European Conference on Complex Systems

ECCS'07, Dresden

Hierarchical analysis of piecewise affine models of gene regulatory networks

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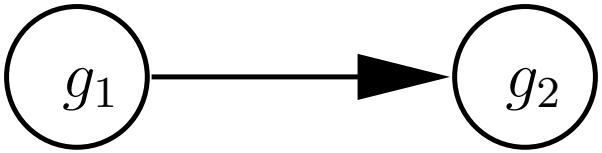
Oct., 1st 2007

Outline

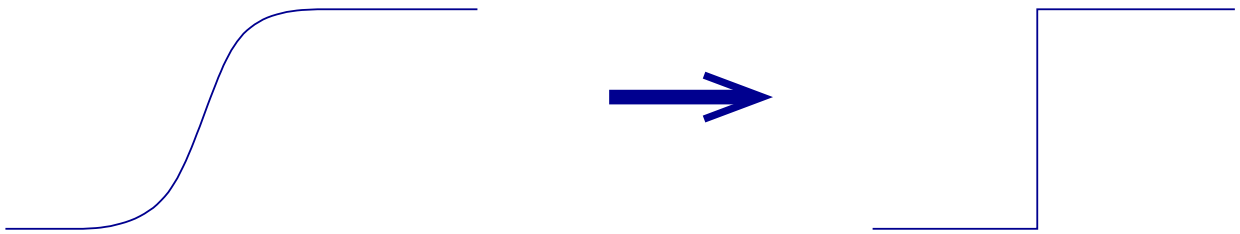
- The piecewise affine framework
- Hierarchical decomposition of PWA systems and asymptotic qualitative analysis
- Threshold elimination and application to biological example

Piecewise affine models of gene regulatory networks



- Vertices g_i: stand for genes. Each g_i is associated to a nonnegative variable: $x_i \in [0, max_i]$ representing the *level of expression* of gene i.

- Edges: stand for sigmoid-like interactions between genes.



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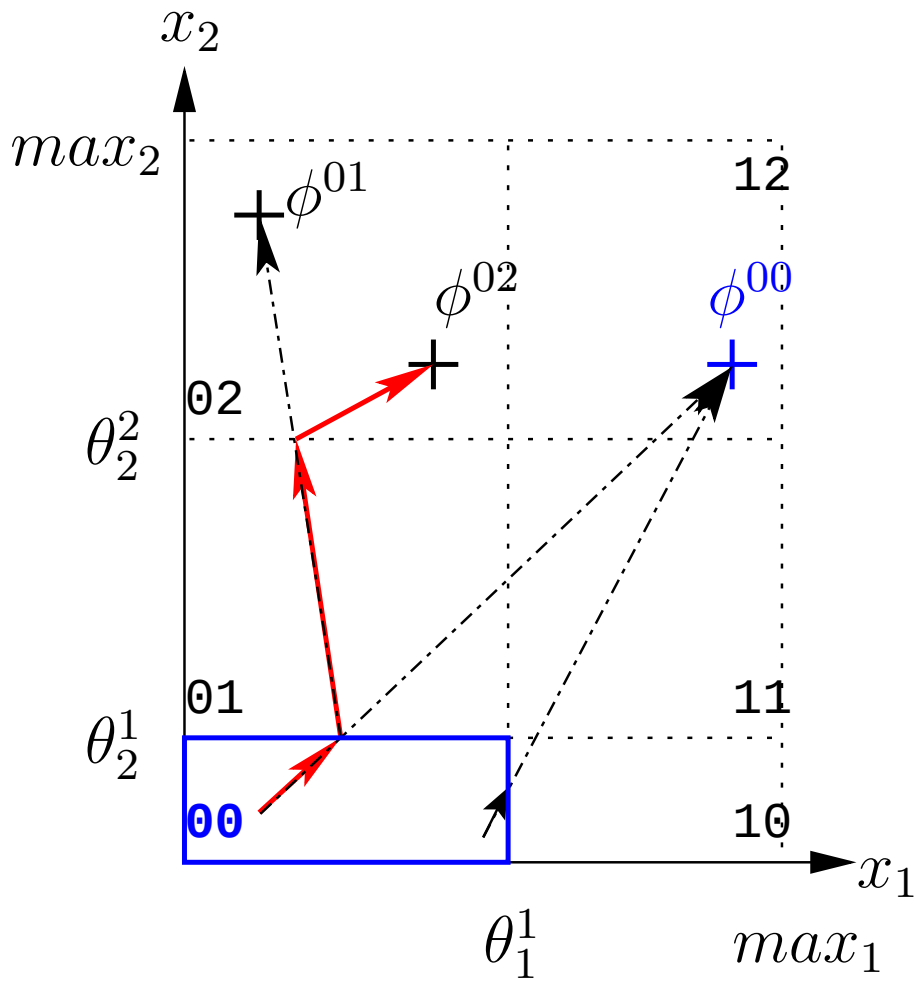
Piecewise affine models of gene regulatory networks

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

In each box $D = \prod_{i=1}^{n} \left]\theta_i^{j_i}, \theta_i^{j_i+1}\right[$, the flow monotonically converges to a unique focal point

Ex: box $00 \longrightarrow \phi^{00} = \left(\frac{\kappa_1^2}{\gamma_1}, \frac{\kappa_2^2}{\gamma_2}\right)$

$\rightsquigarrow$ Here, focal point ϕ^{00} belongs to the box 12.

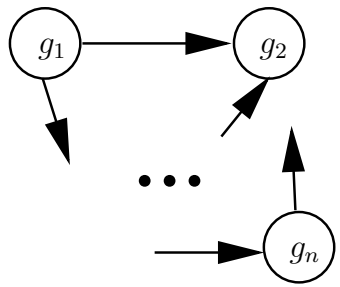


Qualitative analysis of PWA systems

The discrete structure of PWA systems allows a qualitative analysis of their dynamics. [de Jong *et al.* 2005]

- Given a PWA system:

$$\begin{cases} \dot{x}_1 = K_1(x) - \Gamma_1(x)x_1 \\ \dots \\ \dot{x}_n = K_n(x) - \Gamma_n(x)x_n \end{cases}$$



- Together with the relative positions of the focal points:

$$\forall\ D\,, \qquad \forall\, i\,, \quad \theta_i^j < \left(\phi^D\right)_i < \theta_i^{j+1}$$

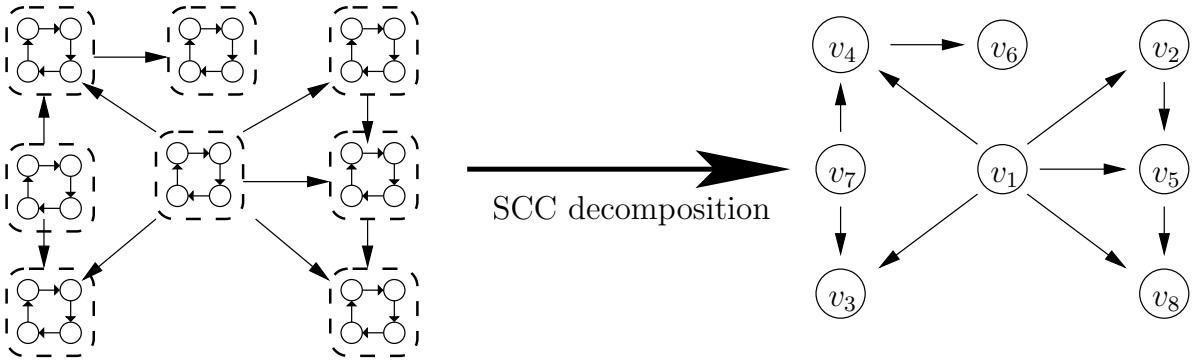
- We can compute qualitative simulations with computer tools such that *Genetic Network Analyser* (GNA) [de Jong *et al.* 2003].

Hierarchical analysis of PWA systems

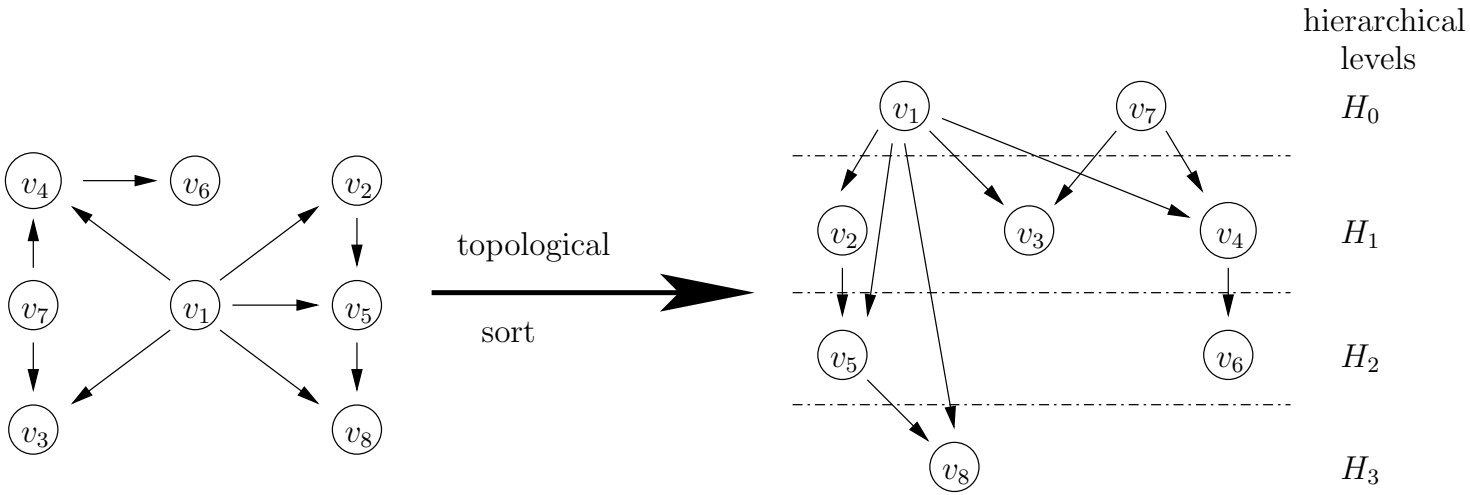
- Hierarchical decomposition of interaction graph
- Asymptotic analysis of triangular PWA system

SCC decomposition and topological sort

- Decomposition of the *interaction graph* in Strongly Connected Components (SCC)



- Topological sort of the SCC graph ($\rightsquigarrow$ *hierarchical organization*).



SCC decomposition and topological sort

This decomposition leads to a triangular form of the ODEs:

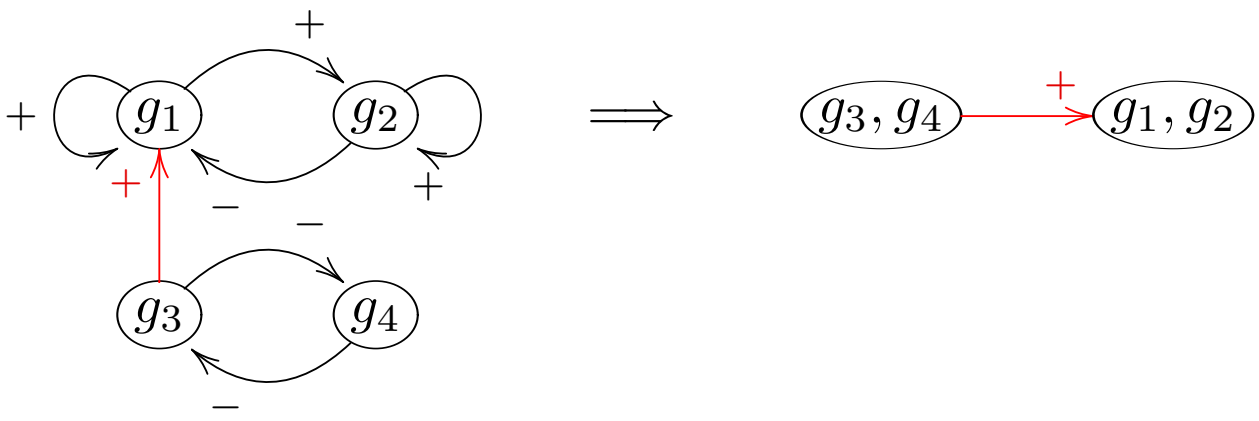
$$x = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_{n-1} \\ x_n \end{pmatrix} \rightsquigarrow \xi = \begin{pmatrix} \xi_1 \\ \vdots \\ \xi_k \end{pmatrix}, \quad \begin{cases} \dot{\xi}_1 = f_1(\xi_1) \\ \dot{\xi}_2 = f_2(\xi_1, \xi_2) \\ \dots \\ \dot{\xi}_k = f_k(\xi_1, \xi_2, \dots, \xi_k) \end{cases}$$

$\Rightarrow$ We are brought to analyze $\mathbf{k}$ $(\leq n)$ **smaller** PWA systems.

Asymptotic analysis of hierarchical PWA systems

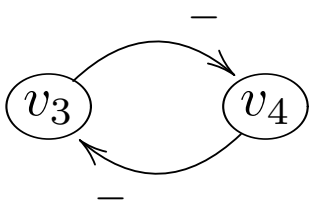
$$(\Sigma)\begin{cases} \dot{x}_1 = \kappa_1^0 + \kappa_1^1 f_1(x) + \kappa_1^2 s^+(x_1,\theta_1^1)s^-(x_2,\theta_2^2)s^+(x_3,\theta_3^1)f_1(x) - \gamma_1 x_1 \\ \dot{x}_2 = \kappa_2^0 + \kappa_2^1 f_2(x) + \kappa_2^2 s^+(x_1,\theta_1^1)s^+(x_2,\theta_2^1)f_2(x) - \gamma_2 x_2 \\ \dot{x}_3 = \kappa_3^0 + \kappa_3^1 s^-(x_4,\theta_4^1) - \gamma_3 x_3 \\ \dot{x}_4 = \kappa_4^0 + \kappa_4^1 s^-(x_3,\theta_3^1) - \gamma_4 x_4 \end{cases}$$

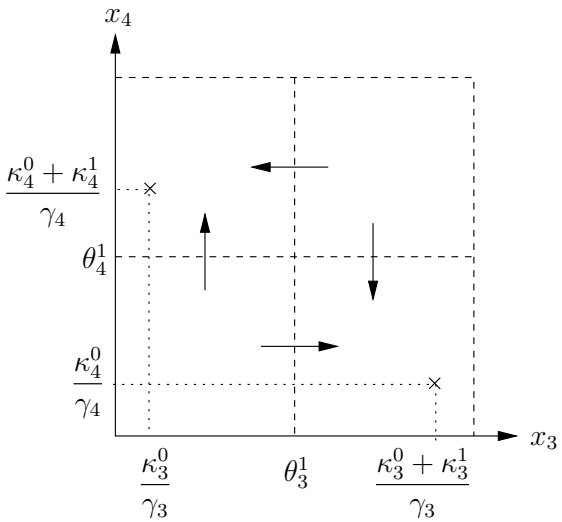
The hierarchization of the interaction graph gives:



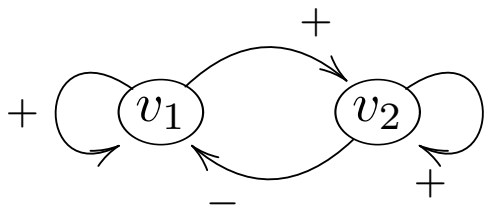
Asymptotic analysis of hierarchical PWA systems

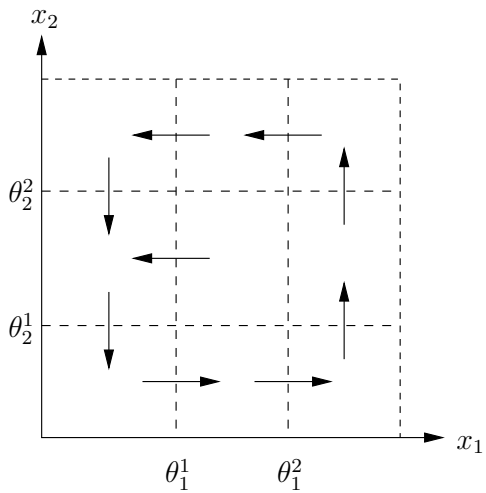
(Σ_1)





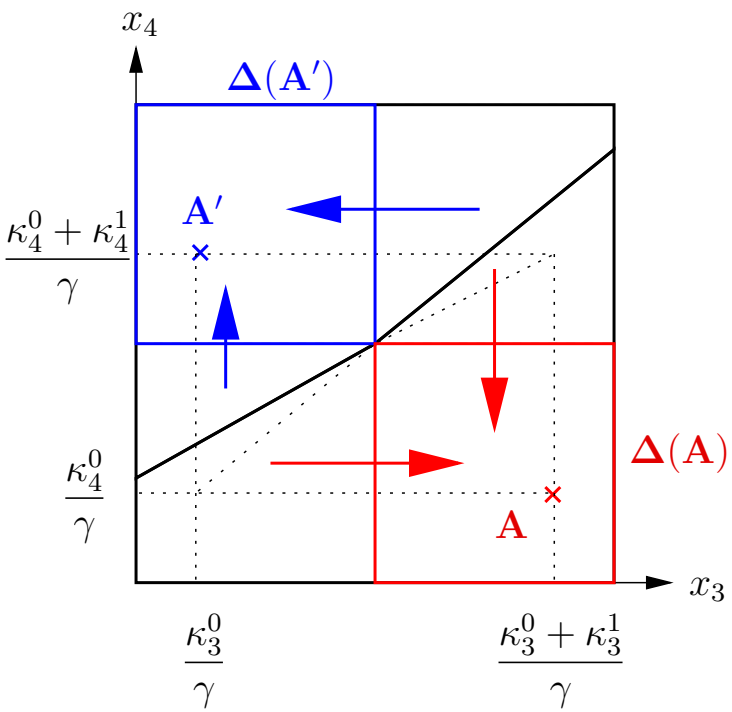
(Σ_2)





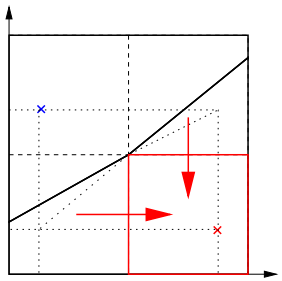
Asymptotic analysis of hierarchical PWA systems

- The first subsystem (Σ_1) is the classical bi-stable switch.
- We have therefore to study 2 cases, according to the initial condition of the first subsystem: (x_3^0, x_4^0):



Asymptotic analysis of hierarchical PWA systems

- First case :

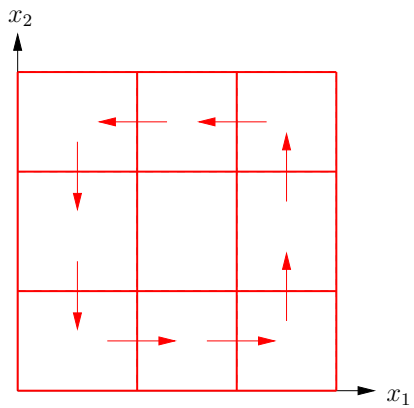


After a *finite time*, we have:

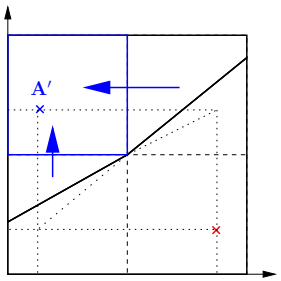
$$s^+(x_3, \theta_3^1) = 1$$

$$\Downarrow$$

The second subsystem (Σ_2) converges towards an attractive cycle:



- Second case :

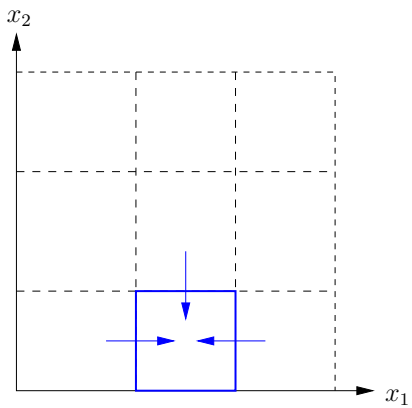


After a *finite time*, we have:

$$s^+(x_3, \theta_3^1) = 0$$

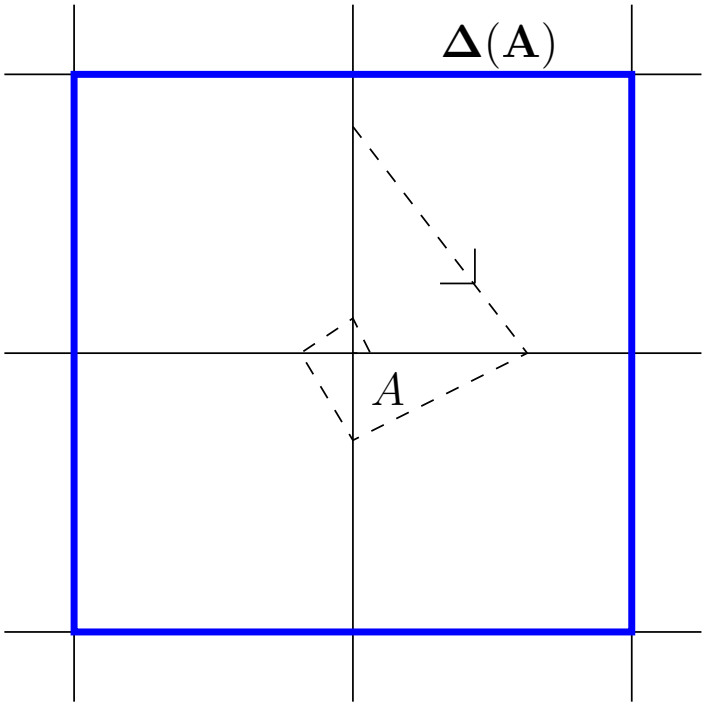
$$\Downarrow$$

The second subsystem (Σ_2) converges towards a steady state:

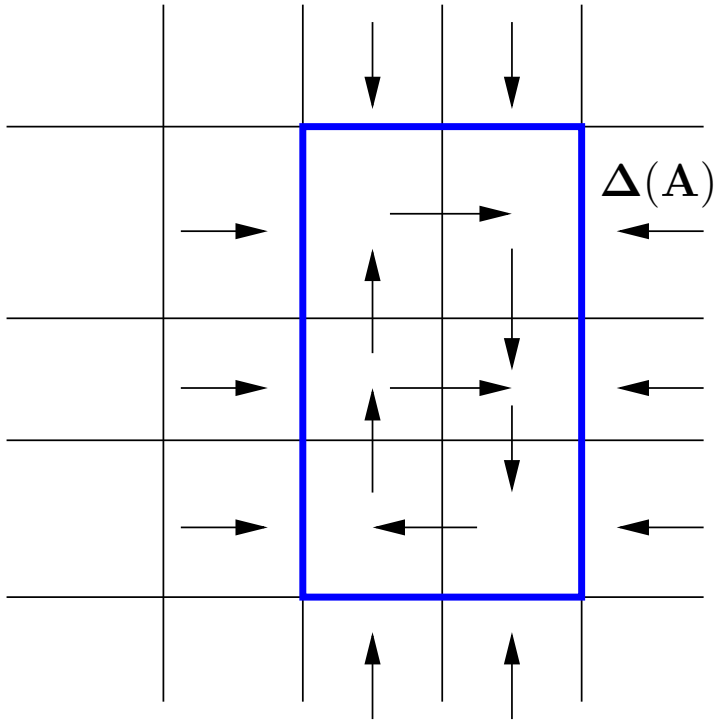


Asymptotic analysis of hierarchical PWA systems

Generalization for other types of attractors:



A singular steady state



A more complex attractor

Asymptotic analysis of hierarchical PWA systems

- The SCC computation allows to decompose a "big" PWA system into a hierarchy of coupled or uncoupled PWA subsystems.

  $\longrightarrow$ Model reduction technique

- It gives a practical way to analyze the qualitative behavior of the initial system thanks to the qualitative analysis of the subsystems.

- The efficiency of this method strongly relies on the efficiency of the SCC decomposition.

  $\longrightarrow$ In some cases, this method can be improved by a simple threshold elimination algorithm.

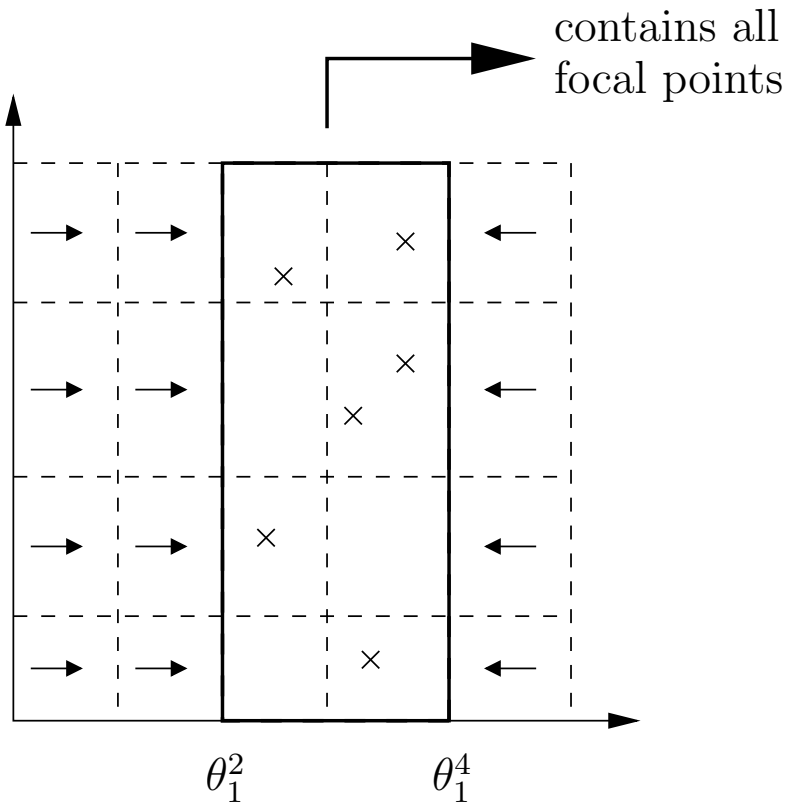
Threshold elimination and hierarchical decomposition

$\rightsquigarrow$ Application to a biological example:

carbon starvation response network in e-coli

[de Jong *et al.* Biosystems, 2006]

The principle of threshold elimination



- In this case, in the direction x_1, after a finite time we have:

$$\begin{cases} s^+(x_1, \theta_1^0) = s^+(x_1, \theta_1^1) = s^+(x_1, \theta_1^2) = 1 \\ s^+(x_1, \theta_1^4) = \cdots = s^+(x_1, \theta_1^{p_1}) = 0 \end{cases}$$

- Injecting these equations in the system, we eliminate thresholds $\theta_1^0, \theta_1^1, \theta_1^2, \theta_1^4, \ldots$
- This can be performed in each direction independently.

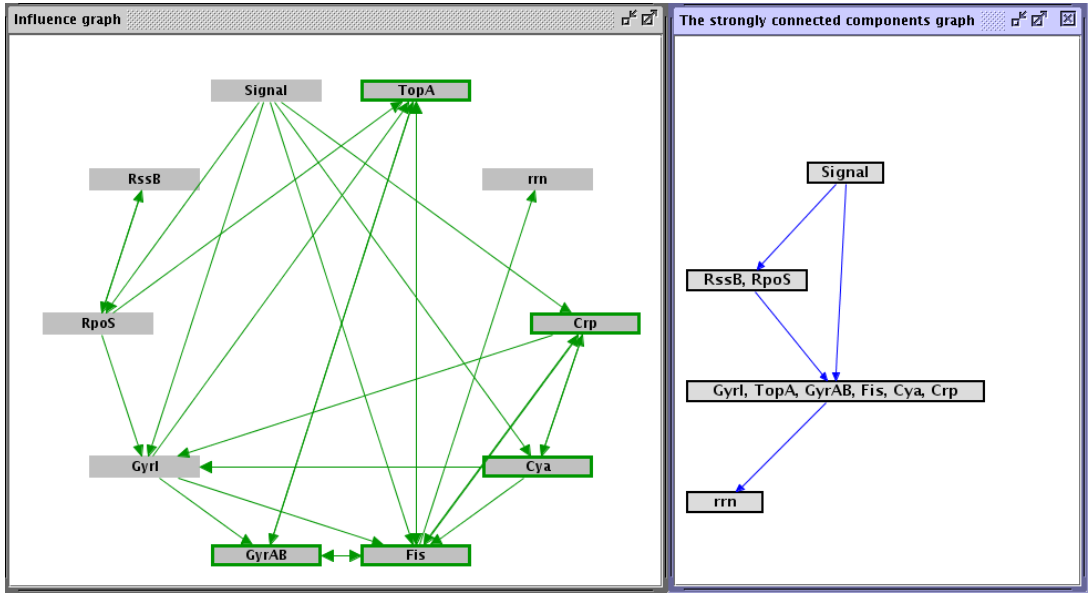
The principle of threshold elimination

Compute the interaction graph $\mathcal{G}_\Sigma$
Compute the hierarchical graph $\mathcal{G}^{scc}$ {The SCC are denoted $C_1, \ldots, C_m$, they are hierarchically ordered: if $1 \leq k_1 < k_2 \leq m$, then there is no edge from C_{k_2} to C_{k_1}.}
for $k = 1$ to m **do**
  repeat
    for $j = 1$ to l **do**
      Compute the set Φ of focal points
      Perform elimination in direction j {Some edges are possibly cut.}
      Compute the new interaction graph
      Compute the new hierarchical graph
      Compute the new set Φ' of focal points
    end for
  until $\Phi' = \Phi$
end for
Build the reduced system (Σ')

Application to a biological example

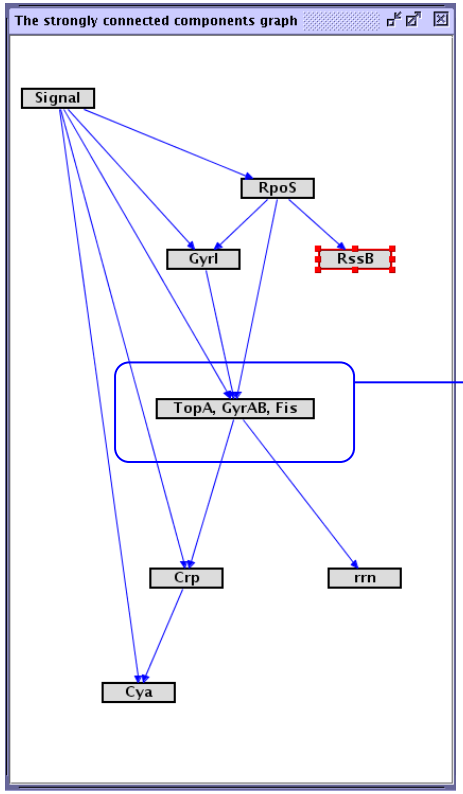
Extended model of carbon starvation response network in e-coli:

- 9 variables,
- 1 input variable



Application to a biological example

Interaction graph after threshold elimination and SCC decomposition:



TopA, *GyrAB* and *Fis* form a group of 3 variables that seems to play a central role in the system behavior

[Grognard *et al.* 2007]

Conclusion

- Models of gene regulatory networks:

  The PWA framework offers a practical way to represent gene interactions dynamics.

  $\rightsquigarrow$ *GNA* software, Qualitative analysis.

- Hierarchical organization:

  it is a general *model reduction* technique, improving in certain cases the qualitative analysis

- The threshold elimination process can be improved, notably considering "*discrete invariants*" of the system:

  discrete invariants $\leftrightarrow$ SCC of the transition graph