A linear algebra approach to understanding the basic reproduction number

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Motivation

- Just because you have the tools and know what to do with them doesn't mean you know why they work.

- The linear algebra techniques of matrix multiplication and inversion may allow us to compute the basic reproduction number, but interpretation requires that we understand what the pieces and operations mean.

- Outline: Next Generation Method, Geometric explanation of why it works, Graph theory methods of interpretation.

Basic reproduction number

- "the average number of secondary cases arising from a typical primary case in an entirely susceptible population"

- In practice, R_0 may not correspond exactly to the above definition, especially when considering extensions like vectors or the environment

- Threshold for the local stability of the disease-free equilibrium (DFE)

Classic SIR example

$$\frac{dS}{dt} = -\beta IS$$

$$\frac{dI}{dt} = \beta IS - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

- In the classic SIR model, R_0 is the contact rate times the average duration of the infectious period
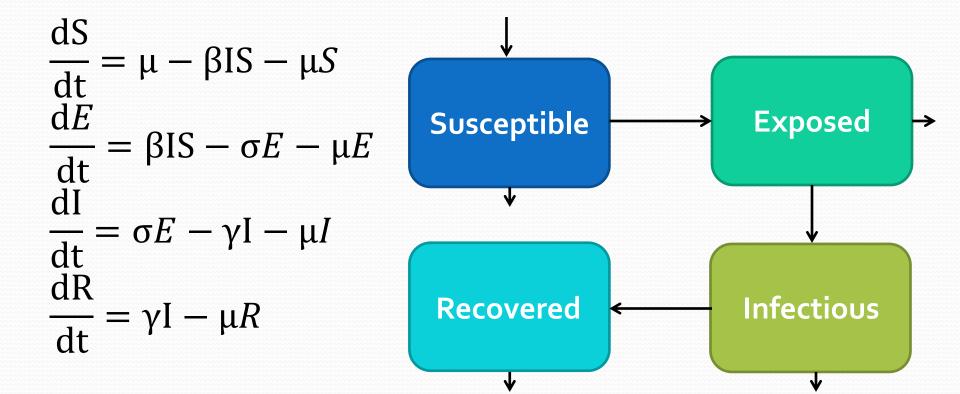
$$R_0 = \beta \times \frac{1}{\gamma}$$

contact rate

average infectious period

Next generation method

- Multiple methods exist to calculate R_0, but the next generation method is one of the most common and rigorous ways.

- Define:
  - Let x be the vector of states and x_0 the DFE
  - For each infected compartment i
    - Let f_i be the rate of influx of newly infected people to compartment i
    - Let v_i be the net transfer of individuals out of compartment i

- Then $\frac{dx_i}{dt} = f_i(x) - v_i(x)$

Example: SEIR with demography

$$\frac{dS}{dt} = \mu - \beta IS - \mu S$$

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

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

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

Example: SEIR with demography

$$\frac{dS}{dt} = \mu - \beta IS - \mu S$$

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

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

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

$$f(x) = \begin{bmatrix} \beta IS \\ 0 \end{bmatrix}$$

$$v(x) = \begin{bmatrix} (\sigma + \mu)E \\ (\gamma + \mu)I - \sigma E \end{bmatrix}$$

Next generation method

- Define:
  - Let F and V be the Jacobians of f and v evaluated at the disease-free equilibrium
- That is

  - $F_{ij} = \dfrac{df_i}{dx_j}\bigg|_{x=x_0}$

  - $V_{ij} = \dfrac{dv_i}{dx_j}\bigg|_{x=x_0}$

$$\text{e.g. } F = \begin{bmatrix} \dfrac{df_E}{dE} & \dfrac{df_E}{dI} \\ \dfrac{df_I}{dE} & \dfrac{df_I}{dI} \end{bmatrix}_{x=x_0}$$
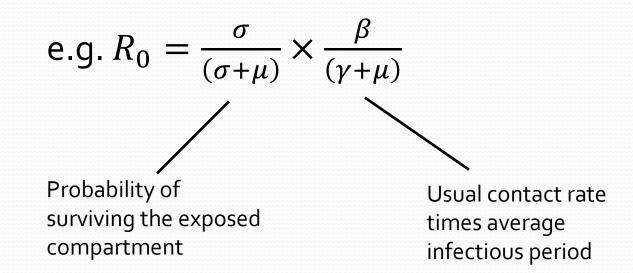
Example: SEIR with demography

$$\frac{dS}{dt} = \mu - \beta IS - \mu S$$

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

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

$$f(x) = \begin{bmatrix} \beta IS \\ 0 \end{bmatrix}$$

$$v(x) = \begin{bmatrix} (\sigma + \mu)E \\ (\gamma + \mu)I - \sigma E \end{bmatrix}$$

$$F = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix}$$

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

Next generation method

- The matrix FV^{-1} is called the next generation matrix

- The basic reproduction number is the spectral radius (largest eigenvalue) of the next generation matrix.
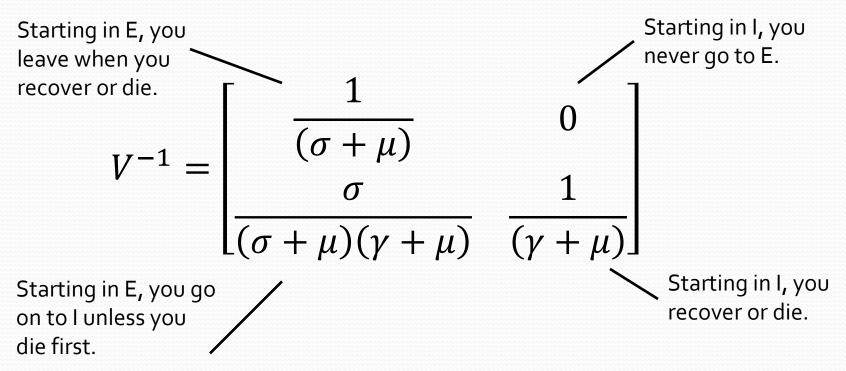
$$\text{e.g. } R_0 = \frac{\sigma}{(\sigma+\mu)} \times \frac{\beta}{(\gamma+\mu)}$$

Probability of surviving the exposed compartment

Usual contact rate times average infectious period

Um, what?
Why FV^{-1}?

Interpreting the NGM

- The (j, k) entry of V^{-1} is the average length of time an individual introduced into compartment k spends in compartment j in its lifetime.

$$V^{-1} = \begin{bmatrix} \dfrac{1}{(\sigma + \mu)} & 0 \\ \dfrac{\sigma}{(\sigma + \mu)(\gamma + \mu)} & \dfrac{1}{(\gamma + \mu)} \end{bmatrix}$$

Interpreting the NGM

- The (j, k) entry of V^{-1} is the average length of time an individual introduced into compartment k spends in compartment j in its lifetime.

Starting in E, you leave when you recover or die.

Starting in I, you never go to E.

$$V^{-1} = \begin{bmatrix} \dfrac{1}{(\sigma + \mu)} & 0 \\[4mm] \dfrac{\sigma}{(\sigma + \mu)(\gamma + \mu)} & \dfrac{1}{(\gamma + \mu)} \end{bmatrix}$$
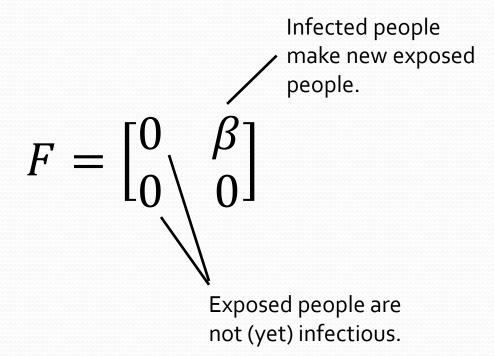
Starting in E, you go on to I unless you die first.

Starting in I, you recover or die.

Interpreting the NGM

- The (i, j) entry of F is the rate at which infected individuals in compartment j produce a new infection in compartment i.

$$F = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix}$$

Interpreting the NGM

- The (i, j) entry of F is the rate at which infected individuals in compartment j produce a new infection in compartment i.

Infected people make new exposed people.

$$F = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix}$$

Exposed people are not (yet) infectious.

Interpreting the NGM

- The (i, k) entry of FV^{-1} is the thus the expected number of new infections in compartment i produced by an infected individual started in k .

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

Interpreting the NGM

- The (i, k) entry of FV^{-1} is the thus the expected number of new infections in compartment i produced by an infected individual started in k .
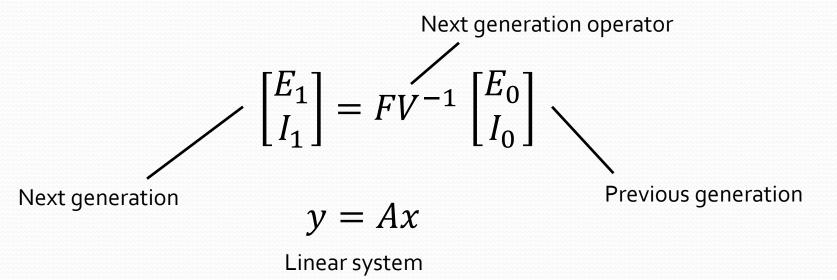
$$FV^{-1} = \begin{bmatrix} \dfrac{\beta\sigma}{(\sigma + \mu)(\gamma + \mu)} & \dfrac{\beta}{(\gamma + \mu)} \\ 0 & 0 \end{bmatrix}$$

Infected people make new exposed, not new infectious.

But why the spectral radius?

Next generation

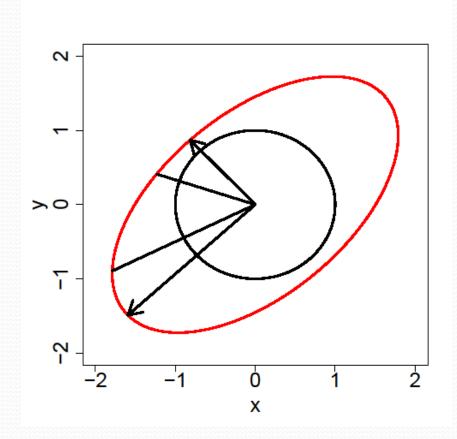- Near the disease free equilibrium, the process of making the next generation is approximately linear.

Next generation operator

$$\begin{bmatrix} E_1 \\ I_1 \end{bmatrix} = FV^{-1} \begin{bmatrix} E_0 \\ I_0 \end{bmatrix}$$

Next generation

Previous generation

$$y = Ax$$

Linear system

- We can use the geometry of linear systems!

Apply a linear transformation to a circle

- The resulting ellipse has major and minor axes.

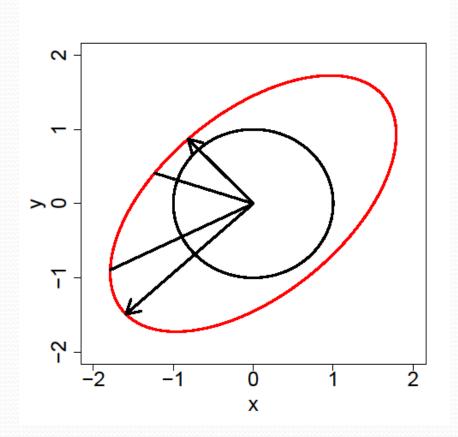- We also note the eigenvectors of the transformation matrix.

$$A = \begin{bmatrix} 1.58 & 0.84 \\ 0.14 & 1.72 \end{bmatrix}$$

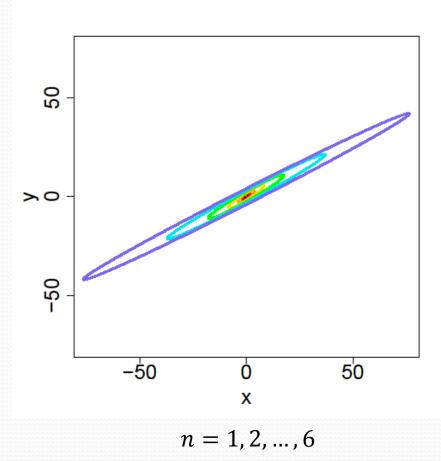# Apply a linear transformation to a circle

- The size of the next generation depends on the initial conditions.

- The largest possible next generation ($\|A\| = 2.18$) is not the same as the largest eigenvalue ($\rho(A) = 2$).
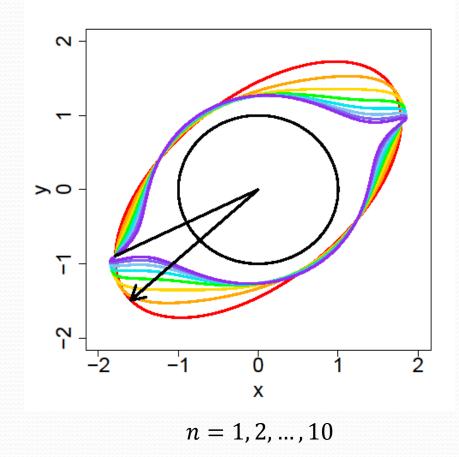
Multiple generations: $A^n x$

- After multiple generations, the ellipse becomes exaggerated, and the relative influence of the eigenvectors changes.

- This tells us about long term behavior.

- But we want AVERAGE behavior.
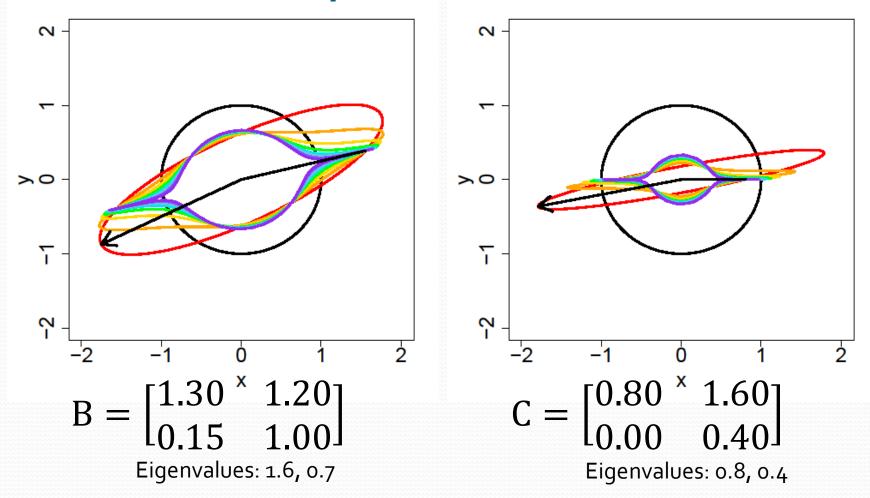
- We need to scale the ellipses.

$n = 1, 2, \ldots, 6$

Scale so that magnitude is $\sqrt[n]{\|A^n x\|}$

- Taking the limit as $n \to \infty$ gives the long run average behavior.

- As n increases, we see $\sqrt[n]{\|A^n\|}$ converging to $\rho(A)$.

- The size of the average next generation will be $\rho(A)$ because (almost every) initial condition converges to lie along the dominant eigenvector.
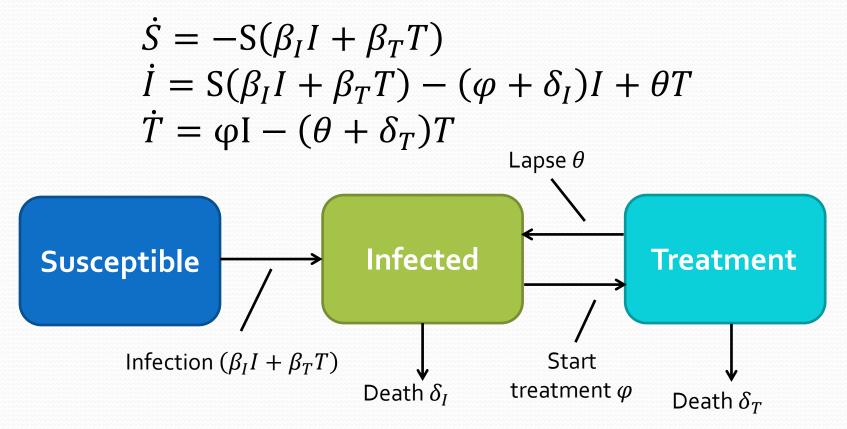
$$n = 1, 2, \ldots, 10$$

More examples

$$B = \begin{bmatrix} 1.30 & 1.20 \\ 0.15 & 1.00 \end{bmatrix}$$

Eigenvalues: 1.6, 0.7

$$C = \begin{bmatrix} 0.80 & 1.60 \\ 0.00 & 0.40 \end{bmatrix}$$

Eigenvalues: 0.8, 0.4

Interpreting the NGM

- We now understand why the spectral radius is the right measure.

- But we still may struggle with interpreting the NGM matrix in terms of our parameters, especially in high dimensional cases.

Example: Treatment compliance

- Infected individuals can go on and off a treatment that reduces their infectivity and mortality rate

$$\dot{S} = -S(\beta_I I + \beta_T T)$$
$$\dot{I} = S(\beta_I I + \beta_T T) - (\varphi + \delta_I)I + \theta T$$
$$\dot{T} = \varphi I - (\theta + \delta_T)T$$

Lapse θ

Susceptible → **Infected** ⇄ **Treatment**

Infection $(\beta_I I + \beta_T T)$

Death δ_I

Start treatment φ

Death δ_T

Example: Treatment compliance

$$f(x) = \begin{bmatrix} S(\beta_I I + \beta_T T) \\ 0 \end{bmatrix}$$

$$F = \begin{bmatrix} \beta_I & \beta_T \\ 0 & 0 \end{bmatrix}$$

$$v(x) = \begin{bmatrix} (\varphi + \delta_I)I - \theta T \\ (\theta + \delta_T)T - \varphi I \end{bmatrix}$$

$$V = \begin{bmatrix} \varphi + \delta_I & -\theta \\ -\varphi & \theta + \delta_T \end{bmatrix}$$
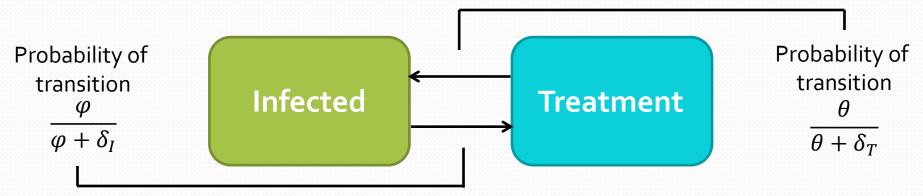
$$V^{-1} = \begin{bmatrix} \dfrac{\theta + \delta_T}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta} & \dfrac{\theta}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta} \\ \dfrac{\varphi}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta} & \dfrac{\varphi + \delta_I}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta} \end{bmatrix}$$

Um, what?

These are average times spent in the compartments?

How do we interpret $(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta$?

Expected number of visits

- How many times, on average, will I not be on treatment? To answer this, first ask, what is the probability that I relapse if I start treatment.
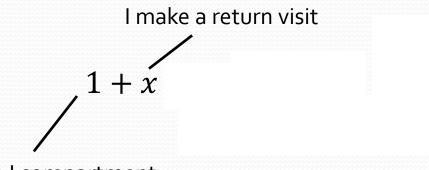
Probability of transition $\dfrac{\varphi}{\varphi + \delta_I}$

Infected

Treatment

Probability of transition $\dfrac{\theta}{\theta + \delta_T}$

- The probability of jumping to treatment and back is
$$\frac{\varphi\theta}{(\varphi+\delta_I)(\theta+\delta_T)}.$$

Expected number of visits

- Let us count the number of visits times the probability of making the visit. This will give us the expected number.

- First define $x := \dfrac{\varphi\theta}{(\varphi+\delta_I)(\theta+\delta_T)}$
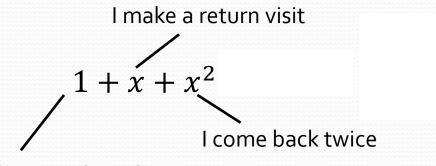
1

I start in the I compartment

Expected number of visits

- Let us count the number of visits times the probability of making the visit. This will give us the expected number.

- First define $x := \dfrac{\varphi\theta}{(\varphi+\delta_I)(\theta+\delta_T)}$

I make a return visit

$$1 + x$$
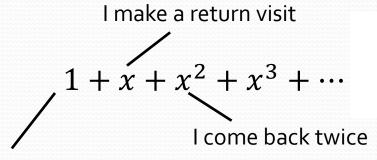
I start in the I compartment

Expected number of visits

- Let us count the number of visits times the probability of making the visit. This will give us the expected number.

- First define $x := \dfrac{\varphi\theta}{(\varphi+\delta_I)(\theta+\delta_T)}$

I make a return visit

$$1 + x + x^2$$

I come back twice

I start in the I compartment

Expected number of visits

- Let us count the number of visits times the probability of making the visit. This will give us the expected number.

- First define $x := \dfrac{\varphi\theta}{(\varphi + \delta_I)(\theta + \delta_T)}$

I make a return visit

$$1 + x + x^2 + x^3 + \cdots$$

I come back twice
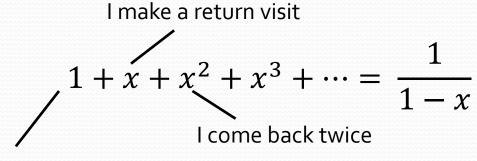
I start in the I compartment

Expected number of visits

- Let us count the number of visits times the probability of making the visit. This will give us the expected number.

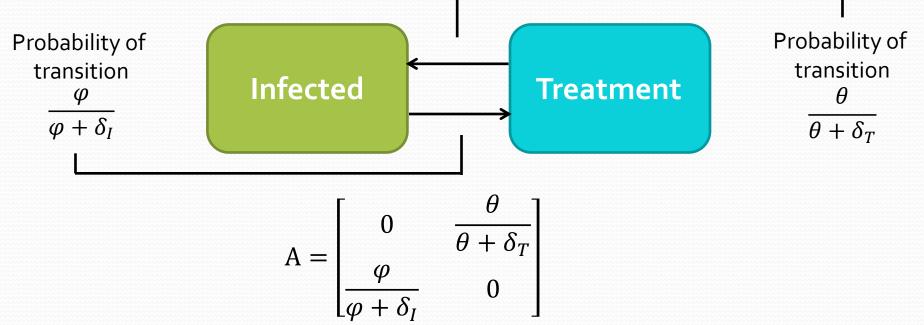- First define $x := \dfrac{\varphi\theta}{(\varphi+\delta_I)(\theta+\delta_T)}$

I make a return visit

$$1 + x + x^2 + x^3 + \cdots = \frac{1}{1-x}$$

I come back twice

I start in the I compartment

Expected number of visits

- So the expected number of visits to I is

$$\frac{1}{1-x} = \frac{1}{1 - \dfrac{\varphi\theta}{(\varphi + \delta_I)(\theta + \delta_T)}} = \frac{(\varphi + \delta_I)(\theta + \delta_T)}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta}$$

- Each visit to I lasts, on average, $\frac{1}{\varphi + \delta_I}$.

- So, I expect to spend

$$\frac{(\varphi + \delta_I)(\theta + \delta_T)}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta} \times \frac{1}{\varphi + \delta_I} = \frac{\theta + \delta_T}{(\varphi + \delta_I)(\theta + \delta_T) - \varphi\theta}$$

much time in the compartment over my infectious lifetime. This is $V^{-1}{}_{1,1}$.

Graph-theoretic interpretation

- Write the adjacency matrix A of the weighted, directed graph of the infected compartments such that $A_{m,n}$ is the probability of moving from compartment n to compartment m

Probability of transition
$$\frac{\varphi}{\varphi + \delta_I}$$

Infected

Treatment

Probability of transition
$$\frac{\theta}{\theta + \delta_T}$$

$$A = \begin{bmatrix} 0 & \dfrac{\theta}{\theta + \delta_T} \\ \dfrac{\varphi}{\varphi + \delta_I} & 0 \end{bmatrix}$$

Graph-theoretic interpretation

- Then

$$M = I + A + A^2 + A^3 + \cdots = (I - A)^{-1}$$

is the matrix who (i, j) entry is the expected number of visits to compartment i if you start in compartment j.

- So we can write V^{-1} as the product of waiting times and this matrix of expected visits

Probability of going T to I

Average time spent in a visit to I

$$V^{-1} = \begin{bmatrix} \dfrac{1}{\varphi + \delta_I} & 0 \\ 0 & \dfrac{1}{\theta + \delta_T} \end{bmatrix} \times \left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \begin{bmatrix} 0 & \dfrac{\theta}{\theta + \delta_T} \\ \dfrac{\varphi}{\varphi + \delta_I} & 0 \end{bmatrix} \right)^{-1}$$

Average time spent in a visit to T

Probability of going I to T

Teaser: R_O and infection control

- The basic reproduction number has implications for infection control. If a fraction of susceptibles greater than $1 - \frac{1}{R_0}$ is permanently protected at birth, an epidemic cannot occur.

- If we want to control not by mass vaccination rather but by targeting subgroups (e.g. only vectors) or specific pathways (e.g. genital-to-genital intercourse), then there exist extensions of R_0, called the *type* and *target reproduction numbers* that can do this.

Questions?

All this—and more!—is written up in a document I can share upon request.