A Plague on Both Houses: Modeling Viral Infection to Control a Pest Outbreak

Anton E. Weisstein

Video IX: Microbial Control

Background on myxoma

Myxoma is a virus that occurs naturally in the South American jungle rabbit *Sylvilagus brasiliensis*. Infection with myxoma virus leads to the disease myxomatosis; this disease is mild in *S. brasiliensis* but almost always lethal in the European rabbit *Oryctolagus cuniculus* (Fenner and Ratcliffe, 1965).

Figure 1. Devastation of pastureland by rabbits. The field on the right is protected by a rabbit-proof fence.

The European rabbit was imported to Australia in 1859 and rapidly became a serious agricultural pest. In an attempt to control the rabbit population, myxoma virus was introduced in Australia in 1950. Mosquitoes quickly spread the disease, decimating rabbit populations: over 99% of rabbits that became infected with myxoma died of the infection (Fenner and Ratcliffe, 1965).

Within a year, however, the mortality rate had dropped to 90%, and it continued to decrease steadily for over a decade. Laboratory studies showed that two factors were responsible: rabbits were evolving resistance to the virus (Marshall and Douglas, 1961), and the virus was simultaneously becoming less deadly (Fenner and Ratcliffe, 1965).

In the end, strains of the virus with mortality rates between 70-95% came to predominate over both milder and more virulent strains (Fenner and Ratcliffe, 1965), leading to partial control of the rabbit population. Further control measures have been undertaken, including introduction of new myxoma vectors (the European and Spanish rabbit fleas), release of a second biological agent (rabbit calcivirus), and physical control methods such as poisoning and shooting. The result is that rabbit numbers are roughly half of what they were in the late 1940s (Williams *et al.*, 1995). Despite all these efforts, however, rabbits continue to cause approximately $600 million (Australian) in agricultural damages each year (Department of Agriculture —Western Australia 2001).

Background on epidemiological models

In 1979, Anderson and May presented a theoretical epidemiological construct which has since become known as an SIR model. The SIR model forms the basis for the *Epidemiology* computer simulation, which is used in several other activities in this book. (See the list of related *Microbes Count!* activities at the end of this lab.) Although the questions posed by the myxoma model could be answered using the simulations in *Epidemiology*, in this activity you will have the opportunity to explore the mathematical model that underlies the computer generated simulations and to develop a deeper understanding of the SIR model.

Under the SIR model, the host population is partitioned into three categories: susceptible individuals (S), infected individuals (I), and individuals who have recovered from infection and thereby become immune to re-infection (R). This framework enables us to describe and predict the course of an epidemic by tracking movement into, out of, and between these compartments. For example, an individual's recovery from infection can be represented as decreasing the value of I by one and increasing the value of R by one. Similarly, if a susceptible individual is born, we note this event by increasing S by one.

Among the most important parameters of such a model are:

- The natural birth and death rates of the host,
- The rates at which hosts die and recover from infection, and
- The rate at which infection spreads from infected to uninfected hosts.

Depending on the model details, additional parameters may also be necessary. In studying the myxoma case, for example, our model should include multiple strains of the virus, each of which may have different host mortality, recovery, and transmission rates. It is also important to consider the manner in which a particular disease is spread. Infections easily spread through casual contact, such as flu and smallpox, spread at rates proportional to the numbers of both susceptible and infected host individuals ($= S \cdot I$). Other infections, such as malaria and myxoma, are transmitted by vectors rather than from host to host; the spread of these diseases therefore depends not only on the numbers of susceptible and infected hosts (S and I), but also on the numbers of uninfected and infected vectors (U and V). Myxoma virus can be transmitted by several vectors including mosquitoes, fleas, and blackflies; for the sake of simplicity, however, our model will include only a single vector species.

Myxoma model

For the sake of simplicity, we will use a discrete-time form of the SIR model. Each time interval therefore reflects a set period of objective time such as a day or a week. We will also make the following simplifying assumptions, not all of which may be biologically realistic:

- Asexual reproduction in both hosts and vectors.
- No population age structure.
- At most one strain can infect a single host or vector individual.
- Recovery from *any* strain confers permanent immunity to *all* strains.
- Infection and recovery do not affect reproductive rates.
- Neonatal infection in hosts but not in vectors.
- No inherited immunity.
- Vectors not affected by infection.

• Infectious vectors remain permanently infectious.

• Positive correlation between virulence and transmissibility (see below).

Again for the sake of simplicity, our model will include only three strains of the virus. The host population will therefore be divided into five compartments: susceptible (S), infected with strain #1, 2, or 3 (I_1, I_2, I_3), and recovered (R). Similarly, the vector population will be divided into four compartments, one for uninfected vectors (U) and one for vectors infected with each of the three strains (V_1, V_2, V_3). Figure 2 shows how individuals move between these compartments.

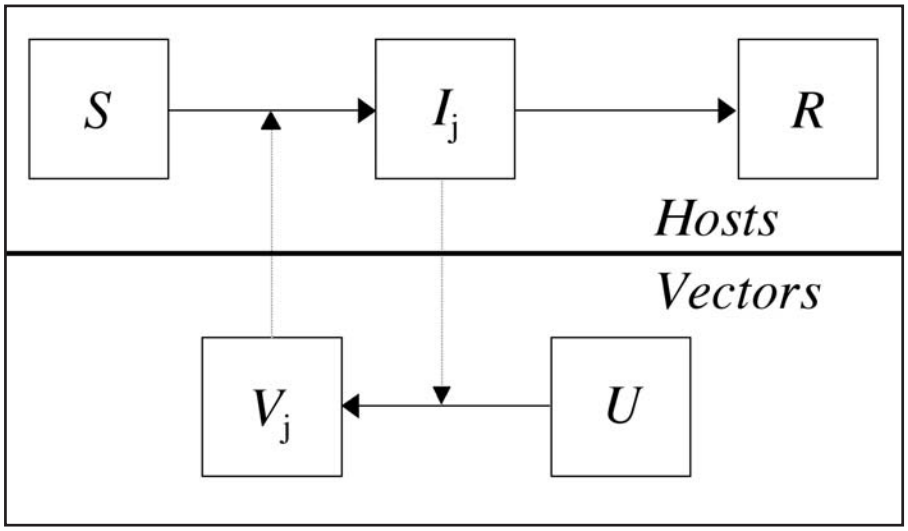

Figure 2: Compartments of the host and vector populations. Hosts move from susceptible to infected to recovered; vectors from uninfected to infected. The dotted lines across populations denote the cycle of virus transmission; thus, transmission by infected vectors causes susceptible hosts to become infected, and transmission by infected hosts causes uninfected vectors to become infected.

We assume logistic growth of the host population. The easiest way to do this is to make the host birth rate *decrease* linearly with population size and the host death rate *increase* linearly with population size. (See Figure 3.)

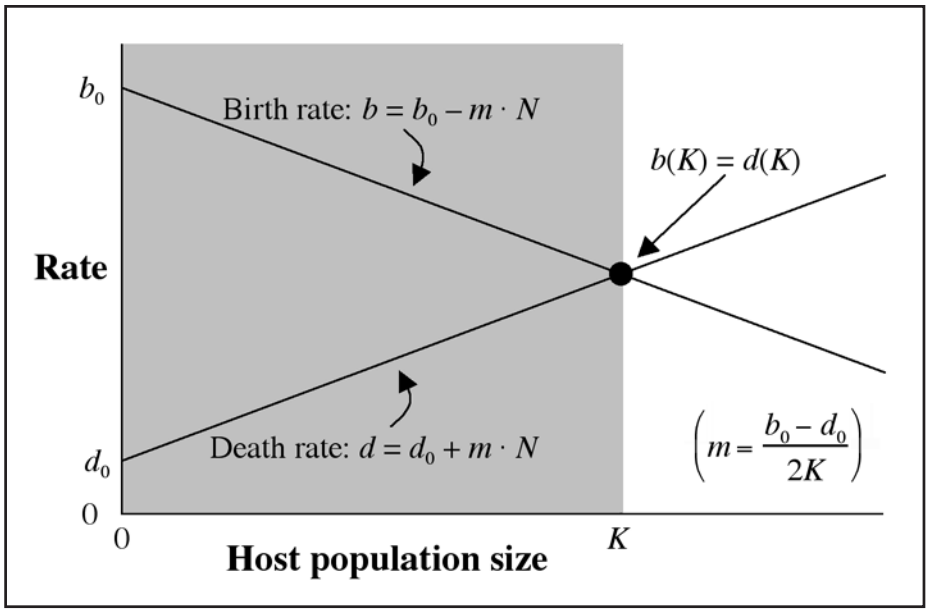

Figure 3: Birth and death rates for a population undergoing logistic growth. As the population size increases, the birth rate falls and the death rate rises. The two lines representing these rates intersect at the population's equilibrium, namely the carrying capacity (K). Below carrying capacity, the population's birth rate exceeds its death rate, so the population will increase; this area is shaded grey. Above carrying capacity, the inequality is reversed, so the population will decrease; this area is shaded white.

Table 1: Key parameters of the model.

Name	Parameter	Representative value	Units
b_0	Host birth rate at N = 0	0.04	births / host
d_0	Host (natural) death rate at $N = 0$	0.01	deaths / host
K	Host carrying capacity	10,000	host individuals
k_j	Host death rate from infection with strain j	0.4	deaths / infected host
r_j	Host recovery rate from infection with strain j	0.2	recoveries / infected host
b'	Vector birth rate	0.2	births / vector
d'	Vector death rate	0.2	deaths / vector
ω	Host-vector contact rate	0.00003	contacts / host / vector
α_j	Vector $\rightarrow$ host transmission rate of strain j	0.4	transmissions / infected vector / susceptible host
β_j	Host $\rightarrow$ vector transmission rate of strain j	0.9	transmissions / infected host / susceptible vector

Table 1 lists key parameters of the model. It's important to understand the interpretation of each parameter so that you can choose biologically meaningful values when running your own simulations. In particular, the host-vector contact rate ω *must* be very small or the simulation will give meaningless results, such as population sizes less than zero. Each strain must also satisfy

$$k_j + r_j \leq 1 - d$$

which states that an infected individual can't die twice, and can't both die and recover.

Finally, some model parameters may be interdependent. For example, many infectious diseases produce a variable viral titer in the host: cases with high titer are generally both more lethal and more easily transmitted to a vector. Myxomatosis follows this general pattern (Fenner and Ratcliffe 1965), so we should choose values k_j and β_j that are positively correlated across strains. It is convenient to order the strains from most virulent (#1) to least virulent (#3); then we need only ensure that $k_1 > k_2 > k_3$ and $\beta_1 > \beta_2 > \beta_3$.

We can describe the model outlined above by the following five recursion equations (Table 2). Each of these equations gives the number of individuals in one compartment (e.g., susceptible hosts) in terms of the model parameters and the compartment sizes at the previous time interval. I urge you to take a few minutes to look at these equations in the context of Figure 2 and see how they encapsulate the model's assumptions. You may find it helpful to recall that addition combines *independent* terms (e.g., newborns vs. adults), multiplication combines

Table 2. Recursion equations used by the model.

(1) New number of susceptible hosts $S(t+1)$ = Susceptible newborn hosts $b[S(t)+R(t)]$ + Existing susceptible hosts… $S(t)$ · who don't die… $(1-d)$ · and don't become infected. $[1-\omega\sum_j \alpha_j V_j(t)]$,

(2) New number of hosts infected with strain j $I_j(t+1)$ = Infected newborn hosts $b \cdot I_j(t)$ + Existing infected hosts… who don't die or recover $I_j(t)\cdot(1-d-k_j-r_j)$ + Existing susceptible hosts… $S(t)$ · who don't die… $(1-d)$ · but do become infected. $[\omega\alpha_j V_j(t)]$,

(3) New number of recovered hosts $R(t+1)$ = Existing recovered hosts… $R(t)$ · who don't die $(1-d)$ + Number of hosts recovering from any strain. $\sum_j r_j I_j(t)$,

(4) New number of uninfected vectors $U(t+1)$ = Newly born vectors $b'[U(t)+\sum_j V_j(t)]$ + Existing uninfected vectors $U(t)$ · who don't die… $(1-d')$ · and don't become infected. $[1-\omega\sum_j \beta_j I_j(t)]$,

(5) New number of vectors infected with strain j $V_j(t+1)$ = Existing infected vectors… $V_j(t)$ · who don't die $(1-d')$ + Existing uninfected vectors… $U(t)$ · who don't die… $(1-d')$ · but do become infected. $[\omega\beta_j I_j(t)]$.

conditional terms (e.g., susceptible hosts who become infected), and subtraction from one represents logical *negation* (e.g., one minus the proportion dying represents the proportion surviving).

Understanding and using the myxoma workbook

The mathematical model developed above is contained in the Microsoft *Excel*® workbook "Myxoma template.xls", located in the Myxoma section of the *Microbes Count!* web site. All the equations have already been entered into the spreadsheet, so all you need to do is choose the parameter values you want, run the model, and interpret the results. See Figure 4.

Columns A-R of row 3 show the state of the host and vector populations at time zero. Scroll to the right to view the initial number of susceptible hosts, hosts infected with each strain, recovered hosts, total hosts, % hosts infected with each strain, number of uninfected vectors, and number of vectors infected with each strain. Some cells are outlined in red: these are initial conditions that you can

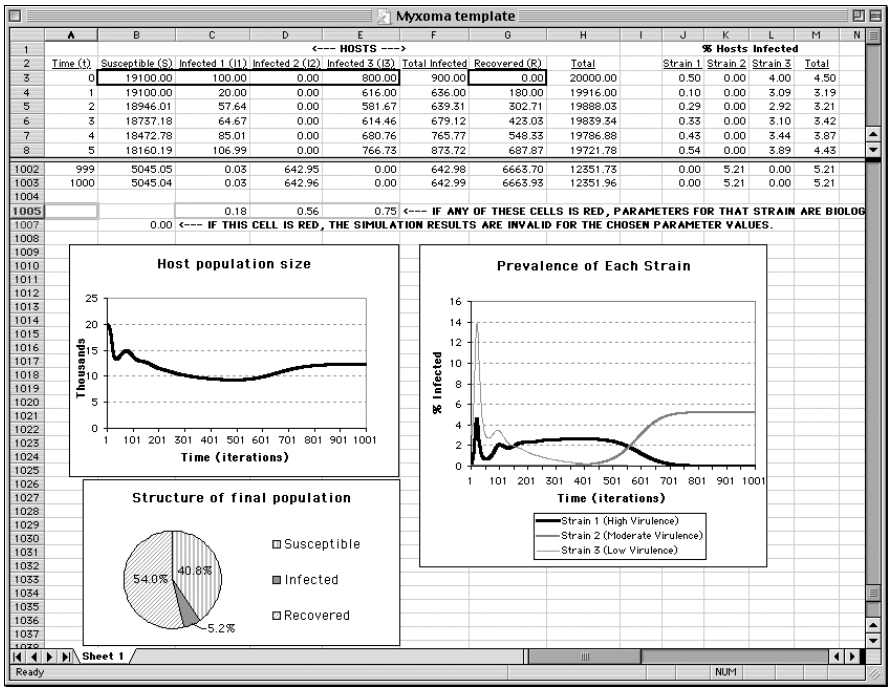

Figure 4: Screen shot of the myxoma workbook, including partial data table and graphs. See text for details.

modify to perform your own simulation. Values in other cells, such as F3 ("Total infected"), are computed from the initial conditions and should not be entered directly.

Column U contains the model parameters such as birth and death rates, carrying capacity, and virulence/transmissibility parameters for each strain. Again, these cells are outlined in red to indicate that new values can be entered into these cells. Note that cell U7, the host-vector contact rate ω, is shaded red to remind you that errors will result unless this value is kept very small, especially when host and/or vector numbers are large.

Rows 4 through 1003 contain iterations of model equations (1)-(5). The screen has been split vertically so you can see both the first few and the last few iterations. The bottom half of the screen contains four "warning" cells that will turn red in case of simulation errors. Be sure to check these cells before interpreting any results!

Also shown are three graphs. "Host population size" plots the size of the host population over time. "Prevalence of each strain" plots the proportion of the host population infected with each of the three strains over time. "Structure of final population" shows the proportion of the host population at time t = 1000 who are susceptible, infected, and recovered. As you conduct your own investigations, you may find it useful to construct additional graphs using *Excel*'s ChartWizard function.

As soon as you change any starting condition or parameter, the workbook will immediately run a simulation using the new value and graph the results. If you want to change several values before running the simulation (for example, if you are setting the initial conditions equal to the final conditions of a previous run),

you must first disable this feature by setting calculations to manual mode. The details of how to do this vary among versions of Excel: consult your version's Help Index for specific instructions. Once calculations are set to manual, the workbook will recalculate only when you use the "Calculate Now". command (see Excel's help Index) or set calculations back to automatic mode.

Investigations

1. Set the host population's carrying capacity (*K*) to 20,000 and introduce a small number of individuals infected with strain 1. Notice the changes in the graphs at the bottom of the worksheet. At what value does the population size stabilize? Why is this less than the carrying capacity? Does the population converge smoothly to that value? How would you interpret the fluctuations in virus prevalence over time?

   Repeat for strains 2 and 3 and compare across strains, recalling that strain #1 is most virulent and strain #3 least virulent. Which strain leads to the greatest reduction in population size? Which strain leads to the greatest % of infected individuals at equilibrium? Are these patterns what you would have expected? Discuss possible explanations.

2. Reduce *K* to 12,000 and repeat the above analysis for each strain. What change do you note in the % infected at equilibrium? What do you think might happen if you reduced the carrying capacity further? Try it and see.

   What you have observed is the epidemiological threshold. Contagious diseases need a certain minimum number of hosts present or else they are lost, although the specific threshold varies from one disease to another. Which of the three strains you examined had the highest threshold and which the lowest? What are the implications of epidemiological thresholds for small and isolated populations? When and how have epidemiological thresholds influenced human history? You may find recent papers by Mitchell and Power (2003) and Torchin *et al.* (2003) of interest in this context.

   Imagine that we are trying to control a disease by eradicating its vector. Set *K* back to its original value of 20,000 and reduce the number of vectors present by 20%. What effect does this change have on the number of infected hosts at equilibrium? Continue reducing the size of the vector population. By how much must you reduce the vector population to eliminate the disease? Is it the same across all three strains? If not, which strain is easiest to eliminate and which is hardest? Is this the same pattern you saw for the strains' host epidemiological threshold? Why or why not?

3. Begin with only strain 1 present and run the worksheet until the system reaches equilibrium. Note the host population size and % infected. Now model the appearance of a mutant strain of the virus by introducing a

single individual infected with strain 2. Run the worksheet, paying particular attention to the graph of % infected. Describe any changes you see. How would you interpret them? Would you obtain the same result if the virus had mutated to strain 3 instead of strain 2? To what extent do your observations match what actually happened with myxoma in Australia?

Try altering the parameters associated with each strain (k, r, α, β), retaining the positive correlation between virulence (k) and transmissibility (β). Repeat the above analysis several times for different parameter values. Does the scenario play out in the same way? What are the implications for understanding the evolution of virulence?

4. As Health Minister for the island nation of Knessy, you know that there are two strains of the mosquito-borne morbidia virus circulating among your citizens, one of which (strain X) is much more lethal than the other (strain A). Fortunately, infections with strain X are sporadic and never seem to spark a widespread epidemic. Still, even the relatively mild illness produced by strain A is a drain on your economy and a cause of significant suffering.

   You have identified four promising intervention strategies to deal with this problem:

   - Formulate an advanced treatment that will speed recovery from strain A.
   - Drain a nearby marshland that harbors a large fraction of the local mosquito population.
   - Develop and release a weakened strain of the virus.
   - Change people's behavior: limit outdoor gatherings, encourage use of insect repellent, etc.

   Unfortunately, your budget will allow you to pursue only one of these strategies. Which one do you choose? Can you suggest other strategies that might be even more successful? Justify your decision based on simulation results as well as any other considerations (e.g. political, ecological, economic) that might be relevant. What additional data might you want to collect before making your decision?

5. Discuss the model's assumptions. Are any of them unrealistic? How might you reformulate the model to incorporate more realistic assumptions? To what extent would this complicate the model's implementation and interpretation?

   What factors influence the relative competitive dominance of different strains? Is it possible to develop a formula for determining which of three strains would be competitively dominant?

   What differences would there be between the vector-based myxoma model and a model of a directly transmissible disease such as influenza? In what ways might these structural differences cause the two models to generate different predictions?

Additional Resources

Available on the *Microbes Count!* web site at http://bioquest.org/microbescount

Text

A PDF copy of this activity, formatted for printing

The "Myxoma template" model file

Related *Microbes Count!* Activities

Chapter 1: Modeling More Mold

Chapter 1: Population Explosion: Modeling Phage Growth

Chapter 6: Tracking the West Nile Virus

Chapter 8: Investigating Predator-Prey Interactions

Chapter 10: Measles in Nakivale Refugee Camp

Chapter 11: Epidemiology: Understanding Disease Spread

Chapter 12: Vaccine: Experimenting with Strategies to Control Infectious Diseases

Unseen Life on Earth Telecourse

Coordinates with Video IX: Microbial Control

Relevant Textbook Keywords

Biological control, Epidemiology, Mathematical modeling

Related Web Sites (accessed on 4/18/03)

Economic and Ecological Impact of Rabbits in Australia
http://rubens.anu.edu.au/student.projects/rabbits/home.html

Microbes Count! Website
http://bioquest.org/microbescount

Unseen Life on Earth: A Telecourse
http://www.microbeworld.org/htm/mam/is_telecourse.htm

References

Anderson, R. M., and R. M. May (1979). Population biology of infectious diseases. *Nature* 280: Part I: 361-367 and Part II: 455-461.

Department of Agriculture—Western Australia (2001). Farmnote 25/2001: European wild rabbit.
http://www.agric.wa.gov.au/agency/pubns/FARMNOTE/2001/f02501.htm

Dwyer, G., S. A. Levin, and L. Buttel (1990). A simulation model of the population dynamics and evolution of myxomatosis. *Ecological Monographs* 60: 423-447.

Fenner, F., and R. N. Ratcliffe (1965). *Myxomatosis*. Cambridge University Press, London, England.

Marshall, I. D., and G. W. Douglas (1961). Studies in the epidemiology of infectious myxomatosis of rabbits. VIII. Further observations on changes in the innate resistance of Australian wild rabbits exposed to myxomatosis. *Journal of Hygiene* 59: 117-122.

Mitchell, C. E., and A. G. Power (2003). Release of invasive plants from fungal and viral pathogens. *Nature* 421: 625-627.

Torchin, M. E., K. D. Lafferty, A. P. Dobson, V. J. McKenzie, and A. M. Kuris (2003). Introduced species and their missing parasites. *Nature* 421: 628-630.

Williams, K., I. Parer, B. Coman, J. Burley, and M. Braysher (1995). Managing vertebrate pest: rabbits. Bureau of Resource Sciences/CSIRO Division of Wildlife and Ecology, Australian Government Publishing Service, Canberra. p. 284.

Figure and Table References

Figure 1. Included with permission, Fenner and Ratcliffe (1965)

Figure 4. Screen shot from the “Myxoma Template.xls” model file.