Dynamical modeling in epidemiology

1. Problematic
2. Writing the equations
3. Analyzing the model

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The challenge of infectious diseases

- **Infectious diseases (ID): still a major cause of death**
  - Humans (tens of millions of deaths per year)
  - Animals (livestock, wild)

- **Since 80s: ID are coming back!**
  - Emergence of new diseases (Avian influenza, Chikungunya…)
  - Re-emergence of old ones (Tuberculosis…)

↳ **ID are a part of life ⇒ New interest for ID**

The goals of epidemiology

- **Understanding:**
  - How ID appear
  - Pathogen strategies
  - Dynamic of host pathogen systems

- **In order to:**
  - Anticipate the impact of ID
  - Evaluate the efficiency of health policies (vaccination…)

↳ **ID cannot be directly observed ⇒ Mathematical models**

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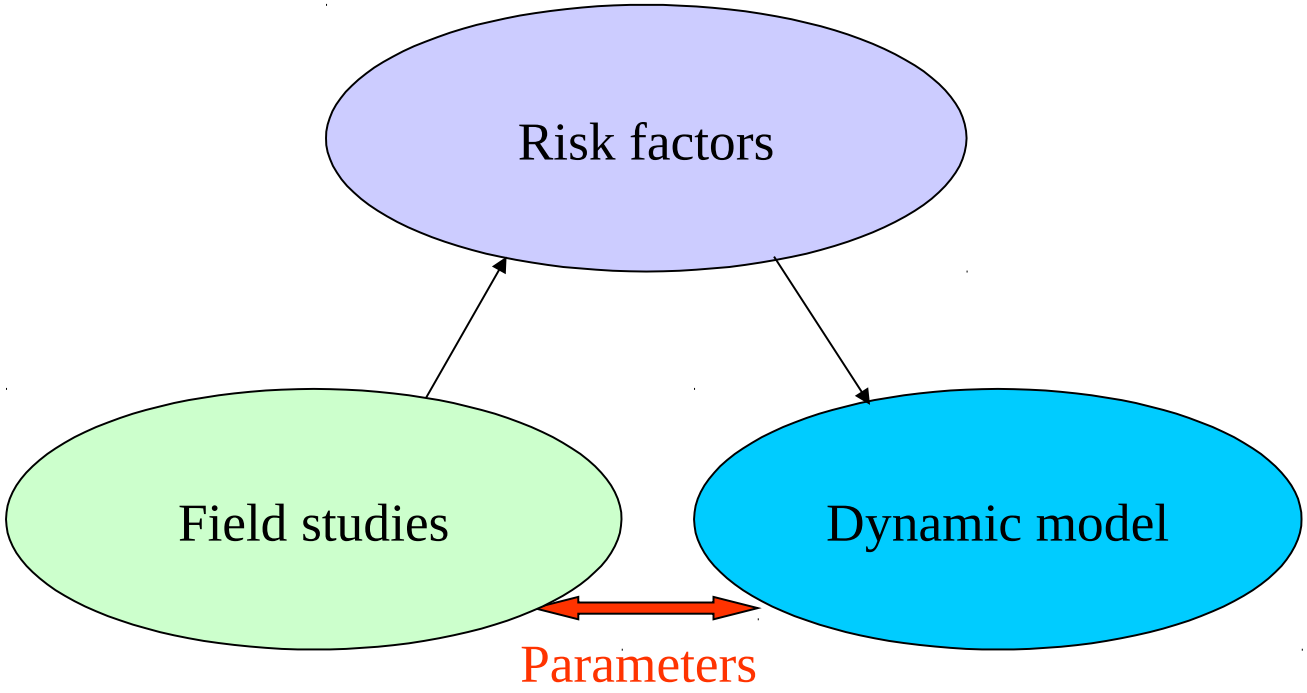
Modeling hypothesizes and parameters



Pictures of (sero)prevalence at different times t

Understanding mechanisms of ID spread

Specificity of host-parasite systems

- **Needed to build a model with:**
  - A host demography model
  - Including the dynamic of pathogen
- **We thus have to model:**
  - Entries and leavings of host individuals in time
  - The transmission of the parasite between infected and susceptible hosts in time
  - If relevant: recovery of infected hosts, loss of immune memory,...

Building a model

- Identifying the biological question
  impact of the disease, efficiency of a vaccination program...
- Formalizing hypothesizes and building the model
  Type of model? Which compartments? Model used for demography and transmission?... Eventually: equations
- Analysis of the model
  Formula for R_0, equilibrium states, stability of the equilibria
  Estimation of model parameters...
- Discussion of the results
  Consistency with observations/known tendencies; criticism/way to improve the model, new biological questions...

Ideally, a model should be simple, general and realistic ⇒ **compromise**

Different classes of mathematical models

- **Can be:**
  - **Discrete** or **continuous** time
  - **Deterministic** (no random fluctuations of parameters and variables) or **stochastic** (with random fluctuations)
- **Here, model in continuous time and deterministic because:**
  - Events having a short time scale (transmission…)
  - First approach: mean behavior of the system

↳ **Compartmental models: majority of dynamical models in epidemiology**

⇒ Compartments chosen in agreement with biological assumptions

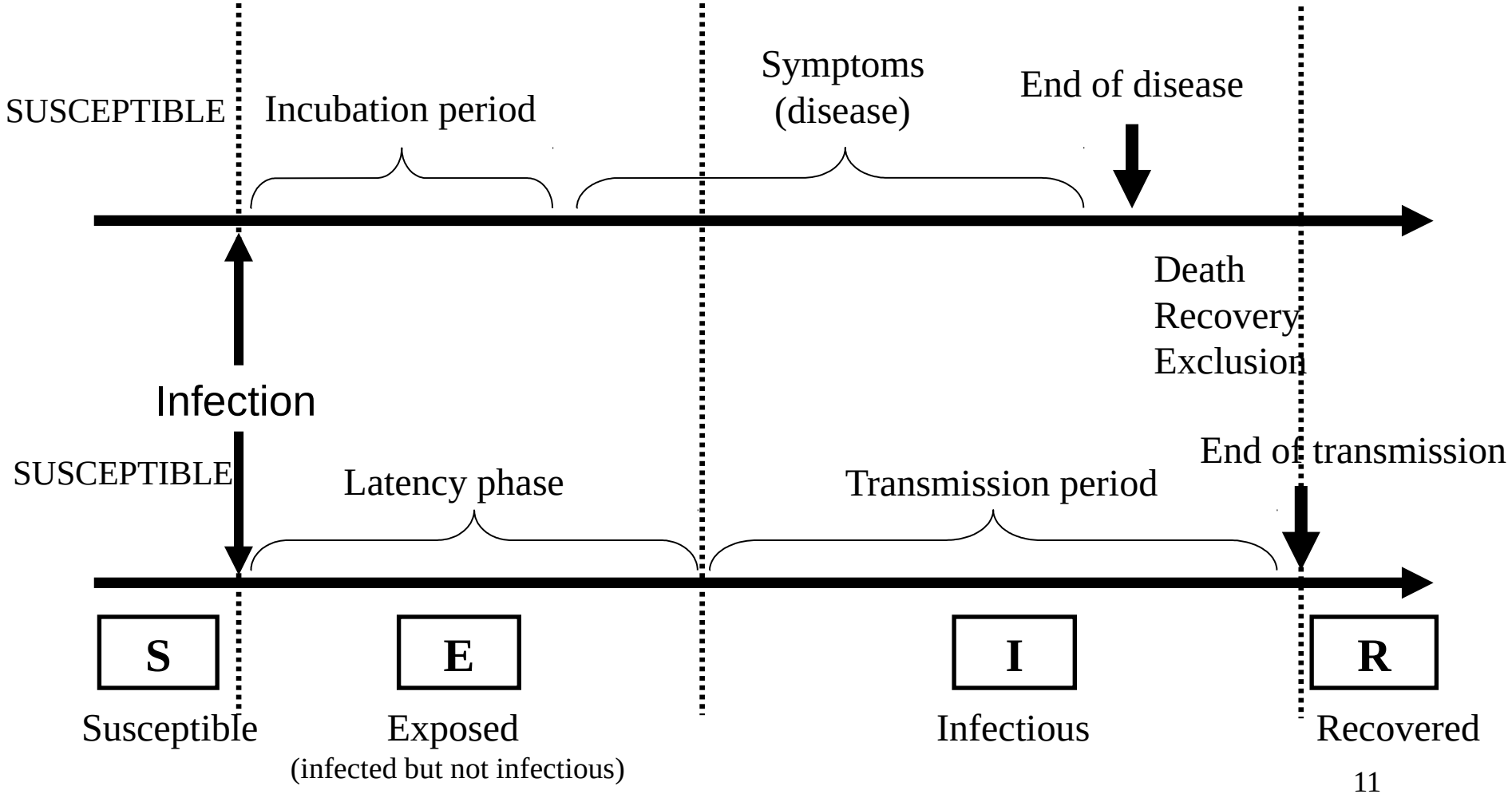
Compartmental models and differential equations (1/2)

- **<u>Characteristics</u>:**
  - Population split into ≠ classes (compartments)
  - Within a compartment, all individuals are assumed equivalent

- **<u>Case of a deterministic model</u>:**
  - Entries and leavings are flows of individuals
  - The evolution of the system in time is entirely determined by initial conditions
    ⇒ No random fluctuations in events' occurrence
  - Useful for studying the mean behavior of the systems

Dynamic of the infection and choice of the compartments

Always take the point of view of the parasite!



Characteristics of host-parasite interactions

- **Virulence**
  - Ability of the parasite to induce troubles in the host :
    - Induced additional mortality
    - pathology
    - Fertility loss
    - …
  - Property of the host-parasite interaction

    (« product » of the exploitation of the host by the parasite)

- **Transmission mode of the parasite**
  - **direct transmission**: horizontal *vs* vertical (from mother to child)
  - **indirect transmission**: water, ground, non hematophage arthropod
  - through **vectors**: arthropod

Compartmental models and differential equations (2/2)

- **<u>Vocabulary</u>:**

  - **flow** : quantity of individuals going from one compartment to another per unit of time (arrows on the flow diagram)

    Unit = individuals/unit of time

  - **rate** : flow divided by the number of individuals in the departure compartment (unit = 1/unit of time)

    ex: a mortality rate *m* in a population of size *N* means that the flow of individuals dying is *m.N*

  - **Mean time spent in a compartment**:

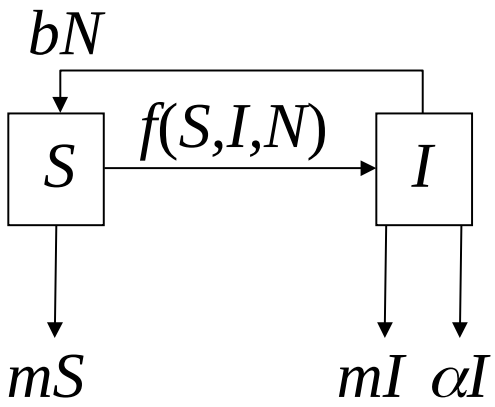
    inverse of the rate of departure from the compartment

    ex: if *m* is the mortality rate, then the mean time spent in the population is 1/*m*. Rem: here 1/*m* is hence the life expectancy!

Example of a chronic infectious disease

- **Hypothesizes**
  - Closed host population
  - Demographic parameters: natality *b*, mortality *m*
  - Direct transmission using the transmission function FT= *f*(*S*,*I*,*N*)
  - No recovery, so no long-lasting immunity
  - Additional mortality for infected individuals: rate α
  - *Example of such a disease?*

- **Flow diagram of the model:**



Example of a chronic infectious disease

- **<u>Writing the ordinary differential equations (ode)</u>**
  - For each compartment X:

    dX/dt = sum of entering flows **<u>minus</u>** sum of leaving flows
  - Provides the evolution of the number of individuals in each compartment in time = the dynamic of the system in time

In our example:

$$\begin{cases} \dfrac{dS}{dt} = b \cdot (S + I) - m \cdot S - f(S,I,N) \\ \dfrac{dI}{dt} = f(S,I,N) - (m + \alpha) \cdot I \end{cases}$$

Incidence function (1/2)

- **Incidence :** number of new cases of infection (or diseases) during a unit of time

In the model : 

f(*S*,*I*,*N*)=incidence and *f* is called **the incidence function**.

- **Efficient individual contact rate λ:** $\lambda(N)=c(N).e_c.e_d$, with:
  - $c(N)$ = frequency of at risk contacts
  - e_c = proportion of at risk contacts with an *I* that leads to the contamination of the *S*
  - e_d = proportion of contaminations that lead to the spread of the parasite within its host (=infection)

$$f(S,I,N)=\lambda(N).\ I/N\ .\ S$$

Number of individuals suscpitble to acquire the infection

Efficient contact rate

Proportion of contacts with infectious individuals

Incidence function (2/2)

- **<u>Representation of the transmission of the infectious agent</u>:**

2 classical models types

Mass action: $\lambda(N) = \beta \cdot N$

Proportionate mixing: $\lambda(N) = \beta$

➢ Frequency of contacts proportional with the size or density of hosts $c(N)=c.N$

Frequency of contacts independent from the size or density of hosts: $c(N)=c$

$S \xrightarrow{f(S,I,N)} I$

$f(S,I,N)=\lambda(N).\ I/N\ .\ S$

f(S,I,N)=β.S.I

$$\begin{cases} \frac{dS}{dt} = -\beta \cdot S \cdot I \\ \frac{dI}{dt} = \beta \cdot S \cdot I \end{cases}$$

OR

f(S,I,N)=β.S.I/N

$$\begin{cases} \frac{dS}{dt} = -\frac{\beta \cdot S \cdot I}{S+I} \\ \frac{dI}{dt} = \frac{\beta \cdot S \cdot I}{S+I} \end{cases}$$

Choosing the model for the incidence function

- **Proportionate mixing**
  - MST
- **Mass action**
  - Aerosol transmission
  - Vector transmission
- **A bit of both**
  - Transmission through aggressive contacts

No strict rule, to be discussed with biologists

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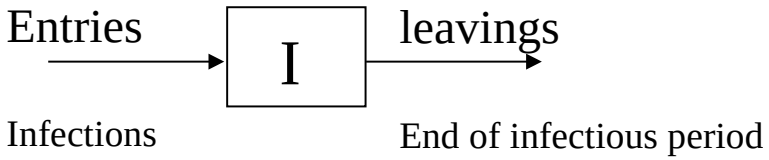
The basic reproduction number $\mathbf{R_0}$ (1/2)

- **Definition**

  R_0 = number of newly infected individuals generated by **1 infected individual** over its infectious period, when he is released into **a fully susceptible population**.



Mathematically,

R_0= (nb of infections per time unit) x (mean duration of the infection)

= (flow entering in I) / (flow leaving I) , for ***I*=1** and ***S*=N**

R_0 is called the **basic reproduction number**

The basic reproduction number $\mathbf{R_0}$ (2/2)

- **If R_0>1**

  One infected individual will cause several new cases before the end of its infectious period: the parasite can spread, ie cause an epidemic. Else if R_0<1, the disease will rapidly go extinct.

Mathematically, R_0>1 means:

(flow entering in I) / (flow leaving I)>1 for ***I*=1** and ***S*=N**

(flow entering in I) - (flow leaving I)>0 for ***I*=1** and ***S*=N**

since $\left.\frac{dI}{dt}\right|_{\substack{I=1\\S\approx N}}$ = (flow entering in I) - (flow leaving I) then $\left.\frac{dI}{dt}\right|_{\substack{I=1\\S\approx N}} > 0$

Which means that I increases. If, on the contrary, R_0<1, then $\left.\frac{dI}{dt}\right|_{\substack{I=1\\S\approx N}} < 0$ and I decreases.

R_0>1 is hence **an epidemic condition**.

Model equilibria: is endemy a possible outcome?

- The state of the system at time *t* is characterized by the number of individuals in **each** compartment.

  Ex: For an SIR model, the state at *t* is given by the **triplet** $(S(t),I(t),R(t))$

- At the equilibrium, the system does not evolve anymore, so all derivative are equal to 0
- (S*,I*,R*) is hence an equilibrium if and only if

$$\begin{cases} \frac{dS}{dt}(S^*,I^*,R^*) = 0 \\ \frac{dI}{dt}(S^*,I^*,R^*) = 0 \\ \frac{dR}{dt}(S^*,I^*,R^*) = 0 \end{cases}$$

- The long term persistence of the parasite is possible if there is an endemic state, ie an equilibrium for which $I^* \neq 0$.

Back to the chronic infectious disease example

- **Expression of the R_0**

  For $I=1$ and $S \approx N$:

$$\begin{cases} \frac{dS}{dt} = b \cdot (S+I) - m \cdot S - \beta SI \\ \frac{dI}{dt} = \beta SI - (m+\alpha) \cdot I \end{cases}$$

$$R_0 = \frac{\beta \cdot S \cdot I}{(m+\alpha) \cdot I} \approx \frac{\beta \cdot N \cdot 1}{(m+\alpha) \cdot 1} = \frac{\beta \cdot N}{m+\alpha}$$

- **Equilibria**

  $dS/dt=dI/dt=0$

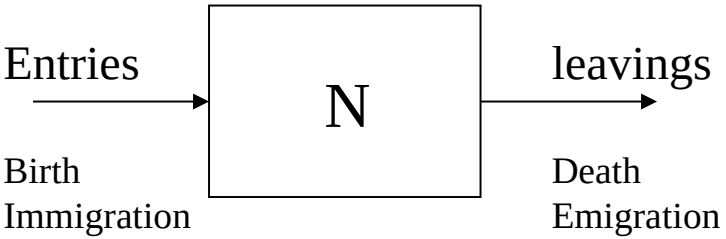
  ⇒ Two equilibrium points: ($S=0$, $I=0$) and

$$\left(S^* = \frac{m+\alpha}{\beta}, I^* = \frac{(b-m) \cdot (m+\alpha)}{\beta \cdot (m+\alpha-b)} \right)$$

  ⇒ Poorly realistic demographic model…: keep a critical attitude!

Modeling host demography (1/3)

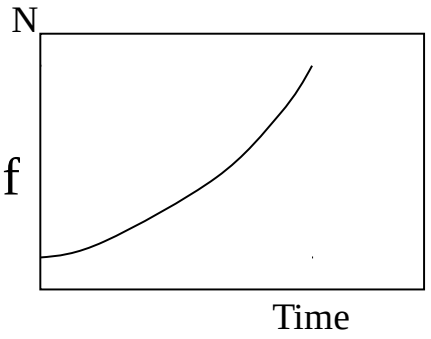
- **Flow diagram:**



- **Continuous time ⇒ differential equations:**
- **<u>Exponential growth</u>:**
  - Example of a closed population (without migrations)
  - Let b =natality rate and m = mortality rate:

$$\frac{dN}{dt} = bN - mN = (b - m)N = rN$$

  - Solving this ode, we find $N=N_0e^{rt}$: exponential growth of the population. r is called the growth rate

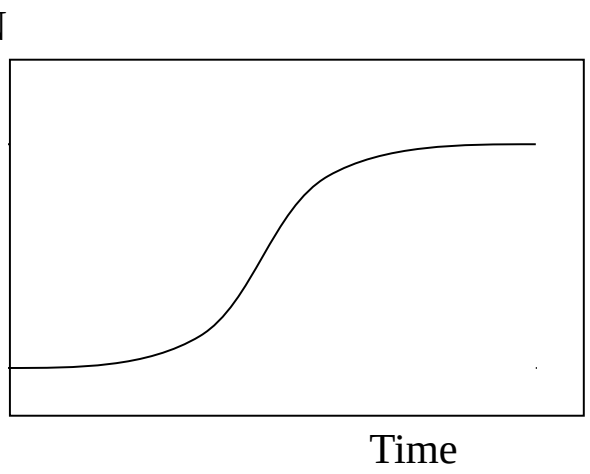


Modeling host demography (2/3)

- **<u>Logistic growth model</u>:**
  - In real life, the growth cannot be infinite
  - Slowed down at large densities (brake term)
  - Density dependent regulation
  - K = carrying capacity of the population (due to resources, shelter,..)
  - The equation becomes

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$

where $-rN/K$ is the brake term



Modeling host demography (3/3)

$$\begin{cases} \dfrac{dS}{dt} = b \cdot (S + I) - m \cdot S - \beta SI \\ \dfrac{dI}{dt} = \beta SI - (m + \alpha) \cdot I \end{cases}$$

Introduction of a density dependence term:
$m(N) = m_0 + aN$

$$\begin{cases} \dfrac{dS}{dt} = b \cdot (S + I) - (m_0 + a(S + I)) \cdot S - \beta SI \\ \dfrac{dI}{dt} = \beta SI - (m_0 + a(S + I) + \alpha) \cdot I \end{cases}$$

Stability of the equilibria

- That an equilibrium exists does not mean it will be reached.

  To be attainable, an equilibrium must be **stable**: if we stay close enough from the equilibrium then we are "attracted".

- To evaluate stability, we use the **Jacobian** matrix, which is the matrix of partial derivatives.

Ex: in the SIR model:

$$\begin{cases} \dfrac{dS}{dt} = f(S,I,R) \\ \dfrac{dI}{dt} = g(S,I,R) \\ \dfrac{dR}{dt} = h(S,I,R) \end{cases} \qquad J = \begin{pmatrix} \dfrac{\partial f}{\partial S} & \dfrac{\partial f}{\partial I} & \dfrac{\partial f}{\partial R} \\ \dfrac{\partial g}{\partial S} & \dfrac{\partial g}{\partial I} & \dfrac{\partial g}{\partial R} \\ \dfrac{\partial h}{\partial S} & \dfrac{\partial h}{\partial I} & \dfrac{\partial h}{\partial R} \end{pmatrix}$$

Then we look at the **sign of the eigenvalues of $J(S^*,I^*,R^*)$**, where (S^*,I^*,R^*) is the equilibrium we want to study :

- If all eigenvalues have a real part < 0 ⇨ STABLE
- If at least one eigenvalue has a real part > 0 ⇨ UNSTABLE