Cell Population Dynamics – Lecture Notes

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February 9, 2021

Chapter - Delay differential equations

Models of self-regulating systems often include discrete delays in the feedback loop to account for the finite time required to perform essential steps before the loop is closed. Such mathematical simplifications are especially welcome in biological applications, where knowledge about the loop steps is usually sparse. This includes maturation and growth times needed to reach reproductive age in a population [1,2], signal propagation along neuronal axons [3], and post-translational protein modifications [4,5]. Introduction of a discrete delay in an ordinary differential equation can destabilize steady states and generate complex dynamics, from limit cycles to chaos [6]. Although the linear stability properties of scalar equations with single discrete delays are fairly well characterized, lumping intermediate steps into a delayed term can produce broad and atypical delay distributions that deviate from discrete delays, and it is still not clear how that affects the stability of the equation [7].

The delayed feedback differential equation of the form

$$\dot{x} = F\Big(x, \int_0^\infty x(t-s)\,d\eta(s)\Big)$$

is a model paradigm in biology and physics [5,8–12]. The first argument of F is the instantaneous part of the loop and the second one, the delayed or retarded part, which closes the feedback loop. The function η is a cumulative probability distribution function, it can be continuous, discrete, or a mixture of continuous and discrete elements. In most cases, the stability of the above equation is related to its linearized equation about one of its steady states $\bar{x}$,

$$\dot{x} = -ax - b\int_0^\infty x(t-s)\,d\eta(s) \tag{1}$$

where the constants a and $b \in \mathbb{R}$ are the negatives of the derivatives of the instantaneous and the delayed parts of F at $x = \bar{x}$,

$$a = -\frac{\partial}{\partial x}F(x,y)\Big|_{x=y=\bar{x}} \quad \text{and} \quad b = -\frac{\partial}{\partial y}F(x,y)\Big|_{x=y=\bar{x}}.$$

Let B be the vector space of continuous and bounded functions on $[-\infty, 0] \to \mathbb{R}$. With the norm $||\phi|| = \sup_{\theta\in[-\infty,0]} |\phi(\theta)|$, $\phi \in B$, B is a Banach space.

Consider the linear retarded functional differential equation

$$\dot{x} = -ax - b\int_0^\infty x(t-s)\,d\eta(s) \tag{2}$$

with real constants a and b. We assume that η is a cumulative probability distribution function: $\eta : [0,\infty) \to [0,1]$ is monotone nondecreasing, right-continuous, $\eta(s) = 0$ for $s < 0$ and $\eta(+\infty) = 1$. The corresponding probability density functional $f(s)$ is given by the generalized derivative $d\eta(s) = f(s)ds$. The following definitions and Theorem follow from Stépán [13].

Solution The function $x : \mathbb{R} \to \mathbb{R}$ is a solution of equation (2) with the initial condition

$$x_\sigma = \phi,\ \sigma \in \mathbb{R},\ \phi \in B, \tag{3}$$

if there exists a scalar $\delta > 0$ such that $x_t \equiv x(t+\theta) \in B$ for $\theta \in [-\infty, 0]$ and x satisfies Eqs. (2) and (3) for all $t \in [\sigma, \sigma+\delta)$.

The notation $x_t(\sigma,\phi)$ is also used to refer to the solution of equation (2) associated with the initial conditions σ and ϕ.

Stability The trivial solution $x = 0$ of equation (2) is stable if for every $\sigma \in \mathbb{R}$ and $\varepsilon > 0$ there exists $\delta = \delta(\varepsilon)$ such that $||x_t(\sigma,\phi)|| < \epsilon$ for any $t \geq \sigma$ and for any function $\phi \in B$ satisfying $||\phi|| < \delta$. The trivial solution $x = 0$ is called asymptotically stable if it is stable, and for every $\sigma \in \mathbb{R}$ there exists $\Delta = \Delta(\sigma)$ such that $\lim_{t\to\infty} ||x_t(\sigma,\phi)|| = 0$ for any $\phi \in B$ satisfying $||\phi|| < \Delta$.

Characteristic equation The function $D : \mathbb{C} \to \mathbb{C}$ given by

$$D(\lambda) = \lambda + a + b\int_0^\infty e^{-\lambda s} d\eta(s),$$

is called the characteristic function of the linear equation (2). The equation $D(\lambda) = 0$ is called the characteristic equation of (2).

The following theorem [13,14] gives a necessary and sufficient condition for the (linear) asymptotic stability of $x = 0$.

Theorem Suppose that there exists $\nu > 0$ such that the following inequality is satisfied:

$$\int_0^\infty e^{\nu s} d\eta(s) < \infty. \tag{4}$$

The solution $x = 0$ of equation (2) is (exponentially) asymptotically stable if and only if all roots of the characteristic equation $D(\lambda) = 0$ have $\Re(\lambda) < 0$.

In particular, when the delay is bounded, i.e. when there is $h > 0$ such that $d\eta(s) = 0$ for all $s > h$, the condition is satisfied, and asymptotic stability is determined by the characteristic equation.

Discrete Delay Differential Equations

When η represents a single discrete delay (η a heaviside function), the asymptotic stability of the zero solution of equation (2) is fully determined by the following theorem, originally due to Hayes [15]. Let $\eta(s) = \mathbb{1}_{[\tau,+\infty)}$, for a constant $\tau > 0$ then equation (2) simplifies to

$$\dot{x} = -ax - bx(t-\tau). \tag{5}$$

Stability of the scalar linear equation with a discrete delay

The generalised differential of η is a Dirac mass centered at τ: $d\eta(s) = \delta(s-\tau)ds$.

Theorem (Hayes) Let the delay probability density be $f(s) = \delta(s-\tau)$, a Dirac mass at τ. The zero solution of equation (2) is asymptotically stable if and only if $a > -b$ and $a \geq |b|$, or if $b > |a|$ and

$$\tau < \frac{\arccos(-a/b)}{\sqrt{b^2 - a^2}}.$$

More generally, the following statements always hold for any delay distribution:

(i) When $a \leq -b$, the characteristic equation of equation (2) has a positive real root.

(ii) When $a \geq |b|$ and $a > -b$, the characteristic equation of equation (2) has no root with positive real part.

Proof. The delay τ being bounded, we can use the characteristic equation to study the asymptotic stability of equations (5). This means that we are looking for exponential solutions, just as in the case of ordinary differential equations. Assume there is a solution $x(t) = \exp(\lambda t)$, for some complex value λ. Then, the characteristic equation is

$$\begin{aligned} \dot{x} = \lambda x(t) &= -ax(t) - bx(t-\tau), \\ \lambda e^{\lambda t} &= -ae^{\lambda t} - be^{\lambda(t-\tau)}, \\ \lambda &= -a - be^{-\lambda\tau}. \end{aligned}$$

The characteristic equation is trancendental, and possesses an infinity of roots for $\tau > 0$, always in pair of complex conjugates. When $\tau = 0$, there is a single root located at $\lambda = -a - b$. This root is negative when $a > -b$, zero when $a = -b$ and positive when $a < -b$. By continuity of the characteristic equation in τ, roots cannot appear in the right-half complex plane. Roots $\lambda = \mu + i\omega$ must be located on the following curve (figure 1),

$$\omega = \pm\sqrt{b^2 e^{-2\mu\tau} - (\mu + a)^2}.$$

When τ is continuously increased from zero, the only way stability can change is when roots cross the imaginary axis, i.e. when $\Re(\lambda) = 0$.

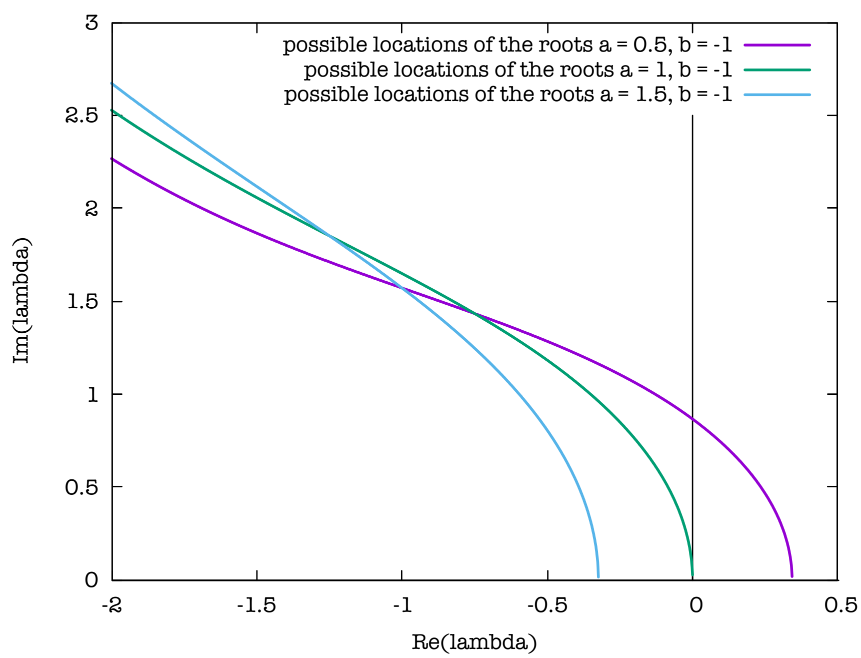

Figure 1: Possible locations of the roots of the characteristic equations, for $a = 0.5, 1.0, and 1.5$, and $b = -1$.

For $a = -b$, the dominant root $\lambda = 0$ for all $\tau \geq 0$. For $a < -b$, there exists a positive root $\lambda > 0$ for all $\tau \geq 0$. For $a > -b$ and τ sufficiently small, all roots have negative real parts. If there is a critical value τ^* such that a pair of roots crosses the imaginary axis, then the delay can destabilise the equilibirum. We obtain , after setting $\lambda = i\omega$, and separating the real and imaginary parts of the characteristic equation,

$$
\begin{aligned}
a + b\cos(\omega\tau) &= 0, \\
\omega - b\sin(\omega\tau) &= 0.
\end{aligned}
$$

The equations can be solved for ω by summing up the squares for get rid of the trigonometric functions. Therefore, there is a pair of imaginary roots when

$$
\tau = \tau^* = \frac{\arccos(-a/b)}{\omega},
$$

where $\omega = \sqrt{b^2 - a^2}$. To finish the proof, it remains to show that the pair of imaginary roots becomes, and stay positive, when $\tau > \tau^*$. To do that, we need to check that the derivative $d\Re(\lambda)/d\tau$ is always positive at $\lambda = \pm i\omega$. The derivative of λ wrt to τ is obtained implicitly by differentiating the characteristic equation. Let $\lambda' = d\lambda/d\tau$, we have

$$
\lambda' + be^{-\lambda\tau}\Big(-\tau\lambda' - \lambda\Big) = 0.
$$

At an imaginary root, $i\omega + a + be^{-i\omega\tau} = 0$, so

$$
\lambda'\Big(1 + \tau a + i\omega\tau\Big) = i\omega\big(-a - i\omega\big).
$$

It follows that

$$
\begin{aligned}
\lambda' &= \frac{i\omega\big(-a - i\omega\big)}{\Big(1 + \tau a + i\omega\tau\Big)}, \\
&= \frac{\big(-ia\omega + \omega^2\big)\big(1 + \tau a - i\omega\tau\big)}{(1 + \tau a)^2 + \omega^2\tau^2}, \\
&= \frac{\omega^2 - i\big(a\omega + a^2\tau\omega + \omega^3\big)}{(1 + \tau a)^2 + \omega^2\tau^2}.
\end{aligned}
$$

The real part of the derivative is strictly positive, since $\omega^2 = b^2 - a^2$. This completes the proof.

Note When τ increases further, there will be several other pairs of root crossing to the right half-complex plane. None of these roots can cross back to the left half-plane. Another way to look a the stability of equation 5 is by fixing the value of τ and finding the region of stability in the (a, b)-plane. This is called a **stability chart** (figure 2). The characteristic equation can be solved parametrically for a and b:

$$
\begin{aligned}
b(\omega) &= \frac{\omega}{\sin(\omega\tau}, \\
a(\omega) &= -\omega\frac{\cos(\omega\tau)}{\sin(\omega\tau)}.
\end{aligned}
$$

The parameters have a periodic denominator. The zeros of the denominator delimit branches of the parametric curve (a, b). Only branches with $b > 0$ are relevant here, and these branches are well-ordered. The first branch corresponds to the interval $\omega \in [0, \pi/\tau)$, and this is the branch that determines the boundary of stability (figure 2, *dashed curve*).

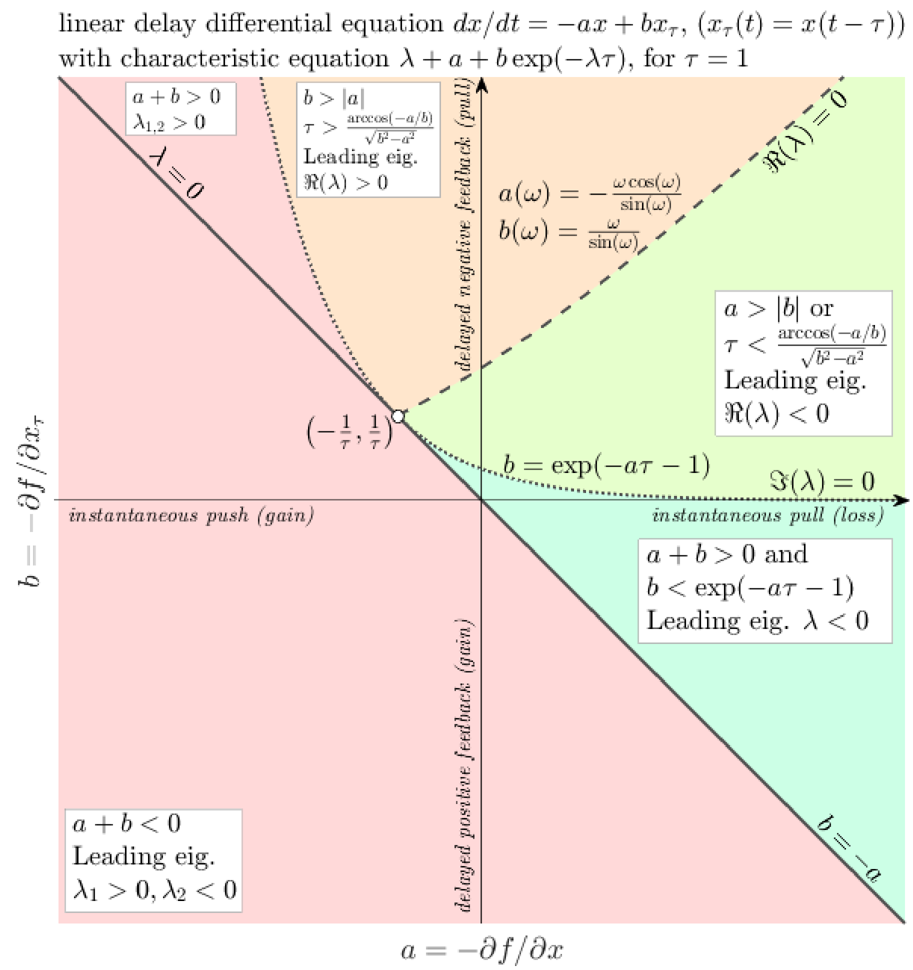

Figure 2: Stability chart for the scalar linear equation with a discrete delay.

Systems with a Discrete Delay

Differential equations often come as a system of equations on the state vector $X \in \mathbb{R}^n$. If we assume that there is a single discrete delay, the system can be expressed as

$$\dot{X}(t) = F\Big(X(t), X(t-\tau)\Big).$$

The linear stability analysis around a steady state $\bar{X}$ follow the same lines as above. Linearisation is performed given that now F is a function from $\mathbb{R}^{2n} \to \mathbb{R}^n$, accounting for the retarded arguments. The linearised system will therefore take the form

$$\frac{dX}{dt} = D_X F(X,Y)\big|_{X=Y=\bar{X}} X + D_Y F(X,Y)\big|_{X=Y=\bar{X}} X(t-\tau) \tag{6}$$

where the matrices $D_X F$ and $D_Y F$ are the Jacobian matrices with respect to the instantaneous and delayed arguments, respectively. Call the Jacobian matrices $A = D_X F(X,Y)\big|_{X=Y=\bar{X}}$ and $B = D_Y F(X,Y)\big|_{X=Y=\bar{X}}$. The characteristic equation is obtained by letting $X = X_0 e^{\lambda t}$, for some vector $X_0 \in \mathbb{R}^n$,

$$\frac{dX}{dt} = \lambda e^{\lambda t} X_0 = e^{\lambda t} A X_0 + e^{\lambda(t-\tau)} B X_0, \tag{7}$$

The exponential terms cancel out, leaving the eigenvalue problem

$$\lambda X_0 = \Big(A + e^{-\lambda\tau} B\Big) X_0. \tag{8}$$

The characteristic equation now reads $D(\lambda) = \det\Big(A + e^{-\lambda\tau} B - \lambda I\Big) = 0$. The determinant has the form of a *quasi-polynomial* $P(\lambda) + Q(\lambda)e^{-\lambda\tau}$), where P and Q are polynomials, with the degree of P equal to n and the degree of Q strictly less than n. For $n = 1$, with the notation of the previous section, we have $P(\lambda) = \lambda + a$ and $Q(\lambda) = b$.

Stability analysis for systems is not as straightforward as in the scalar case. The delay still has an important role in the location of the roots of the characteristic equation, but now roots can cross the imaginary axis either way, making it difficult to count the number of roots with positive real parts. Particular cases can often be treated though.

Examples

Mackey-Glass Equation

The Mackey-Glass equation is a classic delay equation, originally developed to account for the seemingly choatic dynamics in white blood cell numbers in some leukemia patients. The equation for the total white blood cell count (in cells/L blood) is

$$\frac{dx}{dt} = f_0 \frac{x(t-\tau)}{1 + x^h(t-\tau)} - \gamma x. \tag{9}$$

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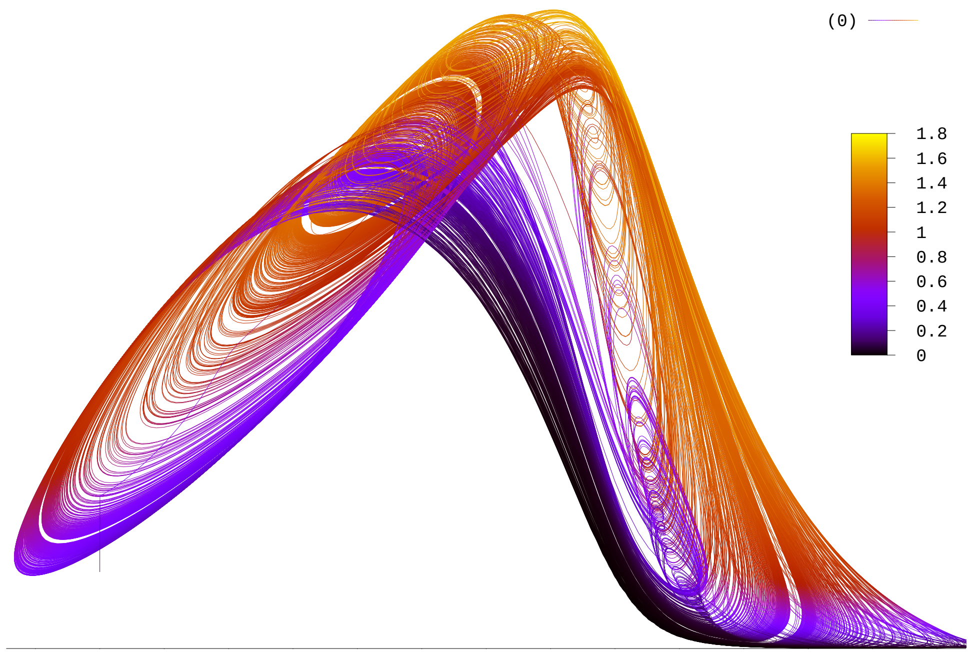

Figure 3: Mackey-Glass equation.

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