Correspondence between discrete and piecewise linear models of gene regulatory networks

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Abstract

We know that some proteins can regulate the expression of genes in a living organism. The regulation of gene expression occurs through networks of regulatory interactions in a non linear way between DNA, RNA, proteins and some molecules, called genetic regulatory networks. It is becoming clear that mathematical models and tools are required to analyze these complex systems.

In the course of his study on gene regulatory networks R. Thomas proposed a discrete framework that mimics the qualitative evolution of such systems. Such discrete models are of great importance because kinetic parameters are often non measurable *in vivo* and available data are often of qualitative nature. Then Snoussi proved consistency between the discrete approach of R. Thomas and Piecewise Linear Differential Equation Systems, which are easy to construct from interaction graph and thresholds of interactions.

Our work focuses on the relationships between both approaches: we will prove a result of correspondence between the two models. Finally, we will give some short description of a Maple program which can compute a discrete path, given the ordinary differential equation and starting box.

Supplementary information: The code for computing discrete path and instructions to use it are available on http://math.unice.fr/∼diener/.

1 Introduction

A gene regulatory network is a set of genes coding for proteins (i.e. each gene expresses itself and produces a specific protein) able to activate or inhibit the expression of the other genes of the set. As the number of genes of the interacting networks is usually high, the possible interactions between them build a network of interactions so complex and intricated that it becomes really difficult to predict for example the consequences on the whole network of the over expression of one gene or under expression of another. Building simplified computational models is thus required to understand the dynamic of these networks.

The most obvious method to model such a network consists of a description in term of systems of differential equations. But as the interactions between genes are considered as non linear and as most of the parameters of the differential equations are impossible to identify, it remains difficult, if not impossible, to understand the dynamic and to predict the behavior of the different genes even knowing the form of the differential model, unless one can simplify the description.

In the early seventies, two kinds of simplified models have been introduced on the same idea: the activation or inhibition of one gene on the expression of another gene have a sigmoid profile which means that the regulation is essentially inefficient when the concentration of the active gene is below a threshold value, its effect increases rapidly around this threshold value and is

saturated for higher concentration. With this in mind, Glass and Kauffman [4] have introduced a special class of piecewise linear differential equations, replacing the sigmoids in the differential equations by Heaviside functions. This leads to a discontinuous system of differential equations that is much more tractable than the original smooth ones. Piecewise linear models have been intensively studied (see [11] for example) and produce lots of interesting results. Another class of even more radically simplified models, the so called *logical models* or *discrete models*, introduced by René Thomas [10], is also build on an on/of version of the regulations but in keeping only in the model the description of the dynamic through a boolean interaction graph. This over simplification is shown to be especially useful in allowing automatic explorations of all possible interactions with a computer ([2],[1] for example).

In this paper we will first present, and illustrate with two typical examples, the two approaches, the piecewise linear and the discrete. Then we will prove a result of correspondence between the two models. Doing this we follow a work of Snoussi [8] who first introduced what he called a *discrete mapping* that maps each piecewise linear differential model to a corresponding discrete model in an automatic way. It is thus important to describe precisely what information contained in the piecewise linear differential model is kept by the discrete model and what is lost.

2 Two examples of gene regulatory networks

Before introducing the general form of the piecewise linear differential model we consider here, let us just show first two typical examples, one is an example of what is called a biological switch and the other example of a biological cycle. These both cases, are only toy examples (with arbitrary chosen coefficients), just for illustration.

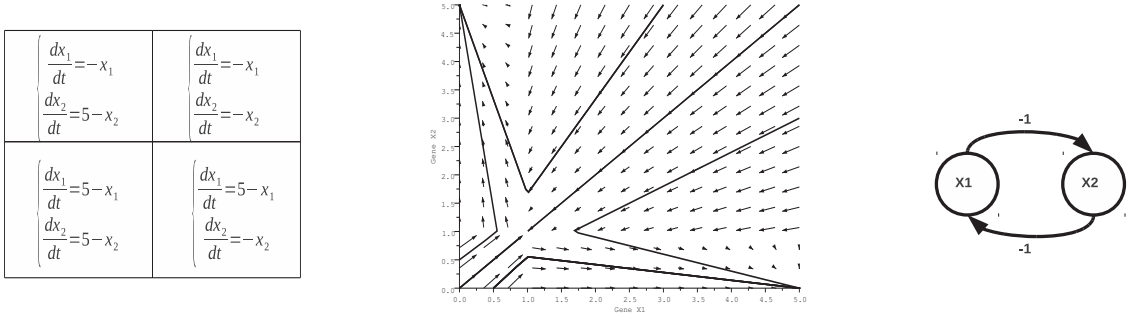

Figure 1: An example of biological switch: the choice of the parameters here is $\gamma_1 = \gamma_2 = \theta_2^1 = \theta_1^2 = 1$ and $k_1^0 = k_2^0 = -k_1^2 = -k_2^1 = 5$. There are 4 boxes in which the differential system is linear, $]0,1[^2$, $]1,5[\times]0,1[$, $]0,1[\times]1,5[$ and $]1,5[^2$. It happens that all trajectories with initial point "below" the diagonal converge to the stable node $(5,0)$ and all the trajectories with initial point above the diagonal converge to the other stable node $(0,5)$. There is a third equilibrium on the diagonal, $(1,1)$, which is a saddle point of the dynamic.

2.1 Example of a biological switch

The first example consists in two genes X_1 and X_2, whose respective level of expression at time t are denoted by $x_1(t)$ and $x_2(t)$ (level of concentration in the two produced proteins). The

model of the dynamic takes into account several effects. First a negative action (inhibition) of the protein produced by the gene X_2 on the expression of the gene X_1, described by

$$\frac{dx_1}{dt} = k_1^0 + k_1^2 I(\theta_2^1, x_2)$$

where k_1^0 is the level of expression of X_1 when X_2 is absent (or inefficient), θ_2^1 is the threshold value of the level of expression of X_2 beyond which the X_2 inhibition of X_1 is assumed to be efficient, k_1^2 is the level of that inhibition and $I(\theta, x)$ is the Heaviside function (equal to 0 for $x < \theta$ and 1 for $x \geq \theta$). A second effect taken into account is the degradation of the protein produced by X_1. The rate of degradation is usually assumed to be proportional to the concentration $x_1(t)$ and then described by

$$\frac{dx_1}{dt} = -\gamma_1 x_1$$

We assume the dynamic of the second gene similar: inhibition by the other gene and decreasing of the level of concentration of its protein due to degradation. This leads to the following differential system:

$$\left\{ \begin{array}{rcl} \frac{dx_1}{dt} & = & k_1^0 + k_1^2 I(\theta_2^1, x_2) - \gamma_1 x_1 \\ \frac{dx_2}{dt} & = & k_2^0 + k_2^1 I(\theta_1^2, x_1) - \gamma_2 x_2 \end{array} \right. \quad (1)$$

It is easy to see that the two thresholds θ_1^2 and θ_2^1 cut the phase space $[0, max_1] \times [0, max_2]$ in 4 domains (or rectangular boxes) in which the differential system is simply linear with constant coefficients and thus easy to solve explicitly. It remains to stick together the trajectories in between the 4 domains to have a good picture of the global behavior (see figure 1). With the chosen set of parameters, the system has two stable equilibrium and an additional equilibria of saddle point type that create for the trajectories a possible switch from one stable equilibrium toward the other one when the initial conditions $(x_1(0), x_2(0))$ change: indeed a small modification of the initial conditions, just crossing the diagonal, is enough to completely modify the evolution of the system. This is the phenomenon of *bistability* or *biological switch*[1]: in one case[2], the system converges to one equilibrium corresponding to a maximal level of expression of X_2 and about no expression of X_1 and in the other case[3], the level of expression of X_1 is maximal and there is about no expression of X_2.

2.2 Example of a biological cycle

The second example is still an example with two genes X_1 and X_2 but we assume now that X_1 activates X_2 and that X_2 activates itself and inhibits X_1. This leads to the following model:

$$\left\{ \begin{array}{l} \frac{dx_1}{dt} = k_1^0 + k_1^2 I(\theta_2^1, x_2) - \gamma_1 x_1 \\ \frac{dx_2}{dt} = k_2^1 I(\theta_1^2, x_1) + k_2^2 I(\theta_2^2, x_2) - \gamma_2 x_2 \end{array} \right. \quad (2)$$

[1]This example is a simplified model of the following situation : the bacteriophage Lambda is a virus able to get into the cell of the Escherichia Coli bacteria and to multiply. The infection of the bacteria by the phage either leads to the destruction of the bacteria (lytic pathways) through a kind of explosion of the cell producing a huge amount of phages able to infect new bacterias, either to a silent integration of the phage genome into the bacteria genome (lysogenic pathway). In the last case, the bacteria will continue to reproduce itself as usual being now resistant to new infection. The choice between lytic and lysogenic pathways is regulated by two antagonist proteins, the protein CI responsible for the lysogenic pathway and the protein CRO responsible for the lytic pathway. These two proteins are encoded by two genes, *ci* and *cro*, whose expression is mutually inhibited by the other.

[2]which corresponds to the lytic pathway

[3]which corresponds to the lysogenic pathway

where the constants have the same meaning as in the first example.
As in the first example, this system is piecewise linear on four boxes delimited by the thresholds.

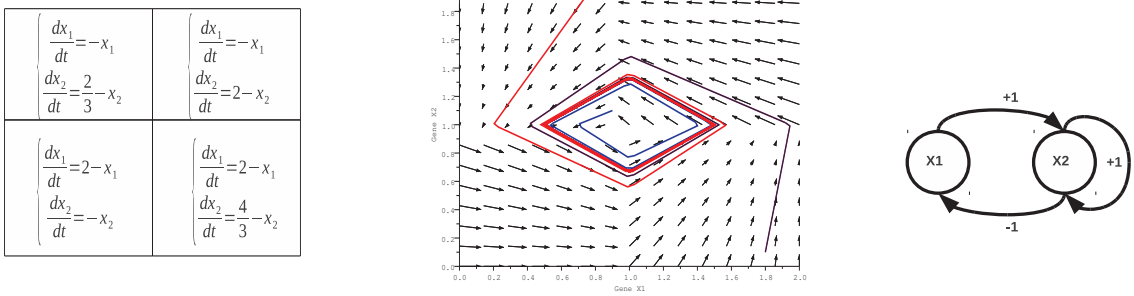

Figure 2: An example of biological cycle: the choice of the parameters here is $\gamma_1 = \gamma_2 = \theta_2^1 = \theta_1^2 = \theta_2^2 = 1$, $k_1^0 = -k_1^2 = 2$, $k_2^1 = \frac{4}{3}$ and $k_2^2 = \frac{2}{3}$. There are 4 boxes in which the system is linear. Whatever its initial condition, all trajectories will spiral toward a unique limit cycle.

It is easy to compute the trajectories in each box and to stick them end to end at the border of the boxes. For a particular choice of the parameters, one can prove that there is a unique attractive cycle (see figure 2), just in computing the first return Poincaré map explicitly.

3 The piecewise linear model

In the paper [3], from which we will adopt here some notations, the piecewise linear model for gene regulatory network we consider is called a *Glass model* because it has been introduced by Glass and Kauffman in [4]. The general form of this model of n genes $X_1, X_2, \ldots, X_n$ is given by

$$\frac{dx}{dt} = f(x) - \Gamma x \tag{3}$$

where $x(t) = (x_1(t), x_2(t), \ldots, x_n(t))$ represents the concentrations of the proteins produced by the n genes, $f(x)$ is a vector whose i^{th} component $f_i(x_1, x_2, \ldots, x_n)$ represents the rate of synthesis of the i-th gene (which depends on the action of the other genes) and Γ is a diagonal matrix whose diagonal coefficients $\Gamma_i^i = \gamma_i$ are the degradation rates of genes. As in the two examples, the rate of synthesis f_i of each gene X_i is the sum of a constant term which represent a basal synthesis rate of this gene and the aggregated contribution of all the genes (including possibly itself) that activate or inhibit it.

$$f_i(x_1, x_2, \ldots, x_n) = k_i^0 + \sum_{j \in T_i} k_i^j I(\theta_j^i, x_j) \tag{4}$$

The numbers θ_j^i are the threshold values of the action of gene X_j on the expression of gene X_i and the coefficient k_i^j is positive when gene X_j is an activator of gene X_i and negative when it is an inhibitor. The sum is on all indices j such that the gene X_j either activates or inhibits the expression of the gene X_i. We denote by T_i, the set of all these indices. Being a concentration of protein, each quantities $x_i(t)$ ranges in some interval $[0, max_i]$ and thus the differential system will be considered only in the bounded domain $\mathcal{B} = \prod_{i=1}^n [0, max_i]$ called the *phase space* of the continuous model. The different thresholds break down the phase space $\mathcal{B}$ in several boxes where the differential system is simply linear (affine) (and thus easy to solve explicitly).

For each $j = 1, \ldots, n$, the set of all thresholds θ_j^i can be ordered in $\sigma_0^j < \sigma_1^j < \sigma_2^j < \ldots < \sigma_{s_j}^j < \sigma_{s_j+1}^j$ where we add $\sigma_0^j = 0$ and $\sigma_{s_j+1}^j = max_j$ as a boundary of the boxes and the different boxes are defined by the following system of n double inequalities:

$$\left\{ \begin{array}{lcccl} \sigma_{s_1}^1 & < & x_1 & < & \sigma_{s_1+1}^1 \\ \ldots & & \ldots & & \ldots \\ \sigma_{s_n}^n & < & x_n & < & \sigma_{s_n+1}^n \end{array} \right. \tag{5}$$

The multi integer (vector of integers) $s = (s_1, s_2, \ldots, s_n)$ which is an element of the set $S = \prod_{j=1}^n \{0, 1, \ldots, s_j\}$ is a level for the different boxes of the phase space $\mathcal{B}$ that we call a *state* of the network. In the piecewise linear model, there is only a finite number of states for the dynamic. Each of them corresponds to one box $\mathcal{B}_s$ of the phase space, delimited by a lower multi threshold $\sigma(s) = (\sigma_{s_1}^1, \ldots, \sigma_{s_n}^n)$ and an upper multi threshold $\sigma(s+\mathcal{I}_n) = (\sigma_{s_1+1}^1, \ldots, \sigma_{s_n+1}^n)$ where $\mathcal{I}_n$ is the vector having all its components equal to 1. The main point is that, in each box $\mathcal{B}_s$, the model (3) is given by the simple linear system

$$\left\{ \begin{array}{lcccl} \frac{dx_1}{dt} & = & k_1(s) & - & \gamma_1 x_1 \\ \ldots & & \ldots & & \ldots \\ \frac{dx_n}{dt} & = & k_n(s) & - & \gamma_n x_n \end{array} \right. \tag{6}$$

where $k_i(s) = f_i(x_1, \ldots, x_n)$ is the value of the synthesis rate f_i in the box B_s. Thus the solutions in the box are easy to compute

$$x_i(t) = \frac{k_i(s)}{\gamma_i} + e^{-\gamma_i t}(x_i(0) - \frac{k_i(s)}{\gamma_i}) \tag{7}$$

for all $i = 1, \ldots, n$, and it is immediately obvious that, inside each box, all solutions tend to a stable equilibrium called the *focal point* of the box. Let's denote $\phi(s) = (\frac{k_1(s)}{\gamma_1}, \ldots, \frac{k_n(s)}{\gamma_n})$ the focal point of $\mathcal{B}_s$. It can be either inside $\mathcal{B}_s$ (including its boundary), if it satisfy the set of double inequalities (5) and it is then a stable equilibrium of the whole dynamic, either outside (in another box $\mathcal{B}_{s'}$, with $s' \neq s$) and in this case the trajectories follow the dynamic given by (7) as long as they have not reached the boundary of $\mathcal{B}_s$ and will simply switch to the new dynamic of the next box when crossing the boundary.

Remark One difficulty with piecewise linear systems of differential equations like our model here is that they are discontinuous differential equations, and, as such, do not behave like smooth systems of differential equations regarding the question of existence and unicity of the solutions. More precisely, it can happens that the boundary between two boxes is a so called *black wall* when the solutions in both boxes point towards the boundary in such a way that it becomes impossible from each side to exit the box and enter the other. When this happens, one can nevertheless define properly a concept of solutions for such piecewise linear system using the Philipov theory of singular (and set valued) solutions, as explained by Gouzé and Sari in [6].

In this paper nevertheless, we will not consider such singular solutions because we will ever stay away from any black wall. All the solutions we will consider will be build only in putting end to end the boundaries of the boxes, the usual (i.e.well defined) solutions inside the different boxes.

Let us make precise what we consider here as a (regular) solution of (3).

Definition A continuous function $(x(t) = (x_1(t), x_2(t), \ldots, x_n(t))$ defined on an interval $t \in [t^-, t^+]$ is called a *regular solution* of (3) if it is differentiable except for at a finite number of points $t^- = t^0 < t^1 < \ldots < t^L < t^{L+1} = t^+$ and satisfy the equation (3) on each open interval $]t^l, t^{l+1}[$ for $l \in \{0, 1, \ldots, L-1\}$.

In restricting our attention to these solutions only, we loose other kind of (singular) solutions, that could exists also, the ones that spend time inside the boundaries of the boxes. But this is singular behavior that we will not consider here.

4 The discrete model

Before introducing the discrete model, let us remark that it is not necessary to start from the piecewise linear model to introduce the discrete model as we will do here. Indeed, even if it was introduced by R.Thomas as a simplification of the (smooth) systems of differential equations used by the biologists, often much too difficult to study by themself, the discrete model have been develop and used successfully as a model of gene regulatory networks without any connection with a piecewise linear model. Nevertheless we will introduce it here, following Snoussi[8] as a discrete version of a piecewise linear model because we do not need to be more general.

4.1 Snoussi's discrete mapping

The first idea, starting with a piecewise linear model (3), is to introduce a directed graph whose vertices are the states $s \in \mathcal{S}$ (one state per box) and whose edges are the transitions $(s \to s')$, where $s' \in \mathcal{S}$ is the state corresponding to the focal point $\phi(s)$ of the box $\mathcal{B}_s$. This application from $\mathcal{S}$ to $\mathcal{S}$ that map each state s to the state s' of its focal point is what Snoussi called the discrete mapping in [8].

But it is easy to understand that this model does not adequately reflect the piecewise linear dynamic except when $\mathcal{B}_s$ and $\mathcal{B}_{s'}$ are two neighboring boxes. Indeed, as soon as the flow exits $\mathcal{B}_s$ to enter the next box, it is driven by a new dynamic and tends to a focal point which is usually no longer $\phi(s)$. This is why Thomas and Snoussi leave this first description, called synchronous, for an asynchronous one, the *State Transition Graph*, or simply *Transition Graph*.

4.2 The transition graph

The transition graph associated with model (3) is the directed graph defined from the previous one with the same vertices $s \in \mathcal{S}$ and with each edge $(s \to s')$ replaced, when s' is not a neighboring state, by one or several edges from s to neighboring states in the following way. Let denote by e^i for any $i \in \{1, \ldots, n\}$ the state having only zero as component except the i^{th} that is equal to 1 and let define $\tau_i^+(s) = s + e^i$ and $\tau_i^-(s) = s - e^i$. In the transition graph each age $(s \to s')$ of the initial synchronous graph will be replaced, except if $s' = s$ or if s' is already a neighboring state, by one edge $(s \to \tau_i^+(s))$ for each i such that the i^{th} component of $\phi(s) - s$ is strictly greater then 1, and one edge $(s \to \tau_i^-(s))$ for each i such that the i^{th} component of $\phi(s) - s$ is strictly lower than -1.

For example, the transition graphs of the two previous examples are given by :

$$\begin{array}{ccc} 01 & \longleftarrow & 11 \\ \uparrow & & \downarrow \\ 00 & \longrightarrow & 10 \end{array} \qquad\qquad \begin{array}{ccc} 01 & \longleftarrow & 11 \\ \downarrow & & \uparrow \\ 00 & \longrightarrow & 10 \end{array} \quad .$$

The first transition graph contains in fact two additional edges, one is $(01 \to 01)$ and the other $(10 \to 10)$, not drawn in the picture.

It appears that, even very simple, transition graphs are useful for the study of gene regulatory network because they keep the main features of the piecewise linear (or smooth) model but they are much more tractable. They probably contribute to the discovery by R.Thomas of the decisive role of negative and positive circuits that remain one of the main result of the theory

of gene regulatory network. Let us recall here this result as a comment on the choice of our two introductory examples. When a gene exerts an influence on the rate of production of a second one who exerts an influence on the production of a third one, and so on, who finally exerts an influence on the first gene itself, they build a network called a *feedback circuit*. There are in fact two kinds of such circuits that have very contrasting roles in the regulatory networks. The presence of the first one, called *positive* because the number of inhibitions is even (as in our first example with two inhibitions), appears to be a necessary condition for multistationarity while the presence of the second, called *negative* because this number is odd (as in our second example), is a necessary condition for the existence of an attractor (such as a limit cycle). These properties have been proved in the mean time (see for example [9],[5],[7]).

5 A correspondence result

In [8], Snoussi studied two simple situations where the information contained in the transition graph are sufficient to deduce, from the knowledge of it only, the dynamic of the original piecewise linear model. The first is the case of a stable equilibrium (if in the transition graph one has an edge $(s \to s)$, then the former system has a stable equilibrium (the converse is obvious) and the second is the case of a particular negative feedback circuit. In this particular case, the focal point of each box $\mathcal{B}_s$ belongs to the next box (the naïve (synchronous) transition graph is already a complete (asynchronous) transition graph.

On the other hand, it is easy to understand that given any path in the transition graph, it is not always true that the flow of the piecewise linear model follows the corresponding sequence of boxes/states. If the transition graph is for example the following:

$$\begin{array}{ccccc} 01 & \longleftarrow & 11 & & 21 \\ \downarrow & & \uparrow & & \uparrow \\ 00 & \longrightarrow & 10 & \longrightarrow & 20 \end{array} \quad .$$

and if we attach our attention to the sequence of edges from 00 to 10 and from 10 to 20, different dynamics can happens for the piecewise linear model. Either some trajectories starting in the box $\mathcal{B}_{00}$ will enter the box $\mathcal{B}_{20}$ after passing through the box $\mathcal{B}_{10}$ (the others will go up to $\mathcal{B}_{11}$) or none of them will reach $\mathcal{B}_{20}$ (all will go up). Thus it is clear on this example that the path $00 \to 10 \to 20$ that exists in the transition graph do not represent well the dynamic of the model. The same conclusion holds for the path $00 \to 10 \to 11$ for which it is either some or possibly all the solutions that are captured by the dynamic of this path. In both cases, the knowledge of the discrete dynamic only do not allow to understand the original dynamic. This is because the transition graph contains two vertices leaving $\mathcal{B}_{10}$, one toward $\mathcal{B}_{11}$ and one toward $\mathcal{B}_{20}$ (as the focal point of the box $\mathcal{B}_{10}$ belongs to $\mathcal{B}_{21}$). This kind of ambiguity are the origin of the problem.

We will state now a sufficient condition on the paths of the transition graph to avoid such an ambiguity. This is the object of the following correspondence result. The sufficient condition is close to the one introduce in [3] (to prove the existence and unicity of a limit cycle), called alignment of the focal points but it is not exactly the same we consider here.

Theorem 5.1 *Consider a piecewise linear model (3), L an integer and let s^1, s^2, ...s^L be a discrete path of length L belonging to the transition graph associated with the model.*

Assume that

1. *each vertex* s^l, $l = 1, \ldots, L-1$, *is* simple, *in the sens that it is only connected with* s^{l+1} *and there is no other edge* $(s^l \to s)$, *for* $s \neq s^{l+1}$, *in the transition graph*
2. *for any edge* $(s^l \to s^{l+1})$ *in the discrete path, the next edge (if any, i.e. if* $l < L-1$*) is not* $(s^{l+1} \to s^l)$

Then for any point $x_0 \in \mathcal{B}_{s^1}$, *not in the boundary of* $\mathcal{B}_{s^1}$, *there is a unique solution of the piecewise linear dynamic* $x(t)$ *defined for* $t \in [0, t^L]$, *with* $x(0) = x_0$, $x(t^L) \in \mathcal{B}_{s^L}$ *and such that* $x(t)$ *will cross successively* $\mathcal{B}_{s^2}$, $\mathcal{B}_{s^3}$, $\ldots$,$\mathcal{B}_{s^{L-1}}$.

Proof Let us first recall that the dynamic of the piecewise linear model is defined in each box $\mathcal{B}_s$ of the phase space by the linear system (6) which is a smooth differential system with well defined solutions in the whole space. As long as a solution stays inside a box, there is no problem for existence and unicity but we need to say what happens for the solution at the boundaries of the boxes. Notice first that any solution of the linear system starting at a point of the boundary of the box either enter the box when t increases or exits the box or neither enter nor exit (possible behavior for points "in the corners"). If all the points of one face, not belonging to the boundary of the face, are initial points of solutions that enter the box, we will call this face an *entrance face*, and same for *exit faces*. Usually, a face of a box is neither an entrance nor an exit face because it contains together initial points of solutions that enter and that exit.

We will show first the following lemma :

Lemma 5.2 *When a vertex* s *of the transition graph is simple (assumption 1 of the theorem), its associated box* $\mathcal{B}_s$ *has a unique exit face and* $2n-1$ *entrance faces unless it contains its own focal point in which case all the faces of the box are entrance faces.*

Proof Let's denote by $s \to s'$ the unique edge starting from the state s. According to the definition of a transition graph, either $s' = s$ or $s' = \tau_i^{\pm}(s)$ for some $i \in \{1, \ldots, n\}$. The case when $s' = s$ corresponds to the case where the focal point of B_s belongs to B_s itself. It has been already noticed by Snoussi that, in this case the focal point is a stable equilibrium of the global dynamic and this implies that all solutions tend to the focal point, staying in B_s. All faces of B_s are then entrance faces.

Now, assume for example that $s' = \tau_i^+(s)$. Let's call the i^{th} *beam* of the box the set defined by the same set of inequalities then the box (5),

$$\sigma(s) \leq x \leq \sigma(s + I_n)$$

except the i^{th} one, $\sigma^i_{s_i} \leq x_i \leq \sigma^i_{s_i+1}$, replaced by $\sigma^i_{s_i} \leq x_i < +\infty$. This beam is an unbounded domain containing the box that also contains its focal point as $s' = \tau_i^+(s)$ because in this case, s' and s differs by only their i^{th} component. As we know the exact solution inside B_s, it is easy to see that each component tends monotonously to the focal point and thus will satisfy all inequalities that define the beam until it leaves the box. This shows that any solution starting in the box will leave it when crossing the face $x_i = \sigma^i_{s_i+1}$, including the solutions starting on any other faces than this one. Thus this face is indeed the only exit face.

This lemma shows the dynamic inside the boxes. The next lemma explain how to stick together the dynamic of two successive boxes.

Lemma 5.3 *Let* $(s^l \to s^{l+1})$ *an edge of the transition graph between two simple vertices (satisfying assumption* 1*) and satisfying also assumption* 2*. Then for any point* $x^l \in \mathcal{B}_{s^l}$, *not in the boundary of* $\mathcal{B}_{s^l}$, *there is a unique regular solution of the piecewise linear dynamic* $x(t)$ *defined for* $t \in [t^l, t^{l+1}]$, *with* $x(t^l) = x^l$, $x(t^{l+1}) \in \mathcal{B}_{s^{l+1}}$.

Proof The solution starting at x^l, well define and unique as long as it stays in B_{s^l}, will exit B_{s^l} through its unique exit face according to assumption 1 and the previous lemma. This exit face is also a face of the next box, $B_{s^{l+1}}$ and the assumption 2 make impossible that it is the exit face of this box too. Thus it is an entrance face of $B_{s^{l+1}}$ and the exit point from B_{s^l} of the solution we consider is then an initial point of a solution of $B_{s^{l+1}}$, well defined and unique. To build the regular solution we want it suffices to put end to end the two solutions until any point $x^{l+1} \in B_{s^{l+1}}$ in order to build a continuous function that is a regular solution.

To prove the theorem, consider any discrete path s^1, s^2, $...s^L$ of length L belonging to the transition graph of the piecewise linear model that satisfy the two assumptions and take any point in the box B_{s^1}. Follow its solution defined in B_{s^1} up to the unique exit face of this box which exists according to the first lemma and which as to be an entrance face of the next box B_{s^2} according to the second lemma. This allows one to define by continuity the solution in a unique way up to a point belonging to B_{s^2}. Starting again from this point, the same argument allows one to define the solution uniquely up to a point of B_{s^3} and so on. As the same reasoning can be repeated for each vertex of the discrete path, the theorem is proved.

6 Computation (using a MAPLE program) of a discrete path given the ordinary differential equation (3) and a starting box

We are concerned in finding out a set of procedures which can provide us automatically whether there exist a closed path or not and given L, it can find out a discrete path of length L starting from a first box. In the MAPLE program we first input the equation (3), all k_i^j's, θ_j^i's, γ_i's and $\mathcal{B} = \prod_{i=1}^n [0, max_i]$. Here, partition of the $\mathcal{B}$ produces several boxes. If one enter as initial condition of a path, any of these boxes and the length L of a path then the program return the path of the Transition graph beginning at the initial box and of length L except if one of the following conditions is not fulfilled for each box along the path:

1. the path exits the space $\mathcal{B}$
2. the hypothesis of being simple (as in the theorem 5.1) is not satisfied
3. the path reaches a stationary box before it reach the length L

The output of this program is like a numerical integration of a differential equation. The program is less precise but together with the theorem it shows the existence of a true trajectory. Hence, it is a tool for analyzing model like (3) of genetic regulatory network.

7 Conclusion

We have shown a sufficient condition for the existence and unicity of regular solutions of a piecewise linear model of gene regulatory network, expressed in terms of its transition graph. It shows that under easy to check assumptions, the considered path of the transition graph is a faithful representation of the piecewise linear flow. It is easy to find examples where these assumptions are not satisfied and nevertheless the conclusion of the theorem remains true. This gives the idea of possible extensions of this correspondence result to some more general cases especially the ones that needs a more careful study as ambiguities exist in the dynamic.

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