Global attractivity of the periodic solution for a periodic model of hematopoiesis

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Hematopoiesis models

Mackey and Glass [1], proposed the following models to describe the hematopoiesis process (the process of production, multiplication, and specialization of blood cells in the bone marrow):

- Hematopoieses with monotone prodution rate

$$z'(t) = -\gamma z(t) + \frac{F_0 \eta^n}{\eta^n + z^n(t-\tau)}, \qquad n > 0; \tag{1}$$

- Hematopoiesis with unimodal prodution rate

$$z'(t) = -\gamma z(t) + \frac{F_0 \eta^n z(t-\tau)}{\eta^n + z^n(t-\tau)}, \qquad n > 1; \tag{2}$$

$z(t)$ density of cells in time t; τ time delay; γ destruction rate;
F_0 maximal prodution rate (only for (1)); η a shape parameter.

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

- With the change of variable $z(t) = \eta x(t)$, eq. (1) becomes

$$x'(t) = -\gamma x(t) + \frac{\beta}{1 + x^n(t-\tau)}, \qquad t \geq 0, \tag{3}$$

where $\beta = F_0/\eta > 0$, $\gamma > 0$, $n > 0$, and $\tau \geq 0$.

[2] E.Liz, M.Pinto, V.Tkachenko, and S.Trofimchuk, Quart. Appl. Math. 63 (2005), 56-70.

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- The unique positive solution K of the equation

$$\gamma K = \frac{\beta}{1 + K^n}$$

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- **Theorem 1** Liz et al (2005)[2]:
The equilibrium K is a global attractor of (3), in the set of positive solutions, if one of the following conditions holds:
  1. $0 < n \leq 1$;
  2. $n > 1$ and $\gamma \leq \frac{1}{\tau} \ln \frac{n^2+1}{n^2-n}$;
  3. $n > 1$, $\gamma > \frac{1}{\tau} \ln \frac{n^2+1}{n^2-n}$, and $e^{-\tau\gamma} > c \ln \frac{c^2+c}{1+c^2}$, where $c = \frac{\gamma n K^{n+1}}{\beta}$.

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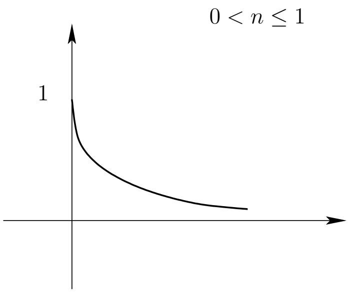
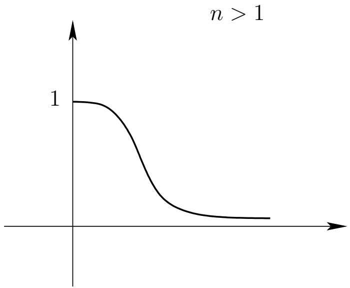
$$g(x) = \frac{1}{1+x^n}$$





Here, we only treat the situation where $0 < n \leq 1$.

- **Periodic Hematopoiesis model**

$$x'(t) = -a(t)x(t) + \frac{b(t)}{1 + x^n(t - \tau(t))}, \qquad t \geq 0, \tag{4}$$

where,
(H) $a, b \in C(\mathbb{R}; (0, \infty))$ and $\tau \in C(\mathbb{R}; [0, \infty))$ are ω-periodic, for $\omega > 0$,

[3] A.Wan and D.Jiang, Kyushu J. Math. 56 (2002), 193-202.

[4] L.Berezansky, E.Braverman, and L.Idels, Appl. Math. Comp. 219 (2013), 4892-4907.

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- **Theorem 2** Wan & Jiang (2002)[3]: Assuming **(H)**, the ω-periodic model (4) has a positive ω-periodic solution, $\tilde{x}(t)$.

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- **Theorem 2** Wan & Jiang (2002)[3]: Assuming **(H)**, the ω-periodic model (4) has a positive ω-periodic solution, $\tilde{x}(t)$.
- **Open Problem 1** Berezansky et al. (2013)[4]: Supposing **(H)** and $0 < n \leq 1$, prove or disprove that all positive solutions of (4) converge to $\tilde{x}(t)$.

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- In 2007, Liu et al. [5], studied the general form of model (4),

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{b_i(t)}{1 + x^n(t - \tau_i(t))}, \qquad t \geq 0, \qquad (5)$$

(H) $a, b_i \in C(\mathbb{R}; (0, \infty))$ and $\tau_i \in C(\mathbb{R}; [0, \infty))$ are ω-periodic, for $\omega > 0$, $m \in \mathbb{N}$, and $i = 1, \dots, m$.

Notation: $\tau(t) = \max_i \tau_i(t)$ and $\tau = \max_t \tau(t)$.

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

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- **Theorem 3** Liu et al.[5]: Assume **(H)** and $0 < n \leq 1$. Then
  (a) Model (5) has a positive ω-periodic solution, $\tilde{x}(t)$;
  (b) The periodic solution $\tilde{x}(t)$ satisfies

$$\tilde{x}(t) \geq x_1 \exp\left(- \sup_{t \in [0,\omega]} \int_{t-\tau}^{t} a(u)du \right) =: X_1, \qquad \text{for all } t \in \mathbb{R},$$

where x_1 is the unique positive solution of the equation

$$\bar{a}x = \sum_{i=1}^{m} \frac{\underline{b}_i}{1 + x^n}, \qquad \bar{a} = \max a(t), \ \underline{b}_i = \min b_i(t).$$

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

Global attractivity

- **Theorem 4** Liu et al. (2007)[5]: Assume **(H)** and $0 < n \leq 1$. The positive ω-periodic solution $\tilde{x}(t)$ of (5) is globally attractive (in the set of all positive solutions), if

$$\frac{nX_1^{n-1}}{1+X_1^n}\frac{e^{A(\omega)}}{e^{A(\omega)}-1}\int_0^\omega \sum_{i=1}^m b_i(s)ds \leq 1, \tag{6}$$

where $A(\omega) = \int_0^\omega a(u)du$.

- **Theorem 5** Faria & Oliveira, (2019)[6]:
  Assume **(H)** and $0 < n \leq 1$. The positive ω-periodic solution $\tilde{x}(t)$ of (5) is globally attractive (in the set of all positive solutions), if there is $T > 0$ such that

$$\frac{nX_1^{n-1}}{(1+X_1^n)^2} \sup_{t\geq T} \int_{t-\tau(t)}^{t} \sum_{i=1}^{m} b_i(s) \exp\left(-\int_s^t a(u)du\right) ds < 1. \quad (7)$$

[6] T. Faria and J.J. Oliveira, Applied Mathematics Letters 94 (2019), 1-7.

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- By easy computations, for all $t > 0$, we prove that

$$\int_{t-\tau(t)}^{t} \sum_{i=1}^{m} b_i(s) \exp\left(-\int_s^t a(u)du\right) ds < \frac{e^{A(\omega)}}{e^{A(\omega)}-1} \int_0^{\omega} \sum_{i=1}^{m} b_i(s) ds.$$

  Thus, Theorem 5 improves the stability criterion presented in Theorem 4.
- The following example shows that condition (7) is strictly less restrictive than condition (6).

[6] T. Faria and J.J. Oliveira, Applied Mathematics Letters 94 (2019), 1-7.

Letting in $n=1$, $m=2$, and
$a(t)=1+\frac{1}{2}\cos(2\pi t)$,
$b_1(t)=\frac{3}{8}\left(1+\frac{1}{2}\cos(2\pi t)\right)$ and $b_2(t)=\frac{3}{8}\left(1+\frac{1}{2}\sin(2\pi t)\right)$,
$\tau_1(t)=\tau_2(t)=\frac{1}{2}(1+\sin(2\pi t))$,
in hematopiesis model (5), we obtain

$$x'(t)=-\left(1+\frac{1}{2}\cos(2\pi t)\right)x(t)+\frac{6+\frac{3}{2}\left(\cos(2\pi t)+\sin(2\pi t)\right)}{8(1+x(t-\frac{1}{2}(1+\sin(2\pi t))))}. \quad (8)$$

In this case, $X_1=\frac{\sqrt{2}-1}{2}e^{-1}$, and condition (7) read as

$$\frac{nX_1^{n-1}}{(1+X_1^n)^2}\sup_{t\geq T}\int_{t-\tau(t)}^{t}\sum_{i=1}^{m}b_i(s)\exp\left(-\int_s^t a(u)du\right)ds\approx 0.64757<1.$$

However, conditon (6) does not hold because

$$\frac{nX_1^{n-1}}{1+X_1^n}\frac{e^{A(\omega)}}{e^{A(\omega)}-1}\int_0^{\omega}\sum_{i=1}^{m}b_i(s)ds\approx 1.10248>1.$$

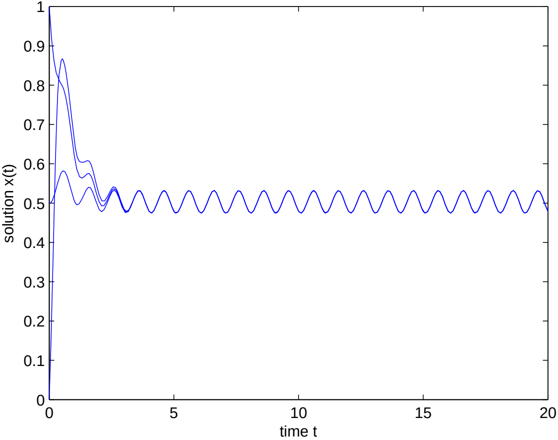

Figure: Three solutions of (8) with initial condition $\varphi_1(\theta) = \cos\theta$, $\varphi_2(\theta) = 0.5e^{\theta}$, and $\varphi_3(\theta) = 0.1 - \mathrm{sen}(\pi\theta)$, for $\theta \in [-1, 0]$, respectively.

Proof of the main result (idea)

- The global stability of the zero equilibrium of the scalar impulsive general delay differential equation

$$y'(t) = -a(t)y(t) + \sum_{i=1}^{m} f_i(t, y_t^i), 0 \leq t \neq t_k,$$
$$y(t_k^+) - y(t_k) = I_k(y(t_k)),\ k \in \mathbb{N},$$

where $y_t^i =, y_{|_{[t-\tau_i(t),t]}}$, and $\tau(t) = \max_i \tau_i(t)$, was studied by Faria & Oliveira and several stability critera are published in

- [7] T. Faria and J.J. Oliveira, *On stability for impulsive delay differential equations and applications to a periodic Lasota-Wazewska model*, Disc. Cont. Dyn. Systems Series B, 21 (2016), 2451-2472.
- [8] T. Faria and J.J. Oliveira, *A note on stability of impulsive scalar delay differential equations*, Electron. J. Qual. Theory Differ. Equ., Paper No. 69 (2016), 1-14.

- Now, we consider the non-impulsive equation

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- and the hypothesis

(A1) $\int_0^{\infty} a(u)\, du = \infty$;

(A2) There are $\lambda_{1,i}, \lambda_{2,i} : [0, \infty) \to [0, \infty)$ piecewise continuous

$$-\lambda_{1,i}(t)\mathcal{M}_t^i(\varphi) \leq f_i\left(t, \varphi_{|_{[-\tau_i(t),0]}}\right) \leq \lambda_{2,i}(t)\mathcal{M}_t^i(-\varphi),\ \ t \geq 0, \varphi \in S^*,$$

$\mathcal{M}_t^i(\varphi) = \max\left\{0, \sup_{\theta\in[-\tau_i(t),0]} \varphi(\theta)\right\}$, S^* an admissible set;

(A3) There is $T > 0$ such that

$$\alpha_1^* \alpha_2^* < 1, \tag{10}$$

where the coefficients $\alpha_j^* := \alpha_j^*(T)$ are given by

$$\alpha_j^* = \sup_{t\geq T} \int_{t-\tau(t)}^{t} \sum_{i=1}^{m} \lambda_{j,i}(s) e^{-\int_s^t a(u)du} ds, \qquad j = 1, 2.$$

- **Theorem 6** Faria & Oliveira (2016)[7]: Assume (A1)-(A3). If $0 \in S^*$, then the zero solution of (9) is globally attractive.

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- **Remark**: In fact, the same conclusion can be obtained under (A1), (A3), and the following weaker version of (A2):

(A2*) for solutions $y(t)$ of (9) with initial condition in S^*,

(i) if $y(t)$ is non-oscillatory, then, for large $t \geq 0$, $f_i(t, y_t^i) \leq 0$ if $y_t^i \geq 0$ and $f_i(t, y_t^i) \geq 0$ if $y_t^i \leq 0$;

(ii) if $y(t)$ is oscillatory, (A2) is satisfied for large t with $\varphi|_{[-\tau_i(t),0]}$ replaced by y_t^i.

- **Notation**: A funtion $z(t)$ is *oscillatory* if it is not eventually zero and it has arbitrarily large zeros; otherwise, it is called *non-oscillatory*.

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$$y'(t) = -a(t)y(t) + \sum_{i=1}^{m} f_i(t, y_t^i), \qquad t \geq 0 \tag{11}$$

with

$$f_i(t, y_t^i) = b_i(t) \left[\frac{1}{1 + (y(t - \tau_i(t)) + \tilde{x}(t - \tau_i(t)))^n} - \frac{1}{1 + \tilde{x}(t - \tau_i(t))^n} \right].$$

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- $a(t) > 0$ is ω- periodic, thus (A1) holds;
- Hypotheses (A2*)(i) holds trivially;
- By Lagrange's Theorem, we have

$$f_i(t, y_t^i) = -\frac{n\xi^{n-1} b_i(t)}{(1 + \xi^n)^2} y(t - \tau_i(t))$$

with $\xi = \xi(t, y, i)$ between
$x(t - \tau_i(t)) = y(t - \tau_i(t)) + \tilde{x}(t - \tau_i(t))$ and $\tilde{x}(t - \tau_i(t))$.

- By Theorem 3, $\tilde{x}(t) \geq X_1$.
- From Liu et al. (2007)[5] , we also know that:
If $y(t) = x(t) - \tilde{x}(t)$ is oscillatory, then $x(t) \geq X_1$ for large t.
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  $$\xi \geq X_1.$$
- As $\sigma \mapsto \frac{n\sigma^{n-1}}{(1+\sigma^n)^2}$ is a non-increasing on $(0, \infty)$, we have
  $$f_i(t, y_t) = \frac{n\xi^{n-1}}{(1+\xi^n)^2} b_i(t)\big(-y(t-\tau_i(t))\big) \leq \frac{nX_1^{n-1}}{(1+X_1^n)^2} b_i(t)\mathcal{M}_t^i(-y_t)$$
  and
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- Thus $(A2^*)$(ii) holds with
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- Thus (A2*)(ii) holds with
  $$\lambda_{1,i}(t) = \lambda_{2,i}(t) = \frac{nX_1^{n-1}}{(1+X_1^n)^2} b_i(t).$$
- Finally, condition (7) is equivalent to (10) with $\alpha_1^* = \alpha_2^*$, and we conclude that $y(t) \to 0$ as $t \to \infty$. The proof is complete.

Final Remarks

- The open problem, to prove or disprove that all positive solutions of periodic model (4) are attracted by the positive periodic solution, remains unresolved;

[8] T. Faria and J.J. Oliveira, Electron. J. Qual. Theory Differ. Equ., Paper No. 69 (2016), 1-14.

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- For periodic model (5), with $n \leq 1$ and impulses, we obtain a more restrictive criterion than (7), if we apply directly the results in the paper [8];
- For periodic model (5) with $n > 1$, Liu et.al.[5] also obtained a global attractivity criterion of the positive periodic solution. In this case, we also obtained a better result, which is a Corollary of a main criterion obtained for periodic model (5) with $n > 1$ and impulses. These results are under review.

[8] T. Faria and J.J. Oliveira, Electron. J. Qual. Theory Differ. Equ., Paper No. 69 (2016), 1-14.

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Thank you