A mathematical periodic model for the hematopoiesis process with predictable abrupt changes

Teresa Faria[a], José J. Oliveira[b]

November 2, 2022

(a) Faculdade de Ciências da Universidade de Lisboa, CMAF
(b) Departamento de Matemática, CMAT, Universidade do Minho

Delay differential equations

Delay differential equations

- $x(t)$ feeling of the water temperature
- $\tau > 0$ delay time
- $F : \mathbb{R} \to \mathbb{R}$ reaction men on the temperature regulator

Delay differential equations

- $x(t)$ feeling of the water temperature
- $\tau > 0$ delay time
- $F : \mathbb{R} \to \mathbb{R}$ reaction men on the temperature regulator

$$x'(t) = F(x(t))$$

Delay differential equations

- $x(t)$ feeling of the water temperature
- $\tau > 0$ delay time
- $F : \mathbb{R} \to \mathbb{R}$ reaction men on the temperature regulator

▶

$$x'(t) = F(x(t - \tau))$$

Delay differential equations

- $x(t)$ feeling of the water temperature
- $\tau > 0$ delay time
- $F : \mathbb{R} \to \mathbb{R}$ reaction men on the temperature regulator

- If the water speed depends of time. $\tau : [0, +\infty) \to [0, +\infty)$

$$x'(t) = F(x(t - \tau(t)))$$

Delay differential equations

- For $\tau \in \mathbb{R}^+$ and $m \in \mathbb{N}$, consider

$$\mathcal{C} := C([-\tau, 0]; \mathbb{R}^m) = \left\{ \varphi : [-\tau, 0] \to \mathbb{R}^m \,\middle|\, \varphi \text{ is continuous} \right\}$$

with the norm

$$\|\varphi\| = \sup_{\theta \in [-\tau, 0]} |\varphi(\theta)|_{\mathbb{R}^m}.$$

Delay differential equations

- For $\tau \in \mathbb{R}^+$ and $m \in \mathbb{N}$, consider

$$\mathcal{C} := C([-\tau, 0]; \mathbb{R}^m) = \left\{ \varphi : [-\tau, 0] \to \mathbb{R}^m \,\middle|\, \varphi \text{ is continuous} \right\}$$

  with the norm

$$\|\varphi\| = \sup_{\theta \in [-\tau, 0]} |\varphi(\theta)|_{\mathbb{R}^m}.$$

- The real space $(\mathcal{C}, \|\cdot\|)$ is a Banach space.

- For $F : [0, +\infty) \times \mathcal{C} \to \mathbb{R}^m$ continuous, we call a delay differential equation to the equation

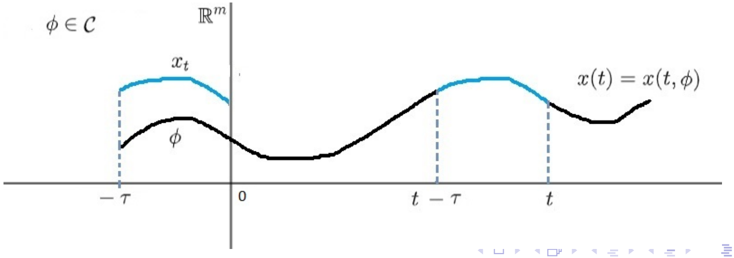
$$\begin{cases} x'(t) = F(t, x_t), & t > 0 \\ x(t) = \phi(t), & t \in [-\tau, 0] \end{cases}$$

- For $F : [0, +\infty) \times \mathcal{C} \to \mathbb{R}^m$ continuous, we call a delay differential equation to the equation

$$\begin{cases} x'(t) = F(t, x_t), & t > 0 \\ x(t) = \phi(t), & t \in [-\tau, 0] \end{cases}$$

- Let $b \in (0, +\infty]$, and $x : [-\tau, b] \to \mathbb{R}^m$ a continuous function. For $t \in [0, b]$, the function $x_t \in \mathcal{C}$ is defined by

$$x_t(\theta) = x(t + \theta), \quad \forall \theta \in [-\tau, 0].$$



Biological models

In what follows, we only consider the scalar case $(m = 1)$ and non-negative time $(t \geq 0)$.

- Scalar biological models

$$x'(t) = -\text{Mortality} + \text{Birth}, \qquad t \geq 0,$$

  where:

  - $x(t)$ is the amount of living beings (animals, plants, cells, etc...);
  - .
  - .
- .
- .

Biological models

In what follows, we only consider the scalar case $(m = 1)$ and non-negative time $(t \geq 0)$.

- Scalar biological models

$$x'(t) = -ax(t) + \text{Birth}, \qquad t \geq 0,$$

  where:

  - $x(t)$ is the amount of living beings (animals, plants, cells, etc...);
  - $a > 0$
  - .

- Mortality: $ax(t)$
- .

Biological models

In what follows, we only consider the scalar case $(m = 1)$ and non-negative time $(t \geq 0)$.

- Scalar biological models

$$x'(t) = -a(t)x(t) + \text{Birth}, \qquad t \geq 0,$$

  where:
  - $x(t)$ is the amount of living beings (animals, plants, cells, etc...);
  - $a : [0, \infty) \to \mathbb{R}^+$ is a periodic continuous function;
  - .
- Mortality: $a(t)x(t)$
- .

Biological models

In what follows, we only consider the scalar case ($m = 1$) and non-negative time ($t \geq 0$).

- Scalar biological models

$$x'(t) = -a(t)x(t) + f(t, x_t), \qquad t \geq 0,$$

  where:
  - $x(t)$ is the amount of living beings (animals, plants, cells, etc...);
  - $a : [0, \infty) \to \mathbb{R}^+$ is a periodic continuous function;
  - $\forall \phi \in \mathcal{C}$, $t \mapsto f(t, \phi)$ is a periodic continuous function.
- Mortality: $a(t)x(t)$
- Birth: $f(t, x_t)$

Biological models

- Scalar biological models

$$x'(t) = -a(t)x(t) + f(t, x_t), \qquad t \geq 0, \tag{1}$$

where:

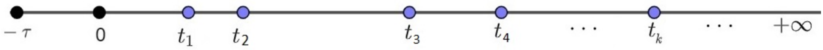
  - $x(t)$ is the amount of living beings (animals, plants, cells, etc...);
  - $a : [0, \infty) \to \mathbb{R}^+$ is a periodic continuous function;
  - $\forall \phi \in \mathcal{C}$, $t \mapsto f(t, \phi)$ is a periodic continuous function.

- Mortality: $a(t)x(t)$
- Birth: $f(t, x_t)$

$\boxed{\text{Only positive solutions are significant: } x(t) > 0}$

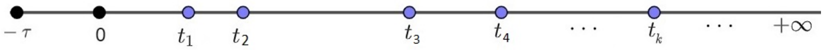
Impulsive biological models

- Assume there are abrupt changes in $x(t)$ at specific times in the future, $(t_k)_{k\in\mathbb{N}}$.

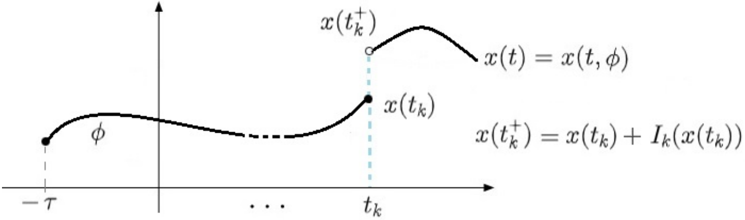


Impulsive biological models

- Assume there are abrupt changes in $x(t)$ at specific times in the future, $(t_k)_{k\in\mathbb{N}}$.



- We mean



- Note that $x(t_k^+) - x(t_k) = I_k(x(t_k))$

Impulsive biological models

- Scalar impulsive delay differential equation

$$\begin{cases} x'(t) = -a(t)x(t) + f(t, x_t), & 0 \leq t \neq t_k, \\ x(t_k^+) = x(t_k) + I_k(x(t_k)), & k = 1, 2, \dots \end{cases}, \qquad (2)$$

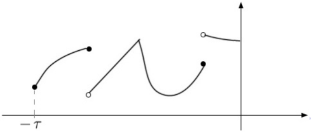
where
  - $(t_k)_{k \in \mathbb{N}}$ such that $0 < t_k \nearrow +\infty$;
  - $I_k : \mathbb{R} \to \mathbb{R}$ continuous;
  - $a : [0, \infty) \to (0, \infty)$ continuous;
  - $f : [0, \infty) \times PC \to [0, \infty)$ with some regularities.

Impulsive biological models

- Scalar impulsive delay differential equation

$$\begin{cases} x'(t) = -a(t)x(t) + f(t, x_t), & 0 \le t \ne t_k, \\ x(t_k^+) = x(t_k) + I_k(x(t_k)), & k = 1, 2, \dots \end{cases}, \qquad (2)$$

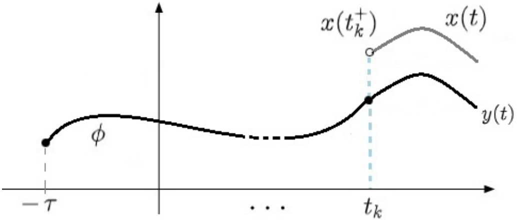
  where
  - $(t_k)_{k\in\mathbb{N}}$ such that $0 < t_k \nearrow +\infty$;
  - $I_k : \mathbb{R} \to \mathbb{R}$ continuous;
  - $a : [0, \infty) \to (0, \infty)$ continuous;
  - $f : [0, \infty) \times PC \to [0, \infty)$ with some regularities.
- $PC = \left\{ \varphi : [-\tau, 0] \to \mathbb{R} \,\middle|\, \varphi \text{ is piecewise continuous} \right\}$



The **key step** to deal with impulsive models.

- For $x(t)$ a solution of (2) on $[0, \infty)$, define

$$y(t) = \prod_{k:0 \leq t_k < t} \frac{x(t_k)}{x(t_k) + I_k(x(t_k))} x(t)$$



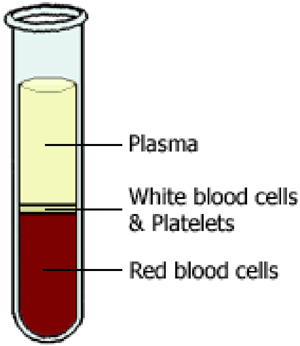
- The function $y(t)$ is continuous and it is solution of

$$y'(t) = -a(t)y(t) + \prod_{k:0 \leq t_k < t} J_k(x(t_k))f(t, x_t), \qquad 0 \leq t \neq t_k.$$

Hematopoiesis process

Process of production, multiplication, regulation, and specialization of blood cells in the bone marrow.

Blood

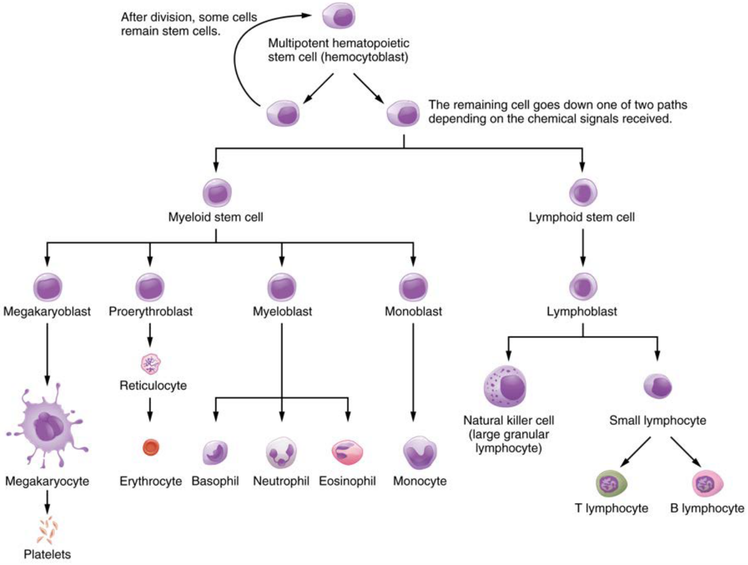


Blood is made by 55% plasma and 45% blood cells.

cells	number cells/$1\mu l$ [2]	
thrombocytes (Platelets)	$15 \times 10^4 \leftrightarrow 40 \times 10^4$	
erythrocytes (red cells)	men	$43 \times 10^5 \leftrightarrow 59 \times 10^5$
	women	$35 \times 10^5 \leftrightarrow 55 \times 10^5$
leukocytes (white cells)	$4500 \leftrightarrow 11000$	

$$1\mu l = 1mm^3$$

[2] L. Dean, *Blood Group and Red Cell Antigens, National Center for Biotechnology Information (US)*, 2005.


After division, some cells remain stem cells.
Multipotent hematopoietic stem cell (hemocytoblast)
The remaining cell goes down one of two paths depending on the chemical signals received.
Myeloid stem cell
Lymphoid stem cell
Megakaryoblast
Proerythroblast
Myeloblast
Monoblast
Lymphoblast
Reticulocyte
Natural killer cell (large granular lymphocyte)
Small lymphocyte
Megakaryocyte
Erythrocyte
Basophil
Neutrophil
Eosinophil
Monocyte
T lymphocyte
B lymphocyte
Platelets

Maturation time in the bone marrow

cells	Maturation time
thrombocytes (Platelets)	$\simeq$7 days [3]
erythrocytes (red blood)	$\simeq$6 days [4]
neutrophils (60% of white blood cells)	$\simeq$15 days [5]

[3] G.P. Langlois, M. Craig, A.R. Humphries et al., *Normal and pathological dynamics of platelets in humans*, J. Math. Biol. 75 (2017), 1411–1462.

[4] J. Bélair, M. C. Mackey, J. M. Mahaffy, *Age-structured and two-delay models for erythropoiesis*, Math. Biosci. 128 (1995), 317–346.

[5] Y. Yan, J. Sugie, *Existence regions of positive periodic solutions for a discrete hematopoiesis model with unimodal production functions* Appl. Math. Model. 68 (2019), 152–168.

Hematopoiesis models

- Consider the scalar biological model (1) periodic

$$x'(t) = -a(t)x(t) + f(t, x_t), \qquad t \geq 0,$$

- where:
  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a(t)$ is the mortality rate at time t;
  - $f(t, x_t)$ is the release of new blood cells in the circulation bloodstream at time t;
  - ;
  - .

Hematopoiesis models

- Consider the scalar biological model periodic

$$x'(t) = -a(t)x(t) + \beta, \qquad t \geq 0,$$

- where:
  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
  - $\beta > 0$ is the production;
  - ;
  - ;
  - .

Hematopoiesis models

- Consider the scalar biological model periodic

$$x'(t) = -a(t)x(t) + \beta(t), \qquad t \geq 0,$$

- where:
    - $x(t)$ is the density of blood cells in circulation at time t;
    - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
    - $\beta : [0, +\infty) \to \mathbb{R}^+$ is the production periodic function;
    - ;
    - ;
    - .

Hematopoiesis models

- Consider the scalar biological model periodic

$$x'(t) = -a(t)x(t) + \frac{\beta(t)}{x(t)}, \qquad t \geq 0,$$

- where:
  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
  - $\beta : [0, +\infty) \to \mathbb{R}^+$ is the production rate periodic function;
  - ;
  - ;
  - .

Hematopoiesis models

- Consider the scalar biological model periodic

$$x'(t) = -a(t)x(t) + \frac{\beta(t)\eta}{\eta + x(t)}, \qquad t \geq 0,$$

- where:
  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
  - $\beta : [0, +\infty) \to \mathbb{R}^+$ is the maximal production rate periodic function;
  - $\eta > 0$ a shape parameter;
  - .

Hematopoiesis models

- Consider the scalar biological model periodic

$$x'(t) = -a(t)x(t) + \frac{\beta(t)\eta}{\eta + x(t-\tau)}, \qquad t \geq 0,$$

- where:
  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
  - $\beta : [0, +\infty) \to \mathbb{R}^+$ is the maximal production rate periodic function;
  - $\eta > 0$ a shape parameter;
  - $\tau \geq 0$ is the time delay.

Hematopoiesis models

- Consider the scalar biological model periodic

$$x'(t) = -a(t)x(t) + \frac{\beta_1(t)\eta}{\eta + x(t-7)} + \frac{\beta_2(t)\eta}{\eta + x(t-6)} + \frac{\beta_3(t)\eta}{\eta + x(t-15)}$$

- where:
  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
  - $\beta_1, \beta_2, \beta_3 : [0, +\infty) \to \mathbb{R}^+$ are the maximal production rate periodic functions;
  - $\eta > 0$ a shape parameter;
  - $\tau \geq 0$ is the time delay.

Hematopoiesis model with several delays

- Thus we can consider

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))}, \qquad t \geq 0$$

where $m \in \mathbb{N}$,

- $x(t)$ is the density of blood cells in circulation at time t;
- $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
- $\beta_i : [0, +\infty) \to \mathbb{R}^+$ are the maximal production rate periodic functions;
- $\tau_i : [0, +\infty) \to [0, +\infty)$ are the periodic delay functions.

Hematopoiesis model with several delays

- Thus we can consider

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))}, \qquad t \geq 0$$

where $m \in \mathbb{N}$,

  - $x(t)$ is the density of blood cells in circulation at time t;
  - $a : [0, +\infty) \to \mathbb{R}^+$ is the mortality rate periodic function;
  - $\beta_i : [0, +\infty) \to \mathbb{R}^+$ are the maximal production rate periodic functions;
  - $\tau_i : [0, +\infty) \to [0, +\infty)$ are the periodic delay functions.

- **Notation:** The maximal delay is $\overline{\tau} = \max_t \tau(t)$, where

$$\tau(t) = \max_i \tau_i(t)$$

Pioneers Hematopoiesis models

Mackey and Glass [1], proposed the following models to describe the hematopoiesis process:

- Hematopoieses with monotone prodution rate

$$z'(t) = -\gamma z(t) + \frac{F_0 \eta^n}{\eta^n + z(t-\tau)^n}, \qquad n > 0; \tag{3}$$

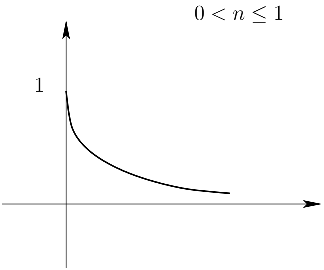
- Hematopoiesis with unimodal prodution rate

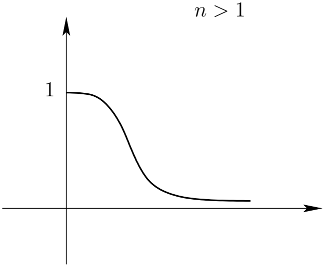
$$z'(t) = -\gamma z(t) + \frac{F_0 \eta^n z(t-\tau)}{\eta^n + z(t-\tau)^n}, \qquad n > 1; \tag{4}$$

$z(t)$ density of cells at time t; τ time delay; γ destruction rate;
F_0 maximal prodution rate (only for (3)); η a shape parameter.

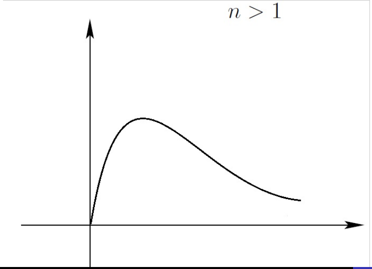
[1] M.C.Mackey, L. Glass, Science 197 (1977) 287-289.

- Monotone prodution rate





- Unimodal prodution rate



Hematopoiesis model with linear impulses

For $(t_k)_k$ an increasing sequence such that $t_k \to \infty$, we consider

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))^n}, & 0 \leq t \neq t_k, \\ \\ x(t_k^+) = (1 + b_k)x(t_k), & k \in \mathbb{N} \end{cases} \tag{5}$$

with $n \in \mathbb{R}^+$ and the impulsive functions are linear, that is

$$I_k(u) = b_k u, \qquad \text{for } b_k \in \mathbb{R}.$$

Note that

$$x(t_k^+) = (1 + b_k)x(t_k) \Leftrightarrow x(t_k^+) = x(t_k) + b_k x(t_k)$$

$$PC_0^+ = \left\{ \varphi \in PC : \varphi(\theta) \geq 0 \text{ for } \theta \in [-\overline{\tau}, 0),\ \varphi(0) > 0 \right\}$$

- **Periodic Hematopoiesis model with linear impulses**

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t-\tau_i(t))^n}, & 0 \le t \ne t_k, \\ x(t_k^+) = (1+b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

- **Periodic Hematopoiesis model with linear impulses**

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t-\tau_i(t))^n}, & 0 \leq t \neq t_k, \\ x(t_k^+) = (1+b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

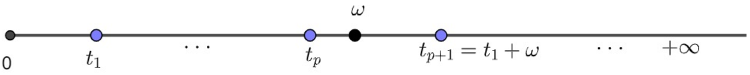
- **(H1)** $a, \beta_i : [0, +\infty) \to (0, \infty)$ and $\tau_i : [0, +\infty) \to [0, +\infty)$ are ω-periodic continuous functions, for some $\omega > 0$;

- **Periodic Hematopoiesis model with linear impulses**

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t-\tau_i(t))^n}, & 0 \le t \ne t_k, \\ x(t_k^+) = (1+b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

- **(H1)** $a, \beta_i : [0, +\infty) \to (0, \infty)$ and $\tau_i : [0, +\infty) \to [0, +\infty)$ are ω-periodic continuous functions, for some $\omega > 0$;
- **(H2)** $\exists p \in \mathbb{N}$ such that $0 < t_1 < \cdots < t_p < \omega$ and

$$t_{k+p} = t_k + \omega, \qquad b_{k+p} = b_k, \qquad k \in \mathbb{N};$$



- **Periodic Hematopoiesis model with linear impulses**

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t-\tau_i(t))^n}, & 0 \le t \neq t_k, \\ x(t_k^+) = (1+b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

- **(H1)** $a, \beta_i : [0, +\infty) \to (0, \infty)$ and $\tau_i : [0, +\infty) \to [0, +\infty)$ are ω-periodic continuous functions, for some $\omega > 0$;
- **(H2)** $\exists p \in \mathbb{N}$ such that $0 < t_1 < \cdots < t_p < \omega$ and

$$t_{k+p} = t_k + \omega, \qquad b_{k+p} = b_k, \qquad k \in \mathbb{N};$$

- **(H3)** $1 + b_k > 0$, $\forall k \in \mathbb{N}$;

- **Periodic Hematopoiesis model with linear impulses**

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t-\tau_i(t))^n}, & 0 \le t \neq t_k, \\ x(t_k^+) = (1+b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

- **(H1)** $a, \beta_i : [0, +\infty) \to (0, \infty)$ and $\tau_i : [0, +\infty) \to [0, +\infty)$ are ω-periodic continuous functions, for some $\omega > 0$;
- **(H2)** $\exists p \in \mathbb{N}$ such that $0 < t_1 < \cdots < t_p < \omega$ and

$$t_{k+p} = t_k + \omega, \qquad b_{k+p} = b_k, \qquad k \in \mathbb{N};$$

- **(H3)** $1 + b_k > 0$, $\forall k \in \mathbb{N}$;
- **(H4)** $\prod_{k=1}^{p}(1+b_k) < e^{\int_0^\omega a(t)dt}$

Existence of periodic solution

- **Theorem 1** Faria & Oliveira [3]:
  Assume **(H1)-(H4)**.
  Then system (5)

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))^n}, & 0 \le t \ne t_k, \\ x(t_k^+) = (1 + b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

  has at least one positive ω-periodic solution.

[3] T. Faria and J.J. Oliveira, *Existence of positive periodic solution for scalar delay differential equations with and without impulses*, J. Dyn. Differ. Equ., 31 (2019), 1223-1245.

Existence of periodic solution

- **Theorem 1** Faria & Oliveira [3]:
  Assume **(H1)-(H4)**.
  Then system (5)

$$\begin{cases} x'(t) = -a(t)x(t) + \displaystyle\sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))^n}, & 0 \le t \neq t_k, \\ x(t_k^+) = (1 + b_k)x(t_k), & k \in \mathbb{N} \end{cases}$$

  has at least one positive ω-periodic solution.

- In what follows, we denote by $x^*(t)$ a positive ω-periodic solution of system (5).

[3] T. Faria and J.J. Oliveira, *Existence of positive periodic solution for scalar delay differential equations with and without impulses*, J. Dyn. Differ. Equ., 31 (2019), 1223-1245.

- **Theorem 2**: Assume **(H1)-(H4)** and $n \in (0,1]$.
  The periodic solution $x^*(t)$ of (5) is GAS, in the set of positive solutions, if there is $T > 0$ such that

$$\alpha_1^*\alpha_2^* < 1 \quad \text{or} \quad \alpha_1\alpha_2 < \frac{9}{2},$$

where $\alpha_j^* = \sup_{t\geq T} \alpha_j^*(t)$, $\alpha_j = \sup_{t\geq T} \alpha_j^*(t)\, e^{\int_{t-\tau(t)}^t a(u)du}$ $(j=1,2)$,

and

$$\alpha_1^*(t) = \int_{t-\tau(t)}^t \sum_{i=1}^m \beta_i(s) \frac{nx^*(s-\tau_i(s))^{n-1}}{[1+x^*(s-\tau_i(s))^n]^2} B_i(s)\, e^{-\int_s^t a(u)\,du}\, ds$$

$$\alpha_2^*(t) = \int_{t-\tau(t)}^t \sum_{i=1}^m \beta_i(s) \frac{x^*(s-\tau_i(s))^{n-1}}{1+x^*(s-\tau_i(s))^n} B_i(s)\, e^{-\int_s^t a(u)\,du}\, ds$$

with $B_i(s) = \prod_{k: t-\tau_i(t)\leq t_k < t} (1+b_k)^{-1}, \quad i = 1, \dots, m.$

In case that $x^*(t)$ is unknown, we have the estimate

$$\mathfrak{m} \leq x^*(t) \leq \mathfrak{M}, \qquad t \geq 0,$$

where

$$\mathfrak{M} = \min\left\{ M\beta\overline{B}, M\overline{B}(e^{A(\omega)} - 1)\, e^{A(\omega)} \left(\max_{t\in[0,\omega]} \frac{\sum_{i=1}^m \beta_i(t)}{a(t)} \right) \right\}$$

$$\mathfrak{m} = \frac{e^{-A(\omega)}\, M\underline{B}}{1 + \mathfrak{M}^n} \max\left\{ \beta, (e^{A(\omega)} - 1) \left(\min_{t\in[0,\omega]} \frac{\sum_{i=1}^m \beta_i(t)}{a(t)} \right) \right\}$$

with $\beta = \int_0^\omega \sum_{i=1}^m \beta_i(s)ds$, $A(\omega) = \int_0^\omega a(u)du$,
$M = \left(\prod_{k=1}^p (1+b_k)^{-1} - e^{-A(\omega)} \right)^{-1}$,
$\overline{B} = \max\left\{ 1, \prod_{k=j}^{j+l} (1+b_k)^{-1} : j = 1, \dots, p, l = 0, \dots, p-1 \right\}$, and
$\underline{B} = \min\left\{ 1, \prod_{k=j}^{j+l} (1+b_k)^{-1} : j = 1, \dots, p, l = 0, \dots, p-1 \right\}$.

Theorem 3: Assume **(H1)-(H4)** and $n > 1$.
The periodic solution $x^*(t)$ of (5) is GAS (in PC_0^+) if, for some $T > 0$, one of the following conditions holds:

(i) $\left(\alpha_1\gamma < \frac{9}{4} \text{ or } \alpha_1^*\gamma^* < 1\right)$ and $\inf_t\{x^*(t)\} \geq \left(\frac{n-1}{n+1}\right)^{\frac{1}{n}}$;

(ii) $\left(\alpha_1\gamma < \frac{9}{4} \text{ or } \alpha_1^*\gamma^* < 1\right)$ and $\sup_t\{x^*(t)\} \leq \left(\frac{n-1}{n+1}\right)^{\frac{1}{n}}$;

(iii) $\gamma < \frac{3}{2}$ or $\gamma^* < 1$,

where $\gamma^* = \sup\limits_{t \geq T} \gamma^*(t)$, $\gamma = \sup\limits_{t \geq T} \gamma^*(t)\, e^{\int_{t-\tau(t)}^t a(u)du}$, with

$$\gamma^*(t) = \rho_n \int_{t-\tau(t)}^{t} \sum_{i=1}^{m} \beta_i(s) B_i(s)\, e^{-\int_s^t a(u)\,du}\, ds,$$

with $\rho_n = \frac{(n+1)^2}{4n}\left(\frac{n-1}{n+1}\right)^{\frac{n-1}{n}}$, $B_i(s)$, α_1, and α_1^* as above.

- No impulsive case ($b_k = 0, \forall k \in \mathbb{N}$)

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))^n}, \quad t \geq 0, \qquad (6)$$

[7] G. Liu, J. Yan and F. Zhang, J. Math. Anal. Appl. 334 (2007), 157-171.

- No impulsive case ($b_k = 0,\ \forall k \in \mathbb{N}$)

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t - \tau_i(t))^n}, \quad t \geq 0, \qquad (6)$$

- **Theorem 5**: Consider $n > 1$ and assume **(H1)**. If

$$\rho_n \sup_{t\in[0,\omega]} \int_{t-\tau(t)}^{t} \sum_{i=1}^{m} \beta_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds < \max\left\{1, \frac{3}{2}\,\mathrm{e}^{-\mathcal{A}}\right\},$$

$\mathcal{A} = \sup_{t\in[0,\omega]} \int_{t-\tau(t)}^{t} a(u)du$ and $\rho_n = \frac{(n+1)^2}{4n}\left(\frac{n-1}{n+1}\right)^{\frac{n-1}{n}}$
then there is a GAS positive ω-periodic solution of (6).

[7] G. Liu, J. Yan and F. Zhang, J. Math. Anal. Appl. 334 (2007), 157-171.

- No impulsive case ($b_k = 0$, $\forall k \in \mathbb{N}$)

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{\beta_i(t)}{1 + x(t-\tau_i(t))^n}, \quad t \geq 0, \qquad (6)$$

- **Theorem 5**: Consider $n > 1$ and assume **(H1)**. If

$$\rho_n \sup_{t\in[0,\omega]} \int_{t-\tau(t)}^{t} \sum_{i=1}^{m} \beta_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds < \max\left\{1, \frac{3}{2}\,\mathrm{e}^{-\mathcal{A}}\right\},$$

$\mathcal{A} = \sup_{t\in[0,\omega]} \int_{t-\tau(t)}^{t} a(u)du$ and $\rho_n = \frac{(n+1)^2}{4n}\left(\frac{n-1}{n+1}\right)^{\frac{n-1}{n}}$
then there is a GAS positive ω-periodic solution of (6).
- Liu et al [7] proved the the same assuming **(H1)**, $n > 1$, and

$$(n-1)^{\frac{n-1}{n}} \frac{\mathrm{e}^{A(\omega)}}{\mathrm{e}^{A(\omega)} - 1} \int_0^{\omega} \sum_{i=1}^{m} \beta_i(s)ds \leq 1.$$

[7] G. Liu, J. Yan and F. Zhang, J. Math. Anal. Appl. 334 (2007), 157-171.

Numerical example

Consider the 1-periodic model

$$\begin{aligned} x'(t) &= -\left(1 + \frac{1}{2}\cos(2\pi t)\right)x(t) + \frac{c_1\left(1 + \frac{1}{2}\cos(2\pi t)\right)}{1 + x(t - 6 - \cos(2\pi t))^n} \\ &\quad + \frac{c_2\left(1 + \frac{1}{2}\sin(2\pi t)\right)}{1 + x(t - 7 - \cos(2\pi t))^n} + \frac{c_3\left(1 + \frac{1}{2}\cos(2\pi t)\right)}{1 + x(t - 15 - \cos(2\pi t))^n}, \end{aligned}$$

where c_1, c_2, c_3 are positive real numbers.

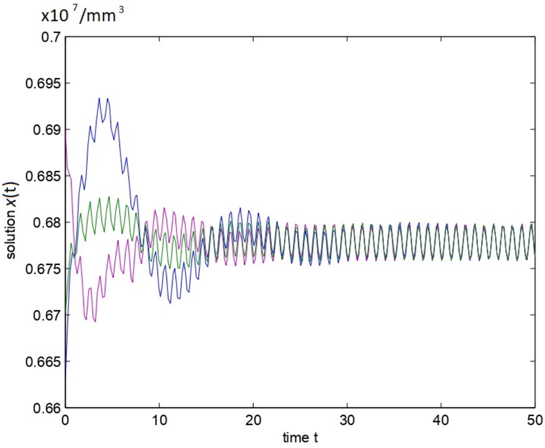


Figure: Numerical simulation of three solutions where $c_1 = 1.1$, $c_2 = 0.03$, $c_3 = 0.001$ and $n = 1.03$, with initial condition $\varphi(\theta) = 0.67$, $\varphi(\theta) = 0.65(1 + 0.02\cos(\theta))$, and $\varphi(\theta) = 0.69(1 + 0.02\sin(\theta))$, for $\theta \in [-16, 0]$, respectively.

Thank you

The presented results are published in

[8] T. Faria and J.J. Oliveira, *Global asymptotic stability for a periodic delay hematopoiesis model with impulses*, Applied Mathematical Modelling 79 (2020) 843-864.