18 $\mathcal{R}_0$

McMaster University

Mathematics and Statistics

$$\int_M d\omega = \int_{\partial M} \omega$$

Mathematics 4MB3/6MB3 Mathematical Biology

Instructor: David Earn

Lecture 18

$\mathcal{R}_0$

Friday 16 February 2018

Announcements

- **Assignment 3** is due Wednesday 28 February 2018, 11:30am.
- **Midterm test:**
  - *Date:* Thursday 8 March 2018
  - *Time:* 7:00pm to 9:00pm
  - *Location:* BSB-B154
- Draft Project Description Document has been posted.
  - Questions?
- **Assignment 4** will be posted soon.
  It is due Monday 12 March 2018, 11:30am.
  - Make sure to complete question 3 on this assignment *before* the midterm test.

$\mathcal{R}_0$: biological definition

The **basic reproduction number** $\mathcal{R}_0$ is:

> *the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual*

e.g., Anderson and May (1991) "Infectious Diseases of Humans"

$\mathcal{R}_0$: more mathematical definition

The **basic reproduction number** $\mathcal{R}_0$ is:

> *the number of new infections produced by a typical infective individual in a population at a disease free equilibrium (DFE)*

van den Driessche and Watmough (2002) *Mathematical Biosciences* **180**, 29–48

$\mathcal{R}_0$: most mathematical definition

The **basic reproduction number** $\mathcal{R}_0$ is:

> *the spectral radius of the next generation operator at a disease free equilibrium (DFE)*

Diekmann, Heesterbeek & Metz (1990) *J. Math. Biol.* **28**, 365–382

Definitions from matrix analysis

Definition (Spectrum of a matrix)

Let M be an $n \times n$ real (or complex) matrix. The **spectrum of M** is

$$\sigma(M) = \{\lambda : Mv = \lambda v \text{ for some non-zero } v \in \mathbb{C}^n\},$$

i.e., $\sigma(M)$ is the set of eigenvalues of M.

Definition (Spectral radius of a matrix)

Let M be an $n \times n$ real (or complex) matrix. The **spectral radius of M** is

$$\rho(M) = \max\{|\lambda| : \lambda \in \sigma(M)\},$$

i.e., $\rho(M)$ is the maximum modulus of the eigenvalues of M.

Computing $\mathcal{R}_0$

- In very simple models, $\mathcal{R}_0$ is the product of the transmission rate and the mean time in the infectious class. *e.g.*, In the SIR model with vital dynamics,

$$\mathcal{R}_0 = \beta \cdot \frac{1}{\gamma + \mu}\,.$$

- When there are multiple infected classes, it is more complicated to compute $\mathcal{R}_0$.
- In the SEIR model, we found (based on a biological argument) that

$$\mathcal{R}_0 = \beta \cdot \frac{\sigma}{\sigma + \mu} \cdot \frac{1}{\gamma + \mu}\,.$$

- Mathematically, the spectral radius of the next generation operator at the DFE is exactly this quantity. With this definition, it is also true that the disease persists if $\mathcal{R}_0 > 1$ and goes extinct if $\mathcal{R}_0 < 1$.

SEIR model (with vital dynamics)

$$\frac{dS}{dt} = \mu N - \frac{\beta SI}{N} - \mu S$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \sigma E - \mu E$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

- Birth and death rate (μ)
- Transmission rate (β)
- Mean latent period ($1/\sigma$)
- Mean infectious period ($1/\gamma$)

Next generation matrix for the SEIR model

- Consider flows in and out of the infected compartments, and highlight flows that correspond to new infections:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} E \\ I \end{pmatrix} = \begin{pmatrix} \beta SI - \sigma E - \mu E \\ \sigma E - \gamma I - \mu I \end{pmatrix}$$

- $\mathcal{F} =$ inflow of new infecteds to infected compartments $= \begin{pmatrix} \beta SI \\ 0 \end{pmatrix}$
- $\mathcal{V} =$ outflow from infected compartments minus inflow of *non-new* infecteds $= \begin{pmatrix} \sigma E + \mu E \\ -\sigma E + \gamma I + \mu I \end{pmatrix}$
- Let $F =$ linearization of $\mathcal{F}$ at DFE
- Let $V =$ linearization of $\mathcal{V}$ at DFE
- Then the **next generation matrix** is FV^{-1}
- Analogous to $\beta\gamma^{-1}$ in simple case.

Interpretation of FV^{-1} as next generation matrix

"To interpret the entries of FV^{-1} and develop a meaningful definition of $\mathcal{R}_0$, consider the fate of an infected individual introduced into compartment k of a disease free population. The (j,k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection. The (i,j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i. Hence, the (i,k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k. Following Diekmann et al. (1990), we call FV^{-1} the next generation matrix for the model and set

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

where $\rho(A)$ denotes the spectral radius of a matrix A."

van den Driessche and Watmough (2002) *Mathematical Biosciences* **180**, 29–48 [page 33]

$\mathcal{R}_0$ via FV^{-1} for the SEIR model

$$\mathcal{F} = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix} \qquad \mathcal{V} = \begin{pmatrix} \sigma E + \mu E \\ -\sigma E + \gamma I + \mu I \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} (\sigma+\mu) & 0 \\ -\sigma & (\gamma+\mu) \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\sigma+\mu} & 0 \\ \frac{\sigma}{(\sigma+\mu)(\gamma+\mu)} & \frac{1}{\gamma+\mu} \end{pmatrix} \implies FV^{-1} = \begin{pmatrix} \frac{\beta\sigma}{(\sigma+\mu)(\gamma+\mu)} & \frac{\beta}{\gamma+\mu} \\ 0 & 0 \end{pmatrix}$$

$$\mathcal{R}_0 = \rho(FV^{-1}) = \beta\sigma/(\sigma+\mu)(\gamma+\mu)$$

- Note wrt previous slide that the $(2,1)$ entry of V^{-1} is the average time an individual who enters the E compartment spends in the I compartment: only a proportion $\sigma/(\sigma+\mu)$ of such individuals make it to the I compartment, where the average time spent—by individuals who get there—is $1/(\gamma+\mu)$.

Computing $\mathcal{R}_0$ for other compartmental ODE models

- The method applied in the previous slides to obtain $\mathcal{R}_0$ for the SEIR model works more generally for a very large class of "reasonable" infectious disease ODE models. "Reasonable" means:
  1. The vector field can be written $\mathcal{F} - \mathcal{V}$, where $\mathcal{F} \geq 0$ corresponds to *new infections* and $\mathcal{V}$ can be written $\mathcal{V} = \mathcal{V}^+ - \mathcal{V}^-$, where $\mathcal{V}^+ \geq 0$ corresponds to *outflow* and $\mathcal{V}^- \geq 0$ corresponds to *inflow of infectives that are not new*.
  2. The biologically relevant part of the state space is forward-invariant. In particular, if a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, nor any other means.
  3. The DFE is stable in the absence of new infection (if there is more than one DFE, $\mathcal{R}_0$ may depend on which one we focus on).
  4. The population size N is constant (or the model is expressed in terms of proportions in each compartment).

Computing $\mathcal{R}_0$ for other compartmental ODE models

Theorem (van den Driessche and Watmough (2002))

If the vector field associated with an ODE infectious disease model satisfies the conditions specified on the previous slide, then

1. *$\mathcal{R}_0$ can be computed as $\rho(FV^{-1})$;*
2. *if $\mathcal{R}_0 < 1$ then the disease-free equilibrium (DFE) is locally asymptotically stable (LAS), whereas if $\mathcal{R}_0 > 1$ then there is a LAS endemic equilibrium (EE).*

$\mathcal{R}_0$ calculation: summary

- The biological method of deriving $\mathcal{R}_0$ is generally more informative in terms of what is going on. But it can be challenging to apply to complex models.
- The formal approach, *i.e.*, $\mathcal{R}_0 = \rho(FV^{-1})$, works in almost any situation you will encounter, even very complicated models with many compartments.
- If possible, it is best to use both methods to find an expression for $\mathcal{R}_0$, and make sure they agree.
- A completely different challenge is to estimate $\mathcal{R}_0$ for a real epidemic from data...

Estimating $\mathcal{R}_0$ based on the SEIR model

- If the SEIR model captures the natural history of some disease well, how can you *estimate* $\mathcal{R}_0 = \dfrac{\beta\sigma}{(\sigma+\mu)(\gamma+\mu)}$?
  - Mean latent period $1/\sigma$
  - Mean infectious period $1/\gamma$
  - Birth rate μ
  - Estimate β via initial growth rate r:
    - For the simplest SIR model, $r = \beta - \gamma$ so $\beta = r + \gamma$.
    - More generally, r is the largest positive (or least negative) real part of the eigenvalues of $F - V$.
    - For SEIR model we find:

$$r = \frac{1}{2}\left(\sqrt{4\beta\sigma + (\gamma-\sigma)^2} - (\gamma+\sigma+2\mu)\right)$$

    - Solving this for β we obtain: $\beta = \dfrac{(r+\sigma+\mu)(r+\gamma+\mu)}{\sigma}$