1

Dynamical system

Let us first consider the Sterile Insect Technique.

Model for the *Sterile Insect Technique*

Recalling that we denote E, A, M_s the density of eggs, adults, and sterile mosquitoes, respectively, the model reads

$$\begin{aligned}
\frac{d}{dt}E &= \beta_E A\left(1-\frac{A}{K}\right)\frac{A}{A+\gamma M_s} - (\tau_E+\delta_E)E,\\
\frac{d}{dt}A &= \beta_A E - \delta_A A,\\
\frac{d}{dt}M_s &= u - \delta_s M_s.
\end{aligned}$$

Dynamical system without control

We first investigate the equilibria in the case $u = 0$.

Equilibria

Under the assumptions $\delta_s > \delta_A$ and $\beta_E \beta_A > \delta_A(\tau_E + \delta_E)$, there are two equilibria :

- The extinction equilibrium $(E_1^*, A_1^*, M_s^*) = (0, 0, 0)$,
- The non-extinction equilibrium $(E_2^*, A_2^*, M_s^*) = \left(\overline{E}_2, \frac{\beta_A}{\delta_A}\overline{E}_2, 0\right)$ with $\overline{E}_2 = K\left(1 - \frac{(\tau_E+\delta_E)\delta_A}{\beta_E\beta_A}\right)$.

Moreover, the non-extinction equilibrium is linearly asymptotically stable, whereas the extinction equilibrium is linearly unstable.

This results implies in particular that the extinction equilibrium can not be reach with this mathematical model. This is the reason why, in some modeling [5], a small Allee effect has been added : replacing β_E by $\beta_E(1 - e^{-\beta'(A+\gamma M_s)})$.

5. H. Bossin, Y. Dumont and M. Strugarek, Using sterilizing males to reduce or eliminate Aedes populations : insights from a mathematical model, Appl. Math. Model., 68 (2019)

Dynamical system with constant control

Let us consider now the case of a constant release function $u = \overline{U}$.

Equilibria

Under above assumptions, if we assume moreover that $\overline{U}$ is large enough, more precisely $\overline{U} > \dfrac{K\delta_s((\tau_E+\delta_E)\delta_A - \beta_E\beta_A)^2}{4(\tau_E+\delta_E)\delta_A\gamma\beta_E\beta_A}$, then there is only one equilibrium :

- The extinction equilibrium $(E_1^*, A_1^*, M_s^*) = (0, 0, \frac{\overline{U}}{\delta_s})$ which is globally asymptotically stable.

As a consequence, when $u = \overline{U}$, the system converges to the extinction steady state, i.e. the population will be eradicated.

- However, after the end of the treatment period (i.e. when $u = 0$), the dynamical system tends to come back to the non-extinction equilibrium, in particular due to spatial reinvasion when system are not insolated. Then it is necessary to perform new releases.
- It is also possible to look for feedback control function, i.e. $u = \Psi(A)$ (cf Presentation of Pierre-Alexandre Bliman).

Dynamical system : an optimal control problem

The question is to know how to optimize the release function to be as close as possible to the *extinction equilibrium* at the end of a treatment period starting at the *non-extinction equilibrium* $(E(t=0), A(t=0)) = (E_2^*, A_2^*)$ [6].

Cost

$$J(u) = \frac{1}{2}E(T)^2 + \frac{1}{2}F(T)^2.$$

Constraints

- The local release of mosquitoes is bounded : $0 \leq u \leq \overline{U}$.
- The total number of mosquitoes used is bounded (production limitation) : $0 \leq \int_0^T u(t)dt \leq C$.

Optimization problem

$$\min_{u \in \mathcal{U}_{\overline{U},C,T}} J(u), \quad \text{with } \mathcal{U}_{\overline{U},C,T} = \left\{ 0 \leq u \leq \overline{U} \text{ a.e., } \int_0^T u(t)dt \leq C \right\}.$$

6. L. Almeida, M. Duprez, Y. Privat, N. V., *Mosquito population control strategies for fighting against arboviruses*, Math. Biosc. Eng. 2019

Dynamical system : optimal control

Existence of an optimal control

We may prove that this minimization problem has a solution u^*. Moreover, assuming that $\overline{U}T > C$, the optimal control strategy uses the maximal amount of mosquitoes, i.e. $\int_0^T u^*(t)\,dt = C$, and there exists $T_0 \in (0,T)$ such that $u^* = 0$ on (T_0, T) (consequence of the PMP).

SKETCH OF PROOF (existence) :

- Let us consider $(u_n)_{n\in\mathbb{N}}$ a minimizing sequence in $\mathcal{U}_{\overline{U},C,T}$, i.e. $\lim_{n\to+\infty} J(u_n) = \inf_{\mathcal{U}_{\overline{U},C,T}} J$.
- Since (u_n) belongs to $\mathcal{U}_{\overline{U},C,T}$ it is uniformly bounded in $L^1 \cap L^\infty(0,T)$. Then, we may extract a subsequence that converges weakly-* in $L^\infty(0,T)$ towards a limit call u. Clearly $u \in \mathcal{U}_{\overline{U},C,T}$. Moreover, $M'_{s,n}$, E_n, A_n are also uniformly bounded. Thus, by Arzela-Ascoli Theorem, we may extract subsequences that converge uniformly.
- Passing into the limit in the system of ODE, the limit satisfies the same differential system. Since by definition of minimizing sequence we have $J(u) = \inf_{\mathcal{U}_{\overline{U},C,T}} J$, it allows us to conclude the proof of existence.

Numerical results

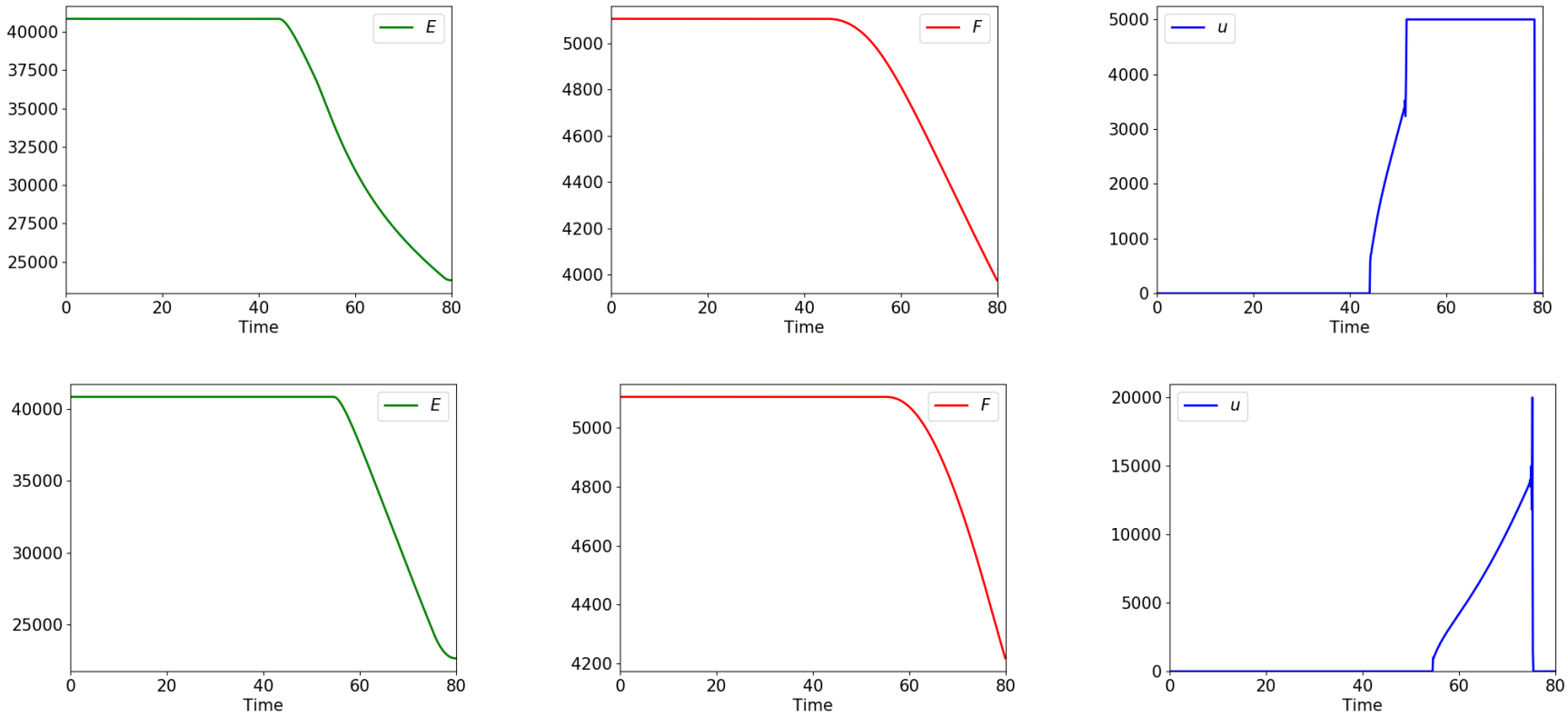

FIGURE – Simulation of the sterile insect technique for $T = 80$, $C = 150000$, $\overline{U} = 5000$ (1st line), 20000 (2nd line).

Numerical results

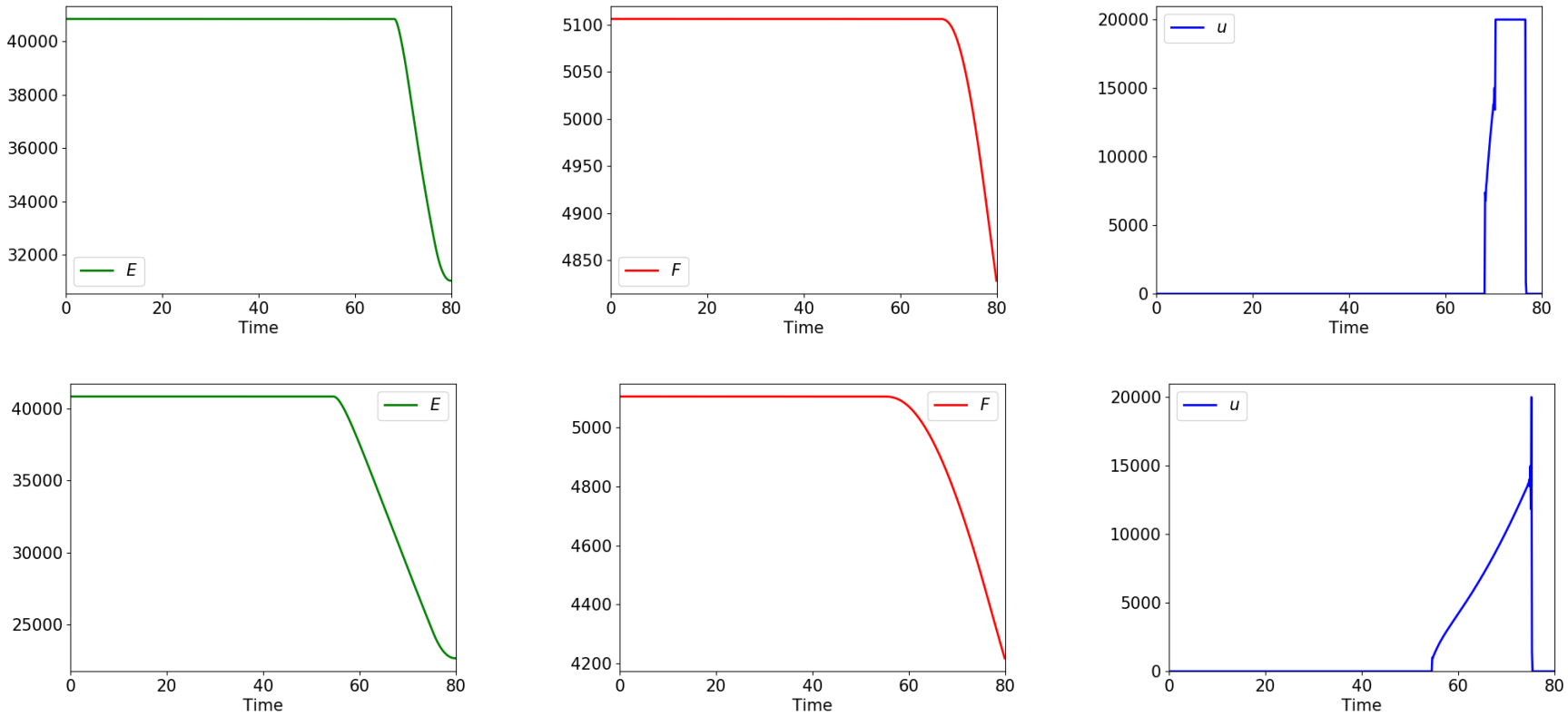

FIGURE – Simulation of the sterile insect technique. Influence of the mating competitiveness of sterilizing males parameter γ. We take $T = 80$, $C = 150000$, $\overline{U} = 20000$ with different values of γ : $\gamma = \frac{1}{3}$ (1st line), 1 (2nd line).

Outline of lecture 1

Mathematical model : Wolbachia strategy

We then consider the dynamical system for the *Wolbachia* strategy that we recall below without releases (i.e. $u = 0$)

$$\begin{aligned}
\frac{d}{dt}E_u &= \beta_E A_u \left(1 - s_h \frac{A_i}{A_u + A_i}\right)\left(1 - \frac{A_u + A_i}{K}\right) - (\tau_E + \delta_E)E_u, \\
\frac{d}{dt}A_u &= \beta_A E_u - \delta_A A_u, \\
\frac{d}{dt}E_i &= (1 - s_f)\beta_E A_i \left(1 - \frac{A_u + A_i}{K}\right) - (\tau_E + \delta_E)E_i, \\
\frac{d}{dt}A_i &= \beta_A E_i - \delta\delta_A A_i.
\end{aligned}$$

The equilibria and their stability are given by the following results.

Mathematical model : Wolbachia strategy

Equilibria and stability

Let us consider that $1 < \delta$, $0 < s_f < 1$, $0 < s_h \leq 1$. We denote $b = \dfrac{\beta_A \beta_E}{(\tau_E + \delta_E)}$.

Assume moreover that $(1 - s_f)b > \delta\delta_A$, $s_h + \dfrac{1-s_f}{\delta} > 1$.
Then there are four distinct non-negative equilibria :

- *Wolbachia* invasion

  $$(E^*_{uW}, A^*_{uW}, E^*_{iW}, A^*_{iW}) := \left(0, 0, K\Big(1 - \frac{\delta\delta_A}{b(1-s_f)}\Big), K\Big(\frac{\beta_A}{\delta\delta_A} - \frac{\beta_A}{b(1-s_f)}\Big)\right)$$

  is stable ;
- *Wolbachia* extinction

  $(E^*_{uE}, A^*_{uE}, E^*_{iE}, A^*_{iE}) := \left(K\Big(1 - \dfrac{\delta_A}{b}\Big), K\Big(\dfrac{\beta_A}{\delta_A} - \dfrac{\beta_A}{b}\Big), 0, 0\right)$ is stable ;
- co-existence steady state $(E^*_{uC}, A^*_{uC}, E^*_{iC}, A^*_{iC})$ is unstable.
- extinction $(0, 0, 0, 0)$ is unstable.

Towards an optimization problem

As a consequence, there are two basins of attraction :

- The basin of attraction of the *Wolbachia invasion* equilibrium ;
- The basin of attraction of the *Wolbachia extinction* equilibrium.

A direct consequence of this result is that it suffices to take u such that at the end of the releases period the solution belongs to the basin of attraction of the *Wolbachia invasion* equilibrium to guarantee the success of this strategy.

Towards an optimization problem

As a consequence, there are two basins of attraction :

- The basin of attraction of the *Wolbachia invasion* equilibrium ;
- The basin of attraction of the *Wolbachia extinction* equilibrium.

A direct consequence of this result is that it suffices to take u such that at the end of the releases period the solution belongs to the basin of attraction of the *Wolbachia invasion* equilibrium to guarantee the success of this strategy.

The question we want to address is the optimisation of the release function u. Hence, we consider the above dynamical system and we assume that at the beginning of the releases, the system is in the *Wolbachia-free* equilibrium

$$E_u(0) = K\left(1 - \frac{\delta_A}{b}\right), \quad A_u(0) = K\left(\frac{\beta_A}{\delta_A} - \frac{\beta_A}{b}\right), \quad E_i(0) = A_i(0) = 0.$$

Towards an optimization problem

We want to optimize the release strategy to be as close as possible to the *Wolbachia*-infected equilibrium at the final time of treatment, denoted T. That is, we want to determine the release function u which minimizes the distance to the desired equilibria :

Cost The cost function is defined by

$$J(u) = \frac{1}{2}\left(E_u(T)^2 + A_u(T)^2 + \left(E_i(T) - E^*_{iW}\right)^2_+ + \left(A_i(T) - A^*_{iW},\right)^2_+\right).$$

Constraints

- The local release of mosquitoes is bounded : $0 \leq u \leq \overline{U}$.
- The total number of mosquitoes used is bounded (production limitation) : $0 \leq \int_0^T u(t)dt \leq C$.

Optimization problem

$$\min_{u \in \mathcal{U}_{\overline{U},C,T}} J(u), \quad \text{with } \mathcal{U}_{\overline{U},C,T} = \left\{0 \leq u \leq \overline{U} \text{ a.e., } \int_0^T u(t)dt \leq C\right\}.$$

Numerical simulations

We may prove that this optimal problem admits (at least) one solution. However, it is more difficult to have a precise description of this optimum, apart with numerical simulations.

TABLE – Values of the parameters.

Parameter	*Name*	*Value*
β_E	Effective fecundity	10
b	Growth rate	3.125
δ_A	Female death rate	0.04
s_h	Probability of cytoplasmic incompatibility	0.9951
$1 - s_f$	Fecundity reduction of infected females with respect to uninfected females	0.95
δ	Increase of mortality for infected mosquitoes	1.25

Numerical results

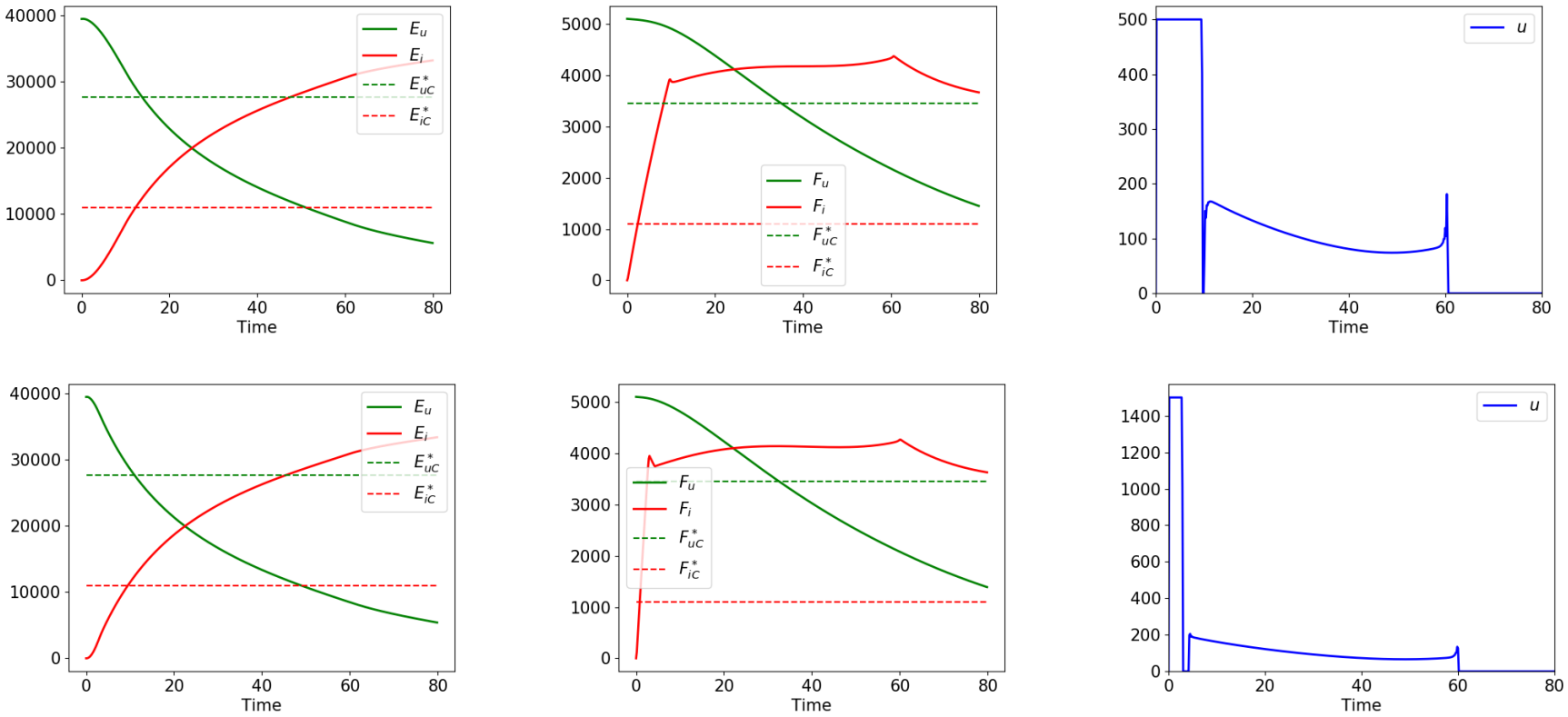

FIGURE – Simulation of the wolbachia technique for $T = 80$, $C = 10000$, $\overline{U} = 500$ (1st line), 1500 (2nd line). The dashed lines correspond to the coexistence equilibria..

Numerical results

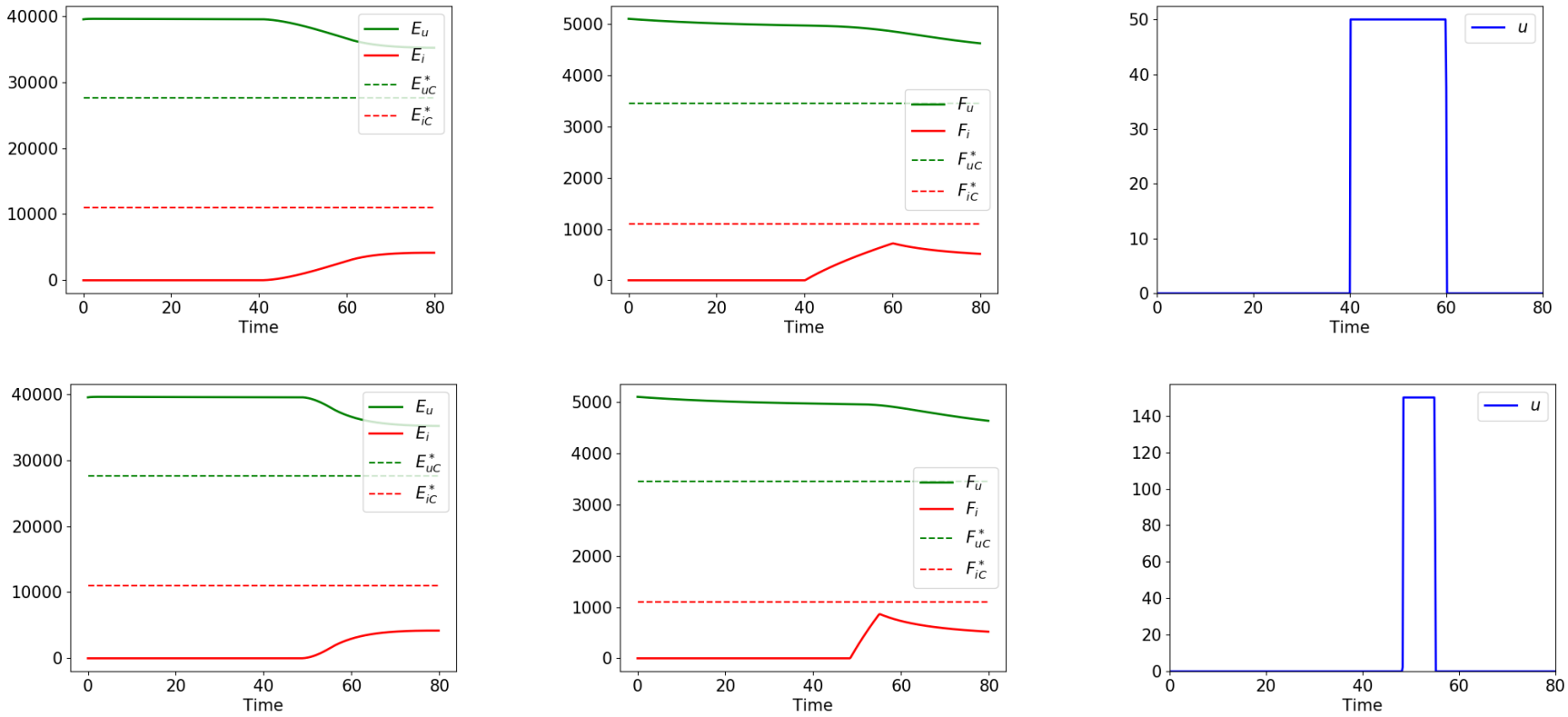

FIGURE – Simulation of the wolbachia technique for $T = 80$, $C = 1000$, $\overline{U} = 50$ (1st line), 150 (2nd line). The dashed lines correspond to the coexistence equilibria..

Outline of lecture 1

Observations

Although we did not find interesting properties for the solutions of the optimization problem, we observe interesting features from the numerical results

- It seems that when the number of mosquitoes available is enough to reach the basin of attraction of the desired equilibrium, the optimal strategy consists in acting strongly at the beginning of the release period.
- On the contrary, when the number of mosquitoes available is not enough, it seems better to act only at the end of the time interval.

These observations can be explained mathematically by approaching the optimization problem to a simpler problem that can be solved.

Mathematical model : Wolbachia strategy

We first recall the dynamical system.

$$
\begin{aligned}
\frac{d}{dt}E_u &= \beta_E A_u \left(1 - s_h \frac{A_i}{A_u + A_i}\right)\left(1 - \frac{A_u + A_i}{K}\right) \\
&\quad - (\tau_E + \delta_E) E_u, \\
\frac{d}{dt}A_u &= \beta_A E_u - \delta_A A_u, \\
\frac{d}{dt}E_i &= (1 - s_f)\beta_E A_i \left(1 - \frac{A_u + A_i}{K}\right) - (\tau_E + \delta_E) E_i, \\
\frac{d}{dt}A_i &= \beta_A E_i - \delta\delta_A A_i + u.
\end{aligned}
$$

Mathematical model : Wolbachia strategy

We first recall the dynamical system.
We assume fast dynamics of the egg compartment.

$$
\begin{aligned}
0 &= \beta_E A_u \left(1 - s_h \frac{A_i}{A_u + A_i}\right)\left(1 - \frac{A_u + A_i}{K}\right) \\
&\quad - (\tau_E + \delta_E) E_u, \\
\frac{d}{dt} A_u &= \beta_A E_u - \delta_A A_u, \\
0 &= (1 - s_f)\beta_E A_i \left(1 - \frac{A_u + A_i}{K}\right) - (\tau_E + \delta_E) E_i, \\
\frac{d}{dt} A_i &= \beta_A E_i - \delta\delta_A A_i + u.
\end{aligned}
$$

Mathematical model : Wolbachia strategy

We deduce from the first and third equation an expression of E_u and E_i with respect to A_u and A_i that we inject in the second and fourth equation. We obtain :

Simplified model for the *Wolbachia* technique

Denoting $b = \frac{\beta_E \beta_A}{\tau_E + \delta_E}$,

$$\begin{cases} \frac{d}{dt} A_i = (1 - s_f) b A_i \left(1 - \frac{A_i + A_u}{K}\right) - \delta \delta_A A_i + u, \\ \frac{d}{dt} A_u = b A_u \left(1 - s_h \frac{A_i}{A_i + A_u}\right)\left(1 - \frac{A_i + A_u}{K}\right) - \delta_A A_u. \end{cases}$$

Mathematical model : equilibria

We first consider the steady states (equilibria) when $u = 0$.

Steady states

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

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

Mathematical model : equilibria

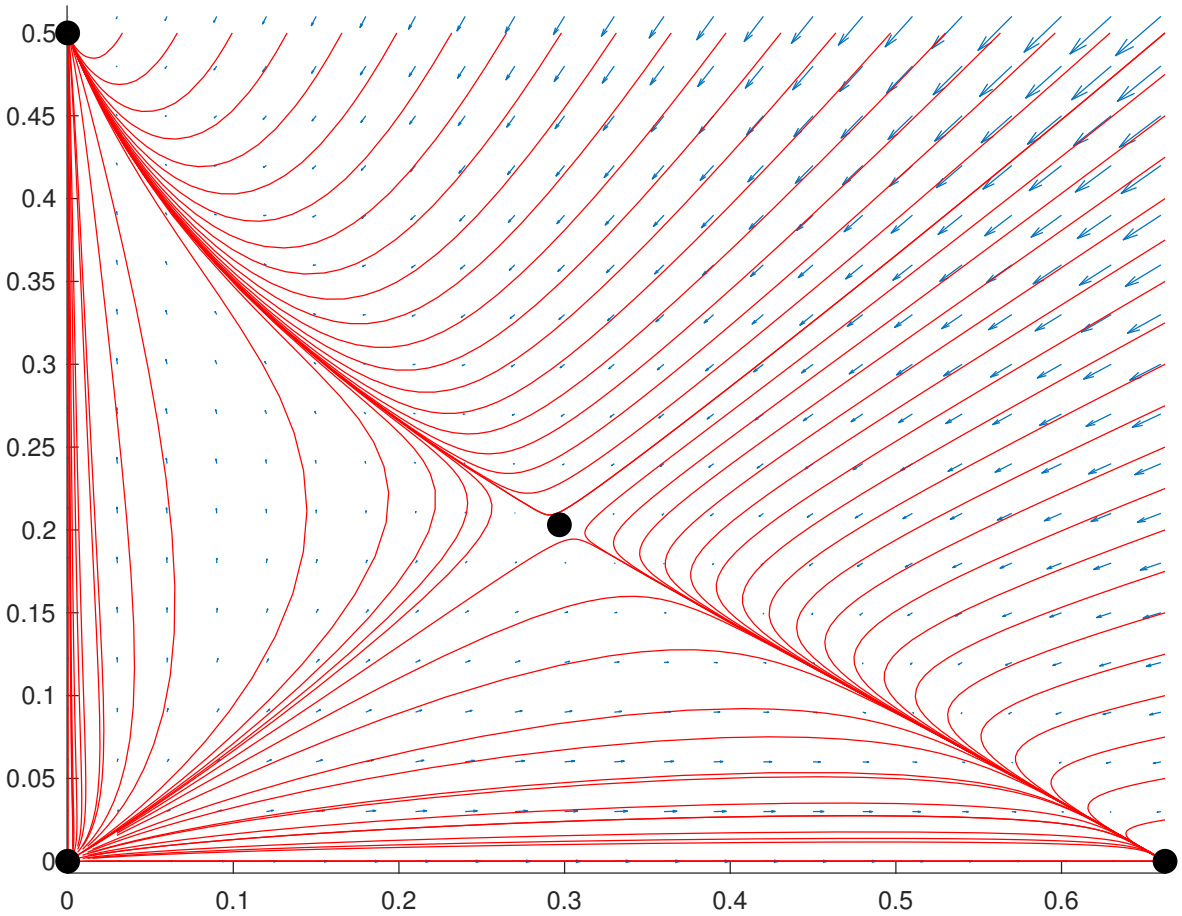

FIGURE – Phase portrait representing the equilibria and their stability for the dynamical system without spatial diffusion

Optimal control problem

As above, we want to optimize the release strategy to be as close as possible to the *Wolbachia*-infected equilibrium at the final time of treatment, denoted T :

Cost

$$J(u) = \frac{1}{2} A_u(T)^2 + \frac{1}{2} (A_{iW}^* - A_i(T))_+^2.$$

Constraints

- The local release of mosquitoes is bounded : $0 \leq u \leq \overline{U}$.
- The total number of mosquitoes used is bounded (production limitation) : $0 \leq \int_0^T u(t)dt \leq C$.

Optimization problem

$$\min_{u \in \mathcal{U}_{\overline{U},C,T}} J(u), \quad \text{with } \mathcal{U}_{\overline{U},C,T} = \left\{ 0 \leq u \leq \overline{U} \text{ a.e.}, \int_0^T u(t)dt \leq C \right\}.$$

Reduction of the optimal problem

Then, we simplify this system by using the large fertility asymptotics : introduce the parameter ϵ such that $b = \frac{b^0}{\epsilon}$ and assume that $\epsilon \ll 1$,

$$\begin{cases} \frac{d}{dt}A_i &= (1-s_f)\frac{b^0}{\epsilon}A_i\left(1-\frac{A_i+A_u}{K}\right) - \delta\delta_u A_i + u, \\ \frac{d}{dt}A_u &= \frac{b^0}{\epsilon}A_u\left(1-s_h\frac{A_i}{A_i+A_u}\right)\left(1-\frac{A_i+A_u}{K}\right) - \delta_u A_u. \end{cases}$$

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$$\begin{cases} \frac{d}{dt}A_i &= (1-s_f)\frac{b^0}{\epsilon}A_i\left(1-\frac{A_i+A_u}{K}\right) - \delta\delta_u A_i + u, \\ \frac{d}{dt}A_u &= \frac{b^0}{\epsilon}A_u\left(1-s_h\frac{A_i}{A_i+A_u}\right)\left(1-\frac{A_i+A_u}{K}\right) - \delta_u A_u. \end{cases}$$

Formally, letting $\epsilon \to 0$, we deduce

$$A_i + A_u = K(1-\epsilon n) + o(\epsilon).$$

Then, we introduce

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

Large fertility asymptotics

After straightforward computations, we find

$$\begin{cases} \dfrac{d}{dt}n = -\dfrac{1-\epsilon n}{\epsilon}(b^0 n(s_h p^2 - (s_f + s_h)p + 1) - \delta_u((\delta - 1)p + 1)) - \dfrac{u}{\epsilon K}, \\ \dfrac{d}{dt}p = p(1-p)(b^0 n(s_h p - s_f) + (1-\delta)\delta_u) + \dfrac{u(1-p)}{K(1-\epsilon n)}. \end{cases}$$

Large fertility asymptotics

After straightforward computations, we find

$$\begin{cases} \dfrac{d}{dt}n = -\dfrac{1-\epsilon n}{\epsilon}(b^0 n(s_h p^2 - (s_f + s_h)p + 1) - \delta_u((\delta - 1)p + 1)) - \dfrac{u}{\epsilon K}, \\ \dfrac{d}{dt}p = p(1-p)(b^0 n(s_h p - s_f) + (1-\delta)\delta_u) + \dfrac{u(1-p)}{K(1-\epsilon n)}. \end{cases}$$

Formally, when $\epsilon \to 0$, assuming the convergence $p \to p_0$ and $n \to n_0$, we deduce from the first equation

$$n_0 = \frac{\delta_u((\delta - 1)p_0 + 1) + u/K}{b^0(s_h {p_0}^2 - (s_f + s_h)p_0 + 1)}.$$

Reduction of the model

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

$$\frac{d}{dt}p_0 = \delta\delta_u s_h \frac{p_0(1-p_0)(p_0-\theta)}{b^0(s_h {p_0}^2 - (s_f+s_h)p_0 + 1)} + \frac{u}{K} \cdot \frac{(1-p_0)(1-s_h p_0)}{s_h {p_0}^2 - (s_f+s_h)p_0 + 1},$$

with

$$\theta = \frac{s_f + \delta - 1}{\delta s_h}.$$

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

Reduction of the optimal problem

This formal derivation can be made rigorous, we obtain that as $\epsilon \to 0$, the system reduces to

Reduced problem

$$\frac{dp}{dt} = f(p) + ug(p),$$

where

$$f(p) = \frac{\delta\delta_u s_h}{b^0} \frac{p(1-p)(p-\theta)}{(1-p)(1-s_h p) + (1-s_f)p}, \qquad \theta = \frac{s_f + \delta - 1}{\delta s_h},$$

$$g(p) = \frac{1}{K} \frac{(1-p)(1-s_h p)}{(1-p)(1-s_h p) + (1-s_f)p}.$$

Reduction of the optimal problem

For the cost functional, we recall our choice

$$J(u) = \frac{1}{2} A_u(T)^2 + \frac{1}{2} (A_{iW}^* - A_i(T))_+^2.$$

Introducing the notation $p = \frac{A_i}{A_i + A_u}$, we have

$$\begin{aligned} J(u) =& \frac{1}{2} ((A_i + A_u)(T)(1 - p(T)))^2 \\ &+ \frac{1}{2} \Big(K(1 - \epsilon \frac{\delta_u \delta}{b^0 (1 - s_f)}) - ((A_i + A_u)(T) p(T)) \Big)_+^2. \end{aligned}$$

Thus, with the fact that $A_i + A_u \to K$, we deduce that

$$J(u) \underset{\epsilon \to 0}{\to} (K(1 - p(T)))^2.$$

Reduced optimal control problem

Reduced optimization problem

$$\min_{u \in \mathcal{U}_{\overline{U},C,T}} (1 - p(T))^2,$$

with $\mathcal{U}_{\overline{U},C,T} = \{0 \leq u \leq \overline{U} \text{ a.e.}, \int_0^T u(t)dt \leq C\}$, where p solves the differential equation

$$\frac{d}{dt}p = f(p) + ug(p), \quad f \text{ bistable}, g > 0 \text{ on } (0,1),\ g(1) = 0.$$

Reduced optimal control problem

This problem is simpler to study than the full system. Indeed, we observe that when $u = 0$,

- if $0 < p < \theta$, then $\frac{d}{dt} p < 0$;
- if $\theta < p < 1$, then $\frac{d}{dt} p > 0$.

In other words, the basin of attraction of 1 is $(\theta, 1)$, outside this domain, the solution move away from 1. Hence to be optimal one expects the solution to go to this basin of attraction as fast as possible. If the solution cannot reach this basin of attraction, it is better to act at the end of the protocol.

Reduction of the optimal problem

Using the Pontryagin Maximum Principle, this observation can be made rigorous and we may prove the following result [7] :

Theorem

Assume $T > C/M$ and above assumptions on the coefficients.
Then, any solution u^* to the reduced optimal problem satisfies $\int_0^T u^*(t)dt = C$ and is bang-bang (*i.e.* equal a.e. to 0 or $\overline{U}$).

Moreover, if (u^ϵ) is a family of minimizers for the optimal problem for the full system. Then, as $\epsilon \to 0$, it converges strongly in $L^1(0,T)$ to a solution of the reduced problem. Moreover, we have

$$\lim_{\epsilon \to 0} \min_{u \in \mathcal{U}_{\overline{U},C,T}} J^\epsilon(u) = \min_{u \in \mathcal{U}_{\overline{U},C,T}} (1 - p(T))^2.$$

This result implies that when ϵ is small the optimum is not far from a bang bang solution. However, from the above numerical result, it seems that it is not bang bang.

7. L. Almeida, Y. Privat, M. Strugarek, N. V., *Optimal releases for population replacement strategies, application to Wolbachia*, SIAM J. Math. Anal. 2019.

Reduction of the optimal problem

Actually, we can get a precise description of the optimum :

- If $\overline{U} \leq \max_{p\in[0,\theta]} -\frac{f(p)}{g(p)}$ then the unique solution is given by $u^* = \overline{U}\mathbf{1}_{[T-C/\overline{U},T]}$.
- Otherwise, defining $C^*(\overline{U}) = \int_0^\theta \frac{\overline{U}dp}{f(p)+\overline{U}g(p)}$, one has
  - if $C < C^*(\overline{U})$ then the solution is unique and equal to $u^* = \overline{U}\mathbf{1}_{[T-C/\overline{U},T]}$;
  - if $C > C^*(\overline{U})$ then the solution is unique and equal to $u^* = \overline{U}\mathbf{1}_{[0,C/\overline{U}]}$;
  - if $C = C^*(\overline{U})$ then there is a continuum of solutions given by $u^*_\lambda = \overline{U}\mathbf{1}_{[\lambda,\lambda+C/\overline{U}]}$ for $\lambda \in [0, T - C/\overline{U}]$.

Outline of lecture 1

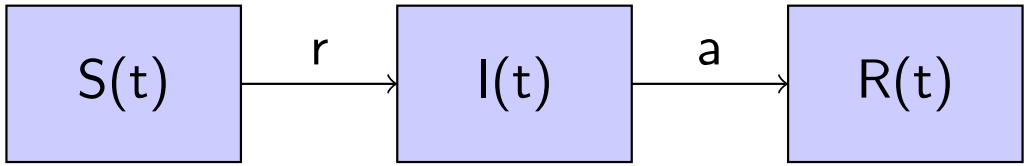
Some historical facts

- In the 18th century, London was strongly affected by an epidemic of smallpox. A controversial solution is *variolation*, which involves contacting individuals with a pustule removed from a patient. This kills the individual or gives him immunity for life. Daniel Bernoulli (Swiss mathematician, 1700-1782) proposes in 1766 a mathematical model describing this epidemic and determines whether or not to practice *variolation*. He proves that by inoculating part of the population, life expectancy was considerably increased.
- In 1911, Sir Ronald Ross (Nobel prize in medicine 1902, 1857-1932) presents the first mathematical model of malaria transmission, which highlights a threshold phenomenon. This is one of the first compartmental models. He is considered one of the founding fathers of mathematical epidemiology.
- In 1927, W.O. Kermarck & A.G. Mac Kendrick use the ideas of R. Ross and propose the SIR model to study the transmission of infection by humans.

Outline of lecture 1

SIR model

In 1927, W.O. Kermack & A. G. McKendrick introduce the so-called compartmental models : population is divided into susceptible individuals (S), infected individuals (I), and removed/recovered individuals (R).



where r is the transmission rate, a is the removal rate.

SIR model

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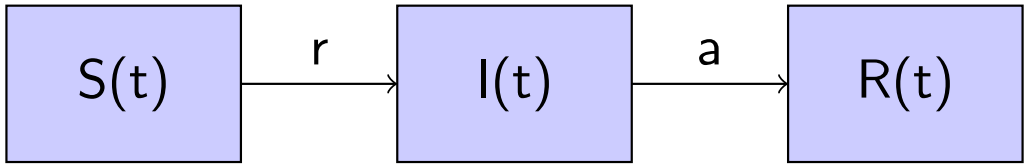

where r is the transmission rate, a is the removal rate.

The SIR system reads

$$\begin{cases} S' &= -r\dfrac{SI}{N} \\ I' &= r\dfrac{SI}{N} - aI \\ R' &= aI \\ N &= S + I + R. \end{cases}$$

complemented by initial data

$$S(0) = S_0, \quad I(0) = I_0, \quad R(0) = 0.$$

SIR model

- **Conservation.**

We first observe that $N = S + I + R$ is a constant. Indeed, $S' + I' + R' = 0$.

- **Equilibria.**

If we calculate the equilibria, we get

$$\begin{cases} 0 &= -r\dfrac{\overline{S}\,\overline{I}}{N} \\ 0 &= r\dfrac{\overline{S}\,\overline{I}}{N} - a\overline{I} \\ 0 &= a\overline{I} \end{cases}$$

Looking to the last equation, it gives $\overline{I} = 0$, which is the only solution. Thus, we expect that the number of infected should converge to 0 to reach the equilibrium.

However, it does not give any information about the number of individuals which has been infected (corresponding to the one in the R compartment at final time).

SIR model

$$\begin{cases} S' &= -r\frac{SI}{N} \\ I' &= r\frac{SI}{N} - aI \\ R' &= aI \end{cases}$$

Question : Knowing r, a, S_0 and I_0, can we know if an epidemic will occur or not ?

SIR model

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Question : Knowing r, a, S_0 and I_0, can we know if an epidemic will occur or not ?

We have $I'(0) = I_0(r\frac{S_0}{N} - a)$.

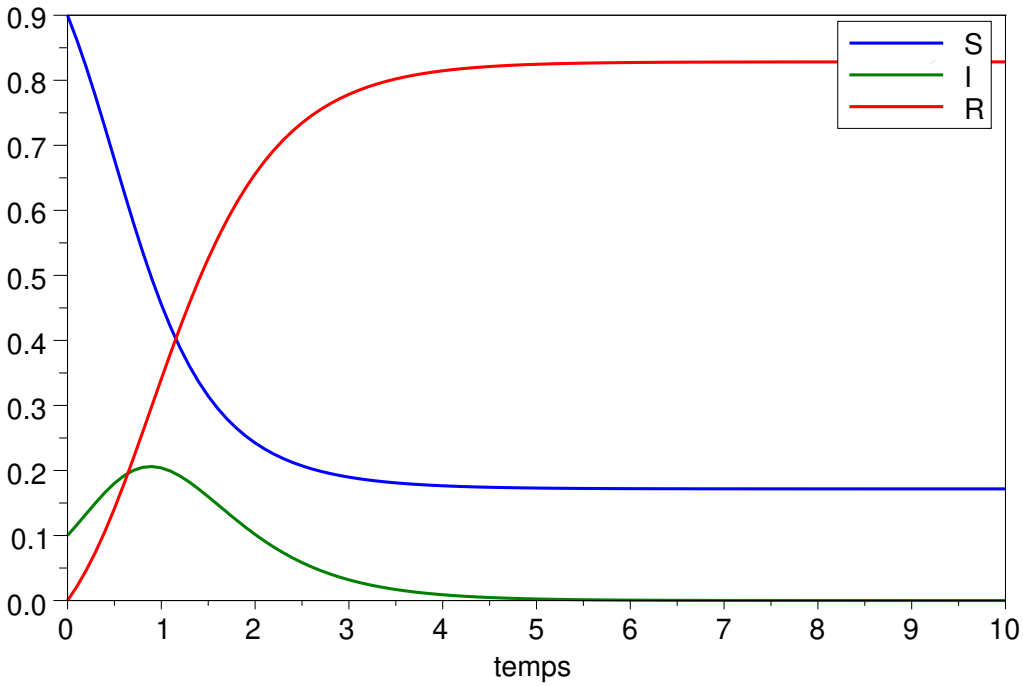
- If $rS_0 < aN$, then $I'(0) < 0$ and since $S' \leq 0$, we always have $I'(t) < 0$. Thus, the number of infected I will diminish until extinction.
- If $rS_0 > aN$, then $I'(0) > 0$. The number of infected individuals will start to increase.

We recover the threshold phenomenon, first noticed by Sir Ronald Ross. We denote $R_0 = \frac{rS_0}{aN}$, called basic reproduction number.

SIR model : numerical observation

Example : In a population where 90% of individuals are susceptibles and 10% are infected ($S_0 = 0.9$, $I_0 = 0.1$).

Case : $r = 4$, $a = 2$, *thus* $R_0 = 1.8$

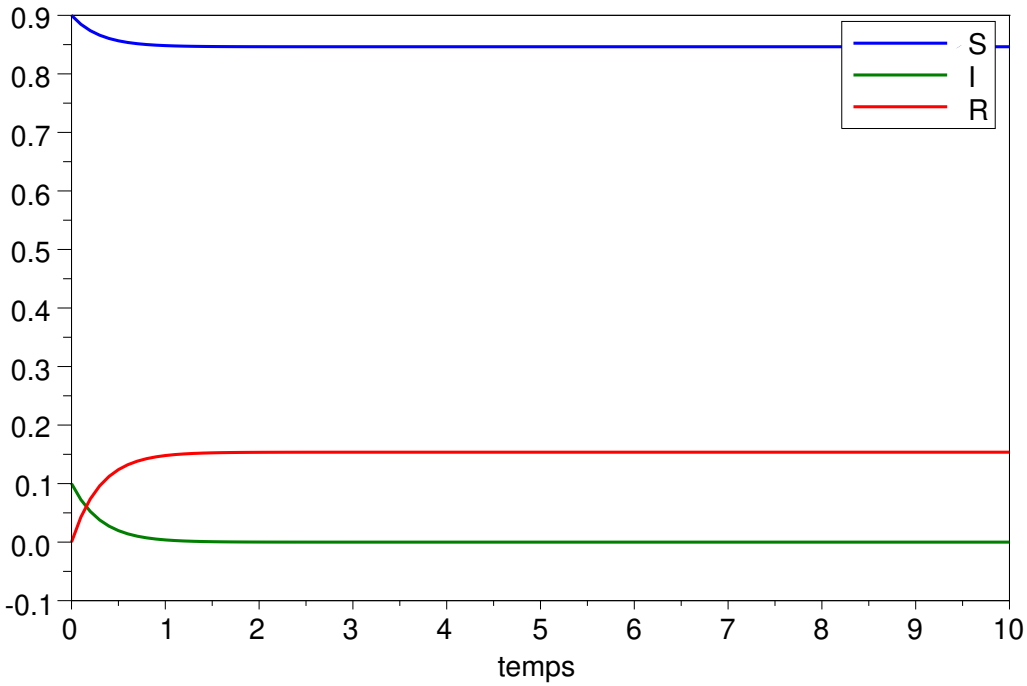


There is a peak of epidemic. At the final time, more than 80% of the population has been infected.

SIR model : numerical observation

Example : In a population where 90% of individuals are susceptibles and 10% are infected ($S_0 = 0.9$, $I_0 = 0.1$).

Case : $r = 2$, $a = 5$, *thus* $R_0 = 0.36$



There is no epidemic. Less than 15% of the population has been infected.

Outline of lecture 1

Basic reproduction number R_0

The basic reproduction number, R_0, is defined as the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population.
This quantity defines the epidemic threshold of a particular infection : if $R_0 < 1$, the infection will die out ; if $R_0 > 1$, the infection will be able to spread, there is an outbreak risk.

Some examples :

Disease	R_0	Disease	R_0
Measles (Rougeole)	12-18	Coqueluche	12-17
Diphtéria	6-7	Smallpox	5-7
Polio	5-7	HIV/AIDS	2-5
SRAS [8]	2-5	H1N1 (Grippe A) [9]	2-4
Dengue [10]	2.5-3.3	Ebola [11]	1.5-2.5

8. (outbreak in China 2003)
9. (outbreak 2009)
10. (Salvador (Brazil) outbreak 2002)
11. (West Africa 2014)

Basic reproduction number R_0

To avoid outbreak, we may try to diminish the value of R_0. In the SIR model, we have

$$R_0 = \frac{rS_0}{aN}.$$

Then, to diminish R_0, one may :

Basic reproduction number R_0

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- diminish r : quarantine, improve hygiene conditions to avoid contact with germs, ... ;

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- increase a : improve treatments ;

Basic reproduction number R_0

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$$R_0 = \frac{rS_0}{aN}.$$

Then, to diminish R_0, one may :

- diminish r : quarantine, improve hygiene conditions to avoid contact with germs, ... ;
- increase a : improve treatments ;
- diminish S_0/N : vaccination campaign. We consider that to stop an outbreak, one needs to vaccine a proportion $\left(1 - \frac{1}{R_0}\right)$ of the population. (Indeed, in this situation we will have $S_0 = \frac{1}{R_0}N$, then the new basic reproduction number will be 1).

Determining R_0 is essential to launch a prevention policy, or a vaccination campaign.
Example : for H1N1, R_0 is between 2 and 4. Thus, one needs to vaccinate between 50 and 75 % of the population.

Basic reproduction number R_0

The basic reproduction number R_0 is a dimensionless number

$$R_0 \propto \left(\frac{\text{infection}}{\text{contact}}\right) \cdot \left(\frac{\text{contact}}{\text{time}}\right) \cdot \left(\frac{\text{time}}{\text{infection}}\right)$$

In a simple model like SIR, the basic reproduction number is easy to compute. Indeed, the transmission rate is r, the mean infection time is $\frac{1}{a}$.

It becomes more tricky when we are considering infection with multiple types of infected individuals, or vector-borne disease, or sexually transmitted infections, ...

Remark : Denoting $i(t)$ the number of infected individuals at time t. If a fraction a leaves the infected compartment by unit of time, then $i'(t) = -ai(t)$, implying $i(t) = e^{-at}i(0)$. Then, the mean infection time is given by $\int_0^\infty e^{-at}dt = \frac{1}{a}$.

Basic reproduction number R_0 : example on the SIR model

Recall the SIR model

$$S' = -r\frac{SI}{N}, \quad I' = r\frac{SI}{N} - aI, \quad R' = aI, \quad N = S + I + R \text{ (constant)}.$$

The equilibrium without infection is given by $(S, I, R) = (S_0, 0, N - S_0)$ where S_0 is the (constant) number of individuals. Let us study the stability of this equilibrium. We linearize around this equilibrium, the linearized variables (s, i, r) verify

$$s' = -r\frac{S_0}{N}i, \quad i' = r\frac{S_0}{N}i - ai, \quad r' = ai.$$

Hence the Jacobian is given by $J = \begin{pmatrix} 0 & -rS_0/N & 0 \\ 0 & rS_0/N - a & 0 \\ 0 & a & 0 \end{pmatrix}$.

The eigenvalues of this matrix are $\{0, rS_0 - a\}$. We deduce :

The steady state without infection is linearly stable provided $rS_0 \leq aN$, i.e. $R_0 \leq 1$.

Hence, the basic reproduction number gives information on the stability of the equilibrium without infection.

Basic reproduction number R_0

Assume that we have a system in which there are multiple discrete types of infected individuals (e.g., mosquitoes and humans ; women and men ; or humans, dogs, and chickens). We define the next generation matrix as the square matrix G in which the ijth element of G, g_{ij}, is the expected number of secondary infections of type i caused by a single infected individual of type j, again assuming that the population of type i is entirely susceptible.
Then, the basic reproduction number is given by the spectral radius of G

$$R_0 = \rho(G) = \sup\{|\lambda|, \lambda \in \ \mathrm{Sp}\,(G)\}.$$

The next generation matrix has a number of desirable properties from a mathematical standpoint. In particular, it is a non-negative matrix and, as such, it is guaranteed that there will be a single, unique eigenvalue which is positive, real, and strictly greater than all the others. This is R_0.

Basic reproduction number R_0

A method to compute the basic reproduction number has been proposed in [Diekmann et al] [12]. We assume to have a system of ODE describing the dynamics of an infection :

1. Determine the variables describing the infected states.
2. Determine the equilibrium without infection and linearize around it only the system for infected states (i.e. compute the Jacobian matrix J).
3. Split the Jacobian matrix $J = T + \Sigma$ where T is the transmission matrix (birth of infected individuals) and Σ is the transition matrix (change of state).
4. We have $R_0 = \rho(-T\Sigma^{-1})$.

Then, we have the fundamental result :

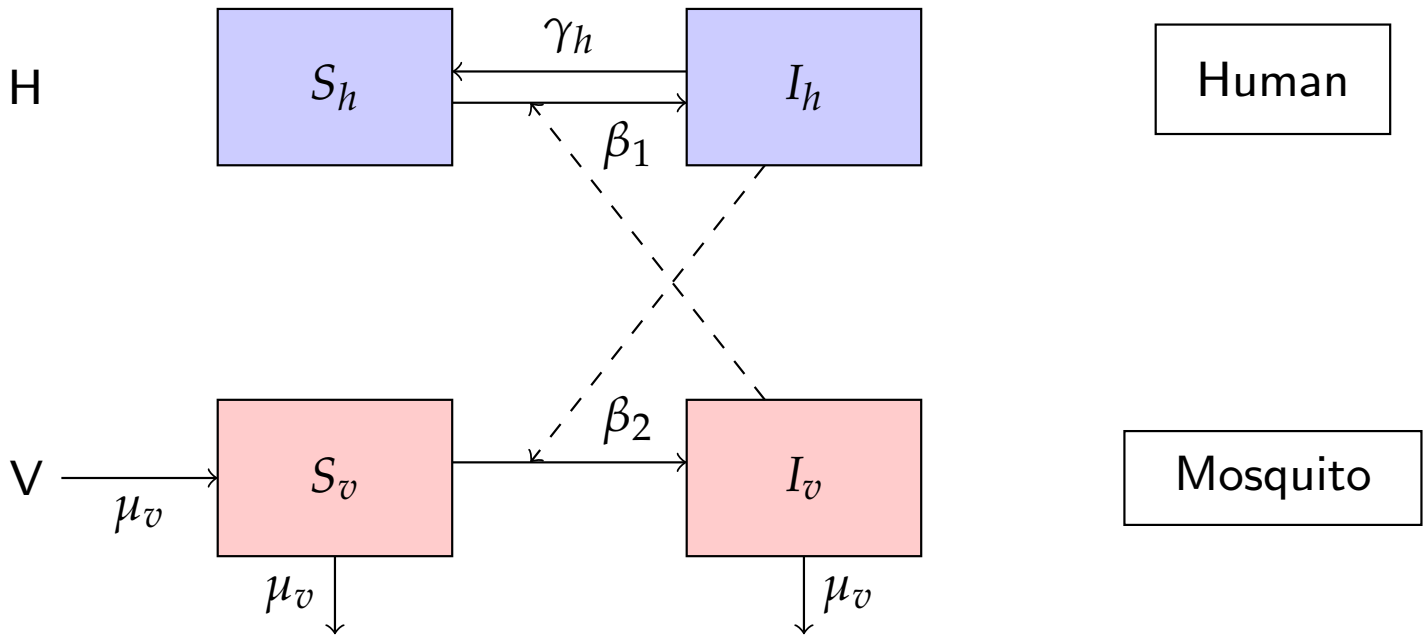
Theorem

Assume that the transmission matrix T is nonnegative, Σ is nonnegative outside the diagonal with $\sup\{ \mathrm{Re}(\lambda), \lambda \in \mathrm{Sp}(\Sigma)\} < 0$.
Then, the equilibrium without infection is linearly stable iff $R_0 \leq 1$.

12. O. Diekmann, J.A. Heersterbeek, J.A.J. Metz, J. Mathematical Biol. 1990

Ross-Macdonald model

Let us consider a model based on the work of Sir Ronald Ross (Nobel prize in 1902) improved later by George Macdonald (1952) for malaria. It is a vector-borne disease, i.e. transmitted by a vector : mosquitoes (mainly of genus *Anopheles*). The dynamical system includes the mosquitoes dynamics and its interaction with human.



Similar models are used for the transmission of Dengue, Chikungunya, Zika, ...

Ross-Macdonald model

The modelling assumptions are :

- Two populations : H (human), V (vector of the disease = mosquito).
- SIS model for the disease for H and V, where we assume that the total population of human is constant (fast dynamics of the disease) and we neglect the recovery rate for mosquitoes (life expectancy too short compared to the duration of the disease).
- Parameters :
  - β_1, β_2 proportions of bites giving rise to an infection to human, respectively, mosquitoes ;
  - γ recovery rate for human ;
  - μ_m death and birth rate for mosquitoes (assumed to be the same).

Ross-Macdonald model

The corresponding system of ODE reads

$$
\begin{aligned}
\frac{dS_h}{dt} &= -\beta_1 \frac{I_v S_h}{H} + \gamma I_h\,, \qquad H = S_h + I_h\,,\\
\frac{dI_h}{dt} &= \beta_1 \frac{I_v S_h}{H} - \gamma I_h\,,\\
\frac{dS_v}{dt} &= -\beta_2 \frac{I_h S_v}{H} + \mu V - \mu S_v\,, \qquad V = S_v + I_v\,,\\
\frac{dI_v}{dt} &= \beta_2 \frac{I_h S_v}{H} - \mu I_v\,.
\end{aligned}
$$

It is clear that the number of human, H, and of mosquitoes, V, are constants.

Ross-Macdonald model

We are now in position to compute the basic reproduction number for this system.

1. There are two infected states : I_h, I_v.
2. Equilibrium without infection : $(S_h, I_h, S_v, I_v) = (H, 0, V, 0)$.
   Linearization around this equilibrium for the infected states

$$\frac{dI_h}{dt} = \beta_1 I_v - \gamma I_h, \qquad \frac{dI_v}{dt} = \beta_2 \frac{V}{H} I_h - \mu I_v.$$

3. Transmission and transition matrices

$$T = \begin{pmatrix} 0 & \beta_1 \\ \beta_2 \frac{V}{H} & 0 \end{pmatrix} \qquad \Sigma = \begin{pmatrix} -\gamma & 0 \\ 0 & -\mu \end{pmatrix}.$$

4. Computation of R_0

$$T\Sigma^{-1} = \begin{pmatrix} 0 & \frac{\beta_1}{\mu} \\ \frac{\beta_2 V}{H\gamma} & 0 \end{pmatrix}.$$

The spectral radius for this latter matrix is then $R_0 = \sqrt{\frac{\beta_1 \beta_2 V}{\gamma \mu H}}$.

A model for dengue transmission

Finally, we consider a model for dengue transmission [13] This model is based on the following modeling assumption :

- The human population is assumed to be constant, i.e. the death rate for human is the same as the birth rate.
- Dengue is a SEI disease for mosquitoes.
- Dengue is a SIR disease for human.

We use the following notations :

- V, S_m, E_m, I_m denote the total number of mosquitoes, the number of susceptible mosquitoes, the number of mosquitoes exposed to the disease, the number of infected mosquitoes, respectively. We have the relation $\boxed{V = S_m + E_m + I_m}$.
- H, S_h, I_h, R_h denote the total number of human, the number of susceptible human, the number of infected human, the number of recovered humand, respectively. We have $\boxed{H = S_h + I_h + R_h}$.

13. From H. Hughes, N. F. Britton, *Modelling the use of Wolbachia to control dengue fever transmission*, Bull. Math. Biol. (2013).

A model for dengue transmission

With these considerations, the model reads

$$\frac{dV}{dt} = bV(1 - \frac{V}{K}) - dV,$$

$$\frac{dE_m}{dt} = ap(V - E_m - I_m)\frac{I_h}{N_h} - eE_m - dE_m, \qquad \frac{dI_m}{dt} = eE_m - dI_m,$$

$$\frac{dS_h}{dt} = \mu H - aqI_m\frac{S_h}{H} - \mu S_h, \qquad \frac{dI_h}{dt} = aqI_m\frac{S_h}{H} - cI_h - \mu I_h.$$

- Parameters are
  - a the biting rate.
  - p the probability of a blood meal leading to mosquito catching dengue from infected human.
  - q the probability of a blood meal leading to human catching dengue from infected mosquito.
  - b, d birth and death rate for mosquitoes, respectively ; e mean incubation time.
  - μ birth and death rate (the same) ; c recovery time.

A model for dengue transmission

We are now in position to compute the basic reproduction number for this system.

1. There are 3 infected states : E_m, I_m, I_h.
2. Equilibrium without infection : $(V, E_m, I_m, S_h, I_h) = (K(1-\frac{d}{b}), 0, 0, H, 0)$. Linearization around this equilibrium for the infected states

$$\frac{dE_m}{dt} = \frac{apK(1-\frac{d}{b})}{H} I_h - (e+d)E_m, \qquad \frac{dI_m}{dt} = eE_m - dI_m,$$
$$\frac{dI_h}{dt} = aqI_m - (c+\mu)I_h.$$

3. Transmission and transition matrices

$$T = \begin{pmatrix} 0 & 0 & \frac{apK(1-\frac{d}{b})}{H} \\ 0 & 0 & 0 \\ 0 & aq & 0 \end{pmatrix} \qquad \Sigma = \begin{pmatrix} -(d+e) & 0 & 0 \\ e & -d & 0 \\ 0 & 0 & -(c+\mu) \end{pmatrix}.$$

4. Computation of R_0 : We have

$$-\Sigma^{-1} = \begin{pmatrix} \frac{1}{d+e} & 0 & 0 \\ \frac{e}{d(d+e)} & \frac{1}{d} & 0 \\ 0 & 0 & \frac{1}{c+\mu} \end{pmatrix}.$$

A model for dengue transmission

Then, using the above approach, we compute

$$T\Sigma^{-1} = \begin{pmatrix} 0 & 0 & \frac{apK(1-\frac{d}{b})}{(c+\mu)H} \\ 0 & 0 & 0 \\ \frac{eaq}{d(d+e)} & \frac{aq}{d} & 0 \end{pmatrix}.$$

The spectral radius for this latter matrix is then $R_0 = \sqrt{\frac{ea^2pqK(1-\frac{d}{b})}{d(d+e)(c+\mu)H}}$.

To be continued ...

Thank you for your attention.