Mathematical Modeling of Infectious Diseases, UCSF

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Compartmental models

We spent a long time last time on the foundations of compartmental modeling. Today we'll take this a little further.

Chains

Show the SEIR model.

Let's find out what the sum of two independent identical exponential distributions is. Consider Y_1, Y_2, and Z:

$$\frac{dY_1}{dt} = -\lambda Y_1$$

$$\frac{dY_2}{dt} = \lambda Y_1 - \lambda Y_2$$

$$\frac{dZ}{dt} = \lambda Y_2$$

If we start off with N people in Y_1 at time 0, and watch how they build up over time in Z, we'll understand what the cumulative distribution function for the sum of two independent exponentials is. Let T be the waiting time distribution of the sum of two independent exponentials is.

$$P(T < t) = Z(t)/N$$

See? Z is the fraction of people for whom this has already happened. Imagine each person has a waiting time T. If you are in Z at time t, then $T < t$. If $T < t$, then you are in Z at time t.

We already know $Y_1(t) = Ne^{-\lambda t}$. We need to use a little trickery to get Y_2. There's a standard trick:

$$\frac{dY_2}{dt} + \lambda Y_2 = \lambda N e^{-\lambda t}.$$

$$e^{\lambda t}\frac{dY_2}{dt} + e^{\lambda t}\lambda Y_2 = \lambda N.$$

$$\frac{d}{dt}\left(e^{\lambda t}Y_2\right) = \lambda N.$$

$$d\left(e^{\lambda t}Y_2\right) = \lambda N dt$$

$$\int_{t=0}^{t=t'} d\left(e^{\lambda t}Y_2\right) = \int_{t=0}^{t=t'} \lambda N dt$$

$$e^{\lambda t'}Y_2(t') - Y_2(0) = \lambda N t'$$

By assumption, everyone is in Y_1 at the beginning, so $Y_2(0) = 0$.

$$e^{\lambda t'}Y_2(t') = \lambda N t'$$

Rearranging and dropping the primes:

$$Y_2(t) = \lambda N t e^{-\lambda t}$$

Finally,

$$\frac{dZ}{dt} = \lambda Y_2(t).$$

We have

$$\frac{1}{N}\frac{dZ}{dt} = \lambda^2 t e^{-\lambda t}.$$

Remember that the fraction of people who have arrived in Z at any time is the cumulative distribution function of the arrival time. We wouldn't mind having that, but actually having the probability density function would be nice too. The PDF is the derivative of the cumulative distribution function; where are we going to get it? We notice that we already have it in the previous equation!

$$f(t) = \frac{d}{dt} P(T < t) = \lambda^2 t e^{-\lambda t}.$$

What distribution has this density? Meet the gamma distribution, with shape parameter 2. The sum of two independent identical exponentials with rate λ is a gamma with shape parameter 2.

The Gamma family comes up all the time. The general formula for the density is

$$f(t) = \frac{\lambda^a}{\Gamma(a)} t^{a-1} e^{-\lambda t}.$$

We won't prove it, but the mean is always a/λ. Here, a is the *shape parameter* and λ is the rate.

The sum of n independent identical exponentials (with rate λ) is a gamma with shape n and rate λ, which we won't show.

Some people call a gamma distribution with integer shape parameter (i.e. a sum of exponentials) an Erlang distribution.

You already have seen the gamma distribution in your life. If the rate parameter is 1/2 and the shape parameter is $n/2$, it's called a *chi square* distribution.

Exercise 1. Find the hazard $\lambda(t)$ for a gamma distribution with shape parameter 2 and rate parameter λ. ∎

General hazard

R_0 for a model with delay (SEIR) model.

Loops

It's common in compartmental modeling to loop back to a previous state. An example is given by herpes simplex virus, where a person can repeatedly have episodes during which transmission is much more likely than when there is no episode (cf. Blower 1998).

Let's imagine for a moment that we are looking at a closed population of people with the disease, and just keeping track of how many have episodes at any given time.

We might assume the rate of relapse is independent of the past history of relapses, and is the same for everyone. Let Y be the number people with symptoms then, and L be the number without. Say the relapse hazard is ζ. Then in a given unit of time, we have each of L people faced with a risk $\zeta\Delta t$ of relapsing. The expected number of relapses is then $L\zeta\Delta t$. This gives us a flow rate per unit time of $L\zeta$.

Similarly, say the rate of recovery (recovery hazard) is ρ. Then the flow rate of people recovering per unit time is $Y\rho$. So we would just write

$$\frac{dL}{dt} = \rho Y - \zeta L$$

and

$$\frac{dY}{dt} = -\rho Y + \zeta L$$

The total population, $N = L + Y$ doesn't change; $dN/dt = 0$.

In fact, why not just divide by N and get equations for the fraction symptomatic over time:

$$\frac{dy}{dt} = -\rho y + \zeta(1 - y).$$

Exercise 2. Show that the equilibrium fraction of symptomatic people in the above simple model is $\bar{y} = \frac{\zeta}{\zeta+\rho}$. Suppose ρ is much smaller than ζ; does the answer make sense? What about if ζ is much larger than ρ? ∎

Let $a = \rho + \zeta$. Then we can write

$$\frac{dy}{dt} = -ay + \zeta$$

This can be looked at as a version of the "immigration-death" process again. We have an inflow at rate ζ and an outflow at rate a.

There's a standard trick to solve it; you don't have to learn the trick, but just understand the solution:

$$\frac{dy}{dt} + ay = \zeta$$

$$e^{at}\left(\frac{dy}{dt} + ay\right) = \zeta e^{at}$$

$$\left(\frac{dy}{dt}e^{at} + ay\right)e^{at} = \zeta e^{at}$$

$$\frac{d}{dt}\left(ye^{at}\right) = \zeta e^{at}$$

$$d\left(ye^{at}\right) = \zeta e^{at}dt$$

$$\int_{t=0}^{t=t'} d\left(ye^{at}\right) = \int_{t=0}^{t=t'} \zeta e^{at}dt$$

$$y(t')e^{at'} - y(0) = \frac{\zeta}{a}\left(e^{at'} - 1\right)$$

Just for simplicity, let's imagine everyone at the beginning was symptomatic, so $y(0) = 1$. Then

$$y(t')e^{at'} = 1 + \frac{\zeta}{a}\left(e^{at'} - 1\right)$$

Now just write t for t':

$$y(t) = \frac{\zeta}{\zeta+\rho}\left(1 - e^{-at}\right) + e^{-at} = \frac{\zeta}{\zeta+\rho}\left(1 - e^{-at}\right) + \frac{\zeta+\rho}{\zeta+\rho}e^{-at}$$

$$y(t) = \frac{\zeta - \zeta e^{-at} + (\zeta+\rho)e^{-at}}{\zeta+\rho}$$

$$y(t) = \frac{\zeta + \rho e^{-at}}{\zeta+\rho} = \frac{\zeta + \rho e^{-(\rho+\zeta)t}}{\zeta+\rho}.$$

Exercise 3. What is the behavior of this equation as $t \to \infty$? Work out the solution if $y(0) = 0$. ▮

Exercise 4. Suppose that births occur randomly in the sense that the rate of new people being added to a population has a constant rate Λ, so the chance of a birth happening in a tiny time interval Δt is $\Lambda\Delta t$. Suppose there are X people, and the per capita death rate is μ. (a) What is the mean waiting time to death, for any individual in the population?
(b) Show

$$X(t + \Delta t) = X(t)(1 - \mu\Delta t) + \Lambda\Delta t$$

if you assume birth/immigration is independent of death.

(c) Now rearrange and take the limit as $\Delta t \to 0$ and get

$$\frac{dX}{dt} = \Lambda - \mu X$$

(d) Find the equilibrium of this system (for what value is $dX/dt = 0$?) Construct an interpretation in terms of a kind of "prevalence equals incidence times duration" in a demographic setting.

∎

Now, we're going to add what we learned about competing risks to what we just learned about loops. Suppose now we have a chance of death, all the time, no matter what stage you are in:

$$\frac{dL}{dt} = -\mu L - \zeta L + \rho Y$$

$$\frac{dY}{dt} = -\mu Y + \zeta L - \rho Y$$

Now, people leave and never come back. The long run equilibrium is zero. What we want to know is how much transmission could a person cause? Or rather, if we started a bunch of people out, how much transmission could they cause?

For your first episode, the removal rate is $\rho + \mu$. The mean duration is $1/(\rho + \mu)$. The chance of death is $\mu/(\rho + \mu)$, and the chance you recovered is $\rho/(\rho + \mu)$. If death occurred, that's it; no more cases. But if you recovered, there's a chance you'll relapse again. What is it? If you recover, your recovery will last on average how long? The time is $1/(\zeta + \mu)$, and there's a chance $\mu/(\zeta + \mu)$ of death before your relapse and a chance $\zeta/(\zeta + \mu)$ that you actually relapse and become an infective again.

If you're an infective, everything is as it was before. There is nothing in the model to distinguish your second relapse from your first. All these distributions are memoryless.

So. What is your total person-time of infection? Let's say it's called T. What we know is that

$$T = \frac{1}{\rho + \mu} + \frac{\rho\zeta}{(\rho + \mu)(\zeta + \mu)} T.$$

The first time is the duration of the current episode. The second term is the chance you recover (instead of dying) times the chance you relapse (insteading of dying in state L).

You can actually go ahead and solve this for T.

We may also reason this way. Let's just call

$$k = \frac{\rho}{\rho + \mu}\frac{\zeta}{\zeta + \mu}.$$

This is the chance that you have another episode, once one infectious episode ends. Let's also call the length of one episode $\tau = 1/(\rho + \mu)$. So another way to look at it is that the number of infectious episodes is going to be

$$1 + k + k^2 + k^3 + \cdots$$

We know $0 \le k < 1$, since we are only interested in $\mu > 0$. Therefore we can add this series up and get $1/(1 - k)$; that is the expected number of episodes for each infective. Each episode lasts τ long, so the expected time is $\tau/(1 - k)$. Is this the solution of the equation

$$T = \tau + kT?$$

This analysis shows you that a loop is actually a kind of chain that never stops.

Let's look at the full epidemic model (Blower 1997):

$$\frac{dX}{dt} = -\beta X \frac{Y}{N} + \Lambda - \mu X$$

$$\frac{dY}{dt} = \beta X \frac{Y}{N} - \mu Y - \rho Y + \zeta L$$

$$\frac{dL}{dt} = -\mu L - \zeta L + \rho Y$$

This is a kind of modified SI model. The analysis above shows what R_0 is for this model.

Do a TB model.

Exercise 5. How long did this assignment take you? ∎