Abstract Interpretation of Dynamics of Biological Regulatory Networks

Loïc Paulevé, Morgan Magnin, Olivier Roux

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IRCCyN / MOVES Team, Nantes (France)

JOBIM 2010 satellite meeting:
Dynamical modelling and simulation of biological networks
10th September 2010

Overview

The use of models for dynamical concurrent systems requires to formally check for dynamical properties:

- Validation of the model / control of the system.
- Hard for large models (state space explosion).

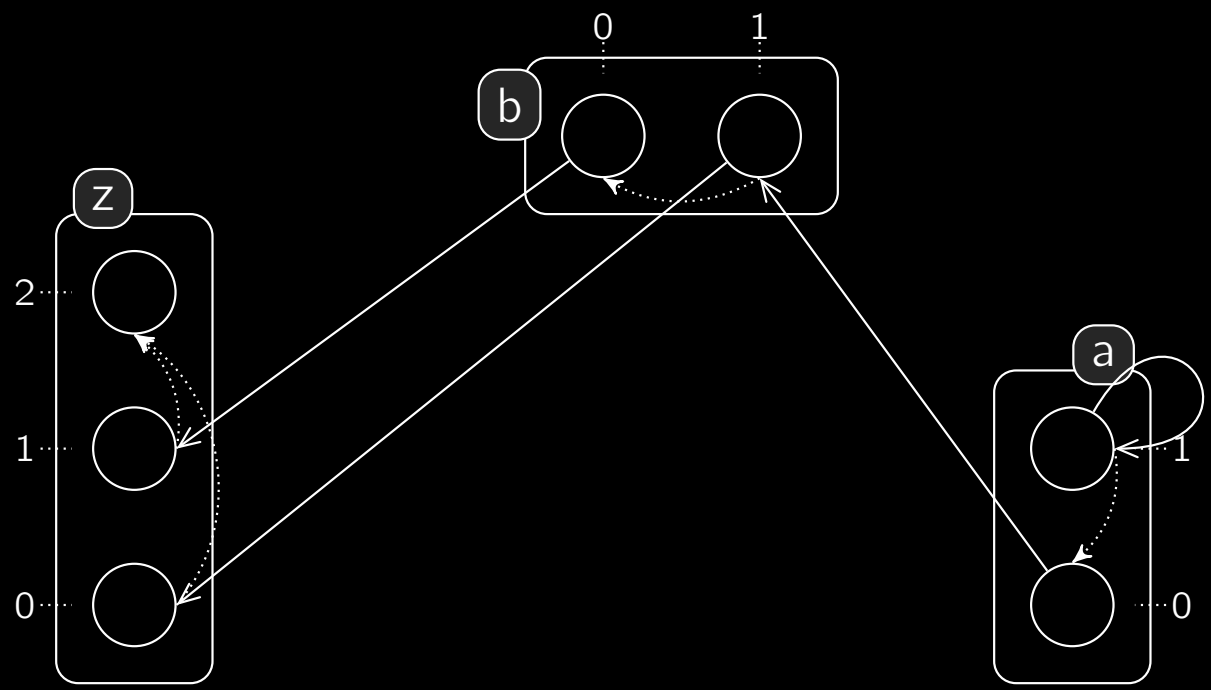
Some solutions

- State space exploration algorithm improvement.
- Automatic reduction of the model.
  - Static analysis of the model (source code).

Outline

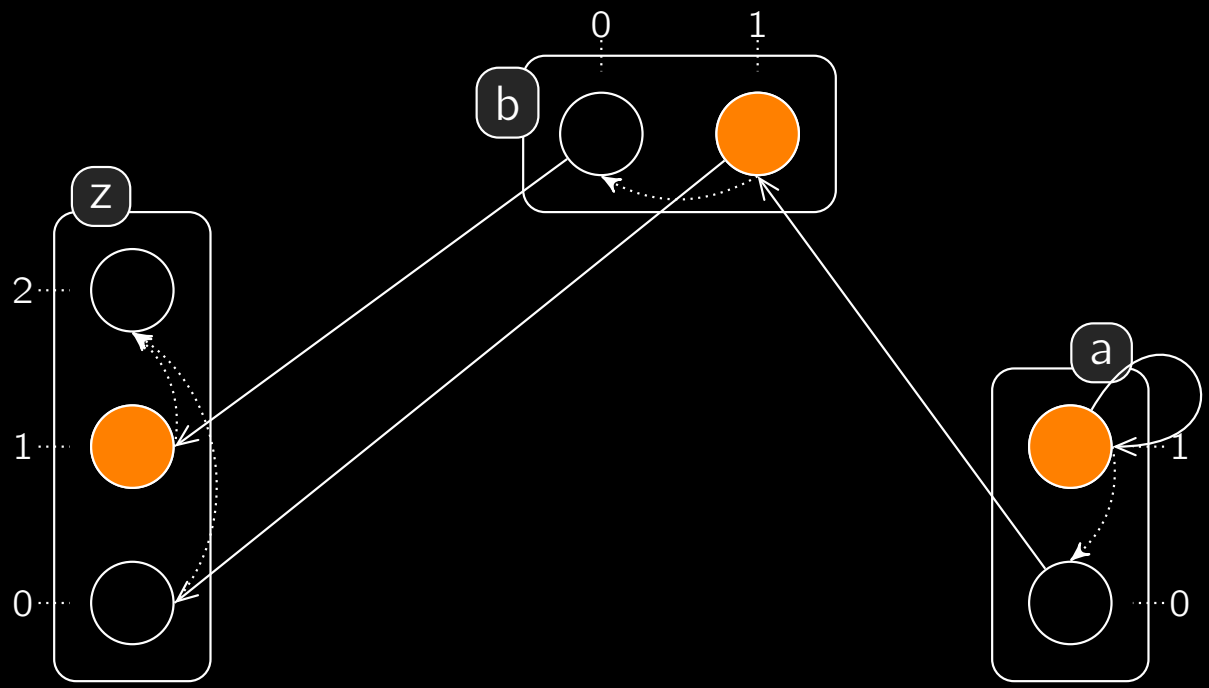
1. Introduction of a formal framework, the Process Hitting.
2. Abstract interpration and static analysis of Process Hittings to prove reachability properties.
3. Application to Biological Regulatory Networks (BRNs) + on-going work.

The Process Hitting Framework



- Sorts: a,b,z; Processes: $a_0, a_1, b_0, b_1, z_0, z_1, z_2$;
- Actions: a_0 hits b_1 to make it bounce to b_0, ...;
- States: $\langle a_1, b_1, z_1 \rangle$, $\langle a_0, b_1, z_1 \rangle$, $\langle a_0, b_0, z_1 \rangle$, ...;
- Restriction of Communicating Finite-State Machines (CFSM).

The Process Hitting Framework



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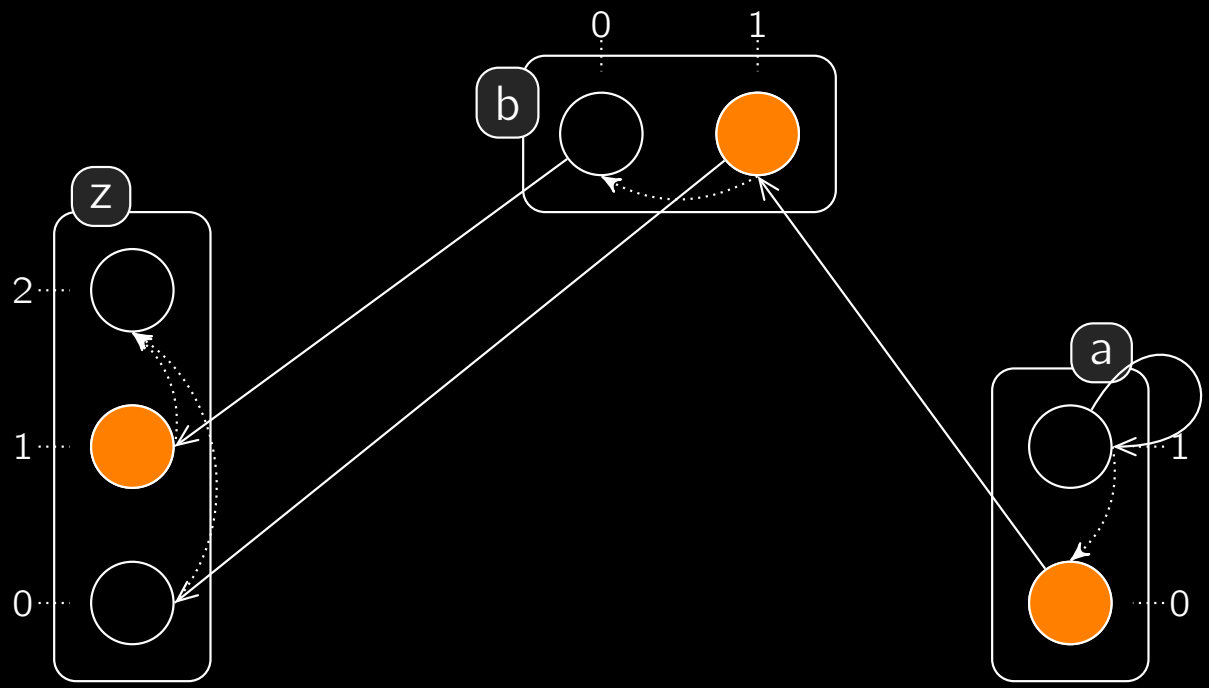

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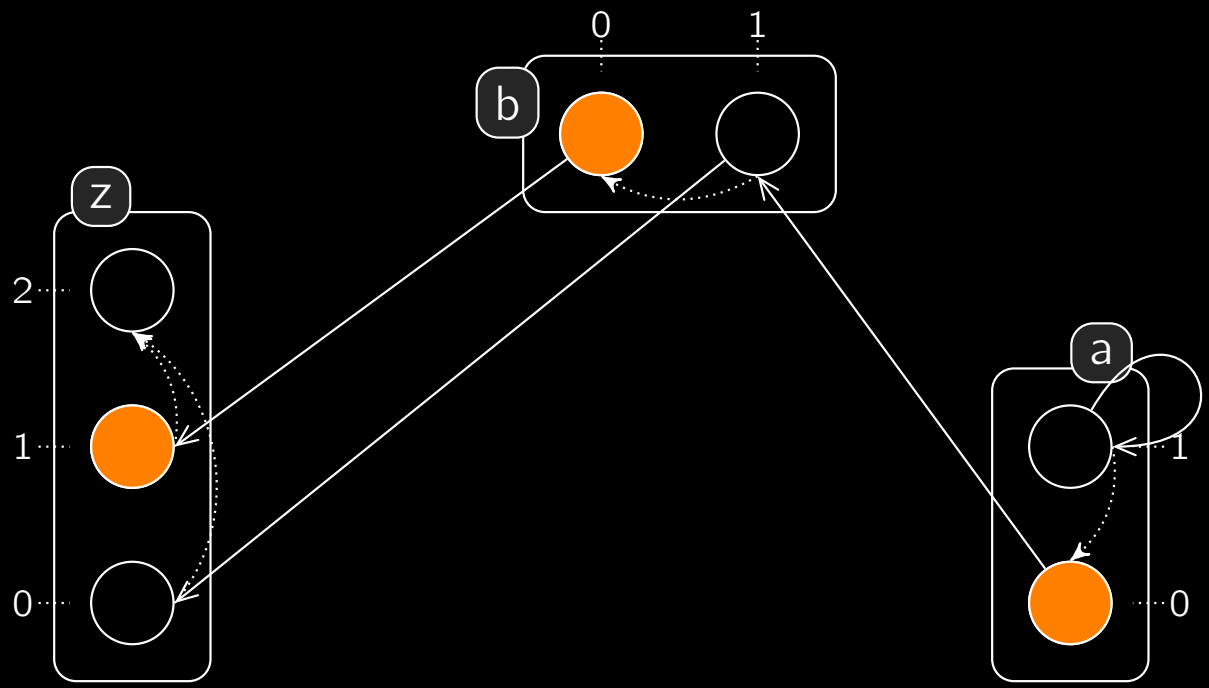

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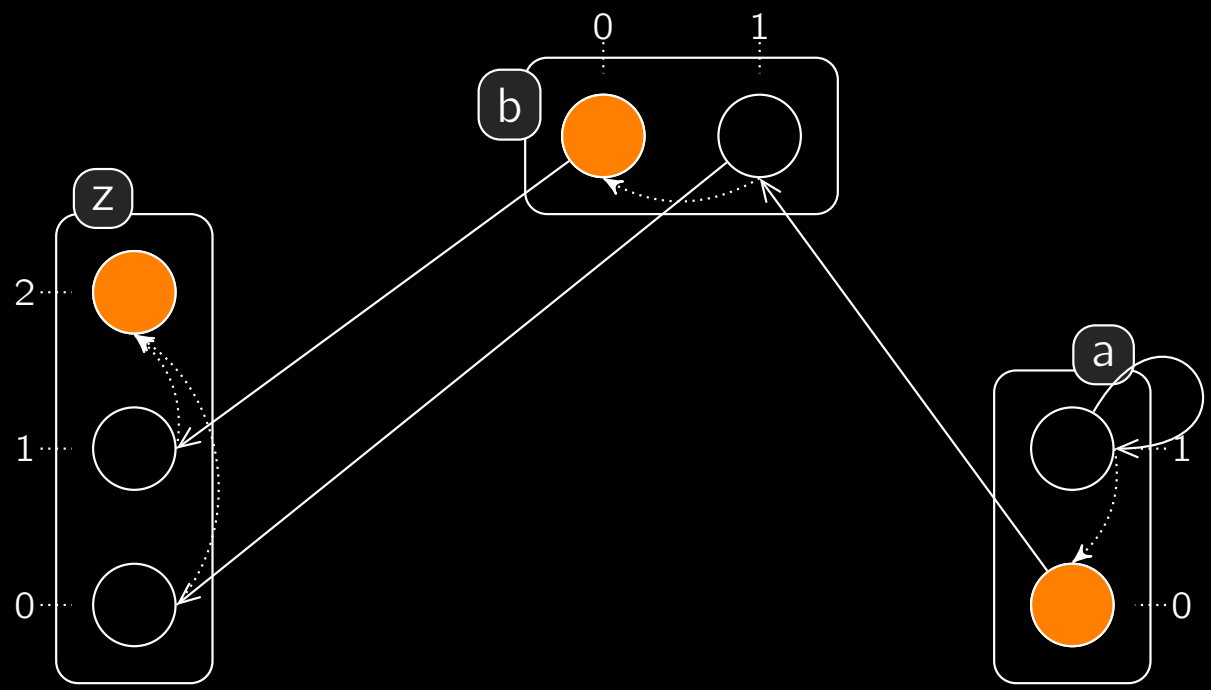

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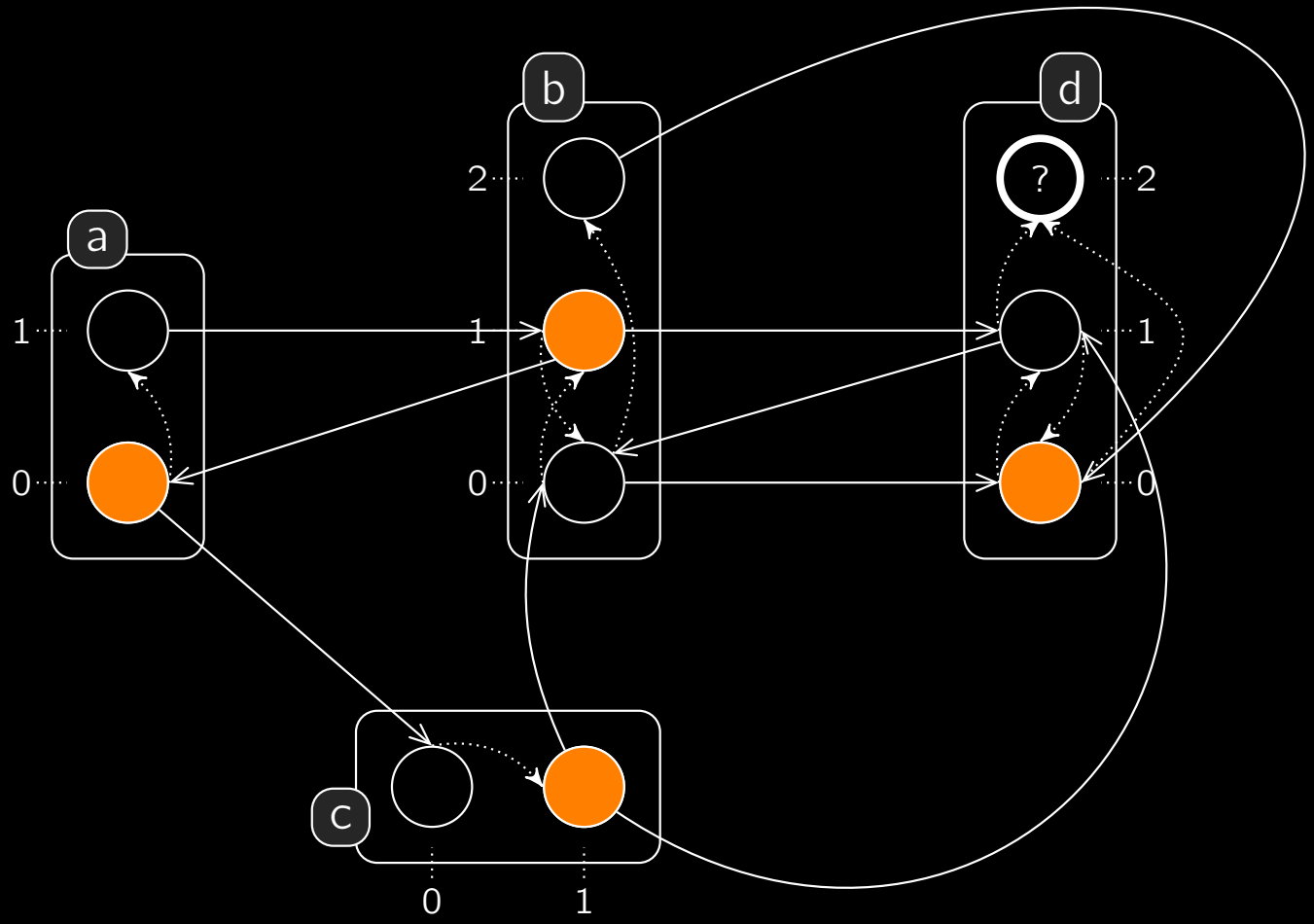
The Process Reachability Problem



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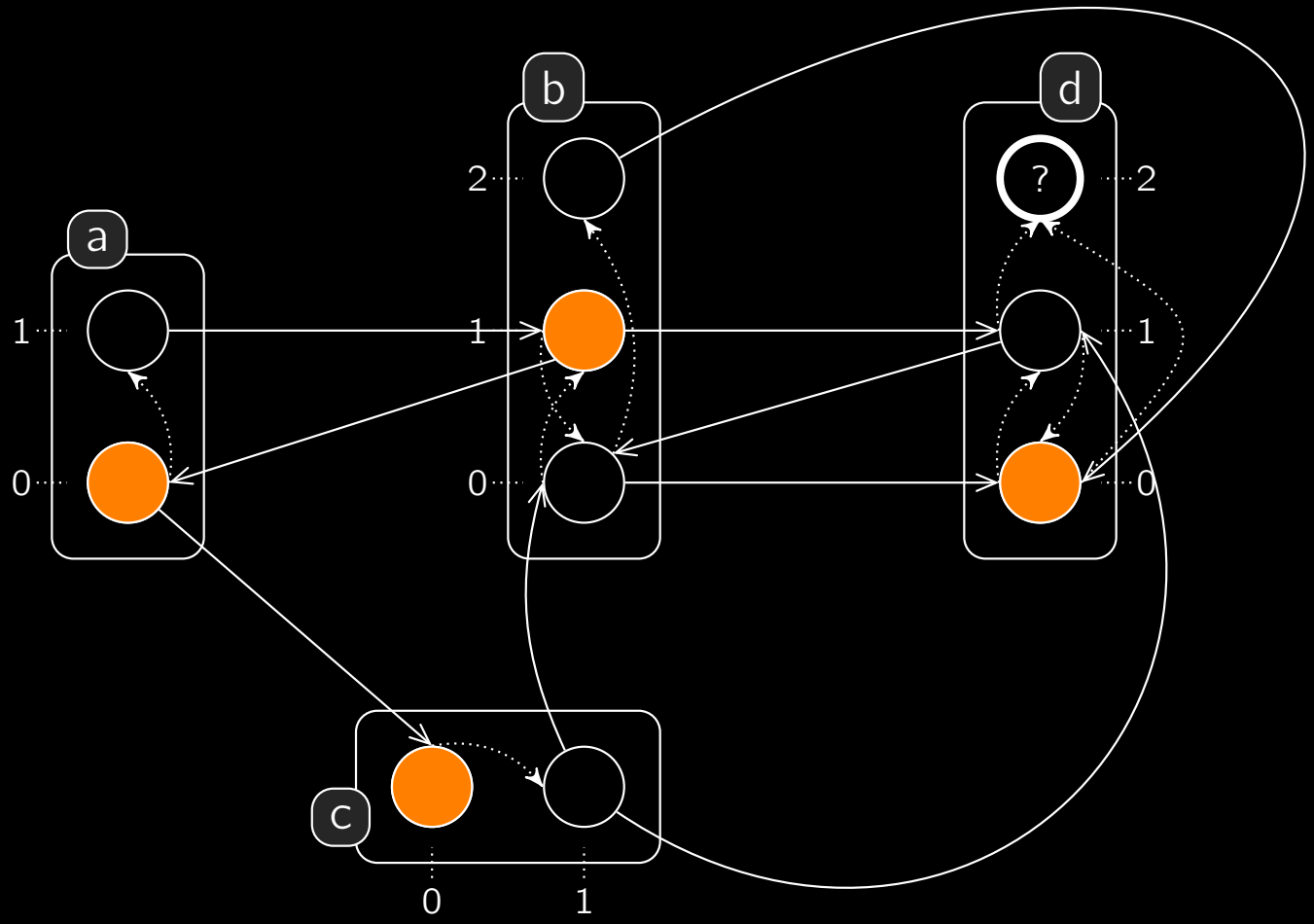

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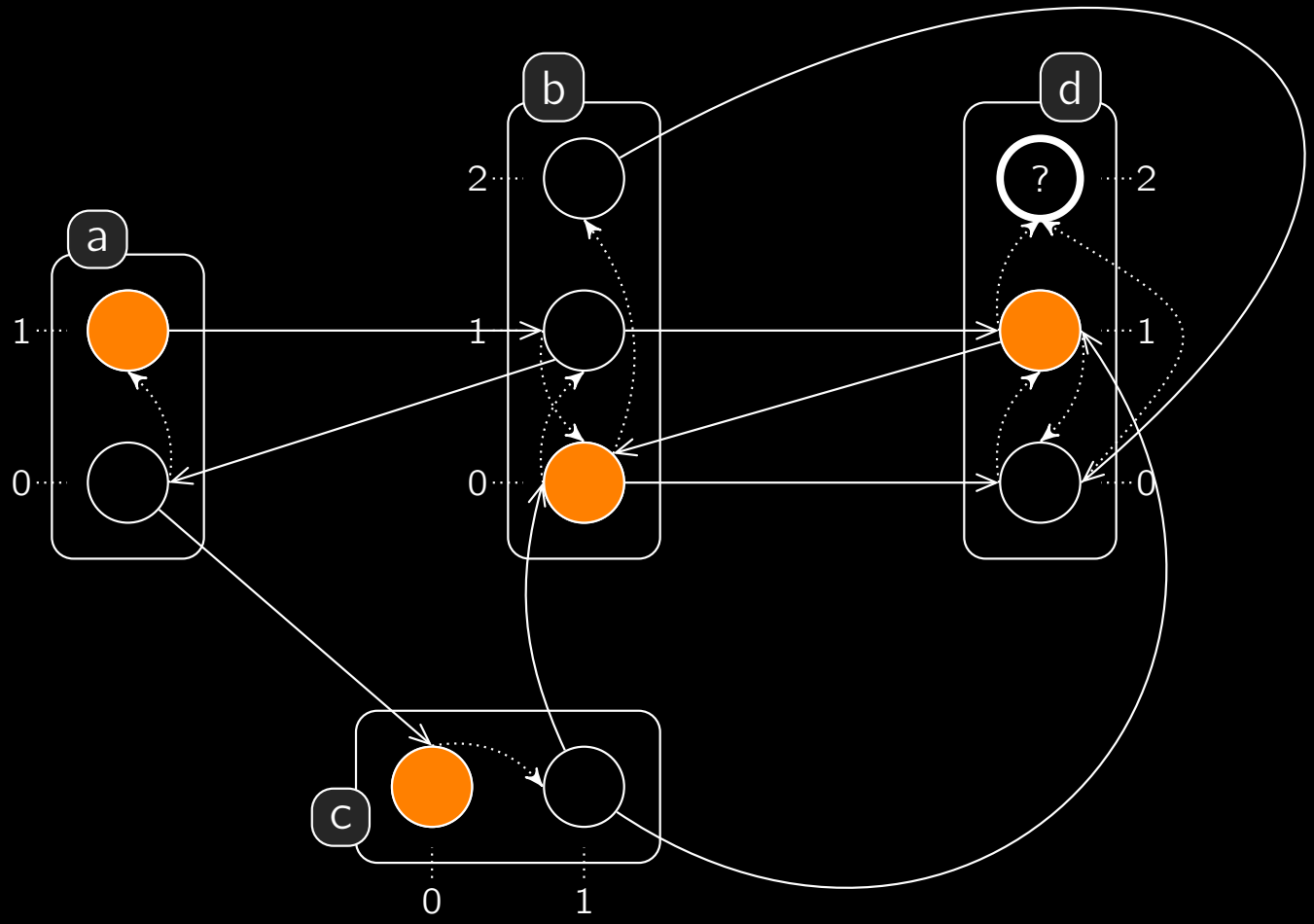

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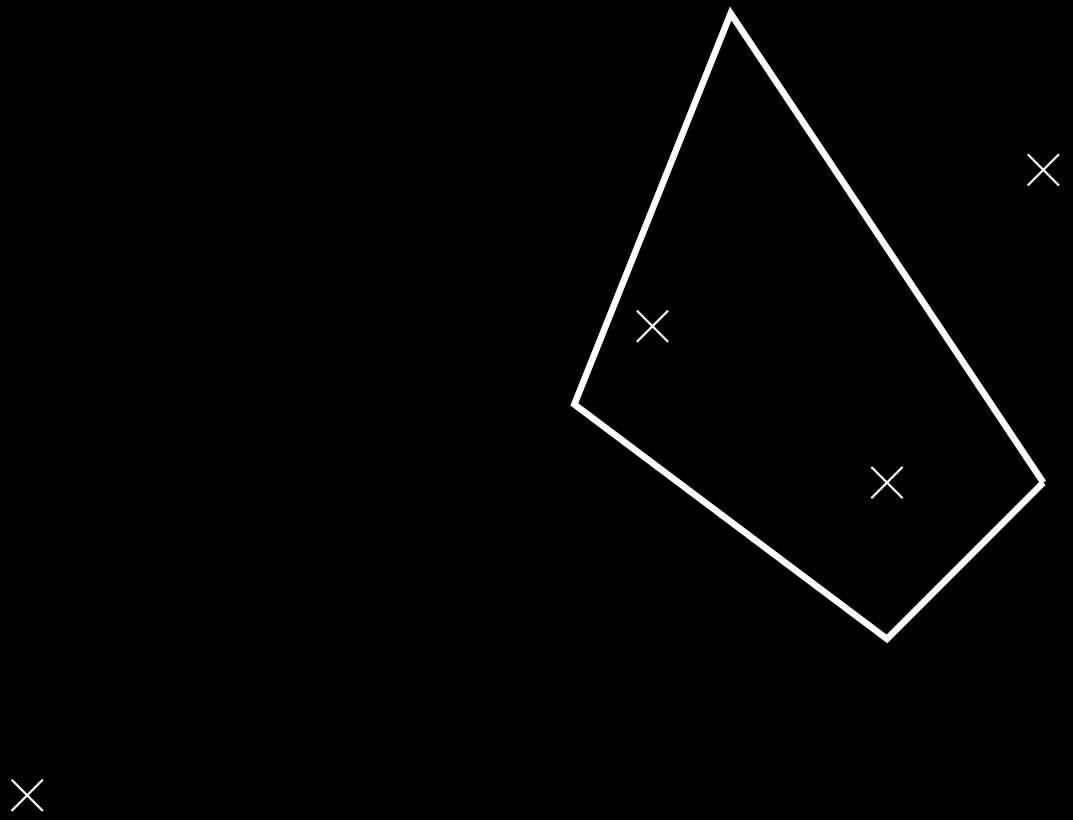
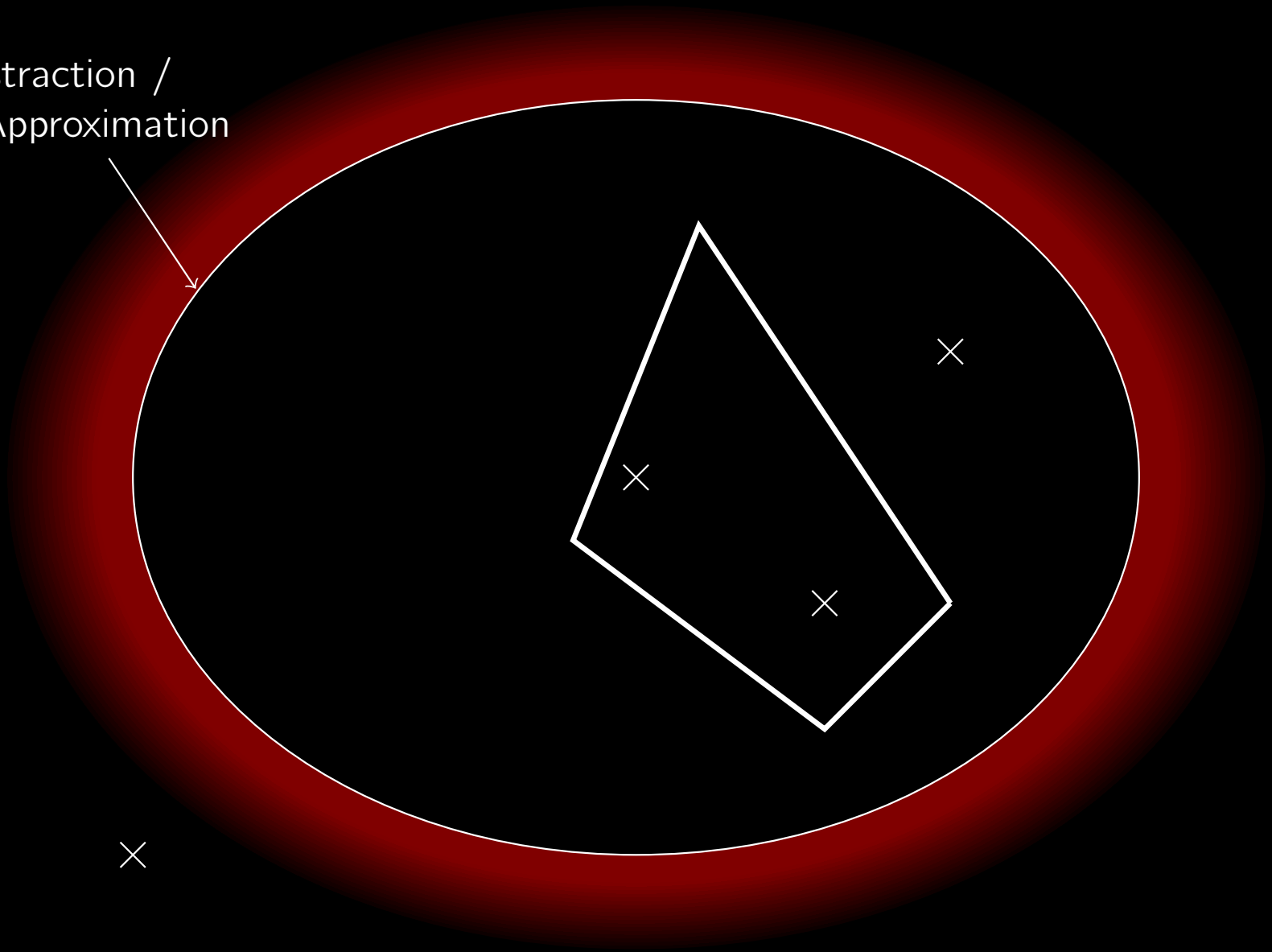
Overall Approach: Over- and Under-Approximation



Overall Approach: Over- and Under-Approximation

1. Abstraction / Over-Approximation



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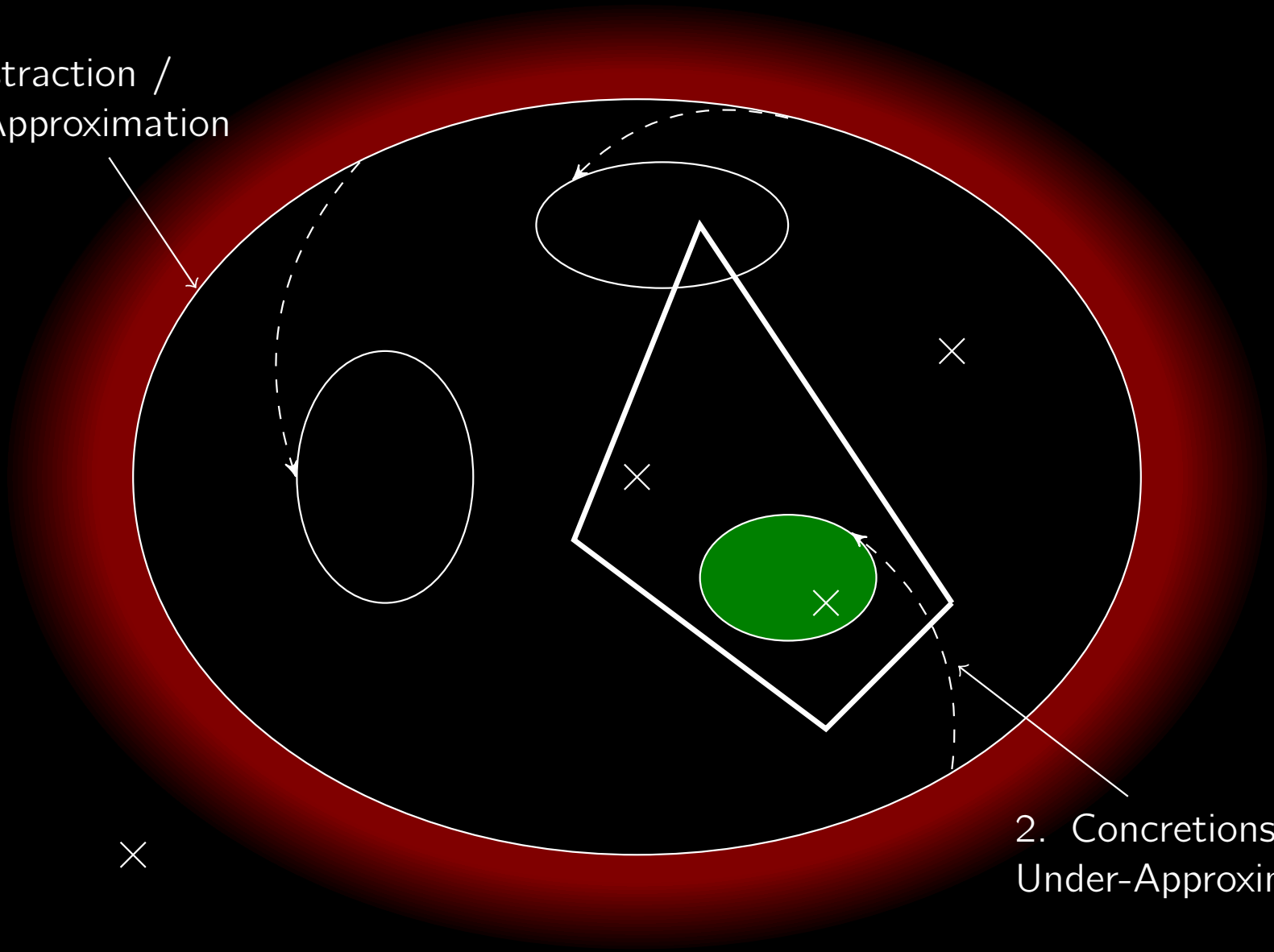
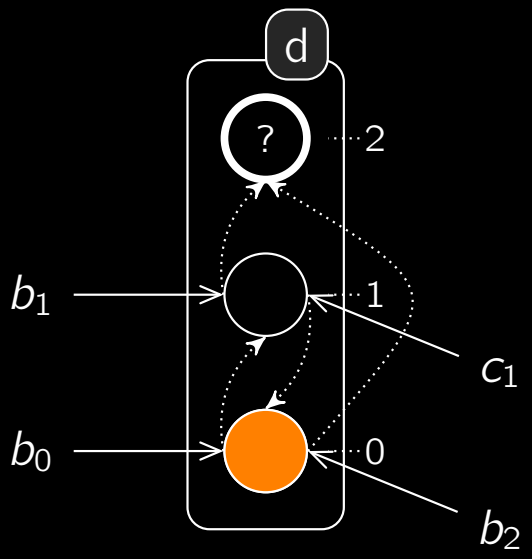


(Abstracted) Bounce Sequences



Objectives

$d_0 \Rsh^* d_2,\ d_1 \Rsh^* d_2,\ \ldots$

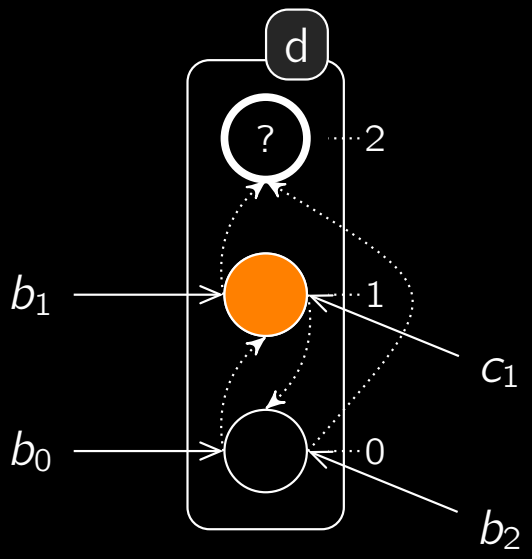
Bounce Sequences

Only minimal sequences are kept.

$$\mathcal{BS}(d_0 \Rsh^* d_2) = \{[b_0 \rightarrow d_0 \Rsh d_1;\ b_1 \rightarrow d_1 \Rsh d_2],\ [b_2 \rightarrow d_0 \Rsh d_2]\}$$

$$\mathcal{BS}(d_1 \Rsh^* d_2) = \{[b_1 \rightarrow d_1 \Rsh d_2],\ [c_1 \rightarrow d_1 \Rsh d_0;\ b_2 \rightarrow d_0 \Rsh d_2]\}$$

(Abstracted) Bounce Sequences



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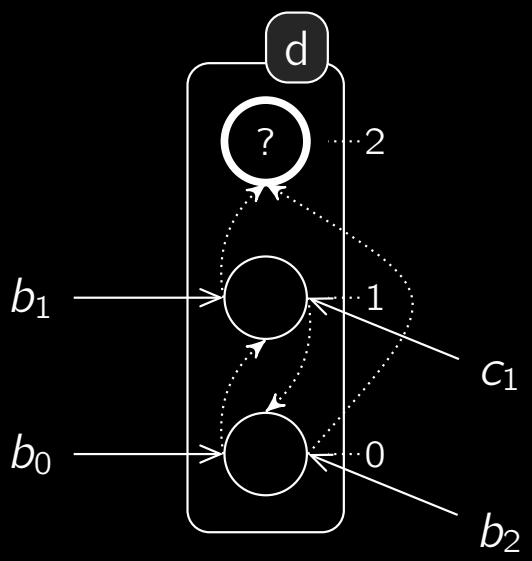
(Abstracted) Bounce Sequences



Objectives

$d_0 \Gamma^* d_2,\ d_1 \Gamma^* d_2,\ \ldots$

Bounce Sequences

Only minimal sequences are kept.

$$\mathcal{BS}(d_0 \Gamma^* d_2) = \{[b_0 \rightarrow d_0 \Gamma d_1; b_1 \rightarrow d_1 \Gamma d_2], [b_2 \rightarrow d_0 \Gamma d_2]\}$$

$$\mathcal{BS}(d_1 \Gamma^* d_2) = \{[b_1 \rightarrow d_1 \Gamma d_2], [c_1 \rightarrow d_1 \Gamma d_0; b_2 \rightarrow d_0 \Gamma d_2]\}$$

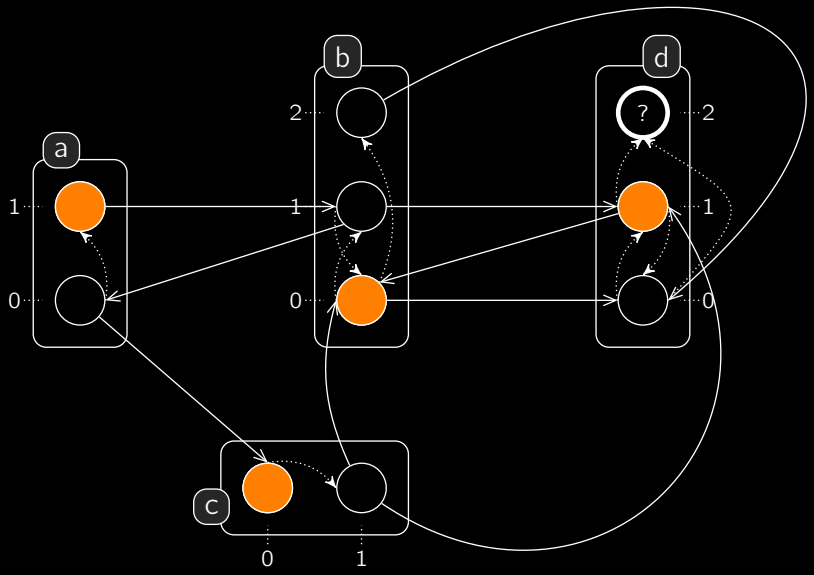
Abstracted Bounce Sequences

Only hitters are kept, and the order is forgotten.

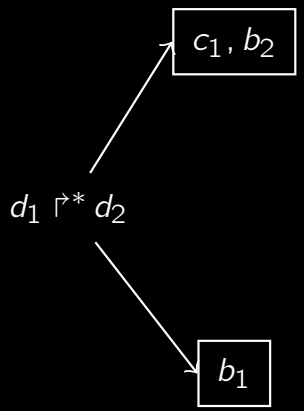
$$\mathcal{BS}\hat{}(d_0 \Gamma^* d_2) = \{\{b_0, b_1\}, \{b_2\}\}$$

$$\mathcal{BS}\hat{}(d_1 \Gamma^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$$

Over-approximation of Process Reachability



- $\mathcal{BS}\hat{}(d_1 \Rsh^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$



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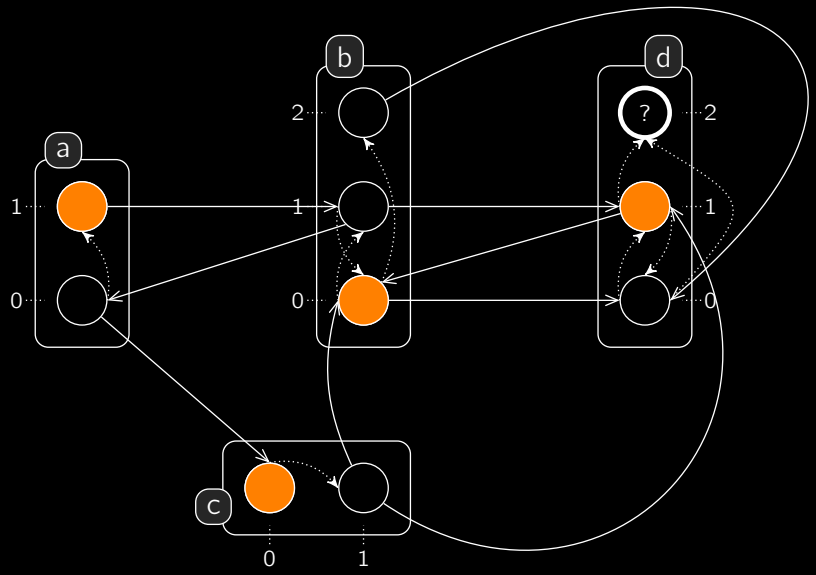
Over-approximation of Process Reachability



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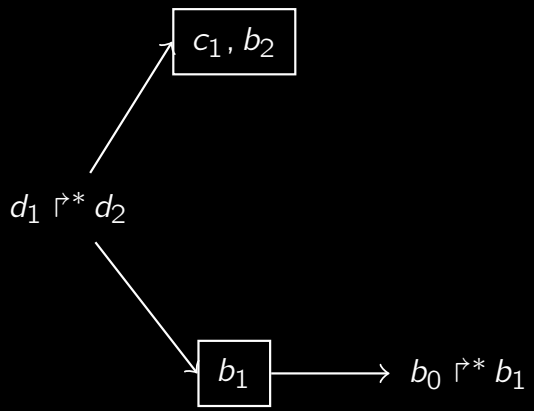

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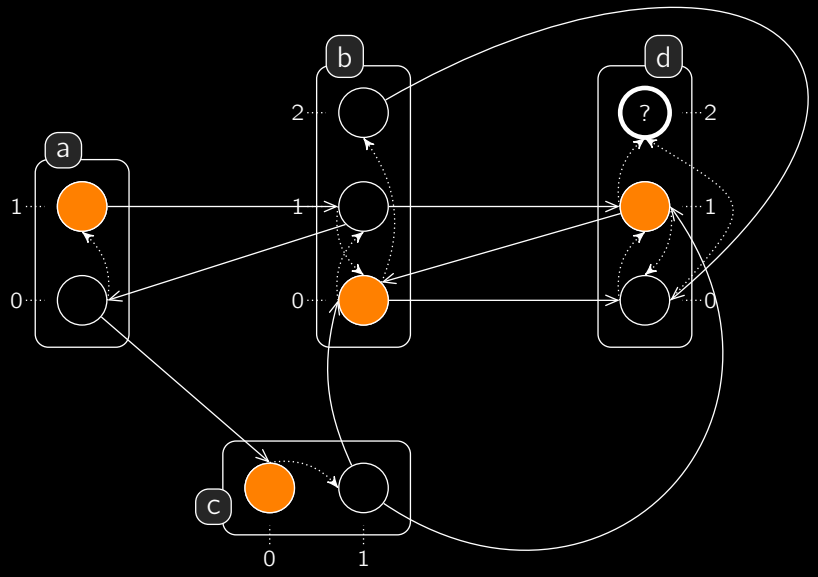

- $\mathcal{BS}\hat{}(d_1 \Rsh^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$
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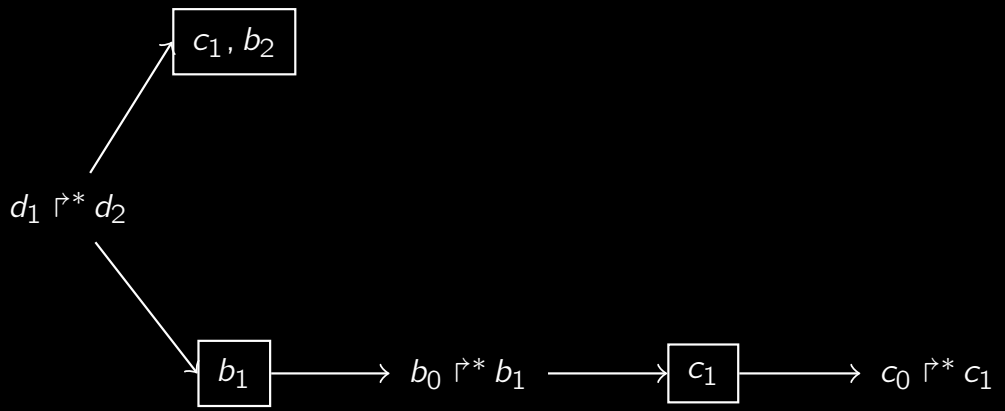

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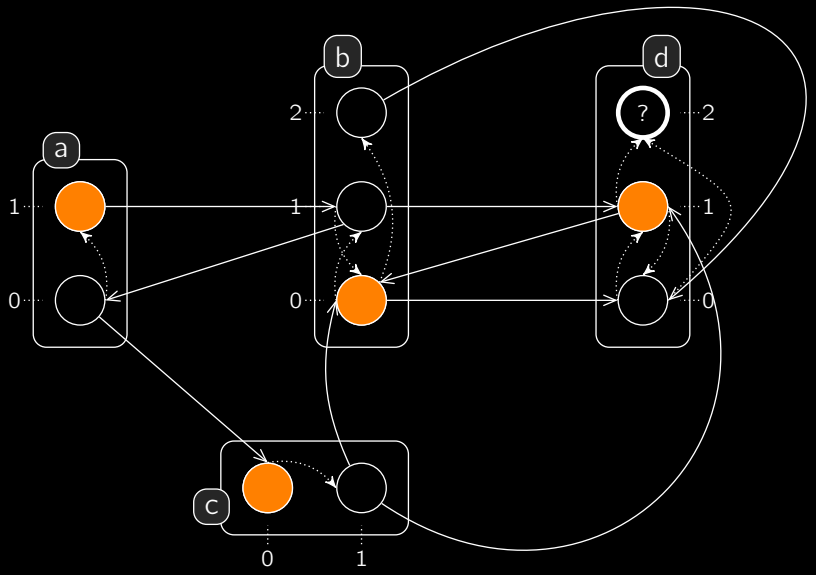
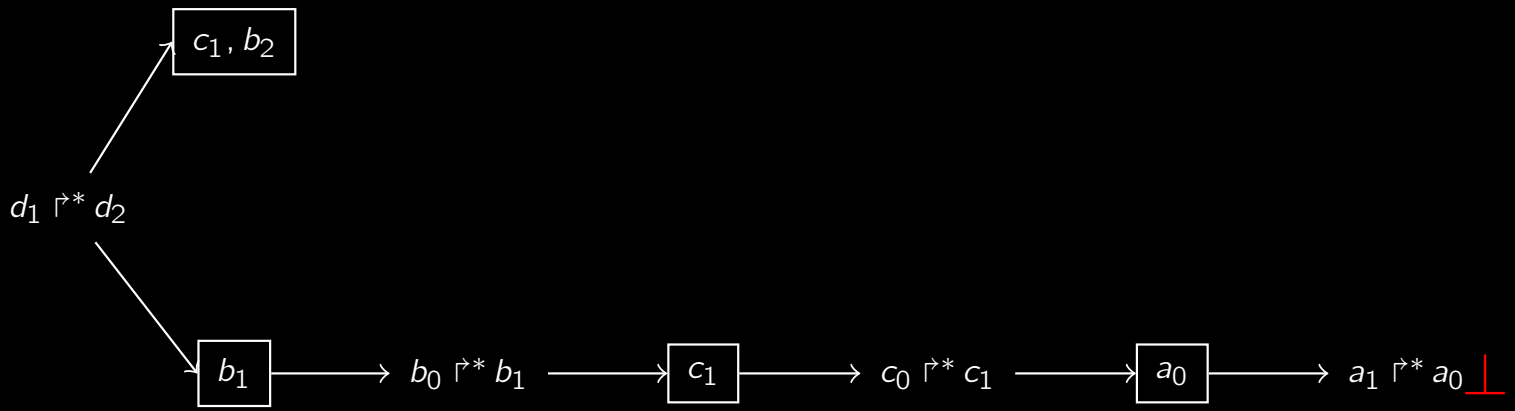


- $\mathcal{BS}\hat{}(d_1 \Rsh^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$
- $\mathcal{BS}\hat{}(b_0 \Rsh^* b_1) = \{\{c_1\}\}$
- $\mathcal{BS}\hat{}(c_0 \Rsh^* c_1) = \{\{a_0\}\}$
- $\mathcal{BS}\hat{}(a_1 \Rsh^* a_0) = \emptyset$



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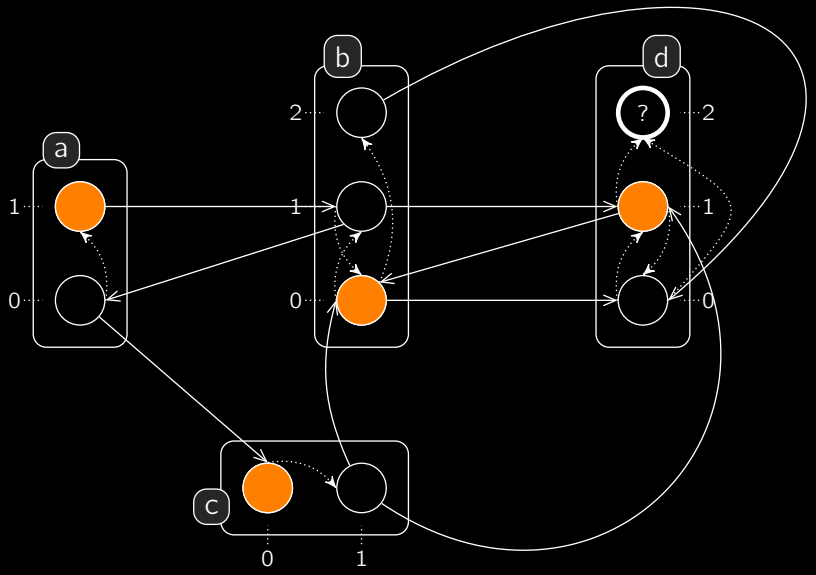

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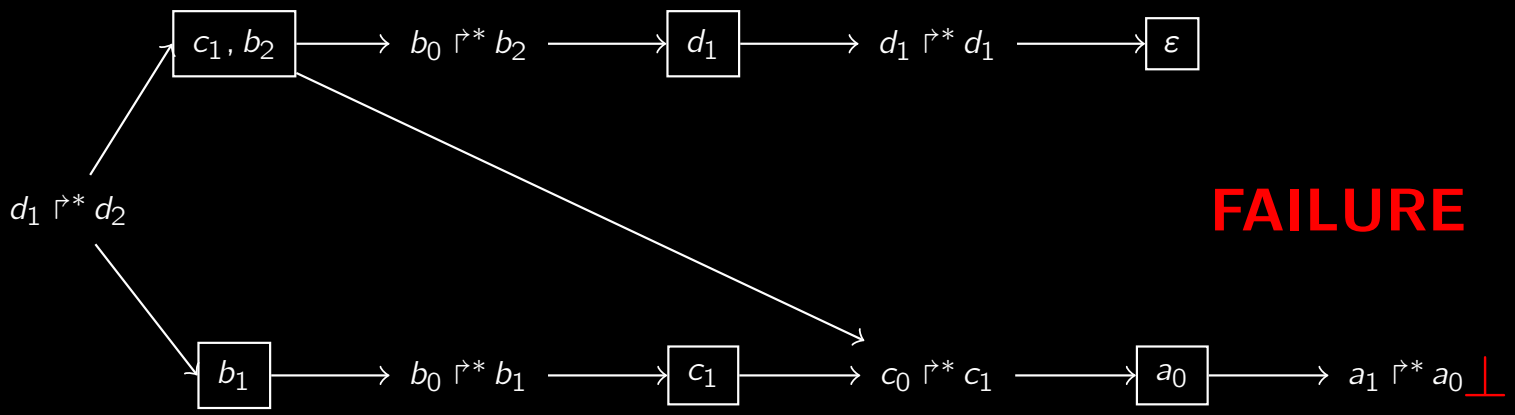
- $\mathcal{BS}\hat{}(a_1 \Rsh^* a_0) = \emptyset$
- $\mathcal{BS}\hat{}(b_0 \Rsh^* b_2) = \{\{d_1\}\}$
- $\mathcal{BS}\hat{}(d_1 \Rsh^* d_1) = \{\varepsilon\}$



FAILURE

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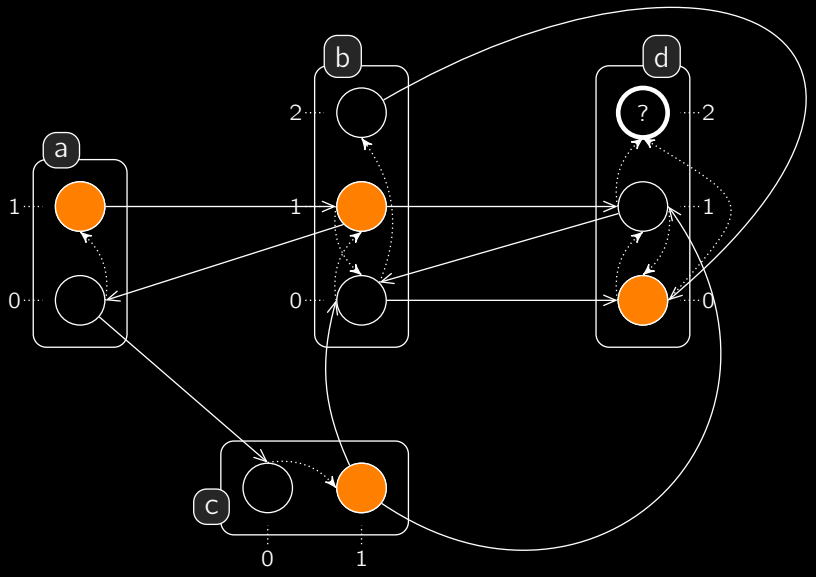
Over-approximation of Process Reachability



- $\mathcal{BS}\hat{}(d_1 \Rsh^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$
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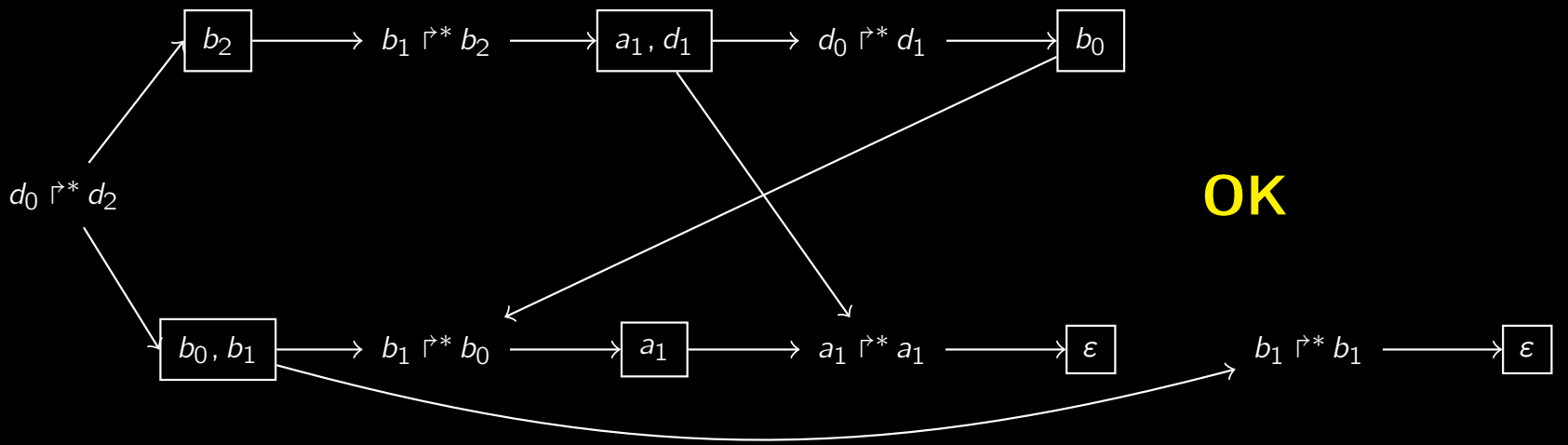
- $\mathcal{BS}\hat{}(d_0 \Rsh^* d_2) = \{\{b_0, b_1\}, \{b_2\}\}$



OK

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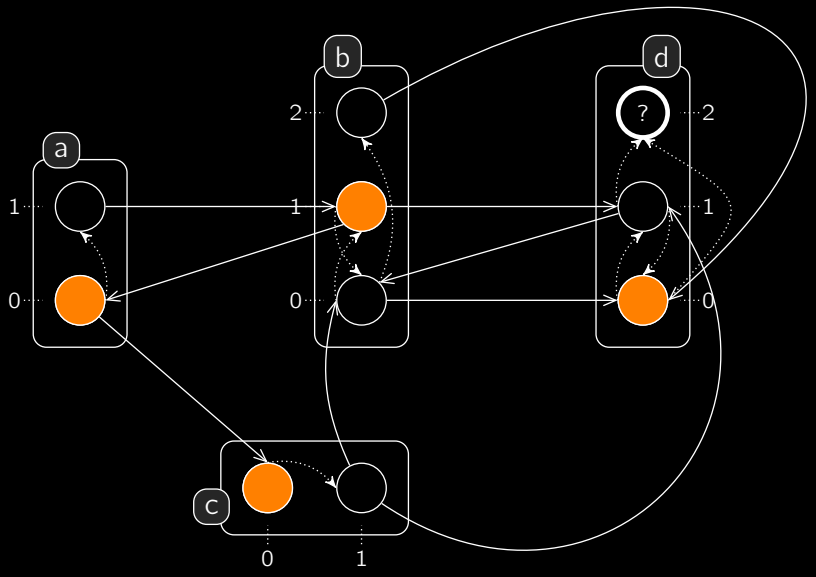

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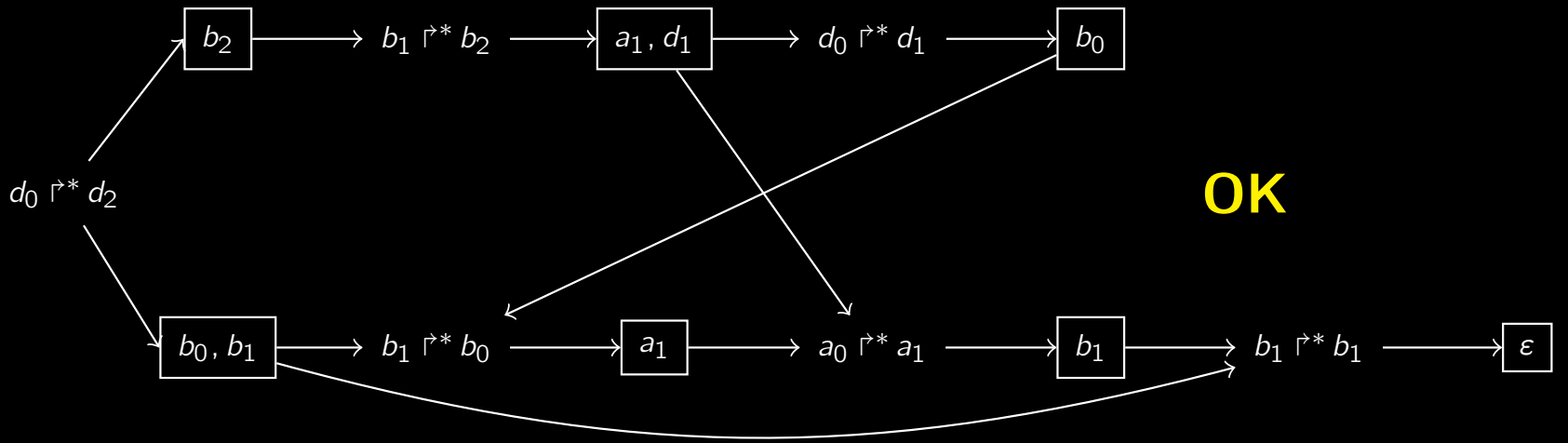

OK

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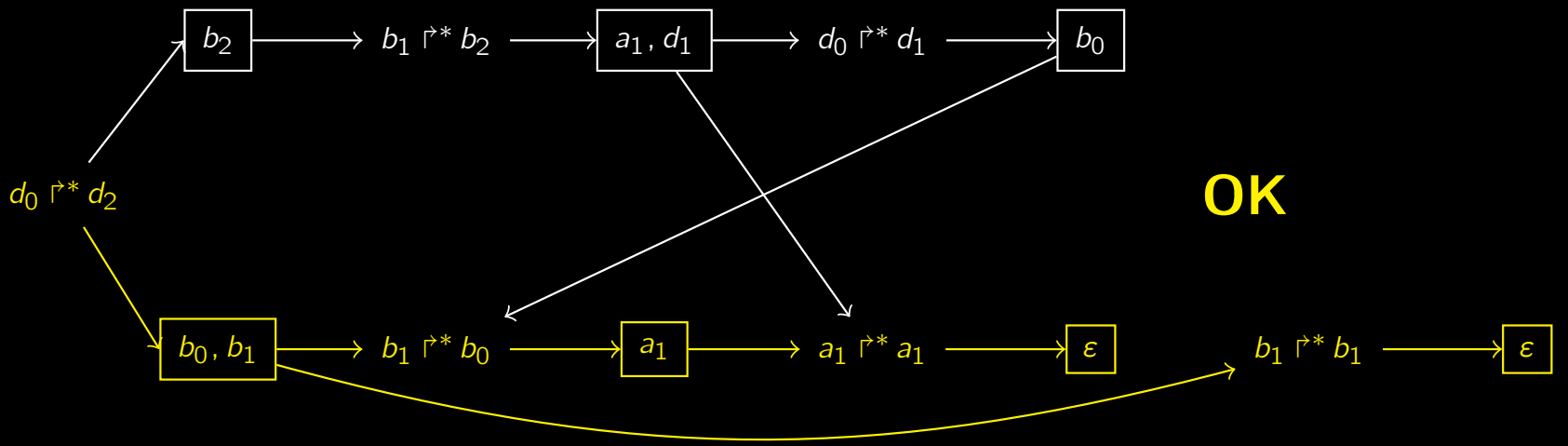
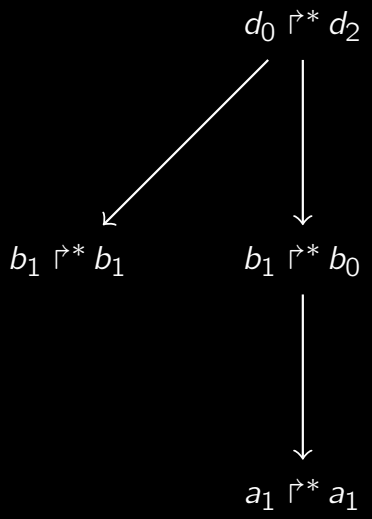
Building concretions





- arbitrary select one way to resolve an objective;
- there must be no cycle.

$\Rightarrow$ ensure all dependencies are reachable:

- whatever the order of resolution;
- whatever the required number of occurrence.

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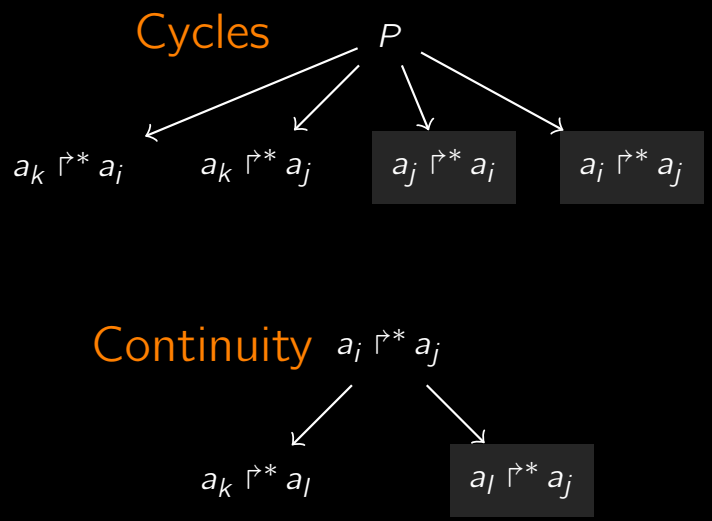
Under-approximation of Process Reachability

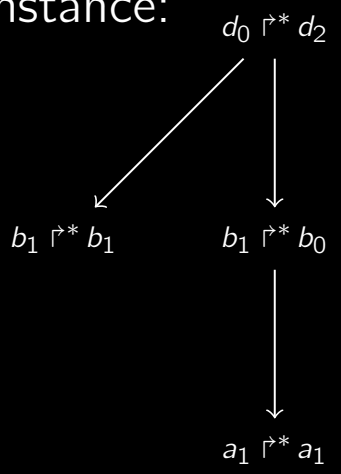
From previous abstraction:

- arbitrary select one way to resolve an objective;
- apply the saturation procedure;
- if all required objectives are possible, then SUCCESS;
- else INCONCLUSIVE, try another concretion.

Saturation procedure:



Instance:



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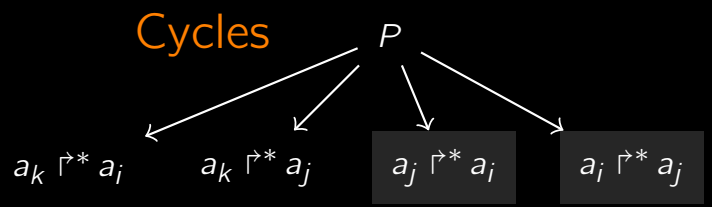

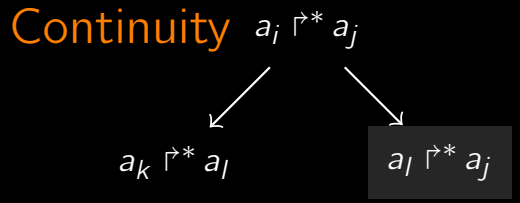

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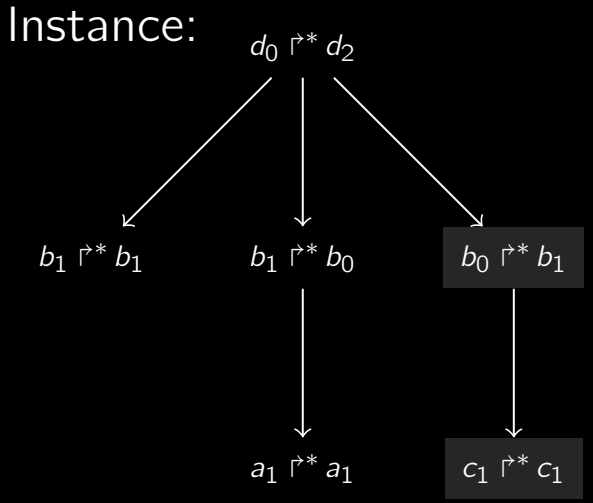

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Under-approximation of Process Reachability

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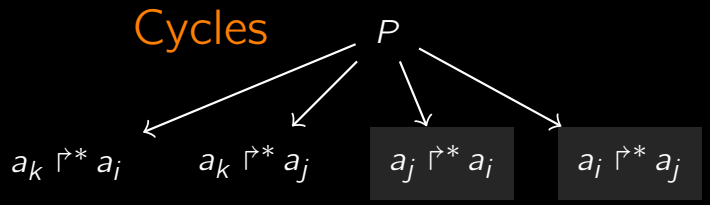
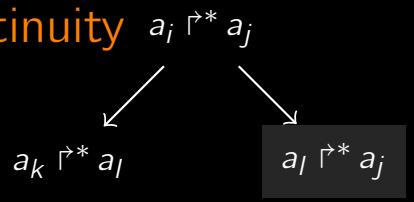
Saturation procedure:

Cycles



Continuity



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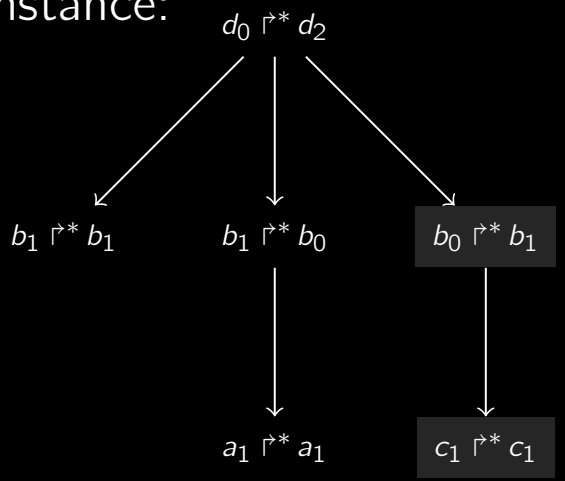

SUCCESS

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Under-approximation of Process Reachability

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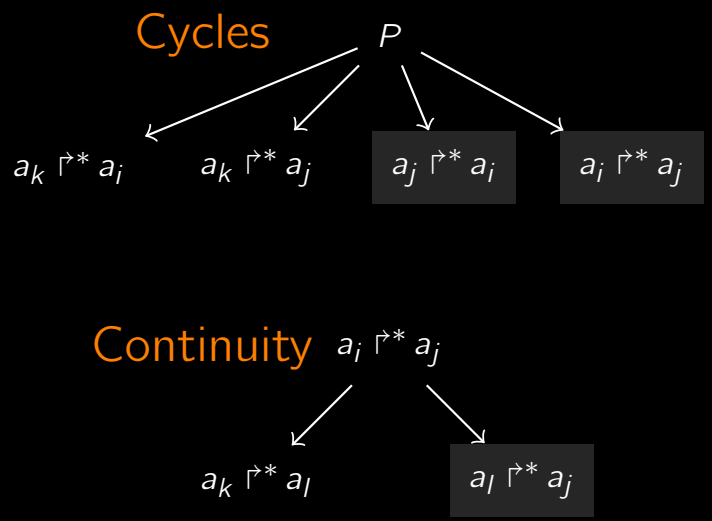
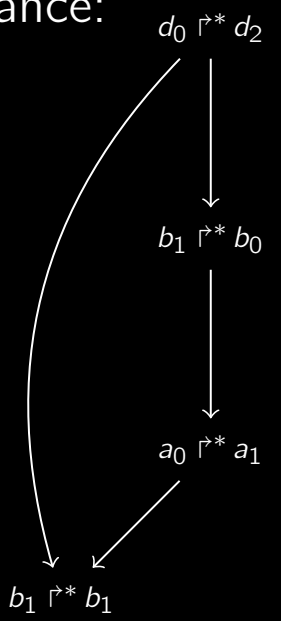
Saturation procedure:



Instance:



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Under-approximation of Process Reachability

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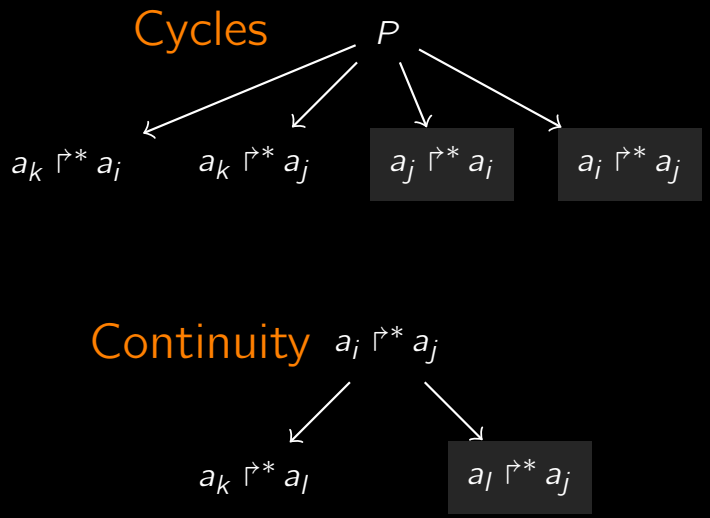

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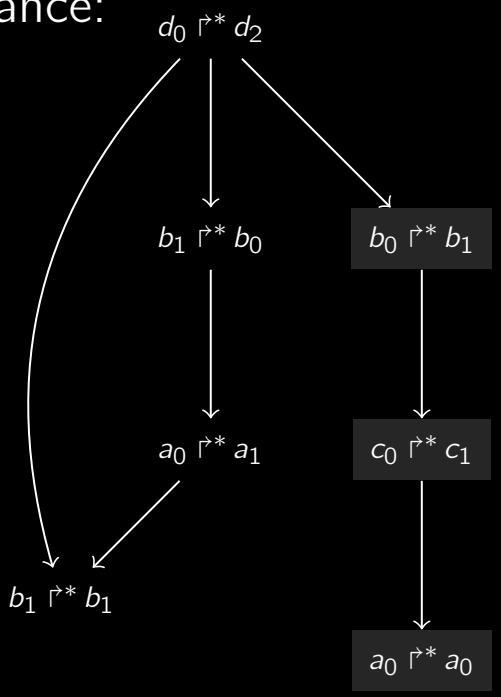

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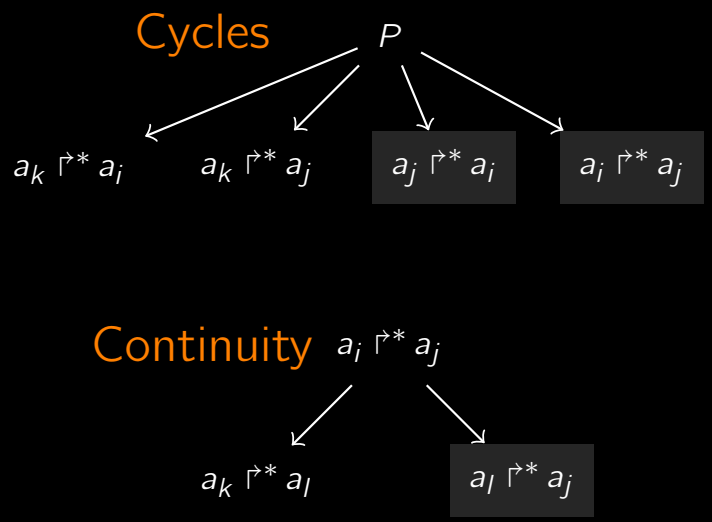

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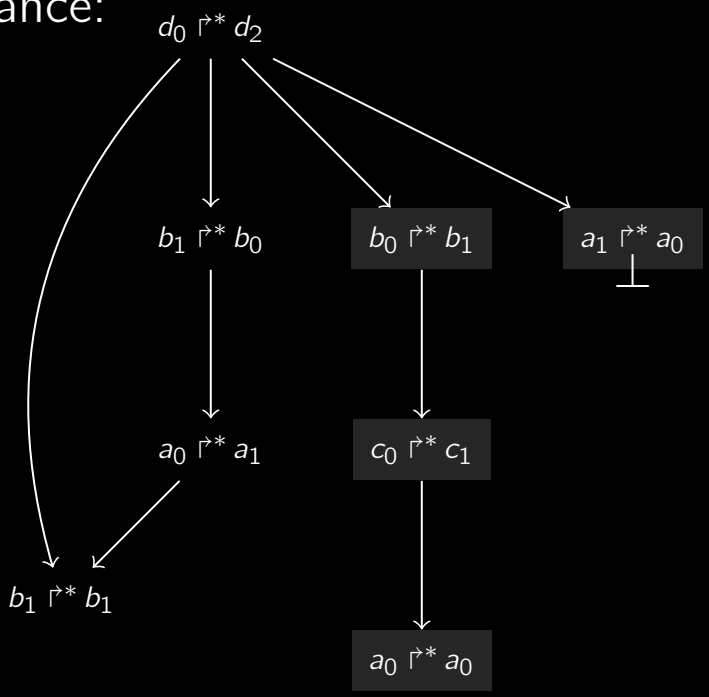

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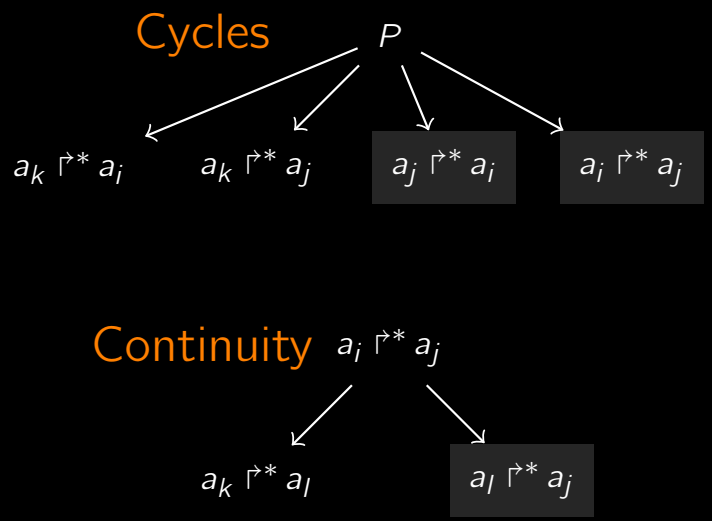

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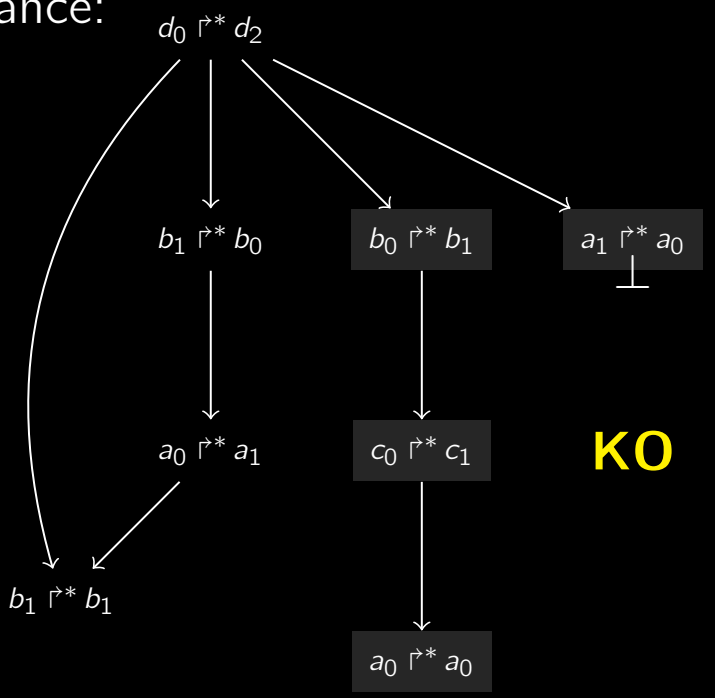

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Pre-Conclusion

Comments

- Quite simple approximations from Process Hittings source code;
- prevent explicit state space exploration;
- abstract stuctures provide information on required steps for reachability.

Complexities

- Computing $\mathcal{BS}\hat{}$ is exponential in the size of the sort;
- other operations are $\approx$ polynomial in the number of sorts.

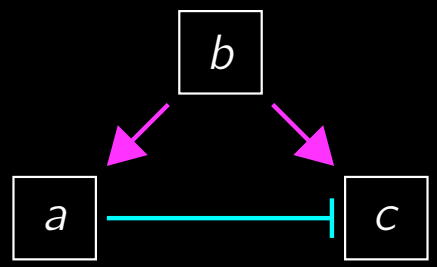
Outlook

- $\mathcal{BS}\hat{}(a_i \not\Rightarrow^* a_j) = \emptyset \Rightarrow a_i$ cannot appear after a_j;
- refine over- and under-approximations with this knowledge:
- reduce inconclusivness.

Biological Regulatory Networks (BRNs)

- Relates components with actions of activation and inhibition;
- each component has a finite number of ordered states;
- the next state of a component is function of its activators/inhibitors.

Interaction graph

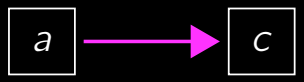


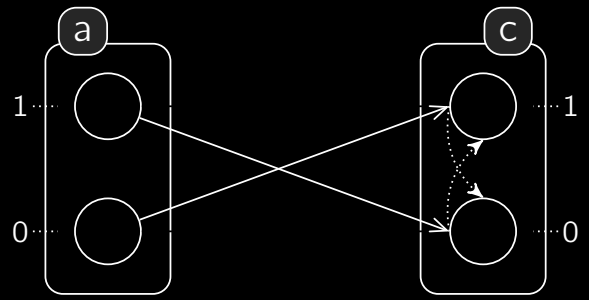
Cooperations

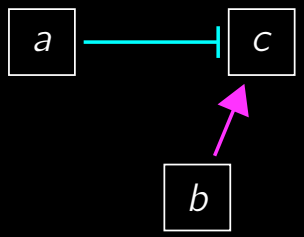
For instance (boolean case): $c = \neg a \wedge b$.

[René Thomas in Journal of Theoritical Biology, 1973] [A. Richard, J.-P. Comet, G. Bernot in Modern Formal Methods and Applications, 2006]

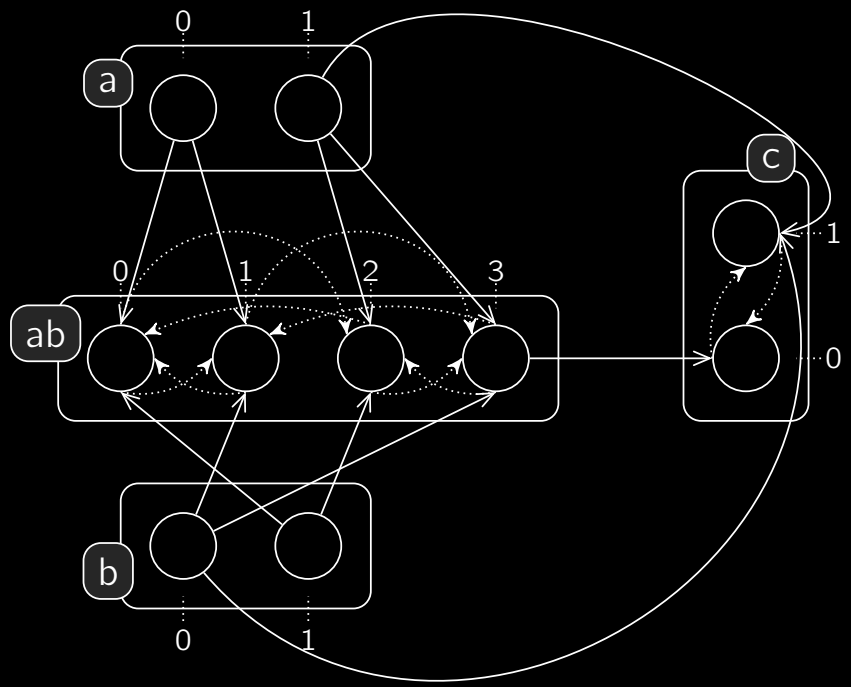
From BRNs to Process Hittings





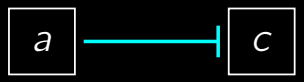


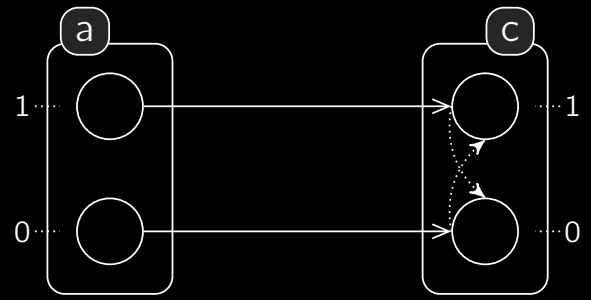
$c = \neg a \wedge b$

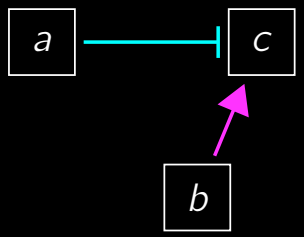


[Paulevé, *et al.* in Trans. in Computational Systems Biology, 2010]

From BRNs to Process Hittings







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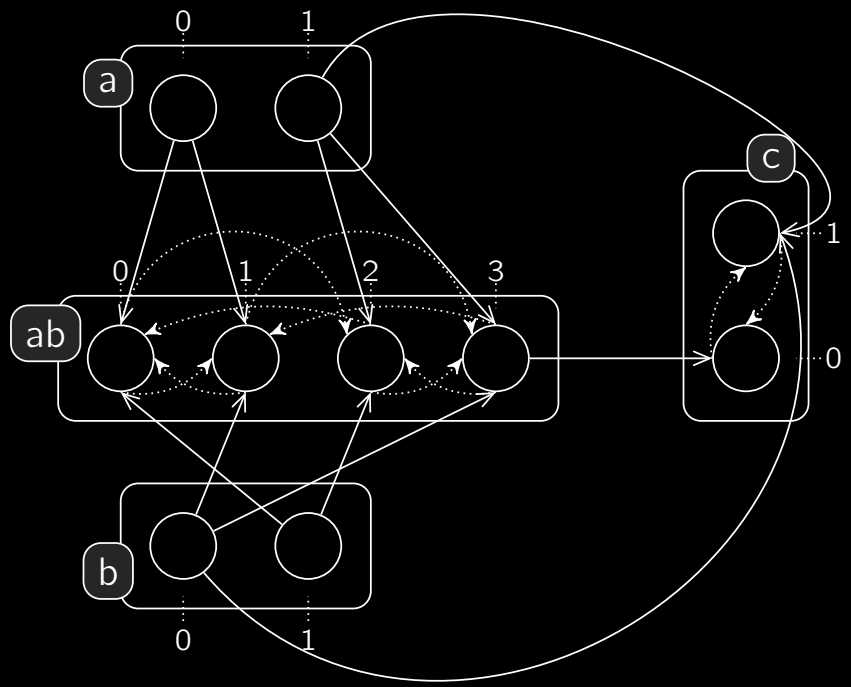

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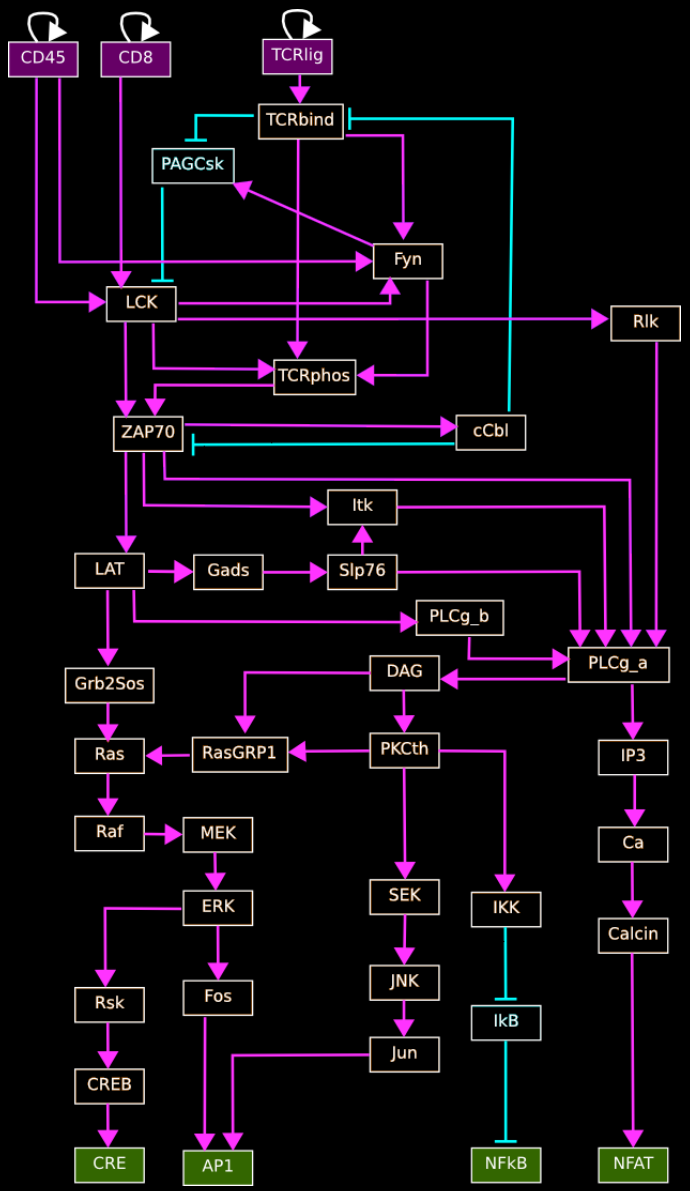

Experimentations

T-Cell Receptor Signalling Pathway

(40 components)

Process Hitting: 53 sorts, 176 processes, 416 actions, largest sort: 32 processes; total: $\approx 10^{22}$ states.

Reachability analysis:

- always conclusive;
- execution time: around $1s$.
- *libddd* framework: from a few seconds to many hours (or out of memory).

Bottleneck: $\mathcal{BS}^\wedge$ computation (large sorts).

[Klamt, *et al.* in BMC Bioinformatics, 2006]
[Naldi, Thieffry, Chaouiya in CMSB 2007]
[http://ddd.lip6.fr]

Conclusion and TODOs

Conclusion

- Efficient method to (semi-)decide process reachability;
- static analysis and abstract interpretation from the model;
- exploit particular structures of the language used (Process Hitting);
- no explicit state space construction;
- promising scalability.

On-going work

- Reduce inconclusivness: exploit partial order of process appearance.
- Extract necessary processes for achieving reachabilities: towards control.
- Software soon at `http://www.irccyn.ec-nantes.fr/~pauleve`.

Future work

- How does the analysis apply to less restricted CFSM?
- Quantitative analysis (eg: probability of reaching a process within a time interval).