LECTURE 2

Equilibrium Stability Analysis &
Next Generation Method

The death of an epidemic

- In SIR equations, let's divide equation for dX/dt by dZ/dt:

  $dX/dZ = -(\beta X Y/N)/(\gamma Y)$

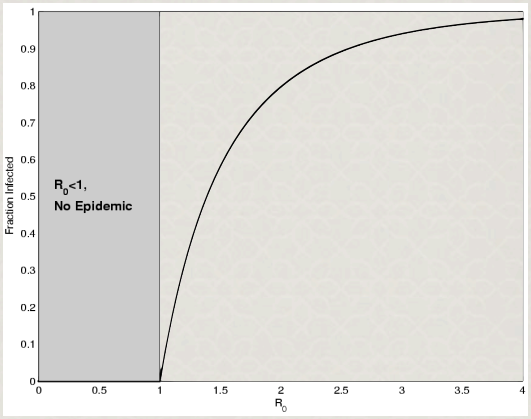
  $= -R_o X/N$

- Integrate with respect to Z
  - $X(t) = X(o)\, e^{-Z(t) R_o/N}$
- When epidemic is over, by definition, we have $X(\infty)$, $Y(\infty)$ $(=o)$, and $Z(\infty)$
- $X(\infty) = N - Z(\infty) = X(o)\, e^{-Z(\infty) R_o/N}$

The death of an epidemic

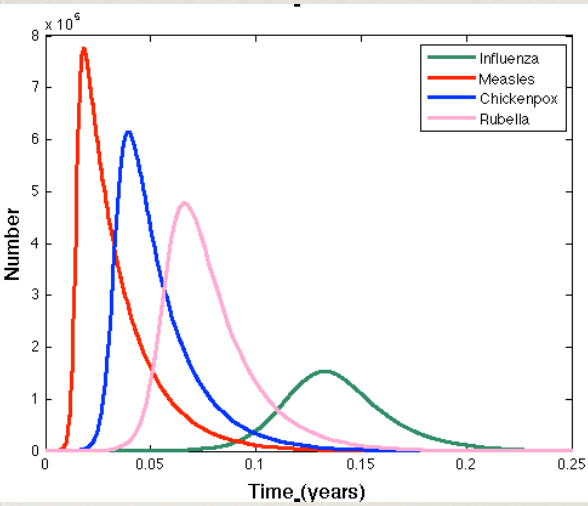
- So, $N - Z(\infty) - X(0)\, e^{-Z(\infty) R_0/N} = 0$
- Solve this numerically ('transcendental' equation)

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



Kermack & McKendrick (1927)

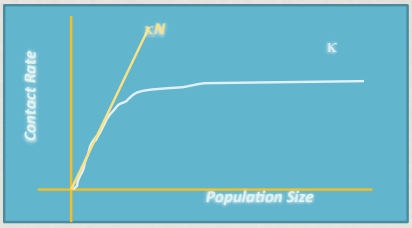
Simple Epidemics



	β	1/γ	R_0
"Measles"	886 yr^{-1}	0.019 yr	17
"Influenza"	180 yr^{-1}	0.011 yr	2
"Chickenpox"	315 yr^{-1}	0.022 yr	7
"Rubella"	200 yr^{-1}	0.025 yr	5

Frequency- or Density-Dependent Transmission?

- Assumed contact rate, κ, constant: 'mixing' is independent of population size: frequency-dependent transmission. Reasonable?
- If we assume contact rate to be κN (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 β and γ, there's now a threshold population density required for invasion

Incorporating virulence

- *Assume infectious individuals die at rate α*

$$\frac{dY}{dt} = \ldots - \gamma Y - \alpha Y$$

Transmission & R_0

Density Dependent

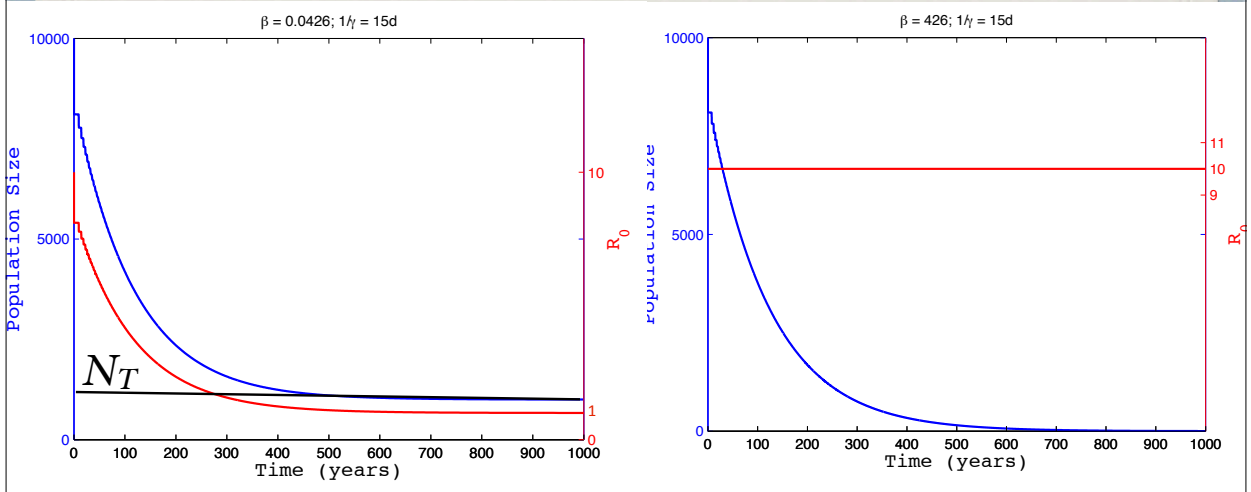
β=0.0426, γ=24, α=18, μ=0.02

N_T = 1000

Frequency Dependent

β=426, γ=24, α=18, μ=0.02

No invasion threshold



FD transmission → pathogen can wipe out host

What should we do?

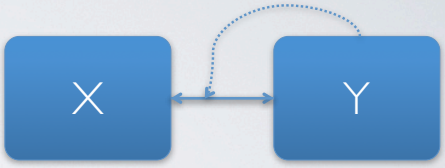
- If population size doesn't change, FD & DD equivalent ($\beta_{FD} = N \times \beta_{DD}$)
- Otherwise:
  - Frequency-dependence generally more appropriate in large populations with heterogenous mixing, STDs, vector-borne pathogens
  - Density-dependence representative of wildlife & livestock diseases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



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

System reduced to a single state variable

What is R_0 here? $R_0 = \frac{\beta}{\gamma}$

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

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

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

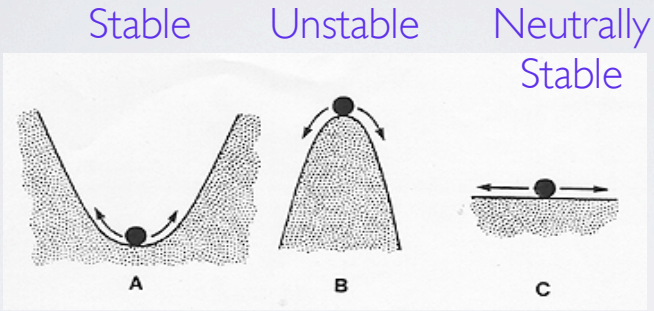
EQUILIBRIUM ANALYSIS

- 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

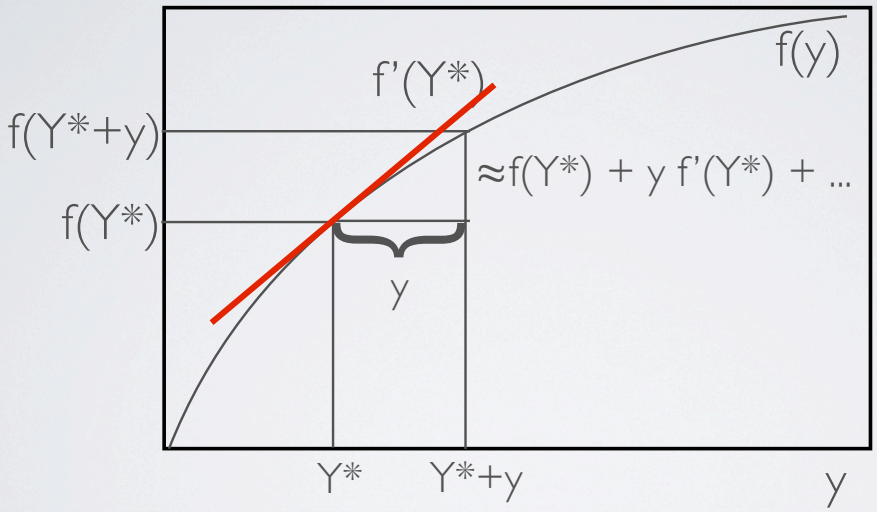
$$\frac{dy}{dt} = f(Y^*) + yf'(Y^*) + y^2 f''(Y^*) + \dots$$

- 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 Λ
- Our perturbation, y(t), will
  1. Grow exponentially if Λ >0 (equilibrium Unstable)
  2. Decay exponentially if Λ <0 (equilibrium Stable)

TAYLOR EXPANSION



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 $Y^* = N(1-\gamma/\beta) = N(1-1/R_0)$

$$f(Y) = \beta Y(1 - \frac{Y}{N}) - \gamma Y$$

$$f'(Y) = \frac{df(Y)}{dY} = \beta - 2\beta\frac{Y}{N} - \gamma$$

SIS MODEL

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

- So, when Y*=0,
  $f'(0) = \beta-\gamma$
  $\Rightarrow<0$ if $\gamma>\beta$ or $R_0<1$

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

STABILITY ANALYSIS

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

$$\frac{dN_i}{dt} = f_i(N_1, N_2, \ldots, N_n) \qquad i = 1, \ldots n$$

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

Keeling & Rohani (2008) pp30-31

Excellent texts: Strang (1986) & Kreyszig (2010)

ADDING A LATENT PERIOD: SEIR MODEL

- 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 (Λ_3) and (assume μ 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

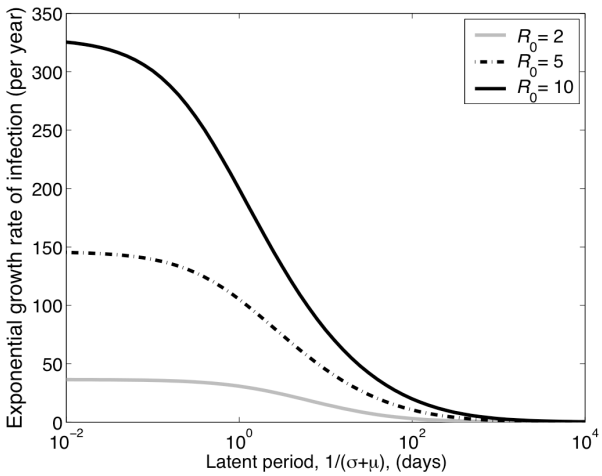
$$I_{SEIR} \approx I(0) \cdot e^{\frac{1}{2}\left(-(\sigma+\gamma)+\sqrt{4(R_0-1)\gamma\sigma+(\gamma+\sigma)^2}\right)}$$

- 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 $\Lambda=(\gamma+\mu)(\beta/(\gamma+\mu)-1)$
   - 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

$$\frac{dx_i}{dt} = \mathcal{F}_i(x, y) - \mathcal{V}_i(x, y) \qquad \text{i=1,..., n}$$

$$\frac{dy_j}{dt} = \mathcal{G}_j(x, y) \qquad \text{j=1,..., m}$$

- $\mathcal{F}_i$ = rate at which ***new infecteds*** enter compartment *i*
- $\mathcal{V}_i$ = transfer of individuals out of and into *i*th compartment

ASSUMPTIONS

I. $\mathcal{F}_i(0,y) = \mathcal{V}_i(0,y) = 0 \ \forall \ y>0$
(no new infections if no infecteds)

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

III. $\mathcal{V}_i(0,y) \leq 0 \ \forall \ y_i \geq 0$
(if compartment empty, can only have inflow)

IV. $\sum_i \mathcal{V}_i(x,y) \geq 0 \ \forall \ x_i \geq 0$ and $y_i \geq 0$
(sum is net outflow)

V. System $y' = \mathcal{G}(0,y)$ 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

$$\frac{dx_i}{dt} = \mathcal{F}_i(x,y) - \mathcal{V}_i(x,y) \qquad i=1,\ldots, n$$

$$\frac{dy_j}{dt} = \mathcal{G}_j(x,y) \qquad j=1,\ldots, m$$

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:

$$F_{ij} = \frac{\partial \mathcal{F}_i}{\partial x_j}(0,y^*) \qquad V_{ij} = \frac{\partial \mathcal{V}_i}{\partial x_j}(0,y^*)$$

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', ρ) 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)

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

$$F = \frac{\partial \mathcal{F}_1}{\partial I} = \beta \qquad V = \frac{\partial \mathcal{V}_1}{\partial I} = \mu + \gamma$$

Hence, $R_0 = \dfrac{\beta}{(\mu + \gamma)}$

NEXT GENERATION METHOD

- SEIR equations (again):

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

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

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

n=2
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

$$F_1 = \beta SI$$

$$F_2 = 0$$

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

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

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

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

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

NEXT GENERATION METHOD

- Now, we write a new matrix V that defines rate of transfer of infectives from one compartment to another

$$V_1 = (\mu + \sigma)E$$

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

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

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

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

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

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:

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

NEXT GENERATION METHOD

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

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

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

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

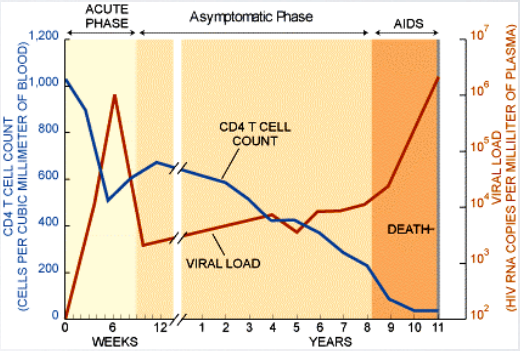
Check: $\sigma \to \infty$, $R_0 = \beta/(\mu+\gamma)$ as for SIR model

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

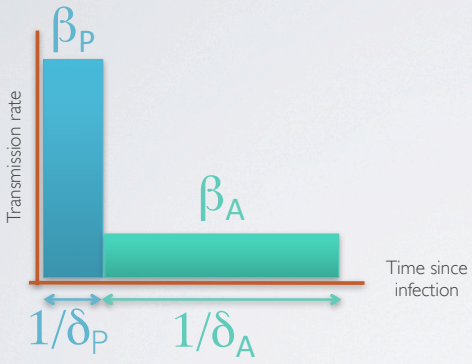
CLASS CHALLENGE: HIV PROGRESSION

Model needs to consider infectivity of different stages and respective durations



Fauci et al. 1995; Ann Intern Med

CLASS CHALLENGE: HIV PROGRESSION



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

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

$$\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}^{-1} = \frac{1}{a_{11}a_{22} - a_{12}a_{21}} \begin{pmatrix} a_{22} & -a_{12} \\ -a_{21} & a_{11} \end{pmatrix}$$

SOLUTION

$$F = \begin{pmatrix} \beta_P & \beta_A \\ 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} \delta_P & 0 \\ -\delta_P & \delta_A \end{pmatrix}$$

$$V^{-1} = \frac{1}{\delta_P \delta_A} \begin{pmatrix} \delta_A & \delta_P \\ 0 & \delta_P \end{pmatrix}$$

SOLUTION … C'TD

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

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

$$R_0 = \frac{\beta_P}{\delta_P} + \frac{\beta_A}{\delta_A}$$