

Lecture 2: Differential-Delay equations.

D. Gurarie

A differential equation, or system: $y' = f(y, t); y(t_0) = y_0$, predicts a (near) future state of the system: $y(t_0 + dt) \approx y_0 + f(y_0, t_0)dt$, from its current state, and thus carries no 'past memory'. This approach is suitable for many mechanical systems, based on Newton's law: the current state (position + velocity) determines its future dynamics.

But in many biological systems reaction does not come as immediate response to stimulation. It often appears with certain time-lags, so such systems are capable to accumulate past memory.

Mathematically we can include time-lag, e.g. T in the model, via *differential-delay* equation:

$$y'(t) = f(y(t), y(t-T), t, \dots) \quad (1)$$

Such equation typically exhibit more complicated dynamic patterns, compared to their DE counterparts.

Linear differential-delay equations

The simplest 1st order linear *differential-delay* equation (DDE)

$$y'(t) + ry(t-T) + by(t) = \dots \quad (2)$$

can be solved by the method of *characteristic polynomial*, same way as all linear DEs (1-st or higher order) with constant coefficients. Indeed, any linear DE, given by differential operator

$$L = D^n + a_1 D^{n-1} + \dots + a_n,$$

$$L[y] = y^{(n)} + a_1 y^{(n-1)} + \dots + a_n y = 0$$

has exponential solutions $\{e^{\lambda t}\}$, whose exponent λ solves *characteristic equation*:

$$p(\lambda) = \lambda^n + a_1 \lambda^{n-1} + \dots + a_n = 0$$

So an n -th order DE has at most n real (or complex) exponential solutions, and its general

solution is a linear combination of those: $y(t) = \sum_k C_k e^{\lambda_k t}$.

Typical examples are

- (i) linear growth/decay: $y' + ay = 0$, with $y(t) = Ce^{-at}$, or
- (ii) linear oscillator: $\ddot{x} + b\dot{x} + \frac{k}{m}x = 0$, with quadratic $p(\lambda)$, and complex roots

$$\lambda = -\alpha \pm i\omega; \quad \alpha = -b/2 - \text{damping rate}; \quad \omega = \sqrt{k/m - b^2/4} - \text{frequency}$$

$$y(t) = \{e^{\lambda t}\}, \text{ or } e^{-\alpha t} (C_1 \cos \omega t + C_2 \sin \omega t)$$

- damped oscillation.

Applying this method to DDE (2), we get solution $y(t) = e^{\lambda t}$, where λ obeys a transcendental equation

$$\boxed{\lambda + re^{-T\lambda} + b = 0} \tag{3}$$

Unlike 1-st order DE such equation will typically have (infinitely) many real and complex solutions. In that sense a DDE (even first order) is an ‘infinite dimensional system’, unlike n-th order DE (n-dimensional system).

Solutions of (3) are given by a generalized ‘log- function’, called *Product-Log*, or *Plog*, inverse function of the complex map: $\boxed{w = ze^z} \Rightarrow \boxed{z = P \log(w)}$, so

$$z + ae^{-z} = 0 \Rightarrow z = \text{Plog}(-a) \tag{4}$$

This function is built in Mathematica (see [notebook](#)) and other standard packages,

$$\lambda + b = \frac{1}{T} \text{Plog}(-rTe^{bT}) = \frac{1}{T} \text{Plog}(-a(T)) \tag{5}$$

Analysis of Plog: DDE: $y' + ay(t-1) = 0$

Real roots

Equation (4) has at most one (or two) real roots, provided $aT > -1/e$

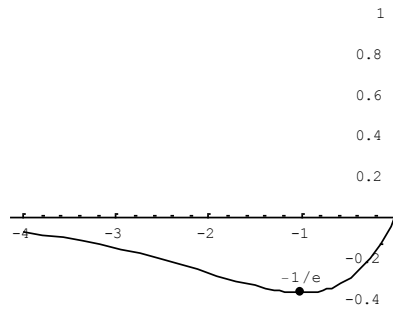


Fig. 1: Function $p(x) = xe^x$

Moreover, positive a have single positive root, while negative range $-1/e < aT < 0$, has two negative roots. Based on real roots, one would conclude that equilibrium $y = 0$ of (3) is unstable for positive growth rate a , and stable for negative (like in DEs). The situation, however is more complicated, as both cases have infinitely many complex roots, that can determine their stability.

Complex roots

Complex $z = u + iv$ has real and imaginary parts satisfying:

$$e^{u+iv} (u + iv) = -a$$

Hence, we get equation for $\text{Im}(z); \text{Re}(z)$

$$\begin{aligned} f(v) &= \frac{v}{\sin v} e^{-v \cot v} = -a \\ u &= -v \cot(v) \end{aligned} \quad (6)$$

Having solved 1st equation (6) for v at a fixed level $v = v_1(a) < v_2(a) < \dots$ we compute real part via 2nd equation: $u_1(a) > u_2(a) > \dots$ (shown in Fig.2).

Stability analysis

Sequences $\{u_n, v_n\}$ have asymptotic formulae

$$v_k \approx \left(2k + \frac{1}{2}\right)\pi; \quad u_k \approx \ln\left(\frac{a}{\pi(2k + 1/2)}\right) \rightarrow -\infty$$

As a increases they undergo a sequence of bifurcations at critical levels $a_k = (2k + 1/2)\pi$ with k unstable complex pairs $\{z_0; \dots; z_k\}, \text{Re}(z_j > 0)$

The entire bifurcation pattern of DDE: $y' + ay(t-1) = 0$

Range a	$u_1 = \text{Re}(z_1)$	$y(t)$	Stability
$[0, 1/e]$	$\lambda_1 < 0$ - real	$c_1 e^{-\lambda_1 t} + c_2 e^{-\lambda_2 t} + \dots$	Stable+ damped osc.
$[1/e, \pi/2]$	$u_j = \text{Re}(z_j) < 0$	$\sum c_j e^{z_j t}$	damped osc.
$[\pi/2, 5\pi/2]$	$u_1 > 0 > u_j$	$c_{\pm} e^{(u_1 \pm iv_1)t} + \sum_{j>1} c_j e^{z_j t}$	1st (Hopf) bifurcation
$[5\pi/2, 9\pi/2]$	$u_1 > u_2 > 0 > u_j$	$c_{\pm} e^{(u_1 \pm iv_1)t} + \sum_{j>1} c_j e^{z_j t}$	2 nd bifurcation

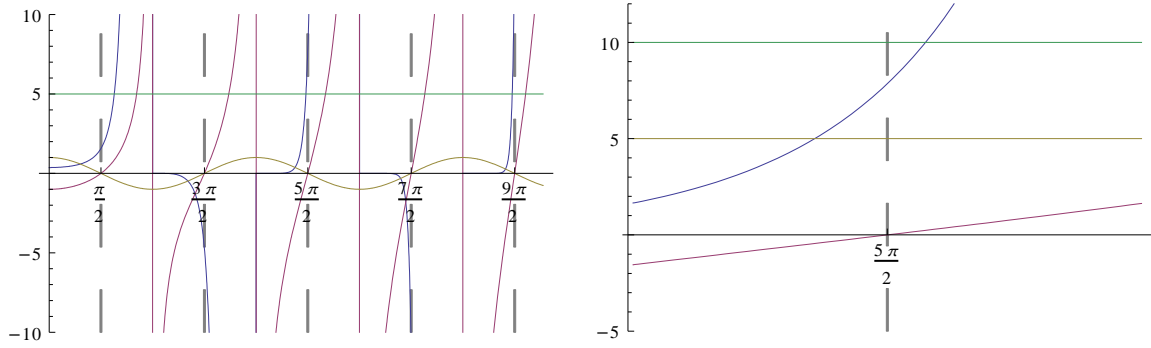


Fig.2: Function $f = \frac{v}{\sin v} e^{-v \cot v}$ (blue), whose levels determine $v = \text{Im}(z)$, and $u = \text{Re}(z) = -v \cot v$ (purple).

Analysis of time lag: DDE: $y' + ry(t-T) = 0$

Here $\lambda = \frac{1}{T} P \log(-rT) = \alpha + i\beta$, and we get equations for the imaginary and real parts of λ

$$f(T\beta) = \frac{T\beta}{\sin(T\beta)} e^{-T\beta \cot(T\beta)} = -rT \quad (7)$$

$$\alpha = -\beta \cot(T\beta)$$

As above system undergoes a sequence of bifurcations at critical lags

$$T_k = \left\{ \frac{\pi}{2r}; \frac{5\pi}{2r}; \frac{9\pi}{2r}; \dots \right\}$$

with critical frequencies $\beta_k = \text{Im}(\lambda_k) = 1$, and amplitudes $\alpha_k(T) \rightarrow 0$.

Nonlinear DDE

We apply the above (linear) analysis to several examples of nonlinear DDE.

1. **Logistic DDE:** $y'(t) = r \left[1 - \frac{y(t-T)}{N} \right] y(t)$. It still can serve as a population model, but

time-lag in the relative growth rate, has to do with *delayed* developmental stages. Some insects (and other organisms) undergo several stages, e.g. larva, pupae etc. So if $y(t)$ represents adult population at time t , its growth rate (at t) depends on the state of the system (i.e. adult females) at time $t-T$, the time it takes to develop from egg to adult.

Many interesting examples of delayed models appear in Physiology, so called periodic (or dynamic) diseases. We shall consider 3 such examples:

2. **Cheyne-Stokes respiration.** Here variable $C(t)$ represents CO₂-level (concentration) in the blood. High level of C turns in a negative feedback mechanism, that is breathing that removes excess CO₂. The feedback response however, does not appear immediately, but has a time lag (it takes the “excess signal” to reach breathing effector channels). The simplest ways to describe such feedback regulation is via DDE

$$\frac{dC(t)}{dt} = p - BV(C(t-T))C(t) \quad (8)$$

with sigmoid (switch) function: $V(y) = \frac{y^m}{a^m + y^m}$; ($m \gg 1$), called Hill function.

Parameter p represents CO₂ – production rate of (due to metabolism), and BV is C -dependent removal rate.

3. **Haematopoiesis** refers to generation of specialized blood cells, which is (partly) regulated by the blood cell population, called $y(t)$. Once again delays come naturally here, and a suitable model (Mackey-Glass 1977) can be written as DDE

$$y'(t) = \lambda(y(t-T)) - \gamma y(t) \quad (9)$$

where new cells are produced at a (delayed) rate $\lambda(y)$, and removed (die out) at a rate

γ . Mackey and Glass proposed function λ in the form: $\lambda(y) = \frac{y}{y^m + a^m}$

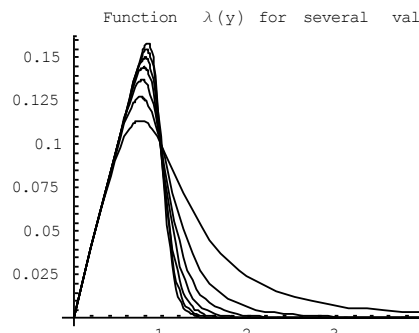


Fig.3: Production function for **Haematopoiesis**

So production rate grows linearly for small y , peaks at $y^* = a(m-1)^{1/m}$, then drops to zero.

4. **Fever control of malaria parasite.** [Malaria parasite](#) undergoes several developmental stages alternating between human and mosquito hosts. After a 7-day incubation period in a human host, following infected bite, it releases large number (10,000-30,000) of short-lived extracellular blood stages, called merozoites. The merozoites rapidly invade red blood cells (RBC). Inside the RBC each parasite undergoes asexual replication over a 48-72 hr period (depending on species). Then it bursts the cell, and releases a dozen of new merozoites to continue the cycle. Such exponential parasitic growth, and the associated destruction of RBC, is mostly responsible for the clinical symptoms of malaria. As the parasite density (parasitemia) reaches a critical (pyrogenic) level, 10^4 parasites/mm³ of blood, the patient will suffer periodic bouts of the acute fever. Fever is one of the natural (non-specific) body responses to invading parasites that attempts to maintain (control) their level at or below a critical value. It serves a first line of immuno-defense. To model this process we introduce parasite density $x(t)$. In the fever-free condition it grows exponentially at a rate $r = .5\ln 12 \approx 1.24/day$. When the fever switches on the growth turns into decay (with a delay of several hours). We assume decay rate proportional to r , βr , ($\beta > 1$). So our model becomes a DDE

$$x'(t) = r \left[1 - \beta V \left(\frac{x(t-T)}{N} \right) \right] x(t) \quad (10)$$

with the Hill function $V = \frac{x^m}{1 + x^m}$, that switched 'on' and 'off' about pyrogenic level N .

In all 3 cases we can find equilibria (same as the corresponding DE w/o delay), and study their linearized stability.

1. **Logistic delay** (rescaled to $N = 1$) gives a linearized DDE of the form

$u'(t) = -ru(t-T)$, where stable (carrying capacity) equilibrium undergoes bifurcation into limit cycle (Hopf) at $rT > \pi/2$ (see [Mathematica notebook](#))

2. **Cheyne-Stokes** after rescaling $u'(t) = 1 - \alpha V(u(t-T))$ gives a linear DDE

$$u' = -Au(t) - Bu(t-T)$$

with coefficients $A = \alpha V^*$; $B = u^* V'^*$, where * indicates values of $V(u)$ or derivative $V'(u)$ at the equilibrium value u^* . The detailed analysis is given in [Mathematica notebook](#). It shows

bifurcation of stable equilibrium into limit cycle behavior, associated with breathing abnormalities.

3. **Haematopoiesis** gives linear DDS $u'(t) = Bu(t-T) - Au(t)$ with $A = \lambda^*$; $B = \gamma$. Here we vary Hill parameter $5 < m < 20$, and find more complicated bifurcations from equilibria to limit cycle, and chaos (details in [Mathematica notebook](#)).

Problem: Study stability and bifurcation in the rescaled fever model, in terms of Hill parameters m , β and dimensionless time rT . Find stability range, estimate period of oscillation at the bifurcation value.