Differential equations with time delay

Marek Bodnar

Faculty of Mathematics, Informatics and Mechanics,
Institute of Applied Mathematics and Mechanics,
University of Warsaw

MIM Colloquium
December 8^{th}, 2016

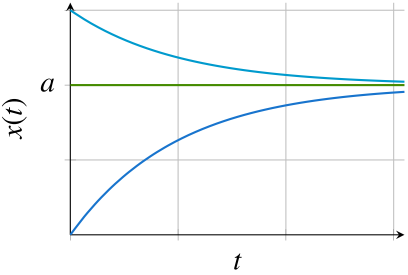
What are delay differential equations?

(Almost) the simplest differential equation

$$x'(t) = a - x(t), \quad x(0) = x_0,$$

has a solution

$$x(t) = a + (x_0 - a)\mathrm{e}^{-t}.$$



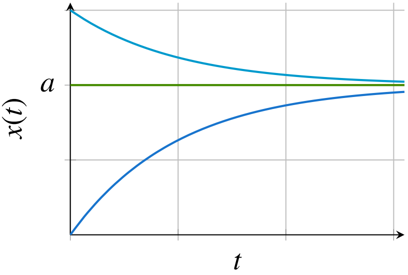
What are delay differential equations?

(Almost) the simplest differential equation

$$x'(t) = a - x(t), \quad x(0) = x_0,$$

has a solution

$$x(t) = a + (x_0 - a)\mathrm{e}^{-t}.$$



Adding time delay obtaining

$$x'(t) = a - x(t-\tau), \quad x(0) = x_0$$

and we cannot solve it since the value of $x(-\tau)$ is not known.

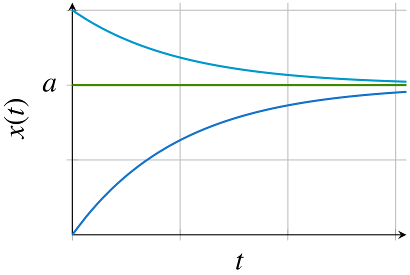
What are delay differential equations?

(Almost) the simplest differential equation

$$x'(t) = a - x(t), \quad x(0) = x_0,$$

has a solution

$$x(t) = a + (x_0 - a)\mathrm{e}^{-t}.$$



Adding time delay obtaining

$$x'(t) = a - x(t-\tau), \quad x(t) = \phi(t), \quad t \in [-\tau, 0],$$

and we need to pose initial condition on the whole interval $[-\tau, 0]$. In general, there are no solutions of this linear equation that can be expressed in terms of elementary functions.

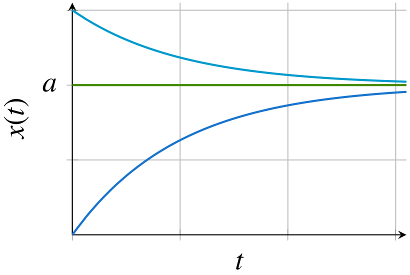
What are delay differential equations?

(Almost) the simplest differential equation

$$x'(t) = a - x(t), \quad x(0) = x_0,$$

has a solution

$$x(t) = a + (x_0 - a)e^{-t}.$$



Adding time delay obtaining

$$x'(t) = a - x(t - \tau), \quad x(t) = \phi(t), \quad t \in [-\tau, 0],$$

and we need to pose initial condition on the whole interval $[-\tau, 0]$. In general, there are no solutions of this linear equation that can be expressed in terms of elementary functions.

Corollary

A proper phase space is a space of functions.

Continuation of a simple example

For some particular parameters (and initial functions) we can find a solution. Set $\tau = \frac{\pi}{2}$ and consider

$$x'(t) = a - x\left(t - \frac{\pi}{2}\right), \quad x(t) = a + \beta\cos(t), \quad \text{for} \quad t \in \left[-\frac{\pi}{2}, 0\right].$$

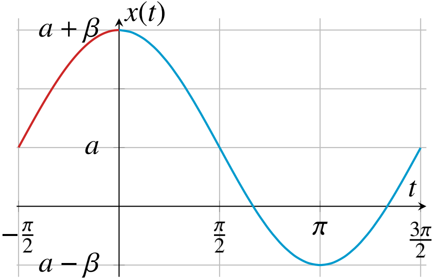
Continuation of a simple example

For some particular parameters (and initial functions) we can find a solution. Set $\tau = \frac{\pi}{2}$ and consider

$$x'(t) = a - x\left(t - \frac{\pi}{2}\right), \quad x(t) = a + \beta\cos(t), \text{ for } t \in \left[-\frac{\pi}{2}, 0\right].$$

The solution is (an easy exercise)

$$x(t) = a + \beta\cos(t).$$



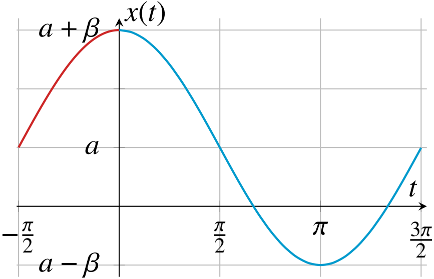
Continuation of a simple example

For some particular parameters (and initial functions) we can find a solution. Set $\tau = \frac{\pi}{2}$ and consider

$$x'(t) = a - x\left(t - \frac{\pi}{2}\right), \quad x(t) = a + \beta\cos(t), \text{ for } t \in \left[-\frac{\pi}{2}, 0\right].$$

The solution is (an easy exercise)

$$x(t) = a + \beta\cos(t).$$



Surprises

- Solution does not converge to a steady state.

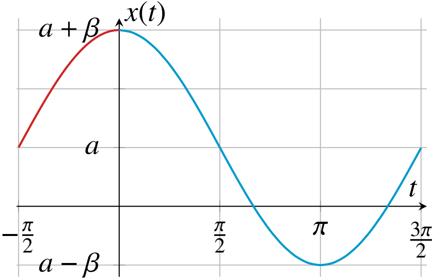
Continuation of a simple example

For some particular parameters (and initial functions) we can find a solution. Set $\tau = \frac{\pi}{2}$ and consider

$$x'(t) = a - x\Big(t - \frac{\pi}{2}\Big), \quad x(t) = a + \beta\cos(t), \text{ for } t \in \Big[-\frac{\pi}{2}, 0\Big].$$

The solution is (an easy exercise)

$$x(t) = a + \beta\cos(t).$$



Surprises

- Solution does not converge to a steady state.
- If $\beta > a$, then solution takes negative values.

Negativity of the solution

$$x'(t) = a - x(t-\tau), \quad x(t) = \phi(t), \quad t \in [-\tau, 0] \qquad (\star)$$

Proposition

For any parameters $a > 0$, $\tau > 0$ there exists an initial function φ such that solution to $(\star)$ takes negative values.

Negativity of the solution

$$x'(t) = a - x(t-\tau), \quad x(t) = \phi(t), \quad t \in [-\tau, 0] \qquad (\star)$$

Proposition

For any parameters $a > 0$, $\tau > 0$ there exists an initial function φ such that solution to $(\star)$ takes negative values.

Proof:

It is enough to take φ such that

- $\varphi(-\tau) > a$;
- $\varphi(0) = 0$. □

Negativity of the solution

$$x'(t) = a - x(t-\tau), \quad x(t) = \phi(t), \quad t \in [-\tau, 0] \qquad (\star)$$

Proposition

For any parameters $a > 0$, $\tau > 0$ there exists an initial function φ such that solution to $(\star)$ takes negative values.

Proof:

It is enough to take φ such that

- $\varphi(-\tau) > a$;
- $\varphi(0) = 0$. □

Corollary

Although delay differential equations look very similar to ordinary differential equations, they are different and intuitions from ODE sometimes do not work.

Logistic equation with delay

$$x'(t) = \alpha x(t-\tau)\Big(1 - x(t-\tau)\Big), \quad x(t) = \varphi(t) \geq 0, \ t \in [-\tau, 0]. \qquad (\diamond)$$

Solution to $(\diamond)$ without delay (i.e. $\tau = 0$)

- All solutions, except the trivial one, converges to 1.
- All solutions are monotonic.
- All solutions are non-negative.

Logistic equation with delay

$$x'(t) = \alpha x(t-\tau)\big(1 - x(t-\tau)\big), \quad x(t) = \varphi(t) \geq 0, \; t \in [-\tau, 0]. \qquad (\diamond)$$

Solution to ($\diamond$) without delay (i.e. $\tau = 0$)

- All solutions, except the trivial one, converges to 1.
- All solutions are monotonic.
- All solutions are non-negative.

The case $\tau > 0$

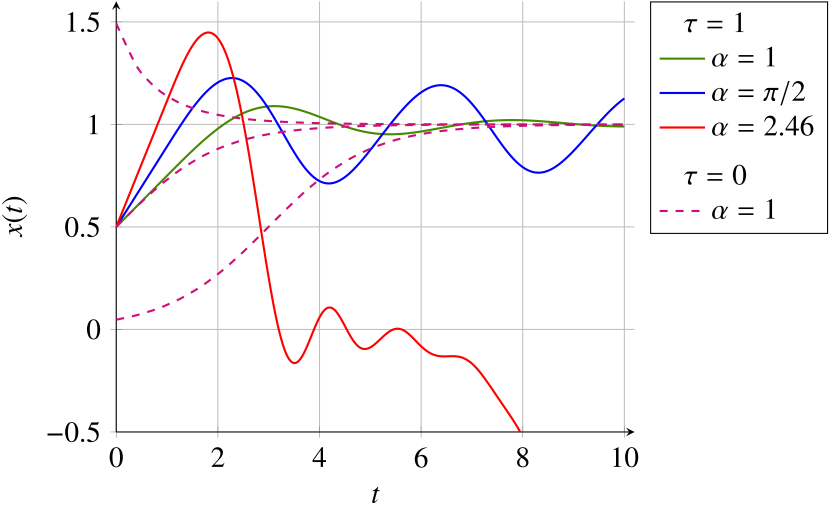
All above statements become false:

- Solutions converges to 1 only if $\alpha\tau < \pi/2$;
- Solutions do not need to be monotonic (even for small $\alpha\tau$);
- Solutions need not to be non-negative.
- Even if $\varphi(t) \in (0, 1]$, then solution to ($\diamond$) are non-negative only for small $\alpha\tau$. For $\alpha\tau > 3.06$ they can take negative values.

M.B. *Appl. Math. Lett.* (2000)

Logistic equation with delay — graph of the solutions

$$\dot{x}(t) = \alpha x(t-\tau)\Big(1 - x(t-\tau)\Big).$$



Hutchinson model and open problem

Hutchinson model

$$x'(t) = \alpha x(t)\Big(1 - x(t-\tau)\Big)$$

- For $\alpha\tau < 37/24$ all solutions converges to $\bar{x} = 1$, except the trivial one.
- At $\alpha\tau = \pi/2$ the Hopf bifurcation occurs (the steady state becomes unstable and periodic solution arises).
- For $\alpha\tau < \pi/2$ the steady state is locally stable.

Hutchinson model and open problem

Hutchinson model

$$x'(t) = \alpha x(t)\Big(1 - x(t-\tau)\Big)$$

- For $\alpha\tau < 37/24$ all solutions converges to $\bar{x} = 1$, except the trivial one.
- At $\alpha\tau = \pi/2$ the Hopf bifurcation occurs (the steady state becomes unstable and periodic solution arises).
- For $\alpha\tau < \pi/2$ the steady state is locally stable.

Wright's hypothesis:

- The steady state is globally stable for all $\alpha\tau < \pi/2$.

Hutchinson model and open problem

Hutchinson model

$$x'(t) = \alpha x(t)\Big(1 - x(t-\tau)\Big)$$

- For $\alpha\tau < 37/24$ all solutions converges to $\bar{x} = 1$, except the trivial one.
- At $\alpha\tau = \pi/2$ the Hopf bifurcation occurs (the steady state becomes unstable and periodic solution arises).
- For $\alpha\tau < \pi/2$ the steady state is locally stable.

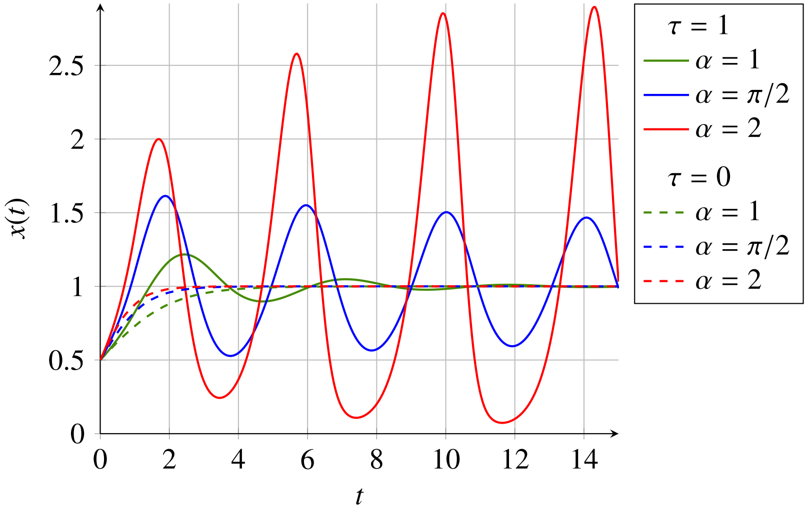
Wright's hypothesis:

- The steady state is globally stable for all $\alpha\tau < \pi/2$.
- It is not known if the hyphothesis is true for $37/24 < \alpha\tau < \pi/2$.

I say few words more about logistic equation later.

Hutchinson model — graph of the solutions

$$\dot{x}(t) = \alpha x(t)\Big(1 - x(t-\tau)\Big).$$



Simple equations — reach and chaotic dynamics

Model of hematopoiesis

- $x(t)$ — size of population of mature red blood cells;
- τ — time for maturation of red blood cells;
- $f(x)$ — non-increasing function that describes mechanism of self-regulation of hematopeisis: more blood cells in the organism $\Longrightarrow$ weaker stimulation of differentiation of steam blood cells.

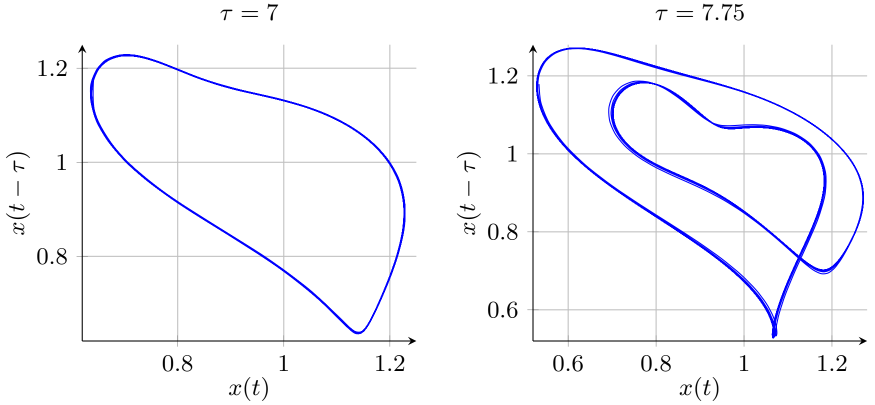
Mackey-Glass equation

After scaling equation reads

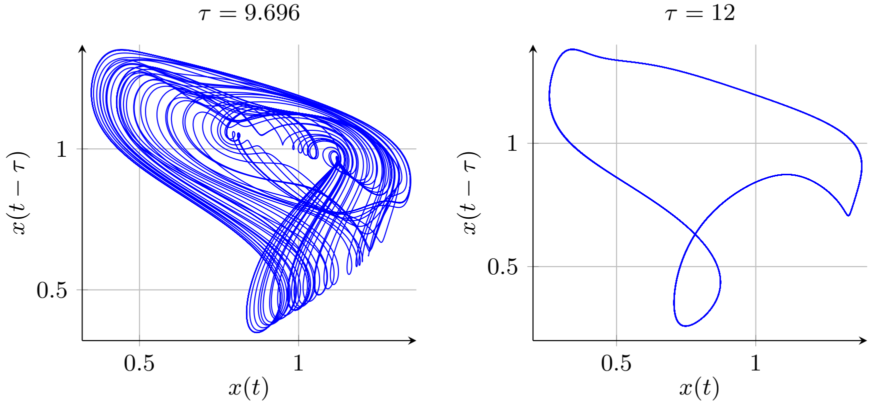
$$x'(t) = \alpha \frac{x(t-\tau)}{1 + x^k(t-\tau)} - \beta x(t).$$

The model exhibits a chaotic behaviour.

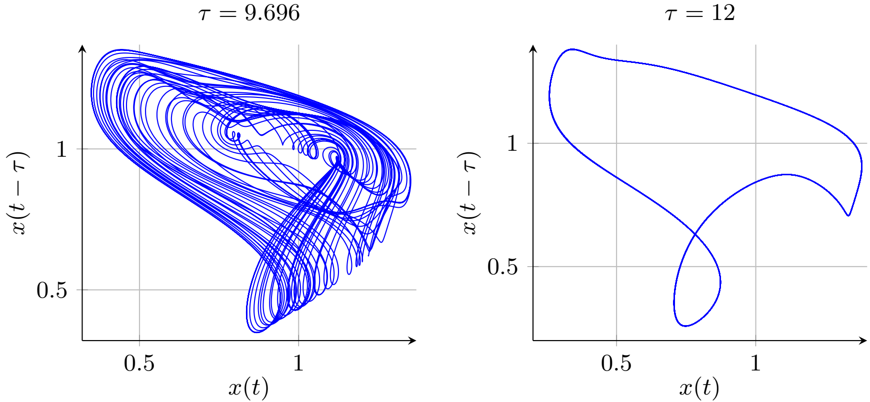
Simple equations — reach and chaotic dynamics



Simple equations — reach and chaotic dynamics



Simple equations — reach and chaotic dynamics



M.C. Mackey, L. Glass, *Science*, (1977).

L. Glass, M.C. Mackey, *Ann. NY. Acad. Sci.*, (1979).

J.D. Farmer, E. Ott, J.A. Yorke, *Physica D*, (1983).

Ważewszka-Czyżewska and Lasota model

Notation

- $x(t)$ — size of red blood cells' population;
- μ — death rate ($1/\mu$ mean time life of a read blood cell);
- ρ — oxygen demand;
- γ — stimulation's level of the system.

Ważewszka-Czyżewska and Lasota equation

It is derived from a transport equation that descries ageing (maturation) of red blood cells

$$x'(t) = -\mu x(t) + \rho e^{-\gamma x(t-\tau)}$$

M. Ważewska-Czyżewska, A. Lasota, *Mat. Stos.* 1976.

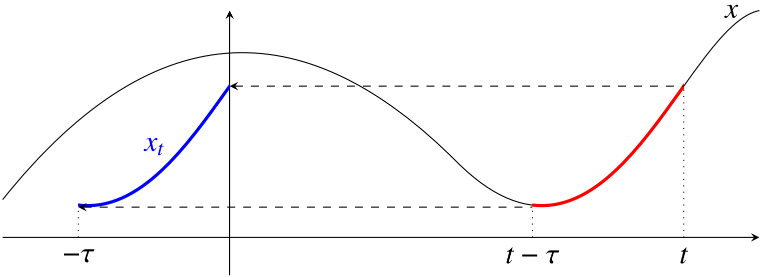
M. Ważewska-Czyżewska, *Erythrokinetics*, 1981

General form of delay differential equation

Derivative at time t_0 may depend on the values of the function on the whole interval $[t_0 - \tau, t_0]$ ($\tau \in \overline{\mathbb{R}}$).

General form of equation with delay

$$\dot{x}(t) = f(t, x_t)$$



What does mean x_t?

It is a function $x_t : [-\tau, 0] \to \mathbb{R}^n$, $x_t(\theta) = x(t + \theta)$ for $\theta \in [-\tau, 0]$.

Phase space

For finite delay ($\tau < \infty$)

Usually we consider the space

$$C = \mathbf{C}([-\tau, 0]; \mathbb{R}^n)\,,$$

of continuous functions defined on $[-\tau, 0]$.

There exist a few papers at which the space L^p is considered.

Regularity of solutions

Assume that $f \in C^k$, then for $1 \le \ell \le k + 1$

$$x_t \in C^{\ell}, \quad \text{for} \quad t \ge t_0 + \ell\tau.$$

Continuation of solutions

Forward continuation

Theorem is very similar to the one for ordinary differential equations, but additional assumption that f is completely continuous is required.

An example on the next slide.

Continuation of solutions

Forward continuation

Theorem is very similar to the one for ordinary differential equations, but additional assumption that f is completely continuous is required.

An example on the next slide.

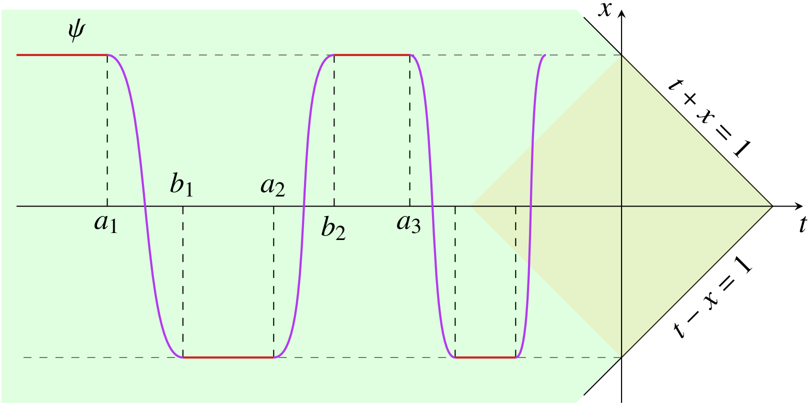
Backward continuation

In general solution of delay cannot be prolonged backward.

Reason: solution of the equation on $[0, \tau]$ is C^1 class, while the function on $[-\tau, 0]$ is only continuous.

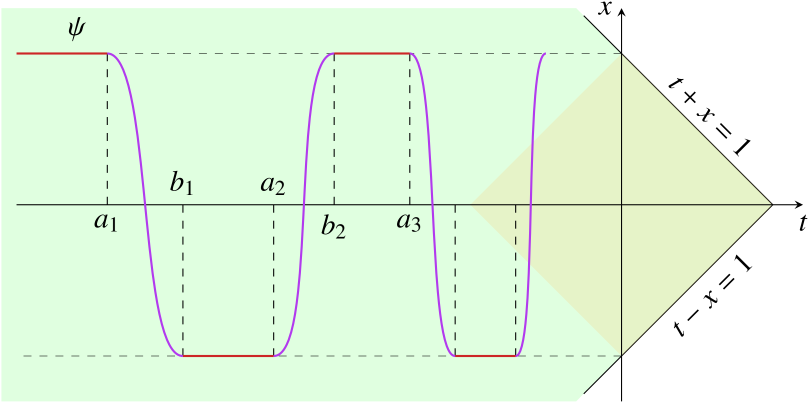
In order to continue solution backward, we need additional "compatibility conditions" (to continue on $[-2\tau, -\tau]$, next one to continue on $[-3\tau, -2\tau]$, and so on).

Non-continuation — example



$$\Delta(t) = t^2, \quad a_k = b_k - \Delta(b_k), \quad a_k, b_k \to 0, \quad h\Big(t - \Delta(t), \psi(t - \Delta(t))\Big) = \psi'(t).$$

Non-continuation — example



$$\Delta(t) = t^2, \quad a_k = b_k - \Delta(b_k), \quad a_k, b_k \to 0, \quad h\Big(t - \Delta(t), \psi(t - \Delta(t))\Big) = \psi'(t).$$

Solution of the equation

$$x'(t) = h\Big(t - \Delta(t), x(t - \Delta(t))\Big), \quad x(t) = 1, \; t \le \sigma < a_1$$

cannot be prolonged for $t \ge 0$.

Why DDEs seem to be similar to ODEs

The most popular form

Equation with discrete delay(s)

$$x'(t) = f\big(t, x(t), x(t-\tau)\big), \quad x(t) = \varphi(t),\ t \in [-\tau, 0]$$

or in a functional form

$$x'(t) = F(t, x_t),\ x_0 = \phi, \quad F(t, \phi) = f\big(t, \varphi(0), \varphi(-\tau)\big), \quad x_t, \varphi \in C.$$

Why DDEs seem to be similar to ODEs

The most popular form

Equation with discrete delay(s)

$$x'(t) = f(t, x(t), x(t-\tau)), \quad x(t) = \varphi(t), \ t \in [-\tau, 0]$$

or in a functional form

$$x'(t) = F(t, x_t), \ x_0 = \phi, \quad F(t, \phi) = f(t, \varphi(0), \varphi(-\tau)), \quad x_t, \varphi \in C.$$

The step method

- $t \in [0, \tau] \implies x(t-\tau) = \varphi(t-\tau)$, so
$$x'(t) = f(t, x(t), \varphi(t-\tau))$$
is non-autonomous ODE.
- We solve equation/prove property on $[0, \tau]$ and
- use mathematical induction to prove it for all $t \geq 0$.

Equation with discrete delay cannot blow-up

Theorem

Let $f : \mathbb{R} \to \mathbb{R}$ be a continuous function and $\tau > 0$ be an arbitrary number. Then for every initial function φ solution to

$$x'(t) = f(x(t-\tau)), \ t \geq 0, \tag{▲}$$

$x(t) = \varphi(t)$ *for* $t \in [-\tau, 0]$*, exists, is unique and defined for all* $t \geq 0$.

Equation with discrete delay cannot blow-up

Theorem

Let $f\colon \mathbb{R} \to \mathbb{R}$ be a continuous function and $\tau > 0$ be an arbitrary number. Then for every initial function φ solution to

$$x'(t) = f(x(t-\tau)), \ t \geq 0, \tag{▲}$$

$x(t) = \varphi(t)$ *for* $t \in [-\tau, 0]$*, exists, is unique and defined for all* $t \geq 0$.

Proof:

- Let $t \in [0, \tau]$. Equation (▲) reads

  $$x'(t) = f(\varphi(t-\tau)).$$

  with initial condition $x(0) = \varphi(0)$.
- We obtain solution on $[0, \tau]$ integrating both sides. Solution is unique, continuous and defined on the whole interval $[0, \tau]$.
- Mathematical induction implies assertion. □

Blow-up — an example

ODE

Solution to

$$x'(t) = x^2(t), \quad x(0) = 1$$

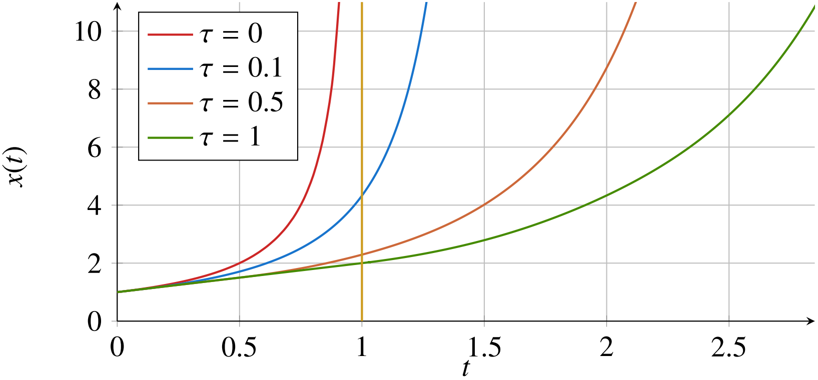
blows up as $t \to 1^-$.

DDE

Solution to

$$x'(t) = x^2(t-\tau), \quad x(t) = 1, t \in [-\tau, 0]$$

is defined on $[-\tau, +\infty)$.



Stability of the steady state

Techniques

1. Liapunov functional theorem, an analogous to the version for ODEs. However, here $V : C \to \mathbb{R}$;
2. Linearization method (the most popular — I will discuss more);
3. Comparison with an appropriate discrete dynamical system (that is studying the behaviour for delay $\longrightarrow +\infty$),

E. Liz, A. Ruiz-Herrera, *J. Diff. Eqs.*, (2013).

M.B., *J. Diff. Eqs*, (2015)

Liapunov functional — an example

Finding Liapunov functional

is as easy (or as difficult) as for ODEs. If we know Liapunov function for ODE version of the system we may try to add some integral term.

Consider

$$x'(t) = -a(t)x^3(t) + b(t)x^3(t-\tau). \qquad (\clubsuit)$$

Assumptions:

- $a, b\colon \mathbb{R} \to \mathbb{R}$ continuous and bounded;
- $a(t) \geq \delta$, $|b(t)| < q\delta$, for $0 < q < 1$.

Liapunov functional — an example

Finding Liapunov functional

is as easy (or as difficult) as for ODEs. If we know Liapunov function for ODE version of the system we may try to add some integral term.

Consider

$$x'(t) = -a(t)x^3(t) + b(t)x^3(t-\tau). \qquad (\clubsuit)$$

Assumptions:

- $a, b \colon \mathbb{R} \to \mathbb{R}$ continuous and bounded;
- $a(t) \geq \delta$, $|b(t)| < q\delta$, for $0 < q < 1$.

To prove global stability of the trivial solution to ($\clubsuit$) we can use the following functional

$$V(\phi) = \frac{\phi^4(0)}{4} + \frac{\delta}{2}\int_{-\tau}^{0} \phi^6(s)\mathrm{d}s, \quad \phi \in C$$

Linear stability theorem

Consider

$$x'(t) = F(x_t) = Lx_t + G(x_t), \quad F(0) = 0, G(0) = 0,$$

where L is linear operator, G is (small) non-linear part.
We look for exponential solution to the linear equation

$$x'(t) = Lx_t, \quad x(t) = ce^{\lambda t}.$$

Zeros of the characteristic equation $W(\lambda) = 0$ determine stability.

- For all zeros λ of W we have $\mathrm{Re}\lambda < 0 \implies$ the steady state is locally stable.
- If there exists zero λ_0 of W such that $\mathrm{Re}\lambda_0 > 0 \implies$ the steady state is unstable.
- If $\mathrm{Re}\lambda_0 = 0$ and $\mathrm{Re}\lambda <\leq 0$ for all zeros of W, the local stability of non-linear system is not determined by the stability of the linear system.

General techniques

If delays are discrete, the characteristic function reads

$$W(\lambda) = P(\lambda) + \sum_{k=1}^{m} Q_k(\lambda)\mathrm{e}^{-\tau_k \lambda},$$

where P and Q_k are polynomials.

Mikhailov criterion

If $n = \deg P > \deg Q$, W has no zeros on imaginary axis. Then the number of zeros in the right-hand complex half-plane is equal to

$$\frac{n}{2} - \frac{1}{\pi}\Delta_{\omega\in[0,+\infty)}\arg W(i\omega).$$

General techniques

If delays are discrete, the characteristic function reads

$$W(\lambda) = P(\lambda) + \sum_{k=1}^{m} Q_k(\lambda)e^{-\tau_k \lambda},$$

where P and Q_k are polynomials.

Mikhailov criterion

If $n = \deg P > \deg Q$, W has no zeros on imaginary axis. Then the number of zeros in the right-hand complex half-plane is equal to

$$\frac{n}{2} - \frac{1}{\pi}\Delta_{\omega\in[0,+\infty)}\arg W(i\omega).$$

Remark

If for τ_k^0 zeros of W crosses imaginary axis (i.e. $W(i\omega_0) = 0$) that the same situation is for

$$\tau_k^j = \tau_k^0 + \frac{2j\pi}{\omega_0}.$$

General techniques

In the simplest case, if

$$W(\lambda) = P(\lambda) + Q(\lambda)e^{-\tau\lambda},$$

where P and Q are polynomials, we can check if the stability changes. If it is so, there exists purely imaginary zero of W.

$$W(i\omega) = P(i\omega) + Q(i\omega)e^{-i\tau\omega} = 0 \implies F(\omega) = \left|P(i\omega)\right|^2 - \left|Q(i\omega)\right|^2 = 0.$$

Theorem

Under some technical assumptions, for $F(\omega_0) = 0$.

$$\mathrm{sign}\left(\frac{\mathrm{d}}{\mathrm{d}\tau} \mathit{Re}\Big(W(\lambda)\Big)\Big|_{\lambda=i\omega_0}\right) = \mathrm{sign}\Big(F'(\omega_0)\Big).$$

K.L. Cooke, P. van den Driessche *Funkcj Ekvacioj* (1986).

One equation with one discrete delay

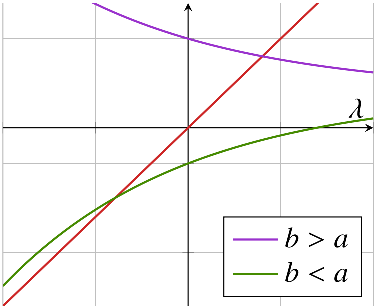
Linear equation reads

$$x'(t) = -ax(t) + bx(t-\tau),$$

and characteristic equation is

$$\lambda + a - b\mathrm{e}^{-\lambda\tau} = 0 \iff \lambda = -a + b\mathrm{e}^{-\lambda\tau}.$$

Real positive zeros



One equation with one discrete delay

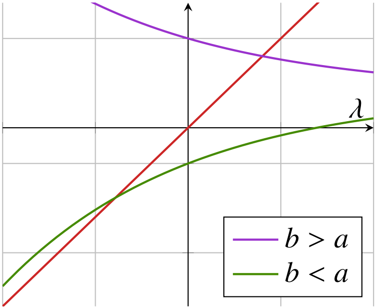
Linear equation reads

$$x'(t) = -ax(t) + bx(t - \tau),$$

and characteristic equation is

$$\lambda + a - be^{-\lambda\tau} = 0 \iff \lambda = -a + be^{-\lambda\tau}.$$

Real positive zeros



Complex zeros

For $b < a$ (stability for $\tau = 0$).

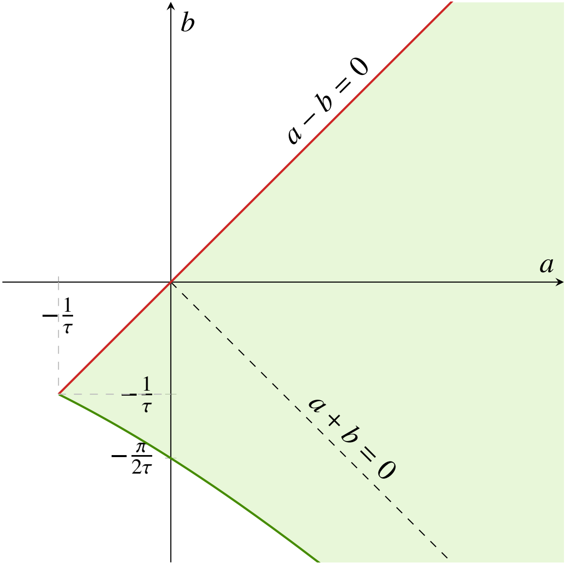
Change in stability $\iff$ there exists $\lambda = i\omega$.

We solve the system

$$a - b\cos(\omega\tau) = 0,$$
$$\omega + b\sin(\omega\tau) = 0.$$

Necessary condition for stability change $|a| \leq |b|$.

Stability region



Border of the stability region are given by:

- $a = b$ for $a \geq -1$
- $\tau = \dfrac{\arccos\left(\frac{a}{b}\right)}{\sqrt{b^2 - a^2}}$

  for $a > -\frac{1}{\tau}$, and

  $b < 0$, $|b| > |a|$

Two equations with one discrete delay

General form of system of two linear equations with delay

$$\begin{aligned} x'(t) &= \alpha_1 x(t) + \beta_1 y(t) + \alpha_2 x(t-\tau) + \beta_2 y(t-\tau) \\ y'(t) &= \gamma_1 x(t) + \delta_1 y(t) + \gamma_2 x(t-\tau) + \delta_2 y(t-\tau) \end{aligned}$$

and characteristic function reads

$$W(\lambda) = \lambda^2 + a_1\lambda + a_0 + \big(b_1\lambda + b_0\big)\mathrm{e}^{-\lambda\tau} + c\mathrm{e}^{-2\lambda\tau},$$

where

$$\begin{aligned} a_1 &= -(\alpha_1 + \delta_2) \\ a_0 &= \alpha_1\delta_1 - \beta_1\gamma_1 \\ b_1 &= -(\alpha_2 + \delta_2) \\ b_0 &= \alpha_1\delta_2 - \beta_1\gamma_2 + \alpha_2\delta_1 - \beta_2\gamma_1 \\ c &= \alpha_2\delta_2 - \beta_2\gamma_2 \end{aligned}$$

Two equations with one discrete delay

$$W(\lambda) = \lambda^2 + a_1\lambda + a_0 + \big(b_1\lambda + b_0\big)\mathrm{e}^{-\lambda\tau} + \ c\mathrm{e}^{-2\lambda\tau} \ ,$$

Two equations with one discrete delay

$$W(\lambda) = \lambda^2 + a_1\lambda + a_0 + \left(b_1\lambda + b_0\right)\mathrm{e}^{-\lambda\tau} + \cancel{c\mathrm{e}^{-2\lambda\tau}},$$

We assume $c = 0$.

Steady state unstable for all $\tau \geq 0$ if

- it is a saddle point for $\tau = 0$ (i.e. $a_0 + b_0 < 0$);
- it is unstable node or unstable focus for $\tau = 0$ (i.e. $a_1 + b_1 > 0$ and $a_0 + b_0 > 0$) and $|a_0| < |b_0|$.

Steady state stable for all $\tau \geq 0$ if

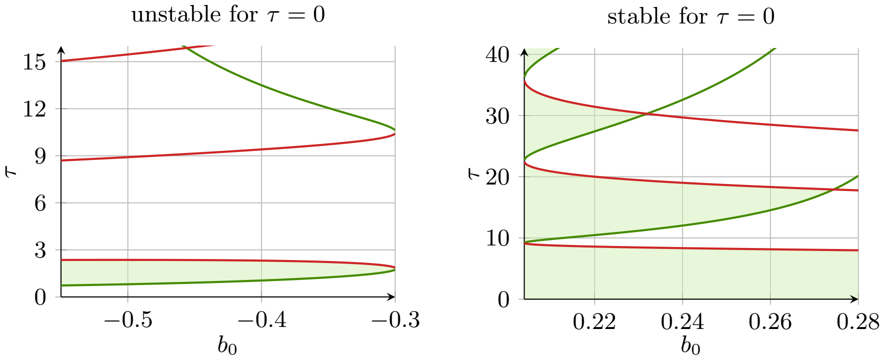
- it is stable for $\tau = 0$ (i.e. $a_0 + b_0 > 0$ and $a_1 + b_1 < 0$) and
  - $(a_1^2 - 2a_0 - b_1^2)^2 < 4(a_0^2 - b_0^2)$ or
  - $a_1^2 > 2a_0 + b_1^2$ and $|a_0| > |b_0|$.

Two equations with one discrete delay

$$W(\lambda) = \lambda^2 + a_1\lambda + a_0 + \big(b_1\lambda + b_0\big)\mathrm{e}^{-\lambda\tau},$$

Otherwise steady state changes its stability with increasing $\tau = 0$.

- If $|a_0| < |b_0| \implies$ only one switch (stable $\to$ unstable);
- If $|a_0| > |b_0|$ and $a_1^2 < 2a_0 + b_1^2$ and $(a_1^2 - 2a_0 - b_1^2)^2 > 4(a_0^2 - b_0^2)$ multiple stability switches are possible.

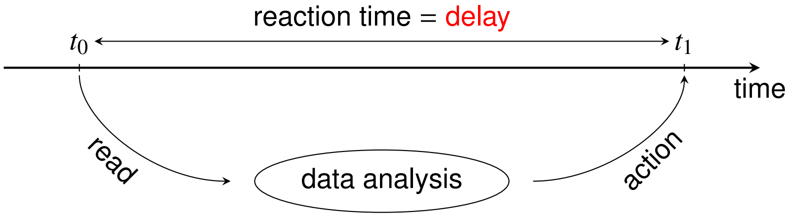


More equations or more delays

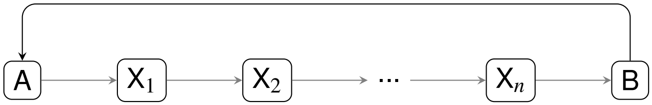
- Situation can be more complex.
- Even for one equation and two discrete delays multiple stability changes are possible.
- If delay distribution is continuous, that is delay term is written as
$$\int_0^{+\infty} \theta(s)x(t-s)\mathrm{d}s,$$
where θ is a probabilistic density on $[0, +\infty)$, then in the characteristic function Laplace transform of θ can be involved.

Why do we need delays?

Control

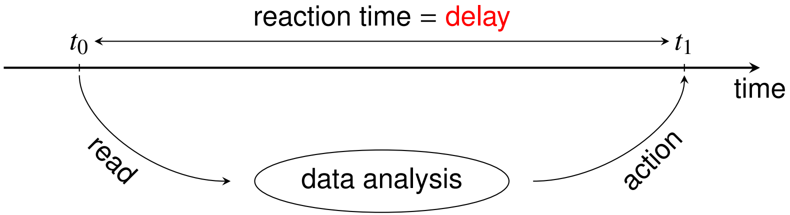


Simplifying more complex system

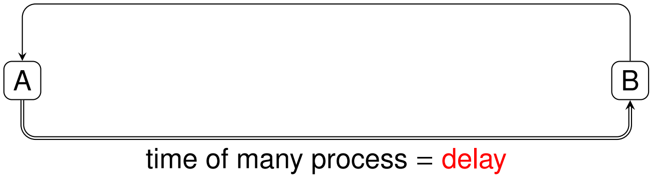


Why do we need delays?

Control



Simplifying more complex system



Where does time delay appear?

In models of

- biological processes eg.
  - tumour growth and cancer therapies,
  - biochemical reactions and gene expression,
  - immune system,
  - spread of epidemic,
- economic processes eg.
  - optimisation of fishing,
  - controlling of pollutions,
- physical and chemical processes eg.
  - lasers,
- sociological processes.

Hutchinson model with treatment function

Assumptions

- x — size of (cancer cells') population;
- death rate $\eta\colon [0,+\infty) \to [0,+\infty)$ includes external force (eg. action of drug)
- *per capita* birth rate is a decreasing function of population size at time $t-\tau$, where τ denotes cells' division time.
- K is called "carrying capacity".

$$x'(t) = r\,x(t)\left(1 - \frac{x(t-\tau)}{K}\right) - \eta(t)\,x(t).$$

Hutchinson model with treatment function

Assumptions

- x — size of (cancer cells') population;
- death rate $\eta\colon [0,+\infty) \to [0,+\infty)$ includes external force (eg. action of drug)
- *per capita* birth rate is a decreasing function of population size at time $t-\tau$, where τ denotes cells' division time.
- K is called "carrying capacity".

$$x'(t) = r\,x(t)\left(1 - \frac{x(t-\tau)}{K}\right) - \boxed{\eta(t)}\,x(t).$$

Hutchinson model with treatment function

Assumptions

- x — size of (cancer cells') population;
- death rate $\eta\colon [0, +\infty) \to [0, +\infty)$ includes external force (eg. action of drug)
- *per capita* birth rate is a decreasing function of population size at time $t - \tau$, where τ denotes cells' division time.
- K is called "carrying capacity".

$$x'(t) = r\,x(t)\left(\boxed{1 - \frac{x(t-\tau)}{K}}\right) - \eta(t)\,x(t).$$

Hutchinson model with treatment function

Assumptions

- x — size of (cancer cells') population;
- death rate $\eta\colon [0, +\infty) \to [0, +\infty)$ includes external force (eg. action of drug)
- *per capita* birth rate is a decreasing function of population size at time $t - \tau$, where τ denotes cells' division time.
- K is called "carrying capacity".

$$x'(t) = r\,x(t)\left(1 - \frac{x(t-\tau)}{\boxed{K}}\right) - \eta(t)\,x(t).$$

Global stability of trivial steady state

$$\begin{aligned} x'(t) &= rx(t)\Big(1 - x(t-\tau)\Big) - \eta(t)x(t), \ \ t \geq 0 \\ x(t) &= \varphi(t) \geq 0, \ \ t \in [-\tau, 0]. \end{aligned} \qquad (\star\star)$$

- If $\eta(t) \equiv \bar{\eta} \geq r$ and $\tau = 0$ then $x(t) \to 0$ as $t \to +\infty$.
- Question: what happens if $\tau > 0$ and η is not constant?

Global stability of trivial steady state

$$\begin{aligned} x'(t) &= rx(t)\Big(1 - x(t-\tau)\Big) - \eta(t)x(t), \ t \geq 0 \\ x(t) &= \varphi(t) \geq 0, \ t \in [-\tau, 0]. \end{aligned} \qquad (\star\star)$$

- If $\eta(t) \equiv \bar{\eta} \geq r$ and $\tau = 0$ then $x(t) \to 0$ as $t \to +\infty$.
- Question: what happens if $\tau > 0$ and η is not constant?

Pharmacokinetic function

- The concentration of drug decays exponentially $\eta'(t) = -\delta\eta(t)$.
- Drug is administrated at points t_j, that is $\eta(t_j) = \lim_{t \to t_j^-} \eta(t) + d_j$.
- Assuming periodic administration of the same dose (d per time unit, κ times per time unit) we get

$$\eta(t) = \frac{d}{\kappa(e^{\delta/\kappa} - 1)} \Big(e^{\delta([\kappa t]+1-\kappa t)/\kappa} - e^{-\delta t}\Big)$$

Global stability of trivial steady state

$$x'(t) = rx(t)\Big(1 - x(t-\tau)\Big) - \eta(t)x(t), \ t \geq 0 \qquad (\star\star)$$
$$x(t) = \varphi(t) \geq 0, \ t \in [-\tau, 0].$$

- If $\eta(t) \equiv \bar{\eta} \geq r$ and $\tau = 0$ then $x(t) \to 0$ as $t \to +\infty$.
- Question: what happens if $\tau > 0$ and η is not constant?

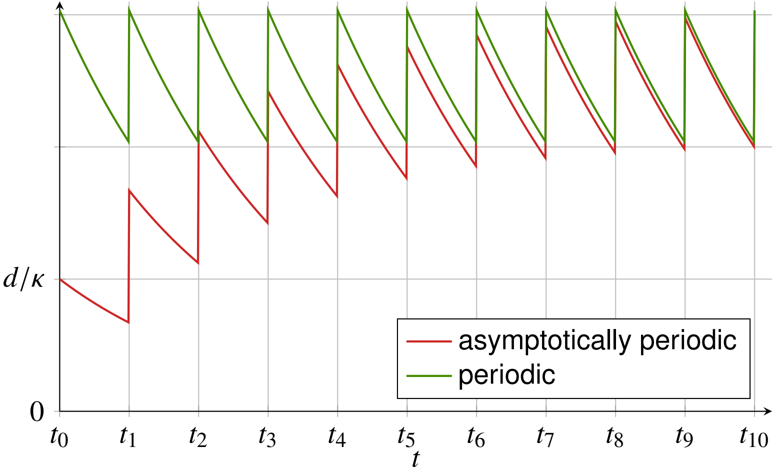
Pharmacokinetic function

- The concentration of drug decays exponentially $\eta'(t) = -\delta\eta(t)$.
- Drug is administrated at points t_j, that is $\eta(t_j) = \lim\limits_{t \to t_j^-} \eta(t) + d_j$.
- Assuming periodic administration of the same dose (d per time unit, κ times per time unit) we get

$$\eta(t) = \frac{d}{\kappa(e^{\delta/\kappa} - 1)}\Big(e^{\delta([\kappa t]+1-\kappa t)/\kappa} - e^{-\delta t}\Big)$$

- This function is almost periodic for large t.

Graph of pharmacokinetic function



Global stability of the steady state

Generalised equation

$$x'(t) = rx(t)f\big(x(t-\tau)\big) - \eta(t)x(t), \qquad (\star\star)$$

- f is strictly decreasing, $f(1) = 0$, and $f(0) = 1$ or $\lim_{x\to 0^+} f(x) = +\infty$.
- η is asymptotically periodic, i.e. $\eta(t) = \eta_p(t) + \eta_r(t)$, where η_p is periodic with period σ, $\eta_r(t) \to 0$ as $t \to +\infty$.
- $\displaystyle\int_0^{+\infty} \eta_r(t)\mathrm{d}t$ is convergent.

Theorem

Under the above assumptions the trivial steady state of $(\star\star)$ is globally stable if and only if

$$\frac{1}{\sigma}\int_0^{\sigma} \eta(t)\mathrm{d}t \geq \lim_{x\to 0^+} f(x).$$

M.B., U. Foryś, M.J. Piotrowska, *Appl. Math. Lett.*, (2013).

System with self regulation(s)

Biological system often need a system that keep amount (concentration) of a substance on a certain level. We assume that decay rate is constant.

- Constant production

$$\text{outside} \xrightarrow{\text{production } a} \boxed{\text{protein}} \xrightarrow{\text{degradation } \mu} \emptyset$$

System with self regulation(s)

Biological system often need a system that keep amount (concentration) of a substance on a certain level. We assume that decay rate is constant.

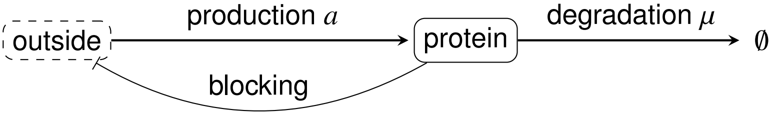
- Constant production $x'(t) = a - \mu x(t)$.

$$\text{outside} \xrightarrow{\text{production } a} \boxed{\text{protein}} \xrightarrow{\text{degradation } \mu} \emptyset$$

System with self regulation(s)

Biological system often need a system that keep amount (concentration) of a substance on a certain level. We assume that decay rate is constant.

- Constant production $x'(t) = a - \mu x(t)$.

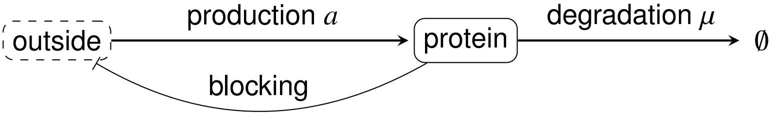


Weakness — the system does not react on its own state.

System with self regulation(s)

Biological system often need a system that keep amount (concentration) of a substance on a certain level. We assume that decay rate is constant.

- Constant production $x'(t) = a - \mu x(t)$.



Weakness — the system does not react on its own state.

- Production is blocked by the presence of the substance.

$$x'(t) = a\,y(t) - \mu x$$
$$y'(t) = \frac{\alpha}{\varepsilon}\big(1 - y(t)\big) - \frac{\beta}{\varepsilon}y(t)x(t)$$

System with self regulation(s)

Biological system often need a system that keep amount (concentration) of a substance on a certain level. We assume that decay rate is constant.

- Constant production $x'(t) = a - \mu x(t)$.

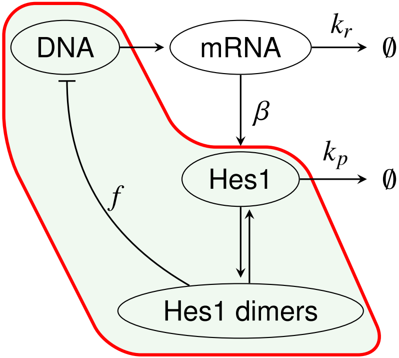
$$\begin{tikzcd} \text{outside} \arrow[r, "\text{production } a"] & \boxed{\text{protein}} \arrow[r, "\text{degradation } \mu"] \arrow[l, bend left, dash, "\text{blocking}"] & \emptyset \end{tikzcd}$$

Weakness — the system does not react on its own state.

- Production is blocked by the presence of the substance.

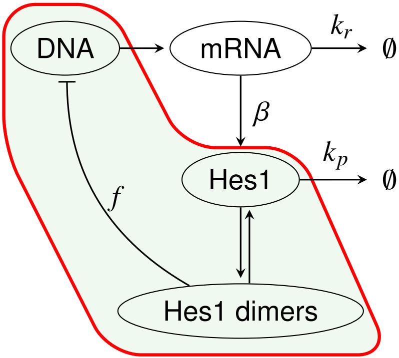
$$\begin{aligned} x'(t) &= a\, y(t) - \mu x \\ y'(t) &= \frac{\alpha}{\varepsilon}\big(1 - y(t)\big) - \frac{\beta}{\varepsilon} y(t)x(t) \end{aligned} \quad \xRightarrow{\varepsilon \to 0} \quad x'(t) = \frac{a}{1 + \frac{\beta}{\alpha}x(t)} - \mu x.$$

Classical Hes1 gene expression model



- Hes1 proteins form dimers and bound to its own DNA blocking transcription.
- Intensity of mRNA production decreases with increasing concentration of the protein (the process is described by a function f)
- In models we describe only concentrations of mRNA and protein.

Classical Hes1 gene expression model



- Hes1 proteins form dimers and bound to its own DNA blocking transcription.
- Intensity of mRNA production decreases with increasing concentration of the protein (the process is described by a function f)
- In models we describe only concentrations of mRNA and protein.

Classical model (N.A. Monk, *Curr. Biol.*, **13**: 1409–1413, (2003))

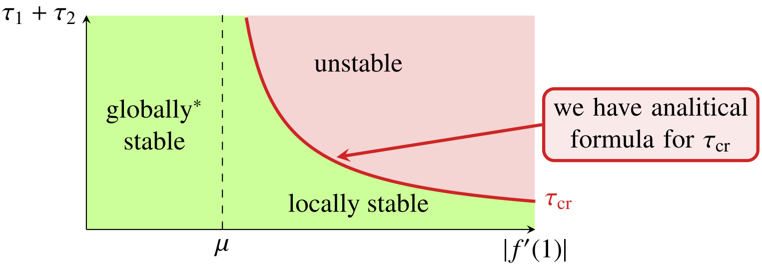
$$\begin{aligned}\dot r(t) &= \boxed{\tilde f(p(t-\tau_r))} - k_r r(t)\,,\\ \dot p(t) &= \beta r(t-\tau_p) - k_p p(t)\,,\end{aligned} \quad \xrightarrow{\text{rescaling}} \quad \begin{aligned}\dot x(t) &= \boxed{f(y(t-\tau_1))} - x(t)\,,\\ \dot y(t) &= x(t-\tau_2) - \mu y(t)\,,\end{aligned}$$

Usually $\quad f(p) = \dfrac{\gamma_r k^h}{k^h + p^h}.$

What is known about model properties

✓ Non-negative, unique, bounded solution globally defined;

→ The (local) stability of the unique postive steady state



If $f'''(1) < -\alpha(f''(1))^2$, then the Hopf bifurcation is supercritical, α depends on $f'(1)$, and model parameters.

S. Bernard et al., *Phil. Trans. R. Soc. A*, (2006)

M.B., A. Bartłomiejczyk, *Non. Anal. RWA*, (2013)

*Global stability proved under additional assumptions

M.B., *J. Diff. Eqs*, (2015)

Numerical simulations can suggest incorect results

For $f(p) = \dfrac{\gamma_r k^h}{k^h + p^h}$ and sufficiently large τ the steady state can loose stability (if the Hill coefficient h is large enough).

- How large should be delay to have sustained oscillation?

Numerical results

τ	damping	period
0	0	
10	240	170
30	870	170
40	1900	170
50	9500	170
80	∞	280

Numerical results from the paper M. Jensen et al. *FEBS Lett.* (2003).

Numerical simulations can suggest incorect results

For $f(p) = \dfrac{\gamma_r k^h}{k^h + p^h}$ and sufficiently large τ the steady state can loose stability (if the Hill coefficient h is large enough).

- How large should be delay to have sustained oscillation?

Numerical results

τ	damping	period
0	0	
10	240	170
30	870	170
40	1900	170
50	9500	170
80	∞	280

Analytical results

For the parameters used for simulations:
Stable oscillations appear for $\tau \approx 41$.

The amplitude of limit cycle is small, around $0,2$, while the amplitude at the beginning of simulation can be large.

Numerical results from the paper M. Jensen et al. *FEBS Lett.* (2003).

Current projects (of M.B. U. Foryś and M.J. Piotrowska)

Currently we are working on mathematical models of tumour, in particular brain tumour in the framework of

- *Mathematical models and methods in description of tumour growth and its therapies.* (NCN, OPUS),
- *Therapy optimization in glioblastoma: An integrative human data-based approach using mathematical models* (James S. Mc. Donnell Foundation), PI: Victor Perez Garcia.

  This is a collaborative project in which many institution are involved, among others
  - Mathematical Oncology Laboratory, Universidad de Castilla-La Mancha, Spain
  - Hospital 12 de Octubre, Madrid, Spain
  - Fundación Hospital de Madrid, HM Hospitals, Spain
  - Department of Neurobiology, Institute for Biological Research, University of Belgrade, Serbia
  - Bern Inselspital, Switzerland.


Thank you for your attention!