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To cite this version:

Vincent Acary, Hidde de Jong, Bernard Brogliato. Numerical simulation of piecewise-linear models of gene regulatory networks using complementarity systems. Optimization: Computation, Theory and Modeling. Workshop III - Complementarity And Its Extensions, Dec 2012, Singapore, Singapore. 2012. hal-00766266

HAL Id: hal-00766266

https://inria.hal.science/hal-00766266v1

Submitted on 31 Jan 2013

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Numerical simulation of piecewise-linear models of gene regulatory networks using complementarity systems

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INRIA Rhône–Alpes, Grenoble.

Workshop 3 on Complementarity and its Extensions. 17 - 21 Dec 2012.
Institute for Mathematical Sciences. National University of Singapore

Joint work with Hidde de Jong and Bernard Brogliato

Bio.

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

"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

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- A first simple network of two genes
- Definition of Piece-Wise Linear (PWL) models

Filippov's solutions
- Notions of Filippov's solutions
- Filippov's extension of PWL models
- Aizerman & Pyatnitskii's extension of PWL models
- Relations between the extensions

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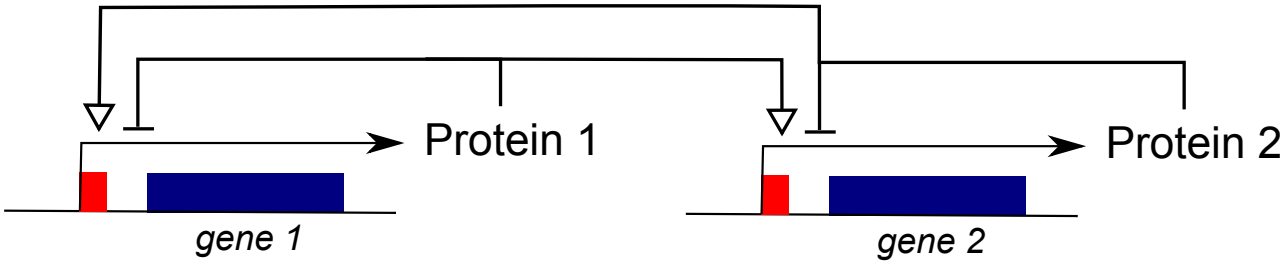
Conclusions & Perspectives

A first simple network of two genes



PWL model corresponding to this network.

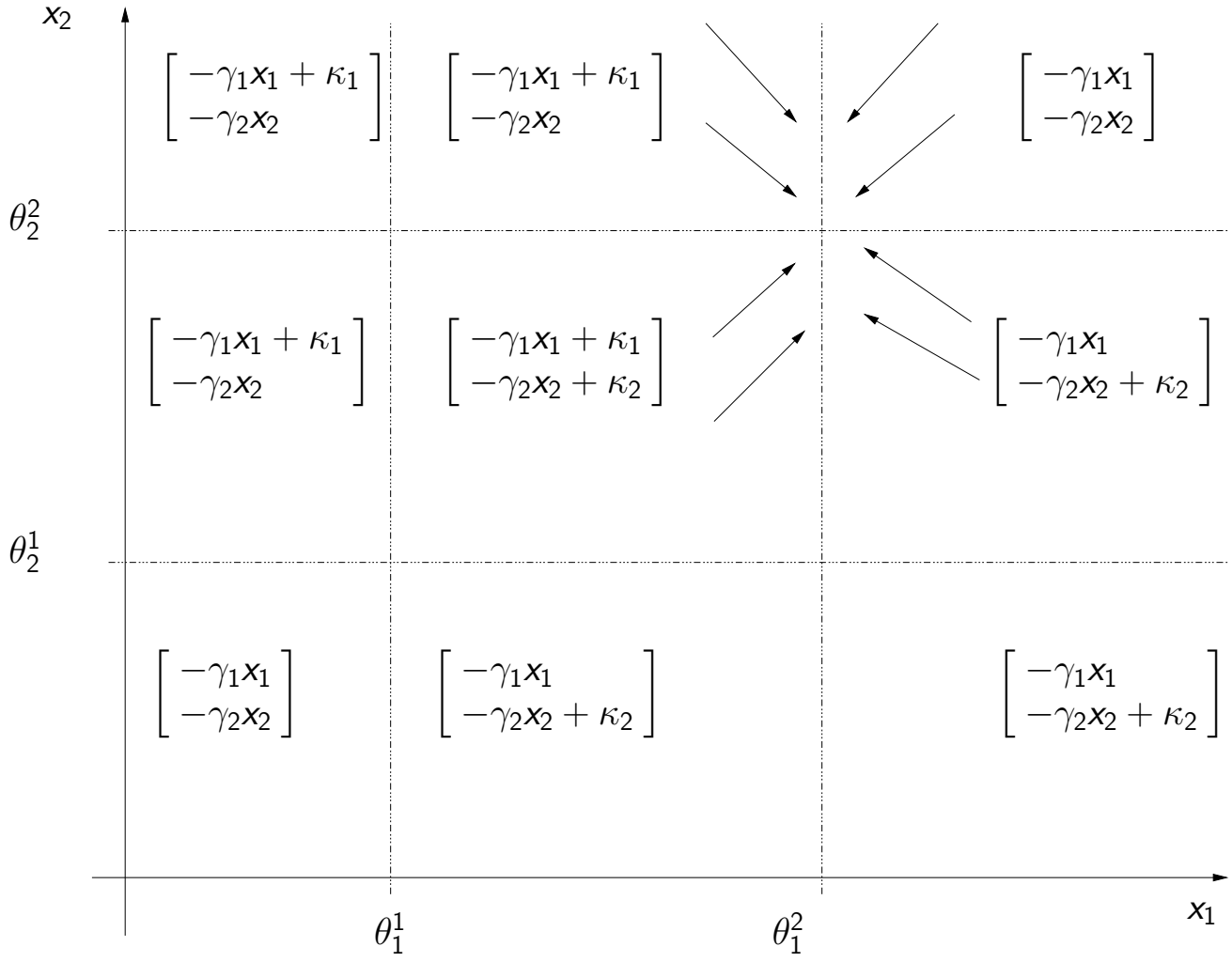
$$\begin{cases} \dot{x}_1 &= -\gamma_1\, x_1 + \kappa_1\, s^+(x_2, \theta_2^1)\, s^-(x_1, \theta_1^2) \\ \dot{x}_2 &= -\gamma_2\, x_2 + \kappa_2\, s^+(x_1, \theta_1^1)\, s^-(x_2, \theta_2^2) \end{cases} \tag{1}$$

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*

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

A first simple network of two genes



Definition of Piece-Wise Linear (PWL) models

Notation

- $x = (x_1, \ldots, x_n)^T \in \Omega$ 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, $i \in \{1, \ldots, n\}$, we distinguish a set of constant, strictly positive threshold concentrations $\{\theta_i^1, \ldots, \theta_i^{p_i}\}$, $p_i > 0$.
- $\Theta = \bigcup_{i \in \{1,\ldots,n\}, k \in \{1,\ldots,p_i\}} \{x \in \Omega \mid x_i = \theta_i^k\}$ 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

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

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,
- $b_i^l\ :\ \Omega \setminus \Theta \to \{0, 1\}$ are so-called Boolean *regulation functions*.

Boolean functions and step functions

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

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

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):

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

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 $p = \sum_{j\in\{1,\dots,n\}} p_j$,

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

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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Notions 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

Discontinuous Dynamics in $\Omega \setminus \Theta$

$$\dot{x}_i = f_i(x) = -\gamma_i \, x_i + b_i(x), \;\; i \in \{1, \ldots, n\}. \tag{3}$$

Definition 3 (F-extension of PWL models)

The F-extension of the PWL model (3) is defined by the differential inclusion

$$\dot{x} \in F(x), \;\; \textit{with } F(x) = \overline{co}\left(\{\lim_{y \to x,\, y \notin \Theta} f(y)\}\right), \;\; x \in \Omega, \tag{7}$$

where $\overline{co}(P)$ denotes the closed convex hull of the set P, and $\{\lim_{y \to x,\, y \notin \Theta} f(y)\}$ the set of all limit values of $f(y)$, for $y \notin \Theta$ and $y \to x$.

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 ?

Aizerman & Pyatnitskii's extension of PWL models

Discontinuous Dynamics in $\Omega \setminus \Theta$

$$\dot{x}_i = f_i(x) = -\gamma_i\, x_i + b_i(x),\ \ i \in \{1, \ldots, n\}. \tag{3}$$

Introduction of selection $\sigma = (\sigma_1^1, \ldots, \sigma_1^{p_1}, \ldots, \sigma_n^1, \ldots, \sigma_n^{p_n})^T \in [0,1]^p$.

Let us define the function $g : \mathbb{R}^p \to \mathbb{R}^n$ by

$$g_i(\sigma) = \sum_{l \in L_n} \kappa_i^l\, \tilde{b}_i^l(\sigma), \quad j \in \{1, \ldots, n\}. \tag{8}$$

where $\tilde{b}_i^l(\cdot)$ are obtained from $b_i^l(\cdot)$ by replacing every occurrence of $s^+(x_j, \theta_j^k)$ and $s^-(x_j, \theta_j^k)$ by σ_j^k and $1 - \sigma_j^k$, respectively.

Reformulation of the PWL model (3)

$$\dot{x}_i = f_i(x) = -\gamma_i\, x_i + g_i(\sigma),\ \ i \in \{1, \ldots, n\}, \tag{9}$$

Aizerman & Pyatnitskii's extension of PWL models

Multi-valued step function

$$S^+(x_j, \theta_j^k) = \begin{cases} 1 & x_j > \theta_j^k \\ [0,1] & x_j = \theta_j^k \\ 0 & x_j < \theta_j^k \end{cases} \quad \text{and } S^-(x_j, \theta_j^k) = \begin{cases} 0 & x_j > \theta_j^k \\ [0,1] & x_j = \theta_j^k \\ 1 & x_j < \theta_j^k \end{cases} . \tag{10}$$

Interesting equivalence. ☺

$$\sigma_j^k \in S^+(x_j, \theta_j^k) \Longleftrightarrow (x_j - \theta_j^k) \in N_{[0,1]}(\sigma_j^k) \tag{11}$$

Aizerman & Pyatnitskii's extension of PWL models

Definition 4 (AP-extension of PWL models)

The AP-extension of a PWL model (3) is defined by the following differential inclusion

$$\dot{x} \in \begin{bmatrix} G_1(x) \\ \vdots \\ G_n(x) \end{bmatrix} = \left\{ \begin{bmatrix} -\gamma_1 x_1 + g_1(\sigma) \\ \vdots \\ -\gamma_n x_n + g_n(\sigma) \end{bmatrix} \middle| \sigma_j^k \in S^+(x_j, \theta_j^k),\ j \in \{1, \dots, n\},\ k \in \{1, \dots, p_j\} \right\} \tag{12}$$

Properties

- Definition related to the Utkin concept of equivalent control method
- Existence of solutions is not so generic. G is not convex !
- Promising extension for Numerics.

➜ Mixed complementarity systems or Differential Variational Inequalities

Relations between the extensions

Proposition 5 ((Machina and Ponosov, 2011))

Under Assumption 1 (multiaffine R.H.S.), $F(x) = \overline{co}(G(x))$ *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

$$\sigma \in S^{+}(x, \theta), \tag{13}$$

   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

$$\sigma \in S^{+}(x, \theta), \tag{14}$$

can equivalently reformulate in the form of an inclusion as

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

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

$$\begin{cases} 0 \leqslant 1 - \sigma \perp (x - \theta)^{+} \geqslant 0 \\ 0 \leqslant \sigma \perp (x - \theta)^{-} \geqslant 0, \end{cases} \tag{16}$$

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

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

Reformulation as MCS/DVI

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

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

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

Reformulation as MCS/DVI

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

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

where $\mathrm{diag}(\gamma) \in \mathbb{R}^{n \times n}$ 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:

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

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

Formulation into MCP/VI

Let us define the vector

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

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

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

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

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

Existence of solutions

Proposition 7

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

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

has a nonempty and compact solution set.

Sketch of the proof

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

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

with

$$h(\sigma) = \theta - Cx = \theta - C\,\mathrm{diag}(1/(1+h\tau\gamma))\,[(I_n - h(1-\tau)\,\mathrm{diag}(\gamma))x_k + h\,g(\sigma)] \tag{26}$$

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

$$\text{(MCP)} \qquad \begin{cases} H(z) = w - v \\ l \leqslant z \leqslant u \\ (u - z)^T v = 0 \\ (z - l)^T w = 0 \end{cases} . \tag{27}$$

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

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

where

$$\begin{aligned} W^{\alpha+1} &= hC\,M^{-1}\,B(\sigma^{\alpha}), \\ q^{\alpha+1} &= CM^{-1}\left[(I_n - h(1-\tau)\mathrm{diag}(\gamma))x_k + hg(\sigma^{\alpha}) + hB(\sigma^{\alpha})\sigma^{\alpha}\right] - \theta. \\ M &= I_n + h\tau\mathrm{diag}(\gamma) \\ B(\sigma) &= \nabla_{\sigma} g(\sigma) \end{aligned}$$

- 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

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

or more compactly

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

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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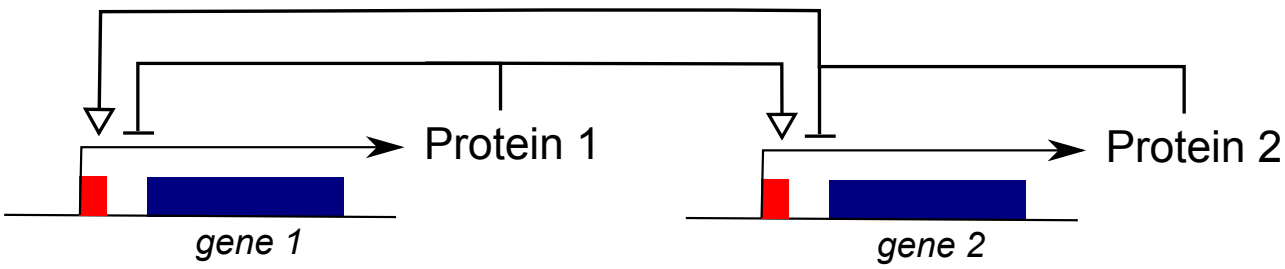
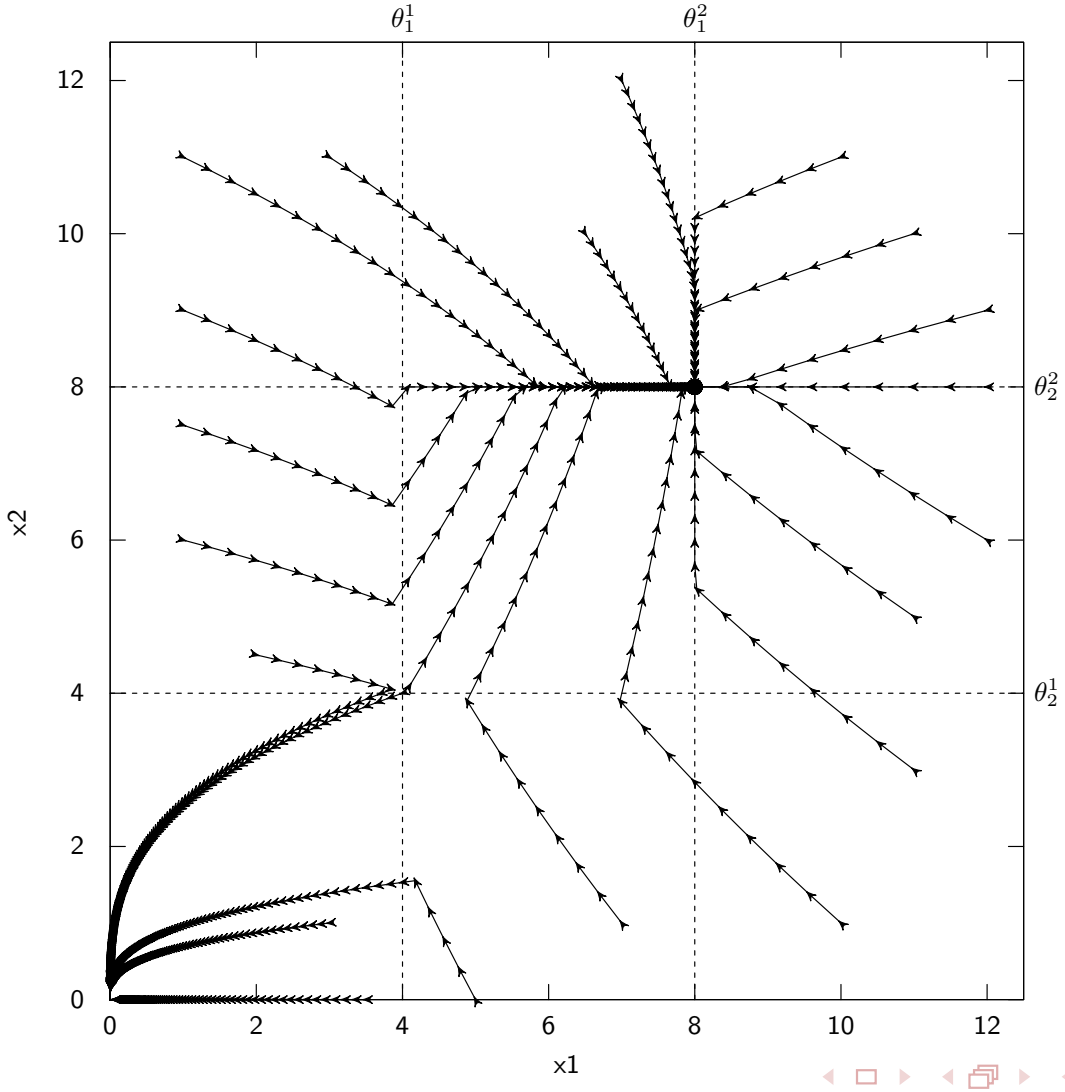


PWL model corresponding to this network.

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

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 $x_2 = \theta_2^2$

Restriction of the domain of interest to $\bar{\Omega} = \Omega \cap (\theta_1^1, +\infty) \times (\theta_1^2, +\infty)$. The original system (19) can be then reduced to

$$\begin{cases} \dot{x} = -\mathrm{diag}(\gamma)x + \bar{B}\bar{\sigma} + \bar{\kappa} \\ \bar{C}x - \bar{\theta} \in N_{[0,1]^2}(\bar{\sigma}) \end{cases} \tag{32}$$

with

$$\bar{\sigma} = \begin{bmatrix} \sigma_2 \\ \sigma_4 \end{bmatrix}, \bar{C} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \bar{\theta} = \begin{bmatrix} \theta_1^2 \\ \theta_2^2 \end{bmatrix}, \bar{B} = \begin{bmatrix} -\kappa_1 & 0 \\ 0 & -\kappa_2 \end{bmatrix}, \bar{\kappa} = \begin{bmatrix} \kappa_1 \\ \kappa_2 \end{bmatrix}. \tag{33}$$

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

Properties

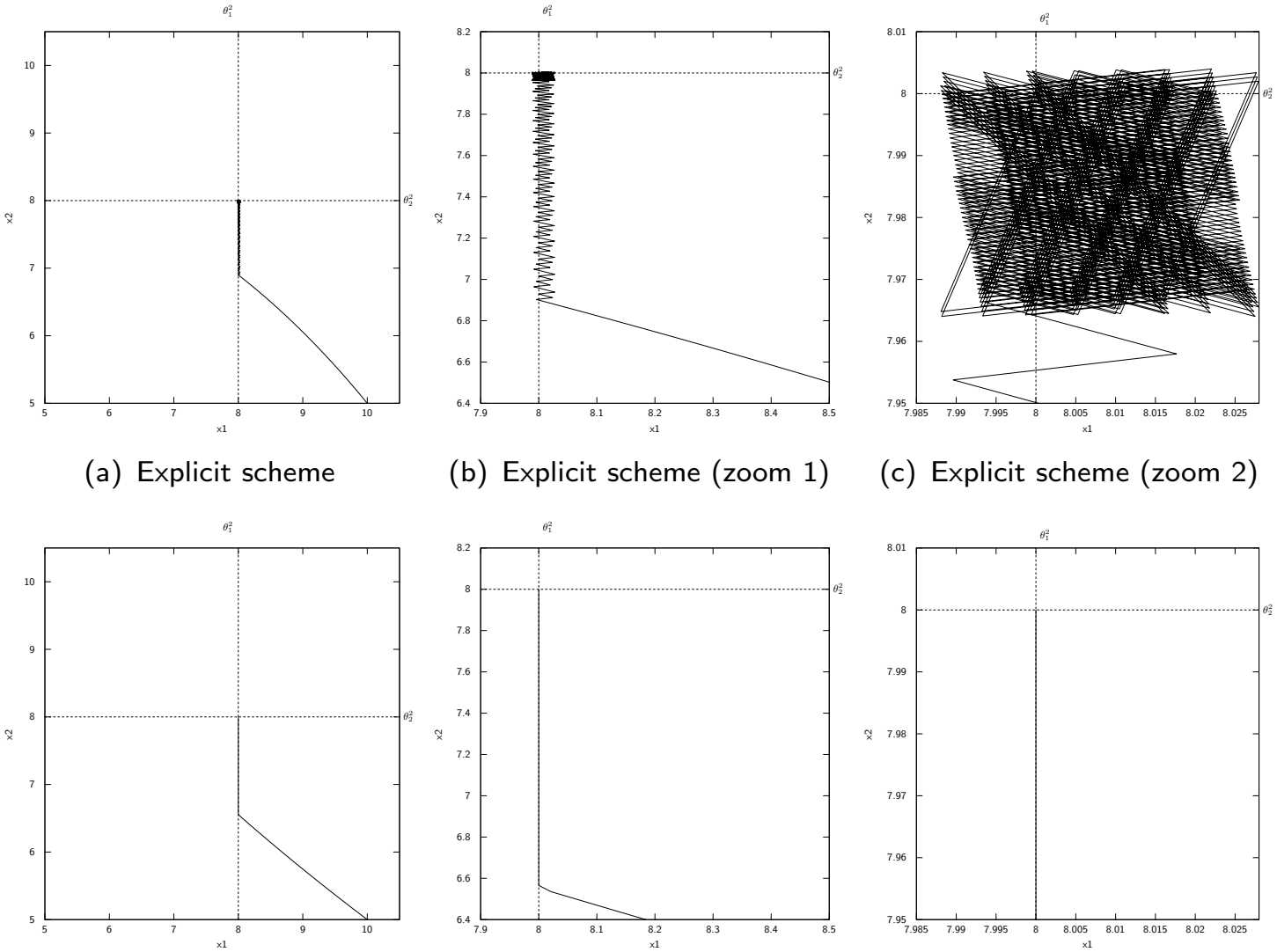
1. The one–step VI

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

   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

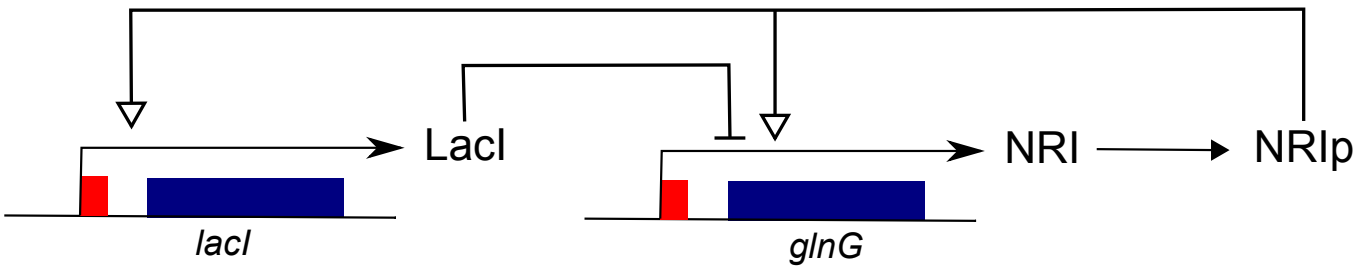
The equilibrium point $\bar{\theta} = (\theta_1^2, \theta_2^2)$ is finite-time stable in $\bar{\Omega}$.

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

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

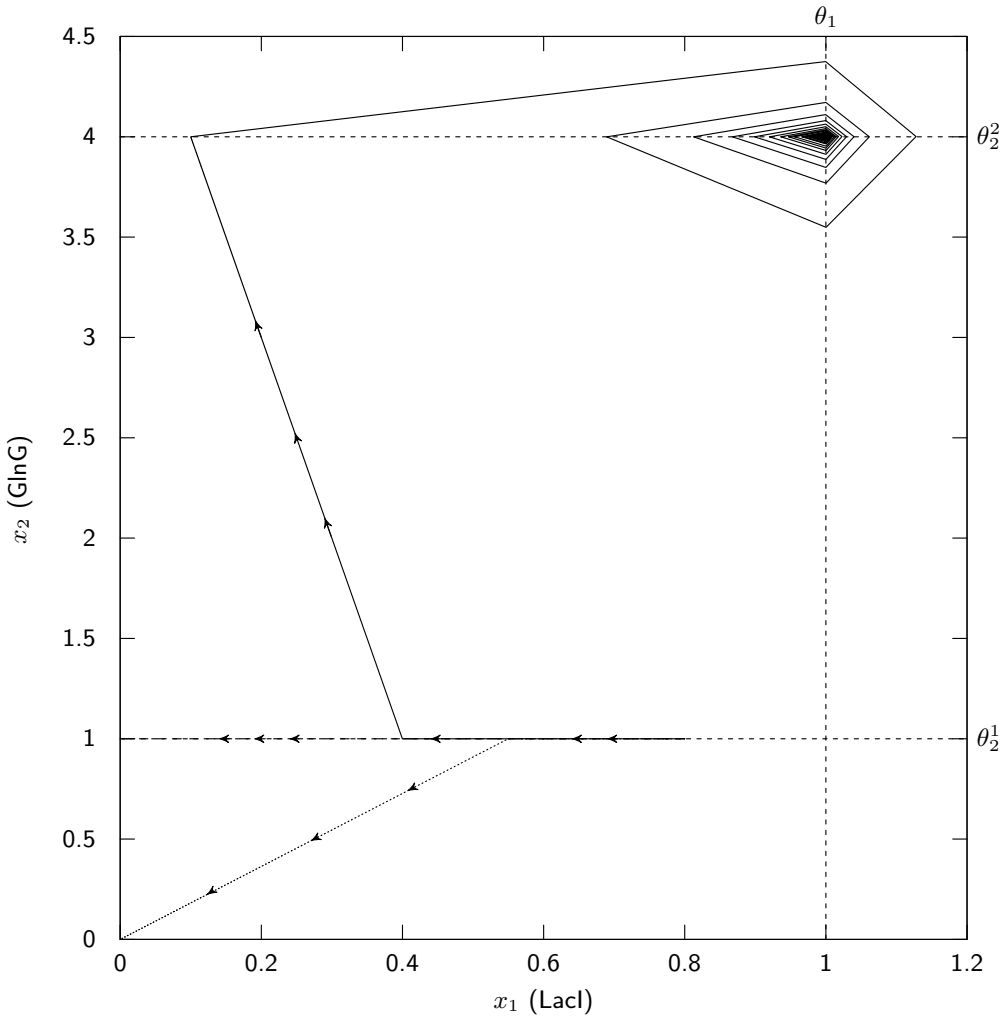
Synthetic oscillator with positive feedback



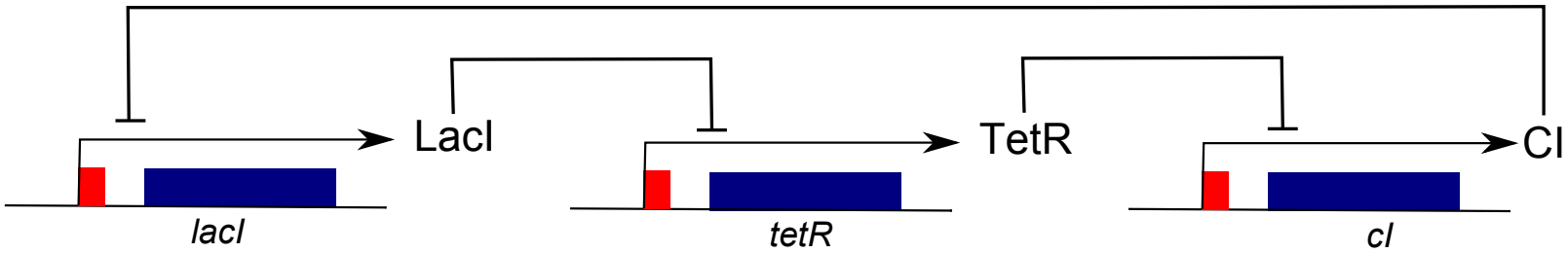
$$\begin{cases} \dot{x}_1 &= -\gamma_1 x_1 + \kappa_1 s^+(x_2, \theta_2^2) \\ \dot{x}_2 &= -\gamma_2 x_2 + \kappa_2 s^-(x_1, \theta_1) s^+(x_2, \theta_2^1) \end{cases} \tag{35}$$

The variables x_1 and x_2 represent the concentrations of the proteins LacI and GlnG, respectively.
The following parameter values have been used in the simulations: $\gamma_1 = \gamma_2 = 0.032$, $\kappa_1 = 0.08$, $\kappa_2 = 0.16$, and $\theta_1 = 1$, $\theta_2^1 = 1$, and $\theta_2^2 = 4$.

Synthetic oscillator with positive feedback



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



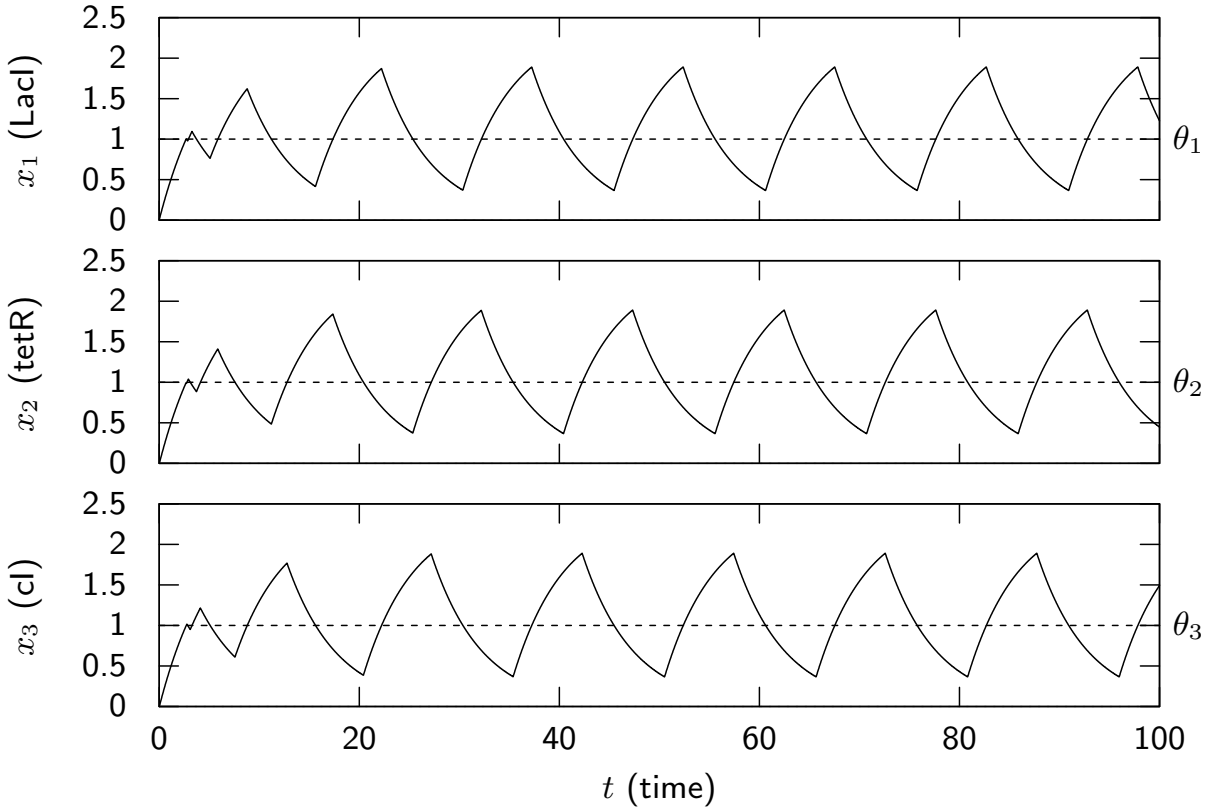
(a)

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

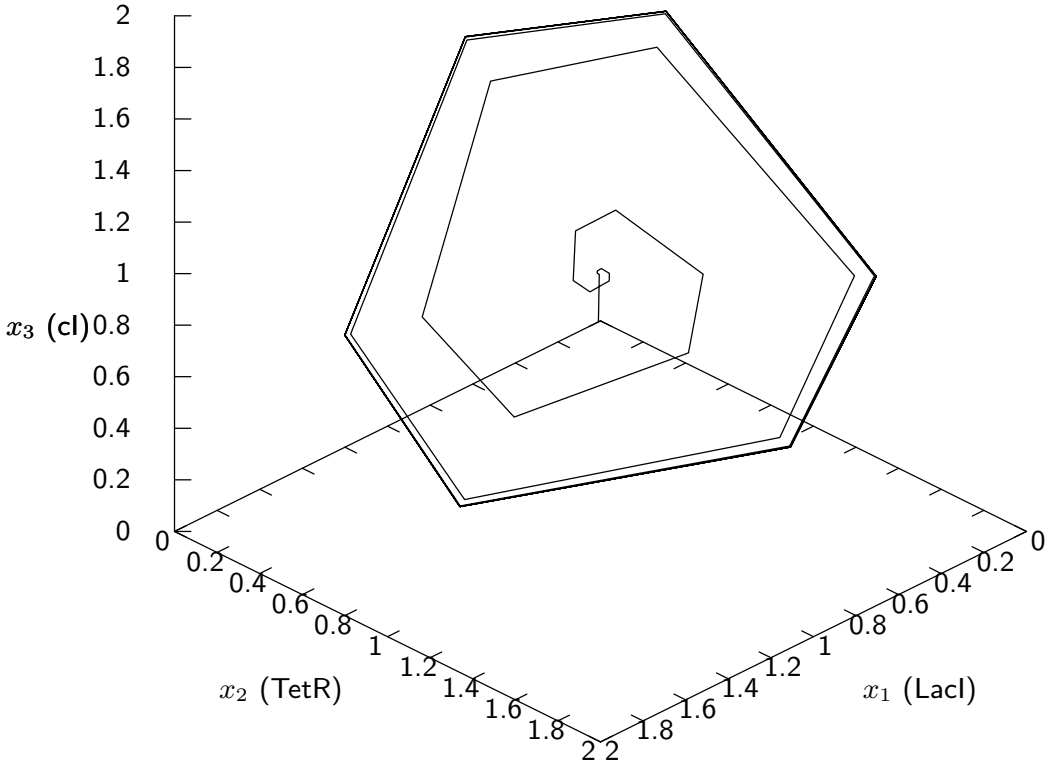
The variables x_1, x_2, and x_3 represent the concentrations of the proteins LacI, TetR, and CI, respectively.

The following parameter values have been used in the simulations:
$\gamma_1 = \gamma_2 = \gamma_3 = 0.2$, $\kappa_1^1 = \kappa_2^1 = \kappa_3^1 = 4.8\,10^{-4}$, $\kappa_1^2 = \kappa_2^2 = \kappa_3^2 = 4.8\,10^{-1}$, 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)



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 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.

Introduction on gene regulatory network modeling
- A first simple network of two genes
- Definition of Piece-Wise Linear (PWL) models

Filippov's solutions
- Notions of Filippov's solutions
- Filippov's extension of PWL models
- Aizerman & Pyatnitskii's extension of PWL models
- Relations between the extensions

Numerical Methods for the AP-extension
- Principles
- Reformulation as MCS/DVI
- The general time-discretization framework.
- Solution methods for MCP

Illustrations
- The first simple network of two genes
- Synthetic oscillator with positive feedback
- Repressilator

Conclusions & Perspectives

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General Piecewise Linear models