Reachability of singular states in Thomas-Snoussi networks

Eric Fanchon

Institut de Biologie Structurale,
Grenoble

GeoCal, feb. 2006

Outline

1. Presentation of multivalued asynchronous (Thomas-Snoussi) networks

2. Results
   - Generalization of Snoussi's theorem
   - Generalization of the 'circuit analysis'
   - Determine the class of singular states which are potentially reachable → reduction of complexity

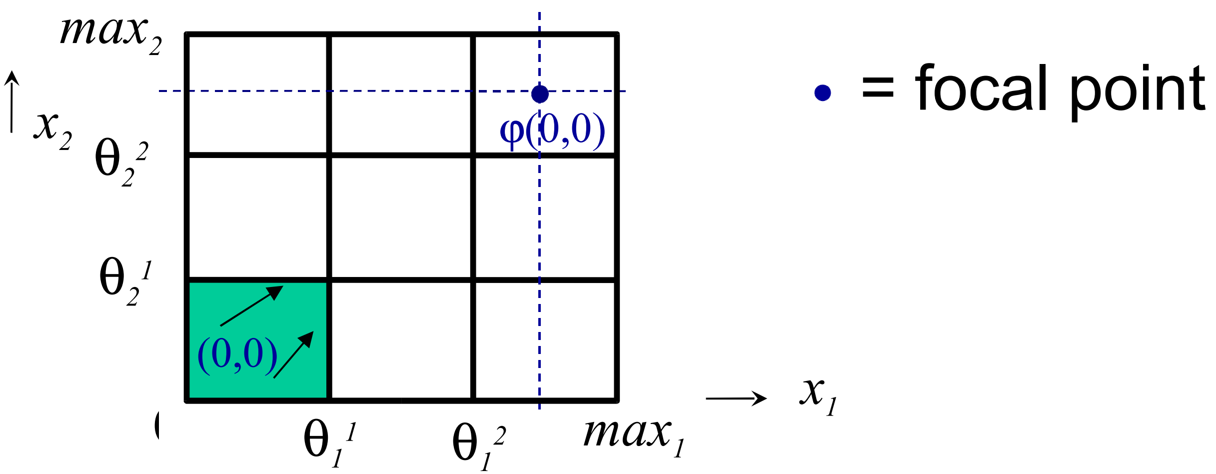
Piecewise-affine systems

$$dx_i/dt = f_i(\mathbf{x}) - \gamma_i x_i \quad \text{with } \gamma_i > 0$$

Rectangular partition

In each regular domain D, the system tends monotonically to a focal point $\varphi(D)$.

Phase portrait : determined by the distribution of focal points



Focal point equations

2d example with two thresholds on each axis :

$$\dot{x}_1 = \kappa_1\, s^-(x_1, \theta_1^{\,2})\, s^-(x_2, \theta_2^{\,1}) - \gamma_1 x_1 = 0$$

$$\dot{x}_2 = \kappa_2\, s^-(x_1, \theta_1^{\,1})\, s^-(x_2, \theta_2^{\,2}) - \gamma_2 x_2 = 0$$

s : step function

x : protein concentration

θ : threshold

κ , γ : kinetic constants

Focal point equations :

$$\varphi_1(\mathbf{x}) = K_1\, s^-(x_1, \theta_1^{\,2})\, s^-(x_2, \theta_2^{\,1})$$

$$\varphi_2(\mathbf{x}) = K_2\, s^-(x_1, \theta_1^{\,1})\, s^-(x_2, \theta_2^{\,2})$$

with $K_1 = \kappa_1/\gamma_1$ and $K_2 = \kappa_2/\gamma_2$

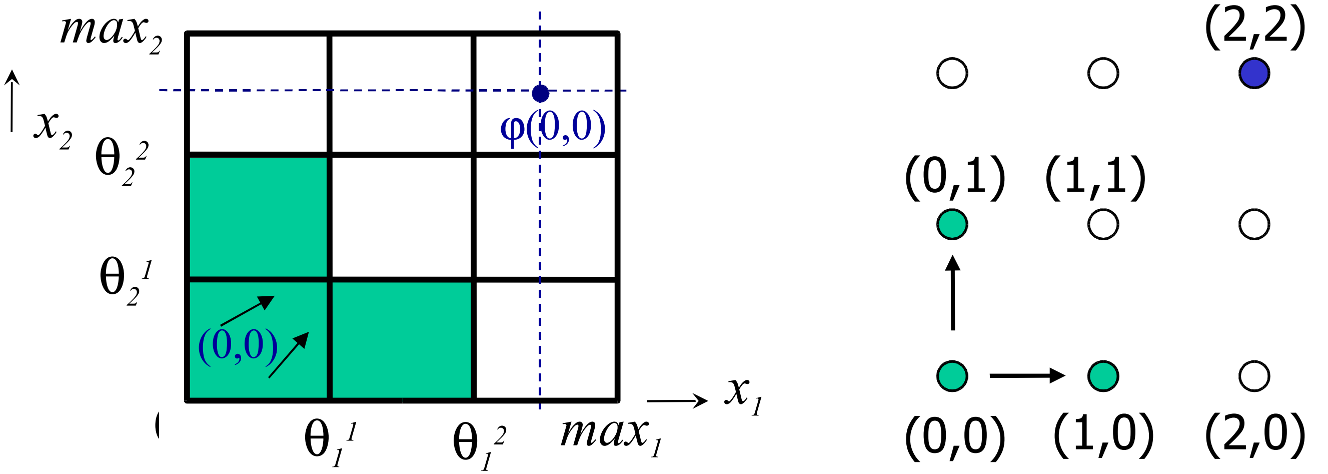
Focal point equations

$$\begin{cases} \dots \\ \varphi_j(x) = g_j(s^\varepsilon(x_i, \theta_i), s^\varepsilon(x_r, \theta_r), \dots) \\ \varphi_k(x) = g_k(s^\varepsilon(x_i, \theta_i), \dots) \\ \dots \end{cases}$$

Discrete abstraction

Instantiation of the parameters
→ transition graph

Transition D → D' : if ∃ trajectory going from *D* to *D'*.



9 states

If the focal point of D is outside D : outgoing transition(s)
Else : D is a (stable) stationary state.

Transition rule

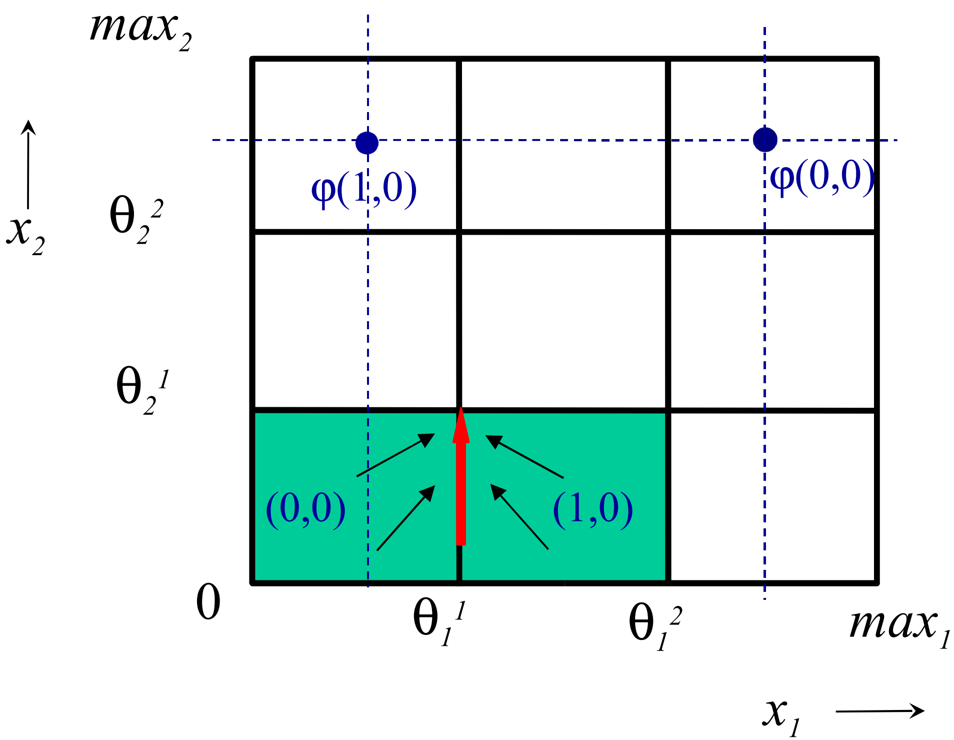
State $\mathbf{x'}$ is a successor of $\mathbf{x}$ if :

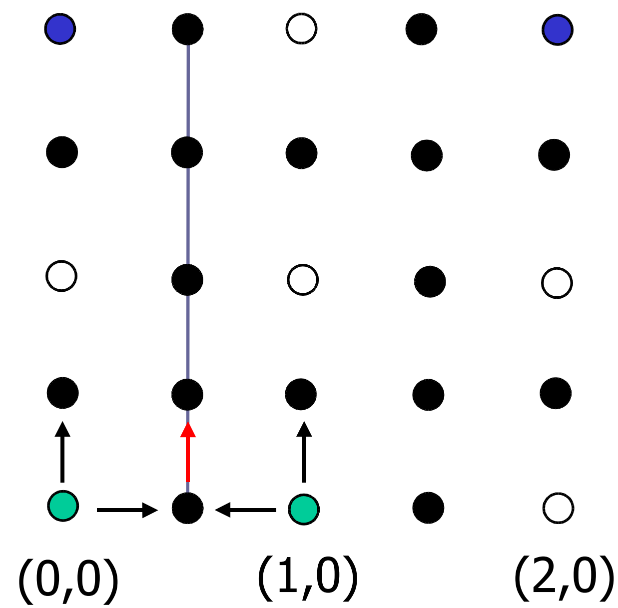
- $\mathbf{x'}$ is adjacent to $\mathbf{x}$

  $\Rightarrow$ there exists at most one component i such that $x'_i \neq x_i$

- If $\varphi_i(\mathbf{x}) > x_i$: $x'_i = x_i + 1$
- If $\varphi_i(\mathbf{x}) < x_i$: $x'_i = x_i - 1$
- If $\varphi_i(\mathbf{x}) = x_i$: $x'_i = x_i$

Black wall





25 states

de Jong, Gouzé et al., Bull. Math. Biology, 66, 301 (2004)
Sliding mode / persistent state

Singular states

- Order of a singular state : number of state components equal to a threshold ($x_i = \theta_i$)

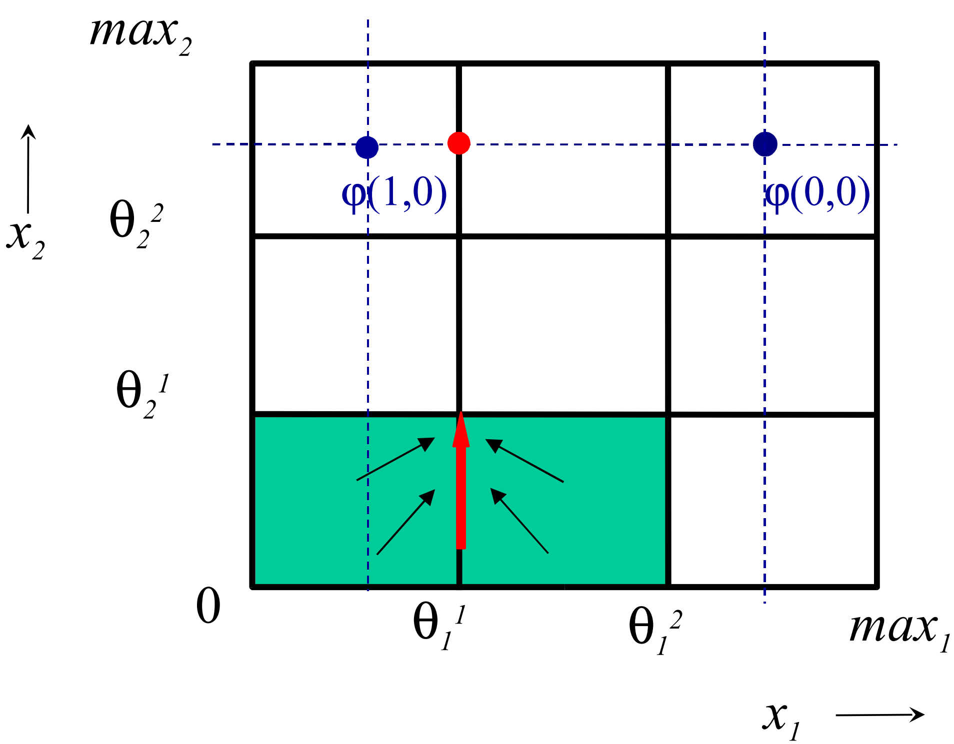
  n=4: $\mathbf{x} = (1, \theta_2, 0, \theta_4)$ → $q(\mathbf{x})=2$

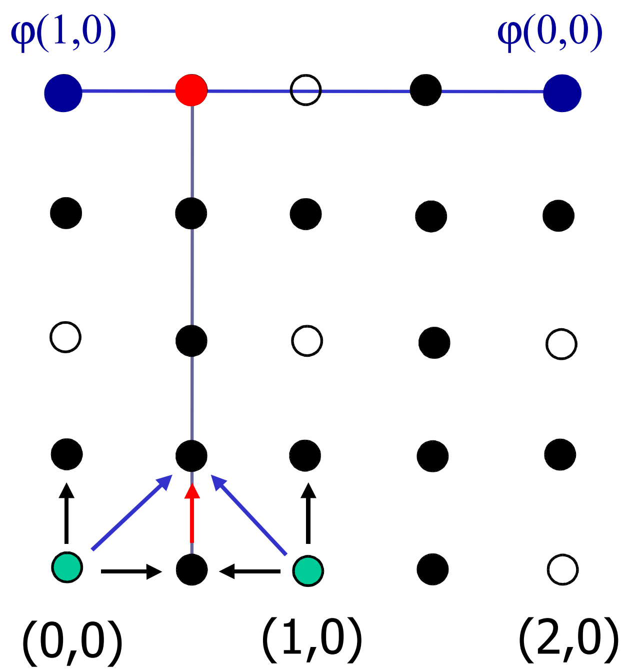
- If n is the dimensionality of the system, the total number of states is increased by a factor α^n,

  $1.5 < \alpha < 2$.

  Ex: 4 thresholds per axis, n=10: $\alpha^n \approx 350$

Formal (discrete) rule

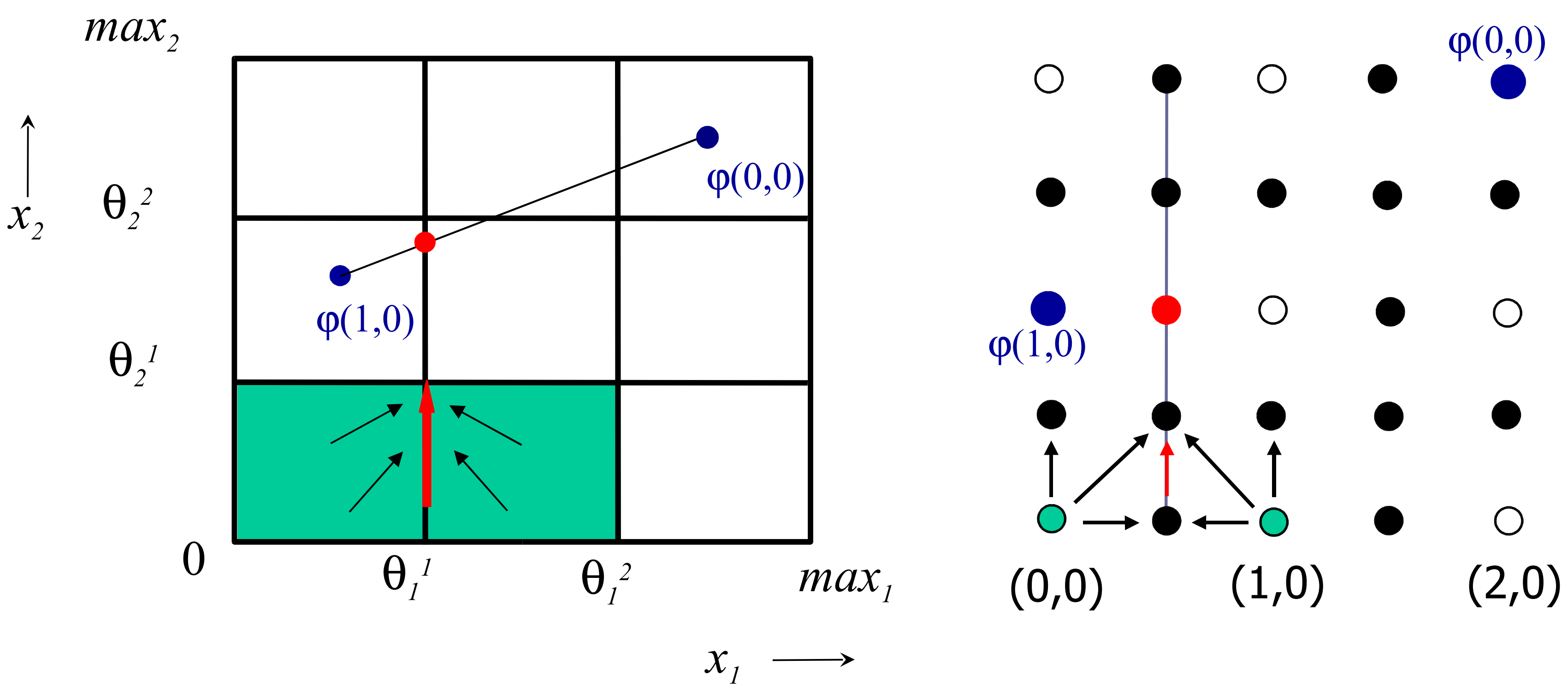




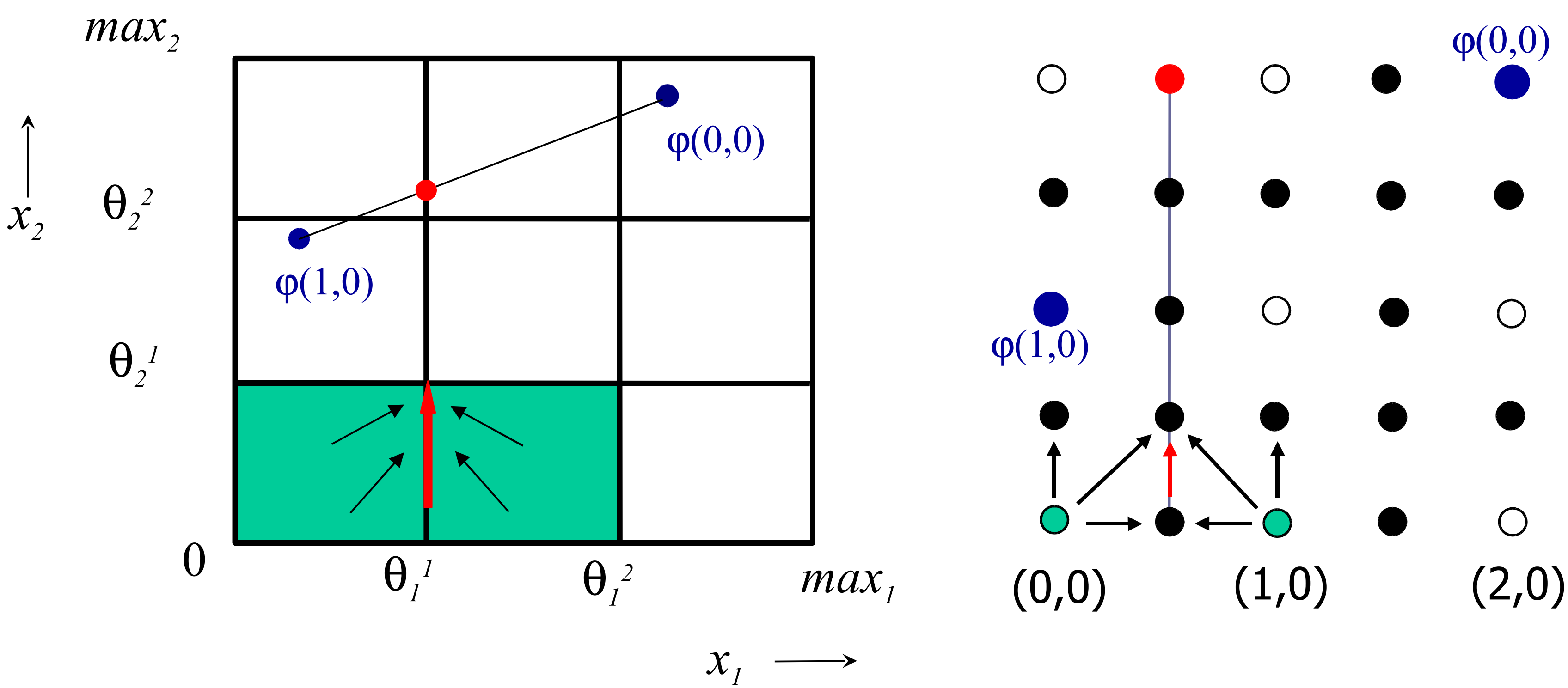
Derived from de Jong, Gouzé et al., Bull. Math. Biology, 66, 301 (2004)

Second abstraction

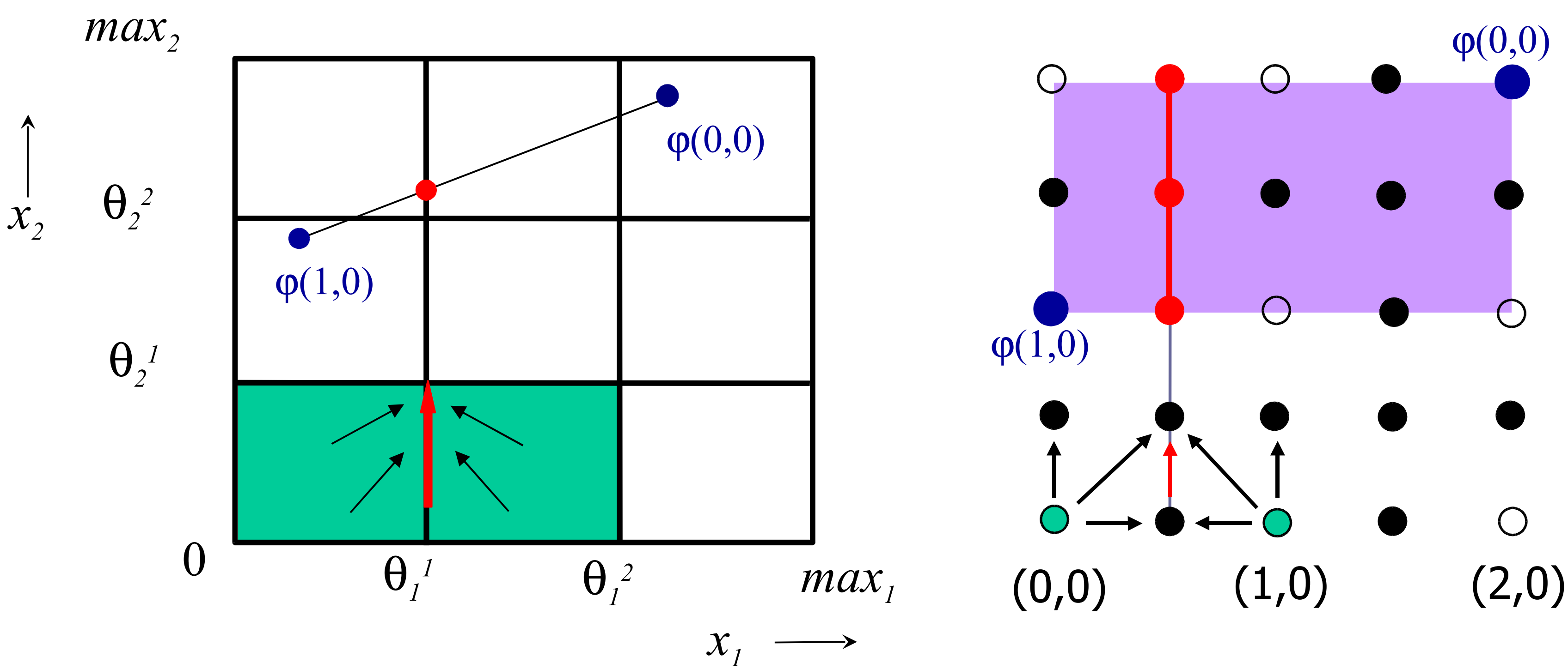
Discretization of the focal point coordinates



Second abstraction



Hyper-rectangular approximation



Superposition of the 3 possibilities

Derived from de Jong, Gouzé et al., Bull. Math. Biology, 66, 301 (2004)

Transition rules

Let **x** be a state and **x'** a state (adjacent to **x**) of lower dimension (i.e.higher order)

Transition **x** → **x'** exists iff :

- The intersection of Rect(**x**) and of the support of **x** is non-empty (**x** is persistant)
- Pour toute composante i qui est régulière dans **x** et singulière dans **x'** :
  - si $x'_i = x_i + \frac{1}{2}$: $\exists y \in \mathrm{Reg}(\mathbf{x}),\ x_i < \varphi_i(\mathbf{y})$
  - si $x'_i = x_i - \frac{1}{2}$: $\exists y \in \mathrm{Reg}(\mathbf{x}),\ x_i > \varphi_i(\mathbf{y})$

Transition graph

Nodes = domains (discrete states)
Arcs = all possible transitions between domains

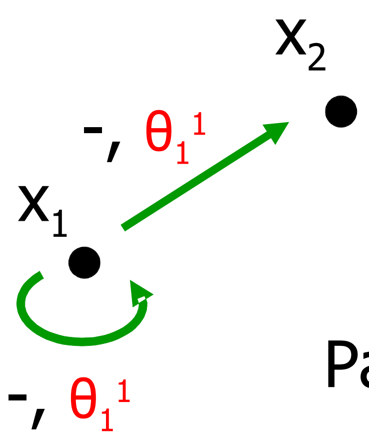
All continuous trajectories are represented by a **path** in the transition graph

The transition graph provides a qualitative view of the phase portrait

Part 2 : General properties

- Generalization of Snoussi's theorem
- Consequences of threshold multiplicities greater than 1
- Generalization of the 'circuit analysis'

Local influence graph



$$\varphi_1(\mathbf{x}) = K_1\,(1 - s^+(x_1, \theta_1^1)\, s^+(x_2, \theta_2^1))$$

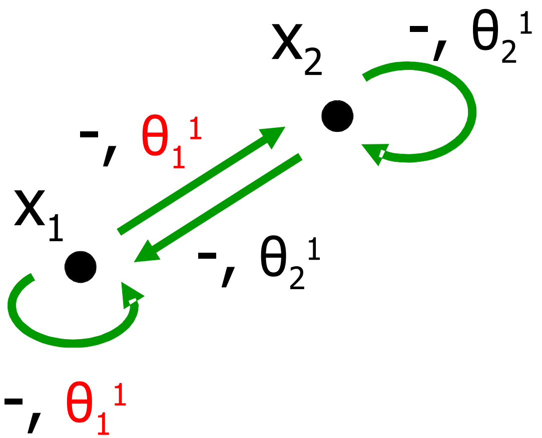
$$\varphi_2(\mathbf{x}) = K_2\,(1 - s^+(x_1, \theta_1^1)\, s^+(x_2, \theta_2^1))$$

Partial graph associated to $(\theta_1^1, 1)$

Jacobian matrix of $\Phi(\mathbf{x})$: $a_{ij} = \partial\Phi_i/\partial x_j \neq 0$ iff j influences i

→ Every singular state $\mathbf{x}$ is associated to a local graph $G(\mathbf{x})$

Global influence graph



$$\varphi_1(\mathbf{x}) = K_1\,(1 - s^+(x_1,\theta_1^1)\; s^+(x_2,\theta_2^1))$$

$$\varphi_2(\mathbf{x}) = K_2\,(1 - s^+(x_1,\theta_1^1)\; s^+(x_2,\theta_2^1))$$

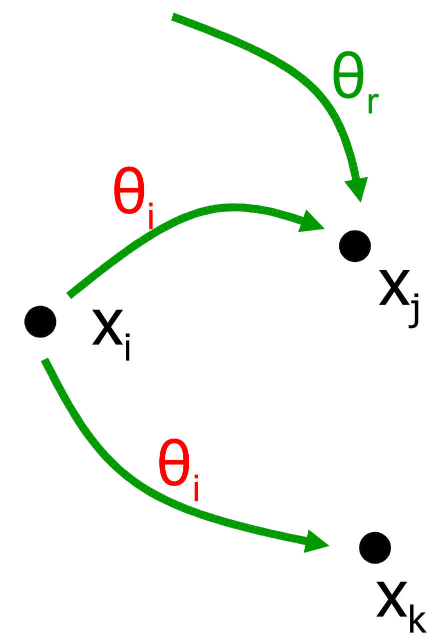
One step function → one arc

Each arc represents a derivative $\partial \Phi_i / \partial x_j$

Threshold multiplicity

- Definition:
  multiplicity of threshold θ_i = number of arcs labelled with θ_i.
- Ex: two genes belonging to the same operon

$$\begin{cases} \ldots \\ \varphi_j(\mathbf{x}) = f_j(s^\varepsilon(x_i,\theta_i), s^\varepsilon(x_r, \theta_r), \ldots) \\ \varphi_k(\mathbf{x}) = f_k(s^\varepsilon(x_i,\theta_i), \ldots) \\ \ldots \end{cases}$$



Link joining the 2 focal points is a slanted segment in the plane (x_j,x_k)

mult(θ_i) = m : m components of focal points may change when θ_i is crossed

Snoussi's theorem

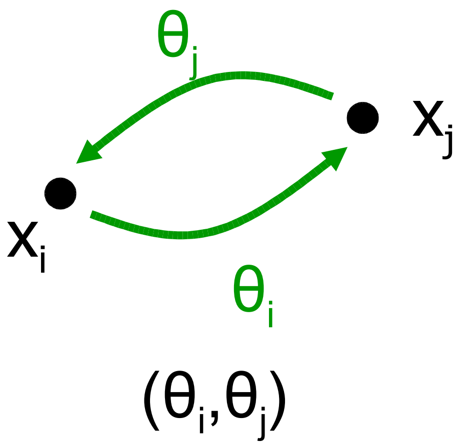
Snoussi & Thomas, Bull. Math. Biol., 55, 973 (1993)

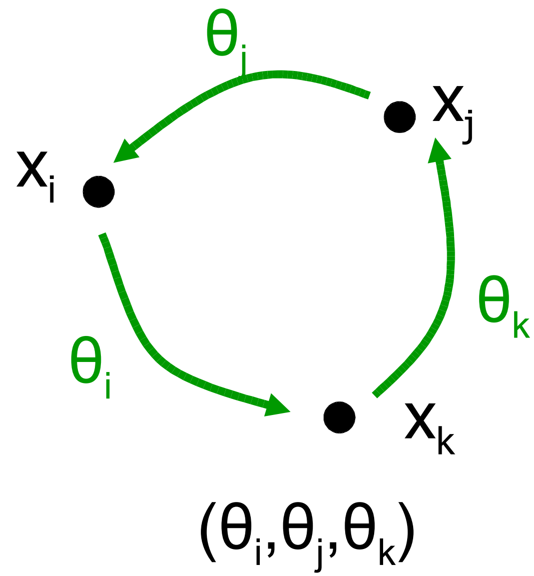
- Two restrictions:
  - Additive systems : $f_i(\mathbf{x}) = k_{i0} + \sum k_{ij}\, \sigma^{\pm(ij)}(x_j, \theta_{ij})$
  - All the thresholds have multiplicity = 1
- Let x be a singular state

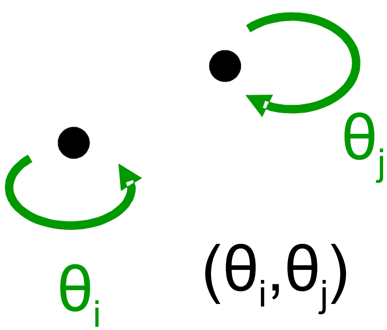
  x persistent $\Rightarrow$ G(x) is a hooping

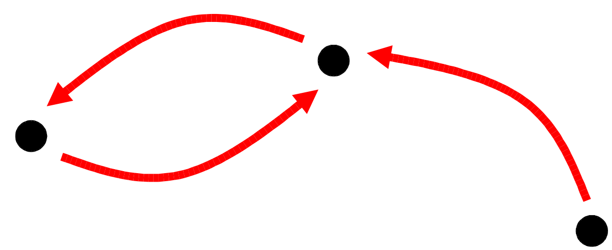
Hooping : circuit or union of disjoint circuits (C. Soulé)

(counter-) examples of hoopings







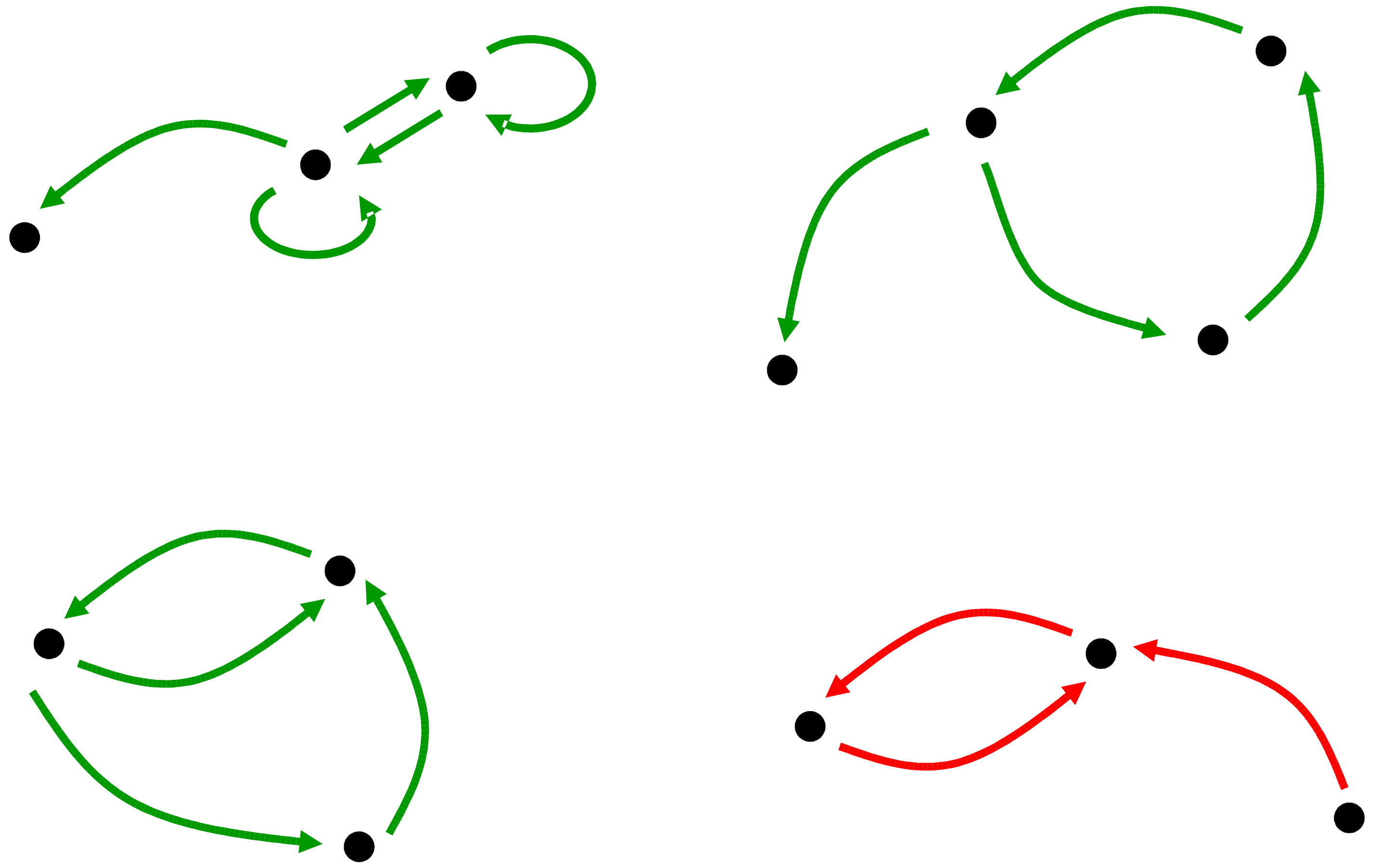


(1) Generalization of Snoussi

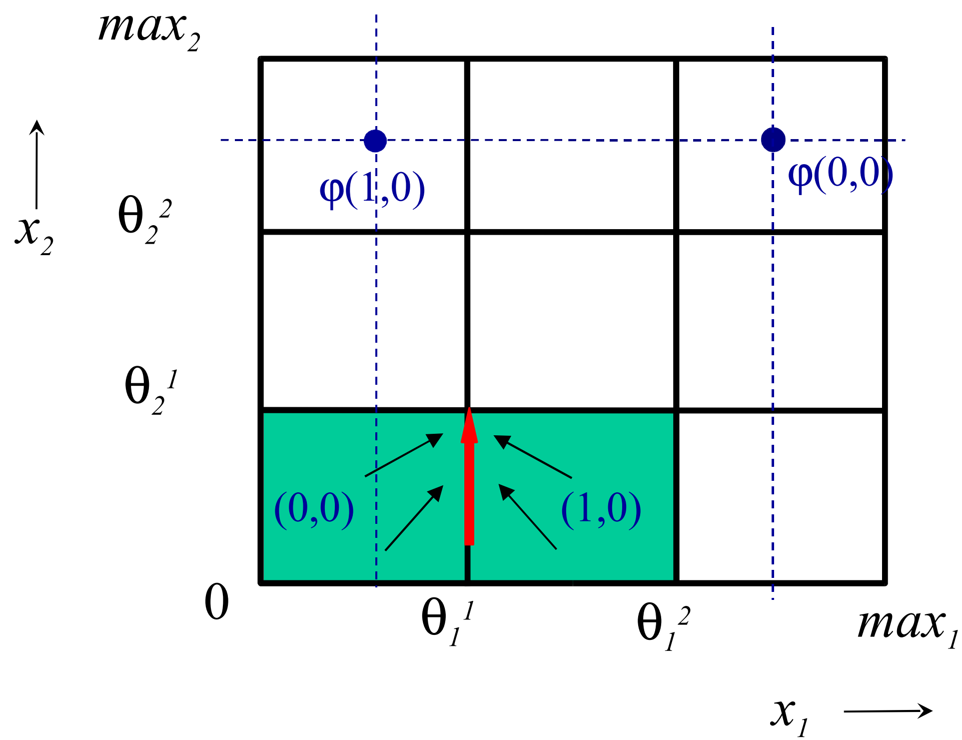
- General validity :
  - Additive or non-additive regulation functions
  - Thresholds of any multiplicity

$$\mathbf{x} \text{ persistent} \Rightarrow \text{indegree}(G(\mathbf{x})) > 0$$

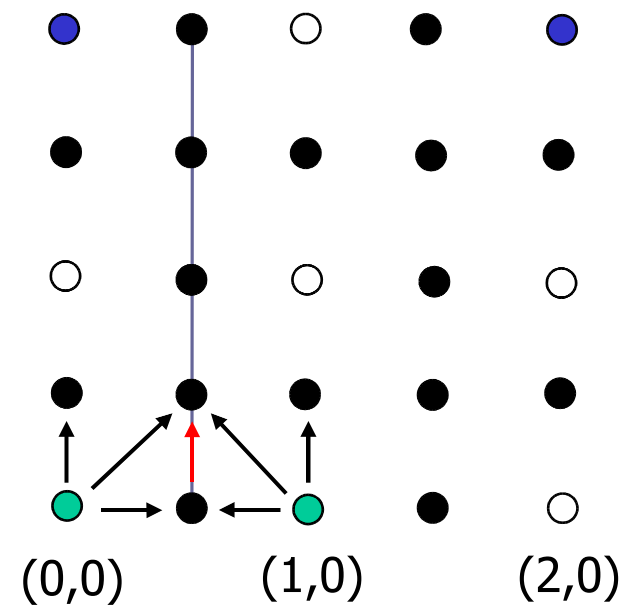
(counter-) examples



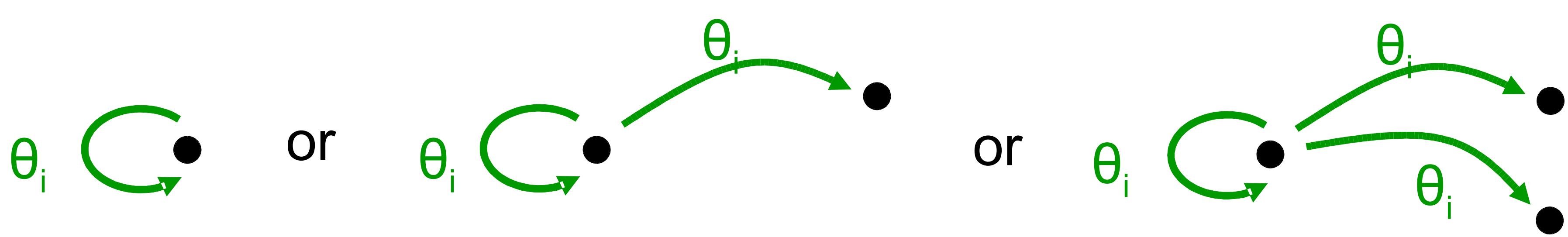
q = 1



max2
x2
θ2 2
θ2 1
φ(1,0)
φ(0,0)
(0,0)
(1,0)
0
θ1 1
θ1 2
max1
x1



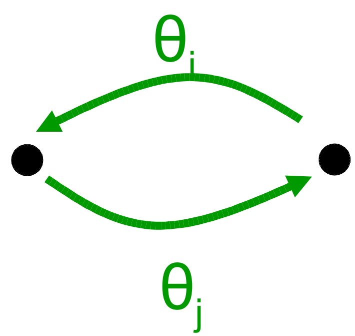
(0,0)
(1,0)
(2,0)



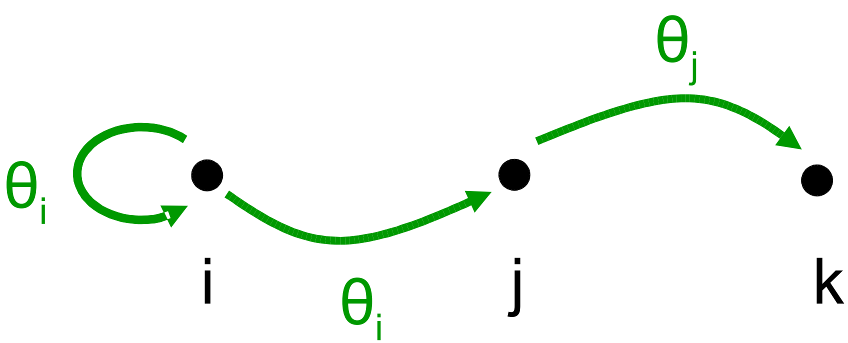
θi
or
θi
θi
or
θi
θi
θi

$\mathbf{q = 2}$

Hooping

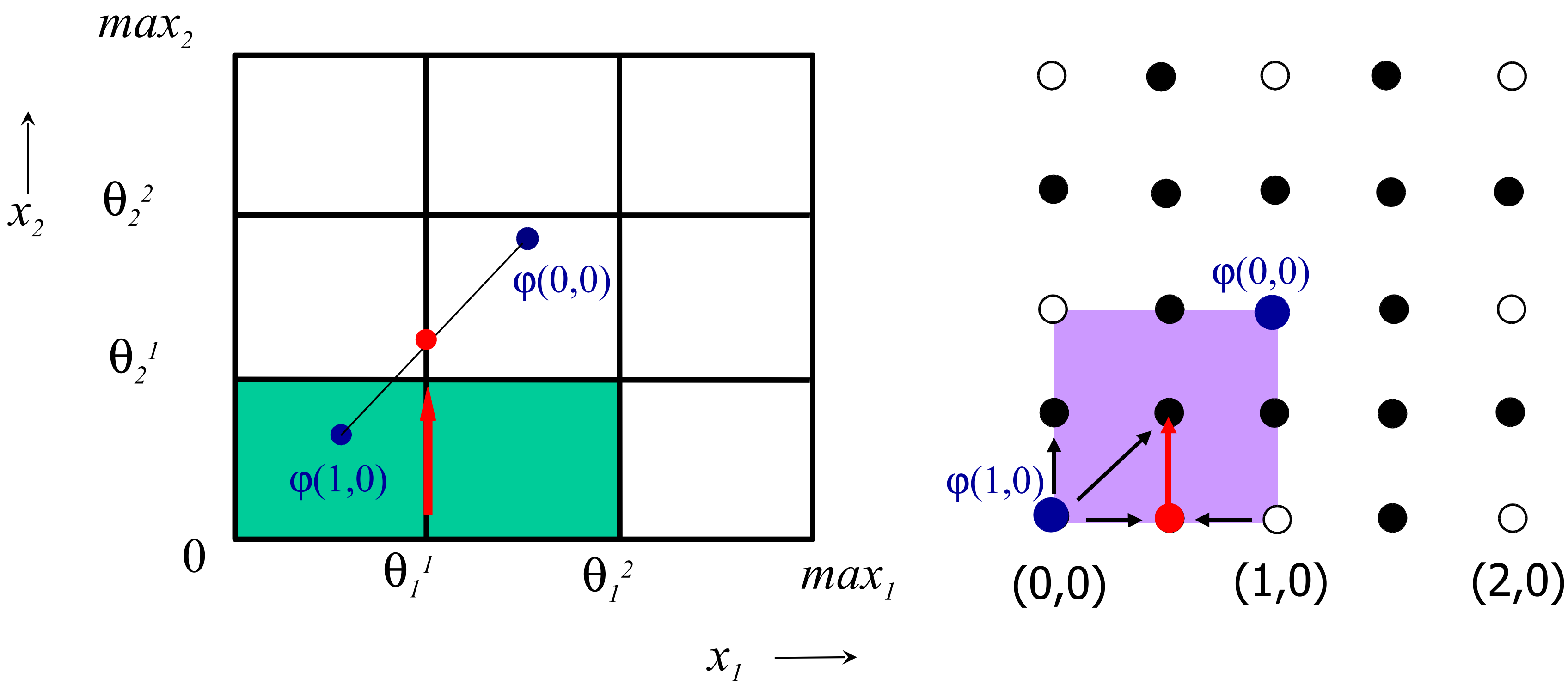


Circuit



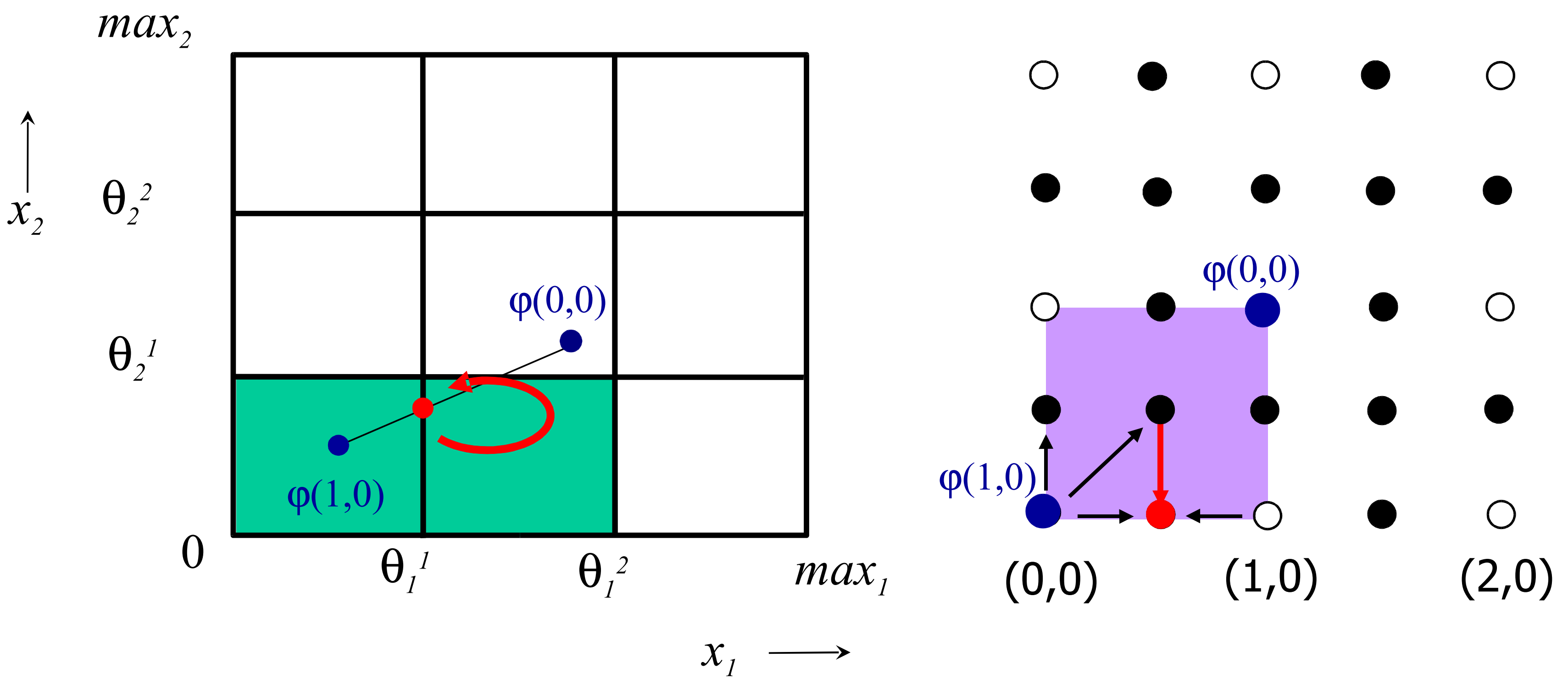
Persistent but not *robustly* persistent

Degeneracy



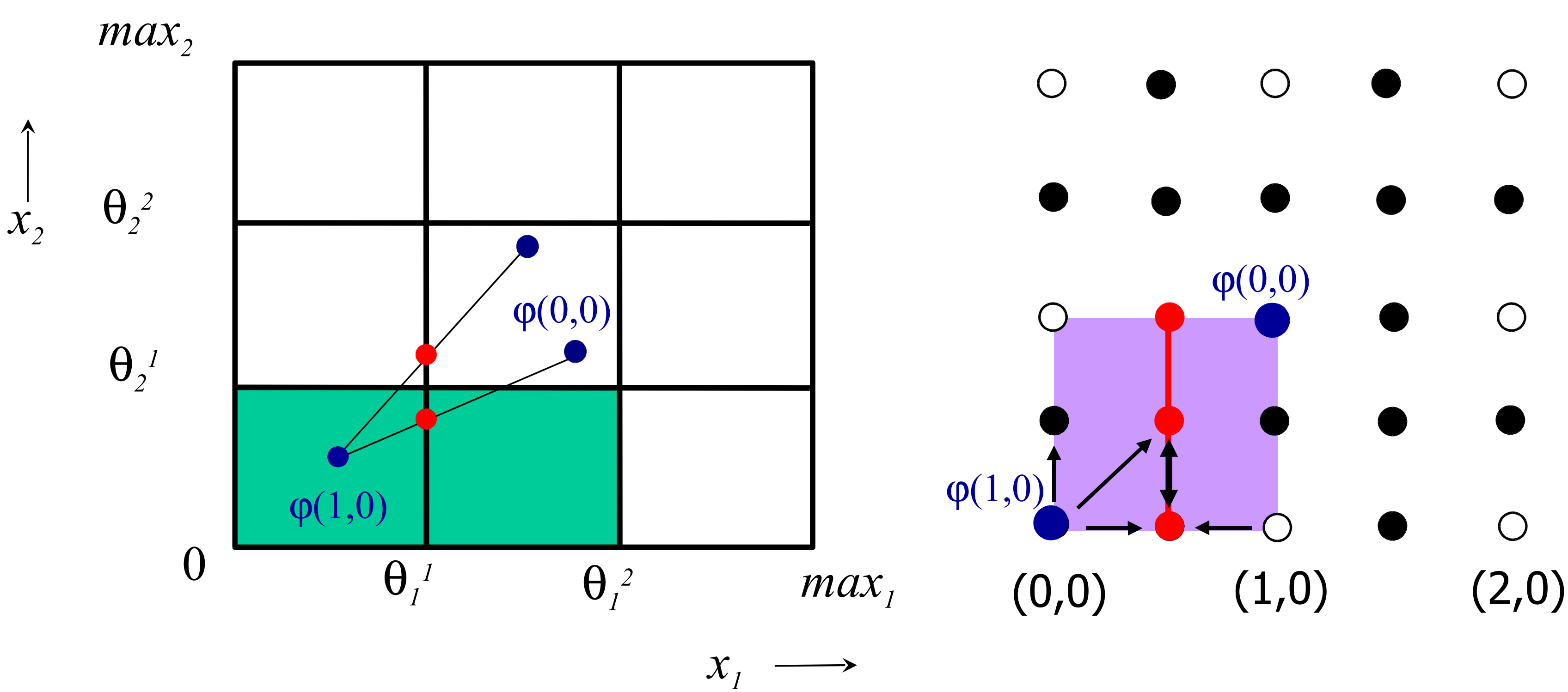
max_2
x_2
θ_2^2
θ_2^1
φ(0,0)
φ(1,0)
0
θ_1^1
θ_1^2
max_1
x_1
φ(0,0)
φ(1,0)
(0,0)
(1,0)
(2,0)

Degeneracy



singular state $(\theta_1^1,0)$ is stationary

Degeneracy



state $(\theta_1^1,0)$ is both stationary and non-stationary!

(2) relationship between multiplicity and degeneracy

- Degeneracy is possible only if singular state x contains at least 1 threshold θ_j with multiplicity > 1

- if all thresholds are such that $m(\theta_j) = 1$: no degeneracy

Reachability of higher orders from regular states

Approximation :

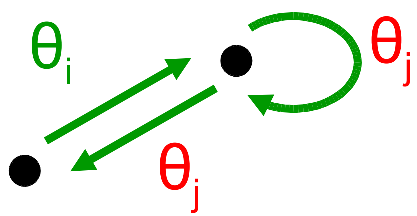
- ‘coincidence’ transitions can safely be ignored

  → no diagonal transitions to states of lower dimension (higher orders)

⇒ a state **x** of order q can be reached:

- directly by a spiralling trajectory converging on **x** → logical cycle in the discrete description. Possible if G(**x**) is a negative circuit.
- by a path of states of order 0, 1,..., q-1 which are *persistent*
- or a combination of the two

Examples



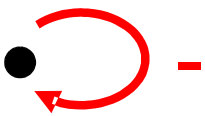
mult(θ_j) = 2

Both (θ_i) and (θ_i,θ_j) can be persistent

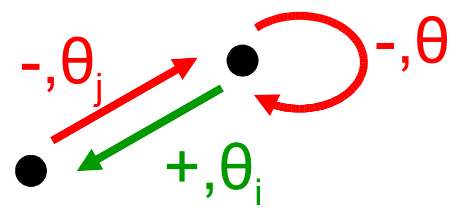
→ possibility to reach q=3

Reachability of higher orders from regular states

- q=1 No condition
- q=2 reachable if q=1 can be persistent and stable

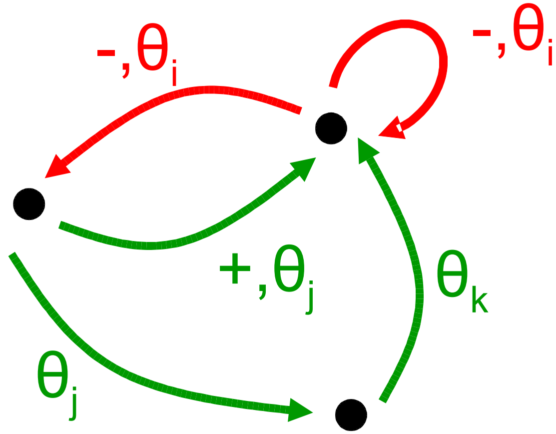


- q=3 previous cond. + possible persistence of q=2



- q=4

  …



Perspectives

- This work is part of a larger project : Formulation of the discrete transition system in Constraint Logic Programming, with Fabien Corblin and Laurent Trilling (LSR, Grenoble)
- Proceedings of WCB05 (Workshop on Constraint Based Methods for Bioinformatics, Spain, 2005), pp 25-34. http://www.dimi.uniud.it/dovier/WCB05/wcb05.pdf

Perspectives :

- Qualitative analysis of phase portrait : steady states, cycles
- Simulations
- Inference of parameters of known behavior
- Behavioral equivalence of two models...

Summary

- Generalization of Snoussi's theorem

- Differences mainly due to thresholds of multiplicity >1

- Analysis in terms of circuits/hoopings in the general case

→ synthesis of two approaches: the logical approach of Thomas et al and the approach of de Jong et al (based on the Filippov method)