

Parametric Analysis and Abstraction of Genetic Regulatory Networks

Michaël Adélaïde and Grégoire Sutre



Lab. Bordelais de Recherche en Informatique, Bordeaux University, France

Genetic Regulatory Networks

- Regulation of gene expression
 - regulation of DNA transcription (binding sites)
 - RNA processing and transport

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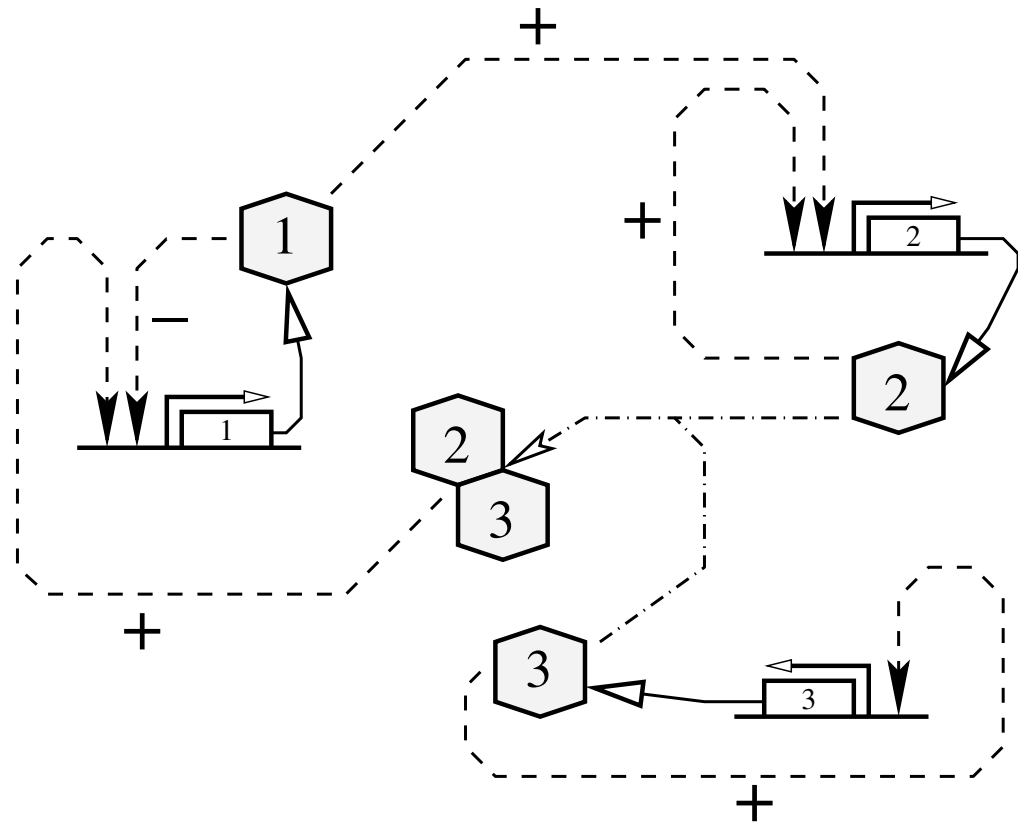
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- Regulation of gene expression
 - regulation of DNA transcription (binding sites)
 - RNA processing and transport
- Network of interactions between DNA, RNA, proteins, ...
 - hard to understand
- Need for formal methods
 - modeling
 - analysis (simulation, model checking)

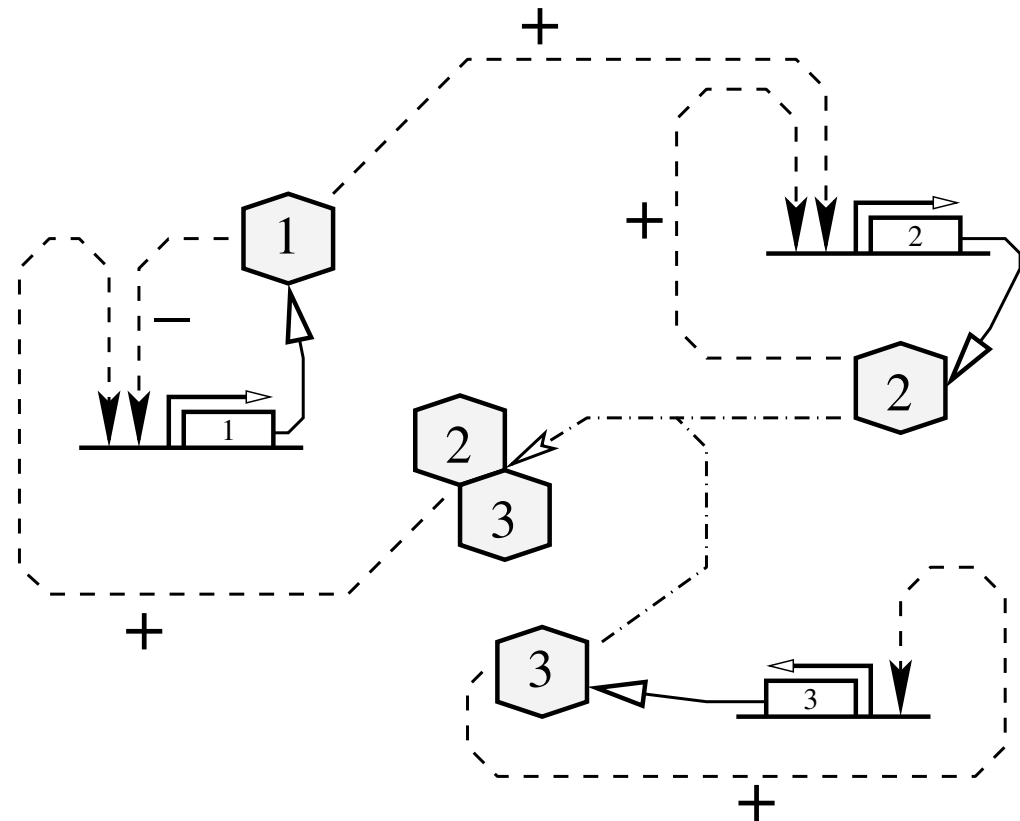
Regulatory Diagrams

- genes
- proteins
- + : activation
- - : inhibition



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- Dynamics: differential equations

- $\frac{d}{dt}x_1 = \kappa_1\zeta^-(x_1, \theta_1) + \kappa'_1\zeta^+(x_{23}, \theta'_1) - \gamma_1x_1$

- ζ^-, ζ^+ : sigmoids

Objectives

- Behavioral analysis of regulatory networks
 - stationary states and attraction basins
 - reachability
 - finite-state qualitative approximations

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- Predictions
 - in silico experiments

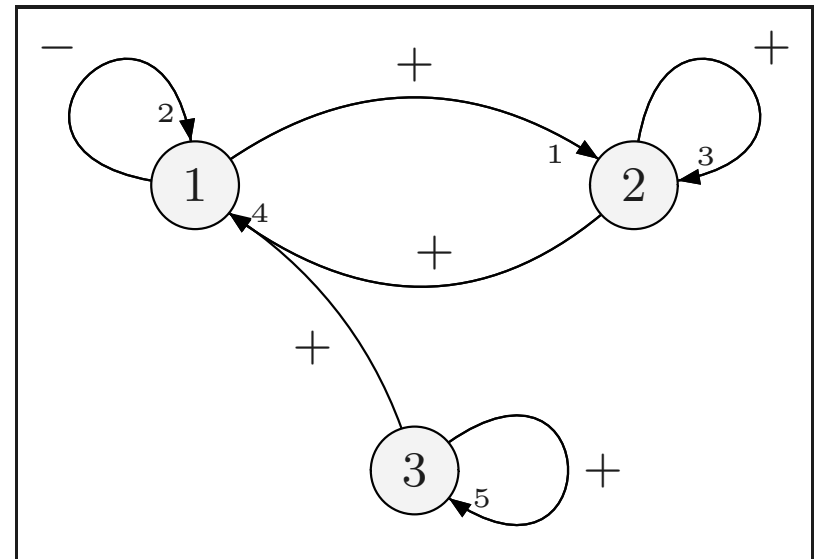
- Model checking
 - validation of models w.r.t. in vivo experiments

Our approach — Outline of the talk

- Regulatory Networks modeled as hypergraphs
- Continuous semantics given by differential inclusions
- Time-abstract semantics: parametric attractor systems
- Symbolic analysis and abstraction
- Tiny case study
- Conclusion and future work

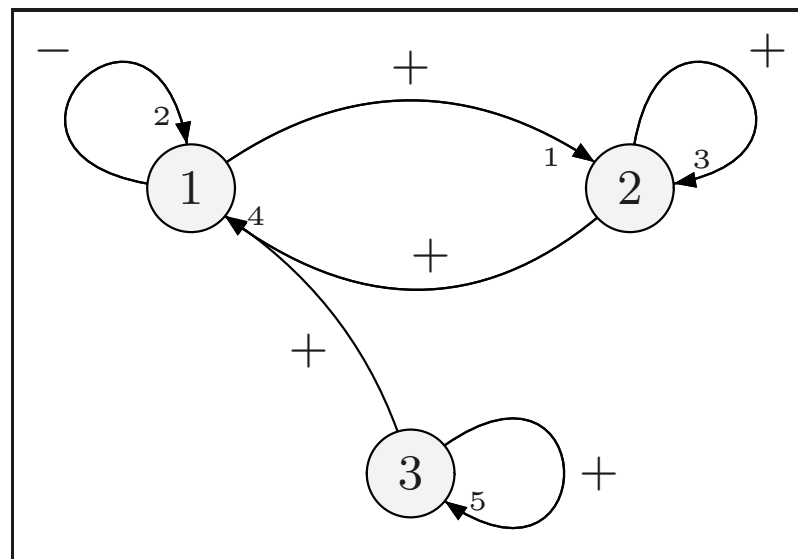
Regulatory Networks

- Directed hypergraph: $\langle V, E, in, out \rangle$
- Sign labeling: $\varepsilon : E \times V \rightarrow \{-, +\}$
- Parameters:
 - $\gamma : V \rightarrow \mathbb{R}_{>0}$
 - $\kappa : E \rightarrow \mathbb{R}_{\geq 0}$
 - $\theta : E \times V \rightarrow \mathbb{R}_{\geq 0}$



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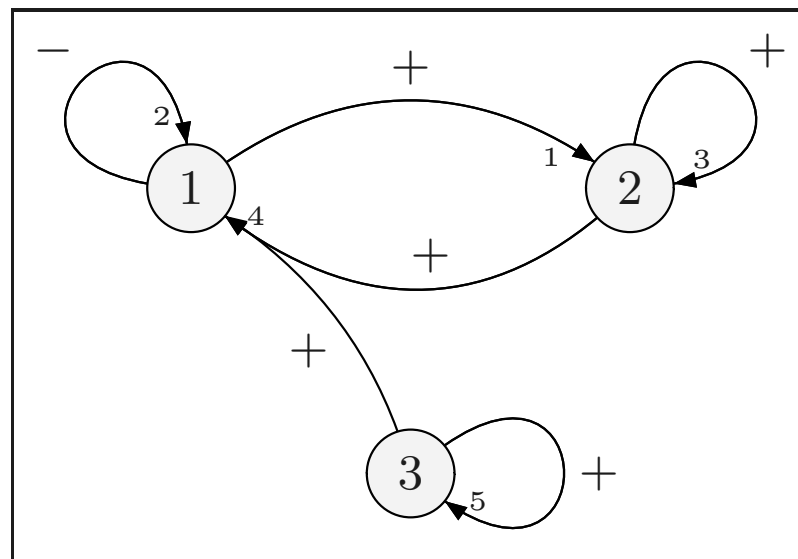
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- state space: $\mathbb{R}_{\geq 0}^V$
- $$\frac{d}{dt} \vec{x}(v) = \sum_{e \in out^{-1}(v)} \kappa(e) \prod_{w \in in(e)} s^{\varepsilon(e,w)}(\vec{x}(w), \theta(e,w)) - \gamma(v) \vec{x}(v)$$
- $s^+, s^- : \mathbb{R} \times \mathbb{R} \rightarrow \{0, 1\}$ are the partial step functions of Heaviside

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- state space: $\mathbb{R}_{\geq 0}^3$

$$\begin{cases} \frac{d}{dt} x_1 &= \kappa_2 s^-(x_1, \theta_{2,1}) + \kappa_4 s^+(x_2, \theta_{4,2}) s^+(x_3, \theta_{4,3}) - \gamma_1 x_1 \\ \frac{d}{dt} x_2 &= \kappa_1 s^+(x_1, \theta_{1,1}) + \kappa_3 s^+(x_2, \theta_{3,2}) - \gamma_2 x_2 \\ \frac{d}{dt} x_3 &= \kappa_5 s^+(x_3, \theta_{5,3}) - \gamma_3 x_3 \end{cases}$$

Trajectories [dJG⁺04]

- $\mathbb{R}_{\geq 0}^V$ partitioned into boxes and walls
- Dynamics within a box B : $\frac{d}{dt} \vec{x} = \vec{\kappa}_B - \vec{\gamma} \cdot \vec{x}$
 - limit point $\vec{\varphi}_B$ with $\vec{\varphi}_B(v) = \frac{\vec{\kappa}_B(v)}{\vec{\gamma}(v)}$
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- When γ is constant, the reachable states within zone z are:

$$z \cap \text{hull}(\{\vec{x}\} \cup \{\vec{\varphi}_B \mid B \in \mathcal{B}(z)\})$$

Parametric attractor systems: syntax

- $\mathcal{A} = \langle V, T, th, K, at \rangle$
 - V is a finite set of components
 - T is a finite set of threshold parameters
 - $th : V \rightarrow \mathbb{P}(T)$ is a threshold mapping
 - K is a finite set of attractor parameters
 - $at : Z(V, T) \rightarrow \mathbb{P}_f(\underbrace{\mathbb{L}(K)}^V)$ is an attractor mapping

linear expressions over K with coefficients in \mathbb{Q}

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- Zones: $Z(V, T)$
 - location of $v \in V$: partial mapping $l : T \rightarrow \{-, 0, +\}$ defined on $th(v)$ and such that $\text{card}(l^{-1}(\{0\})) \leq 1$
 - zone: mapping z from V to $\{-, 0, +\}^T$ such that $z(v)$ is a location of v

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- $Q = \{(z, \vec{x}, \theta, \kappa) \mid z \in Z(V, T), \theta \in \mathbb{R}_{\geq 0}^T, \kappa \in \mathbb{R}_{\geq 0}^K, \vec{x} \in \llbracket z \rrbracket_{\theta}\}$
 - $\llbracket z \rrbracket_{\theta} \subseteq \mathbb{R}_{\geq 0}^V$: interpretation of zone z w.r.t threshold valuation $\theta \in \mathbb{R}_{\geq 0}^T$

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- $\Sigma = \Delta(V, T) \cup \Lambda(V, T)$
 - $\Delta(V, T) = \{\delta(z) \mid z \in Z(V, T)\}$
 - $\Lambda(V, T) : \text{vectors of labels for threshold crosses (e.g. } \perp, - \xrightarrow{t} 0)$

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- $\Sigma = \Delta(V, T) \cup \Lambda(V, T)$
- $(z, \vec{x}, \theta, \kappa) \xrightarrow{\sigma} (z', \vec{x}', \theta', \kappa')$ if $(\theta, \kappa) = (\theta', \kappa')$ and either:
 - $\sigma = \delta(z)$, and $z = z'$, and $\vec{x}' \in \text{hull}(\{\vec{x}\} \cup \llbracket \text{at}(z) \rrbracket_{\kappa})$ (C)
 - $\sigma \in \Lambda(V, T)$, and $z \xrightarrow{\sigma}_{V, T} z'$, and $\vec{x} = \vec{x}'$ (D)

Symbolic transition systems [HM00]

- $\mathcal{S} = \langle Q, \Sigma, \rightarrow, R \rangle$
 - $\langle Q, \Sigma, \rightarrow \rangle$ labeled transition system
 - R subset of $\mathbb{P}(Q)$
 - $Q \in R$, and R closed under set operations (\cap, \setminus)
 - R closed under post and pre: $\underbrace{\text{post}(r, \sigma)} \in R$ and $\text{pre}(r, \sigma) \in R$
 $\{q' \in Q \mid \exists q \in r, q \xrightarrow{\sigma} q'\}$

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- Effectivity:
 - regions are finitely presented
 - all operations on regions ($\cap, \setminus, \stackrel{?}{=} \emptyset$, post and pre) are computable

Symbolic analysis of param. attr. systems

- Real arithmetic $\langle \mathbb{R}, +, \times, \leq \rangle$ is a decidable theory
- Regions: subsets of Q definable in real arithmetic
- Transition relation \rightarrow definable in real arithmetic

Theorem

Parametric attractor systems are effective symbolic transition systems

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Theorem

Parametric attractor systems are effective symbolic transition systems

- Regions are linear in V
 - non-linearities may only appear between parameters

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- k -precise abstraction $\mathcal{S}_k^\#(\mathcal{A}) = (Q_k^\#, \Sigma, \rightarrow_k^\#)$

- $Q_k^\#$: partition of Q induced by

$$P_k^\# = \{\text{pre}(Q, w) \mid w \in \Delta(V, T)(\Lambda(V, T)\Delta(V, T))^i, i \leq k\}$$

- $r \xrightarrow[k]^\sigma r'$ if $\text{pre}(r', \sigma) \cap r \neq \emptyset$

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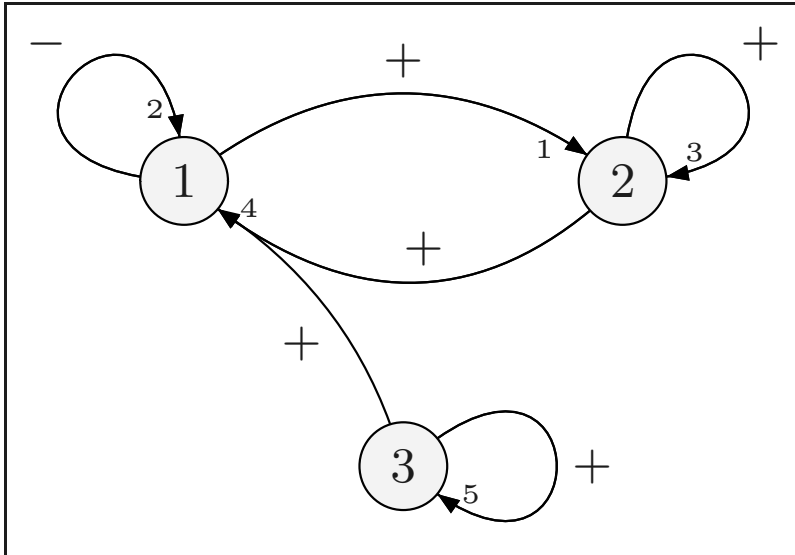
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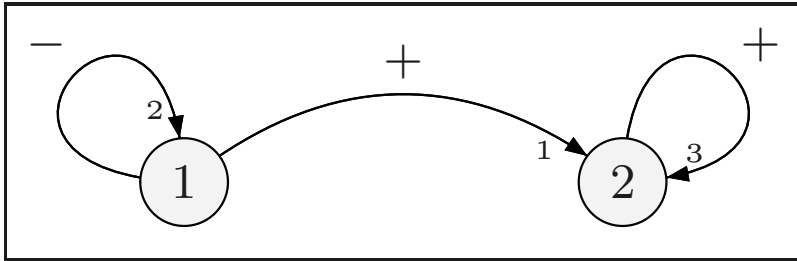
$\mathcal{S}_k^\#(\mathcal{A})$ is an abstraction of $\mathcal{S}(\mathcal{A})$ that has the same traces of length at most k as $\mathcal{S}(\mathcal{A})$

Case study: simplified example



- Uniform degradation rate ($\gamma = 1$)
- Simplification:
 - assume that x_3 is too low initially
 - we may remove vertex 3

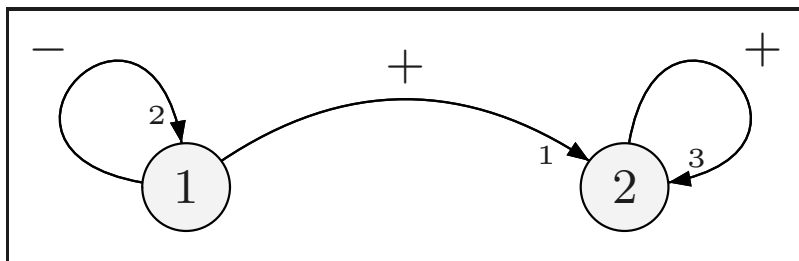
Case study: simplified example



■ state space: $\mathbb{R}_{\geq 0}^3$

■
$$\begin{cases} \frac{d}{dt}x_1 = \kappa_2 s^-(x_1, \theta_2) - x_1 \\ \frac{d}{dt}x_2 = \kappa_1 s^+(x_1, \theta_1) + \kappa_3 s^+(x_2, \theta_3) - x_2 \end{cases}$$

Case study: simplified example



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- Parametric attractor system: $\mathcal{A} = \langle V, T, th, K, at \rangle$ with:

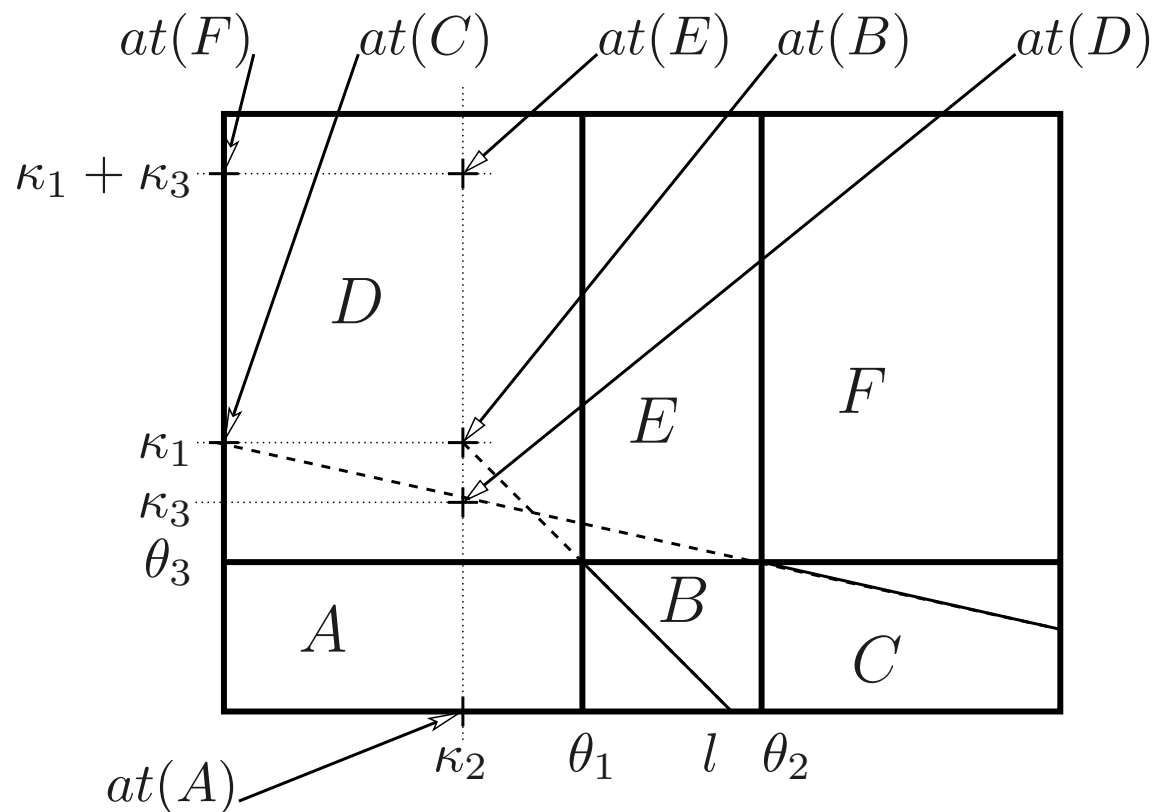
- $V = \{v_1, v_2\}, T = \{t_1, t_2, t_3\}, K = \{k_1, k_2, k_3\}$

- $th(v_1) = \{t_1, t_2\}, th(v_2) = \{t_3\}$

- $at : Z(V, T) \rightarrow \mathbb{P}_f(\mathbb{L}(K)^V)$ defined in the obvious way

- if $z(v_1) = \{t_1 \mapsto -, t_2 \mapsto -\}$ and $z(v_2) = \{t_3 \mapsto +\}$ then $at(z) = \{(k_2, k_3)\}$

Case study: attractors

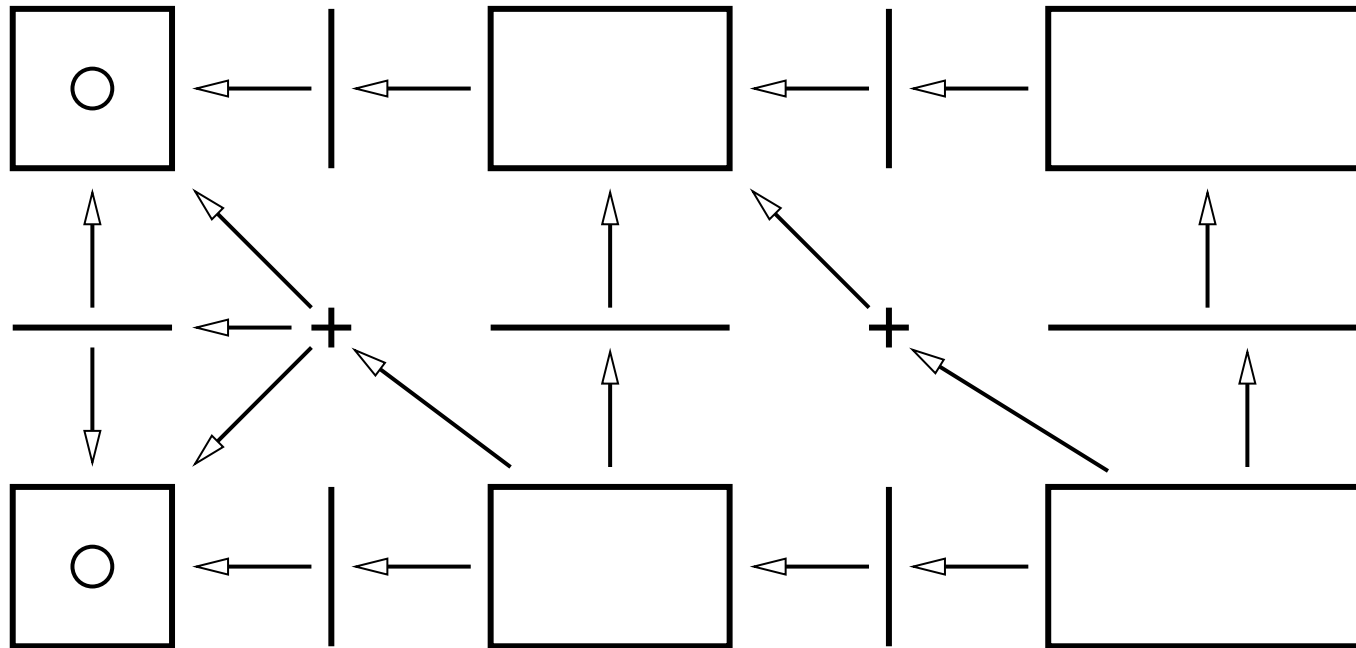


- $0 < \kappa_2 < \theta_1$

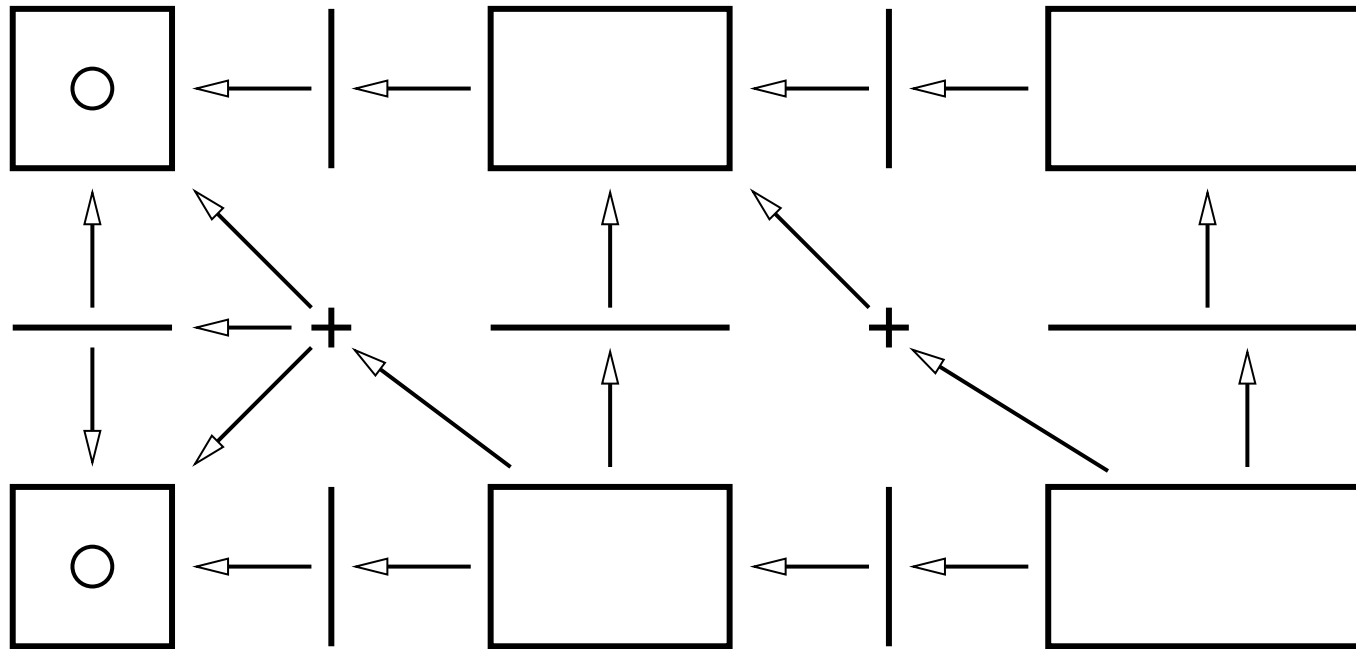
- $0 < \theta_3 < \kappa_3 < \kappa_1$

- $\theta_1 < \underbrace{\frac{\kappa_1(\theta_1 - \kappa_2)}{\kappa_1 - \theta_3} + \kappa_2}_l < \theta_2$

Case study: 0-precise abstraction

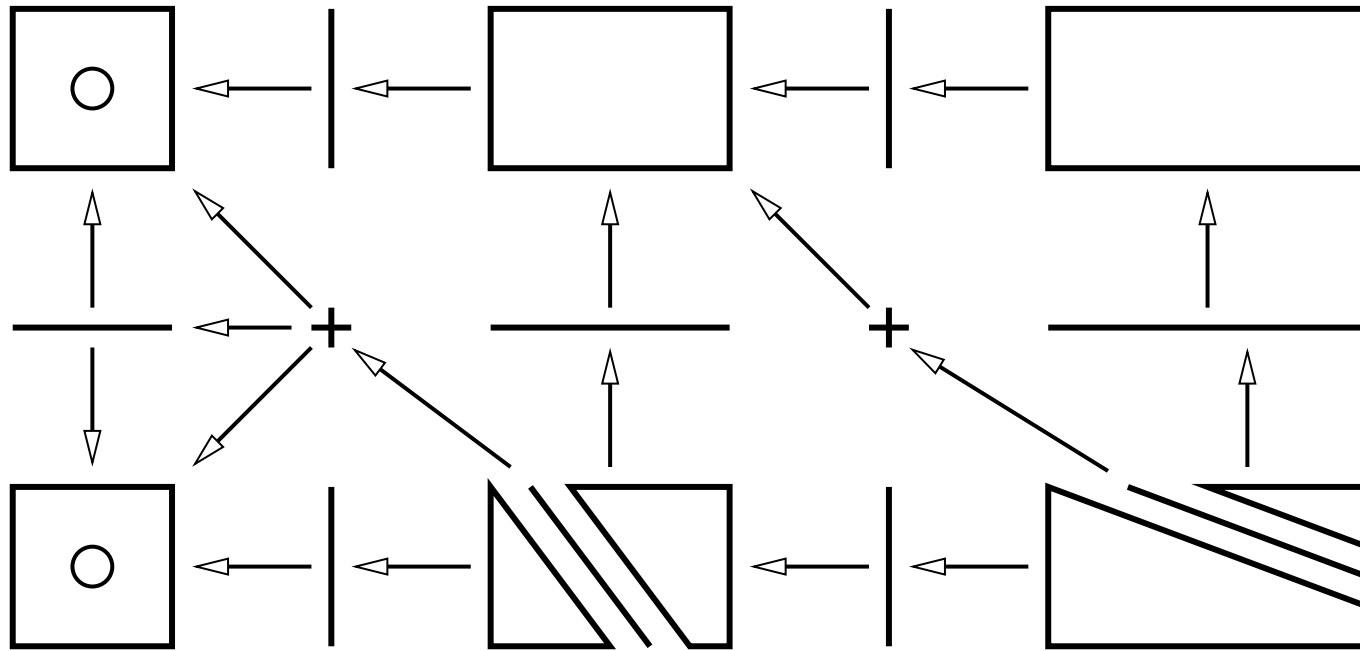


Case study: 0-precise abstraction



- Both stationary states reachable from zone (C)

Case study: 1-precise abstraction



- Stationary state in (A) not reachable from zone (C)

Conclusion and future work

- Regulatory networks with a uniform degradation rate
- time-abstract semantics: parametric attractor systems
 - new class of hybrid systems
- Parametric attractor systems are effective symbolic transition systems
 - decidability of bounded-reachability properties
 - computation of arbitrarily precise abstractions
- Perspectives:
 - practical feasibility of this approach
 - decidability of reachability for parametric attractor systems

References

- [dJG⁺04] Hidde de Jong, Jean-Luc Gouze, , Celie Hernandez, Michel Page, Tewfik Sari, and Johannes Geiselmann. Qualitative simulation of genetic regulatory networks using piecewise-linear models. *Bulletin of Mathematical Biology*, 66:301–340, 2004.
- [HM00] T. A. Henzinger and R. Majumdar. A classification of symbolic transition systems. In *Proc. 17th Ann. Symp. Theoretical Aspects of Computer Science (STACS'2000), Lille, France, Feb. 2000*, volume 1770 of *Lecture Notes in Computer Science*, pages 13–34. Springer, 2000.