

Mathematical Modeling of Infectious Diseases, UCSF

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1 Hazard

Last time we were working with a basic stochastic model of an epidemic, and we made a few quick approximations and derived some equations that are often called “the” Kermack-McKendrick model. We went from a stochastic model in discrete time to a deterministic model in continuous time. In fact, we’ll see some stochastic models in continuous time as well as some deterministic models in discrete time. All in good time.

This week one of the things we need to do is deepen our understanding of continuous time systems and their relation to discrete time systems, among other things.

First of all, we are going to have to talk about continuous random variables. There won’t really be time to review this theory in detail, but some key facts you will need are as follows. For a discrete variable, we had a probability function p_i that told us the chance the variable took on the value i . But in the continuous world, what matters is the probability the variable falls in various intervals; this probability is specified by giving a *cumulative distribution function*. Say our variable is called X , and somebody has provided us with the cumulative distribution function of X , which is $F(x) = P(X \leq x)$. We’re going to look at continuous random variables with *continuous* cumulative distribution function. (For the purists, we’re actually being even more restrictive: we’re ruling out a bunch of strange random variables that have what are called *singular* distributions; the ones we look at are called *absolutely continuous*).

Exercise 1. Show or argue that for continuous CDF F ,

$$P(X \in [a, b]) = P(X \in (a, b]) = P(X \in [a, b)) = P(X \in (a, b)) = F(b) - F(a).$$

You have seen this sort of thing before in your statistical studies. For example, you may have been asked to find the chance a standard normal variable is between -1 and 1, etc. ■

Exercise 2. Show or argue that for any real random variable with a continuous cdf, the cdf F should obey $\lim_{x \rightarrow -\infty} F(x) = 0$, $\lim_{x \rightarrow \infty} F(x) = 1$, and $dF/dx \geq 0$ if you can differentiate it—but $F(x_1) \geq F(x_2)$ for $x_1 > x_2$ no matter what (tell me why a CDF can’t “go down”). ■

Often we work with the *probability density function*, $f(x) = dF/dx$. The density of a standard normal is $f(x) = ke^{-x^2/2}$. Let’s find k ; we know

$$\int_{-\infty}^{\infty} f(x)dx = 1$$

for any probability density function. So

$$k \int_{-\infty}^{\infty} e^{-x^2/2} dx = 1.$$

If we do that integral, one over it will be k . This isn’t the easiest integral in the world to do; there’s a famous trick: square it and transform coordinates, but we won’t have time to do this. Instead, the answer is, believe it or not, $\int_{-\infty}^{\infty} e^{-x^2/2} dx = \sqrt{2\pi}$!

So the standard normal density is

$$f(x) = \frac{1}{\sqrt{2\pi}} e^{-x^2/2}.$$

The general normal is

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

which has two parameters μ and σ .

For any continuous variable, the expected value is $EX = \int_{-\infty}^{\infty} xf(x)dx$, which is just the continuous version of the formula we had before for discrete variables. Let’s write the mean of the standard normal:

$$EX = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} xe^{-x^2/2} dx.$$

Simplest thing to do here is notice the thing you’re integrating is symmetric, with as much below 0 as above it. Each half can be integrated, but they’ll cancel out and leave 0. We

don't care what the integral of each half is, but it's important that the integral be possible; there are symmetric variables with perfectly nice densities that don't work in this integral.

We're going to need an important idea, that of *hazard*. Suppose some event is supposed to happen, and we want to study the waiting time T for it. Take $T \geq 0$. The hazard $\lambda(t)$ is the chance per unit time the event is about to happen, if it hasn't happened yet. Formally:

$$\lambda(t) = \frac{P(T \in (t, t + dt])}{dtP(T > t)}.$$

This is commonly discussed for nonnegative waiting time random variables. What does this even mean? First, $P(T > t) = 1 - F(t)$ with F as the CDF. The quantity $P(T \in (t, t + dt]) = F(t + dt) - F(t) \approx f(t)dt$. So we could write this definition as

$$\lambda(t) = \frac{f(t)}{1 - F(t)}.$$

2 The Exponential Distribution

Let's think about it. What if λ is constant? A fixed hazard, unchanging in time. Then just from the definition, we would have

$$\lambda = \frac{f(t)}{1 - F(t)}.$$

So

$$\lambda(1 - F(t)) = \frac{dF}{dt}.$$

We could express this in terms of the *survival function*, the chance the event hasn't happened yet: $P(T > t) = S(t) = 1 - F(t)$. So

$$\lambda S(t) = -\frac{dS}{dt}.$$

or

$$\frac{dS}{dt} = -\lambda S(t).$$

Let's solve this:

$$\frac{dS}{S} = -\lambda dt$$

Integrate both sides:

$$\int_{t=0}^{t_1} \frac{dS}{S} = \int_{t=0}^{t_1} (-\lambda dt)$$

$$\log(S(t_1)/S(0)) = -\lambda t_1$$

$$S(t_1)/S(0) = e^{-\lambda t_1}$$

By definition, $S(0) = 1$; at the beginning, it hasn't happened. So

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

and

$$F(t) = 1 - e^{-\lambda t}.$$

with

$$f(t) = \frac{dF}{dt} = \lambda e^{-\lambda t}.$$

This distribution is called the *exponential* distribution. A random variable representing a waiting time with constant hazard is called an exponential distribution.

Exercise 3. Let T be an exponential waiting time variable with hazard λ . Show that

$$ET = \int_0^\infty t \lambda e^{-\lambda t} = \frac{1}{\lambda}.$$

■

Suppose T is an exponential waiting time with hazard λ . Suppose that we are at time t_0 and it hasn't happened; what is the distribution of the amount of future time to wait given it hasn't happened by time t_0 ? We need the conditional distribution of $T - t_0$ given $T > t_0$. Let's compute it by finding its survival function as a function of say u :

$$P(T - t_0 > u | T > t_0) = \frac{P(T - t_0 > u)}{S(t_0)}.$$

But $P(T - t_0 > u) = P(T > t_0 + u) = S(t_0 + u)$. The survival function of an exponential is just exponential, so

$$P(T - t_0 > u | T > t_0) = \frac{S(t_0 + u)}{S(t_0)} = \frac{e^{-\lambda(t_0 + u)}}{e^{-\lambda t_0}} = e^{-\lambda u}.$$

That's the survival function of an exponential with hazard λ ; the conditional distribution of how much longer there is to wait is always the same, no matter how long you've waited! This property is called *memorylessness* and you've seen it with the geometric. Now you know the exponential is memoryless also. It is a lot harder to prove, but it turns out the ONLY (absolutely) continuous memoryless distribution is the exponential.

Here is another nice fact about the exponential. Let T_1 and T_2 be independent exponential waiting times, with hazards λ and μ respectively. Let T be the smaller of the two; $T = T_1 \wedge T_2 = \min(T_1, T_2)$. Let's get the distribution of T . Looking at the survival function:

$$P(T > t_0) = P(T_1 \wedge T_2 > t_0) = P(T_1 > t_0 \text{ and } T_2 > t_0).$$

Look closely: the event that the smaller of T_1 and T_2 is greater than some time t_0 is *exactly the same event* as both $T_1 > t_0$ and $T_2 > t_0$. So the same event has the same probability. Now, though, we invoke independence:

$$P(T > t_0) = P(T_1 > t_0 \text{ and } T_2 > t_0) = P(T_1 > t_0)P(T_2 > t_0) = e^{-\lambda t_0} e^{-\mu t_0}.$$

Then,

$$P(T > t_0) = e^{-\lambda t_0} e^{-\mu t_0} = e^{-(\lambda + \mu)t_0}.$$

That is the survival function of an exponential with hazard $\lambda + \mu$. *The minimum of two independent exponentials is itself exponential, with hazard given by the sum of the two independent hazards.* This works in fact for any number of independent exponentials.

Let's do one more quick thing. Imagine a constant hazard, and look at tiny time steps. Let's specifically pick a time t ; divide the time from 0 to t into N steps, and make N big. Each tiny step of length t/N is going to be thought of as a Bernoulli trial; with hazard λ we

can write $p_N = \lambda t/N$, where here we put a subscript N on the p to remind us. Geometrically, the chance the event hasn't happened yet by time t is just

$$(1 - p_N)^N$$

or

$$(1 - \lambda t/N)^N.$$

Here, let's take the limit as $N \rightarrow \infty$.

$$L = \lim_{N \rightarrow \infty} (1 - \lambda t/N)^N.$$

Write

$$\log(L) = \log \left(\lim_{N \rightarrow \infty} (1 - \lambda t/N)^N \right).$$

Now, $\log$ is continuous:

$$\log(L) = \log \lim_{N \rightarrow \infty} \log(1 - \lambda t/N)^N$$

$$\log(L) = \log \lim_{N \rightarrow \infty} N \log(1 - \lambda t/N)$$

Transform to $w = 1/N$:

$$\log(L) = \log \lim_{w \rightarrow 0} \frac{\log(1 - \lambda w t)}{w}$$

This is indeterminate form $0/0$, so Prof. L'Hopital will come help us out:

$$\log(L) = \log \lim_{w \rightarrow 0} \frac{1/(1 - \lambda w t) \cdot (-\lambda t)}{1} = -\lambda t$$

Then of course,

$$L = e^{-\lambda t}$$

and this is the survival function of the exponential. So you can think of an exponential as a limit of a geometric where you have more and more tiny little Bernoulli trials; as you make the number of trials go up, the success per trial goes down proportionally. It is the same limit we took for the Poisson.

3 Modeling with The Exponential Distribution

3.1 Decay

Imagine there are N individuals in a population, and each has hazard of dying in the next dt given by λ .

We can model this probabilistically, and think of N as a random variable evolving in time. Death occurs randomly, and so we have a fluctuating random quantity. Or we can model this deterministically. Let's do the latter first.

Suppose we just think of death happening independently. Then we have N independent Bernoulli trials, each with success probability λdt . We therefore expect $N\lambda dt$ deaths each dt . Let's then model this by writing

$$N(t + dt) = N(t) - N(t)\lambda dt.$$

Rearranging,

$$\frac{N(t + dt) - N(t)}{dt} = -\lambda N(t)$$

and so taking $dt \rightarrow 0$:

$$\frac{dN}{dt} = -\lambda N(t)$$

Here, we can solve as before and find $N(t) = N(0)e^{-\lambda t}$, exponential decay.

Exercise 4. Suppose the hazard of mortality is 1 per week. What is the fraction living after 1/2 week? 1 week? 2 weeks? What is the half-life (time till mortality reaches 50%)? ■

3.2 Branches

Now, suppose we have N individuals, and two independent causes of death. Each has hazard λ and μ , say. We already know that the removal from the living state is going to be exponential, with hazard $\lambda + \mu$. We can accumulate the number of deaths of type 1 in Z_1 and of type 2 in Z_2 .

$$N(t + dt) = N(t) - (\lambda + \mu)Ndt.$$

But

$$Z_1(t + dt) = Z_1(t) + \lambda N dt.$$

Why? The chance of death during time dt , for any person, due to cause 1, is λdt . So the expected number of deaths due to cause 1 is $\lambda N dt$. In fact it is just that simple.

We could ponder this another moment. We could reason: the chance of death is actually

$$1 - (1 - \lambda dt)(1 - \mu dt) = 1 - (1 - \lambda dt - \mu dt + \lambda\mu(dt)^2) = \lambda dt + \mu dt - \lambda\mu(dt)^2$$

which is $(\lambda + \mu)dt$ to first order.

Similarly,

$$Z_2(t + dt) = Z_2(t) + \mu N dt.$$

These become

$$\frac{dN}{dt} = -(\lambda + \mu)N$$

and

$$\begin{aligned}\frac{dZ_1}{dt} &= \lambda N \\ \frac{dZ_2}{dt} &= \mu N\end{aligned}$$

Here, $N = N_0 e^{-(\lambda+\mu)t}$. At the end of time, nobody's left. Then,

$$dZ_1 = \lambda N dt = \lambda N_0 e^{-(\lambda+\mu)t} dt$$

Integrating,

$$Z_1(\infty) - Z_1(0) = \lambda N_0 \int_0^\infty e^{-(\lambda+\mu)t} dt$$

Here $Z_1(0) = 0$.

$$Z_1(\infty) = \lambda N_0 \frac{-1}{\lambda + \mu} (0 - 1) = N_0 \frac{\lambda}{\lambda + \mu}.$$

So at the end, the causes of death accumulate cases proportional to the hazard ratio. The one with twice the hazard gets twice the deaths.

Exercise 5. Suppose juveniles mature at rate γ , and have mortality rate μ in the juvenile state. What is the fraction of creatures that die in the juvenile state? ■

3.3 Loops

3.4 Chains

Exercise 6. How long did this assignment take you? ■