PhD defense

Algebraic Modeling of the Multi-Scale Dynamics of Biological Regulatory Networks

Maxime FOLSCHETTE

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

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Rapporteurs : Jean-Paul COMET, Professeur des universités, Université de Nice – Sophia Antipolis
Anne SIEGEL, Directrice de recherche CNRS, IRISA (CNRS & Université Rennes 1), Inria Rennes

Examinateurs : Mireille RÉGNIER, Directrice de recherche Inria, École polytechnique & Université Paris-Sud 11
Denis THIEFFRY, Professeur des universités, École normale supérieure

Directeur de thèse : Olivier ROUX, Professeur des universités, École centrale de Nantes
Co-encadrant de thèse : Morgan MAGNIN, Maître de conférences, École centrale de Nantes

The Modeling/Analysis duality

Modeling a system is the first step towards its comprehension

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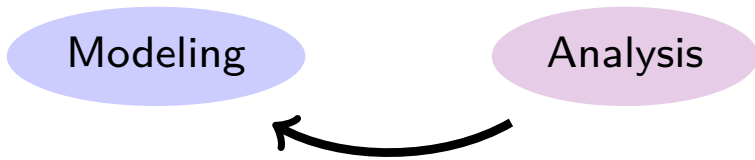

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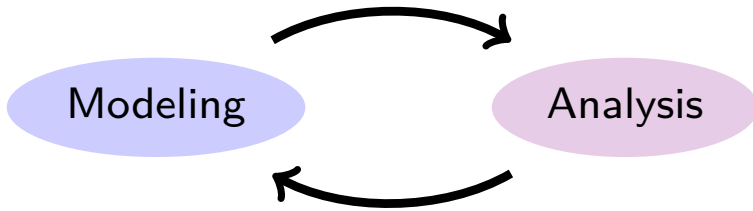

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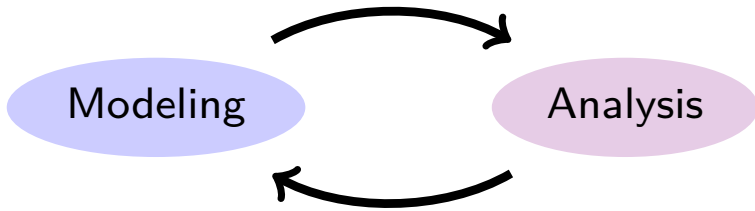

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The modeling and analysis steps of a system are strongly linked

Overview of This Presentation

State of the Art of the modeling of biological regulatory networks

- Discrete asynchronous representations and Thomas modeling
- Standard Process Hitting

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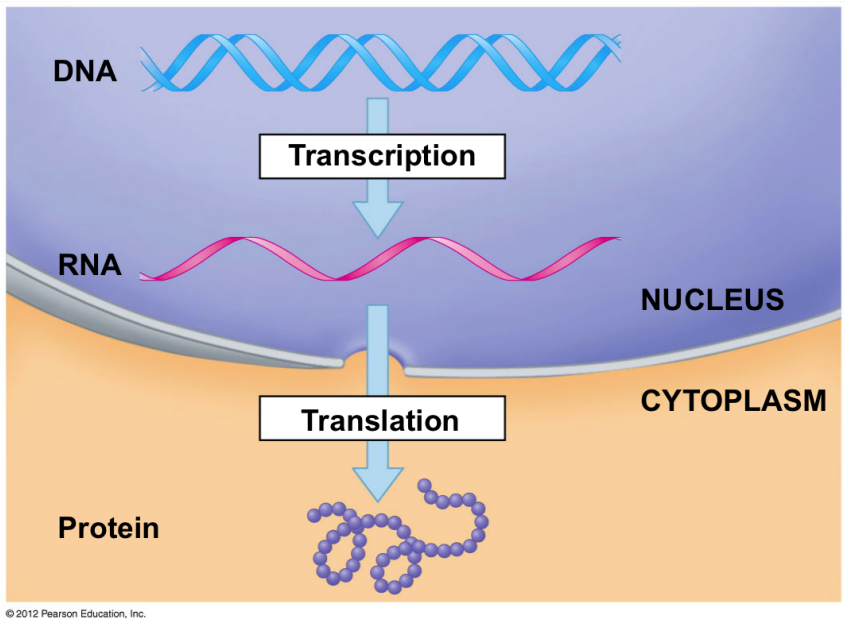
Analysis of the Process Hitting

- Correction of the cooperative sorts
- Static analysis of reachability
- Equivalences and links with other formalisms

Abstractions of the Representation



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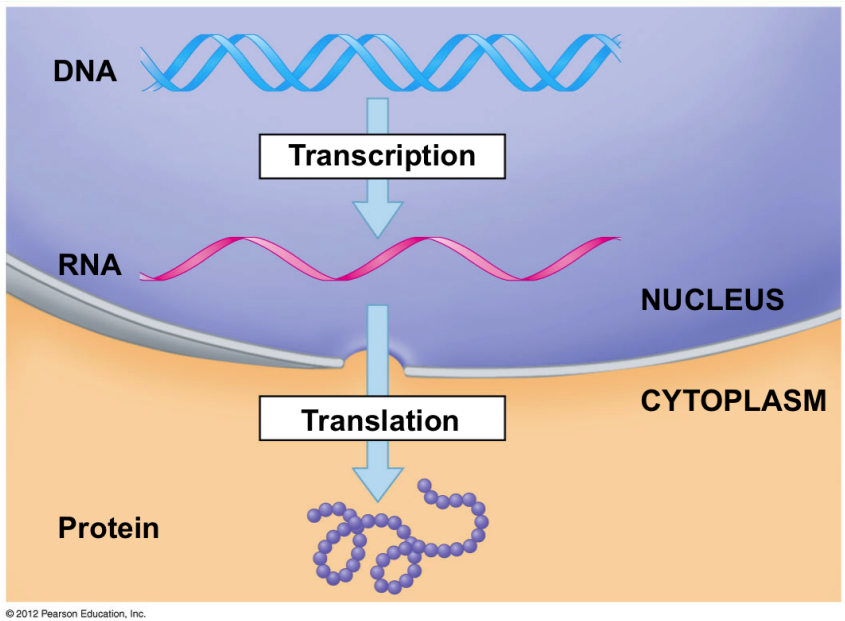

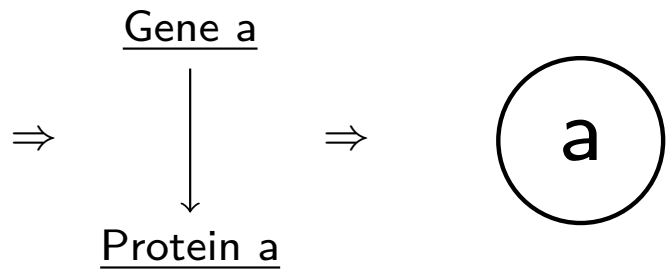

Discretization and Asynchronism

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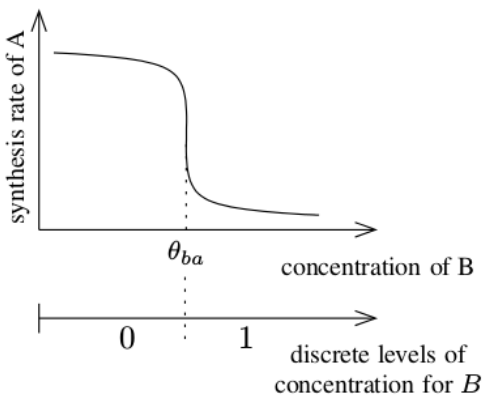

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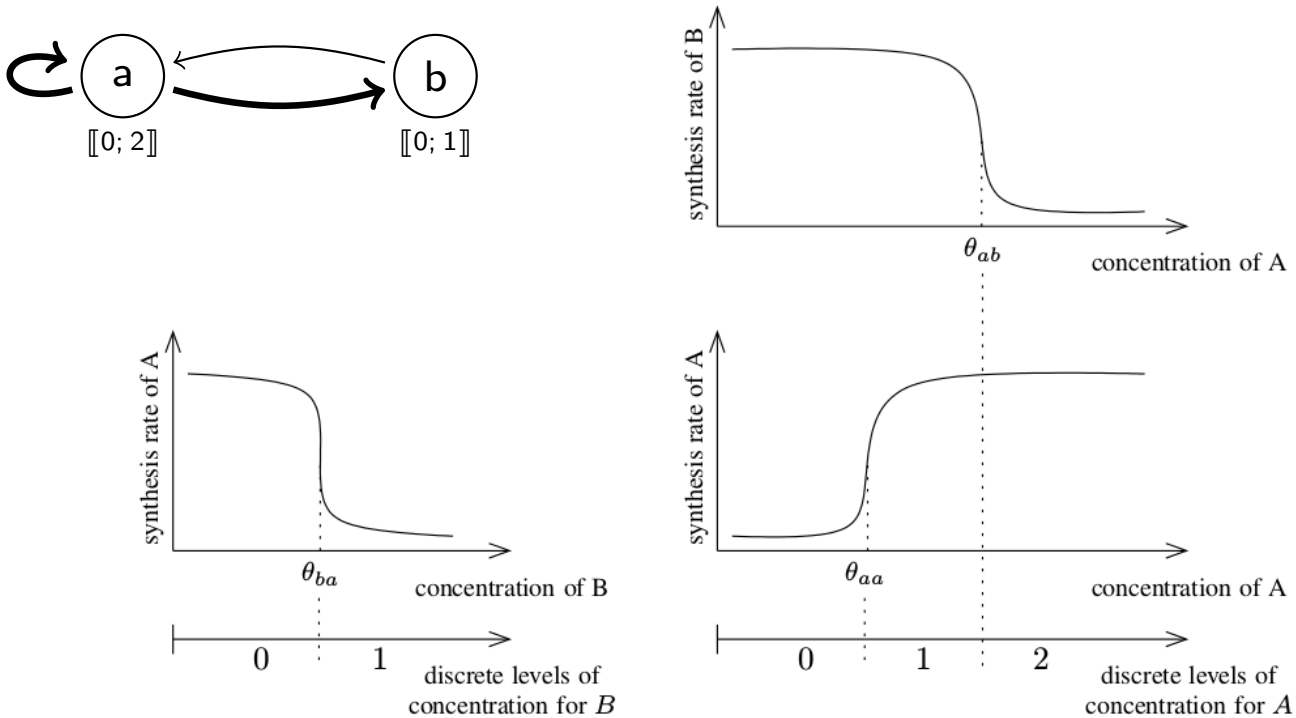

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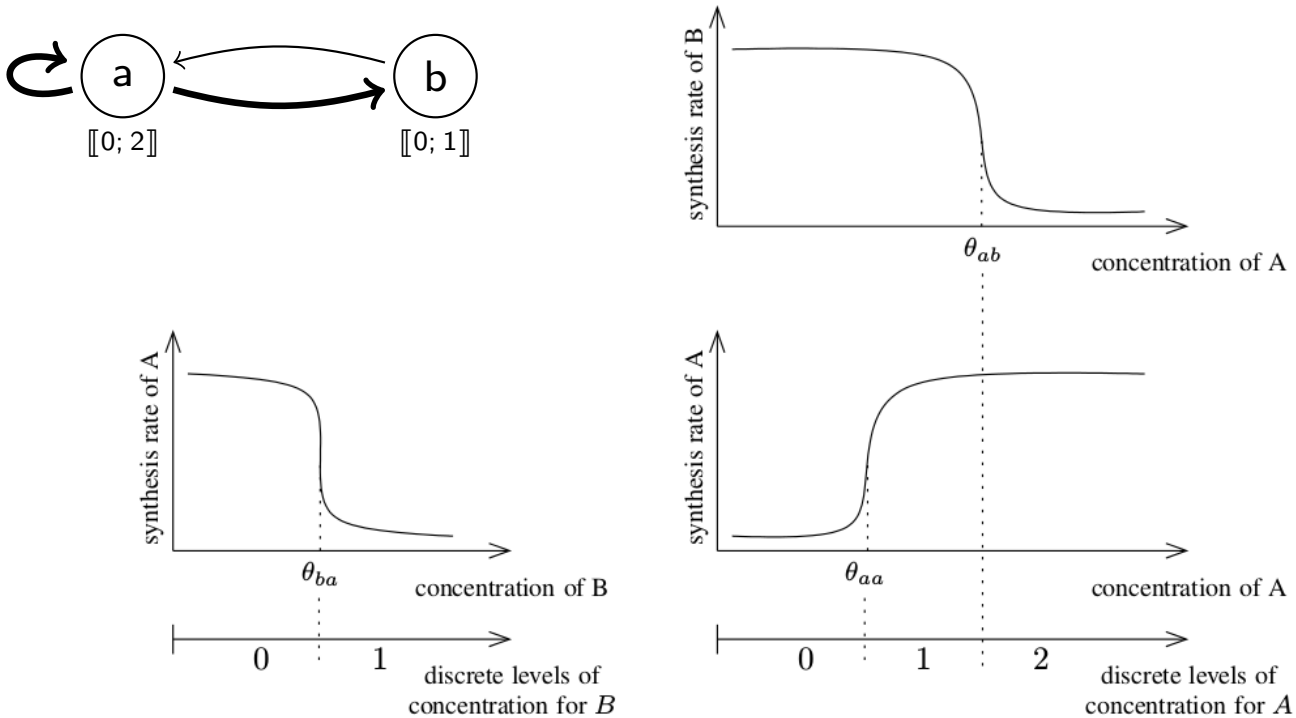

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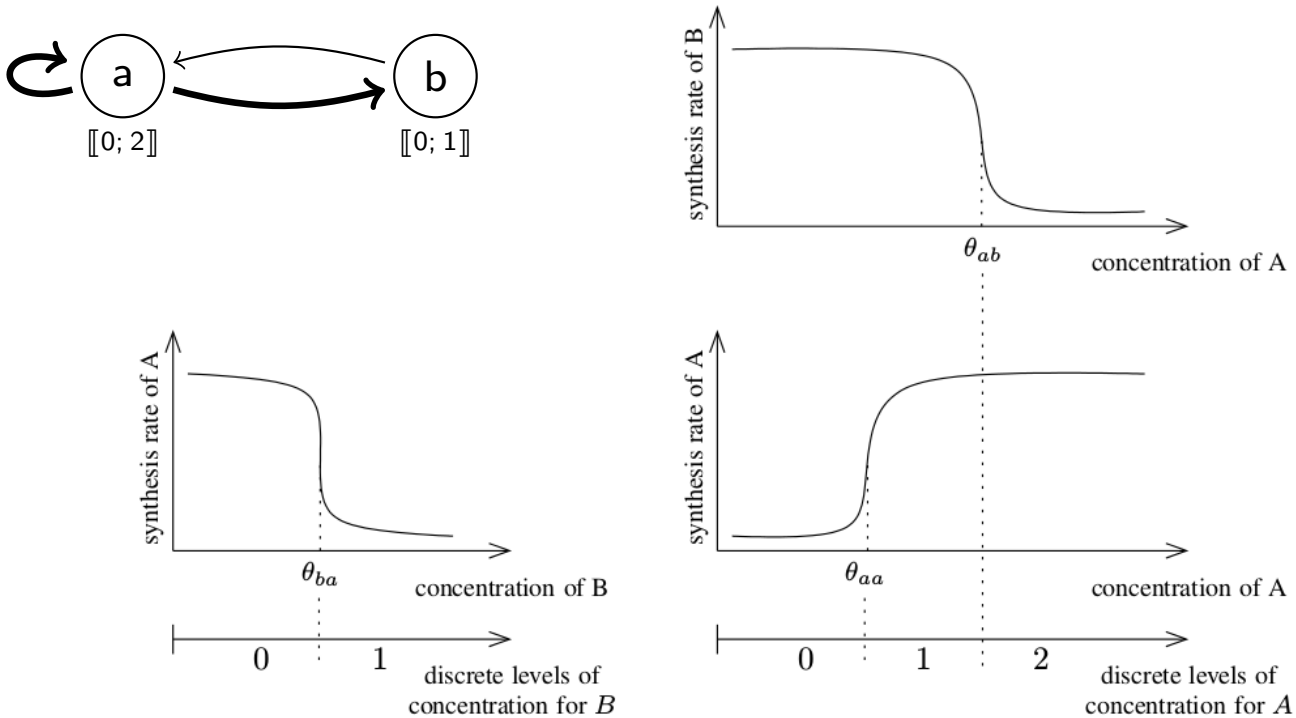

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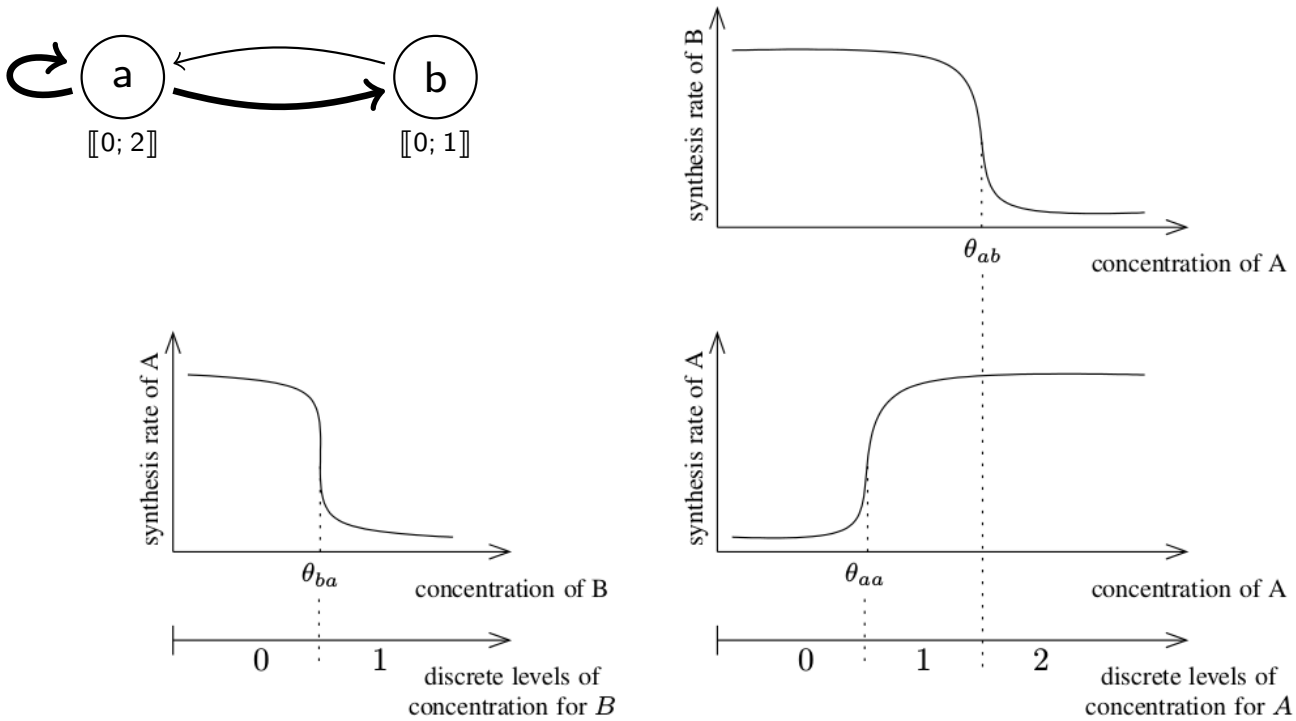

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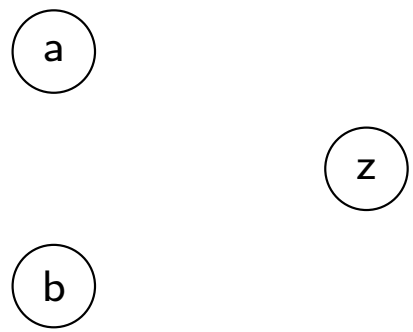
  → Abstracted as thresholds or **discrete levels**
- Continuous variations of the real values
  → **Unitary** dynamics
- Simultaneous crossings of two thresholds never occurs
  → **Asynchronous** dynamics

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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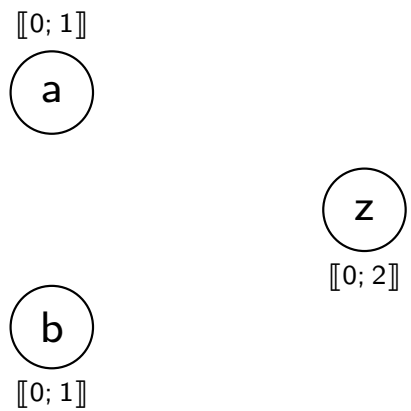

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- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

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	$f^z(a,b)$
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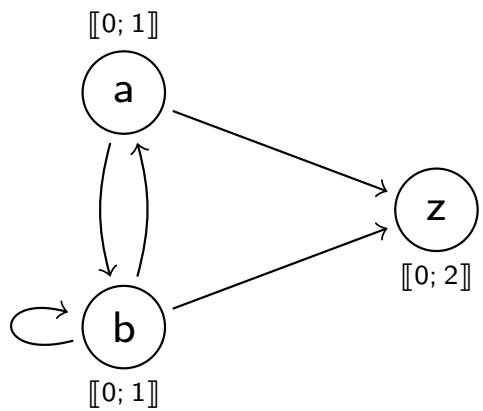

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- Signs and thresholds on the edges $a \xrightarrow{+1} z$

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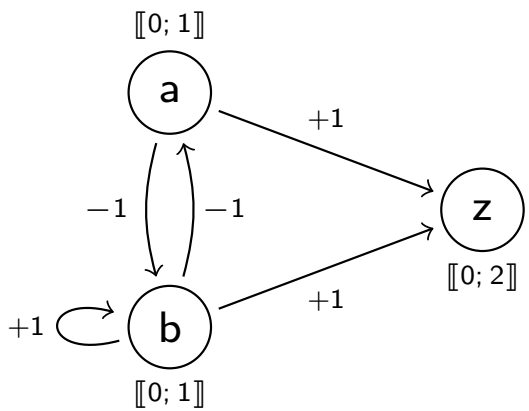
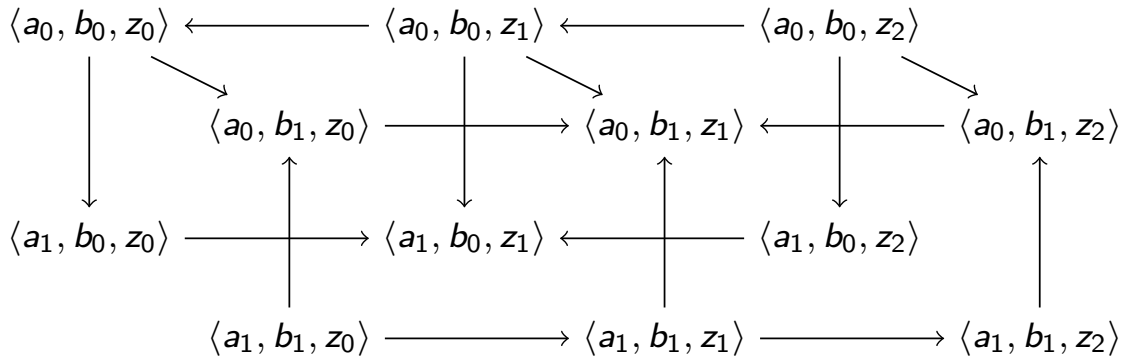


Analysis of Thomas Modeling

The State graph is computed in a unitary and asynchronous fashion



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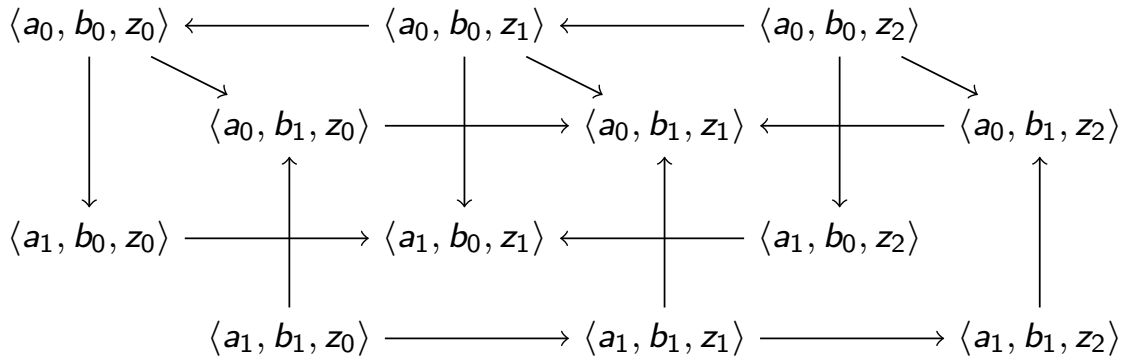

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Some works all to link the structure of the model and some dynamic properties:

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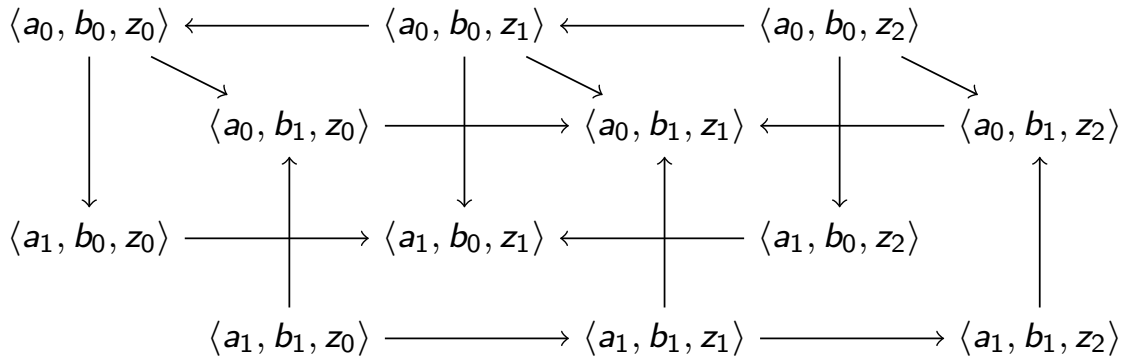

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But reachability properties require to compute the whole state graph:
Example: From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?

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

Standard Process Hitting

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

Standard Process Hitting is:

- Well-adapted to the modeling of BRNs
- An **atomistic and qualitative** modeling (explicit & discrete expression levels)
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Several missing features:

- Faulty representation **cooperations**
- **Possible enrichment** of the expressivity
  → Which requires to adapt the previous tools

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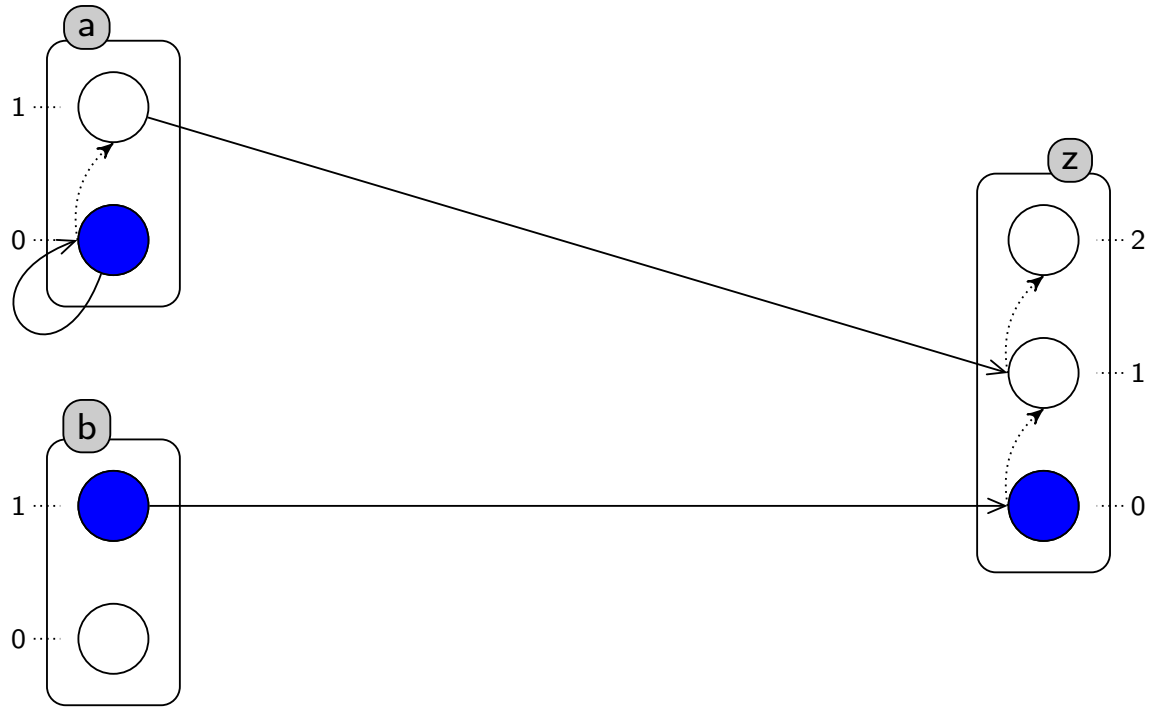

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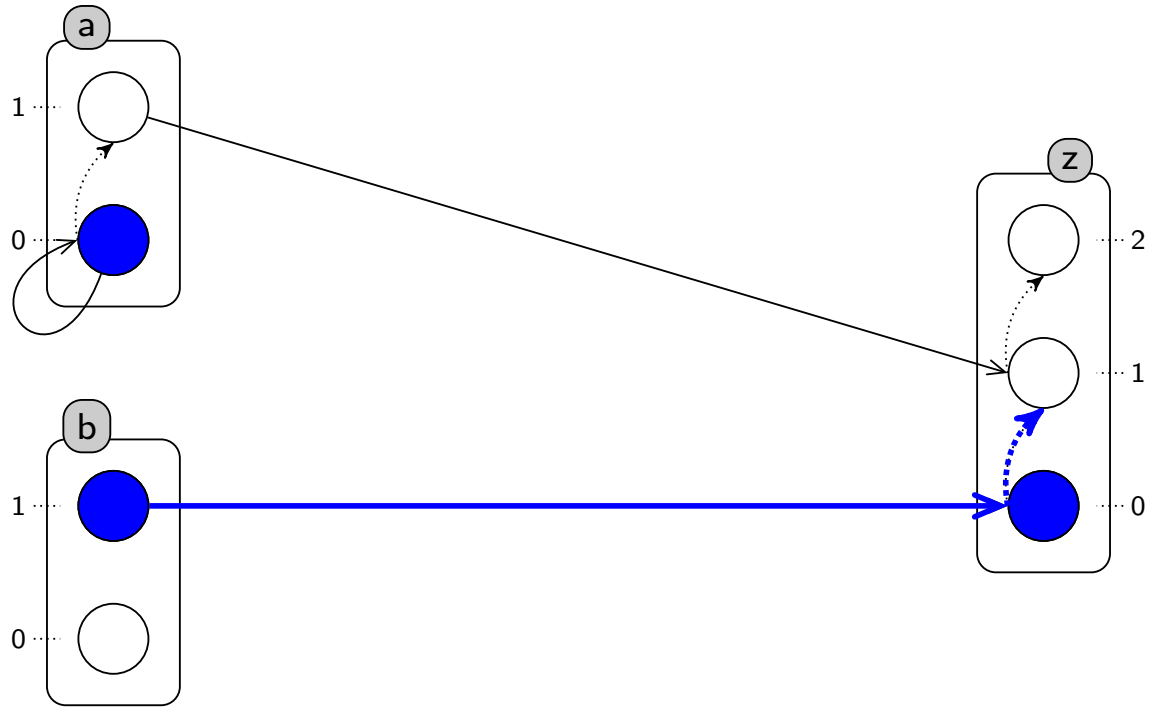

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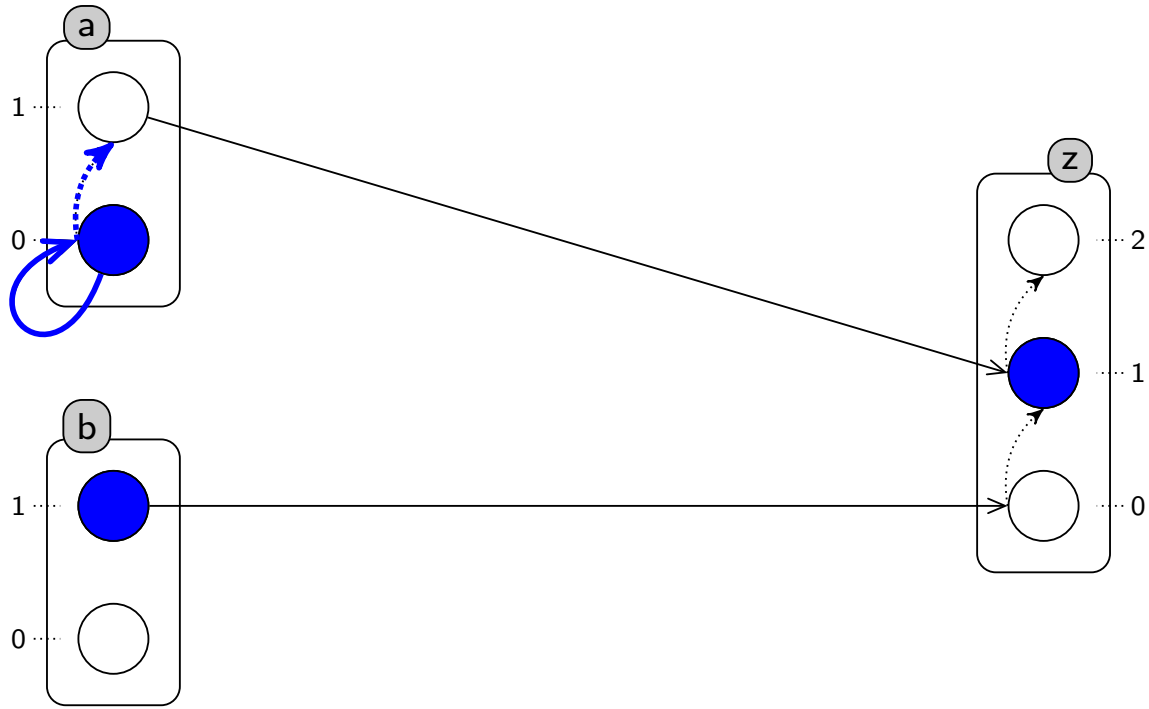

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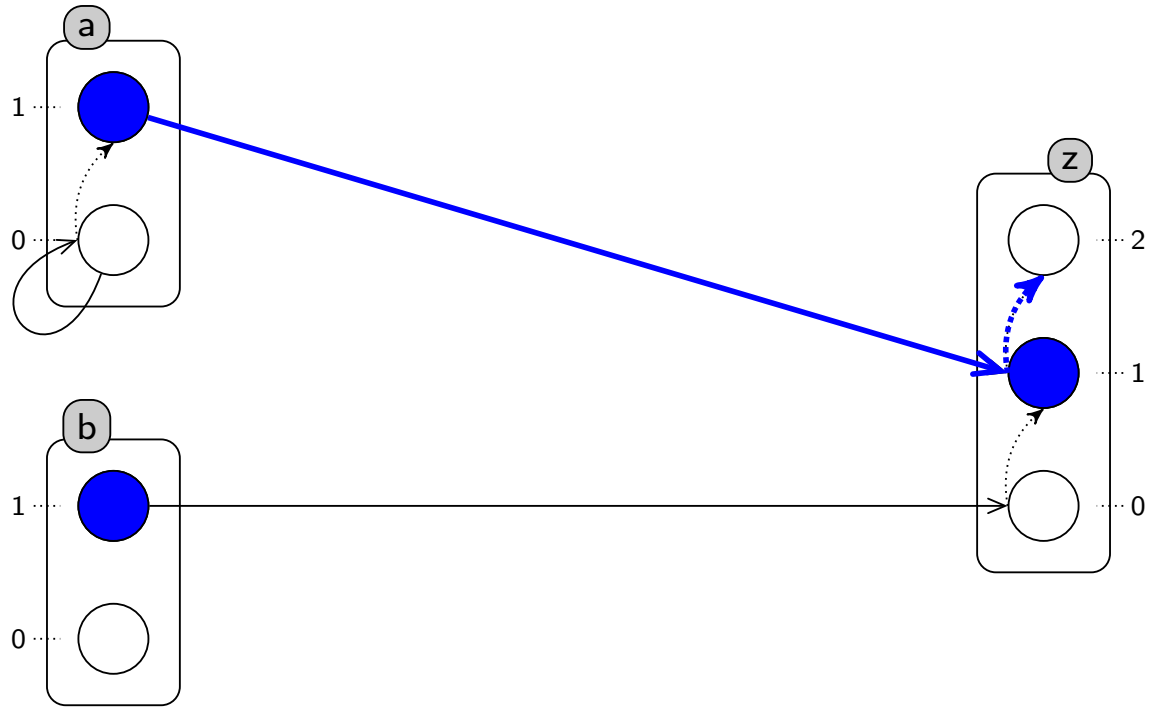

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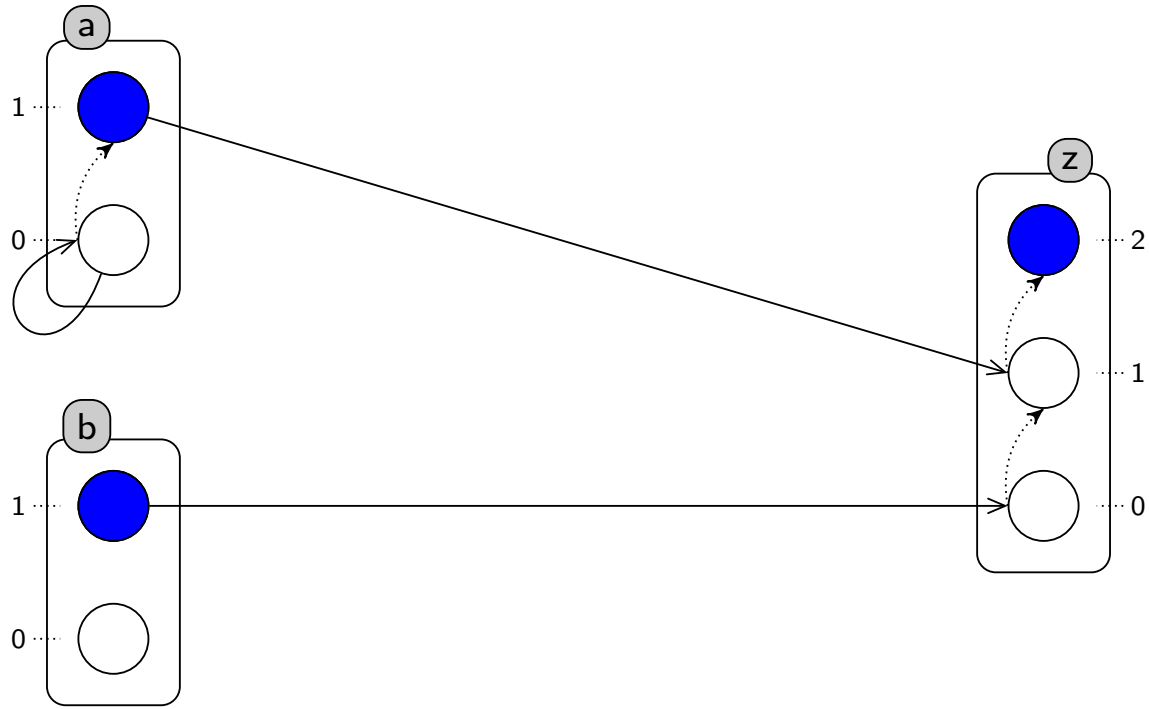

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Cooperations

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Cooperation between a_1 and b_1: $\underline{a_1 \wedge b_1} \rightarrow z_0 \uparrow z_1$

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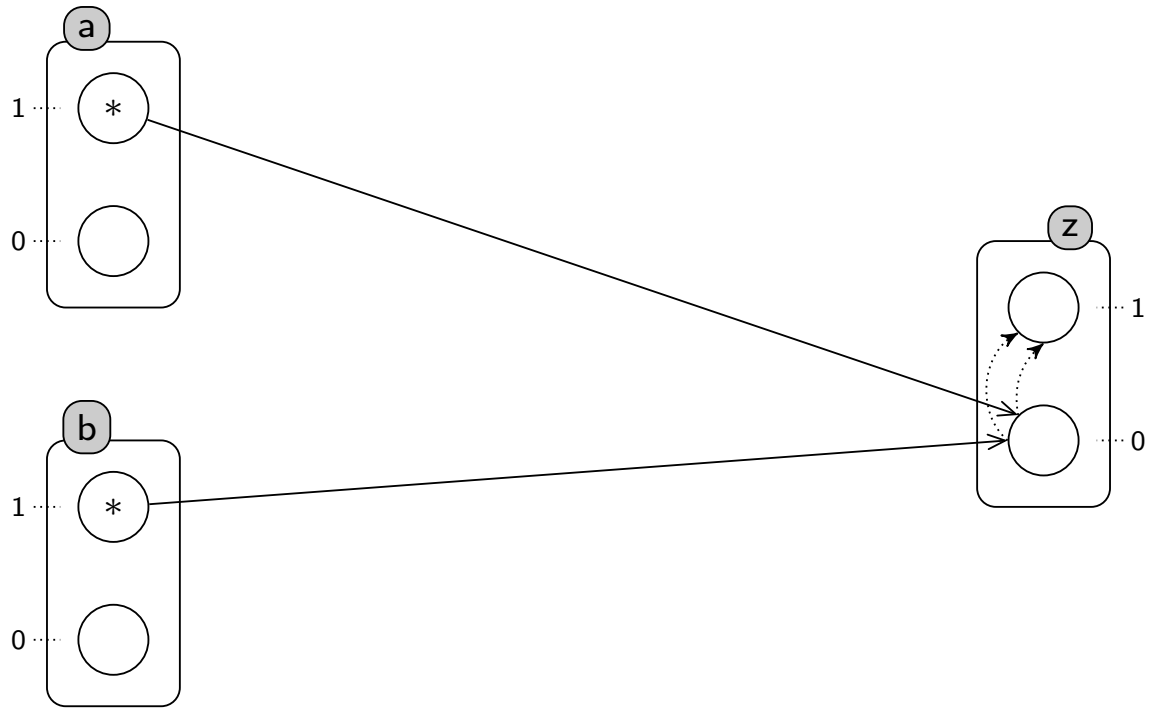

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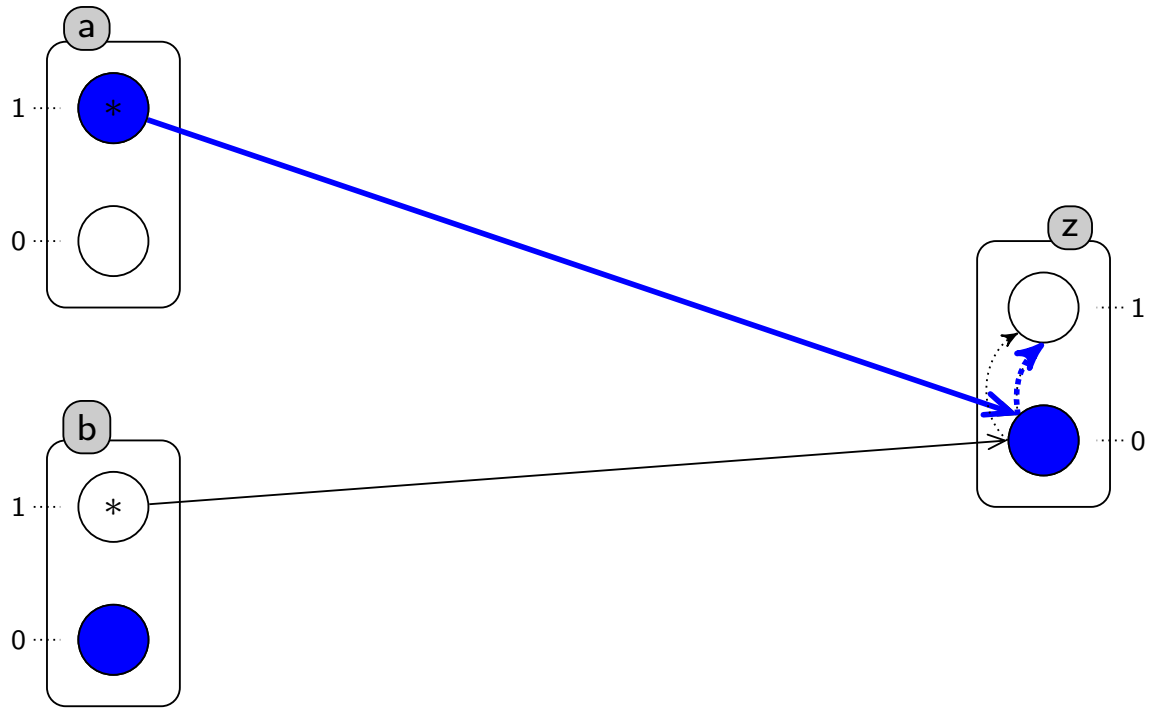

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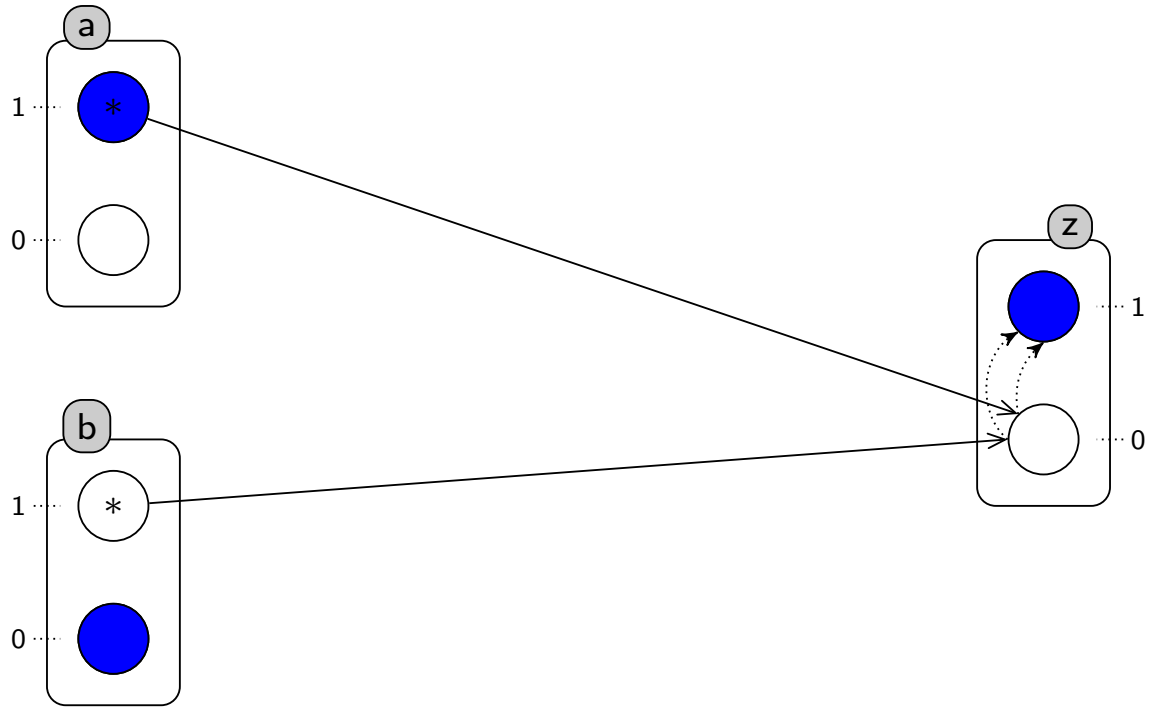

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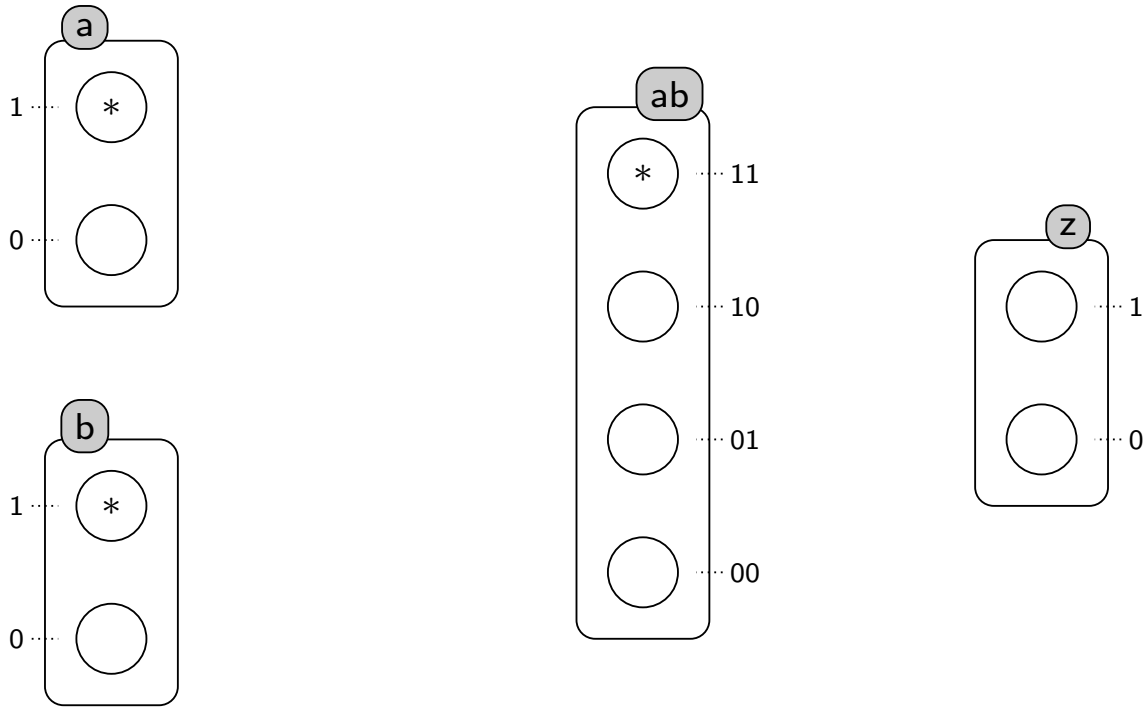

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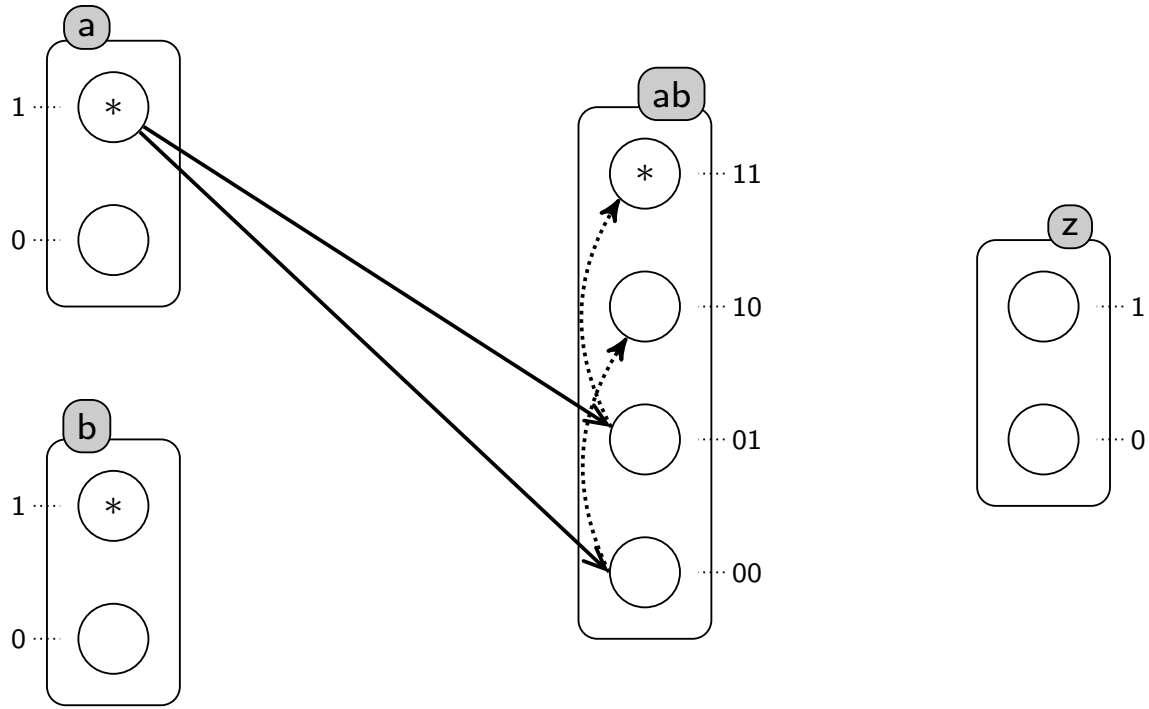

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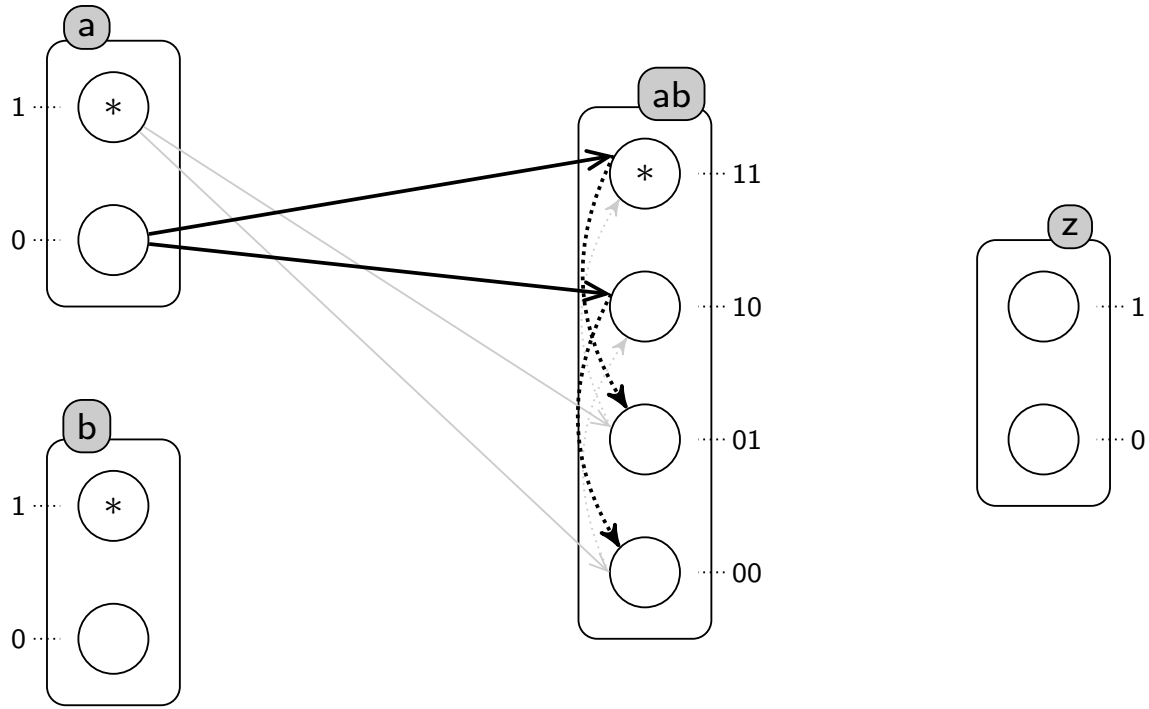

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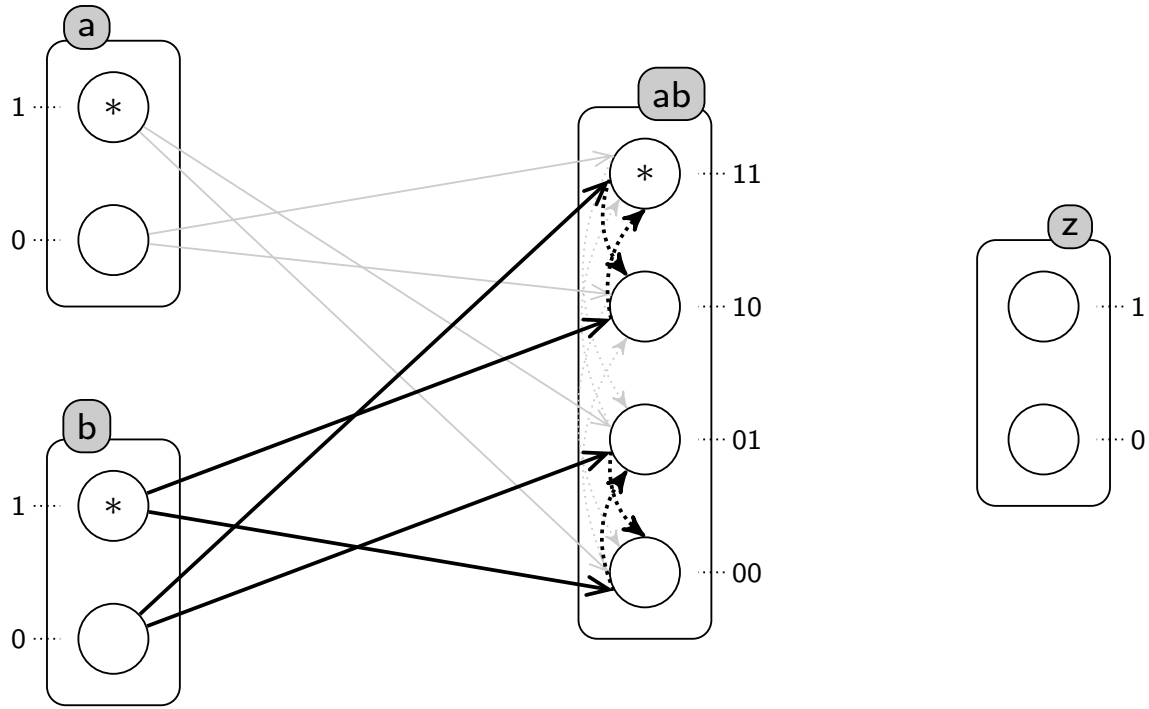

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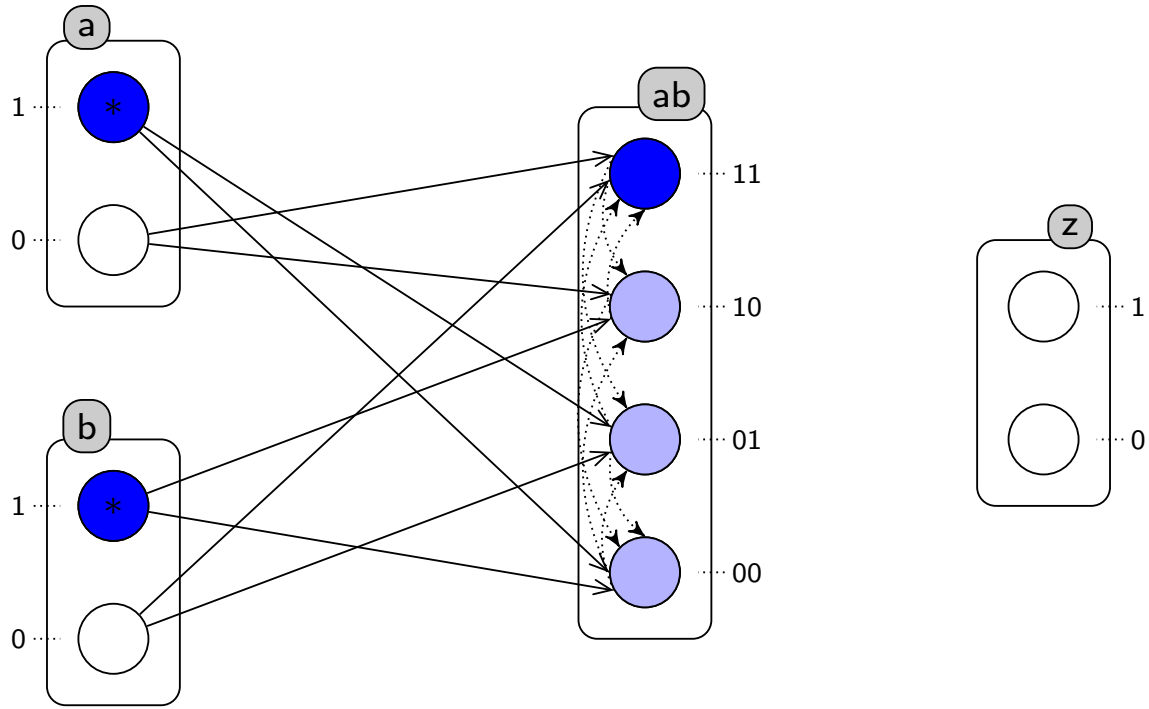

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Each configuration is represented by one process $\underline{a_1 \wedge b_1} \Rightarrow ab_{11}$

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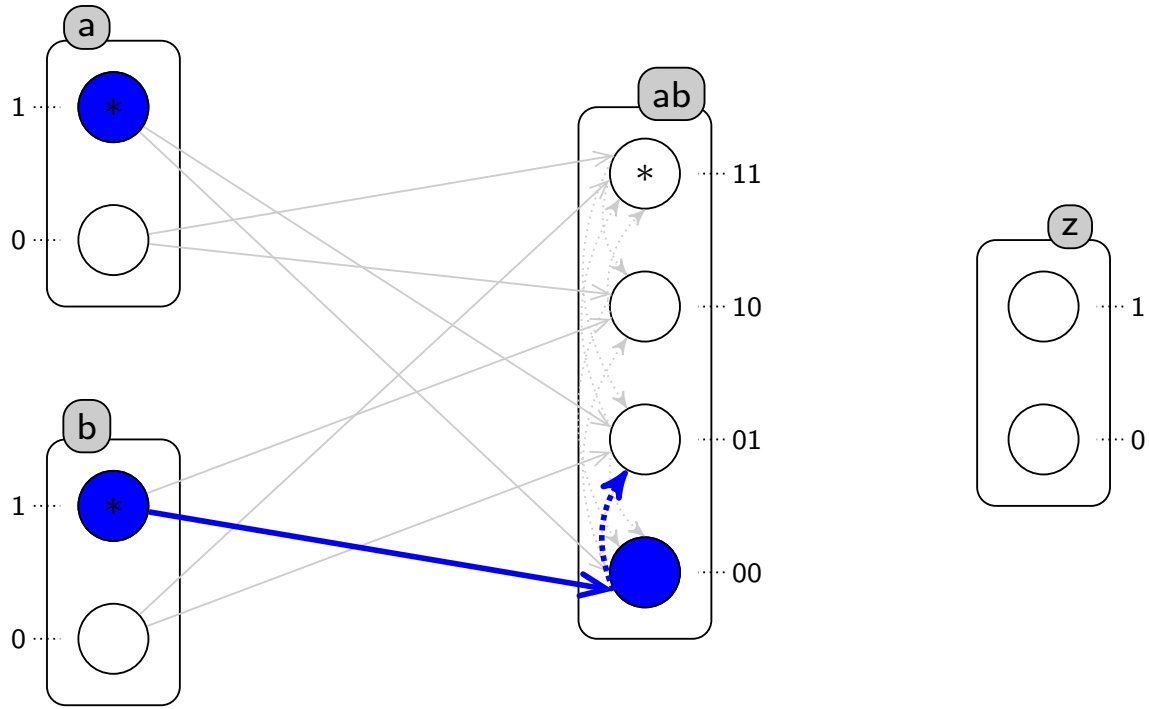

Cooperation between a_1 and b_1: $\underline{a_1 \wedge b_1} \rightarrow z_0 \uparrow z_1$

Solution: a **cooperative sort** ab to express $\underline{a_1 \wedge b_1}$

Each configuration is represented by one process $\underline{a_1 \wedge b_1} \Rightarrow ab_{11}$

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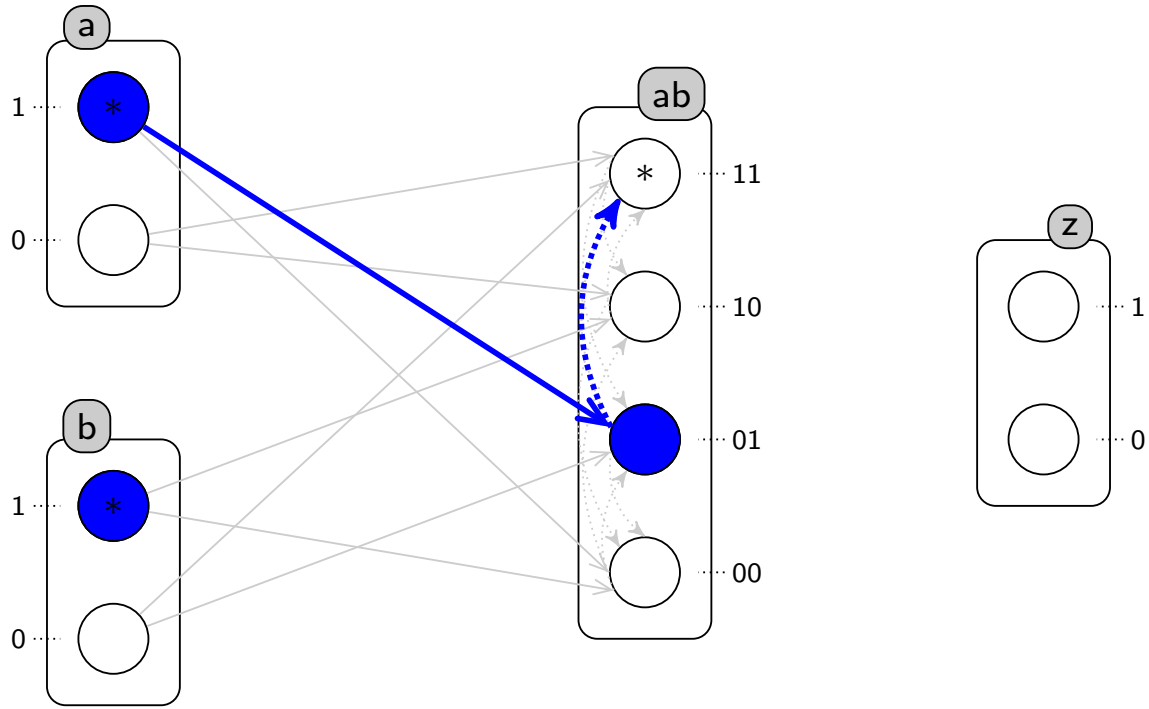

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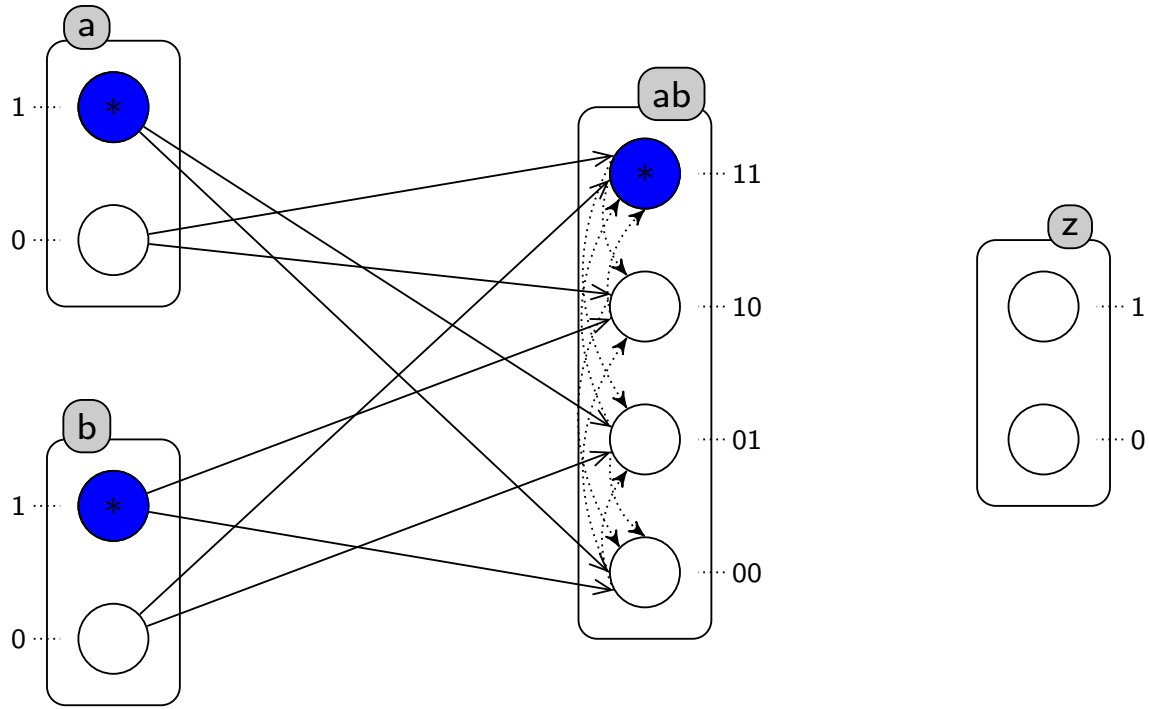

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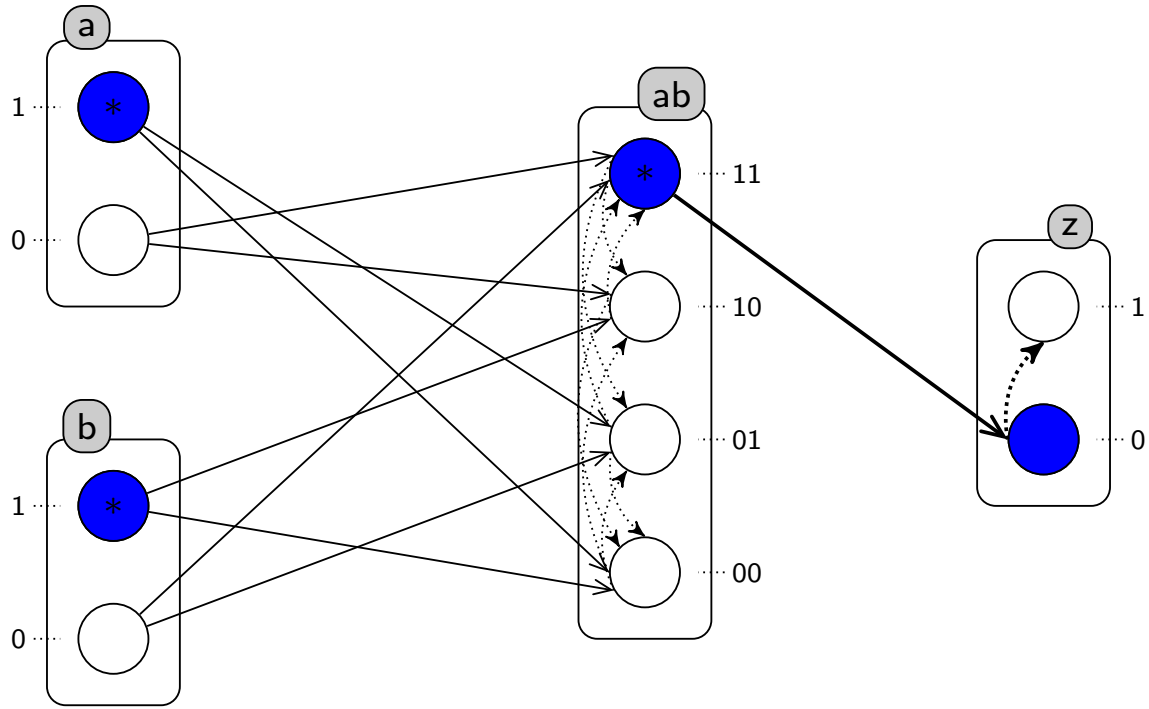

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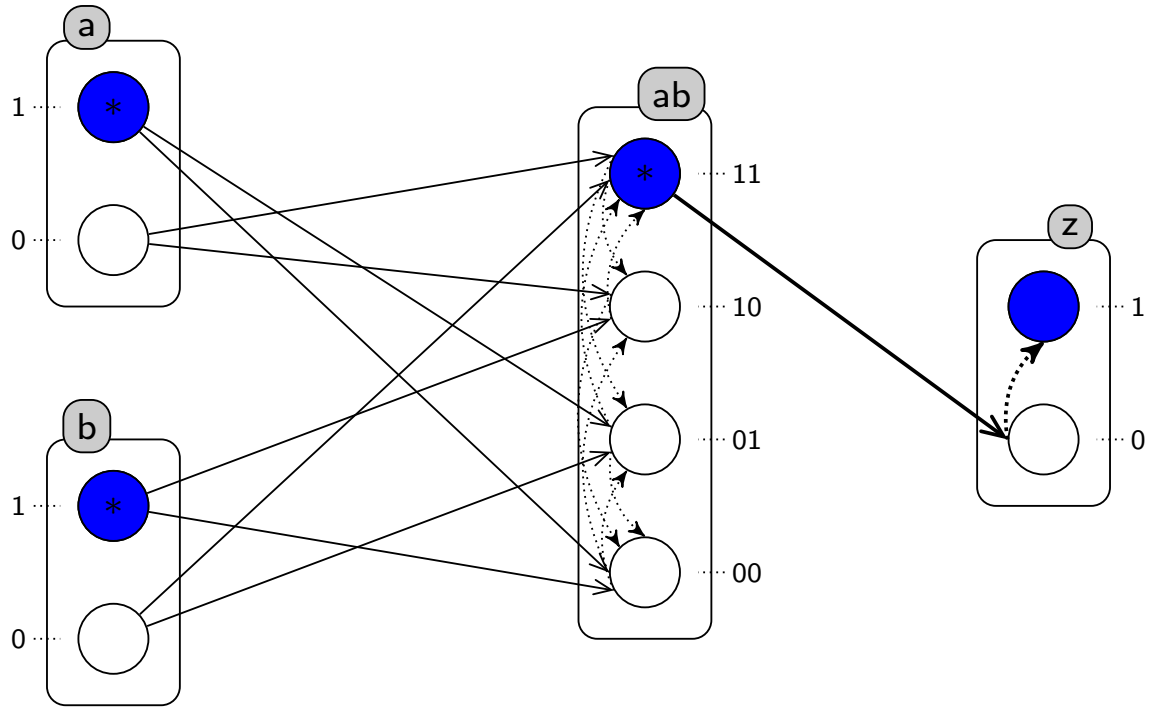

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Approximations for the Reachability Analysis

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

Check reachability properties:

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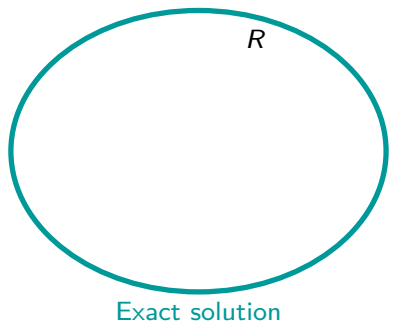

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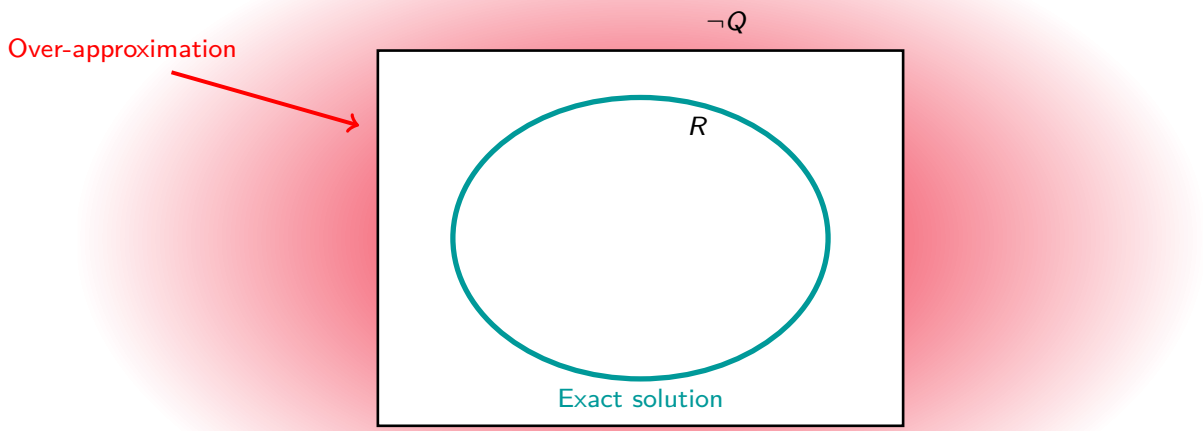

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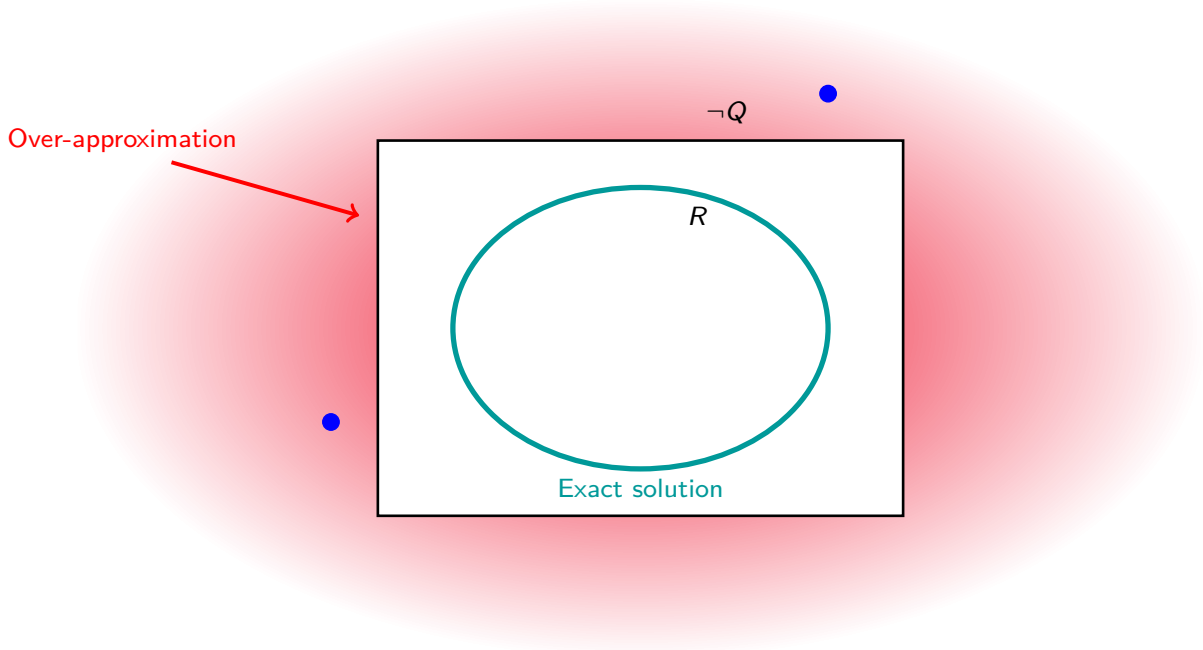

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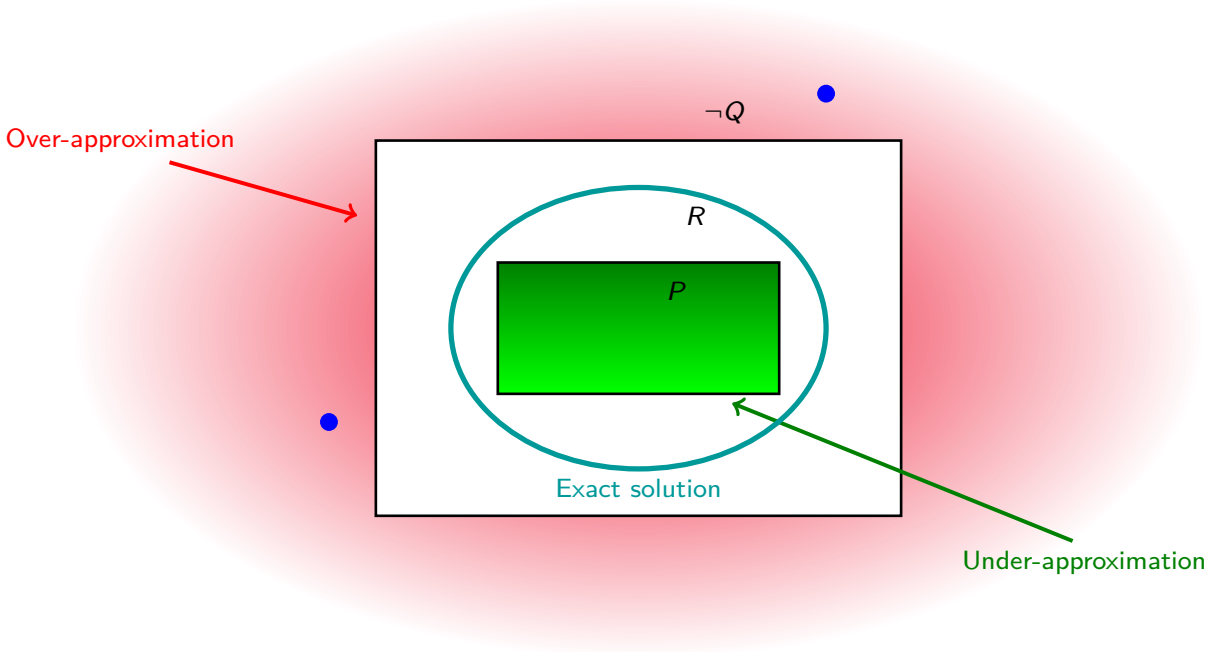

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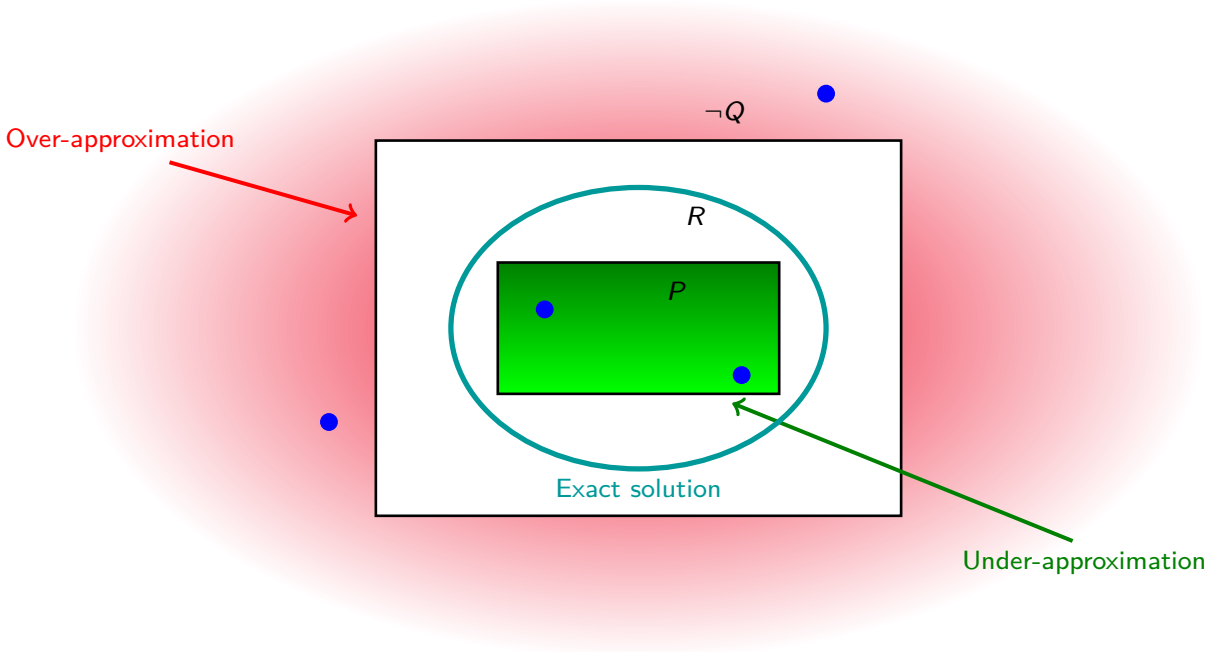

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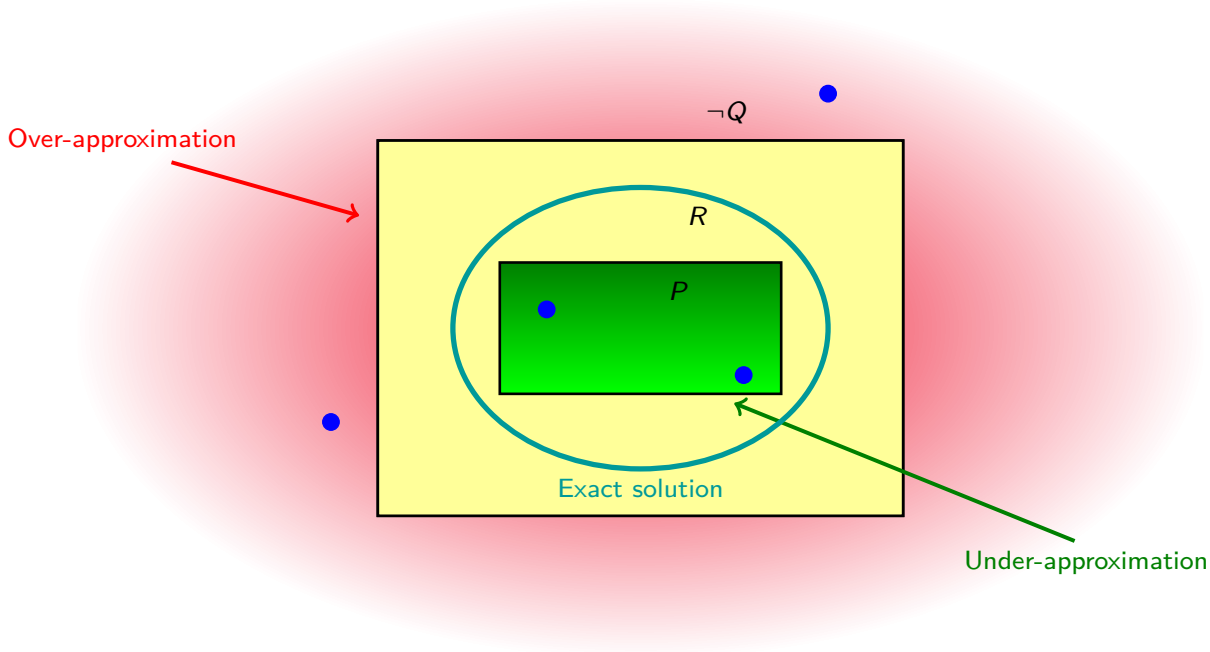

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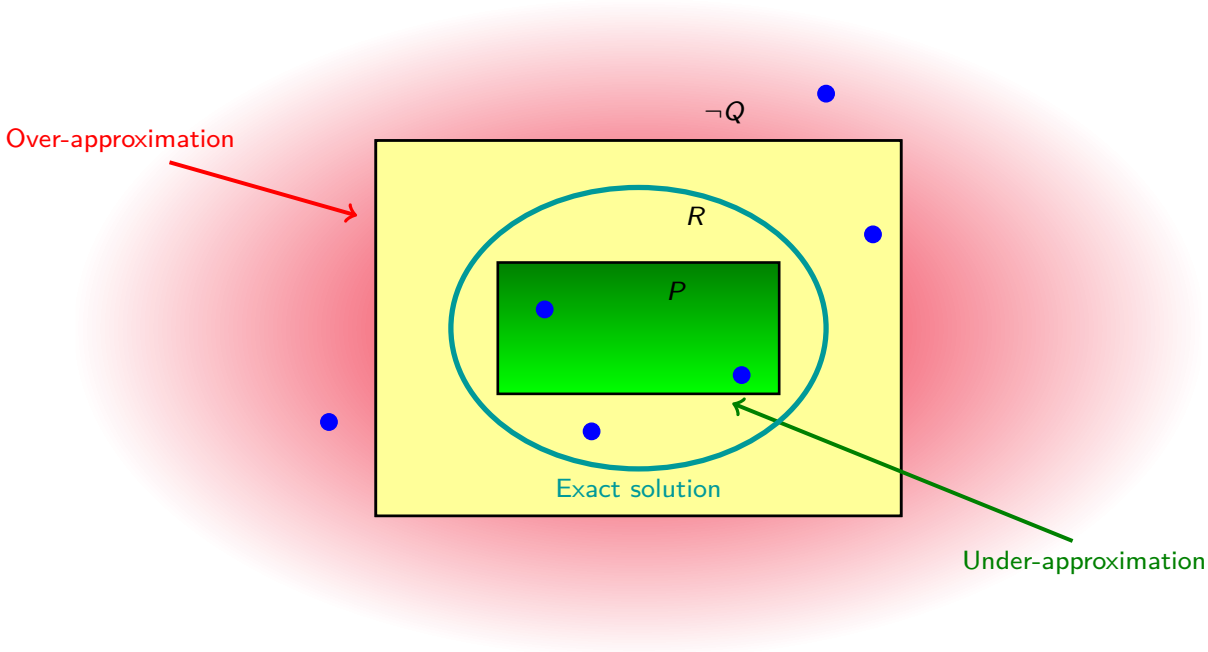

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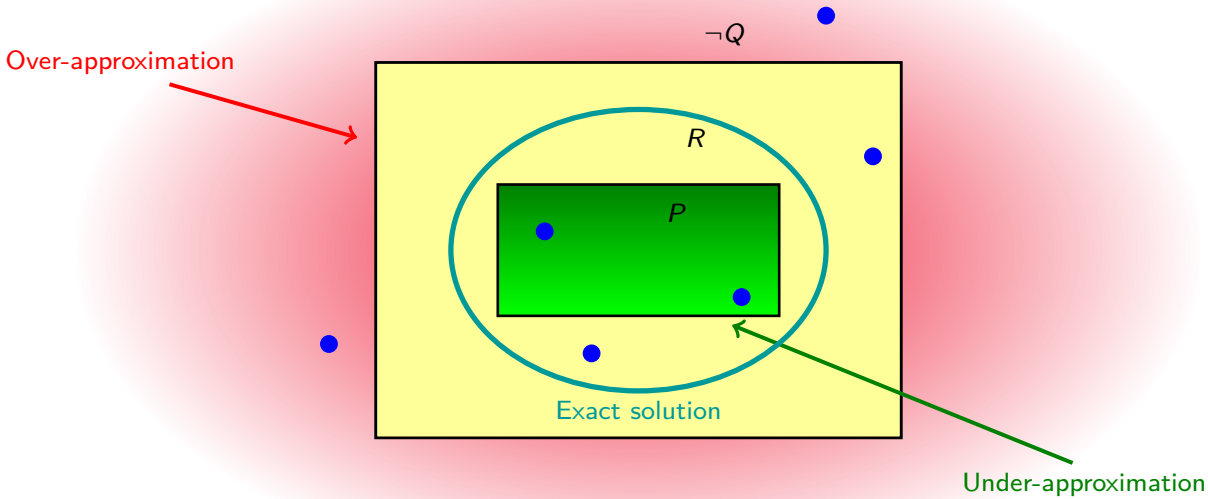
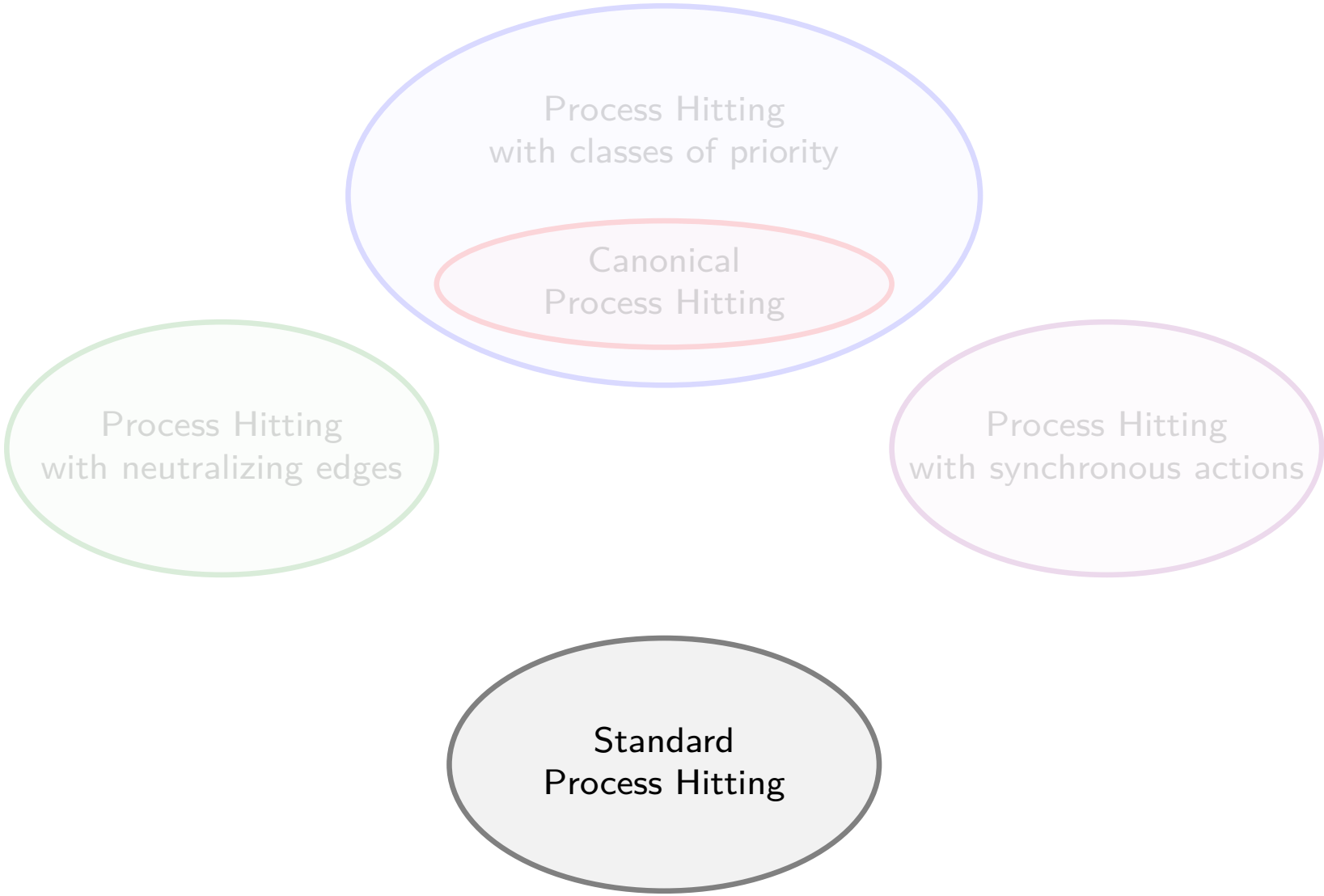


Polynomial complexity in the number of sorts
Exponential complexity in the number of processes in each sort

→ Efficient for big models with few expression levels

Standard Process Hitting



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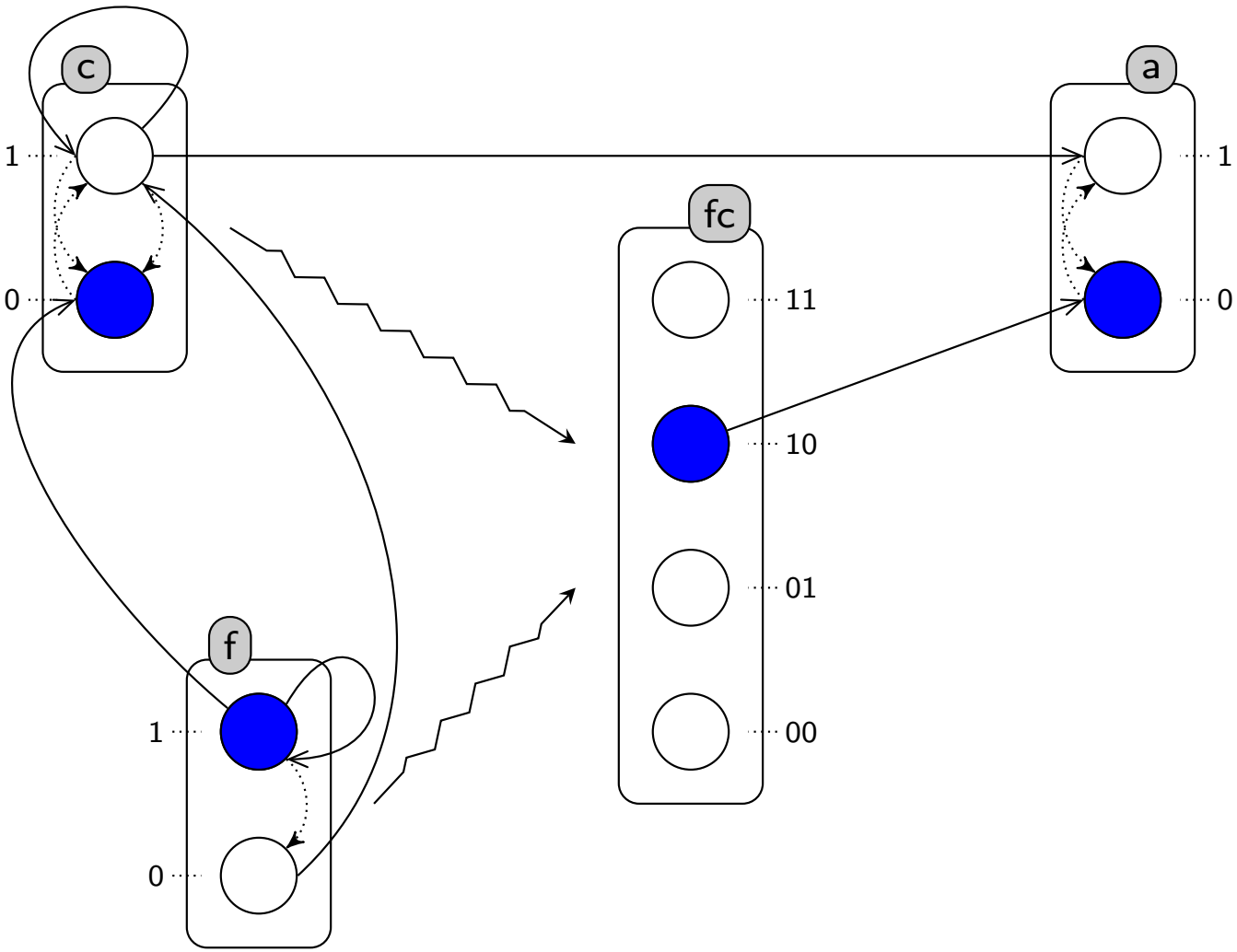

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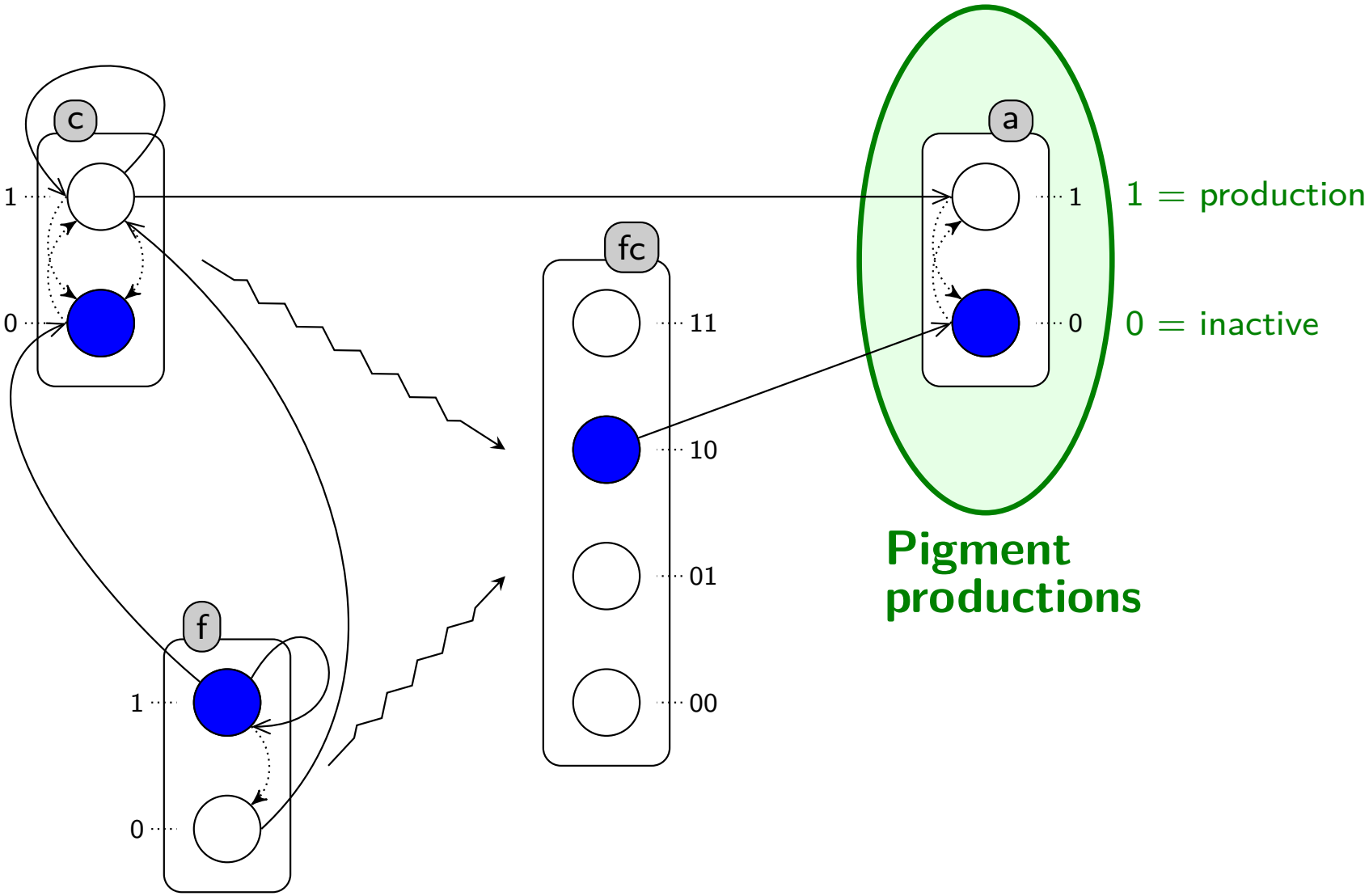

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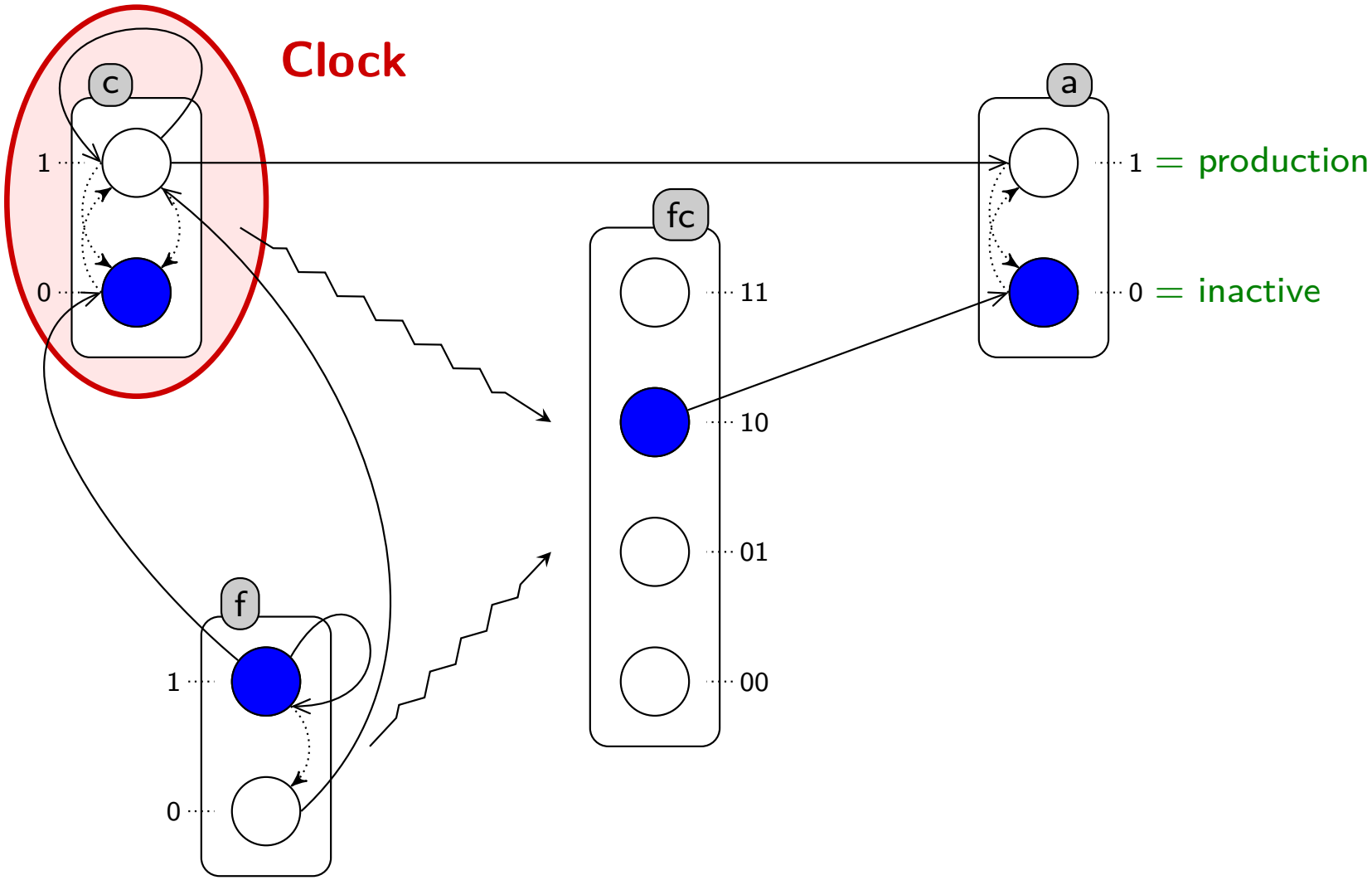

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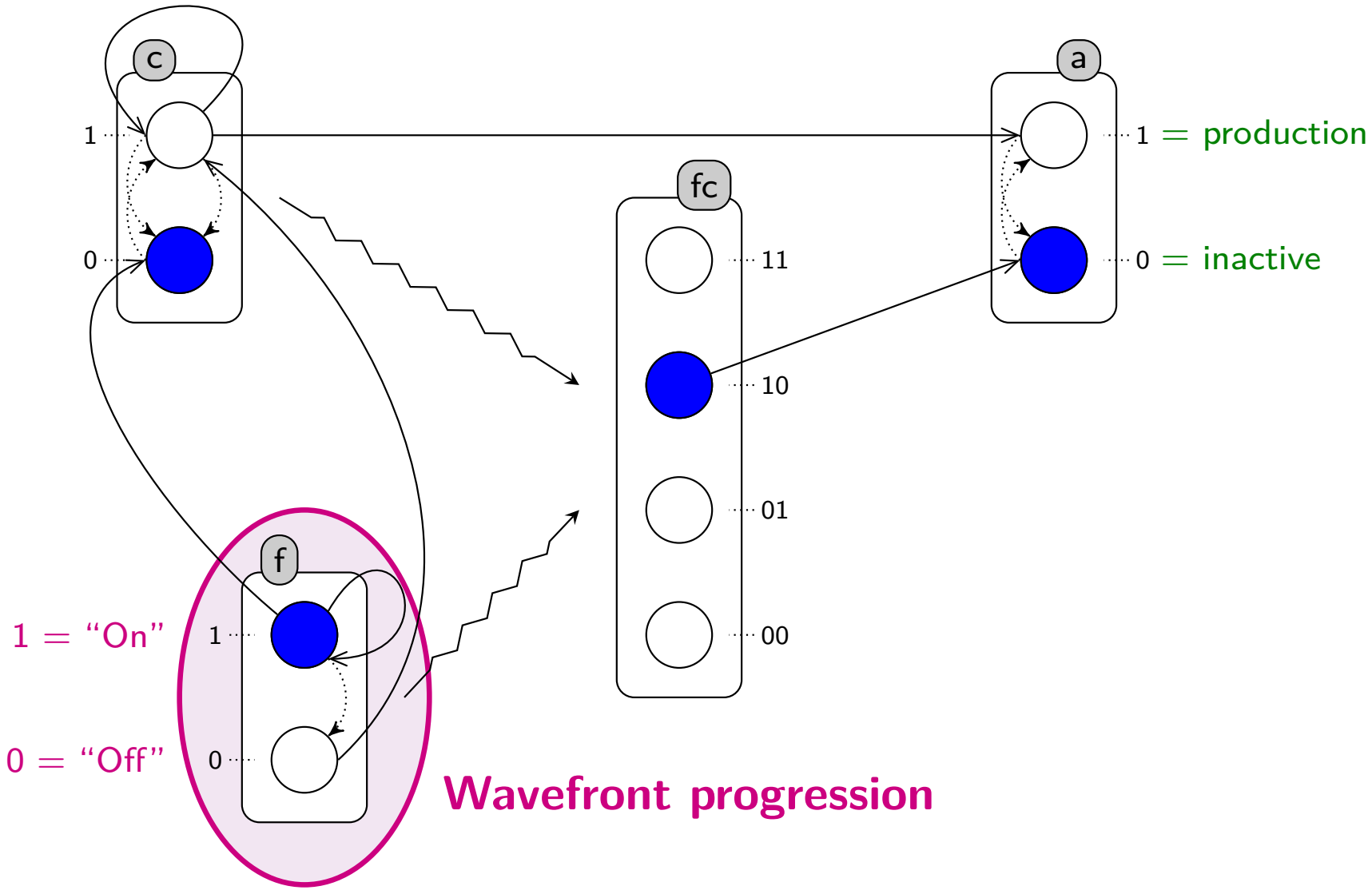

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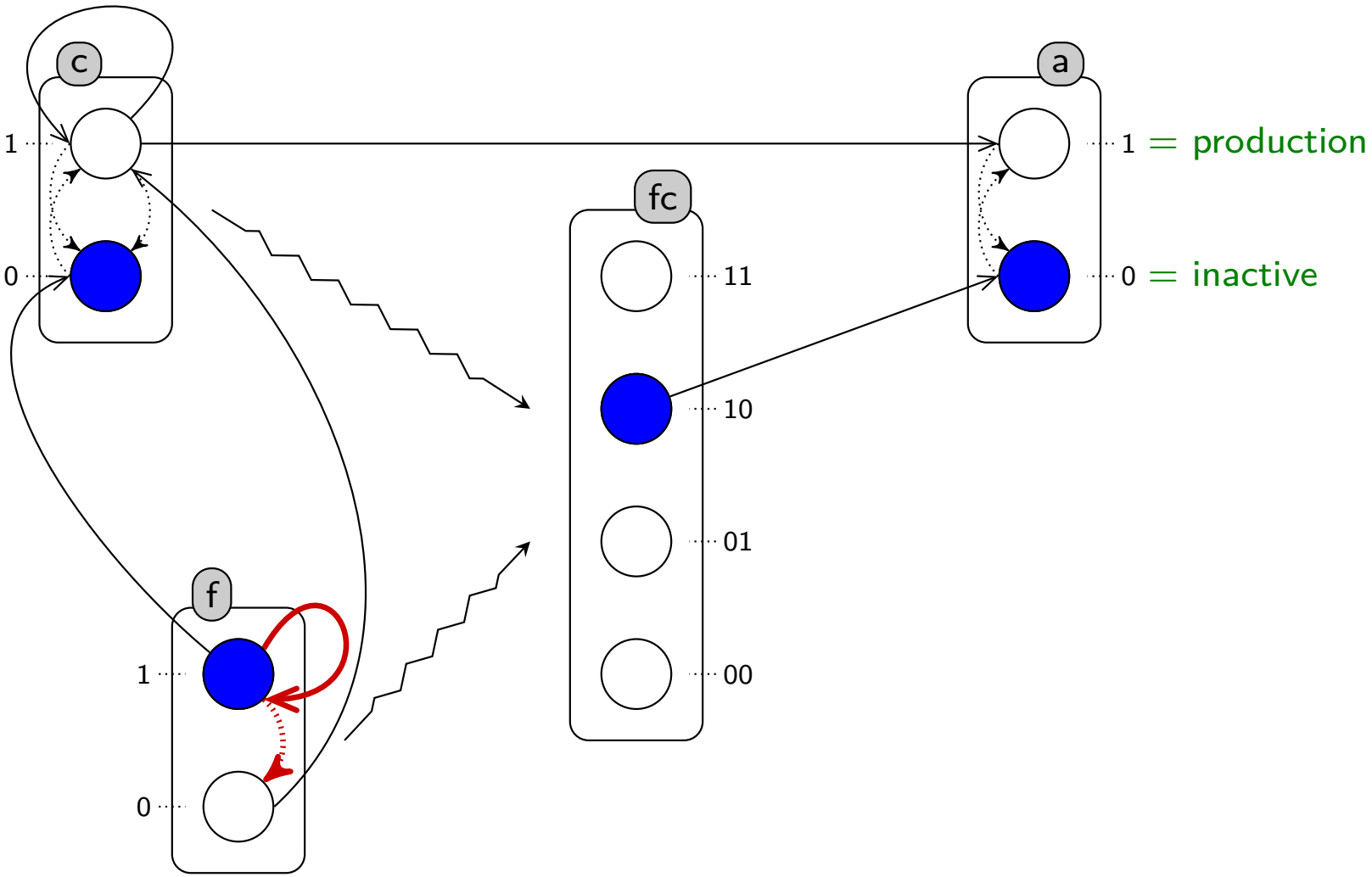

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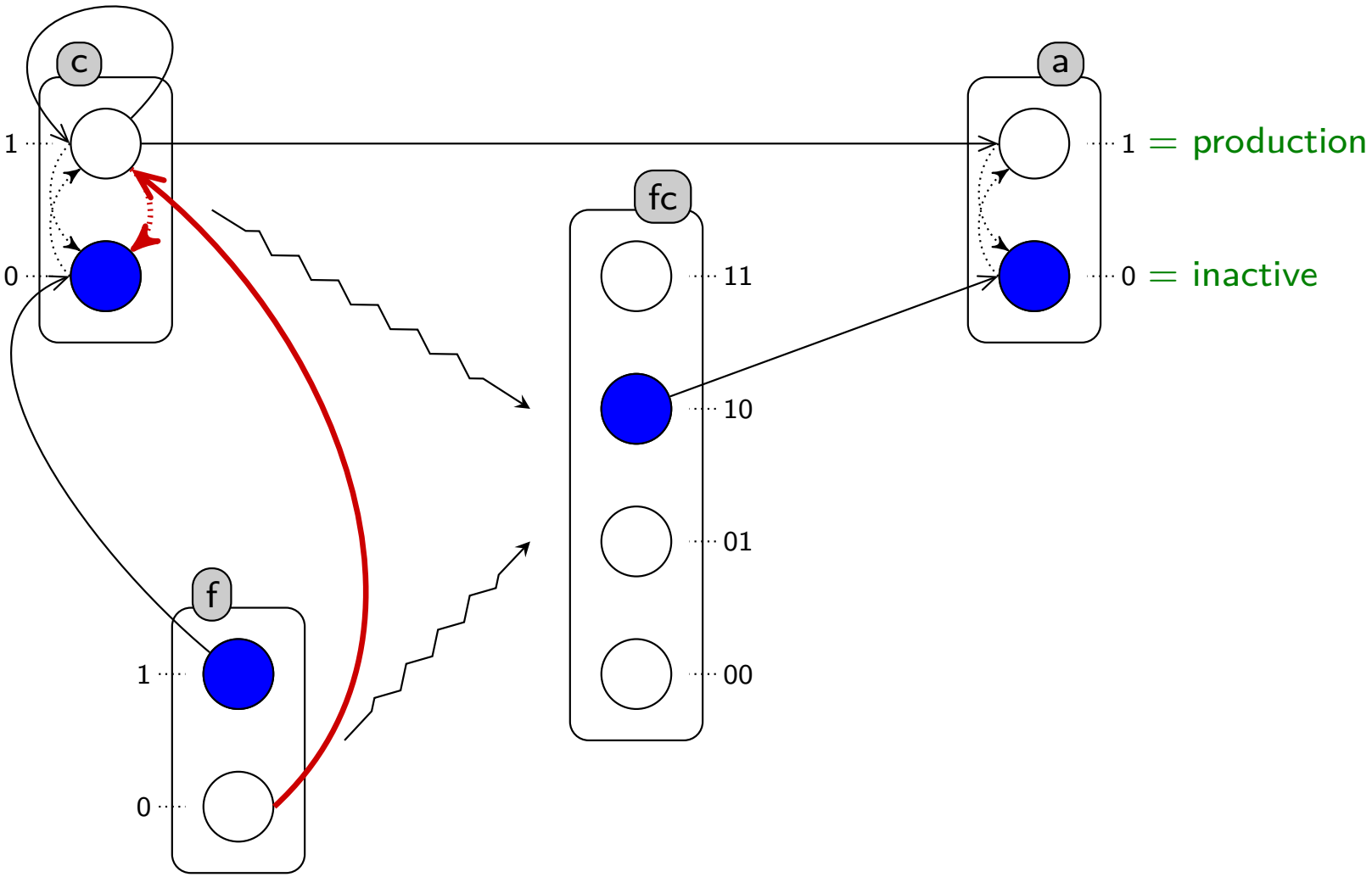

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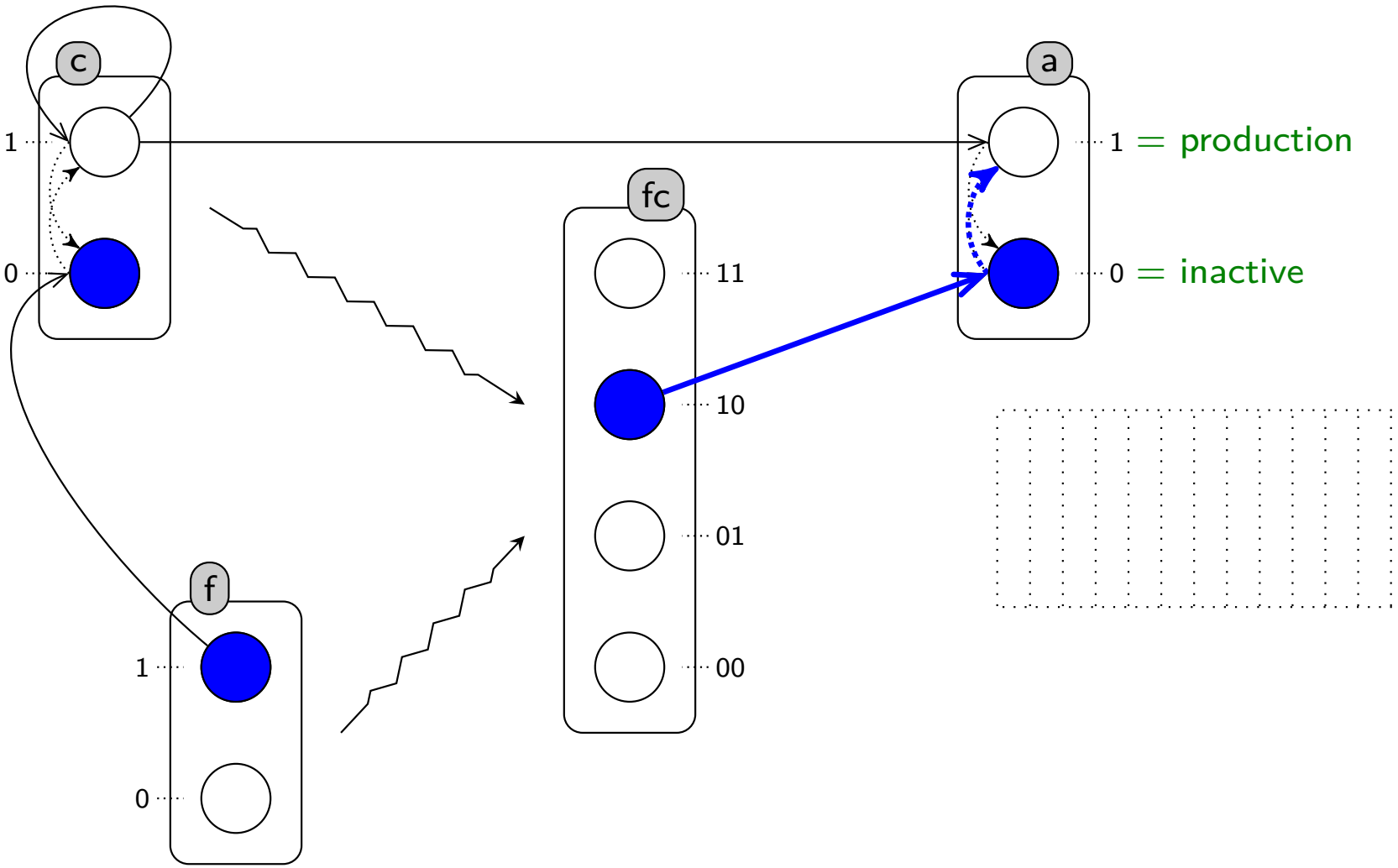

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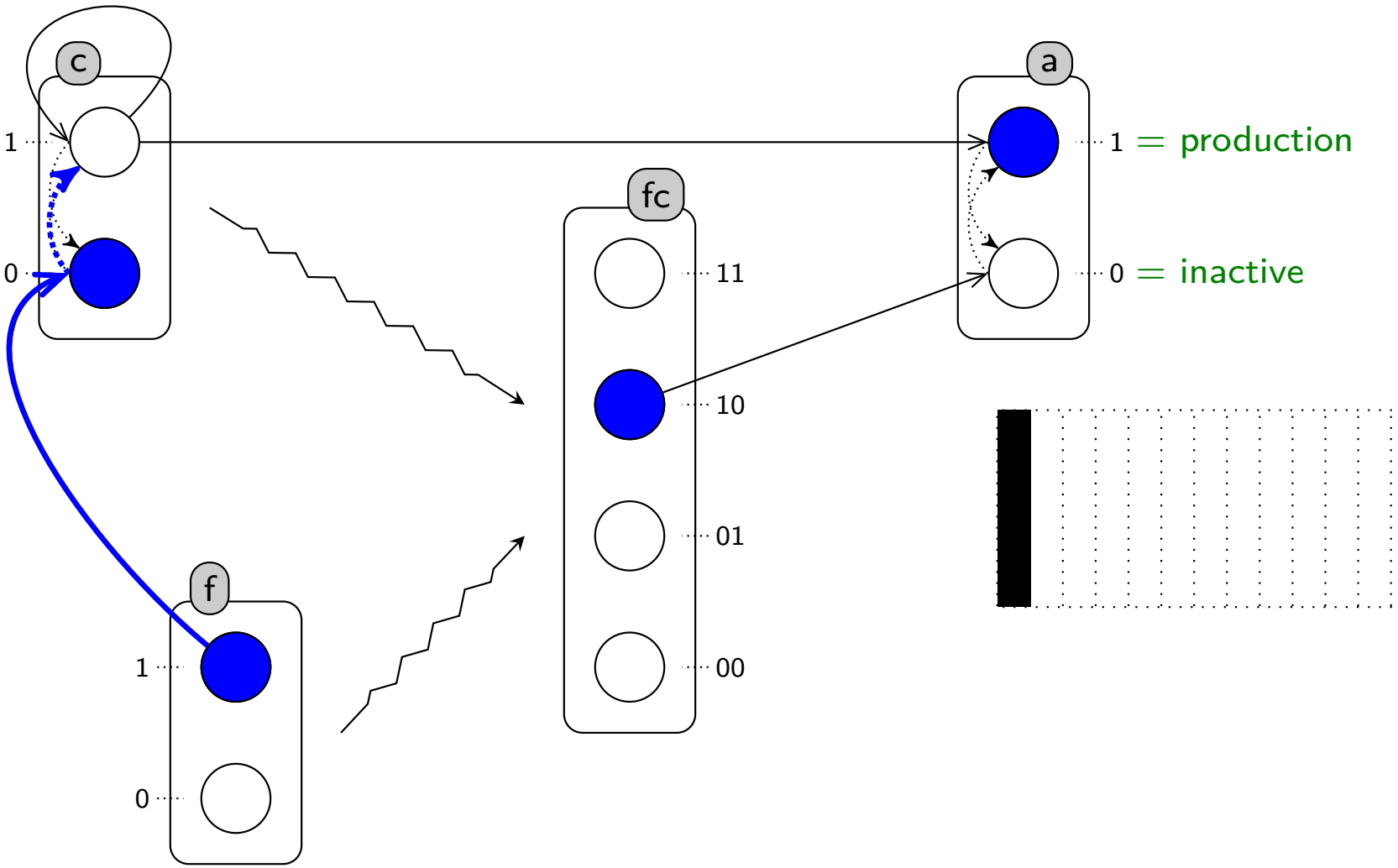

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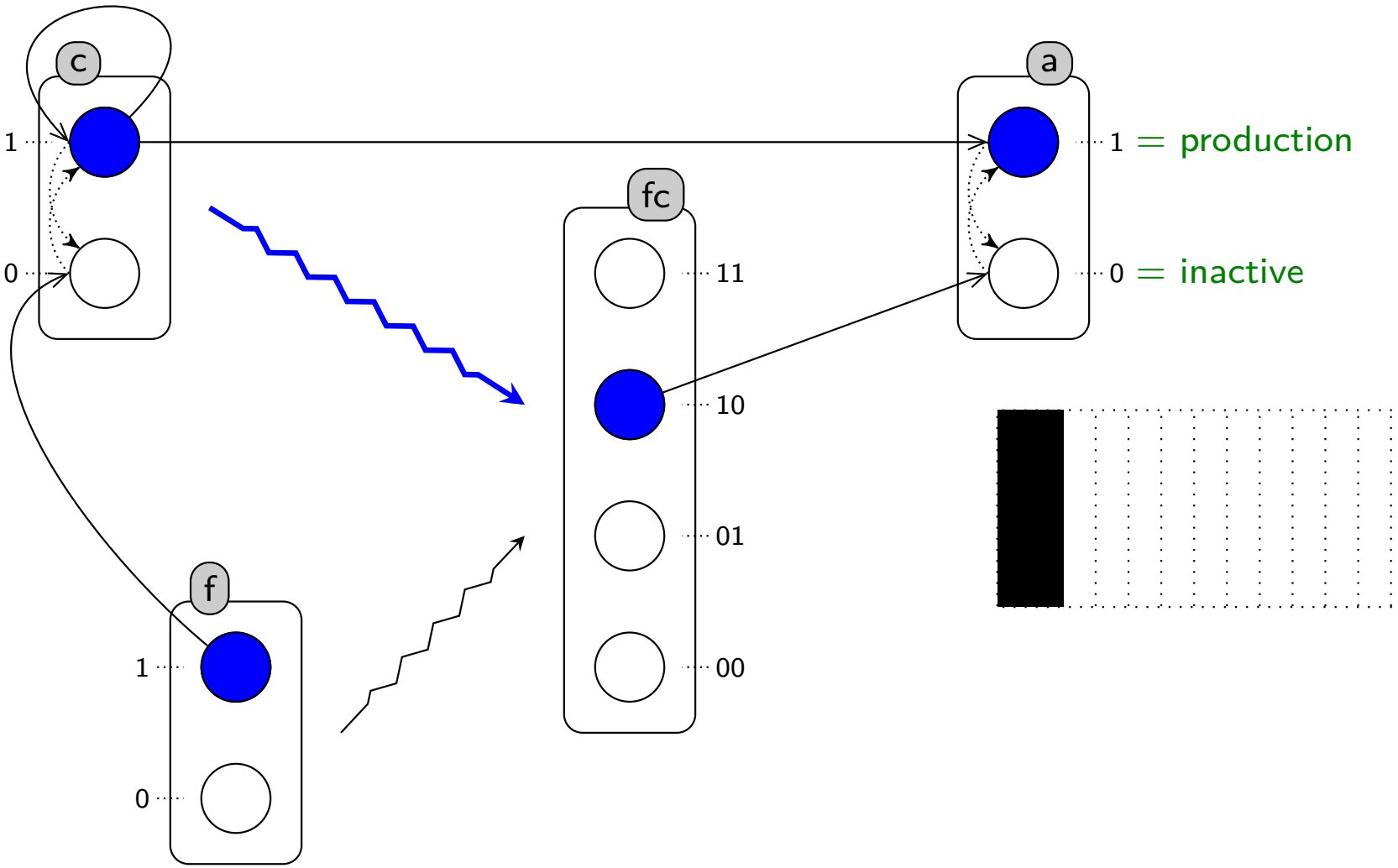

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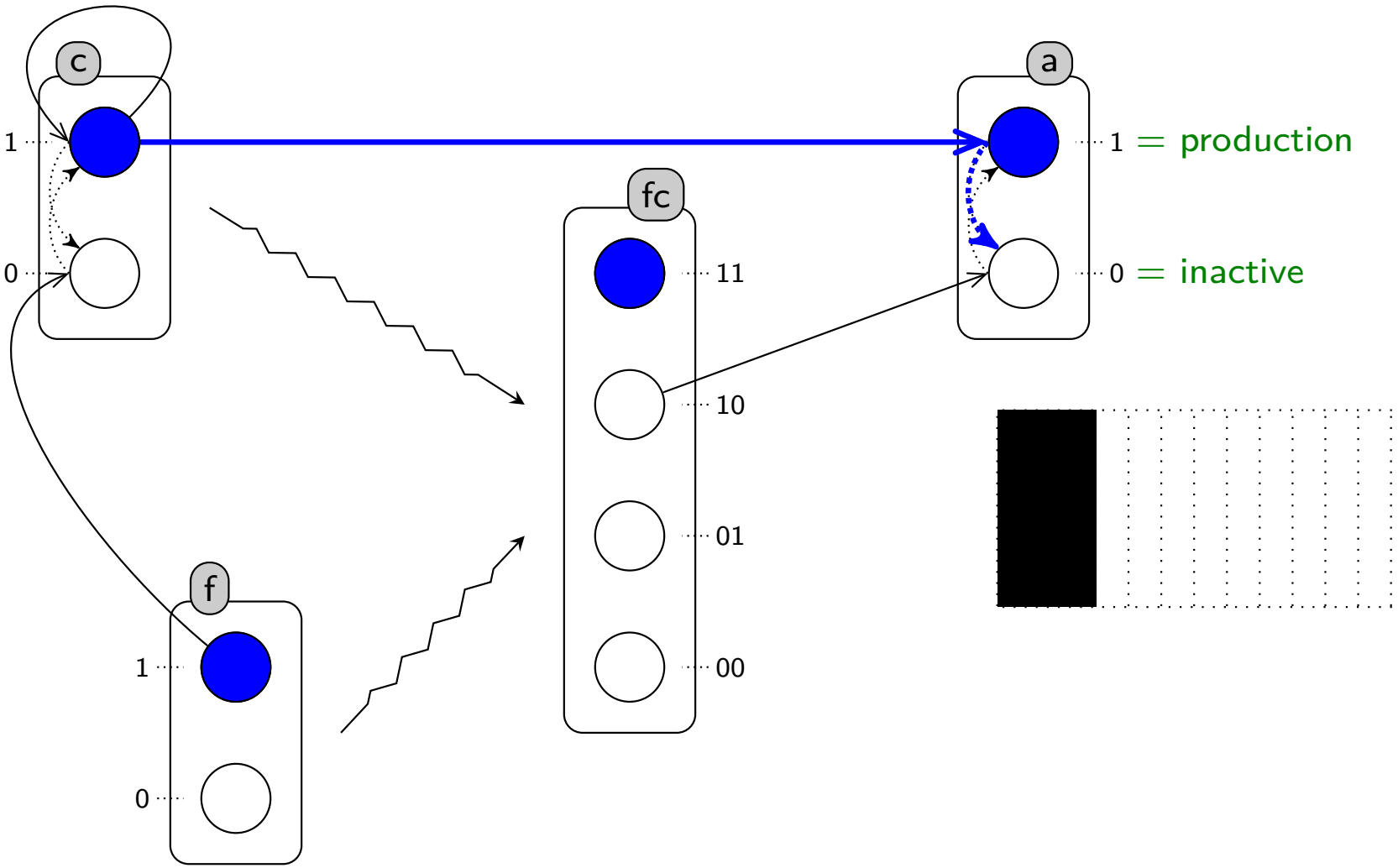

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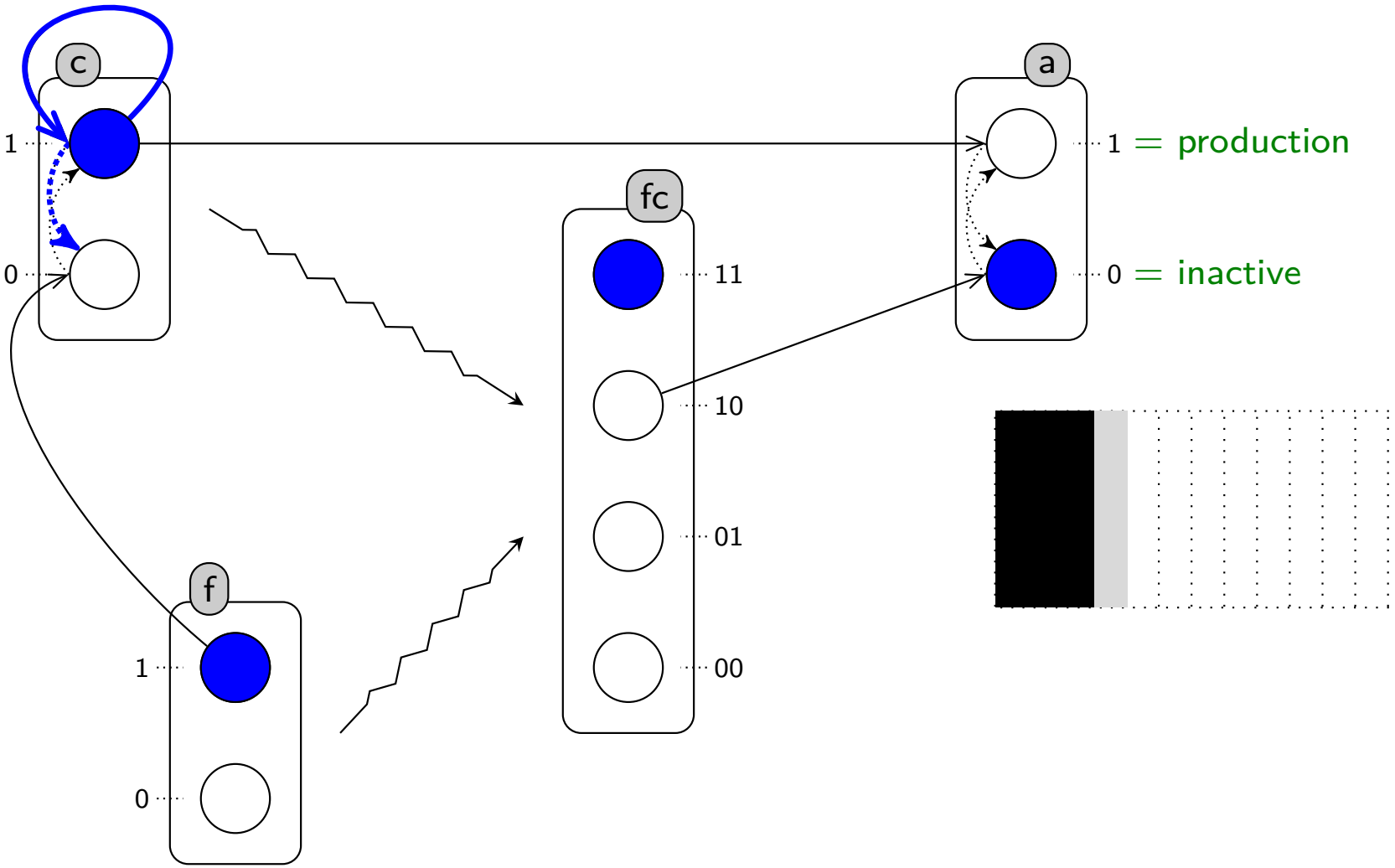

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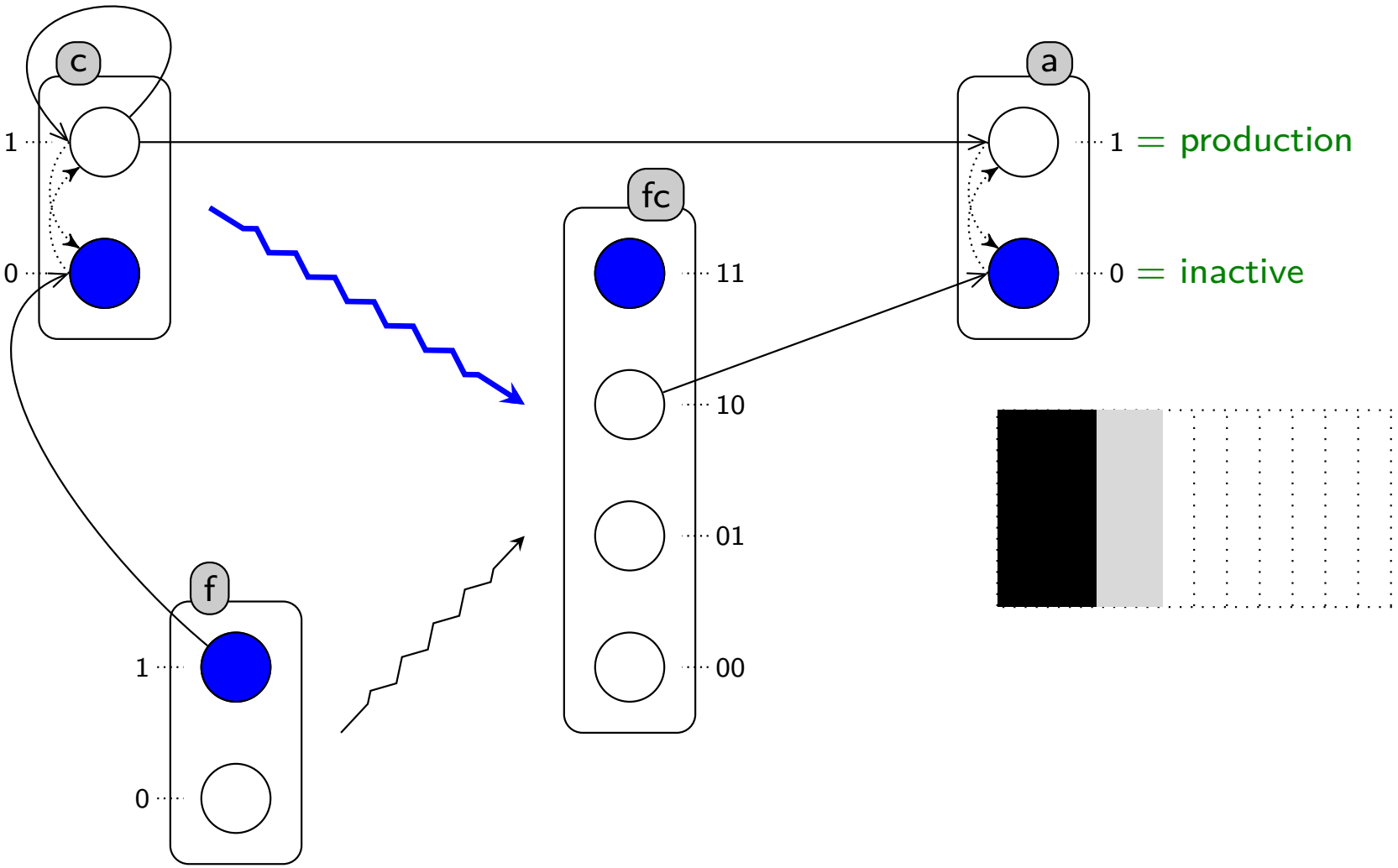

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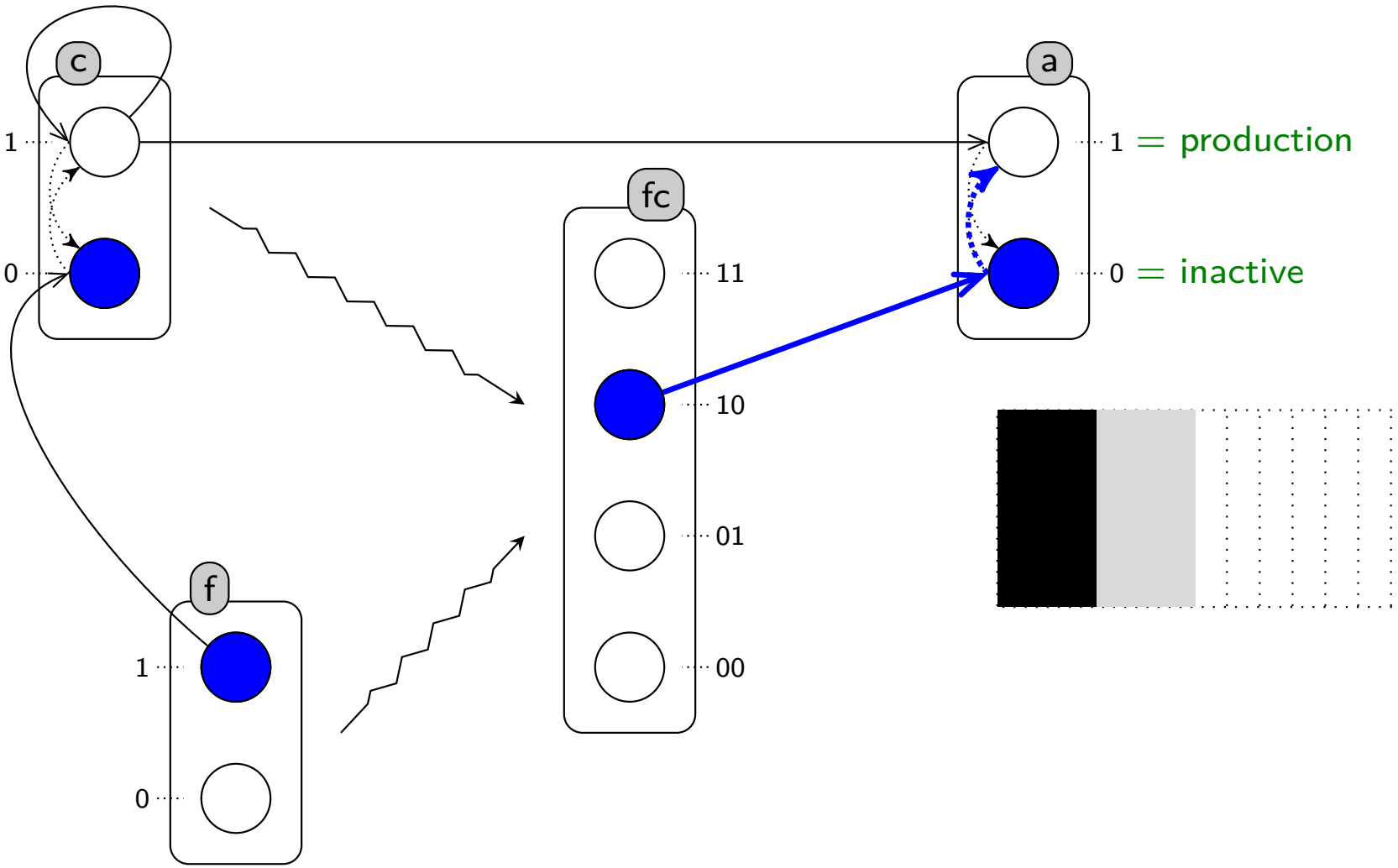

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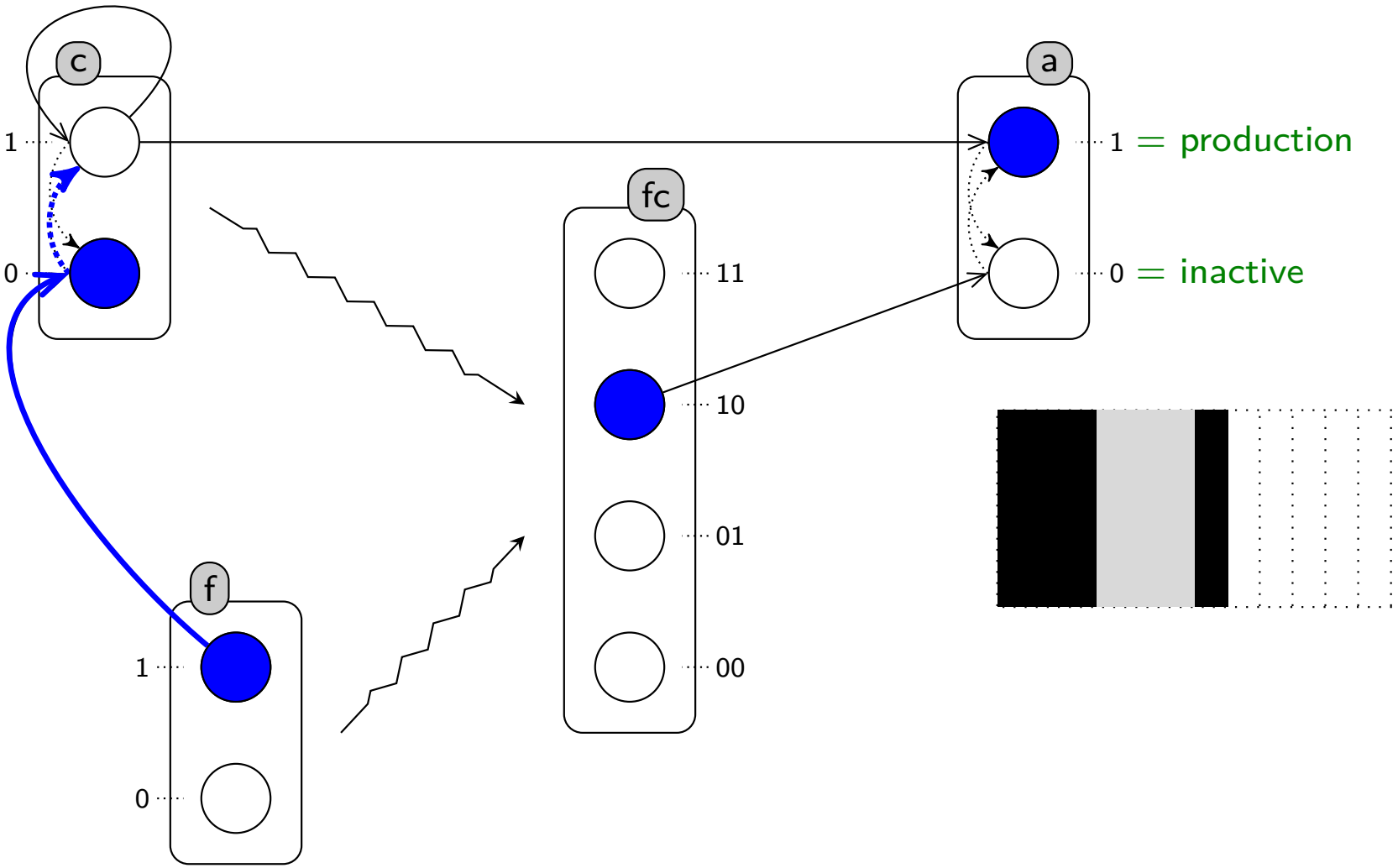

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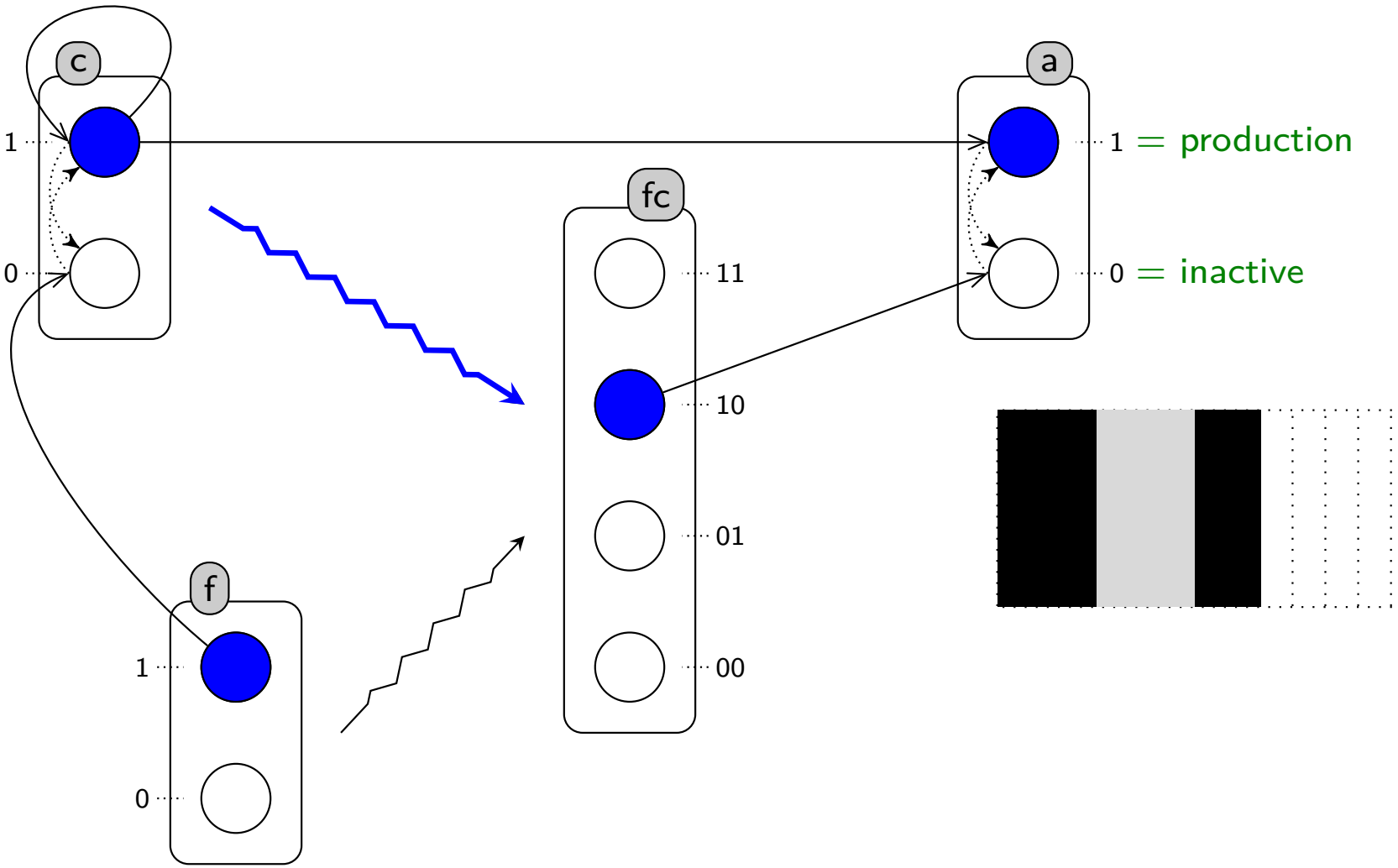

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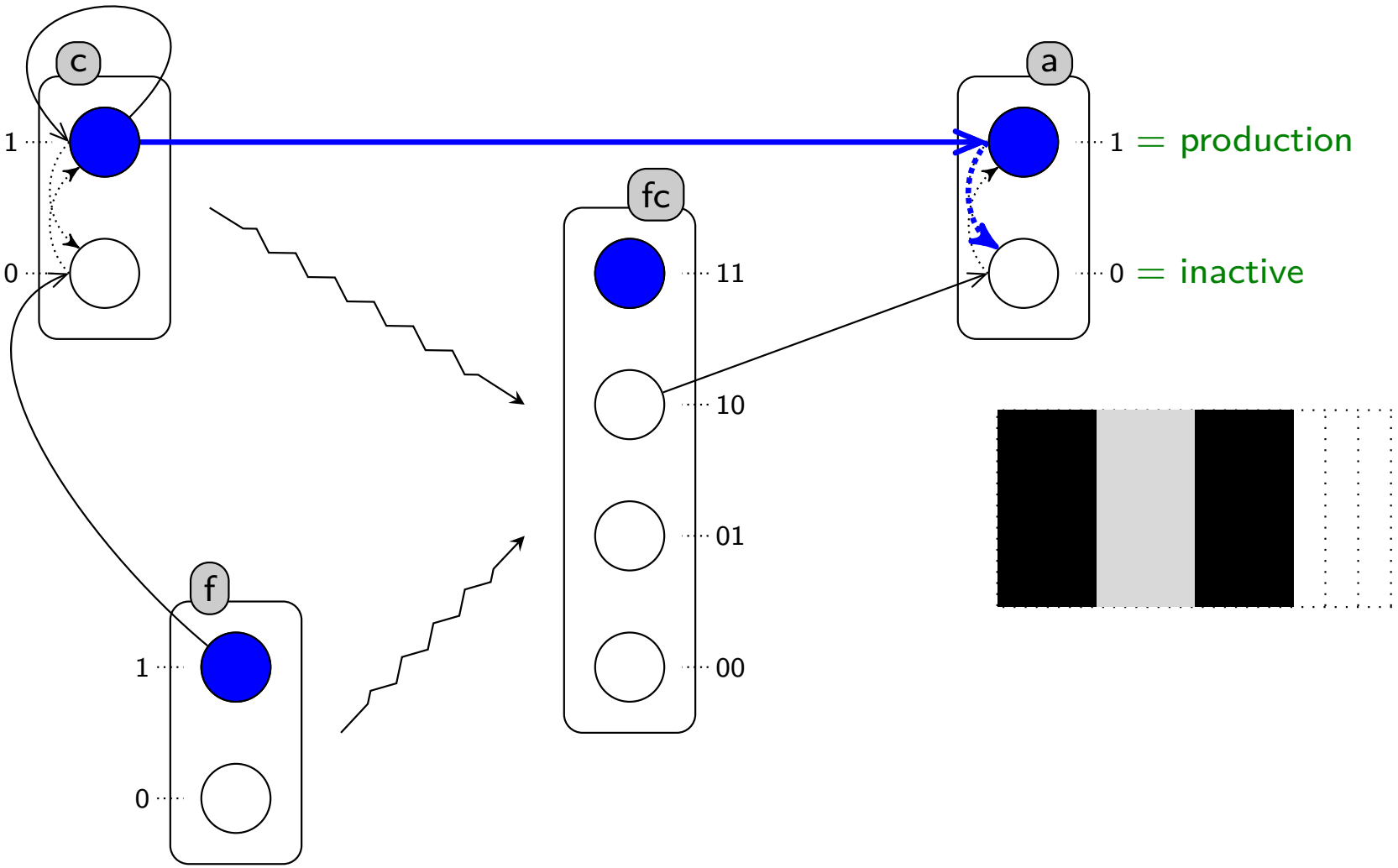

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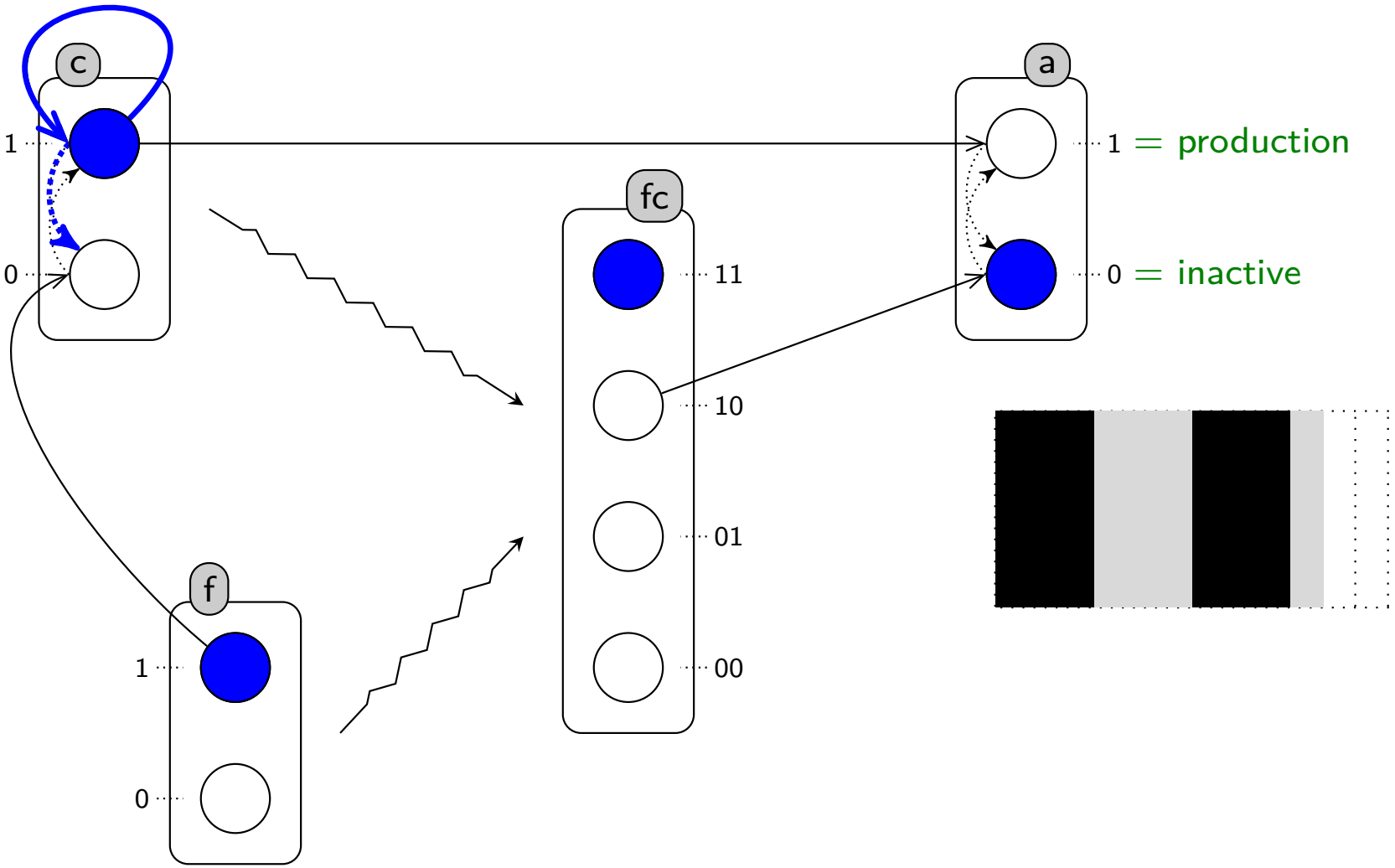

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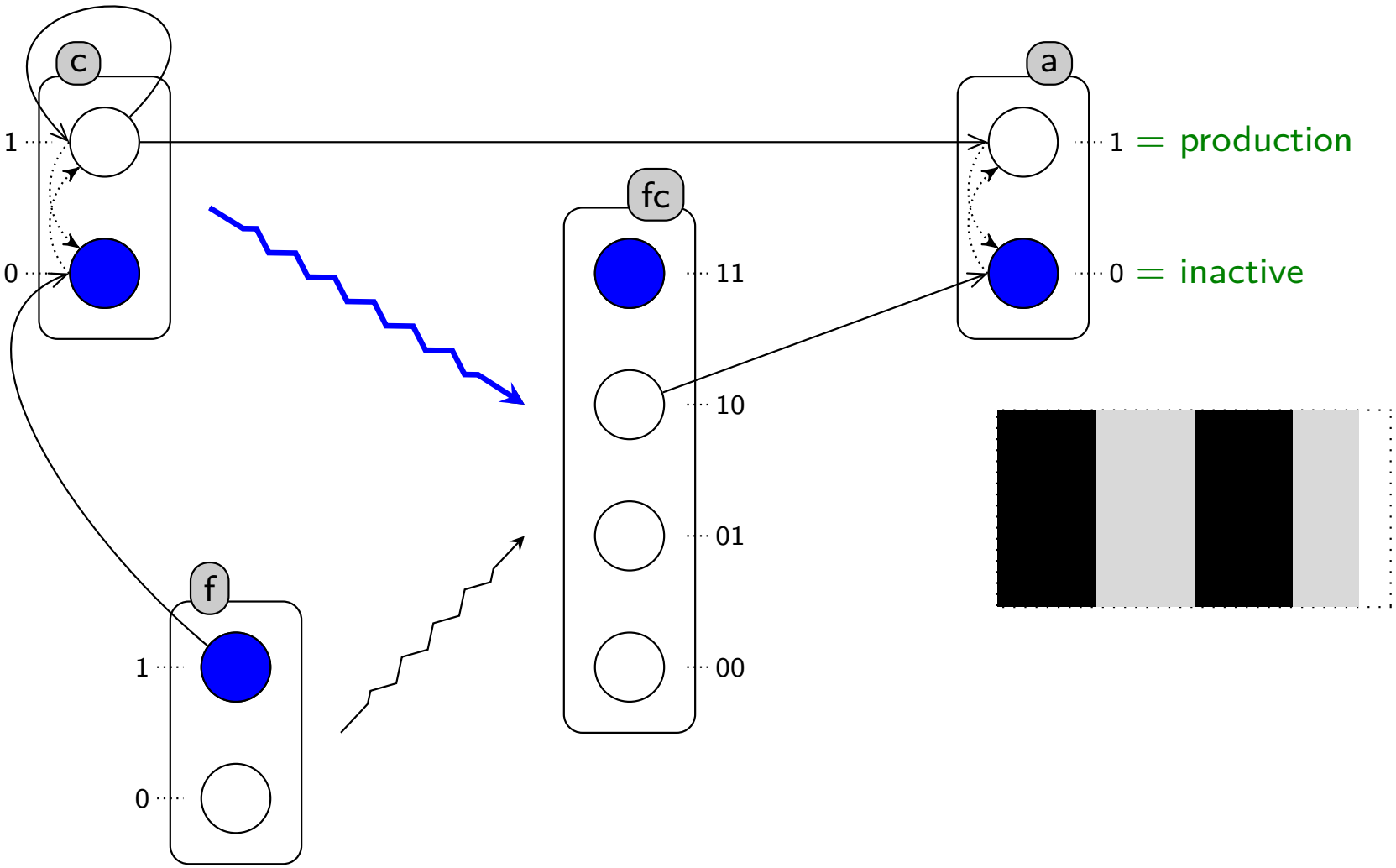

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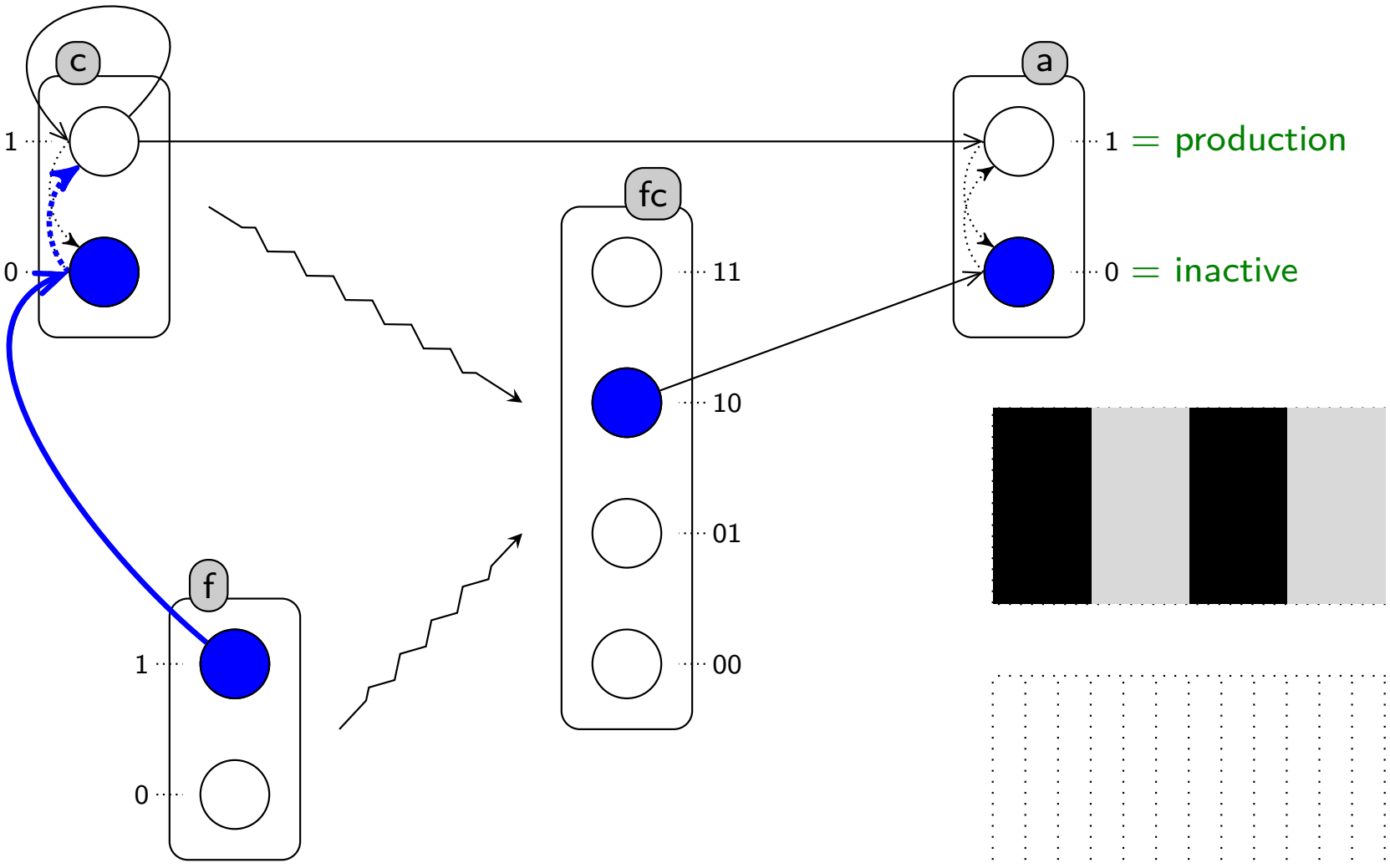

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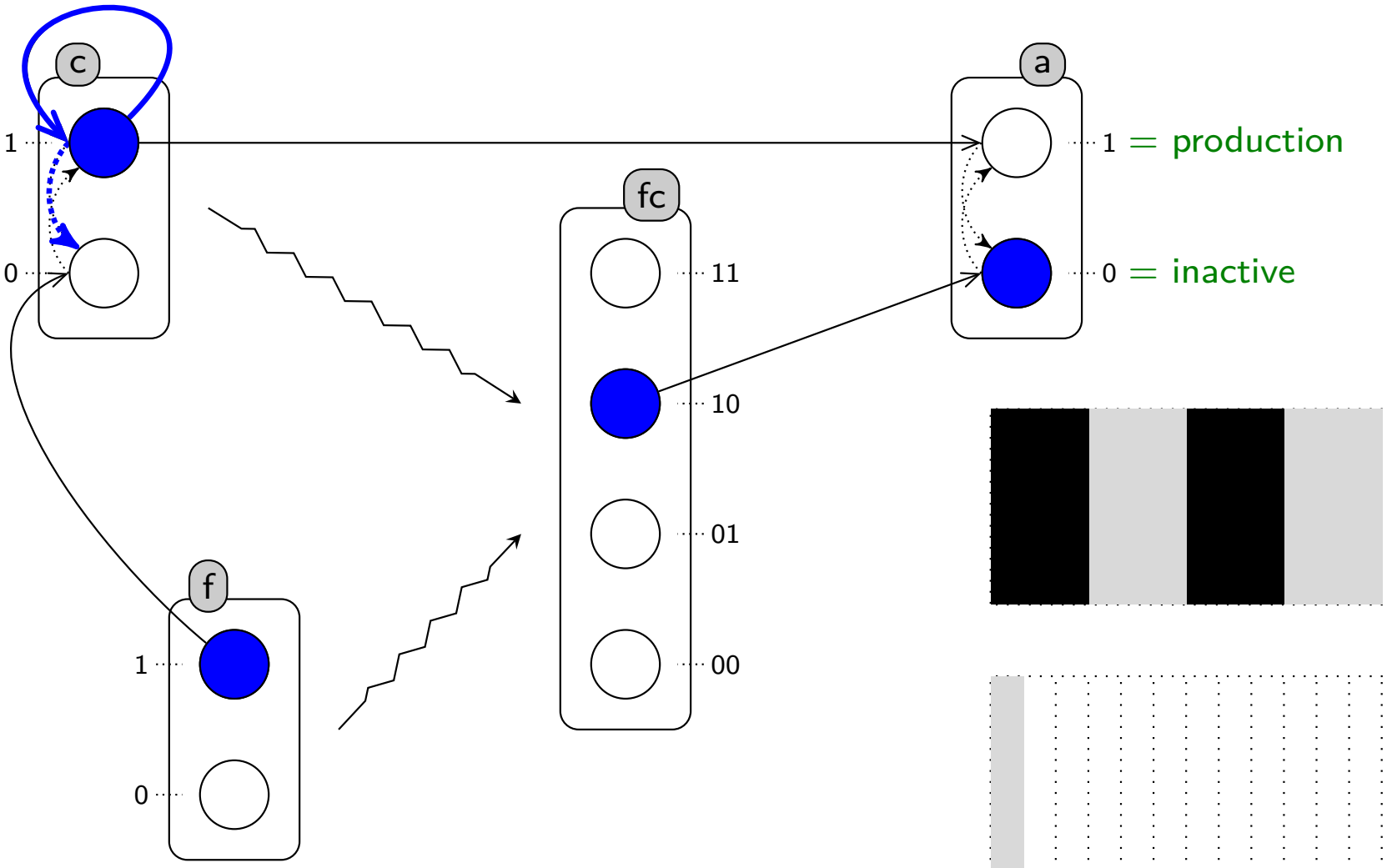

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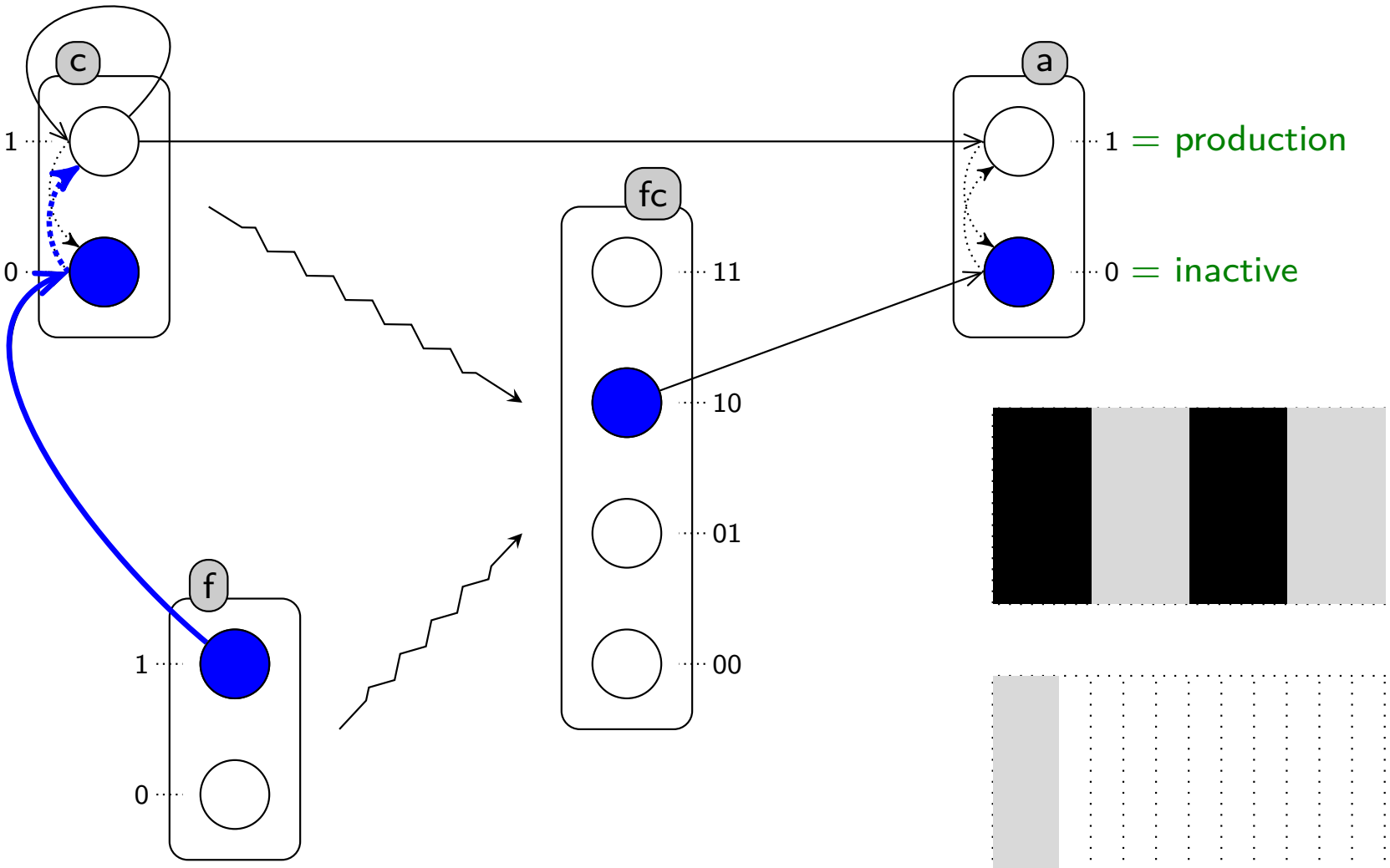

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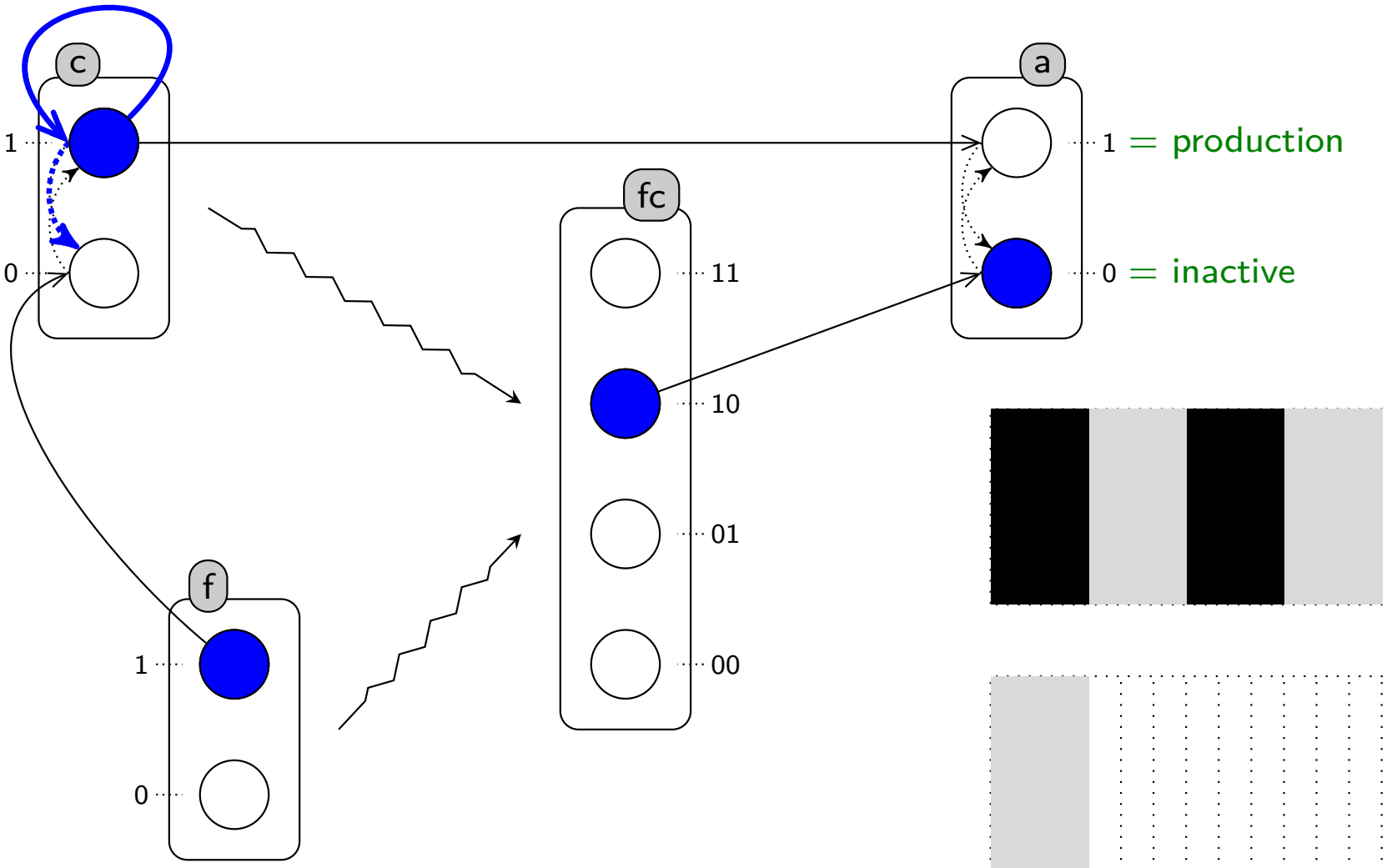

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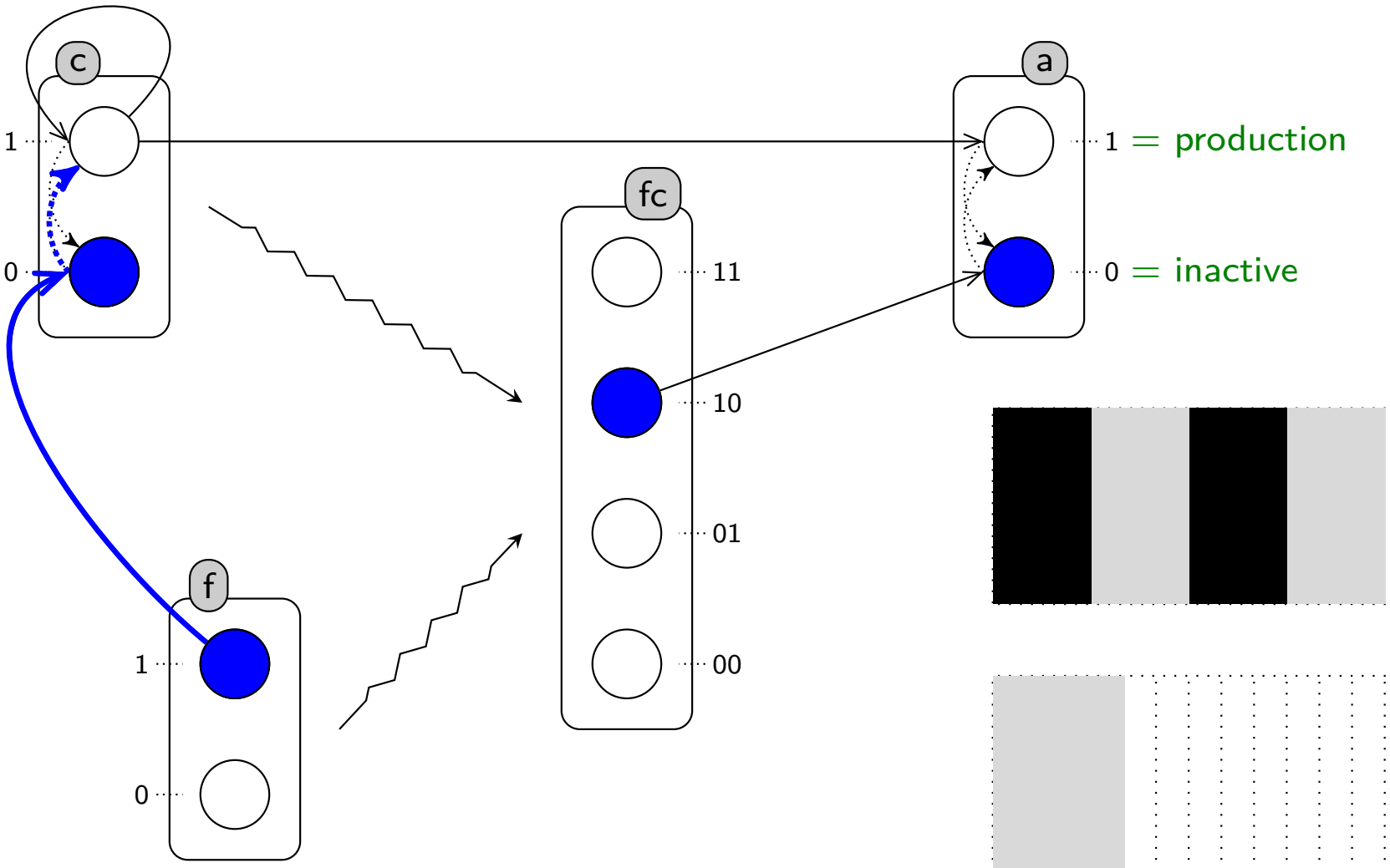

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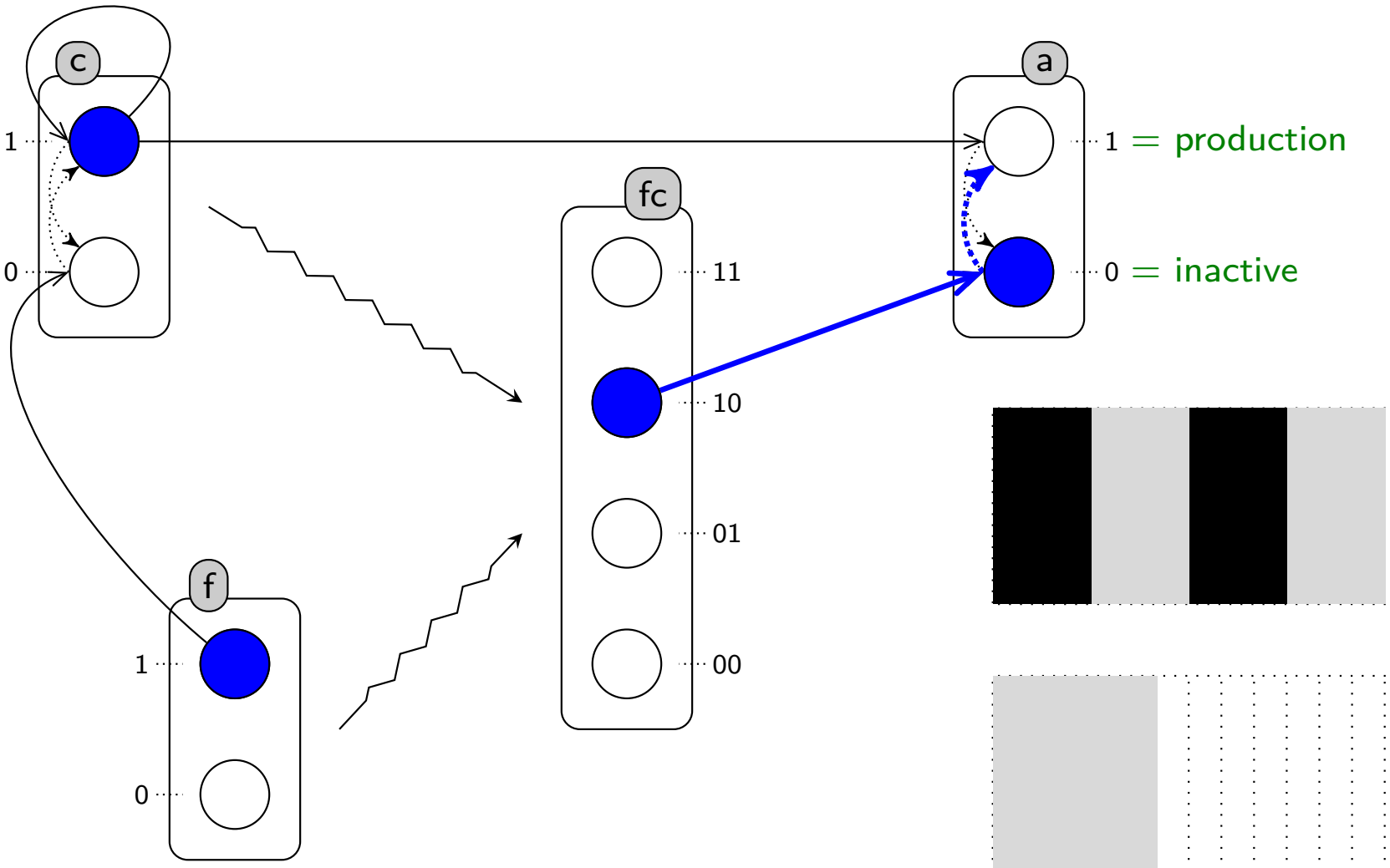

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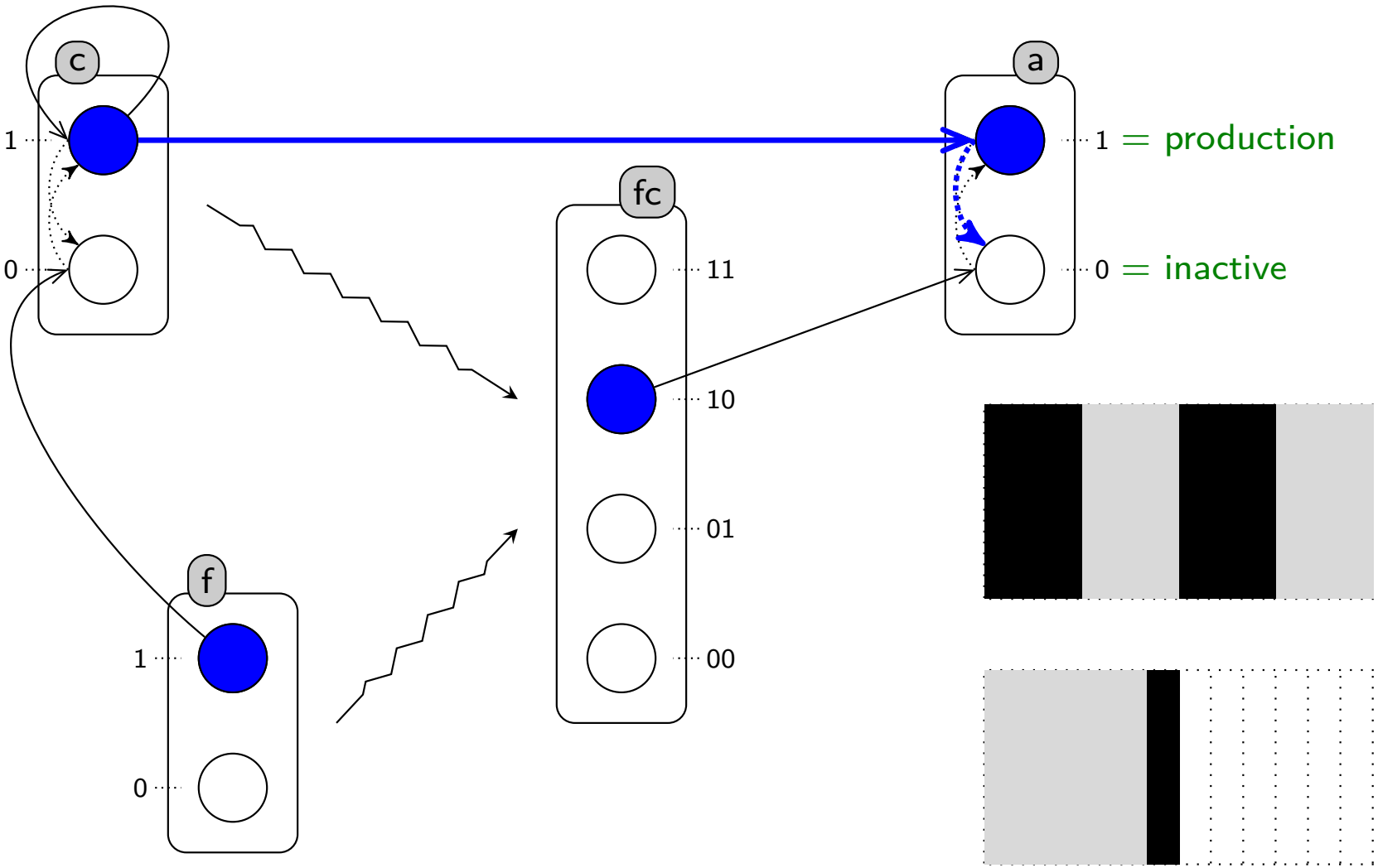

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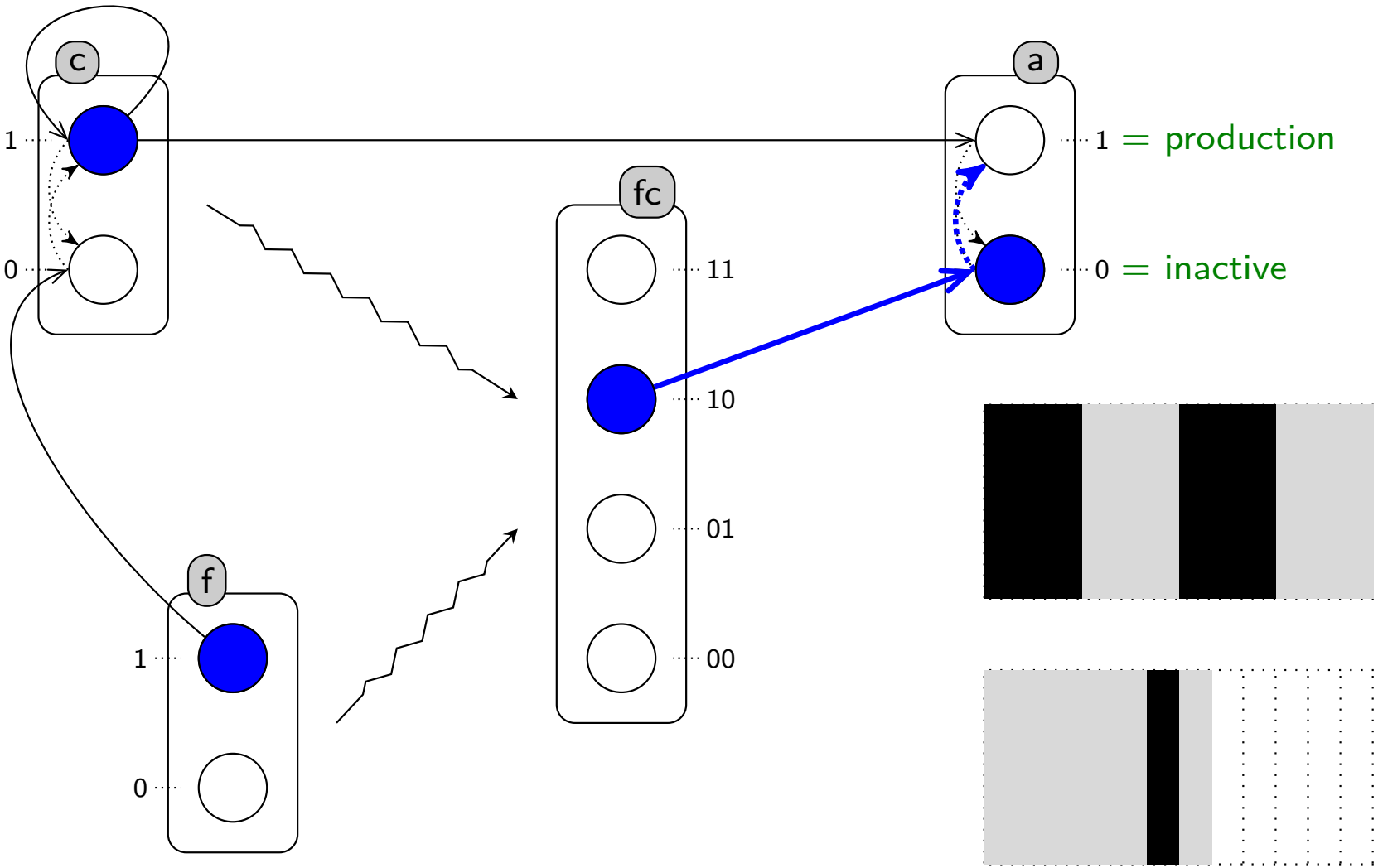

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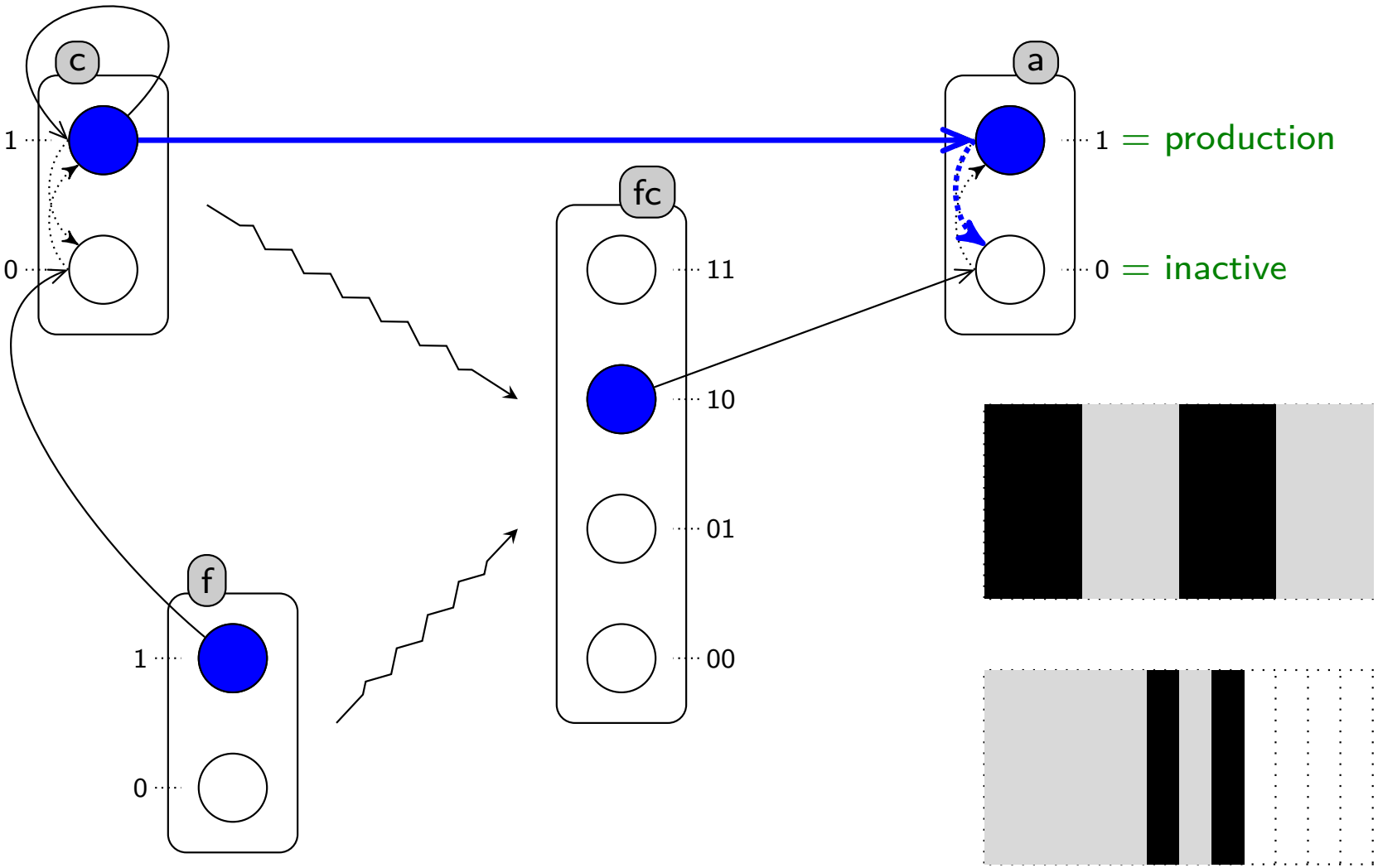

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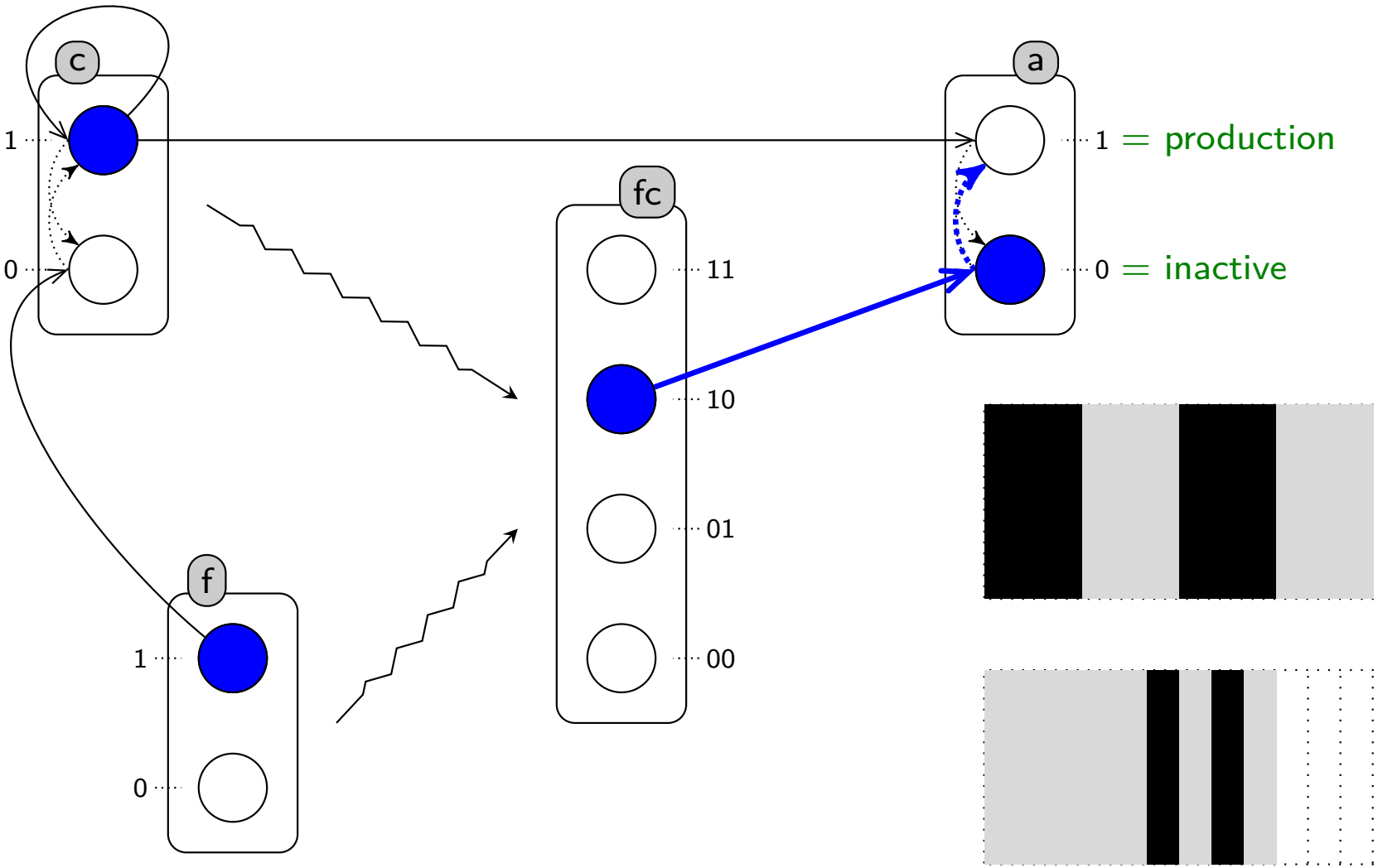

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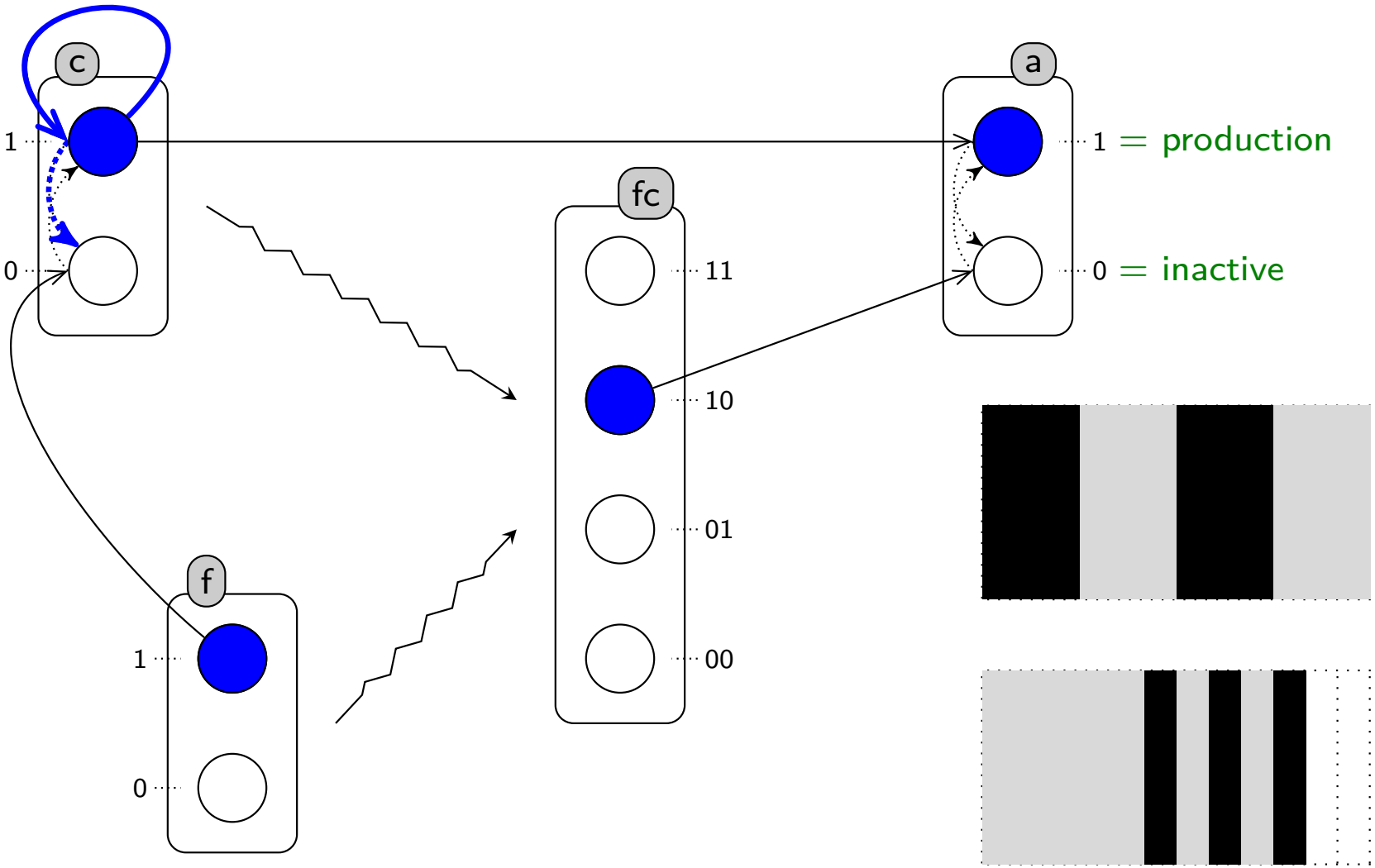

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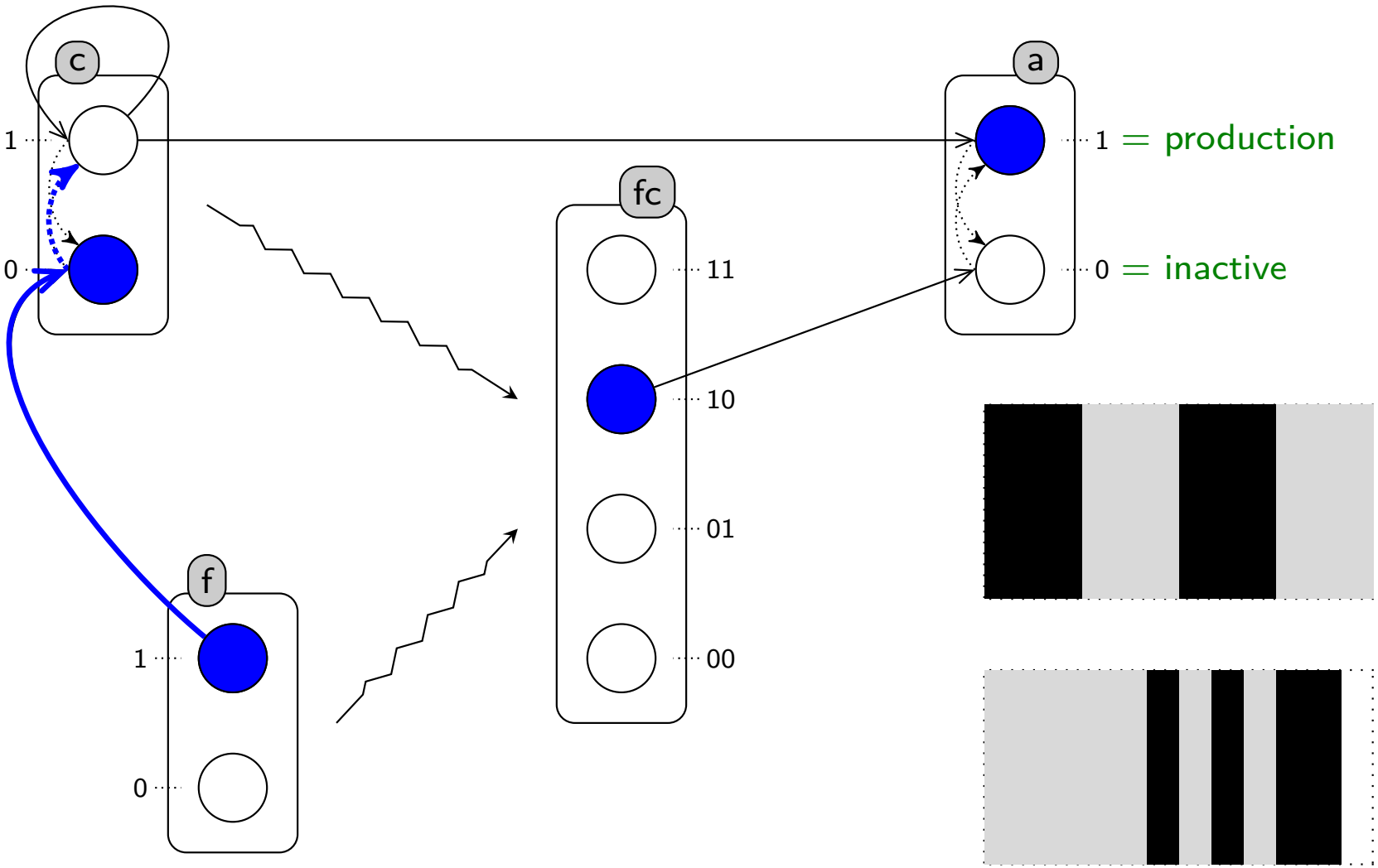

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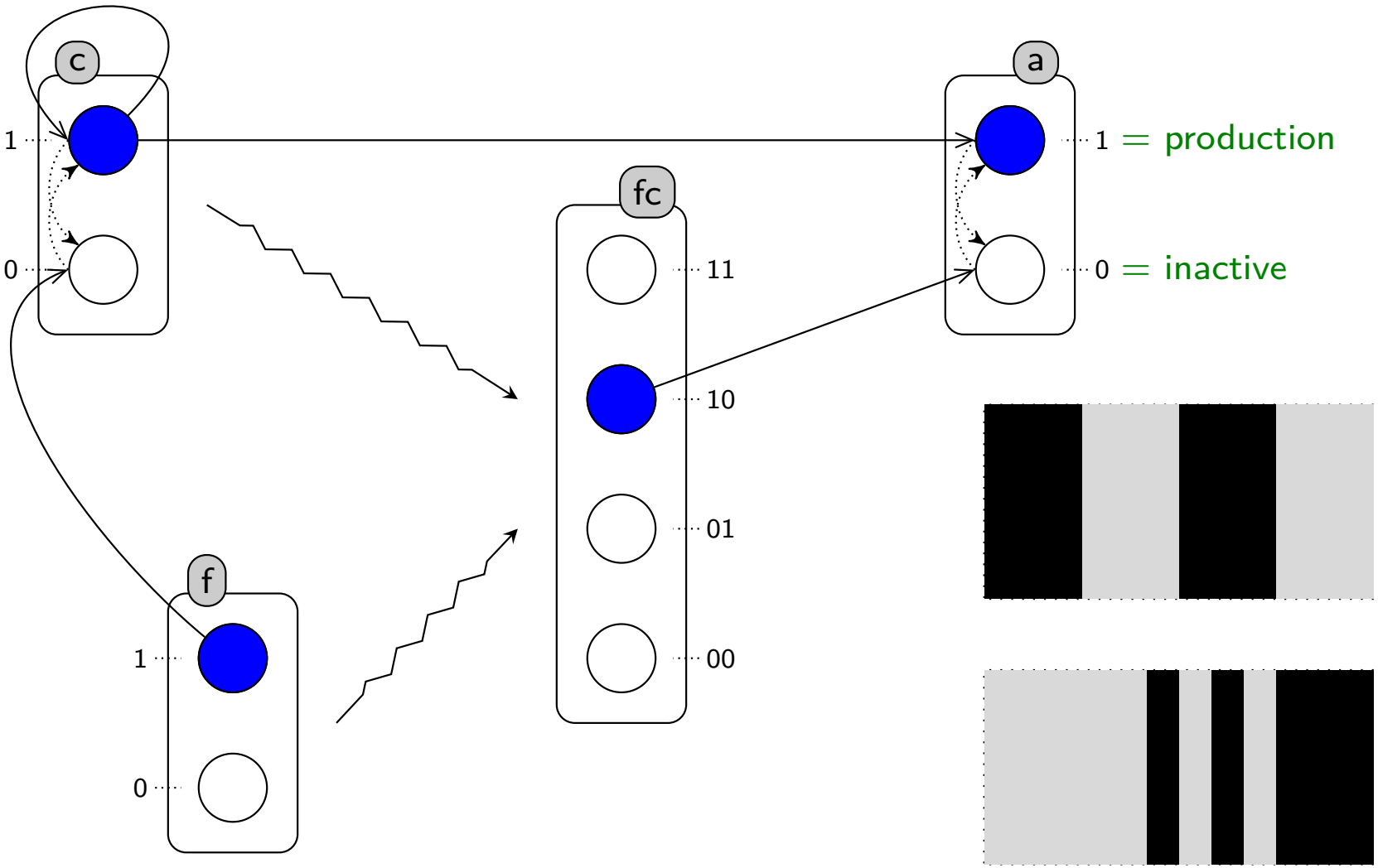
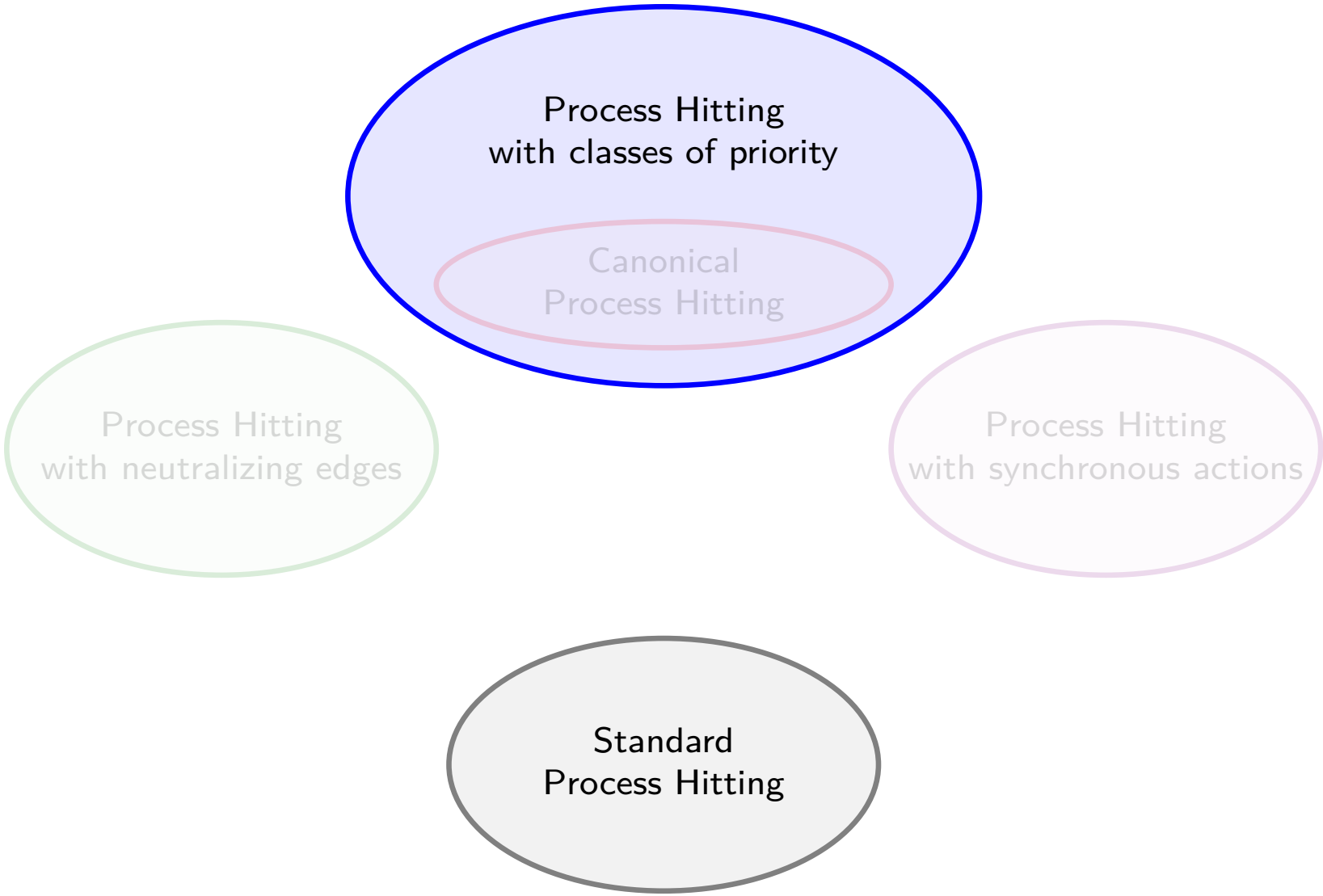


Process Hitting with Classes of Priorities



Addition of classes of priorities

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]

- Each action is associated to a discrete priority
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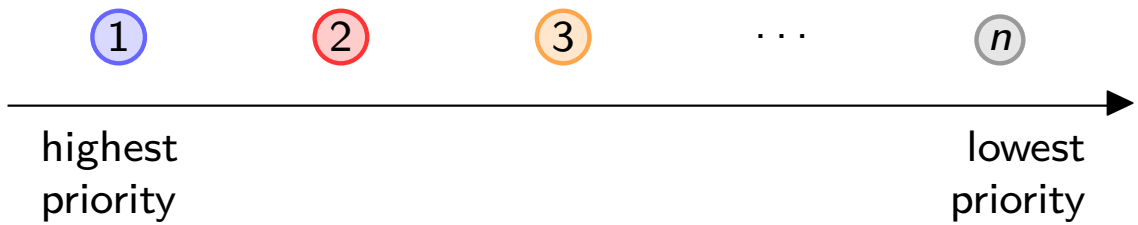

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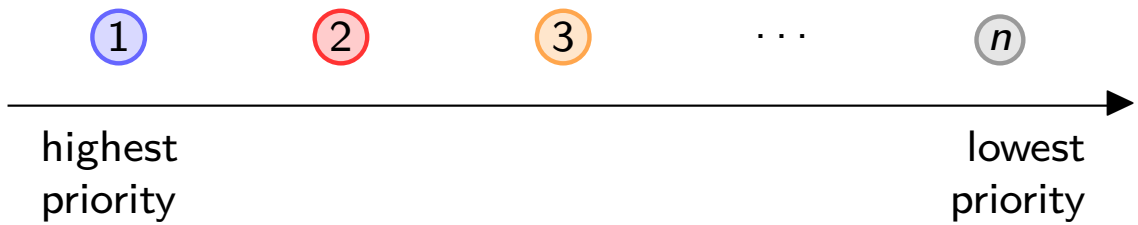

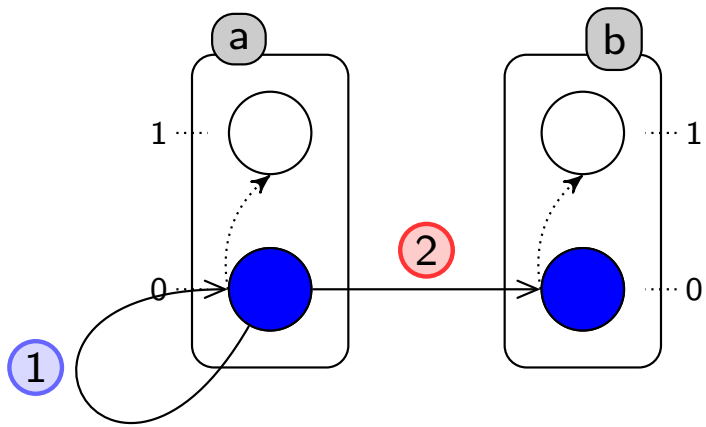

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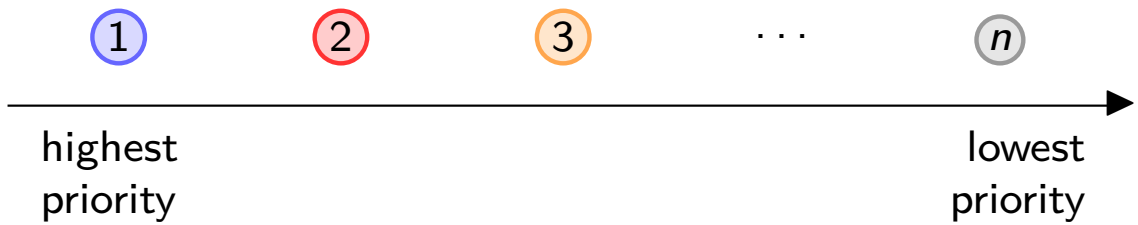

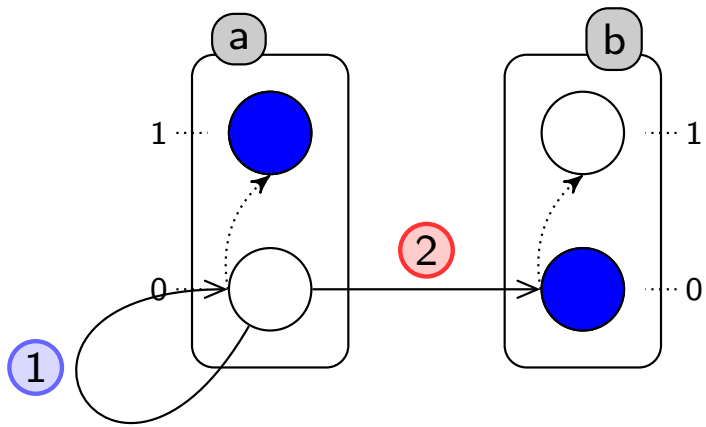

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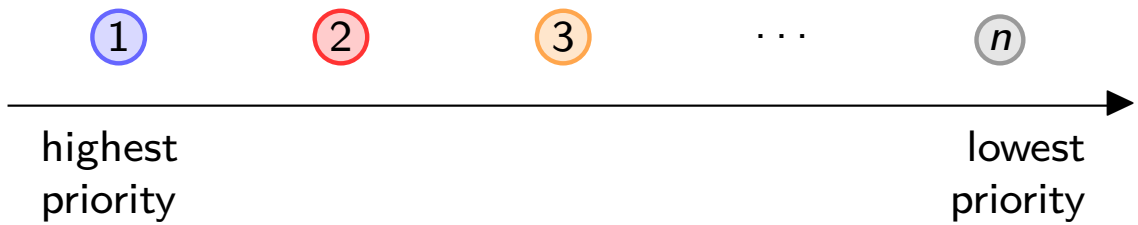
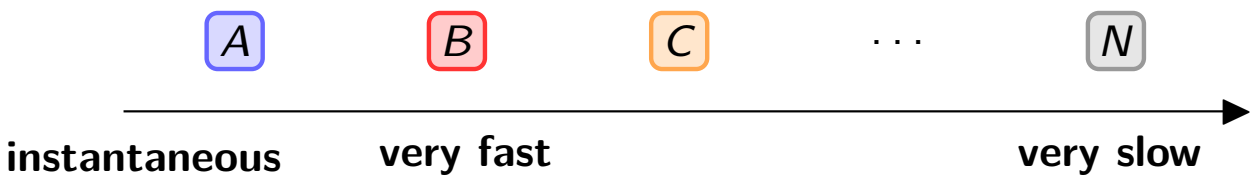


- Allow to model classes of actions with similar speeds or temporal parameters



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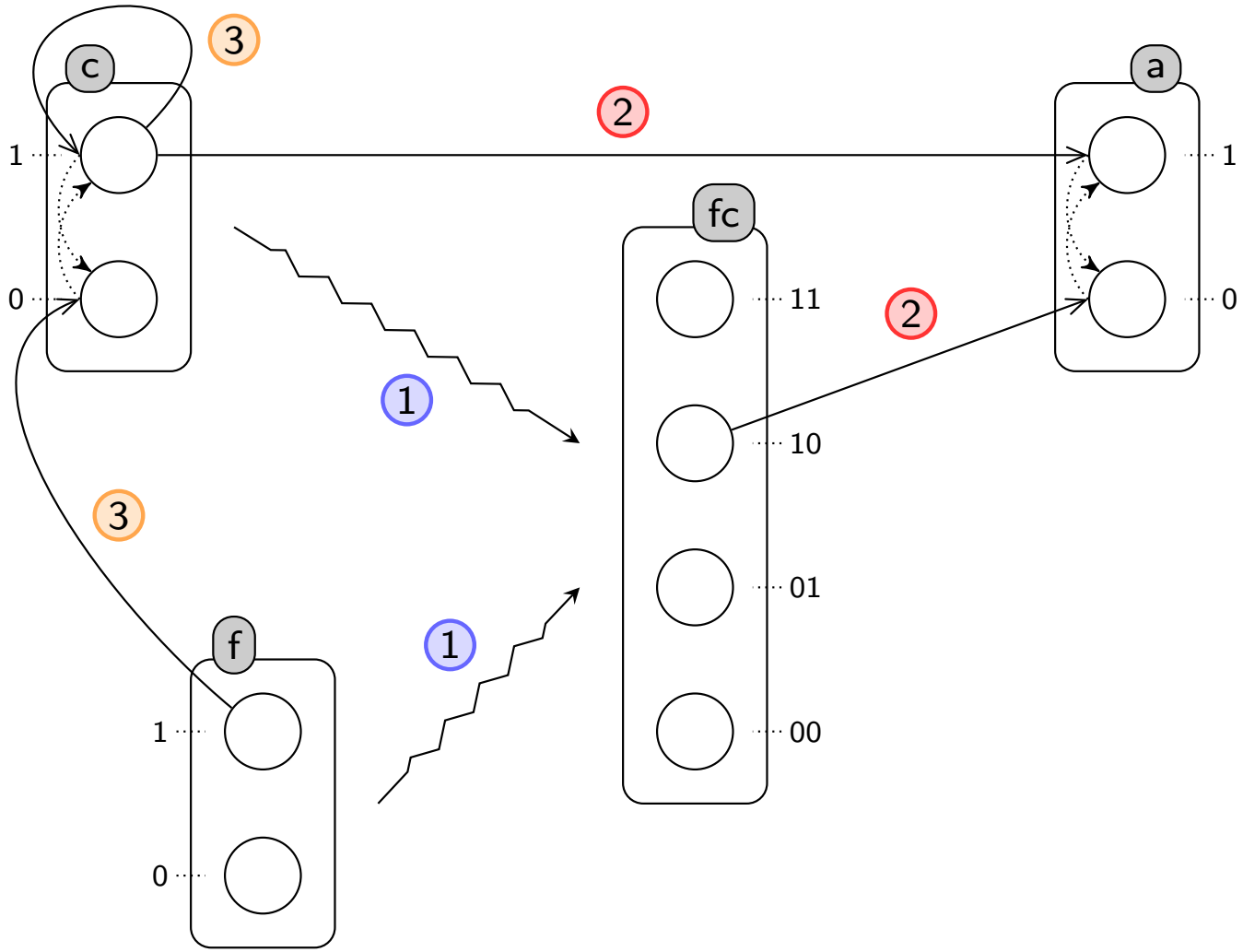

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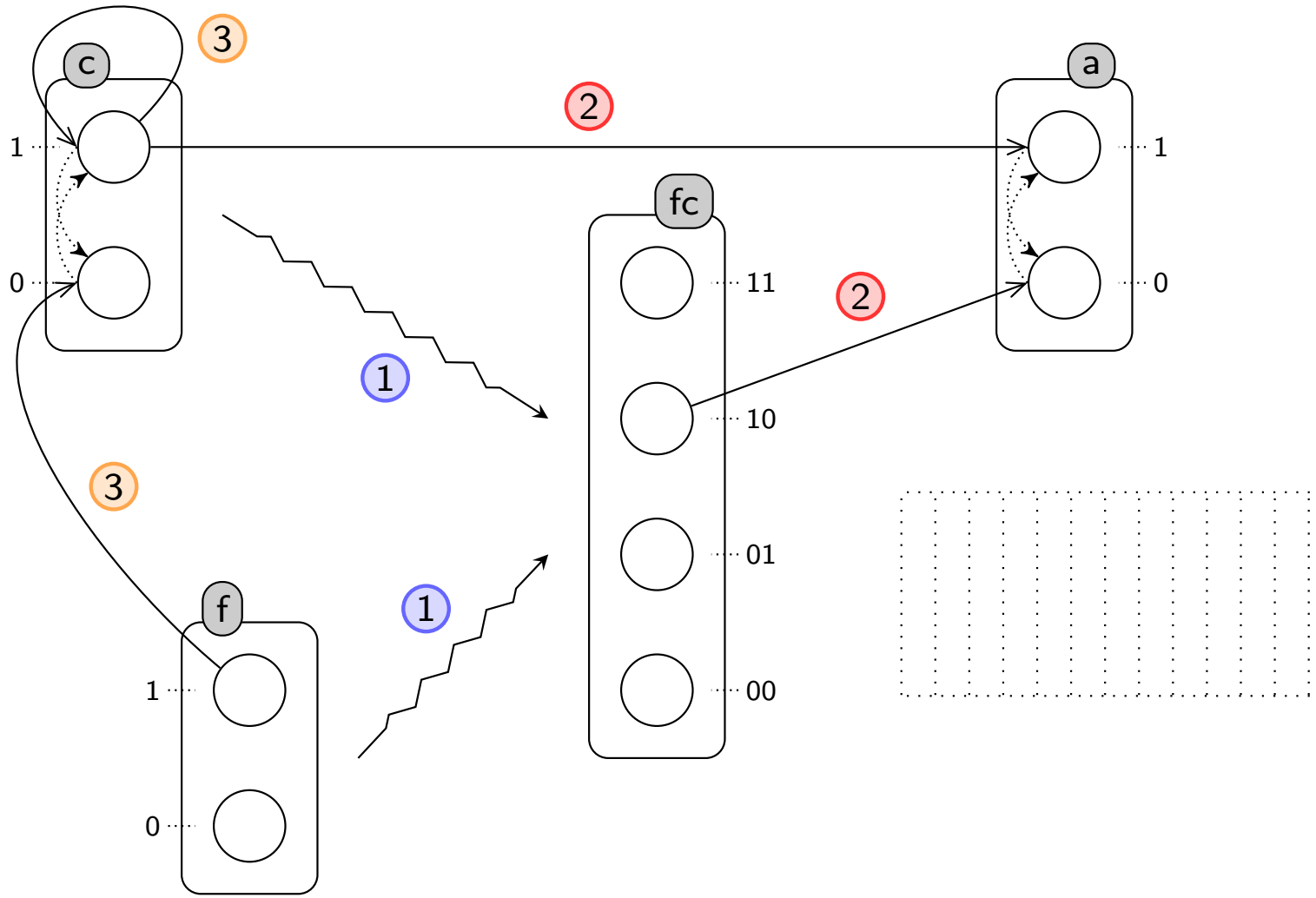

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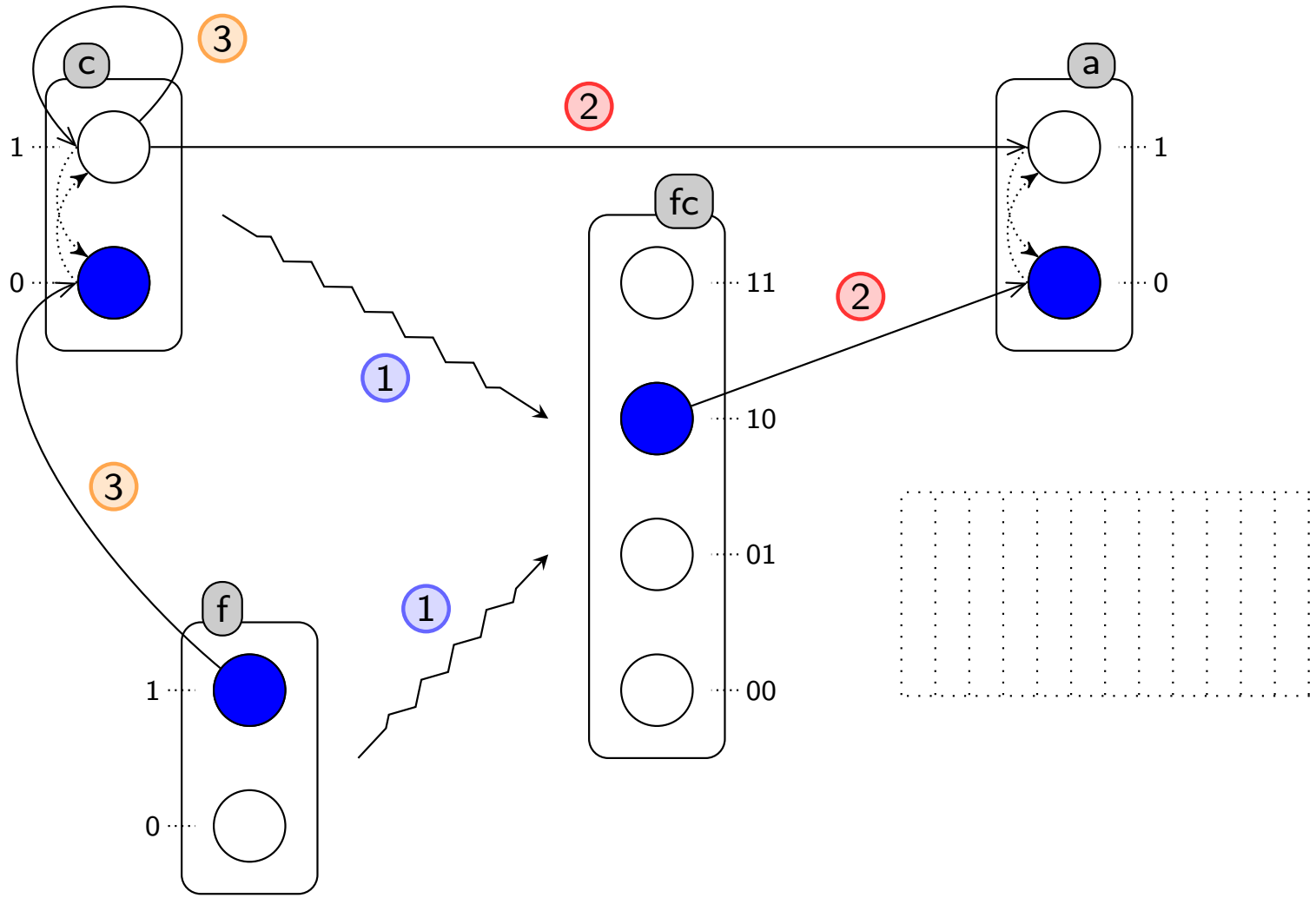

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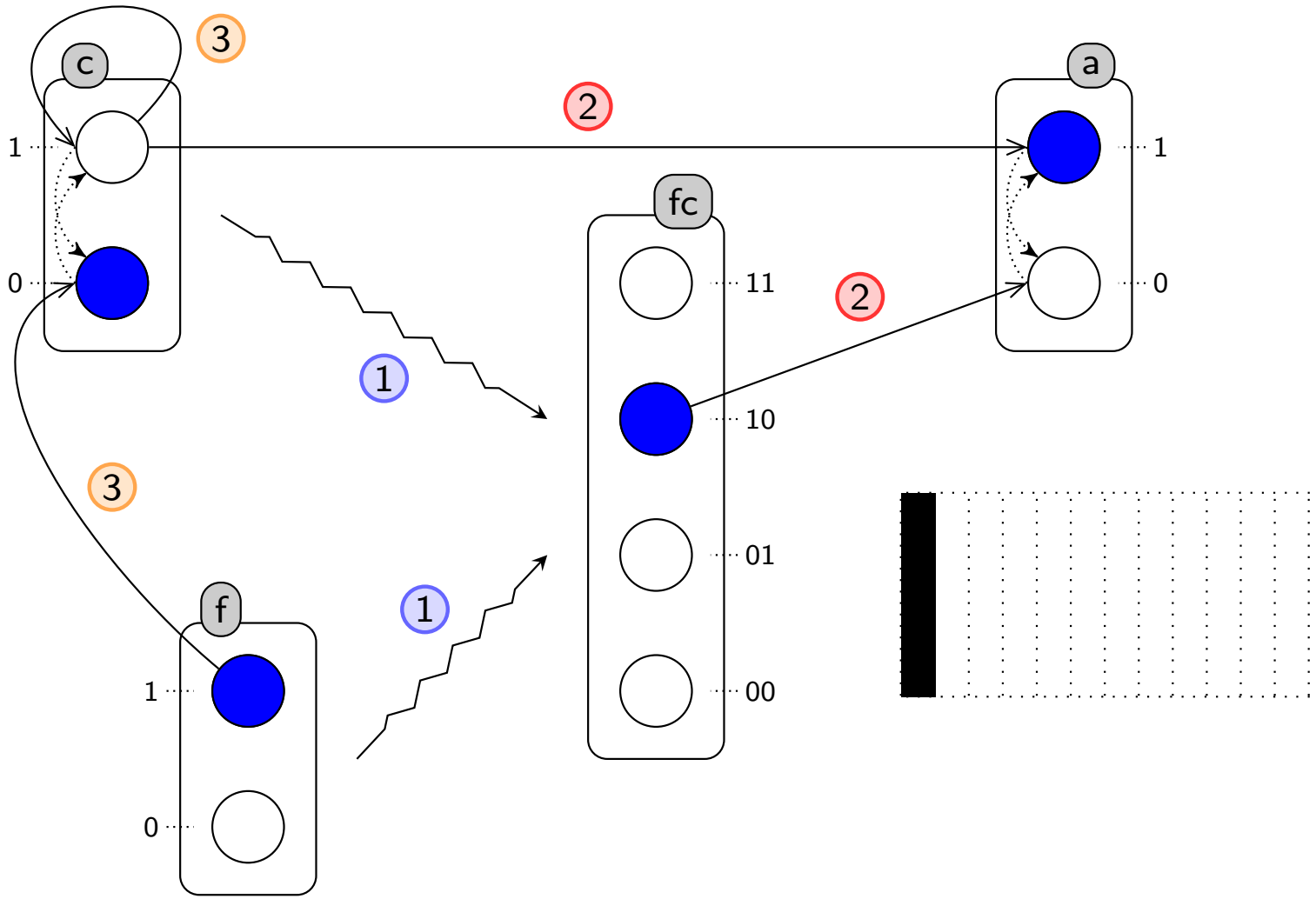

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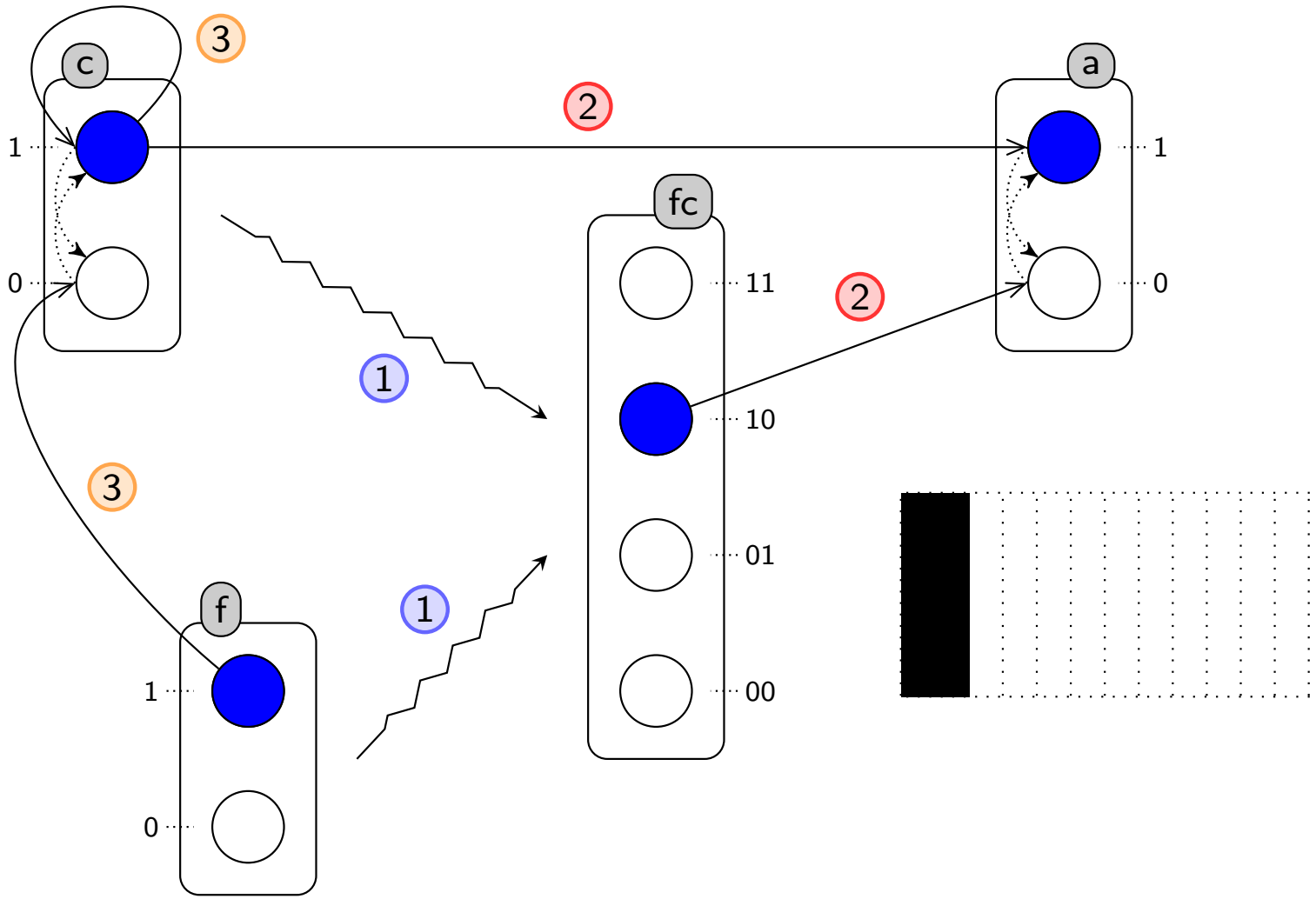

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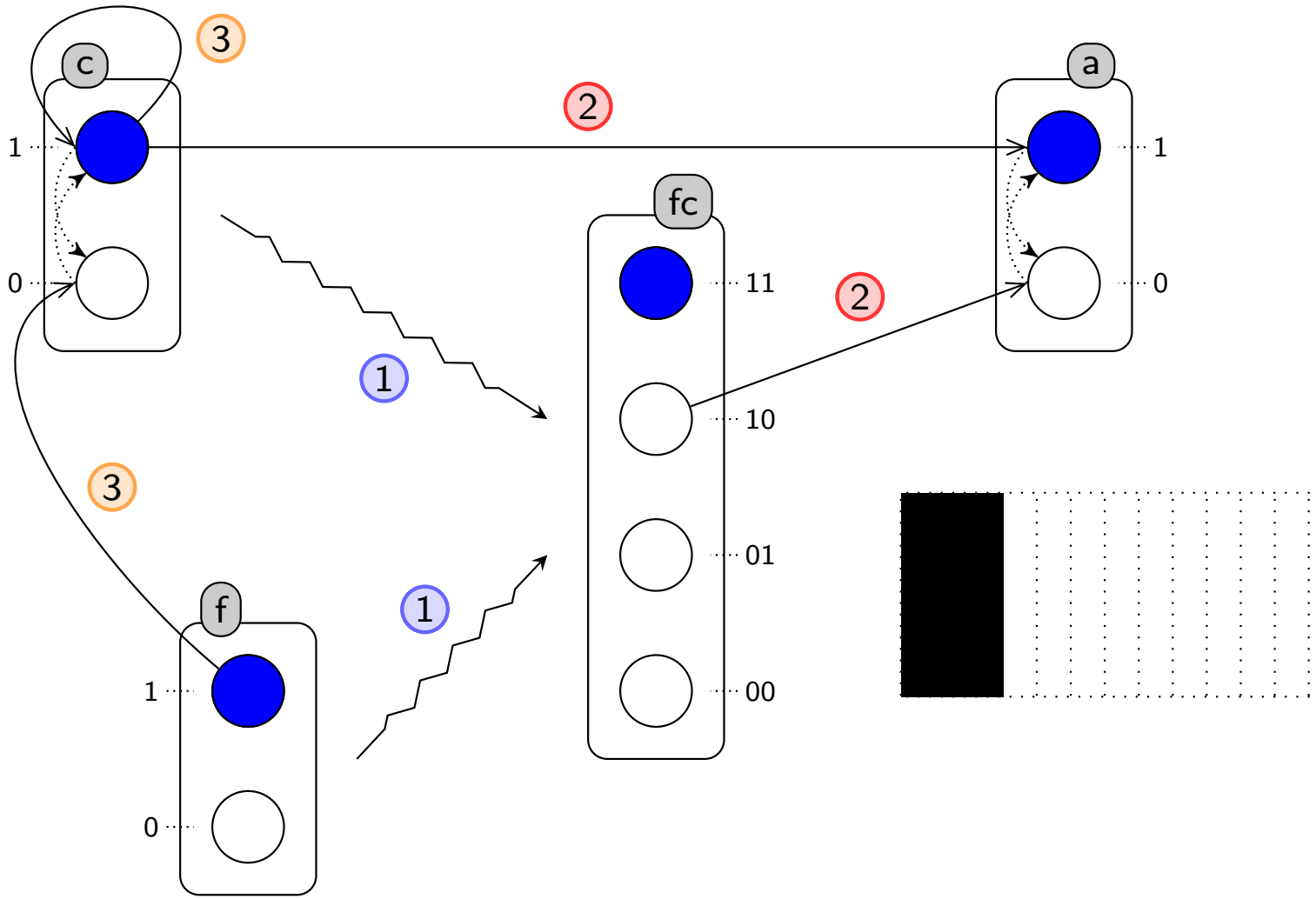

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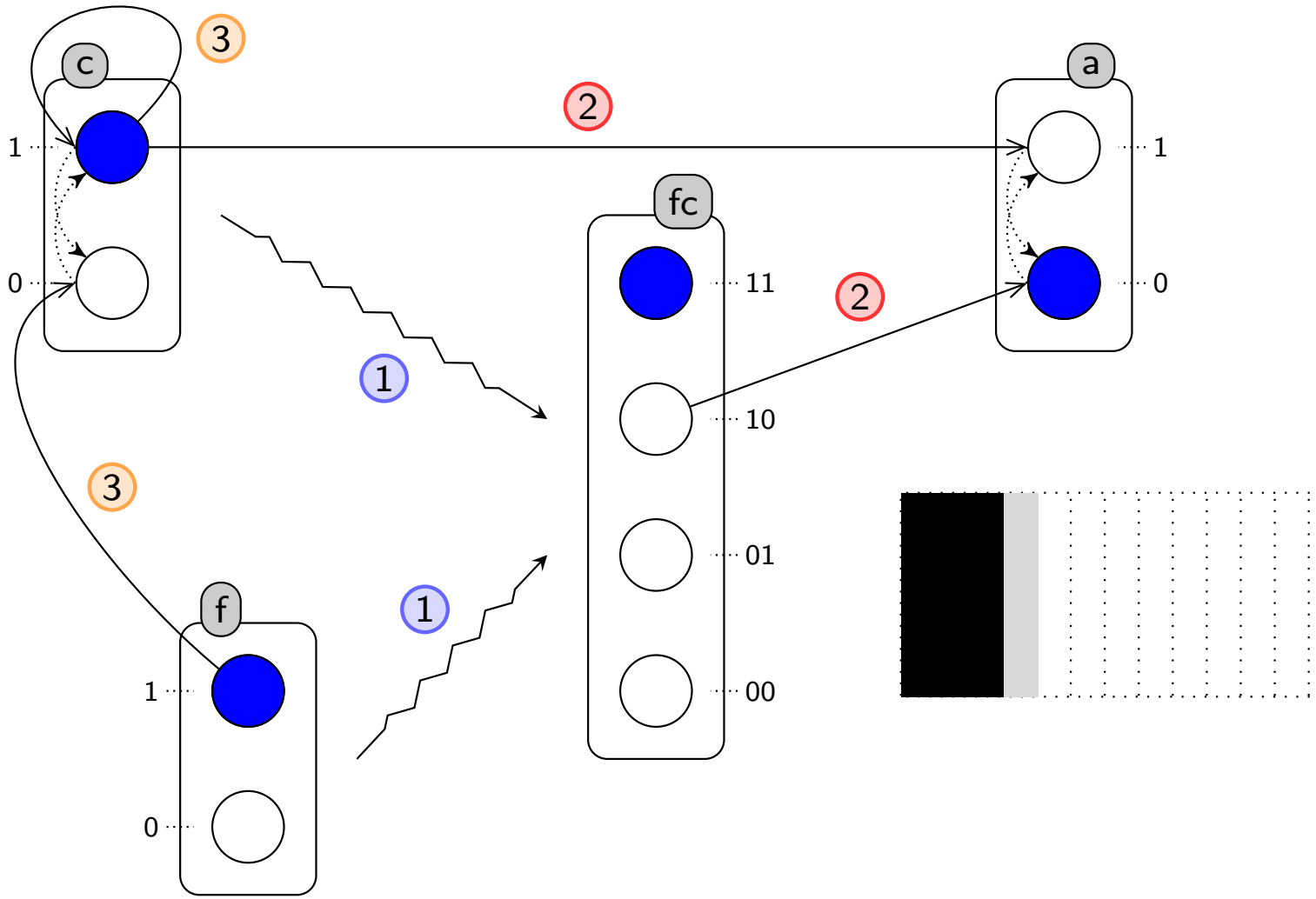

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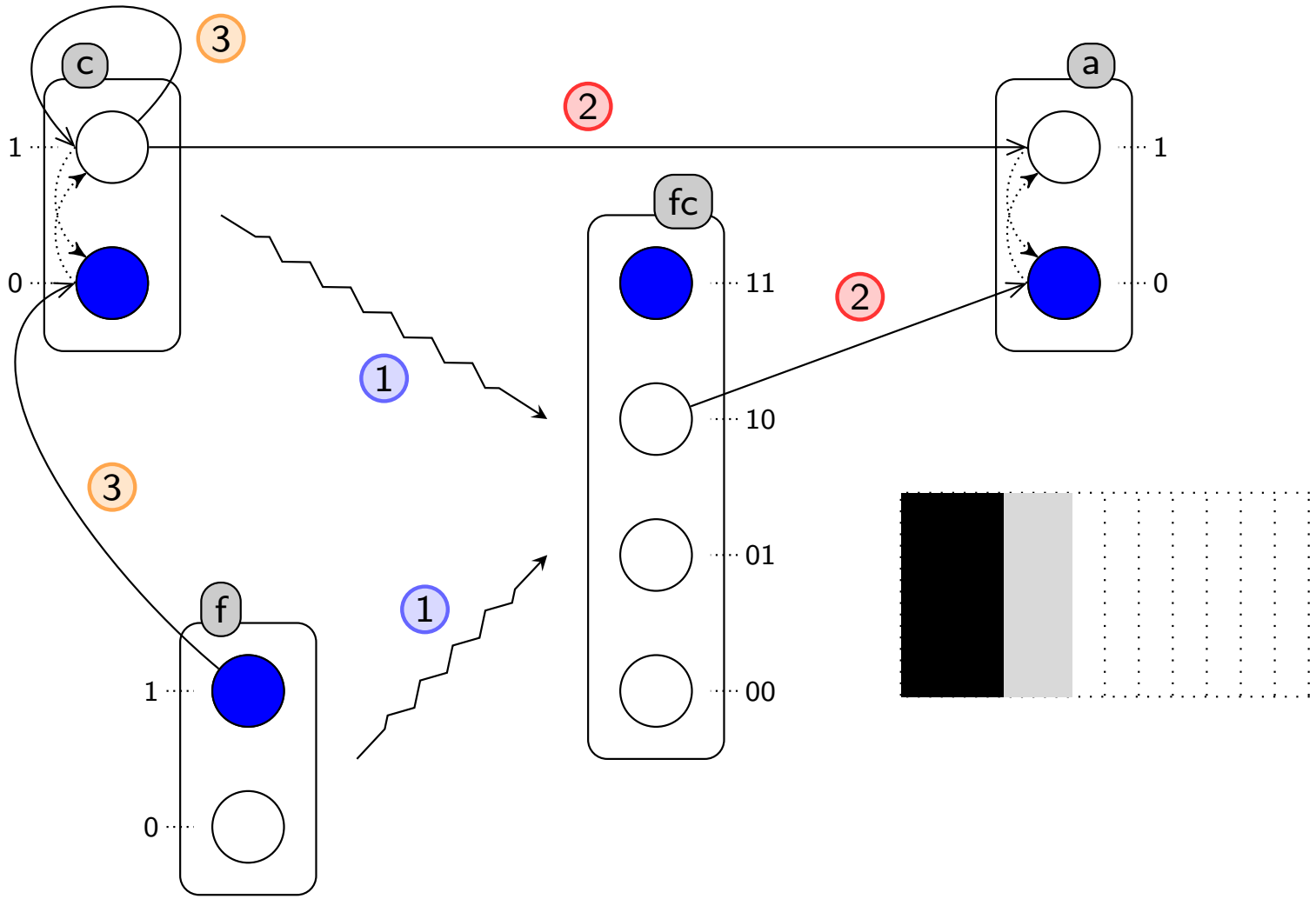

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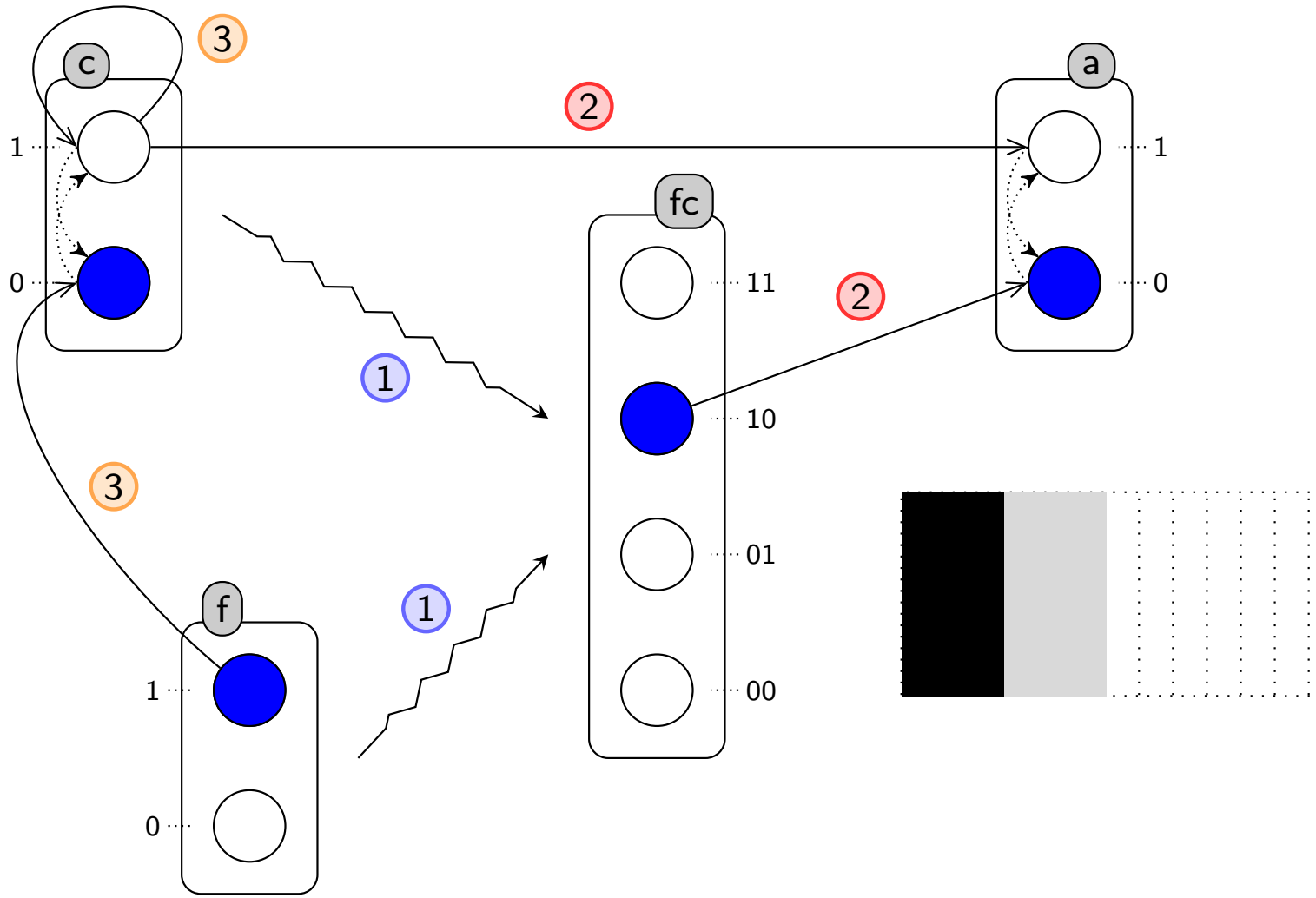

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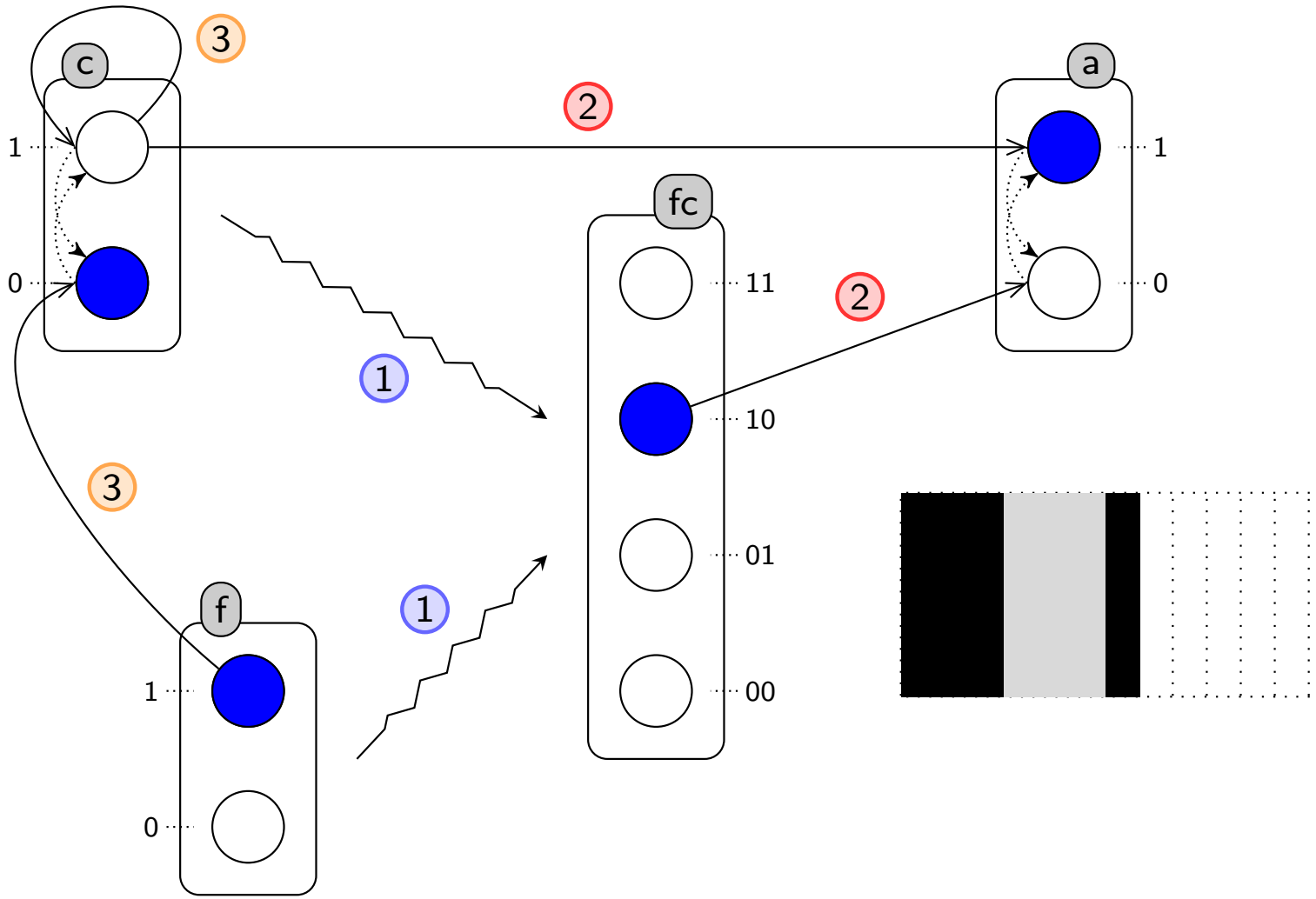

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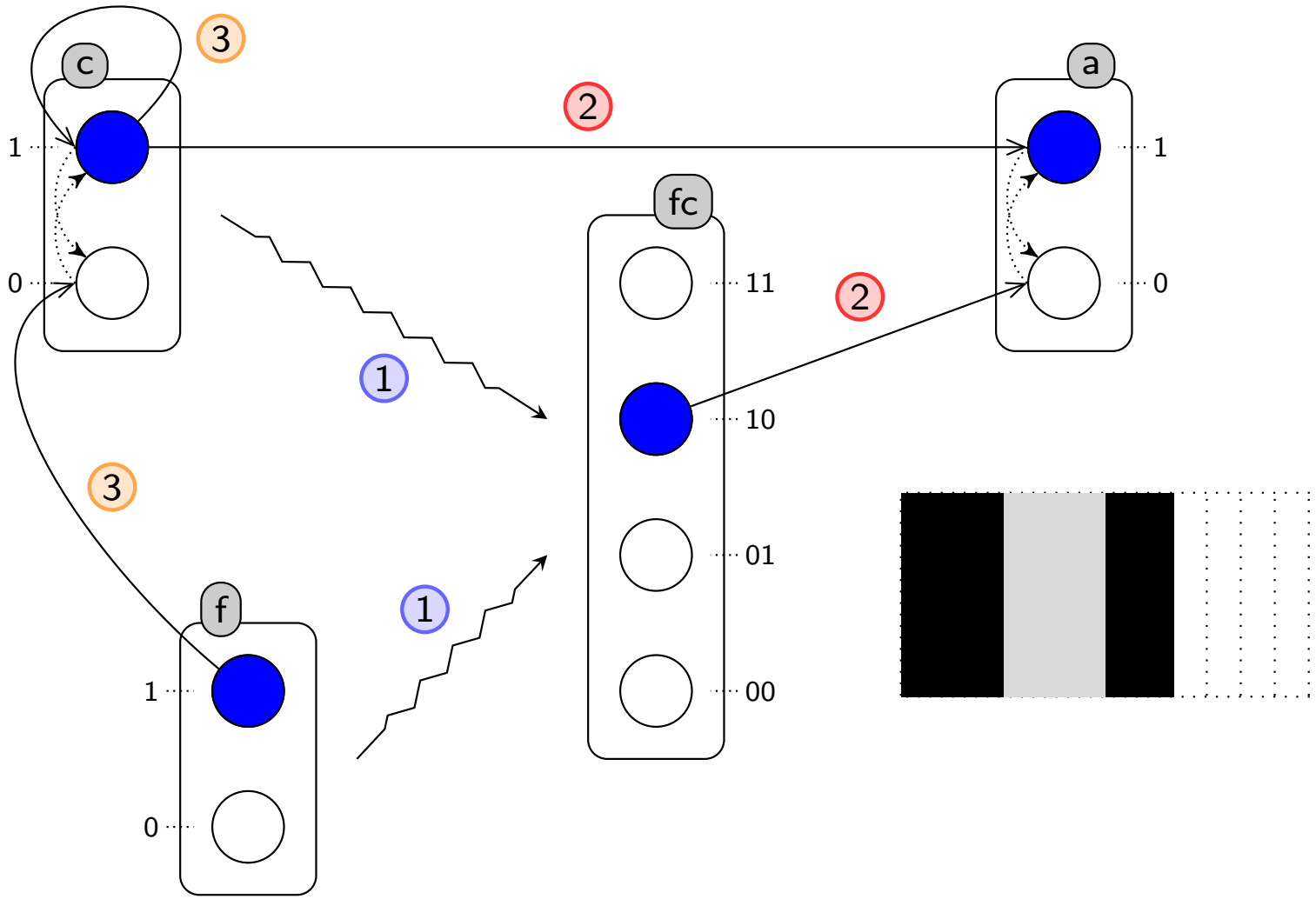

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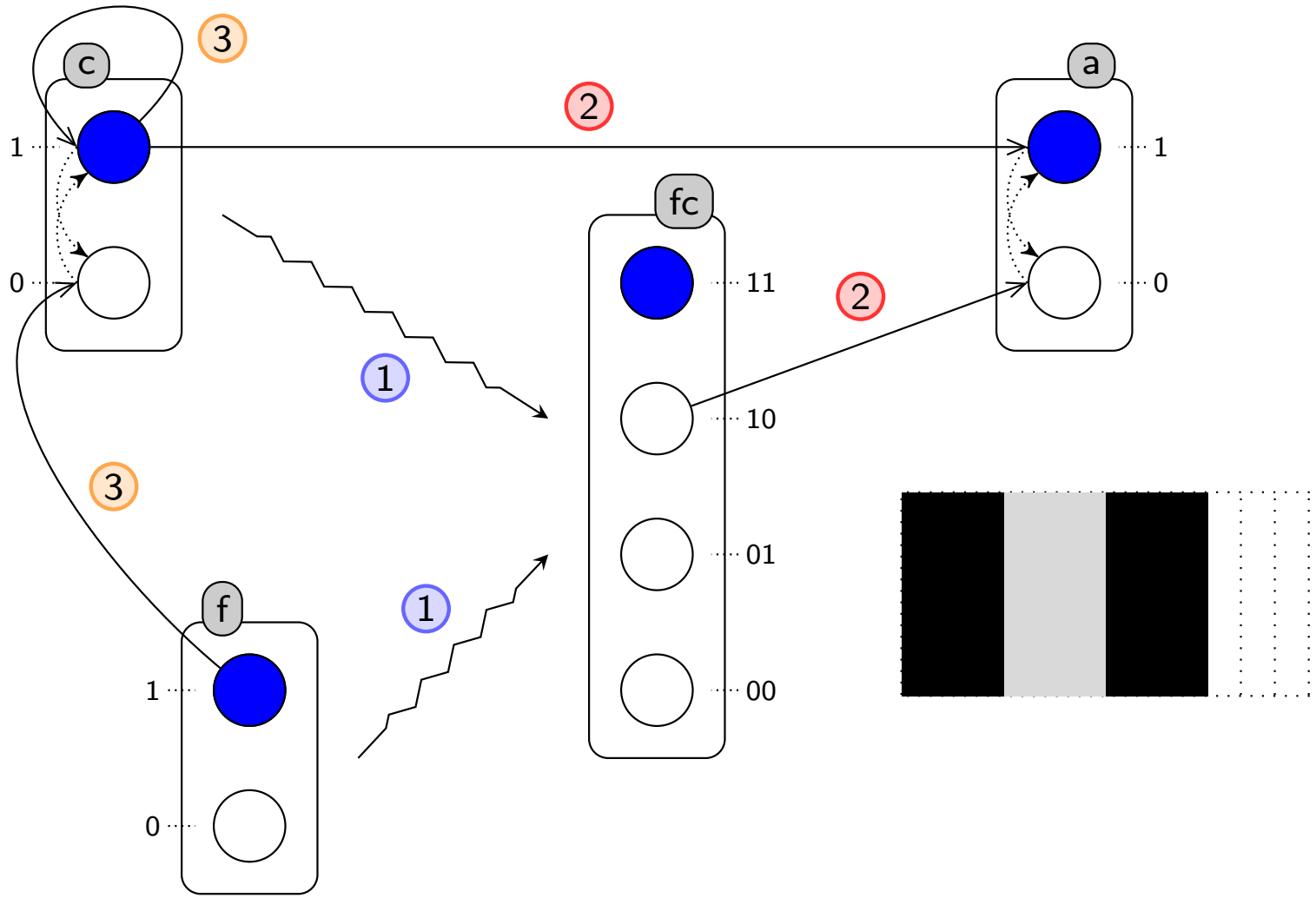

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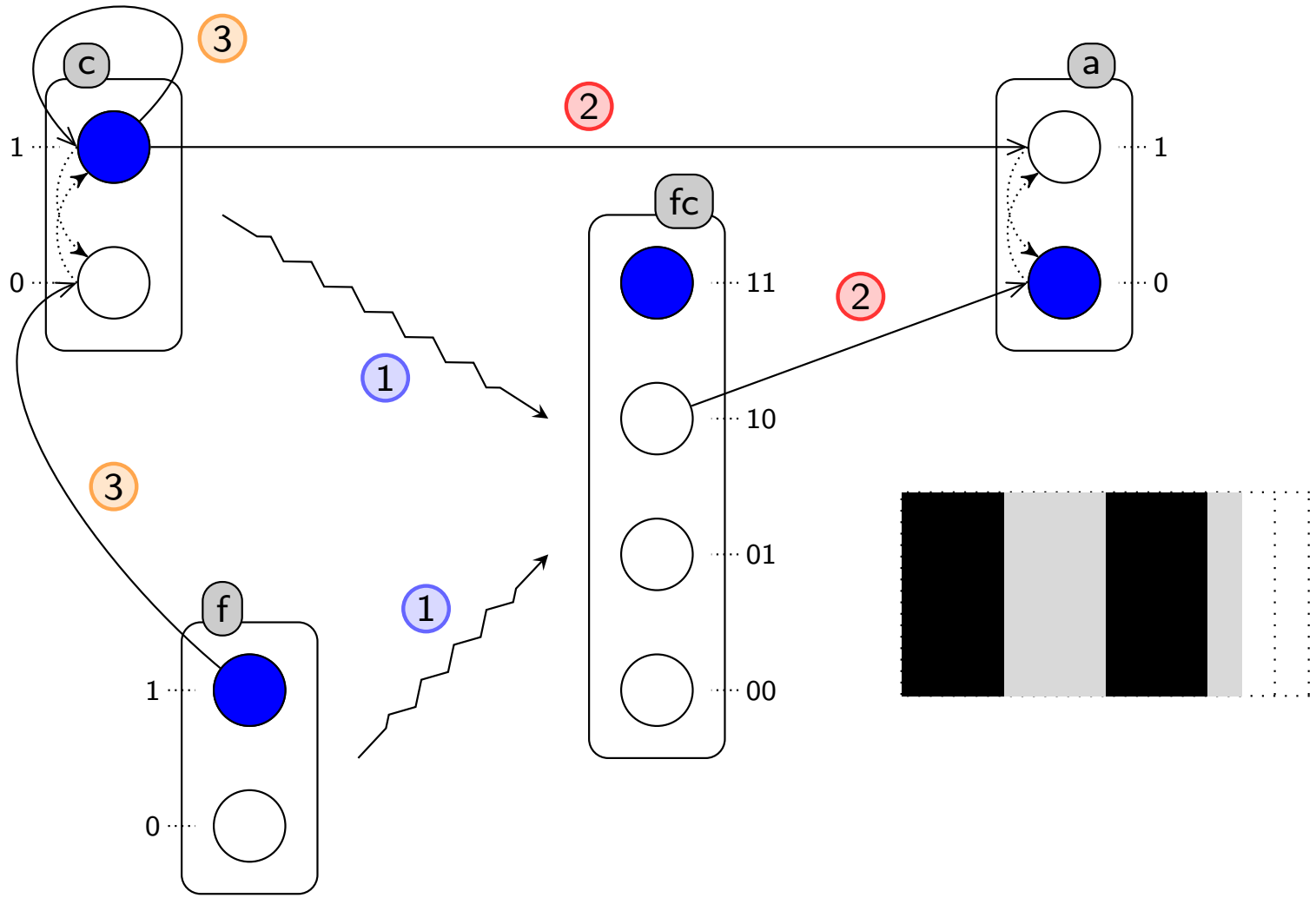

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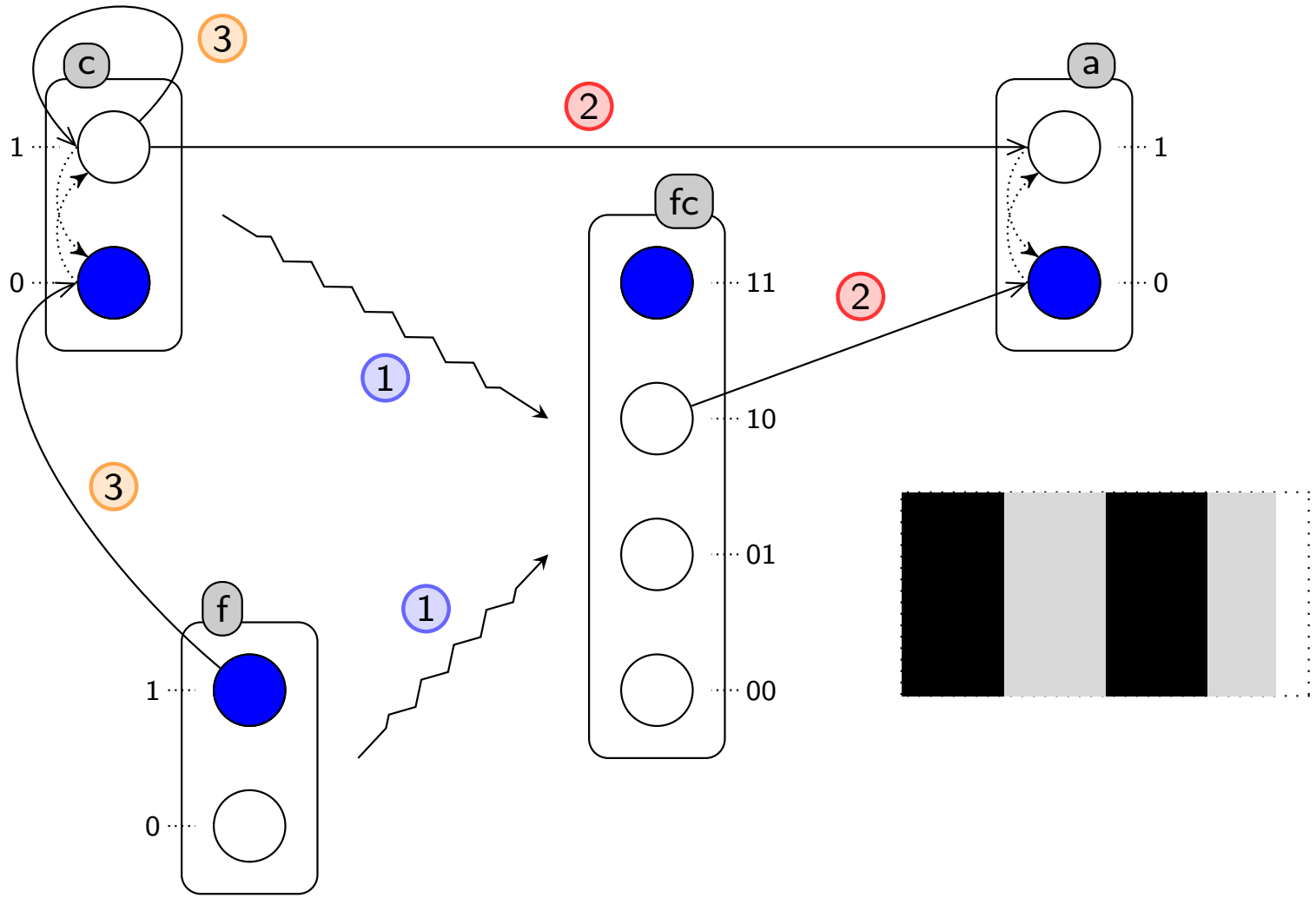

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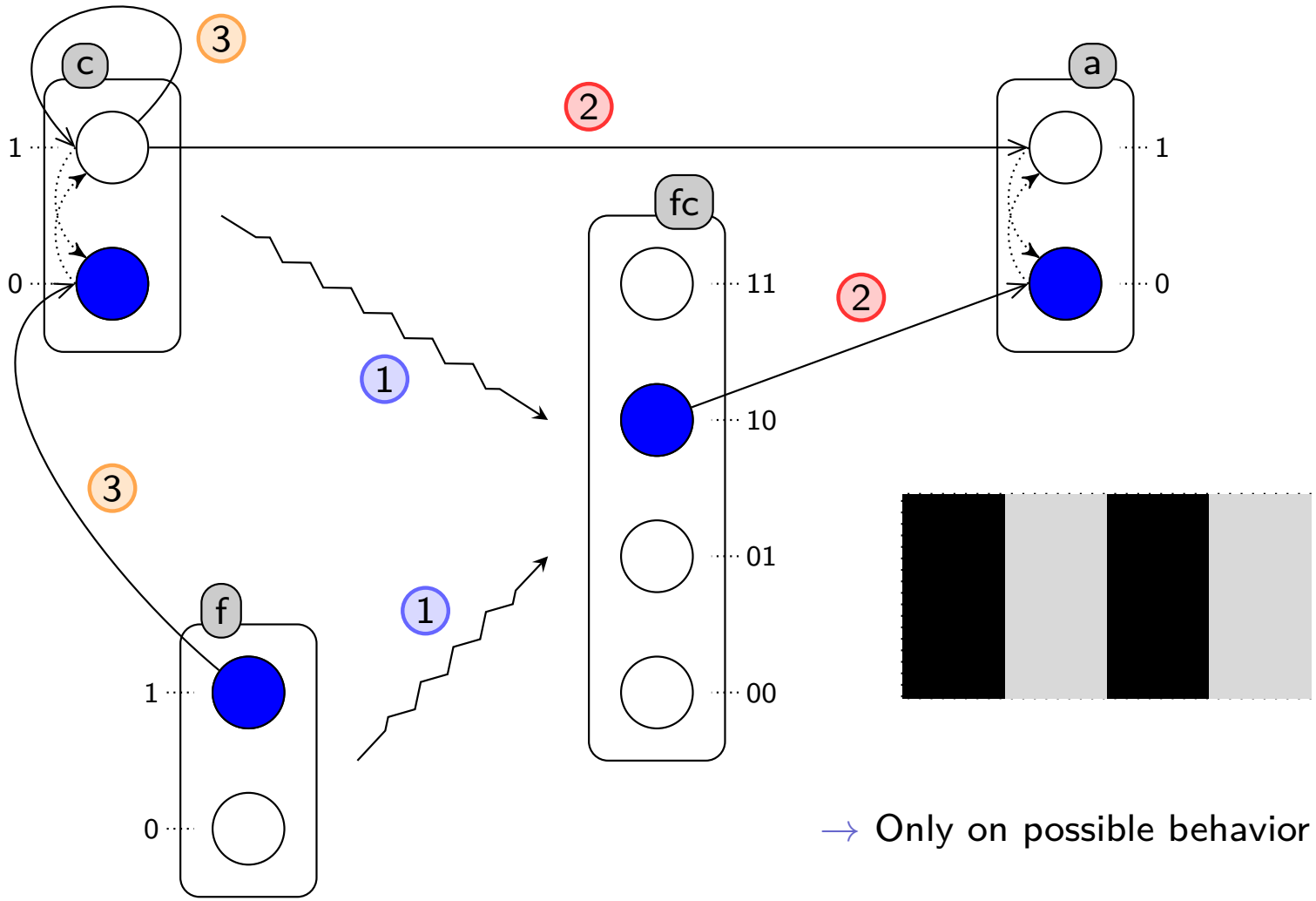
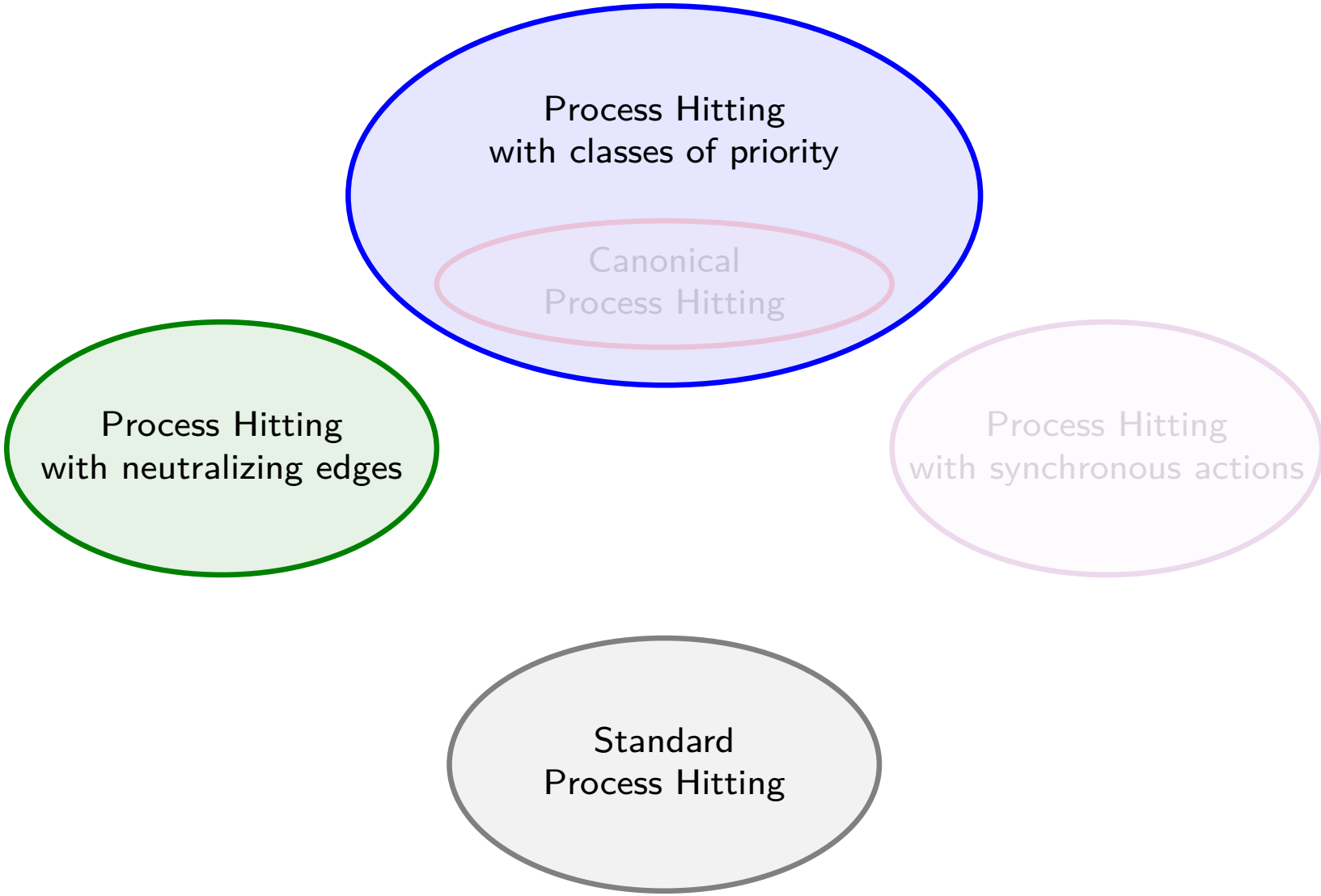


→ Only on possible behavior

Process Hitting with Neutralizing Edges



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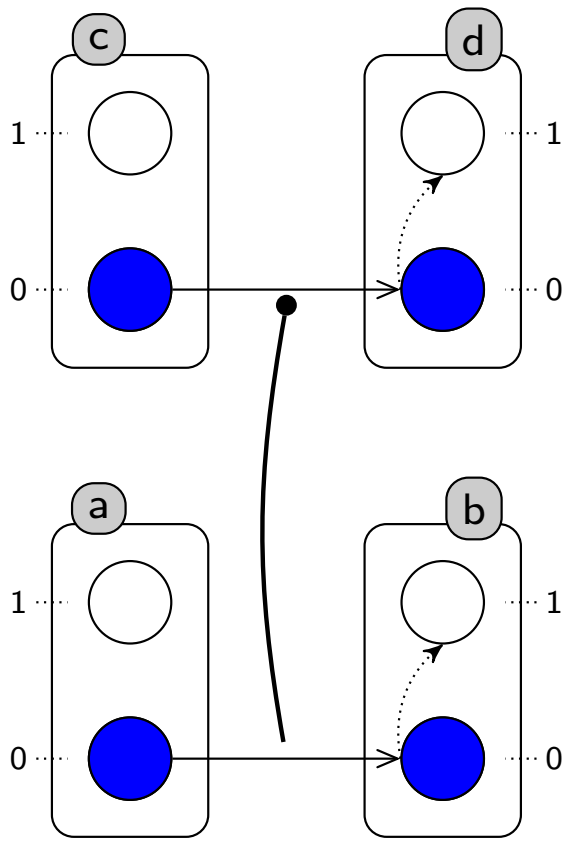

- Integration of temporal data about relative reaction speeds
- Atomistic preemptions between actions similar to "atomistic priorities"

$c_0 \rightarrow d_0 \Rsh d_1$ cannot be plays **while**

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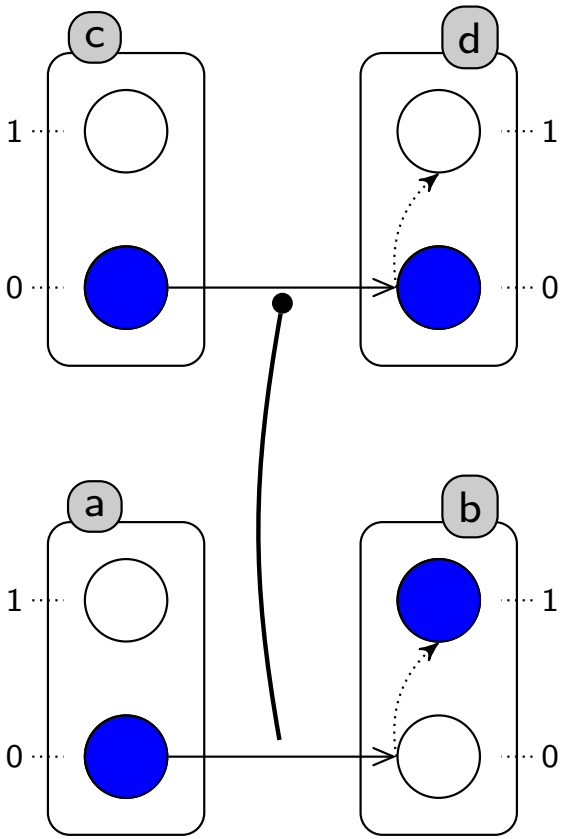

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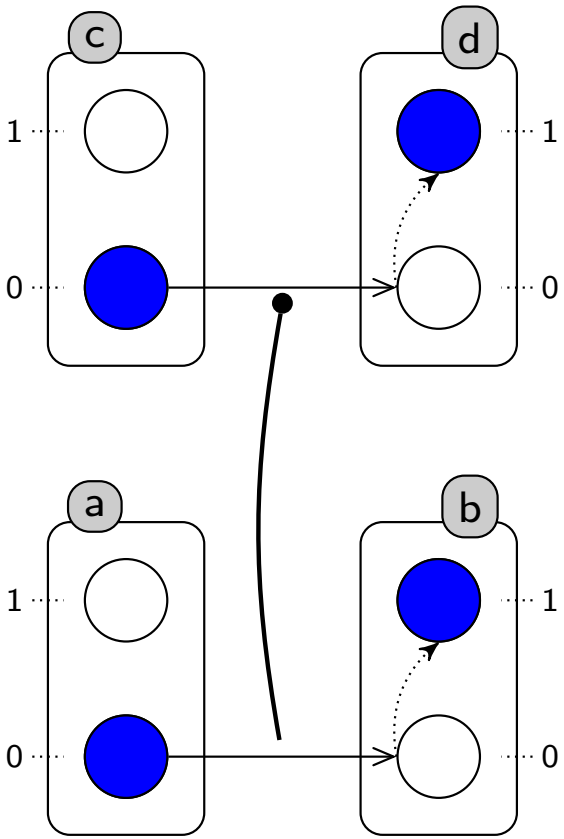

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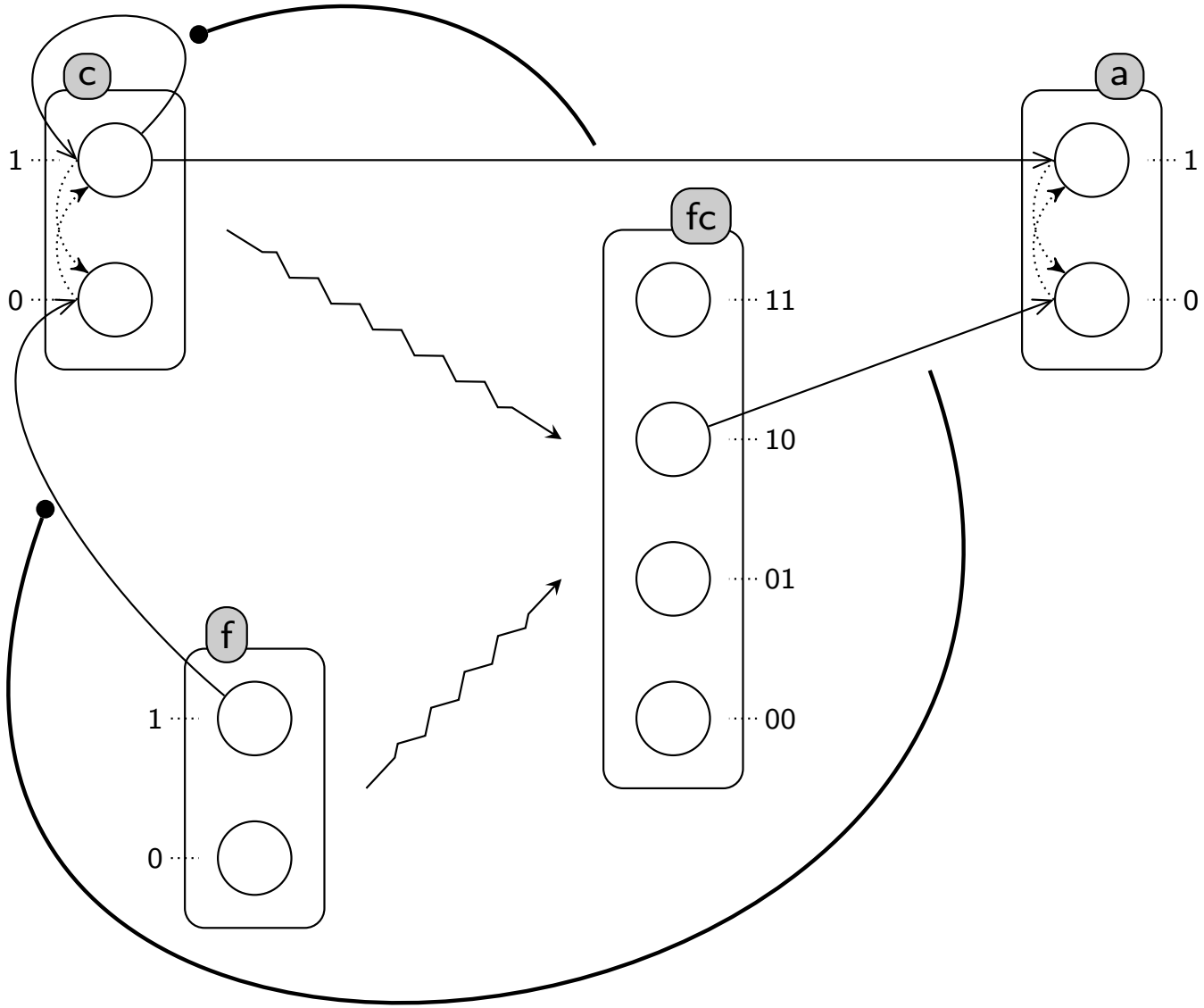
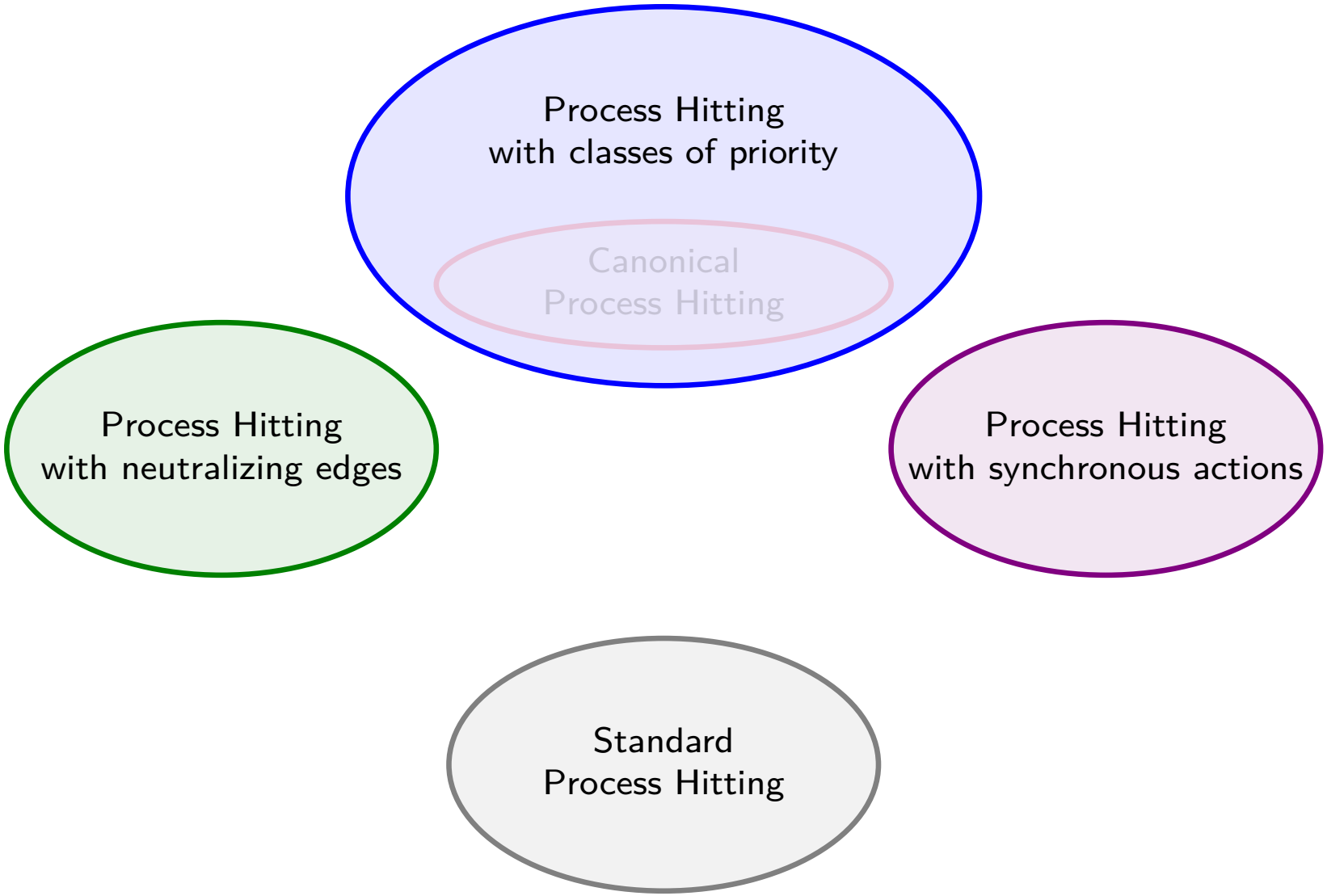


Process Hitting with Synchronous Actions



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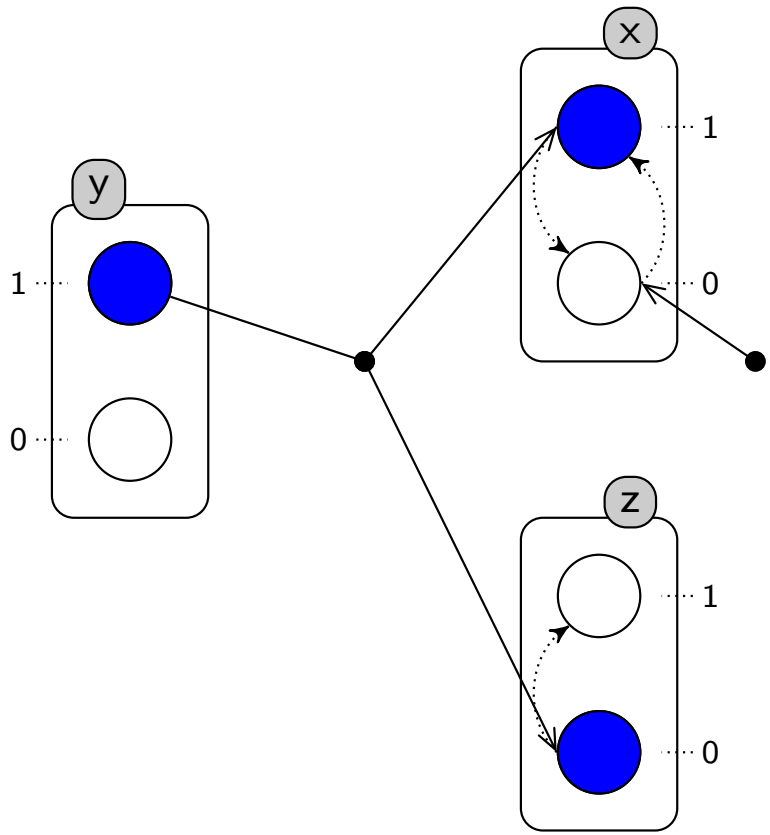


- Synchronizations between actions:
  - All catalysts must be present
  - Reactants are consumed all together
  - Simultaneous creation of the products
- Representation of biochemical equations:

$$X \xrightarrow{Y} Z$$

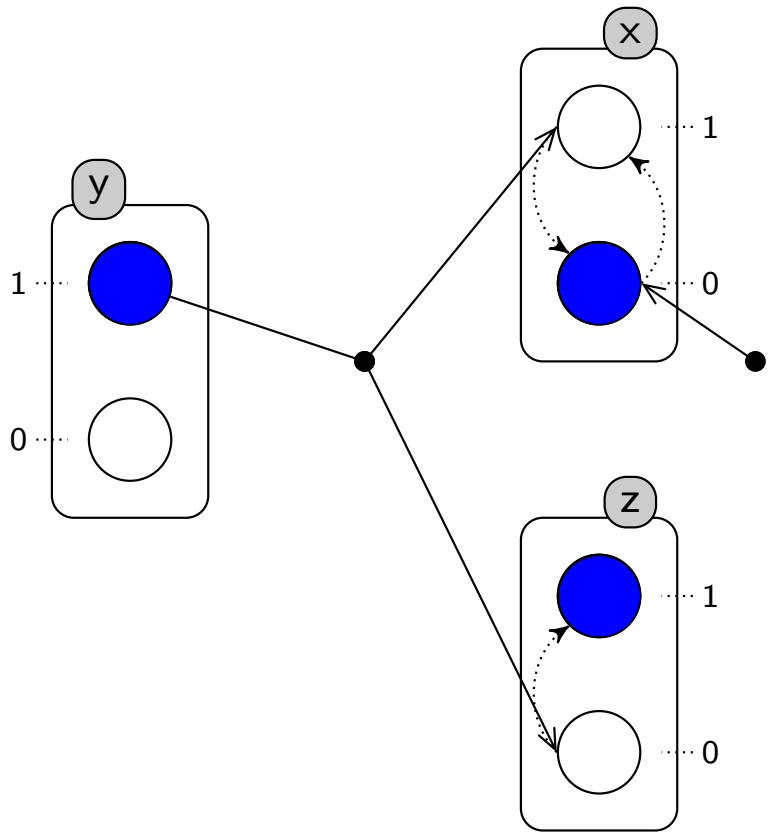
under the form:

$$h_2 = \{x_1, y_1, z_0\} \rightarrowtail \{x_0, z_1\}$$

All processes of A
must be present to play $A \rightarrowtail B$

After the play of $A \rightarrowtail B$,
all processes of B are present

Addition of Synchronous Actions



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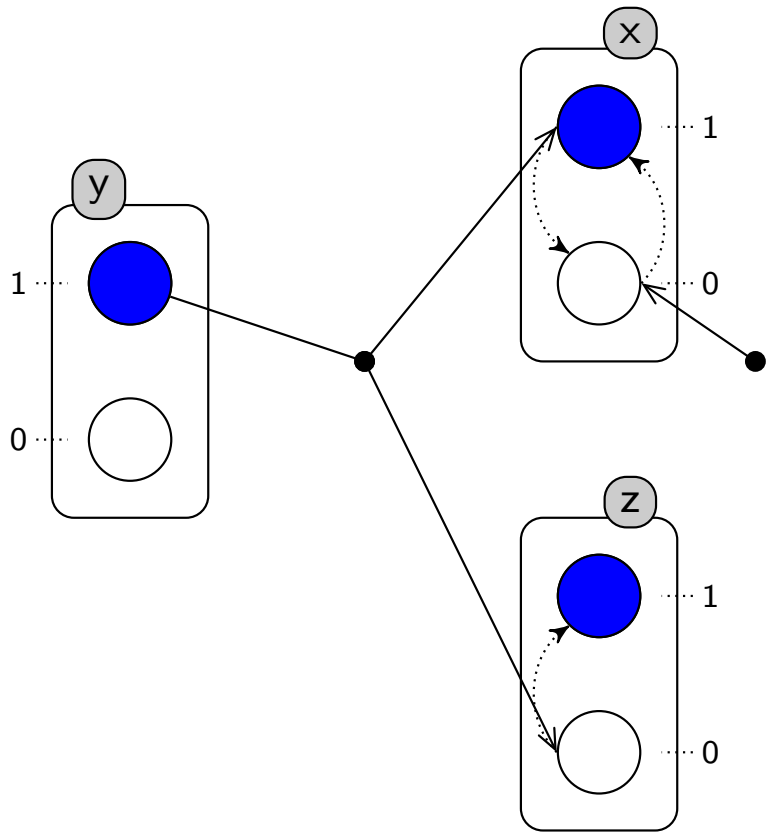

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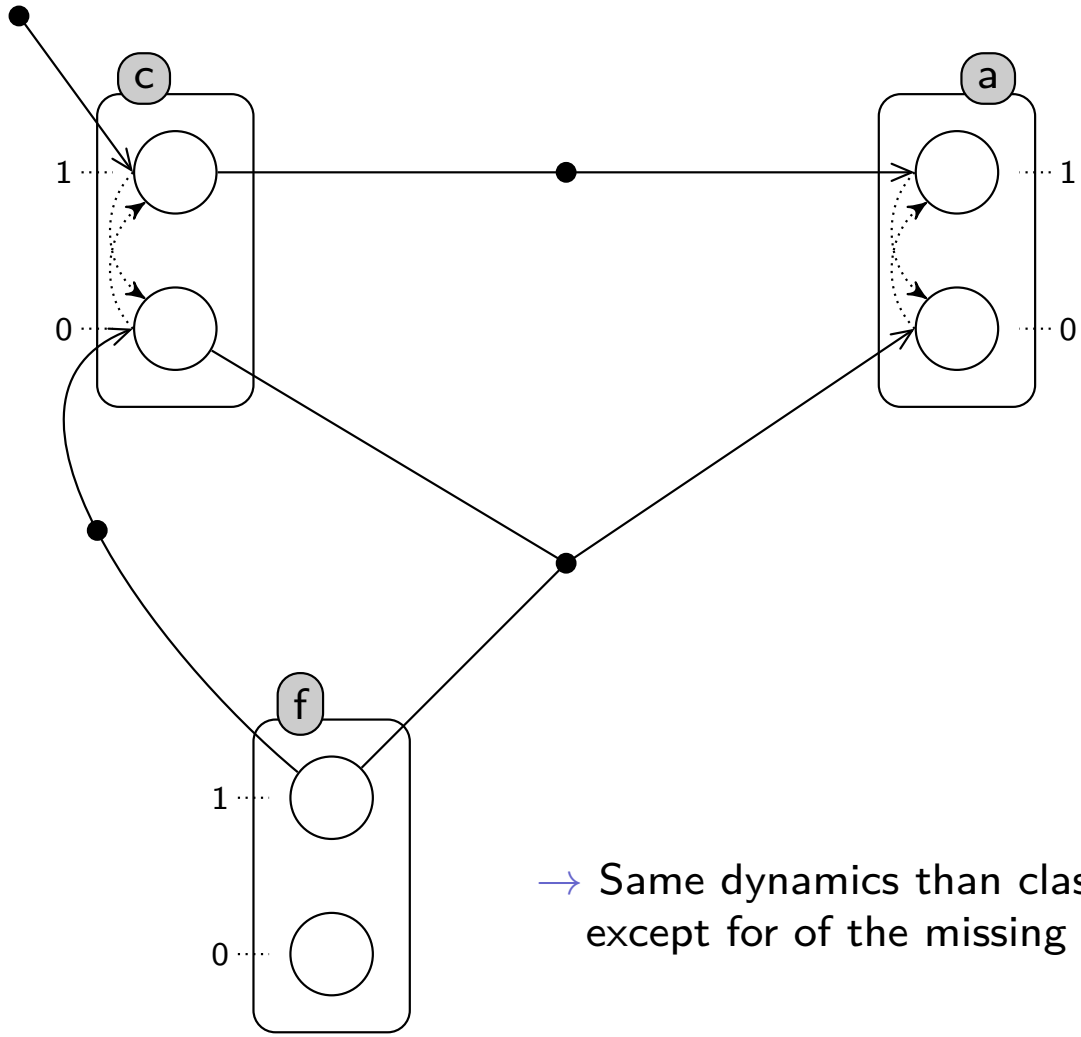
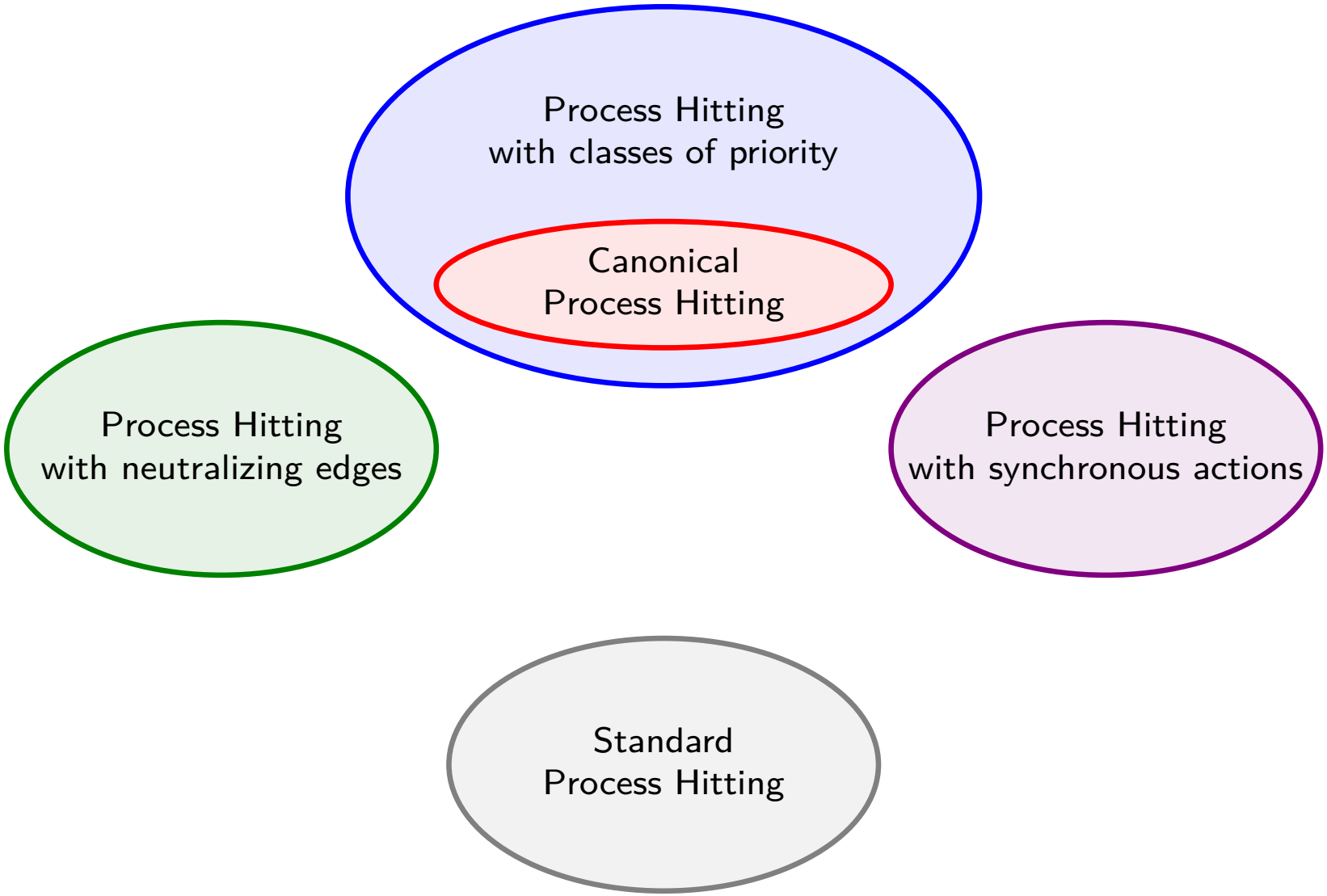
Use of Synchronous Actions



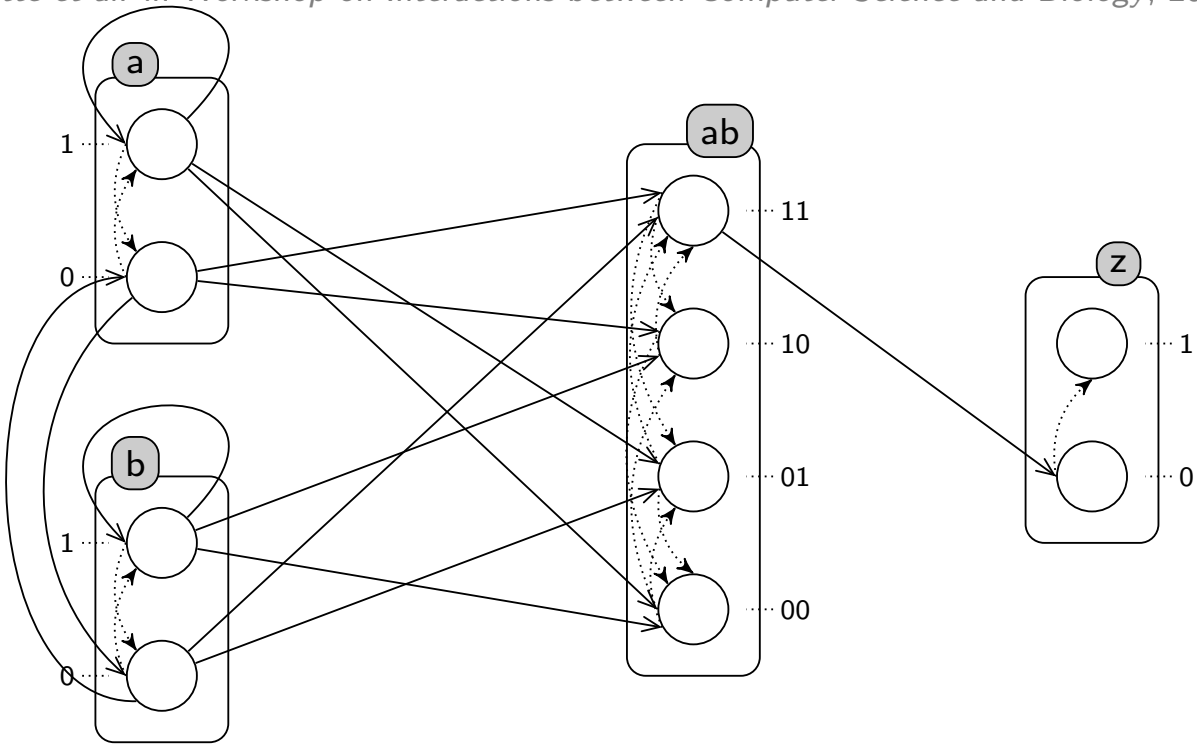
→ Same dynamics than classes of priorities, except for of the missing cooperative sort

Canonical Process Hitting



Temporal Shift in Cooperative Sorts

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



Drawback: the cooperative sorts are too "loose" (temporal shift)

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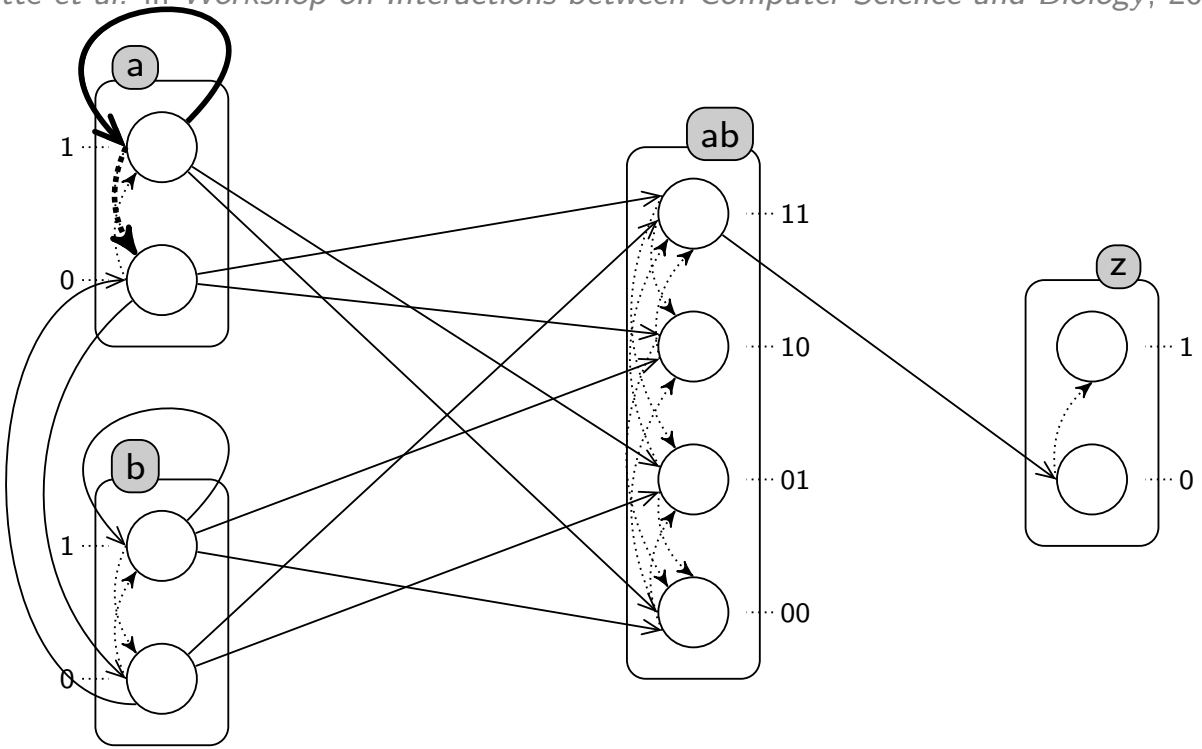

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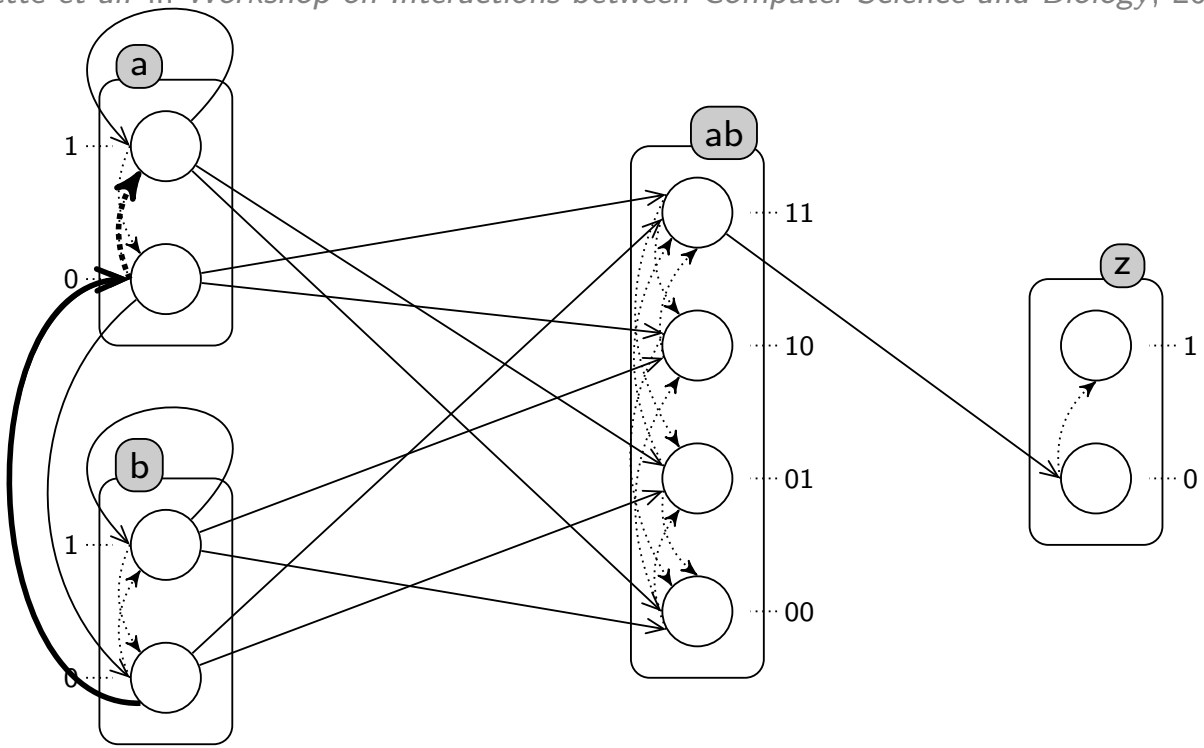

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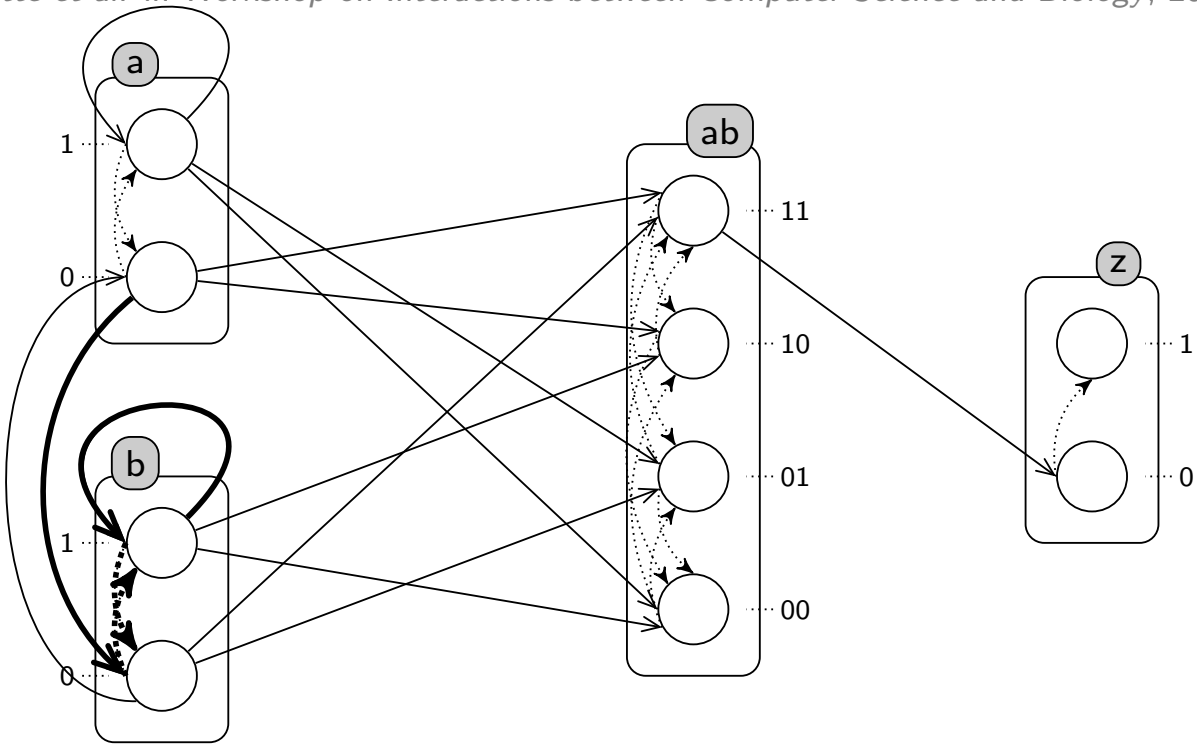

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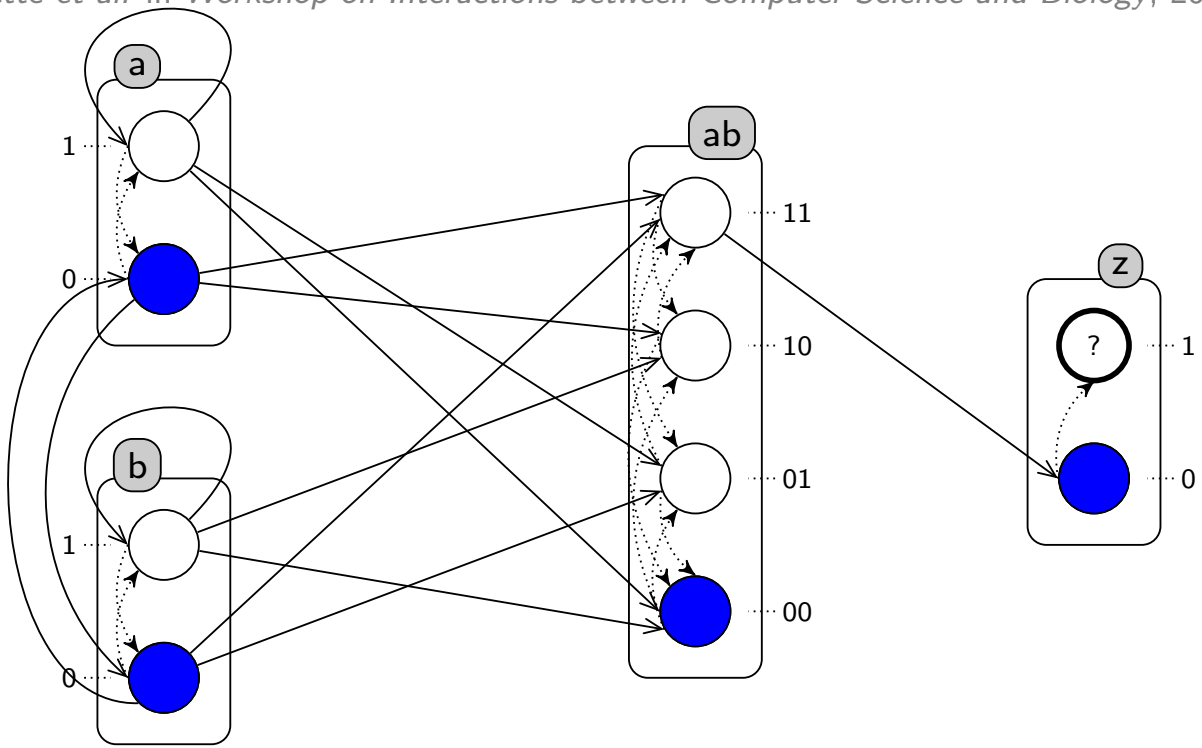

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$\langle a_0, b_0, ab_{00}, z_0 \rangle$

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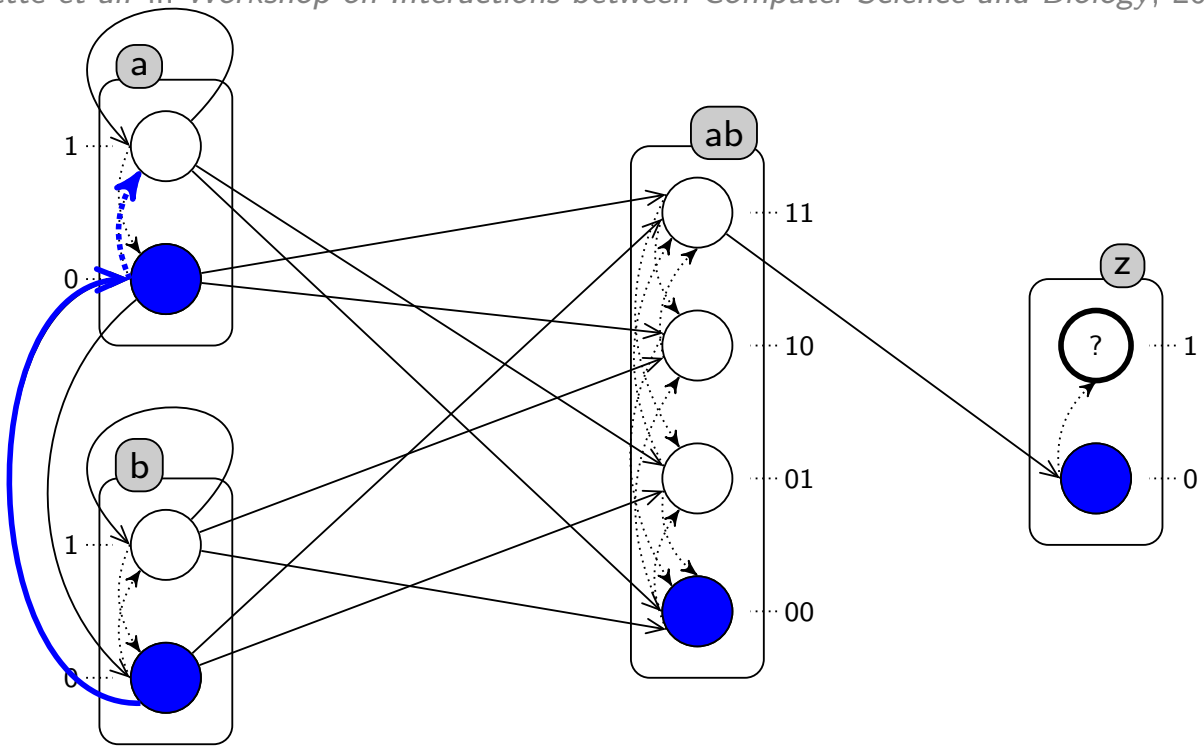

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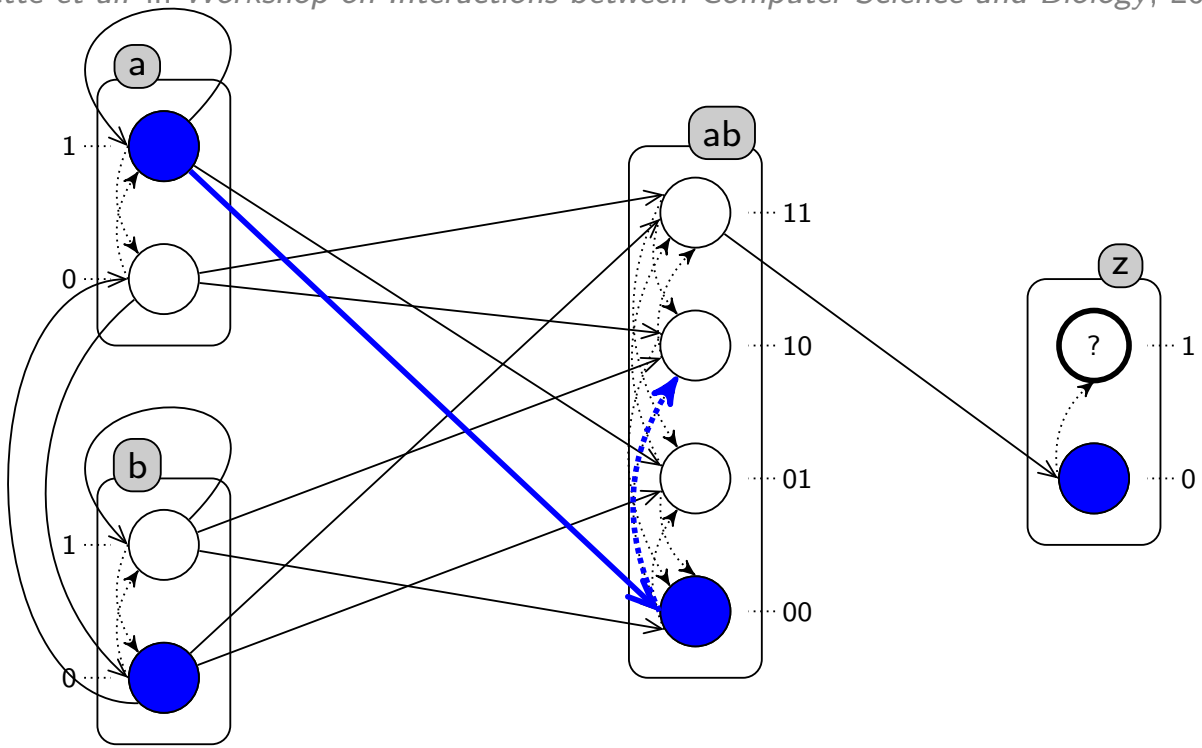

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$\langle a_0, b_0, ab_{00}, z_0 \rangle \rightarrow \langle a_1, b_0, ab_{00}, z_0 \rangle$

Temporal Shift in Cooperative Sorts

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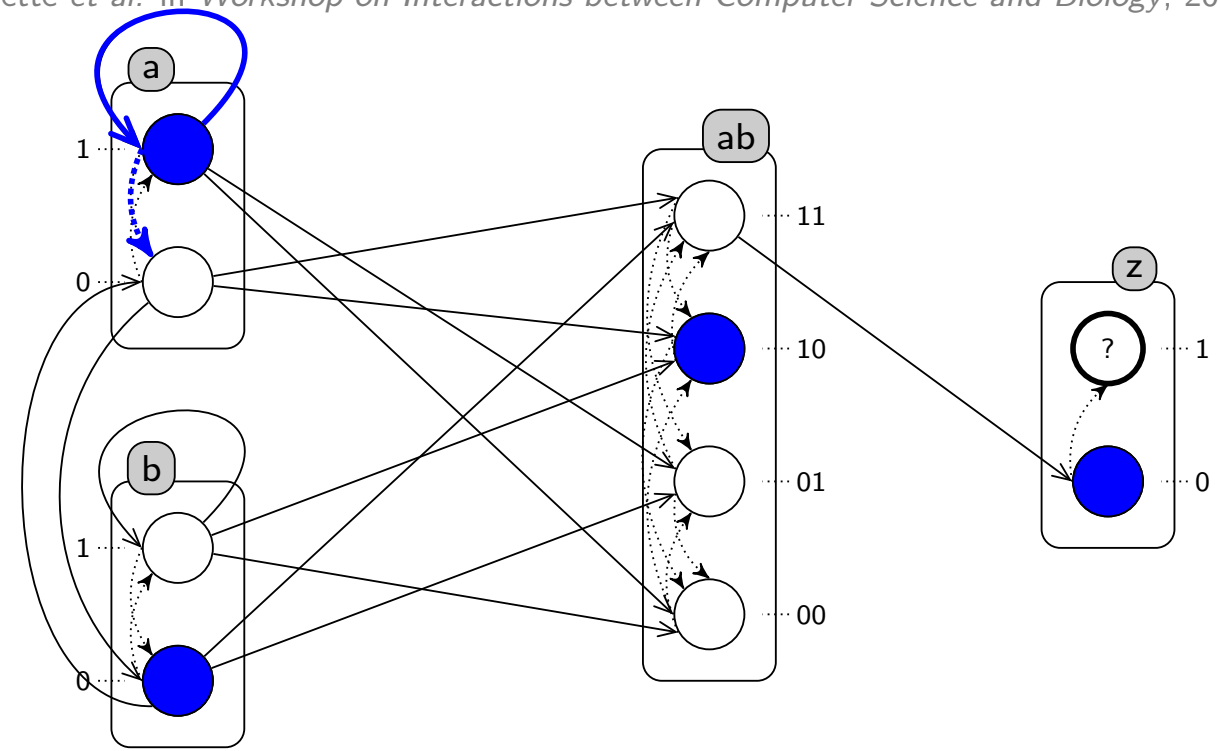

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$\langle a_0, b_0, ab_{00}, z_0 \rangle \rightarrow \langle a_1, b_0, ab_{00}, z_0 \rangle \rightarrow \langle a_1, b_0, ab_{10}, z_0 \rangle$

Temporal Shift in Cooperative Sorts

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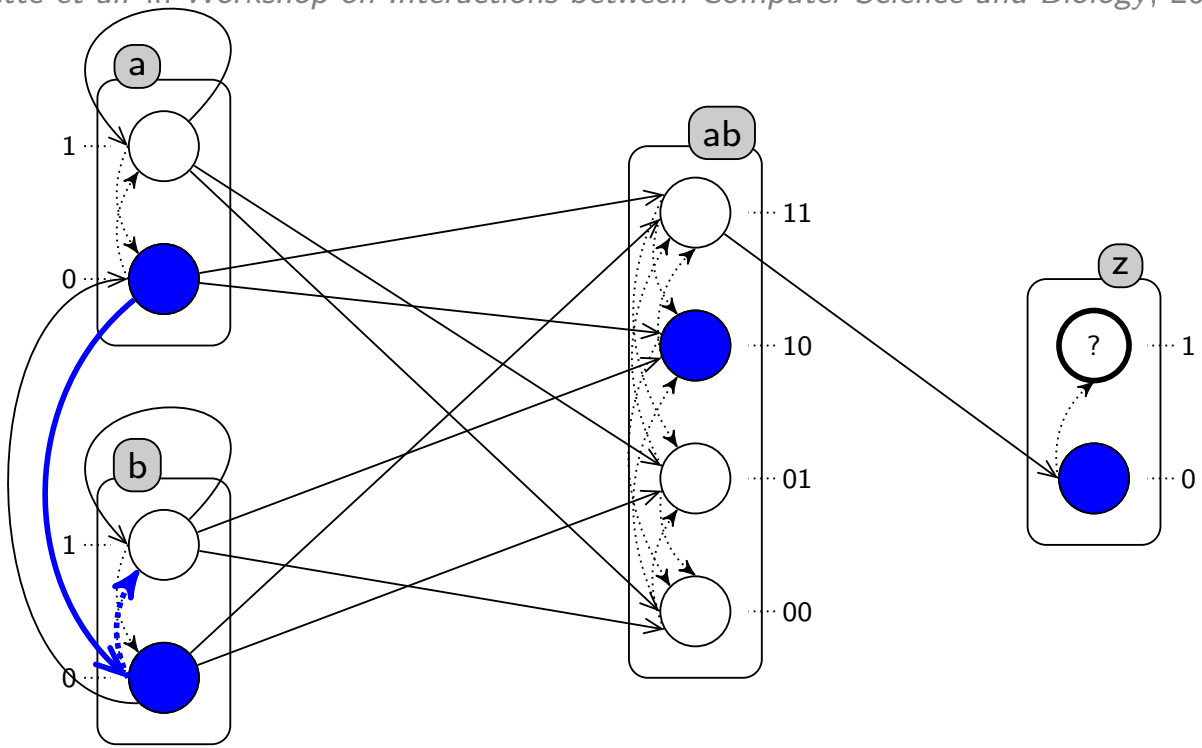

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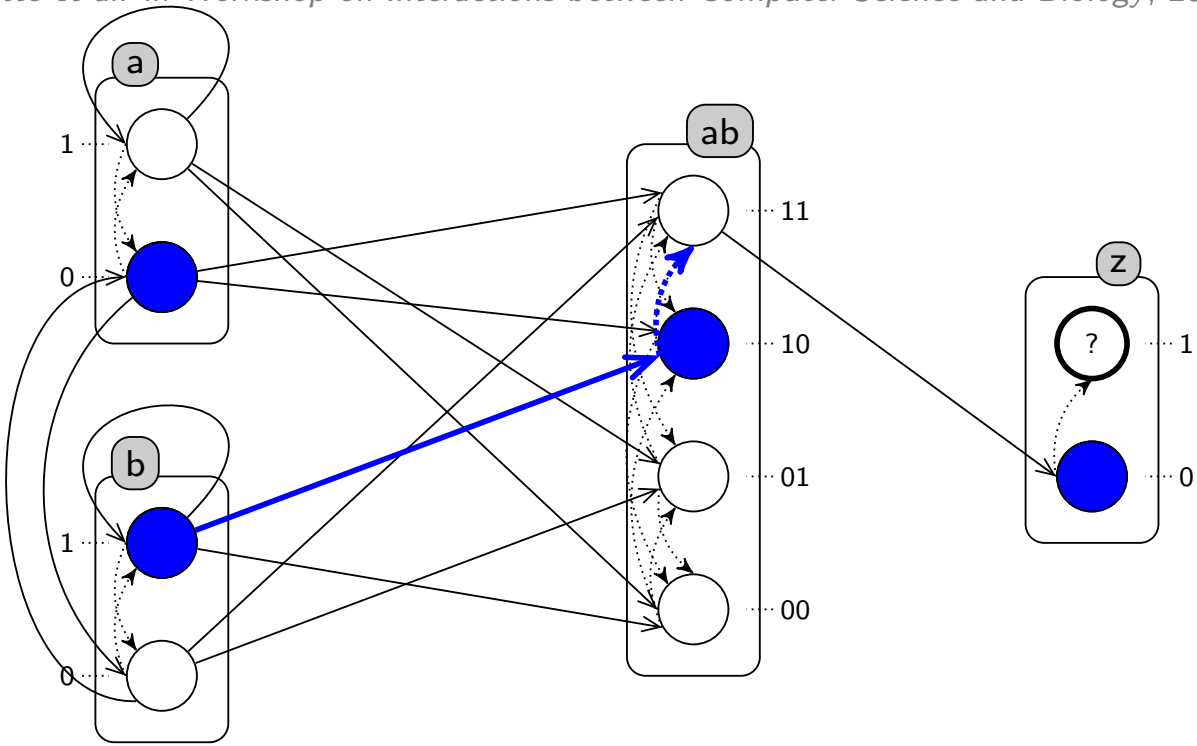

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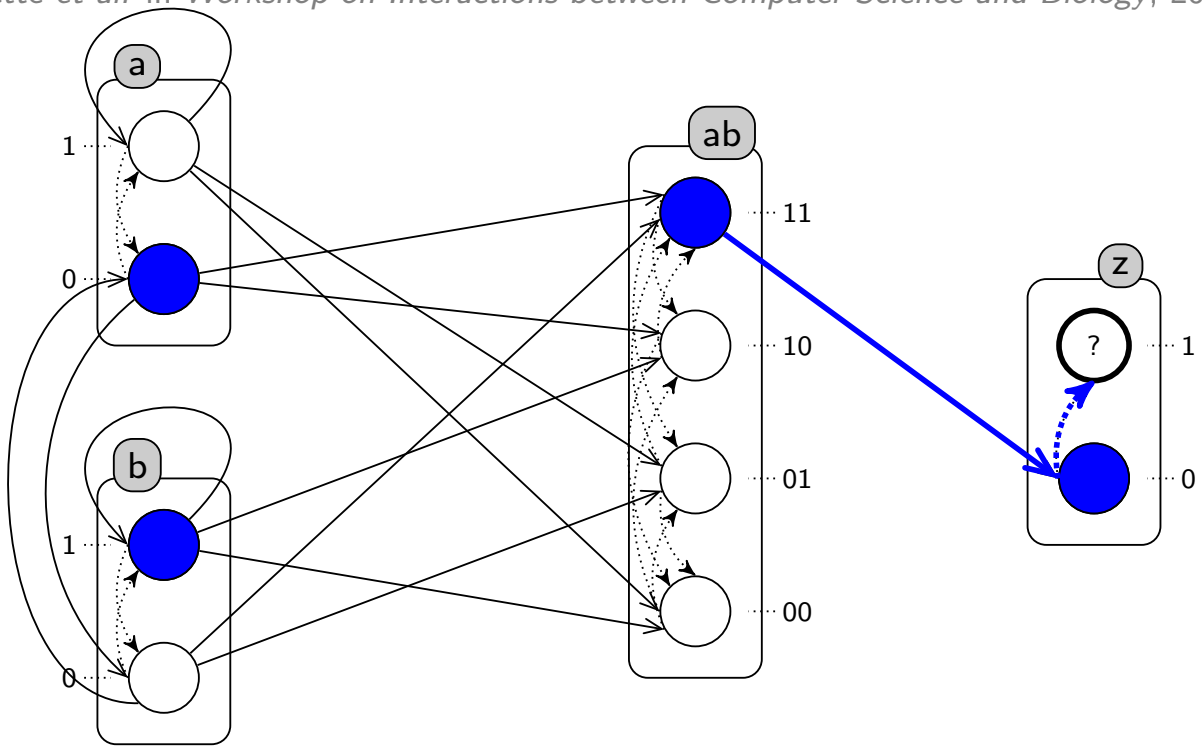
$\rightarrow \langle a_0, b_1, ab_{10}, z_0 \rangle$

Temporal Shift in Cooperative Sorts

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



Drawback: the cooperative sorts are too "loose" (temporal shift)

$\langle a_0, b_0, ab_{00}, z_0 \rangle \to \langle a_1, b_0, ab_{00}, z_0 \rangle \to \langle a_1, b_0, ab_{10}, z_0 \rangle \to \langle a_0, b_0, ab_{10}, z_0 \rangle$
$\to \langle a_0, b_1, ab_{10}, z_0 \rangle \to \langle a_0, b_1, ab_{11}, z_0 \rangle$

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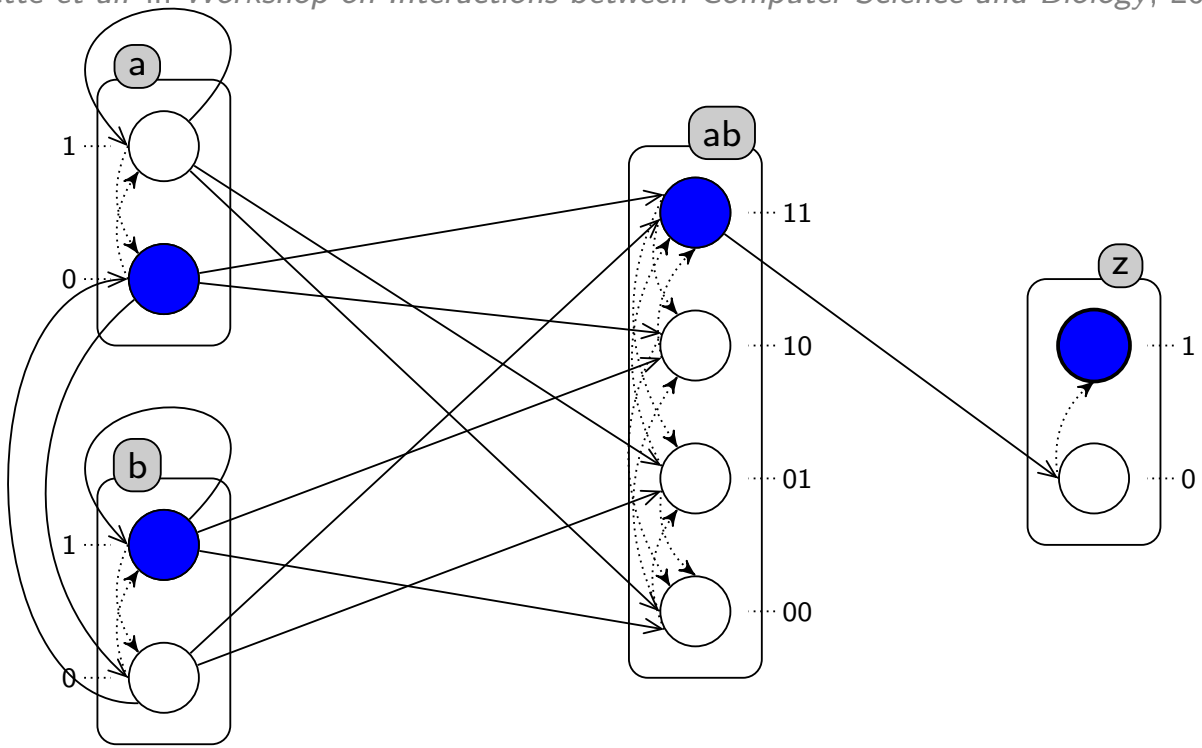

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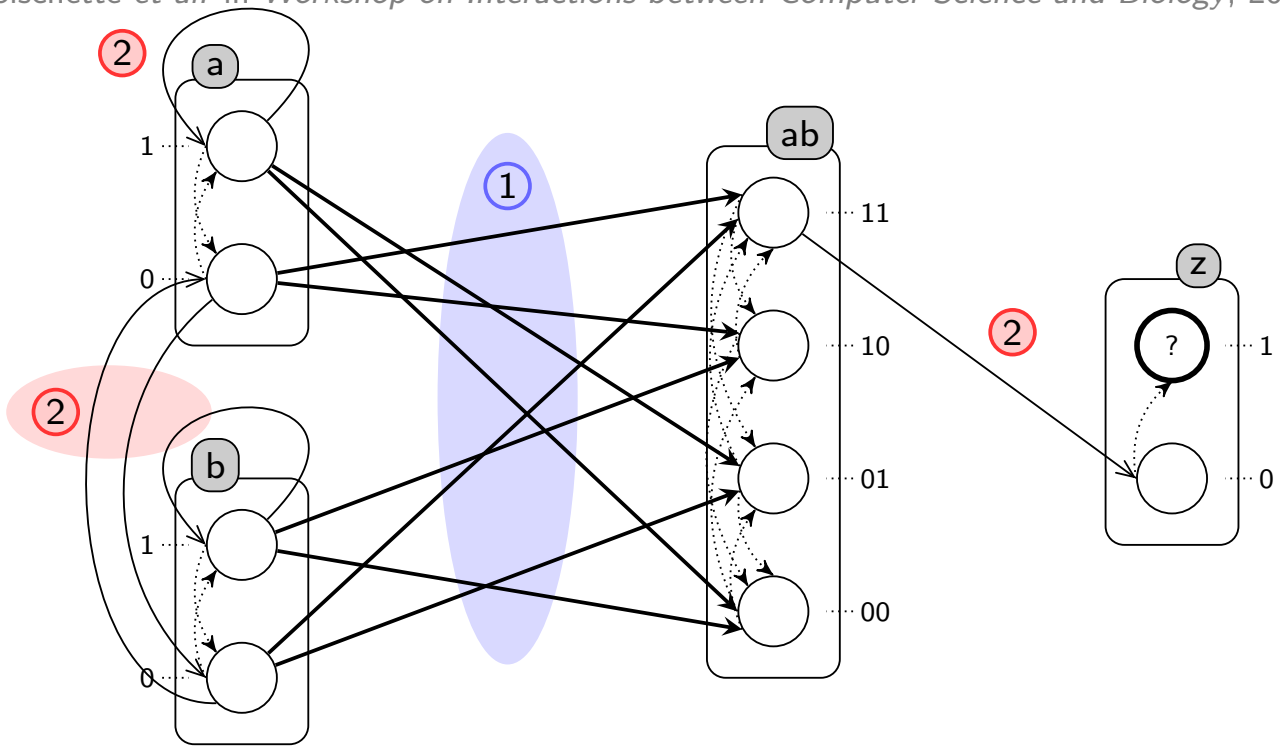
$\to \langle a_0, b_1, ab_{10}, z_0\rangle \to \langle a_0, b_1, ab_{11}, z_0\rangle \to \langle a_0, b_1, ab_{11}, z_1\rangle$

Expected behavior: $a_1 \wedge b_1$ **simultaneously** i.e. "in the same state"
Obtained behavior: $\mathbf{P}(a_1) \wedge \mathbf{P}(b_1)$ with $\mathbf{P}$ = "previously"

Canonical Process Hitting

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



- Primary actions (updating cooperative sorts) → (1)
  non-biological / non-controllable actions
- Secondary actions (all the other ones) → (2)
  biological / controllable actions / with delays

Canonical Process Hitting

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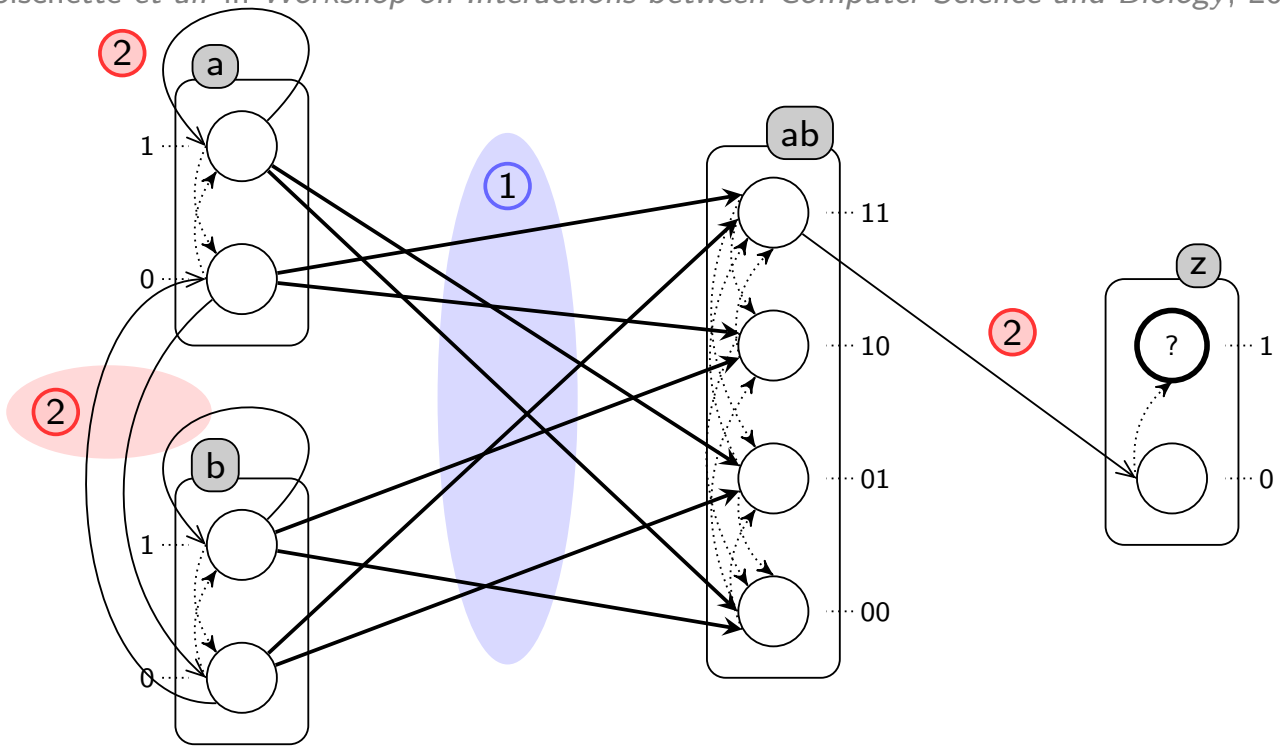

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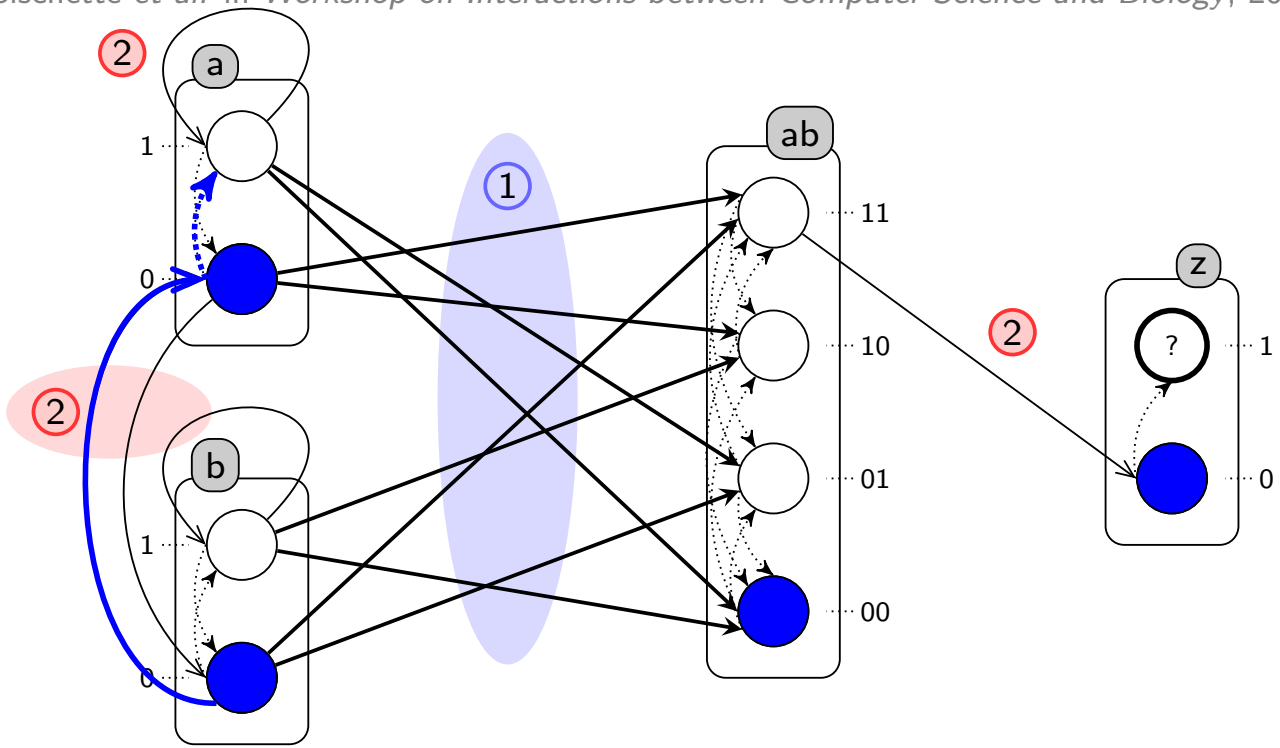

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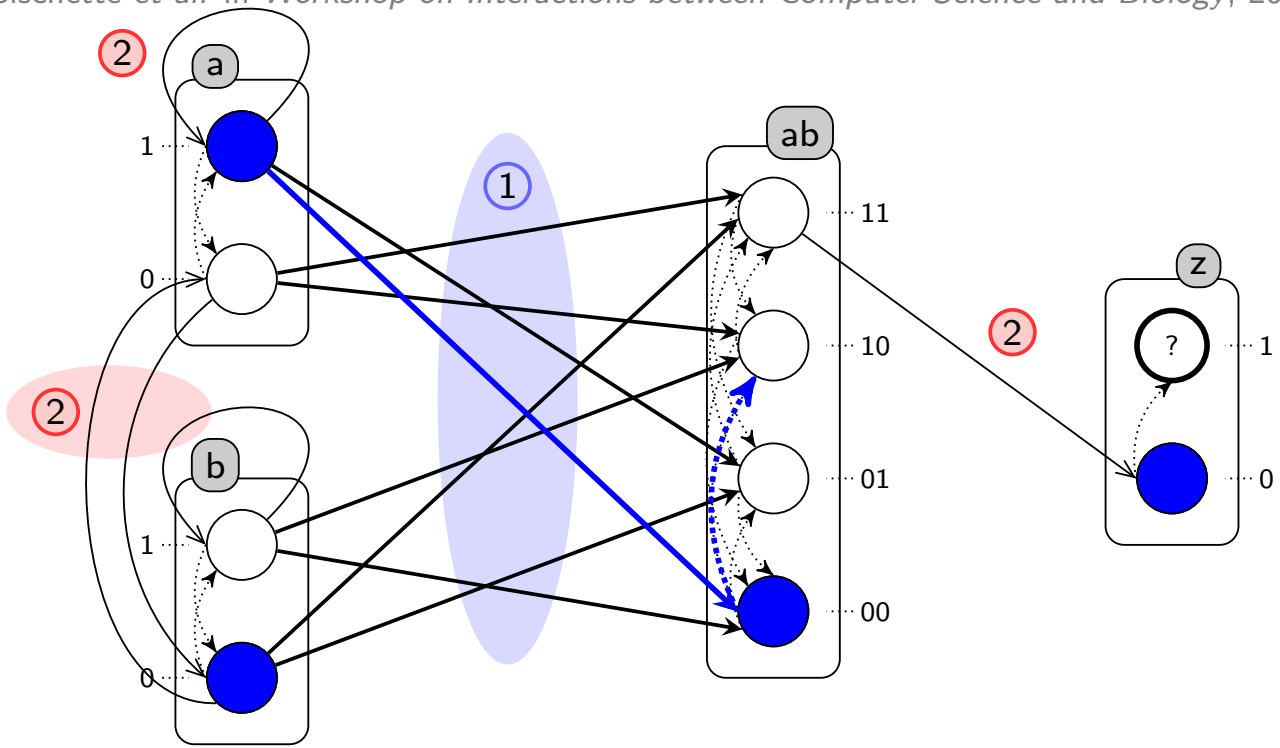

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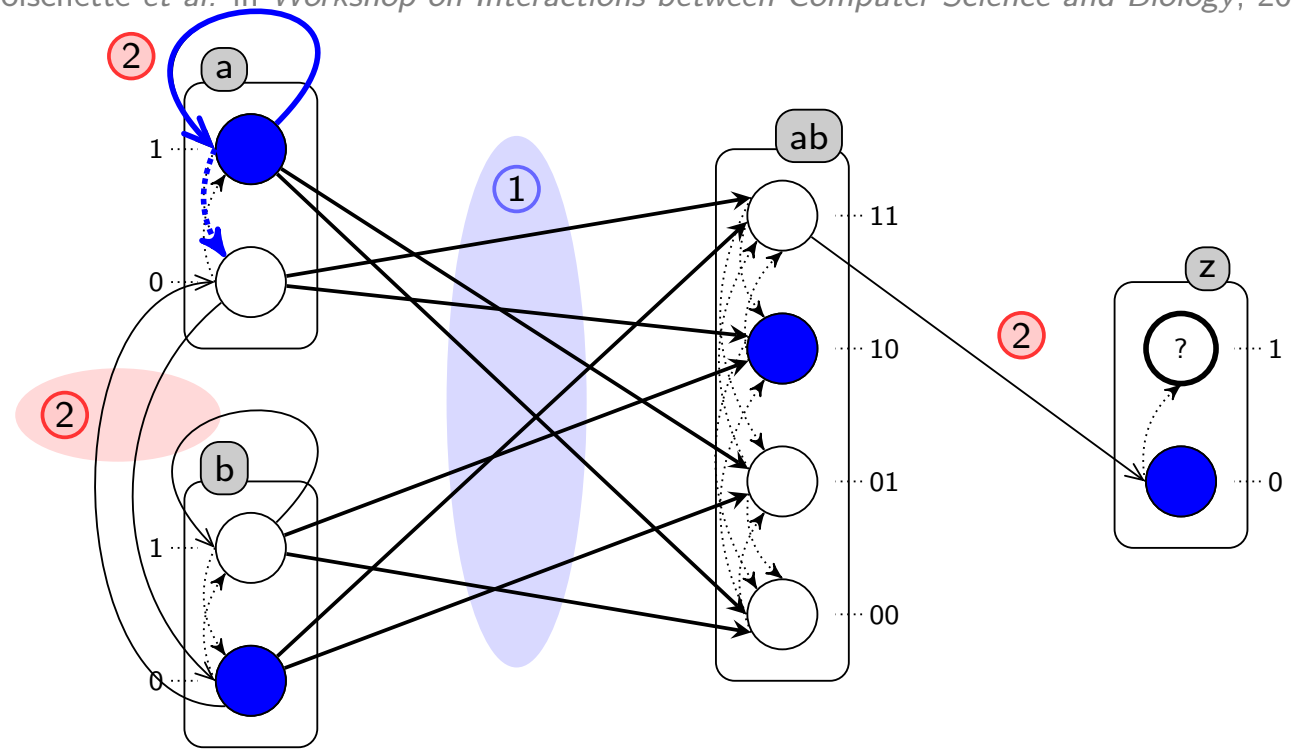

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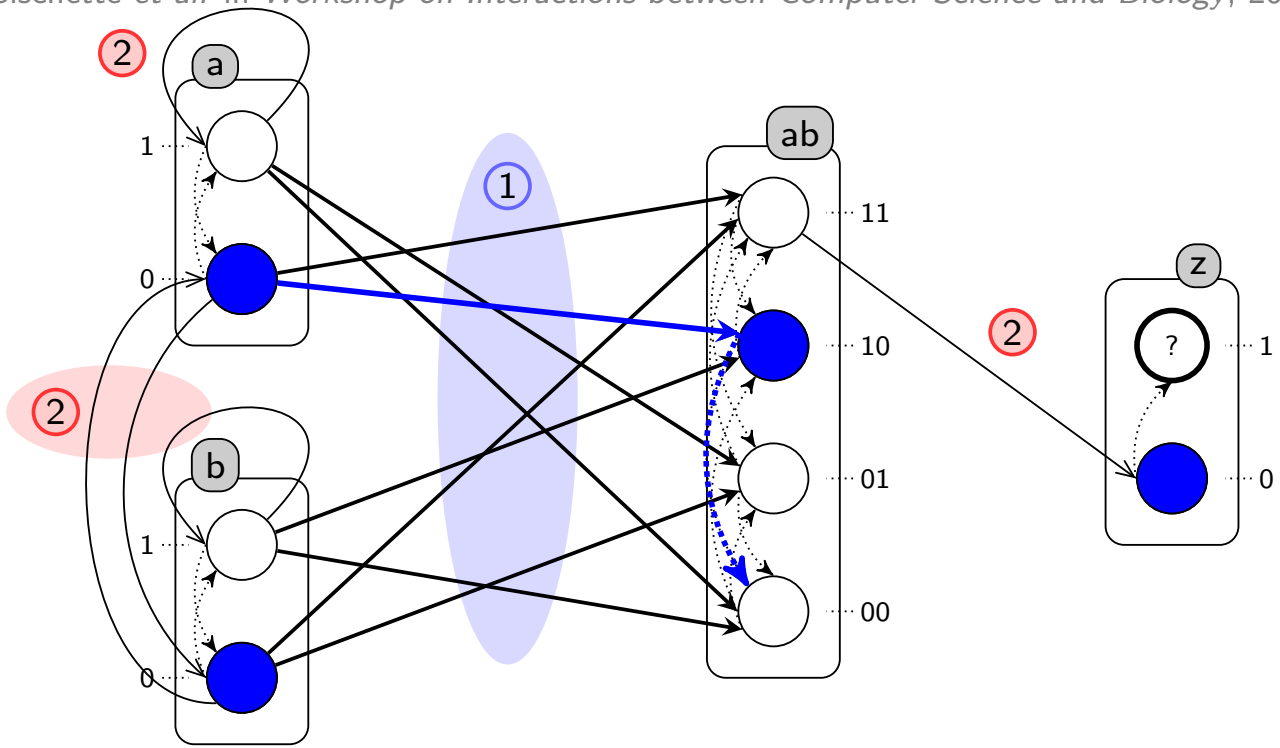

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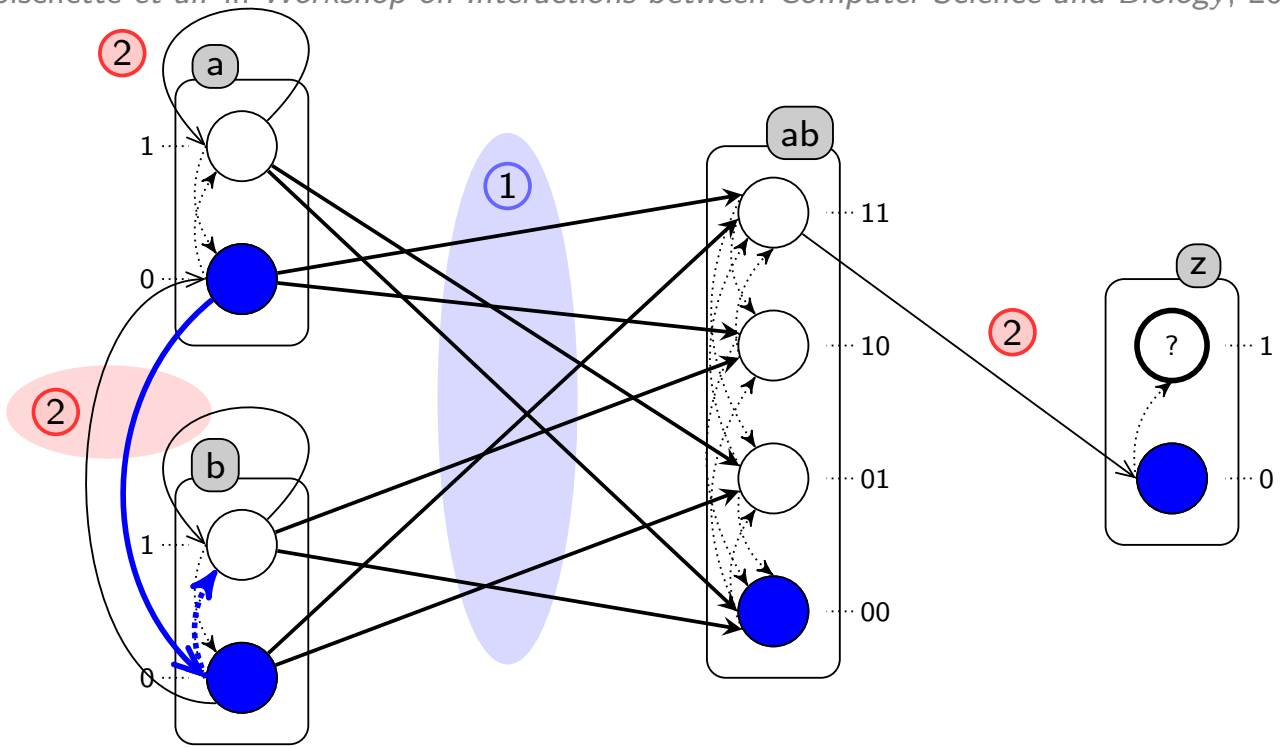

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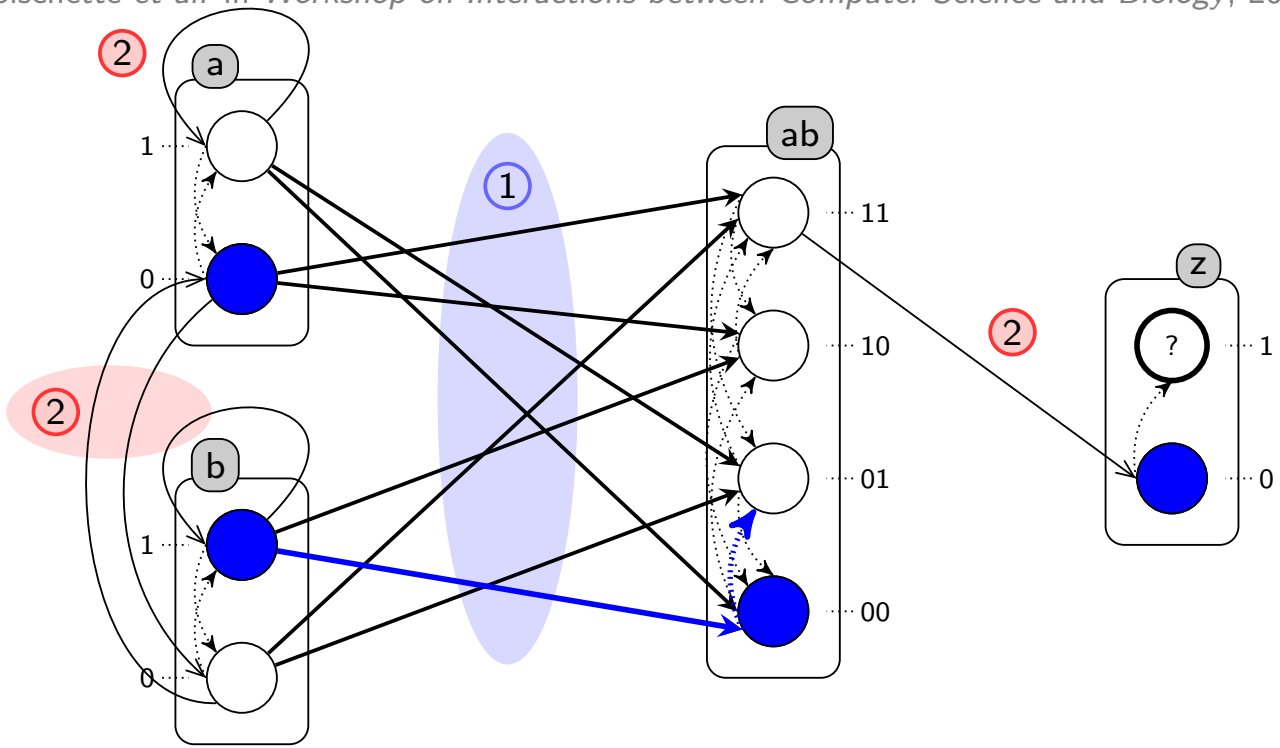

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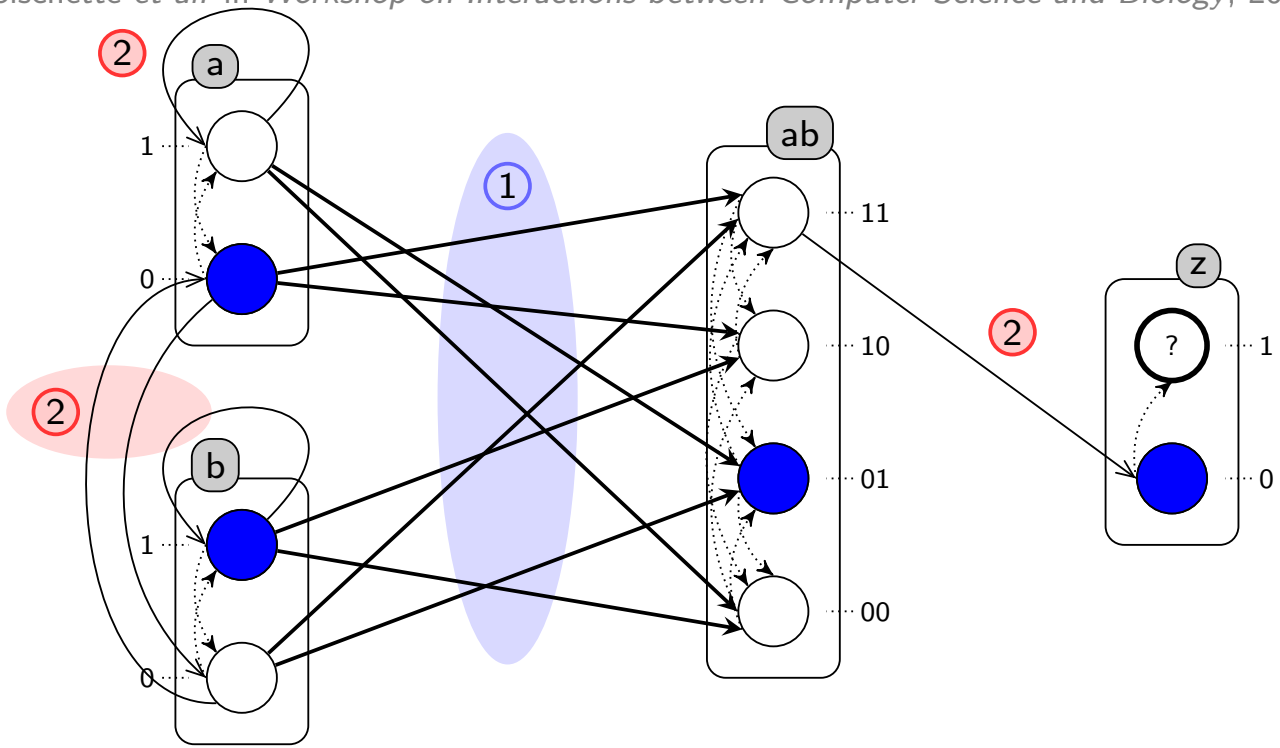

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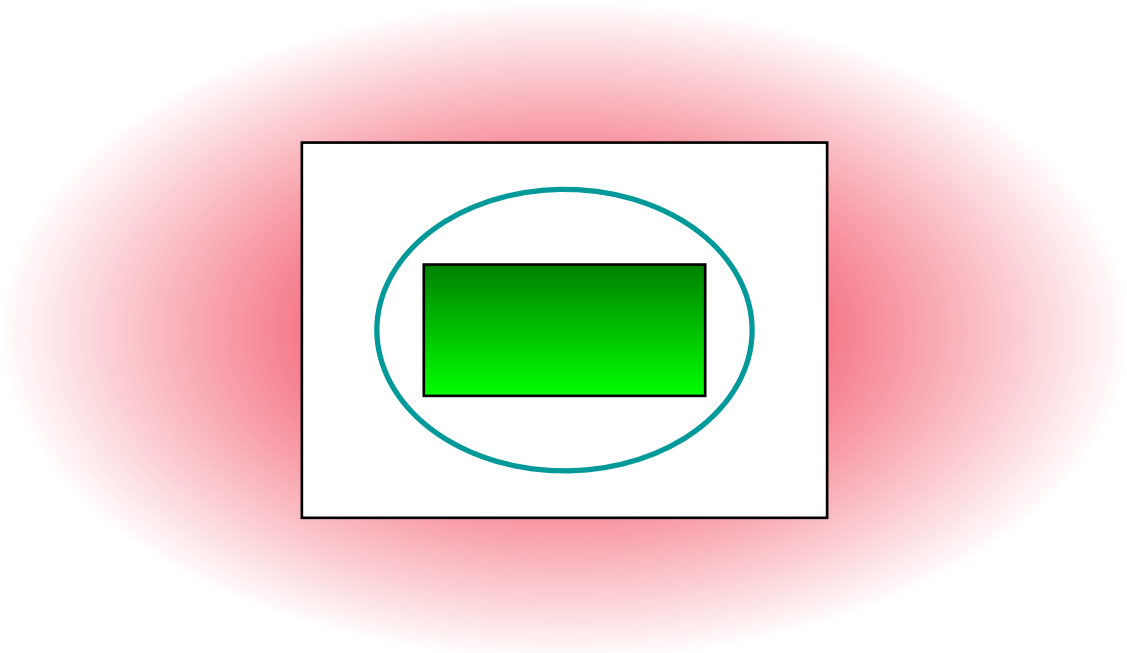
Static Analysis of Canonical Process Hitting

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]

Adding priorities restricts the possible dynamics (preemptions)

→ Invalidates the previous under-approximation



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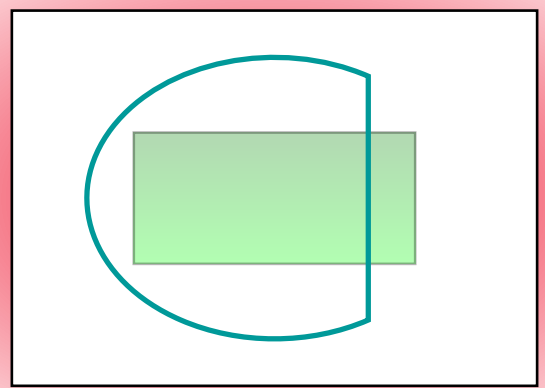

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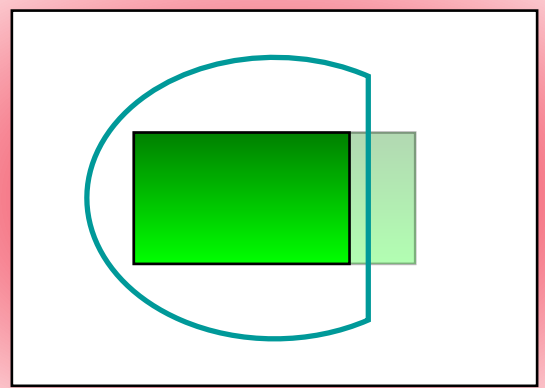

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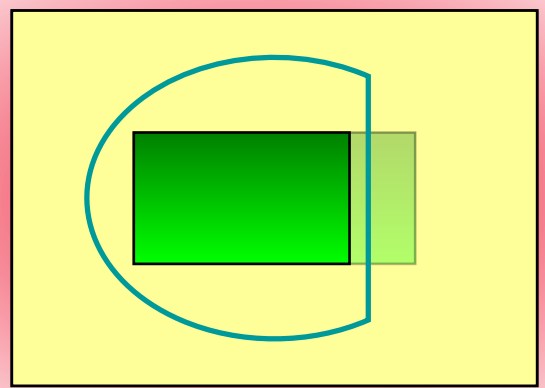

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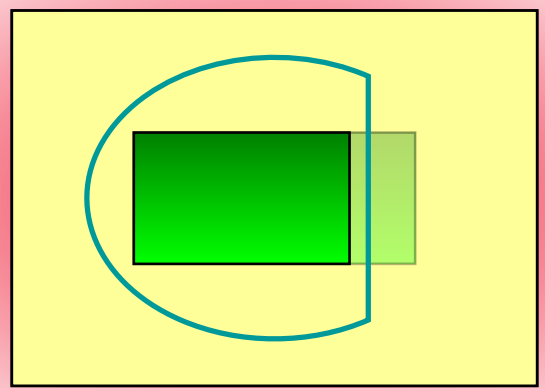

Similar complexity for a more expressive formalism

→ Still efficient for big models

→ Finer under-approximation

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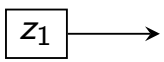

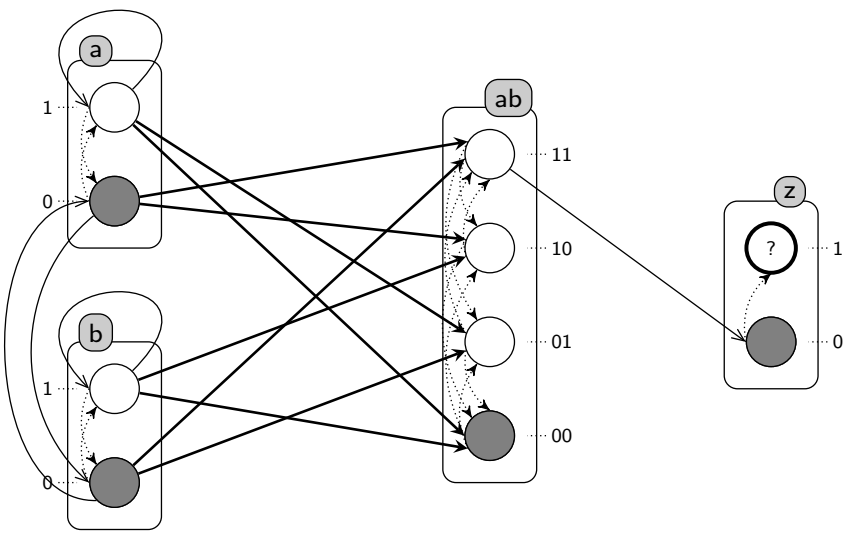

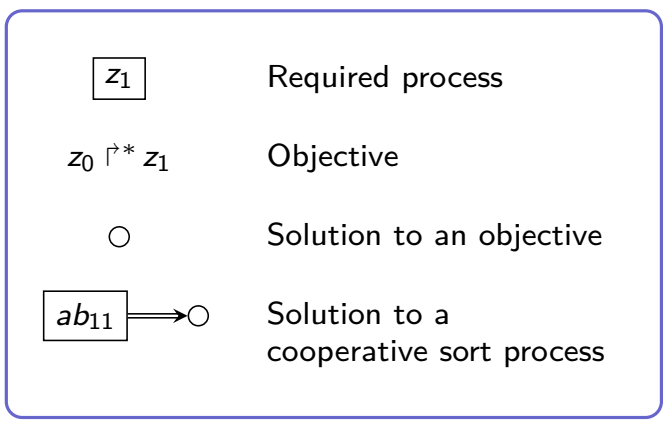

Static Analysis of Canonical Process Hitting

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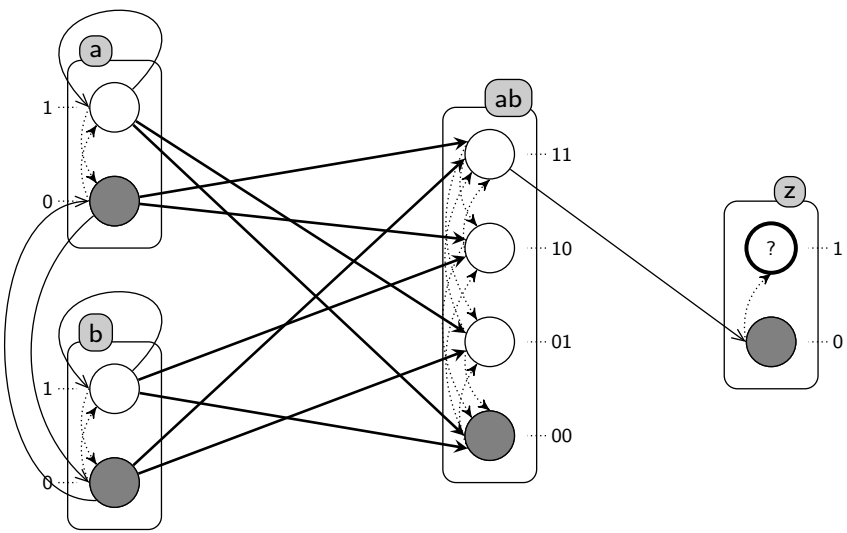
$\boxed{z_1} \longrightarrow z_0 \,\vec{\lceil}^{*}\, z_1 \longrightarrow$



$\boxed{z_1}$	Required process
$z_0 \,\vec{\lceil}^{*}\, z_1$	Objective
○	Solution to an objective
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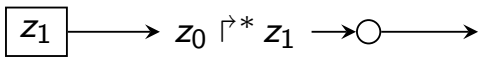

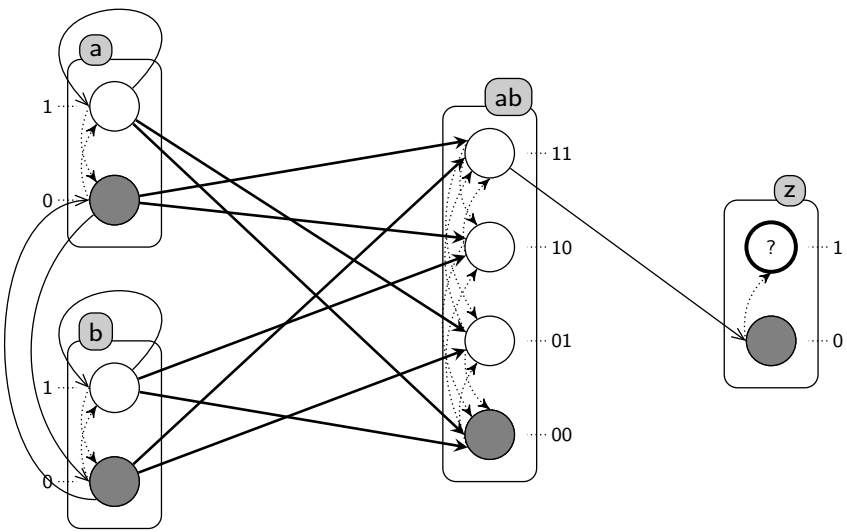

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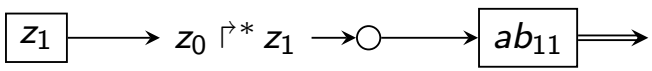

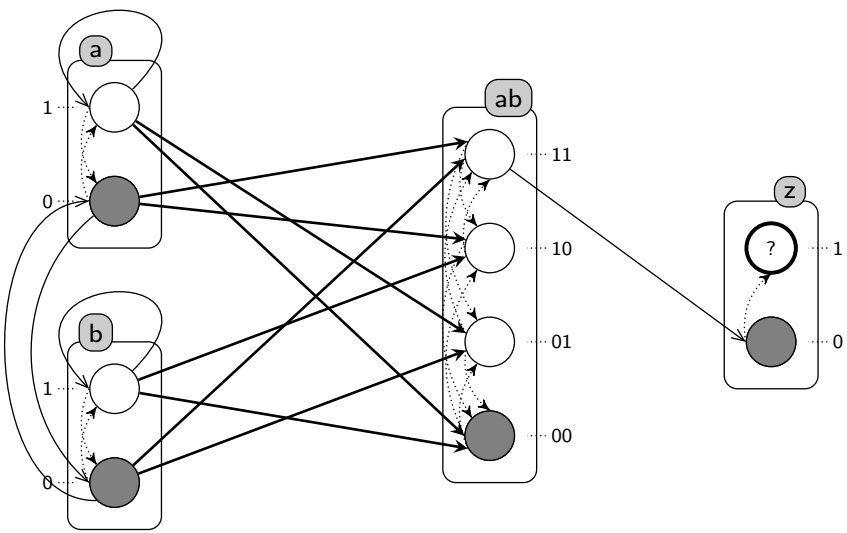

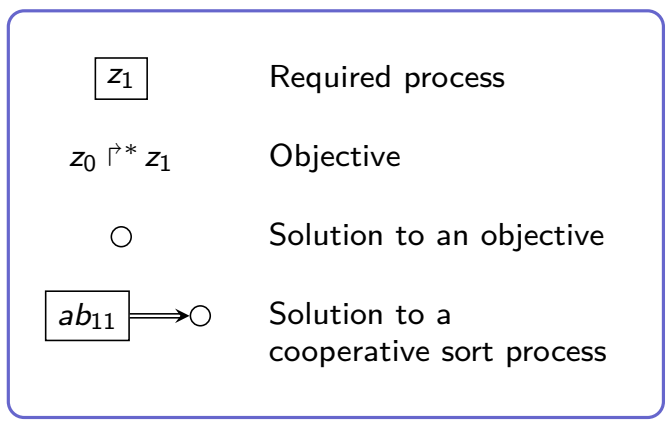

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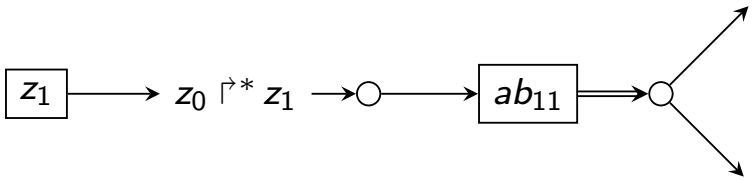

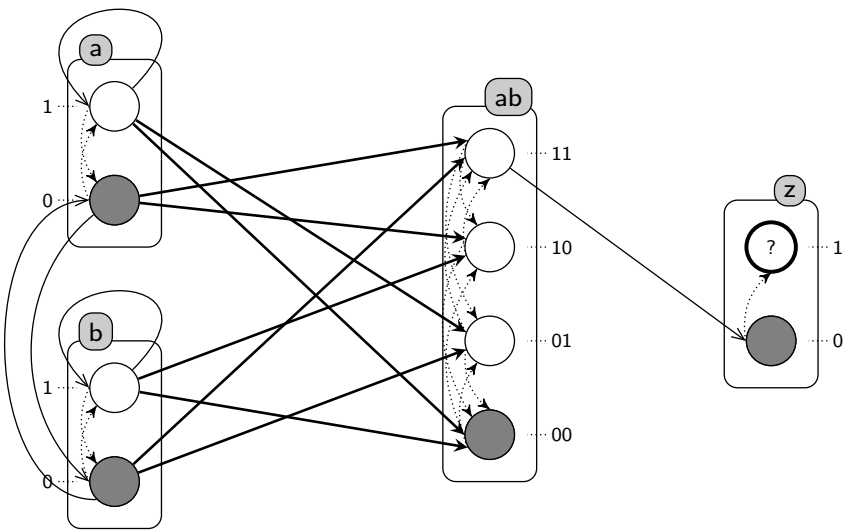

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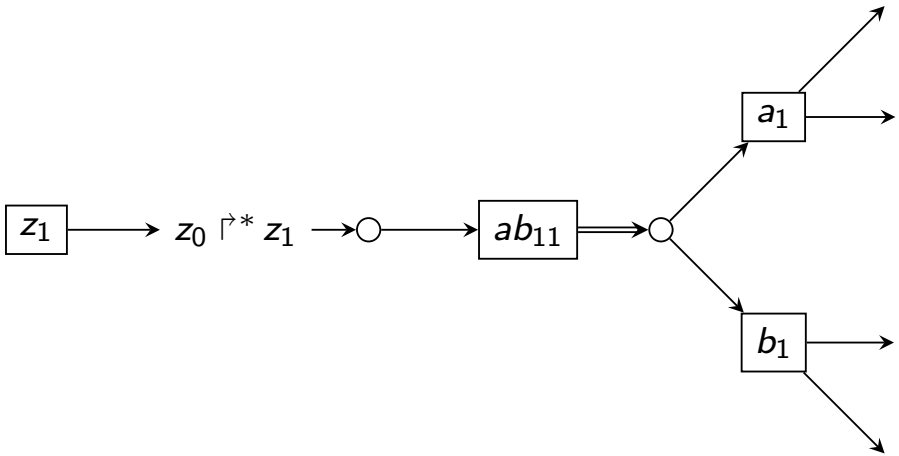

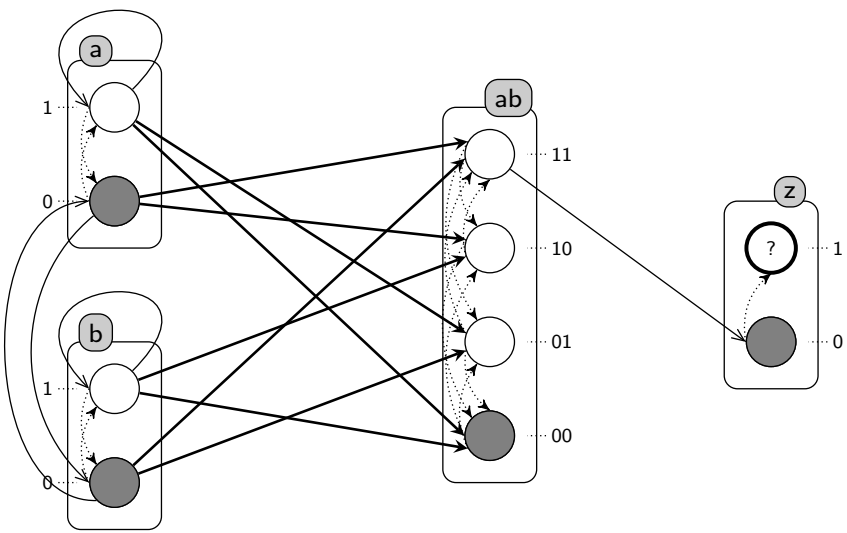

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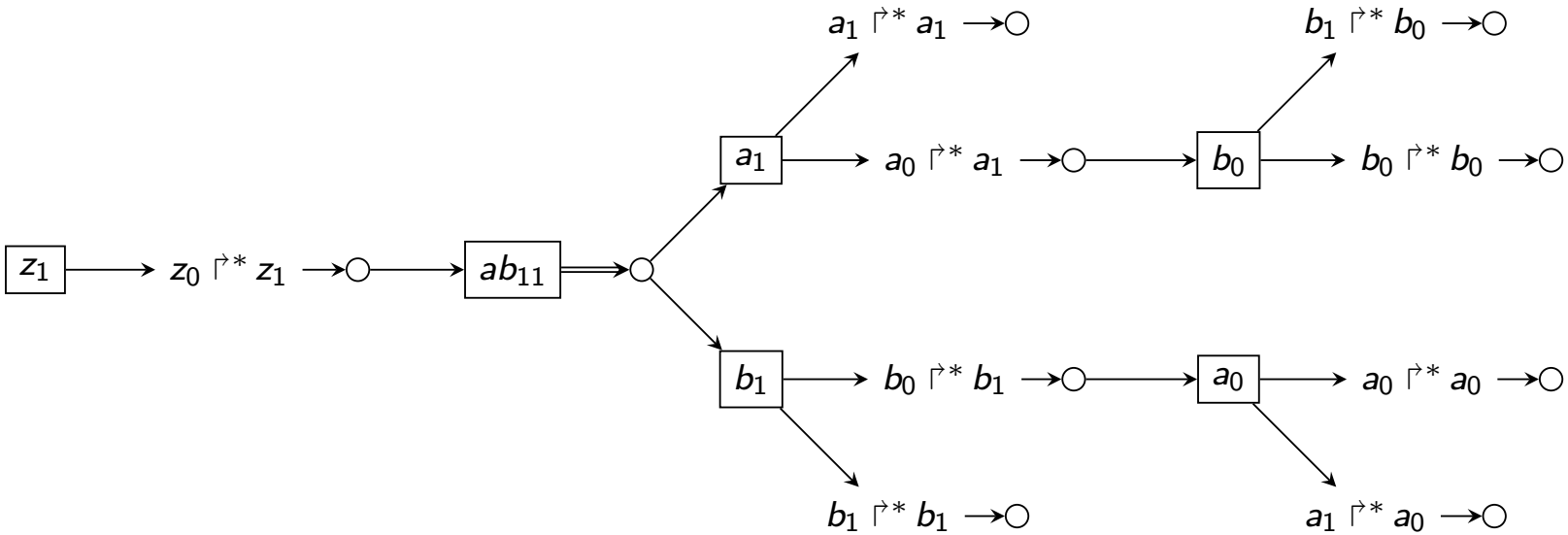

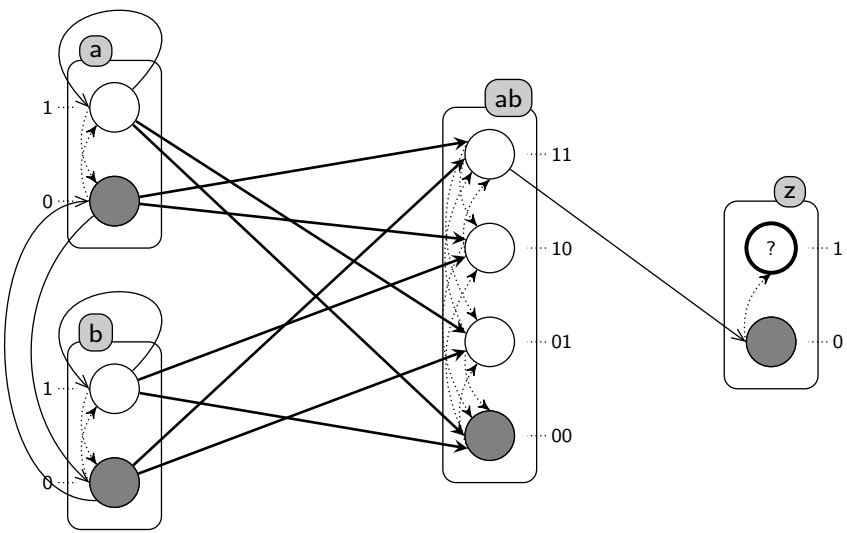

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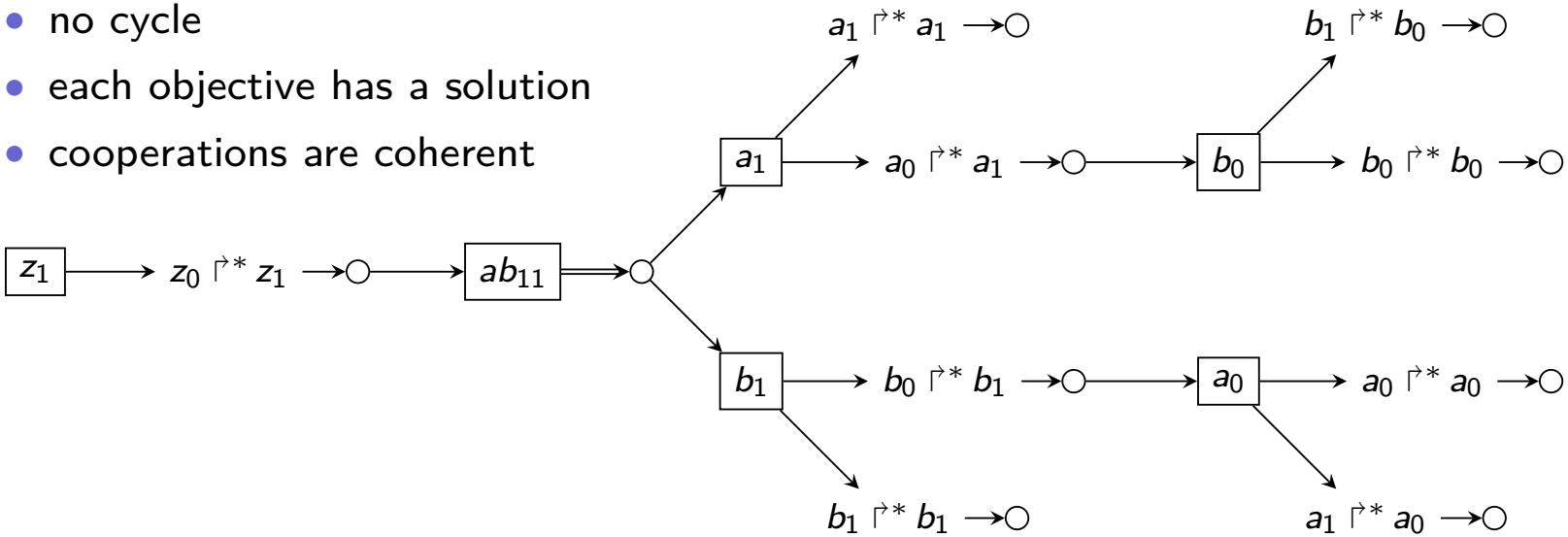
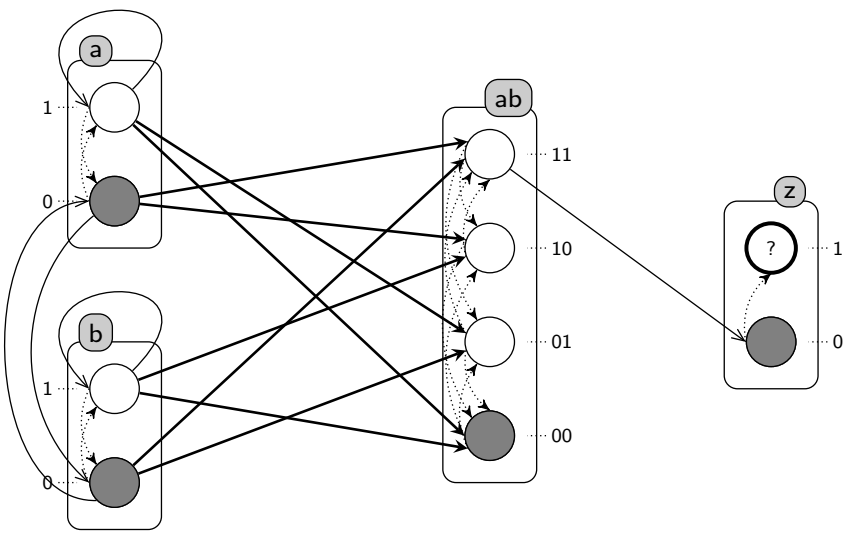
Static Analysis of Canonical Process Hitting

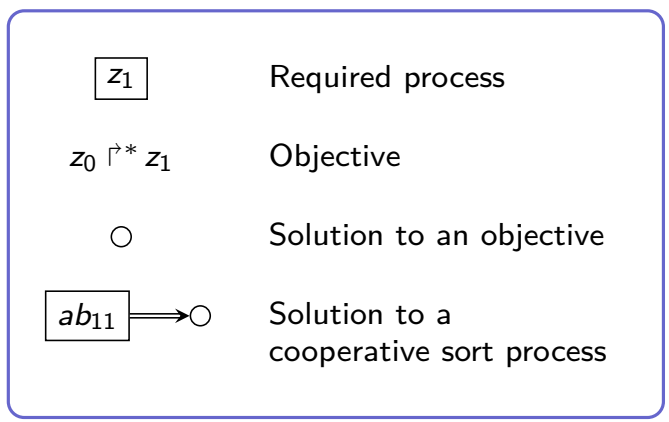
[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]

Sufficient condition:

- no cycle
- each objective has a solution
- cooperations are coherent







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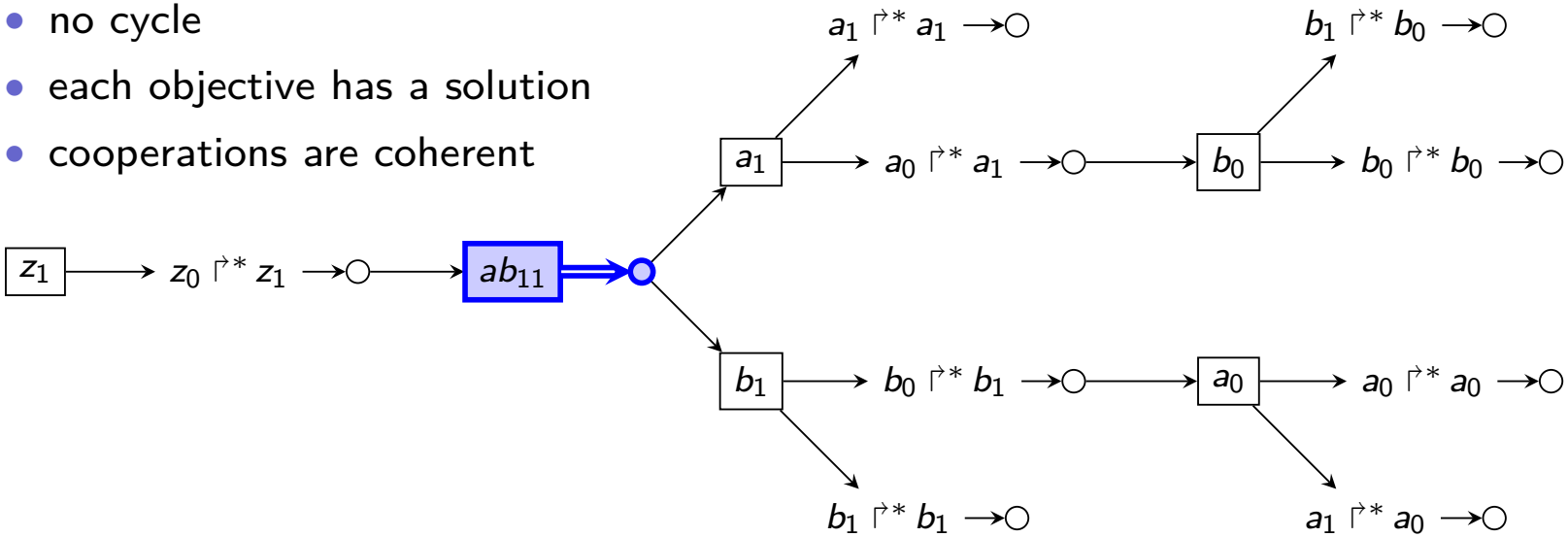

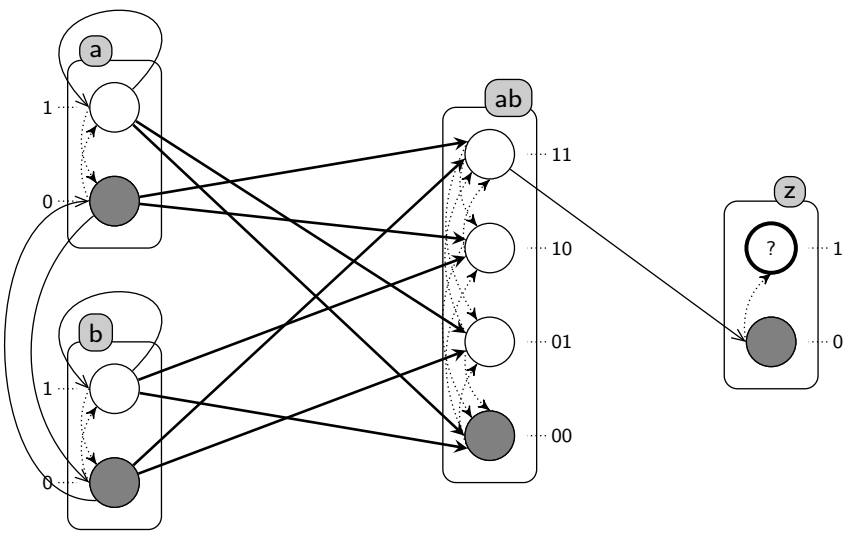

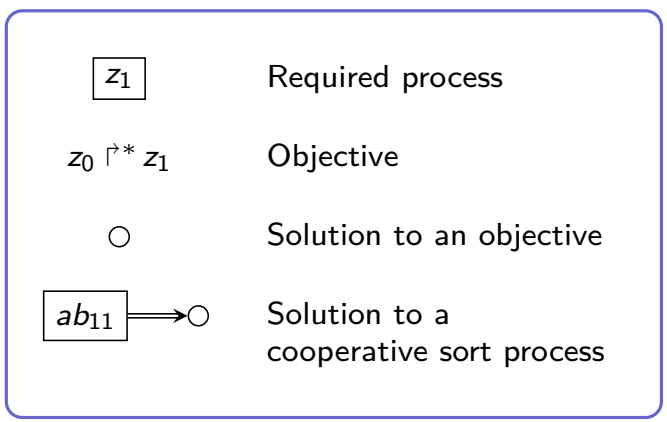

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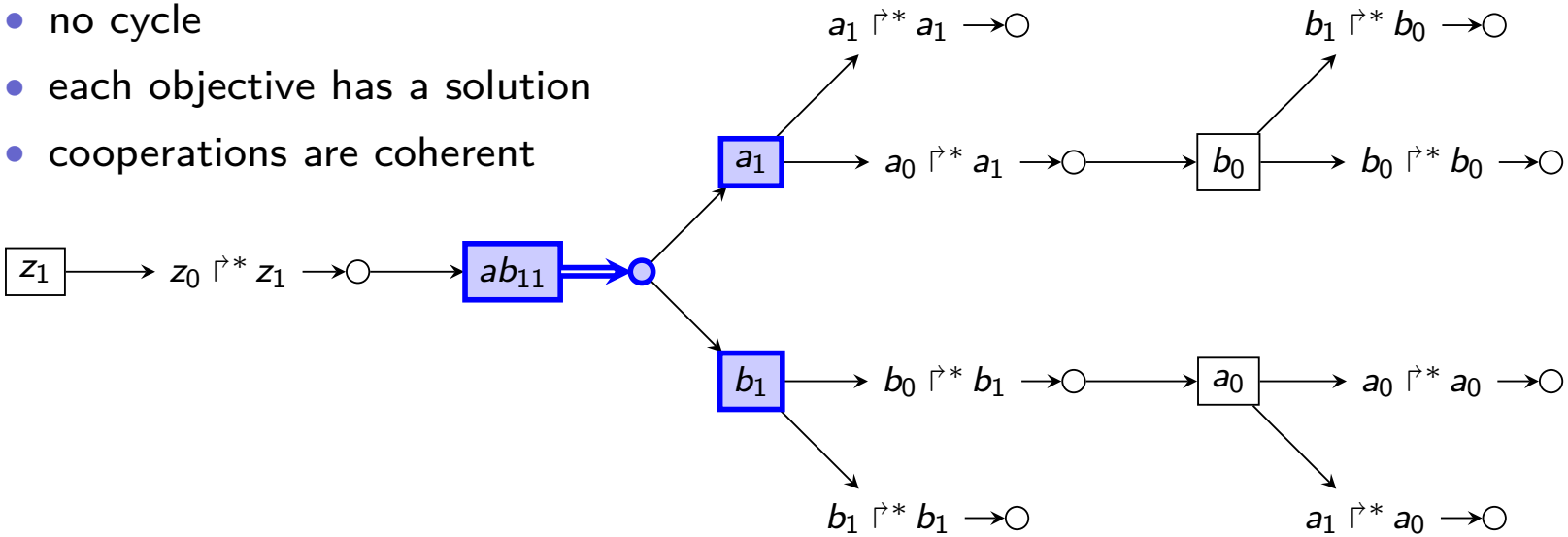
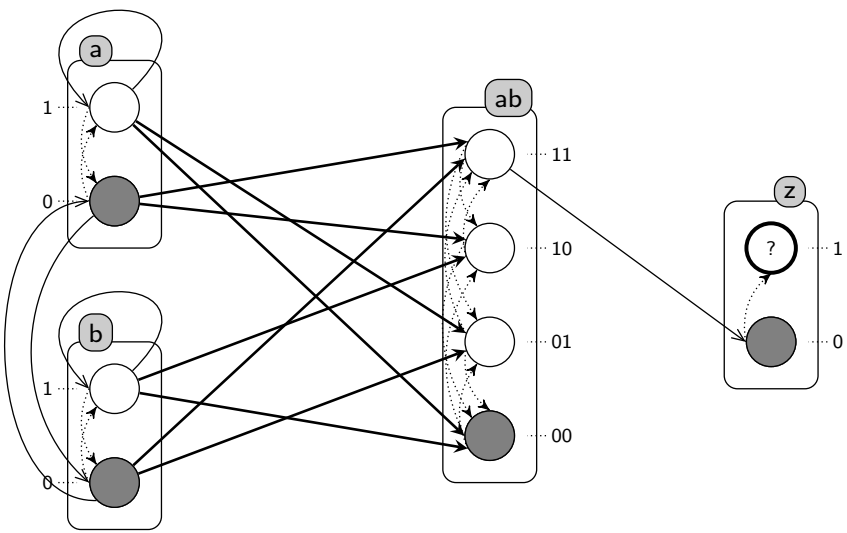
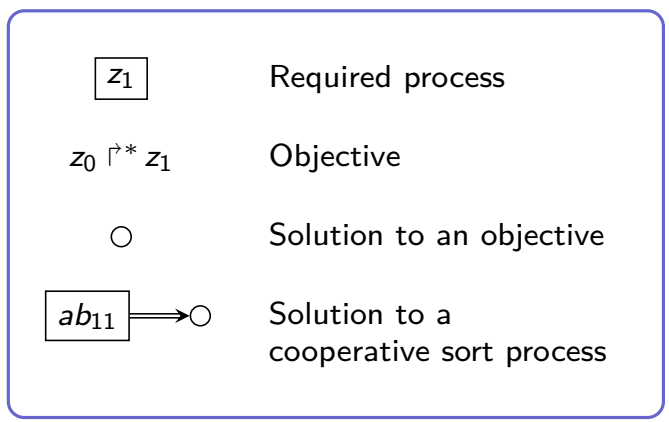




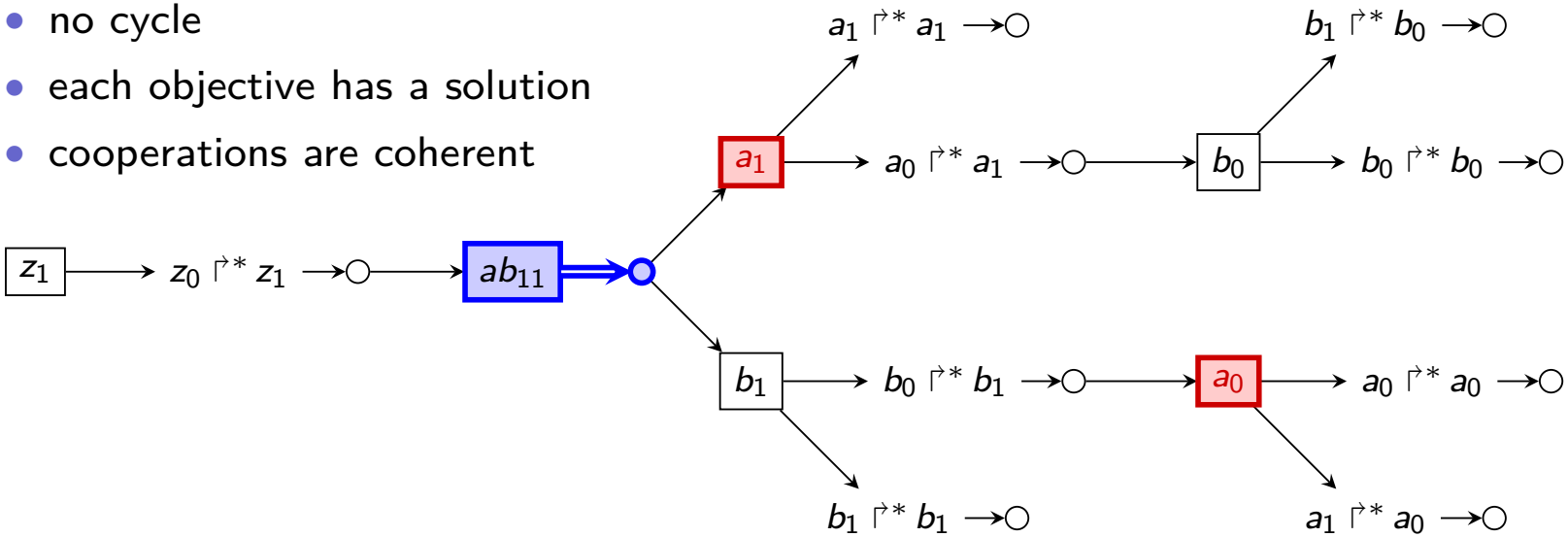


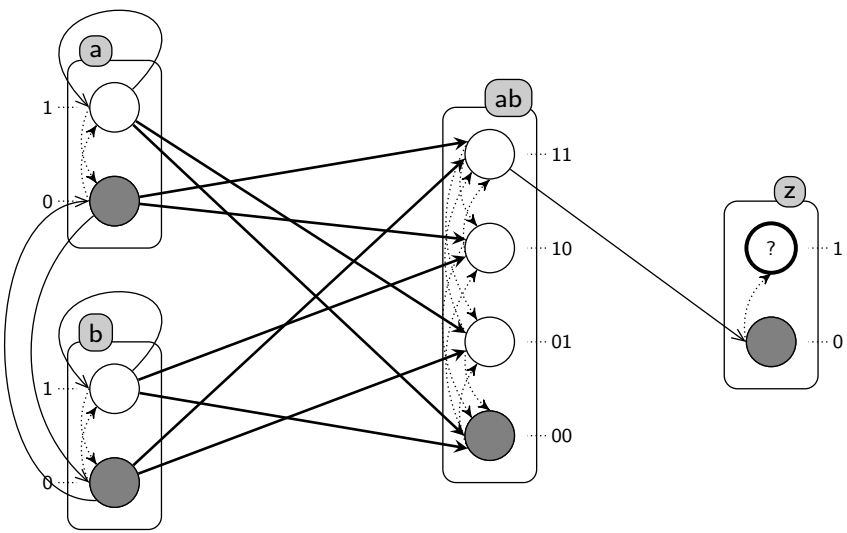
Static Analysis of Canonical Process Hitting

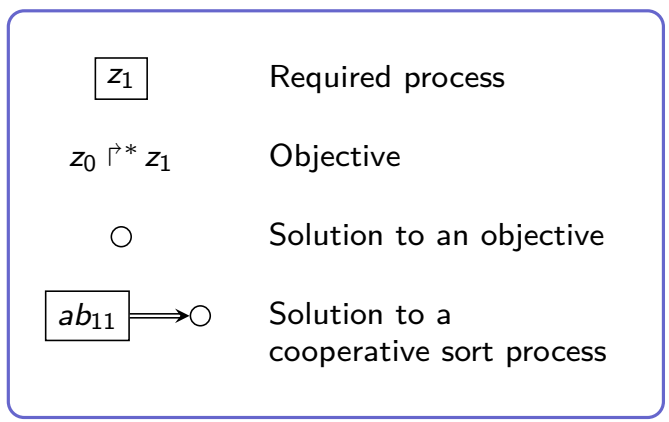
[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]

Sufficient condition:

- no cycle
- each objective has a solution
- cooperations are coherent







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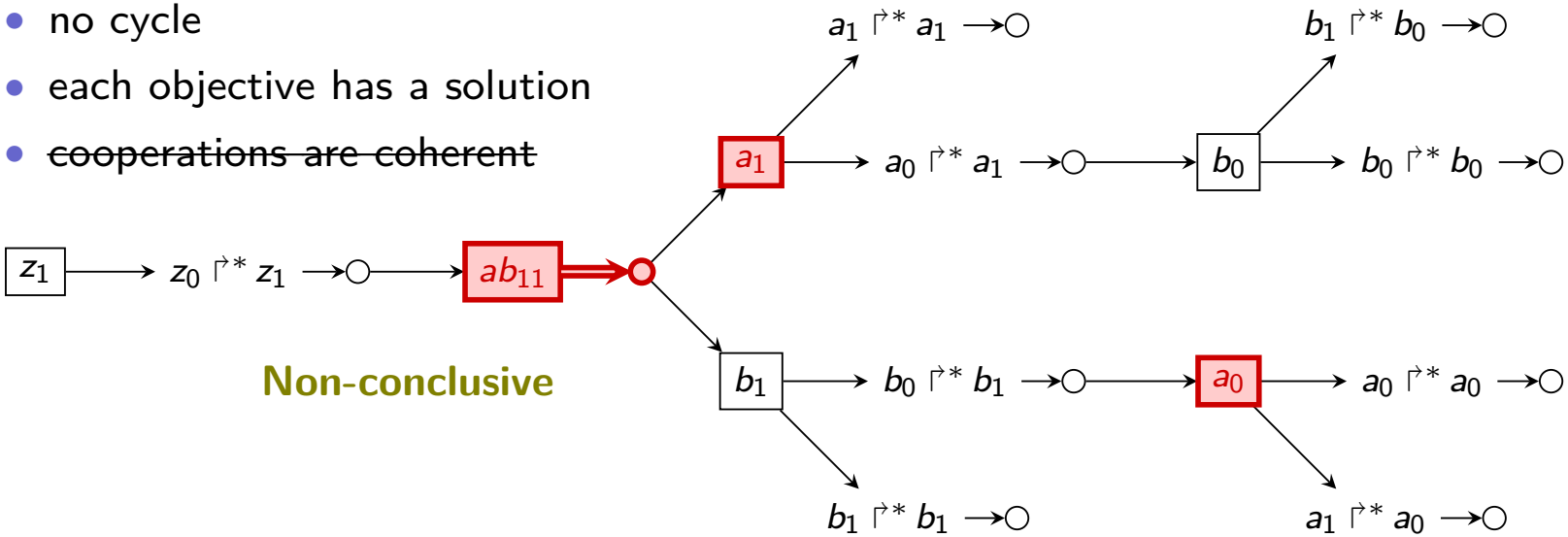
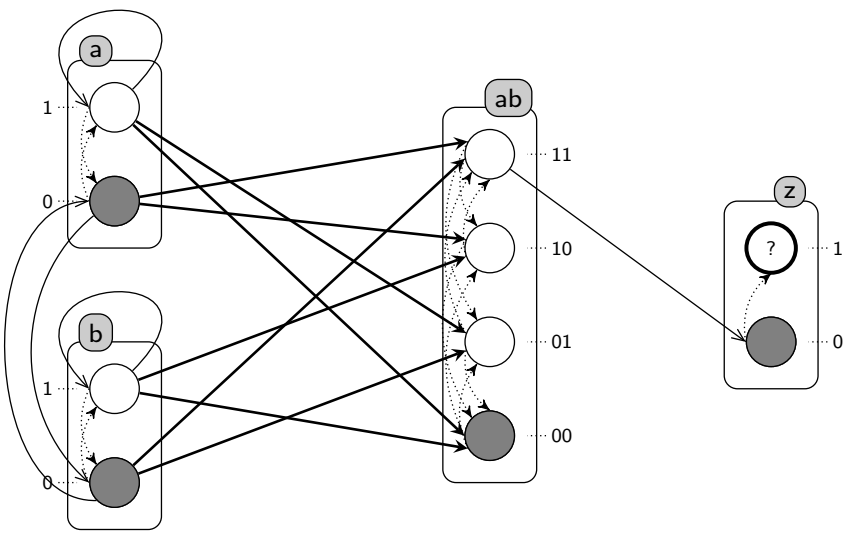
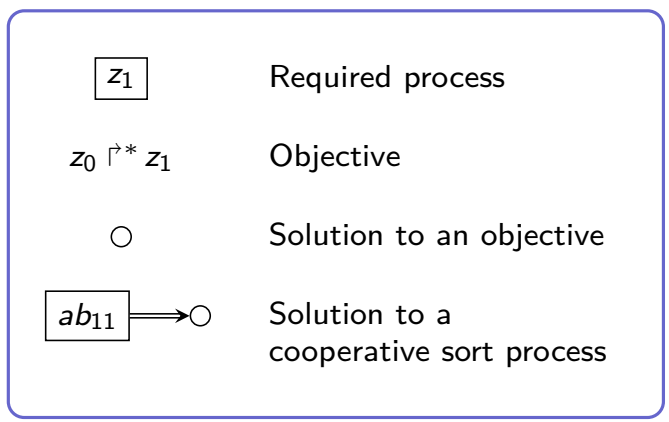


Non-conclusive





Implementation of the Static Analysis Into PINT

Complexity:

- Computation of the local causality graph:
  - Polynomial in the number of sorts
  - Exponential in the number of processes of each sort
- Analysis of the graph (sufficient condition):
  - Polynomial in the size of the graph

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Makes the study of large networks tractable:

Modèle	Sortes	Processus	Actions	États	libddd[1]	GINsim[2]	PINT
egfr20	35	196	670	2^{64}		$<$1s	**0.02s**
tcrsig40	54	156	301	2^{73}		∞	**0.02s**
tcrsig94	133	448	1124	2^{194}	[13min – ∞]		**0.03s**
egfr104	193	748	2356	2^{320}			**0.16s**

[1] LIP6/Move [Couvreur *et al.*, *Lecture Notes in Computer Science*, 2002]
[2] TAGC/IGC [Chaouiya, Naldi, Thieffry, *Methods in Molecular Biology*, 2012]

egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
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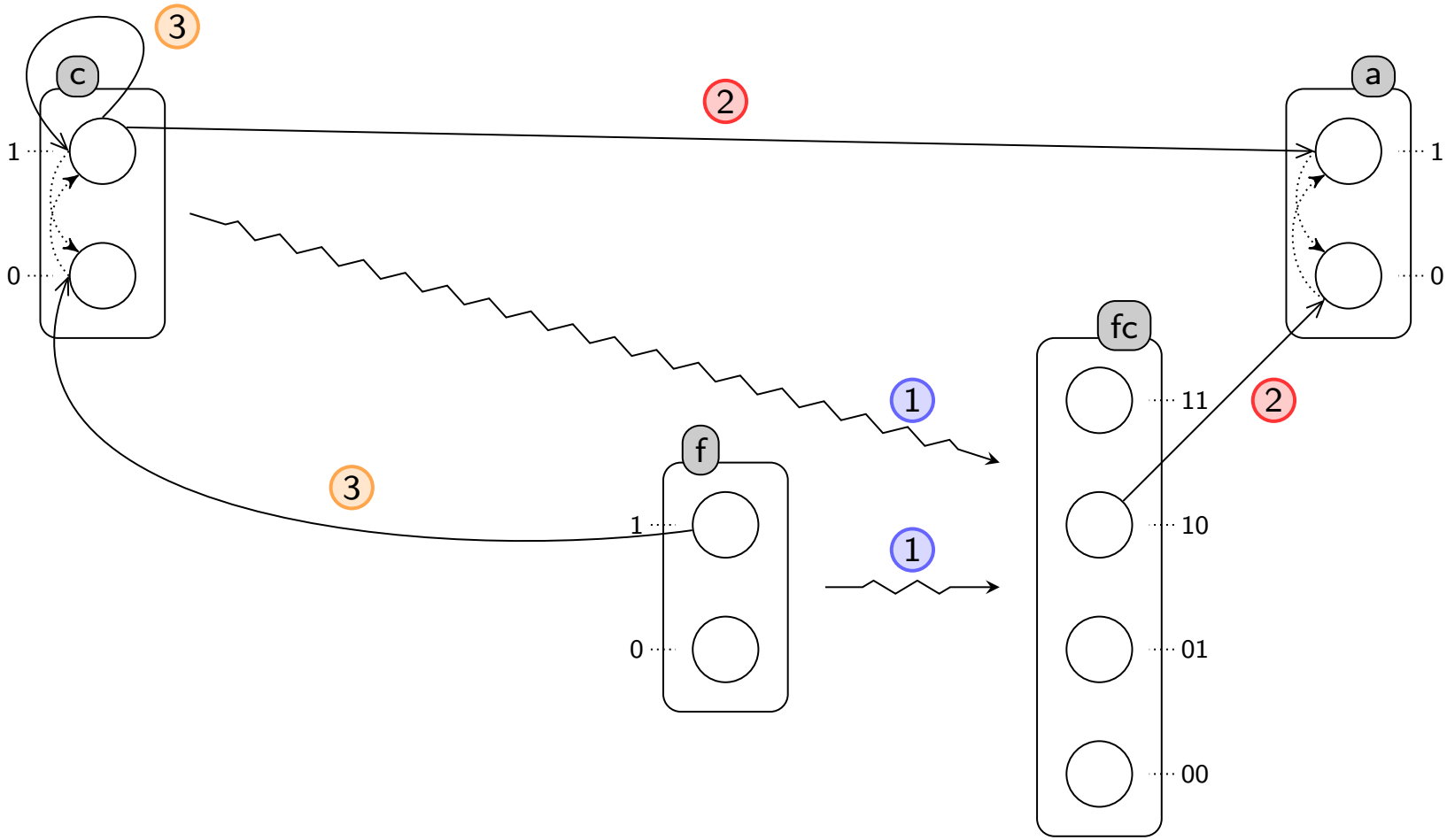
Formal Translation Into Canonical Form



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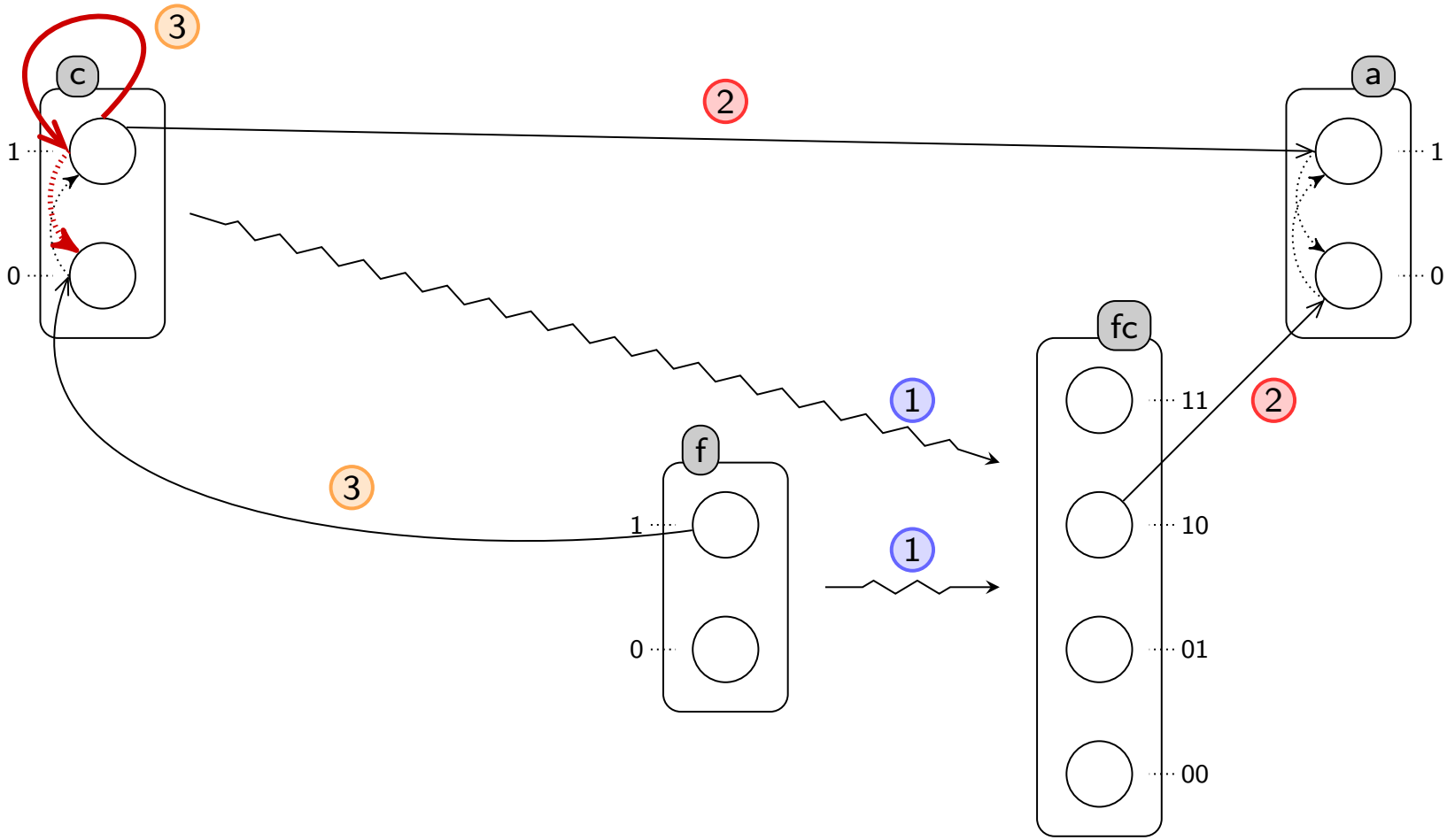

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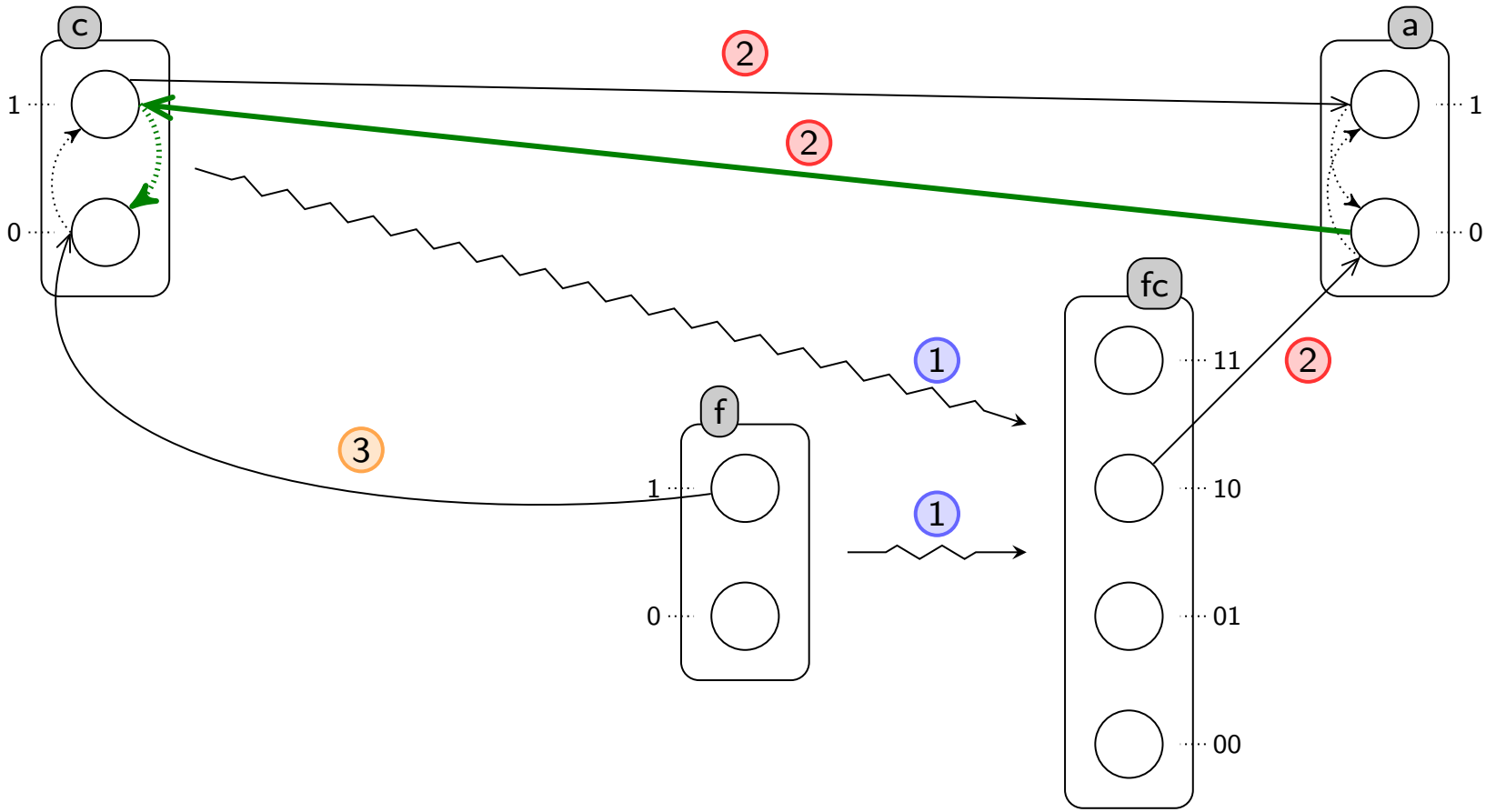

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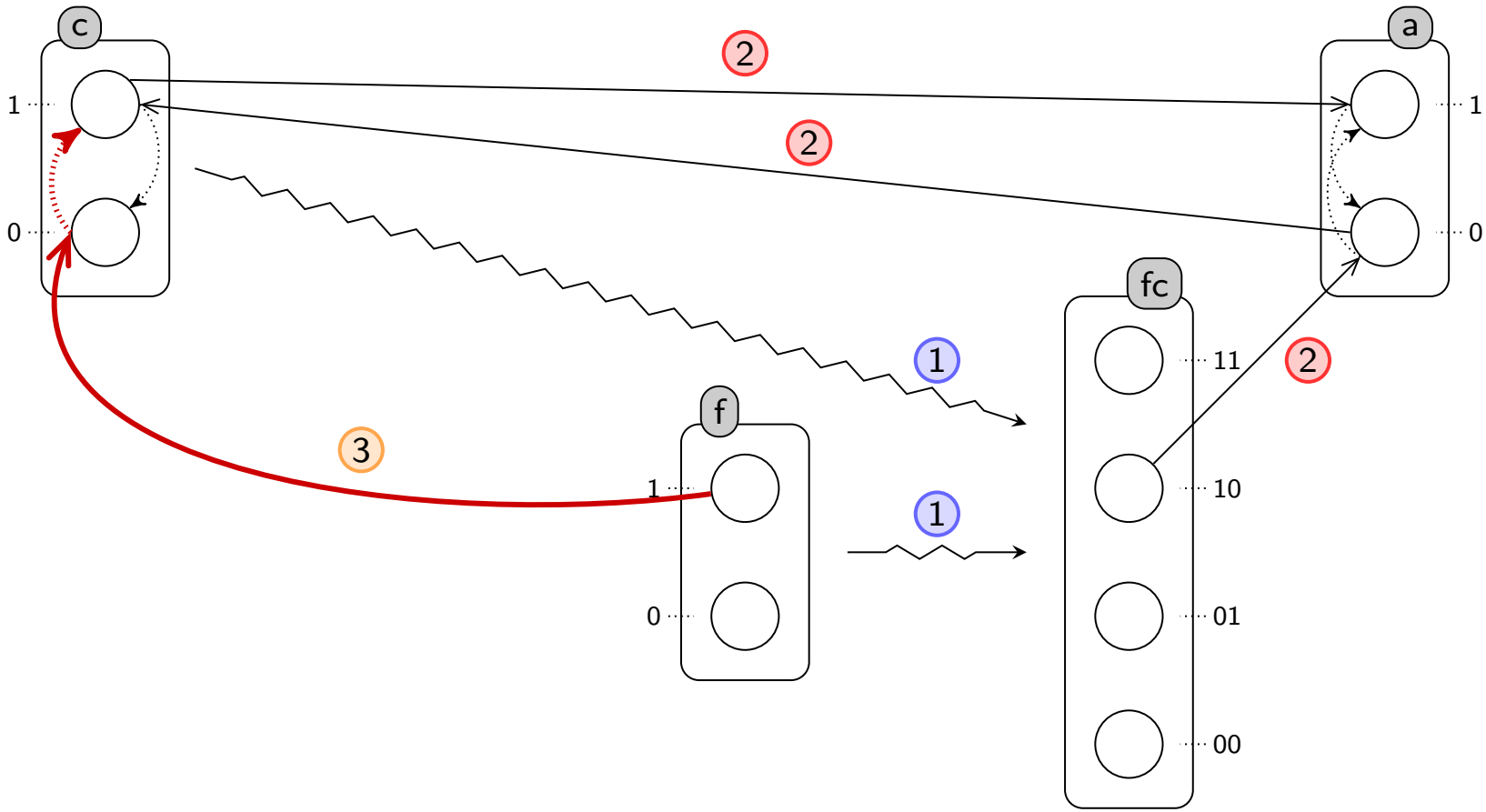

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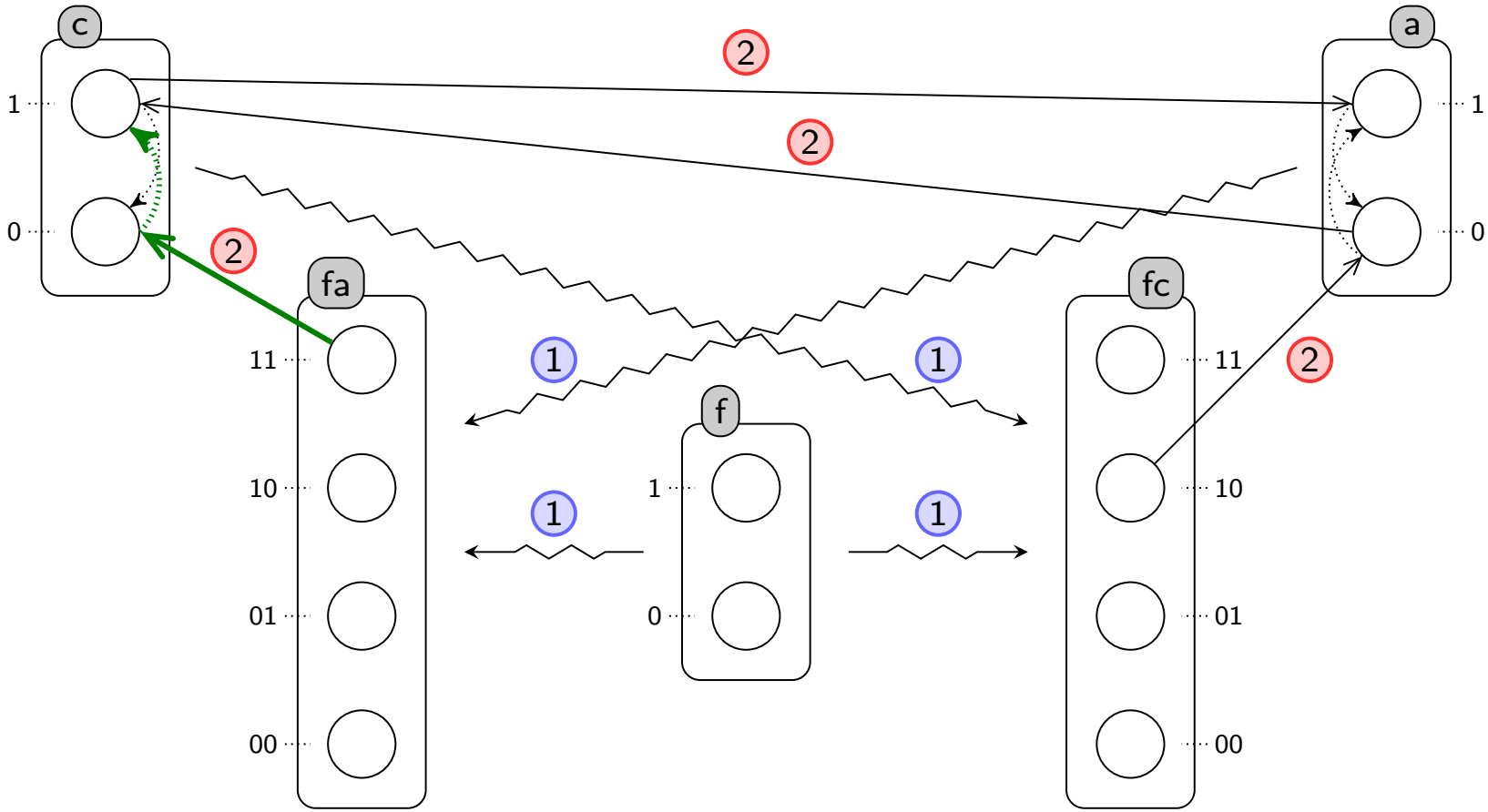

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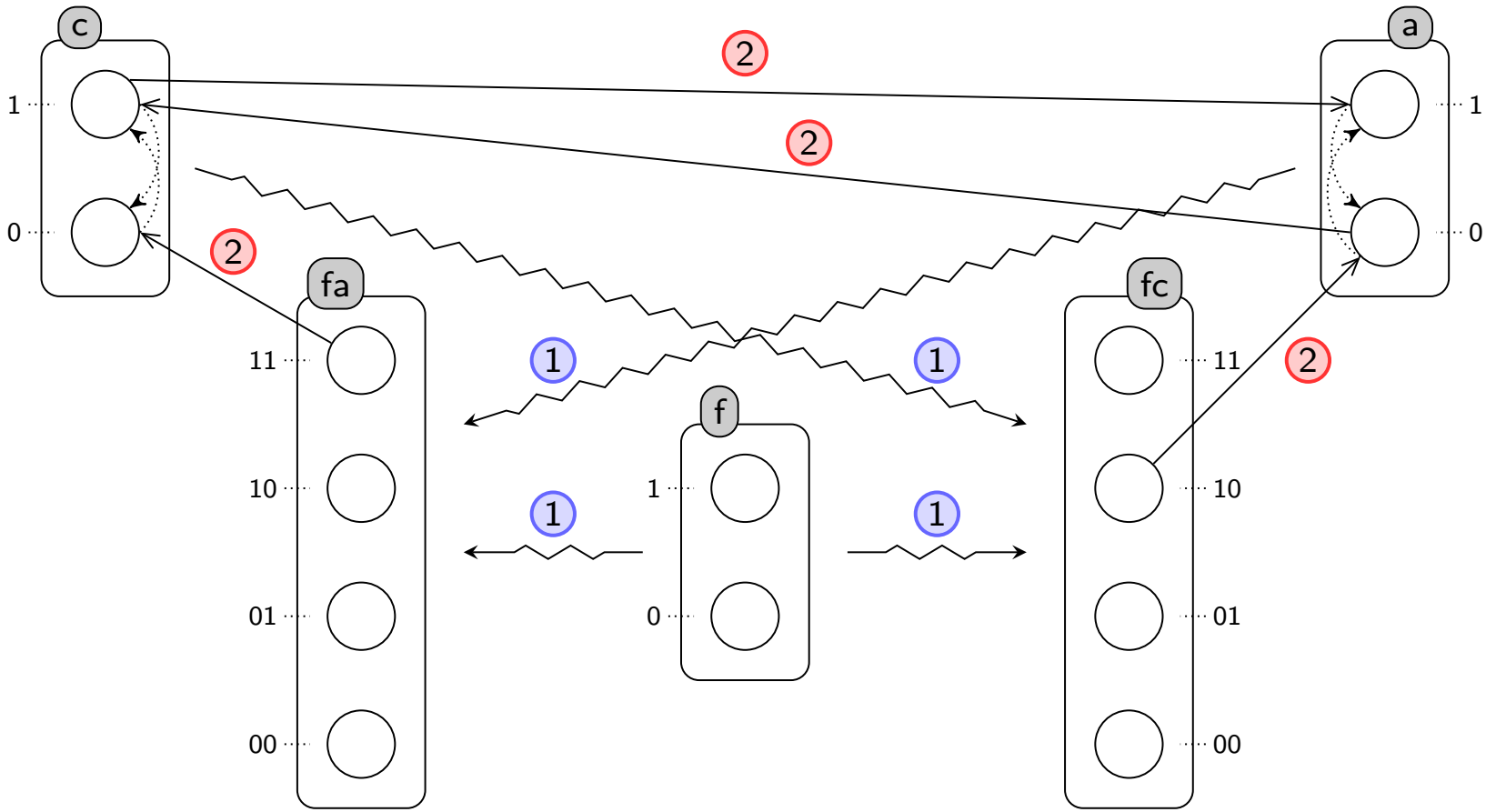
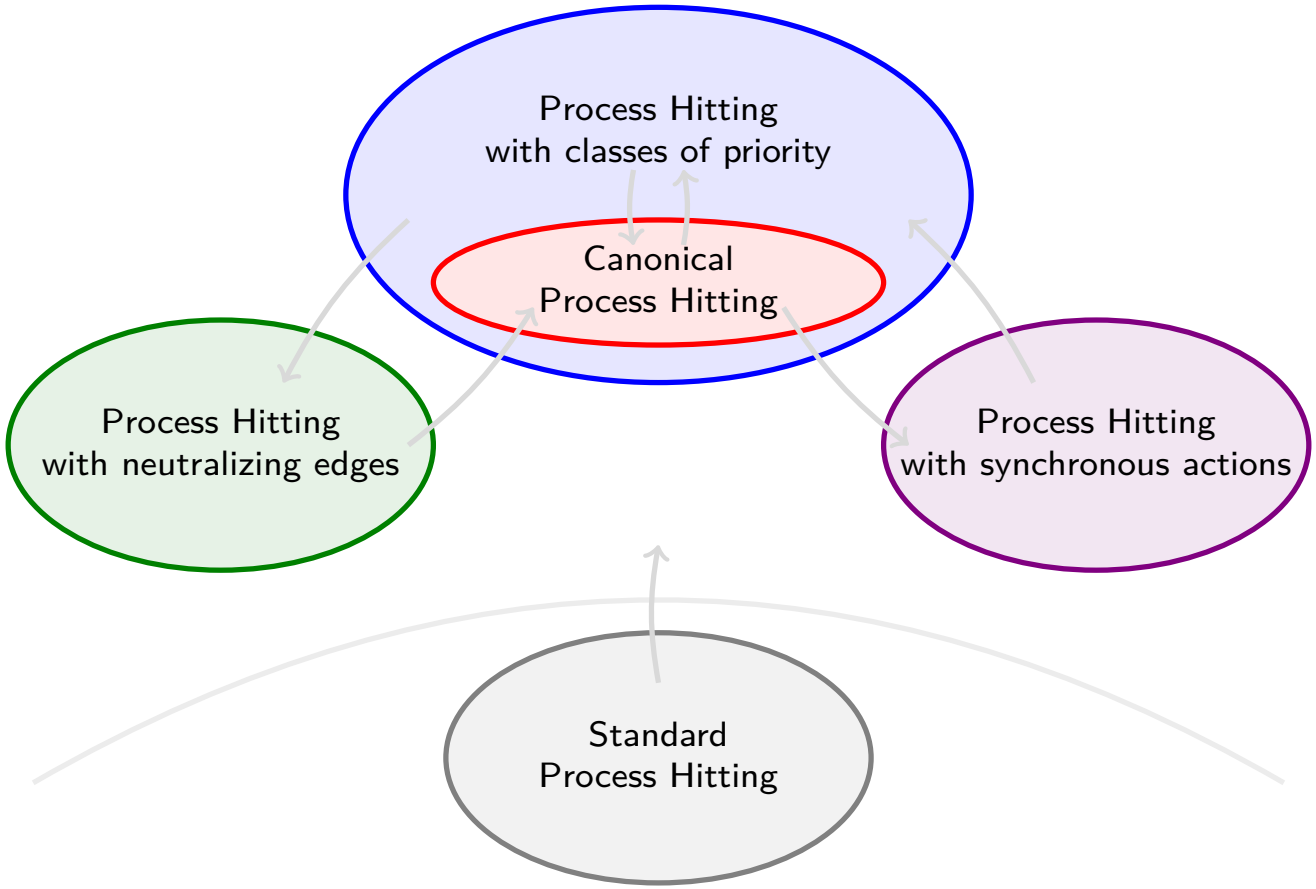


→ Same dynamics (with supplemental cooperative sorts)

→ The canonical form can be computed for all Process Hitting extensions, with classes of priorities, neutralizing edges or synchronous actions

Equivalence Between Process Hitting Extensions



All developed enrichments have the same expressivity

- Expressive power improved
- Can always be translated to the canonical form
- But sometimes at the cost of an exponential translation

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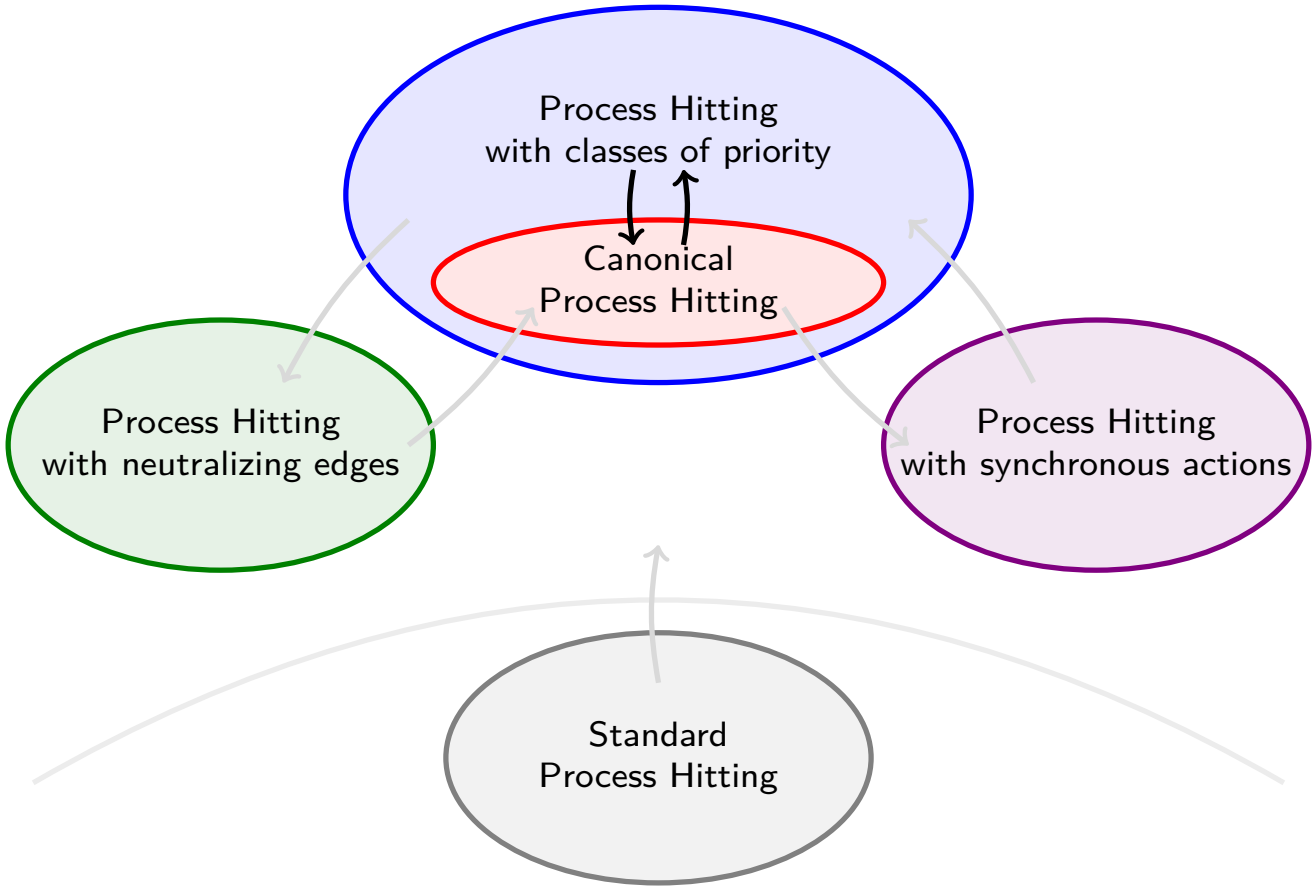

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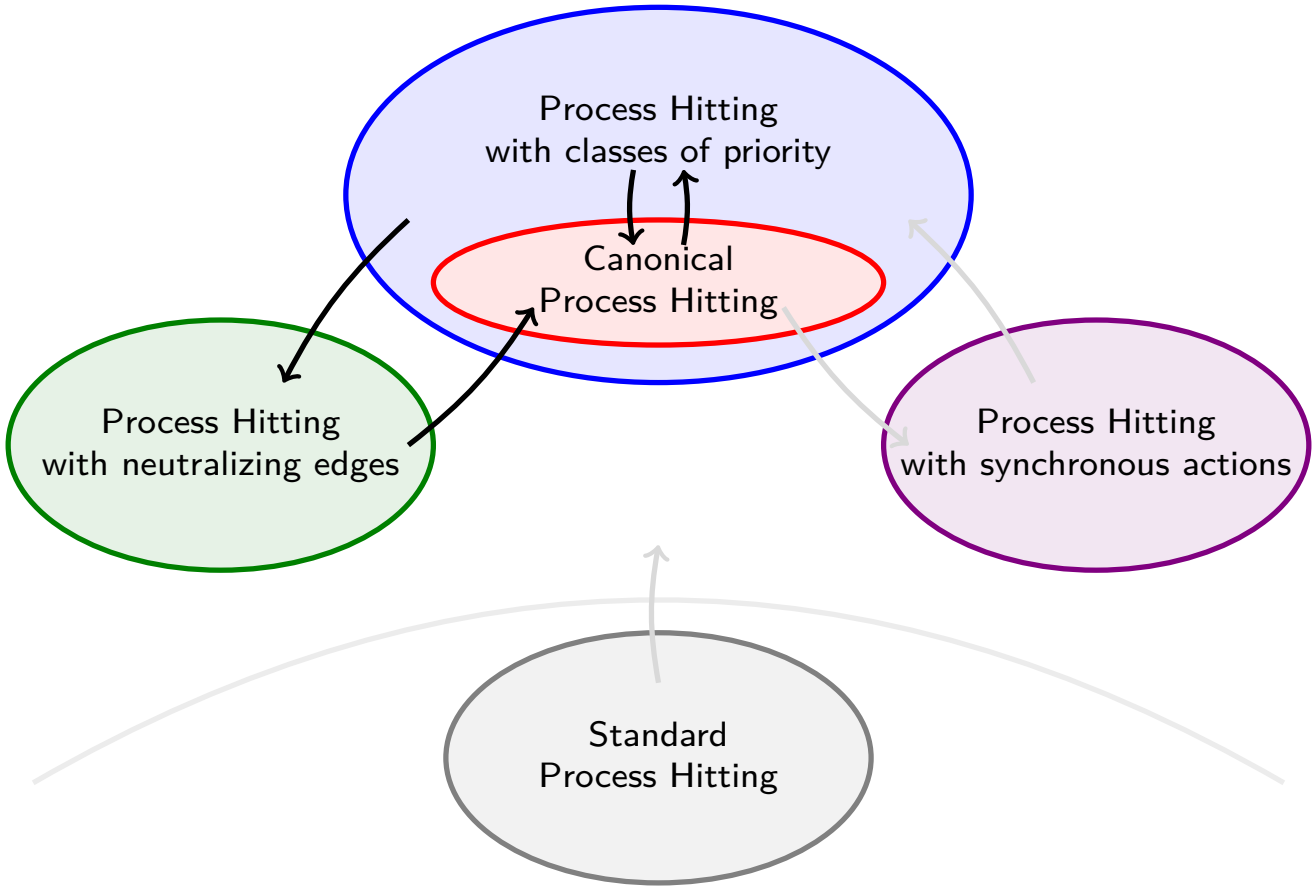

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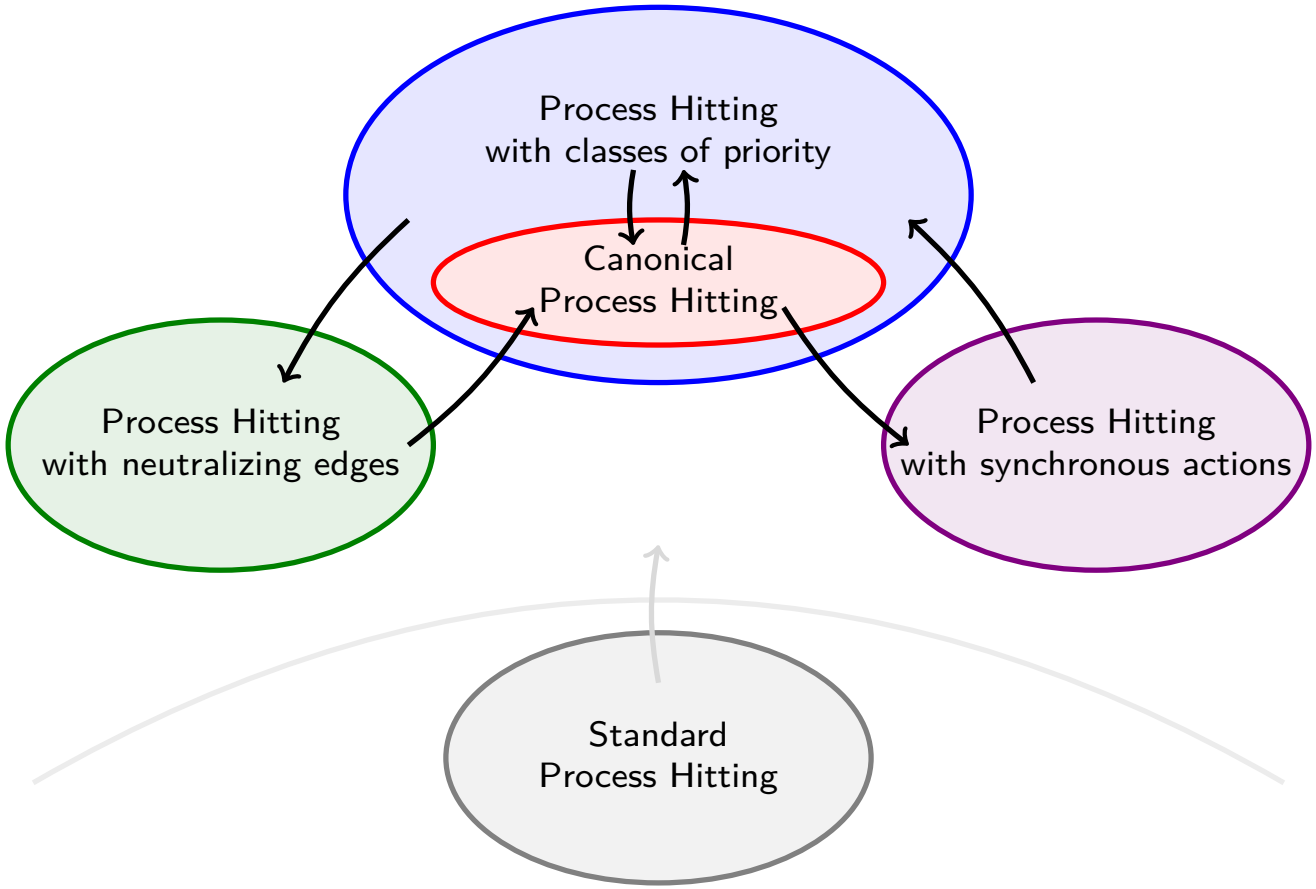

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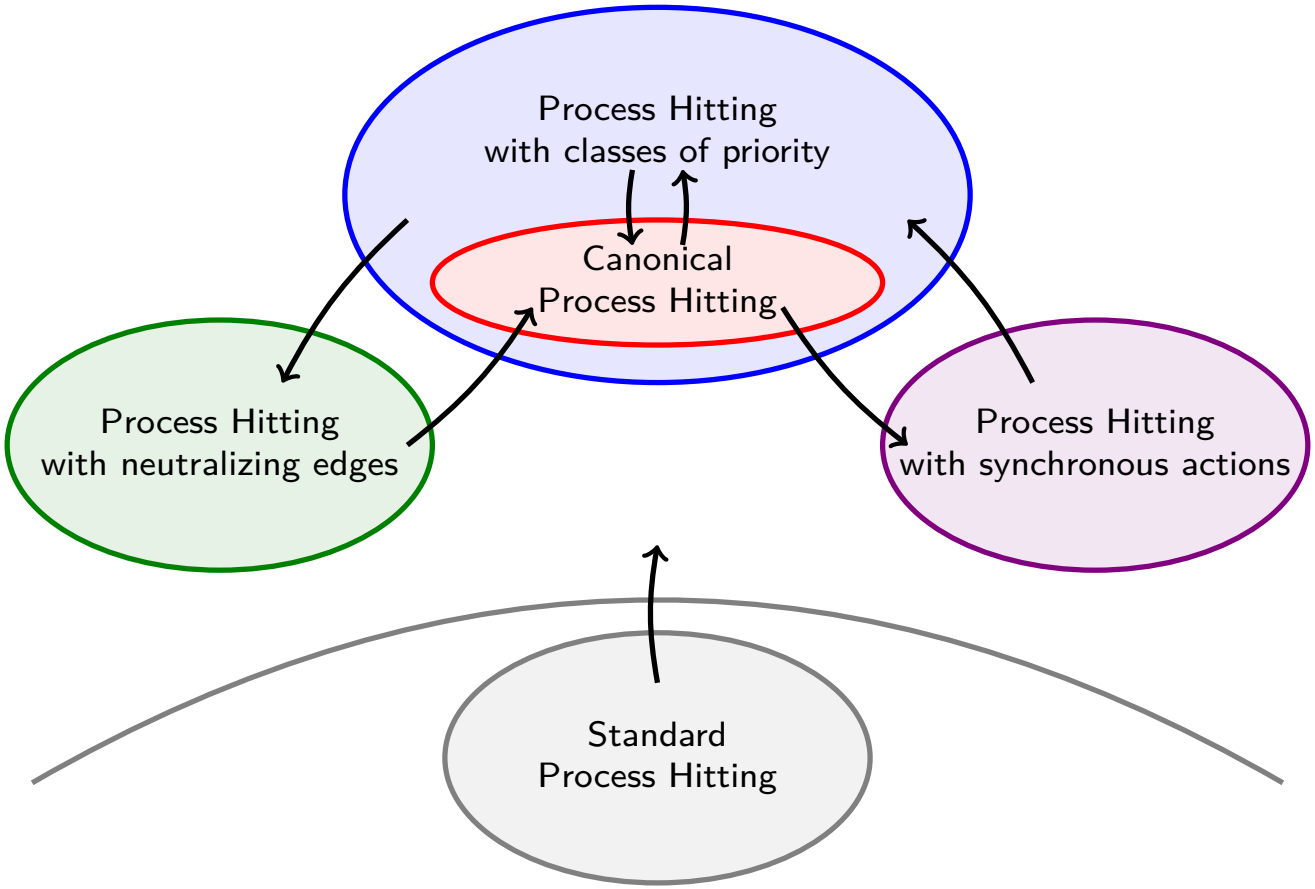

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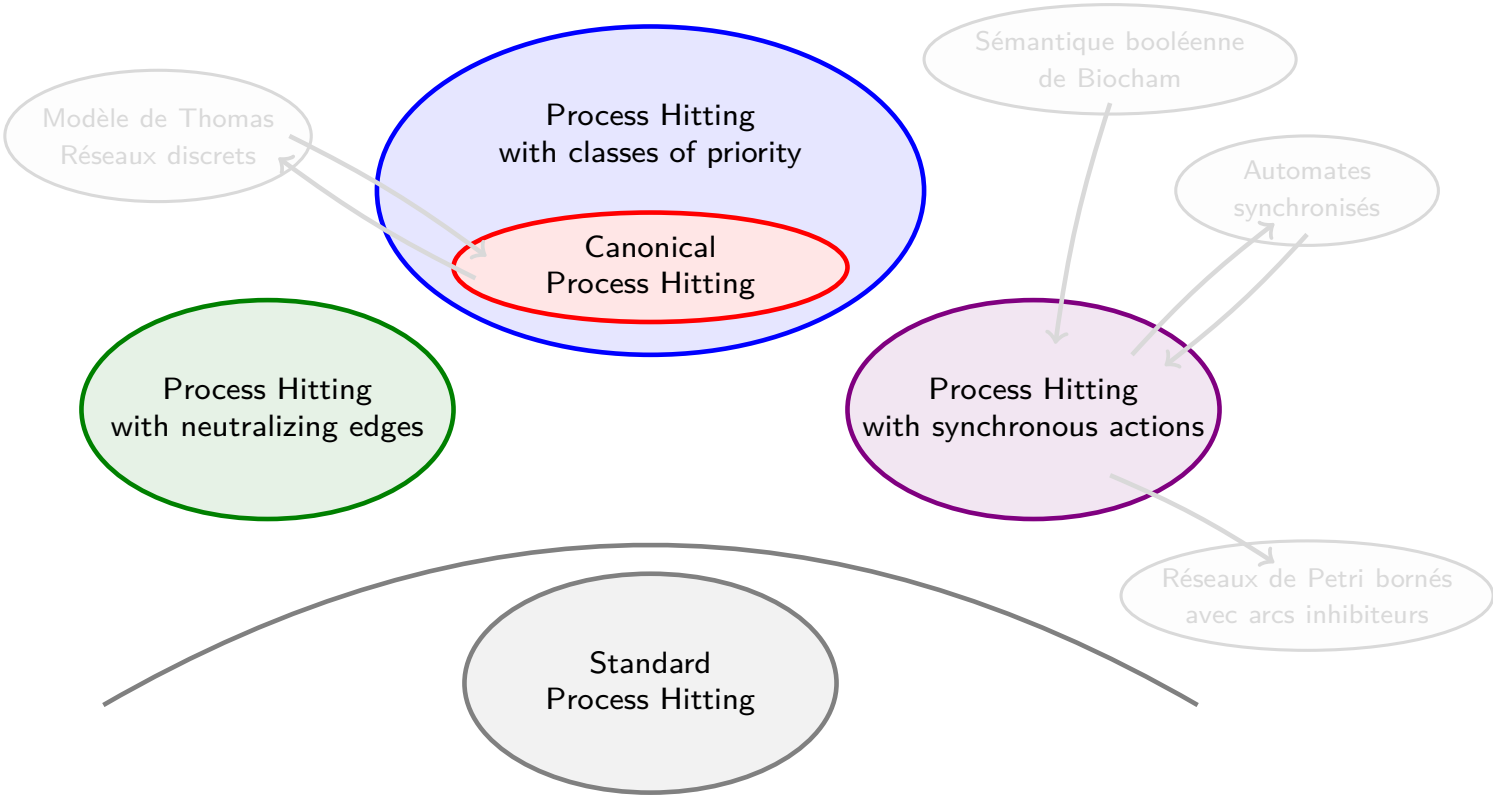
Translation From and To Other Discrete Models



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- Equivalence with synchronous automata networks
- Translation towards (bounded) Petri nets with inhibitor arcs
- Translation from the Boolean semantics of Biocham

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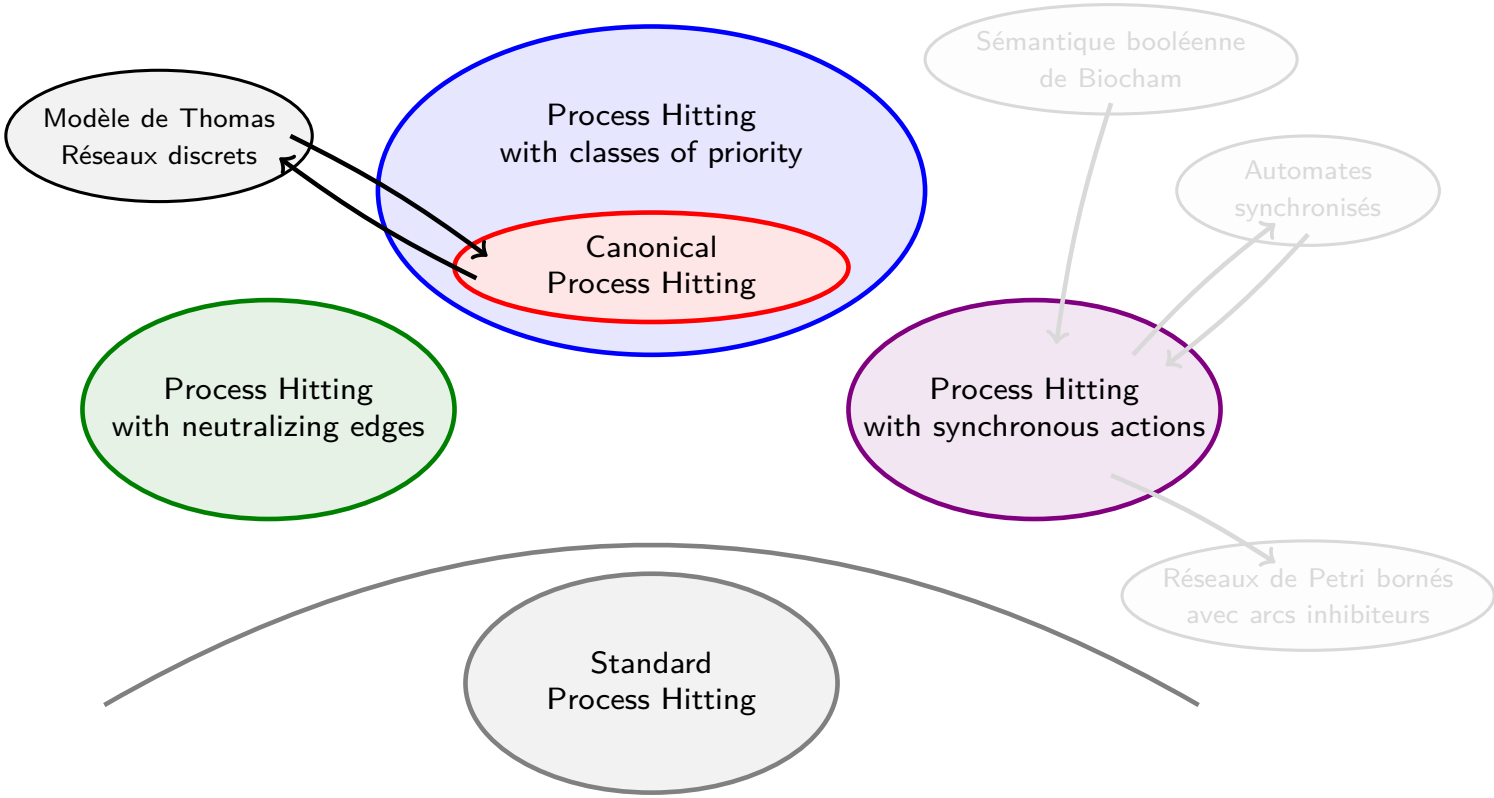

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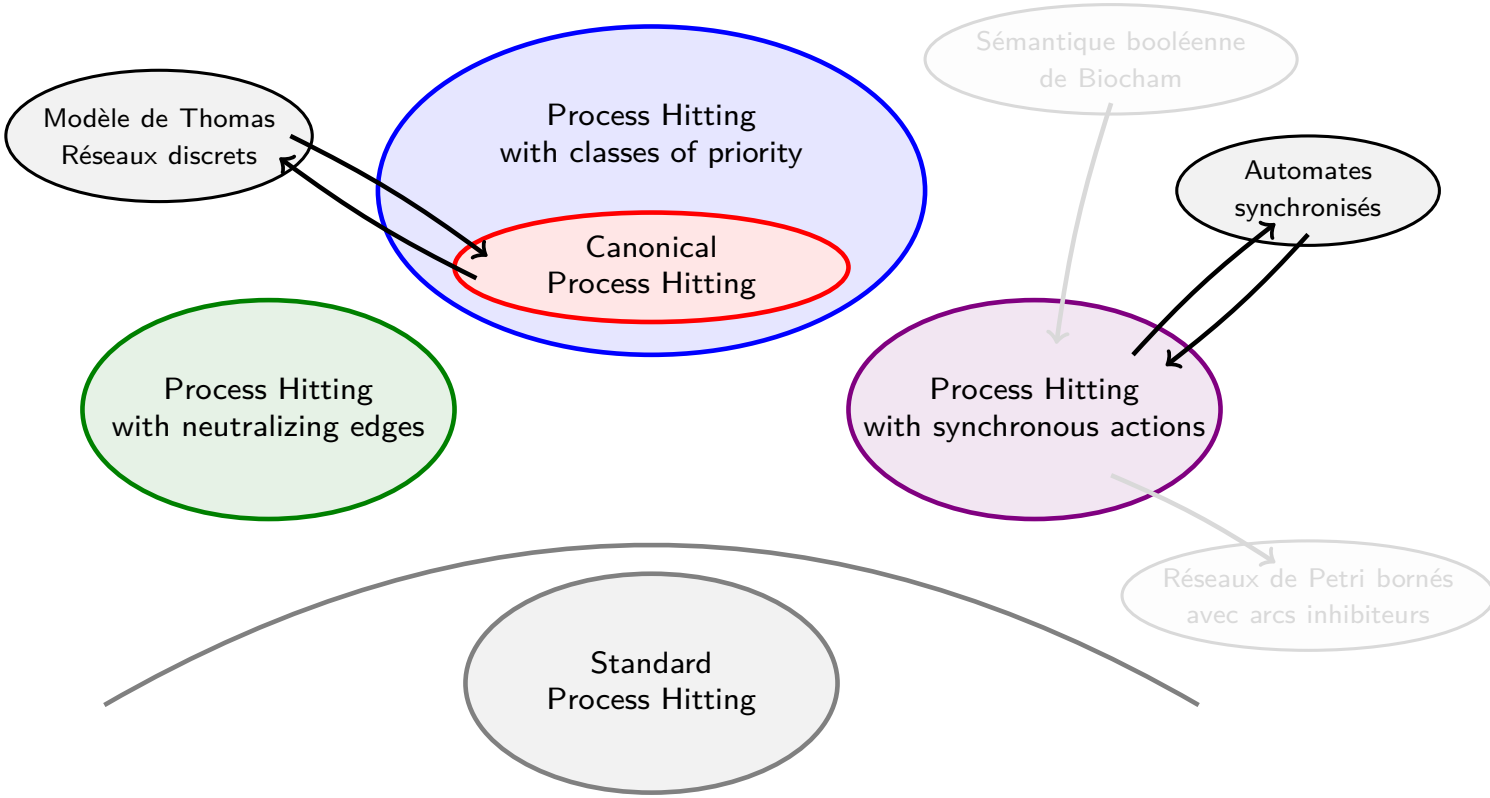

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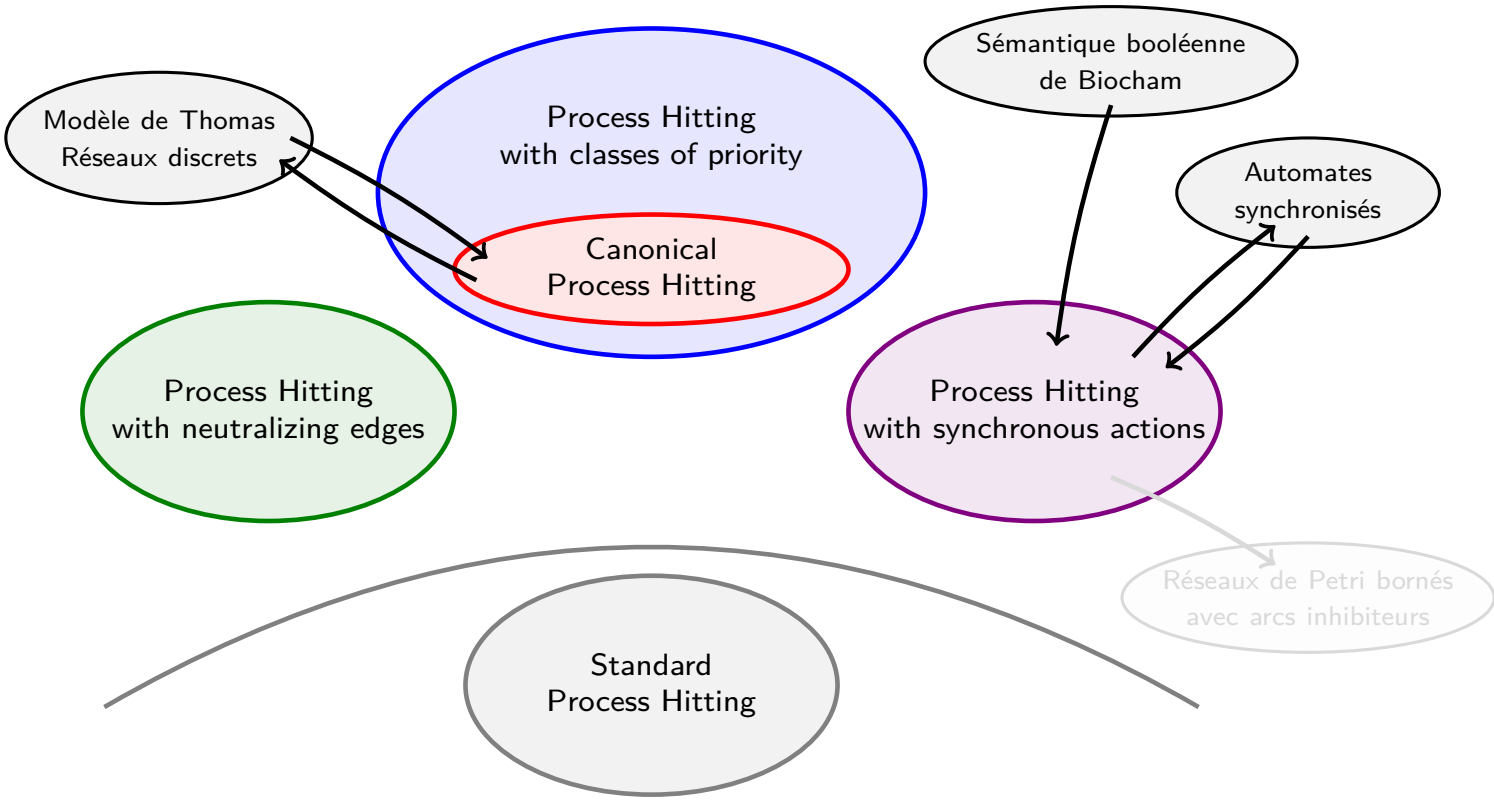

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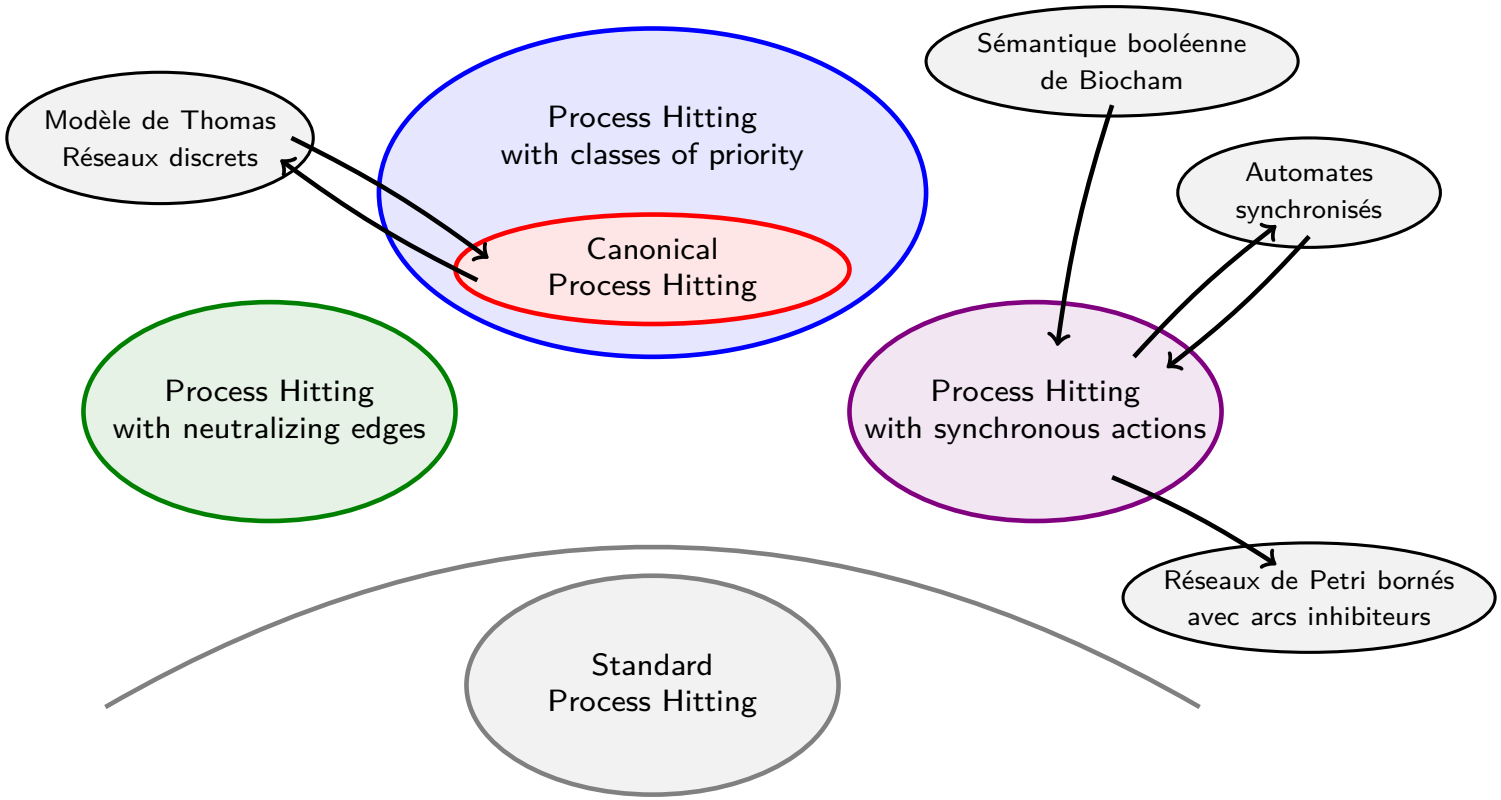

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Translation To Thomas Modeling

[Folschette *et al.* in *Computational Methods in Systems Biology*, 2012]

- Two successive inferences: 1) interaction graph; 2) parameters
- Exhaustive analysis of the local dynamics for each regulator
- enumeration of all parametrizations compatible with the dynamics

Complexity:
Linear in the number of genes,
Exponential in the number of regulators of one component

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	Models			Inference the IG		Inference of parameters	
Name	Sorts	Processes	Actions	Duration	Edges	Durations	Parameters
egfr20	22	152	399	**1s**	50	**1s**	191
tcrsig40	14	156	301	**1s**	54	**1s**	143
tcrsig94	39	448	1124	**13s**	169	∞	2.10^9
egfr104	89	748	2356	**4min**	241	**1min 30s**	$1.10^6/2.10^6$

egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin *et al.*, 2009]
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General Conclusion

Standard Process Hitting allows to represent biological regulatory networks in an **atomistic** fashion:

- Existing efficient static analysis
- But temporal shift issues
- Limited modeling power

Extensions of the Process Hitting to improve the expressivity:

- Rectification of the temporal shift $\rightarrow$ Strictly higher expressivity
- Allows to abstract temporal parameters
- New links to other formalisms (Thomas, PN, etc.)

Static analysis of the Canonical Process Hitting:

- Efficient analysis of reachability properties
- Applicable to the extensions at the cost of a translation
- New kind of property: simultaneous activation

Outlooks

New **exploitation** possibilities:

- Modeling and analysis of full databases
- Study of uncontrollable behaviors or punctual perturbations
- Research of interesting properties (attractors, oscillations, ...)

Improvement of the static analysis:

- Refining in order to reduce the non-conclusiveness
- New methods using by-products such as the local causality graph
- New properties to check (temporal logic, counters, ...)

Enrichment of the **modeling power**:

- Dynamical classes of priorities
- Guarded actions or complex logic gates
- New model checking tools (Hoare logic, ...)

Collaborations

Participation to the **ANR blanc** project **BioTempo** (March 2011 – November 2014):

"Language, time representations and hybrid models
for the analysis of incomplete models in molecular biology"

Task 3: Introduce synchronization and continuous time in chronological models: programming language, multi-clocks and hybrid systems

3 months PhD internship (March – May 2012):
National Institute of Informatics (Tokyo, Japan)
Invited in the team of **Katsumi Inoue**

"Automated Reasoning and Hypothesis
Finding for Systems Biology"

Partnership organized with AtlanSTIC Financial participation of Centrale Initiatives

Personal Contributions

Book chapter:

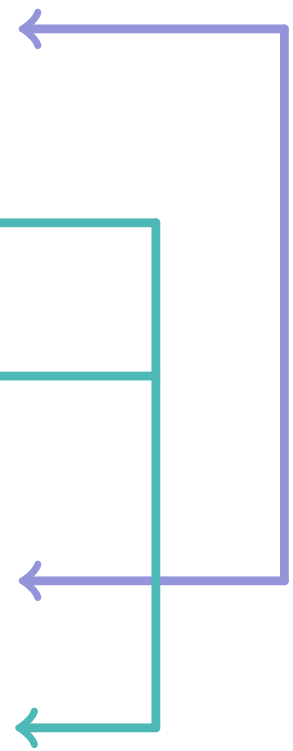
- Paulevé, Chancellor, **Folschette**, Magnin, Roux :
  Analyzing Large Network Dynamics with Process Hitting,
  Logical Modeling of Biological Systems, août 2014

Conferences and workshops:

- **Folschette**, Paulevé, Magnin, Roux :
  Under-approximation of reachability in multivalued asynchronous networks,
  CS2Bio'13, *Electronic Notes in Theoretical Computer Science*, Vol. 299, 2013
  sélectionné pour un numéro spécial de *Theoretical Computer Science*
- **Folschette**, Paulevé, Inoue, Magnin, Roux :
  Concretizing the process hitting into biological regulatory networks,
  CMSB'12, *Lecture Notes in Computer Science*, 2012
- **Folschette**, Paulevé, Inoue, Magnin, Roux :
  Abducing Biological Regulatory Networks from Process Hitting models,
  ECML-PKDD'12 / LDSSB'12, 2012

Current journal submissions:

- **Folschette**, Paulevé, Magnin, Roux :
  Sufficient Conditions for Reachability in Automata Networks with Priorities,
  soumis à un numéro spécial de *Theoretical Computer Science*
- **Folschette**, Paulevé, Inoue, Magnin, Roux :
  Constructing Biological Regulatory Networks from Process Hitting models,
  en cours de révision pour *Theoretical Computer Science*
- Paulevé, **Folschette**, Magnin, Roux :
  Analyses statiques de la dynamique des réseaux d'automates indéterministes,
  soumis à un numéro spécial de *Technique et Science Informatiques*



Thank you for your attention

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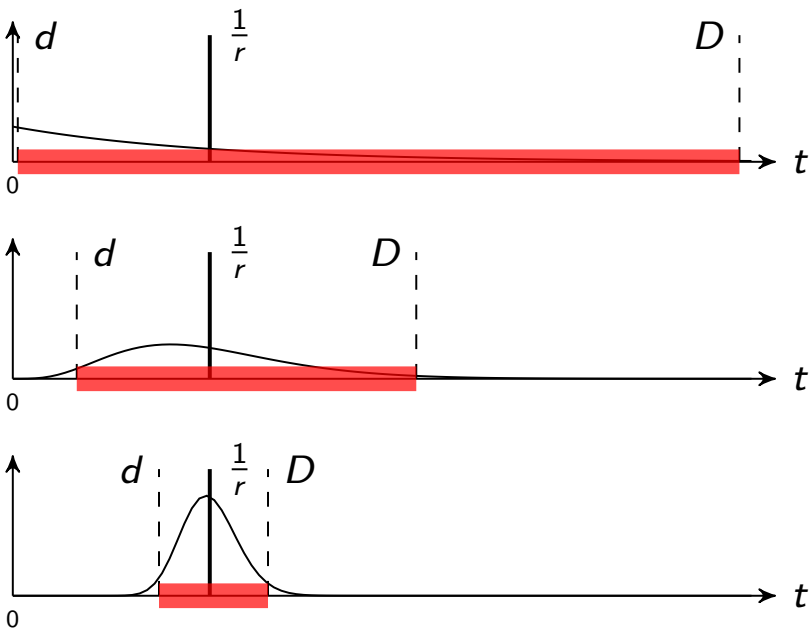
Stochastic Parameters

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

- Introduction of temporal properties
- Stochastic parameters (r, sa) equivalent to a **firing interval** $[d; D]$



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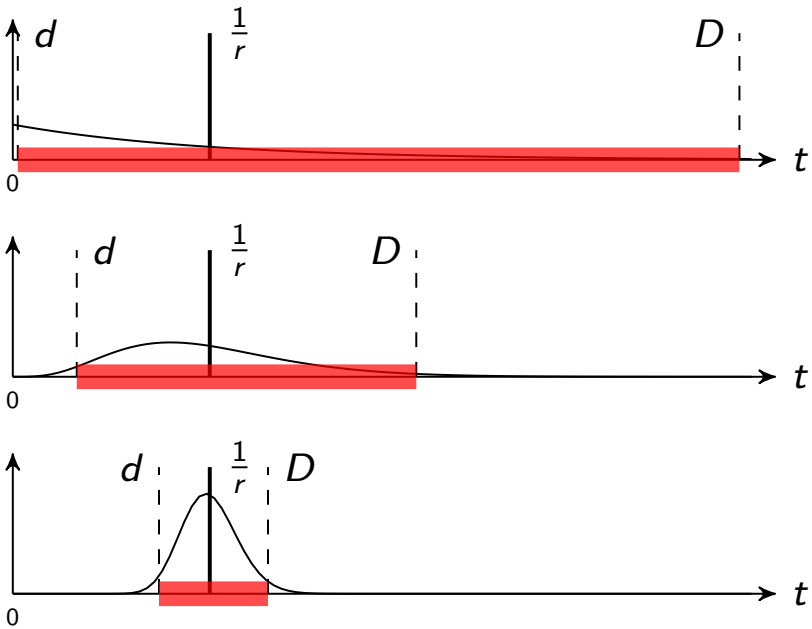
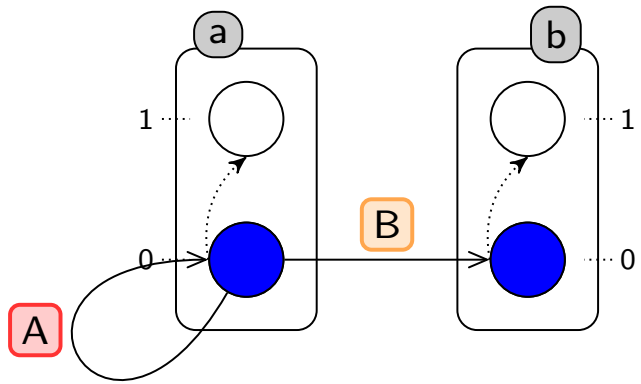
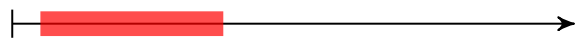


Intervalle de tir



$a_0 \rightarrow b_0 \Rightarrow b_1$ (B)

$a_0 \rightarrow a_0 \Rightarrow a_1$ (A)

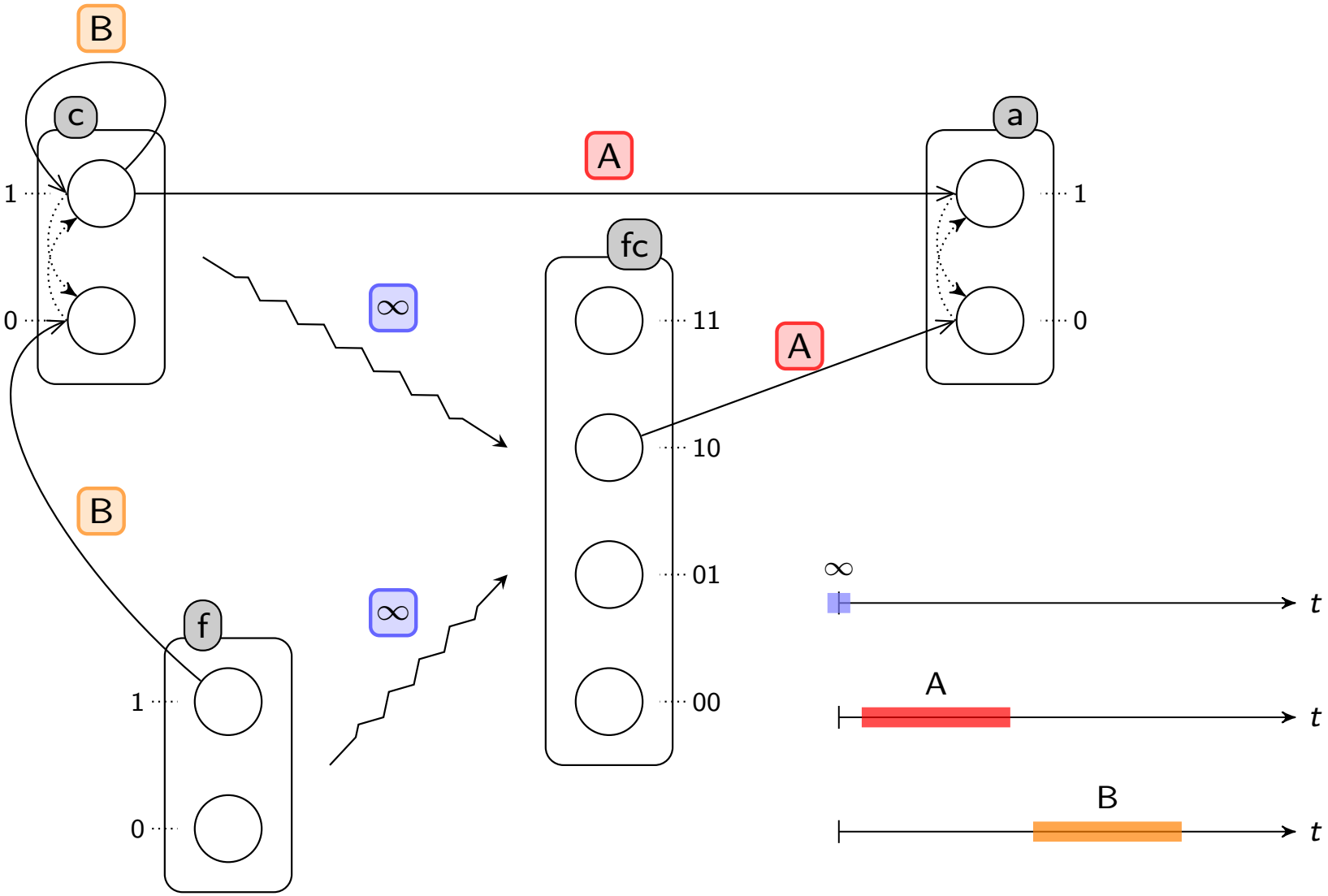


$\rightarrow$ **Very low probability** to reach b_1

- Simulation $\rightarrow$ not formal
- *Model-checking* $\rightarrow$ High complexity for an acceptable precision

Use of Stochastic Parameters

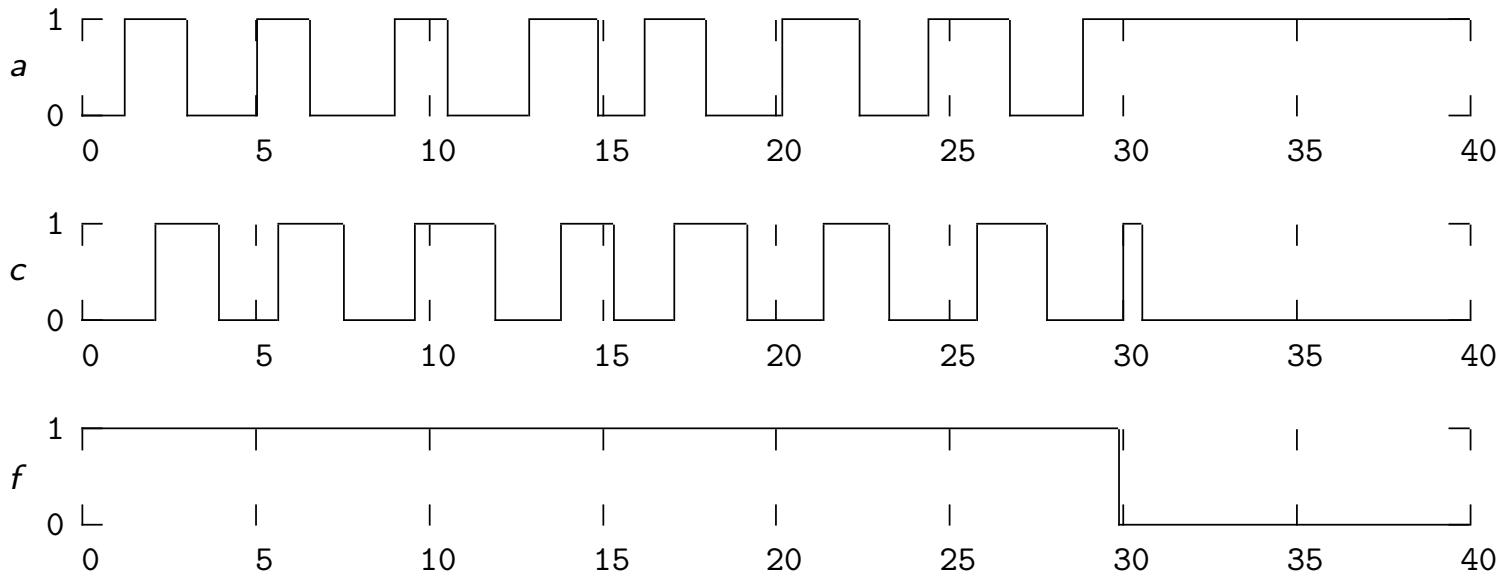
[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]



Temporal Simulation

[Paulevé (PhD thesis), 2011]

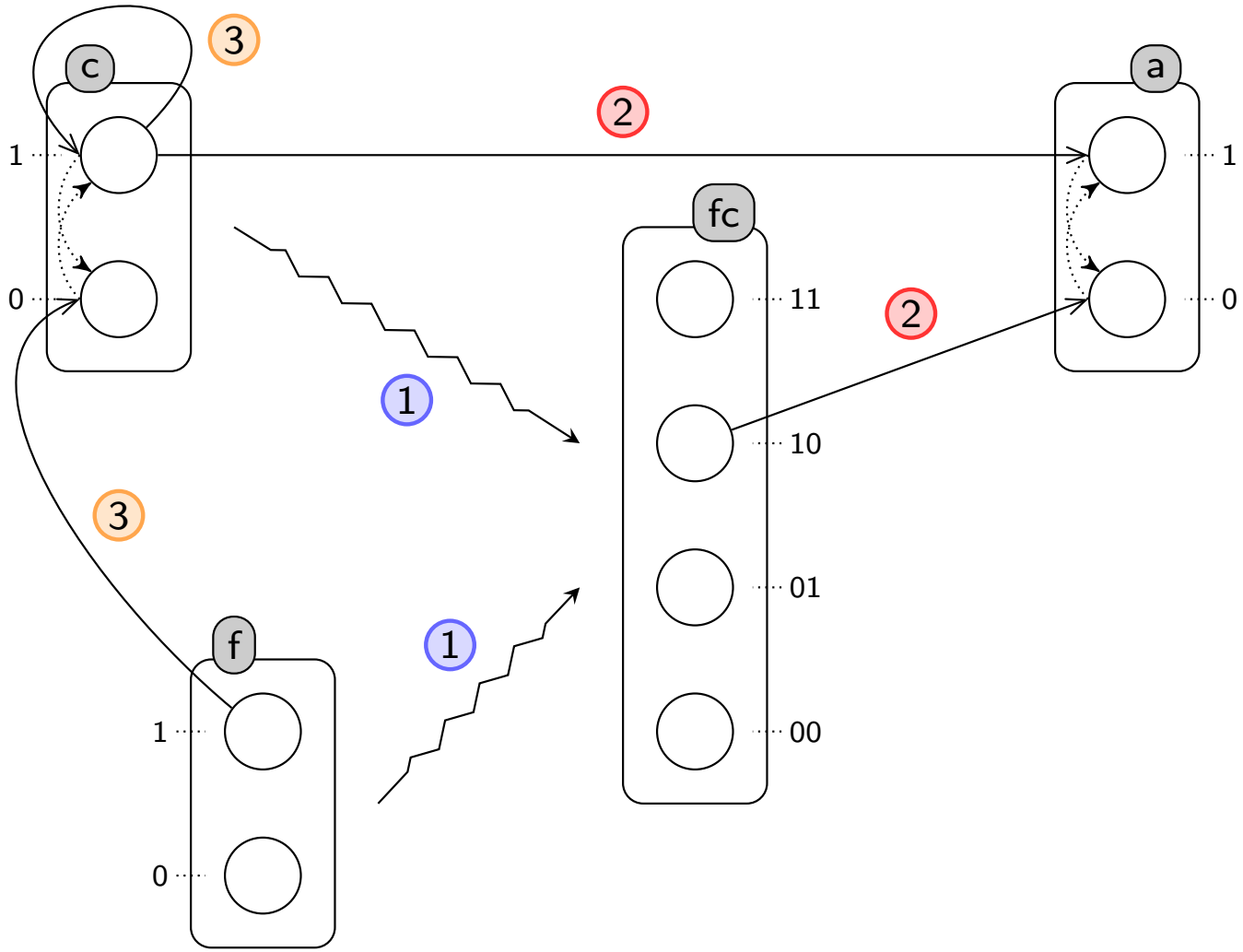
- Simulation with stochastic parameters:



- Other possible analysis: stochastic model checkers (PRISM)
  → But combinatoric explosion: PRISM fails for more than 5 components

Use of Classes of Priorities

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



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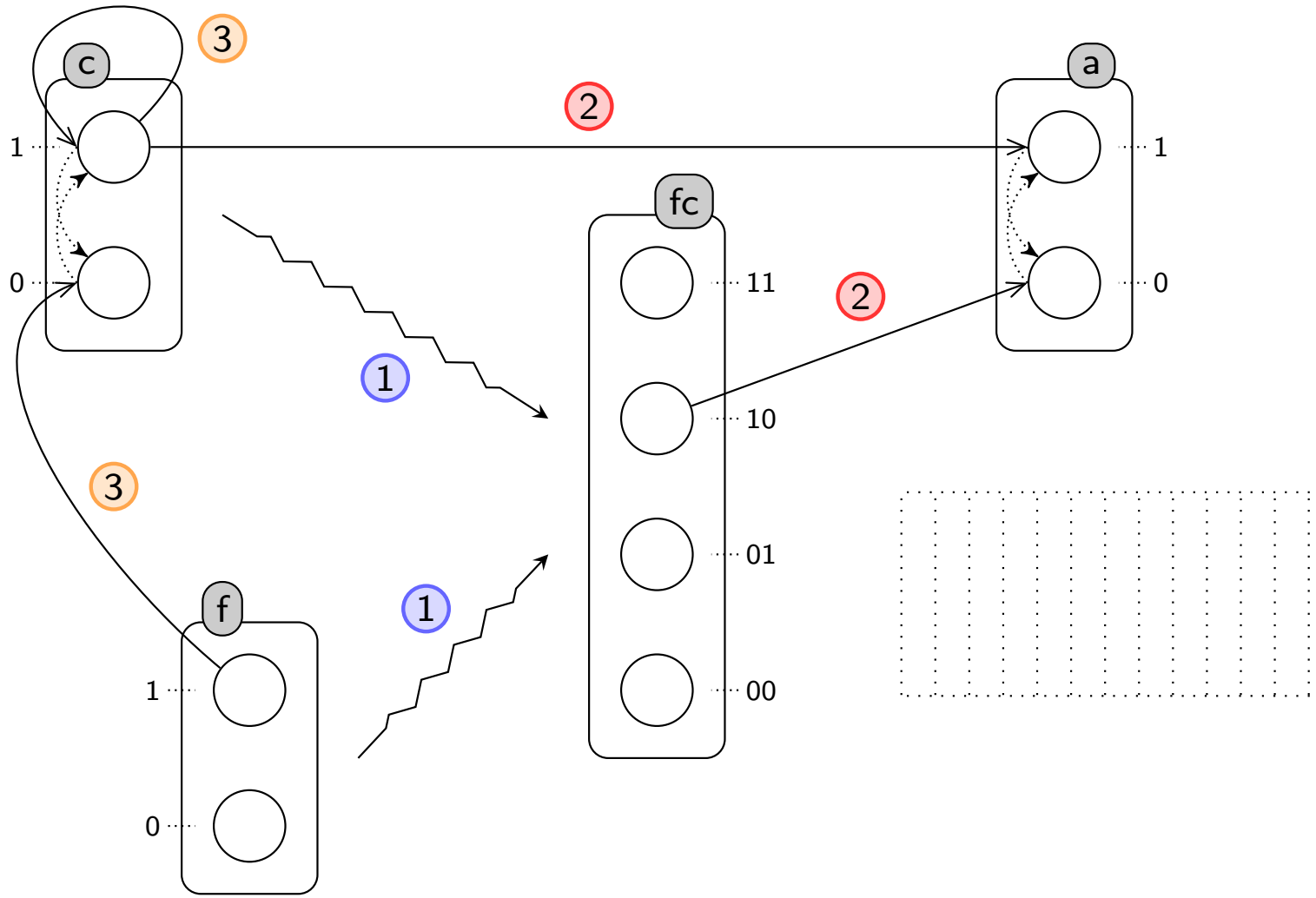

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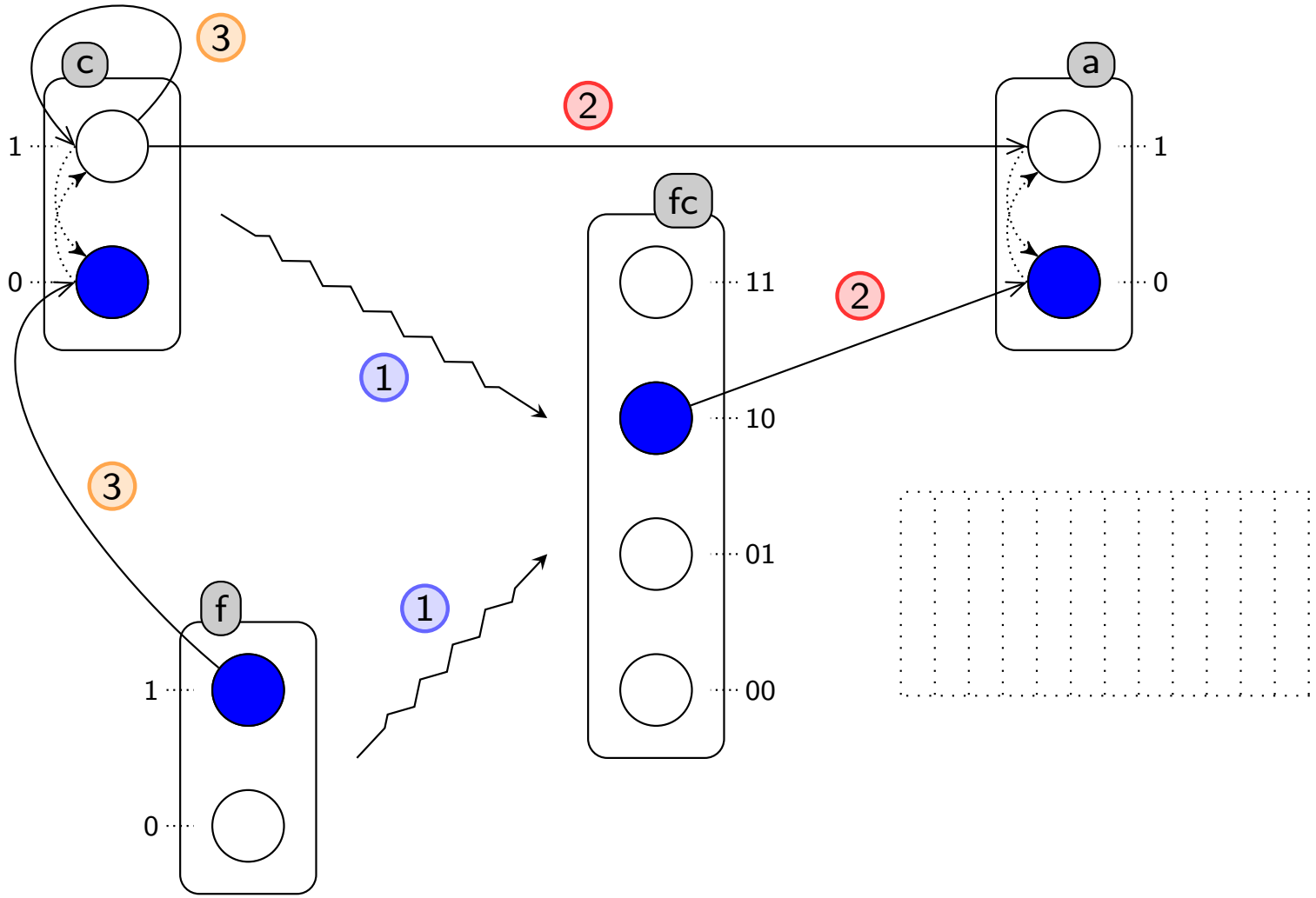
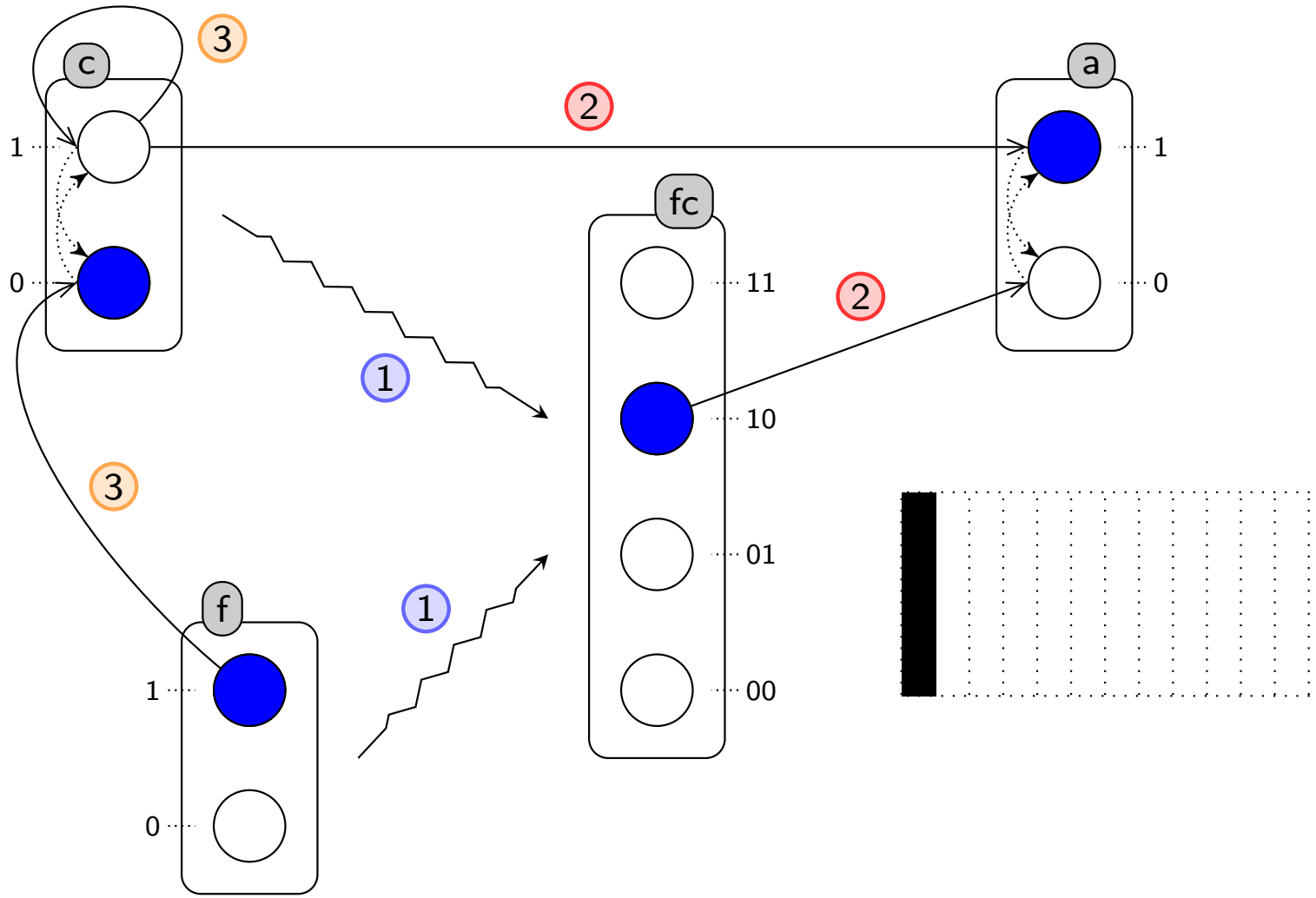


Use of Classes of Priorities

[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



Use of Classes of Priorities

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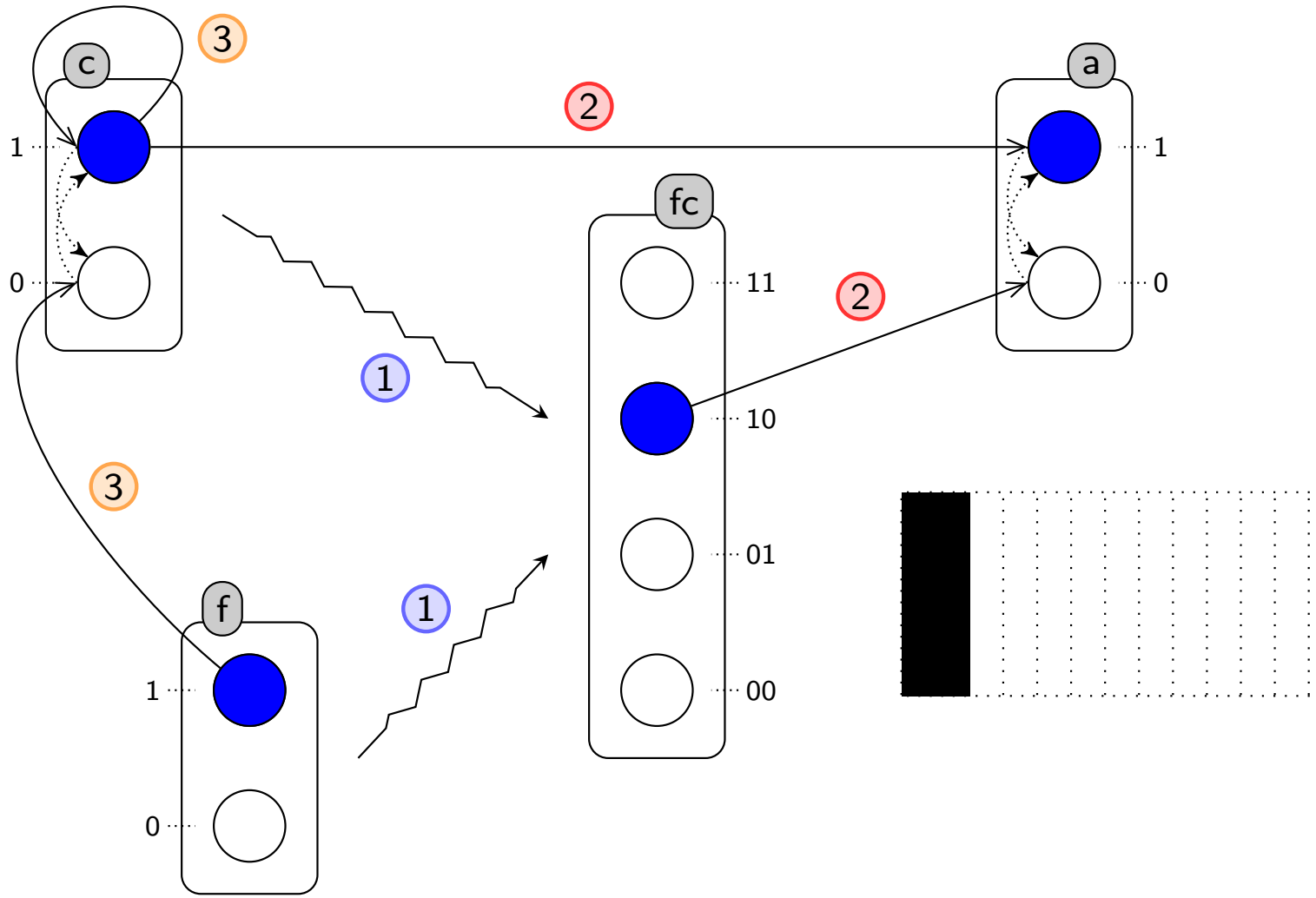

Use of Classes of Priorities

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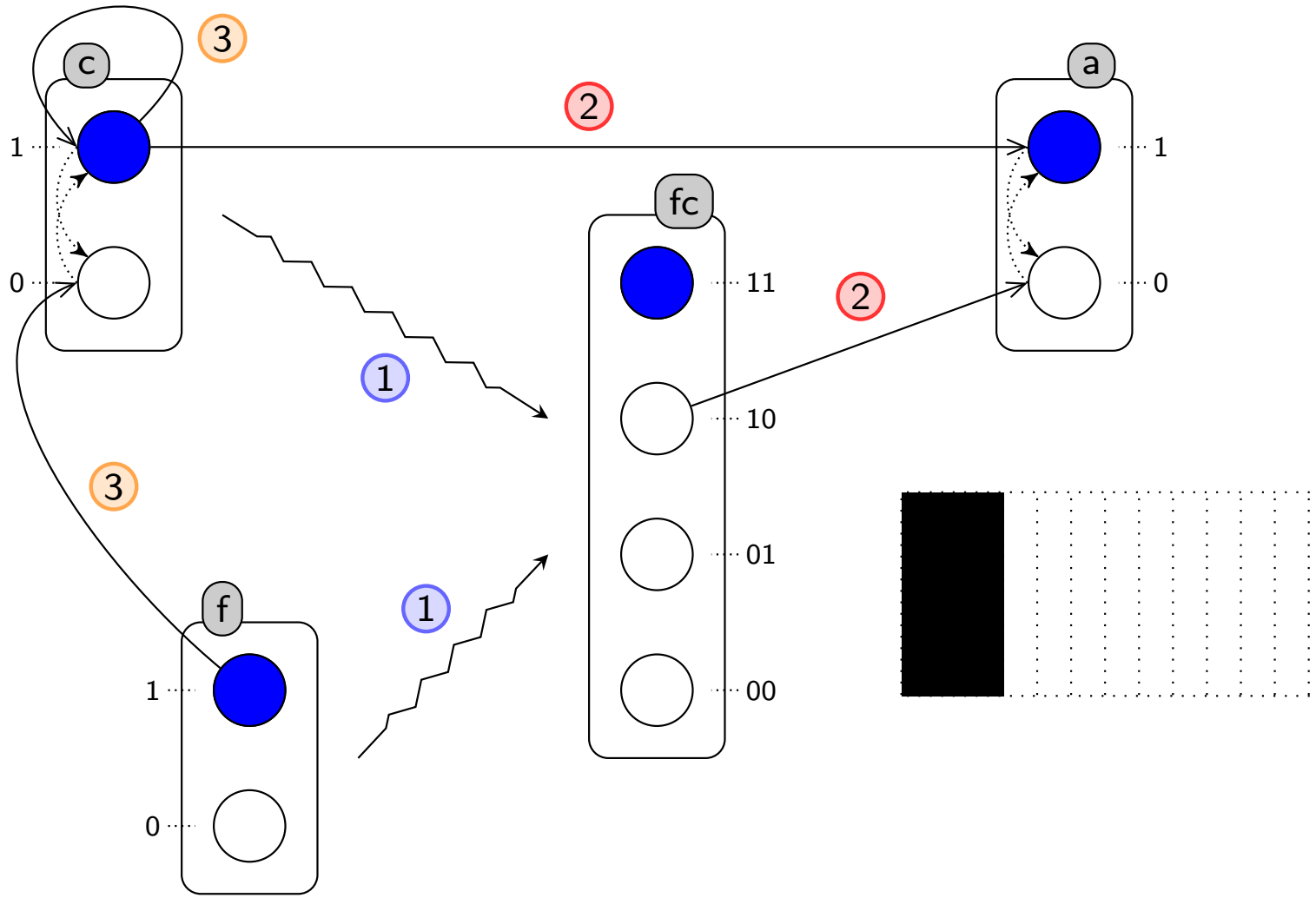

Use of Classes of Priorities

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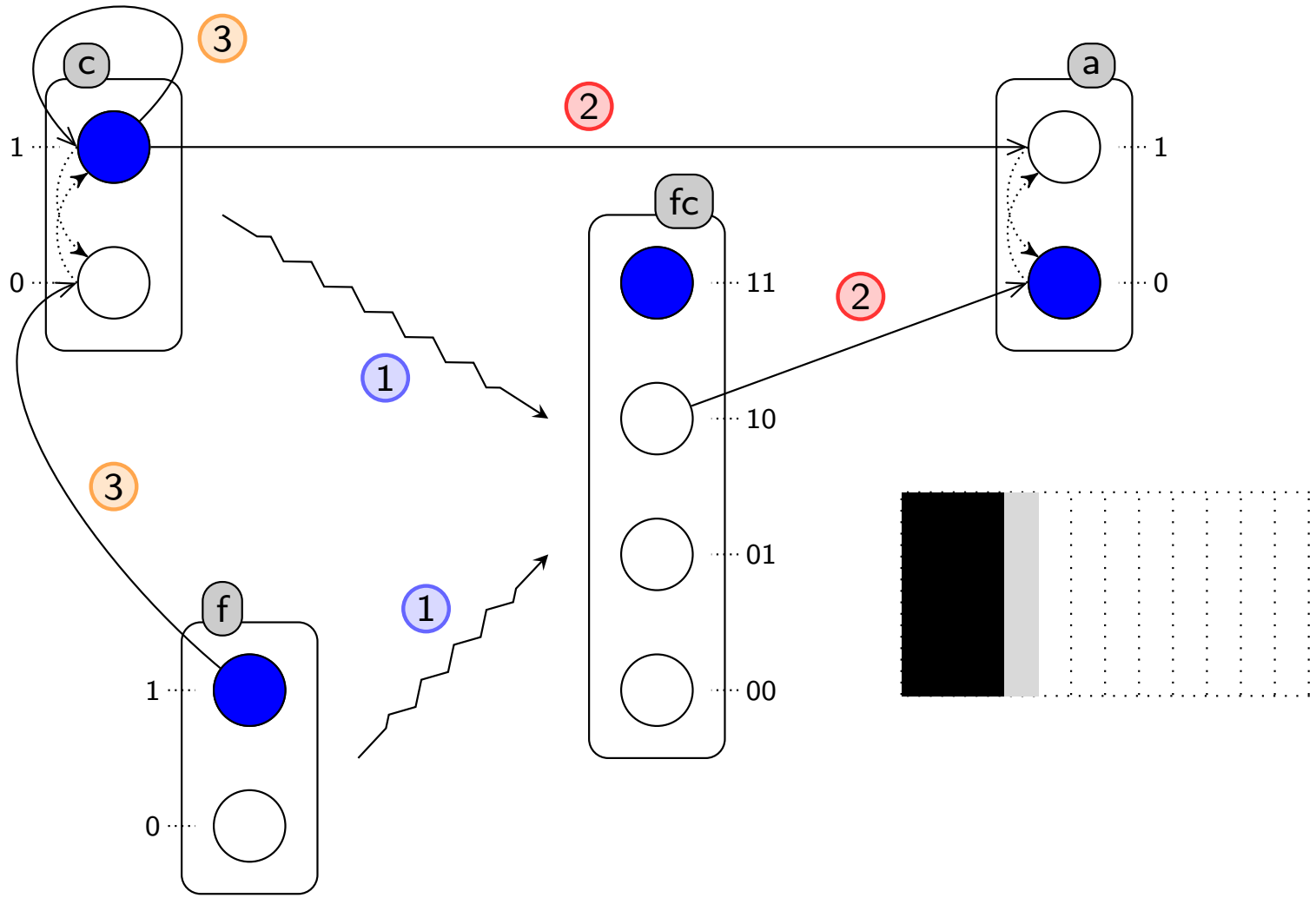

Use of Classes of Priorities

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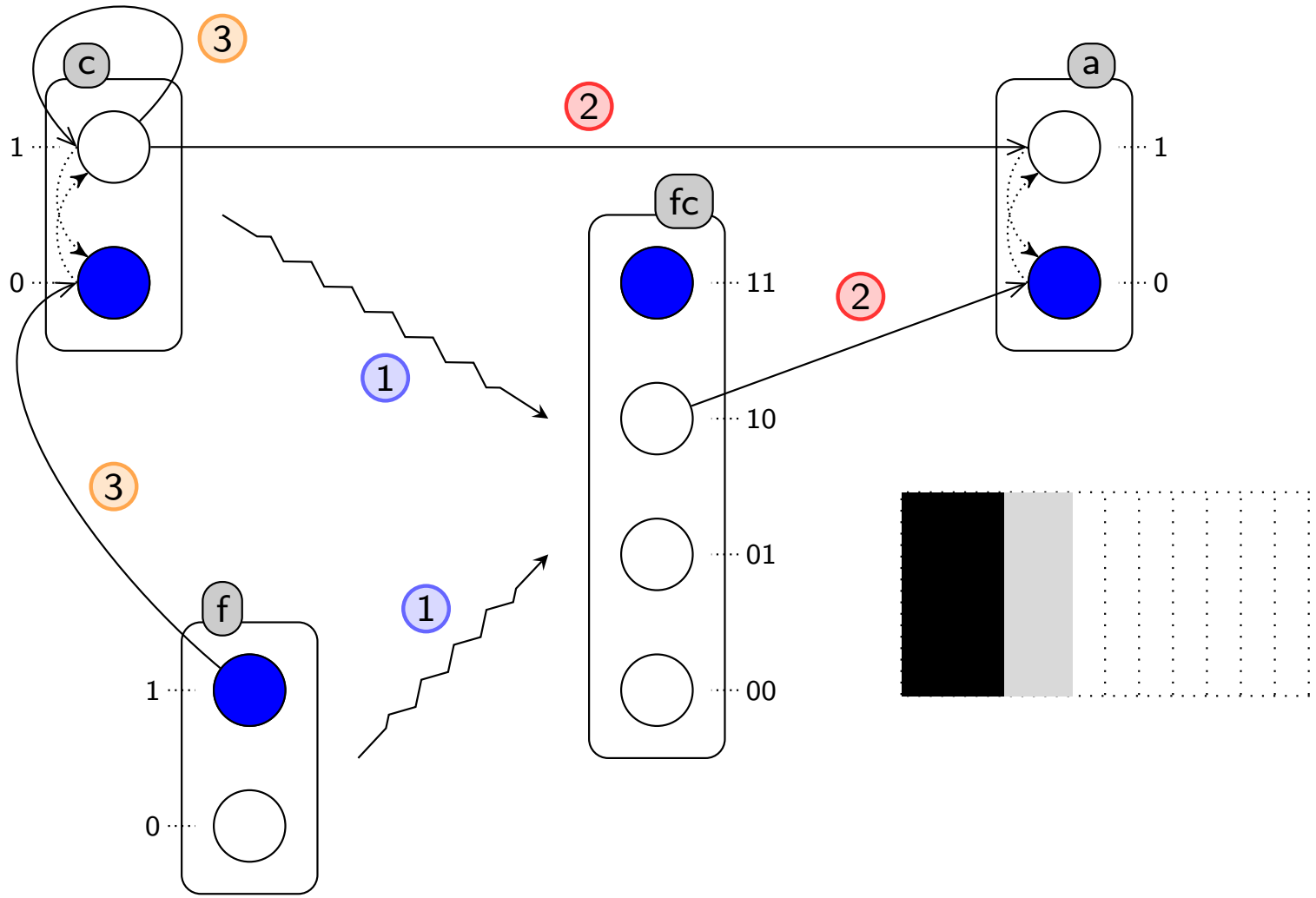

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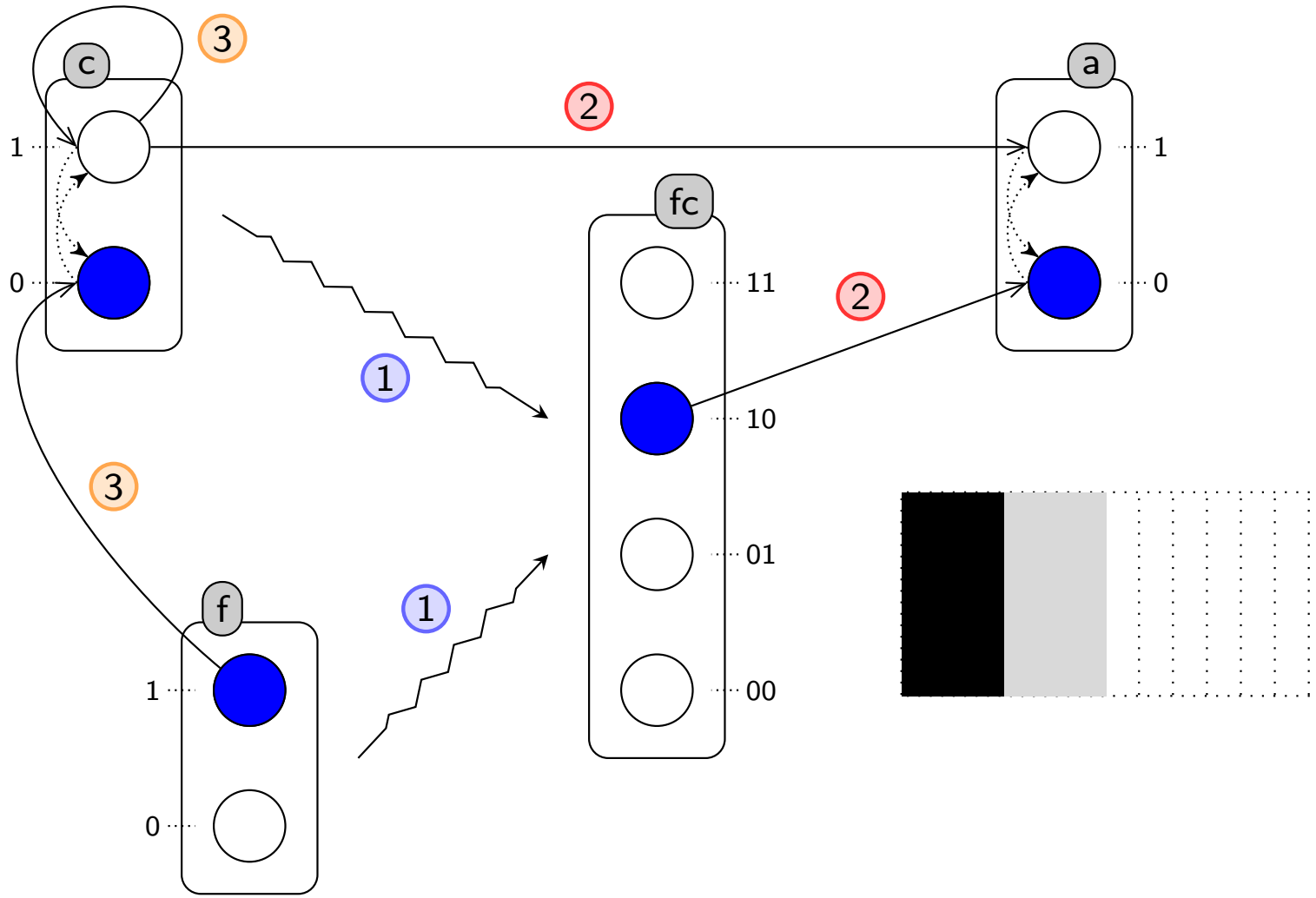

Use of Classes of Priorities

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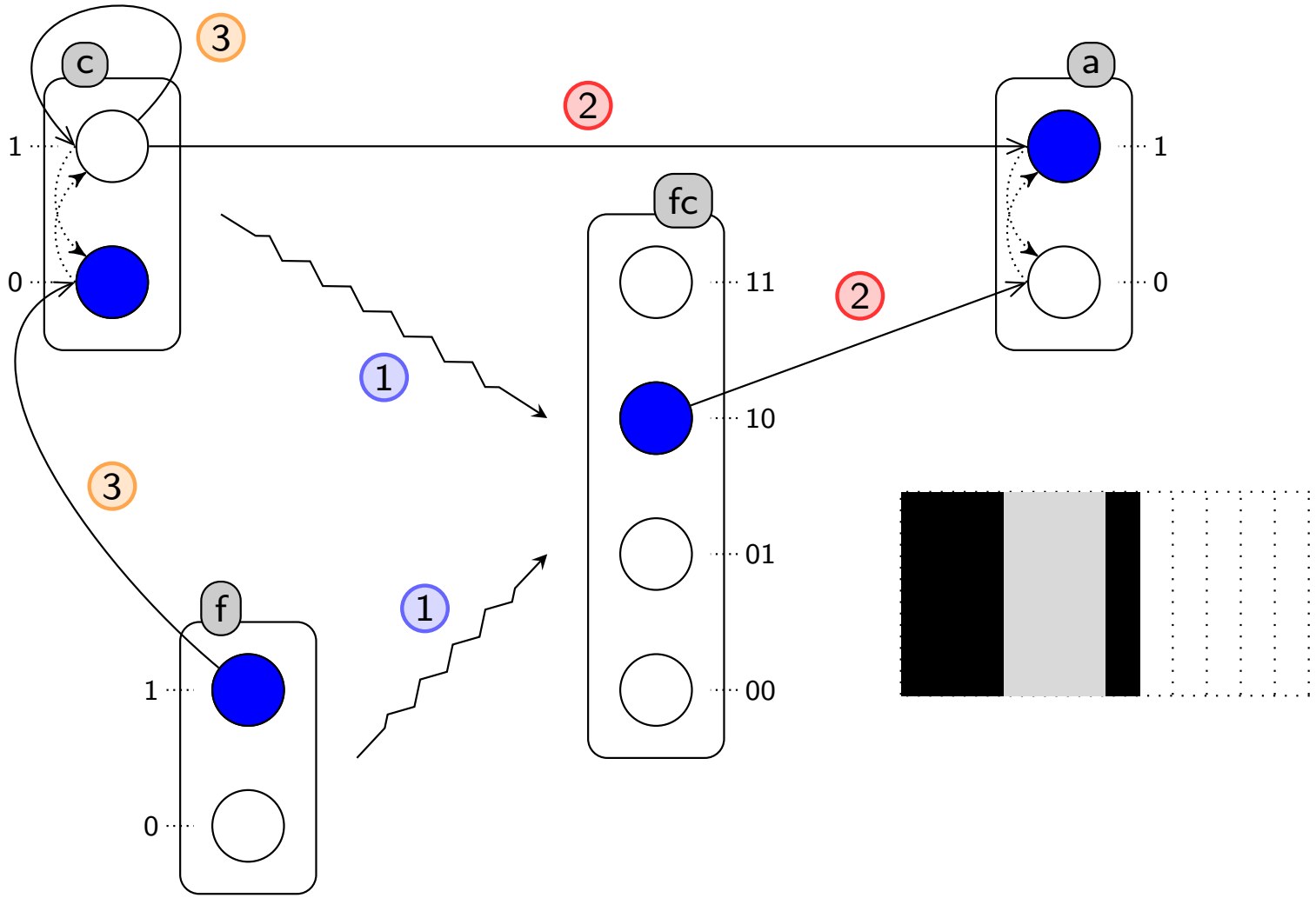

Use of Classes of Priorities

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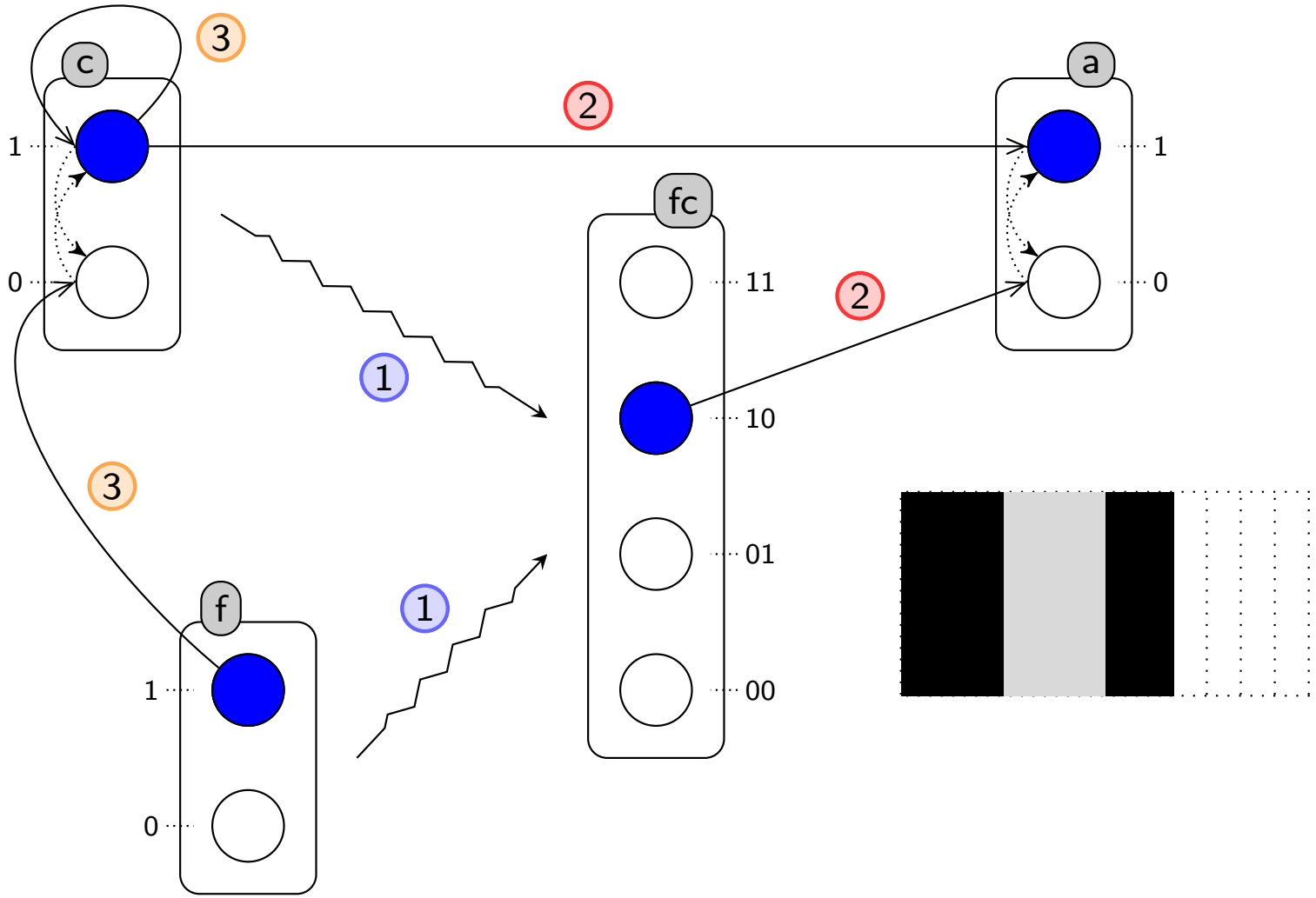

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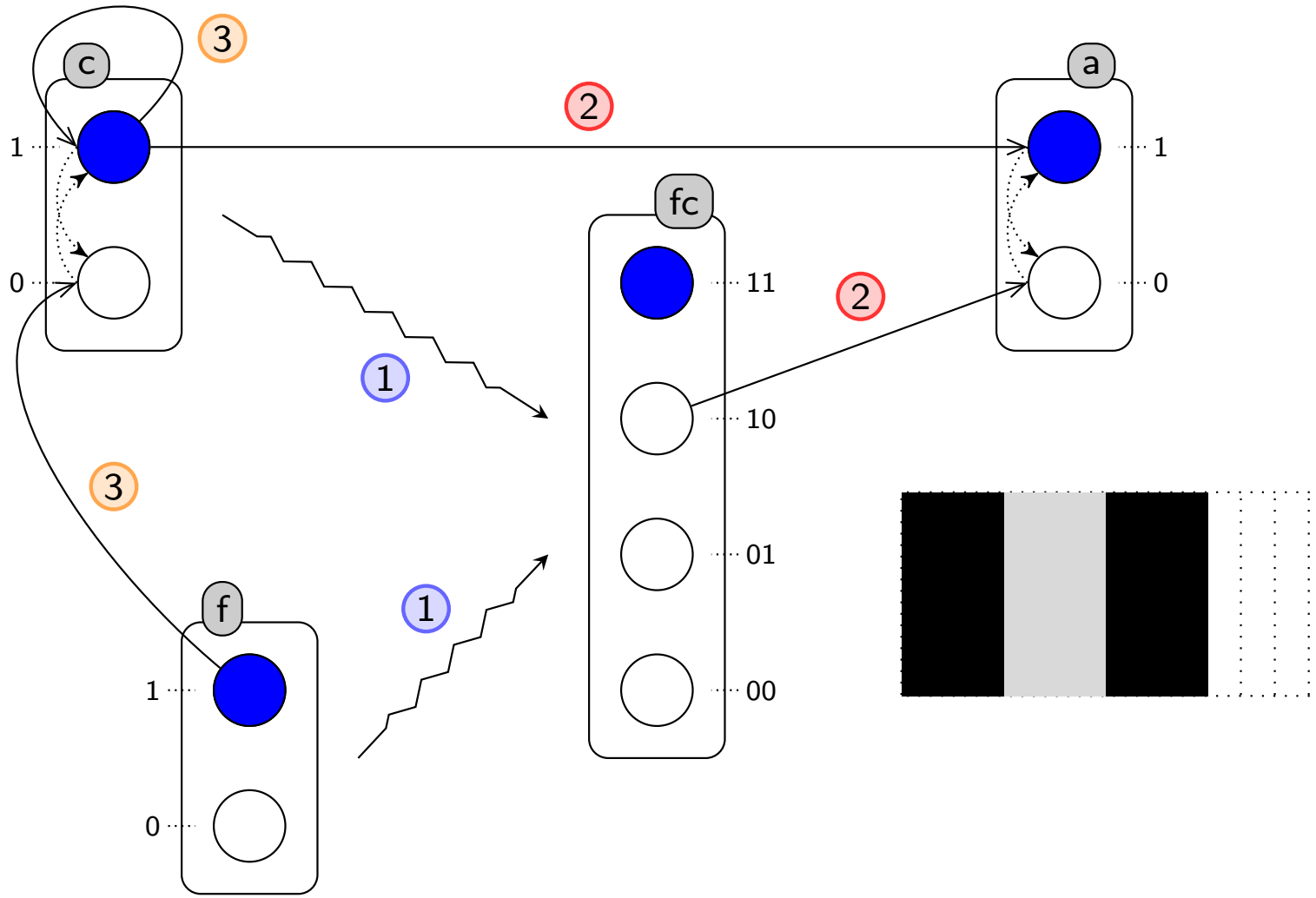

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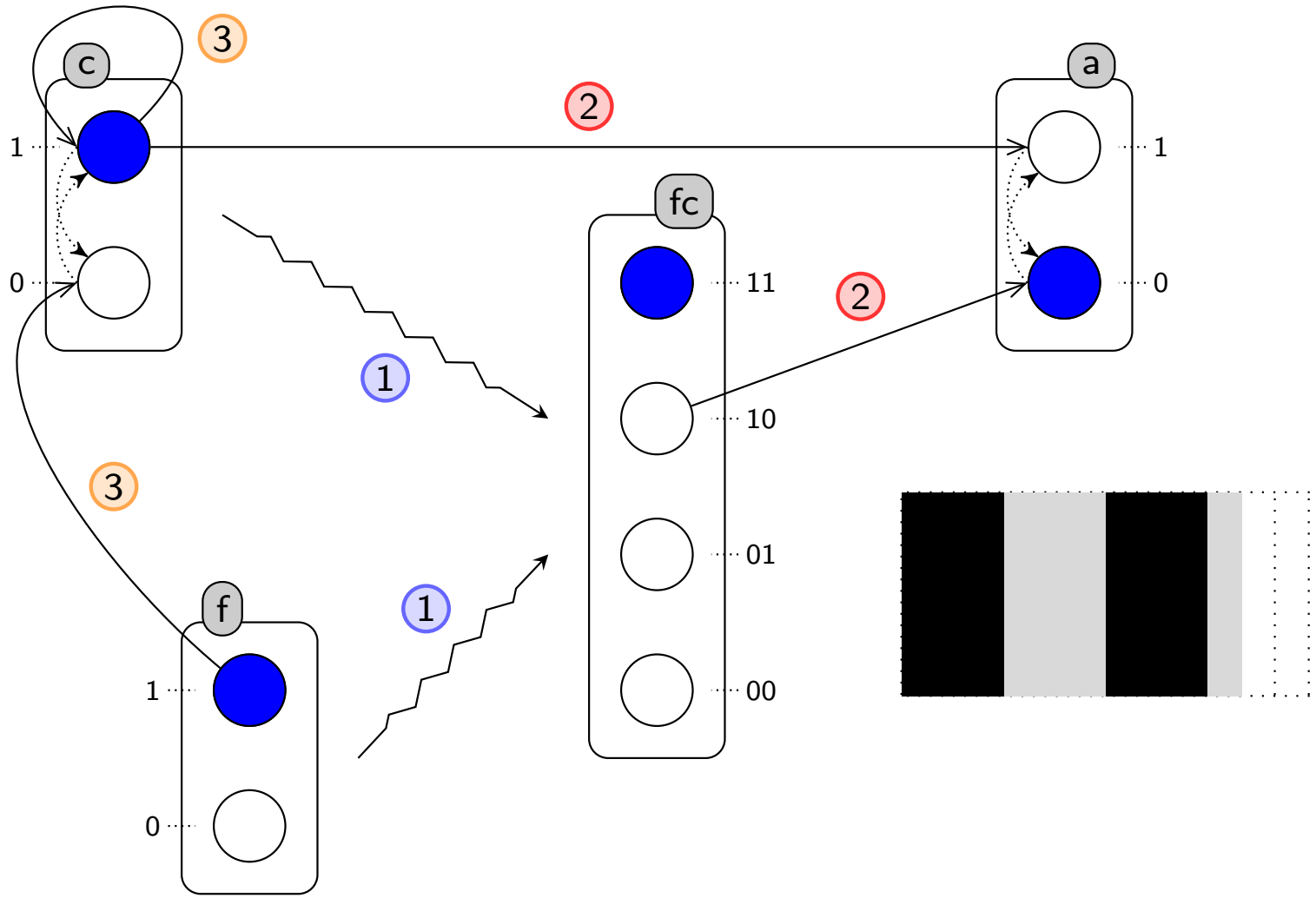

Use of Classes of Priorities

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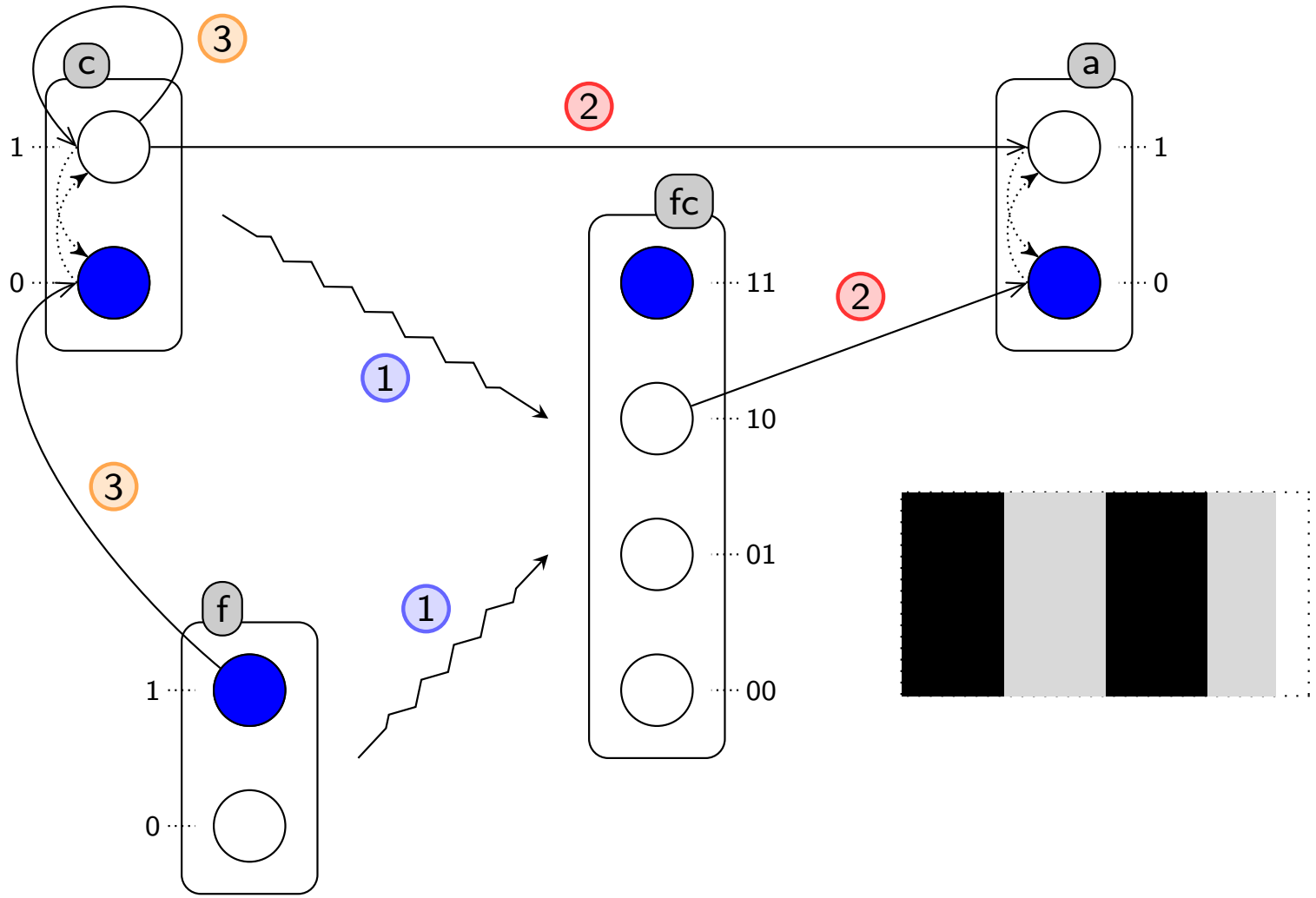

Use of Classes of Priorities

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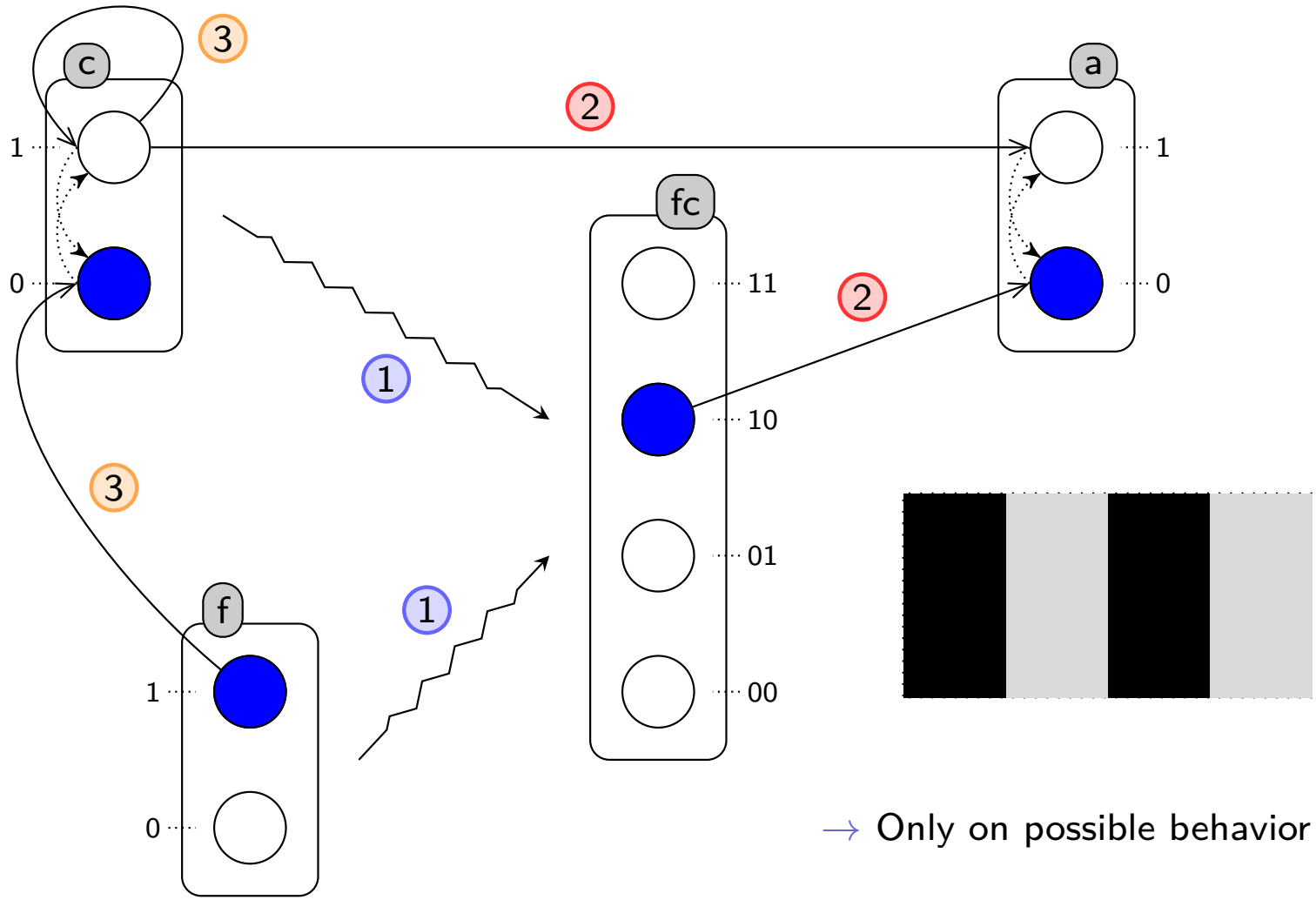
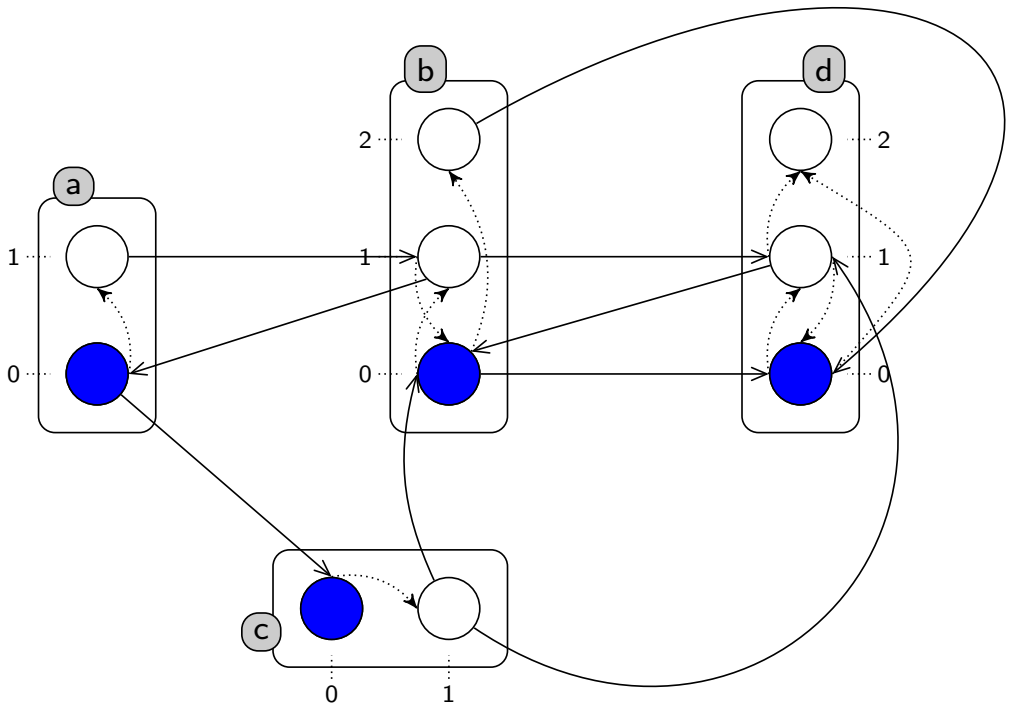


→ Only on possible behavior

Static analysis: successive reachability

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

Successive reachability of processes:



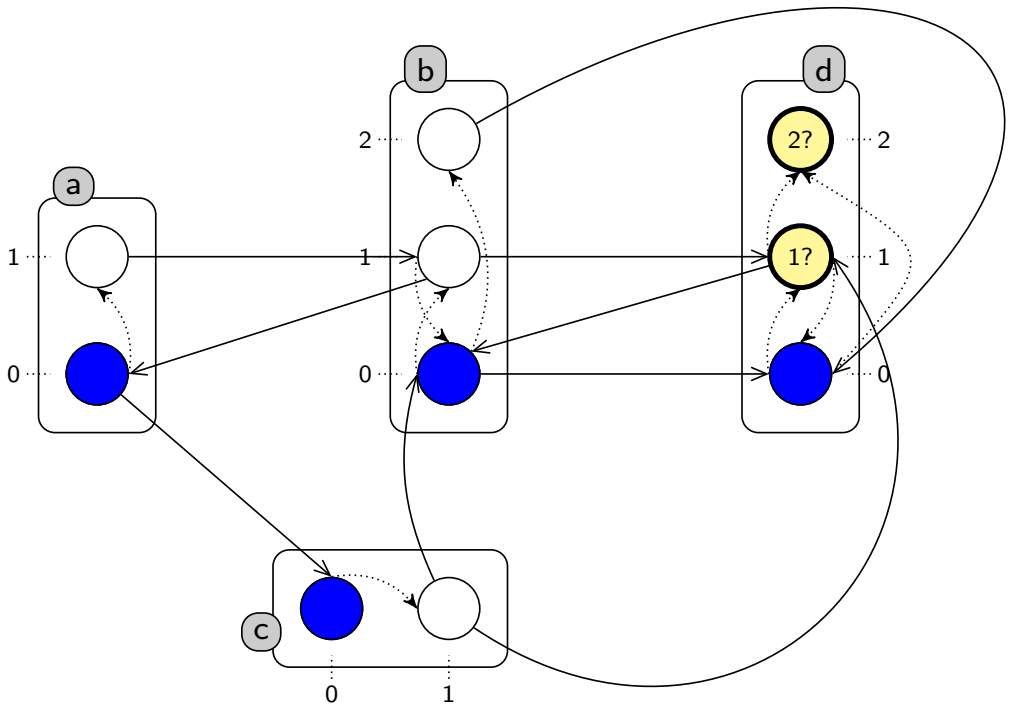
- Initial state

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

Static analysis: successive reachability

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

Successive reachability of processes:

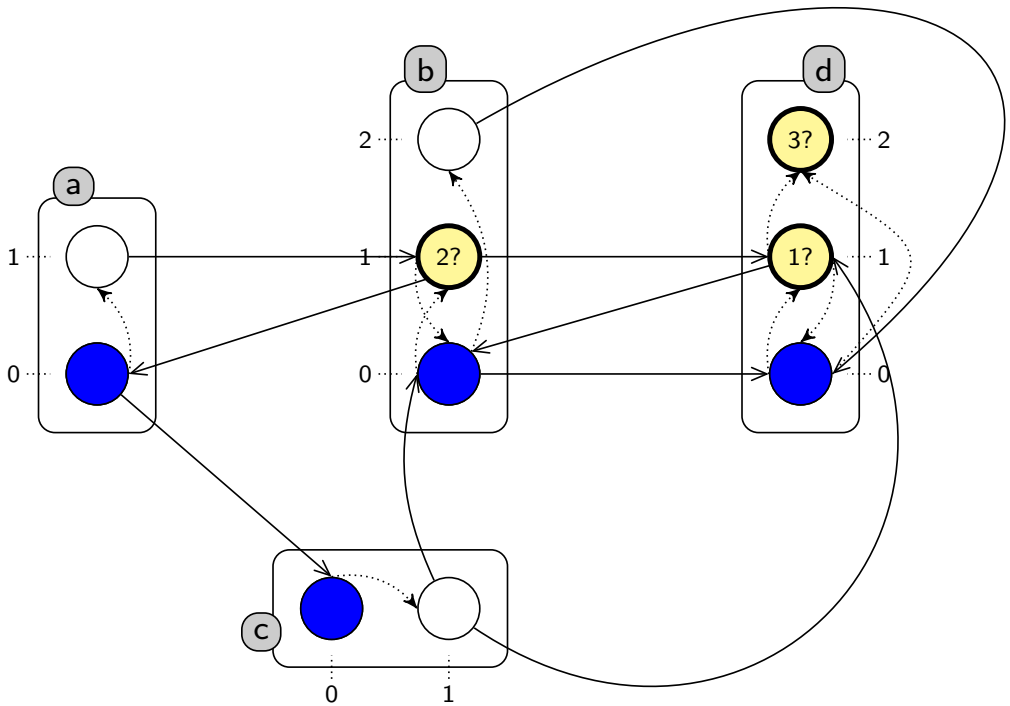


- Initial state $\langle a_1, b_0, c_0, d_0 \rangle$
- Objectives $[\ \Rsh d_1 \ :: \Rsh d_2\ ]$

Static analysis: successive reachability

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

Successive reachability of processes:



- Initial state

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

- Objectives

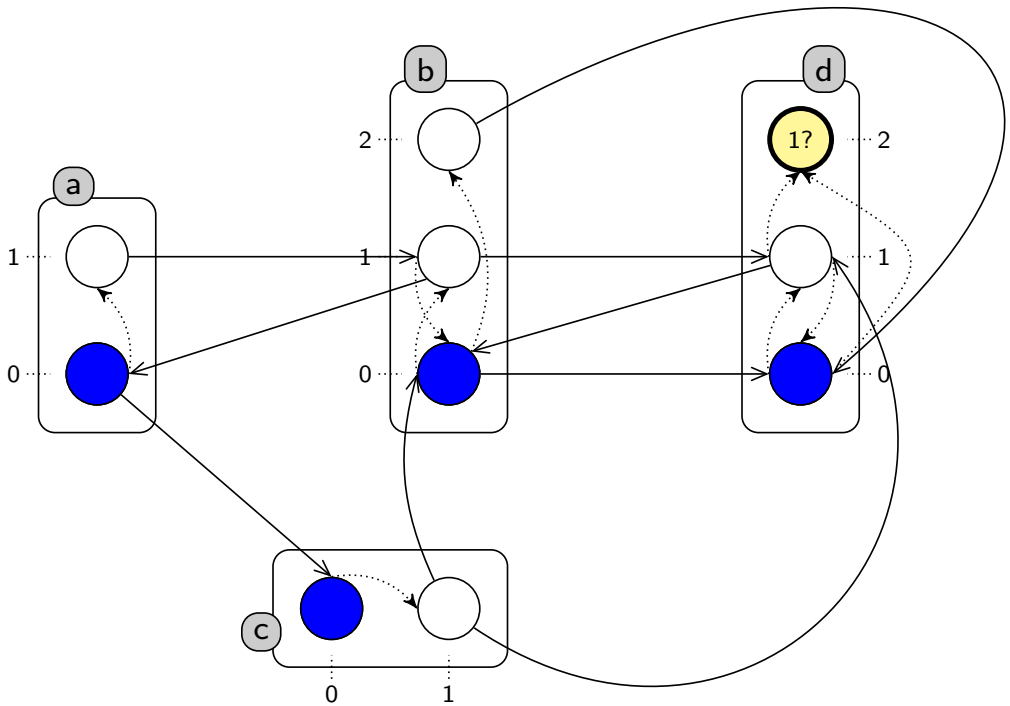
$[\ \Rsh\ d_1\ ::\ \Rsh\ d_2\ ]$

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

Static analysis: successive reachability

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

Successive reachability of processes:



- Initial state

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

- Objectives

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

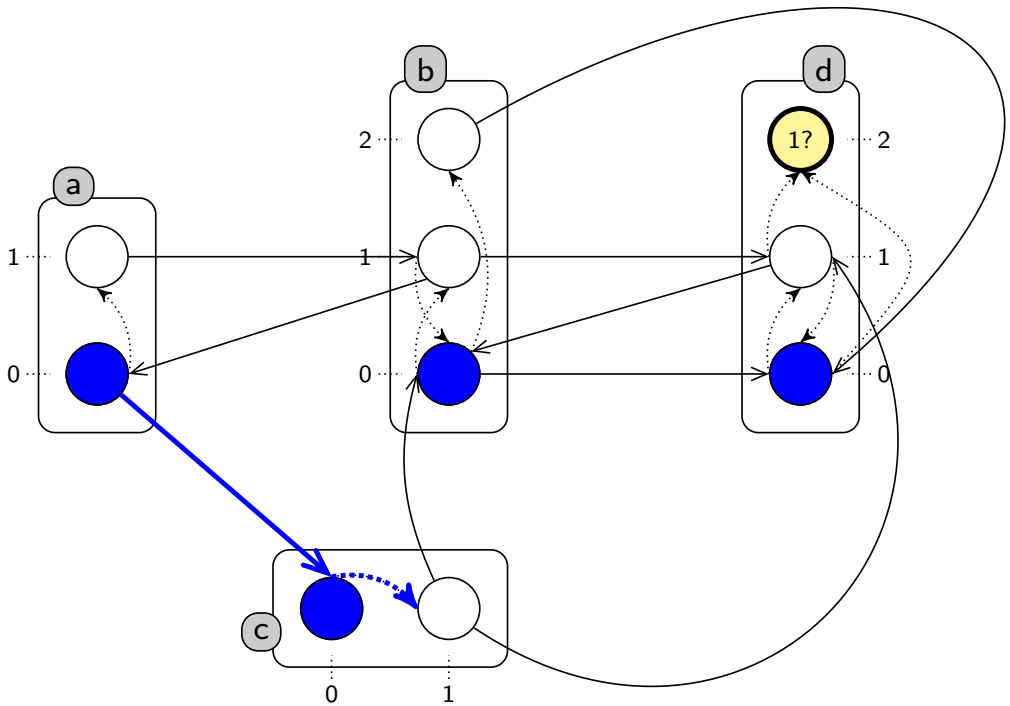
$$[\ \Rsh\ d_1 :: \Rsh\ b_1 :: \Rsh\ d_2\ ]$$

$$[\ \Rsh\ d_2\ ]$$

Static analysis: successive reachability

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

Successive reachability of processes:



- Initial state

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

- Objectives

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

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

$[\ \Rsh\ d_2\ ]$

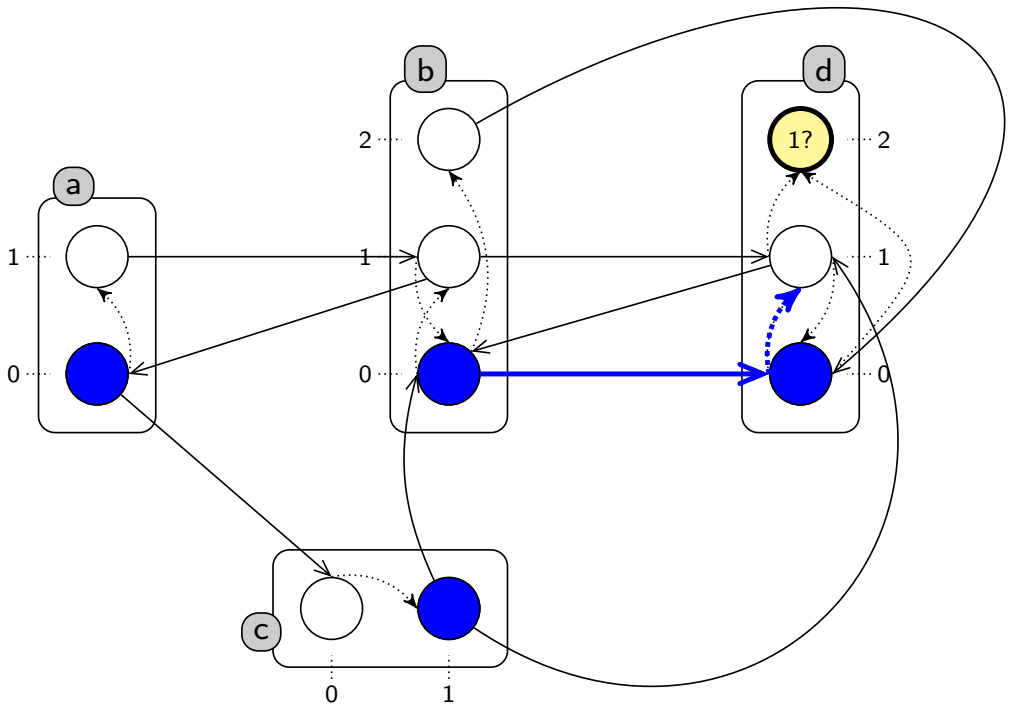
$\rightarrow$ Concretization of the objective = scenario

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

Static analysis: successive reachability

[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

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

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

$[\ \Rsh\ d_2\ ]$

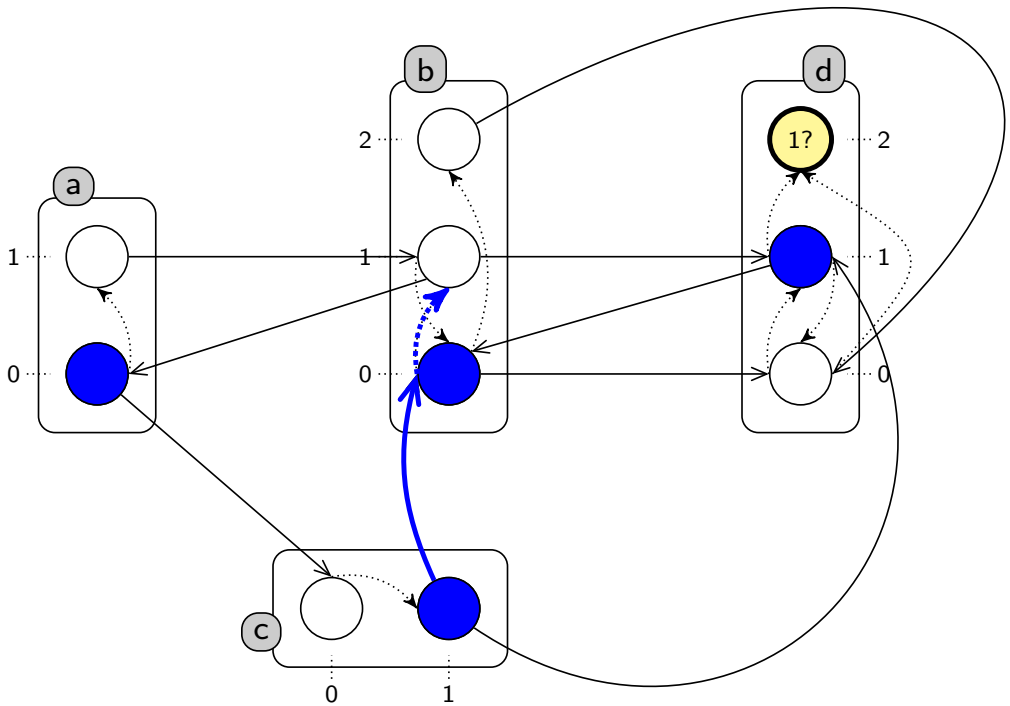
$\rightarrow$ Concretization of the objective = scenario

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

Static analysis: successive reachability

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

Successive reachability of processes:



- Initial state

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

- Objectives

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

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

$[\ \Rsh\ d_2\ ]$

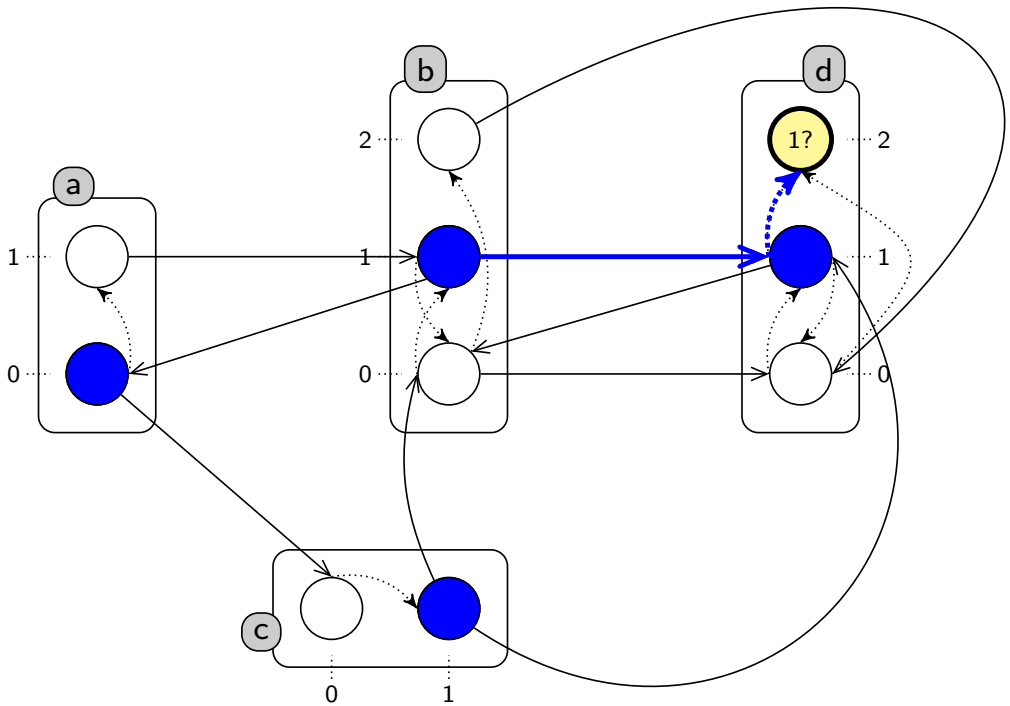
$\rightarrow$ Concretization of the objective = scenario

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

Static analysis: successive reachability

[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

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

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

$[\ \Rsh\ d_2\ ]$

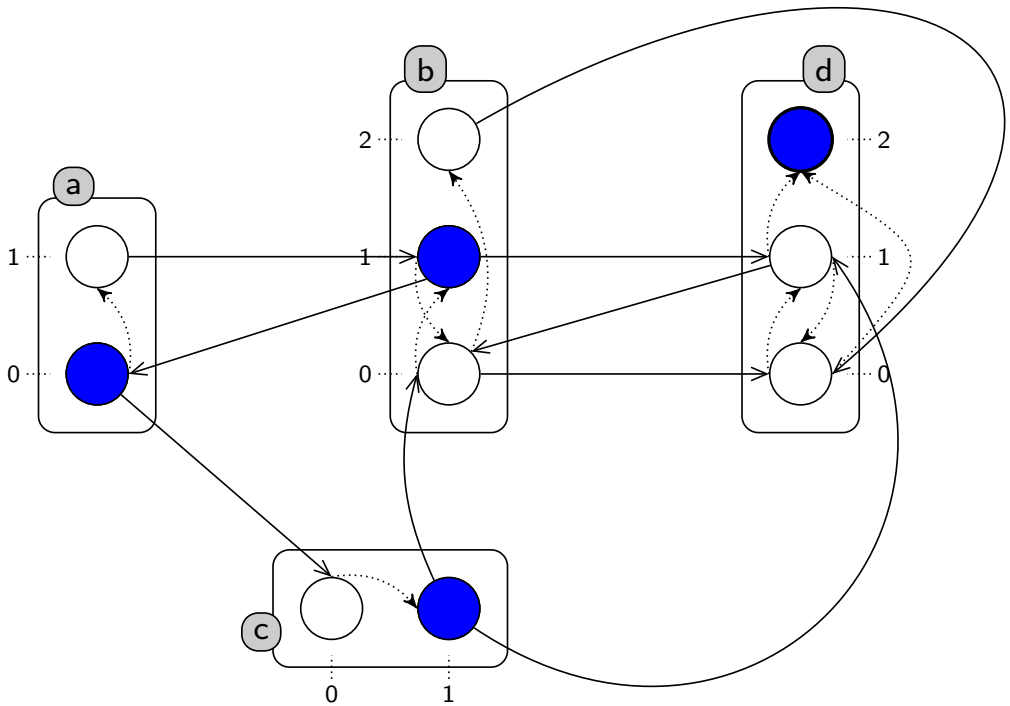
$\rightarrow$ Concretization of the objective = scenario

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

Static analysis: successive reachability

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

Successive reachability of processes:



- Initial state

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

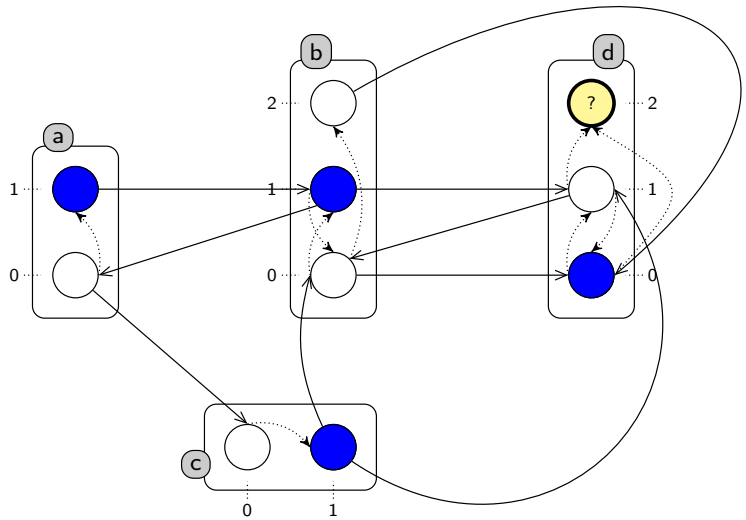
- Objectives

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

$\rightarrow$ Concretization of the objective = scenario

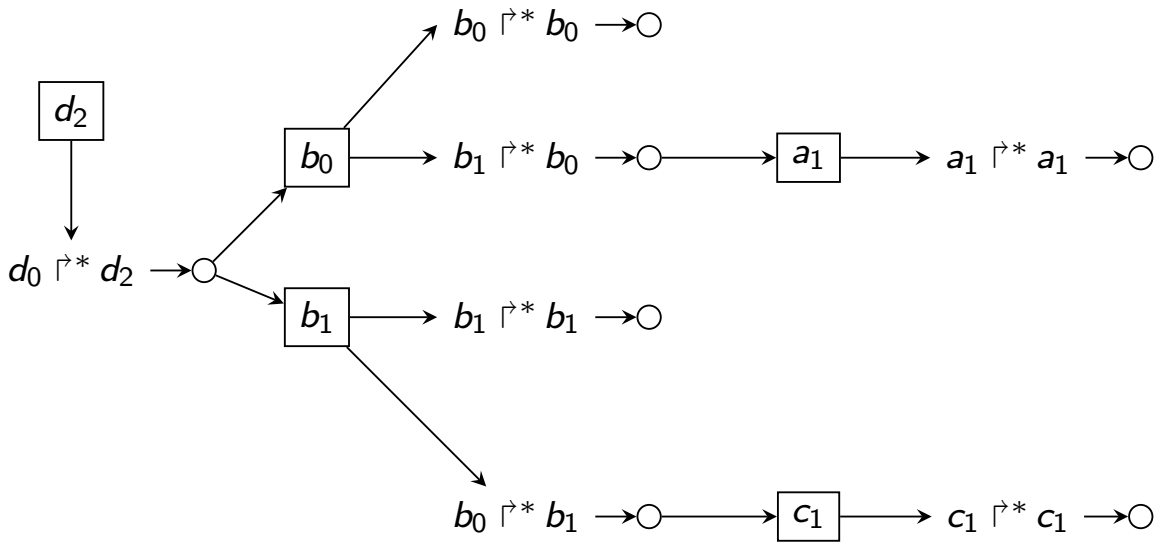
$$a_0 \rightarrow c_0\ \Rsh\ c_1 :: b_0 \rightarrow d_0\ \Rsh\ d_1 :: c_1 \rightarrow b_0\ \Rsh\ b_1 :: b_1 \rightarrow d_1\ \Rsh\ d_2$$

Under-approximation



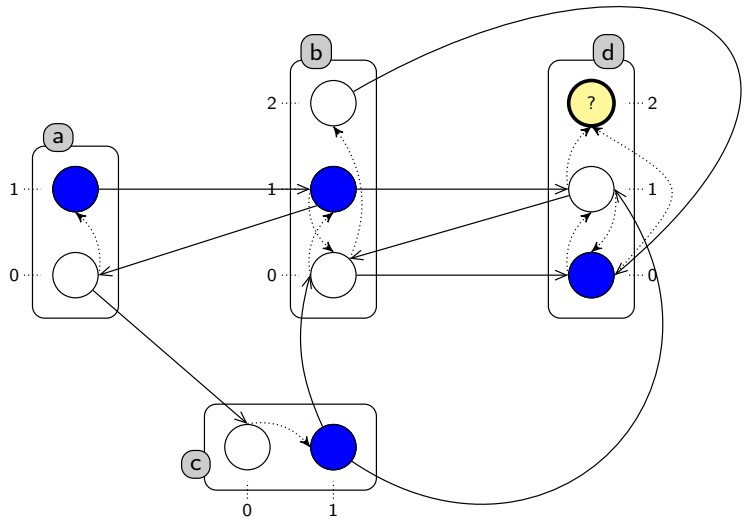
Sufficient condition:

- no cycle
- each objective has a solution



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

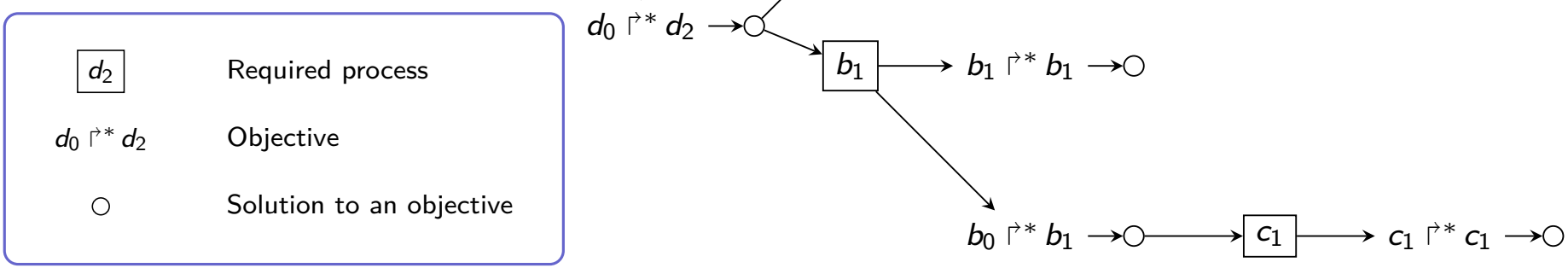
Under-approximation



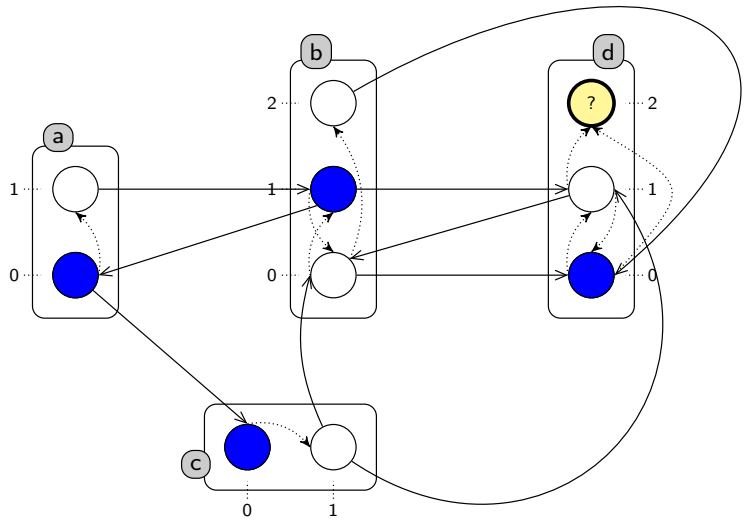
Sufficient condition:

- no cycle
- each objective has a solution

R is **true**

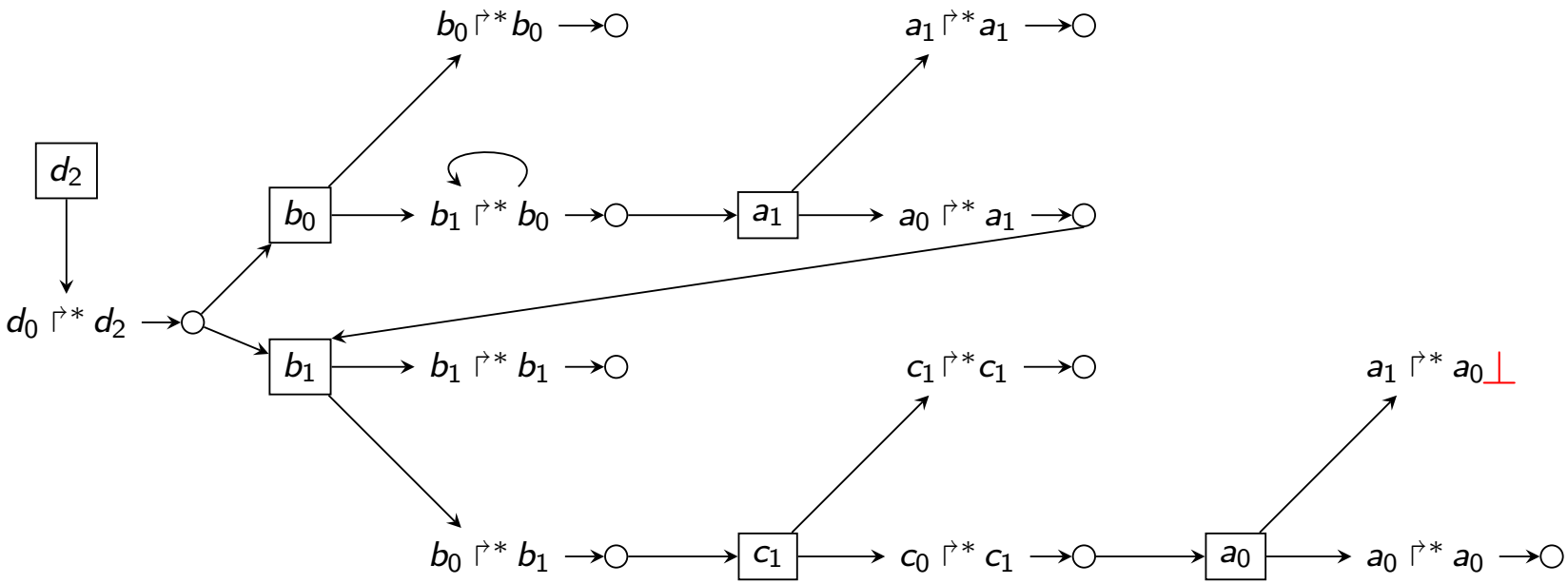


Under-approximation

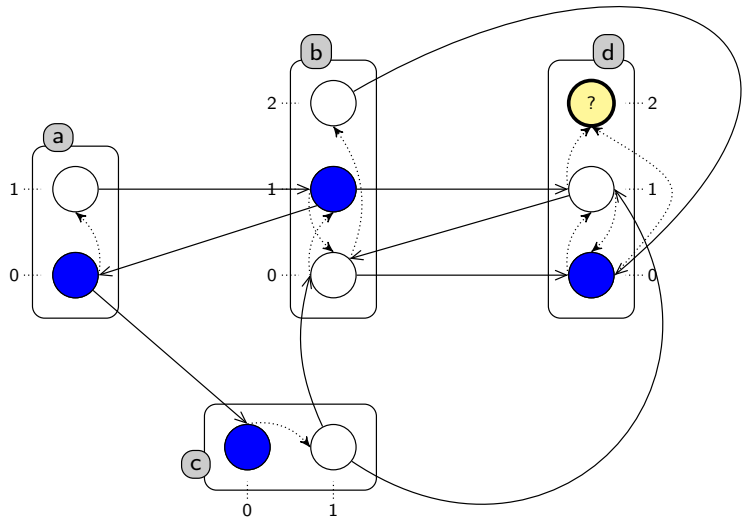


Sufficient condition:

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



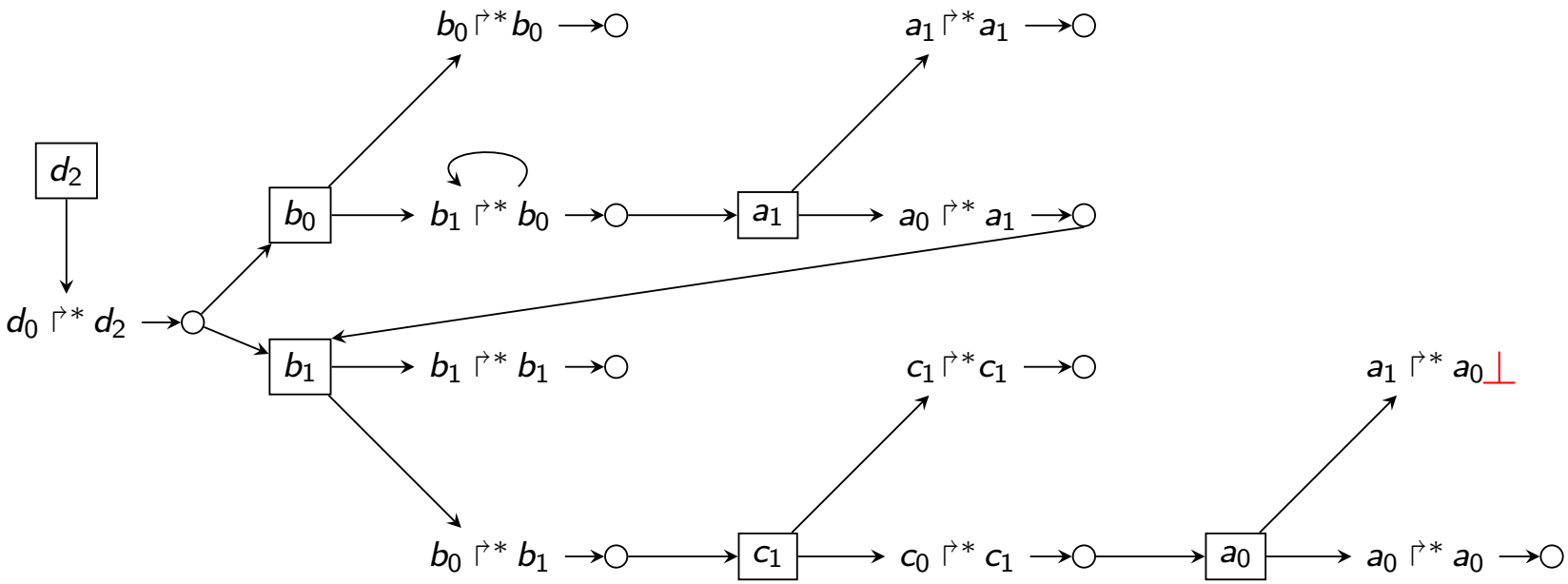
Under-approximation



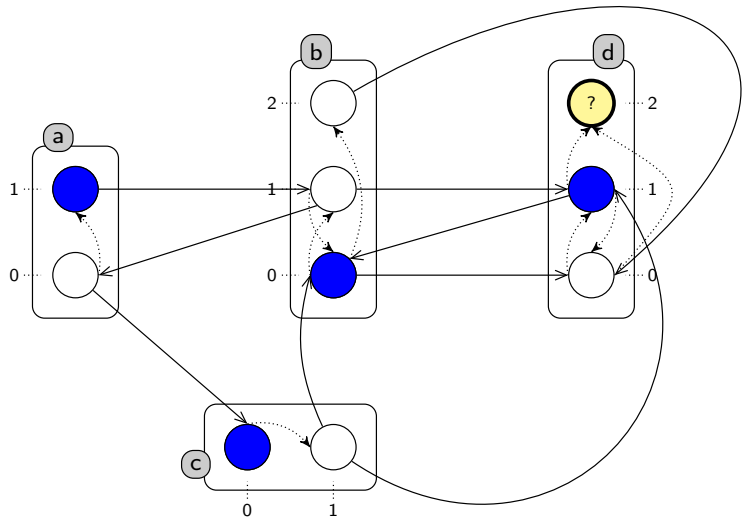
Sufficient condition:

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

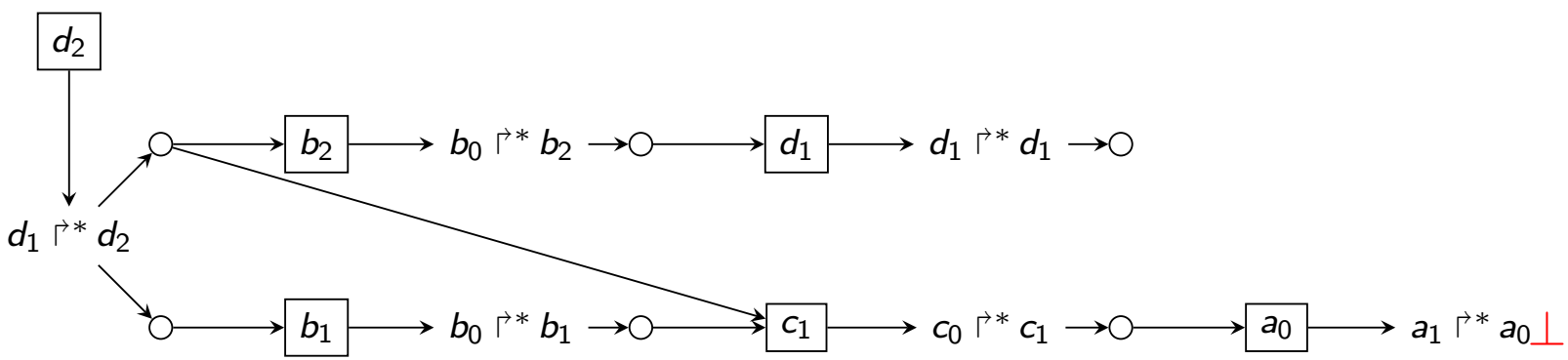
Inconclusive



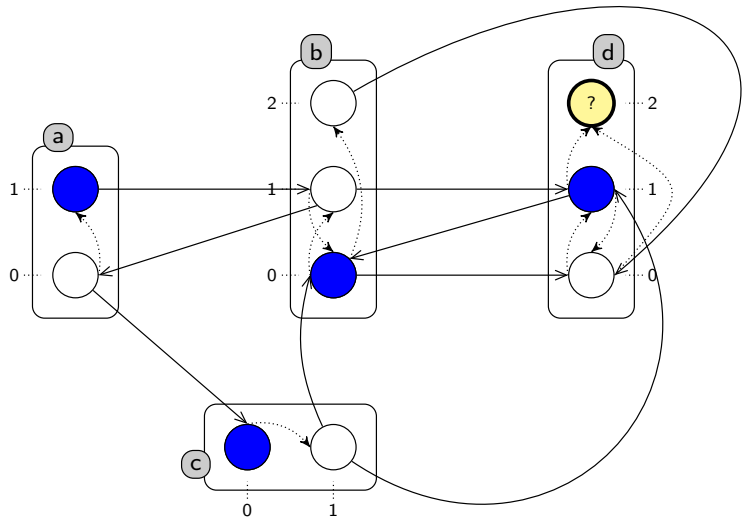
Over-approximation



Necessary condition:



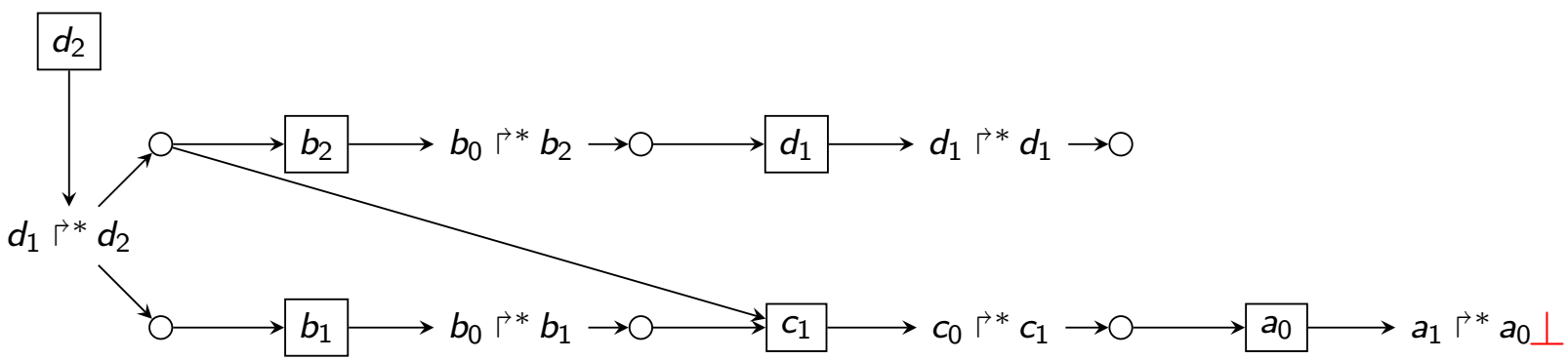
Over-approximation



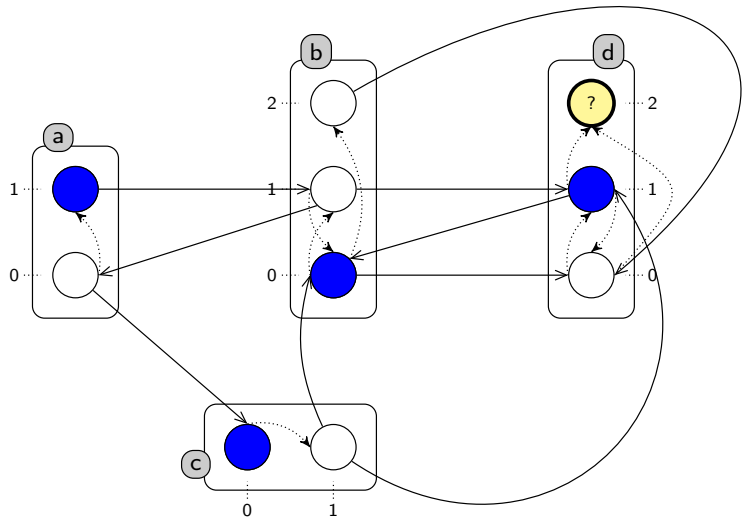
Necessary condition:

There exists a traversal with no cycle

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



Over-approximation



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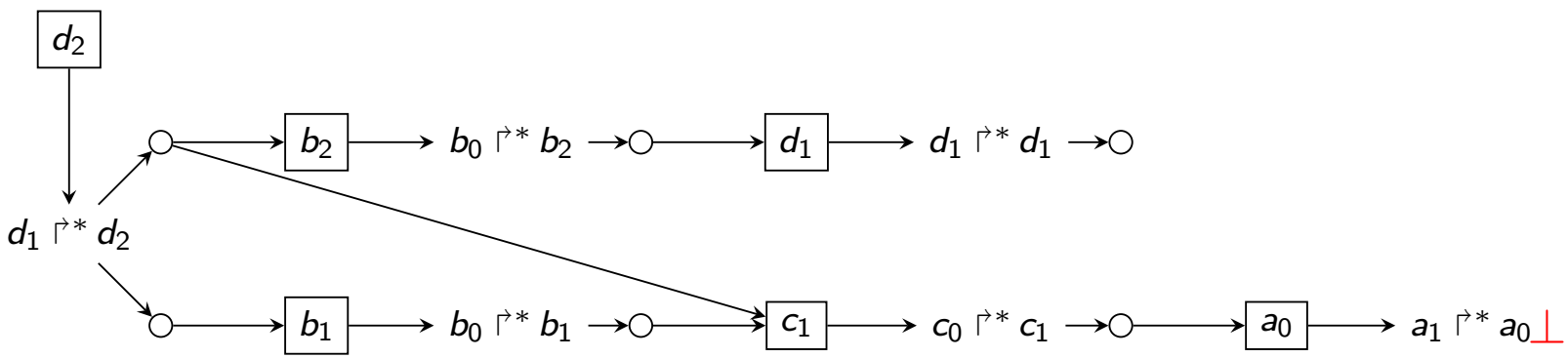
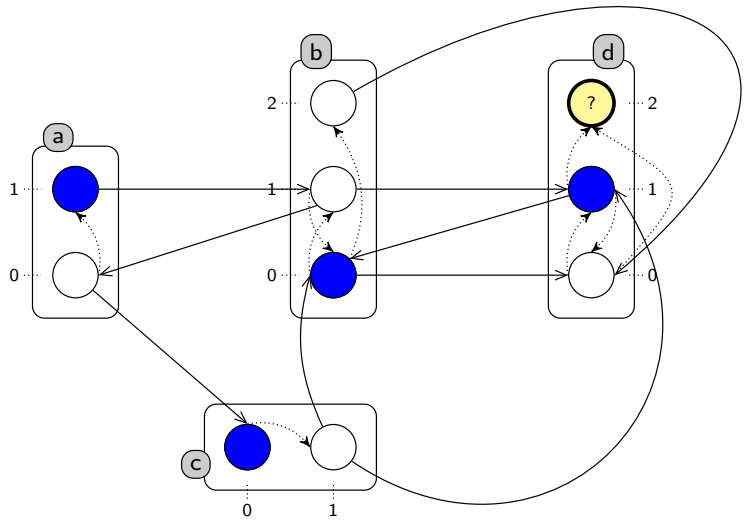


Over-approximation

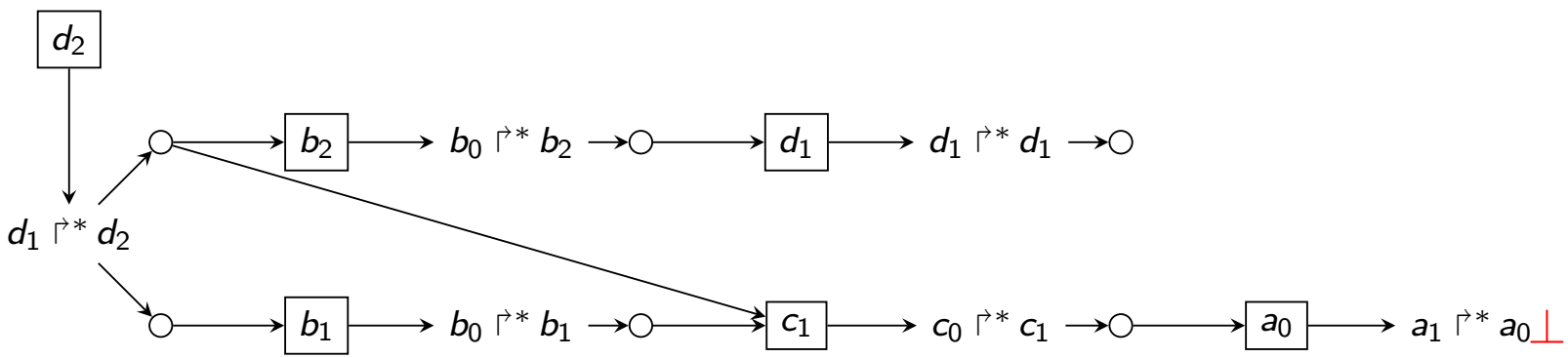


Necessary condition:

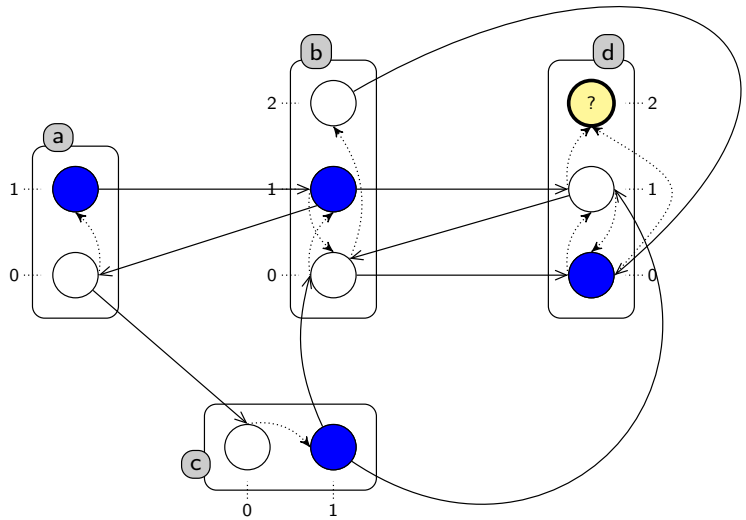
~~There exists a traversal~~ with no cycle

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

R is **false**



Over-approximation



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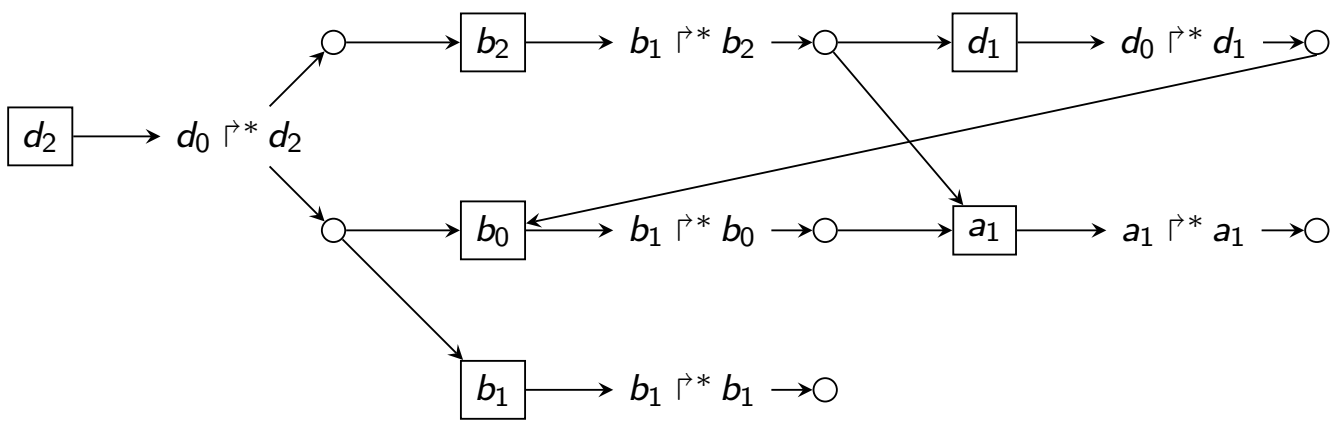
- process → follow all objectives



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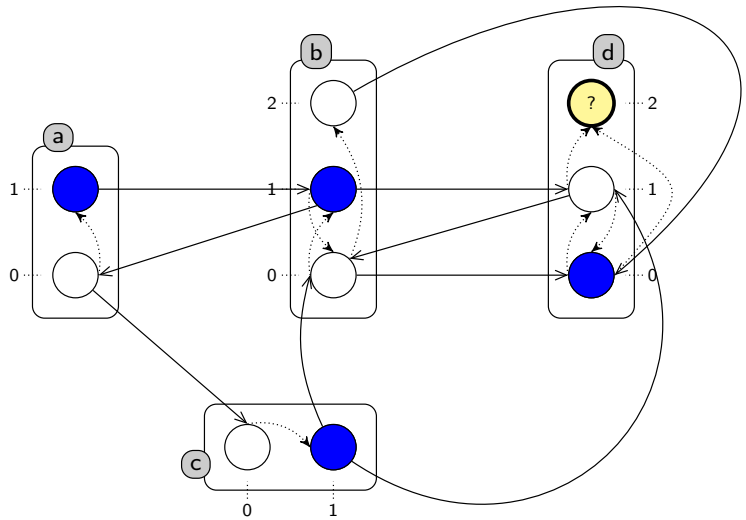

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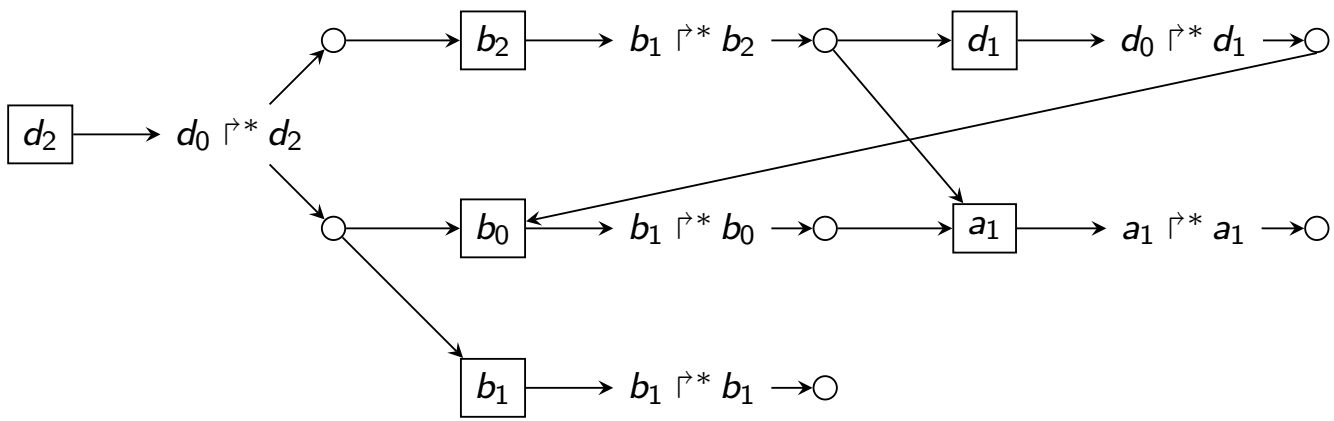
Inconclusive

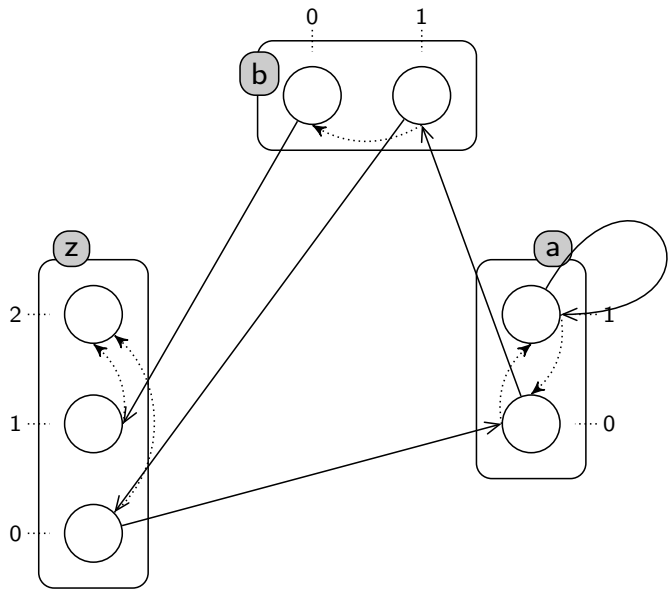


Static Analysis: Fixed Points

[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



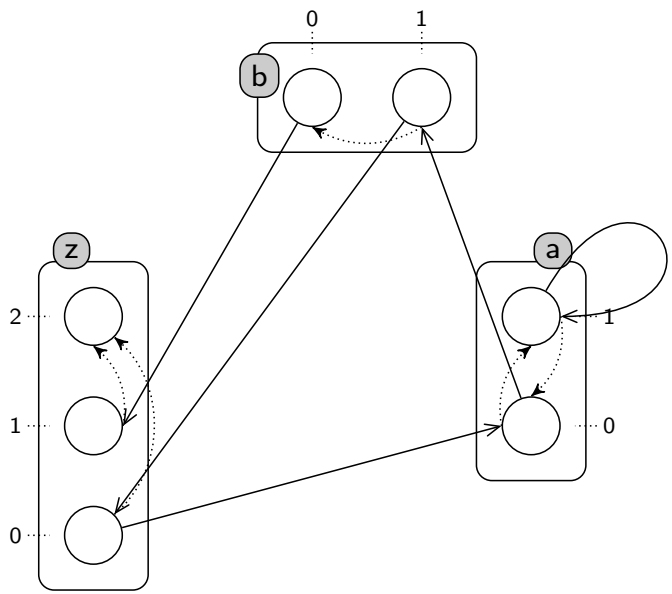
Static Analysis: Fixed Points

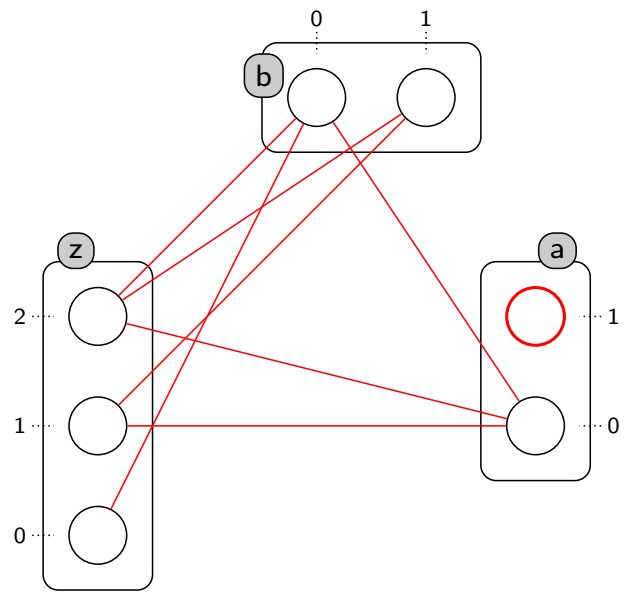
[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]

Fixed point = state where no action can be fired

→ avoid couples of processes bounded by an action

→ Hitless Graph





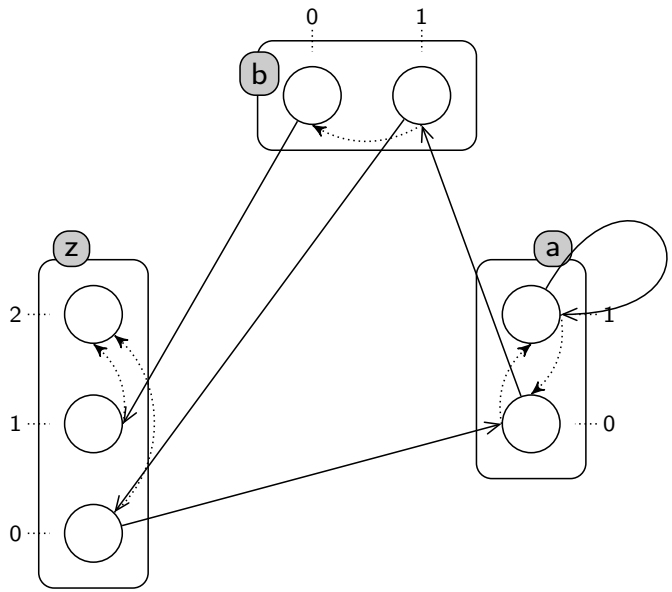
Static Analysis: Fixed Points

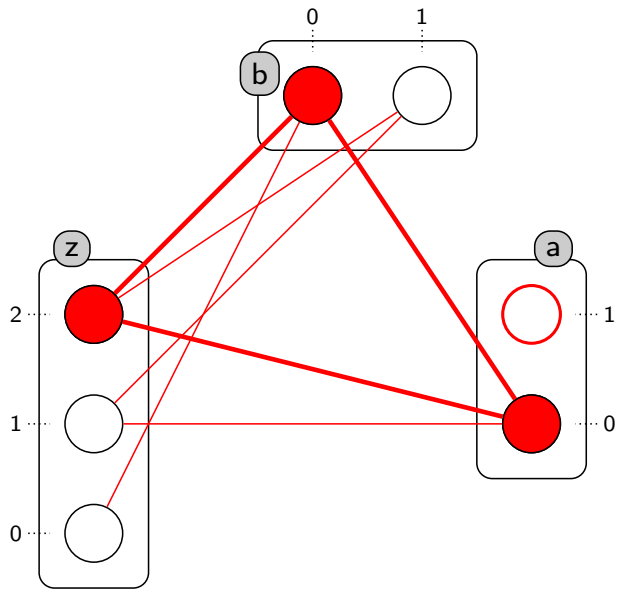
[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]

Fixed point = state where no action can be fired

→ avoid couples of processes bounded by an action

→ Hitless Graph → **n-cliques** = fixed points





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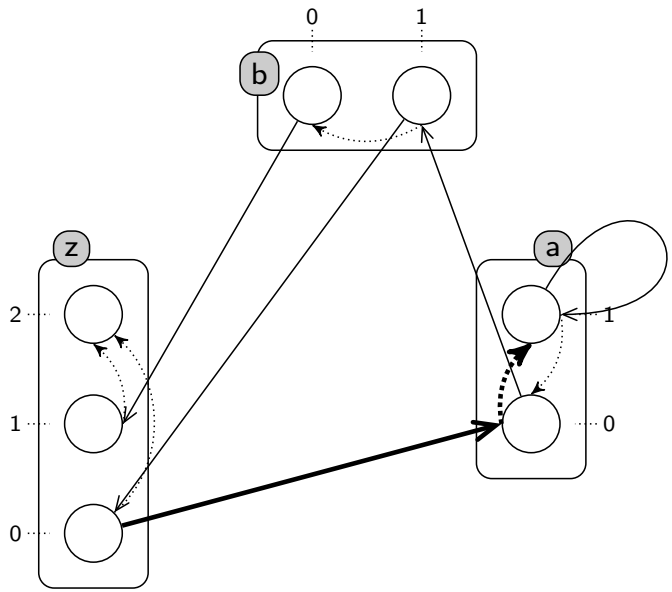

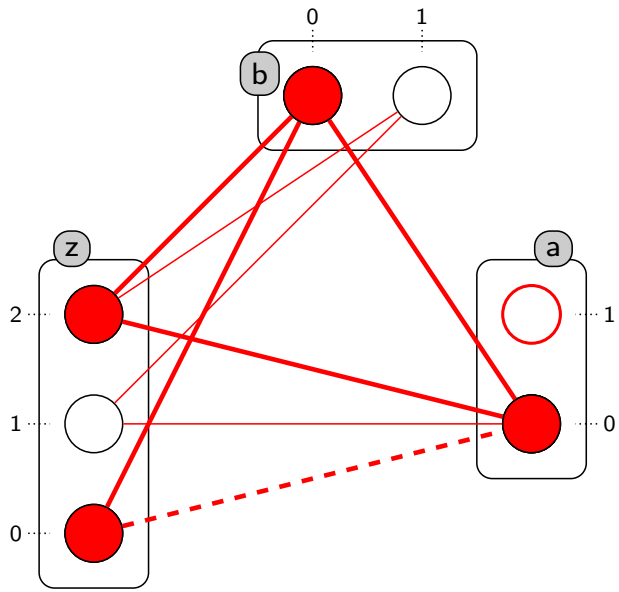

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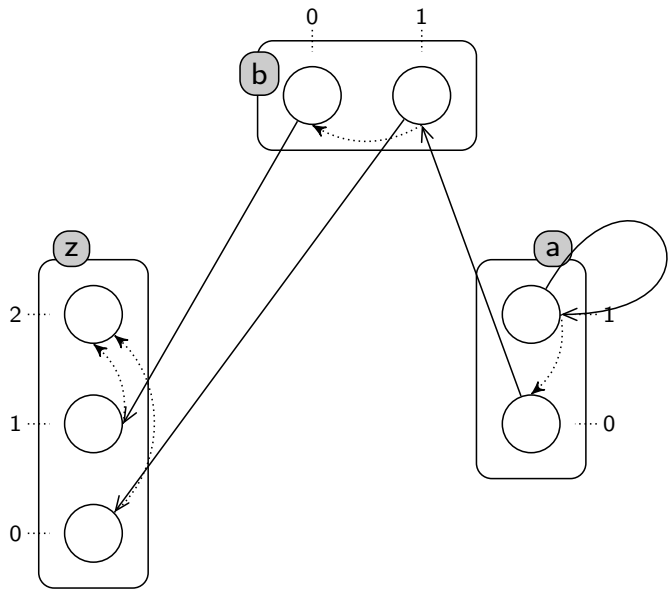

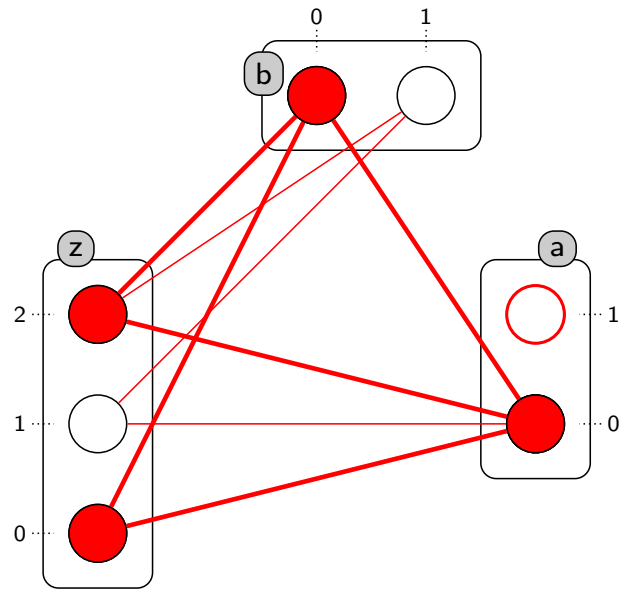

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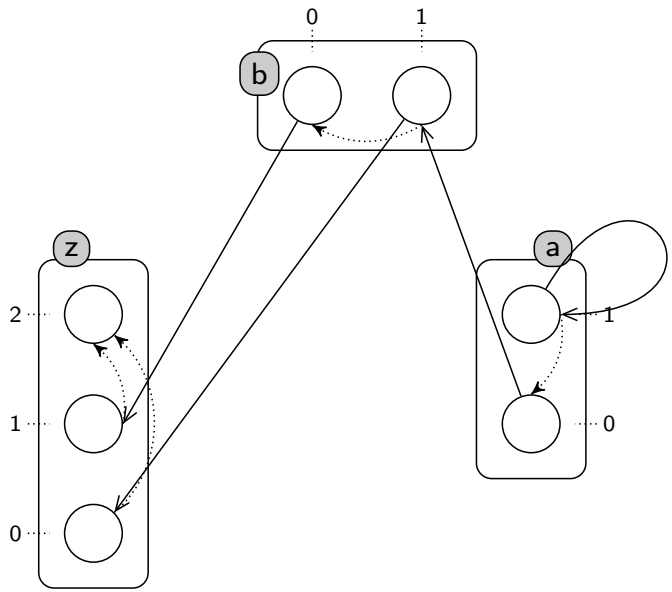

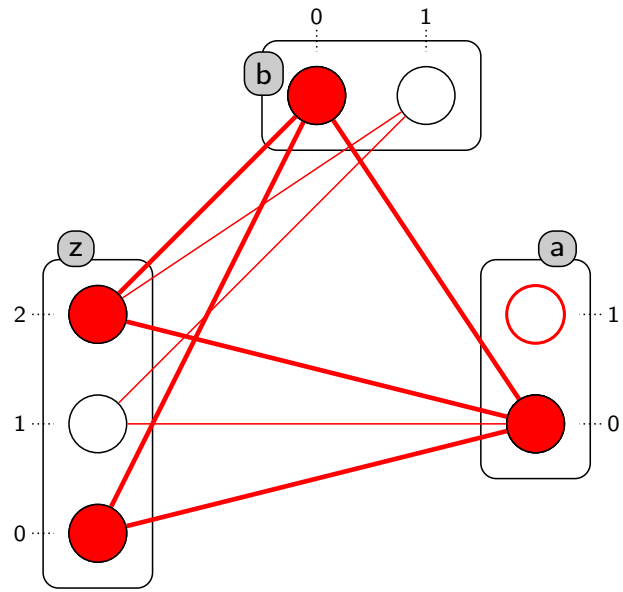

Exponential complexity w.r.t. the number of sorts