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On stability analysis of genetic regulatory networks represented by delay-differential equations

Laurie Haustenne * **Georges Bastin** ** **Jean-Michel Coron** ***
Laetitia Fontaine * **Pascal Hols** *

* *Biochimie et Génétique Moléculaire Bactérienne, Institut des Sciences de la Vie, Université catholique de Louvain, 1348 Louvain-la-Neuve, Belgium.*

** *Department of Mathematical Engineering, ICTEAM, Université catholique de Louvain, 4, Avenue G. Lemaitre, 1348 Louvain-La-Neuve, Belgium.*

*** *Laboratoire Jacques-Louis Lions, Université Pierre et Marie Curie, Institut Universitaire de France, 4, Place Jussieu, 75252 Paris Cedex, France.*

Abstract: The purpose of this note is to give a short presentation of a general method for the stability analysis of the steady-states of genetic regulatory networks represented by delay-differential equations. Two complementary ways are investigated: a frequency domain approach which applies to linearized models and gives necessary and sufficient conditions for the local steady-state stability, a Lyapunov approach derived from the viewpoint of hyperbolic PDE systems which gives sufficient conditions for global stability. These methods are illustrated with the example of the "toggle switch".

Keywords: Genetic regulatory network, Hyperbolic system, Lyapunov function, Stability.

1. INTRODUCTION

We are concerned with continuous time models of genetic networks when "time delays are included to allow for the time required for transcription, translation, and transport" (Smolen et al. [2000]). The network dynamics are therefore represented by delay-differential equations whose solutions evolve in the positive orthant. It is well known that these systems may have multiple steady-states or equilibria. A critical issue is to determine the stability of these equilibria. The purpose of this paper is to give a concise, but instrumental, presentation of a general method which can be used for the stability analysis of the steady-states of genetic regulatory networks represented by delay-differential equations. Two complementary ways are investigated: a frequency domain approach which applies to linearized models and gives necessary and sufficient conditions for the local steady-state stability, a Lyapunov approach derived from the viewpoint of hyperbolic PDE systems which gives sufficient conditions for global stability. These methods are illustrated with the example of the "toggle switch".

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2. MATHEMATICAL MODEL

We consider a genetic regulatory network which involves n genes interconnected through activator or repressor proteins. As illustrated in Fig.1, the expression of the i-th gene in the network ($i = 1, \ldots, n$) is represented by the following standard delay-differential system (see e.g. Bernot et al. [2013]):

$$\begin{aligned} \frac{dM_i(t)}{dt} &= b_i + h_i(P_k(t-\tau_k)) - \delta_i M_i(t), \\ \frac{dP_i(t)}{dt} &= \alpha_i M_i(t-\tau_{n+i}) - \beta_i P_i(t), \end{aligned} \tag{1}$$

where, at time t, $M_i(t)$ is the density of mRNA molecules and P_i the density of proteins expressed by the i-th gene. The constants b_i and α_i denote respectively the basal transcription rate and the specific translation rate. The constants β_i and δ_i are the natural degradation rate coefficients. The constant delays τ_i and τ_{n+i} are the times needed for transcription and translation respectively. The function h_i describes the feedback control of the expression of the i-th gene by a protein which is produced by another or the same gene in the network. More precisely, the function $h_i(P_k)$ means that the transcription of the i-th gene may be activated or repressed by the density P_k of the protein expressed by the k-th gene of the network (with the possibility that $k \neq i$ or $k = i$). It may therefore be

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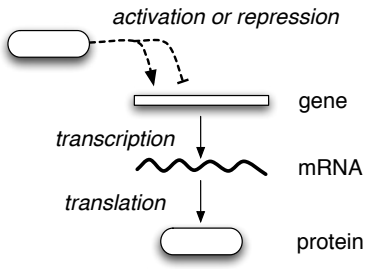

Fig. 1. Scheme of genetic transcription and translation with activation or repression.

either an activation Hill function of the form

$$h_i(P_k) = \frac{\upsilon_i P_k^{m_i}}{k_i^{m_i} + P_k^{m_i}}, \tag{2}$$

or an inhibition Hill function of the form

$$h_i(P_k) = \frac{\upsilon_i k_i^{m_i}}{k_i^{m_i} + P_k^{m_i}}, \tag{3}$$

where υ_i, k_i and m_i are constant parameters with υ_i the maximal transcription rate, k_i the half-saturation coefficient and m_i the so-called Hill coefficient.

A steady-state of the system is a constant solution M_i^*, P_i^*, $i = 1, \ldots, n$, of the dynamical system (1) i.e. a solution of the algebraic system

$$\begin{aligned} b_i + h_i(P_k^*) - \delta_i M_i^* &= 0, \\ \alpha_i M_i^* - \beta_i P_i^* &= 0. \end{aligned} \tag{4}$$

Let us define the deviations of P_i and M_i with respect to a steady-state M_i^*, P_i^*:

$$m_i(t) = M_i(t) - M_i^*, \qquad p_i(t) = P_i(t) - P_i^*. \tag{5}$$

With these coordinates, the model (1) is alternatively written under the form

$$\begin{aligned} \frac{dm_i(t)}{dt} &= g_i(p_k(t-\tau_k))p_k(t-\tau_k) - \delta_i m_i(t), \\ \frac{dp_i(t)}{dt} &= \alpha_i m_i(t-\tau_{n+i}) - \beta_i p_i(t), \end{aligned} \tag{6}$$

where the function g_i is defined such that

$$g_i(p)p = h_i(P^* + p) - h_i(P^*). \tag{7}$$

The linearization, around zero, of the system (6) is then given by

$$\begin{aligned} \frac{dm_i(t)}{dt} &= g_i(0)p_k(t-\tau_k) - \delta_i m_i(t), \\ \frac{dp_i(t)}{dt} &= \alpha_i m_i(t-\tau_{n+i}) - \beta_i p_i(t). \end{aligned} \tag{8}$$

In the next section we study the stability of the linear system (8) in the frequency domain.

3. FREQUENCY DOMAIN STABILITY

We introduce the following vector notations:

$$\mathbf{m} = \begin{pmatrix} m_1 \\ \vdots \\ m_n \end{pmatrix}, \qquad \mathbf{p} = \begin{pmatrix} p_1 \\ \vdots \\ p_n \end{pmatrix}, \tag{9}$$

Using the Laplace transform, the linear system (8) is written in the frequency domain as

$$\begin{aligned} \mathbf{m} &= (sI_n + D)^{-1} F(s)\mathbf{p}, \\ \mathbf{p} &= (sI_n + B)^{-1} AE(s)\mathbf{m}, \end{aligned} \tag{10}$$

with the following matrix definitions:

$$\begin{aligned} A &= \mathrm{diag}\{\alpha_1, \ldots, \alpha_n\}, \\ B &= \mathrm{diag}\{\beta_1, \ldots, \beta_n\}, \\ D &= \mathrm{diag}\{\delta_1, \ldots, \delta_n\}, \\ E(s) &= \mathrm{diag}\{e^{-s\tau_{n+1}}, \ldots, e^{-s\tau_{2n}}\}, \\ F(s) &= \text{matrix with entry } [F(s)]_{ik} = g_i(0)e^{-s\tau_k} \text{ if } k \sim i \\ &\quad \text{and 0 otherwise.} \end{aligned}$$

The notation "diag" means that the matrix is diagonal. The notation $k \sim i$ means that the protein expressed by the k-th gene is an activator or a repressor of the i-th gene transcription.

The system (10) is a feedback system as shown in Fig.2. The poles of the system are the roots of the characteristic

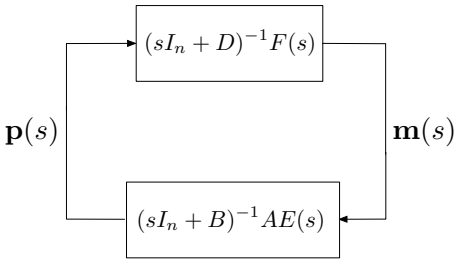

Fig. 2. The linearized model of a genetic network viewed as a feedback system.

equation

$$\det\left[I - (sI_n + B)^{-1}AE(s)(sI_n + D)^{-1}F(s)\right] = 0. \tag{11}$$

The following theorem gives the condition for the system stability.

Theorem 1. *The linear system* (8) *is exponentially stable if and only if the poles of the system have strictly negative real parts and are bounded away from zero.*

This theorem directly follows, as a special case, from [Hale and Verduyn-Lunel, 2002, Section 3] and [Michiels and Niculescu, 2007, Section 1.2]).

In the next section, as an example of how this theorem can be used, we consider the model of a "toggle switch".

4. EXAMPLE: THE TOGGLE SWITCH

A toggle switch (Fig. 3) is a system of two genes that repress each other (see e.g. Smits et al. [2008], Veening et al. [2008] and the references therein). In the case of the toggle switch, the general model (1) is specialized as follows:

$$\begin{aligned} \frac{dM_1(t)}{dt} &= b_1 + h_1(P_2(t-\tau_2)) - \delta_1 M_1(t), \\ \frac{dP_1(t)}{dt} &= \alpha_1 M_1(t-\tau_3) - \beta_1 P_1(t), \end{aligned} \tag{12}$$

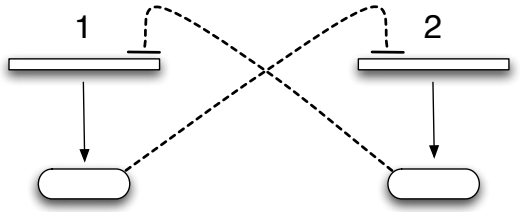

Fig. 3. Toggle switch.

$$\begin{aligned}\frac{dM_2(t)}{dt} &= b_2 + h_2(P_1(t-\tau_1)) - \delta_2 M_2(t),\\ \frac{dP_2(t)}{dt} &= \alpha_2 M_2(t-\tau_4) - \beta_2 P_2(t),\end{aligned} \tag{13}$$

with

$$\begin{aligned}h_1(P_2) &= \frac{\upsilon_1 k_1^{m_1}}{k_1^{m_1} + P_2^{m_1}},\\ h_2(P_1) &= \frac{\upsilon_2 k_2^{m_2}}{k_2^{m_2} + P_1^{m_2}}.\end{aligned} \tag{14}$$

Depending on the numerical values of the constant coefficients and parameters, the system may have 1, 2 or 3 steady-states. The linearization around any of these steady-states is written

$$\begin{aligned}\frac{dm_1(t)}{dt} &= g_1(0)p_2(t-\tau_2) - \delta_1 m_1(t),\\ \frac{dp_1(t)}{dt} &= \alpha_1 m_1(t-\tau_3) - \beta_1 p_1(t),\\ \frac{dm_2(t)}{dt} &= g_2(0)p_1(t-\tau_1) - \delta_2 m_2(t),\\ \frac{dp_2(t)}{dt} &= \alpha_2 m_2(t-\tau_4) - \beta_2 p_2(t).\end{aligned} \tag{15}$$

Then, using formula (11), it is a matter of a few computations to show that the characteristic equation is

$$\underbrace{s^4 + a_3 s^3 + a_2 s^2 + a_1 s^1 + a_0}_{\psi(s)} - \underbrace{\alpha_1\alpha_2 g_1(0) g_2(0)}_{\chi} e^{-s\tau} = 0$$

with

$$\begin{aligned}\tau &= \tau_1 + \tau_2 + \tau_3 + \tau_4,\\ a_0 &= \beta_1\beta_2\delta_1\delta_2,\\ a_1 &= (\beta_1+\beta_2)\delta_1\delta_2 + \beta_1\beta_2(\delta_1+\delta_2),\\ a_2 &= \beta_1\beta_2 + \delta_1\delta_2 + (\beta_1+\beta_2)(\delta_1+\delta_2),\\ a_3 &= \beta_1 + \beta_2 + \delta_1 + \delta_2.\end{aligned}$$

In order to analyze the stability of the poles in function of the time-delay τ, we follow the procedure of Walton and Marshall [1987].

The first step is to examine the stability when $\tau = 0$. In that case, it follows from a straightforward application of the Routh-Hurwitz criterion that the poles are stable if and only if

$$a_0 - \alpha_1\alpha_2 g_1(0) g_2(0) > 0, \tag{16}$$

$$a_1 a_2 a_3 > a_1^2 + a_3^2(a_0 - \alpha_1\alpha_2 g_1(0) g_2(0)). \tag{17}$$

In the second step, we compute the following polynomial in ω^2:

$$\begin{aligned}W(\omega^2) &= \psi(j\omega)\psi(-j\omega) - \chi^2\\ &= \omega^8 + b_3\omega^6 + b_2\omega^4 + b_1\omega^2 + b_0\end{aligned}$$

with

$$\begin{aligned}b_0 &= a_0^2 - \chi^2,\\ b_1 &= a_1^2 - 2a_0a_2,\\ b_2 &= a_2^2 - 2(a_0 + a_1a_3),\\ b_3 &= 2a_2 + a_3.\end{aligned}$$

Then, if conditions (16) and (17) are satisfied and if $W(\omega^2)$ has no positive real roots, the system (15) is stable for all $\tau \geqslant 0$. In contrast, if $W(\omega^2)$ has positive real roots, there is a maximum value of τ beyond which the system becomes unstable.

5. LYAPUNOV STABILITY

Since a genetic regulatory network is inherently a nonlinear system having, possibly, multiple steady-states, the frequency domain approach, based on linearization, has a fundamental limitation: it gives conditions that ensure only the *local* stability of the steady-states. By this, it is meant that if the initial conditions are slightly perturbed, then the system returns to the equilibrium. In order to determine larger domains of convergence (and even to guarantee *global* stability in the case where the genetic network has a single steady-state), it is more appropriate (and less easy !) to use the Lyapunov approach. For this purpose, we introduce the auxiliary independent variable $z \in [0,1]$, and we consider that the protein and mRNA densities $p_i = P_i - P_i^*$ and $m_i = M_i - M_i^*$ now depend on the two variables t and z and satisfy the partial differential equations

$$\begin{aligned}\partial_t p_i(t,z) + \frac{1}{\tau_i}\partial_z p_i(t,z) &= 0,\\ \partial_t m_i(t,z) + \frac{1}{\tau_{n+i}}\partial_z m_i(t,z) &= 0,\end{aligned} \tag{18}$$

under the boundary conditions

$$\begin{aligned}\frac{dm_i(t,0)}{dt} &= g_i(p_k(t,1))p_k(t,1) - \delta_i m_i(t,0),\\ \frac{dp_i(t,0)}{dt} &= \alpha_i m_i(t,1) - \beta_i p_i(t,0),\end{aligned} \tag{19}$$

The model (18)-(19) is identical to the delay-differential model (6) which has been used above since the transport equations (18) are, by definition, equivalent to

$$p_i(t,1) = p_i(t-\tau_i, 0), \quad m_i(t,1) = m_i(t-\tau_{n+i}, 0). \tag{20}$$

We introduce the following candidate Lyapunov function

$$\begin{aligned}V = \int_0^1 \Bigg[&\sum_{i=1}^n q_i\tau_i p_i^2(t,z)e^{-\mu\tau_i z}\\ &+ \sum_{i=1}^n q_{n+i}\tau_{n+i} m_i^2(t,z)e^{-\mu\tau_{n+i}z}\Bigg] dz\\ &+ \frac{1}{2}\sum_{i=1}^n w_i p_i^2(t,0) + \frac{1}{2}\sum_{i=1}^n w_{n+i} m_i^2(t,0),\end{aligned} \tag{21}$$

with positive parameters μ, q_i, q_{n+i}, w_i, w_{n+i} to be determined. With matrix notations, this function is rewritten

$$V = \int_0^1 \big[\mathbf{p}^T(t,z)Q_1T_1E_1(\mu,z)\mathbf{p}(t,z) + \mathbf{m}^T(t,z)Q_2T_2E_2(\mu,z)\mathbf{m}(t,z)\big]dz + \frac{1}{2}\big[\mathbf{p}^T(t,0)W_1\mathbf{p}(t,0) + \mathbf{m}^T(t,0)W_2\mathbf{m}(t,0)\big], \quad (22)$$

with

$$\begin{aligned} Q_1 &= \mathrm{diag}\{q_i,\, i=1,\dots,n\}, \\ Q_2 &= \mathrm{diag}\{q_{n+i},\, i=1,\dots,n\}, \\ T_1 &= \mathrm{diag}\{\tau_i,\, i=1,\dots,n\}, \\ T_2 &= \mathrm{diag}\{\tau_{n+i},\, i=1,\dots,n\}, \\ E_1(\mu,z) &= \mathrm{diag}\{e^{-\mu\tau_i z},\, i=1,\dots,n\}, \\ E_2(\mu,z) &= \mathrm{diag}\{e^{-\mu\tau_{n+i} z},\, i=1,\dots,n\}, \\ W_1 &= \mathrm{diag}\{w_i,\, i=1,\dots,n\}, \\ W_2 &= \mathrm{diag}\{w_{n+i},\, i=1,\dots,n\}. \end{aligned}$$

Using integration by parts, it can be shown that the time derivative of V, along the system solutions, is

$$\frac{dV}{dt} = -\mu V - \mathbf{X}^T\mathcal{M}(\mu,\mathbf{p}(t,1))\mathbf{X}, \quad (23)$$

with the vector $\mathbf{X}$ and the matrix $\mathcal{M}(\mu,\mathbf{p})$ defined as

$$\mathbf{X}^T = \begin{pmatrix}\mathbf{p}^T(t,0) & \mathbf{m}^T(t,0) & \mathbf{p}^T(t,1) & \mathbf{m}^T(t,1)\end{pmatrix}^T \quad (24)$$

$$\mathcal{M}(\mu,\mathbf{p}) = \begin{pmatrix} W_1B - Q_1 & 0 & 0 & -W_1A \\ 0 & W_2D - Q_2 & -W_2G(\mathbf{p}) & 0 \\ 0 & 0 & Q_1E_1(\mu,1) & 0 \\ 0 & 0 & 0 & Q_2E_2(\mu,1) \end{pmatrix} \quad (25)$$

We have the following theorem.

Theorem 2. *There exists $\mu > 0$ sufficiently small such that V is a strict exponentially decreasing Lyapunov function along the solutions the system (18)-(19) with $\mathbf{p} \in \mathbb{R}_+^n$ if there exist $q_i > 0$, $q_{n+i} > 0$, $w_i > 0$, $w_{n+i} > 0$ such that the matrix $\mathcal{M}(0,\mathbf{p})$ is positive definite for all $\mathbf{p} \in \mathbb{R}_+^n$.*

In the next section, we use again the toggle switch as an example of how this theorem can be used.

6. EXAMPLE: THE TOGGLE SWITCH

For the toggle switch example, the general model (18)-(19) is specialized as follows:

$$\begin{aligned} &\partial_t p_1(t,z) + \frac{1}{\tau_1}\partial_z p_1(t,z) = 0, \\ &\partial_t p_2(t,z) + \frac{1}{\tau_2}\partial_z p_2(t,z) = 0, \\ &\partial_t m_1(t,z) + \frac{1}{\tau_3}\partial_z m_1(t,z) = 0 \\ &\partial_t m_2(t,z) + \frac{1}{\tau_4}\partial_z m_2(t,z) = 0, \end{aligned}$$

$$\begin{aligned} &\frac{dm_1(t,0)}{dt} = g_1(p_2(t,1))p_2(t,1) - \delta_1 m_1(t,0), \\ &\frac{dp_1(t,0)}{dt} = \alpha_1 m_1(t,1) - \beta_1 p_1(t,0), \\ &\frac{dm_2(t,0)}{dt} = g_2(p_1(t,1))p_1(t,1) - \delta_2 m_2(t,0), \\ &\frac{dp_2(t,0)}{dt} = \alpha_2 m_2(t,1) - \beta_2 p_2(t,0). \end{aligned}$$

For this system, the matrix $\mathcal{M}(0,\mathbf{p})$ is

$$\mathcal{M}(0,\mathbf{p}) = \begin{pmatrix} \mathcal{M}_{11} & \mathcal{M}_{12} \\ 0 & \mathcal{M}_{22} \end{pmatrix}, \quad (26)$$

with

$$\mathcal{M}_{11} = \begin{pmatrix} w_3\beta_1 - q_1 & 0 & 0 & 0 \\ 0 & w_4\beta_2 - q_2 & 0 & 0 \\ 0 & 0 & w_1\delta_1 - q_3 & 0 \\ 0 & 0 & 0 & w_2\delta_2 - q_4 \end{pmatrix},$$

$$\mathcal{M}_{12} = \begin{pmatrix} 0 & 0 & -w_3\alpha_1 & 0 \\ 0 & 0 & 0 & -w_4\alpha_2 \\ 0 & -w_1g_1(p_2) & 0 & 0 \\ -w_2g_2(p_1) & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{M}_{22} = \begin{pmatrix} q_1 & 0 & 0 & 0 \\ 0 & q_2 & 0 & 0 \\ 0 & 0 & q_3 & 0 \\ 0 & 0 & 0 & q_4 \end{pmatrix}.$$

This matrix is positive definite if and only if the leading principal minors of the symmetric matrix $\mathcal{M}(0,\mathbf{p}) + \mathcal{M}^T(0,\mathbf{p})$ are all positive. This leads to the following inequalities:

$$\begin{aligned} &0 < w_3\beta_1 - q_1 \\ &0 < w_4\beta_2 - q_2 \\ &0 < w_1\delta_1 - q_3 \\ &0 < w_2\delta_2 - q_4 \\ &0 < (w_1\delta_1 - q_3)q_2 - (1/4)w_1^2g_1^2(p_2) \\ &0 < (w_2\delta_2 - q_4)q_1 - (1/4)w_2^2g_2^2(p_1) \\ &0 < (w_3\beta_1 - q_1)q_3 - (1/4)w_3^2\alpha_1^2 \\ &0 < (w_4\beta_2 - q_2)q_4 - (1/4)w_4^2\alpha_1^2. \end{aligned}$$

Hence, the system is stable for any τ_i if there exist positive values of q_i and w_i such that these inequalities are satisfied.

7. FINAL REMARKS

In this paper, we have presented two ways for analyzing the stability of steady-states in genetic regulatory networks represented by delay-differential equations: a frequency domain approach and a Lyapunov approach. The two methods are complementary. The advantage of the frequency domain method is to give necessary and sufficient conditions but the stability is local. In contrast, the Lyapunov method may give global stability results but the stability conditions are only sufficient and can be conservative in some instances.

In this paper, for simplicity, we have restricted the presentation to networks where each gene can be controlled by

one protein at most. The analysis can easily be extended to situations where a gene can be controlled by several proteins simultaneously. In fact, both Theorems 1 and 2 hold exactly as they are, provided the definitions of the matrices $F(s)$ and $G(\mathbf{p})$ are adequately extended.

The Lyapunov method of this paper is derived from the viewpoint of hyperbolic systems and easy to implement (see Bastin and Coron [2014] for more details). An alternative approach, based on Lyapunov-Krasovskii functionnals, has been used in other papers with a special emphasis on the robustness issue, see e.g. Wang et al. [2008], Ren and Cao [2008].

An application to the genetic network of the basic mechanism for the competence development in *Streptococcus thermophilus* (see Haustenne et al. [2015] and Fontaine et al. [2013]) is in progress.

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