LECTURE 2
Equilibrium Stability Analysis &
Next Generation Method
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

\[
\frac{dX}{dt} = \gamma Y - \beta X \frac{Y}{N}
\]
\[
\frac{dY}{dt} = \beta X \frac{Y}{N} - \gamma Y
\]

System reduced to a single state variable

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

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

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

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)
To determine stability properties of equilibria, we need to calculate *dominant* ‘eigenvalue’.
• 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

\[
f(y) 
\approx f(Y^*) + y f'(Y^*) + \ldots
\]
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 \( Y^* = N(1 - \gamma/\beta) = N(1 - 1/R_0) \)

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

\[ f'(Y) = \frac{df(Y)}{dY} = \beta - 2\beta \frac{Y}{N} - \gamma \]
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 ($x_i^2, x_ix_j$ 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: \( S + E + I + R = 1 \)
SEIR MODEL

• 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

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

- 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 $\Lambda = (\gamma + \mu) \left(\beta/({\gamma + \mu})-1\right)$
   • As long as $\beta/({\gamma + \mu}) > 1$, disease-free equilibrium is unstable and pathogen successfully invades

2. Use “next generation method” or “Spectral Radius method” (see Diekmann et al. 1990; *J. Math. Biol.* and Heffernan et al. 2005; *J. R. Soc. Interface*)
NEXT GENERATION METHOD

• Useful 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
NEXT GENERATION METHOD

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

- \( F_i \) = rate at which **new infecteds** enter compartment \( i \)
- \( V_i \) = transfer of individuals out of and into \( i \)th compartment
ASSUMPTIONS

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

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

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

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

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

\[
\frac{dS}{dt} = \mu - \beta SI - \mu S
\]
\[
\frac{dI}{dt} = \beta SI - \gamma I - \mu I
\]
\[
\frac{dR}{dt} = \gamma I - \mu R
\]

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

\[
\mathcal{F}_1 = \beta SI
\]
\[
\mathcal{V}_1 = (\mu + \gamma)I
\]
\[
\mathcal{G}_1 = \mu - \beta SI - \mu S
\]
\[
\mathcal{G}_2 = \gamma I - \mu R
\]
LINEARIZATION

General system

\[
\frac{dx_i}{dt} = F_i(x, y) - V_i(x, y) \quad \text{for } i=1,\ldots, n
\]

\[
\frac{dy_j}{dt} = G_j(x, y) \quad \text{for } j=1,\ldots, m
\]

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 x 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 \( j \).
NEXT 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

\[ \frac{dS}{dt} = \mu - \beta SI - \mu S \]
\[ \frac{dI}{dt} = \beta SI - \gamma I - \mu I \]
\[ \frac{dR}{dt} = \gamma I - \mu R \]

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

\[ \mathcal{F}_1 = \beta SI \]
\[ \mathcal{V}_1 = (\mu + \gamma)I \]
\[ \mathcal{G}_1 = \mu - \beta SI - \mu S \]
\[ \mathcal{G}_2 = \gamma I - \mu R \]

\[ F = \frac{\partial \mathcal{F}_1}{\partial I} = \beta \quad V = \frac{\partial \mathcal{V}_1}{\partial I} = \mu + \gamma \]

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

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

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

We deal with these two ‘infected’ compartments

\( n=2 \)
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.

$$F_1 = \beta SI$$

$$F_2 = 0$$

$$F = \begin{pmatrix}
    \frac{\partial(\beta SI)}{\partial E} & \frac{\partial(\beta SI)}{\partial I} \\
    0 & 0
\end{pmatrix} = \begin{pmatrix}
    0 & \beta \\
    0 & 0
\end{pmatrix}$$

$$\frac{dS}{dt} = \mu - (\beta I + \mu)S$$

$$\frac{dE}{dt} = \beta IS - (\mu + \sigma)E$$

$$\frac{dI}{dt} = \sigma E - (\mu + \gamma)I$$
Now, we write a new matrix $V$ that defines rate of transfer of infectives from one compartment to another

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

$$V = \begin{pmatrix} \mu + \sigma & 0 \\ -\sigma & \mu + \gamma \end{pmatrix}$$

$$\frac{dS}{dt} = \mu - (\beta I + \mu) S$$
$$\frac{dE}{dt} = \beta I S - (\mu + \sigma) E$$
$$\frac{dI}{dt} = \sigma E - (\mu + \gamma) I$$
NEXT GENERATION METHOD

• 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:

\[
FV^{-1} = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix}
\begin{pmatrix}
  \frac{\mu + \gamma}{(\mu + \gamma)(\mu + \sigma)} & 0 \\
  \frac{\sigma}{(\mu + \gamma)(\mu + \sigma)} & \frac{\mu + \sigma}{(\mu + \gamma)(\mu + \sigma)}
\end{pmatrix}
\]
This is Next Generation Operator. $R_0$ given by largest eigenvalue of this matrix:

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

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

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

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

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

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

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

\[
\begin{pmatrix}
  a_{11} & a_{12} \\
  a_{21} & a_{22}
\end{pmatrix}^{-1}
= \frac{1}{a_{11}a_{22} - a_{12}a_{21}}
\begin{pmatrix}
  a_{22} & -a_{12} \\
  -a_{21} & a_{11}
\end{pmatrix}
\]
\[
F = \begin{pmatrix}
\beta_P & \beta_A \\
0 & 0
\end{pmatrix} \quad V = \begin{pmatrix}
\delta_P & 0 \\
-\delta_P & \delta_A
\end{pmatrix} \quad V^{-1} = \frac{1}{\delta_P \delta_A} \begin{pmatrix}
\delta_A & \delta_P \\
0 & \delta_P
\end{pmatrix}
\]

\[
FV^{-1} = \begin{pmatrix}
\beta_P & \beta_A \\
0 & 0
\end{pmatrix} \begin{pmatrix}
\frac{1}{\delta_P} & 0 \\
\frac{1}{\delta_A} & \frac{1}{\delta_A}
\end{pmatrix}
\]

\[
|FV^{-1}| = \begin{pmatrix}
\frac{\beta_P}{\delta_P} + \frac{\beta_A}{\delta_A} - \Lambda & \frac{\beta_A}{\delta_A} \\
0 & -\Lambda
\end{pmatrix} = 0
\]

\[
R_0 = \frac{\beta_P}{\delta_P} + \frac{\beta_A}{\delta_A}
\]