AN INTRODUCTION TO THE BASIC REPRODUCTIVE NUMBER IN MATHEMATICAL EPIDEMIOLOGY

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3 WHAT TO DO WITH A $R_0$?

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Kermack-McKendrick SIR model

- 1905: plague epidemic in Mumbai

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

**Question:** How can we prevent such an epidemic?
Kermack-McKendrick SIR model

- 1927: first model to understand epidemic process

![SIR model diagram](image)

\[
\begin{align*}
\frac{dS(t)}{dt} &= -\beta S(t)I(t) \\
\frac{dI(t)}{dt} &= \beta S(t)I(t) - \gamma I(t) \\
\frac{dR(t)}{dt} &= \gamma I(t)
\end{align*}
\]

**Question**: Can we extract a tool to measure the disease risk?
At the early beginning...

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

\[ \mathcal{R}_0 = \int_0^\infty P(a) \beta(a) \, da \]

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

1. **A brief history of $R_0$**

2. **A recipee for $R_0$ calculation**

3. **What to do with a $R_0$ ?**

4. **Main difficulties arising with structured PDE models**
The next generation matrix

An efficient method for $R_0$ calculation in ODE epidemic models
[Van Den Driessche & Watmough (2002)]

$$\dot{x}(t) = f(x(t)), \quad x = (x_1, \ldots, x_p, x_{p+1}, \ldots, x_n)^T$$

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

with

- $F_i$ flux of newly infected
- $V_i^+$ (resp. $V_i^-$) other entering fluxes (resp. leaving fluxes)
**The next generation matrix**

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

\[
D_{x^*} \mathcal{F} = \begin{pmatrix} 0 & 0 \\ 0 & F \end{pmatrix}, \quad D_{x^*} \mathcal{V} = \begin{pmatrix} \Box & \Box \\ 0 & V \end{pmatrix}
\]

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

The \( R_0 \) value related to the epidemic system \( \dot{x}(t) = f(x(t)) \) is given by

\[
R_0 = \rho(-FV^{-1})
\]

Sketch of proof:

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

Some remarks:

- $-FV^{-1}$ is the "next generation matrix"
  → interpretation

- requires to determine the DFE $x^*$

- $x^*$ is locally asymptotically stable when $\mathcal{R}_0 < 1$

- efficiency: reduction method!
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What to do with a $R_0$?

$R_0$ 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:

\[
\begin{align*}
S & \xrightarrow{\beta I} I \\
I & \xrightarrow{\gamma} R
\end{align*}
\]

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 $R_0 = 0.7$
Example 1: Measure of epidemic risk & prediction

**Figure:** SIR model, simulation with $R_0 = 0.9$
**Example 1: Measure of epidemic risk & prediction**

**Figure:** SIR model, simulation with $R_0 = 1$
Example 1: Measure of epidemic risk & prediction

Figure: SIR model, simulation with $R_0 = 1.5$
**Example 1: Measure of epidemic risk & prediction**

**Figure:** SIR model, simulation with $R_0 = 3$
Example 1: Measure of epidemic risk & prediction

Figure: SIR model, simulation with $R_0 = 5$
Example 1: Measure of epidemic risk & prediction

Figure: SIR model, simulation with $R_0 = 5$
Example 2: Control strategy

1- Malaria and Ross’ "Mosquito theorem"

Ross model

\[
\begin{align*}
\frac{dI_H(t)}{dt} &= ab_1 I_M \frac{H - I_H}{H} - \gamma I_H \\
\frac{dI_M(t)}{dt} &= ab_2 (M - I_M) \frac{I_M}{M} - \mu I_M
\end{align*}
\]

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 / mosquito and time unit
- \(b_1\) proba that a bite generates a human infection
- \(b_2\) proba that a mosquito becomes infected
- \(1/\gamma\) infection period for human
- \(1/\mu\) mosquito lifespan
Example 2: Control strategy

DFE \((0, 0)\)

\[
F = \begin{pmatrix}
0 & ab_1 \\
\frac{ab_2 M}{H} & 0
\end{pmatrix}
\]

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

\[
\mathcal{R}_0 = \rho(-FV^{-1}) = \sqrt{\frac{a^2 b_1 b_2 M}{\gamma \mu H}}
\]

→ Emphasizes the Ross' "Mosquitoe theorem"!
Example 2: Control strategy

DFE \((0, 0)\)

\[
F = \begin{pmatrix}
0 & ab_1 \\
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\]

\[
R_0 = \rho(-FV^{-1}) = \sqrt{\frac{a^2 b_1 b_2 M}{\gamma \mu H}}
\]

→ Emphasizes the Ross' "Mosquitoe theorem"!
Example 2: Control strategy

2- "Herd immunity" in disease vaccination

SEIS model - Assumptions:
- no vertical transmission
- exposure period
- no natural immunity
- healed become susceptible

\[ \Lambda \]

\[ S \]  \[ \beta I \]  \[ E \]  \[ \alpha \]  \[ I \]  \[ \mu \]  \[ \mu + \gamma \]
Example 2: Control strategy

SEIS model

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

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

\[F = \begin{pmatrix} 0 & 0 \\ 0 & \frac{\beta \Lambda}{\mu} \\ 0 & -\frac{\beta \Lambda}{\mu} \end{pmatrix} \]

\[V = \begin{pmatrix} 0 & -\frac{\beta \Lambda}{\mu} \\ -\frac{\beta \Lambda}{\mu} & \alpha \\ -\frac{\beta \Lambda}{\mu} & \frac{\beta \Lambda}{\mu} \end{pmatrix} \]

\[R_0 = \rho(-FV^{-1}) = \frac{\alpha \beta \Lambda}{\mu(\mu + \alpha)(\mu + \gamma)}\]
Example 2: Control strategy

SEIS model

\[
\begin{align*}
\frac{dS(t)}{dt} &= (1 - \epsilon)\Lambda - \beta S(t)I(t) - \mu S(t) \\
\frac{dE(t)}{dt} &= \beta S(t)I(t) - (\alpha + \mu)E(t) \\
\frac{dI(t)}{dt} &= \alpha E - (\gamma + \mu)I(t)
\end{align*}
\]

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

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

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

\[\tilde{R}_0 = (1 - \epsilon) R_0\]

Vaccination of a proportion \(\epsilon\) of new borns: \(\epsilon > 1 - \frac{1}{R_0} \Rightarrow \tilde{R}_0 < 1!\)
| Disease    | $R_0$ | Herd immunity |
|------------|-------|---------------|
| Mumps      | 4-7   | 75-86 %       |
| Polio      | 5-7   | 80-86 %       |
| Small pops | 5-7   | 80-85 %       |
| Diphtheria | 6-7   | 85 %          |
| Rubella    | 6-7   | 83-85 %       |
| Measles    | 12-18 | 83-94 %       |

**Table:** $R_0$ and herd immunity thresholds for vaccine-preventable diseases [Am. J. Prev. Med., 20 (2001)]
### Table: \( R_0 \) and herd immunity thresholds for vaccine-preventable diseases [Am. J. Prev. Med., 20 (2001)]

| Disease       | \( R_0 \) | 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 %      |

→ Eradication in 1977!
**Example 3: Impact of biodiversity on the disease dynamics**

Trophically transmitted parasite: *Echinococcus multilocularis*
**Example 3: Impact of biodiversity on the disease dynamics**

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

\[
\begin{align*}
\frac{dz_S}{dt} &= b_z z - \left( m_z + (b_z - m_z) \frac{z_S + z_I}{k_z} \right) z_S \\
\frac{dx_i S}{dt} &= b x_i - \left( m + (b - m) \frac{x_j S + x_j I}{k} \right) x_i S - \Phi_i(x_1, x_2) \frac{x_i S}{x_i} z \\
\frac{dz}{dt} &= - \left( m_z + (b_z - m_z) \frac{z_S + z_I}{k_z} \right) z_I \\
\frac{dx_i I}{dt} &= - \left( m + (b - m) \frac{x_j S + x_j I}{k} \right) x_i I - \Phi_i(x_1, x_2) \frac{x_i I}{x_i} z + z_I \Gamma_i x_i S
\end{align*}
\]
**Example 3**: Impact of biodiversity on the disease dynamics

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

\[
\begin{align*}
\frac{dz_S}{dt} &= b_z z - \left( m_z + (b_z - m_z) \frac{zS + zI}{k_z} \right) zS \\
\frac{dx_iS}{dt} &= bx_i - \left( m + (b - m) \frac{\sum x_jS + x_jI}{k} \right) x_iS - \Phi_i(x_1, x_2) \frac{x_iS}{x_i} z - zS \sum_i \eta_i \Phi_i(x_1, x_2) \frac{x_iS}{x_i} - \mu zI \\
\frac{dz_I}{dt} &= -\left( m_z + (b_z - m_z) \frac{zS + zI}{k_z} \right) zI + zS \sum_i \eta_i \Phi_i(x_1, x_2) \frac{x_iS}{x_i} - \mu zI \\
\frac{dx_iI}{dt} &= -\left( m + (b - m) \frac{\sum x_jS + x_jI}{k} \right) x_iI - \Phi_i(x_1, x_2) \frac{x_iS}{x_i} z + zI \Gamma_i x_iS
\end{align*}
\]
**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:
   
   \[
   -FV^{-1} = \begin{pmatrix}
   0 & \frac{\eta_1 z^* \Phi_1(x_1^*, x_2^*)}{x_1^* b} & \frac{\eta_2 z^* \Phi_2(x_1^*, x_2^*)}{x_2^* b} \\
   \frac{\Gamma_1 x_1^*}{b z + \mu} & 0 & 0 \\
   \frac{\Gamma_2 x_2^*}{b z + \mu} & 0 & 0
   \end{pmatrix}
   \]

3. Basic reproductive number:

   \[
   R_0 = \sqrt{\frac{z^*}{b(b z + \mu)}} \times (\eta_2 \Gamma_2 \Phi_2(x_1^*, x_2^*) + \eta_1 \Gamma_1 \Phi_1(x_1^*, x_2^*))
   \]

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 □
**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!

\[
R_0 = \sqrt{\frac{z^*}{b(b_z + \mu)}} \times (\eta_2 \Gamma_2 \Phi_2(x_1^*, x_2^*) + \eta_1 \Gamma_1 \Phi_1(x_1^*, x_2^*))
\]

**Figure:** Impact of prey availability on \(R_0\), with \(\Gamma_1 = \Gamma_2\) (left) and \(\Gamma_1 < \Gamma_2\) (right)
**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!**

\[
R_0 = \sqrt{\frac{z^*}{b(z + \mu)}} \times (\eta_2 \Gamma_2 \Phi_2(x_1^*, x_2^*) + \eta_1 \Gamma_1 \Phi_1(x_1^*, x_2^*))
\]

**Figure:** Impact of prey availability on \(R_0\), with \(\Gamma_1 = \Gamma_2\) (left) and \(\Gamma_1 < \Gamma_2\) (right)
**Example 3: Impact of biodiversity on the disease dynamics**

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

→ The total of prey impacts the effect of biodiversity on the epidemic risk (dilution/amplification)
Example 3: Impact of biodiversity on the disease dynamics

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

→ The total of prey impacts the effect of biodiversity on the epidemic risk (dilution/amplification)
Example 4: Extinction VS. persistence

The DFE is locally asymptotically stable whenever $R_0 < 1$ and unstable if $R_0 > 1$.

- Can we say more than "locally" when $R_0 < 1$?
- Persistence of the disease when $R_0 > 1$? $\Rightarrow$ the instability of DFE is not enough!
- And what about $R_0 = 1$?

**Definition (uniform persistence)**

The disease is uniformly persistent if

$$\exists \varepsilon > 0, \forall I_0 > 0 \Rightarrow \liminf_{t \to +\infty} I(t) \geq \varepsilon.$$
Example 4: Extinction VS. persistence

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**Definition (uniform persistence)**

The disease is uniformly persistent if

$$\exists \varepsilon > 0, \ \forall I_0 > 0 \Rightarrow \lim_{t \to +\infty} \inf I(t) \geq \varepsilon.$$
**Example 4: Extinction VS. persistence**

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

\[
\begin{align*}
\frac{dS(t)}{dt} &= \Lambda - \beta S(t)I(t) - \mu_S S(t) \\
\frac{dI(t)}{dt} &= \beta S(t)I(t) - \mu_I I(t)
\end{align*}
\]

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

\[\bar{x} = \left( \frac{1}{R_0}, \frac{\mu_S}{\mu_I} \left(1 - \frac{1}{R_0}\right) \right) \text{ Endemic Equilibrium (EE) with}\]

\[R_0 = \frac{\beta \Lambda}{\mu_S \mu_I}\]

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

- \(R_0 \leq 1 \Rightarrow \text{DFE is globally stable;}
- \(R_0 > 1 \Rightarrow \text{EE is globally stable}\)

Remark: uniform persistence when \(R_0 > 1\)!
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

Some extensions:

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

→ 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 $\frac{di}{dt} = \sigma(i)$

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

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 $\sigma(i) = \nu i$,

\[
R_0 = \frac{\gamma}{\mu_0} \int_{i^-}^{+\infty} \frac{1}{\nu i} \int_{i^-}^{i} \Phi(s) e^{-\int_{s}^{i} \frac{\mu(l)}{\nu l} dl} ds
\]
SI structured models in epidemiology

Infection load-structured model

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

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

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 $\sigma(i) = \nu i$,

\[
\mathcal{R}_0 = \frac{\gamma}{\mu_0} \int_{i^-}^{+\infty} \frac{1}{\nu i} \int_{i^-}^{i} \Phi(s)e^{-\int_{s}^{i} \frac{\mu(l)}{\nu l} dl} ds
\]
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 $R_0$ depends on the structure variable
- the local stability properties through linearization fail
- global stability: infinite dimensional Lyapunov functions (global attractor, but the stability fails $\Rightarrow$ 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!