

ON TWO QUALITATIVE REPRESENTATIONS OF A GENETIC REGULATORY NETWORK

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Abstract

There is an increasing interest in the study of genetic regulatory networks, and in addition to experimental tools, specific tools for modelling and simulation recently emerged, allowing systematic behaviour prediction of large complex systems. Since there is a usual lack of information of biochemical reaction networks, qualitative simulation tools, requiring only specification of inequality-like algebraic constraints, are preferred to quantitative ones. Starting from a simple piecewise-linear model of a *two genes regulatory network* (TGNR) described in the literature, this paper proposes an alternate qualitative modelling technique, which extends a *hybrid control systems* (HCS) framework from control engineering. The thresholds protein concentrations partition the state space into hyperrectangular open regions and the resulting qualitative model is basically a logical abstraction of the families of continuous trajectories mapped to this partition. The relations of this model to numerical simulation results and a comparison with the corresponding qualitative model in the *Genetic Network Analyzer* (GNA) approach are presented.

Key words

biological systems, hybrid control systems, piecewise-linear systems, qualitative models.

1 Introduction and motivation

In addition to experimental approaches, computer tools for modelling and simulation of cellular processes, involving diverse components and complex interactions, receive an increasing interest from researchers [Takashi et al., 2002]. The basic challenge is: given sufficient information about the biochemical system, can the software tool predict its behaviour? Quantitative models of biological

reaction networks, based on differential equations, require specification of numerical values for kinetic parameters and molecular concentrations, which usually are not exactly known.

In contrast, qualitative modelling and simulation tools, based on algebraic inequality-like restrictions imposed to the state variables, have recently emerged as an efficient approach in systems biology. Such an example is the *Genetic Network Analyzer* (GNA), adapted for qualitative simulation of genetic regulatory networks [de Jong et al., 2003a;b]. The basic model is a *piecewise-linear* (PL) differential system, whose right-hand side changes when the state variables, represented by protein concentrations, reach given threshold values. The evolution of continuous trajectories through the partition derived from the threshold limits is abstracted to a qualitative model, which is basically a logic automaton: the discrete states correspond to partition domains in the continuous state space while transitions occur when threshold limits are crossed.

This paper proposes an alternate qualitative modelling approach, based on a *hybrid control systems* (HCS) framework, firstly introduced by Antsaklis and his co-workers [Stiver, Antsaklis and Lemmon, 1994]. For a *two-genes regulatory network* (TGNR) PL model, a *discrete event* abstraction, called DES-plant, is constructed and compared to the corresponding GNA qualitative model reported in the literature. Also, a switching control law is deduced and implemented in MATLAB simulation experiments, making possible a comparison between the TGNR qualitative evolutions and their numerical counterparts in the partitioned state space. The paper is organized as follows. The basic PL model of genetic regulatory networks is presented in Section 2, followed by a presentation of the HCS framework in Section 3. The core is the construction of the DES-plant abstraction, which translates the interaction between

the continuous trajectories and the hypersurfaces of the state partition. The qualitative DES-plant model of the TGNR, simulation experiments and a comparative discussion are presented in Section 4, followed by concluding remarks.

2 A piecewise linear model of a TGNR

The piecewise-linear model of genetic regulatory networks dynamics, firstly introduced by [Glass and Kaufmann, 1973] and used by [de Jong et al., 2003] for qualitative simulation with the GNA tool is

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}) - \mathbf{g}(\mathbf{x})\mathbf{x}, \quad \mathbf{x} \geq \mathbf{0}, \quad (1)$$

with $\mathbf{x} \in \mathbf{R}^n$ a vector of cellular protein concentration, $\mathbf{f} = (f_1, \dots, f_n)'$, $\mathbf{g} = \text{diag}(g_i)_{i=1:n}$.

For each $i \in 1:n$, $f_i : \mathbf{R}_{\geq 0}^n \rightarrow \mathbf{R}_{\geq 0}$ is

$$f_i(\mathbf{x}) = \sum_{l=1}^{L_i} k_{il} b_{il}(\mathbf{x}), \quad (2)$$

where $k_{il} > 0$ is a rate parameter, $b_{il} : \mathbf{R}_{\geq 0}^n \rightarrow \{0,1\}$ is a *regulation function* and L_i a possible empty set of indices. The function $b_{il}(\mathbf{x})$ is a combination of step functions $s^\pm(x_i, \theta_i^j)$, with $s^+(x_i, \theta_i^j) = 0$, for $x_i < \theta_i^j$, $s^+(x_i, \theta_i^j) = 1$, for $x_i > \theta_i^j$, and $s^-(x_i, \theta_i^j) = 1 - s^+(x_i, \theta_i^j)$, where $\theta_i^j \geq 0$ are threshold values. Usually the regulation of protein degradation is $g_i(\mathbf{x}) = \gamma_i > 0$, $i = 1:n$.

The PL model of a TGNR example discussed in [de Jong et al., 2003a;b] and depicted in Figure 1 is

$$\begin{cases} \dot{x}_1 = k_1 s^-(x_1, \theta_1^2) s^+(x_2, \theta_2^1) - \gamma_1 x_1 \\ \dot{x}_2 = k_2 s^-(x_1, \theta_1^1) s^-(x_2, \theta_2^2) - \gamma_2 x_2 \end{cases} \quad (3)$$

where

$$k_i > 0, \quad 0 < \theta_i^1 < \theta_i^2, \quad k_i - \gamma_i \theta_i^2 > 0, \quad i = 1:2. \quad (4)$$

3 A HCS framework and the DES-plant model

In the HCS structure, the continuous plant is controlled, through an interface, by a discrete event controller (Figure 2).

Starting from a partition of the continuous state-space, the plant coupled to the interface is abstracted to a *discrete event system* (DES), called DES-plant, and then the controller is built within the DES theory.

In the sequel, a technique used for DES-plant model construction is applied to design a qualitative model of the TGNR. Firstly, the structure of the HCS is reviewed in brief.

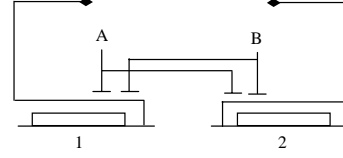


Figure 1. The example of TGNR in [de Jong et al., 2003]; the genes 1 and 2 code each one for regulatory protein (A and B).

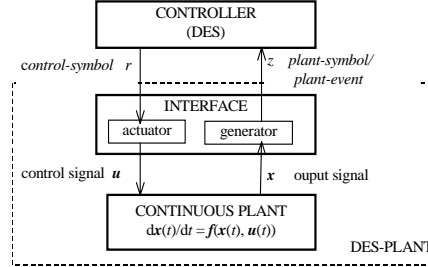


Figure 2. The architecture of a HCS.

3.1 The structure of the HCS

The *continuous plant* is modelled by the differential system

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t)), \quad (5)$$

where $\mathbf{x}(t) \in X \subseteq \mathbf{R}^n$ and $\mathbf{u}(t) \in U \subseteq \mathbf{R}^m$ are the state and control vector respectively, at time $t \in \mathbf{R}$. X is the continuous state space. The set of admissible control values $U = \{\mathbf{u}_1, \dots, \mathbf{u}_M\}$ is bijectively mapped to the *alphabet of control-symbols*

$$\tilde{\mathbf{R}} = \{r_1, \dots, r_M\}. \quad (6)$$

The *interface* converts signals between the plant and the controller and it comprises the *actuator* and the *event generator*. Consider the bijective function between control values and the related alphabet, $\gamma : \tilde{\mathbf{R}} \rightarrow U$, $\gamma(r_m) = \mathbf{u}_m$, $m = 1:M$.

The *actuator* converts a string of control-symbols $\omega_r = r(0), r(1), \dots, r(k), \dots$, $\omega_r \in \tilde{\mathbf{R}}^*$, - with k the logical time - to a vector of piecewise constant control-signals for the plant $\mathbf{u}(t) = \sum_{k \geq 0} \gamma(r(k)) \cdot I(t, t_c(k), t_c(k+1))$, where $t_c(k) \in \mathbf{R}$ is the moment when $r(k)$ is received from the DES controller, $t_c(k) < t_c(k+1)$, $\forall k > 0$ and $I : \mathbf{R} \times \mathbf{R} \times \mathbf{R} \rightarrow \{0, 1\}$ is a characteristic function defined by $I(t, \alpha, \beta) = 1$, if $\alpha \leq t < \beta$ and $I(t, \alpha, \beta) = 0$, if else.

The *state space partition*. The *event generator* converts the plant's state trajectory $\mathbf{x}(\cdot)$, evolving in the partitioned state space, into a string of plant-symbols. Consider a set of N indexed smooth functionals, with $N \geq 1$ a natural number,

$$S_h^N = \{h_i : X \rightarrow \mathbf{R} \mid h_i \in C^1, i=1:N\}, \quad (7)$$

which defines the *partition* of the state space X . Each functional $h_i \in S_h^N$ satisfies

$$\nabla_a(h_i) \neq \mathbf{0}, \quad \forall a \in \ker(h_i). \quad (8)$$

Each hypersurface $\ker(h_i) = \{\mathbf{x} \in X \mid h_i(\mathbf{x}) = 0\}$, $i \in 1:N$, separates the continuous state space into two disjoint half-spaces, respectively,

$$\begin{aligned} H_i^+ &= \{\mathbf{x} \in X \mid h_i(\mathbf{x}) > 0\}, \\ H_i^- &= \{\mathbf{x} \in X \mid h_i(\mathbf{x}) < 0\}. \end{aligned} \quad (9)$$

The hypersurfaces $\ker(h_i)$, $i=1:N$, partition the state space X into $\hat{Q} \leq 2^N$ disjoint open cells. Consider $DX = X \mid Fr$, with $Fr = \bigcup_{i=1}^N \ker(h_i)$. The *equivalence relation* induced by S_h^N is $rel \subset DX \times DX$, defined by $(\mathbf{x}_a, \mathbf{x}_b) \in rel \Leftrightarrow h_i(\mathbf{x}_a)h_i(\mathbf{x}_b) > 0, \forall h_i \in S_h^N$.

The *cellular space* $DX_{/rel} = C$ is the set of all *classes of equivalence* of the relation rel . Consequently, in each cell, any functional h_i , $i \in 1:N$, has a *constant* sign. Each cell is bijectively labelled with a symbol from the *alphabet of the plant's discrete states*

$$\tilde{P} = \{p_1, \dots, p_{\hat{Q}}\}. \quad (10)$$

Define $\text{sgn} : \mathbf{R} \rightarrow \mathbf{R}$, $\text{sgn}(y) = -1$, if $y < 0$, $\text{sgn}(y) = 0$, if $y = 0$ and $\text{sgn}(y) = 1$, if $y > 0$. The *quality function* $\mathbf{b} : X \rightarrow \{-1, 0, 1\}^N$ is defined by

$$\mathbf{b}(\mathbf{x}) = (\text{sgn}(h_1(\mathbf{x})) \dots \text{sgn}(h_N(\mathbf{x})))'. \quad (11)$$

The value $\mathbf{b}(\mathbf{x})$ is *consistent* if and only if $\text{sgn}(h_i(\mathbf{x})) \neq 0, \forall h_i \in S_h^N$ and *inconsistent* if else [Oltean, 2001]. Denote $c_q \in C$ the cell of the state space partition labelled with $p_q \in \tilde{P}$ and $\mathbf{b}(\mathbf{x}) = \mathbf{b}_q$, $\forall \mathbf{x} \in c_q$, the qualitative state of p_q , $q=1:\hat{Q}$. The set of all consistent qualitative values, or *qualitative states*, is

$$B = \{\mathbf{b}_1, \dots, \mathbf{b}_{\hat{Q}}\}. \quad (12)$$

The discrete states $p_q, p_s \in \tilde{P}$ are *adjacent* if $\exists h_i \in S_h^N$ s.t. the vectors $\mathbf{b}_q, \mathbf{b}_s \in B$ satisfy the relations: $b_q^j b_s^j = -1, b_q^j b_s^j = 1, \forall j \in 1:N, j \neq i$.

The *open adjacency boundary* between two discrete states $p_q, p_s \in \tilde{P}$, separated by the

hypersurface $\ker(h_i)$ is:

$$\begin{aligned} A(h_i, p_q, p_s) &= \{\mathbf{x} \in X : \text{sgn}(h_i(\mathbf{x})) = 0\}, \\ \text{sgn}(h_j(\mathbf{x})) &= b_q^j, \quad \forall j \neq i, j \in 1:N\}. \end{aligned} \quad (13)$$

with $A(h_i, p_q, p_s) = A(h_i, p_s, p_q) \subseteq \ker(h_i)$.

A *plant-event* denoted $(i+)$ or $(i-)$, $i \in 1:N$, occurs whenever the continuous trajectory $\mathbf{x}(\cdot)$ crosses the hypersurface $\ker(h_i)$, $h_i \in S_h^N$, in the positive or negative direction, respectively. A *sufficient condition* for the occurrence of a plant-event $(i+)$ at the time $t_e \in \mathbf{R}$ is

$$h_i(\mathbf{x}(t_e)) = 0 \wedge \dot{h}_i(\mathbf{x}(t_e)) > 0, \quad (14)$$

which means that, at $t_e \in \mathbf{R}$, the continuous trajectory $\mathbf{x}(\cdot)$ crosses $\ker(h_i)$ in the *positive* direction, from H_i^- to H_i^+ . A similar condition can be formulated for the plant-event $(i-)$. The *alphabet of plant-symbols* is

$$\tilde{Z} = \{z_{1+}, z_{1-}, \dots, z_{N+}, z_{N-}\} \cup \{\varepsilon\} \quad (15)$$

where ε is the *silent event* and the plant-symbol z_{i+}/z_{i-} , $i \in 1:N$, is sent through the generator whenever the associated plant-event $(i+)/(i-)$ occurs (Figure 3).

The *DES-plant* model is the automaton $G_p = \{\tilde{P}, \tilde{R}, f_p, \tilde{Z}, g_p\}$, where \tilde{P} is the set of discrete states, \tilde{R} is the *input* alphabet of control-symbols, \tilde{Z} is the output alphabet of plant-symbols, $f_p : \tilde{P} \times \tilde{R} \rightarrow 2^{\tilde{P}}$ is the state transition function and $g_p : \tilde{P} \times \tilde{P} \rightarrow \tilde{Z}$ is the output function. The dynamical equations are: $p(k+1) \in f_p(p(k), r(k))$, $g_p(p(k), p(k+1)) = z(k+1)$, where $\forall k \geq 0$, $p(k), p(k+1) \in \tilde{P}$, $z(k+1) \in \tilde{Z}$, $r(k) \in \tilde{R}$. If $p(k) = p(k+1)$, i.e. if no hypersurface is crossed, then $z(k+1) = \varepsilon$, which is the *silent event*.

The *DES controller* is a deterministic Moore machine $G_c = \{\tilde{S}, \tilde{Z}, f_c, s_0, \tilde{R}, g_c\}$, where \tilde{S} is the finite set of discrete states, $s_0 \in \tilde{S}$ is the initial state, \tilde{Z} is the input alphabet, \tilde{R} is the output alphabet, $f_c : \tilde{S} \times \tilde{Z} \rightarrow \tilde{S}$ is the state transition function and $g_c : \tilde{S} \rightarrow \tilde{R}$ is the output function. The dynamical equations are: $f_c(s(k), z(k+1)) = s(k+1)$, with $s(0) = s_0$, $g_c(s(k+1)) = r(k+1)$, with $g_c(s(0)) = r(0)$, and $s(k), s(k+1) \in \tilde{S}$, $z(k+1) \in \tilde{Z}$, $r(k) \in \tilde{R}$, $\forall k \geq 0$.

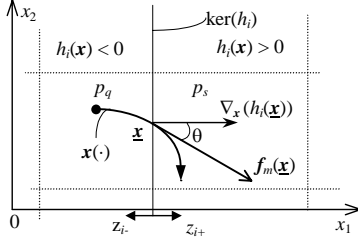


Figure 3. The occurrence of a plant event ($i+$) and of a discrete state transition $p_q \rightarrow p_s$ in a DES-plant - an example.

If there is no hysteresis, the DES controller coupled to the interface behaves like a switching control law

$$\mathbf{u}^*(\mathbf{x}) = F(\text{sgn}(h_1(\mathbf{x})), \dots, \text{sgn}(h_N(\mathbf{x}))), \quad (16)$$

with $F: \mathbf{R}^N \rightarrow \mathbf{R}^m$.

3.2 A criterion for the qualitative construction of the DES-plant model

Consider the following assumptions.

A0. In the HCS, the plant events do *not* occur simultaneously. \diamond

A1. (*absence of inflexion points at the crossing moments*). Given $\forall h_i \in S_h^N$, $\forall \mathbf{u}_m \in U \sim \tilde{R}$ and $\forall \mathbf{x}_0 \in X$, with $\mathbf{x}(\cdot)$ the solution of $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}_m)$, $\mathbf{x}(0) = \mathbf{x}_0$, the function $h_i \circ \mathbf{x}: \mathfrak{T} \rightarrow \mathbf{R}$, $\mathfrak{T} \subseteq \mathbf{R}$ interval, has the property: if $\exists t_e \in \mathfrak{T} \subseteq \mathbf{R}$ with $h_i(\mathbf{x}(t_e)) = 0$ and $[dh_i(\mathbf{x}(t))/dt]_{t=t_e} = 0$, then t_e is *not* an inflexion point. \diamond

A2. (*constant trajectories orientation on the crossing border*). $\forall p_q, p_s \in \tilde{P}$, $\forall \mathbf{u}_m \in U$, if p_q, p_s are adjacent on $\ker(h_i)$, $h_i \in S_h^N$, then, $\text{sgn}(\langle \mathbf{f}(\mathbf{x}, \mathbf{u}_m), \text{grad}_{\mathbf{x}}(h_i) \rangle)$ is constant for $\forall \mathbf{x} \in A(h_i, p_q, p_s)$. \diamond

A3. $\forall c_q \in C$ and $\forall \mathbf{u}_m \in U$, the family of solutions of $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}_m)$, $\mathbf{x}(0) = \mathbf{x}_0 \in c_q$ either crosses the border of c_q at some $t_e > 0$, or it remains within the cell c_q . \diamond

Consequence of A1: the trajectories do not pass through the intersection of two or several hypersurfaces of the partition (7). \diamond

Denote in (5)

$$\mathbf{f}_m(\mathbf{x}) = \mathbf{f}(\mathbf{x}, \mathbf{u}_m), \quad \forall \mathbf{u}_m \in U. \quad (17)$$

Assuming that **A0** is true, a plant-event ($i+$) occurs if and only if $\exists \underline{\mathbf{x}} \in \ker(h_i)$ and $r_m \in \tilde{R}$ s.t. $\mathbf{x}(t_e) = \underline{\mathbf{x}}$, $\mathbf{u}(t) = \gamma(r_m)$, $t \in (t_e^-, t_e^+)$ and $\mathbf{f}_m'(\underline{\mathbf{x}}) \cdot \nabla_{\mathbf{x}}(h_i) > 0$ [Oltean, et al., 2000], as illustrated in Figure 3 (and similarly ($i-$)). Also, in

$$(15), \dot{h}_i(\mathbf{x}(t)) = \langle \nabla_{\mathbf{x}(t)}(h_i), \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t)) \rangle.$$

Criterion 1 [Oltean, et al., 2000]. Assume that **A0-A3** are true and consider $p_q, p_s \in \tilde{P}$ and $r_m \in \tilde{R}$ in G_p . Then: A) $p_s \in f_p(p_q, r_m) \Leftrightarrow p_q, p_s$ are adjacent on some $\ker(h_i)$, $h_i \in S_h^N$ and

$$b_q^i(\mathbf{f}_m'(\underline{\mathbf{x}}) \nabla_{\mathbf{x}}(h_i)) < 0, \quad \forall \underline{\mathbf{x}} \in A(h_i, p_q, p_s), \quad (18)$$

with b_q^i is the i^{th} component of $\mathbf{b}_q \in B$ and B) if $p_s \in f_p(p_q, r_m)$, then $g_p(p_q, p_s) = z_{i+} \in \tilde{Z}$ (or $z_{i-} \in \tilde{Z}$) $\Leftrightarrow b_q^i = -1$ (or $b_q^i = 1$, respectively). \diamond

Based on Criterion 1, the DES-plant automaton can be constructed *without integrating* the equations (5).

4 The qualitative model of the TGNR as a DES-plant abstraction in a HCS

Based on the HCS representation of the TGNR PL model, the discrete dynamics deduced from the DES-plant automaton is compared to the discrete dynamics in the GNA qualitative model, on one side, and to numerical simulation results of the PL TGNR model, on the other side

4.1 Construction of the DES-plant automaton

Based on the model (3) with constraints (4), consider the state space partition defined by

$$\begin{aligned} h_1(\mathbf{x}) &= x_1 - \theta_1^1, & h_2(\mathbf{x}) &= x_1 - \theta_1^2, \\ h_3(\mathbf{x}) &= x_2 - \theta_2^1, & h_4(\mathbf{x}) &= x_2 - \theta_2^2. \end{aligned} \quad (19)$$

Denote the control values in (3)

$$\begin{aligned} \mathbf{u}_1 &= (k_1, k_2)', & \mathbf{u}_2 &= (k_1, 0)', \\ \mathbf{u}_3 &= (0, k_2)', & \mathbf{u}_4 &= (0, 0)'. \end{aligned} \quad (20)$$

and, with notation (17), define

$$\begin{aligned} \mathbf{f}_1(\mathbf{x}) &= (k_1 - \gamma_1 x_1, k_2 - \gamma_2 x_2)', \\ \mathbf{f}_2(\mathbf{x}) &= (k_1 - \gamma_1 x_1, -\gamma_2 x_2)', \\ \mathbf{f}_3(\mathbf{x}) &= (-\gamma_1 x_1, k_2 - \gamma_2 x_2)', \\ \mathbf{f}_4(\mathbf{x}) &= (-\gamma_1 x_1, -\gamma_2 x_2)'. \end{aligned} \quad (21)$$

The TGNR model (3) can be rewritten as

$$\dot{x}_1 = u_1(\mathbf{x}) - \gamma_1 x_1, \quad \dot{x}_2 = u_2(\mathbf{x}) - \gamma_2 x_2, \quad (22)$$

with the components of the *switching law* (16)

$$\begin{aligned} u_1(\mathbf{x}) &= 0.25k_1[1 - \text{sgn}(h_2(\mathbf{x}))][1 - \text{sgn}(h_3(\mathbf{x}))], \\ u_2(\mathbf{x}) &= 0.25k_2[1 - \text{sgn}(h_1(\mathbf{x}))][1 - \text{sgn}(h_4(\mathbf{x}))]. \end{aligned} \quad (23)$$

Based on the state space partition and on the qualitative states specified in Figure 4a and applying Criterion 1, the DES-plant model of the TGNR in Figure 4b is obtained.

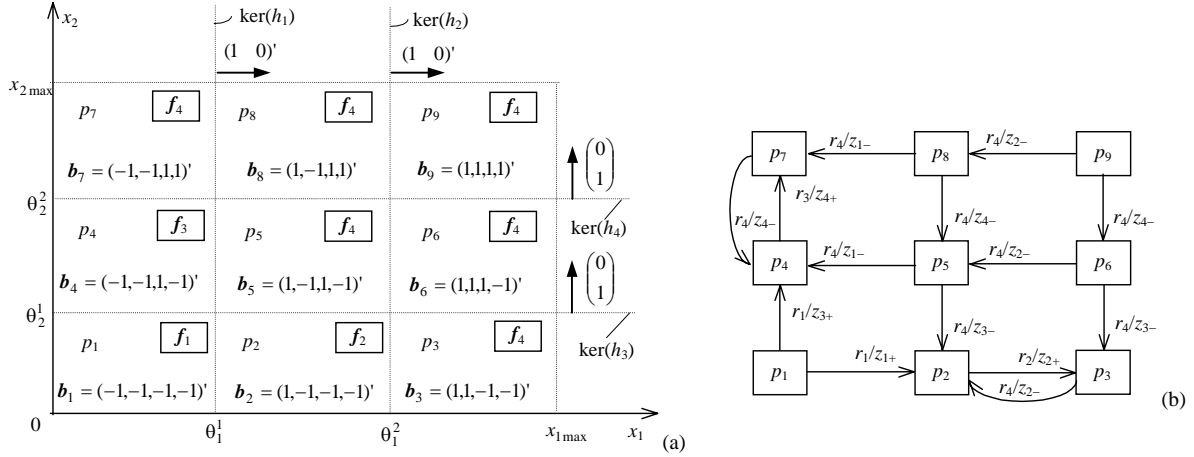


Figure 4. (a) The state space partition of TGNR in the HCS framework, including the qualitative states \mathbf{b}_i , the symbolic states p_i , $i = 1 : 9$ and the local continuous state velocities f_j , $j = 1 : 4$ (24). (b) DES-plant automaton of the TGNR.

For example the transition $p_1 \xrightarrow{z_{1+}^{r_1}} p_2$ takes place because p_1 and p_2 are adjacent on $\ker(h_1)$ and $\mathbf{b}_1^1(\mathbf{f}_1^1(\mathbf{x})\nabla_{\mathbf{x}}(h_1)) = -(k_1 - \gamma_1 x_1, k_2 - \gamma_2 x_2) \cdot \begin{pmatrix} 1 \\ 0 \end{pmatrix} < 0$ for $\forall \mathbf{x} \in \{\mathbf{x} \in \mathbf{R}^2 \mid x_1 = \theta_1^1 \wedge 0 < x_2 < \theta_2^1\}$.

Remark 1. Note that **A0** does not hold for the system (22)-(23). However, this assumption regards only isolated trajectories, so it is “generically” true. \diamond

4.2 MATLAB simulation experiments. A comparison with the GNA qualitative model

In contrast with the partition in Figure 4a, considered in the HCS framework, the partition proposed by de Jong and colleagues [2003a;b], within the GNA qualitative approach (Figure 5) includes, as studied domains, not only open regions, but also *isolated points* (like D^7) or *cell boundaries* (like D^6 or D^2); these are not taken into account as discrete states in the DES-plant automaton in Figure 4b. The corresponding differences are illustrated in the sub-graphs in Figure 6.

The results of simulation experiments based on MATLAB implementation of equations (22)-(23), are depicted in Figure 7 and 8. Despite that fact that the qualitative model in the HCS does *not* capture the trajectories evolving through the intersection of the partition hypersurfaces (see *Remark 1*), such continuous evolutions are generated in MATLAB, when implementing (22)-(23), as illustrated in Figure 7 by the trajectory started in \mathbf{x}_{03} .

In the GNA qualitative approach, there are trajectories ending on the switching domains D_4 and D^{16} , which belong in fact to the hypersurfaces of the partition.

In the HCS framework, simulation experiments

show that these trajectories switch on the boundary between two adjacent cells and execute a cycle between the corresponding discrete states of the DES-plant model: examples are the trajectories starting in \mathbf{x}_{01} and \mathbf{x}_{02} in Figure 7 and also all the trajectories in Figure 8.

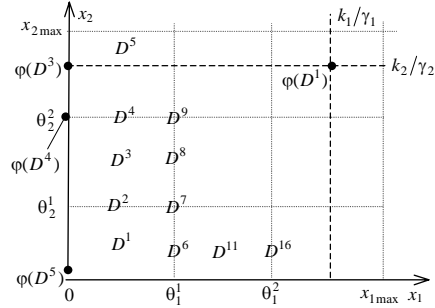


Figure 5. State space partition in [de Jong et al., 2003]: $\varphi(D^i)$ - target equilibria of the regulatory domains D^i , $i = 1 : 3$; D^2 , D^4 - switching domains; compared to Figure 4a, $D^7 = \ker(h_1) \cap \ker(h_3)$.

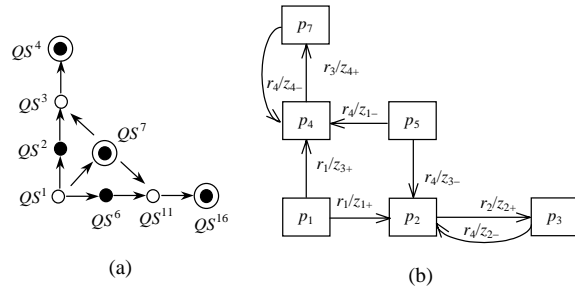


Figure 6. (a) Transition graph resulting from GNA simulation of the TGNR starting in D^1 , QS^i - qualitative states associated to D^i in Figure 5, respectively; (b) the sub-graph corresponding to the DES-plant model in Figure 4b; D^7 (QS^7) has no correspondent.

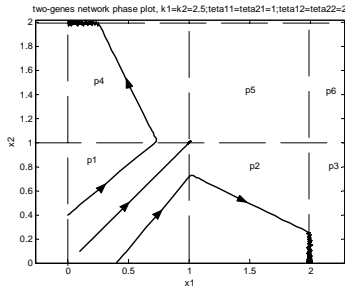


Figure 7. Simulation experiment of the TGRN system started in p_1 : the qualitative evolutions are $p_1(p_2p_3)^*$ for $x_{01} = (0.4, 0)'$, $p_1(p_4p_7)^*$ for $x_{02} = (0, 0.4)'$; for $x_{03} = (0.1, 0.1)'$ the trajectory ends at $\ker(h_1) \cap \ker(h_3)$.

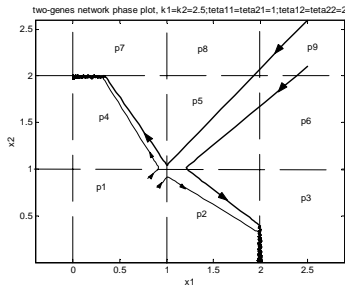


Figure 8. Simulation experiment of the TGRN system: the qualitative evolutions starting in p_1 (thin lines) are $p_1(p_2p_3)^*$ for $x_{01} = (0.9, 0.8)'$; $p_1(p_4p_7)^*$ for $x_{02} = (0.8, 0.9)'$; the qualitative evolutions starting in p_9 are $p_9p_8p_5(p_4p_7)^*$ for $x_{03} = (2.5, 2.6)'$ and $p_9p_6p_5(p_2p_3)^*$ for $x_{04} = (2.5, 2.1)'$.

5 Concluding remarks

The study of qualitative models is important for behaviour prediction in systems biology, where in general parameter values are known only to reside within regions or intervals. In state space terms, biochemical interaction processes are usually adequately described by classes of PL differential systems, with protein concentrations as state variables and first-order discontinuous functions in the right-hand side. Qualitative modelling firstly implies building a state space partition, based on the threshold limits in the discontinuous functions. The resulting model has discrete states and discrete transitions.

Starting from the hybrid nature of a family of genetic regulatory networks models, for which de Jong and colleagues has proposed GNA qualitative approaches [2003a;b], this paper introduces an alternate procedure for qualitative model building, with origins in a framework in control engineering.

In contrast with the GNA qualitative model, the proposed partitioning takes into account only *open regions* as domains or *cells*, which drives to a less detailed but more robust qualitative model. Within the limits of assumptions **A0-A3**, the qualitative evolutions of the TGRN studied example are successfully checked against MATLAB simulation experiments. Only **A0** does not hold for the studied

TGNA model, but the referred trajectories are isolated. If the qualitative evolution of the DES-plant model comprises a final cycle between two discrete states, this corresponds to switching of the simulated continuous trajectory on the adjacency boundary between the corresponding open cells.

Also, if the assumptions **A0-A3** hold, the construction procedure is simple and robust, and does not imply exact knowledge of numerical values for systems parameters: a discrete transition models a family of continuous trajectories crossing the boundary between adjacent domains. Deducing a discrete transition in the DES-plant model implies only the evaluation of the *sign of the scalar product* between the state velocity and the gradient of the crossed hypersurface on the adjacency boundary. Thus it is enough to know if the system parameters meet algebraic inequality-like constraints.

Future research directions imply the investigation of procedures for automated DES-plant model construction, in view of behaviour prediction of high order PL models. Also, automated testing of **A0-A3** can be considered for classes of differential systems.

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