Delay equations in biology

I start with a very elementary example:

$$\frac{dx}{dt} = rx(t)(1 - x(t-\tau)) \tag{1}$$

which is a growth model in which the saturation effect is delayed. You can think of it as follows. Cella are born but don't consume resources until they reach a certain age. So, our question is what happens? A simple integration of this equation with $x(0) = .1$, $r = 2, \tau = 1$ and $x(t) = 0, t \in [-1, 0)$ shows nice oscillations. How does this happen?

An Aside Here is the XPP code for the above delay equation:

```
x'=r*x*(1-delay(x,tau))
par r=2,tau=1
init x=0.1
@ delay=5
done
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Curiously, most courses in dynamics never cover delay equations which have a rather rich behavior. Philosophically, I have always thought delay equations arise as a simplification that is due to our ignorance of what is physically going on during the delay period. However, they are convenient to use and generally provide a nice mechanism for oscillatory behavior.

There are two fixed points to this equation, $x^* = 1, x^* = 0$. We'd like to look at the stability of these. The linearized equation is

$$\frac{dy}{dt} = ry(1 - x^*) - rx^* y(t - \tau).$$

At $x^* = 0$, this is just

$$y' = ry$$

which is unstable since $r > 0$. However, at $x^* = 1$, we obtain

$$y'(t) = -ry(t - \tau).$$

As usual, we look for solutions of the form, $y(t) = \exp(\lambda t)$ leading to the equation

$$\lambda = -re^{-\lambda\tau}.$$

A simple graphical plot reveals that there are no real roots to this equation. Heowever, there can be infinitely ,many complex roots. Thus, we have to establish when their real parts are negative. Let $\nu = \lambda\tau$ and replace r by $R = r\tau$ so that this equation can be written as

$$\nu e^{\nu} + R = 0. \tag{2}$$

Clearly, if the real part of ν is positive, then so is that of λ since $\tau > 0$. Equations like this have been studied by many and there are a large number of specific results for them. Let's see if we can find a pure imaginary root. For if this is the case, then we expect that small changes in R will move the root onto one side or the other of the imaginary axis and we will get instability. Let $\nu = i\omega$. This leads to a pair of equations

$$\begin{aligned} \omega \sin \omega &= R \\ \omega \cos \omega &= 0 \end{aligned}$$

The second of these has infinitely many such roots, the first (nontrivial) of which is $\pi/2$. This gives a value of $R = \pi/2$. Thus, if $r = 2$, then we expect an instability at around $\pi/4 \approx 0.78$. If you numerically integrate the equations with $\tau = 0.8$ and $r = 2$, you find a nice periodic orbit with period 3.31. The analysis predicts a period of around π which is pretty good. (Why does it predict a period of π?)

This is rather handwavy in that we haven't really proven that there is instability as we change R. For this we appeal to the following theorem:

THEOREM 1(Hayes) *All the roots of $pe^z + q - ze^z = 0$ where p and q are real have negative real parts if and only if*

(a) $p < 1$, *and*

(b) $p < -q < \sqrt{a_1^2 + p^2}$

where a_1 is a root of $a = p \tan a$ such that $0 < a < \pi$. If $p = 0$, we take $a_1 = \pi/2$.

Applying this theorem to our equation (2), we see that we must have $r\tau < \pi/2$ for stability. Thus, the critical value of the delay is $\pi/(2r)$. The Hopf bifurcation theorem allows one to show that near the onset of instability, there will be small amplitude periodic solutions for the delay equation.

There are other theorems which we can use, but they are complicated and as with most delay equations, apply only to special cases. Instead, I will describe a nice geometric method for determining when it is possible the destabilize a rest state *by increasing the delay.* When there is a single delay, the exponential polynomial we obtain has the form:

$$H(\lambda) = P(\lambda) + Q(\lambda)e^{-\lambda\tau}. \tag{3}$$

We first state a theorem on absolute stability.

THEOREM 2(Brauer, JDiff Eq 69:185-191,1987) *Suppose that*

1. $P(\lambda) \neq 0$ *for* $\Re\lambda \geq 0$,
2. P, Q *are real polynomials,*
3. $|Q(i\omega)| < |P(i\omega)|$ *for all* $\omega \neq 0$,

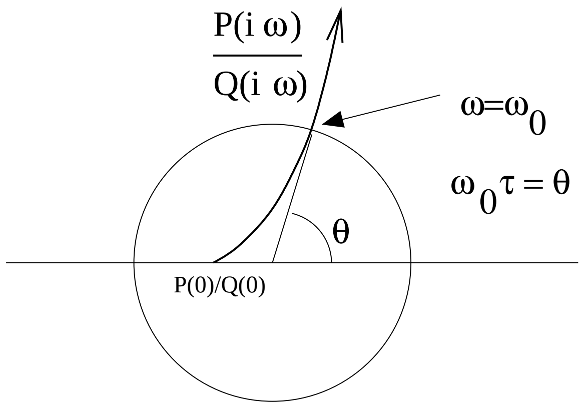

Figure 1: Illustration of delay destabilization

4.

$$\lim_{|\lambda|\to\infty, \Re\lambda>0} \left|\frac{Q(\lambda)}{P(\lambda)}\right| = 0$$

Then all the roots of $H(\lambda) = 0$ have strictly negative real parts.

This theorem gives conditions guaranteeing that delays cannot destabilize a system. We now illustrate a way to see when they do. That is, suppose we introduce a delay into a system. Then under what circumstances can this lead to instability when in absence of delay, there was no instability.

We wish to see when roots to $H(z) = 0$ cross the imaginary axis as the delay varies. To obtain this, we make the following observation. If they cross the imaginary axis, then there must be a root to $H(i\omega) = 0$.. We can rewrite this as

$$e^{-i\omega\tau} = \frac{P(i\omega)}{Q(i\omega)} \equiv M(i\omega).$$

As ω moves negatively, the left hand side simply tracks the unit circle moving in a counterclockwise manner. The right-hand side plots out a curve in the complex plane. Typically, the polynomial, P has higher degree than Q so that for ω large in magnitude, $M(i\omega)$ will lie outside the unit circle. Suppose that $|P(0)/Q(0)| < 1$. Then for small ω M lies inside the unit circle and thus as ω gets big, M will cross the unit circle (as long as P has no imaginary roots). Thus, there is a particular value of ω, ω_0 for which $M(-i\omega_0)$ lies on the unit circle. Suppose this happens at angle θ. Then, we obtain the critical value of the delay,

$$\tau\omega_0 = \theta$$

and have shown delay-induced instability. For the logistic model, this is trivial. M tracks up the imaginary axis, crossing at $\theta = \pi/2$ which is exactly what we found before.

I turn now to a somewhat odd example. This is a partial differential equation with "age structuring." Age structured models arise in many systems where one wants to track the number of organisms at a certain age. I am going to present a simple model that has some cool behavior. Basically, the idea in this very simple model is that all ages can reproduce but at a rate depending on the resourses. The resources are used only by those organisms older than a certain age. I will first derive a discrete age model and proceed to the formal continuum limit. Let $u(a,t)$ be the population of organisms at age, a. Then

$$\frac{du(a,t)}{dt} = -\mu u(a,t) + g[(u(a-\delta a,t) - u(a,t))]/\delta a$$

The first term on the right is the intrinsic death rate. The second term is the growth of organisms at age $a - \delta a$ to organisms of age a, and the last term is the growth of age a to age $a + \delta a$. We will assume infinite age to avaoid a condition at large ages. The one question that comes to mind is what happens at $a = \delta a$. Then we have $u(0,t)$ as the incoming population. This is precisely where the births come in. Proceeding to the continuum limit, we obtain the partial differential equation

$$u_t(a,t) + u_a(a,t) + u(a,t) = 0$$

where we have rescaled time and age to eliminate g, μ. Don't despair if you haven't seen a PDE. This one is very simple to solve for our purposes. We need a condition at $a = 0$ to account for births:

$$u(0,t) = B(t)$$

where $B(t)$ is the births that come into the system. For example, suppose B is just a constant. Then we can look for a time-independent solution, $u(a,t) = U(a)$ representing the steady state. This leads to the ODE:

$$U_a + U = 0 \qquad U(0) = B$$

which has the nice solution, $U(a) = Be^{-a}$. Thus, there are lots of babies and not many old folks. Suppose now that the births depend on the total population over some minimal age. That is,

$$B(t) = r \int_M^\infty u(a,t)\ da.$$

Again we look for stationary solutions. We find that $U(a) = Ce^{-a}$. as before. However, we must have

$$U(0) = C = r \int_M^\infty Ce^{-a}\ ds = rCe^{-M}$$

which has only $C = 0$ as a solution or C is arbitrary if we pick $re^{-M} = 1$. Thus, there are essentially no nontrivial stationary solutions to this problem. Suppose that anyone can reproduce but at a rate dependent on the resources and these are limited by the adults only. This leads ot

$$B(t) = r\int_0^\infty u(a,t)\ da\left(1 - \int_A^\infty u(a,t)\ da\right).$$

This is like the delay model we examined above. We will solve this and also study the stability of the stationary solution. We are interested in whether delaying the consumption can cause instability. It makes sense – if we delay the consumption, then lots of offspring can occur which grow older and grab everything causing a lowering of the birth rate and a return of the resources. As above, lets look for a stationary solution, $u(a,t) = U(a)$. We see that

$$U_a + U = 0$$

which has a solution, $U(a) = Ce^{-a}$. We must then have:

$$U(0) = C = r\int_0^\infty Ce^{-a}\ da\left(1 - \int_A^\infty Ce^{-a}\ da\right)$$

which implies

$$C = rC(1 - Ce^{-A}).$$

$C = 0$ is the trivial solution and $C = e^A(1 - 1/r)$. Some things are clear from this. First, $r > 1$ is necessary for positive solutions. Second, the longer you delay consumption, the larger the population. (The lesson is that to keep the population down, give your kids whatever they want!) Now we want to analyze the stability of this system. We let $u(a,t) = U(a) + v(a,t)$ where v is a small perturbation Substitution into the full equation and using the fact that $U_a + U = 0$, we get

$$v_t + v_a + v = 0$$

and

$$v(0,t) = \int_0^\infty v(a,t)\ da[r(1 - Ce^{-A})] - \int_A^\infty v(a,t)\ darC.$$

Making use of the fact that $r(1 - Ce^{-A}) = 1$ and the definition of C, we obtain

$$v(0,t) = \int_0^\infty v(a,t)\ da - \int_A^\infty v(a,t)\ dae^A(r-1).$$

Since the whole thing is time independent, we look for solutions of the form, $v(a,t) = e^{\lambda t}w(a)$ with $w(a)$ integrable over the whole line. If $\Re\lambda > 0$ for some solution to this, then $U(a)$ is unstable. Plugging this in, we get

$$\lambda w + w_a + w = 0$$

which has a solution, $w(a) = w(0)e^{-(\lambda+1)a}$. Applying this to the boundary condition, we get

$$w(0) = \frac{w(0)}{\lambda+1} - \frac{w(0)e^{-(\lambda+1)A}}{\lambda+1}e^A(r-1).$$

Dividing by $w(0)$ (which can't be zero, otherwise it is not an eigenfunction) and multiplying by $\lambda + 1$ (which cannot be zero for otherwise, w is not integrable), we simplify this to

$$\lambda = -(r-1)e^{-\lambda A}.$$

Finally, multiplying by A and letting $z = A\lambda$, we get

$$A(1-r) - ze^z = 0$$

which is covered by the Theorem 1 and implies ($p = 0$, so $a_1 = \pi/2$ and $q = A(1-r)$) that for stability,

$$1 < r < 1 + \frac{\pi}{2A}.$$

Homework

1. See how far along you can get in the analysis of the stability and fixed points of the famous Mackey-Glass equation. I have chosen parameters so that the fixed points are easy to find:

$$\frac{dx}{dt} = -x(t)/2 + \frac{1}{1 + x(t-\tau)^k}$$

   where $k > 0, \tau \geq 0$ are the two parameters. In particular, find conditions on p guaranteeing that there are delay induced instabilities. Use Theorem 2 to find conditions on p such that the fixed point is always stable.

2. Study the stability of the origin for the delayed neural network model

$$\frac{du}{dt} = -u(t) + \tanh(\alpha u(t) - \beta u(t-\tau))$$

   All parameters are positive. The derivative of tanh at the origin is 1.