MATH 8410 – Mathematical Epidemiology

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Objective of the course

Introduction to mathematical epidemiology ("math epi"):

▶ problems considered
▶ methods:
  ▶ modelling
  ▶ mathematical analysis
  ▶ numerical investigations
  ▶ interpretation
Outline – ODE

- SIS with demography: $R_0$
- SIR without demography: final size of an epidemic
- SEIRS in constant population
- SEIR in non-constant population
- Other ODE models:
  - Role of vaccination
  - Bistability
  - Logistic demography
- Large scale systems: metapopulations (spread in discrete space)
Outline – Infinite dimension

- Sojourn time in compartments
- SIS with arbitrary sojourn in compartments
- SIS with vaccination
- “Compartment age”
- Age structuration
- Spatial spread of epidemics in continuous space
Outline – Stochastic models

- Why stochasticity?
- Stochastic equivalents of deterministic models
SIS model with demography

Size of an epidemic (SIR model of Kermack and McKendrick)

SIRS model with constant population

SLIRS model with constant population

More on incidence functions

Next generation method

Modèle SEIRS – Propriétés globales

SEIRS en population non constante

Herd immunity

Effet de la vaccination – États bistables
Compartments

Consider a population. We want to model the spread of an infectious disease in this population. We suppose that individuals can be in one of two (epidemiological) states:

- they are **susceptible** (to the disease) if they are not harbouring the infectious pathogen,
- they are **infectious** if they harbour the pathogen and are actively spreading it to others.

This defines two **compartments**. The object of the modelling exercise is to find how to describe the evolution of the number of individuals in each compartment.

The type of model we obtain is called a **compartamental model**.
We denote:

- $S(t)$ the number of susceptible individuals,
- $I(t)$ the number of infectious individuals,
- $N(t) = S(t) + I(t)$ the total population.

The following hypotheses describe a disease for which the incubation period is very short.

We also assume that infection affects individuals only for a limited period of time.
Susceptible individuals

Assume that susceptible individuals

- are born at a rate $d$ that is proportional to the total population $N$
- die at the *per capita* rate $d$ (i.e., $d$ is proportional to the number of susceptible individuals).

In an epidemic model, birth and death are relative to susceptibility, not necessarily “real” birth and death.

Since all newborns are susceptible, we are not accounting for *vertical transmission* of the disease from a parent to a newborn.
Infectious individuals

Assume that infectious individuals

- die at the *per capita* rate $d$,
- recover at the *per capita* rate $\gamma$.

We ignore **disease induced mortality**: the disease is not severe enough to cause death.
Interactions – Infection

When a contact takes place between an infectious and a susceptible individual, the infectious pathogen can be transmitted.

The function $f(S, I)$ of $S$ and $I$ that describes this process goes under two different names, depending on how it is written (and thus the underlying “philosophy”):

- **incidence,**
- **force of infection.**

In both cases, the function consists of two components:

- a count of the number of contacts that take place,
- a description of the probability that such a contact is infecting, i.e., that the pathogen is transmitted.
Incidence is defined in (classical) epidemiology as the number of new infections per time period.

In ODE context, equivalent to “rate at which new infections are generated, per unit time”.

Most frequently used forms are mass action incidence,

\[ f(S, I) = \beta SI \]

and proportional (or standard) incidence,

\[ f(S, I) = \beta \frac{SI}{S + I} \]

In both cases, \( \beta \) is the disease transmission coefficient. It has different units in the two forms.
Mass action incidence

\[ f(S, I) = \beta SI \quad (1) \]

In the case of (1), it is assumed that all susceptible individuals can meet all infectious individuals ("mass action" comes from chemistry).

If the population is large, this hypothesis is not very realistic.

Popular nonetheless because this is a "friendly" nonlinearity.

Here, \( \beta \) has units.
Standard incidence

Case of a larger population.

\[ f(S, I) = \beta \frac{SI}{S + I} \] (2)

Each infectious individual meets a proportion of the susceptible individuals (or vice versa: each susceptible meets a proportion of the infectious individuals).

Can be tricky if \( \lim_{t \to \infty} S(t) + I(t) = 0 \) (for instance, the disease drives the population to extinction).

Here, \( \beta \) has units..
Flow diagram

\[ \begin{align*}
S & \quad \beta \text{SI} / N \\
I & \quad \gamma \text{I} \\
dN & \quad \text{dS} \\
dI & \quad \text{dI}
\end{align*} \]
The model

Choose standard incidence (2),

\[
S' = dN - dS - \beta \frac{SI}{N} + \gamma I \tag{3a}
\]

\[
I' = \beta \frac{SI}{N} - dI - \gamma I \tag{3b}
\]

Consider the IVP consisting of this system together with initial conditions \( S(0) = S_0 \geq 0 \) and \( I(0) = I_0 \geq 0 \).
Remarks

- (3) is an SIS model, (susceptible-infectious-susceptible).

- If $\gamma = 0$ (no recovery), then the model is an SI-type model. In this case, this is a chronic infectious disease, an infected individual remains infectious their whole life (but the disease is not lethal, there is no disease induced mortality).

- Diseases with this type of characteristics are bacterial diseases caused by *staphylococcus aureus, streptococcus pyogenes, chlamydia pneumoniae* or *neisseria gonorrhoeae*. 
Demography and susceptibility

The notion of “birth” and “death” in epidemic models is relative to susceptibility to the disease under consideration.

A model that describes the spread of human immunodeficiency virus (HIV) in an at risk population such as IDU would consider for instance

- birth as the beginning of the practice of the risky behaviour,
- death as the end of the risky behaviour (either by actual death or because the individual ceases to inject).
Analysis of the system

System (3) is nonlinear.

In principle, should use the usual planar methods.

Here, however, we can find an explicit solution.
Dynamics of $N$

We have

$$N' = (S + N)'$$
$$= dN - dS \frac{SI}{N} + \gamma I + \beta \frac{SI}{N} - dl - \gamma l$$
$$= dN - d(S + I)$$
$$= 0$$

Therefore, for all $t$, $N(t) \equiv N_0 := S_0 + I_0$. 
Proportions

\[ s = \frac{S}{N} \quad i = \frac{I}{N} \]

Remark that \( s + i = (S + I)/N = 1 \). The derivative of \( i \) is given by

\[ i' = \frac{I'N - IN'}{N^2} = \frac{I'}{N} - \frac{iN'}{N} \]

Since \( N' = 0 \),

\[ i' = \frac{I'}{N} \]

Substitute the RHS of (3b) in this equation gives

\[ i' = \beta \frac{SI}{N^2} - d \frac{I}{N} - \gamma \frac{I}{N} = \beta si - (d + \gamma)i \]
System in proportions

Since \( s + i = 1 \), we can substitute \( s = 1 - i \) in the latter equation, giving
\[
i' = \beta(1 - i)i - (d + \gamma)i.
\]

Therefore, the system \textit{in proportions} is given by

\[
\begin{align*}
  s &= 1 - i \\
  i' &= \beta(1 - i)i - (d + \gamma)i
\end{align*}
\]

Since \( N \) is constant, solutions to (3) are deduced directly from those of (4), and we now concentrate on (4).
Rewrite (4b) as

$$i' - (\beta - (d + \gamma))i = -\beta i^2$$

(5)

This is a Bernoulli equation, which, using the change of variables $u = i^{-1}$, gives the linear equation

$$-u' - (\beta - (d + \gamma))u = -\beta$$

i.e.,

$$u' + (\beta - (d + \gamma))u = \beta$$

(6)
An integrating factor is given by

\[ \mu(t) = \exp \left( \int P(t) \, dt \right) = e^{(\beta-(d+\gamma))t} \]

and as a consequence

\[ \mu(t)u = \frac{\beta}{\beta - (d + \gamma)} e^{(\beta-(d+\gamma))t} + C \]

for \( C \in \mathbb{R} \). Thus, finally,

\[ u = \frac{\beta}{\beta - (d + \gamma)} + Ce^{-(\beta-(d+\gamma))t} \]
The initial condition $i_0 = l_0/N$ can be written $u(0) = 1/i_0$. As a consequence,

$$u(0) = \frac{1}{i_0} = \frac{\beta}{\beta - (d + \gamma)} + C$$

which implies that

$$C = \frac{\beta - (d + \gamma) - i_0\beta}{i_0(\beta - (d + \gamma))}$$
Thus, the solution of the linear equation (6) is given by

\[
\begin{align*}
    u &= i_0 \beta + (\beta - (d + \gamma) - i_0 \beta) e^{-(\beta-(d+\gamma))t} \\
    &= \frac{i_0 \beta (1 - e^{-(\beta-(d+\gamma))t}) + (\beta - (d + \gamma)) e^{-(\beta-(d+\gamma))t}}{i_0 (\beta - (d + \gamma))}
\end{align*}
\]

and that of (5) is

\[
\begin{align*}
    i(t) &= \frac{i_0 (\beta - (d + \gamma))}{i_0 \beta (1 - e^{-(\beta-(d+\gamma))t}) + (\beta - (d + \gamma)) e^{-(\beta-(d+\gamma))t}}
\end{align*}
\]
In summary, the solution to (4) is given by

\[ i(t) = \frac{i_0(\beta - (d + \gamma))}{i_0\beta(1 - e^{-(\beta-(d+\gamma))t}) + (\beta - (d + \gamma))e^{-(\beta-(d+\gamma))t}} \]  

(7a)

and

\[ s(t) = 1 - i(t) \]  

(7b)
Observing (7a),

\[ i(t) = \frac{i_0(\beta - (d + \gamma))}{i_0 \beta (1 - e^{-(\beta - (d + \gamma))t}) + (\beta - (d + \gamma))e^{-(\beta - (d + \gamma))t}} \]  \hfill (7a)

it is clear that there are two cases:

- If \( \beta - (d + \gamma) < 0 \), then \( \lim_{t \to \infty} e^{-(\beta - (d + \gamma))t} = +\infty \), so 
  \[ \lim_{t \to \infty} i(t) = 0 \] and \( \lim_{t \to \infty} s(t) = 1 \).

- If \( \beta - (d + \gamma) > 0 \), then \( \lim_{t \to \infty} e^{-(\beta - (d + \gamma))t} = 0 \); thus, 
  \[ \lim_{t \to \infty} i(t) = \frac{\beta - (d + \gamma)}{\beta} \] and 
  \[ \lim_{t \to \infty} s(t) = 1 - \frac{\beta - (d + \gamma)}{\beta}. \]
The basic reproduction number $\mathcal{R}_0$

Reformulate the result in the epidemiological context using the *basic reproduction number*, usually denoted $\mathcal{R}_0$. Let

$$\mathcal{R}_0 = \frac{\beta}{d + \gamma}$$

We then have the following equivalences:

$$\mathcal{R}_0 < 1 \iff \beta - (d + \gamma) < 0$$
$$\mathcal{R}_0 > 1 \iff \beta - (d + \gamma) > 0$$

Also,

$$\frac{\beta - (d + \gamma)}{\beta} = 1 - \frac{1}{\mathcal{R}_0}$$
Summary in “epidemiological terms”

**Theorem**

For system (3), defining

\[ R_0 = \frac{\beta}{d + \gamma} \]

we have the following alternative:

- If \( R_0 < 1 \), then
  - \( \lim_{t \to \infty} s(t) = 1 \)
  - \( \lim_{t \to \infty} i(t) = 0 \),

  *the disease goes extinct.*

- If \( R_0 > 1 \), then
  - \( \lim_{t \to \infty} s(t) = \frac{1}{R_0} \)
  - \( \lim_{t \to \infty} i(t) = 1 - \frac{1}{R_0} \),

  *the disease becomes endemic.*
Remarks about $\mathcal{R}_0$

- $\mathcal{R}_0$ determines the propension of a disease to establish itself in a population.

- The aim of a control measure is thus to reduce $\mathcal{R}_0$ to values smaller than 1.

- The “verbal” definition of $\mathcal{R}_0$ is the average number of secondary infections produced when an infectious individual is introduced into a completely susceptible population.

- Remark for our naive model, $1/(d + \gamma)$ is the average sojourn time in the $I$ compartment before death or recovery and $\beta$ is linked to the probability of transmitting the infection.
Case $R_0 > 1$

Also, remark that the higher $R_0$, the higher the proportion of infectious individuals in the population. As a consequence, $R_0$ is also an indicator of the infectiousness of the diseases.
A few sample values of $R_0$ (from Anderson and May)

The value of $R_0$ can be estimated with data.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Location</th>
<th>Period</th>
<th>$R_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Cirencester, England</td>
<td>1947-50</td>
<td>13-14</td>
</tr>
<tr>
<td></td>
<td>England and Wales</td>
<td>1950-68</td>
<td>16-18</td>
</tr>
<tr>
<td></td>
<td>Kansas, USA</td>
<td>1918-21</td>
<td>5-6</td>
</tr>
<tr>
<td></td>
<td>Ontario, Canada</td>
<td>1912-3</td>
<td>11-12</td>
</tr>
<tr>
<td></td>
<td>Willesden, England</td>
<td>1912-3</td>
<td>11-12</td>
</tr>
<tr>
<td></td>
<td>Ghana</td>
<td>1960-8</td>
<td>14-15</td>
</tr>
</tbody>
</table>
SIS model with demography

Size of an epidemic (SIR model of Kermack and McKendrick)

SIRS model with constant population

SLIRS model with constant population

More on incidence functions

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Modèle SEIRS – Propriétés globales

SEIRS en population non constante

Herd immunity

Effet de la vaccination – États bistables
Epidemic – Size of an epidemic

Before, we were considering a problem of endemicity, i.e., the long term behaviour of an infectious disease.

Here, we consider only the first epidemic peak.

▶ Does it always take place?
▶ When an epidemic goes through a population, are all individuals infected?

Questions originally asked by Kermack and McKendrick in 1927.
The SIR model without demography

Suppose that

- the time interval considered is small enough that the demographic component can be neglected. (We say the model does not include *vital dynamics*.)
- Incidence is mass action function (1).

Consider the Kermack and McKendrick model:

\[ S' = -\beta SI \quad (8a) \]
\[ I' = (\beta S - \gamma)I \quad (8b) \]
\[ R' = \gamma I \quad (8c) \]
Reduction of the problem

The system contains a third compartment for *removed* individuals.

However, this compartment does not influence the dynamics of $S$ and $I$ ($R$ does not appear in $S'$ or $I'$).

Furthermore, $N' = (S + I + R)' = 0$ and thus $N$ is constant. So the dynamics of $R$ can be deduced from that of $S$ and $I$ by using the fact that $R = N - S - I$.

So consider the subsystem consisting of equations (8a) and (8b).
Equilibria

Let us seek equilibria of (8). From (8b),

- either $\bar{S} = \alpha / \beta$,
- or $\bar{I} = 0$.

Substituting in (8a) gives

- in the first case, the equilibrium $(\bar{S}, \bar{I}) = (\alpha / \beta, 0)$,
- in the second case, any $\bar{S} \geq 0$ is an equilibrium (continuum of equilibria).

Classic methods have problems with non-isolated equilibria.
Plan B..

Let us consider the dynamics of

\[ \frac{dl}{dS} \]

We have

\[ \frac{dl}{dS} = \frac{dl}{dt} \frac{dt}{dS} = \frac{l'}{S'} \]

\[ = \frac{\beta SI - \gamma l}{-\beta SI} \]

\[ = \frac{\gamma}{\beta S} - 1 \]
The equation
\[ \frac{dl}{dS} = \frac{\gamma}{\beta S} - 1 \]
is easy to integrate, giving
\[ I(S) = \frac{\gamma}{\beta} \ln S - S + C \]
where \( C \in \mathbb{R} \). The initial condition \( I(S_0) = I_0 \) gives \( C = S_0 + I_0 - \frac{\gamma}{\beta} \ln S_0 \) and the solution to (8) is a function of \( S \),
\[ I(S) = S_0 + I_0 - S + \frac{\gamma}{\beta} \ln \frac{S}{S_0} \]
Note also that

\[ R(S) = N - S - I(S) = R_0 - \frac{\gamma}{\beta} \ln \frac{S}{S_0} \]

The equation

\[ I(S) = S_0 + I_0 - S + \frac{\gamma}{\beta} \ln \frac{S}{S_0} \]

describes trajectories in the \((S, I)\) plane corresponding to initial conditions \((S_0, 1 - S_0)\) (and \(R_0 = 0\)).
Suppose that the total population is normalised, i.e., $N = 1$.

Then $R = 1 - S - I$.

Let

$$R_0 = \frac{\beta}{\gamma}$$

If not normalized, take $R_0 = \frac{\beta S_0}{\gamma}$. 
Proportion de susceptibles
Proportion d'infectieux
$(1/R_0, I_M)$
Let \((S(t), I(t))\) be a solution of \((8)\).

- If \(R_0S_0 \leq 1\), then \(I(t)\) tends to 0 when \(t \to \infty\).
- If \(R_0S_0 > 1\), then \(I(t)\) first reaches a maximal value
  
  \[
  1 - \frac{1}{R_0} - \frac{\ln(R_0S_0)}{R_0}
  \]

  then goes to 0 as \(t \to \infty\).

- The proportion \(S(t)\) of susceptibles is a decreasing function and its limit \(S(\infty)\) is the unique solution in \((0, 1/R_0)\) of the transcendental equation
  
  \[
  1 - S(\infty) + \frac{\ln[S(\infty)/S_0]}{R_0} = 0
  \]
Summary

We have seen

- an SIS model for endemicity, with demography, where we characterised a threshold, $R_0$, such that when $R_0 < 1$, the disease goes extinct whereas when $R_0 > 1$, the disease becomes established in the population (becomes endemic).

- An SIR *epidemic* model without vital dynamics, where the presence or absence of an epidemic wave is characterized by the value of $R_0$. 
SIS model with demography

Size of an epidemic (SIR model of Kermack and McKendrick)

**SIRS model with constant population**

SLIRS model with constant population

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SEIRS en population non constante

Herd immunity

Effet de la vaccination – États bistables
When a pathogen (or any foreign object) enters the body, it triggers an *immune response*.

Modelling the immune system is another branch of mathematical biology, very close to mathematical epidemiology (the models are often very similar if not identical).

The immune system has *memory*: antibodies generated to ward off infection with a given pathogen are produced for some amount of time after the infection, giving better immunity against reinfection by the same infectious agent.

Immunity is either permanent (⇒ SIR) or temporary (⇒ SIRS).
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### Incubation periods

- **SIS and SIR:** progression from S to I instantaneous.

#### Several incubation periods:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yersinia Pestis</td>
<td>2-6 days</td>
</tr>
<tr>
<td>Ebola haemorrhagic fever (HF)</td>
<td>2-21 days</td>
</tr>
<tr>
<td>Marburg HF</td>
<td>5-10 days</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>1-3 weeks</td>
</tr>
<tr>
<td>Tse-tse</td>
<td>weeks–months</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>months–years</td>
</tr>
</tbody>
</table>
Hypotheses

- There is demography. New individuals are born at a rate proportional to the total population.
- There is no vertical transmission: all “newborns” are susceptible.
- The disease is non-lethal, it causes no additional mortality.
- New infections occur at the rate $f(S, I, N)$.
- There is a period of incubation for the disease.
- There is a period of time after recovery during which the disease confers immunity to reinfection.
The model is as follows:

\[ S' = d(N - S) - f(S, I, N) + \nu R \]  
\[ L' = f(S, I, N) - (d + \varepsilon)L \]  
\[ I' = \varepsilon L - (d + \gamma)I \]  
\[ R' = \gamma I - (d + \nu)R \]

Meaning of the parameters:

- \(1/\varepsilon\) average duration of the incubation period.
- \(1/\gamma\) average duration of infectious period.
- \(1/\nu\) average duration of immune period.
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More on incidence functions

Suppose transmission occurs at the rate

\[ f(S, I, N) \]

- \( f \) is the rate at which new cases are generated per unit time, often called the incidence or incidence function.

- Depends on the number \( S(t) \) of susceptible individuals, \( I(t) \) of infectious individuals and, potentially, of the total population \( N(t) \).

- The choice of an appropriate function is hard, often the hardest and most uncertain part of epidemic modelling.
Mass action incidence

\[ f(S, I) = \beta SI \]  

(1)

An incidence function of the form (1) is called *mass action incidence*.

- Assumes homogeneous mixing of infectious and susceptible individuals in the population.
- Strong hypothesis: every individual can potentially meet every other individual.
- If every individual is a vertex in a graph and contacts are the edges, then mass action is an Erdos-Renyi graph.
Standard incidence

The other most frequently used incidence function takes the form

\[ f(S, I, N) = \beta \frac{SI}{N} \]  

(2)

and is called *standard* or *proportional* incidence.

In the case of (2), each susceptible individual can meet a fraction of the infectious individuals (we can also think in terms of infectious individuals meeting a fraction of the susceptible individuals).

**Remark**

When the total population is constant, set \( \beta \) in (1) to be \( \tilde{\beta} = \beta / N \) in (2) \( \Rightarrow \) the forms (1) and (2) are equivalent when the total population is constant.
General incidence

\[ f(S, I) = \beta S^q I^p \]  \hspace{1cm} (10)

An incidence function of the form (10) is often called *general incidence*. Such functions are generally used in a parameter identification context: additionally to finding \( \beta \), one can seek \( p \) and \( q \) to get the best possible fit to data.

Has also been used theoretically in obtaining global asymptotic stability of the SEIR (SLIR) model.

Can be used to implement a required number of contacts.
Incidence with refuge

The following function models a refuge effect:

\[
 f(S, I, N) = \begin{cases} 
 \beta I \left( N - \frac{I}{q} \right), & \text{if } I < qN \\
 0, & \text{if } I \geq qN 
\end{cases}
\]  

(11)

Here, only the proportion \(0 < q < 1\) of the population is really susceptible, for example because of spatial heterogeneities.
Negative binomial incidence

The following is called negative binomial incidence:

\[ f(S, I) = kS \ln \left(1 + \beta \frac{I}{k}\right) \]  \hspace{1cm} (12)

For small values of \( k \), this function describes a very aggregated infection, while for \( k \to \infty \), this is mass action incidence.
Asymptotic contact

The asymptotic contact function takes the form

\[ f(S, I) = \frac{N}{1 - \varepsilon + \varepsilon N} \frac{F(S, I)}{N} \]  \hspace{1cm} (13)

where \( F \) is one of the incidence functions previously described.

When \( \varepsilon = 0 \), contacts are proportional to \( N \), while when \( \varepsilon = 1 \), contacts are independent of \( N \).
Asymptotic transmission takes the form

\[ f(S, I) = \beta \frac{SI}{c + S + I} \]  

(14)

where \( c \) is a constant.

For instance, an incidence function of the form

\[ \frac{C(N)}{N} F(S, I) \]

with \( C(N) = \frac{N}{(1 - \varepsilon + \varepsilon N)} \) the function describing the rate of contact and \( F(S, I) \) the function describing disease transmission, the latter assumed in the form (12).
SIS model with demography

Size of an epidemic (SIR model of Kermack and McKendrick)

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The basic reproduction number $R_0$

Used frequently in epidemiology (not only math epi).

**Definition ($R_0$)**

The basic reproduction number $R_0$ is the average number of secondary cases generated by the introduction of an infectious individual in a wholly susceptible population.

- If $R_0 < 1$, then on average, each infectious individual infects less than one other person, so the epidemic has chances of dying out.
- If $R_0 > 1$, then on average, each infectious individual infects more than one other person and the disease can become established in the population (or there will be a major epidemic).
Computation of $\mathcal{R}_0$

Mathematically, $\mathcal{R}_0$ is a bifurcation parameter aggregating some of the model parameters and such that the disease free equilibrium (DFE) loses its local asymptotic stability when $\mathcal{R}_0 = 1$ is crossed from left to right.

- As a consequence, $\mathcal{R}_0$ is found by considering the spectrum of the Jacobian matrix of the system evaluated at the DFE.
- The matrix quickly becomes hard to deal with (size and absence of “pattern”) and the form obtained is not unique, which is annoying when trying to interpret $\mathcal{R}_0$. 
Example of the SIS model

Take SIS normalized to $N = 1$.

\[
S' = d - dS - \beta SI + \gamma I \\
I' = \beta SI - (d + \gamma)I
\]

DFE: $(\bar{S}, \bar{I}) = (1, 0)$.

\[
J_{ESM} = \begin{pmatrix}
-d & \gamma - \beta \bar{S} \\
\beta \bar{I} & \beta \bar{S} - (d + \gamma)
\end{pmatrix} = \begin{pmatrix}
-d & \gamma - \beta \\
0 & \beta - (d + \gamma)
\end{pmatrix}
\]

From this, we get the eigenvalues $-d$ and $\beta - (d + \gamma)$.

$\Rightarrow$ LAS of the DFE is governed by the sign of $\beta - (d + \gamma)$.

So we find the same $R_0$ that we had found earlier.

But the problem quickly becomes untractable.
The next generation operator

Diekmann and Heesterbeek, characterized in the ODE context by van den Driessche and Watmough.

Consider only individuals harbouring the pathogen, in a vector $\mathcal{I}$, and form the vectors

- $\mathcal{F}$ of infection fluxes,
- $\mathcal{V}$ of other fluxes (with $-$ sign),

so that

$$\mathcal{I}' = \mathcal{F} - \mathcal{V}$$

Then compute the Fréchet derivatives $D\mathcal{F}$ and $D\mathcal{V}$ with respect to the infected variables $\mathcal{I}$ and evaluate $F = D\mathcal{F}(DFE)$ and $V = D\mathcal{V}(DFE)$. Then

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

where $\rho$ is the spectral radius.
Theorem (van den Driessche and Watmough)

Suppose that the DFE exists. Let then $\mathcal{R}_0$ be defined by

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

with matrices $F$ and $V$ as indicated before. Then,

- if $\mathcal{R}_0 < 1$, the DFE is LAS,
- if $\mathcal{R}_0 > 1$, the DFE is unstable.