An introdution to the basic reproductive number in mathematical epidemiology

CIMPA SCHOOL 'Mathematical models in biology and medicine'
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Kermack-McKendrick SIR model

- 1905 : plague epidemic in Mumbai

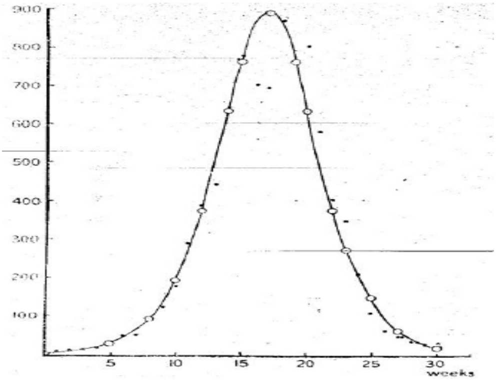


Figure: K.-McK. *Proc. R. Soc. Lond. A* **(115)**, 1927

<u>Question</u> : How can we prevent such an epidemic ?

Kermack-McKendrick SIR model

- 1927 : first model to understand epidemic process

$$\boxed{S} \xrightarrow{\beta I} \boxed{I} \xrightarrow{\gamma} \boxed{R}$$

SIR model

$$\begin{cases} \frac{dS(t)}{dt} = -\beta S(t)I(t) \\ \frac{dI(t)}{dt} = \beta S(t)I(t) - \gamma I(t) \\ \frac{dR(t)}{dt} = \gamma I(t) \end{cases}$$

Question : Can we extract a tool to measure the disease risk ?

From an heuristic definition of $\mathcal{R}_0$...

At the early begining...

1. A demographic concept [Böckh (1886) – Dublin & Lotka (1925)] :

$$\mathcal{R}_0 = \int_0^\infty \underbrace{\mathcal{P}(a)}_{\text{survival}} \underbrace{\beta(a)}_{\text{fertility}} \, da$$

2. Extension to epidemiology :
   - "Mosquitoe theorem" [Ross (1911)]
   - Pest epidemic in Mumbai [Kermack & McKendrick (1927)]
   - Link with demographic concept [MacDonald (1952)]

Epidemiological concept

$\mathcal{R}_0$: number of secondary infections resulting from a single primary infection into an otherwise susceptible population.

Why is $\mathcal{R}_0$ a threshold marker of epidemic ? $\rightarrow$ introduction of p infected individuals $\Rightarrow (\mathcal{R}_0)^k p$ infected individuals after step k.

… to a mathematical definition of $\mathcal{R}_0$

Mathematical translation through dynamical systems
[Diekmann & Heersterbeck (1990)]

Mathematical translation

$\mathcal{R}_0$: bifurcation threshold that ensures ($\mathcal{R}_0 < 1$) or not ($\mathcal{R}_0 > 1$) the stability of a specific equilibrium point, the disease-free equilibrium (DFE)

- Finite and infinite dimensional systems ;
- Determine the DFE ;
- Linked to spectral properties of the linearized problem about the DFE

Question : How can we calculate a $\mathcal{R}_0$?

Contents

The next generation matrix

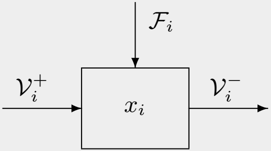
An efficient method for $\mathcal{R}_0$ calculation in ODE epidemic models
[Van Den Driessche & Watmough (2002)]

$$\dot{x}(t) = f(x(t)), \qquad x = (x_1 \ldots, x_p, \underbrace{x_{p+1}, \ldots, x_n}_{\text{infected}})^T$$

$$f(x) = \mathcal{F}(x) + \underbrace{\mathcal{V}(x)}_{=(\mathcal{V}^+ - \mathcal{V}^-)(x)}$$

with

- $\mathcal{F}_i$ flux of newly infected
- $\mathcal{V}_i^+$ (resp. $\mathcal{V}_i^-$) other entering fluxes (resp. leaving fluxes)



The next generation matrix

With DFE $x^* = (x_1^*, \ldots, x_p^*, 0, \ldots, 0)$,

$$D_{x^*}\mathcal{F} = \begin{pmatrix} 0 & 0 \\ 0 & F \end{pmatrix}, \qquad D_{x^*}\mathcal{V} = \begin{pmatrix} \square & \square \\ 0 & V \end{pmatrix}$$

Theorem [Van Den Driessche & Watmough, Math. Biosci., 180 (2002)]

The $\mathcal{R}_0$ value related to the epidemic system $\dot{x}(t) = f(x(t))$ is given by

$$\mathcal{R}_0 = \rho(-FV^{-1})$$

Sketch of proof :

- $-FV^{-1} \geq 0$ (Metzler matrices theory)
- the spectral radius is an eigenvalue (Perron-Frobenius theorem)
- linearization + Varga theorem

$\square$

The next generation matrix

Some remarks :

- $-FV^{-1}$ is the "next generation matrix"
  $\rightarrow$ interpretation
- requires to determine the DFE x^*
- x^* is locally asymptotically stable when $\mathcal{R}_0 < 1$
- efficiency : reduction method !

Contents

What to do with a $\mathcal{R}_0$?

$\mathcal{R}_0$ utility through 4 examples :

1. Measure of epidemic risk & prediction
2. Control strategy ("herd immunity")
3. Impact of biodiversity on the disease dynamics
4. Extinction VS. persistence

Example 1 : Measure of epidemic risk & prediction

SIR model of Kermack-McKendrick :

$$\boxed{S} \xrightarrow{\beta I} \boxed{I} \xrightarrow{\gamma} \boxed{R}$$

SIR model

$$\begin{cases} \frac{dS(t)}{dt} = -\beta S(t) I(t) \\ \frac{dI(t)}{dt} = \beta S(t) I(t) - \gamma I(t) \\ \frac{dR(t)}{dt} = \gamma I(t) \end{cases}$$

DFE $x^* = (S^*, 0, 0)$, $F = \beta S^*$, $V = -\gamma$

$$\mathcal{R}_0 = \frac{\beta S^*}{\gamma}$$

Example 1 : Measure of epidemic risk & prediction

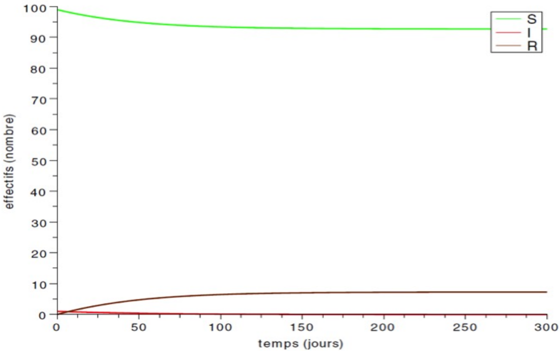


Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 0.7}$

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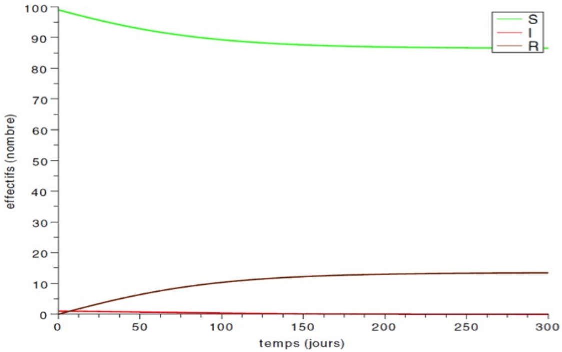

Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 0.9}$

Example 1 : Measure of epidemic risk & prediction

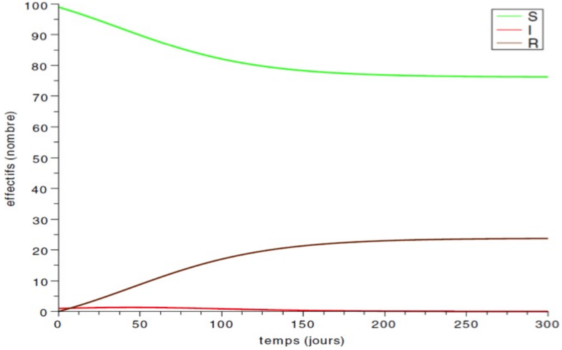

Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 1}$

Example 1 : Measure of epidemic risk & prediction

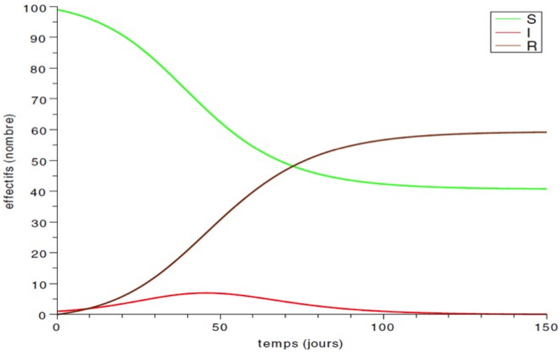

Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 1.5}$

Example 1 : Measure of epidemic risk & prediction

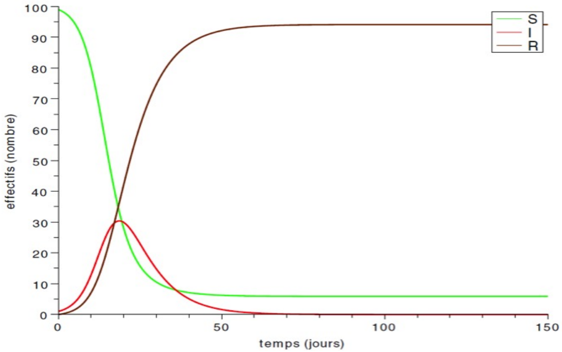

Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 3}$

Example 1 : Measure of epidemic risk & prediction

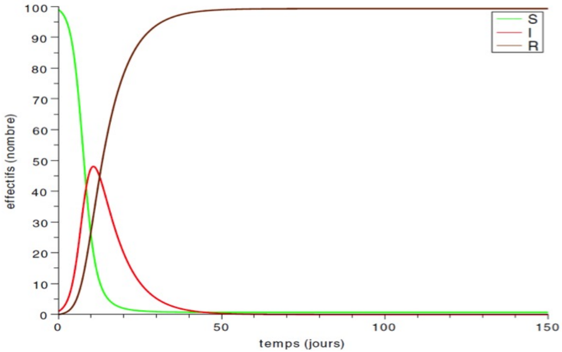

Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 5}$

Example 1 : Measure of epidemic risk & prediction

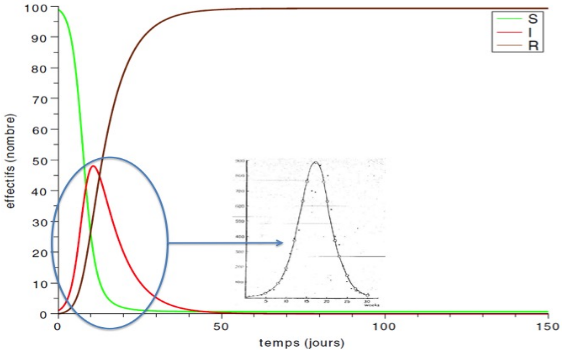

Figure: SIR model, simulation with $\boxed{\mathcal{R}_0 = 5}$

Example 2 : Control strategy

1- Malaria and Ross' "Mosquitoe theorem"

Ross model

$$\begin{cases} \frac{dI_H(t)}{dt} = ab_1 I_M \frac{H-I_H}{H} - \gamma I_H \\ \frac{dI_M(t)}{dt} = ab_2(M-I_M)\frac{I_M}{M} - \mu I_M \end{cases}$$

with

- H (resp. M) constant population of humans (resp. mosquitoes)
- I_H (resp I_M) number of infected humans (resp. mosquitoes)
- a number of bites / mosquitoe and time unit
- b_1 proba that a bite generates a human infection
- b_2 proba that a mosquitoe becomes infected
- $1/\gamma$ infection period for human
- $1/\mu$ mosquitoe lifespan

Example 2 : Control strategy

DFE $(0,0)$

$$F = \begin{pmatrix} 0 & ab_1 \\ \frac{ab_2M}{H} & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} -\gamma & 0 \\ 0 & -\mu \end{pmatrix}$$

$$\mathcal{R}_0 = \rho(-FV^{-1}) = \sqrt{\frac{a^2b_1b_2M}{\gamma\mu H}}$$

$\longrightarrow$ Emphasizes the Ross' "Mosquitoe theorem" !

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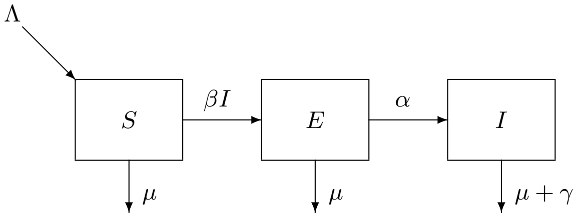
Example 2 : Control strategy

2- "Herd immunity" in disease vaccination

SEIS model - Assumptions :

- no vertical transmission
- exposure period
- no natural immunity
- healed become susceptible



Example 2 : Control strategy

SEIS model

$$\begin{cases} \frac{dS(t)}{dt} = \Lambda - \beta S(t)I(t) - \mu S(t) \\ \frac{dE(t)}{dt} = \beta S(t)I(t) - (\alpha+\mu)E(t) \\ \frac{dI(t)}{dt} = \alpha E - (\gamma+\mu)I(t) \end{cases}$$

$x^* = \left(\frac{\Lambda}{\mu}, 0, 0\right)$ DFE

$$F = \begin{pmatrix} 0 & 0 \\ 0 & \frac{\beta\Lambda}{\mu} \end{pmatrix}$$

$$V = \begin{pmatrix} 0 & -(\alpha+\mu) \\ -(\gamma+\mu) & \alpha \end{pmatrix}$$

$$\mathcal{R}_0 = \rho(-FV^{-1}) = \frac{\alpha\beta\Lambda}{\mu(\mu+\alpha)(\mu+\gamma)}$$

Example 2 : Control strategy

SEIS model

$$\begin{cases} \frac{dS(t)}{dt} = (1-\epsilon)\Lambda - \beta S(t)I(t) - \mu S(t) \\ \frac{dE(t)}{dt} = \beta S(t)I(t) - (\alpha+\mu)E(t) \\ \frac{dI(t)}{dt} = \alpha E - (\gamma+\mu)I(t) \end{cases}$$

$x^* = \left(\frac{(1-\epsilon)\Lambda}{\mu}, 0, 0\right)$ DFE

$F = \begin{pmatrix} 0 & 0 \\ 0 & \frac{\beta(1-\epsilon)\Lambda}{\mu} \end{pmatrix}$

$V = \begin{pmatrix} 0 & -(\alpha+\mu) \\ -(\gamma+\mu) & \alpha \end{pmatrix}$

$$\tilde{\mathcal{R}_0} = (1-\epsilon)\mathcal{R}_0$$

Vaccination of a proportion ϵ of new borns : $\epsilon > 1 - \frac{1}{\mathcal{R}_0} \Rightarrow \tilde{\mathcal{R}_0} < 1$!

Disease	$\mathcal{R}_0$	Herd immunity
Mumps	4-7	75-86 %
Polio	5-7	80-86 %
Small pops	5-7	80-85 %
Diphteria	6-7	85 %
Rubella	6-7	83-85 %
Measles	12-18	83-94 %

Table: $\mathcal{R}_0$ and herd immunity thresholds for vaccine-preventable diseases [**Am. J. Prev. Med.**, 20 (2001)]

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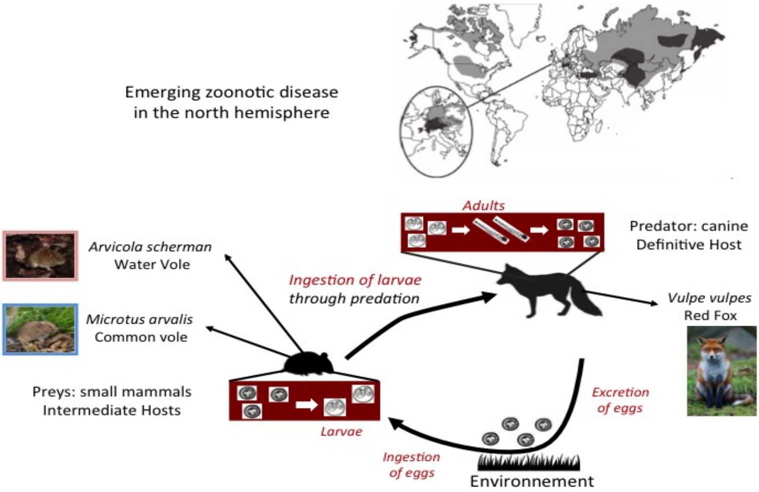
$\longrightarrow$ Eradication in 1977 !

Example 3 : Impact of biodiversity on the disease dynamics

Trophically transmitted parasite : *Echinococcus multilocularis*



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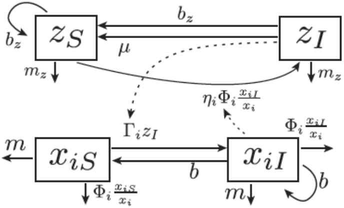

Echinococcus transmission model [Baudrot, Perasso, Fritsch & Raoul (2016)]

growth **predation** **epidemic**

$$\frac{dz_S}{dt} = b_z z - \left(m_z + (b_z - m_z)\frac{z_S + z_I}{k_z}\right) z_S - z_S \sum_i \eta_i \Phi_i(x_1, x_2)\frac{x_{iI}}{x_i} + \mu z_I$$

$$\frac{dx_{iS}}{dt} = b x_i - \left(m + (b - m)\frac{\sum_j x_{jS} + x_{jI}}{k}\right) x_{iS} - \Phi_i(x_1, x_2)\frac{x_{iS}}{x_i} z - z_I \Gamma_i x_{iS}$$

$$\frac{dz_I}{dt} = - \left(m_z + (b_z - m_z)\frac{z_S + z_I}{k_z}\right) z_I + z_S \sum_i \eta_i \Phi_i(x_1, x_2)\frac{x_{iI}}{x_i} - \mu z_I$$

$$\frac{dx_{iI}}{dt} = - \left(m + (b - m)\frac{\sum_j x_{jS} + x_{jI}}{k}\right) x_{iI} - \Phi_i(x_1, x_2)\frac{x_{iI}}{x_i} z + z_I \Gamma_i x_{iS}$$

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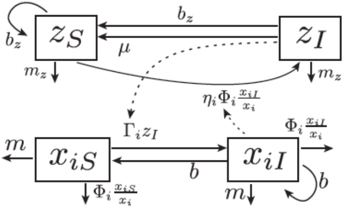

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$$\frac{dx_{iI}}{dt} = -\left(m + (b - m)\frac{\sum_j x_{jS} + x_{jI}}{k}\right) x_{iI} \quad - \Phi_i(x_1, x_2)\frac{x_{iI}}{x_i} z + \quad z_I \Gamma_i x_{iS}$$

Example 3 : Impact of biodiversity on the disease dynamics

Theorem [Baudrot et al., JTB, 397 (2016)]

1. existence of DFE $(z^*, x_1^*, x_2^*, 0, 0, 0)$
2. Next generation matrix :

$$-FV^{-1} = \begin{pmatrix} 0 & \dfrac{\eta_1 z^* \Phi_1(x_1^*, x_2^*)}{x_1^* b} & \dfrac{\eta_2 z^* \Phi_2(x_1^*, x_2^*)}{x_2^* b} \\ \dfrac{\Gamma_1 x_1^*}{b_z + \mu} & 0 & 0 \\ \dfrac{\Gamma_2 x_2^*}{b_z + \mu} & 0 & 0 \end{pmatrix}$$

3. Basic reproductive number :

$$\mathcal{R}_0 = \sqrt{\frac{z^*}{b(b_z + \mu)} \times (\eta_2 \Gamma_2 \Phi_2(x_1^*, x_2^*) + \eta_1 \Gamma_1 \Phi_1(x_1^*, x_2^*))}$$

Sketch of proof :

- Model reduction with different time scales (parasite cycle VS. host dynamics)
- change of variables $(x_1, x_2) \mapsto \left(x_1 + x_2, \frac{x_1}{x_1 + x_2}\right)$ to get the DFE $\square$

Example 3 : Impact of biodiversity on the disease dynamics

Eco-epidemiological question : How variability in host competence impacts the parasite dynamics ?

→ Density-dependant dilution of the parasite !

$$\mathcal{R}_0 = \sqrt{\frac{z^*}{b(b_z+\mu)} \times \left(\eta_2 \Gamma_2 \Phi_2(x_1^*, x_2^*) + \eta_1 \Gamma_1 \Phi_1(x_1^*, x_2^*)\right)}$$

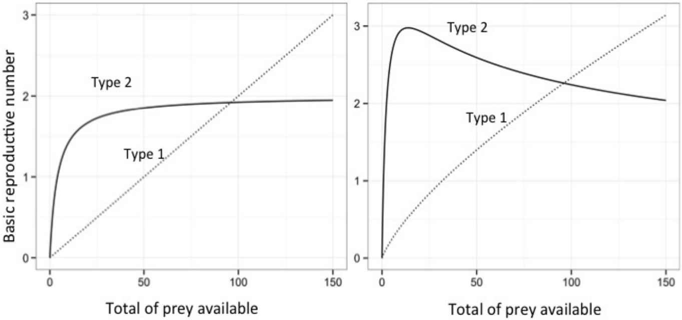

Figure: Impact of prey availability on $\mathcal{R}_0$, with $\Gamma_1 = \Gamma_2$ (left) and $\Gamma_1 < \Gamma_2$ (right)

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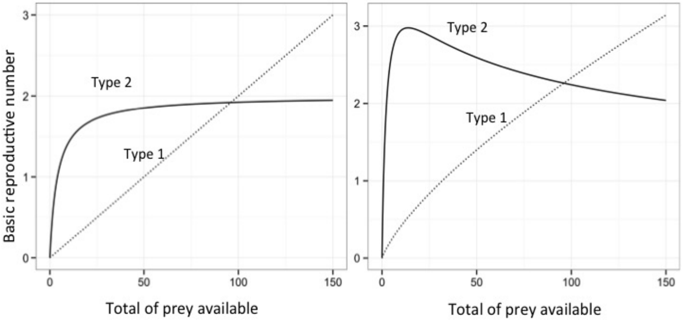

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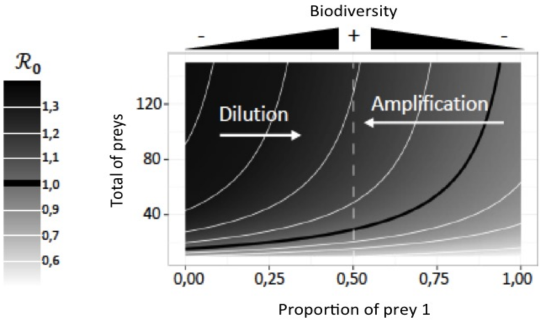
→ The total of prey impacts the effect of biodiversity on the epidemic risk (dilution/amplification)



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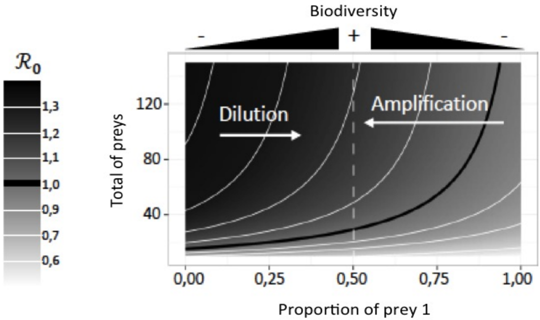

Example 4 : Extinction VS. persistence

The DFE is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

- Can we say more than "locally" when $\mathcal{R}_0 < 1$?
- Persistence of the disease when $\mathcal{R}_0 > 1$? $\rightarrow$ the instability of DFE is not enough !
- And what about $\mathcal{R}_0 = 1$?

Definition (uniform persistence)

The disease is uniformly persistent if

$$\exists \varepsilon > 0, \forall I_0 > 0 \Rightarrow \liminf_{t \to +\infty} I(t) \geq \varepsilon.$$

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Global stability properties [Korobeinikov & Wake, (2002)]

$$\begin{cases} \frac{dS(t)}{dt} = \Lambda - \beta S(t)I(t) - \mu_S S(t) \\ \frac{dI(t)}{dt} = \beta S(t)I(t) - \mu_I I(t) \end{cases}$$

$x^* = \left(\frac{\Lambda}{\mu_S}, 0\right)$ DFE

$\bar{x} = \left(\frac{1}{\mathcal{R}_0}, \frac{\mu_S}{\mu_I}(1 - \frac{1}{\mathcal{R}_0})\right)$ Endemic Equilibrium (EE) with

$$\mathcal{R}_0 = \frac{\beta\Lambda}{\mu_S\mu_I}$$

Theorem [Korobeinikov & Wake, Appl. Math. Lett., 15 (2002)]

- $\mathcal{R}_0 \leq 1 \Rightarrow$ DFE is globally stable ;
- $\mathcal{R}_0 > 1 \Rightarrow$ EE is globally stable

Remark : uniform persistence when $\mathcal{R}_0 > 1$!

Example 4 : Extinction VS. persistence

Idea of the proof : use of Lyapunov functions

$$L(S,I) = \bar{S} g\left(\frac{S}{\bar{S}}\right) + \bar{I} g\left(\frac{I}{\bar{I}}\right)$$

with the key function $g(z) = z - 1 - \ln(z)$ L satisfies

- L is definite positive
- $\|(S,I)\| \to \infty \Rightarrow L(S,I) \to \infty$
- $\frac{d[L(S(t),I(t)]}{dt} < 0$

Theorem of Lyapunov $\Rightarrow$ global stability

$\square$

Some extensions :

- SIR, SIRS and SIS [Korobeinikov & Wake]
- Multi-strains SIR, SIS models [Bichara, Iggidr & Sallet (2014)]

Contents

SI structured models in epidemiology

$\longrightarrow$ population structured according to variable of

- age of infection
- immunity level
- infection load
- time before detection...

in

- the transmission process
- the evolution of the disease

Applications : nosocomial infections, HIV, salmonella, BSE-Bovine Spongiform Encephalopathy, Scrapie, CWD-Chronic Wasting Disease, Influenza...

References : Diekmann & Heesterbeek, Gurtin & MacCamy, Ianelli, Magal, Thieme, Webb, Laroche & Perasso...

SI structured models in epidemiology

Infection load-structured model

* infection load $i \geq i^-$
* evolution $\frac{di}{dt} = \sigma(i)$

$$\begin{cases} \frac{dS}{dt} = \gamma - \mu_0 S - \Theta(t, S(t)) - S\mathcal{H}(I) \\ \frac{\partial I(t,i)}{\partial t} + \frac{\partial(\sigma(i)I(t,i))}{\partial i} = -\mu(i)I + \Phi(i)S(t)\mathcal{H}(I) \\ \sigma(i^-)I(t,i^-) = \Theta(t, S(t)) \end{cases}$$

with $\mathcal{H}(I) = \int_{i^-}^{+\infty} \beta(i)I(t,i)di$

Theorem [Perasso & Razafison, Siam J. Appl. Math., 74(5) (2014)]

For $\Theta \equiv 0$ and $\sigma(i) = \nu i$,

$$\mathcal{R}_0 = \frac{\gamma}{\mu_0} \int_{i^-}^{+\infty} \frac{1}{\nu i} \int_{i^-}^{i} \Phi(s) e^{-\int_s^i \frac{\mu(l)}{\nu l} dl} \, ds$$

SI structured models in epidemiology

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What is different ?

The structure variable implies to deal with infinite dimensional systems !

So, if we want to apply the next generation matrix method...

- requires a suitable theoretical framework (functional spaces)
- no matrices but differential operators
- the spectral properties are different (essential spectrum)
- the expression of $\mathcal{R}_0$ depends on the structure variable
- the local stability properties through linearization fail
- global stability : infinite dimensional Lyapunov functions (global attractor, but the stability fails -> Lasalle invariance principle)

But some results...

- age of infection models : local stability of DFE [Castillo-Chavez & Feng (1998)] ; global stability of DFE & of EE [Magal, McCluskey & Webb (2010-2013)]
- infection load models (with exponential growth) : local stability of DFE & EE [Perasso & Razafison (2014)]
- two structuring variables : global stability of the DFE [Laroche & Perasso (2016)]

THANK YOU!