Journée MDSC

Analysing Biological Networks with Exhaustive and Abstract Methods

Analyse des réseaux biologiques par des méthodes exhaustives et d'approximation

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2016/05/24

Overview of This Presentation

Frameworks: the models we will talk about

- **Thomas modeling** (historically widespread)
- **Asynchronous Automata Networks** (generalization)

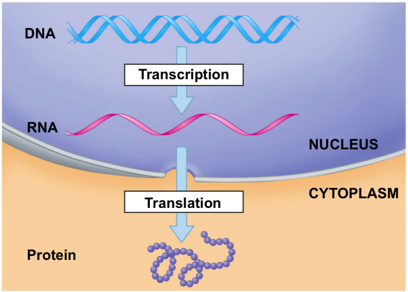
Exhaustive analyses: classical model-checking approaches with a high complexity

- Modal logic with an explicit fixed point: **μ-calculus**
- Logic programming: **Answer Set Programming**

Static analyses: approximations of the dynamics for lower complexity

- **Classical results** of static analysis
- **Abstract interpretation**: a finer approach

Abstractions of the Representation



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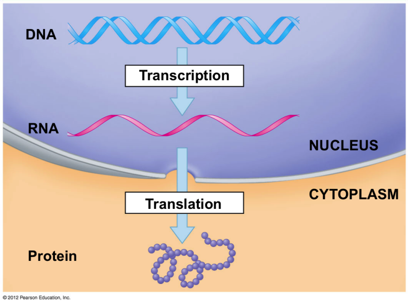

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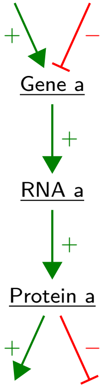

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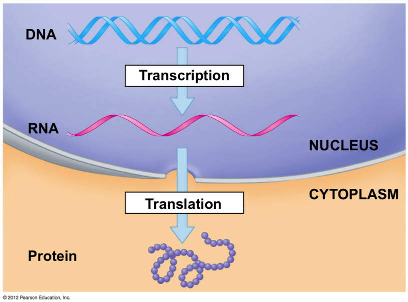
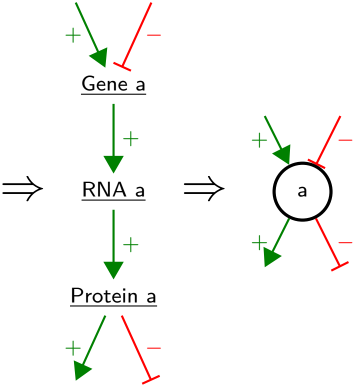
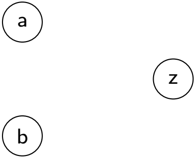




Discrete Networks / Thomas Modeling

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

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



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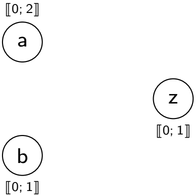
- A set of components $N = \{a, b, z\}$
- A set of discrete expression levels for each component $a \in \mathbb{F}^a = [\![0; 2]\!]$
- The set of global states $\mathbb{F} = \mathbb{F}^a \times \mathbb{F}^b \times \mathbb{F}^z$



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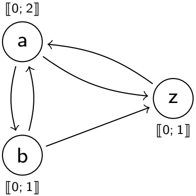
- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

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



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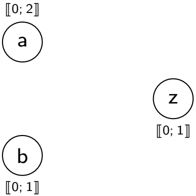

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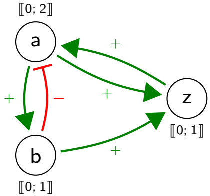

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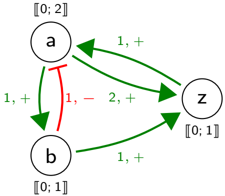
- Signs on the edges $a \xrightarrow{+} z$ or signs + thresholds $a \xrightarrow{2,+} z$



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

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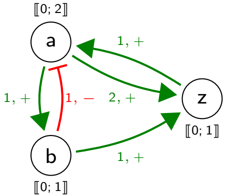
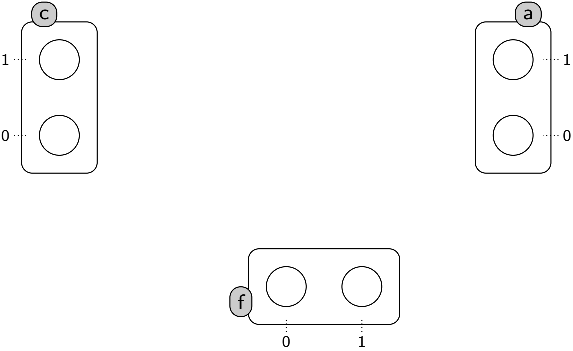


Asynchronous Automata Networks (AAN)
Enriched Process Hitting (PH)



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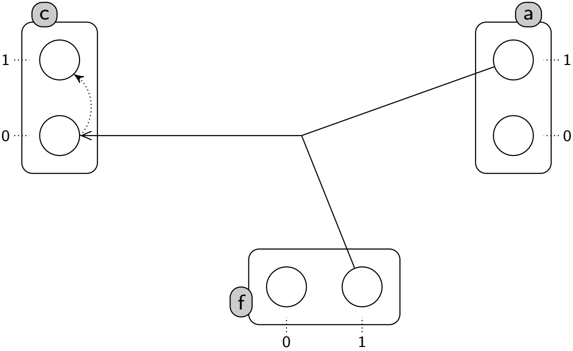

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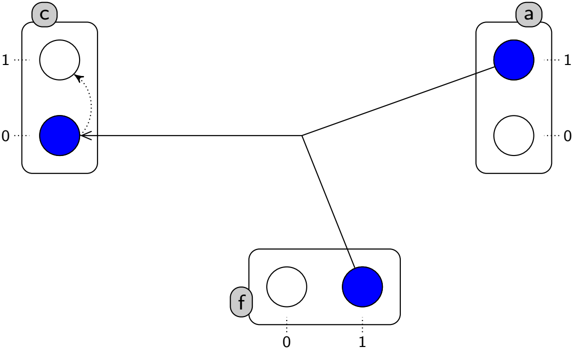

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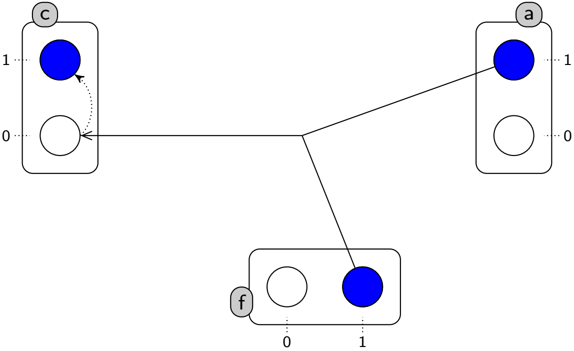
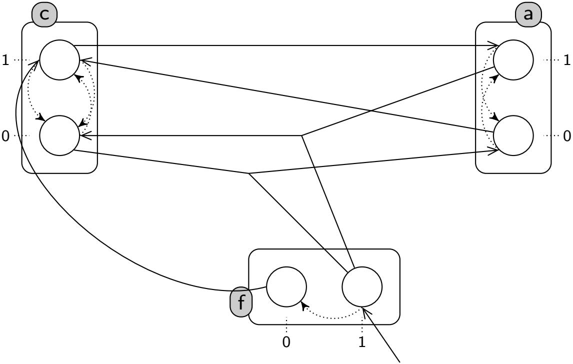


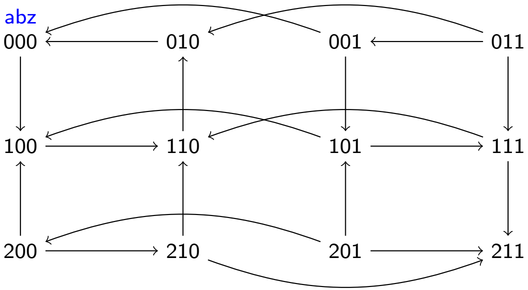
Asynchronous Automata Networks (AAN)
Enriched Process Hitting (PH)

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



State-graph

The state-graph depicts the whole dynamics
Computation: **exponential** in the size of the model



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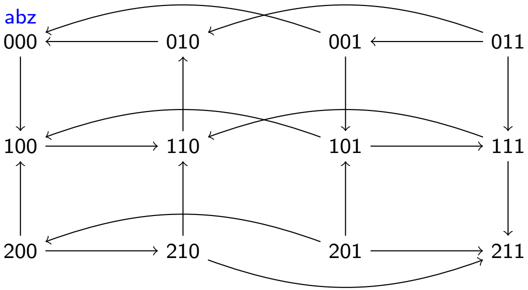

Attractor = minimal set of states from which the dynamics cannot escape

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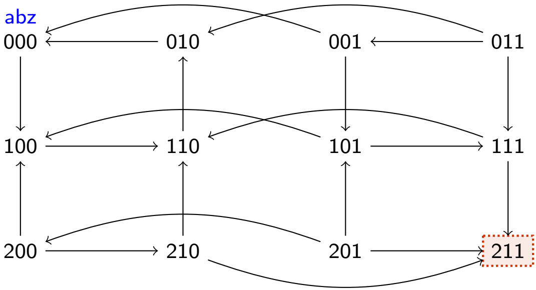
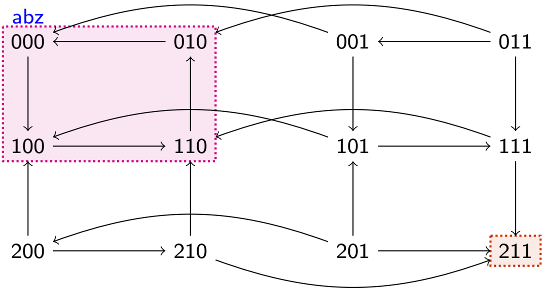


Attractor = minimal set of states from which the dynamics cannot escape

- **Stable state** (state with no successors)

State-graph

The state-graph depicts the whole dynamics
Computation: **exponential** in the size of the model

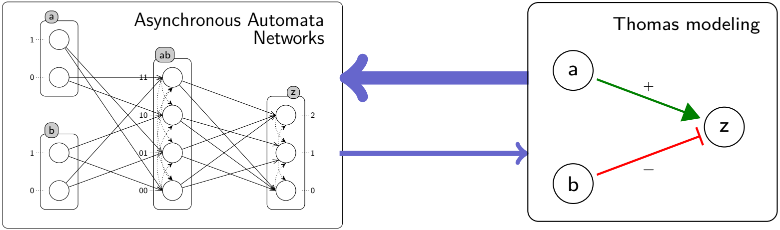


Attractor = minimal set of states from which the dynamics cannot escape

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

Translations Between AAN and Thomas Modeling

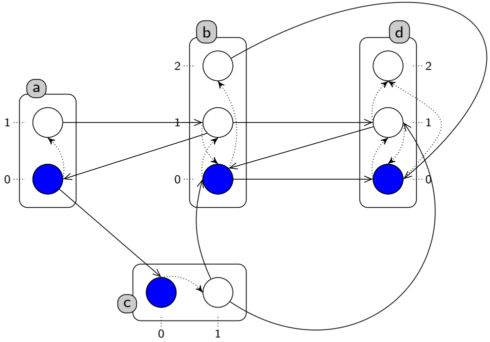
[Folschette *et al.*, *Theoretical Computer Science*, 2015a]
[Folschette *et al.*, *CS2Bio'13*, 2013]



- Asynchronous Automata Networks encompass Thomas modeling
- Mutual translations developed
- Results are also mutually applicable

The Reachability Problem

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]

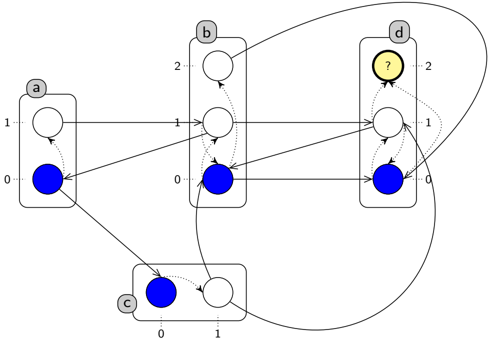


- Initial state

$\langle a_1, b_0, c_0, d_0 \rangle$

The Reachability Problem

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]



- Initial state

$\langle a_1, b_0, c_0, d_0 \rangle$

- Objective

$[\ d_2\ ]$

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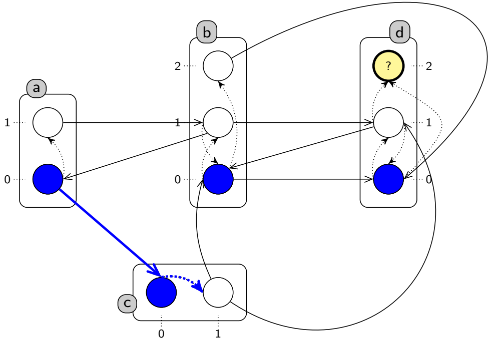

- Initial state

$\langle a_1, b_0, c_0, d_0 \rangle$

- Objective

$[\ d_2\ ]$

→ Concretization of the objective = scenario

$$\underline{a_0 \rightarrow c_0 \upharpoonright c_1} :: b_0 \rightarrow d_0 \upharpoonright d_1 :: c_1 \rightarrow b_0 \upharpoonright b_1 :: b_1 \rightarrow d_1 \upharpoonright d_2$$

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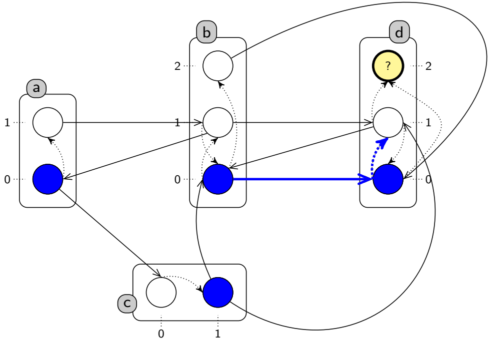

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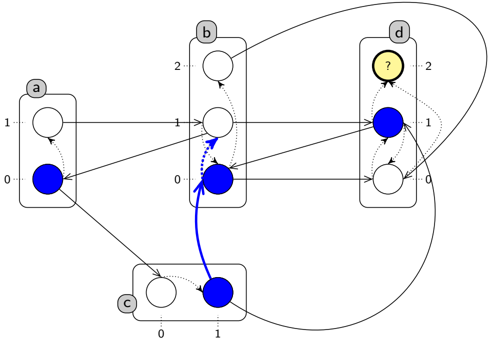

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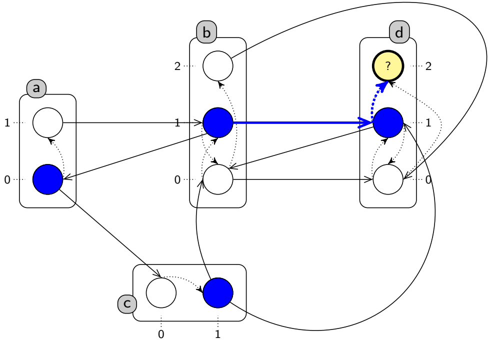

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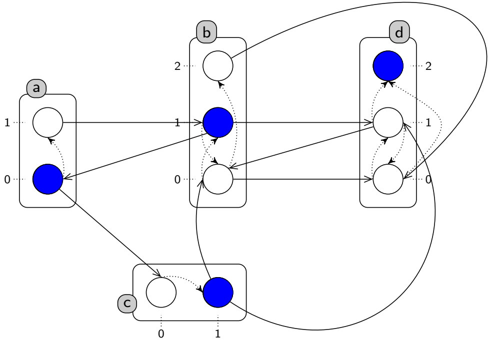
$$a_0 \rightarrow c_0 \upharpoonright c_1 :: b_0 \rightarrow d_0 \upharpoonright d_1 :: c_1 \rightarrow b_0 \upharpoonright b_1 :: \underline{b_1 \rightarrow d_1 \upharpoonright d_2}$$

The Reachability Problem

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]



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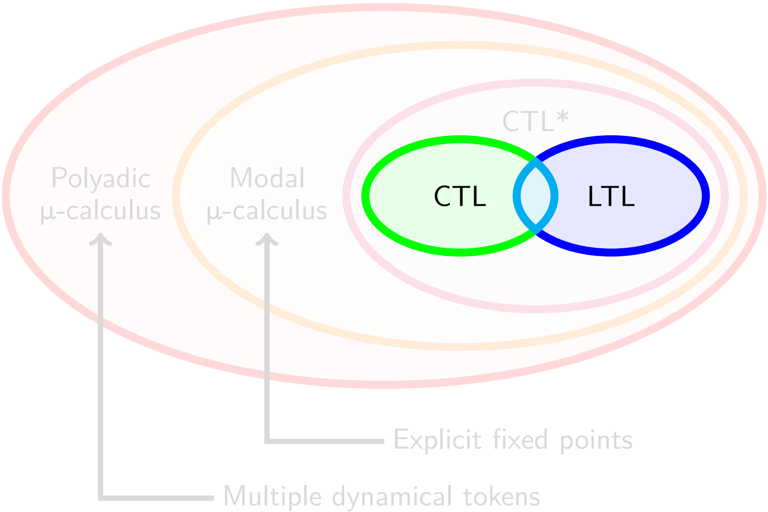
The Polyadic µ-caculus



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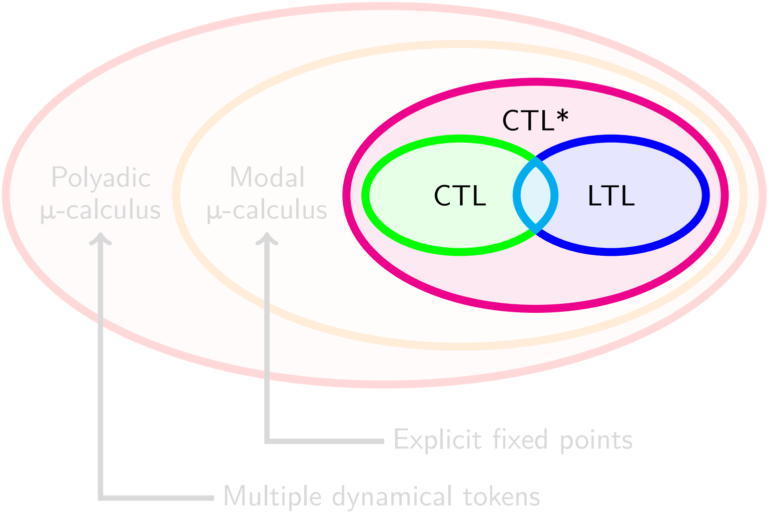

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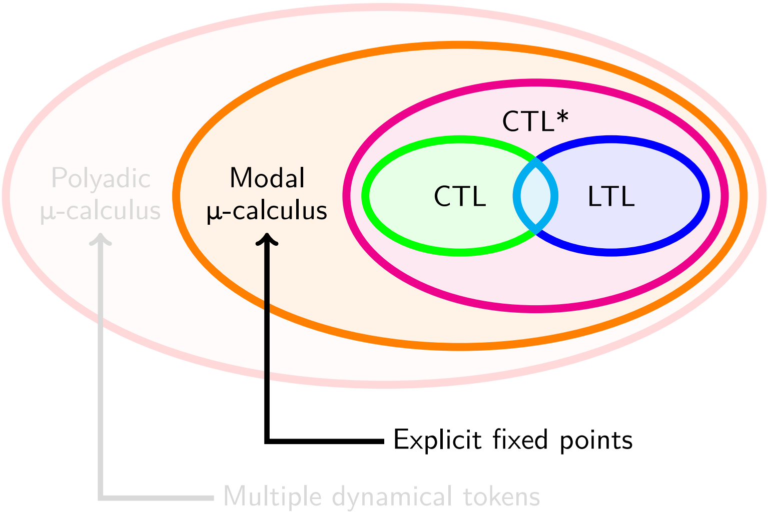

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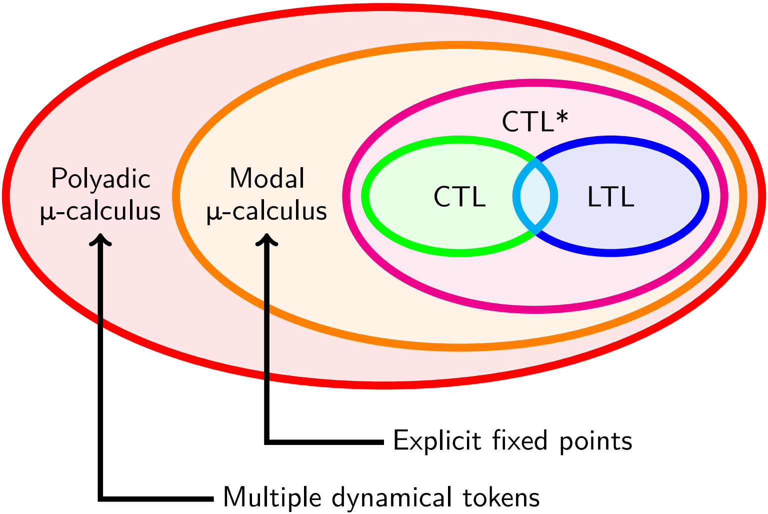

CTL*

CTL

LTL

Polyadic
μ-calculus

Modal
μ-calculus

Explicit fixed points

Multiple dynamical tokens

The Modal μ-calculus

LTL: Implicit fixed point of the "Until" operator
$p\ U\ q \equiv$ "Either q, or p and the next state also verifies $p\ U\ q$"

(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 manipulations:
- $i = j$ ("make 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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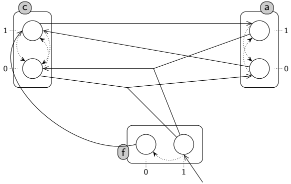
Applications of the Polyadic μ-calculus



Objective: Unify formulas for many dynamical problems

Not always possible with classical temporal logics (LTL, CTL, CTL*):

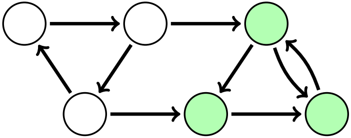
1) From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?
$(a = 0 \wedge b = 0 \wedge z = 0) \Rightarrow \mathrm{EF}(z = 2)$

2) Does $(0, 0, 0)$ belong to an attractor?
$(a = 0 \wedge b = 0 \wedge z = 0) \Rightarrow \mathrm{N}\bot \vee \mathrm{AG}(\mathrm{EF}(a = 0 \wedge b = 0 \wedge z = 0))$

3) What is the set of attractors of the model?
??? — Requires a quantification on the set of all states

Idea: Use polyadic μ-calculus with one token per automata

Search for Attractors with Polyadic µ-calculus

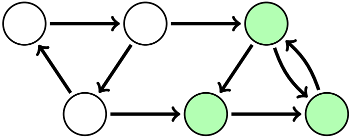


🟢 = belongs to an attractor

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

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

Search for Attractors with Polyadic µ-calculus



🟢 = belongs to an attractor

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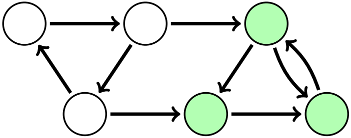

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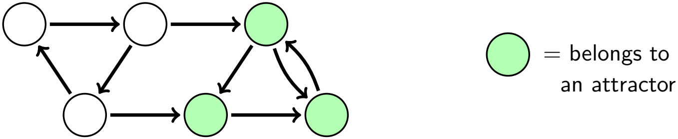

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Conclusion on Polyadic µ-calculus

Properties expressed so far:

- Enumeration of attractors
- Enumeration of switches
- Bisimulation between two models (regarding a set of observables)
- Highlighting Zeno behaviors

Aim: Unification of properties without quantifiers

Complexity: Exponential (equivalent to building the state graph)

Outlooks:

- New formulas
- Implementation
- Generate µ-calculus formulas? (More readable interface)

Answer Set Programming

Answer Set Programming (ASP): Declarative & logic programming

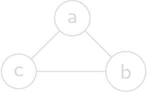
Rule: $head \leftarrow body.$
"If *body* is true, then *head* must be true (usual logical consequence)"

Fact: $head.$
"*head* is always true"

Constraint: $\bot \leftarrow body.$
"If *body* is true, it invalidates the whole answer set"

Example:

$node(a).\ node(b).\ node(c).$
$edge(a,b).\ edge(b,c).\ edge(a,c).$
$edge(X,Y) \leftarrow edge(Y,X).$



Solving: Finding the minimal set of atoms satisfying the problem

```
node(a) node(c) node(b)
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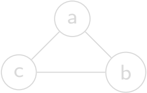

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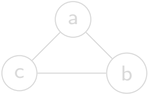

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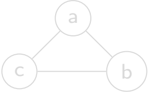

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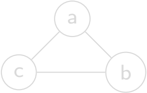

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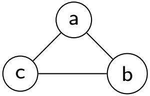

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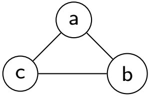

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Cardinalities: $min \ \{ \ atom : enum \ \} \ max \leftarrow body.$

- Enumerates all atoms of the form *atom* according to the variables of *enum*
- Keep between *min* and *max* possibilities
- Creates as many answer sets as there are combinations

General method:

1) **Enumerate** of all candidate combinations using cardinalities

$color(red). \ color(green). \ color(blue).$

$1 \ \{ \ attrib(X, C) : color(C) \ \} \ 1 \leftarrow node(X).$

```
Answer set 1: attrib(b,red) attrib(c,red) attrib(a,red)
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Answer set 3: attrib(b,red) attrib(c,green) attrib(a,blue)
   ⋮ (27 answer sets)
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2) **Filter out** the undesired candidates using constraints

$\bot \leftarrow attrib(X, C), attrib(Y, C), edge(X, Y).$

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ASP for Model-checking

[Ben Abdallah, Folschette, Roux, Magnin, *BIBM'15*, 2015]

Usage: Describe the problem instead of its resolution

Stable states enumeration

1) Describe the model with facts (automata, actions)
2) Describe what a playable action is with rules
3) Enumerate all states with cardinalities
4) Filter out states with a playable action

Reachability analysis (reaching a given state)

1) Describe the model with facts (automata, actions, initial & target states)
2) Create the dynamics:
    - describe playability with rules
    - enumerate potential futures with cardinalities and constraints
3) Filter out paths that don't end in the target state

Conclusion on ASP for Model-checking

[Ben Abdallah, Folschette, Roux, Magnin, *BIBM'15*, 2015]

Complexity: Exponential (exhaustive computation of the dynamics)
But strong heuristics that give good results

Models		Stable states	Reachability analysis		
Name	States	ASP	libddd[1]	GINsim[2]	ASP
egfr20	2^{64}	**0.017s**	1min 55s	2min 32s	**12s**
tcrsig40	2^{73}	**0.021s**	∞	∞	**4min 28s**

[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]

Pros: Very flexible (programming language),
The complexity taken care of by the solver

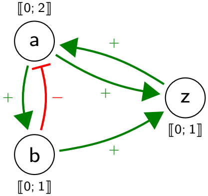
Outlooks:

- New properties to check (reverse reachability, Eden gardens)
- Optimizations (exclude cycles)

Static Analysis of Thomas Modeling

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

Conjectures of René Thomas:



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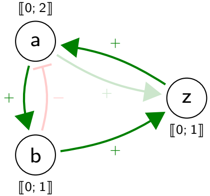
Conjectures of René Thomas:

- Multiple **stable states** ⇒ positive cycle in the graph



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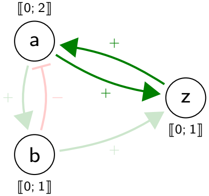

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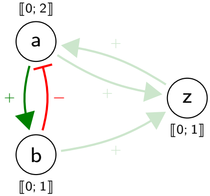

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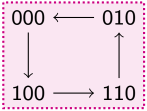

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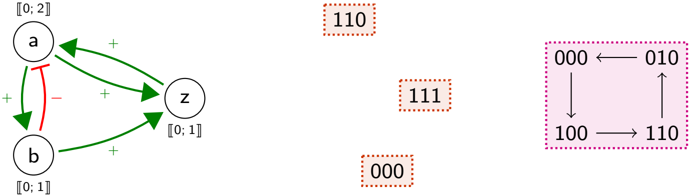


Proofs: [Remy, Ruet & Thieffry, *Advances in Applied Mathematics*, 2008]
[Richard, *Advances in Applied Mathematics*, 2010]
[Richard & Comet, *Discrete Applied Mathematics*, 2007]

Static Analysis of Thomas Modeling

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

Contrapositives:

- No positive cycle in the graph ⇒ The **stable state** (if any) is unique
- No negative cycle in the graph ⇒ No **complex attractor** (only stable states)

Other results:

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

Complexity: Usually very low (searching for all cycles)

Limitations: Very broad results on the dynamics
(cannot predict the evolution of one particular component)

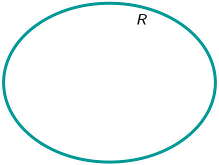
→ **Need for more precise methods**

Over- and Under-approximations

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]

→ Directly checking R is hard (**exponential**)

→ Rather check **approximations** P and Q so that: $P \Rightarrow R \Rightarrow Q$
Computing P or Q is much simpler (roughly **polynomial**)



Exact solution

Over- and Under-approximations

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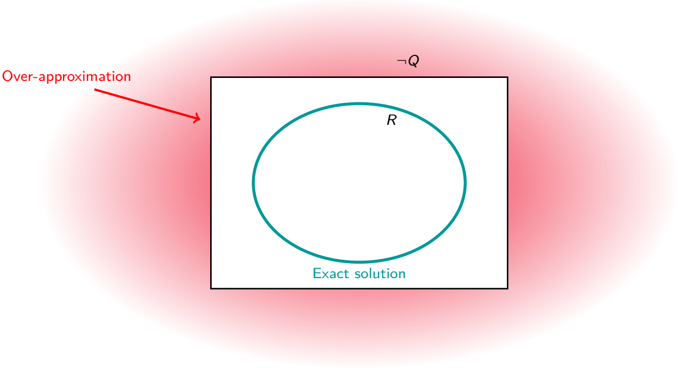

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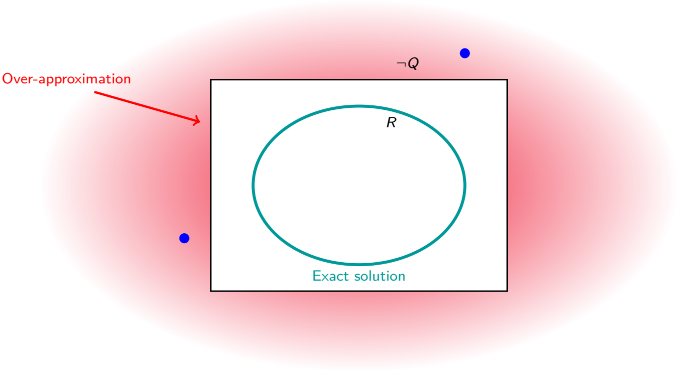

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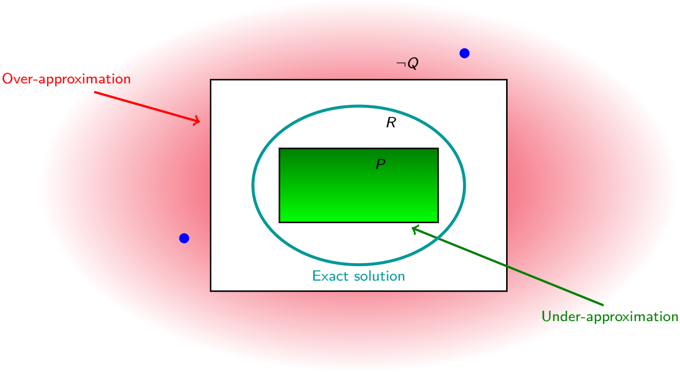

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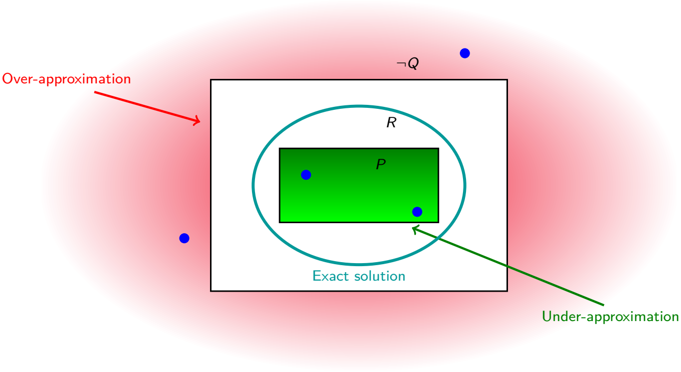

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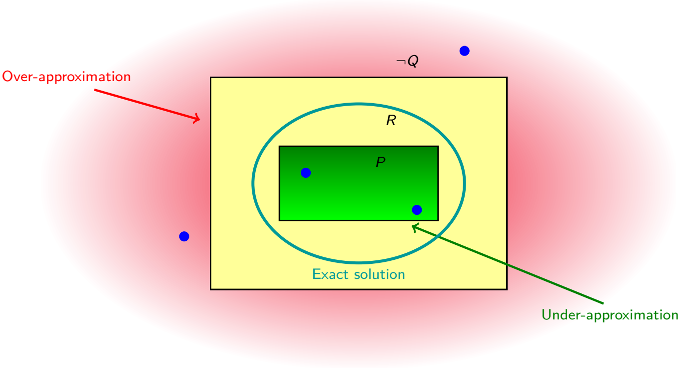

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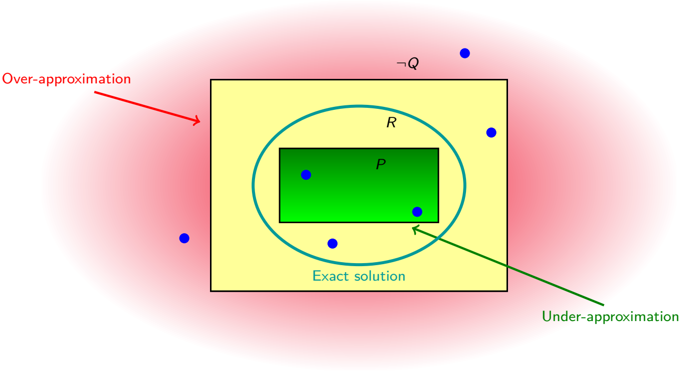
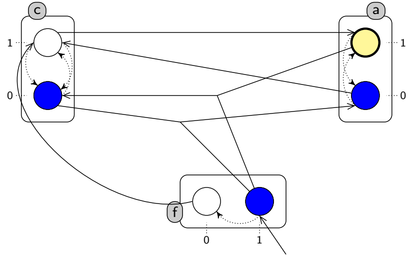
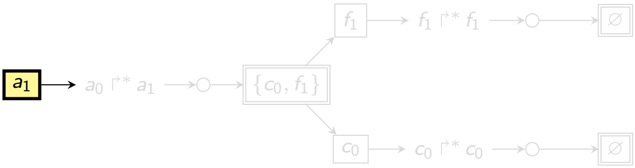


Abstract Interpretation (Under-approximation)

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



- No conflict
- All leaves are $\boxed{\boxed{\varnothing}}$



$\boxed{a_1}$

$a_0 \Rsh^* a_1$

$\{c_0, f_1\}$

f_1

$f_1 \Rsh^* f_1$

$\varnothing$

c_0

$c_0 \Rsh^* c_0$

$\varnothing$

$$\{c_0, f_1\} \rightarrow a_0 \Rsh a_1$$

Abstract Interpretation (Under-approximation)

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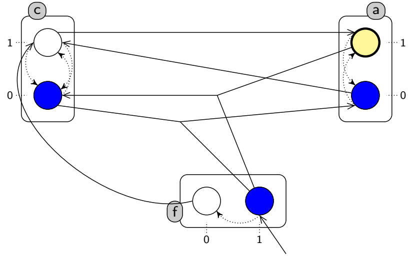

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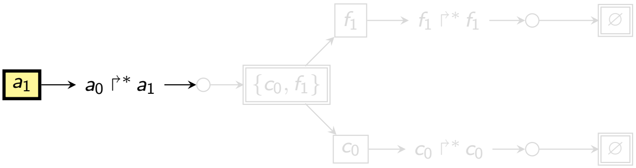

$\boxed{a_1} \longrightarrow a_0 \Rsh^* a_1 \longrightarrow \circ \longrightarrow \boxed{\boxed{\{c_0, f_1\}}}$

$\boxed{f_1} \longrightarrow f_1 \Rsh^* f_1 \longrightarrow \circ \longrightarrow \boxed{\boxed{\varnothing}}$

$\boxed{c_0} \longrightarrow c_0 \Rsh^* c_0 \longrightarrow \circ \longrightarrow \boxed{\boxed{\varnothing}}$

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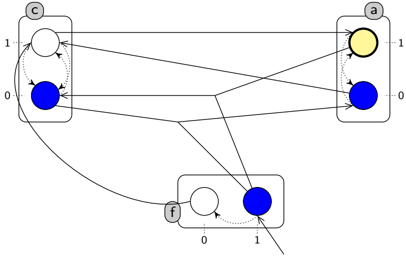

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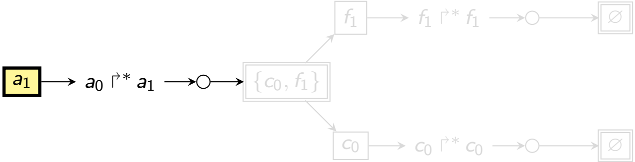
- All leaves are $\boxed{\emptyset}$



$\boxed{a_1} \longrightarrow a_0 \Rsh^* a_1 \longrightarrow \bigcirc \longrightarrow \boxed{\{c_0, f_1\}}$

$\boxed{f_1} \longrightarrow f_1 \Rsh^* f_1 \longrightarrow \bigcirc \longrightarrow \boxed{\emptyset}$

$\boxed{c_0} \longrightarrow c_0 \Rsh^* c_0 \longrightarrow \bigcirc \longrightarrow \boxed{\emptyset}$

$$\{c_0, f_1\} \to a_0 \Rsh a_1$$

Abstract Interpretation (Under-approximation)

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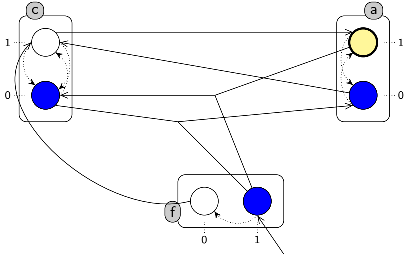

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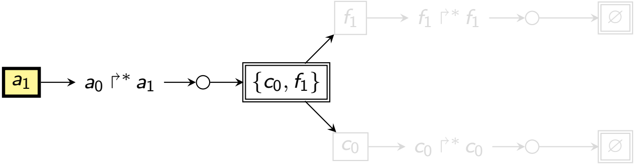


$a_1 \longrightarrow a_0 \upharpoonright^* a_1 \longrightarrow \circ \longrightarrow \boxed{\{c_0, f_1\}}$

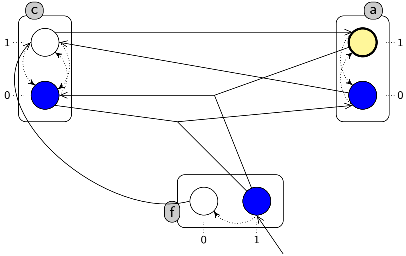
$f_1 \longrightarrow f_1 \upharpoonright^* f_1 \longrightarrow \circ \longrightarrow \boxed{\varnothing}$

$c_0 \longrightarrow c_0 \upharpoonright^* c_0 \longrightarrow \circ \longrightarrow \boxed{\varnothing}$

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

Abstract Interpretation (Under-approximation)

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



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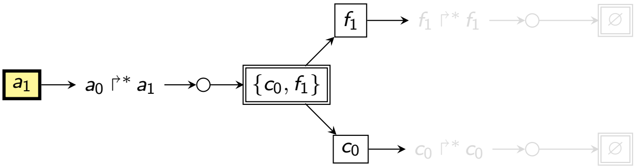

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$\boxed{f_1} \longrightarrow f_1 \Rsh^* f_1 \longrightarrow \circ \longrightarrow \boxed{\boxed{\varnothing}}$

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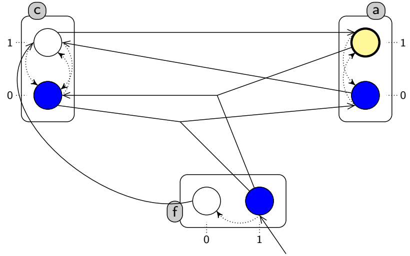

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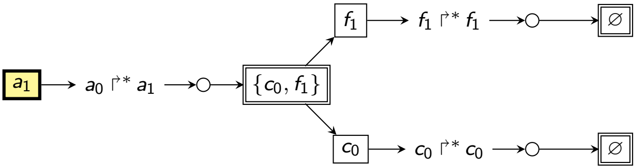

$\boxed{a_1}$ → $a_0 \Rsh^* a_1$ → ○ → $\boxed{\{c_0, f_1\}}$

$\boxed{\{c_0, f_1\}}$ → $\boxed{f_1}$ → $f_1 \Rsh^* f_1$ → ○ → $\boxed{\varnothing}$

$\boxed{\{c_0, f_1\}}$ → $\boxed{c_0}$ → $c_0 \Rsh^* c_0$ → ○ → $\boxed{\varnothing}$

$$\{c_0, f_1\} \rightarrow a_0 \Rsh a_1$$

Abstract Interpretation (Under-approximation)

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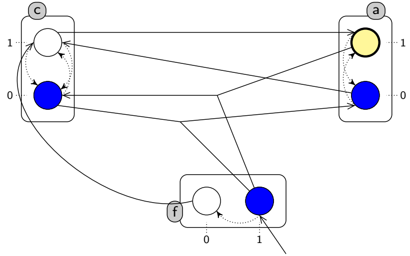

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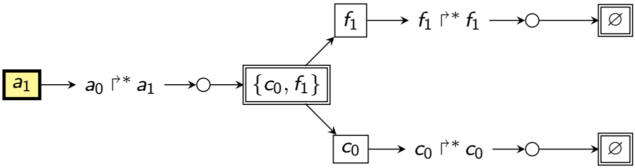

$a_1 \rightarrow a_0 \Rsh^* a_1 \rightarrow \circ \rightarrow \{c_0, f_1\}$

$\{c_0, f_1\} \rightarrow f_1 \rightarrow f_1 \Rsh^* f_1 \rightarrow \circ \rightarrow \varnothing$

$\{c_0, f_1\} \rightarrow c_0 \rightarrow c_0 \Rsh^* c_0 \rightarrow \circ \rightarrow \varnothing$

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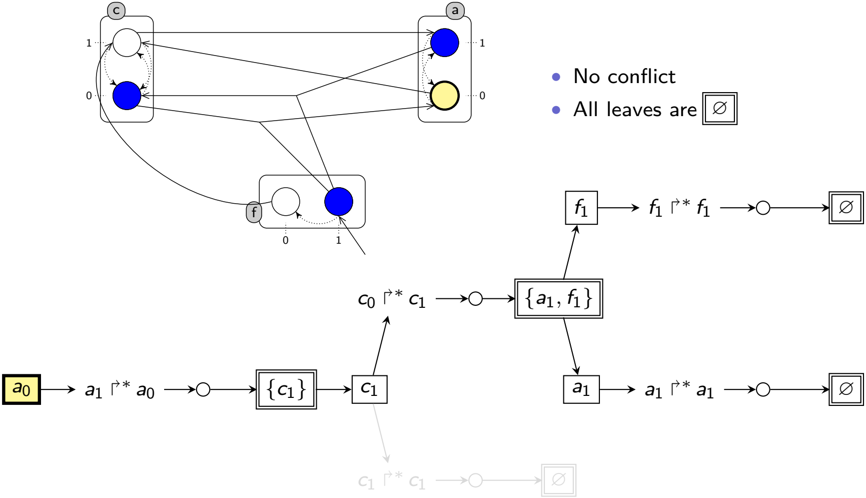
Abstract Interpretation (Under-approximation)

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



- No conflict
- All leaves are $\boxed{\boxed{\varnothing}}$

$\boxed{a_0} \rightarrow a_1 \Rsh^* a_0 \rightarrow \circ \rightarrow \boxed{\boxed{\{c_1\}}} \rightarrow \boxed{c_1}$

$\boxed{c_1} \rightarrow c_0 \Rsh^* c_1 \rightarrow \circ \rightarrow \boxed{\boxed{\{a_1, f_1\}}}$

$\boxed{\boxed{\{a_1, f_1\}}} \rightarrow \boxed{f_1} \rightarrow f_1 \Rsh^* f_1 \rightarrow \circ \rightarrow \boxed{\boxed{\varnothing}}$

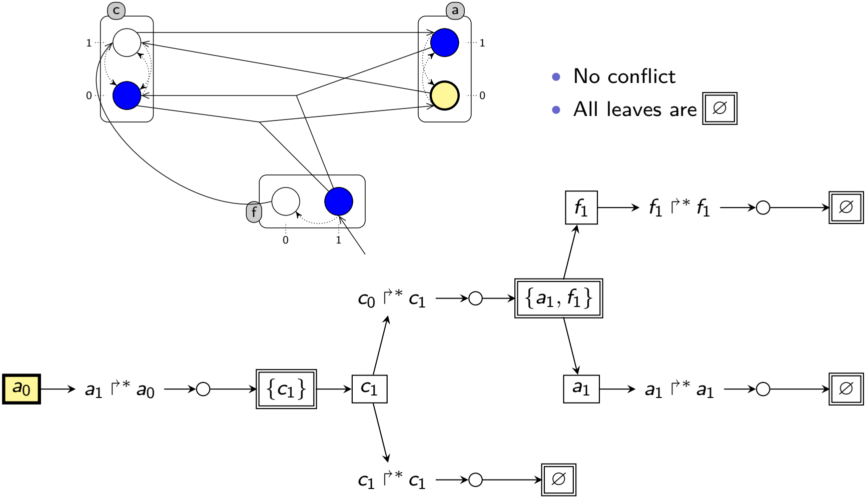
$\boxed{\boxed{\{a_1, f_1\}}} \rightarrow \boxed{a_1} \rightarrow a_1 \Rsh^* a_1 \rightarrow \circ \rightarrow \boxed{\boxed{\varnothing}}$

$\boxed{c_1} \rightarrow c_1 \Rsh^* c_1 \rightarrow \circ \rightarrow \boxed{\boxed{\varnothing}}$

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

Abstract Interpretation (Under-approximation)

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



- No conflict
- All leaves are $\boxed{\varnothing}$

$\boxed{a_0} \rightarrow a_1 \Rsh^* a_0 \rightarrow \circ \rightarrow \boxed{\{c_1\}} \rightarrow \boxed{c_1}$

$\boxed{c_1} \rightarrow c_0 \Rsh^* c_1 \rightarrow \circ \rightarrow \boxed{\{a_1, f_1\}}$

$\boxed{\{a_1, f_1\}} \rightarrow \boxed{f_1} \rightarrow f_1 \Rsh^* f_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{\{a_1, f_1\}} \rightarrow \boxed{a_1} \rightarrow a_1 \Rsh^* a_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{c_1} \rightarrow c_1 \Rsh^* c_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$$\{a_1, f_1\} \rightarrow c_0 \Rsh c_1 \quad :: \quad \{c_1\} \rightarrow a_1 \Rsh a_0$$

Abstract Interpretation (Under-approximation)

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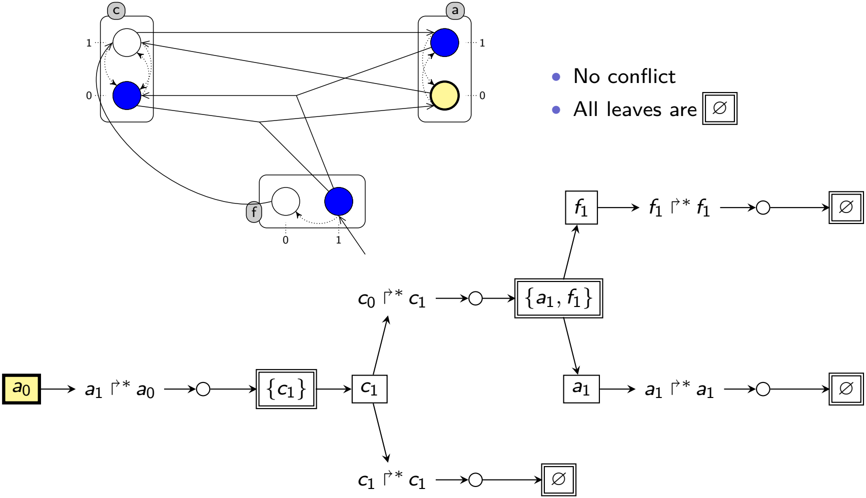

- No conflict
- All leaves are $\boxed{\varnothing}$

$\boxed{a_0} \rightarrow a_1 \upharpoonright^* a_0 \rightarrow \circ \rightarrow \boxed{\{c_1\}} \rightarrow \boxed{c_1}$

$\boxed{c_1} \rightarrow c_0 \upharpoonright^* c_1 \rightarrow \circ \rightarrow \boxed{\{a_1, f_1\}}$

$\boxed{c_1} \rightarrow c_1 \upharpoonright^* c_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{\{a_1, f_1\}} \rightarrow \boxed{f_1} \rightarrow f_1 \upharpoonright^* f_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{\{a_1, f_1\}} \rightarrow \boxed{a_1} \rightarrow a_1 \upharpoonright^* a_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

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

Abstract Interpretation (Under-approximation)

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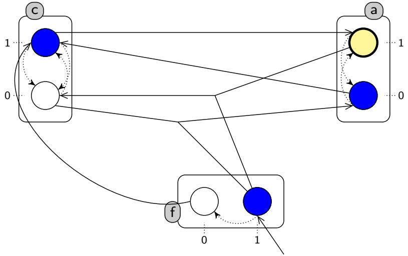
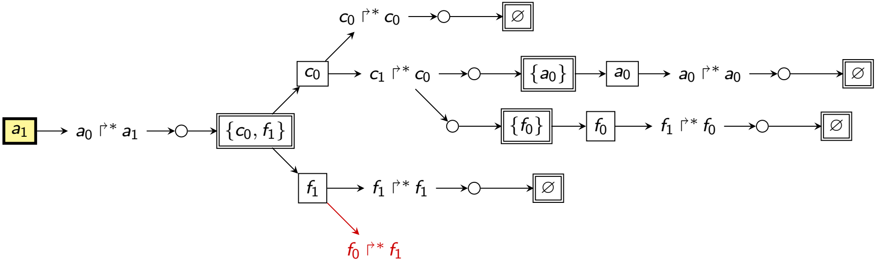


- No conflict
- ~~All leaves are $\boxed{\emptyset}$~~



a_1

$a_0 \Rsh^* a_1$

$\{c_0, f_1\}$

c_0

$c_0 \Rsh^* c_0$

$\emptyset$

$c_1 \Rsh^* c_0$

$\{a_0\}$

a_0

$a_0 \Rsh^* a_0$

$\emptyset$

$\{f_0\}$

f_0

$f_1 \Rsh^* f_0$

$\emptyset$

f_1

$f_1 \Rsh^* f_1$

$\emptyset$

$f_0 \Rsh^* f_1$

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

Abstract Interpretation (Under-approximation)

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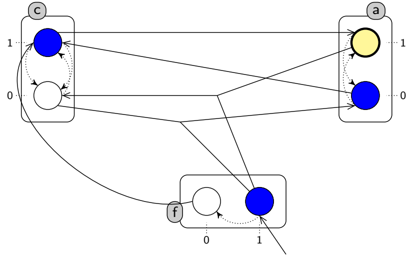

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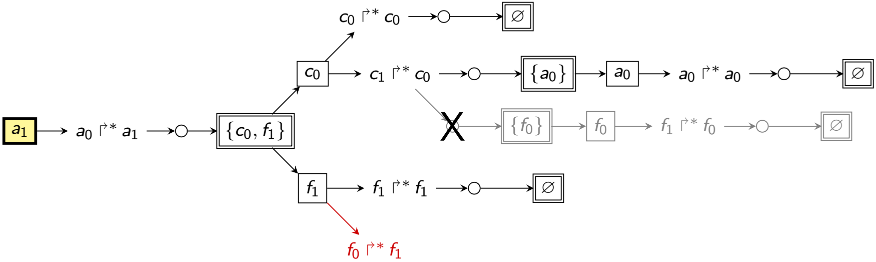

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$\boxed{c_0} \rightarrow c_0 \Rsh^* c_0 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{c_0} \rightarrow c_1 \Rsh^* c_0 \rightarrow \circ \rightarrow \boxed{\{a_0\}} \rightarrow \boxed{a_0} \rightarrow a_0 \Rsh^* a_0 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$c_1 \Rsh^* c_0 \rightarrow$ X $\rightarrow \boxed{\{f_0\}} \rightarrow \boxed{f_0} \rightarrow f_1 \Rsh^* f_0 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{f_1} \rightarrow f_1 \Rsh^* f_1 \rightarrow \circ \rightarrow \boxed{\varnothing}$

$\boxed{f_1} \rightarrow f_0 \Rsh^* f_1$

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

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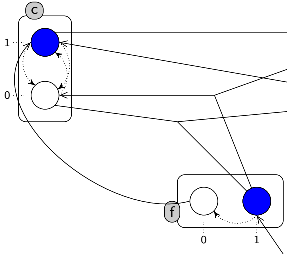

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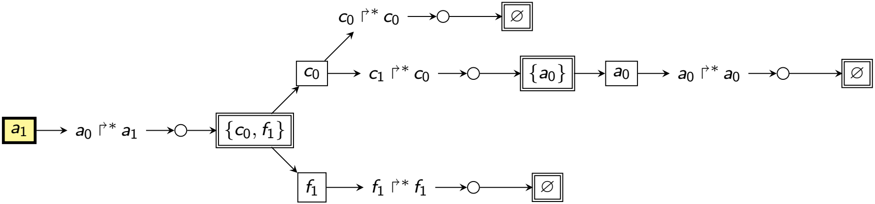

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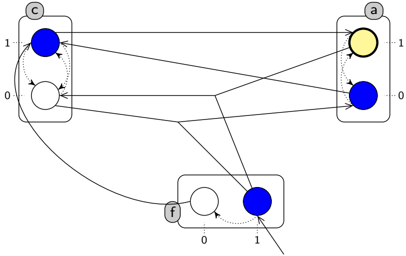

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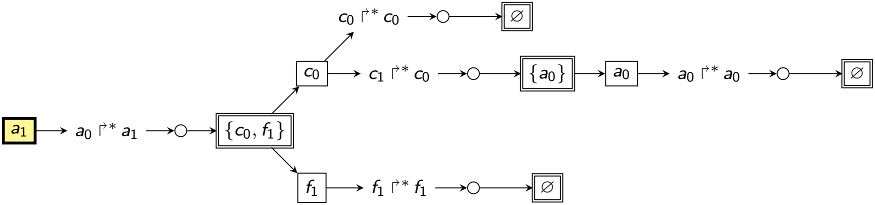

$$\{a_0\} \rightarrow c_1 \upharpoonright c_0 \;::\; \{c_0, f_1\} \rightarrow a_0 \upharpoonright a_1$$

Implementation of the Abstract Interpretation

Complexity:

- Computation of the local causality graph:
    - Polynomial in the number of automata
    - Exponential in the number of local states of each automata (usually very low, max. 4)
- Analysis of the graph (sufficient condition):
    - Polynomial in the size of the abstract graph
- Enumeration of the subsets of solutions (if needed):
    - Exponential in the size of the abstract graph

→ Very efficient on biological networks: **many components with few local states**

Model	Automata	Actions	States	libddd[1]	GINsim[2]	PINT[3]
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]

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egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
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Summary & Conclusion

- Discrete modeling = coherent abstraction of real biochemical phenomena
  - → Discrete Networks / Thomas modeling
  - → Asynchronous Automata Networks
  - → ...And other extensions related to Asynchronous Automata Networks
- Polyadic μ-calculus
  - → More generic than CTL*
  - → Examples: enumeration of attractors, switches, bisimulation...
  - → Ongoing implementation
- Answer Set Programming
  - → Logic programming works!
  - → Powerful heuristics giving good performances
- Static analysis by abstract interpretation
  - → (Only) reachability properties (CTL operator EF)
  - → Very efficient (polynomial complexity)
  - → Broad range of models (translations of Thomas models)

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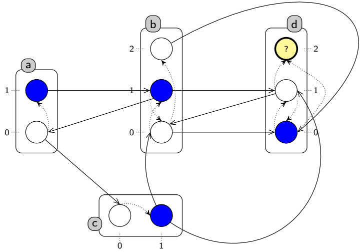
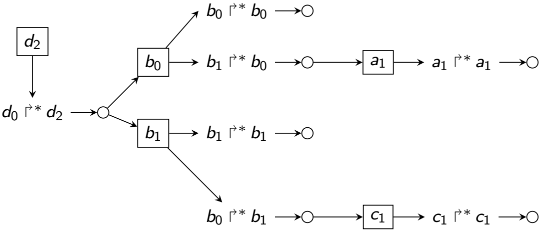
- Emna Ben Abdallah, Maxime Folschette, Olivier Roux, Morgan Magnin. Exhaustive analysis of dynamical properties of Biological Regulatory Networks with Answer Set Programming. *IEEE International Conference on Bioinformatics and Biomedicine (BIBM'15)*, 281–285, IEEE. November 2015.

Under-approximation





$\boxed{d_2}$

$d_0 \Rsh^* d_2$

$\boxed{b_0}$

$\boxed{b_1}$

$b_0 \Rsh^* b_0$

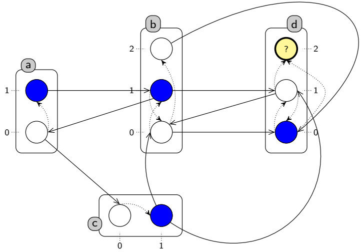
$b_1 \Rsh^* b_0$ → $\boxed{a_1}$ → $a_1 \Rsh^* a_1$

$b_1 \Rsh^* b_1$

$b_0 \Rsh^* b_1$ → $\boxed{c_1}$ → $c_1 \Rsh^* c_1$

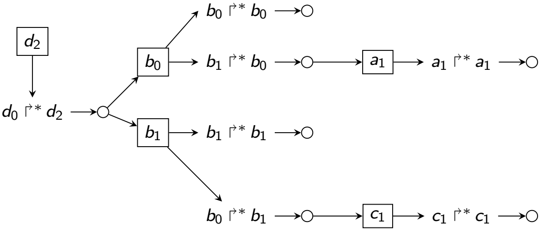
$\boxed{d_2}$	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution



$\boxed{d_2}$

$d_0 \Rsh^* d_2$

$\boxed{b_0}$

$\boxed{b_1}$

$b_0 \Rsh^* b_0$

$b_1 \Rsh^* b_0$

$b_1 \Rsh^* b_1$

$b_0 \Rsh^* b_1$

$\boxed{a_1}$

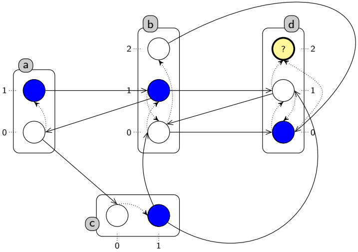
$a_1 \Rsh^* a_1$

$\boxed{c_1}$

$c_1 \Rsh^* c_1$

$\boxed{d_2}$	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

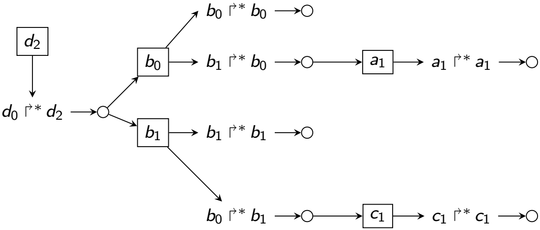
Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution

P is **true** $\Rightarrow$ R is **true**



$\boxed{d_2}$

$d_0 \Rsh^{*} d_2 \longrightarrow \bigcirc$

$\boxed{b_0}$ $\longrightarrow$ $b_0 \Rsh^{*} b_0 \longrightarrow \bigcirc$

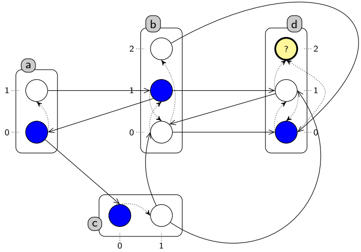
$\boxed{b_0}$ $\longrightarrow$ $b_1 \Rsh^{*} b_0 \longrightarrow \bigcirc \longrightarrow \boxed{a_1} \longrightarrow a_1 \Rsh^{*} a_1 \longrightarrow \bigcirc$

$\boxed{b_1}$ $\longrightarrow$ $b_1 \Rsh^{*} b_1 \longrightarrow \bigcirc$

$\boxed{b_1}$ $\longrightarrow$ $b_0 \Rsh^{*} b_1 \longrightarrow \bigcirc \longrightarrow \boxed{c_1} \longrightarrow c_1 \Rsh^{*} c_1 \longrightarrow \bigcirc$

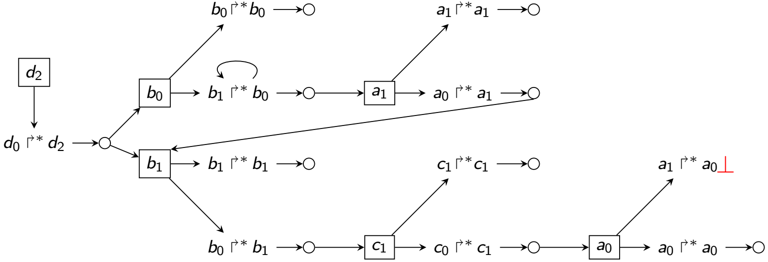
$\boxed{d_2}$	Required process
$d_0 \Rsh^{*} d_2$	Objective
○	Solution to an objective

Under-approximation



Sufficient condition:

- no cycle
- ~~each objective has a solution~~



$b_0 \Rsh^* b_0$

$a_1 \Rsh^* a_1$

d_2

b_0

$b_1 \Rsh^* b_0$

a_1

$a_0 \Rsh^* a_1$

$d_0 \Rsh^* d_2$

b_1

$b_1 \Rsh^* b_1$

$c_1 \Rsh^* c_1$

$a_1 \Rsh^* a_0 \bot$

$b_0 \Rsh^* b_1$

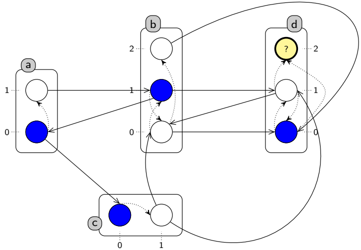
c_1

$c_0 \Rsh^* c_1$

a_0

$a_0 \Rsh^* a_0$

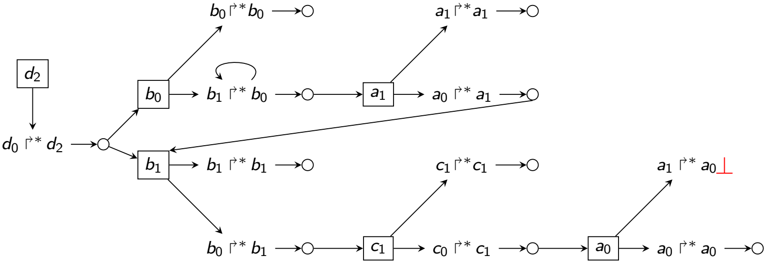
Under-approximation



Sufficient condition:

- no cycle
- ~~each objective has a solution~~

P is **false** ⇒ **Inconclusive**



d_2

$d_0 \Rsh^* d_2$

b_0

b_1

$b_0 \Rsh^* b_0$

$b_1 \Rsh^* b_0$

$b_1 \Rsh^* b_1$

$b_0 \Rsh^* b_1$

a_1

$a_1 \Rsh^* a_1$

$a_0 \Rsh^* a_1$

c_1

$c_1 \Rsh^* c_1$

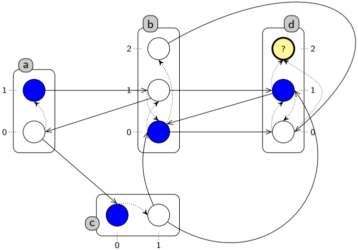
$c_0 \Rsh^* c_1$

a_0

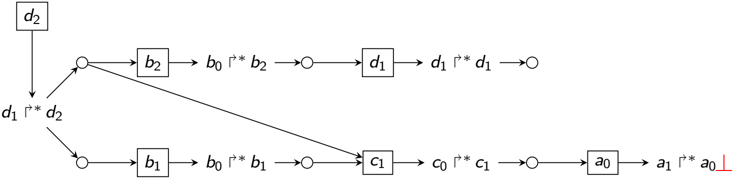
$a_1 \Rsh^* a_0 \bot$

$a_0 \Rsh^* a_0$

Over-approximation



Necessary condition:



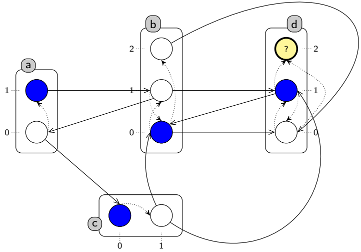
$\boxed{d_2}$

$d_1 \Rsh^{*} d_2$

$\boxed{b_2}$ $b_0 \Rsh^{*} b_2$ $\boxed{d_1}$ $d_1 \Rsh^{*} d_1$

$\boxed{b_1}$ $b_0 \Rsh^{*} b_1$ $\boxed{c_1}$ $c_0 \Rsh^{*} c_1$ $\boxed{a_0}$ $a_1 \Rsh^{*} a_0 \bot$

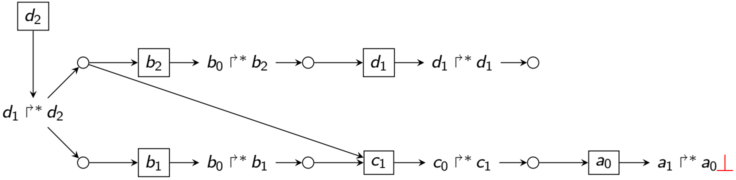
Over-approximation



Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives



d_2

$d_1 \Rsh^* d_2$

b_2

$b_0 \Rsh^* b_2$

d_1

$d_1 \Rsh^* d_1$

b_1

$b_0 \Rsh^* b_1$

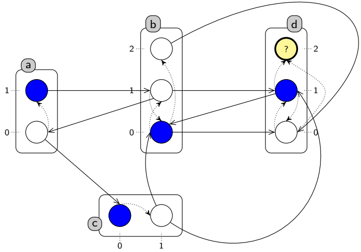
c_1

$c_0 \Rsh^* c_1$

a_0

$a_1 \Rsh^* a_0 \bot$

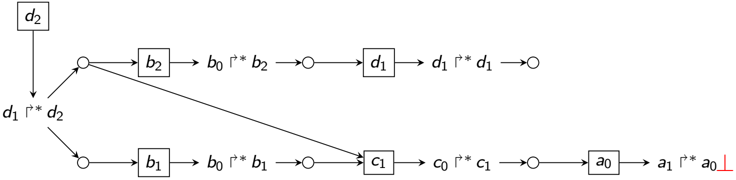
Over-approximation



Necessary condition:

~~There exists a traversal~~ with no cycle

- ~~objective → follow **one** solution~~
- solution → follow **all** processes
- process → follow **all** objectives

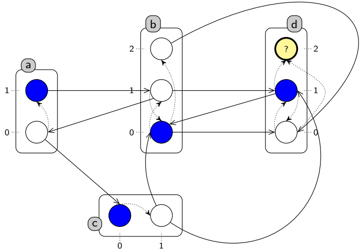

d_2

$d_1 \Rsh^* d_2$

b_2 $b_0 \Rsh^* b_2$ d_1 $d_1 \Rsh^* d_1$

b_1 $b_0 \Rsh^* b_1$ c_1 $c_0 \Rsh^* c_1$ a_0 $a_1 \Rsh^* a_0 \bot$

Over-approximation

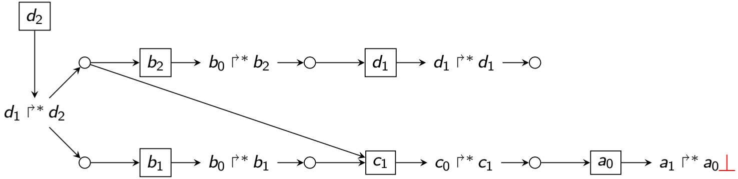


Necessary condition:

~~There exists a traversal~~ with no cycle

- ~~objective → follow **one** solution~~
- solution → follow **all** processes
- process → follow **all** objectives

Q is **false** ⇒ R is **false**



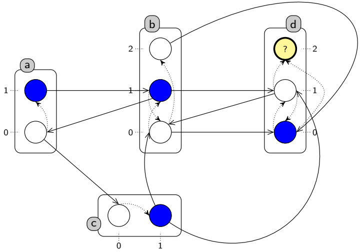
d_2

$d_1 \Rsh^* d_2$

b_2 $b_0 \Rsh^* b_2$ d_1 $d_1 \Rsh^* d_1$

b_1 $b_0 \Rsh^* b_1$ c_1 $c_0 \Rsh^* c_1$ a_0 $a_1 \Rsh^* a_0 \bot$

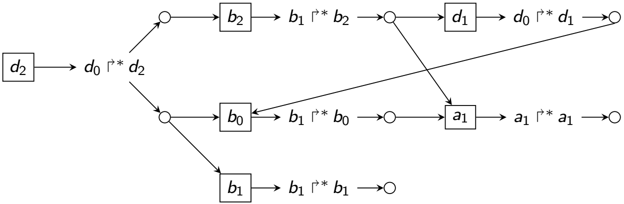
Over-approximation



Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives



d_2 → $d_0 \Rsh^* d_2$

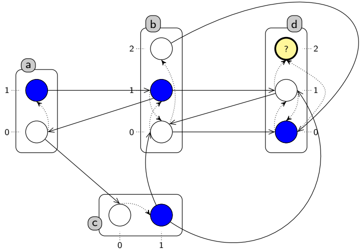
b_2 → $b_1 \Rsh^* b_2$

d_1 → $d_0 \Rsh^* d_1$

b_0 → $b_1 \Rsh^* b_0$

a_1 → $a_1 \Rsh^* a_1$

b_1 → $b_1 \Rsh^* b_1$



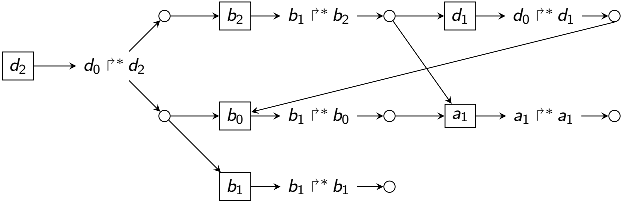
Over-approximation

Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives

R **is true** ⇒ **Inconclusive**



$\boxed{d_2}$

$d_0 \Rsh^* d_2$

$\boxed{b_2}$

$b_1 \Rsh^* b_2$

$\boxed{d_1}$

$d_0 \Rsh^* d_1$

$\boxed{b_0}$

$b_1 \Rsh^* b_0$

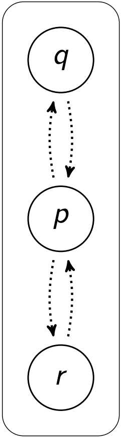
$\boxed{a_1}$

$a_1 \Rsh^* a_1$

$\boxed{b_1}$

$b_1 \Rsh^* b_1$

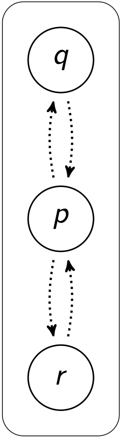
Examples with Modal µ-calculus



No tokens: only one evolution is studied

Atomic property (p**,** q**,** r**)**
$[\![p]\!] = \{p\}$

Examples with Modal µ-calculus



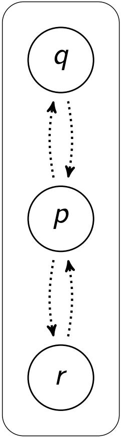
No tokens: only one evolution is studied

Atomic property (*p*, *q*, *r*)

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

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

Examples with Modal μ-calculus



No tokens: only one evolution is studied

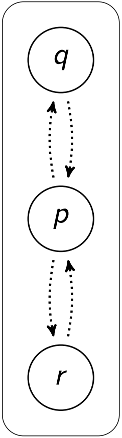
Atomic property (p, q, r)

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

Possible future (“may”)

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

Examples with Modal μ-calculus



No tokens: only one evolution is studied

Atomic property (*p*, *q*, *r*)

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

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

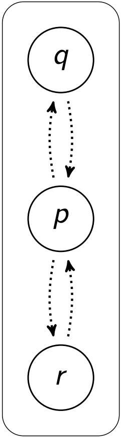
Possible future ("may")

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

Necessary future ("must")

$[\![\square\ q]\!] = \varnothing$

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")

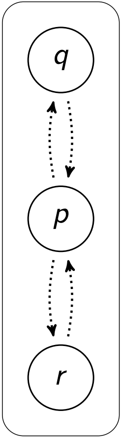
$[\![\Diamond\ q]\!] = \{p\}$

Necessary future ("must")

$[\![\Box\ q]\!] = \varnothing$

$[\![\Box\ p]\!] = \{q; r\}$

Examples with Polyadic µ-calculus

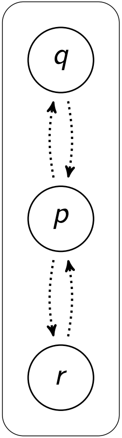


Atomic property (p, q, r)

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

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

Examples with Polyadic μ-calculus



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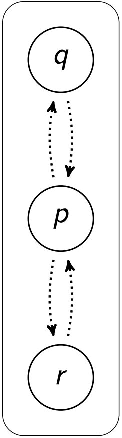
Token affectation ($i \leftarrow j$)

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

Examples with Polyadic µ-calculus



Atomic property (p, q, r)

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

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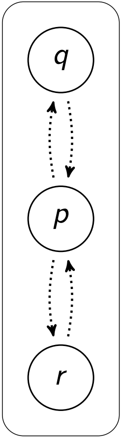
Token affectation ($i \leftarrow j$)

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

Token comparison ($i = j$)

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

Examples with Polyadic μ-calculus



Atomic property (p, q, r)

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

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

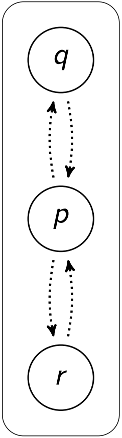
Token comparison ($i = j$)

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

Possible future (“may”)

$[\![\Diamond_1\ q]\!] = \{(p, p); (p, q); (p, r)\}$

Examples with Polyadic μ-calculus



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 ($i = j$)

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

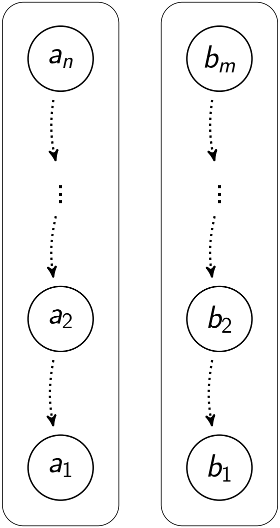
Possible future (“may”)

$[\![\Diamond_1\ q]\!] = \{(p, p); (p, q); (p, r)\}$

Necessary future (“must”)

$[\![\Box_1\ q]\!] = \varnothing$

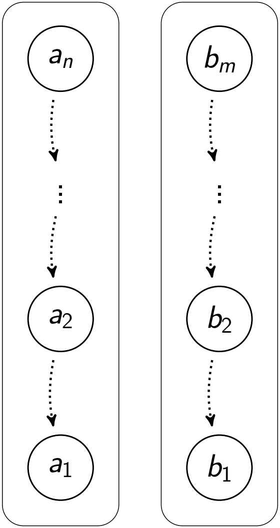
Examples with Polyadic µ-calculus



Least fixed point (μ)

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

Examples with Polyadic μ-calculus



Least fixed point (μ)

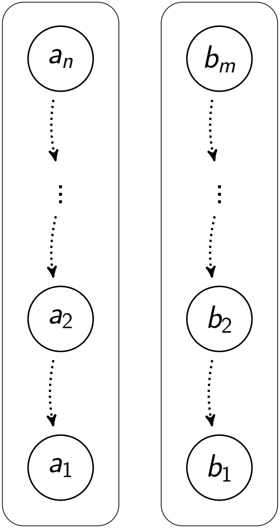
$$\phi = \mu X.(\Box_1\bot \wedge \Box_2\bot) \vee \Diamond_1\Diamond_2 X$$

Iterations:

$$[\![\phi]\!]_0 = \varnothing$$
$$[\![\phi]\!]_1 = \{(a_1, b_1)\}$$
$$[\![\phi]\!]_2 = \{(a_1, b_1); (a_2, b_2)\}$$
$$[\![\phi]\!]_3 = \{(a_1, b_1); (a_2, b_2); (a_3, b_3)\}$$

⋮

Examples with Polyadic µ-calculus



Least fixed point (μ)

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

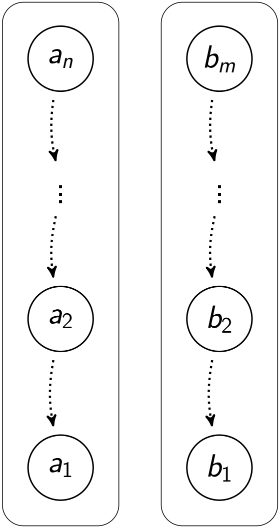
Iterations:

$$\llbracket\phi\rrbracket_0 = \varnothing$$
$$\llbracket\phi\rrbracket_1 = \{(a_1, b_1)\}$$
$$\llbracket\phi\rrbracket_2 = \{(a_1, b_1); (a_2, b_2)\}$$
$$\llbracket\phi\rrbracket_3 = \{(a_1, b_1); (a_2, b_2); (a_3, b_3)\}$$
$$\vdots$$

Generalization:

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

Examples with Polyadic µ-calculus



Least fixed point (μ)

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

Iterations:

$$[\![\phi]\!]_0 = \varnothing$$
$$[\![\phi]\!]_1 = \{(a_1, b_1)\}$$
$$[\![\phi]\!]_2 = \{(a_1, b_1); (a_2, b_2)\}$$
$$[\![\phi]\!]_3 = \{(a_1, b_1); (a_2, b_2); (a_3, b_3)\}$$
$$\vdots$$

Generalization:

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

Idea: use one (or n) token per automata