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SWITCHING MODELING, STABILITY AND REGULATION FOR BIOLOGICAL SYSTEMS: GENOMICS

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Abstract: This work describes the modeling, stability and regulation problem for a class of biological dynamical systems. The class of biological dynamical systems considered in this paper, are genomical systems described in terms of genetic regulatory networks. Genetic regulatory networks, connect genes by a set of boolean rules (switching conditions given in terms of concentration thresholds) in order to simulate the expression patterns presented in real cells. At the lowest level the evolution of proteins is continuous, discreteness arises when the concentration of enabling quantities is above the threshold, thus exhibiting an hybrid behavior. As a result, two modeling approaches are considered: the first one, based on place-transition Petri nets, describes the behavior of the protein concentration when there is a state change due to some concentration threshold, without being interested in the protein's concentration state at its lowest

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level. In the second approach, given in terms of dynamical colored Petri nets (DCPN), everything is taken in to consideration. Once the model is obtained the stability and regulation problems for genetic regulatory systems, employing Lyapunov methods are addressed.

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1. Introduction

This work describes the modeling, stability and regulation problem for a class of biological dynamical systems. The paper provides a new mathematical technique for the careful study of the complex dynamical interactions between the components of these systems. The approach proposed, is qualitative without dealing with the numerical details. The class of biological dynamical systems considered in this paper, are genomical systems described in terms of genetic regulatory networks [1, 2]. Genetic regulatory networks have received a major impetus from the recent development of experimental techniques allowing the measurement of proteins of gene expression in a massively parallel way, besides giving insight in to the essential regulatory mechanisms in cells. Genetic regulatory networks, connect genes by a set of boolean rules (switching conditions given in terms of concentration thresholds) in order to simulate the expression patterns presented in real cells. The set of boolean rules simulate the network chemical reactions in which regulatory proteins control genes that provide other regulators (proteins) which in turn control the synthesis and degradation of other genes. At the lowest level the evolution of proteins is continuous, discreteness arises when the concentration of enabling quantities is above the threshold, thus exhibiting an hybrid behavior. As a result, two modeling approaches are considered. The first one, based on place-transition Petri nets, describes the behavior of the protein concentration when there is a state change due to some concentration threshold, without being interested in the protein's concentration state at its lowest level. In the second approach, given in terms of dynamical colored Petri nets (DCPN), the continuous protein's concentration evolution as well as its behavior when there is a state change due to some concentration threshold, are taken in to consideration. Once the model is obtained the stability and regulation problems for genetic regulatory

systems, employing Lyapunov methods are addressed. Stability and regulation properties translate in to the presence or absence of: conservation relations, equilibrium points (a pre-specified behavior for therapeutic purposes), regeneration of states, etc. Even the divergence of these properties can be of interest indicating some type of defect. The paper is organized as follows. Section 1 presents the problem to be solved as well as the methodology. In Section 2, the stability theory for difference equations and its application to discrete event systems modeled with Petri nets as well as the definition of DCPN are recalled. In Section 3 a mathematical framework for genetic regulatory networks is given. In Section 4, a simple genetic regulatory system which illustrates the concepts discussed in the previous sections is considered, and finally, some concluding remarks are given.

2. Preliminaries

Notation. $N = \{0, 1, 2, ...\}$, $N_{n_0}^+ = \{n_0,\ n_0 + 1,..., n_0 + k, ...\}$, $n_0 \geq 0$, $Z = \{.... - 2, -1, 0, 1, 2, ...\}$, $R_+ = [0, \infty)$. Given $x, y \in R^n$, we usually denote the relation "$\leq$" to mean componentwise inequalities with the same relation, i.e., $x \leq y$ is equivalent to $x_i \leq y_i, \forall i$. A function $f(n, x)$, $f : N_{n_0}^+ \times R^n \to R^n$ is called nondecreasing in x if given $x, y \in R^n$ such that $x \geq y$ and $n \in N_{n_0}^+$ then, $f(n, x) \geq f(n, y)$.

Consider systems of first ordinary difference equations given by

$$x(n + 1) = f[n, x(n)], \quad x(n_o) = x_0, \quad n \in N_{n_0}^+, \tag{1}$$

where $n \in N_{n_0}^+$, $x(n) \in R^n$ and $f : N_{n_0}^+ \times R^n \to R^n$ is continuous in $x(n)$.

Definition 2.1. The n vector valued function $\Phi(n, n_0, x_0)$ is said to be a solution of (1) if $\Phi(n_0, n_0, x_0) = x_0$ and $\Phi(n + 1, n_0, x_0) = f(n, \Phi(n, n_0, x_0))$ for all $n \in N_{n_0}^+$.

Definition 2.2. (see [3, 4]) The system (1) is said to be:

i) Practically stable, if given (λ, A) with $0 < \lambda < A$, then

$$\|x_0\| < \lambda \Rightarrow \|x(n, n_0, x_0)\| < A,\ \forall n \in N_{n_0}^+,\ n_0 \geq 0.$$

ii) Uniformly practically stable, if it is practically stable for every $n_0 \geq 0$.

iii) Stable if $\forall\ \varepsilon > 0\ \exists\ \eta = \eta(\varepsilon, n_0) > 0$ such that if $x_0 < \eta \Rightarrow \mid x(n, n_0, u_0) \mid < b(\varepsilon)$ for $n \geq n_0$.

iv) Uniformly stable if it is stable but η does not depend on n_0.

v) Asymptotically stable if in addition to being stable $\lim_{n\to\infty} \|x_n\| = 0$.

The following class of function is defined.

Definition 2.3. A continuous function $a : [0, \infty) \to [0, \infty)$ is said to belong to class $\mathcal{K}$ if it is strictly increasing and $a(0) = 0$.

Consider a Lyapunov function $v(n, x(n))$, $v : N_{n_0}^{+} \times R^n \to R_+$ and define the variation of v relative to (1) by

$$\Delta v = v(n+1, x(n+1)) - v(n, x(n)). \tag{2}$$

Then, the following result concerns the practical stability of (1).

Theorem 2.1. (see [4]) *Let $v : N_{n_0}^{+} \times R^n \to R_+$ be a continuous function in x, such that $b(\|x\|) \leq v(n, x(n)) \leq a(\|x\|)$ for $b, a \in \mathcal{K}$ and*

$$\Delta v(n, x(n)) \leq w(n, v(n, x(n)))$$

holds for $n \in N_{n_0}^{+}$, $x(n) \in R^n$, where $w : N_{n_0}^{+} \times R_+ \to R$ is a continuous function in the second argument. Assume that : $g(n, u) \triangleq u + w(n, u)$ is nondecreasing in u, $0 < \lambda < A$ are given and finally that $a(\lambda) < b(A)$ is satisfied. Then, the stability properties of

$$u(n+1) = g(n, u(n)),\ u(n_0) = u_0 \geq 0, \tag{3}$$

imply the corresponding stability properties of the system (1).

Now, we extend our last theorem, to the case of several Lyapunov functions. Consider a vector Lyapunov function $v(n, x(n))$, $v : N_{n_0}^{+} \times R^n \to R_+^p$, and define the variation of v relative to (1). Then, the following result concerns the practical stability of (1).

Theorem 2.2. *Let $v : N_{n_0}^{+} \times R^n \to R_+^p$ be a continuous function in x, define the function $v_0(n, x(n)) = \sum_{i=1}^{p} v_i(n, x(n))$ such that satisfies the estimates*

$$b(\|x\|) \leq v_0(n, x(n)) \leq a(\|x\|) \text{ for } a, b \in \mathcal{K} \text{ and}$$

$$\Delta v(n, x(n)) \leq w(n, v(n, x(n)))$$

for $n \in N_{n_0}^{+}$, $x(n) \in R^n$, where $w : N_{n_0}^{+} \times R_+^p \to R^p$ is a continuous function in the second argument.

Assume that : $g(n, e) \triangleq e + w(n, e)$ is nondecreasing in e, $0 < \lambda < A$ are given and finally that $a(\lambda) < b(A)$ is satisfied. Then, the practical stability properties of

$$e(n+1) = g(n, e(n)),\ e(n_0) = e_0 \geq 0, \tag{4}$$

imply the corresponding practical stability properties of system (1).

Fixing a particular form on the function $w(n,e)$ one obtains different kinds of stability performance, this is summarized in the next result

Corolary 2.1. (see [4]) *In Theorem 2.1 and Theorem 2.2:*

i). If $w(n,e) \equiv 0$ we get uniform practical stability of (1) which implies structural stability.

ii). If $w(n,e) = -c(e)$, for $c \in \mathcal{K}$, we get uniform practical asymptotic stability of (1).

2.1. Stability, Stabilization and/or Regulation of Discrete Event Systems Modeled with Place-Transition Petri Nets, see [5]

Definition 2.4. A Petri net is a 5-tuple, $PN = \{P, T, F, W, M_0\}$, where:

$P = \{p_1, p_2, ..., p_m\}$is a finite set of places,
$T = \{t_1, t_2, ..., t_n\}$ is a finite set of transitions,
$F \subset (P \times T) \cup (T \times P)$ is a set of arcs,
$W : F \to N_1^+$ is a weight function,
M_0: $P \to N$ is the initial marking,
$P \cap T = \emptyset$ and $P \cup T \neq \emptyset$.

A Petri net structure without any specific initial marking is denoted by N. A Petri net with the given initial marking is denoted by (N, M_0). Notice that if $W(p,t) = \alpha$ (or $W(t,p) = \beta$) then, this is often represented graphically by α, (β) arcs from p to t (t to p) each with no numeric label.

Let $M_k(p_i)$ denote the marking (i.e., the number of tokens) at place $p_i \in P$ at time k and let $M_k = [M_k(p_1), ..., M_k(p_m)]^T$ denote the marking (state) of PN at time k. A transition $t_j \in T$ is said to be enabled at time k if $M_k(p_i) \geq W(p_i, t_j)$ for all $p_i \in P$ such that $(p_i, t_j) \in F$. It is assumed that at each time k there exists at least one transition to fire. If a transition is enabled then, it can fire. If an enabled transition $t_j \in T$ fires at time k then, the next marking for $p_i \in P$ is given by

$$M_{k+1}(p_i) = M_k(p_i) + W(t_j, p_i) - W(p_i, t_j). \tag{5}$$

Let $A = [a_{ij}]$ denote an $n \times m$ matrix of integers (the incidence matrix), where $a_{ij} = a_{ij}^+ - a_{ij}^-$ with $a_{ij}^+ = W(t_i, p_j)$ and $a_{ij}^- = W(p_j, t_i)$. Let $u_k \in \{0,1\}^n$ denote a firing vector where if $t_j \in T$ is fired then, its corresponding firing vector is $u_k = [0, ..., 0, 1, 0, ..., 0]^T$ with the one in the j-th position in the vector and zeros everywhere else. The matrix equation (nonlinear difference equation)

describing the dynamical behavior represented by a Petri net is:

$$M_{k+1} = M_k + A^T u_k, \tag{6}$$

where if at step k, $a_{ij}^- < M_k(p_j)$ for all $p_i \in P$ then, $t_i \in T$ is enabled and if this $t_i \in T$ fires then, its corresponding firing vector u_k is utilized in the difference equation to generate the next step. Notice that if M' can be reached from some other marking M and, if we fire some sequence of d transitions with corresponding firing vectors $u_0, u_1, ..., u_{d-1}$ we obtain that

$$M' = M + A^T u, \ u = \sum_{k=0}^{d-1} u_k. \tag{7}$$

Let $(N_{n_0}^+, d)$ be a metric space, where $d : N_{n_0}^+ \times N_{n_0}^+ \to R_+$ is defined by

$$d(M_1, M_2) = \sum_{i=1}^{m} \zeta_i \|M_1(p_i) - M_2(p_i)\|, \quad \zeta_i > 0, \quad i = 1, ..., m$$

and consider the matrix difference equation which describes the dynamical behavior of the discrete event system modeled by a Petri net (7) then we have the following proposition.

Proposition 2.1. *Let N be a Petri net. N is uniform practical stable if there exists a Φ strictly positive m vector such that*

$$\Delta v = u^T A\Phi \leq 0. \tag{8}$$

Moreover, N is uniform practical asymptotic stability if the following equation holds

$$\Delta v = u^T A\Phi \leq -c(e), \ \text{for } c \in \mathcal{K}. \tag{9}$$

Lemma 2.1. *Let suppose that Proposition (2.1) holds then,*

$$\Delta v = u^T A\Phi \leq 0 \Leftrightarrow A\Phi \leq 0. \tag{10}$$

Definition 2.5. Let N be a Petri net. N is said to be stabilizable if there exists a firing transition sequence with transition count vector u such that system (7) remains bounded.

Proposition 2.2. *Let N be a Petri net. N is stabilizable if there exists a firing transition sequence with transition count vector u such that the following equation holds*

$$\Delta v = A^T u \leq 0. \tag{11}$$

Remark 2.1. It is important to underline that by fixing a particular u, which satisfies (11), we restrict the coverability tree to those markings (states) that are finite. The technique can be utilized to get some type of regulation and/or eliminate some undesirable events (transitions).

2.2. Stability, Stabilization and/or Regulation of Discrete Event Systems Modeled with Colored Petri nets, see [6]

In this section, we define the concepts of colored Petri nets, marking, step, firing rule and incidence matrix (for which the theory of multi-sets is recalled). Colored Petri nets have undergone several revisions using expressions to specify the incidence matrices and markings, but for Lyapunov analysis the function representation as presented here is preferred. Next, we show how by applying Theorem 2.1 and Theorem 2.2, we obtain the generalization of Proposition 2.1 and Proposition 2.2 to systems modeled by colored Petri nets. Colored Petri nets are common high level Petri nets in which the tokens are identified.

Definition 2.6. A multi-set m, over a non-empty set S, is a function $m : S \to N$ which we represent as a formal sum:

$$\sum_{s \in S} m(s)'s.$$

By S_{MS} we denote the set of all multi-sets over S. The non-negative integers $\{m(s) : s \in S\}$ are the coefficients of the multi-set. $s \in S$ iff $m(s) \neq 0$.

Definition 2.7. Addition, scalar multiplication , comparison and size of multi-sets are defined in the following way, for all $m_1, m_2, m_3 \in S_{MS}$ and all $n \in N$:

i) $m_1 + m_2 = \sum_{s \in S}(m_1(s) + m_2(s))'s$ (addition).

ii) $n * m = \sum_{s \in S}(n * m(s))'s$ (scalar multiplication).

iii) $m_1 \neq m_2 = \exists s \in S : m_1(s) \neq m_2(s)$ (comparison).

iv) $m_1 \leq m_2 = \forall s \in S : m_1(s) \leq m_2(s)$ ($\geq$ and $=$ are defined analogously to $\leq$).

v) $\mid m \mid = \sum_{s \in S} m(s)$ ($\mid m \mid = 0$ iff $m = \emptyset$ the empty multi-set) (size).

When $\mid m \mid = \infty$ we say that m is infinite. Otherwise m is finite. When $m_1 \leq m_2$ we also define substraction:

vi) $m_2 - m_1 = \sum_{s \in S}(m_2(s) - m_1(s))'s$ (substraction).

Remark 2.2. Weighted-sets w over a set S (denoted by S_{WS}) are defined in exactly the same way as multi-sets except that we replace N by Z, i.e.,

we allow negative coefficients. The operations for weighted-sets are similar to the operations with multi-sets. However, scalar multiplication is defined for negative integers and substraction is defined also for all weighted-sets.

Definition 2.8. A colored Petri net is a 7-tuple,

$$\text{CPN} = (\Omega, P, T, C, A^+, A^-, M_0),$$

where:

- Ω is a finite set of non-empty sets, called colors,
- P is the set of places,
- T is the set of transitions,
- $P \cap T = \emptyset$ and $P \cup T \neq \emptyset$,
- $C : P \cup T \longrightarrow \Omega$ is the color function, where Ω is the set of finite non-empty sets,
- $A^+(A^-) : C(p) \times C(t) \rightarrow N$ is the forward (backward) incidence matrix of $P \times T$,
- M_0 , the initial marking, is a vector indexed by the elements of P, where $M_0(p)$: $C(p) \rightarrow N$.

Remark 2.3. The forward and backward incidence matrices, are matrices of size $P \times T$ with coefficients in N which, consequently, define linear applications from $C(t)$ to $C(p)_{MS}$. The initial marking $M_0(p)$ takes its values in $C(p)_{MS}$.

Definition 2.9. A marking of CPN is a function M defined on P, such that $M(p) \in C(p)_{MS}$ for all $p \in P$.

Definition 2.10. A step of CPN is a function X defined on T, such that $X(t) \in C(t)_{MS}$ for all $t \in T$.

Definition 2.11. The transition firing rule is given by:

- A step X is enabled in a marking M iff the following property holds $\forall p \in P$, $M(p) \geq \sum_{t \in T} A^-(p,t)(X(t))$, which can also be written as $M \geq A^- * X$, where $*$ denotes generalized matrix-multiplication. We then say that t is enabled or firable under the marking M.

- Firing a transition t leads to a new marking M_1 defined by: $\forall p \in P$, $M_1(p) = M(p) + \sum_{t \in T} A^+(p,t)(X(t)) - \sum_{t \in T} A^-(p,t)(X(t))$, or in general $M_1 = M + A^+ * X - A^- * X$.

Remark 2.4. The condition $M(p) \geq \sum_{t \in T} A^-(p,t)(X(t))$ tells us that the multi-set of all the colors, which are removed from p when t occurs (for all $t \in X$), is required to be less than or equal to the marking of p. It is important to mention that the generalized matrix-multiplication, (when it is defined), behaves in relation to the size operation as follows:

$$\mid A_1 * A_2 \mid = \mid A_1 \mid * \mid A_2 \mid .$$

Definition 2.12. The incidence matrix of a colored Petri net is defined by: $A = A^+ - A^-$, $A(p,t) \in C(t) \to C(p)_{WS}$, where $A(p,t)$ is a linear mapping whose associated matrix $P \times T$ takes values in Z.

Remark 2.5. When a transition t is fired with respect to a color $c_t \in C(t)$ then, for every color $c_p \in C(p)$, $A(c_p, c_t)$ gives the number of colors c_p to be added to (if the number is positive) or to be removed from (if the number is negative) place p. Notice that if $M^{'}$ can be reached from a marking M, i.e., there exists a sequence of enabled steps whose associated transitions have been fired, then we obtain that

$$M^{'} = M + A * X. \tag{12}$$

Definition 2.13. Let a place $p \in P$, a non negative $n \in N$ be given then, n is an integer bound for p iff: $\forall M^{'}$ reachable from M: $\mid M'(p) \mid \leq n$.

Let $(N_{n_0}^+, d)$ be a metric space, where $d : N_{n_0}^+ \times N_{n_0}^+ \to R_+$ is defined by

$$d(M_1, M_2) = \sum_{i=1}^{m} \zeta_i \| (M_1(p_i)(c_p) - M_2(p_i)(c_p)) \| ,$$
$$\zeta_i > 0, \quad \forall c_p \in C(p_i), \quad i = 1, ..., m, \tag{13}$$

and consider equation (12), which defines a continuous function in $(N_{n_0}^+, d)$. Now, we are ready to state the two main results of this section.

Proposition 2.3. *Let CPN be a colored Petri net, CPN is uniform practical stable if there exists a strictly positive linear mapping $\Phi : C(p)_{WS} \to U_{WS}$ (with U normally one of the color sets already used in CPN) such that:*

$$\Delta v = \mid \Phi * A * X \mid \leq 0. \tag{14}$$

Remark 2.6. The condition given by equation (14) with strictly equality sign is equivalent to the condition:

$$\Phi * A = 0_f,$$

where 0_f is the zero function. The solution of this equation is not an easy task. However, different methods have been proposed, drawing heavily on results from linear algebra and linear programming.

Proposition 2.4. *Let CPN be a colored Petri net, CPN is stabilizable if there exists a step X such that*

$$\Delta v =\mid A * X \mid \leq 0. \tag{15}$$

2.3. Dynamical Colored Petri Nets, see [8]

Definition 2.14. A place $p \in P$ is said to be a dynamical place if its marking obeys the following equation:

$$M'(p) = \begin{cases} M(p) + \sum_{t \in T} A(p,t)(X(t)) \text{ if } X \text{ switches}, \\ \mathcal{L}(M(p), X) \text{ if } X \text{ is fixed}, \end{cases} \tag{16}$$

where $\mathcal{L}$ is a differential operator. Then, p is said to have the internal dynamics property.

Definition 2.15. A dynamical colored Petri net (DCPN) is a colored Petri net such that there is at least one $p \in P$ that has the internal dynamics property.

3. Mathematical Framework for Genetic Regulatory Networks

Let $\{p_i\}_{i=1}^n$ denote the cellular protein concentrations and consider $\Sigma \subseteq R^n, \Sigma = \Sigma_1 \times \Sigma_2 \times \cdots \Sigma_n$ with $\Sigma_i = \{p_i \in R_+ : 0 \leq p_i \leq \text{ Max}\{p_i\}\}$, $i = 1, ..., n$. Let $\theta_i^j : j = 1, ..., q, i = 1, ..., n$ be a set of different threshold concentrations, associated to the p_i proteins, such that $\theta_i^1 < \theta_i^2 < \cdots < \theta_i^q <$ Max $\{p_i\}$ then, Σ admits the following decomposition:

$$\begin{aligned} \Sigma &= \cup_{k=1}^{(2q+1)^i} D_1^k \times D_2^k \times \cdots D_n^k; \\ D_1^l \times D_2^l \times \cdots D_n^l &\neq D_1^m \times D_2^m \times \cdots D_n^m \quad \text{for } \ l \neq m, \\ l, m &= 1, ..., (2q+1)^i, \quad i = 1, ..., n, \end{aligned} \tag{17}$$

where each D_i^k for i fixed, takes one and only one of the forms shown below:

$$\begin{aligned}
D_i^k &= \{p_i \in R_+ : 0 \leq p_i < \theta_i^1\},\\
D_i^k &= \{p_i \in R_+ : p_i = \theta_i^1\},\\
D_i^k &= \{p_i \in R_+ : \theta_i^1 < p_i < \theta_i^2\},\\
D_i^k &= \{p_i \in R_+ : p_i = \theta_i^2\},\\
&\vdots\\
D_i^k &= \{p_i \in R_+ : \theta_i^{q-1} < p_i < \theta_i^q\},\\
D_i^k &= \{p_i \in R_+ : p_i = \theta_i^q,\\
D_i^k &= \{p_i \in R_+ : \theta_i^q < p_i \leq \text{ Max}\,\{p_i\}\}.
\end{aligned}$$

Definition 3.1. Let Σ be given by (17) then fix k, if for some of the D_i^k strict equality is achieved then $D_1^k \times D_2^k \times \cdots D_n^k \subsetneqq \Sigma$ is called a switching set.

Definition 3.2. The order of a switching set is equal to the number of i', $i = 1, ..., n$, where equality is achieved.

Definition 3.3. A set which is not a switching set is called a regulatory set.

In a regulatory set, the evolution of proteins is continuous having the possibility of staying there forever or leaving it by crossing a switching set. In a switching set the protein's trajectories, either transverse the set continuously or they slide continuously towards an equilibrium point. As a result, two modeling approaches are considered: the first one, based on place-transition Petri nets, describes the behavior of the protein concentration when there is a state change due to some concentration threshold, without being interested in the protein's concentration state at its lowest level (the protein concentration states at the regulatory and switching sets are frozen). In the second approach, given in terms of dynamical colored Petri nets (DCPN), the continuous protein's concentration evolution as well as its behavior when there is a state change due to some concentration threshold, are taken in to consideration. Once these models are obtained, the stability and regulation problems for genetic regulatory systems are addressed by applying the results given in the previous sections. This is next illustrated by means of an example.

4. A Simple Genetic Regulatory System

Consider a simple genetic regulatory network of two genes each coding for a regulatory protein p_1 and p_2 which control the expression of both genes. Let

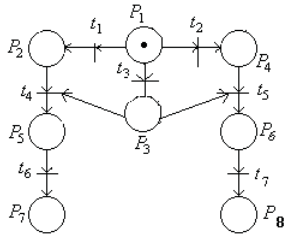

Figure 1:

θ_i^j; $j = 1, 2$, $i = 1, 2$ be the different threshold concentrations associated with p_1 and p_2 subject to: $\theta_1^1 < \theta_1^2 <$ Max $\{p_1\}$ and $\theta_2^1 < \theta_2^2 <$ Max $\{p_2\}$ then, $\Sigma \subseteq R^2$ is partitioned in to 9 regulatory sets and 16 switching sets.

Case 1) Place-transition model.

This case considers the evolution of proteins p_1 and p_2 by just taking in to account the changes produced by the switching sets. Assuming that the evolution of the proteins starting from the regulatory set $D_1^1 \times D_2^1$ is given by the following diagram:

$$D_1^1 \times D_2^1 \rightarrow \begin{cases} D_1^1 \times D_2^2 \rightarrow D_1^1 \times D_2^3 \rightarrow D_1^1 \times D_2^4 \\ \qquad\qquad\qquad\quad \uparrow \\ \qquad\qquad D_1^2 \times D_2^2 \\ \qquad\qquad\qquad\quad \downarrow \\ D_1^2 \times D_2^1 \rightarrow D_1^3 \times D_2^1 \rightarrow D_1^4 \times D_2^1 \end{cases} \tag{18}$$

(understanding that the occurrence of $D_1^1 \times D_2^2 \rightarrow D_1^1 \times D_2^3 \rightarrow D_1^1 \times D_2^4$, $D_1^2 \times D_2^2$ and $D_1^2 \times D_2^1 \rightarrow D_1^3 \times D_2^1 \rightarrow D_1^4 \times D_2^1$ is mutually exclusive), where: $D_1^1 \times D_2^1 = \{0 \leq p_1 < \theta_1^1\} \times \{0 \leq p_2 < \theta_2^1\}$;

$D_1^1 \times D_2^2 = \{0 \leq p_1 < \theta_1^1\} \times \{p_2 = \theta_2^1\}$; $D_1^2 \times D_2^2 = \{p_1 = \theta_1^1\} \times \{p_2 = \theta_2^1\}$; $D_1^2 \times D_2^1 = \{p_1 = \theta_1^1\} \times \{0 \leq p_2 < \theta_2^1\}$; ...; $D_1^1 \times D_2^4 = \{0 \leq p_1 < \theta_1^1\} \times \{p_2 = \theta_2^2\}$; $D_1^4 \times D_2^1 = \{p_1 = \theta_1^2\} \times \{0 \leq p_2 < \theta_2^1\}$ and $D_1^1 \times D_2^4$, $D_1^4 \times D_2^1$ are switching sets with stable equilibrium points, the place-transition Petri net model takes the form shown in Figure 1:

Having the following specifications:

Places: $p_1 = D_1^1 \times D_2^1$, $p_2 = D_1^1 \times D_2^2$, $p_3 = D_1^2 \times D_2^2$, $p_4 = D_1^2 \times D_2^1$, $p_5 = D_1^1 \times D_2^3$, $p_6 = D_1^3 \times D_2^1$, $p_7 = D_1^1 \times D_2^4$ and $p_8 = D_1^4 \times D_2^1$ (the protein's concentration state at the regulatory and switching sets).

Transitions: $t_1, t_2, ..., t_7$: the change of state produced by the activation of the respective threshold(s).

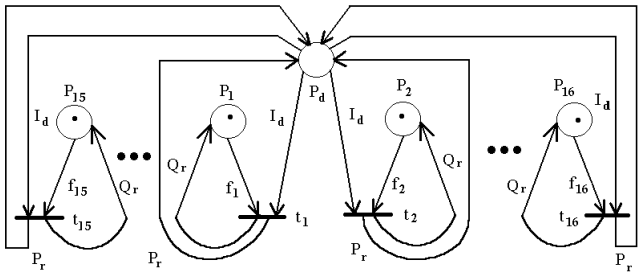

Figure 2:

Initial marking: $M_0(p_1) = 1$, $M_0(p_2) = M_0(p_3) = ... = M_0(p_7) = 0$.

From the incidence matrix of the place-transitions Petri net, given by

$$A = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ -1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & -1 & -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & -1 & -1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 0 & 1 \end{bmatrix},$$

picking $\Phi = [1, 1, 1, 1, 2, 2, 2, 2]$, $\Phi > 0$ the condition $A\Phi = 0$ is satisfied concluding stability. Now that stability has been achieved, (assuming that that the thresholds can be set as desired), the objective is to design a control law such that the state given by the place $p_7 = D_1^1 \times D_2^4$ will be attained for some therapeutic purposes. Then, using the theory given in Subsection 2.1 and [7], the control law which solves the problem results to be $u = [1, 0, 0, 1, 0, 1, 0]$.

Case 2) DCPN model, see [8].

This case considers the evolution of proteins p_1 and p_2, at its lowest level as well as its behavior when there is a state change due to some concentration threshold. More precisely, the protein's concentration state at its lowest level is modeled by equation (16) when X is fixed, while when there is a state change produced by the activation of one of the switching sets, is given when X switches. The DCPN model is shown in Figure 2, where:

Places: p_d : Cellular protein concentrations state (dynamical place), $p = p_1 = p_2 = ... = p_{16}$: the possible switches states, defined by the switching sets.

$C(p_d) = R_+$

$C(p) = \{\cdot\}$

Transitions: t_1 : switching set 1 is active, t_2 : switching set 2 is active,..., t_{16} : switching set 16 is active.

$C(t_1) = C(t_2) = ... = C(t_{16}) = (R_+ \times \{\cdot\})$

$f_1(M(p_d))(= f_2(M(p_d)) = ... = f_{16}(M(p_d))) = if$ ($M(p_d)$ is such that the switching set 1(or 2 or 3 or 4 or...or 16) is activated) *then* $1\cdot$ *else* $\emptyset$

$I_d(M(p_d)) = 1'M(p_d)$, identity function,

$P_r(M(p_d), \{\cdot\}) = 1'M(p_d)$, projection function,

$Q_r(M(p_d), \{\cdot\}) = \{\cdot\}$, projection function.

The initial marking is:

$M_0(p_d) = 1M_0(p_d)$ (some initial state which belongs to $D_1^1 \times D_2^1$),

$M_0(p) = 1\cdot$.

The incidence matrix of the dynamical coloured Petri net shown in Figure 2, is given by

$$A = \begin{bmatrix} -I_d + P_r & -I_d + P_r & -I_d + P_r & -I_d + P_r & -I_d + P_r & \cdots & -I_d + P_r \\ -f_1 + Q_r & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & -f_2 + Q_r & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & -f_3 + Q_r & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & -f_4 + Q_r & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 & \ddots & \ddots & \vdots \\ \vdots & \vdots & \cdots & \vdots & \ddots & -f_{15} + Q_r & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & -f_{16} + Q_r \end{bmatrix}$$

stability is concluded by picking $\Phi : C(p)_{WS} \to U_{WS}$, ($U_{WS} = R$), equal to:

$$\Phi = \begin{bmatrix} I_d & I_d & \cdots & I_d \end{bmatrix}$$

Proof. Computing equation (14), one gets

$$\begin{aligned} -I_d(I_d(R_+)) + I_d(P_r(R_+, \{\cdot\})) - I_d(f_1(R_+)) + I_d(Q_r(R_+, \{\cdot\})) = \emptyset\,, \\ -I_d(I_d(R_+)) + I_d(P_r(R_+, \{\cdot\})) - I_d(f_2(R_+)) + I_d(Q_r(R_+, \{\cdot\})) = \emptyset\,, \\ \vdots \\ -I_d(I_d(R_+)) + I_d(P_r(R_+, \{\cdot\})) - I_d(f_{16}(R_+)) + I_d(Q_r(R_+, \{\cdot\})) = \emptyset\,, \end{aligned}$$

which proves our assertion. □

For this modeling approach it is not possible to obtain regulation, since there is no control of the protein's concentration evolution at regulatory domains, so unless, some extra conditions are imposed, the state given by the switching set $D_1^1 \times D_2^4$ can not be attained as was done in Case 1.

5. Conclusions

This work addressed the modeling, stability and regulation problem for genomical dynamical systems. Two modeling approaches were considered: the first one, based on place-transition Petri nets, and a second one based on dynamical colored Petri nets (DCPN). Stability was successfully proven in both cases. However regulation to some desired state was just possible to attain for the place-transition model, for the DCPN model this was not the case unless some extra conditions are imposed on the protein's concentration evolution.

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