Global asymptotic stability

MATH 8xyz – Lecture 14

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The University of Manitoba campuses are located on original lands of Anishinaabeg, Ininew, Anisininew, Dakota and Dene peoples, and on the National Homeland of the Red River Métis.
We respect the Treaties that were made on these territories, we acknowledge the harms and mistakes of the past, and we dedicate ourselves to move forward in partnership with Indigenous communities in a spirit of Reconciliation and collaboration.

Outline

Endemic SIRS-type models with demography

What if there's another guest at the party?

Last remarks

Endemic SIRS-type models with demography

What if there's another guest at the party?

Last remarks

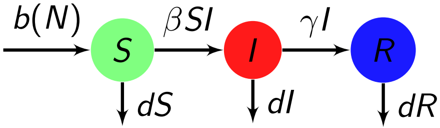
Two potential variations on the Kermack-McKendrick model

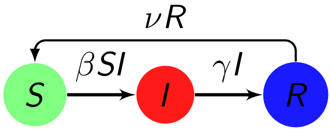
- Add *vital dynamics*, i.e., consider demographic processes

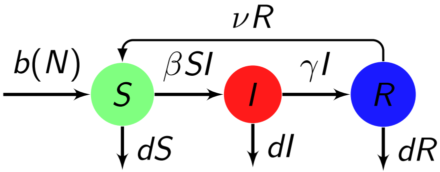
- Individuals do not die from the disease; after recovering, individuals are *immune* from infection for some time

- We can of course combine both!

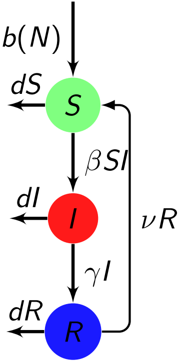
Potential variations







The model



$$S' = b(N) + \nu R - dS - \beta SI \tag{1a}$$

$$I' = \beta SI - (d+\gamma)I \tag{1b}$$

$$R' = \gamma I - (d+\nu)R \tag{1c}$$

Consider the initial value problem consisting in (1) to which we adjoin initial conditions $S(0) = S_0 \geq 0$, $I(0) = I_0 \geq 0$ and $R(0) = R_0 \geq 0$

Typically, we assume $N_0 = S_0 + I_0 + R_0 > 0$ to avoid a trivial case

Birth and death are *relative*

Remark that the notions of *birth* and *death* are relative to the population under consideration

E.g., consider a model for human immunodeficiency virus (HIV) in an at-risk population of intravenous drug users. Then

- birth is the moment the at-risk behaviour starts
- death is the moment the at-risk behaviour stops, whether from "real death" or because the individual stops using drugs

Choosing a form for demography

Before we proceed with the analysis proper, we must discuss the nature of the assumptions on demography

To do this, we consider the behaviour of the total population

$$N(t) = S(t) + I(t) + R(t)$$

Behaviour of the total population

Summing the equations in (1)

$$N' = b(N) - dN \tag{2}$$

There are three common ways to define $b(N)$ in (2)

1. $b(N) = b$
2. $b(N) = bN$
3. $b(N) = bN - cN^2$

Case 3 leads to logistic dynamics of the total population and is not discussed here

Case of a birth rate constant *per capita*

If $b(N) = bN$, then birth in (2) satisfies $N'/N = b$; we say that birth is **constant *per capita***

In this case, (2) takes the form

$$N' = bN - dN = (b - d)N$$

with initial condition $N(0) = N_0$

The solution to this scalar autonomous ODE is easy

$$N(t) = N_0 e^{(b-d)t}, \quad t \geq 0$$

Thus there are 3 possibilities:

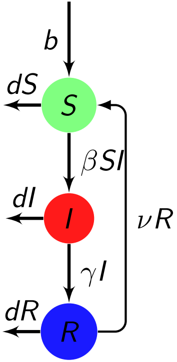
- if $b > d$, $N(t) \to \infty$, the total population explodes
- if $b = d$, $N(t) \equiv N_0$, the total population remains constant
- if $b < d$, $N(t) \to 0$, the total population collapses

From now on, assume $b(N) = b$

- We want a reasonable case, we could therefore suppose that $b(N) = d$, which would lead to a constant total population

- However, this is a little reductive, so we choose instead $b(N) = b$, which, we will see, works as well even though it can initially be thought of as not being very realistic

The model (for good this time)



$$S' = b + \nu R - dS - \beta SI \tag{3a}$$

$$I' = \beta SI - (d+\gamma)I \tag{3b}$$

$$R' = \gamma I - (d+\nu)R \tag{3c}$$

Consider the initial value problem consisting in (3) to which we adjoin initial conditions $S(0) = S_0 \geq 0$, $I(0) = I_0 \geq 0$ and $R(0) = R_0 \geq 0$

Typically, we assume $N_0 = S_0 + I_0 + R_0 > 0$ to avoid a trivial case

Endemic SIRS-type models with demography

Is the system well-posed?

For an ODE epidemiological model

- Do solutions to (3) exist and are they unique?
- Is the positive cone invariant under the flow of (3)?
- Are solutions to (3) bounded? Some models have unbounded solutions but they are rare and will need to be considered specifically

Solutions exist and are unique

- The vector field is always C^1, implying that solutions exist and are unique

If we had instead considered an incidence of the form $f(S, I, N) = \beta SI/N$ and, say, demography with $b(N) = bN$, then some discussion might have been needed if $b < d$

Invariance of $\mathbb{R}^3_+$ under the flow (1)

Let us start by assuming that $I(0) = I_0 = 0$. Then (3b) remains $I' = 0$, meaning that the SR-plane (i.e., the set $\{I = 0\}$) is positively invariant under the flow of (3)

On that plane, (3) reduce to

$$S' = b + \nu R - dS \tag{4a}$$
$$R' = -(d + \nu)R \tag{4b}$$

$\implies$ a solution with $I_0 > 0$ cannot enter the plane $\{I = 0\}$. Indeed, suppose that $I_0 > 0$ but $\exists t_\star > 0$ such that $I(t_\star) = 0$. Then at $(S(t_\star), I(t_\star) = 0, R(t_\star))$, there are two solutions to (3): the one we just generated as well as the one governed by (4)

This contradicts uniqueness of solutions to (3)

Invariance of $\mathbb{R}_+^3$ under the flow (2)

We saw that $I(t) > 0$ if $I(0) > 0$

Suppose now that $S = 0$. Equation (3a) is then

$$S' = b + \nu R > 0$$

So if $S(0) = S_0 > 0$, then $S(t) > 0$ for all t. If, on the other hand, $S_0 = 0$, then $S(t) > 0$ for $t > 0$ small; from what we just saw, this is then also true for all $t > 0$

We say the vector field points *inward*

$\implies$ S cannot become zero

Do the same for R

To summarise, for invariance

For simplicity, denote $\mathbb{R}^\star = \mathbb{R} \setminus \{0\}$

- If $(S(0), I(0), R(0)) \in \mathbb{R}_+ \times \mathbb{R}_+^\star \times \mathbb{R}_+$, then $\forall t > 0$,
$$(S(t), I(t), R(t)) \in (\mathbb{R}_+^\star)^3$$
- If $(S(0), I(0), R(0)) \in \mathbb{R}_+ \times \{0\} \times \mathbb{R}_+$, then $\forall t \geq 0$,
$$(S(t), I(t), R(t)) \in \mathbb{R}_+^\star \times \{0\} \times \mathbb{R}_+$$

The model is therefore satisfactory in that it does not allow solutions to become negative

Remark – Know your audience

This reasoning has its place in an MSc of PhD manuscript: you need to demonstrate that you know what to do and how to do it

In a research paper, this is not really necessary and actually often superfluous; the statement *it is easy to show that solutions exist uniquely and that the positive orthant is invariant under the flow of the system* is typically sufficient

(However, be sure to cover your bases: don't show the proof in the paper but have it in your notes.. *it is easy to show* can be a dangerous statement if it is not easy...)

The total population is asymptotically constant

Since $b(N) = b$, the total population equation (2) takes the form

$$N' = b - dN$$

This equation has a unique equilbrium $N^\star = b/d$ and it is very easy to check that this equilibrium is GAS: this is a scalar autonomous equation, so solutions are monotone; they increase to $N^\star$ if $N_0 < N^\star$ and decrease to $N^\star$ if $N_0 > N^\star$

So we can work at the limit $N^\star$ where $R = N^\star - (S + I)$ and thus drop the equation for R

Boundedness

It follows from what we just saw that the positive cone $\mathbb{R}_+^3$ is (positively) invariant under the flow of (3)

Since $N(t) \to N^\star$, we deduce that solutions of (3) are bounded

Seeking equilibria

We seek $S = S^\star, I = I^\star, R = R^\star$ such that

$$0 = b + \nu R - dS - \beta SI \tag{5a}$$
$$0 = \beta SI - (d+\gamma)I \tag{5b}$$
$$0 = \gamma I - (d+\nu)R \tag{5c}$$

From (5b), either $I^\star = 0$ or $\beta S - (d+\gamma) = 0$, i.e., $S^\star = (d+\gamma)/\beta$

When $I^\star = 0$, substituting $I^\star = 0$ into (5c) implies that $R^\star = 0$ and, in turn, substituting $I^\star = R^\star = 0$ into (5c) gives $S^\star = b/d$. This gives the disease-free equilibrium (DFE)

$$\boldsymbol{E}_0 := (S^\star, I^\star, R^\star) = \left(\frac{b}{d}, 0, 0\right) \tag{6}$$

We return to $S^\star = (d+\gamma)/\beta$ in a while

Classic method for computing $\mathcal{R}_0$

$\mathcal{R}_0$ is the surface in parameter space where the DFE loses its LAS

To find $\mathcal{R}_0$, we therefore study the LAS of the DFE

In an arbitrary (S, I, R), the Jacobian matrix of (3) takes the form

$$J_{(S,I,R)} = \begin{pmatrix} -d-\beta I & -\beta S & \nu \\ \beta I & \beta S-(d+\gamma) & 0 \\ 0 & \gamma & -(d+\nu) \end{pmatrix} \tag{7}$$

The LAS of the DFE depends on the sign of the real parts of the eigenvalues of (7) at that equilibrium point, so we evaluate

$$J_{\boldsymbol{E}_0} = \begin{pmatrix} -d & -\beta S^\star & \nu \\ 0 & \beta S^\star - (d+\gamma) & 0 \\ 0 & \gamma & -(d+\nu) \end{pmatrix} \tag{8}$$

Block upper triangular matrix $\implies$ eigenvalues are $-d < 0$, $-(d+\nu) < 0$ and $\beta S^\star - (d+\gamma)$

$\implies$ LAS of the DFE determined by sign of $\beta S^\star - (d+\gamma)$

Sign of $\beta S^\star - (d+\gamma)$

Recall that at the DFE (6), $S^\star = b/d$, so

$$\text{sign}(\beta S^\star - (d+\gamma)) = \text{sign}\left(\beta \frac{b}{d} - (d+\gamma)\right)$$

So the DFE is LAS if

$$\beta \frac{b}{d} < d + \gamma \iff \frac{\beta}{d+\gamma}\,\frac{b}{d} < 1$$

Denote

$$\mathcal{R}_0 = \frac{\beta}{d+\gamma}\,\frac{b}{d} \tag{9}$$

(We sometimes emphasise that $b/d = N^\star$, the total population, and thus write $\mathcal{R}_0 = \beta N^\star/(d+\gamma)$)

Seeking equilibria (2)

Now consider the second EP where $S^\star = (d+\gamma)/\beta = N^\star/\mathcal{R}_0$

Write (5c) as $R^\star = \gamma I^\star/(d+\nu)$

Since $S^\star + I^\star + R^\star = N^\star$, this means that

$$N^\star - S^\star - I^\star = \gamma I^\star/(d+\nu)$$

so substituting $S^\star = N^\star/\mathcal{R}_0$,

$$\left(1 + \frac{\gamma}{d+\nu}\right) I^\star = \left(1 - \frac{1}{\mathcal{R}_0}\right) N^\star$$

So finally

$$I^\star = \left(1 - \frac{1}{\mathcal{R}_0}\right) \frac{d+\nu}{d+\nu+\gamma} N^\star$$

The EEP

The **endemic equilibrium** (EEP) of (3) is

$$\boldsymbol{E}_\star := (S^\star, I^\star, R^\star) = \left(\frac{1}{\mathcal{R}_0}\ N^\star, \left(1-\frac{1}{\mathcal{R}_0}\right)\ \frac{d+\nu}{d+\nu+\gamma}\ N^\star, N^\star-(S^\star+I^\star)\right) \tag{10}$$

Remark that $\boldsymbol{E}_\star$ is **not biologically relevant** when $\mathcal{R}_0 \leq 1$

Theorem 1

Let the basic reproduction number be

$$\mathcal{R}_0 = \frac{\beta}{d+\gamma}\ N^\star \tag{9}$$

and consider the EP of (3)*: the DFE*

$$\boldsymbol{E}_0 = \left(\frac{b}{d}, 0, 0\right) \tag{6}$$

and the EEP

$$\boldsymbol{E}_\star = \left(\frac{1}{\mathcal{R}_0}\ N^\star, \left(1 - \frac{1}{\mathcal{R}_0}\right)\ \frac{d+\nu}{d+\nu+\gamma}\ N^\star, N^\star - (S^\star + I^\star)\right) \tag{10}$$

- *If* $\mathcal{R}_0 < 1$*, then* $\boldsymbol{E}_0$ *is LAS and* $\boldsymbol{E}_\star$ *is not biologically relevant*
- *If* $\mathcal{R}_0 > 1$*, then* $\boldsymbol{E}_0$ *is unstable and* $\boldsymbol{E}_\star$ *is biologically relevant*

As you can probably guess, if $\mathcal{R}_0 > 1$, then $\boldsymbol{E}_\star$ is not only biologically relevant but actually also LAS

Recall the Jacobian

$$J_{(S,I,R)} = \begin{pmatrix} -d-\beta I & -\beta S & \nu \\ \beta I & \beta S-(d+\gamma) & 0 \\ 0 & \gamma & -(d+\nu) \end{pmatrix} \tag{7}$$

$$= \begin{pmatrix} -\beta I & -\beta S & \nu \\ \beta I & \beta S-\gamma & 0 \\ 0 & \gamma & -\nu \end{pmatrix} - d\mathbb{I}$$

From this, we get that $-d$ is an eigenvalue of J

- there is a theorem that tells us that if $\lambda \in \sigma(M)$, then $\lambda + k \in \sigma(M + k\mathbb{I})$ ($\sigma(M)$ is the spectrum of M, the set of eigenvalues of M)
- the first matrix on the second line has all column sums zero so has a zero eigenvalue

We could continue and after some blood, sweat and tears, get that $J_{\boldsymbol{E}_\star}$ has its eigenvalues with negative real parts when $\boldsymbol{E}_\star$ is biologically relevant, i.e., when $\mathcal{R}_0 > 1$

With even more blood, sweat and tears, we can actually show that the result is *global*

We express that on the next slide

Theorem 2

Let the basic reproduction number be defined by (9) *and consider the DFE* (6) *and the EEP* (10)

- *If* $\mathcal{R}_0 < 1$, *then* $\boldsymbol{E}_0$ *is globally asymptotically stable (GAS) and* $\boldsymbol{E}_\star$ *is not biologically relevant*
- *If* $\mathcal{R}_0 > 1$, *then* $\boldsymbol{E}_0$ *is unstable and* $\boldsymbol{E}_\star$ *is GAS*

In other words

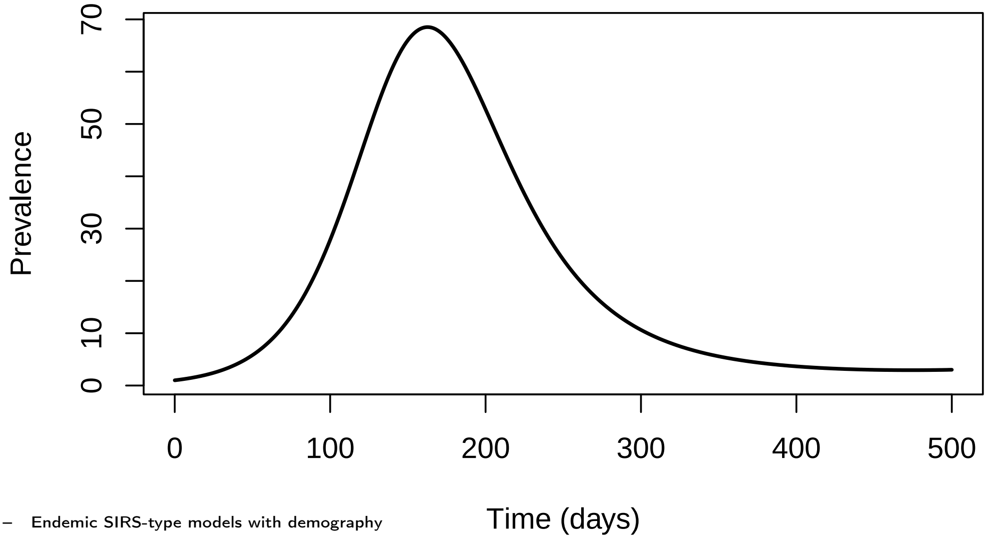
- when $\mathcal{R}_0 < 1$, then all solutions go to the DFE, the disease goes extinct
- when $\mathcal{R}_0 > 1$, then all solutions go to the EEP, the disease becomes endemic

Endemic SIRS-type models with demography

- The SIRS model(s)
- Mathematical analysis of the SIRS model
- **Some numerics with the SIRS model**
- Herd immunity in the SIRS model
- SLIRS model with constant population
- Computing $\mathcal{R}_0$ more efficiently
- A better vaccination model?

```r
library(deSolve)
rhs_SIRS <- function(t, x, p) {
  with(as.list(c(x, p)), {
    dS = b + nu * R - d * S - beta * S * I
    dI = beta * S * I - (d + gamma) * I
    dR = gamma * I - (d + nu) * R
    return(list(c(dS, dI, dR)))
  })
}
# Initial conditions
N0 = 1000
I0 = 1
R0 = 0
IC = c(S = N0-(I0+R0), I = I0, R = R0)
# "Known" parametres
d = 1/(80*365.25)
b = N0 * d
```

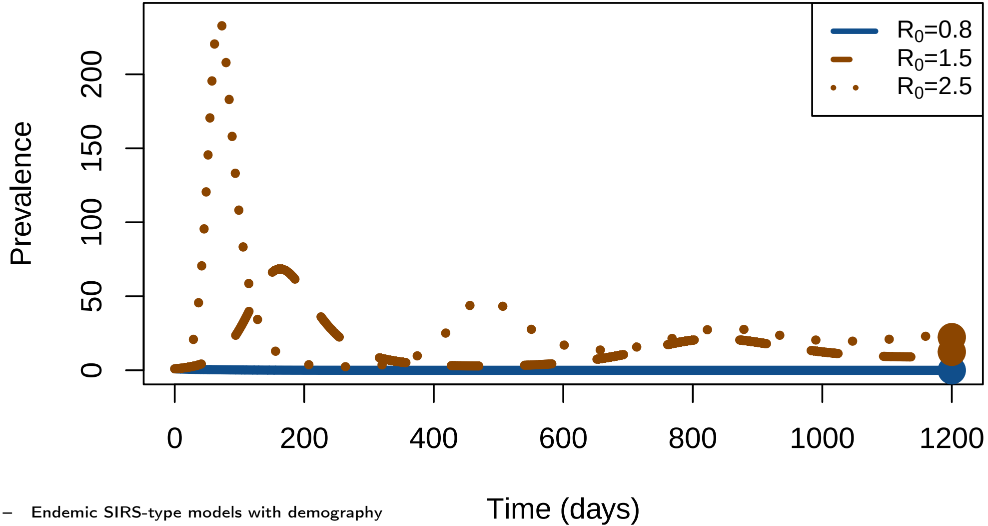
```r
gamma = 1/14
nu = 1/365.25
# Set beta s.t. R_0 = 1.5
R_0 = 1.5
beta = R_0 * (d + gamma) / (N0-I0-R0)
params = list(b = b, d = d, gamma = gamma, beta = beta, nu = nu)
times = seq(0, 500, 1)
# Call the numerical integrator
sol_SIRS <- ode(y = IC, times = times, func = rhs_SIRS,
                parms = params, method = "ode45")
# Plot the result
plot(sol_SIRS[,"time"], sol_SIRS[,"I"],
     type = "l", lwd = 2,
     xlab = "Time (days)", ylab = "Prevalence")
```


Prevalence
0
10
30
50
70
0
100
200
300
400
500
Time (days)

I just did ...

What I advise not to do: illustrate a mathematical result without adding anything to the result itself

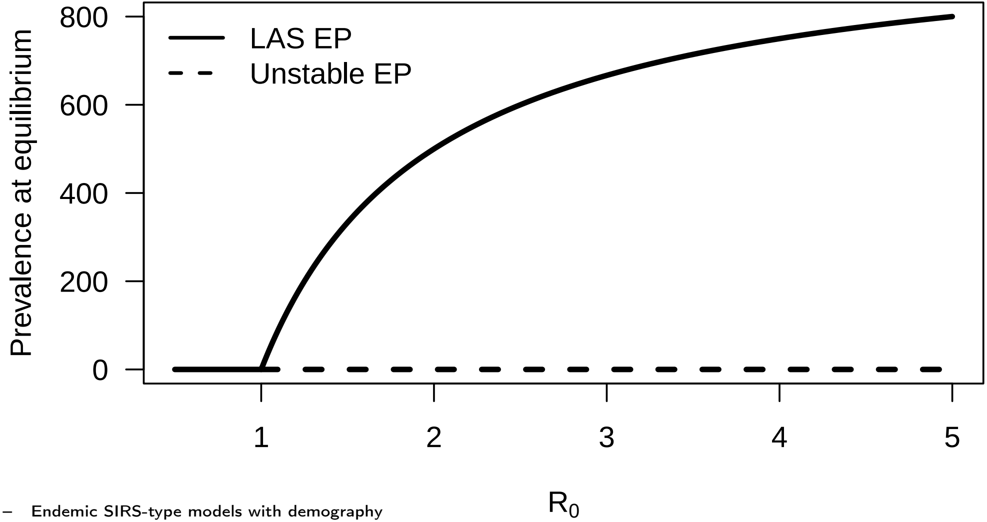
Let us make things a bit better. See the code


Prevalence
0
50
100
150
200
0
200
400
600
800
1000
1200
Time (days)
R0=0.8
R0=1.5
R0=2.5

We could continue, but with a model this simple, there is little more to do: the 3 parameters of the system are combined within $\mathcal{R}_0$ and the latter summarises the dynamics well

We are going to show something important: the bifurcation diagram

We saw that when $\mathcal{R}_0 < 1$, $I \to 0$, whereas when $\mathcal{R}_0 > 1$, $I \to (1 - 1/\mathcal{R}_0)N$. Let us represent this (code)


800
600
400
200
0
Prevalence at equilibrium
LAS EP
Unstable EP
1
2
3
4
5
R0

Endemic SIRS-type models with demography

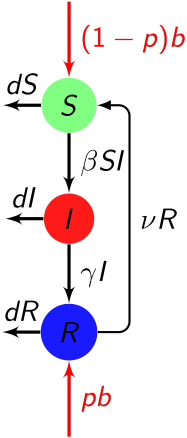
- The SIRS model(s)
- Mathematical analysis of the SIRS model
- Some numerics with the SIRS model
- **Herd immunity in the SIRS model**
- SLIRS model with constant population
- Computing $\mathcal{R}_0$ more efficiently
- A better vaccination model?

An SIRS model with vaccination

Take SIRS model (3) and assume the following

- Vaccination takes newborn individuals and moves them directly into the removed compartment, without them becoming infected/infectious
- A fraction p is vaccinated at birth

The model



$$S' = (1-p)b + \nu R - dS - \beta SI \tag{11a}$$
$$I' = \beta SI - (d+\gamma)I \tag{11b}$$
$$R' = bp + \gamma I - (d+\nu)R \tag{11c}$$

Consider the initial value problem consisting in (11) to which we adjoin initial conditions $S(0) = S_0 \geq 0$, $I(0) = I_0 \geq 0$ and $R(0) = R_0 \geq 0$

Typically, we assume $N_0 = S_0 + I_0 + R_0 > 0$ to avoid a trivial case

This modification doesn't change much

Equation (2) for the total population is unchanged

The Jacobian (7) at arbitrary point is also unchanged

The DFE is affected, though; as a consequence, so is the reproduction number

The DFE for the SIRS vaccination model

Considering (11) at equilibrium and substituting $I^\star = 0$ into this system gives

$$\begin{aligned} 0 &= (1-p)b + \nu R^\star - dS^\star \\ 0 &= bp - (d+\nu)R^\star \end{aligned}$$

which we rewrite as the linear system

$$\begin{pmatrix} d & -\nu \\ 0 & d+\nu \end{pmatrix} \begin{pmatrix} S^\star \\ R^\star \end{pmatrix} = \begin{pmatrix} (1-p)b \\ bp \end{pmatrix}$$

Thus

$$\begin{aligned} \begin{pmatrix} S^\star \\ R^\star \end{pmatrix} &= \frac{1}{d(d+\nu)} \begin{pmatrix} d+\nu & \nu \\ 0 & d \end{pmatrix} \begin{pmatrix} (1-p)b \\ pb \end{pmatrix} \\ &= \frac{1}{d(d+\nu)} \begin{pmatrix} (d+\nu)(1-p)b + pb\nu \\ pbd \end{pmatrix} \end{aligned}$$

As a consequence, the DFE takes the form

$$\boldsymbol{E}_0^v := (S^\star, I^\star, R^\star) = \left(\left(1 - p + \frac{p\nu}{d+\nu}\right) N^\star, 0, \frac{pd}{d+\nu} N^\star\right) \tag{12}$$

Substituting (12) into the eigenvalue that determines stability of the DFE, $\beta S^\star - (d+\gamma)$, we get

$$\begin{aligned} \beta S^\star - (d+\gamma) < 0 &\iff \frac{\beta}{d+\gamma} S^\star < 1 \\ &\iff \frac{\beta}{d+\gamma}\left(1 - p + \frac{p\nu}{d+\nu}\right) N^\star < 1 \end{aligned}$$

So we define

$$\mathcal{R}_0^v = \frac{\beta}{d+\gamma}\left(1 - p + \frac{p\nu}{d+\nu}\right) N^\star \tag{13}$$

Herd immunity

Therefore

- $\mathcal{R}_0^{\mathrm{v}} < \mathcal{R}_0$ if $p > 0$
- To control the disease, $\mathcal{R}_{\mathsf{v}}$ must take a value less than 1, i.e.,

$$\mathcal{R}_{\mathsf{v}} < 1 \iff p > 1 - \frac{1}{\mathcal{R}_0} \tag{14}$$

By vaccinating a fraction $p > 1 - 1/\mathcal{R}_0$ of newborns, we thus are in a situation where the disease is eventually eradicated

This is **herd immunity** (*bis repetita*)

Endemic SIRS-type models with demography

Incubation periods

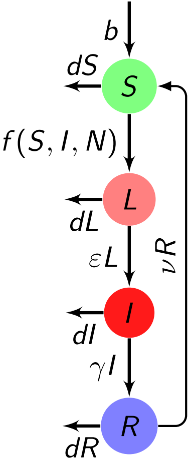
- SIS and SIR: progression from S to I is instantaneous
- Several incubation periods:

Disease	Incubation period
Yersinia Pestis	2-6 days
Ebola haemorrhagic fever (HF)	2-21 days
Marburg HF	5-10 days
Lassa fever	1-3 weeks
Tse-tse	weeks–months
HIV/AIDS	months–years

Hypotheses

- There is demography
- New individuals are born at a constant rate b
- There is no vertical transmssion: 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 (immune period)

SLIRS



The model is as follows:

$$S' = b + \nu R - dS - f(S, I, N) \tag{15a}$$
$$L' = f(S, I, N) - (d + \varepsilon)L \tag{15b}$$
$$I' = \varepsilon L - (d + \gamma)I \tag{15c}$$
$$R' = \gamma I - (d + \nu)R \tag{15d}$$

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

Endemic SIRS-type models with demography

ELSEVIER

Mathematical Biosciences 180 (2002) 29–48

Mathematical Biosciences

www.elsevier.com/locate/mbs

Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission

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Dedicated to the memory of John Jacquez

The basic reproduction number $\mathcal{R}_0$

Used frequently in epidemiology (not only math epi)

Definition 3 (R_0)

The basic reproduction number $\mathcal{R}_0$ is the average number of secondary cases generated by the introduction of an infectious individual in a wholly susceptible population

- If $\mathcal{R}_0 < 1$, then on average, each infectious individual infects less than one other person, so the epidemic has chances of dying out
- If $\mathcal{R}_0 > 1$, 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 $\mathcal{R}_0$

Preliminary setup of PvdD & Watmough 2002

$x = (x_1, \ldots, x_n)^T$, $x_i \geq 0$, with the first $m < n$ compartments the infected ones

X_s the set of all disease free states:

$$X_s = \{x \geq 0 | x_i = 0, i = 1, \ldots, m\}$$

Distinguish new infections from all other changes in population

- $F_i(x)$ rate of appearance of new infections in compartment i
- $V_i^+(x)$ rate of transfer of individuals into compartment i by all other means
- $V_i^-(x)$ rate of transfer of individuals out of compartment i

Assume each function continuously differentiable at least twice in each variable

$$x_i' = f_i(x) = F_i(x) - V_i(x), \quad i = 1, \ldots, n$$

where $V_i = V_i^- - V_i^+$

Some assumptions

- **(A1)** If $x \geq 0$, then $F_i, V_i^+, V_i^- \geq 0$ for $i = 1, \ldots, n$

Since each function represents a directed transfer of individuals, all are non-negative

- **(A2)** If $x_i = 0$ then $V_i^- = 0$. In particular, if $x \in X_s$, then $V_i^- = 0$ for $i = 1, \ldots, m$

If a compartment is empty, there can be no transfer of individuals out of the compartment by death, infection, nor any other means

- **(A3)** $F_i = 0$ if $i > m$

The incidence of infection for uninfected compartments is zero

- **A4** If $x \in X_s$ then $F_i(x) = 0$ and $V_i^+(x) = 0$ for $i = 1, \ldots, m$

Assume that if the population is free of disease then the population will remain free of disease; i.e., there is no (density independent) immigration of infectives

One last assumption for the road

Let x_0 be a DFE of the system, i.e., a (locally asymptotically) stable equilibrium solution of the disease free model, i.e., the system restricted to X_s. We need not assume that the model has a unique DFE

Let $Df(x_0)$ be the Jacobian matrix $[\partial f_i/\partial x_j]$. Some derivatives are one sided, since x_0 is on the domain boundary

(A5) If $F(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts

Note: if the method ever fails to work, it is usually with (A5) that lies the problem

Stability of the DFE as function of $\mathcal{R}_0$

Theorem 4

Suppose the DFE exists. Let then

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

with matrices F and V obtained as indicated. Assume conditions (A1) through (A5) hold. Then

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

Important to stress *local* nature of stability that is deduced from this result. We will see later that even when $\mathcal{R}_0 < 1$, there can be several positive equilibria

Direction of the bifurcation at $\mathcal{R}_0 = 1$

μ bifurcation parameter s.t. $\mathcal{R}_0 < 1$ for $\mu < 0$ and $\mathcal{R}_0 > 1$ for $\mu > 0$ and x_0 DFE for all values of μ and consider the system

$$x' = f(x, \mu) \tag{16}$$

Write

$$D_x f(x_0, 0) = D(\mathcal{F}(x_0) - \mathcal{V}(x_0))|_{\mathcal{R}_0=1}$$

as block matrix

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

Write $[\alpha_{\ell k}]$, $\ell = m+1, \dots, n$, $k = 1, \dots, m$ the $(\ell - m, k)$ entry of $-J_4^{-1} J_3$ and let v and w be left and right eigenvectors of $D_x f(x_0, 0)$ s.t. $vw = 1$

Let

$$a = \sum_{i,j,k=1}^{m} v_i w_j w_k \left(\frac{1}{2} \frac{\partial^2 f_i}{\partial x_j \partial x_k}(x_0, 0) + \sum_{\ell=m+1}^{n} \alpha_{\ell k} \frac{\partial^2 f_i}{\partial x_j \partial x_\ell}(x_0, 0) \right) \tag{17}$$

$$b = v D_{x\mu} f(x_0, 0) w = \sum_{i,j=1}^{n} v_i w_j \frac{\partial^2 f_i}{\partial x_j \partial \mu}(x_0, 0) \tag{18}$$

Theorem 5

Consider model (16) with $f(x, \mu)$ satisfying conditions (A1)–(A5) and μ as described above

Assume that the zero eigenvalue of $D_x f(x_0, 0)$ is simple

Define a and b by (17) and (18); assume that $b \neq 0$. Then $\exists \delta > 0$ s.t.

- *if $a < 0$, then there are LAS endemic equilibria near x_0 for $0 < \mu < \delta$*
- *if $a > 0$, then there are unstable endemic equilibria near x_0 for $-\delta < \mu < 0$*

Example of the SLIRS model (15)

Variation of the infected variables in (15) are described by

$$
\begin{aligned}
L' &= f(S, I, N) - (\varepsilon + d)L \\
I' &= \varepsilon L - (d + \gamma)I
\end{aligned}
$$

Write

$$
\mathcal{I}' = \begin{pmatrix} L \\ I \end{pmatrix}' = \begin{pmatrix} f(S, I, N) \\ 0 \end{pmatrix} - \begin{pmatrix} (\varepsilon + d)L \\ (d + \gamma)I - \varepsilon L \end{pmatrix} =: \mathcal{F} - \mathcal{V} \tag{19}
$$

Denote

$$f_L^\star := \frac{\partial}{\partial L} f\bigg|_{(S,I,R)=\boldsymbol{E}_0} \qquad f_I^\star := \frac{\partial}{\partial I} f\bigg|_{(S,I,R)=\boldsymbol{E}_0}$$

the values of the partials of the incidence function at the DFE $\boldsymbol{E}_0$

Compute the Jacobian matrices of vectors $\mathcal{F}$ and $\mathcal{V}$ at the DFE $\boldsymbol{E}_0$

$$F = \begin{pmatrix} f_L^\star & f_I^\star \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \varepsilon + d & 0 \\ -\varepsilon & d + \gamma \end{pmatrix} \tag{20}$$

Thus

$$V^{-1} = \frac{1}{(d+\varepsilon)(d+\gamma)} \begin{pmatrix} d+\gamma & 0 \\ \varepsilon & d+\varepsilon \end{pmatrix}$$

Also, in the case N is constant, $\partial f/\partial L = 0$ and thus

$$FV^{-1} = \frac{f_I^\star}{(d+\varepsilon)(d+\gamma)} \begin{pmatrix} \varepsilon & d+\varepsilon \\ 0 & 0 \end{pmatrix}$$

As a consequence,

$$\mathcal{R}_0 = \varepsilon \frac{f_I^\star}{(d+\varepsilon)(d+\gamma)}$$

Theorem 6

Let

$$\mathcal{R}_0 = \frac{\varepsilon f_I^\star}{(d+\varepsilon)(d+\gamma)} \tag{21}$$

Then

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

It is important here to stress that the result we obtain concerns the **local** asymptotic stability. We see later that even when $\mathcal{R}_0 < 1$, there can be several locally asymptotically stable equilibria

Application

The DFE is

$$(\bar{S}, \bar{L}, \bar{I}, \bar{R}) = (N, 0, 0, 0)$$

- Mass action incidence (frequency-dependent contacts):

$$f_I^\star = \beta \bar{S} \Rightarrow \mathcal{R}_0 = \frac{\epsilon \beta N}{(\epsilon + d)(\gamma + d)}$$

- Standard incidence (proportion-dependent contacts):

$$f_I^\star = \frac{\beta \bar{S}}{N} \Rightarrow \mathcal{R}_0 = \frac{\epsilon \beta}{(\epsilon + d)(\gamma + d)}$$

Links between SLIRS-type models

$$
\begin{aligned}
S' &= b + \nu R - dS - f(S, I, N) \\
L' &= f(S, I, N) - (d + \varepsilon)L \\
I' &= \varepsilon L - (d + \gamma)I \\
R' &= \gamma I - (d + \nu)R
\end{aligned}
$$

SLIR	SLIRS where $\nu = 0$
SLIS	Limit of SLIRS when $\nu \to \infty$
SLI	SLIR where $\gamma = 0$
SIRS	Limit of SLIRS when $\varepsilon \to \infty$
SIR	SIRS where $\nu = 0$
SIS	Limit of SIRS when $\nu \to \infty$
	Limit SLIS when $\varepsilon \to \infty$
SI	SIS where $\nu = 0$

Values of $\mathcal{R}_0$

$(\bar{S}, \bar{I}, \bar{N})$ values of S, I and N at DFE. Denote $\bar{f}_I = \partial f / \partial I(\bar{S}, \bar{I}, \bar{N})$.

SLIRS	$\frac{\varepsilon \bar{f}_I}{(d+\varepsilon)(d+\gamma)}$
SLIR	$\frac{\varepsilon \bar{f}_I}{(d+\varepsilon)(d+\gamma)}$
SLIS	$\frac{\varepsilon \bar{f}_I}{(d+\varepsilon)(d+\gamma)}$
SLI	$\frac{\varepsilon \bar{f}_I}{(d+\varepsilon)(d+\gamma)}$
SIRS	$\frac{\varepsilon \bar{f}_I}{d+\gamma}$
SIR	$\frac{\bar{f}_I}{d+\gamma}$
SIS	$\frac{\bar{f}_I}{d+\gamma}$
SI	$\frac{\bar{f}_I}{d+\gamma}$

Endemic SIRS-type models with demography

- The SIRS model(s)
- Mathematical analysis of the SIRS model
- Some numerics with the SIRS model
- Herd immunity in the SIRS model
- SLIRS model with constant population
- Computing $\mathcal{R}_0$ more efficiently
- **A better vaccination model?**

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GLOBAL RESULTS FOR AN EPIDEMIC MODEL WITH VACCINATION THAT EXHIBITS BACKWARD BIFURCATION*

JULIEN ARINO†, C. CONNELL MCCLUSKEY†, AND P. VAN DEN DRIESSCHE†

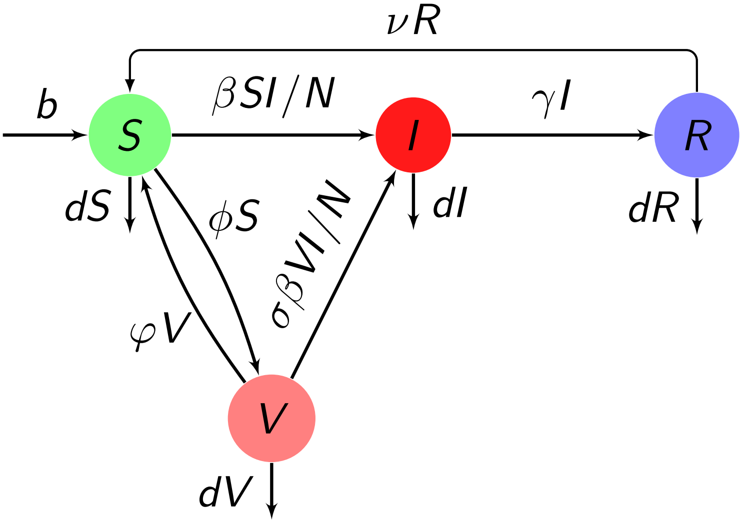
Abstract. Vaccination of both newborns and susceptibles is included in a transmission model for a disease that confers immunity. The interplay of the vaccination strategy together with the vaccine efficacy and waning is studied. In particular, it is shown that a backward bifurcation leading to bistability can occur. Under mild parameter constraints, compound matrices are used to show that each orbit limits to an equilibrium. In the case of bistability, this global result requires a novel approach since there is no compact absorbing set.

Key words. epidemic model, vaccination, backward bifurcation, compound matrices, global dynamics

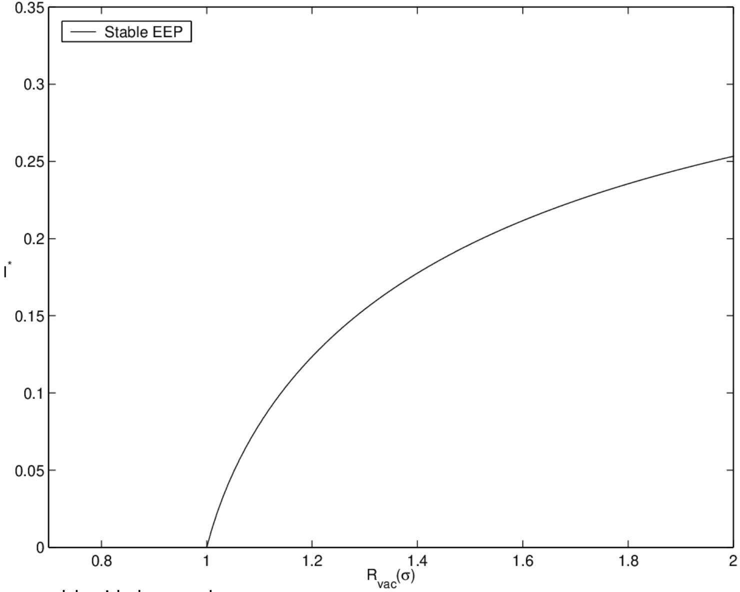
AMS subject classifications. 92D30, 34D23

DOI. 10.1137/S0036139902413829

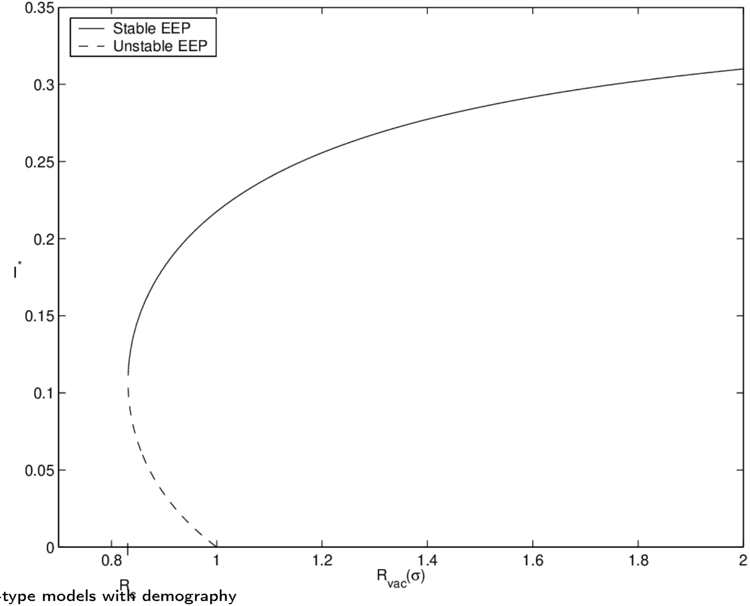
SLIRS with vaccination

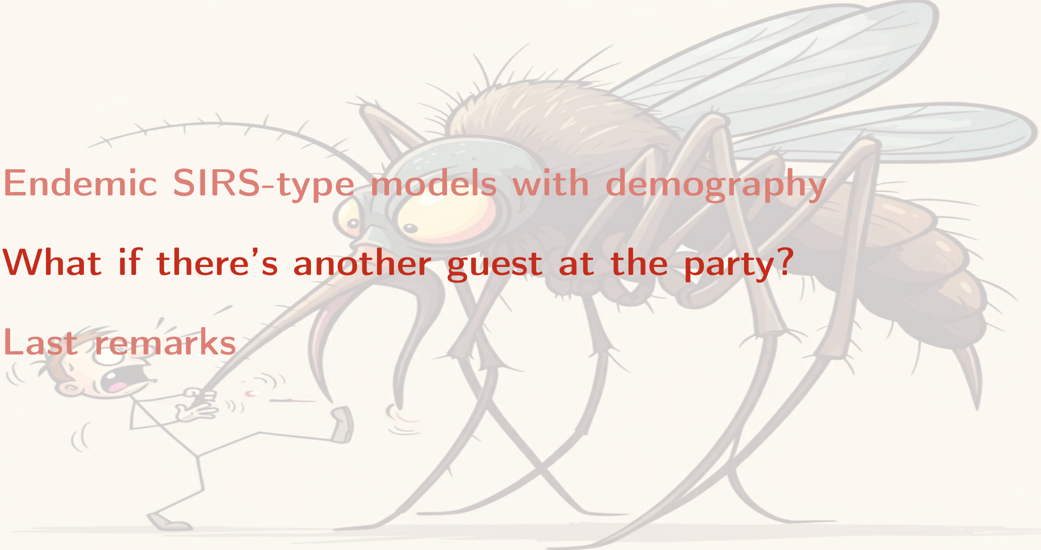


The usual situation



What can happen with vaccination – Backward bifurcation





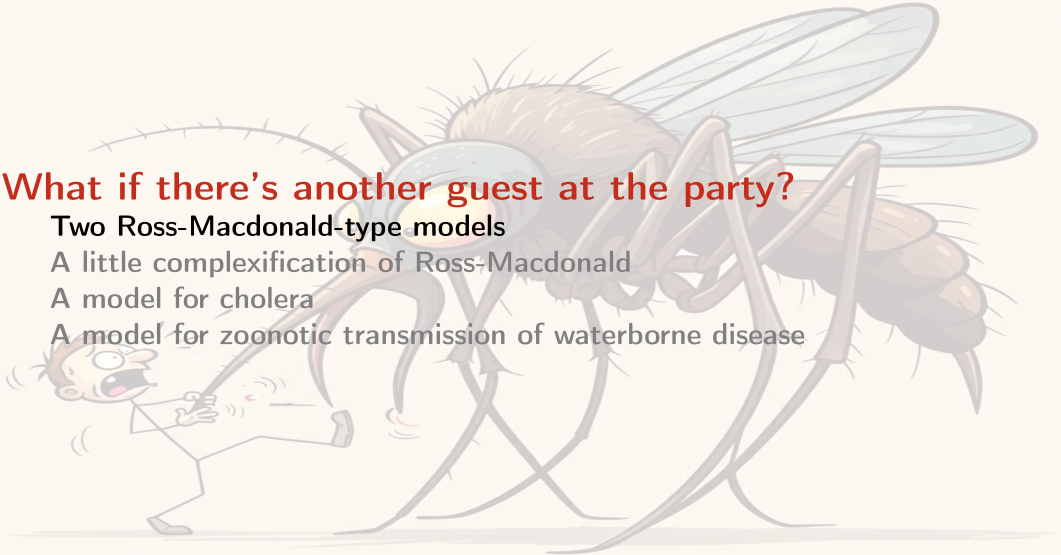
Endemic SIRS-type models with demography

What if there's another guest at the party?

Last remarks

What if there's another guest at the party?

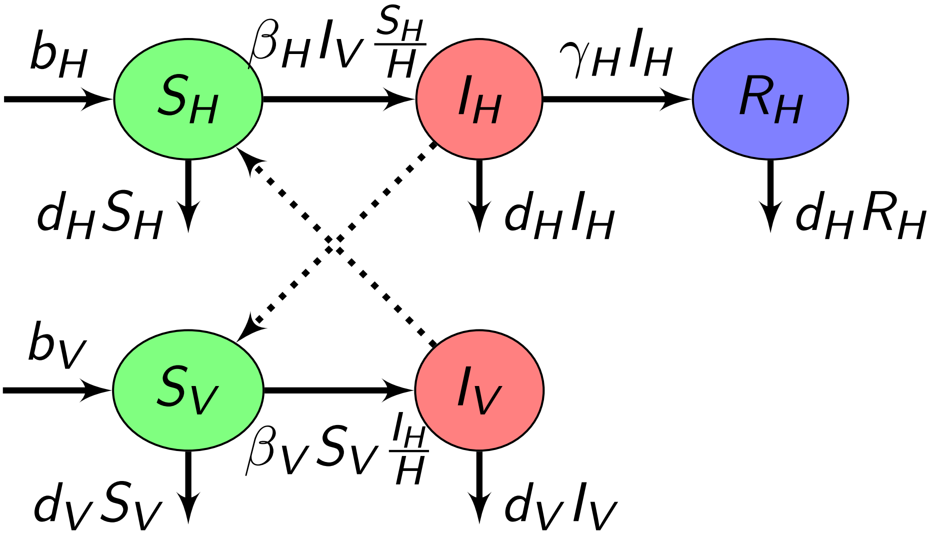
- **Two Ross-Macdonald-type models**
- A little complexification of Ross-Macdonald
- A model for cholera
- A model for zoonotic transmission of waterborne disease



See, e.g., Simoy & Aparicio, Ross-Macdonald models: Which one should we use?, *Acta Tropica* (2020)

Ross introduced the model in 1911. Later "tweaked" by Macdonald to include mosquito latency period

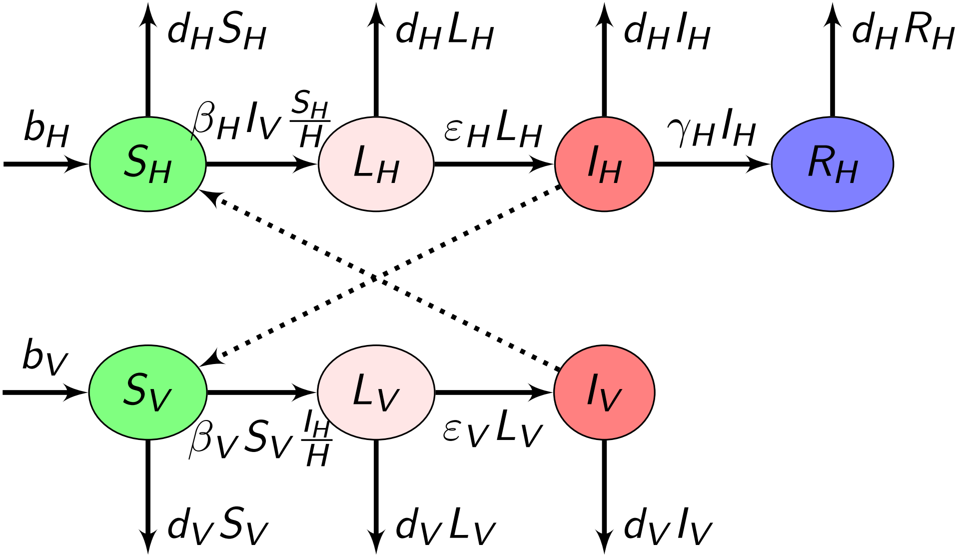
Here, I show a version in the paper cited, with some notation changed


b_H
S_H
$\beta_H I_V \frac{S_H}{H}$
I_H
$\gamma_H I_H$
R_H
$d_H S_H$
$d_H I_H$
$d_H R_H$
b_V
S_V
I_V
$\beta_V S_V \frac{I_H}{H}$
$d_V S_V$
$d_V I_V$

Reproduction number

$$\mathcal{R}_0 = \frac{\beta_H \beta_V}{(\gamma_H + \gamma_V) d_V} \; \frac{V^\star}{H^\star} \tag{22}$$

where $H^\star$ and $V^\star$ are the total host and vector populations, respectively


$d_H S_H$
$d_H L_H$
$d_H I_H$
$d_H R_H$
b_H
$\beta_H I_V \frac{S_H}{H}$
$\varepsilon_H L_H$
$\gamma_H I_H$
S_H
L_H
I_H
R_H
b_V
S_V
L_V
I_V
$\beta_V S_V \frac{I_H}{H}$
$\varepsilon_V L_V$
$d_V S_V$
$d_V L_V$
$d_V I_V$

Reproduction number

$$\mathcal{R}_0 = \frac{\beta_H \beta_V}{(\gamma_H + \gamma_V) d_V} \frac{\varepsilon_V}{d_V + \varepsilon_V} \frac{\varepsilon_H}{d_H + \varepsilon_H} \frac{V^\star}{H^\star} \tag{23}$$

where $H^\star$ and $V^\star$ are the total host and vector populations, respectively

Here

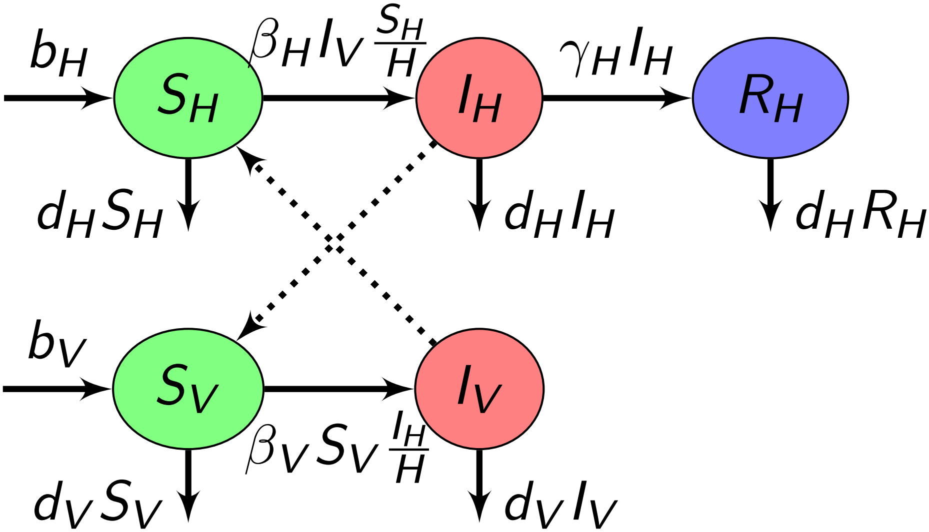
$$f_X = \frac{\varepsilon_X}{d_X + \varepsilon_X}$$

are the fractions of latent individuals (of type $X = \{V, H\}$) who survive the latency period

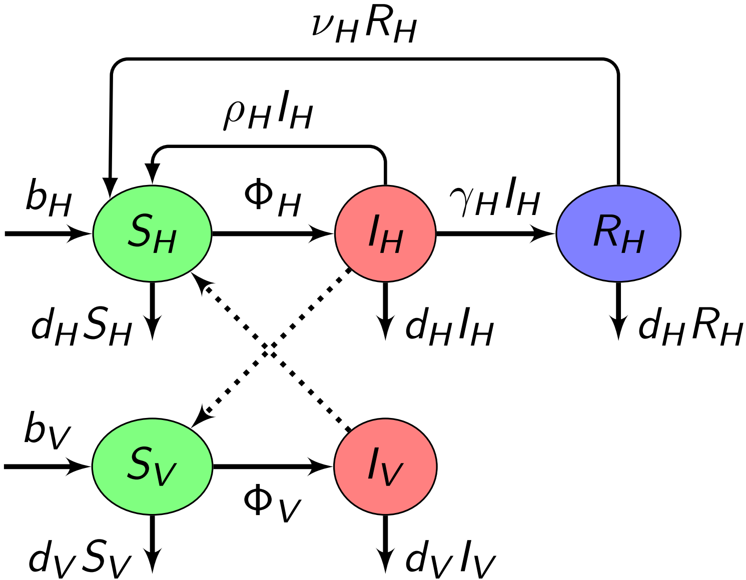
What if there's another guest at the party?

- Two Ross-Macdonald-type models
- **A little complexification of Ross-Macdonald**
- A model for cholera
- A model for zoonotic transmission of waterborne disease

Recall this guy?



Let us add a few arrows



Arino, Ducrot & Zongo, A metapopulation model for malaria with transmission-blocking partial immunity in hosts, Journal of Mathematical Biology (2012)

Incidence functions take the form

$$\Phi_H = b_H(H,V)\sigma_{VH}\frac{I_V}{V}$$

and

$$\Phi_V = b_V(H,V)\left(\sigma_{HV}\frac{I_H}{H} + \hat{\sigma}_{HV}\frac{R_H}{H}\right)$$

where b_H and b_V are numbers per unit time of mosquito bites a human has and the number of humans a mosquito bites, respectively

Parameters of the incidence function

- σ_{HV} probability of transmission of the parasite (in gametocyte form) from an infectious human to a susceptible mosquito
- $\hat{\sigma}_{HV}$ probability of transmission of the parasite (in gametocyte form) from a semi-immune human to a susceptible mosquito
- σ_{VH} probability of transmission of the parasite (in sporozoite form) from an infectious mosquito to a susceptible human

Additional parameter that can be factored in (all per unit time)

- a_H maximum number of mosquito bites a human can receive
- a_V number of times one mosquito would "want to" bite humans
- a average number of bites given to humans by each mosquito

People to read for malaria models (IMOBO)

See also the work of

- Gideon Ngwa at the University of Buea
- Nakul Chitnis at the Swiss Tropical and Public Health Institute

Many others...

More complex models may be needed for malaria

Timing of processes is critical in malaria

Plasmodium life cycle in the mosquito is commensurate with mosquito lifetime

Need models that are able to account for that, because ODEs are not really good at this (see beginning of Stochastic systems lecture)

Mathematics becomes more complicated

What if there's another guest at the party?

- Two Ross-Macdonald-type models
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- A model for cholera
- A model for zoonotic transmission of waterborne disease

Research article

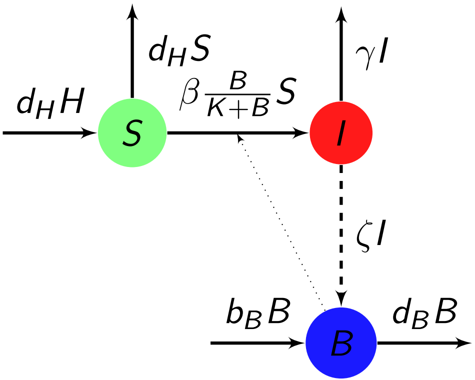
Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir

Cláudia Torres Codeço*

Address: Programa de Computação Científica Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

E-mail: Cláudia Torres Codeço* - codeco@malaria.procc.fiocruz.br
*Corresponding author

Codeço's model



$$S' = d_H(H - S) - \beta \frac{B}{K+B} S \tag{24a}$$

$$I' = \beta \frac{B}{K+B} S - \gamma I \tag{24b}$$

$$B' = (b_B - d_B)B + \zeta I \tag{24c}$$

K concentration of cholera in water giving 50% chance of catching it

Note that the dashed arrow from I to B is not a flow: individuals do not convert into *vibrio cholerae*

What if there's another guest at the party?

- Two Ross-Macdonald-type models
- A little complexification of Ross-Macdonald
- A model for cholera
- **A model for zoonotic transmission of waterborne disease**

Bull Math Biol (2016) 78:169–183
DOI 10.1007/s11538-015-0136-y

ORIGINAL ARTICLE

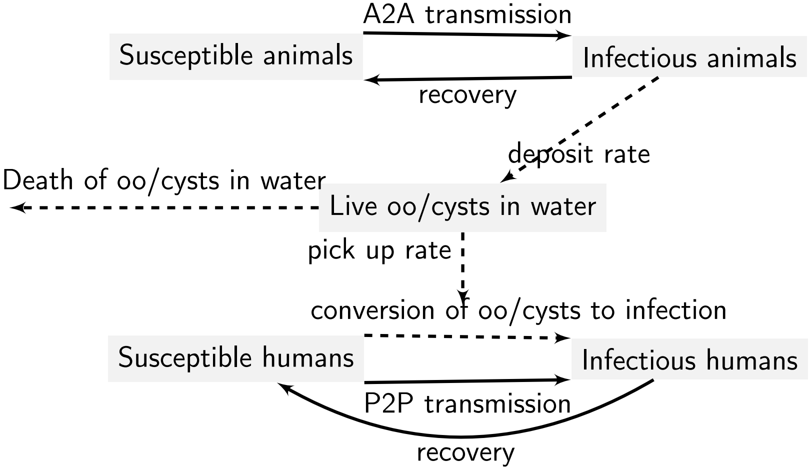
Zoonotic Transmission of Waterborne Disease: A Mathematical Model

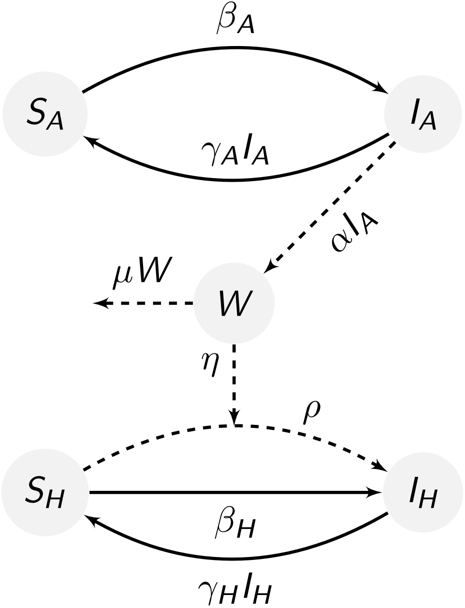
Edward K. Waters[1] · Andrew J. Hamilton[2] · Harvinder S. Sidhu[3] · Leesa A. Sidhu[3] · Michelle Dunbar[4]

Zoonotic transmission of waterborne disease

Zoonoses are animal diseases that are transmitted to humans

Model here used for instance to model Giardia transmission from possums to humans


A2A transmission
Susceptible animals
Infectious animals
recovery
deposit rate
Death of oo/cysts in water
Live oo/cysts in water
pick up rate
conversion of oo/cysts to infection
Susceptible humans
Infectious humans
P2P transmission
recovery


β_A
S_A
I_A
$\gamma_A I_A$
αI_A
μW
W
η
ρ
S_H
I_H
β_H
$\gamma_H I_H$

The full model

$$
\begin{aligned}
{S_A}' &= -\beta_A S_A I_A + \gamma_A I_A && (25a)\\
{I_A}' &= \beta_A S_A I_A - \gamma_A I_A && (25b)\\
W' &= \alpha I_A - \eta W(S_H + I_H) - \mu W && (25c)\\
{S_H}' &= -\rho\eta W S_H - \beta_H S_H I_H + \gamma_H I_H && (25d)\\
{I_H}' &= \rho\eta W S_H + \beta_H S_H I_H - \gamma_H I_H && (25e)
\end{aligned}
$$

Considered with $N_A = S_A + I_A$ and $N_H = S_H + I_H$ constant

Simplified model

Because N_A and N_H are constant, (25) can be simplified:

$$
\begin{aligned}
{I_A}' &= \beta_A N_A I_A - \gamma_A I_A - \beta_A I_A^2 && \text{(26a)}\\
W' &= \alpha I_A - \eta W N_H - \mu W && \text{(26b)}\\
{I_H}' &= \rho\eta W(N_H - I_H) + \beta_H N_H I_H - \gamma_H I_H - \beta_H I_H^2 && \text{(26c)}
\end{aligned}
$$

Three EP: DFE $(0,0,0)$; endemic disease in humans because of H2H transmission; endemic in both H and A because of W

Three EP: DFE $(0,0,0)$; endemic disease in humans because of H2H transmission; endemic in both H and A because of W

Let

$$\mathcal{R}_{0A} = \frac{\beta_A}{\gamma_A} N_A \quad \text{and} \quad \mathcal{R}_{0H} = \frac{\beta_H}{\gamma_H} N_H \tag{27}$$

- DFE LAS if $\mathcal{R}_{0A} < 1$ and $\mathcal{R}_{0H} < 1$, unstable if $\mathcal{R}_{0A} > 1$ or $\mathcal{R}_{0H} > 1$
- If $\mathcal{R}_{0H} > 1$ and $\mathcal{R}_{0A} < 1$, (26) goes to EP with endemicity only in humans
- Endemic EP with both A and H requires $\mathcal{R}_{0A} > 1$ and $\mathcal{R}_{0H} < 1$

Note that proof is **not** global

Endemic SIRS-type models with demography

What if there's another guest at the party?

Last remarks

To simplify or not to simplify?

- In the KMK epidemic model (**??**) and the SIRS endemic model (3), since the total population is constant or asymptotically constant, it is possible to omit one of the state variables since $N^\star = S + I + R$
- We often use $R = N^\star - S - I$
- This can greatly simplify some computations
- Whether to do it or not is a matter of preference

To normalise or not to normalise?

- In the KMK epidemic model (??) and the SIRS endemic model (3), since the total population is constant or asymptotically constant, it is possible to normalise to $N = 1$
- This can greatly simplify some computations
- However, I am not a big fan: it is important to always have the "sizes" of objects in mind
- If you do normalise, at least for a paper destined to mathematical biology, always do a "return to biology", i.e., interpret your results in a biological light, which often implies to return to original values

Where we are

- An *epidemic* SIR model (the KMK SIR) in which the presence or absence of an epidemic wave is characterised by the value of $\mathcal{R}_0$
- The KMK SIR has explicit solutions (in some sense). **This is an exception!**
- An *endemic* SIRS model in which the threshold $\mathcal{R}_0 = 1$ is such that, when $\mathcal{R}_0 < 1$, the disease goes extinct, whereas when $\mathcal{R}_0 > 1$, the disease becomes established in the population
- Some simple variations on these models
- A few models for vector-borne or water-borne diseases

Global properties of the SLIRS model

SLIRS - Mukherjee, Chattopadhyay Tapaswi

SLIRS (SEIRS) with constant birth d, per capita death d and incidence function

$$f(S,I,N) = \beta S^q I^p$$

They establish uniform boundedness, then define

$$V(S,E,I) = \frac{1}{2}\left((S-S^\star)^2 + (E-E^\star)^2 + (I-I^\star)^2\right)$$

Mukherjee, Chattopadhyay Tapaswi, Math. Comput. Modelling 18 (1993)

Matrix A and theorem

Defining

$$A = \begin{pmatrix} \beta I^{*p} g(S) + d + \nu & \frac{1}{2}(\nu - \beta I^{*p} g(S)) & \frac{1}{2}(\beta S^q h(I) + \nu) \\ \frac{1}{2}(\nu - \beta I^{*p} g(S)) & \varepsilon + d & -\frac{1}{2}(\beta S^q h(I) + \varepsilon) \\ \frac{1}{2}(\beta S^q h(I) + \nu) & -\frac{1}{2}(\beta S^q h(I) + \varepsilon) & \gamma + d \end{pmatrix}$$

with functions g and h such that

$$S^q - S^{*q} = (S - S^\star) g(S), \quad I^p - I^{*p} = (I - I^\star) h(I)$$

Theorem: The function V is such that $V' < 0$ if

- $4(\beta I^{*p} g(S) + d + \nu)(\varepsilon + d) > (\nu - \beta I^{*p} g(S))^2$
- $\det A > 0$

Clearly, hard to check in practice, so the system is studied in other ways.

Li Muldowney (1995)

Li Muldowney (1995)

$$
\begin{aligned}
S' &= d - \beta S^q I^p - dS \\
L' &= \beta S^q I^p - (\varepsilon + d)L \\
I' &= \varepsilon L - (\gamma + d)I \\
R' &= \gamma I - dR
\end{aligned}
$$

Li, Muldowney PvdD - CAMQ (1999)

SLIRS (SEIRS) with incidence

$$f(S, I, N) = \beta g(I) S$$

where g such that $g(0) = 0$, $g(I) > 0$ for $I \in (0, 1]$ and $g \in C^1(0, 1]$. Normalize total population to $S + E + I + R = 1$. Additional assumption on g:

(H) $c = \lim_{I \to 0^+} \frac{g(I)}{I} \leq +\infty$; when $0 < c < +\infty$, $g(I) \leq cI$ for small I

Basic reproduction number

We have

$$\frac{\partial \overline{f}}{\partial I} = \beta \frac{\partial \overline{g}}{\partial I}$$

Since $\dfrac{\partial \overline{g}}{\partial I} = \lim_{I \to 0^+} \dfrac{g(I)}{I} = c$,

$$\mathcal{R}_0 = \frac{c\beta\varepsilon}{(d+\varepsilon)(d+\gamma)}$$

Uniform persistence theorem

Theorem: If $g(I)$ satisfies (H), then the system with incidence $f(S,I,N) = \beta S^q I^p$ is uniformly persistent $\iff \mathcal{R}_0 > 1$.

The system is **uniformly persistent** if there exists $0 < \epsilon_0 < 1$ such that any solution $(S(t), E(t), I(t), R(t))$ of SEIRS with initial conditions $(S(0), E(0), I(0), R(0)) \in \overset{\circ}{\Gamma}$ satisfies

$$\liminf_{t\to\infty} S(t) \geq \epsilon_0, \quad \liminf_{t\to\infty} E(t) \geq \epsilon_0$$
$$\liminf_{t\to\infty} I(t) \geq \epsilon_0, \quad \liminf_{t\to\infty} R(t) \geq \epsilon_0$$

No closed orbits theorem

Theorem: Suppose the incidence $f(S, I, N) = \beta S^q I^p$ satisfies (H) and

$$|g'(I)|I \leq g(I) \text{ for } I \in (0, 1]$$

Suppose additionally that $\mathcal{R}_0 > 1$ and one of the conditions

is satisfied, where

$$\eta_0 = \min_{I \in [\epsilon_0, 1]} g(I) > 0$$

and ϵ_0 is as previously defined. Then there is no rectifiable closed curve invariant under the SEIRS flow. Moreover, every semi-trajectory in Γ converges to an equilibrium.
The proof uses compound matrices (see later).

Lyapunov function for SLIR and SLIS

Andrei Korobeinikov considers an SLIR with normalized constant population 1 and vertical transmission:

$$
\begin{aligned}
S' &= d - \beta SI - pdI - qdL - dS \\
L' &= \beta SI + pdI - (\varepsilon + d - qd)L \\
I' &= \varepsilon L - (\gamma + d)I
\end{aligned}
$$

- p proportion of newborns from I who are I at birth
- q proportion of newborns from L who are L at birth
- R does not influence the system dynamics, so is not shown

Equilibria

- DFE: $E_0 = (1, 0, 0)$ - EE: $E^\star = (S^\star, L^\star, I^\star)$ with

$$S^\star = \frac{1}{\mathcal{R}_0^v} \quad L^\star = \frac{d}{\varepsilon + d}\left(1 - \frac{1}{\mathcal{R}_0^v}\right)$$

$\mathrm{I}^\star = \frac{d\varepsilon}{(\varepsilon+d)(\gamma+d)}\left(1 - \frac{1}{\mathcal{R}_0^v}\right) where \mathcal{R}_0^v = \frac{\beta\varepsilon}{(\gamma+d)(\varepsilon+d)-qd(\varepsilon+d)-pd\varepsilon} is the basic reproduction number with vertical transmission. We have \mathrm{R}_0 =$
$\mathcal{R}_0^v$ iff $p = q = 0$. Also, $\mathcal{R}_0^v = 1$ when $\mathcal{R}_0 = 1$.
$E^\star$ is biologically valid only when $\mathcal{R}_0^v > 1$.

Lyapunov function

We use the function
$$V = \sum a_i(x_i - x_i^\star \ln x_i)$$

Theorem:

- If $\mathcal{R}_0 > 1$, then (**??**)-(**??**) has the GAS equilibrium $E^\star$
- If $\mathcal{R}_0 \leq 1$, then (**??**)-(**??**) has the DFE E_0 GAS and $E^\star$ is not biologically valid

Compound matrices

The compound matrix method

- Extension of Dulac's criterion to higher-dimensional systems - Useful to rule out periodic orbits - Was very popular for a while, but main limitation: - Becomes difficult to use when system dimension ≥ 4

Fiedler reference

See Fiedler Special Matrices and Their Applications in Numerical Mathematics (2013) for details. Let $A = (a_{ij})$, $i = 1, \ldots, m$, $j = 1, \ldots, n$ an $m \times n$ matrix and k an integer, $1 \leq k \leq \min(m, n)$. Let $M = \{1, \ldots, m\}$ and $N = \{1, \ldots, n\}$, $M^{(k)}$ and $N^{(k)}$ the sets of k-tuples of elements of M and N ordered lexicographically, respectively.

k-th compound matrix

The k-th compound matrix $A^{(k)}$ of A is the $C(m,k) \times C(n,k)$ matrix, with rows indexed by elements of $M^{(k)}$ and columns by elements of $N^{(k)}$, such that the element $A^{(k)}(I,J)$, $I \in M^{(k)}$, $J \in N^{(k)}$ is the determinant $\det A(I,J)$. $A(I,J)$ is the submatrix of A consisting of rows in I and columns in J. Another interpretation of $A^{(k)}$ is as the k-th exterior product of A.

Additive compound matrix

Suppose A is an $n \times n$ matrix. The matrix $(I + tA)^{(k)}$ is a $C(n,k) \times C(n,k)$ matrix whose elements are polynomials in t of degree at most k. Grouping monomials of the same degree in t:

$$(I + tA)^{(k)} = A^{(k,0)} + tA^{(k,1)} + \cdots + t^k A^{(k,k)}$$

where the matrices $A^{(k,s)}$ do not depend on t. The matrix $A^{(k,1)}$ is the k-th **additive compound matrix** of A and is denoted $A^{[k]}$. It satisfies

$$A^{[k]} = \lim_{h \to 0} \left(\frac{1}{h} \left((I + hA)^{(k)} - I^{(k)} \right) \right)$$

This can also be written as

$$A^{[k]} = D_+ (I + hA)^{(k)} |_{h=0}$$

where D_+ is the right derivative.

Theorem for additive compound matrix

Theorem: Suppose $A = (a_{pq})$. Then, for $I, J \in N^{(k)}$

$$A^{[k]}(I,J) = \begin{cases} \sum_{p \in I} a_{pp} & \text{if } J = I \\ 0 & \text{if } |I \cap J| \leq k-2 \\ (-1)^{\sigma} a_{pq} & \text{if } |I \cap J| = k-1 \end{cases}$$

where p is the element of $I \setminus (I \cap J)$, q is the element of $J \setminus (I \cap J)$ and σ is the number of elements of $I \cap J$ between p and q.

Case k=2

When $k = 2$: **Theorem:** Suppose $A = (a_{ij})$. For all $i = 1, \ldots, C(n, 2)$, let $(i) = (i_1, i_2)$ be the i-th element of the lexicographic order of pairs (i_1, i_2) of integers with $1 \leq i_1 < i_2 \leq n$. Then the element (i, j) of $A^{[2]}$ is

$$a_{ij} = \begin{cases} a_{i_1 i_1} + a_{i_2 i_2} & \text{if } (j) = (i) \\ (-1)^{r+s} a_{i_r j_s} & \text{if exactly one element } i_r \text{ of } (i) \text{ does not appear in } (j) \text{ and } j_s \text{ does not a} \\ 0 & \text{if no element of } (i) \text{ appears in } (j) \end{cases}$$

where p is the element in $I \setminus (I \cap J)$, q is the element in $J \setminus (I \cap J)$ and σ is the number of elements of $I \cap J$ between p and q.

Example

Let

$$A_2 = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}, \quad A_3 = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}$$

$$A_4 = \begin{pmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & a_{43} & a_{44} \end{pmatrix}$$

Example continued

Then

$$A_2^{[2]} = a_{11} + a_{22}, \quad A_3^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{pmatrix}$$

Example continued 2

$$A_4^{[2]} = \begin{pmatrix} a_{11}+a_{22} & a_{23} & a_{24} & -a_{13} & -a_{14} & 0 \\ a_{32} & a_{11}+a_{33} & a_{34} & a_{12} & 0 & -a_{14} \\ a_{42} & a_{43} & a_{11}+a_{44} & 0 & a_{12} & a_{13} \\ -a_{31} & a_{21} & 0 & a_{22}+a_{33} & a_{34} & -a_{24} \\ -a_{41} & 0 & a_{21} & a_{43} & a_{22}+a_{44} & a_{23} \\ 0 & -a_{41} & a_{31} & -a_{42} & a_{32} & a_{33}+a_{44} \end{pmatrix}$$

$$A_3^{[3]} = a_{11} + a_{22} + a_{33}$$

$$A_4^{[3]} = ()$$

Theorem for compound matrices

Theorem: Let A, B be two $n \times n$ matrices. Then

- The number of nonzero off-diagonal elements of $A^{[k]}$ is $C(n-2, k-1)$ times the number of nonzero off-diagonal elements of A
- $A^{[1]} = A$, $A^{[n]} = \mathrm{tr} A$
- $(A+B)^{[k]} = A^{[k]} + B^{[k]}$ (hence the name additive)
- Let S be a nonsingular $n \times n$ matrix. Then

$$(SAS)^{[k]} = S^k A^{[k]} (S^{-1})^{(k)}$$

Theorem for eigenvalues

Theorem: Let A be a real $m \times m$ matrix. For A to have all eigenvalues with strictly negative real parts, it is necessary and sufficient that

- the second additive compound matrix $A^{[2]}$ has all eigenvalues with strictly negative real parts
- $(-1)^m \det(A) > 0$

Role in stability

Consider the differential equation

$$x' = f(x)$$

Theorem: A sufficient condition for a periodic orbit $\gamma = \{p(t) : 0 \leq t \leq \omega\}$ of $x' = f(x)$ to be asymptotically orbitally stable with asymptotic phase is that the linear system

$$z'(t) = \left(\frac{\partial f^{[2]}}{\partial x}(p(t)) \right) z(t)$$

is asymptotically stable.

Li Muldowney (1995)

Global stability in metapopulations

Remarks on global stability in metapopulations

- Unlike local analysis, there is no algorithm to systematically address this problem - It is handled case by case. Two examples in the rest of this lecture - Some elements of systematic global theory: work by Zhisheng Shuai and collaborators, mainly - The question, as often: is global stability really important? It depends on the context of the work...

|P|-SLIRS model

Consider a particular case of the $|\mathcal{P}|$-SLIRS system with constant birth

$$
\begin{aligned}
S_p' &= b_p + \nu_p R_p - \Phi_p - d_p S_p + \sum_{q\in\mathcal{P}} m_{Spq} S_q \\
L_p' &= \Phi_p - (\varepsilon_p + d_p) L_p + \sum_{q\in\mathcal{P}} m_{Lpq} L_q \\
I_p' &= \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q\in\mathcal{P}} m_{Ipq} I_q \\
R_p' &= \gamma_p I_p - (\nu_p + d_p) R_p + \sum_{q\in\mathcal{P}} m_{Rpq} R_q
\end{aligned}
$$

and standard incidence

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p}$$

Arino van den Driessche, Fields Inst. Commun. 48:1-13 (2006)

Global stability theorem for |P|-SLIRS

Theorem: Compute $\mathcal{R}_0$ as explained earlier. If $\mathcal{R}_0 < 1$, then the DFE of the $|\mathcal{P}|$-SLIRS system is globally asymptotically stable.

Proof for |P|-SLIRS

Since $S_p \leq N_p$ for all t, it follows that $\Phi_p \leq \beta_p N_p I_p / N_p = \beta_p I_p$, and equation for L_p gives the inequality

$$L'_p \leq \beta_p I_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q$$

To use a comparison theorem, define a linear system consisting of the equations for L_p and I_p:

$$L'_p = \beta_p I_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p + \delta_p) I_p + \sum_{q \in \mathcal{P}} m_{Ipq} I_q$$

Proof continued

- The linear system above has matrix $F - V$ as its coefficient matrix, so (by arguments in the proof of the $\mathcal{R}_0$ result of van den Driessche Watmough) satisfies $\lim_{t\to\infty} L_p = 0$ and $\lim_{t\to\infty} I_p = 0$ for $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ - Using a comparison theorem, these limits also hold for the nonlinear subsystem - It follows by the same reasoning as before that $\lim_{t\to\infty} R_p = 0$ and $\lim_{t\to\infty} S_p = N_p^\star$

Thus, when $\mathcal{R}_0 < 1$, the DFE is GAS, the disease dies out.

|S||P|-SLIRS (multi-species)

Consider the system with total constant population, equal movement for all states and irreducible

$$
\begin{aligned}
S'_{sp} &= d_{sp}N_{sp} + \nu_{sp}R_{sp} - \Phi_{sp} - d_{sp}S_{sp} + \textstyle\sum_{q\in\mathcal{P}} m_{spq}S_{sq} \\
L'_{sp} &= \Phi_{sp} - (\varepsilon_{sp} + d_{sp})L_{sp} + \textstyle\sum_{q\in\mathcal{P}} m_{spq}L_{sq} \\
I'_{sp} &= \varepsilon_{sp}L_{sp} - (\gamma_{sp} + d_{sp})I_{sp} + \textstyle\sum_{q\in\mathcal{P}} m_{spq}I_{sq} \\
R_{sp} &= \gamma_{sp}I_{sp} - (\nu_{sp} + d_{sp})R_{sp} + \textstyle\sum_{q\in\mathcal{P}} m_{spq}R_{sq}
\end{aligned}
$$

and standard incidence

$$\Phi_{sp} = \sum_{k\in\mathcal{S}} \beta_{skp}\frac{S_{sp}I_{kp}}{N_p}$$

Arino et al., Math. Med. Biol. 22(2):129-142 (2005)

Global stability theorem for |S||P|-SLIRS

Theorem: For the $|\mathcal{S}||\mathcal{P}|$-SLIRS model, define $\mathcal{R}_0$ as above. If $\mathcal{R}_0 < 1$, then the DFE is GAS.

Proof for |S||P|-SLIRS

To establish GAS of the DFE when $\mathcal{R}_0 < 1$, consider the non-autonomous system consisting of the equations for L_{sp}, I_{sp}, R_{sp}, where L_{sp} is written as

$$L'_{sp} = \sum_{j\in\mathcal{S}} \beta_{sjp}(N_{sp} - L_{sp} - I_{sp} - R_{sp})\frac{I_{jp}}{N_{jp}} - (d_{sp} + \varepsilon_{sp})L_{sp} + \sum_{q\in\mathcal{P}} m_{spq}L_{sq} - \sum_{q\in\mathcal{P}} m_{sqp}L_{sp}$$

where S_{sp} is replaced by $N_{sp} - L_{sp} - I_{sp} - R_{sp}$, and N_{sp} solves

$$\frac{d}{dt}N_{sp} = \sum_{q\in\mathcal{P}} m_{spq}N_{sq}$$

Proof continued

By similar reasoning as for the DFE, we have

$$\lim_{t\to\infty} N_{sp}(t) = N_{sp}^{\star} > 0$$

Write the non-autonomous system as

$$x' = f(t, x)$$

where x is the $3|\mathcal{S}||\mathcal{P}|$-dimensional vector of L_{sp}, I_{sp}, R_{sp}. The DFE corresponds to $x = 0$. $N_{sp}(t) \to N_{sp}^{\star}$ as $t \to \infty$.

Proof continued 2

Substitute the limit $N_{sp}^{\star}$ for N_{sp} in the equation for L_{sp}:

$$L'_{sp} = \sum_{j \in \mathcal{S}} \beta_{sjp}(N_{sp}^{\star} - L_{sp} - I_{sp} - R_{sp}) \frac{I_{jp}}{N_{jp}^{\star}} - (d_{sp} + \varepsilon_{sp}) L_{sp} + \sum_{q \in \mathcal{P}} m_{spq} L_{sq}$$

The non-autonomous system is *asymptotically autonomous*, with limiting system

$$x' = g(x)$$

Proof continued 3

To show that 0 is GAS for the limiting system, consider the linear system

$$x' = \mathcal{L}x$$

where x is the $3|\mathcal{S}||\mathcal{P}|$-dimensional vector of L_{sp}, I_{sp}, R_{sp}. In $\mathcal{L}$, replace S_{sp}/N_{jp} by $N^\star_{sp}/N^\star_{jp}$. The equations for I_{sp} and R_{sp} are not affected, while the equation for L_{sp} becomes

$$L'_{sp} = \sum_{j\in\mathcal{S}} \beta_{sjp} \frac{N^*_{sp}}{N^*_{jp}} I_{jp} - (d_{sp} + \varepsilon_{sp}) L_{sp} + \sum_{q\in\mathcal{P}} m_{spq} L_{sq}$$

Comparing the nonlinear and linear systems, $g(x) \leq \mathcal{L}x$ for all $x \in \mathbb{R}_+^{3|\mathcal{S}||\mathcal{P}|}$.

Proof continued 4

In the linear system, the equations for L_{sp} and I_{sp} do not involve R_{sp}. Let $\tilde{x}$ be the part of x corresponding to E_{sp} and I_{sp}, and $\tilde{\mathcal{L}}$ the corresponding submatrix. The method used for the DFE can be applied to prove stability of $\tilde{x} = 0$ for the subsystem $\tilde{x}' = \tilde{\mathcal{L}}\tilde{x}$, with $\tilde{\mathcal{L}} = F - V$. If $\mathcal{R}_0 < 1$, then $\tilde{x} = 0$ is a stable equilibrium of the subsystem. When $\tilde{x} = 0$, the equation for R_s becomes

$$R_s' = (\mathcal{M}_s - D_s)R_s$$

with $R_s = (R_{s1}, \ldots, R_{s|\mathcal{P}|})^T$, $D_s = \mathrm{diag}(d_{s1}, \ldots, d_{s|\mathcal{P}|})$.

Proof continued 5

From previous results, $-\mathcal{M}_s$ is a singular M-matrix and $-\mathcal{M}_s + D_s$ is a nonsingular M-matrix for all D_s. Thus, the equilibrium $R_s = 0$ of this linear system is stable. Therefore, the equilibrium $x = 0$ of the linear system is stable when $\mathcal{R}_0 < 1$. Using a standard comparison theorem, it follows that 0 is a GAS equilibrium of the limiting system.

Final conclusion

When $\mathcal{R}_0 < 1$, the linear system has a unique equilibrium (the DFE) since its coefficient matrix $F - V$ is nonsingular. Global stability follows from results on asymptotically autonomous systems.

Bibliography I