Stability and Hopf Bifurcation for a Cell Population Model with State-Dependent Delay

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Hematopoiesis and stem cells

Hematopoiesis leads to the **production** and **regulation** of blood cells.

Stem cells differentiate in mature blood cells, under the action of **growth factors**.

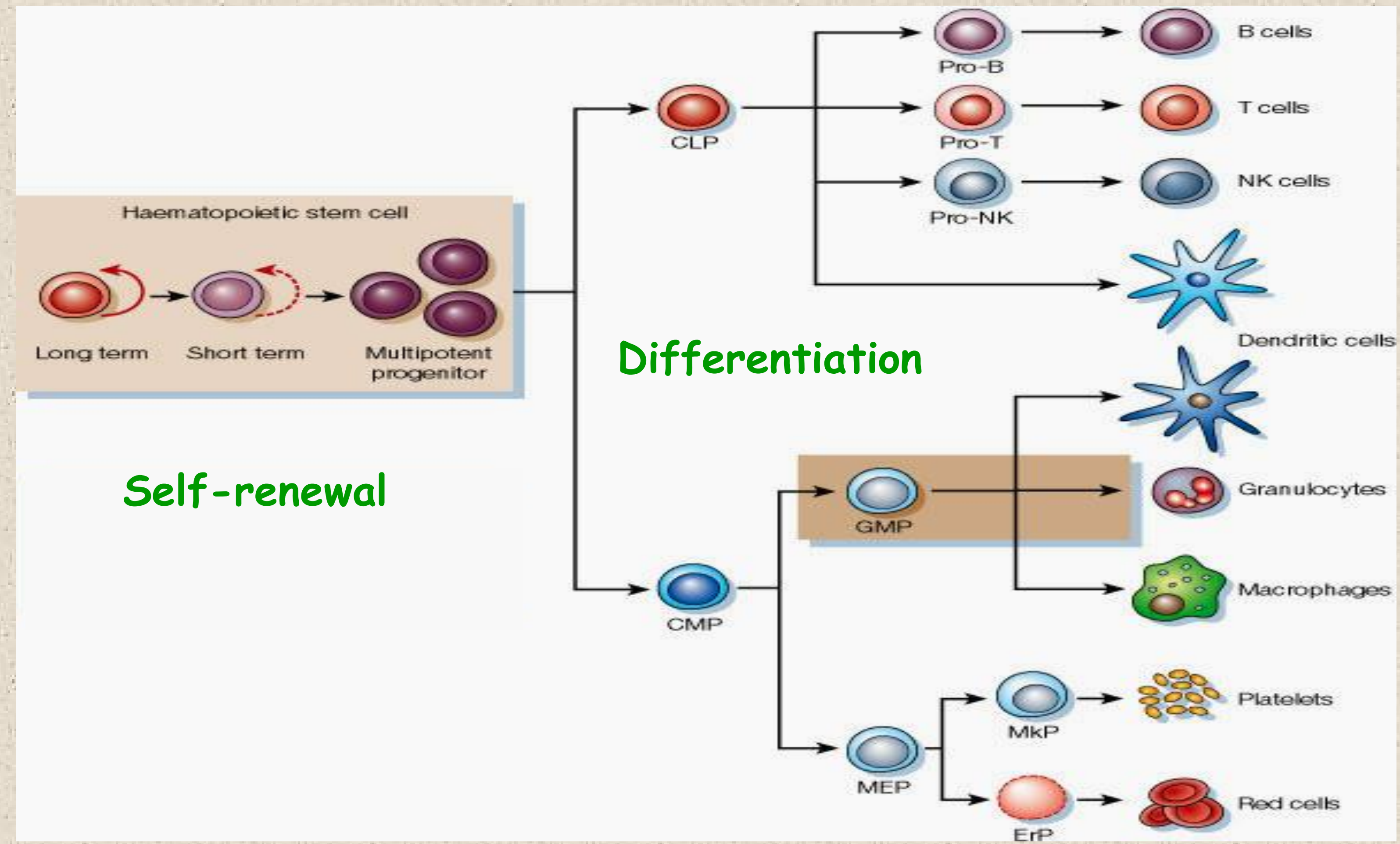
The hematopoiesis is located in the **bone marrow**.

The growth factor mainly involved in the regulation of red blood cells production is the famous **EPO**.

Stem cells have unique capacities of **differentiation** and to generate **identical** cells.

Hematopoiesis and stem cells

Primitive Stem Cells → Committed Stem Cells → Precursors → Mature Cells



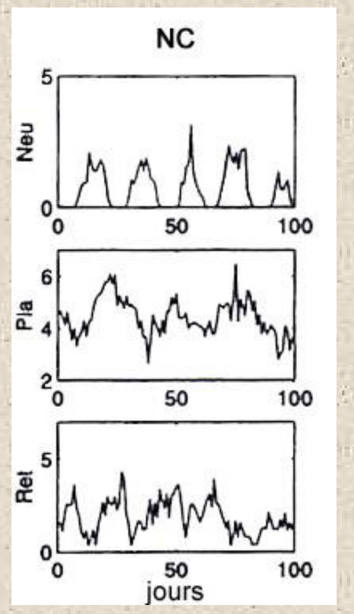
Reya et al. 2001 Nature 414:105-111

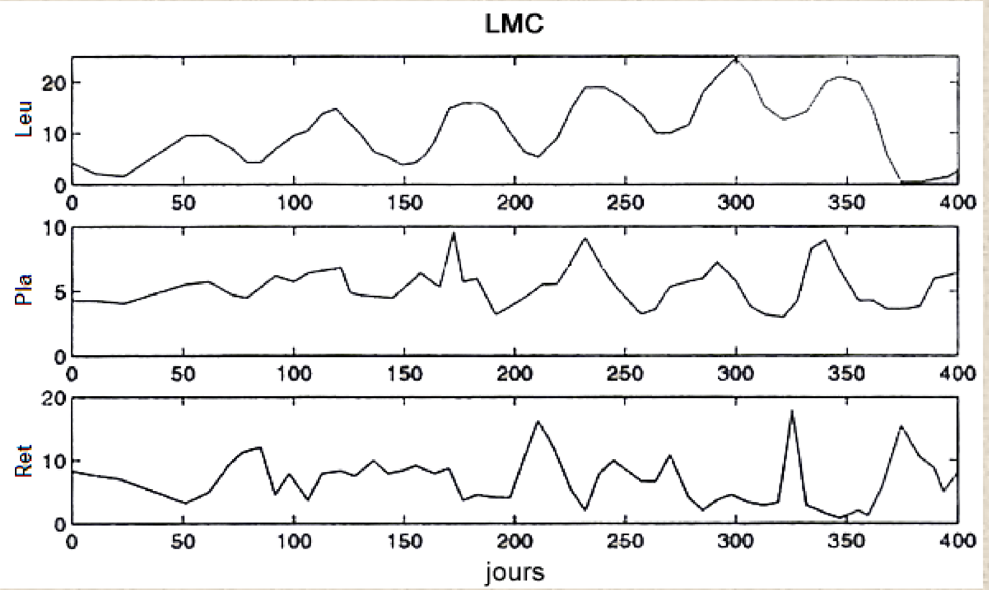
Periodic Hematological Diseases

They are diseases affecting blood cells and characterized by **significant oscillations** of blood cells counts, varying from **days to months**.

Because of their dynamical properties, these diseases offer an almost unique opportunity for understanding the hematopoiesis process.

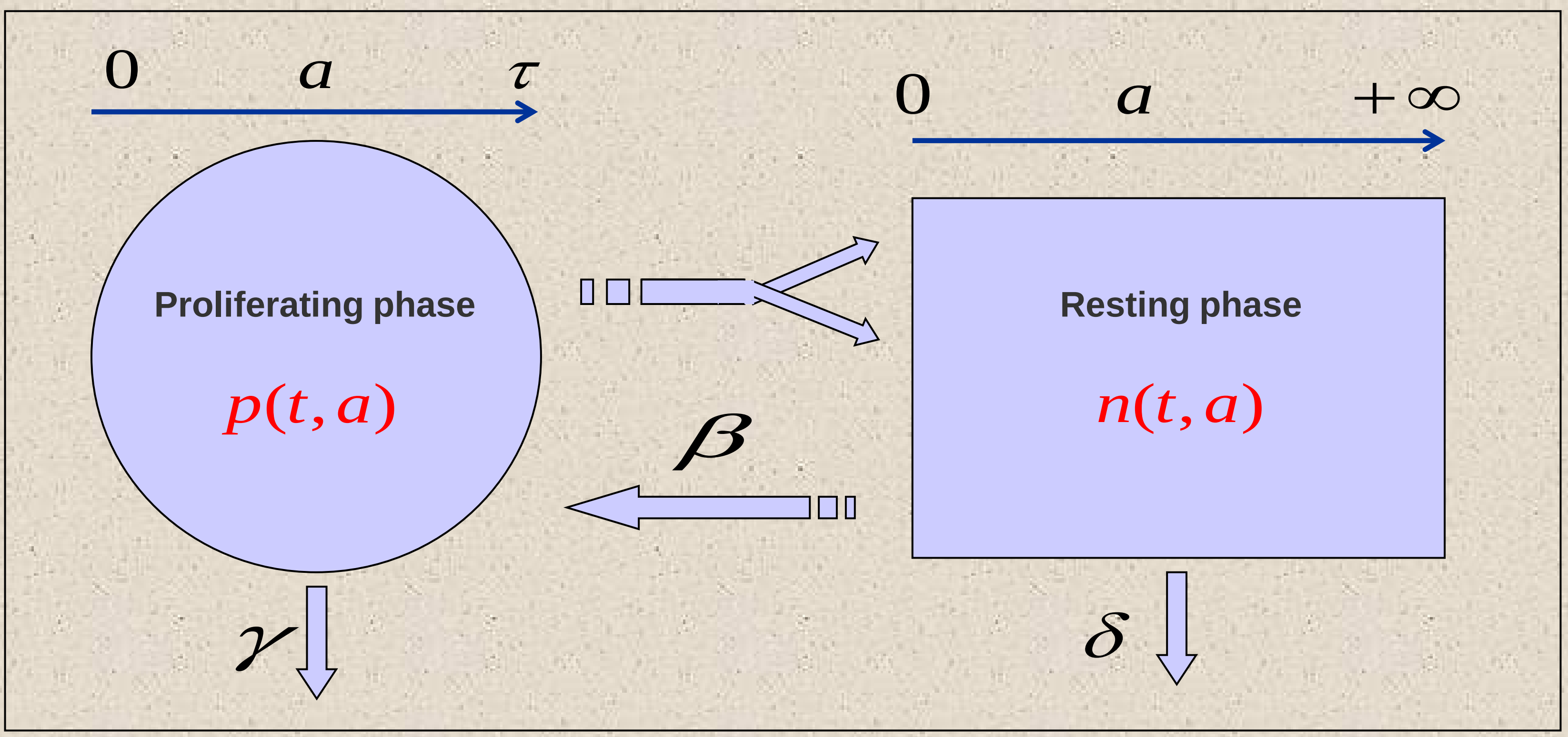
- **Periodic auto-immune hemolytic anemia**, red blood cells, **16 - 17** days;
- **Cyclical thrombocytopenia**, platelets, **20 - 40** days;
- **Cyclical neutropenia**, all blood cells, **19 - 21** days;
- **Periodic chronic myelogenous leukemia**, all blood cells, **40 - 80** days.





The Mackey's model

Hematopoiesis has been studied **mathematically** since **1978** by **Mackey** and his group.
Mackey proposed the first model.
It consists in a **system of two compartments: proliferating and resting phase.**



$$\begin{cases} \dfrac{\partial p}{\partial t}(t,a) + \dfrac{\partial p}{\partial a}(t,a) = -\gamma p(t,a), & 0 < a < \tau, \\ \dfrac{\partial n}{\partial t}(t,a) + \dfrac{\partial n}{\partial a}(t,a) = -\left(\delta + \beta(N(t))\right) n(t,a), & a > 0, \end{cases}$$

$$\begin{cases} n(t,0) = 2p(t,\tau), \\ n(t,\infty) = 0, \\ p(t,0) = \int_0^{+\infty} \beta(N(t)) n(t,a) da = \beta(N(t)) N(t). \end{cases}$$

$$N(t) = \int_0^{+\infty} n(t,a) da, \qquad P(t) = \int_0^{\tau} p(t,a) da.$$

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By integrating over the age and using the boundary conditions, we obtain the following system.

$$\frac{dN}{dt}(t) = -\big(\delta + \beta(N(t))\big) N(t) + 2\,p(t,\tau),$$

$$\frac{dP}{dt}(t) = -\gamma P(t) + p(t,0) - p(t,\tau),$$

$$= -\gamma P(t) + \beta(N(t)) N(t) - p(t,\tau).$$

By the characteristics' method, we obtain

$$\frac{da}{dt}=1 \quad \Longrightarrow \quad p(t,a)=\begin{cases} p(0,a-t)\mathrm{e}^{-\gamma t}, & 0\le t<a, \\ p(t-a,0)\mathrm{e}^{-\gamma a}, & 0\le a\le t. \end{cases}$$

Then, we obtain

$$p(t,a)=\begin{cases} p_0(a-t)\mathrm{e}^{-\gamma t}, & \text{if } 0\le t<a, \\ \beta\big(N(t-a)\big)N(t-a)\mathrm{e}^{-\gamma a}, & \text{if } 0\le a\le t. \end{cases}$$

For $t>\tau$

$$p(t,\tau)=\beta\big(N(t-\tau)\big)N(t-\tau)\mathrm{e}^{-\gamma\tau}.$$

$$\begin{cases} \dfrac{dN}{dt}(t)=-\big(\delta+\beta\big(N(t)\big)\big)N(t)+2e^{-\gamma\tau}\beta\big(N(t-\tau)\big)N(t-\tau), \\ \dfrac{dP}{dt}(t)=-\gamma P(t)+\beta\big(N(t)\big)N(t)-e^{-\gamma\tau}\beta\big(N(t-\tau)\big)N(t-\tau). \end{cases}$$

$$\frac{dN}{dt}(t) = -\left(\delta + \beta\left(N(t)\right)\right)N(t) + 2e^{-\gamma\tau}\beta\left(N(t-\tau)\right)N(t-\tau). \qquad (1)$$

A steady state of this equation is a stationary solution $\bar{N} \geq 0$.

It satisfies

$$-\left(\delta + \beta\left(\bar{N}\right)\right)\bar{N} + 2e^{-\gamma\tau}\beta\left(\bar{N}\right)\bar{N} = 0.$$

Then

$$\bar{N} = 0 \quad \text{or} \quad \left(2e^{-\gamma\tau} - 1\right)\beta\left(\bar{N}\right) = \delta,$$

provided that $\tau < \frac{1}{\gamma}\ln\left(\frac{2\beta(0)}{\beta(0)+\delta}\right).$

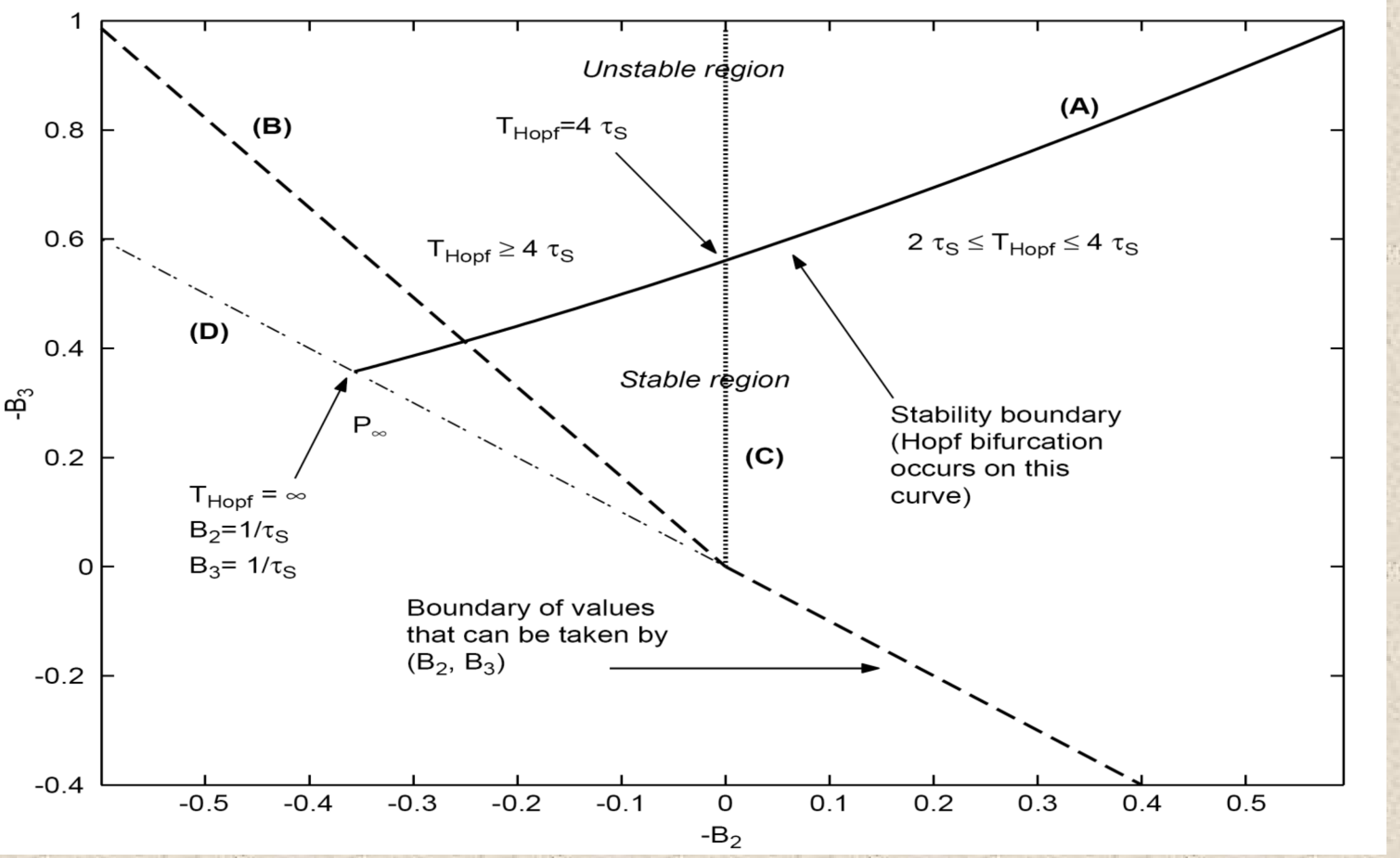
The linearization of equation (1) about $\bar{N}$ leads to

$$\frac{dx}{dt}(t) = ax(t) + bx(t-\tau),$$

with

$$\begin{cases} a = -\left(\delta + \beta(\bar{N}) + \beta'(\bar{N})\bar{N}\right), \\ b = 2e^{-\gamma\tau}\left(\beta(\bar{N}) + \beta'(\bar{N})\bar{N}\right). \end{cases}$$

$$\frac{dN}{dt} = -\left(\delta + \beta\left(N(t)\right)\right)N(t) + 2e^{-\gamma\tau}\beta\left(N(t-\tau)\right)N(t-\tau).$$



S. Bernard, J. Belair and M.C. Mackey.
Journal of Theoretical Biology (2003)

$$B_2 = a = -\left(\delta + \beta\left(\bar{N}\right) + \beta'\left(\bar{N}\right)\bar{N}\right),$$

$$B_3 = b = 2e^{-\gamma\tau}\left(\beta\left(\bar{N}\right) + \beta'\left(\bar{N}\right)\bar{N}\right).$$

Cell cycle variability

Many authors have tried to improve Mackey's model, particularly to better take into account cell cycle duration.

Cell cycle duration variability has been the subject of numerous modeling works (for instance, Alarcon and Tindall (2007), and Tyson and Novak (2001)).

In this work, we focus on the influence of the number of cells on the cell cycle durations.

$$
\begin{cases}
\dfrac{\partial n}{\partial t} + \dfrac{\partial n}{\partial a} = -\left(\delta + \beta(N(t)\right) n, \quad a > 0,\ t > 0, & (2) \\
\dfrac{\partial p}{\partial t} + \dfrac{\partial p}{\partial a} = -\gamma p, \quad 0 < a < \tau(N(t)),\ t > 0, & \\
n(t,0) = 2p(t, \tau(N(t))), \quad t > 0, & (3) \\
p(t,0) = \beta\left(N(t)\right) N(t), \quad t > 0. & (4)
\end{cases}
$$

$\tau : \left[0, +\infty\right) \to \left[0, +\infty\right)$ is an increasing function.

Integrating (2) with respect to the age variable and using the condition (3) we obtain

$$N'(t) = -\left(\delta + \beta(N(t)\right) N(t) + 2\,p(t,\tau(N(t))), \quad t > 0. \qquad (5)$$

Using the method of characteristics, we obtain for $t > \tau(N(t))$

$$p(t,\tau(N(t))) = e^{-\gamma\tau\left(N(t)\right)}\beta\left(N\left(t-\tau\left(N(t)\right)\right)\right)N\left(t-\tau\left(N(t)\right)\right). \qquad (6)$$

We deduce that $N(t)$ satisfies the following state-dependent delay differential equation.

$$N'(t) = -\big(\delta + \beta(N(t)\big)N(t) \\ + 2e^{-\gamma\tau(N(t))}\beta\Big(N\big(t-\tau\big(N(t)\big)\big)\Big)N\big(t-\tau\big(N(t)\big)\big). \qquad (7)$$

The existence and uniqueness of a solution of (7) defined on $[0,+\infty)$ for an initial condition belonging to C^1, the space of continuously differentiable function on $[-\tau_{\max},0]$, follows from Mallet-Paret et al. (1994).

$$N'(t) = -\left(\delta + \beta(N(t)\right) N(t) + 2e^{-\gamma\tau\left(N(t)\right)}\beta\left(N\left(t-\tau\left(N(t)\right)\right)\right) N\left(t-\tau\left(N(t)\right)\right). \qquad (7)$$

A steady state $\bar{N} \geq 0$ of equation (7) satisfies

$$\delta\bar{N} = \left(2e^{-\gamma\tau\left(\bar{N}\right)} - 1\right)\beta(\bar{N})\bar{N}.$$

(7) has two steady states $\bar{N} \equiv 0$ and $\bar{N} \equiv N^* > 0$, provided that

$$\tau_0 = \inf_{x \geq 0} \tau(x) < \frac{1}{\gamma} \ln\left(\frac{2\beta(0)}{\beta(0) + \delta} \right). \qquad (8)$$

If (8) holds, then $\bar{N} \equiv 0$ is unstable.

If (8) does not hold, then $\bar{N} \equiv 0$ is L.A.S.

The characteristic equation for the trivial steady state is given by

$$\Delta_0(\lambda) = \lambda + \delta + \beta(0) - 2\beta(0) e^{-\gamma \tau_0} e^{-\lambda \tau_0}.$$

Considering Δ_0 as a function of real λ, one obtains that Δ_0 is an increasing function with a unique real root $\lambda_0 \in \mathbb{R}$. When (8) holds, then $\Delta_0(0) < 0$, so $\lambda_0 > 0$, which proves the instability of the trivial steady state.
Conversely, when (8) does not hold, $\Delta_0(0) \geq 0$ and $\lambda_0 \leq 0$. One can show that all roots $\lambda \neq \lambda_0$ of Δ_0 satisfy $\mathrm{Re}(\lambda) < \lambda_0$. Consequently, the local asymptotic stability straightforwardly follows when (8) does not hold.

If

$$\tau_0 \geq \frac{1}{\gamma}\ln\left(\frac{2\beta(0)}{\beta(0)+\delta}\right),$$

then $\bar{N} \equiv 0$ is locally asymptotically stable.

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then $\bar{N} \equiv 0$ is globally asymptotically stable.

Consider the Lyapunov function $V:\mathbb{R}^+ \to \mathbb{R}^+$ given by

$$V(x) = \frac{x^2}{2}.$$

Define $p:\mathbb{R}^+ \to \mathbb{R}^+$ by $p(x) = x\exp\left(2\alpha\tau\sqrt{2x}\right),\ x \in \mathbb{R}^+,$

with $0 < \alpha < \min\left\{\gamma, \gamma - \frac{1}{\tau_0}\ln\left(2\beta(0)/\delta\right)\right\}.$

Let N be a solution of (7) such that, for $t \geq 0,\ \theta \in [-\tau_{\max}, 0],$

$$V(N(t+\theta)) < p(V(N(t))).$$

Then, for $t \geq 0$

$$\dot{V}(N(t)) \leq -\left[\delta - 2\,\mathrm{e}^{-(\gamma-\alpha)\tau(N(t))}\,\beta(0)\right].$$

We focus on the L.A.S of N^* and a local Hopf bifurcation.

We assume the function τ is given by $\tau(x) = \mu\tilde{\tau}(x)$, where μ is a positive parameter.

$$N'(t) = -\left(\delta + \beta(N(t)\right) N(t) \\ + 2e^{-\gamma\mu\tilde{\tau}\left(N(t)\right)}\beta\left(N\left(t - \mu\tilde{\tau}\left(N(t)\right)\right)\right) N\left(t - \mu\tilde{\tau}\left(N(t)\right)\right).$$

We assume that $\tau_0 < \frac{1}{\gamma}\ln\left(\frac{2\beta(0)}{\beta(0)+\delta}\right)$. That is

$\beta(0) > \delta$ and $0 \le \mu < {}^{1}\!/_{\tilde{\tau}(0)\gamma} \ln\left(\frac{2\beta(0)}{\beta(0)+\delta}\right) := \overline{\mu}.$

The positive steady state N^* depends then on the parameter μ and is given implicitly by

$$\left(2e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} - 1\right)\beta\left(N^*(\mu)\right) = \delta, \qquad \mu \in [0, \overline{\mu}).$$

Thus, by using the Implicit Functions Theorem, N^* is a decreasing continuously differentiable function of μ.
Taking μ as a real parameter, our purpose is to prove the existence of the local Hopf bifurcation.
The characteristic equation associated with $N^*(\mu)$ is written as

$$\Delta(\lambda, \mu) = \lambda + b(\mu) + c(\mu)e^{-\lambda\mu\tilde{\tau}(N^*(\mu))}.$$

where, for $\mu \in [0, \overline{\mu})$,

$$b(\mu) = \delta + \overline{\beta}(\mu) + \mu\tilde{\tau}'(N^*(\mu))\overline{\alpha}(\mu)e^{-\gamma\mu\tilde{\tau}(N^*(\mu))},$$

$$c(\mu) = -2\overline{\beta}(\mu)e^{-\gamma\mu\tilde{\tau}(N^*(\mu))},$$

$$\overline{\alpha}(\mu) = 2\gamma\beta(N^*(\mu))N^*(\mu), \quad \overline{\beta}(\mu) = \beta(N^*(\mu)) + \beta'(N^*(\mu))N^*(\mu).$$

$N^*(\mu)$ is locally asymptotically stable for $\mu = 0$ and the stability can be lost as μ increases away from 0, with $\mu < \overline{\mu}$, only if purely imaginary characteristic roots appear.
We investigate the existence of purely imaginary roots. Using $1 - 2e^{-\gamma\mu\tilde{\tau}(N^*(\mu))} < 0$, it is obvious that $\Delta(0, \mu) = b(\mu) + c(\mu) > 0$, so $\lambda = 0$ is not a characteristic root.

Let $\omega > 0$. Separating real and imaginary parts, we obtain

$$\begin{cases} \omega = c(\mu)\sin(\omega\mu\tilde{\tau}(N^*(\mu))), \\ b(\mu) = -c(\mu)\cos(\omega\mu\tilde{\tau}(N^*(\mu))). \end{cases}$$

One can note that if $i\omega$ is a purely imaginary root then so is $-i\omega$.
A necessary condition to have purely imaginary roots is

$$| c(\mu) | > | b(\mu) | .$$

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$$\mid c(\mu) \mid > \mid b(\mu) \mid .$$

Adding the squares of both sides in the last system, eigenvalues $i\omega(\mu)$, with $\omega(\mu) > 0$ and $\mu \in \left[0, \mu^*\right)$, must satisfy

$$\omega(\mu) = \left(c^2(\mu) - b^2(\mu)\right)^{\frac{1}{2}} \quad \text{for } \mu \in \left[0, \mu^*\right).$$

Then, we look for $\mu \in \left[0, \mu^*\right)$ solution of

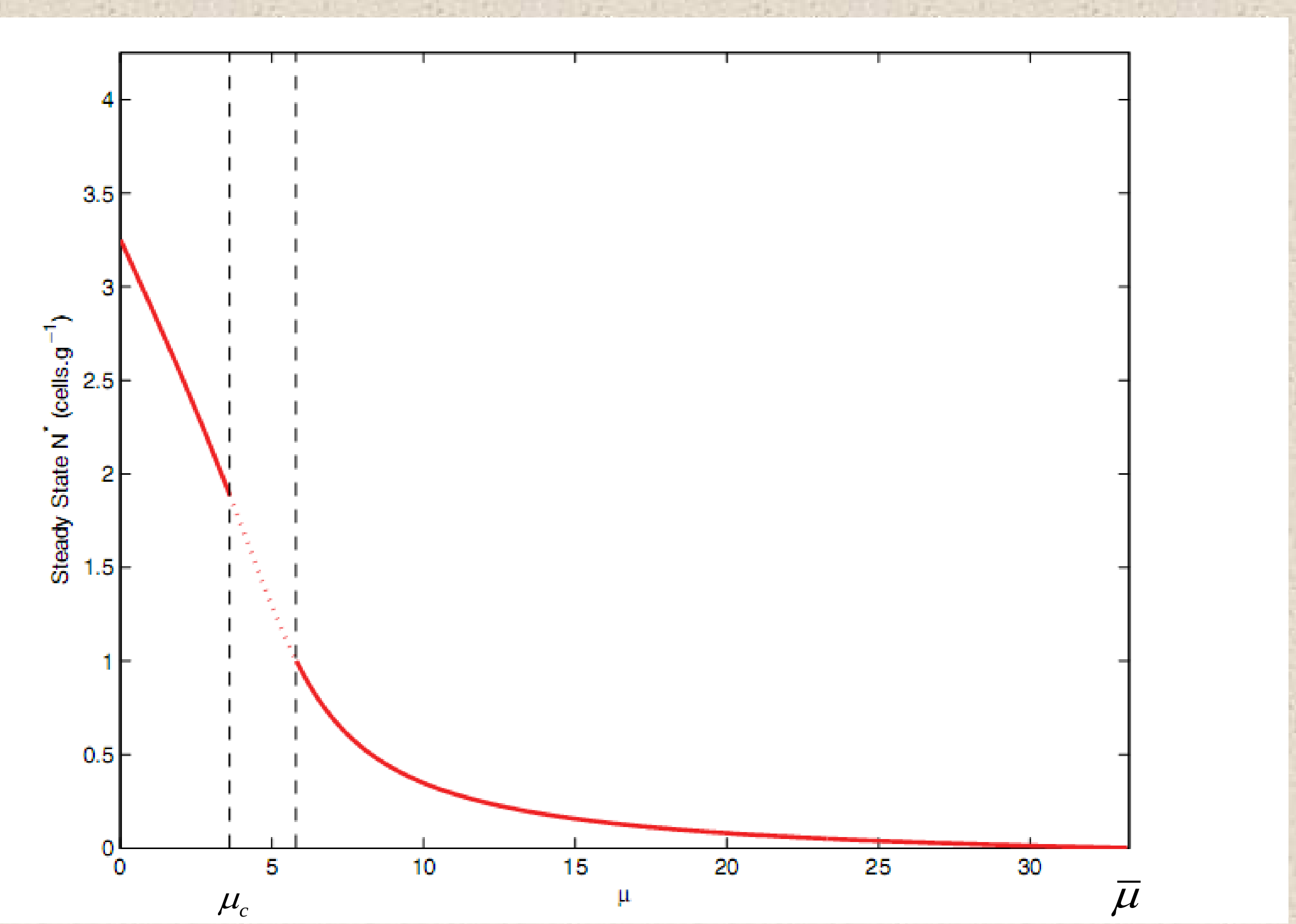
$$\mu\tau(N^*(\mu))\left(c^2(\mu)-b^2(\mu)\right)^{\frac{1}{2}} = \arccos\left(-\frac{b(\mu)}{c(\mu)}\right)+2k\pi, \quad k \in \mathbb{N}.$$

That is a solution of

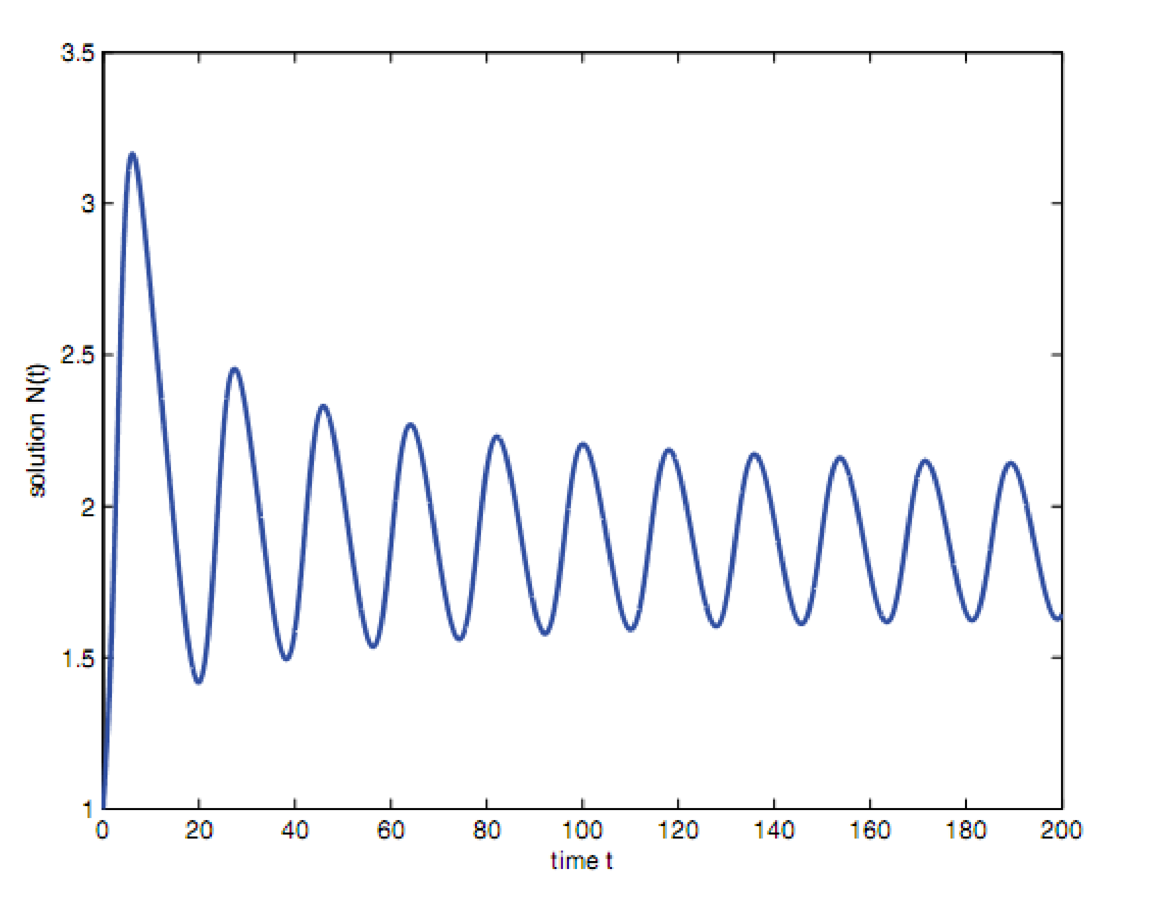
$$Z_k(\mu) := \mu - \frac{\arccos\left(-\frac{b(\mu)}{c(\mu)}\right)+2k\pi}{\tau(N^*(\mu))\left(c^2(\mu)-b^2(\mu)\right)^{\frac{1}{2}}} = 0, \quad \mu \in \left[0, \mu^*\right).$$

$Z_k(0) < 0$ and $\lim_{\mu\to\mu^*} Z_k(\mu) = -\infty.$

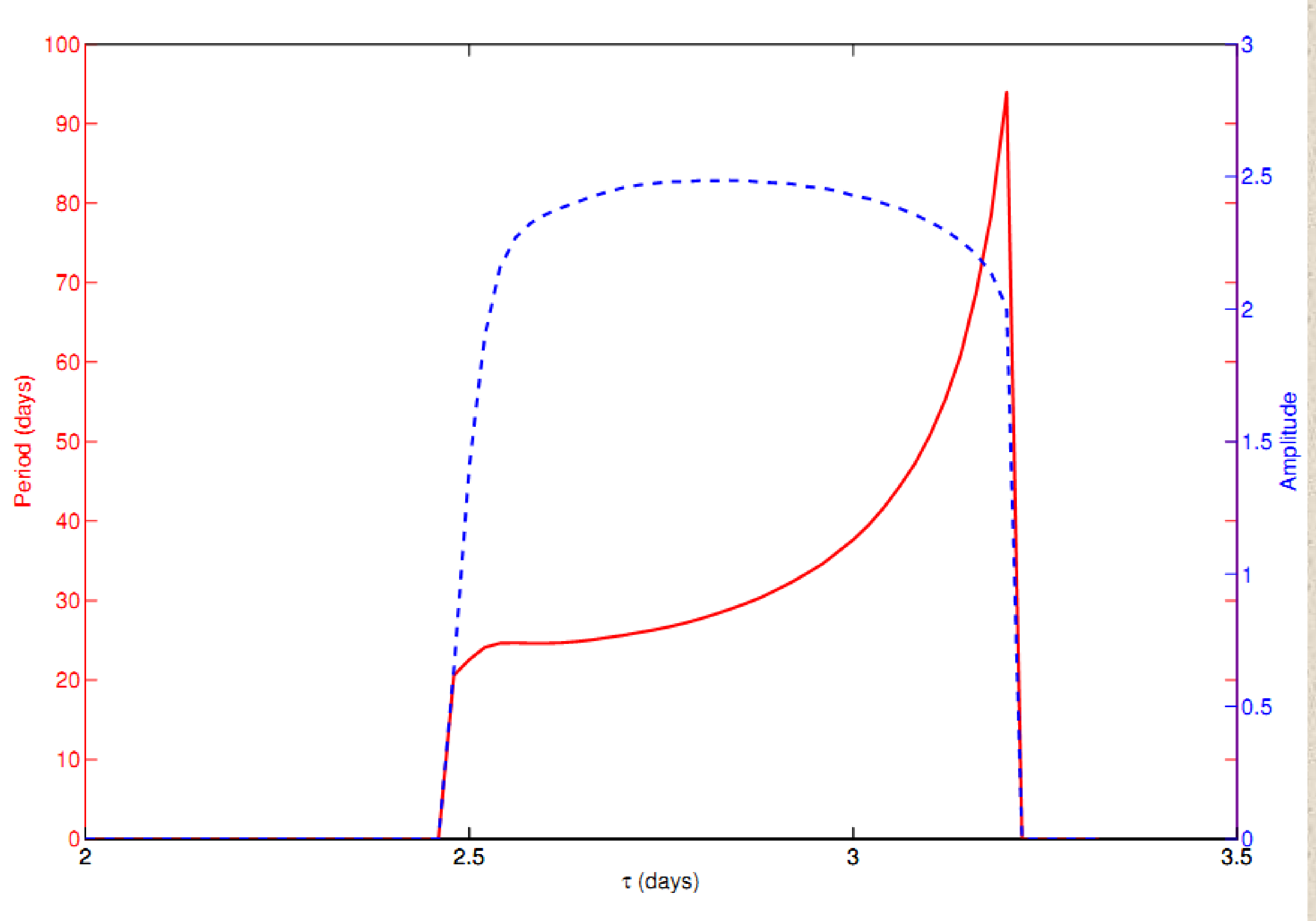
If Z_k has no root on $\left[0, \mu^*\right)$, then Z_j, with $j > k$, does not have roots.



The solid line corresponds to stable values of the steady state, whereas the dotted lines account for unstable values of positive steady state.



Periodic solution at the Hopf bifurcation.



M. Adimy, F. Crauste, My L. Hbid et R. Qesmi. SIAM J. Appl. Math, (2010).