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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Overview of This Presentation

Frameworks: the models we will talk about

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

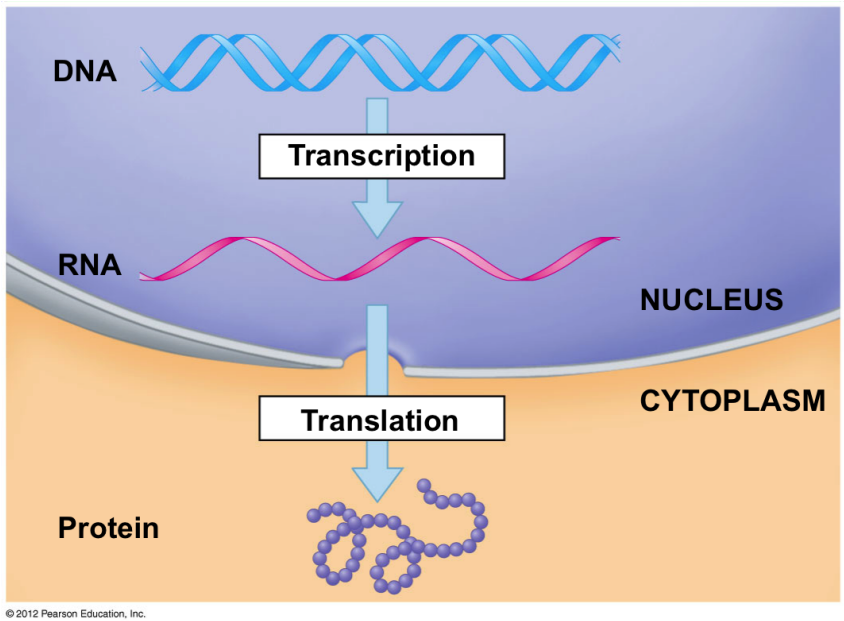
Exhaustive analyses: classical model-checking approaches with a high complexity

- 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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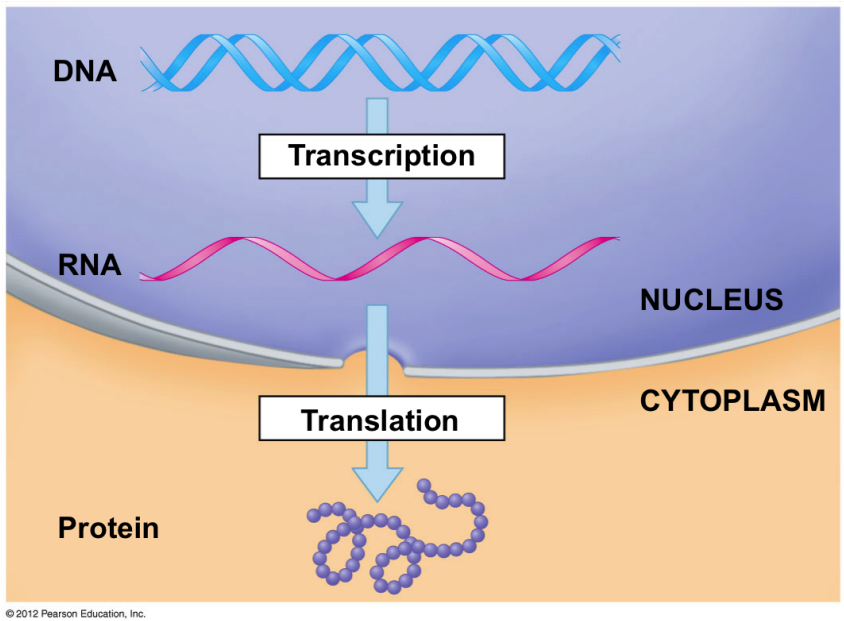

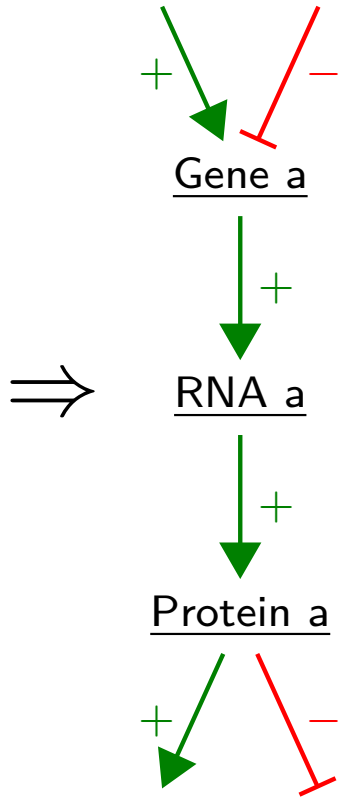

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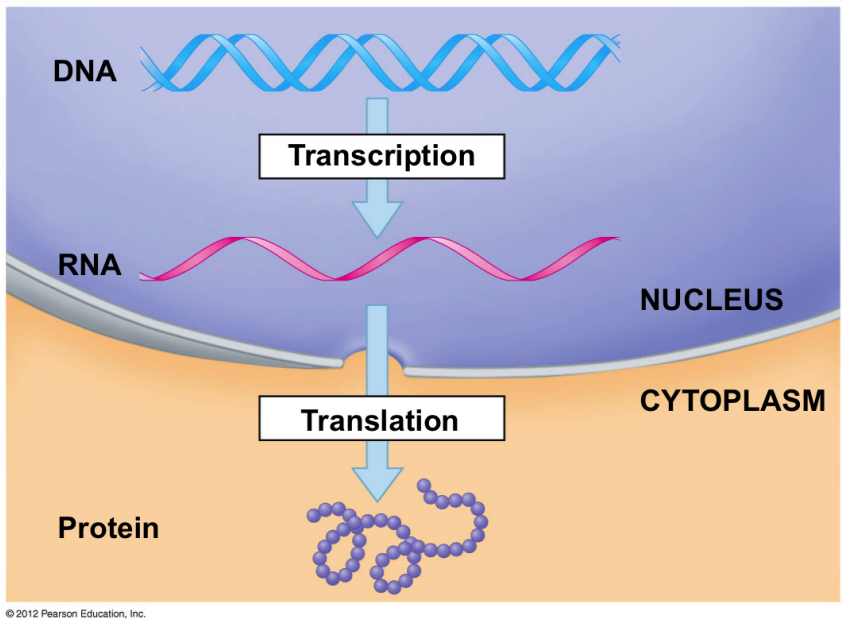
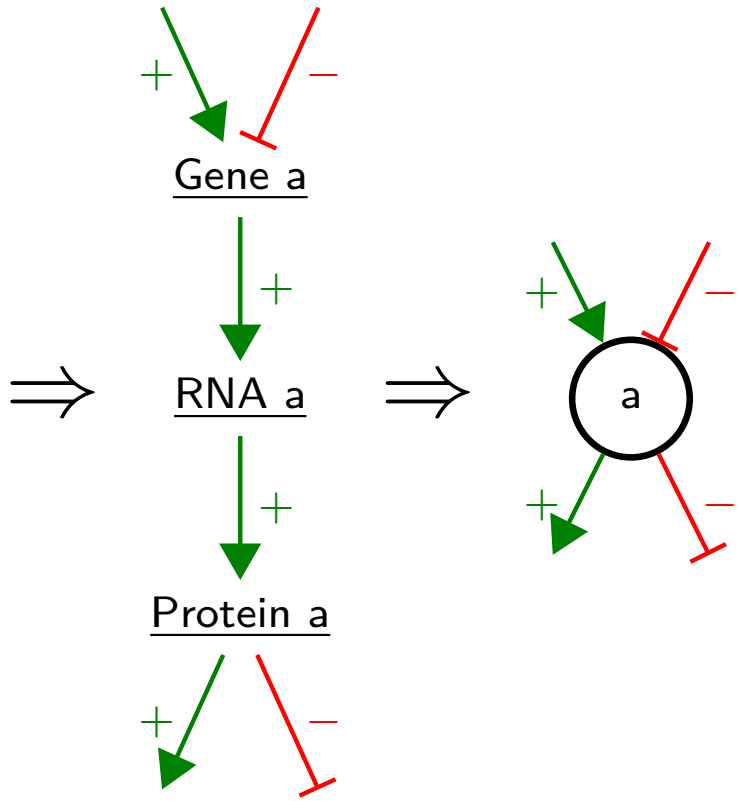
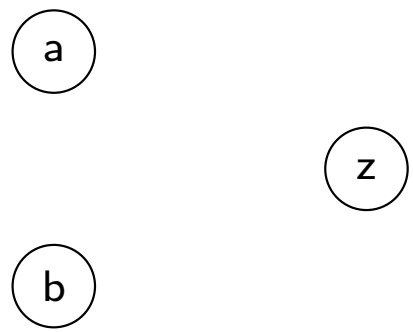




Discrete Networks / Thomas Modeling

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

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



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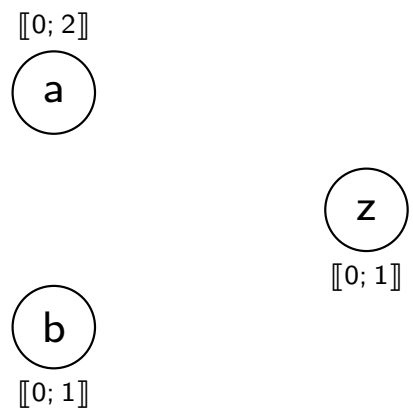
- A set of components $N = \{a, b, z\}$
- A set of discrete expression levels for each component $a \in \mathbb{F}^a = [\![0; 2]\!]$
- The set of global states $\mathbb{F} = \mathbb{F}^a \times \mathbb{F}^b \times \mathbb{F}^z$



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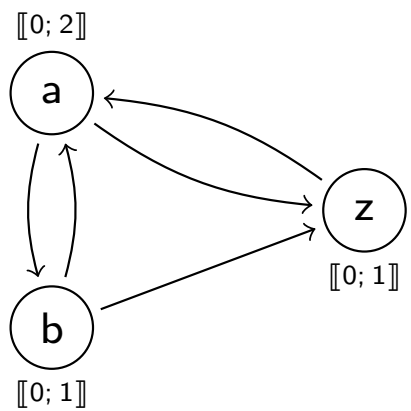
- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

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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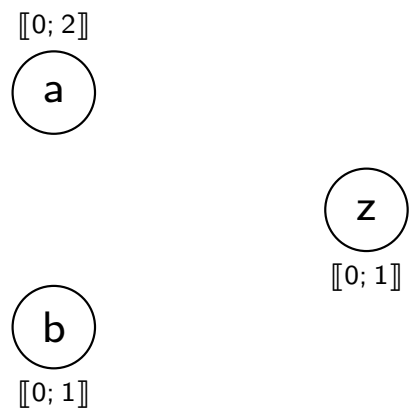

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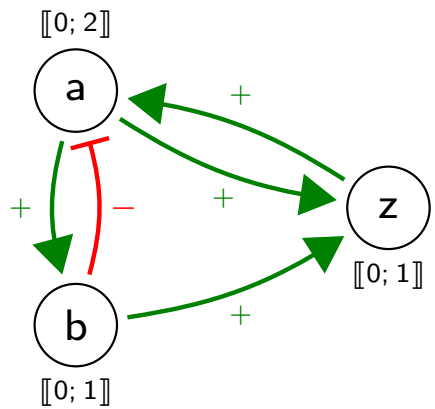

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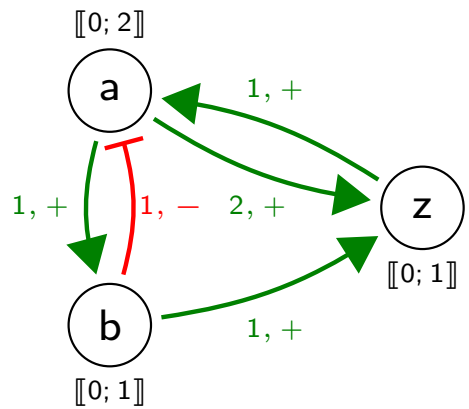

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- Signs on the edges $a \xrightarrow{+} z$ or signs + thresholds $a \xrightarrow{2,+} z$
- Discrete parameters / evolution functions $f^a : \mathbb{F} \to \mathbb{F}^a$

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

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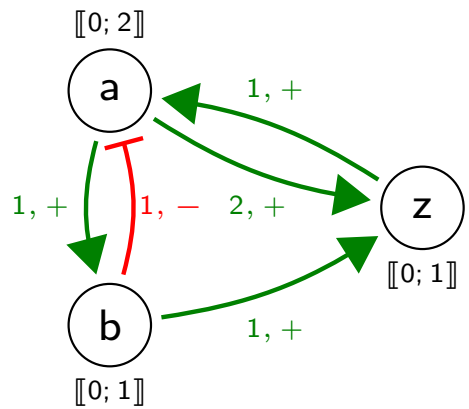
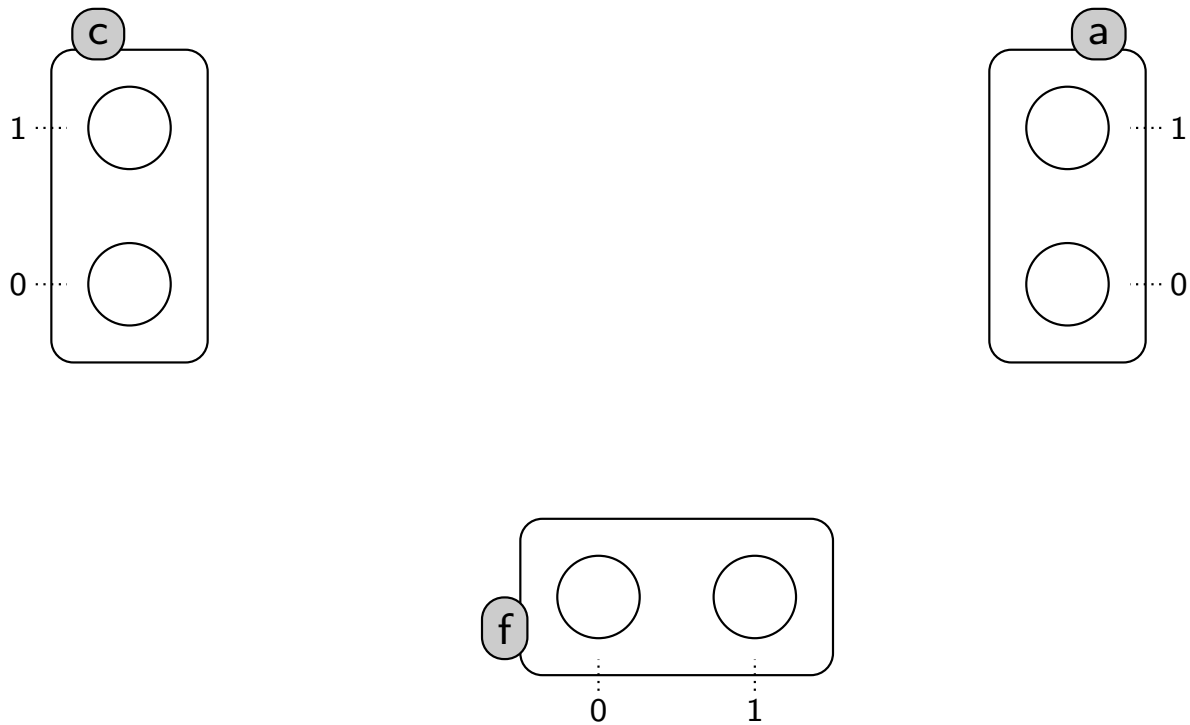


Asynchronous Automata Networks (AAN)
Enriched Process Hitting (PH)



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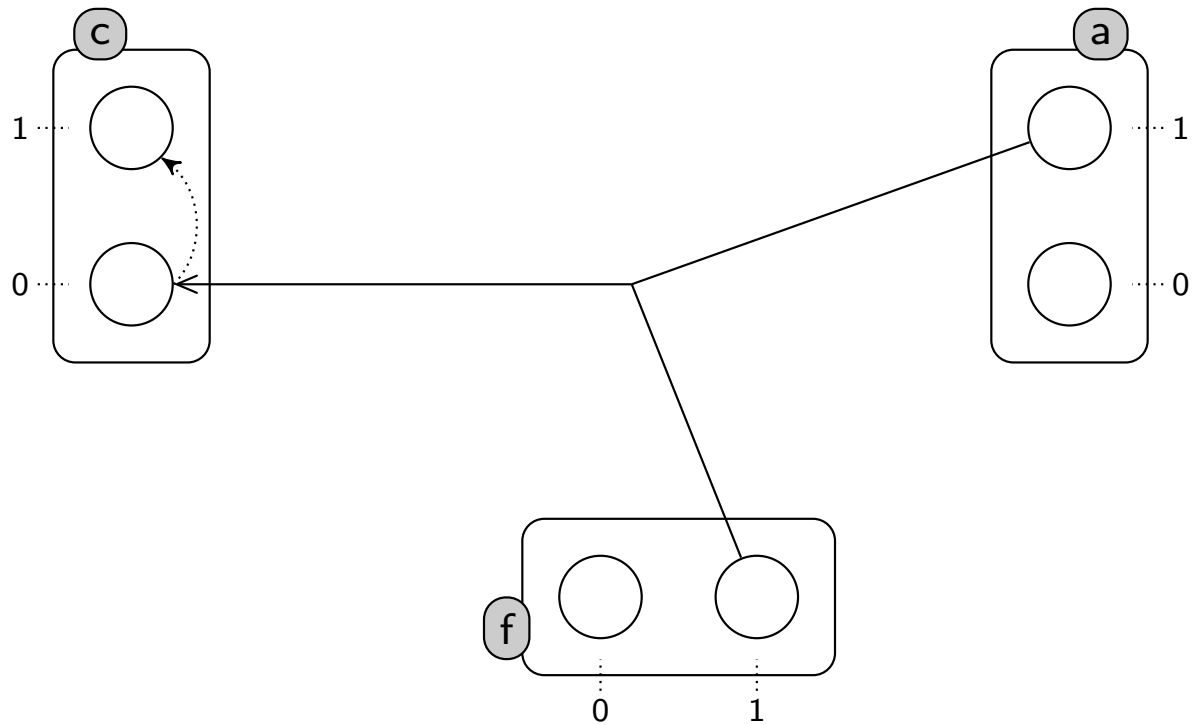

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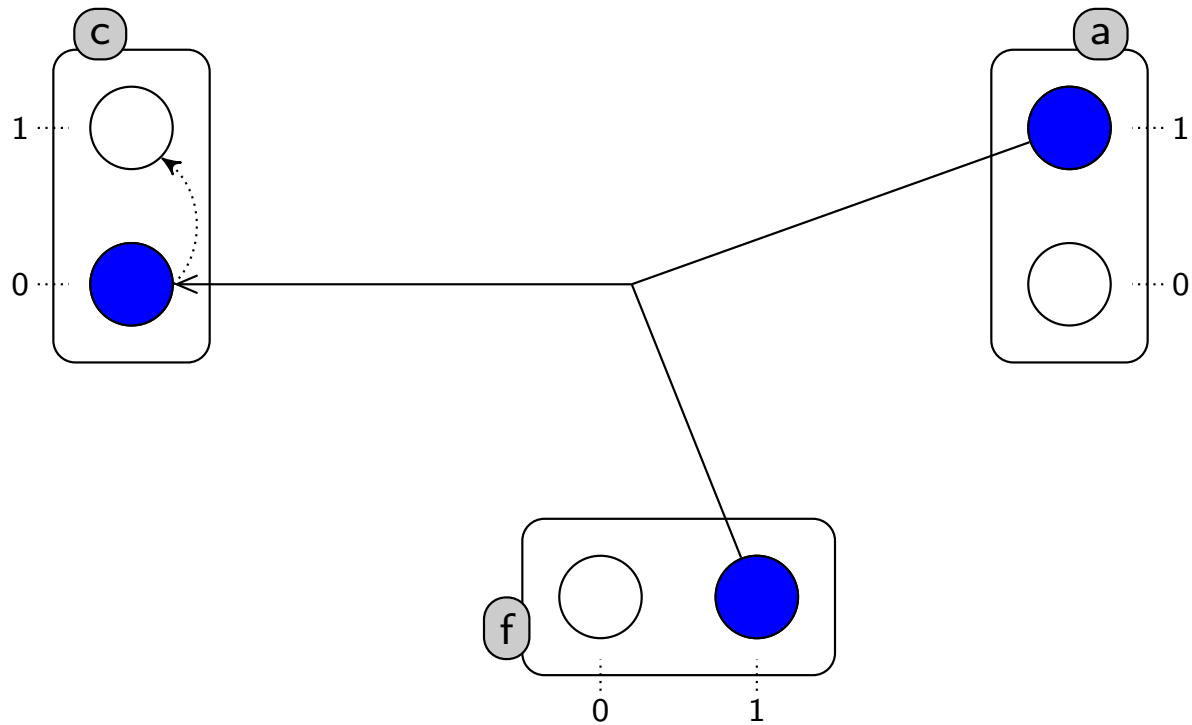

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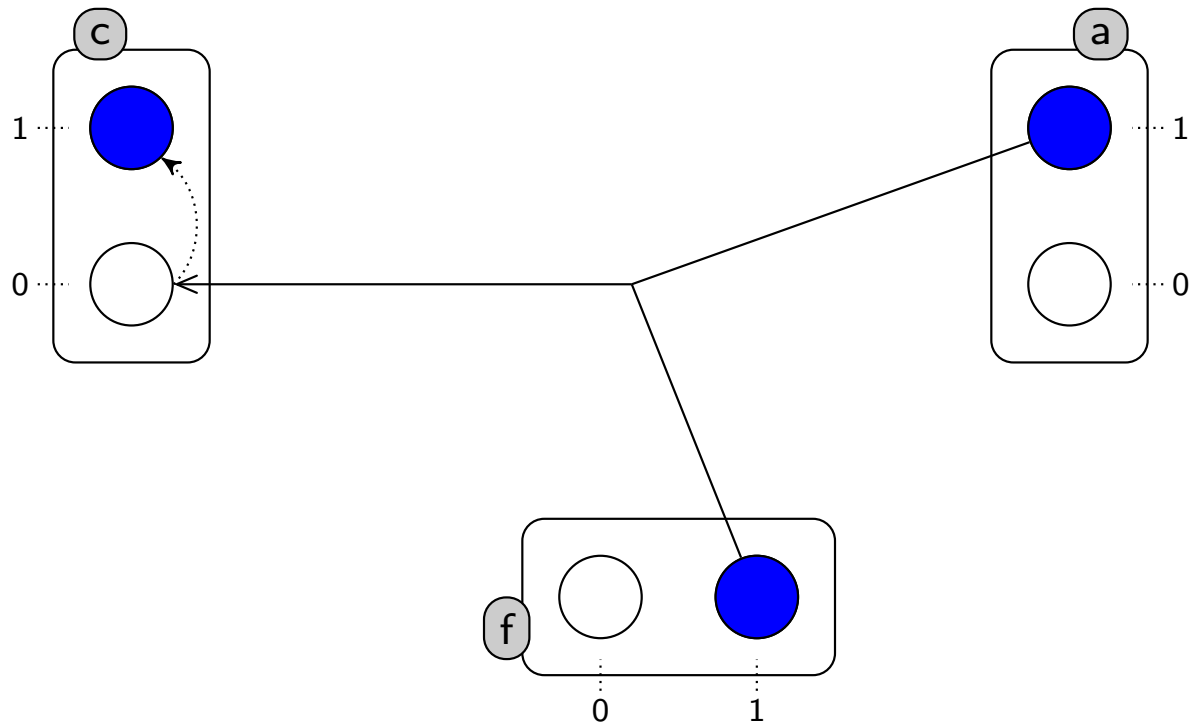
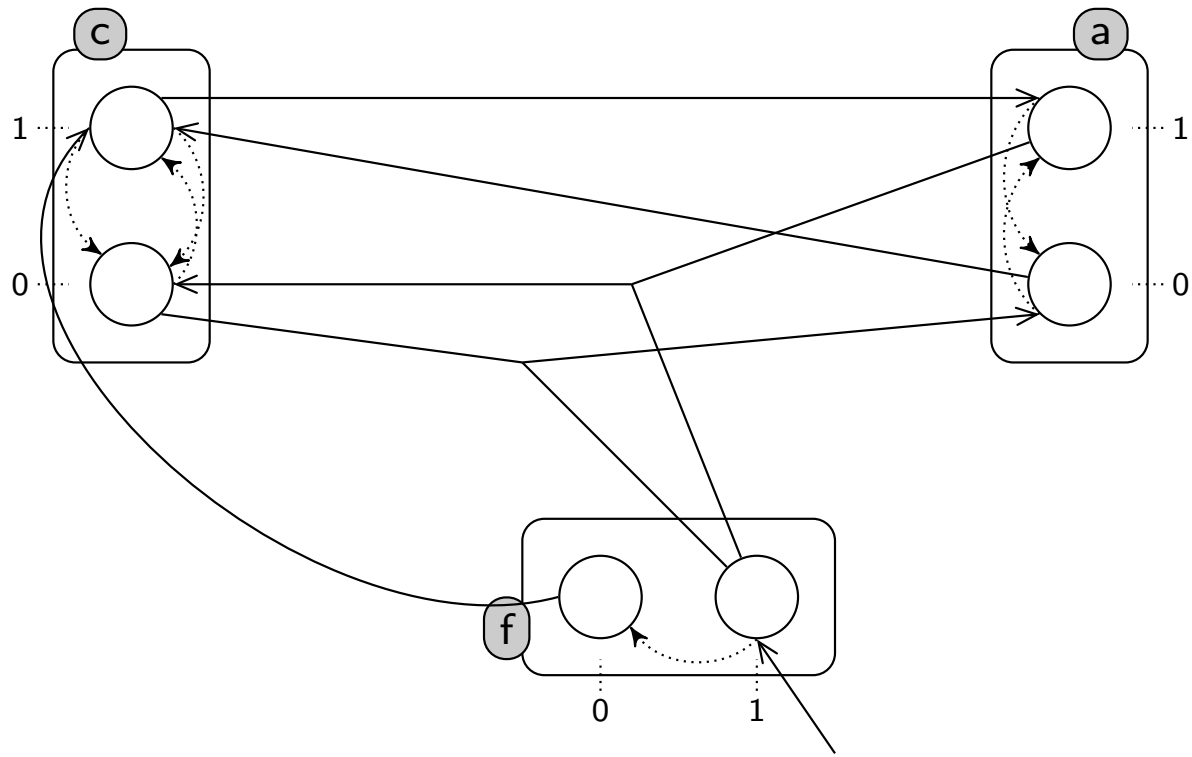


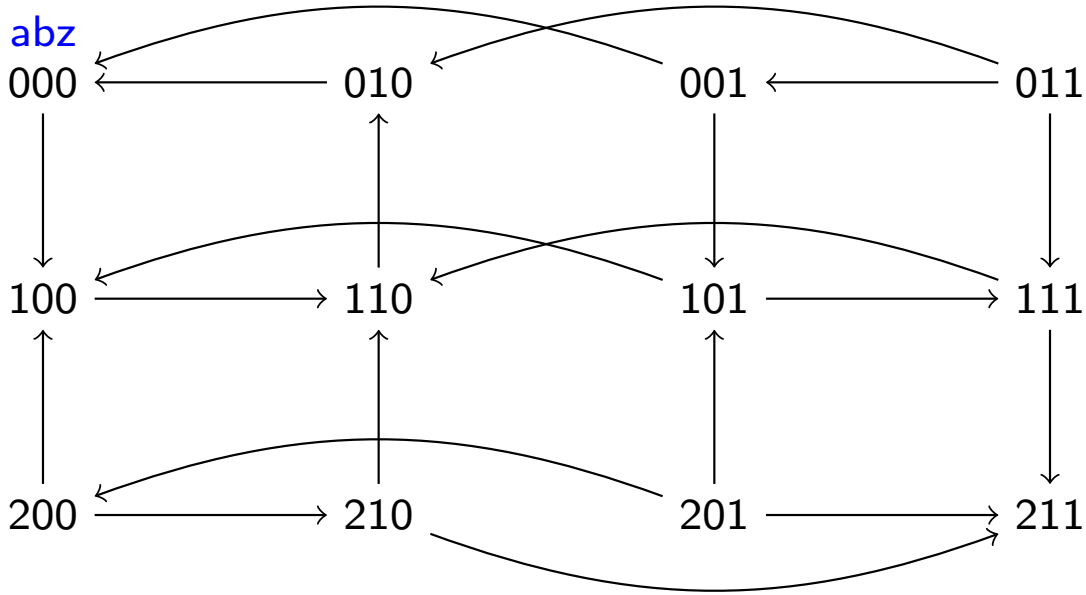
Asynchronous Automata Networks (AAN)
Enriched Process Hitting (PH)

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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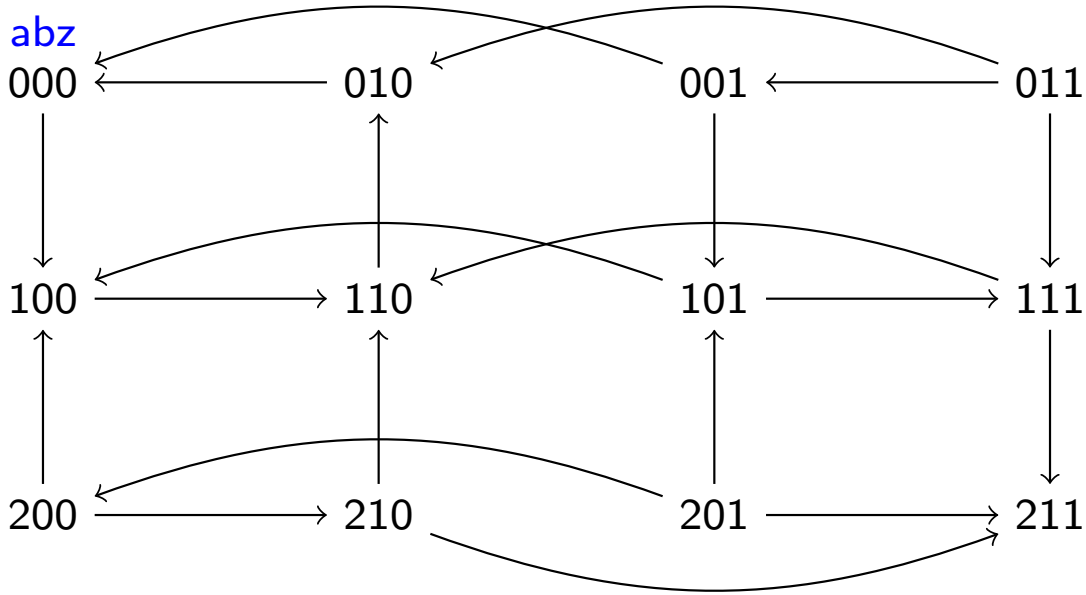

Attractor = minimal set of states from which the dynamics cannot escape

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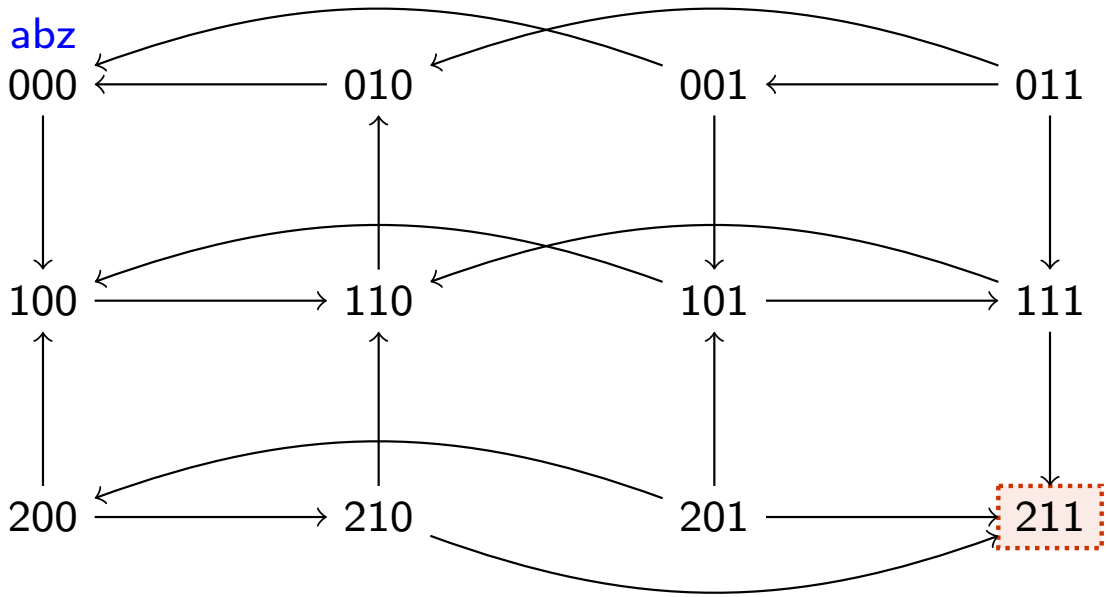

Attractor = minimal set of states from which the dynamics cannot escape

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

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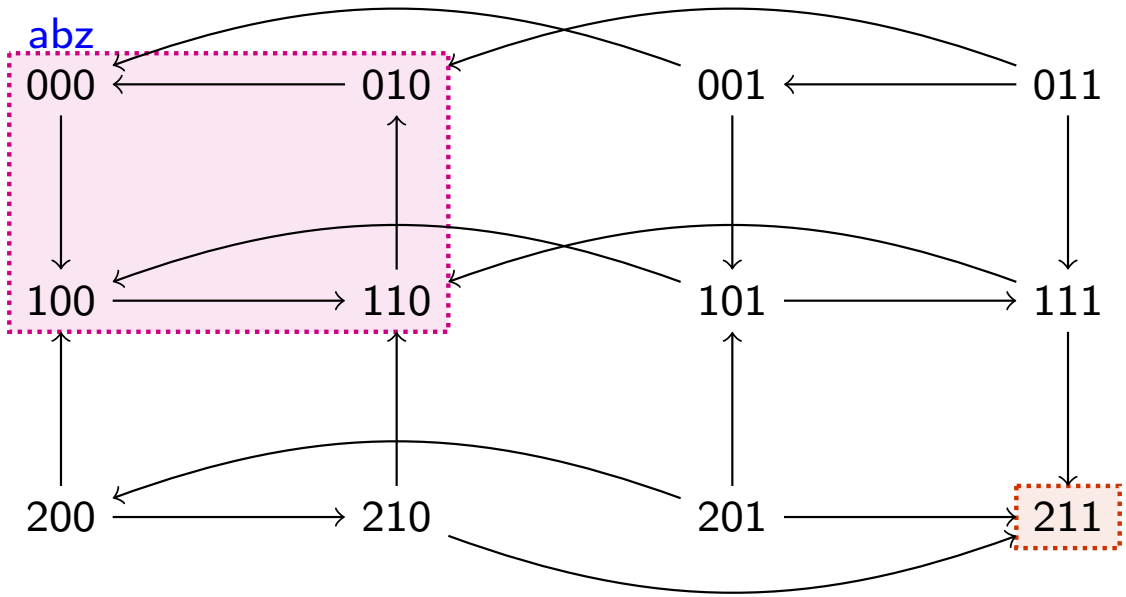
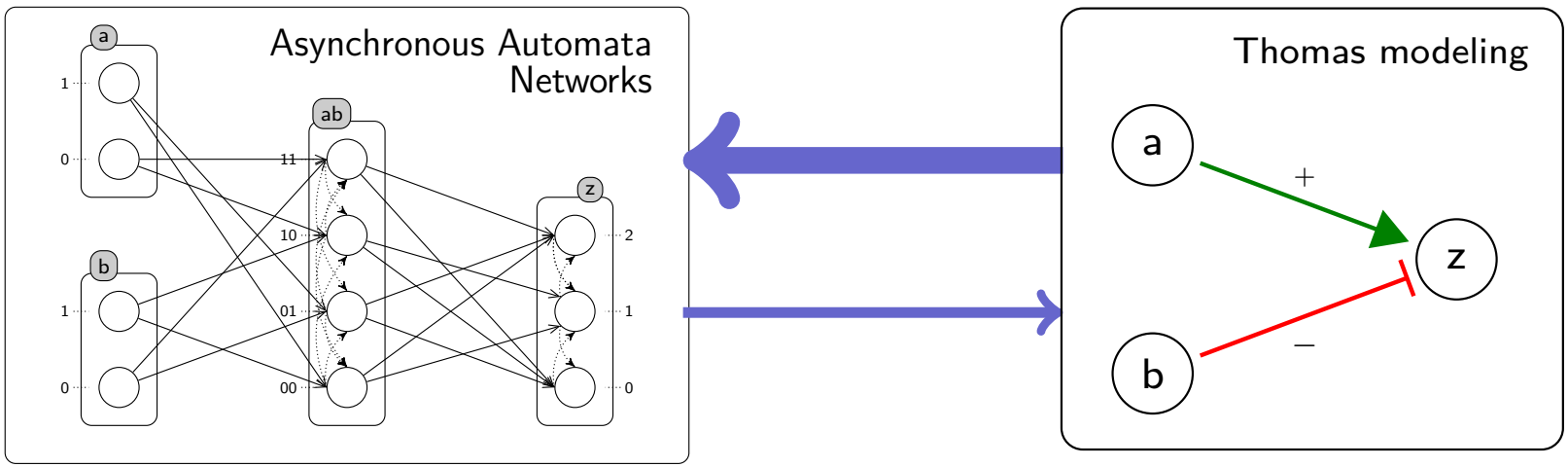


Attractor = minimal set of states from which the dynamics cannot escape

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

Translations Between AAN and Thomas Modeling

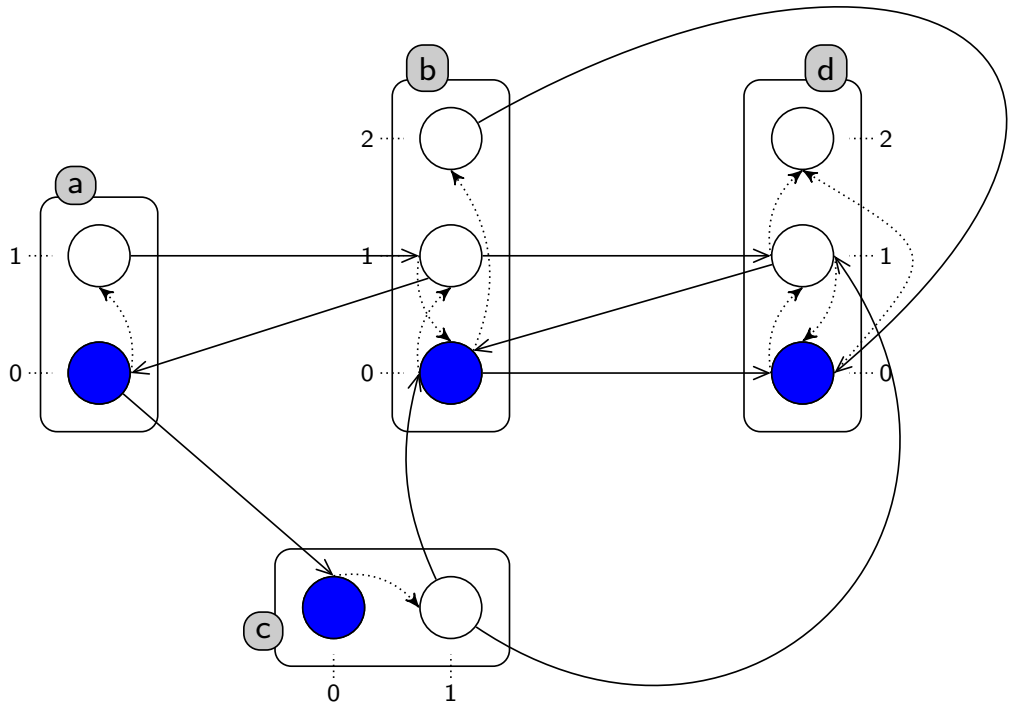
[Folschette *et al.*, *Theoretical Computer Science*, 2015a]
[Folschette *et al.*, *CS2Bio'13*, 2013]



- 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

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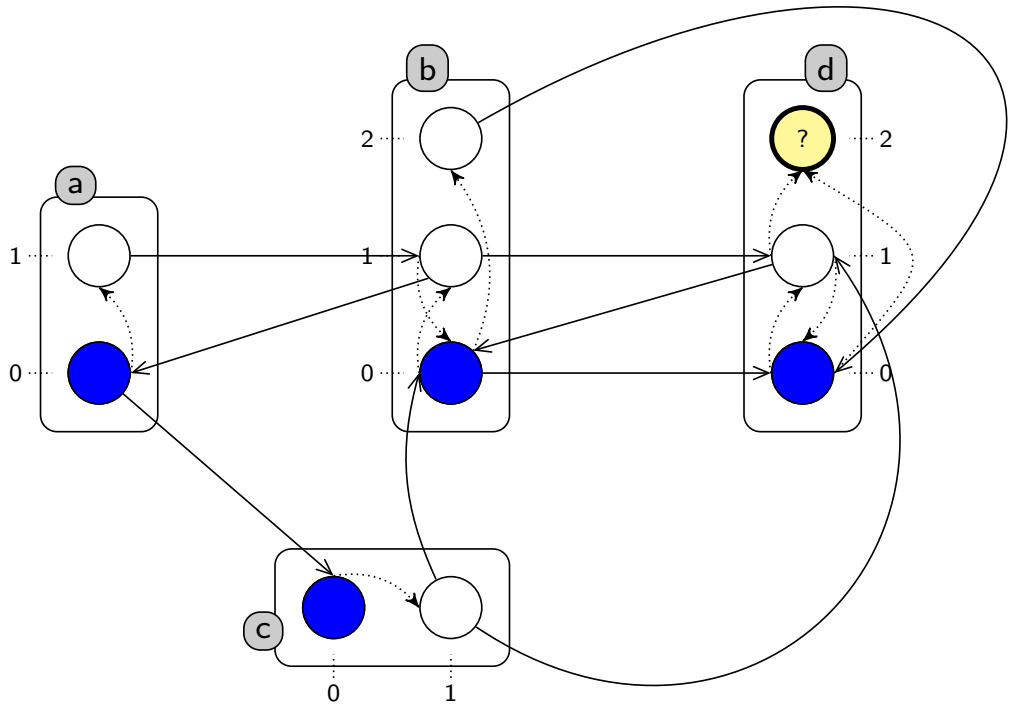

- Initial state $\langle a_1, b_0, c_0, d_0 \rangle$
- Objective $[\ d_2\ ]$

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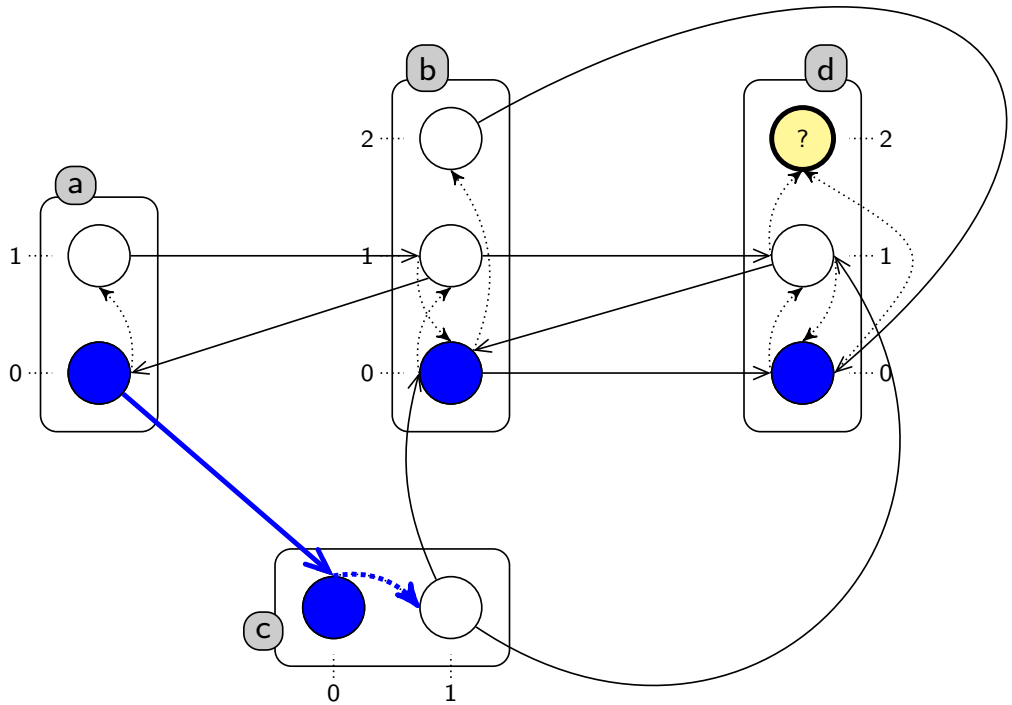

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$\rightarrow$ Concretization of the objective = scenario

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

The Reachability Problem

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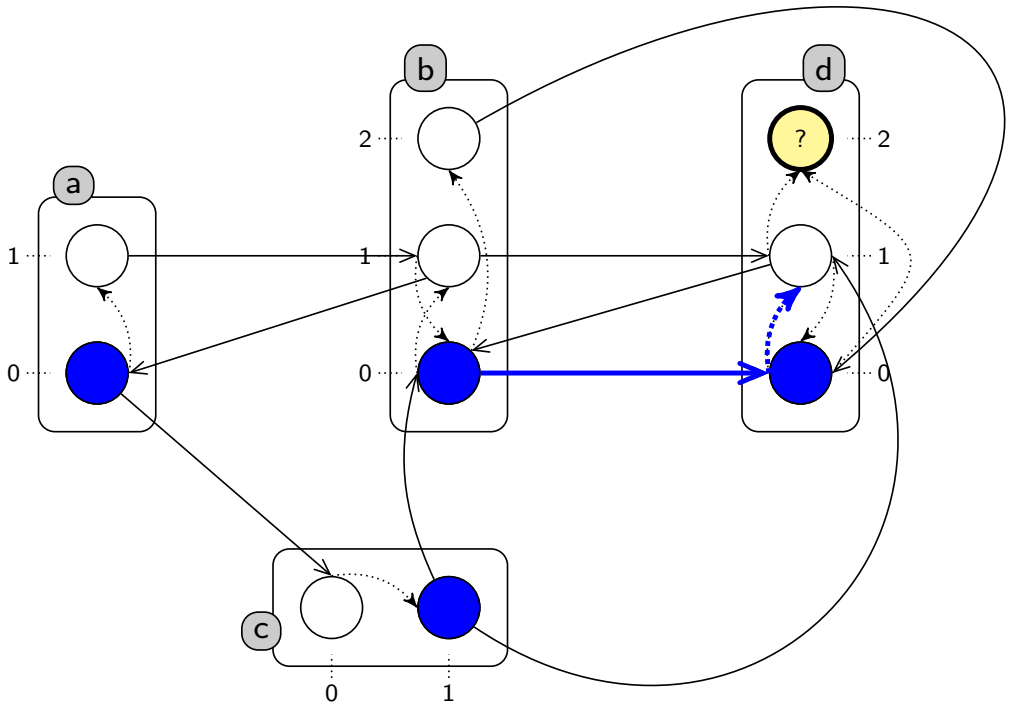

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$$a_0 \rightarrow c_0 \Rsh c_1 :: \underline{b_0 \rightarrow d_0 \Rsh d_1} :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$$

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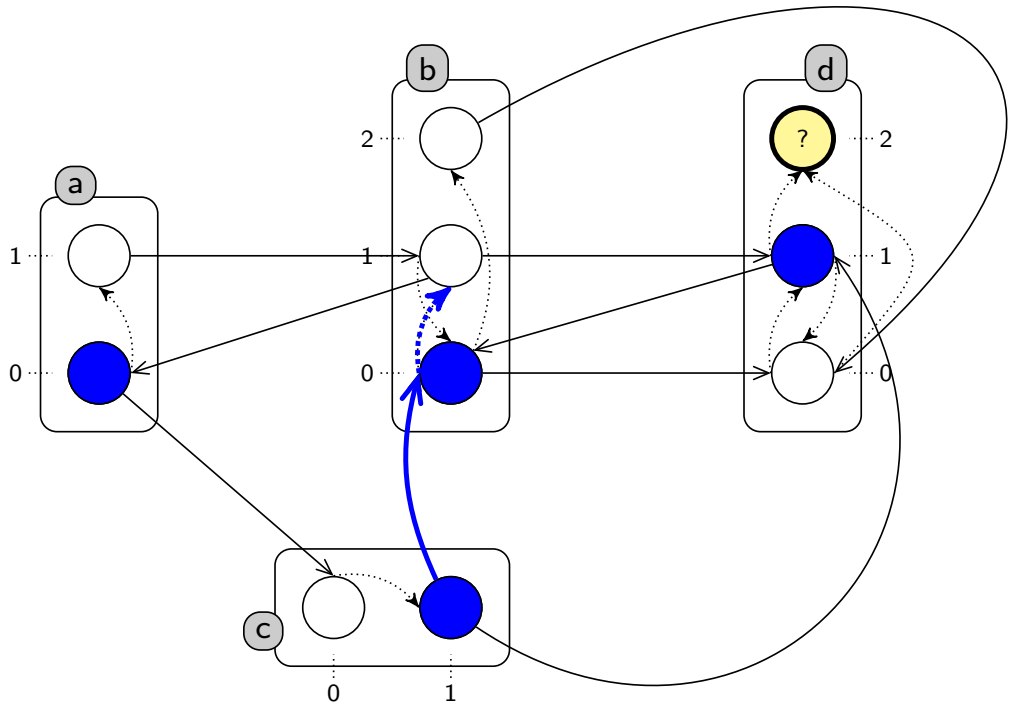
[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]



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The Reachability Problem

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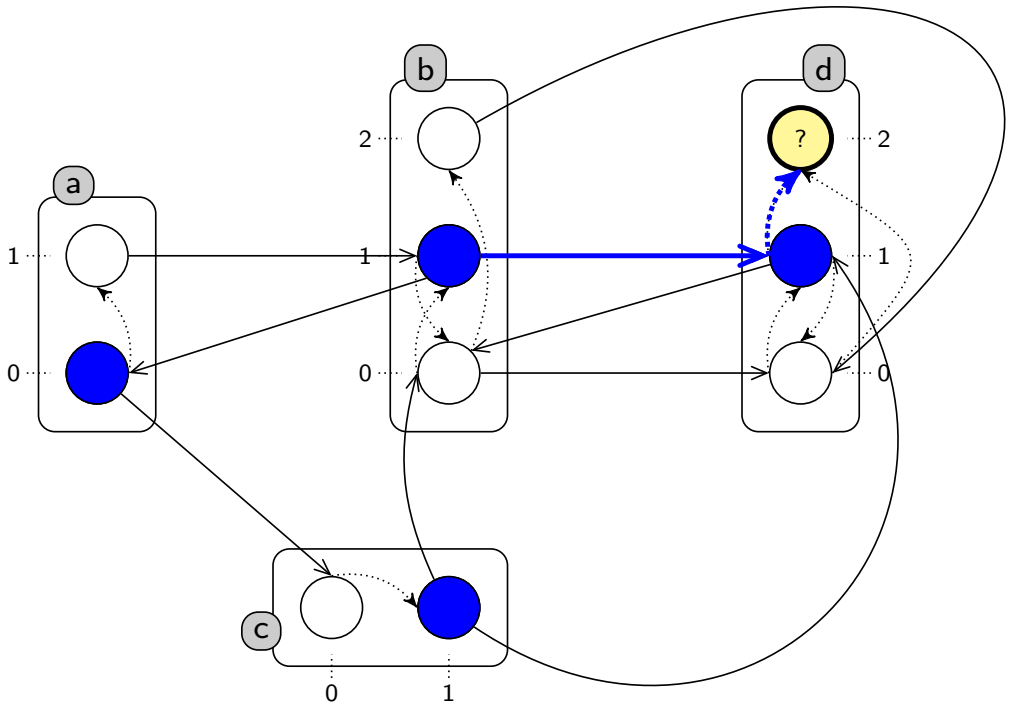

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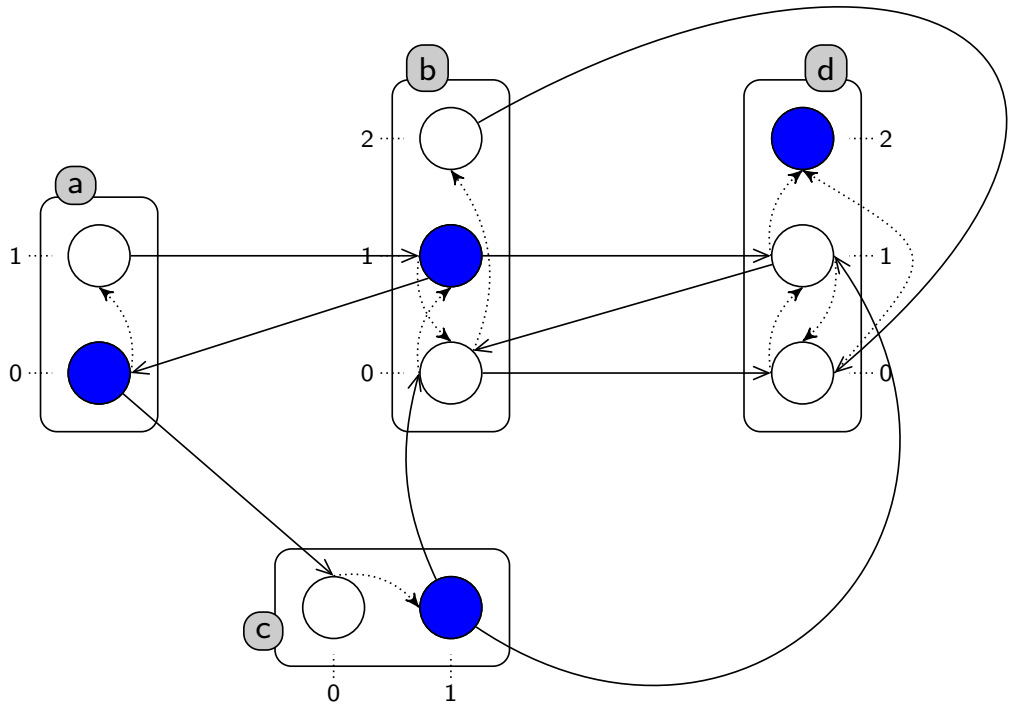

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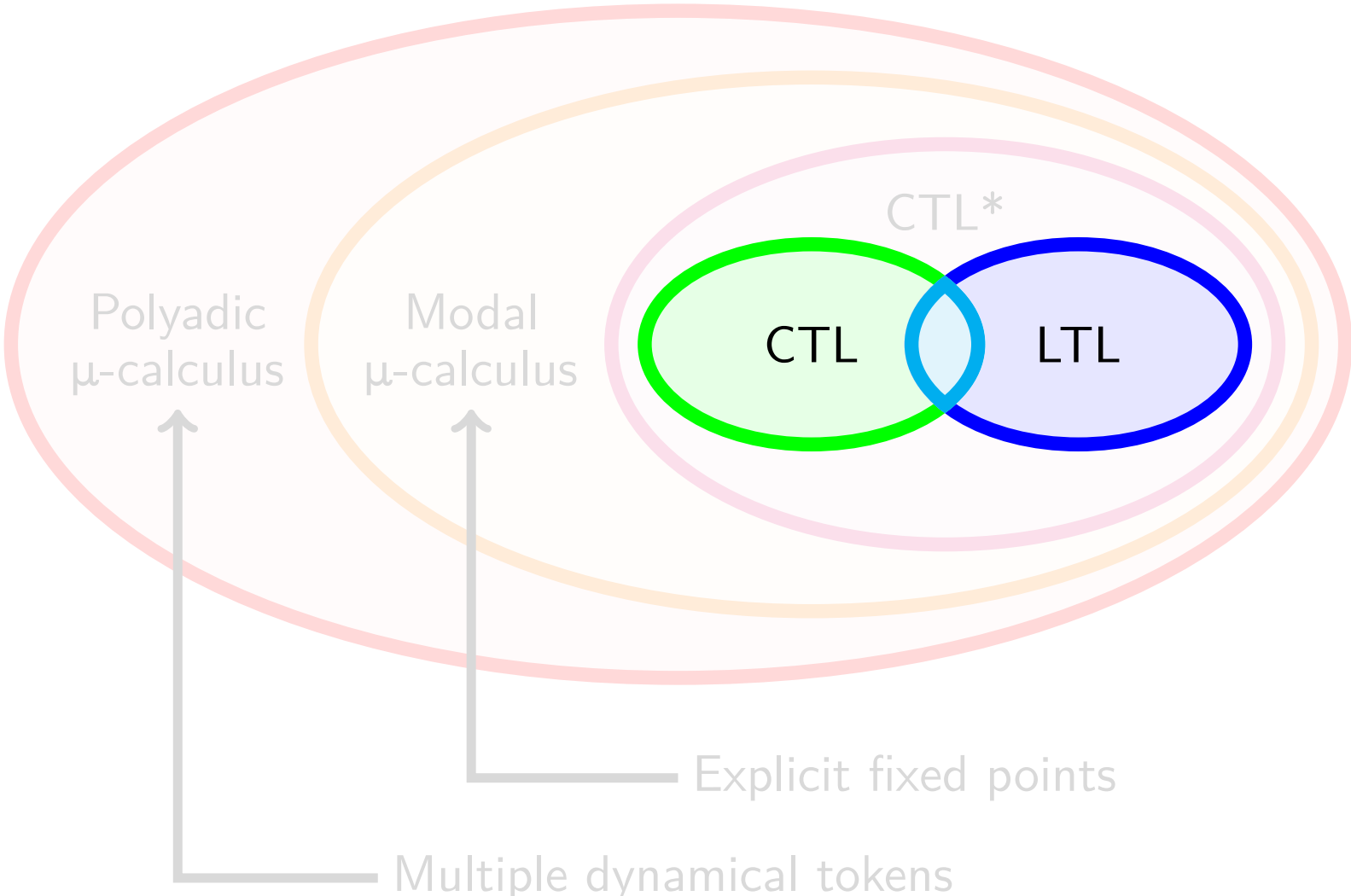
The Polyadic μ-caculus



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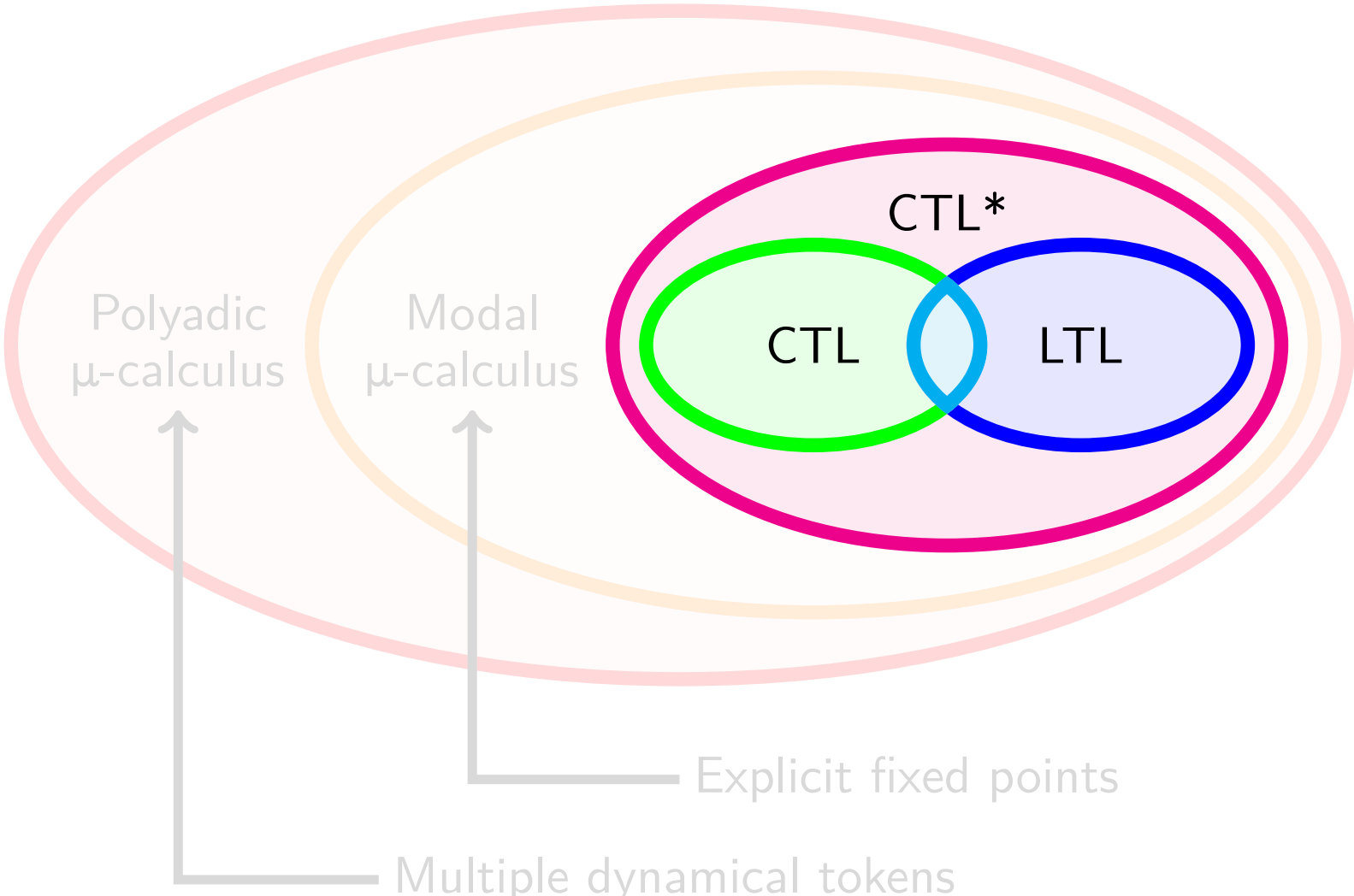

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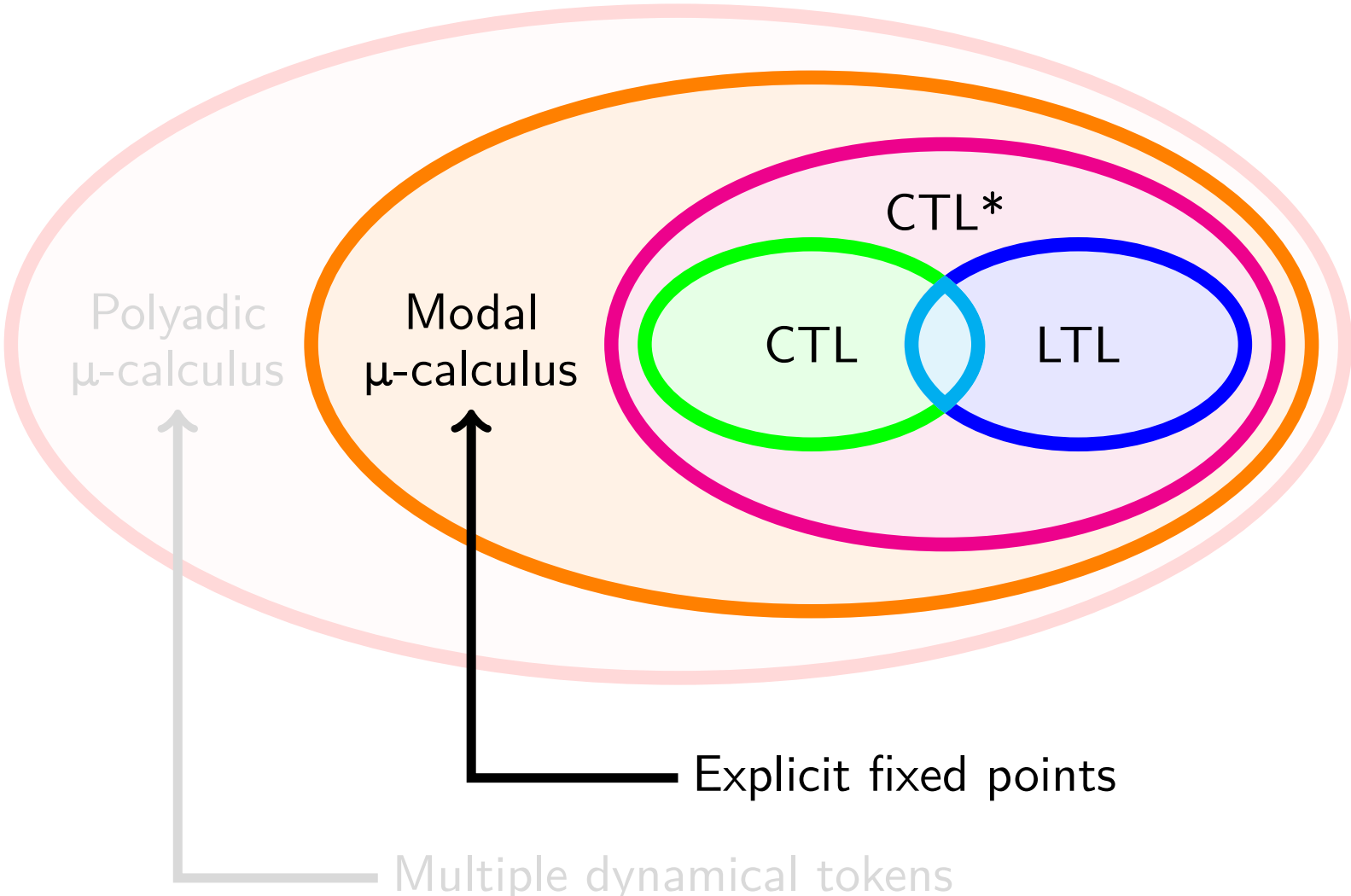

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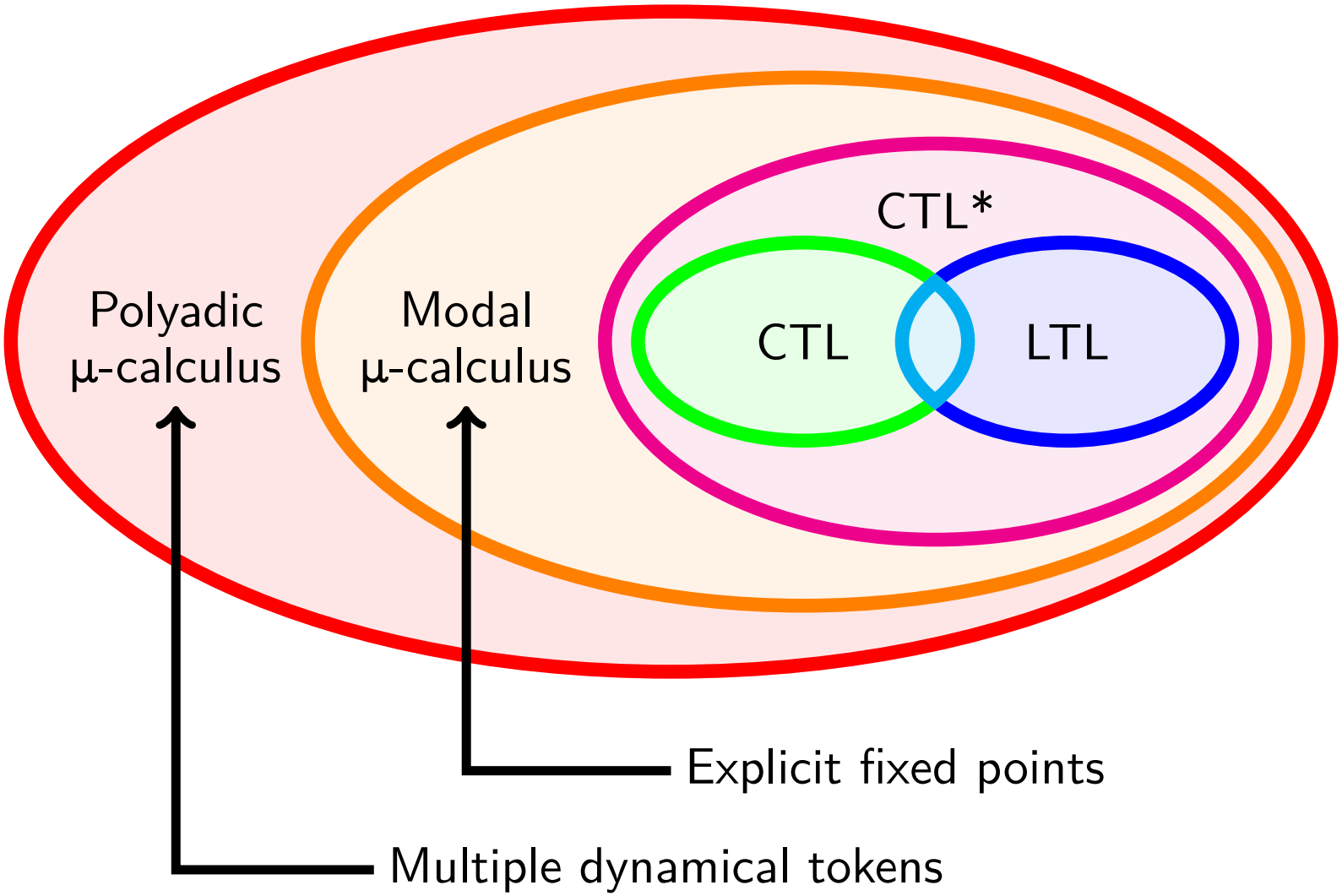

The Modal μ-calculus

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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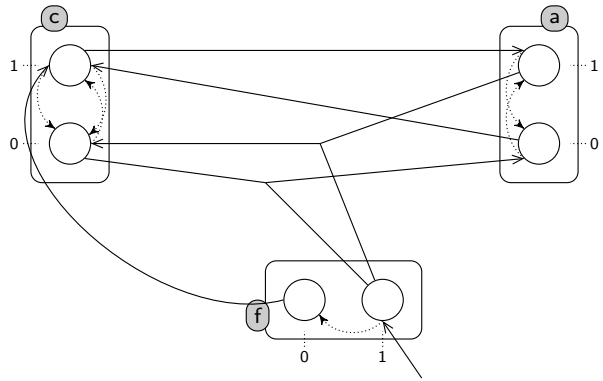
- $i \leftarrow j$ ("move token i to the position of token j")

Applications of the Polyadic μ-calculus



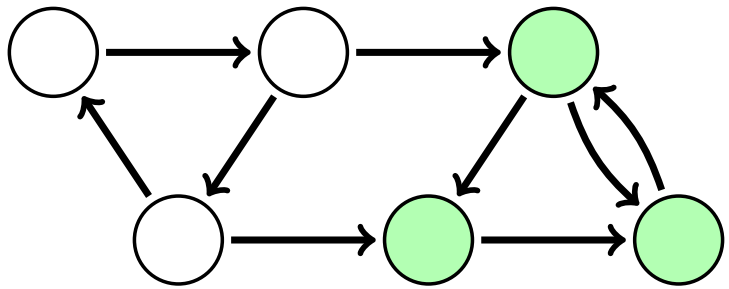
Objective: Unify formulas for many dynamical problems

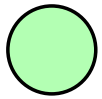
Not always possible with classical temporal logics (LTL, CTL, CTL*):

1) From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?
   $(a = 0 \wedge b = 0 \wedge z = 0) \Rightarrow \mathsf{EF}(z = 2)$
2) Does $(0, 0, 0)$ belong to an attractor?
   $(a = 0 \wedge b = 0 \wedge z = 0) \Rightarrow \mathsf{N}\bot \vee \mathsf{AG}(\mathsf{EF}(a = 0 \wedge b = 0 \wedge z = 0))$
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

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

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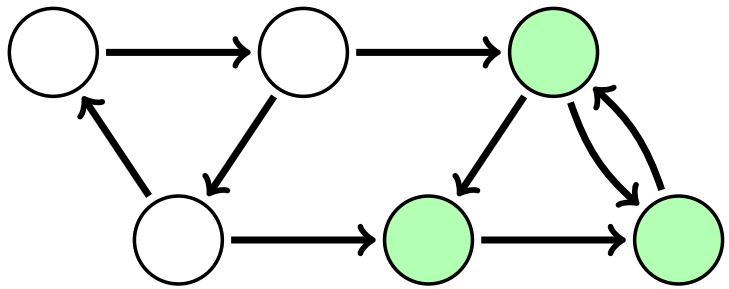

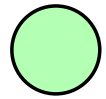

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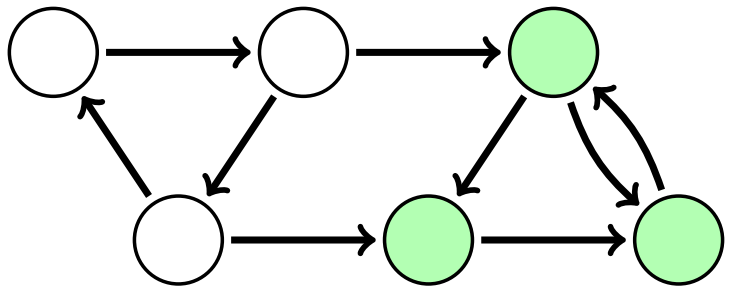

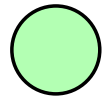

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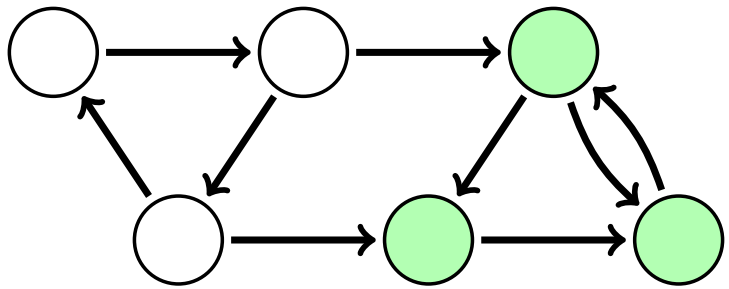

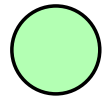

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Conclusion on Polyadic μ-calculus

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)
edge(a,b) edge(b,c) edge(a,c)
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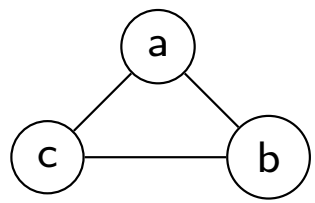

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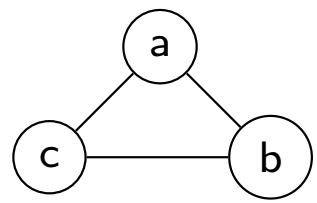

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Cardinalities: $min\ \{\ atom : enum\ \}\ max \leftarrow body.$

- 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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   .
   .
   . (27 answer sets)
```

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

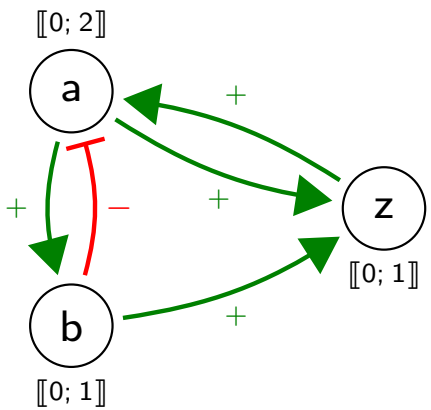
Outlooks:

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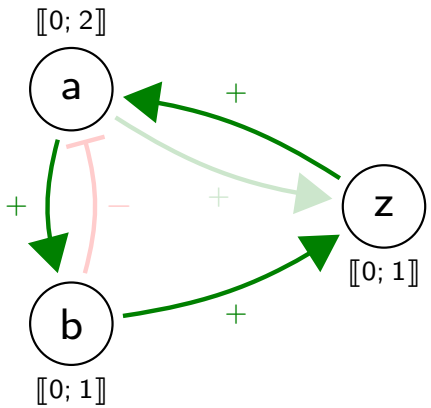
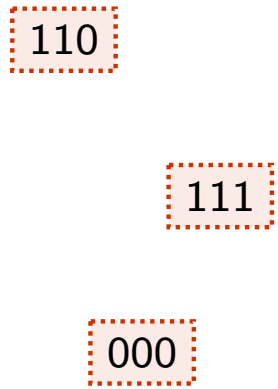
- Multiple **stable states** ⇒ positive cycle in the graph





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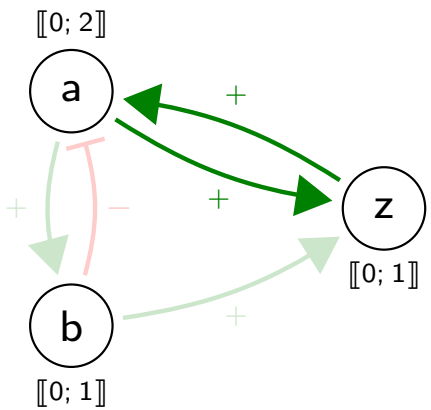

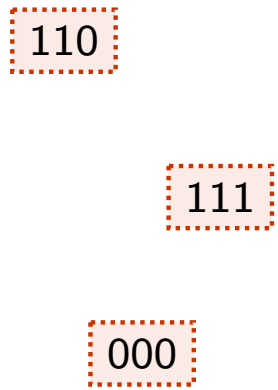

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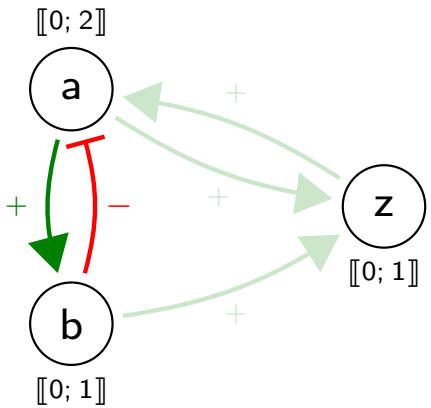

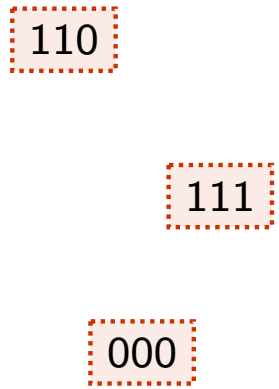

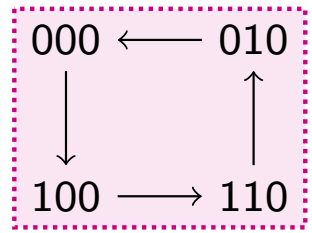

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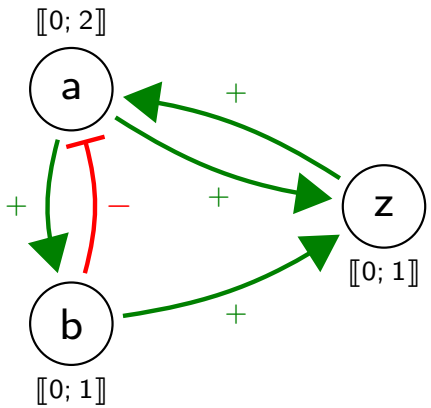

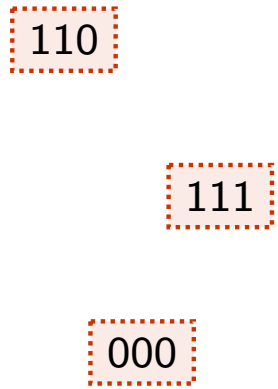

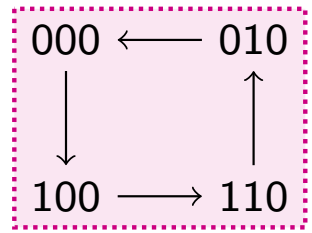

Proofs: [Remy, Ruet & Thieffry, *Advances in Applied Mathematics*, 2008]
[Richard, *Advances in Applied Mathematics*, 2010]
[Richard & Comet, *Discrete Applied Mathematics*, 2007]

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[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)

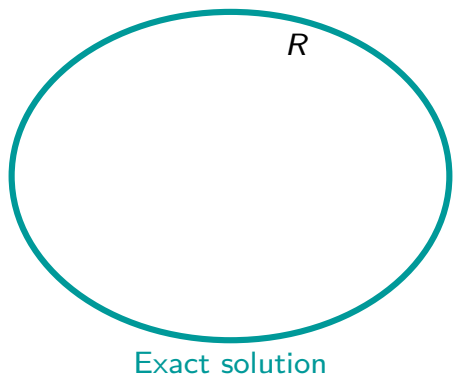
→ **Need for more precise methods**

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**)



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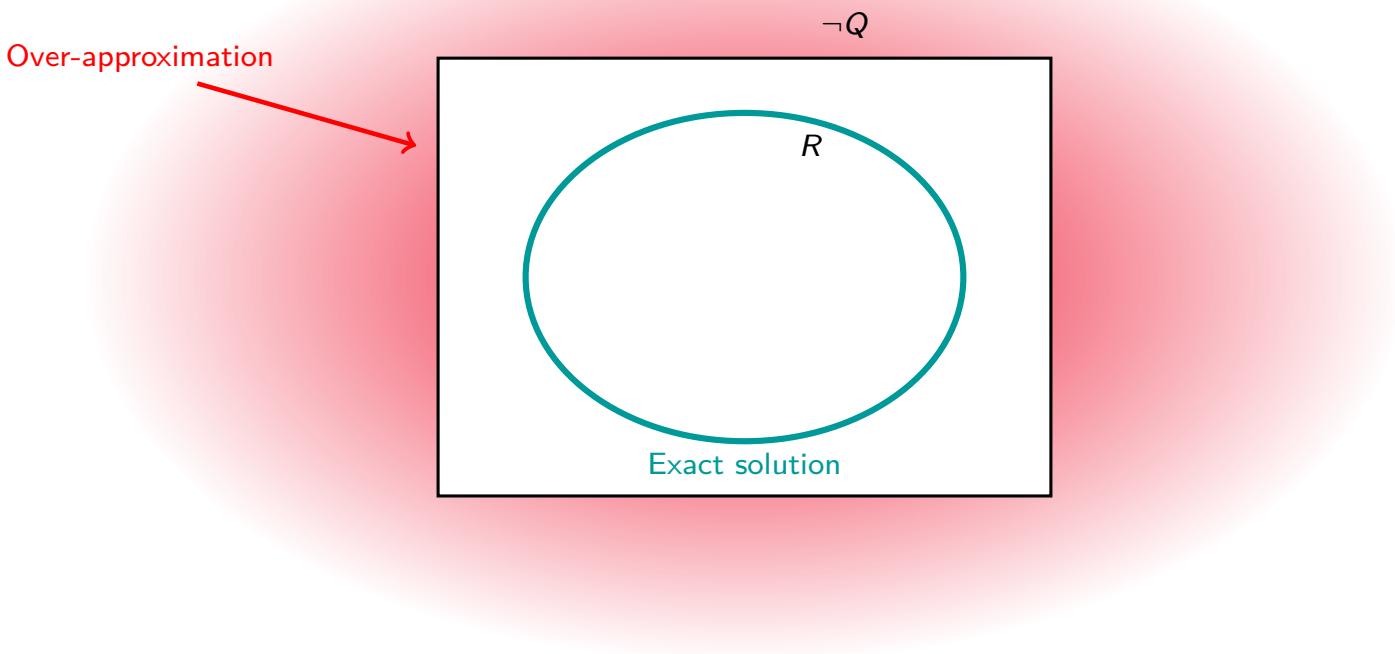

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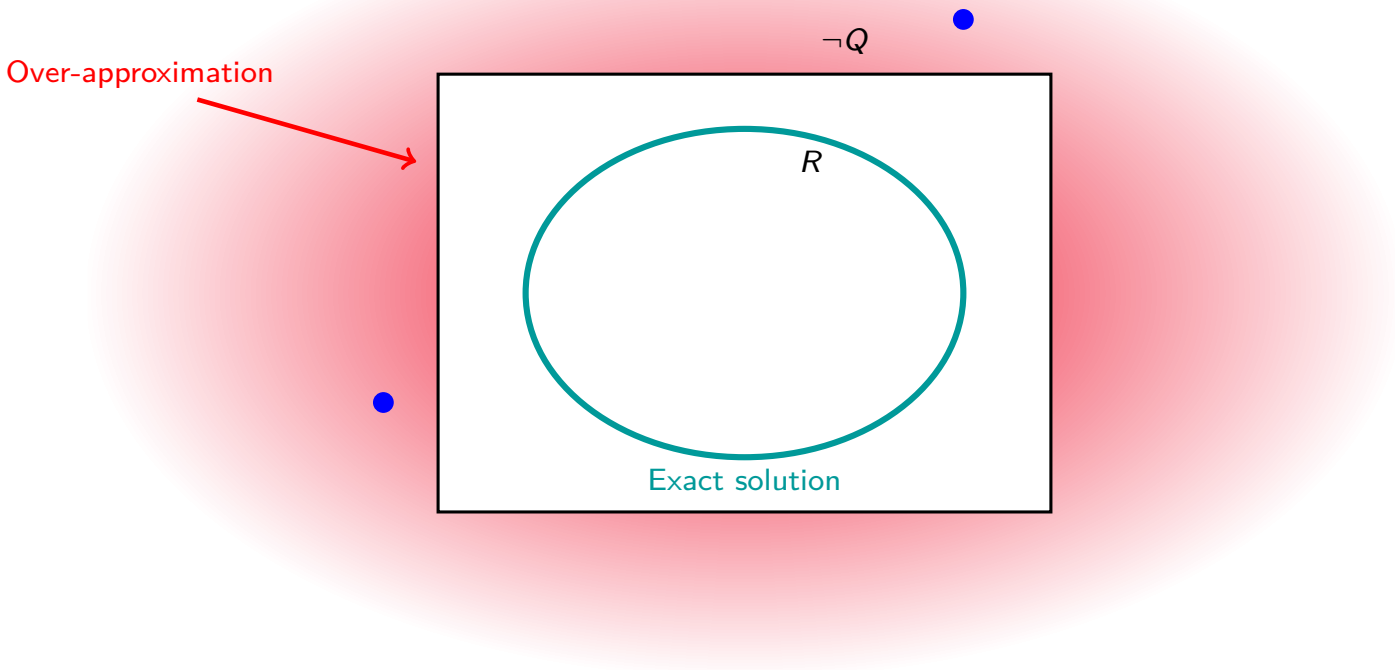

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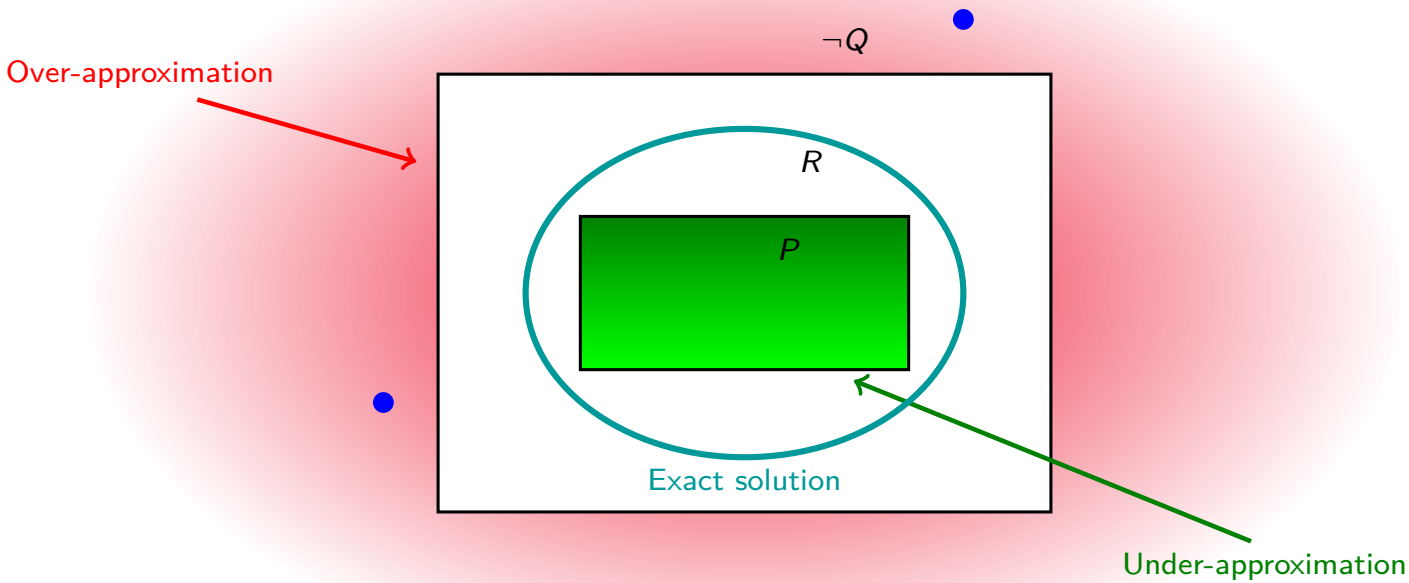

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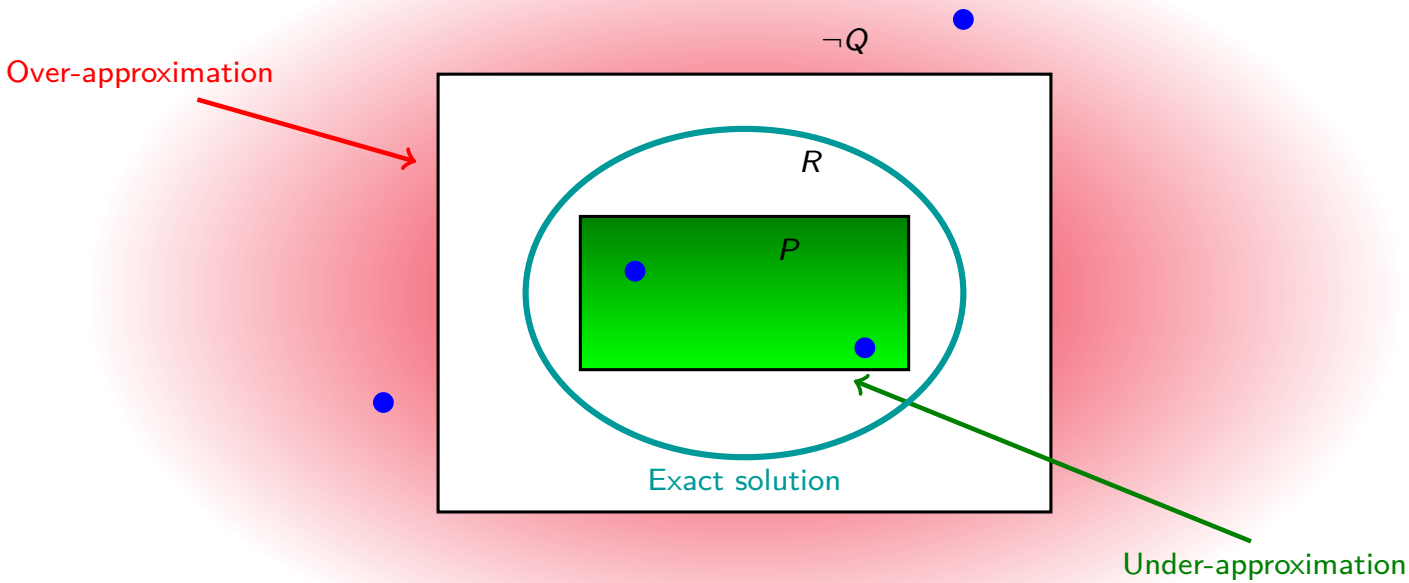

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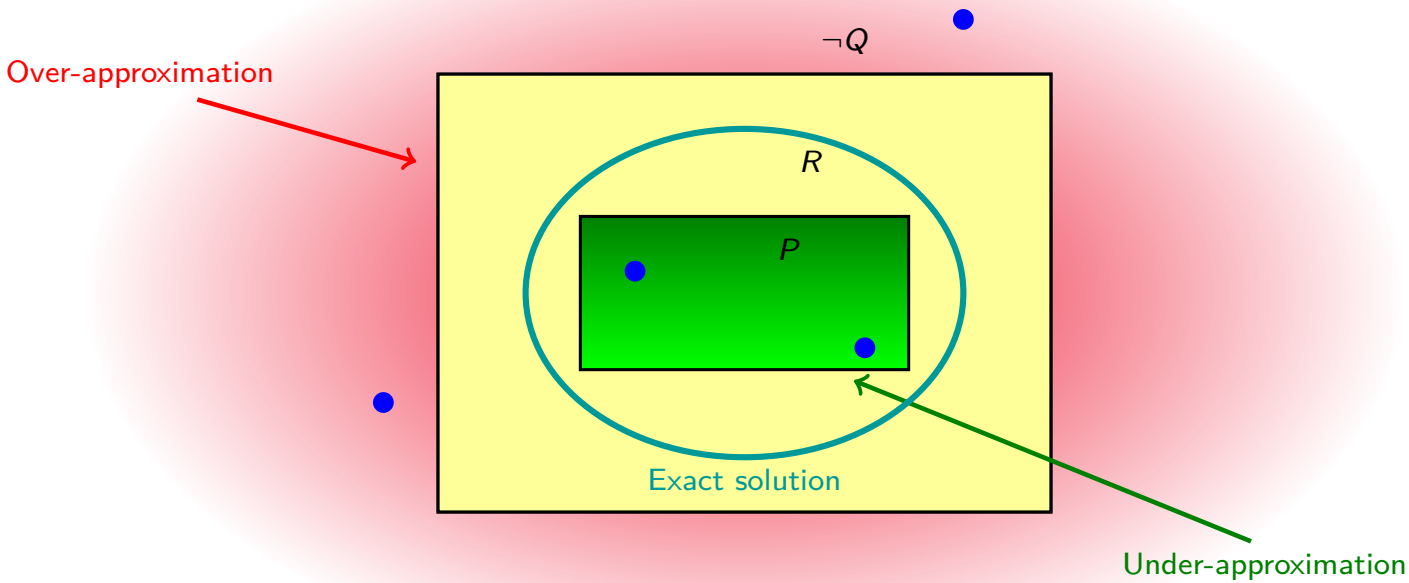

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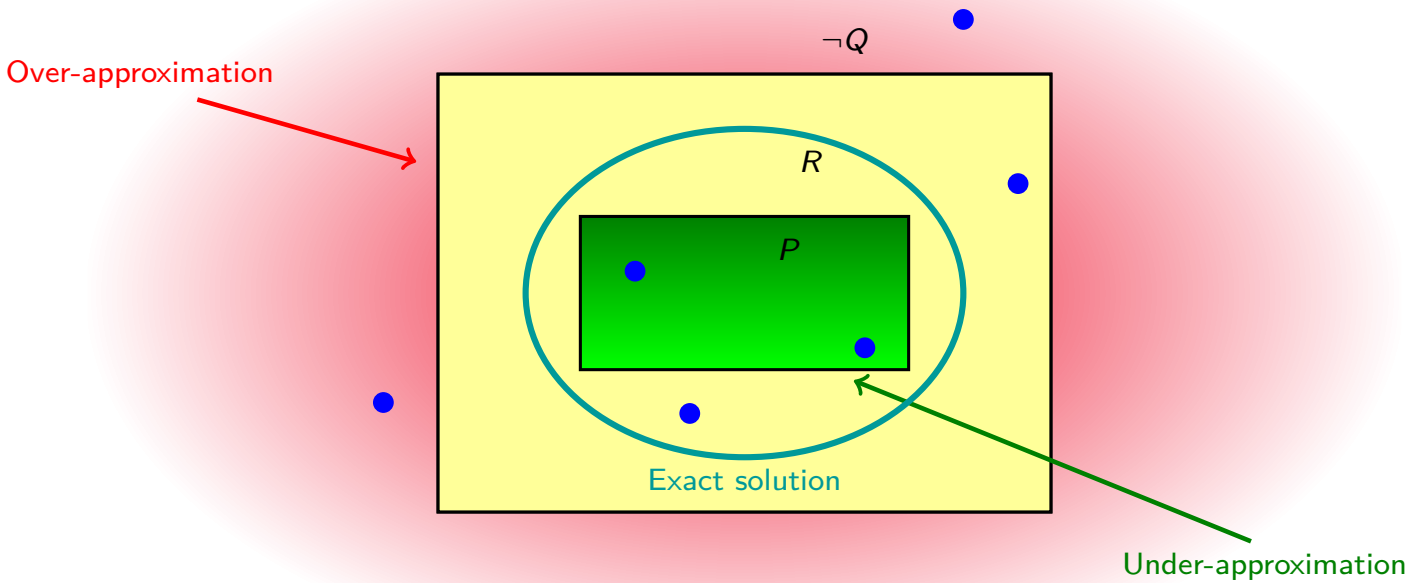

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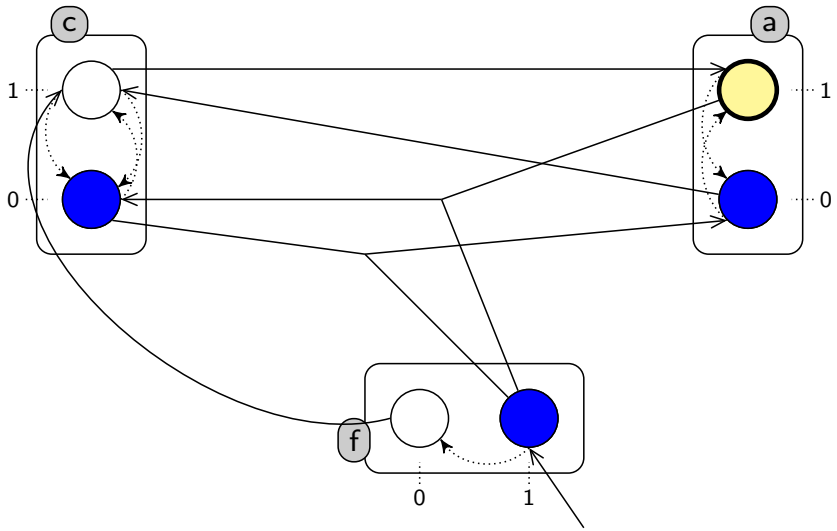

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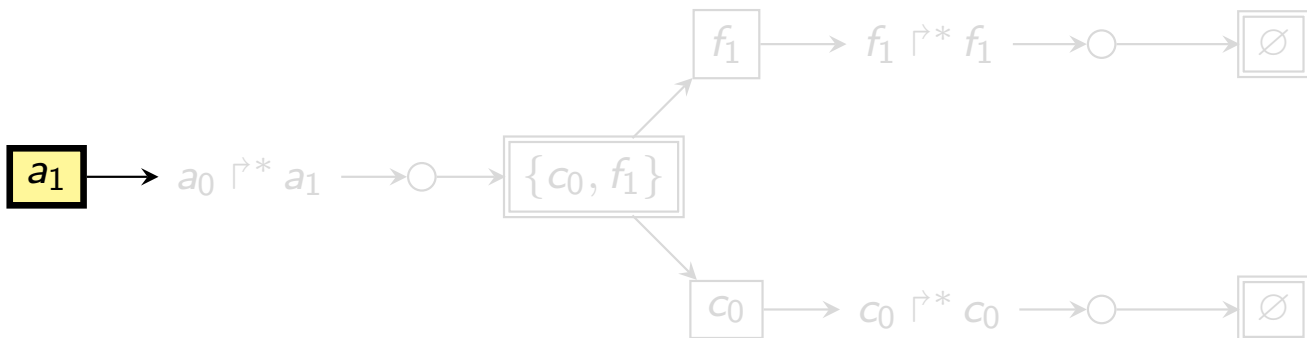

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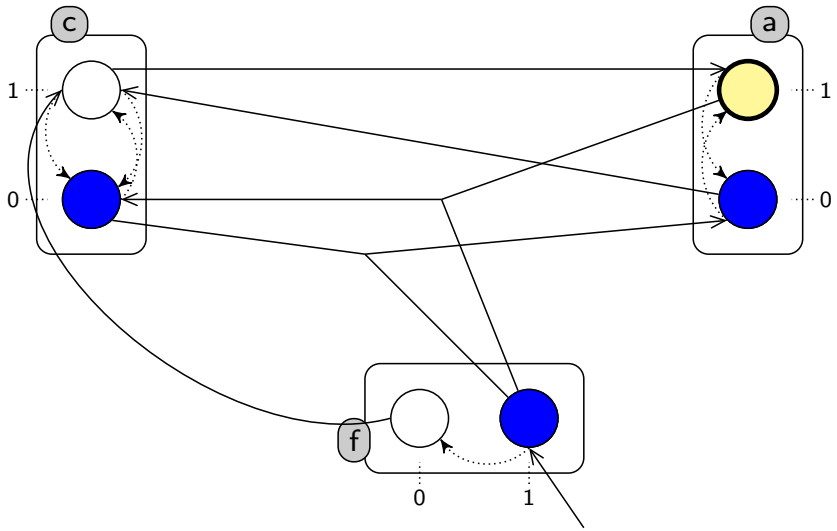

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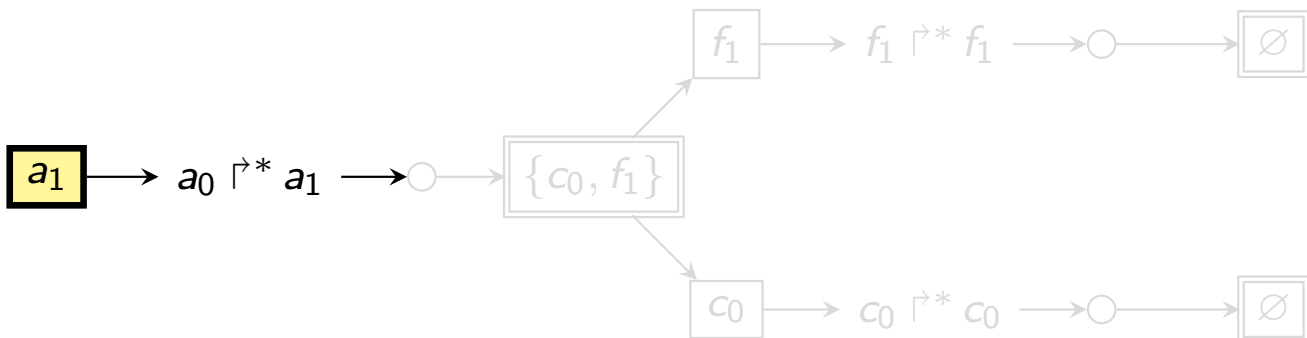

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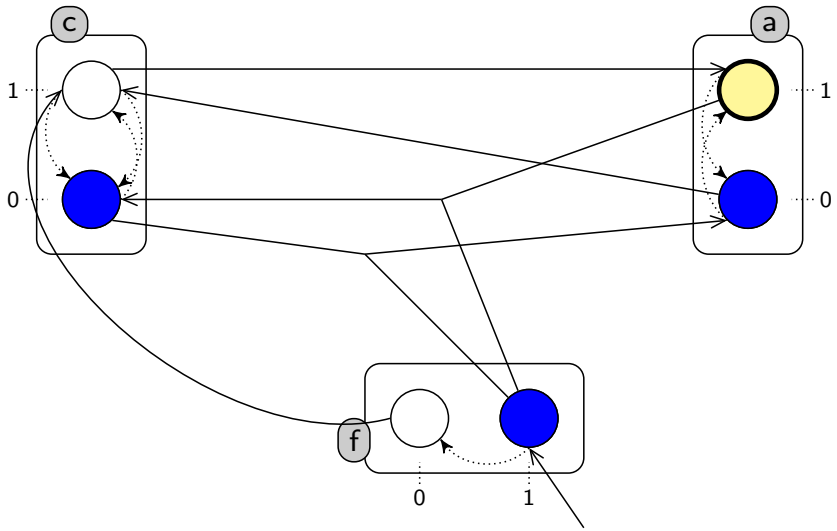

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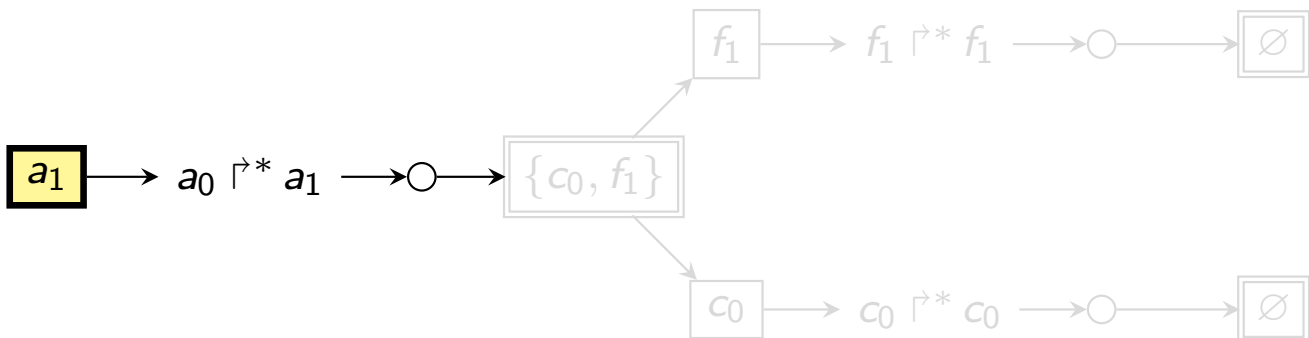

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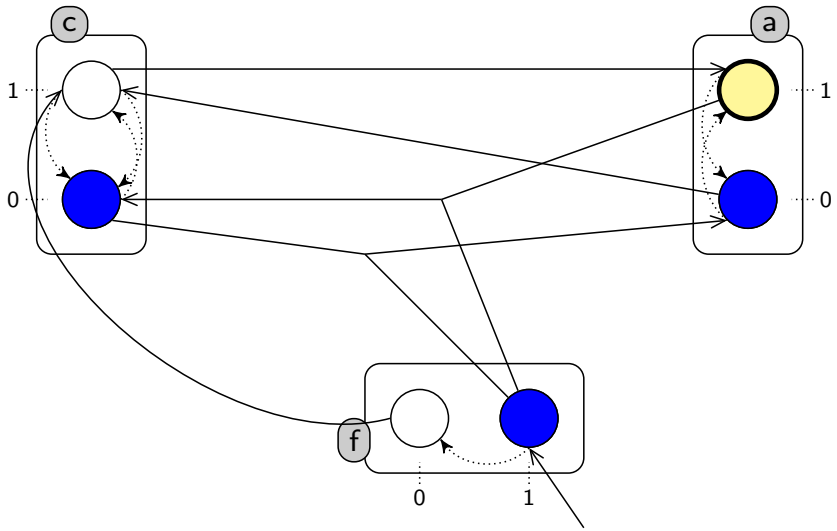

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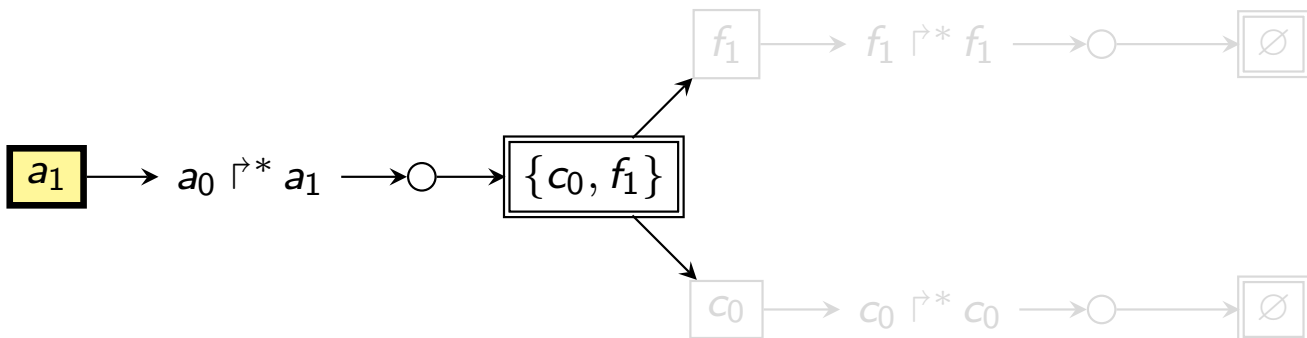

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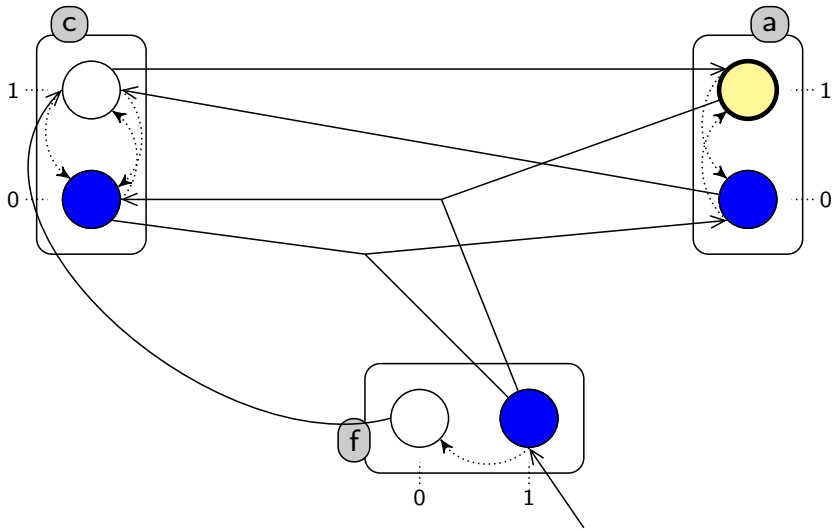

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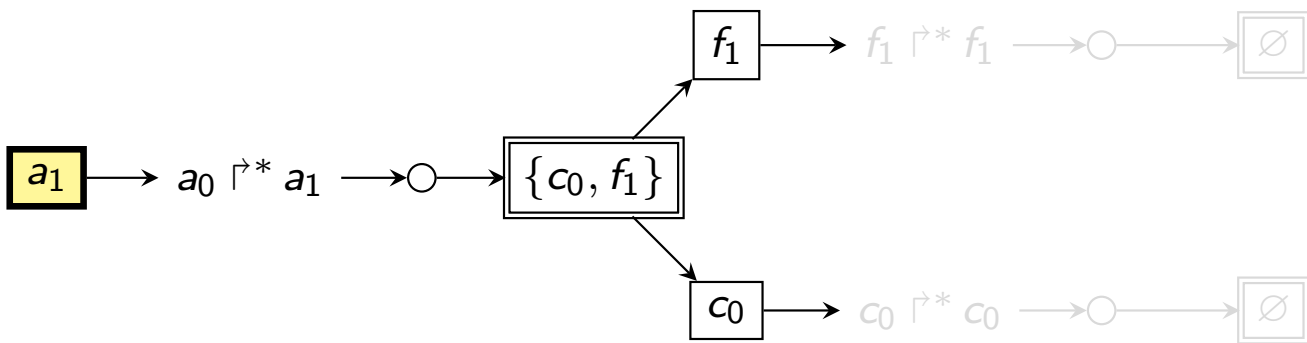

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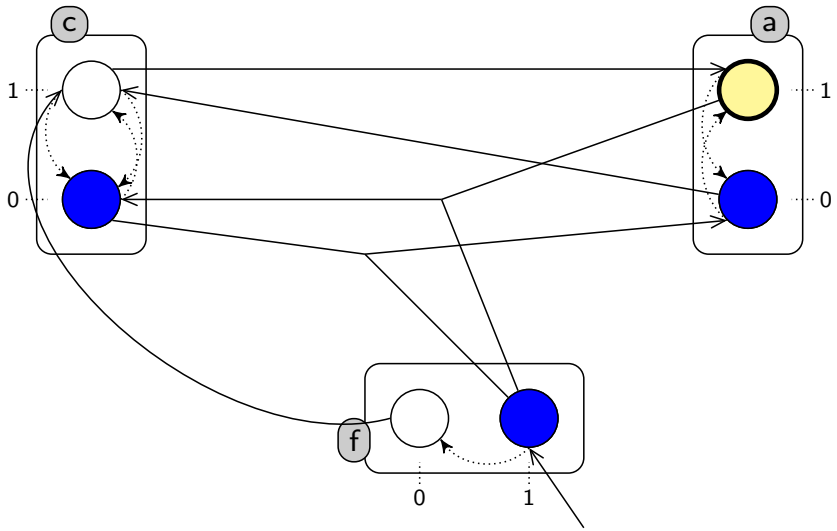

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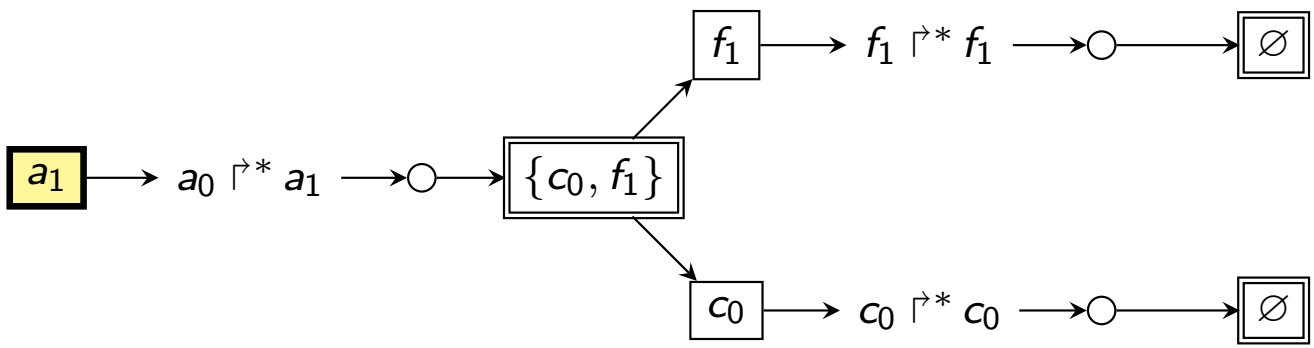

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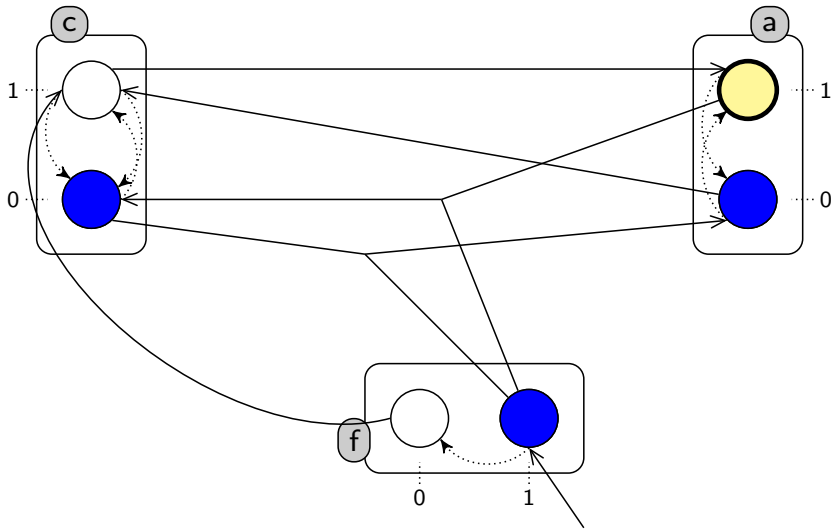

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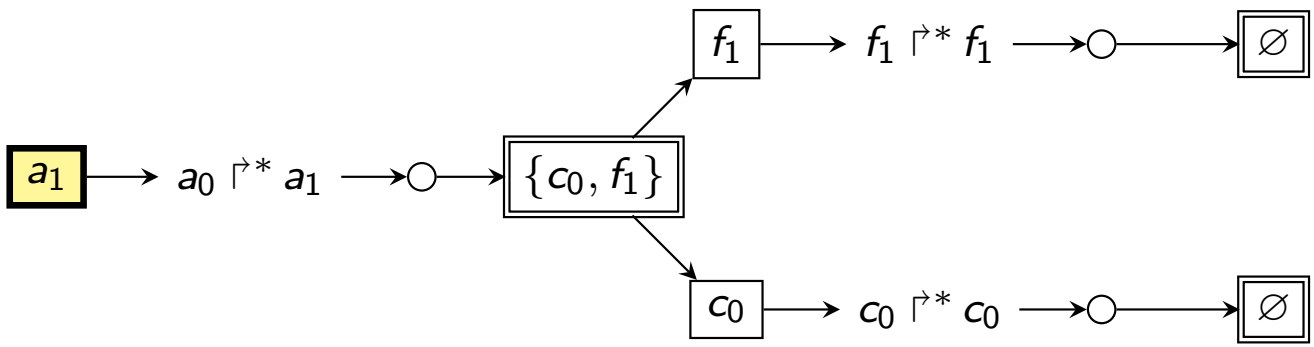

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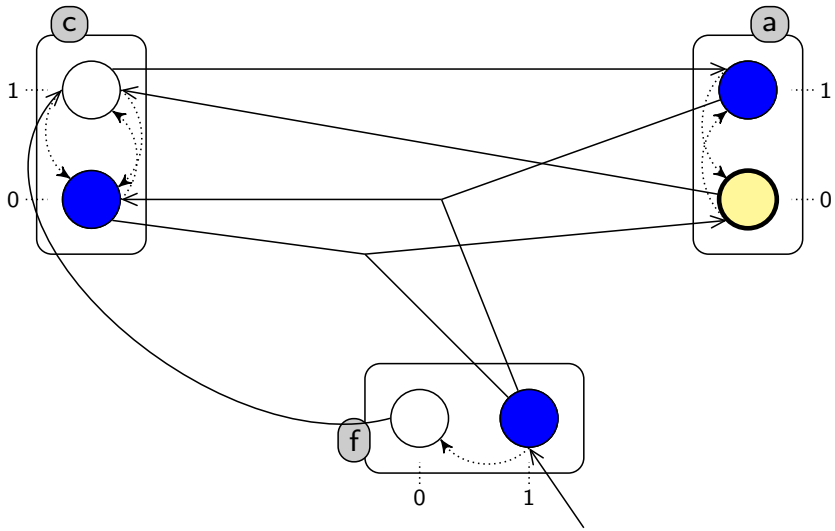

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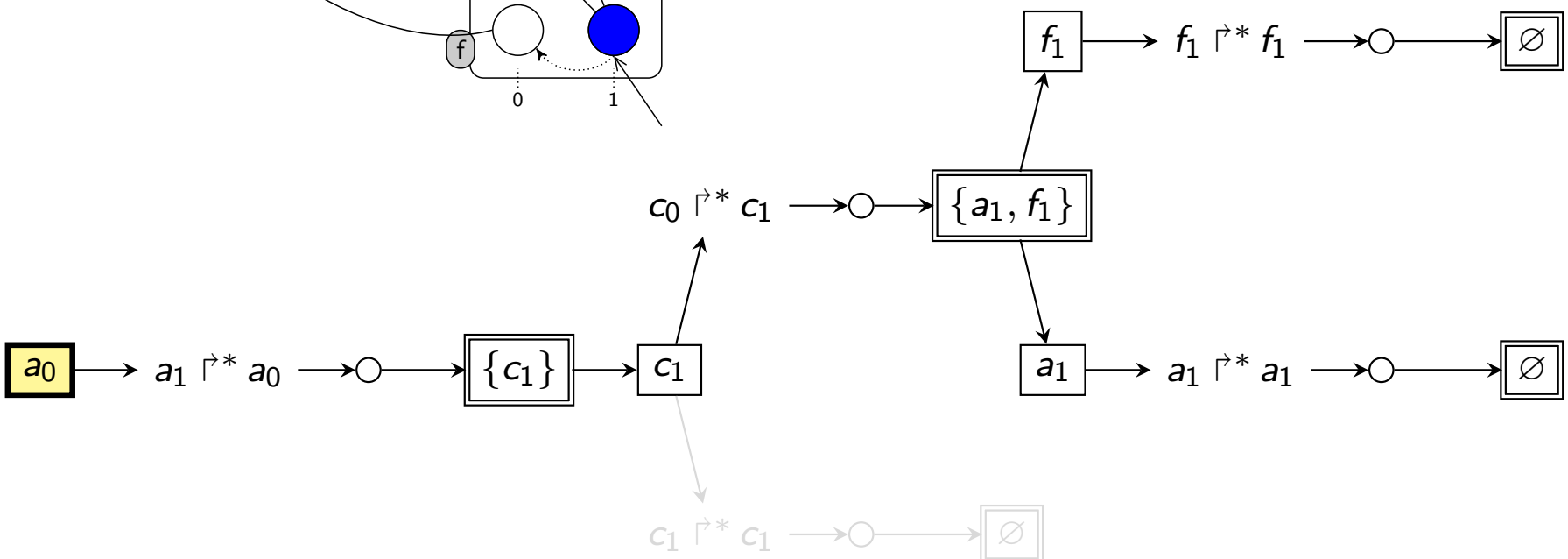

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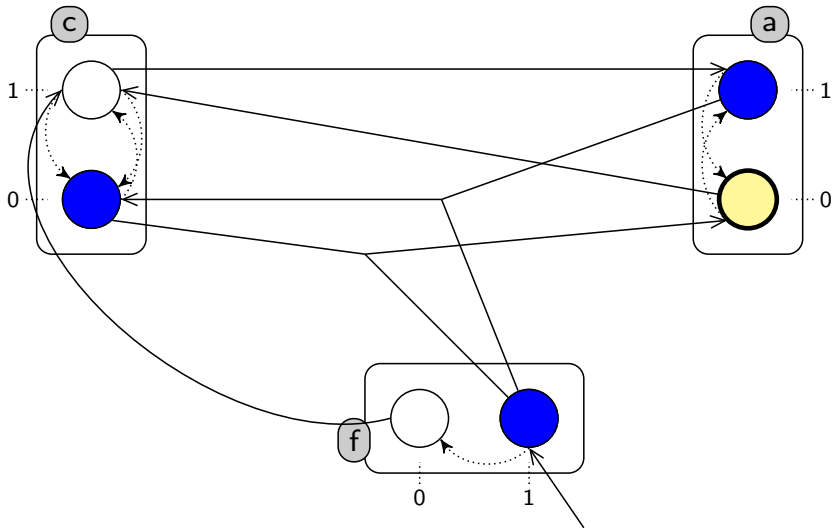

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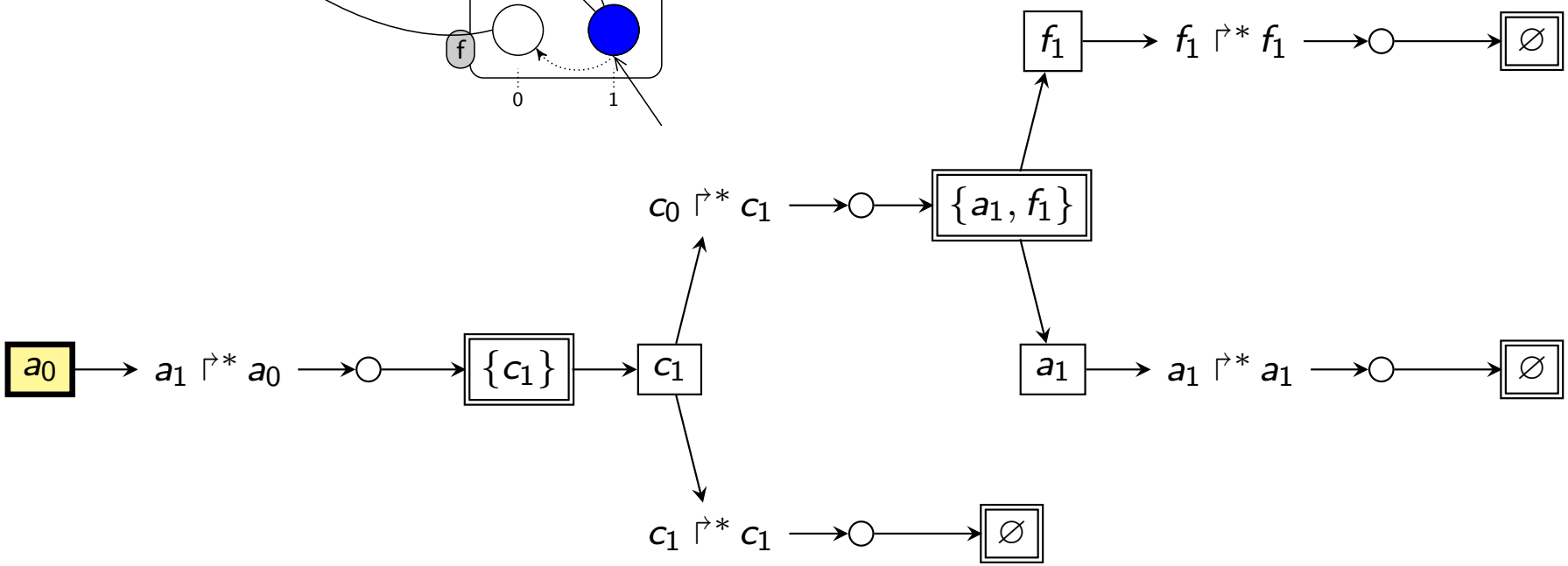

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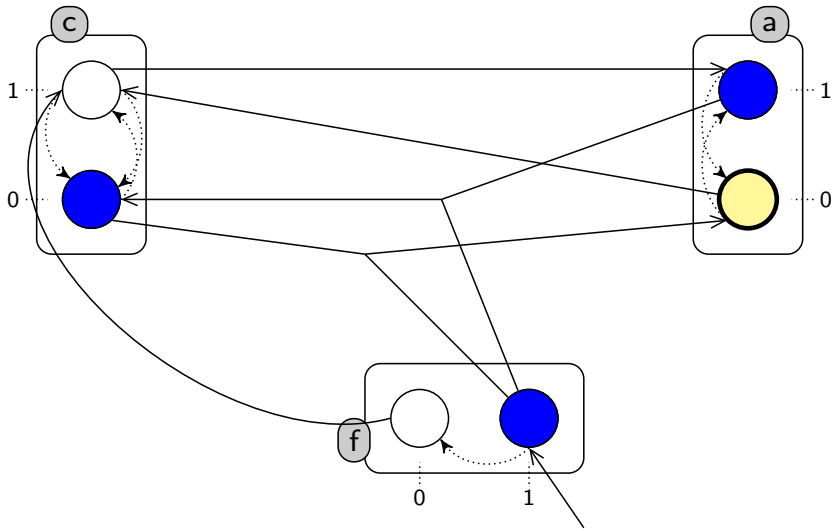

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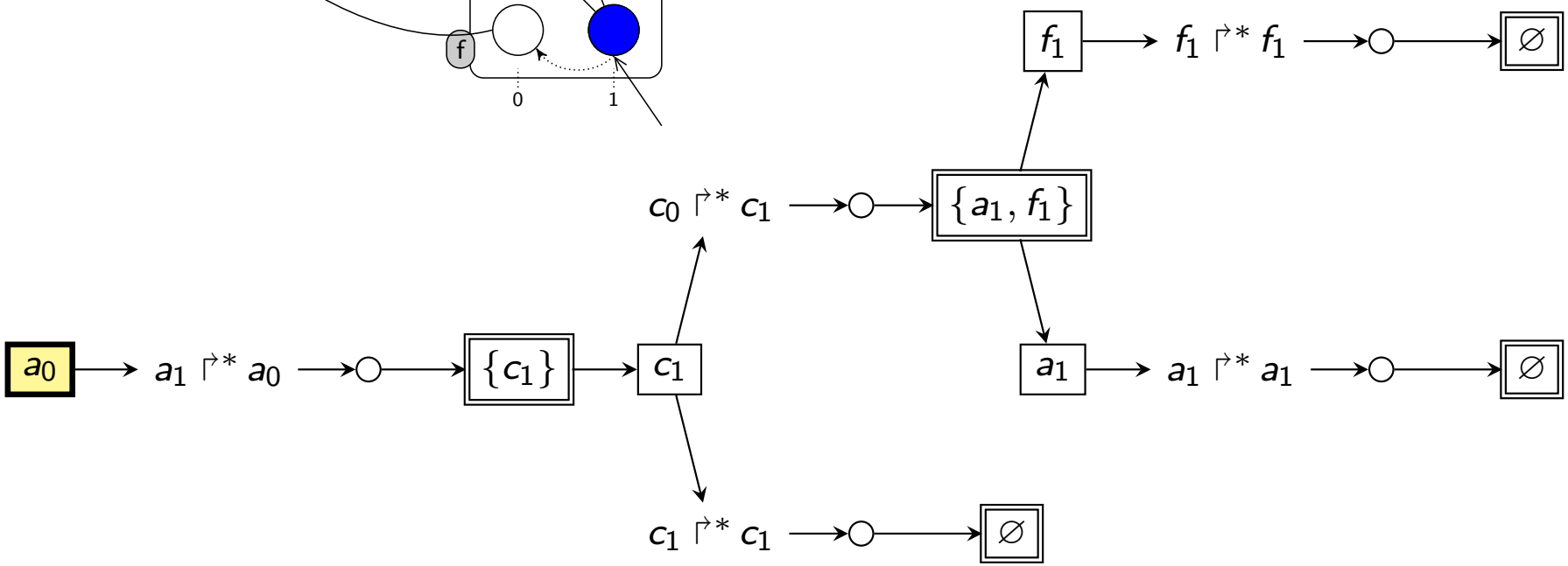

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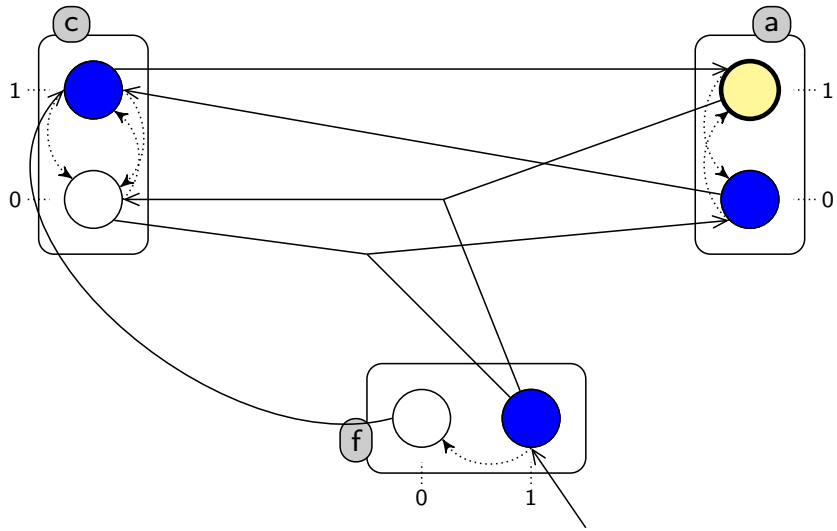

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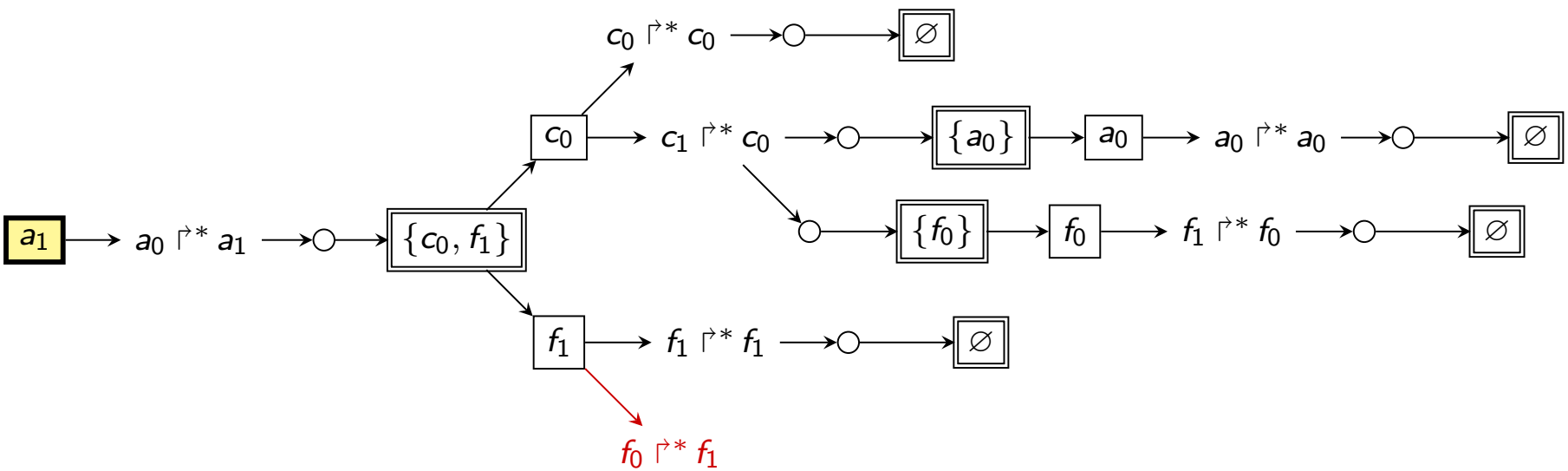

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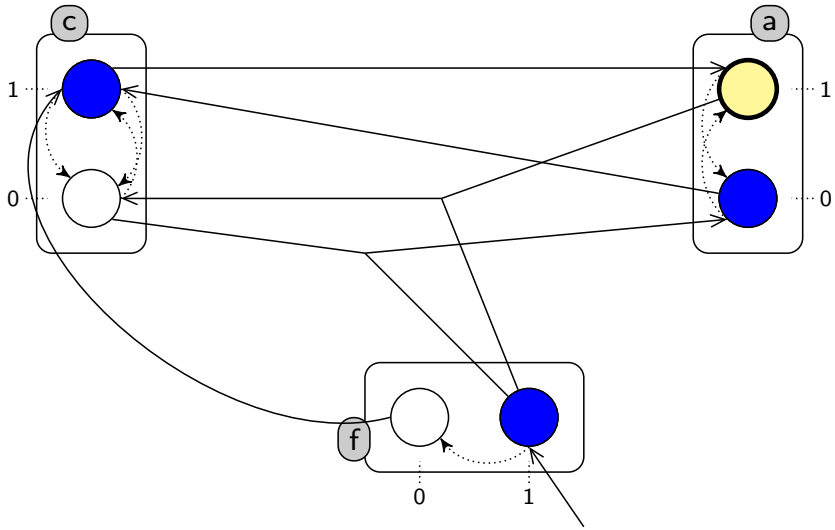

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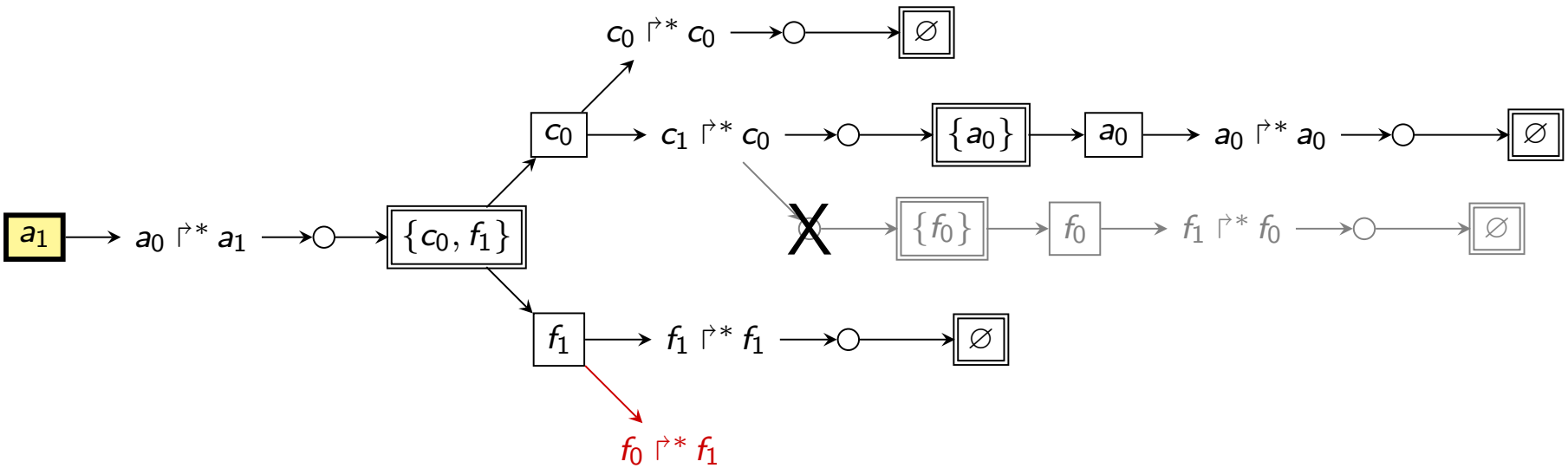

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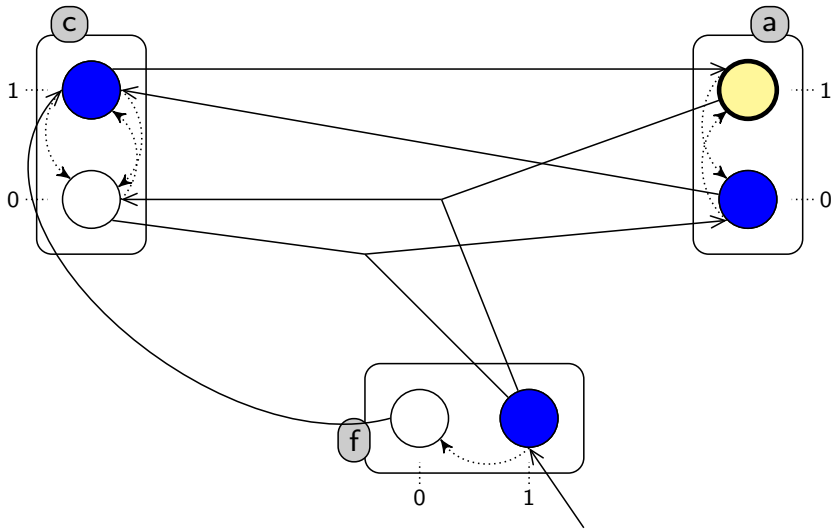

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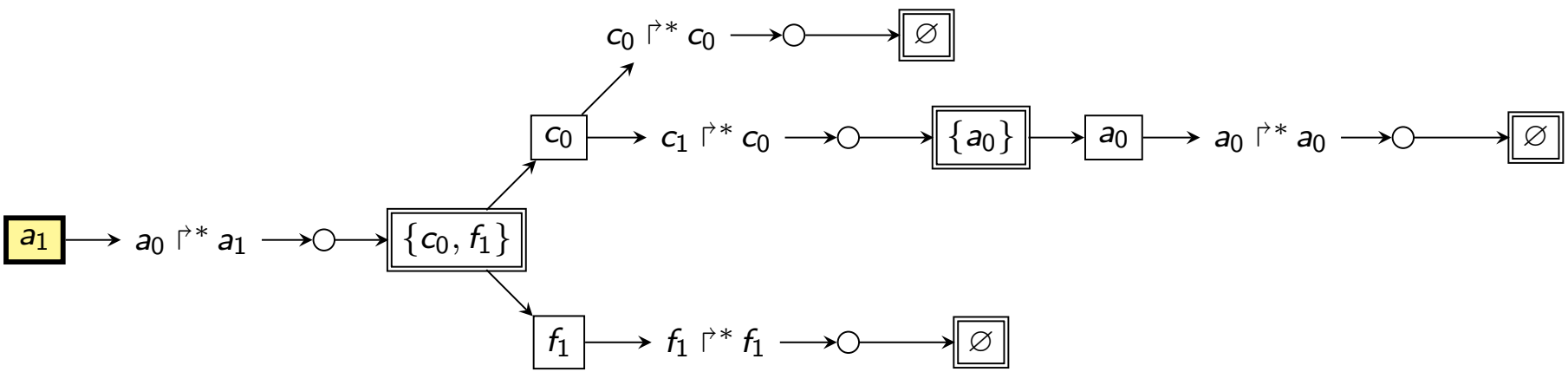

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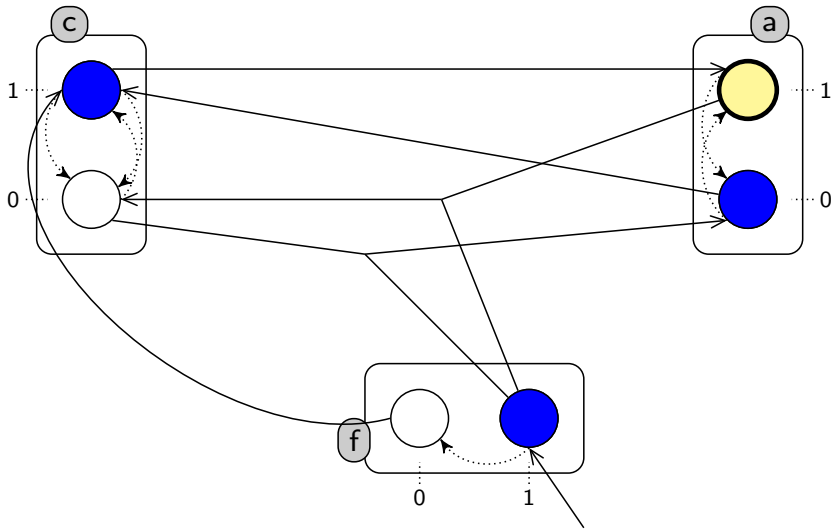

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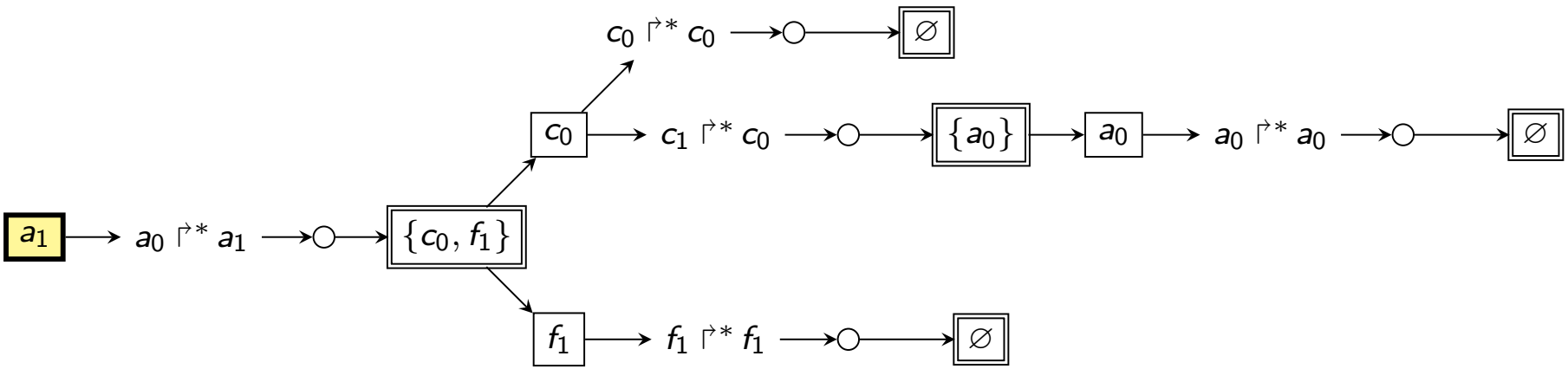

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Implementation of the Abstract Interpretation

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]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga *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)
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Bibliography

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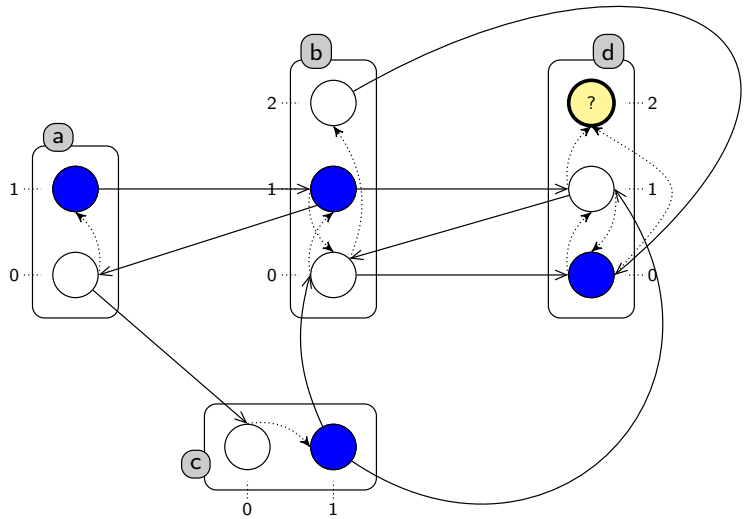
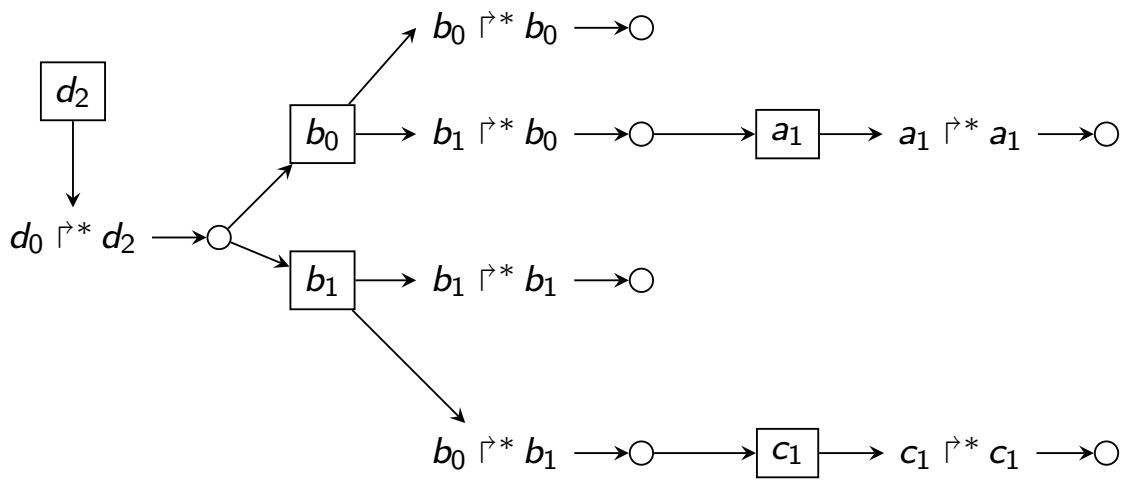
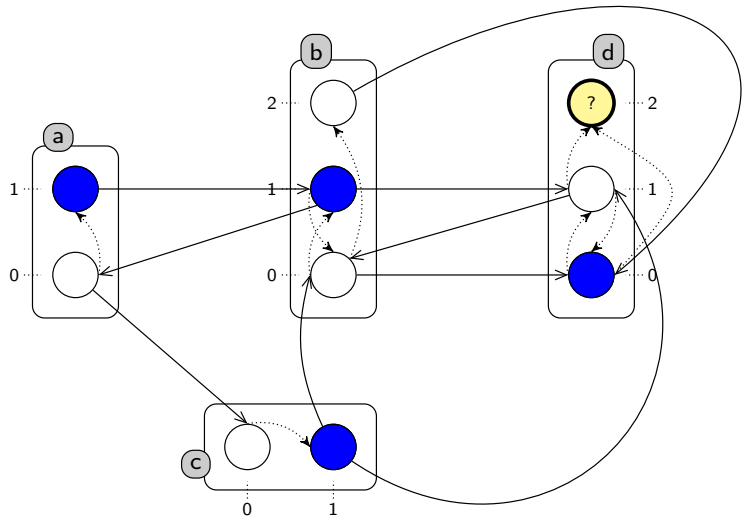
Under-approximation





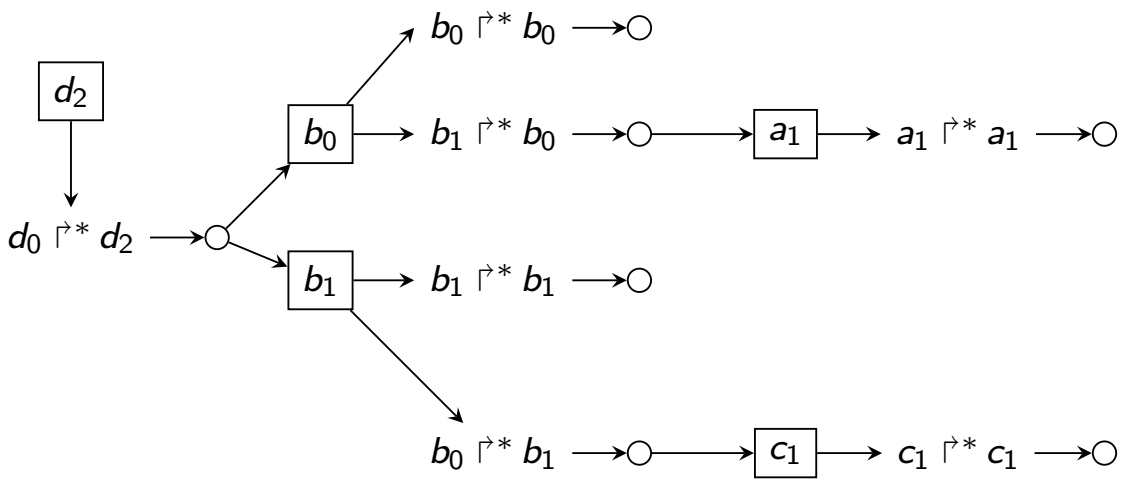
d_2	Required process
$d_0 \Gamma^* d_2$	Objective
○	Solution to an objective



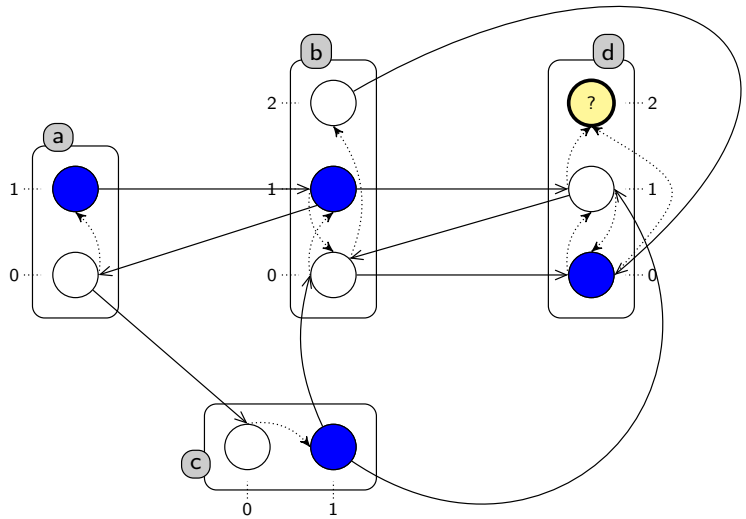
Under-approximation

Sufficient condition:

- no cycle
- each objective has a solution



d_2	Required process
$d_0 \lceil^* d_2$	Objective
○	Solution to an objective

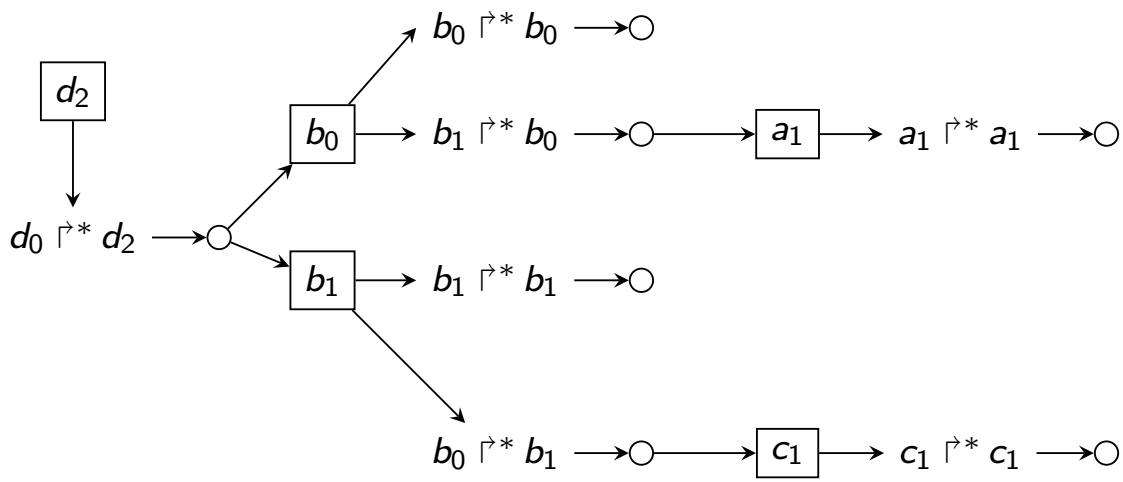


Under-approximation

Sufficient condition:

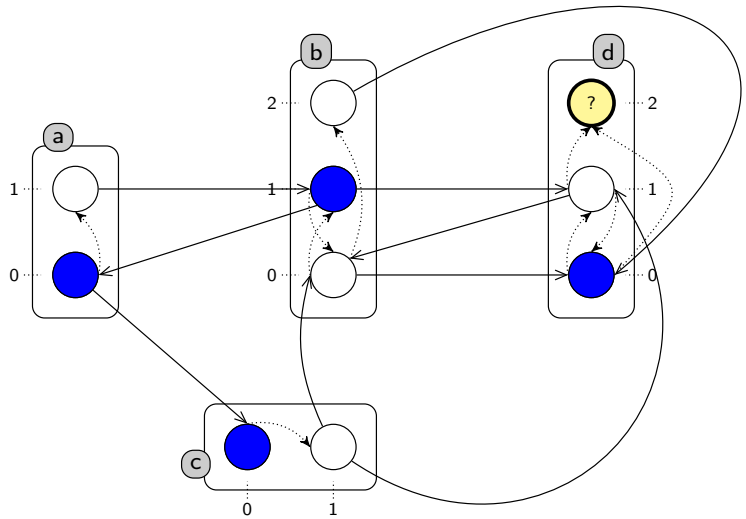
- no cycle
- each objective has a solution

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



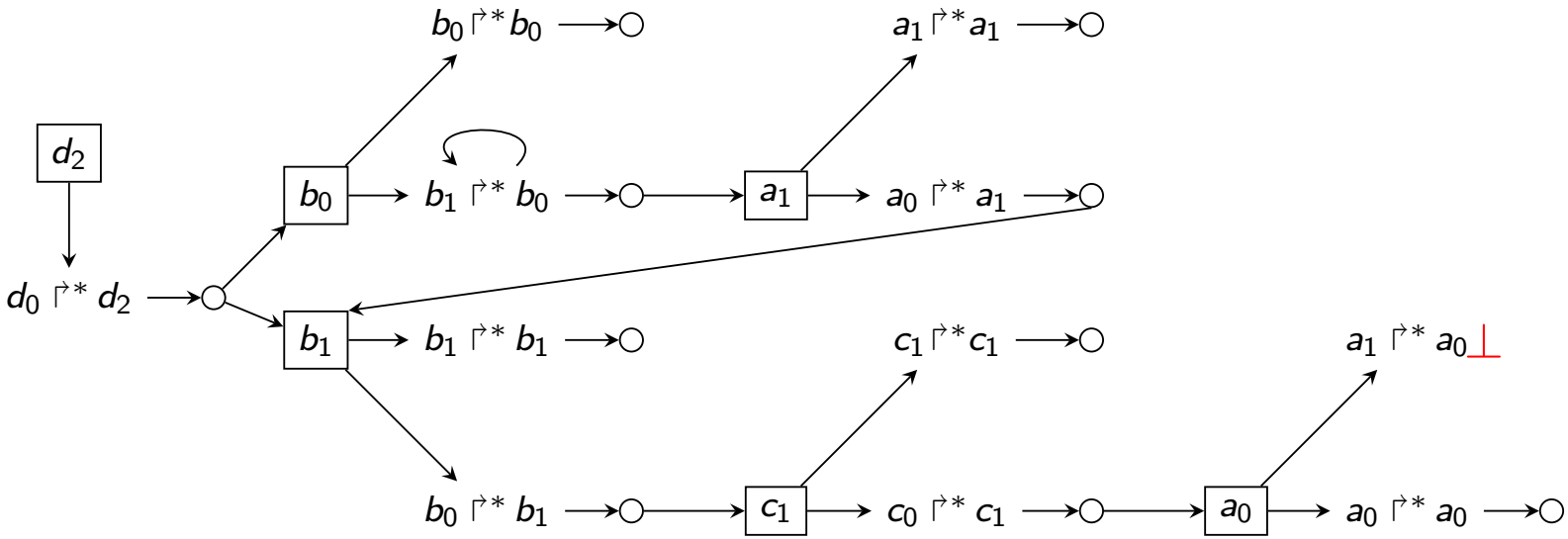
$\boxed{d_2}$	Required process
$d_0 \lceil^* d_2$	Objective
○	Solution to an objective

Under-approximation

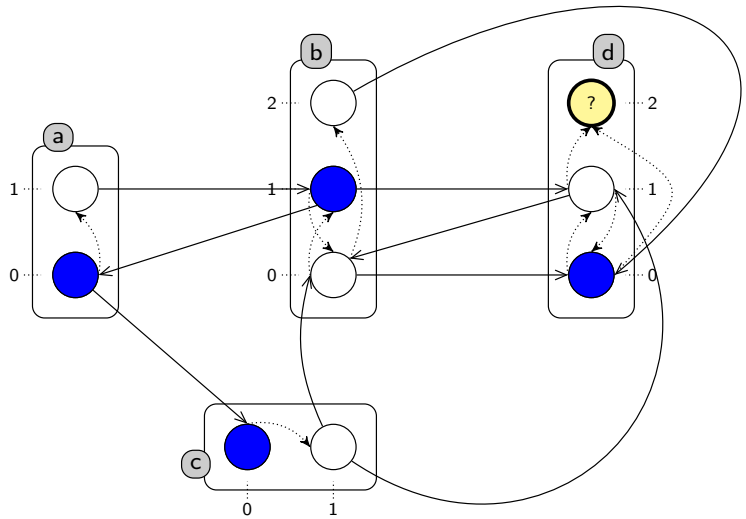


Sufficient condition:

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



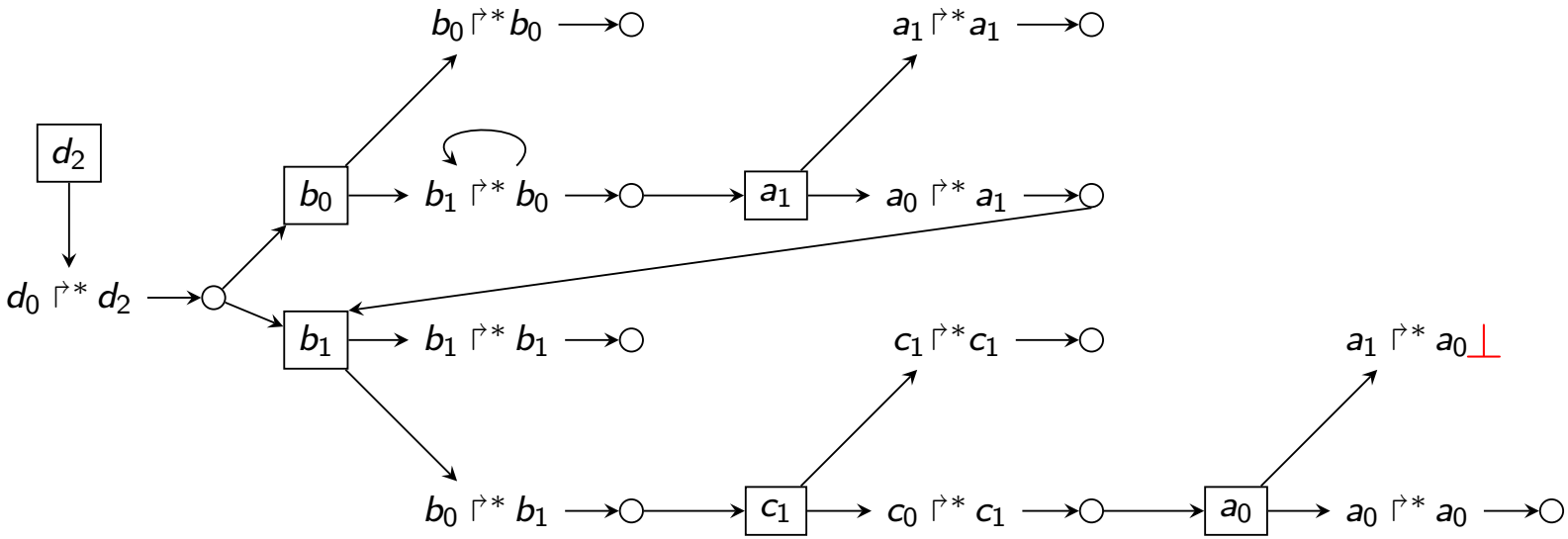
Under-approximation



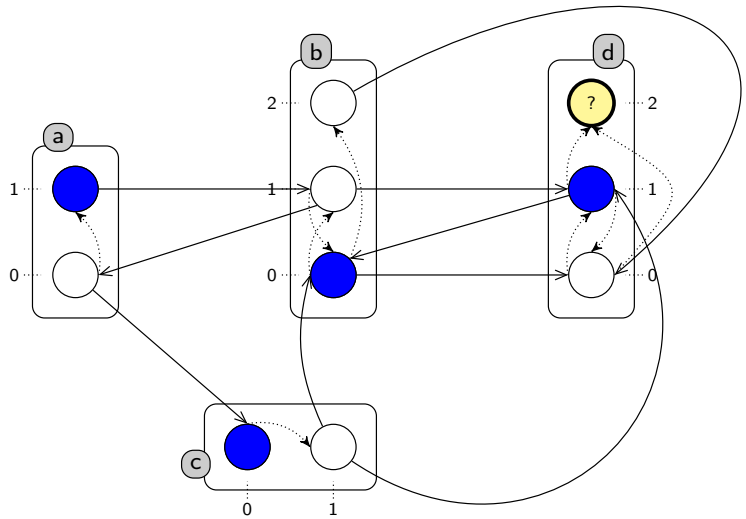
Sufficient condition:

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

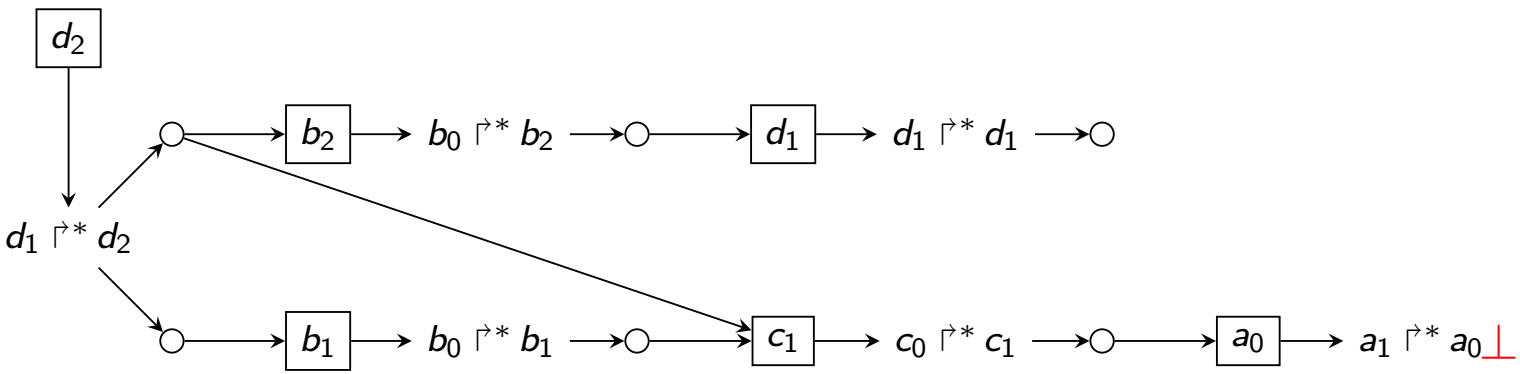
P is **false** $\Rightarrow$ **Inconclusive**

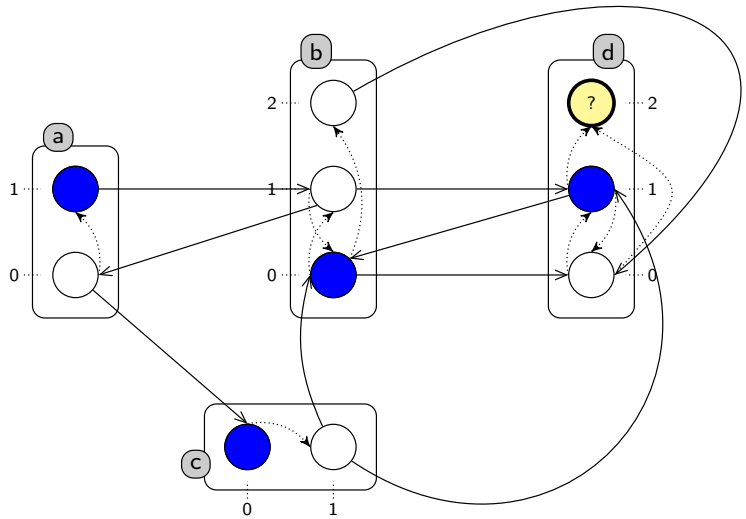


Over-approximation



Necessary condition:



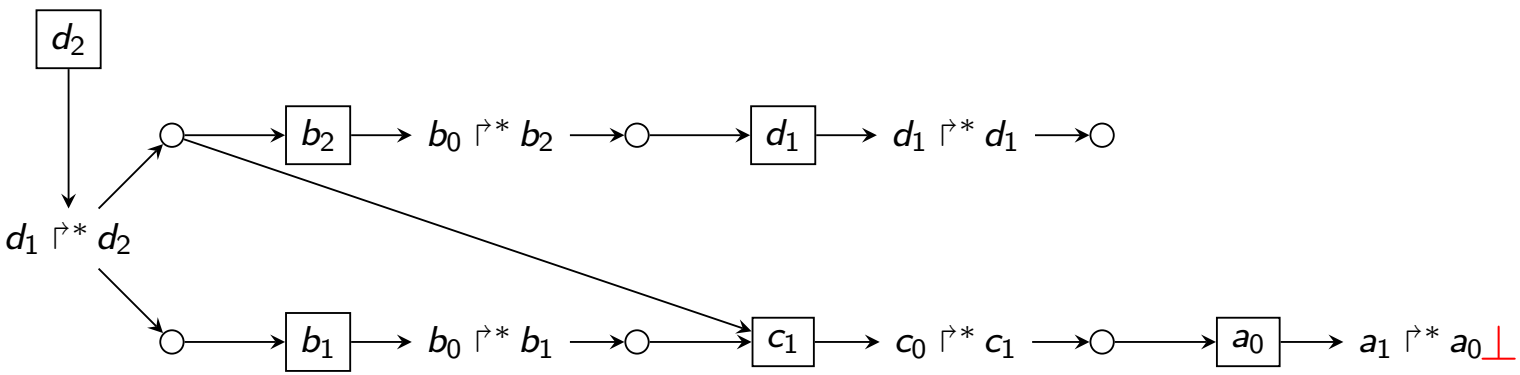


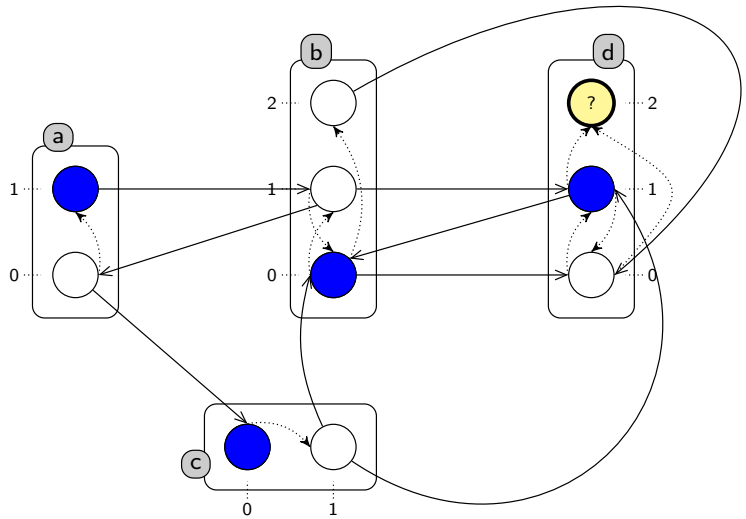
Over-approximation

Necessary condition:

There exists a traversal with no cycle

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





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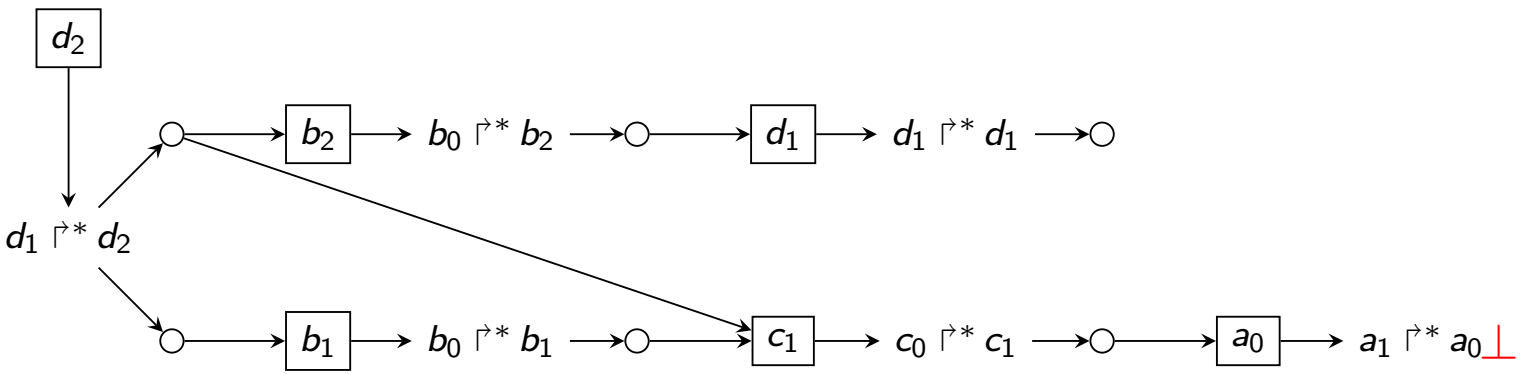
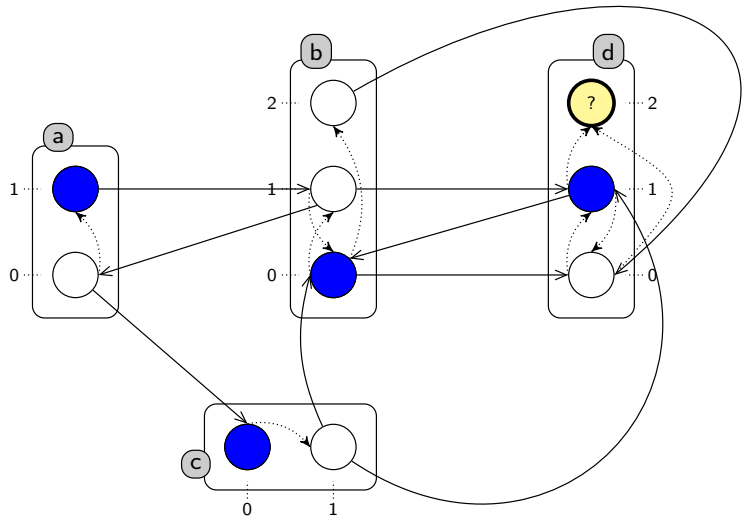




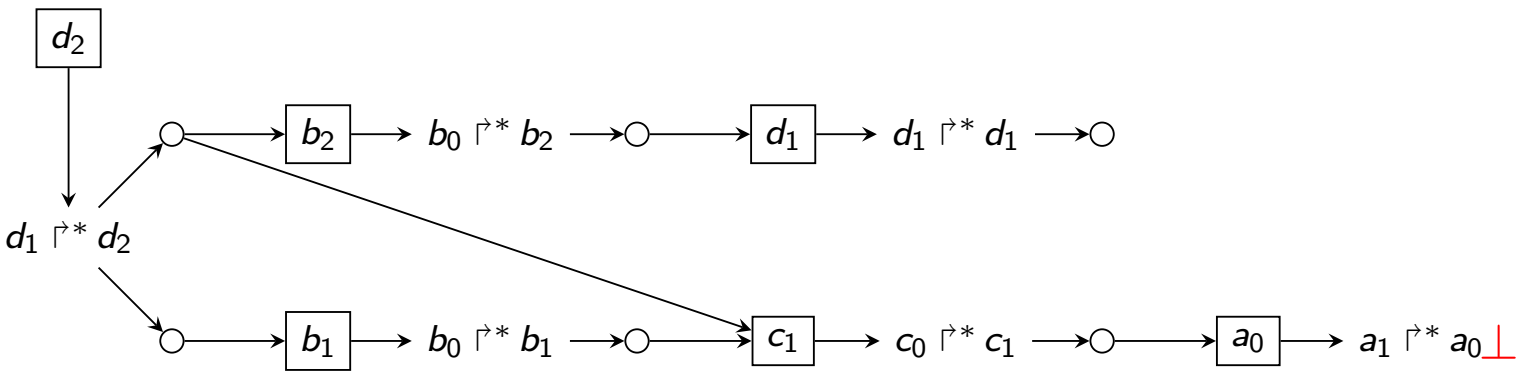
Over-approximation

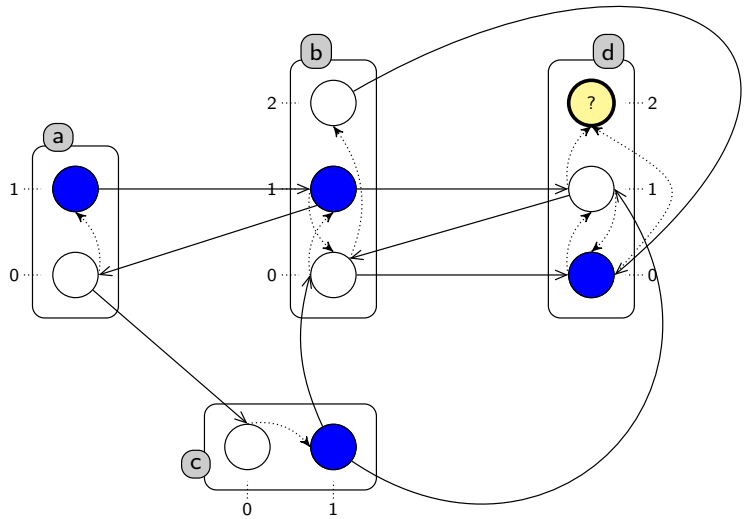
Necessary condition:

~~There exists a traversal~~ with no cycle

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

Q is **false** $\Rightarrow$ R is **false**





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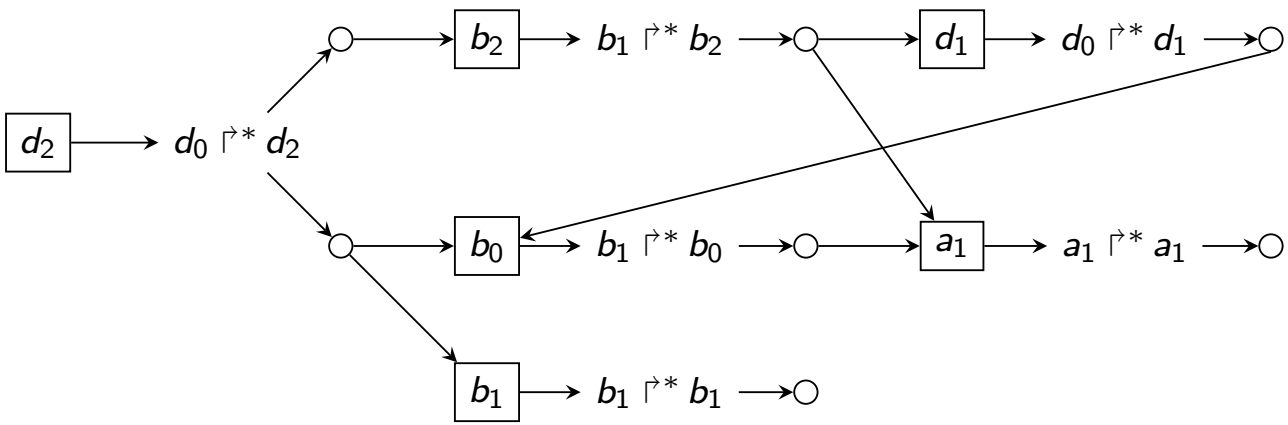

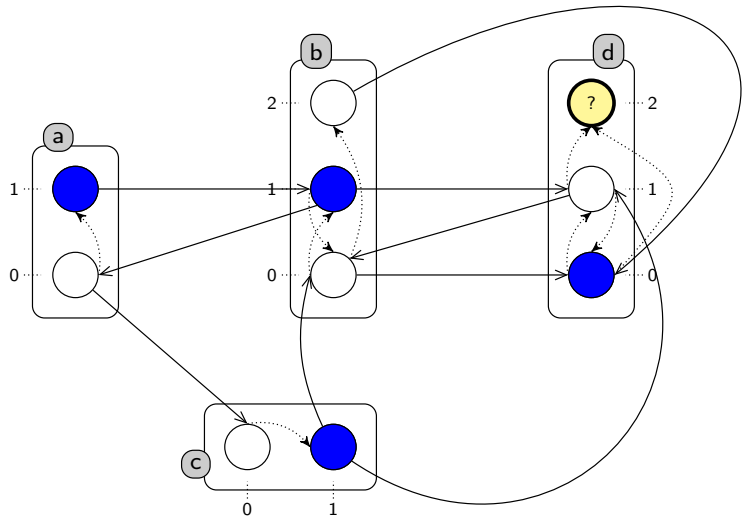

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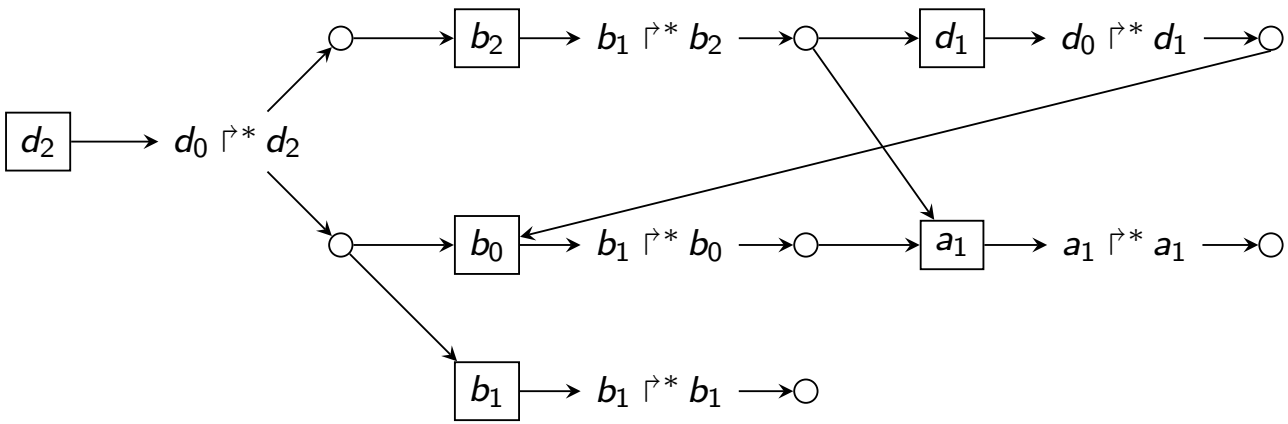
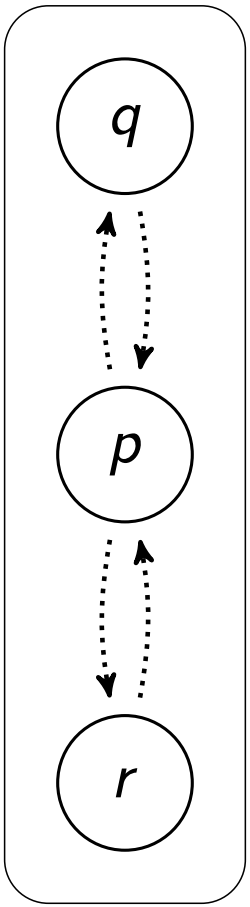
- process → follow **all** objectives

R is true ⇒ Inconclusive



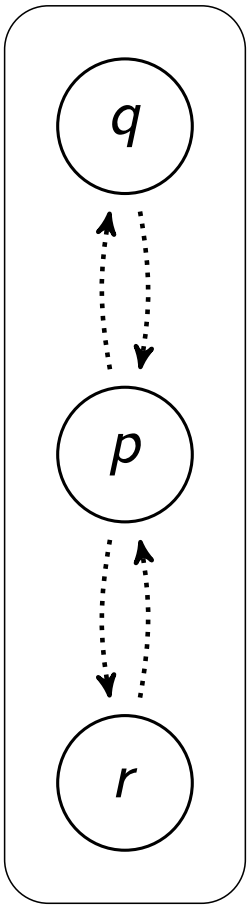
Examples with Modal μ-calculus



No tokens: only one evolution is studied

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

Examples with Modal μ-calculus



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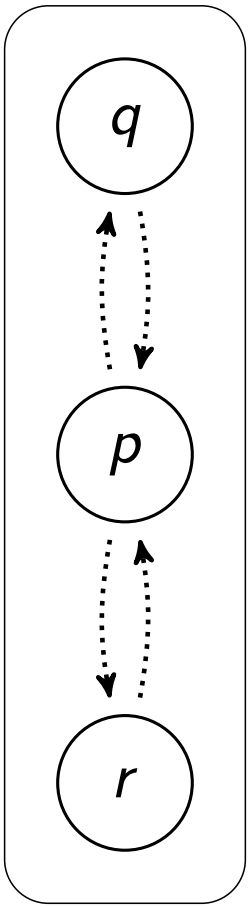

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Possible future ("may")

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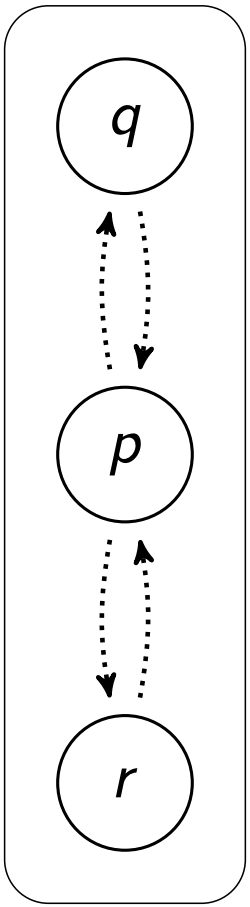

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Necessary future (“must”)

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

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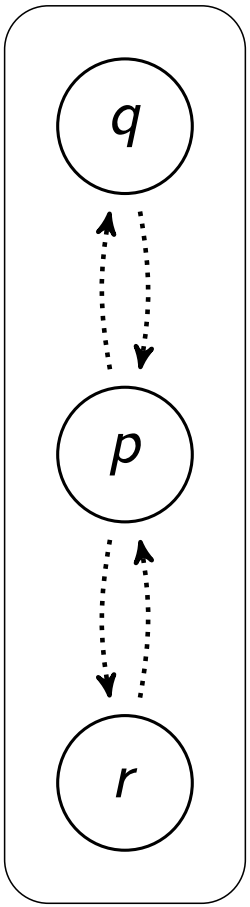

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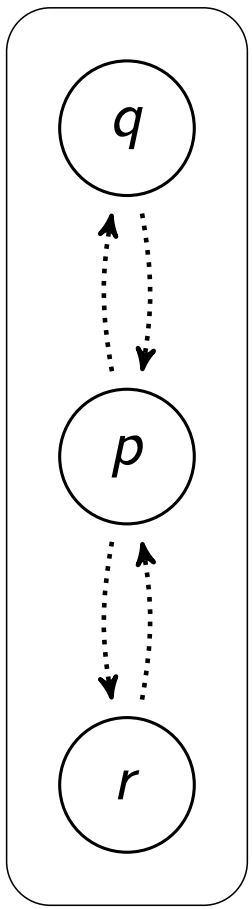
Examples with Polyadic μ-calculus

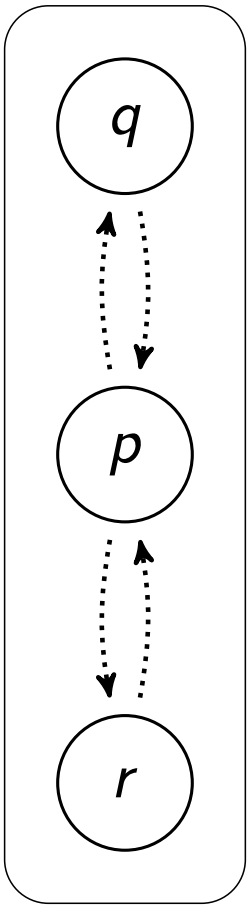


Atomic property (p, q, r)

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

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

Examples with Polyadic μ-calculus



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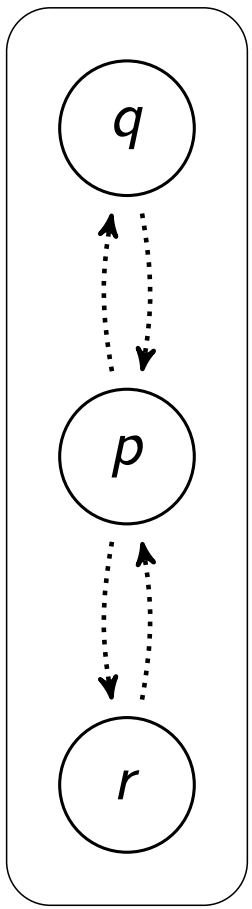
Token affectation ($i \leftarrow j$)

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

Examples with Polyadic μ-calculus



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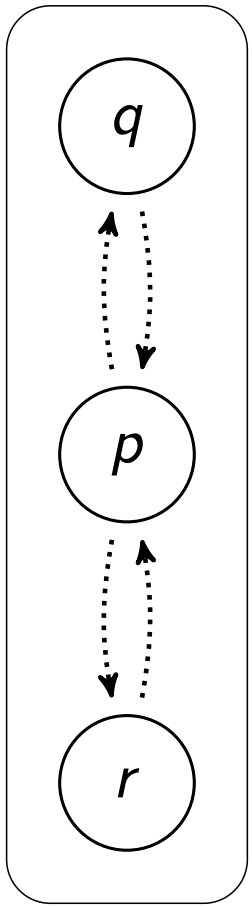

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$[\![\Diamond_1\ q]\!] = \{(p, p); (p, q); (p, r)\}$

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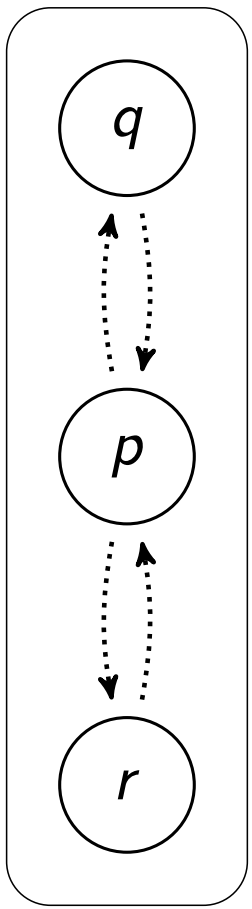

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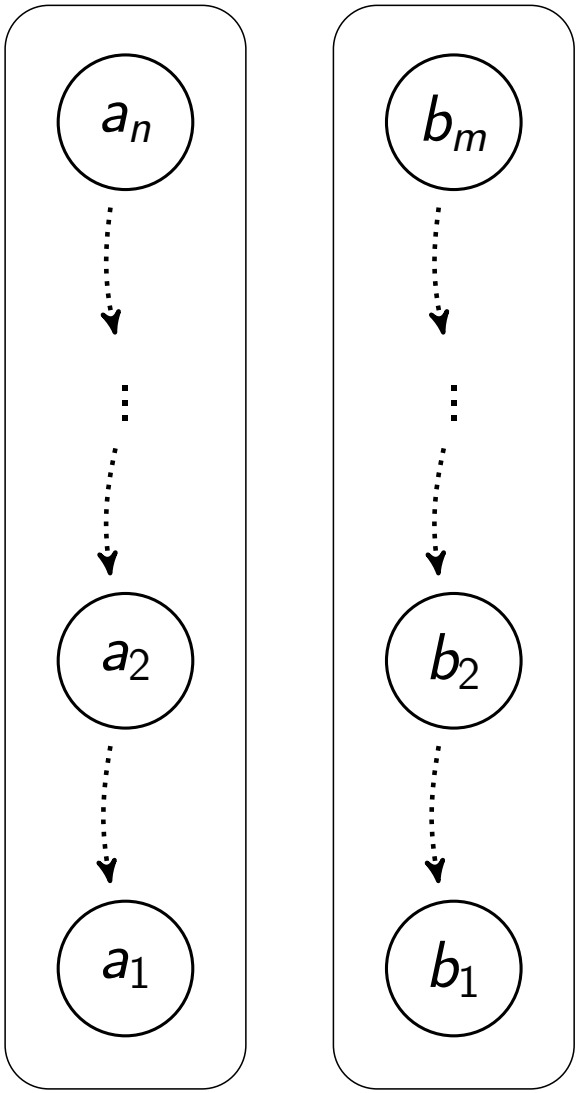
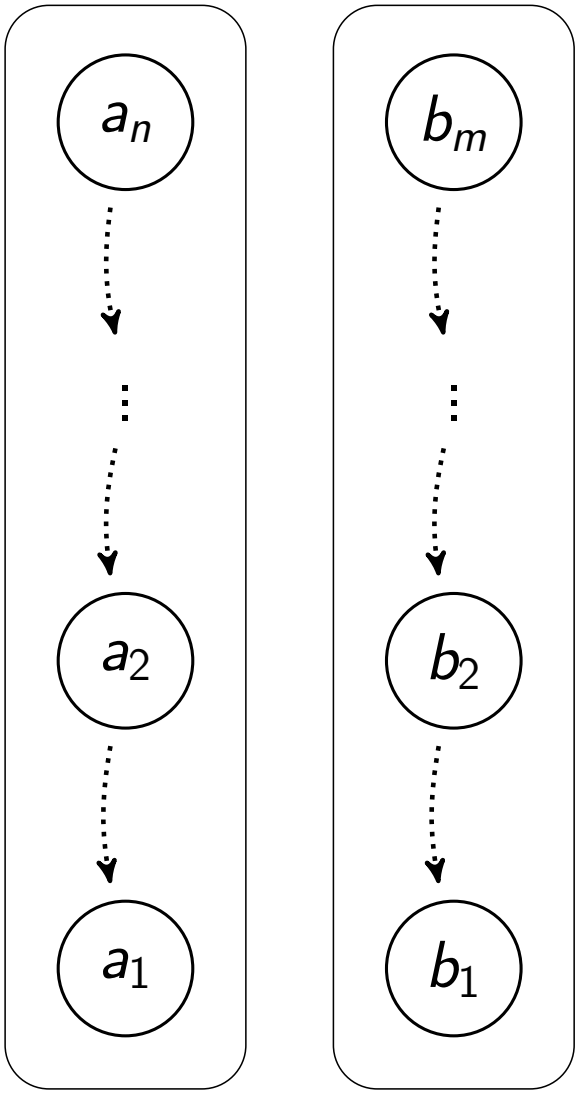


Least fixed point (μ)

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

Examples with Polyadic μ-calculus



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Iterations:

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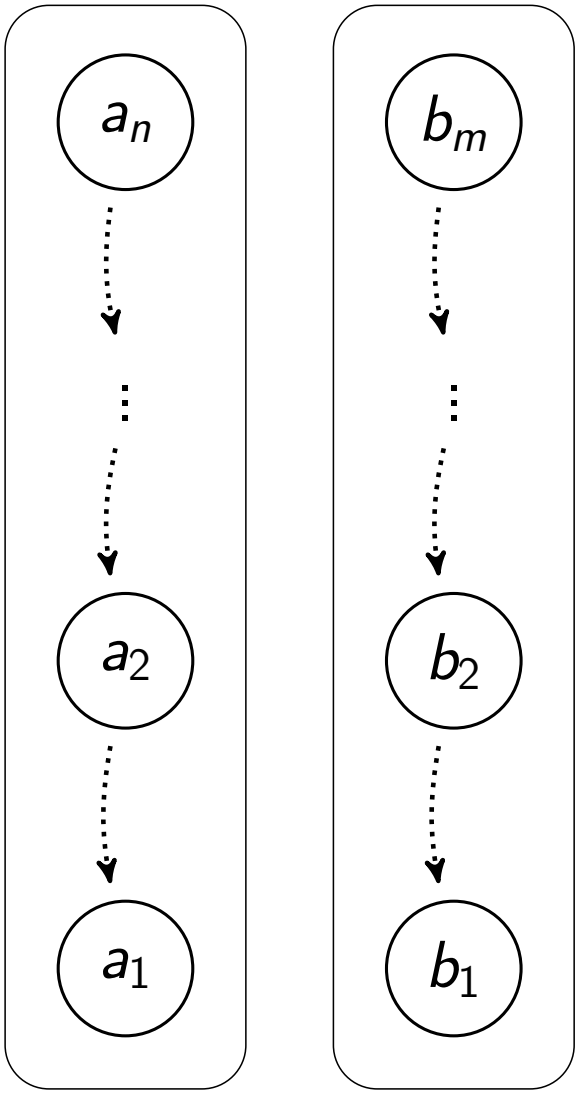
$$\vdots$$

Examples with Polyadic μ-calculus



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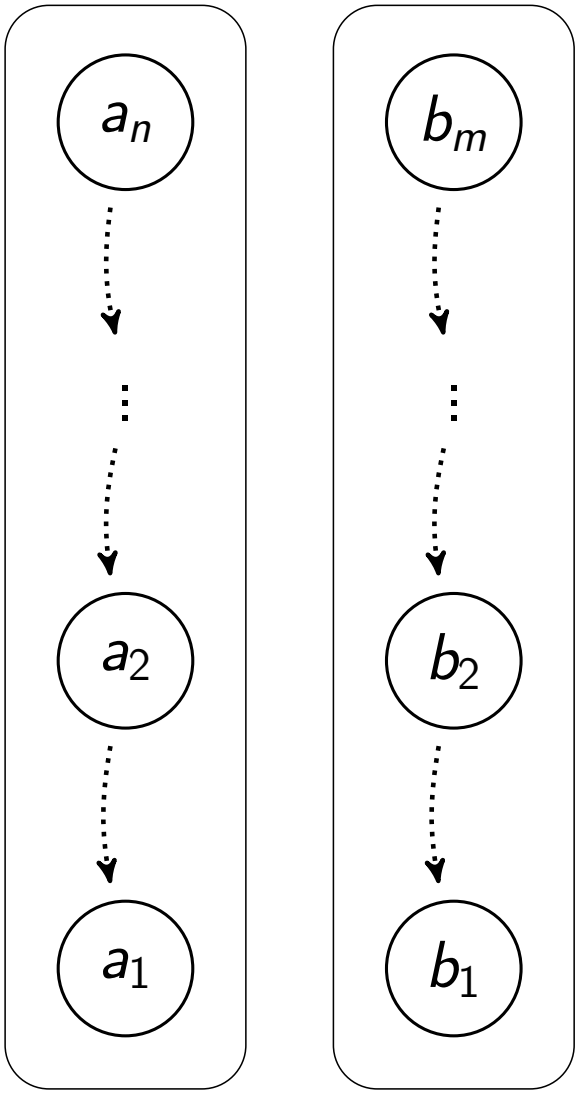
Generalization:

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

Examples with Polyadic μ-calculus



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Idea: use one (or n) token per automata