Mathematical Modeling of Infectious Diseases, UCSF

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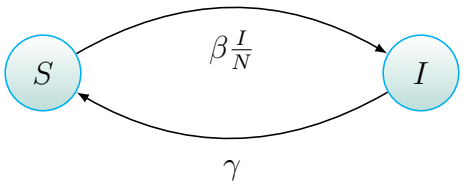
The SIS model

We will look today at the classical SIS (susceptible-infective-susceptible) model.



Here, the population is divided into susceptible (S) and infective (I), with total number $N = S + I$; the prevalence fraction is I/N. We assume the force of infection is $\lambda = \beta\frac{I}{N}$. We assume exponential recovery (recovery at constant hazard γ). The model is then

$$\frac{dS}{dt} = -\beta S\frac{I}{N} + \gamma I$$

$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I$$

We can just write this as one equation:

$$\frac{dI}{dt} = \beta(N - I)\frac{I}{N} - \gamma I.$$

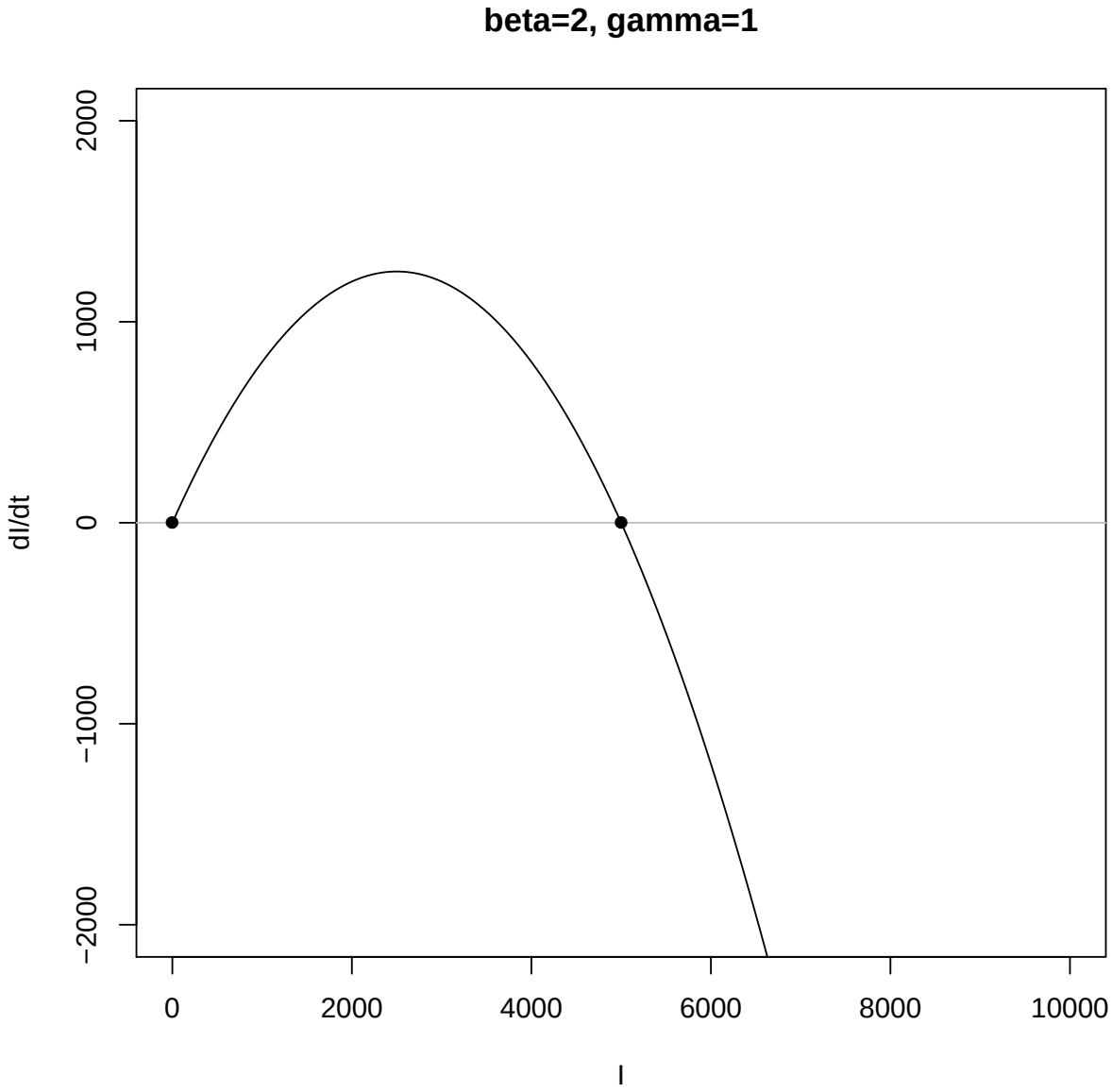
This is a nonlinear ordinary differential equation, since I and it's derivatives appear to powers other than 1.

The dimensions of γ are reciprocal time; it is a rate. Note that β in this model also has dimensions of rate as well.

Note that $dN/dt = dS/dt + dI/dt = 0$; the total population doesn't change in this model.

Let's plot the right hand side. First, let us pick $\beta = 2$ per year and suppose $\gamma = 1$ per year, and let's take $N = 10000$ say.

```r
nmax <- 10000
itmp <- seq(0,nmax,by=1)
cur.beta <- 2
cur.gamma <- 1
plot(itmp,cur.beta*(nmax-itmp)*itmp/nmax - cur.gamma*itmp,xlab="I",ylab="dI/dt",type="l"
abline(h=0,col="gray")
points( ((cur.beta-cur.gamma)/cur.beta)*nmax, 0,pch=16 )
points( 0, 0,pch=16 )
```



In fact the graph is of course a parabola. One zero is at $I = 0$; if there are no infectives, then the number of infectives doesn't change. It makes sense: if nobody has the disease, then nobody ever gets it. This model is therefore excluding importation, immigration, and evolution.

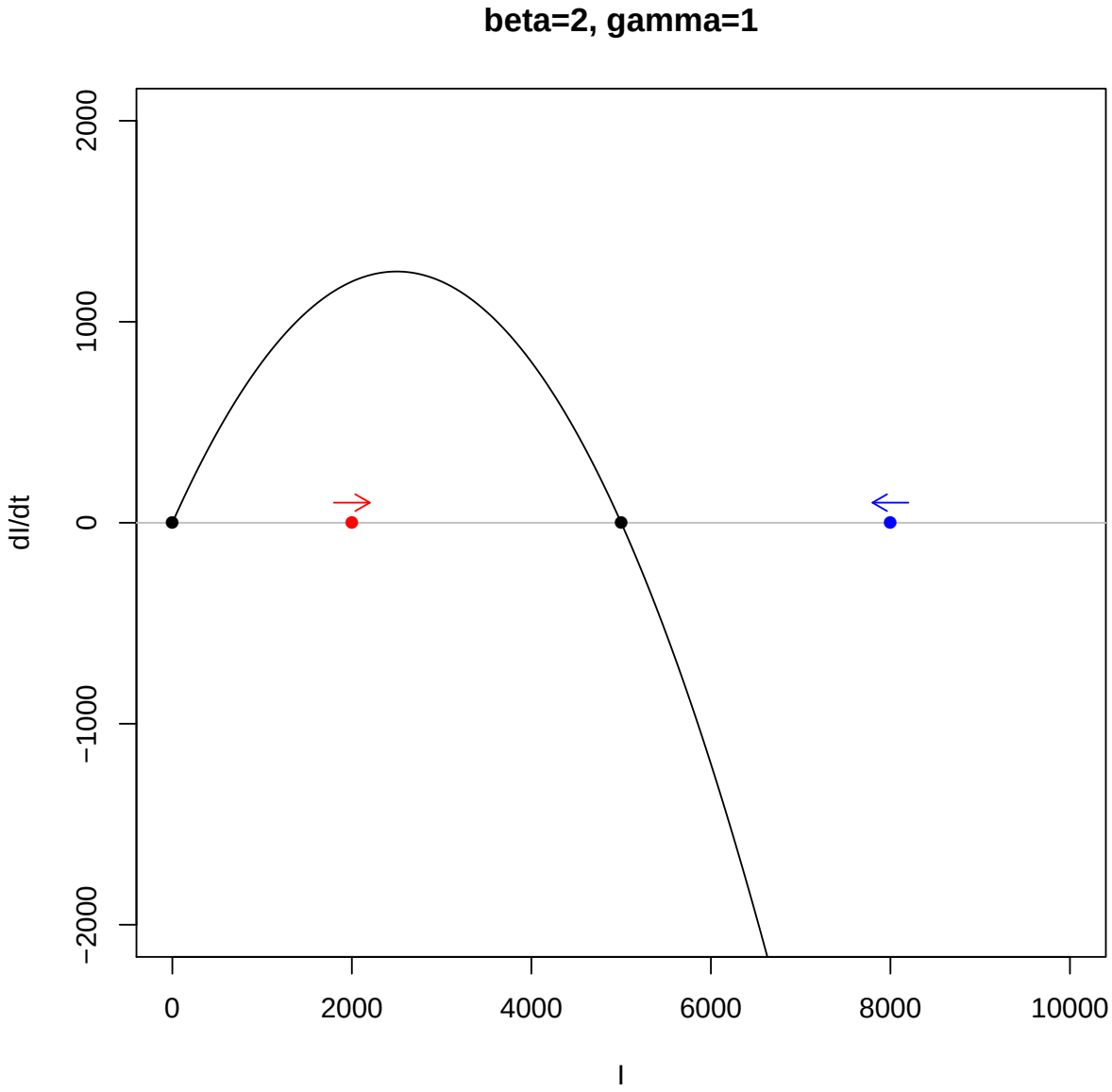
Where is the other root of the parabola? It is at I^* such that

$$\beta(N - I^*)/N = \gamma.$$

This is just from substituting into the dI/dt equation above. What we get is that the prevalence fraction I^*/N is $(\beta - \gamma)/\beta$. If I^* takes this value, then the rate of production of new cases exactly balances recovery, and again the number of infectives does not change.

What does this mean? Say you have a value of $I = 2000$ (a prevalence fraction of 0.2).

```
nmax <- 10000
itmp <- seq(0,nmax,by=1)
cur.beta <- 2
cur.gamma <- 1
plot(itmp,cur.beta*(nmax-itmp)*itmp/nmax - cur.gamma*itmp,xlab="I",ylab="dI/dt",type="l"
abline(h=0,col="gray")
points( ((cur.beta-cur.gamma)/cur.beta)*nmax, 0,pch=16 )
points( 0, 0,pch=16 )
points( 2000, 0, pch=16, col="red")
arrows( 1800, 100, 2200, 100, length=0.1, col="red")
points( 8000, 0, pch=16, col="blue")
arrows( 8200, 100, 7800, 100, length=0.1, col="blue")
```



We know the rate of change of I has to be given by the equation. We have 2 per year times 10000 - 2000 times 0.2 = 3200 new infections per year for the first term. And we will have 2000 times 1 per year = 2000 recoveries per year for the second. The total rate of change is 1200 per year, in the positive direction. So if $I = 2000$, the rate of change is positive—the red dot in the plot is moving to the right at a speed of 1200 per year.

If we happened to be at the value $I = 5000$, what happens? Then we have a new infection rate of 2 per year, $\times(10000 - 5000) \times 0.5$, which is 5000 per year. The number of recoveries is $\gamma I = 5000$ per year also, so the system is in equilibrium.

If we were at say $I = 8000$, then what? We would have a new infection rate of 2 per year, times $10000 - 8000$, times 0.8. There are lots of infectives—so the susceptibles are at high risk. But there aren't that many of them; the total new infection rate is back down to 3200 per year again. But the recovery rate is 8000 per year; we're going to be losing infectives faster than we gain them. If the system is at the blue point and $I = 8000$, then the rate of change is negative. I is decreasing—the blue dot is moving left. The parabola keeps going down (even though I cut the graph off).

Can the dot cross from the left of the equilibrium at 5000 over to the right? No way. The velocity is zero at the equilibrium; if it were there, it could never leave. In fact, the system will never actually get there either. Before we move on, let's ask two more questions. What if the value of I were 12000 say? Well, it can't be. There are only 10000 people, so I is restricted to the range $[0, 10000]$. What if the equations somehow tried to create solutions that went outside this range? That model wouldn't be well posed.

It turns out we can actually solve this whole system. That's pretty lucky in a way. Normally nice closed form analytic solutions just don't happen for realistic systems.

Let's do it. First, since N is a constant, I'd like to just change variables please, over to say $y = I/N$. Then we have

$$\frac{dy}{dt} = \beta y(1 - y) - \gamma y.$$

which is

$$\int \frac{dy}{\beta y(1 - y) - \gamma y} = \int dt = t + C.$$

Here C is a constant of integration.

The denominator factors on the left: $\beta y(1 - y) - \gamma y = y(\beta - \gamma - \beta y)$. Let's solve it only for the case $\beta - \gamma > 0$, and we use the usual trick:

$$\begin{aligned}\frac{1}{y(\beta - \gamma - \beta y)} &= \frac{A}{y} + \frac{B}{\beta - \gamma - \beta y} \\ &= \frac{A(\beta - \gamma - \beta y)}{y(\beta - \gamma - \beta y)} + \frac{By}{\beta - \gamma - \beta y}\end{aligned}$$

$$= \frac{A\beta - A\gamma - A\beta y + By)}{y(\beta - \gamma - \beta y)}$$

So this will all work if $A = 1/(\beta - \gamma)$ and $B = A\beta$. So:

$$\int \frac{dy}{\beta y(1-y) - \gamma y} = \int \frac{dy}{(\beta - \gamma)y} + \int \frac{\beta dy}{(\beta - \gamma)(\beta - \gamma - \beta y)}.$$

$$= \frac{\ln(y)}{\beta - \gamma} - \frac{1}{\beta - \gamma}\ln(\beta - \gamma - \beta y).$$

$$= \frac{1}{\beta - \gamma}\ln\left(\frac{y}{\beta - \gamma - \beta y}\right).$$

We then have

$$\frac{1}{\beta - \gamma}\ln\left(\frac{y}{\beta - \gamma - \beta y}\right) = t + C$$

Just for a moment, let $a = \beta - \gamma$:

$$\ln\left(\frac{y}{a - \beta y}\right) = at + C$$

$$\frac{y}{a - \beta y} = C'e^{at}.$$

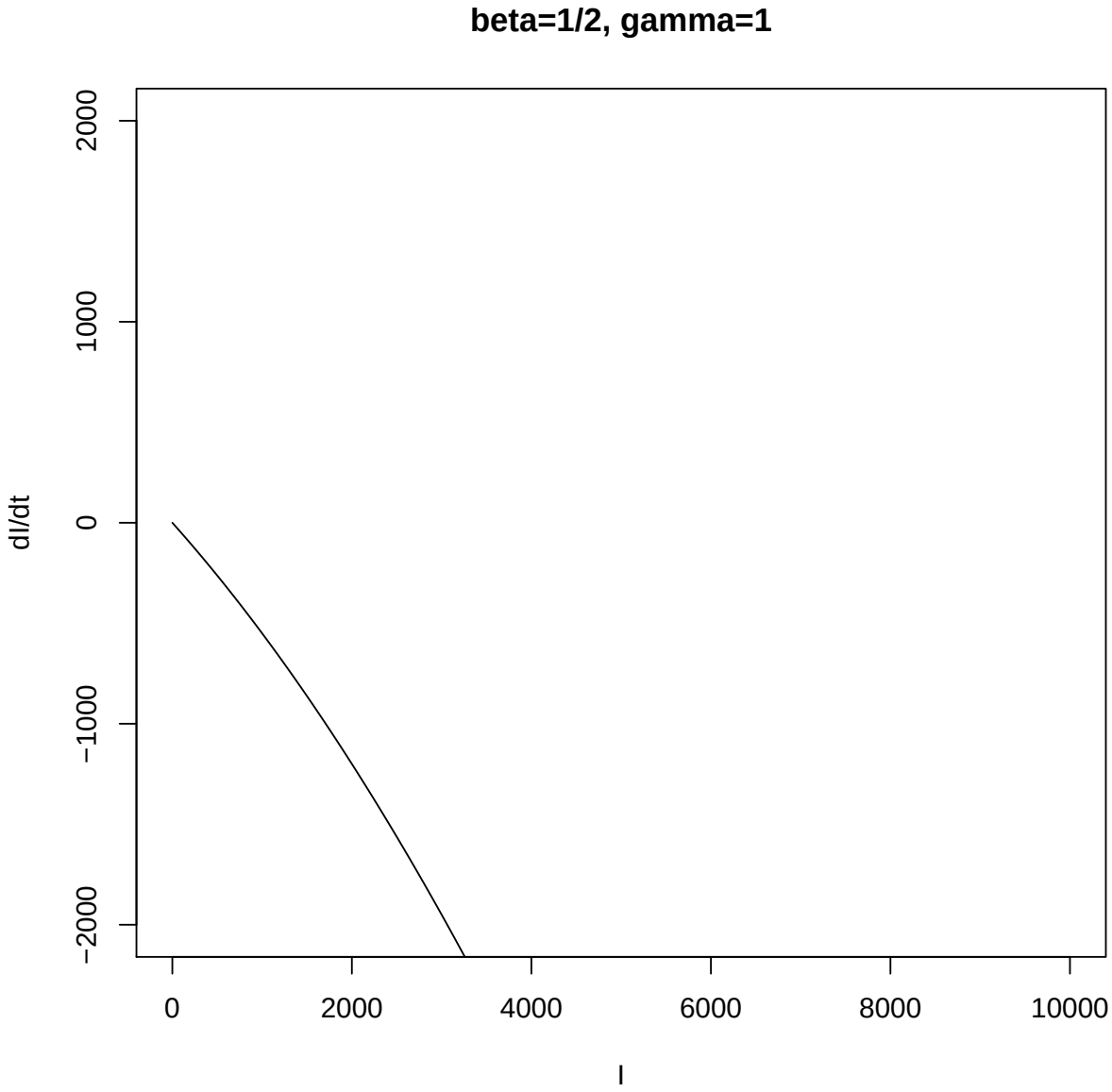
Rearrange this and apply the initial condition $y(t) = y_0$ and you get

$$y = \frac{\beta - \gamma}{\beta y_0 + (\beta(1 - y_0) - \gamma)e^{-(\beta-\gamma)t}}.$$

Does it make sense? As $t \to \infty$, this just becomes the equilibrium $(\beta - \gamma)/\beta$, so at least it makes that sense. This curve shows logistic growth in time.

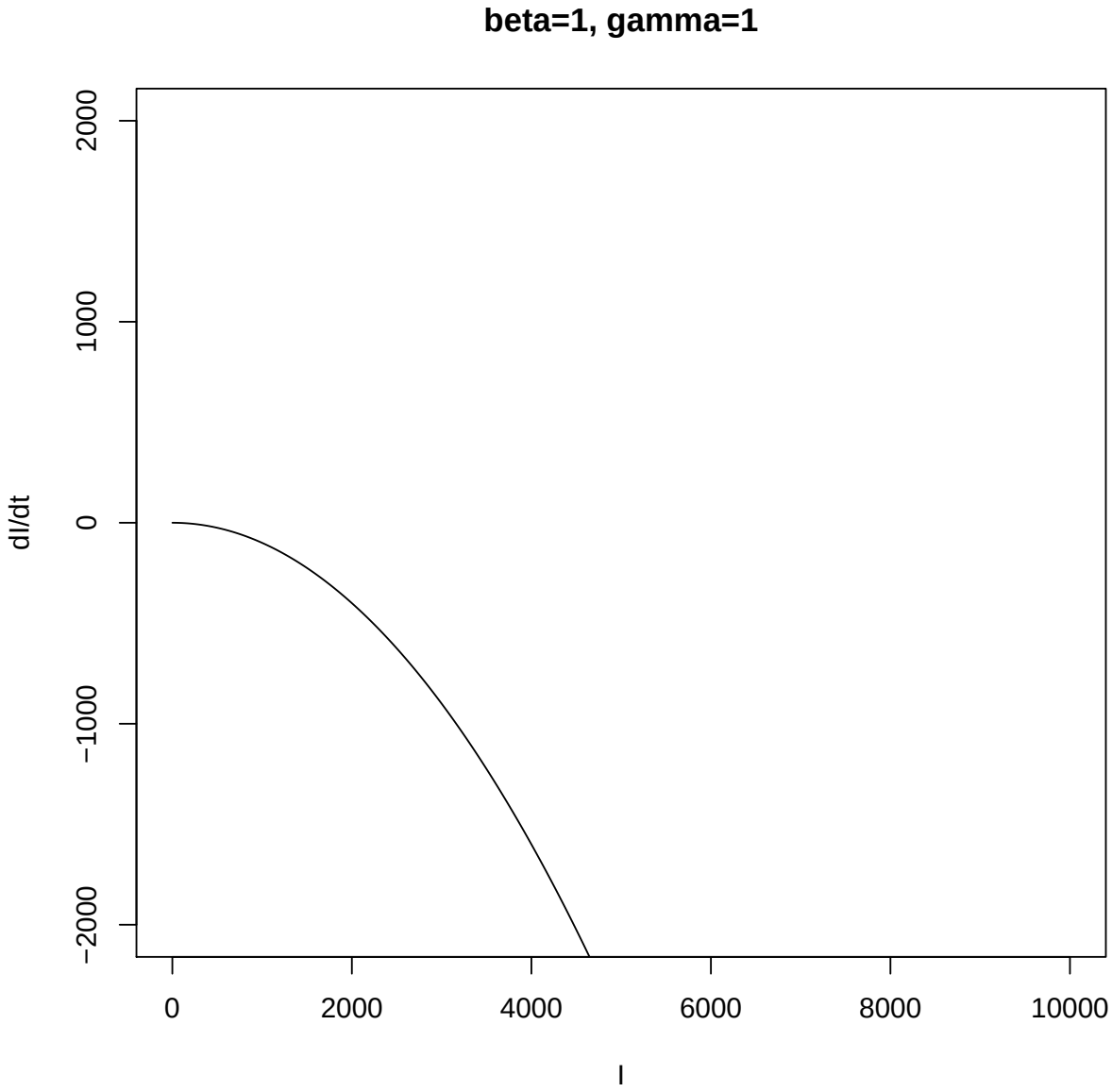
But what if $\beta - \gamma < 0$? A positive equilibrium does not exist, and we'll discuss it more in a moment. Let's look at the right hand side for $\beta = 0.5$ per year and $\gamma = 1$ per year:

```
nmax <- 10000
itmp <- seq(0,nmax,by=1)
cur.beta <- 0.5
cur.gamma <- 1
plot(itmp,cur.beta*(nmax-itmp)*itmp/nmax - cur.gamma*itmp,xlab="I",ylab="dI/dt",type="l"
```



What happens if $\beta = \gamma$ exactly? Not particularly believable in reality—why would two different processes have rates that equal each other right down to infinitely many decimals?

```
nmax <- 10000
itmp <- seq(0,nmax,by=1)
cur.beta <- 1
cur.gamma <- 1
plot(itmp,cur.beta*(nmax-itmp)*itmp/nmax - cur.gamma*itmp,xlab="I",ylab="dI/dt",type="l"
```



Suppose we consider the following. Let's follow only the very first infectives; let $I^{(0)}$ be the number of them. By definition, we can't get any more—you were either there at the beginning or you were not. Let's let $I^{(+)}$ be the number of new infectives caused by the initial group of infectives—I mean the total number ever caused. This variable is meant to be a cumulative incidence; it is counting the flow into a state, and not worrying about the

actual number of infectives. Imagine just counting the number of people who ever enter a room on a given day and not keeping track of who leaves.

So we will have for the first generation

$$\frac{dI^{(0)}}{dt} = -\gamma I^{(0)}.$$

They decay away exponentially just like we assumed all infectives do in this model. We know the solution to this equation is $I^{(0)} = I^{(0)}e^{-\gamma t}$. The size of the original cohort is an exponential function. We know the initial size of the starting group of infectives, $I^{(0)}(0)$, and this decays away in time. As time passes, the size of the starting group of infectives is smaller as they recover.

But while they're still infective, they cause new infections. The incidence term *from them* is $\beta S I^{(0)}/N$. We know after a while there are other infectives, second or later generation infectives, and those infectives will keep transmitting disease too. But we're not talking about those. We're talking about transmission from the first generation, and this happens at rate $\beta S I^{(0)}/N$.

Let's now assume that $I^{(0)}$ is much less than N, and that over the course of the first generation, the size of the second generation will also be small compared to N. So we'll never put much of a dent in N, and we can just take $S = N$. Eventually the epidemic might grow and render this assumption no longer useful. But while we have it, we have incidence from the first generation of $\beta I^{(0)}$. So the cumulative incidence $I^{(+)}$ follows

$$\frac{dI^{(+)}}{dt} = \beta I^{(0)}.$$

So

$$I^{(+)}(t) = \int_0^t \beta I^{(0)}(t')dt' = \beta \int_0^t I^{(0)}(0)e^{-\gamma t'}dt'$$

$$I^{(+)}(t) = \beta I^{(0)}(0) \int_0^t e^{-\gamma t'}dt' = \beta I^{(0)}(0) \left(-\frac{1}{\gamma}\right)\left(e^{-\gamma t} - 1\right)$$

which becomes

$$I^{(+)}(t) = \frac{\beta I^{(0)}(0)(1 - e^{-\gamma t})}{\gamma}.$$

In the far future, as $t \to \infty$, the number of secondary cases generated per initial starting case is therefore β/γ, which is the basic reproduction number for this model.

Chains

In the simple model we just looked at, there was no waiting time between infection and disease or infectivity. But really there is always some delay, and for some problems, it is important enough to consider. A common design motif in epidemic models is to construct a delay using exponential states. In fact it's possible with branches, loops, and chains to construct an arbitrarily good approximation to any waiting time. But what you often see is a simple model where infective people enter an "exposed" waiting state E. Let's take a moment to learn more about how chains of states work.

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. ∎

Loops

Loops form another design motif. In fact the SIS model shows a loop; once you recover, you become susceptible again and the prior history is forgotten. 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 $0 \leq k < 1$, 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.

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