The death of an epidemic

In SIR equations, let’s divide equation for \( \frac{dX}{dt} \) by \( \frac{dZ}{dt} \):

\[
\frac{dX}{dZ} = - \frac{\beta \frac{X Y}{N}}{\gamma Y} = - \frac{R_0 X}{N}
\]

Integrate with respect to \( Z \):

\[
X(t) = X(0) e^{- \frac{R_0}{N} t}
\]

When epidemic is over, by definition, we have \( X(\infty), \)
\( Y(\infty) = 0 \), and \( Z(\infty) \)

\[
X(\infty) = N - Z(\infty) = X(0) e^{- \frac{R_0}{N} \infty}
\]
The death of an epidemic

- So, \( N - Z(\infty) - X(\infty) e^{-Z(\infty) R_0/N} = 0 \)
- Solve this numerically (‘transcendental’ equation)

\( R_0 < 1 \) means no Epidemic

Epidemic dies out because there are too few infectives, not because of too few susceptibles

Kermack & McKendrick (1927)

Simple Epidemics

<table>
<thead>
<tr>
<th>Disease</th>
<th>( \beta ) (yr(^{-1}))</th>
<th>( 1/\gamma ) (yr)</th>
<th>( R_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Measles”</td>
<td>886</td>
<td>0.019</td>
<td>17</td>
</tr>
<tr>
<td>“Influenza”</td>
<td>180</td>
<td>0.011</td>
<td>2</td>
</tr>
<tr>
<td>“Chickenpox”</td>
<td>315</td>
<td>0.022</td>
<td>7</td>
</tr>
<tr>
<td>“Rubella”</td>
<td>200</td>
<td>0.025</td>
<td>5</td>
</tr>
</tbody>
</table>
**Frequency- or Density-Dependent Transmission?**

- Assumed contact rate, $\kappa$, constant: ‘mixing’ is independent of population size: *frequency-dependent transmission*. Reasonable?
- If we assume contact rate to be $\kappa N$ (increases with ‘crowding’), then transmission rate is
  - $dX/dt = -\beta XY$
- Called *density-dependent transmission*

**Does it Matter?**

- Again, pathogen invasion if $dY/dt > 0$
- If initially everyone susceptible ($X=N$),
  - $\beta NY - \gamma Y > 0 \Rightarrow Y(\beta N - \gamma) > 0$
- In this case, we define $R_0 = \beta N / \gamma$, so need $R_0 > 1$
- Hence, for any particular $\beta$ and $\gamma$, there’s now a *threshold population density* required for invasion
Incorporating virulence

Assume infectious individuals die at rate $\alpha$.

\[
\frac{dY}{dt} = \ldots - \gamma Y - \alpha Y
\]
What should we do?

- If population size doesn’t change, FD & DD equivalent \( \beta_{FD} = N \times \beta_{DD} \)
- Otherwise:
  - Frequency-dependence generally more appropriate in large populations with heterogenous mixing, STDs, vector-borne pathogens
  - Density-dependence representative of wildlife & livestock diseases (especially with smaller population sizes)

LONG-TERM DYNAMICS

- So far, looked at start and end of a simple epidemic
- In other settings, would like to know systems dynamics in the long run
- Use equilibrium analysis
STDS AND SIS MODEL

Simple model for a non-immunising infection, that is only cleared through treatment

\[
\begin{align*}
\frac{dX}{dt} &= \gamma Y - \beta X \frac{Y}{N} \\
\frac{dY}{dt} &= \beta X \frac{Y}{N} - \gamma Y
\end{align*}
\]

System reduced to a single state variable

Recall that \(N=X+Y\), so we can rewrite this system as

\[
\begin{align*}
\frac{dY}{dt} &= \beta(N - Y) \frac{Y}{N} - \gamma Y \\
\frac{dY}{dt} &= \beta Y \left(1 - \frac{Y}{N}\right) - \gamma Y
\end{align*}
\]

What is \(R_0\) here?

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

EQUILIBRIUM ANALYSIS

- Can study properties of model at equilibrium (setting rates of change = 0)

- Setting \(dY/dt = 0\), we get
  \[
  \beta(N - Y)Y/N - \gamma Y = 0,
  \]
  So \(Y(\beta(N-Y)/N - \gamma) = 0\)

- Satisfied whenever \(Y=0\) or \(Y=N - N\gamma/\beta = N(1 - 1/R_0)\)
- Eqm points are: 0 and \(N(1 - 1/R_0)\)
- So, under what circumstances do we see each state?
STABILITY ANALYSIS

- So, we have two equilibria – one where pathogen persists and one where it is absent
- What are conditions that determine when we observe one or other?
- For answer to this question, we need to carry out linear stability analysis
- Basic idea is to start at an equilibrium point and introduce a slight change (a ‘perturbation’) and establish whether this perturbation grows (unstable) or decays (stable)

EQUILIBRIUM STABILITY

To determine stability properties of equilibria, we need to calculate dominant ‘eigenvalue’
LINEAR STABILITY ANALYSIS: 1-D CASE

- Assume we have a single state variable
  \[ \frac{dY}{dt} = f(Y) \]

- So, at equilibrium point \( Y^* \), \( f(Y^*) = 0 \)
- Now, we're interested in knowing what happens if we slightly 'perturb' equilibrium
- Let \( Y = Y^* + y \) (\( y << Y^* \)), substitute in ODE
  \[ \frac{d(Y + y)}{dt} = \frac{dy}{dt} = f(Y^* + y) \]

LINEAR STABILITY ANALYSIS: 1-D CASE

- \( f(N^* + n) \) can be expressed as a Taylor expansion
  \[ \frac{dy}{dt} = f(Y^*) + y f'(Y^*) + y^2 f''(Y^*) + \ldots \]
  - Note: \( f' \) means derivative of \( f \) with respect to \( Y \)
- We end up with a linear ODE, solution to which is
  \[ y(t) = y(0)e^{f'(Y^*)t} \]

- \( f'(N^*) \) is 'eigenvalue' -- from now on, we'll call it \( \Lambda \)
- Our perturbation, \( y(t) \), will
  1. Grow exponentially if \( \Lambda > 0 \) (equilibrium Unstable)
  2. Decay exponentially if \( \Lambda < 0 \) (equilibrium Stable)
TAYLOR EXPANSION

\[
\begin{align*}
f(Y*) & \approx f(Y*) + y f'(Y*) + ...
\end{align*}
\]

SIS MODEL

\[
\frac{dY}{dt} = \beta Y \left(1 - \frac{Y}{N}\right) - \gamma Y
\]

- System is in equilibrium as long as
  - \(Y* = 0\) (or \(X* = N\)) ... ie DFE
  - \(or Y* = N(1-\gamma/\beta) = N(1-1/R_0)\)

\[
\begin{align*}
f(Y) &= \beta Y \left(1 - \frac{Y}{N}\right) - \gamma Y \\
f'(Y) &= \frac{df(Y)}{dY} = \beta - 2\beta \frac{Y}{N} - \gamma
\end{align*}
\]
SIS MODEL

\[ f'(Y) = \beta - 2\beta \frac{Y}{N} - \gamma \]

- So, when \( Y^*=0 \),
  \[ f'(0) = \beta - \gamma \]
  \[ \Rightarrow <0 \text{ if } \gamma > \beta \text{ or } R_0 < 1 \]

- When \( Y^*=N(1-\gamma/\beta) \),
  \[ f'(Y^*) = -\beta + \gamma \]
  \[ \Rightarrow <0 \text{ if } \beta > \gamma \text{ or } R_0 > 1 \]

STABILITY ANALYSIS

- Let's do this in general terms
- For a system containing \( n \) state variables, we have

\[ \frac{dN_i}{dt} = f_i(N_1, N_2, \ldots, N_n) \quad i = 1, \ldots n \]

- Now, we perturb equilibrium \((N_i = N_i^* + x_i, x_i << N_i^*)\), Taylor
  expand \( f_i() \) and ignore higher order terms \((x_i^2, x_ix_j \text{ etc})\)

- Growth of perturbations \((x_i, i=1,n)\) given by linear set of
  ODEs

Keeling & Rohani (2008) pp30-31

• Incorporating a latent period takes into account transition from *infected but not yet infectious* to *infectious*

\[
\frac{dS}{dt} = \mu - \beta SI - \mu S
\]

\[
\frac{dE}{dt} = \beta SI - (\sigma + \mu)E
\]

\[
\frac{dI}{dt} = \sigma E - (\gamma + \mu)I
\]

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

Note: \( S + E + I + R = 1 \)

---

• In qualitative ways, this addition makes little difference
• System still possesses two equilibria: DFE \((1,0,0)\) and an endemic equilibrium

\[
(S^*, E^*, I^*) = \left( \frac{1}{R_0}, \frac{\mu(\mu + \gamma)}{\beta \sigma} (R_0 - 1), \frac{\mu}{\beta} (R_0 - 1) \right)
\]

Expression for \( R_0 \) is now

\[
R_0 = \frac{\beta \sigma}{(\mu + \gamma)(\mu + \sigma)}
\]
INVASION PHASE: SIR

• Consider Jacobian for SIR model, evaluated at disease free equilibrium

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

- We worked out that two eigenvalues are \( \Lambda_{1,2} = -\mu \)
- Third is \( \Lambda_3 = \beta - (\mu + \gamma) = (R_0 - 1)(\mu + \gamma) \)
- So, initial dynamics of I class are driven by this largest eigenvalue (\( \Lambda_3 \))
  and (assume \( \mu \) is small) are given by

\[
I_{SIR} \approx I(0) \times e^{(R_0-1)\gamma t}
\]

INVASION PHASE: SEIR

• If we do exactly same thing for SEIR model (straightforward but more involved), we get

\[
I_{SEIR} \approx I(0) \cdot e^{\frac{1}{2} \left( -(\sigma + \gamma) + \sqrt{4(R_0 - 1)\gamma\sigma + (\gamma + \sigma)^2} \right)}
\]

- This seems pretty unwieldy. Let’s see what happens if we assume \( \gamma = \sigma \)

\[
I_{SEIR} \approx I(0) \times e^{(\sqrt{R_0 - 1})\gamma t}
\]

- So, in comparison with SIR model, invasion speed in SEIR model scales with \( \sqrt{R_0} \)
THE INVASION PHASE: SEIR

DERIVING EXPRESSION FOR $R_0$

1. Examine eigenvalues at disease-free equilibrium
   - Show system has two eigenvalues, $\Lambda = -\mu$ and $\Lambda = (\gamma + \mu) \left(\frac{\beta}{\gamma + \mu} - 1\right)$

   - As long as $\beta/(\gamma + \mu) > 1$, disease-free equilibrium is unstable and pathogen successfully invades

• Usefull when host population can be split into disjoint categories (representing epidemiological complexities)
• Establishes # of transmissions generated by typical infected in susceptible population

• Denote $x = \{x_1, x_2, \ldots, x_n\}$ represent $n$ infected host compartments
• Denote $y = \{y_1, y_2, \ldots, y_m\}$ represent $m$ other host compartments

\[ \frac{dx_i}{dt} = F_i(x, y) - V_i(x, y) \quad i=1,\ldots, n \]
\[ \frac{dy_j}{dt} = G_j(x, y) \quad j=1,\ldots, m \]

• $F_i = \text{rate at which new infecteds enter compartment } i$
• $V_i = \text{transfer of individuals out of and into } i\text{th compartment}$
ASSUMPTIONS

I. $F_i(0,y) = V_i(0,y) = 0 \forall y>0$
   (no new infections if no infecteds)

II. $F(x,y) \geq 0 \forall x_i \geq 0$ and $y_i \geq 0$
    (no new infections if no infecteds)

III. $V_i(0,y) \leq 0 \forall y_i \geq 0$
     (if compartment empty, can only have inflow)

IV. $\sum_i V_i(x,y) \geq 0 \forall x_i \geq 0$ and $y_i \geq 0$
    (sum is net outflow)

V. System $y' = G(0,y)$ has unique asymptotically stable equilibrium, $y^*$

SIR MODEL

\[
\begin{align*}
\frac{dS}{dt} &= \mu - \beta SI - \mu S \\
\frac{dI}{dt} &= \beta SI - \gamma I - \mu I \\
\frac{dR}{dt} &= \gamma I - \mu R \\
\end{align*}
\]

Here, $n=1$, $m=2$, $x=I$, $y = (S,R)$

$F_1 = \beta SI$

$V_1 = (\mu + \gamma)I$

$G_1 = \mu - \beta SI - \mu S$

$G_2 = \gamma I - \mu R$
LINEARIZATION

General system

\[ \frac{dx_i}{dt} = F_i(x, y) - V_i(x, y) \quad i=1,\ldots, n \]
\[ \frac{dy_j}{dt} = G_j(x, y) \quad j=1,\ldots, m \]

can decouple x-system from y-system when close to disease-free equilibrium, \( y^* \)

\[ \frac{dx}{dt} = (F - V)x \]

where \( F \) and \( V \) are \( n \times n \) matrices:

\[ F_{ij} = \frac{\partial F_i}{\partial x_j}(0, y^*) \quad V_{ij} = \frac{\partial V_i}{\partial x_j}(0, y^*) \]

NEXT GENERATION METHOD

\[ \frac{dx}{dt} = (F - V)x \]

If \( F=0 \) (no new infections), \( x = x(0)e^{-Vt} \).

Expected number of secondary cases produced by an initial case is

\[ \int_0^\infty Fe^{-Vt}x(0)dt = F \left( \int_0^\infty e^{-Vt}dt \right) x(0) = FV^{-1}x(0) \]

Next Generation Matrix, \( K = FV^{-1} \).

Entry \( K_{ij} \) represents expected number of secondary cases in compartment \( i \) by an individual in compartment \( j \).
NEW GENERATION METHOD

• Next generation operator \((FV^{-1})\) gives rate at which individuals in compartment \(j\) generate new infections in compartment \(i\) times average length of time individual spends in single visit to compartment \(j\)

• \(R_0\) is given by dominant eigenvalue (or ‘spectral radius’, \(\rho\)) of \(FV^{-1}\), ie \(R_0 = \rho(FV^{-1}) = \rho(K)\)

SIR MODEL

\[
\begin{align*}
\frac{dS}{dt} &= \mu - \beta SI - \mu S \\
\frac{dI}{dt} &= \beta SI - \gamma I - \mu I \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{align*}
\]

Here, \(n=1, m=2, x=I, y=(S,R)\)

\[
\begin{align*}
F &= \frac{\partial F_1}{\partial I} = \beta \\
V &= \frac{\partial V_1}{\partial I} = \mu + \gamma
\end{align*}
\]

Hence, \(R_0 = \frac{\beta}{(\mu + \gamma)}\)
• SEIR equations (again):

\[
\begin{align*}
\frac{dS}{dt} &= \mu - (\beta I + \mu)S \\
\frac{dE}{dt} &= \beta IS - (\mu + \sigma)E \\
\frac{dI}{dt} &= \sigma E - (\mu + \gamma)I
\end{align*}
\]

We deal with these two ‘infected’ compartments

How do we use Next Generation Method to work out \( R_0 \) for this model?

**NEXT GENERATION METHOD**

• Write down matrix \( F \), which defines rate of new infections in different compartments, differentiated with respect to \( E \) and \( I \) and evaluated at disease-free equilibrium

\[
F_1 = \beta SI \\
F_2 = 0 \\
F = \begin{pmatrix} \frac{\partial(\beta SI)}{\partial E} & \frac{\partial(\beta SI)}{\partial I} \\ 0 & 0 \end{pmatrix}
\]

\[
F = \begin{pmatrix} \beta S^* \\ 0 \\ 0 \end{pmatrix} = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix}
\]

\[
\begin{align*}
\frac{dS}{dt} &= \mu - (\beta I + \mu)S \\
\frac{dE}{dt} &= \beta IS - (\mu + \sigma)E \\
\frac{dI}{dt} &= \sigma E - (\mu + \gamma)I
\end{align*}
\]
Now, we write a new matrix $V$ that defines rate of transfer of infectives from one compartment to another.

\[
V_1 = (\mu + \sigma)E \\
V_2 = (\mu + \gamma)I - \sigma E
\]

\[
\begin{pmatrix}
\mu + \sigma & 0 \\
-\sigma & \mu + \gamma
\end{pmatrix}
\]

\[
\frac{dS}{dt} = \mu - (\beta I + \mu)S \\
\frac{dE}{dt} = \beta IS - (\mu + \sigma)E \\
\frac{dI}{dt} = \sigma E - (\mu + \gamma)I
\]

Recall that inverse of

\[
\begin{pmatrix}
a & b \\
c & d
\end{pmatrix}
\]

is

\[
\frac{1}{ad - bc}
\begin{pmatrix}
d & -b \\
-c & a
\end{pmatrix}
\]

So, we get:

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

This is Next Generation Operator. \( R_0 \) given by largest eigenvalue of this matrix:

\[
|FV^{-1}| = \begin{vmatrix} \frac{\beta \sigma}{(\mu+\gamma)(\mu+\sigma)} & \frac{\beta(\mu+\sigma)}{(\mu+\gamma)(\mu+\sigma)} \\ 0 & 0 \end{vmatrix} - \Lambda
\]

\[ R_0 = \frac{\beta \sigma}{(\mu+\gamma)(\mu+\sigma)} \]

Check: \( \sigma \to \infty \), \( R_0 = \beta/(\mu+\gamma) \) as for SIR model

**LECTURE SUMMARY**

- Linear Stability Analysis
- SIR/SEIR endemic eqm stable if \( R_0 > 1 \)
- Approach to eqm via damped oscillations
  - Period given by \( 2\pi \sqrt{(AG)} \)
- Adding latent period, SEIR model
- Affects speed of epidemic take-off
- Next Generation Method to derive expression for \( R_0 \) for *any* model
CLASS CHALLENGE: HIV PROGRESSION

Model needs to consider infectivity of different stages and respective durations

Fauci et al. 1995; Ann Intern Med

CLASS CHALLENGE: HIV PROGRESSION

Equations:
\[
\begin{align*}
    \frac{dS}{dt} &= -(\beta_P I_P + \beta_A I_A) S \\
    \frac{dI_P}{dt} &= (\beta_P I_P + \beta_A I_A) S - \delta_P I_P \\
    \frac{dI_A}{dt} &= \delta_P I_P - \delta_A I_A \\
\end{align*}
\]

Show:
\[
R_0 = \frac{\beta_P}{\delta_P} + \frac{\beta_A}{\delta_A}
\]
HINT: YOU’LL NEED TO KNOW

$$\begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix} = a_{11}a_{22} - a_{12}a_{21}$$

$$\left( \begin{array}{cc} a_{11} & a_{12} \\ a_{21} & a_{22} \end{array} \right)^{-1} = \frac{1}{a_{11}a_{22} - a_{12}a_{21}} \left( \begin{array}{cc} a_{22} & -a_{12} \\ -a_{21} & a_{11} \end{array} \right)$$

SOLUTION

$$F = \left( \begin{array}{cc} \beta_p & \beta_A \\ 0 & 0 \end{array} \right) \quad V = \left( \begin{array}{cc} \delta_p & 0 \\ -\delta_p & \delta_A \end{array} \right)$$

$$V^{-1} = \frac{1}{\delta_p \delta_A} \left( \begin{array}{cc} \delta_A & \delta_p \\ 0 & \delta_p \end{array} \right)$$
$FV^{-1} = \begin{pmatrix} \beta_p & \beta_A \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\delta_p} & 0 \\ \frac{1}{\delta_A} & \frac{1}{\delta_A} \end{pmatrix}$

$|FV^{-1}| = \begin{pmatrix} \frac{\beta_p}{\delta_p} + \frac{\beta_A}{\delta_A} - \Lambda & \frac{\beta_A}{\delta_A} \\ \delta_p & \delta_A \end{pmatrix} = 0$

$R_0 = \frac{\beta_p}{\delta_p} + \frac{\beta_A}{\delta_A}$