

# Biological phenomena : description, modelling and mathematical approach

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## Introduction

This course aims at focusing on the use of mathematics to describe, understand, model biological phenomena. A particular focus will be paid on the mathematical modelling.

- Aims.** Use complementary skills of biologists, physicists and mathematicians to understand, describe, predict observed phenomena.
- Issues.** Issues are important in particular in term of medical applications and prevention policy.
- Way.** **Mathematical modelling**, mathematical tools from analysis to statistics and numerical simulation.

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**Way.** **Mathematical modelling**, mathematical tools from analysis to statistics and numerical simulation.

The outline of the lecture will be the following

- **Lecture 1 : Generalities and Modelling**
  - Mathematical model in population dynamics.
  - Dynamical systems, SIR models, basic reproduction number.
- **Lecture 2 : Parabolic model in population dynamics**
  - Propagation phenomena, traveling waves.
  - Turing instabilities.
- **Lecture 3 : Mathematical models of tumor growth**

# Lecture 1

## Generalities and Modelling

# Outline of lecture 1

## 1 Population dynamics

- Malthus model
- Verhulst model
- Allee effect
- Lotka-Volterra system

## 2 Parabolic equations in biology

- Reaction-diffusion systems in population dynamics
- Reaction kinetics

## 3 Dynamical system in biology

- Existence and uniqueness theory
- Equilibria and stability

## 4 Mathematical epidemiology

- Introduction
- SIR model
- Basic reproduction number  $R_0$
- Examples of compartmental models

## Introduction

We focus on the dynamics of a population of individuals (men, animals, cells, bacteria, ...) which we characterize by its density (or number) at time  $t \geq 0$  denoted  $N(t)$ .

$N(t)$  : number of individuals at time  $t \geq 0$ .

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**Goal** : knowing the density (or number) at time  $t = 0$ , denoted  $N_0$ , try to predict the population dynamics for future times  $t \geq 0$  depending on some observed phenomena.

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## Population dynamics : Malthus

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In this model, only two phenomena are taken into account :

- **birth**, with a rate  $b > 0$  (mean number of individuals generated by one individual by unit of time) : for  $N$  individuals, during a time interval  $\delta t$ , the number of birth is  $bN\delta t$  ;
- **death**, with a rate  $d > 0$ .

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Taking the limit  $\delta t \rightarrow 0$ , we get

$$N'(t) = bN(t) - dN(t).$$

## Population dynamics : Malthus

Malthus model (1798)

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This very simple model allows us to observe two phenomena :

- If  $b > d$ , we have an **exponential growth** of the size of the population (sometimes call **Malthusian** growth).
- If  $b < d$ , we have **extinction** of the population.

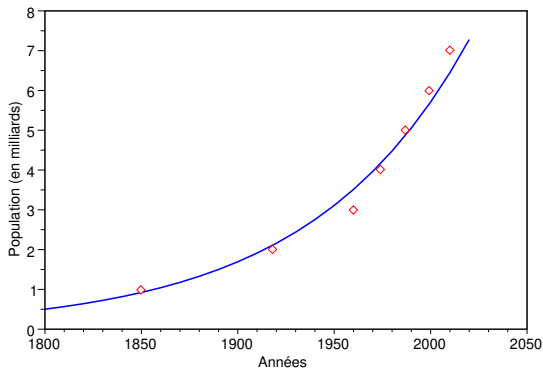
$r = b - d$  is called the **growth rate**.



## Population dynamics : Malthus

This is a too simple model to be realistic. Nevertheless, looking for long time scale of the world human population :

Année	1750	1850	1918	1960	1974	1987	1999	2010
Population (in billions)	0.5	1	2	3	4	5	6	7



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## Population dynamics : Verhulst

In 1838, Pierre-François Verhulst (Belgian mathematician, 1804-1849) refined the Malthus model by proposing a growth rate depending on the size of the population :

- When  $N$  is small, same growth rate as for the Malthus model ;
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### Verhulst model (1838)

$$N'(t) = r \left( 1 - \frac{N(t)}{K} \right) N(t), \quad N(0) = N_0.$$

$r$  : growth rate ;  $K$  : environmental capacity.

## Population dynamics : Verhulst

### Verhulst model

$$N'(t) = r\left(1 - \frac{N(t)}{K}\right)N(t), \quad N(0) = N_0.$$

We notice that :

- If  $N \in [0, K]$ , then  $(1 - \frac{N}{K})N \geq 0$ , thus  $N' \geq 0$  : The size of the population increases.
- If  $N > K$ , then  $(1 - \frac{N}{K})N < 0$ , thus  $N' < 0$  : The size of the population decreases.

As a consequence  $N$  is a **bounded** function.

## Population dynamics : Verhulst

### Verhulst model

$$N'(t) = r \left( 1 - \frac{N(t)}{K} \right) N(t), \quad N(0) = N_0.$$

This Cauchy problem can actually be solved explicitly by noticing that

$$\frac{N'(t)}{N(t) \left( 1 - \frac{N(t)}{K} \right)} = \frac{N'(t)}{N(t)} + \frac{N'(t)}{K - N(t)} = r.$$

Thus,

$$\frac{d}{dt} \left( \ln(N(t)) - \ln(K - N(t)) \right) = r.$$

Integrating in time it gives,

$$\ln \left( \frac{N(t)}{K - N(t)} \right) = rt + \ln \left( \frac{N_0}{K - N_0} \right).$$

## Dynamique des populations : Verhulst

After calculation, it gives

$$N(t) = \frac{KN_0}{(K - N_0)e^{-rt} + N_0}.$$

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- If  $N_0 > 0$ , then  $\lim_{t \rightarrow +\infty} N(t) = K$ .



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### Verhulst model

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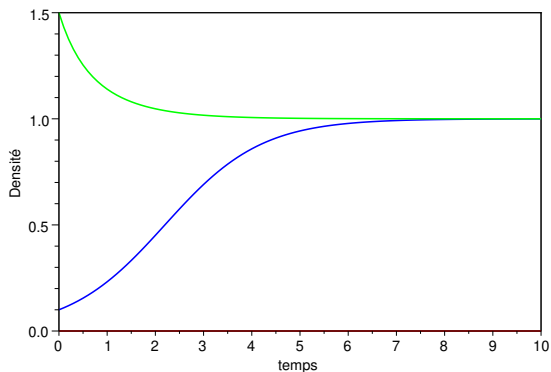
We remark that  $N(t) = 0$  and  $N(t) = K$  are constant solutions to this ODE. Such solutions are called **equilibria**.

Except for the case where the density is initially 0, all solutions converge to the stationary state  $N(t) = K$

We say that the steady state  $N = K$  is **stable**  $\Rightarrow$  **monostable** case.

## Population dynamics : equilibria

Numerical example of solutions for  $K = 1$ ,  $r = 1$  and for 3 values of  $N_0$  :  $N_0 = 0$  (red),  $N_0 = 0.1$  (blue),  $N_0 = 1.5$  (green).



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## Allee effect, bistability

In the case of, for instance, *endangered and rare species*, an other phenomena should be taken into account : [Allee effect](#).

There is a negative effect of growth when the population density is too low. This may be due, for example, to the scarcity effect, the consanguinity effect, the difficulty of meeting a partner for populations with low density, ...

We choose a growth rate under the form  $(1 - N)(N - \theta)$ , with  $\theta \in (0, 1)$ . It is :

- negative if  $0 < N < \theta$ ,
- positive if  $\theta < N < 1$ .

Denoting  $N(t)$  population density at time  $t$ , the model with Allee effect reads :

$$N'(t) = (1 - N(t))(N(t) - \theta)N(t), \quad \theta \in ]0, 1[, \quad N(0) = N_0.$$

## Allee effect

$$N'(t) = (1 - N(t))(N(t) - \theta)N(t), \quad \theta \in ]0, 1[, \quad N(0) = N_0.$$

**Equilibria.** We look for  $\bar{N}$  such that

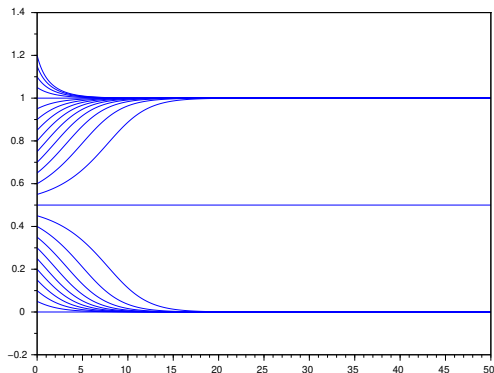
$$(1 - \bar{N})(\bar{N} - \theta)\bar{N} = 0.$$

Thus, there are 3 equilibria : 0,  $\theta$  and 1.

- Stability.**
- If  $N \in ]0, \theta[$ ,  $N' < 0$  thus  $N$  decreases  $\Rightarrow$  0 is stable.
  - If  $N \in ]\theta, 1[$ ,  $N' > 0$  thus  $N$  increases  $\Rightarrow$  1 is stable.
  - Thus  $\theta$  is unstable.

## Allee effect

**Allee effect** : population density should be higher than a threshold to avoid extinction.



Example of a numerical simulation for the equation  $y' = y(1-y)(y-0.5)$  for different initial data ranging from 0 to 1.2.

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## Predator-Prey model of Lotka-Volterra

In 1920, Alfred J. Lotka and Vito Volterra proposed a model to describe the dynamics of two species in interaction : preys and predators. Their model is based on several assumptions :

- The prey population finds ample food at all times.
- The food supply of the predator population depends entirely on the size of the prey population.
- The rate of change of populations is proportional to its size.
- During the process, the environment does not change in favour of one species, and genetic adaptation is inconsequential.
- Predators have limitless appetite.



## Predator-Prey model of Lotka-Volterra

Denoting  $n$  the density of preys and  $p$  the density of predators. The system reads

$$\begin{aligned}n' &= n \left( \underbrace{a}_{\text{birth rate}} - \underbrace{bp}_{\text{predation}} \right), \\p' &= p \left( \underbrace{cn}_{\text{predation}} - \underbrace{d}_{\text{death rate}} \right).\end{aligned}$$

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**Equilibria.** We look for  $(\bar{n}, \bar{p})$  solution to

$$0 = \bar{n}(a - b\bar{p}), \quad 0 = \bar{p}(c\bar{n} - d).$$

There are two couples of solutions  $(0,0)$  and  $(\frac{d}{c}, \frac{a}{b})$ .

## Predator-Prey model of Lotka-Volterra

For the Lotka-Volterra system, there is an **energy** (conserved quantity). Indeed, we notice that

$$\frac{cn - d}{n}n'(t) = \frac{a - bp}{p}p'(t).$$

Integrating in time, we deduce that

$$cn(t) - d \ln(n(t)) = a \ln(p(t)) - bp(t) + \text{Cste}.$$

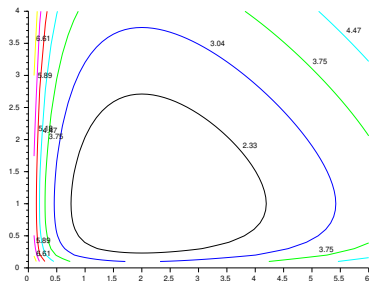
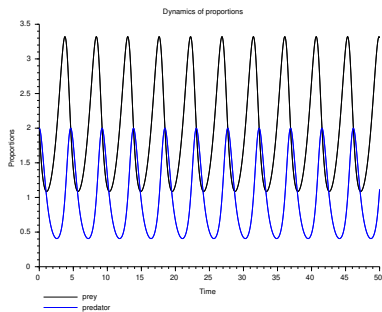
As a consequence the quantity

$$H(t) = cn(t) + bp(t) - d \ln(n(t)) - a \ln(p(t)),$$

is constant.

## Predator-Prey model of Lotka-Volterra

As a consequence the trajectories in the phase plane  $(n, p)$  of the solutions belongs to the **level sets** of the **energy  $H$** .



The level sets of  $H$  being closed (see figure on the right), the solutions are periodic in time (see figure on the left).

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## Reaction-diffusion-advection systems

We include the spatial dependency. Let us consider  $I$  species in interaction. We denote  $n_i(t, x)$  the density of a species  $i$ ,  $i = 1, \dots, I$ , at time  $t$ , position  $x \in \mathbb{R}^d$ . We assume that individuals

- move randomly according to **Brownian motions** (diffusion process),
- are subjected to an external **force field**  $U(t, x) \in \mathbb{R}^d$ ,
- growth, die, interact together ; it is modeled through a **reaction term**.

The system governing the dynamics of the interacting system of populations  $n_i$  reads,  $i = 1, \dots, I$ ,

$$\partial_t n_i \quad \underbrace{-D_i \Delta n_i}_{\text{active motion}} \quad + \quad \underbrace{\operatorname{div}(U_i(t, x)n_i)}_{\text{oriented drift}} \quad = \quad \underbrace{n_i R_i(t, x, n_1, \dots, n_I)}_{\text{reaction term}}.$$

The quantity  $D_i > 0$  is the diffusion coefficient.

Such system enters into the class of **parabolic equations**.

## Reaction-diffusion-advection systems

Such systems should be complemented by

- Initial data

$$n_i(t = 0, x) = n_i^0, \quad i = 1, \dots, I.$$

- Boundary conditions if the domain  $\Omega \subset \mathbb{R}^d$  is bounded. Two classical boundary conditions are given by :

**Dirichlet boundary conditions** (the value at the boundary is prescribed)

$$u = u_b \quad \text{on } \partial\Omega.$$

**Neumann boundary conditions** (the flux at the boundary is prescribed)

$$\partial_\nu u = \gamma \quad \text{on } \partial\Omega.$$

- If  $\Omega = \mathbb{R}^d$  we usually assume that functions goes to 0 at infinity (i.e. belongs to some  $L^p(\mathbb{R}^d)$  space).

## Reaction term

A family of reaction terms is given by

$$R_i(n_1, \dots, n_I) = r_i + \sum_{j=1}^I c_{ij} n_j,$$

- $r_i$  intraspecific growth rate of species  $i$  ;
- $c_{ij}$  interaction effect of species  $j$  on species  $i$ . Usually  $c_{ii} < 0$  to model intraspecific competition, for  $i \neq j$ , one can distinguish :
  - If  $c_{ij} < 0$ ,  $c_{ji} > 0$ ,  $i$  is a prey for  $j$  and  $j$  is a predator for  $i$  ;
  - If  $c_{ij} > 0$ ,  $c_{ji} > 0$ , mutualistic interaction (both species help the other and benefit from it) ;
  - If  $c_{ij} < 0$ ,  $c_{ji} < 0$ , competition (both species compete for example for the same food).



## Examples

- Heat equation

$$\partial_t n - \Delta n = 0.$$

- Fisher/KPP equation (1937)

$$\partial_t n - \Delta n = rn\left(1 - \frac{n}{K}\right).$$

- Allen-Cahn equation (1979)

$$\partial_t n - \Delta n = n(1-n)(n-\theta), \quad \theta \in (0,1).$$

- Fokker-Planck equation

$$\partial_t n - \Delta n - \operatorname{div}(n\nabla n) = 0.$$

- Lotka-Volterra prey-predator system

$$\partial_t n - D_1 \Delta n = n(r_1 - bp),$$

$$\partial_t p - D_2 \Delta p = p(cn - r_2),$$

Then  $c_{12} = -b < 0$  and  $c_{21} = c > 0$ .

## General properties

In all generality, we consider the reaction-diffusion system,  $i = 1, \dots, I$ , on  $\mathbb{R}^d$

$$\partial_t n_i - D_i \Delta n_i = n_i R_i, \quad n_i(t=0) = n_i^0.$$

### Nonnegativity principle

Assume that  $n_i^0 \geq 0$ ,  $n_i^0 \in L^2(\mathbb{R}^d)$ , and that  $|R_i(t, x)| \leq \Gamma(t)$  with  $\Gamma$  a locally bounded function. Then  $n_i(t, x) \geq 0$ .

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**Proof** (formal) We use the so-called Stampacchia method. Let  $p_i = -n_i$ , we have

$$\partial_t p_i - D_i \Delta p_i = p_i R_i.$$

We denote  $(p_i)_+ = \max(p_i, 0)$  the positive part of  $p_i$ . We multiply by  $(p_i)_+$  and integrate, using the Green formula

$$\frac{1}{2} \frac{d}{dt} \int_{\mathbb{R}^d} (p_i)_+^2 dx + D_i \int_{\mathbb{R}^d} |\nabla (p_i)_+|^2 dx = \int_{\mathbb{R}^d} (p_i)_+^2 R_i dx.$$

### Reminder : Green formula

$$\int_{\Omega} u \Delta v dx = \int_{\partial\Omega} u \partial_\nu v d\sigma + \int_{\Omega} \nabla u \cdot \nabla v dx.$$

## General properties

$$\frac{1}{2} \frac{d}{dt} \int_{\mathbb{R}^d} (p_i)_+^2 dx + D_i \int_{\mathbb{R}^d} |\nabla (p_i)_+|^2 dx = \int_{\mathbb{R}^d} (p_i)_+^2 R_i dx.$$

By assumption  $|R_i(t, x)| \leq \Gamma(t)$ . Thus

$$\frac{1}{2} \frac{d}{dt} \int_{\mathbb{R}^d} (p_i)_+^2 dx \leq \Gamma(t) \int_{\mathbb{R}^d} (p_i)_+^2 dx.$$

As a consequence, we have

$$\int_{\mathbb{R}^d} (p_i)_+^2 dx \leq e^{\int_0^t 2\Gamma(s) ds} \int_{\mathbb{R}^d} (p_i(t=0))_+^2 dx = 0.$$

Thus  $(p_i)_+ = 0$ , which implies  $n_i \geq 0$ .

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## Reaction kinetics

Let us denote  $n_i$  the molecular concentrations of species  $i$ ,

$$\partial_t n_i - \underbrace{D_i \Delta n_i}_{\text{molecular diffusion}} + \underbrace{n_i L_i = G_i}_{\text{reaction terms}}, \quad t \geq 0, x \in \mathbb{R}^d, i = 1, \dots, I.$$

Reaction terms are given by the *law of mass action* : the rate of a reaction is proportional to the concentrations of the reactants.

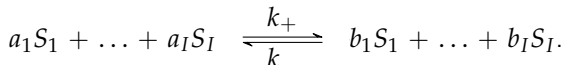
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Reaction terms are given by the *law of mass action*: the rate of a reaction is proportional to the concentrations of the reactants.

For example, consider the reversible reaction



It leads to the reaction rate

$$\partial_t n_i - D_i \Delta n_i + \underbrace{a_i k_+ \prod_{j=1}^I n_j^{a_j} + b_i k_- \prod_{j=1}^I n_j^{b_j}}_{\text{loss terms}} = \underbrace{b_i k_+ \prod_{j=1}^I n_j^{a_j} + a_i k_- \prod_{j=1}^I n_j^{b_j}}_{\text{gain terms}}.$$

## Reaction kinetics

The latter equation may be rewritten

$$\partial_t n_i - D_i \Delta n_i = (b_i - a_i) \left( k_+ \prod_{j=1}^I n_j^{a_j} - k_- \prod_{j=1}^I n_j^{b_j} \right).$$

### Entropy property

Denoting

$$S(t, x) = \sum_{i=1}^I (n_i \ln(n_i) + \sigma_i - 1), \quad \text{with} \quad \sum_{i=1}^I \sigma_i (a_i - b_i) = \ln k_+ - \ln k_-.$$

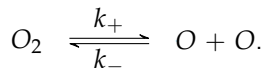
There are different possible choice for the constant  $\sigma_i$ . In all cases, we have the *entropy dissipation property*

$$\frac{d}{dt} \int_{\mathbb{R}^d} S(t, x) dx + \sum_{i=1}^I D_i \int_{\mathbb{R}^d} \frac{|\nabla n_i|^2}{n_i} dx \leq 0.$$



## Reaction kinetics : examples

### Dioxygene dissociation



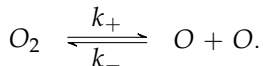
Denoting  $n_1 = [O_2]$  and  $n_2 = [O]$ ,

$$\partial_t n_1 - D_1 \Delta n_1 - k_+ n_1 = k_- n_2^2,$$

$$\partial_t n_2 - D_2 \Delta n_2 - 2k_- n_2^2 = 2k_+ n_1.$$

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Properties :

- Conservation

$$\frac{d}{dt} \int_{\mathbb{R}^d} (2n_1 + n_2) dx = 0.$$

- Entropy

$$S(t) = \int_{\mathbb{R}^d} (n_1(\ln(k_+ n_1) - 1) + n_2(\ln(\sqrt{k_-} n_2) - 1)) dx,$$

is a nonincreasing quantity.

## Reaction kinetics : examples

Indeed, computing

$$\begin{aligned}
 \frac{d}{dt} S(t) &= \int_{\mathbb{R}^d} (\partial_t n_1 \ln(k_+ n_1) + \partial_t n_2 \ln(\sqrt{k_-} n_2)) dx \\
 &= \int_{\mathbb{R}^d} (D_1 \Delta n_1 \ln(k_+ n_1) + D_2 \Delta n_2 \ln(\sqrt{k_-} n_2)) dx \\
 &\quad + \int_{\mathbb{R}^d} (-k_+ n_1 + k_- (n_2)^2) (\ln(k_+ n_1) - 2 \ln(\sqrt{k_-} n_2)) dx \\
 &= - \int_{\mathbb{R}^d} (D_1 \frac{|\nabla n_1|^2}{n_1} + D_2 \frac{|\nabla n_2|^2}{n_2}) dx \\
 &\quad - \int_{\mathbb{R}^d} (k_+ n_1 - k_- (n_2)^2) (\ln(k_+ n_1) - \ln(k_- n_2^2)) dx.
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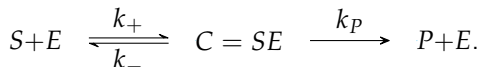
Since the function  $\ln$  is nondecreasing the latter term is nonpositive.

Thus,

$$\frac{d}{dt}S(t) \leq 0.$$

## Reaction kinetics : enzymatic reactions

**Enzymatic reactions (Michaelis & Menten (1913))** A substrate  $S$  can be transformed into a product  $P$ , but this reaction occurs only if an enzyme  $E$  is present :



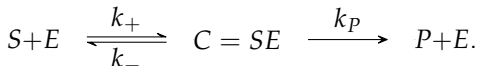
We neglect molecular diffusion :

$$\begin{aligned} \frac{dn_S}{dt} &= k_- n_C - k_+ n_S n_E ; & \frac{dn_E}{dt} &= (k_- + k_P) n_C - k_+ n_S n_E ; \\ \frac{dn_C}{dt} &= k_+ n_S n_E - (k_- + k_P) n_C ; & \frac{dn_P}{dt} &= k_P n_C. \end{aligned}$$

This reaction comes with the initial data  $n_S^0 > 0$ ,  $n_E^0 > 0$ ,  $n_C^0 = n_P^0 = 0$ .

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This reaction comes with the initial data  $n_S^0 > 0$ ,  $n_E^0 > 0$ ,  $n_C^0 = n_P^0 = 0$ .

### ■ Conservation quantities

$$n_E(t) + n_C(t) = n_E^0 + n_C^0 = n_E^0 ; \quad n_S(t) + n_C(t) + n_P(t) = n_S^0 + n_C^0 + n_P^0 = n_S^0.$$

## Reaction kinetics

Using this two algebraic relation, we may simplify into

$$\begin{aligned}\frac{dn_S}{dt} &= k_- n_C - k_+ n_S (n_E^0 - n_C) ; \\ \frac{dn_C}{dt} &= k_+ n_S (n_E^0 - n_C) - (k_- + k_P) n_C .\end{aligned}$$

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We may simplified further the system by assuming a quasi-static approximation on  $n_C$ , i.e. fast dynamics of the complex  $SE$ .

From the second equation, we deduce the relation

$$n_C = \frac{k_+ n_S n_E^0}{k_- + k_P + k_+ n_S} .$$

Injecting into the first equation, we obtain the *so-called* [Michaelis-Menten law](#)

$$\frac{dn_S}{dt} = -k_P n_E^0 \frac{n_S}{\frac{k_- + k_P}{k_+} + n_S} .$$

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## Cauchy problem

Many problems in biology may be modelled by a system of differential equation.

### Cauchy problem

Let  $T > 0$ ,  $f : [0, T] \times \mathbb{R}^d \rightarrow \mathbb{R}^d$ ,  $y_0 \in \mathbb{R}^d$ .

A Cauchy problem is the given of a differential system and an initial data :

$$\begin{cases} y'(t) = f(t, y(t)), & t \in [0, T], \\ y(0) = y_0. \end{cases} \quad (C)$$

- When the function  $f$  does not depend on the time, the system is called *autonomous*.
- A differential equation of order  $n$  may be rewritten into a system of order 1 in dimension  $n$  by using the variable  $Y(t) = (y(t), y'(t), \dots, y^{(n-1)}(t))$ .

## Cauchy problem : linear case

Let  $A \in \mathcal{M}_n(\mathbb{R})$ ,  $B : [0, T] \rightarrow \mathbb{R}^n$ , it is easy to solve the linear problem

$$y'(t) = Ay(t) + B(t), \quad y(0) = y_0.$$

The solution is given by

$$y(t) = \exp(tA)y_0 + \int_0^t \exp((t-s)A)B(s) ds,$$

where we recall that the exponential of a matrix is given by

$$\exp(A) = \sum_{k=0}^{\infty} \frac{1}{k!} A^k.$$

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If the matrix  $A$  is diagonalizable :  $\exists P \in GL_n(\mathbb{R})$  such that  $P^{-1}AP = D$ , then

$$\exp(tA) = P \exp(tD)P^{-1} = P \begin{pmatrix} e^{t\lambda_1} & 0 & \dots & 0 \\ 0 & e^{t\lambda_2} & \ddots & \vdots \\ & \ddots & \ddots & 0 \\ 0 & & 0 & e^{t\lambda_n} \end{pmatrix} P^{-1}.$$

## Cauchy problem : existence theory

### Definition

- We say that  $(I, y)$  is a *local solution* of  $(C)$  iff  $I \subset [0, T]$  is an interval containing 0 and  $y : I \rightarrow \mathbb{R}^d$  is differentiable and satisfies  $(C)$ .
- We say that  $(J, z)$  is an *extension* of  $(I, y)$  iff  $I \subset J$  and  $\forall t \in I, y(t) = z(t)$ .
- We say that  $(I, y)$  is a *maximal solution* if we cannot extend it on a strictly bigger interval.
- If  $I = [0, T]$ , we say that the solution is *global*.

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### Cauchy-Lipschitz theorem

Assume  $f$  is continuous on  $[0, T] \times \mathbb{R}^d$ , locally Lipschitz continuous with respect to its second variable uniformly with respect to  $t$ . Then, the Cauchy problem (C) admits an unique maximal solution.

Moreover, if we denote  $[0, b)$  the interval of existence, if  $b < T$ , then  $\lim_{t \rightarrow b^-} \|y(t)\| = +\infty$ .

## Cauchy problem : existence theory

### Cauchy-Lipschitz theorem (global version)

Assume  $f$  is continuous on  $[0, T] \times \mathbb{R}^d$  and globally Lipschitz continuous with respect to its second variable uniformly with respect to  $t$ . Then, the Cauchy problem (C) admits an unique global solution.



## Cauchy problem : existence theory

### Cauchy-Lipschitz theorem (global version)

Assume  $f$  is continuous on  $[0, T] \times \mathbb{R}^d$  and globally Lipschitz continuous with respect to its second variable uniformly with respect to  $t$ . Then, the Cauchy problem (C) admits a unique global solution.

#### Remark :

- $f$  locally Lipschitz continuous with respect to its second variable uniformly with respect to  $t$  :

$$\forall y \in \mathbb{R}^d, \exists V_y \subset \mathbb{R}^d (y \in V_y), \exists L_y > 0, \quad \forall x, \tilde{x} \in V_y, \forall t \in [0, T], \\ \|f(t, x) - f(t, \tilde{x})\| \leq L_y \|x - \tilde{x}\|.$$

- $f$  globally Lipschitz continuous with respect to its second variable uniformly with respect to  $t$  :

$$\exists L > 0, \forall x, \tilde{x} \in \mathbb{R}^d, \forall t \in [0, T], \quad \|f(t, x) - f(t, \tilde{x})\| \leq L \|x - \tilde{x}\|.$$

## Cauchy problem : examples

Some important examples :

- Consider the Cauchy problem

$$y' = y^2, \quad y(0) = y_0 > 0.$$

The solution is given by  $y(t) = \frac{y_0}{1 - y_0 t}$ .

It exists only on  $[0, \frac{1}{y_0})$  and blows up at time  $\frac{1}{y_0}$ .

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It exists only on  $[0, \frac{1}{y_0})$  and blows up at time  $\frac{1}{y_0}$ .

- Consider the Cauchy problem

$$y' = \sqrt{y}, \quad y(0) = 0.$$

Then,  $y(t) = \frac{t^2}{4}$  and  $y(t) = 0$  are two solutions for this problem. Hence there is no uniqueness. Indeed the assumption in the Cauchy-Lipschitz theorem are not satisfied.

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## Equilibrium

In this section we focus on *autonomous systems* and we assume to have existence of a *global* solution on  $[0, +\infty)$ .

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

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

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

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### Definition

- An **equilibrium** is a stationary solution, i.e.  $\bar{y} \in \mathbb{R}^d$  such that  $f(\bar{y}) = 0$ .
- An equilibrium is **stable** if  $\forall \varepsilon > 0, \exists \delta > 0$  such that  $\forall y \in B(\bar{y}, \delta)$ ,  $\phi(t, y) \in B(\bar{y}, \varepsilon)$ .
- An equilibrium is **asymptotically stable** if it is stable and  $\exists \eta > 0$  such that  $\forall y \in B(\bar{y}, \eta), \|\phi(t, y) - \bar{y}\| \xrightarrow[t \rightarrow +\infty]{} 0$ .
- An equilibrium is **unstable** if it is not stable.

## Linear case

Let us investigate the system  $Y' = AY$  with  $A \in \mathcal{M}_d(\mathbb{C})$ .

- **Equilibrium** :  $\bar{Y} \in \mathbb{R}^d$  such that  $A\bar{Y} = 0$ , i.e.  $\bar{Y} \in \text{Ker}A$ .
- **Flow** :  $\phi(t, Y_0) = e^{tA}Y_0$ .
- **Stability analysis** :  $\phi(t, Y_0) - \bar{Y} = e^{tA}Y_0 - \bar{Y} = e^{tA}(Y_0 - \bar{Y})$ . Thus,  $\bar{Y}$  is stable iff  $e^{tA}$  is bounded,  $\bar{Y}$  is asymptotically stable iff  $\lim_{t \rightarrow +\infty} e^{tA} = 0$ .

If  $A$  is diagonalizable, denoting  $\lambda_1, \dots, \lambda_d$  its eigenvalues, there exists  $P \in GL_d(\mathbb{C})$  such that

$$\exp(tA) = P \exp(tD)P^{-1} = P \begin{pmatrix} e^{t\lambda_1} & 0 & \dots & 0 \\ 0 & e^{t\lambda_2} & \ddots & \vdots \\ & \ddots & \ddots & 0 \\ 0 & & 0 & e^{t\lambda_d} \end{pmatrix} P^{-1}.$$

As a consequence,  $\bar{Y}$  is stable iff  $\text{Re}(\lambda_i) \leq 0$ ,  $i = 1, \dots, n$ ;  $\bar{Y}$  is asymptotically stable iff  $\text{Re}(\lambda_i) < 0$ ,  $i = 1, \dots, n$ .

## Linear case

If  $A$  is not diagonalizable, then we can triangulate  $A$  : there exists  $P \in GL_d(\mathbb{C})$  such that

$$\exp(tA) = P \exp(tD) P^{-1} = P \begin{pmatrix} e^{t\lambda_1} & * & \dots & 0 \\ 0 & e^{t\lambda_2} & \ddots & \vdots \\ & \ddots & \ddots & * \\ 0 & & 0 & e^{t\lambda_d} \end{pmatrix} P^{-1}.$$

We compute for an eigenspace  $\text{Ker}(A - \lambda I)$ , if  $B = \lambda I + N$  with  $N$  nilpotent (i.e.  $N^p = 0$  for some  $p \geq 1$ ),

$$e^{tB} = e^{\lambda t} e^{tN} = e^{\lambda t} \sum_{k=0}^{p-1} \frac{t^k}{k!} N^k.$$

The latter polynomial of degree  $p - 1$  is bounded only if  $p = 1$ .

As a consequence the equilibrium is stable only if, for all eigenvalues  $\lambda \in Sp(A)$ ,  $\text{Re}(\lambda) < 0$  or  $\text{Re}(\lambda) = 0$  and the corresponding eigenspace is diagonalizable.



## Stability

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

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

We deduce some stability results on the non-linear problem  $y' = f(y)$  from a stability analysis on the linear problem  $z' = Df(\bar{y})z$ .

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### Proposition

Let us consider the Cauchy problem  $(C_0)$ , let  $\bar{y}$  be an equilibrium ( $f(\bar{y}) = 0$ ). Denoting  $(\lambda_1, \dots, \lambda_k)$  ( $k \leq d$ ) the eigenvalues of  $Df(\bar{y})$ . Then the equilibrium is (linearly) **asymptotically stable** if  $\operatorname{Re}(\lambda) < 0$  for all eigenvalues  $\lambda \in \operatorname{Sp}(A)$ .

## Examples in one dimension

In one dimension, for the problem

$$y' = f(y), \quad y(0) = y_0.$$

- The equilibria are the roots of  $f : \bar{y} \in \mathbb{R}$  such that  $f(\bar{y}) = 0$ .
- The stability is given by the sign of the derivative :  
If  $f'(\bar{y}) < 0$ , then  $\bar{y}$  is linearly asymptotically stable ;  
If  $f'(\bar{y}) > 0$ , then  $\bar{y}$  is linearly unstable.

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  - If  $f'(\bar{y}) > 0$ , then  $\bar{y}$  is linearly unstable.

Let us come back to the examples in the first course : Verhulst model

$$N'(t) = rN\left(1 - \frac{N}{K}\right),$$
$$N(0) = N_0.$$

The equilibria are 0 and  $K$ . We notice that  $f'(0) > 0$  and  $f'(K) < 0$ . Then 0 is linearly unstable and  $K$  is linearly asymptotically stable.

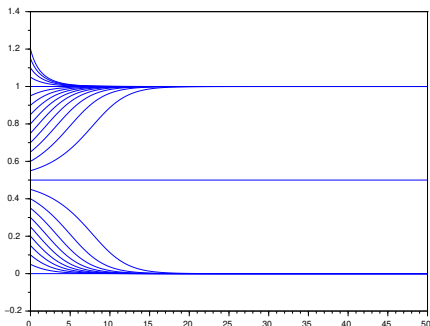
## Examples : Allee effect

For the model with Allee effect

$$N'(t) = N(1 - N)(N - \theta), \quad 0 < \theta < 1,$$

$$N(0) = N_0.$$

The equilibria are 0,  $\theta$  and 1. We notice that  $f'(0) < 0$ ,  $f'(\theta) > 0$  and  $f'(K) < 0$ . Then  $\theta$  is linearly unstable and 0 and  $K$  are linearly asymptotically stable.



## Examples : Spruce budworm model

Spruce budworm is a serious pest for conifers and is responsible for important damage in forests in North America. The following model has been proposed to model the dynamics of this insect



Let  $N(t)$  denote the density of this insect at time  $t > 0$ ,  $r_B$  reproduction rate,  $K_B$  environmental capacity,  $p$  predation function by birds.

$$\frac{d}{dt}N = r_B N \left(1 - \frac{N}{K_B}\right) - p(N).$$

To describe the predation function, we make the following assumptions : predation is weak when  $N$  is small (birds goes in another place), predation is saturated for large  $N$  (birds cannot eat too much). For example we take the function

$$p(N) = \frac{BN^2}{A^2 + N^2}.$$

## Examples : Spruce budworm model

$$\frac{d}{dt}N = r_B N \left(1 - \frac{N}{K_B}\right) - \frac{BN^2}{A^2 + N^2}.$$

We adimensionnalize the system by setting  $u = \frac{N}{A}$ ,  $r = \frac{Ar_B}{B}$ ,  $q = \frac{K_B}{A}$ ,  $\tau = \frac{Bt}{A}$ .  
Then the equation reads

$$\begin{aligned} \frac{du}{d\tau} &= \frac{1}{A} \frac{dN}{dt} \frac{dt}{d\tau} = \frac{1}{B} \frac{dN}{dt} = \frac{1}{B} \left( r_B A u \left(1 - \frac{Au}{K_B}\right) - \frac{Bu^2}{1 + u^2} \right) \\ &= ru \left(1 - \frac{u}{q}\right) - \frac{u^2}{1 + u^2}. \end{aligned}$$

This change of variable allows us to pass from 4 parameters ( $r_B, K_B, B, A$ ) to 2 parameters ( $r, q$ ).

## Examples : Spruce budworm model

The final model reads

$$\frac{du}{d\tau} = ru\left(1 - \frac{u}{q}\right) - \frac{u^2}{1 + u^2}, \quad u(0) = u_0.$$

- **Existence.** By Cauchy-Lipschitz theorem, there exists a maximal solution. Moreover, if  $u(t) > q$ , we have  $u' < 0$  thus  $u$  is decreasing. By uniqueness, since  $u = 0$  is a solution, we deduce that if  $u_0 > 0$ , then for any  $t > 0$ ,  $u(t) > 0$ . We conclude that  $0 < u \leq \max(q, u_0)$ . Thus, we have existence of a *global solution* (the solution can not blow up).
- **Equilibria.** We have to solve the equation

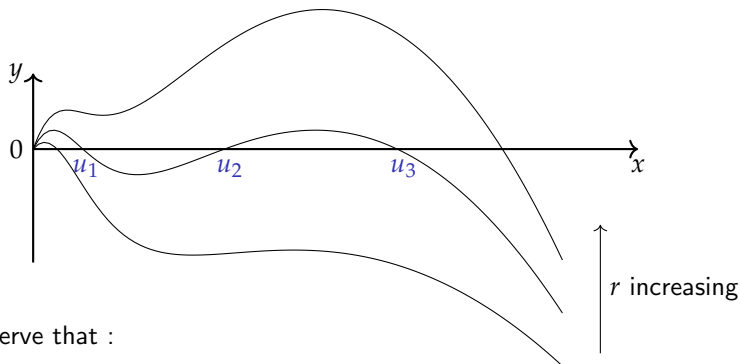
$$ru\left(1 - \frac{u}{q}\right) = \frac{u^2}{1 + u^2}$$

Thus  $u = 0$  or  $r\left(1 - \frac{u}{q}\right) = \frac{u}{1 + u^2}$  for which there are 1, 2 or 3 solutions depending on  $r$  and  $q$ .



## Examples : Spruce budworm model

For  $q$  fixed, by increasing or decreasing  $r$  there may be 2, 3, or 4 steady states.



We observe that :

- 0 and  $u_2$  are always unstable ;
- $u_1$  and  $u_3$  are always stable.

When decreasing  $r$  enough, there is only one stable steady state  $u_1$ , waiting long enough, the total population stabilizes at the density  $u_1$ .

Moreover, we can notice an hysteresis phenomenon.

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  - Lotka-Volterra system
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  - Reaction-diffusion systems in population dynamics
  - Reaction kinetics
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  - SIR model
  - Basic reproduction number  $R_0$
  - Examples of compartmental models

## Some historical facts

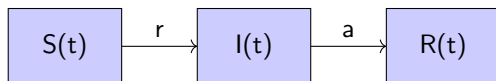
- In the 18th century, London was strongly affected by an epidemic of smallpox. A controversial solution is *variolation*, which involves contacting individuals with a pustule removed from a patient. This kills the individual or gives him immunity for life. [Daniel Bernoulli](#) (Swiss mathematician, 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.

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## SIR model

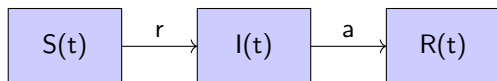
In 1920, W.O. Kermack & A. G. McKendrick introduce the so-called **compartmental models** : population is divided into **susceptible** individuals (**S**), **infected** individuals (**I**), and **removed/recovered** individuals (**R**).



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

## SIR model

In 1920, 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.

The SIR system reads

$$\left\{ \begin{array}{l} S' = -rSI \\ I' = rSI - aI \\ R' = aI \end{array} \right.$$

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

$$\begin{cases} 0 & = & -r\bar{S}\bar{I} \\ 0 & = & r\bar{S}\bar{I} - a\bar{I} \\ 0 & = & a\bar{I} \end{cases}$$

Looking to the last equation, it gives  $\bar{I} = 0$ , 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

$$\begin{cases} S' &= -rSI \\ I' &= rSI - aI \\ R' &= aI \end{cases}$$

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



## SIR model

$$\begin{cases} S' &= -rSI \\ I' &= rSI - aI \\ R' &= aI \end{cases}$$

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

We have  $I'(0) = I_0(rS_0 - a)$ .

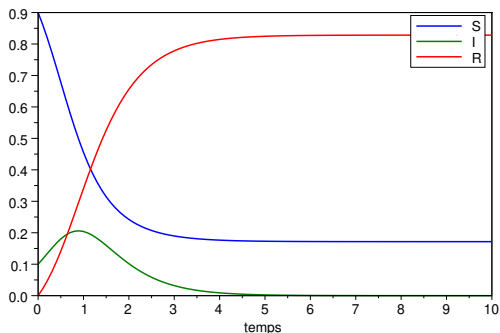
- If  $rS_0 < a$ , then  $I'(0) < 0$  and since  $S' \leq 0$ , we always have  $I'(t) < 0$ . Thus, the number of infected  $I$  will diminish until extinction.
- If  $rS_0 > a$ , then  $I'(0) > 0$ . The number of infected individuals will start to increase.

We recover the threshold phenomenon, first noticed by Sir Ronald Ross. We denote  $R_0 = \frac{rS_0}{a}$ , 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  $R_0 = 1.8$

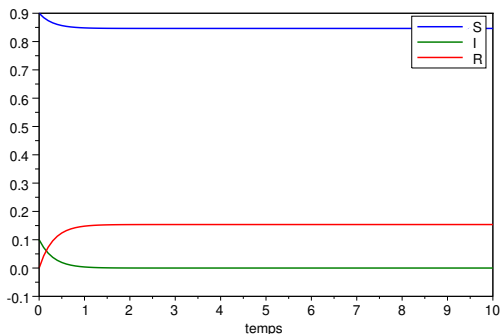


There is a peak of epidemic. At the final time, more than 80% of the population has been infected.

## 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.

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## 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
SARS <sup>1</sup>	2-5	H1N1 (Grippe A) <sup>2</sup>	2-4
Influenza <sup>3</sup>	2-3	Ebola <sup>4</sup>	1.5-2.5

1. (outbreak in China 2003)
2. (outbreak 2009)
3. (grippe espagnole 1918)
4. (West Africa 2014)

## 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

$$S' = -rSI, \quad I' = rSI - aI, \quad R' = aI.$$

The equilibrium without infection is given by  $(S, I, R) = (S_0, 0, 0)$  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

$$s' = -rS_0i, \quad i' = rS_0i - ai, \quad r' = ai.$$

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

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

The steady state without infection is linearly stable provided  $rS_0 - a \leq 0$ , 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  $ij$ th 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  $G$

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

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]<sup>5</sup>. 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  $\Sigma$  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,  $\Sigma$  is nonnegative outside the diagonal with  $\sup\{\operatorname{Re}(\lambda), \lambda \in \operatorname{Sp}(\Sigma)\} < 0$ .

Then, the equilibrium without infection is linearly stable iff  $R_0 \leq 1$ .

5. O. Diekmann, J.A. Heesterbeek, J.A.J. Metz, J. Mathematical Biol. 1990

## Basic reproduction number $R_0$

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

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

Then, to diminish  $R_0$ , one may :

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- **increase  $a$**  : improve treatments ;

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

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

Then, to diminish  $R_0$ , one may :

- **diminish  $r$**  : quarantine, improve hygiene conditions to avoid contact with germs, ... ;
- **increase  $a$**  : improve treatments ;
- **diminish  $S_0$**  : vaccination campaign. We consider that to stop an outbreak, one needs to vaccinate a proportion  $\left(1 - \frac{1}{R_0}\right)$  of the population.

*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 $R_0$

Determine  $R_0$  is essential to launch a prevention policy, or a vaccination campaign.



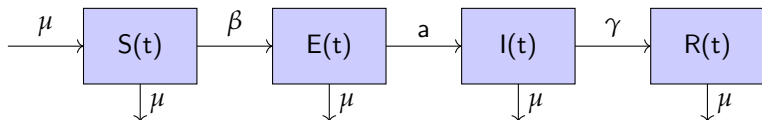
**FIGURE** – Extracted picture from the movie *Contagion* (by S. Soderbergh in 2011) in which a scientist, interpreted by Kate Winslet explain the spread of an outbreak thanks to  $R_0$ .

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## SEIR model

We add a compartment to take into account an incubation period during which individuals are infected but not infectious. The new compartment is denoted  $E$  (exposed).



The parameters are :

- $\mu$  death rate which is assumed to be equal to the birth rate (such that the total population is constant);
- $\beta$  rate of infection ;
- $a$  transition rate from exposed to infected ;
- $\gamma$  recovery rate.



## SEIR model

The corresponding system of ODE reads

$$\begin{cases} S' &= \mu N - \mu S - \beta \frac{I}{N} S \\ E' &= \beta \frac{I}{N} S - (\mu + a) E \\ I' &= a E - (\mu + \gamma) I \\ R' &= \gamma I - \mu R, \end{cases}$$

where  $N = S + E + I + R$  is the total number of individuals, which is constant. We follow the strategy enumerate above

- 1 There are two infected states :  $E, I$ , two non infected states :  $S, R$ .
- 2 Equilibrium without infection is  $S = N, E = I = R = 0$ . Linearized system around the equilibrium reads for infected states

$$E'(t) = \beta I - (\mu + a) E, \quad I'(t) = a E - (\mu + \gamma) I.$$

- 3 Transmission and transition matrices

$$T = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix}, \quad \Sigma = \begin{pmatrix} -(a + \mu) & 0 \\ a & -(\mu + \gamma) \end{pmatrix}.$$

## SEIR model

Finally the basic reproduction number for the SEIR model is given by

$$R_0 = \rho(-T\Sigma^{-1}) = \frac{a\beta}{(\gamma + \mu)(a + \mu)}.$$

Indeed,

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

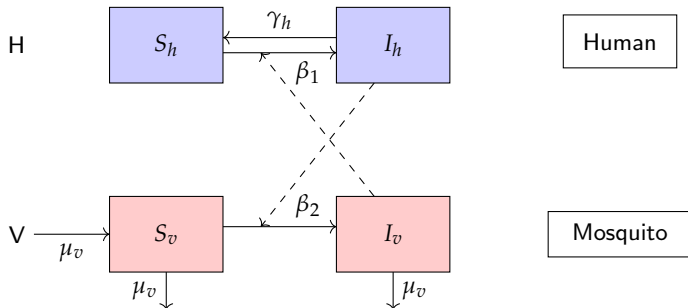
Then, we can compute

$$-T\Sigma^{-1} = \begin{pmatrix} \frac{a\beta}{(a+\mu)(\gamma+\mu)} & \frac{\beta}{\mu+\gamma} \\ 0 & 0 \end{pmatrix}.$$

It is a triangular matrix. Hence its eigenvalues are given in the diagonal.

## 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 :**
  - $\beta_1, \beta_2$  proportions of bites giving rise to an infection to human, respectively, mosquitoes ;
  - $\gamma$  recovery rate for human ;
  - $\mu_m$  death and birth rate for mosquitoes (assumed to be the same).

## Ross-Macdonald model

The corresponding system of ODE reads

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

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

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

- 3 Transmission and transition matrices

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

- 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  $R_0 = \sqrt{\frac{\beta_1 \beta_2 V}{\gamma \mu H}}$ .