Modelling, Simulation, and Large-Scale Model Checking of Biological Regulatory Networks

Loïc Paulevé, Morgan Magnin, Olivier Roux

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DTU - 10th March 2011

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Other people I work with

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Microsoft Research, Cambridge, UK
Stochastic simulation

Adrien Richard
I3S, Nice, France
Biological Regulatory Networks

Overview

Computer science for systems biology

- Models for dynamical concurrent systems.
- Validation of the model / control of the system.

- We focus on Biological Regulatory Networks (BRNs).
- We introduce a new modelling framework: the Process Hitting.

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The Process Hitting [Paulevé, Magnin, Roux in TCSB 2011]

- *Elementary* framework for dynamical complex systems;
- Applied to BRNs; not limited to.
- Stochastic and Time dimensions (simulation + standard model checking).
- Software available (PINT - `http://processhitting.wordpress.com`).

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Large-scale model checking (dynamical properties)

- Cope with state space explosion.
- Our approach: Static Analysis of the model.
- Static analysis by Abstract Interpretation.

Outline

1. Introduction to BRNs
2. The Process Hitting
3. Stochastic and Time Parameters
4. Scalable Analysis of Dynamics
   - Dynamics Properties from BRN Interaction Graph
   - Fix Points
5. Abstract Interpretation of Scenarios
6. Applications
7. Discussion

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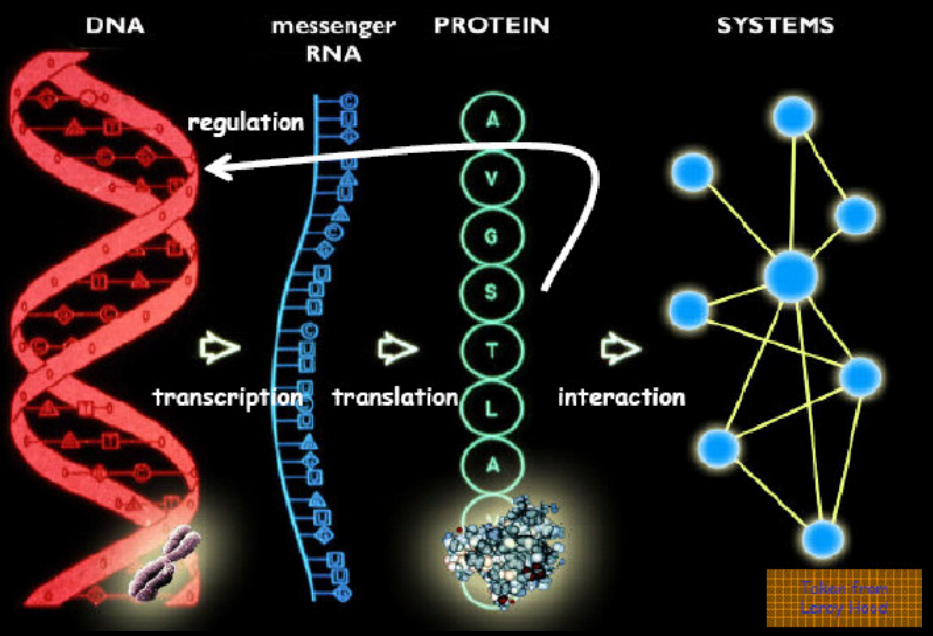
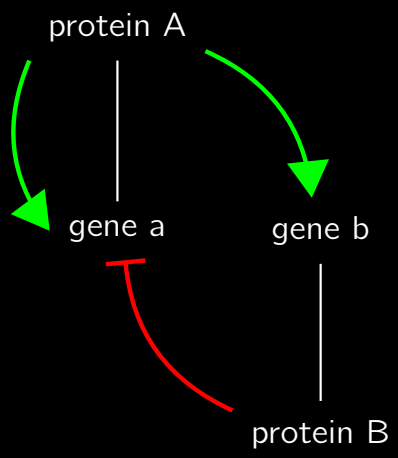
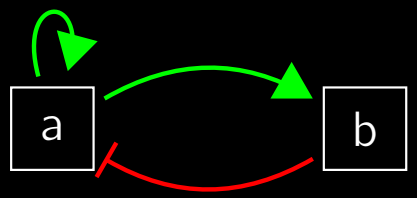
Biological Regulatory Networks (BRNs)







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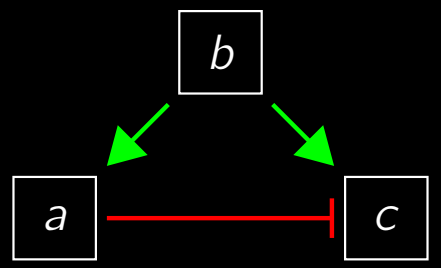
Biological Regulatory Networks (BRNs)

- 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

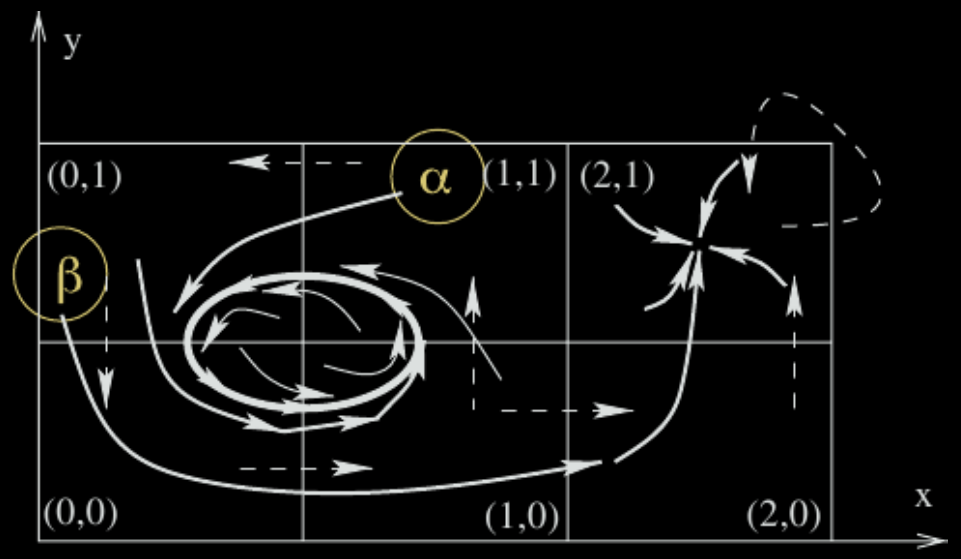


Cooperations

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]

Quantitative Features



Some current work

- Time(d), Stochastic Petri Nets [Heiner],
- Continuous-time Markov Chains (PRISM) [Kwiatkowska, Parker],
- Biocham [Fages], Kappa [Danos, Feret, Fontana, Krivine],
- Timed Automata [Siebert, Bockmayr],
- Linear Hybrid Automata [Ahmad, Roux].

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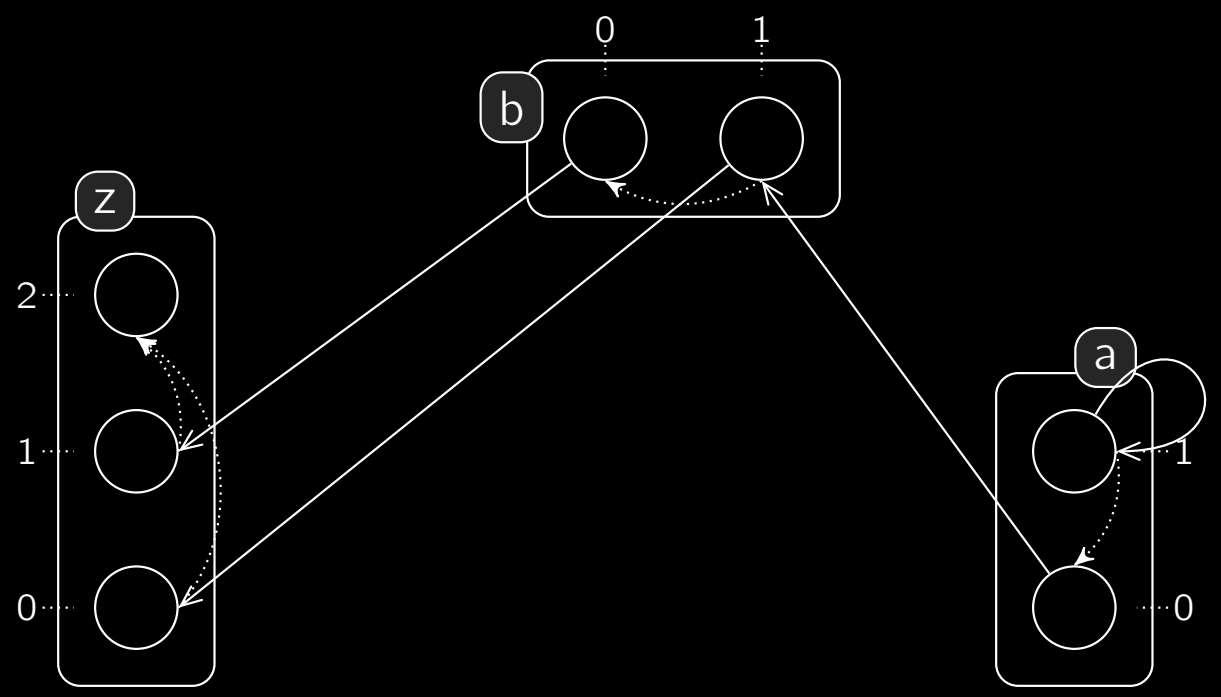
The Process Hitting Framework

[Paulevé, Magnin, Roux in TCSB 2011]



- 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).

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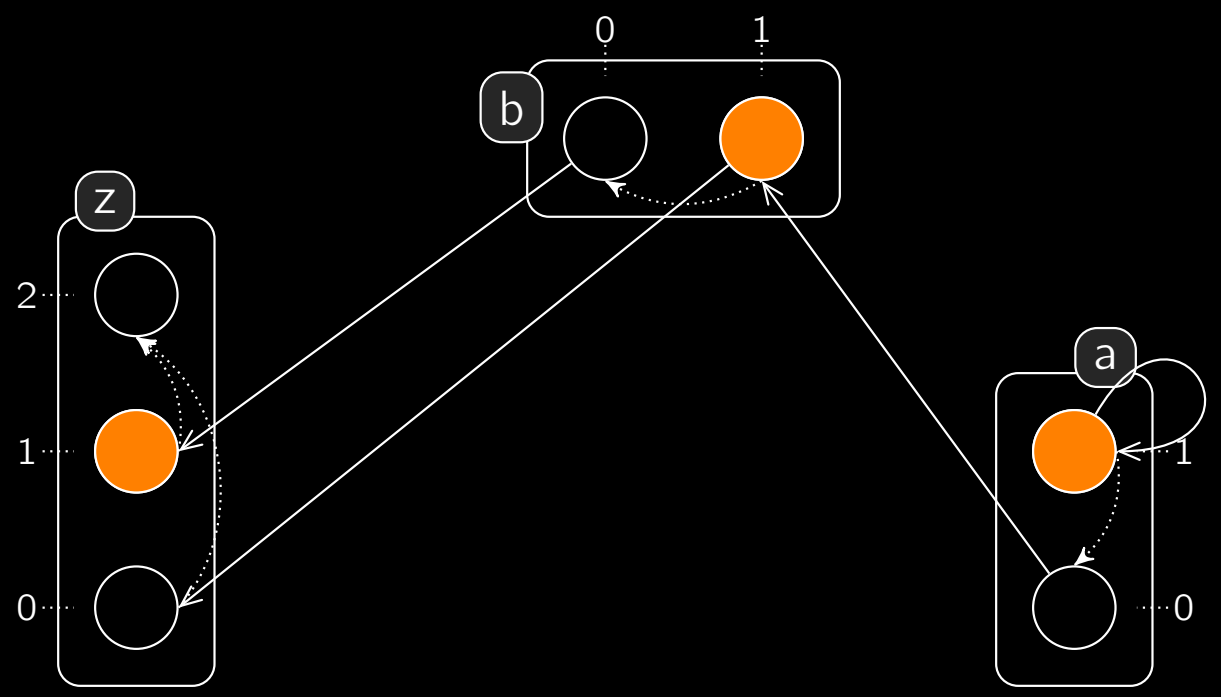

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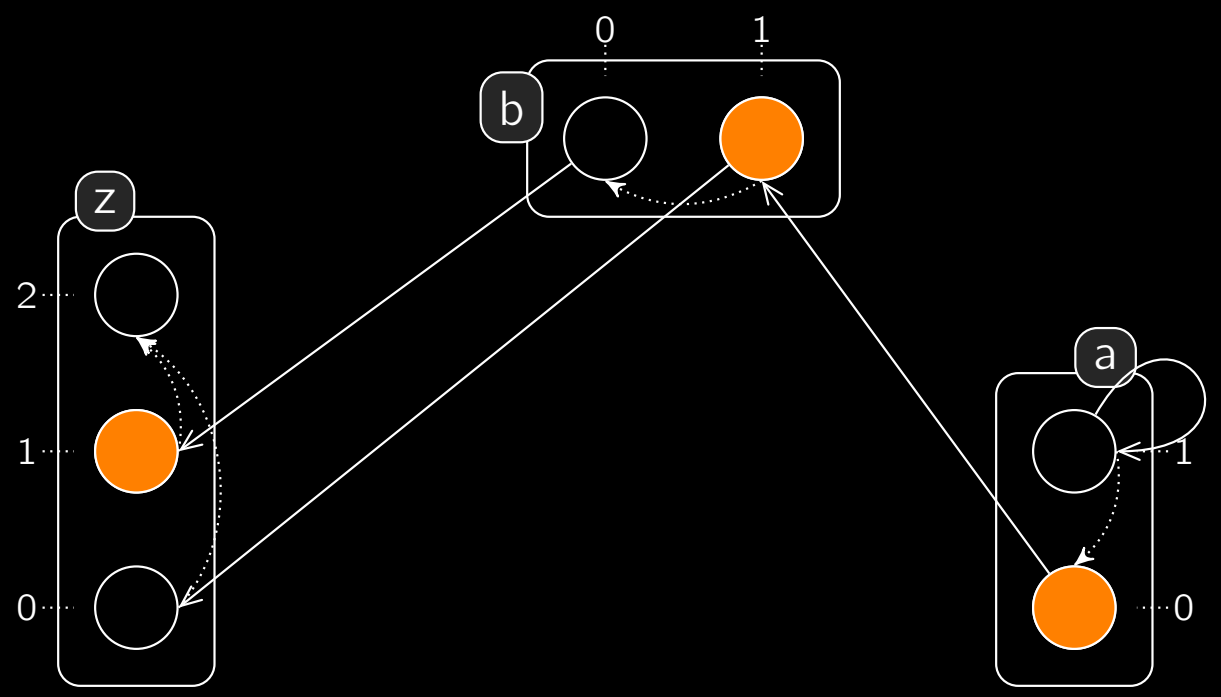

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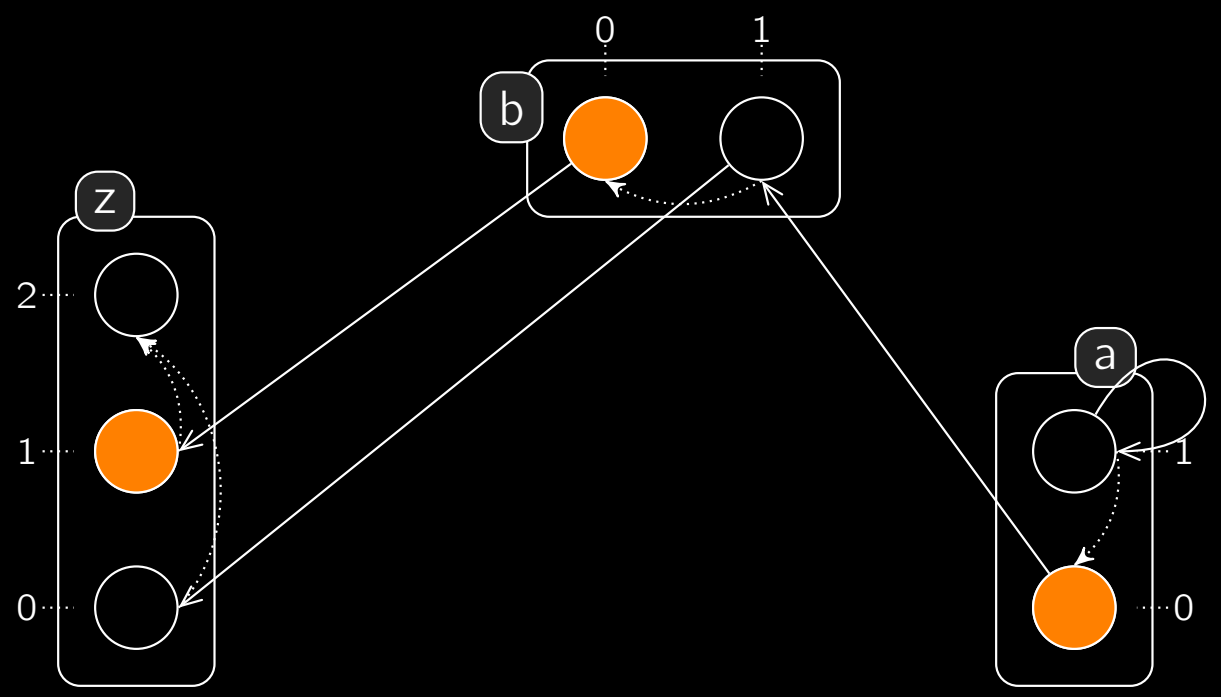

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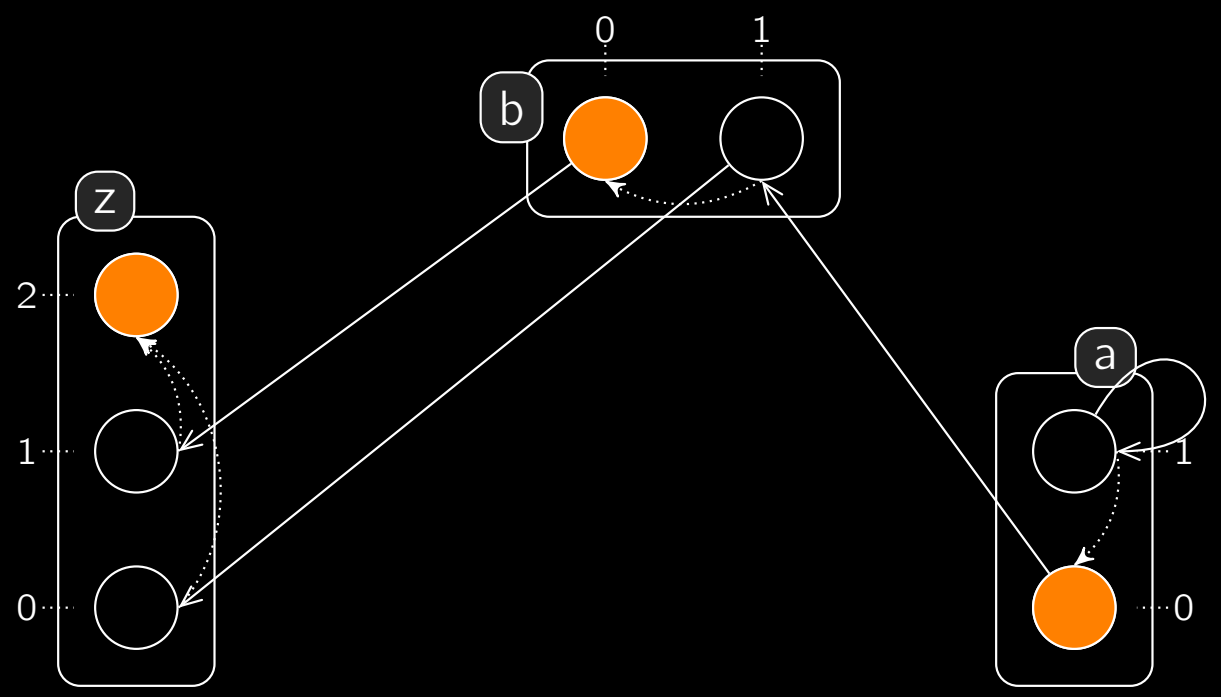

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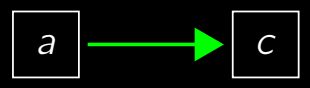
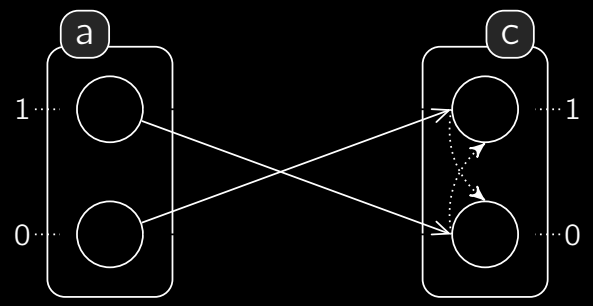
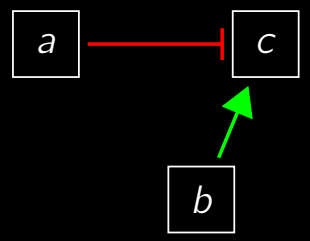
From BRNs to Process Hittings







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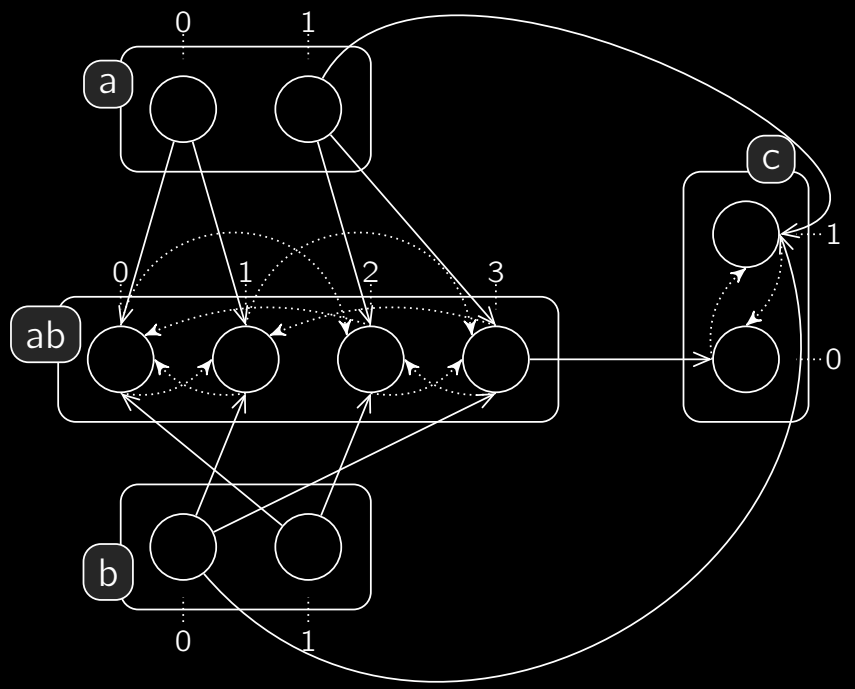

[Paulevé, Magnin, Roux in Trans. in Computational Systems Biology, 2011]

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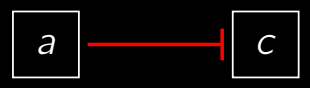

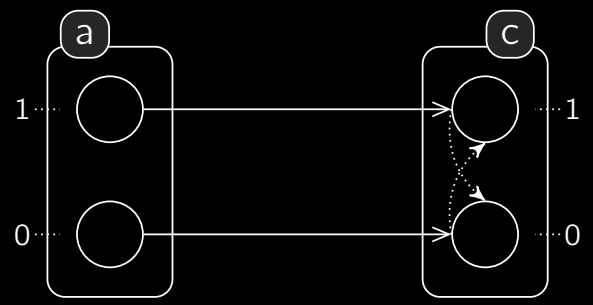

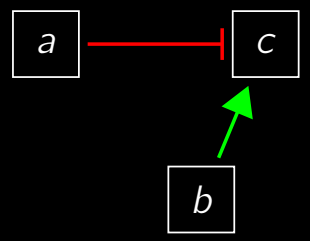

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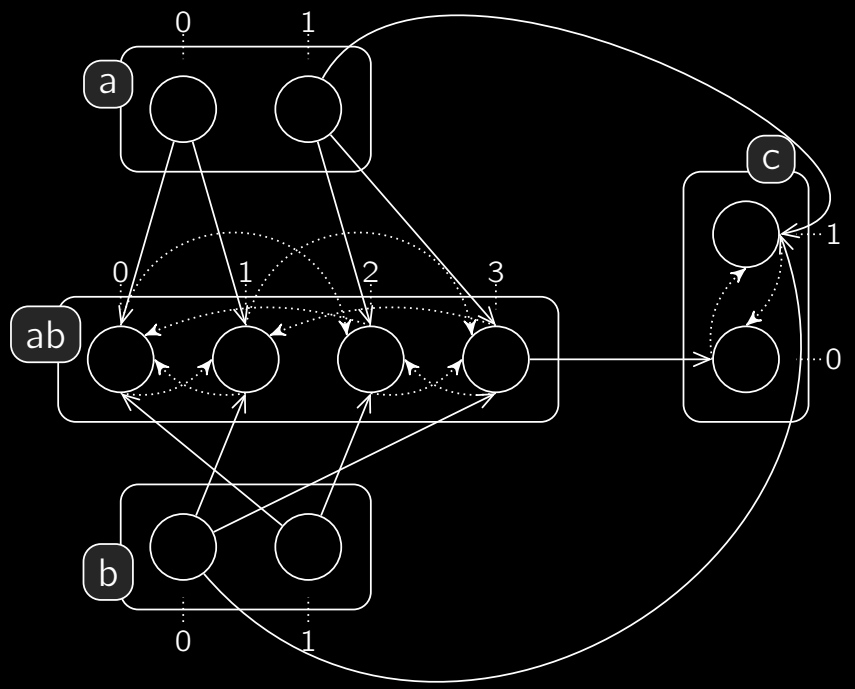

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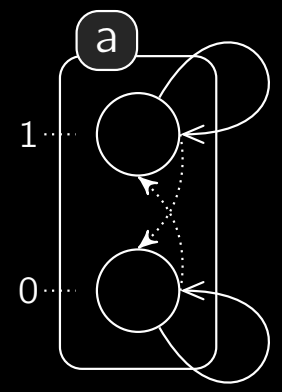
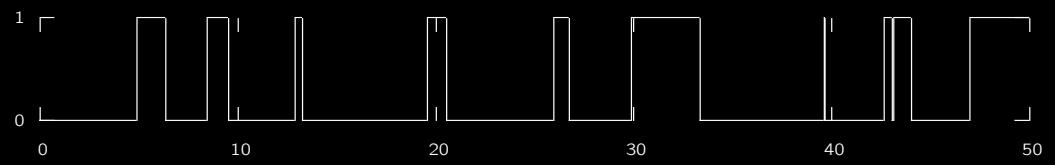
Stochasticity Absorption Factor

[Paulevé, Magnin, Roux in IEEE TSE, 2010]

- Stochastic (Markovian) dimension is prominent
- ... but no precise time features;
- Exponential distribution: mean r^{-1}; variance r^{-2}.





sa=1

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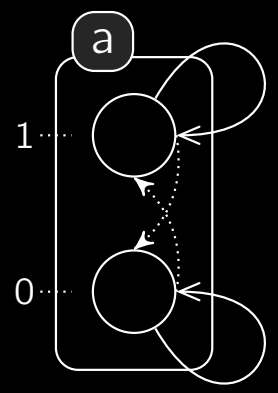
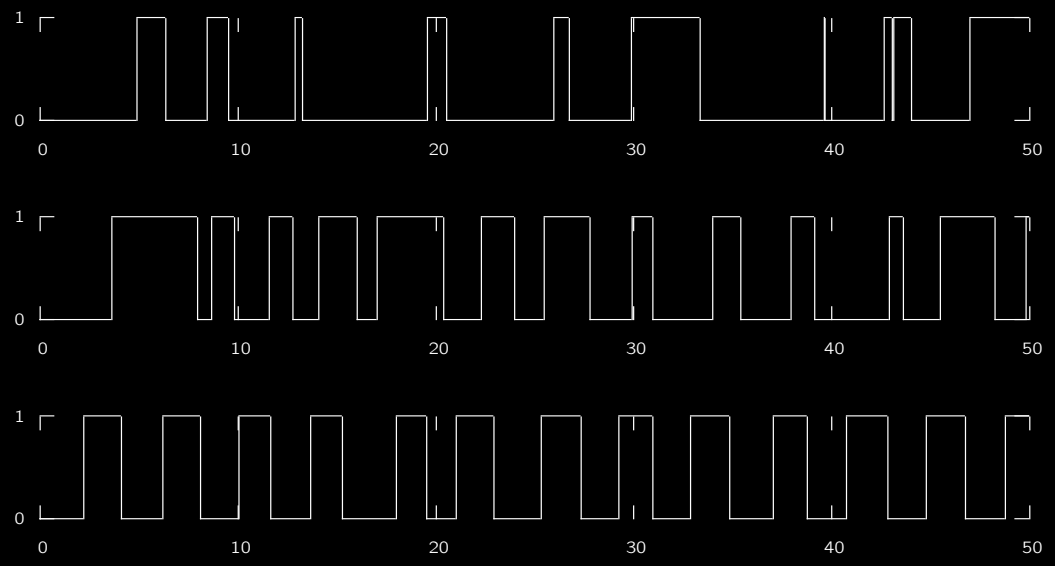
- Exponential distribution: mean r^{-1}; variance r^{-2}.
- Provide a stochasticity absorption factor sa:
- duration follows the sum of sa exponentials of rate $r.sa$;
- mean r^{-1}; variance $r^{-2}sa^{-1}$ (Erlang distribution).





sa=1

sa=5

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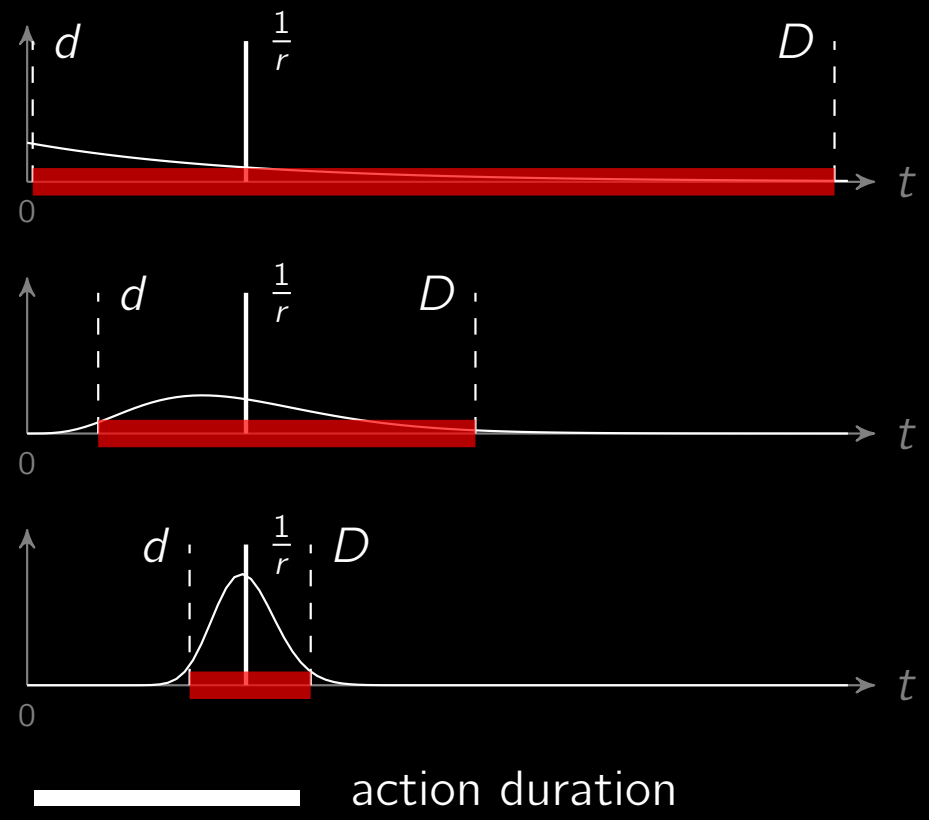
Stochastic and Time Parameters

[Paulevé, Magnin, Roux in IEEE TSE, 2010]

- Specify either (r, sa), or its firing interval $[d; D]$,
- which is the confidence interval at confidence coefficient $1 - \alpha$.
- We have estimators to translate $[d; D]$ to (r, sa).



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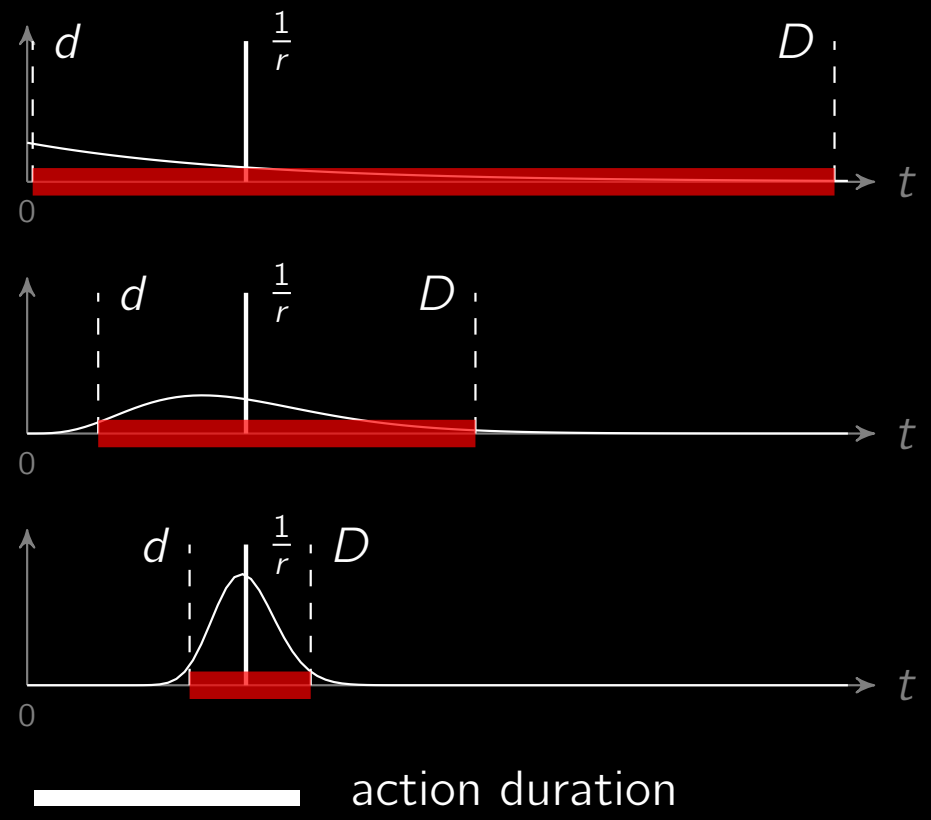

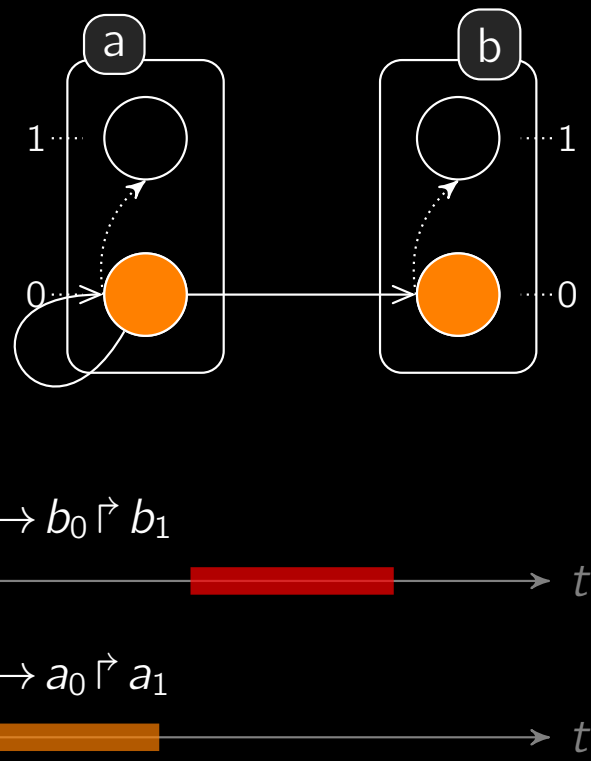

$\Rightarrow b_1$ is reached at a very low probability.

Simulation and Model Checking

Probabilistic Model Checking

- Translation from the Erlang stochastic π-calculus to PRISM.
- Applies to the Process Hitting as well.
- Not tractable with large stochasticiy absorption factors;
- but there is hope in symmetry reductions, or abstractions of sequences of transitions, or ...

Simulation

- Non-Markovian simulation using the
- Generic abstract machine for stochastic process calculi [Paulevé, Youssef, Lakin, Phillips at CMSB 2010].
- Process Hitting simulator implemented in PINT.

Challenge: scalable inference of stochastic and time parameters...

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Challenge: scalable inference of stochastic and time parameters...
... still open; prior need for scalable qualitative analyses.

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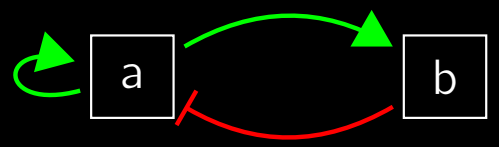
Dynamics Properties from BRN Interaction Graph

An interaction graph can describe a large set of different dynamics (think to different cooperations between components).



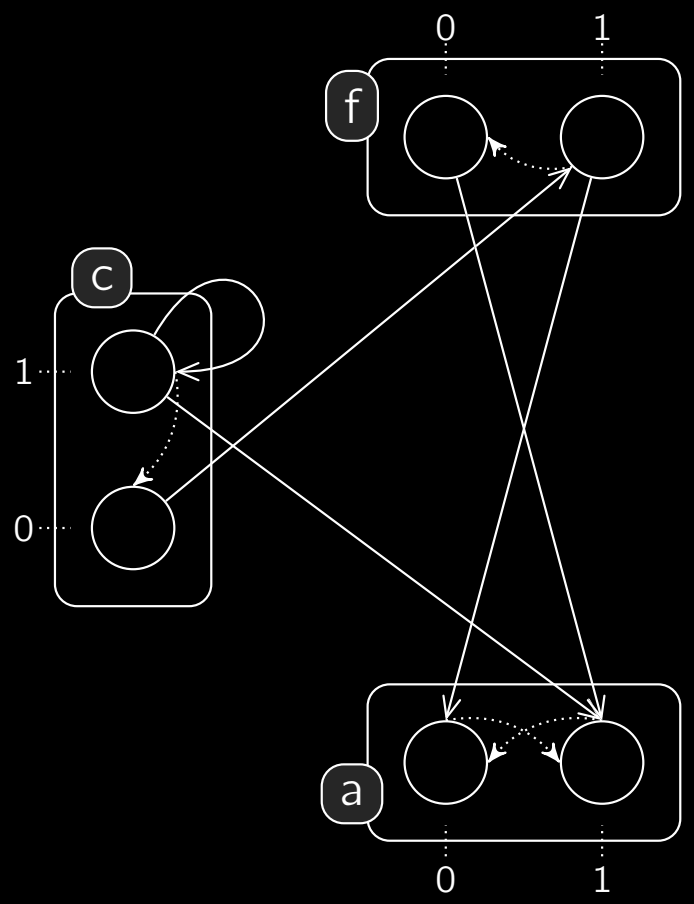
Mathematical work on relationship between the interaction graph and dynamical properties:

- Multi-stationnarity requires a positive circuit (René Thomas conjecture) [Soule in ComPlexUs, 2003] [Richard, Comet in Discrete Appl. Math., 2007].
- Sustained oscillations requires a negative circuit (René Thomas conjecture) [Remy, *et al.* in Adv. Appl. Math., 2008] [Richard in Adv. Appl. Math., 2010].
- The maximum number of fixed points can be characterized [Aracena in Bul. of Mathematical Biology, 2008]; [Richard in Discrete Appl. Math., 2009].
- Topological Fixed Points [Paulevé, Richard in CRAS 2010].

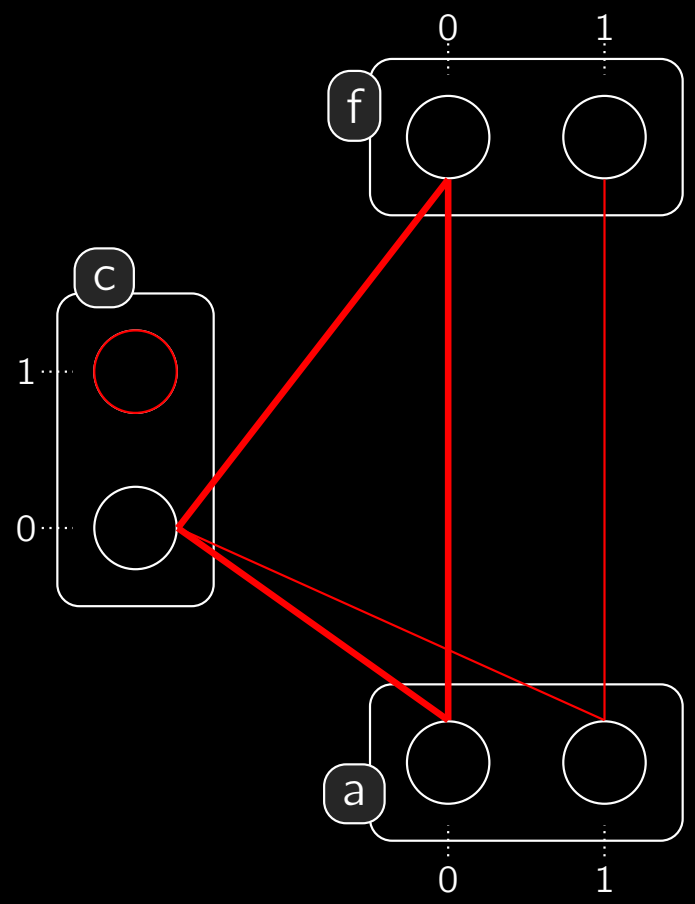
Fix Points

[Paulevé, Magnin, Roux in TCSB 2011]

Process Hitting



Hitless graph

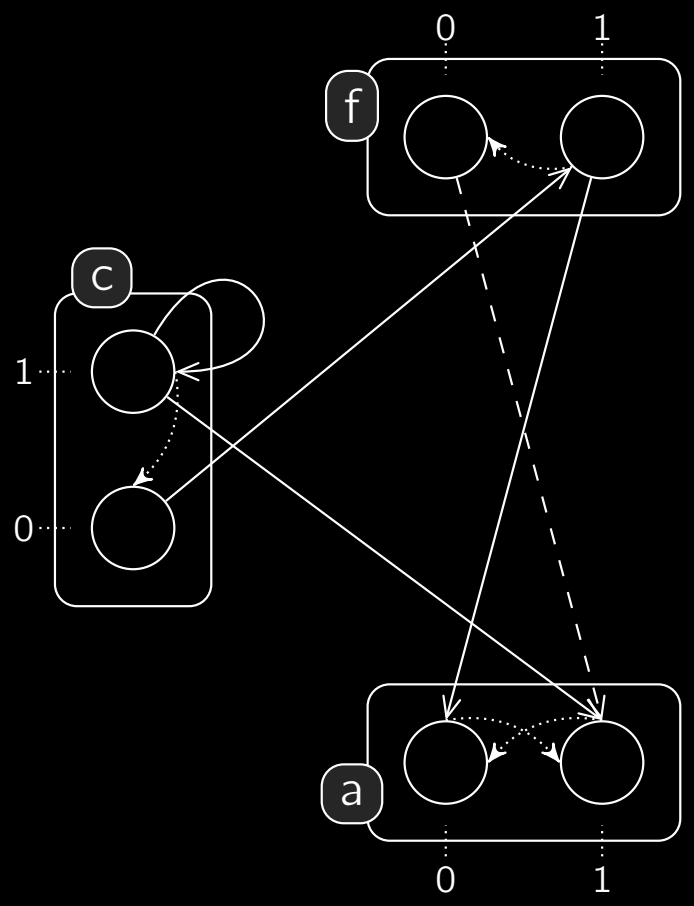


n-cliques <u>are</u> fix points

Fix Points

[Paulevé, Magnin, Roux in TCSB 2011]

Process Hitting



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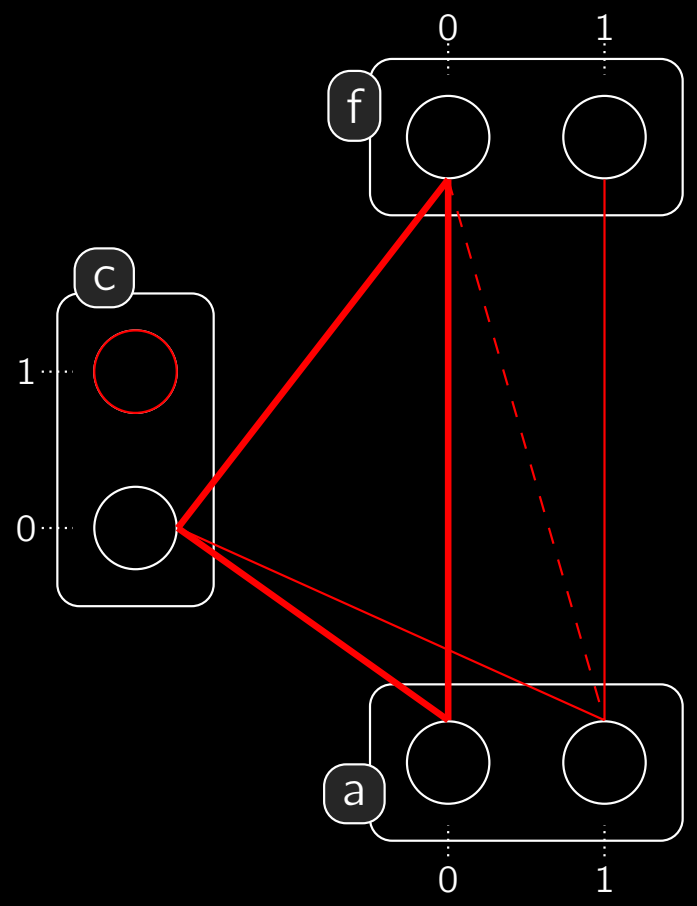

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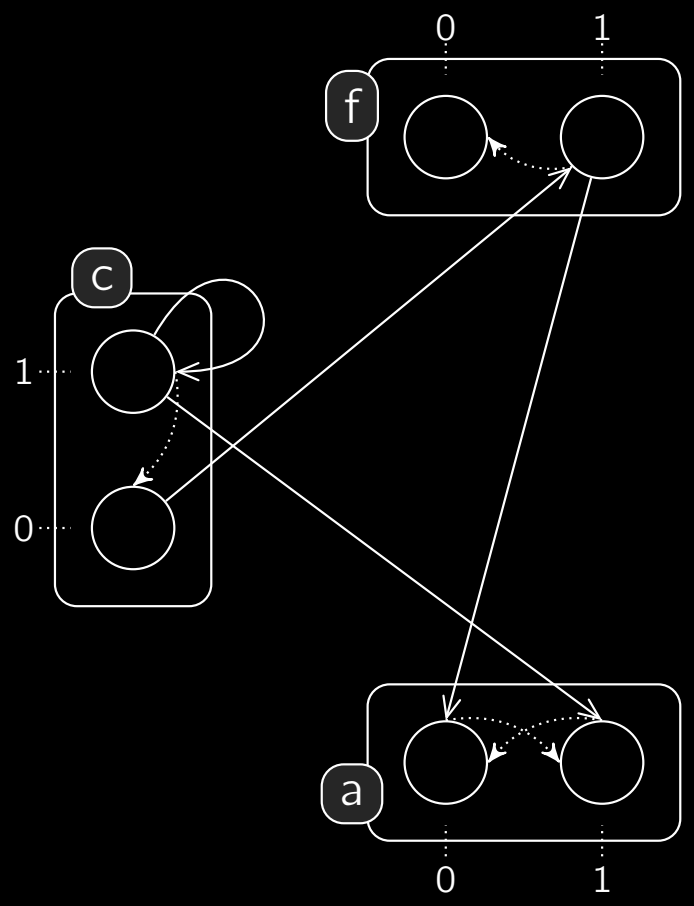

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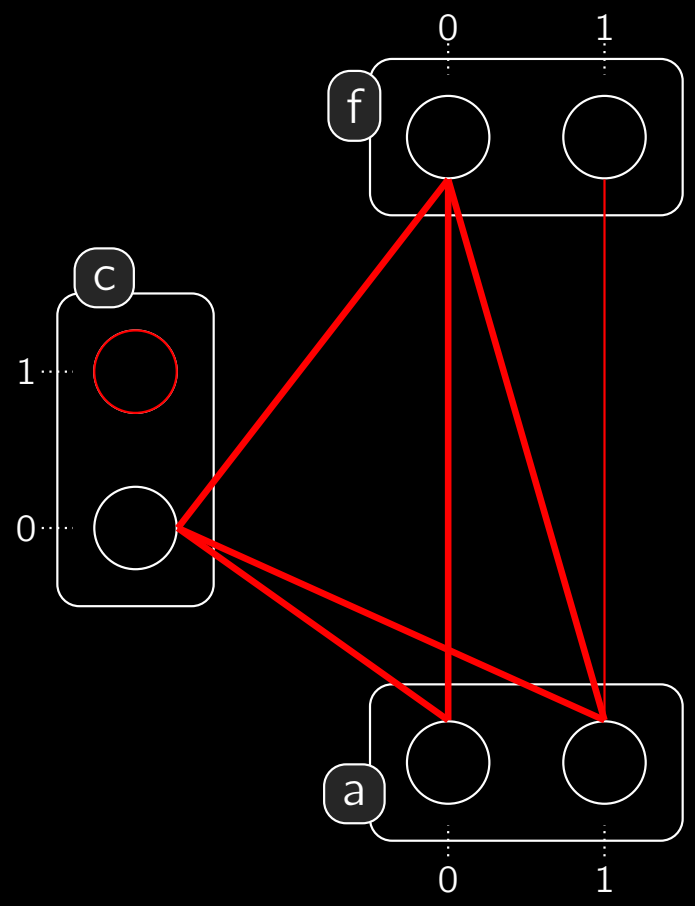

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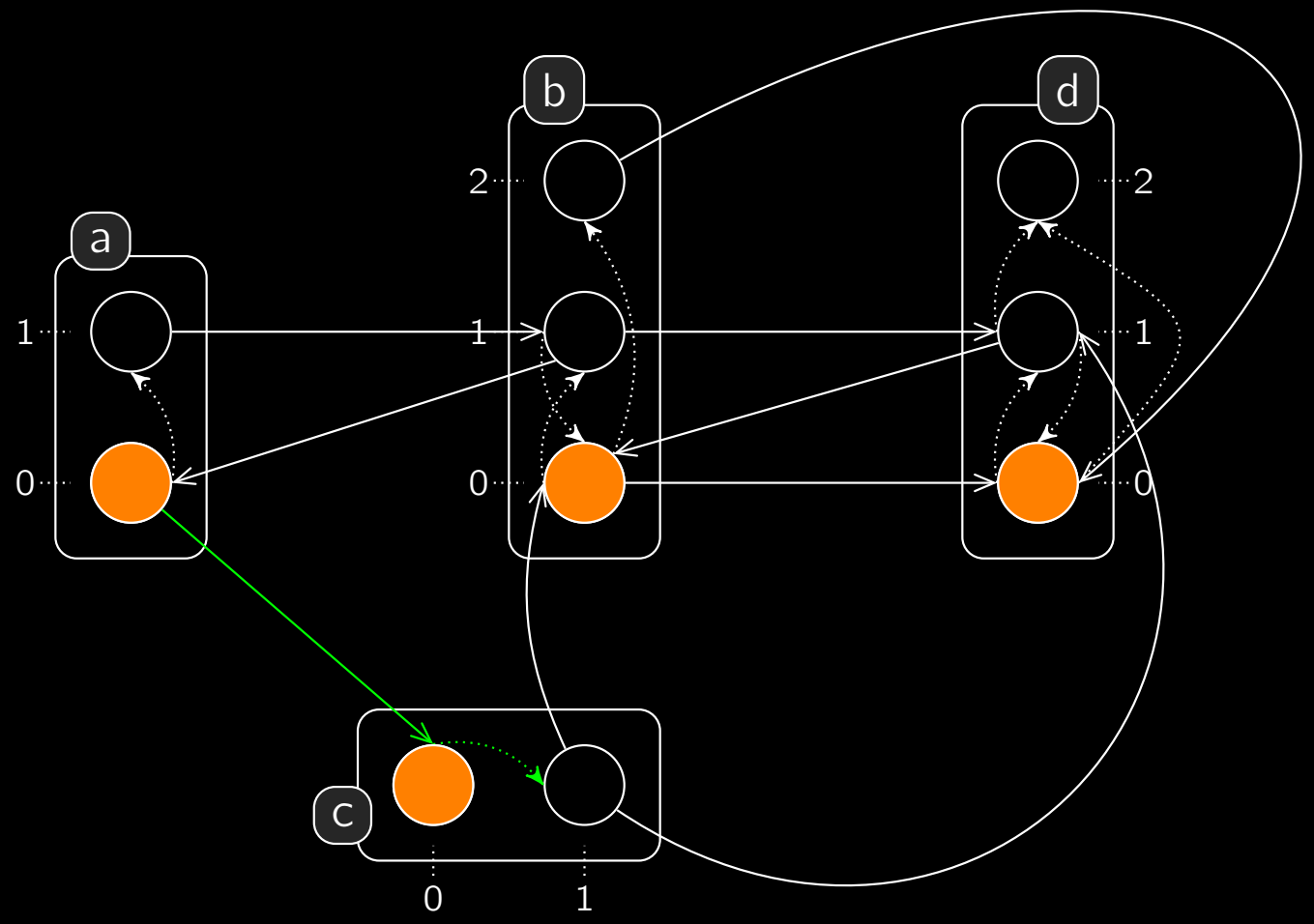
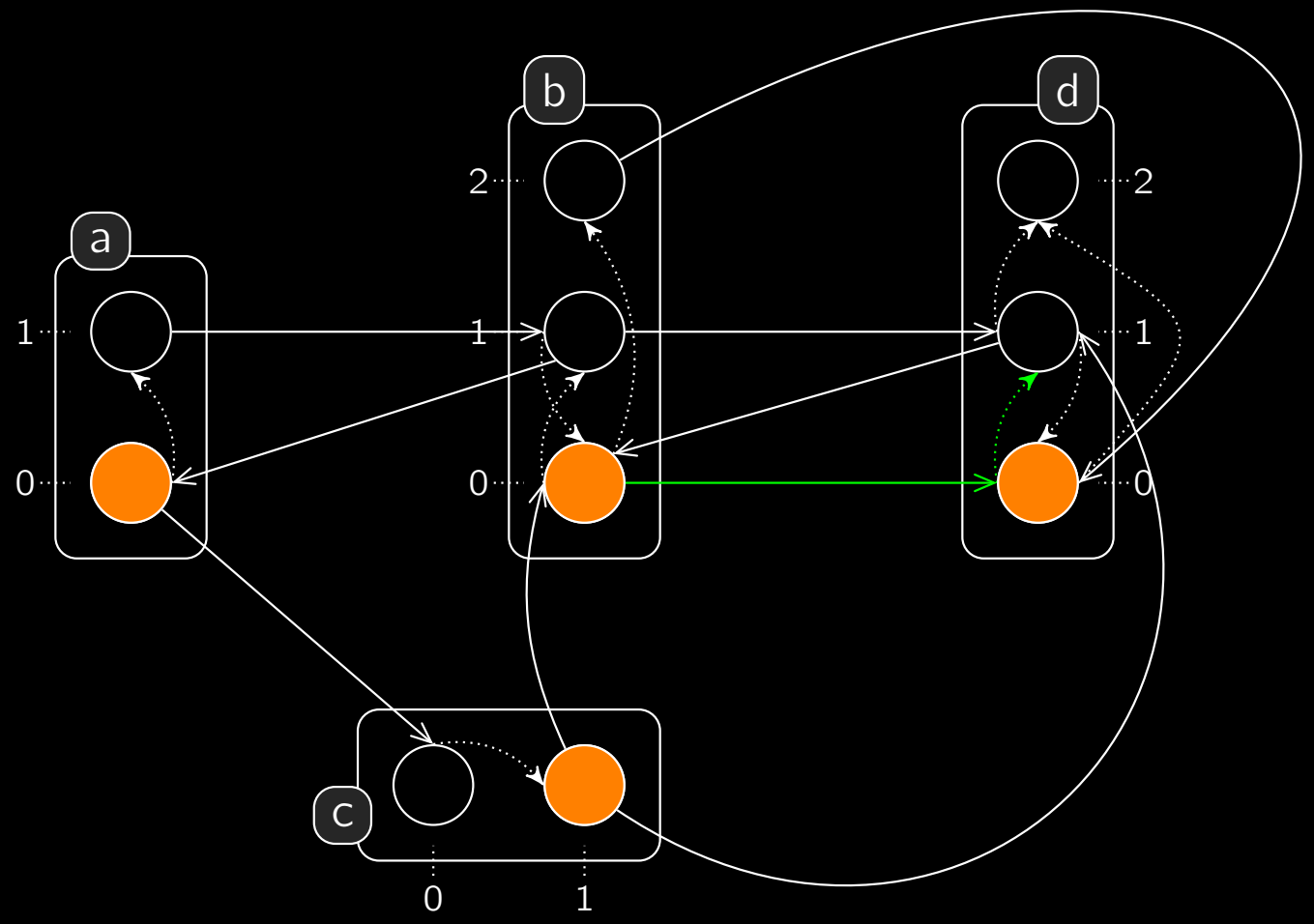


$a_0 \rightarrow c_0 \lceil c_1 :: b_0 \rightarrow d_0 \lceil d_1 :: c_1 \rightarrow b_0 \lceil b_1 :: b_1 \rightarrow d_1 \lceil d_2$

Loïc Paulevé, Morgan Magnin, Olivier Roux

Scenarios



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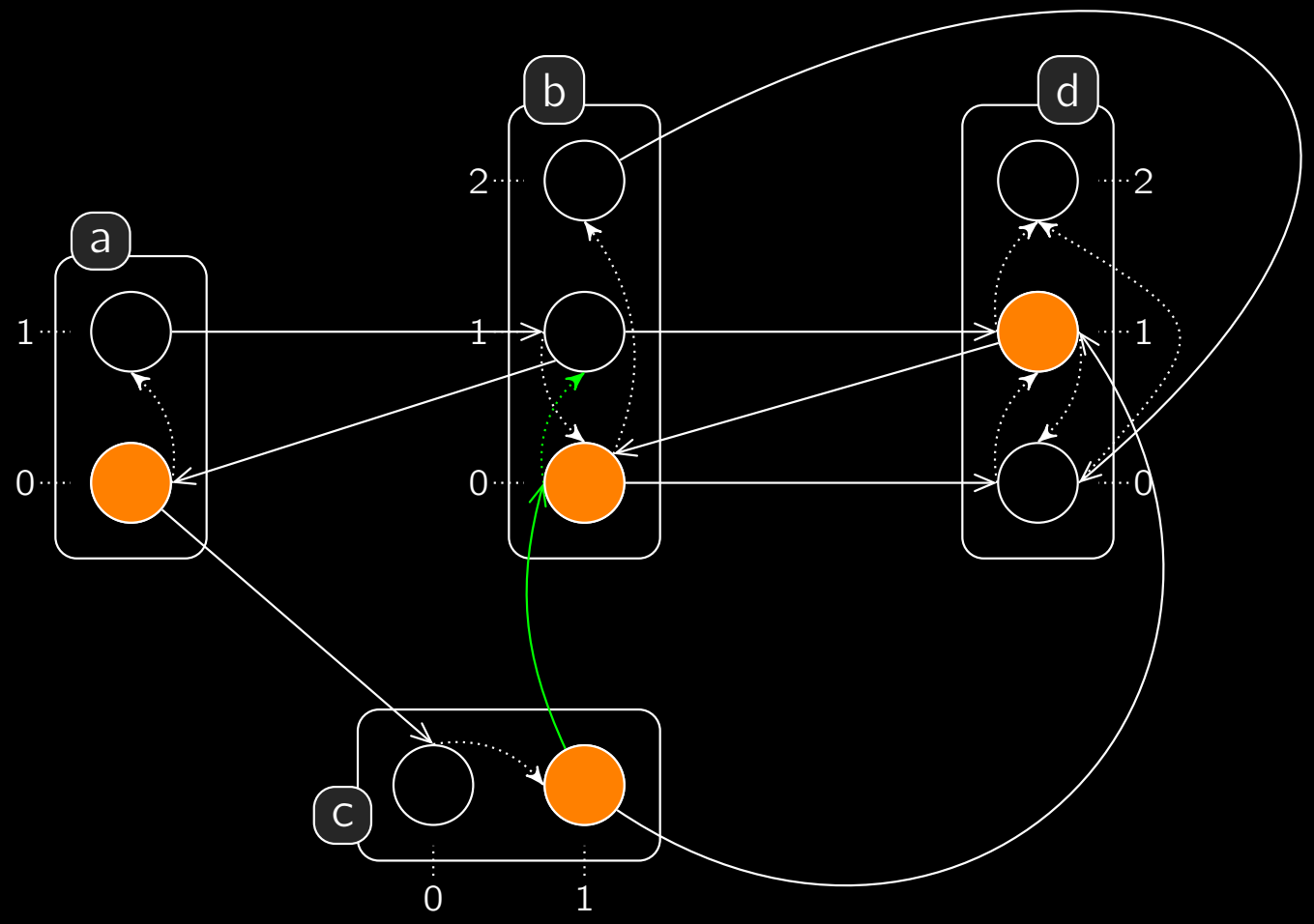

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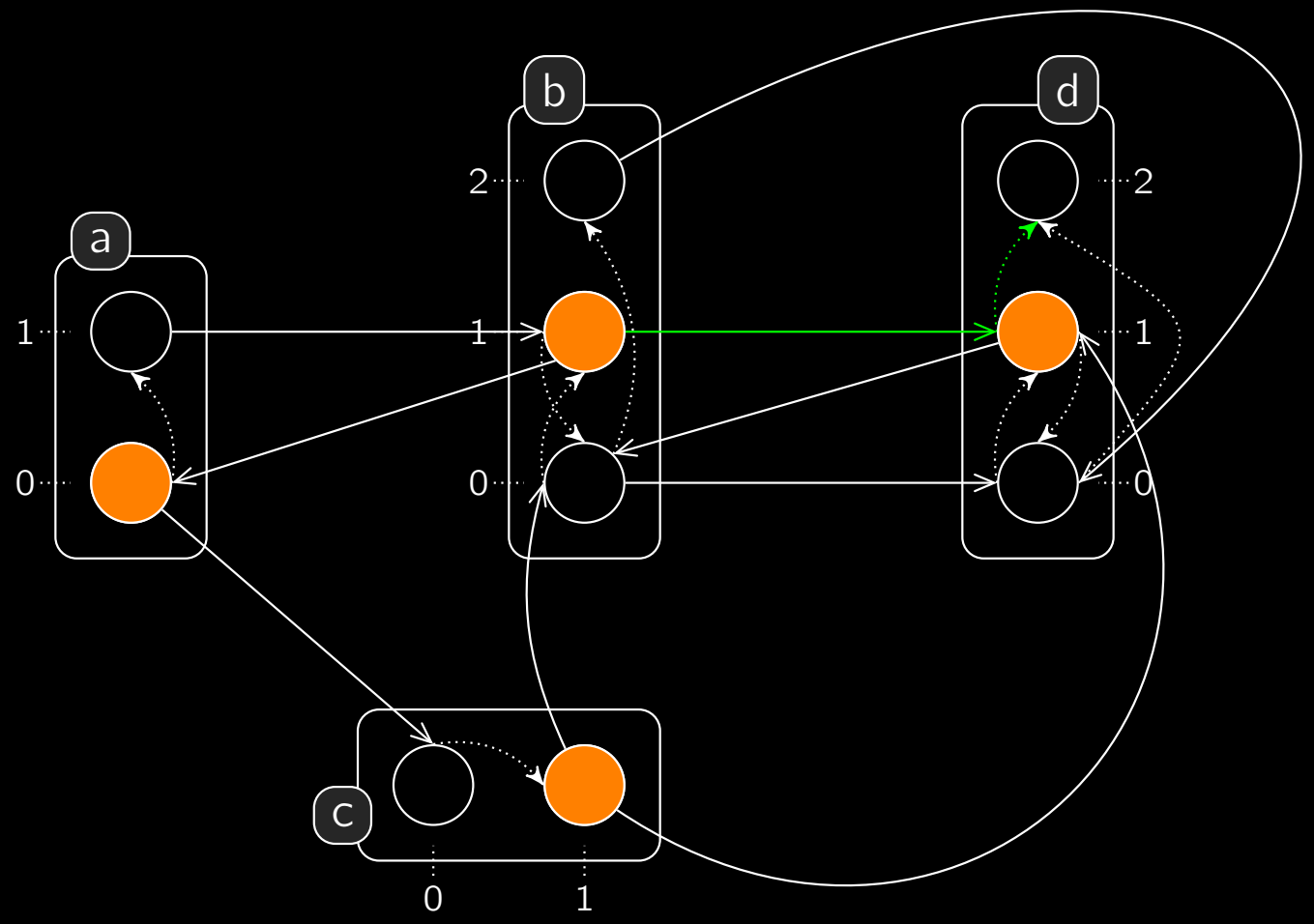

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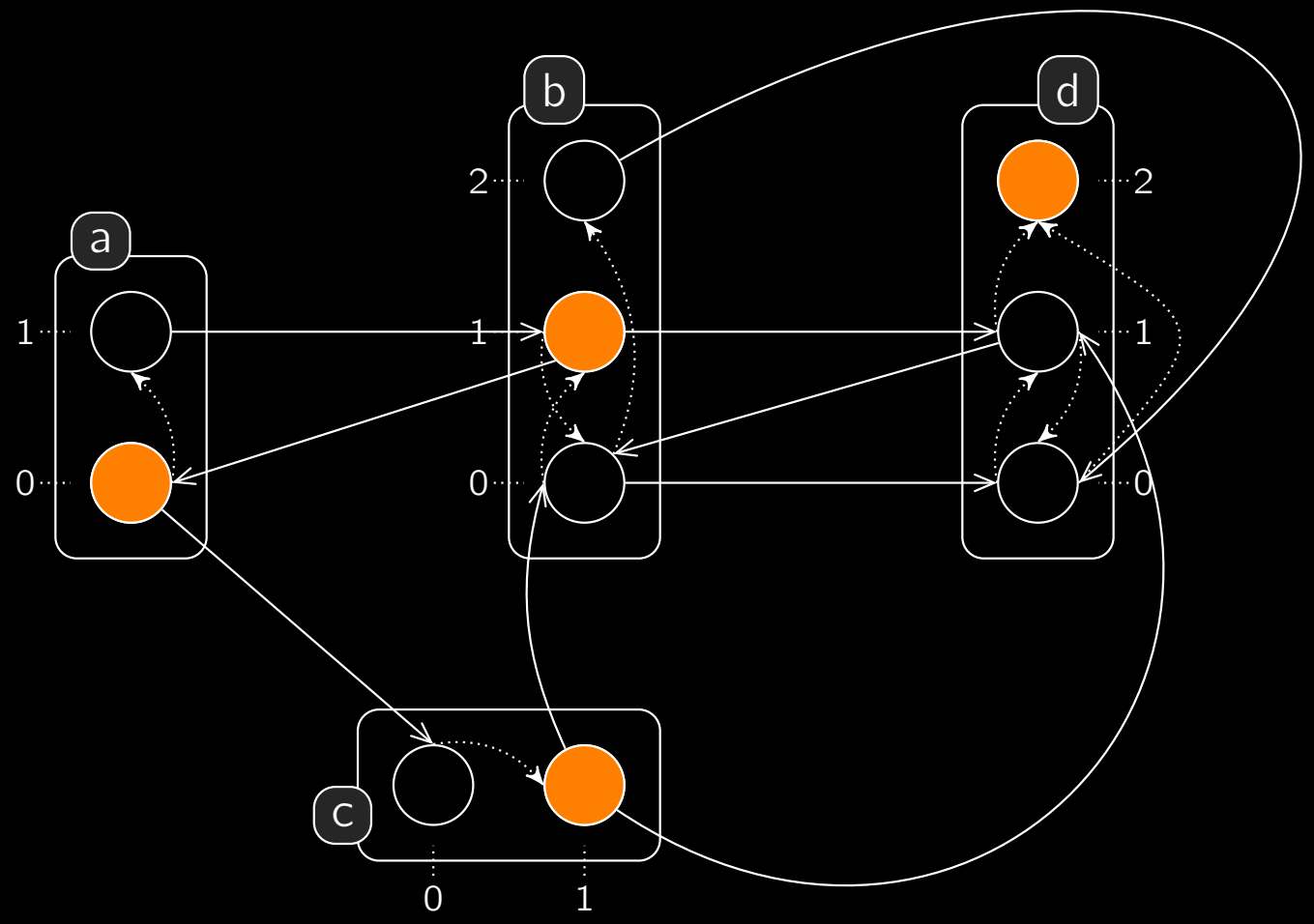

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Abstract Interpretation of Scenarios

[Paulevé, Magnin, Roux at SASB 2010 + MSCS submitted]

Scenarios – Successively playable actions.

- E.g. $\delta = a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow d_0 \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$.

Context — For each sort, subset of initial processes.

- E.g. $\varsigma = \langle a_0, b_0, b_2, c_0, d_0 \rangle$.

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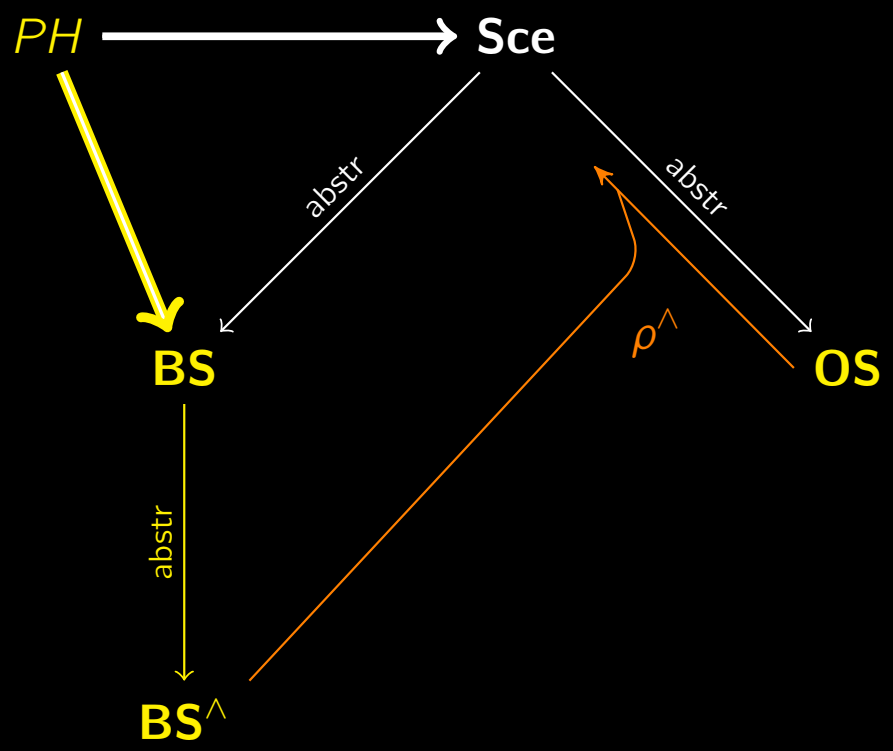
Overall approach

- 2 orthogonal abstractions;
- Bounce Sequences **BS**;
- Objective Sequences **OS**;
- Concretization: $\gamma_\varsigma : \mathbf{OS} \mapsto \wp(\mathbf{Sce})$;
- Refinements: $\rho : \mathbf{OS} \mapsto \wp(\mathbf{OS})$;
- $\gamma_\varsigma(\omega) = \gamma_\varsigma(\rho(\omega))$.



Two Orthogonal Abstractions

$$a_0 \rightarrow c_0 \lceil^{\rightarrow} c_1 :: b_0 \rightarrow d_0 \lceil^{\rightarrow} d_1 :: c_1 \rightarrow b_0 \lceil^{\rightarrow} b_1 :: b_1 \rightarrow d_1 \lceil^{\rightarrow} d_2$$

Abstraction by Objective Sequences

- $c_0 \lceil^{\rightarrow *} c_1 :: d_0 \lceil^{\rightarrow *} d_1 :: b_0 \lceil^{\rightarrow *} b_1 :: d_1 \lceil^{\rightarrow *} d_2;$

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- $c_0 \Rsh^* c_1 :: d_0 \Rsh^* d_1 :: b_0 \Rsh^* b_1 :: d_1 \Rsh^* d_2$;
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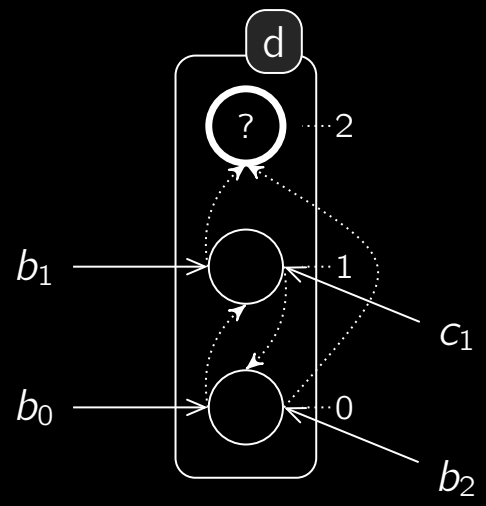

E.g.: $b_0 \rightarrow d_0 \lceil d_1 :: b_1 \rightarrow d_1 \lceil d_2 \ (d_0 \lceil^* d_2)$

Two Orthogonal Abstractions

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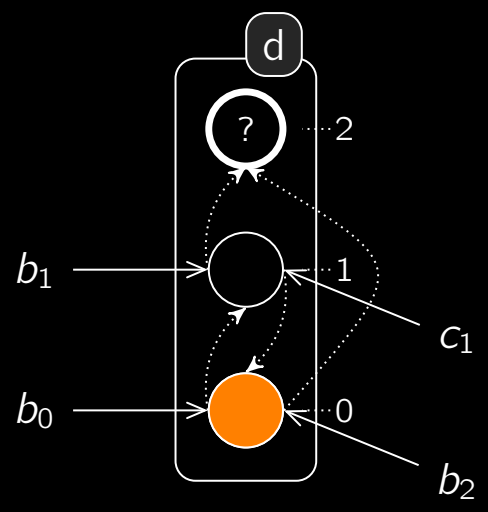

E.g.: $b_0 \rightarrow d_0 \lceil^{\rightarrow} d_1 :: b_1 \rightarrow d_1 \lceil^{\rightarrow} d_2$ $(d_0 \lceil^{\rightarrow *} d_2)$
$\Rightarrow$ can be computed off-line:

- $\mathbf{BS}(d_0 \lceil^{\rightarrow *} d_2) = \{b_0 \rightarrow d_0 \lceil^{\rightarrow} d_1 :: b_1 \rightarrow d_1 \lceil^{\rightarrow} d_2,$
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- $\mathbf{BS}^{\wedge}(d_0 \lceil^{\rightarrow *} d_2) = \{\{b_0, b_1\}, \{b_2\}\}$.

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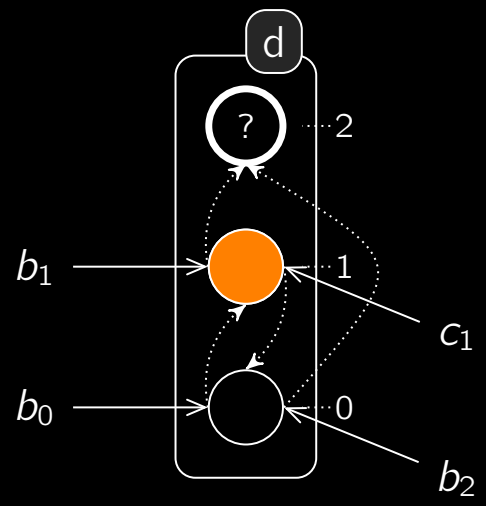
Abstraction by Bounce Sequences



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- $\mathbf{BS}(d_1 \Rsh^* d_2) = \{b_1 \rightarrow d_1 \Rsh d_2,$
  $c_1 \rightarrow d_1 \Rsh d_0 :: b_2 \rightarrow d_0 \Rsh d_2\}$;
- $\mathbf{BS}^\wedge(d_1 \Rsh^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$.

Objective Sequence Refinements

$$\gamma_\varsigma(\omega) = \{\delta \in \textbf{Sce} \mid \omega \text{ abstracts } \delta \wedge \mathrm{support}(\delta) \subseteq \varsigma\}.$$

Idea: the more details we know, the better $\gamma_\varsigma(\omega)$ should be understood.

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Objective Refinement by $\mathbf{BS}^\wedge$: $\rho^\wedge$

$\mathbf{Obj} \times \wp(\mathbf{BS}^\wedge)$	$\wp(\mathbf{OS})$
$d_0 \Rsh^* d_2$, $\{\{b_0, b_1\}, \{b_2\}\}$	$\star \Rsh^* b_0 :: b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$, $\star \Rsh^* b_1 :: b_1 \Rsh^* b_0 :: d_0 \Rsh^* d_2$, $\star \Rsh^* b_2 :: d_0 \Rsh^* d_2$
$\gamma_\varsigma(d_0 \Rsh^* d_2)$	$= \gamma_\varsigma(\rho^\wedge(d_0 \Rsh^* d_2, \mathbf{BS}^\wedge(d_0 \Rsh^* d_2)))$

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Generalization to **OS** refinements: $\widetilde{\rho}$

$\mathbf{OS} \times \wp(\mathbf{BS}^\wedge)$	$\wp(\mathbf{OS})$
$\omega, \mathbf{BS}^\wedge$	$\mathrm{interleave}\begin{pmatrix}\omega' \\ \omega_{1..n-1}\end{pmatrix} :: \omega_{n..\lvert\omega\rvert}$ where $n \in \mathbb{I}^\omega$ and $\omega' :: \omega_n \in \rho^\wedge(\omega_n, \mathbf{BS}^\wedge(\omega_n))$
$\gamma_\varsigma(\omega)$	$= \gamma_\varsigma(\widetilde{\rho}(\omega, \mathbf{BS}^\wedge))$

Objective Sequence Concretizability

a.k.a. Process Reachability Problem

$\gamma_s(a_i \Rsh^* a_j :: \ldots :: z_k \Rsh^* z_l) \neq \emptyset$?

CTL: $EF(s[a] = a_j \wedge EF(\cdots \wedge EF(s'[z] = z_l) \ldots))$.

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Over-approximation

- Un-ordered: $\gamma_s(\omega) \neq \emptyset \Longrightarrow \gamma_s(\omega_n) \neq \emptyset, \forall n \in \mathbb{I}^\omega$
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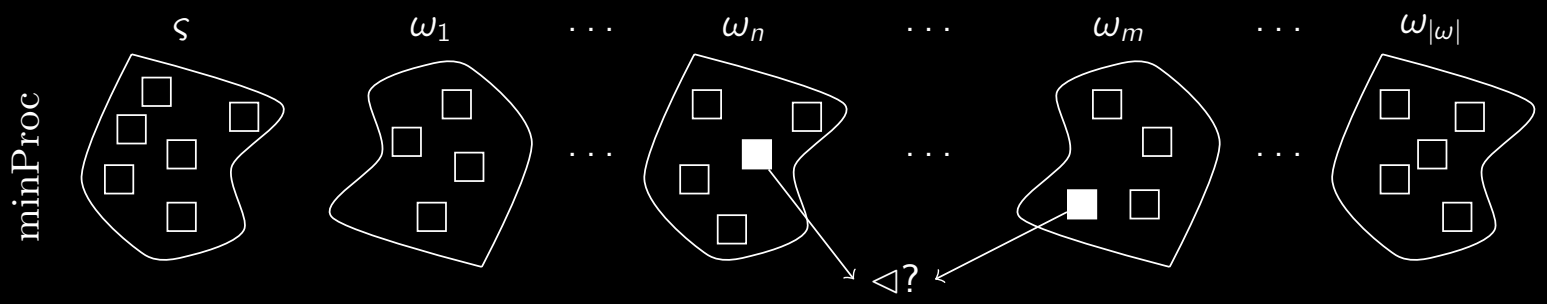
- Process occurrences order constaints ($a_i \lhd a_j$):



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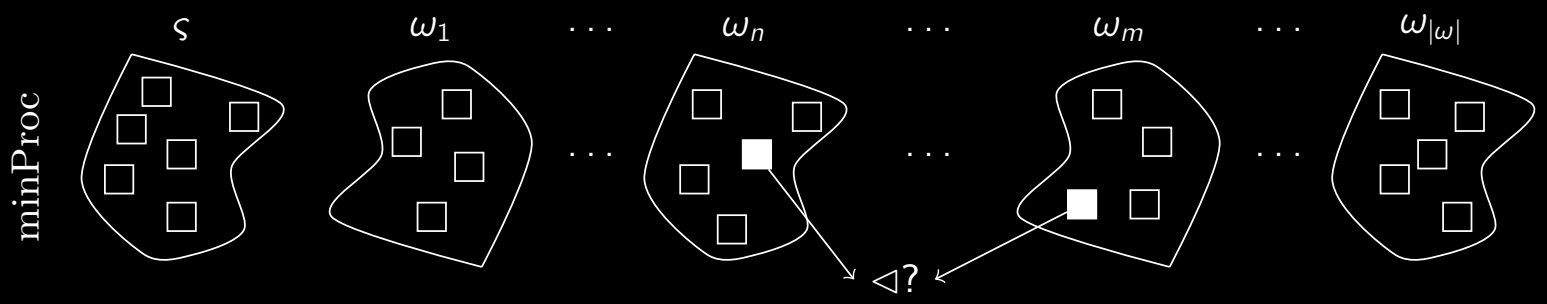

Under-approximation

- Sufficient condition: impose a particular structure of scenarios.

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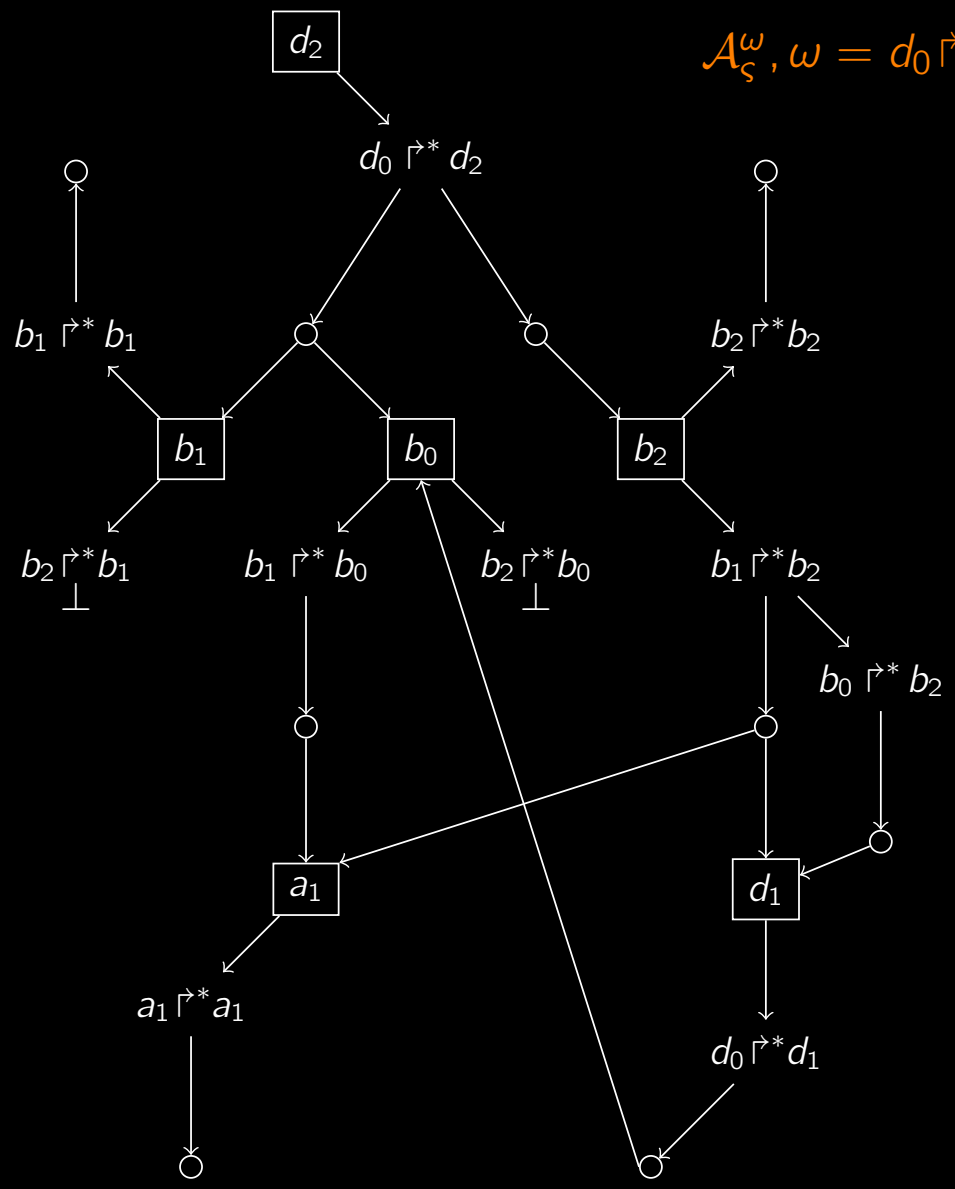
Implementation of Over-approximations

$\mathcal{A}^{\omega}_{\varsigma}, \omega = d_0 \Rsh^* d_2, \varsigma = \langle a_1, b_1, b_2, c_1, d_0 \rangle$



Legend

Requirement

$a_j \longrightarrow a_i \Rsh^* a_j$

Solution

$(\{b_i, c_j\} \in \mathbf{BS}^{\wedge}(a_i \Rsh^* a_j))$

$a_i \Rsh^* a_j \longrightarrow \bigcirc \to b_i, c_j$

Continuity

$a_i \Rsh^* a_j \longrightarrow a_k \Rsh^* a_j$

Trivial solution

$a_i \Rsh^* a_j \longrightarrow \bigcirc$

No solution

$a_i \Rsh^* a_j$
$\perp$

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Complexities

Data structures

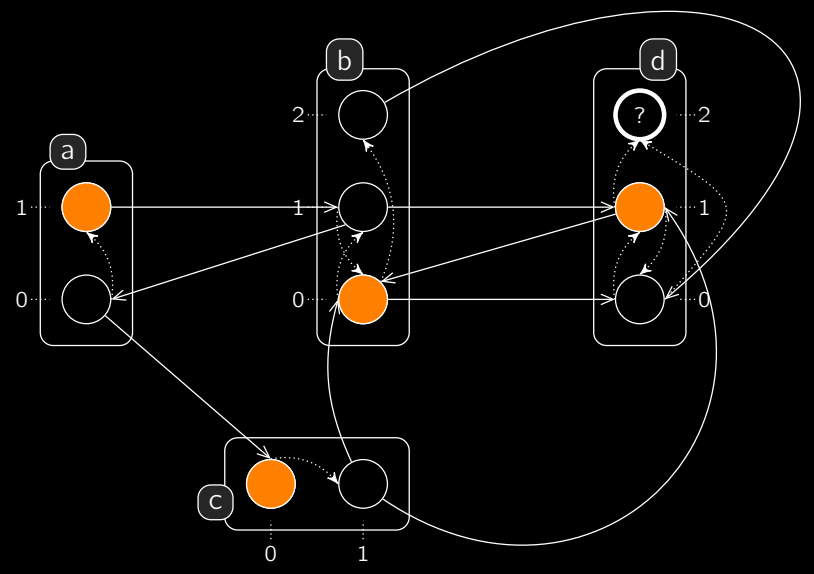
- Computing **BS** is exponential in the number of processes in a single sort.
- Computing $\mathbf{BS}^{\wedge}$ is faster, but still exponential.
- The size of $\mathcal{A}_{\varsigma}^{\omega}$ is $\approx$ polynomial in the number of processes.

Analyses

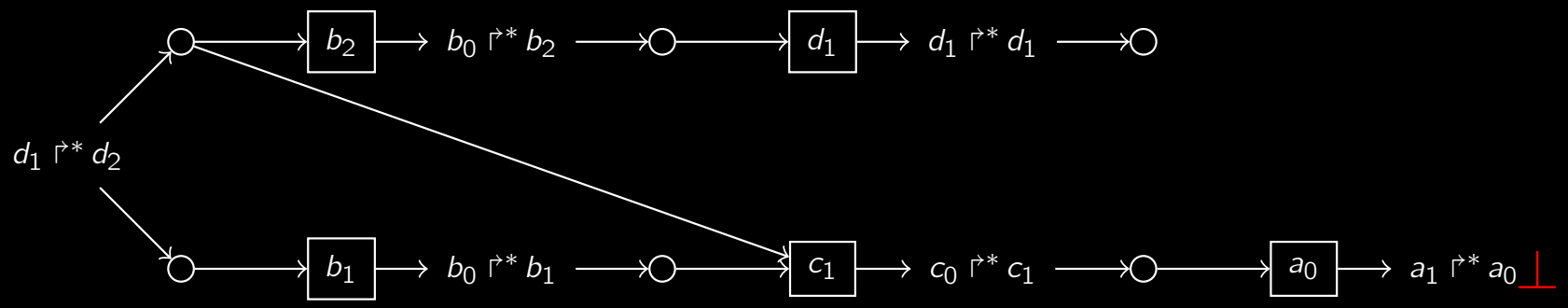
- Over-approximations are polynomial in the size of $\mathcal{A}_{\varsigma}^{\omega}$.
- Under-approximation is polynomial in the size of $\mathcal{A}_{\varsigma}^{\omega}$; and can be applied a number of times exponential in the number of solutions of a single objective.

$\Longrightarrow$ efficient with a small number of processes per sort; while a very large number of sorts can be handled.

Un-ordered Over-approximation



- $\gamma_\varsigma(\omega) \neq \emptyset \Longrightarrow \gamma_\varsigma(\omega_n) \neq \emptyset, \forall n \in \mathbb{I}^\omega$ (recursive reasoning with $\rho^\wedge : \mathbf{Obj} \mapsto \wp(\mathbf{OS})$).
- Necessary condition: there always exists a solution ending with a trivial objective.



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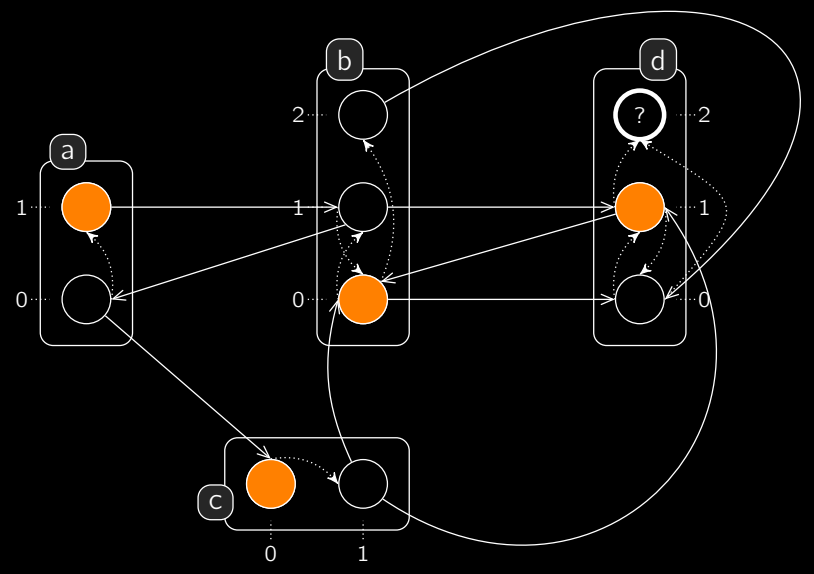

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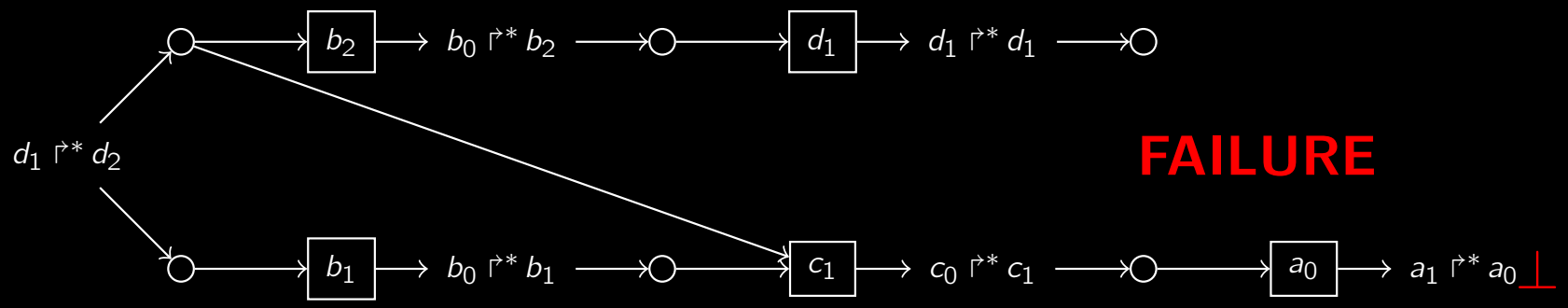

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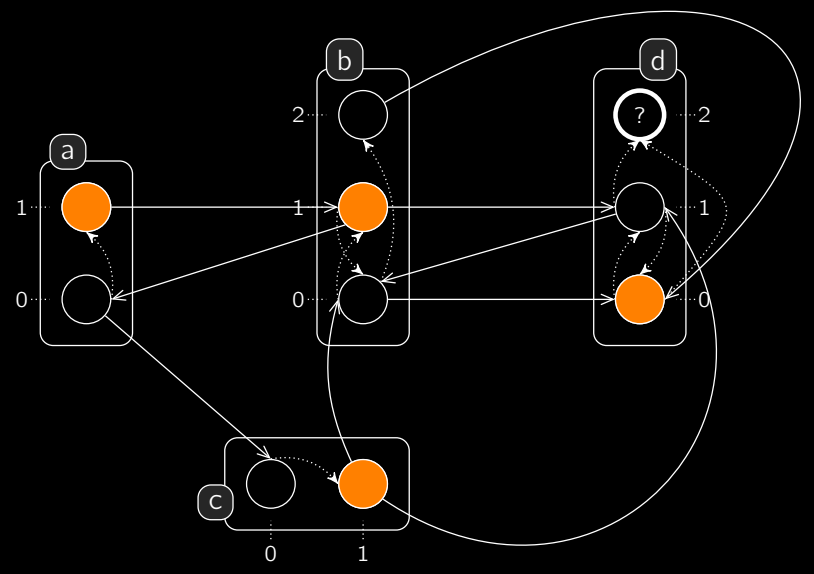

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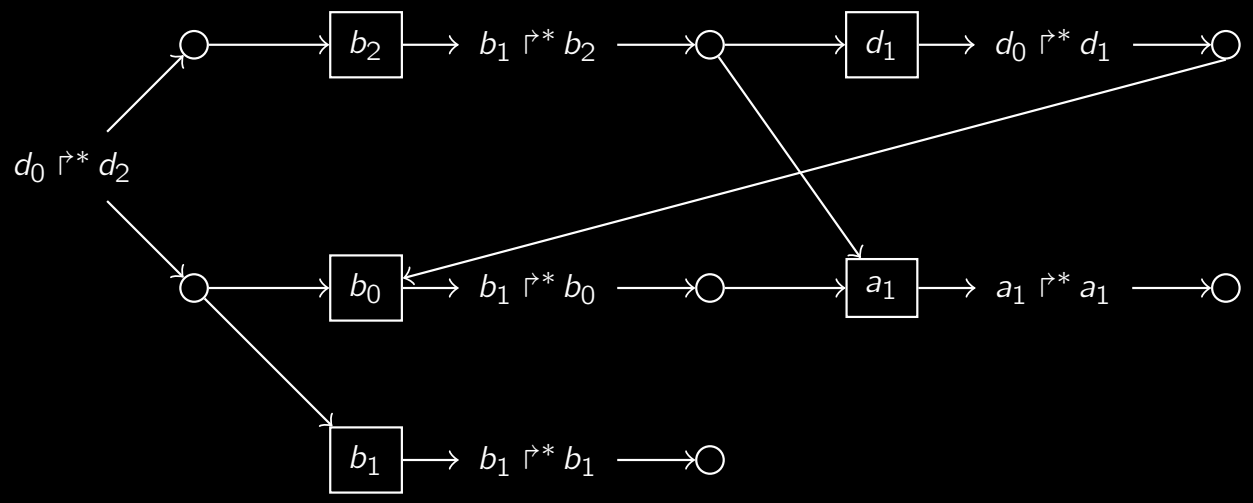

OK

Ordered Over-approximation

Goal: $\gamma_\varsigma(a_1 \Rsh^* a_0 :: \omega) \neq \emptyset \Longrightarrow \gamma_{max\varsigma}(\omega) \neq \emptyset$

- If $a_0 \notin \varsigma$, $\exists c_i \rightarrow a_? \Rsh a_0$, hence $max\varsigma[a] = \{a_0\}$ and $max\varsigma[c] = \{c_i\}$:
$$\delta_{1..n} :: c_i \rightarrow a_? \Rsh a_0 :: \delta_{m..|\delta|} \text{ — } \delta_{m..|\delta|} \in \gamma_{\varsigma'}(\omega) \ .$$
- For all other sorts, use the saturated context of $\lceil \mathcal{A}^\omega_\varsigma \rceil$:
$$\lceil \mathcal{A}^\omega_\varsigma \rceil = \mathrm{lfp}\ \left(\mathcal{A}^\omega_\varsigma \mapsto \mathcal{A}^\omega_{\varsigma \Cap \mathrm{procs}(\mathcal{A}^\omega_\varsigma)} \right) \ .$$
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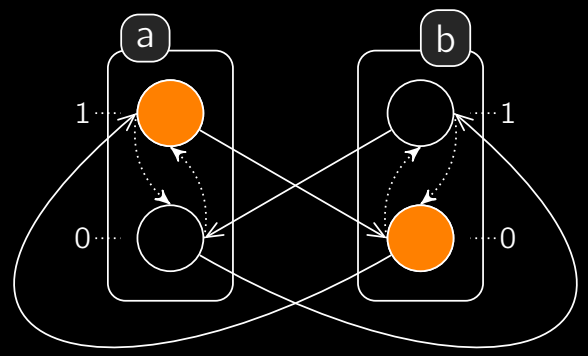

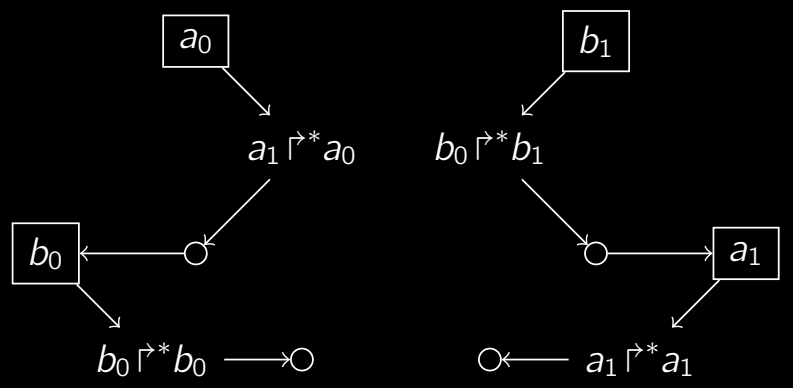

$\gamma_{\langle a_1, b_0 \rangle}(a_1 \lceil^* a_0 :: b_0 \lceil^* b_1) \neq \emptyset$

Ordered Over-approximation

Goal: $\gamma_\varsigma(a_1 \Rsh^* a_0 :: \omega) \neq \emptyset \implies \gamma_{max\varsigma}(\omega) \neq \emptyset$

- If $a_0 \notin \varsigma$, $\exists c_i \rightarrow a_? \Rsh a_0$, hence $max\varsigma[a] = \{a_0\}$ and $max\varsigma[c] = \{c_i\}$:
$$\delta_{1..n} :: c_i \rightarrow a_? \Rsh a_0 :: \delta_{m..|\delta|} \text{ — } \delta_{m..|\delta|} \in \gamma_{\varsigma'}(\omega) \ .$$
- For all other sorts, use the saturated context of $\lceil \mathcal{A}^\omega_\varsigma \rceil$:
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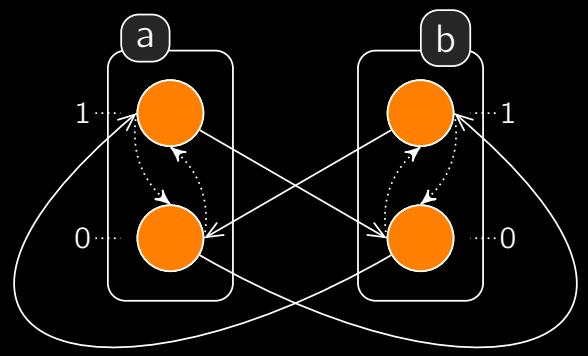

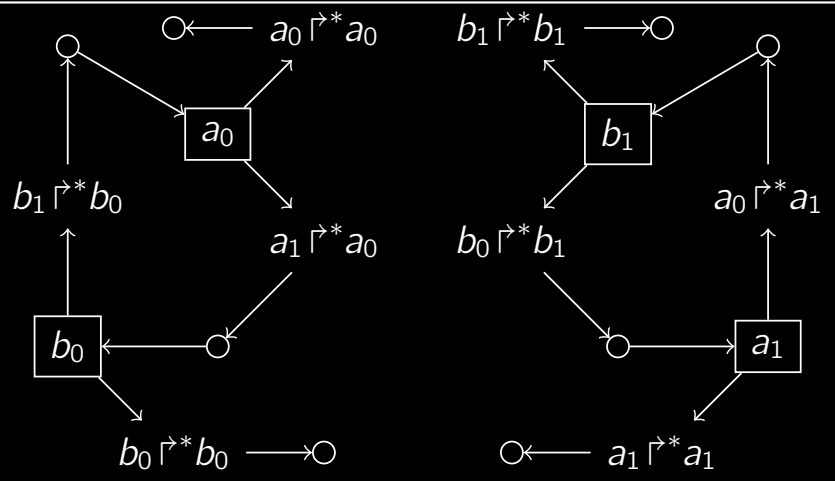

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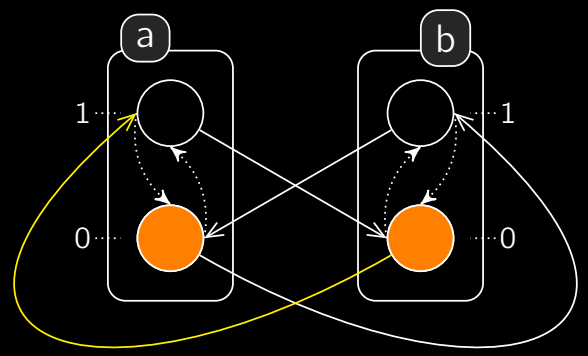

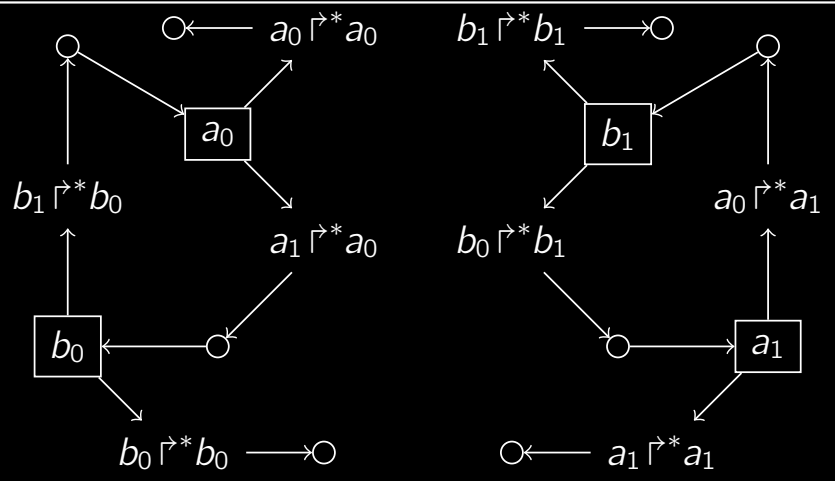

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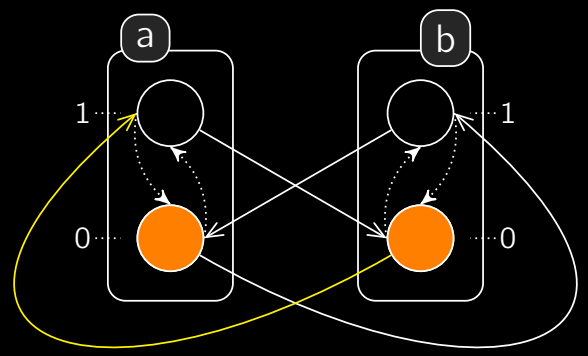
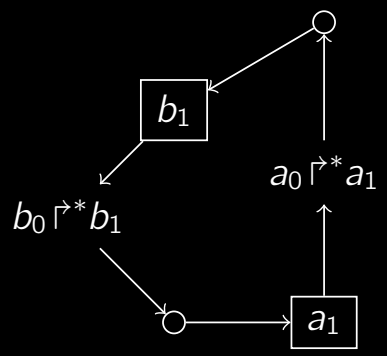




$\gamma_{\langle a_1, b_0 \rangle}(a_1 \Rsh^* a_0 :: b_0 \Rsh^* b_1) \neq \emptyset \implies \gamma_{\langle a_0, b_0 \rangle}(b_0 \Rsh^* b_1) \neq \emptyset$ **FAILURE**

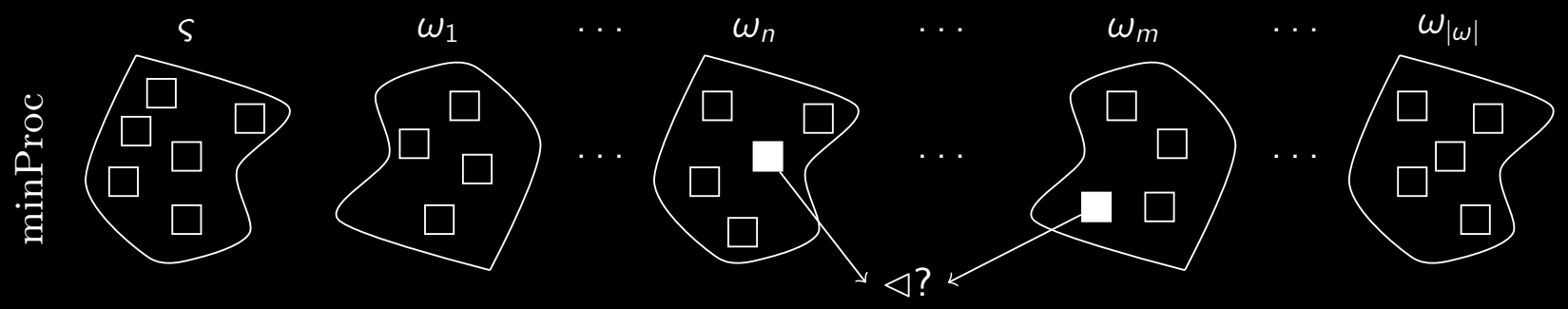
Process Occurrences Order Constraints

$a_j \lhd a_i \iff$ no scenario can be abstracted by $a_i \lceil^{*} a_j$.

Uncovering Order Constraints

$\mathbf{BS}(a_i \lceil^{*} a_j) = \emptyset \implies a_j \lhd a_i$

Idea of Over-Approximation



Based on the ordered over-approximation ($\lceil \mathcal{A}^{\omega}_{\varsigma} \rceil$):

- $\mathrm{minProc}_{\varsigma}(\omega_n) = \{p \in \mathbf{Proc} \mid p$ occurs in all solutions of $\omega_n\}$;
- $\begin{cases} \{a_i \in \varsigma\} & \text{if } n = 0 \\ \mathrm{minProc}_{max\varsigma}(\omega_n) & \text{otherwise,} \\ & \text{with } max\varsigma = \mathrm{maxCtx}(\varsigma, w, n-1) \end{cases}$.

Under-approximation

Idea: force a particular shape for scenarios.

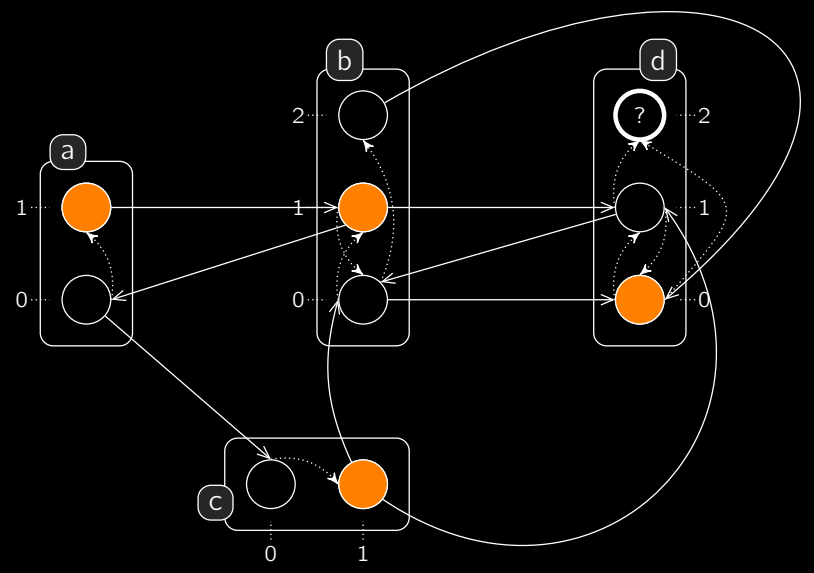
- "top-down" resolution: ignore interleaving requirements:
- if $a_i \Rsh^* a_j$ needs b_i and c_i, resolve $\star \Rsh^* b_i$, then $\star \Rsh^* c_i$ (and conversely), etc.

Implementation

- Abstract structure $\lceil \mathcal{B}_\varsigma^\omega \rceil$ very similar to $\lceil \mathcal{A}_\varsigma^\omega \rceil$, *except that*:
- some solutions can be ignored;
- (maximal continuity, instead of minimal).

Sufficient condition

- $\lceil \mathcal{B}_\varsigma^\omega \rceil$ has no cycle; and
- all referenced objectives have at least one solution.



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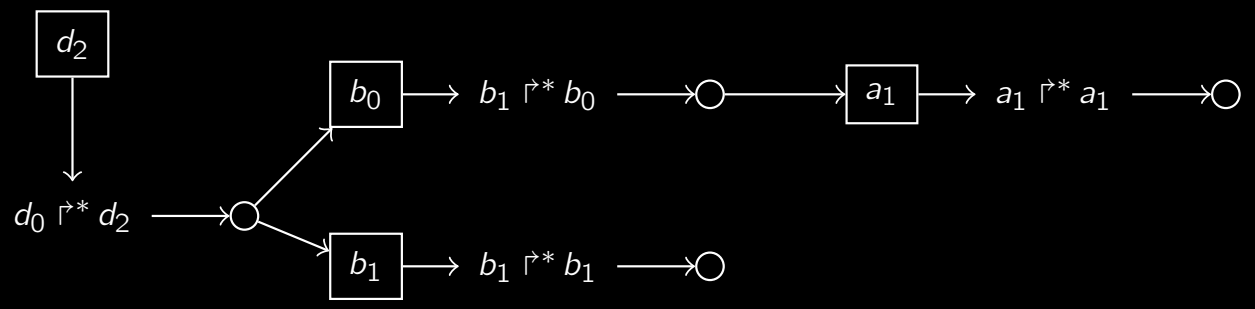
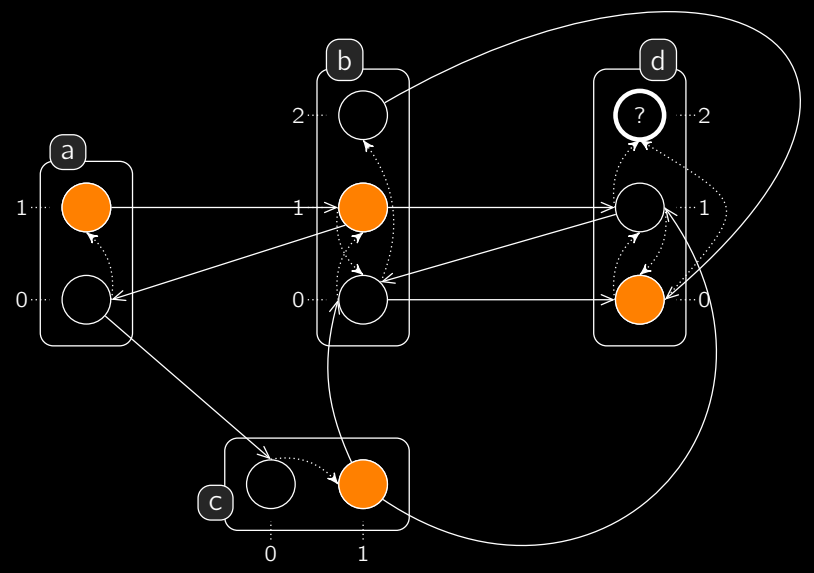
Remark: may be more conclusive on refined ω.





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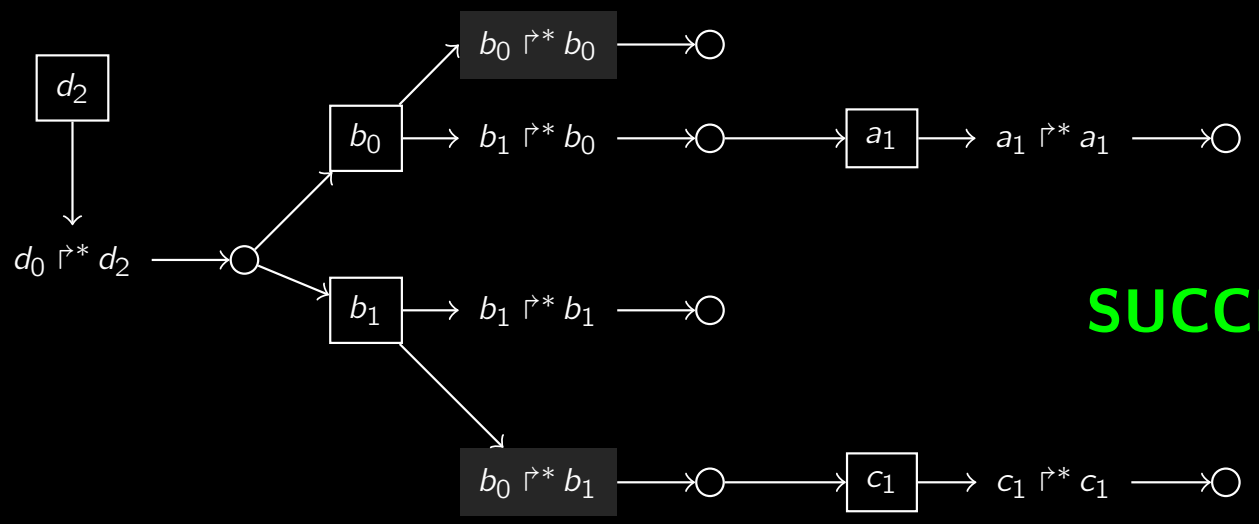
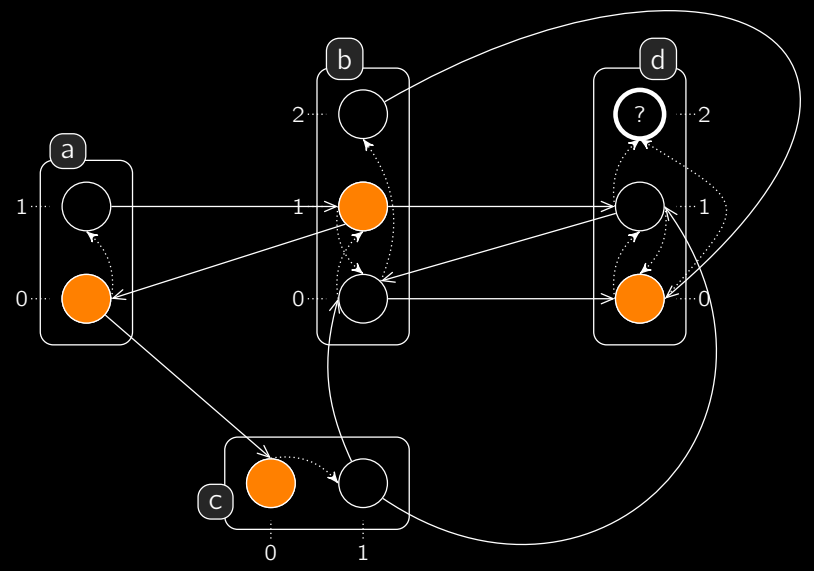


SUCCESS



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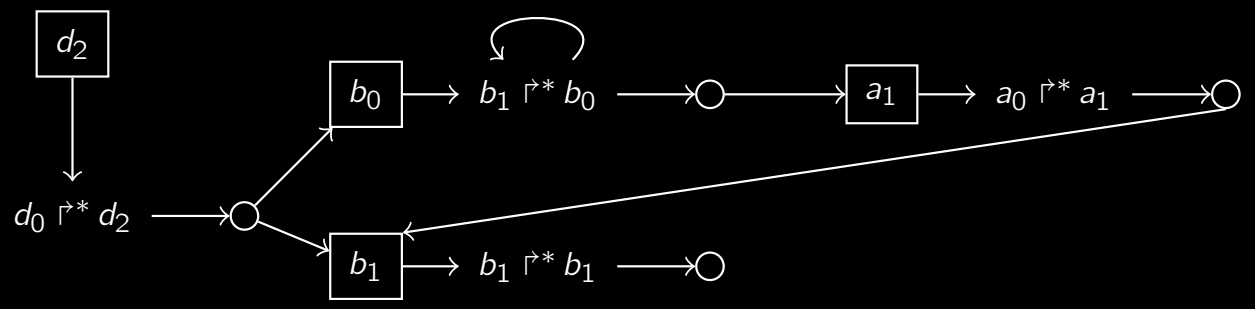

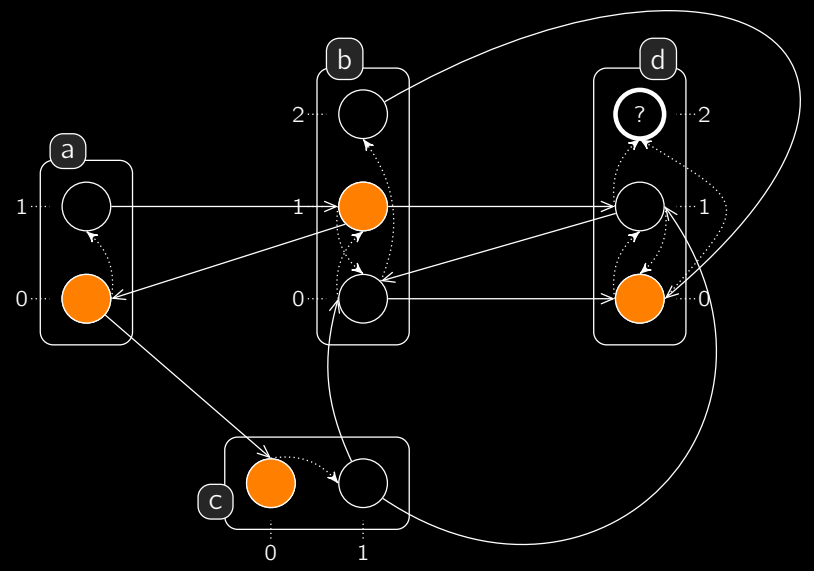

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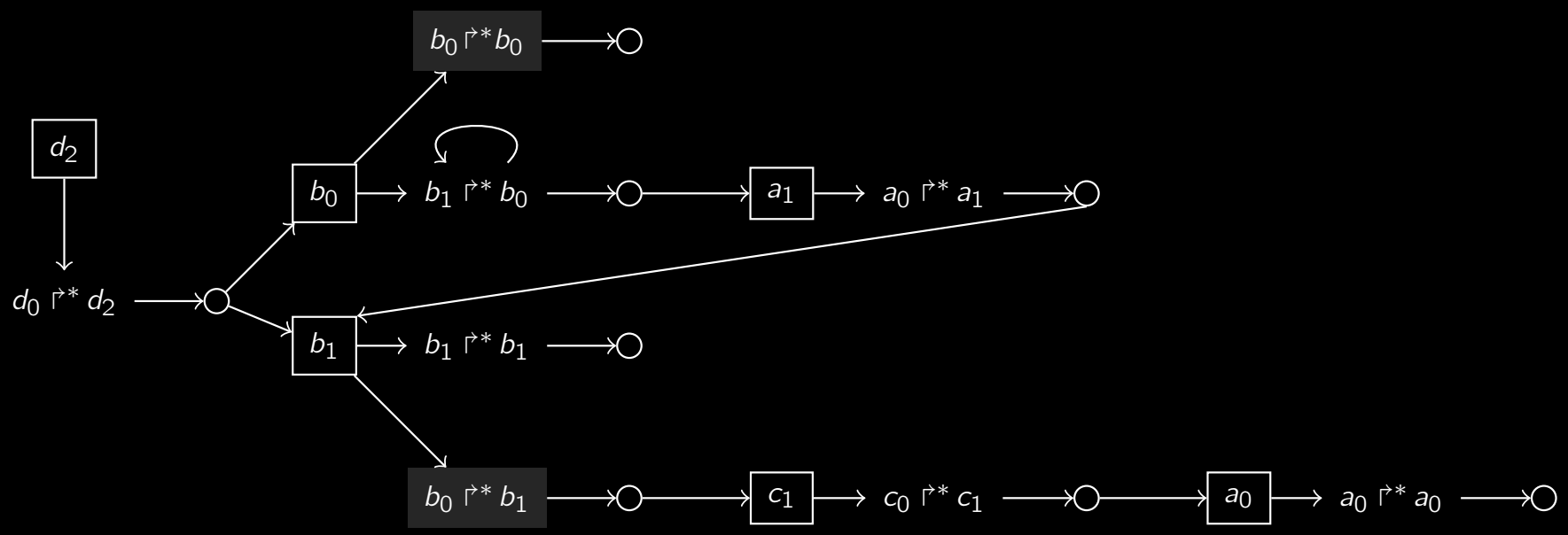

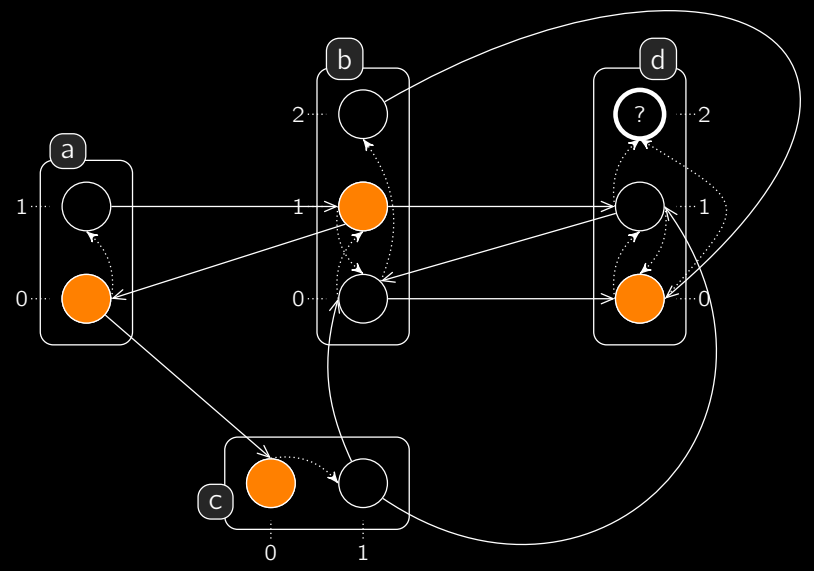

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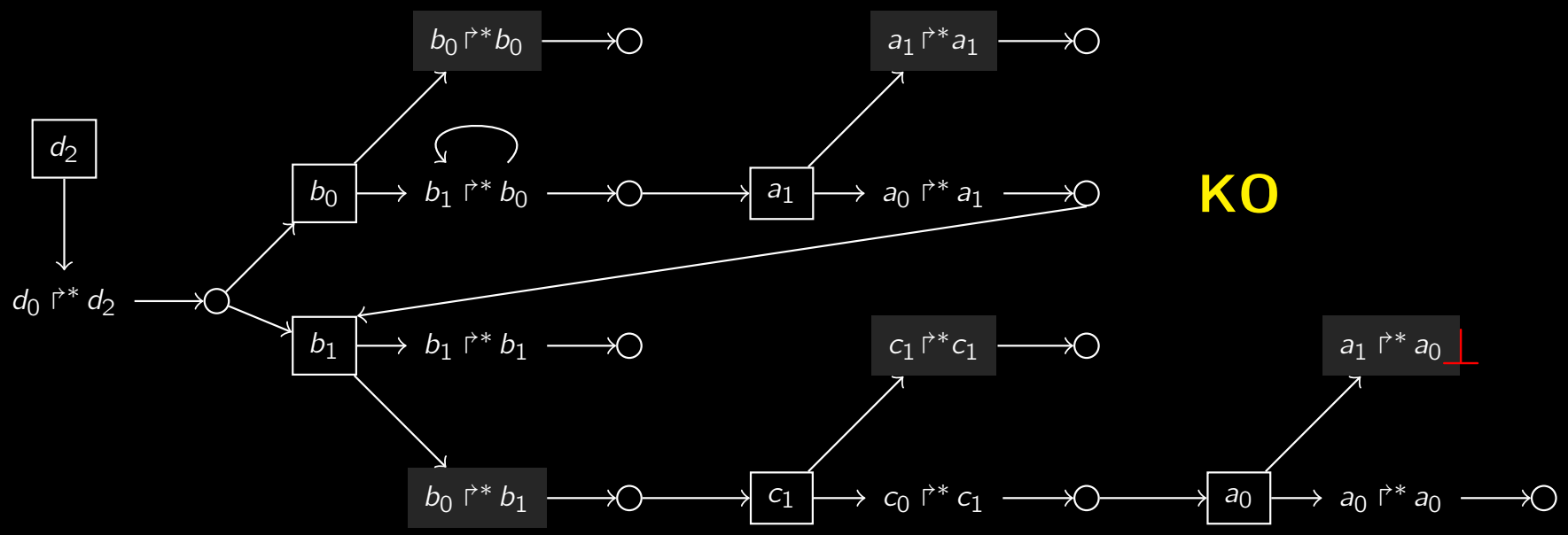

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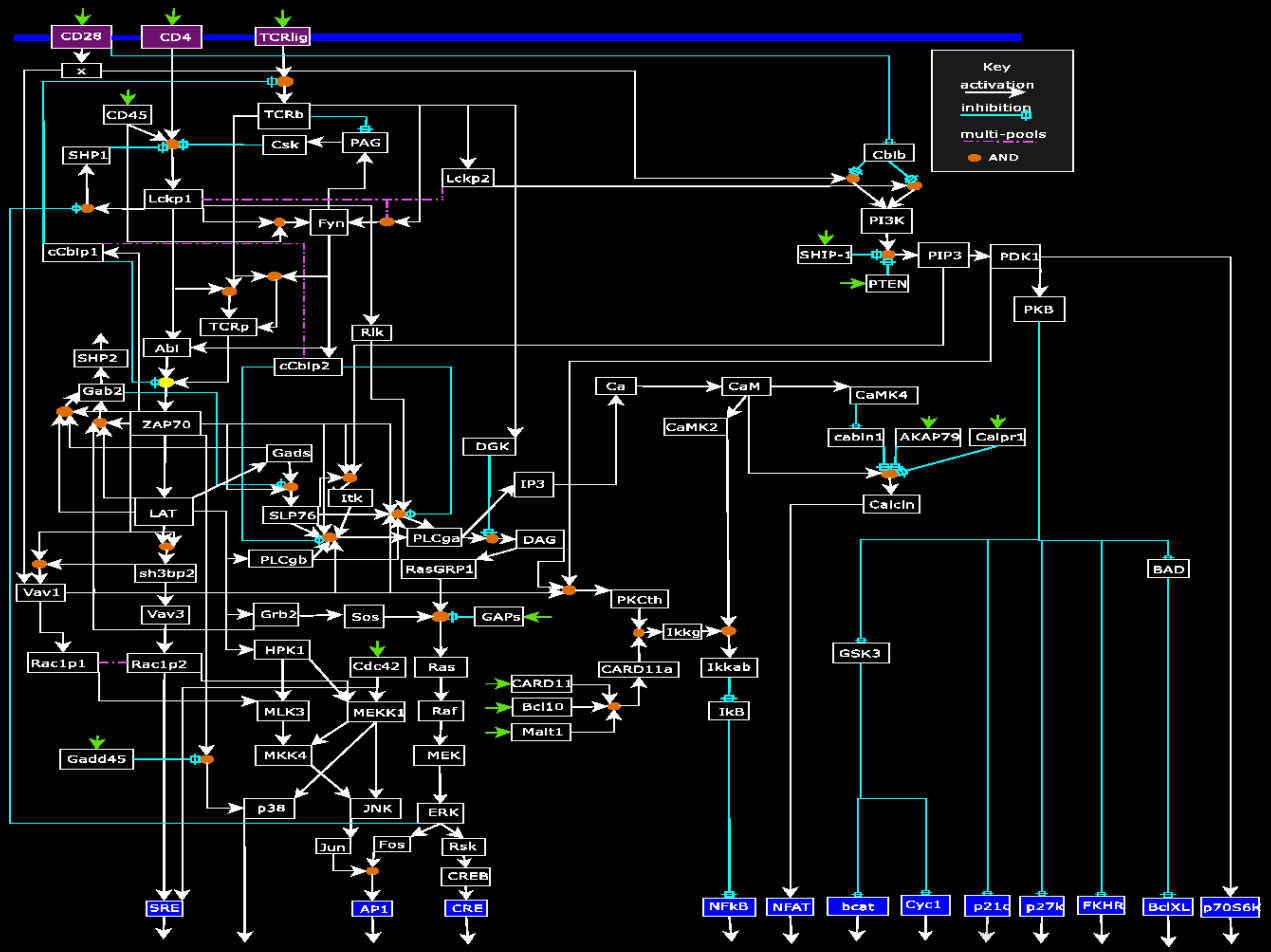
Outline

1. Introduction to BRNs
2. The Process Hitting
3. Stochastic and Time Parameters
4. Scalable Analysis of Dynamics
   - Dynamics Properties from BRN Interaction Graph
   - Fix Points
5. Abstract Interpretation of Scenarios
6. Applications
7. Discussion

T-Cell Receptor Signalling Pathway

(94 components)



[Saez-Rodriguez, *et al.* in PLoS Comput Biol, 07]

Process Hitting
133 sorts,
448 processes,
1124 actions:
$\approx 2 \cdot 10^{58}$ states.

Reachability analysis always conclusive; around 0.01*s* (compared to *libddd*: out of memory). [http://ddd.lip6.fr]

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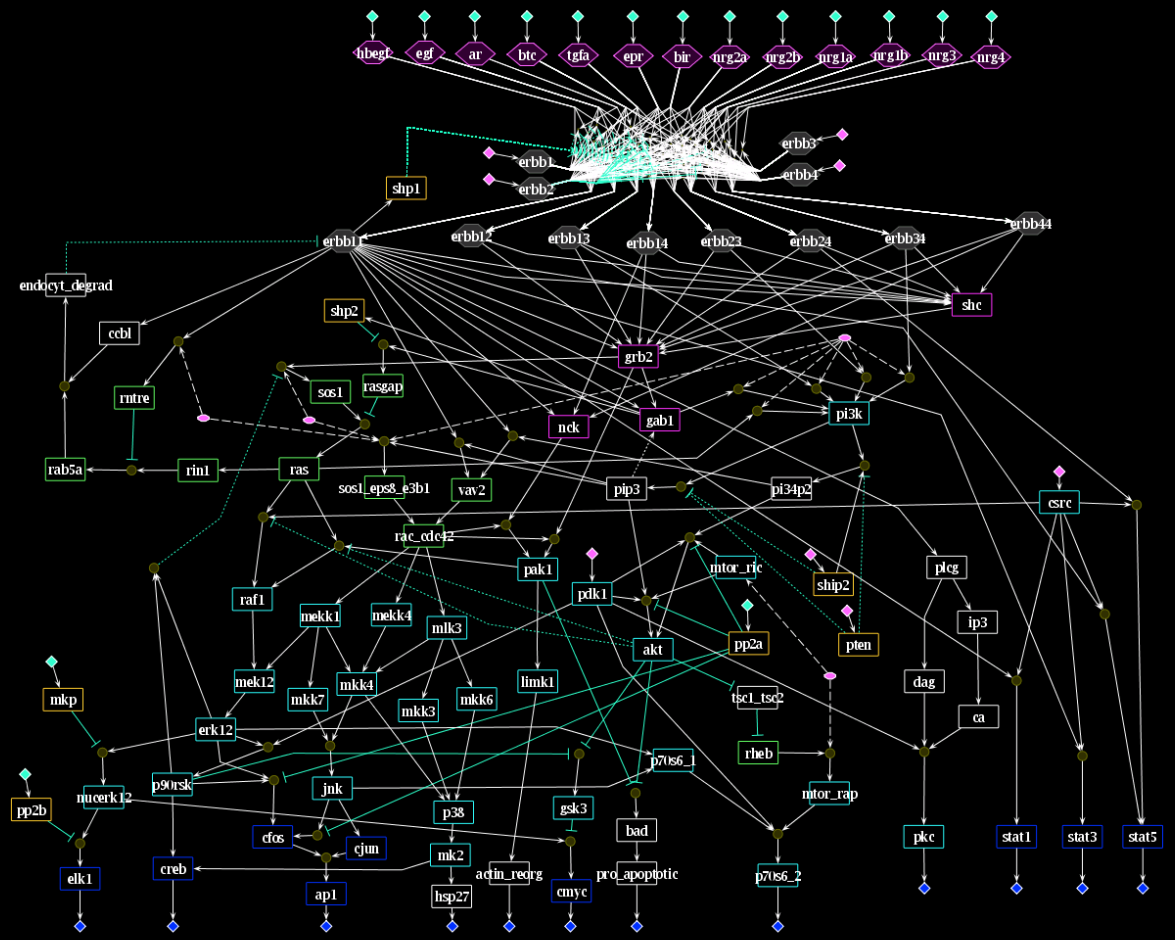
EGFR/ErbB Signalling

(104 components)



[Samaga, *et al.* in PLoS Comput Biol, 2009]

Process Hitting
193 sorts,
748 processes,
2356 actions:
$\approx 2 \cdot 10^{96}$ states.

Reachability analysis always conclusive; around 0.05*s* (compared to *libddd*: out of memory). [http://ddd.lip6.fr]

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Conclusion and Outlook

The Process Hitting

- *Elementary* framework for dynamical complex systems;
- Applied to BRNs; not limited to.
- Generic tuning of time features within stochastic models (simulation + standard model checking).
- Software available (PINT - `http://processhitting.wordpress.com`).

Static Analysis by Abstract Interpretation of Process Hitting

- Very efficient over- and under-approximations of process reachability;
- Extract necessary processes for achieving reachabilities: towards control.
- Future work may establish other dynamical properties: attractors, etc.

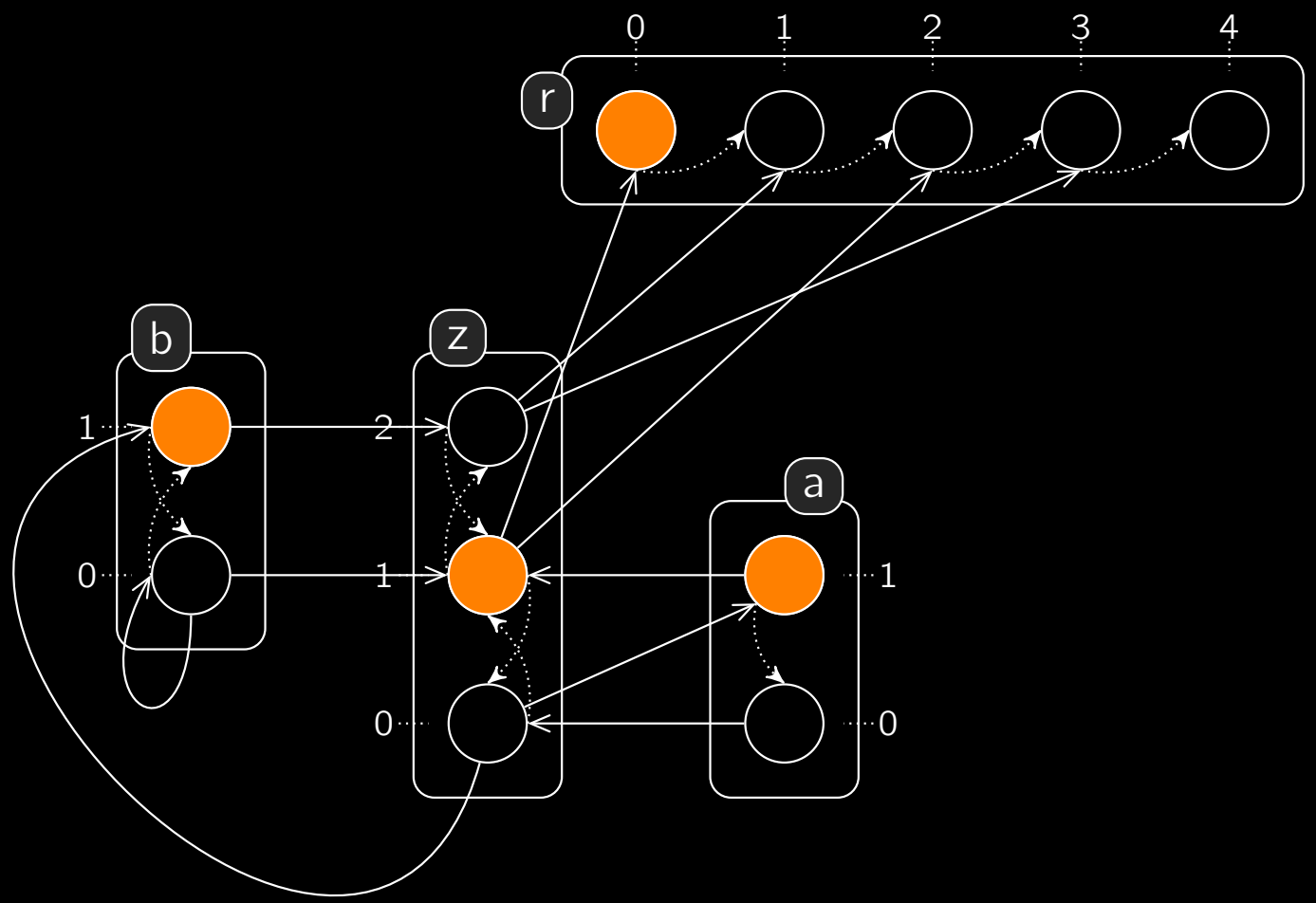
Towards Quantitative Analysis

- Extension to the Process Hitting with Priorities.
- Two classes of actions: instantaneous and non-instantaneous.

Bonus

...

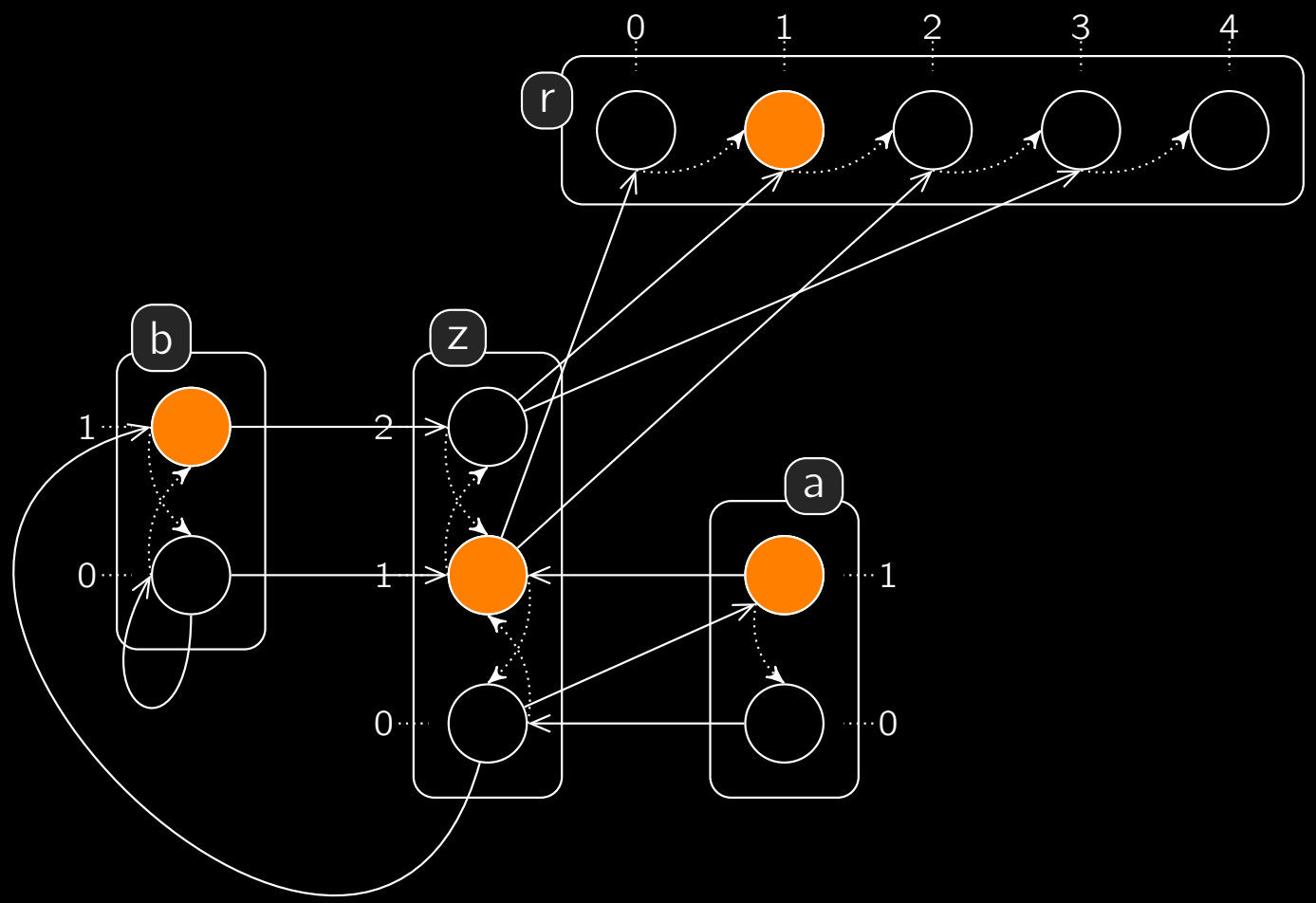
Toy Example



$\mathbf{BS}(r_0 \lceil^{*} r_4) = \{[z_1 \rightarrow r_0 \lceil r_1, z_2 \rightarrow r_1 \lceil r_2, z_1 \rightarrow r_2 \lceil r_3, z_2 \rightarrow r_3 \lceil r_4]\}$

Objective sequence to check: $z_1 \lceil^{*} z_2, z_2 \lceil^{*} z_1, z_1 \lceil^{*} z_2$.

Toy Example



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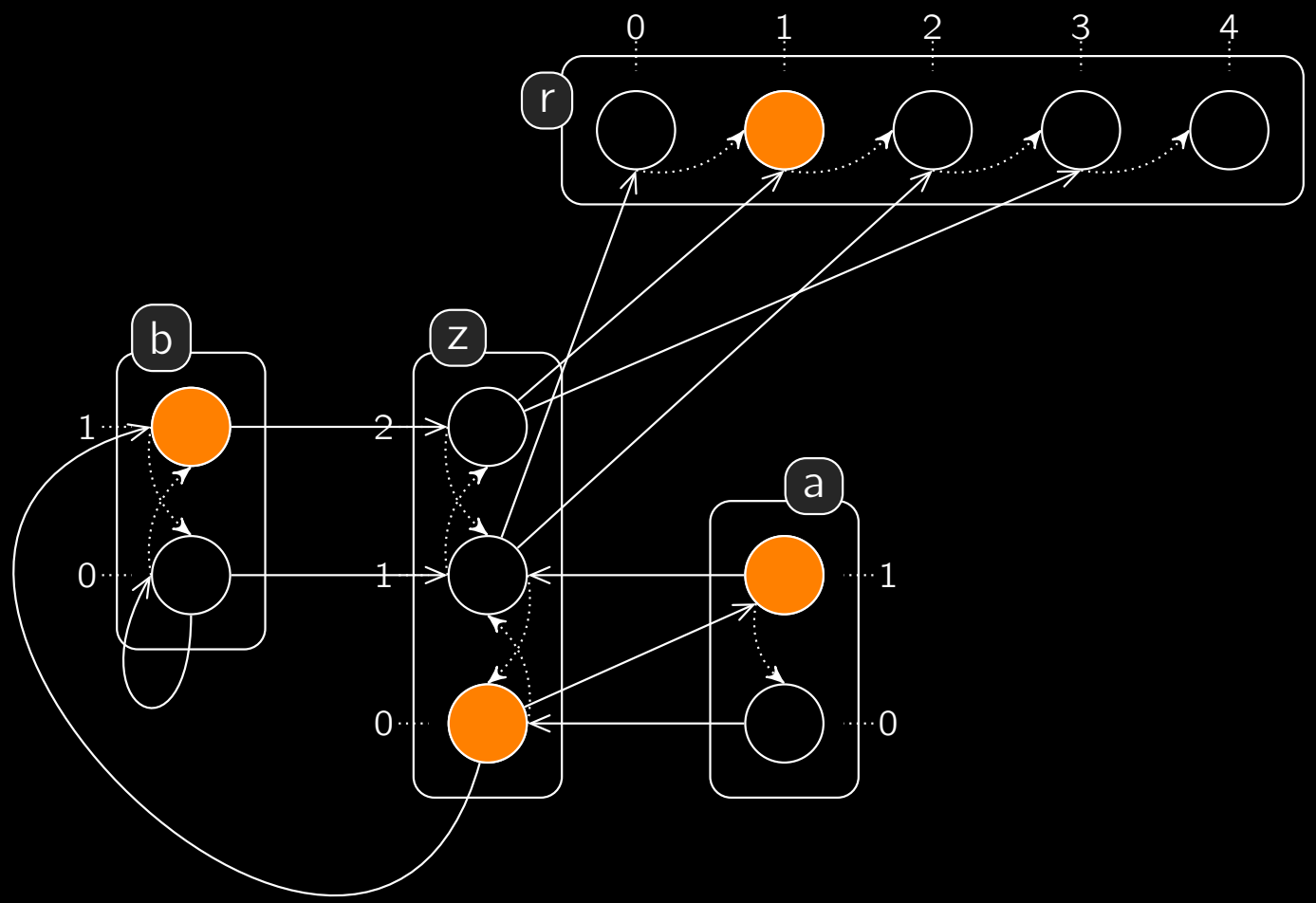

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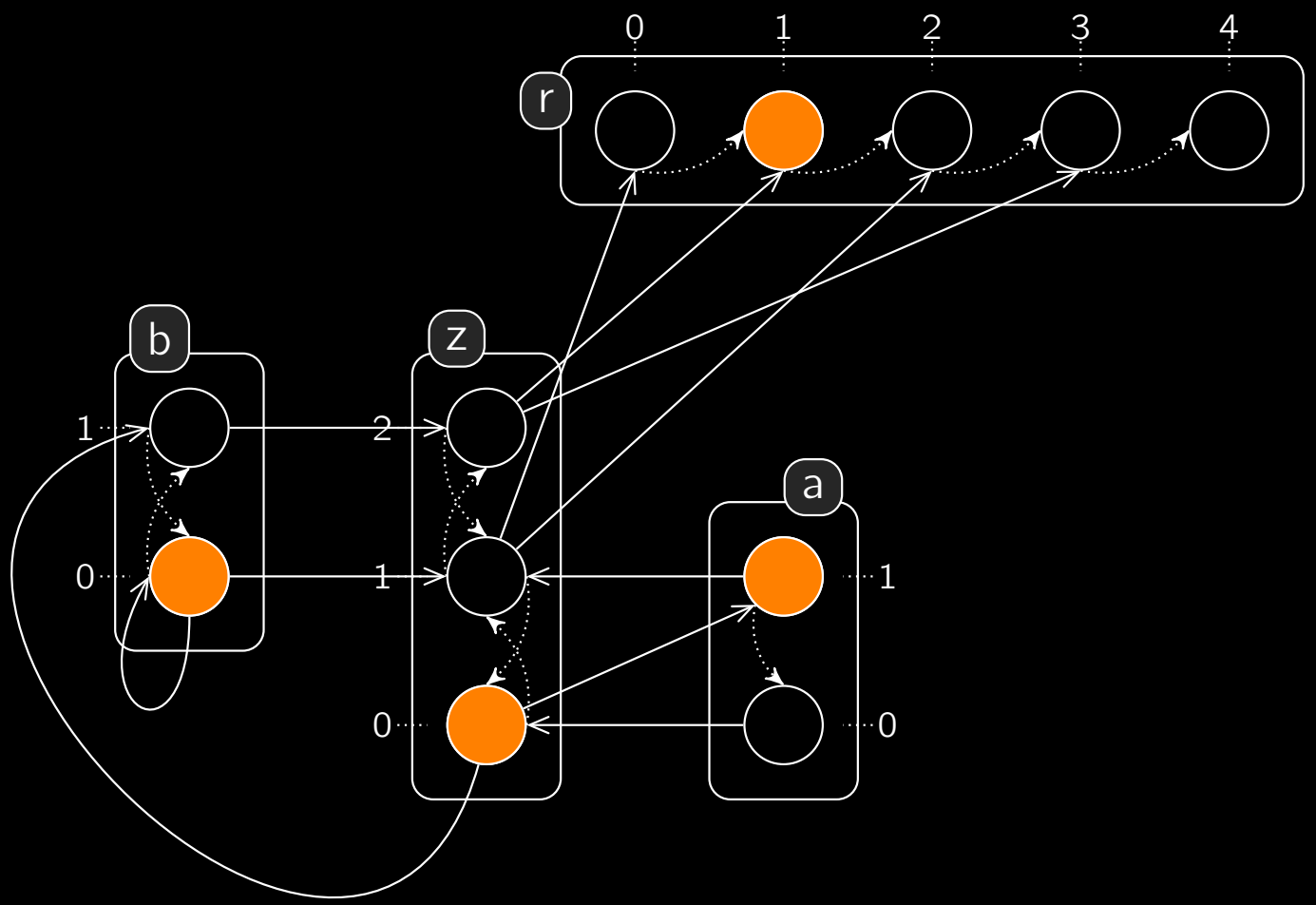

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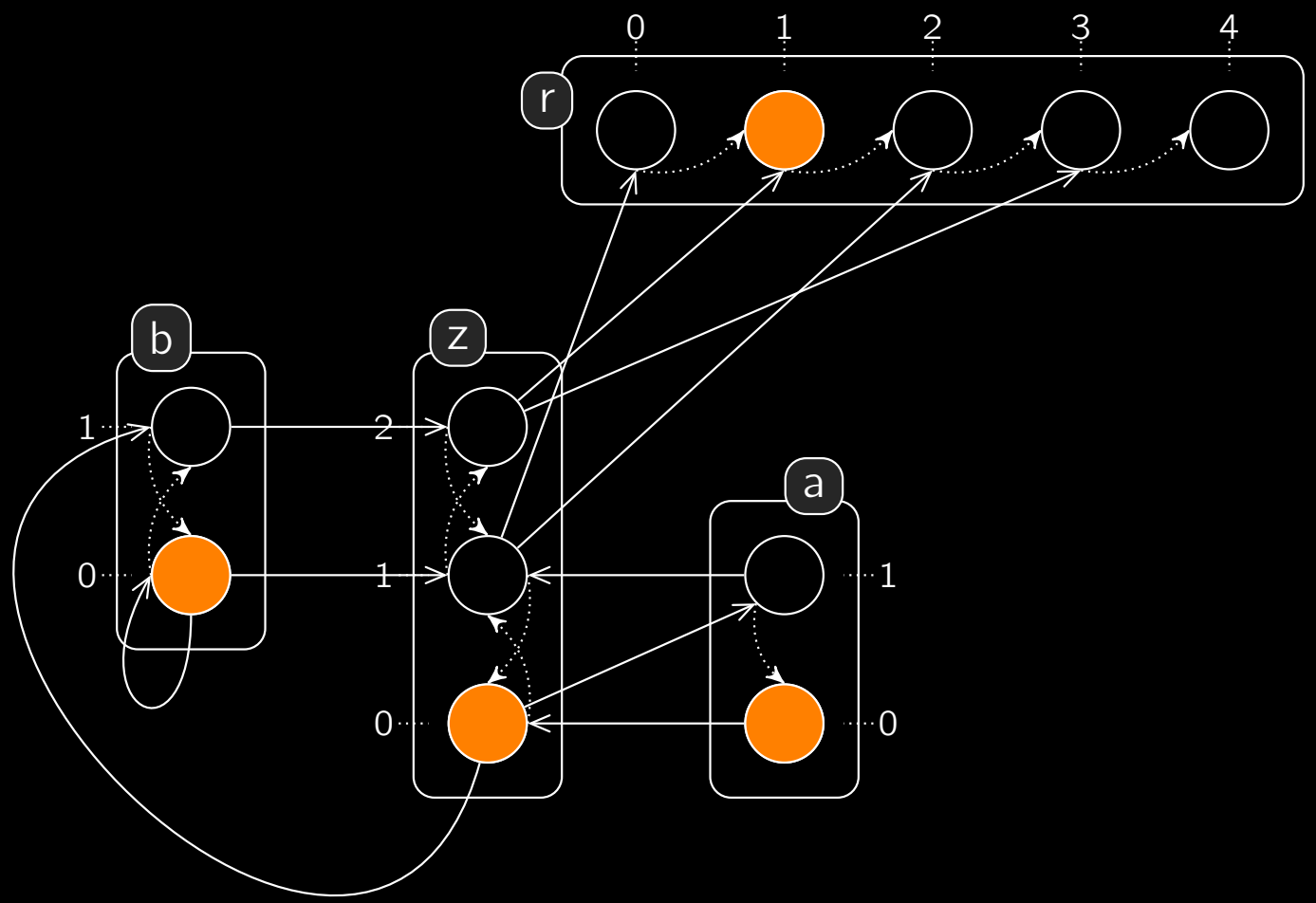

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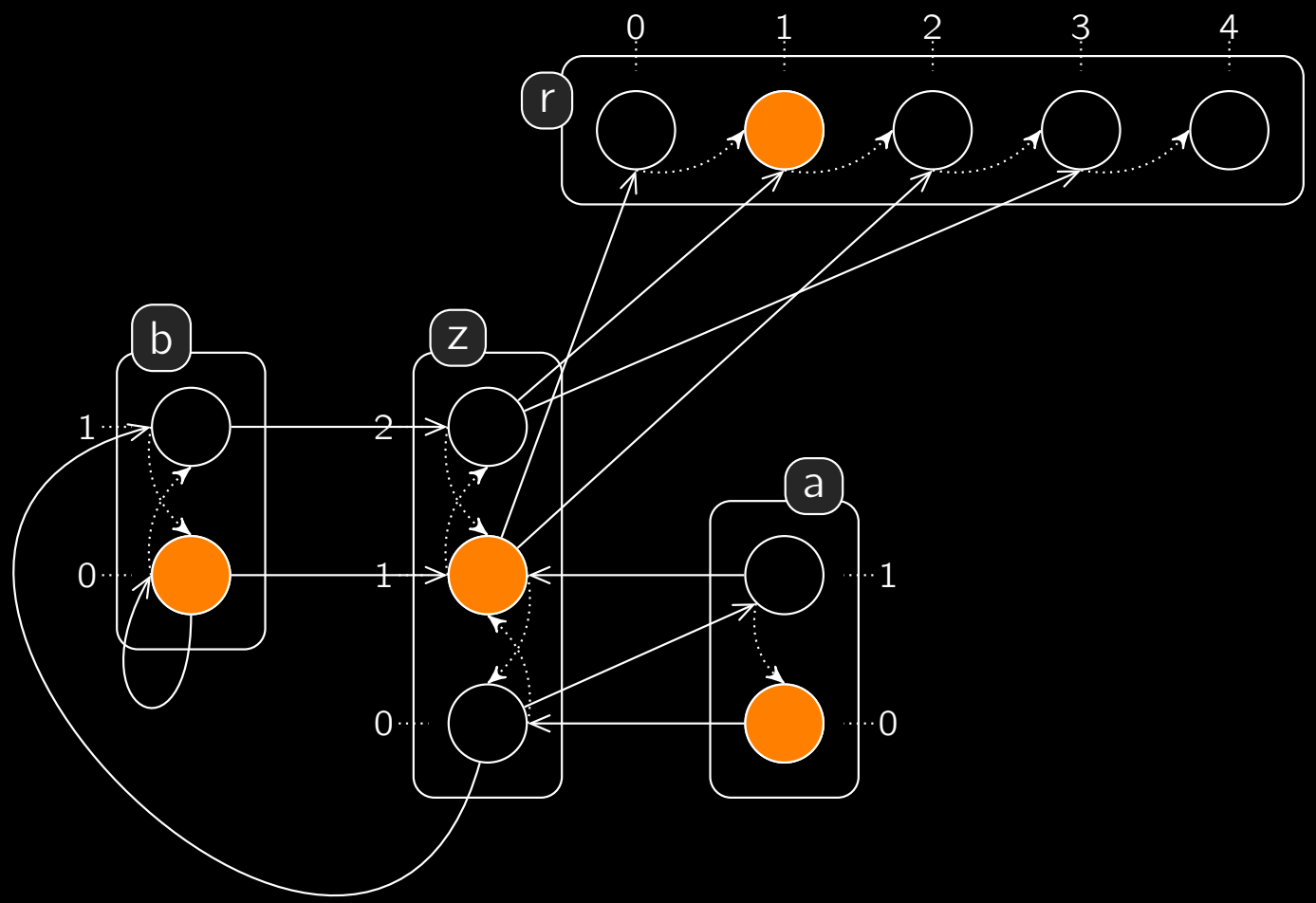

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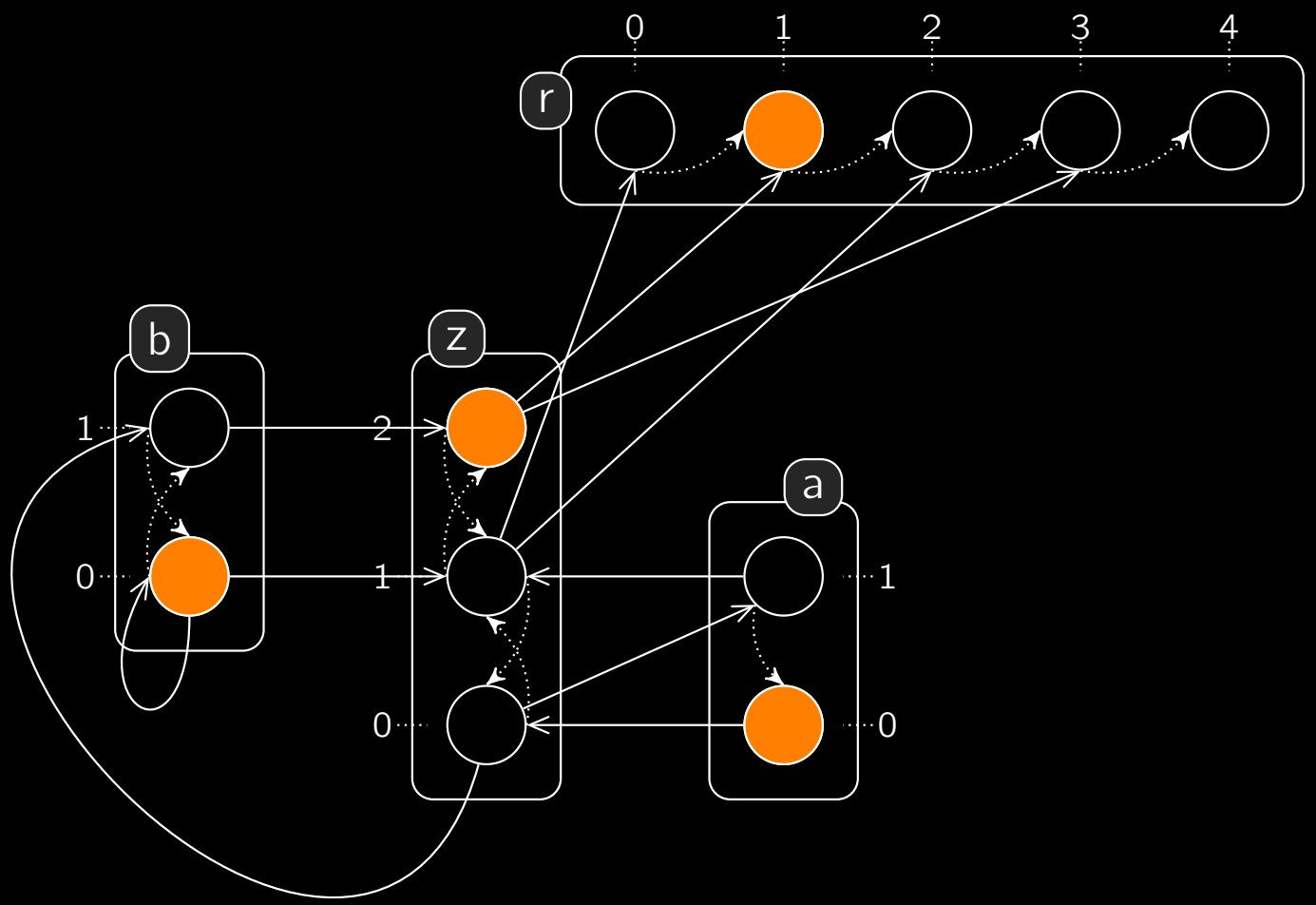

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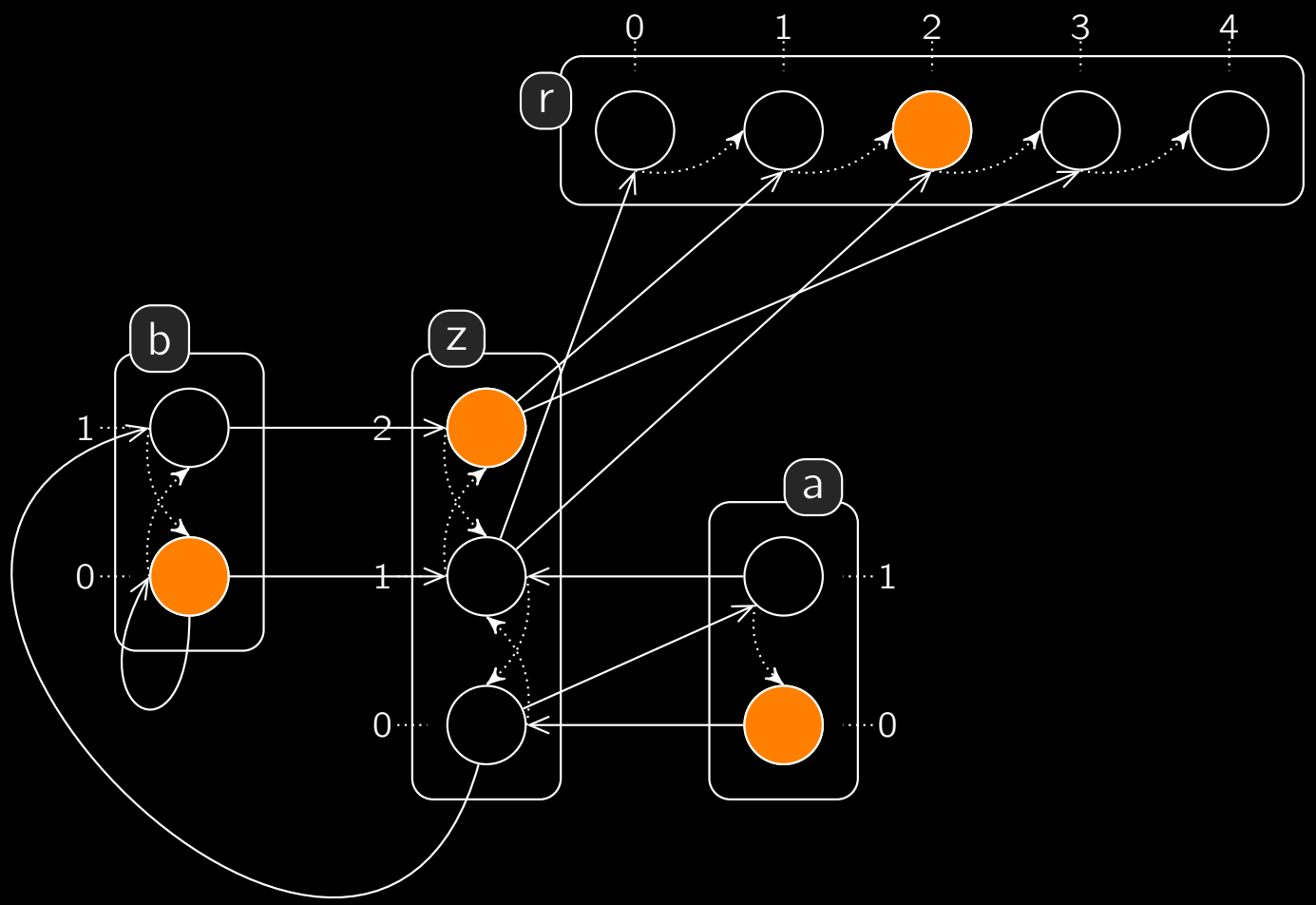

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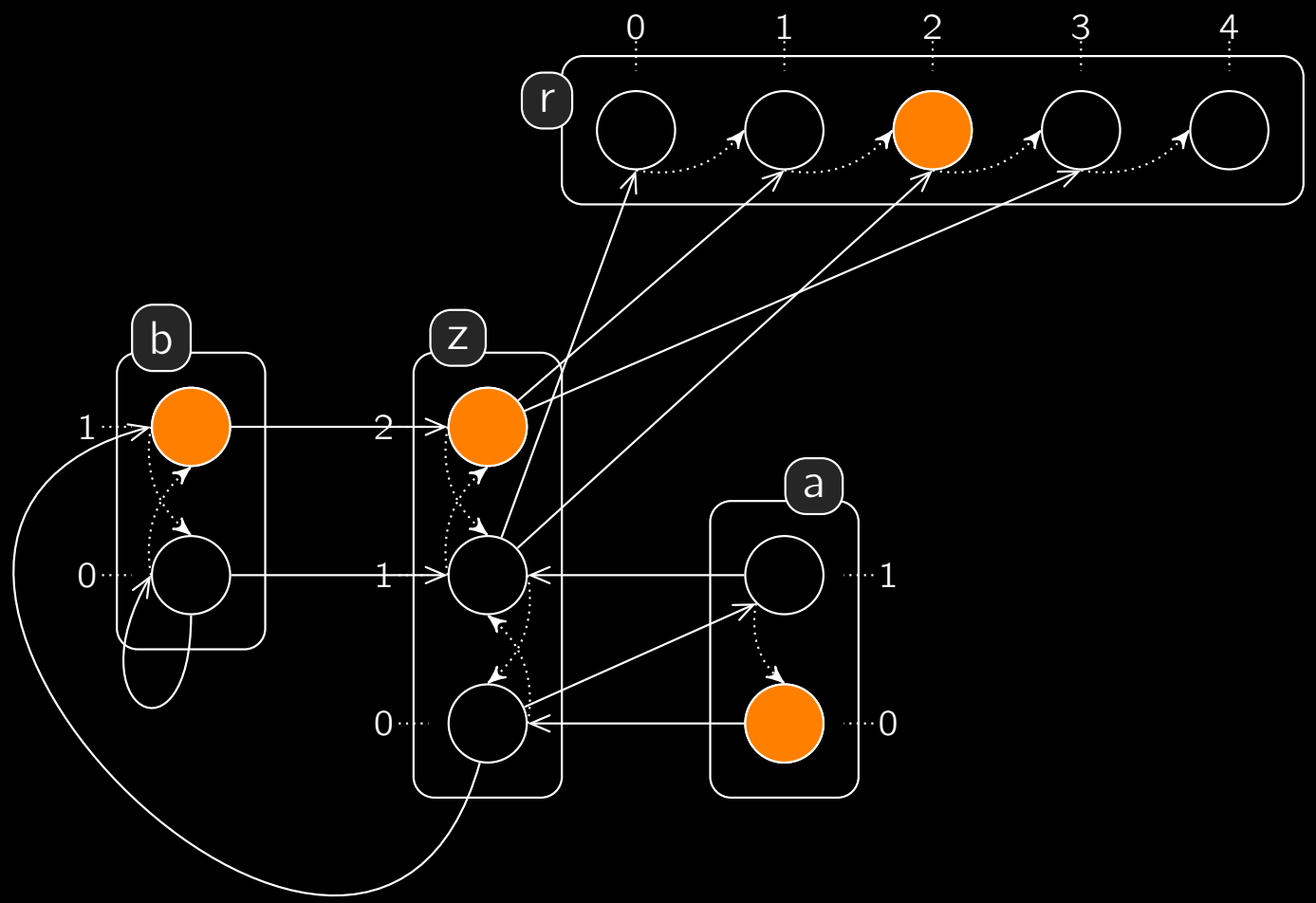

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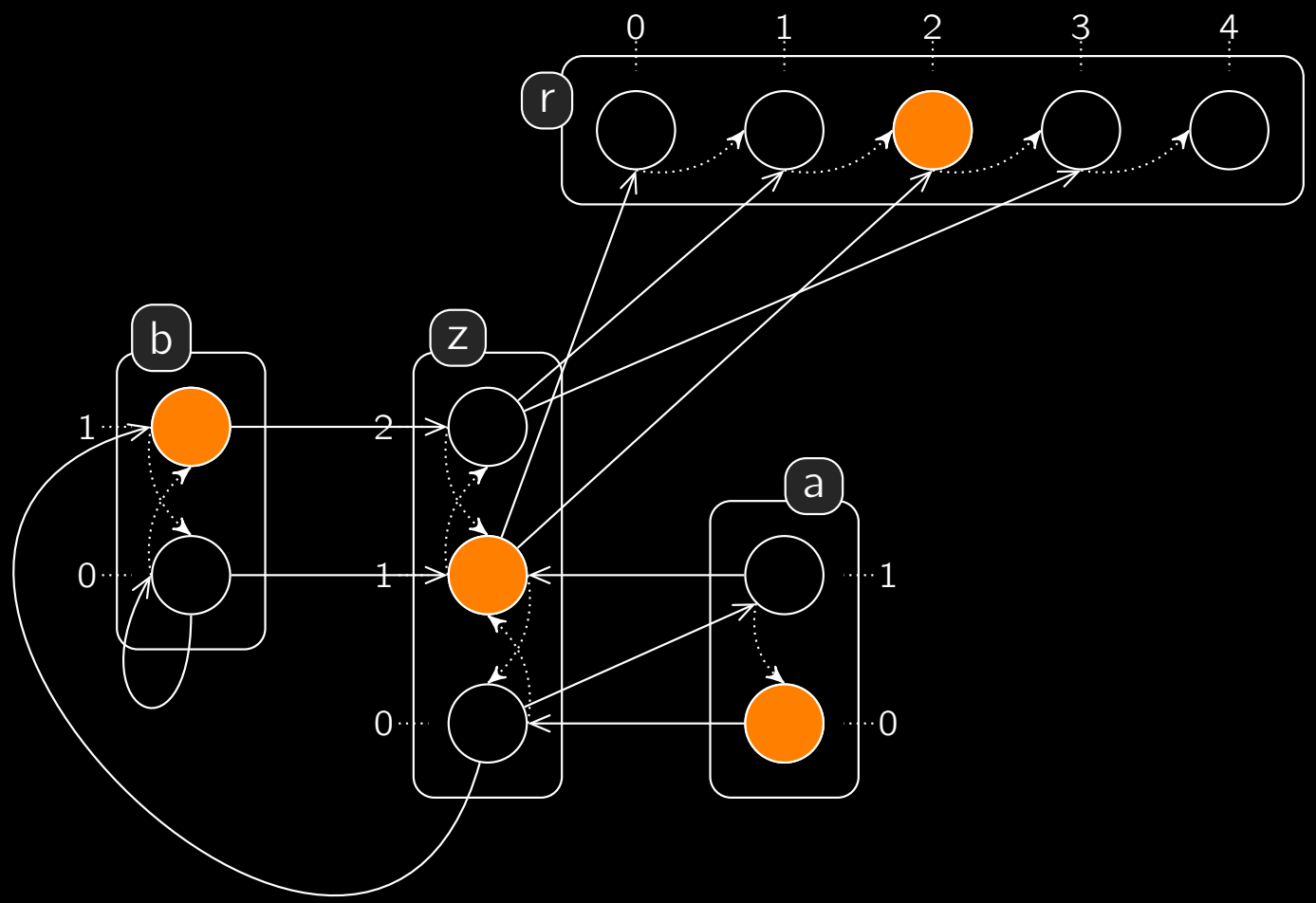

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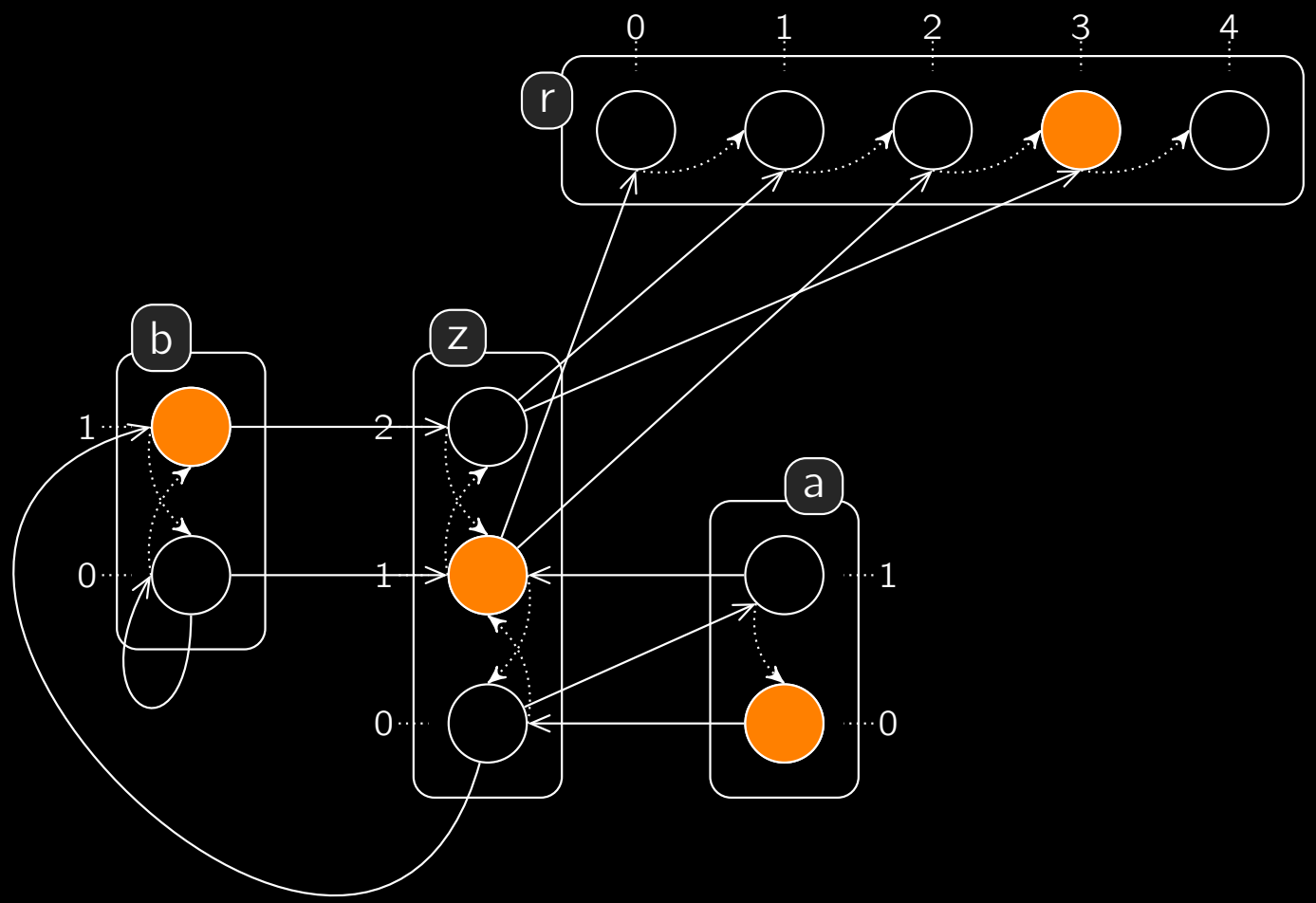
Objective sequence to check: $z_1 \lceil^* z_2, z_2 \lceil^* z_1, z_1 \lceil^* z_2$.

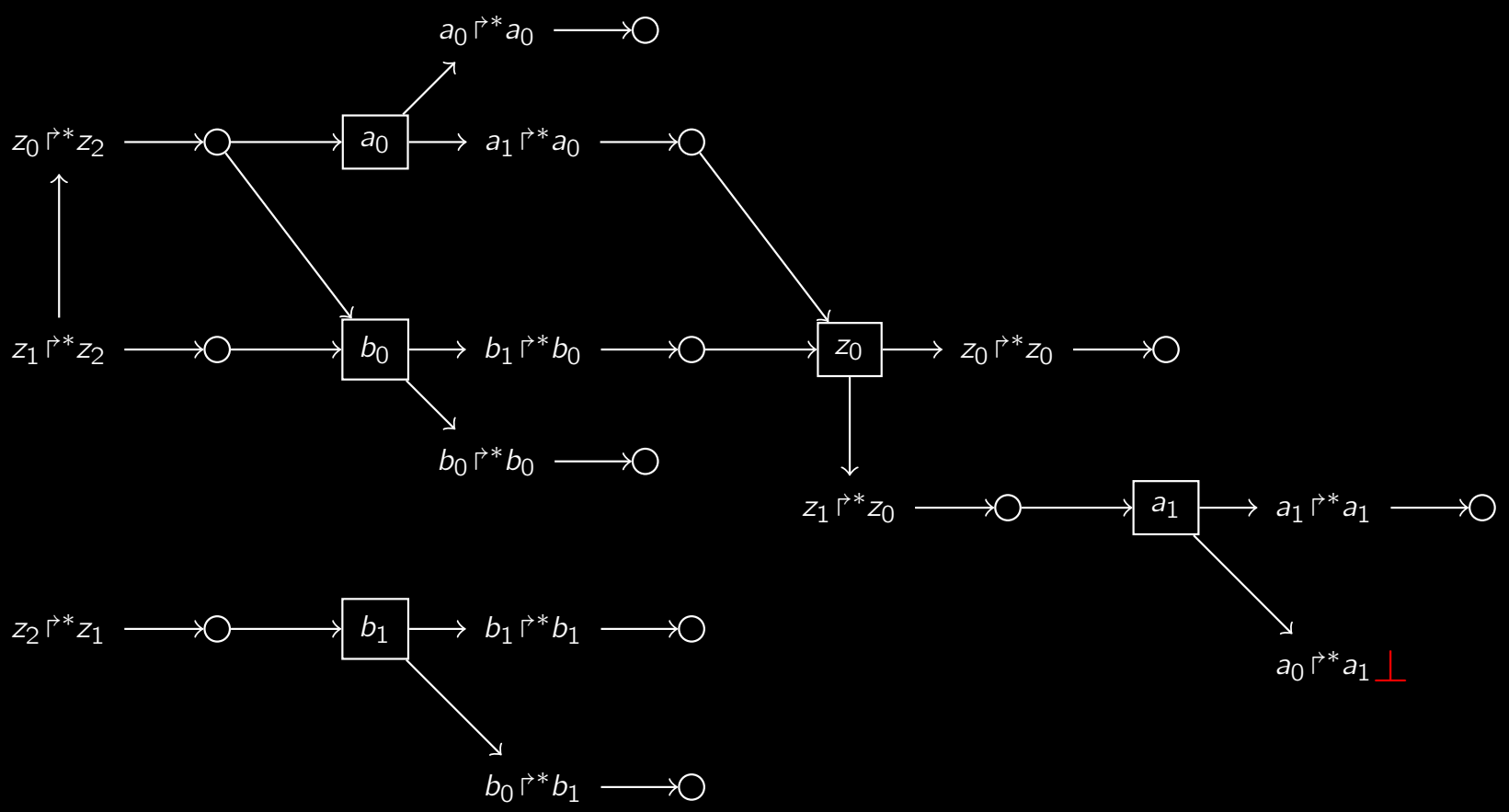
Toy Example



$\mathbf{BS}(r_0 \lceil^* r_4) = \{[z_1 \rightarrow r_0 \lceil r_1, z_2 \rightarrow r_1 \lceil r_2, z_1 \rightarrow r_2 \lceil r_3, z_2 \rightarrow r_3 \lceil r_4]\}$

Objective sequence to check: $z_1 \lceil^* z_2, z_2 \lceil^* z_1, z_1 \lceil^* z_2$.

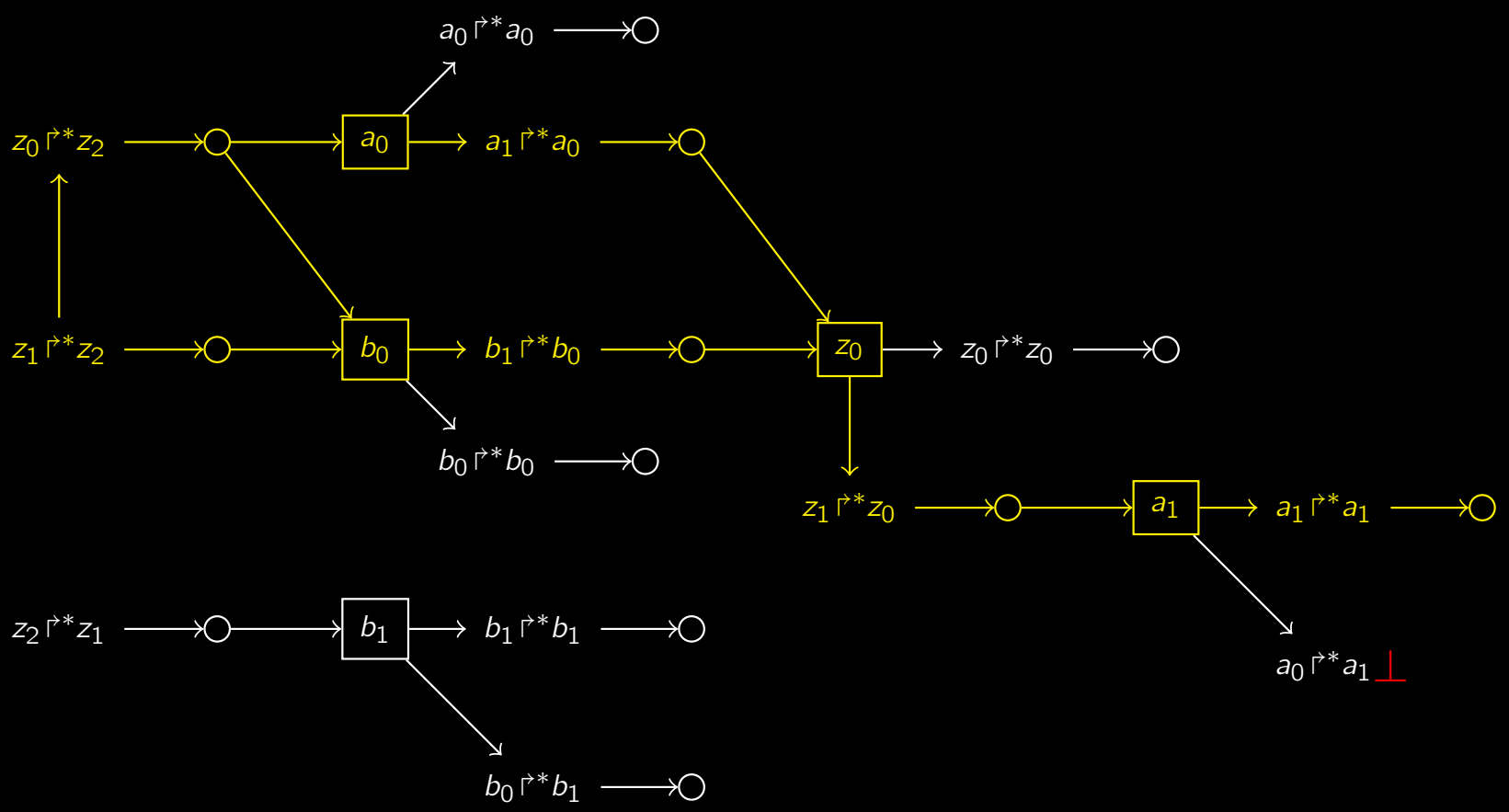
Saturated Abstract Structure of Example



$a_1 \lhd a_0$

	s	$z_1 \Rsh^* z_2$	$z_2 \Rsh^* z_1$	$z_1 \Rsh^* z_2$
minPROC	a_1, b_1, z_1			
$max\varsigma$	a_1, b_1, z_1			

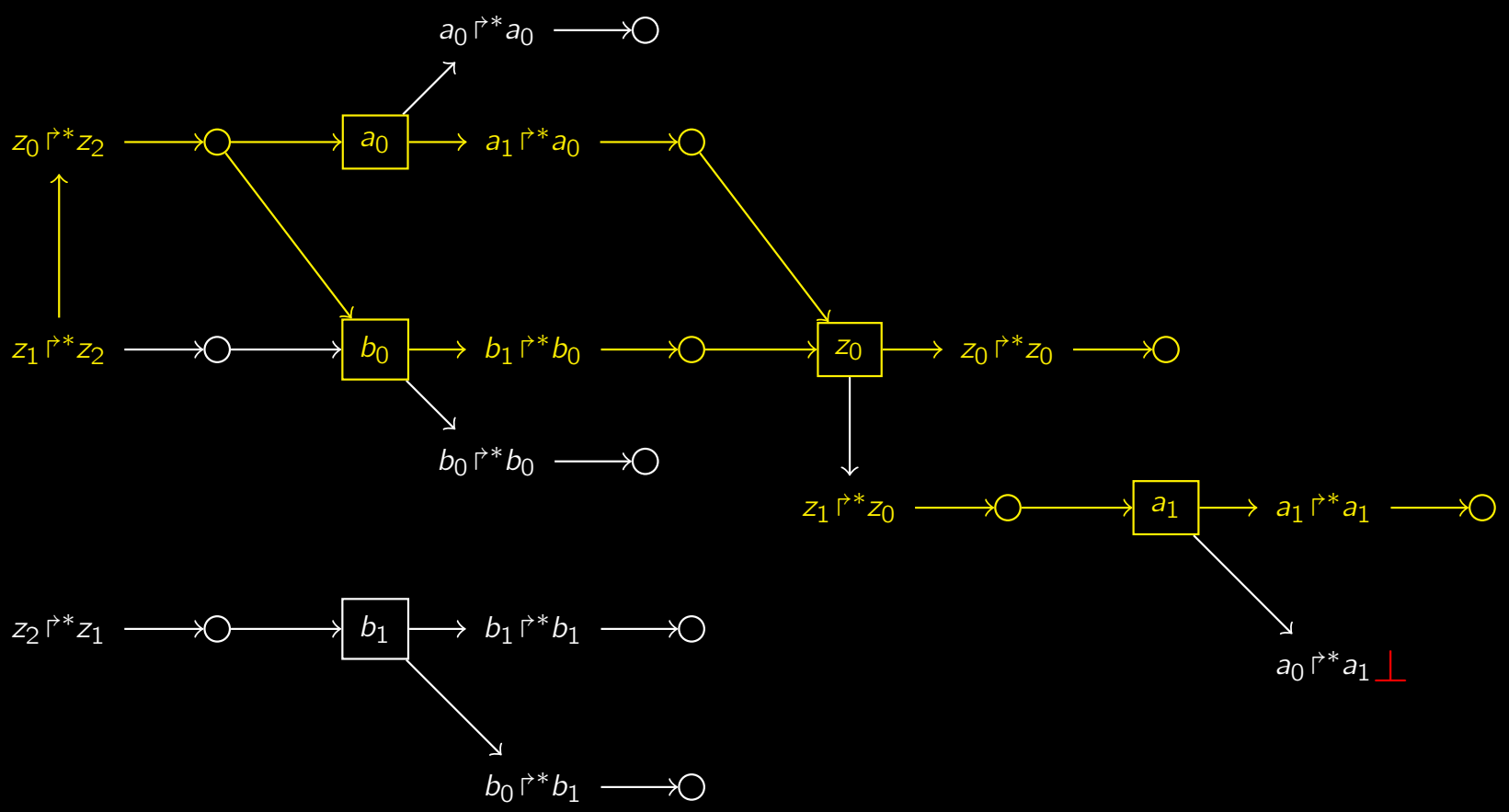
Saturated Abstract Structure of Example



$a_1 \lhd a_0$

	s	$z_1 \Rsh^* z_2$	$z_2 \Rsh^* z_1$	$z_1 \Rsh^* z_2$
minPROC	a_1, b_1, z_1			
$max\varsigma$	a_1, b_1, z_1			

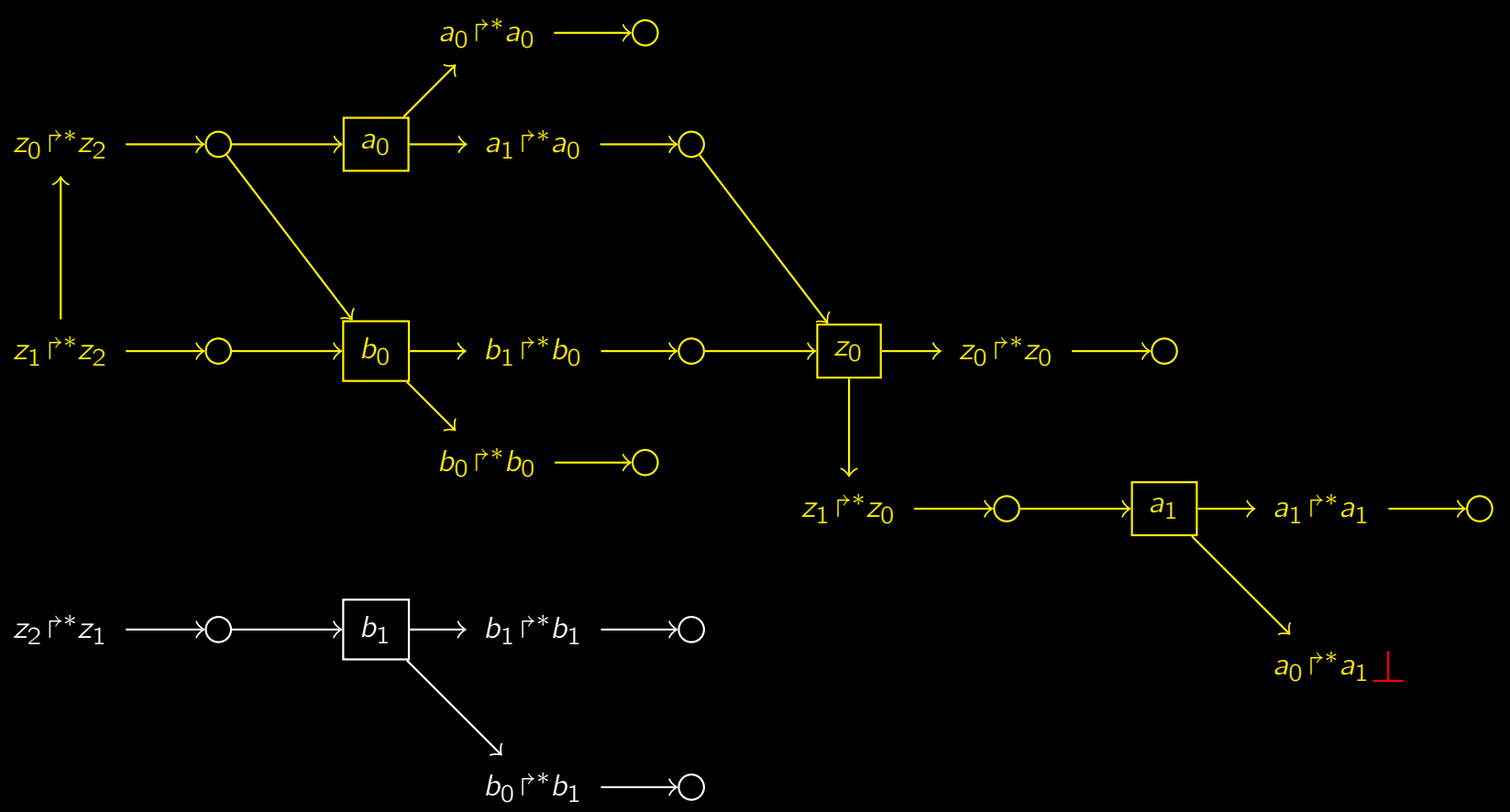
Saturated Abstract Structure of Example



$a_1 \lhd a_0$

	s	$z_1 \Rsh^* z_2$	$z_2 \Rsh^* z_1$	$z_1 \Rsh^* z_2$
minPROC	a_1, b_1, z_1	a_0, a_1, b_0 z_0, z_2		
$max\varsigma$	a_1, b_1, z_1			

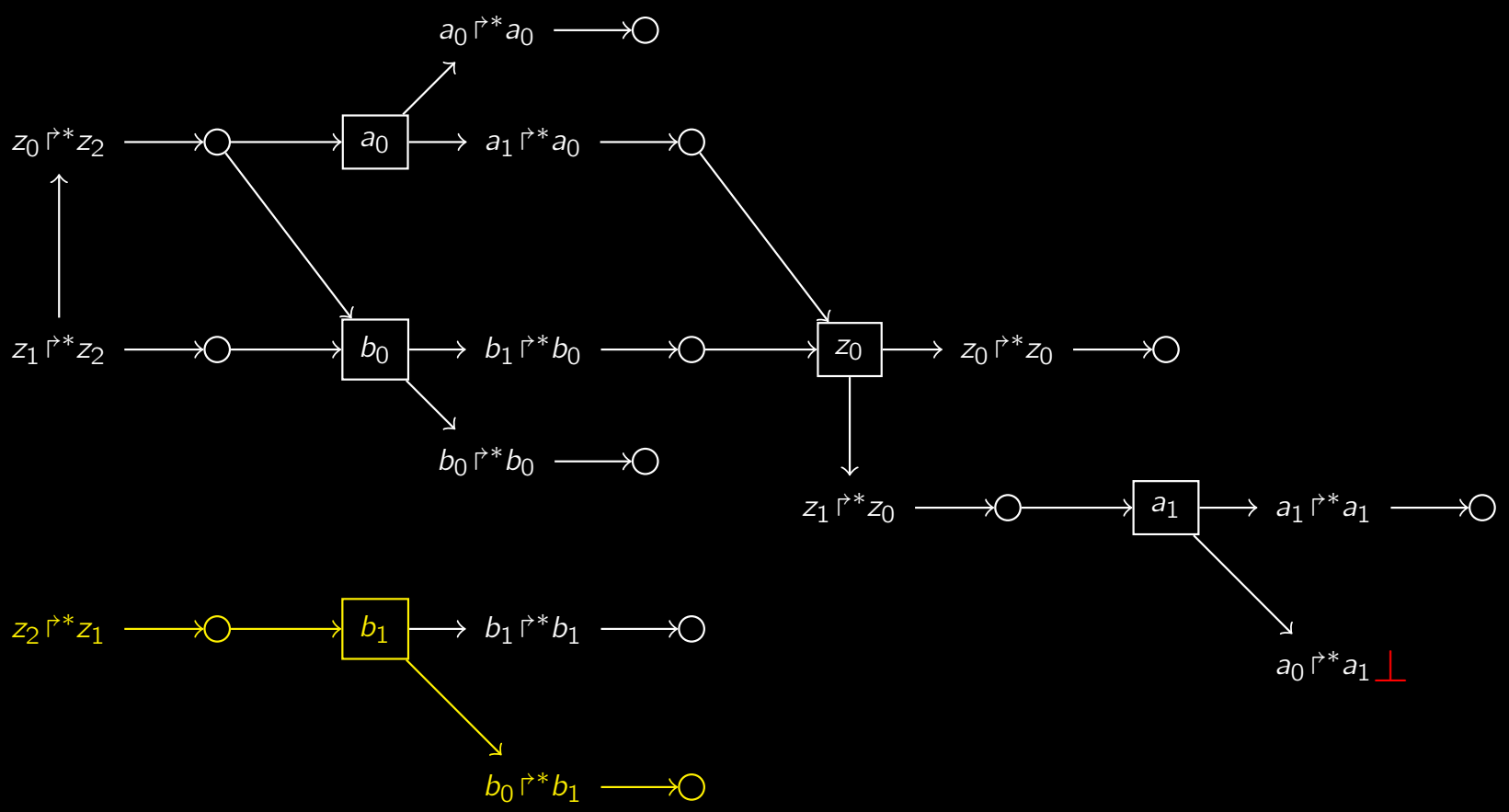
Saturated Abstract Structure of Example



$a_1 \lhd a_0$

	s	$z_1 \Rsh^* z_2$	$z_2 \Rsh^* z_1$	$z_1 \Rsh^* z_2$
minPROC	a_1, b_1, z_1	a_0, a_1, b_0 z_0, z_2		
$max\varsigma$	a_1, b_1, z_1	a_0, a_1, b_0 z_2		

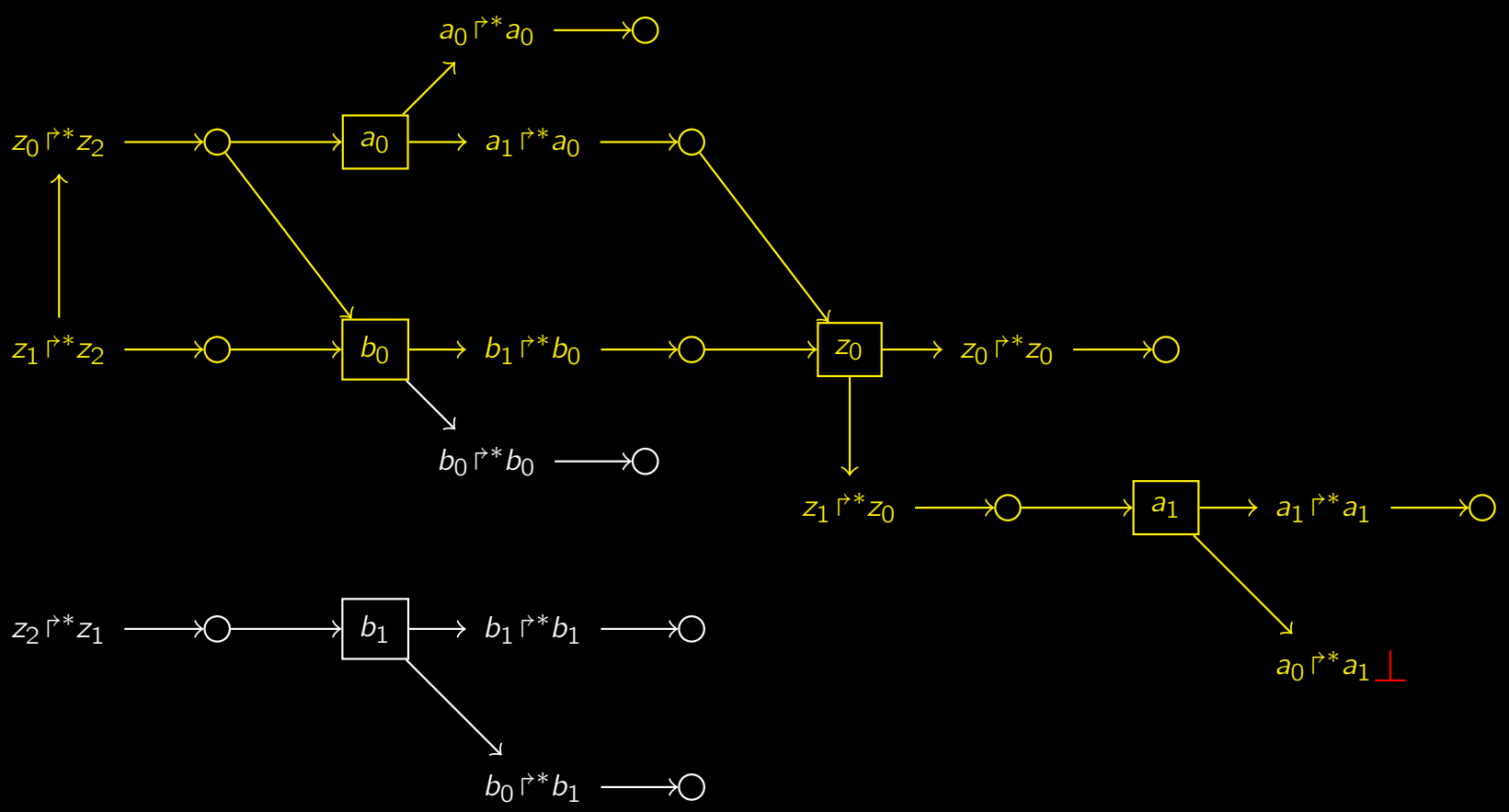
Saturated Abstract Structure of Example



$a_1 \lhd a_0$

	s	$z_1 \Rsh^* z_2$	$z_2 \Rsh^* z_1$	$z_1 \Rsh^* z_2$
minPROC	a_1, b_1, z_1	a_0, a_1, b_0 z_0, z_2	b_1, z_1	
$max\varsigma$	a_1, b_1, z_1	a_0, a_1, b_0 z_2	a_0, a_1, b_1 z_1	

Saturated Abstract Structure of Example



$a_1 \lhd a_0$

	s	$z_1 \Rsh^* z_2$	$z_2 \Rsh^* z_1$	$z_1 \Rsh^* z_2$
minPROC	a_1, b_1, z_1	a_0, a_1, b_0 z_0, z_2	b_1, z_1	a_0, a_1, b_0 z_0, z_2
$max\varsigma$	a_1, b_1, z_1	a_0, a_1, b_0 z_2	a_0, a_1, b_1 z_1	