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

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Abstract— **We consider linear systems with distributed delays where delay kernels are assumed to be finite duration impulse responses of finite dimensional systems. We show that stability analysis for this class of systems can be reduced to stability analysis of linear systems with discrete delays, for which many algorithms are available in the literature. The results are illustrated on a mathematical model of hematopoietic cell maturation dynamics.**

I. Introduction

Distributed delay system models appear in a wide range of applications, such as, logistics [8], traffic flow [27], microorganism growth [24], and hematopoiesis [1], [2], [4].

Algebraic theory of systems with distributed and lumped delays is well established, see e.g. [14], [16] where realization and control properties are studied within this framework. Also, stability analysis for systems with distributed delays has been studied by many researchers, see [25] for a list of early works and [11], [12], [13], [17], [19], [20], [21], [28], [29], [30] for some other relevant results. In particular, [11], [12], [13] deal with piecewise constant delay kernels. In [20] the delay kernel is a gamma-distribution, and in [21], [30] rational delay kernels are considered. The setting in [28] covers, in an indirect way, exponential delay kernels; the main discussion there is on the analytic solution of Lyapunov functional equation.

Distributed delay kernels considered in this paper are finite duration impulse responses of finite dimensional systems, i.e., they consist of finite linear combinations of exponential terms and the Dirac delta. A simpler form of this type of systems has been considered in the motivating example section of [30]. We will generalize a result of [30] on scalar systems to a larger class of linear systems with distributed delays. In particular, stability analysis of such systems will be reduced to the analysis of systems with lumped delays for which many computationally effective algorithms are available, see e.g. [9], [12], [22] and references therein.

As an application example we will consider the linearized model of hematopoietic cell maturation dynamics appearing in [3]. This model of hematopoiesis is particularly dedicated to represent the evolution dynamics of Acute Myeloblastic Leukemia (AML), a cancerous hemopathy for which mathematical modeling has been limited so far. We should also point out that therapies for AML have remained unchanged for the last 40 years, relying mainly on the cytotoxic drug Cytosine Arabinoside, with only partial successes (see e.g., [15], [26] and following review articles in the latter journal). The model we consider is structured both in discrete cell differentiation status $k = 1,2,\ldots N$ and in continuous cell physiological age a ($0 \leq a < h_k$ in the k^{th} proliferating cell compartment, $a \geq 0$ in the resting cell compartments).

It has been shown that the process of formation and development of blood cells can be modeled by using time delay system models, see e.g. [1]–[7], [18], [23], where non-linear discrete or distributed delay models appear. The linearized model of [3] can be seen as a cascade connection of N scalar systems with distributed delays. Therefore, the stability of each individual scalar system determines local stability of the cell differentiation model proposed.

The paper is organized as follows. In section 2 we discuss the scalar case where the delay kernel is a single exponential term. In this section we make connections with some earlier results, and pose the multivariable version of the problem. In Section 3 the stability analysis of distributed delay systems with exponential kernels is reduced to the analysis of a higher order system with lumped delays. In Section 4 the results are applied to a mathematical model of hematopoietic cell maturation dynamics taken from [3]. Concluding remarks are made in Section 5.

II. Delay Kernel with Single Exponential Term

In order to motivate our main problem let us consider the following scalar system taken from [29], [30]

$$\dot{x}(t) = -ax(t) + \int_0^h be^{-\alpha\theta}x(t-\theta)d\theta \qquad (1)$$

where a, b, α and h are fixed real numbers, h is positive and $x(t)$ is a real valued function, with known initial condition, $x(\theta)$, for $\theta \in [-h \ , \ 0]$. We want to determine stability conditions in terms of given parameters. When $a > 0$, the system is stable for $h = 0$. So, we may pose the following problem: find the smallest $h > 0$ (as a function of a, b and α) destabilizing the system. There are several approaches to this problem, including [10] and [30], where different conditions are obtained for stability of (1). Here we take an alternative approach which considers the characteristic equation

$$s + a - F(s) = 0 \qquad (2)$$

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where $F(s)$ is the Laplace transform of the extended delay kernel

$$f(t) = \begin{cases} b\ e^{-\alpha t} & \text{for } 0 \le t \le h \\ 0 & \text{for } t > h. \end{cases} \tag{3}$$

If we assume $x(\theta) = 0$ for $\theta \in [-h\ ,\ ,0)$ and $x(0) = x_o \neq 0$, then the input-output stability of the system $(x(t),\ t \ge 0$ is the output due to an impulsive input $x_o\delta(t))$ is determined by checking the roots of the characteristic equation (2). In this case we have a retarded delay system, and hence input-output stability is equivalent to having all roots of (2) in the open left half plane, $\mathbb{C}_-$. In this setting, it is easy to verify that

$$F(s) = b\ \frac{1-e^{-h(s+\alpha)}}{s+\alpha}. \tag{4}$$

In [30] the author discusses the question whether the stability bound (5) given below is tight (i.e. it is also necessary) or not, but does not give a conclusive answer.

Proposition 1. Let a, b, α, h be positive numbers. All roots of (2) are in $\mathbb{C}_-$ if and only if

$$\frac{b\ (1-e^{-h\alpha})}{a\ \alpha} < 1. \tag{5}$$

Proof. Clearly, all roots of (2) are in $\mathbb{C}_-$ if and only if the Nyquist graph of $G(j\omega)$ does not encircle -1, where

$$G(s) = -(s+a)^{-1}F(s).$$

Note that the function $\angle G(j\omega) + \pi$ is

$$\tan^{-1}\left(\frac{e^{-h\alpha}\sin(h\omega)}{1-e^{-h\alpha}\cos(h\omega)}\right) - \tan^{-1}(\omega/a) - \tan^{-1}(\omega/\alpha),$$

where $\angle G(j\omega)$ is the phase of $G(j\omega)$. Then the result follows from the claim that $\angle G(j\omega) = -\pi$ only at $\omega = 0$, and $\angle G(j\omega) < -\pi$ for $\omega > 0$. Therefore $G(j\omega)$ does not encircle -1 if and only if $G(0) > -1$, which is equivalent to (5).

Now in order to prove the above claim it is sufficient to show that

$$\ell(\omega) := \frac{\omega}{\alpha} > \frac{e^{-h\alpha}\sin(h\omega)}{1-e^{-h\alpha}\cos(h\omega)} =: r(\omega) \tag{6}$$

for $\omega > 0$. Clearly $\ell(0) = r(0) = 0$ and $\ell(\omega)$ has constant derivative $1/\alpha$. The right hand side, $r(\omega)$, has the derivative

$$\frac{d}{d\omega}r(\omega) = he^{-h\alpha}\frac{\cos(h\omega) - e^{-h\alpha}}{(1-e^{-h\alpha}\cos(h\omega))^2}$$

and the derivative is maximum at $\omega = 0$. A careful examination shows that for positive h and α we have

$$\frac{1}{\alpha} > h\ \frac{e^{-h\alpha}}{1-e^{-h\alpha}}.$$

This proves (6), which implies the result. □

At this point we should also mention that the above result can also be deduced from [10] and [3] where a model of hematopoietic stem cell dynamics is analyzed.

Next we show here that $a > 0$ is not a sufficient condition when $b < 0$ (see [30] where this question is discussed): as an example let us take $b = -300$, $a = 10$, $h = 0.25$ and $\alpha = 1$, the Nyquist plot is as shown in Figure 1. Since G is stable $G(j\omega)$ should not encircle -1 for feedback system stability, however, we see one encirclement.

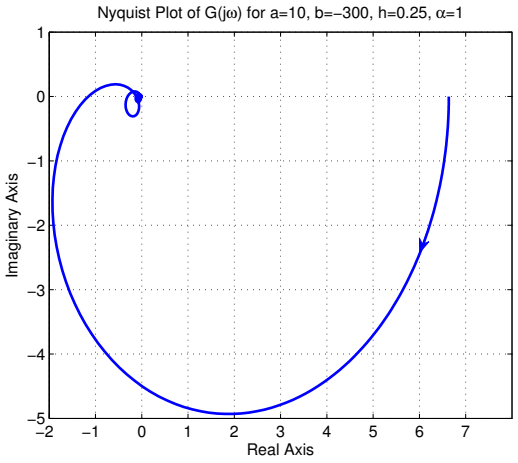

Fig. 1. Nyquist plot of $G(j\omega)$ for $a = 10$, $b = -300$, $h = 0.25$ and $\alpha = 1$.

Let us now consider the system (1) with $a < 0$. In this case when $b = 0$, or $h = 0$, the system is unstable. So, we can see the distributed delay term as a feedback control which tries to stabilize the open-loop unstable system. It is interesting to investigate the stabilizing b and h pair for a given $a < 0$ and α. Clearly if $b > 0$ there is no hope to stabilize the system (the right hand side of (1) becomes positive for all positive initial conditions). So, consider only $b < 0$ when $a < 0$. The characteristic equation is $1 + G(s) = 0$, where

$$G(s) = \frac{|b|}{(s-|a|)}\ \frac{(1-e^{-h(s+\alpha)})}{(s+\alpha)}.$$

In this case feedback system is stable if and only if $G(j\omega)$ encircles -1 once in the counter clockwise direction. This is equivalent to the following three conditions:

$$G(0) < -1 \tag{7}$$

$$\frac{\mathrm{d}}{\mathrm{d}\omega}\angle G(j\omega)\Big|_{\omega=0} > 0 \tag{8}$$

$$-1 < G(j\omega_1) \tag{9}$$

where $\omega_1 > 0$ is the smallest ω for which $\angle G(j\omega) = -\pi$.

For this system it is easy to check that the second condition (8) is equivalent to

$$\frac{h\alpha}{e^{h\alpha}-1} > 1 - \frac{\alpha}{|a|}. \tag{10}$$

In particular, when $|a| \le \alpha$, (10) holds for all $h > 0$. When $|a|/\alpha > 1$ then (10) specifies an upper bound for $h\alpha$.

Let us now examine the special case $a = -1$, $\alpha = 1$. For these fixed parameters (7) is equivalent to having

$$G(0) = -|b|(1-e^{-h}) < -1.$$

Since $|a| = \alpha > 0$ and $h > 0$ the second condition (8) holds as discussed above. For $a = -1$ and $\alpha = 1$ we have

$$\angle G(j\omega) = -\pi + \tan^{-1}\left(\frac{\sin(h\omega)}{e^h - \cos(h\omega)}\right)$$

which gives $\omega_1 = \pi/h$. So, the third condition (9) is equivalent to $b < 0$ and

$$|b| \ \frac{1+e^{-h}}{(\pi/h)^2+1} < 1.$$

Thus, combining all the above conditions we obtain the following result.

Proposition 2. Let $a = -1$, $\alpha = 1$, $b < 0$ and $h > 0$. Then (2) has all roots in $\mathbb{C}_-$ if and only if

$$\frac{1}{(1-e^{-h})} < |b| < \frac{(\pi/h)^2+1}{1+e^{-h}}. \qquad (11)$$

□

Figure 2 shows the allowable range of $|b|$ as a function of h, determined from (11).

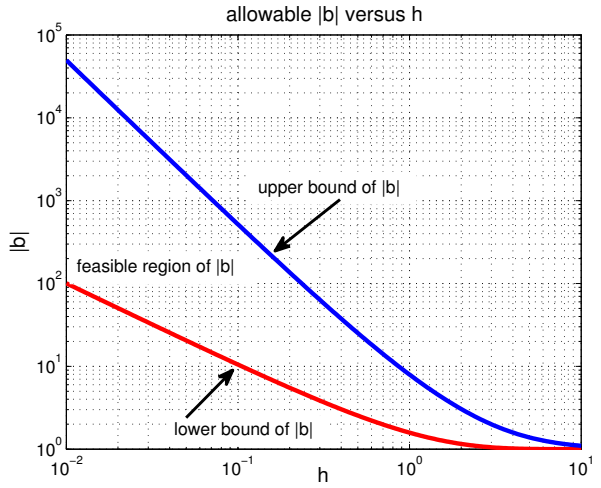

Fig. 2. Allowable range of $|b|$ as a function of h when $a = -1$, and $\alpha = 1$.

We now briefly discuss the multivariable version of the above problem:

$$\dot{x}(t) = Ax(t) + \int_0^h B(\theta)x(t-\theta)d\theta \qquad (12)$$

where A is an $n \times n$ Hurwitz matrix, and $B(\cdot)$ is an $n \times n$ piecewise continuous matrix function, bounded on $[0\ ,\ h]$. The characteristic equation is

$$\det(sI - A - F(s)) = 0$$

where F is the Laplace transform of the delay kernel, i.e.,

$$F(s) = \int_0^h B(t)e^{-st}dt. \qquad (13)$$

Suppose there exists b_o such that

$$\int_0^h \|B(t)\|dt \le b_o,$$

then $\|F\|_\infty \le b_o$. The small gain theorem says that the feedback system formed by $(sI-A)^{-1}$ and $F(s)$ is stable if

$$\|(sI-A)^{-1}\|_\infty < 1/b_o. \qquad (14)$$

This is exactly the same sufficient condition obtained in [29].

III. Transformation to a Lumped Delay Form

The second sufficient condition found in [30], for stability of (1), is derived by transforming the distributed delay system to another system with lumped delay. We now generalize this idea for the MIMO systems in the form (12).

A. Impulse Response of a Finite Dimensional System Restricted to $[0\ ,\ h]$

First we consider the case where $B(\cdot)$ is the impulse response of a strictly proper finite dimensional system restricted to the finite interval $[0\ ,\ h]$; more precisely,

$$B(\theta) = C_o e^{A_o\theta}B_o\ , \quad \theta \in [0\ ,\ h] \qquad (15)$$

for some given real matrices A_o, B_o, C_o of compatible dimensions such that (A_o, B_o) is controllable and (C_o, A_o) is observable. Now, the Laplace transform of the delay kernel as defined by (13) can be computed:

$$F(s) = C_o(sI-A_o)^{-1}B_o - C_o e^{A_o h}(sI-A_o)^{-1}B_o e^{-hs}. \qquad (16)$$

Let us define

$$w(t) = \int_0^h B(\theta)x(t-\theta)d\theta$$

then $\dot{x}(t) = Ax(t) + w(t)$, where w can be seen as the output of the linear system F whose input is x. A particular realization of this system is

$$\begin{aligned} \dot{x}_d(t) &= A_o x_d(t) + B_o x(t)\ , \quad x_d(0) = 0 \\ w(t) &= C_o x_d(t) - C_o e^{A_o h}x_d(t-h). \end{aligned}$$

Combining x and x_d, let $z(t) = \begin{bmatrix} x(t) \\ x_d(t) \end{bmatrix}$, then we have

$$\dot{z}(t) = \begin{bmatrix} A & C_o \\ B_o & A_o \end{bmatrix} z(t) + \begin{bmatrix} 0 & -C_o e^{A_o h} \\ 0 & 0 \end{bmatrix} z(t-h). \qquad (17)$$

For a given set of parameters, A, A_o, B_o, C_o, h, there are several numerically efficient techniques to check stability of the system (17), see e.g. [9], [12], [22].

Remark. The model (17) remains valid even when the "delay" h is time-varying. In order to see this let us consider

$$w(t) := \int_0^{h(t)} C_o e^{A_o\theta}B_o x(t-\theta)d\theta. \qquad (18)$$

Then, we claim that $w(t)$ can be obtained from

$$\begin{aligned} \dot{x}_d(t) &= A_o x_d(t) + B_o x(t)\ , \quad x_d(0) = 0 \qquad (19) \\ w(t) &= C_o x_d(t) - C_o e^{A_o h(t)}x_d(t-h(t)). \qquad (20) \end{aligned}$$

To prove this claim, first, note that the solution of (19) is

$$x_d(t) = \int_0^t e^{A_o\tau}B_o x(t-\tau)d\tau \quad t \ge 0.$$

Therefore, (20) gives

$$w(t) = C_o x_d(t) - \int_0^{t-h(t)} C_o e^{A_o(\tau+h(t))} B_o x(t-h(t)-\tau) d\tau$$

which is equivalent to

$$w(t) = \int_0^t C_o e^{A_o \tau} B_o x(t-\tau) d\tau - \int_{h(t)}^t C_o e^{A_o \sigma} B_o x(t-\sigma) d\sigma$$

and hence (19)-(20) gives $w(t)$ defined in (18).

B. Impulse Responses of Several Finite Dimensional Systems Restricted to Sub-Intervals of $[0\ ,\ h]$

The above discussion can be generalized to the case where $B(\theta)$ is in the form (15) on several sub-intervals of $[0\ ,\ h]$. More precisely,

$$B(\theta) = B_k e^{A_k \theta} C_k \quad , \quad \text{for} \quad \theta \in [h_k\ ,\ h_{k+1}) \qquad (21)$$

for $k = 1, \ldots, n$, where $h_1 = 0 < h_2 < \cdots < h_{n+1} = h$. As before, we assume that (A_k, B_k) is controllable and (C_k, A_k) is observable. Let us now define

$$w_k(t) = \int_{h_k}^{h_{k+1}} B_k e^{A_k \theta} C_k x(t-\theta) d\theta$$

then $\dot{x}(t) = Ax(t) + \sum_{k=1}^n w_k(t)$, and each w_k is the output of the following system with lumped delays

$$\begin{aligned} \dot{x}_{dk}(t) &= A_k x_{dk}(t) + B_k x(t-h_k)\ , \quad x_{dk}(0) = 0 \\ w_k(t) &= C_k x_{dk}(t) - C_k e^{A_k \tau_k} x_{dk}(t-\tau_k). \end{aligned}$$

where $\tau_k = (h_{k+1} - h_k)$, $k = 1, \ldots, n$.

Defining $z(t) = [x(t), x_{d1}(t), \ldots, x_{dn}(t)]^{\mathrm{T}}$, we get a new system equation of the form

$$\dot{z}(t) = \widehat{A}_1 z(t) + \sum_{k=2}^n \widehat{A}_k z(t-h_k) + \sum_{k=1}^n \widehat{B}_k z(t-\tau_k)$$

for some fixed matrices $\widehat{A}_k$ and $\widehat{B}_k$, for $k = 1, \ldots, n$, computed from the original problem data.

In the above discussion it is possible to include additional Dirac delta terms in $B(\theta)$. For example if

$$B(\theta) = B_k e^{A_k \theta} C_k + D_k \delta(\theta - h_k^d)$$

for $\theta \in [h_k\ ,\ h_{k+1})$, and $h_k \le h_k^d \le h_{k+1}$, then $w_k(t)$ contains an additional term $D_k x(t-h_k^d)$, which is a lumped delay term. Thus, any Dirac delta term in the distributed delay kernel give rise to a lumped delay term.

In conclusion, if the delay kernel consists of impulse responses of finite dimensional systems, restricted to finite intervals, then stability analysis can be done using a linear system with lumped delays only, that is obtained from the above transformation technique.

IV. Application to Hematopoiesis

There have been a number of studies where mathematical models for the process of formation and development of blood cells (hematopoiesis) are proposed and studied. See for example the works [1]–[7], [18], [23], where non-linear discrete or distributed delay models appear. Most recently, in [3] a system of N differential equations with distributed delays is introduced to model cell differentiation and to study acute myelogenous leukemia. The linearization of the model in [3], around the equilibrium point of interest, leads to a linear system whose characteristic equation is in the form

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

where

$$F_k(s) = \int_0^{h_k} b_k e^{-\gamma_k \theta} f_k(\theta) e^{-s\theta} d\theta$$

h_k, γ_k are positive constants, a_k and b_k are constants and f_k is a positive valued function such that

$$\int_0^{h_k} f_k(\theta) d\theta = 1.$$

In [3], the authors show numerically that a blockade of one of the biological processes described by the model, namely the differentiation rate from the k^{th} proliferating to the $(k+1)^{\text{th}}$ resting cell subpopulation, for one given maturation stage k, $0 \le k \le N$, yields in the model what is observed in the clinic of acute leukemias: overproduction in the bone marrow and release in the bloodstream of immature cells (myeloblasts).

In this model, a key function is the probability f_k for a cell in the proliferative k^{th} subpopulation to divide. In their numerical studies, Adimy et al. use the Dirac measure δ_{h_k} ($0 \le a < h_k$ for proliferating cells) for this probability, but a more general form for f_k in the model is

$$f_k(\theta) = g_k(\theta) e^{-\int_0^\theta g_k(u) du}, \text{ for } 0 \le \theta \le h_k, \text{ otherwise } 0,$$

where the division rate $g_k \ge 0$ must satisfy the condition

$$\int_0^{h_k} g_k(u) du = +\infty,$$

for f_k to be a probability density. Note here that from this condition one can deduce that, equivalently to the definition of f_k from the division rate g_k, one can write

$$g_k(\theta) = f_k(\theta) \left[\int_\theta^{h_k} f_k(u) du \right]^{-1}.$$

Unfortunately, we have no access to the actual division rate as a function of age in the proliferating cell subpopulations, be it for cancer or for normal cells, and we must content ourselves with speculations on the form of g_k, knowing that no cell divides at the beginning (in age) of the proliferative phase, and all cells will have divided after age h_k.

We propose to use more regular probability densities on $[0, h_k)$, such as

$$f_k(\theta) = \frac{m}{e^{m h_k} - 1} e^{m\theta}, \quad m \text{ integer } > \gamma_k, \qquad (22)$$

whence $g_k(\theta) = \dfrac{m}{e^{m(h_k-\theta)}-1}$ for the division rate, or also

$$f_k(\theta) = e^{\frac{h_k^{-m+1}}{m-1}} . \frac{e^{-\frac{(h_k-\theta)^{-m+1}}{m-1}}}{(h_k-\theta)^m},$$

coming from $g_k(\theta) = (h_k-\theta)^{-m}$, m integer > 1, or more generally from any g_k positive convex function on $[0\ ,\ h_k)$ with a sharp increase when θ approaches h_k, such that $\int_0^{h_k} g_k(u)du = +\infty$.

Following Adimy et al., we define:

- δ_k, death rate in the resting k^{th} subpopulation,
- $\mu_k = \dfrac{d}{dx}[x\beta_k(x)]\Big|_{x=x^*}$, where β_k is the reintroduction function from the resting k^{th} subpopulation into the proliferative k^{th} subpopulation and x^* is an equilibrium point,
- L_k $(0 \le L_k \le 1)$ is the rate of proliferating cells that divide without differentiation, i.e., that remain in the k^{th} compartment; setting L_k to 1 means blocking cell differentiation at stage k,
- F_k is the Laplace transform of the function $\theta \mapsto \begin{cases} b_k e^{-\gamma_k\theta} f_k(\theta) & \text{when} \quad 0 \le \theta \le h_k \quad \text{and} \\ 0 \quad \text{when} \quad \theta > h_k \end{cases}$
  where γ_k is the death rate in the proliferative k^{th} subpopulation, f_k is the mitosis (=cell division) probability density in this same subpopulation, an event that must occur before the age limit h_k for these cells, and $b_k = 2\mu_k L_k$,

which allows to write the characteristic equation for the linearized system, valid in the neighborhood of an equilibrium point, as:

$$s + \delta_k + \mu_k - F_k(s) = 0.$$

In the first, more analytically tractable, case mentioned above (note that μ_k, and hence also $\mu_k + \delta_k$ may be negative, so that absolute values matter), the sufficient stability condition (14) obtained at the end of Section II reads: all roots of $(s + \delta_k + \mu_k - F_k(s)) = 0$ are in $\mathbb{C}_-$ if

$$\frac{|\delta_k + \mu_k|}{2|\mu_k|L_k} > \frac{m}{(m-\gamma_k)} \quad \frac{e^{(m-\gamma_k)h_k}-1}{e^{mh_k}-1}.$$

In the case of a positive μ_k, we have the following necessary and sufficient condition of stability: all roots of $(s + \delta_k + \mu_k - F_k(s)) = 0$ are in $\mathbb{C}_-$ if and only if

$$\frac{\delta_k + \mu_k}{2\mu_k L_k} > \frac{m}{(m-\gamma_k)} \quad \frac{e^{(m-\gamma_k)h_k}-1}{e^{mh_k}-1}.$$

From a physiological point of view, in the case of a positive μ_k, the ratio $\dfrac{\delta_k + \mu_k}{2\mu_k L_k}$ may be interpreted as follows: if one assesses, in the system that has been linearized around a steady state, the balance between influx and efflux of cells in and out of the k^{th} non-proliferating compartment (x_k), then the linear stability condition involves only movements of cells at the k^{th} level, since the input from differentiated, lately divided, cells from the $(k-1)^{\text{th}}$ compartment, contributing to non-diagonal terms is not taken into account by analyzing the eigenvalues of the triangular jacobian matrix (whether or not linearization around a steady state is actually sufficient to completely investigate the stability of the initial nonlinear biological system is another problem, which we will not discuss here). Hence at the k^{th} differentiation compartment level, the cell efflux is measured by the quantities δ_k (death) and μ_k, whereas the influx is measured by the quantity $2L_k$. In this respect, the ratio $\dfrac{\delta_k + \mu_k}{\mu_k}$ is a measure of the excess efflux due to cell death (excess with respect to 1 for efflux due only to the reintroduction rate at steady state). The complete ratio $\dfrac{\delta_k + \mu_k}{2\mu_k L_k}$ may be seen as a balance term between efflux and influx: the ratio efflux/influx must be greater than a given quantity (on the right hand side of the inequation above) to ensure stability rather than explosion. Furthermore, this right hand side term, related to the choice of f_k in our example, is readily seen as a decreasing function of γ_k, the death term in the proliferative compartment, which means that increasing γ_k will naturally relax the constraint on the minimum allowable $\dfrac{\delta_k + \mu_k}{2\mu_k L_k}$ that ensures stability.

Of course, different choices of f_k lead to other stability conditions which can be computed using the technique of Section III.

Now, considering therapeutic objectives, note that it is already clear from the real part of the general characteristic equation,

$$\sigma + \delta_k + \mu_k \left\{ 1 - 2L_k \int_0^{h_k} e^{-(\gamma_k+\sigma)\theta} f_k(\theta)\cos(\omega\theta)d\theta \right\} = 0,$$

(where we used $s = \sigma + j\omega$) that increasing L_k, i.e. decreasing cell differentiation at stage k, will result in a destabilization of the linearized system around its steady state, a destabilization that can be made up for by e.g., increasing the death rates γ_k or δ_k. Naturally, this can also be seen even more neatly on the particular stability condition that we have derived in the case of our example (see above).

The effect of therapies in the case of AML may firstly be thought of in this theoretical context as being exerted on the death rates in the proliferative and resting compartments, increasing these death rates, γ_k or δ_k, respectively. Since agents used in the clinic of AML, such as classical Cytosine Arabinoside (Aracytin$^{\text{TM}}$), or more recent ones, coupled to monoclonal antibodies, such as Gemtuzumab-Ozogamicin (Mylotarg$^{\text{TM}}$), usually act by blocking DNA synthesis in the proliferating S-phase of the cell division cycle, γ_k is likely to be in this model the main or only theoretical target for these drugs. Secondly, other therapeutic molecules might also be used, exerting their effects by blocking reintroduction from rest to proliferation, i.e., by decreasing μ_k in this model. Such a function could be pharmacologically achieved by a mechanism totally independent of the previously described, cytotoxic, one, e.g., by growth factor receptor antagonizing molecules. Thirdly, in an even more distant future, one can think of acting by drugs not to kill diseased cells, but to redirect them in the physiological direction. That could be done by releasing differentiation, in this model by

decreasing L_k, by hoped-for redifferentiation therapies, that unfortunately are not, to our best knowledge, available so far in the clinic of AML. And finally, combining drugs acting on these different mechanisms in a synergistic way is also an option for the future, that could benefit from this sketched theoretical therapeutic framework.

The stability analysis that we performed in the frame of this hematopoiesis model [3] may thus provide therapeutists with theoretical conditions to combine different molecules, acting on different targets, in a coherent and optimized way.

V. Concluding Remarks

In this paper linear systems with distributed delays are studied. We have seen that when the delay kernel is finite sum of impulse responses of finite dimensional systems, restricted to finite time interval, it is possible to transform the distributed delay system to an equivalent system with lumped delays only. Some simple sufficient conditions for delay dependent stability are derived using the small gain theorem, these are in agreement of the earlier results of [29], [30]. For the scalar case we have shown that the sufficient condition of [29] is necessary as well.

This technique is applied to a mathematical model of cell differentiation taken from [3] where application to acute myelogenous leukemia (AML) is considered. We notice that in the simulation section of [3] the functions $f_k(\theta)$ are taken as Dirac delta, which directly give a lumped delay system (i.e., one can argue that in this case we do not have a distributed delay system). The possibility to use smoother functions for the f_k allowed us to perform a stability study in a slightly more general case.

We have proposed a stability analysis method from which one can infer stabilization principles for therapeutic control by drugs that are used or may be used in the future. More precisely, we have investigated possible theoretical targets in the model, and how they should be controlled, having in mind known or searched-for anti-cancer molecules, some of which are already in use in the clinic of AML.

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