
MODELING INFECTIOUS DISEASES

LEARNING OBJECTIVES

- Familiarize students with principles of infectious disease modeling, including assumptions, parameterization, and usage
- Understand the influence of contact rate and heterogeneity on disease dynamics
- Understand how models can be used to predict outcomes of disease control strategies

WEBSITE

This tutorial uses an interactive website, Epidemix, developed by the Royal Veterinary College and Epi-Interactive (Muellner *et al.*, 2018, *Epidemics*)

<https://royalveterinarycollege.shinyapps.io/epidemix/>

ORIENTATION

- This platform allows for exploring multiple types of models, which can be selected in the upper left corner.
- The left-hand pane shows details of different parameters and model structures that can be controlled by the user. To explore any of these options, click “edit”. The “info” button provides more information on what each option controls.
- Throughout this tutorial, we will be using an acute, highly transmissible pathogen (loosely based on Foot-and-mouth disease in swine) to explore disease modeling
- Discussion questions are ***bolded and italicized***. These should be answered (as well as the tables) as your assignment.

EXERCISE 1: WITHIN-HERD DYNAMICS – HOW FAST DOES THE PATHOGEN SPREAD?

- First, select the *model type*: “Stochastic Homogenous COMP”
 - This model assumes homogenous mixing of a closed population (no births/deaths) of 100 animals. The attributes of the population can be viewed or changed in the *Define Host Population Features* option
 - “COMP” stands for compartmental model, meaning that this model operates as a state-transition model where all individuals can be modeled as in one of several infection states (i.e, Susceptible, Infected, Vaccinated, etc.). The evolution of the number of units in each compartment is simulated over time and tracked collectively.
 - Stochastic (as opposed to deterministic) models simulate transitions of units between infection states as associated with underlying probabilities and models as random processes.
- Setup: Go to *Select infection states*, click edit, and check I.a, I.s., and R. This option sets the different infection states for the compartmental model.
 - S = Susceptible → I.a. = Infectious-asymptomatic → I.s = Infectious-symptomatic → Recovered
- Setup: Go to *Define infection and transmission features*. We will revise the time course of infection to look more similar to FMD (Kinsley *et al.*, 2017, *Frontiers in Vet Med.*)
 - *Length of asymptomatic period (days)* = set to 2 days
 - *Length of symptomatic period (days)* = set to 6 days

- *Mode of transmission*: Select density-dependent
- *Daily number of effective contacts* = Number of units to which an infected can transmit per day. Leave as is for now, though FMD would actually have a higher rate
- On the main panel, click “Show graph” to give you a line graph of the number of animals in each state over time.
 - ***What is the maximum number of I.s. individuals at any one time point (peak size of the epidemic)?***
 - We focus on I.s because in this exercise because it’s the only part of the epidemic that is “observable” in real life.
 - ***What percentage of individuals become infected (clue: look at number of recovered individuals at the end)? Why do you think all individuals do not become infected?***
- Click on “Investigate variability” and then “Show graph”. Remember, this is a stochastic model that incorporates randomness. Thus, we have to run the model multiple times to get an overall picture of the average behavior. By default, the model is run 10 times. The “Show mean” tab shows the overall average over time. The “Investigate variability” shows the overall mean over time, but also the 10th and 90th percentiles to get an idea of the range of outcomes that may be possible.
 - From the “Choose Infection State” drop down menu, select “Infectious-symptomatic” to view the variability in the output related to I.s.
 - The middle line is the mean number of I.s individuals over time, and the lower and upper lines are the 10th and 90th percentile.
 - The 10th and 90th interval can be interpreted as 80% of epidemic outcomes are predicted to fall within this range (i.e., normal behavior)
- In Table 1, record your observations about the mean, 10th and 90th percentile of the peak number of I.s, as well as the day that the peak occurs (contact rate = 0.4). You can eye-ball this from the graphs.
- Now, change the *Daily number of effective contacts* to 0.8 (i.e., double the contact rate). Record the same information in Table 1 for this more transmissible disease. Remember to hit “Show graph” every time you change a parameter.

Table 1. Peak number of Infectious-symptomatic farms (I.s) at any point during the epidemic.

	Mean I.s	10 th percentile	90 th percentile	Day of peak
Contact rate = 0.4				
Contact rate = 0.8				

- ***What conclusions do you draw from this comparison about the overall size of the epidemic when we change contact rate?***

EXERCISE 2: WITHIN-HERD MODEL: HOW SOON WOULD WE BE ABLE TO DETECT THE DISEASE?

- We would like to estimate how long it would take to detect a disease a farm, assuming that the only form of surveillance being performed is observations of clinical signs. This is more complex than just using the incubation period of the pathogen, because a single infected animal may not be noticed by farm personnel. The time to detection is useful to a) understand how long we should monitor farms

prior to allowing it to move animals during an outbreak (we assume that if the farm still has no clinical animals by day X, then the farm is unlikely to be infected); and b) for between-herd models, to help understand how long a farm will remain in the population before being detected and depopulated.

- We assume that a producer would identify a potential issue with vesicular disease if 5% of the population were symptomatic. Inspect the mean behavior of the model from Exercise 1 (with default contact rate of 0.4) and note at what day the number of I.s individuals first exceed 5% (remember, the population size is 100).
- ***Is the time to detection longer or shorter than you would have expected? What concerns would you have about the risk this farm poses to other farms during this period?***

EXERCISE 3: PERSISTENCE ON A FARM

- Let's return to our within-herd example to talk about some of the assumptions we made in our modeling
- Set up the model as in Exercise 1 (or the defaults for the "Stochastic Homogenous COMP" will work too)
- Note that we look at the mean behavior of the outbreak, the pathogen eventually goes extinct in the population.
- However, besides homogenous mixing, one of the assumptions of the model is that it is a closed population with no births or deaths.
- Let's take a typical population of piglets on a sow farm (we will ignore the sows for now). We know that the population turns over every 21 days or so, as weaned piglets are moved off the farm and new susceptible piglets are born.
 - ***Hypothesize how the constant turn-over of piglets every 21 days will affect disease dynamics?***
- We can test this assumption by going to *Define host population* and changing "Closed" to "open."
 - Set the *Duration of presence of unit in a population* to 21.
- ***Examine the mean behavior of the disease. What has changed?***
- The constant influx of new susceptibles means that the pathogen never goes extinct and persists and a low prevalence. One common method to deal with this is to vaccinate sows so that maternal antibodies are passed to piglets. Our model does not explicitly have maternal antibodies, but we can play with the immune status of the population through vaccination (here, we are pretending that the proportion of animals that are "vaccinated" are the ones that are protected from clinical disease through maternal antibodies).
 - Experiment with the *Proportion vaccinated (protected)* in the "choose control strategy" tab, starting at 0.1, to see if you can eliminate the disease from the farm

EXERCISE 4: BETWEEN-HERD SPATIAL MODEL: WHAT IS THE BEST STRATEGY TO CONTAIN THE DISEASE?

- Between-herd models for acute pathogens often consider the farm as the epidemic unit (i.e., the farm is considered in one of several infection states). This is because the disease spreads rapidly within a farm

and thus the farm can be considered in a discrete class (e.g., infected or not infected). Computationally, this simplifies the model.

- We know that a population of farms violate assumptions of homogenous mixing (i.e., the probability of contact is not equal between all pairs of farms). This is because farms occur on landscapes, and their spatial distribution influences which farm can infect which other farms; farms are more likely to be infected by nearby farms than farms that are farther away.
- Select the *model type*: “Stochastic Spatial IBM.”
 - IBM stands for “individual based model,” which means that the infection status of every farm is tracked (rather than just the collective number of farms in each group)
 - Set-up: Check the I.a state in *Select infection states to consider*. Leave the R and I.s boxes checked as well.
 - Set-up: In the *Define infection and transmission* features, change the Length of the asymptomatic and symptomatic periods to 2 and 8 days, respectively. Set number of infected units at start of simulation to 1
 - Set-up: In *Define spatial specific population* section, change *Clustering* to spatial clustering (more realistic than random) and set *Proportion of parents* to 0.3 (controls how much clustering there is)
 - In the “*Choose control strategy*” section, turn off vaccination
 - Select “closed” in the *Define host population features* section
- Now, let’s run the model assuming that there are no control measures. As before, you can click on “Show mean” or “Show variability”, then “Show graph” to see the overall dynamics of the epidemic.
- In the main panel, click on “Explore individual timesteps...”
 - Two sliders appear. The first controls which day (time step) you are looking at in the model
 - The second shows which simulation run you are looking at (Remember, this is a stochastic model, so we ran it 10 different times).
 - The scatterplot below is a map of the study area, which each circle representing a farm
 - Click the triangle button (Play) that is below the first slider to play the simulation.
 - If nothing happens (potentially because no transmission occurs), move the second slider to look at a different simulation run.
 - **How would you describe the overall patterns of spread?**
- In Table 2, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).
- Now, assume that you want to model a control strategy. Let’s say that the control strategy to be used is depopulation of infected (and detected) farms. Based on Exercise 2, detection would occur at around 7 days.
 - Go to *Choose control strategy* in the left-hand pain. Click on “*Culling*” and set the *Reduced length of symptomatic infectious period* to 5 days (7 days at detection – two of which were the asymptomatic period), Make sure to click “show graph” for each time you change something.
 - **Describe the map showing spread over time.**

- In Table 2, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).
- **How do you results compare for no control and depopulation?**
- Perhaps an even better option would be to preemptively depopulation all farms within a certain ring around a detected farm (i.e., farms that are within 10 km of an infected/detected farm).
 - In the *Control* section, set the *Pre-emptive cull radius* to 10
 - **Describe the map showing spread over time. How does the pattern of the appearance of green farms change as compared to the previous scenario?**
- In Table 2, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).

Table 2. Peak number of Infectious-symptomatic farms (I.s) at any point during the epidemic.

	Mean I.s	10 th percentile	90 th percentile
No control			
Culling detected farms (5 days)			
Culling detected farms + ring cull			

- **Based on your analysis, which strategy would be most effective in limiting the size of the epidemic?**
- **What other factors would you want to consider (both in terms of the models or for the actual feasibility of the strategy)?**

EXERCISE 5: BETWEEN-HERD NETWORK MODEL: TARGETED VACCINATION?

- As with the spatial model, between-herd network models for acute pathogens often consider the farm as the epidemic unit (i.e., the farm is considered in one of several infection states). This is because the disease spreads rapidly within a farm and thus the farm can be considered in a discrete class (e.g., infected or not infected)
- We know that a population of farms violate assumptions of homogenous mixing. Not only does the spatial distribution of farms influence spread, but animal movements between farms (i.e., contact) has major implications for disease spread.
- Select the *model type*: “Stochastic Network IBM.”
 - IBM stands for “individual based model,” which means that the infection status of every farm is tracked (rather than just the collective number of farms in each group)
 - Set-up: In the *Network specific population* section, change average number of contacts to 2 and the probability of transmission to 0.2.
 - Set-up: In the *Select Infection states to consider*: Check Ia, Is, and R.

- Set-up: Set number of infected units at start of simulation to 1 in the *Define infection and transmission features* section. Also, change the lengths of the asymptomatic and symptomatic periods to 5 and 5.
 - Set-up: Turn off *Culling* in the *Control* section.
- Now, let's run the model assuming that there are no control measures. As before, you can click on "Show mean" or "Show variability", then "Show graph" to see the overall dynamics of the epidemic.
- In the main panel, click on "Explore individual timesteps..."
 - Two sliders appear. The first controls which day (time step) you are looking at in the model
 - The second shows which simulation run you are looking at (Remember, this is a stochastic model, so we ran it 10 different times).
 - In this case, we now see the network of connections among farms.
 - Click the triangle button (Play) that is below the first slider to play the simulation.
 - If nothing happens (potentially because no transmission occurs), move the second slider to look at a different simulation run.
 - **How would you describe the overall patterns of spread? Is the pattern of recovered farms random?**

- In Table 3, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs). Also record the mean cumulative infected (i.e., the number recovered).

- Now, assume that you want to model vaccination.
 - Go to *Choose control strategy* in the left-hand pain. Click on "Vaccination" and set the 0.1 (10% of population is vaccinated, assuming a vaccine that offers complete protection). Make sure to click "show graph" for each time you change something.
 - **Describe the map showing spread over time.**

 - In Table 3, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).

- Unfortunately, you discover you don't have enough vaccine to vaccinated even 10% of the farms. You will only be able to vaccinate 5%.
 - **First, hypothesize what you think will happen.**

 - **Describe the map showing spread over time and the locations of vaccinated farms.**
 - In Table 3, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).

- Because you were lucky enough to have taken advanced epidemiology in vet school, you remember that targeted vaccination based on contact networks could help you use the vaccine more efficiently.
 - **First, hypothesize what you think will happen.**

 - **Describe the map showing spread over time and the locations of vaccinated farms.**

- In Table 3, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).

SUPER-SPREADERS

- Finally, real-world networks often have “Super-spreaders” which are nodes in the network that have a disproportionately large number of connections.
- In the *Network type* section under the *Define network specific parameters* section, change the type to “Heterogenous”. Also, turn-off control
 - Go to the *Explore individual timesteps*.
 - **How does this network look different than before? What do you hypothesize about the size of outbreaks here?**
- In Table 3, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).
- Let’s try a targeted control strategy in this network (5%).
 - In Table 3, record your observations about the mean, 10th and 90th percentile of the peak number of I.s (as seen in the line graphs).
- **What do you conclude about control of infectious disease in this population? Does network structure help you predict the epidemic size and optimal control strategy?**

Table 3. Peak number of Infectious-symptomatic farms (I.s) at any point during the epidemic.

	Mean I.s	10 th percentile	90 th percentile	Cumulative infected (Recovered)
No control				
Vaccinate 10%				
Vaccinate 5%				
Vaccinate 5% - targeted				
Heterogenous:				
No control				
Vaccinate 5% - targeted				