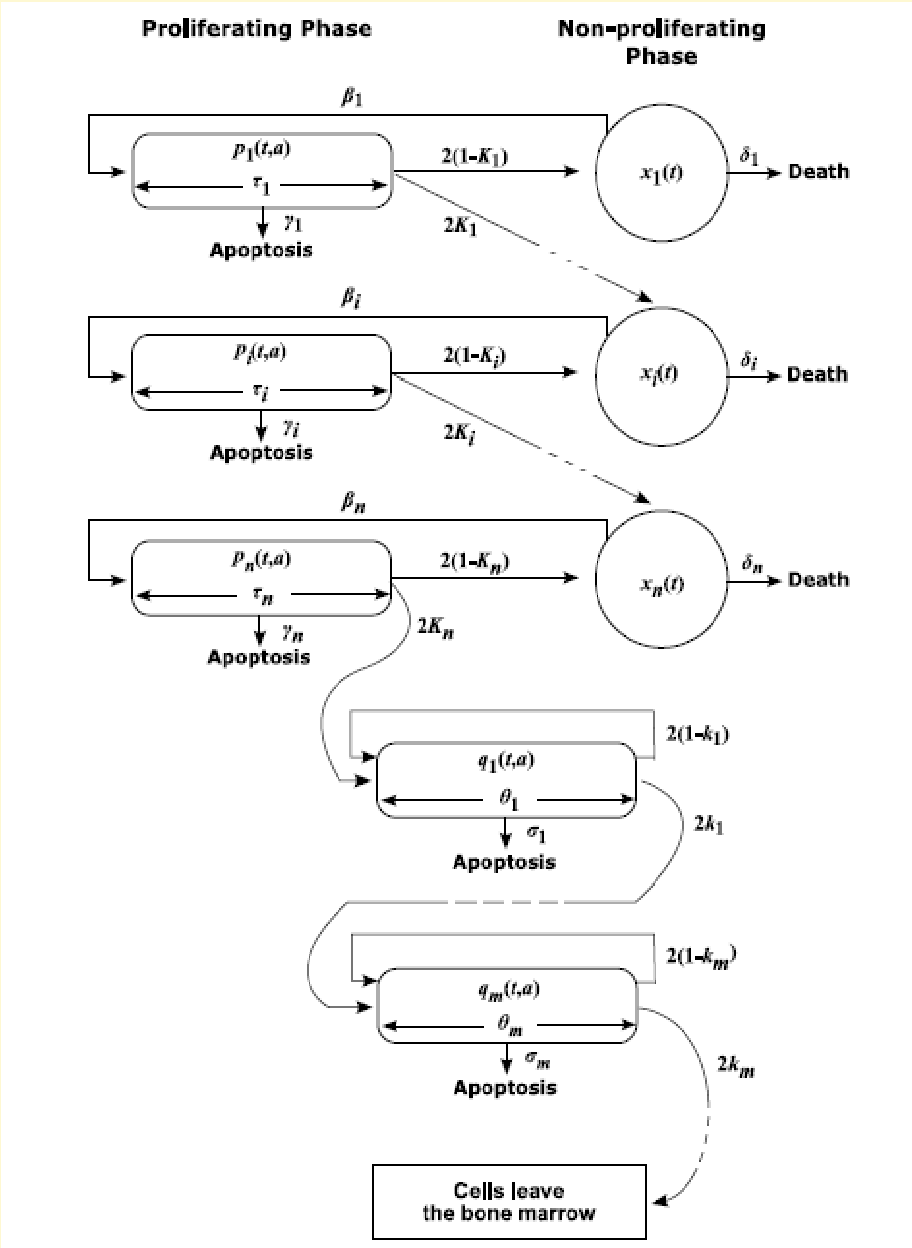
Stability Analysis of Systems with Distributed Delays and Application to Hematopoietic Cell Maturation Dynamics

Hitay Özbay, Catherine Bonnet, Jean Clairambault

A Model of Cell Dynamics from Adimy, Crauste, El Abdllaoui (2008):



x_i total density of resting cells

δ_i and γ_i death rates

a cell age (time spent in a compartment)

y_i total density of proliferating cells

proliferating cells can divide between the moment they enter the proliferating phase and a maximal time τ_i

Mathematical model

$$
\begin{aligned}
\frac{d}{dt}x_i(t) &= -(\delta_i + \beta_i(x_i(t))\; x_i(t) \\
&\quad +2(1-K_i)\int_0^{\tau_i} e^{-\gamma_i a} f_i(a)\beta_i(x_i(t-a))x_i(t-a)da \\
&\quad +2K_{i-1}\int_0^{\tau_{i-1}} e^{-\gamma_{i-1} a} f_{i-1}(a)\beta_{i-1}(x_{i-1}(t-a))x_{i-1}(t-a)da
\end{aligned}
$$

$$
\begin{aligned}
\frac{d}{dt}y_i(t) &= -\gamma_i\; y_i(t) \\
&\quad \underbrace{+\beta_i(x_i(t))x_i(t) - \int_0^{\tau_i} e^{-\gamma_i a} f_i(a)\beta_i(x_i(t-a))x_{i-1}(t-a)da}_{\text{can be seen as an external input}}
\end{aligned}
$$

$i = 2, 3, 4 \ldots.$

$$\int_0^{\tau_i} f_i(\theta)d\theta = 1$$

Linearization

$$\mu_i := \frac{\partial}{\partial x_i}\left(x_i \beta_i(x_i)\right)\Big|_{x=x_e} \qquad L_i := (1-K_i)$$

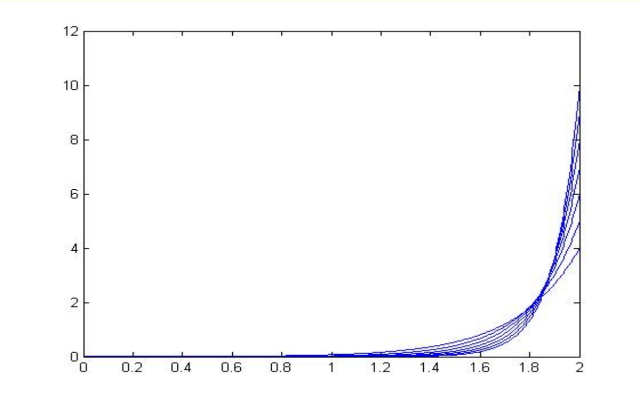
$$F_k(s) := 2L_k\mu_k \int_0^{\tau_k} e^{-\gamma_k\theta} f_k(\theta) e^{-s\theta} d\theta$$

Linearized model is stable if and only if all the roots of the following characteristic equation are in open left half plane

$$\prod_{k=1}^{n}(s+\delta_k+\mu_k-F_k(s))=0$$

Selection of $f_k(\theta)$ plays an important role in the stability analysis as well as the parameters L_k, δ_k, μ_k.

Considering



$$f_k(\theta) = \frac{m}{e^{m\tau_k} - 1} e^{m\theta} \quad \text{for} \quad 0 < \theta < \tau_k$$

m is an integer greater than γ_k then

★ has all its roots in the open left half plane if and only if

$$\frac{1}{2L_k} \left(\frac{\delta_k + \mu_k}{\mu_k} \right) > \left(\frac{m}{m - \gamma_k} \right) \frac{e^{(m-\gamma_k)\tau_k} - 1}{e^{m\tau_k} - 1}$$

Adjustments of the parameters → stability.

In particular, when m is very large, the above stability condition becomes

$$\frac{1}{2L_k} \left(\frac{\delta_k + \mu_k}{\mu_k} \right) > e^{-\gamma_k \tau_k}$$

Problems to be studied:

1. Consider time varying parameters and investigate stability conditions, e.g.

$$\gamma_k = \gamma_{ko} + \frac{A}{B + D(t)} \quad \text{and} \quad L_k = \frac{\widehat{A}\ \widehat{D}(t)}{\widehat{B} + \widehat{D}(t)}$$

2. Consider piecewise constant, or piecewise linear parameters

3. Consider different forms of $f_k(\theta)$

4. Validation of the stability analyses for the above cases with simulations.

5. Justification of the mathematical model using data collection.

These problems will be studied with participation of
Houda Benjelloun (stagiaire) and Andre Fioravanti (PhD student).