KUBIC-NII Joint Seminar on Bioinformatics 2014

Perturbations and Recovery Costs in Biological Regulatory Networks with Process Hitting

Maxime FOLSCHETTE

MeForBio / IRCCyN / École centrale de Nantes (Nantes, France)
maxime.folschette@irccyn.ec-nantes.fr
http://maxime.folschette.name/

Ongoing work with: **Morgan MAGNIN** and **Katsumi INOUE**

2014/11/17

Studying the Perturbations of a Biological Model

Biological models are well-known for being resilient

- Alternative pathways
- Restoration of oscillations

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Observe or measure this in qualitative models:

- Running the models → slow and inefficient
- Model checking → requires powerful methods
- Resilience times → requires timing data
- Observation of specific characteristics → **impact degree**

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Refine this analysis with new model checking methods:

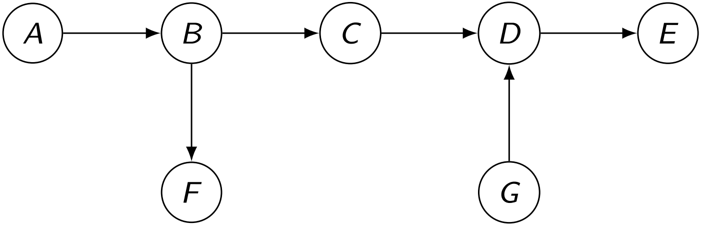
- The Process Hitting framework
- Efficient **reachability analysis**
- Finer study of the perturbations

Impact Degree

[Jiang, Tamura, Ching, Akutsu in *Communications and Computer Sciences*, 2013]

Reaction networks = set of species consumed and produced by reactions

- Reaches an equilibrium state



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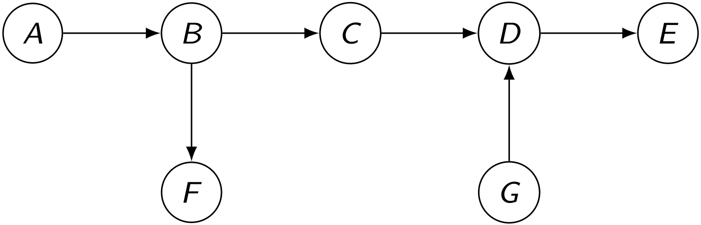

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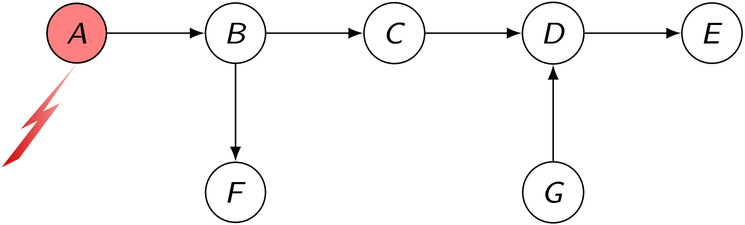

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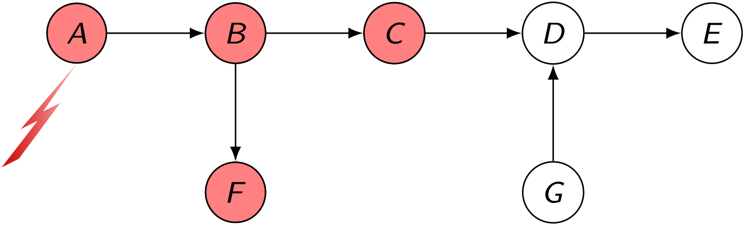

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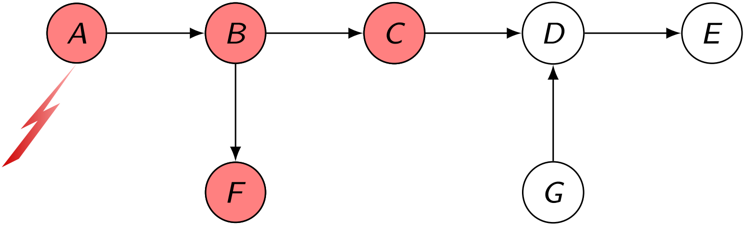

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- Notion of importance/criticality of a node
- Highlights the resilience of biological systems (alternative paths)

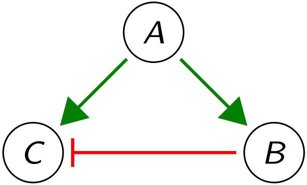
Application to regulation networks

Model from [Comet, Bernot in *Nice Spring school on Modelling and simulation of biological processes in the context of genomics*, 2010]

Regulation networks = set of species regulated by other species

→ The regulating species are not consumed

→ Negative regulations → Not always a steady state



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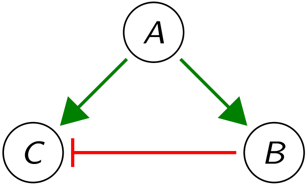

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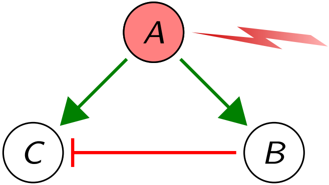

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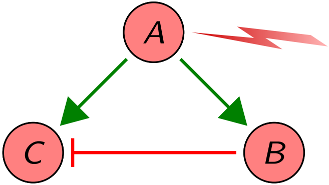

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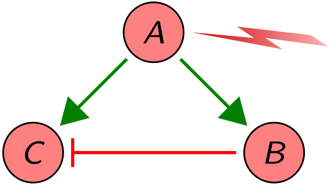

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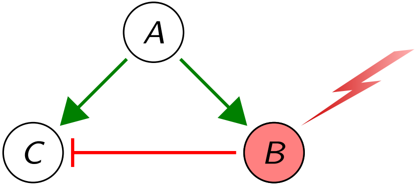

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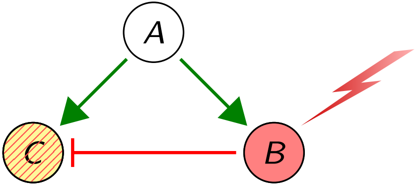

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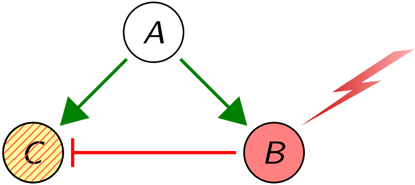

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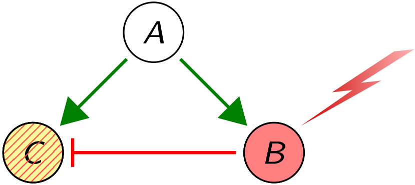
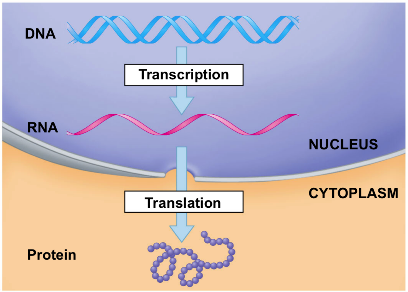


New notion of **impact degree**

- Number of species that are completely turned off → For A: 3
- Number of species whose behavior is modified → For B: $1 + 1 = 2$

→ Requires a more precise study of the behavior

Abstractions of the Representation



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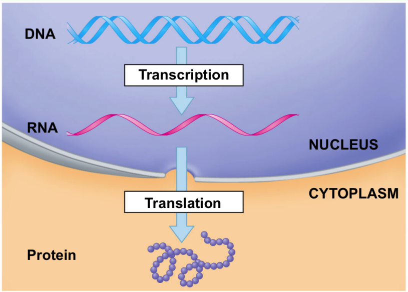
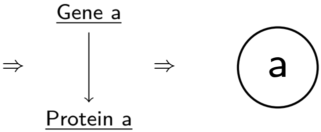
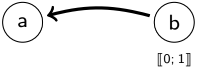
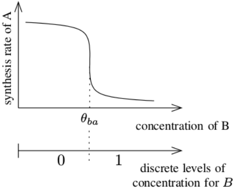




Discretization and Asynchronism

[Richard, Comet, Bernot (tutorial), 2008]





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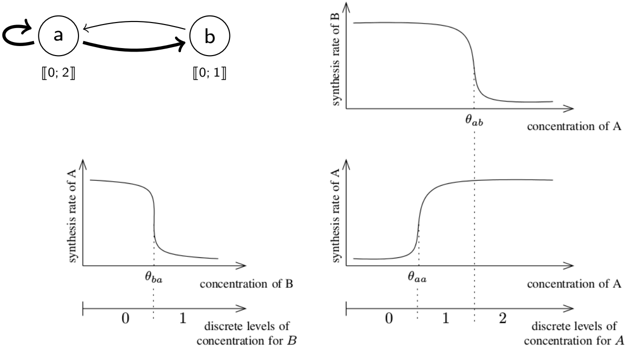

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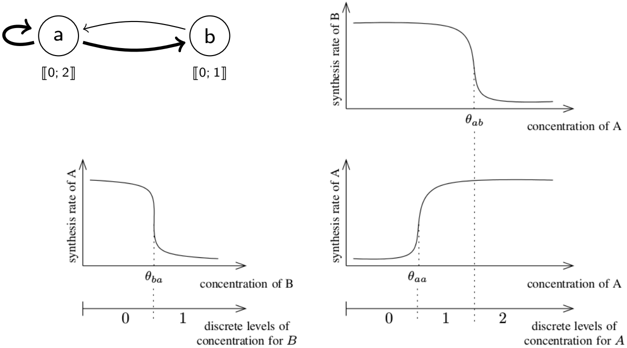

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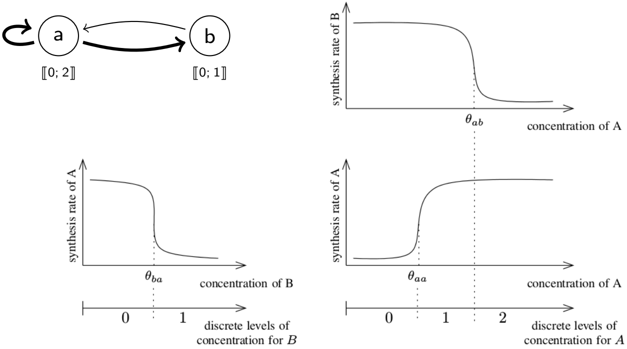

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- Continuous variations of the real values
  → **Unitary** dynamics

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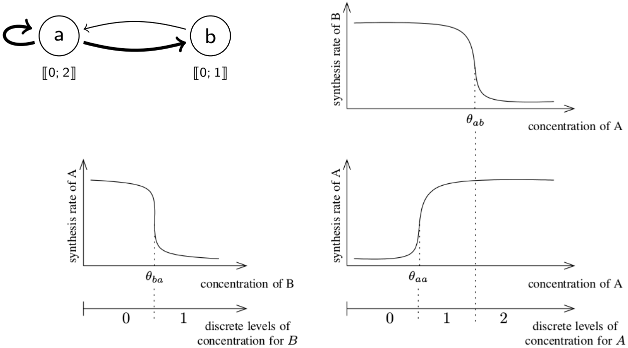
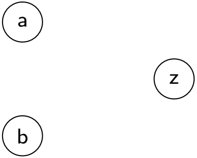


- Unknown real values of concentrations or continuous activity levels
  $\rightarrow$ Abstracted as thresholds or **discrete levels**
- Continuous variations of the real values
  $\rightarrow$ **Unitary** dynamics
- Simultaneous crossings of two thresholds never occurs
  $\rightarrow$ **Asynchronous**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

Discrete Networks / Thomas Modeling

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

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



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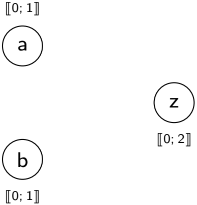

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- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

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

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

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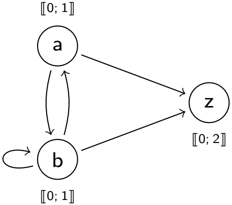
1	1	**2**



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- Signs and thresholds on the edges $a \xrightarrow{+1} z$

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a	b	$f^b(a, b)$
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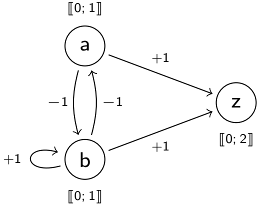
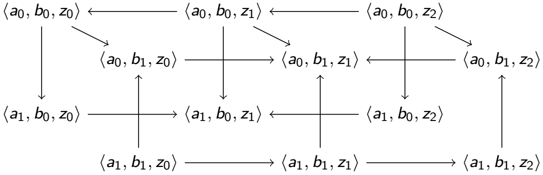


Analysis of Thomas Modeling

The State graph is computed in a unitary and asynchronous fashion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→ **Exponential** size in the number of components

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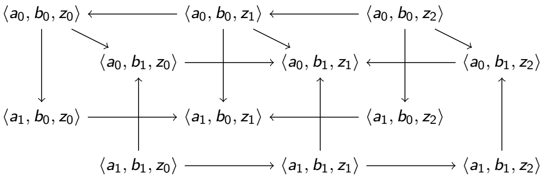
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Some works link the structure of the model to some dynamic properties:

- **Thomas' conjectures** (conditions for multi-stationarity or sustained oscillations)
    - Boolean case: [Remy, Ruet, Thieffry in *Advances in Applied Mathematics*, 2008]
    - Multivalued case: [Richard, Comet in *Discrete Applied Mathematics*, 2007]

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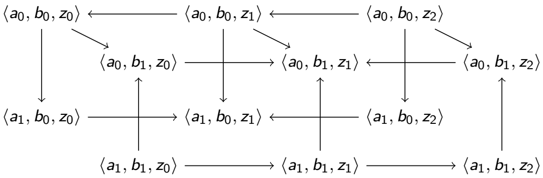
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But reachability properties require to compute the whole state graph:
Example: From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?

- **Temporal logics**
  - CTL: [Bernot, Comet, Richard, Guespin in *Journal of Theoretical Biology*, 2004]
  - LTL: [Ito, Izumi, Hagihara, Yonezaki in *BioInformatics and BioEngineering*, 2010]

Process Hitting

[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]

The **Process Hitting** is:

- A recent formalism well-adapted to the modeling of BRNs
- An **atomistic, qualitative and asynchronous** modeling (explicit & discrete expression levels)
- **Simple but powerful** dynamics (constraints on the form of actions)

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- **Reachability analysis** by abstract interpretation
- Fixed points enumeration
- Stochastic parameters

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Previously developed tools:

- **Reachability analysis** by abstract interpretation
- Fixed points enumeration
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→ The **reachability analysis** is very efficient (polynomial time)
→ The Process Hitting is also well-adapted to study **large BRNs**

Standard Process Hitting

[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]

Sorts: components a, b, z

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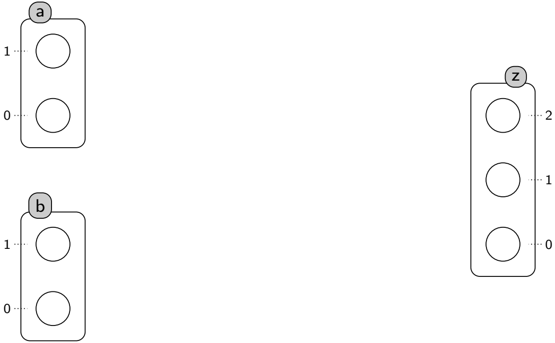

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Processes: local states / discrete expression levels z_0, z_1, z_2

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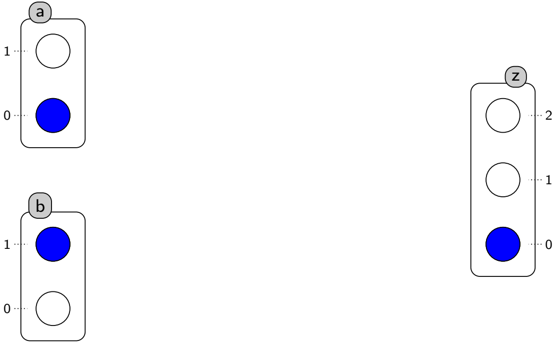

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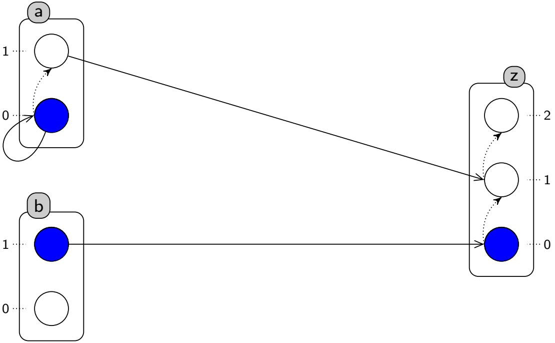

Sorts: components $a, \ b, \ z$

Processes: local states / discrete expression levels $z_0, \ z_1, \ z_2$

States: sets of active processes $\langle a_0, b_1, z_0 \rangle$

Actions: dynamics $b_1 \rightarrow z_0 \upharpoonright z_1, \ a_0 \rightarrow a_0 \upharpoonright a_1, \ a_1 \rightarrow z_1 \upharpoonright z_2$

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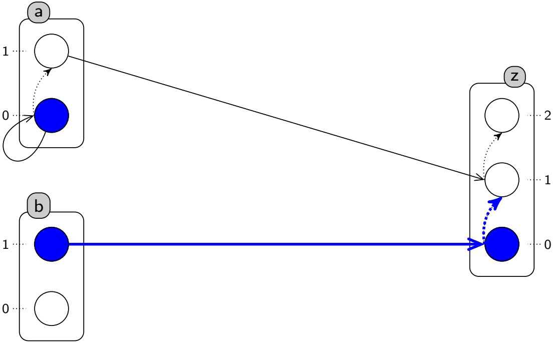

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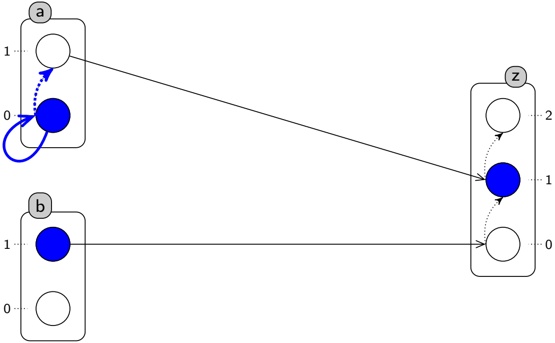
Processes: local states / discrete expression levels z_0, z_1, z_2

States: sets of active processes $\langle a_0, b_1, z_0 \rangle$

Actions: dynamics $\underline{b_1 \rightarrow z_0 \upharpoonright z_1}$, $a_0 \rightarrow a_0 \upharpoonright a_1$, $a_1 \rightarrow z_1 \upharpoonright z_2$

Standard Process Hitting

[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]



Sorts: components a, b, z

Processes: local states / discrete expression levels z_0, z_1, z_2

States: sets of active processes $\langle a_0, b_1, z_1 \rangle$

Actions: dynamics $b_1 \rightarrow z_0 \Rsh z_1$, $\underline{a_0 \rightarrow a_0 \Rsh a_1}$, $a_1 \rightarrow z_1 \Rsh z_2$

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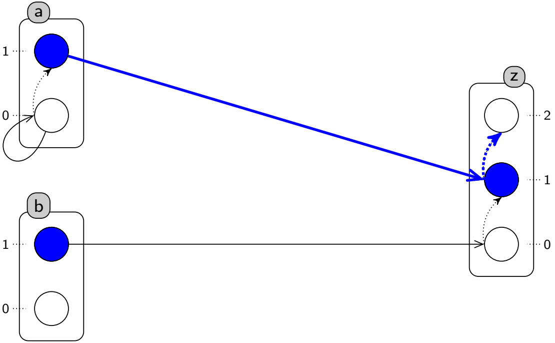

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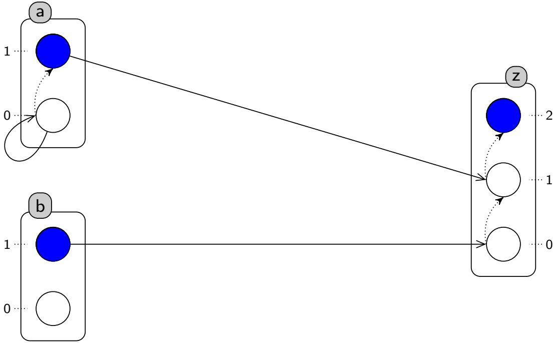

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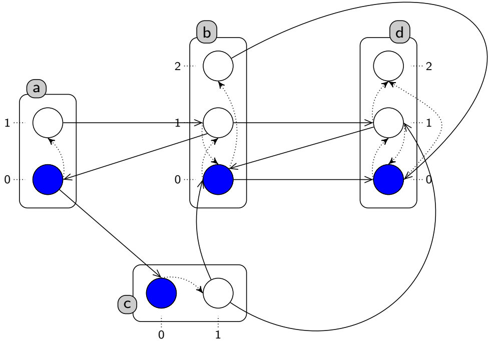
Static analysis: successive reachability

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

Successive reachability of processes:



- Initial state

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

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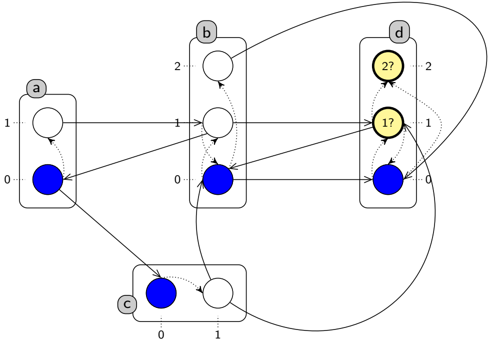
[Paulevé *et al.* in *Mathematical Structures in Computer Science*, 2012]

Successive reachability of processes:



- Initial state

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

- Objectives

$[\ \Rsh d_1 \ :: \Rsh d_2\ ]$

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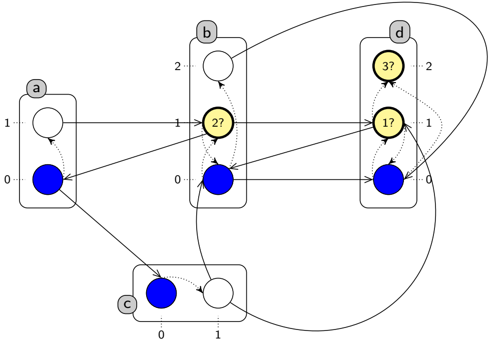

- Initial state

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

- Objectives

$$[\ \Rsh d_1 :: \Rsh d_2\ ]$$
$$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$$

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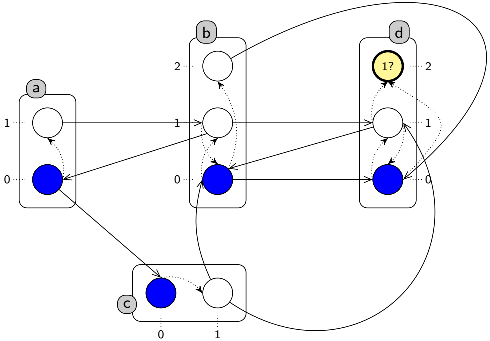

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$[\ \Rsh d_1 :: \Rsh d_2\ ]$

$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$

$[\ \Rsh d_2\ ]$

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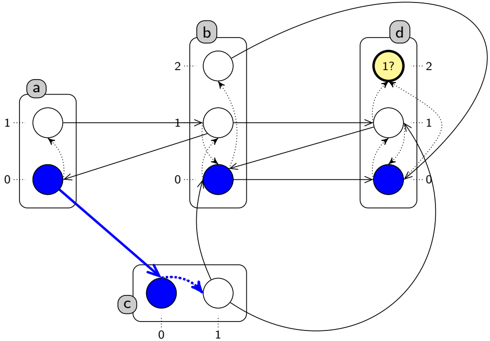

- Initial state

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

- Objectives

$$[\ \Rsh d_1\ ::\ \Rsh d_2\ ]$$
$$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$$
$$[\ \Rsh d_2\ ]$$

$\rightarrow$ Concretization of the objective = scenario

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

Static analysis: successive reachability

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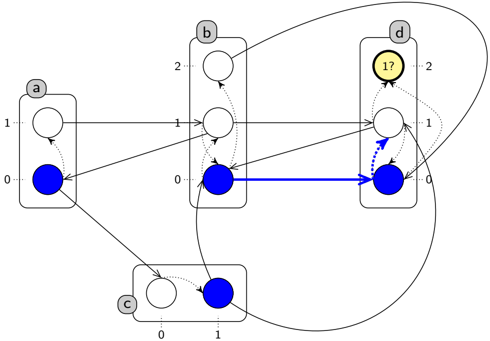

- Initial state

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

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$[\ \Rsh d_1 :: \Rsh d_2\ ]$

$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$

$[\ \Rsh d_2\ ]$

$\rightarrow$ Concretization of the objective = scenario

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

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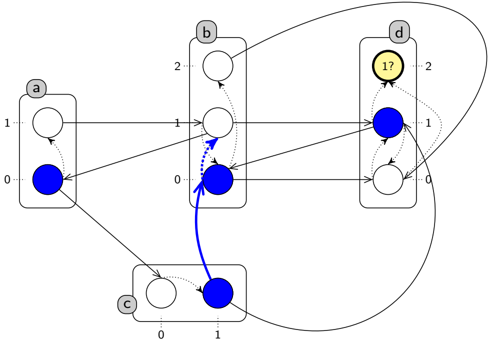

- Initial state

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

- Objectives

$[\ \Rsh d_1 :: \Rsh d_2\ ]$

$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$

$[\ \Rsh d_2\ ]$

$\rightarrow$ Concretization of the objective = scenario

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

Static analysis: successive reachability

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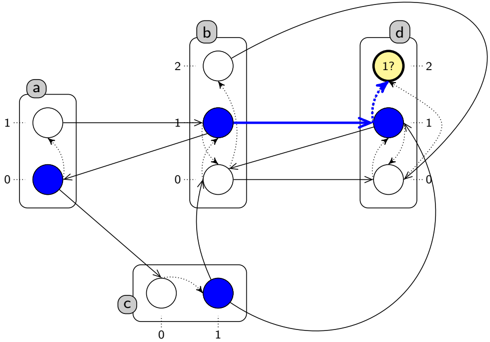
Successive reachability of processes:



- Initial state

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

- Objectives

$$[\ \Rsh d_1 :: \Rsh d_2\ ]$$
$$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$$
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→ Concretization of the objective = scenario

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

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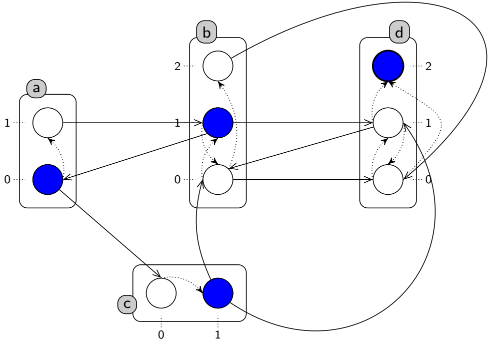
Successive reachability of processes:



- Initial state

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

- Objectives

$[\ {\Rsh}\, d_1 :: {\Rsh}\, d_2\ ]$

$[\ {\Rsh}\, d_1 :: {\Rsh}\, b_1 :: {\Rsh}\, d_2\ ]$

$[\ {\Rsh}\, d_2\ ]$

$\rightarrow$ Concretization of the objective = scenario

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

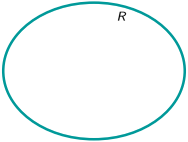
Approximations for the Reachability Analysis

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

Check reachability properties:

« From an initial state s_0, is it possible to reach a state s_n where a_i is active? »

Approximations: P and Q, built so that $P \Rightarrow R \Rightarrow Q$



Exact solution

Approximations for the Reachability Analysis

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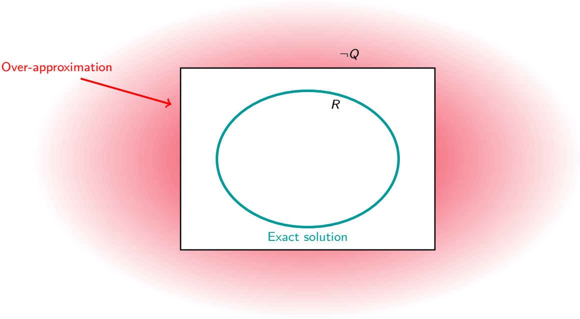

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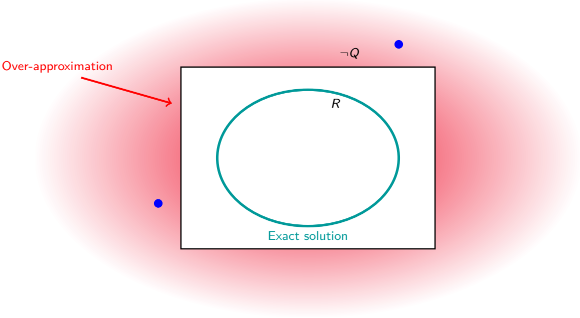

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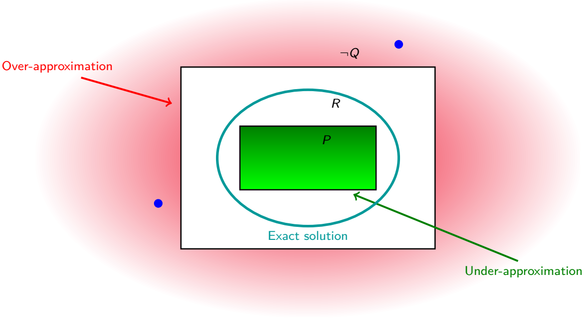

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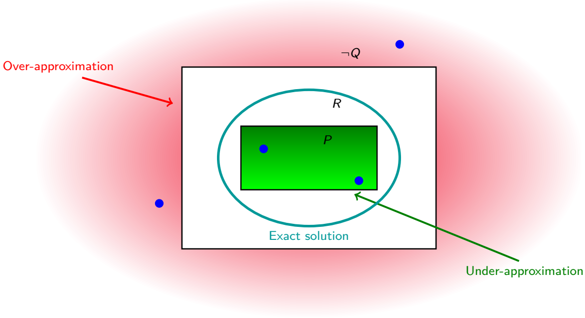

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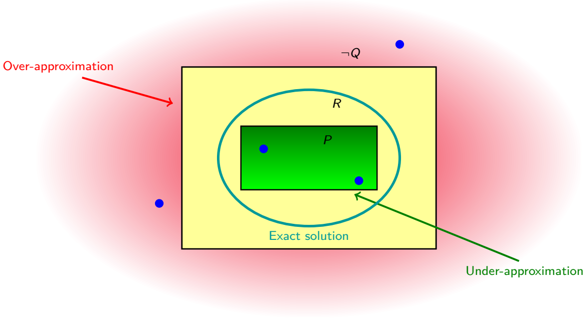

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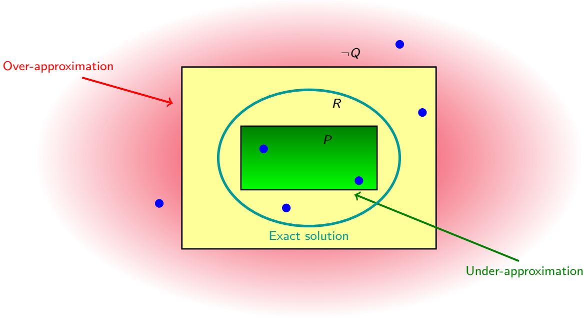

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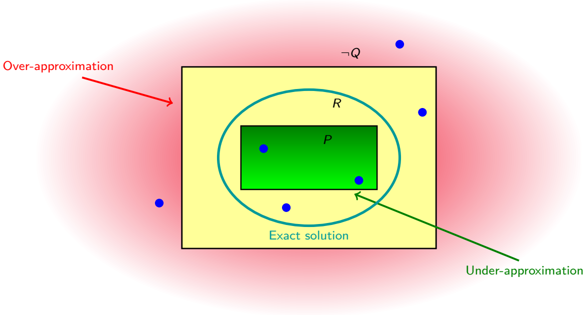

Polynomial complexity in the number of sorts
Exponential complexity in the number of processes in each sort

→ Efficient for big models with few expression levels

Implementation & Execution times

PINT**: Existing free OCaml library**

→ Compiler + tools for Process Hitting models
→ Documentation & examples: `https://github.com/pauleve/pint`

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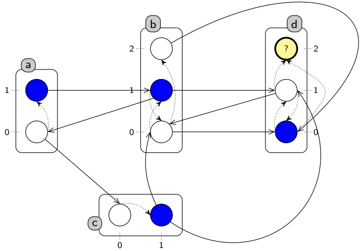
Computation time for various reachability analyses:

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

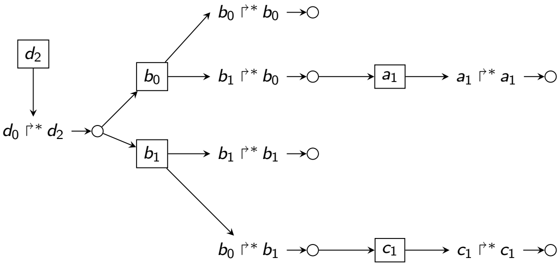
egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga *et al.*, 2009]
tcrsig40 : T-Cell Receptor (40 composants) [Klamt *et al.*, 2006]
tcrsig94 : T-Cell Receptor (94 composants) [Saez-Rodriguez *et al.*,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

Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution



$\boxed{d_2}$

$d_0 \Rsh^* d_2$ → ○

$\boxed{b_0}$

$b_0 \Rsh^* b_0$ → ○

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

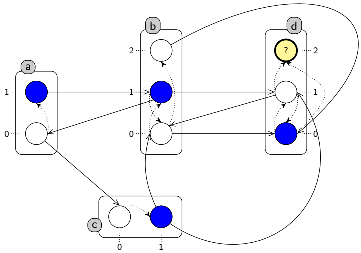
$\boxed{b_1}$

$b_1 \Rsh^* b_1$ → ○

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

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

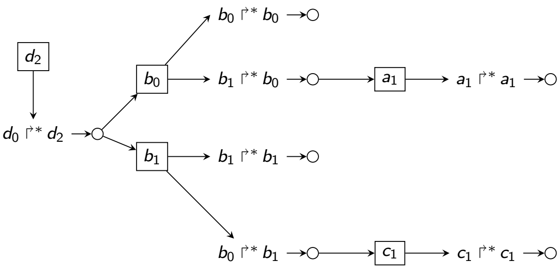
Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution

R is **true**



$\boxed{d_2}$

$d_0 \Rsh^* d_2 \rightarrow$ ○

$\boxed{b_0}$

$b_0 \Rsh^* b_0 \rightarrow$ ○

$b_1 \Rsh^* b_0 \rightarrow$ ○ $\rightarrow \boxed{a_1} \rightarrow a_1 \Rsh^* a_1 \rightarrow$ ○

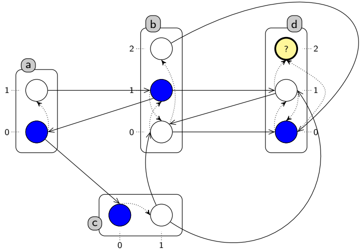
$\boxed{b_1}$

$b_1 \Rsh^* b_1 \rightarrow$ ○

$b_0 \Rsh^* b_1 \rightarrow$ ○ $\rightarrow \boxed{c_1} \rightarrow c_1 \Rsh^* c_1 \rightarrow$ ○

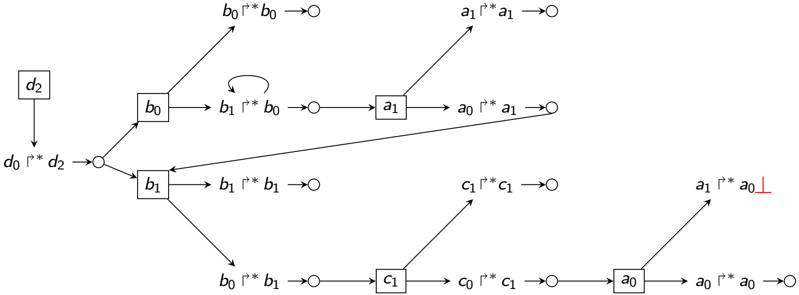
$\boxed{d_2}$	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

Under-approximation

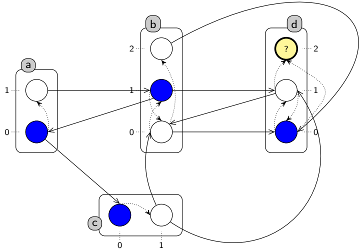


Sufficient condition:

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



Under-approximation



Sufficient condition:

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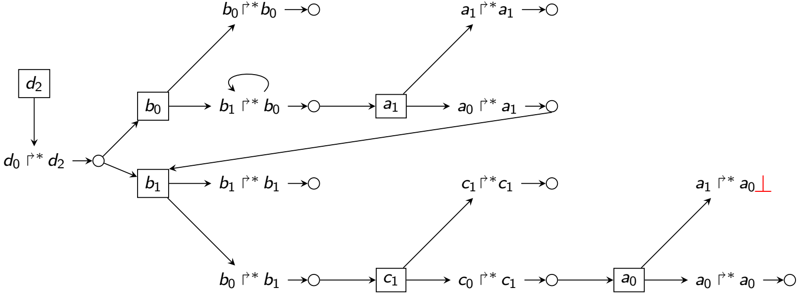
- ~~each objective has a solution~~

Inconclusive



$\boxed{d_2}$

$d_0 \Rsh^{*} d_2$

$\boxed{b_0}$

$b_0 \Rsh^{*} b_0$

$b_1 \Rsh^{*} b_0$

$\boxed{a_1}$

$a_1 \Rsh^{*} a_1$

$a_0 \Rsh^{*} a_1$

$\boxed{b_1}$

$b_1 \Rsh^{*} b_1$

$b_0 \Rsh^{*} b_1$

$\boxed{c_1}$

$c_1 \Rsh^{*} c_1$

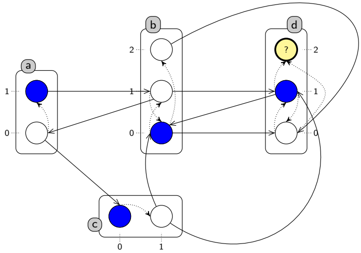
$c_0 \Rsh^{*} c_1$

$\boxed{a_0}$

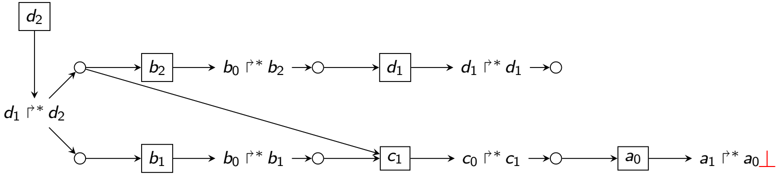
$a_1 \Rsh^{*} a_0 \bot$

$a_0 \Rsh^{*} a_0$

Over-approximation



Necessary condition:

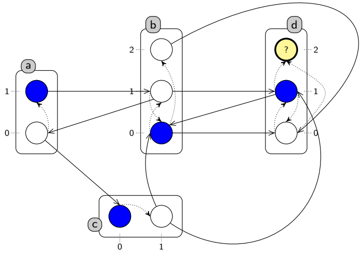

$\boxed{d_2}$

$d_1 \upharpoonright^* d_2$

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

$\boxed{b_1}$ $b_0 \upharpoonright^* b_1$ $\boxed{c_1}$ $c_0 \upharpoonright^* c_1$ $\boxed{a_0}$ $a_1 \upharpoonright^* a_0 \perp$

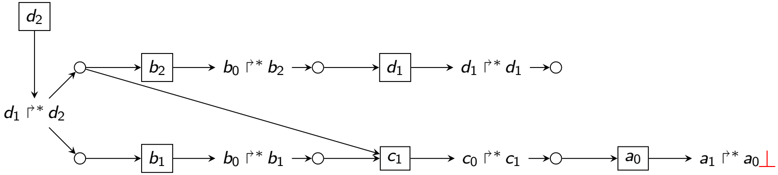
Over-approximation



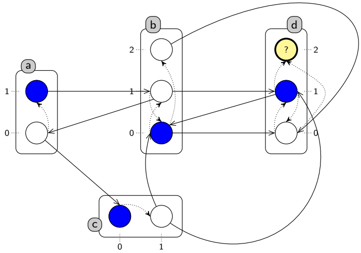
Necessary condition:

There exists a traversal with no cycle

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



Over-approximation



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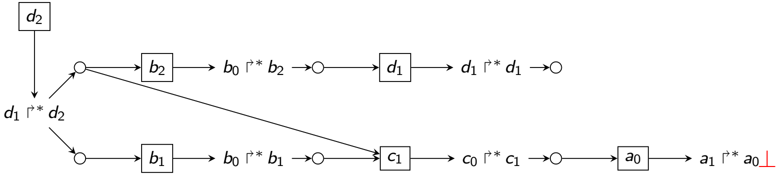


d_2

$d_1 \Rsh^{*} d_2$

b_2

$b_0 \Rsh^{*} b_2$

d_1

$d_1 \Rsh^{*} d_1$

b_1

$b_0 \Rsh^{*} b_1$

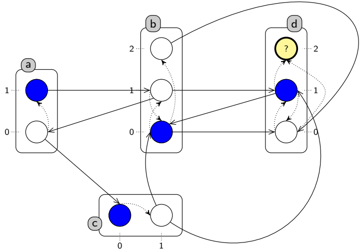
c_1

$c_0 \Rsh^{*} c_1$

a_0

$a_1 \Rsh^{*} a_0 \bot$

Over-approximation

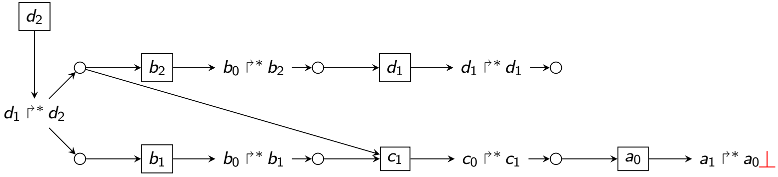


Necessary condition:

~~There exists a traversal~~ with no cycle

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

R is **false**



d_2

$d_1 \Rsh^* d_2$

b_2

$b_0 \Rsh^* b_2$

d_1

$d_1 \Rsh^* d_1$

b_1

$b_0 \Rsh^* b_1$

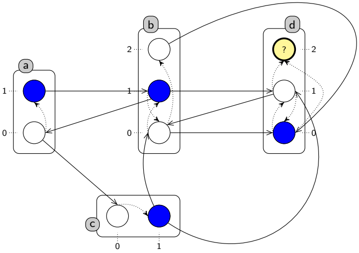
c_1

$c_0 \Rsh^* c_1$

a_0

$a_1 \Rsh^* a_0 \perp$

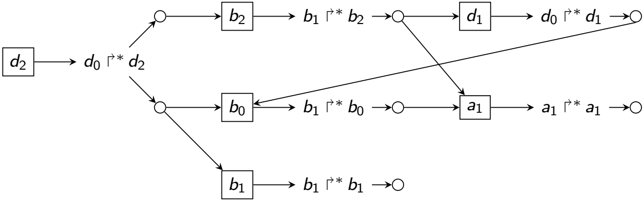
Over-approximation



Necessary condition:

There exists a traversal with no cycle

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



$\boxed{d_2}$

$d_0 \Rsh^* d_2$

$\boxed{b_2}$

$b_1 \Rsh^* b_2$

$\boxed{d_1}$

$d_0 \Rsh^* d_1$

$\boxed{b_0}$

$b_1 \Rsh^* b_0$

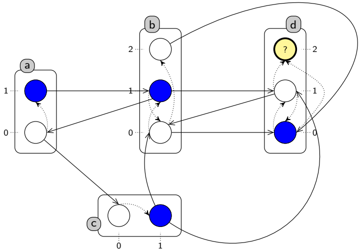
$\boxed{a_1}$

$a_1 \Rsh^* a_1$

$\boxed{b_1}$

$b_1 \Rsh^* b_1$

Over-approximation



Necessary condition:

There exists a traversal with no cycle

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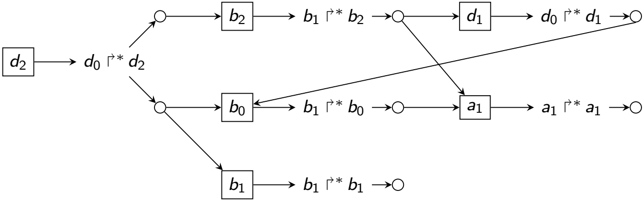
- process → follow all objectives

Inconclusive



d_2 $d_0 \Rsh^{*} d_2$

b_2 $b_1 \Rsh^{*} b_2$ d_1 $d_0 \Rsh^{*} d_1$

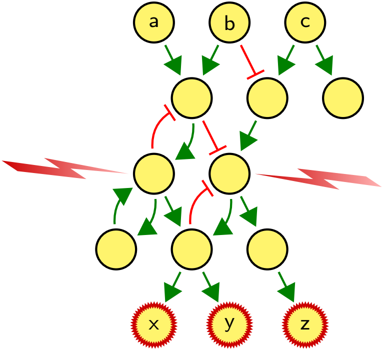
b_0 $b_1 \Rsh^{*} b_0$ a_1 $a_1 \Rsh^{*} a_1$

b_1 $b_1 \Rsh^{*} b_1$

Cut sets

[Paulevé, Andrieux, Koeppl in *Computer Aided Verification*, 2013.]

Cut set = set of nodes whose knockout is sufficient to turn off some outputs



- "Absolute" vision of possible perturbations
- Need for an intermediate point of view → Finer analysis

Cut sets

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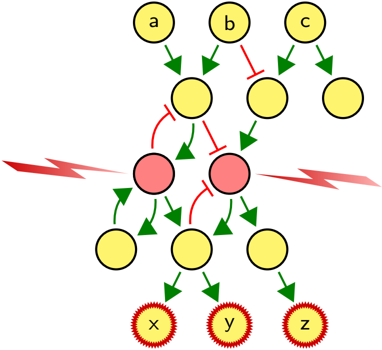

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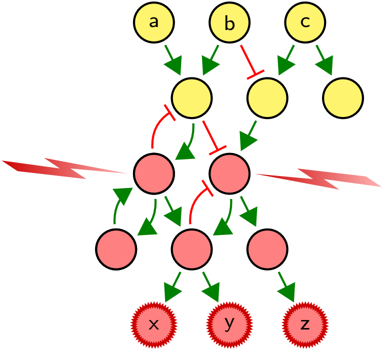

- "Absolute" vision of possible perturbations
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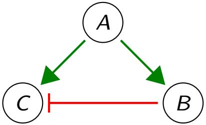
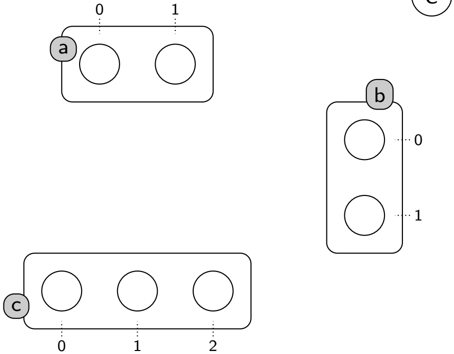
Translation in Process Hitting





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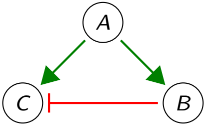

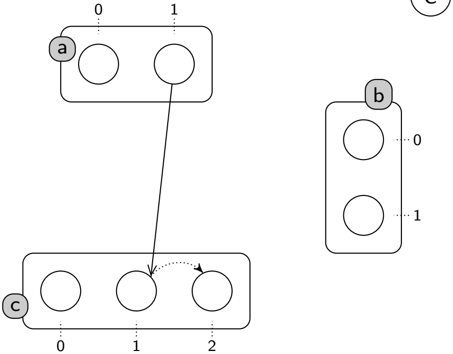

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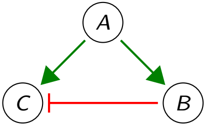

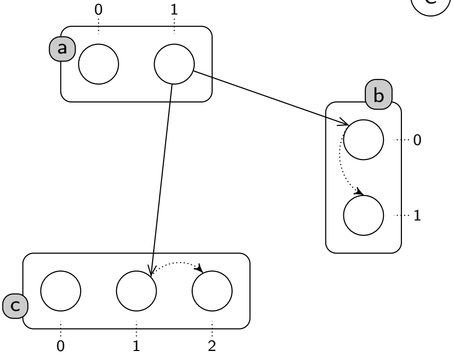

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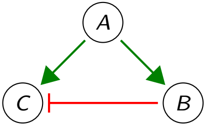

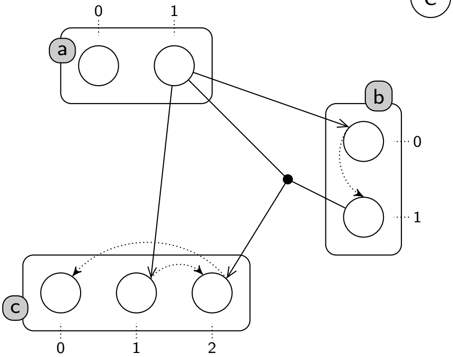

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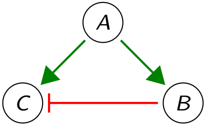

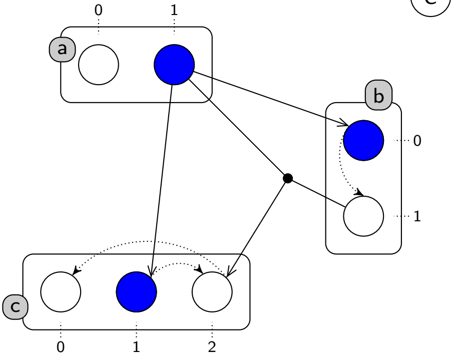

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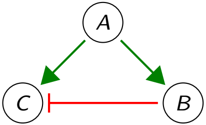

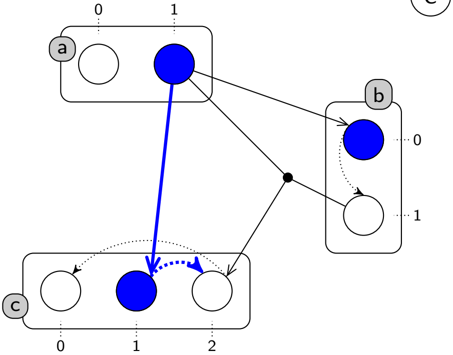

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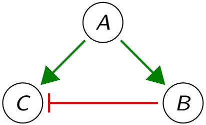

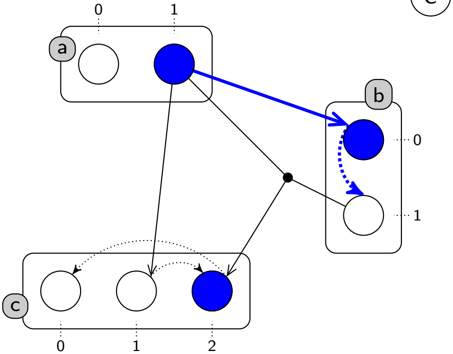

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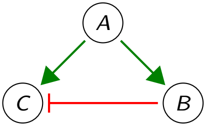

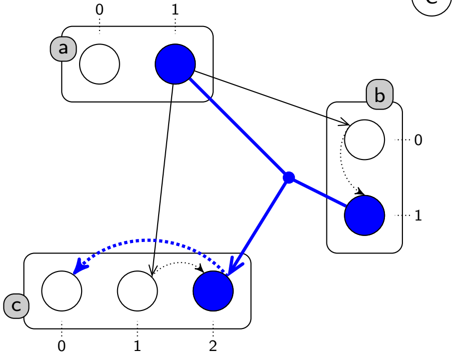

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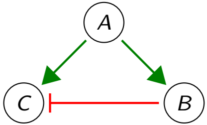
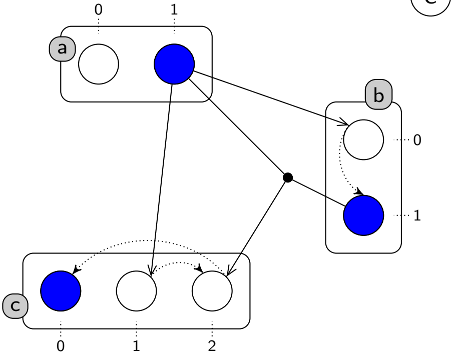
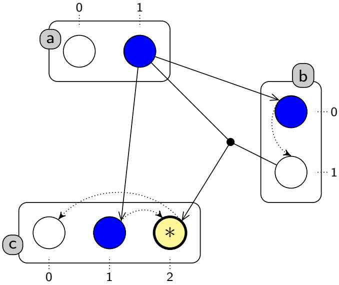




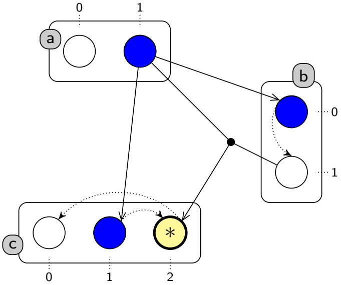
Detailed application of the Static Analysis



Graph of local causality:

$\boxed{c_0}$	Required process
$c_1 \upharpoonright^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis

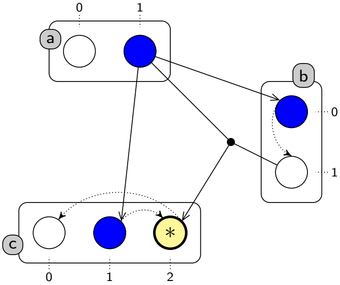


Graph of local causality:

$\boxed{c_2}$

$\boxed{c_0}$	Required process
$c_1 \Rsh^{*} c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



Graph of local causality:

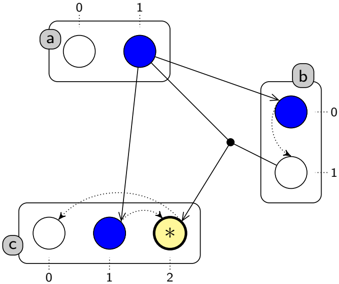
$\boxed{c_2} \longrightarrow c_1 \Rsh^* c_2$

$\boxed{c_0}$ Required process

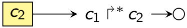
$c_1 \Rsh^* c_0$ Objective

○ Solution to an objective

Detailed application of the Static Analysis



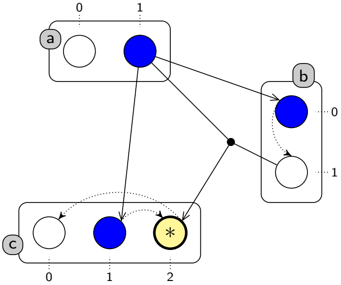
Graph of local causality:



$\boxed{c_2} \longrightarrow c_1 \Rsh^{*} c_2 \longrightarrow \bigcirc$

$\boxed{c_0}$	Required process
$c_1 \Rsh^{*} c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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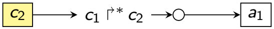

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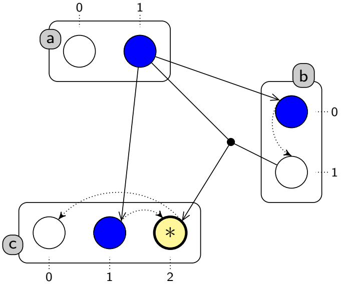
Detailed application of the Static Analysis



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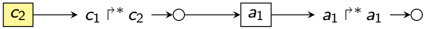

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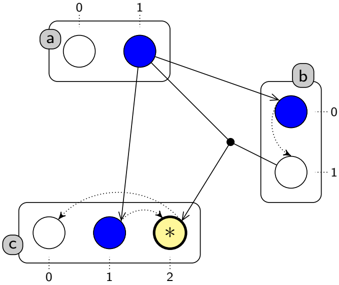
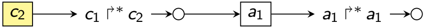


Sufficient condition:

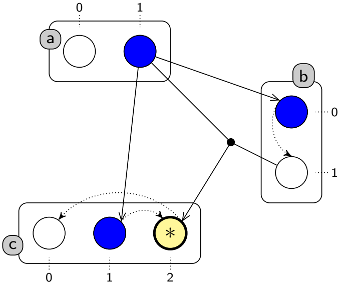
- no cycle
- each objective has a solution
- no contradiction between synchronous requirements

Graph of local causality:



$\boxed{c_0}$	Required process
$c_1 \Rsh^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



Sufficient condition:

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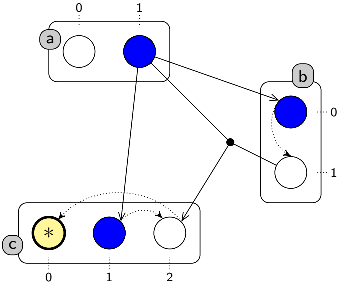
Graph of local causality:

OK

$$\boxed{c_2} \longrightarrow c_1 \Rsh^* c_2 \longrightarrow \bigcirc \longrightarrow \boxed{a_1} \longrightarrow a_1 \Rsh^* a_1 \longrightarrow \bigcirc$$

$\boxed{c_0}$	Required process
$c_1 \Rsh^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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Graph of local causality:

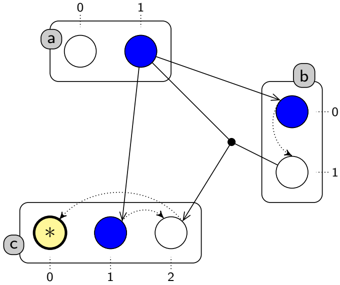
OK

$$\boxed{c_2} \longrightarrow c_1 \Rsh^* c_2 \longrightarrow \circ \longrightarrow \boxed{a_1} \longrightarrow a_1 \Rsh^* a_1 \longrightarrow \circ$$

$$\boxed{c_0}$$

$\boxed{c_0}$	Required process
$c_1 \Rsh^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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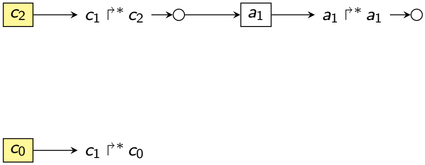
Graph of local causality:

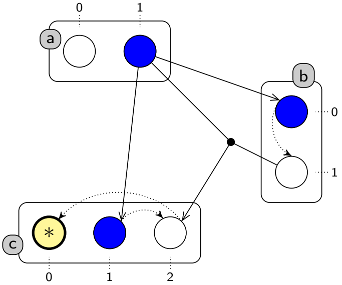
OK


$$\boxed{c_2} \longrightarrow c_1 \upharpoonright^* c_2 \longrightarrow ○ \longrightarrow \boxed{a_1} \longrightarrow a_1 \upharpoonright^* a_1 \longrightarrow ○$$

$$\boxed{c_0} \longrightarrow c_1 \upharpoonright^* c_0$$

$\boxed{c_0}$	Required process
$c_1 \upharpoonright^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



Sufficient condition:

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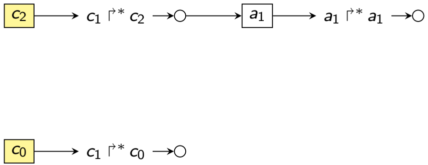
Graph of local causality:

OK

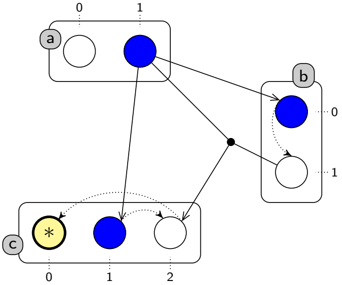


$\boxed{c_2} \longrightarrow c_1 \Rsh^* c_2 \longrightarrow \bigcirc \longrightarrow \boxed{a_1} \longrightarrow a_1 \Rsh^* a_1 \longrightarrow \bigcirc$

$\boxed{c_0} \longrightarrow c_1 \Rsh^* c_0 \longrightarrow \bigcirc$

$\boxed{c_0}$	Required process
$c_1 \Rsh^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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Graph of local causality:

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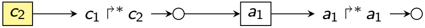
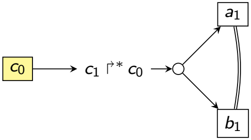
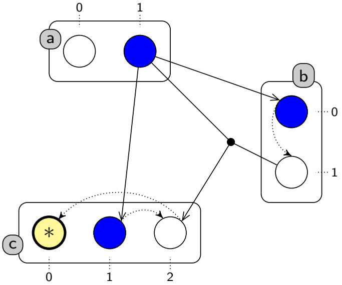




$\boxed{c_0}$	Required process
$c_1 \Rsh^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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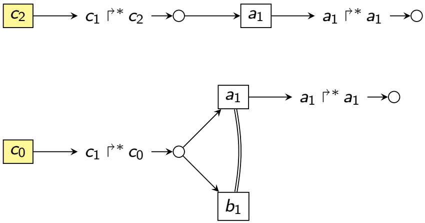

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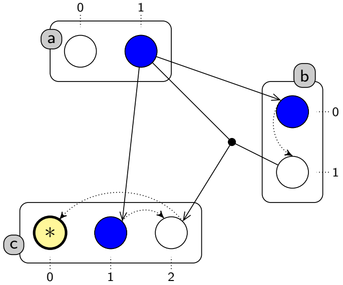
Detailed application of the Static Analysis



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Graph of local causality:

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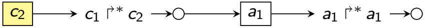
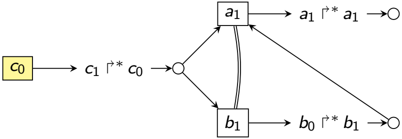


$\boxed{c_2}$ → $c_1 \Rsh^* c_2$ → ○ → $\boxed{a_1}$ → $a_1 \Rsh^* a_1$ → ○



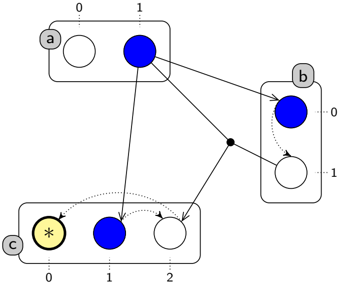
$\boxed{c_0}$ → $c_1 \Rsh^* c_0$ → ○

$\boxed{a_1}$ → $a_1 \Rsh^* a_1$ → ○

$\boxed{b_1}$ → $b_0 \Rsh^* b_1$ → ○

$\boxed{c_0}$	Required process
$c_1 \Rsh^* c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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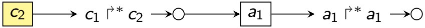
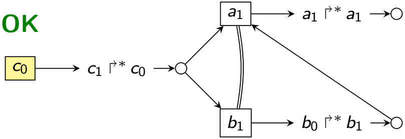
Graph of local causality:

OK



OK



$\boxed{c_0}$	Required process
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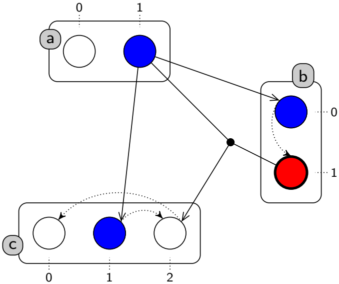
○	Solution to an objective

Detailed application of the Static Analysis



Sufficient condition:

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Graph of local causality:

$\boxed{c_0}$	Required process
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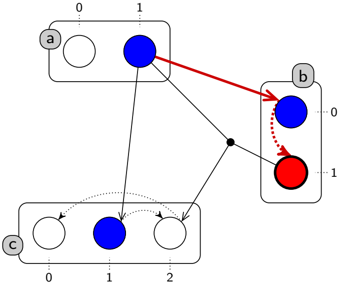
○	Solution to an objective

Detailed application of the Static Analysis



Sufficient condition:

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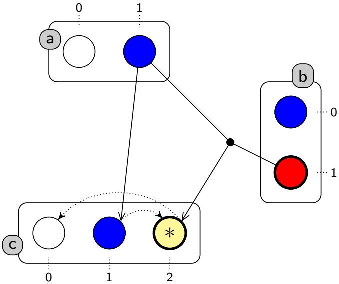
Graph of local causality:

$\boxed{c_0}$	Required process
$c_1 \upharpoonright^{*} c_0$	Objective
○	Solution to an objective

Detailed application of the Static Analysis



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Graph of local causality:

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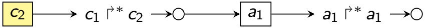

$\boxed{c_0}$	Required process
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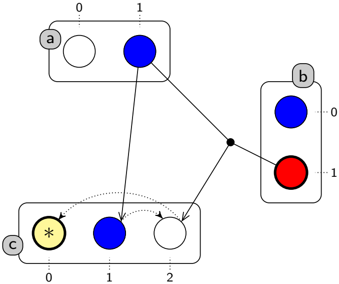

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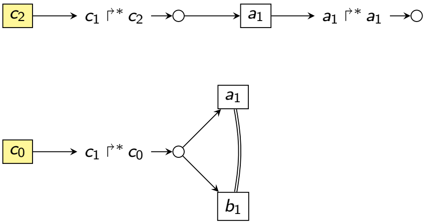

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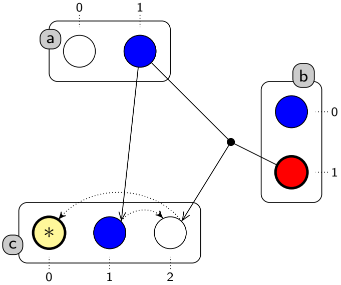

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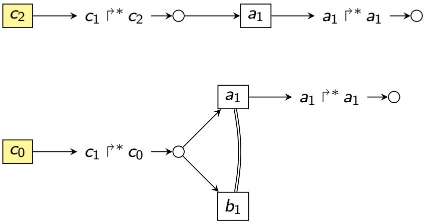

$\boxed{c_2} \rightarrow c_1 \Rsh^* c_2 \rightarrow ○ \rightarrow \boxed{a_1} \rightarrow a_1 \Rsh^* a_1 \rightarrow ○$

$\boxed{c_0} \rightarrow c_1 \Rsh^* c_0 \rightarrow ○$

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$\boxed{b_1}$

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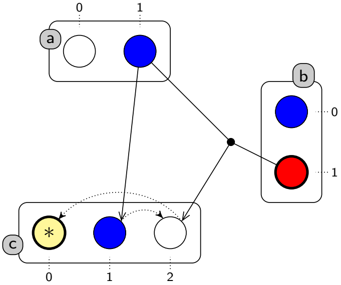

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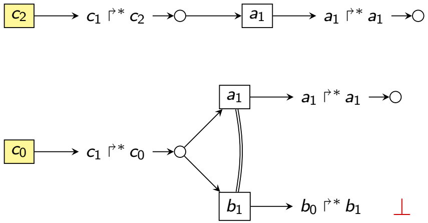

$\boxed{c_2} \longrightarrow c_1 \Rsh^* c_2 \longrightarrow \bigcirc \longrightarrow \boxed{a_1} \longrightarrow a_1 \Rsh^* a_1 \longrightarrow \bigcirc$

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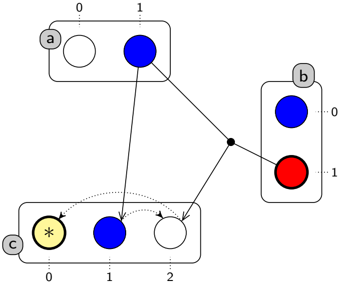

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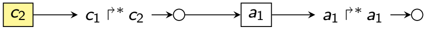

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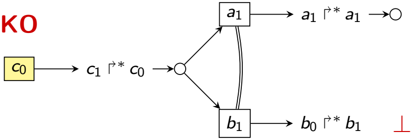

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Alternative Paths

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→ Knocking out a component in a path may reveal an alternative path

- Resilience ⇒ existence of alternative paths (cf. cut sets)
- New path ⇒ New costs or new delays

Conclusion

The Process Hitting allows to represent biological regulatory networks:

- Qualitative and atomistic modeling
- Existing efficient **reachability analysis**
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Quantification of the perturbation using Process Hitting:

- Adapted notion of **impact degree** (multiple values)
- Thanks to the powerful **reachability analysis**
- Additional properties with the graph of local causality

Thank you!

Do you have questions

or suggestions?

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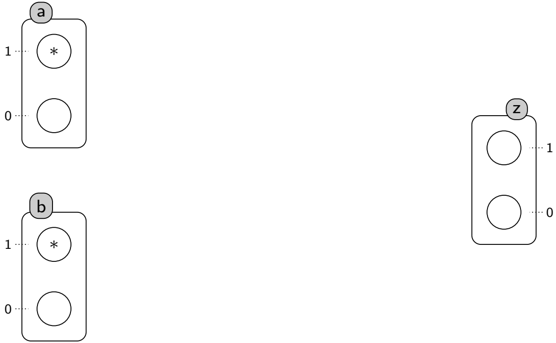
Cooperations

[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]



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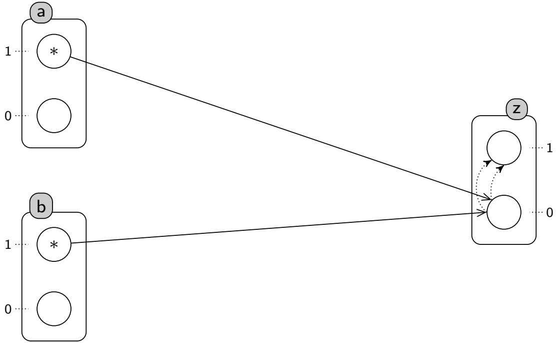

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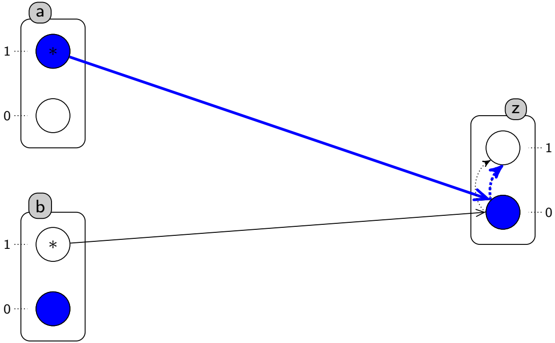

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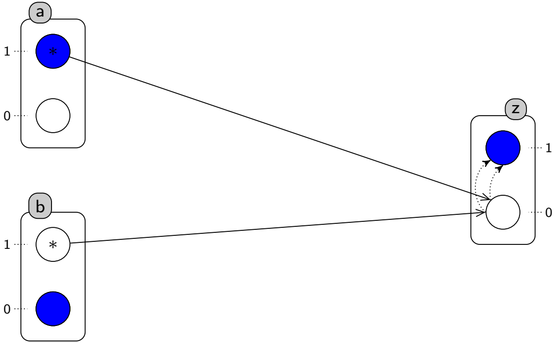

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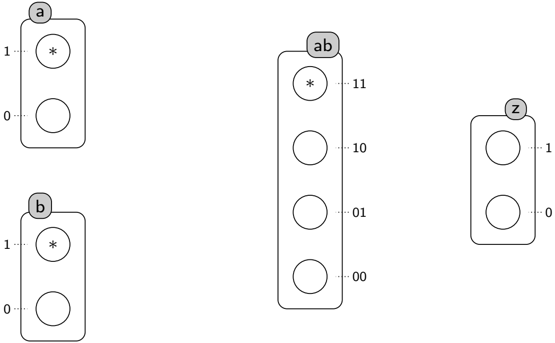

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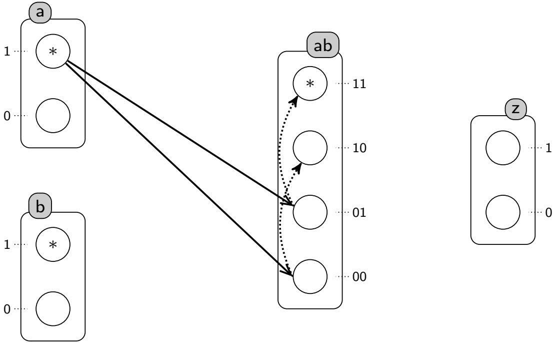

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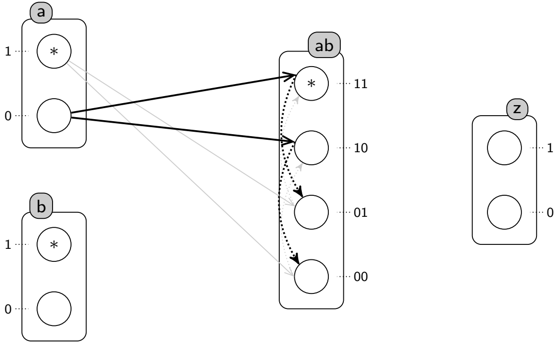

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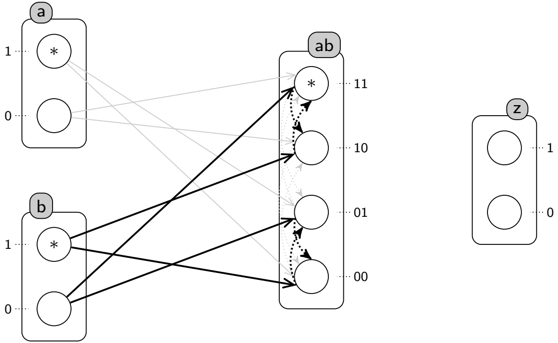

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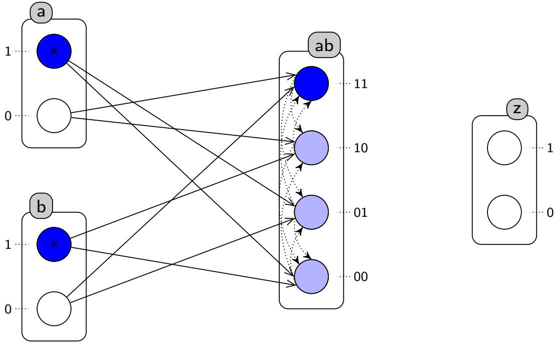

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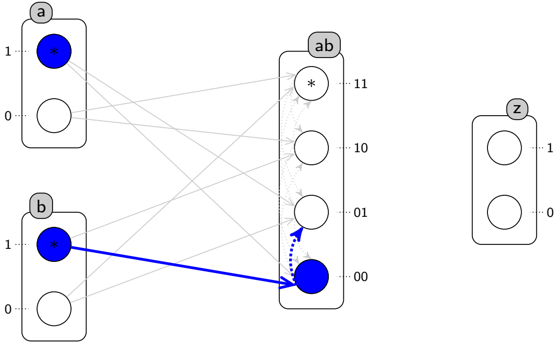

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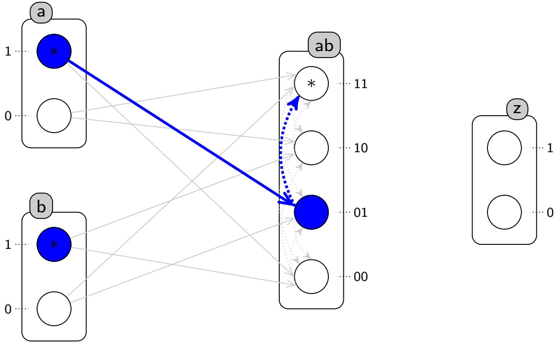

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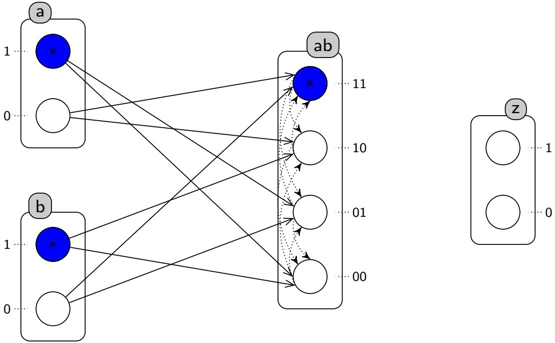

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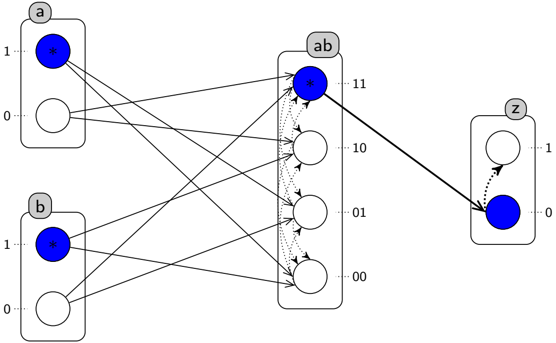

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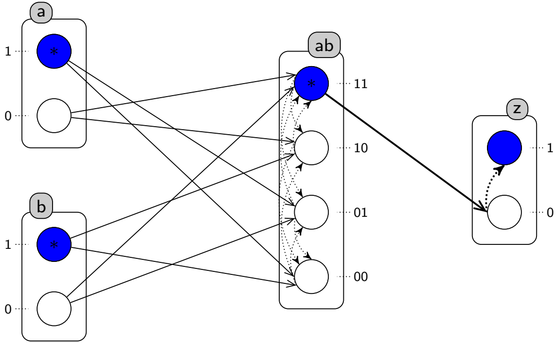

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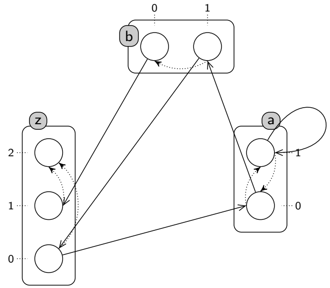
Static Analysis: Fixed Points

[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]

Fixed point = state where no action can be fired

→ avoid couples of processes bounded by an action



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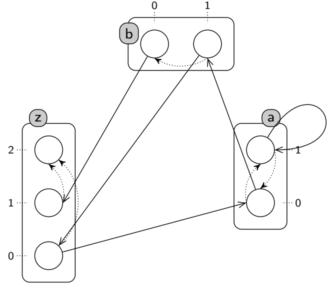

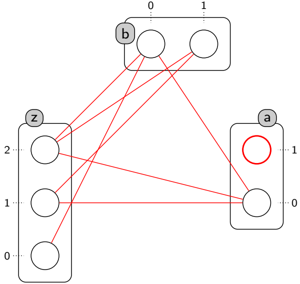

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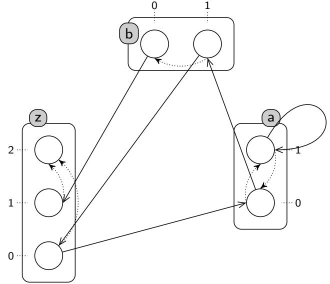

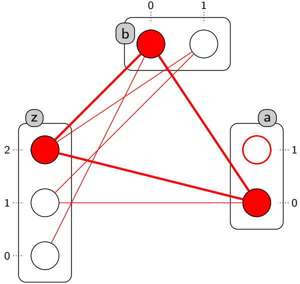

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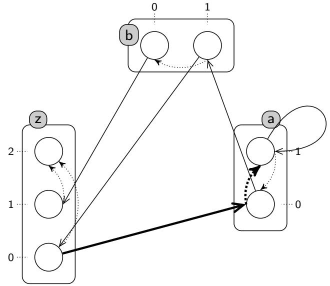

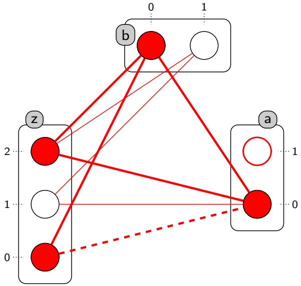

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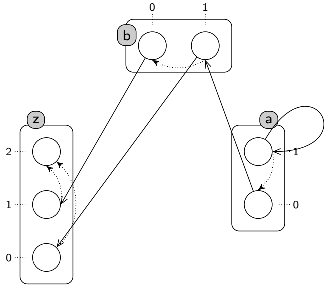

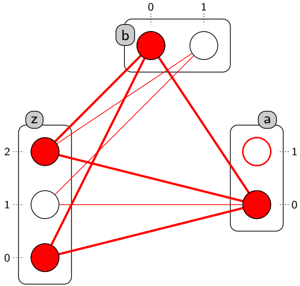

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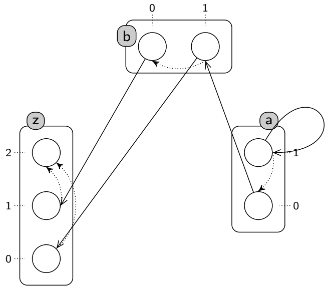

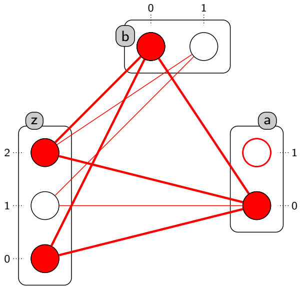

Exponential complexity w.r.t. the number of sorts