MDSC team seminar

Qualitative modeling and dynamical analysis of Biological Regulatory Networks using Asynchronous Automata Networks

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2015/09/28

The Modeling/Analysis duality

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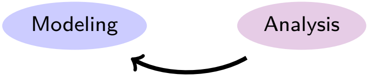

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- The modeling tools must be adapted to the observed properties

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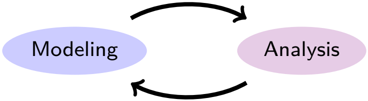

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- The size of the model increases the analysis duration

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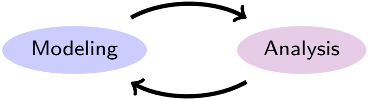

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The modeling and analysis steps of a system are strongly linked

Overview of This Presentation

Abstracting biological models

- Abstraction of biological components
- Discrete, asynchronous and unitary representations

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Examples of **discrete models**

- Discrete Networks (Thomas modeling)
- Asynchronous Automata Networks
- Other extensions of the Process Hitting formalism

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- Discrete Networks (Thomas modeling)
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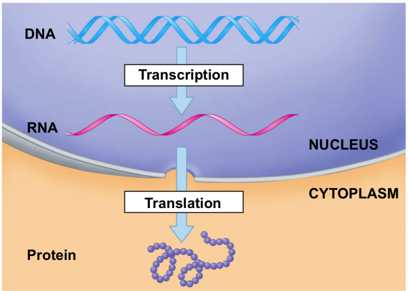
Analysis of the dynamics of discrete models

- Static analysis on the structure
- Abstract interpretation
- A μ-calculus approach

Abstractions of the Representation



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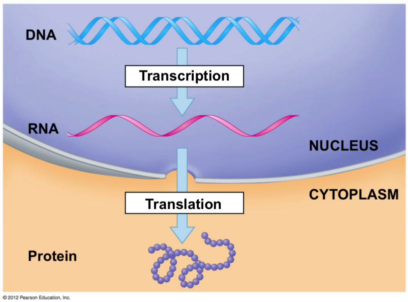

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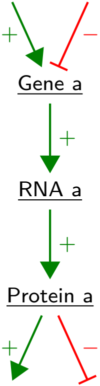

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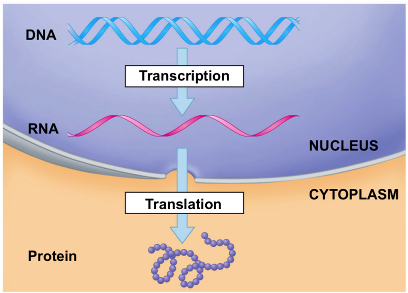
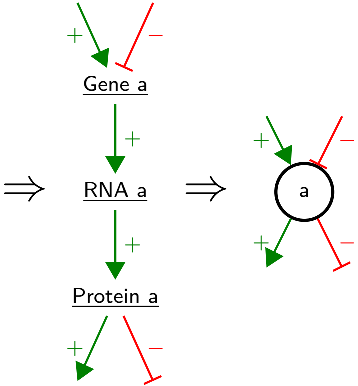
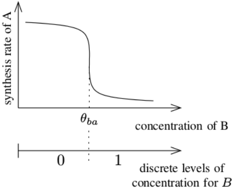




Discretization and Asynchronism

[Richard, *Advances in Applied Mathematics*, 2010]



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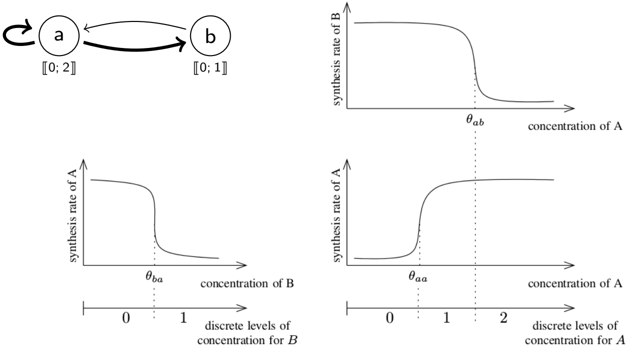

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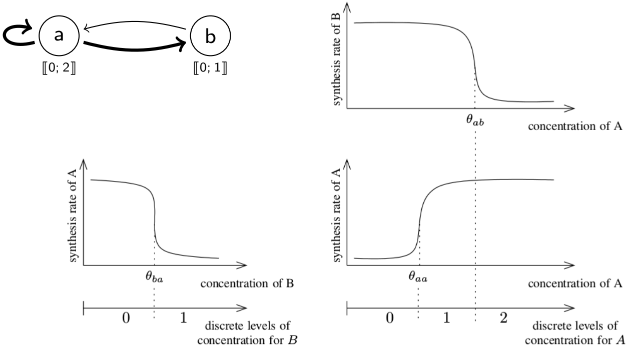

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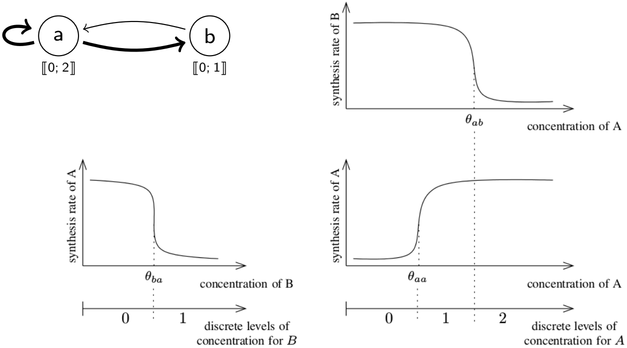

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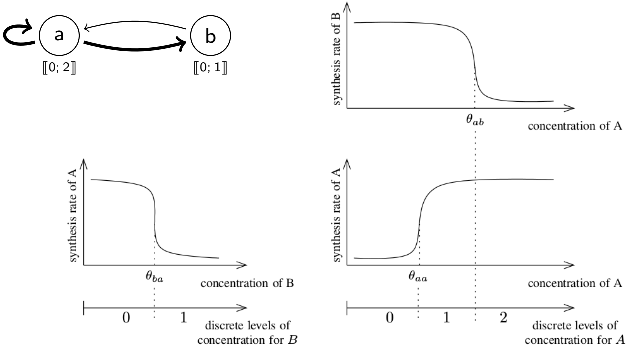
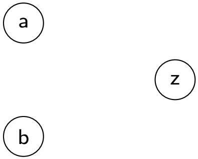


- Unknown real values of concentrations or continuous activity levels
  $\longrightarrow$ Abstracted as thresholds or **discrete levels**
- Continuous variations of the real values
  $\longrightarrow$ **Unitary** dynamics
- Simultaneous crossings of two thresholds never occurs
  $\longrightarrow$ **Asynchronous** dynamics

Discrete Networks / Thomas Modeling

[Kauffman in *Journal of Theoretical Biology*, 1969]
[Thomas in *Journal of Theoretical Biology*, 1973]

- A set of components $N = \{a, b, z\}$



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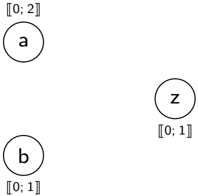

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a	$f^b(a)$
0	**0**
1	**1**
2	**1**

z	b	$f^a(z, b)$
0	0	**1**
0	1	**0**
1	0	**1**
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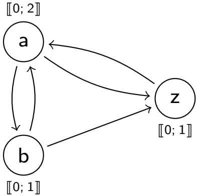

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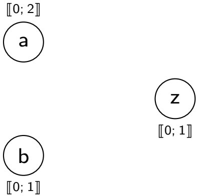

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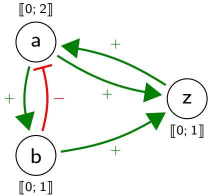

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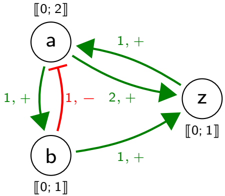

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- Discrete parameters / evolution functions $f^a : \mathbb{F} \to \mathbb{F}^a$

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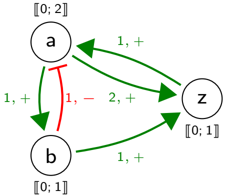

State-graph of a Discrete Network

Several semantics exist regarding the updates:

- Synchronous (deterministic)
- **Asynchronous** (non-deterministic)
- Generalized (even more non-deterministic)

In every case, exponential size in the number of components

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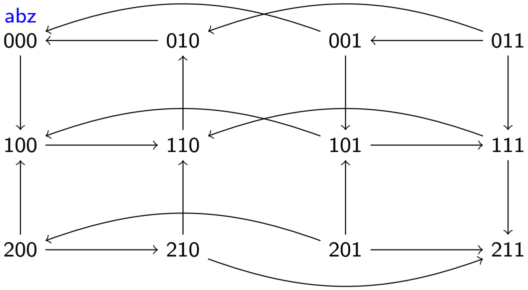

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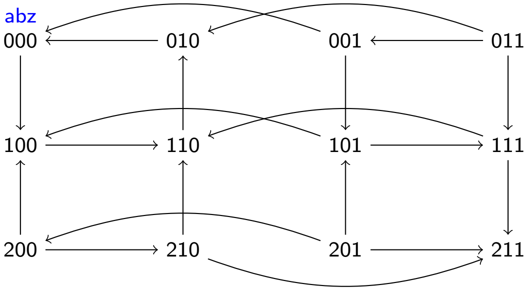

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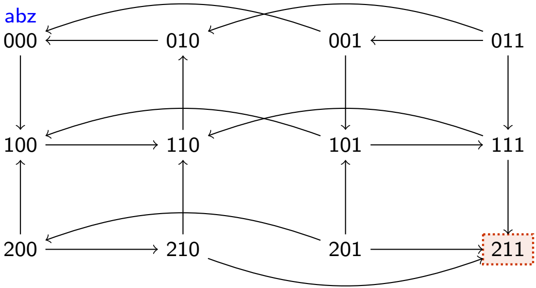

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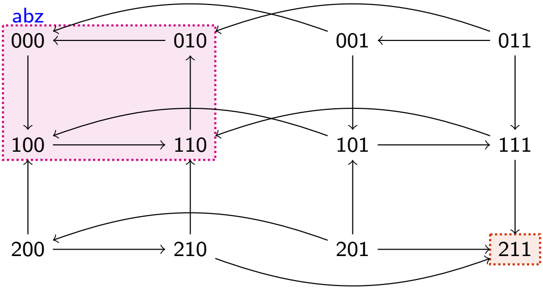

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- **Stable state** (state with no successors)
- **Complex attractor** (loop or composition of loops)

Static Analysis of Discrete Networks

[Thomas in *Numerical Methods in the Study of Critical Phenomena*, 1981]
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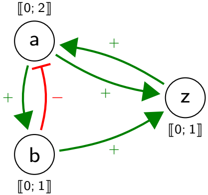
Conjectures of René Thomas:



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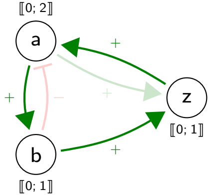

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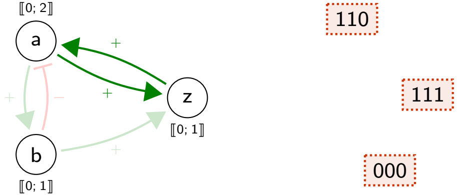

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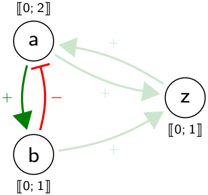

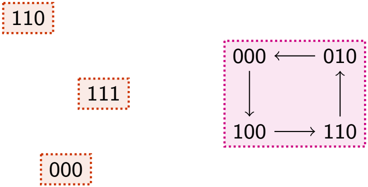

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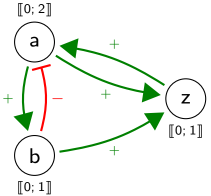

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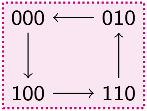

Proofs:
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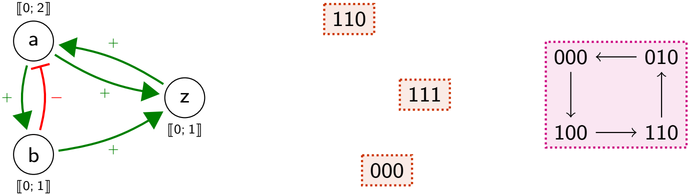

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Other results:

- Lower & upper bounds of the number of attractors
- Functionality of the cycles
- Sufficient condition for no stable state / Topological stable states

Dynamic Analysis of Discrete Networks

- These static analysis results are not sufficient to predict the dynamics of independent components.

Examples that cannot be tackled:

1) From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?
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More precise but require to compute the whole state graph

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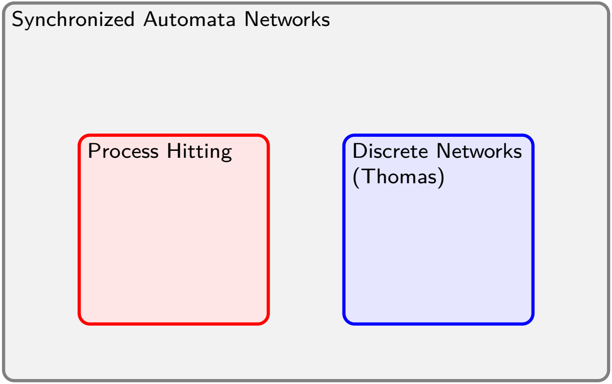
- Applications of CTL and LTL

Check a property on a given model: NuSMV, LibDDD, ...
Create a model for which a property holds: SMBioNet, SPuTNIk, ...
[Bernot, Comet, Richard, Guespin in *Journal of Theoretical Biology*, 2004]

The Enriched Process Hitting



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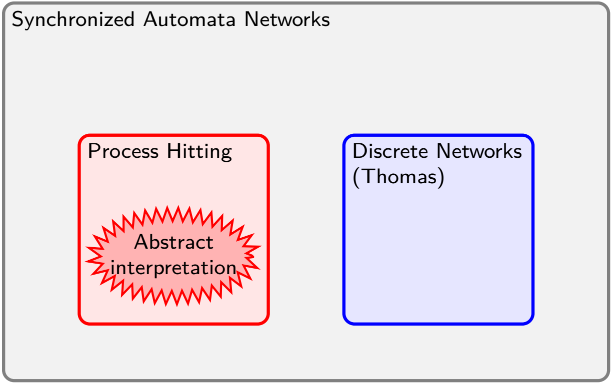

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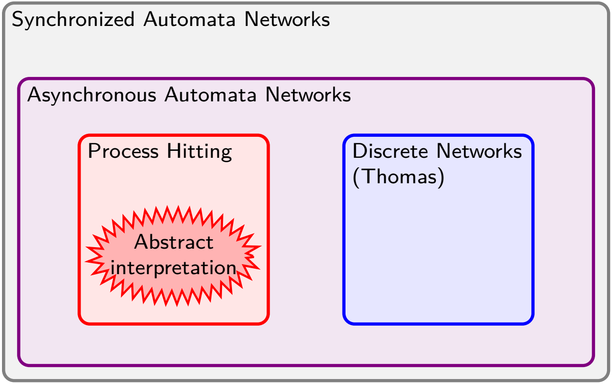

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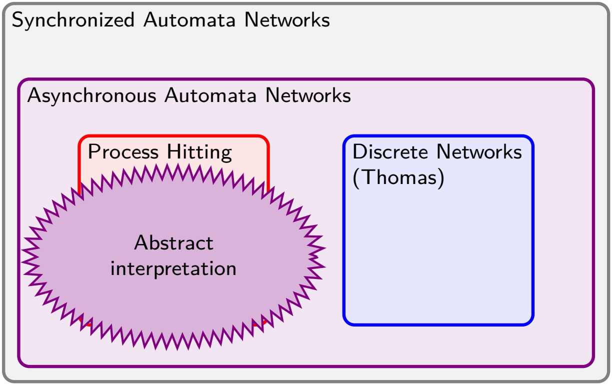
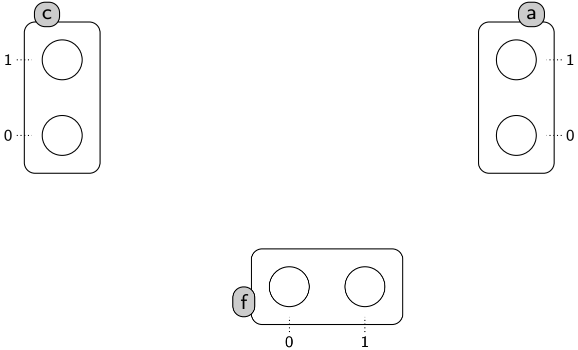


Example of enriched Process Hitting Model



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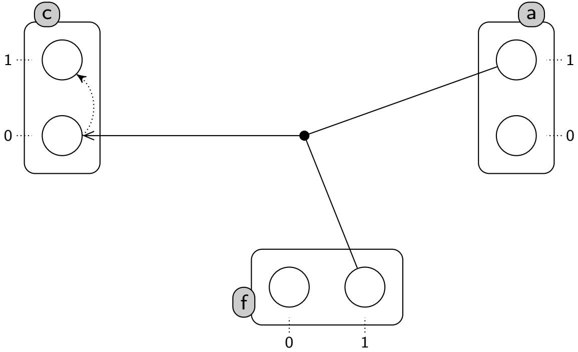

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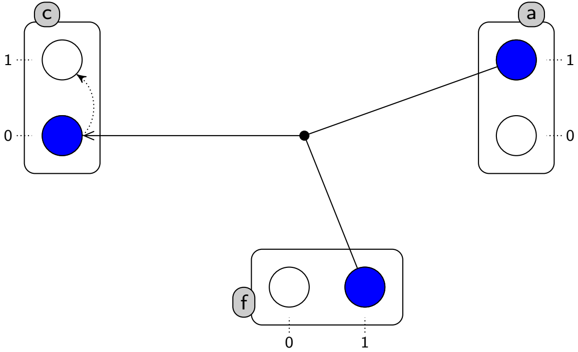

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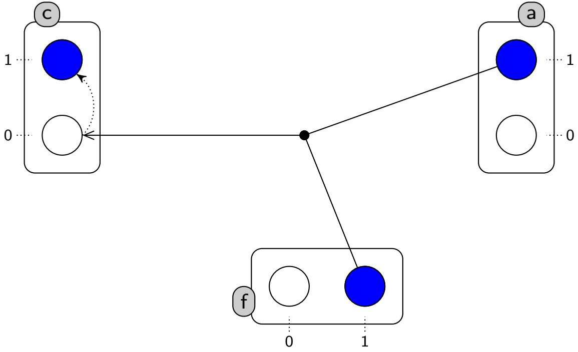

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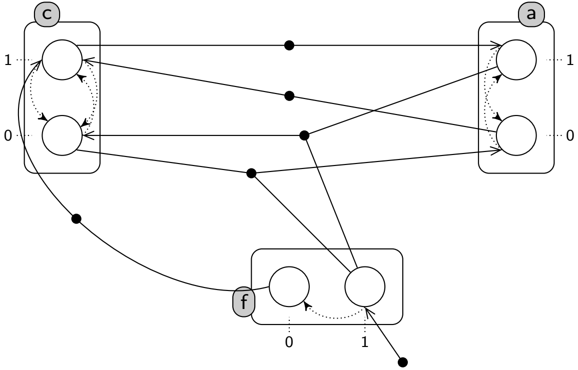
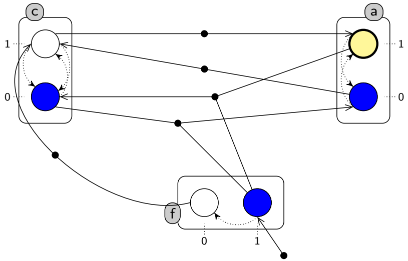
Model from [François *et al.* in Molecular Systems Biology, 2007]



Static analysis



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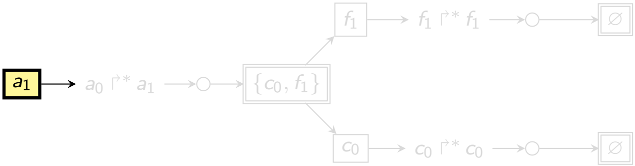

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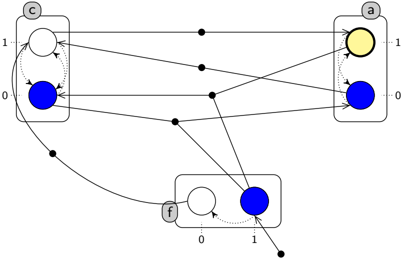

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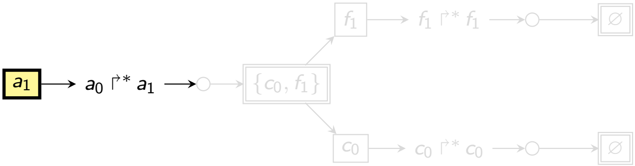

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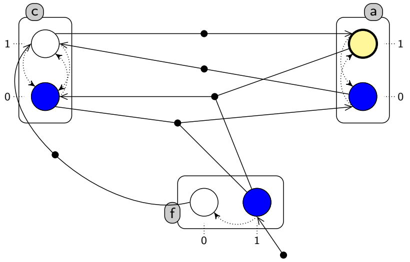

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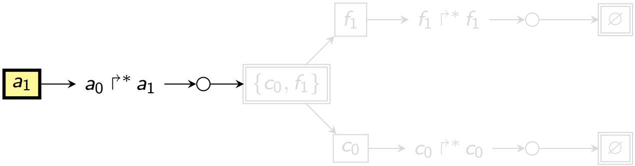

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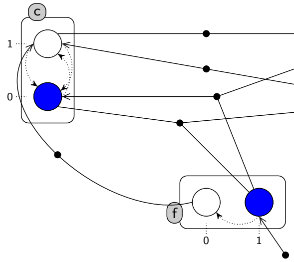

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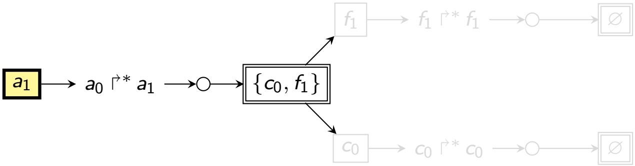

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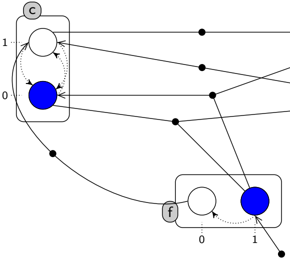

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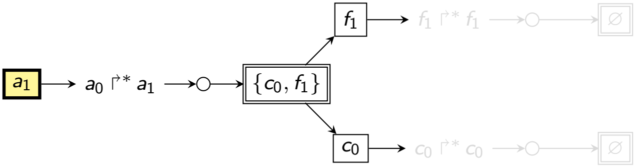

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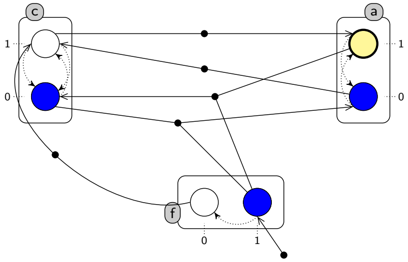

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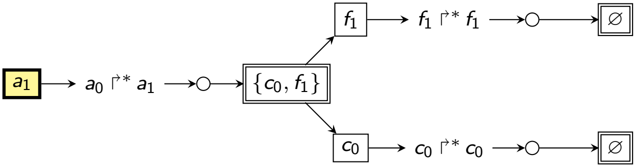

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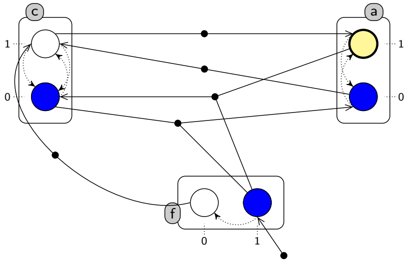

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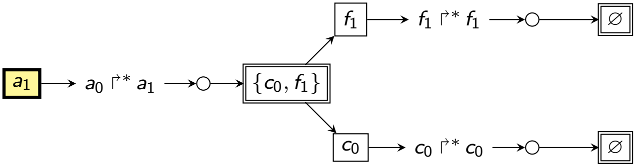

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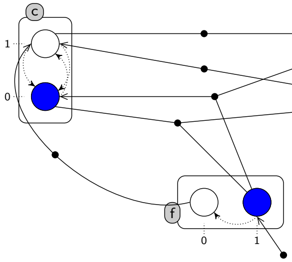

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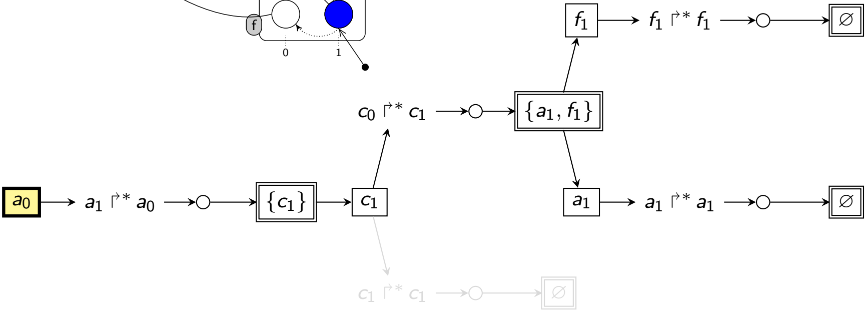

$$\{a_1, f_1\} \rightarrow c_0 \upharpoonright c_1 \;::\; \{c_1\} \rightarrow a_1 \upharpoonright a_0$$

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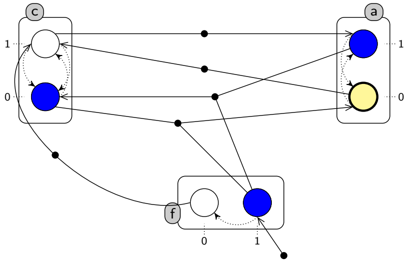

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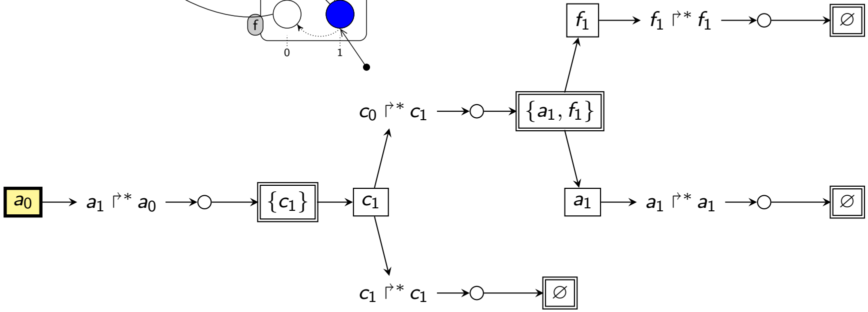

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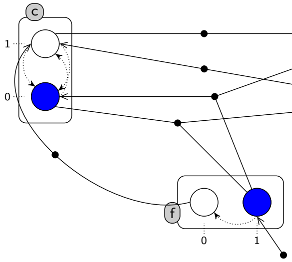

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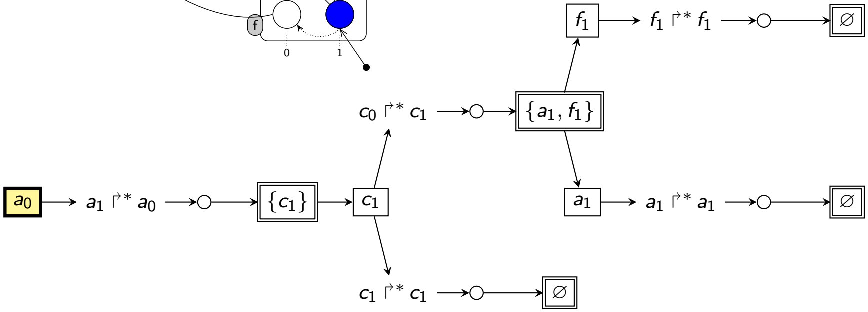

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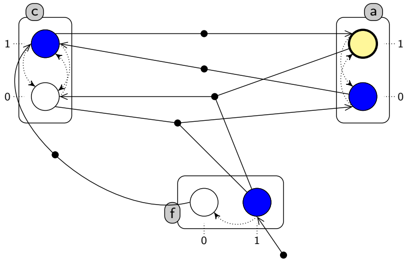

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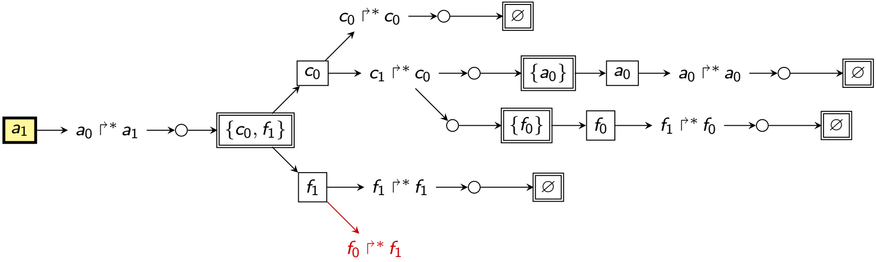

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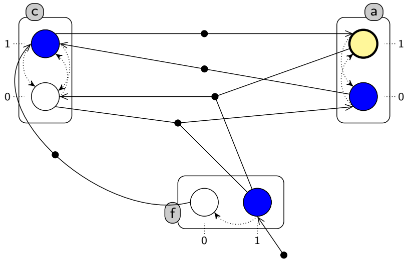

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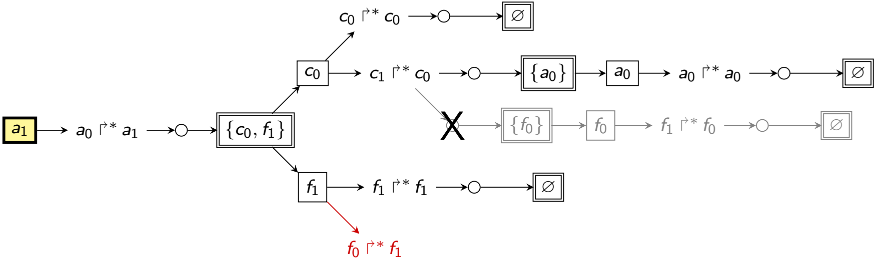

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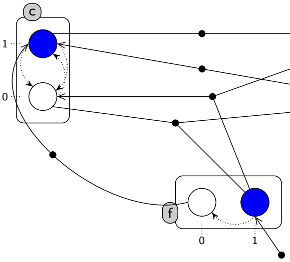

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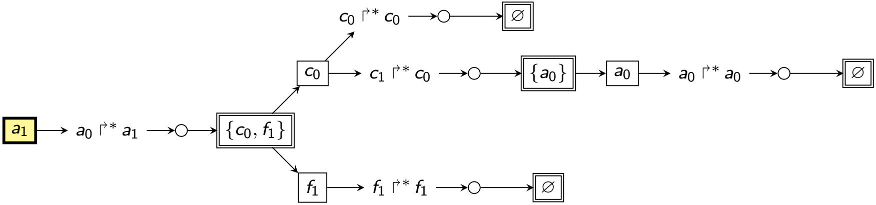

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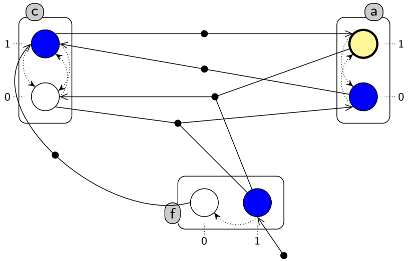

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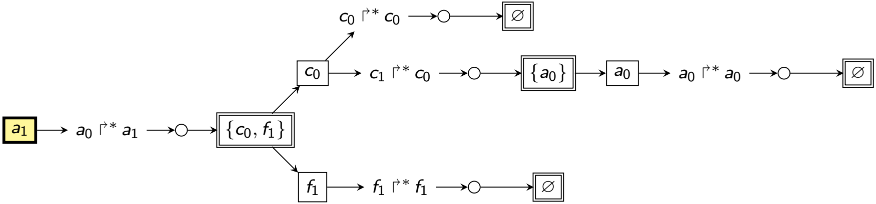

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Implementation of the Static Analysis Into PINT

Complexity:

- Computation of the local causality graph:
  - Polynomial in the number of sorts
  - Exponential in the number of processes of each sort
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Makes the study of large networks tractable:

Model	Automata	Actions	States	libddd[1]	GINsim[2]	PINT
egfr20	35	670	2^{64}		$<$1s	**0.02s**
tcrsig40	54	301	2^{73}		∞	**0.02s**
tcrsig94	133	1124	2^{194}	[$>$1min − ∞]		**0.03s**
egfr104	193	2356	2^{320}	[$>$1min − ∞]		**0.16s**

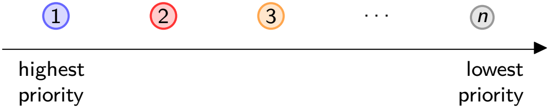
[1] LIP6/Move [Couvreur *et al.*, *Lecture Notes in Computer Science*, 2002]
[2] TAGC/IGC [Chaouiya, Naldi, Thieffry, *Methods in Molecular Biology*, 2012]

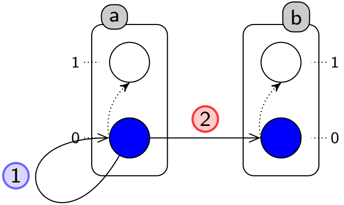
egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga *et al.*, 2009]
tcrsig40 : T-Cell Receptor (40 composants) [Klamt *et al.*, 2006]
tcrsig94 : T-Cell Receptor (94 composants) [Saez-Rodriguez *et al.*, 2007]

Classes of priorities

[Folschette *et al.* in *Theoretical Computer Science*, 2015b]

- Each action is associated to a discrete priority
- An action is playable only if no other action with higher priority is playable





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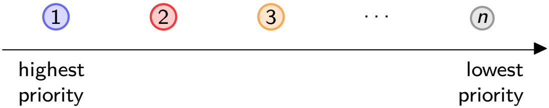

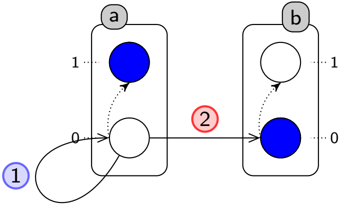

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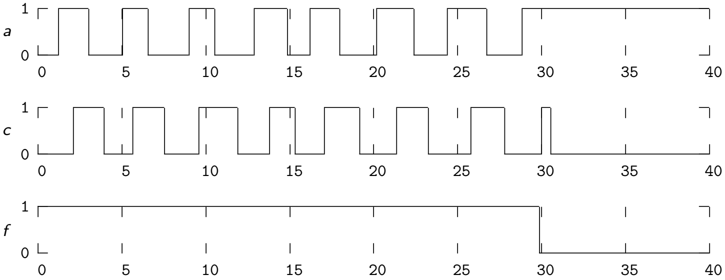
Temporal Simulation

[Paulevé (PhD thesis), 2011]

- Simulation with stochastic parameters:



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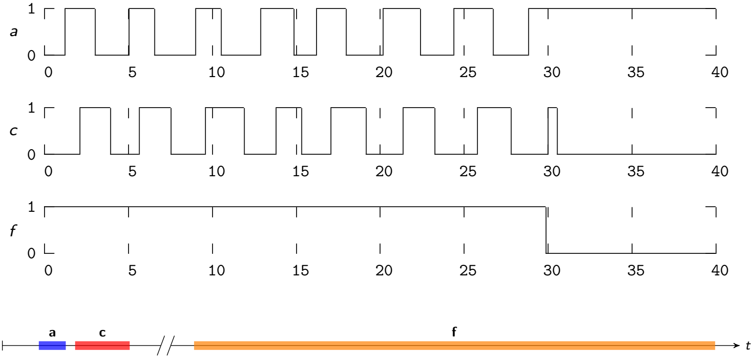

Stochastic parameters:

- **a** $= [0.742; 1.29]$ (mean 1)
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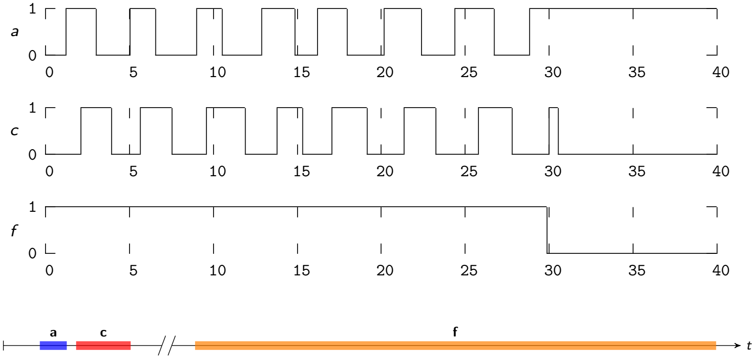

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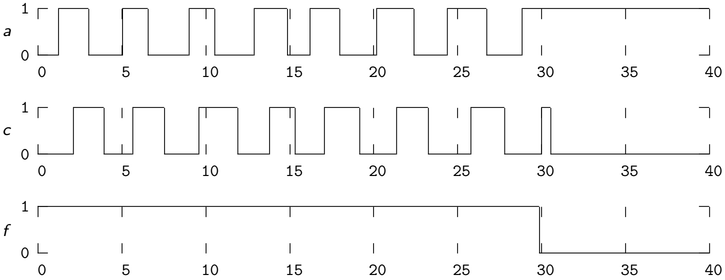

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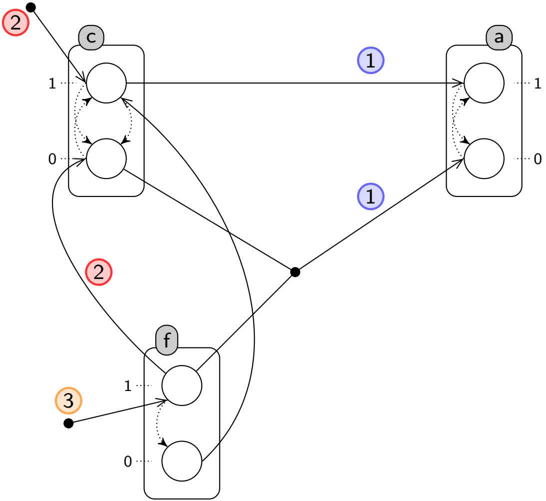
Example with Classes of Priorities



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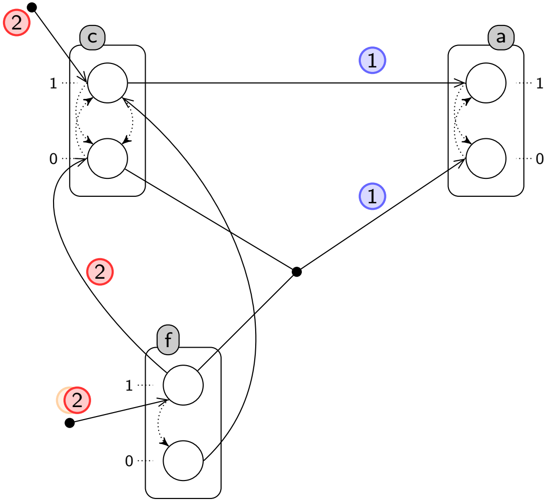
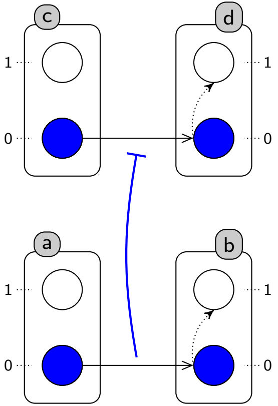


Neutralizing Edges



- Integration of temporal data about relative reaction speeds
- Atomistic preemptions between actions similar to “atomistic priorities”

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$a_0 \rightarrow b_0 \upharpoonright b_1$ is playable

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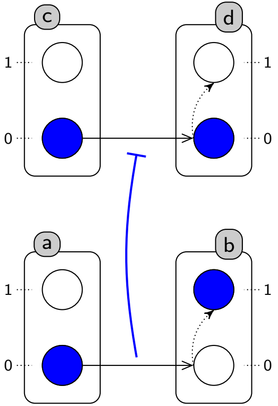

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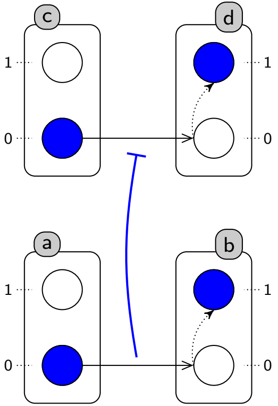

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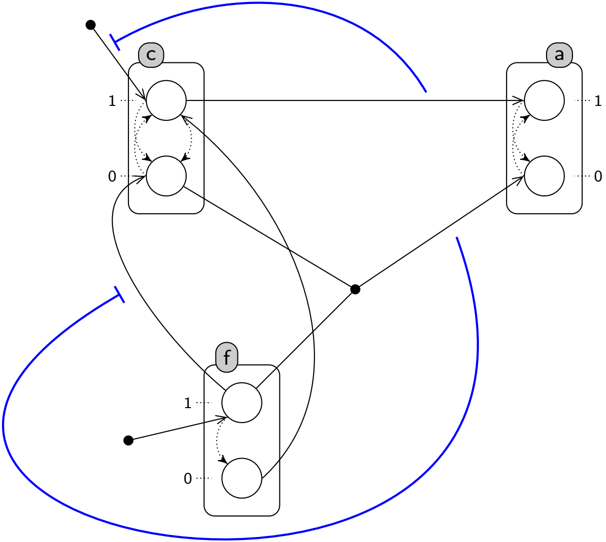
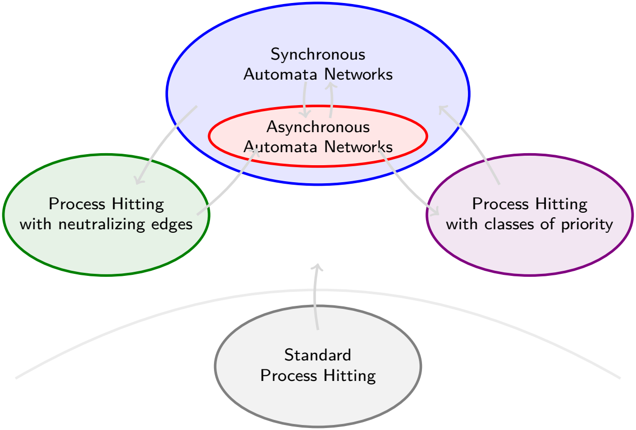


Equivalence Between Process Hitting Extensions



All developed enrichments have the same expressivity

- Expressive power improved
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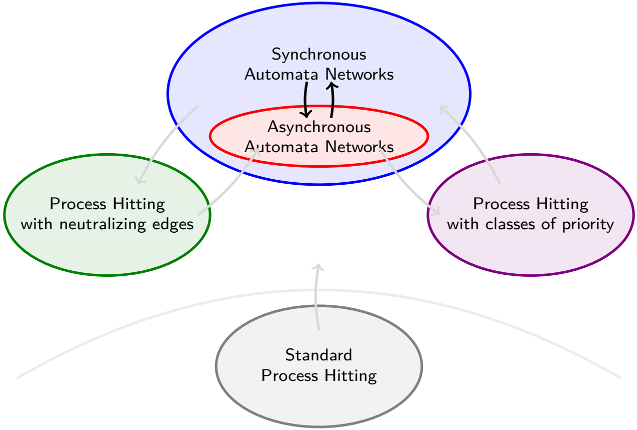

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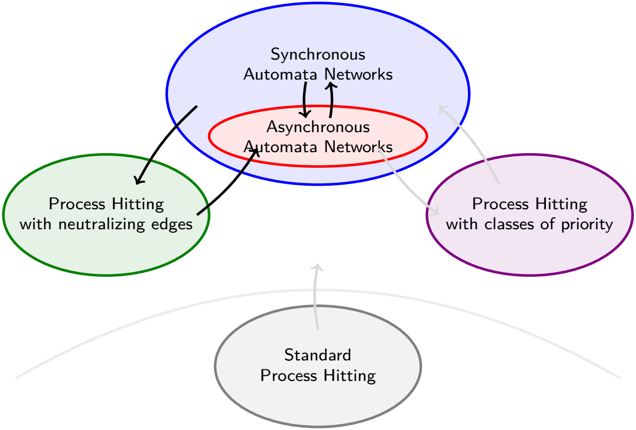

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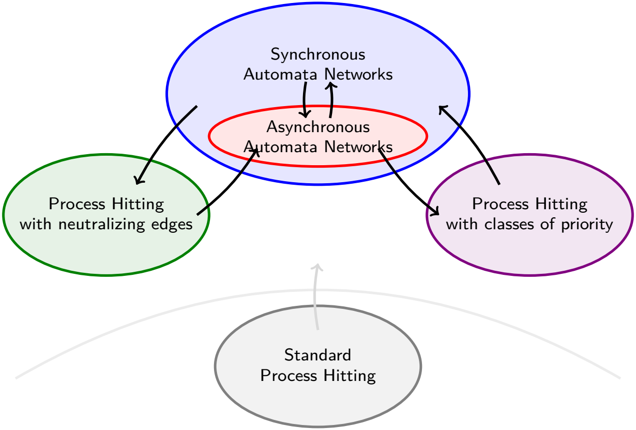

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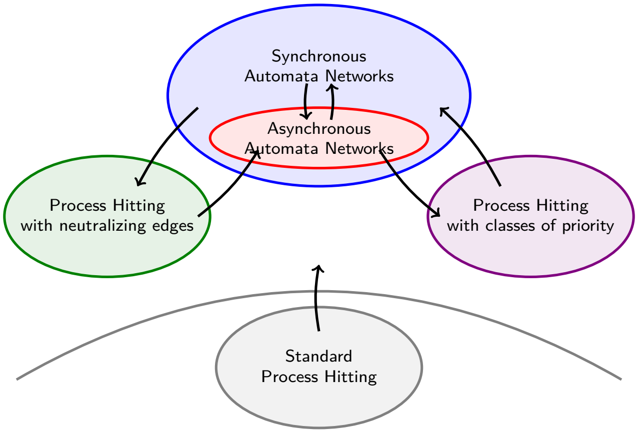

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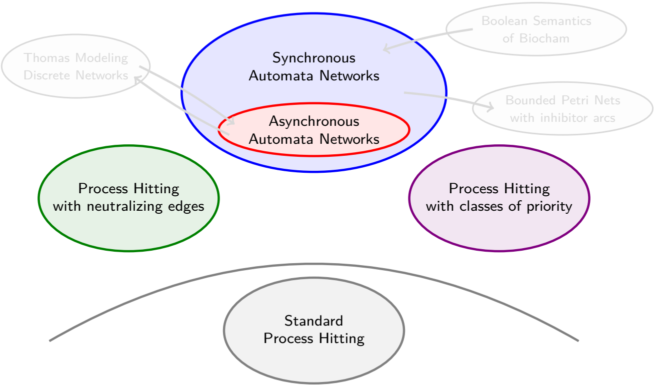
Translation From and To Other Discrete Models



- Equivalence with Discrete Networks / Thomas modeling
- Translation towards (bounded) Petri nets with inhibitor arcs
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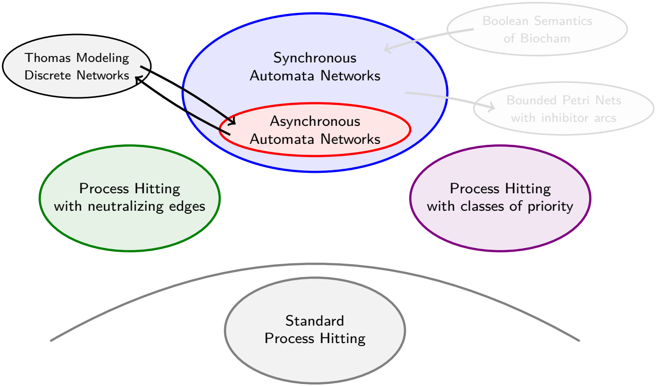

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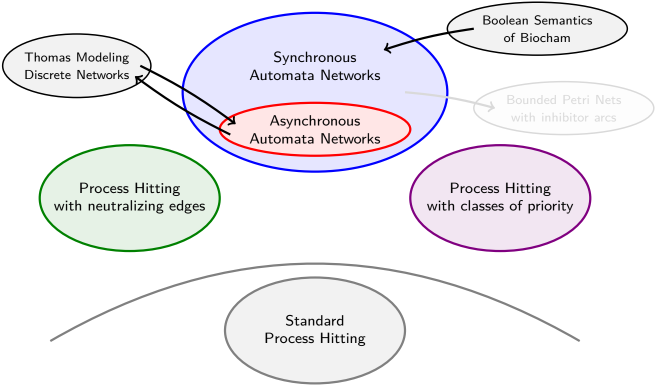

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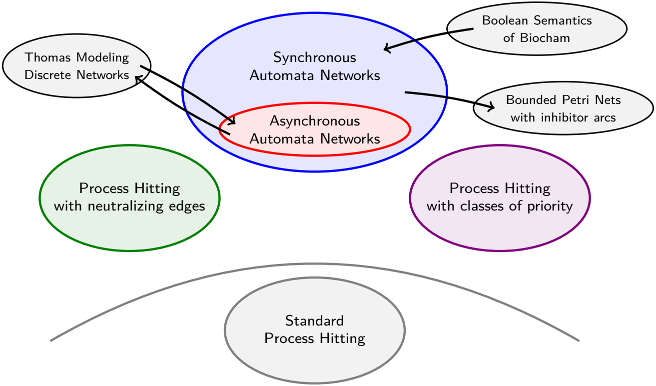

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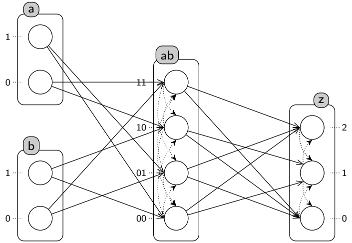
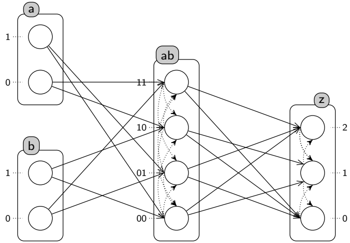
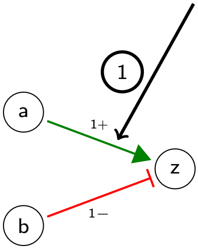
Inferring a BRN with Thomas' parameters



ω		$k_{z,\omega}$
a	b	
−	+	1
−	−	0
+	+	2
+	−	1

Inferring a BRN with Thomas' parameters





ω		$k_{z,\omega}$
a	b	
$-$	$+$	1
$-$	$-$	0
$+$	$+$	2
$+$	$-$	1

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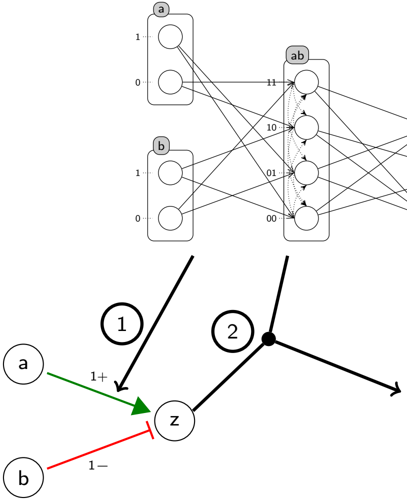

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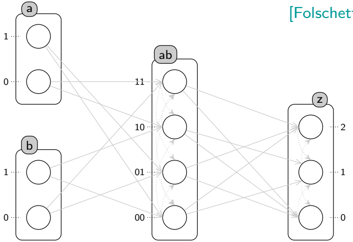
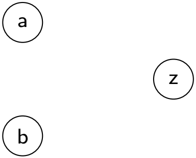
Inferring the Interaction Graph

[Folschette *et al.* in *Theoretical Computer Science*, 2015a]





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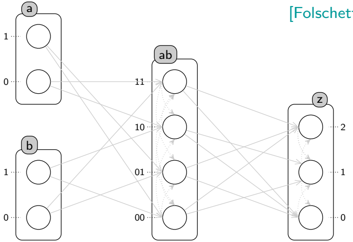

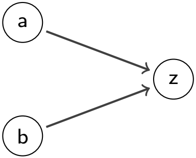

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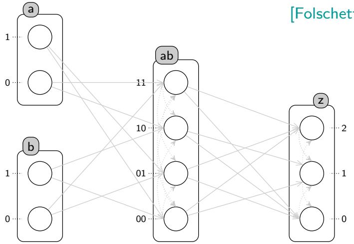

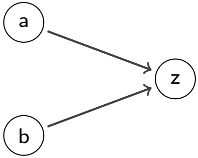

→ **Exhaustive search in all possible configurations**

Inferring the Interaction Graph

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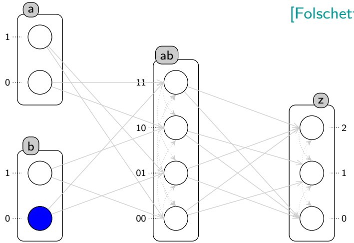

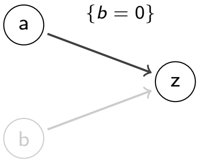

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Inferring the Interaction Graph

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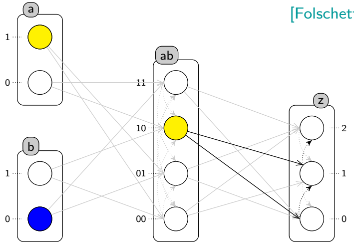

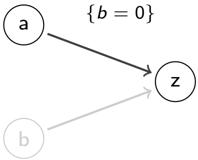

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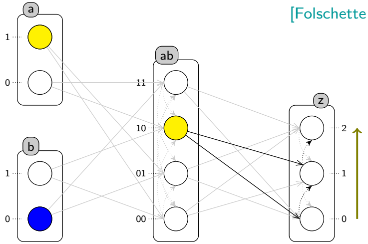

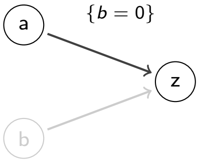

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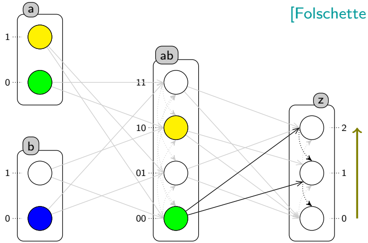

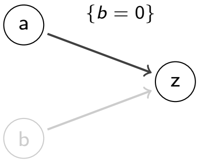

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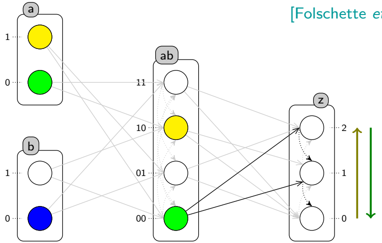

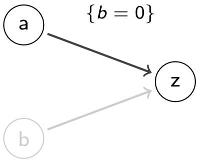

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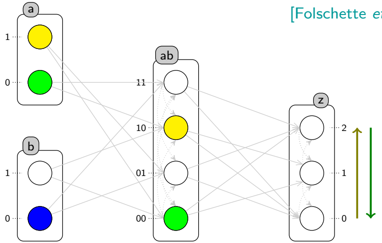

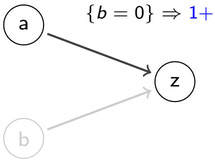

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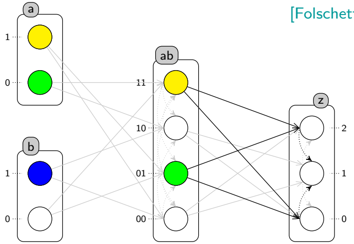

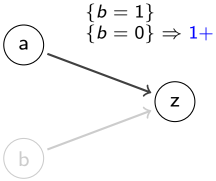

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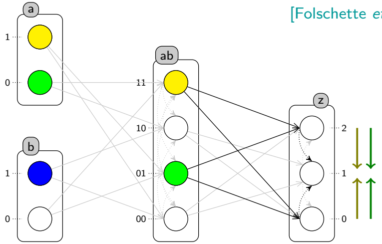

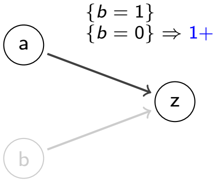

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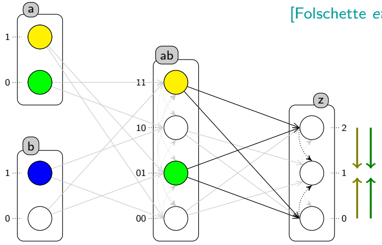

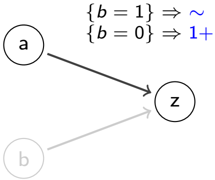

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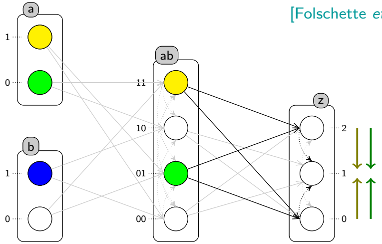

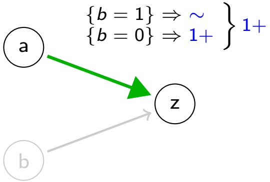

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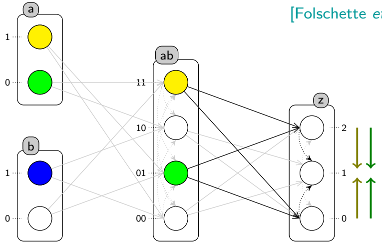

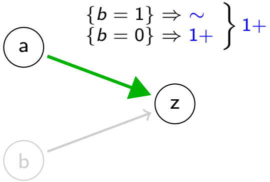

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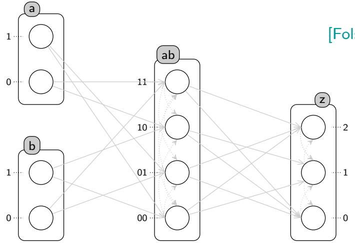
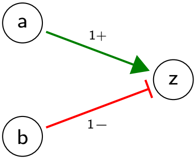
Problematic cases:

→ No focal processes (cycle)
→ Opposite influences $(+ \ \& \ -)$
} ⇒ Unsigned edge

Inferring Parameters

[Folschette *et al.* in *Theoretical Computer Science*, 2015a]

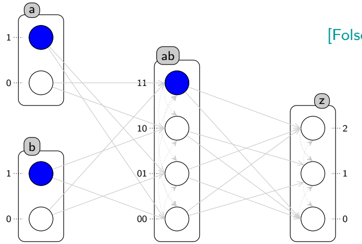


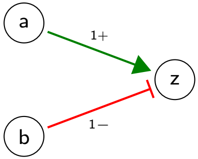


ω		$k_{z,\omega}$
a	b	
$-$	$+$	
$-$	$-$	
$+$	$+$	
$+$	$-$	

Inferring Parameters

[Folschette *et al.* in *Theoretical Computer Science*, 2015a]





ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	

1. For each configuration of resources $[\omega = \{a^+, b^-\}]$

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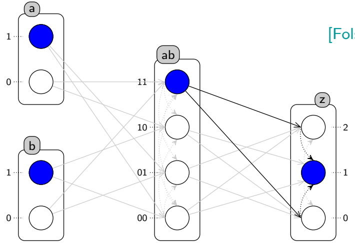

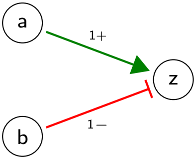

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	

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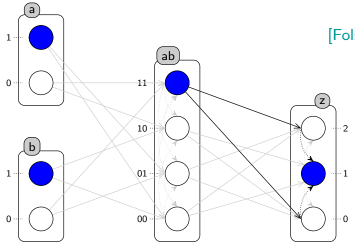

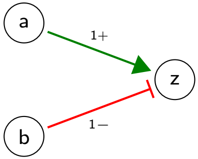

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	1

1. For each configuration of resources [$\omega = \{a^+, b^-\}$]
   find the **focal processes**. If possible, conclude. [$k_{z,\{a^+,b^-\}} = 1$]

Inferring Parameters

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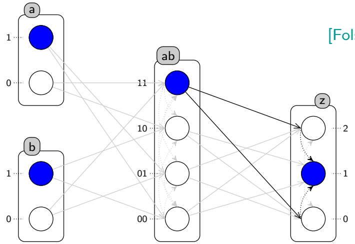

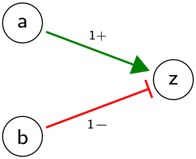

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−	−	
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   Inconclusive cases:

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Inferring Parameters

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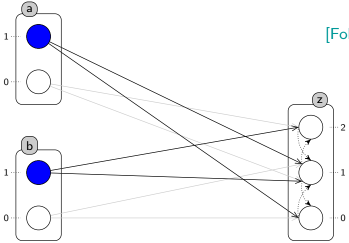

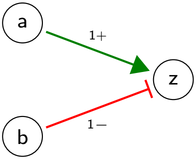

ω		$k_{z,\omega}$
a	b	
$-$	$+$	?
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   Inconclusive cases:
   - Behavior cannot be represented as a BRN
   - Lack of cooperation (no focal processes)

2. If some parameters could not be inferred, enumerate all admissible parametrizations, regarding:
   - Biological constraints [Bernot *et al.* in *Concurrent Models in Molecular Biology*, 2007]
   - The dynamics of the Process Hitting

$[k_{z,\{a^+,b^-\}} \in \{0;1;2\};\ k_{z,\{a^-,b^+\}} \in \{0;1;2\}]$

Translation to Thomas Modeling

[Folschette *et al.* in *Theoretical Computer Science*, 2015a]

- Two successive inferences: 1) interaction graph; 2) parameters
- Exhaustive analysis of the local dynamics for each regulator
- enumeration of all parametrizations compatible with the dynamics

Complexity:
Linear in the number of genes,
Exponential in the number of regulators of one component

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Models				Inference the IG		Inference of parameters	
Name	Sorts	Processes	Actions	Duration	Edges	Durations	Parameters
egfr20	42	152	399	**1s**	51	**1s**	192
tcrsig40	54	156	305	**1s**	55	**1s**	143
tcrsig94	133	448	1082	**100s**	197	**1s**	578
egfr104	193	744	2304	**200s**	280	**3s**	27'496

egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga *et al.*, 2009]
tcrsig40 : T-Cell Receptor (40 composants) [Klamt *et al.*, 2006]
tcrsig94 : T-Cell Receptor (94 composants) [Saez-Rodriguez *et al.*, 2007]

The Modal μ-calculus

LTL: Example of the "Until" operator

$p\ U\ q \equiv$ "Either q, or p and the next state also verifies $p\ U\ q$"

$\Rightarrow$ Implicit fixed point

(Modal) μ-calculus makes such fixed points explicit

$$\varphi = p \mid \neg\varphi \mid \varphi \wedge \varphi \mid \varphi \vee \varphi \mid \Diamond\varphi \mid \Box\varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X$$

- Basic property: p ("p is verified in this node")
- Modal operators: $\Box$ ("for all successors"), $\Diamond$ ("there exists a successor")
- Fixed points: μ (least fixed point), ν (greatest fixed point)

Polyadic (modal) μ-calculus allows to manipulate several tokens in parallel

$$\varphi = p_i \mid i \leftarrow j \mid i = j \mid \neg\varphi \mid \varphi \wedge \varphi \mid \varphi \vee \varphi \mid \Diamond_i\varphi \mid \Box_i\varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X$$

- Token manipulation:
  $i = j$ ("tokens i and j point to the same node")
  $i \leftarrow j$ ("move token i to the position of token j")

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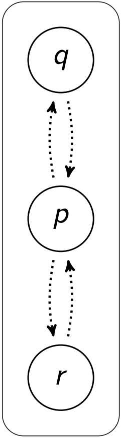
- Fixed points: μ (least fixed point), ν (greatest fixed point)

Polyadic (modal) μ-calculus allows to manipulate several tokens in parallel

$$\varphi = p_i \mid i \leftarrow j \mid i = j \mid \neg\varphi \mid \varphi \wedge \varphi \mid \varphi \vee \varphi \mid \Diamond_i\varphi \mid \Box_i\varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X$$

- Token manipulation:
  $i = j$ ("tokens i and j point to the same node")
  $i \leftarrow j$ ("move token i to the position of token j")

Examples with Modal μ-calculus



No tokens: only one evolution is studied

Atomic property (p, q, r)

$[\![p]\!] = \{p\}$

$[\![q \vee r]\!] = \{q; r\}$

Possible future ("may")

$[\![\Diamond\ q]\!] = \{p\}$

Necessary future ("must")

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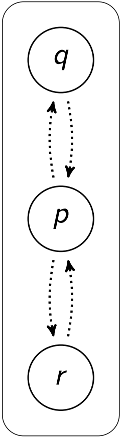

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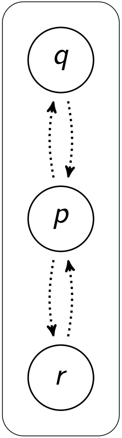

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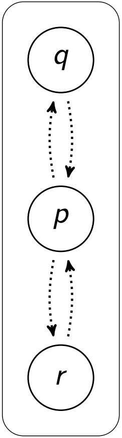

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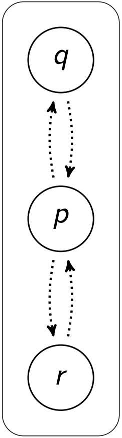

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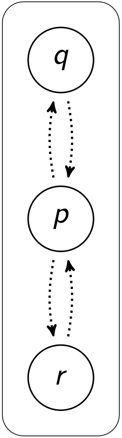

Atomic property (p, q, r)

$[\![p_1 \wedge r_2]\!] = \{(p, r)\}$

$[\![p_1]\!] = \{(p, p); (p, q); (p, r)\}$

Token affectation ($i \leftarrow j$)

$[\![\{2 \leftarrow 1\}\ p_1 \wedge p_2]\!] = \{(p, p); (p, q); (p, r)\}$

Token comparison ($i = j$)

$[\![1 = 2]\!] = \{(p, p); (q, q); (r, r)\}$

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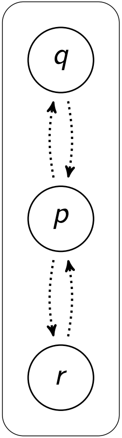

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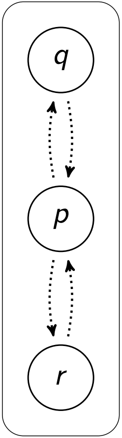

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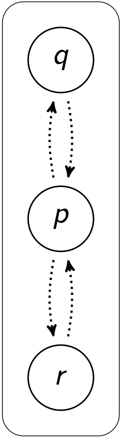

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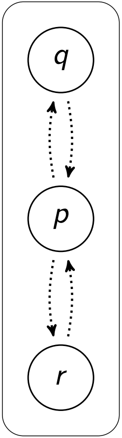

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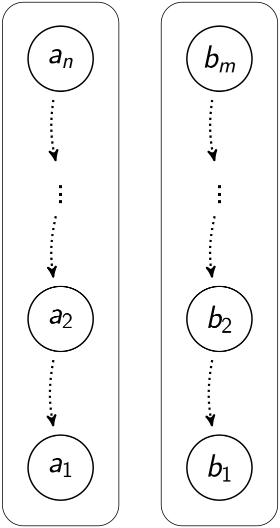

Least fixed point (μ)

$\phi = \mu X.(\Box_1 \bot \wedge \Box_2 \bot) \vee \Diamond_1 \Diamond_2 X$

Iterations:

$[\![\phi]\!]_0 = \varnothing$
$[\![\phi]\!]_1 = \{(a_1, b_1)\}$
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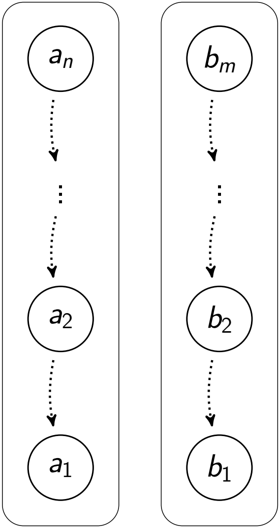
Generalization:

$[\![\phi]\!] = \{(a_i, b_i) \mid i \in [1; \min(m, n)]\}$

Idea: use one (or n) token per automata

Examples with Polyadic μ-calculus



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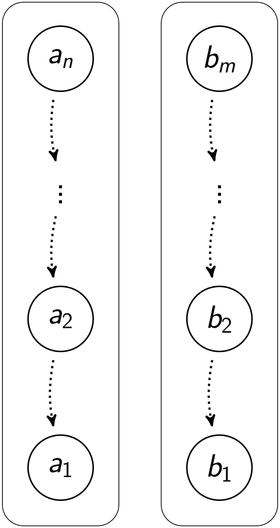

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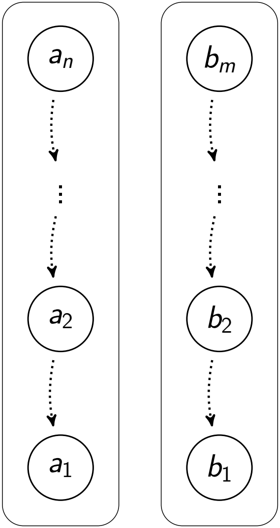

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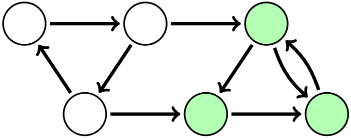
Search for Attractors with Polyadic μ-calculus



$$\varphi_{\text{att}} = \{\boldsymbol{y} \leftarrow \boldsymbol{x}\}\nu W.\underbrace{\underbrace{(\mu Z.\,(\boldsymbol{x} = \boldsymbol{y}) \vee (\Diamond_{\boldsymbol{x}} Z))}_{\varphi_{\text{reach}}} \wedge (\Box_{\boldsymbol{x}} W)}_{\varphi_{\text{explore}}}$$

- $[\![\varphi_{\text{reach}}]\!] = \{(s; t) \mid s \rightarrow^* t\}$
  $\varphi_{\text{reach}} \equiv$ "There exists a path from $\boldsymbol{x}$ to $\boldsymbol{y}$"
- $[\![\varphi_{\text{explore}}]\!] = \{(s; t) \mid \forall s', s \rightarrow^* s' \Rightarrow s' \rightarrow^* t\}$
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- $[\![\varphi_{\text{att}}]\!] = \{(s; s) \mid \forall s', s \rightarrow^* s' \Rightarrow s' \rightarrow^* s\}$
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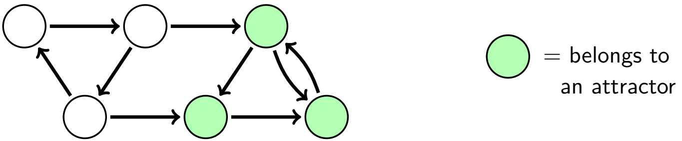

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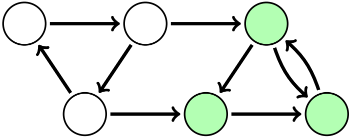

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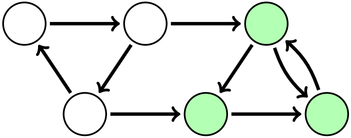

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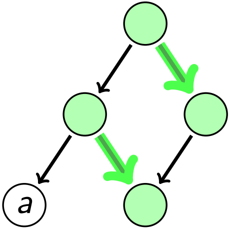
Search for Switches with Polyadic μ-calculus



$$\varphi_{\text{switch}}(\boldsymbol{a}) = \overbrace{\left(\mu W.(\boldsymbol{x} = \boldsymbol{a}) \vee (\Diamond_{\boldsymbol{x}} W)\right)}^{\varphi_{\text{reach}}} \wedge$$
$$\Diamond_{\boldsymbol{x}}\{\boldsymbol{x} \leftarrow \boldsymbol{y}\}\underbrace{\left(\nu Z.\neg(\boldsymbol{y} = \boldsymbol{a}) \wedge (\Box_{\boldsymbol{y}} Z)\right)}_{\varphi_{\text{noreach}}}$$

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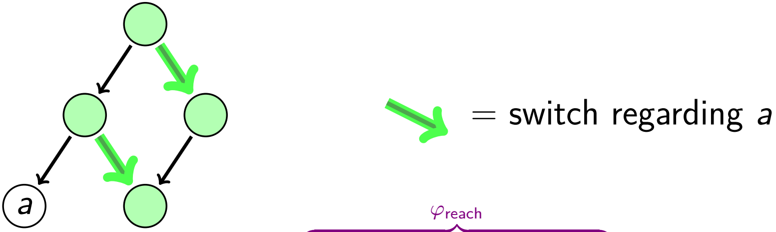

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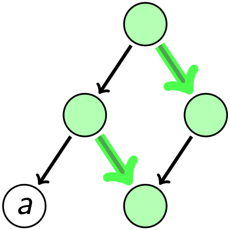

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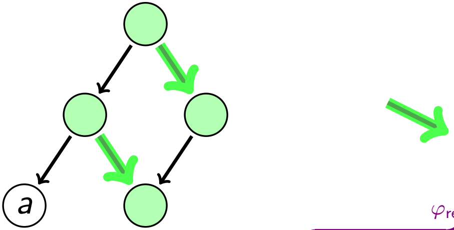

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Bisimulation with Polyadic µ-calculus

Generic **bisimulation** between two models:

$$\varphi_{\text{bisim}} = \nu X.(\bigwedge_{p \in P} p_1 \Leftrightarrow p_2) \wedge (\Box_1 \Diamond_2 X \wedge \Box_2 \Diamond_1 X)$$

Bisimulation only on two sets of **observable components** O and O':

$$\varphi_{\text{bisim-obs}} = \nu X.(\bigwedge_{p \in P} \bigwedge_{(i;j) \in C} p_i \Leftrightarrow p_j) \wedge (\Box^*_{\overline{O}} \Box_O \Diamond^*_{\overline{O'}} \Diamond_{O'} X)$$

Summary & Conclusion

- Discrete modeling = coherent abstraction of real biochemical phenomena
  - → Discrete Networks / Thomas modeling
  - → Asynchronous Automata Networks
  - → Other extensions of the Process Hitting
- Static analysis based on the structure
  - → Results on attractors (multiple stable states / complex attractors)
  - → But results are not always fine enough
- Static analysis by abstract interpretation
  - → Reachability properties
  - → Very efficient (polynomial complexity)
  - → Broad rand of models (+ translations)
  - → But only one kind of property (CTL operator *EF*)
- μ-calculus
  - → More generic than CTL*
  - → Example: enumeration of attractors
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  - → Asynchronous Automata Networks
  - → Other extensions of the Process Hitting
- Static analysis based on the structure
  - → Results on attractors (multiple stable states / complex attractors)
  - → But results are not always fine enough
- Static analysis by abstract interpretation
  - → Reachability properties
  - → Very efficient (polynomial complexity)
  - → Broad rand of models (+ translations)
  - → But only one kind of property (CTL operator *EF*)
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Thank you