

# Parametric Analysis and Abstraction of Genetic Regulatory Networks

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

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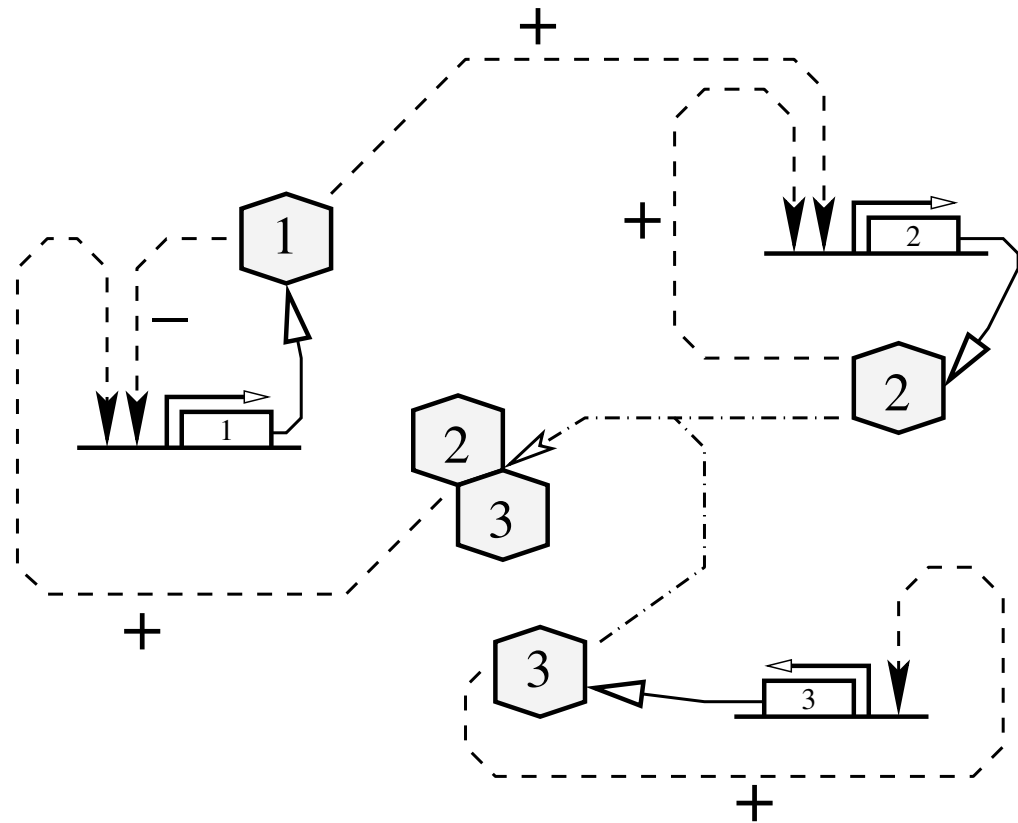
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- Regulation of gene expression
  - regulation of DNA transcription (binding sites)
  - RNA processing and transport
- Network of interactions between DNA, RNA, proteins, ...
  - hard to understand
- Need for formal methods
  - modeling
  - analysis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

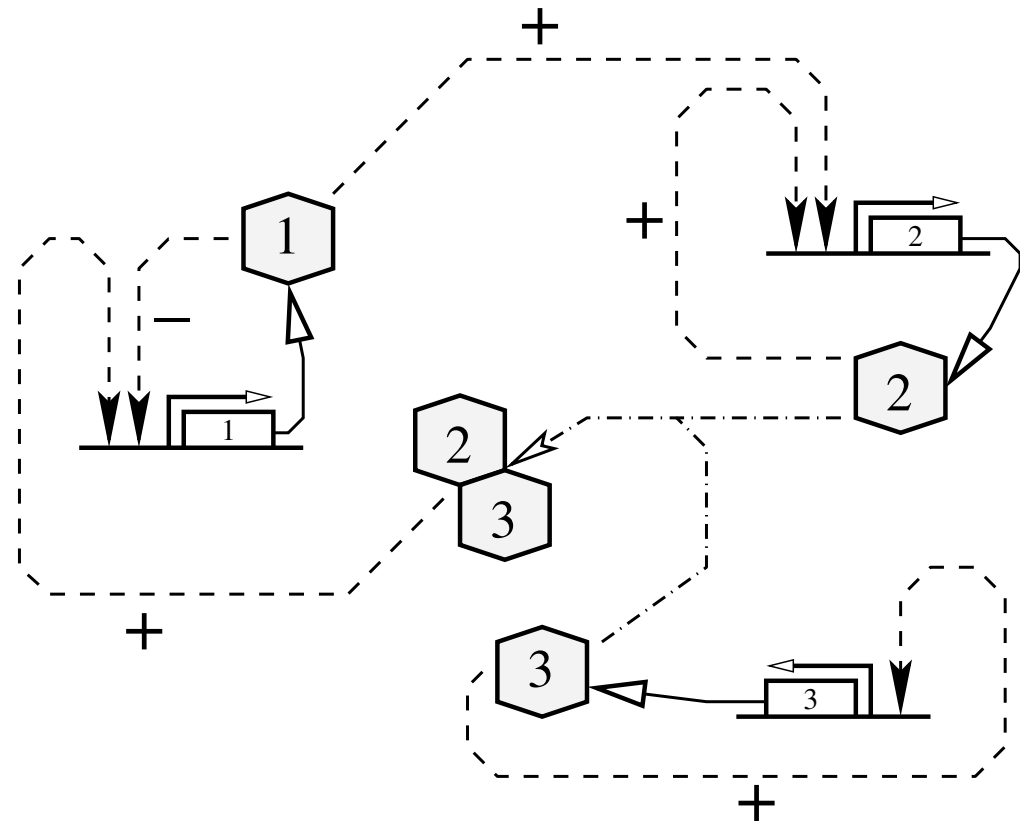
# Regulatory Diagrams

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



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- Dynamics: differential equations

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

- $\zeta^-, \zeta^+$  : sigmoids

# Objectives

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

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- Behavioral analysis of regulatory networks
  - stationary states and attraction basins
  - reachability
  - finite-state qualitative approximations
- Predictions
  - in silico experiments
- Model checking
  - validation of models w.r.t. in vivo experiments

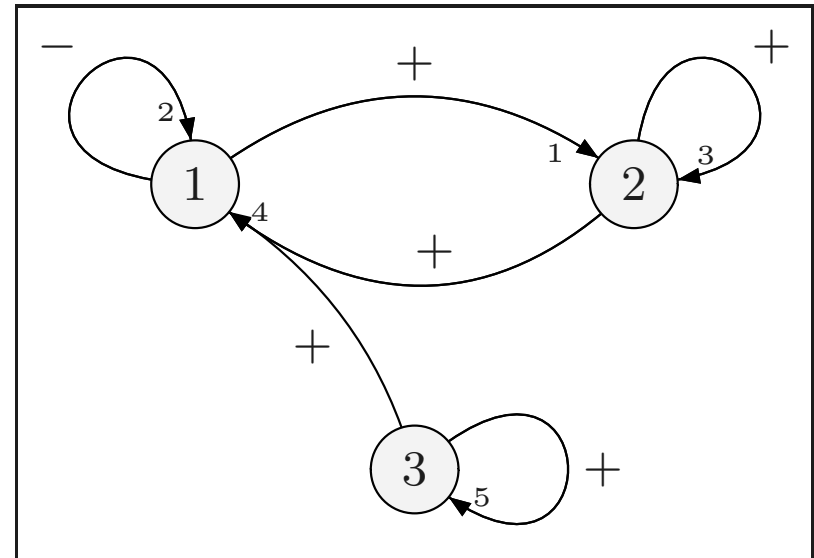


# Our approach — Outline of the talk

- 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

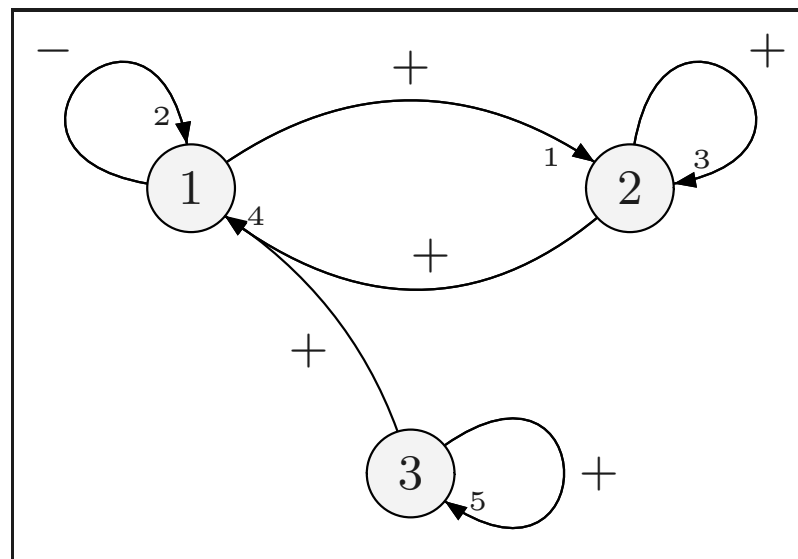
# Regulatory Networks

- 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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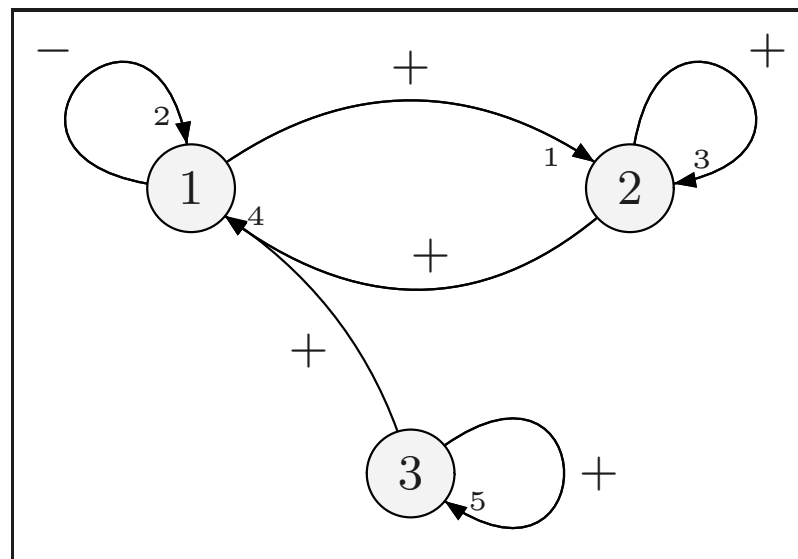
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- state space:  $\mathbb{R}_{\geq 0}^V$
- $$\frac{d}{dt} \vec{x}(v) = \sum_{e \in out^{-1}(v)} \kappa(e) \prod_{w \in in(e)} s^{\varepsilon(e,w)}(\vec{x}(w), \theta(e,w)) - \gamma(v) \vec{x}(v)$$
- $s^+, s^- : \mathbb{R} \times \mathbb{R} \rightarrow \{0, 1\}$  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<sup>+</sup>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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- Dynamics within any zone  $z$  (box or wall):

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- When  $\gamma$  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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*linear expressions over  $K$  with coefficients in  $\mathbb{Q}$*
  
- 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  $\vec{x}' \in \text{hull}(\{\vec{x}\} \cup \llbracket at(z) \rrbracket_{\kappa})$  (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  $\text{pre}(r, \sigma) \in R$   
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 $\{q' \in Q \mid \exists q \in r, q \xrightarrow{\sigma} q'\}$
  
- Effectivity:
  - regions are finitely presented
  - all operations on regions  $(\cap, \setminus, \stackrel{?}{=} \emptyset, \text{post and pre})$  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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- Regions are linear in  $V$ 
  - non-linearities may only appear between parameters

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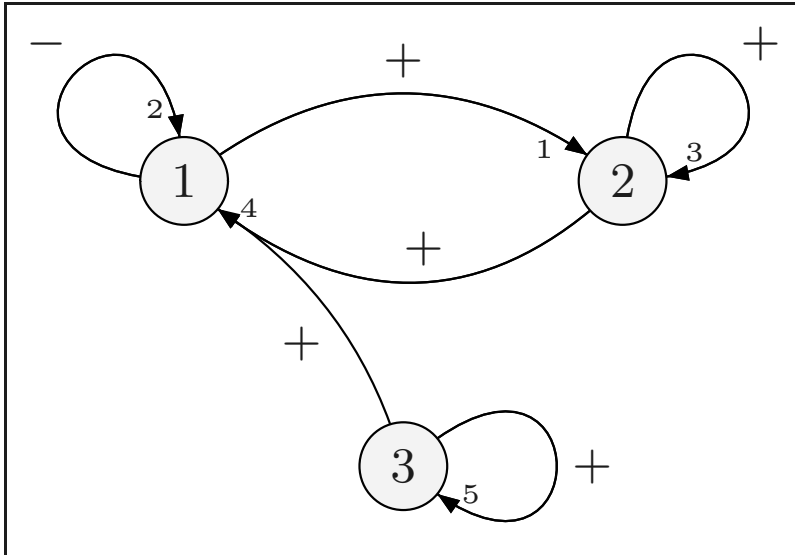
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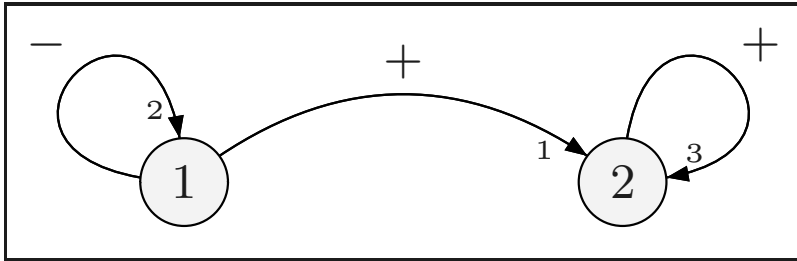
$\mathcal{S}_k^\#(\mathcal{A})$  is an abstraction of  $\mathcal{S}(\mathcal{A})$  that has the same traces of length at most  $k$  as  $\mathcal{S}(\mathcal{A})$

# Case study: simplified example



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

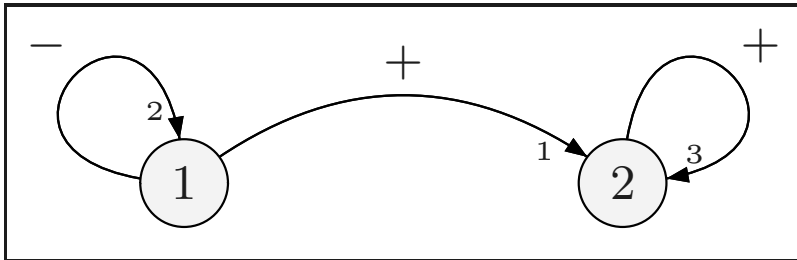
# Case study: simplified example



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

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

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

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

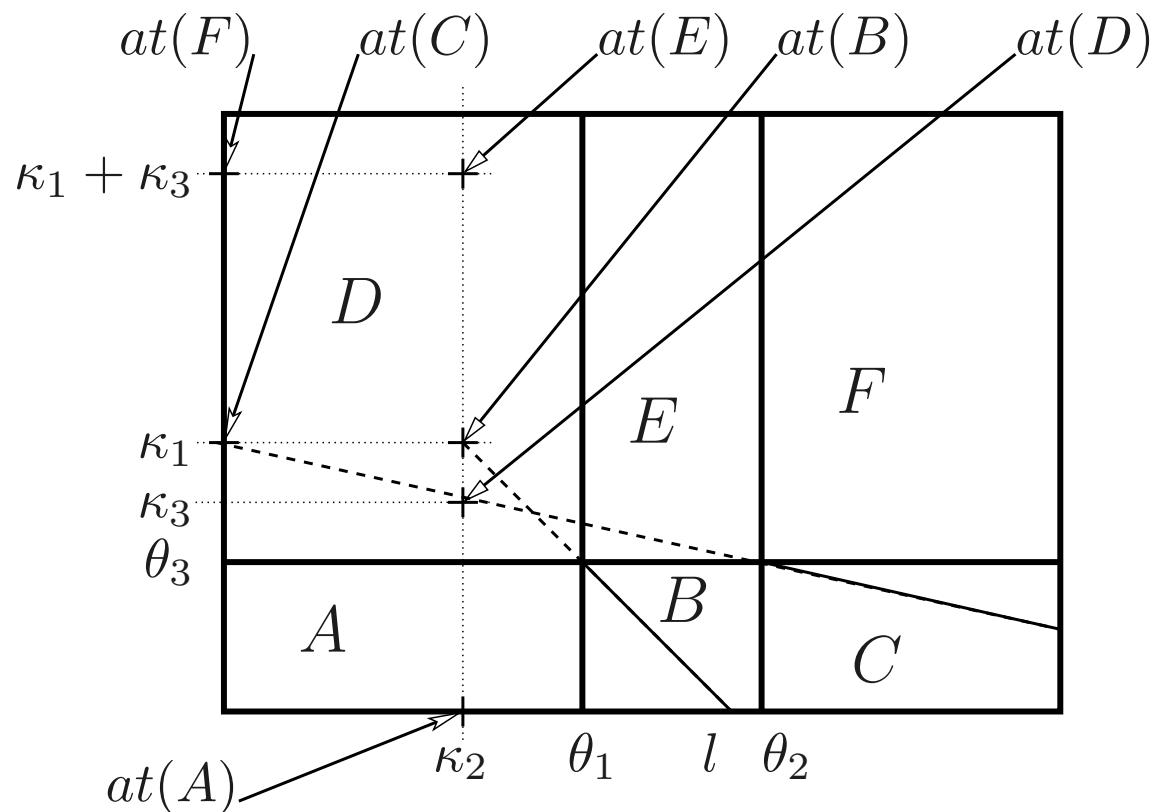
- $th(v_1) = \{t_1, t_2\}, th(v_2) = \{t_3\}$

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

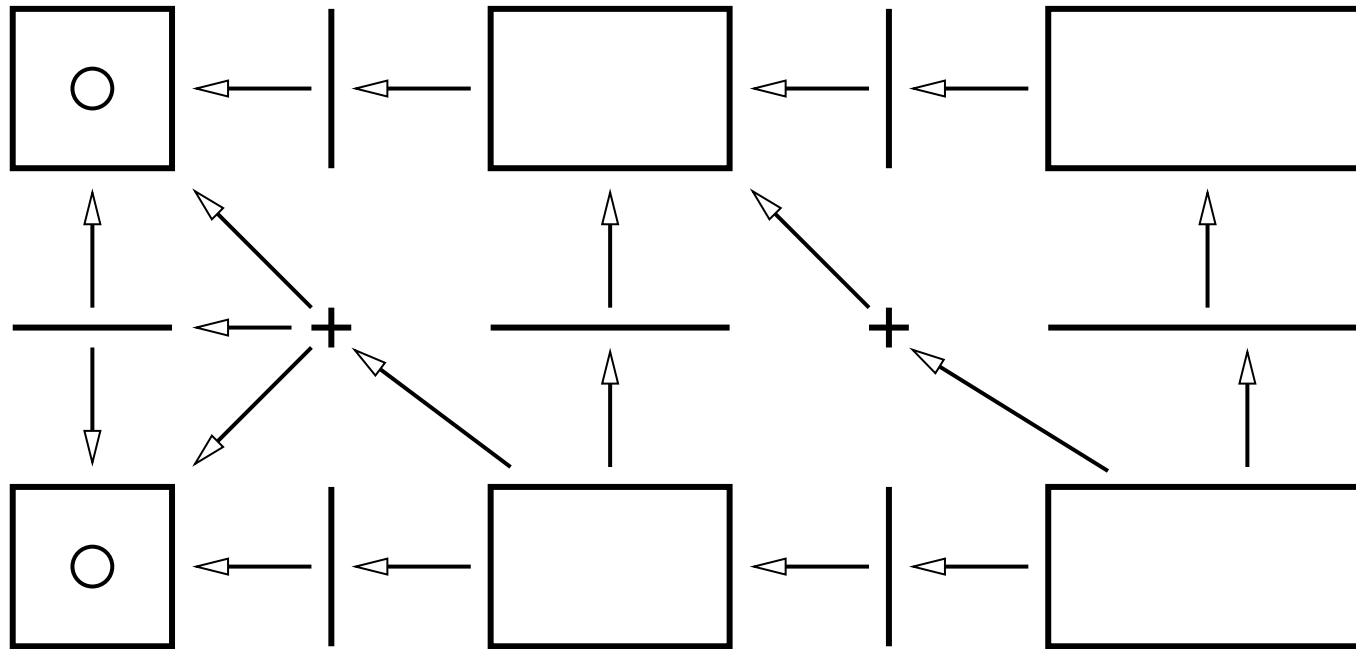


- $0 < \kappa_2 < \theta_1$

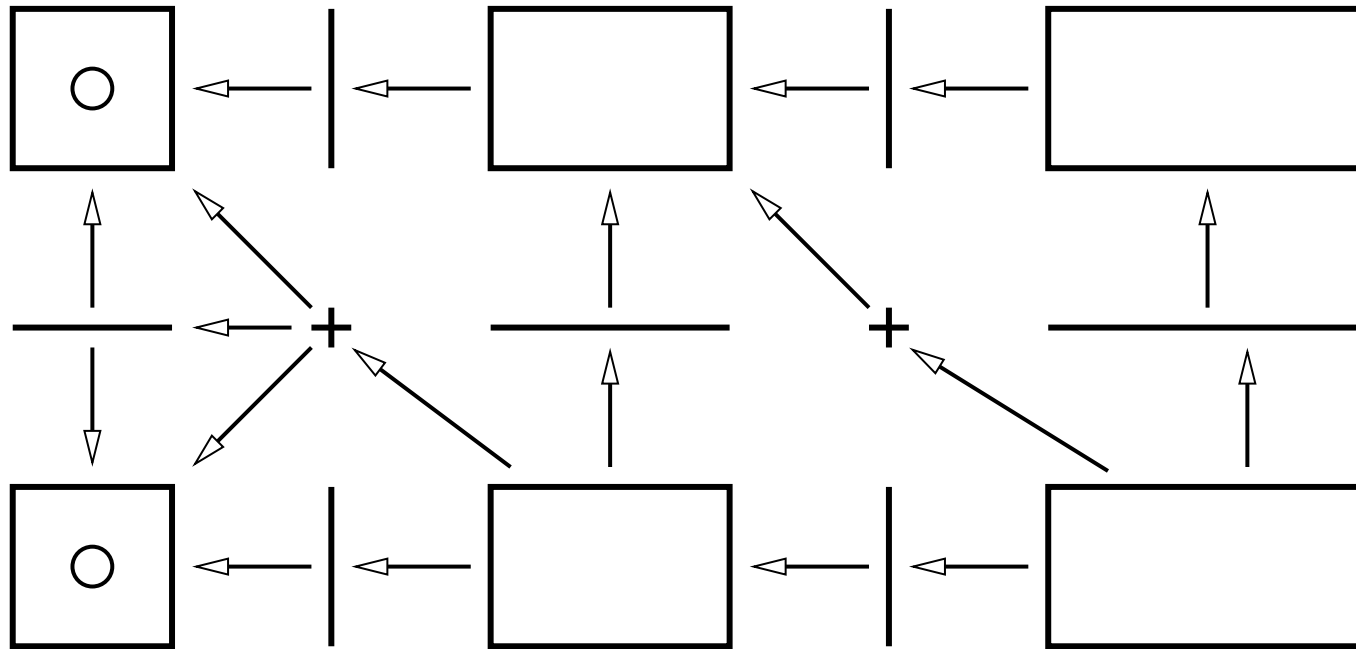
- $0 < \theta_3 < \kappa_3 < \kappa_1$

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

# Case study: 0-precise abstraction

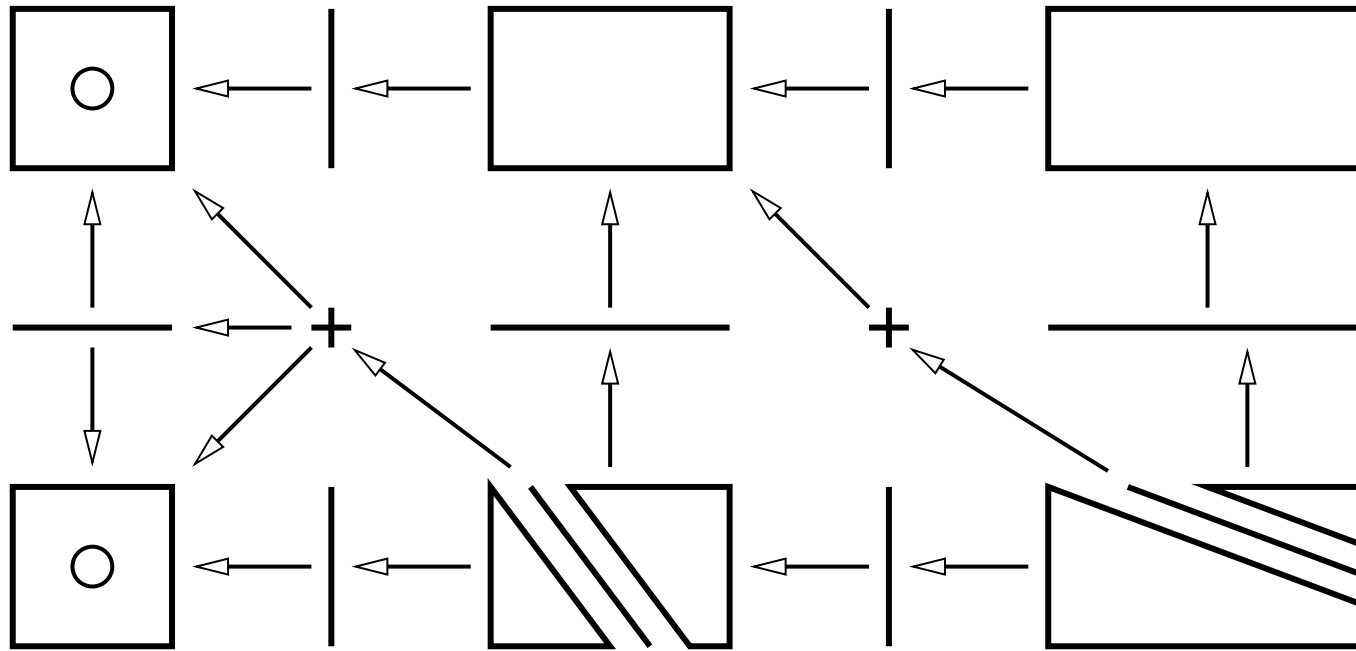


# Case study: 0-precise abstraction



- 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<sup>+</sup>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.