Algorithm for identification of piecewise smooth hybrid systems; application to eukaryotic cell cycle regulation

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Abstract. We discuss piecewise smooth hybrid systems as models for regulatory networks in molecular biology. These systems involve both continuous and discrete variables. The discrete variables allow to switch on and off some of the molecular interactions in the model of the biological system. Piecewise smooth hybrid models are well adapted to approximate the dynamics of multiscale dissipative systems that occur in molecular biology. We show how to produce such models by a top down approach that use biological knowledge for a guided choice of important variables and interactions. Then we propose an algorithm for fitting parameters of the piecewise smooth models from data. We illustrate some of the possibilities of this approach by proposing hybrid versions of eukaryotic cell cycle regulation.

Key words: systems biology, hybrid models, cell cycle

1 Introduction

Hybrid systems are widely used in automatic control theory to cope with situations arising when a finite-state machine is coupled to mechanisms that can be modeled by differential equations [MS00]. It is the case of robots, plant controllers, computer disk drives, automated highway systems, flight control, etc. The general behavior of such systems is to pass from one type of smooth dynamics (mode) described by one set of differential equations to another smooth dynamics (mode) described by another set of differential equations. The command of the modes can be performed by one or several discrete variables. The mode change can be accompanied or not by jumps (discontinuities) of the trajectories.

Depending on how the discrete variables are changed there may be several types of hybrid systems: switched systems [SWM$^+$07], multivalued differential automata [Tav87], differential equations with discontinuous vector fields [FA88], piecewise affine [DJGH$^+$04] and piecewise smooth systems [DB08]. Notice that

in the last two cases, the mode changes when the trajectories attain some smooth manifolds.

Piecewise affine hybrid systems have been used to model dynamics of gene networks [DJGH$^+$04,GRW07]. In these models, the gene variables evolve towards discrete values (attractors). The transient dynamics leading to attractors is considered to be piecewise affine where the linear part of the dynamical equations is defined by a diagonal matrix with negative entries. The transitions between discrete attractors are dictated by the relative position of the above variables with respect to some thresholds. Piecewise-affine hybrid models can be effectively used in verification studies, for instance computing the set of reachable states of a model. Identification of piecewise-affine models is a difficult problem approached elsewhere with various methods such as affine approximations of vector fields [DMT10] and discrete/continuous optimization algorithms [BBG00].

Although sufficient for certain applications like gene networks, piecewise affine models are less adapted to describe phenomena where the dynamics between two successive discrete events is strongly nonlinear. A typical example of such phenomena is the machinery of the cell cycle. Proteolytic degradation of the cyclins is switched on rapidly by the cyclin dependent kinase complexes but between two successive switchings the complexes have non-linear dynamics implying several positive (autocatalytic processes) and negative feed-back loops. These non-linear processes contribute to the robustness of the mechanism.

The idea of piecewise smooth systems arises naturally in the context of biochemical systems with multiple separated timescales. The dynamics of a multiscale, dissipative, large model, can be reduced to the one of a simpler model, called dominant subsystem [RGZL08,GRZ10,GR08]. The dominant subsystem depends on the comparison among the time scales of the large model. For nonlinear models, the dominant subsystem (which can be assimilated to a mode) is only piecewise constant and can change several times during the dynamics. The model reduction methods proposed in [GR08,RGZL08] generate dominant subsystems whose reactions rates are multivariate monomials of the concentration variables, like in the well-known S-systems [SV87]. Indeed, when applied to models using mass action kinetics, quasi-steady state and quasi-equilibrium approximations [GRZ10] lead to lumped models in which the reactions rates result from solving systems of polynomial equations. In general, these polynomials contain only a few terms (fewnomials). The solutions of such systems are much simplified in the case of total separation of the nonconstant terms in the fewnomials and lead to monomial rates. The rate of the same reaction can be represented by different monomials in different dominant subsystems (modes). For instance, the rate of a Michaelis-Menten mechanism depends linearly on the concentration of the substrate for small concentrations and is constant at saturation. We expect that more general rate laws [LUK10] can be treated similarly in our approach.

In this paper we propose a heuristic to construct appropriate modes and adequate piecewise smooth models by using a top-down approach. Then, we

show how the parameters of the hybrid model can be identified from data or from trajectories produced by existing smooth, but more complex models.

2 Hybrid models

We consider the so-called hybrid dynamical systems (HDS) consisting of two components: a continuous part, u, satisfying the equations

$$\frac{du_i}{dt} = f_i(u(t), s(t)), \quad t > 0, \tag{2.1}$$

where $u(t) = (u_1(t), u_2(t), ..., u_n(t)) \in \mathbf{R}^n$, and a discrete part $s(t) \in S$, where S is a finite set of states. We consider that there is an increasing series $\tau_0 = 0 < \tau_1 < \ldots < \tau_k < \ldots$ such that the discrete variables are piecewise constant on the intervals $[\tau_i, \tau_{i+1}[$ and that they change values at $t = \tau_k$. The continuous variables can also have discrete jumps at $t = \tau_k$.

Typically, in molecular networks, the continuous variables are protein concentrations and the discrete states may be gene or protein activities described by boolean variables $s(t) = (s_1(t), s_2(t), ..., s_m(t))$, where $s_j(t) \in \{0, 1\}$.

There are several possible ways to define the evolution of the s variables. Rather generally, this can be done by a time continuous Markov chain with transition probabilities $p(s, s', u)$ from the state s to the state s' (per unit time) depending on current state $u(t)$. However, in many molecular regulatory networks, transition probabilities dependence on u is not smooth. For instance, the probability for s to jump is close to one if u goes above some threshold value, and close to zero if u is smaller than the threshold. We can, in certain cases, neglect the transition time with respect to the time needed for u variables to change. Assuming that some of the discrete variables contribute to production of u and that other contribute to the degradation of u we obtain a general model of hybrid piece-wise smooth dynamical system

$$\begin{aligned} \frac{du_i}{dt} &= \sum_{k=1}^{N} s_k P_{ik}(u) + P_i^0(u) - \sum_{l=1}^{M} \tilde{s}_l Q_{il}(u) - Q_i^0(u), \\ s_j &= H(\sum_{k=1}^{n} w_{jk} u_k - h_j), \quad \tilde{s}_l = H(\sum_{k=1}^{M} \tilde{w}_{lk} u_k - \tilde{h}_l), \end{aligned} \tag{2.2}$$

where H is the unit step function $H(y) = 1$, $y \geq 0$, and $H(y) = 0$, $y < 0$, $P_{ik}, P_i^0, Q_{il}, Q_i^0$ are positive, smooth functions of u representing production, basal production, consumption, and basal consumption, respectively. Here $w, \tilde{w}$ are matrices describing the interactions between the u variables, $i = 1, 2, ..., n$, $j = 1, 2, ..., N$, $l = 1, ..., M$ and $h, \tilde{h}$ are thresholds.

One will usually look for solutions of the piecewise-smooth dynamics (2.2) such that trajectories of $\boldsymbol{u}$ are continuous. However, we can easily extend the above definitions in order to cope with jumps of the continuous variables. Similarly to impact systems occurring in mechanics [DB08], the jumps of the continuous variables can be commanded by the following rule: $\boldsymbol{u}$ instantly changes

to $\boldsymbol{p}_j^{\pm}(\boldsymbol{u})$ whenever a discrete variable $\hat{s}_j = H(\sum_{k=1}^{n} \hat{w}_{jk} u_k - \hat{h}_j)$ changes. The $\pm$ superscripts correspond to changes of $\hat{s}_j$ from 0 to 1 and from 1 to 0, respectively. We can consider reversible jumps in which case the functions $\boldsymbol{p}_j^{\pm}(\boldsymbol{u})$ satisfy $\boldsymbol{p}^+ \circ \boldsymbol{p}^- = Id$. The typical example in molecular biology is the cell cycle. In this case, the command to divide at the end of mitosis is irreversible and corresponds to $\boldsymbol{p}_j^{+}(\boldsymbol{u}) = \boldsymbol{u}/2$. No return is possible, $\boldsymbol{p}_j^{-}(\boldsymbol{u}) = \boldsymbol{u}$.

The class of models (2.2) is too general. We will restrict ourselves to a subclass of piecewise smooth systems where smooth production and degradation terms are assumed multivariate monomials in u, plus some basal terms:

$$\begin{aligned} P_{ik}(\mathbf{u}) &= a_{ik} u_1^{\alpha_1^{ik}} \dots u_n^{\alpha_n^{ik}}, \\ P_i^0(\mathbf{u}) &= a_i^0 \\ Q_{il}(\mathbf{u}) &= \tilde{a}_{il} u_1^{\tilde{\alpha}_1^{il}} \dots u_n^{\tilde{\alpha}_n^{il}} \\ Q_i^0(\mathbf{u}) &= \tilde{a}_i^0 u_i \end{aligned} \tag{2.3}$$

which will be chosen according to an heuristic presented in the next sections.

This restriction does not reduce the power of the method. As argued in the introduction, the monomial rates represent good approximations for nonlinear networks of biochemical reactions with multiple separated timescales [RGZL08,GR08]. More generally, rational functions are good candidates for general rate laws [LUK10]. However, when concentrations are very large or very small the monomial laws are recovered. For instance, Michaelis Menten, Hill, or Goldbeter-Koshland reactions switch from a saturated regime where rates are constant to a small concentration regime where rates follow power laws. Finally, by methods described in [Vak02,VG03] one can show that the above subclass of models can approximate with arbitrary precision any structurally stable dynamics.

These models have several advantages with respect to standard models in molecular biology and neuroscience based on differential equations. They allow us to simulate, in a fairly simple manner, discontinuous transitions occurring in such systems (see a typical graph describing time evolution of protein concentration within cellular cell cycle, Fig.5.1). The discontinuous transitions result either from fast processes or from strongly non-linear (thresholding) phenomena. This class of models is also scalable in the sense that more and more details can be introduced at relatively low cost, by increasing the number of discrete variables and the size of the interaction matrices.

The definition of the rates slightly extends the one used in S-systems, introduced by Savageau [SV87]. Our choice was motivated by the fact that S-systems proved their utility as models for metabolic networks whose dynamics we want to encompass by considering the modes. The introduction of basal terms avoids spurious long living states when some products have zero concentrations.

3 Regulated reaction graphs and hybrid reaction schemes

Interaction mechanisms in molecular biology can be schematized as regulated reaction graphs.

A regulated reaction graph is a quadruple (V, R, E, E_r). The triplet (V, R, E), where $E \subset V \times R \cup R \times V$, defines a reaction bipartite graph, ie $(x, y) \in E$ iff $x \in V, y \in R$ and x is a substrate of R, or $x \in R, y \in V$ and y is a product of x. $E_r \subset V \times R$ is the set that defines regulations, $(x, z) \in E_r$ if the rate of the reaction $z \in R$ depends on $x \in V$ and x is not a substrate of R.

Similar structures of regulated reactions where proposed elsewhere for non-hybrid models [LUK10].

In order to define a hybrid model we first need a *hybrid reaction scheme*. This consists in saying, for each given species, whether its production/degradation can be switched on and off and by which species, also which species modulate the production/degradation of a given species in a smooth way. This means specifying a partition of the regulations $E_r = E_r^d \cup E_r^c$. A regulation $(x, r) \in E_r^d$ is discrete if the decision to switch on and off the reaction r depends (among others) on x. Discrete interactions manifest themselves punctually as a consequence of thresholding and/or of rapid phenomena. The continuous regulations guide the dynamics of the modes. Similarly, there is a partition of the reactions $R = R^s \cup R^c$. A reaction r belongs to the switched reactions $r \in R^s$ if $(x, r) \in E_r^d$, for some $x \in V$. The role of the regulators (continuous if they modulate the reaction rate, discrete if they contribute to switching it on and off) should be indicated on the graph together with the signs of the regulations.

4 Identification of piecewise smooth models

We would like to develop methods allowing to find the parameters of a model from the class introduced above that best describes the observed trajectories of a biological system. These trajectories can come from experiments or can be produced by non-hybrid models. In both situations we obtain a model whose parameters can be easily interpreted in biological terms. The hybrid model can be further analyzed or used to model more complex situations.

In the following we present a reverse engineering algorithm that works well for systems with sharp transitions.

Data. n trajectories (time series) $u_1(t), ..., u_n(t)$ given at time moments $t_0, t_1, ..., t_N$. A regulated reaction graph (the smooth/discrete partition of the regulations can be unspecified).

Output. A model of the type (2.2), (2.3) with values of the parameters that fit well the data.

The algorithm has several steps, some of them involving several alternative numerical solutions. For some of the steps the choice of the numerical solution was adapted to the application presented in the paper, which is the reconstruction of a hybrid cell cycle oscillator.

I. Choice of hybrid reaction scheme and of monomials giving the smooth part of the rates.

The reaction rates have the forms given by (2.3). The monomial exponents $\alpha_{ij}, \tilde{\alpha}_j^i$, the rate functions defining the modes, the mode switching and the jumps can be obtained from the following heuristic rules:

i) If a reaction j is activated then $\alpha_j^i = 1$ for all activators and $\alpha_j^i = -1$ for all inhibitors i in the absence of cooperativity. Cooperativity may be taken into account by considering $|\alpha_j^i| > 1$.

ii) Basal rates are constant for reactions without substrates and proportional to the concentration of the substrate otherwise.

iii) If activated reactions are present with intermittence, their non-basal rates are multiplied by discrete variables s_i; this defines the mode switching.

iv) If a continuous variable u_i is known to induce a jump decision (for instance cell division), it should appear in the definition of the jump discrete variables $\hat{s}$. The functions $\mathbf{p}(\mathbf{u})$ follow from biological observations.

Once the hybrid reaction scheme chosen, we want to fit the remaining model parameters in order to reproduce the observed dynamics.

II. Detection of the events locations.

We look for K time intervals $I_1, I_2, ..., I_K$. The dynamics on each of the intervals is smooth, it is given by (2.2) with the s variables fixed. Mode transitions (change of the variables) occur at the borders of these intervals. We denote the switching times as $\tau_1, ...\tau_K$.

Finding τ_k is a problem of singularity detection. This could be done by various methods, for example by wavelet analysis. Here we decided to use the derivatives of the reaction rates to locate the mode switching events. The peaks of these derivatives indicate the positions of switching events, whereas the sign of the derivatives indicate the sign of the change (activation if positive, inactivation if negative). With this simple criterion we are able to reconstruct the sequence of modes which is defined by the values of the boolean variables $s(t)$.

III. Determining the mode internal parameters.

The previous steps define a set of modes and the static event location. Given a choice of the modes internal parameters the hybrid trajectories can be integrated without knowing the discrete regulations (this will allow the dynamic event location at the next step): the values of s between two successive events are enough. Modes internal parameters are obtained by optimization. Let $u_i^{modes}(t)$ be the continuous hybrid trajectories obtained by integrating the modes between the calculated transition times. We use a parallel version of Lam's simulated annealing algorithm [CDR99] to minimize the following objective function:

$$F = \sum_{i,k} C_k (u_i^{modes}(t_k) - u_i(t_k))^2,$$

where C_k are positive weights. The choice of the weights depends on the dynamical features one wants to reproduce. For instance, for the cell cycle application we choose weights that increase with time. We thus penalize large time deviations that can arise from the loss of synchronicity among variables u_i and avoid the period misfit that could arise between the hybrid and the smooth dynamics after dynamic event location.

IV. Determining the mode control parameters and dynamic event location.

Let $s_m = H(\sum_{(m,j)\in E^r} w_{mj}u_j - h_j)$ be the discrete variables determined above. Let s_k^m be the constant values of s_m on I_k. Consider now the optimal trajectories $u_i^{modes*}(t_l)$ obtained before.

Then, one should have

$$(\sum_{(m,j)\in E^r} w_{mj}u_j^{modes*}(t_l) - h_j)s_k^m > 0, \text{for all } t_l \in I_k, \tag{4.1}$$

which is a linear programming problem for w_{mj} that can be resolved (if it has a solution) in polynomial time.

5 Examples

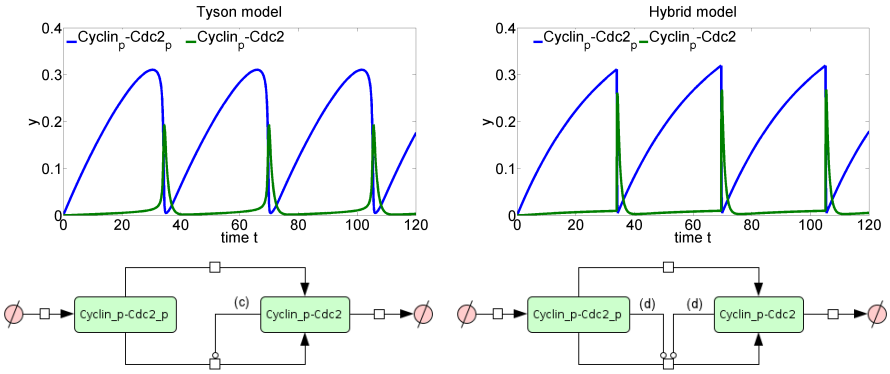

Fig. 5.1. (Top Left) Trajectories of the non-hybrid model by Tyson [Tys91]. (Top Right) Trajectories of the hybrid model. (Bottom Left) Reaction graph of the non-hybrid model. (Bottom Right) Reaction graph of the hybrid model.

A simple cell cycle model As a simple example let us consider the minimal model proposed by Tyson for Cdc2 and Cyclin interactions [Tys91]. This model, which contains initially 6 species and 9 reactions, can be reduced to only 2 species and 4 reactions (details of the reduction will be given elsewhere), while keeping the same dynamics. The two species left are Cyclin-Cdk complexes, with two phosphorylation states: phosphorylation of both monomers ($Cpp := Cyclin_p.Cdc2_p$), or only Cyclin phosphorylated ($Cp := Cyclin_p.Cdc2$).

$$\begin{aligned} \frac{d[Cpp]}{dt} &= k_1 - k_4'[Cpp] - k_4[Cpp][Cp]^2 \\ \frac{d[Cp]}{dt} &= -k_6[Cp] + k_4'[Cpp] + k_4[Cpp][Cp]^2 \end{aligned} \tag{5.1}$$

The regulated reaction graph and the hybrid scheme are represented in Fig.5.1. The dynamics of this model is quite simple. The linear dephosphorylation is slower than the production of Cpp. This create an accumulation of Cpp. Then at some threshold the Cp produced activates the second, faster, dephosphorylation, which drains the accumulated Cpp. Here we model this second, faster reaction as an hybrid reaction, totally controlled by thresholds. This is justified by the observed peaks of the rate derivative (Fig.5.2) and leads to the following hybrid model:

$$\begin{aligned} \frac{d[Cpp]}{dt} &= \tilde{k}_1 - \tilde{k}'_4[Cpp] - \tilde{k}_4 s[Cpp] \\ \frac{d[Cp]}{dt} &= -\tilde{k}_6[Cp] + \tilde{k}'_4[Cpp] + \tilde{k}_4 s[Cpp] \end{aligned} \tag{5.2}$$

where $s = H(w_1[Cpp] + w_2[Cp] - h)$ is the boolean variable.

After the parameter fit we find that w_1 and w_2 are both positive.

For this model no jumps of the continuous variables are needed. Indeed, at the end of mitosis, all continuous variables have small values. Bringing their values to half would not change much the behavior of the model.

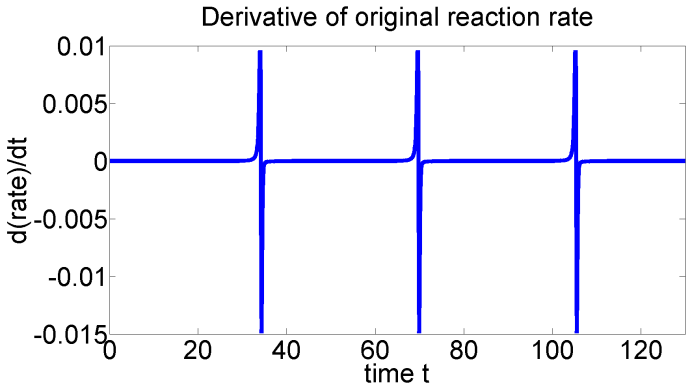

Fig. 5.2. Rate derivative for the simple cell cycle model.

Generic mammalian cell cycle model A complex example with mode switching and jumps is obtained from Novak and Tyson 2006 generic cell cycle model [Csi06]. The generic model contains four different versions, each of them reproduce the cell cycle for a different eukaryote organism : Mammalians, Xenopus embryo, Budding yeast, Fission Yeast. Our study will only focus on the mammalian version. This model contains 12 species and 34 reactions.

We briefly discuss the steps of the algorithm applied to this model.

Choice of the hybrid scheme. Four of these reactions are typically switch-like, following Goldbeter-Koshland kinetics. Another reaction is following Hill kinetics, and also shows switch-like behavior. These reactions are replaced by switched reactions whose rates are simplified monomial rate multiplied by a boolean variable.

For instance the reaction that produces Cyclin-B, induced by the cell mass, is defined by the following kinetic rate:

$$\mathrm{R} = \mathrm{ksb}_{pp}\,[\mathrm{Mass}]\,\mathrm{GK}(\mathrm{kafb}\,[\mathrm{CycB}], \mathrm{kifb}, \mathrm{Jafb}, \mathrm{Jifb}) \tag{5.3}$$

In this case we can replace the Goldbeter-Koshland (GK) function by a boolean variable (see Fig.5.3) and obtain the following simpler rate:

$$\mathrm{R}' = \mathrm{ksb}_{pp}\,[\mathrm{Mass}]\,\mathrm{s} \tag{5.4}$$

where s is a boolean variable.

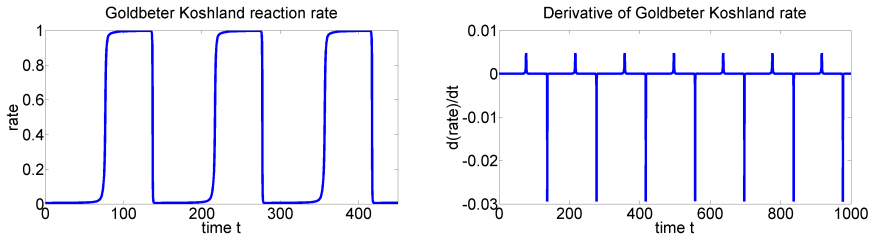

Fig. 5.3. left: Reaction flow of the GK function, right: Derivative of reaction flow of the GK function.

Detection of the transitions. Static event locations follow from the positions of the peaks of the derivative of the reactions rates with respect to time. For the reaction considered above, we find 2 peaks per period of the cell cycle model (see Fig. 5.3), which correspond to switching the reaction from an active state to an inactive one and back. At the end of this step, we obtain a list of the transitions points for each switched reaction, and the status of the switched reactions during each mode (ie between successive transitions) as boolean variables.

Fitting the hybrid model parameters. Once we have this definition, we can fit the model, using the parallel simulated annealing algorithm. As a control we can see the results of the fitting on the rate of the reaction considered above (Fig.5.4).

Computing the mode control parameters. The final goal is to obtain a dynamic definition of these events location, by computing the regulation matrix w and the thresholds h for all the boolean variables.

For instance, the reaction discussed is controlled by the function $f(u) = -37.32[CycA] - 1.694[CycB] - 173.7[CycE] - 177.8[APCP] + 331.2[Cdc20a] + 97.8[Cdc20i] - 78.5[Cdh1] - 107.1[CKI] + 0.3481Mass + 53.52[pB] + 1337[TriA] +$

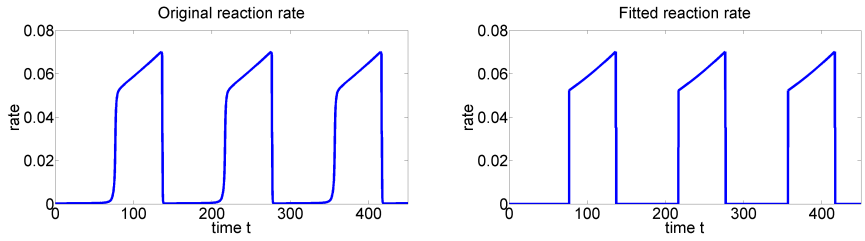

Fig. 5.4. left: Original reaction flow, right: Hybrid reaction flow.

39.57$[TriE]$, which is the parameter of the Heaviside function. The sign of this event function will control the state of the reaction, keeping it inactive if the function is negative, and activating the reaction when the function is positive (Fig.5.5).

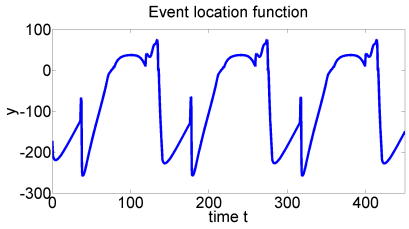

Fig. 5.5. Event location function, ie the Heaviside function parameter.

On Fig.5.6, we can see the trajectories of the hybrid model (with dynamic event location), compared to those of the original model.

6 Conclusion

The results that we present are a proof of principle that piecewise smooth hybrid models can be constructed with a simple heuristic from basic information about biochemical interactions. Using this class of hybrid models instead of piecewise-linear approximations provides, in many situations, a better balance between discrete and smooth interactions. The identification algorithm proposed in the paper combines the static location of the events, the identification of the modes by simulated annealing, and the identification of the mode control parameters by dynamic location. The hardest step of this algorithm is the simulated annealing. Furthermore, for large models, we expect several solutions for the mode control parameters. We are currently improving the algorithm to cope with these situations. A better choice of the modes dictated by model reduction techniques could reduce the time for simulated annealing. Also, we are investigating the use of event location functions that are linear in the logarithms of the continuous

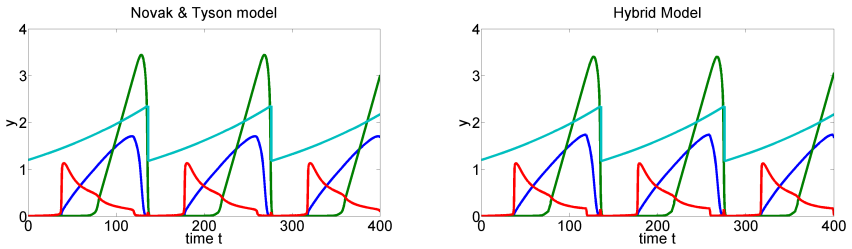

Fig. 5.6. (Left) Trajectories of four main variables of the non-hybrid model by Novak and Tyson [NT04]. (Right) Trajectories of the hybrid model. (blue : Cyclin-A, green : Cyclin-B, red : Cyclin-C, aqua : cell size)

variables. According to the ideas of the introduction, these nonlinear location functions will indicate changes of the dominant monomials in the rate functions, more accurately than the linear location functions. Moreover, they can be obtained directly from the initial smooth model without the need to solve (eventually undetermined) dynamic location inequations. Improved segmentation techniques are needed for future application of the algorithm directly to data.

In the future we will apply the heuristic and the fitting algorithm to model complex situations when signaling pathways interact with the eucaryotic cell cycle. The resulting hybrid models will also be used to investigate emerging properties of regulatory networks such as viability and robustness.

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