Mathematical Analysis of Epidemiological Models III

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What is R_0?

Basic Reproduction Number
Net Reproductive Rate

"the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible" (Anderson & May, 1991)

Why is R_0 important?

- For a wholly susceptible host population,

  $R_0 > 1$ pathogen can invade.

  $R_0 < 1$ pathogen cannot invade.

- When a pathogen is present in the population, often, but not always,

  $R_0 < 1$ pathogen will die out of the population.

The effective reproduction number, R

If the population is not wholly susceptible, then we have R, the effective reproduction number.

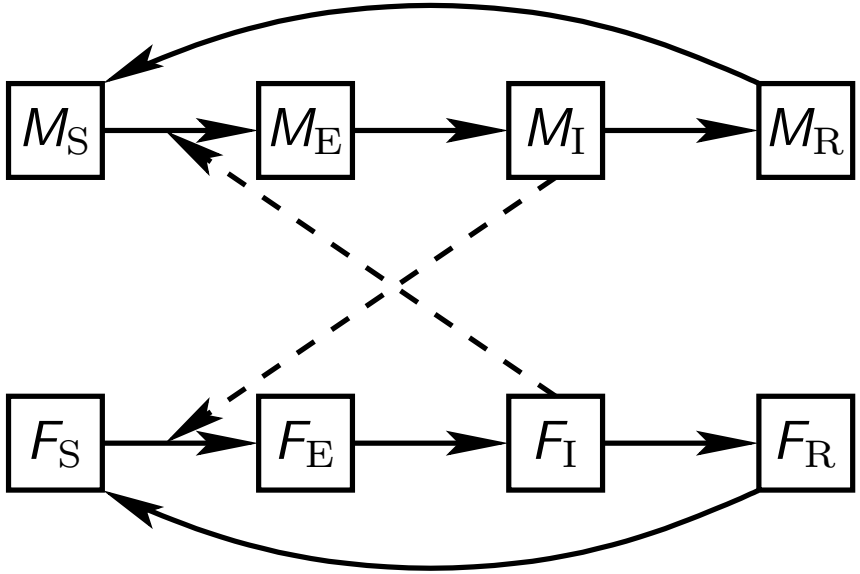
- Pathogen already present
- Vaccinated population

How to compute R_0?

- Heuristic methods
- Systematic method

  P. van den Driessche & James Watmough, 2002, "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission", *Mathematical Biosciences*, 180: 29–48.

Example model for STI



$$\frac{dM_S}{dt} = \omega_M M_R - \beta_M \frac{F_I}{F} M_S \qquad \frac{dF_S}{dt} = \omega_F F_R - \beta_F \frac{M_I}{M} F_S$$

$$\frac{dM_E}{dt} = \beta_M \frac{F_I}{F} M_S - \tau_M M_E \qquad \frac{dF_E}{dt} = \beta_F \frac{M_I}{M} F_S - \tau_F F_E$$

$$\frac{dM_I}{dt} = \tau_M M_E - \gamma_M M_I \qquad \frac{dF_I}{dt} = \tau_F F_E - \gamma_F F_I$$

$$\frac{dM_R}{dt} = \gamma_M M_I - \omega_M M_R \qquad \frac{dF_R}{dt} = \gamma_F F_I - \omega_M F_R$$

Procedure

Decide which states are infected

We need to decide which states are infected and which are uninfected.

In the STI model,
Infected: $M_{\mathrm{E}}, F_{\mathrm{E}}, M_{\mathrm{I}}, F_{\mathrm{I}}$
Uninfected: $M_{\mathrm{S}}, F_{\mathrm{S}}, M_{\mathrm{R}}, F_{\mathrm{R}}$

Procedure

Find disease-free equilibrium (or other equilibrium)

Set $\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = 0$ for all model state variables to find equilibrium.
Also, for disease-free equilibrium, there are no infected people.

Procedure

Find disease-free equilibrium (or other equilibrium)

$$0 = \omega_{\mathrm{M}} M_{\mathrm{R}} - \beta_{\mathrm{M}} \frac{0}{F} M_{\mathrm{S}} \qquad 0 = \omega_{\mathrm{F}} F_{\mathrm{R}} - \beta_{\mathrm{F}} \frac{0}{M} F_{\mathrm{S}}$$

$$0 = \beta_{\mathrm{M}} \frac{0}{F} M_{\mathrm{S}} - \tau_{\mathrm{M}} 0 \qquad 0 = \beta_{\mathrm{F}} \frac{0}{M} F_{\mathrm{S}} - \tau_{\mathrm{F}} 0$$

$$0 = \tau_{\mathrm{M}} 0 - \gamma_{\mathrm{M}} 0 \qquad 0 = \tau_{\mathrm{F}} 0 - \gamma_{\mathrm{F}} 0$$

$$0 = \gamma_{\mathrm{M}} 0 - \omega_{\mathrm{M}} M_{\mathrm{R}} \qquad 0 = \gamma_{\mathrm{F}} 0 - \omega_{\mathrm{F}} F_{\mathrm{R}}$$

$$M_{\mathrm{S}} = F_{\mathrm{S}} = \frac{P}{2}$$

$$M_{\mathrm{E}} = F_{\mathrm{E}} = M_{\mathrm{I}} = F_{\mathrm{I}} = M_{\mathrm{R}} = F_{\mathrm{R}} = 0$$

$$M = F = \frac{P}{2}$$

Procedure

Decide which terms are new infections

From the right-hand sides of the equations for the infected states, decide which terms represent new infections, $\mathcal{F}$.
The remainder are $-\mathcal{V}$.

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathcal{F} - \mathcal{V}$$

$\mathcal{F}$ is the rate of production of new infections.

$\mathcal{V}$ is the transition rates between states.

Procedure

Decide which terms are new infections

$$\begin{aligned}
\frac{\mathrm{d}M_\mathrm{E}}{\mathrm{d}t} &= \beta_\mathrm{M}\frac{F_\mathrm{I}}{F}M_\mathrm{S} - \tau_\mathrm{M}M_\mathrm{E}\\
\frac{\mathrm{d}F_\mathrm{E}}{\mathrm{d}t} &= \beta_\mathrm{F}\frac{M_\mathrm{I}}{M}F_\mathrm{S} - \tau_\mathrm{F}F_\mathrm{E}\\
\frac{\mathrm{d}M_\mathrm{I}}{\mathrm{d}t} &= \tau_\mathrm{M}M_\mathrm{E} - \gamma_\mathrm{M}M_\mathrm{I}\\
\frac{\mathrm{d}F_\mathrm{I}}{\mathrm{d}t} &= \tau_\mathrm{F}F_\mathrm{E} - \gamma_\mathrm{F}F_\mathrm{I}
\end{aligned}$$

$$\mathcal{F} = \begin{bmatrix} \beta_\mathrm{M}\frac{F_\mathrm{I}}{F}M_\mathrm{S} \\ \beta_\mathrm{F}\frac{M_\mathrm{I}}{M}F_\mathrm{S} \\ 0 \\ 0 \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} \tau_\mathrm{M}M_\mathrm{E} \\ \tau_\mathrm{F}F_\mathrm{E} \\ -\tau_\mathrm{M}M_\mathrm{E} + \gamma_\mathrm{M}M_\mathrm{I} \\ -\tau_\mathrm{F}F_\mathrm{E} + \gamma_\mathrm{F}F_\mathrm{I} \end{bmatrix}$$

Procedure

Take derivatives at equilibrium

$$\mathbf{F} = \frac{\mathrm{d}\mathcal{F}}{\mathrm{d}\mathbf{x}} = \begin{bmatrix} \frac{\mathrm{d}\mathcal{F}_1}{\mathrm{d}x_1} & \cdots & \frac{\mathrm{d}\mathcal{F}_1}{\mathrm{d}x_n} \\ \vdots & & \vdots \\ \frac{\mathrm{d}\mathcal{F}_n}{\mathrm{d}x_1} & \cdots & \frac{\mathrm{d}\mathcal{F}_n}{\mathrm{d}x_n} \end{bmatrix} \qquad \mathbf{V} = \frac{\mathrm{d}\mathcal{V}}{\mathrm{d}\mathbf{x}} = \begin{bmatrix} \frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}x_1} & \cdots & \frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}x_n} \\ \vdots & & \vdots \\ \frac{\mathrm{d}\mathcal{V}_n}{\mathrm{d}x_1} & \cdots & \frac{\mathrm{d}\mathcal{V}_n}{\mathrm{d}x_n} \end{bmatrix}$$

These are the rates for new infections and transitions near the equilibrium.

Procedure

Take derivatives at equilibrium

At the disease-free equilibrium,

$$M_{\mathrm{S}} = F_{\mathrm{S}} = M = F = \frac{P}{2},$$
$$M_{\mathrm{E}} = F_{\mathrm{E}} = M_{\mathrm{I}} = F_{\mathrm{I}} = M_{\mathrm{R}} = F_{\mathrm{R}} = 0$$

$$\mathcal{F} = \begin{bmatrix} \beta_{\mathrm{M}} \frac{F_{\mathrm{I}}}{F} M_{\mathrm{S}} \\ \beta_{\mathrm{F}} \frac{M_{\mathrm{I}}}{M} F_{\mathrm{S}} \\ 0 \\ 0 \end{bmatrix}, \quad \mathbf{F} = \begin{bmatrix} 0 & 0 & 0 & \beta_{\mathrm{M}} \frac{M_{\mathrm{S}}}{F} \\ 0 & 0 & \beta_{\mathrm{F}} \frac{F_{\mathrm{S}}}{M} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & \beta_{\mathrm{M}} \\ 0 & 0 & \beta_{\mathrm{F}} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\mathcal{V} = \begin{bmatrix} \tau_{\mathrm{M}} M_{\mathrm{E}} \\ \tau_{\mathrm{F}} F_{\mathrm{E}} \\ -\tau_{\mathrm{M}} M_{\mathrm{E}} + \gamma_{\mathrm{M}} M_{\mathrm{I}} \\ -\tau_{\mathrm{F}} F_{\mathrm{E}} + \gamma_{\mathrm{F}} F_{\mathrm{I}} \end{bmatrix}, \quad \mathbf{V} = \begin{bmatrix} \tau_{\mathrm{M}} & 0 & 0 & 0 \\ 0 & \tau_{\mathrm{F}} & 0 & 0 \\ -\tau_{\mathrm{M}} & 0 & \gamma_{\mathrm{M}} & 0 \\ 0 & -\tau_{\mathrm{F}} & 0 & \gamma_{\mathrm{F}} \end{bmatrix}$$

Procedure

Find $\mathbf{V}^{-1}$

$\mathbf{V}^{-1}$ gives the times spent in each state.
In general, finding the inverse is difficult by hand, but computer algebra (Sage, Maple, Mathematica) takes care of that.

$$\mathbf{V}^{-1} = \begin{bmatrix} \frac{1}{\tau_{\mathrm{M}}} & 0 & 0 & 0 \\ 0 & \frac{1}{\tau_{\mathrm{F}}} & 0 & 0 \\ \frac{1}{\gamma_{\mathrm{M}}} & 0 & \frac{1}{\gamma_{\mathrm{M}}} & 0 \\ 0 & \frac{1}{\gamma_{\mathrm{F}}} & 0 & \frac{1}{\gamma_{\mathrm{F}}} \end{bmatrix}$$

Procedure

Find $\mathbf{FV}^{-1}$

$\mathbf{FV}^{-1}$ gives the total production of new infections over the course of an infection.

$$\mathbf{F} = \begin{bmatrix} 0 & 0 & 0 & \beta_{\mathrm{M}} \\ 0 & 0 & \beta_{\mathrm{F}} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad \mathbf{V}^{-1} = \begin{bmatrix} \frac{1}{\tau_{\mathrm{M}}} & 0 & 0 & 0 \\ 0 & \frac{1}{\tau_{\mathrm{F}}} & 0 & 0 \\ \frac{1}{\gamma_{\mathrm{M}}} & 0 & \frac{1}{\gamma_{\mathrm{M}}} & 0 \\ 0 & \frac{1}{\gamma_{\mathrm{F}}} & 0 & \frac{1}{\gamma_{\mathrm{F}}} \end{bmatrix}$$

$$\mathbf{FV}^{-1} = \begin{bmatrix} 0 & \frac{\beta_{\mathrm{M}}}{\gamma_{\mathrm{F}}} & 0 & \frac{\beta_{\mathrm{M}}}{\gamma_{\mathrm{F}}} \\ \frac{\beta_{\mathrm{F}}}{\gamma_{\mathrm{M}}} & 0 & \frac{\beta_{\mathrm{F}}}{\gamma_{\mathrm{M}}} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

Procedure

Find $\rho(\mathbf{FV}^{-1})$

The largest eigenvalue λ_0 gives the fastest growth of the infected population.

$$\left(\mathbf{FV}^{-1}\right)^N \to \lambda_0^N \mathbf{v}_0 \quad \text{for large } N.$$

So $R_0 = \lambda_0$.

$$\mathbf{FV}^{-1} = \begin{bmatrix} 0 & \frac{\beta_{\mathrm{M}}}{\gamma_{\mathrm{F}}} & 0 & \frac{\beta_{\mathrm{M}}}{\gamma_{\mathrm{F}}} \\ \frac{\beta_{\mathrm{F}}}{\gamma_{\mathrm{M}}} & 0 & \frac{\beta_{\mathrm{F}}}{\gamma_{\mathrm{M}}} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\sigma(\mathbf{FV}^{-1}) = \left\{0, \sqrt{\frac{\beta_{\mathrm{F}}\beta_{\mathbf{M}}}{\gamma_{\mathrm{M}}\gamma_{\mathbf{F}}}}, -\sqrt{\frac{\beta_{\mathrm{F}}\beta_{\mathbf{M}}}{\gamma_{\mathrm{M}}\gamma_{\mathbf{F}}}}\right\} \implies R_0 = \sqrt{\frac{\beta_{\mathrm{F}}\beta_{\mathbf{M}}}{\gamma_{\mathrm{M}}\gamma_{\mathbf{F}}}}$$

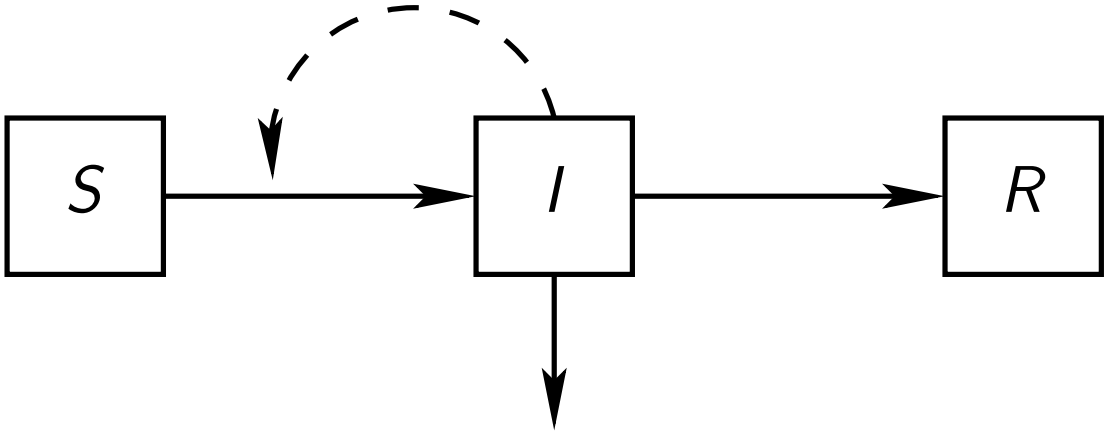
Alternative interpretation

If we had chosen only F_{E} & F_{I} to be infected states, then

$$R_0 = \frac{\beta_{\mathrm{F}} \beta_{\mathbf{M}}}{\gamma_{\mathrm{M}} \gamma_{\mathbf{F}}}$$

More complex models

Flu



$$\frac{\mathrm{d}S_a}{\mathrm{d}t} = -\lambda_a S_a$$

$$\frac{\mathrm{d}I_a}{\mathrm{d}t} = \lambda_a S_a - (\gamma_a + \nu_a) I_a, \qquad \lambda_a = \frac{\sigma_a}{N} \sum_{\alpha=1}^{17} \phi_{a\alpha} \beta_\alpha I_\alpha,$$

$$\frac{\mathrm{d}R_a}{\mathrm{d}t} = \gamma_a I_a, \qquad \text{for } a = 1, \ldots, 17$$

More complex models

Flu

- I_a are infected states
- Equilibrium is everyone susceptible, with given age structure
- New-infection term is $\lambda_a S_a$, so

$$\mathcal{F} = \lambda \otimes \mathbf{S}, \quad \mathcal{V} = (\gamma + \nu) \otimes \mathbf{I}$$

- Then

$$\mathbf{F} = \left\{ \left[\sigma \otimes \frac{\mathbf{S}}{N} \right] \beta^{\mathrm{T}} \right\} \otimes \phi, \quad \mathbf{V} = \mathrm{diag}\,(\gamma + \nu)$$

- And

$$\mathbf{F}\mathbf{V}^{-1} = \left\{ \left[\sigma \oslash (\gamma + \nu) \otimes \frac{\mathbf{S}}{N} \right] \beta^{\mathrm{T}} \right\} \otimes \phi$$

More complex models

Flu

Putting in parameter values from the pandemics, we get

1918 $R_0 = 1.2$

1957 $R_0 = 1.3$