

Models of Infectious Disease

Formal Demography

Stanford Spring Workshop in Formal Demography

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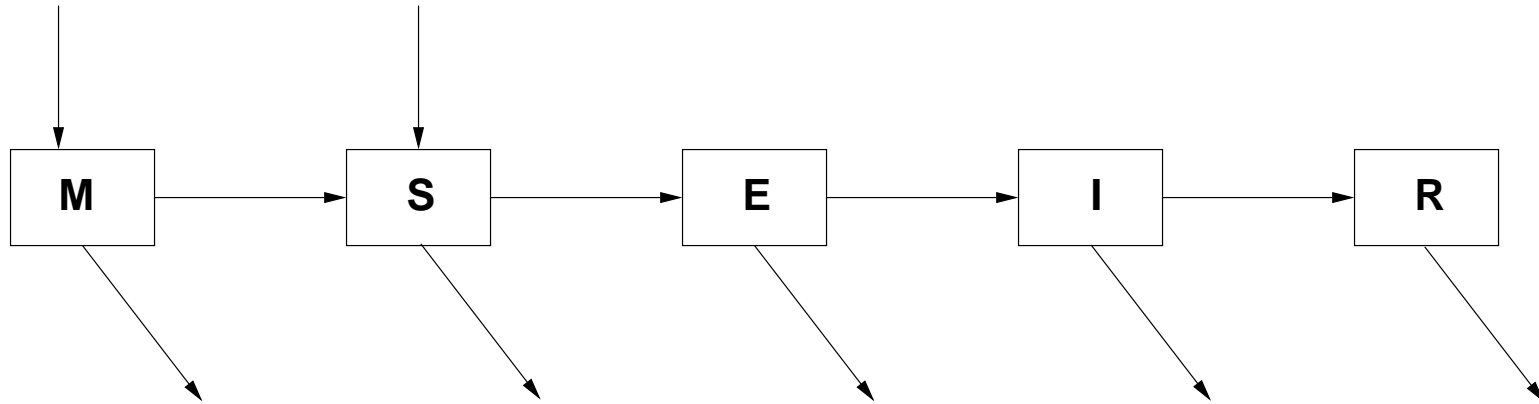
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Outline

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2. Simple Epidemic
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 - (b) Epidemic Curve 2: Incidence
 - (c) Reality Check: Real Epidemic Curves Are Messy
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Compartments: State Diagram



M : maternal protection

S : susceptible

E : exposed

I : infected

R : removed

A Simple Model of An Infectious Disease

Consider a closed population population of N individuals

There are two states:

- Susceptible
- Infected

Initially I_0 are infected

$N - I_0$ are therefore susceptible

We assume the population is **well mixed**

The probability that a susceptible and infectious individual meet is proportional to their abundances, with **effective transmission rate** β

Simple Epidemic Continued

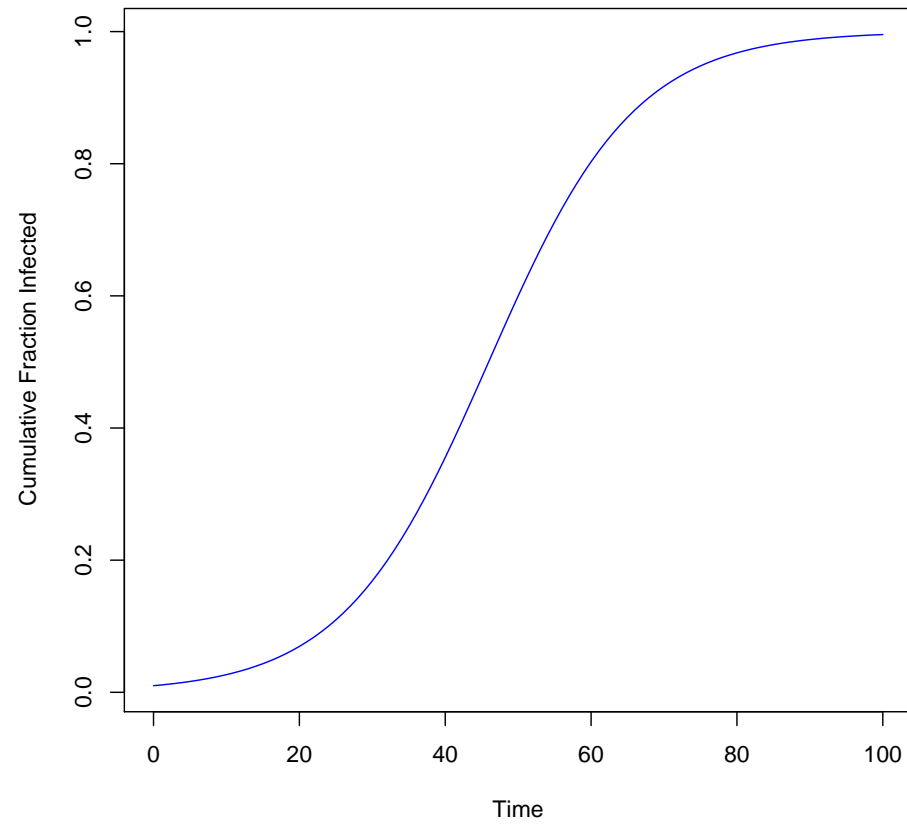
Write $s = S/N$ and $i = I/N$

$$\frac{di}{dt} = \beta i(1 - i). \quad (1)$$

To calculate the number infected at time t , $i(t)$, integrate this equation from time zero to time t , yielding:

$$i(t) = \frac{1}{1 + \frac{1-i_0}{i_0} e^{-\beta t}} \quad (2)$$

This equation yields what is known as the **epidemic curve**



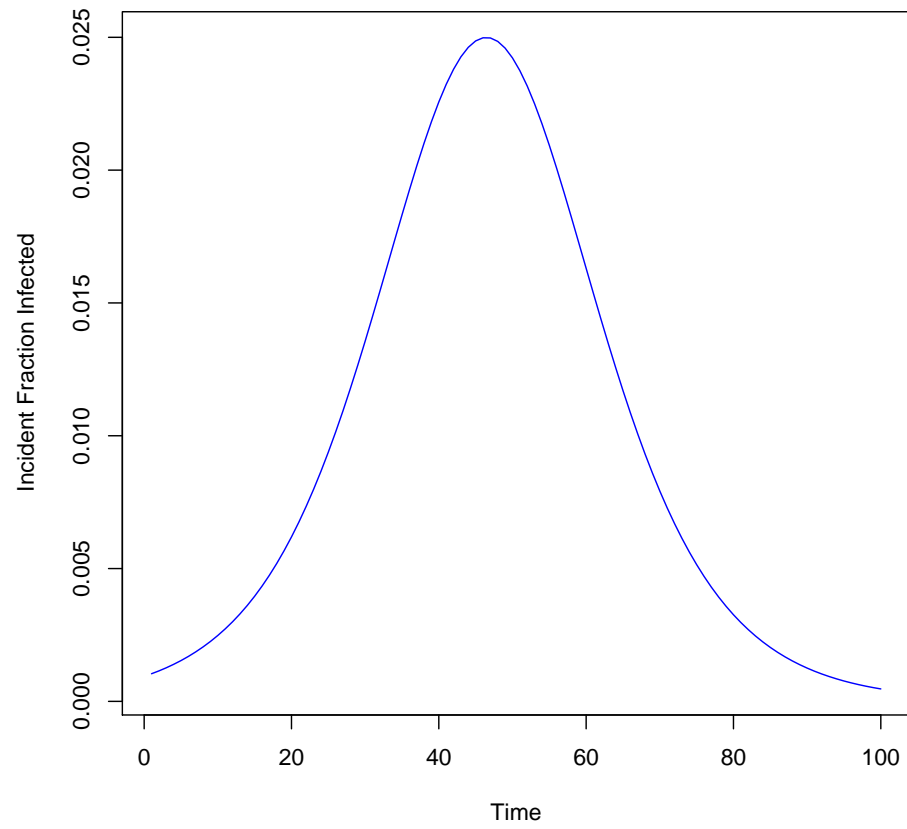
```
epi.curve <- expression(1/(1+ (exp(-beta*t)*(1-a0)/a0)))  
a0 <- .01  
beta <- 0.1  
t <- seq(0,100,1)  
plot(t,eval(epi.curve),type="l",col="blue",  
      xlab="Time", ylab="Cumulative Fraction Infected")
```

Interpreting the Epidemic Curve

This figure plots the cumulative **prevalence** of the infection

We might also want to know about the shape of the **incidence** of infection, that is, the number of new cases per unit time

```
a <- eval(epi.curve)
b <- diff(a)
plot(1:100,b,type="l",col="blue",
     xlab="Time", ylab="Incident Fraction Infected")
```



More Interpretations of the Epidemic Curve

This is the classic **epidemic curve**

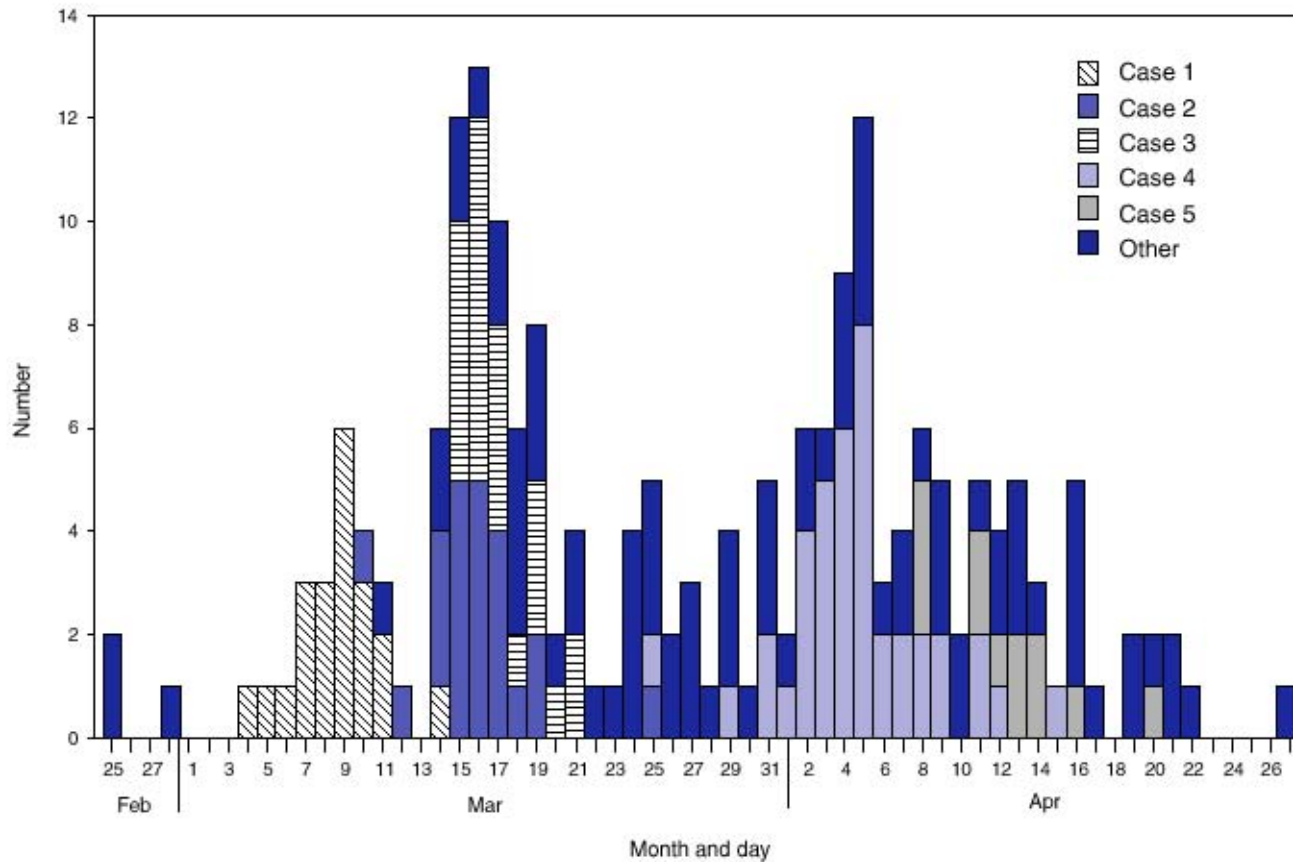
The epidemic curve is “bell-shaped”, but not completely symmetric

There is a greater force of infection early on

Note that in the limit $t \rightarrow \infty$, **everyone in the population becomes infected**

Real Curves Are a Bit More Messy

FIGURE 1. Number of probable cases of severe acute respiratory syndrome,* by date of fever onset and reported source of infection — Singapore, February 25–April 30, 2003



* n = 201.

General Epidemic: The Basic *SIR* Model

A population is comprised of three compartments:

Susceptible Segment not yet infected, disease-free (S)

Infected Segment infected *and* infectious (I)

Removed Recovered (usually) with lifelong immunity (R)

Model Assumptions:

1. Constant (closed) population size
2. Constant rates (e.g., transmission, removal rates)
3. No demography (i.e., births and deaths)
4. Well-mixed population

SIR Continued

Write $s = S/N$, $i = I/N$, $r = R/N$

$$\frac{ds}{dt} = -\beta si \quad (3)$$

$$\frac{di}{dt} = \beta si - \nu i \quad (4)$$

$$\frac{dr}{dt} = \nu i \quad (5)$$

where,

β effective contact rate

ν removal rate

Numerical Solution of the *SIR* Model

Use R library `odesolve`

write a function that we will call `sir`

function takes three arguments `y`, `t`, and `p`, for the initial conditions, time scope, and parameter values respectively

Create list of parameters `pars`, which contains the two parameters of the model β and ν

```
library(odesolve)
pars <- c("beta"=0.05,"nu"=0.075)
times <- seq(0,10,0.1)
y0 <- c(100,1,0)

sir <- function(t,y,p) {
  yd1 <- -p["beta"] * y[1]*y[2]
  yd2 <- p["beta"] * y[1]* y[2] - p["nu"]*y[2]
  yd3 <- p["nu"]*y[2]
  list(c(yd1,yd2,yd3),c(N=sum(y)))
}
```

```
sir.out <- lsoda(y0,times,sir,pars)
```

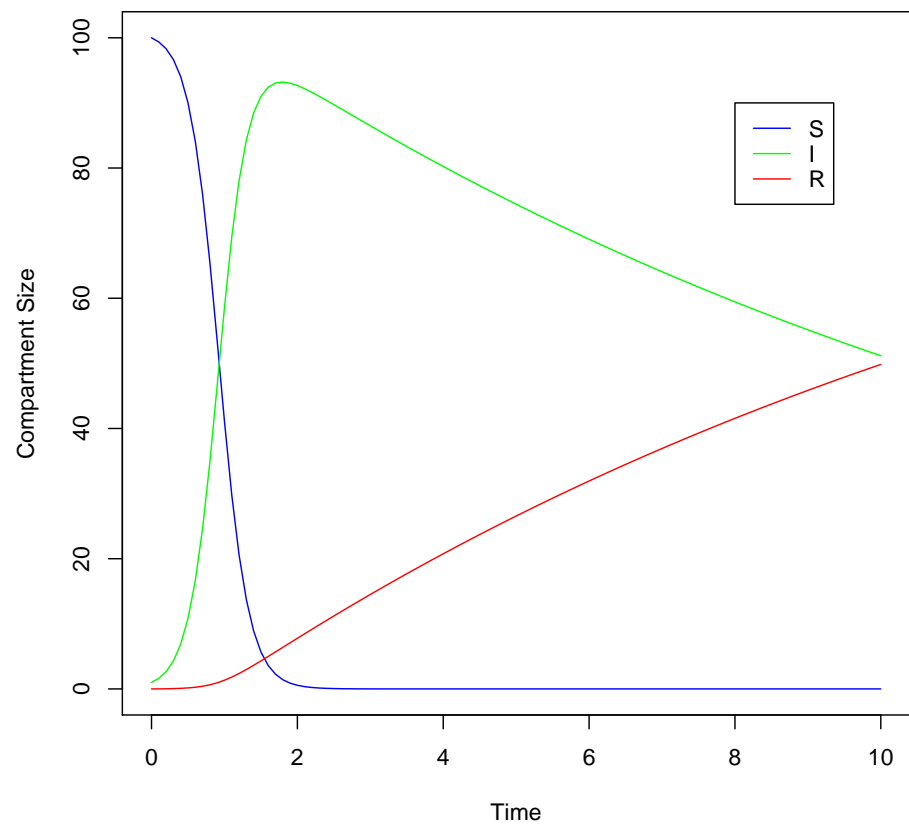
```
sir.out
```

	time	1	2	3	N
[1,]	0.0	1.000000e+02	1.000000	0.0000000000	101
[2,]	0.1	9.935633e+01	1.633984	0.009686266	101
[3,]	0.2	9.831563e+01	2.658889	0.025480797	101
[4,]	0.3	9.665093e+01	4.297969	0.051096592	101
[5,]	0.4	9.403313e+01	6.874588	0.092284864	101
[6,]	0.5	9.002495e+01	10.817430	0.157625403	101

```
...
```

plot the results of this solution

```
plot(sir.out[,1],sir.out[,2],type="l",col="blue",xlab="Time",  
      ylab="Compartment Size")  
lines(sir.out[,1],sir.out[,3],col="green")  
lines(sir.out[,1],sir.out[,4],col="red")  
legend(8,90,c("S","I","R"),col=c("blue","green","red"),lty=c(1,1,1))
```



Conditions for an Epidemic

An epidemic occurs if the number of infecteds increases, i.e., $di/dt > 0$

$$\beta si - \nu i > 0$$

$$\frac{\beta si}{\nu} > i$$

At the outset of an epidemic, $s \approx 1$

$$\frac{\beta}{\nu} = \mathcal{R}_0 > 1$$

Basic Reproduction Number

\mathcal{R}_0 is the **basic reproduction number** of the epidemic

- ▶ **Basic Reproduction Number** (\mathcal{R}_0): the expected number of secondary infections generated by a single, typical infection in a completely susceptible population

Note that Hethcote (2000) refers to the quantity β/ν as σ , the “contact rate”

In general

$$\mathcal{R}_0 \geq \sigma \geq \mathcal{R}$$

where \mathcal{R} is the reproduction number at some time other than the outset of the epidemic

When we model fractions of infected individuals in a closed population (i.e., $i = I/N$ instead of I) $\mathcal{R}_0 = \sigma$

When we model I , $\mathcal{R}_0 = \frac{\beta N}{\nu}$

Simplifying the System (a bit)

Anderson & May (1991) note that the above system of equations can be re-written in terms of the force of infection

Since $S + I + R = N$, the equation 5 is again redundant

Anderson & May (1991) also note that it is frequently convenient to think about epidemics in terms of proportions of the population susceptible, infected, etc.

Write $x = S/N$ and $y = I/N$

Now, A&M show that we can re-write equations 4 and 5 as:

$$\frac{dx}{dt} = \mu - (\mu + \lambda(t)) x(t) \quad (6)$$

$$\frac{d\lambda}{dt} = (\nu + \mu) \lambda(t) (R_0 x(t) - 1) \quad (7)$$

where we write the combination of parameters

$$\frac{\beta N}{\nu + \mu} = R_0$$

This, of course, is the basic reproduction number again

and $N = 1$ in our system

Deriving the Anderson & May Parameterization

We start out with the initial parameterization, just scaled to represent fractions of the population susceptible and infectious ($x = S/N$ and $y = I/N$)

$$\frac{dx}{dt} = \mu - \beta xy - \mu x \quad (8)$$

$$\frac{dy}{dt} = \beta xy - (\nu + \mu)y \quad (9)$$

Now replace $\lambda = \beta y$, noting again that $\mathcal{R}_0 = \beta/(\mu + \nu)$

While it is important to note that x and the force of infection will definitely be functions of time (i.e., $x(t)$, $\lambda(t)$), we drop the the t 's for notational simplicity

$$\frac{dx}{dt} = \mu - x(\lambda - \mu) \quad (10)$$

$$\frac{dy}{dt} = \lambda \left(x - \frac{1}{\mathcal{R}_0} \right) \quad (11)$$

Need to note that $\dot{\lambda} = \beta \dot{y}$, so we need to multiply through by β

Therefore, multiply by $\mathcal{R}_0(\nu + \mu) = \beta$ (since we are trying to get rid of β and put all the equations in terms of λ , the force of infection)

After a little bit of algebra, we find that this recovers the equation [7](#)

Early Growth of the Epidemic

We'd like to know what happens to an epidemic following the introduction of a pathogen

We assume that the inoculum for the epidemic was very small (usually a single infected individual)

therefore, $x(t) \approx 1$ for small t

In addition, it is almost always the case that $\nu \gg \mu$

for the early part of the epidemic, we can assume $\mu \approx 0$

Substitute these values into the dynamical equation for the force of infection, λ

$$\frac{d\lambda}{dt} \approx \nu(R_0 - 1)\lambda$$

This is (once again) an equation for exponential growth, the solution of which is:

$$\lambda(t) = \lambda(0)e^{\Lambda t}$$

where $\Lambda = \nu(R_0 - 1)$, and the $\lambda(0)$ is the initial seed value of the force of infection
 $\lambda(0) = \beta I(0)$

Endemic Equilibria

Since we now care about longer time scales, we can consider things like equilibria of the model

To find the equilibria, set our dynamical equations equal to zero

First, we'll do x^* (**Note that to get x^* , we solve the equation for λ and vice-versa**)

$$\frac{d\lambda}{dt} = (\nu + \mu) \lambda(t) (\mathcal{R}_0 x(t) - 1) = 0$$

$$\lambda \mathcal{R}_0 x - \lambda = 0$$

$$x^* = \frac{1}{\mathcal{R}_0}$$

Solving for λ^* is only slightly trickier

$$\mu - (\mu + \lambda(t))x(t) = 0$$

$$\lambda = \mu\left(\frac{1}{x} - 1\right)$$

Since we already solved for the equilibrium value for x , we substitute this back in

$$\lambda^* = \mu(R_0 - 1)$$

Will the Epidemic Infect Everyone?

Re-write the SIR equations:

$$\begin{aligned}\frac{ds}{dt} &= -\beta si & (12) \\ \frac{di}{dt} &= \beta si - \nu i \\ \frac{dr}{dt} &= \nu i\end{aligned}$$

Divide equation 5 by equation 4

$$\frac{di}{ds} = -1 + \frac{\nu}{\beta s}$$

Final Size of the Epidemic

Multiply both sides by ds

$$di = \left(-1 + \frac{\nu}{\beta s}\right)ds$$

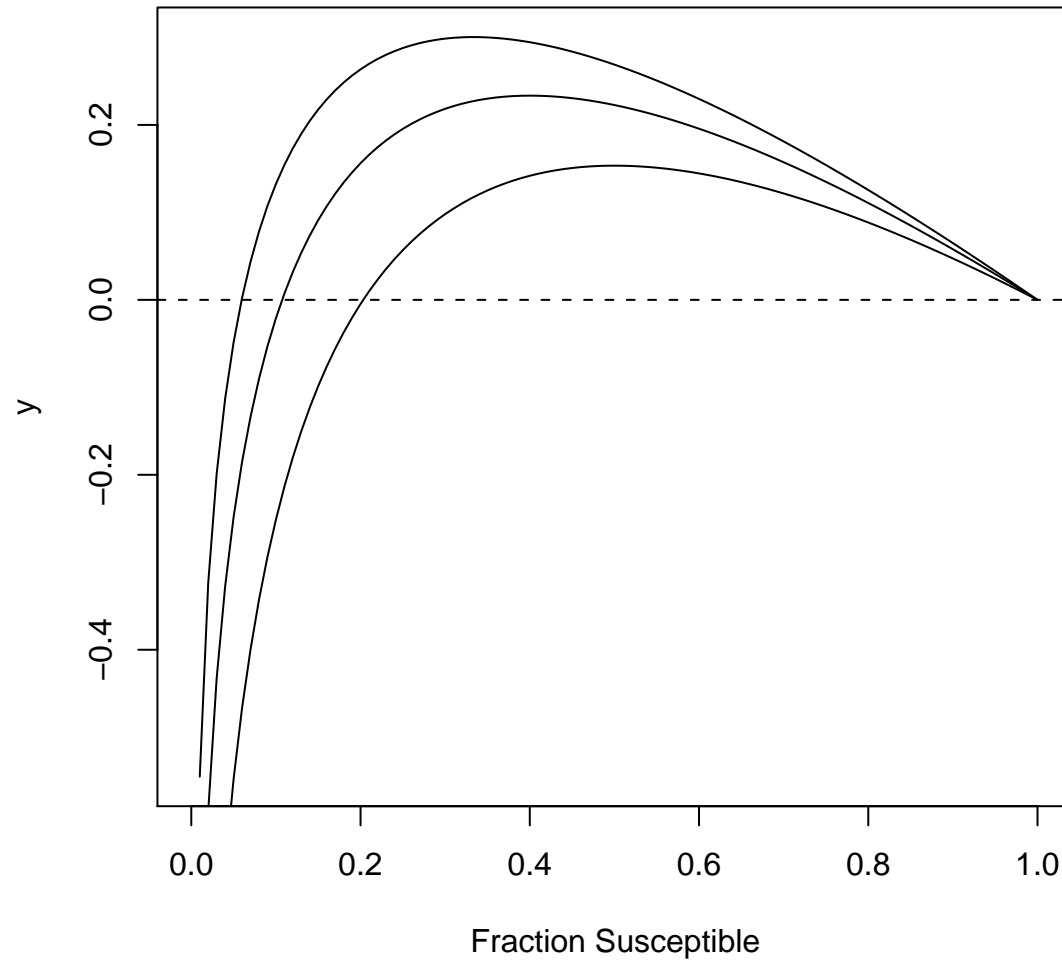
Integrating this (and doing a little algebra) yields

$$\log(s_\infty) = \mathcal{R}_0(s_\infty - 1) \quad (13)$$

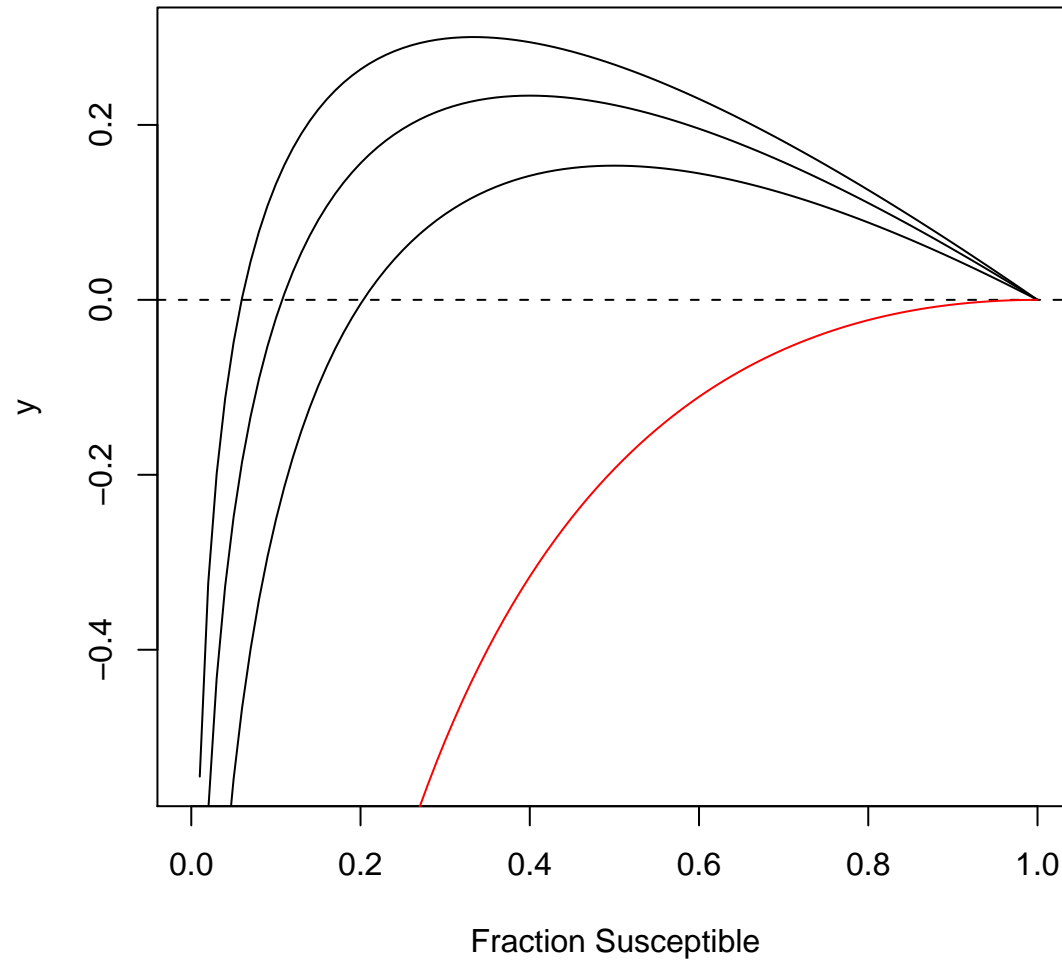
This is the “final size” of the epidemic which is an implicit equation for s_∞ , the number of susceptibles at the end of the epidemic

When $\mathcal{R}_0 > 1$, this equation has exactly two roots, only one of which lies in the interval $(0, 1)$

$$\mathcal{R}_0 > 1$$



$$\mathcal{R}_0 \leq 1$$



Analyzing the Effective Contact Rate, β

Effective contact rate is the per capita rate of infection given contact

- ▶ This is like a rate constant in a thermodynamic equation

Mechanistically, this will involve

- The transmissibility of the pathogen (τ)
- The frequency of contact (\bar{c})

We assumed removal rate was constant \Rightarrow Exponentially distributed

Expected time to removal (δ) is therefore $1/\nu$

$$\mathcal{R}_0 = \tau \bar{c} \delta \quad (14)$$

\mathcal{R}_0 is simply the product of the transmissibility, mean contact rate, and the duration of infection

Interpretation: Expected number of secondary infections in a rarefied population produced by a single typical infection

This is a very important result because it tells us how to control epidemics

Reduce Transmissibility, τ : Develop vaccines, get people to use barrier contraceptives, use anti-retrovirals (e.g., acyclovir for HSV-2, or HAART for HIV)

Decrease Mean Contact, \bar{c} : Isolation/Quarantine, health education programs

Reduce Length of Infectious Period, δ : therapeutics, antibiotic treatment of bacterial infections, care of ulcerations, boost innate immune response

This is essentially the entire theoretical basis of public health interventions for infectious diseases!

How Many People Should We Vaccinate?

Say that we can successfully immunize a fraction $0 < p \leq 1$ of the population

How big does p need to be?

Define \mathcal{R}^* to be the reproduction number of the immunized population

$$\mathcal{R}^* \leq \mathcal{R}_0(1 - p)$$

Since our threshold criterion is for $\mathcal{R}^* < 1$, we can easily solve this inequality for p

Denote the critical fraction successfully immunized as p_c

$$p_c = 1 - (1/\mathcal{R}_0)$$

Not surprisingly, as \mathcal{R}_0 increases, so does the critical vaccination fraction

Critical Values of p for Selected Infections

Infection	\mathcal{R}_0	p	Ref
Measles	18.8	0.95	(Anderson & May 1991)
Pertusis	3.8-5.6	0.74-0.82	(Anderson & May 1991)
Smallpox	4-10	0.75-0.90	(Anderson & May 1991)
Chancroid	1.1	0.10	(Anderson & May 1991)
Influenza (1918)	1.8	0.44	(Mills et al. 2004)
SARS	2.7-3.6	0.63-0.72	(Wallinga & Teunis 2005)
Malaria (Africa)	3.9-31.6 [†]	0.74-0.97	(Smith et al. 2007)

[†] interquartile range for 121 populations

Why Do We Care So Much About \mathcal{R}_0 Anyway?

\mathcal{R}_0 Provides **five** fundamental insights into the dynamics of an infectious disease:

1. \mathcal{R}_0 is the **threshold parameter**, determining whether or not there will be an epidemic
2. \mathcal{R}_0 determines the **initial rate of increase** of an epidemic (i.e., during its exponential growth phase)
3. \mathcal{R}_0 determines the **final size** of the epidemic (i.e., what fraction of susceptibles will ultimately be infected over the course of the outbreak)
4. \mathcal{R}_0 determines the **endemic equilibrium** fraction of susceptibles in the population ($= 1/\mathcal{R}_0$)
5. \mathcal{R}_0 determines the **critical vaccination threshold** ($= 1/\mathcal{R}_0$)

An Example of an Endemic/Epidemic Model

Plot of a hypothetical (and unlikely!) disease's dynamics reproduced from Anderson & May (1991)

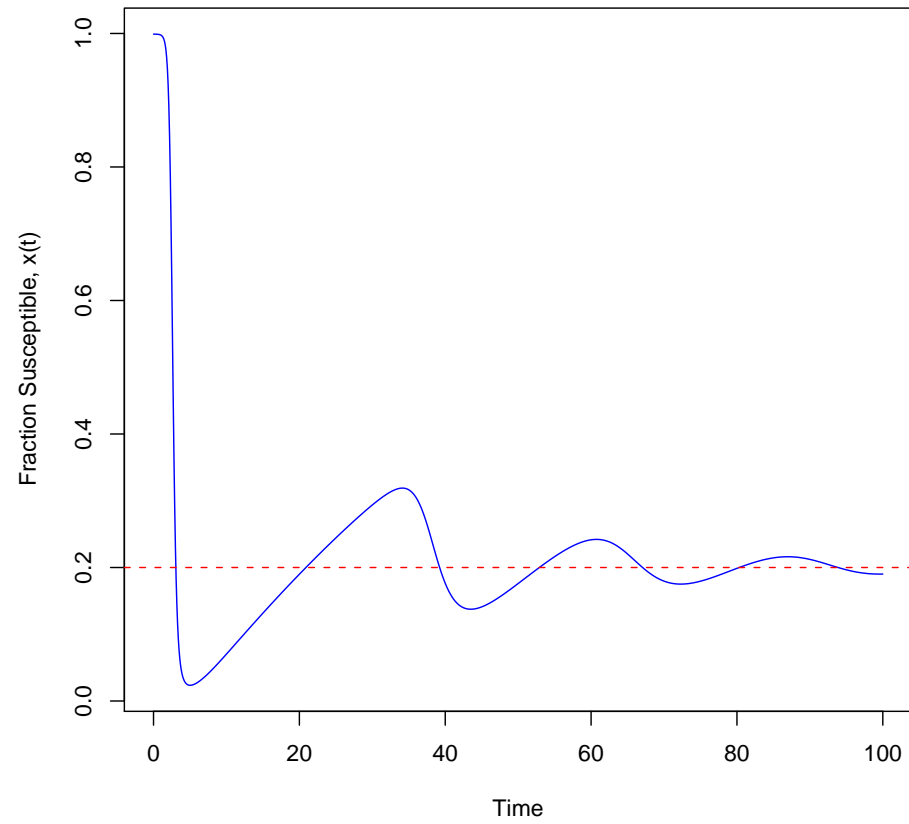
The parameters are $\mu = 1/70$, $\nu = 1$, and $R_0 = 5$,

Here is some R code to reproduce Anderson & May's plot

```
lambda.dyn <- function(t,y,p){
  yd1 <- p["mu"] - (p["mu"]+y[2])*y[1]
  yd2 <- (p["mu"] + p["nu"]) * y[2] * (p["R0"]*y[1] - 1)
  list(c(yd1,yd2))
}

pars <- c("R0"=5,"nu"=1.0,"mu"=0.014)
times <- seq(0,100,.1)
y0 <- c(.999,1e-4)
lambda.out <- lsoda(y0,times,lambda.dyn,pars)
plot(lambda.out[,1],lambda.out[,2],type="l",col="blue",
  xlab="Time",ylab="Fraction Susceptible, x(t)")
abline(h=.2,lty=2,col="red")
```

Approach to Equilibrium



Is the Equilibrium Stable?

How do we calculate the stability of a model that has more than one dimension?

For the one-dimensional models (e.g., the density-dependent population growth models), the process was:

- Calculate the equilibria
- Linearize the model around the equilibrium using a Taylor series approximation
- If the solution to the linearized equilibrium was less than zero, the equilibrium was stable

There is a straightforward extension of this procedure to the multivariate case

A model with multiple variables is stable if and only if the real part of the eigenvalues of the model's **Jacobian Matrix** are less than zero

Great. What's a Jacobian matrix?

write

$$F(x, \lambda) = \frac{dx}{dt} = \mu - (\mu + \lambda(t))x(t),$$

and

$$G(x, \lambda) = \frac{d\lambda}{dt} = (\nu + \mu) \lambda(t) (R_0 x(t) - 1)$$

The Jacobian is:

$$\mathbf{J} = \begin{pmatrix} \partial F / \partial x & \partial F / \partial \lambda \\ \partial G / \partial x & \partial G / \partial \lambda \end{pmatrix}$$

For the *SIR* model variant of equations 6 and 7, the Jacobian is:

$$\mathbf{J} = \begin{pmatrix} -\lambda - \mu & -x \\ R_0 \lambda (\mu + \nu) & (-1 + R_0 x) (\mu + \nu) \end{pmatrix} \quad (15)$$

Using the equilibrium values of x and λ

$$x^* = 1/\mathcal{R}_0,$$

and

$$\lambda^* = \mu(R_0 - 1)$$

along with the parameter values given before ($\mu = 1/70$, $\nu = 1$, and $R_0 = 5$)

The Jacobian is

$$\mathbf{J} = \begin{pmatrix} -0.07142857 & -0.2 \\ 0.28979592 & 0 \end{pmatrix}$$

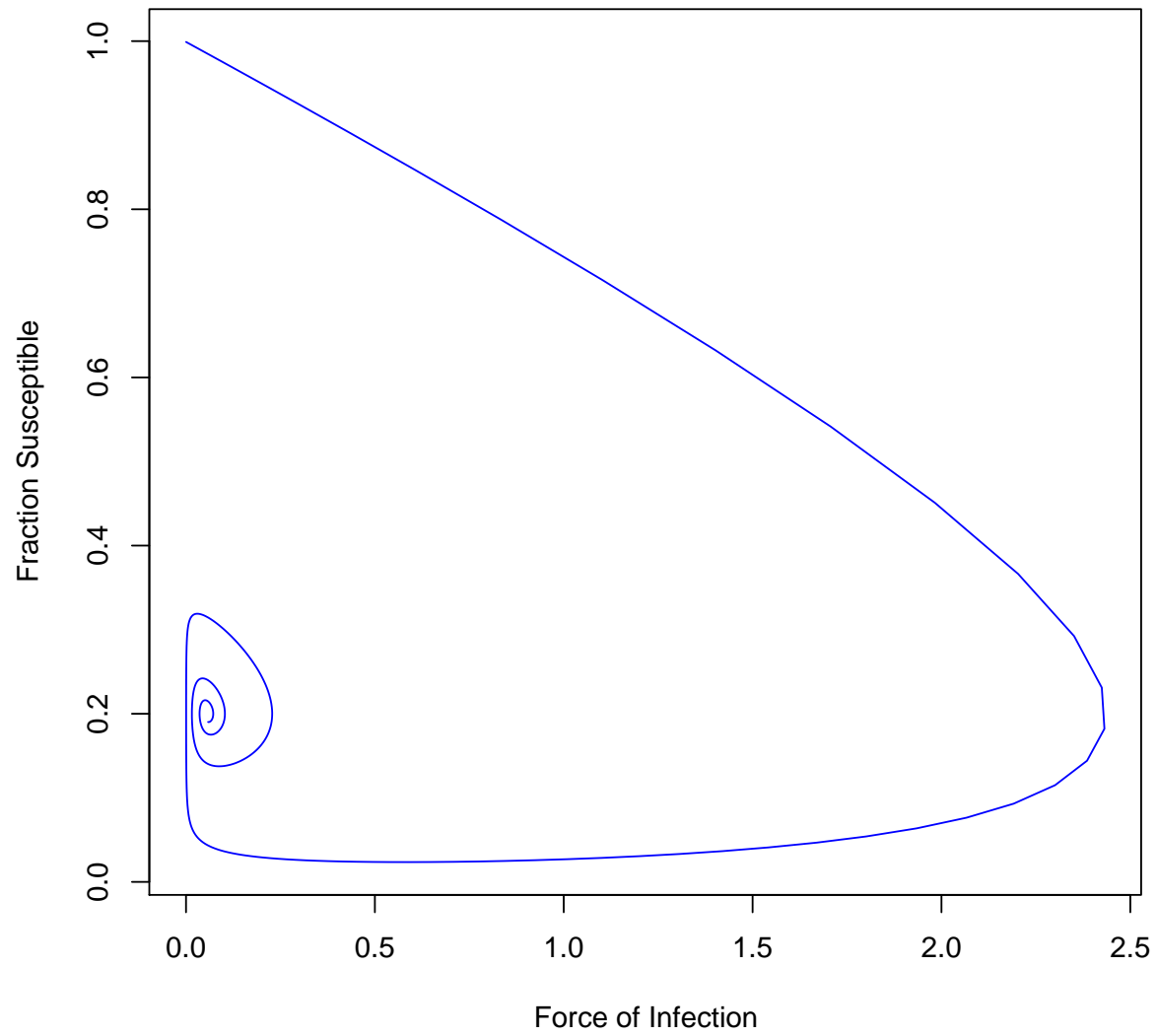
And the eigenvalues of this matrix are

$$\{-0.0357143 - 0.238083 i, -0.0357143 + 0.238083 i\}$$

The real parts of both eigenvalues are negative so the equilibrium $\{x^*, \lambda^*\}$ is asymptotically stable

```
plot(lambda.out[,3],lambda.out[,2],type="l",col="blue",  
      xlab="Force of Infection", ylab="Fraction Susceptible")
```

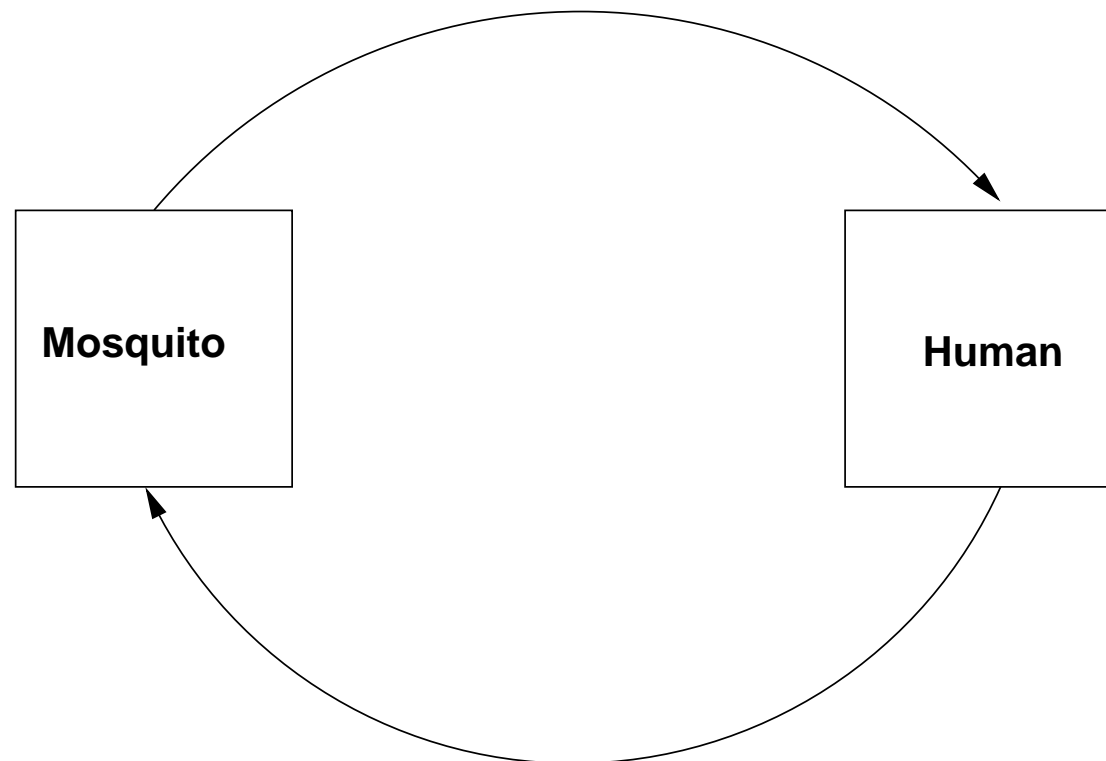
We can see this graphically by plotting the *phase plane* of the model



Structured Epidemic Models

How do you define \mathcal{R}_0 when you have a structured epidemic model?

Consider malaria transmission:



\mathcal{R}_0 for Multi-Host Epidemics

\mathcal{R}_0 is defined as the expected number of secondary cases generated by a single typical index case in a completely susceptible population

What if you have different types of susceptible hosts? What is *typical*?

- Malaria: Mosquitoes and humans
- HIV: Women and Men
- Chagas: Bugs and Humans (& Dogs)
- Lyme: Ticks, Mice, Deer, Humans

\mathcal{R}_0 generalizes very easily to these cases

Next Generation Matrix

Define a square matrix \mathbf{G} where the ij th element is the expected number of type i cases caused by infectious individuals of type j (again, in a completely susceptible population)

Call the ij th element of \mathbf{G} , g_{ij}

Essentially, each element of the matrix is a mini reproduction number that counts just those infections to type i caused by type j

Call these the within- and between-type reproduction numbers

For a two-host model, we have

$$\mathbf{G} = \begin{bmatrix} g_{11} & g_{12} \\ g_{21} & g_{22} \end{bmatrix}$$

For notational convenience replace these subscripted g 's with the letters a, b, c, d (these have nothing to do with the a, b, c, d of a two-way epidemiological table)

$$\mathbf{G} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

where a is the number of type 1 cases caused by infectious individuals of type 1; b is the type 1 caused by type 2; c is type 2 caused by type 1; and d is type 2 caused by type 2

We assume that approximately every individual in each of the types is susceptible

\mathcal{R}_0 is the larger of the two roots of the so-called *characteristic equation*:

$$\lambda_{\pm} = \frac{a + d}{2} \pm \sqrt{\left(\frac{a + d}{2}\right)^2 - ad + bc}$$

\mathcal{R}_0 can be easily calculated numerically for models with more types of susceptibles/infecteds

Example: A Sexually Transmitted Infection

Assume a population in which all transmission is heterosexual

Note that men are frequently far more efficient transmitters than women

Say that the typical infectious woman will, on average, infect half a man in a completely susceptible male population and that a typical infectious man will infect 5 women in a completely susceptible female population

What is \mathcal{R}_0 ?

$$\mathbf{G} = \begin{bmatrix} 0 & 0.5 \\ 5 & 0 \end{bmatrix}$$

$$\mathcal{R}_0 = \frac{0+0}{2} + \sqrt{\left(\frac{0+0}{2}\right)^2 - (0 \cdot 0) + (0.5 \cdot 5)} = \sqrt{2.5} = 1.58$$

Bad news...

Calculating the Next Generation Matrix

Consider the next generation matrix \mathbf{G} . It is comprised of two parts: F and V^{-1} , where

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j} \right] \quad (16)$$

$$V = \left[\frac{\partial V_i(x_0)}{\partial x_j} \right] \quad (17)$$

The F_i are the new infections

The V_i transfers of infections from one compartment to another

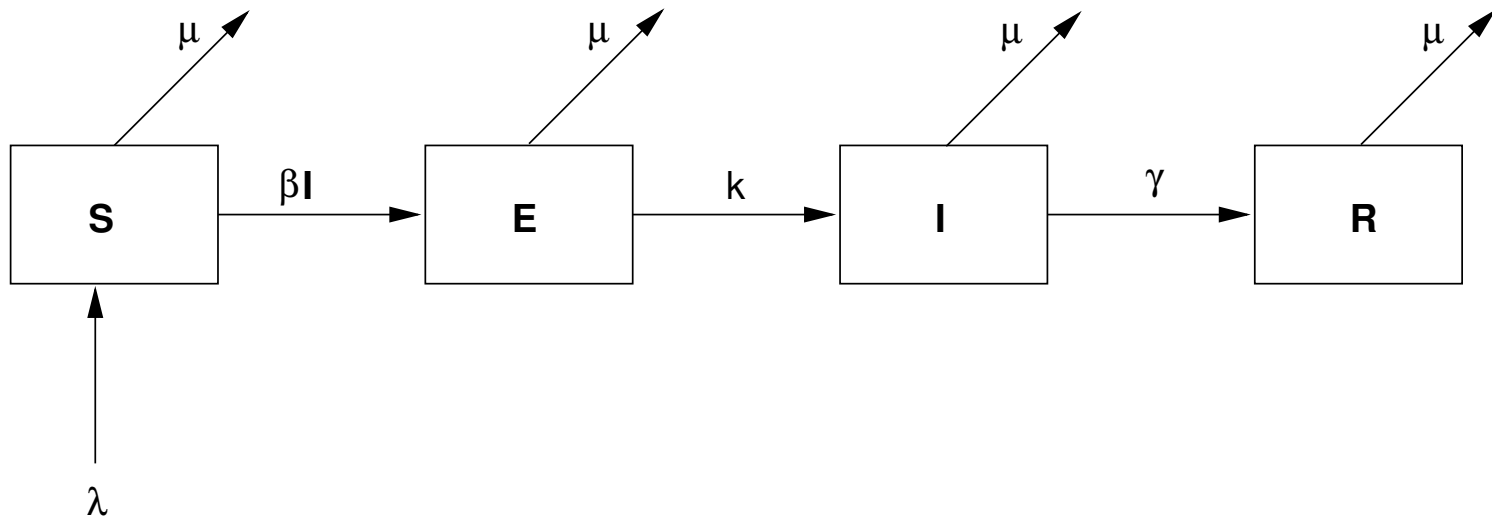
x_0 is the disease-free equilibrium state

\mathcal{R}_0 is the dominant eigenvalue of the matrix $\mathbf{G} = FV^{-1}$.

Example: SEIR Epidemic

Consider a Susceptible-Exposed-Infected-Removed (SEIR) Epidemic

This is an appropriate model for a disease where there is a considerable post-infection incubation period in which the exposed person is not yet infectious



The SEIR Model Consists of Four Differential Equations

$$\dot{S} = -\beta SI + \lambda - \mu S \quad (18)$$

$$\dot{E} = \beta SI - (\mu + k)E \quad (19)$$

$$\dot{I} = kE - (\gamma + \mu)I \quad (20)$$

$$\dot{R} = \gamma I - \mu R \quad (21)$$

β is the effective contact rate

λ is the “birth” rate of susceptibles

μ is the mortality rate

k is the progression rate from exposed (latent) to infected

γ is the removal rate

Next Generation Matrix for SEIR Model

There are two disease states but only one way to create new infections:

$$V = \begin{pmatrix} \frac{\beta\lambda}{\mu} & 0 \\ 0 & 0 \end{pmatrix} \quad (22)$$

In contrast, there are various ways to move between the states:

$$V = \begin{pmatrix} 0 & k + \mu \\ \gamma + \mu & -k \end{pmatrix} \quad (23)$$

\mathcal{R}_0 is the leading eigenvalue of the matrix FV^{-1} , which is

$$\mathcal{R}_0 = \frac{k\beta\lambda}{\mu(k + \mu)(\gamma + \mu)}$$

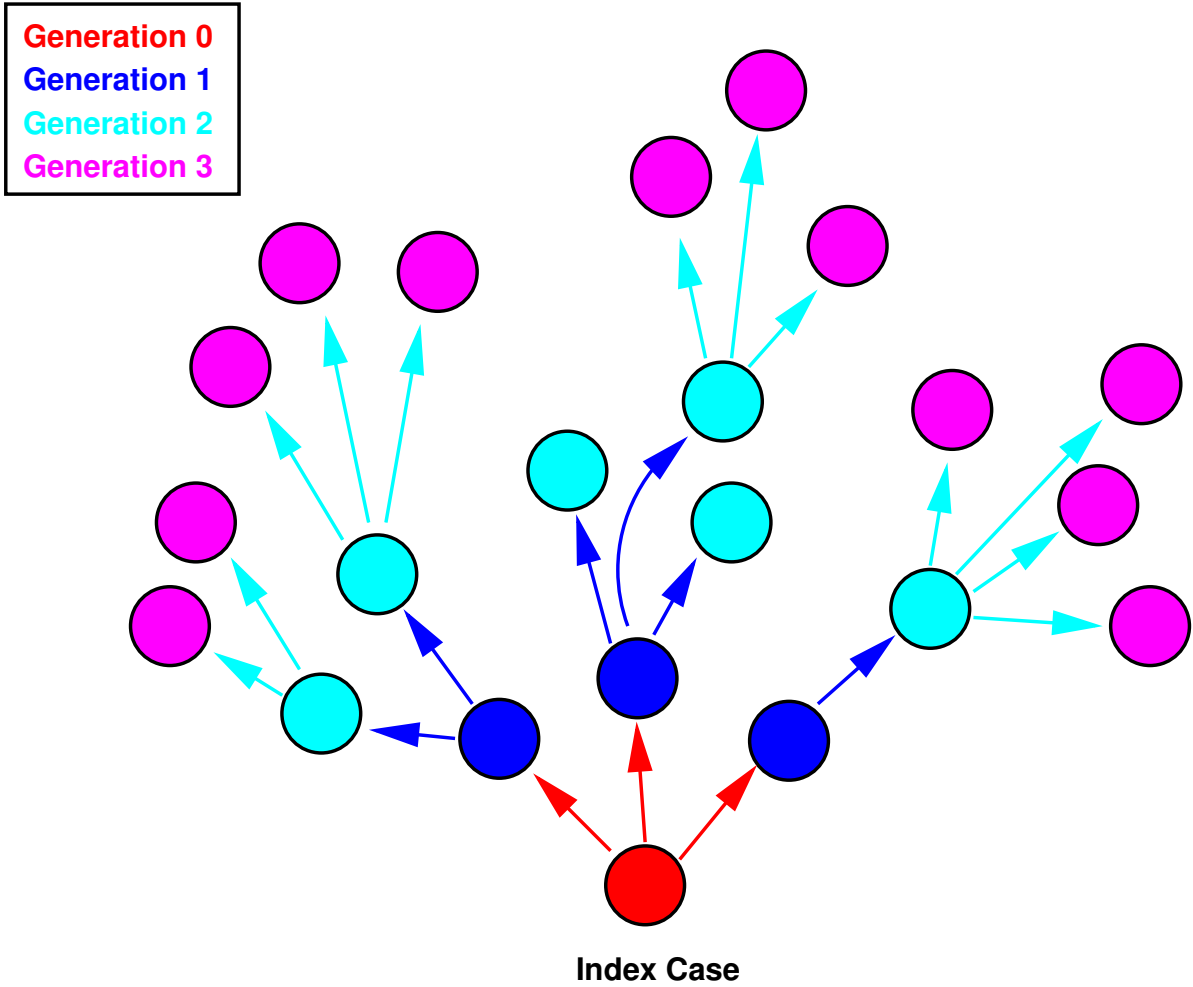
What is a Generation?

In demography, \mathcal{R}_0 is the ratio of total population size from the start to the end of a generation, (roughly) the mean age of childbearing $\mathcal{R}_0 = e^{rT}$

Generations in epidemic models are the waves of secondary infection that flow from each previous infection

If \mathcal{R}_i denotes the reproduction number of the i th generation, then \mathcal{R}_0 is simply the number of infections generated by the index case, i.e., generation zero

Generations



Virulence: Trade-Offs

Assume that virulence is proportional to *parasitemia*, the number of circulating copies of the pathogen in the host

Sustained transmission of the pathogen requires that $\mathcal{R}_0 > 1$

We can easily imagine trade-offs between the components of \mathcal{R}_0

Higher virulence means that *given contact* between a susceptible and infectious individual, transmission is more likely (more parasite copies means a greater chance of successful colonization)

Higher virulence means that contact is less likely because infected hosts are sick (or dead!)

We can build this reasoning into a model of \mathcal{R}_0

Evolution of Optimal Virulence

Assume an infection with no recovery

Assume two forms of mortality: background (μ) and disease-induced (δ)

Denote virulence x

Assume that both transmissibility and disease-induced mortality are functions of x

Our value of \mathcal{R}_0 is the ratio of the rate of new infections to the rate of removal (in this case, only by death)

$$\mathcal{R}_0 = \frac{\beta(x)}{\mu + \delta(x)}$$

We find the optimal value of x by differentiating with respect to x and setting equal to zero

Use the quotient rule and do a little algebra to reveal that

$$\frac{d\beta(x)}{d\delta(x)} = \frac{\beta(x^*)}{\mu + \delta(x^*)}$$

where x^* indicates the optimum value

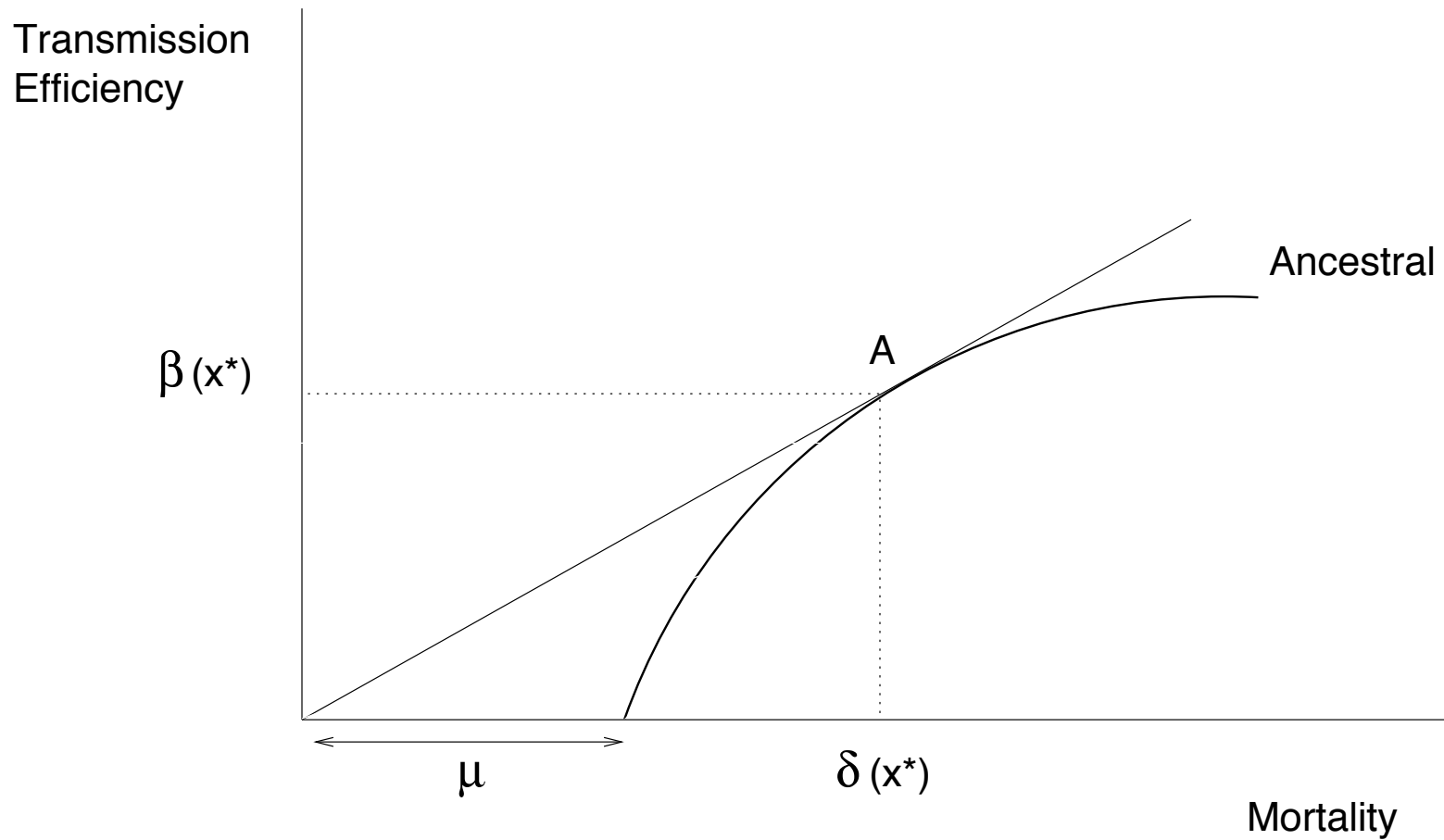
This has a straightforward geometrical interpretation

The trade-off between transmissibility and disease-induced mortality is satisfied where a line, rooted at the origin, is tangent to the curve that relates transmissibility to total mortality

Consider an example in which an ancestral pathogen gives rise to a descendant in which transmissibility is less efficient (a common case for emerging infectious diseases)

What happens to virulence?

Graphical Interpretation of Optimal Virulence



Graphical Interpretation of Optimal Virulence

