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

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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”.

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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”.

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]):

\[
\frac{dM_i(t)}{dt} = b_i + h_i(P_k(t - \tau_k)) - \delta_i M_i(t),
\]

\[
\frac{dP_i(t)}{dt} = \alpha_i M_i(t - \tau_{n+i}) - \beta_i P_i(t),
\]

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 \( \alpha_i \) denote respectively the basal transcription rate and the specific translation rate. The constants \( \beta_i \) and \( \delta_i \) are the natural degradation rate coefficients. The constant delays \( \tau_i \) and \( \tau_{n+i} \) 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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given by

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

where

with activation or repression.

We introduce the following vector notations:

3. FREQUENCY DOMAIN STABILITY

We introduce the following vector notations:

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

\[ \mathbf{m} = (sI_n + D)^{-1}F(s)\mathbf{p}, \]

\[ \mathbf{p} = (sI_n + B)^{-1}AE(s)\mathbf{m}, \]

with the following matrix definitions:

\[ A = \operatorname{diag}\{\alpha_1, \ldots, \alpha_n\}, \]

\[ B = \operatorname{diag}\{\beta_1, \ldots, \beta_n\}, \]

\[ D = \operatorname{diag}\{\delta_1, \ldots, \delta_n\}, \]

\[ E(s) = \operatorname{diag}\{e^{-st_{n+1}}, \ldots, e^{-st_2}\}, \]

\[ F(s) = \text{matrix with entry } [F(s)]_{ik} = g_i(0)e^{-st_k} \text{ if } k \sim i \]

and 0 otherwise.

The notation “\( \operatorname{diag} \)” 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 equation

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

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:

\[ \frac{dM_1(t)}{dt} = b_1 + h_1(P_2(t - \tau_2)) - \delta_1M_1(t), \]

\[ \frac{dP_1(t)}{dt} = \alpha_1M_1(t - \tau_3) - \beta_1P_1(t), \]
The linearization, around zero, of the system (6) is then

\[ \frac{dM_2(t)}{dt} = b_2 + h_2(P_1(t - \tau_1)) - \delta_2 M_2(t), \]

\[ \frac{dP_2(t)}{dt} = \alpha_2 M_2(t - \tau_4) - \beta_2 P_2(t), \]

with

\[ h_1(P_2) = \frac{\nu_1 k_{m_1}}{k_{m_1} + P_2^{m_1}}, \]

\[ h_2(P_1) = \frac{\nu_2 k_{m_2}}{k_{m_2} + P_1^{m_2}}. \]

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

\[ \frac{dm_1(t)}{dt} = g_1(0)p_2(t - \tau_2) - \delta_1 m_1(t), \]

\[ \frac{dp_1(t)}{dt} = \alpha_1 m_1(t - \tau_3) - \beta_1 p_1(t), \]

\[ \frac{dm_2(t)}{dt} = g_2(0)p_1(t - \tau_1) - \delta_2 m_2(t), \]

\[ \frac{dp_2(t)}{dt} = \alpha_2 m_2(t - \tau_4) - \beta_2 p_2(t). \]

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

\[ s^4 + a_4 s^3 + a_3 s^2 + a_2 s + \alpha_0 = \omega^4 + \frac{1}{\tau} \delta_1 s^3 + \beta_1 s^2 + \beta_2 s + \alpha_0 \]

\[ \psi(s) \]

with

\[ \tau = \tau_1 + \tau_2 + \tau_3 + \tau_4, \]

\[ a_0 = \beta_1 \beta_2 \delta_1 \delta_2, \]

\[ a_1 = (\beta_1 + \beta_2) \delta_1 \delta_2 + \beta_1 \beta_2 (\delta_1 + \delta_2), \]

\[ a_2 = \beta_1 \beta_2 + \delta_1 \delta_2 + (\beta_1 + \beta_2) (\delta_1 + \delta_2), \]

\[ a_3 = \beta_1 + \beta_2 + \delta_1 + \delta_2. \]

In order to analyze the stability of the poles in function of the time-delay \( \tau \), 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

\[ a_0 - \alpha_1 \alpha_2 g_1(0) g_2(0) > 0, \]

\[ a_1 a_2 a_3 > a_1^2 + a_2^2 (a_0 - \alpha_1 \alpha_2 g_1(0) g_2(0)). \]

In the second step, we compute the following polynomial in \( \omega^2 \):

\[ W(\omega^2) = \psi(j\omega)\psi(-j\omega) - \chi^2 \]

\[ = \omega^8 + b_3 \omega^6 + b_2 \omega^4 + b_1 \omega^2 + b_0 \]

with

\[ b_0 = a_0^2 - \chi^2, \]

\[ b_1 = a_1^2 - 2a_0 a_2, \]

\[ b_2 = a_2^2 - 2(a_0 + a_1 a_3), \]

\[ b_3 = 2a_2 + a_3. \]

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 \( \tau \geq 0 \). In contrast, if \( W(\omega^2) \) has positive real roots, there is a maximum value of \( \tau \) beyond which the system becomes unstable.

5. LYAPUNOV STABILITY

Since a genetic regulatory network is inherently a non-linear 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 simple 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 \( p_i = P_i - P_i^0 \) and \( m_i = M_i - M_i^0 \) now depend on the two variables \( t \) and \( z \) and satisfy the partial differential equations

\[ \partial_t p_i(t, z) + \frac{1}{\tau_i} \partial_z p_i(t, z) = 0, \]

\[ \partial_t m_i(t, z) + \frac{1}{\tau_{n+i}} \partial_z m_i(t, z) = 0, \]

under the boundary conditions

\[ \frac{dm_i(t, 0)}{dt} = g_i(p_k(t, 1))p_k(t, 1) - \delta_i m_i(t, 0), \]

\[ \frac{dp_i(t, 0)}{dt} = \alpha_i m_i(t, 1) - \beta_i p_i(t, 0), \]

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

\[ p_i(t, 1) = p_i(t - \tau_i, 0), \]

\[ m_i(t, 1) = m_i(t - \tau_{n+i}, 0). \]

We introduce the following candidate Lyapunov function

\[ V = \int_0^1 \left[ \sum_{i=1}^n q_i \tau_i p_i^2(t, z) e^{-\mu \tau_i z} \right] + \sum_{i=1}^n q_{n+i} \tau_{n+i} m_i^2(t, z) e^{-\mu \tau_{n+i} z} \right] dz \]

\[ + \sum_{i=1}^n w_i p_i^2(t, 0) + \frac{1}{2} \sum_{i=1}^n w_{n+i} m_i^2(t, 0), \]

with positive parameters \( \mu, q_i, q_{n+i}, w_i, w_{n+i} \) to be determined. With matrix notations, this function is rewritten
In the next section, we use again the toggle switch as an example. For the toggle switch example, the general model (18)-(19) is specialized as follows:

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

with

\[
\begin{align*}
\begin{bmatrix} Q_1 & W_1 \\ W_1^T & Q_2 \end{bmatrix} &+ \begin{bmatrix} m_1 & m_2 \\ M_1 & M_2 \end{bmatrix} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix},
\end{align*}
\]

where

\[
\begin{align*}
Q_1 &= \text{diag}\{q_i, i = 1, \ldots, n\}, \\
Q_2 &= \text{diag}\{q_{n+i}, i = 1, \ldots, n\}, \\
W_1 &= \text{diag}\{w_i, i = 1, \ldots, n\}, \\
W_2 &= \text{diag}\{w_{n+i}, i = 1, \ldots, n\}.
\end{align*}
\]

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

\[
\frac{dV}{dt} = -\mu V - X^T M(\mu, p(t, 1)) X,
\]

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

\[
X = \begin{pmatrix} p(t, 0) \\ m(t, 0) \\ p(t, 1) \\ m(t, 1) \end{pmatrix},
\]

\[
M(\mu, p) = \begin{pmatrix} W_1 - Q_1 & 0 & 0 & -W_1 A \\ 0 & W_2 D - Q_2 & -W_2 G(p) & 0 \\ 0 & 0 & Q_1 E_1(\mu, 1) & 0 \\ 0 & 0 & 0 & Q_2 E_2(\mu, 1) \end{pmatrix},
\]

with

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

For this system, the matrix $M(0, p)$ is

\[
M(0, p) = \begin{pmatrix} M_{11} & M_{12} \\ 0 & M_{22} \end{pmatrix},
\]

with

\[
M_{11} = \begin{pmatrix} w_3 \beta_1 - q_1 & 0 & 0 & 0 \\ 0 & w_4 \beta_2 - q_2 & 0 & 0 \\ 0 & 0 & w_1 \delta_1 - q_3 & 0 \\ 0 & 0 & 0 & w_2 \delta_2 - q_4 \end{pmatrix},
\]

\[
M_{12} = \begin{pmatrix} 0 & 0 & -w_3 \alpha_1 & 0 \\ 0 & 0 & 0 & -w_4 \alpha_2 \\ -w_2 \gamma_2(p_1) & 0 & 0 & 0 \\ 0 & 0 & 0 & q_1 \end{pmatrix},
\]

\[
M_{22} = \begin{pmatrix} q_1 & 0 & 0 & 0 \\ 0 & q_2 & 0 & 0 \\ 0 & 0 & q_3 & 0 \\ 0 & 0 & 0 & q_4 \end{pmatrix}.
\]

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

\[
\begin{align*}
0 &< w_3 \beta_1 - q_1, \\
0 &< w_4 \beta_2 - q_2, \\
0 &< w_1 \delta_1 - q_3, \\
0 &< w_2 \delta_2 - q_4, \\
0 &< (w_1 \delta_1 - q_3)q_2 - (1/4) w_2^2 g_1^2(p_2), \\
0 &< (w_2 \delta_2 - q_4)q_1 - (1/4) w_1^2 g_2^2(p_1), \\
0 &< (w_3 \beta_1 - q_1)q_3 - (1/4) w_3^2 \alpha_1^2, \\
0 &< (w_4 \beta_2 - q_2)q_4 - (1/4) w_4^2 \alpha_2^2.
\end{align*}
\]

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

6. EXAMPLE: THE TOGGLE SWITCH

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

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

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 $G(p)$ 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 functionals, 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.

REFERENCES


