Fields Institute Summer Workshop on Mathematics of Antimicrobial Resistance
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Introduction (Recapitulation)

The materials presented below usually form part of a short course, and follow a session during which students evaluate the so-called "SIR" (susceptible-infectious-recovered) or Kermack-McKendrick model qualitatively. I assume that most of you are familiar with that material…in short, we explore the concept of basic and effective reproductive numbers for infectious diseases ("R_0" and "R_e", respectively), the relationship between Re and the critical number of susceptibles necessary for an epidemic to emerge, and the relationship between R_0 and the proportion of the population that needs to be vaccinated (or naturally immune) to prevent epidemics if an infectious individual arrives in the population. At this point in the course, we have also discussed the role that "regeneration" of susceptible individuals, through birth, migration or loss of immunity, plays in driving cyclic oscillations in the incidence of infectious diseases.

Students, however, often wish to fit models to data. However, many of you wish to develop simple models that describe clinical or public health challenges that you face in your hospital or agency. In **Part A** of this exercise, we will discuss how SIS, SIR, and SIRS models can be created using data that may be easily accessible in the clinical or public health settings (or which may be publicly available via the Web). In **Part B** of this exercise, we will evaluate a model by Marc Lipsitch that is based on the "SIS" model, and which can be used to gain intuition into challenges we currently face related to control of antimicrobial resistant organisms (ARO) in hospitals and in the community.

Part A: Introduction to Model Parameterization Using Available Data

2. Fitting an SIR Model Using Surveillance Data

This practical is based on a course taught by D.F. and John Edmunds at meetings of the Society for Medical Decision Making a few years ago. The idea here is to allow you to "get your hands dirty" trying to come up with estimates for some key model parameters based on data that may be available to you via public health surveillance, epidemic curves, or other sources. We will focus for the most part on estimating R_0: as we saw last week, once we know R_0 we can back into estimates of the "force of infection" (λ), the transmission coefficient (β), at least by making some simplifying assumptions about the nature of the population we are modeling.

2.1 Estimating R_0 when Disease is Endemic

The basic reproduction number, R_0, has such an influence on the epidemiology of infectious diseases that there are many ways we can use observed patterns of

infection to estimate its value. We will be concentrating here on some of the most common techniques used for vaccine preventable infections. As should be apparent by now, the host-pathogen relationship approximated by the SIR model is a dynamic system that tends to settle at (or oscillate around) an equilibrium. Think back to our session yesterday where we showed that:

$$R_e = R_0 \times s^*$$

where s* was the fraction (as opposed to the number) of susceptible individuals when the disease is at equilibrium. At equilibrium, $R_e = 1$.

2.1.1. Write out an expression for R_0 based on s*.

2.1.2. What data sources could you use to estimate s* for typical childhood infections, such as measles or chickenpox?

2.2 Estimating R_0 Using Age at Infection and Age-Seroprevalence Data

A. Average Age at Infection

It turns out that, in an SIR-type system that includes age structure (i.e., individuals transition between age groups, as well as S, I, and R compartments), there is a relationship between the average age at first infection (A), life expectancy (L), and R_0. Assuming a "rectangular" demography (relatively little death until older age groups, as opposed to the "triangular" demography seen in less-developed countries):

$$R_0 = L/A$$

2.2.1. This relation is derived using calculus, but can you come up with an intuitive explanation for this relation? Hint: think of what a serological profile would look like if everyone was infected exactly at the average age at infection.

There is a slightly less intuitive relationship for populations with type II (constant hazard) mortality as may be seen in low-income countries. Such countries have a more "triangular" age distribution, and in this context R_0 can be approximated as

$$R_0 = 1+L/A$$

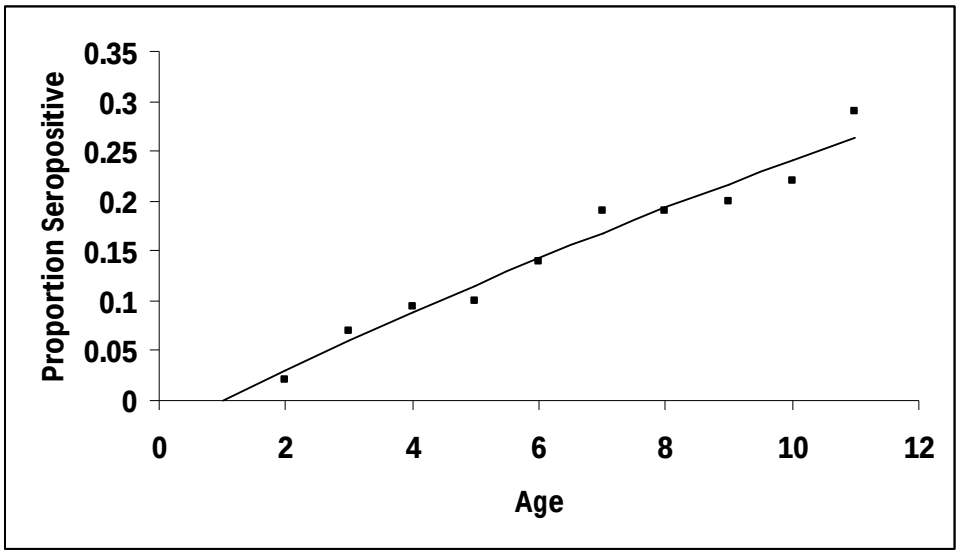
B. Force of Infection

If we have a **constant force of infection** (λ) (rate at which susceptibles become infected) we can describe infection over time using an exponential hazard function, such that the rate of infection can be approximated as:

$$\lambda = 1/A$$

Not infrequently, we have age-specific estimates of susceptibility and immunity; we refer to these as **age-seroprevalence data**. If we assume that a disease is at equilibrium (such that changes in disease incidence by age groups are a function of disease biology, rather than "cohort effects") we can back into estimates of λ.

Suppose we have the following age-seroprevalence data (black dots). The black curve represents a fitted exponential hazard function with $\lambda = 0.03$. We can also estimate hazards using the relation:



$$\lambda = -\ln((S_n)/(S_{n-1}))/t$$

2.2.2. Use this relation to estimate FOI for this disease, using seroprevalence of 14% at age 6. Assume that seroprevalence at birth is 0%.

2.2.3. Based on the FOI you estimated above, what would R_0 be in a "rectangular" population with a life expectancy of 75 years? In a "triangular" population with a life-expectancy of 50 years?

Note that the relation $\lambda = pcI$ can also be useful (where p = probability of transmission conditional on contact, and c = contact rate per unit time). Suppose we

have an estimate of the prevalence of infection in a population at any given time, and we estimate FOI from age-seroprevalence data. This allows us to estimate pc as a composite quantity.

Our approach above assumes that the force of infection in a given population is constant over time, but of course this is unlikely to be the case, for both behavioural and biological reasons. We can derive age-specific estimates of I, and use these to evaluate "who acquired infection from whom" using matrix approaches, but such approaches are beyond the scope of what we will be able to cover today.

2.3. Estimating R_0 in Systems without Long-Lasting Immunity

Thus far, we have discussed models where recovery from infection confers long-lasting immunity, but there are many infectious diseases for which infection confers either short-term or effectively no immunity, and these include a number of common (or formerly common) pathogens such as *S. pneumoniae, H. influenzae* serogroup B (Hib), *Chlamydia trachomatis*, and *N. gonorrhoeae*. We can create an "SIS" model, in which the *I* compartment would change at a rate:

$$dI/dt = +\beta SI-(\mu+\gamma)I$$

Here we are letting "S" and "I" represent the proportion, rather than the number, of individuals susceptible or infected at a given point in time. At equilibrium, the number of individuals moving into the infected state equals the number moving out, so:

$$dI/dt = \beta S^*I^*-(\mu+\gamma)I^* = 0$$

$$\beta S^*=(\mu+\gamma)$$

$$\beta/(\mu+\gamma) = 1/S^*$$

It turns out that the left hand side of this equation is equivalent to R_0. Since $S^* = (1-I^*)$, we can rewrite this as:

$$R_0 = 1/(1-I^*)$$

Where I^*, is equilibrium prevalence of infection.

2.3.1. It turns out that asymptomatic carriage of *Neisseria meningitidis* occurs in about 10% of the population every year. What is the approximate R_0 for *N. meningitidis*?

A recent DLSPH graduate (Laura Kinlin) published a manuscript showing that serogroup C meningococcal disease has almost disappeared in Ontario with the introduction of a conjugate vaccine that prevents meningococcal carriage (Kinlin L.M., Rapid identification of herd effects with the introduction of serogroup C meningococcal conjugate vaccine in Ontario, Canada, 2000-2006. Vaccine 2009; 27(11):1735-40). The drop in cases appeared very shortly after the vaccine was introduced, and despite the fact only a small proportion of the population had been vaccinated against serogroup C meningococcus. Think back to our last session: we derived the following relation for critical fraction to vaccinate for herd immunity:

$$P_c = 1 - (1/R_0)$$

2.3.2. Based on your estimate for R_0 in (2.3.1), above, what fraction of the Ontario population would have to be vaccinated for herd immunity against *N. meningitidis*.

2.4. Estimating R in Systems with Periodic Oscillation

Last session we discussed the fact that SIR systems will oscillate around s* as the disease reaches an endemic equilibrium in the population. What we saw in our SIR model with births and deaths was a gradual increase in the interval between epidemics, and a gradual decrease in the total number of cases in each successive epidemic. However, the time between the first and second epidemic spikes in this system approximates the "intrinsic oscillatory period". The background reading for this session included a short paper by Jonathan Dushoff and colleagues (*Dushoff J, et al. Dynamical resonance can account for seasonality of influenza epidemics. PNAS 2004;101;16915-16916*). In this article, the authors point out that when a "forcing factor" (e.g., changes in transmission due to seasonally varying meteorological factors or behaviors) occurs at the same frequency as the "internal oscillatory frequency", we get sustained oscillation in disease incidence. Dushoff and colleagues note that the "internal oscillatory period" for an infectious disease (T) is:

$$T = 2\pi(DL/(R_0-1))^{1/2}$$

Where D is duration of disease, and L is life expectancy (or, for diseases with transient immunity, time until immunity is lost).

Rearranging this expression we get:

$$R_0 = (4\pi^2 DL/T^2)+1$$

2.4.1. For pertussis, *D* is around 2 weeks; *L* is around 10 years. Outbreaks of pertussis occur approximately every 3 years. Estimate the approximate R_0 for pertussis based on these data.

2.4.2. Consider the statement above that *L* represents either life expectancy in the population or duration of immunity. Why are these interchangeable from the point of view of incidence of infection in a SIR model?

2.4.3. What does the above equation tell you about the impact of duration of immunity on estimates of R_0 for a given interepidemic period? Does this make sense? Can you explain this relation in words (try to include the concept of s* and *Re* in your explanation)? Try to work through the same exercise for *D*.

2.4.4. Would a disease with an interepidemic period of 8 years be estimated to have a higher or lower value for R_0 than that estimated for pertussis, above?

3. Estimation of R_0 from Epidemic Curves: Example from SARS

An extremely important and relatively straightforward means of estimating R_0 comes from evaluation of epidemic curves. This technique was used in real-time to estimate the R_0 for SARS and such techniques would be used in the event of an influenza pandemic. Open up the spreadsheet Session2.xls, and make sure that you are on the worksheet called "SARS".

The spreadsheet is organized as follows: there are 2 parameters in the top left corner that refer to the average incubation period, and the average duration of infection. We will assume that these are known (i.e. we will not be estimating them). We will also assume a constant infectious period and that each infected individual is equally infectious throughout their infectious period (this probably isn't true, but it will make the calculations simpler). Thus, if the incubation period is about 5 days, and the duration of infection is 14 days then the average time from one generation of infections to the next is 12 days (5+14/2). At the very beginning of such an epidemic we can neglect to keep track of the depletion in susceptibles as the

epidemic progresses, as the number of individuals in the population that are not susceptible will be negligible. Under these circumstances a single case will generate:

- R_0 cases after the first generation
- R_0^2 cases in the 2 generation
- R_0^3 cases in the 3 generation
- Etc., etc.

So the number of cases *t* generations after the initial case (which we will call I_t) is:

$$I_t = R_0^t$$

And the cumulative number of cases observed up to generation t is simply:

$$\Sigma\, It$$

We can utilize this to estimate R_0 from the epidemic curve. In the example given we use "least squares" estimates to derive a best guess of R_0. That is, we choose a value of R_0, then compare the sum of the squared differences between the model and the data. We keep choosing values of R_0 until we can minimise the sum of the squared differences between the data and the model.

3.1. Change the values of R_0 and see what happens to sum of the squared differences. Also observe how this affects the graph (which compares the model results with the data). Try and choose a value of R_0 that minimizes the squared differences between the model and data.

3.2. Excel has an add-in program called Solver, which will run through lots of values of a cell and choose the one that fulfils certain criteria (either maximizes a value in another cell, or minimizes it, or sets it to zero). To get Excel to do this we must first run Solver tell it which cell it has to change, and which one it is trying to minimize (or maximize, or set to zero). In our case we want to minimize cell **G16** (sum of the squared differences) by changing cell **I18** (R_0).

Run solver: Tools menu then Solver. If Solver is not installed on your computer, then go to Tools | Add-ins, then tick the "Solver Add-in" option. If this still doesn't work, then you should share with someone who has "Solver" working. Compare your value (from doing it manually) to that obtained by Solver.

3.2.1. What do you think of the fit of the model to the data? How could you improve this fit? Why do you think that, for an R_0 value that provides a reasonable fit to the first few weeks of SARS data, later model estimates tend to be much higher than the observed case numbers (hint: think about the definition of R_0 as opposed to R_e?

3.2.2. Were we right to be worried about SARS?

3.2.3. What is the relationship between the inter-generation period and our estimate of R_0?

3.3. A paper by Lipsitch et al[1]., on the approximate value of R_0 for SARS in Singapore, describes the following relation between R_0, generation time, latent period, and "force of infection" (estimated using the methods described in section 2.2, above), as:

$$R_0 = 1 + \lambda v + f(1-f)(\lambda v)^2$$

Where λ is FOI, f is the latent period (time period between infection and infectiousness), and v is the generation time (or serial interval, as it is called in the Lipsitch paper).

The Impact of Control

3.4. You may have noted that there is a tendency for a model that is well-fitted to earlier case counts to overshoot later case counts. As noted above, this in part reflects the fact that individuals don't tend to stand idly by when an epidemic is noted: public health authorities may institute control measures, concerned citizens may change their behaviour, alcohol-based hand sanitizer use may go up, and so on. We can add a "discount factor" to our simple model to reflect the fact that R is "deflated" through behaviours and interventions as time goes on. This simple fix changes the number of new cases in each generation to:

$$I_t = R_0^t/(1+d)^t$$

Here, *d* is simply a discount factor with a value between 0 and 1. Run Solver again, but this time minimize cell **G16** (sum of the squared differences) by changing both cell **I18** (R_0) and **I19** (d).

3.4.1. What happens to model fit when *d* is included in the model?

3.4.2. What happens to the baseline value for R_0 when *d* is included in the model?

3.4.3. Try to articulate, in words, the difference between the model you fit without *d* and that fit with *d.*

[1] *Lipsitch M, et al., Transmission Dynamics and Control of Severe Acute Respiratory Syndrome. Science 2003; 300: 1966-70.*

4. The Richards Growth Model

The Richards growth model is a type of logistic model first described in the 1950s and intended for application to biological processes. Professor Ying Hsieh has investigated the application of the model to infectious diseases[2]. The model has some attractive properties; in particular, it can be fit to the kind of epidemic curves that are commonly publicly available on the web during outbreaks, it can be used to project the final epidemic size while the outbreak is still in progress, and it can also be used to identify "inflection points" (time points when epidemic growth moves from accelerating growth to decelerating growth).

4.1 The basic model describes the number of infections in some generation (t) as:

$$I(t) = K/[1+e^{(-r(t-tm))}]^{1/a}$$

Here, r is the per capita growth rate of the infected population; K is the carrying capacity for total infections (i.e., the final epidemic size); and a is the exponent of deviation from the standard logistic curve (which basically defines how steep the logistic curve is). The quantity t_m is a parameter related to the "turning point" of the epidemic, which is basically the time point at which growth transitions from accelerating growth to decelerating growth (and which would be analogous to the time point where Re = 1 in an SIR model); it is possible to back into an expression for the turning point via the relation:

$$t_m = t_i + \ln(a)/r$$

Thus t_m equals t_i if a = 1, t_i can be calculated as t_m-ln(a)/r for values of a close to 1. A second useful property of this model involves calculation of R, which is exp(rT) (with T = the generation time or time interval between succeeding generations of cases. T is often approximated as the latent period + ½ the infectious period).

4.1.1. Return to the spreadsheet and click on the tab labelled "SARS Richards". You'll see a table that looks very similar to that we used to fit our last model. However, at the right side of the data table, there is a smaller table labelled "Richards parameters". Try playing with the values for tm, r, a, and K and see what happens to model projections (red line).

4.1.2. Now use Solver again. Ask Solver to minimize the sum of squares (**F17**) by changing the values of cells **I8**:**I11**. What is the sum of squares difference here, relative to what you obtained with the "discounted" model on the last worksheet?

4.1.3. What is the final epidemic size projected by the model? Does this match the observed data?

[2] You can find a good introductory reference at this url: http://www.cdc.gov/ncidod/eid/vol12no01/05-0396.htm. The citation is Hsieh YS, Cheng YS. Real-time forecast of multiphase outbreak. Emerging Infectious Diseases 2006.

4.1.4. The turning point for the epidemic is approximated in cell **I13** (and is presented in *days* rather than *generations* in order to match the X-axis scale on the graph). This point is represented as a blue "X" on the X-axis of the graph. Recall that the change from R > 1 to R < 1 can be identified on a standard epidemic curve (incident cases per unit time) as the point where the curve peaks. This corresponds to the transition from accelerating growth to decelerating growth of the epidemic. Scroll down on the worksheet…you should see an epidemic curve there. Does the turning point estimated by the Richards model fall where you expected? Why or why not?

4.1.5. As noted above, R_0 can be approximated from the Richards model as R_0 as exp(rT) where T = generation time. This model is actually parameterized using single generations as time units, so $r = R_0$. What is the best-fit value for R_0 in this model. How does it differ from prior estimates derived during this session. Is it a true "R_0"?

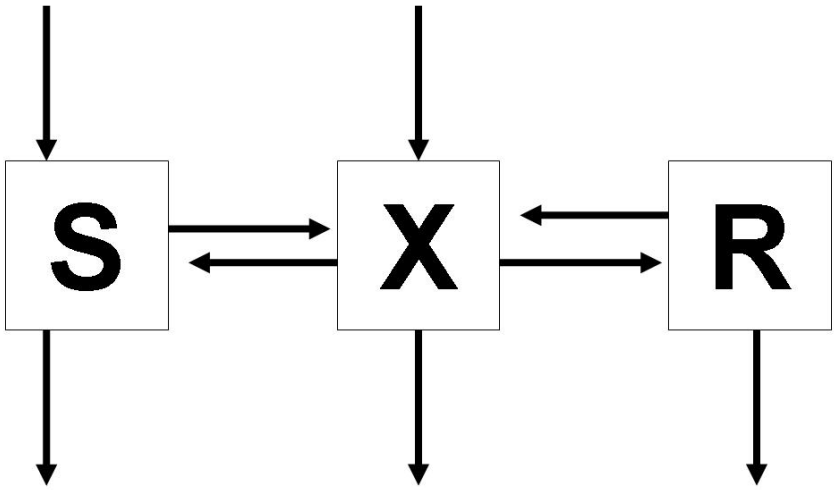
Part B: A Simple Mathematical Model of Antimicrobial Resistance

1. A Simple Resistance Model

This section is based (loosely) on a (simplified) version of the model published by Marc Lipsitch, Carl Bergstrom, and Bruce Levin in *Proceedings of the National Academy of Sciences*, 2000 (*PNAS* 2000; 97(4): 1938-43), which we will post on the Workshop website. Marc alluded to this paper, which was really a landmark, in his lecture to us on Monday.

Notation alert: if you're like me, you may find that your brain has a tough time switching gears in terms of the arbitrary state names in Marc's model: here, *X* represents those susceptible to colonization/infection with the microbe of interest, while *S* represents infection with a susceptible strain of the microbe, and *R* represents infection with an antibiotic resistant strain. To avoid *further* confusion, I am going to leave this notation as is! So: X = su**x**sceptible, S = colonized with **s**usceptible microbe and *R* = colonized with **r**esistant strain!

We are going to work with a simplified version of this model; I have drawn the model compartments below (note that our model corresponds to only the lower half of the paper's **Figure 1B**, as all individuals in our population can be treated). Individuals enter the population either uncolonized with the microbe of interest, or colonized with a susceptible strain (in other words, we are assuming that resistant microbes are only acquired in the closed world of the hospital, the long-term care facility, the daycare, or whatever we are trying to represent with this simple model).



5.1 What are a few of the assumptions we are making in this model? Are they realistic? Do you think this model can provide any valuable insights without being more realistic (no right or wrong answer to the latter question, but perhaps a good time to think about what we are trying to achieve via modeling)?

5.2 Let's call our total population size *N*, where $N = S + X + R$. Now that we have described allowed transitions in the model, let's add some parameters (the rates at which individuals flow between compartments). We will define our parameters as:

a. mu (or the Greek letter μ) = the rate at which individuals move in and out of the population. You can think of this as the admission or discharge rate in a hospital, for example. At steady state, the admission rate = the discharge rate.
b. m = the equilibrium prevalence of colonization/infection in the community.
c. beta (the Greek letter β) = the probability of transmission x the contact rate (we called this "pc" in our last exercise).
d. c_f = fitness cost associated with resistance. This is the proportionate reduction in β associated with the ability of the bacterium to withstand infection with antibiotic #1.
e. gamma (the Greek letter γ) = 1/(duration of colonization or infection), or the rate that colonization or infection is lost in the absence of treatment.
f. t1 ($\tau 1$ in the Lipsitch paper) = the rate at which infected individuals are exposed to antibiotic #1. This antibiotic eradicates *S* type infections but not *R* type infections.

g. t2 ($\tau 2$ in the Lipsitch paper) = the rate at which infected individuals are exposed to antibiotic #2. Both strains are susceptible to this antibiotic.

5.2.1. Now let's try to describe movement between model compartments using the parameters described above. Let's start with individuals susceptible to infection (*X*). Write out expressions for the number of individuals who move in to this group as a result of hospital admission, and the number of individuals who move out of this group due to hospital discharge, per unit time. Write these expressions on the appropriate arrows in the figure above (and feel free to crib from the Lipsitch paper if you need a bit of help getting started):

- Now write expressions for the number of individuals who move out of the *X* compartment per unit time as a result of contact with individuals in the *S* and *R* compartments (note that these expressions should look very similar (but c_f will be present in only one of them!). Again, write these expressions on the appropriate arrows above.

- Lastly, write out the expressions for the rate at which infected/colonized individuals return to the *X* compartment following either treatment or natural clearance of the microbe. Again, these two expressions should look similar (and should be written on the appropriate arrows above, yet again).

5.2.2. Now sum up the three groups of expressions you have written down in response to the questions above. The sum of these expressions is *dX/dt*, or the rate of change in the *X* per time increment.

$dX/dt =$

5.2.3. Can you perform the same exercise for *dS/dt* and *dR/dt*? Again, write out the expressions that describe flow into and out of these

compartments, and write them in the appropriate place on the figure above. Sum them up for both states and write the formulae for *dS/dt* and *dR/dt* below:

dR/dt =

dS/dt =

6. Numerical Example

Click on the worksheet entitled "abx model". You will see several rows of parameter values on a yellow background; these correspond to the model parameters listed in section 5, above. Below the parameter values, on a green background, are the initial conditions of the hospital population; the way the model is set up, there is a single case of antibiotic resistant infection in the population.

6.1 Look at the initial prevalence of colonization/infection. Ideally, the prevalence (green curve) you see on the bottom graph should match the value for *m*. Try changing the value of *m*: what happens? What level does prevalence of infection settle out at over time? What happens to the prevalence of resistance (bottom graph, orange curve) over time?

6.2 Set prevalence back to 0.30. Now change the initial number of individuals with resistant infection to 150. What happens to prevalence over time? What happens to the proportion of individuals with resistant infection over time? Given that all individuals entering the population have susceptible infections, and the individuals with resistant infection at baseline are long gone, where do the new resistant infections come from?

6.3 Keep the number of individuals with resistant infection at baseline high. Now turn your attention to the value for c_f (fitness cost) which has been set to zero. Change this value to 0.01. This will result in the value of β for individuals in the *R* class being reduced by 1% (i.e., 99% of the value for individuals in the *S* class). Now what happens to the number of individuals in the *R* group over time? Try experimenting with different values for c_f? How do these affect prevalence of resistance over time? What happens if you use a *negative* value for c_f (in other words, resistant strains are *more* transmissible than susceptible strains over time)?

Note About "Dynamic Equilibria"

You may have noticed above that when there is no fitness cost associated with resistance, the proportion of individuals in the R state stay approximately where they are at baseline (on the time scale we are using here; it is true that this proportion will drop gradually on a longer time scale due to importation of individuals in only the *S* and *X* classes). We refer to this type of situation as a "dynamic (because people are coming and going) equilibrium". When a fitness cost is added, in the absence of selective pressure from antibiotic therapy, the proportion of individuals in R drops from its initial value, and settles at or near zero. Thus in the presence of a fitness cost, an equilibrium value for R is zero, but in the absence of such a cost, an equilibrium value is whatever R is at baseline. In the presence of a "negative" fitness cost (that is, the resistant strain is more transmissible than the susceptible strain) we get almost total replacement of susceptibles by resistant infections, which assume the equilibrium prevalence previously occupied by susceptibles (or slightly more than that equilibrium prevalence due to slightly higher β).

7. Fitness and Selective Pressure

7.1. Set c_f back to zero, and set the initial number of individuals in the *R* state back to 1. Now add treatment with antibiotic #1 by changing t1 to 1. Remember that antibiotic #1 is the agent to which class *S* is susceptible, but class *R* is resistant. What happens to the proportion of resistant strains now? What happens to the prevalence of infection overall (*S*+*R*) over time?

7.2. Without changing the proportion of individuals treated with antibiotic #1, add a fitness cost for resistance, by changing c_f to 0.02. What happens to the prevalence of infection and resistant infection? What happens to the proportion of infections caused by *R* strains?

7.3. Try changing c_f and the rate of treatment with antibiotic #1 in parallel. What is the relationship between these two parameters and the prevalence of resistant infection? As c_f increases, what do you need in order to maintain resistant infections at a high level?

7.4. You have the option of adding a second antibiotic treatment (t2). Do so now. What happens to prevalence of infection as you increase the rate of treatment with this second agent? What happens to the proportion of strains resistant to antibiotic 1?

7.5. In the original manuscript by Lipsitch and colleagues, the model was structured so that individuals' treatment histories could be tracked. The authors pointed out that, paradoxically, increased use of antibiotic #2 was associated with a decline in the prevalence of resistant infections, but exposure to antibiotic #2 increased the risk of *individuals* acquiring resistant infection. Can you reconcile these two findings? Why is this an important insight for those interested in a nuanced interpretation of the epidemiologic literature related to antibiotic resistance? (Hint: how would a case-control study of risk factors for antibiotic resistance be performed?)[3]

8. More About Dynamic Equilibria

8.1. As you saw above in Section 2.3, it is possible to estimate numerical values for the number of individuals in a given class at equilibrium by setting the differential equations that characterize the system to zero, and solving for values in terms of model parameters; this involves relatively straightforward algebra but nonetheless is beyond the scope of what we hope to achieve this morning. However, turning back to the manuscript by Lipsitch and colleagues, we see that they used this approach to identify non-zero equilibrium conditions for resistant bacteria in the population, under different degrees of ecological pressure from antibiotics 1 and 2, in the special case where there is no fitness cost to resistance. In the manuscript, *R* will remain > 0 where:

$$R_0 > \tau 1/(\tau 1 - m\mu)$$

Note that this is the R_0 for the resistant strain; recall that m is the probability of colonization with the susceptible strain among those admitted to the institution, and μ is the admission/discharge rate for a population of fixed size.

8.1.1. Click on the worksheet entitled "equilibrium". You will see yellow cells with values for m and μ and green cells with values for $R_0 > \tau 1$. You will also see a graph with values for R_0 and $\tau 1$ plotted against each other.

8.1.1.1. Qualitatively, what happens to $\tau 1$ necessary for persistence as the R_0 for resistant strains increases? Is this a linear relationship? Why or why not? What does this tell you about the potential contribution of transmissibility of a given strain to our ability to control antibiotic resistance via antibiotic stewardship?

[3] If you are interested in exploring this issue further, consider reading a classic paper by (ex-pat Canadian) Anthony D. Harris of University of Maryland on control selection in case-control studies of antimicrobial resistance. The issues discussed are not identical, but are closely related. See: Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. Clin Infect Dis. 2001; 32(7):1055-61.

8.1.1.2. Manipulate the values for m and μ. What happens to the scale on the *Y*-axis as you increase m? What does this tell you about the role that normal "commensal" flora play in limiting the transmission of ARO? How is this effect diminished as the rate of exposure to antibiotic #1 increases?

8.1.1.3. Repeat this exercise, changing the value of μ. What is the relationship between μ and the threshold $\tau 1$ for a given value of R_0? What does this suggest about the relative importance of emergency rooms and long-term care facilities or rehab centers in the emergence of nosocomial AROs? Can you explain this effect in words? (Hint: given that individuals are admitted in either the *S* or *X* state, what needs to happen for them to transition to the *R* state?).