Advances in Systems and Synthetic Biology
Modelling Complex Biological Systems in the Context of Genomics
Thematic Research School 2013

— Student workshop —

Introduction to the Process Hitting and inference of its underlying Biological Regulatory Network

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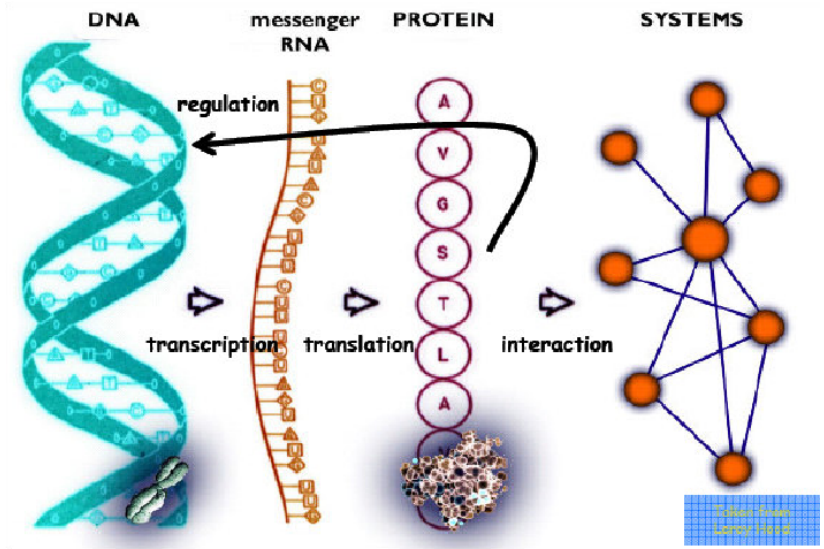
Joint work with:
Loïc PAULEVÉ, Katsumi INOUE, Morgan MAGNIN, Olivier ROUX

Context and Aims

MeForBio team: Algebraic modeling to study complex dynamical biological systems



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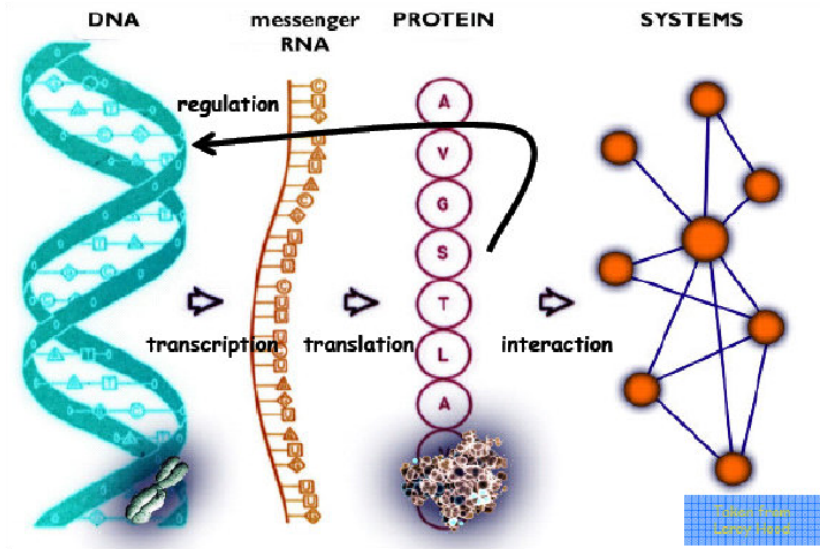
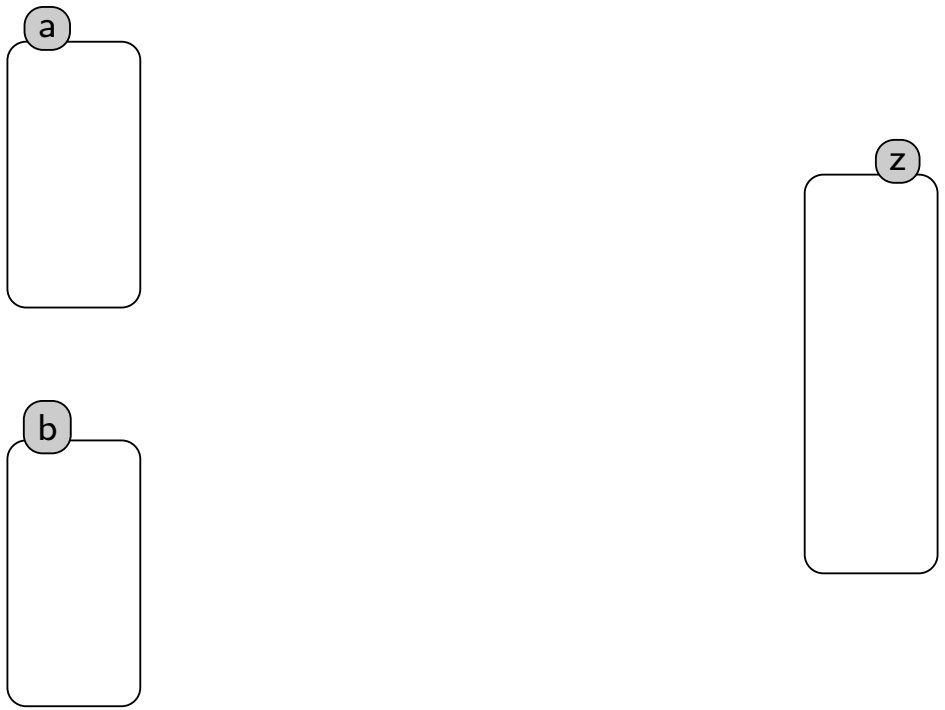


1) Two main models
   - Historical model: **Biological Regulatory Network (René Thomas)**
   - New developed model: **Process Hitting**

2) Allow efficient translation from Process Hitting to BRN

The Process Hitting modeling

[Paulevé, Magnin, Roux in Transactions on Computational Systems Biology, 2011]



Sorts: components a, b, z

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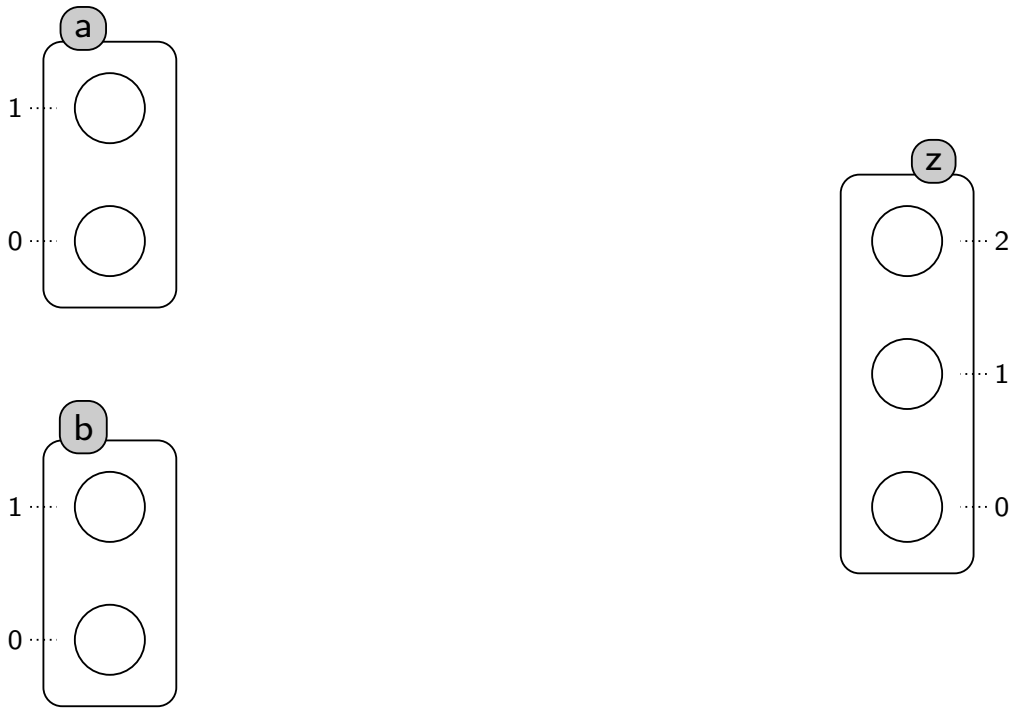

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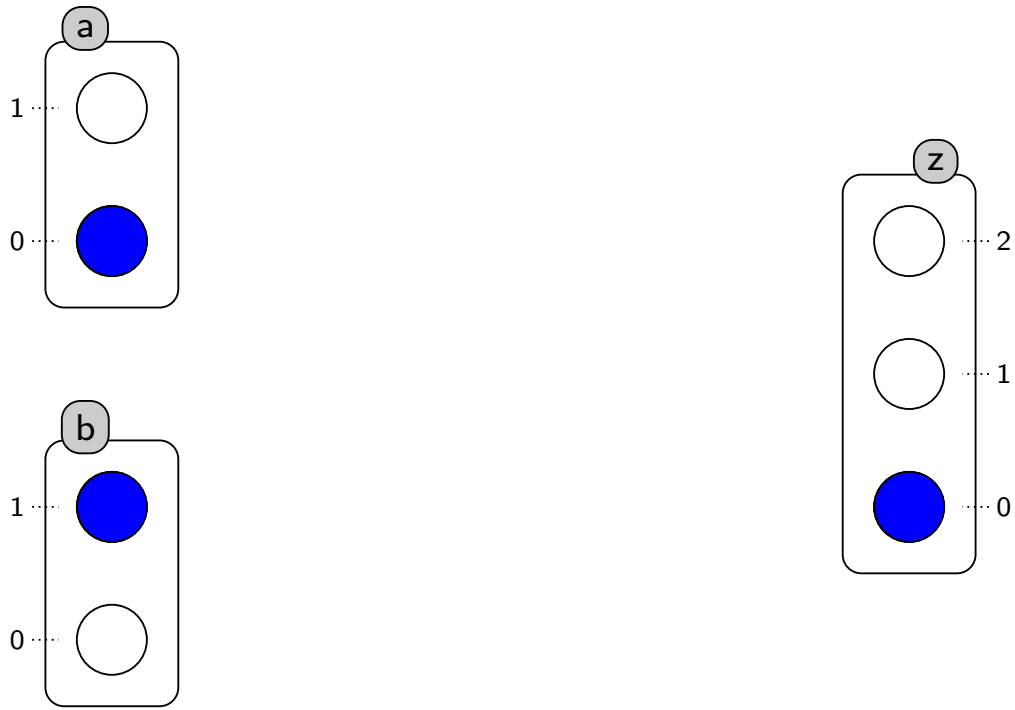

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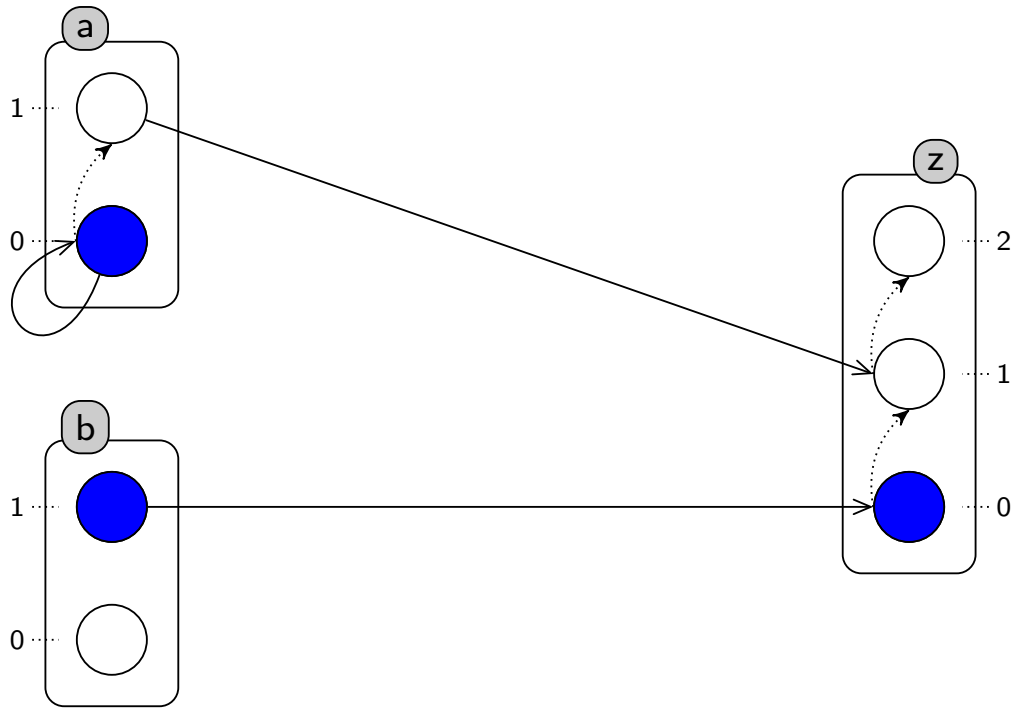

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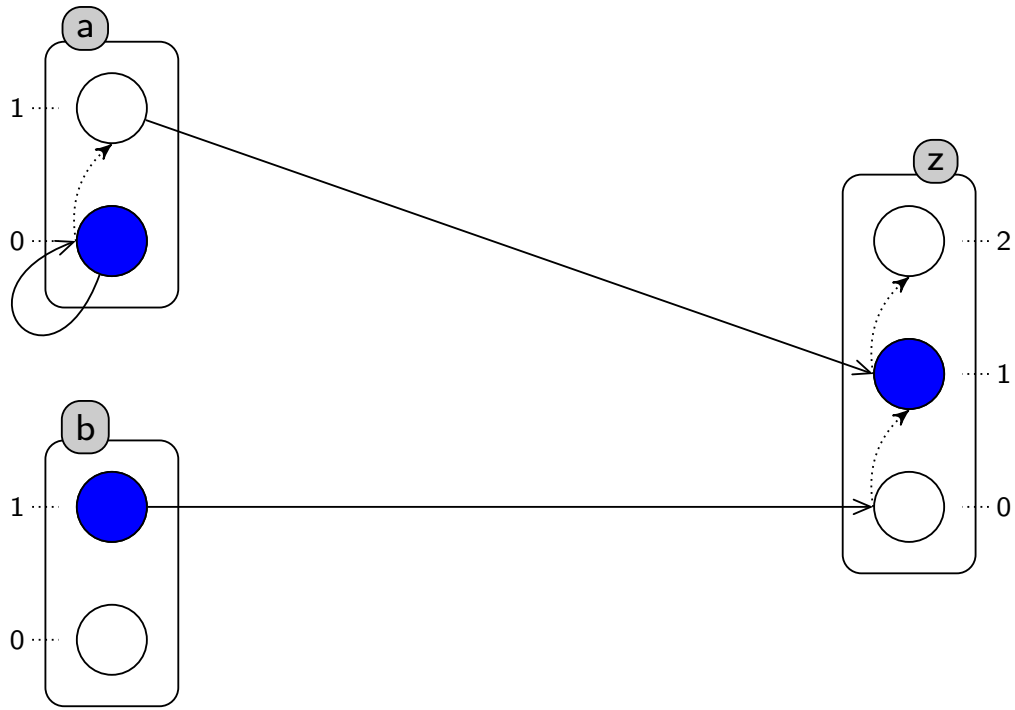

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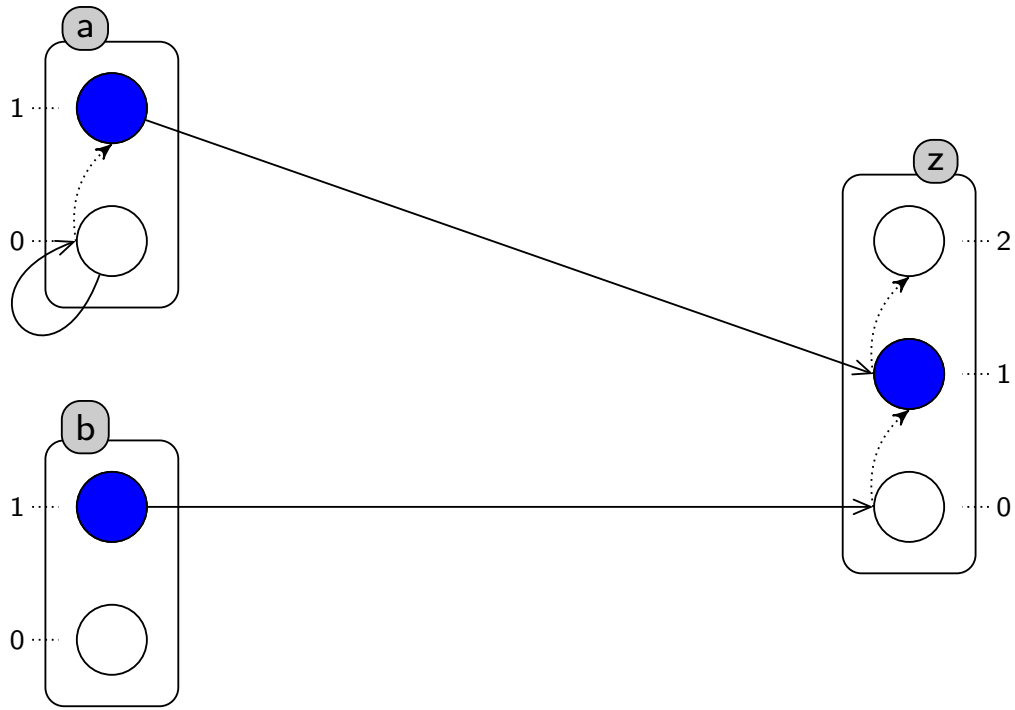

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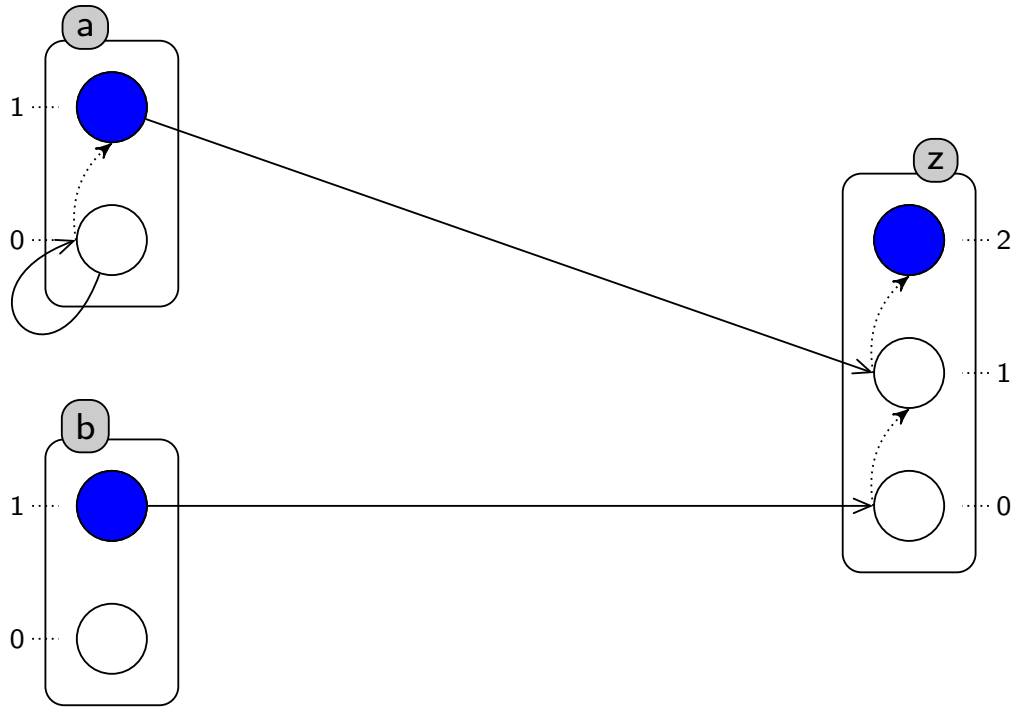

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Adding cooperations

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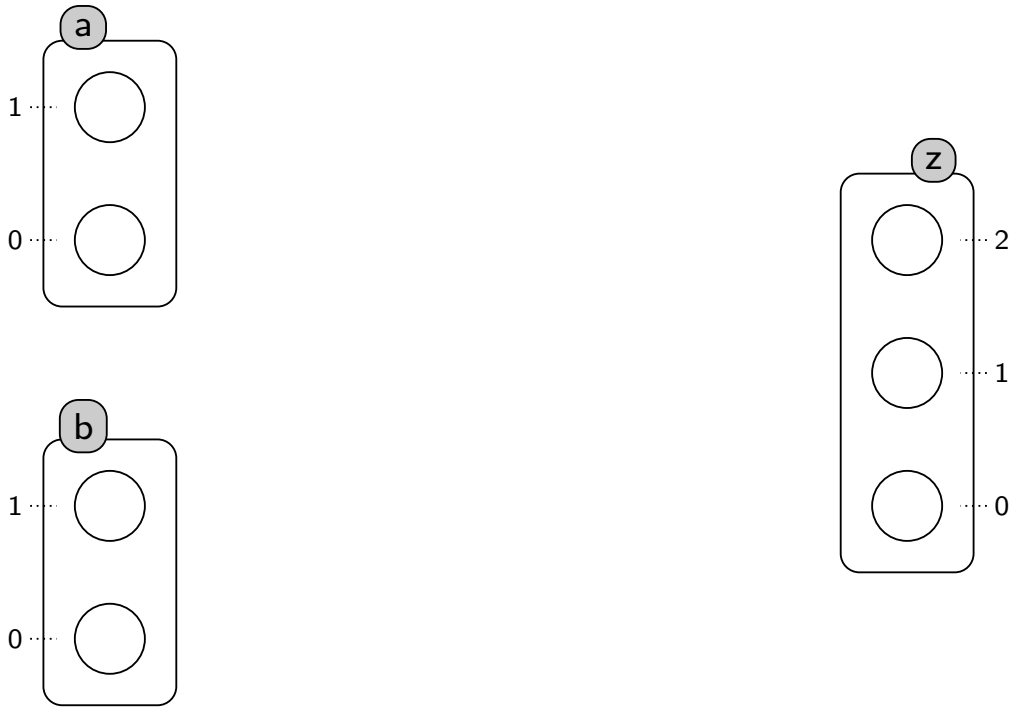

How to introduce some **cooperation** between sorts? $a_1 \wedge b_0 \rightarrow z_1 \Rsh z_2$

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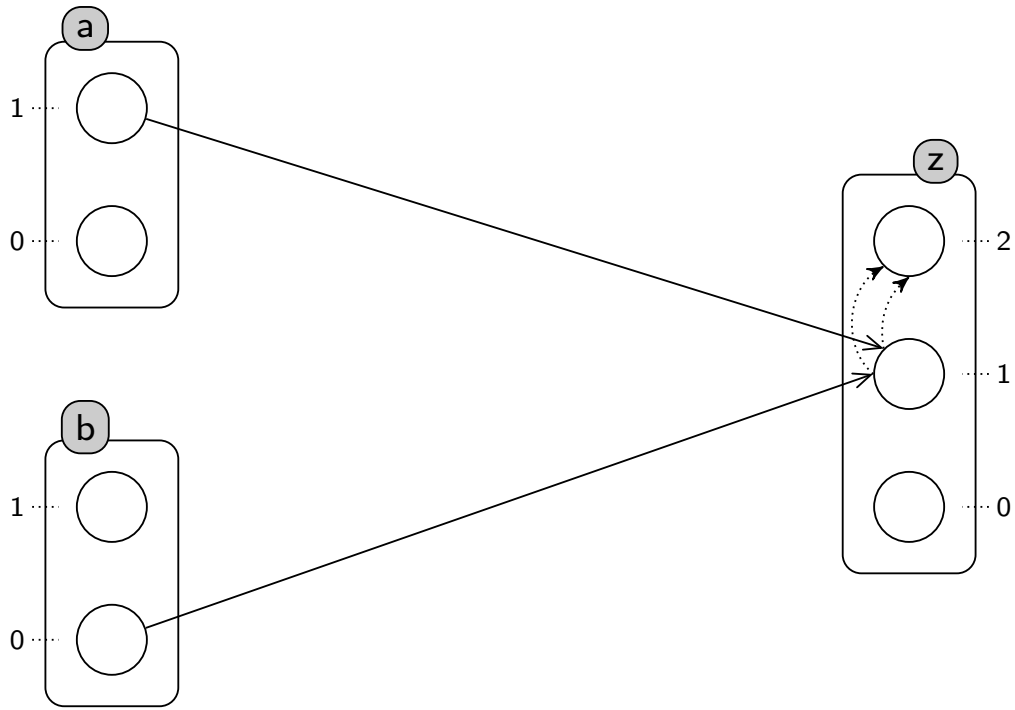

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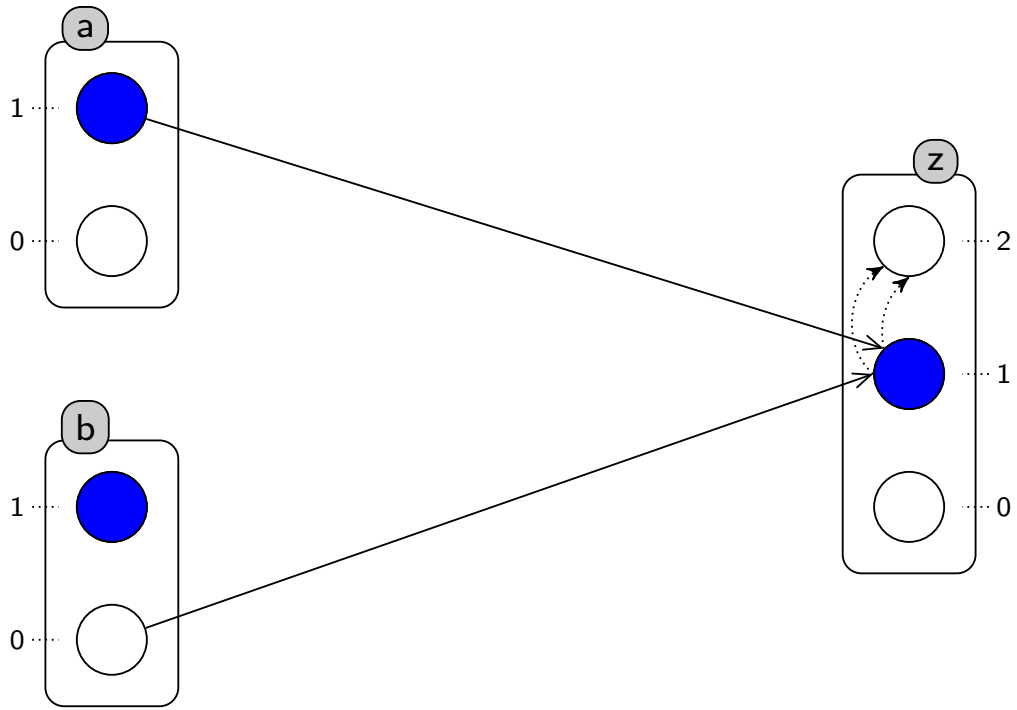

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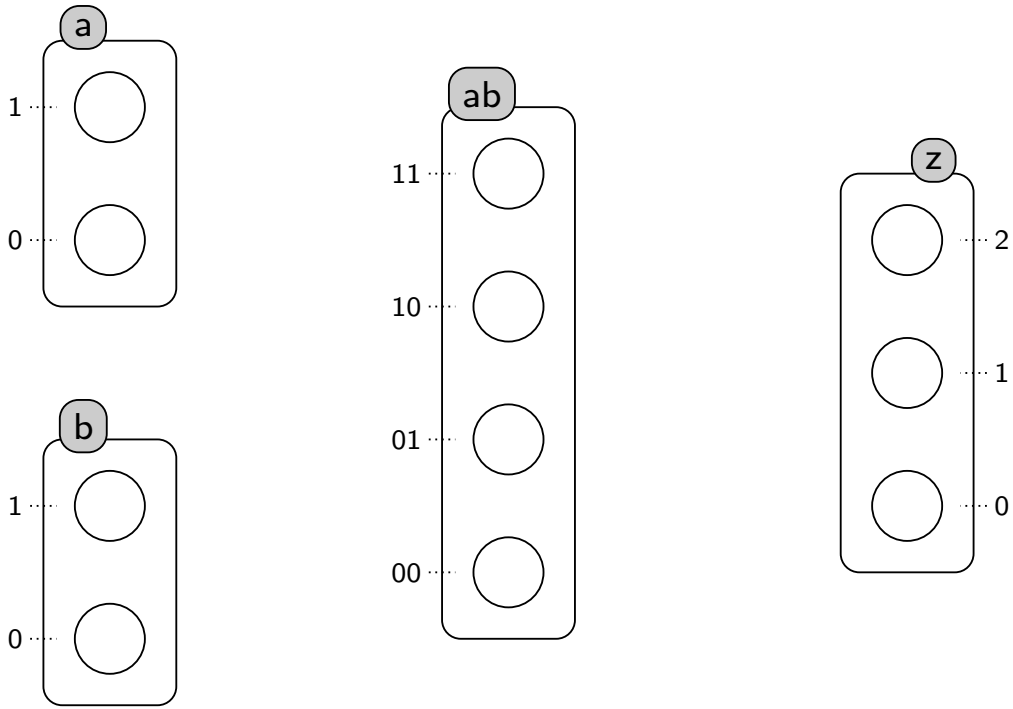

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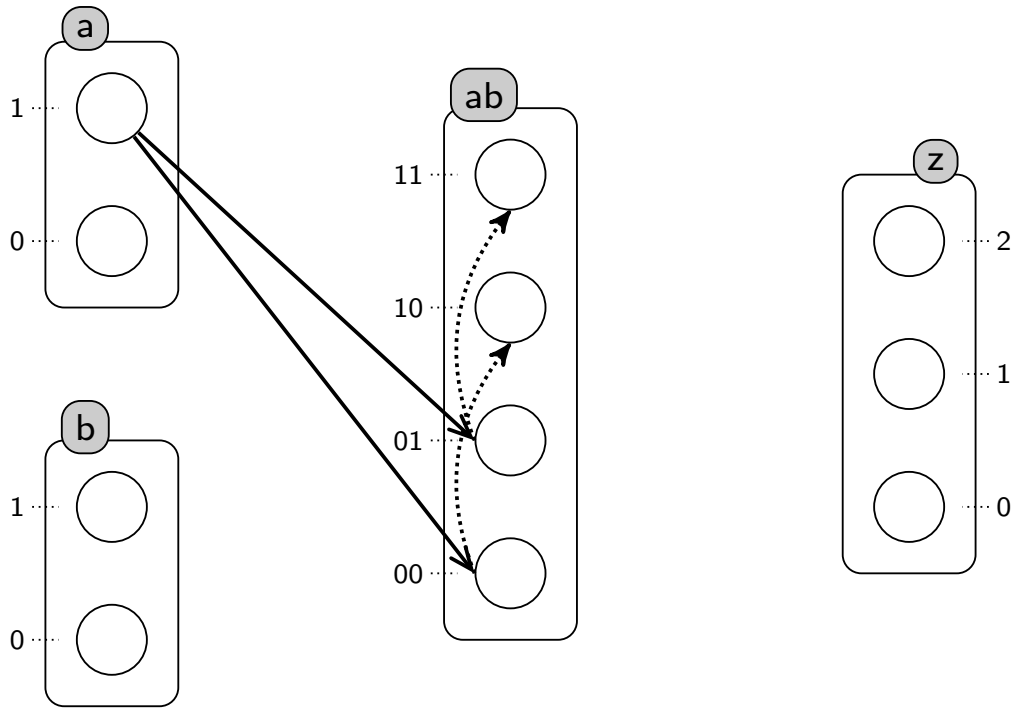

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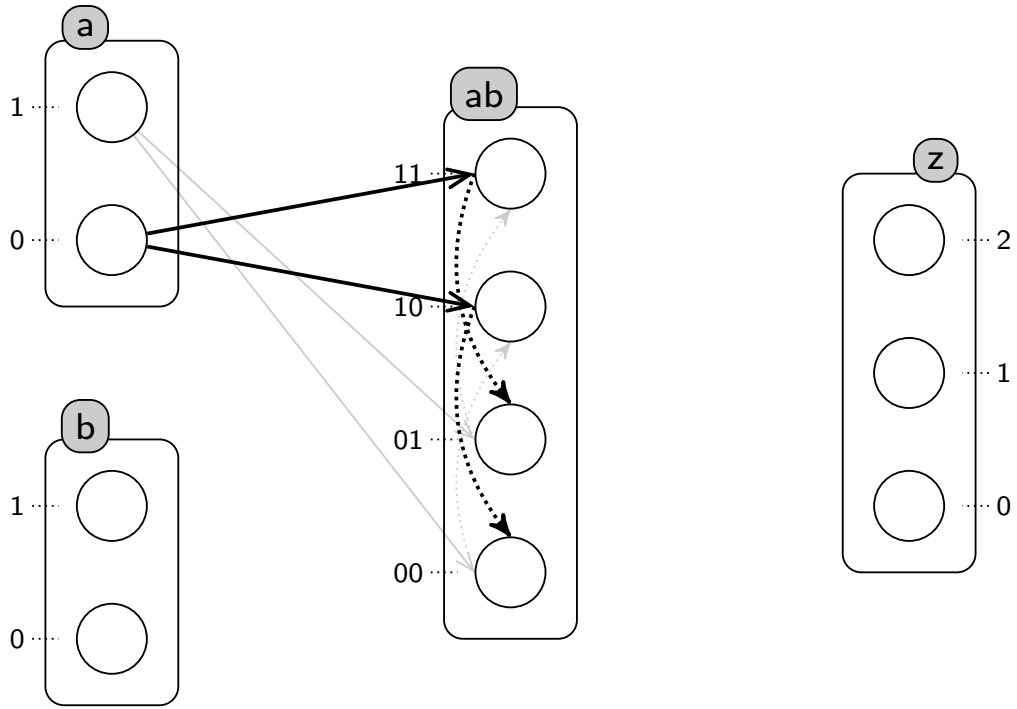

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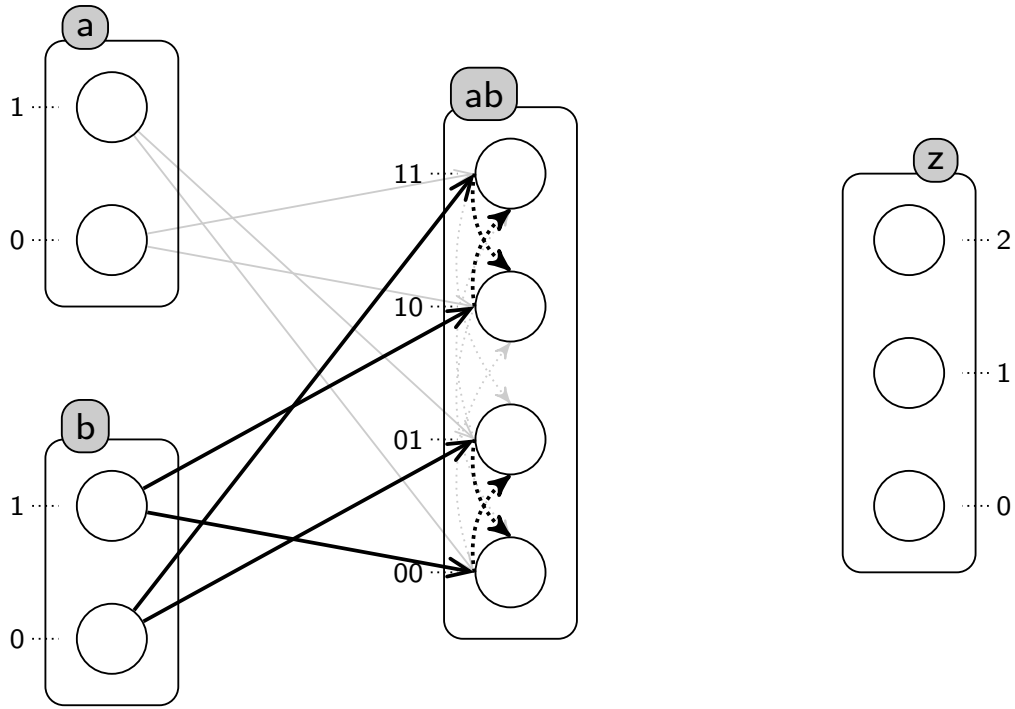

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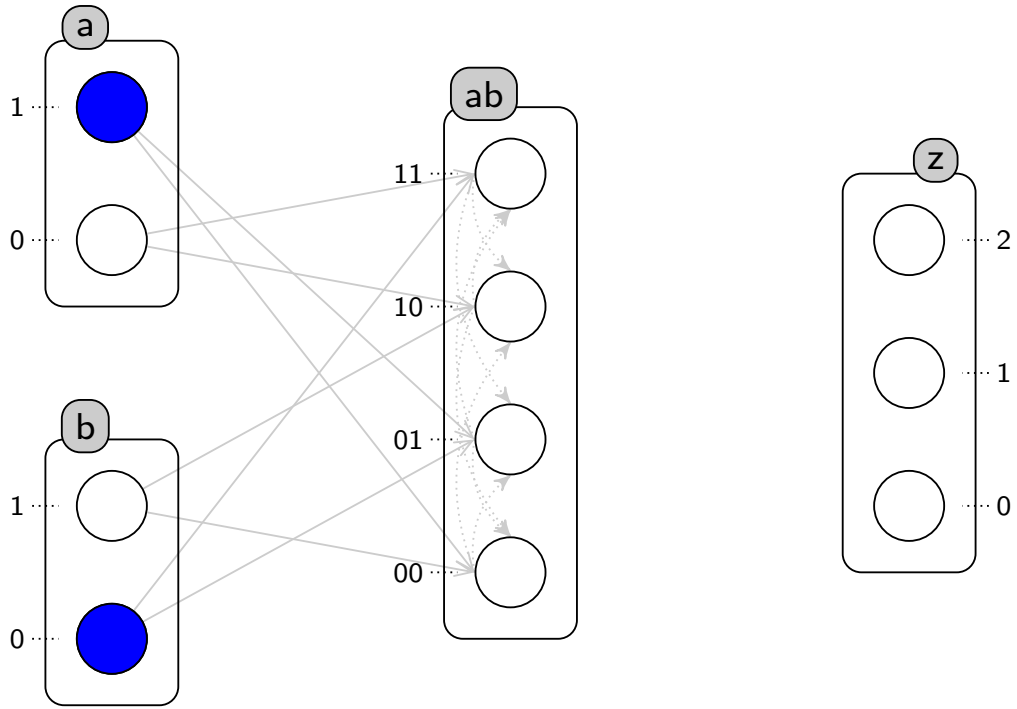

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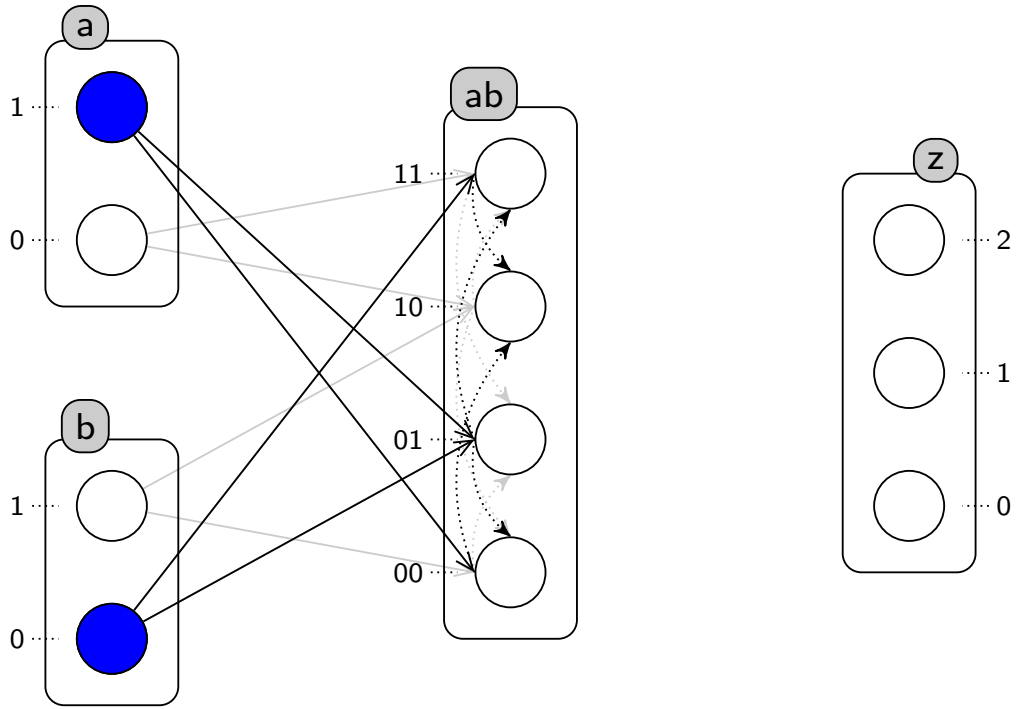

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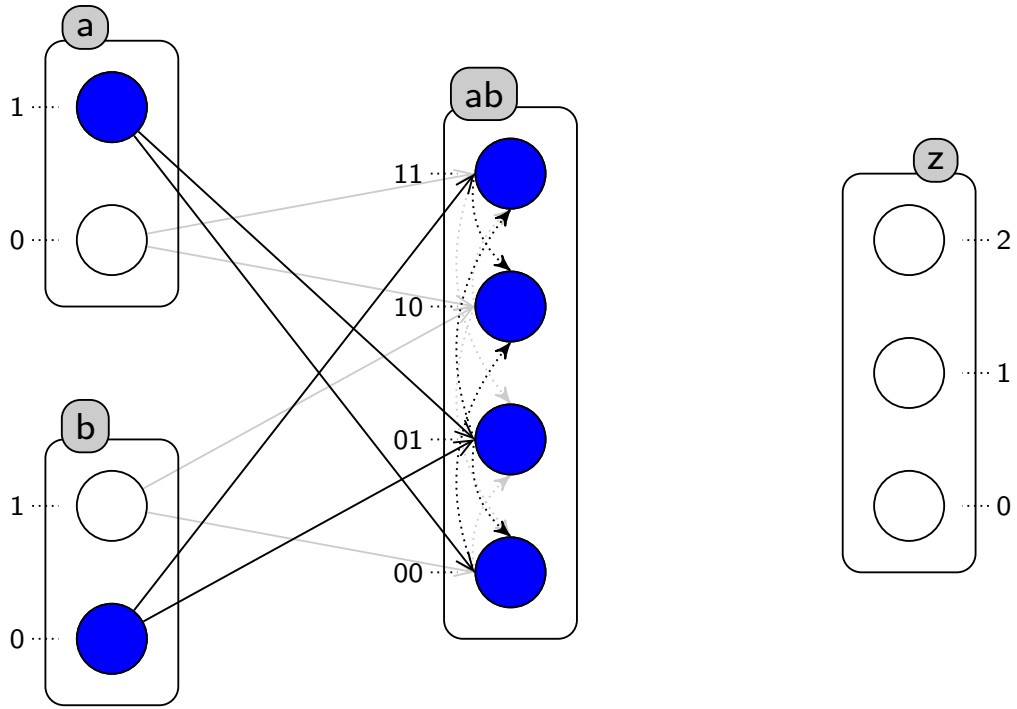

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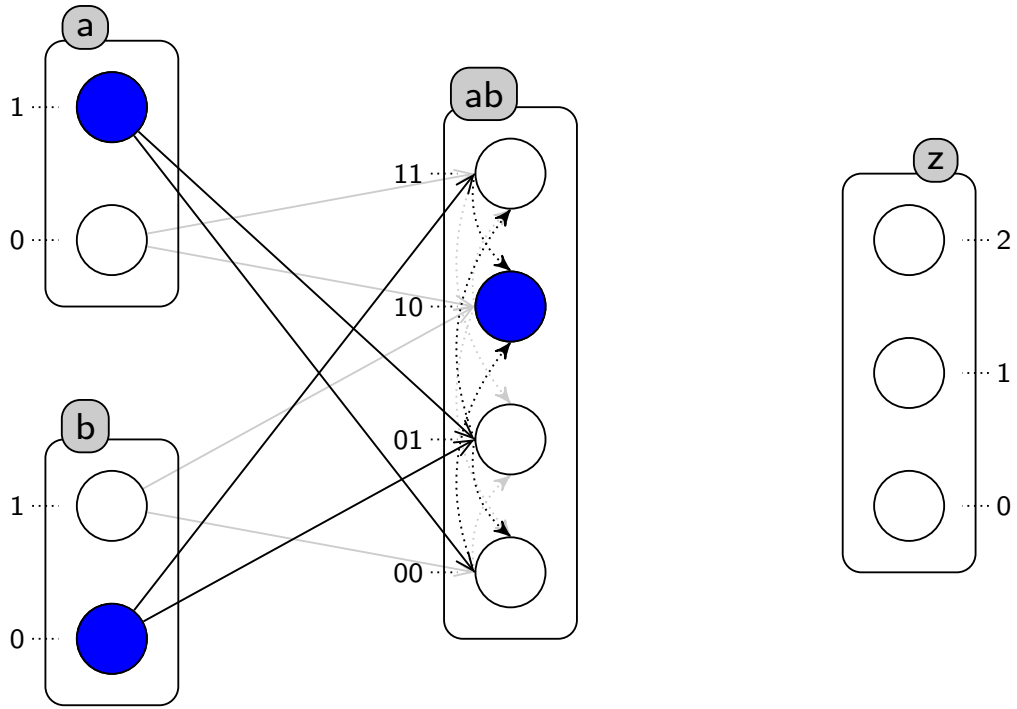

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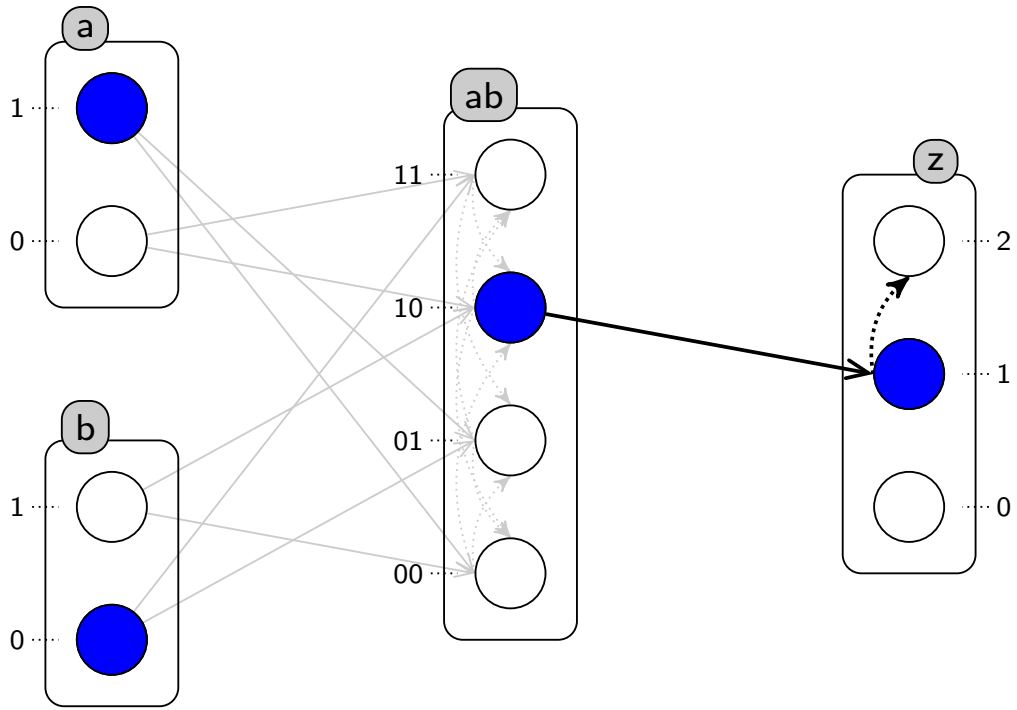

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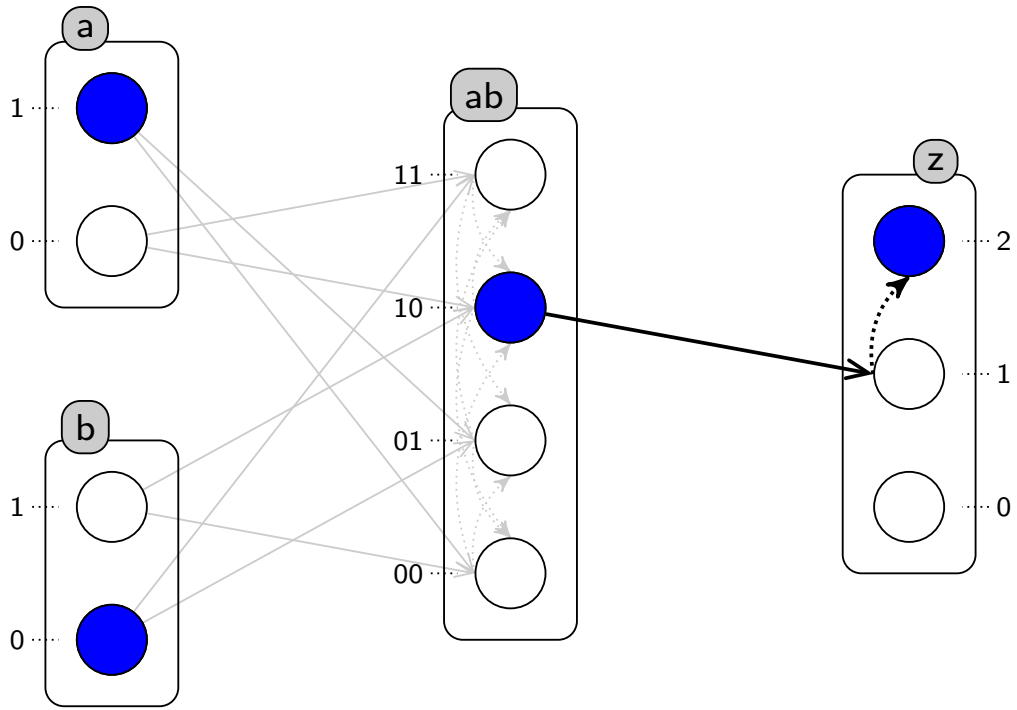

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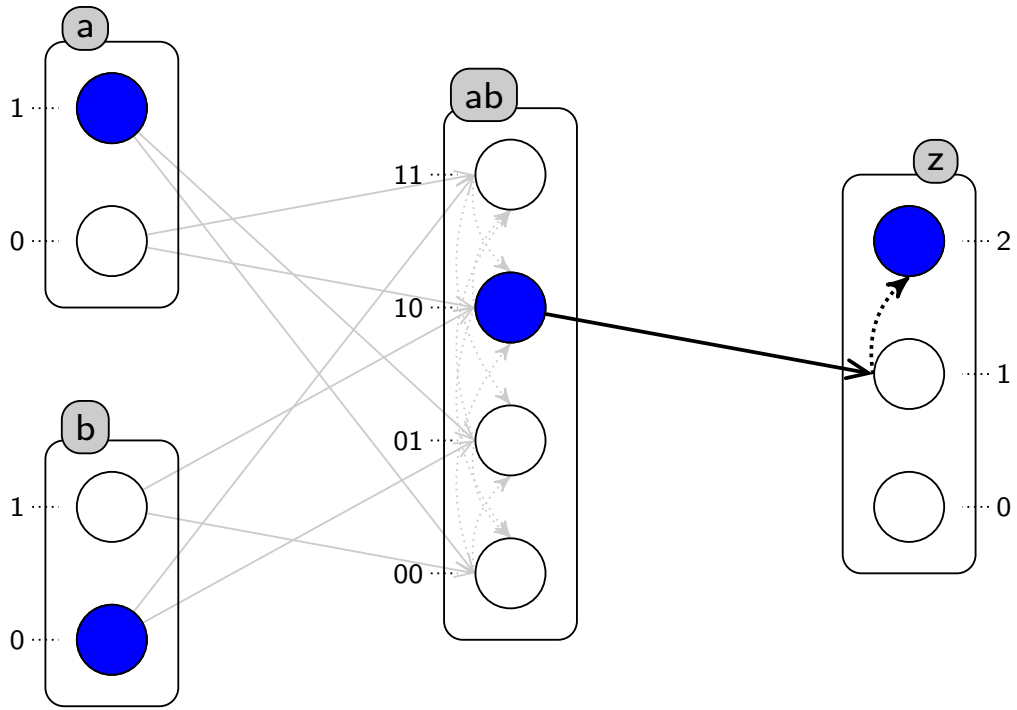

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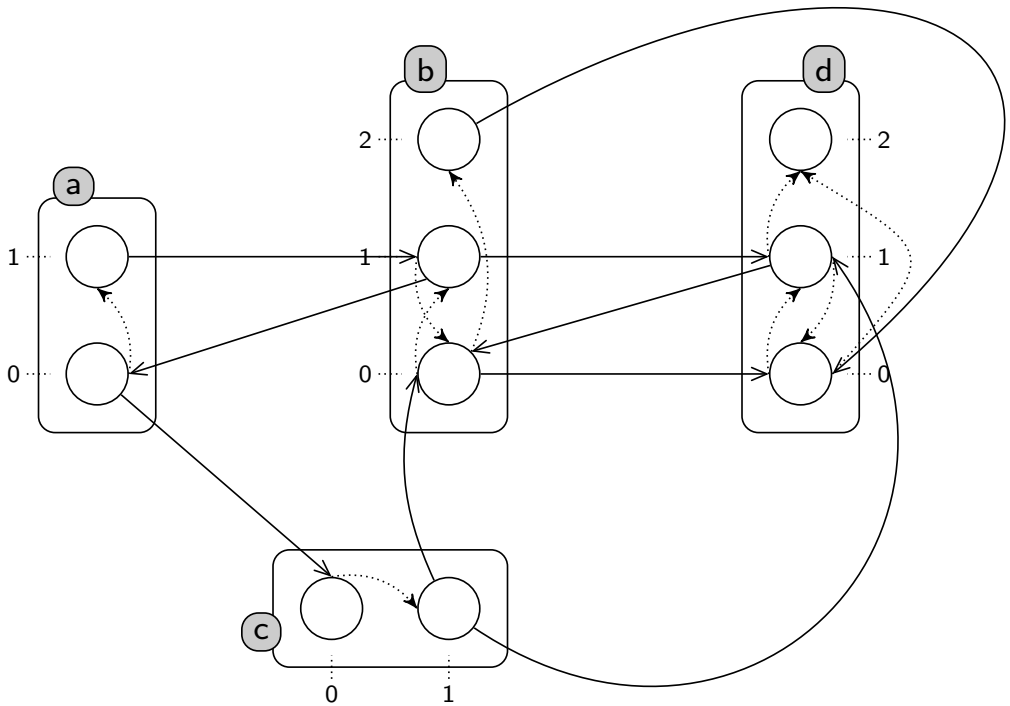
Advantage: regular sort; drawbacks: complexity, temporal shift

Static analysis: successive reachability

[Paulevé, Magnin, Roux in Mathematical Structures in Computer Science, 2012]

Successive reachability of processes:



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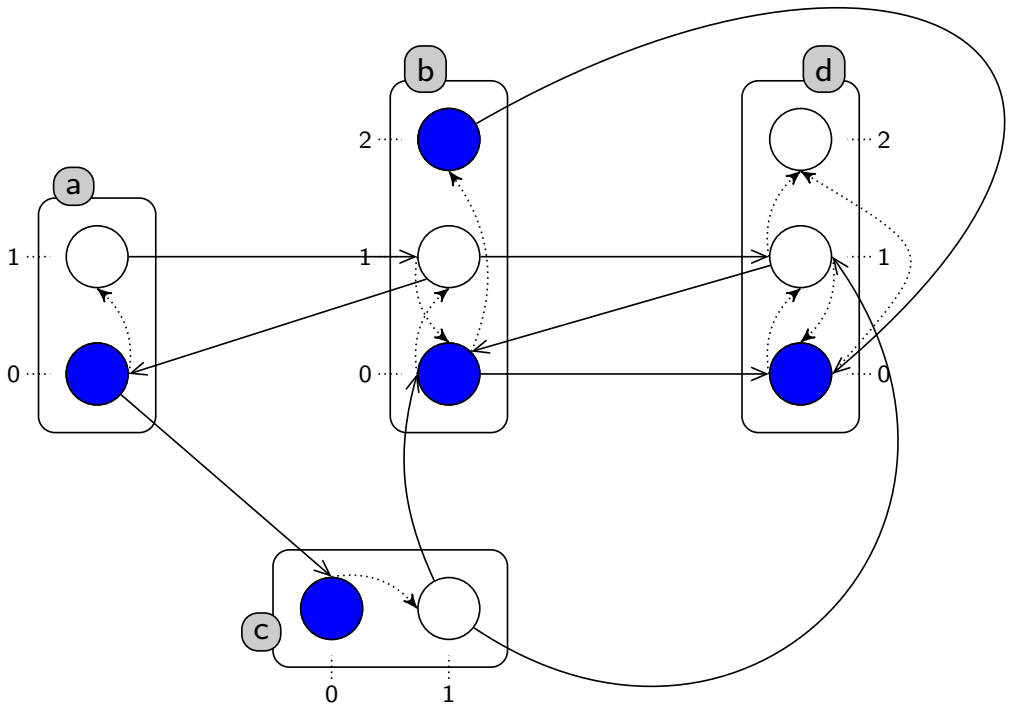

- Initial context

$$\langle a_1, \{b_0, b_1\}, c_0, z_0 \rangle$$

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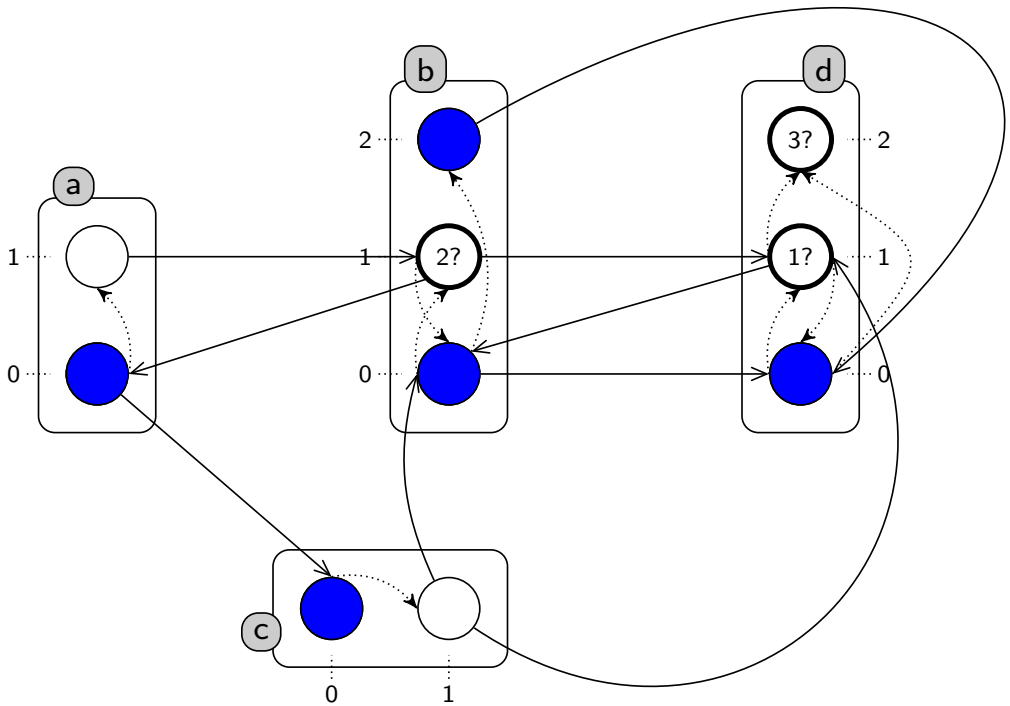

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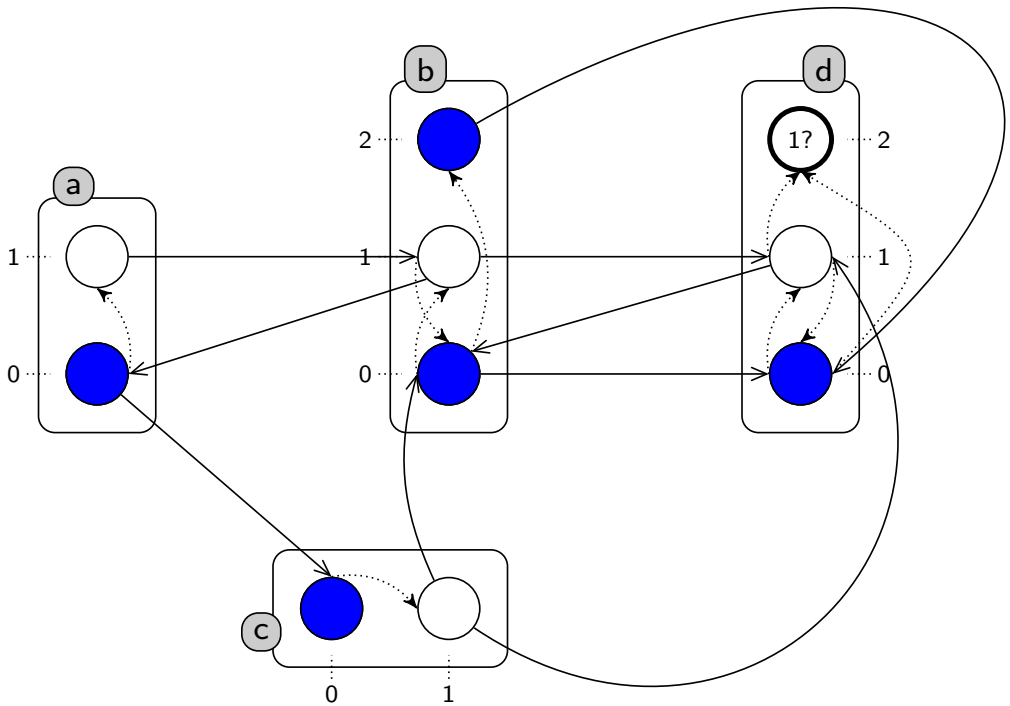

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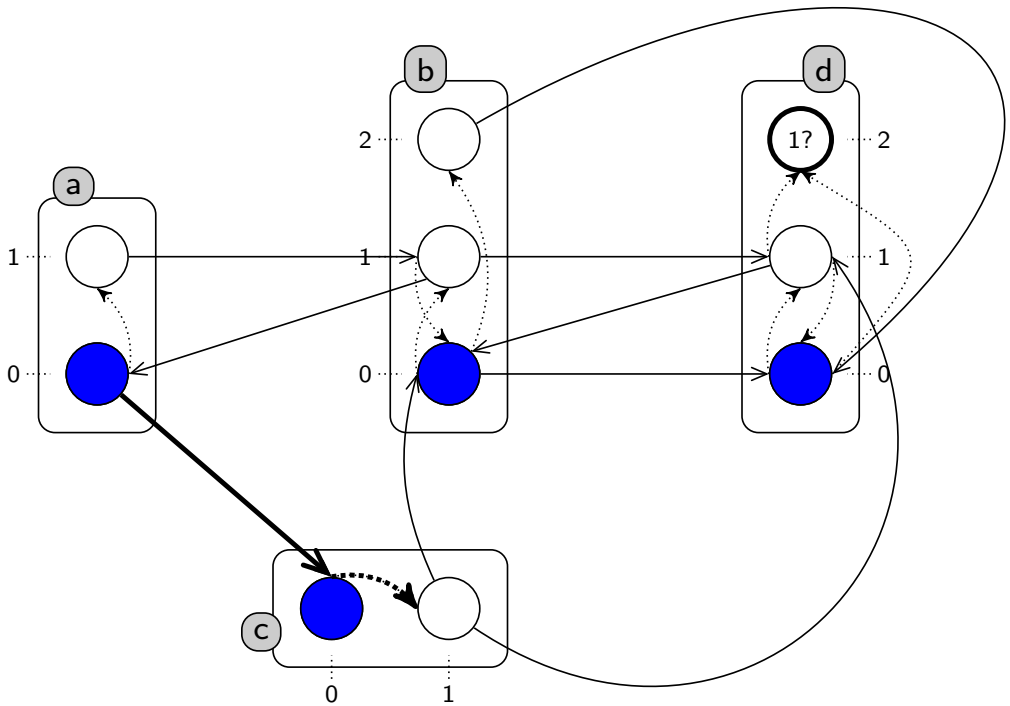

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$\rightarrow$ Concretization of the objective = scenario

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

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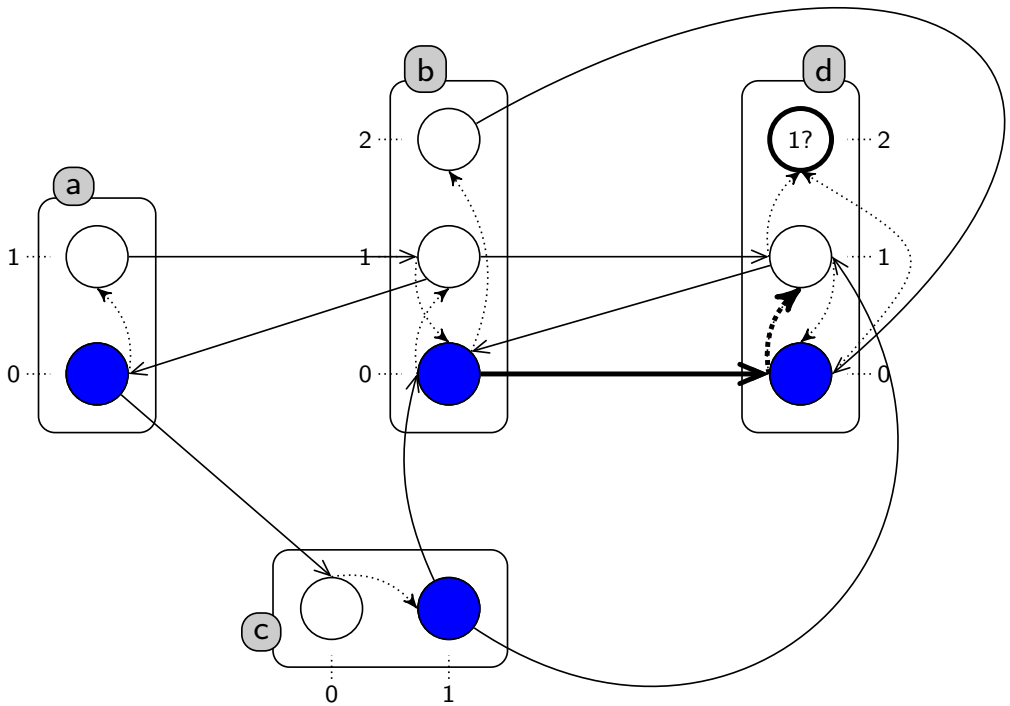

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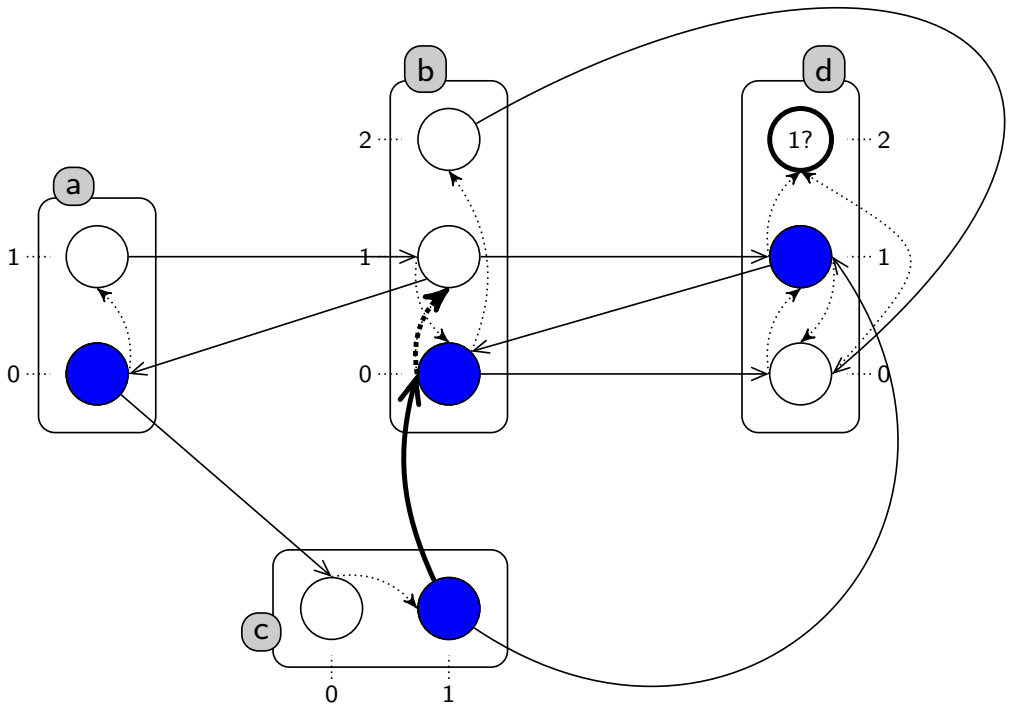

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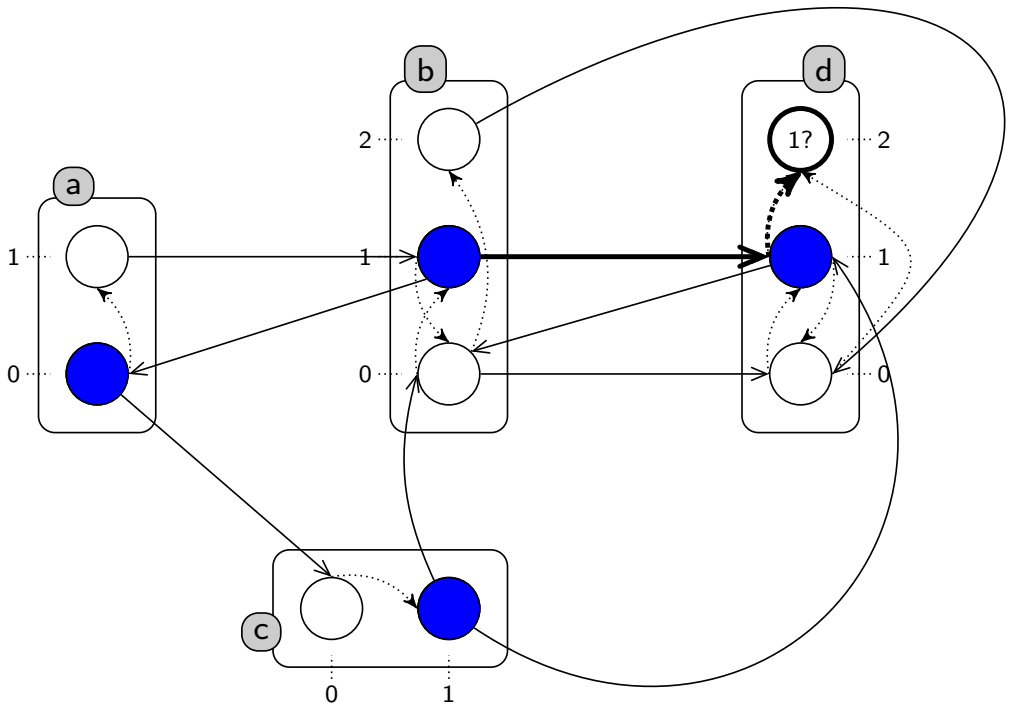

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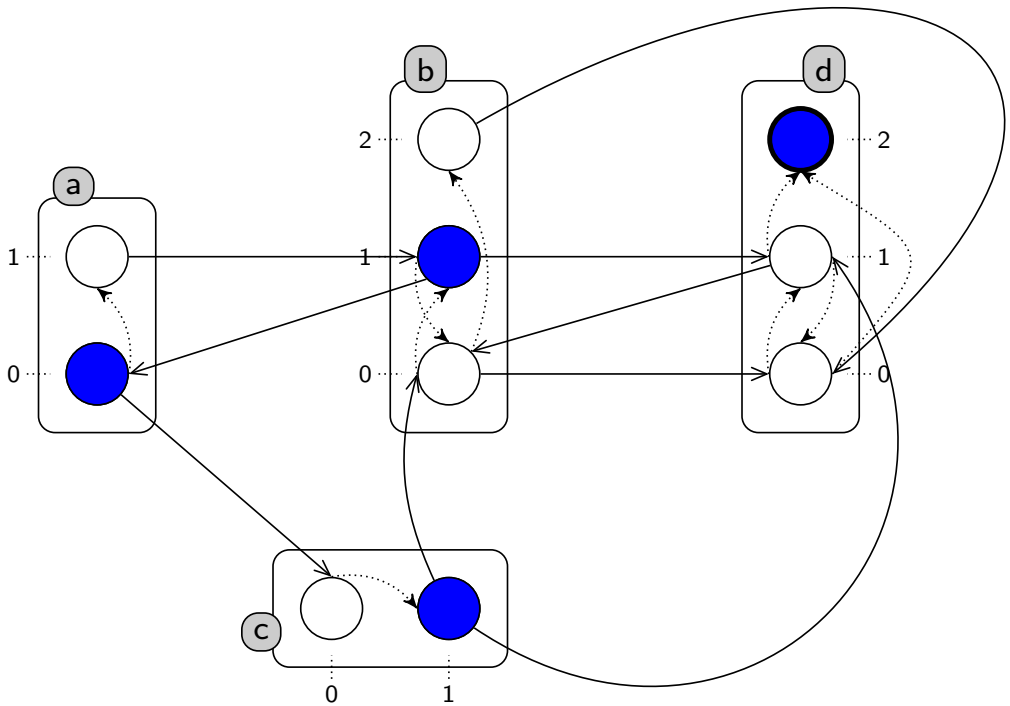

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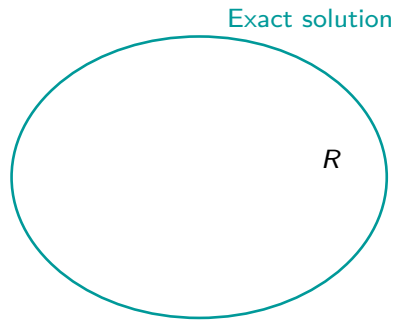
Over- and Under-approximations

[Paulevé, Magnin, Roux in Mathematical Structures in Computer Science, 2012]

Static analysis by abstractions:

→ Directly checking an objective sequence R is hard

→ Rather check the approximations P and Q, where $P \Rightarrow R \Rightarrow Q$:



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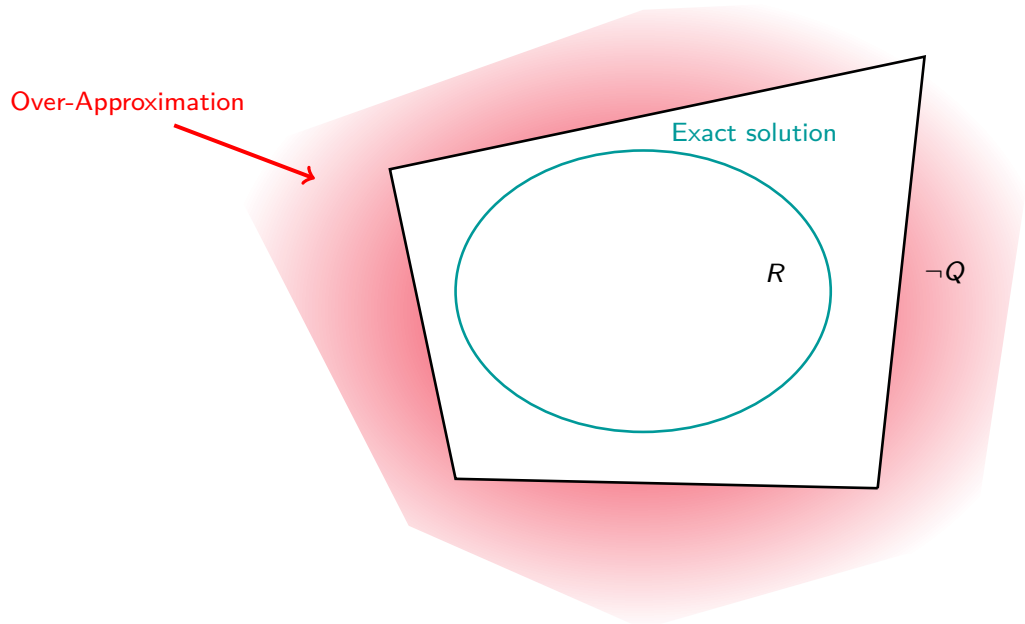

Over- and Under-approximations

[Paulevé, Magnin, Roux in Mathematical Structures in Computer Science, 2012]

Static analysis by abstractions:

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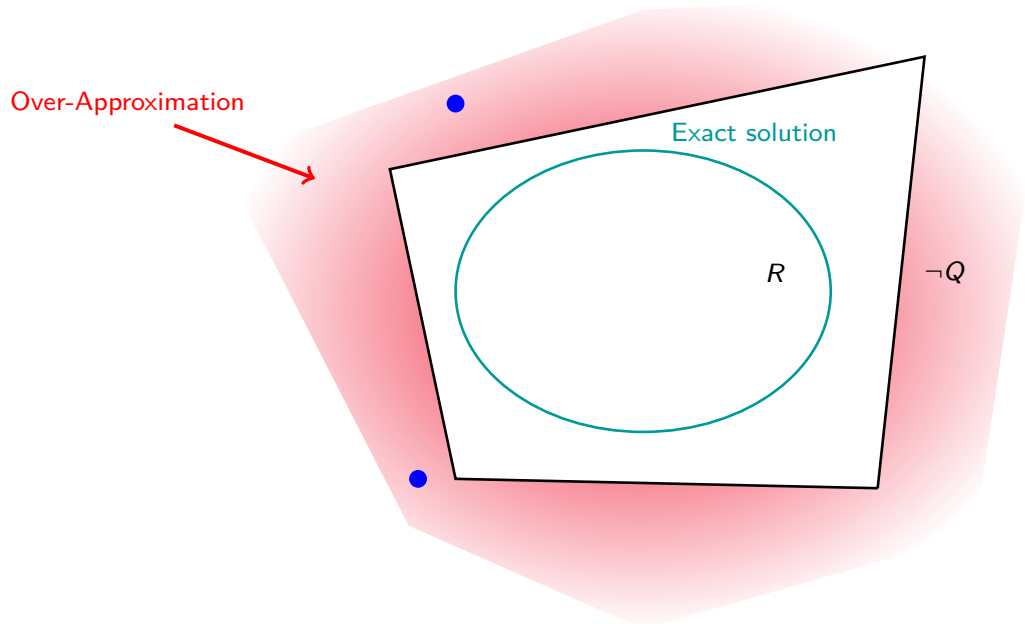

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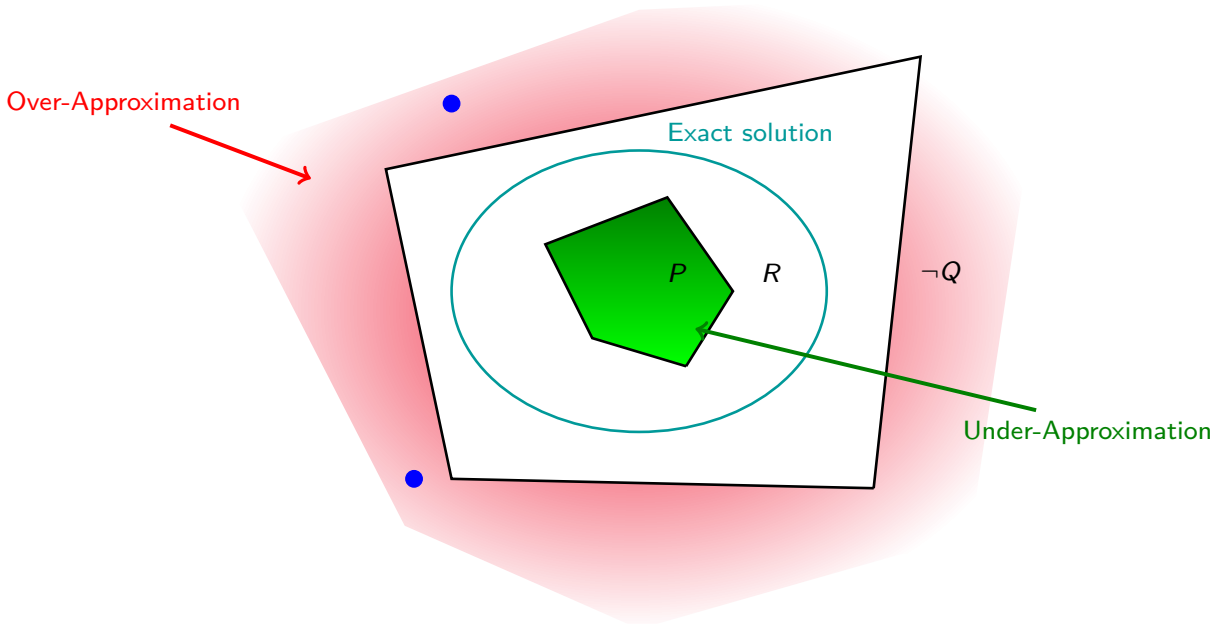

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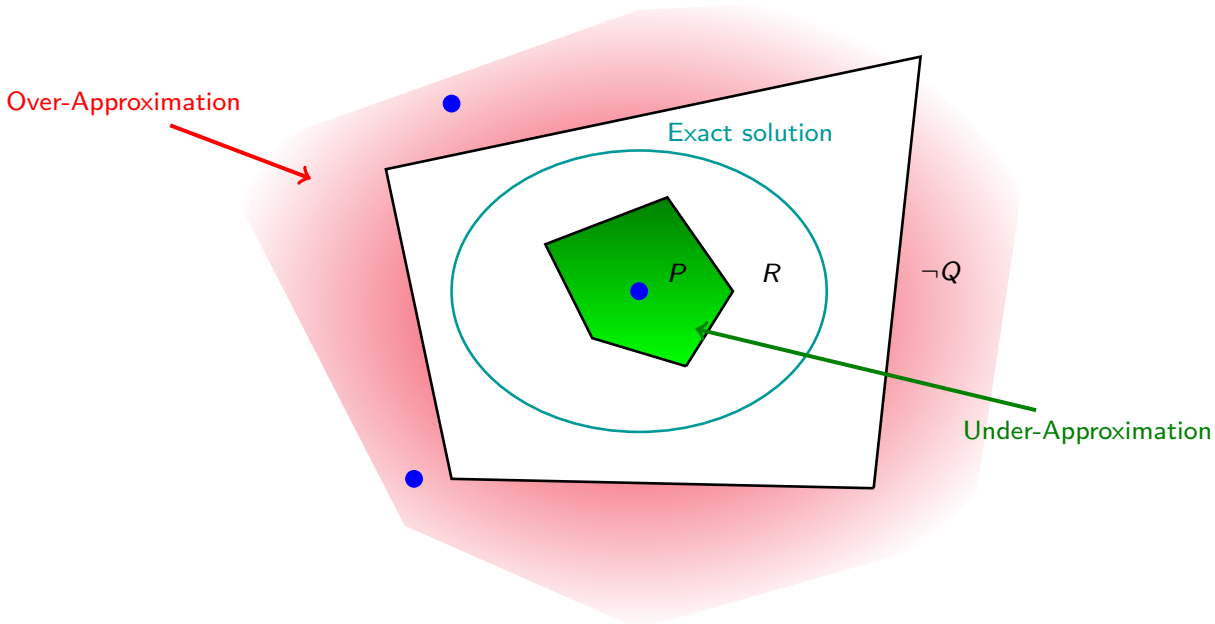

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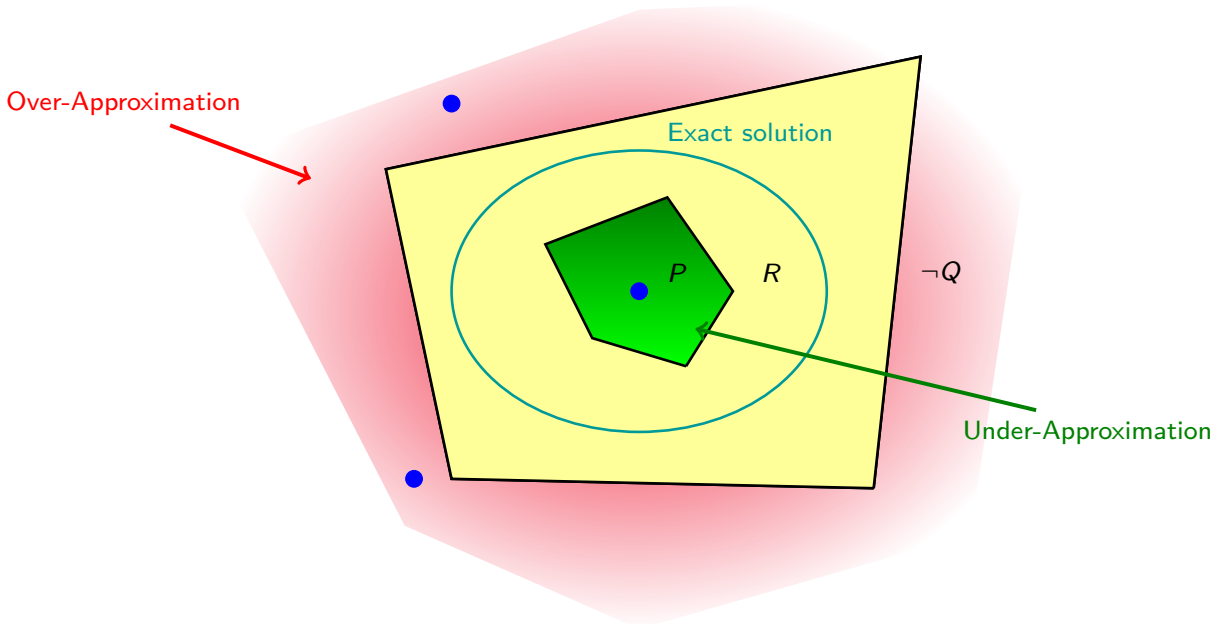

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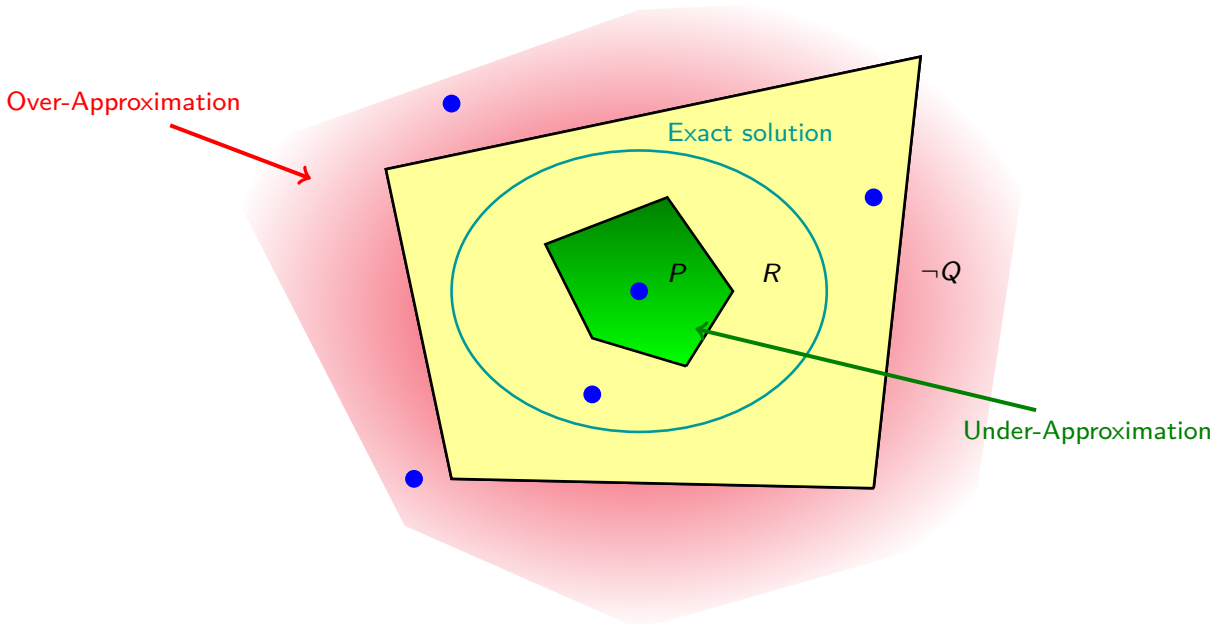

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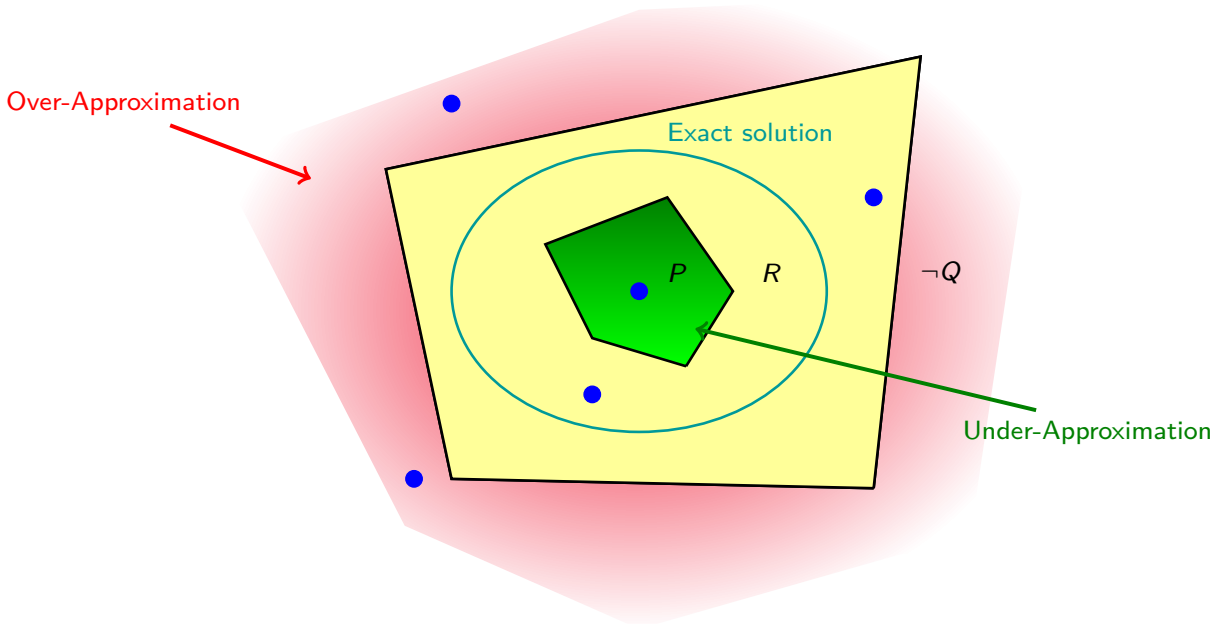

Polynomial w.r.t. the number of sorts and
exponential w.r.t. the number of processes in each sort

→ Efficient for big models with few levels of expression

Implementation & Execution times

PINT: **Existing free OCaml library**

→ Compiler + tools for Process Hitting models
→ Documentation & examples: http://processhitting.wordpress.com/

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Computation time for various reachability analyses:

Model	Sorts	Procs	Actions	States	Biocham[1]	libddd[2]	PINT
egfr20	35	196	670	2^{64}	[3s–∞]	[1s–150s]	**0.007s**
tcrsig40	54	156	301	2^{73}	[1s–∞]	[0.6s–∞]	**0.004s**
tcrsig94	133	448	1124	2^{194}	∞	∞	**0.030s**
egfr104	193	748	2356	2^{320}	∞	∞	**0.050s**

[1] Inria Paris-Rocquencourt/Contraintes
[2] LIP6/Move

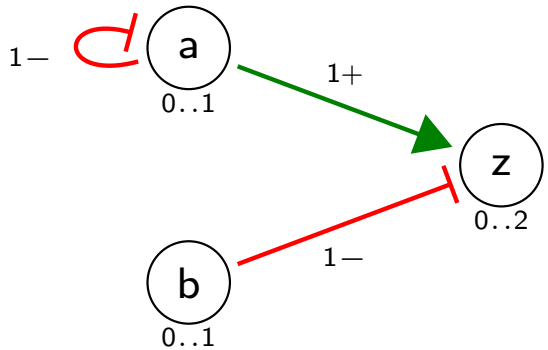
egfr20: [Epidermal Growth Factor Receptor, by Özgür Sahin *et al.*]
egfr104: [Epidermal Growth Factor Receptor, by Regina Samaga *et al.*]
tcrsig40: [T-Cell Receptor Signaling, by Steffen Klamt *et al.*]
tcrsig94: [T-Cell Receptor Signaling, by Julio Saez-Rodriguez *et al.*]

The Process Hitting modeling

- **Dynamic** modeling with an **atomistic** point of view
  - → Independent actions
  - → Cooperation modeled with cooperative sorts
- Efficient **static analysis**
  - → Reachability of a process can be computed in **polynomial time** in the number of sorts
- Useful for the study of **large biological models**
  - → Up to hundreds of sorts
- (Future) extensions
  - → Actions with priorities
  - → Continuous time with clocks?

Biological Regulatory Network (Thomas' modeling)

[Richard, Comet, Bernot in Modern Formal Methods and App., 2006]



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

ω	$k_{a,\omega}$
a	
$+$	1
$-$	0

$k_{b,\omega}$
1

Proposed by René Thomas in 1973, several extensions since then

Historical bio-informatics model for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

Biological Regulatory Network (Thomas' modeling)

[Richard, Comet, Bernot in Modern Formal Methods and App., 2006]

Interaction Graph

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Interaction Graph: structure of the system (genes & interactions)

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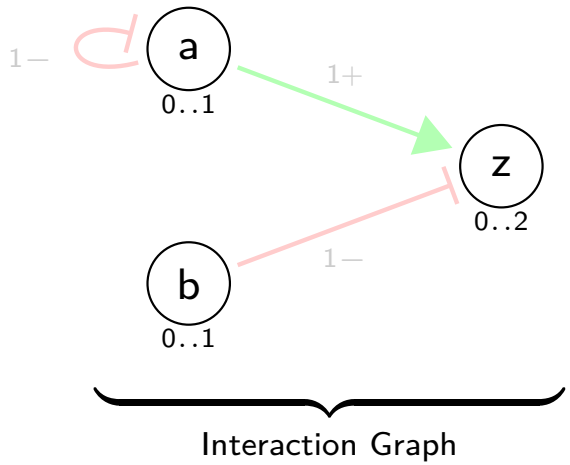

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Interaction Graph: structure of the system (genes & interactions)

Nodes: genes

→ Name *a*, *b*, *z*

→ Possible values (levels of expression) 0..1, 0..2

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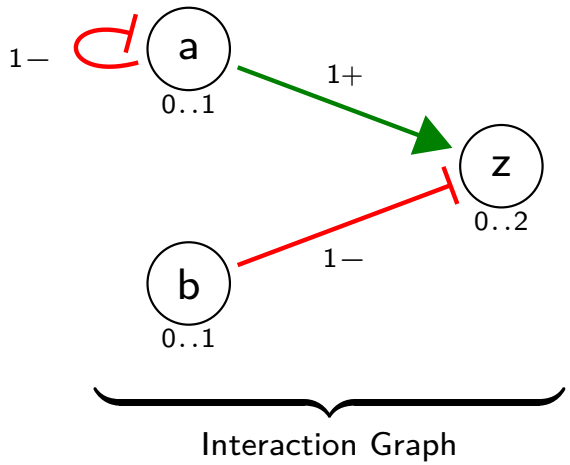

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Interaction Graph: structure of the system (genes & interactions)

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→ Possible values (levels of expression) 0..1, 0..2

Edges: interactions

→ Threshold 1

→ Type (activation or inhibition) + / −

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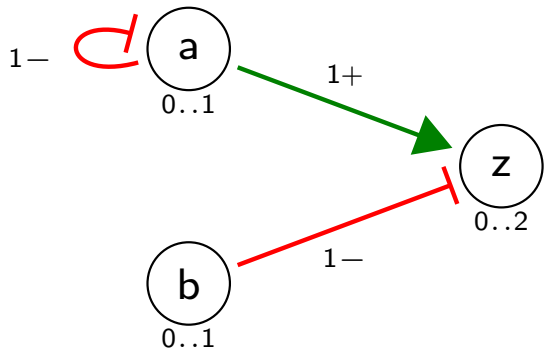

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Parametrization

Parametrization: strength of the influences (cooperations)

Maps of tendencies for each gene

→ To any **influences of predecessors** ω

→ Corresponds a **parameter** $k_{x,\omega}$

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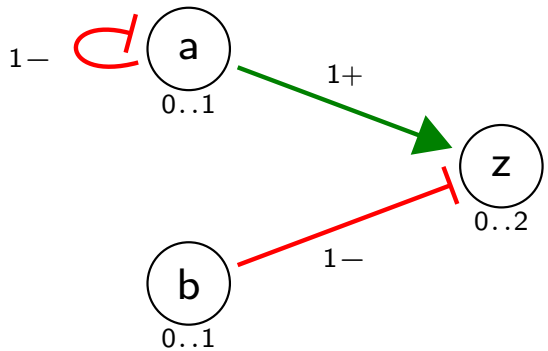

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"$k_{z,\{a^+,b^+\}} = 2$" means: "z tends to 2 when $a \geq 1$ and $b < 1$"

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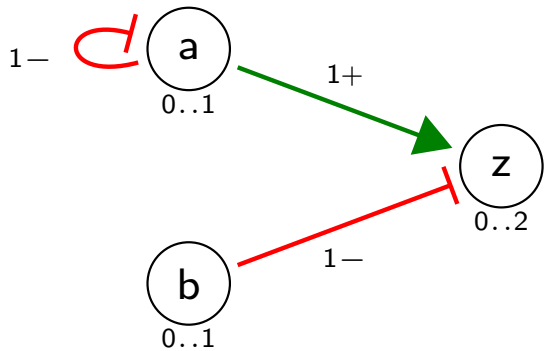

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Biological Regulatory Network

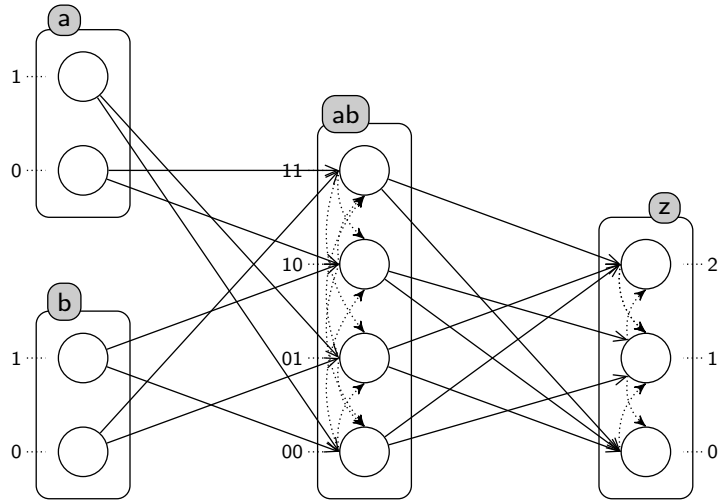
→ All needed information to run the model or study its dynamics:

- Build the State Graph
- Find reachability properties, fixed points, attractors
- Other properties...

→ **Strengths**: well adapted for the study of biological systems

→ **Drawbacks**: inherent complexity; needs the full specification of cooperations

Inferring a BRN with Thomas' parameters



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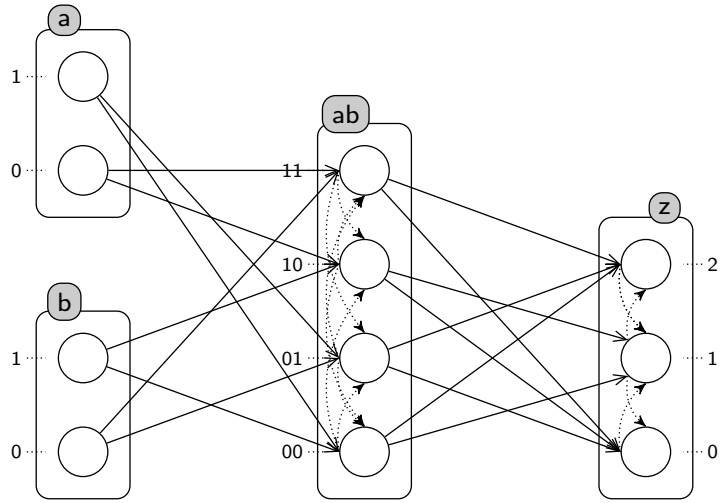

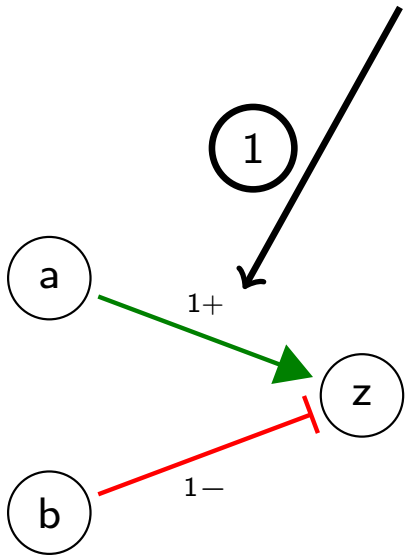

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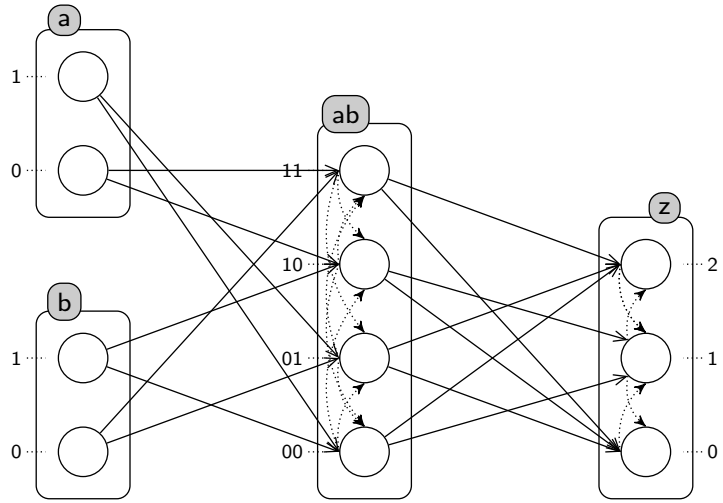

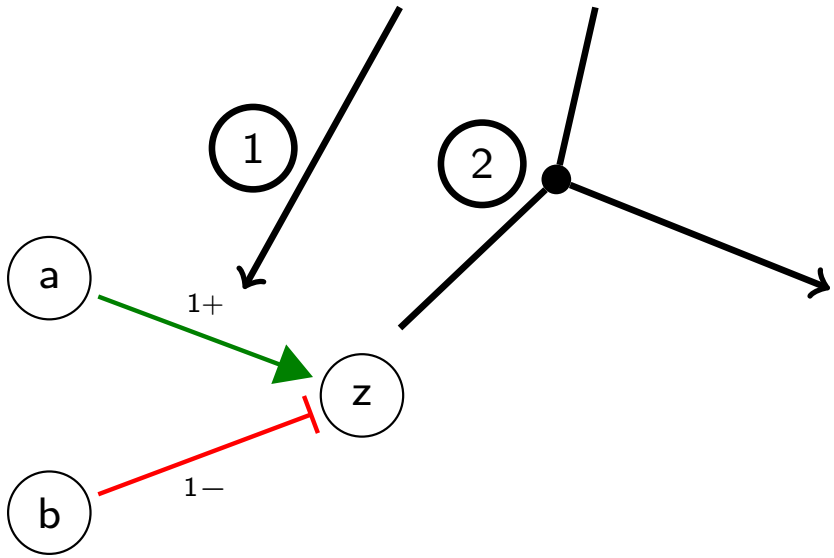

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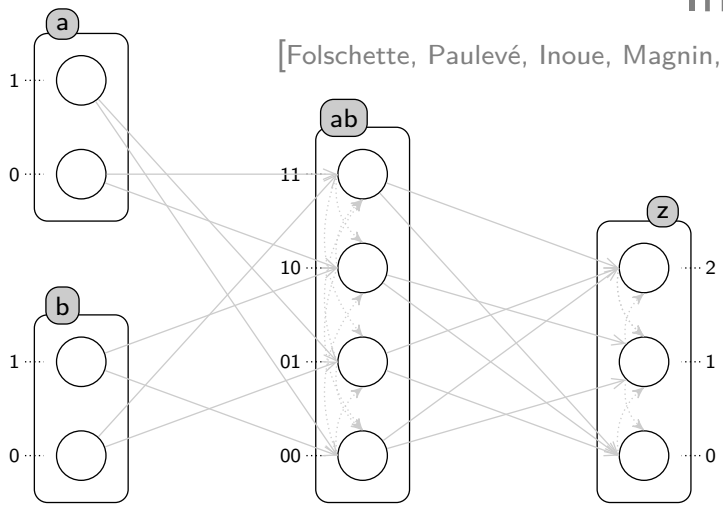

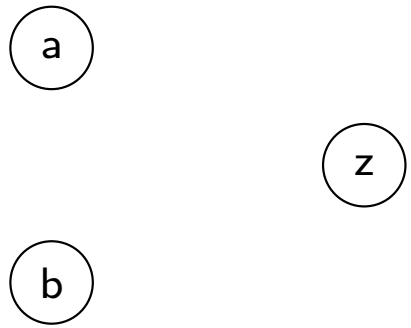

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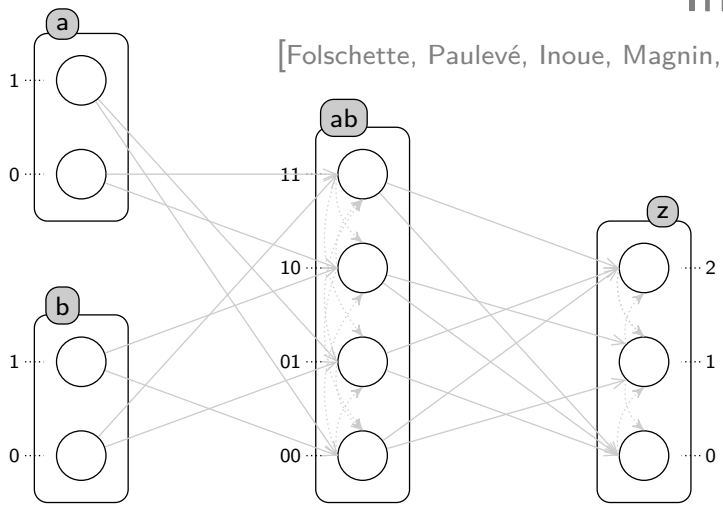

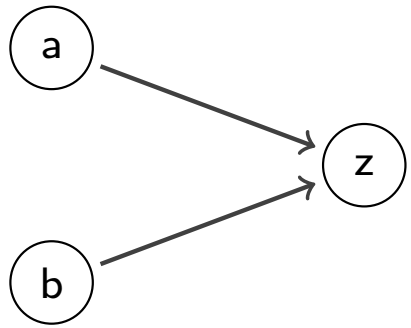

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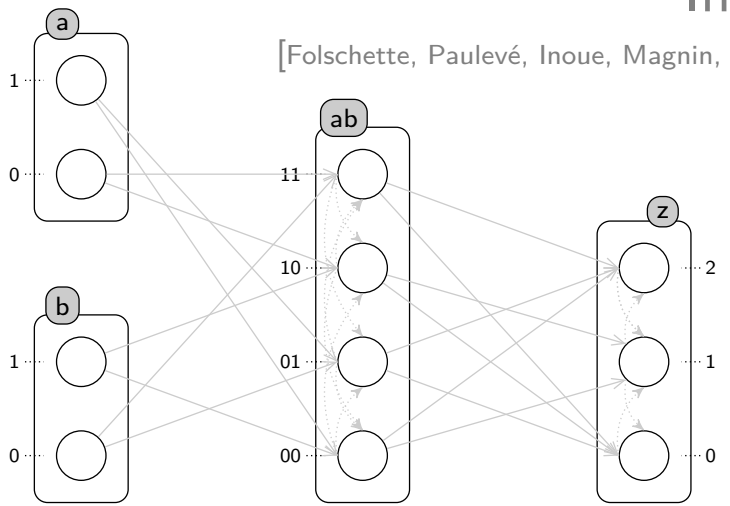

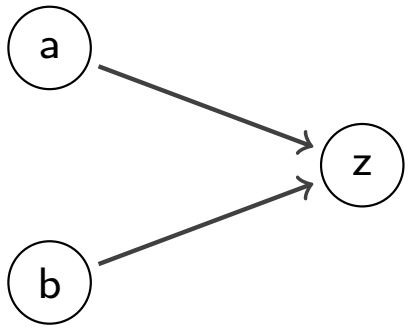

→ **Exhaustive search in all possible configurations**

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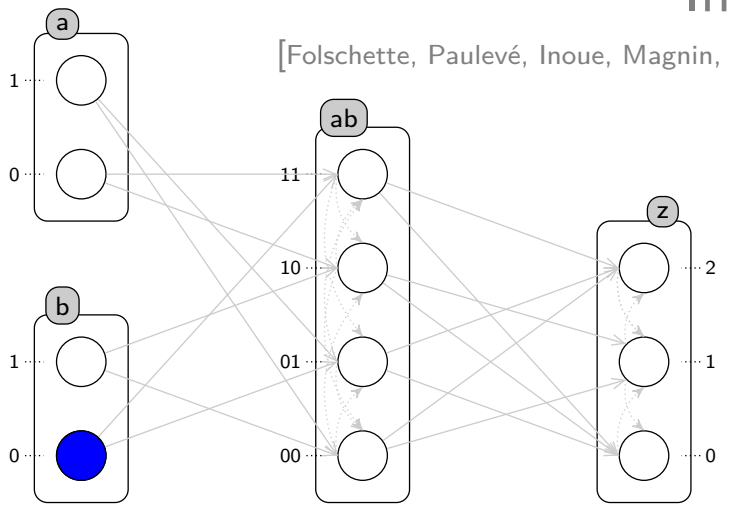

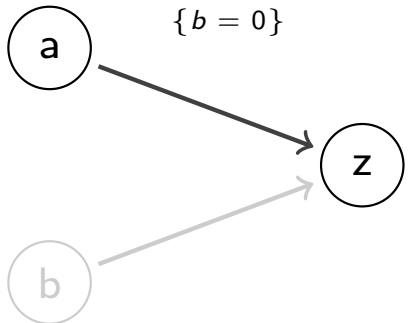

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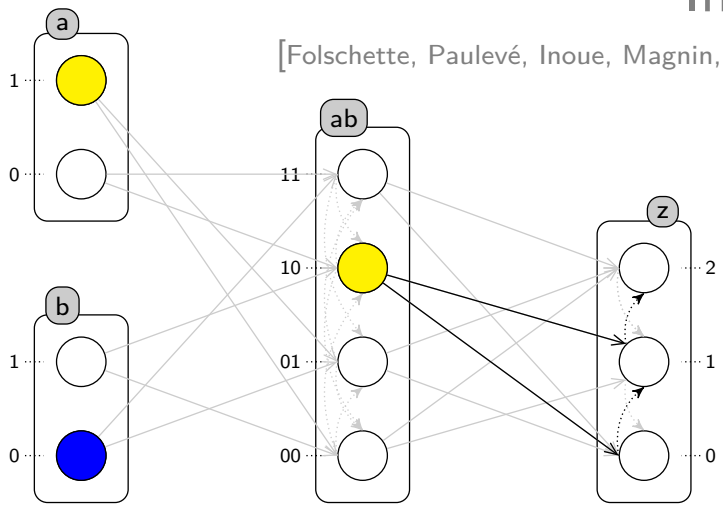

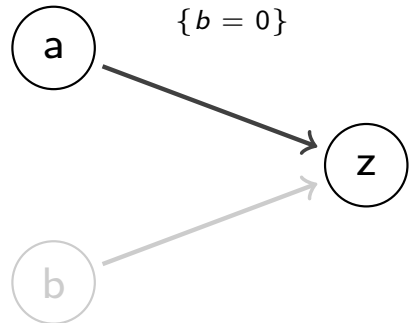

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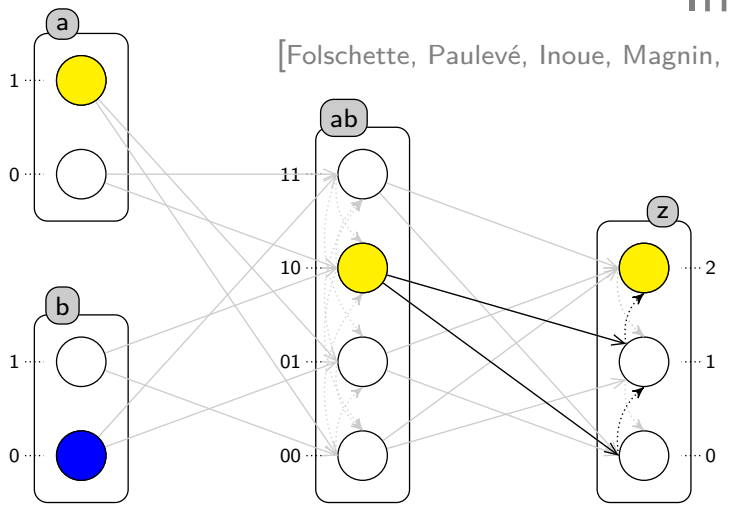

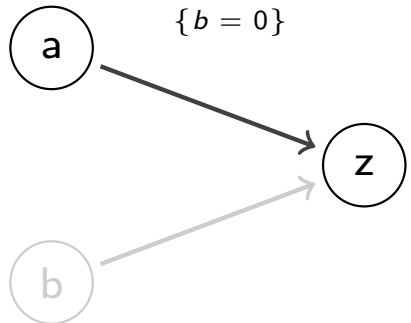

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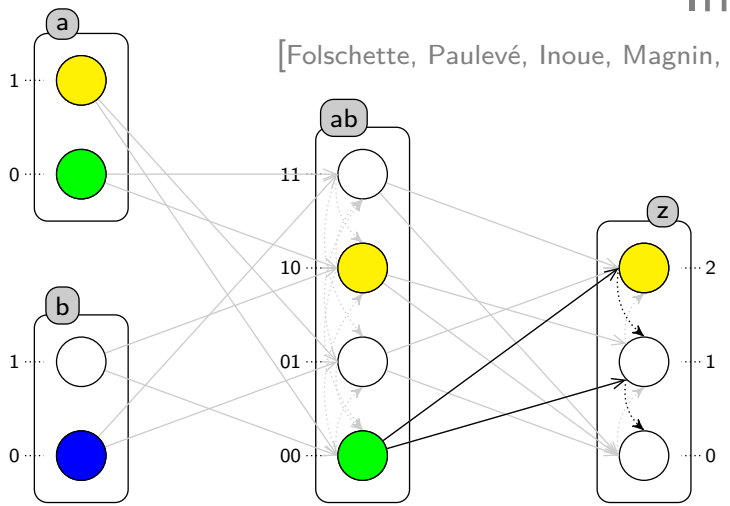

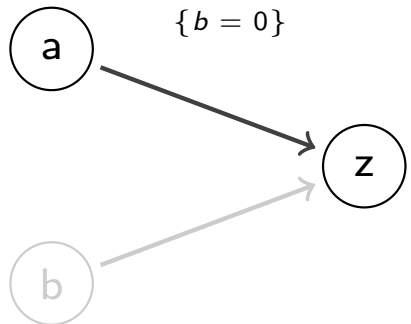

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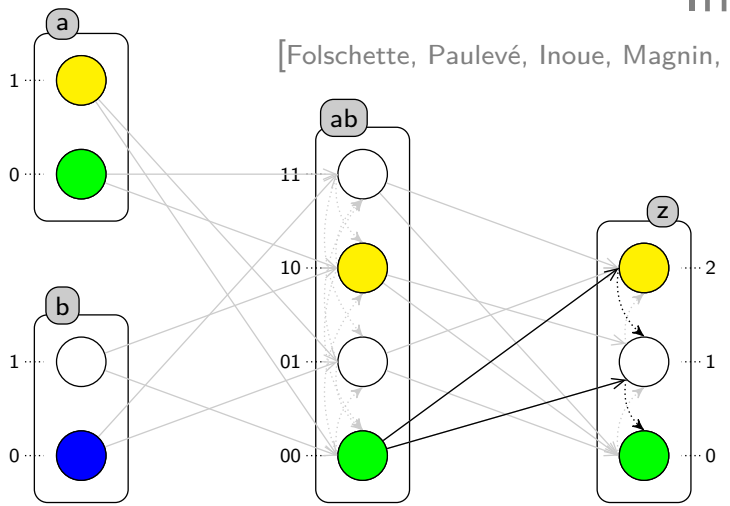

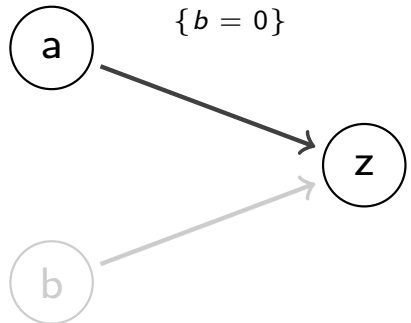

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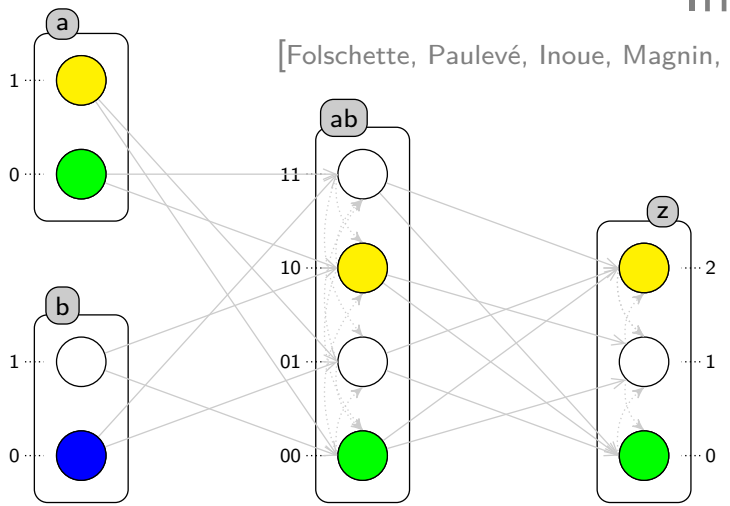

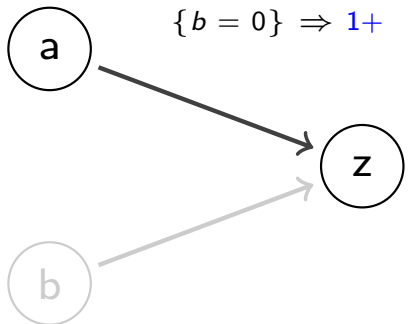

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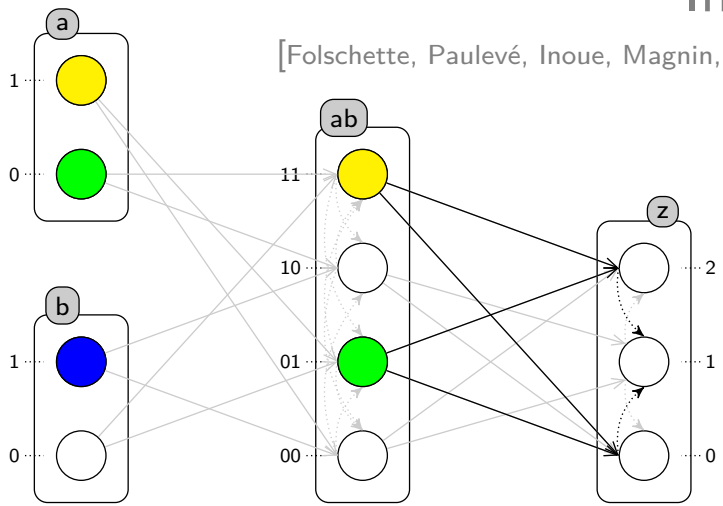
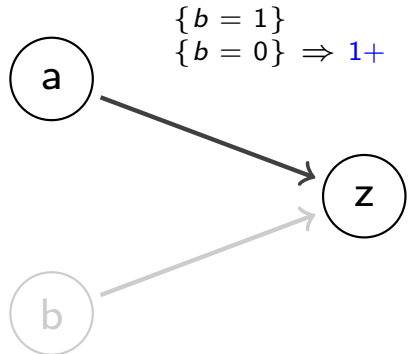
2. Change the active process of this regulator [a_0, a_1] and watch the **focal processes**.
3. Conclude locally: $(a_0 \Rsh a_1 \Rightarrow z_0 \Rsh z_2) \Rightarrow$ activation $(+)$ & threshold $= 1$.

Inferring the Interaction Graph

[Folschette, Paulevé, Inoue, Magnin, Roux in Computational Methods in Systems Biology, 2012]





→ **Exhaustive search in all possible configurations**

1. Pick one regulator [a], and choose an active process for all the others [b_0].
2. Change the active process of this regulator [a_0, a_1] and watch the **focal processes**.
3. Conclude locally: ($a_0 \Rsh a_1 \Rightarrow z_0 \Rsh z_2$) ⇒ activation ($+$) & threshold = 1.
4. Iterate

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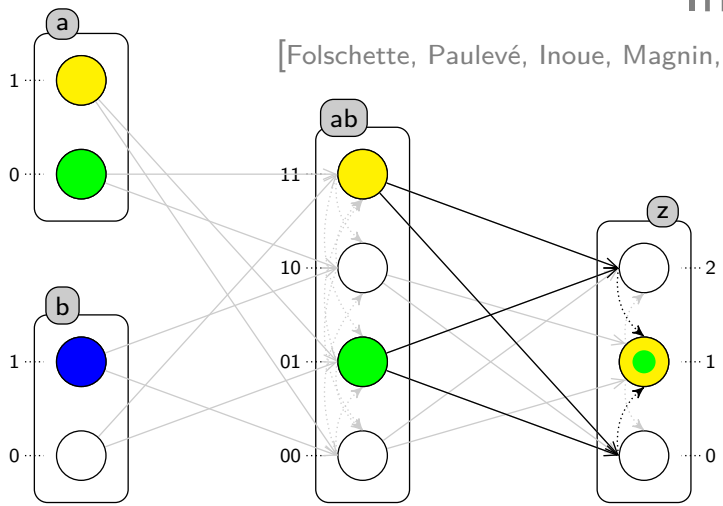

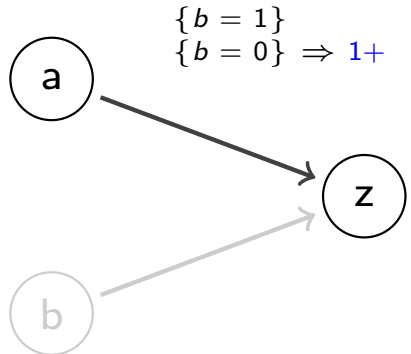

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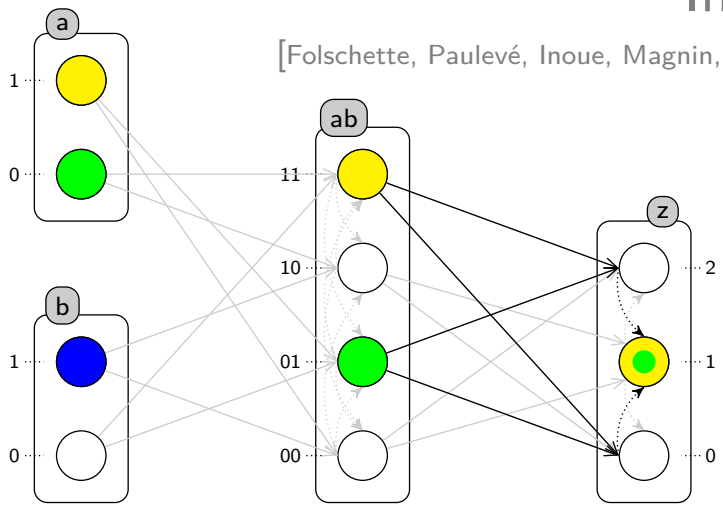

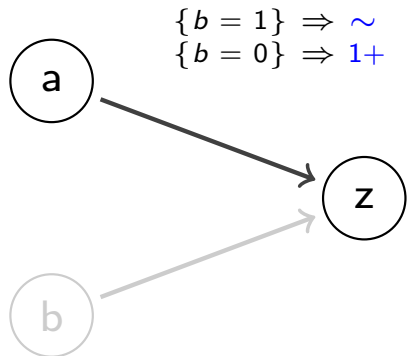

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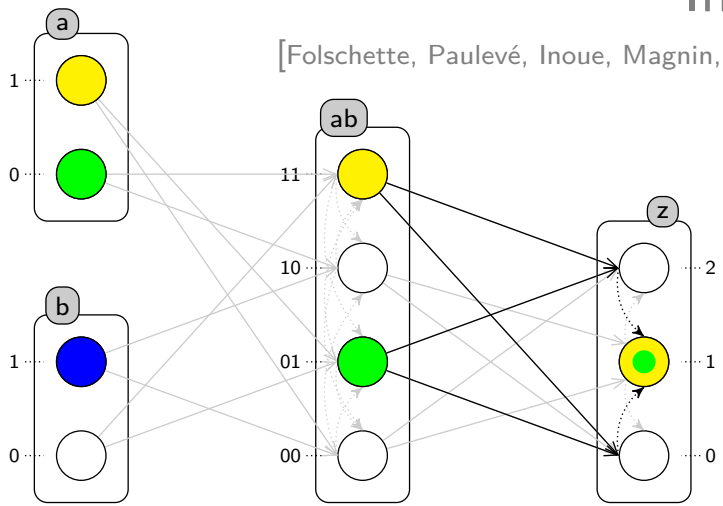

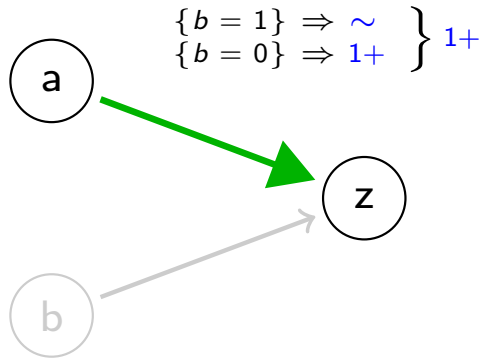

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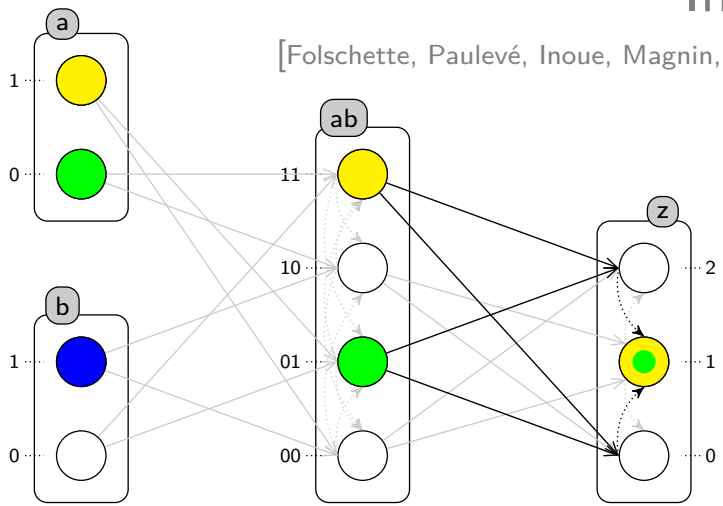

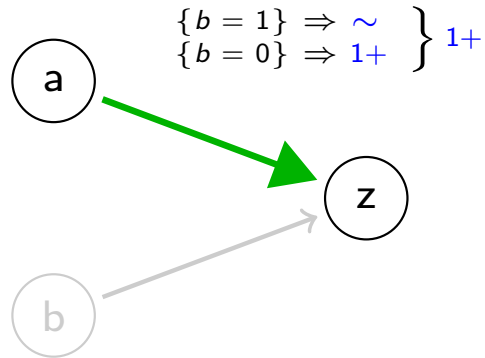

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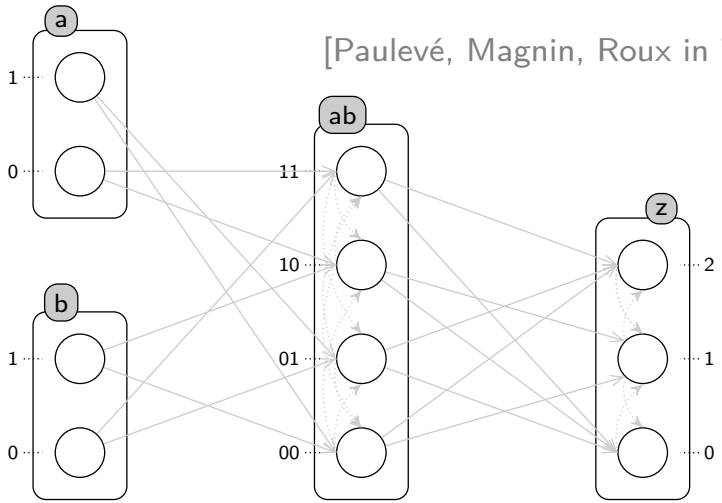
Problematic cases:

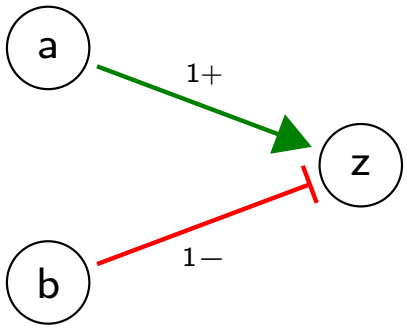
→ No focal processes (cycle)
→ Opposite influences ($+$ & $-$)

} ⇒ Unsigned edge

Inferring Parameters

[Paulevé, Magnin, Roux in Transactions on Computational Systems Biology, 2011]





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

Inferring Parameters

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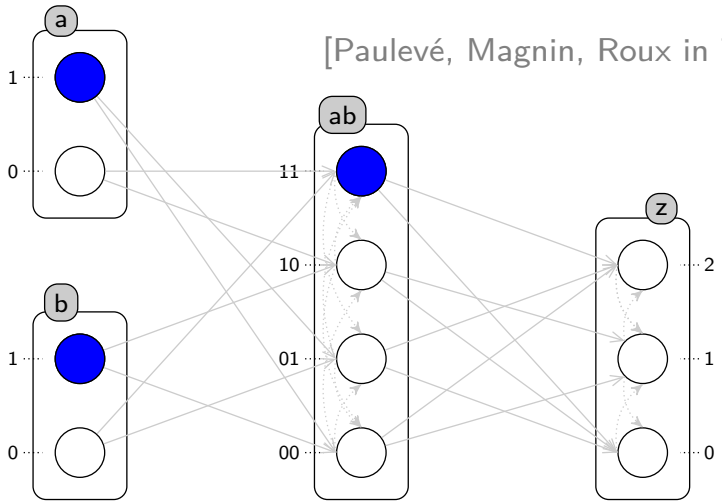

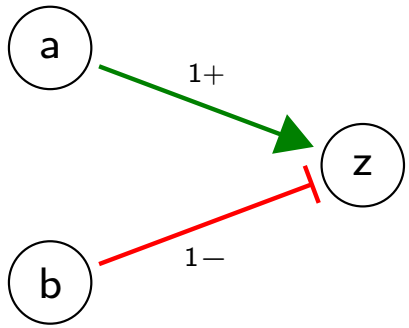

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	

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

Inferring Parameters

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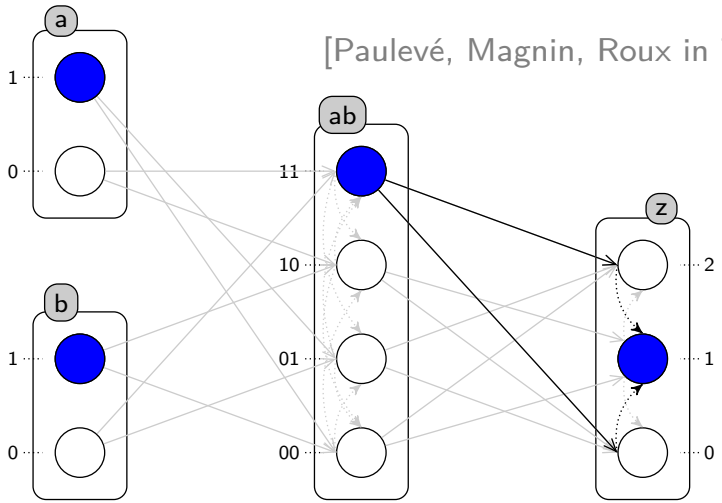

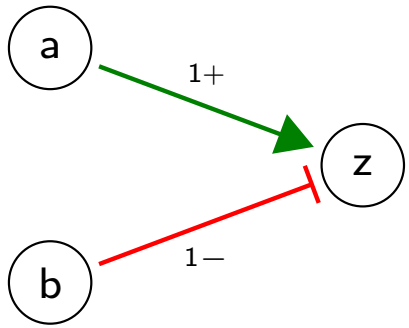

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	

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

Inferring Parameters

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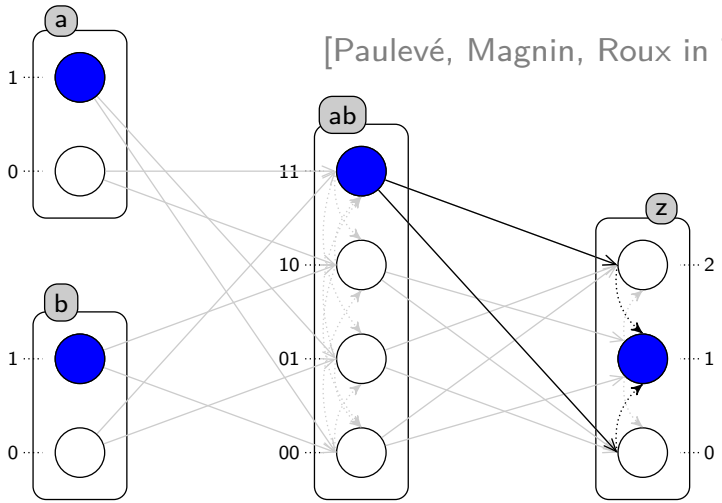

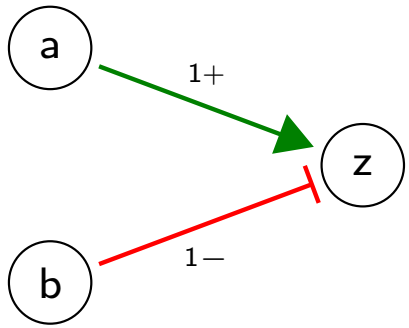

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	1

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

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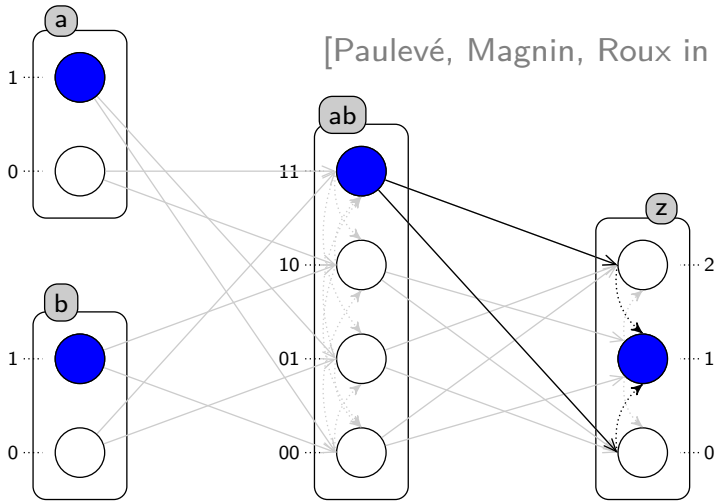

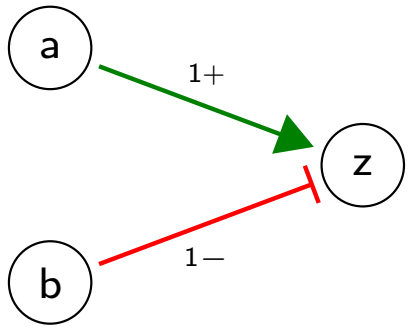

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
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   Inconclusive cases:
   - Behavior cannot be represented as a BRN
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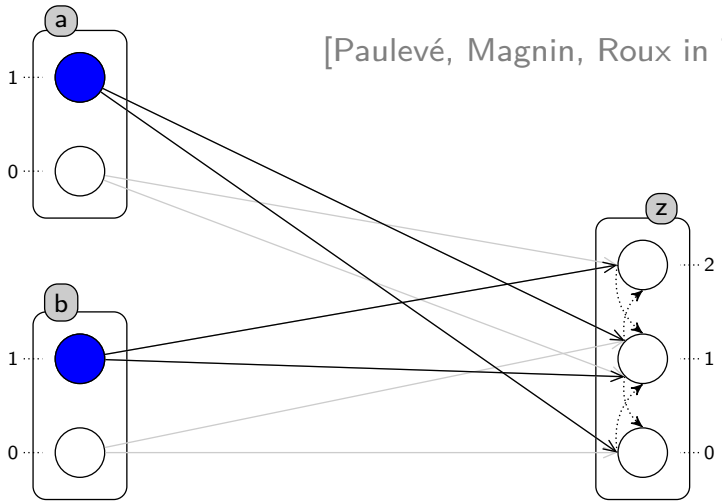

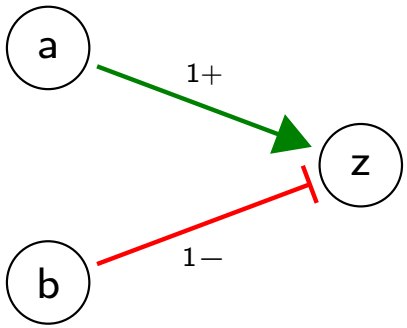

ω		$k_{z,\omega}$
a	b	
−	+	?
−	−	0
+	+	2
+	−	?

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

   Inconclusive cases:
   - Behavior cannot be represented as a BRN
   - Lack of cooperation (no focal processes)

2. If some parameters could not be inferred, enumerate all admissible parametrizations, regarding:
   - Biological constraints
   - The dynamics of the Process Hitting

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

Implementation

Workflow:

- Read and translate the models with **OCaml**
  → Integrated to PINT
- Express the problem in **ASP** (logic programming)
  → Solved with **Clingo** (**Gringo** + **Clasp**)

Complexity: linear in the number of genes, exponential in the number of regulators of one gene

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Model specifications				IG inference		Parameters inference	
Name	S+CS	P	A	Δt	Edges	Δt	Parameters
egfr20	**20**+22	152	399	**1s**	50	**1s**	191
tcrsig40	**40**+14	156	301	**1s**	54	**1s**	143
tcrsig94	**94**+39	448	1124	**13s**	169	∞	2.10^9
egfr104	**104**+89	748	2356	**4min**	241	**1min 30s**	$1.10^6/2.10^6$

S = Sorts CS = Cooperative sorts P = Processes A = Actions

egfr20: [Epidermal Growth Factor Receptor, by Özgür Sahin *et al.*]
egfr104: [Epidermal Growth Factor Receptor, by Regina Samaga *et al.*]
tcrsig40: [T-Cell Receptor Signaling, by Steffen Klamt *et al.*]
tcrsig94: [T-Cell Receptor Signaling, by Julio Saez-Rodriguez *et al.*]

Summary

1. Inference of the **complete Interaction Graph**
2. Inference of the **possibly partial Parametrization**
3. Enumerate all full & **admissible Parametrizations**

   → Exhaustive approaches

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Conclusion

Existing translation: René Thomas $\rightsquigarrow$ Process Hitting

New translation: Process Hitting $\rightsquigarrow$ René Thomas

→ New **formal link** between the two models

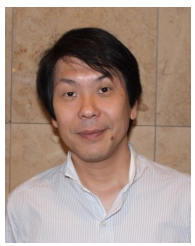
→ More **visibility** to the Process Hitting

Joint work

Inoue Laboratory: National Institute of Informatics / Sokendai / Tokyo (Japan)

MeForBio: IRCCyN / École Centrale de Nantes / Nantes (France)

BISON: Institut für Automatik / ETH / Zürich (Switzerland)



Katsumi INOUE
Professor & team leader

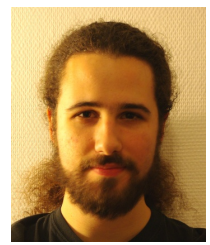
Inoue Laboratory

Loïc PAULEVÉ
Post-doc

BISON

Olivier ROUX
Professor & team leader

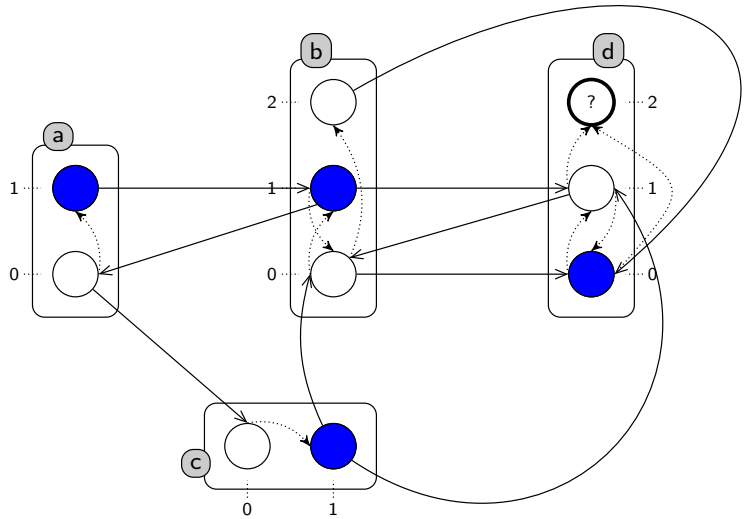
Morgan MAGNIN
Associate professor



Maxime FOLSCHETTE
2^{nd} year PhD student

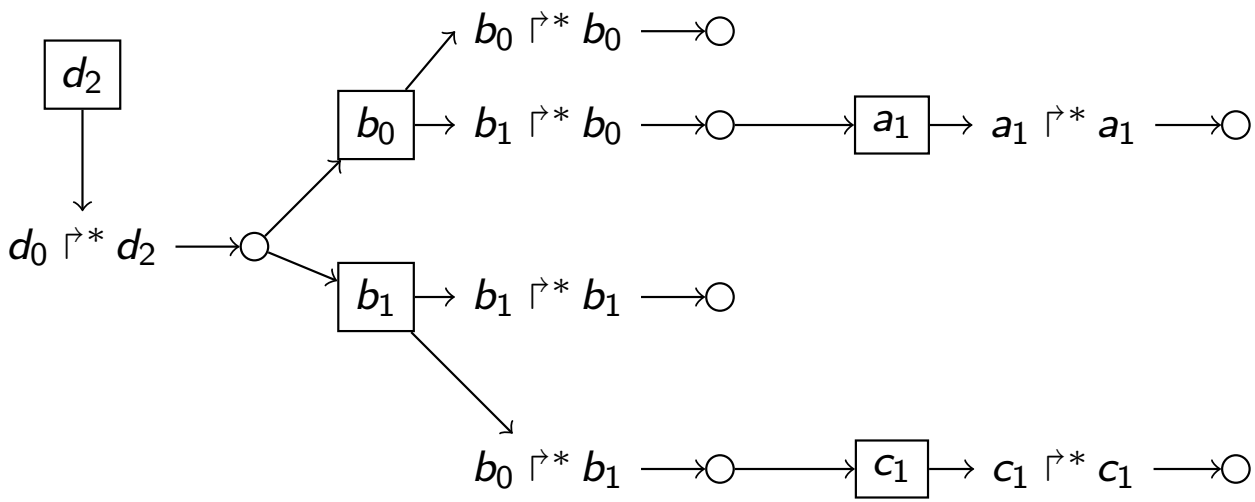
MeForBio

Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution



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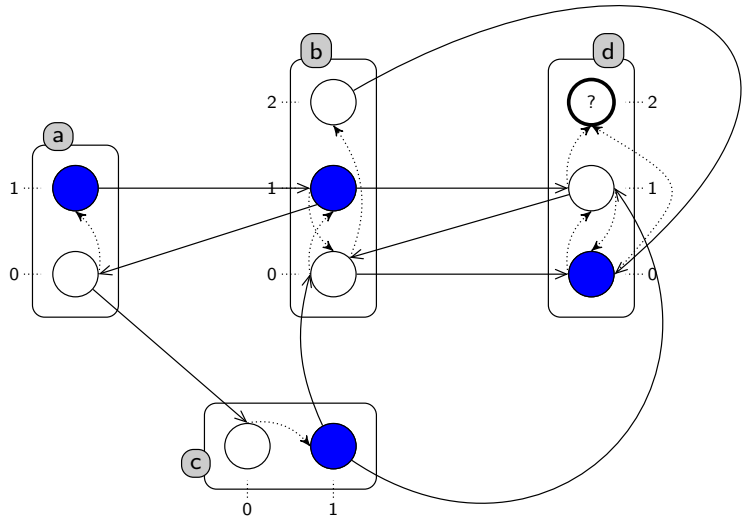

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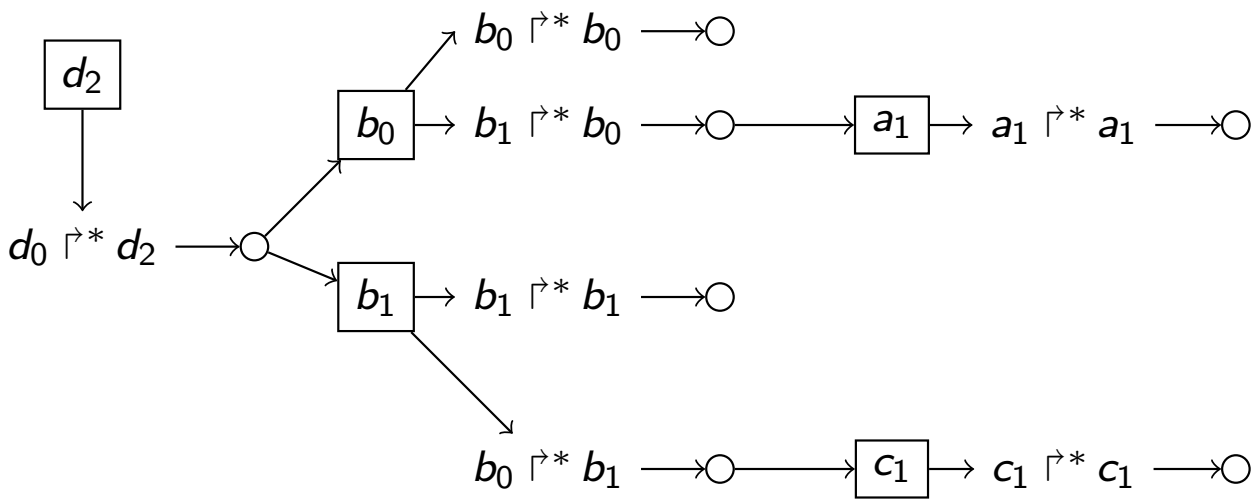
R is **true**



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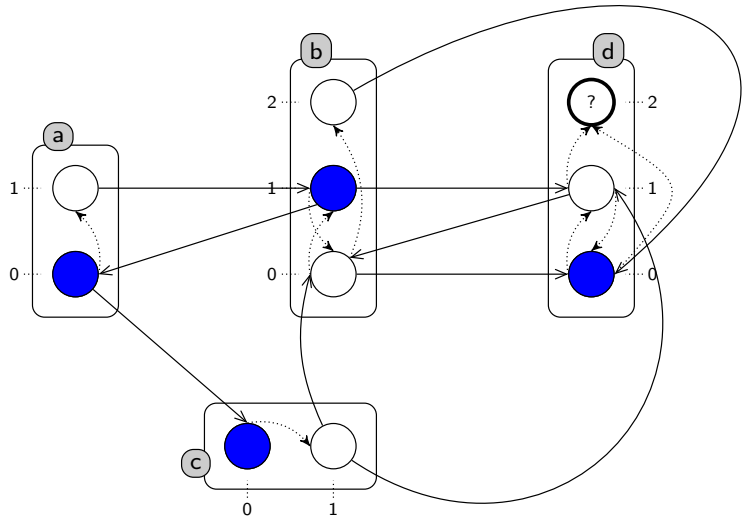

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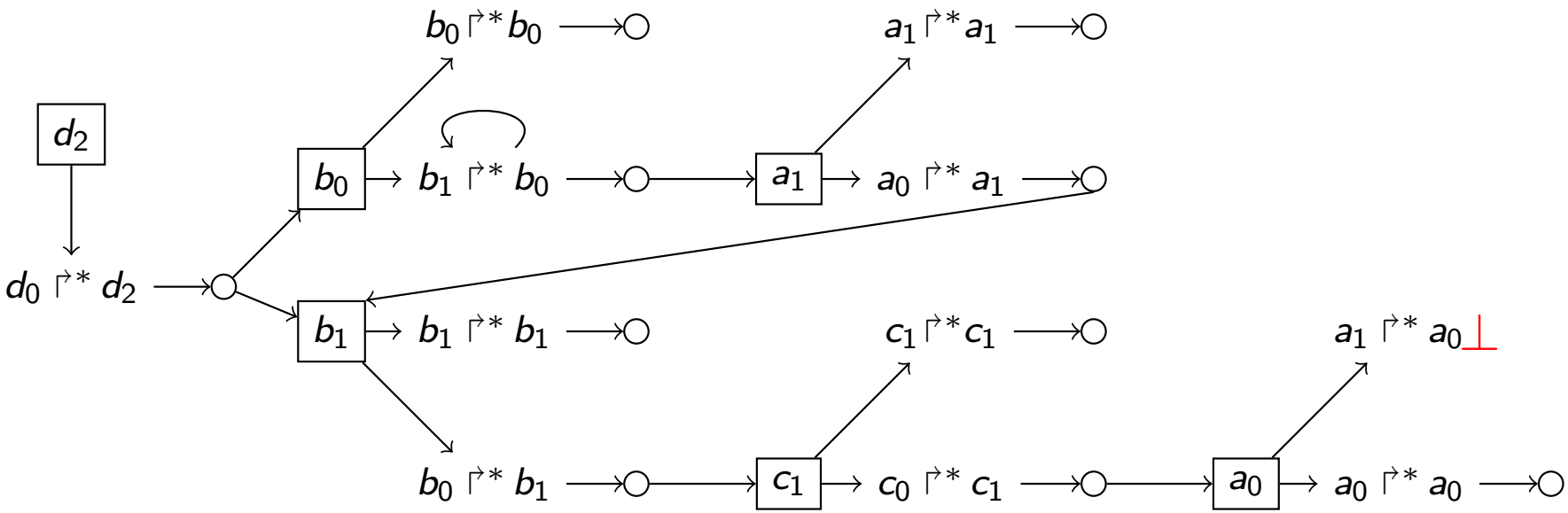

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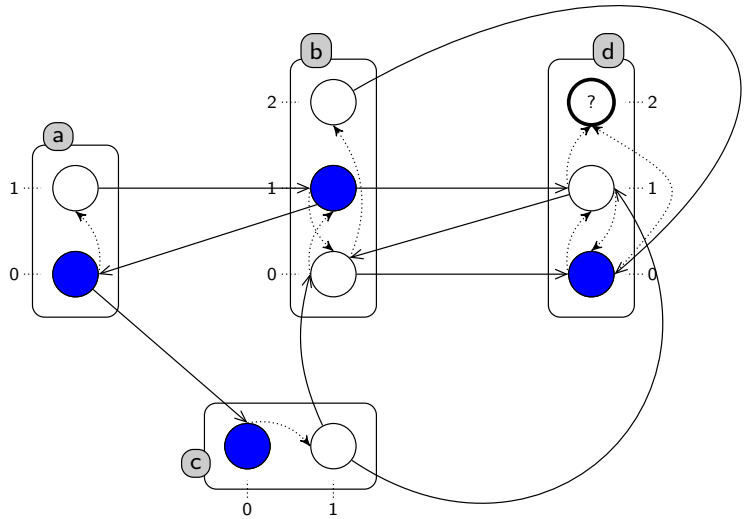

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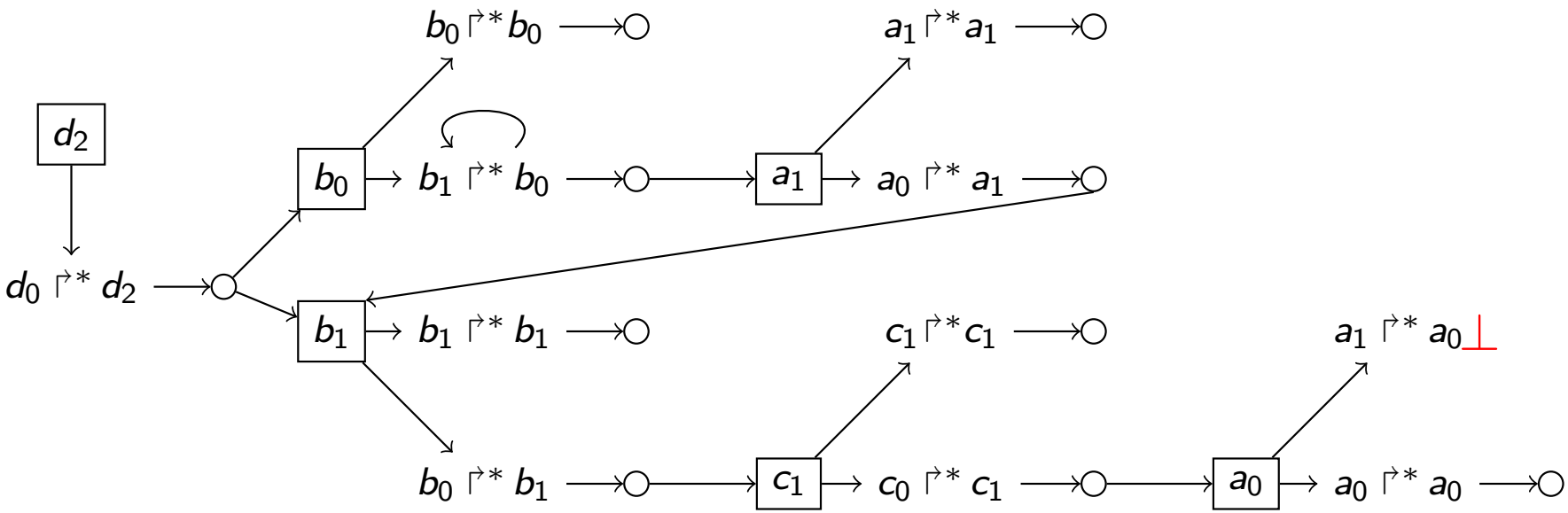
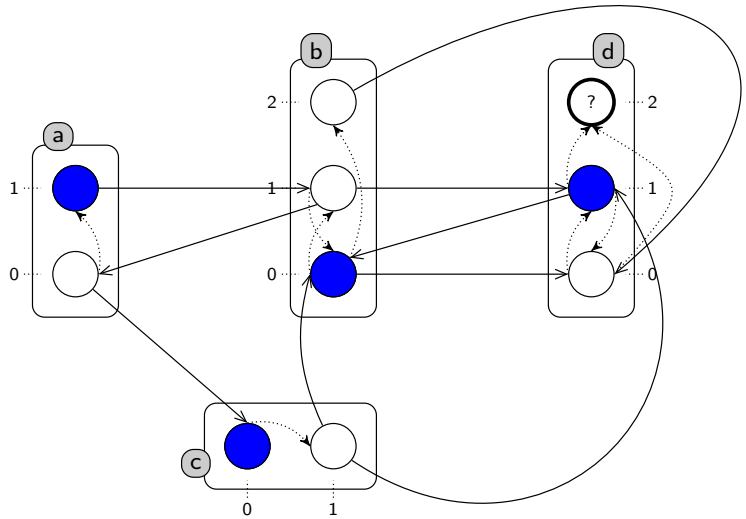
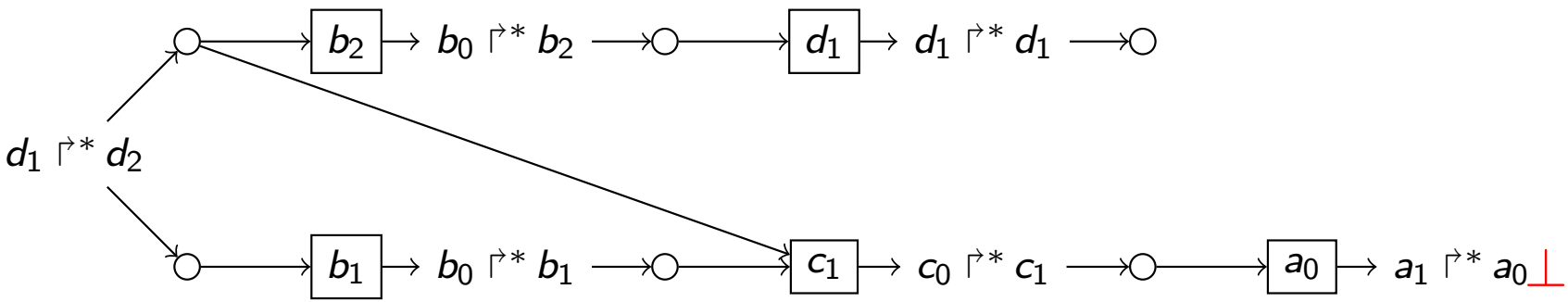
Inconclusive



Over-approximation



Necessary condition:



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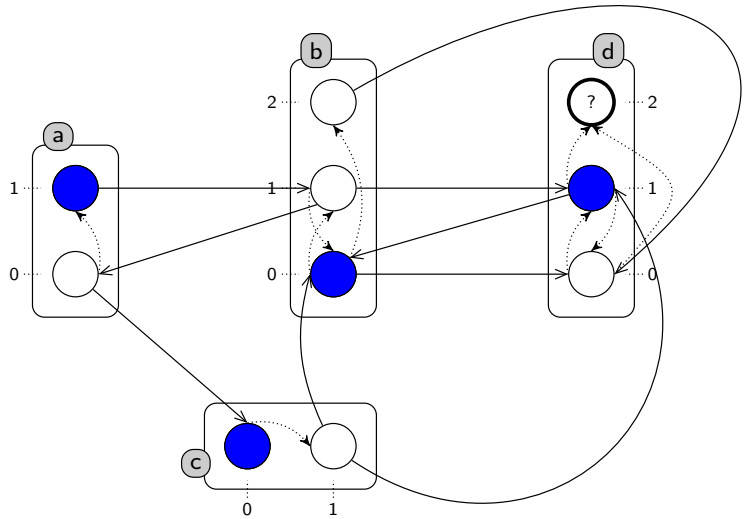
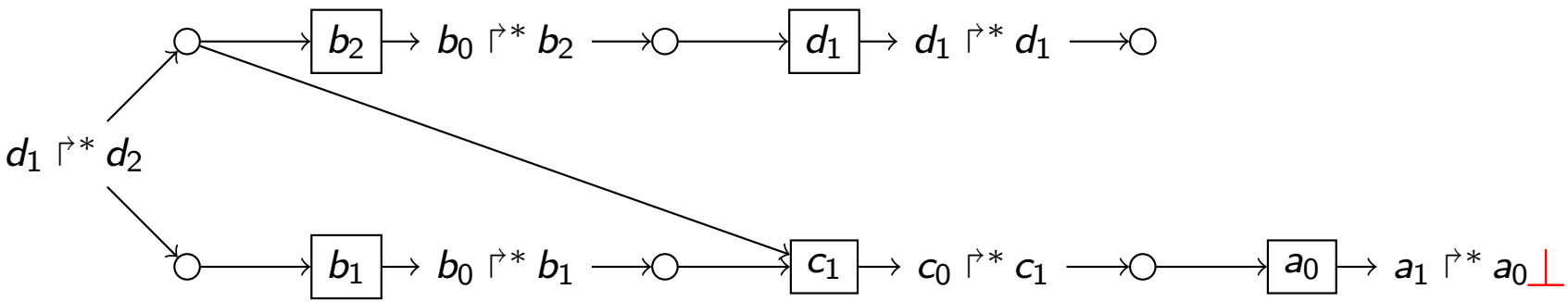


Necessary condition:

There exists a traversal with no cycle

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



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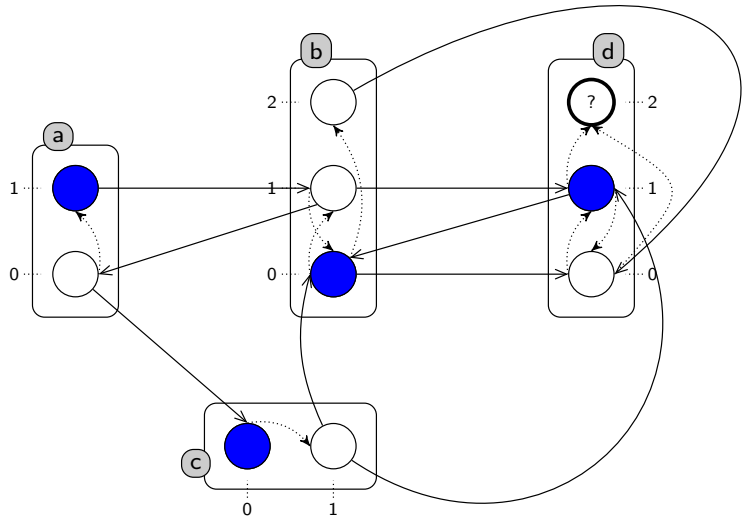

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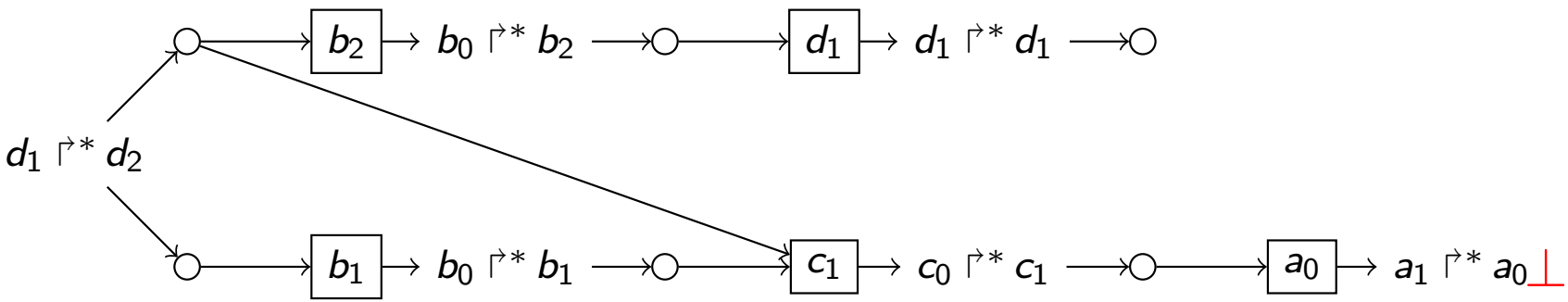

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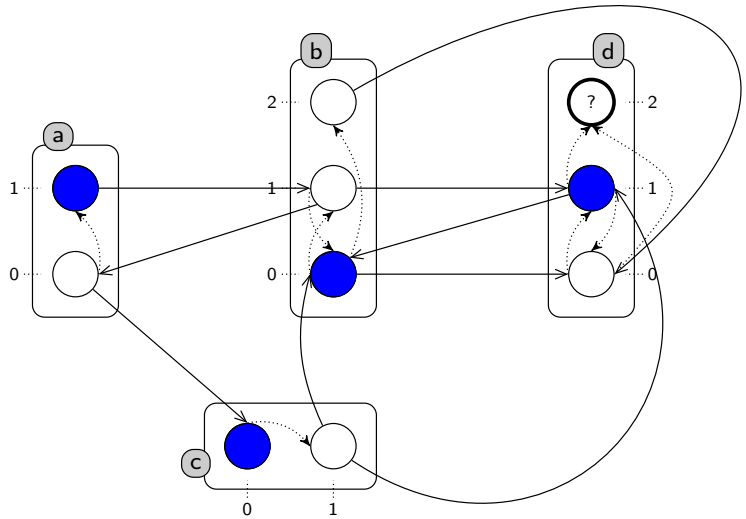
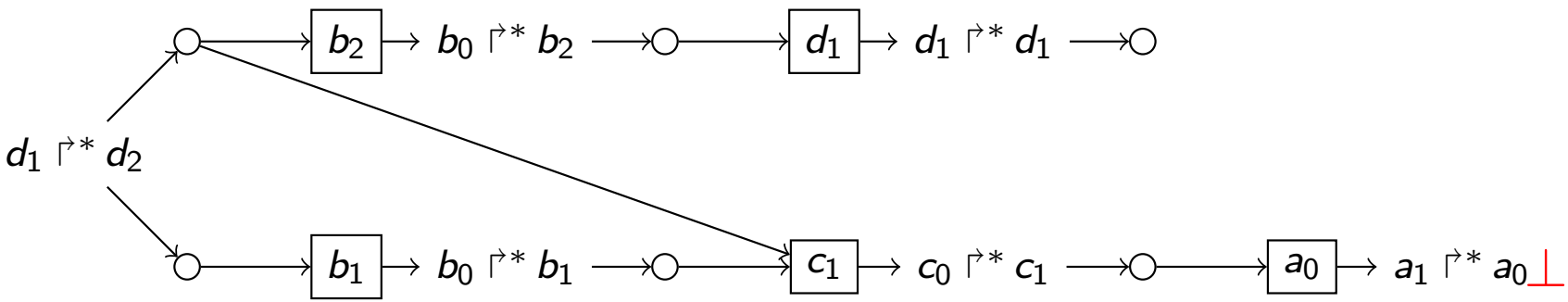


Necessary condition:

~~There exists a traversal~~ with no cycle

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

R is **false**



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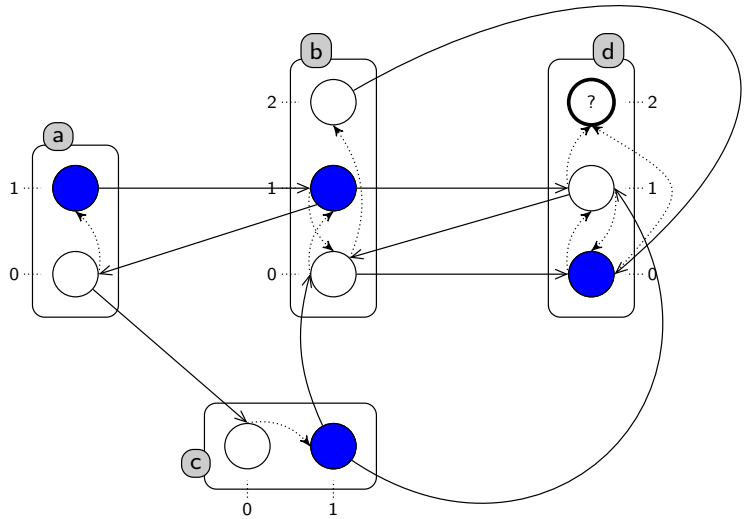

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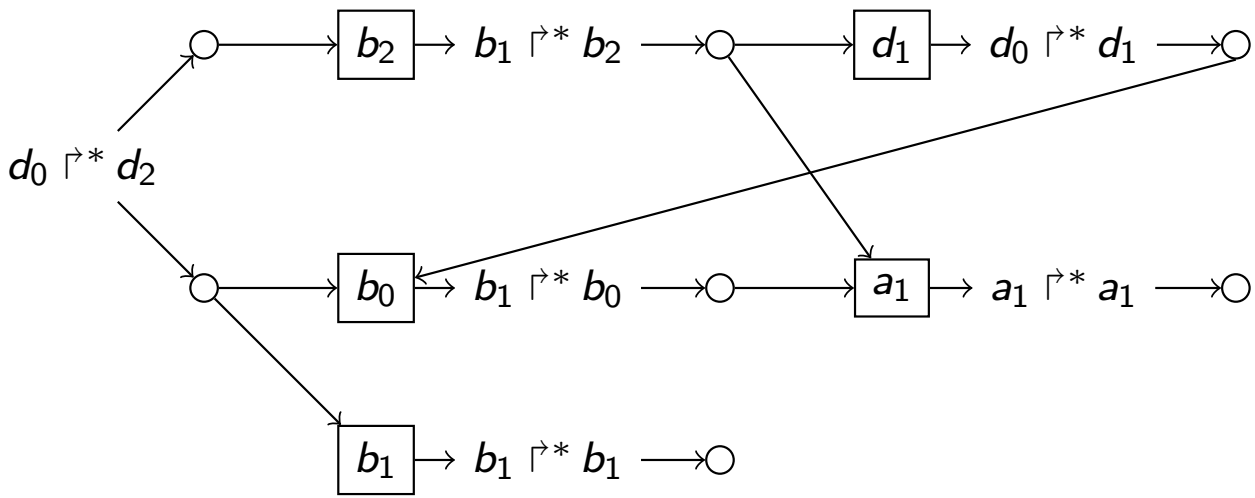
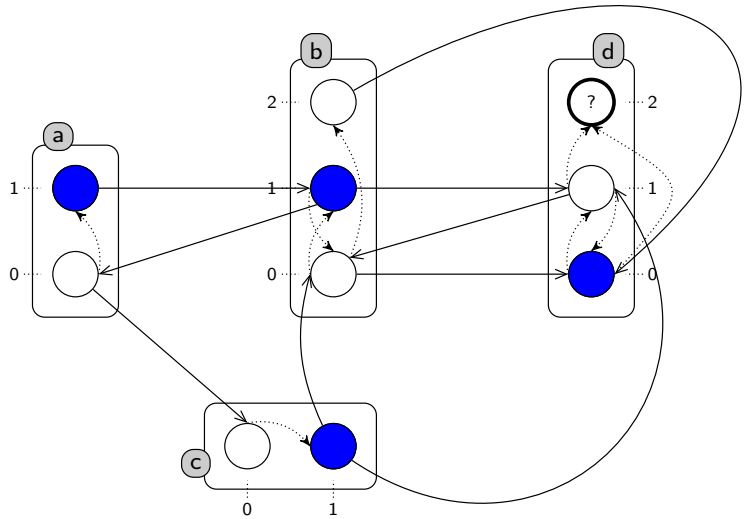


Over-approximation



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There exists a traversal with no cycle

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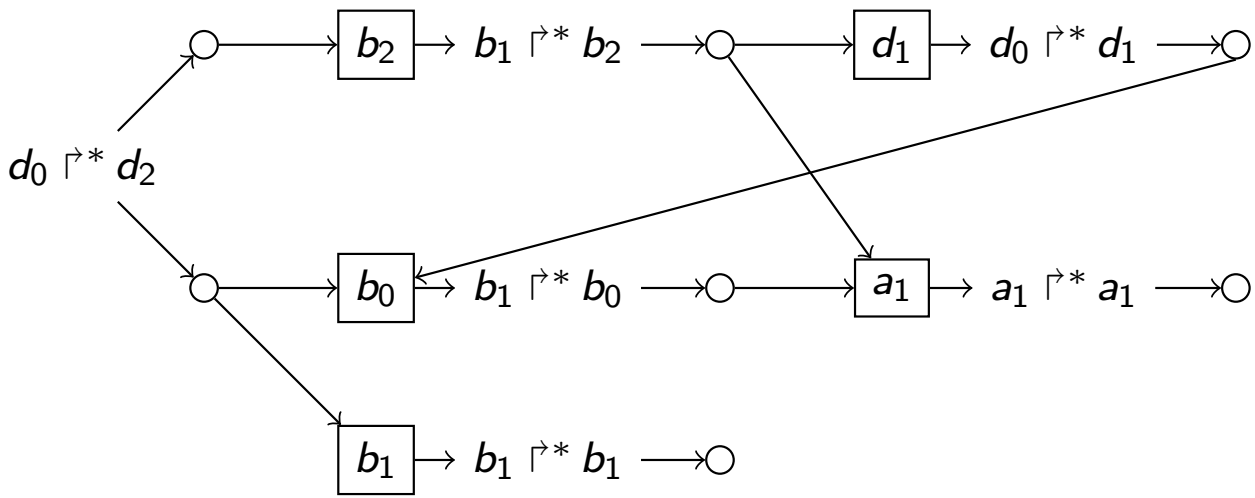

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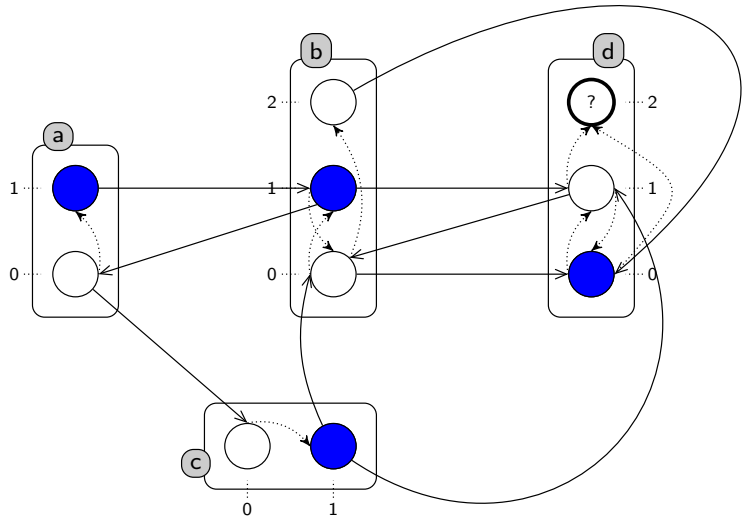

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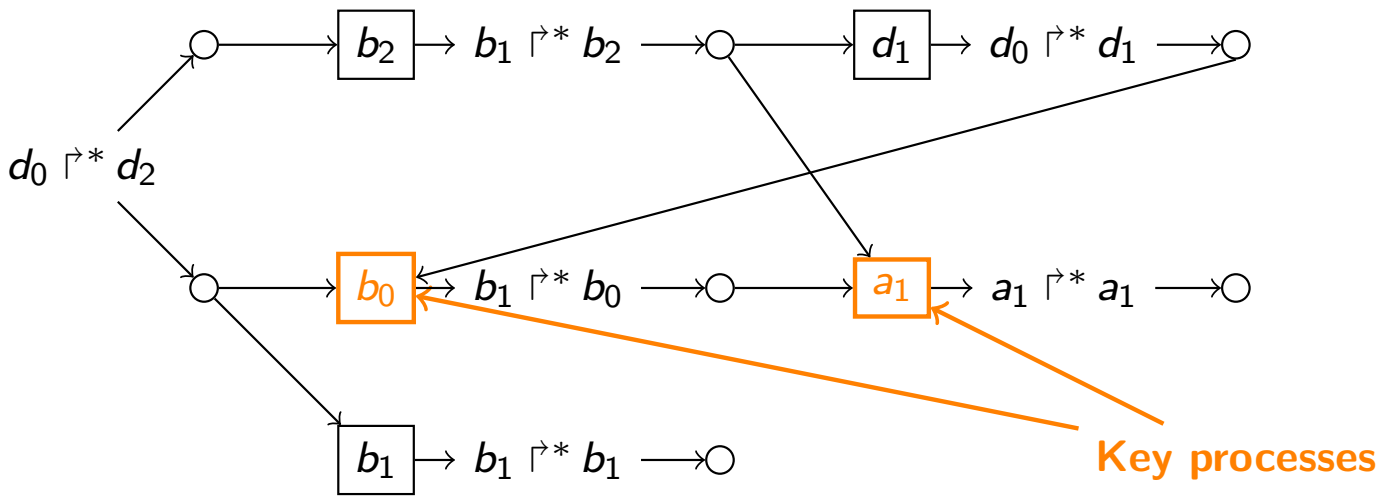

Static Analysis: Fixed Points

[Paulevé, Magnin, Roux in Transactions on Computational Systems Biology, 2011]

Fixed point = state where no action can be fired

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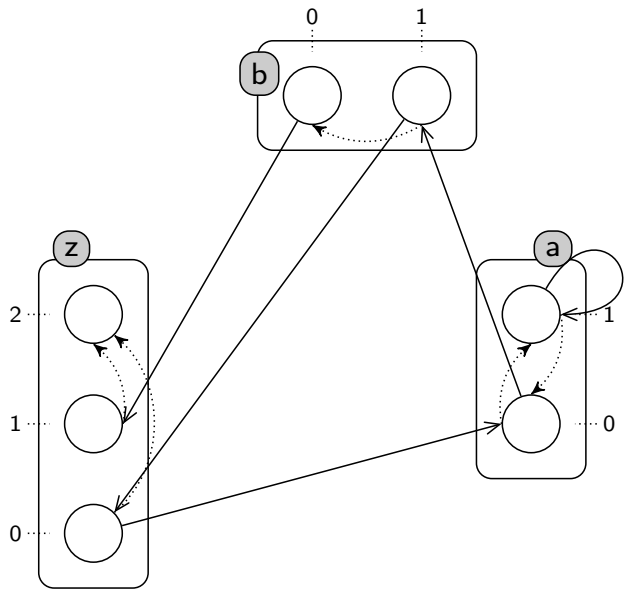

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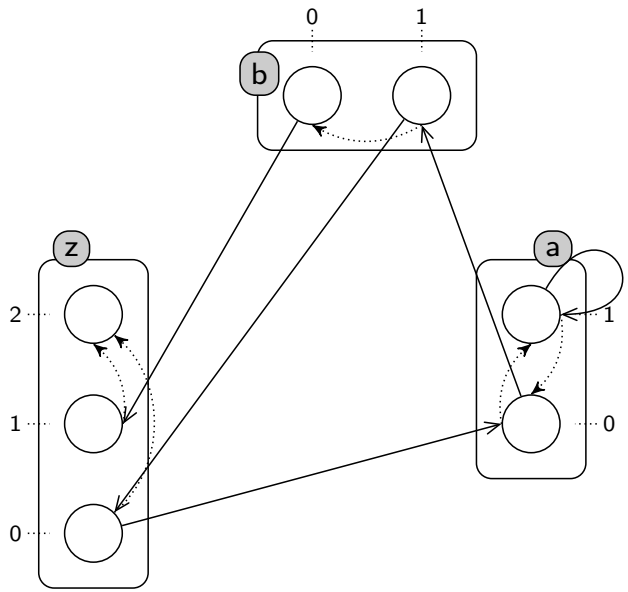

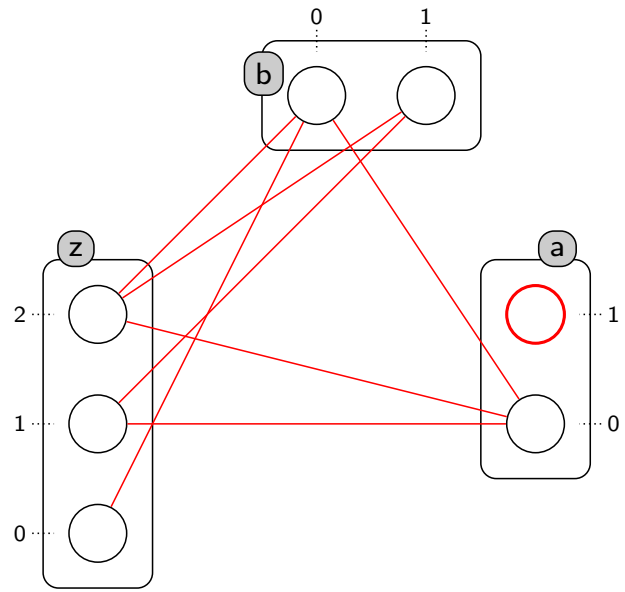

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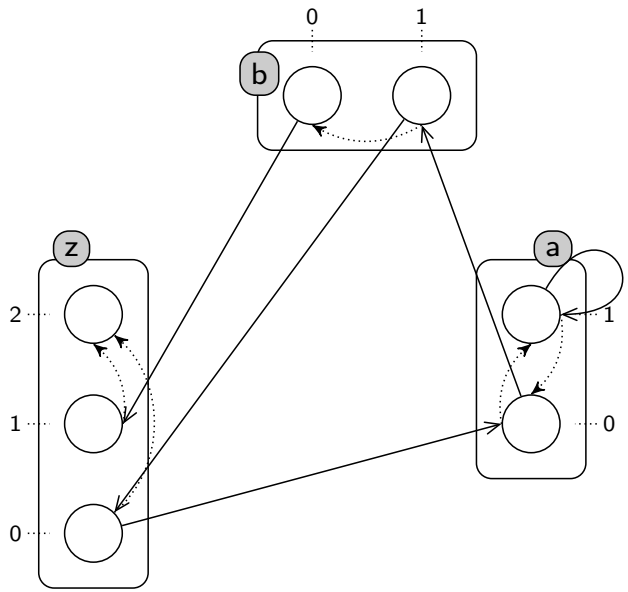

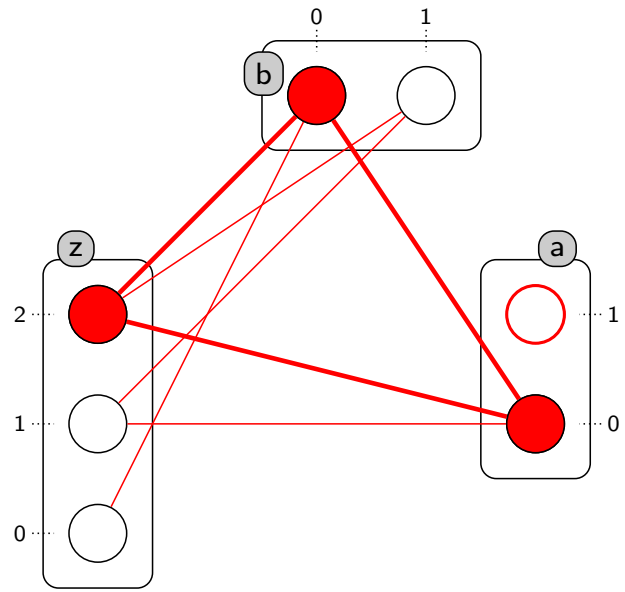

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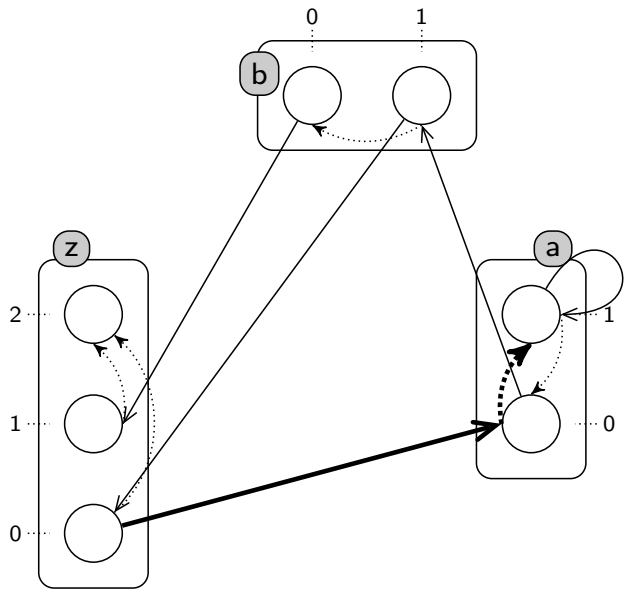

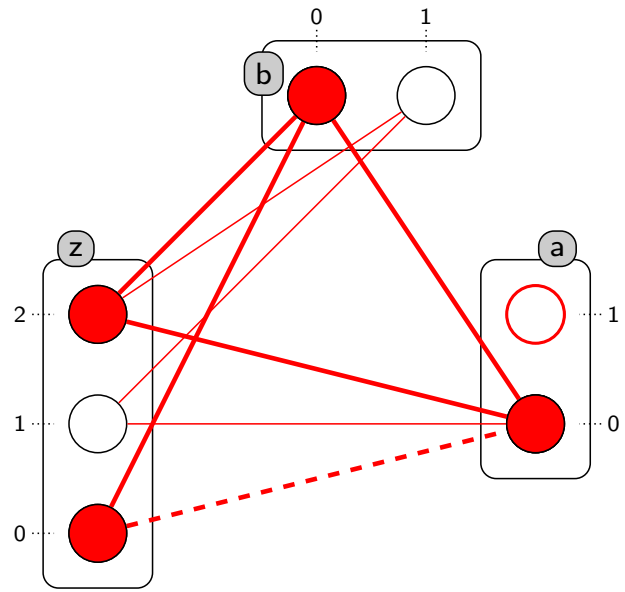

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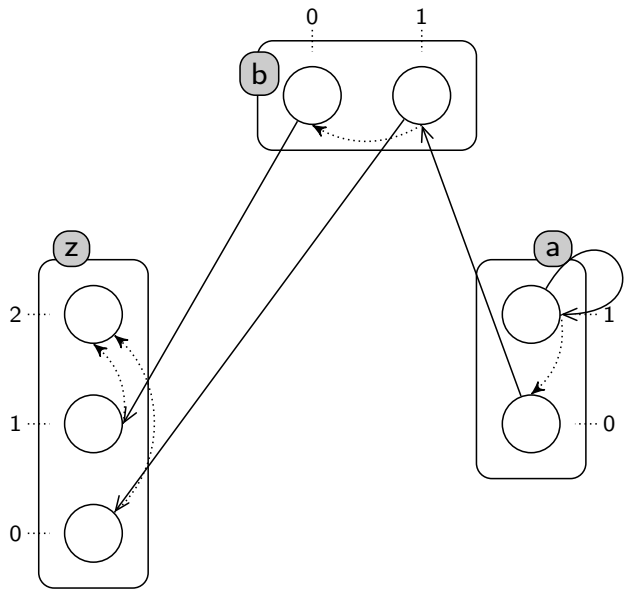

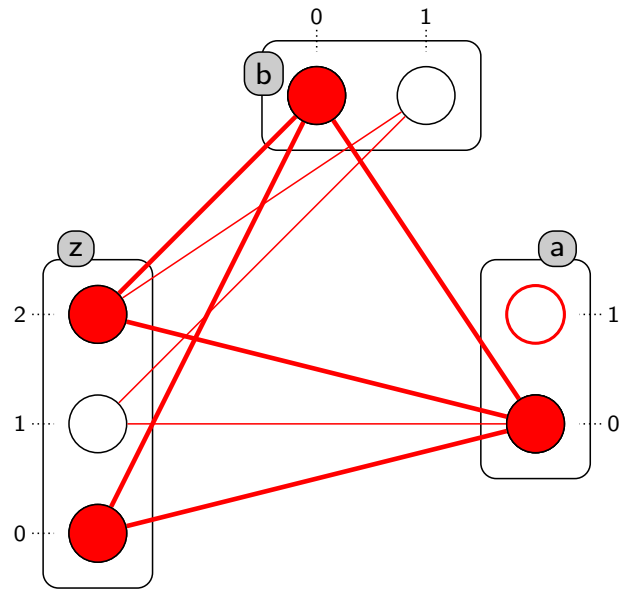

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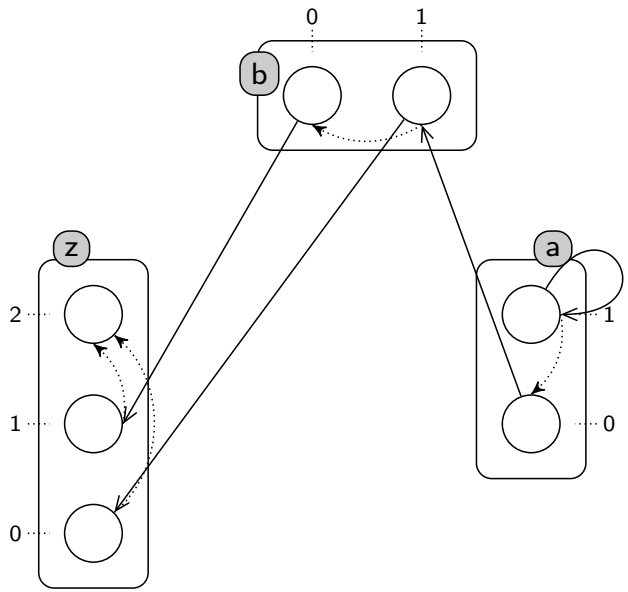

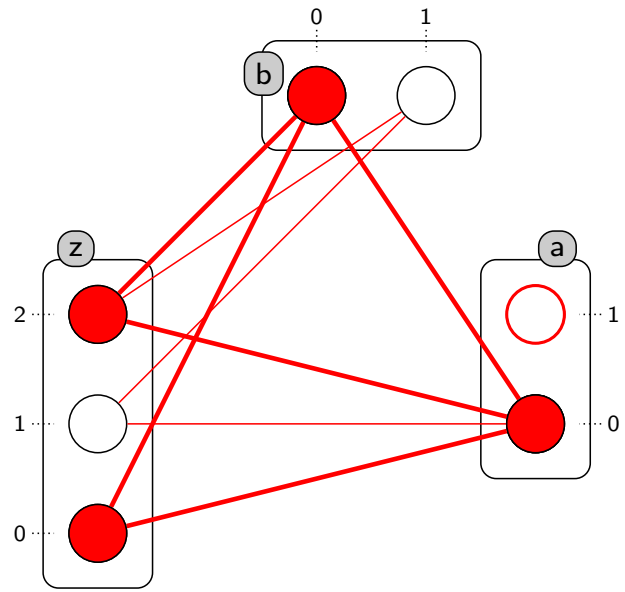

Exponential complexity w.r.t. the number of sorts

Stochastic Features

[Paulevé, Magnin, Roux in Transactions on Computational Systems Biology, 2011]

- Introduces time features
- Parameters: either (r, sa), or the **firing interval** $[d; D]$.

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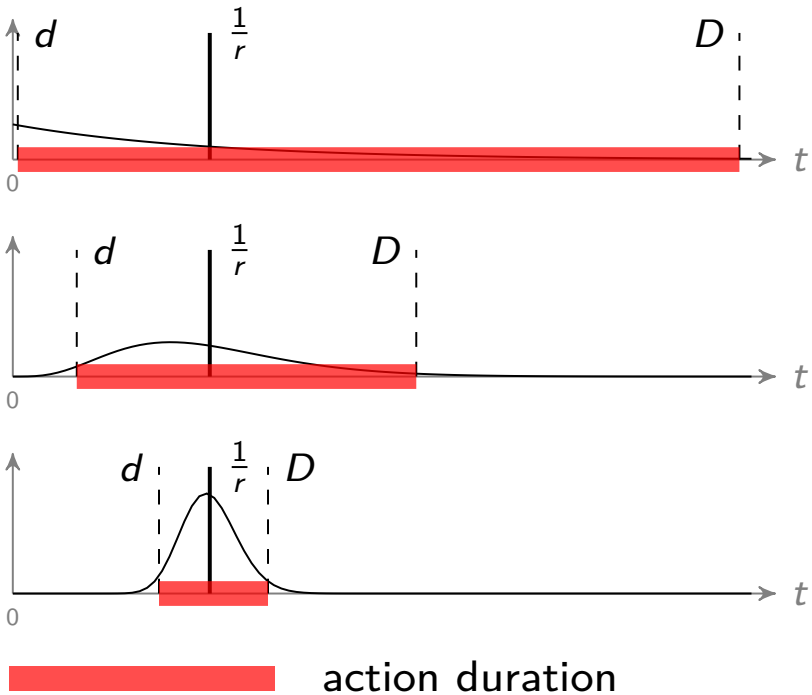

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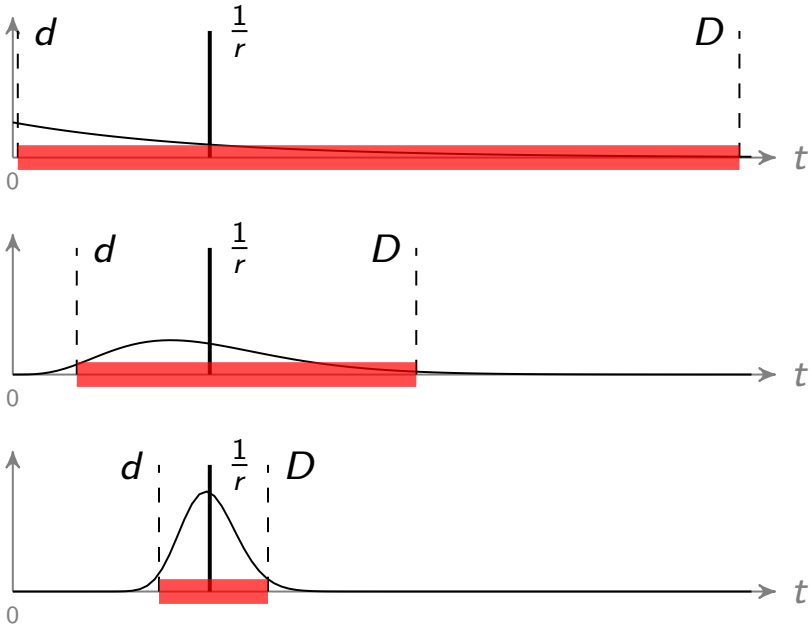
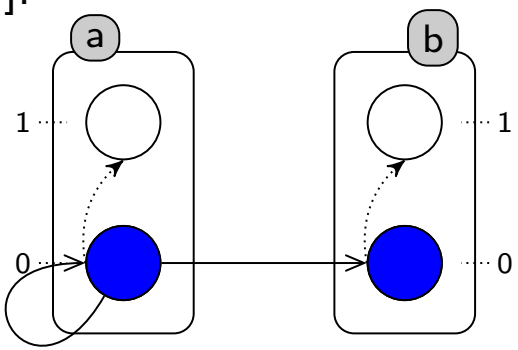


action duration



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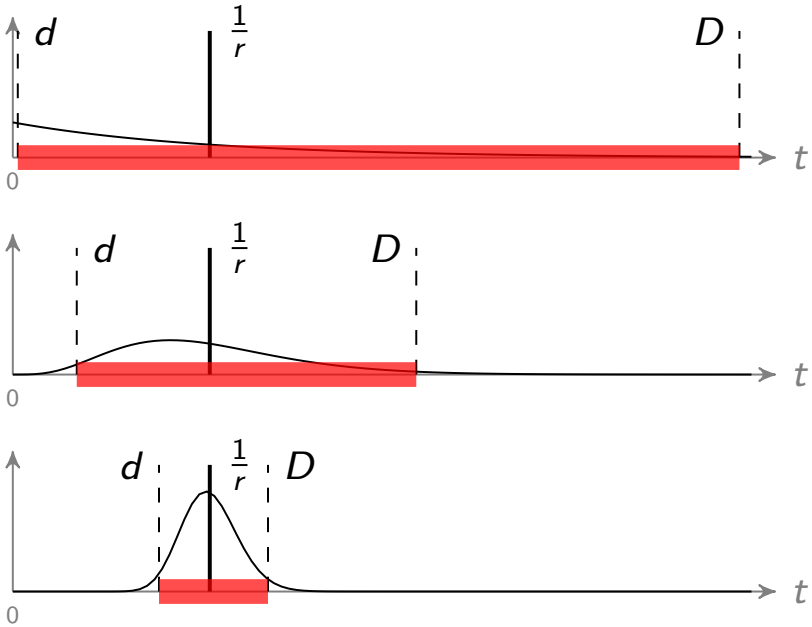

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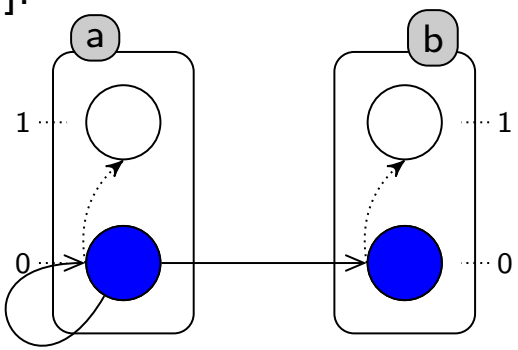

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