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## ► To cite this version:

Irinel-Constantin Morarescu, Silviu-Iulian Niculescu. Some remarks on the stability of cell-to-cell spread models with distributed delays. 3rd IFAC Symposium on System Structure and Control, Oct 2007, Iguaçu, Brazil. <10.3182/20071017-3-BR-2923.00100>. <hal-02293051>

**HAL Id: hal-02293051**

**<https://hal.science/hal-02293051v1>**

Submitted on 20 Sep 2019

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# SOME REMARKS ON THE STABILITY OF CELL-TO-CELL SPREAD MODELS WITH DISTRIBUTED DELAYS

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Abstract: In this paper, we focus on the stability of some low-order distributed delay models describing cell-to-cell spread mechanisms in some well-mixed configuration. The stability analysis will be performed in the delay-parameter space defined by the mean delay and by the corresponding gap. We will explicitly compute the crossing frequency set, and the stability crossing curves by using a frequency-domain approach. An illustrative example encountered in HIV-1 infection will complete the presentation. Copyright © IFAC 2007

Keywords: distributed delay; biology; stability; crossing curves.

## 1. INTRODUCTION

Various biology model representations include a particular common element used to describe a reaction chain (distributed character, see, e.g.

In the sequel, we will focus on some particular class of dynamical models describing cell-to-cell spread mechanisms. Such systems are generally encountered in HIV-1 modeling as mentioned by

The remaining paper is organized as follows: the problem formulation and some comments on the system modeling can be found in Section 2. Section 3 includes the characterization of the stability regions in the delay-parameter set defined by the mean delay value and by the corresponding gap. An illustrative example corresponding to a HIV-1 model is presented in Section 4. Some concluding remarks end the paper. The notations are standard and explained when used for the first time.

## 2. PROBLEM FORMULATION, AND SYSTEM MODEL

In the sequel, we study a two-dimensional model of cell-to-cell spread mechanism, assuming that infection is spread directly from infected cells to healthy cells and neglecting the effects of free virus. The intracellular incubation period is given by a probability distribution and the model is given by two differential equations with distributed delay. More precisely, we consider the system

$$\begin{cases} \frac{dC}{dt} = r_C C(t) \left(1 - \frac{C(t) + I(t)}{C_m}\right) - k_I C(t) I(t), \\ \frac{dI}{dt} = k'_I \int_{-\infty}^t C(\theta) I(\theta) g(t - \theta) d\theta - d_I I(t), \end{cases} \quad (1)$$

where  $C$  ( $I$ ) represents the concentration of healthy (infected) cells,  $r_C$  is the reproductive rate of healthy cells,  $C_m$  is the effective carrying capacity of the system,  $k_I$  represents the infection of healthy cells by the infected cells in a *well-mixed* system,  $k'_I/k_I$  is

the fraction of cells surviving the incubation period,  $d_I$  is the death rate of infected cells,  $g$  is a probability distribution that defines the infectious process history. Explicitly, we assume that the cells which are productively infectious at time  $t$  were infected  $\theta$  time ago, where  $\theta$  is distributed according to the probability density  $g$ . Such a model is also encountered in the HIV-1 infection mechanisms as pointed out by

The initial conditions of the system (1) are defined as follows

$$C(t) = \phi(t) \geq 0, \quad I(t) = \psi(t) \geq 0, \quad t \in (-\infty, 0],$$

where  $\phi$  and  $\psi$  are continuous function on  $(-\infty, 0]$ .

The probability density  $g$  that appears in system (1) is often replaced by some Dirac densities  $g(\theta) = \delta(\theta)$ ,  $g(\theta) = \delta(\theta - \tau)$  where  $\tau$  is a constant or by a gamma distributed kernel

$$g(\theta) := \frac{\alpha^{n+1}\theta^n}{n!} e^{-\alpha\theta}$$

where  $\alpha > 0$  and  $n$  is a positive integer (see, for instance,

When  $g(\theta) = \delta(\theta)$  one obtains the following ordinary differential equations (ODE):

$$\begin{cases} \frac{dC}{dt} = r_C C(t) \left(1 - \frac{C(t) + I(t)}{C_m}\right) - k_I C(t) I(t), \\ \frac{dI}{dt} = k'_I C(t) I(t) - d_I I(t). \end{cases} \quad (2)$$

The initial conditions are

$$C(0) = C_0 \geq 0, \quad I(0) = I_0 \geq 0,$$

where  $C_0$  and  $I_0$  are constant.

When  $g(\theta) = \delta(\theta - \tau)$  where  $\tau$  is a constant, the system (1) becomes the following delay differential equations (DDE) with a discrete delay:

$$\begin{cases} \frac{dC}{dt} = r_C C(t) \left(1 - \frac{C(t) + I(t)}{C_m}\right) - k_I C(t) I(t), \\ \frac{dI}{dt} = k'_I C(t - \tau) I(t - \tau) - d_I I(t). \end{cases} \quad (3)$$

The initial conditions are

$$C(t) = \phi(t) \geq 0, \quad I(t) = \psi(t) \geq 0, \quad t \in [-\tau, 0],$$

where  $\phi$  and  $\psi$  are continuous function on  $[-\tau, 0]$ .

Finally, when

$$g(\theta) := \frac{\alpha^{n+1}\theta^n}{n!} e^{-\alpha\theta},$$

we get a DDE with distributed delay. According to

In general, there is a short intracellular "eclipse phase" (often referred as "latency", see also the infection with HIV-1). During this period the cell is infected but has not yet begun producing virus.

The system (1) has three equilibrium points: the trivial equilibrium  $(0, 0)$ , the healthy equilibrium  $(C_m, 0)$  and the infected equilibrium  $(\bar{C}, \bar{I})$ , where

$$\bar{C} = \frac{d_I}{k'_I}, \quad \bar{I} = \frac{r_C(k'_I C_m - d_I)}{k'_I(r_C + k_I C_m)}$$

if  $k'_I > d_I/C_m$ . Note that the equilibrium points of the model do not depend on the choice of the probability density  $g$ . The interesting problem concerns the stability of the infected equilibrium point  $(\bar{C}, \bar{I})$ . Setting  $C = \bar{C} + x$ ,  $I = \bar{I} + y$  where  $x$  and  $y$  are small, and linearizing, one obtains the characteristic equation:

$$\Delta(\lambda) = \lambda^2 + p\lambda + r + (s\lambda + q)G(\lambda), \quad (4)$$

where the coefficients above are given by:

$$p = \frac{d_I(k'_I C_m + r_C)}{k'_I C_m}, \quad q = \frac{r_C d_I(k'_I C_m - 2d_I)}{k'_I C_m},$$

$$r = \frac{r_C d_I^2}{k'_I C_m}, \quad s = -d_I,$$

and  $G(\lambda)$  is the Laplace transform of  $g(t)$ . Next, replacing  $g$  with the gamma distribution with a gap defined by (??) we get the following particular characteristic function:

$$\Delta(\lambda; T, \tau) := (\lambda^2 + p\lambda + r)(1 + \lambda T)^n + (s\lambda + q)e^{-\lambda\tau}. \quad (5)$$

### 3. STABILITY CHARACTERIZATION IN THE DELAY PARAMETER SET

In the sequel, we derive the stability regions of (5) in the delay parameter space  $(T, \tau)$ . In this sense, we will start by discussing a more general parameter-dependent characteristic equation described by the following quasipolynomial:

$$\Delta(\lambda; T, \tau) = P(\lambda)(1 + \lambda T)^n + Q(\lambda)e^{-\lambda\tau} = 0. \quad (6)$$

where  $P$  and  $Q$  are polynomials with real coefficients such that  $\deg(Q) < \deg(P)$  (see, e.g.

*Assumption I.*  $P(0) + Q(0) \neq 0$ ;

*Assumption II.*  $P(\lambda)$  and  $Q(\lambda)$  do not have common zeros;

*Assumption III.* If  $P(\lambda) = \alpha$ ,  $Q(\lambda) = \beta$ , where  $\alpha, \beta$  are real constants, then  $|\alpha| \neq |\beta|$ ;

*Assumption IV.*  $P(0) \neq 0$ ,  $|P(0)| \neq |Q(0)|$ ;

*Assumption V.*  $P'(j\omega) \neq 0$  whenever  $P(j\omega) = 0$ .

It is easy to see that in our case study, i.e. characteristic function  $\Delta(\lambda; T, \tau)$  given by (5), the Assumptions I and V are automatically satisfied, and the other reduces to some simple comparison of  $P(0) = p$  with  $Q(0) = q$ . Indeed, Assumption I is equivalent to  $k'_I C_m \neq d_I$  which is automatically satisfied since, by hypothesis, we focus on the stability around a particular equilibrium, for which  $k'_I > d_I/C_m$ .

Using the methodology proposed by

#### 3.1 Frequency crossing set computation

Another useful concept is the *frequency crossing set*  $\Omega$ , which is defined as the collection of all  $\omega > 0$

such that there exists a delay-parameter pair  $(T, \tau)$  such that  $\Delta(j\omega; T, \tau) = 0$ . In other words, as the parameters  $T$  and  $\tau$  vary, the characteristic roots may cross the imaginary axis at  $j\omega$  if and only if  $\omega \in \Omega$ . Without any loss of generality, we can consider that  $\Omega \subset \mathbb{R}_+$ .

In the context of equation (6), the characterization of the frequency crossing set is given by the following:

**Proposition 1.** Given any  $\omega > 0$ ,  $\omega \in \Omega$  if and only if it satisfies

$$0 < |P(j\omega)| \leq |Q(j\omega)|. \quad (7)$$

Consider now in more detail the inequality (7). First at all, it is easy to see that  $\Omega$  is *bounded*, that is there exists a real positive number  $M > 0$ , such that for all  $\omega \in \Omega$ ,  $\omega < M$ . Indeed, since  $\deg(P) > \deg(Q)$ , then  $\lim_{\omega \rightarrow \infty} |Q(j\omega)| / |P(j\omega)| = 0$ , and thus there exists some high-frequency  $\omega_h > 0$  such that  $|P(j\omega)| > |Q(j\omega)|$ , for all  $\omega \geq \omega_h$ , and thus for all  $\omega > \omega_h$ , (7) cannot be satisfied.

Next,  $\Omega$  consists of a *finite set of intervals of finite length*. Indeed, it is easy to see that there are only a finite number of solutions of each of the following two equations

$$P(j\omega) = 0, \quad (8)$$

and

$$|P(j\omega)| = |Q(j\omega)|, \quad (9)$$

because  $P$  and  $Q$  are both co-prime polynomials with  $P(0) + Q(0) \neq 0$ . Therefore,  $\Omega$ , which is the collection of  $\omega$  satisfying (7), consists of a finite number of intervals. Denote these intervals as  $\Omega_1, \Omega_2, \dots, \Omega_N$ . Then  $\Omega = \bigcup_{k=1}^N \Omega_k$ .

Without any loss of generality, we may order these intervals from left to right, i.e., for any  $\omega_1 \in \Omega_{k_1}$ ,  $\omega_2 \in \Omega_{k_2}$ ,  $k_1 < k_2$ , we have  $\omega_1 < \omega_2$ .

### 3.2 Stability crossing curves characterization

Using the results and the notations above, we arrive to the following characterization of the stability crossing curves:

**Proposition 2.** The set  $\mathcal{T}$  consists of all the pairs  $(T, \tau)$  given by

$$T = \frac{1}{\omega} \left( \left| \frac{Q(j\omega)}{P(j\omega)} \right|^{2/n} - 1 \right)^{1/2}, \quad (10)$$

$$\begin{aligned} \tau = \tau_m = \frac{1}{\omega} (\angle Q(j\omega) - \angle P(j\omega) - n \arctan(\omega T) \\ + \pi + 2m\pi), \end{aligned} \quad (11)$$

$m = 0, \pm 1, \pm 2, \dots,$

where  $\omega \in \Omega$  represents a crossing frequency.

We will not restrict  $\angle Q(j\omega)$  and  $\angle P(j\omega)$  to a  $2\pi$  range. Rather, we allow them to vary continuously within each interval  $\Omega_k$ . Thus, for each fixed  $m$ , (10) and (11) represent a continuous curve. We denote such a curve as  $\mathcal{T}_m^k$ . Therefore, corresponding to a given interval  $\Omega_k$ , we have an infinite number of continuous stability crossing curves  $\mathcal{T}_m^k$ ,  $m = 0, \pm 1, \pm 2, \dots$ . It should be noted that, for some  $m$ , part or the entire curve may be outside of the range  $\mathbb{R}_+^2$ , and therefore, may not be physically meaningful. The collection of all the points in  $\mathcal{T}$  corresponding to  $\Omega_k$  may be expressed as

$$\mathcal{T}^k = \bigcup_{m=-\infty}^{+\infty} (\mathcal{T}_m^k \cap \mathbb{R}_+^2).$$

Obviously,  $\mathcal{T} = \bigcup_{k=1}^N \mathcal{T}^k$ .

### 3.3 Classification of stability crossing curves

Let the left and right end points of interval  $\Omega_k$  be denoted as  $\omega_k^\ell$  and  $\omega_k^r$ , respectively. Due to Assumptions IV and V, it is not difficult to see that each end point  $\omega_k^\ell$  or  $\omega_k^r$  must belong to one, and only one, of the following three types:

**Type 1.** It satisfies the equation (9).

**Type 2.** It satisfies the equation (8).

**Type 3.** It equals 0.

Denote an end point as  $\omega_0$ , which may be either a left end or a right end of an interval  $\Omega_k$ . Then the corresponding points in  $\mathcal{T}_m^k$  may be described as follows.

If  $\omega_0$  is of type 1, then  $T = 0$ . In other words,  $\mathcal{T}_m^k$  intersects the  $\tau$ -axis at  $\omega = \omega_0$ .

If  $\omega_0$  is of type 2, then as  $\omega \rightarrow \omega_0$ ,  $T \rightarrow \infty$  and  $\tau \rightarrow$

$$\frac{1}{\omega_0} \left( \angle Q(j\omega_0) - \lim_{\omega \rightarrow \omega_0} \angle P(j\omega) - \frac{n\pi}{2} + \pi + m2\pi \right). \quad (12)$$

Obviously,

$$\lim_{\omega \rightarrow \omega_0} \angle P(j\omega) = \angle \left[ \frac{d}{d\omega} P(j\omega) \right]_{\omega \rightarrow \omega_0} \quad (13)$$

if  $\omega_0$  is the left end point  $\omega_k^\ell$  of  $\Omega_k$ , and

$$\lim_{\omega \rightarrow \omega_0} \angle P(j\omega) = \angle \left[ \frac{d}{d\omega} P(j\omega) \right]_{\omega \rightarrow \omega_0} + \pi \quad (14)$$

if  $\omega_0$  is the right end point  $\omega_k^r$  of  $\Omega_k$ . In other words,  $\mathcal{T}_m^k$  approaches a horizontal line. Obviously, only  $\omega_1^\ell$  may be of type 3. Due to non-singularity assumption IV, if  $\omega_1^\ell = 0$ , we must have  $0 < |P(0)| < |Q(0)|$ . In this case, as  $\omega \rightarrow 0$ , both  $T$  and  $\tau$  approach  $\infty$ . In fact,  $(T, \tau)$  approaches a straight line with slope

$$\tau/T \rightarrow \frac{(\angle Q(0) - \angle P(0) - n \arctan \alpha + \pi + m2\pi)}{\alpha}, \quad (15)$$

where

$$\alpha = \left( \left| \frac{Q(0)}{P(0)} \right|^{2/n} - 1 \right)^{1/2}.$$

We say an interval  $\Omega_k$  is of type  $\ell r$  if its left end is of type  $\ell$  and its right end is of type  $r$ . We may accordingly divide these intervals into the following 6 types.

**Type 11.** In this case,  $\mathcal{T}_m^k$  starts at a point on the  $\tau$ -axis, and ends at another point on the  $\tau$ -axis.

**Type 12.** In this case,  $\mathcal{T}_m^k$  starts at a point on the  $\tau$ -axis, and the other end approaches  $\infty$  along a horizontal line.

**Type 21.** This is the reverse of type 12.  $\mathcal{T}_m^k$  starts at  $\infty$  along a horizontal line, and ends at the  $\tau$ -axis.

**Type 22.** In this case, both ends of  $\mathcal{T}_m^k$  approach horizontal lines.

**Type 31.** In this case,  $\mathcal{T}_m^k$  begins at  $\infty$  with an asymptote of slope expressed in (15). The other end is on the  $\tau$ -axis.

**Type 32.** In this case,  $\mathcal{T}_m^k$  again begins at  $\infty$  with an asymptote of slope expressed in (15). The other end approaches  $\infty$  along a horizontal line.

Several examples covering the cases mentioned above can be found in

### 3.4 Crossing direction characterization

Next, introduce the following notations:

$$\begin{aligned} R_0 &= Re \left( \frac{j}{\lambda} \frac{\partial \Delta(\lambda, T, \tau)}{\partial \lambda} \right)_{\lambda=j\omega}, \\ I_0 &= Im \left( \frac{j}{\lambda} \frac{\partial \Delta(\lambda, T, \tau)}{\partial \lambda} \right)_{\lambda=j\omega}, \\ R_1 &= Re \left( \frac{1}{\lambda} \frac{\partial \Delta(\lambda, T, \tau)}{\partial T} \right)_{\lambda=j\omega}, \\ I_1 &= Im \left( \frac{1}{\lambda} \frac{\partial \Delta(\lambda, T, \tau)}{\partial T} \right)_{\lambda=j\omega}, \\ R_2 &= Re \left( \frac{1}{\lambda} \frac{\partial \Delta(\lambda, T, \tau)}{\partial \tau} \right)_{\lambda=j\omega}, \\ I_2 &= Im \left( \frac{1}{\lambda} \frac{\partial \Delta(\lambda, T, \tau)}{\partial \tau} \right)_{\lambda=j\omega}, \end{aligned}$$

the crossing direction is given by the following:

**Proposition 3.** Let  $\omega \in \Omega$  and  $(T, \tau) \in \mathcal{T}$  such that  $j\omega$  is a simple solution of (6) and

$$\Delta(j\omega'; T, \tau) \neq 0, \forall \omega' > 0, \omega' \neq \omega$$

(i.e.  $(T, \tau)$  is not an intersection point of two curves or different sections of a single curve of  $\mathcal{T}$ ). Then a pair of solutions of (6) cross the imaginary axis to the right, through  $\lambda = \pm j\omega$  if

$$R_2 I_1 - R_1 I_2 > 0.$$

The crossing is to the left if the inequality is reversed.

## 4. ILLUSTRATIVE EXAMPLE

Consider now the case of a cell-to-cell spread model representing HIV infection mechanisms with  $C_m =$

$$2 \times 10^6/mL, k_I = 2 \times 10^{-6}/mL/day, k'_I = 1.5 \times 10^{-6}, d_I = 0.3/day, r_C = 0.68/day \text{ (see$$

## REFERENCES

- Baker, C.T.H., G.A. Bocharov and F.A. Rihan (1999). *A report on the use of delay differential equations in numerical modelling in the biosciences*. Numerical Analysis Report No. **343**, Manchester Centre for Computational Mathematics, Manchester.
- Culshaw, R.V., S. Ruan and G. Webb (2003). A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay. *J. Math. Biology*, vol. **46**, pp. 425–444.
- Cushing, J.M. (1981). Volterra integrodifferential equations in population dynamics. in *Mathematics of Biology* (M. IANNALLI, EDS. Ligouri Editore: Naples), 81–148.
- Gopalsamy, K. (1992). *Stability and oscillations in delay differential equations of population dynamics*, Kluwer Academic, Math. Its Appl., **74**.
- Gourley, S.A. and Y. Kuang (1994). A delay reaction-diffusion model of the spread of bacteriophage infection. *Internal Note Arizona State University*, 1994.
- Hoppensteadt, F.C. and C.S. Peskin (1992). *Mathematics in Medicine and Life Sciences*, Springer-Verlag: New York, TAM, **10**.
- Kuang, Y. (1993). *Delay differential equations with applications in population dynamics*, Academic Press: Boston.
- Leonard, R., Zagury, D., Desports, I., Bernard, J., Zagury, J.-F. and R.C. Gallo (1988). Cytopathic effect of human immunodeficiency virus in T4 cells is linked to the last stage of virus infection. *Proc. Natl. Acad. Sci. USA*, vol. **85**, pp. 3570–3574.
- MacDonald, N. (1989). *Biological delay systems: linear stability theory*. (Cambridge University Press, Cambridge).
- Mittler, J.E., B. Sulzer, A.U. Neumann and A.S. Perelson (1998). Influence of delayed viral production on viral dynamics in HIV-1 infected patients. *Math. Biosciences* vol. **152**, pp. 143–163.
- Morărescu, C.I. (2006). *Qualitative analysis of distributed delay systems: Methodology and algorithms*, Ph.D. thesis, University of Bucharest/Université de Technologie de Compiègne, September.
- Murray, J.D. (1993). *Mathematical Biology*, Springer: Berlin (2nd Edition), BioMath., **18**.
- Niculescu, S.-I., W. Michiels, I.C. Morărescu, and K. Gu (2007). Geometric ideas in the stability analysis of delay systems in biosciences. in *Biology and control theory: current challenges*, LNCIS, **357**, Springer-Verlag: Berlin, 217–259.
- Spouge, J.L., R.I. Shrager, and D.S. Dimitrov (1996). HIV-1 infection kinetics in tissue cultures, *Math. Biosciences*, vol. **138**, pp. 1–22.
- Vielle, B. and G. Chauvet. (1998). Delay equation analysis of human respiratory stability, *Math. Biosciences*, vol. **152**, pp. 105–122.