Models for Understanding and Controlling Global Infectious Diseases HUMBIO 154D / HRP 204

Session 9

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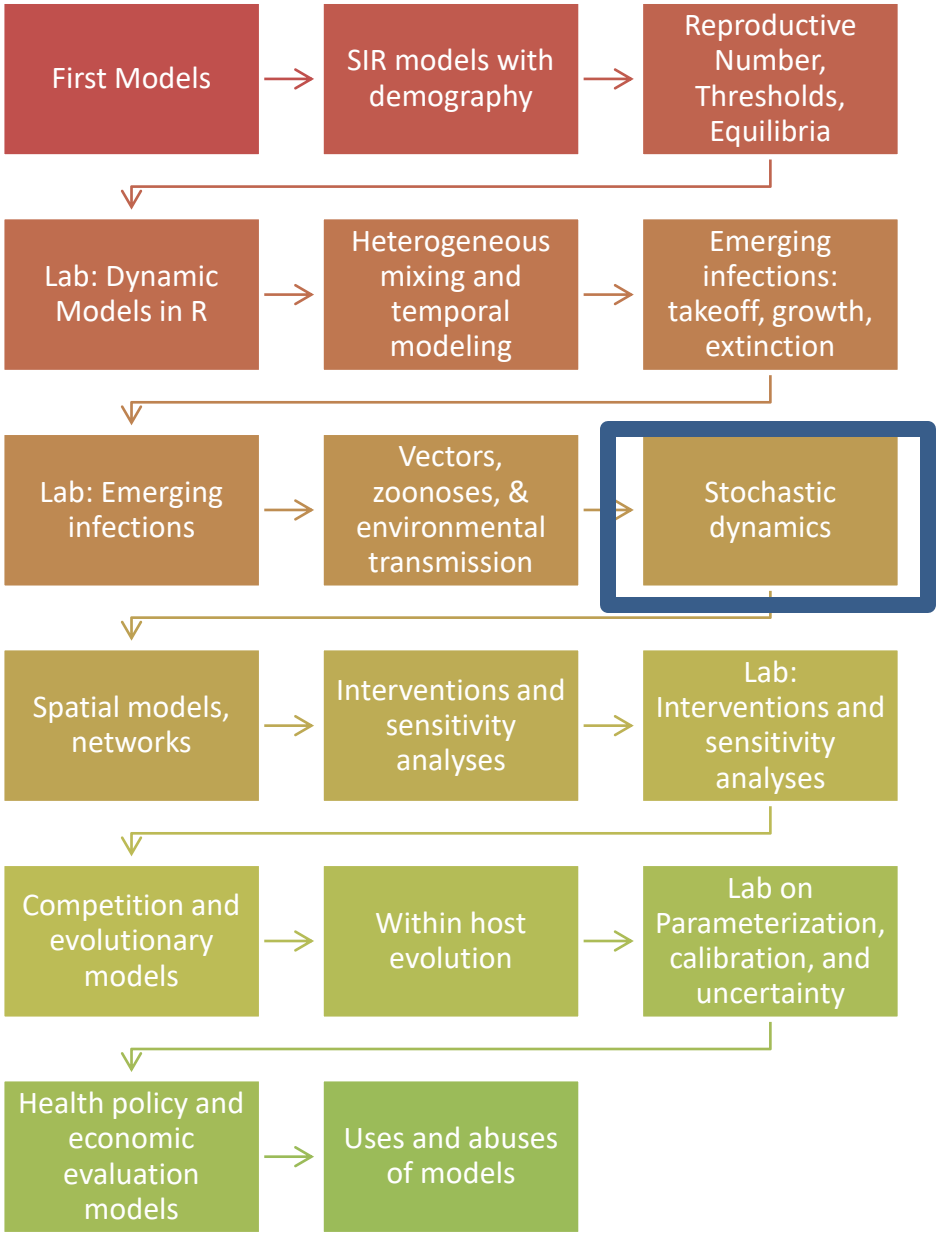
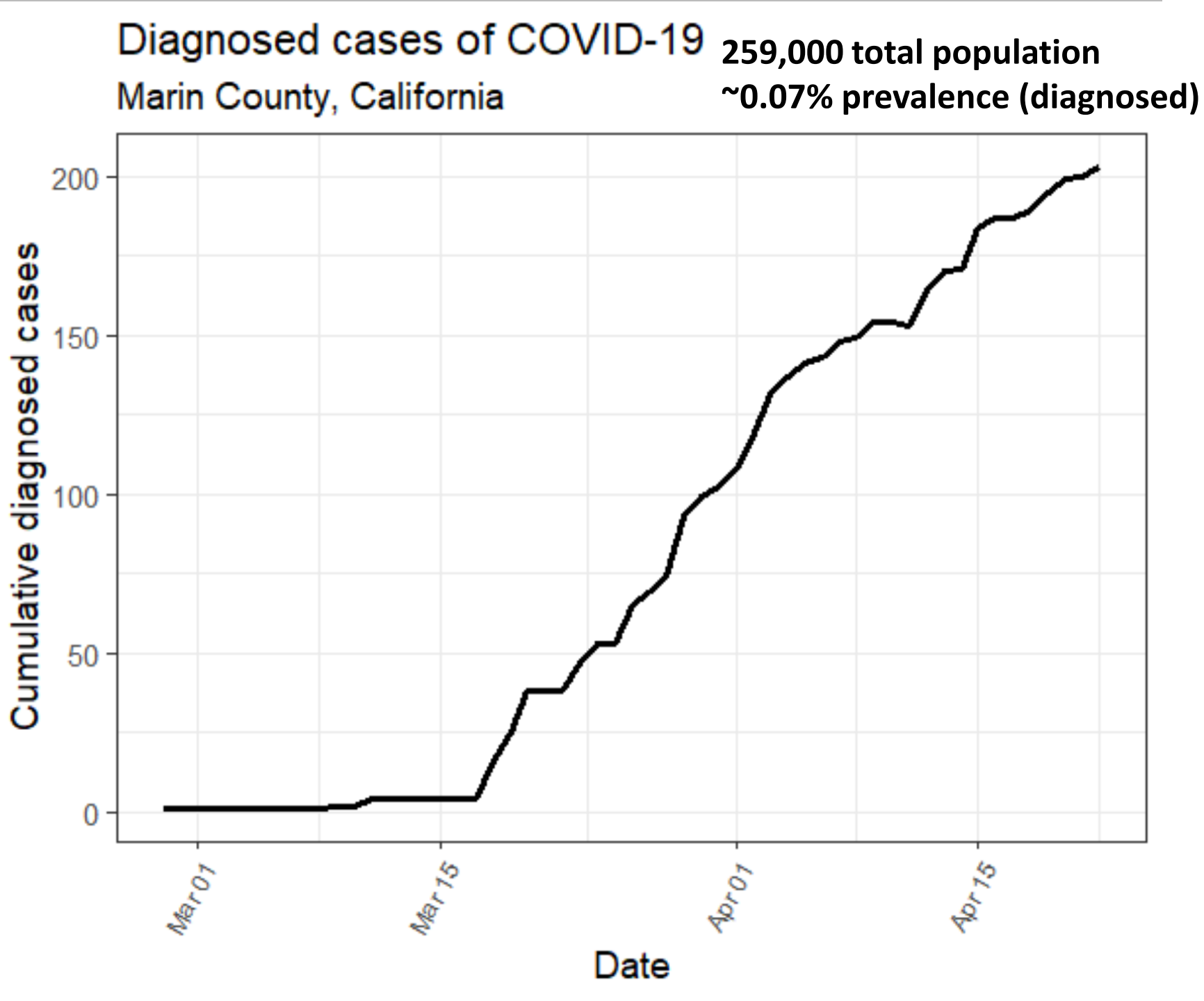
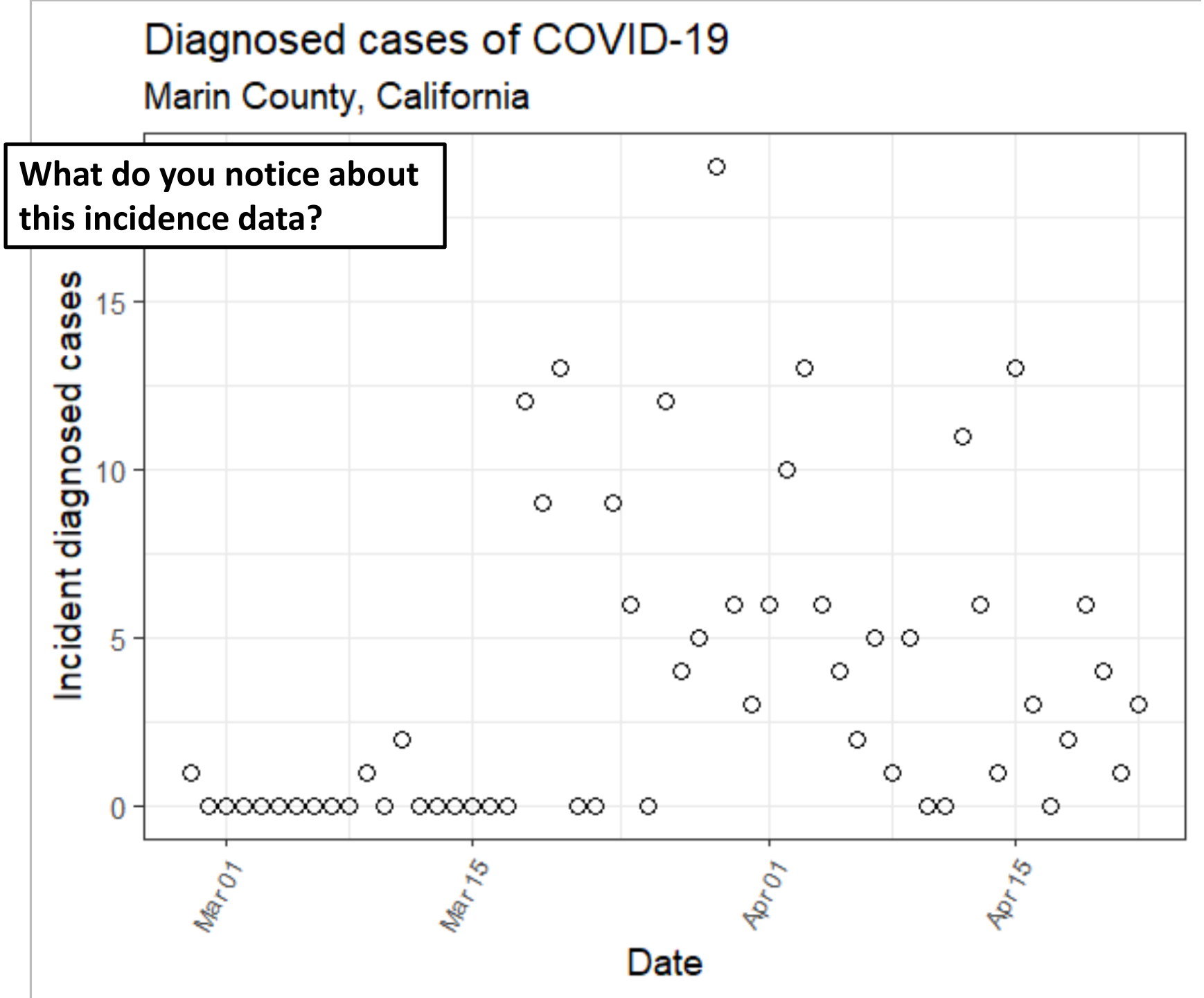
2020

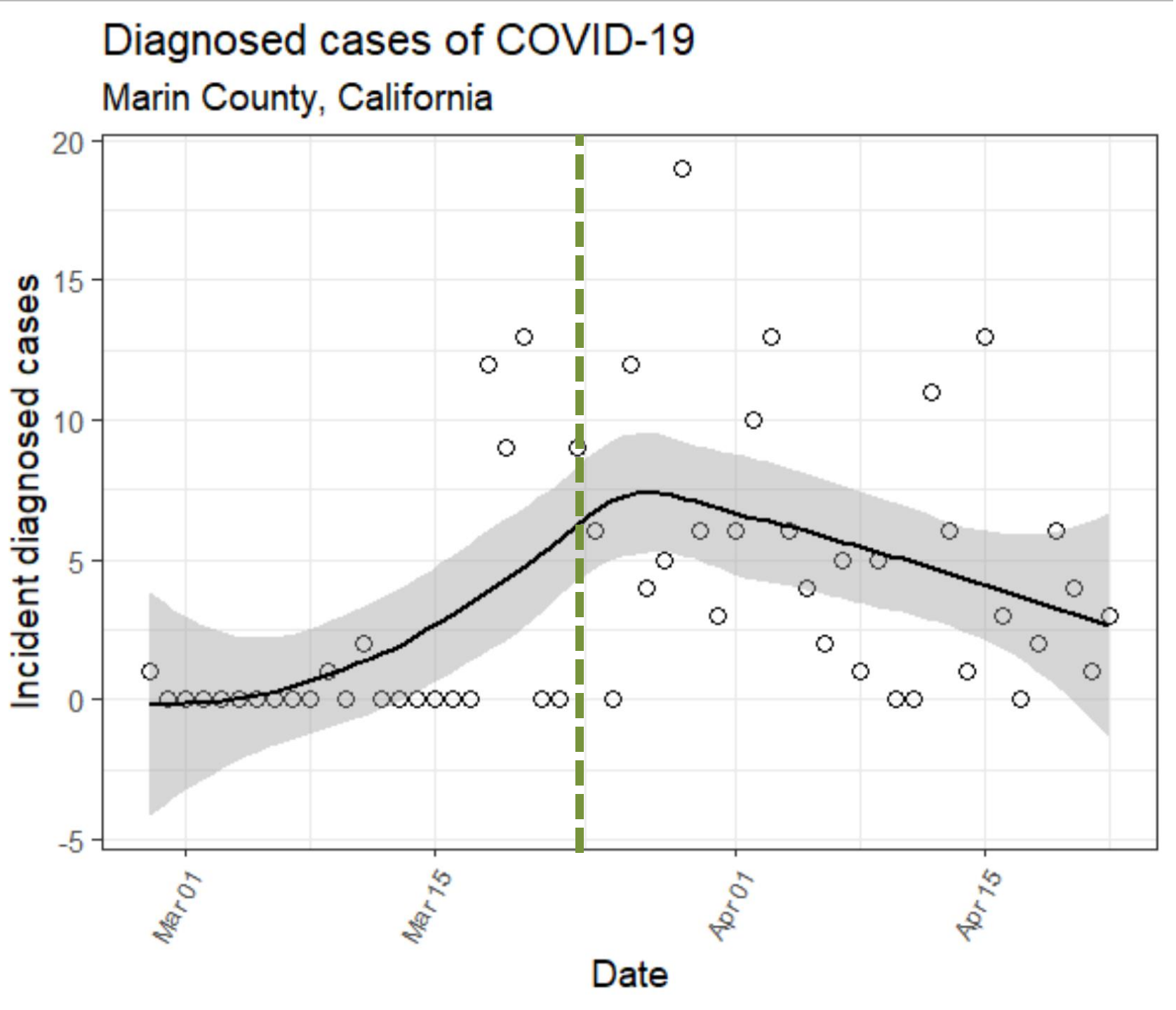
Course Roadmap



“THE REAL WORLD CONTAINS RANDOMNESS”


Diagnosed cases of COVID-19
Marin County, California
259,000 total population
~0.07% prevalence (diagnosed)
Cumulative diagnosed cases
200
150
100
50
0
Mar 01
Mar 15
Apr 01
Apr 15
Date


Diagnosed cases of COVID-19
Marin County, California
What do you notice about this incidence data?
Incident diagnosed cases
0
5
10
15
Mar 01
Mar 15
Apr 01
Apr 15
Date


Diagnosed cases of COVID-19
Marin County, California
Incident diagnosed cases
20
15
10
5
0
-5
Mar 01
Mar 15
Apr 01
Apr 15
Date

Practical Questions

How and when does stochasticity/randomness make the predictions/insights from the models we have been examining to date less applicable?

What patterns should we expect to see in real-world dynamics of infectious diseases because of stochasticity/randomness?

Learning Objectives

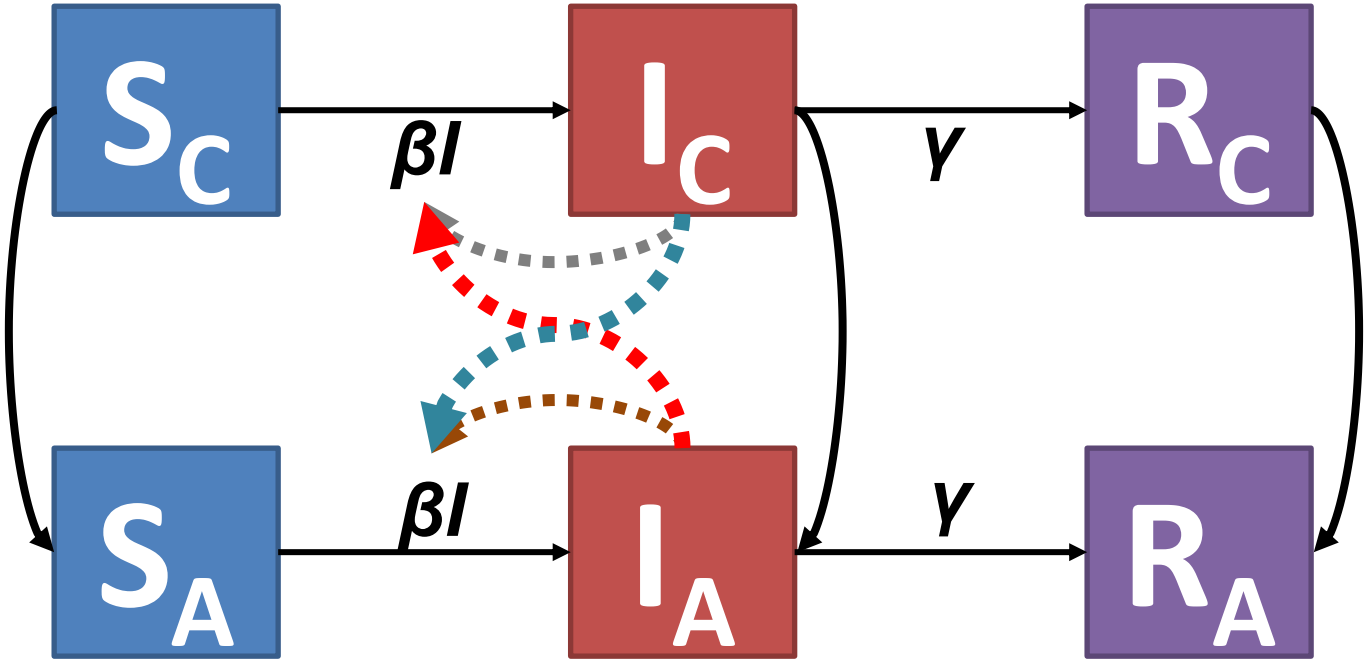
- Define continuous versus discrete and explain how they characterize model differences
- Define deterministic versus stochastic and explain how they characterize model differences
- Understand how stochastic continuous time models differ from deterministic continuous time models
- Understand how stochastic discrete time models differ
- Describe stochastic extinction/fade-out and the conditions under which it is more likely
- Describe the critical community size threshold
- Describe importation and how it relates to the likelihood of extinction/critical community size

Continuous vs. Discrete

- Apply to
  - Quantities being modeled
  - Time steps in the model

Continuous vs. Discrete

- Apply to
  - **<u>Quantities being modeled: Continuous</u>**
  - Time steps in the model



Continuous vs. Discrete

- Apply to
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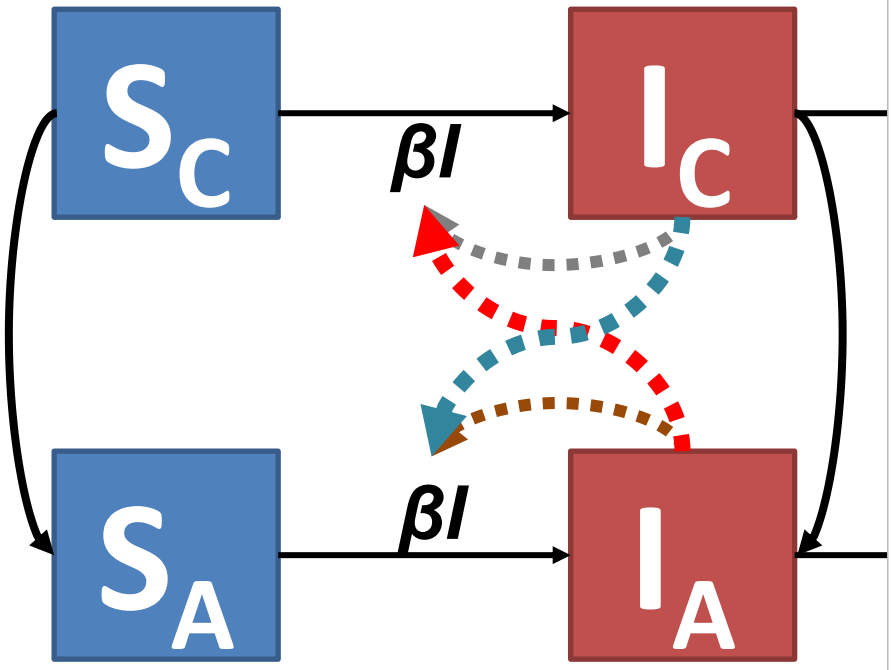
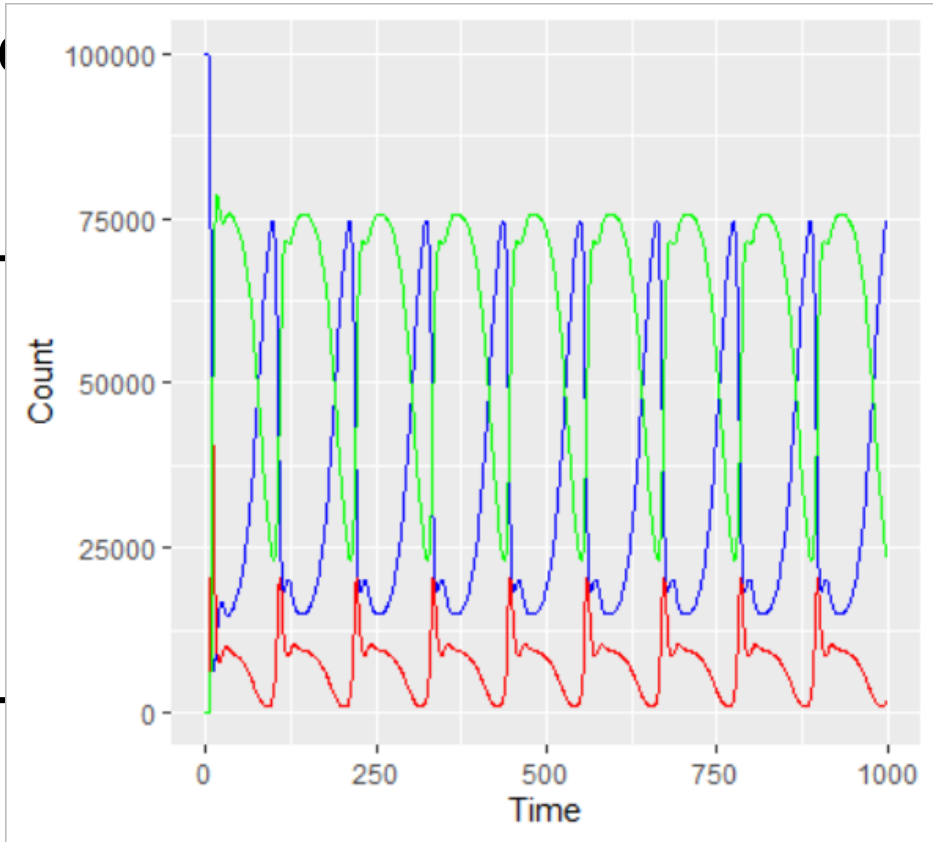
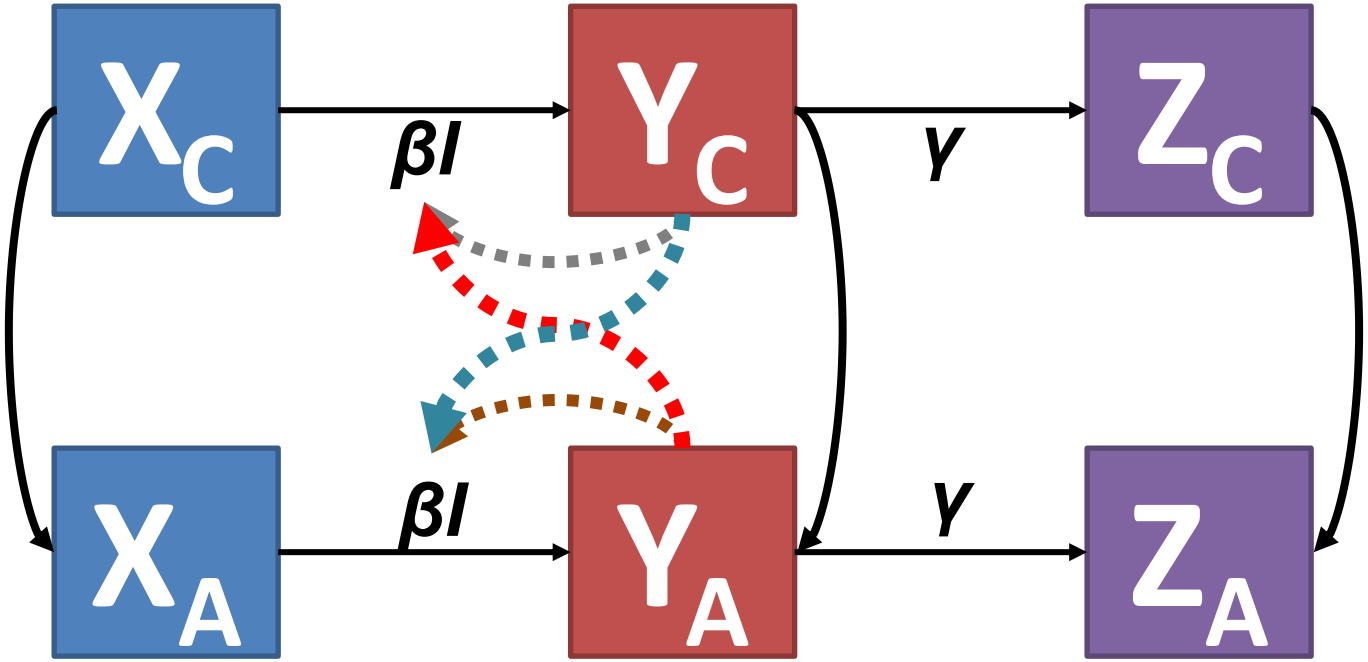
  - Time steps in the mo





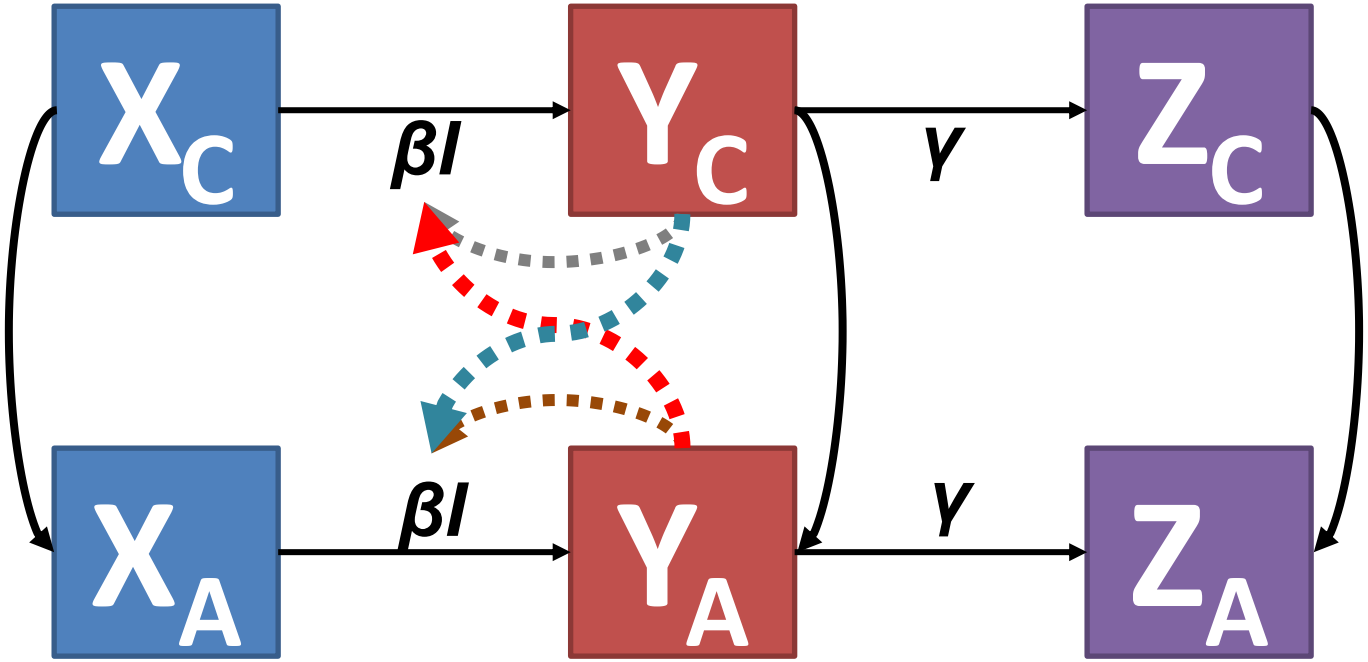
Continuous vs. Discrete

- Apply to
  - **<u>Quantities being modeled: Continuous</u>**
  - Time steps in the model



Continuous vs. Discrete

- Apply to
  - **Quantities being modeled: Discrete**
  - Time steps in the model



Continuous vs. Discrete

- Apply to
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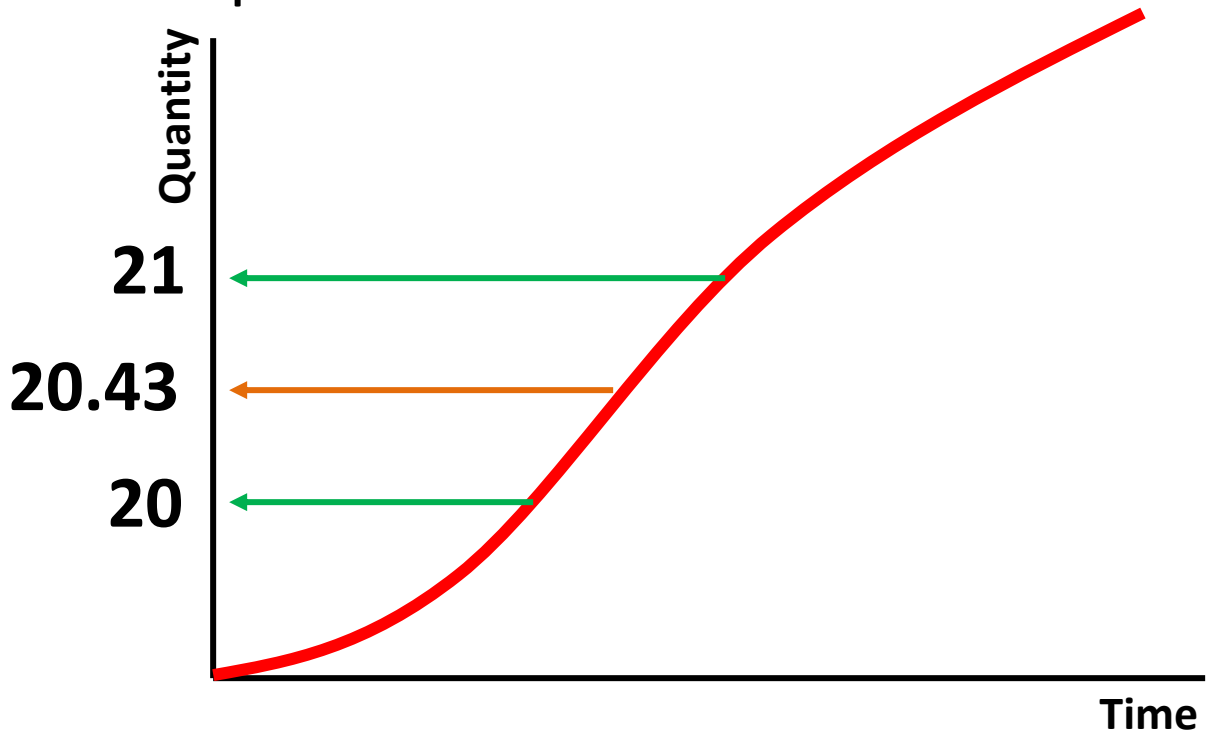
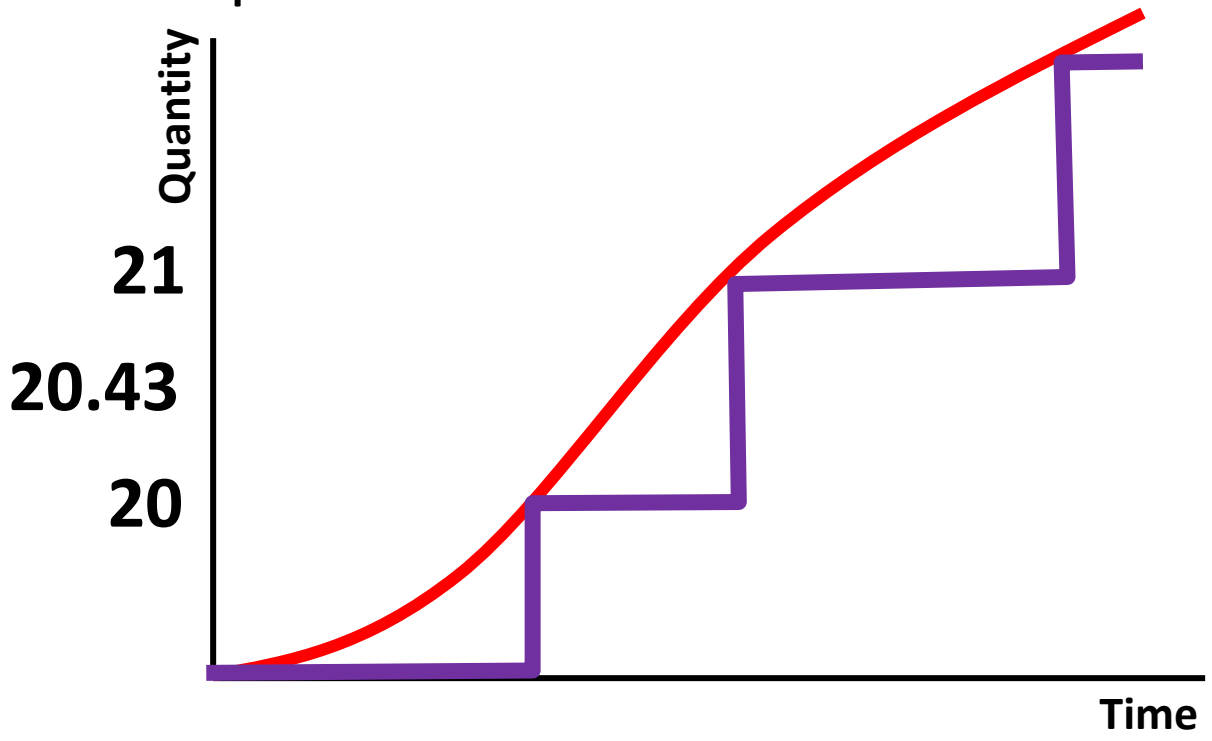
  - Time steps in the model



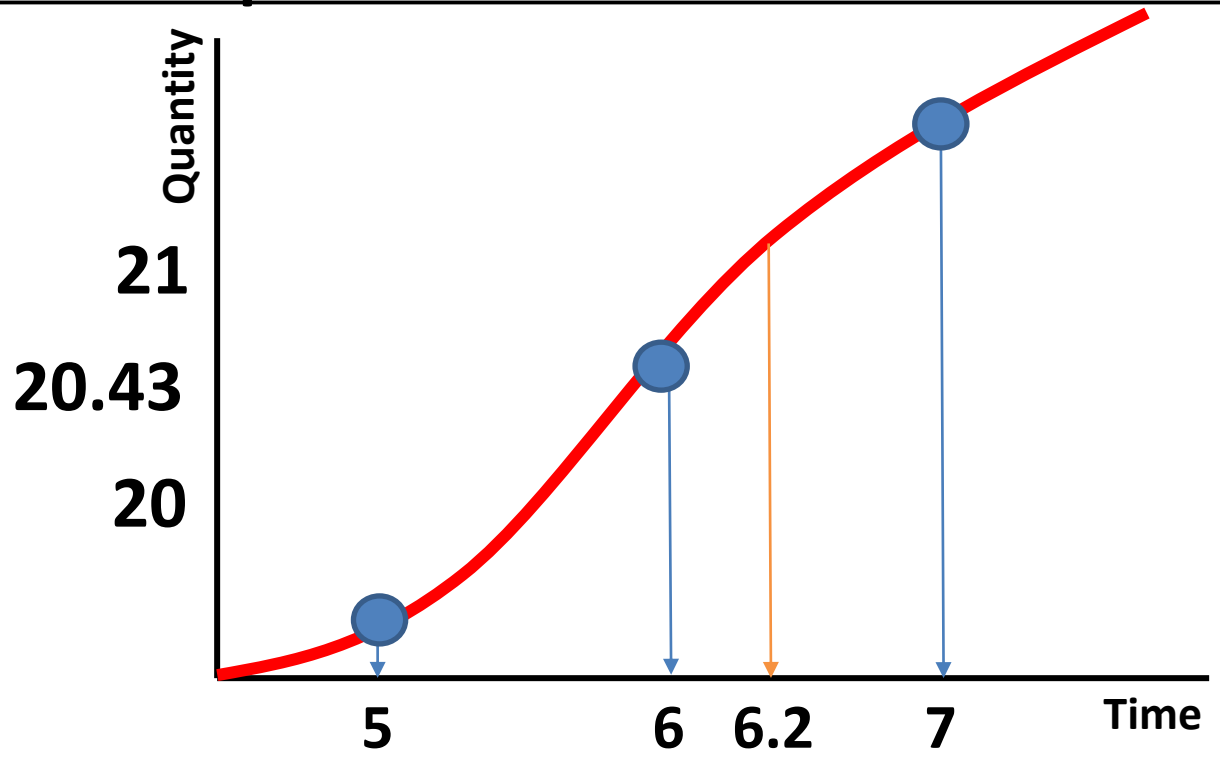
Continuous vs. Discrete

- Apply to
  - **<u>Quantities being modeled: Discrete</u>**
  - Time steps in the model



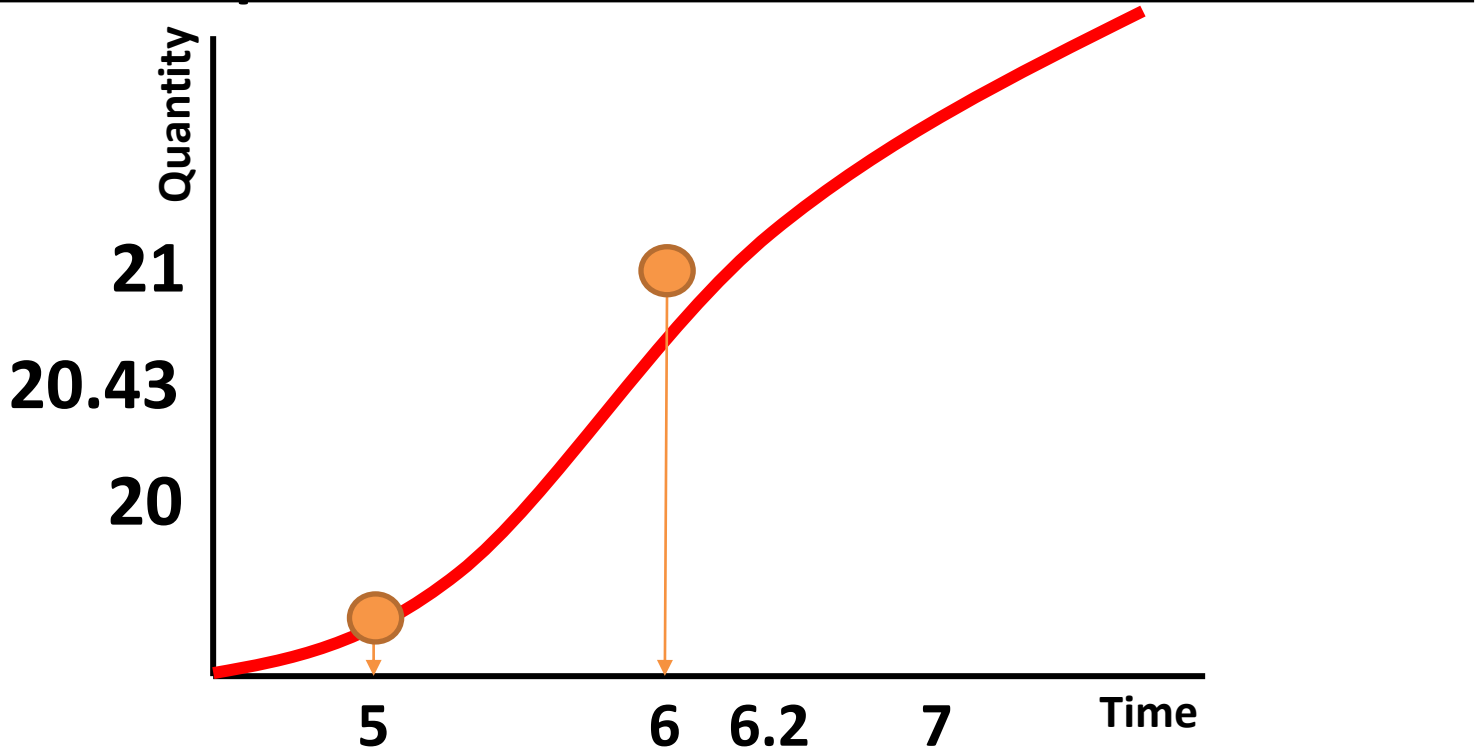
Continuous vs. Discrete

- Apply to
  - Quantities being modeled: Discrete
  - **Time steps in the model: Continuous vs. Discrete**



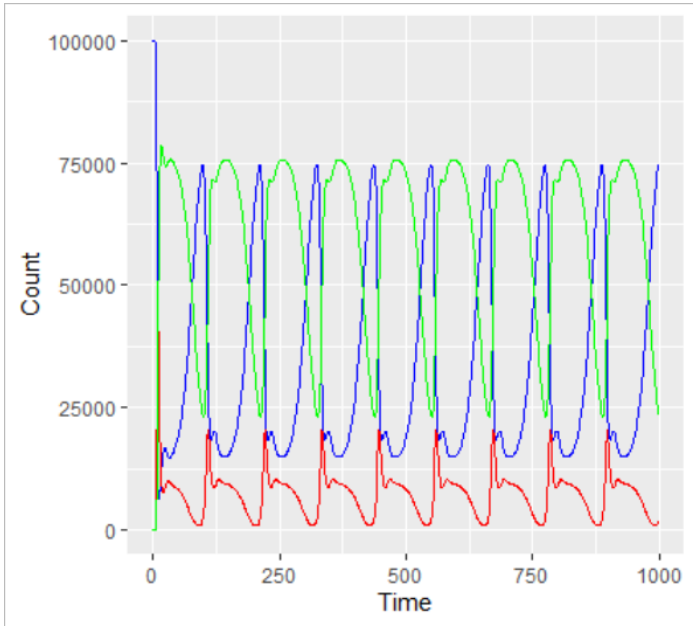
Continuous vs. Discrete

- Apply to
  - Quantities being modeled: **Discrete**
  - **Time steps in the model: Continuous vs. Discrete**



Deterministic vs. Stochastic

- **Deterministic:** Each time I run one of our differential equation models (SI, SIS, SIR, SEIR, etc), with the same parameter inputs (gamma, beta, etc.), I get the same values out



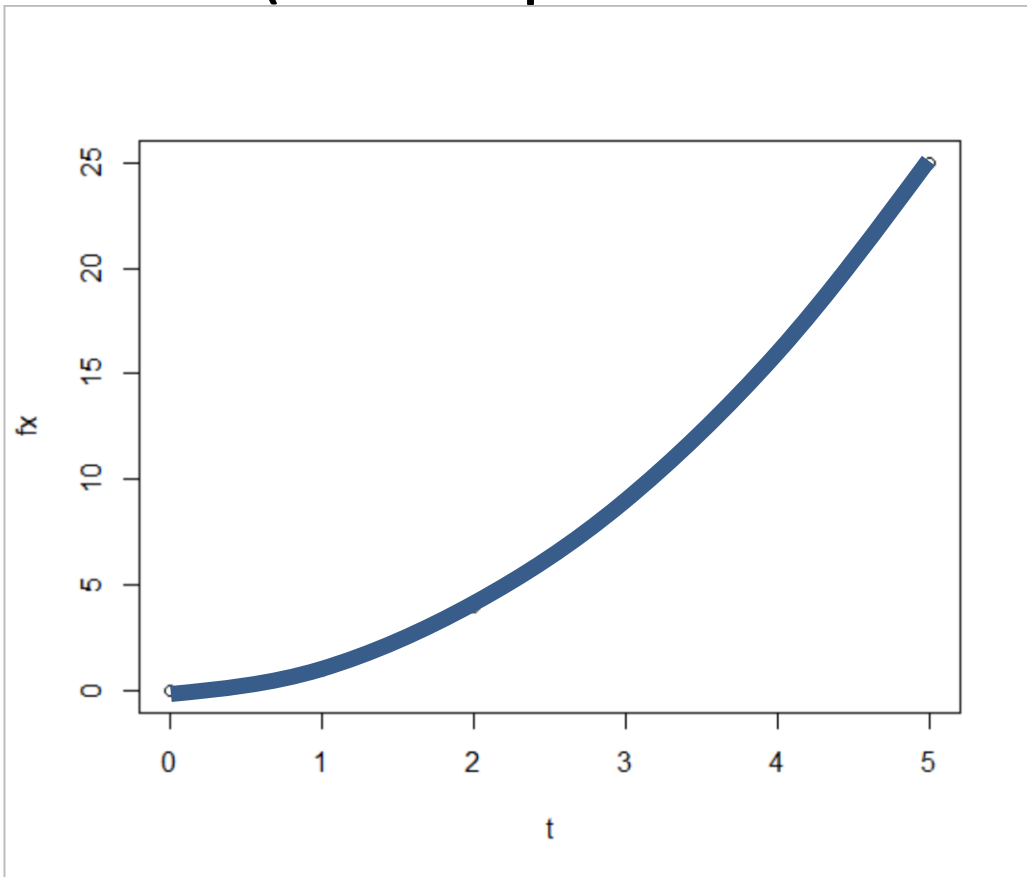
Values out can have complex patterns, but they are the same each time

Deterministic vs. Stochastic

- Our ODEs are functions of input parameters and time {S(t), I(t), R(t)} = f_ODE(params, t)
- For stochastic, let's think about simpler functions that just depend on parameters (actually 1 parameter) (we sample them onces per simulation and not once per time point per simulation)
- So let's let f(parameter) = parameter*t^2

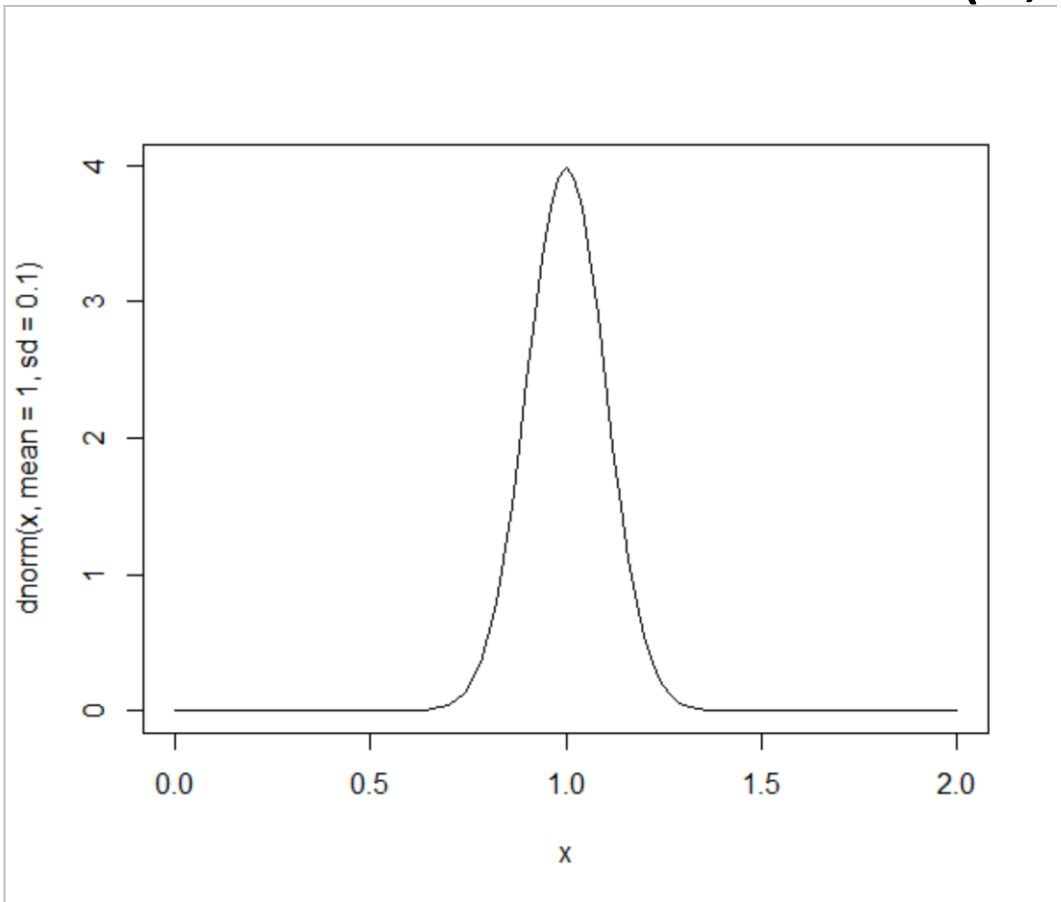
Deterministic vs. Stochastic

- The deterministic version of f(parameter) = parameter*t^2 is: (where parameter = x = 1)



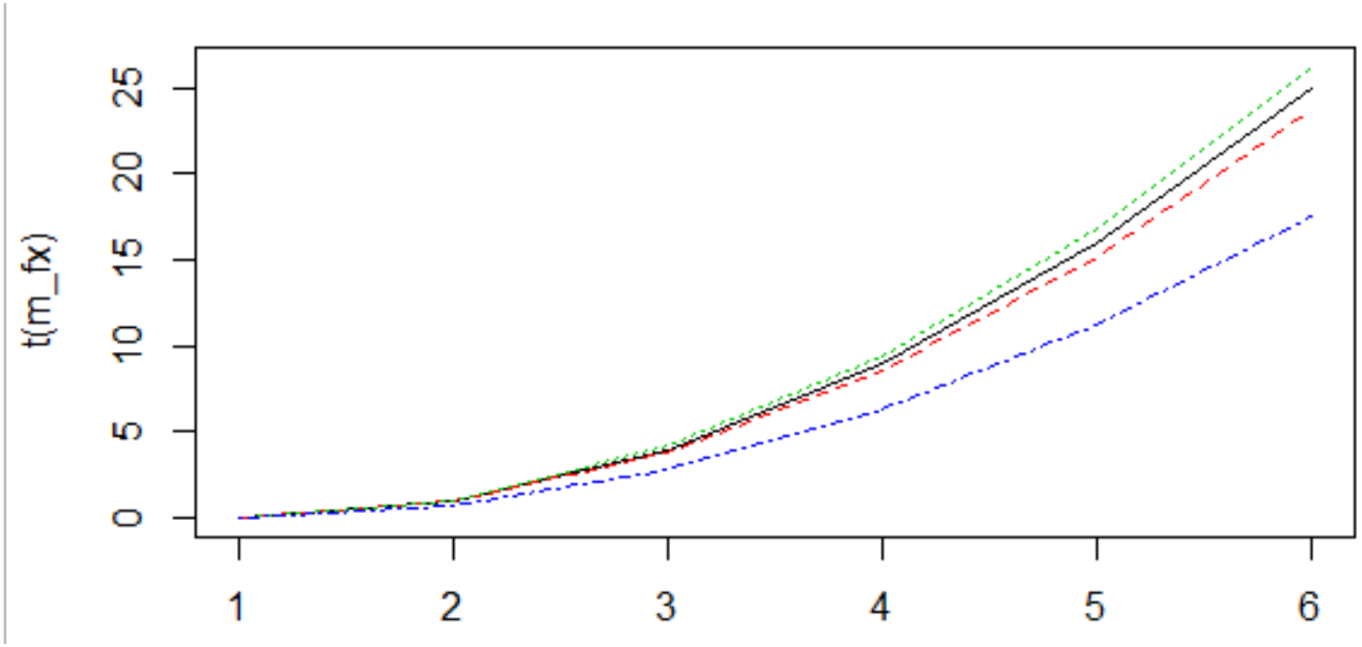
Deterministic vs. Stochastic

- The stochastic version of f(parameter) = parameter*t^2 : let's let x ~ 1+Normal(0,0.1)



Deterministic vs. Stochastic

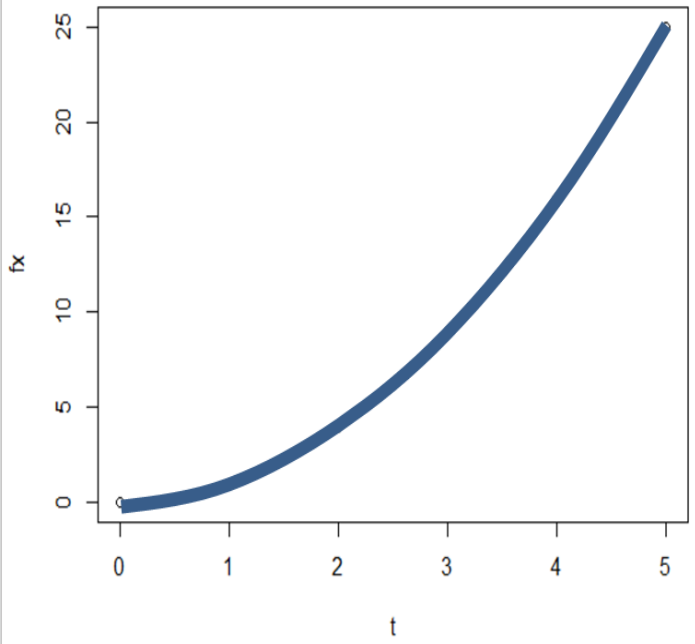
- The stochastic version of f(parameter) = parameter*t^2 : so when sample of x is < 1 then line rises more slowly (blue) or more rapidly (green)



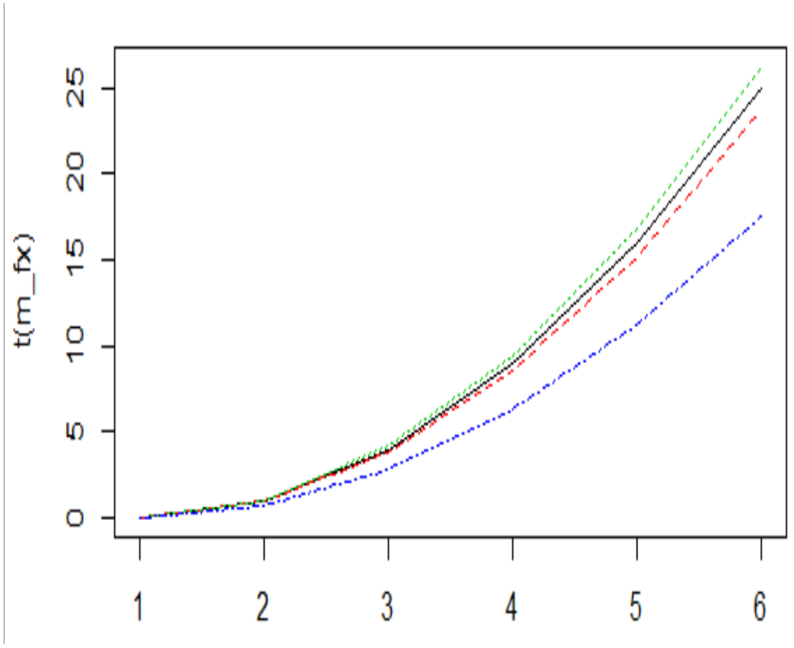
Deterministic vs. Stochastic

- This means that our model (with same parameter(s)) does not produce the same output each time it is run: it is stochastic

Deterministic



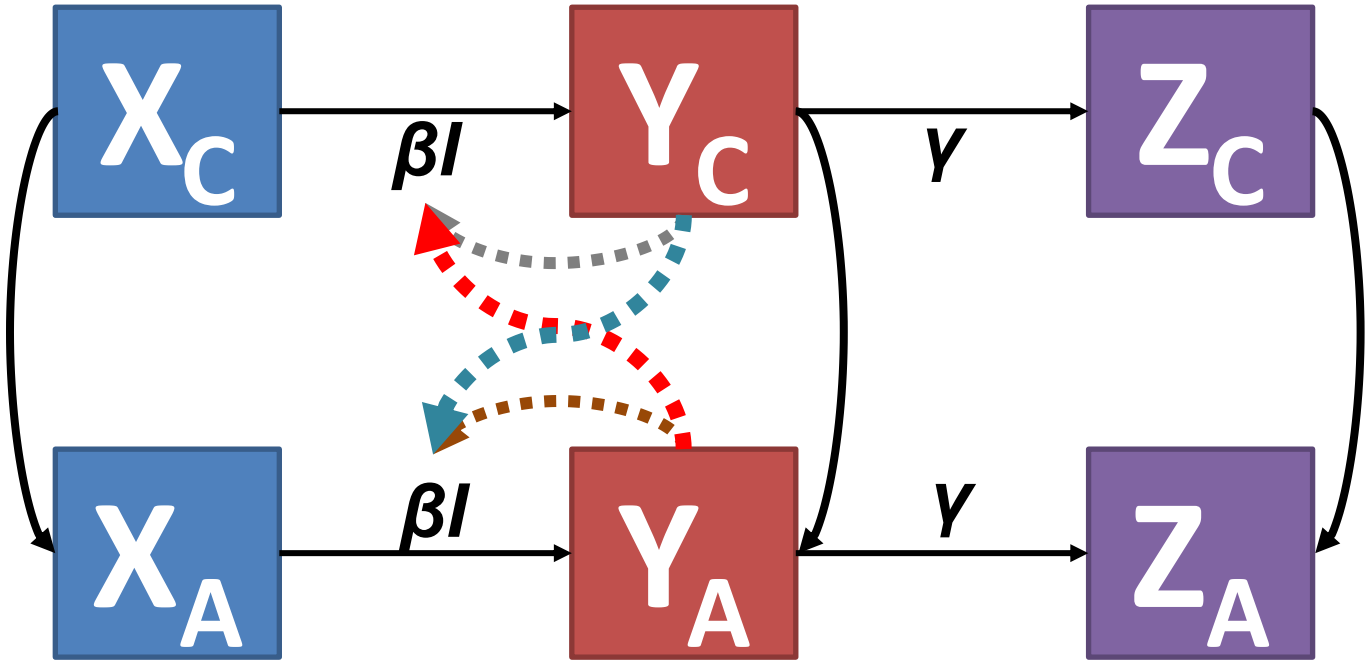
Stochastic



Nerd Aside: Random Numbers

- Chapter talks about a Random Number Generator (RNG)
- What it actually means is a Pseudo-Random Number Generator
- Why?
  - Because computers cannot really do random things themselves
  - What they can do is things whose patterns are very hard to predict
    - Given that I have seen a lot of samples from a stream of "random numbers" sampled from an RNG, it will be nearly impossible to predict the next

What real-world randomness should be reflected in the model?



1. Everyone has an average 4 contacts per week but this month it happened to be lower (like seasonal forcing but not a predictable sine wave)
2. The virus is more transmissible in cold damp conditions, but some weeks will be warmer and dryer
3. Some people who get infected took a lot longer (or a lot less time) to recover than 1/gamma (average duration of infectiousness)

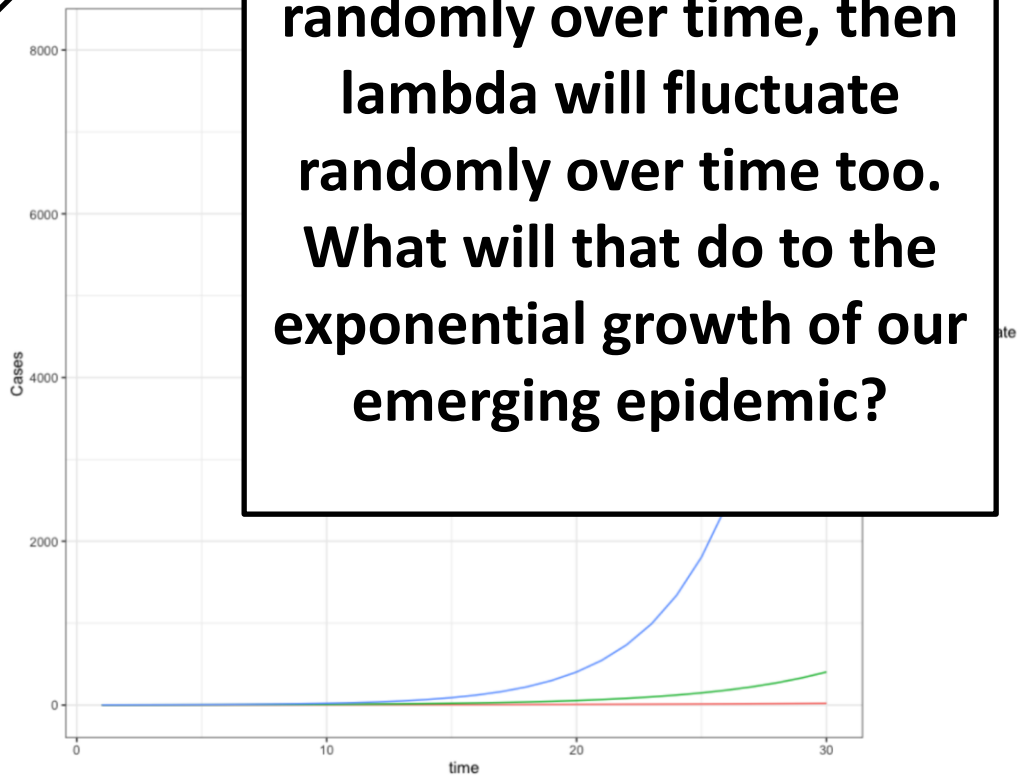
We will first illustrate random ODE model parameters with a simpler model: recall…

A constant growth rate mean growth in cases

$$\frac{dI}{dt} = \Lambda I$$

$\Lambda = (\beta - \gamma)$ = growth rate

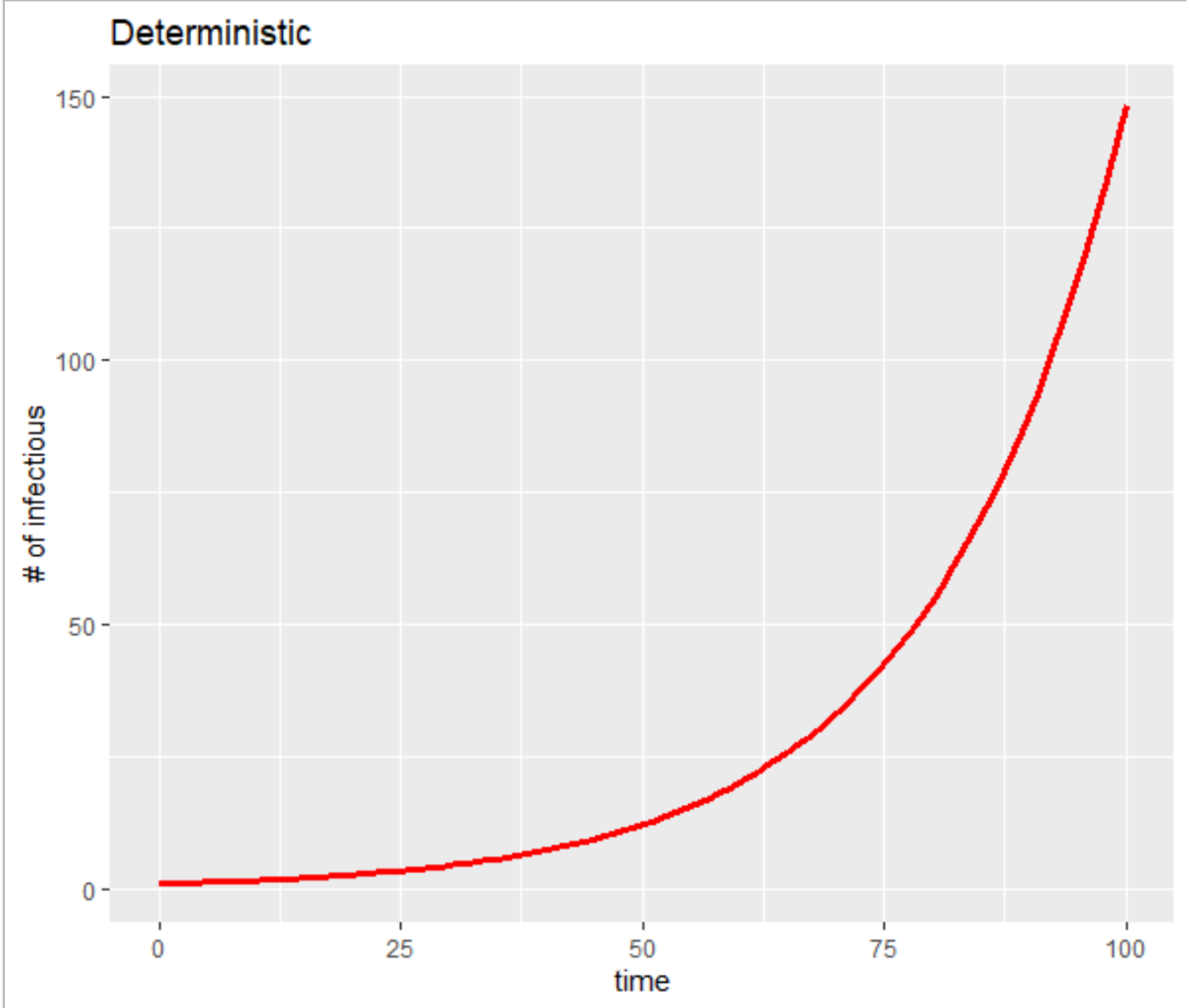
$$I(t) = I(0)e^{\Lambda t}$$



If we imagine that either beta or gamma fluctuate randomly over time, then lambda will fluctuate randomly over time too. What will that do to the exponential growth of our emerging epidemic?

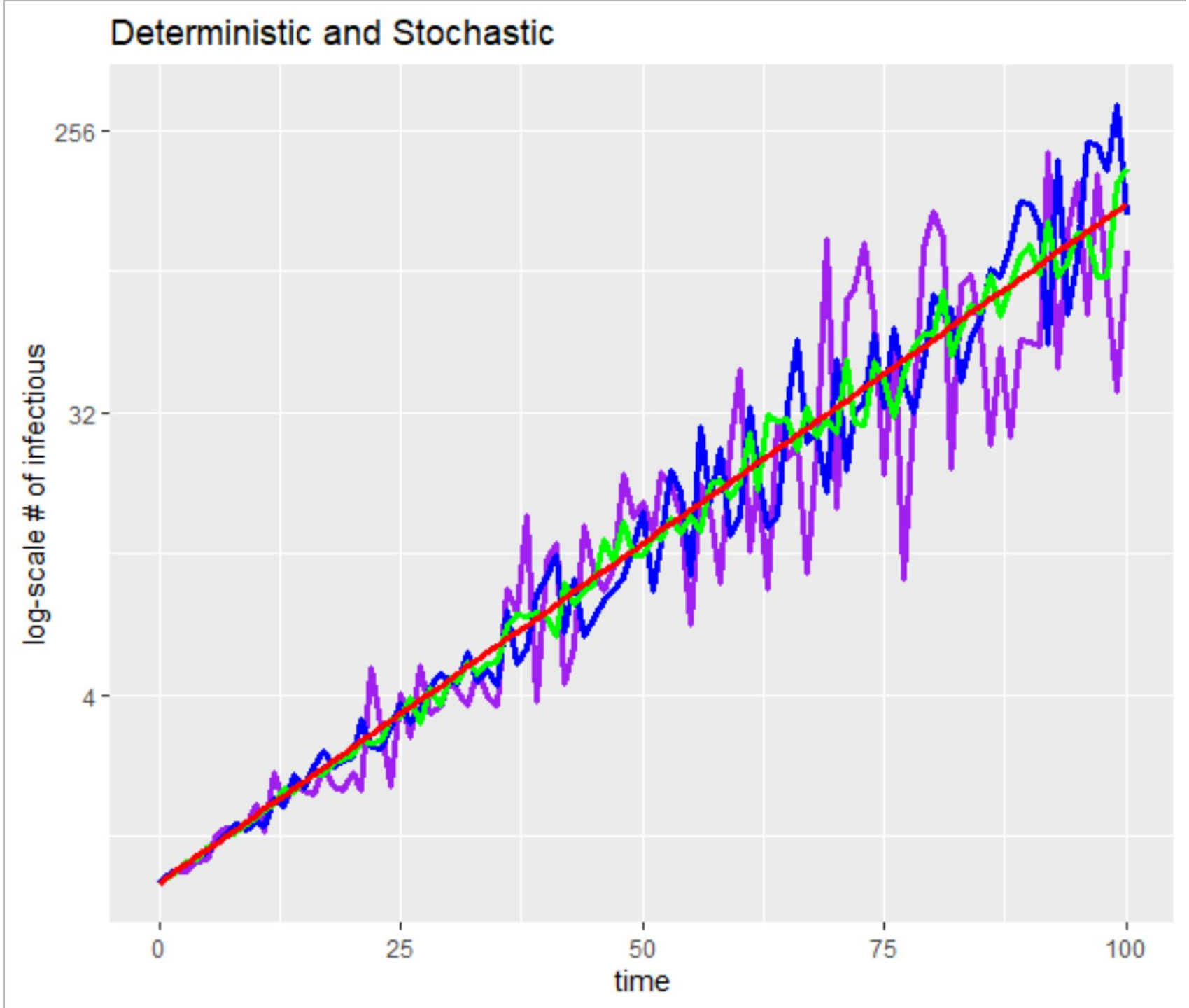
Code for the deterministic exponential growth model

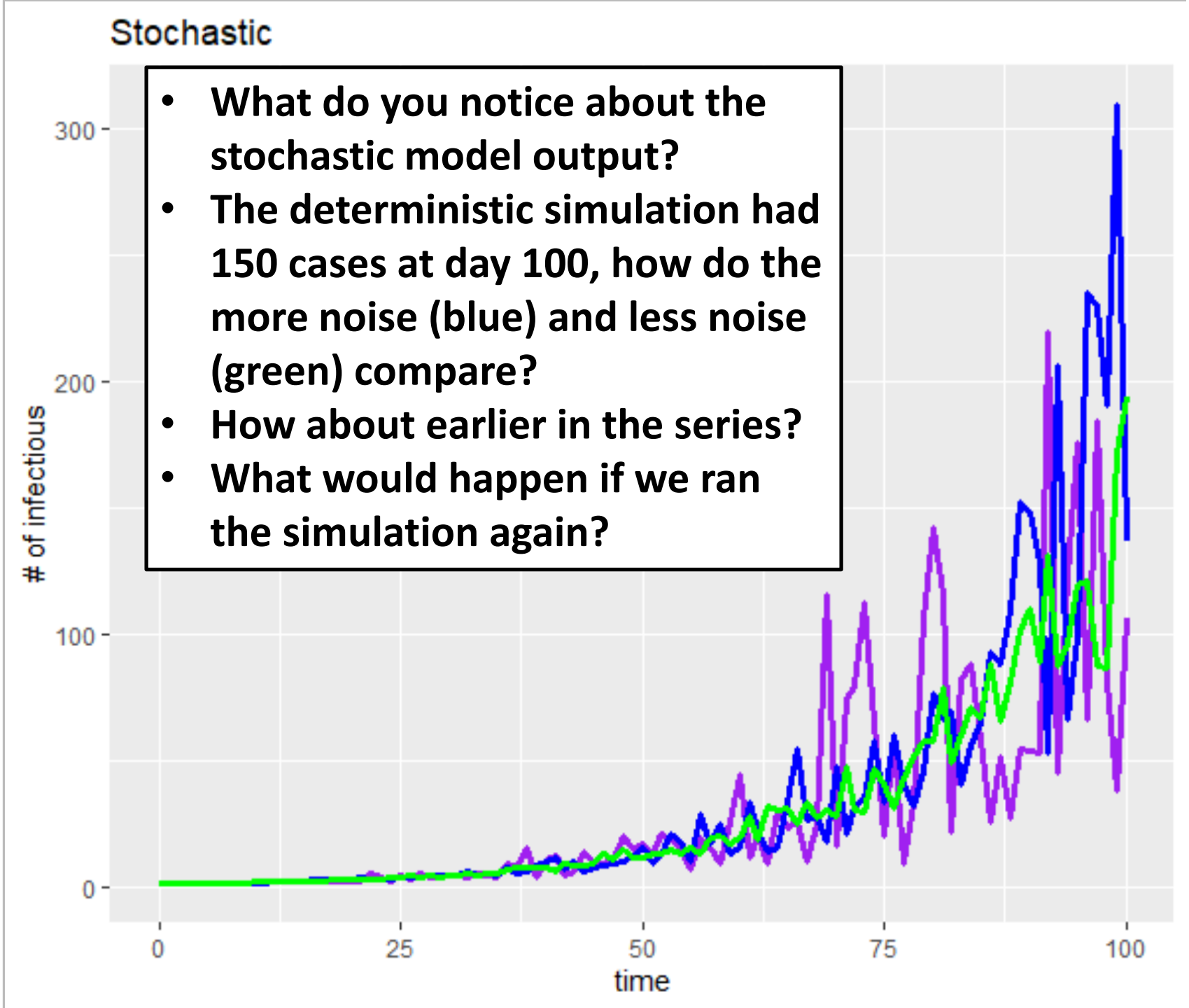
```
r_transmission  <- 0.03
c_contacts      <- 5
c_beta          <- r_transmission * c_contacts
c_gamma         <- 1/10
c_lambda        <- (c_beta - c_gamma)

c_end_time      <- 100
v_times         <- seq(0, c_end_time)
v_lambdas       <- rep(c_lambda, length(v_times))

c_I0            <- 1

do_emergence <- function(I0, lambdas, times) {
  It <- I0 * exp(lambdas * times)
  return(It)
}

v_It            <- do_emergence(c_I0, v_lambdas, v_times)
```

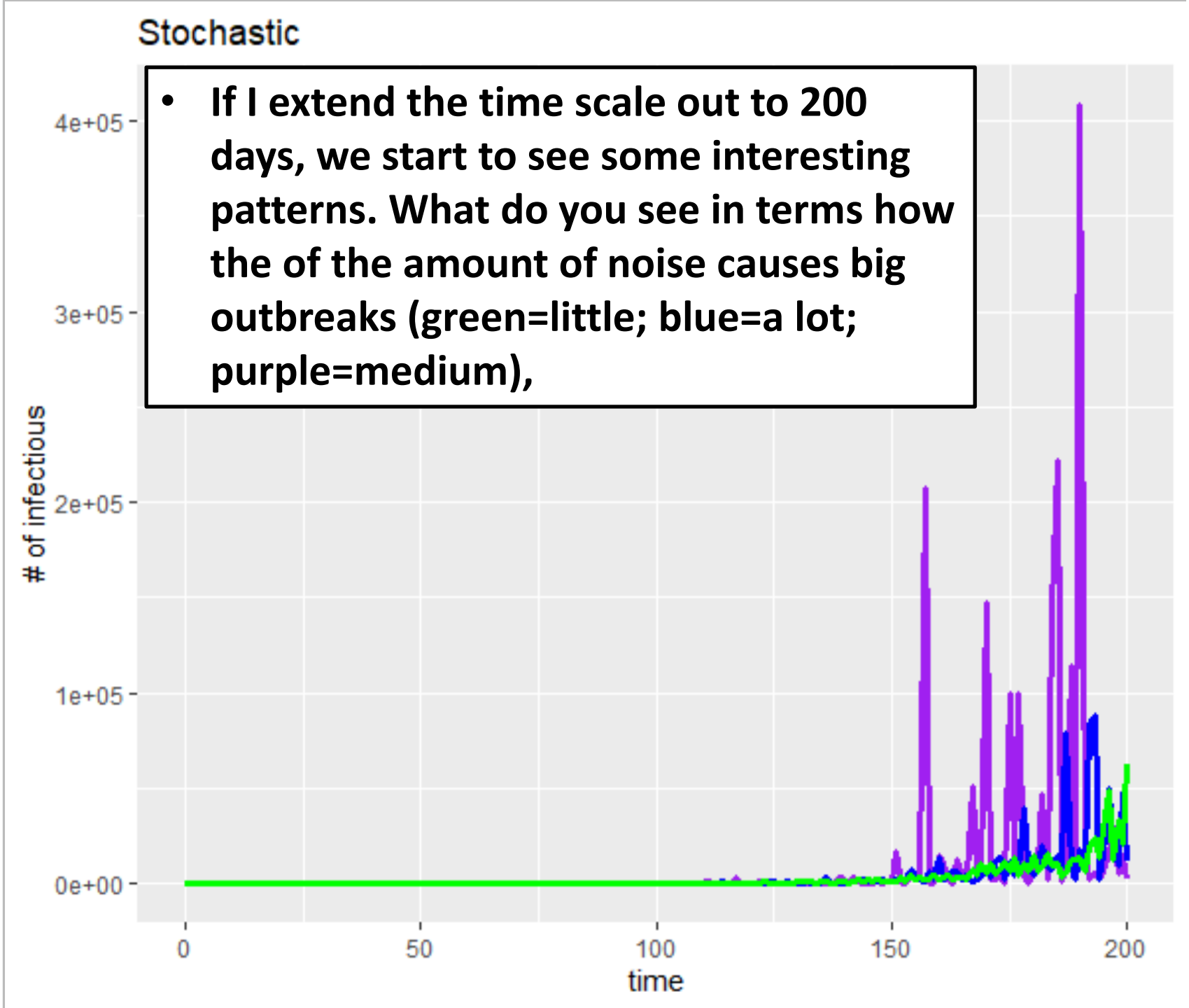

Deterministic
150
100
50
0
# of infectious
0
25
50
75
100
time

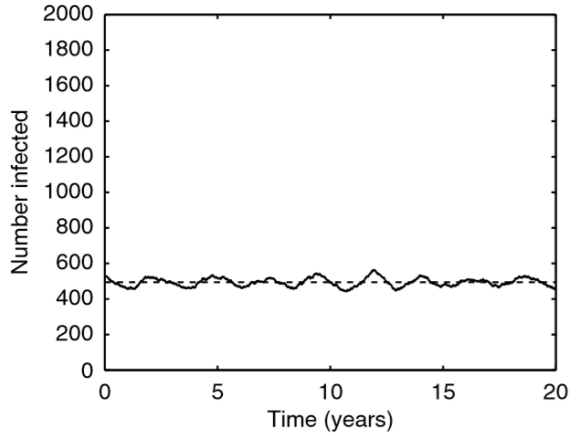
Code for the deterministic exponential growth model

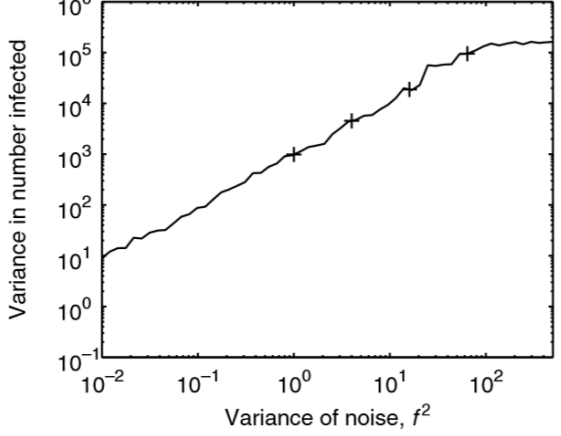
```
v_lambdas_noise <- v_lambdas + rnorm(length(v_lambdas))/200

v_It_noise      <- do_emergence(c_I0, v_lambdas_noise,
                                v_times)

v_lambdas_noise_l <- v_lambdas + rnorm(length(v_lambdas))/400

v_It_noise_l      <- do_emergence(c_I0, v_lambdas_noise_l,
                                  v_times)

v_lambdas_noise_m <- v_lambdas + rnorm(length(v_lambdas))/100

v_It_noise_m      <- do_emergence(c_I0, v_lambdas_noise_m,
                                  v_times)
```

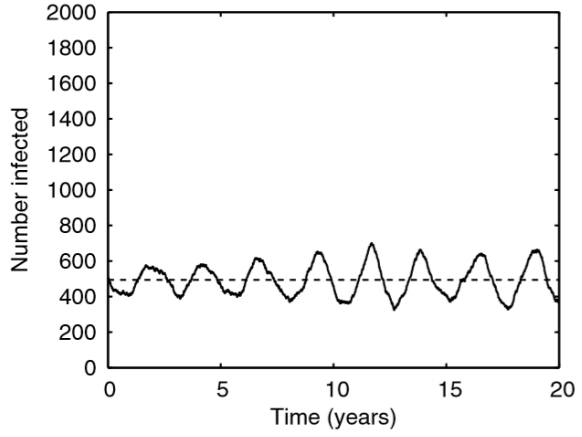

Deterministic and Stochastic
256
32
4
log-scale # of infectious
0
25
50
75
100
time

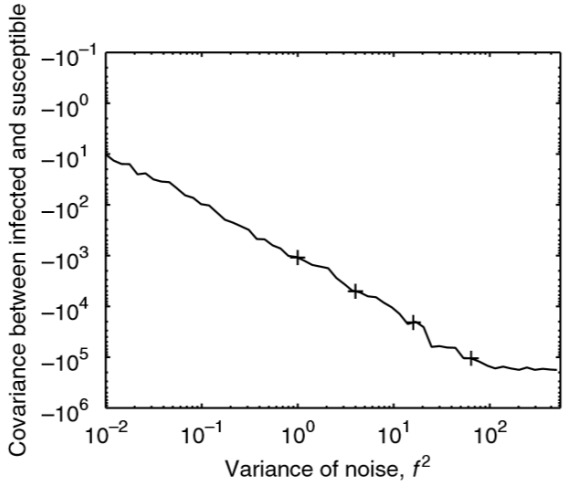

Stochastic
What do you notice about the stochastic model output?
The deterministic simulation had 150 cases at day 100, how do the more noise (blue) and less noise (green) compare?
How about earlier in the series?
What would happen if we ran the simulation again?
300
200
100
0
# of infectious
0
25
50
75
100
time

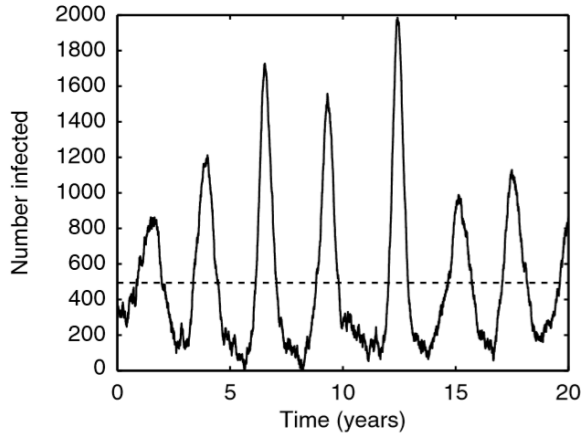

Stochastic
• If I extend the time scale out to 200 days, we start to see some interesting patterns. What do you see in terms how the of the amount of noise causes big outbreaks (green=little; blue=a lot; purple=medium),
4e+05
3e+05
2e+05
1e+05
0e+00
# of infectious
0
50
100
150
200
time











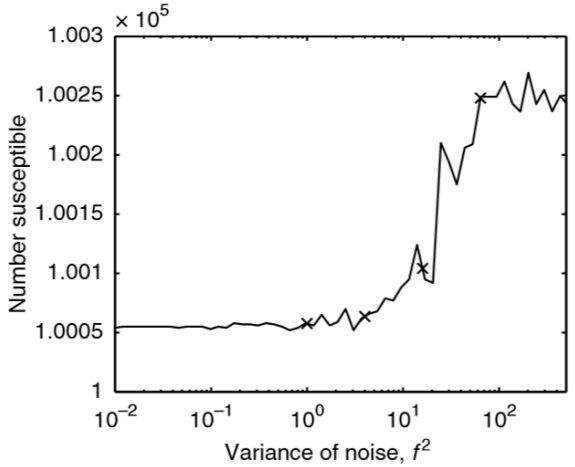
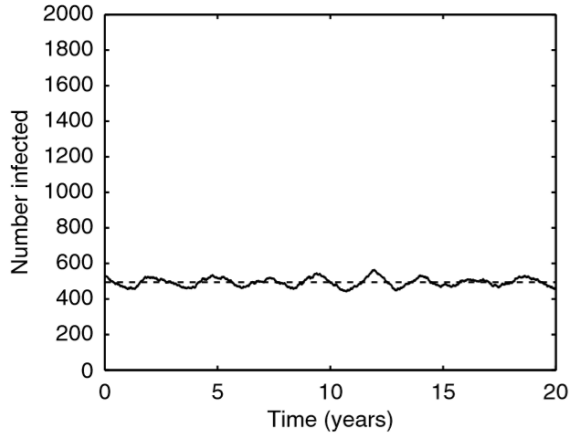
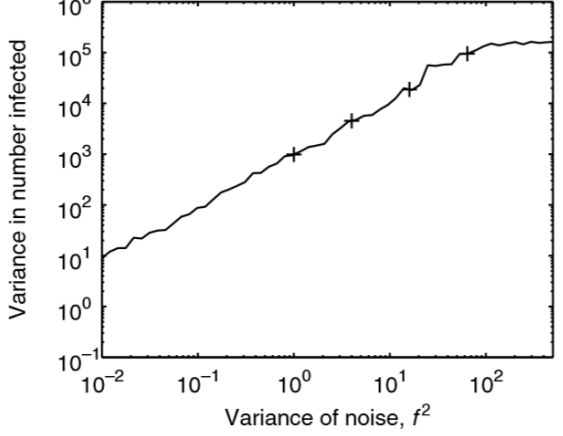
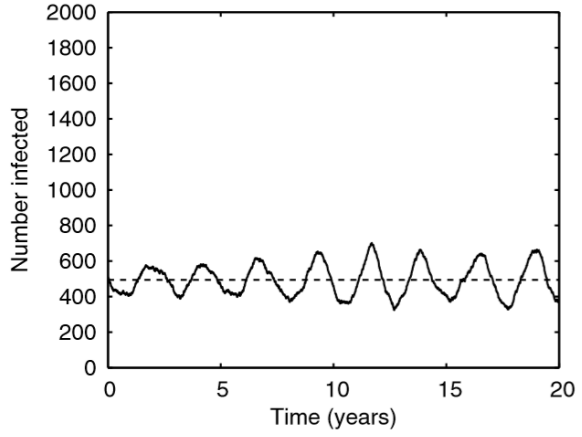


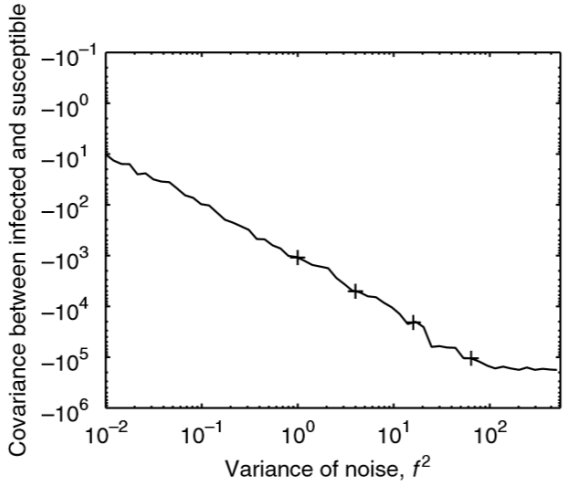
Figure 6.2 (SIR model)

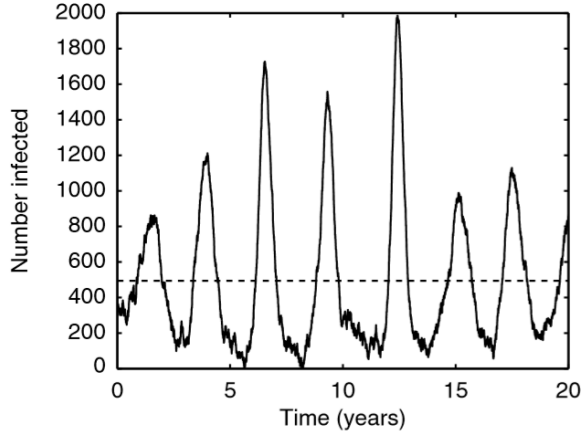
- **Left panels show fluctuations in # of infected individuals.**
  - **Upper has little random noise in Beta**
  - **Middle medium noise**
  - **Lower has a lot of noise**
- **What do you notice about the differences?**











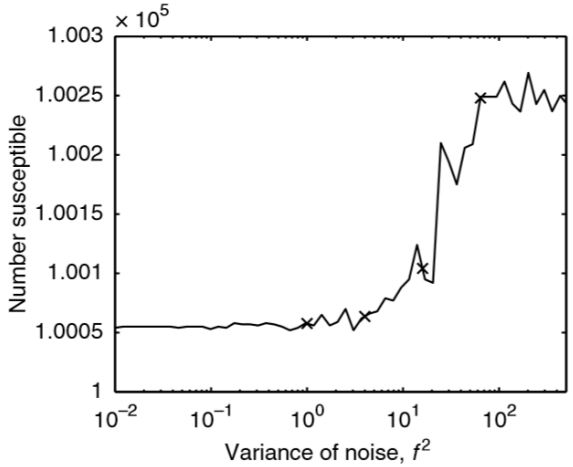
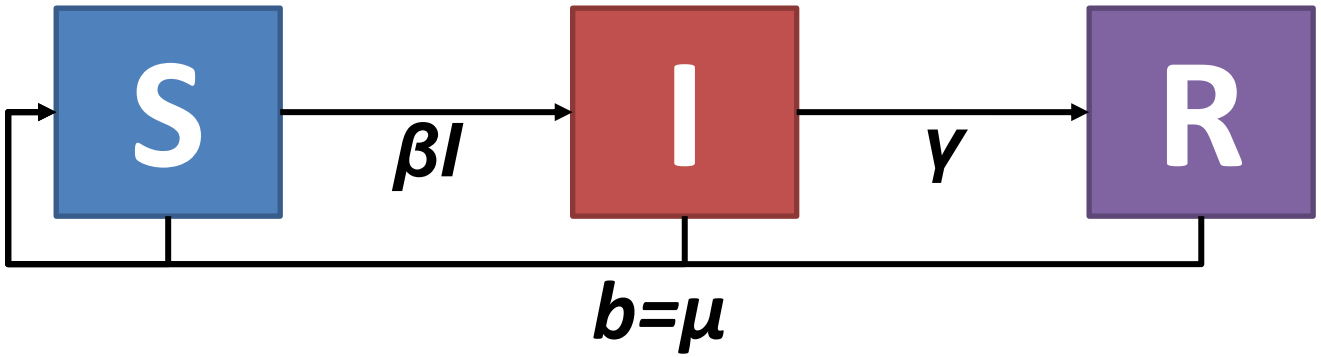


Figure 6.2 (SIR model)

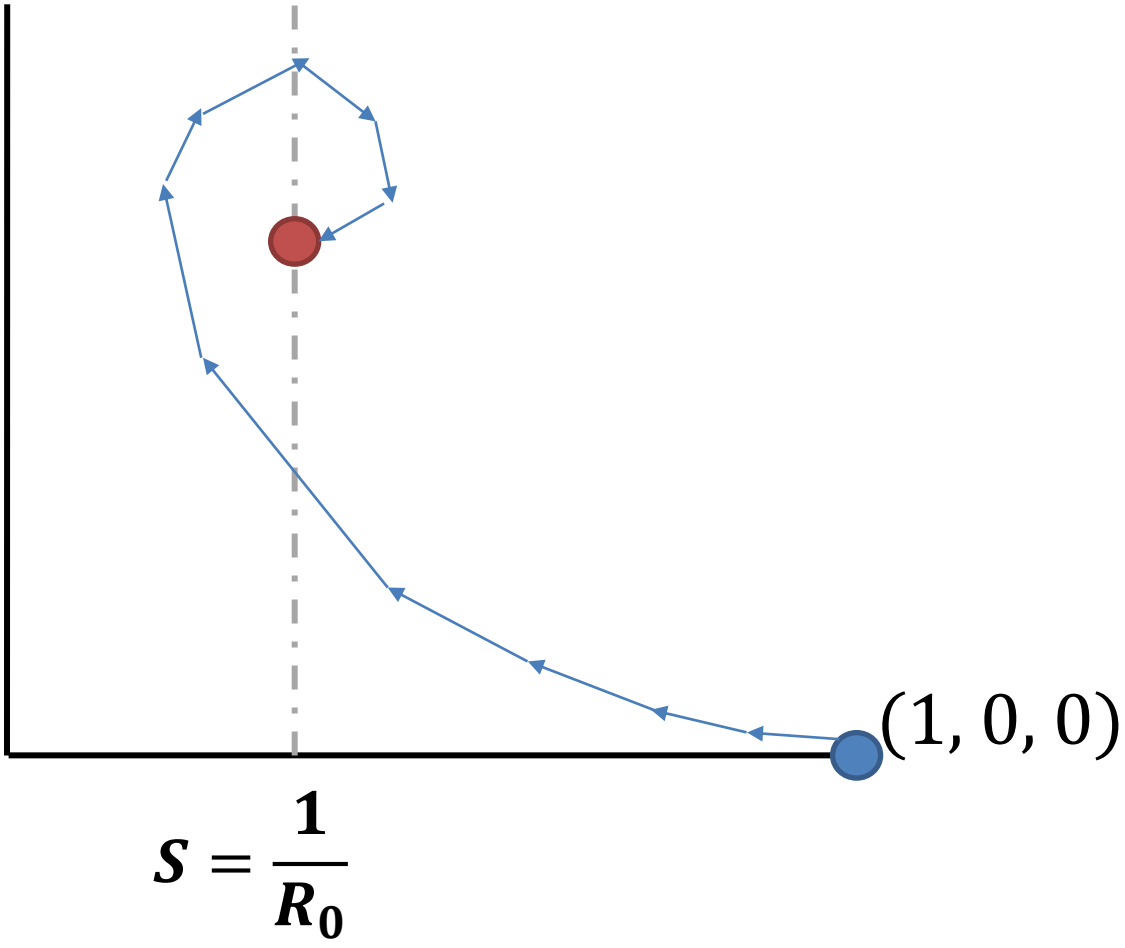
- **Right panels show measures of variance.**
- **Focus on the lowest panel**
- **When there is more noise (the right of the x-axis), there are more susceptibles on average**
- **The middle panel shows that the covariance between infectious and susceptibles becomes more strongly negative with more noise**
- **What is going on?**

What drives the high amplitude epidemics?

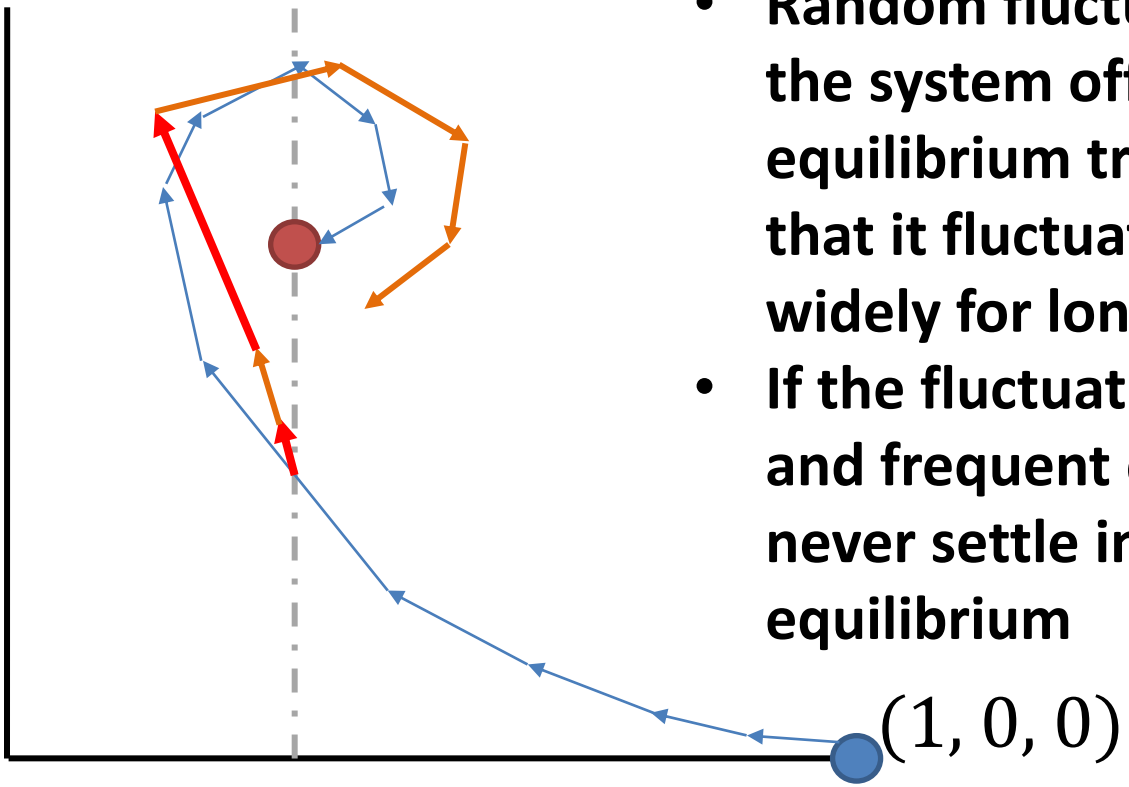


- When β randomly fluctuates below its mean, then
- the number of Susceptibles increases, and
- the number of Infectious falls, but
- With more Susceptibles and
- with the potential for β to randomly fluctuate above its mean,
- we can get a large and rapid epidemic rise which
- depletes the Susceptibles leading to a lower trough…

SIR model with demography: Equilibria and Stability

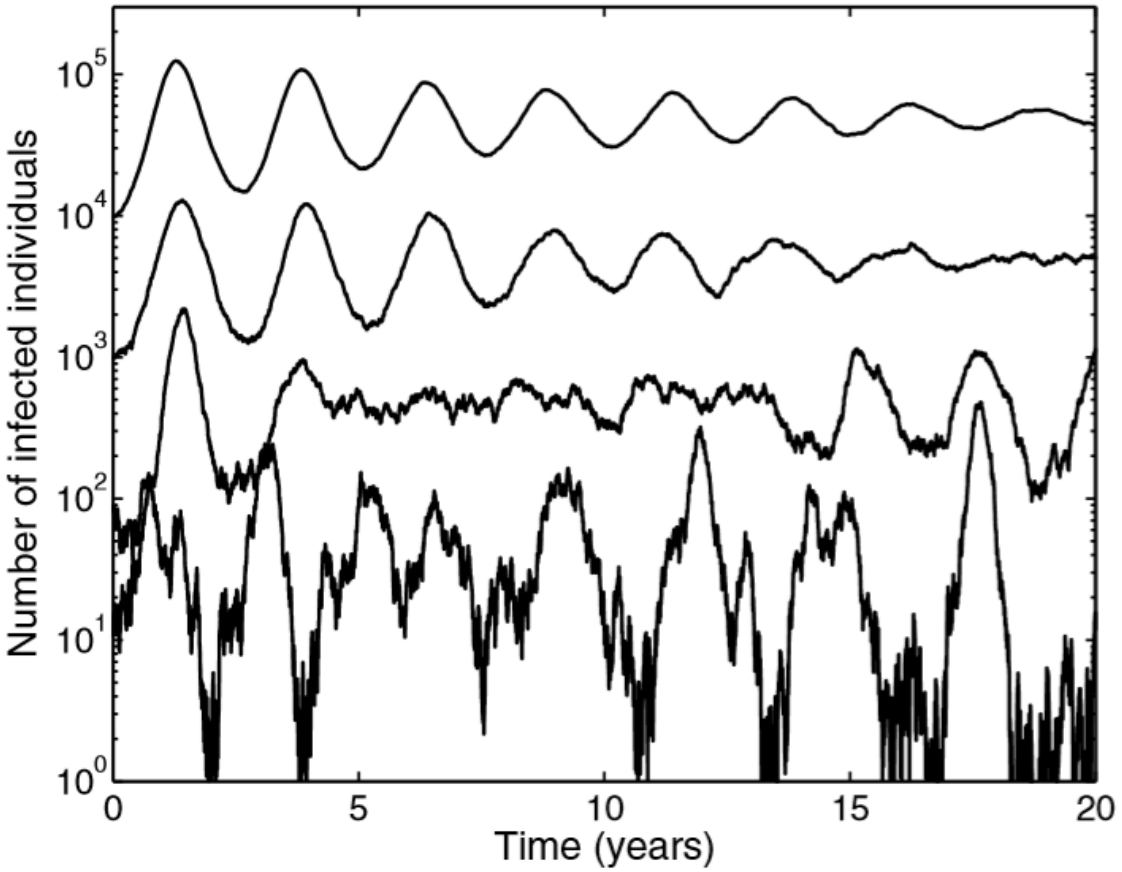


SIR model with demography: Equilibria and Stability



- Random fluctuations knock the system off of its damped equilibrium trajectory so that it fluctuates more widely for longer
- If the fluctuations are large and frequent enough it may never settle into its equilibrium

Scaled noise (relative to population size)

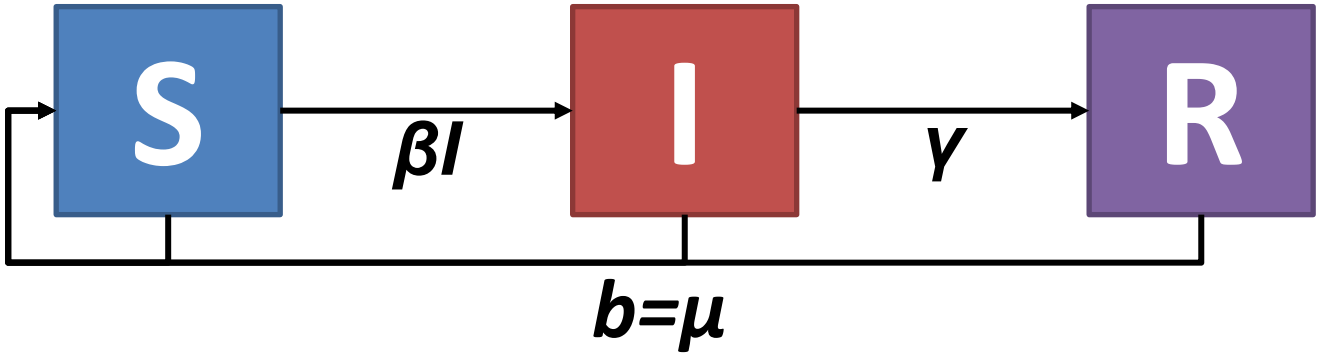


When noise is scaled relative to the population size, then small population sizes take longer and have more trouble getting into their stable endemic equilibrium … Let's talk more about this

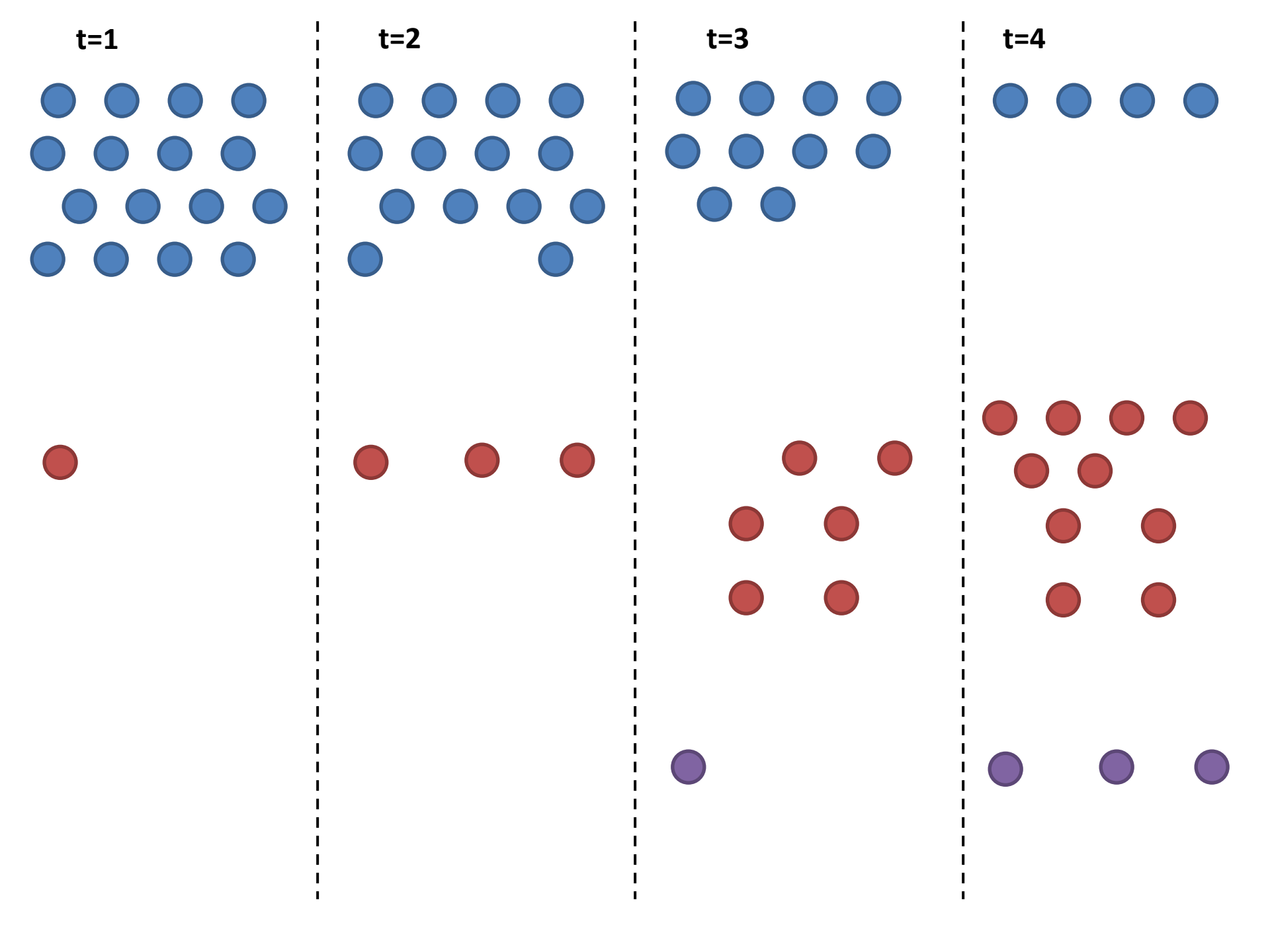
UP UNTIL NOW:
RANDOM FLUCTUATIONS IN PARAMETERS FOR CONTINUOUS QUANTITY, CONTINUOUS TIME MODELS

NOW LET'S CONSIDER DISCRETE QUANTITY DISCRETE TIME MODELS (SIMPLE INDIVIDUAL-BASED MODELS)

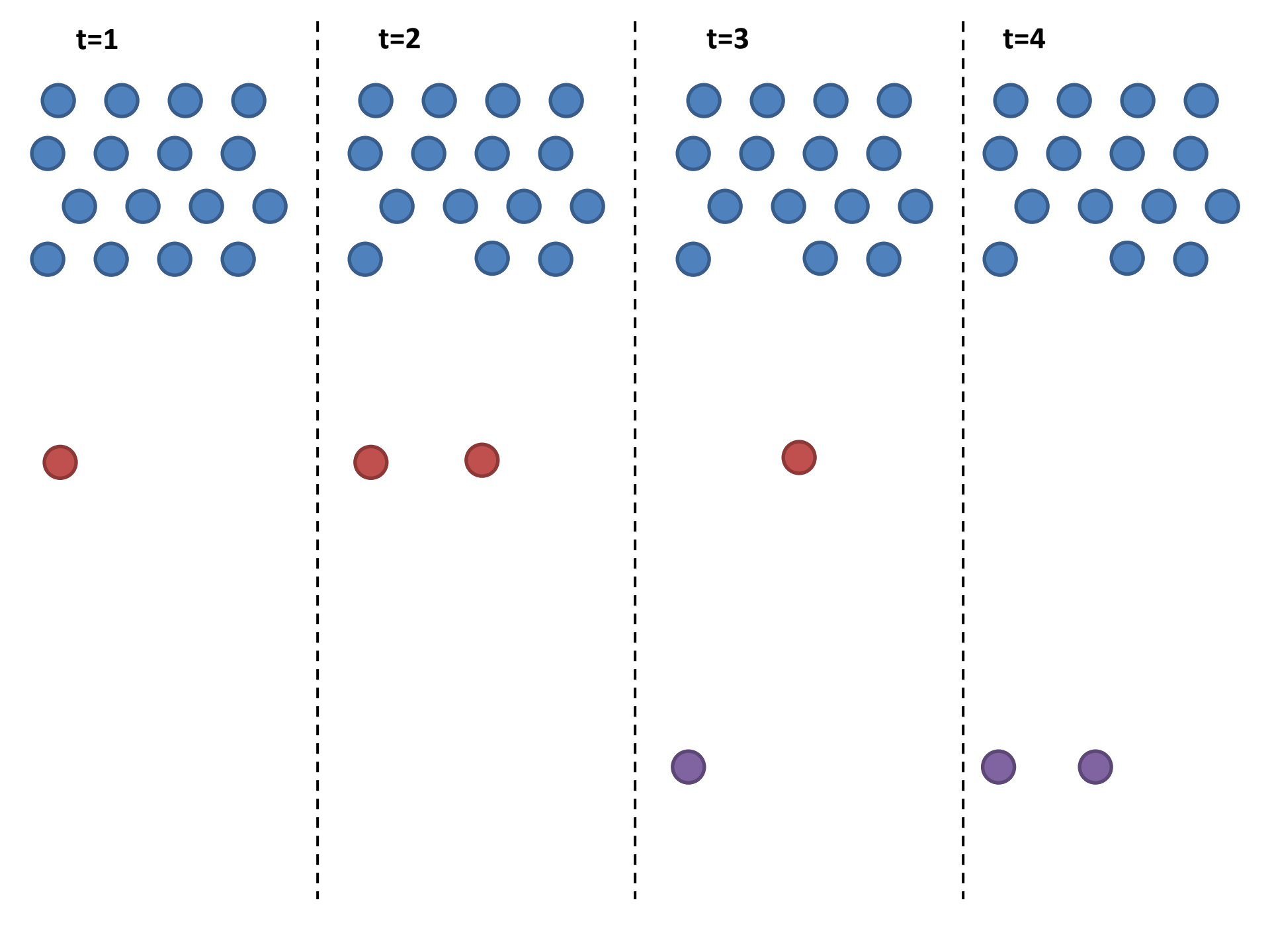
States people are in: Susceptible (blue); Infectious (red); Recovered (purple)



CASE (SIMULATION) 1: EPIDEMIC TAKE-OFF


t=1
t=2
t=3
t=4

CASE (SIMULATION) 2: EPIDEMIC FADE-OUT


t=1
t=2
t=3
t=4

Simple Individual Based Model

- Tracks counts of Susceptibles (X), Infectious (Y), and Recovered (Z)
- Each discrete time step,
  - Chance of each Y infecting each X: Causes count of X to go down and Y to go up by this amount
  - Chance of each Y recovering: Causes count of Y to go down and Z to go up by this amount
  - Chance of each Z having immunity wane: Causes count of Z to go down and X to go up by this amount

Simple Individual Based Model

- For populations (N=X+Y+Z) of different sizes (10^3, 10^4, 10^5, 10^7) we do the following:
  - Run the model 200 times with each model run over 1000 days
  - For each model run, plot the counts of Infectious (Y) over time (ordering these by the # of infectious days)
- Let's look at the model code and the plotted results

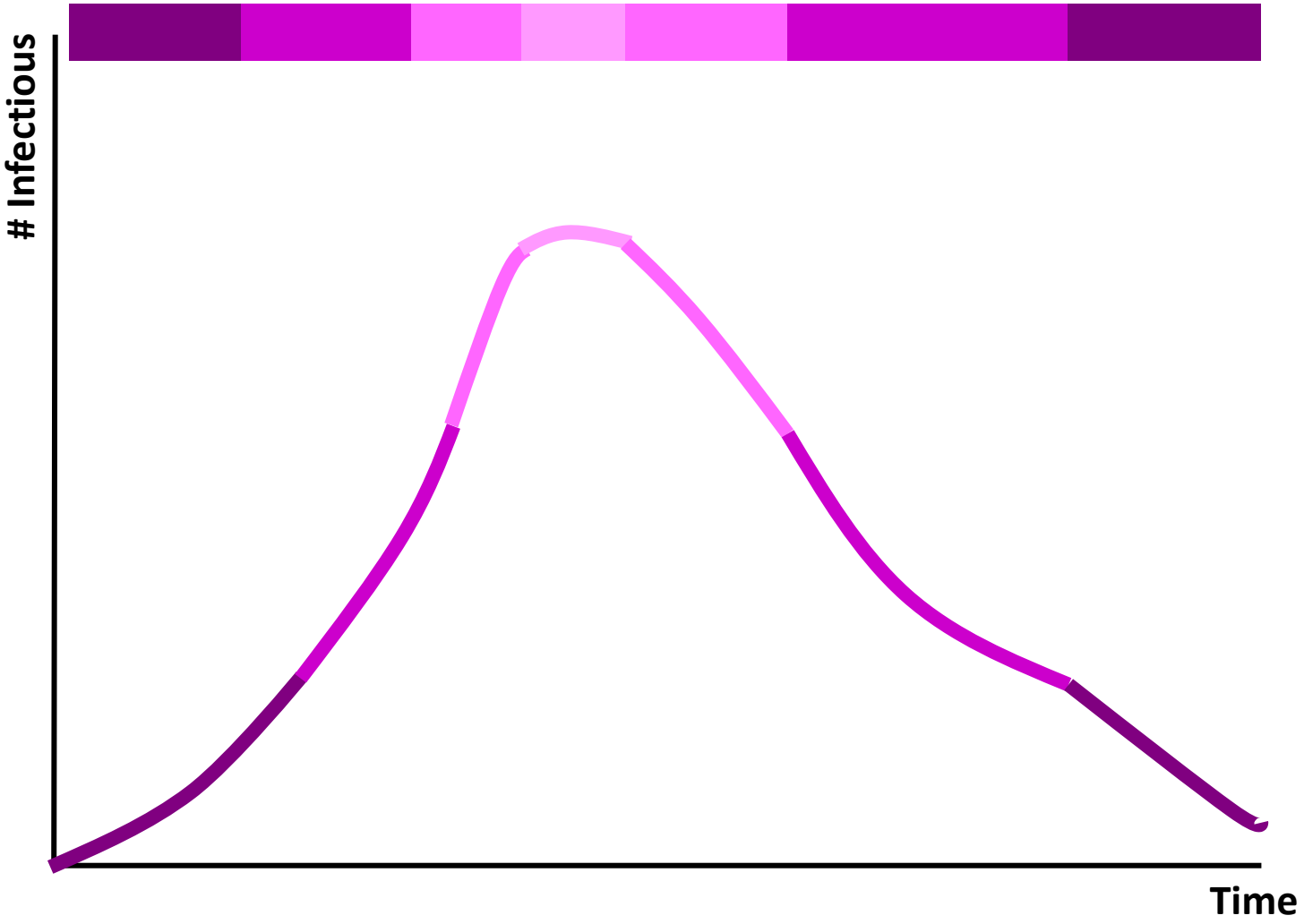
```
# PARAMETER INTIATLIZATION
r_transmission  <- 0.03
c_contacts      <- 5
c_beta          <- r_transmission * c_contacts
c_gamma         <- 1/10
c_omega         <- 1/400
beta_mult <- 1.25
c_end_time <- 1000
n_sims <- 200
pidx <- 1
```

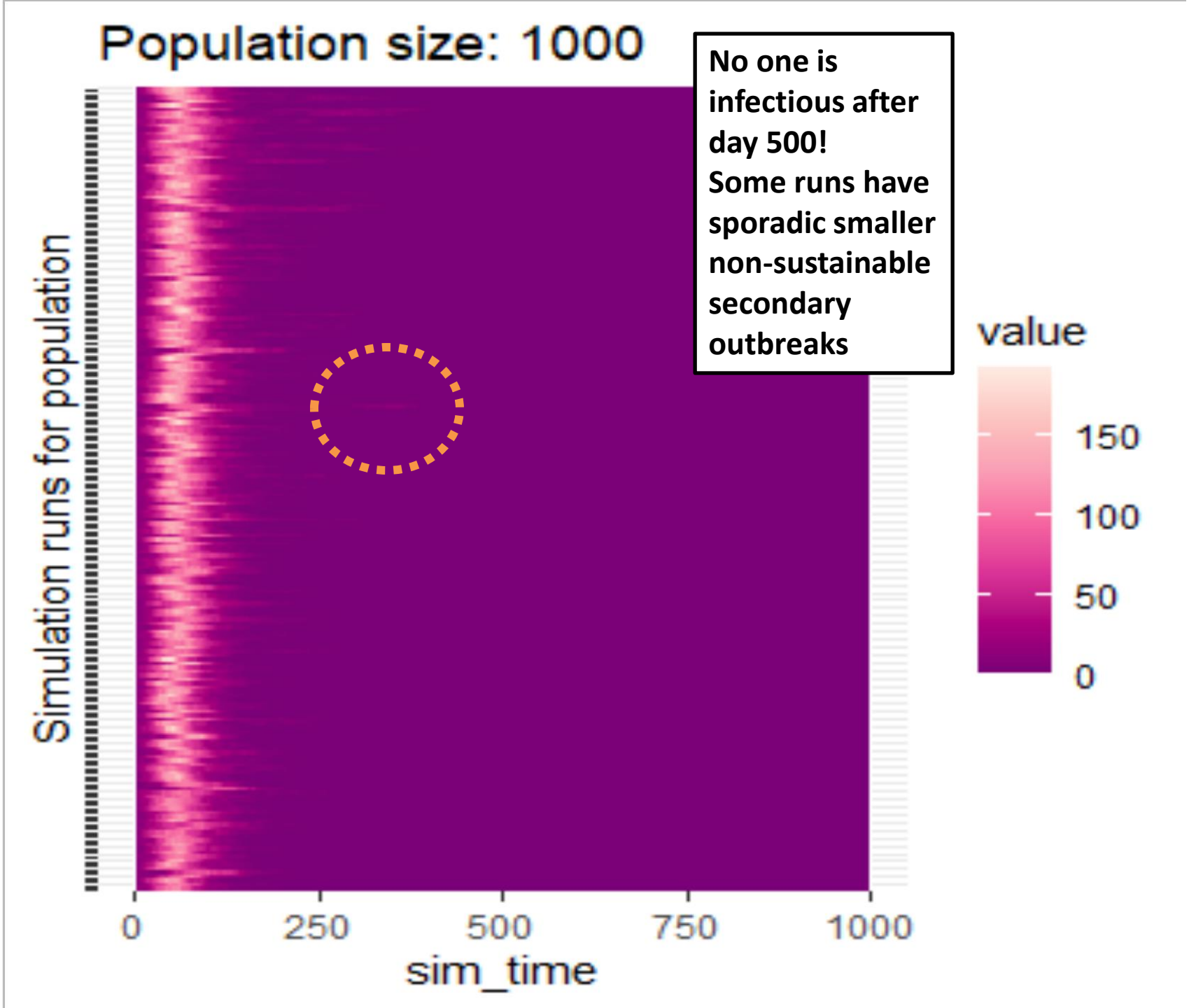
```
# THE LOOP TO ANALYZE DIFFERENT POPULATION SIZES
for(pop_size in c(1000, 10000, 100000, 10000000))
{
  # INITIALIZATION:
  c_Ninit <- pop_size

  # START WITH 10 INFECTIOUS (Y)
  c_Yinit <- 10

  # EVERYONE ELSE IS SUSCEPTIBLE (X)
  c_Xinit <- c_Ninit - c_Yinit

  # MATRIX TO HOLD SIMULATION OUTPUTS
  m_sims <- c()
```

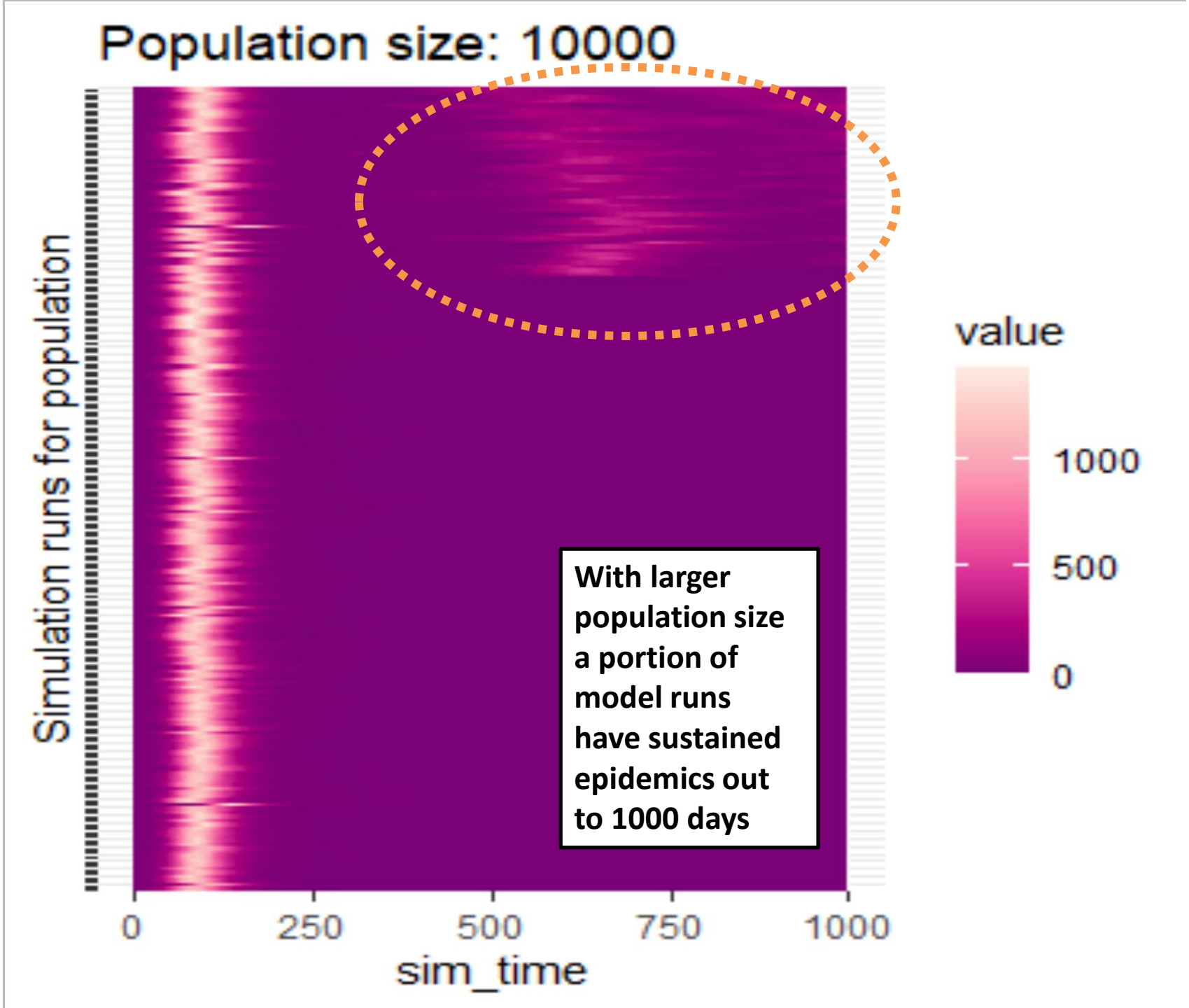
```
for(ss in 1:n_sims) {
    # INITIALIZE THE MATRIX WE WILL USE TO KEEP
    # TRACK OF COUNTS OF X, Y, Z
    m_trace <- matrix(0, nrow = c_end_time+1, ncol = 3)

    # INIT STARTING POPULATION
    for(j in 1:ncol(m_trace)) {
      m_trace[1,j] <- ifelse(j==1, c_Xinit,
                             ifelse(j==2, c_Yinit, 0))
    }

    # SEE NEXT SLIDE FOR CODE FOREACH MODEL TIME STEP

    m_sims <- rbind(m_sims, m_trace[,2])
}
```

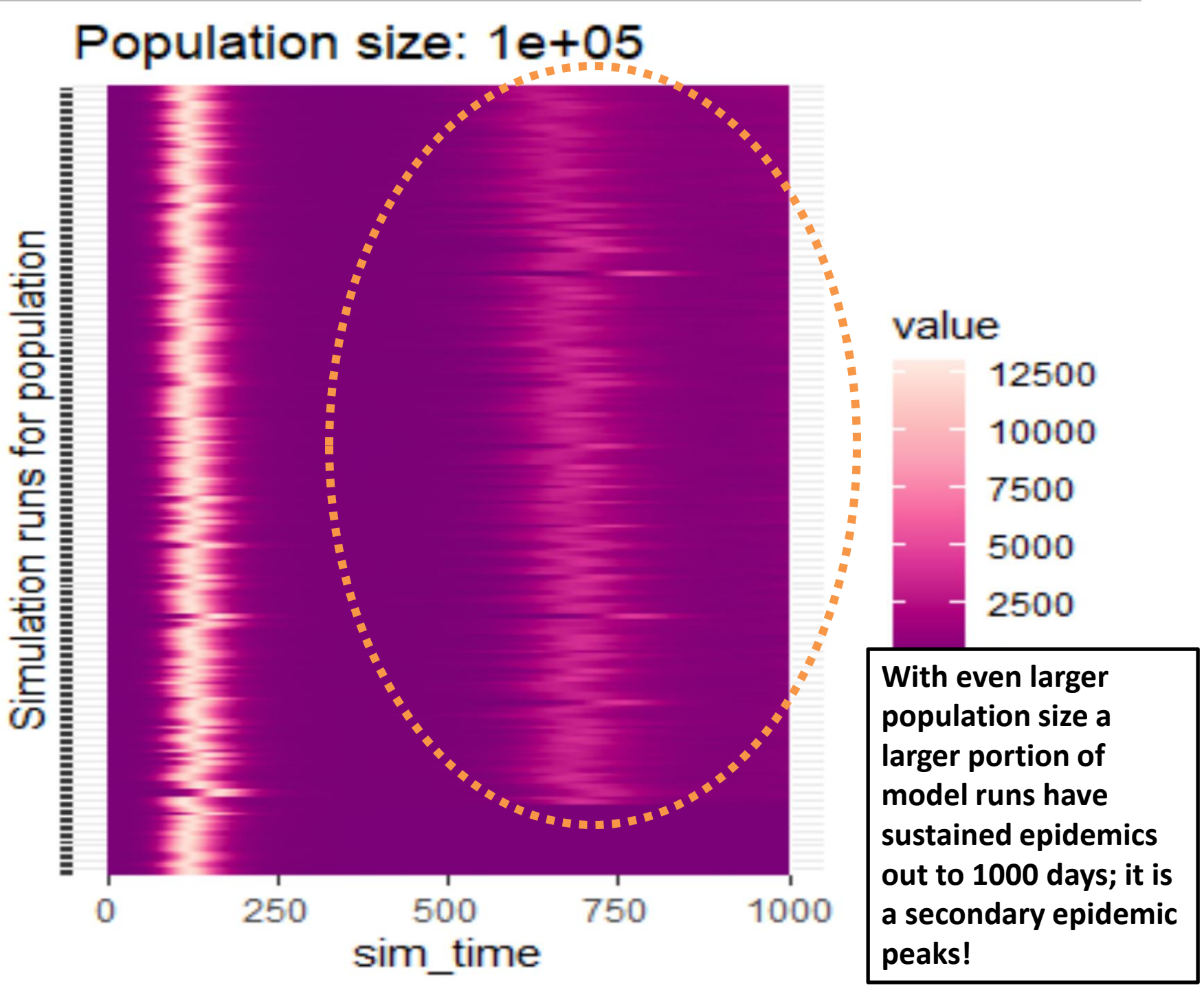
```
for(i in 2:nrow(m_trace)) {
     # CURRENT POPULATION AND INFECTIOUS
     N_prev <- sum(m_trace[i-1,])
     Y_prev <- m_trace[i-1,2]

     # CONVERT FROM RATES TO PERIOD PROBABILITIES
     p_transmission <- 1-exp(-1*(beta_mult*c_beta))
     p_recovery     <- 1-exp(-1*(c_gamma))
     p_waning       <- 1-exp(-1*(c_omega))

     # CHANGES ARE BINOMIAL DISTRIBUTED
     deltaX <- rbinom(1, m_trace[i-1,1],
                         p_transmission*Y_prev/N_prev)
     deltaY <- rbinom(1, m_trace[i-1,2],p_recovery)
     deltaZ <- rbinom(1, m_trace[i-1,3],p_waning)

     UPDATE COUNTS FROM TIME i-1 TO TIME i
     m_trace[i, 1] <- m_trace[i-1, 1] - deltaX + deltaZ
     m_trace[i, 2] <- m_trace[i-1, 2] + deltaX - deltaY
     m_trace[i, 3] <- m_trace[i-1, 3] + deltaY - deltaZ
}
```

Orientation: We plot the prevalent infectious cases for each simulation run, coloring it by the magnitude; We sort these plots by the area under the curve (# of infectious days)

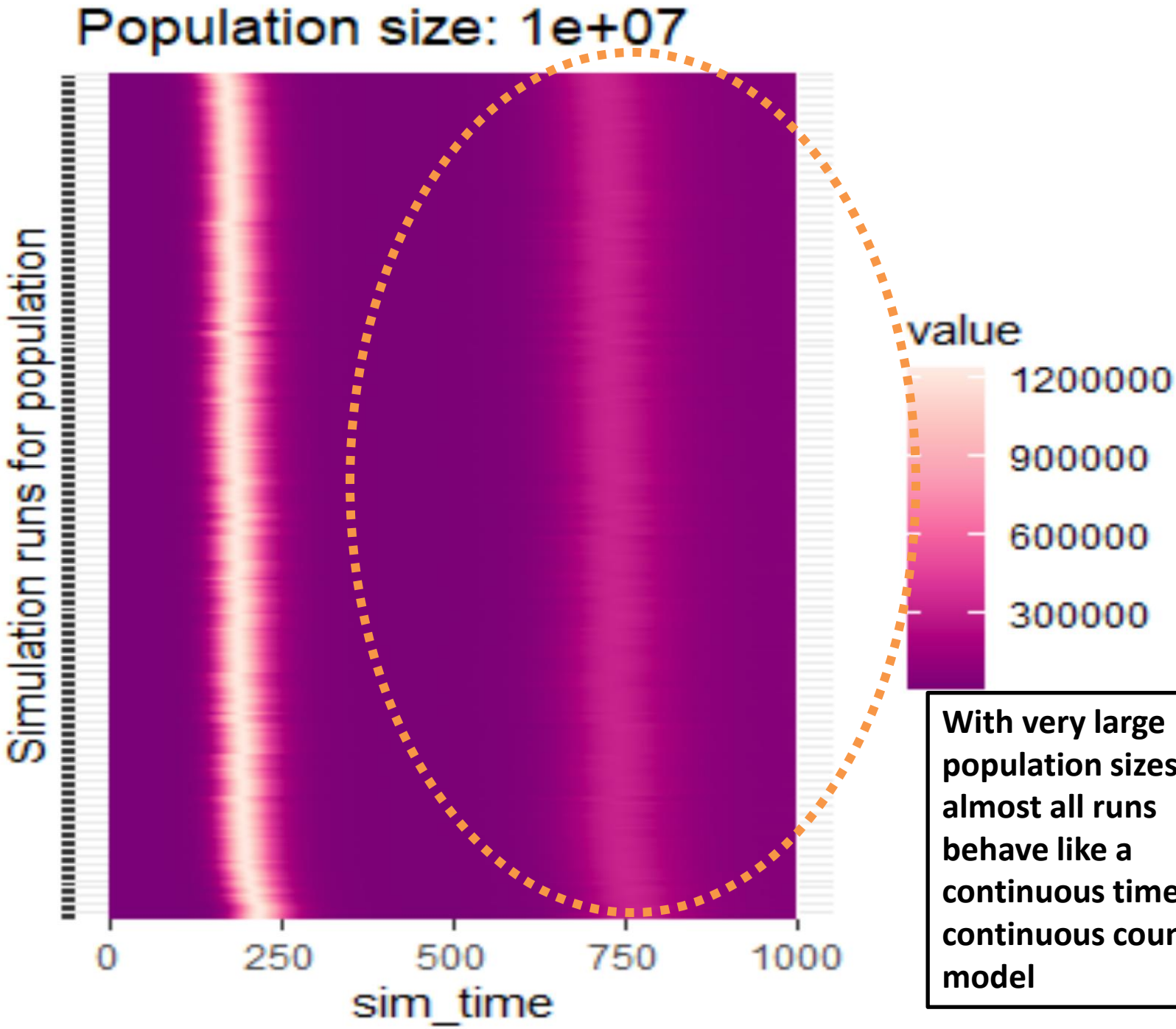



Population size: 1000
No one is infectious after day 500!
Some runs have sporadic smaller non-sustainable secondary outbreaks
Simulation runs for population
value
150
100
50
0
0
250
500
750
1000
sim_time


Population size: 10000
Simulation runs for population
0
250
500
750
1000
sim_time
value
1000
500
0
With larger population size a portion of model runs have sustained epidemics out to 1000 days



With even larger population size a larger portion of model runs have sustained epidemics out to 1000 days; it is a secondary epidemic peaks!

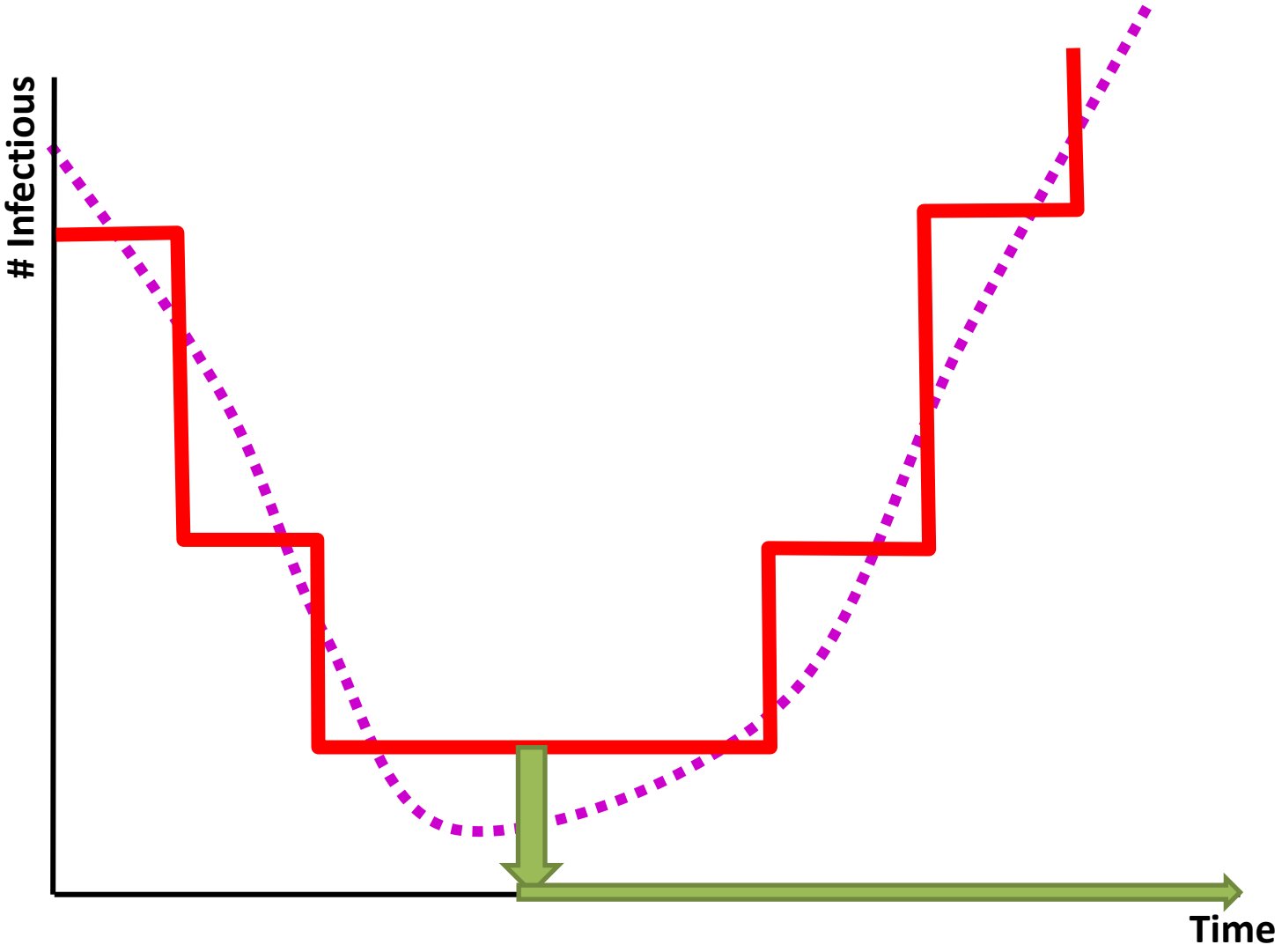


With very large population sizes, almost all runs behave like a continuous time, continuous count model

Stochastic Fade-out/Extinction

- In continuous/deterministic models, when the infection prevalence is low, the rate of growth of infectious individual is large
- This is true for the stochastic individual model, but there is a chance that the # of infectious will go to 0 and then there will be no further growth

Stochastic Fade-out/Extinction

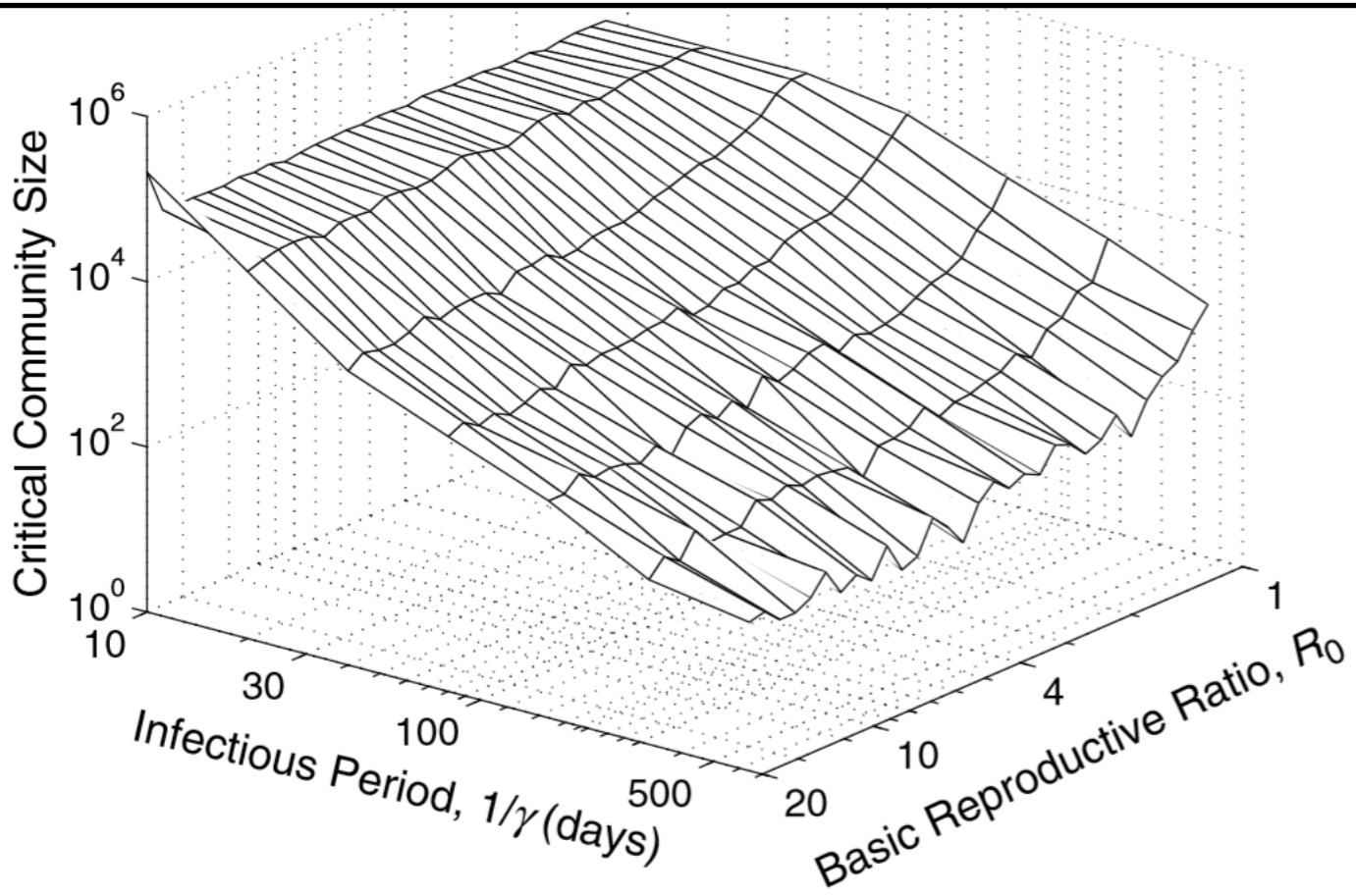


Stochastic Fade-out/Extinction

- What sorts of conditions make stochastic fade-out more likely?
  - Diseases with large fluctuations in prevalence (seasonal forcing)
  - Diseases with low R_0
    - Probability extinct = <% of time recovery before transmitting> + <% of time transmission occurs>*(Probability extinct)^2
    - $P_{ext} = \frac{\gamma}{\beta+\gamma} + \frac{\beta}{\beta+\gamma}(P_{ext})^2 \rightarrow P_{ext} = \frac{\gamma}{\beta} = \frac{1}{R_0}$
  - Small populations
- Less variable (non-exponential) infectious periods, higher fraction susceptible make extinction less likely

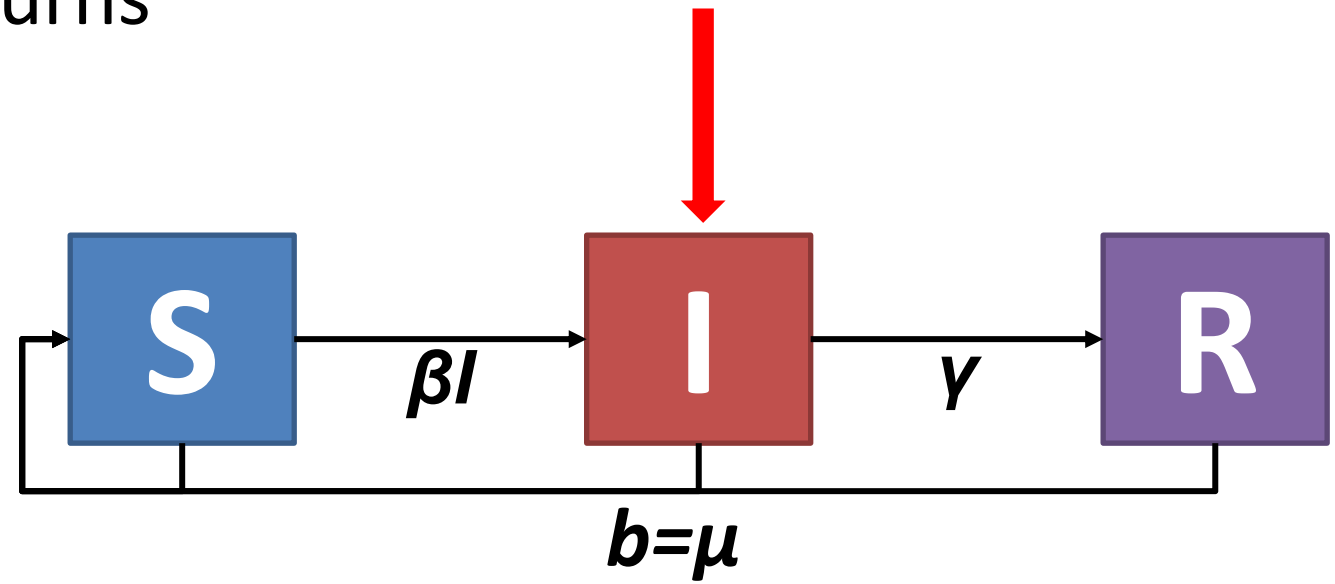
Critical Community Size

The Critical Community Size (CCS) is defined as the smallest population size that does not suffer disease extinction.

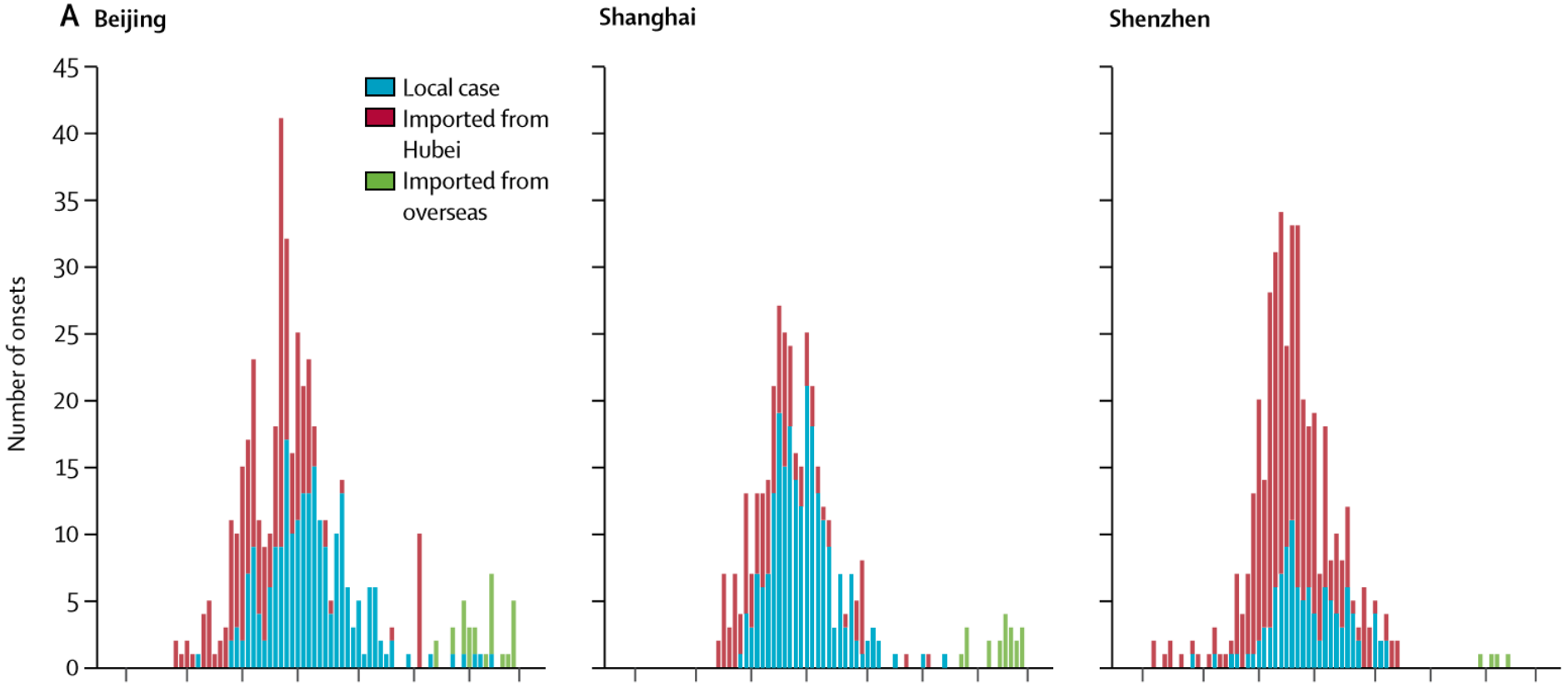


Importance of importations

- Importation: Infectious individuals arrive from outside OR susceptible person temporarily leaves, while away becomes infected, and returns



COVID19 Importation Stories



Important Announcements