

Ordinary differential equations with discontinuous right-hand sides as complementarity systems. Application to gene regulatory networks.

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Joint work with Hidde de Jong and Bernard Brogliato
INRIA Rhône-Alpes, Grenoble.

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One of the father of Nonsmooth Mechanics and Convex Analysis



Jean Jacques Moreau (1923 – 2014)

Bio.

Team-Project BIPOP. INRIA. Centre de Grenoble Rhône-Alpes

“One of the Jean Jacques Moreau’s fan club”. Convex Analysis and Nonsmooth Mechanics.

- ▶ Scientific leader : Bernard Brogliato
- ▶ Nonsmooth dynamical systems : Modeling, analysis, simulation and control.
- ▶ Nonsmooth Optimization : Analysis & algorithms. (Claude Lemaréchal & Jérôme Malick)

Personal research themes

- ▶ Nonsmooth Dynamical systems. Higher order Moreau’s sweeping process. Complementarity systems and Filippov systems
- ▶ Modeling and simulation of switched electrical circuits
- ▶ Discretization method for sliding mode control and optimal control.
- ▶ Formulation and numerical solvers for Coulomb’s friction and Signorini’s problem. Second order cone programming.
- ▶ Time-integration techniques for nonsmooth mechanical systems

Outline

Outline

- ▶ Basic facts on piecewise linear modeling of gene regulatory network
- ▶ Notion of Filippov solutions
 - ▶ Filippov extension
 - ▶ Aizerman & Pyatnitskii extension
- ▶ Mixed Complementarity Systems formulation
- ▶ Numerical time-integration
- ▶ Illustrations
- ▶ Conclusions & perspectives.

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- A first simple network of two genes

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- Filippov's extension of PWL models

- Aizerman & Pyatnitskii's extension of PWL models

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- Synthetic oscillator with positive feedback

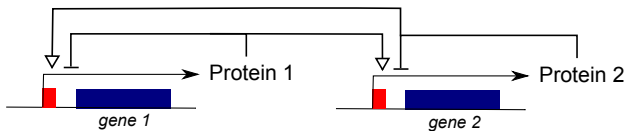
- Repressilator

Extensions to general affine piecewise smooth systems

- General affine piecewise smooth systems

Conclusions & Perspectives

A first simple network of two genes



PWL model corresponding to this network.

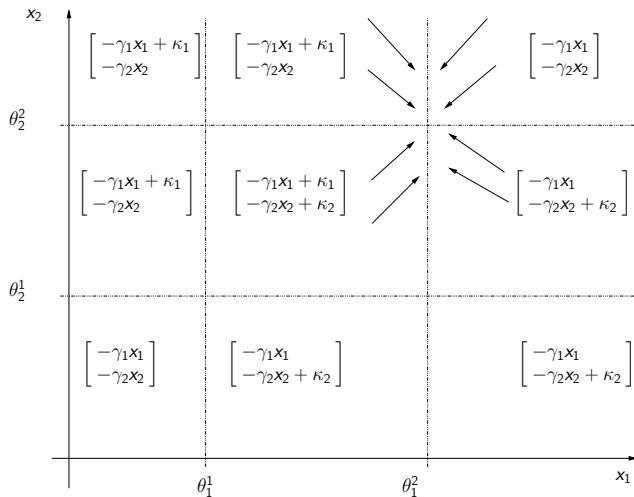
$$\begin{cases} \dot{x}_1 &= -\gamma_1 x_1 + \kappa_1 s^+(x_2, \theta_2^1) s^-(x_1, \theta_1^2) \\ \dot{x}_2 &= -\gamma_2 x_2 + \kappa_2 s^+(x_1, \theta_1^1) s^-(x_2, \theta_2^2) \end{cases} \quad (1)$$

where

- ▶ x_1, x_2 are cellular protein or RNA concentrations
- ▶ κ_1, κ_2 and γ_1, γ_2 are positive synthesis and degradation constants, respectively,
- ▶ $\theta_1^1, \theta_1^2, \theta_2^1, \theta_2^2$ are constant strictly positive threshold concentrations of regulation
- ▶ s^+ and s^- are *step functions*

$$s^+(x_j, \theta_j^k) = \begin{cases} 1 & \text{if } x_j > \theta_j^k \\ 0 & \text{if } x_j < \theta_j^k \end{cases} \quad \text{and} \quad s^-(x_j, \theta_j^k) = \begin{cases} 0 & \text{if } x_j > \theta_j^k \\ 1 & \text{if } x_j < \theta_j^k \end{cases}, \quad (2)$$

A first simple network of two genes



Definition of Piece-Wise Linear (PWL) models

Notation

- ▶ $x = (x_1, \dots, x_n)^T \in \Omega$ a vector of cellular protein or RNA concentrations, where $\Omega \subset \mathbb{R}_+^n$ is a bounded n -dimensional hyperrectangular subspace of \mathbb{R}_+^n
- ▶ For each concentration variable x_i , $i \in \{1, \dots, n\}$, we distinguish a set of constant, strictly positive threshold concentrations $\{\theta_i^1, \dots, \theta_i^{p_i}\}$, $p_i > 0$.
- ▶ $\Theta = \bigcup_{i \in \{1, \dots, n\}, k \in \{1, \dots, p_i\}} \{x \in \Omega \mid x_i = \theta_i^k\}$ the subspace of Ω defined by the threshold hyperplanes.

Definition of Piece-Wise Linear (PWL) models

Definition 1 (PWL model)

A *PWL model* of a gene regulatory network is defined by a set of coupled differential equations

$$\dot{x}_i = f_i(x) = -\gamma_i x_i + b_i(x) = -\gamma_i x_i + \sum_{l \in L_i} \kappa_i^l b_i^l(x), \quad i \in \{1, \dots, n\}, \quad (3)$$

where

- ▶ κ_i^l and γ_i are positive synthesis and degradation constants, respectively,
- ▶ $L_i \subset \mathbb{N}$ are sets of indices of regulation terms,
- ▶ $b_i^l : \Omega \setminus \Theta \rightarrow \{0, 1\}$ are so-called Boolean *regulation functions*.

Boolean functions and step functions

Step functions can be associated with Boolean variables X_j^k such that

$$\begin{aligned} X_j^k(x) &= (x_j > \theta_j^k) = s^+(x_j, \theta_j^k) \\ \bar{X}_j^k(x) &= (x_j < \theta_j^k) = s^-(x_j, \theta_j^k), \end{aligned} \quad (4)$$

where \bar{X} denotes the complemented variables of X .

Definition of Piece-Wise Linear (PWL) models

Generically, any Boolean function $b_i^l(x)$ can be rewritten in minterm disjunctive normal form (DNF):

$$b_i^l(x) = \sum_{\alpha=0}^{2^p-1} c_{i,\alpha}^l m_{\alpha}(x), \quad (5)$$

with $c_{i,\alpha}^l \in \{0, 1\}$. For the set of variables $X_j^k, j \in \{1, \dots, n\}, k \in \{1, \dots, p_j\}$, we have 2^p minterms, with $p = \sum_{j \in \{1, \dots, n\}} p_j$,

$$m_{\alpha}(x) = \prod_{j=1}^n \prod_{k=1}^{p_j} \mathcal{X}_j^k(x), \quad \alpha \in \{0, \dots, 2^p - 1\}. \quad (6)$$

where $\mathcal{X}_j^k(x)$ is a literal defined either as the Boolean variable X_j^k or its negation \bar{X}_j^k .

Assumption 1

The regulation functions $b_i^l(\cdot)$ are multiaffine functions, that is, they are affine with respect to each $s^+(x_j, \theta_j^k)$, for $j \in \{1, \dots, n\}$ and $k \in \{1, \dots, p_j\}$.

Assumption 1 can be shown to be generic for all regulation functions corresponding to Boolean functions written in minterm disjunctive normal form.

Assumption 2

Every step function $s^+(x_j, \theta_j^k)$, with $j \in \{1, \dots, n\}$ and $k \in \{1, \dots, p_j\}$, occurs in at most one $b_i(\cdot)$, $i \in \{1, \dots, n\}$.

Assumption 2 is a rather weak modeling assumption, in the sense that there is usually no compelling biological reason for two genes to be regulated at exactly the same threshold.

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Concept of Filippov's solutions

ODE with discontinuous R.H.S.

- ▶ Step functions $s^\pm(x_j, \theta_j^k)$ gives rise to mathematical complications, because the step functions are undefined and discontinuous at $x_j = \theta_j^k$.
- ▶ Reformulation as differential inclusions

$$\dot{x} \in F(x)$$

Numerous options for defining the set-valued function F .

- ▶ Filippov's definition of solutions as a absolutely-continuous function $x(\cdot)$ such that $\dot{x}(t) \in F(x(t))$ holds almost everywhere on $[t_0, T]$ with $x(t_0) = x_0$.

Filippov's extension of PWL models

Properties

- ▶ Classical definition of Filippov's extension
- ▶ Existence of solutions under mild assumptions
- ▶ Uniqueness is not ensured.

Issues: Hardly tractable formulation for Numerics

$$\dot{x} \in F(x)$$

General time-discretization scheme. (Dontchev and Lempio, 1992)

$$\frac{x_{k+1} - x_k}{h} \in F(x_k)$$

- ▶ How to practically build $F(x)$?
- ▶ How to compute and to choose a selection $\sigma \in F(x)$?
- ▶ How to avoid numerical chattering ?

Filippov's solutions – 18/45

Relations between the extensions

Proposition 5 ((Machina and Ponosov, 2011))

Under Assumption 1 (multiaffine R.H.S.), $F(x) = \overline{\text{co}}(G(x))$ for all $x \in \Omega$.

Comments

- ▶ Every Filippov solution with the AP-extension is a Filippov solution with the F-extension
- ▶ Not sufficient to ensure the existence of a solution.

Proposition 6

Under Assumptions 1 and 2, $F(x) = G(x)$ for all $x \in \Omega$.

Comments

- ▶ We retrieve the existence of solutions.

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Principles

1. A reformulation of the set-valued relation

$$\sigma \in S^+(x, \theta), \quad (13)$$

into inclusion into normal cones, Complementarity Problems (CP) and finite-dimensional Variational Inequalities (VI)

2. An implicit event-capturing time-stepping scheme, mainly based on the backward Euler scheme which allows to deal with the switch-like behaviour and the sliding motion
3. The use of efficient numerical solvers for the *one-step problem* which results from the time-discretization of the CP/VI formulation of the problem

Reformulation as MCS/DVI

The relation

$$\sigma \in S^+(x, \theta), \quad (14)$$

can be equivalently reformulated in the form of an inclusion as

$$(x - \theta) \in N_{[0,1]}(\sigma). \quad (15)$$

In turn, the relation (15) are equivalent to the complementarity conditions

$$\begin{cases} 0 \leq 1 - \sigma \perp (x - \theta)^+ \geq 0 \\ 0 \leq \sigma \perp (x - \theta)^- \geq 0, \end{cases} \quad (16)$$

where the symbol $x \perp y$ means $x^T y = 0$ and y^+, y^- respectively stand for the positive and negative parts of y . Finally, an equivalent formulation of (15) is given by the following VI : find $\sigma \in [0, 1]$ such that

$$(\theta - x)^T (\sigma - \sigma') \geq 0 \text{ for all } \sigma' \in [0, 1]. \quad (17)$$

Reformulation as MCS/DVI

Let us now define the affine function $y : \mathbb{R}^n \rightarrow \mathbb{R}^p$ such that

$$y(x) = Cx - \theta = \begin{bmatrix} x_1 - \theta_1^1 \\ \vdots \\ x_1 - \theta_1^{p_1} \\ \vdots \\ x_n - \theta_1^n \\ \vdots \\ x_n - \theta_1^{p_n} \end{bmatrix}^T \in \mathbb{R}^p \quad (18)$$

where $C \in \mathbb{R}^{p \times n}$ with $C_{ij} \in \{0, 1\}$ and $\theta = [\theta_1^1, \dots, \theta_1^{p_1}, \dots, \theta_n^1, \dots, \theta_n^{p_n}]^T$.

Reformulation as MCS/DVI

The AP-extension of the PWL system in Definition 4 can be written compactly as

$$\begin{cases} \dot{x} = -\text{diag}(\gamma)x + g(\sigma) \\ y(x) = Cx - \theta \in N_{[0,1]^p}(\sigma) \end{cases} \quad (19)$$

where $\text{diag}(\gamma) \in \mathbb{R}^{n \times n}$ is the diagonal matrix made of the components $\gamma_i, i = 1 \dots n$.

- We get
- ▶ Mixed Complementarity Systems (MCS)
 - or
 - ▶ Differential Variational Inequalities (DVI)

An event-capturing scheme. The *one-step* problem

The proposed time discretization of (19) over a time-interval $[t_k, t_{k+1}]$ of length h :

$$\begin{cases} x_{k+1} = x_k - h \operatorname{diag}(\gamma)x_{k+\tau} + h g(\sigma_{k+1}), \\ y_{k+1} = Cx_{k+1} - \theta, \\ y_{k+1} \in N_{[0,1]^p}(\sigma_{k+1}). \end{cases} \quad (20)$$

with the initial condition $x_0 = x(t_0)$. $x_{k+\tau} = \tau x_{k+1} + (1 - \tau)x_k$ for $\tau \in [0, 1]$

Formulation into MCP/VI

Let us define the vector

$$z_{k+1} = \begin{bmatrix} x_{k+1} \\ \sigma_{k+1} \end{bmatrix} \in \mathbb{R}^{n+m}, \quad (21)$$

and the function $H : \mathbb{R}^{n+m} \rightarrow \mathbb{R}^{n+m}$ as

$$H(z_{k+1}) = \begin{bmatrix} x_{k+1} - x_k + h \operatorname{diag}(\gamma)x_{k+\tau} - h g(\sigma_{k+1}) \\ \theta - Cx_{k+1} \end{bmatrix}. \quad (22)$$

Then the problem (20) can be recast into the following inclusion

$$-H(z_{k+1}) \in N_{\mathbb{R}^n \times [0,1]^p}(z_{k+1}). \quad (23)$$

Existence of solutions

Proposition 7

Let $H : \mathbb{R}^{n+m} \rightarrow \mathbb{R}^{n+m}$ be the function defined in (22). Under Assumption 1, the problem to find $z \in \mathbb{R}^n \times [0, 1]^p$ such that

$$-H(z) \in N_{\mathbb{R}^n \times [0, 1]^p}(z), \quad (24)$$

has a nonempty and compact solution set.

Sketch of the proof

- Substitute x_{k+1} in the inclusion to get a reduced inclusion

$$-h(\sigma) \in N_{[0, 1]^p}(\sigma) \quad (25)$$

with

$$h(\sigma) = \theta - Cx = \theta - C \operatorname{diag}(1/(1 + h\tau\gamma)) [(I_n - h(1 - \tau) \operatorname{diag}(\gamma))x_k + hg(\sigma)] \quad (26)$$

- h is continuous and $[0, 1]^p$ is compact convex

Apply Corollary 2.2.5 (Facchinei and Pang, 2003, page 148)

Solution methods

Definition 8 (Mixed complementarity Problem(MCP) (Dirkse and Ferris, 1995))

Given a function $H : \mathbb{R}^{n+m} \rightarrow \mathbb{R}^{n+m}$ and lower and upper bounds $l, u \in \mathbb{R}^{n+m}$, the Mixed complementarity Problem (MCP) is to find $z \in \mathbb{R}^{n+m}$ and $w, v \in \mathbb{R}_+^{n+m}$ such that

$$(MCP) \quad \begin{cases} H(z) = w - v \\ l \leq z \leq u \\ (u - z)^T v = 0 \\ (z - l)^T w = 0 \end{cases} \quad (27)$$

Numerical algorithms

- ▶ MILES (Rutherford, 1993) classical Newton–Josephy method,
- ▶ PATH (Ralph, 1994 ; Dirkse and Ferris, 1995)
- ▶ NE/SQP (Gabriel and Pang, 1992 ; Pang and Gabriel, 1993) generalized Newton’s method based on the minimum function
- ▶ QPCOMP (Billups and Ferris, 1995) NE/SQP
- ▶ SMOOTH (Chen and Mangasarian, 1996) smooth approximations of the NCP,
- ▶ SEMISMOOTH (DeLuca et al., 1996) semismooth Newton with Fischer–Burmeister function,
- ▶ ...

Enumerative solution methods

- With the classical Newton–Josephy method linearization, we get a MLCP

$$\begin{cases} y^{\alpha+1} = W^{\alpha+1} \sigma^{\alpha+1} + q^{\alpha+1} \\ y^{\alpha+1} \in N_{[0,1]^p}(\sigma^{\alpha+1}) \end{cases}, \quad (28)$$

where

$$W^{\alpha+1} = hC M^{-1} B(\sigma^\alpha),$$

$$q^{\alpha+1} = CM^{-1} [(I_n - h(1 - \tau)\text{diag}(\gamma))x_k + hg(\sigma^\alpha) + hB(\sigma^\alpha)\sigma^\alpha] - \theta.$$

$$M = I_n + h\tau\text{diag}(\gamma)$$

$$B(\sigma) = \nabla_\sigma g(\sigma)$$

- Efficient enumerative solvers (see for instance (Al-Khayyal, 1987 ; Sherali et al., 1998 ; Júdice et al., 2002))

Enumerating several solutions corresponding to various modes

Qualitative insight on the nature of solutions

Stationary Points

Finding stationary points of the AP-extension of PWL systems is equivalent to solve the following MCP

$$\begin{cases} 0 = -\text{diag}(\gamma)x + g(\sigma) \\ y(x) = Cx - \theta \in N_{[0,1]^p}(\sigma) \end{cases} \quad (29)$$

or more compactly

$$C\text{diag}(1/(1 + \gamma))g(\sigma) - \theta \in N_{[0,1]^p}(\sigma) \quad (30)$$

With the same reasoning as in the proof of Proposition 7, the VI/CP (30) has a nonempty compact set of solutions.

We have just to checked that some solutions belong to Ω

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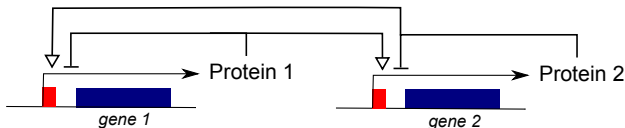
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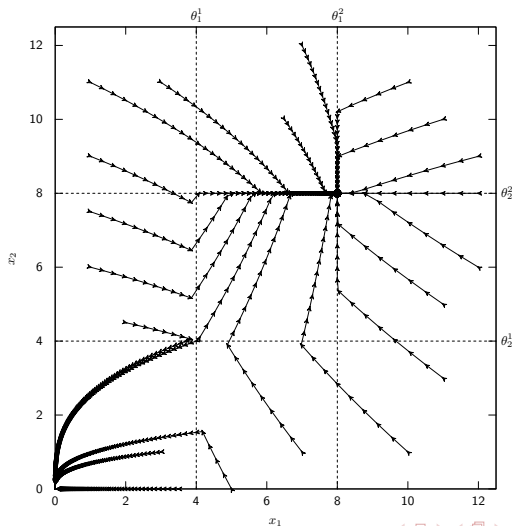


PWL model corresponding to this network.

$$\begin{cases} \dot{x}_1 &= -\gamma_1 x_1 + \kappa_1 s^+(x_2, \theta_2^1) s^-(x_1, \theta_1^1) \\ \dot{x}_2 &= -\gamma_2 x_2 + \kappa_2 s^+(x_1, \theta_1^2) s^-(x_2, \theta_2^2) \end{cases} \quad (31)$$

The parameters are: $\theta_1^1 = \theta_2^1 = 4$, $\theta_1^2 = \theta_2^2 = 8$, $\kappa_1 = \kappa_2 = 40$, $\gamma_1 = 4.5$ and $\gamma_2 = 1.5$.

Different trajectories of system (1) depicting the nature of the three equilibria.



Reduced study around the stationary point $x_1 = \theta_1^2$ and $x_2 = \theta_2^2$

Properties

1. The one-step VI

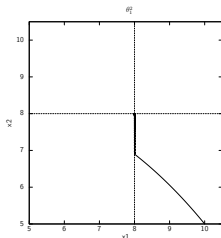
$$\bar{\theta} - \bar{C} \text{diag}(1/(1 + h\tau\gamma)) [(I_n - h(1 - \tau) \text{diag}(\gamma))x_k + h\bar{B}\bar{\sigma} + h\bar{\kappa}] \in N_{[0,1]^2}(\bar{\sigma}) \quad (34)$$

is strongly monotone and has an unique solution (see (Facchinei and Pang, 2003, Theorem 2.3.3))

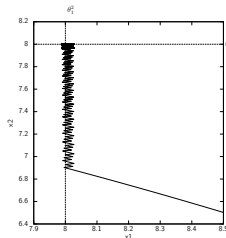
2. No numerical chattering in comparison with explicit schemes (Dontchev and Lempio, 1992)

Application of Lemma 3 in (Acary and Brogliato, 2010).

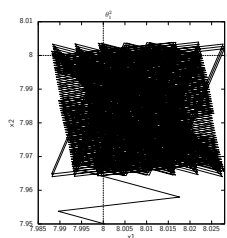
Reduced study around the stationary point $x_1 = \theta_1^2$ and $x_2 = \theta_2^2$



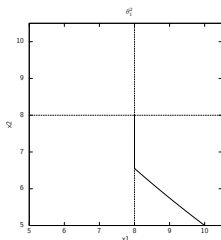
(a) Explicit scheme



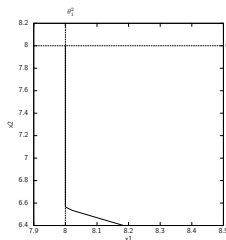
(b) Explicit scheme (zoom 1)



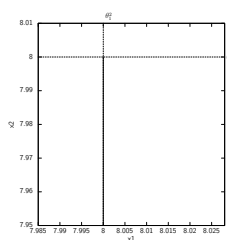
(c) Explicit scheme (zoom 2)



(d) Implicit scheme



(e) Implicit scheme (zoom 1)



(f) Implicit scheme (zoom 2)

Reduced study around the stationary point $x_1 = \theta_1^2$ and $x_2 = \theta_2^2$

Lemma 9

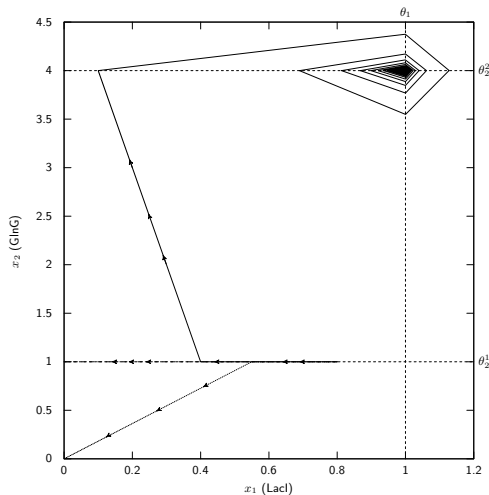
The equilibrium point $\bar{\theta} = (\theta_1^2, \theta_2^2)$ is finite-time stable in $\bar{\Omega}$.

Sketch of the proof

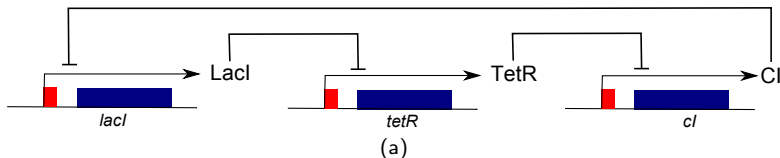
- ▶ Recast into monotone DI, $\dot{z} \in T(z)$
- ▶ Use Lyapunov function $V(z) = \frac{1}{2}z^T z$
- ▶ Since $0 \in T(0)$ and $B_r(0) \in T(0), r > 0$, then we have

$$\dot{V}(z) - r\sqrt{V(z)} \leq 0$$

Synthetic oscillator with positive feedback



Repressilator consisting of three genes (Elowitz and Leibler, 2000)



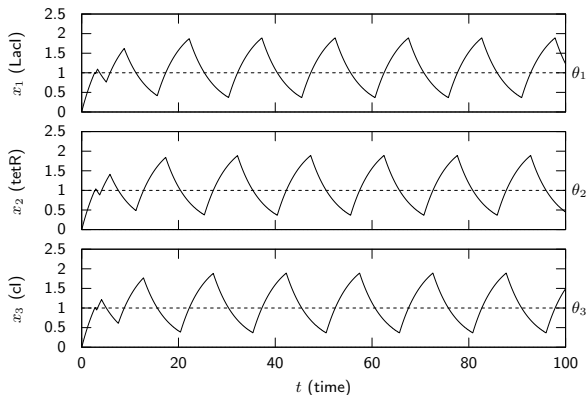
$$\begin{cases} \dot{x}_1 &= -\gamma_1 x_1 + \kappa_1^1 + \kappa_1^2 s^-(x_3, \theta_3) \\ \dot{x}_2 &= -\gamma_2 x_2 + \kappa_2^1 + \kappa_2^2 s^-(x_1, \theta_1) \\ \dot{x}_3 &= -\gamma_3 x_3 + \kappa_3^1 + \kappa_3^2 s^-(x_2, \theta_2) \end{cases} \quad (36)$$

The variables x_1 , x_2 , and x_3 represent the concentrations of the proteins LacI, TetR, and CI, respectively.

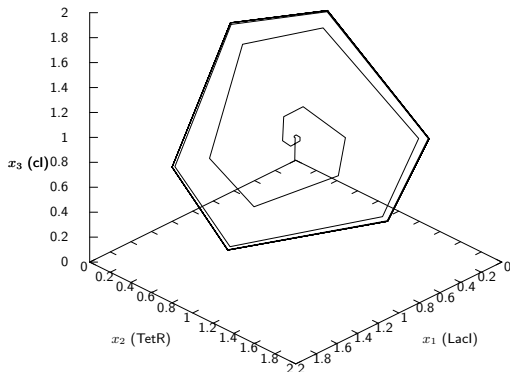
The following parameter values have been used in the simulations:

$\gamma_1 = \gamma_2 = \gamma_3 = 0.2$, $\kappa_1^1 = \kappa_2^1 = \kappa_3^1 = 4.8 \cdot 10^{-4}$, $\kappa_1^2 = \kappa_2^2 = \kappa_3^2 = 4.8 \cdot 10^{-1}$, and $\theta_1 = \theta_2 = \theta_3 = 1$.

Repressilator consisting of three genes (Elowitz and Leibler, 2000)



Repressilator consisting of three genes (Elowitz and Leibler, 2000)



General affine piecewise smooth systems

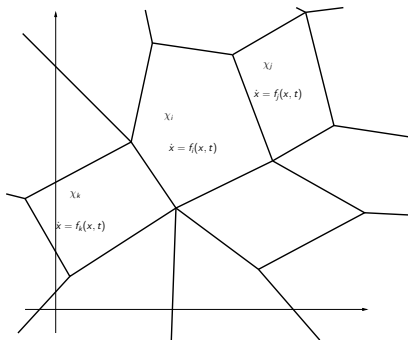


Figure : Partitioning

Ordinary differential equations with discontinuous right-hand sides as complementarity systems. Application to gene regulatory networks.

└ Extensions to general affine piecewise smooth systems

└ General affine piecewise smooth systems

General affine piecewise smooth systems

Conclusions & Perspectives

Conclusions

1. Development of numerical simulation methods for AP-extensions of PWL models, integrated in existing simulation platform.
2. Equivalence of different solution concepts for PWL models (F- and AP-extensions) under reasonable biological assumptions, which means that simulation methods are broadly applicable.
3. MCS/DVI formulation permits theoretical investigations (stability, finite-time convergence, ...)
4. Demonstrate practical usefulness of approach by numerical simulation of dynamics of three synthetic networks (good qualitative correspondence with data).

Perspectives

1. Simulation of real networks with 100 up to 1000 genes.
2. Extension to general polyhedral switching affine system (PSAS) and to piecewise smooth systems
3. Convergence without monotony, convex RHS, or one-sided Lipschitz condition.
4. Higher order event-driven schemes
5. General stability theory when only attractive surfaces are involved in a subset of interest.

Thank you for your attention.

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