FMV team — Oberseminar

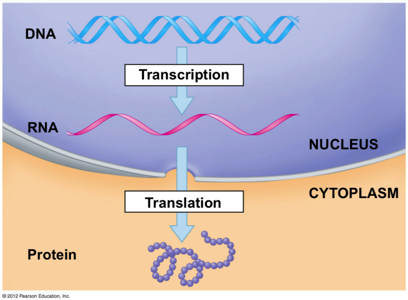
Some Methods and Results on Biological Regulatory Networks

Maxime FOLSCHETTE

FMV team / Department of Electronics & Informatics / University of Kassel
maxime.folschette@uni-kassel.de
http://maxime.folschette.name/

2015/06/18

Abstractions of the Representation



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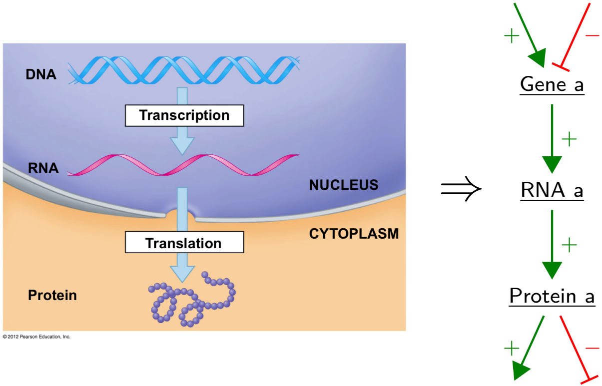

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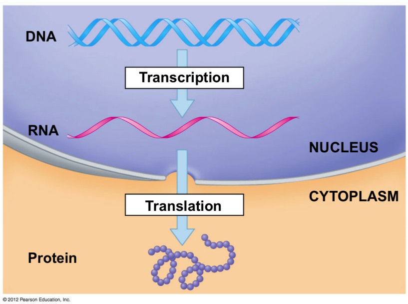

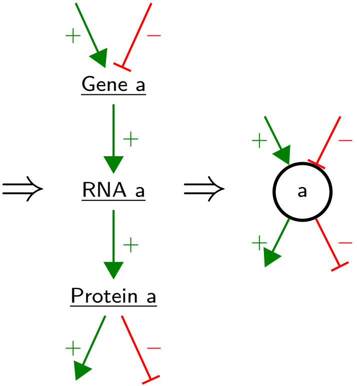

Discrete Networks / Thomas Modeling

[Kauffman in *Journal of Theoretical Biology*, 1969]
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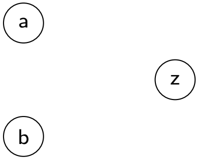
- A set of components $N = \{a, b, z\}$



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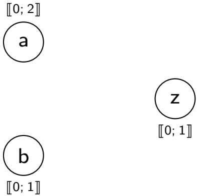
- A set of components $N = \{a, b, z\}$
- A set of discrete expression levels for each component $a \in \mathbb{F}^a = [\![0; 2]\!]$
- The set of global states $\mathbb{F} = \mathbb{F}^a \times \mathbb{F}^b \times \mathbb{F}^z$



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- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

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**
1	1	**2**

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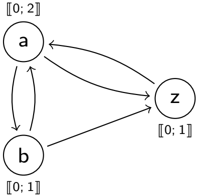

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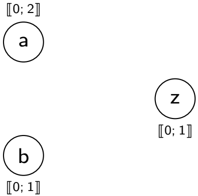

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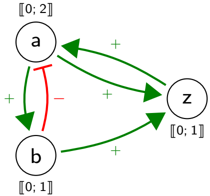
- Signs on the edges $a \xrightarrow{+} z$



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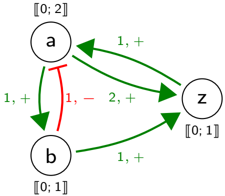

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- Signs on the edges $a \xrightarrow{+} z$ or signs + thresholds $a \xrightarrow{2,+} z$
- Discrete parameters / evolution functions $f^a : \mathbb{F} \to \mathbb{F}^a$

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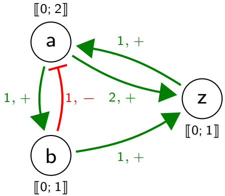

State-graph of a Discrete Network

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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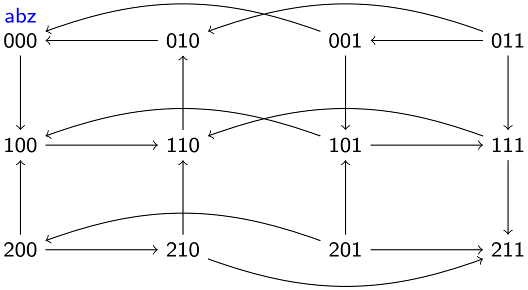

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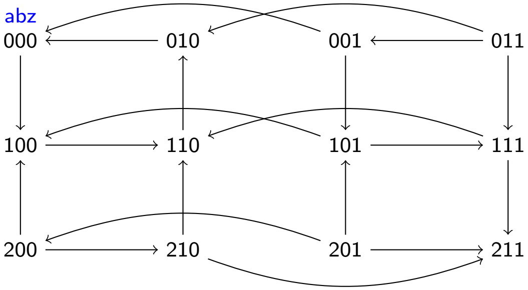

Attractor = minimal set of states from which the dynamics cannot escape
= terminal strongly connected component

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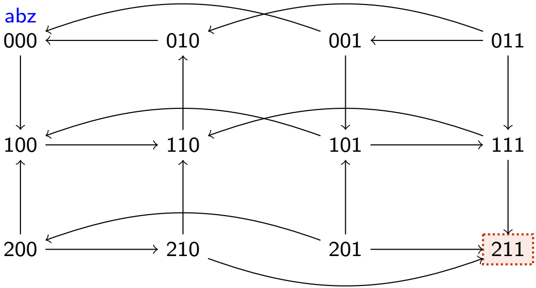

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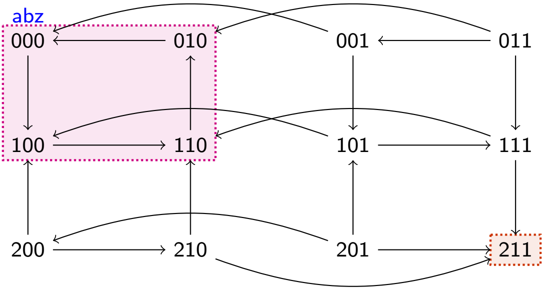

Attractor = minimal set of states from which the dynamics cannot escape
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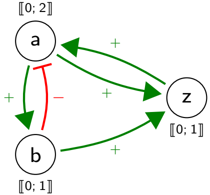
- **Stable state** (state with no successors)
- **Complex attractor** (loop or composition of loops)

Static Analysis of Discrete Networks

[Thomas in *Numerical Methods in the Study of Critical Phenomena*, 1981]
[Paulevé & Richard, *Electronic Notes in Theoretical Computer Science* 2012]

Conjectures of René Thomas:



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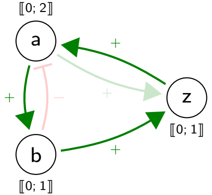

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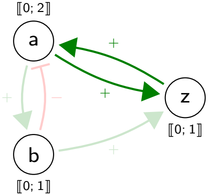

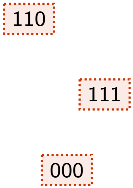

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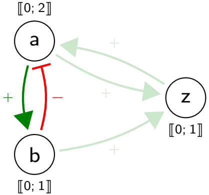

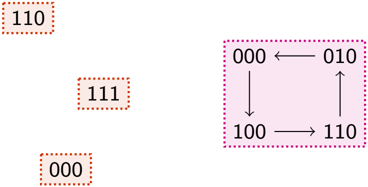

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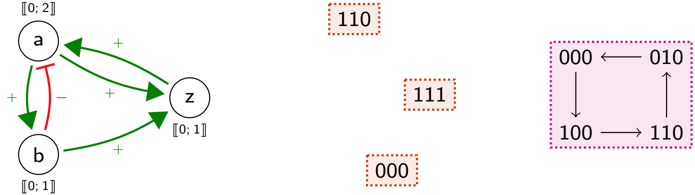

Proofs:
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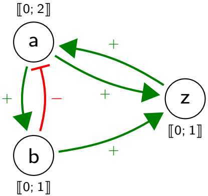

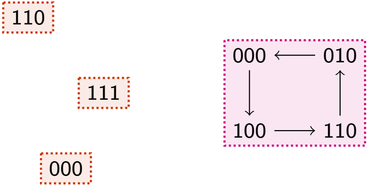

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Other results:

- 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

- The static analysis results are too weak to predict the dynamics of independent components.

Examples:

1) From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?
2) Does $(0, 0, 0)$ belong to an attractor?
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- Temporal logics (LTL, CTL, CTL*)

More precise but require to compute the whole state graph

Examples:
1) $(a = 0 \land b = 0 \land z = 0) \Rightarrow \mathrm{EF}(z = 2)$
2) $(a = 0 \land b = 0 \land z = 0) \Rightarrow \mathrm{AG}(\mathrm{EF}(a = 0 \land b = 0 \land z = 0))$
3) ???

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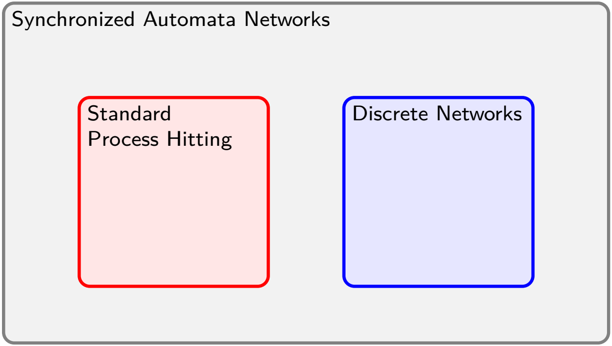
3) ???

- Applications

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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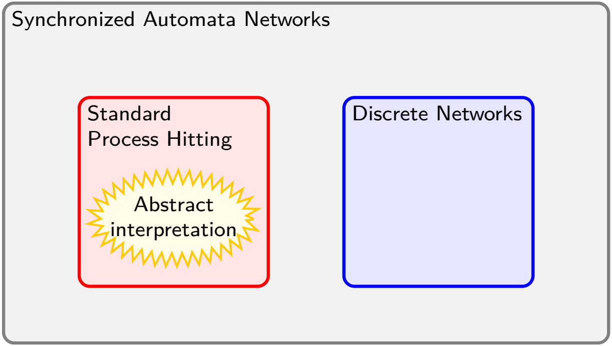

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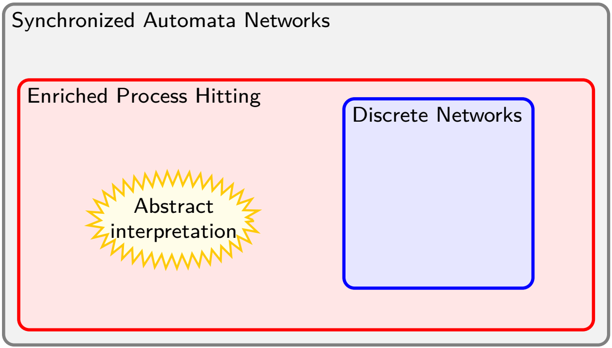

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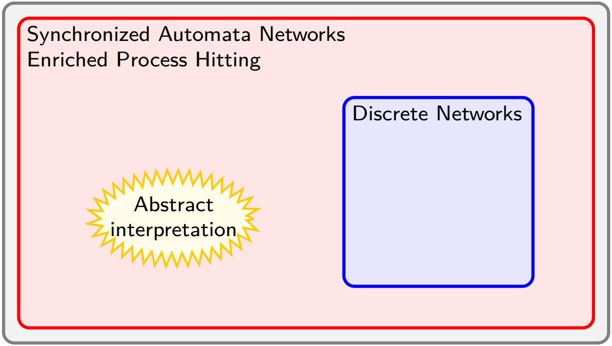
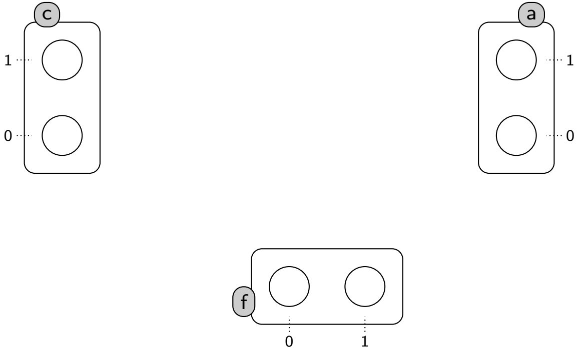


Example of enriched Process Hitting Model



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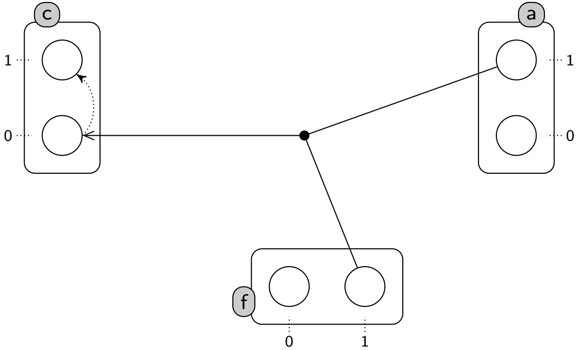

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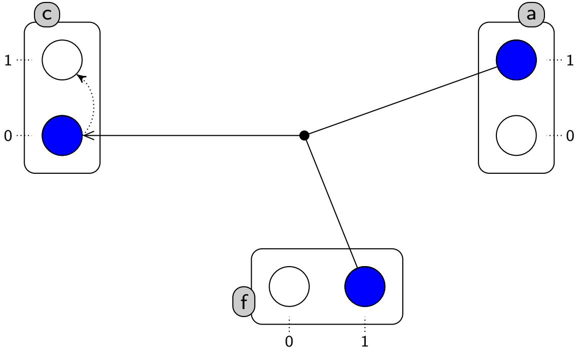

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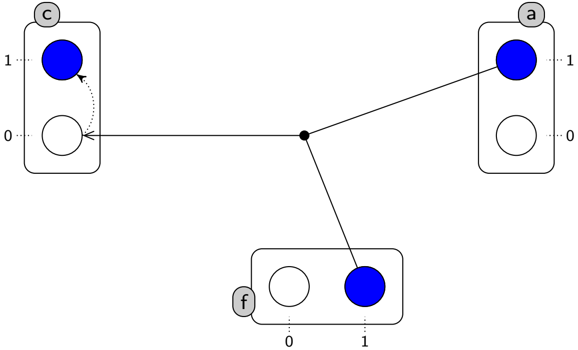

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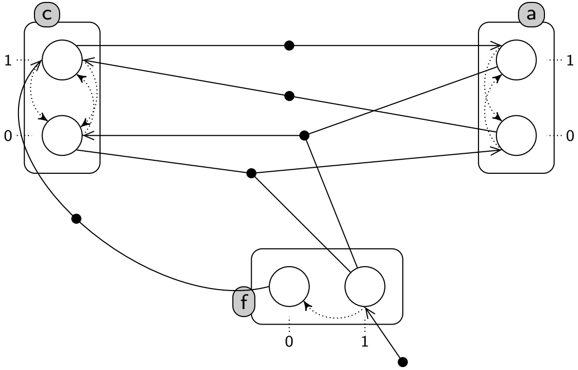
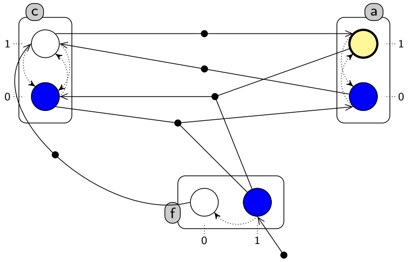
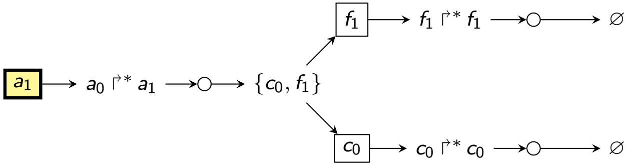


Static analysis



- No conflict
- All leaves are ∅



$$\delta = \{c_0, f_1\} \rightarrow a_0 \upharpoonright a_1$$

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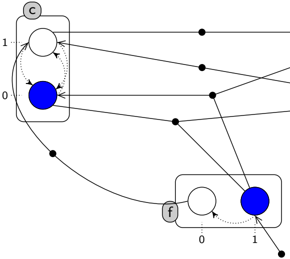

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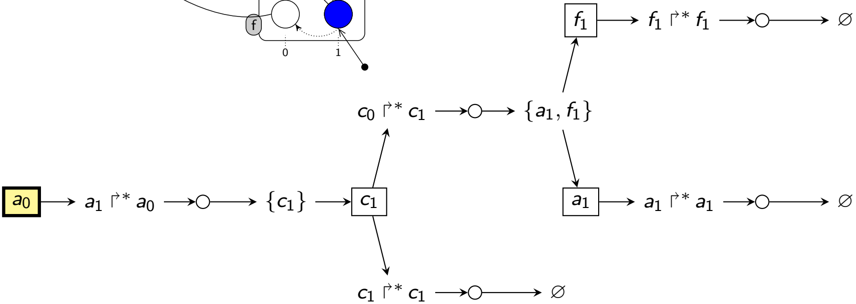
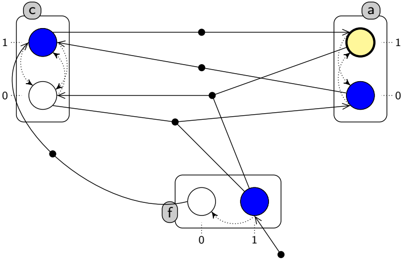


$$\delta = \{a_1, f_1\} \rightarrow c_0 \upharpoonright c_1 :: \{c_1\} \rightarrow a_1 \upharpoonright a_0$$

Static analysis



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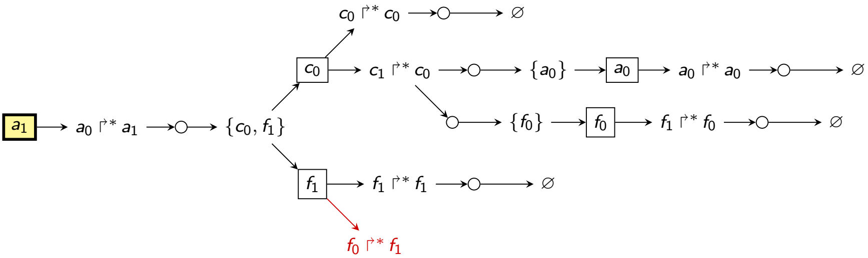

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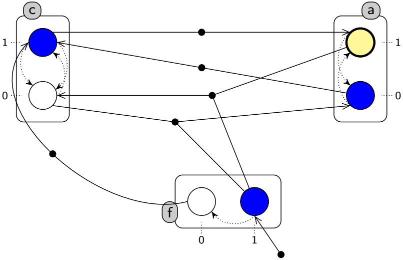

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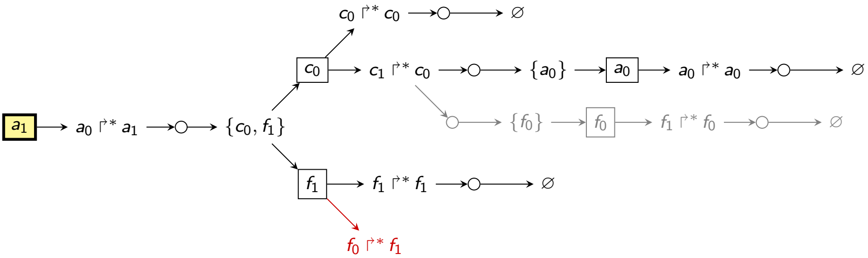

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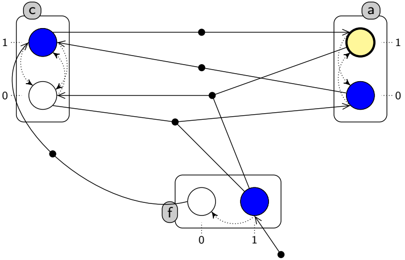

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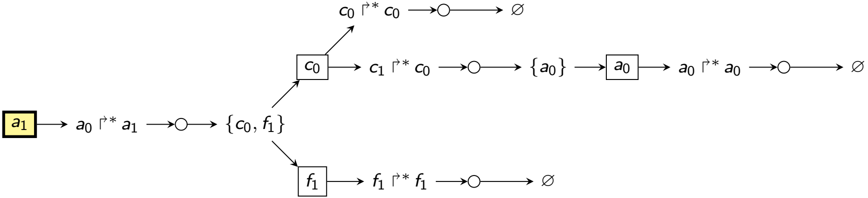

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Search for Attractors with Polyadic μ-calculus

$$\underbrace{\{②\leftarrow①\}\underbrace{\nu Y.(\Box_{①} Y \wedge \underbrace{\mu Z.(① = ② \vee \Diamond_{①} Z)}_{\psi})}_{\psi'}}_{\psi''}$$

- $[\![\psi]\!] = \{(s;t) \mid s \to^* t\}$
  $\psi \equiv$ "There exists a path from ① to ②"
- $[\![\psi']\!] = \{(s;t) \mid \forall s', s \to^* s' \Rightarrow s' \to^* t\}$
  $\psi' \equiv$ "All successors of ① can reach ②"
- $[\![\psi'']\!] = \{(s;s) \mid \forall s', s \to^* s' \Rightarrow s' \to^* s\}$
  $\psi'' \equiv$ "① belongs to an attractor"

Adapting to the semantics

- The formulas are currently adapted for state space graphs

$$\{② \leftarrow ①\}\nu Y.(\Box_{①} Y \wedge \mu Z.(① = ② \vee \Diamond_{①} Z))$$

Adapting to the semantics

- The formulas are currently adapted for state space graphs
- How to apply them directly to the initial models (in Process Hitting)?

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Other Uses of Polyadic μ-calculus

- Search for cycles

$$\mu X.\{⓶ \leftarrow ⓵\}\underbrace{\Diamond_{⓵}(\mu Y.⓵ = ⓶ \vee \Diamond_{⓵} Y)}_{\psi} \vee \Diamond_{⓵} X$$

where $\psi \equiv$ "there exists a path that brings back to token ⓶"

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Branchings in the dynamics that prevent going backward

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  - → Formula for the enumeration of attractors
  - → More ongoing work: cycles, switches...

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Thank you