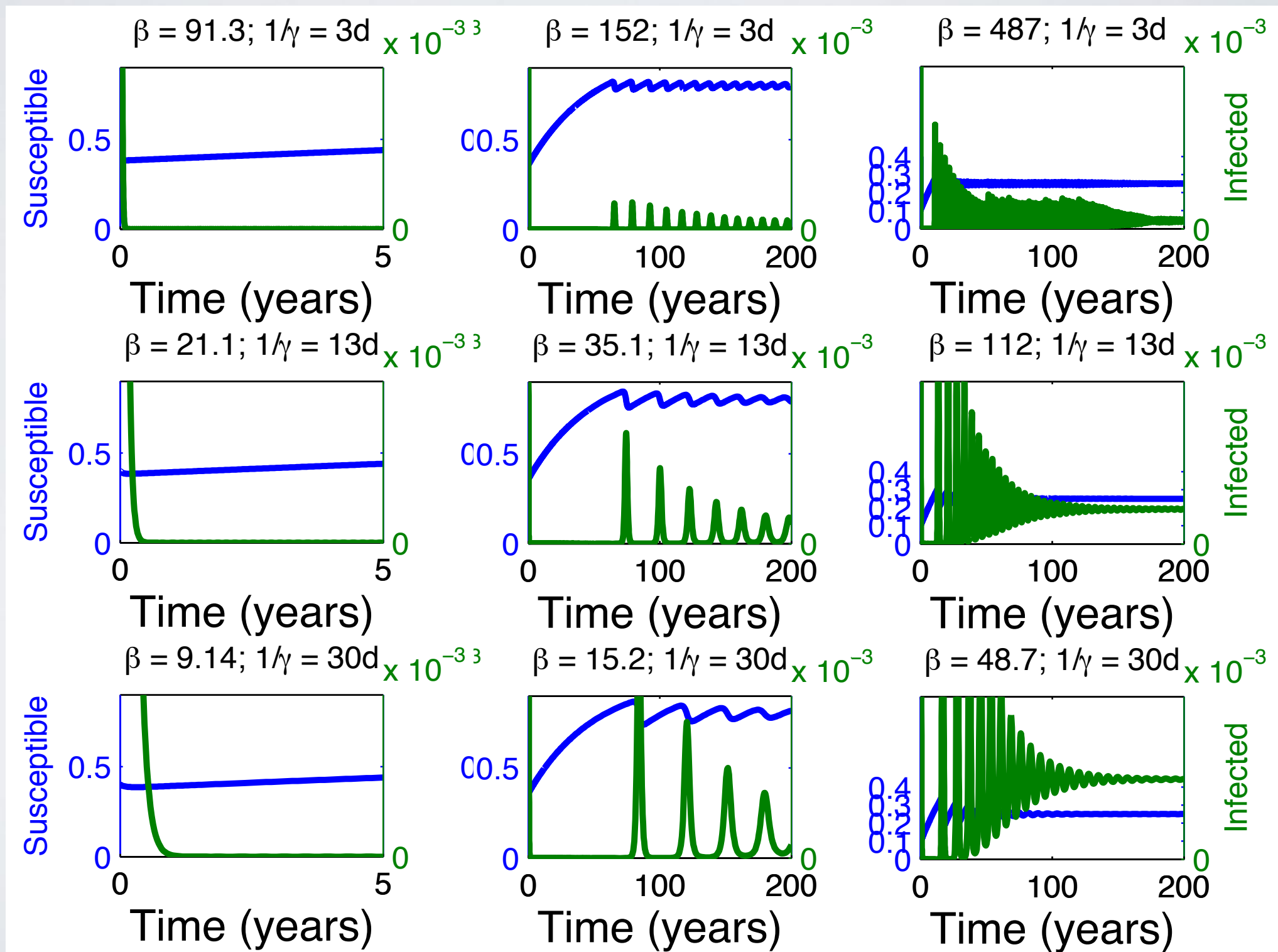


LECTURE 2

Equilibrium Stability Analysis &
Next Generation Method

MODEL OUTPUT

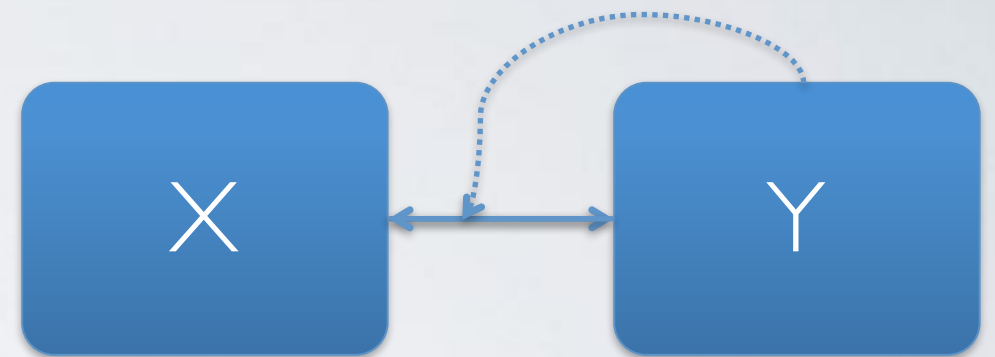


LONG-TERM DYNAMICS

- 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



$$\begin{aligned}\frac{dX}{dt} &= \gamma Y - \beta X \frac{Y}{N} \\ \frac{dY}{dt} &= \beta X \frac{Y}{N} - \gamma Y\end{aligned}$$

System reduced to a single state variable

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

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

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

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 $N(1-1/R_0)$

STABILITY ANALYSIS

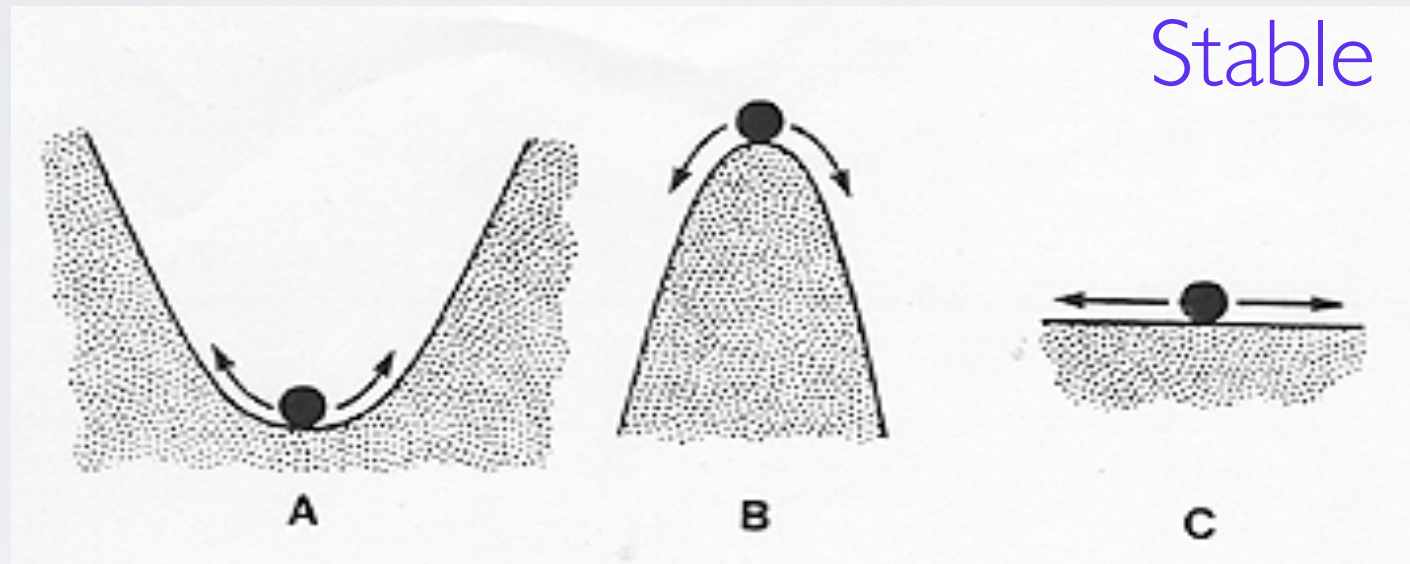
- So, we have two equilibria – one where pathogen persists and one where it is absent
- What are conditions that determine when we observe one or other?
- For answer to this question, we need to carry out *linear stability analysis*
- Basic idea is to start at an equilibrium point and introduce a slight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

EQUILIBRIUM STABILITY

Stable

Unstable

Neutrally
Stable



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 $Y = Y^* + y$ ($y \ll Y^*$), substitute in ODE

$$\frac{d(Y + y)}{dt} = \frac{dy}{dt} = f(Y^* + y)$$

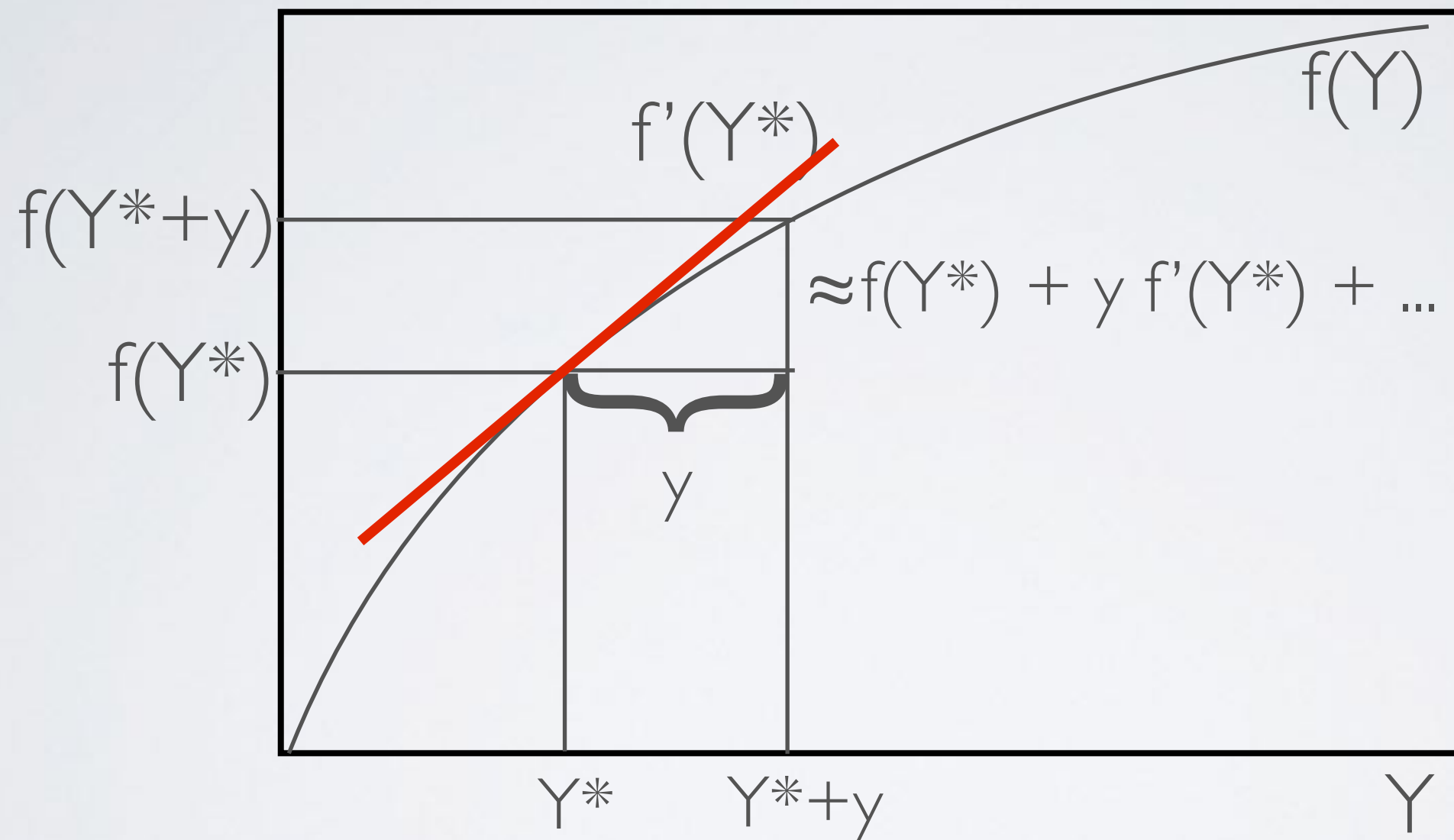
LINEAR STABILITY ANALYSIS: 1-D CASE

- $f(Y^*+y)$ can be expressed as a Taylor expansion

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

- Note: f' means derivative of f with respect to Y

TAYLOR EXPANSION



LINEAR STABILITY ANALYSIS: 1-D CASE

- $f(Y^*+y)$ can be expressed as a Taylor expansion

$$\frac{dy}{dt} = f(Y^*) + y f'(Y^*) + \frac{1}{2} y^2 f''(Y^*) + \dots$$

- Note: f' means derivative of f with respect to Y
- We end up with a linear ODE, solution to which is

$$y(t) = y(0)e^{f'(Y^*)t}$$

- $f'(Y^*)$ is 'eigenvalue' -- from now on, we'll call it Λ
- Our perturbation, $y(t)$, will

1. Grow exponentially if $\Lambda > 0$ (equilibrium **Unstable**)

2. Decay exponentially if $\Lambda < 0$ (equilibrium **Stable**)

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 $Y^*=0$,

$$f'(0) = \beta - \gamma$$

$\Rightarrow < 0$ 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

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

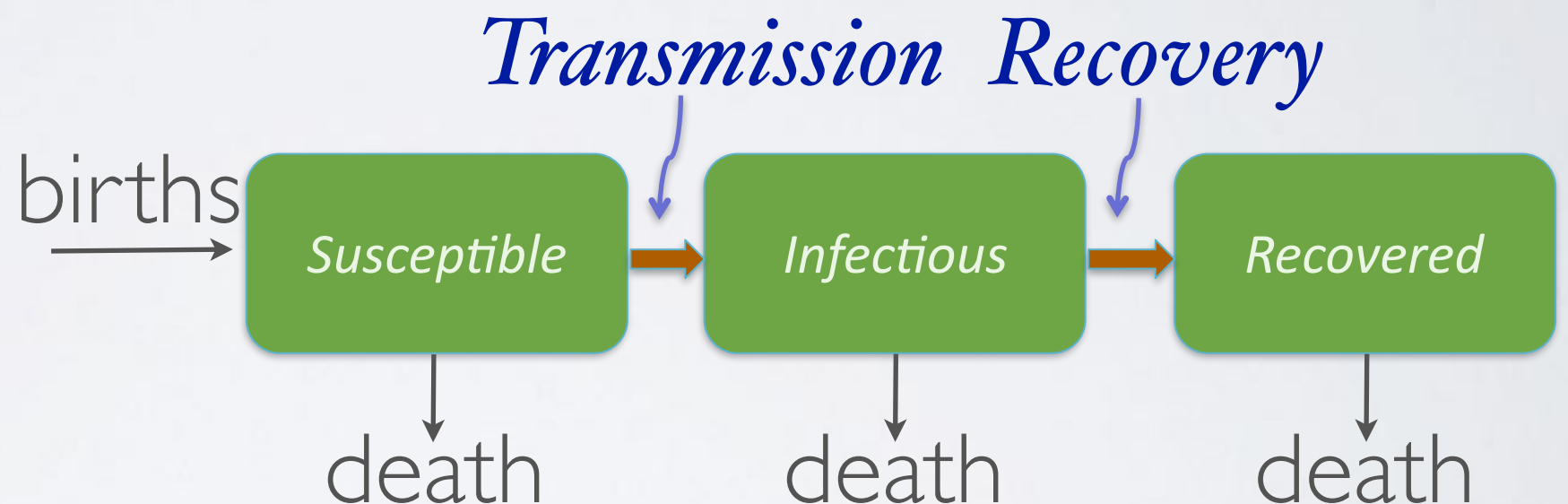
- Now, we perturb equilibrium ($N_i = N_i^* + x_i$, $x_i \ll N_i^*$), Taylor expand $f_i()$ and ignore higher order terms (x_i^2 , $x_i x_j$ etc)
- Growth of perturbations (x_i , $i = 1, \dots, n$) given by linear set of ODEs

SIR MODEL WITH DEMOGRAPHY

- Move on to thinking about recurrent epidemics, facilitated by replenishment of susceptible pool via naïve births

$$\begin{aligned}\frac{dS}{dt} &= \mu - \beta SI - \mu S \\ \frac{dI}{dt} &= \beta SI - (\gamma + \mu)I \\ \frac{dR}{dt} &= \gamma I - \mu R\end{aligned}$$

$$S+I+R = 1 \quad R_0 = \frac{\beta}{(\mu + \gamma)}$$



- μ is both per capita host birth and death rate
- Population size assumed constant
- Host life expectancy given by $1/\mu$

EQUILIBRIUM ANALYSIS - SIR

- Get $S^* = 1/R_0$ and $I^* = \mu/\beta (R_0 - 1)$ (check)
- So, at endemic equilibrium, we have

$$(S^*, I^*, R^*) = \left(\frac{1}{R_0}, \frac{\mu}{\beta} (R_0 - 1), 1 - \frac{1}{R_0} - \frac{\mu}{\beta} (R_0 - 1) \right)$$

This equilibrium is only (biologically) feasible as long as $R_0 > 1$

Note: we also have $(S^*, I^*, R^*) = (1, 0, 0)$

This is called disease-free equilibrium (DFE) stable only if $R_0 < 1$

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 dI/dt for SIR model, evaluated at disease free equilibrium

$$\begin{aligned}\frac{dI}{dt} &= \beta SI - (\mu + \gamma)I \\ &= \beta I - (\mu + \gamma)I\end{aligned}$$

- Can solve this wrt t

$$I_{SIR} \approx I(0) \times e^{\beta - (\mu + \gamma)t}$$

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

INVASION PHASE: SEIR

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

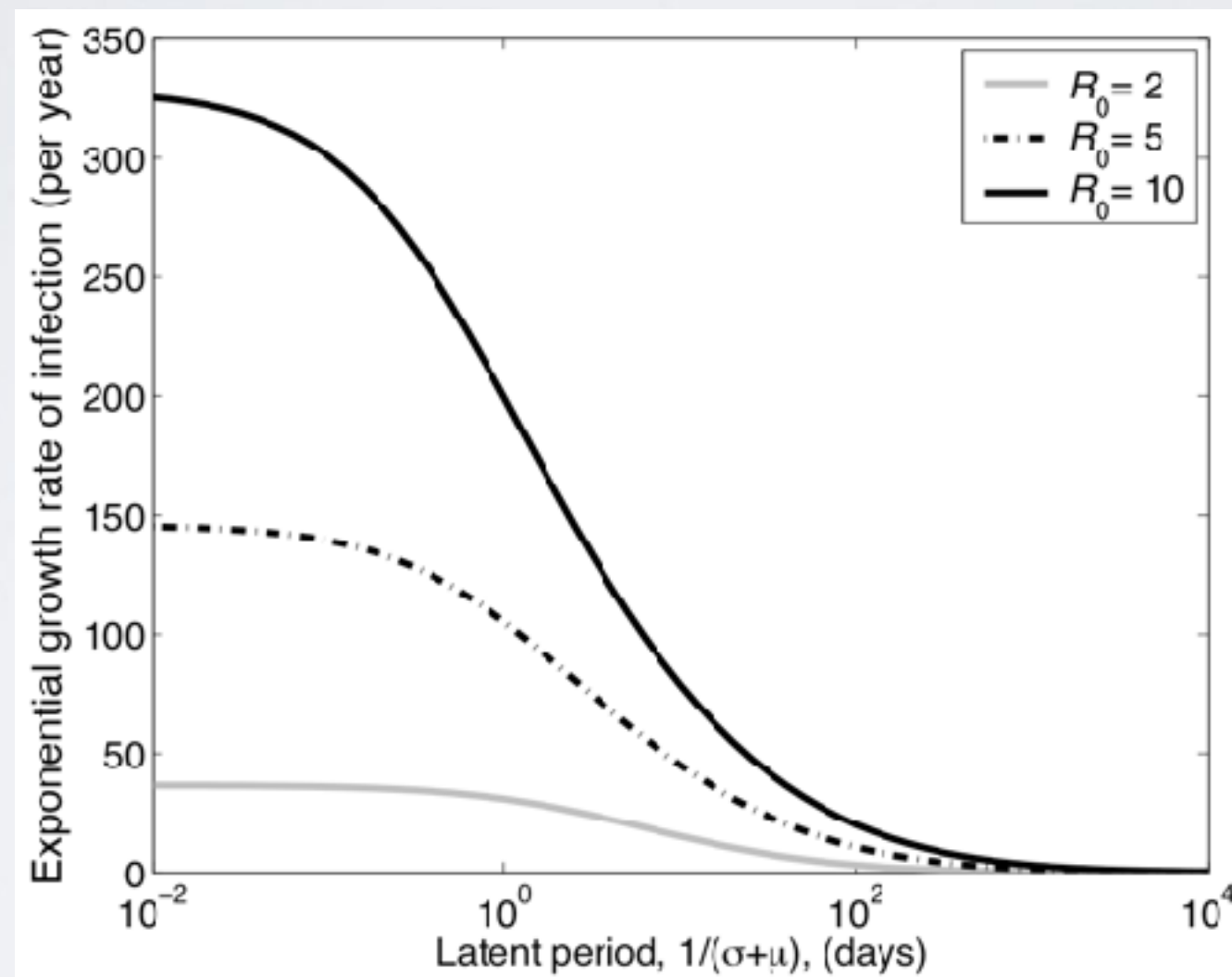
$$I_{SEIR} \approx I(0) \cdot e^{\frac{1}{2} \left(-(\sigma + \gamma) + \sqrt{4(R_0 - 1)\gamma\sigma + (\gamma + \sigma)^2} \right)}$$

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

NEXT GENERATION METHOD

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

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

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

ASSUMPTIONS

- I. $\mathcal{F}_i(0,y) = \mathcal{V}_i(0,y) = 0 \quad \forall y > 0$
(no new infections if no infecteds)
- II. $\mathcal{F}_i(x,y) \geq 0 \quad \forall x_i \geq 0 \text{ and } y_i \geq 0$
(no new infections if no infecteds)
- III. $\mathcal{V}_i(0,y) \leq 0 \quad \forall y_i \geq 0$
(if compartment empty, can only have inflow)
- IV. $\sum_i \mathcal{V}_i(x,y) \geq 0 \quad \forall x_i \geq 0 \text{ and } y_i \geq 0$
(sum is net outflow)
- V. System $y' = \mathcal{G}(0,y)$ has unique asymptotically stable equilibrium, y^*

SIR MODEL

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

$$\begin{aligned}\frac{dS}{dt} &= \mu - \beta SI - \mu S \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I \\ \frac{dR}{dt} &= \gamma I - \mu R\end{aligned}$$

$$\mathcal{F}_1 = \beta SI$$

$$\mathcal{V}_1 = (\mu + \gamma)I$$

$$\mathcal{G}_1 = \mu - \beta SI - \mu S$$

$$\mathcal{G}_2 = \gamma I - \mu R$$

LINEARIZATION

General system

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

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

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:

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

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

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

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

$$\mathcal{F}_1 = \beta SI$$

$$\mathcal{V}_1 = (\mu + \gamma)I$$

$$\mathcal{G}_1 = \mu - \beta SI - \mu S$$

$$\mathcal{G}_2 = \gamma I - \mu R$$

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

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

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:

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

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

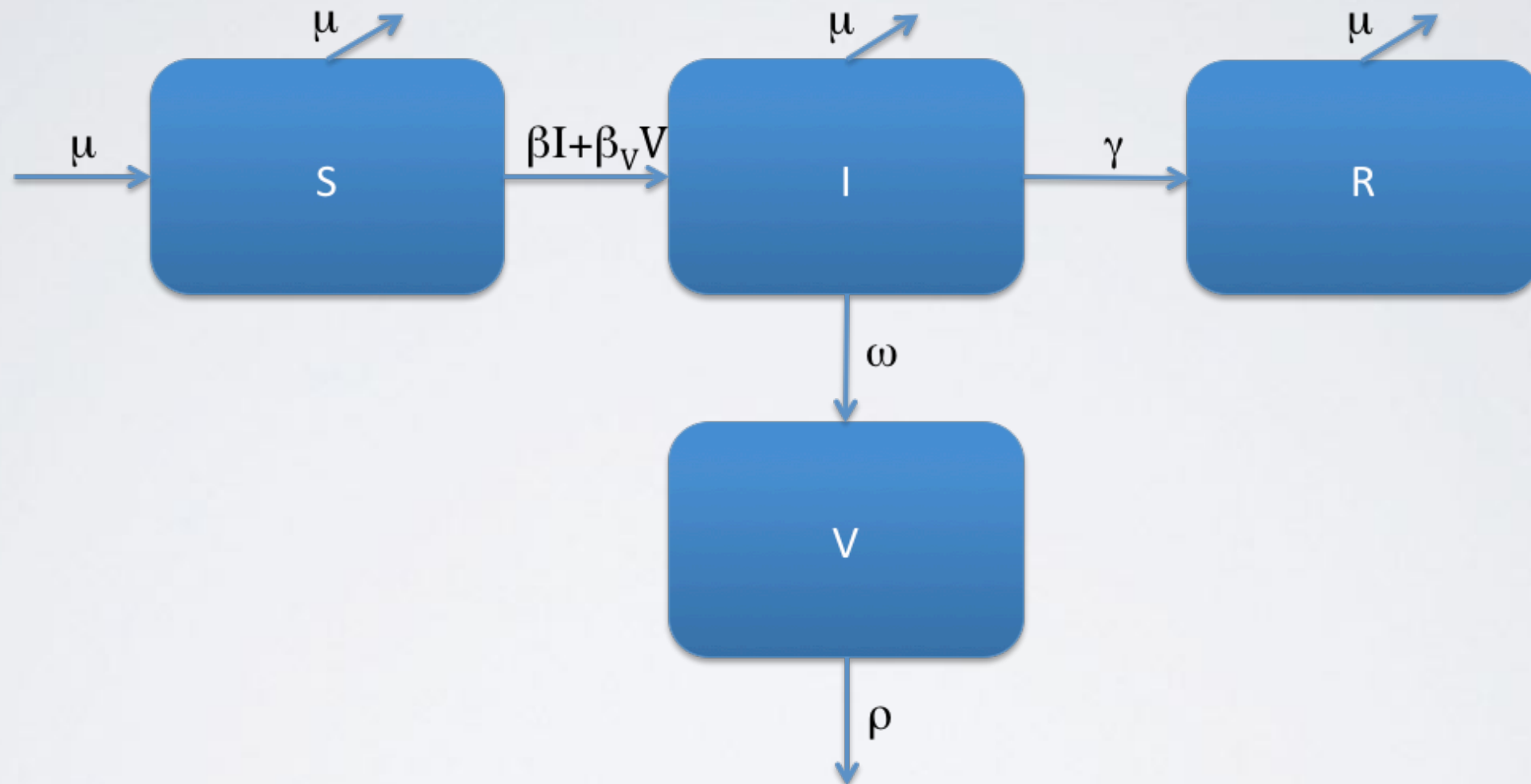
Check: $\sigma \rightarrow \infty$, $R_0 = \beta/(\mu+\gamma)$ as for SIR model

ANOTHER EXAMPLE

For some infectious diseases (eg avian influenza viruses), transmission thought to occur via two distinct pathways.

1. Susceptible hosts (birds) may become infected as a result of direct contact with an infectious individual
2. OR, birds may also become infected via contact with (ie drinking) contaminated water at rate β_v . Each infectious individual sheds virus into environment at a rate ω , and virus in environmental reservoir (denoted by V) decays at a rate ρ

FLOW DIAGRAM



$$\frac{dS}{dt} = \mu(1 - S) - (\beta I + \beta_V V)S$$

$$\frac{dI}{dt} = (\beta I + \beta_V V)S - (\mu + \gamma)I$$

$$\frac{dV}{dt} = \omega I - \rho V$$

NEXT GENERATION MATRIX

- Matrix F , defines new infections in different compartments

$$F_1 = \beta SI + \beta_V SV; \quad F_2 = 0$$

$$F = \begin{pmatrix} \beta & \beta_V \\ 0 & 0 \end{pmatrix}$$

$$\frac{dS}{dt} = \mu(1 - S) - (\beta I + \beta_V V)S$$

$$\frac{dI}{dt} = (\beta I + \beta_V V)S - (\mu + \gamma)I$$

$$V_1 = (\mu + \gamma)I; \quad V_2 = \rho V - \omega I$$

$$\frac{dV}{dt} = \omega I - \rho V$$

$$V = \begin{pmatrix} (\mu + \gamma) & 0 \\ -\omega & \rho \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{(\mu + \gamma)} & 0 \\ \frac{\omega}{\rho(\mu + \gamma)} & \frac{1}{\rho} \end{pmatrix}$$

NEXT GENERATION MATRIX

- Next Generation Operator given by

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

- Work out spectral radius ($\det(FV^{-1} - \lambda I) = 0$):

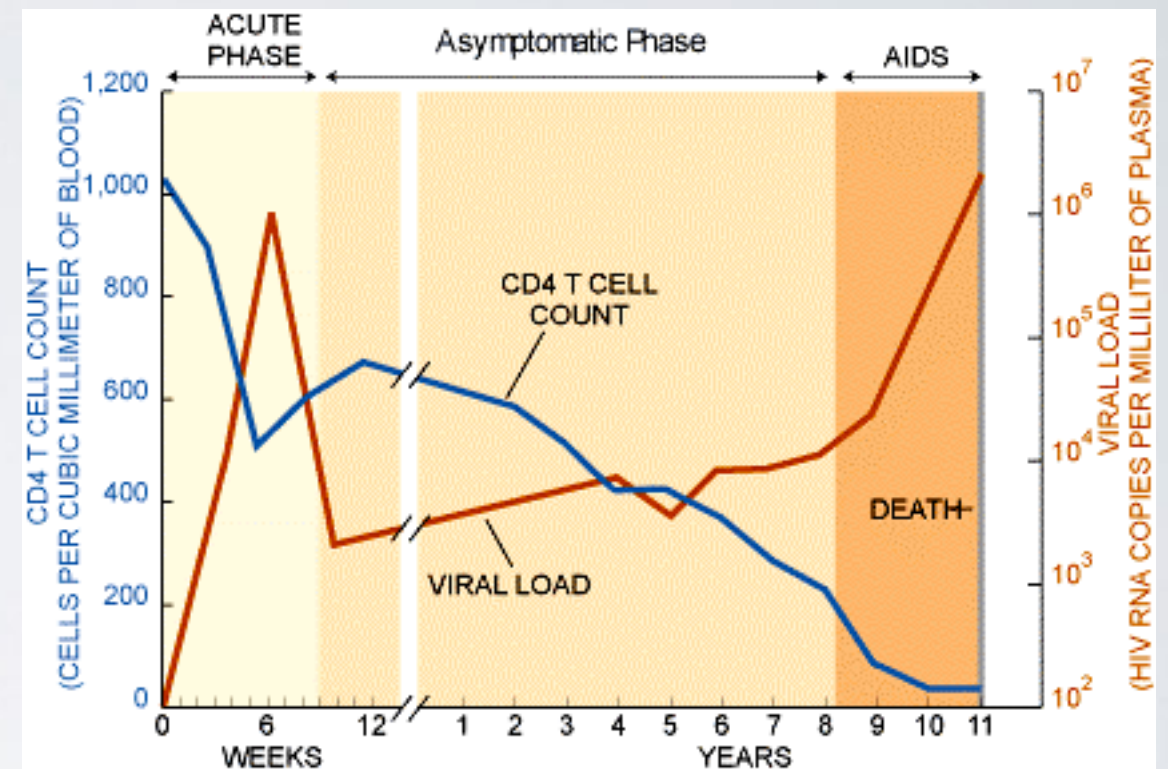
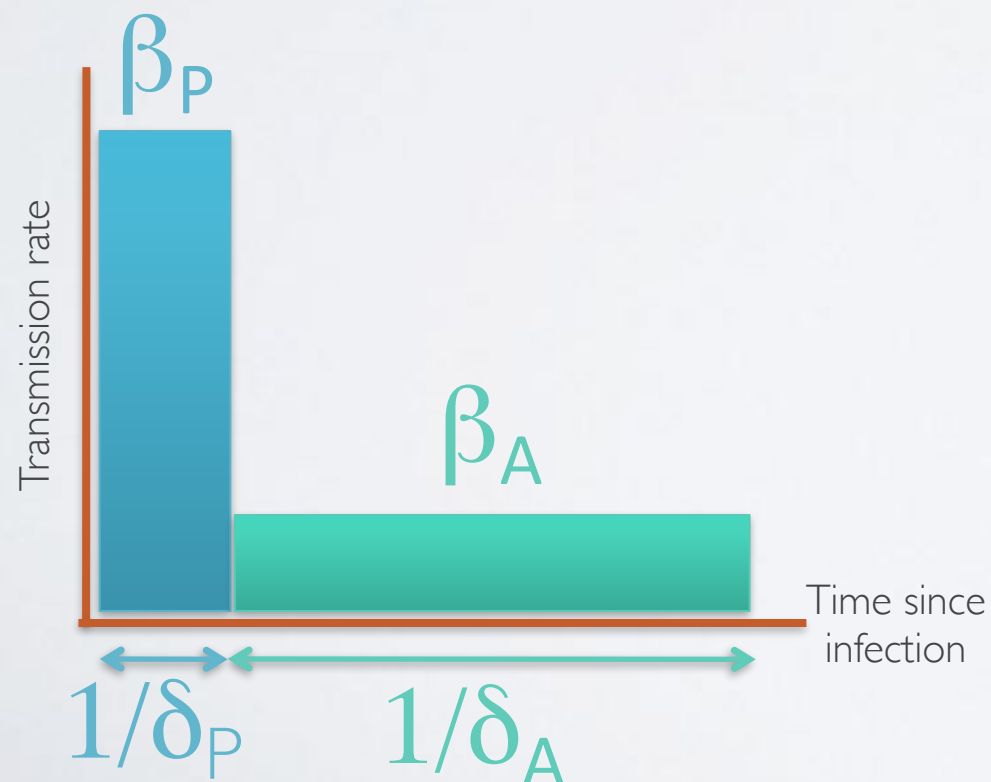
$$R_0 = \frac{\beta}{(\mu + \gamma)} + \frac{\beta_V \omega}{\rho(\mu + \gamma)}$$

LECTURE SUMMARY ...

- Linear Stability Analysis
- SIR/SEIR endemic eqm stable if $R_0 > 1$
- 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

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

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

SOLUTION

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

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

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

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