Modeling hematopoietic cell population dynamics for Acute Myeloid Leukemia with perspectives in control

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Outline

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1. Introduction

Blood cell production

Hematopoiesis is the process of formation of blood cells.
It is initiated in the bone marrow by hematopoietic stem cells (HSCs)

HSCs can

- proliferate
- self-renew
- differentiate in multiple lineages

Proliferation: Cell cycle (growth phase). At the end of this cycle cell division occurs.
Self-renewal: At cell division HSCs produce a daughter with the same biological properties as the parent
Differentiation: At cell division a cell with greater maturity (progenitor) is produced.

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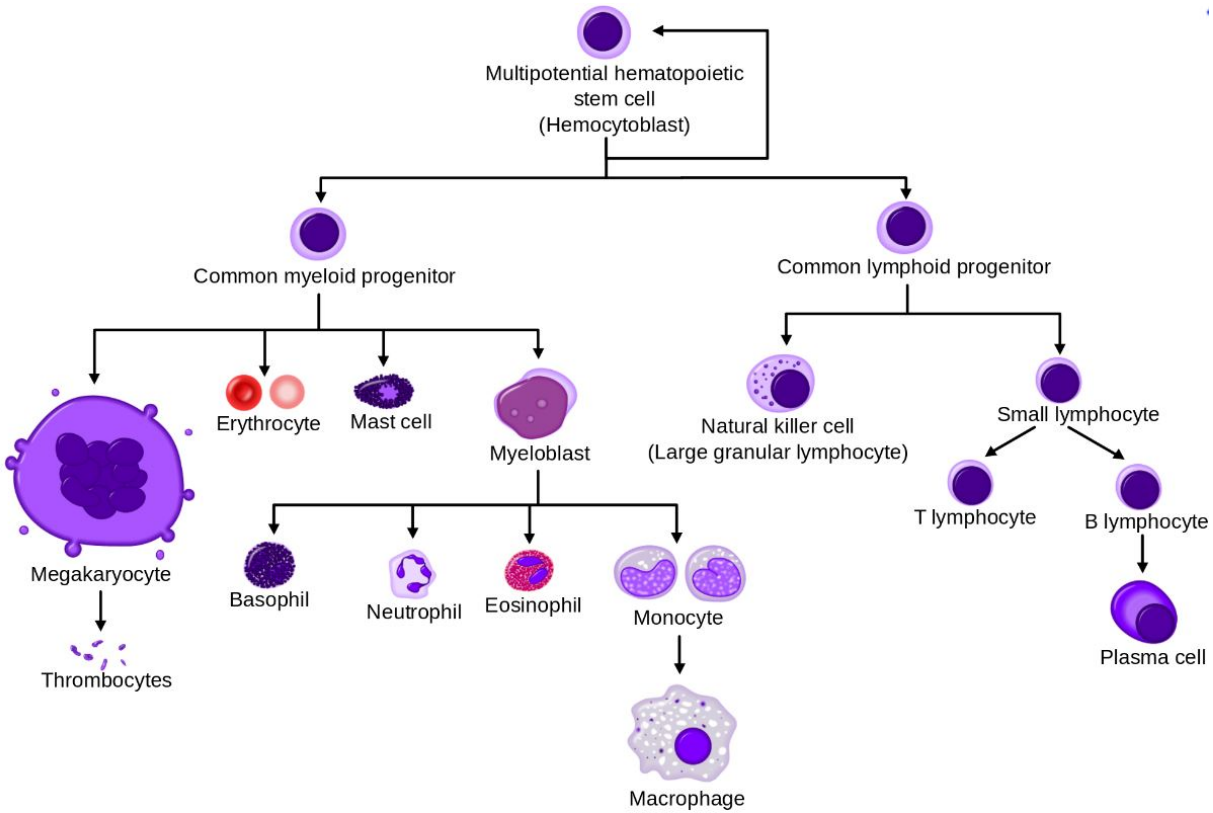
Hematopoiesis and its disorders



Cancers arising from hematopoietic cells are called leukemias.
The classification of different forms of leukemias relies on the progression of the disease (acute or chronic) as well as the type of cell affected (myeloid, lymphoid).

Blood cell production and Acute Myeloid Leukemia (AML)

- **Acute Myeloid Leukemia** is characterized by an overproduction in the bone marrow and realease in the bloodstream of immature cells (myeloblasts).
- According to OMS, the diagnosis of AML is established by demonstrating involvement of more than 20% of the blood and/or bone marrow by leukemic myeloblasts.
- AML combines at least two molecular events: a blockade of the differentiation and an advantage of the proliferation.
- Promyelocytic leukemia : main problem is blockade of the differentiation.
- Leukemias which present a high level of FLTt-3 duplication (main problem is proliferation)

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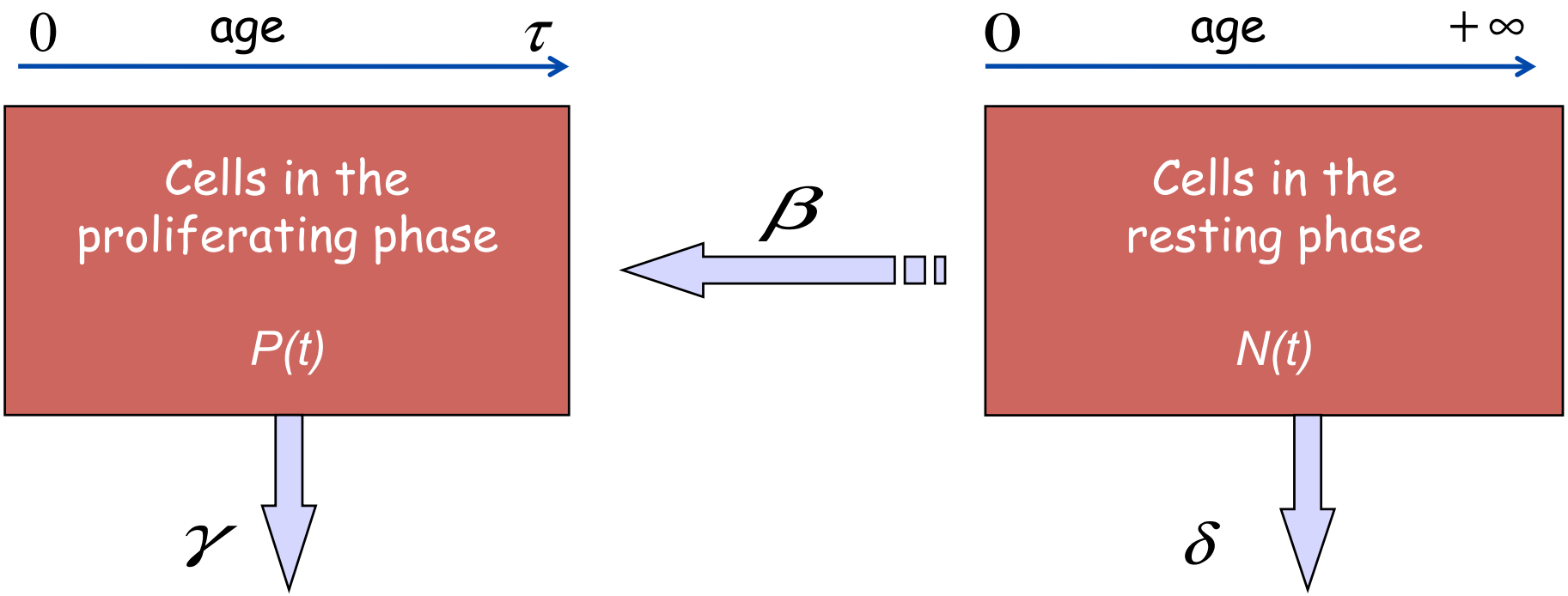
State of the Art: Mackey

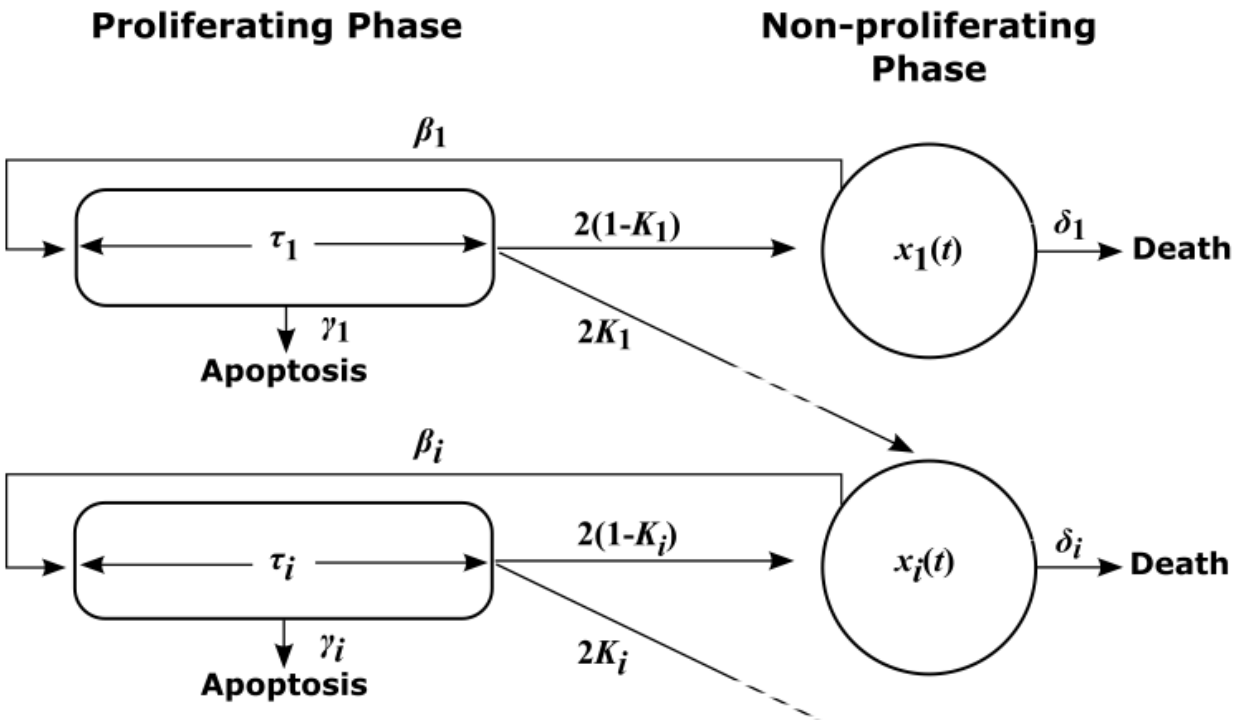
- One of the first mathematical models on hematopoiesis was proposed by Mackey at the end of the 1970's (ODE).



$$\begin{cases} \frac{d}{dt}N(t) = & -(\delta+\beta(N(t)))N(t)+2e^{-\gamma\tau}\beta(N(t-\tau))N(t-\tau), \\ \frac{d}{dt}P(t) = & -\gamma P(t)+\beta(N(t))N(t)-e^{-\gamma\tau}\beta(N(t-\tau))N(t-\tau). \end{cases}$$

State of the Art: Adimy et al.

- Adimy et al (2008) proposed a PDE based model including several compartments conected in series.



Discrete-maturity model

Structured age model proposed by Adimy et al (2008)

$$\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial a} = -(\gamma_i + g_i(a))\, p_i, \quad 0 < a \text{ (age)} < \tau_i,\ t\text{(time)} > 0$$

$$\frac{\partial r_i}{\partial t} + \frac{\partial r_i}{\partial a} = -(\delta_i + \beta_i)\, r_i, \quad a > 0,\ t > 0,$$

β_i depends on x_i where $x_i(t) := \int_0^\infty r(t,a)da$

$$r_i(t,0) = 2(1-K_i)\int_0^{\tau_i} g_i(a)p_i(t,a)da + 2K_{i-1}\int_0^{\tau_{i-1}} g_{i-1}(a)p_{i-1}(t,a)da$$

$$p_i(t,0) = \int_0^\infty \beta_i(x_i(t))r_i(t,a)da = \beta_i(x_i(t))x_i(t)$$

$r_i(0,a)$ $a \geq 0$ and $p_i(0,a)$ $a \in [0,\tau_i]$ given

Mathematical assumptions of the model

- $f_i(.)$, cell divisions (mitosis),

$$f_i(a) \geq 0 \text{ for all } a \in [0, \tau_i], \text{ and } \int_0^{\tau_i} f_i(a)da = 1. \tag{1}$$

- $\beta_i(\cdot)$ are differentiable and decreasing functions

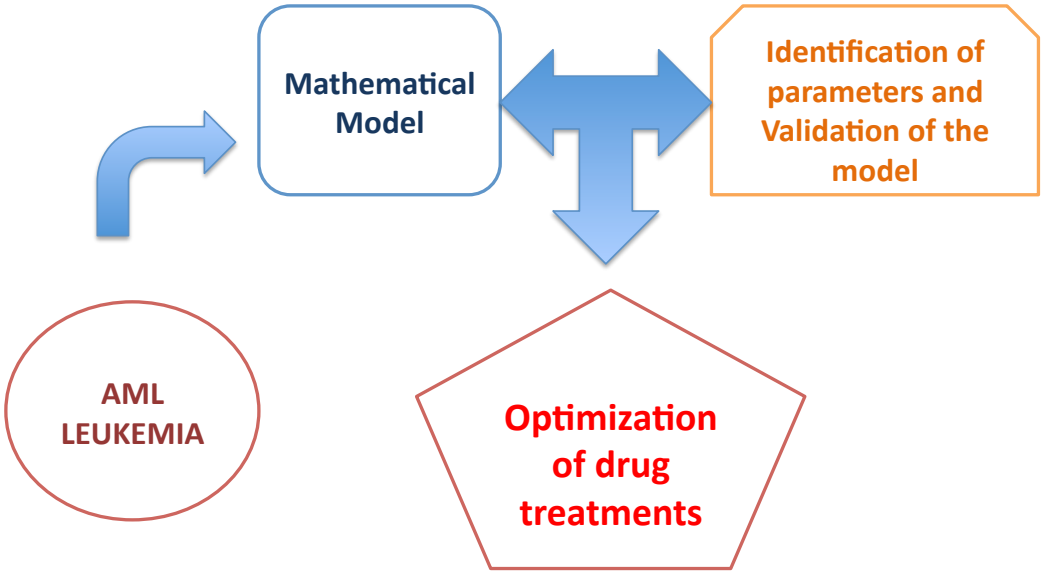
$$\lim_{y \to +\infty} \beta_i(y) = 0$$
$$\left(\beta_i(x) = \frac{\beta_i(0)}{1 + bx^n}, \quad \beta_i(0) > 0, b > 0, n > 0 \right). \tag{2}$$

- The parameters δ_i, K_i, $L_i = 1 - K_i$ τ_i and γ_i are positive.
- We introduce the parameters:

$$C_i = \int_0^{\tau_i} e^{-\gamma_i l} f_i(l)dl, \quad \alpha_i = 2L_iC_i - 1 > 0. \tag{3}$$

Scope and Objectives

We are interested in Leukemias which present a high level of Flt-3 duplication.



Question: how to optimally combine

- cytotoxic drug which acts on apoptose (γ) during phase S of the cell cycle.
- Anti-Flt3 drug (AC220) which acts on the fast self-renewal of cells.

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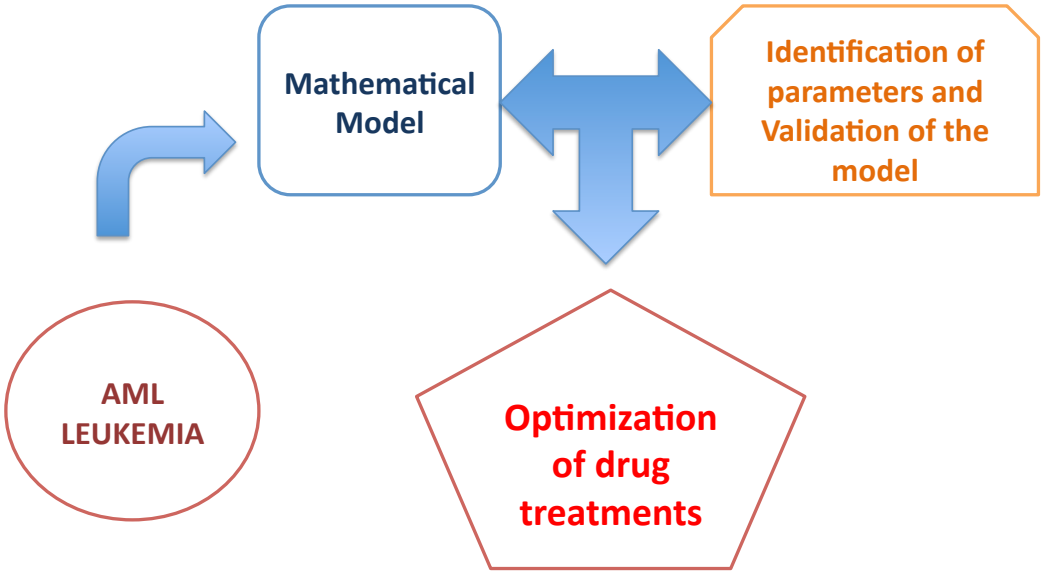

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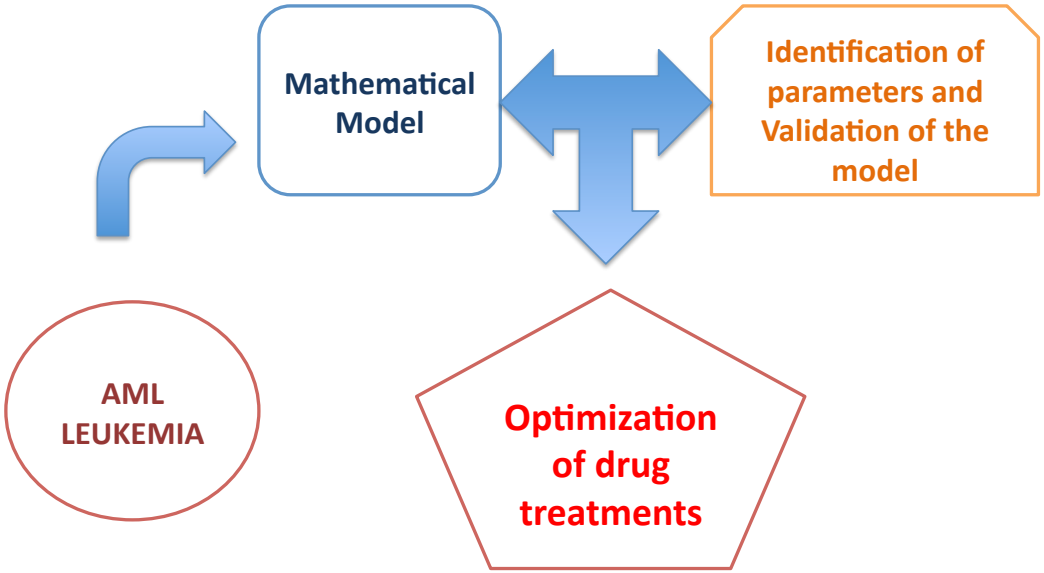

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The first step is to obtain a mathematical model of AML with the following characteristics:

- The self renewal phenomenon is written in two parts where the fast and slow dynamics are separated.
- The phases of the cell cycle are considered ($\mathbf{G_1}$, $\mathbf{S}$, $\mathbf{G_2}$ and $\mathbf{M}$).

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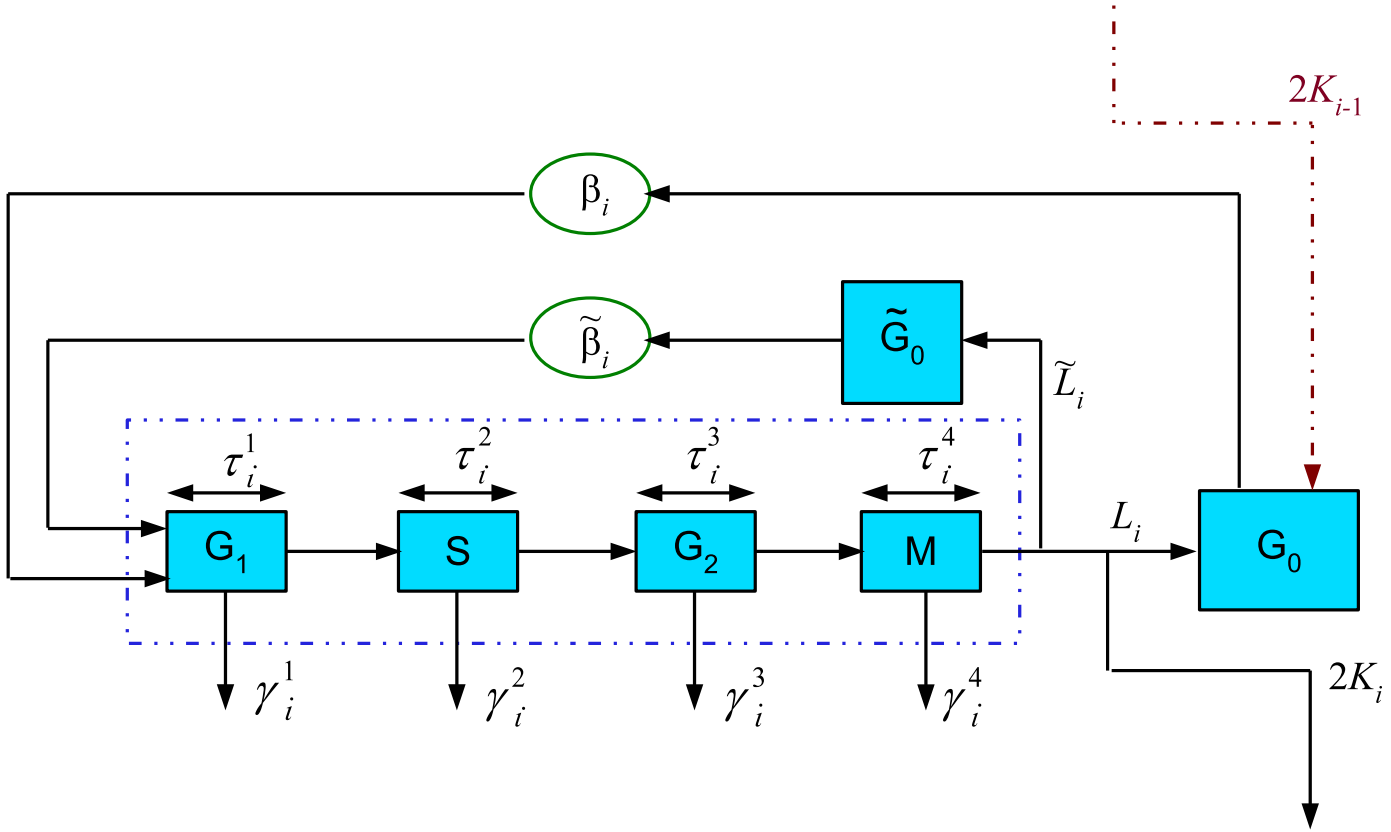
State of the Art: Avila et al.



- $L_i = 2\sigma_i(1-K_i)$ and $\tilde{L}_i = 2(1-\sigma_i)(1-K_i)$
- β_i and $\tilde{\beta}_i$: reintroduction functions of the form $\dfrac{\beta(0)}{1+bx^N}$ (Hill function).
- γ_i^1, γ_i^2, γ_i^3 and γ_i^4: apoptosis rate in $\mathbf{G_1}$, $\mathbf{S}$, $\mathbf{G_2}$ and $\mathbf{M}$ phases.
- τ_i^1, τ_i^2, τ_i^3 and τ_i^4: time elapsed in $\mathbf{G_1}$, $\mathbf{S}$, $\mathbf{G_2}$ and $\mathbf{M}$ phases.

Identification of the parameters

Experiments at St Antoine Hospital on patients' blood: only hyperleucocytic patients are considered ie 1 patient/month

- Build experiments (the kind of parameters we want to identify are not usually of interest for biologists) took a lot of time
- Phases G_2 and M cannot be separated
- Only two different stages of maturity can be identified (stems cells and mature cells)
- The apoptosis rates γ_1, γ_2 and γ_3 cannot be identified separately
- Difficult to identify β
- Probably a patient-dependant model

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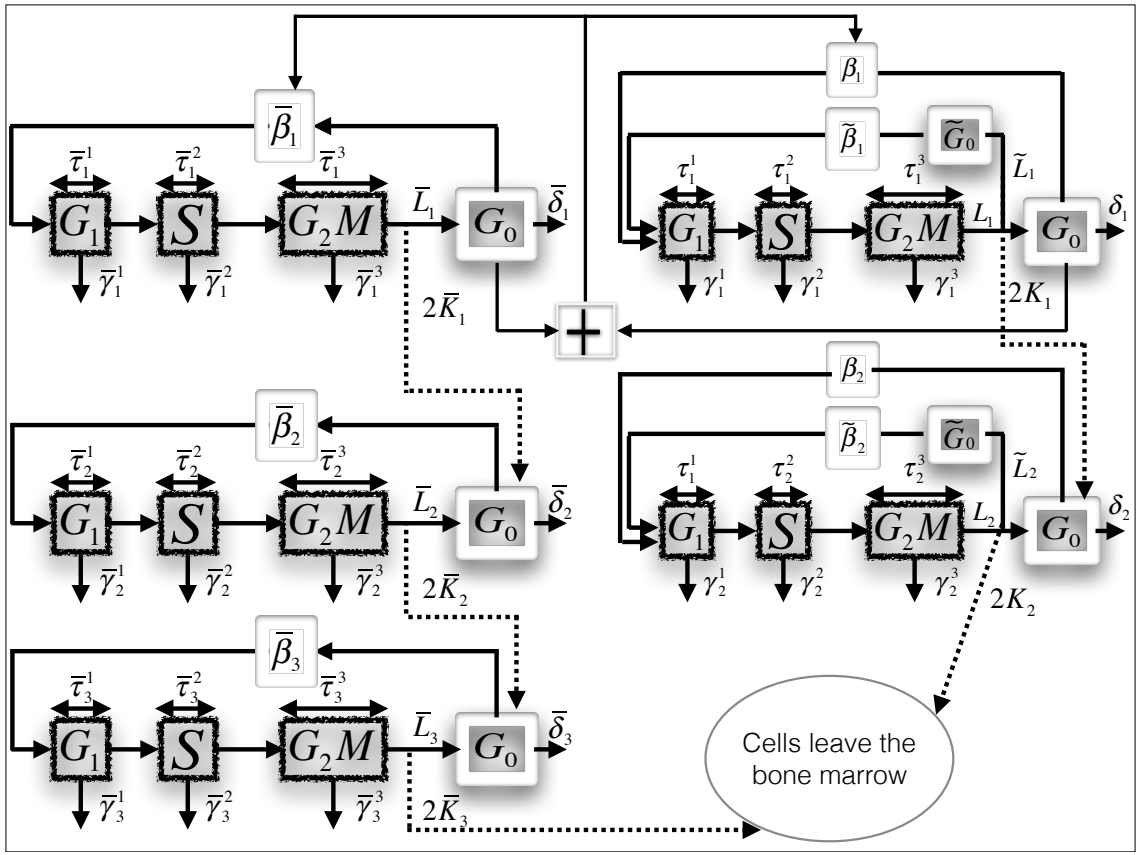
Interconnected model of healthy cells (left) and cancer cells (right).



Mathamatical model of cancer cells.

We denote by $p_i(t,a)$, $l_i(t,a)$, $n_i(t,a)$ and $r_i(t,a)$ the cancer cell populations of the G_1, S, G_2M and G_0 phases respectively
at the *ith* compartment, with age $a \geq 0$ at time $t \geq 0$.

The dynamical behavior of the cancer cells is represented by:

$$\begin{cases} \frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial a} = -\left(\gamma_i^1 + g_i^p(a)\right) p_i, & 0 < a < \tau_i^1, \quad t > 0, \\ \frac{\partial l_i}{\partial t} + \frac{\partial l_i}{\partial a} = -\left(\gamma_i^2 + g_i^l(a)\right) l_i, & 0 < a < \tau_i^2, \quad t > 0, \\ \frac{\partial n_i}{\partial t} + \frac{\partial n_i}{\partial a} = -\left(\gamma_i^3 + g_i^n(a)\right) n_i, & 0 < a < \tau_i^3, \quad t > 0, \\ \frac{\partial r_1}{\partial t} + \frac{\partial r_1}{\partial a} = -\left(\delta_1 + \beta_1(z(t))\right) r_1, & a > 0, \quad t > 0, \\ \frac{\partial r_2}{\partial t} + \frac{\partial r_2}{\partial a} = -\left(\delta_2 + \beta_2\left(\int_0^{+\infty} r_2(t,a)\,da\right)\right) r_2, & a > 0, \quad t > 0, \\ \frac{\partial \tilde{r}_i}{\partial t} + \frac{\partial \tilde{r}_i}{\partial a} = -\tilde{\beta}_i\left(\int_0^{+\infty} \tilde{r}_i(t,a)\,da\right) \tilde{r}_i, & a > 0, \quad t > 0. \end{cases}$$

- $g_i^p(a)$, $g_i^l(a)$, $g_i^n(a)$: division rates in $\mathbf{G_1}$, $\mathbf{S}$ and $\mathbf{G_2M}$ phases.

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Mathematical model of healthy cells.

The dynamical behavior of the healthy cells is represented by:

$$\begin{cases} \dfrac{\partial \bar{p}_j}{\partial t} + \dfrac{\partial \bar{p}_j}{\partial a} = -\left(\bar{\gamma}_j^1 + \bar{g}_j^{\bar{p}}(a)\right)\bar{p}_j, & 0 < a < \bar{\tau}_j^1, \quad t > 0, \\ \dfrac{\partial \bar{l}_j}{\partial t} + \dfrac{\partial \bar{l}_j}{\partial a} = -\left(\bar{\gamma}_j^2 + \bar{g}_j^{\bar{l}}(a)\right)\bar{l}_j, & 0 < a < \bar{\tau}_j^2, \quad t > 0, \\ \dfrac{\partial \bar{n}_j}{\partial t} + \dfrac{\partial \bar{n}_j}{\partial a} = -\left(\bar{\gamma}_j^3 + \bar{g}_j^{\bar{n}}(a)\right)\bar{n}_j, & 0 < a < \bar{\tau}_j^3, \quad t > 0, \\ \dfrac{\partial \bar{r}_1}{\partial t} + \dfrac{\partial \bar{r}_1}{\partial a} = -\left(\bar{\delta}_1 + \bar{\beta}_1\left(z(t)\right)\right)\bar{r}_1, & a > 0, \quad t > 0, \\ \dfrac{\partial \bar{r}_j}{\partial t} + \dfrac{\partial \bar{r}_j}{\partial a} = -\left(\bar{\delta}_j + \bar{\beta}_j\left(\int_0^{+\infty} \bar{r}_j(t,a)\,da(t)\right)\right)\bar{r}_j, & a > 0, \quad t > 0. \end{cases}$$

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Mathematical model

- At the compartments $i = 1, 2$,

$$x_i(t) := \int_0^{+\infty} r_i(t,a)\,da$$

$\longrightarrow$ total population of resting cells at the time t

$$\tilde{x}_i(t) := \int_0^{+\infty} \tilde{r}_i(t,a)\,da$$

$\longrightarrow$ total population of fast-self renewing cells at the time t

- At the compartments $j = 1, 2, 3$

$$\bar{x}_j(t) := \int_0^{+\infty} \bar{r}_j(t,a)\,da$$

$\longrightarrow$ total population of resting healthy cells

- The interconnection between the cancer and healthy cells occurs at their first comparments by means of the common feedback of resting cells $z(t) := x_1(t) + \bar{x}_1(t)$, which acts on the functions β_1 and $\bar{\beta}_1$.

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Division rates

- The division rate g is a continuous function such that $\int_0^\tau g(a)da = +\infty$
- An important property directly related to the division rate g is that it define a probability distribution:

$$f(a) = g(a)\, e^{-\int_0^a g(s)ds}, \text{ on } [0, \tau)$$

satisfy $\int_0^\tau f(a)\, da = 1$.

- We study division rates of the form

$$g(a) = \frac{m}{e^{m(\tau - a)} - 1}, \qquad 0 \leq a < \tau \tag{4}$$

where the integer $m \geq 2$. Its probability distribution is given by

$$f(a) = \frac{m}{e^{m\tau} - 1} e^{ma}, \qquad 0 \leq a \leq \tau.$$

Distributed Delay Differential Equation Model

By using the method of characteristics we obtain the following systems of distributed delay differential equations

$$
\begin{aligned}
\dot{x}_1(t) &= -(\delta_1+\beta_1(x_1(t)+\bar{x}_1(t)))x_1(t)+L_1\left(h_1^3*h_1^2*h_1^1*\omega_1\right)(t),\\
\dot{\tilde{x}}_1(t) &= -\tilde{\beta}_1(\tilde{x}_1(t))\tilde{x}_1(t)+\tilde{L}_1\left(h_1^3*h_1^2*h_1^1*\omega_1\right)(t),\\
\dot{\bar{x}}_1(t) &= -\left(\bar{\delta}_1+\bar{\beta}_1(x_1(t)+\bar{x}_1(t))\right)\bar{x}_1(t)+\bar{L}_1\left(\bar{h}_1^3*\bar{h}_1^2*\bar{h}_1^1*\bar{\omega}_1\right)(t),
\end{aligned}
$$

$$
\begin{aligned}
\dot{x}_2(t) &= -(\delta_2+\beta_2(x_2(t)))x_2(t)+L_2\left(h_2^3*h_2^2*h_2^1*\omega_2\right)(t)\\
&\quad +2K_1\left(h_1^3*h_1^2*h_1^1*\omega_1\right)(t),\\
\dot{\tilde{x}}_2(t) &= -\tilde{\beta}_2(\tilde{x}_2(t))\tilde{x}_2(t)+\tilde{L}_2\left(h_2^3*h_2^2*h_2^1*\omega_2\right)(t),\\
\dot{\bar{x}}_2(t) &= -\left(\bar{\delta}_2+\bar{\beta}_2(\bar{x}_2(t))\right)\bar{x}_2(t)+\bar{L}_2\left(\bar{h}_2^3*\bar{h}_2^2*\bar{h}_2^1*\bar{\omega}_2\right)(t)\\
&\quad +2\bar{K}_1\left(\bar{h}_1^3*\bar{h}_1^2*\bar{h}_1^1*\bar{\omega}_1\right)(t),
\end{aligned}
$$

$$
\dot{\bar{x}}_3(t) = -\left(\bar{\delta}_3+\bar{\beta}_3(\bar{x}_3(t))\right)\bar{x}_3(t)+\bar{L}_3\left(\bar{h}_3^3*\bar{h}_3^2*\bar{h}_3^1*\bar{\omega}_3\right)(t),
$$

.

3. Distributed Delay Differential Equation Model Stability Analysis

Simple model

$$
\begin{aligned}
\dot{x}_i(t) &= -(\delta_i + \beta_i(x_i(t)))x_i(t) \\
&\quad +2L_i \int_0^{\tau_i} e^{-\gamma a} f_i(a)\beta_i(x_i(t-a))x_i(t-a)da \\
&\quad +2(1-K_{i-1}) \int_0^{\tau_{i-1}} e^{-\gamma_{i-1} a} f_{i-1}(a) w_{i-1}(t-a)da \\
\dot{y}_i(t) &= -\gamma_i y_i(t) + \\
&\quad \beta_i(x_i(t))x_i(t) - \int_0^{\tau_i} e^{-\gamma a} f_i(a)\beta_i(x_i(t-a))x_i(t-a)da
\end{aligned}
$$

where $K_0 = 0$

Time-domain or frequency domain ?

Time-domain (state-space description)

Ordinary Differential Equations

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t) \\ y(t) &= Cx(t) \\ x(0) &= 0 \end{aligned}$$

$\xrightarrow{\mathscr{L}}$

Frequency domain (input-output description)

$$\hat{y}(s) = \mathscr{L}(y) = \mathscr{L}(g * u) = \boxed{G(s)}\ \hat{u}(s) = \boxed{C(sI - A)^{-1}B}\ \hat{u}(s)$$

Stability in an input-output framework

Stability

$$\sup_{u \in L^2, u \neq 0} \frac{\|Gu\|_{L^2}}{\|u\|_{L^2}} = \|G\|_{H_\infty} < \infty$$

$H_\infty = \{$fonctions which are analytic and bounded dans $\{\mathrm{Re}\, s > 0\}\}$.

For finite-dimensional systems:

G is H_∞-stable $\iff$ G has no poles in the closed right half-plane

Delay systems

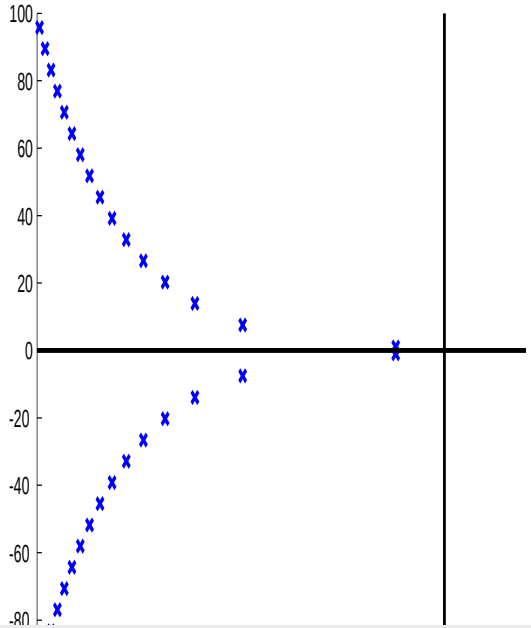
$$G(s) = \frac{t(s) + \sum_{i=1}^{N'} t_i(s) e^{-is\tau}}{p(s) + \sum_{k=1}^{N} q_k(s) e^{-ks\tau}} = \frac{n(s)}{d(s)} \quad \text{où} \quad \deg p \geq \deg t \geq \deg t_i \quad i \in \mathbb{N}_{N'}$$

Retarded : $\deg p > \deg q_k \quad k \in \mathbb{N}_N$

Neutral : $\exists k \in \mathbb{N}_N \quad \deg p = \deg q_k$

$$\dot{x} = x(t-\tau) + u(t-\tau)$$

$$\dot{x} + \dot{x}(t-\tau) = u(t-\tau)$$



Delay systems

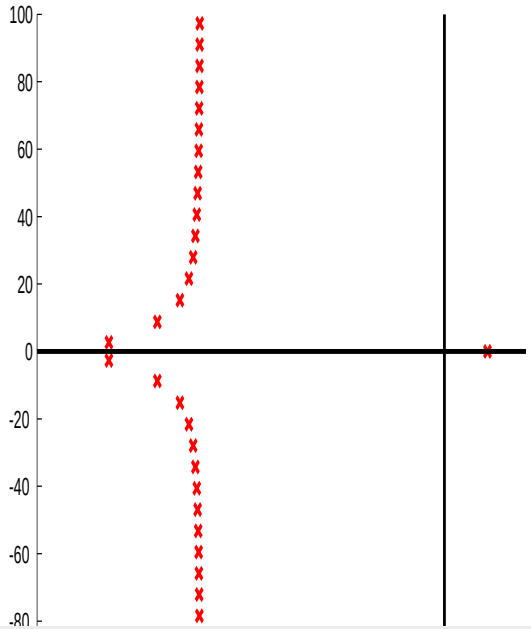
$$G(s) = \frac{t(s) + \sum_{i=1}^{N'} t_i(s) e^{-is\tau}}{p(s) + \sum_{k=1}^{N} q_k(s) e^{-ks\tau}} = \frac{n(s)}{d(s)} \quad \text{où} \quad \deg p \geq \deg t \geq \deg t_i \quad i \in \mathbb{N}_{N'}$$

Retarded : $\deg p > \deg q_k \quad k \in \mathbb{N}_N$

Neutral : $\exists k \in \mathbb{N}_N \quad \deg p = \deg q_k$

$$\dot{x} = x(t-\tau) + u(t-\tau)$$

$$\dot{x} + \dot{x}(t-\tau) = u(t-\tau)$$



Delay systems

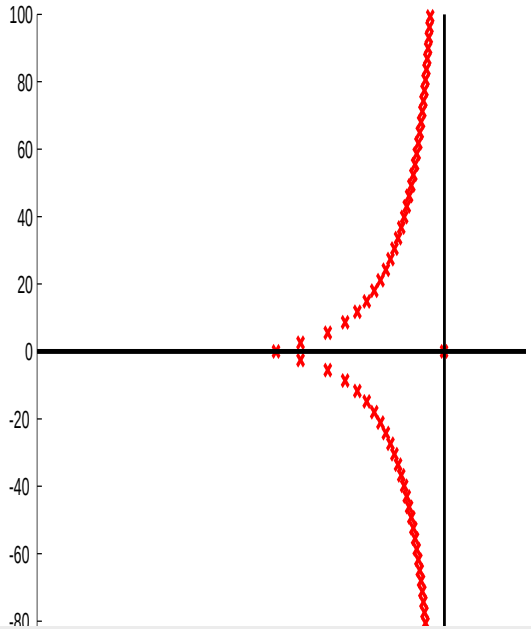
$$G(s) = \frac{t(s) + \sum_{i=1}^{N'} t_i(s) e^{-is\tau}}{p(s) + \sum_{k=1}^{N} q_k(s) e^{-ks\tau}} = \frac{n(s)}{d(s)} \quad \text{où} \quad \deg p \geq \deg t \geq \deg t_i \quad i \in \mathbb{N}_{N'}$$

Retarded : $\deg p > \deg q_k \quad k \in \mathbb{N}_N$

Neutral : $\exists k \in \mathbb{N}_N \quad \deg p = \deg q_k$

$$\dot{x} = x(t-\tau) + u(t-\tau)$$

$$\dot{x} + \dot{x}(t-\tau) = u(t-\tau)$$



Delay systems

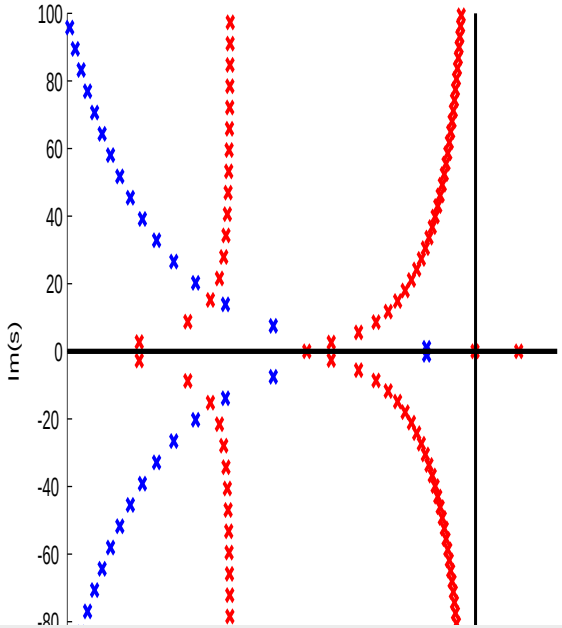
$$G(s) = \frac{t(s) + \sum_{i=1}^{N'} t_i(s) e^{-is\tau}}{p(s) + \sum_{k=1}^{N} q_k(s) e^{-ks\tau}} = \frac{n(s)}{d(s)} \quad \text{où} \quad \deg p \geq \begin{matrix} \deg t \\ \deg t_i \end{matrix} \quad i \in \mathbb{N}_{N'}$$

Retarded : $\deg p > \deg q_k \quad k \in \mathbb{N}_N$

Neutral : $\exists k \in \mathbb{N}_N \quad \deg p = \deg q_k$

$$\dot{x} = x(t-\tau) + u(t-\tau)$$

$$\dot{x} + \dot{x}(t-\tau) = u(t-\tau)$$



H_∞-stability of retarded delay systems

For retarded delay systems:

G is H_∞-stable $\iff$ G has no poles in the closed right half-plane

same NSC for asymptotic and exponential stability

Equilibrium points of the simple model (healthy model)

Here we are interested by strictly positive equilibrium points

The system admits a unique strictly positive equilibrium point if and only if

$$\beta_1(0) > \frac{\delta_1}{2(1-K)\int_0^\tau e^{-\gamma t} f(t)dt - 1} \tag{5}$$

Moreover, the positive steady state can be computed from

$$\beta_i(x_i^e) = \frac{1}{\alpha_i}\left(\delta_i - \frac{2K_{i-1}C_{i-1}\beta_{i-1}(x_{i-1}^e)x_{i-1}^e}{x_i^e}\right) \tag{6}$$

Stability results for the simple model (input-output techniques)

Theorem

Let x^e be the unique strictly positive equilibrium point and $\mu := \frac{d}{dx} x\beta(x)|_{x^e}$.

If $\mu > 0$, le system is locally asymptotically stable iff

$$2(1-K)\int_0^\tau e^{-\gamma t} f(t)dt < \frac{\delta+\mu}{\mu}$$

If $\mu < 0$ and $\delta > |\mu|$, the system is locally asymptotically stable iff

$$2(1-K)\int_0^\tau e^{-\gamma t} f(t)dt < \frac{\delta-|\mu|}{|\mu|} M_0, \quad M_0 > 1$$

Equilibrium points of the interconnected model

We call x_1^e, $\tilde{x}_1^e$, $\bar{x}_1^e$, x_2^e, $\tilde{x}_2^e$, $\bar{x}_2^e$ and $\bar{x}_3^e$ the equilibrium points of the coupled system. The origin, $x_1^e = \tilde{x}_1^e = \bar{x}_1^e = x_2^e = \tilde{x}_2^e = \bar{x}_2^e = \bar{x}_3^e = 0$, is an equilibrium point.

$$\beta_1 \left(x_1^e + \bar{x}_1^e\right) = -c_1 \delta_1, \tag{7}$$

$$\tilde{\beta}_1 \left(\tilde{x}_1^e\right) = -\tilde{c}_1 \delta_1 \left(\frac{x_1^e}{\tilde{x}_1^e}\right), \tag{8}$$

$$\bar{\beta}_1 \left(x_1^e + \bar{x}_1^e\right) = -\frac{\bar{\delta}_1}{1 - \bar{L}_1 \bar{H}_1 (0)}, \tag{9}$$

$$\beta_2 \left(x_2^e\right) = -c_2 \left(\alpha_1 \delta_2 - 2K_1 H_1 (0) \delta_1 \left(\frac{x_1^e}{x_2^e}\right)\right), \tag{10}$$

$$\tilde{\beta}_2 \left(\tilde{x}_2^e\right) = -\tilde{c}_2 \left(\alpha_1 \delta_2 x_2 - 2K_1 H_1 (0) \delta_1 x_1^e\right) \left(\frac{1}{\tilde{x}_2^e}\right), \tag{11}$$

$$\bar{\beta}_2 \left(\bar{x}_2^e\right) = \frac{-\bar{\delta}_2 + 2\bar{K}_1 \bar{H}_1 (0) \bar{\beta}_1 \left(\bar{x}_1^e\right) \left(\frac{\bar{x}_1^e}{\bar{x}_2^e}\right)}{1 - \bar{L}_2 \bar{H}_2 (0)}, \tag{12}$$

$$\bar{\beta}_3 \left(\bar{x}_3^e\right) \frac{-\bar{\delta}_3 + 2\bar{K}_2 \bar{H}_2 (0) \bar{\beta}_2 \left(\bar{x}_2^e\right) \left(\frac{\bar{x}_2^e}{\bar{x}_3^e}\right)}{1 - \bar{L}_3 \bar{H}_3 (0)},$$

Equilibrium points

We are interested in non negative equilibrium points
Use properties of β functions (non negative, decreasing)

$$c_1 \delta_1 < \beta_1(0), \tag{13}$$

$$-\frac{\bar{\delta}_1}{(1-\bar{L}_1 \bar{H}_1(0))} < \bar{\beta}_1(0), \tag{14}$$

$$\frac{1}{L_1+\tilde{L}_1} < H_1(0) < \frac{1}{\tilde{L}_1}, \tag{15}$$

$$\frac{1}{\bar{L}_1} < \bar{H}_1(0), \tag{16}$$

$$\frac{1}{L_2+\tilde{L}_2} < H_2(0) < \frac{1}{\tilde{L}_2}, \tag{17}$$

$$\frac{1}{\bar{L}_2} < \bar{H}_2(0), \tag{18}$$

$$\frac{1}{\bar{L}_3} < \bar{H}_3(0).$$

Equilibrium points

- The perturbation of a healthy solution i.e. $x_1(t) = 0$, $\tilde{x}_1(t) = 0$, $\bar{x}_1(t) > 0$, $x_2(t) = 0$, $\tilde{x}_2(t) = 0$, $\bar{x}_2(t) > 0$ and $\bar{x}_3(t) > 0$ for all $t \geq 0$,may provoke the born of cancer cells.
- Necessary and sufficient conditions for the existence of a unique equilibrium point $\bar{x}_1^e > 0$, $\bar{x}_2^e > 0$ and $\bar{x}_3^e > 0$ when $x_1^e = \tilde{x}_1^e = x_2^e = \tilde{x}_2^e = 0$

Model linearization

Consider the following perturbed trajectories: $X_1(t) := x_1(t) - x_1^e$, $\tilde{X}_1(t) := \tilde{x}_1(t) - \tilde{x}_1^e$, $\bar{X}_1(t) := \bar{x}_1(t) - \bar{x}_1^e$, $X_2(t) := x_2(t) - x_2^e$, $\tilde{X}_2(t) := \tilde{x}_2(t) - \tilde{x}_2^e$, $\bar{X}_2(t) := \bar{x}_2(t) - \bar{x}_2^e$ and $\bar{X}_3(t) := \bar{x}_3(t) - \bar{x}_3^e$. The linearized model is given by

$$
\begin{aligned}
\dot{X}_1(t) &= -(\delta_1 + \mu_1) X_1(t) - c_{12} \bar{X}_1(t) + L_1 \left(h_1^3 * h_1^2 * h_1^1 * W_1\right)(t), \\
\dot{\tilde{X}}_1(t) &= -\tilde{\mu}_1 \tilde{X}_1(t) + \tilde{L}_1 \left(h_1^3 * h_1^2 * h_1^1 * W_1\right)(t), \qquad (19) \\
\dot{\bar{X}}_1(t) &= -\left(\bar{\delta}_1 + \bar{\mu}_1\right) \bar{X}_1(t) - c_{15} X_1(t) + \bar{L}_1 \left(\bar{h}_1^3 * \bar{h}_1^2 * \bar{h}_1^1 * \bar{W}_1\right)(t), \qquad (20) \\
\dot{X}_2(t) &= -(\delta_2 + \mu_2) X_2(t) + L_2 \left(h_2^3 * h_2^2 * h_2^1 * W_2\right)(t) \\
&\quad + 2K_1 \left(h_1^3 * h_1^2 * h_1^1 * W_1\right)(t), \qquad (21) \\
\dot{\tilde{X}}_2(t) &= -\tilde{\mu}_2 \tilde{X}_2(t) + \tilde{L}_2 \left(h_2^3 * h_2^2 * h_2^1 * W_2\right)(t), \qquad (22) \\
\dot{\bar{X}}_2(t) &= -\left(\bar{\delta}_2 + \bar{\mu}_2\right) \bar{X}_1(t) + \bar{L}_2 \left(\bar{h}_2^3 * \bar{h}_2^2 * \bar{h}_2^1 * \bar{W}_2\right)(t) \\
&\quad + 2\bar{K}_1 \left(\bar{h}_1^3 * \bar{h}_1^2 * \bar{h}_1^1 * \bar{W}_1\right)(t), \qquad (23) \\
\dot{\bar{X}}_3(t) &= -\left(\bar{\delta}_3 + \bar{\mu}_3\right) \bar{X}_3(t) + \bar{L}_3 \left(\bar{h}_3^3 * \bar{h}_2^3 * \bar{h}_3^1 * \bar{W}_3\right)(t) \\
&\quad + 2\bar{K}_2 \left(\bar{h}_2^3 * \bar{h}_2^2 * \bar{h}_2^1 * \bar{W}_2\right)(t). \qquad (24)
\end{aligned}
$$

Stability Analysis

The linear system is stable if and only if $1/\det(A(s))$ is stable, where

$$A(s) := \begin{pmatrix} & & & 0 & 0 & 0 & 0 \\ & A_1(s) & & 0 & 0 & 0 & 0 \\ & & & 0 & 0 & 0 & 0 \\ a_{41}(s) & a_{42}(s) & a_{43}(s) & & & & 0 \\ 0 & 0 & 0 & & A_2(s) & & 0 \\ a_{61}(s) & 0 & a_{63}(s) & & & & 0 \\ 0 & 0 & 0 & 0 & 0 & a_{76}(s) & a_{77}(s) \end{pmatrix},$$

Consequently, since the matrix $A(s)$ has a block lower triangular form with diagonal blocks $A_1(s)$, $A_2(s)$ and $a_{77}(s)$ we have

$$\det(A(s)) = \det(A_1(s))\det(A_2(s))a_{77}(s) \tag{25}$$

Stability Analysis

Theorem

Suppose that $\bar{\delta}_1 + \bar{\mu}_1 > 0$, $\delta_1 + \mu_1 > 0$, $\tilde{\mu}_1 > 0$, $\bar{\delta}_2 + \bar{\mu}_2 > 0$, $\delta_2 + \mu_2 > 0$, $\tilde{\mu}_2 > 0$, $\bar{\delta}_3 + \bar{\mu}_3 > 0$,

$$H_1(0) < \frac{\delta_1 + \mu_1}{2(1-K_1)(|\mu_1| + (1-\sigma_1)\delta_1)} \tag{26}$$

$$\bar{H}_1(0) < \frac{\bar{\delta}_1 + \bar{\mu}_1}{2(1-\bar{K}_1)|\bar{\mu}_1|} \tag{27}$$

$$H_2(0) < \frac{\delta_2 + \mu_2}{2(1-K_2)(|\mu_2| + (1-\sigma_2)\delta_2)} \tag{28}$$

$$\bar{H}_2(0) < \frac{\bar{\delta}_2 + \bar{\mu}_2}{2(1-\bar{K}_2)|\bar{\mu}_2|} \tag{29}$$

$$\bar{H}_3(0) < \frac{\bar{\delta}_3 + \bar{\mu}_3}{2(1-\bar{K}_3)|\bar{\mu}_3|}. \tag{30}$$

Then the system linearized at the equilibrium point $x_1^e = 0$, $\tilde{x}_1^e = 0$, $\bar{x}_1^e > 0$, $x_2^e = 0$, $\tilde{x}_2^e = 0$, $\bar{x}_2^e > 0$ *and* $\bar{x}_3^e > 0$ *is* H_∞ *stable. In particular, the nonlinear system is locally asymptotically stable.*

Numerical example

Let us study a system with two compartments with $\delta_1 = 2$, $\bar{\delta}_1 = 7$, $\delta_2 = 1.5$, $\bar{\delta}_2 = 0.85$, $\bar{\delta}_3 = 1.4$, $K_1 = 0.1$, $\bar{K}_1 = 0.2$, $K_2 = 0.1$, $\bar{K}_2 = 0.2$, $\bar{K}_3 = 0.4$, $\sigma_1 = 0.9$, $\sigma_2 = 0.8$, and the other parameters as indicated in the following Table.

i	$\beta_i(0)$	$\tilde{\beta}_i(0)$	$\bar{\beta}_i(0)$	b_i	$\tilde{b}_i$	$\bar{b}_i$	N_i	$\tilde{N}_i$	$\bar{N}_i$
1	2	1	15	1	0.1	1	2	2	3
2	1	1	1	1	0.3	1	4	4	3
3	-	-	6	-	-	1	-	-	4

i	m_i^1	m_i^2	m_i^3	τ_i^1	τ_i^2	τ_i^3	γ_i^1	γ_i^2	γ_i^3
1	3	1	2	0.3	0.1	0.2	0.03	0.01	0.02
2	3	1	2	0.3	0.1	0.2	0.05	0.01	0.08

i	$\bar{m}_i^1$	$\bar{m}_i^2$	$\bar{m}_i^3$	$\bar{\tau}_i^1$	$\bar{\tau}_i^2$	$\bar{\tau}_i^3$	$\bar{\gamma}_i^1$	$\bar{\gamma}_i^2$	$\bar{\gamma}_i^3$
1	3	1	2	1.3	0.1	0.2	0.03	0.01	0.02
2	3	1	2	0.3	0.1	0.2	0.03	0.01	0.02
3	3	4	2	0.3	0.5	0.2	0.03	0.01	0.02

Simulation results

The resulting equilibrium point is $\bar{x}_1^e = 0.5608$, $\bar{x}_2^e = 3.3188$, $\bar{x}_3^e = 0.1295$, $x_1^e = \tilde{x}_1^e = x_2^e = \tilde{x}_2^e = 0$ with the parameters $\mu_1 = 1.5215$, $\tilde{\mu}_1 = 1$, $\bar{\mu}_1 = 7.0159$, $\mu_2 = 1$, $\tilde{\mu}_2 = 1$, $\bar{\mu}_2 = -0.0511$ and $\bar{\mu}_3 = 0.9913$.
The local stability conditions are satisfied:

$$H_1(0) = 0.992 < \frac{\delta_1 + \mu_1}{2(1-K_1)(|\mu_1| + (1-\sigma_1)\delta_1)} = 1.136,$$

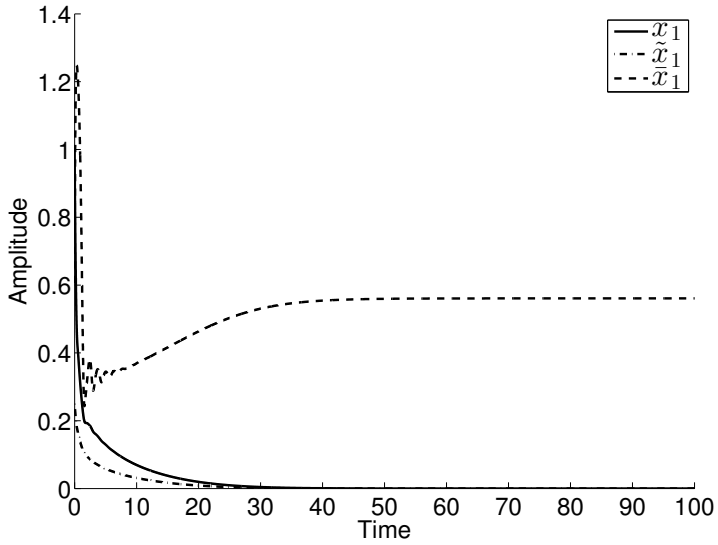
$$\bar{H}_1(0) = 0.968 < \frac{\bar{\delta}_1 + \bar{\mu}_1}{2(1-\bar{K}_1)|\bar{\mu}_1|} = 1.246,$$

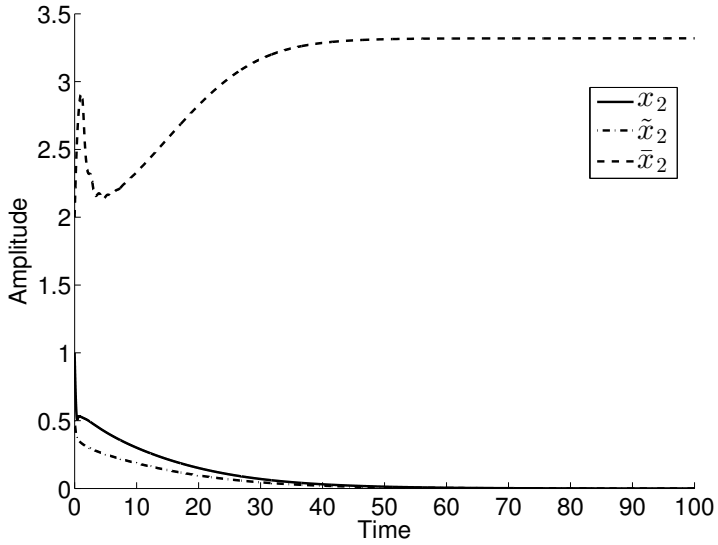
$$H_2(0) = 0.981 < \frac{\delta_2 + \mu_2}{2(1-K_2)(|\mu_2| + (1-\sigma_2)\delta_2)} = 1.068,$$

$$\bar{H}_2(0) = 0.922 < \frac{\bar{\delta}_2 + \bar{\mu}_2}{2(1-\bar{K}_2)|\bar{\mu}_1|} = 9.7659,$$

$$\bar{H}_3(0) = 0.989 < \frac{\bar{\delta}_3 + \bar{\mu}_3}{2(1-\bar{K}_3)|\bar{\mu}_3|} = 1.028.$$

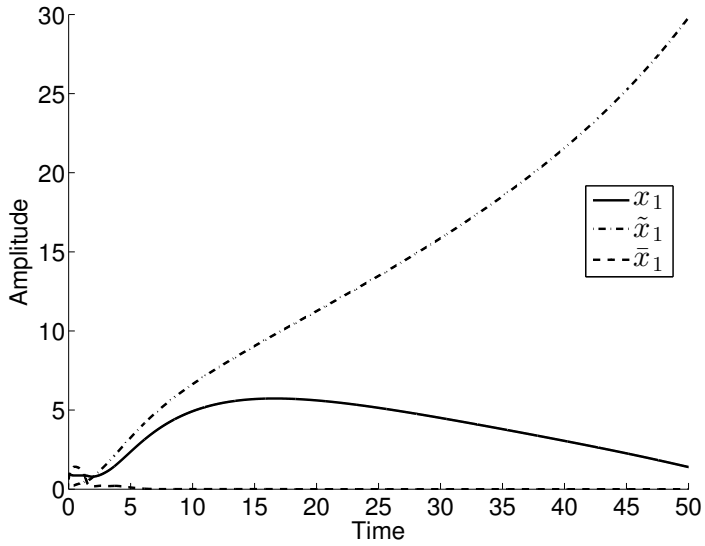
Simulation results





Simulation results

Further simulations showed that decreasing σ_1 and σ_2, and fixing the remaining parameters as in the previous example the local stability condition is no longer satisfied. For example, when $\sigma_1 = 0.4$ and $\sigma_2 = 0.5$ the states $\tilde{x}_1$ and $\tilde{x}_2$ are far from their equilibrium value



Time-varying parameters

To model the action of drugs the two drugs:

$\longrightarrow$ we need to take σ and γ depending on t.

Time-domain methods are helpful to get a first insight

Stability results for the simple model (time-domain)

The function β is assumed to be locally Lipschitz

Trivial equilibrium point

Theorem

The system admits the origin as a **globally asymptotically stable** equilibrium point if for all i

$$\beta_i(0) < \frac{\delta_i}{2(1-K_i)\int_0^\tau e^{-\gamma_i t} f(t)dt - 1} \tag{31}$$

If

$$\beta_1(0) > \frac{\delta_1}{2(1-K_i)\int_0^\tau e^{-\gamma_1 t} f(t)dt - 1} \tag{32}$$

no positive solution converges to the trivial equilibrium point

Example 1:

Choosing $f_i(a) = \frac{m_i}{e^{m_i\tau_i}-1}e^{m_i a}$, with $m_i > 0$ for all $i \in [1,n]$.

$\delta_1 = 1.25$, $L_1 = 1 - K_1 = 0.85$, $m_1 = 5$, $\tau_1 = 1.2$, $\gamma_1 = 0.22$ and $\beta_1(x) = \frac{1}{1+x^2}$. ($\Rightarrow \delta_1 - \alpha_1\beta_1(0) = 0.88$)

$\delta_2 = 1$, $L_2 = 1 - K_2 = 0.8$, $m_2 = 7$, $\tau_2 = 1.3$, $\gamma_2 = 0.33$ and $\beta_2(x) = \frac{3}{1+x^3}$. ($\Rightarrow \delta_2 - \alpha_2\beta_2(0) = 0.72$)

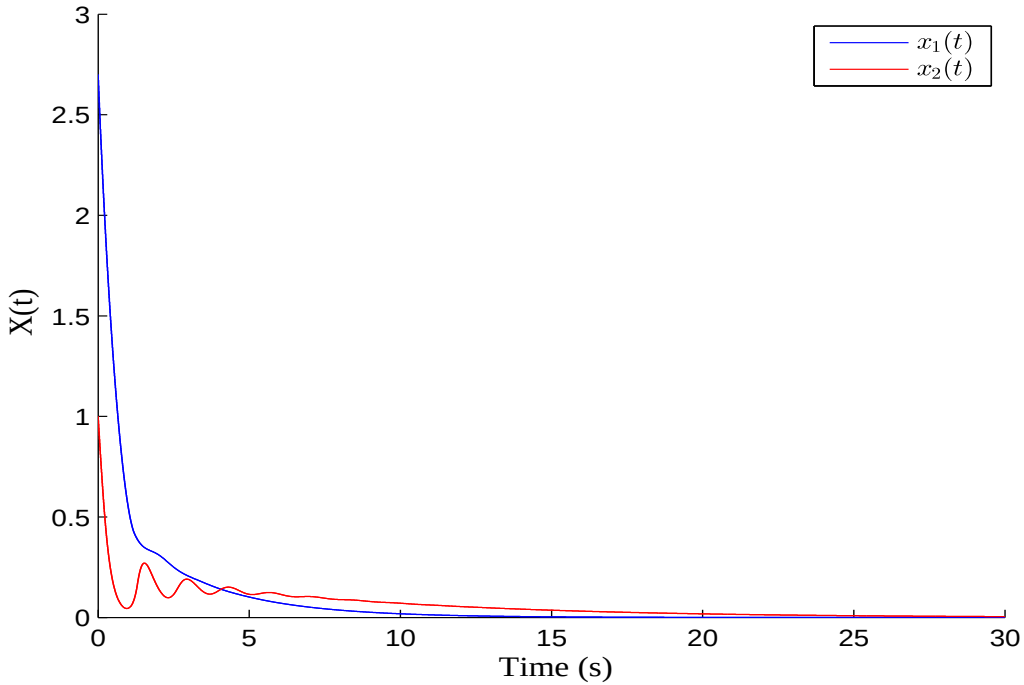


Figure 1: Trajectories of the states x_1 and x_2.

Stability results for the simple model (time-domain)

Let $K_i(t) + L_i(t) = 1$ and $L_i(t) \in [L_{i\min}, L_{i\ max}] \subset (0,1)$

Corollory

The conditions

$$\beta_i(0) < \frac{\delta_i}{2(1 - K_{i\ min}) \int_0^\tau e^{-\gamma_i t} f(t) dt - 1} \tag{33}$$

ensures that the origin of the system (with time-varying parameters) is globally exponentially stable.

Stability results for the simple model (time-domain)

Strictly positive equilibrium point

Theorem

The conditions

$$2(1-K_i)\int_0^{\tau_i} e^{-\gamma_i t} f(t)dt < \frac{\delta_i + \mu_i}{|\mu_i|}$$

ensure that the non linear system is asymptotically (exponentially) stable

We can get an approximation of the basin of attraction

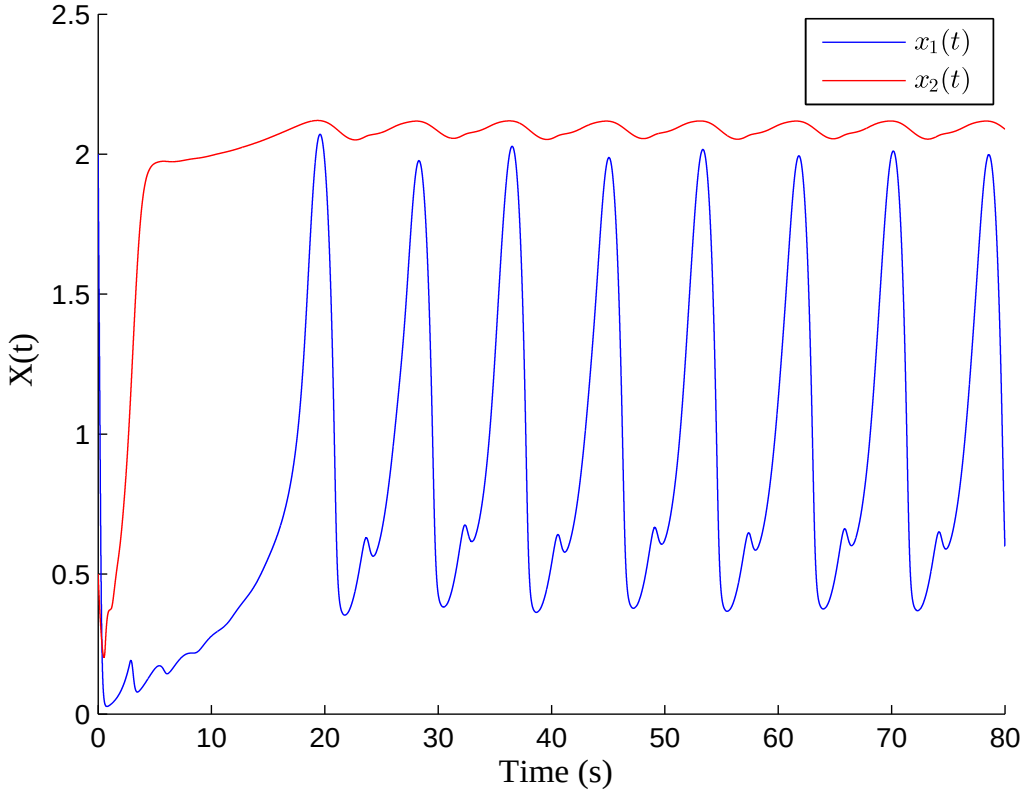
Example 2:

$\delta_1 = 2.1$, $L_1 = 0.985$, $m_1 = 1$, $\tau_1 = 2.81165$, $\gamma_1 = 0.095$ and $\beta_1(x) = \frac{8}{1+x^3}$.

$\Rightarrow (\alpha_1 = 0.63, x_1^e = 1.1226, \varsigma_1 = -26.2113)$.

$\delta_2 = 0.2$, $L_2 = 0.95$, $m_2 = 10$, $\tau_2 = 0.6332$, $\gamma_2 = 0.085$ and $\beta_2(x) = \frac{2}{1+x^3}$.

$\Rightarrow (\alpha_2 = 0.81, x_2^e = 2.1136, \varsigma_2 = -14.5370)$.



Example 3:

For i=1: $\delta_1 = 0.1356$, $K_1 = 0.05$, $\beta_1(x) = \frac{0.5}{1+x^2}$, $\gamma_1 = 0.3$, $m_1 = 10$, $\tau_1 = 1.109402$.

For i=2: $\delta_2 = 0.1669$, $K_2 = 0.07$, $\beta_2(x) = \frac{1}{1+x^4}$, $\gamma_2 = 0.4$, $m_2 = 10$, $\tau_2 = 1.2$.

For i=3: $\delta_3 = 0.3559$, $K_3 = 0.085$, $\beta_3(x) = \frac{3}{1+x^2}$, $\gamma_3 = 0.45$, $m_3 = 2$, $\tau_3 = 1.36$.

$\alpha_1 = 0.40422$, $\alpha_2 = 0.19888$ et $\alpha_3 = 0.20422$.

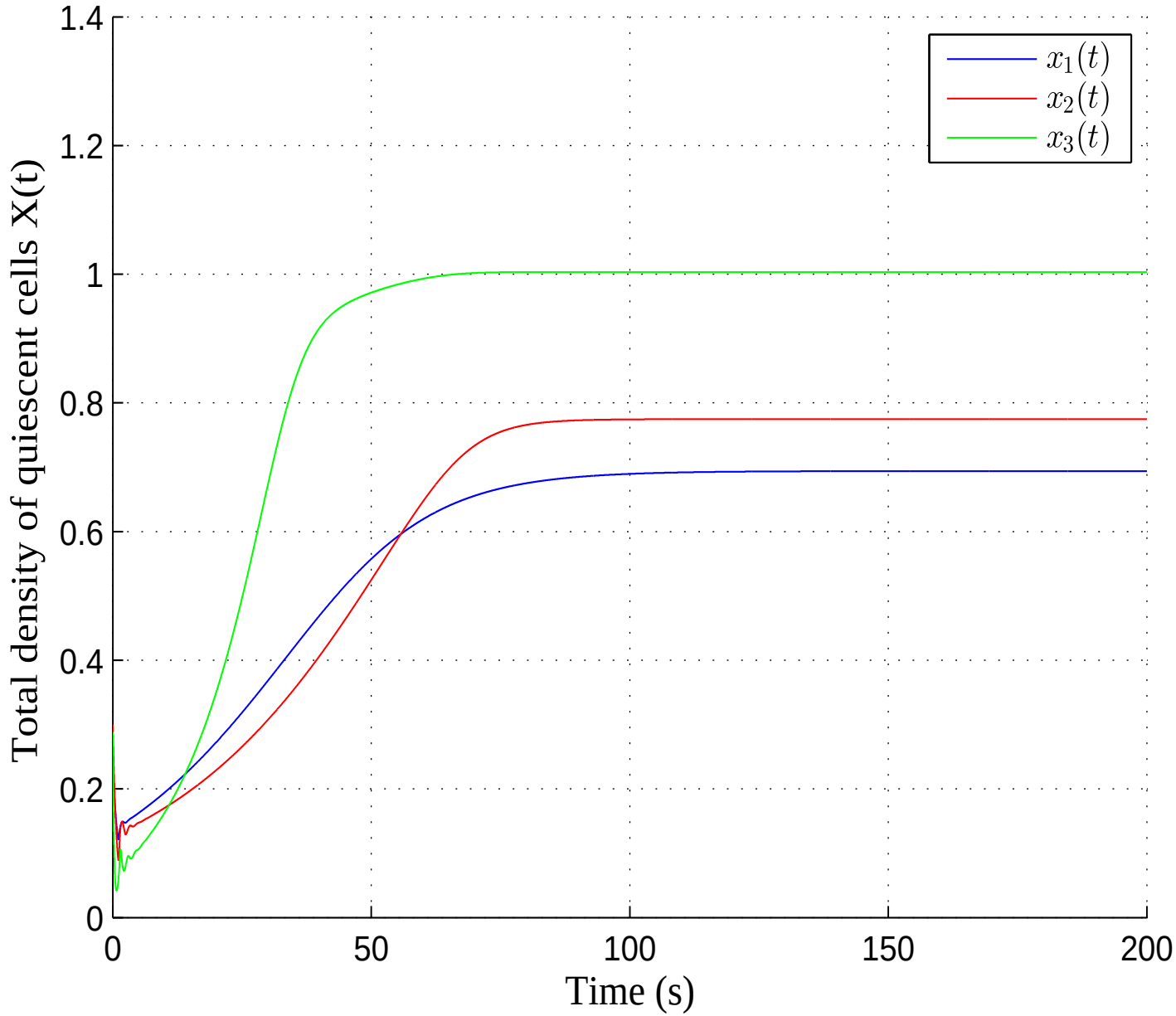
$X^e = (0.7, 0.782, 1.005)$.

$0 < \delta_i < \delta_{i+1}$, $0 < K_i < K_{i+1}$, $0 < \tau_i < \tau_{i+1}$ and $0 < x_i^e < x_{i+1}^e$, for all $i \geq 1$.

For i=1: $\beta_1^* = 0.2505 > 0$, $\varsigma_1 = 0.0892 > 0$.

For i=2: $\beta_2^* = 0.1023 > 0$, $\varsigma_2 = 0.0249 > 0$.

For i=3: $\beta_3^* = 0.3484 > 0$, $\varsigma_3 = 0.3395 > 0$.


1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
50
100
150
200
Total density of quiescent cells X(t)
Time (s)
$x_1(t)$
$x_2(t)$
$x_3(t)$

4. Conclusion and future work

Conclusions and Future work

- We have proposed a multi-stage interconnected model of healthy cells and cancer cells of AML.
- Stability may be lost when fast self-renewal is high
- Model the fast self-renewal phenomenon without quiescent phase.
- Full analysis with time-varying parameters $\gamma(t)$ and $\sigma(t)$.
- PK/PD models