Public seminar of team Lifeware

Modeling and analysis of large regulatory networks with the Process Hitting framework

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2015/04/01

The Modeling/Analysis duality

Modeling a system is the first step towards its comprehension

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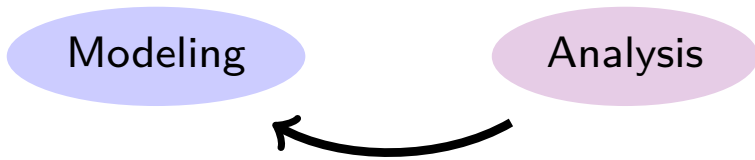

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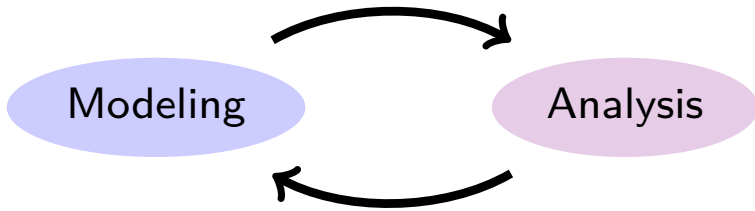

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- The level of details changes the quantity of obtained info
- The size of the model increases the analysis duration

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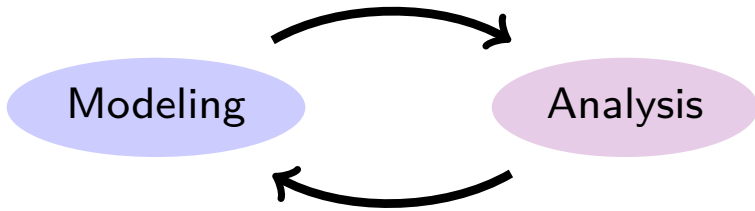

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The modeling and analysis steps of a system are strongly linked

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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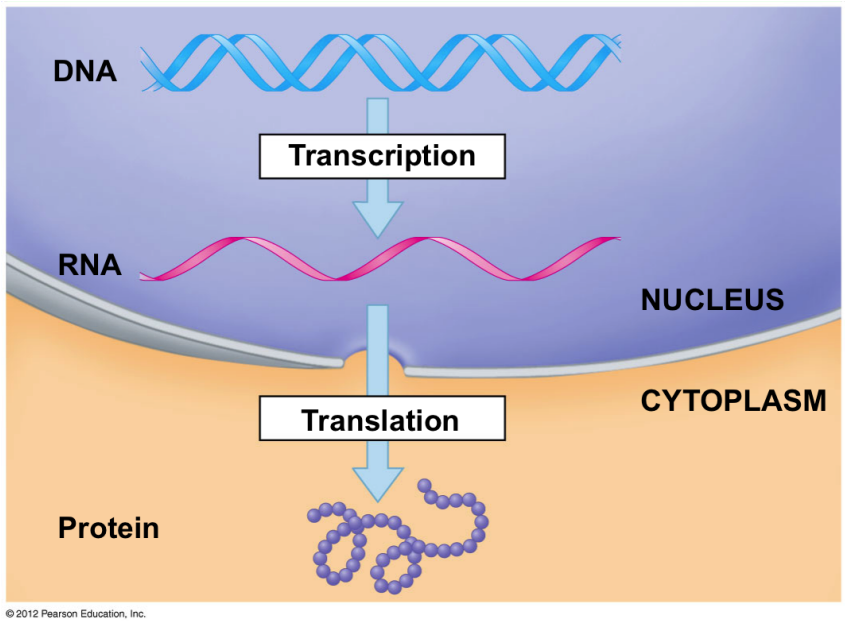
Analysis of the Process Hitting

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

Abstractions of the Representation



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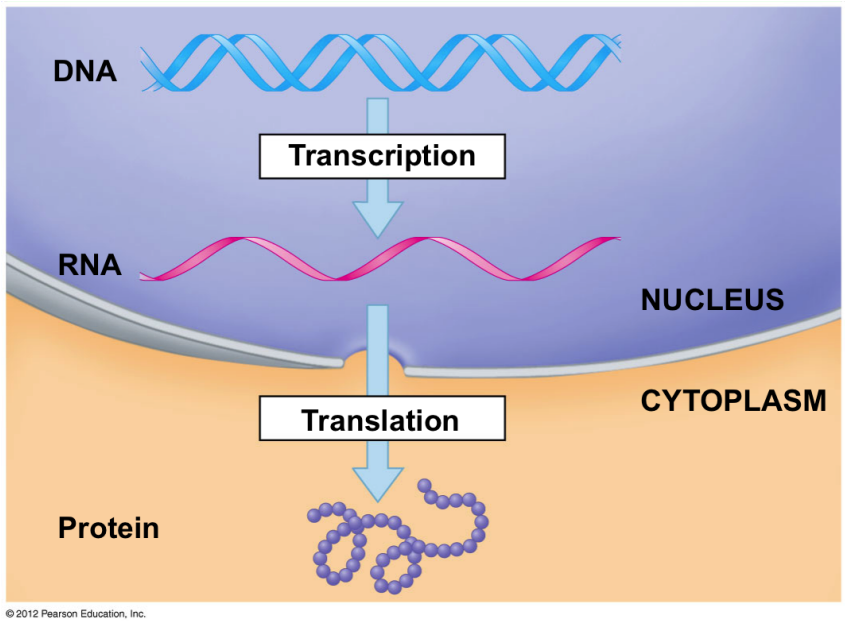
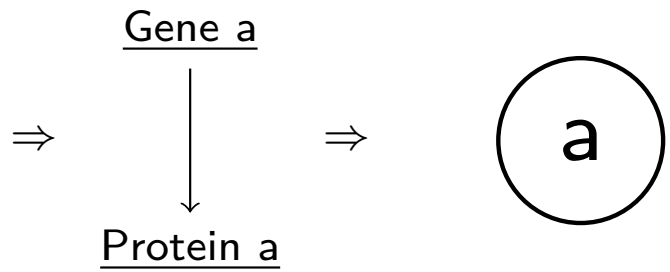
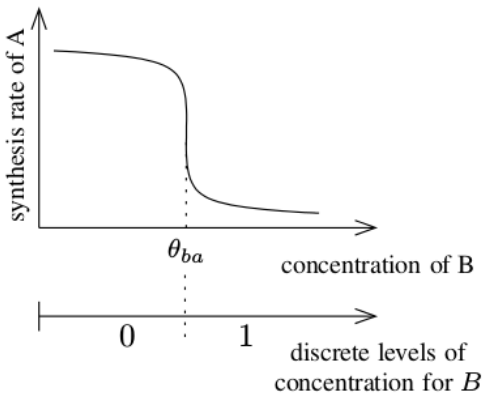




Discretization and Asynchronism

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



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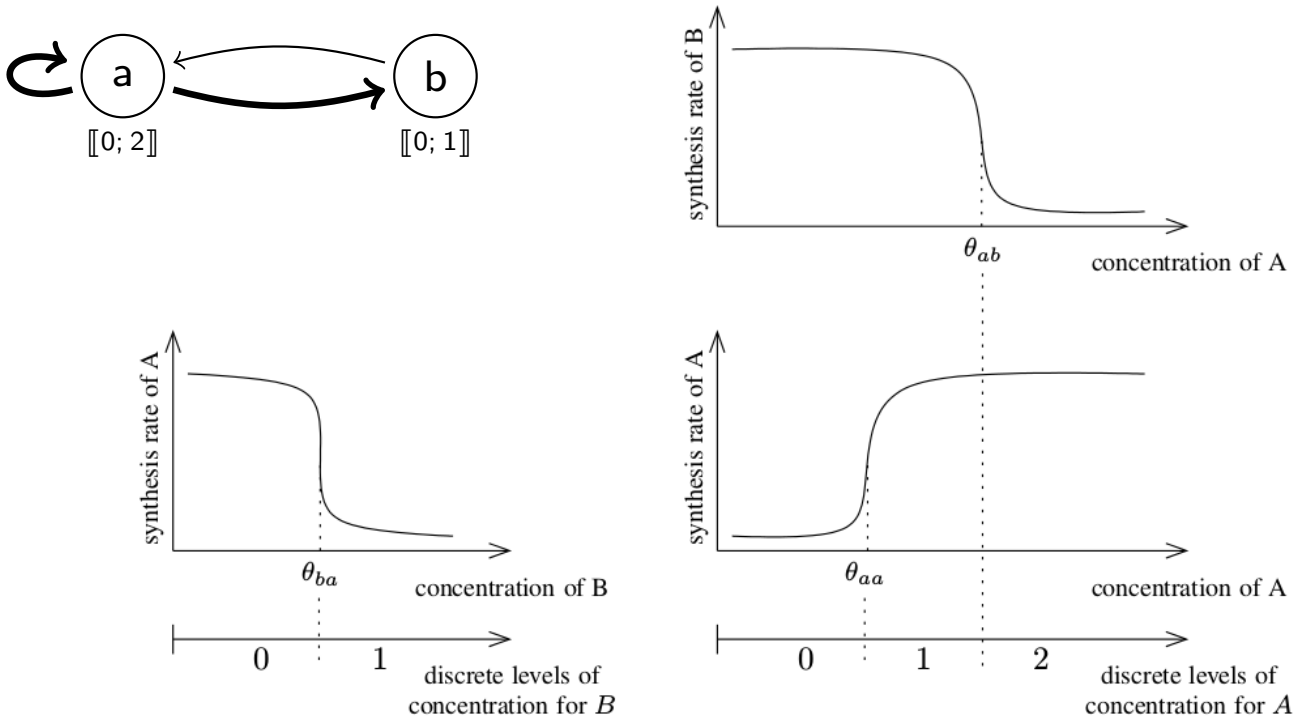

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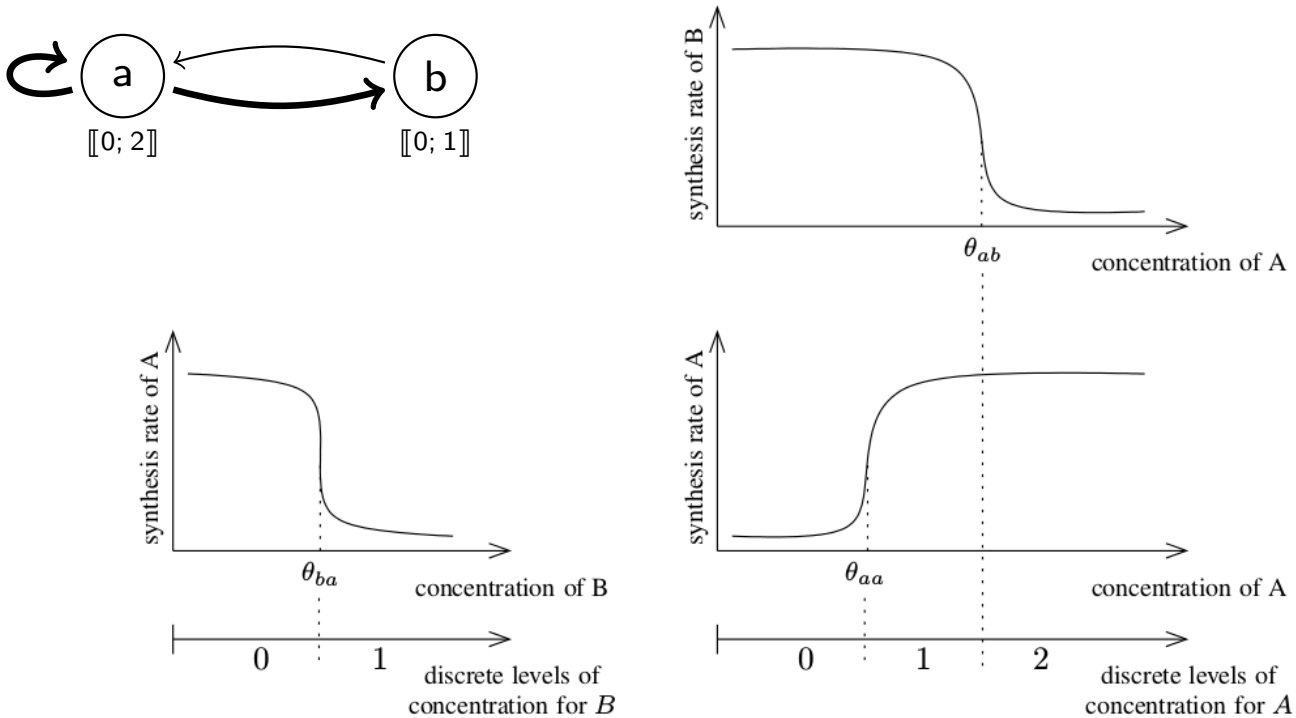

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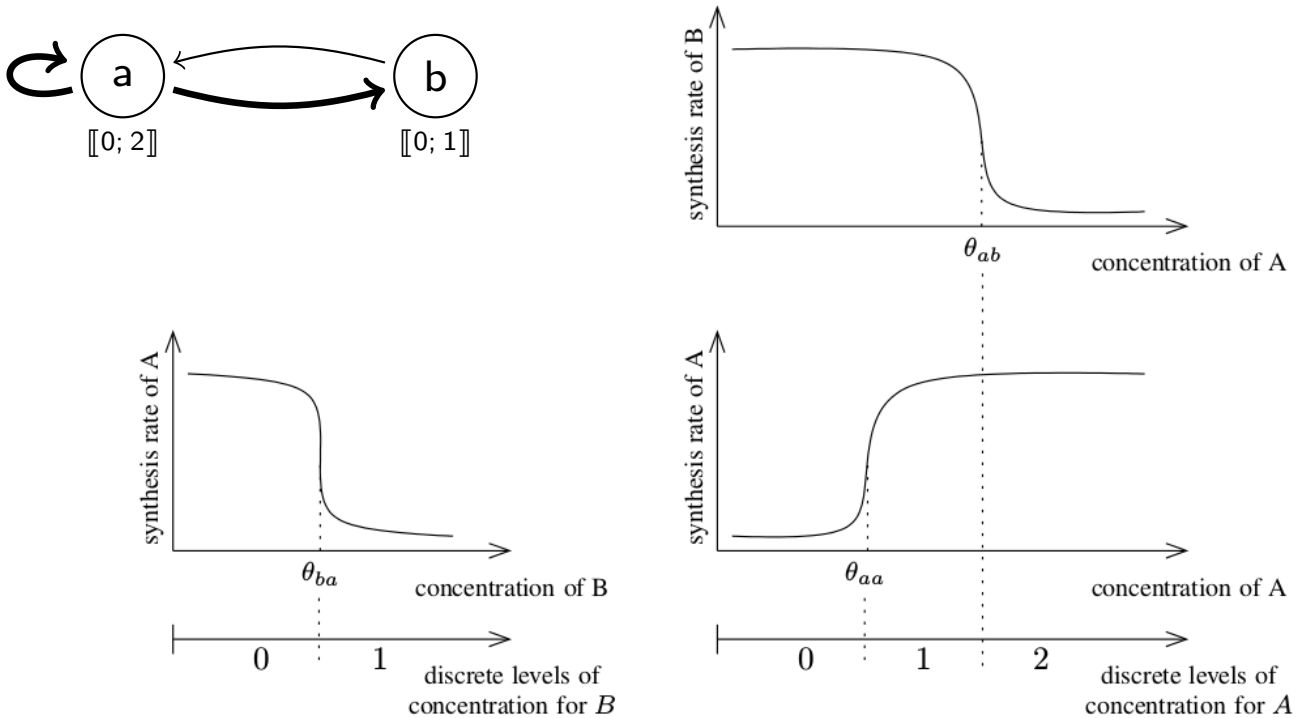

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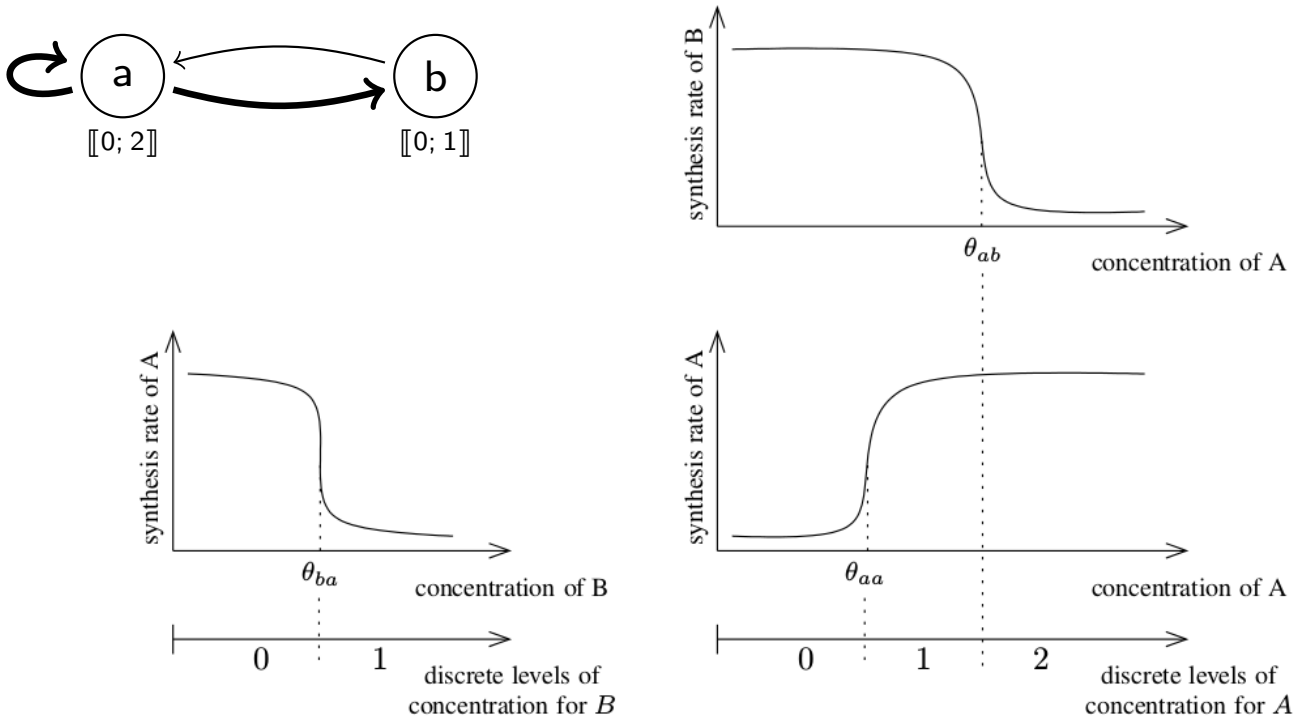

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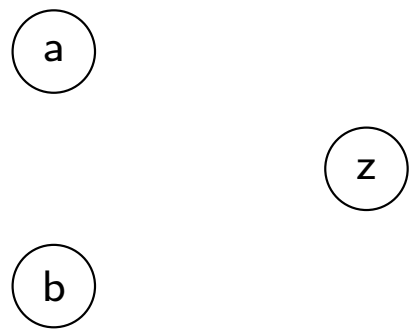
- Continuous variations of the real values
  → **Unitary** dynamics
- Simultaneous crossings of two thresholds never occurs
  → **Asynchronous** dynamics

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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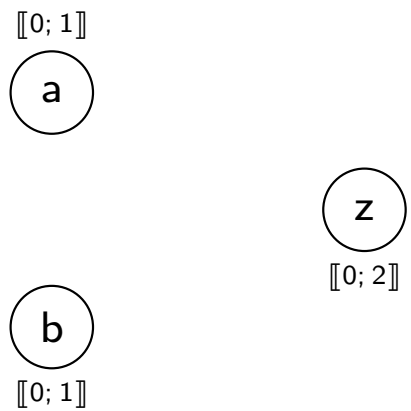

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- An evolution function for each component $f^z : \mathbb{F} \to \mathbb{F}^z$

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

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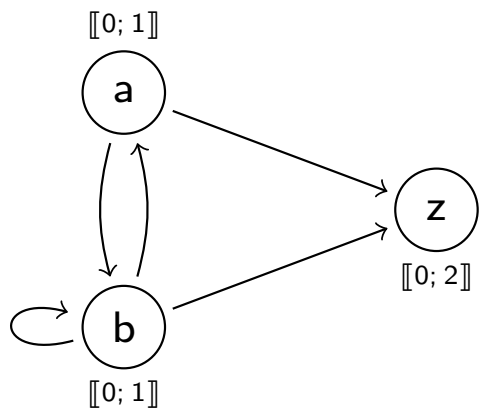

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- Signs and thresholds on the edges $a \xrightarrow{+1} z$

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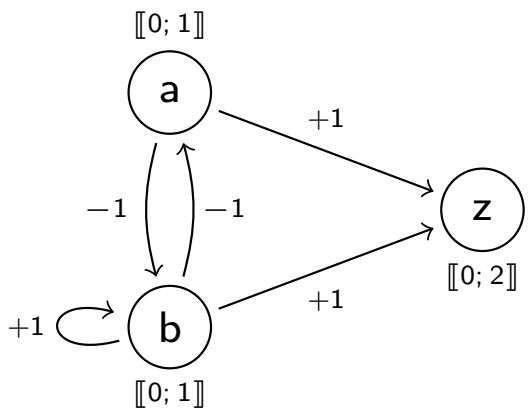
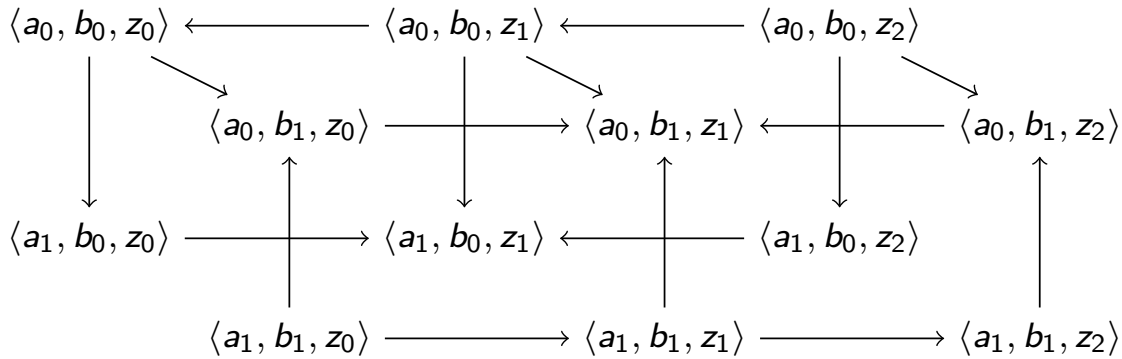


Analysis of Thomas Modeling

The State graph is computed in a unitary and asynchronous fashion



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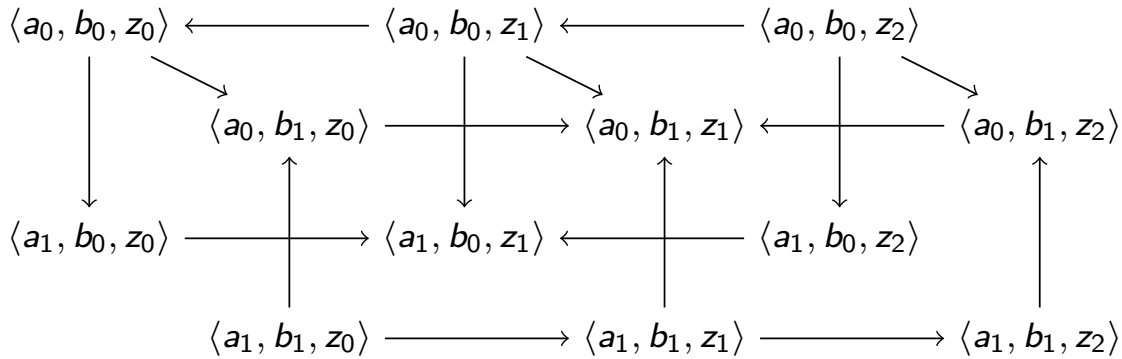

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Some works all to link the structure of the model and some dynamic properties:

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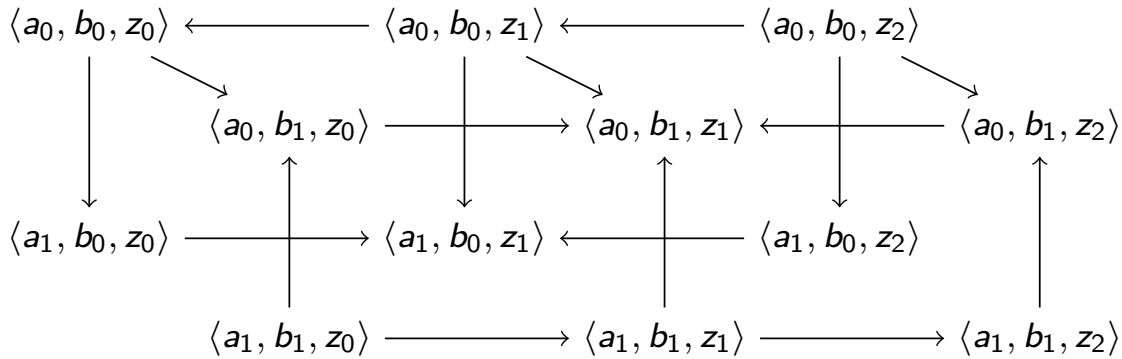

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But reachability properties require to compute the whole state graph:
Example: From the initial state $(a, b, z) = (0, 0, 0)$, is it possible to reach $z = 2$?

- **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)
- **Simple but powerful** dynamics (constraints on the form of actions)

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- Stochastic parameters

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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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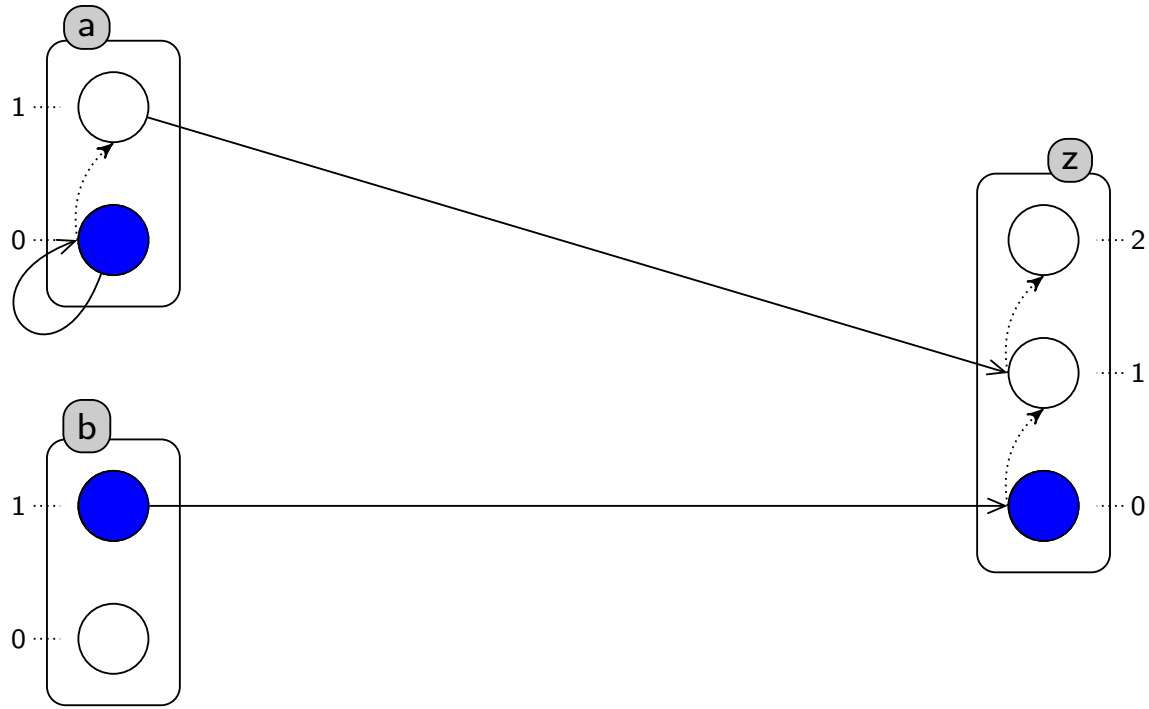

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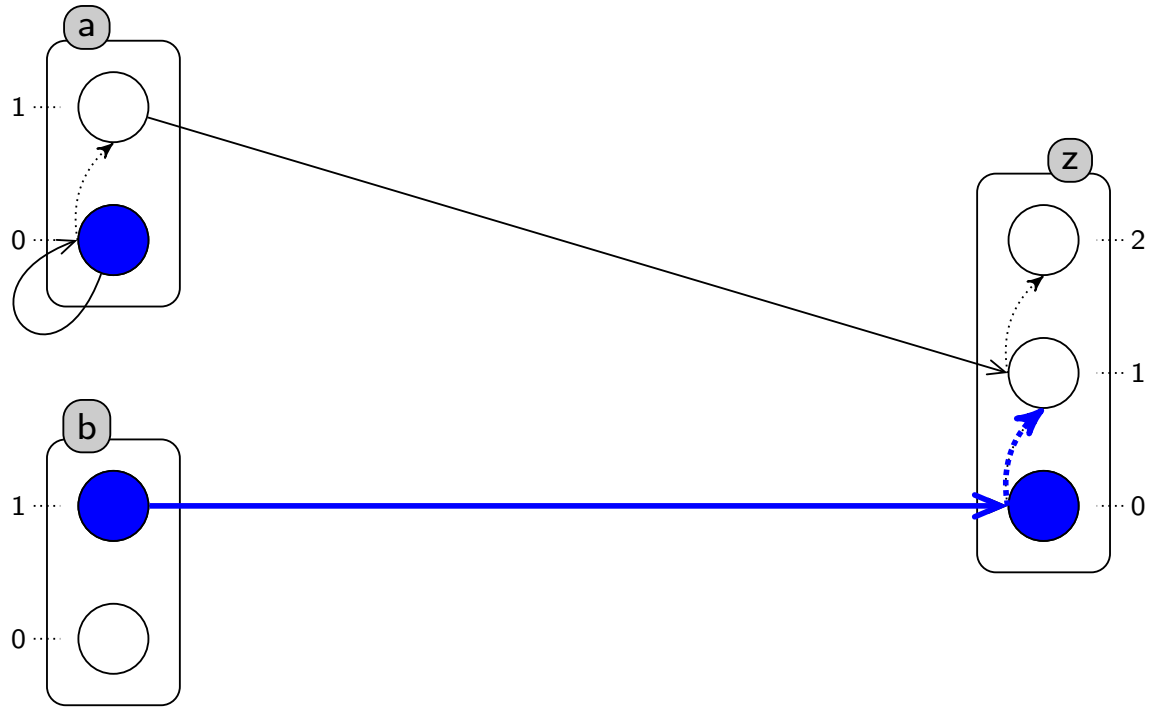

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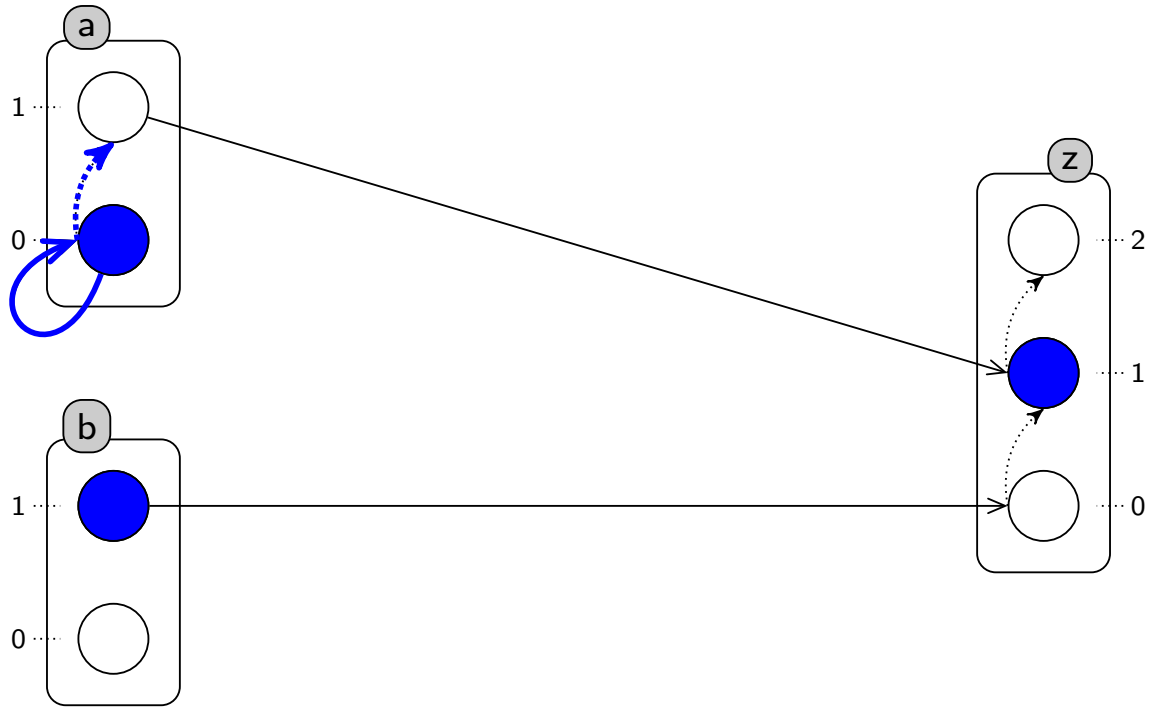

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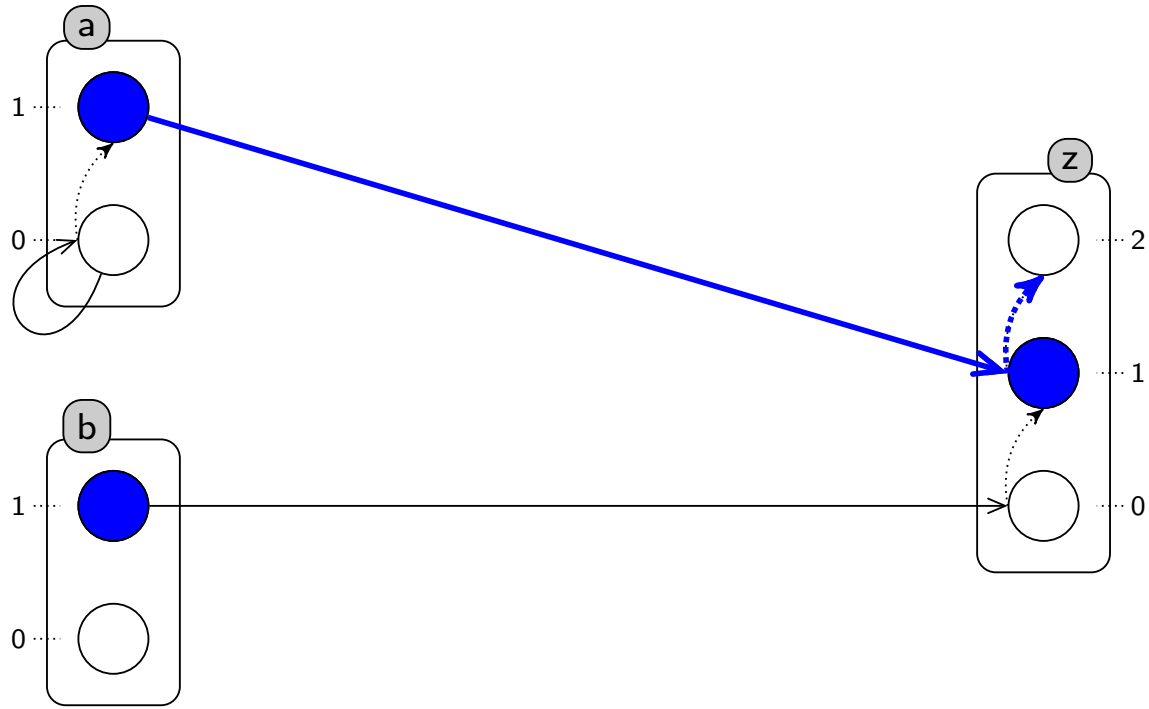

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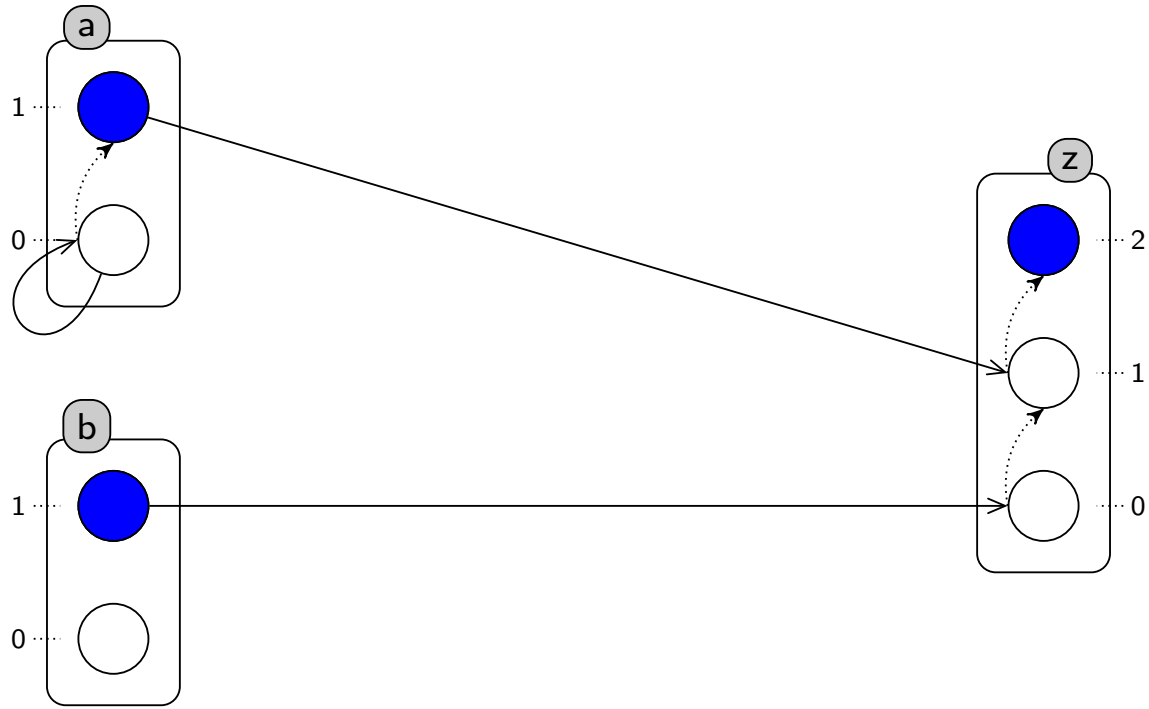

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Cooperations

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

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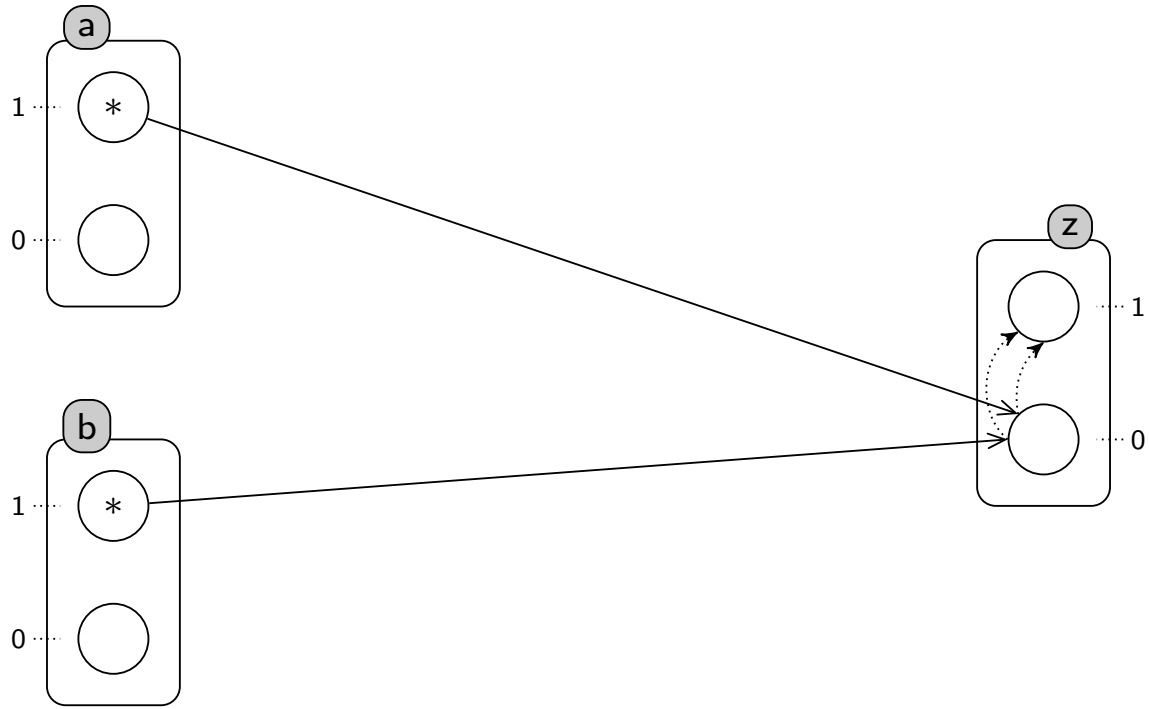

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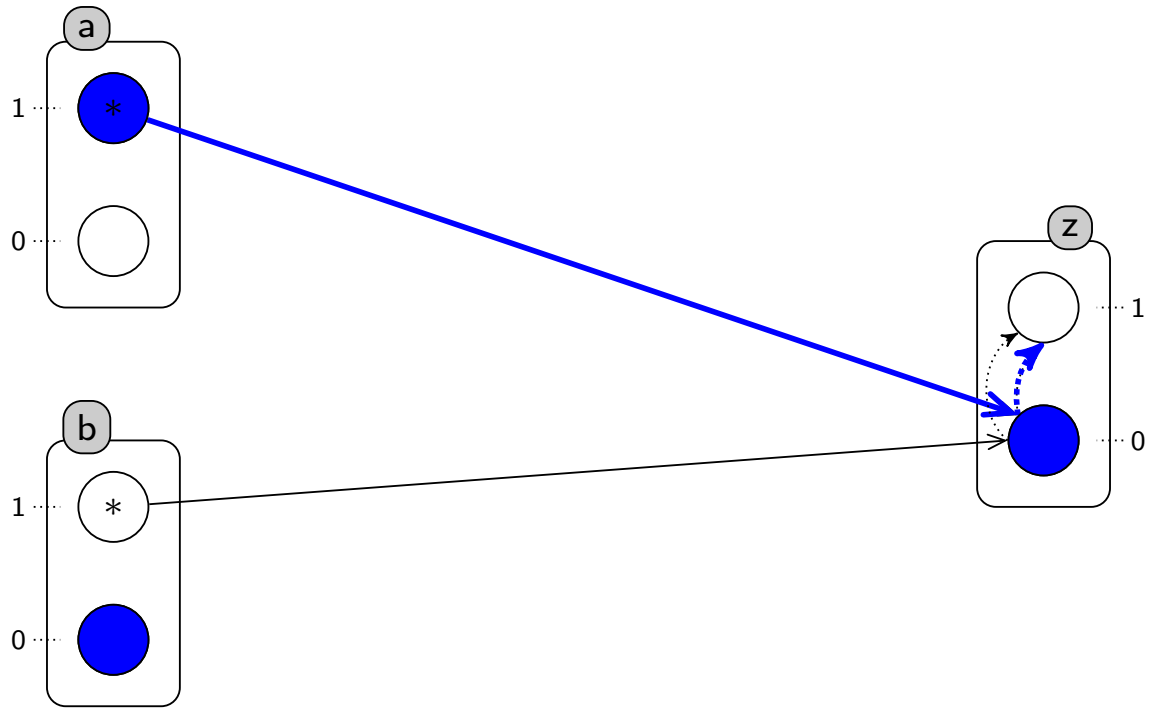

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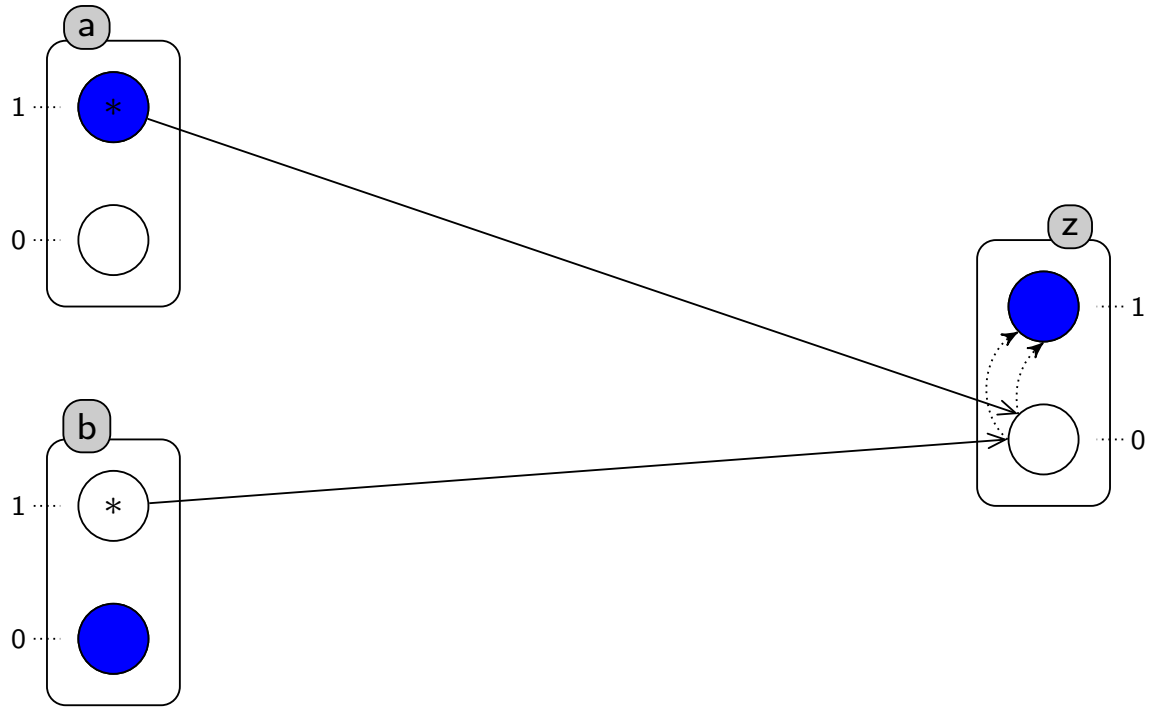

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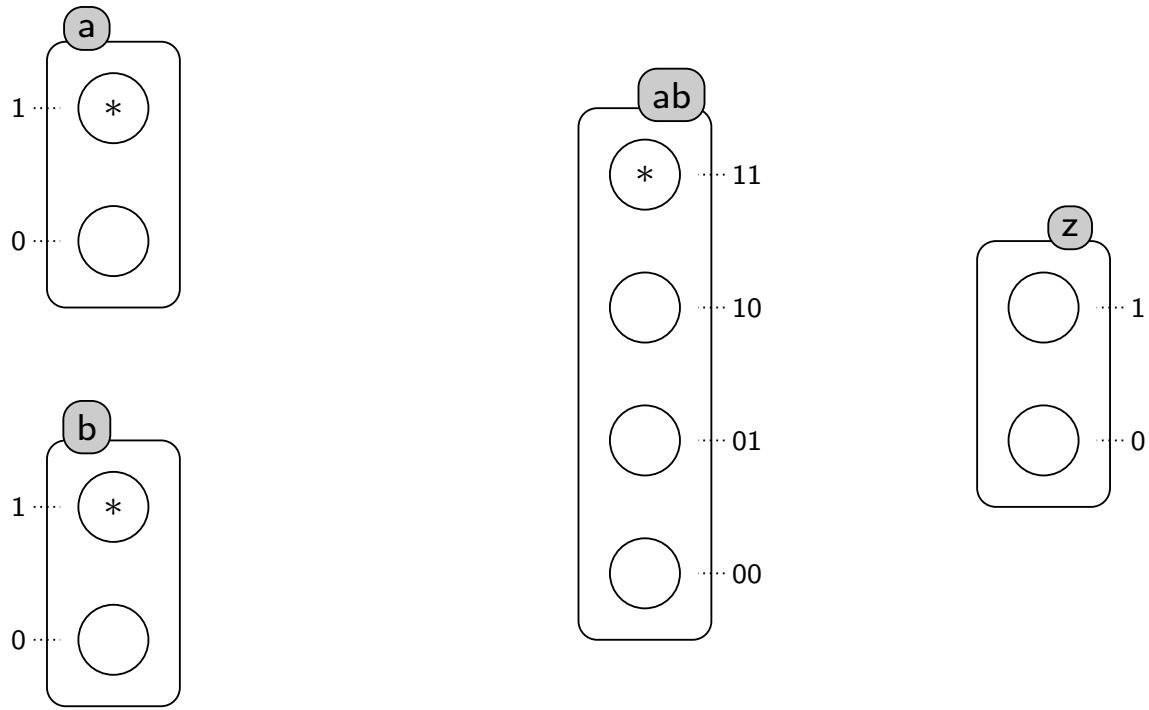

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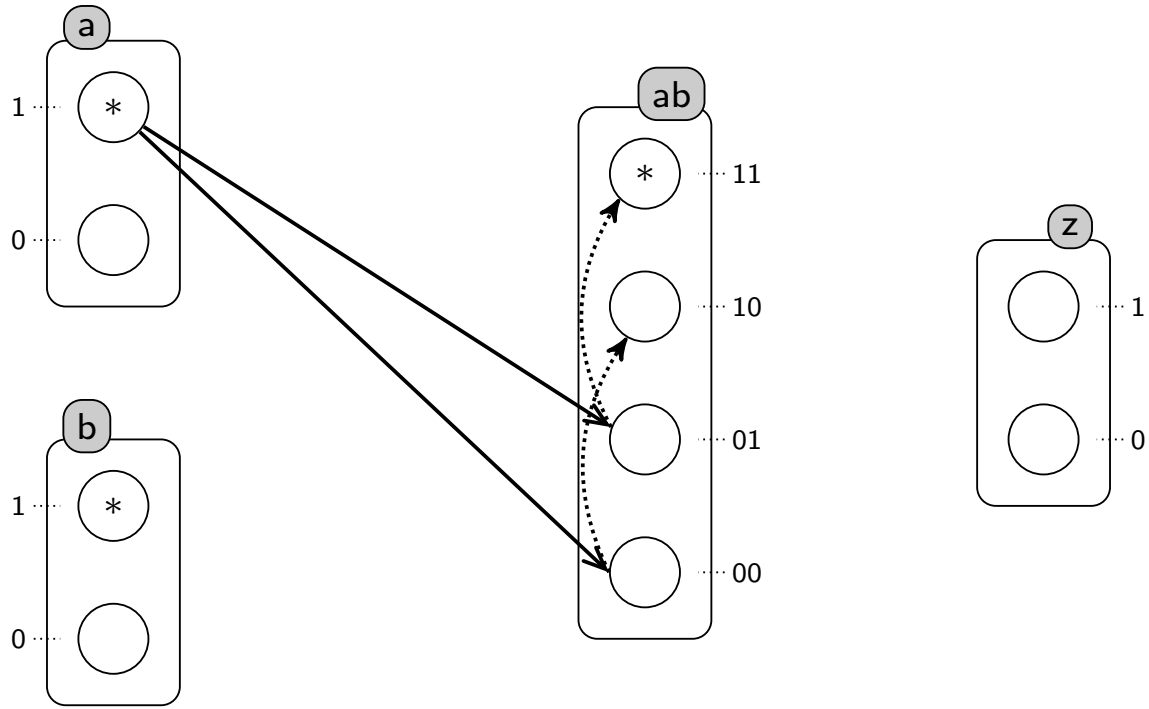

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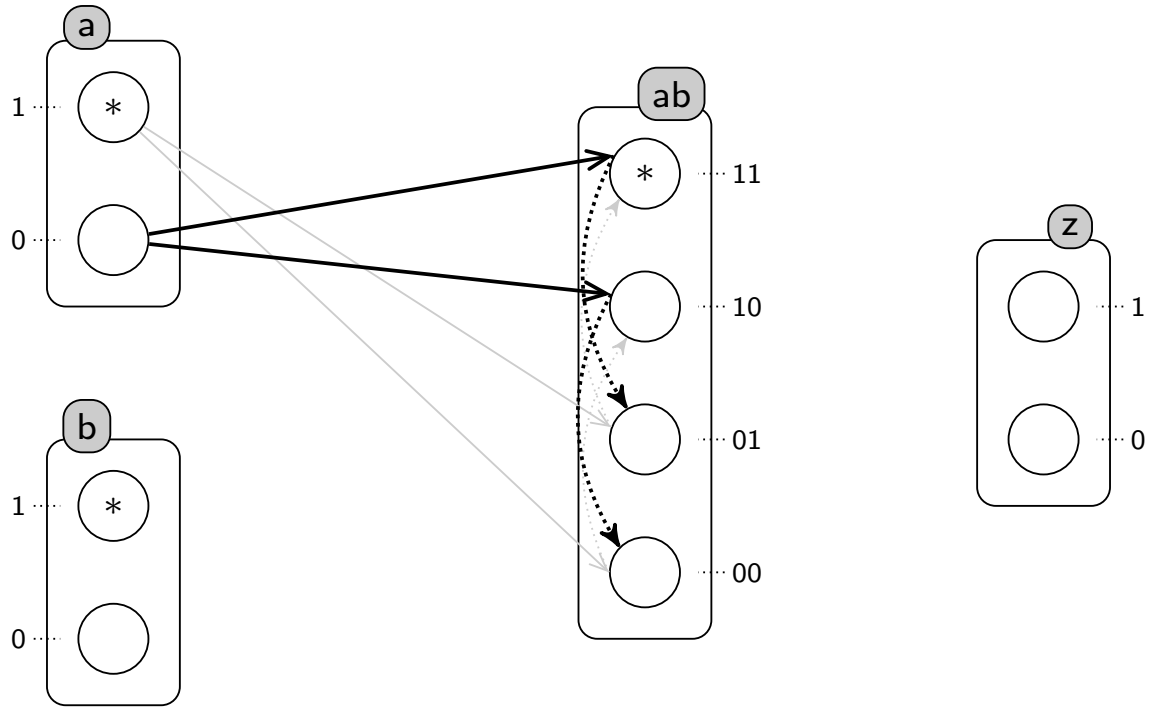

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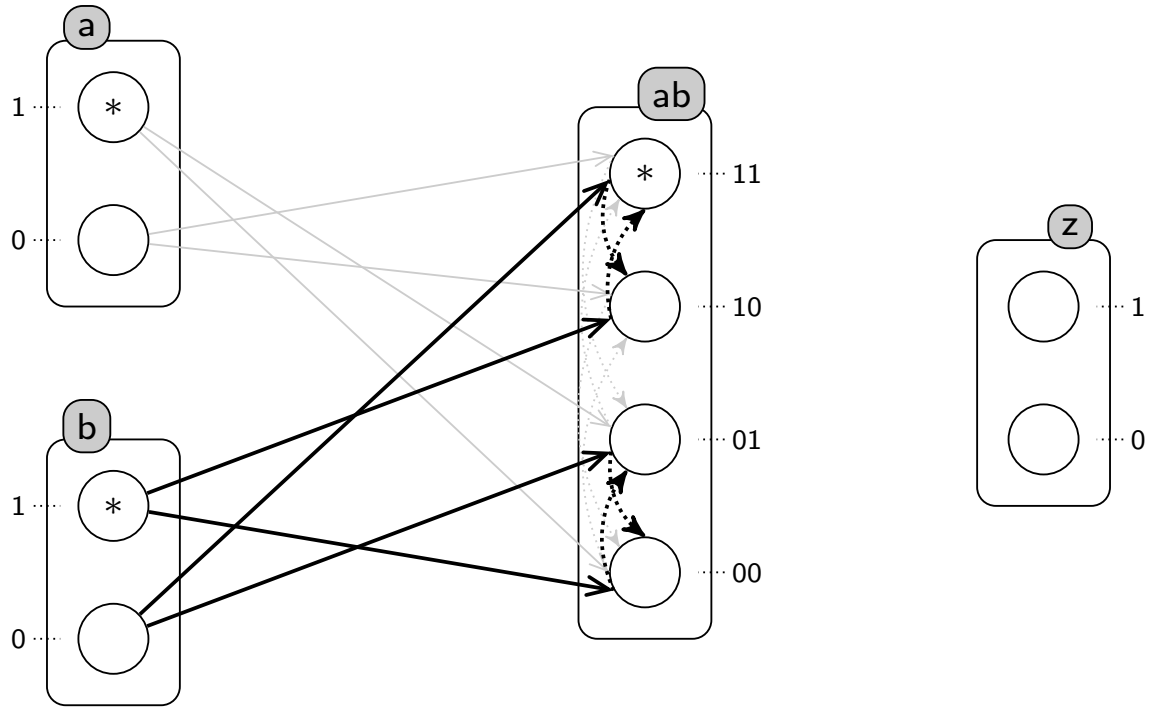

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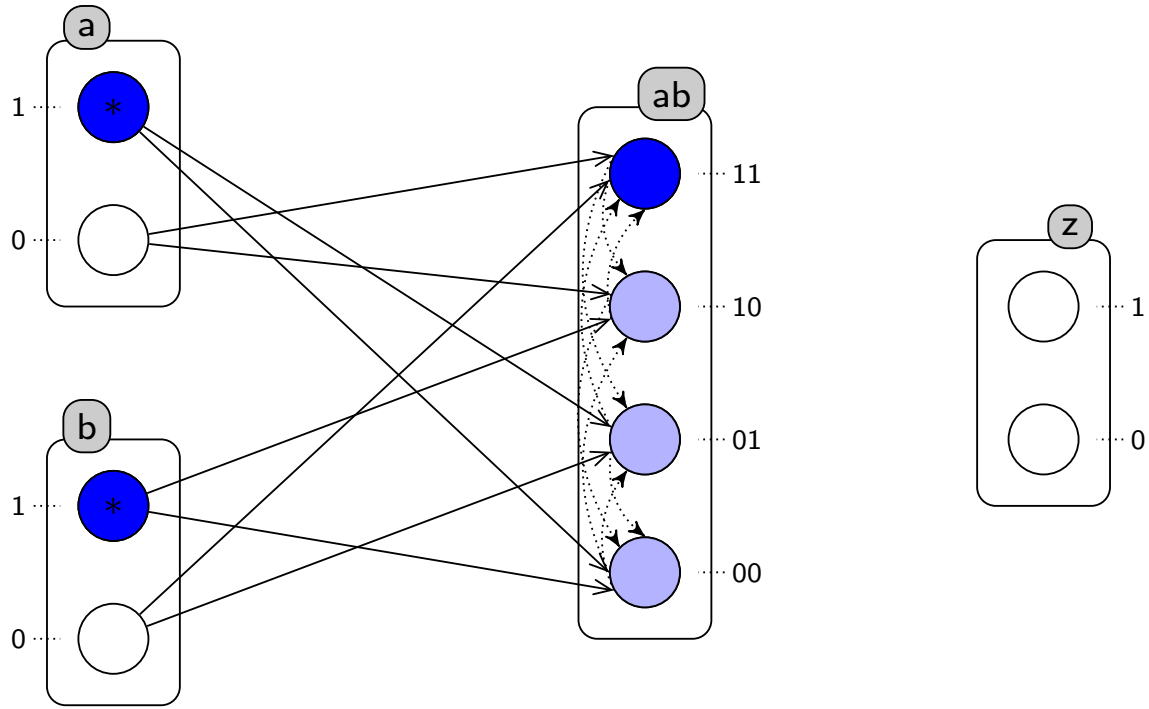

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Solution: a **cooperative sort** ab to express $\underline{a_1 \wedge b_1}$

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

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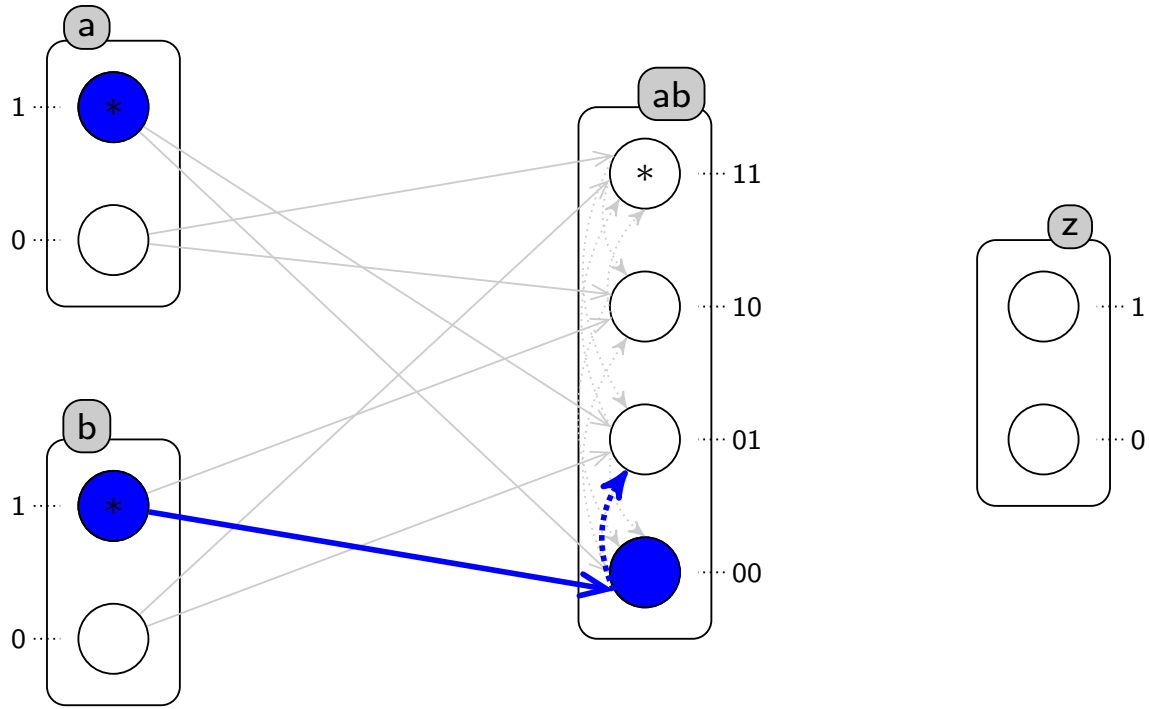

Cooperation between a_1 and b_1: $\underline{a_1 \wedge b_1} \rightarrow z_0 \nearrow z_1$

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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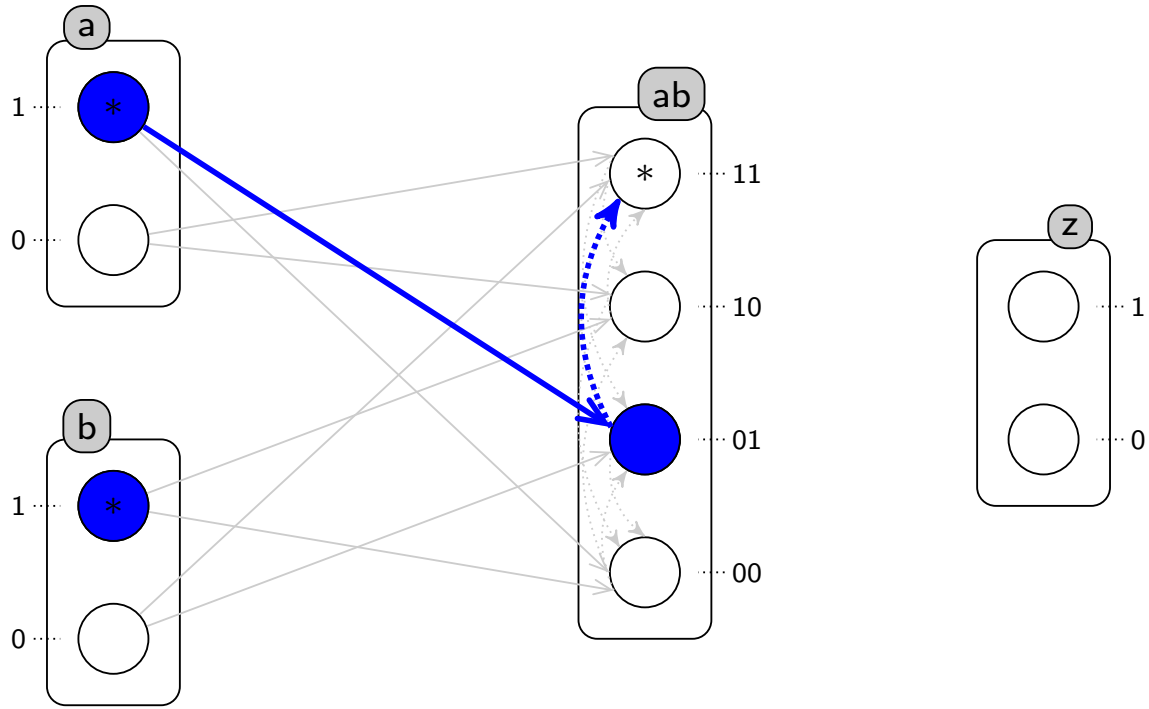

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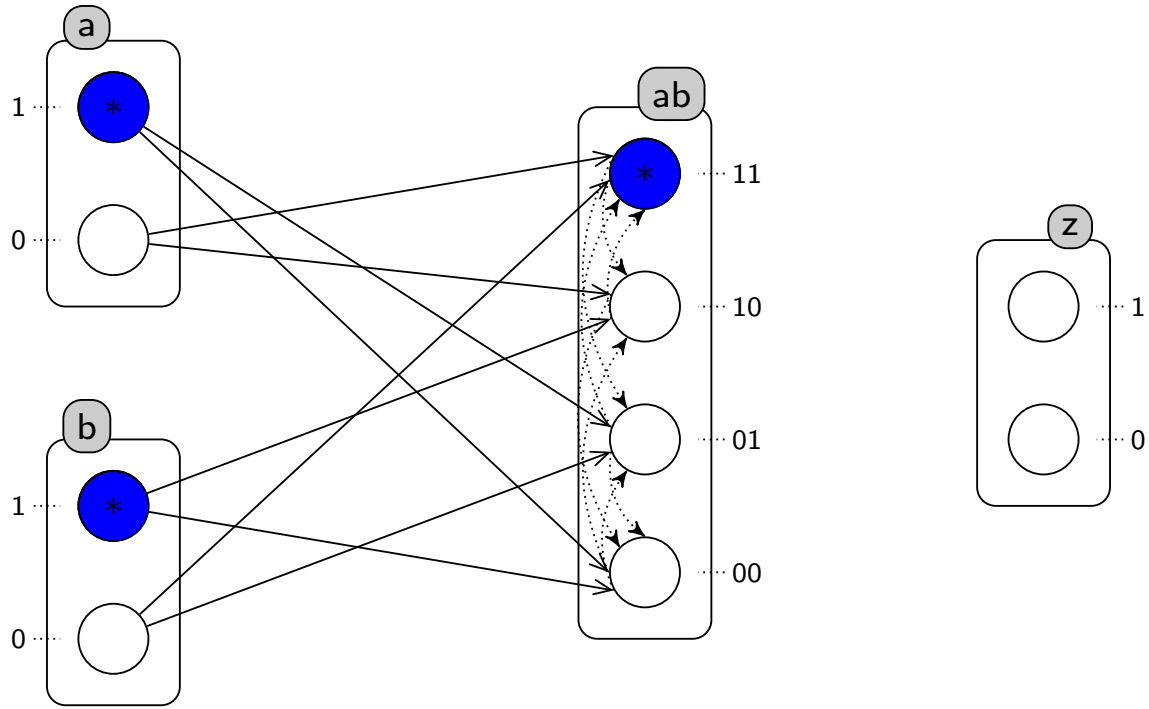

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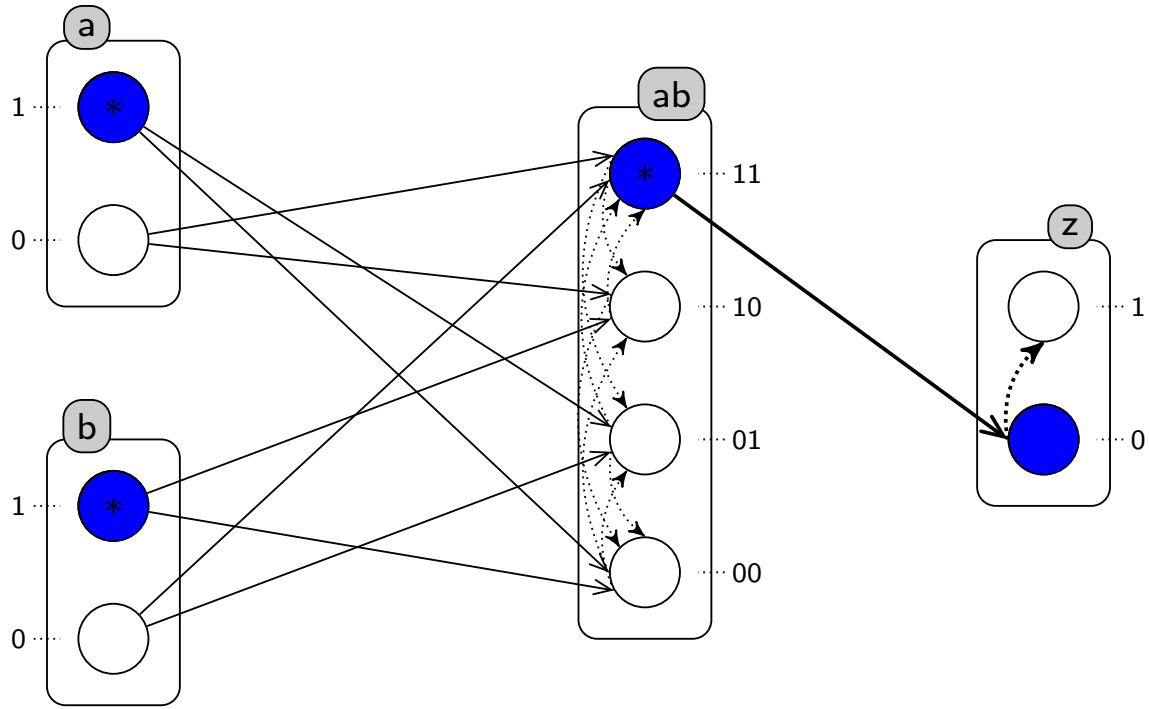

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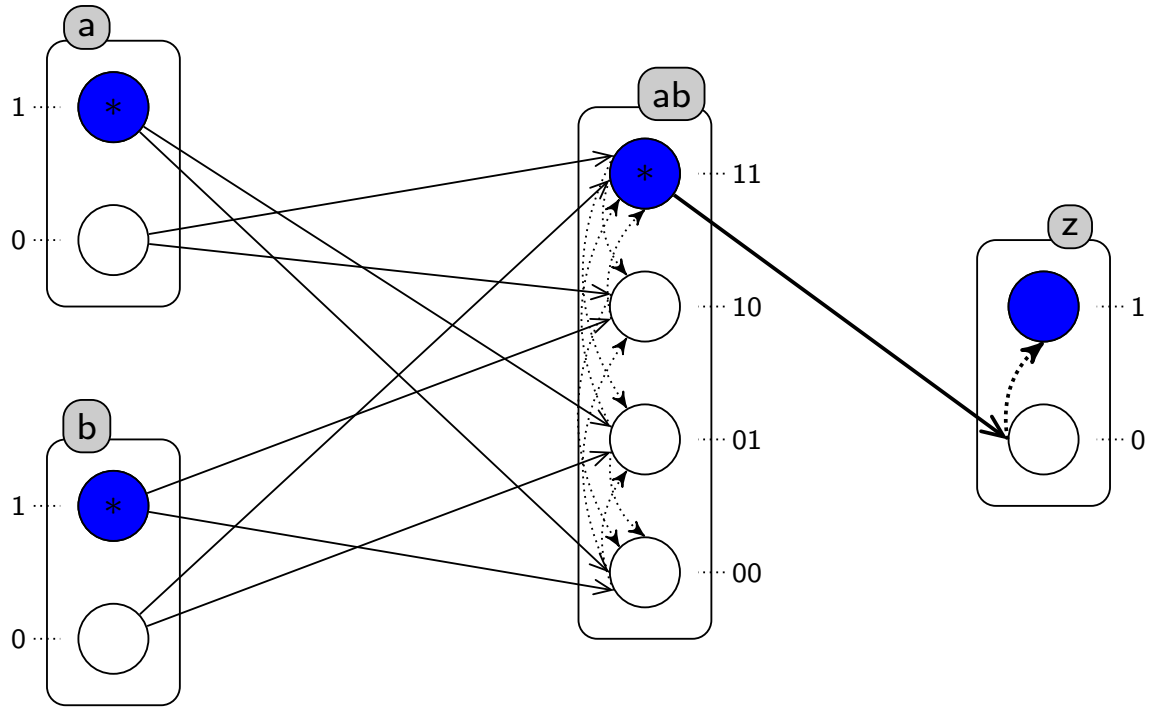

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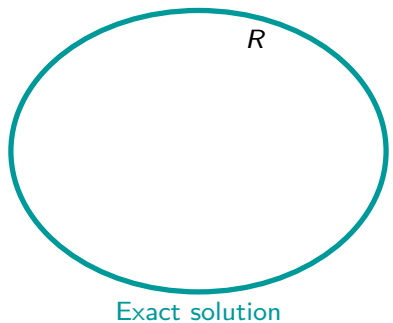
Approximations for the Reachability Analysis

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

Check reachability properties:

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

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



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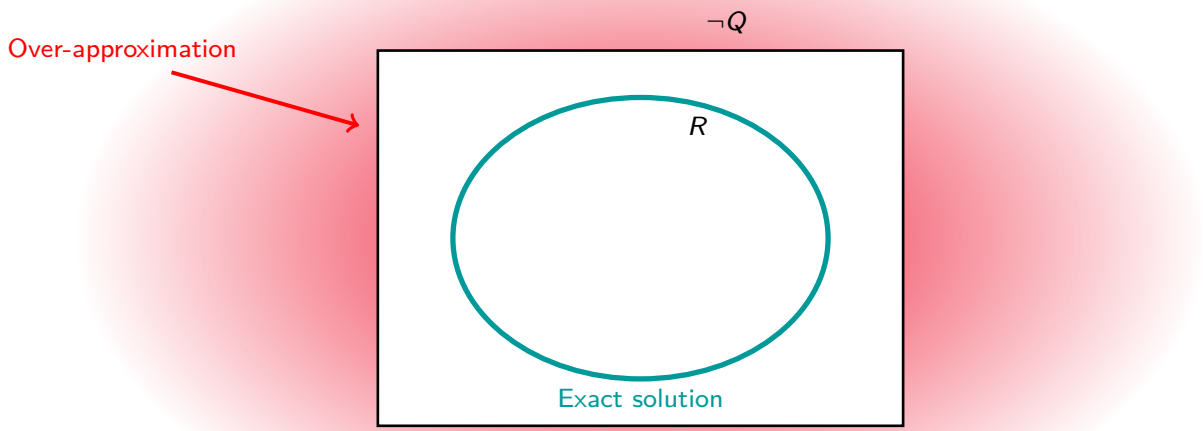

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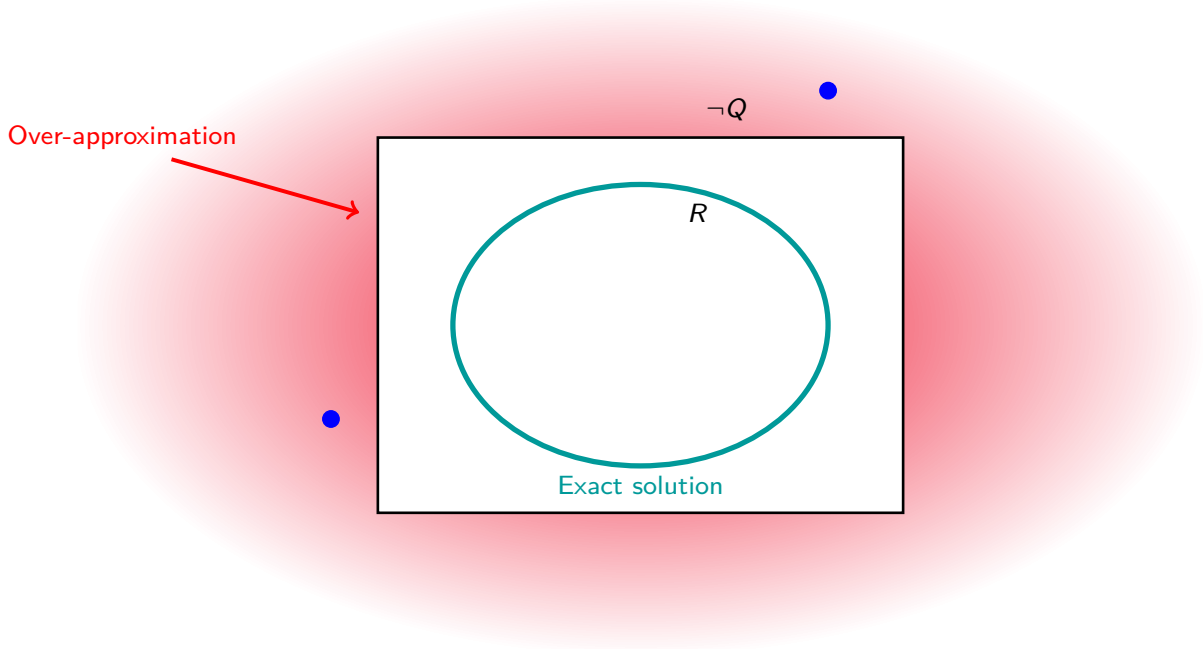

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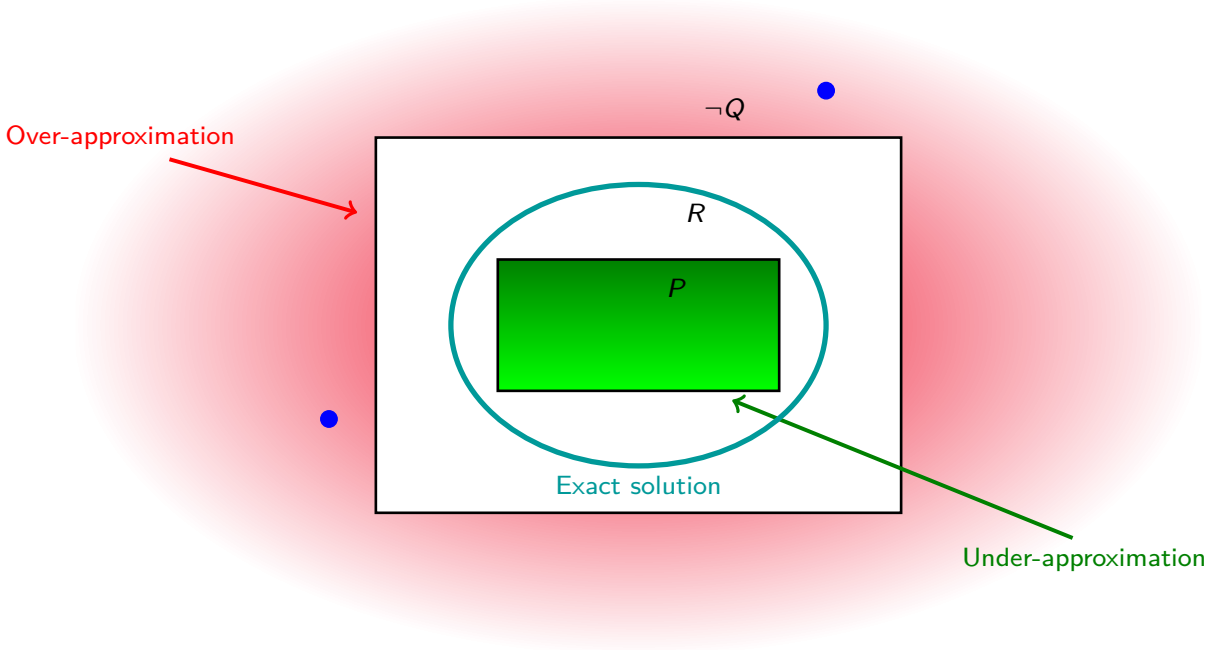

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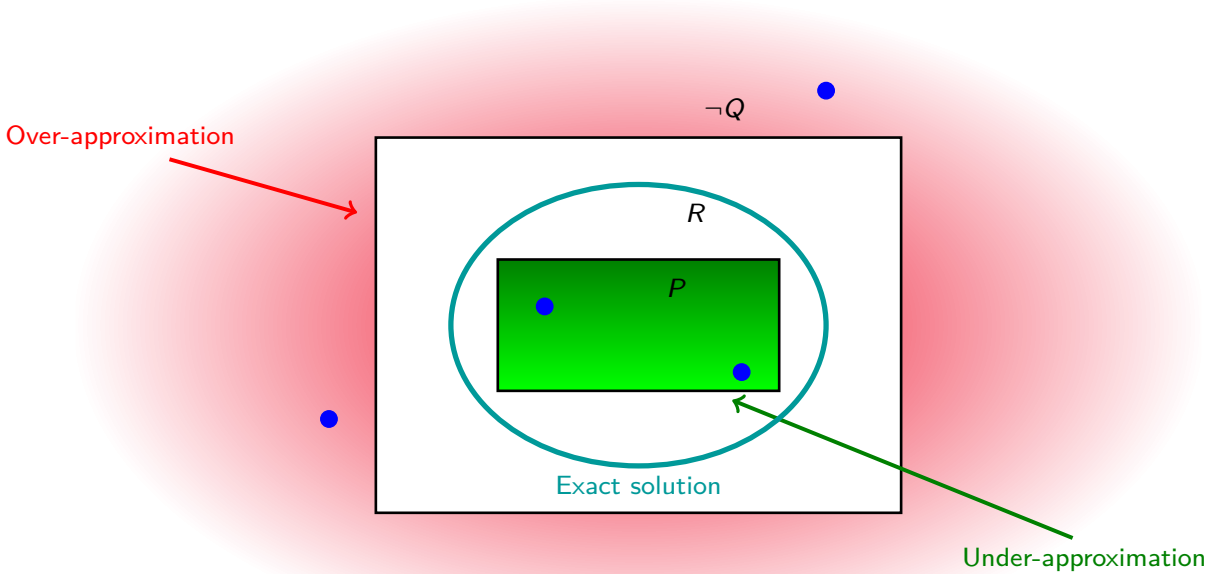

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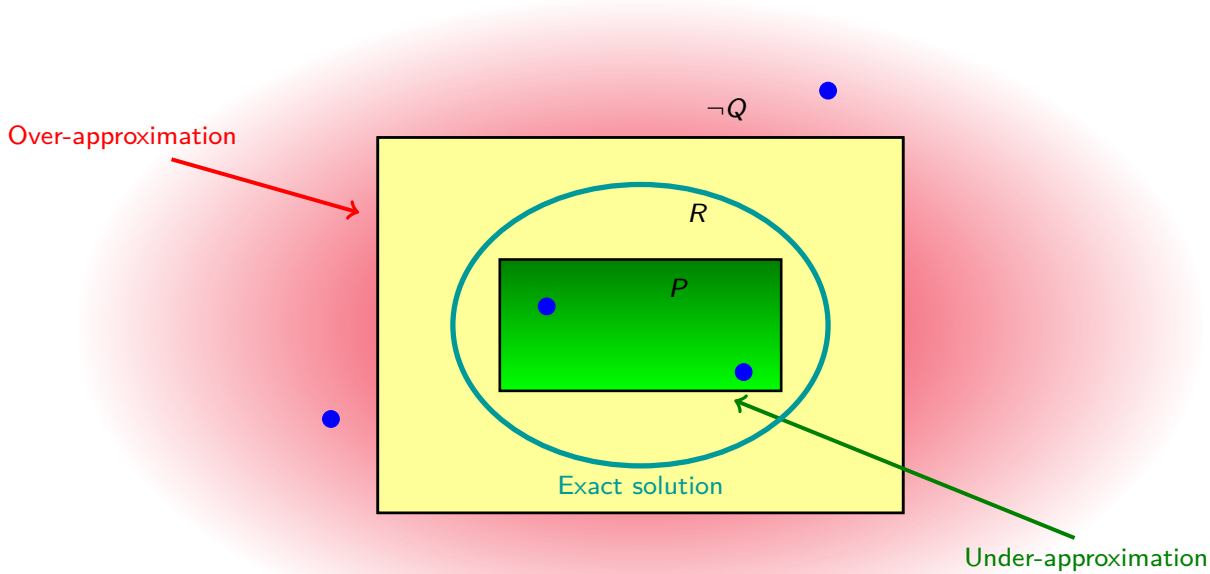

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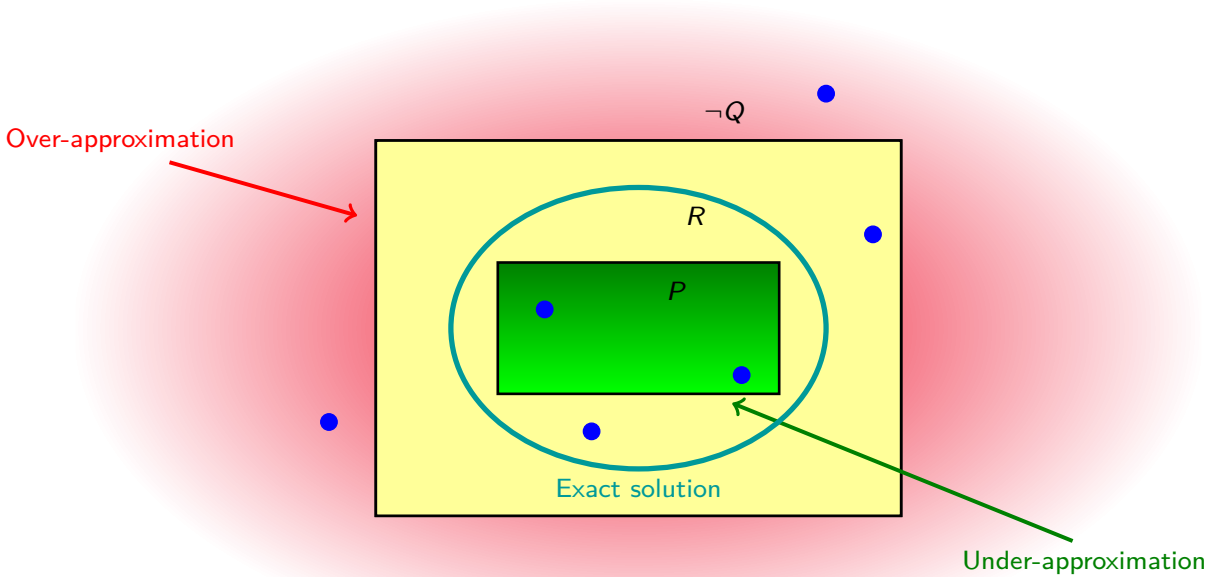

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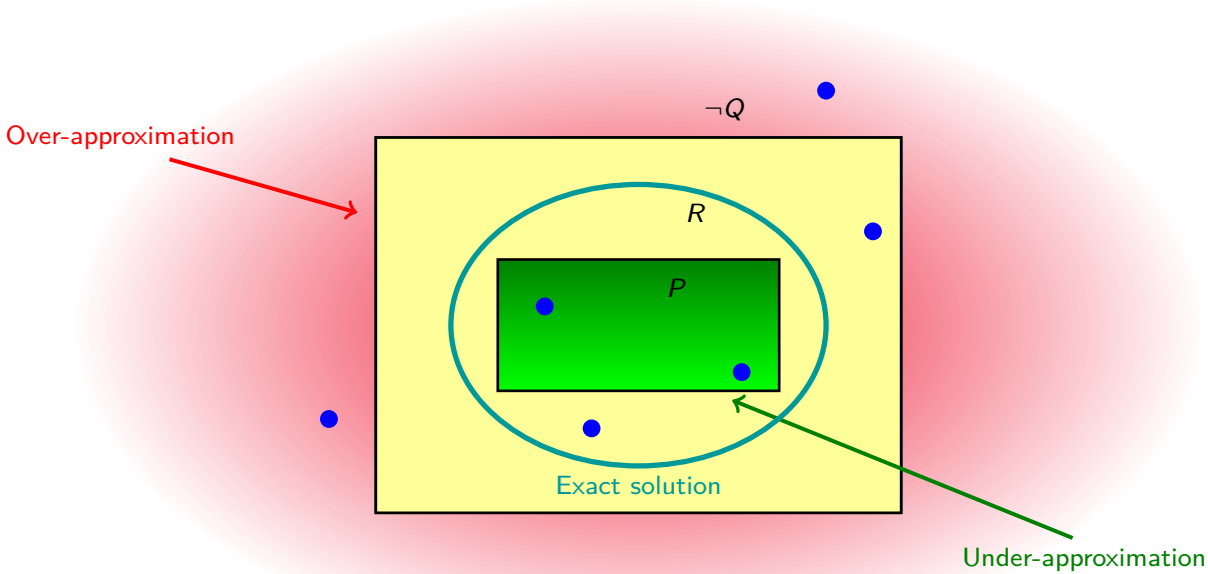
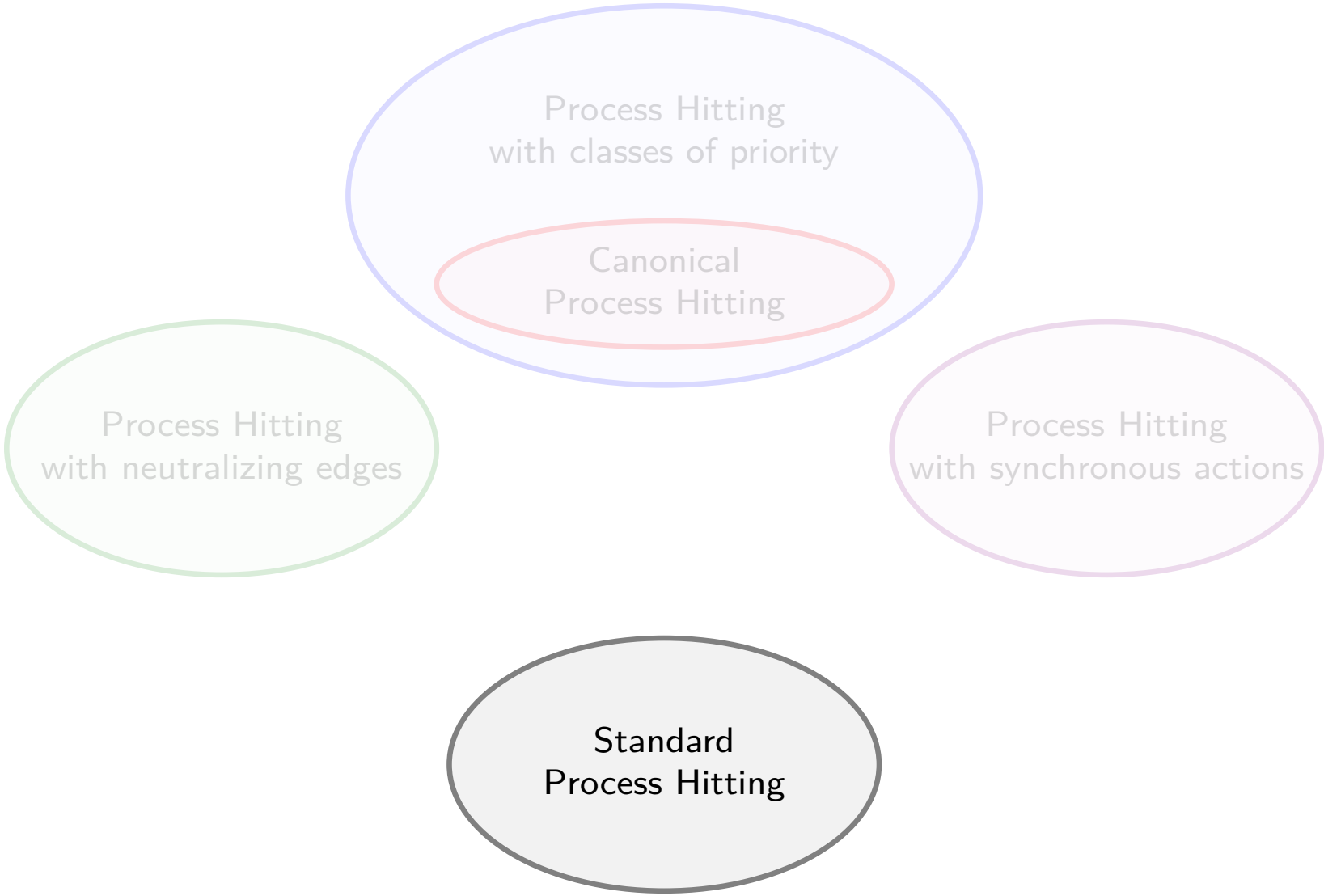


Polynomial complexity in the number of sorts
Exponential complexity in the number of processes in each sort

→ Efficient for big models with few expression levels

Standard Process Hitting



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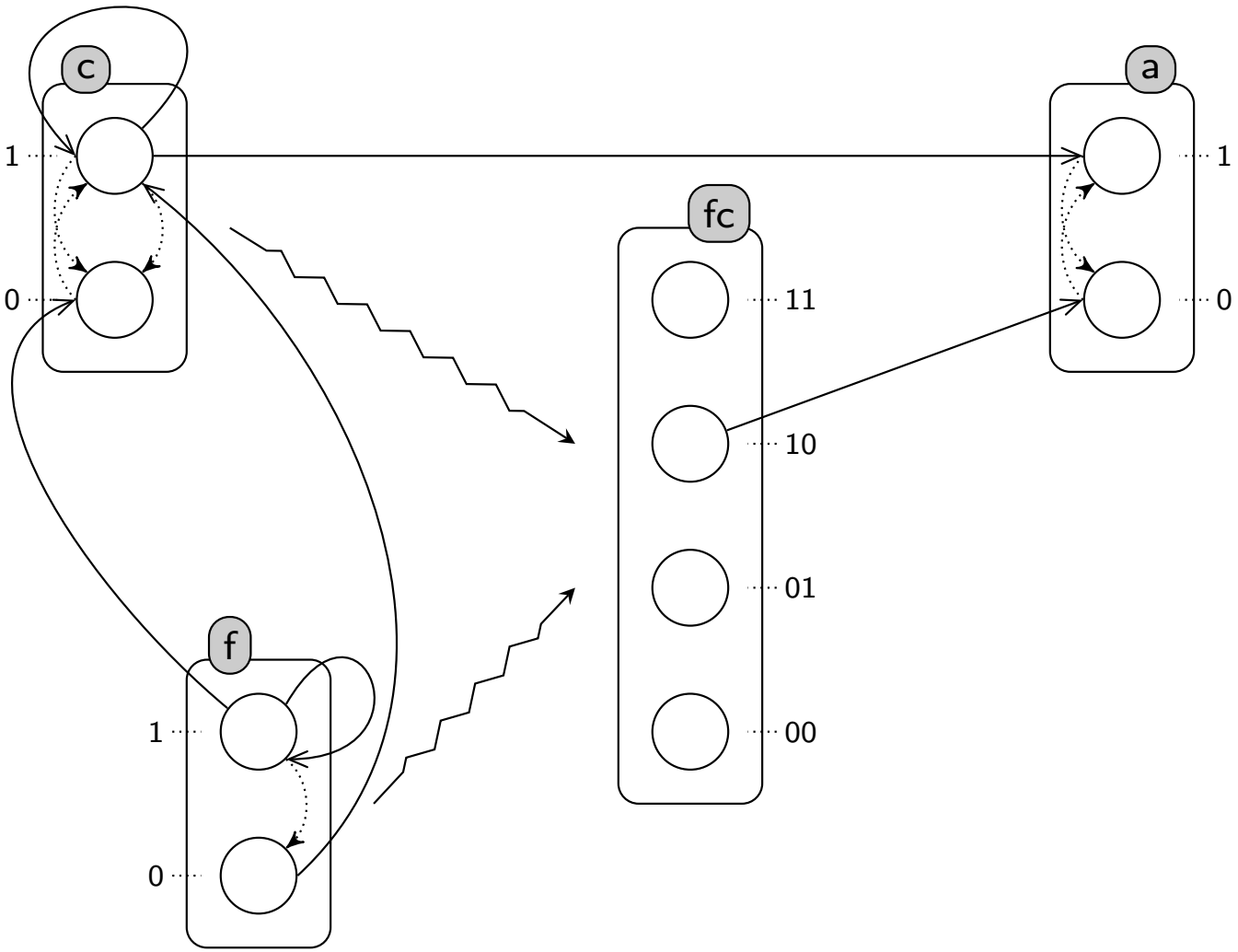

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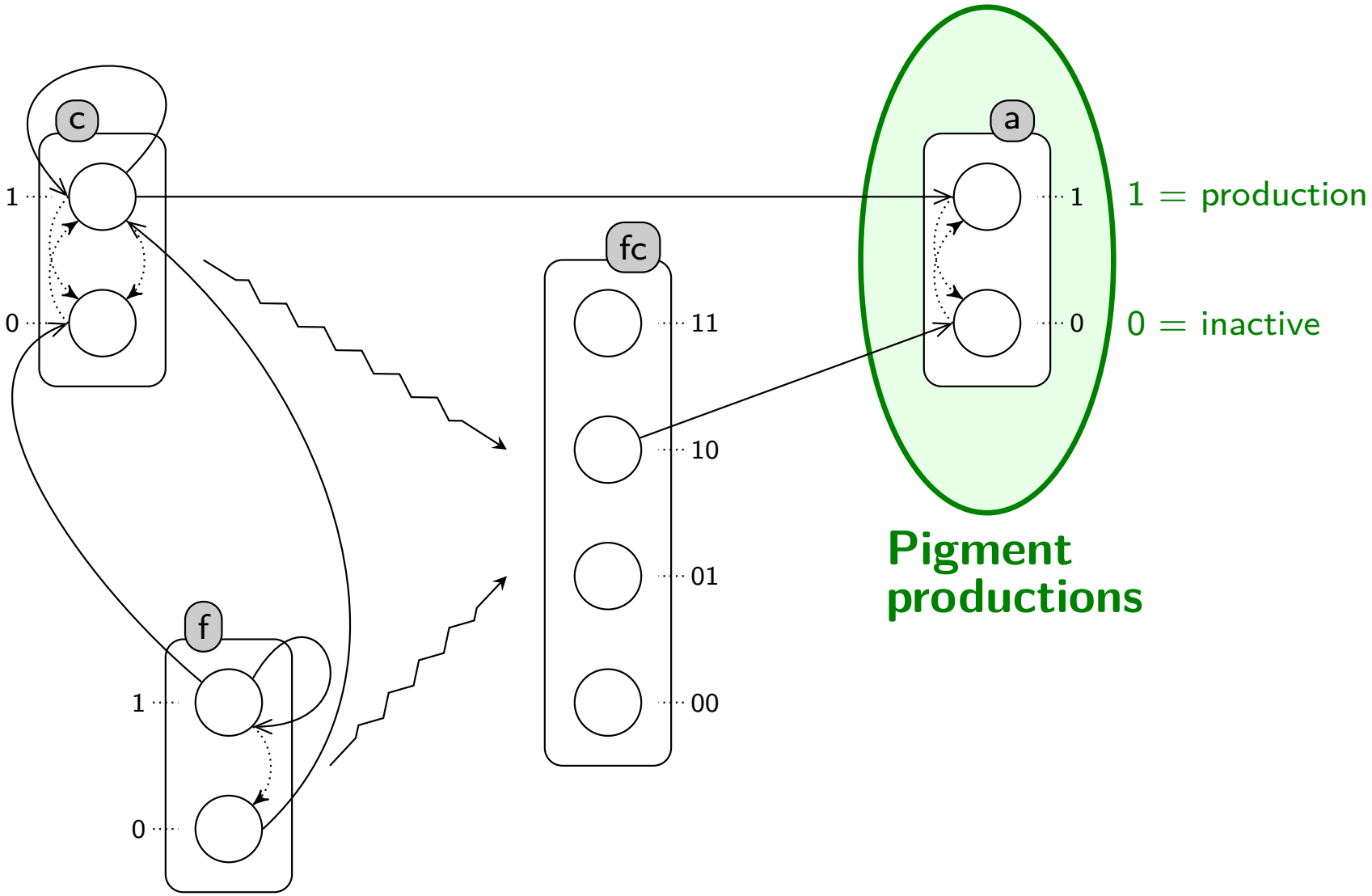

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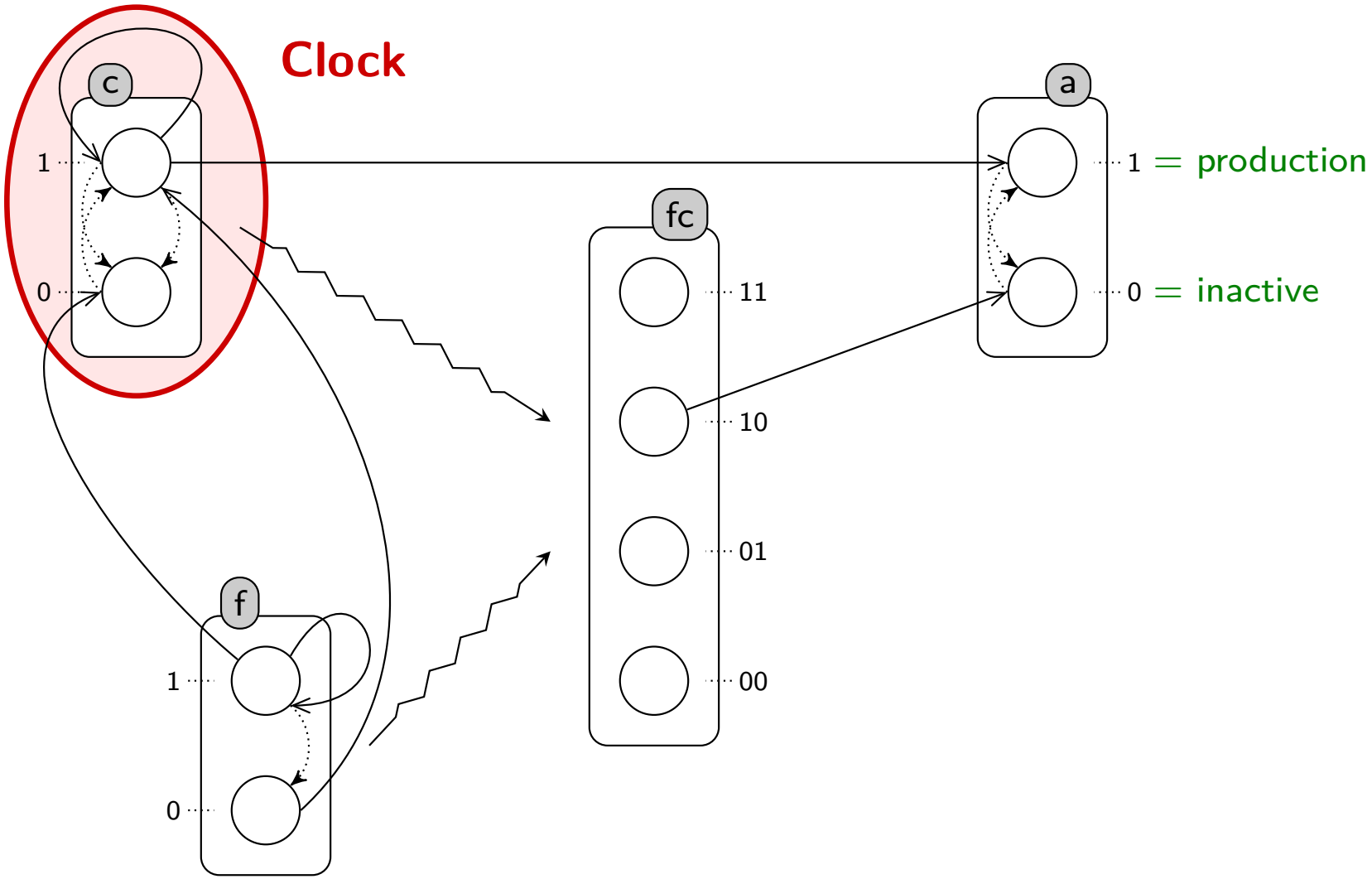

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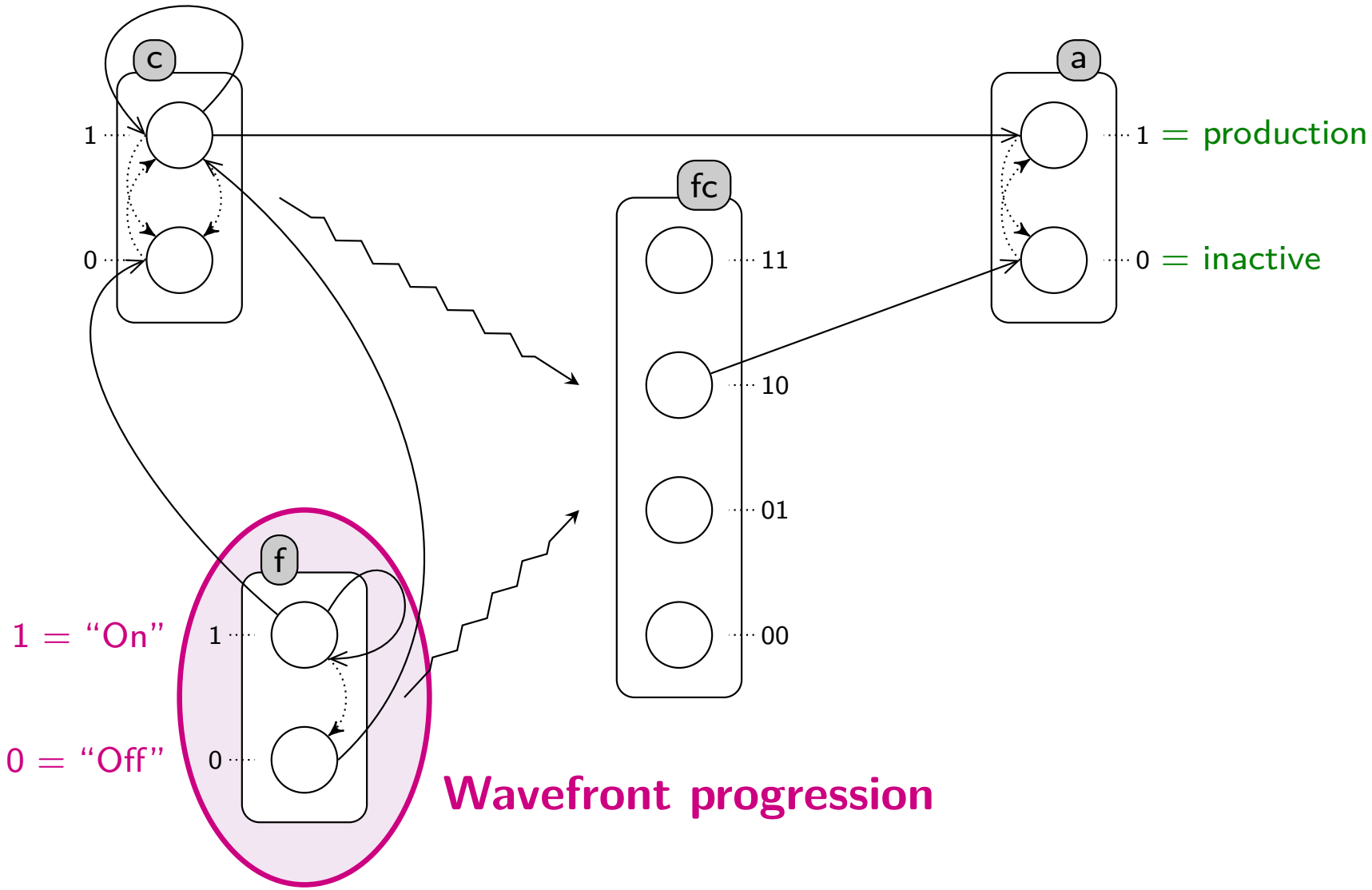

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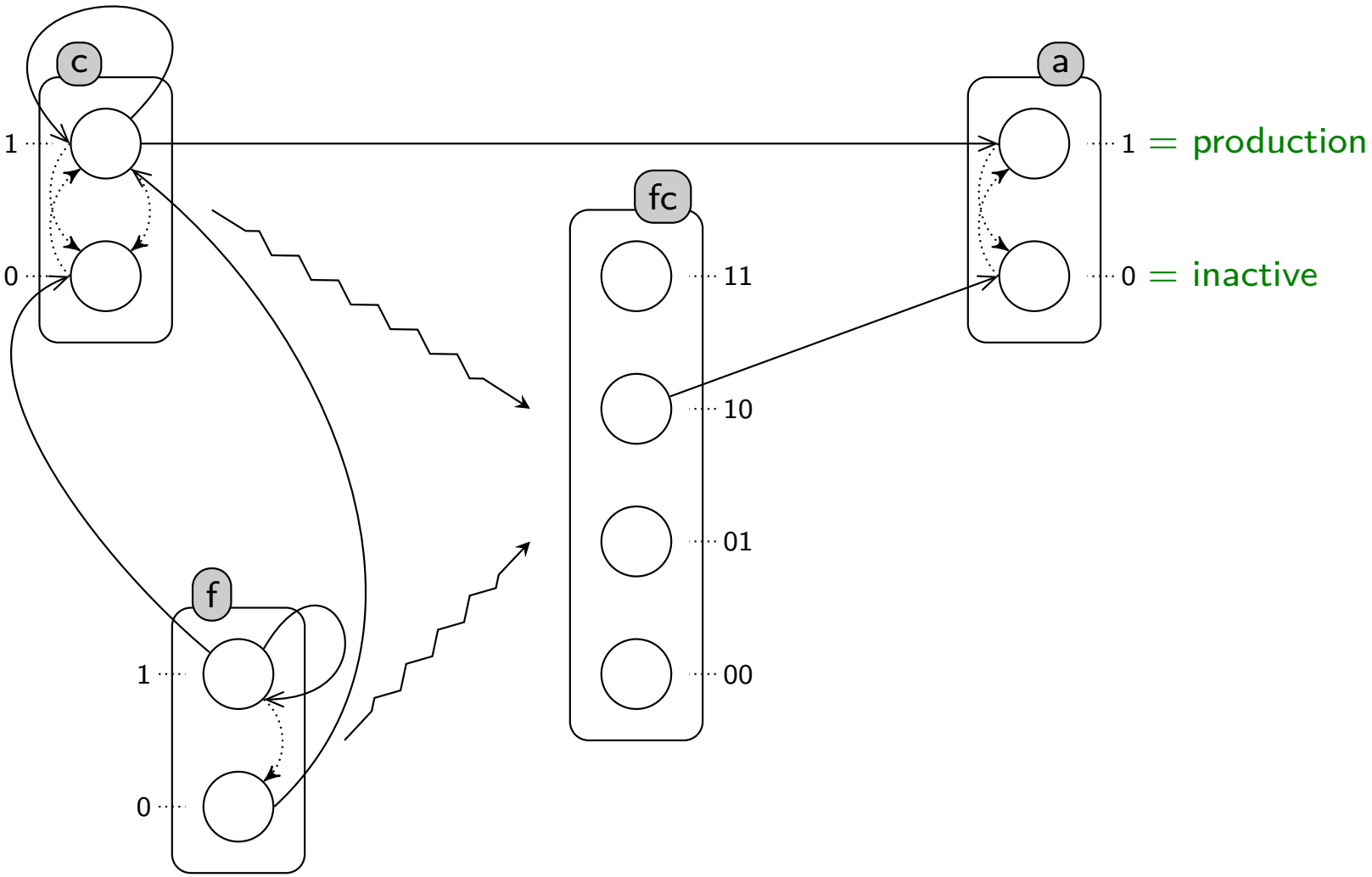

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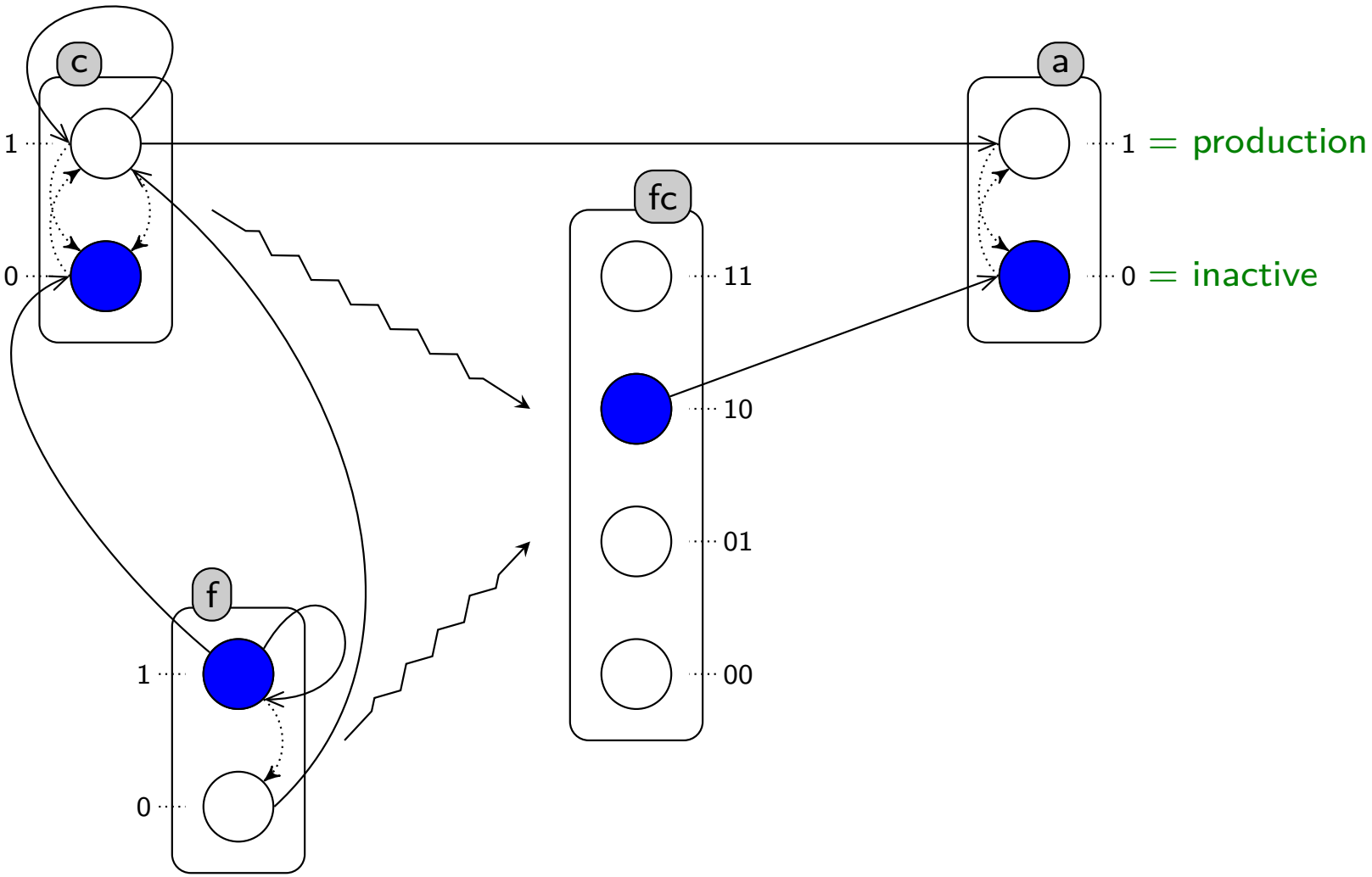

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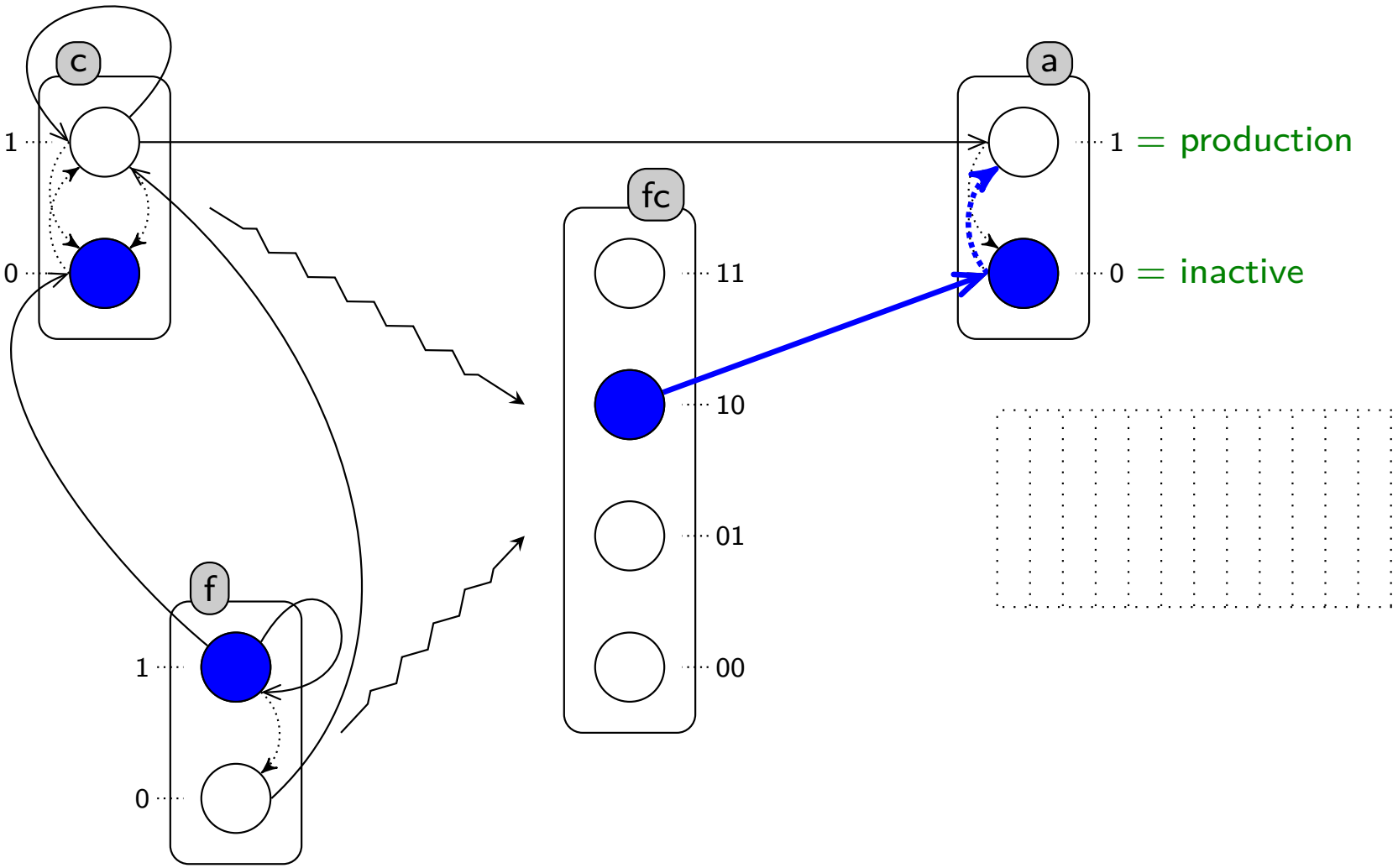

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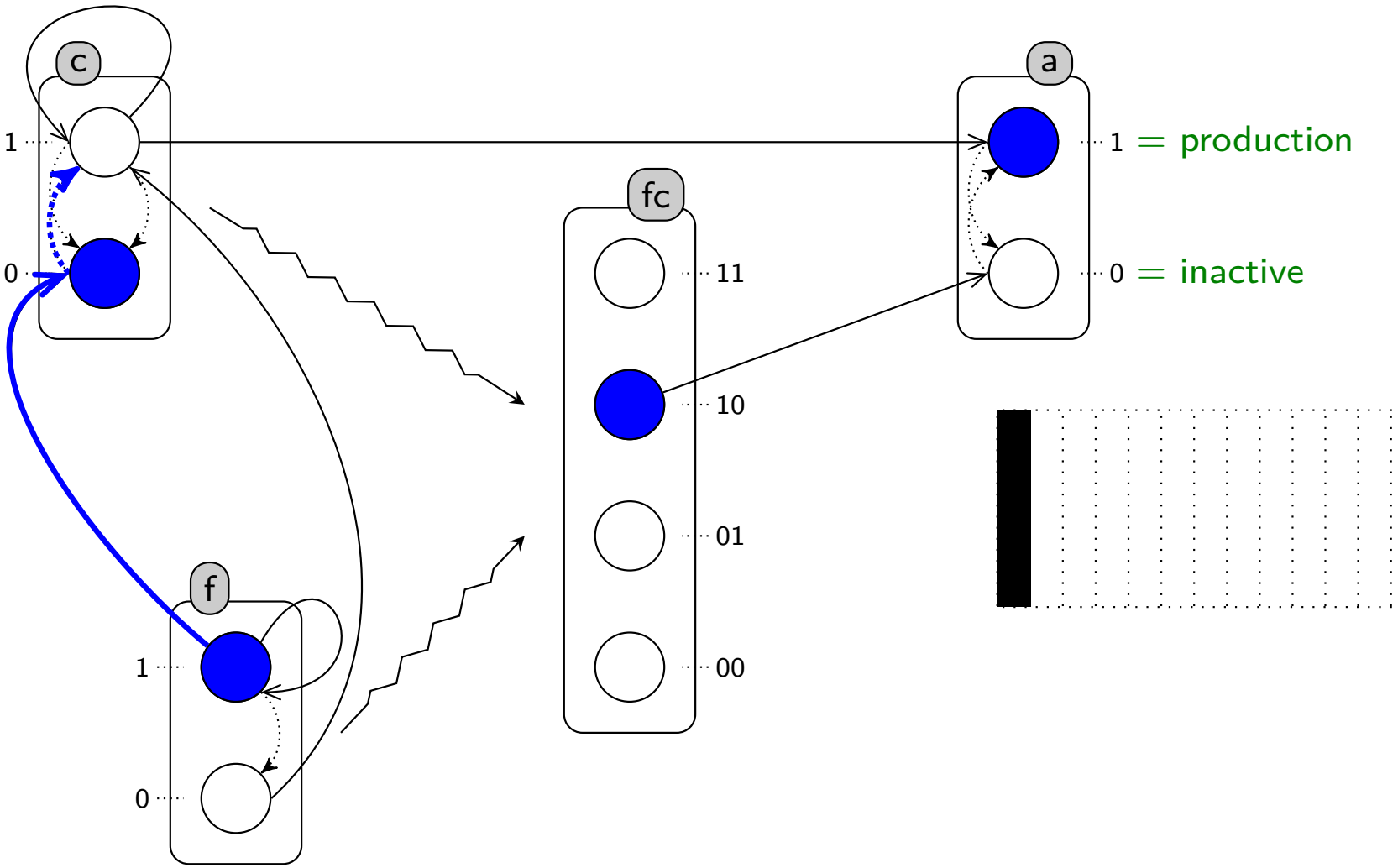

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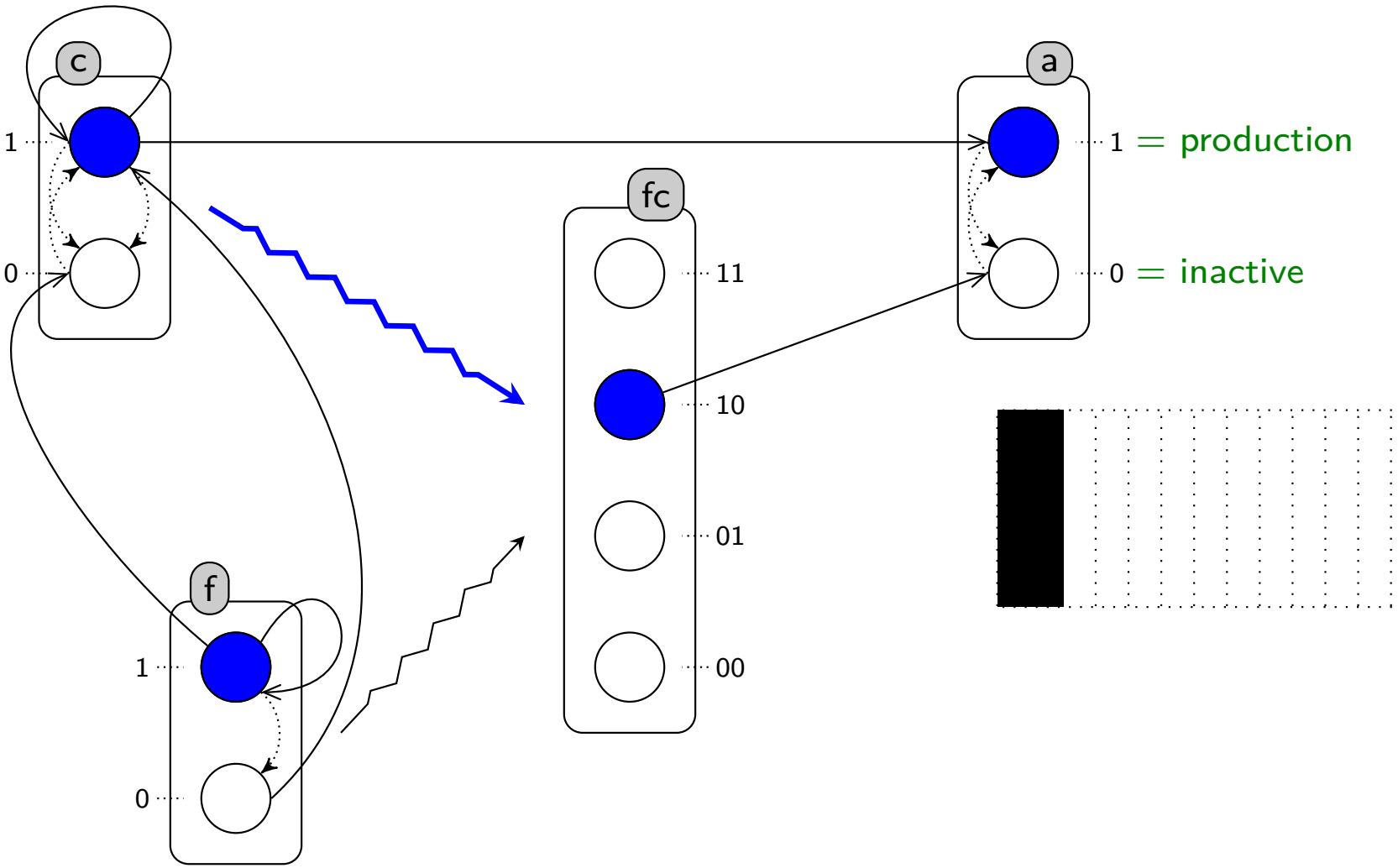

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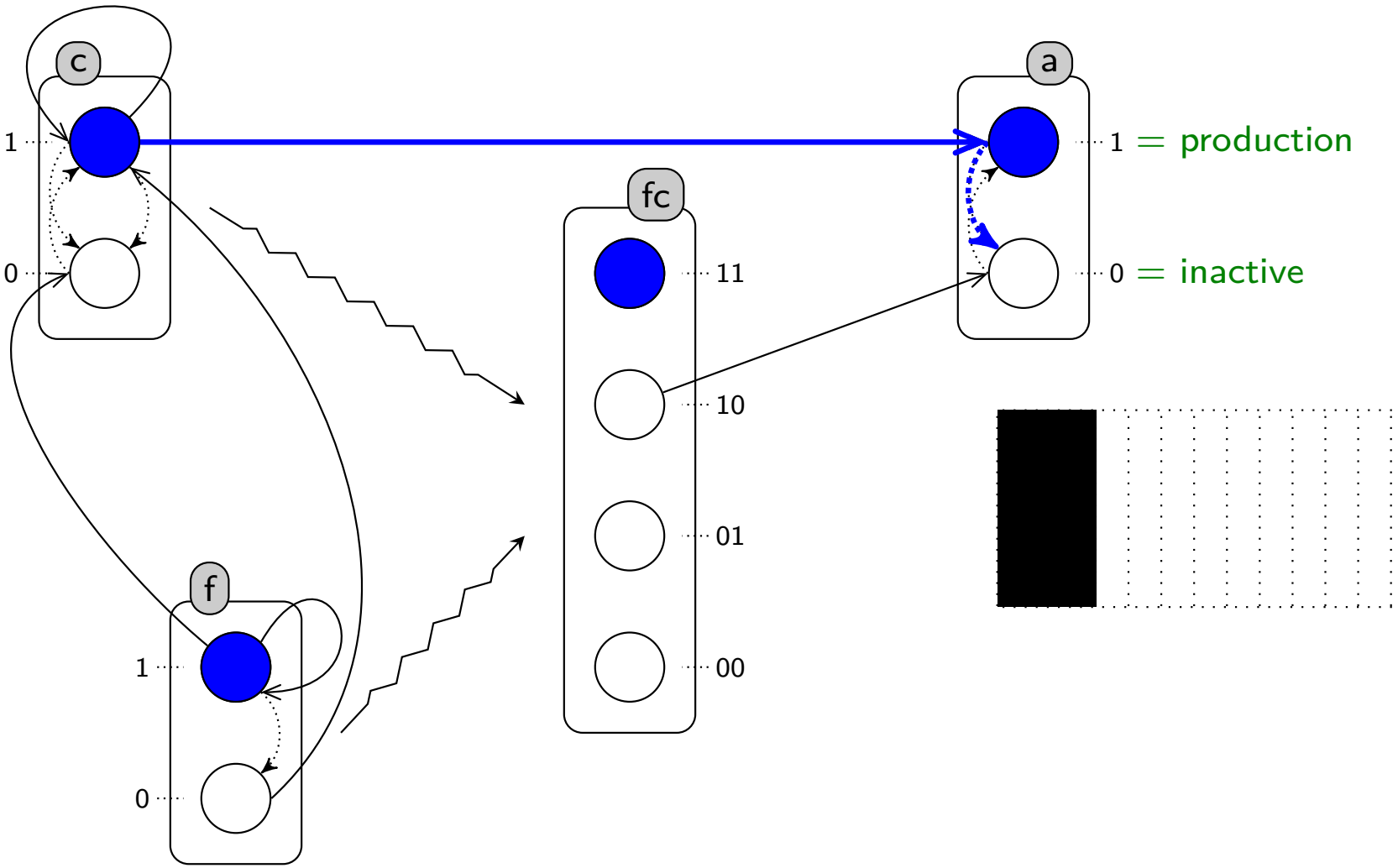

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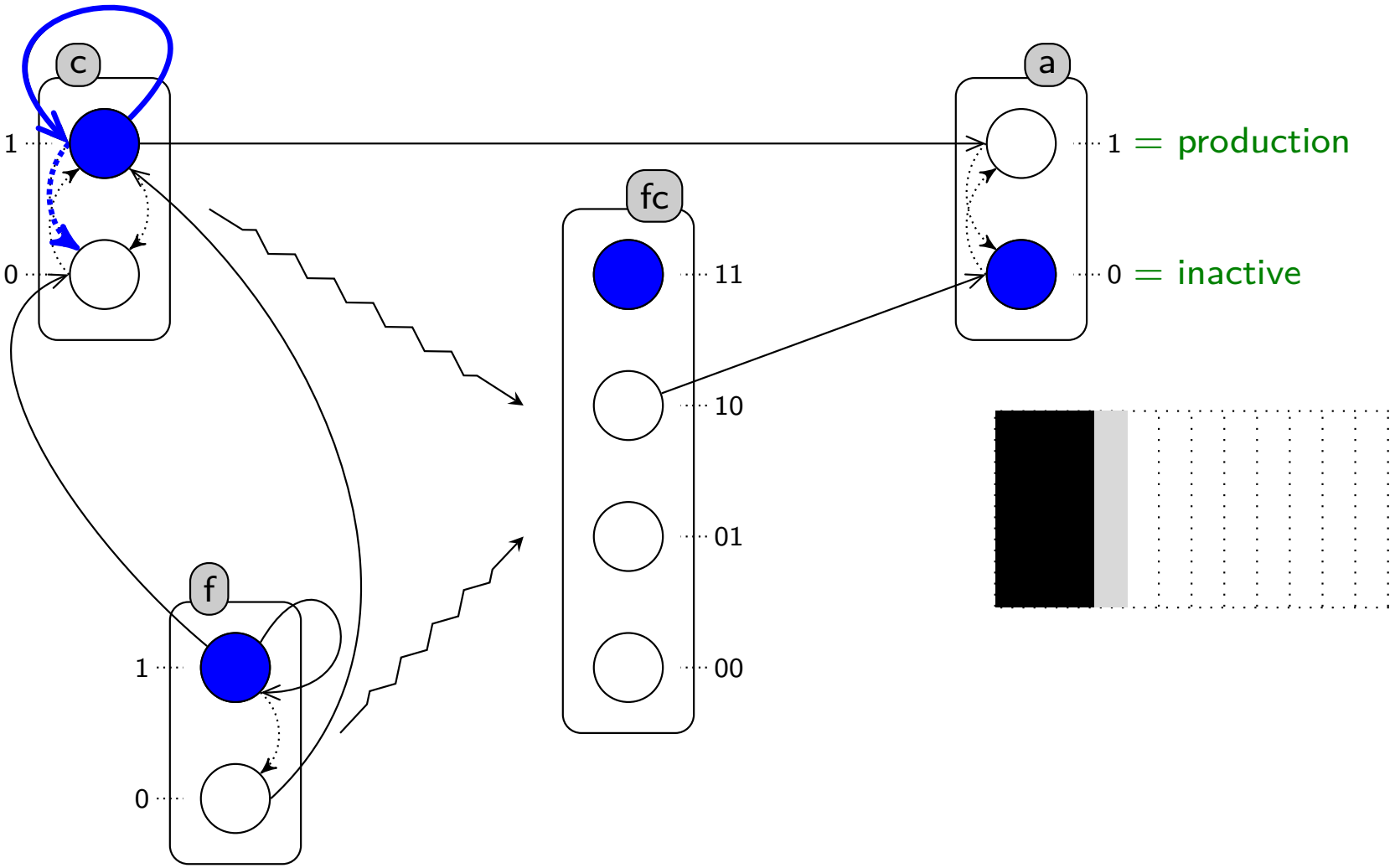

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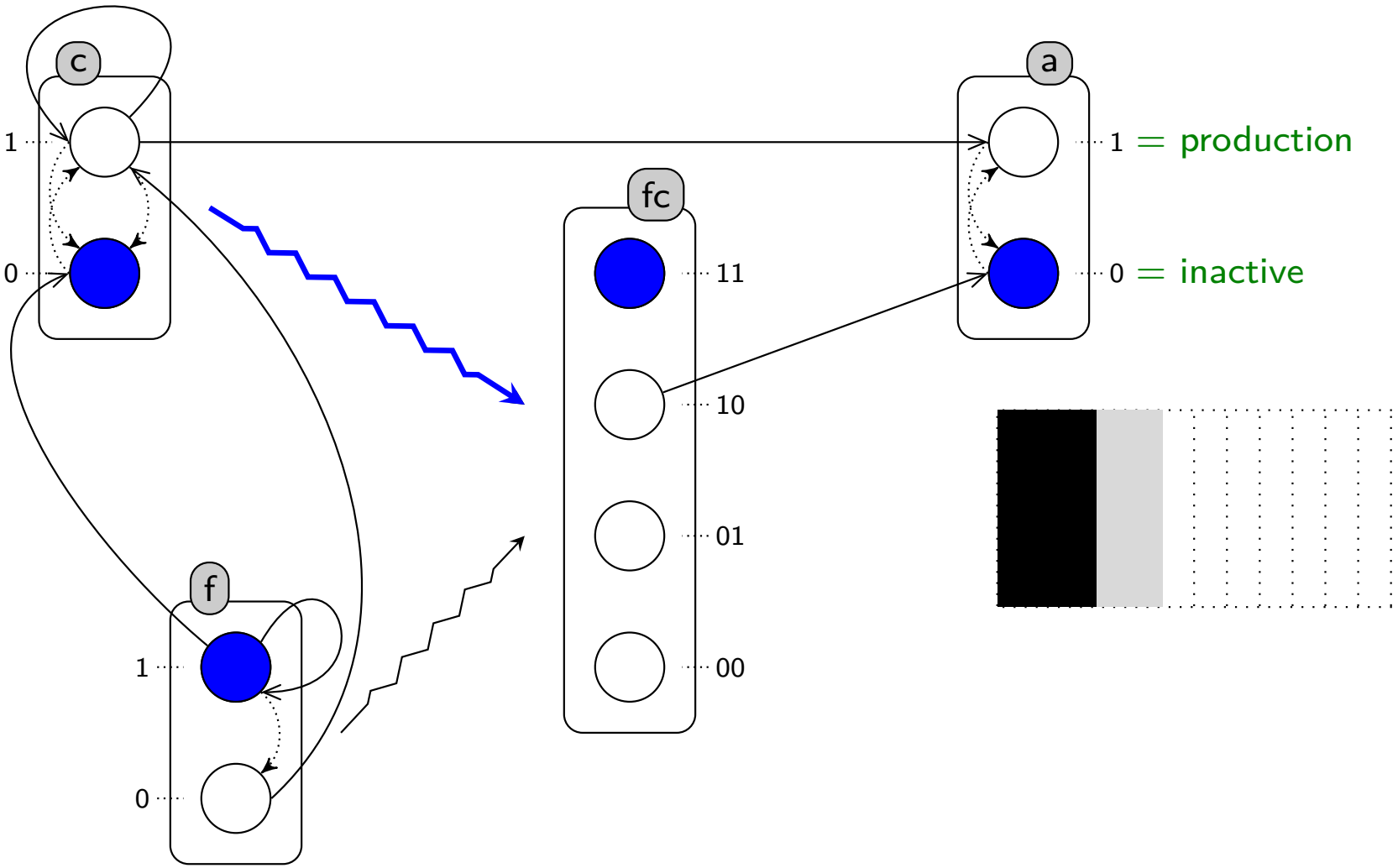

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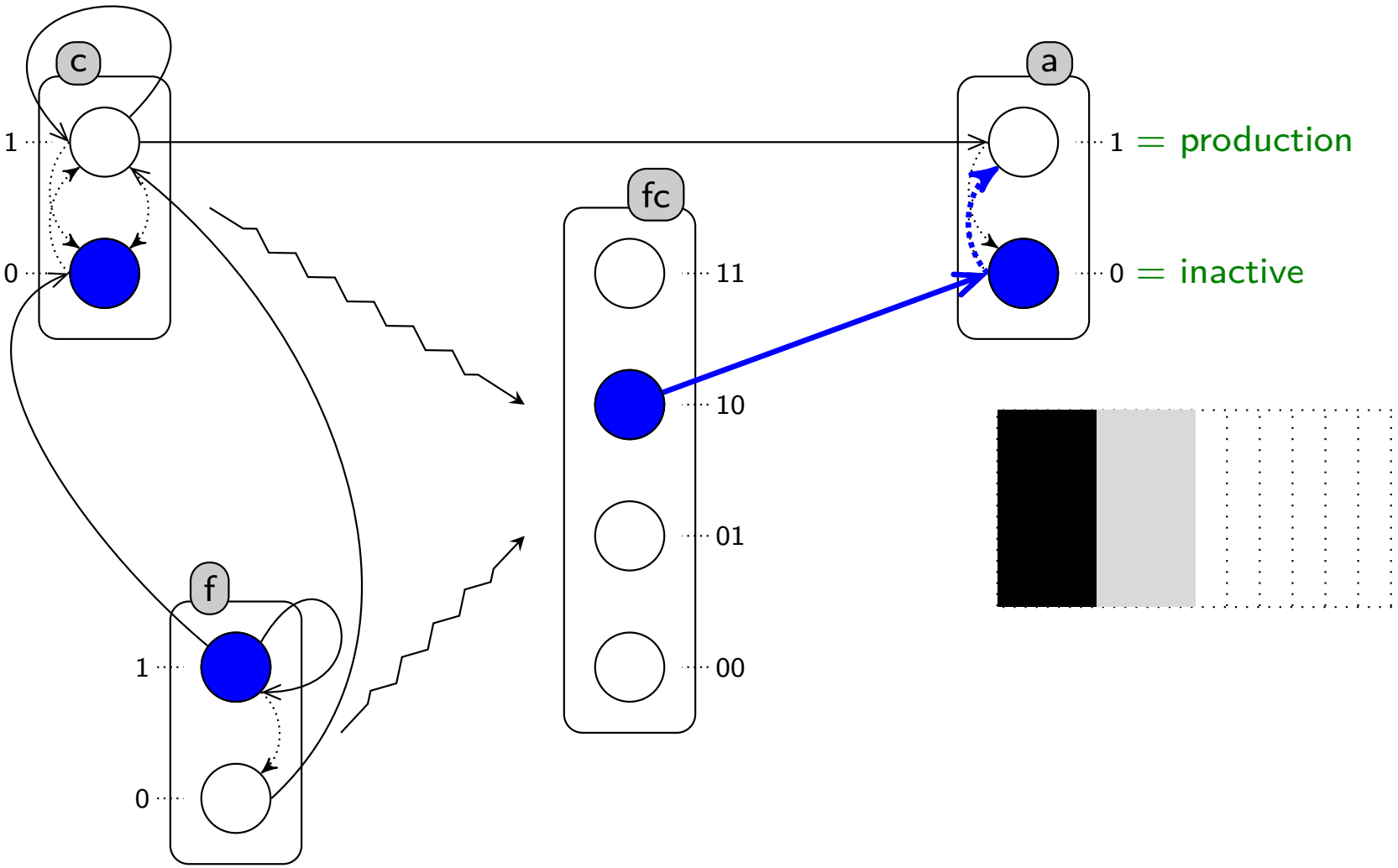

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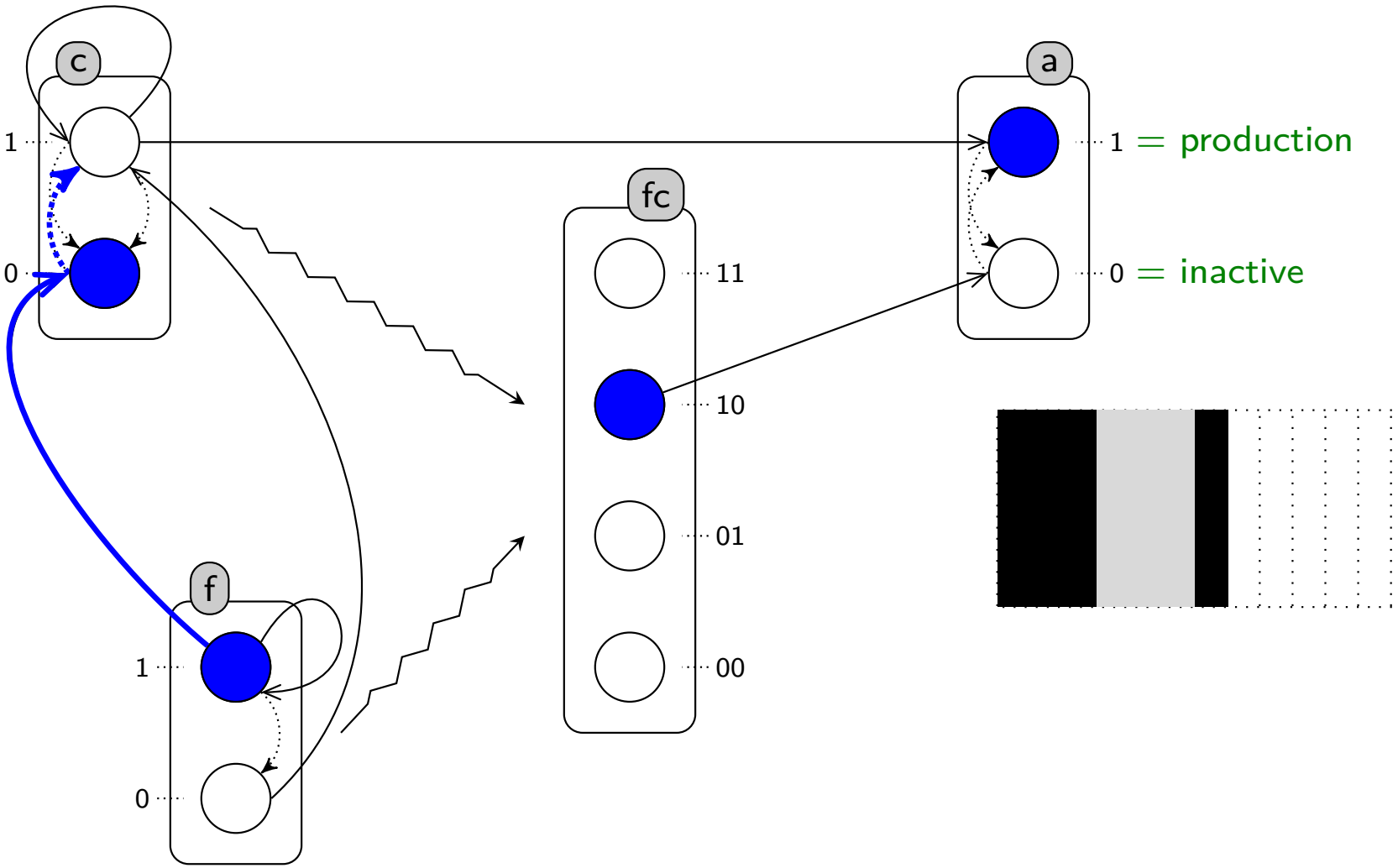

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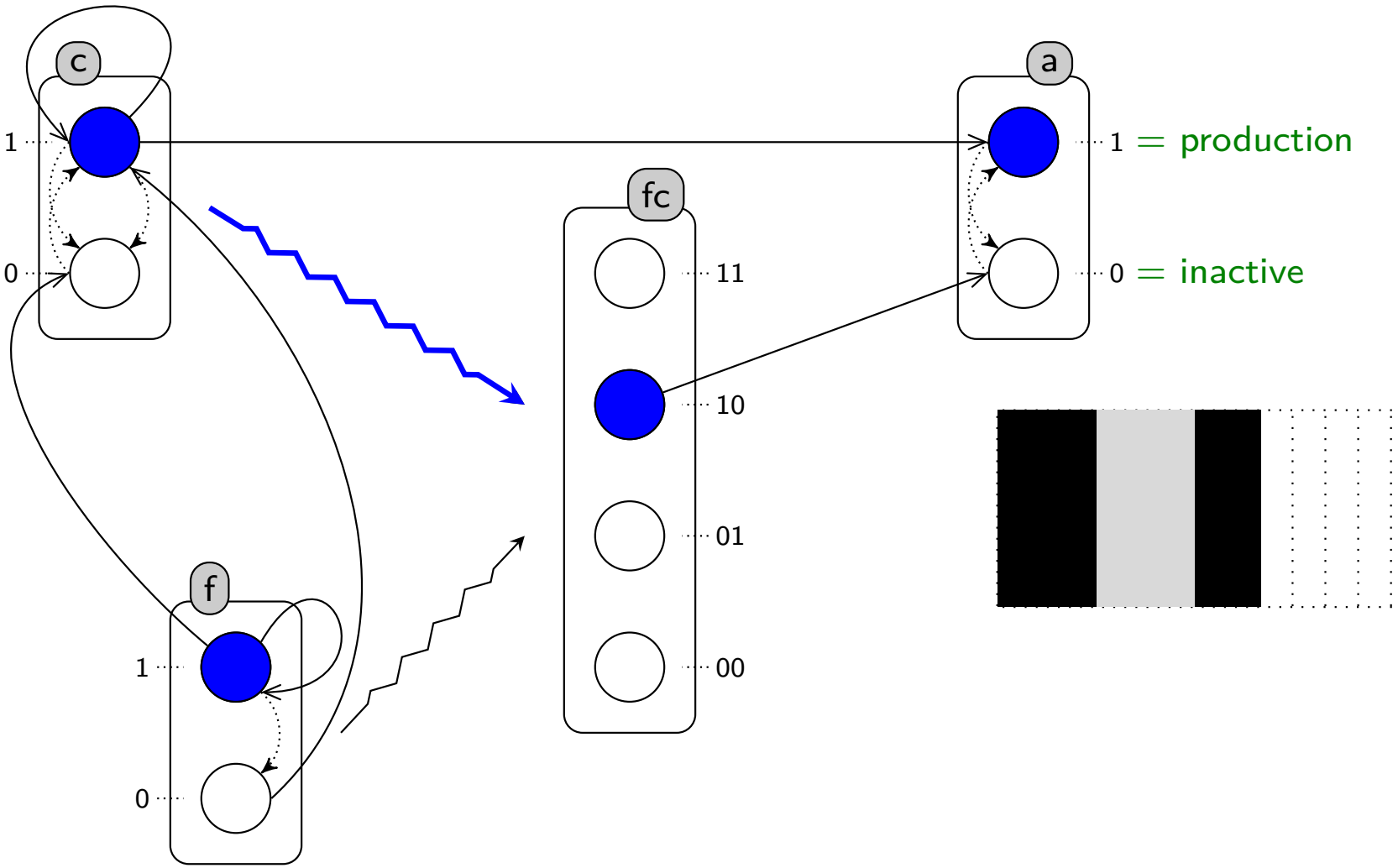

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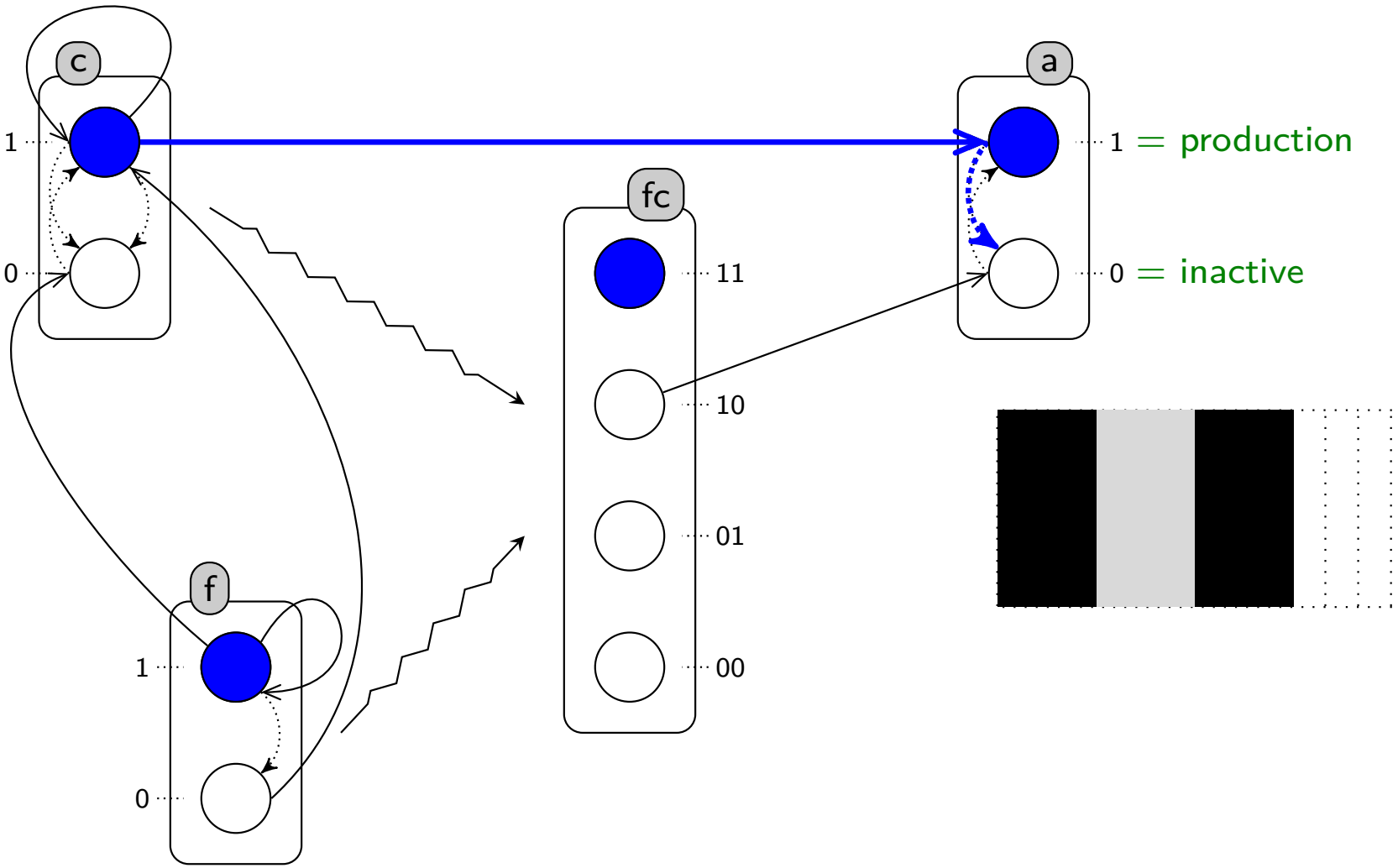

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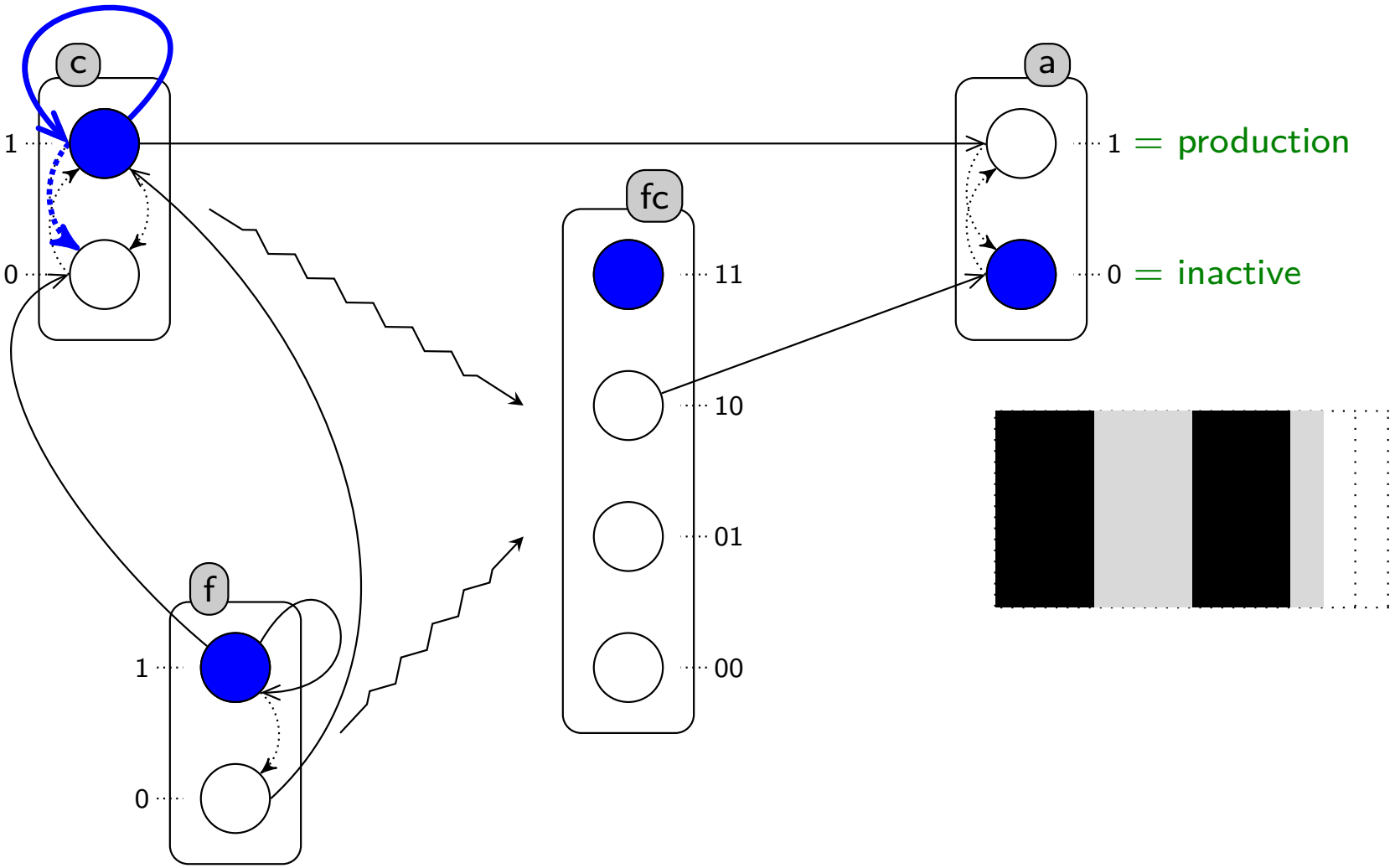

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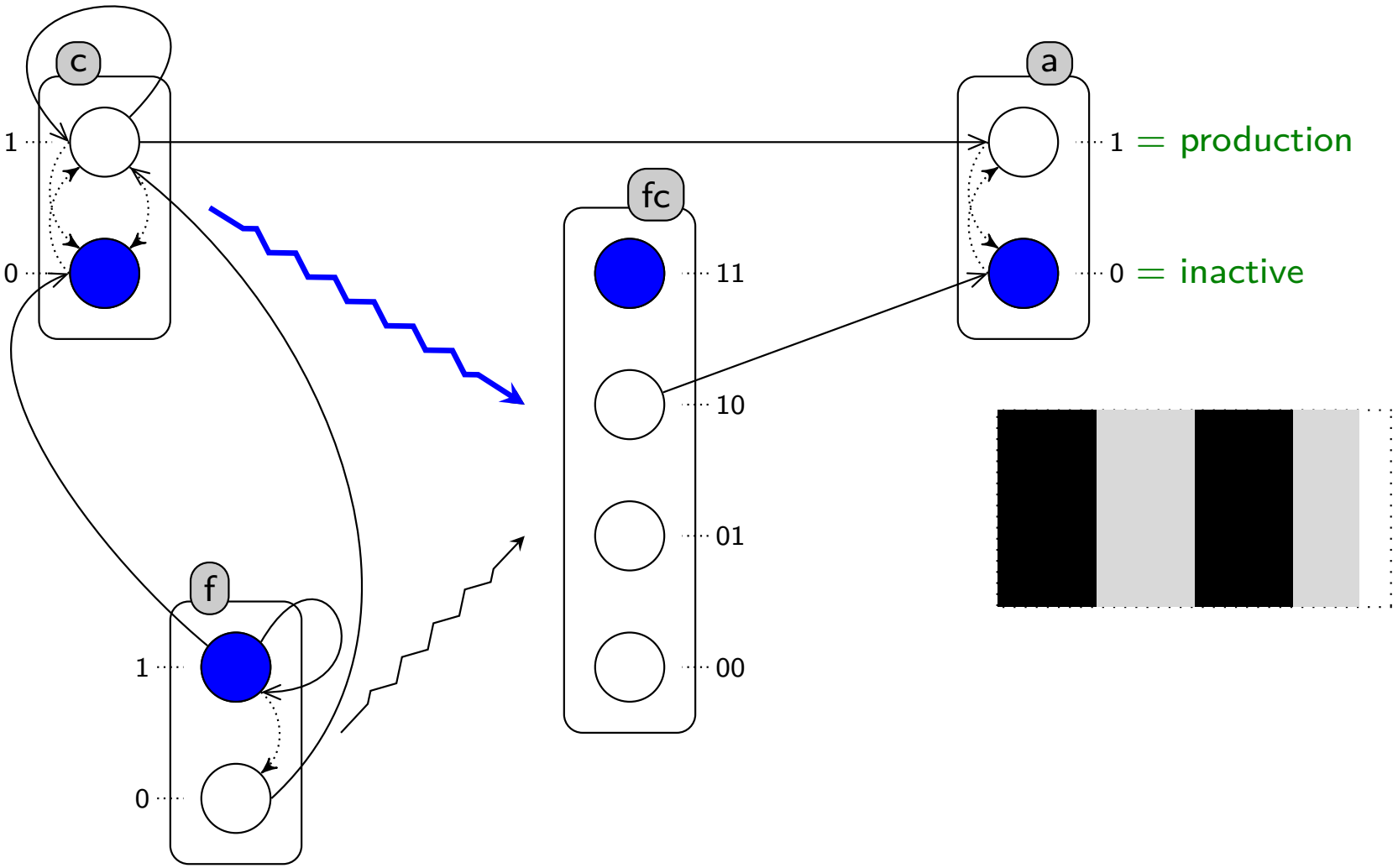

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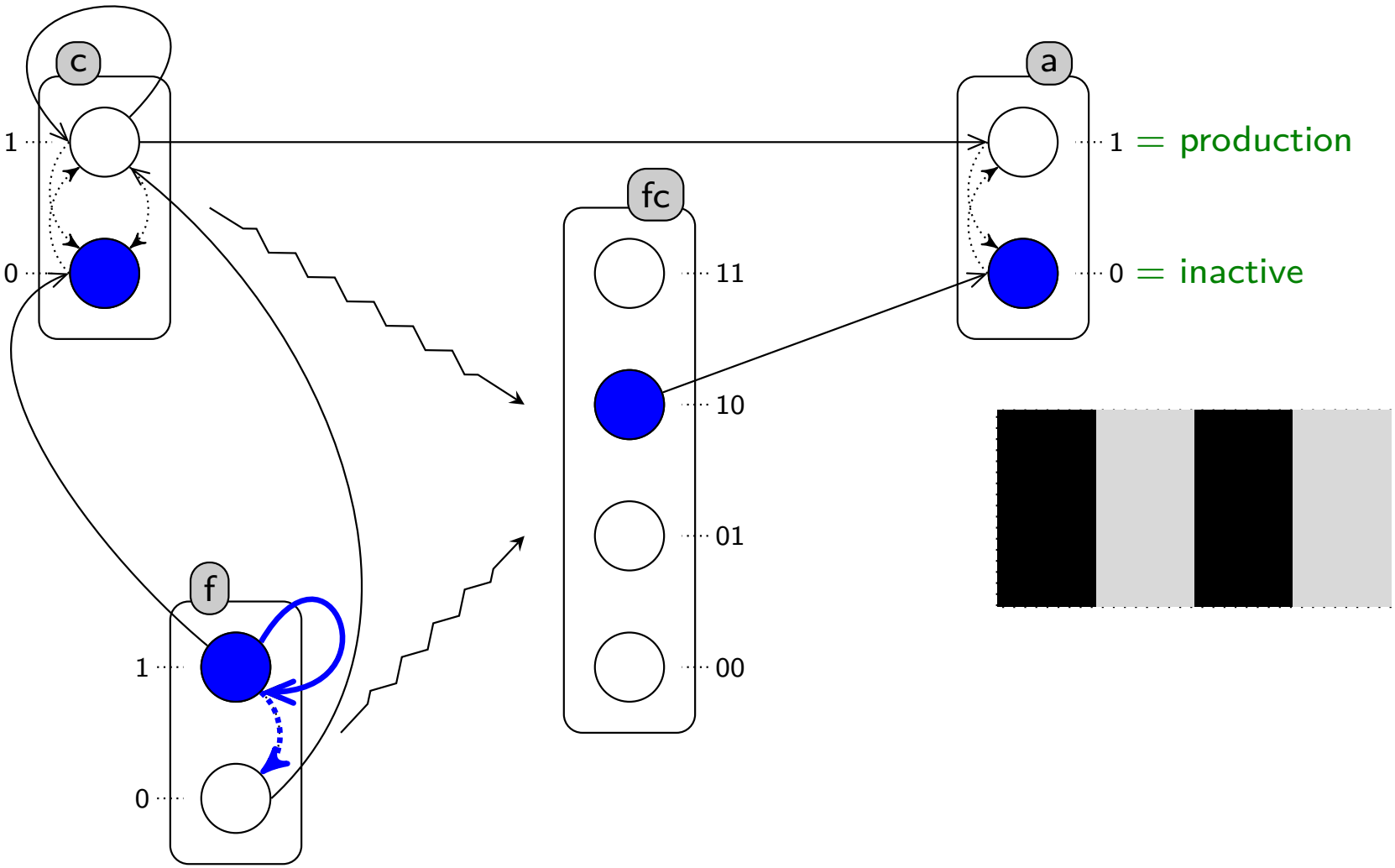

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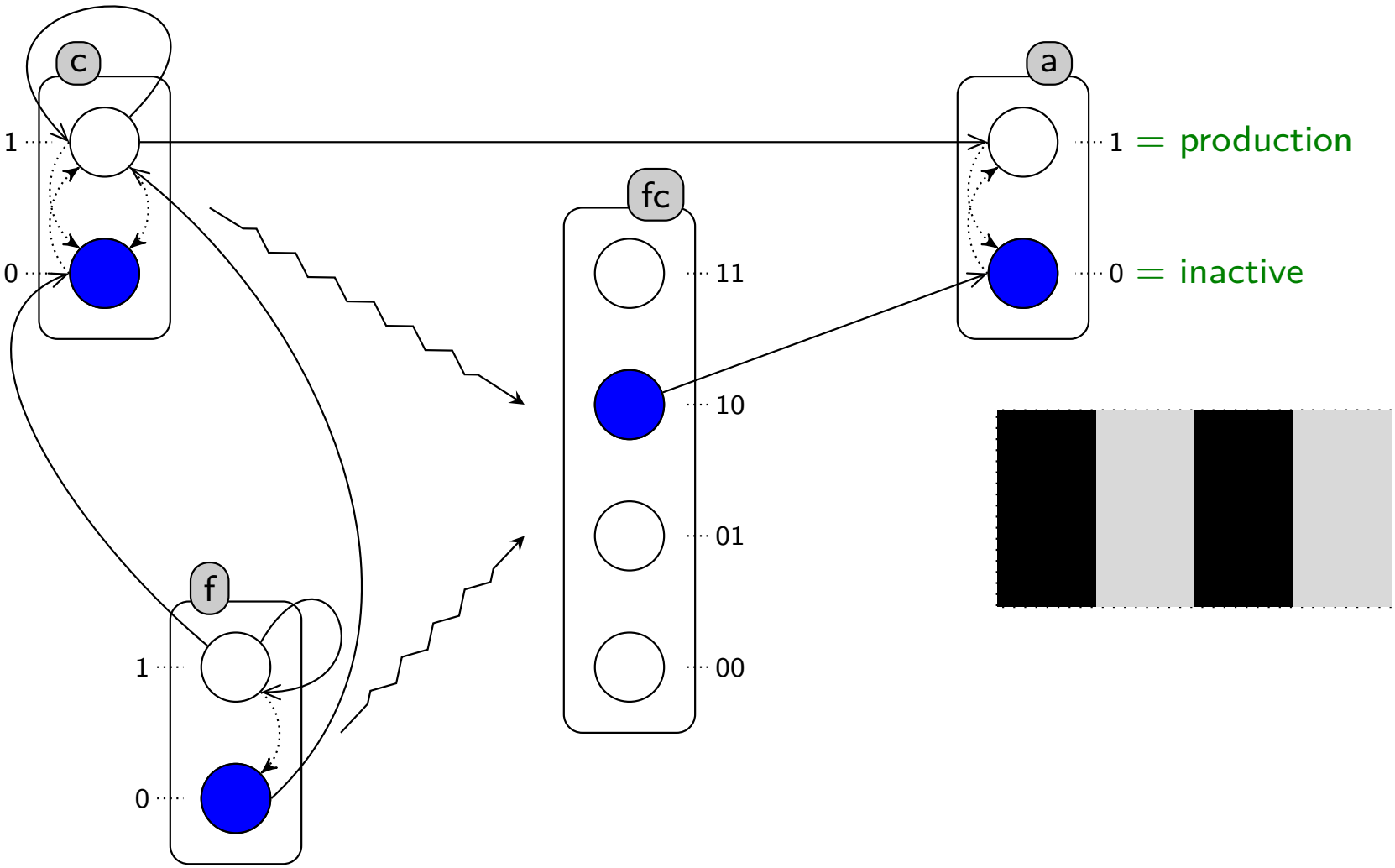

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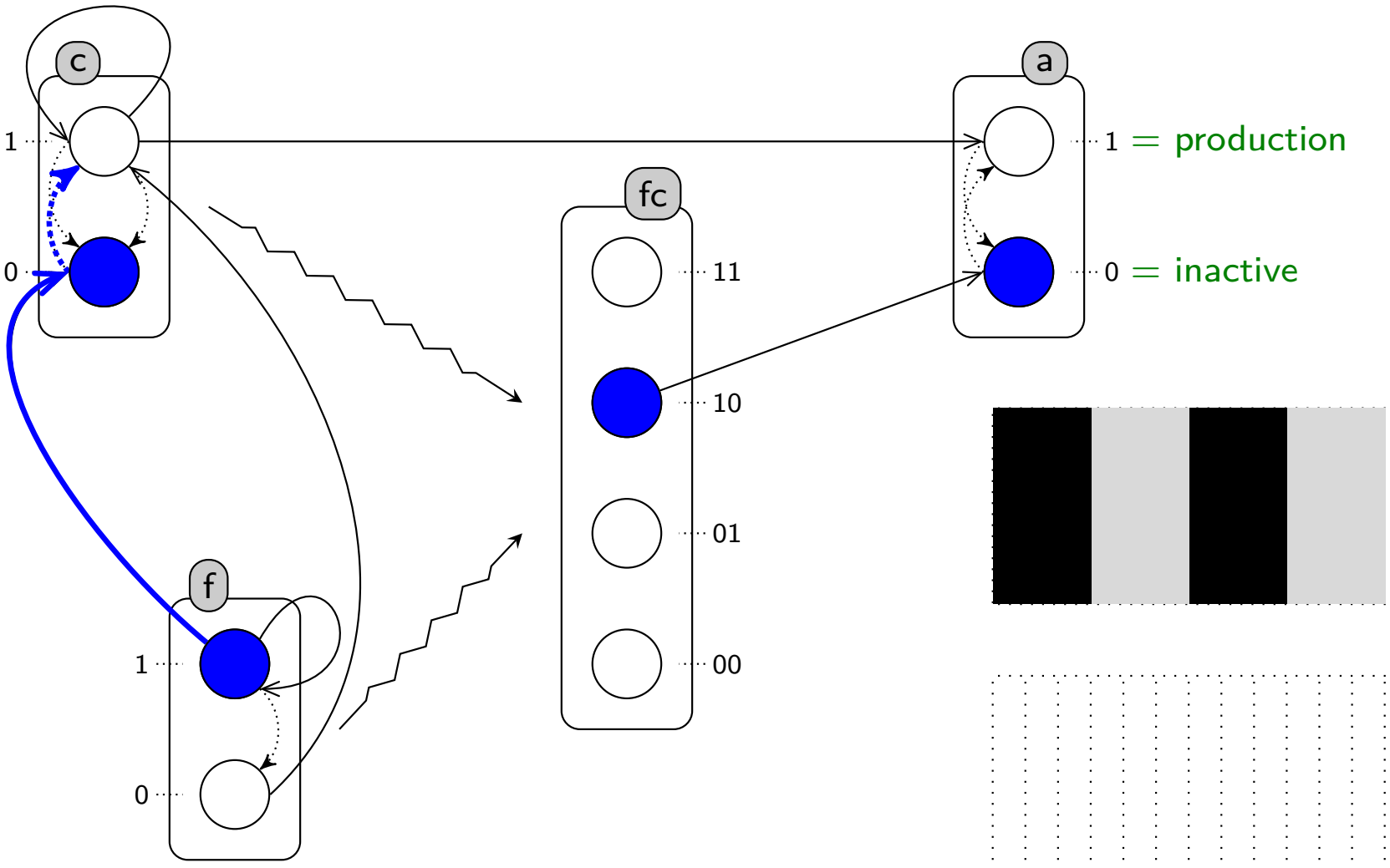

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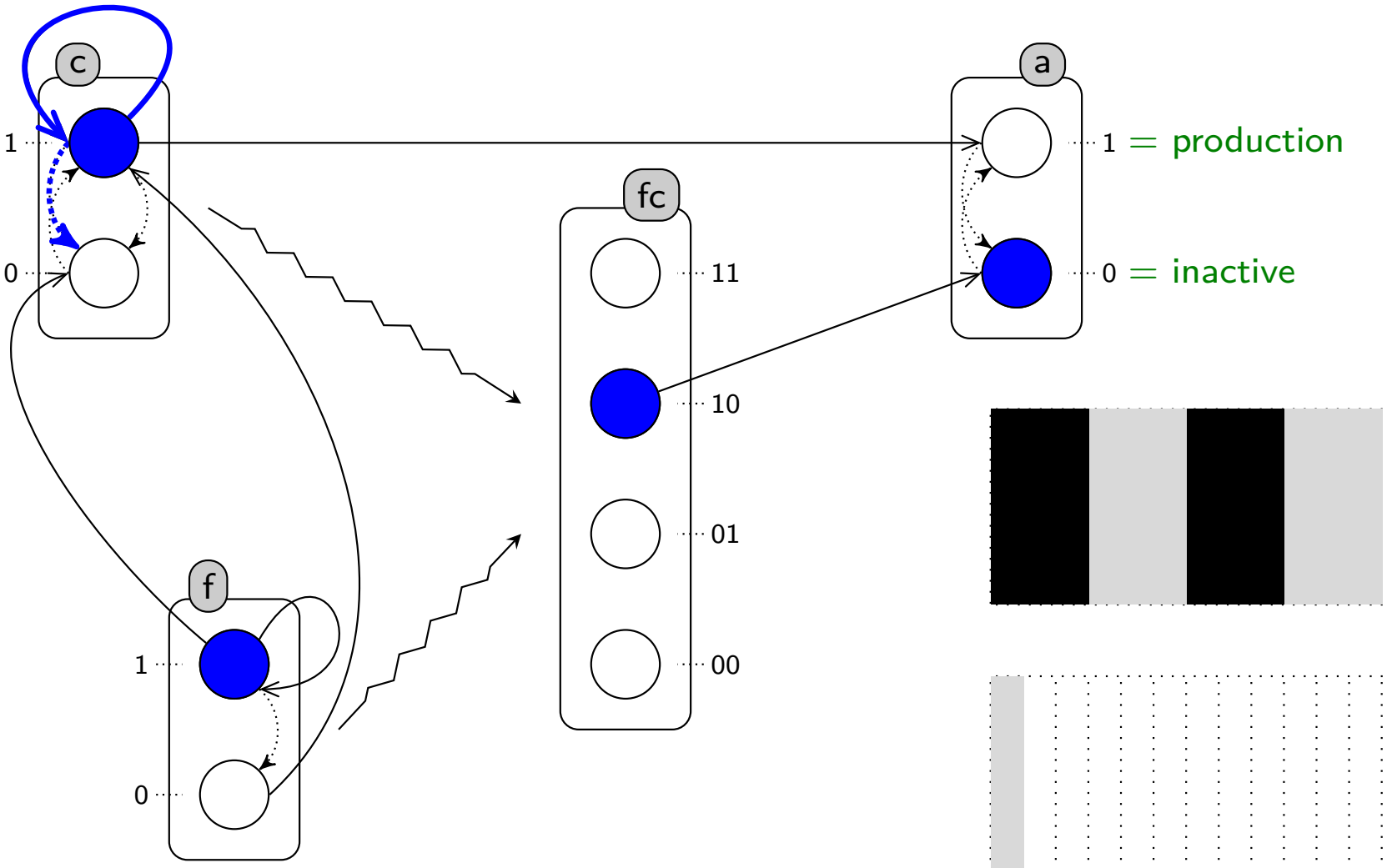

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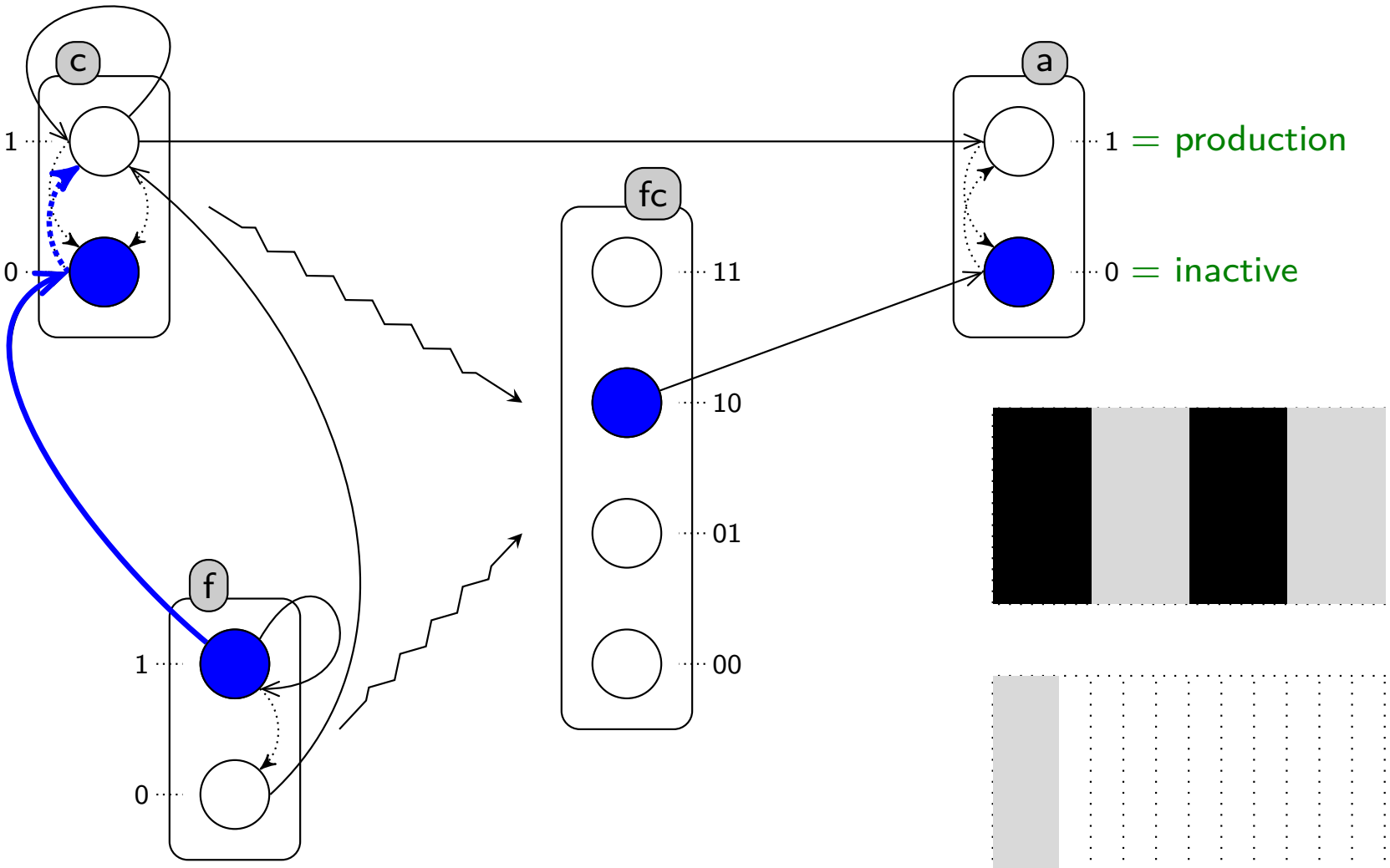

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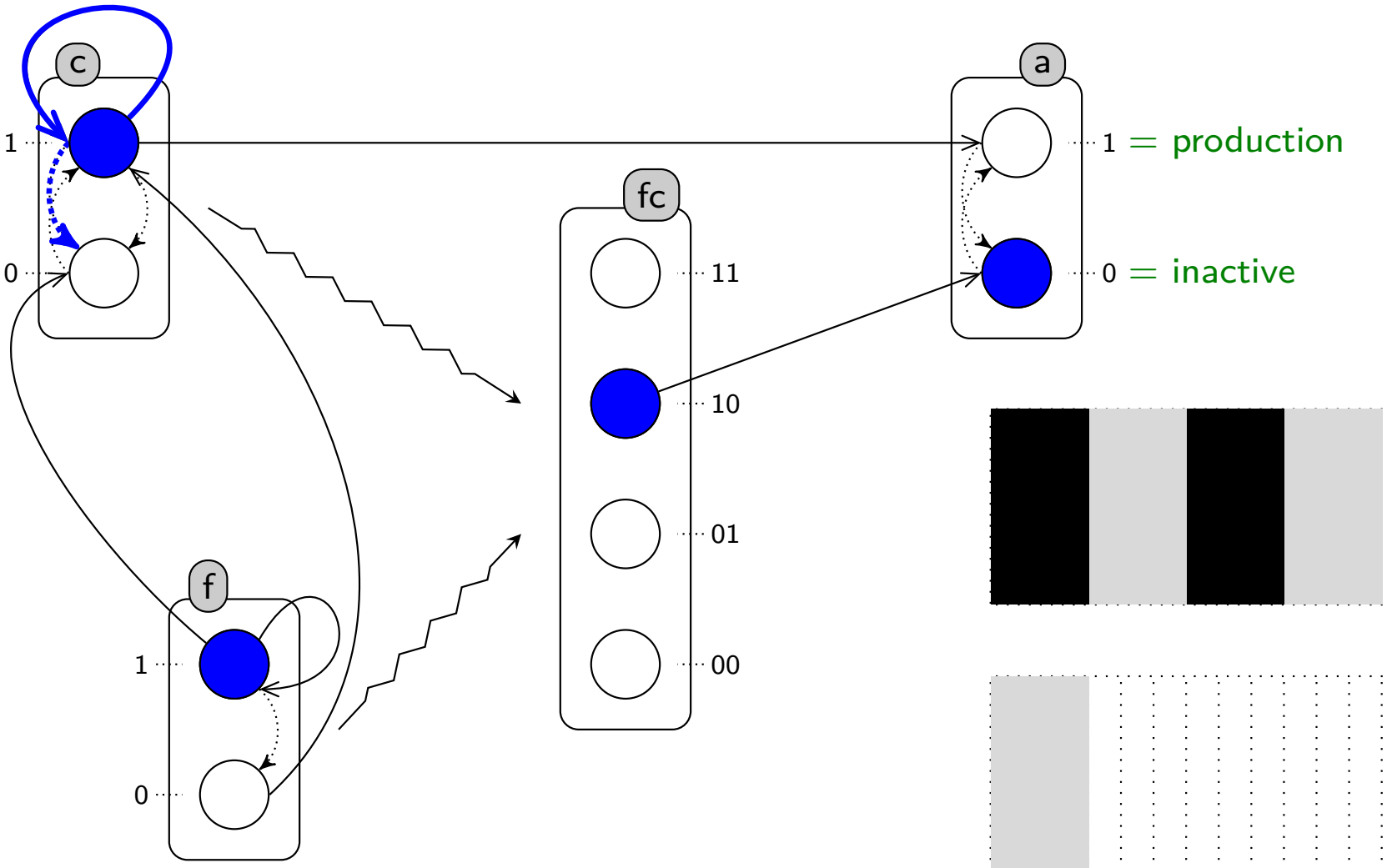

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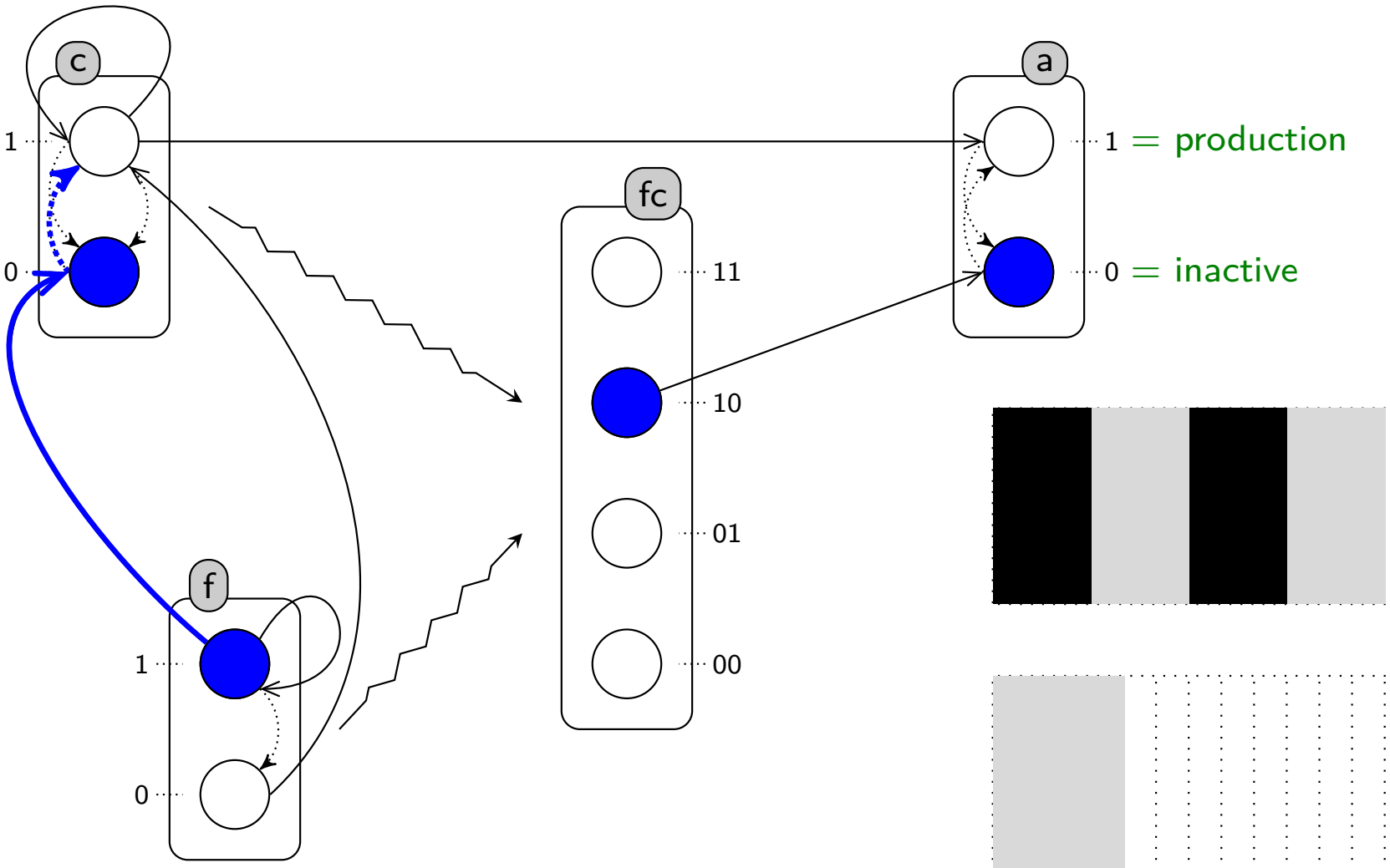

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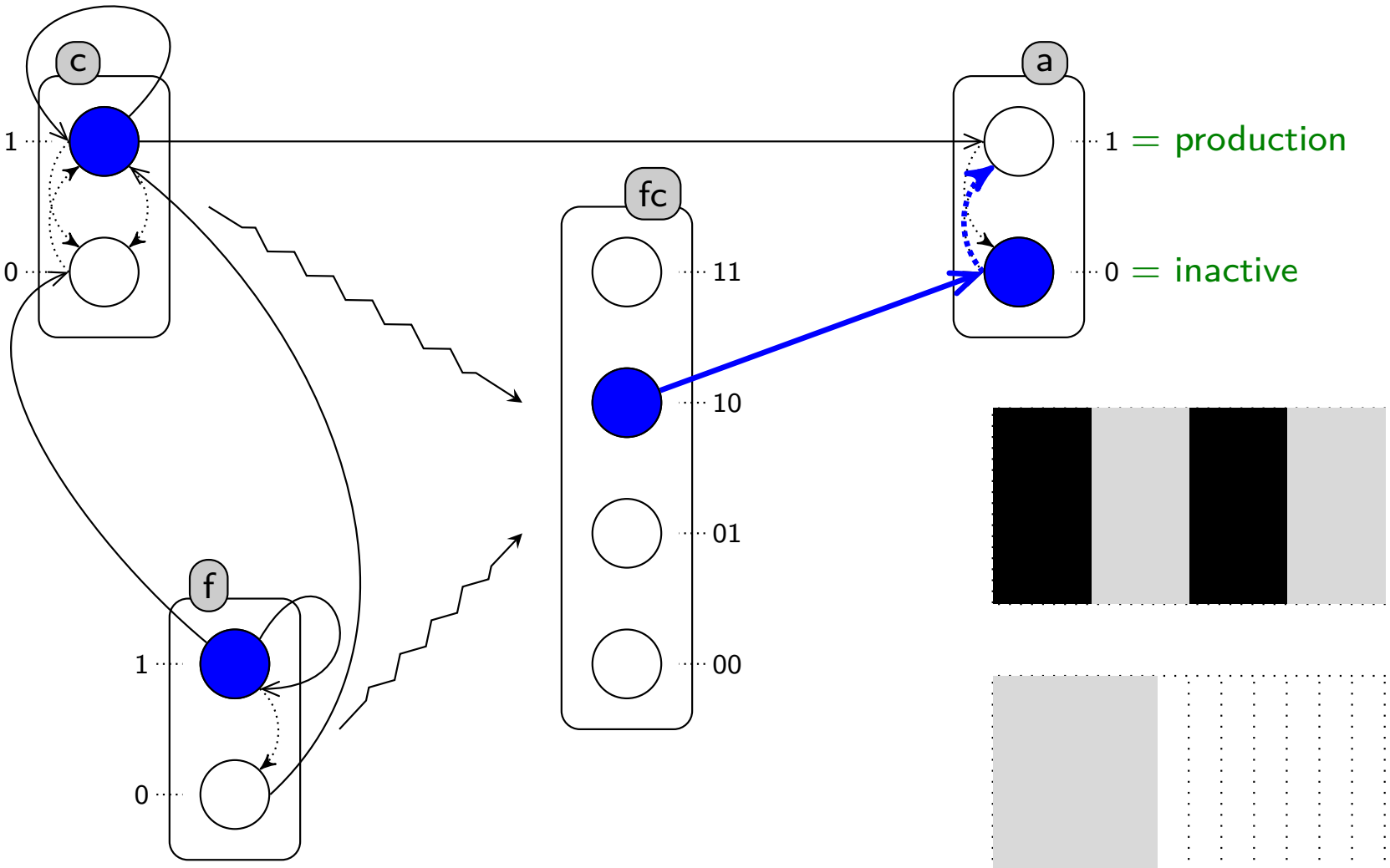

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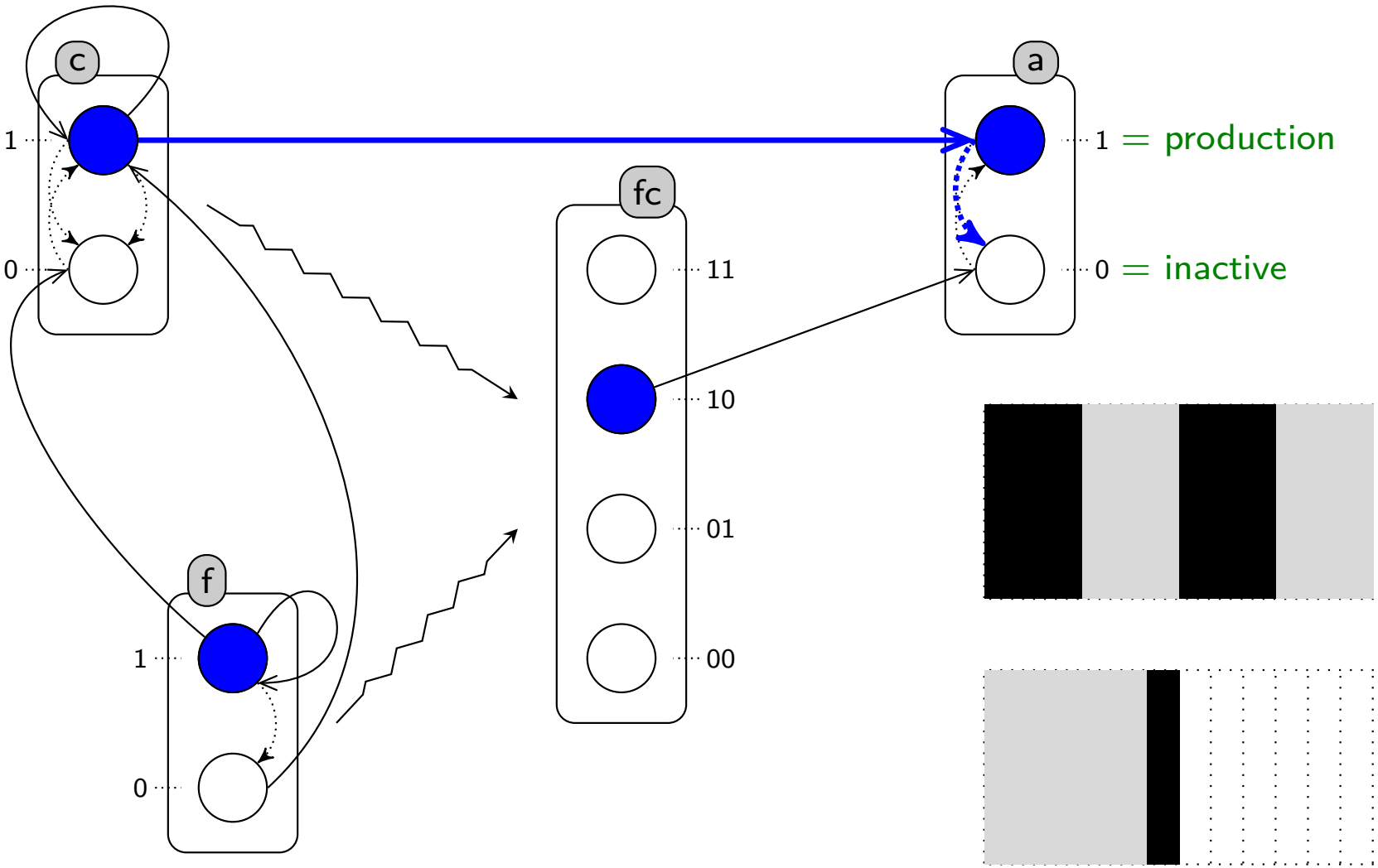

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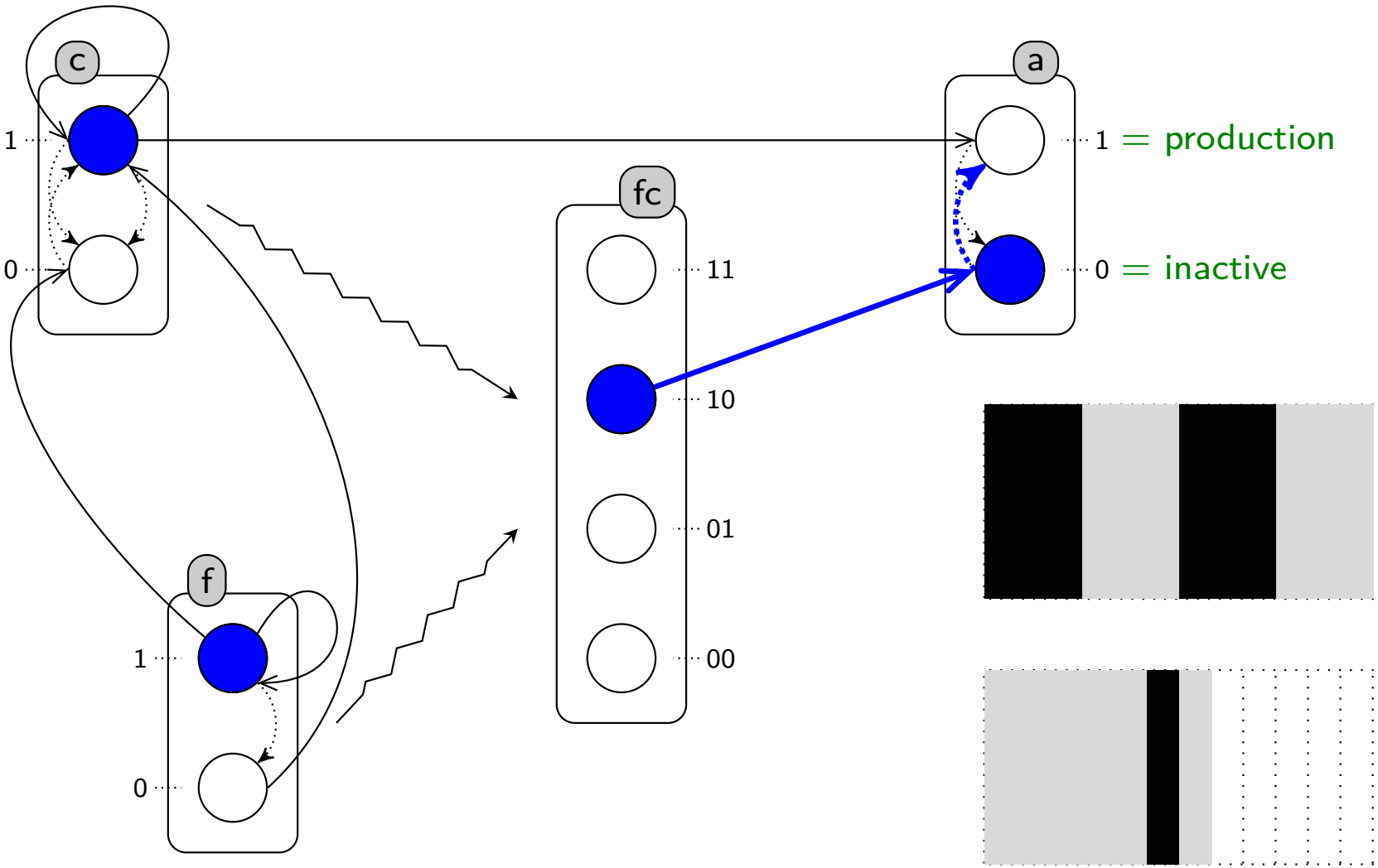

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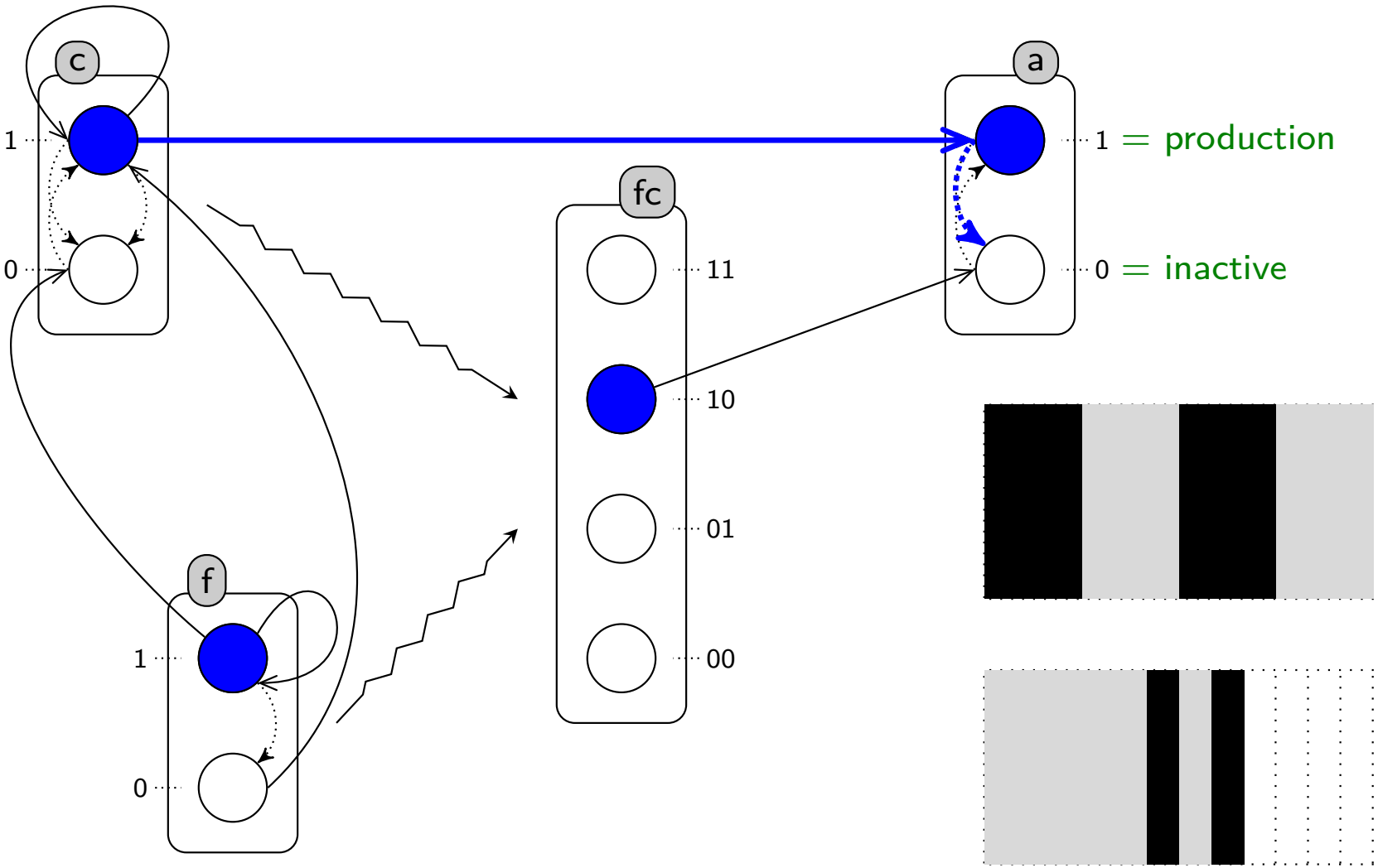

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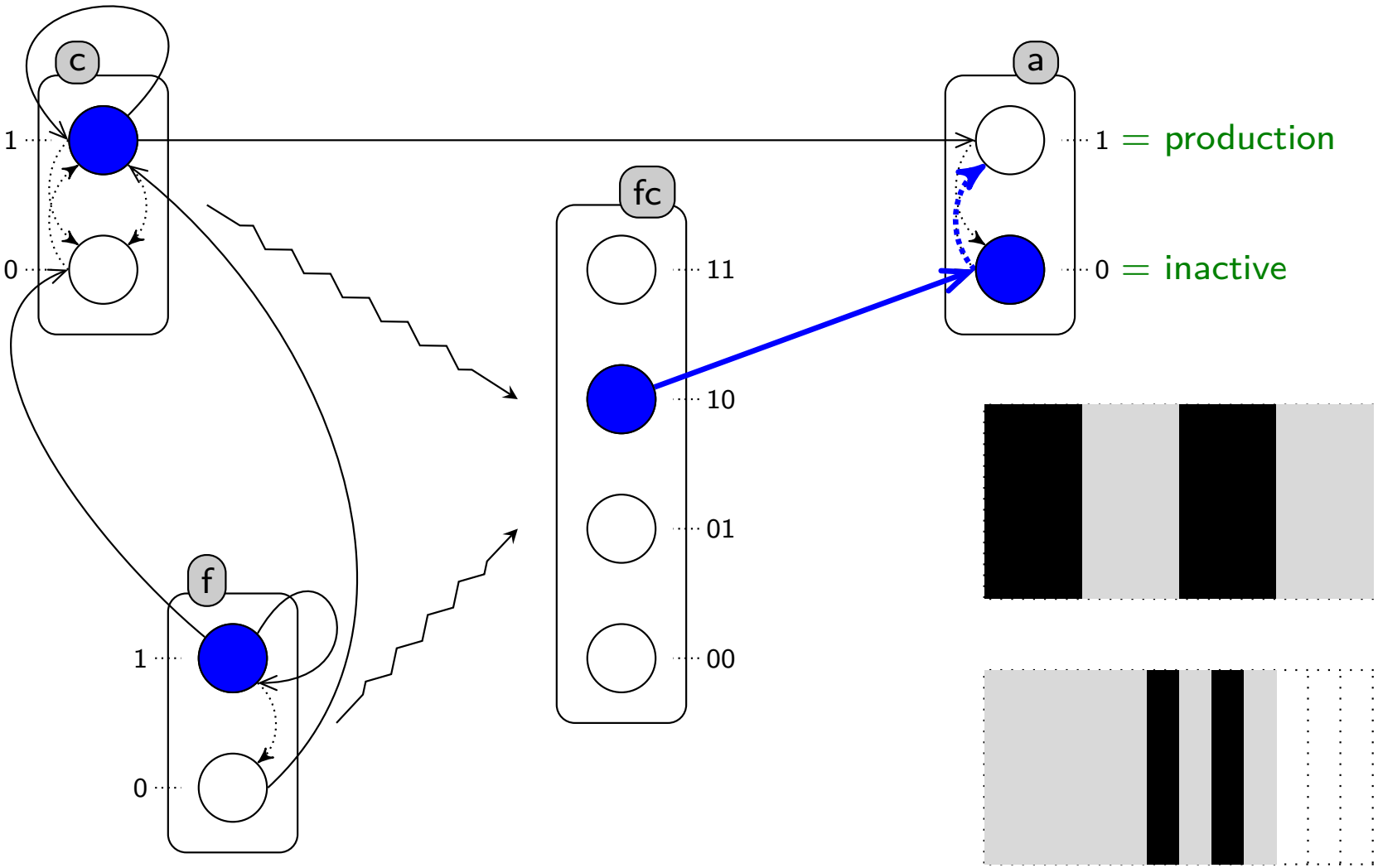

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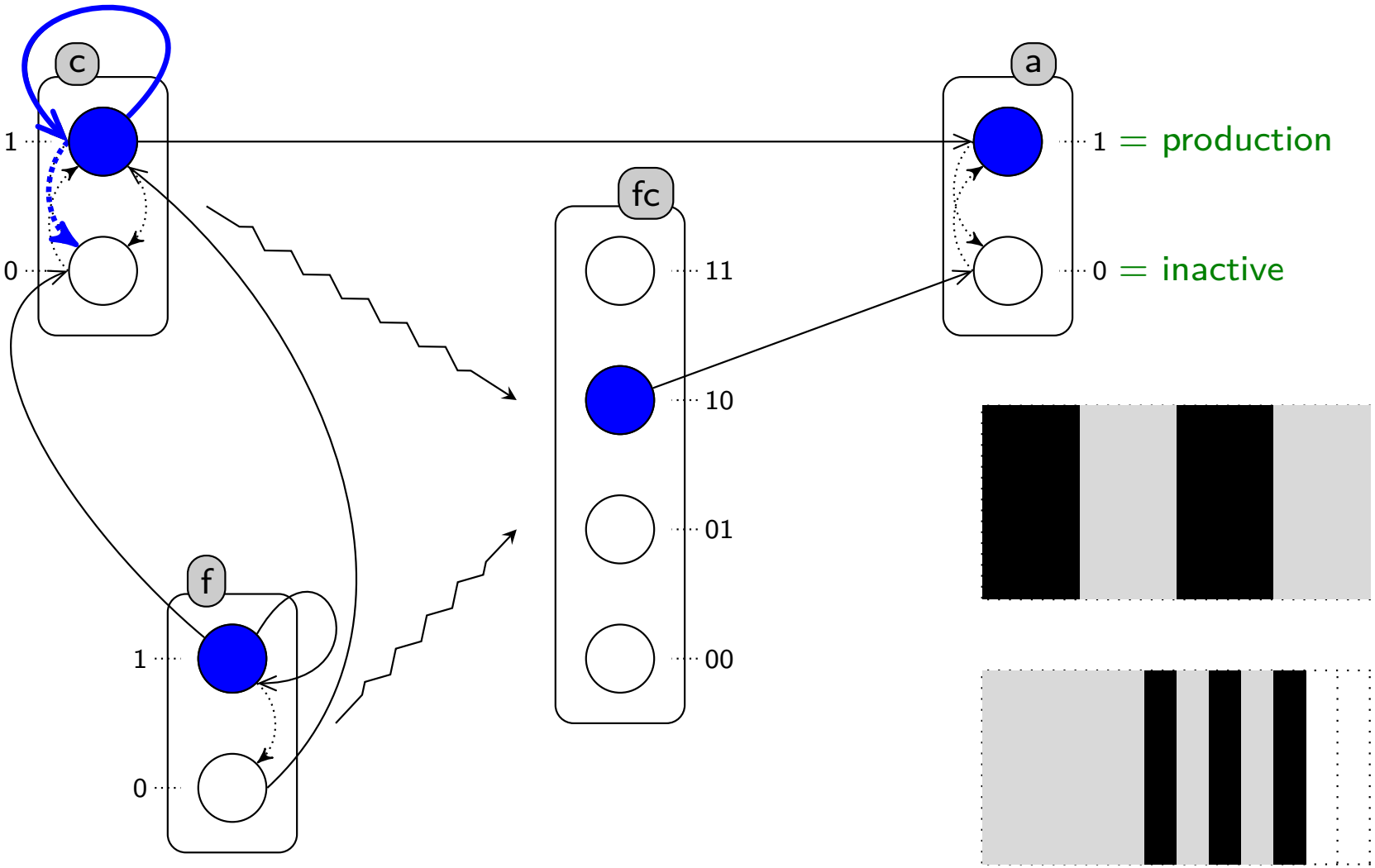

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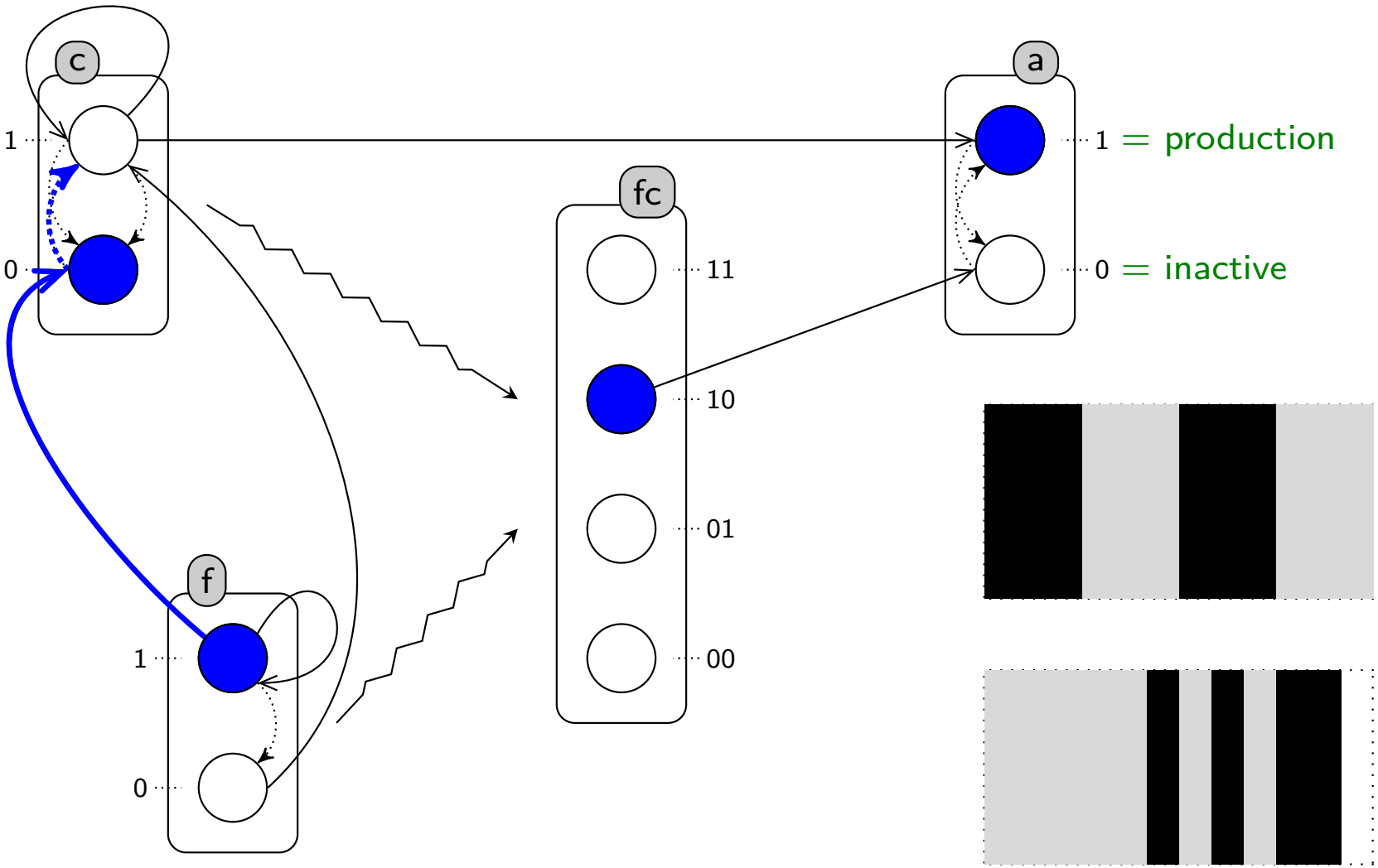

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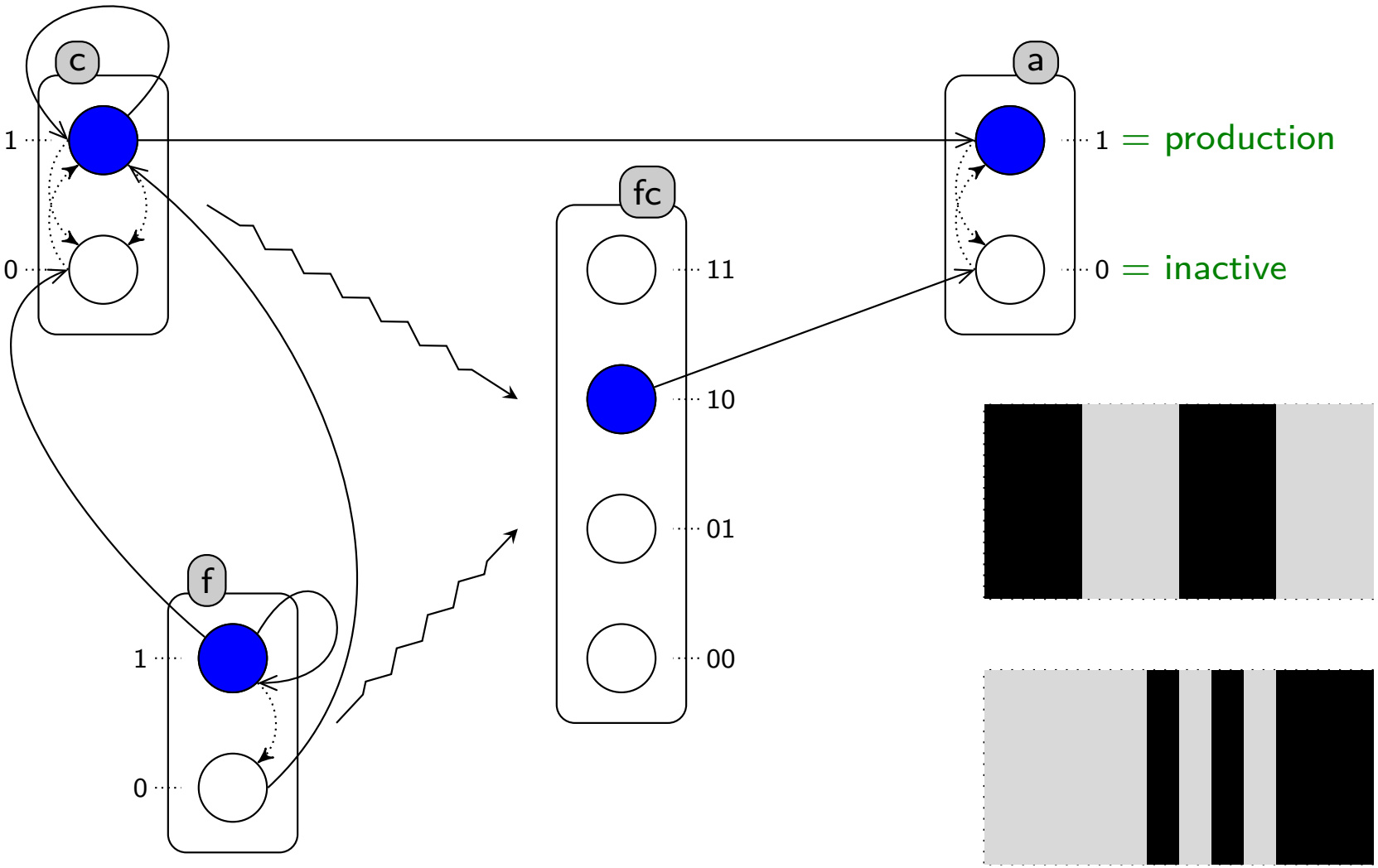
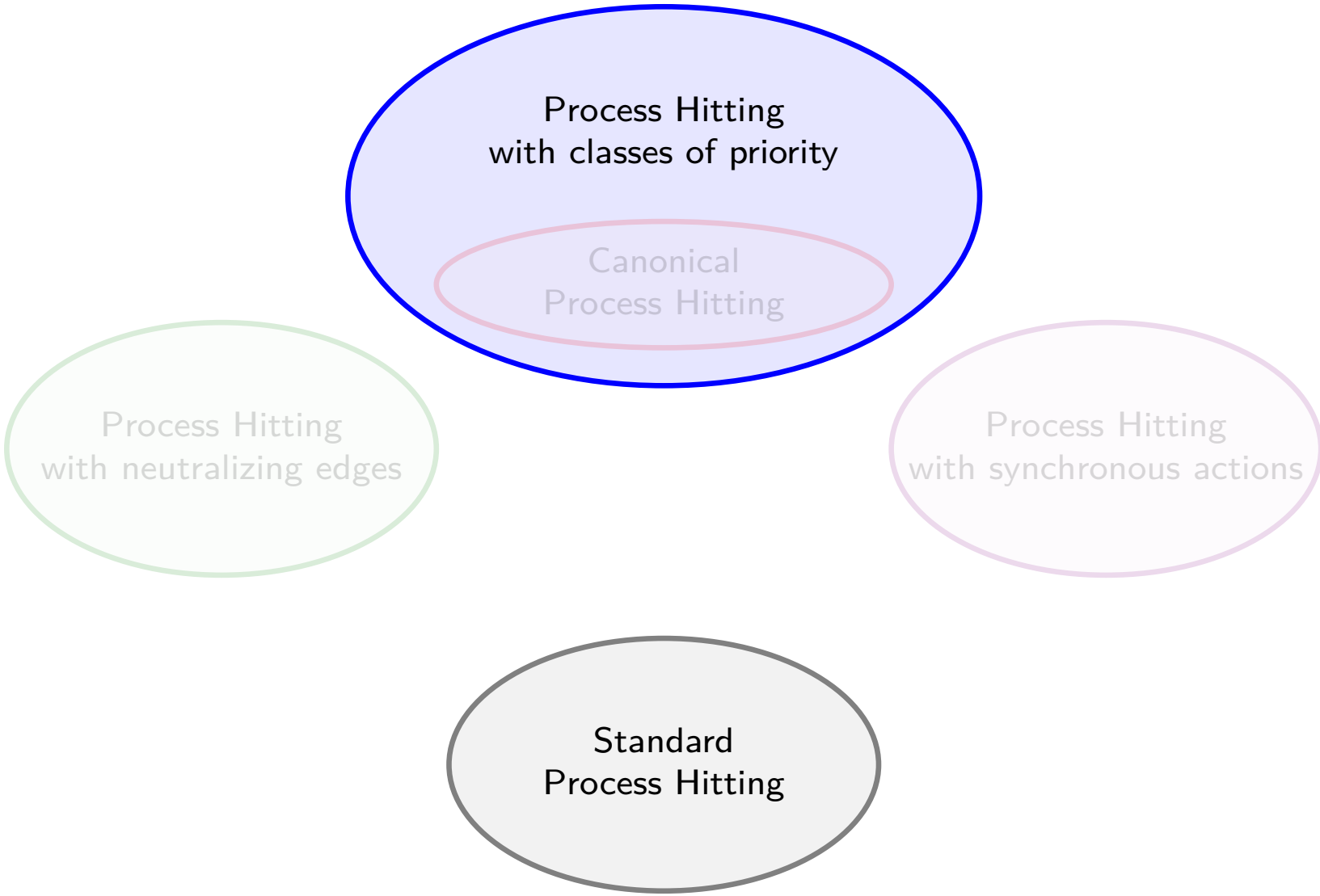


Process Hitting with Classes of Priorities



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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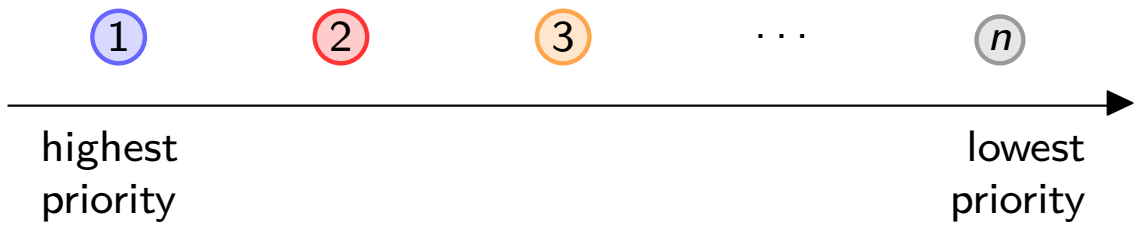

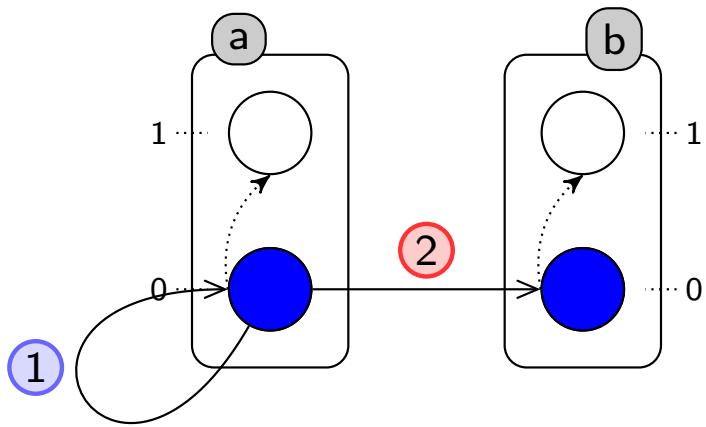

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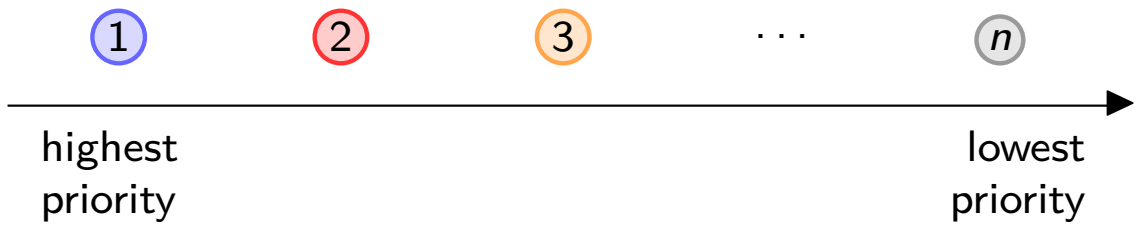

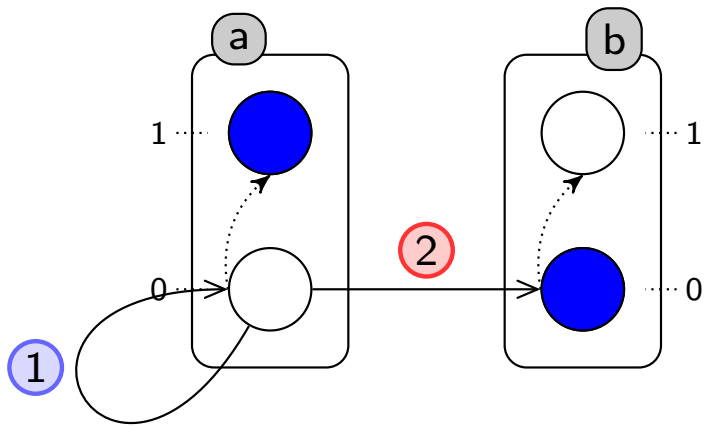

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Use of the Classes of Priorities

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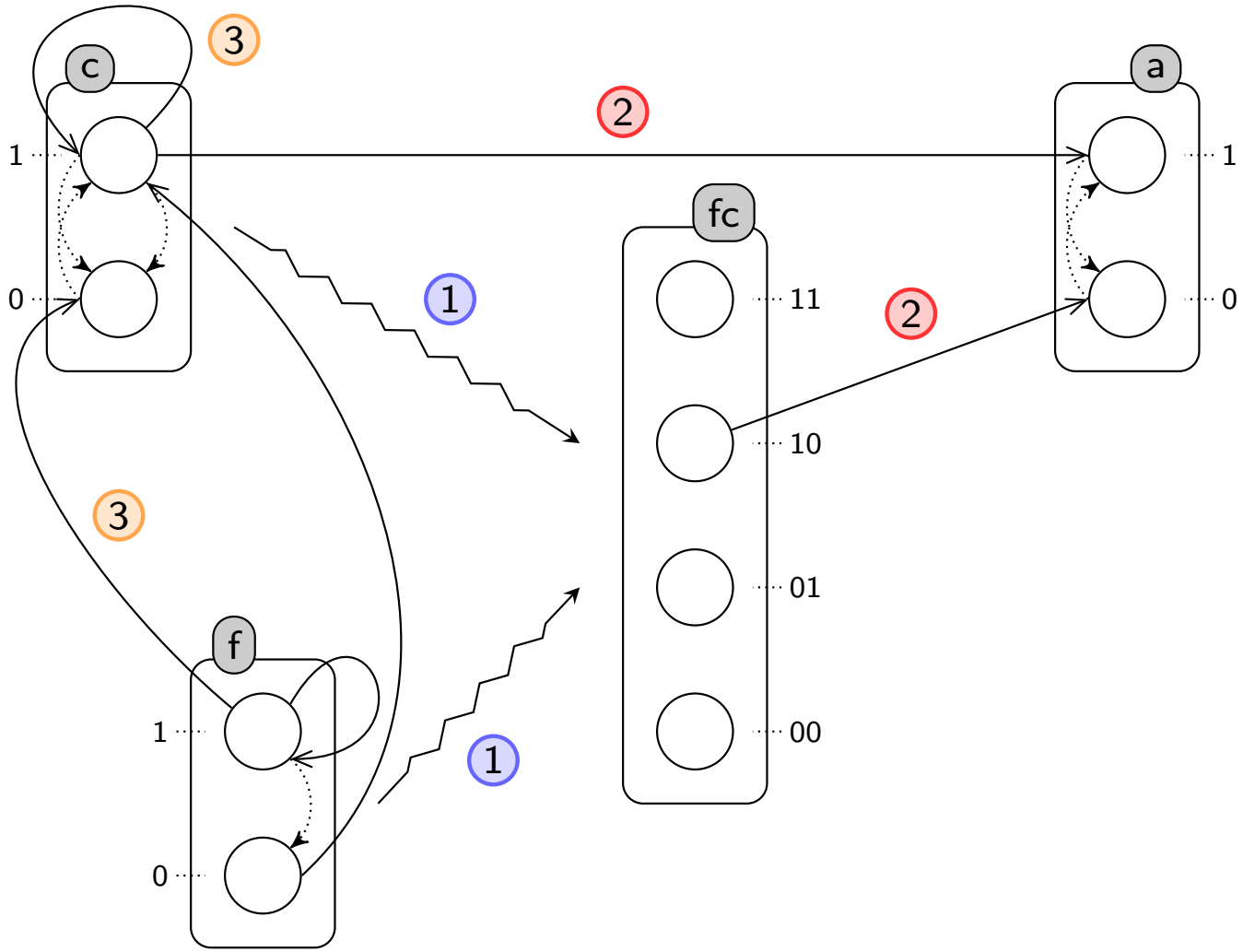

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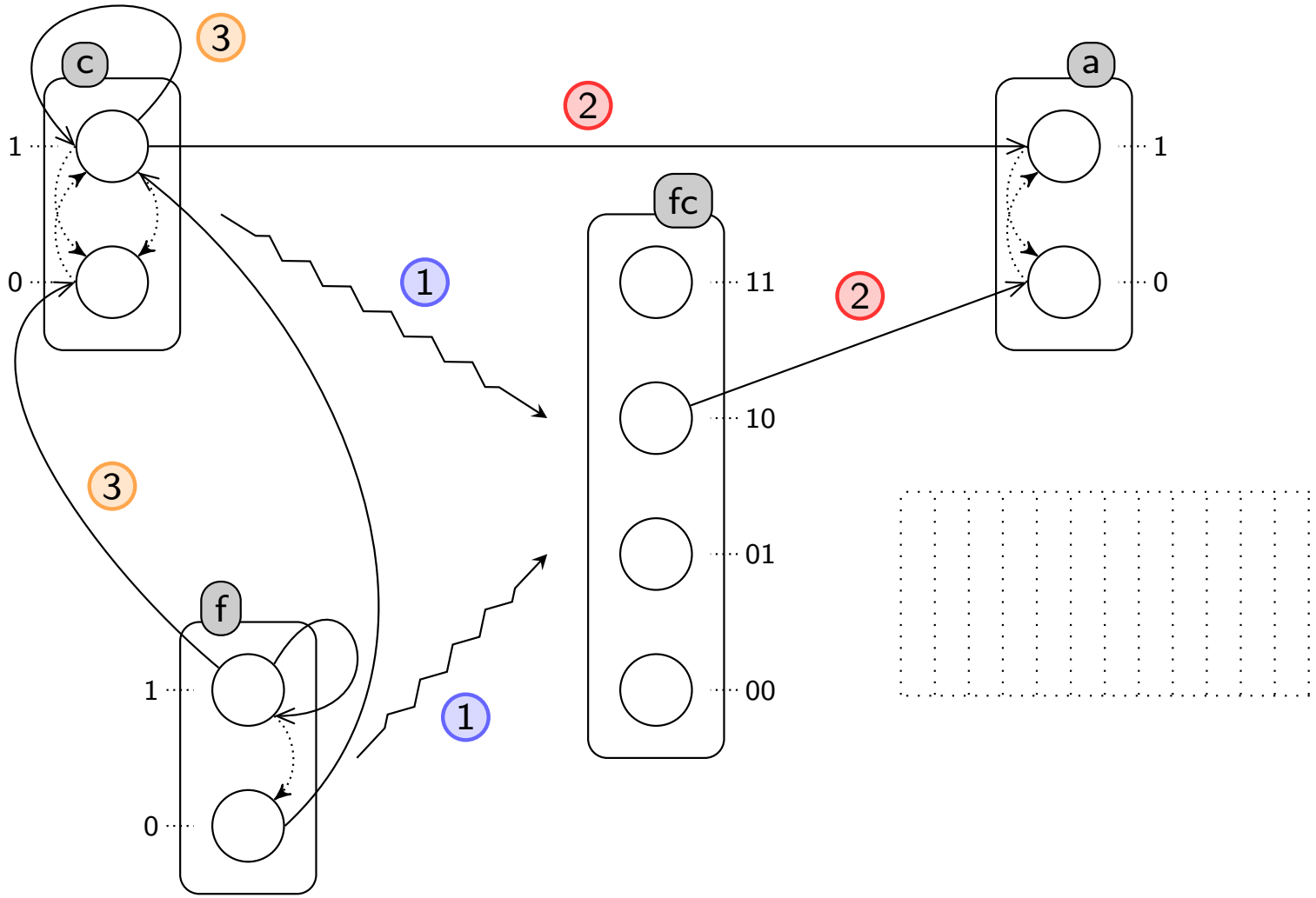

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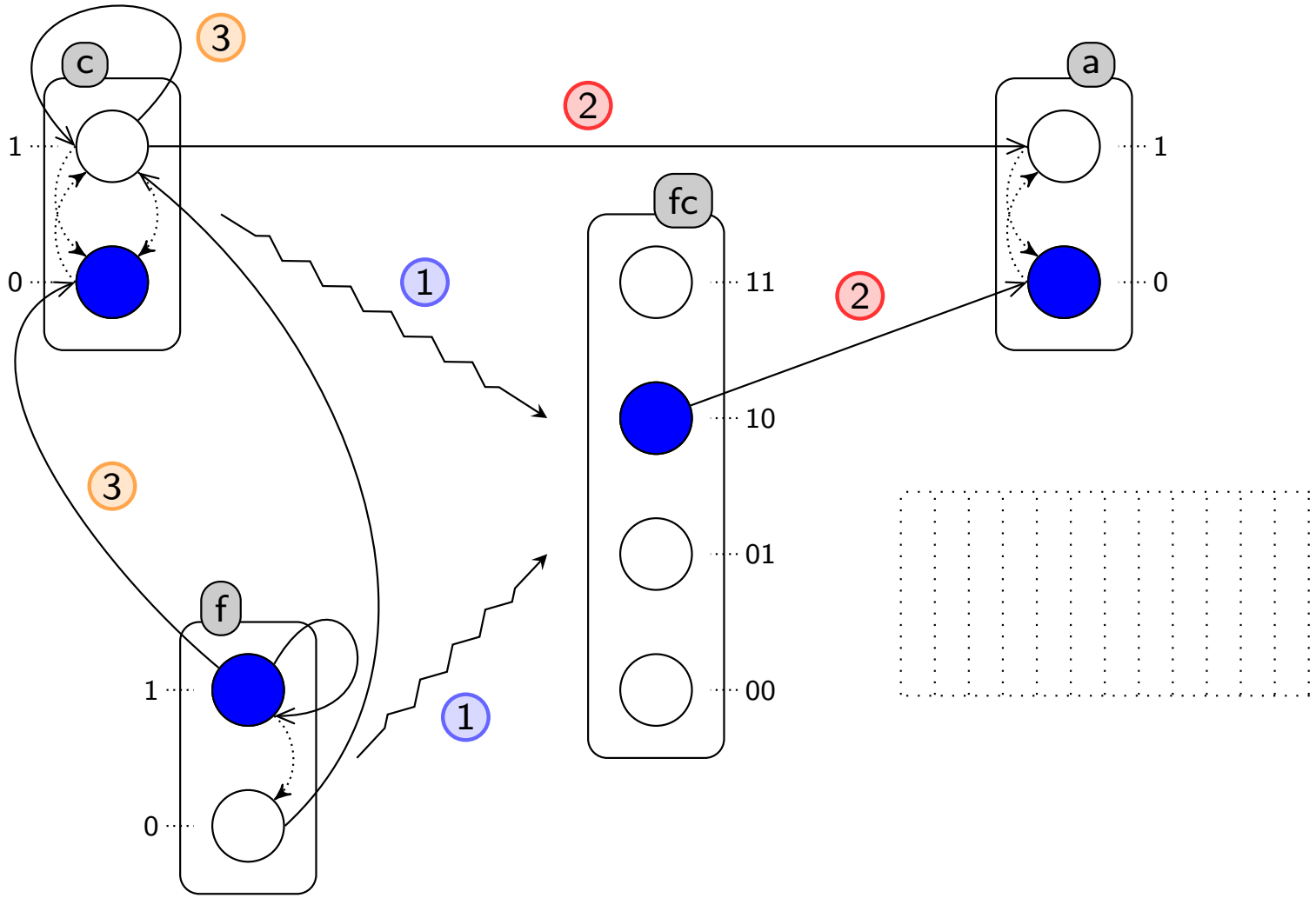

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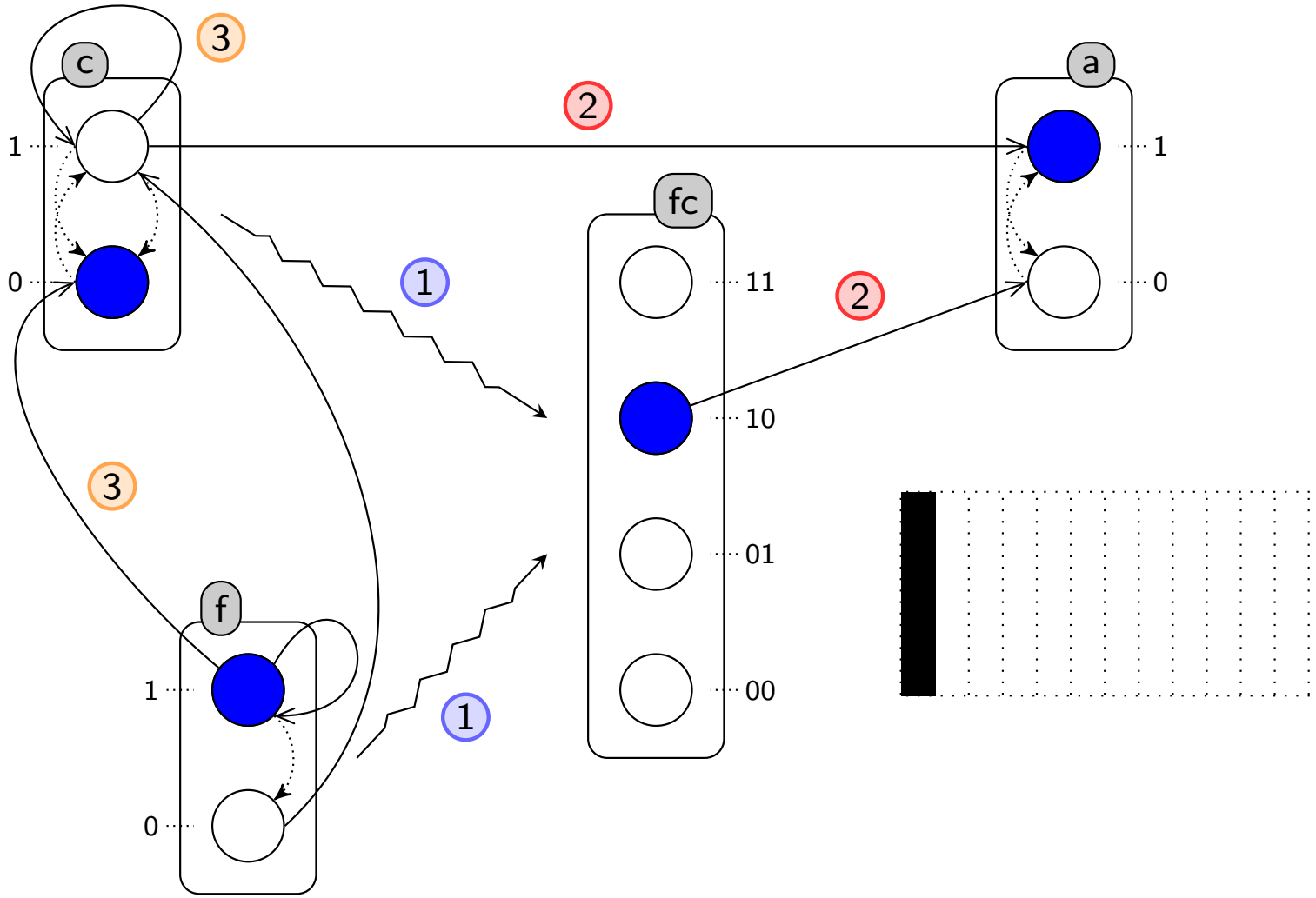

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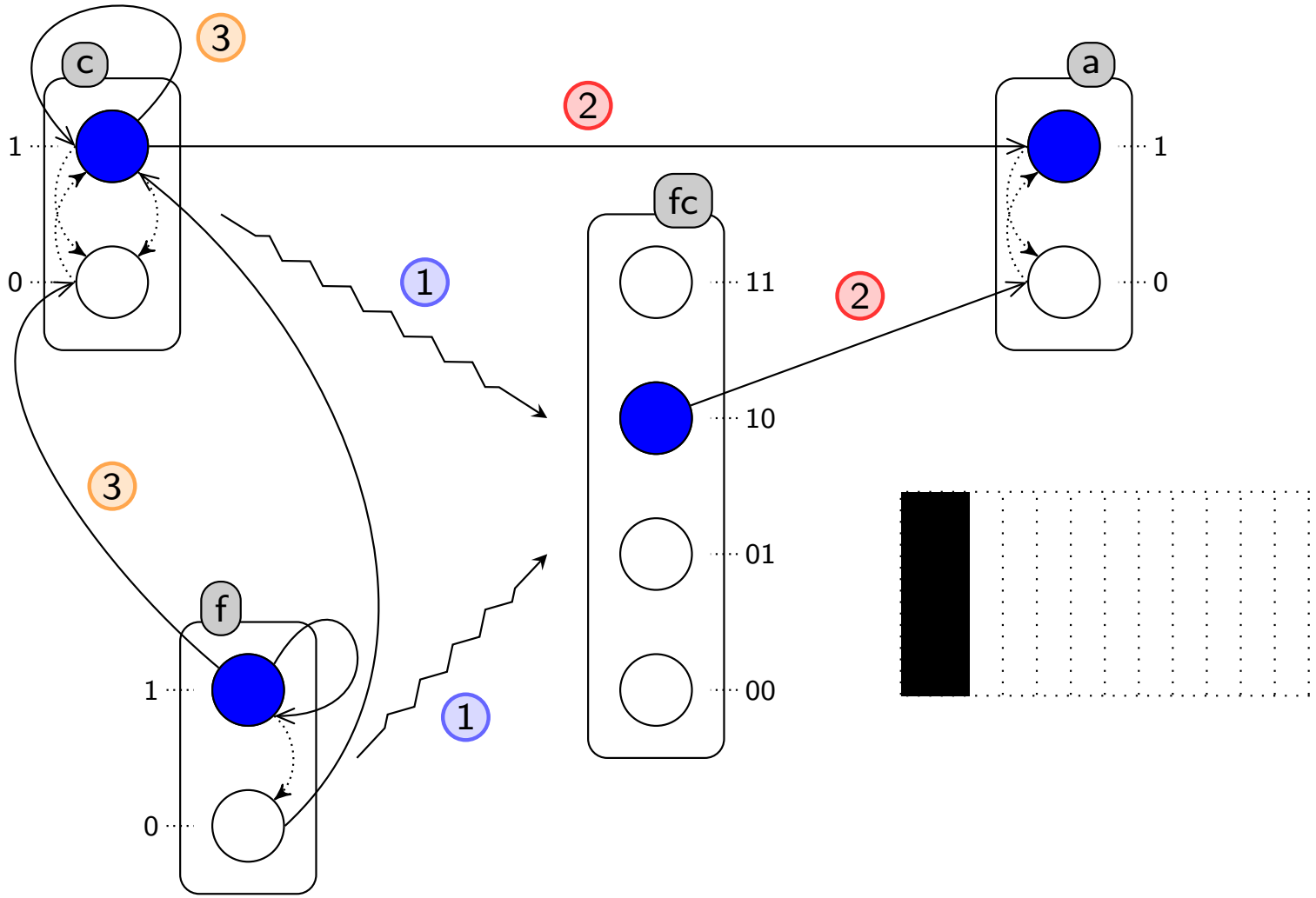

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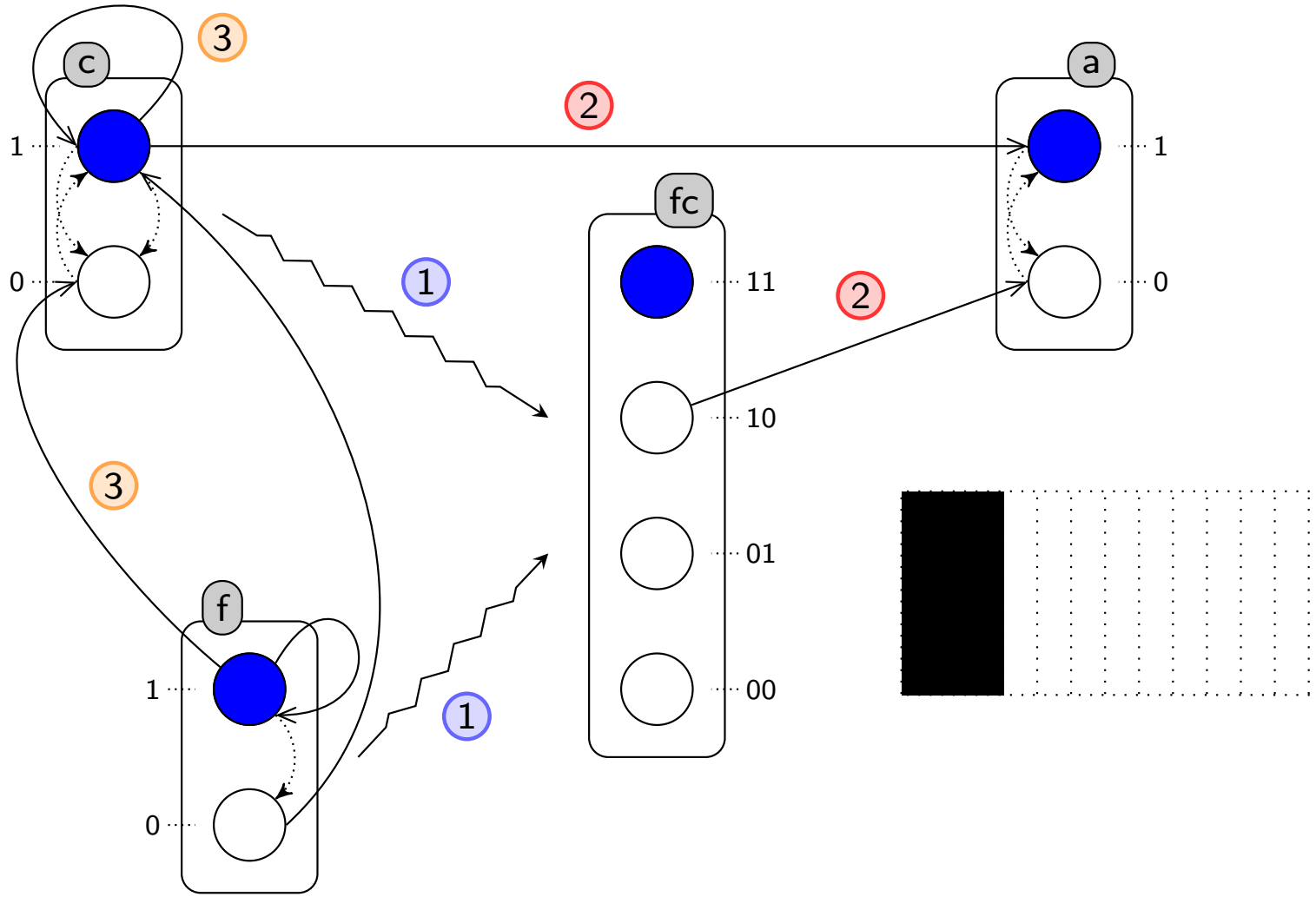

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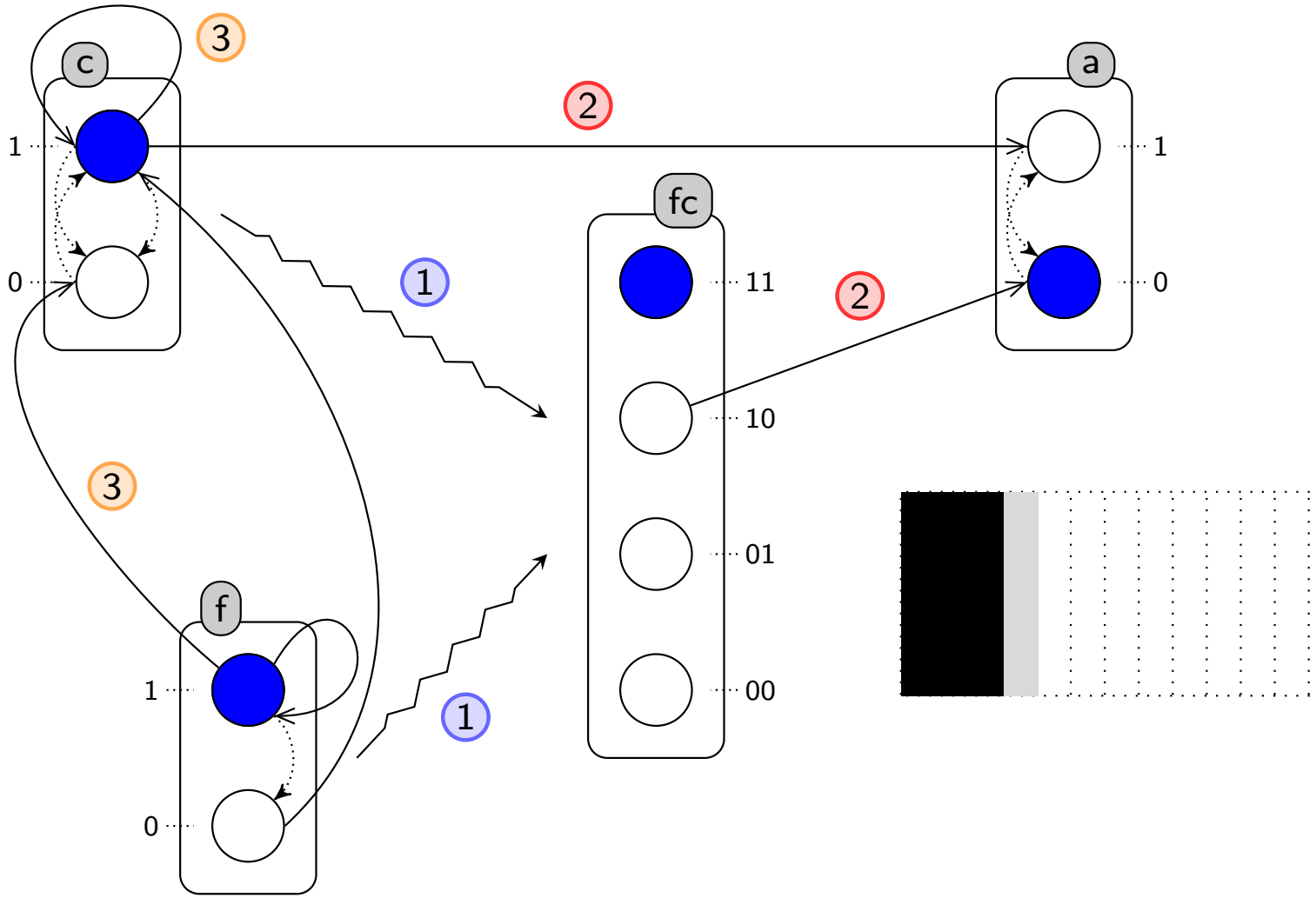

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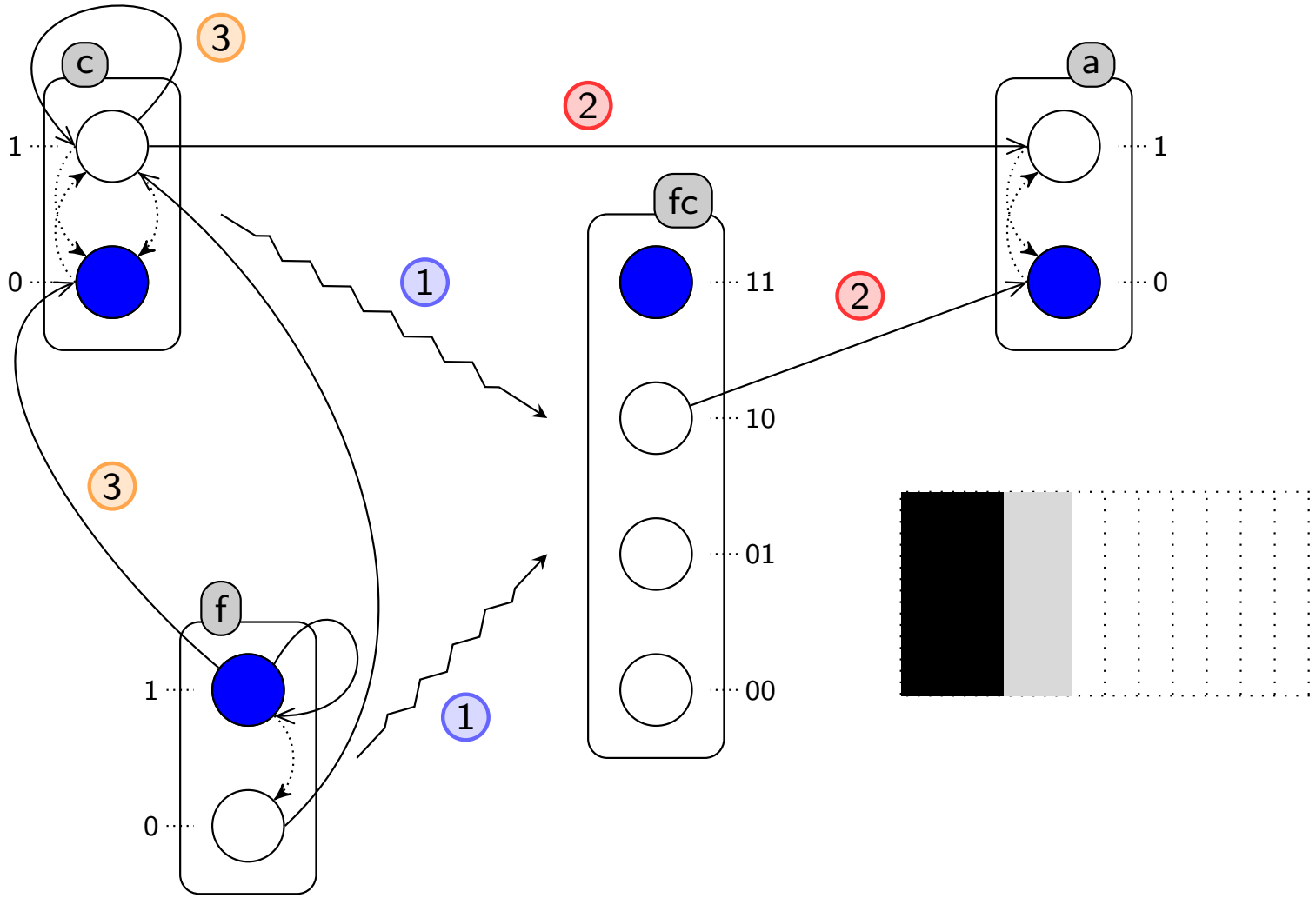

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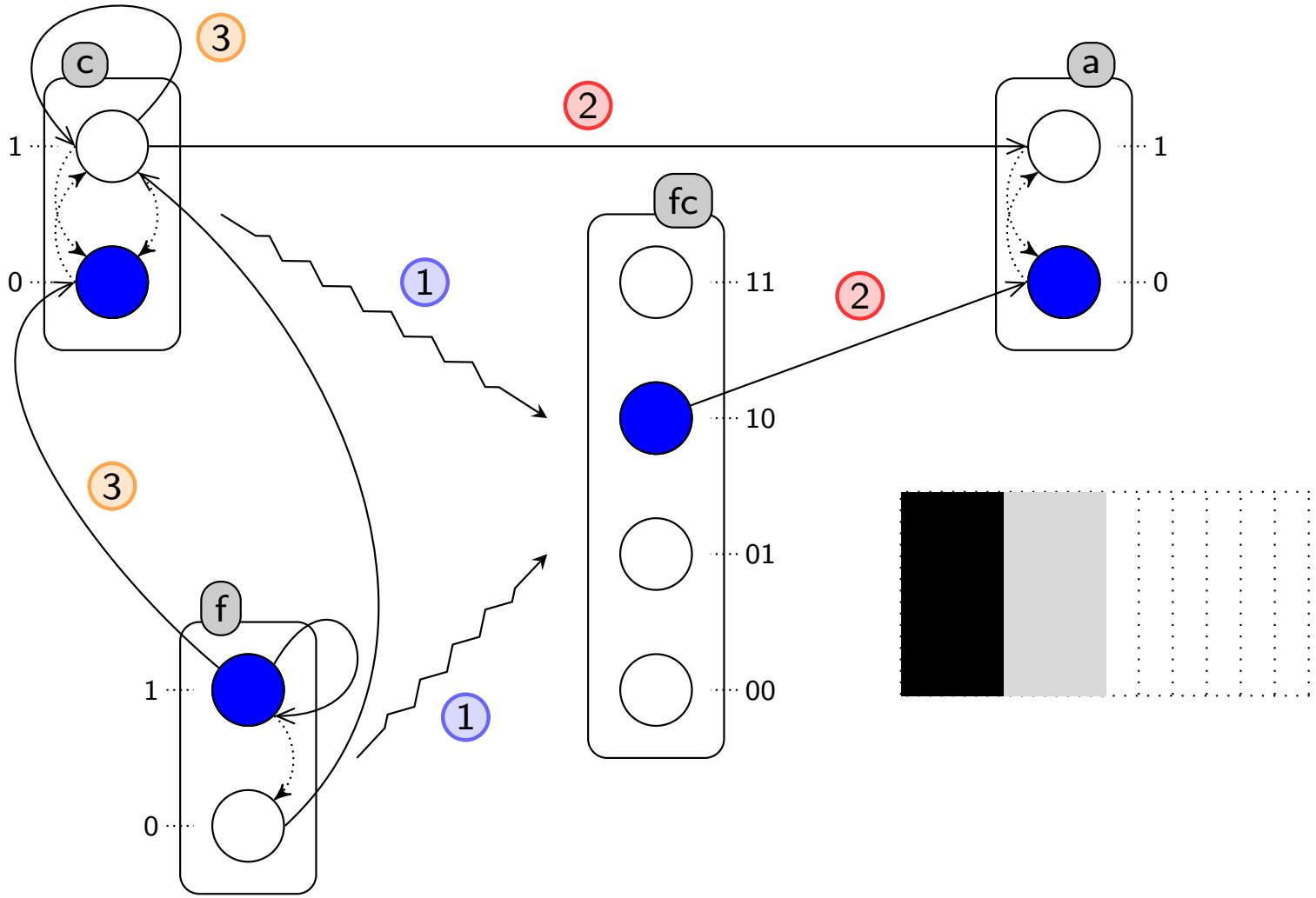

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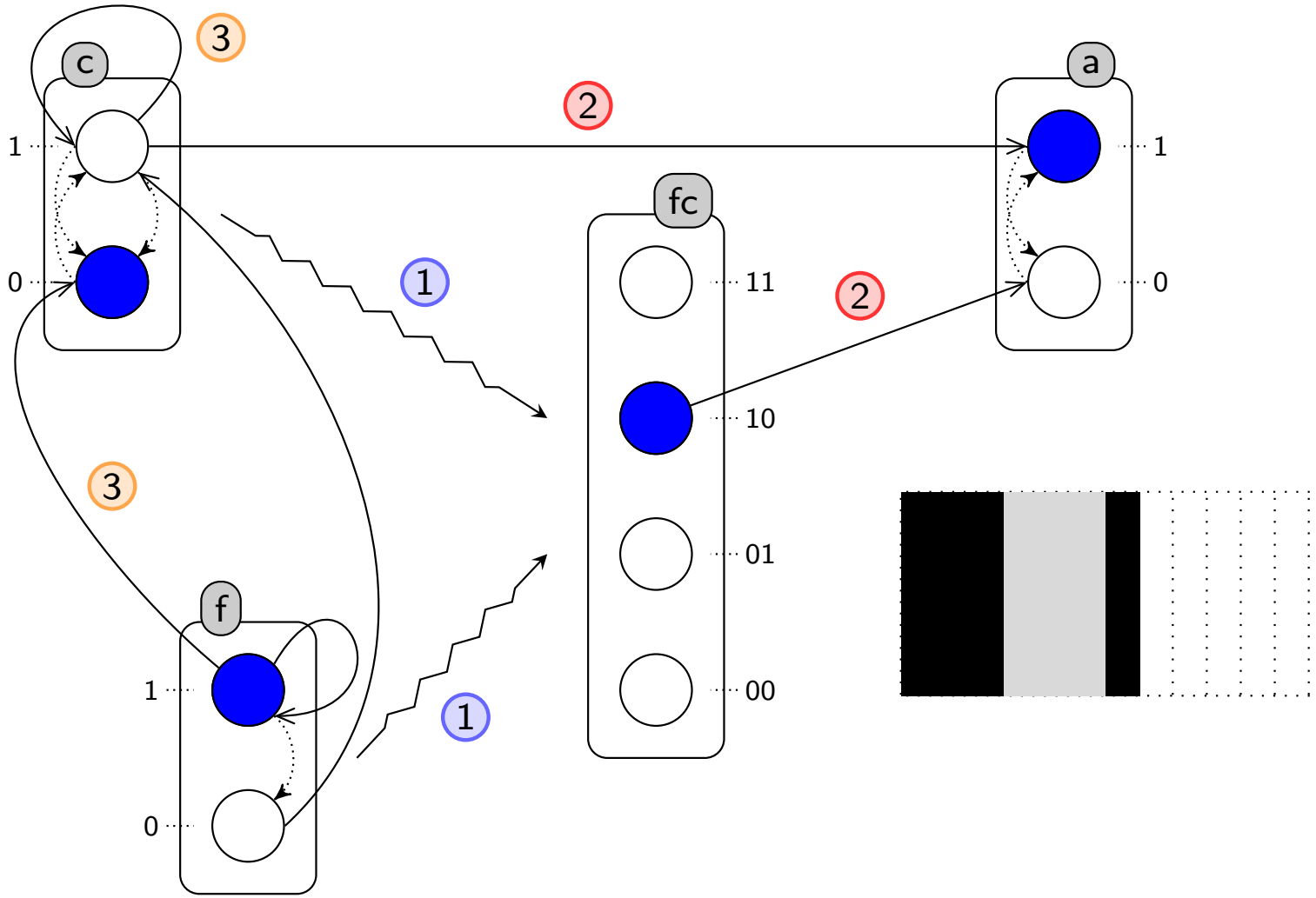

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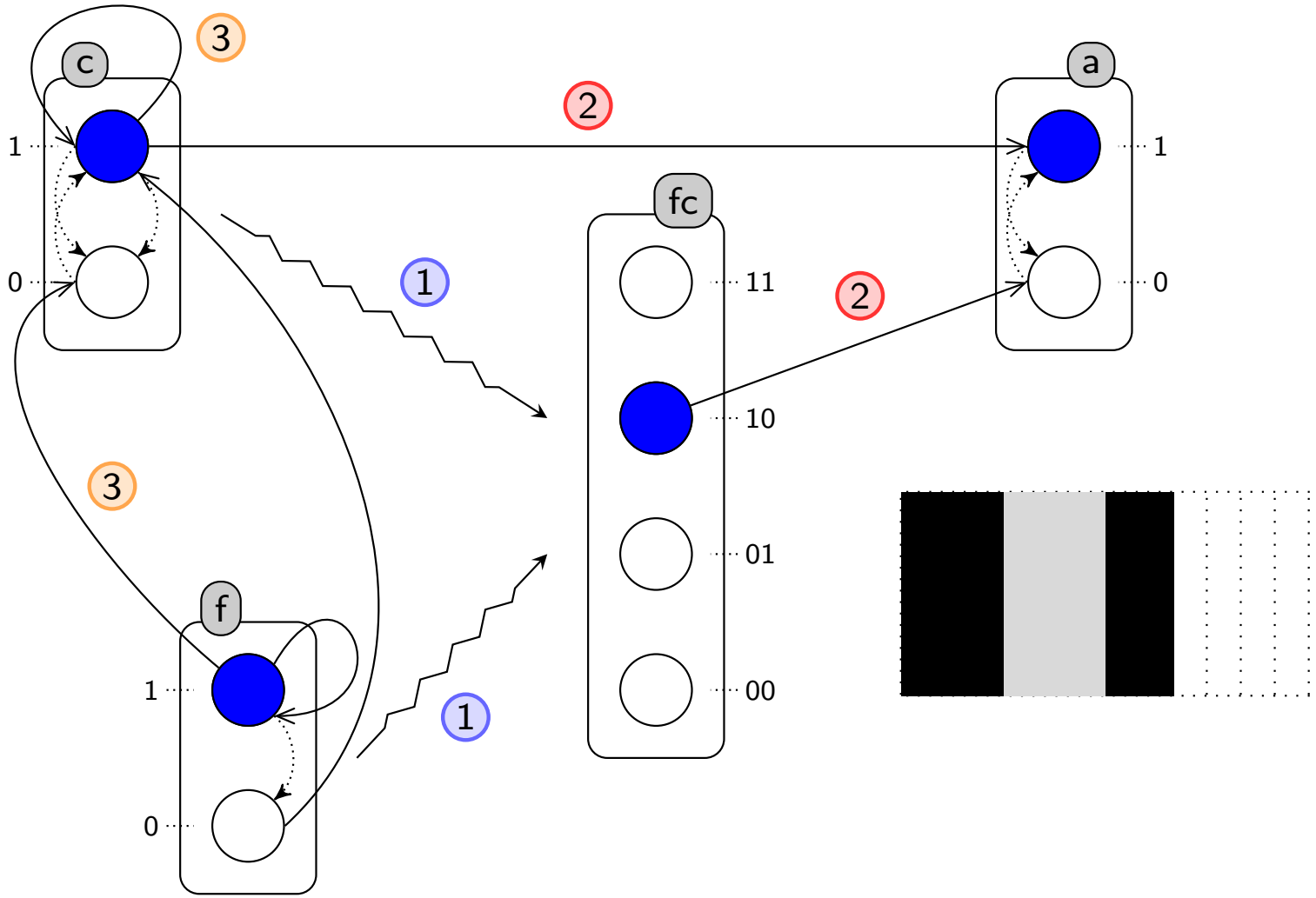

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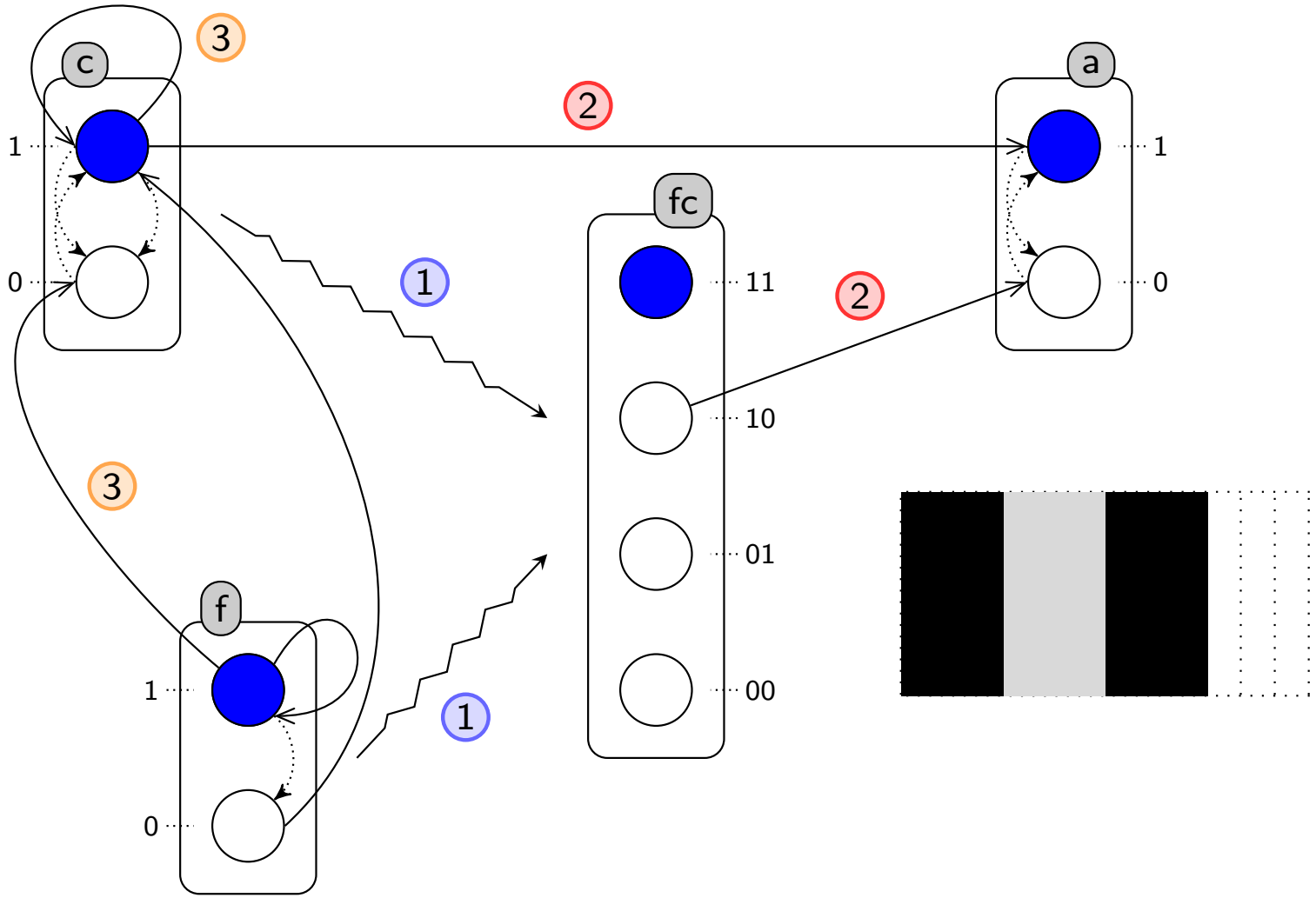

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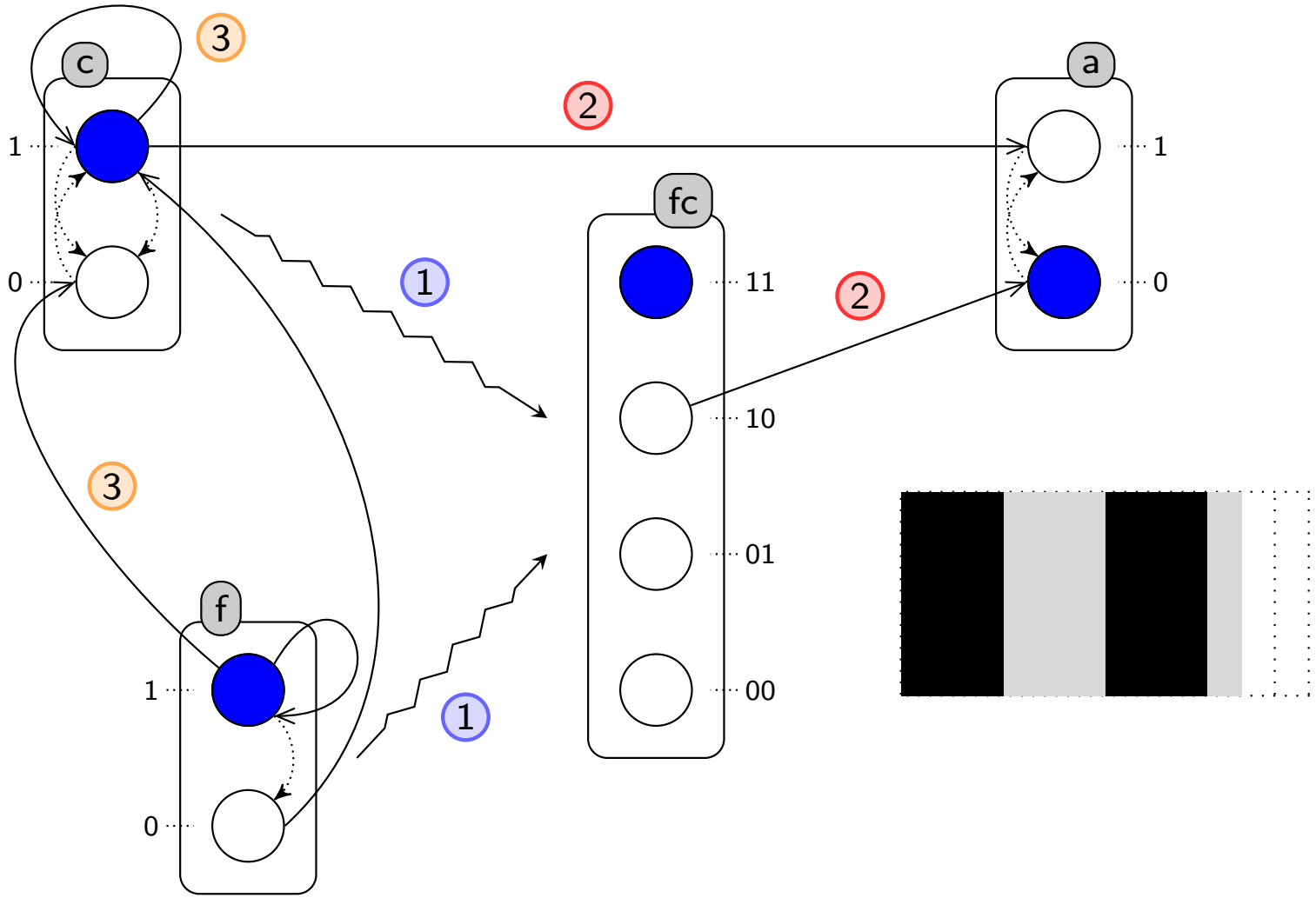

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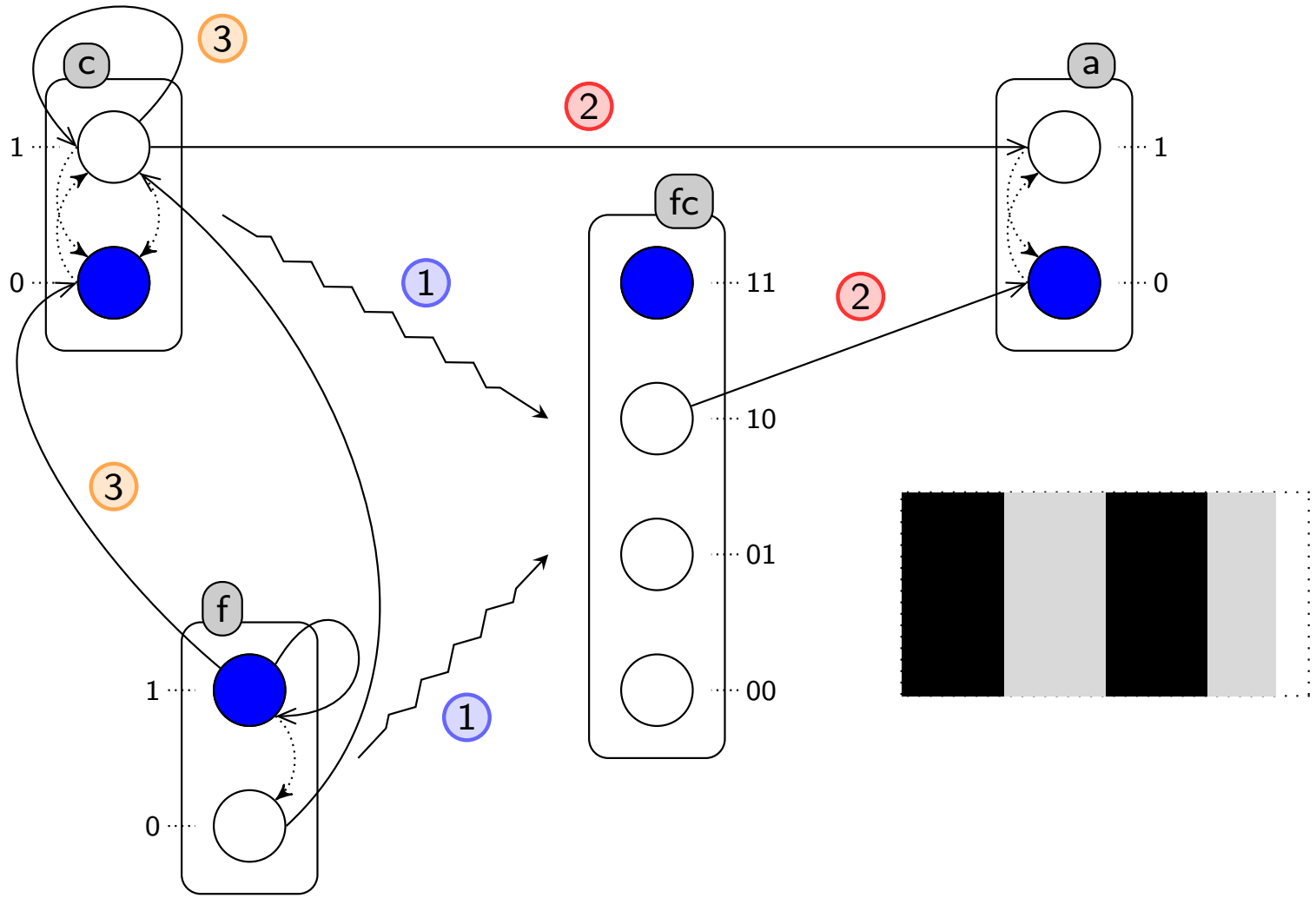

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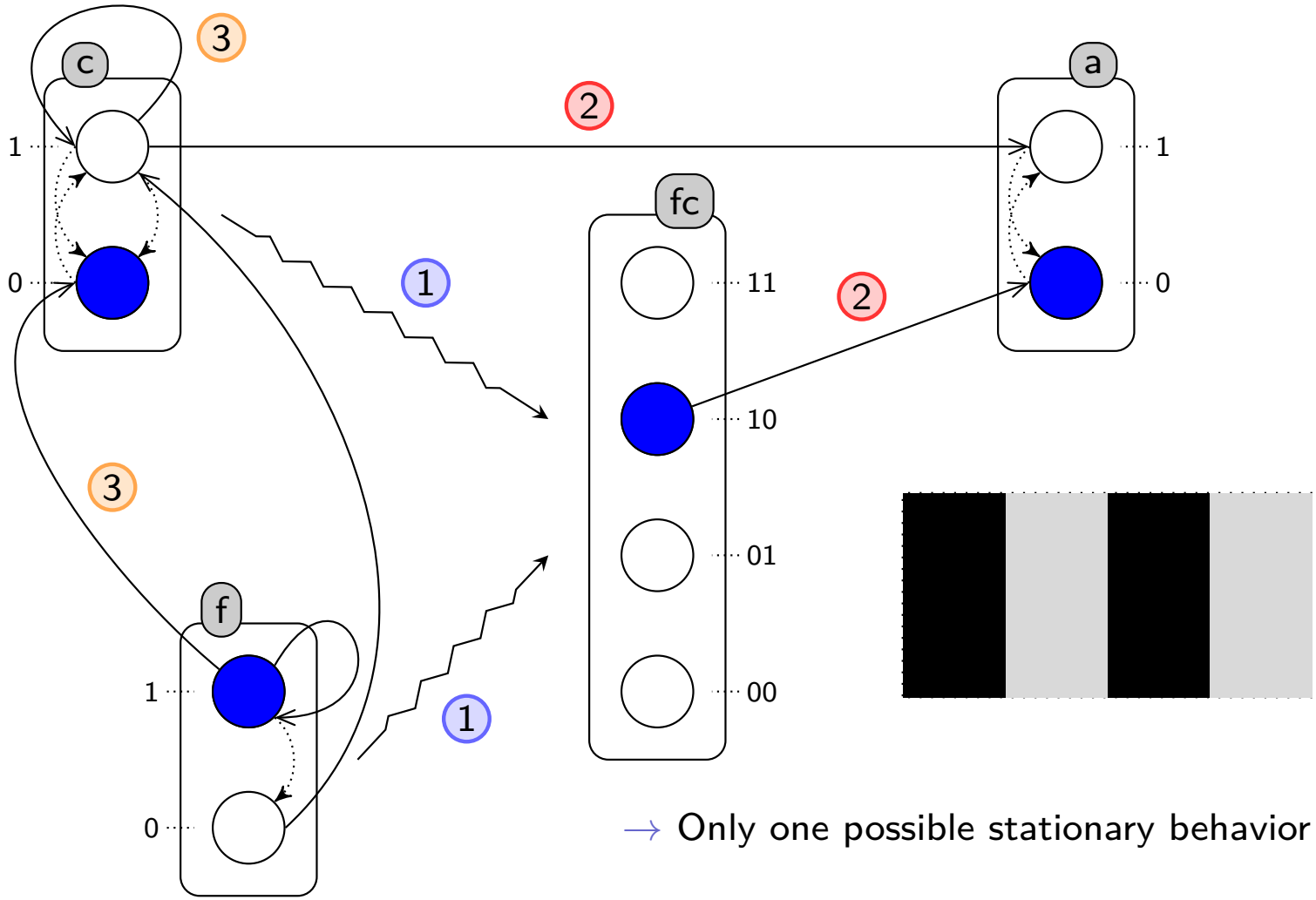
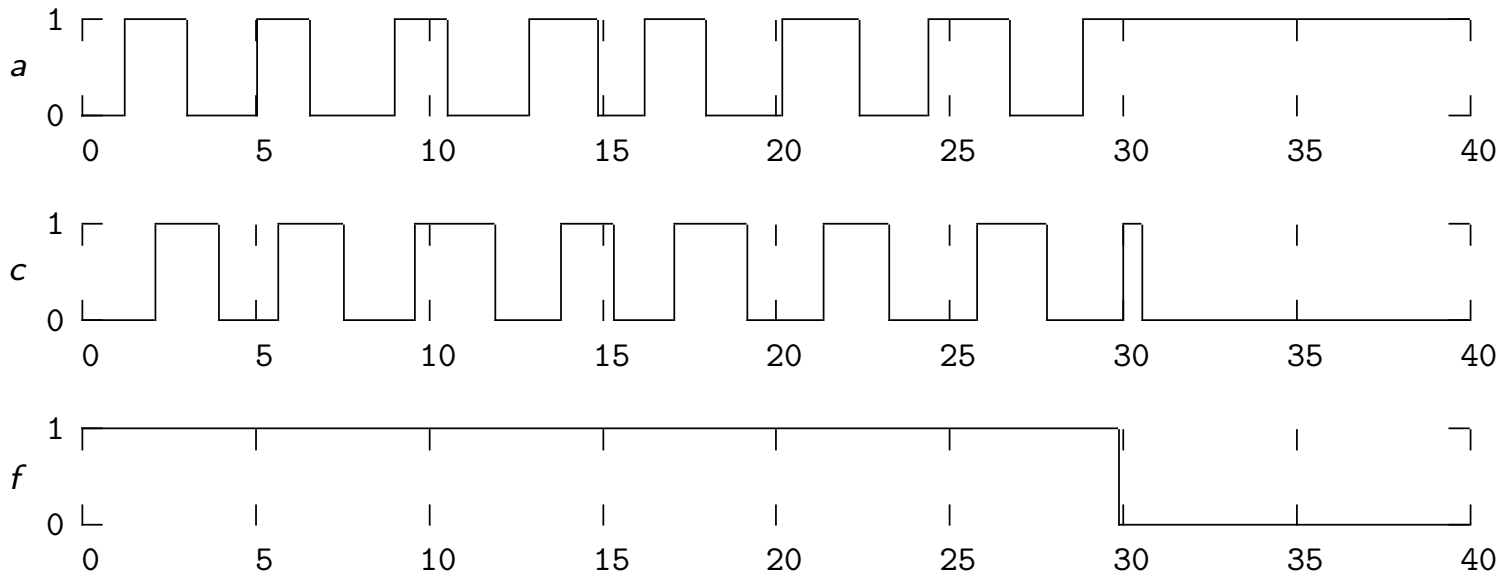


→ Only one possible stationary behavior

Abstraction of Temporal Parameters

[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

Addition of classes of priorities

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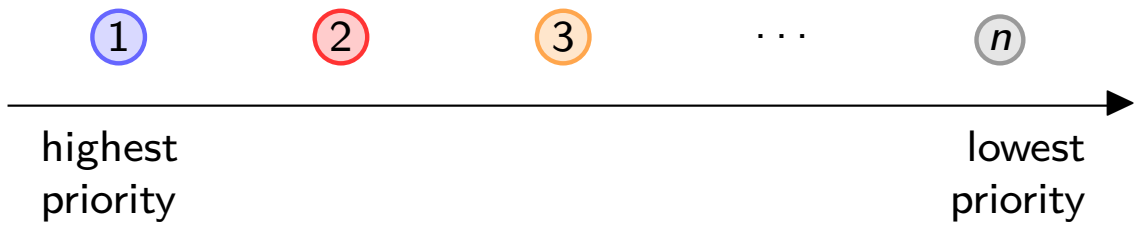
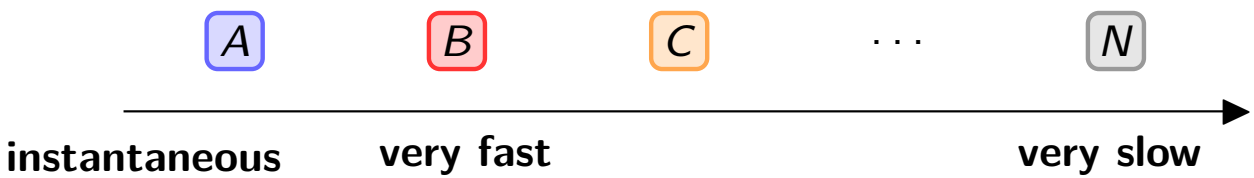


- Allow to model classes of actions with similar speeds or temporal parameters



Limitation of the Classes of Priorities

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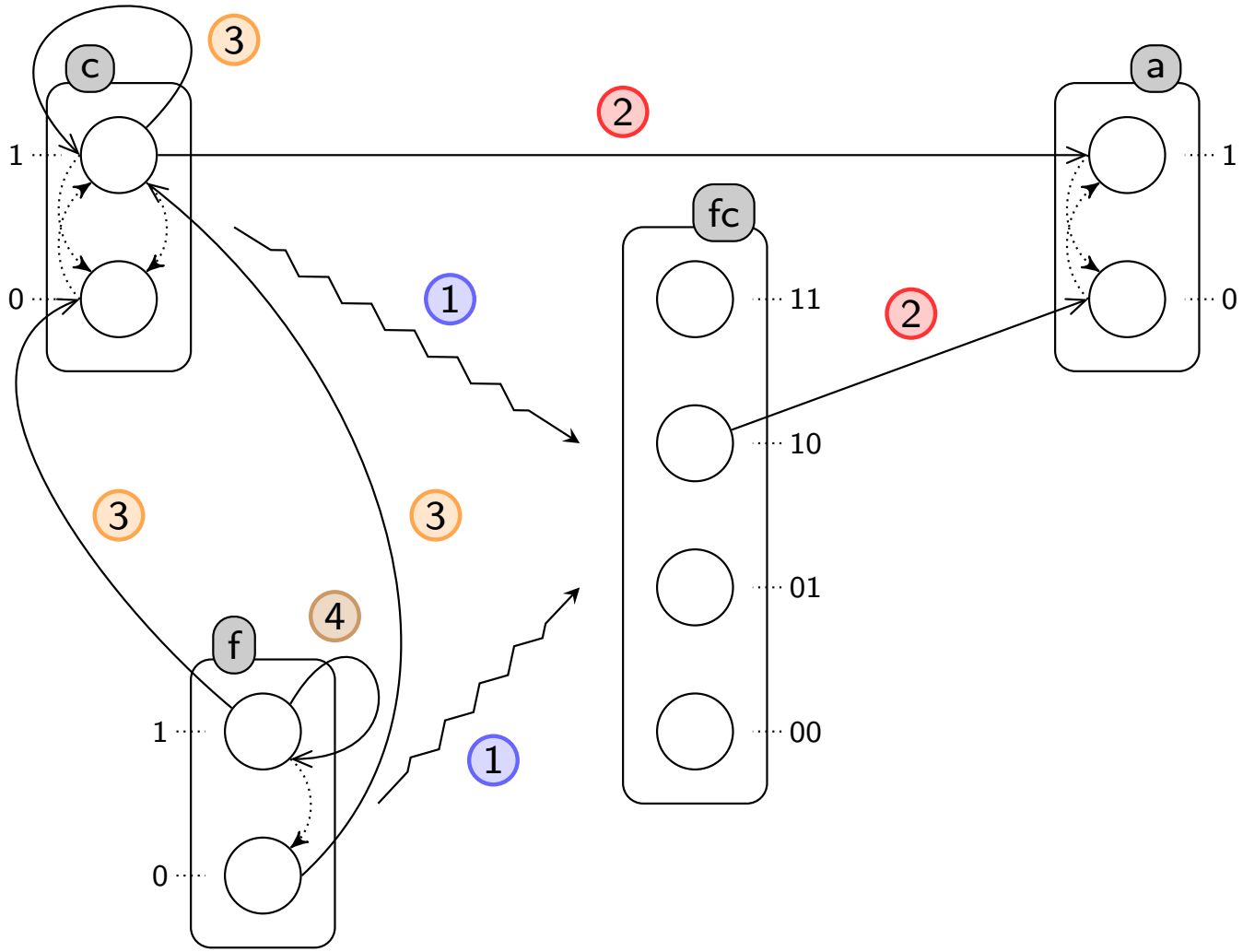

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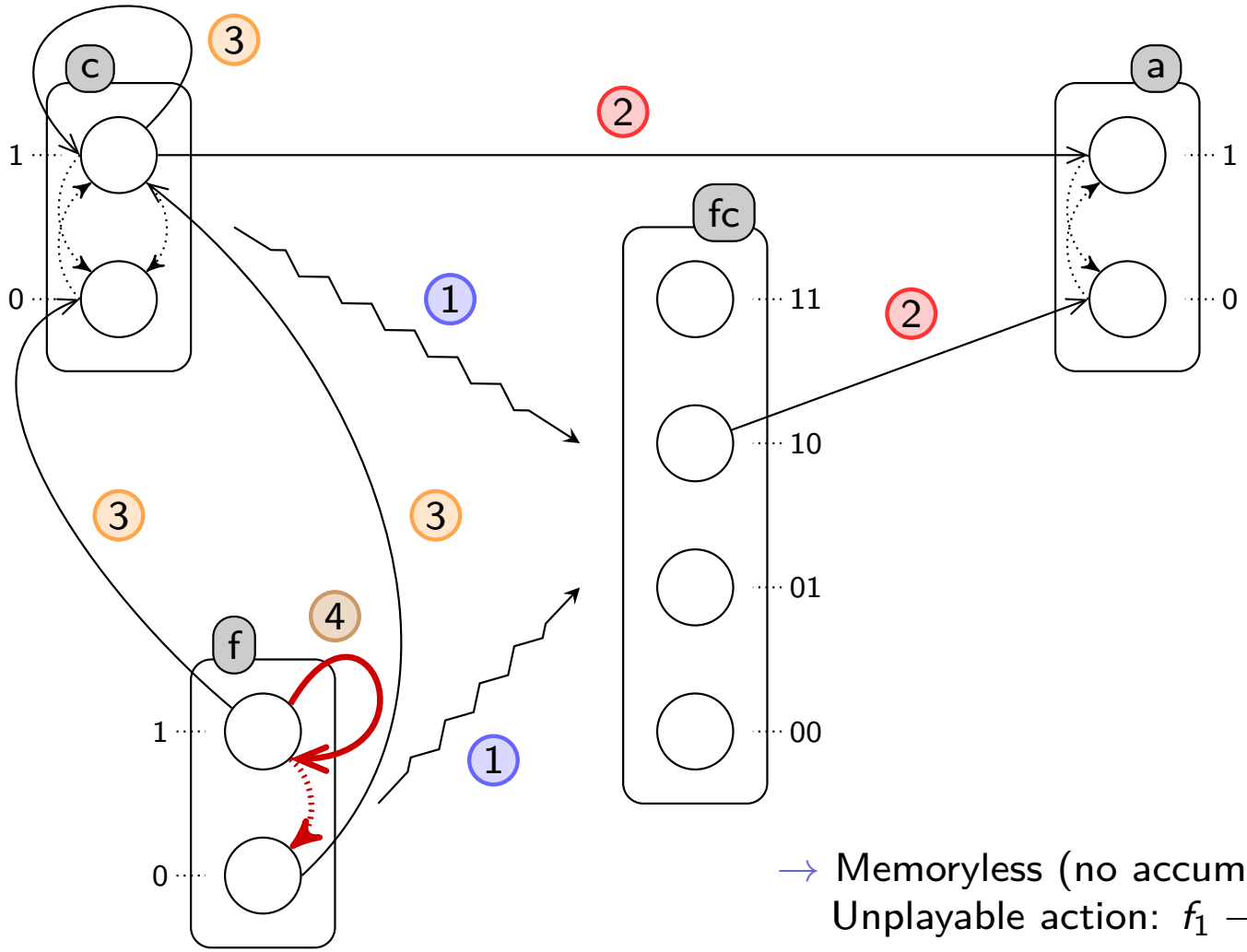

→ Memoryless (no accumulation)
Unplayable action: $f_1 \rightarrow f_1 \not\vdash f_0$

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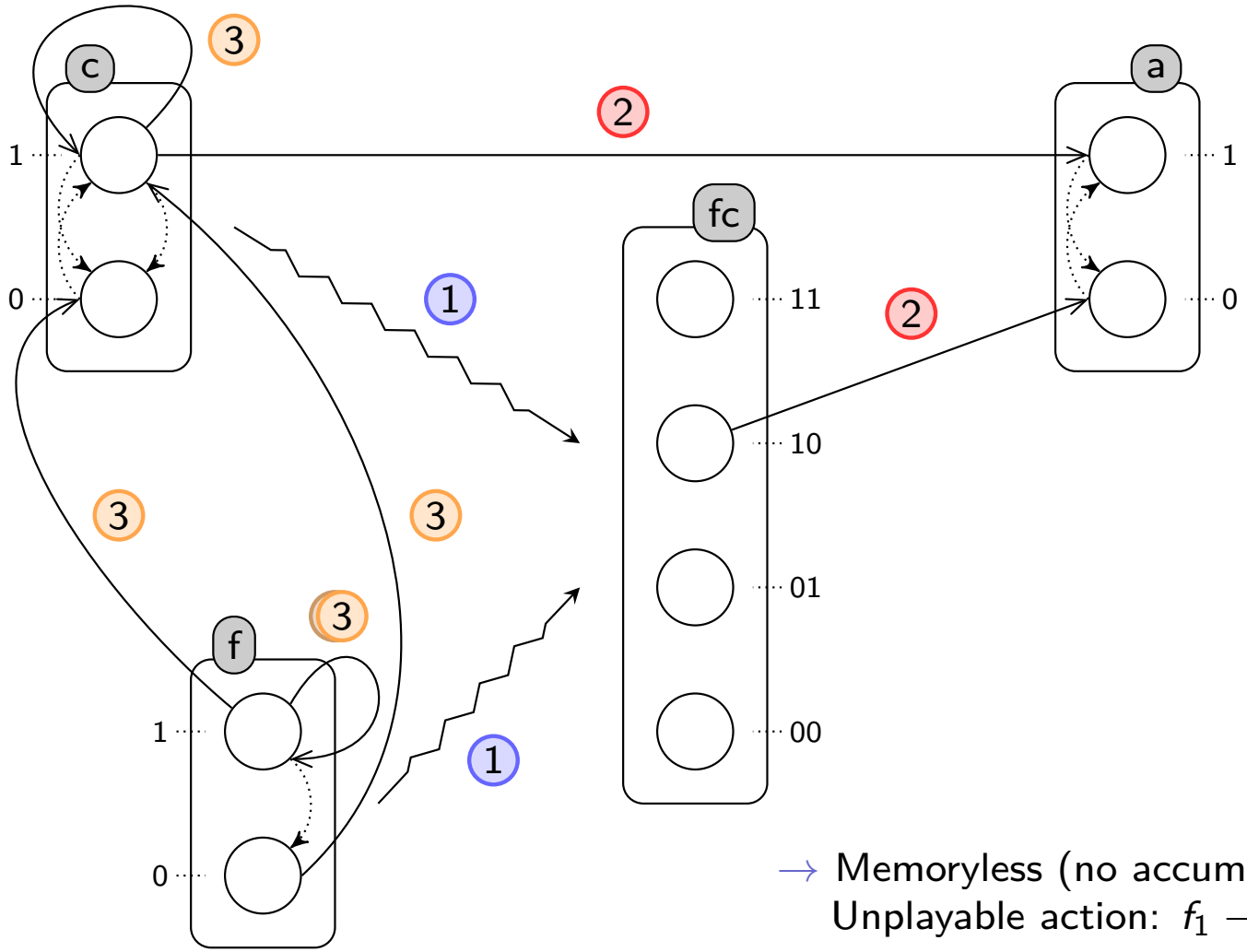

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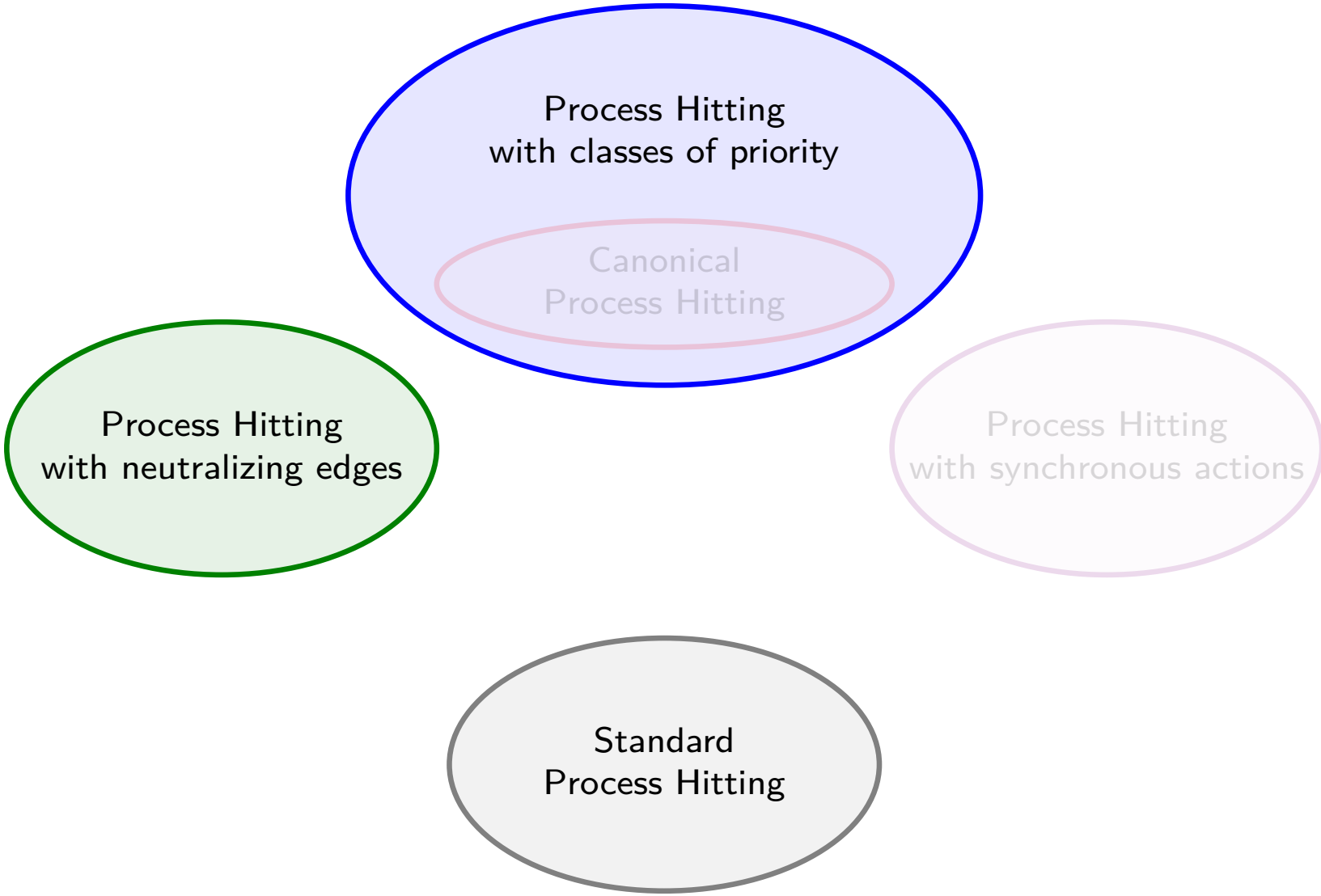
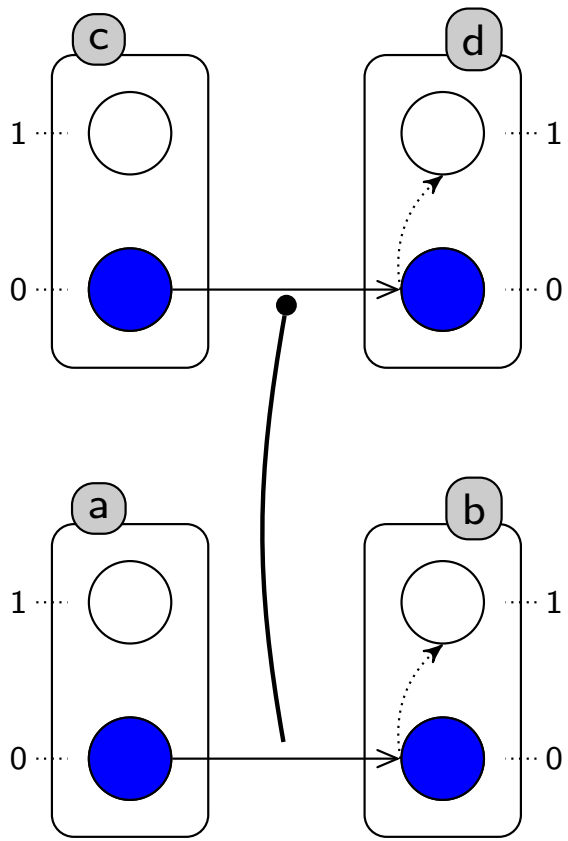
Process Hitting with Neutralizing Edges



Addition of Neutralizing Edges



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

$c_0 \rightarrow d_0 \overset{\uparrow}{\Gamma} d_1$ cannot be plays **while**

$a_0 \rightarrow b_0 \overset{\uparrow}{\Gamma} b_1$ is playable

$\rightarrow d_1$ is **always** reached after b_1

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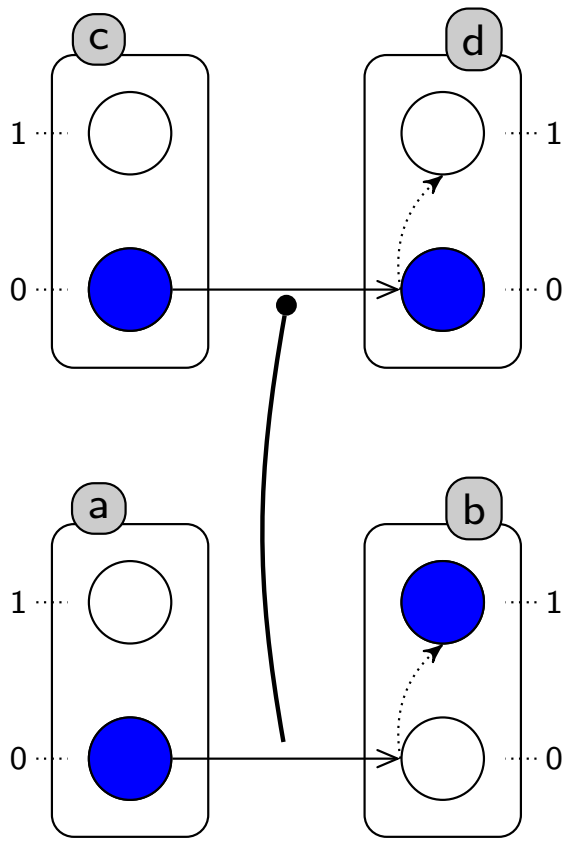

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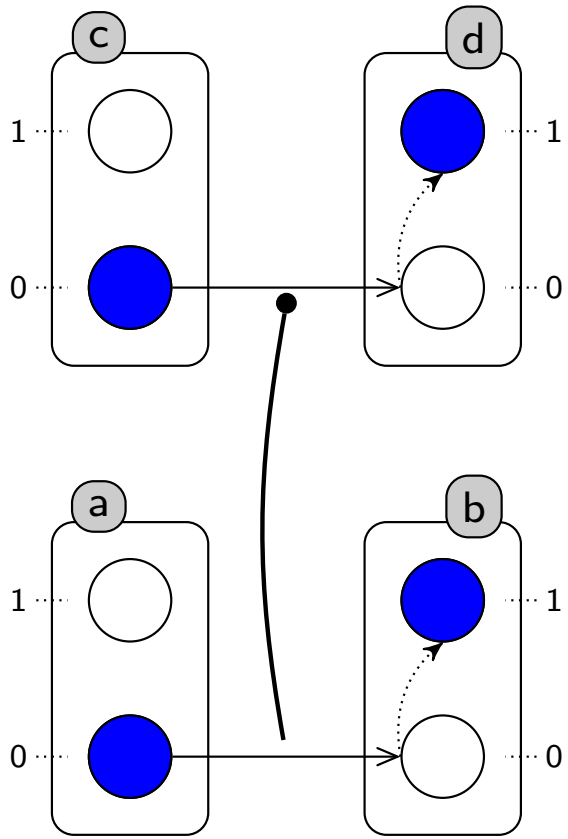

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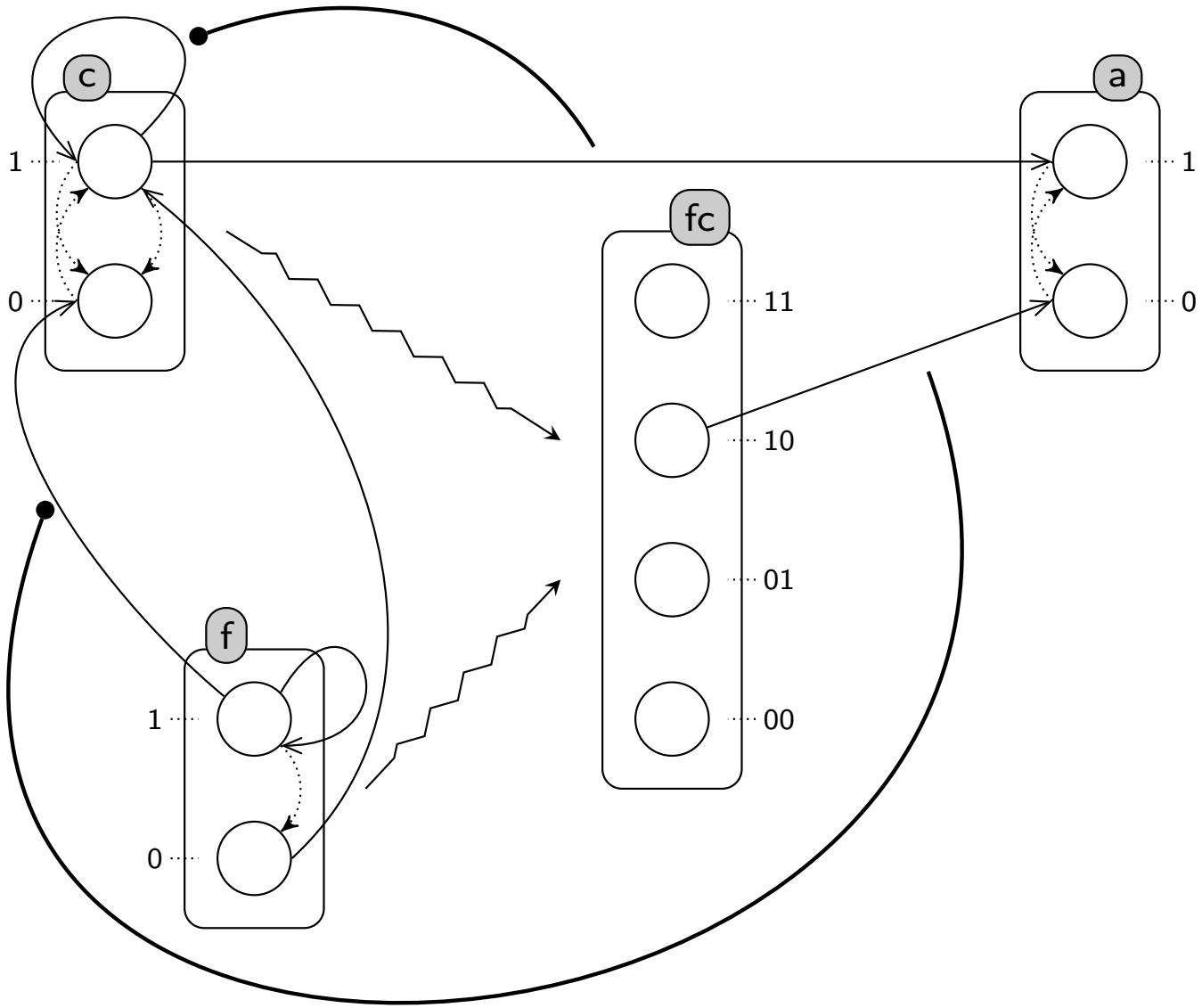
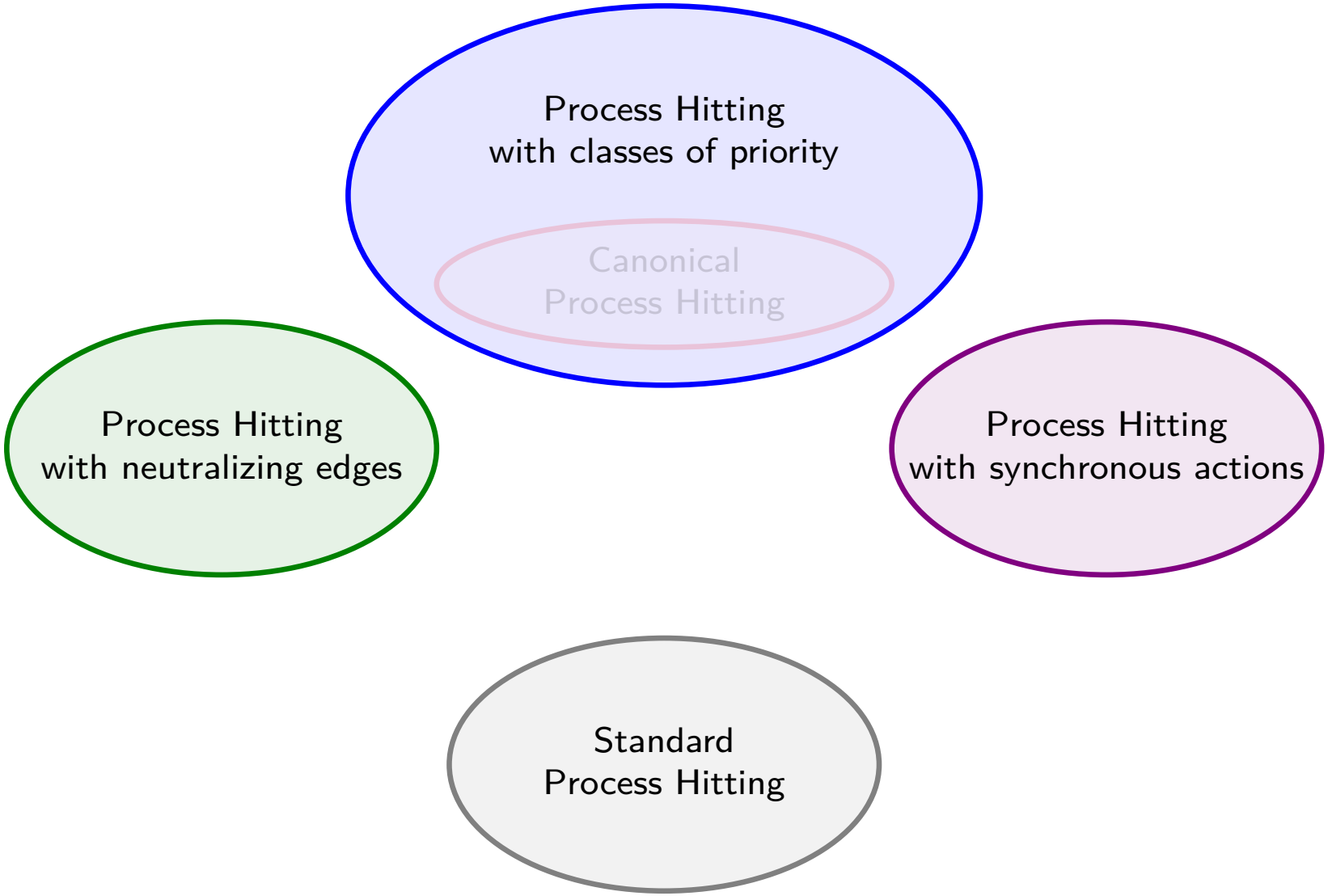


Process Hitting with Synchronous Actions



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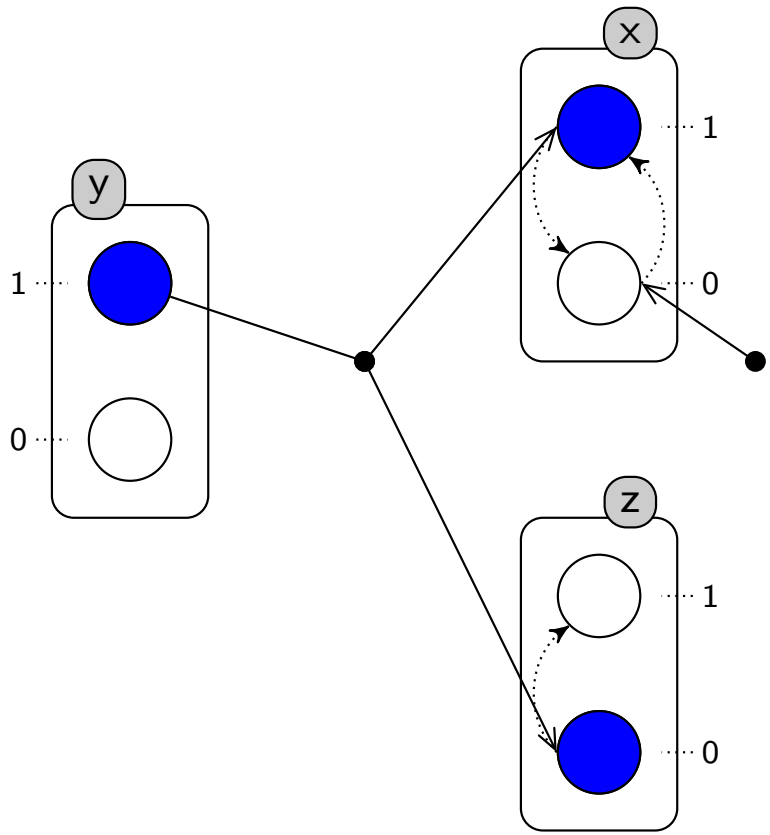

- Synchronizations between actions:
  - All catalysts must be present
  - Reactants are consumed all together
  - Simultaneous creation of the products
- Representation of biochemical equations:

$$X \xrightarrow{Y} Z$$

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 $A \rightarrowtail B$,
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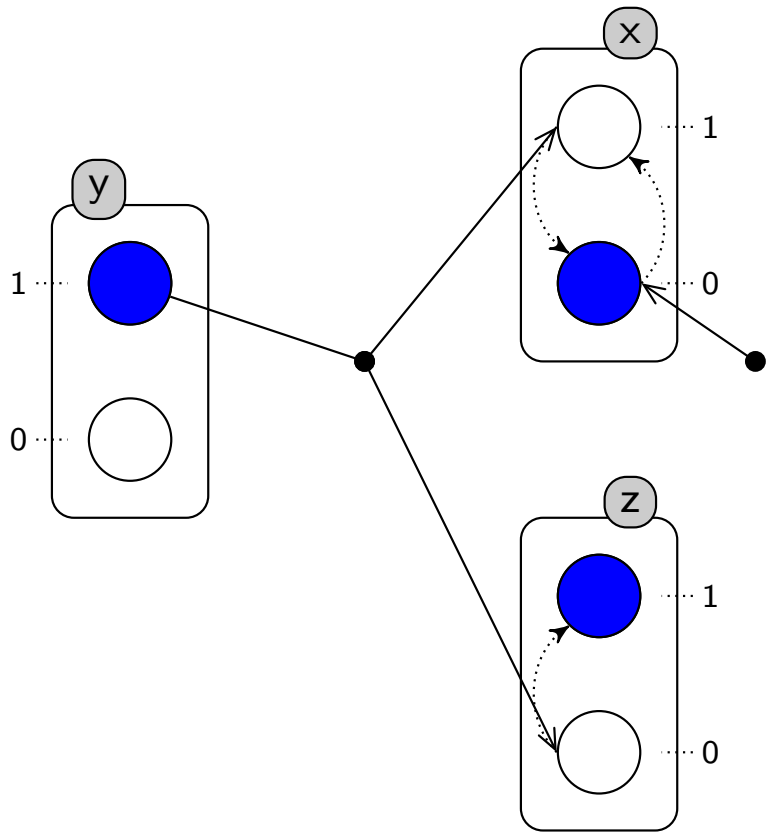
Addition of Synchronous Actions



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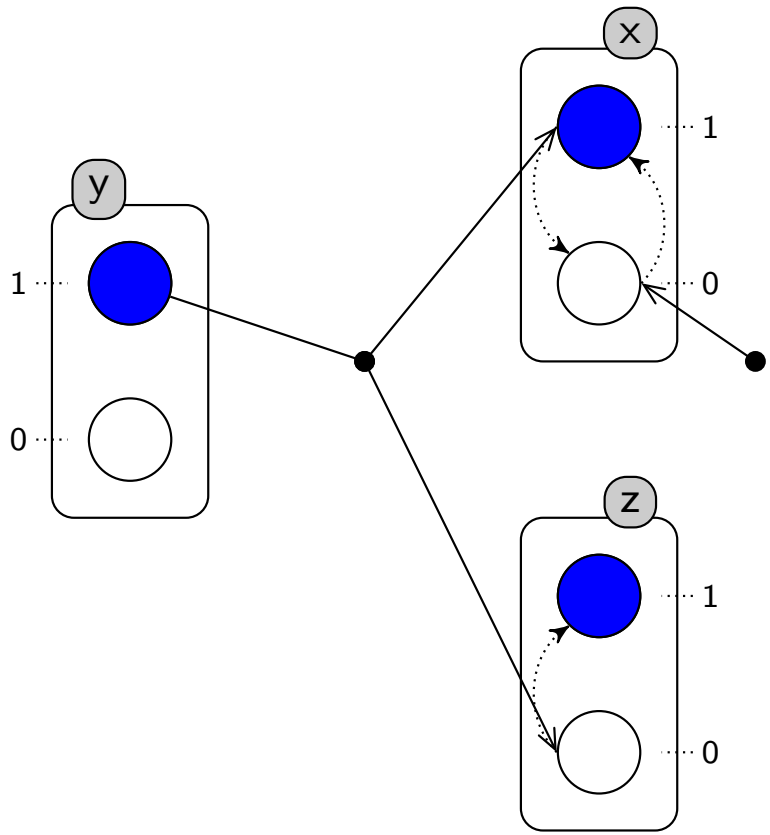

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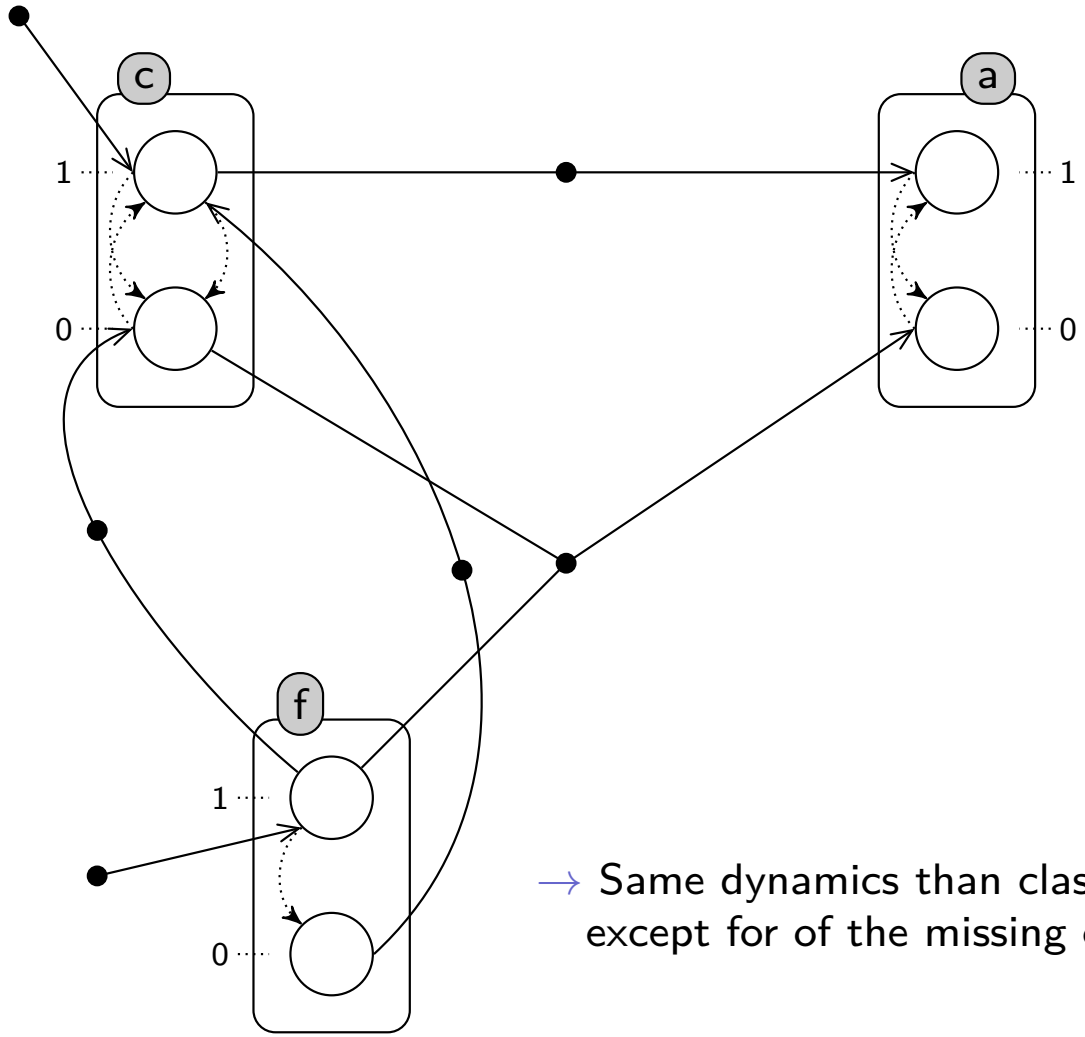
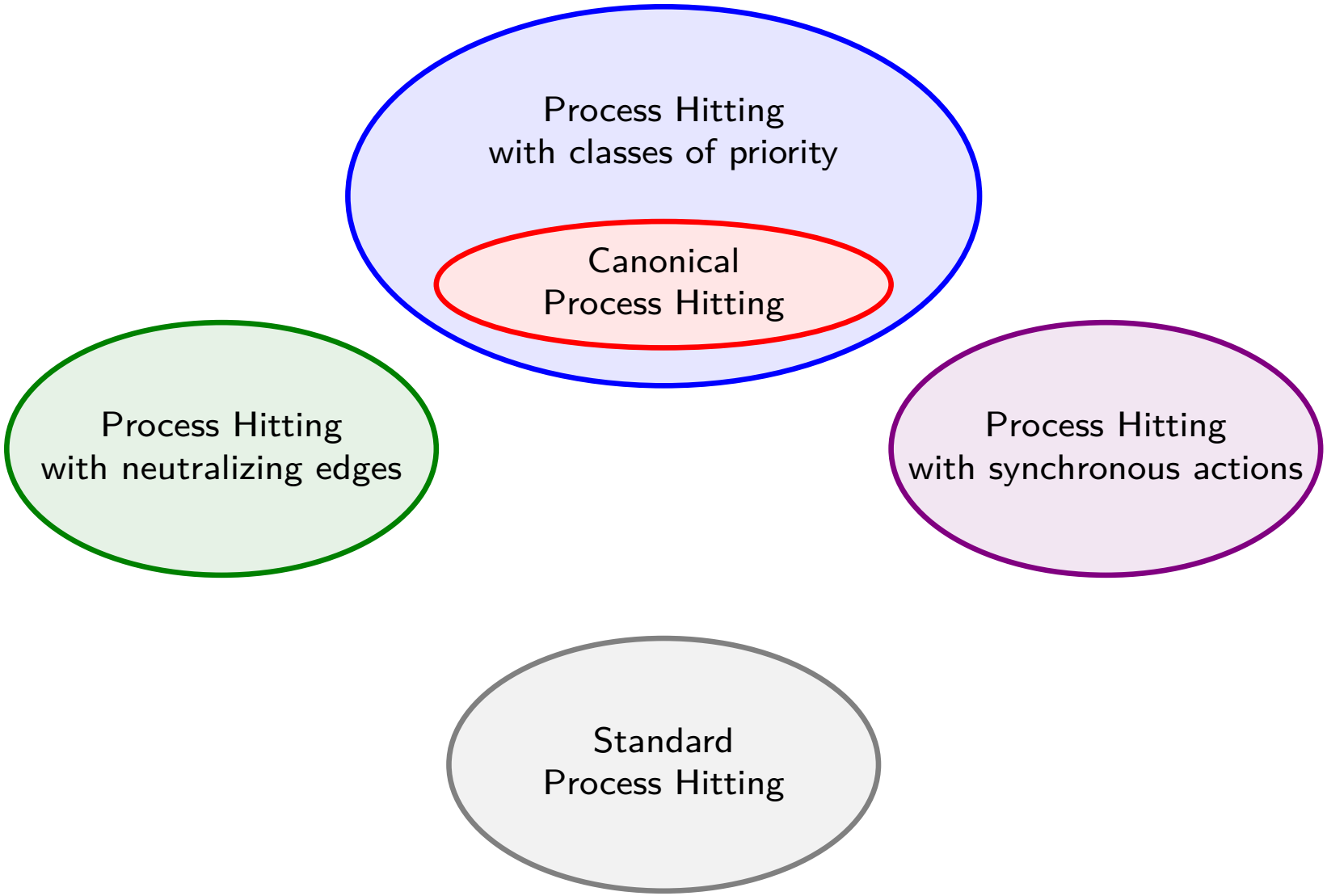
Use of Synchronous Actions



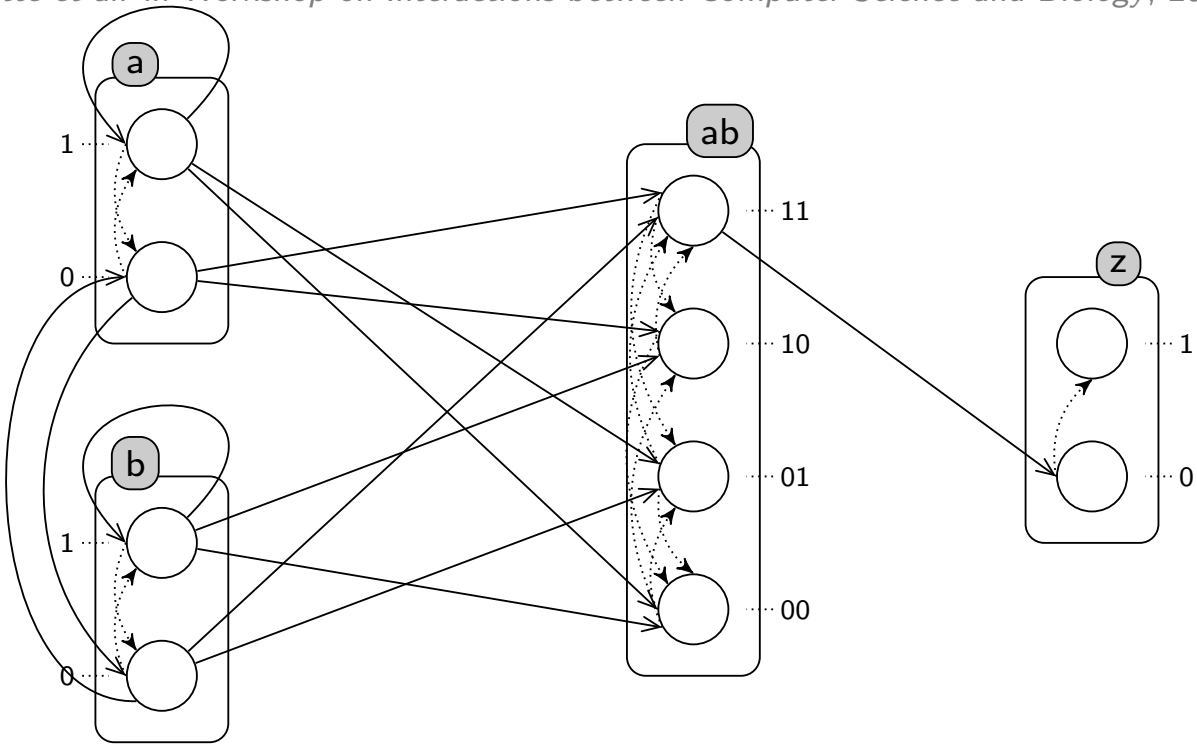
→ Same dynamics than classes of priorities, except for of the missing cooperative sort

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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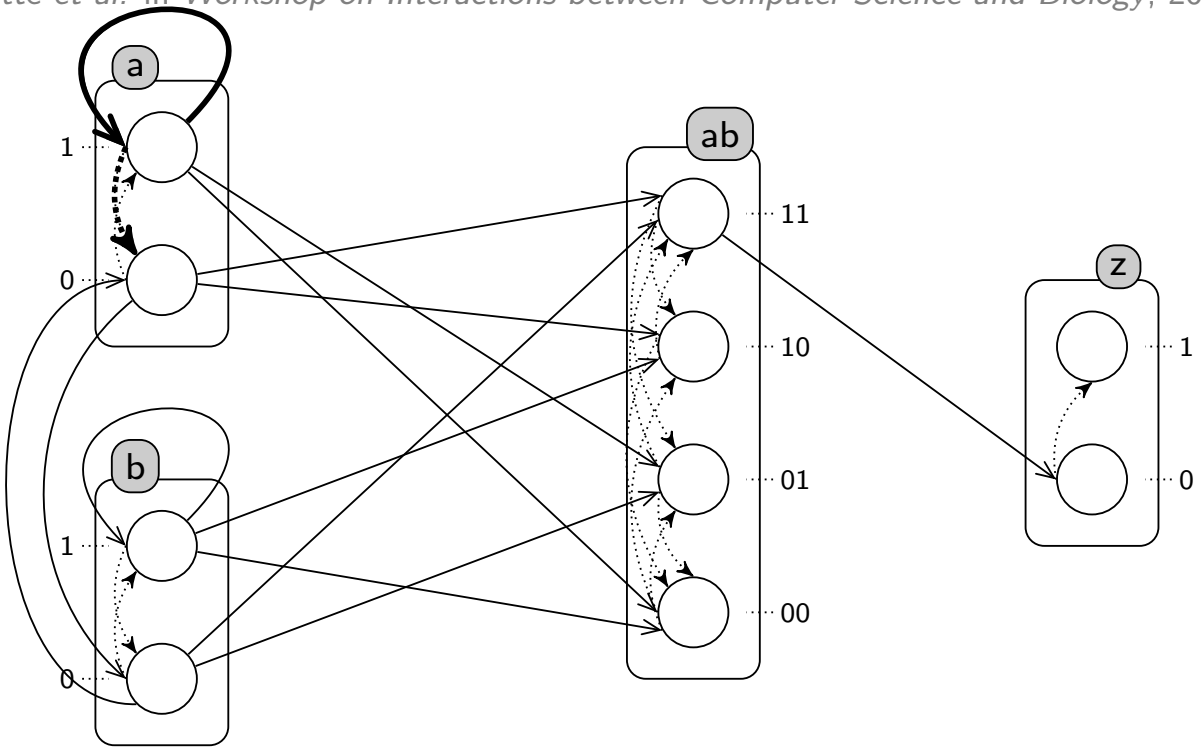

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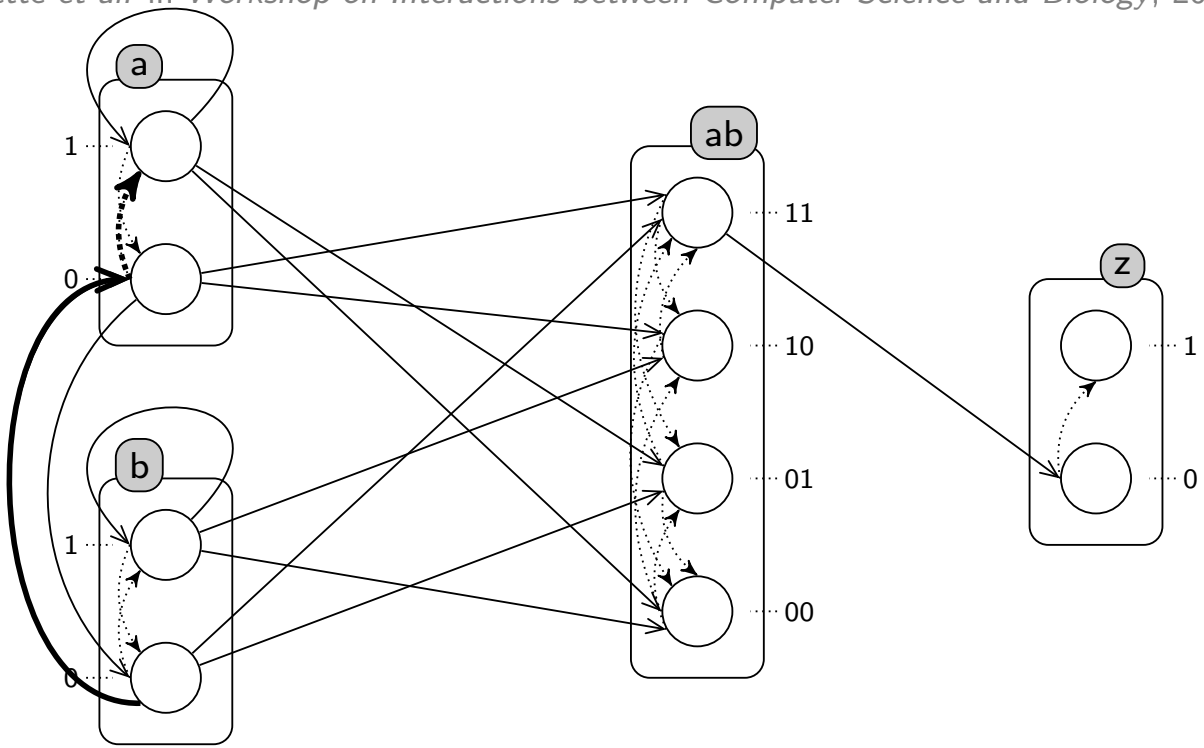

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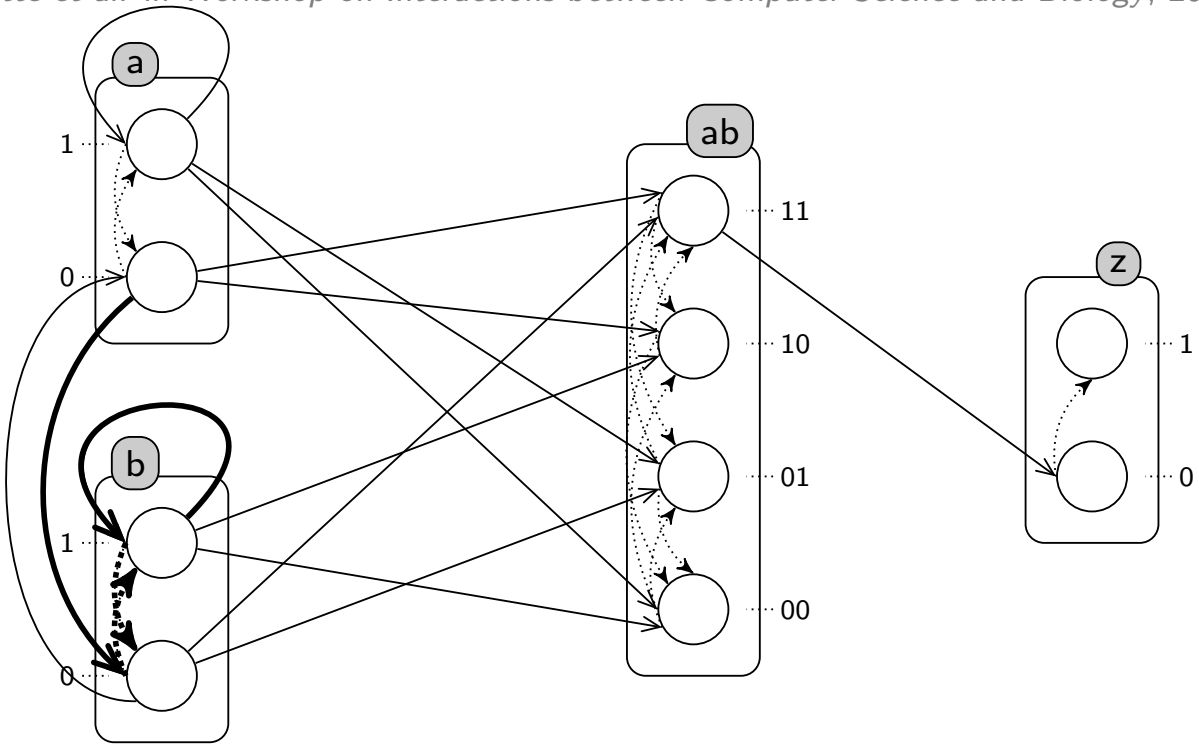

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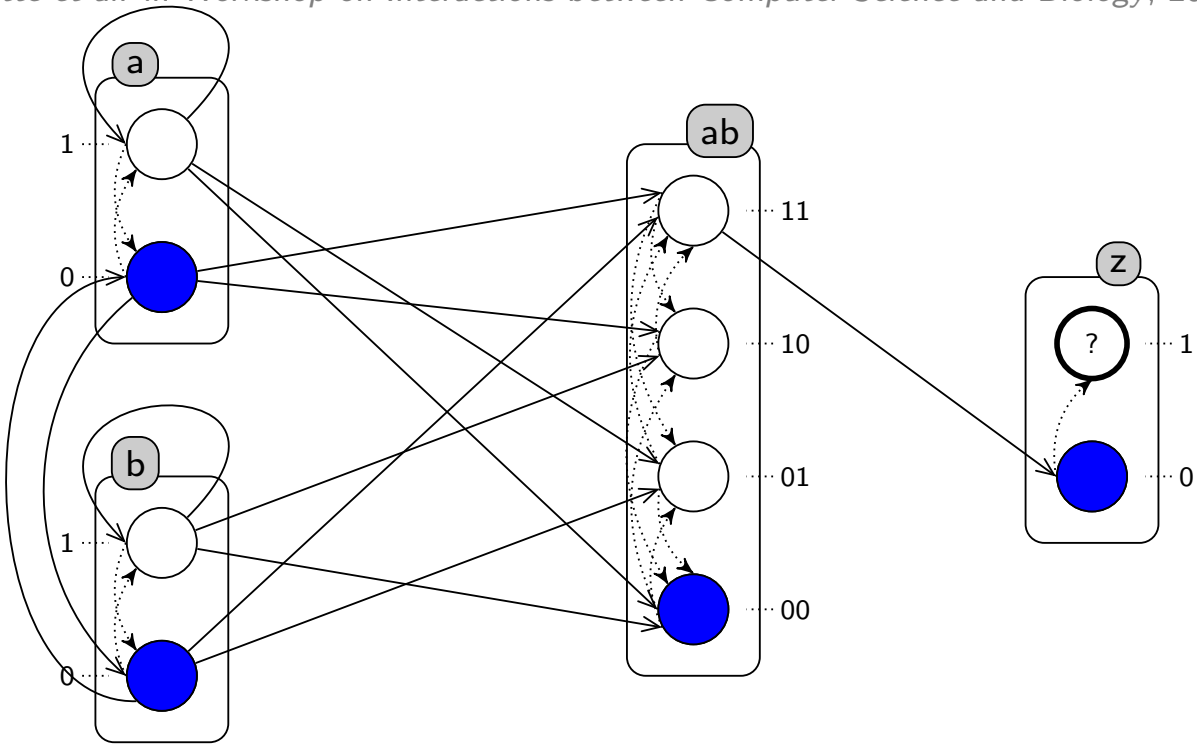

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$\langle a_0, b_0, ab_{00}, z_0 \rangle$

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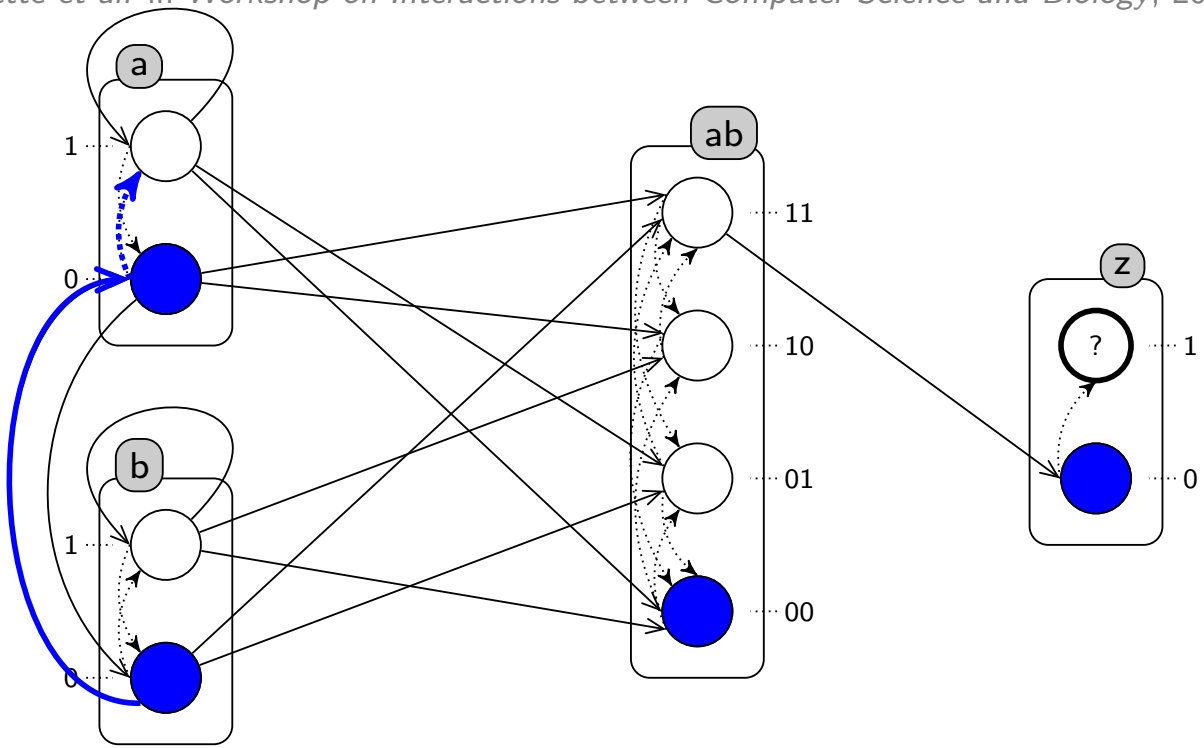
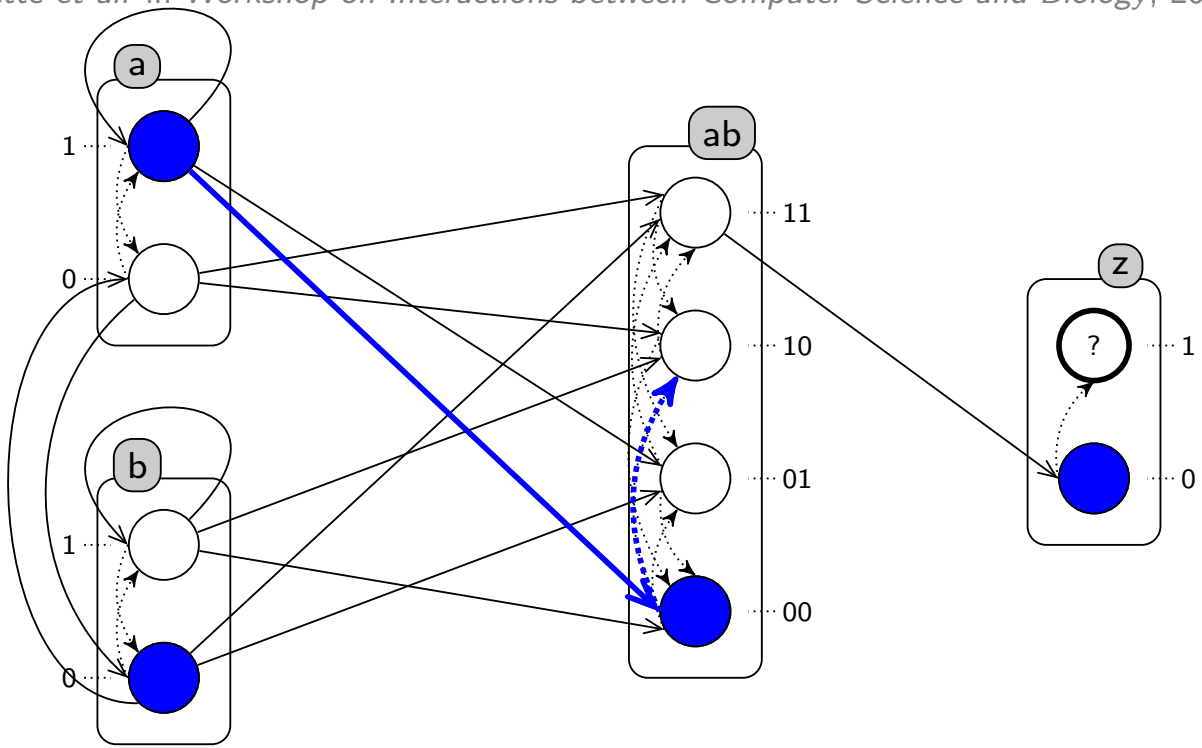


Drawback: the cooperative sorts are too "loose" (temporal shift)

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

Temporal Shift in Cooperative Sorts

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

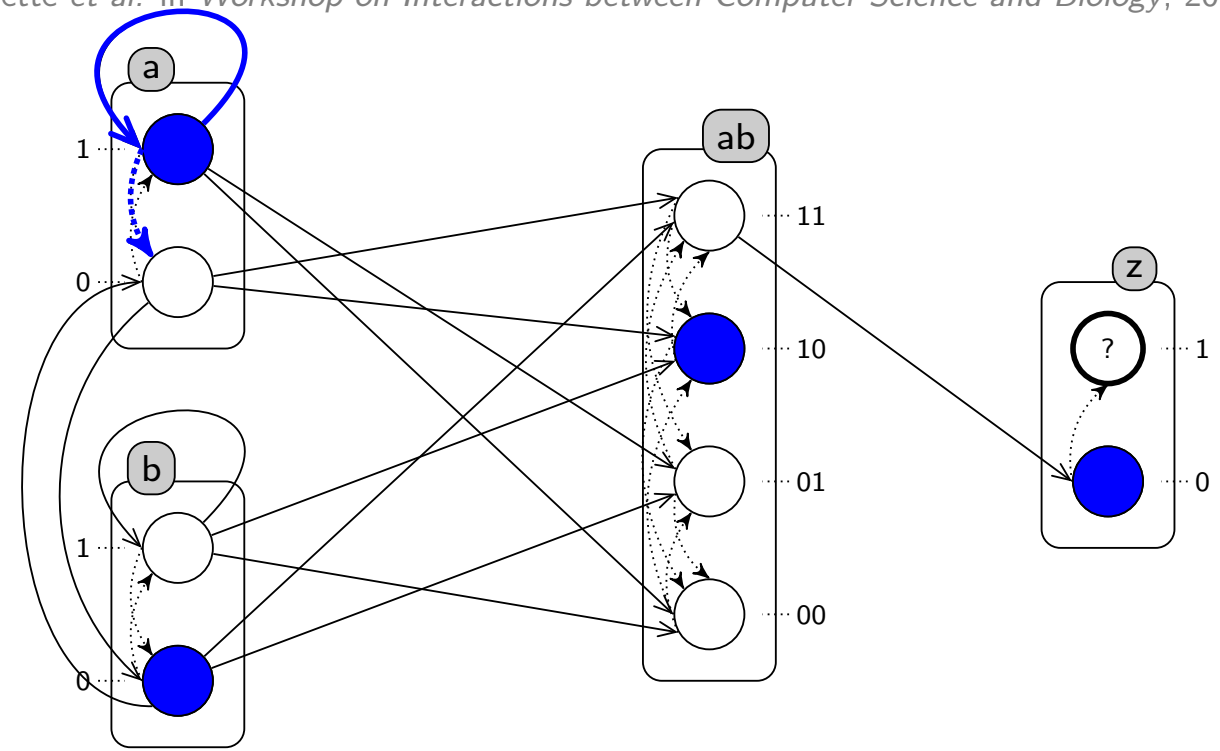


Drawback: the cooperative sorts are too "loose" (temporal shift)

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

Temporal Shift in Cooperative Sorts

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



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

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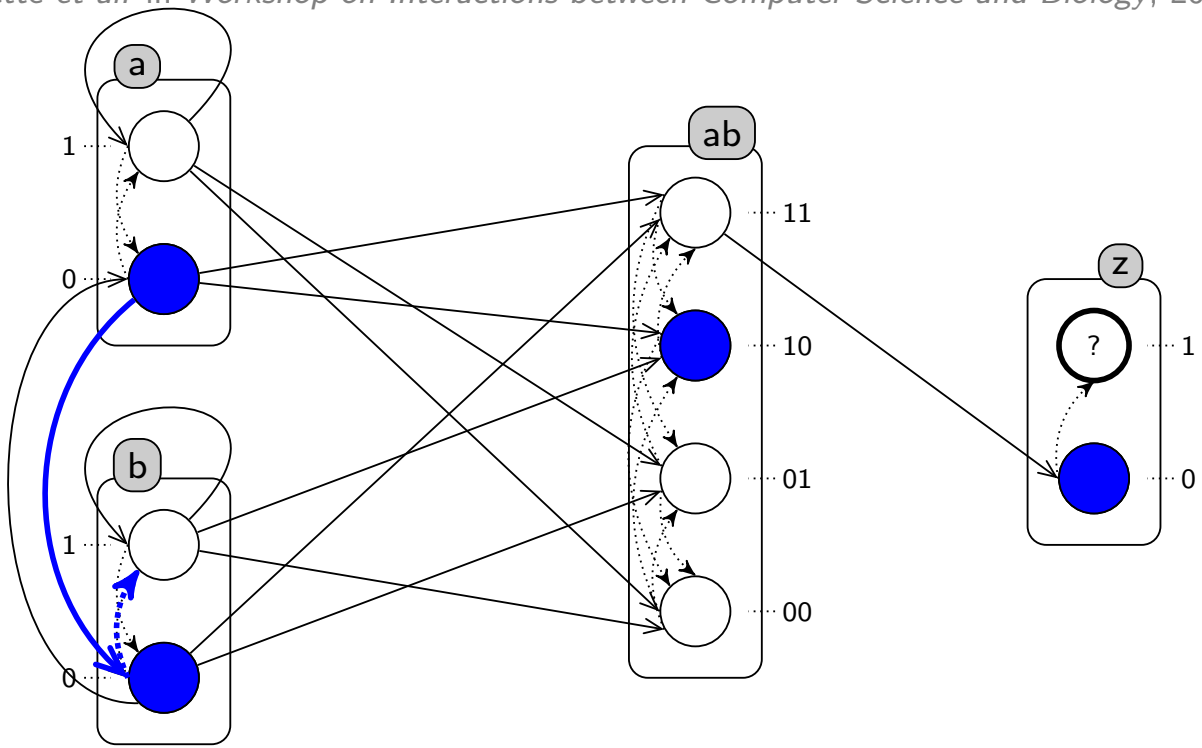

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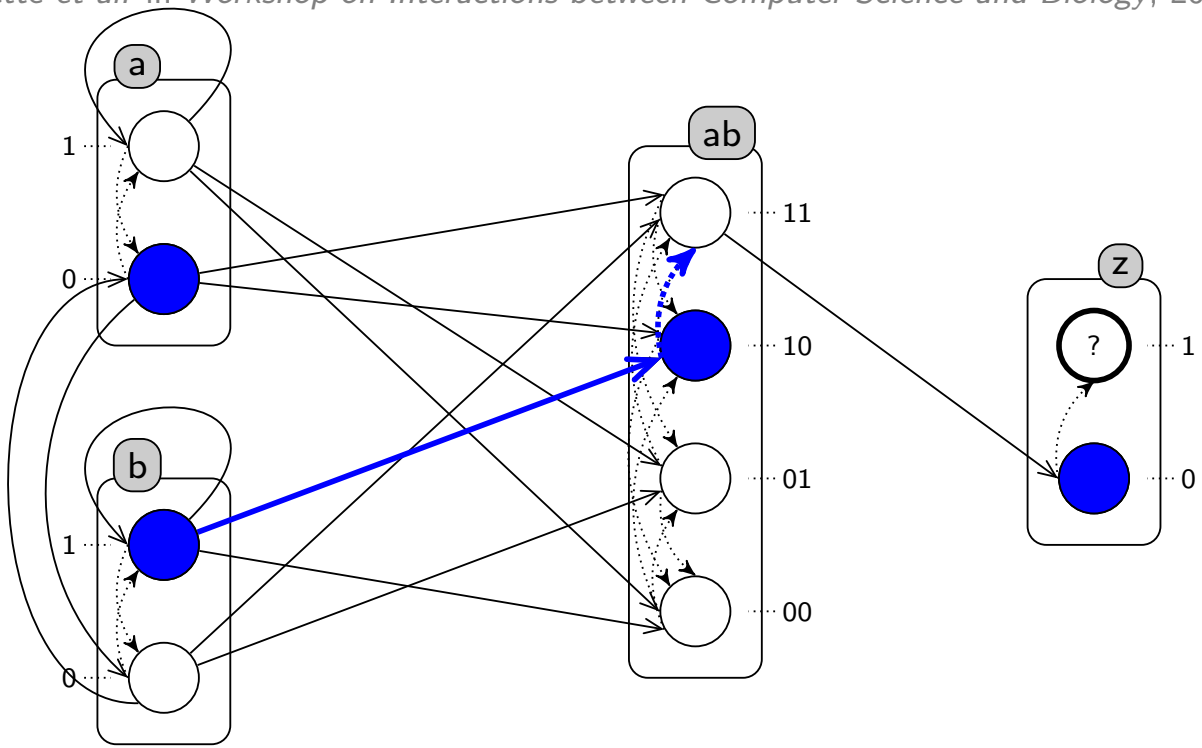

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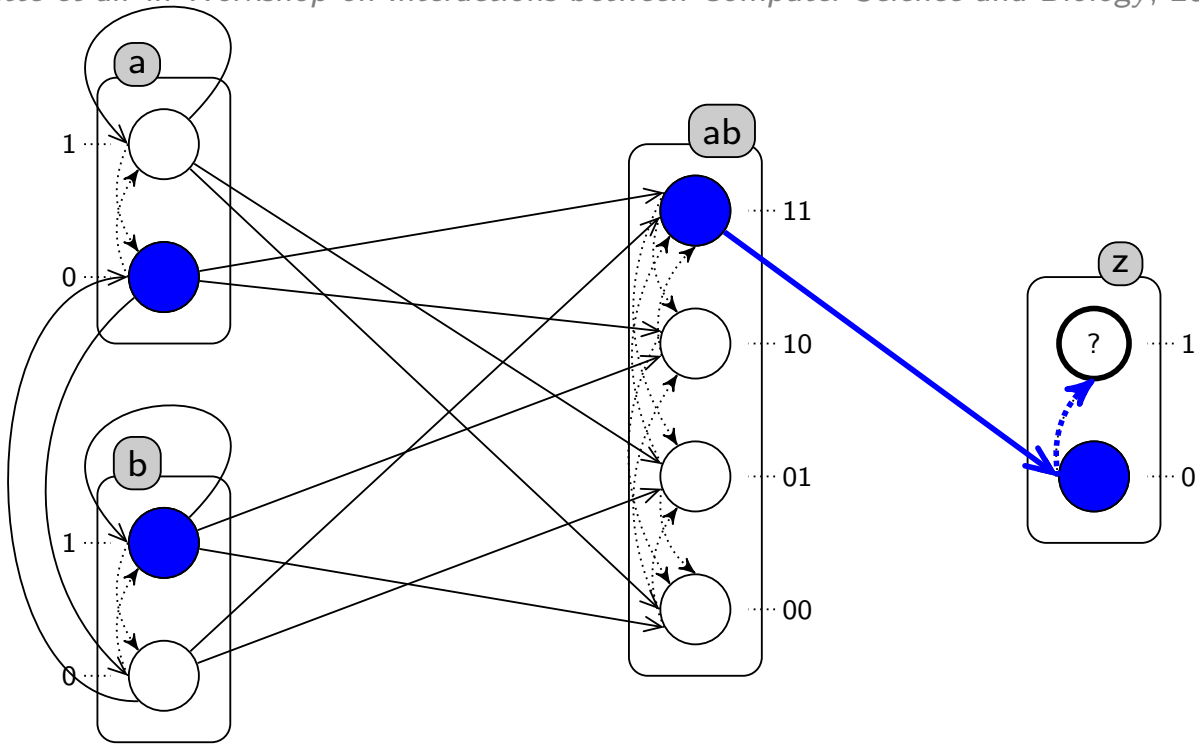

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$\rightarrow \langle a_0, b_1, ab_{10}, z_0 \rangle \rightarrow \langle a_0, b_1, ab_{11}, z_0 \rangle$

Temporal Shift in Cooperative Sorts

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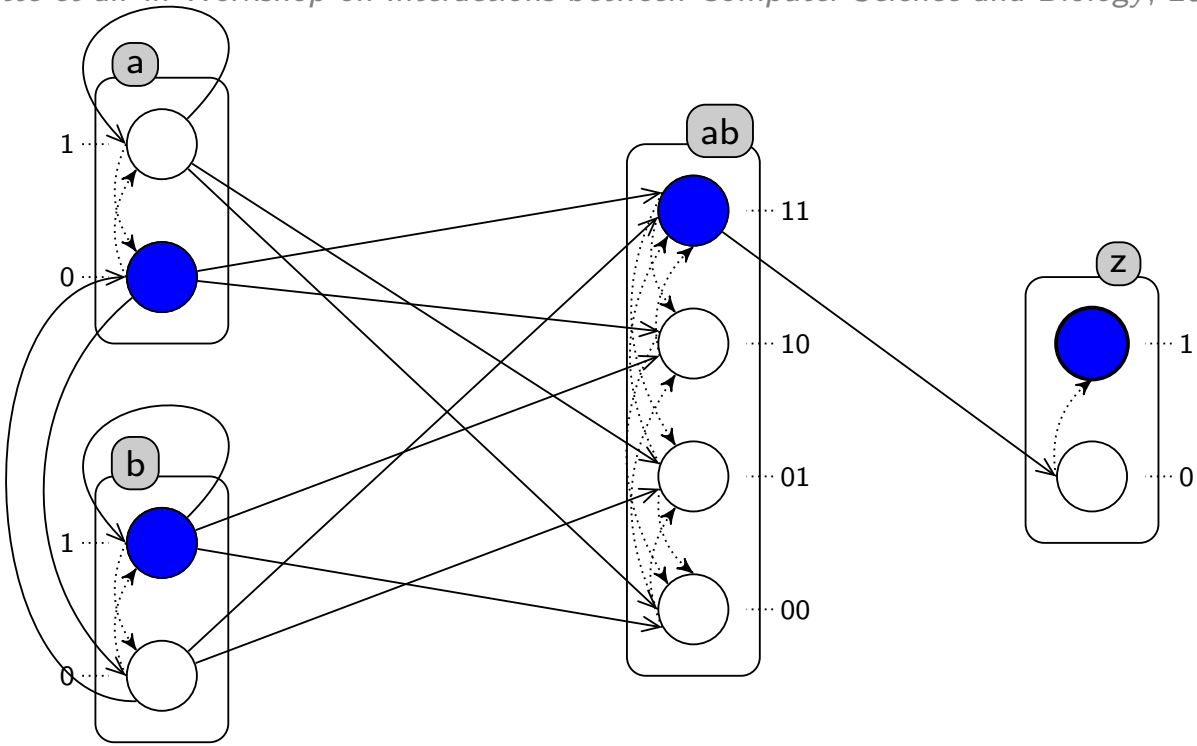

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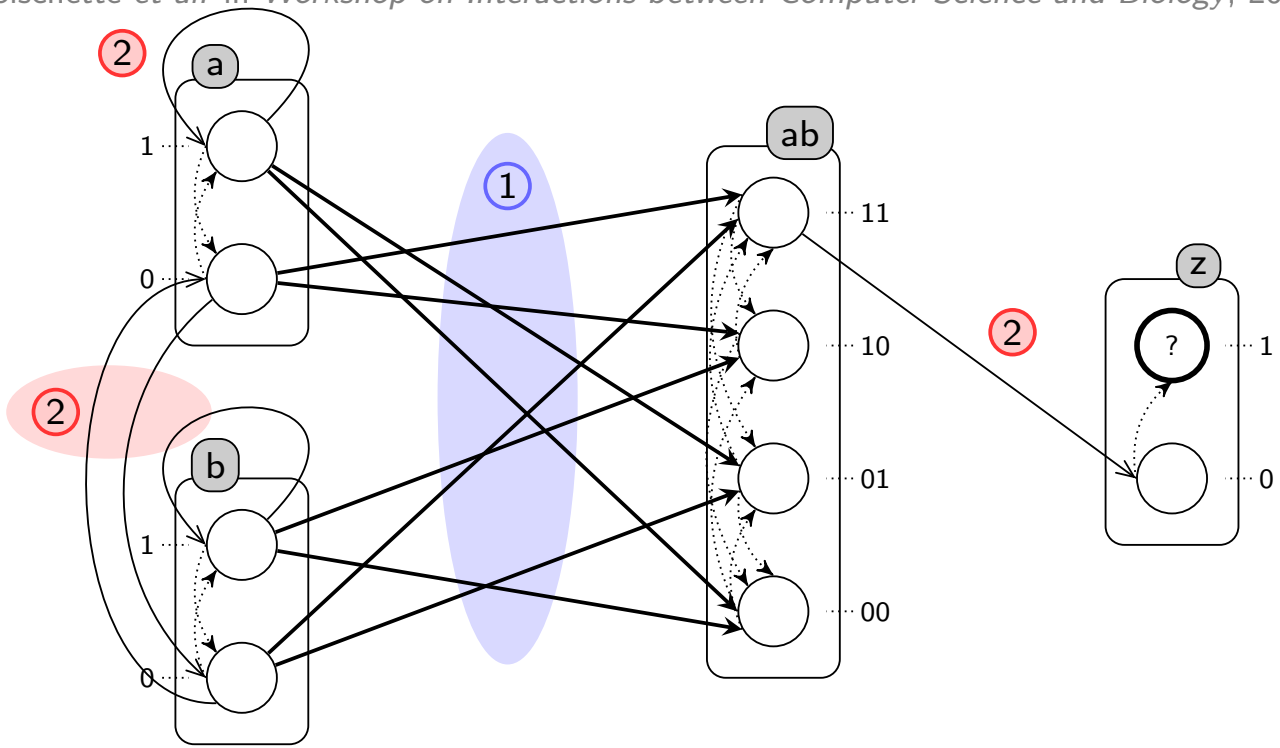
Expected behavior: $a_1 \wedge b_1$ **simultaneously** i.e. "in the same state"
Obtained behavior: $\mathbf{P}(a_1) \wedge \mathbf{P}(b_1)$ with $\mathbf{P}$ = "previously"

Canonical Process Hitting

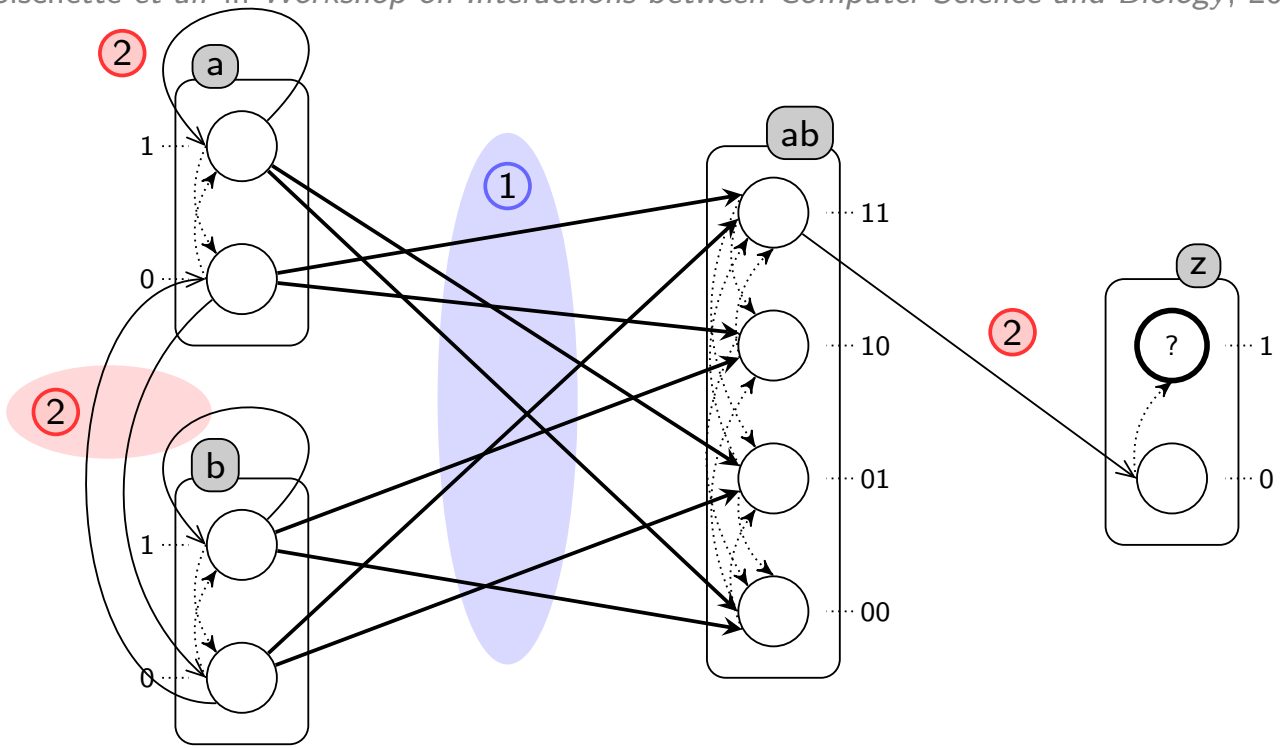
[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



- 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

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



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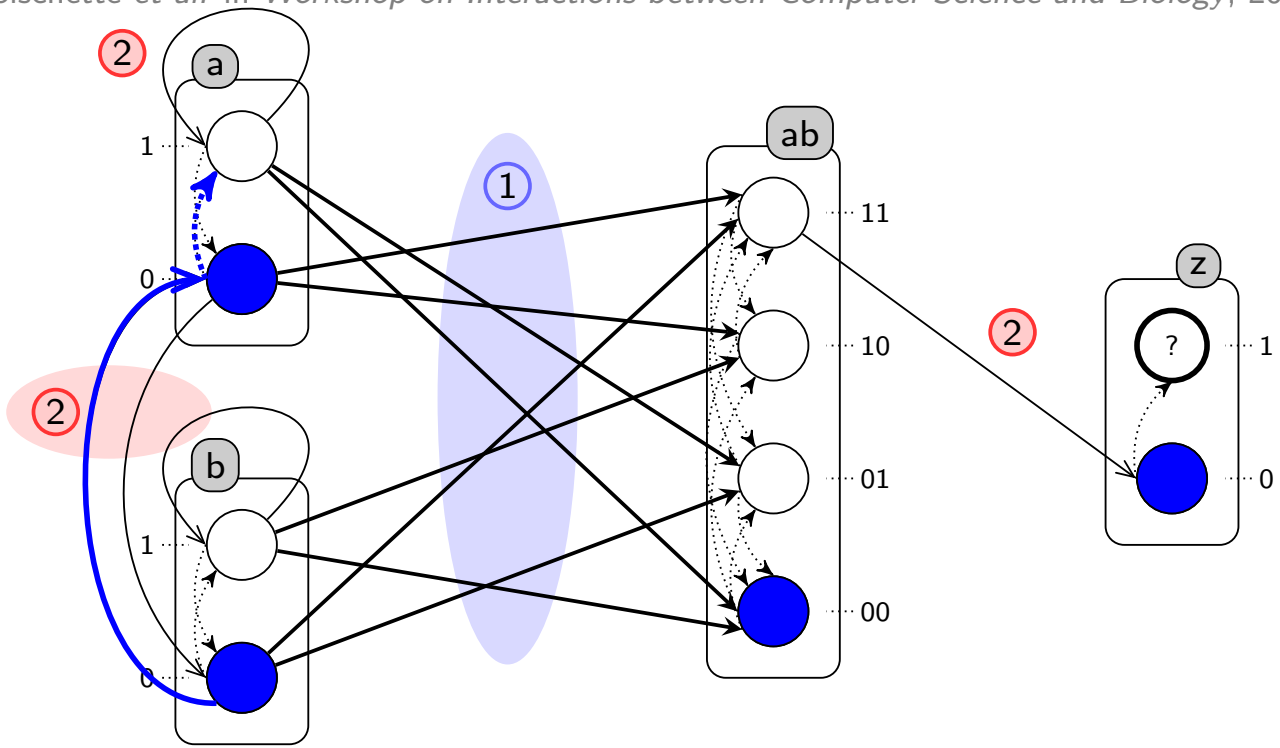

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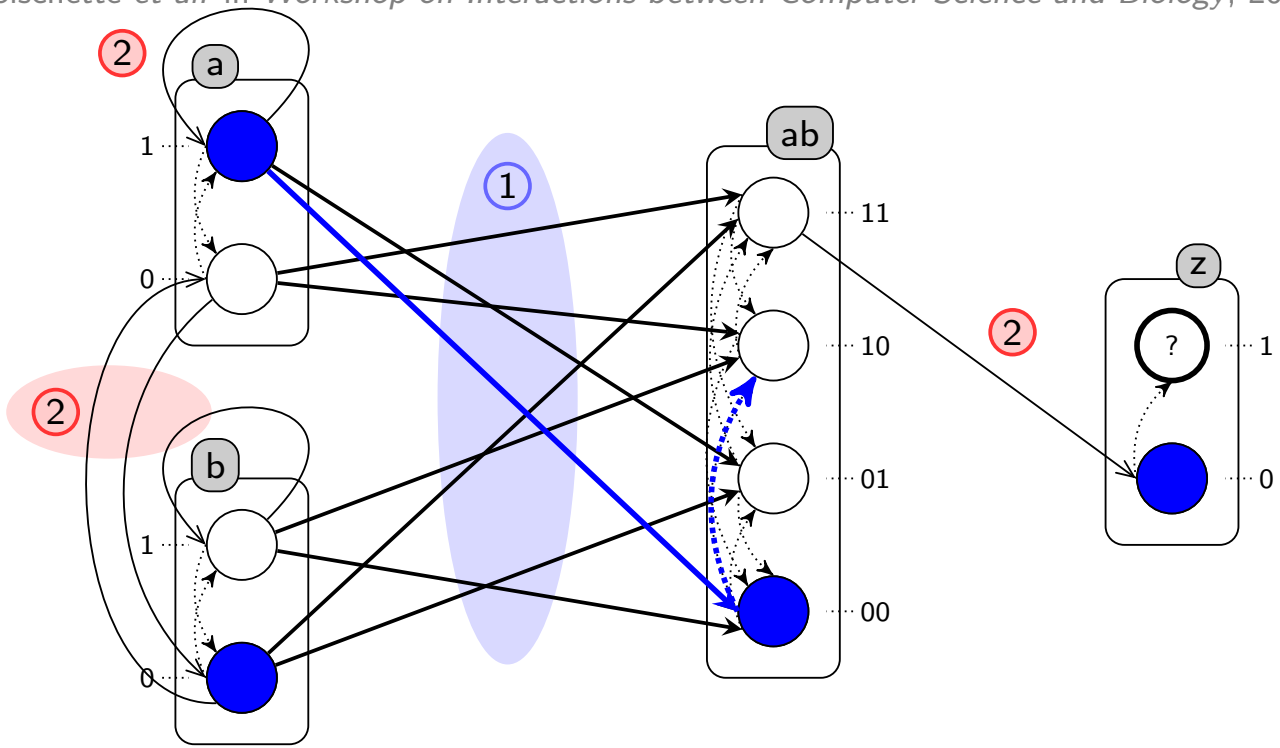

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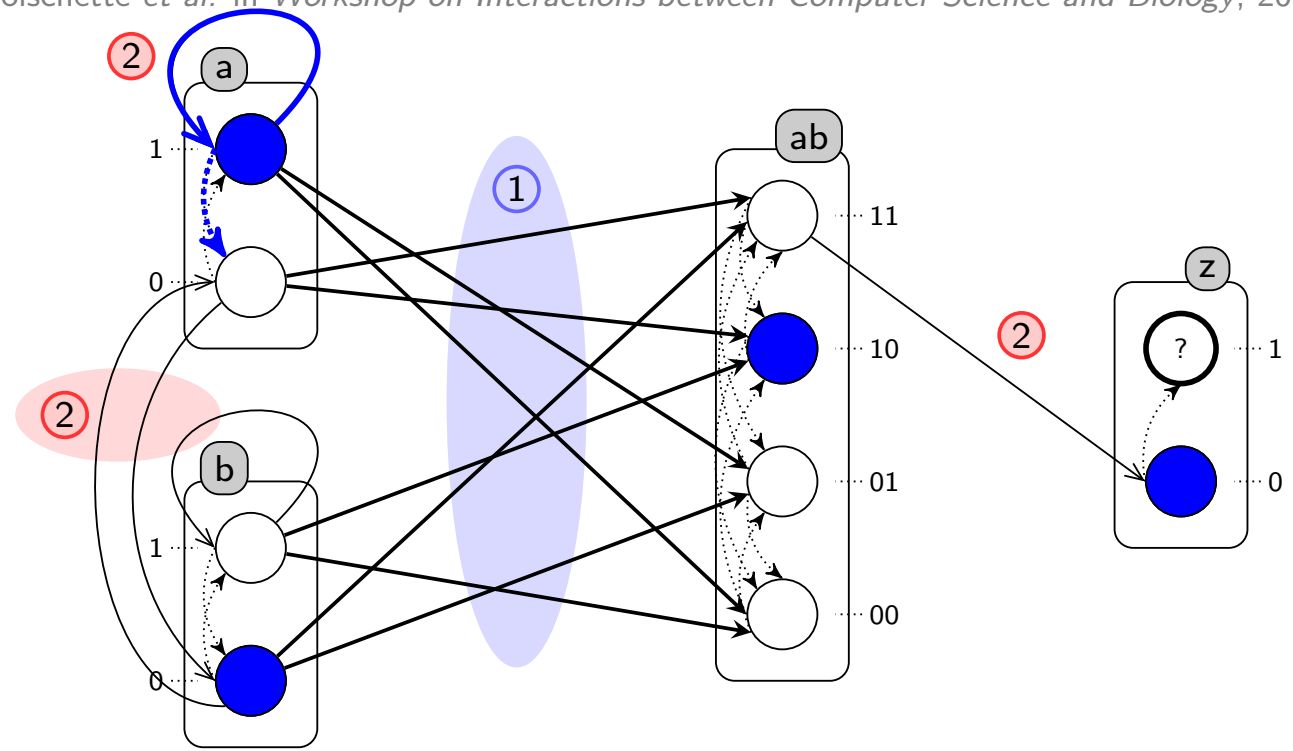

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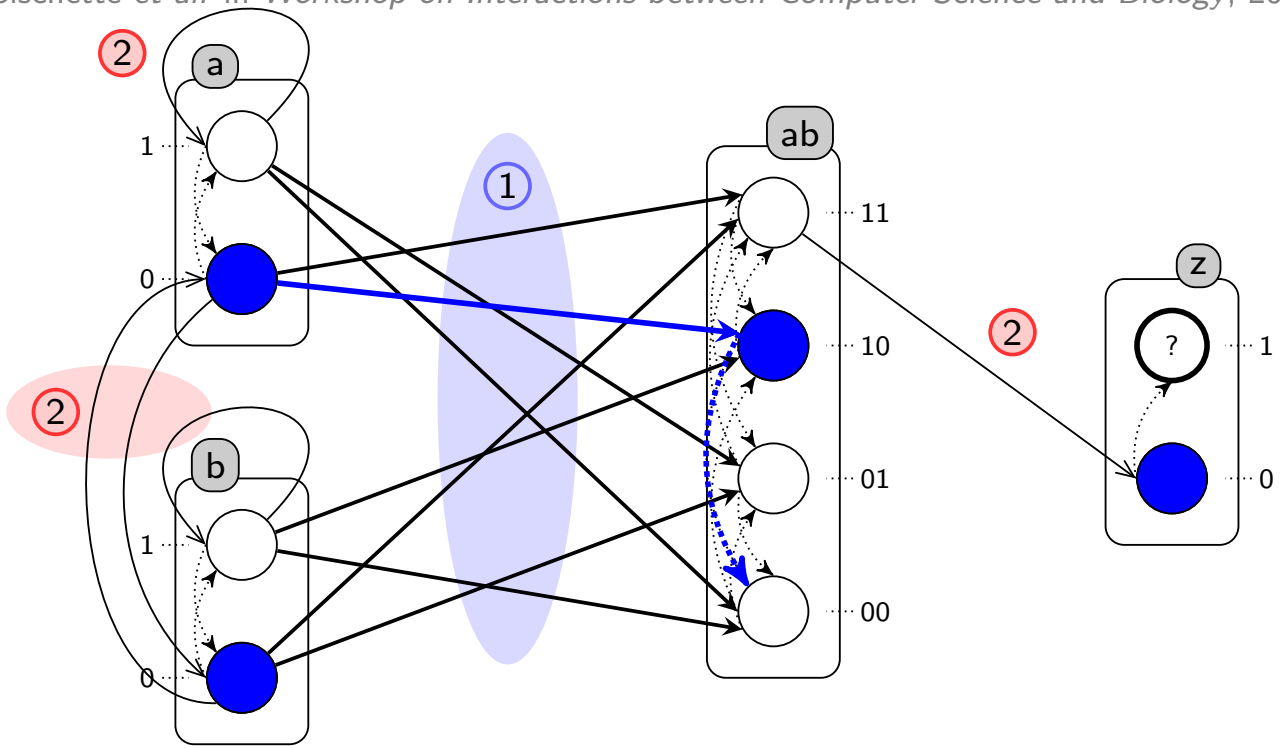

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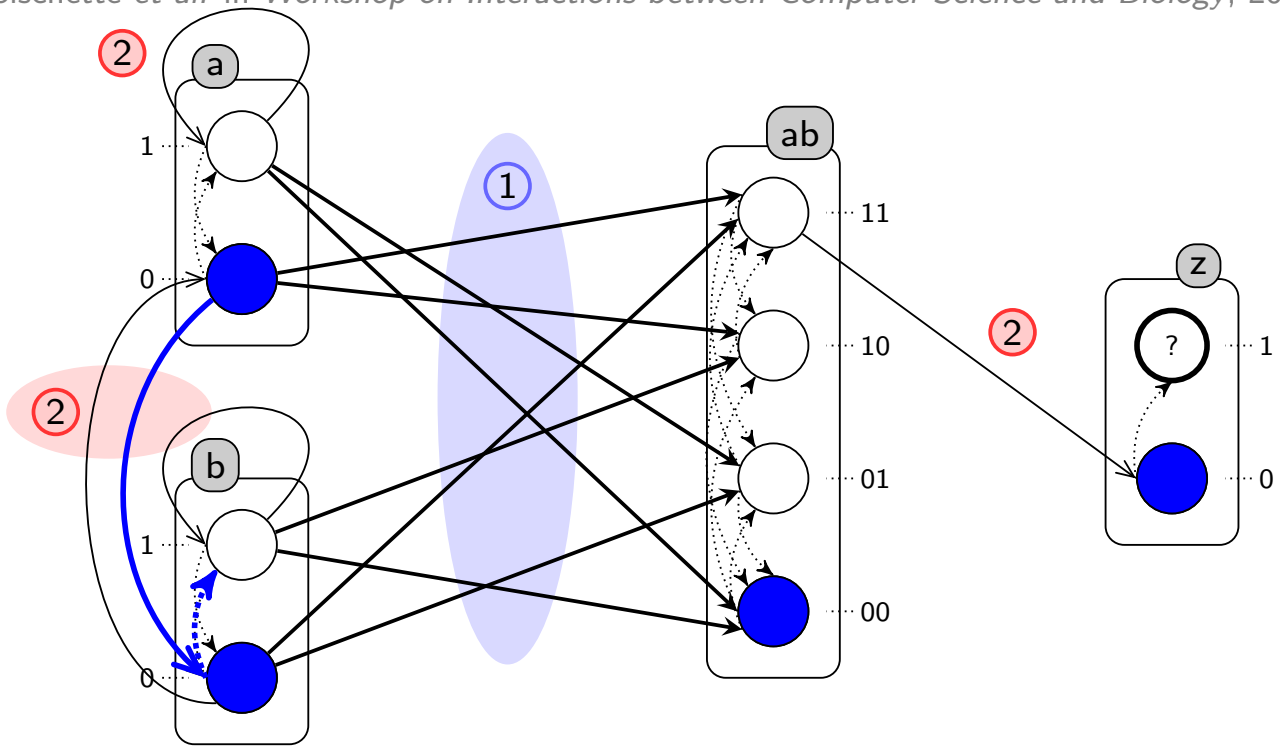

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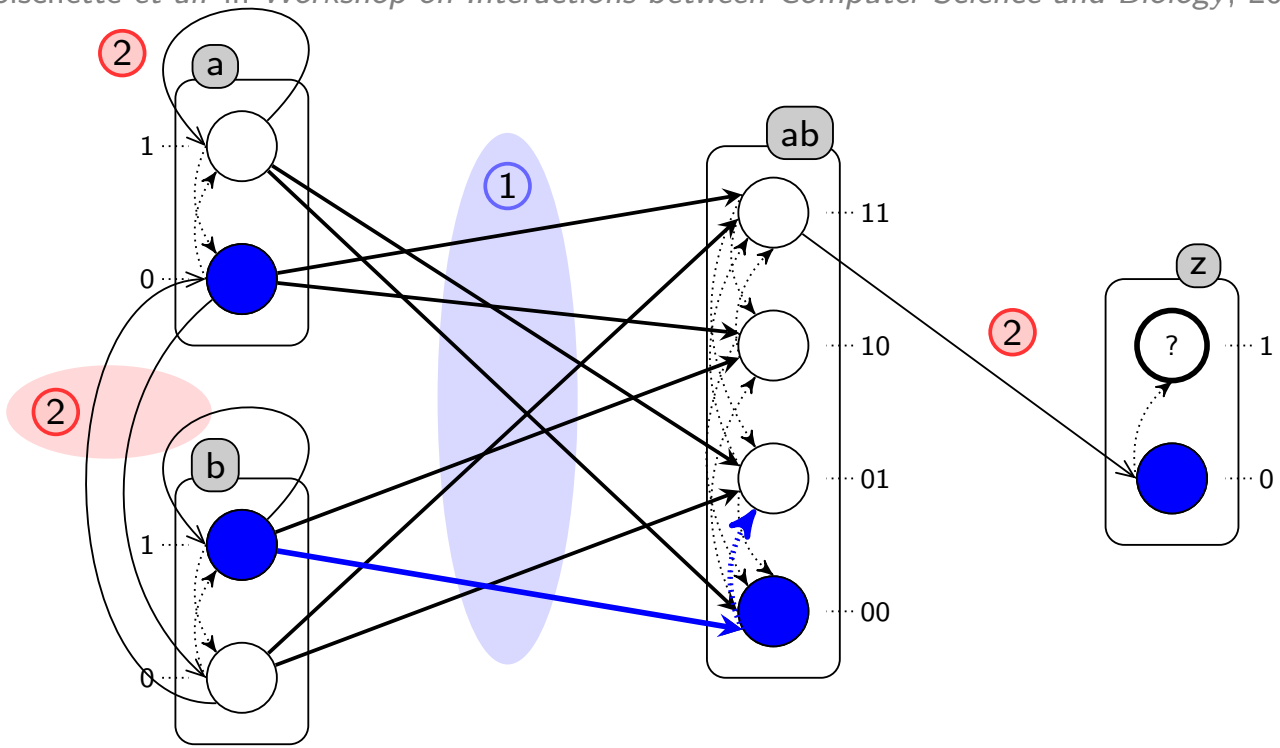

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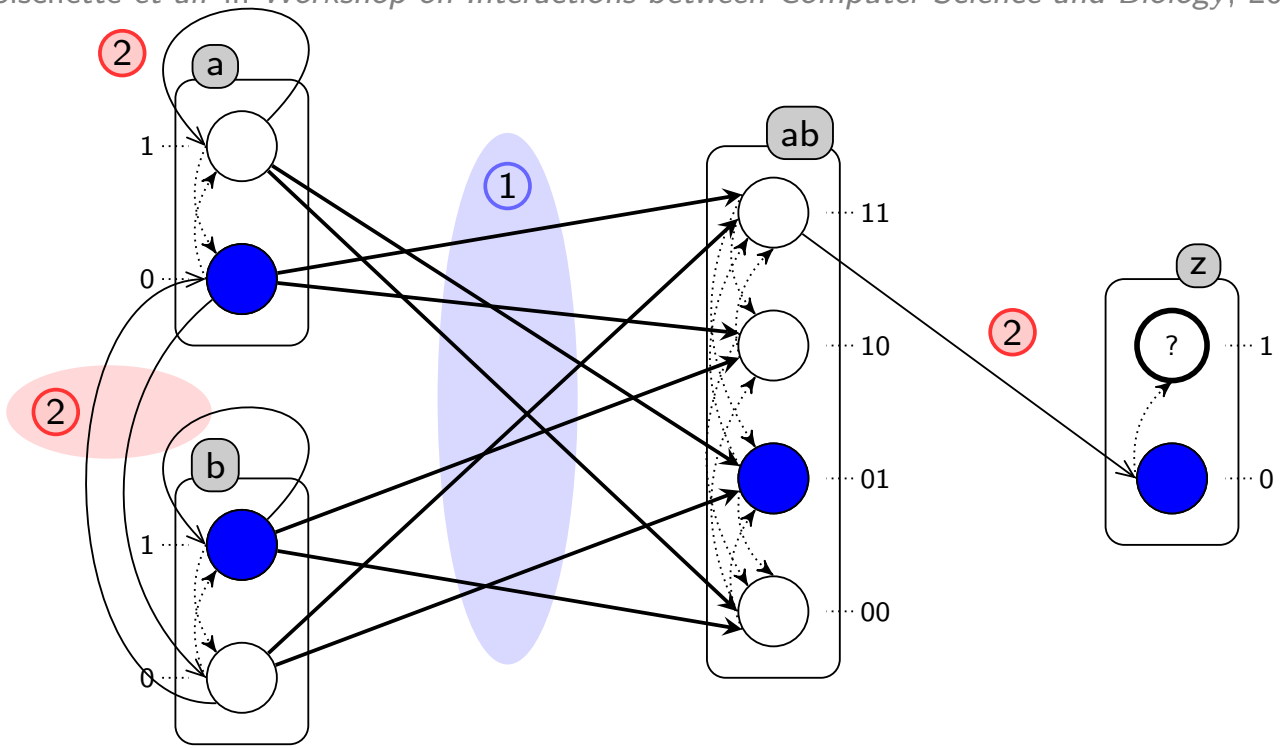

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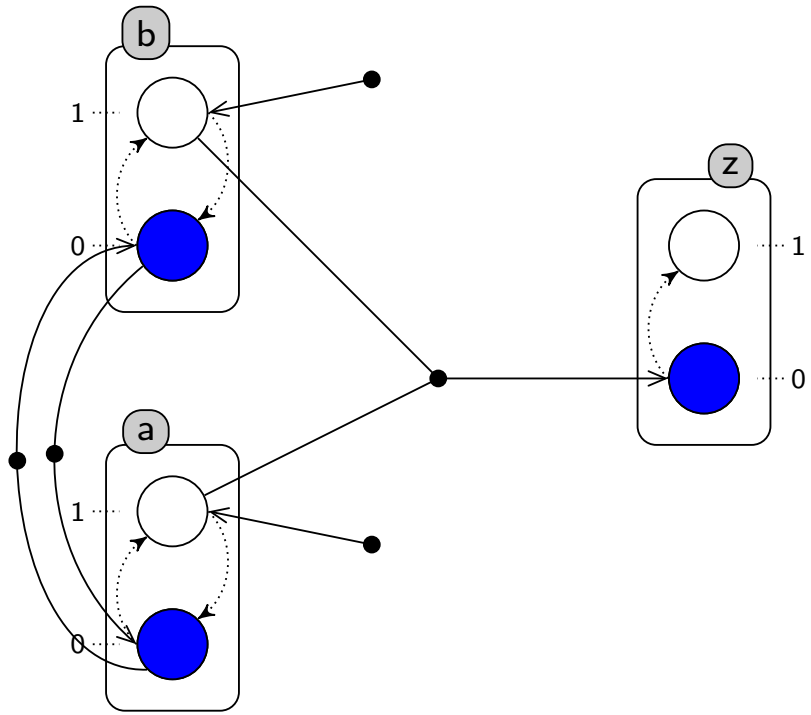
Canonical Process Hitting with Synchronous Actions



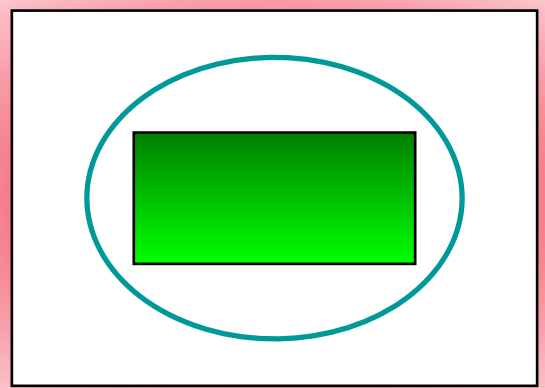
- Equivalent dynamics
- Sub-class of synchronous automata networks
- No priorities (no ill-formed model)
- No interfering updates and less intertwining

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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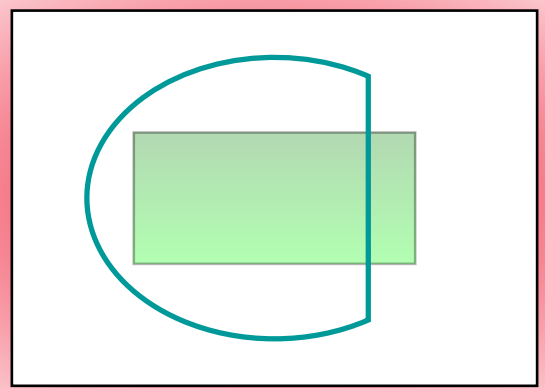

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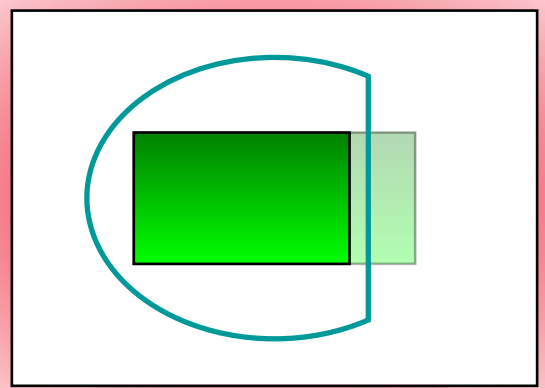

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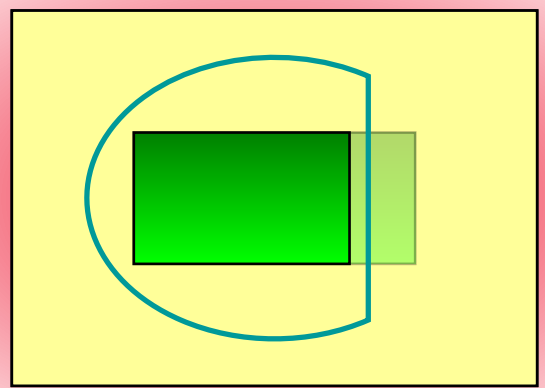

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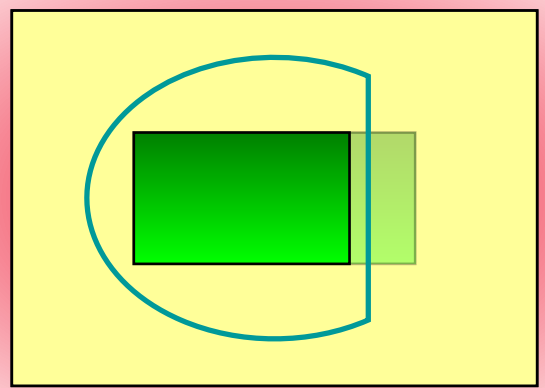


Similar complexity for a more expressive formalism

→ Still efficient for big models

→ Finer under-approximation

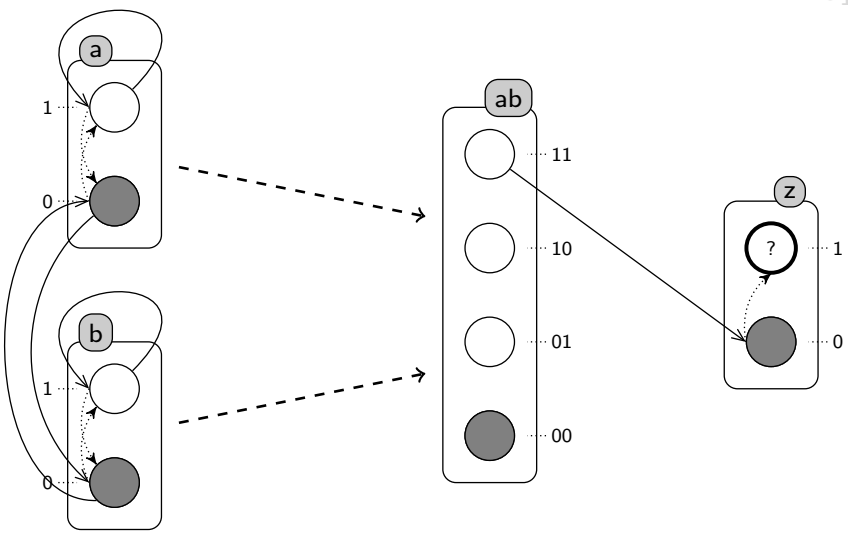
Static Analysis of Canonical Process Hitting

[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

Non-conclusive



$\boxed{z_1}$	Required process
$z_0 \Uparrow^* z_1$	Objective
○	Solution to an objective
$\boxed{\{a_1, b_1\}}$	Synchronization of several processes

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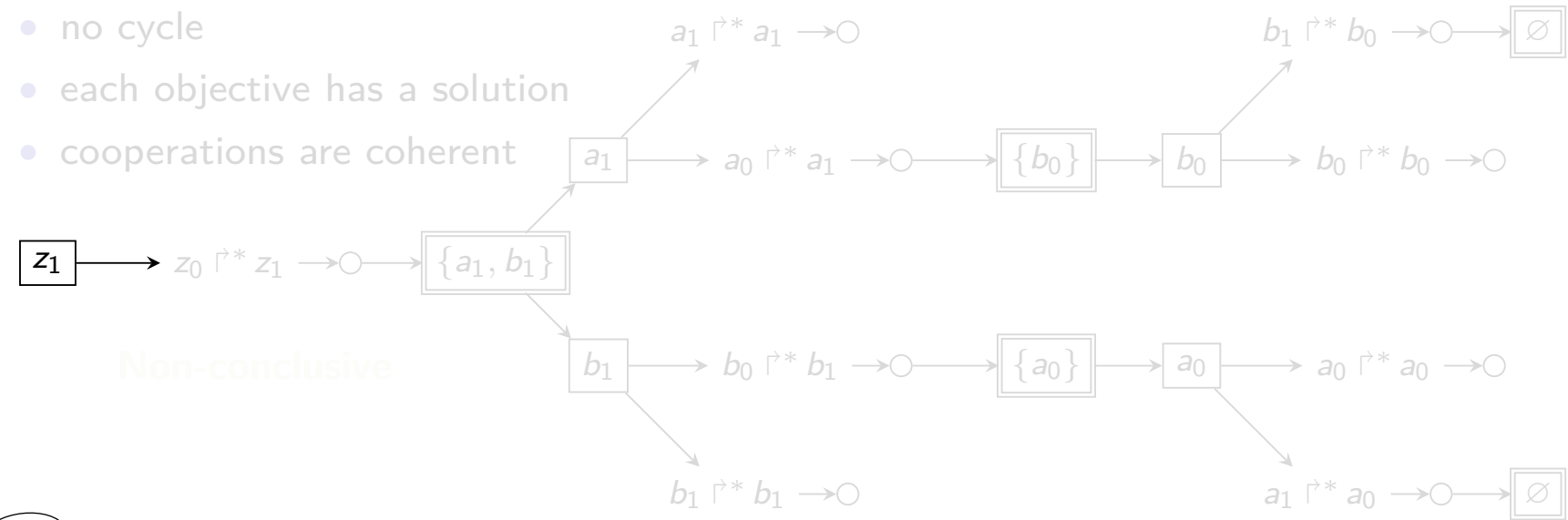

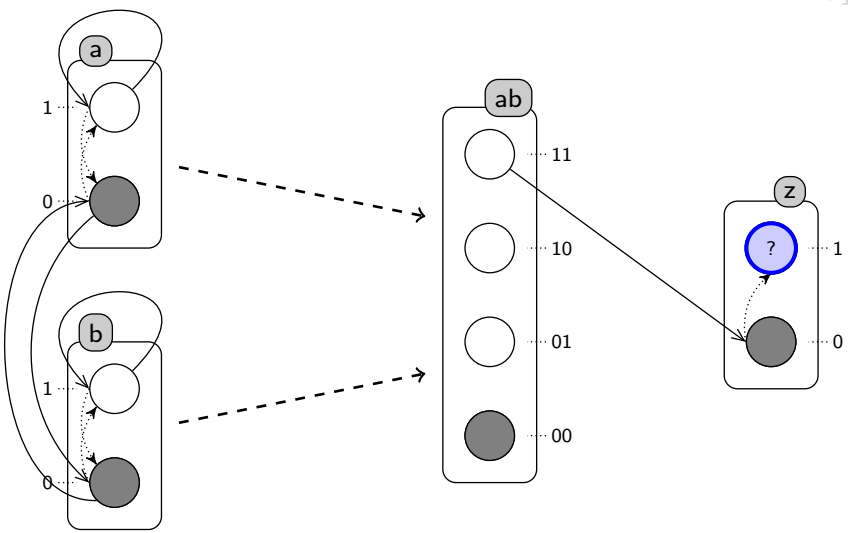

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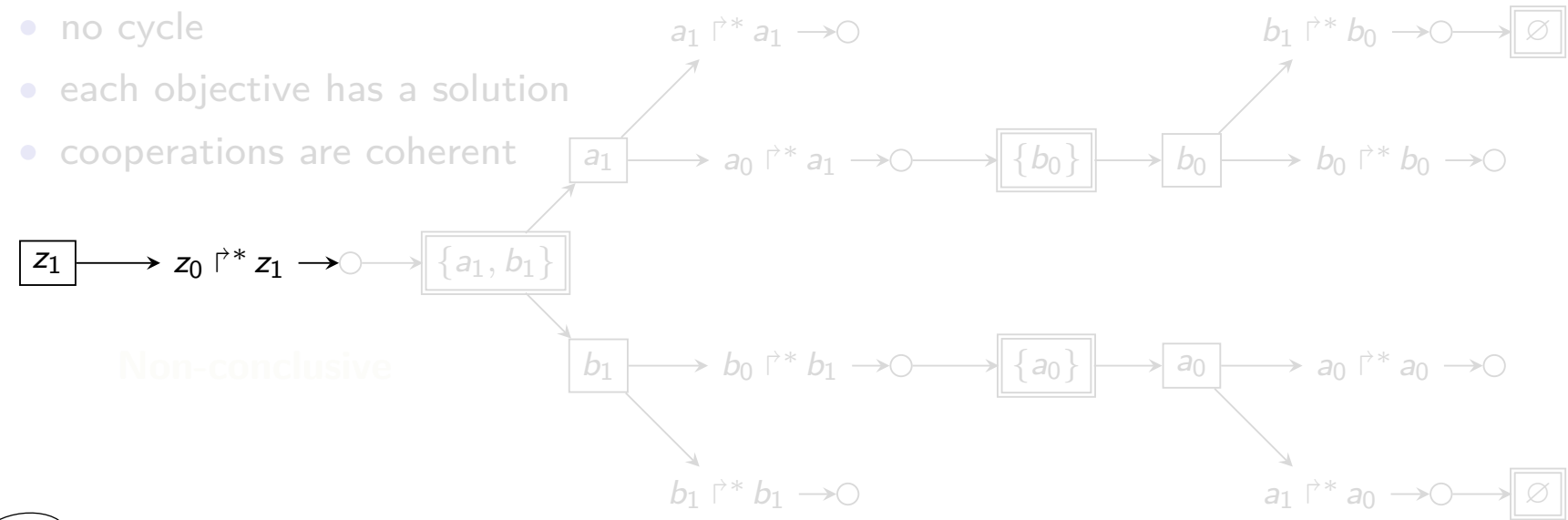

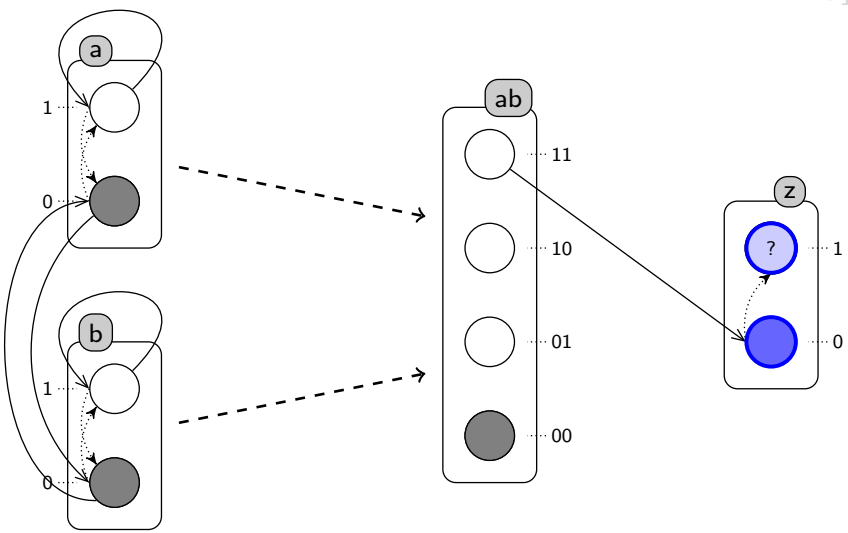

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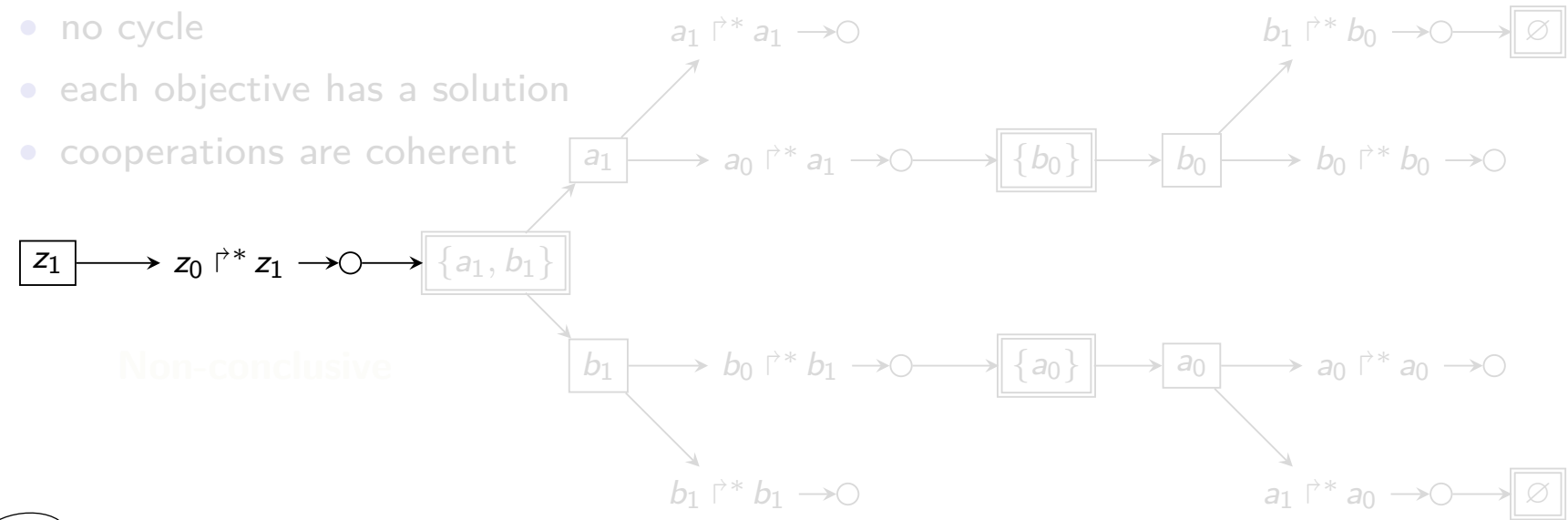

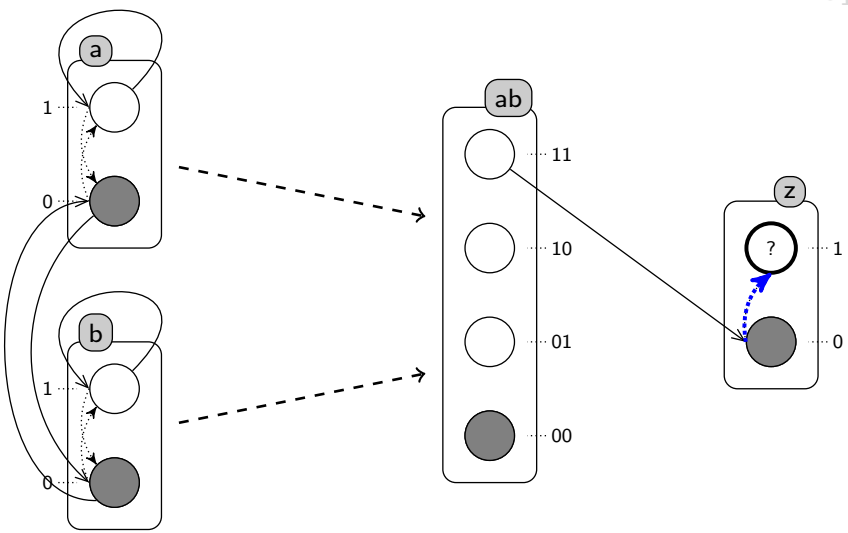

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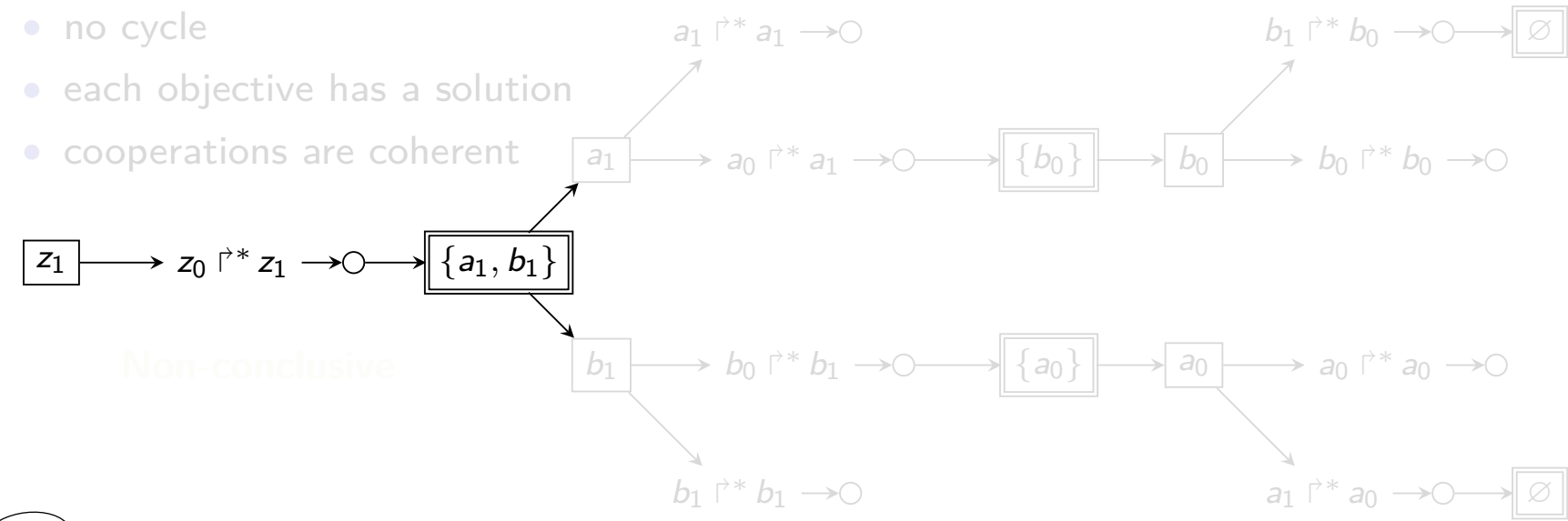

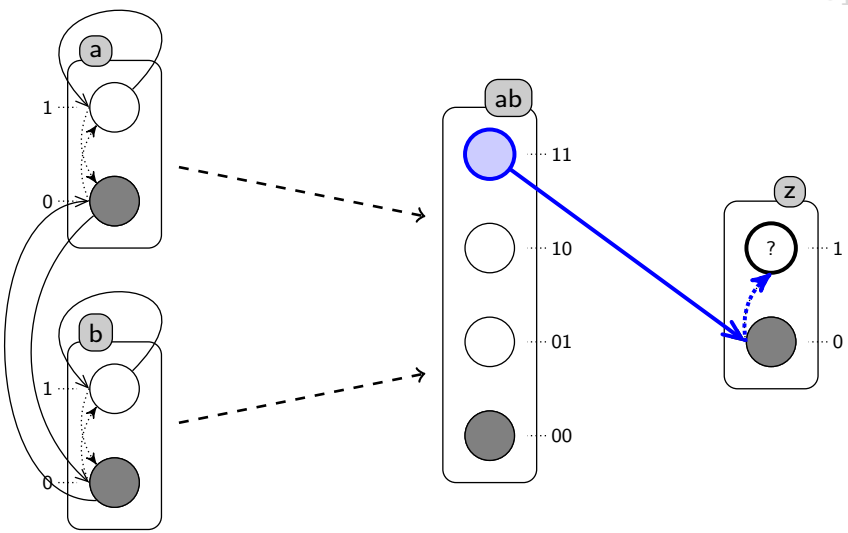

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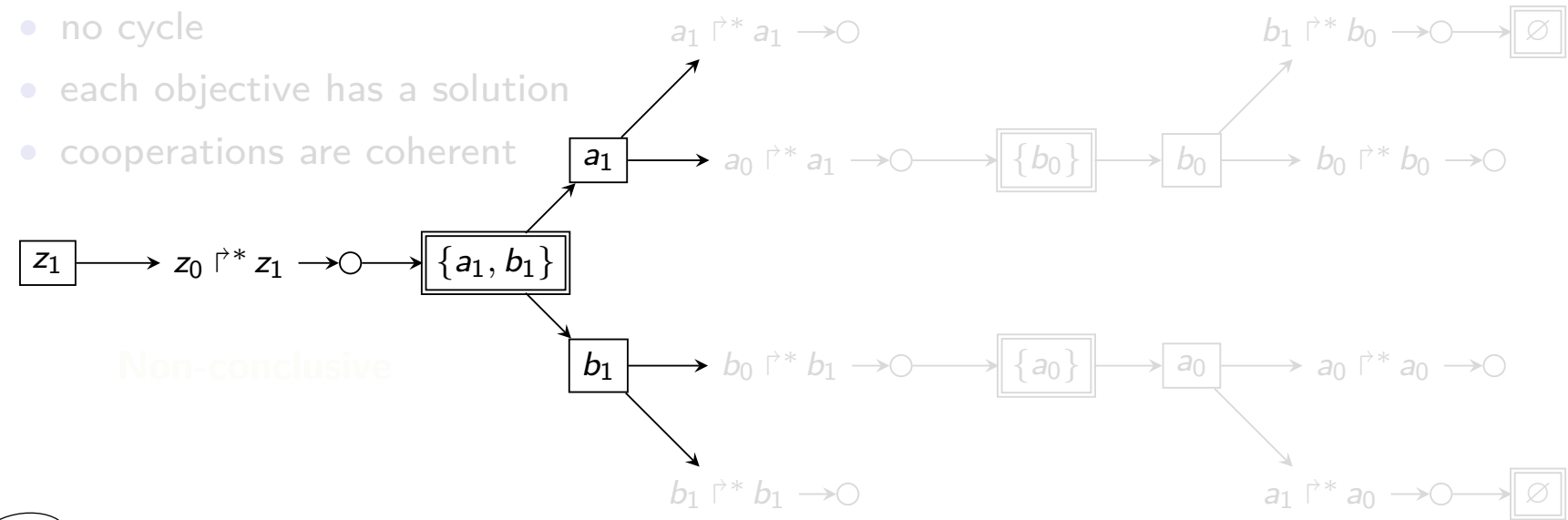

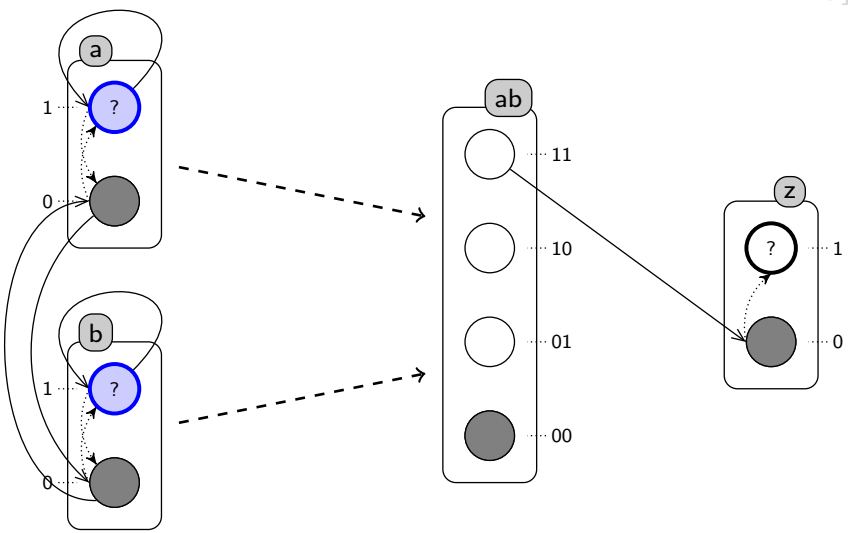

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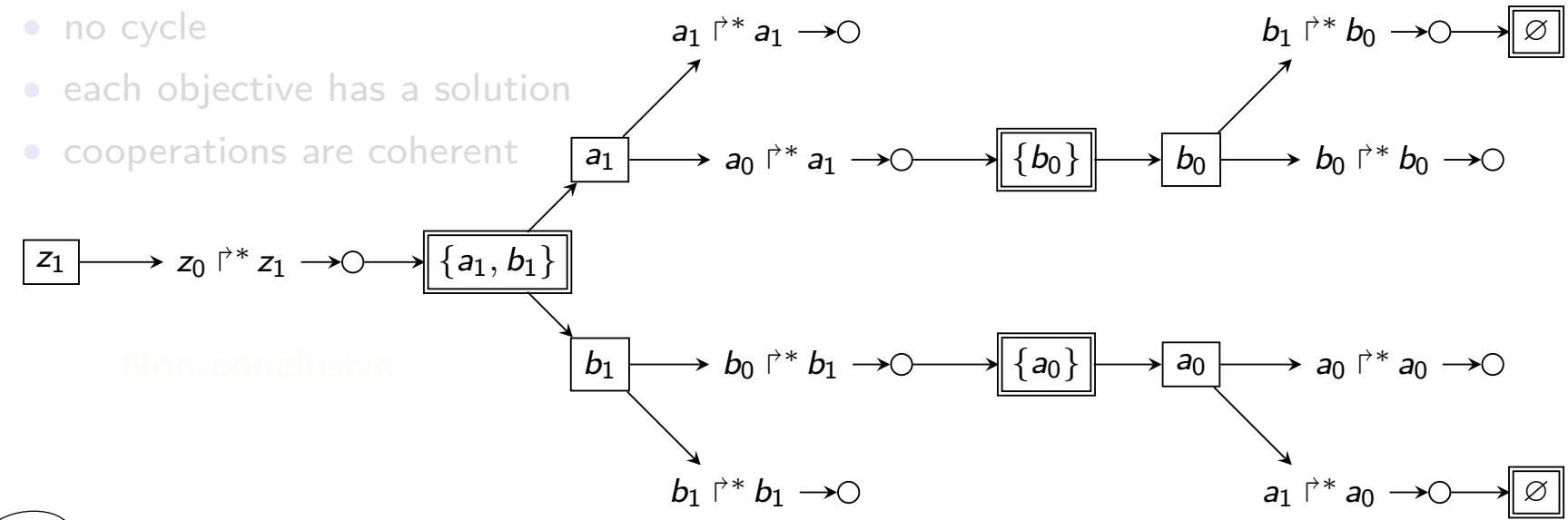

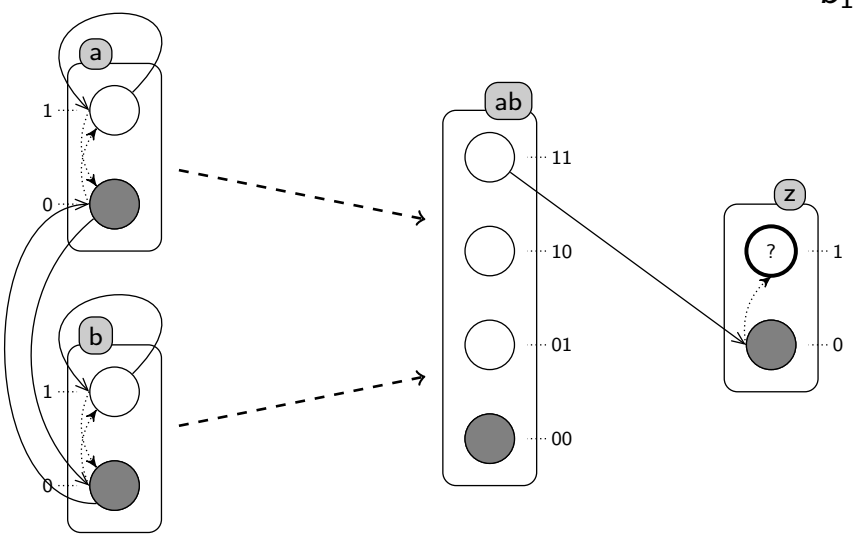

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$z_0 \Rsh^* z_1$	Objective
○	Solution to an objective
$\{a_1, b_1\}$	Synchronization of several processes

Static Analysis of Canonical Process Hitting

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

Sufficient condition:

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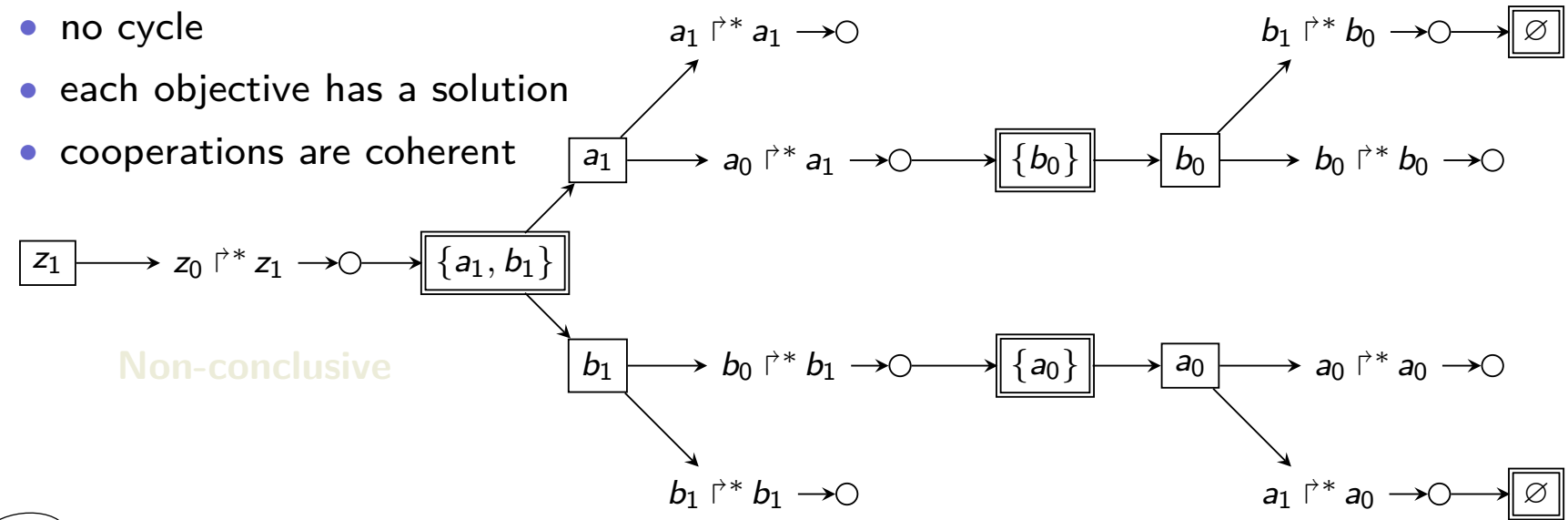

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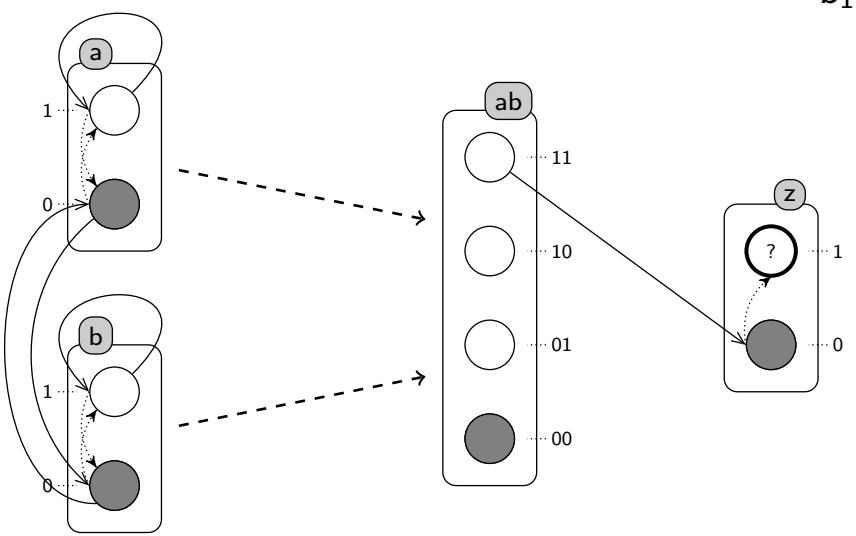

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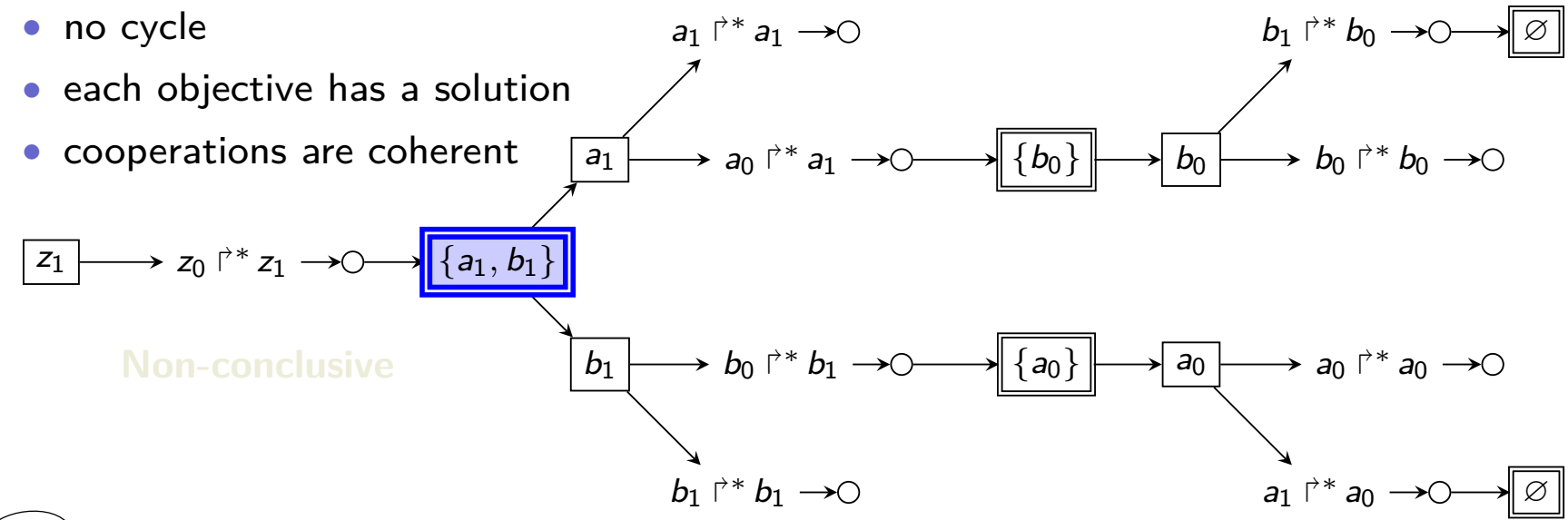

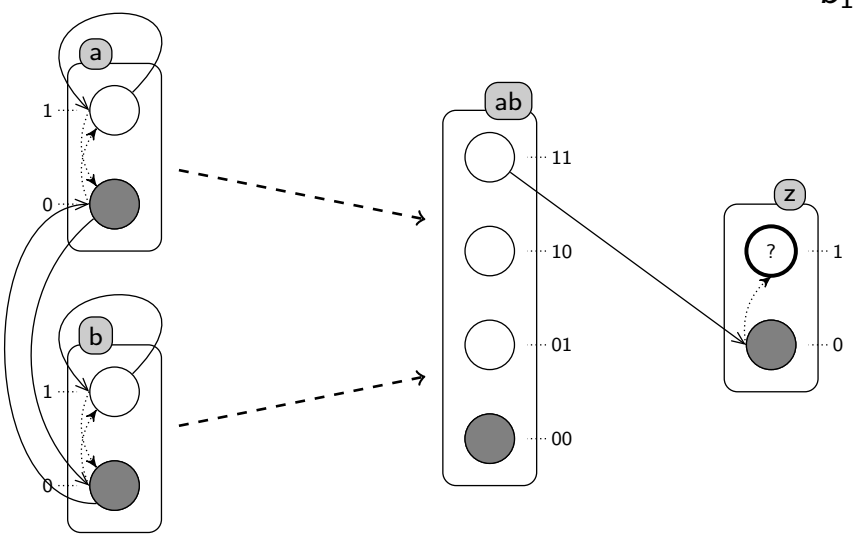

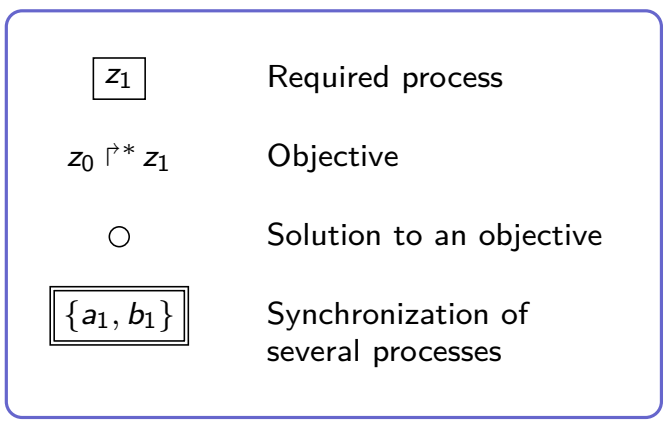

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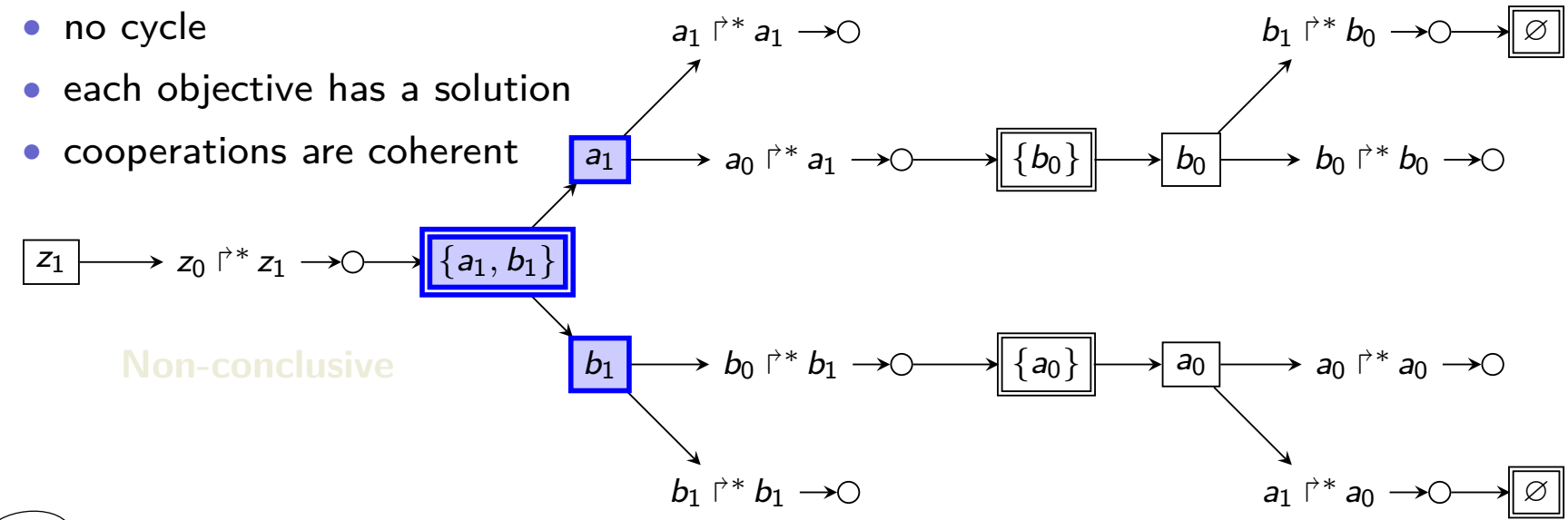

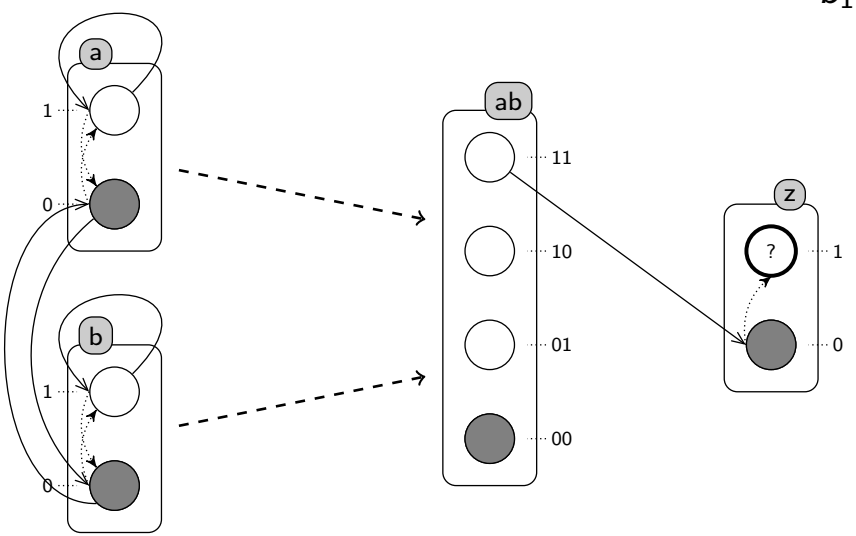

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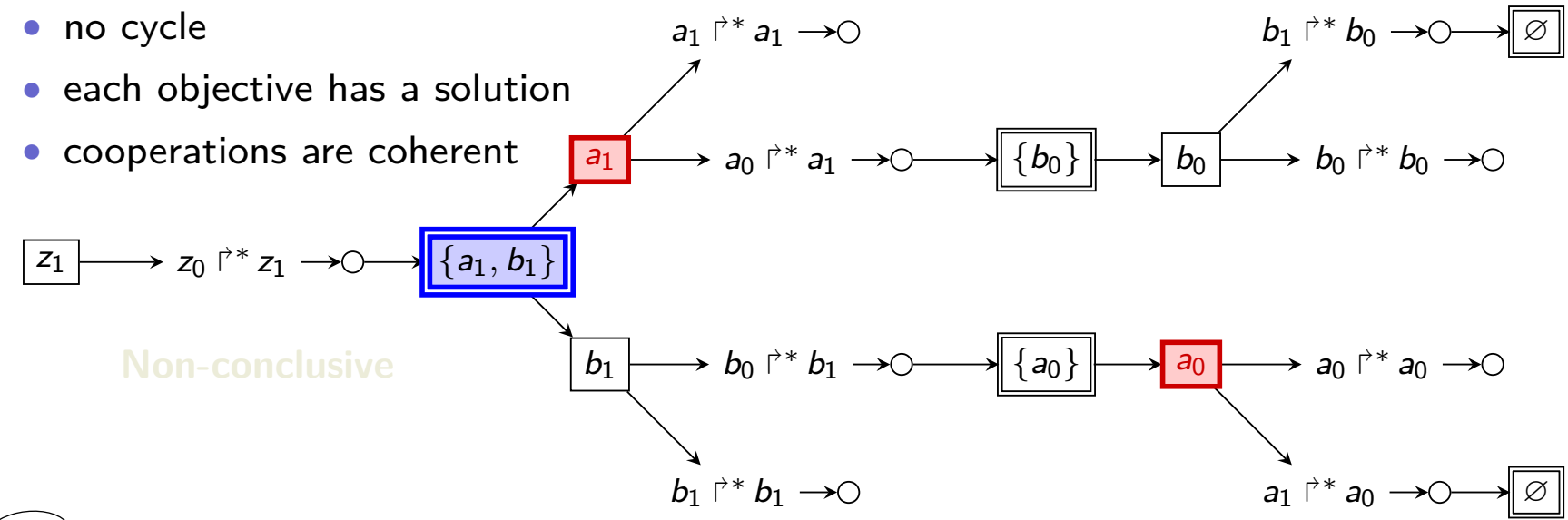

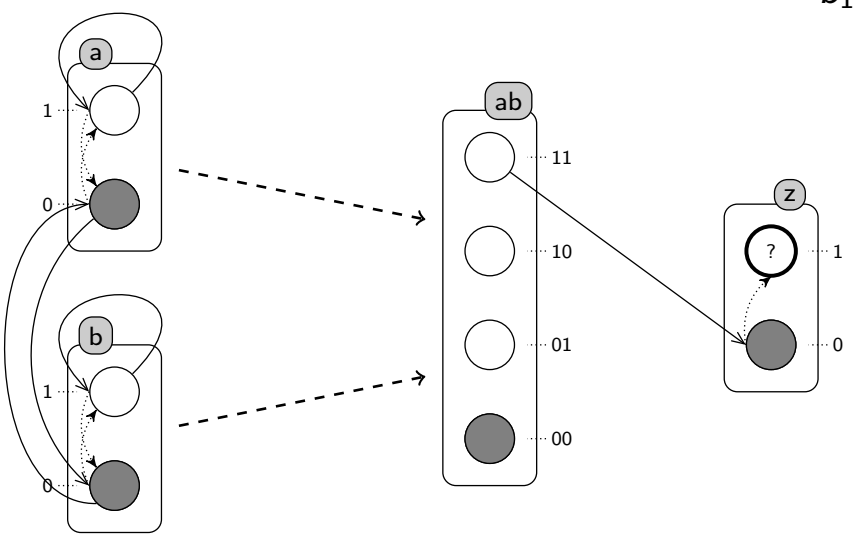

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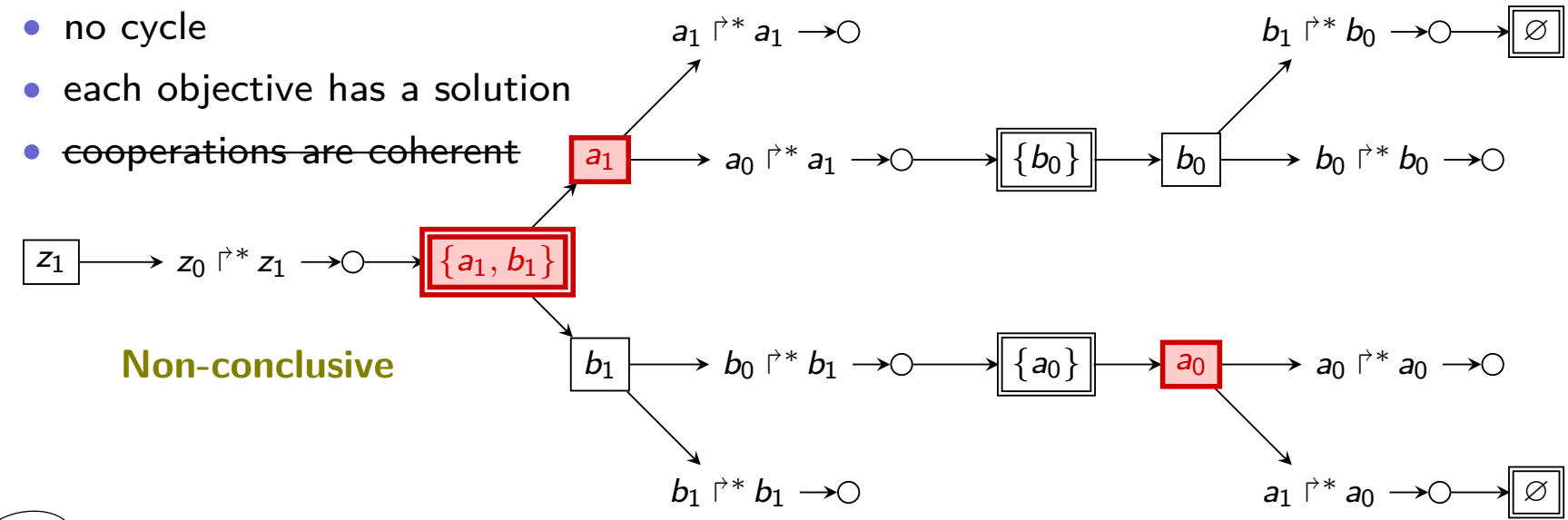

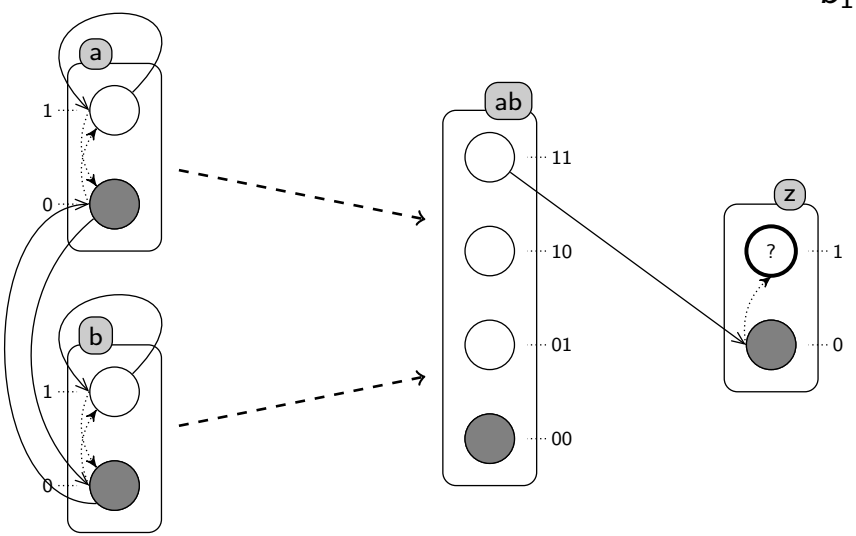

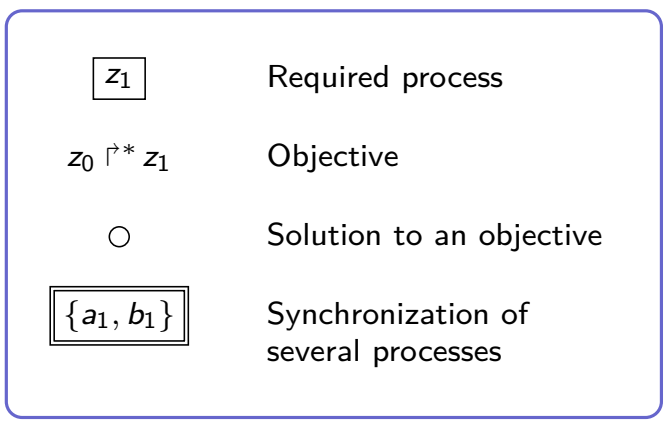

Implementation of the Static Analysis Into PINT

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):
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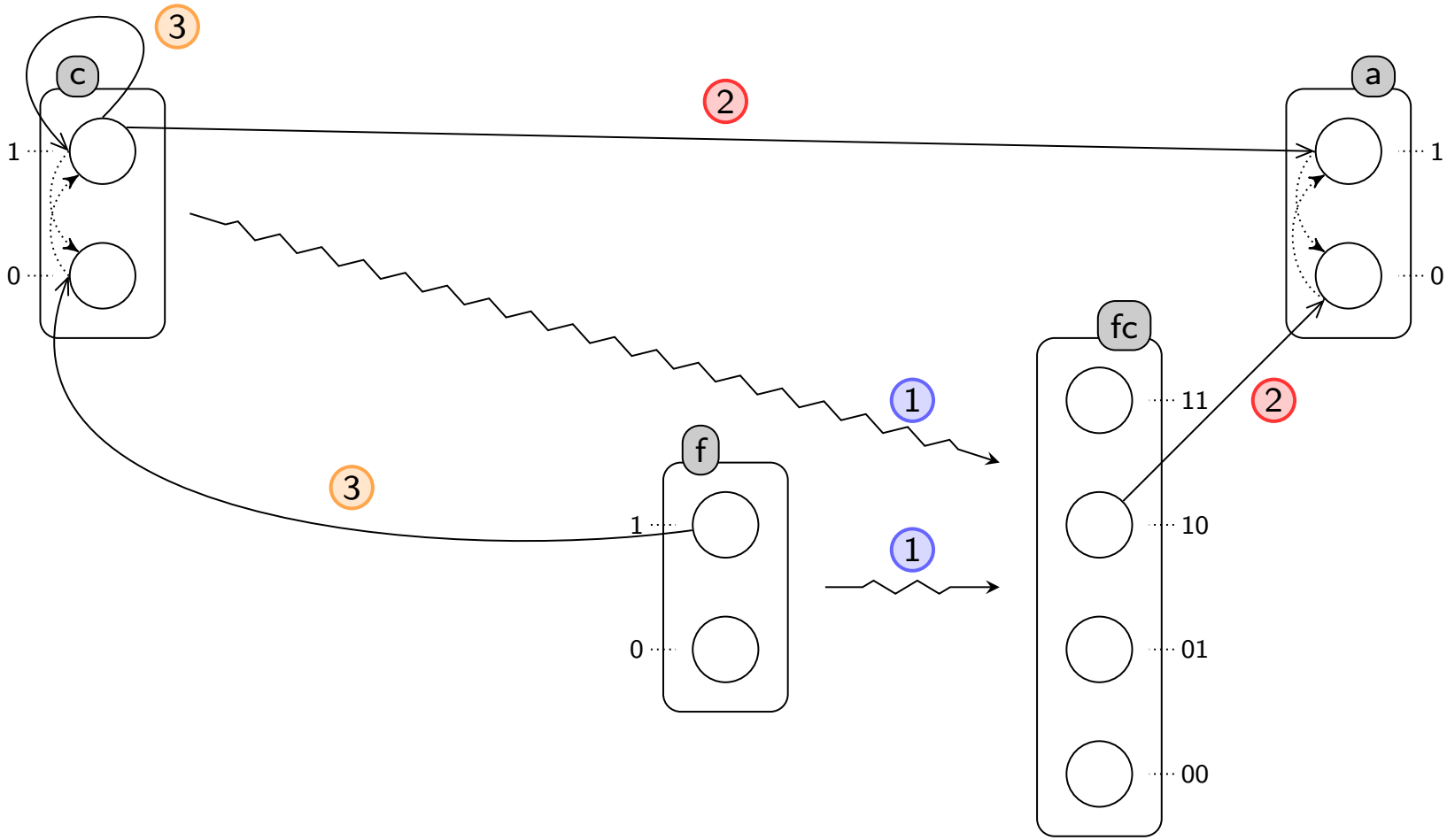
Makes the study of large networks tractable:

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

Formal Translation Into Canonical Form



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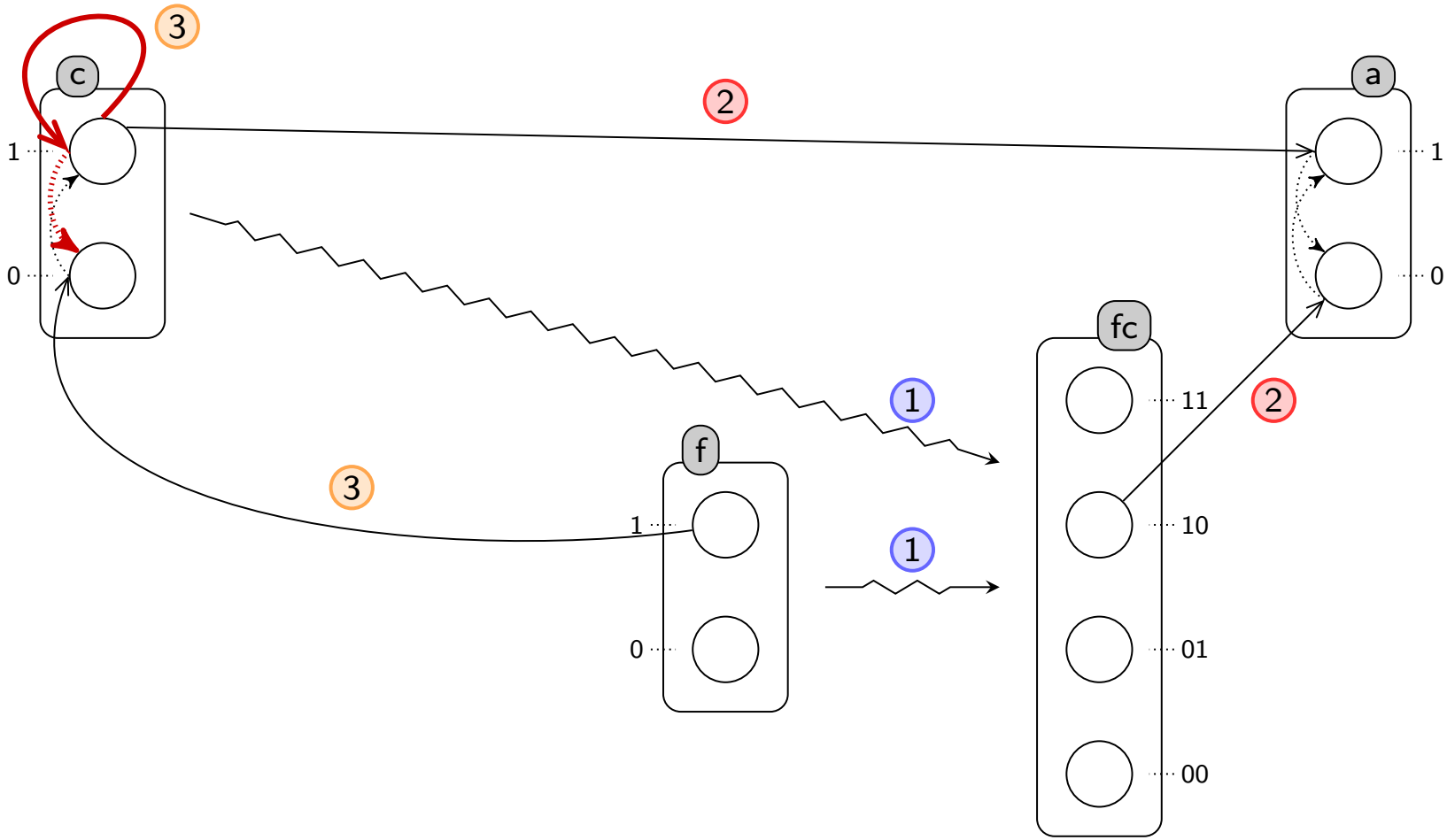

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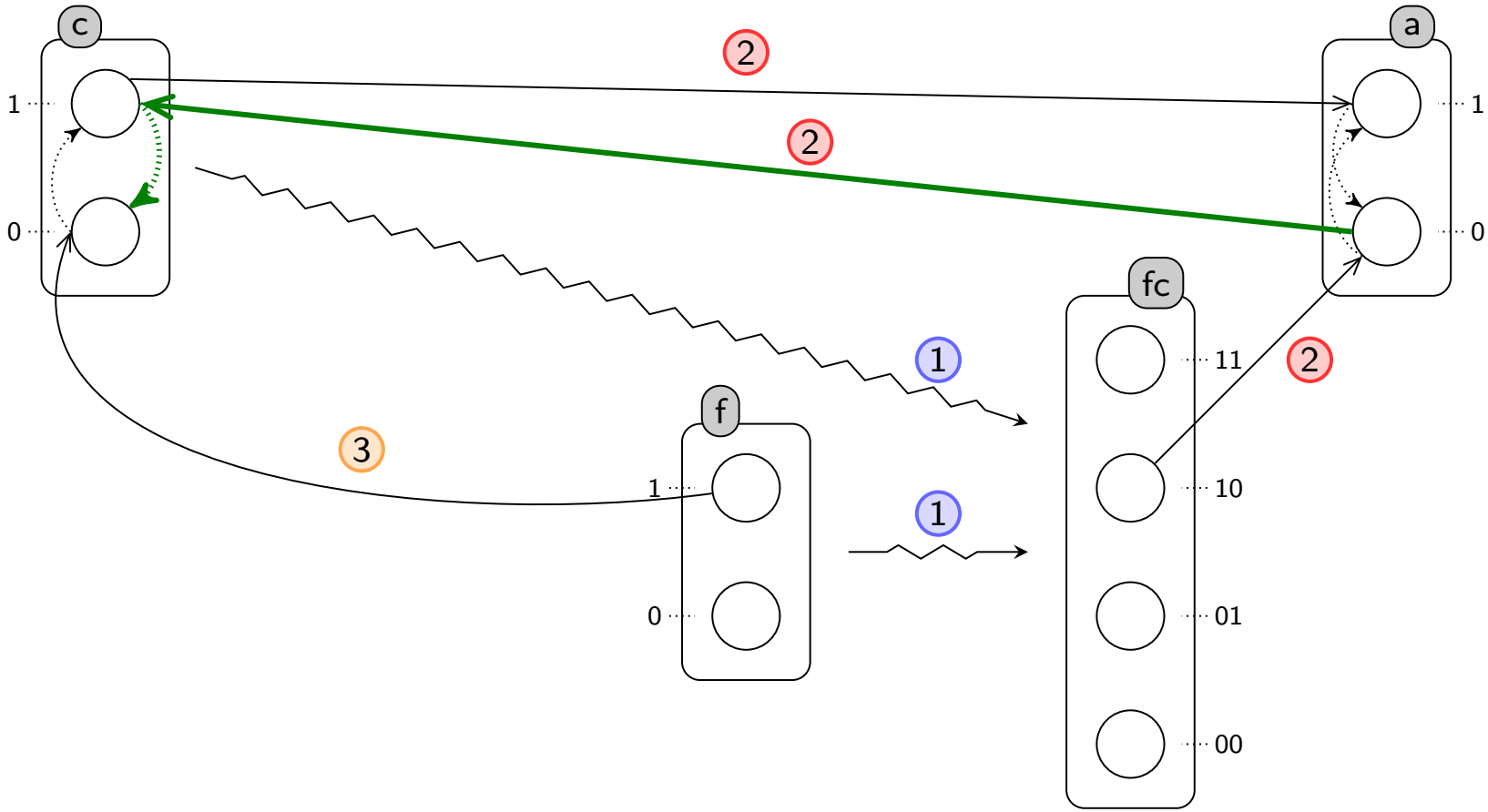

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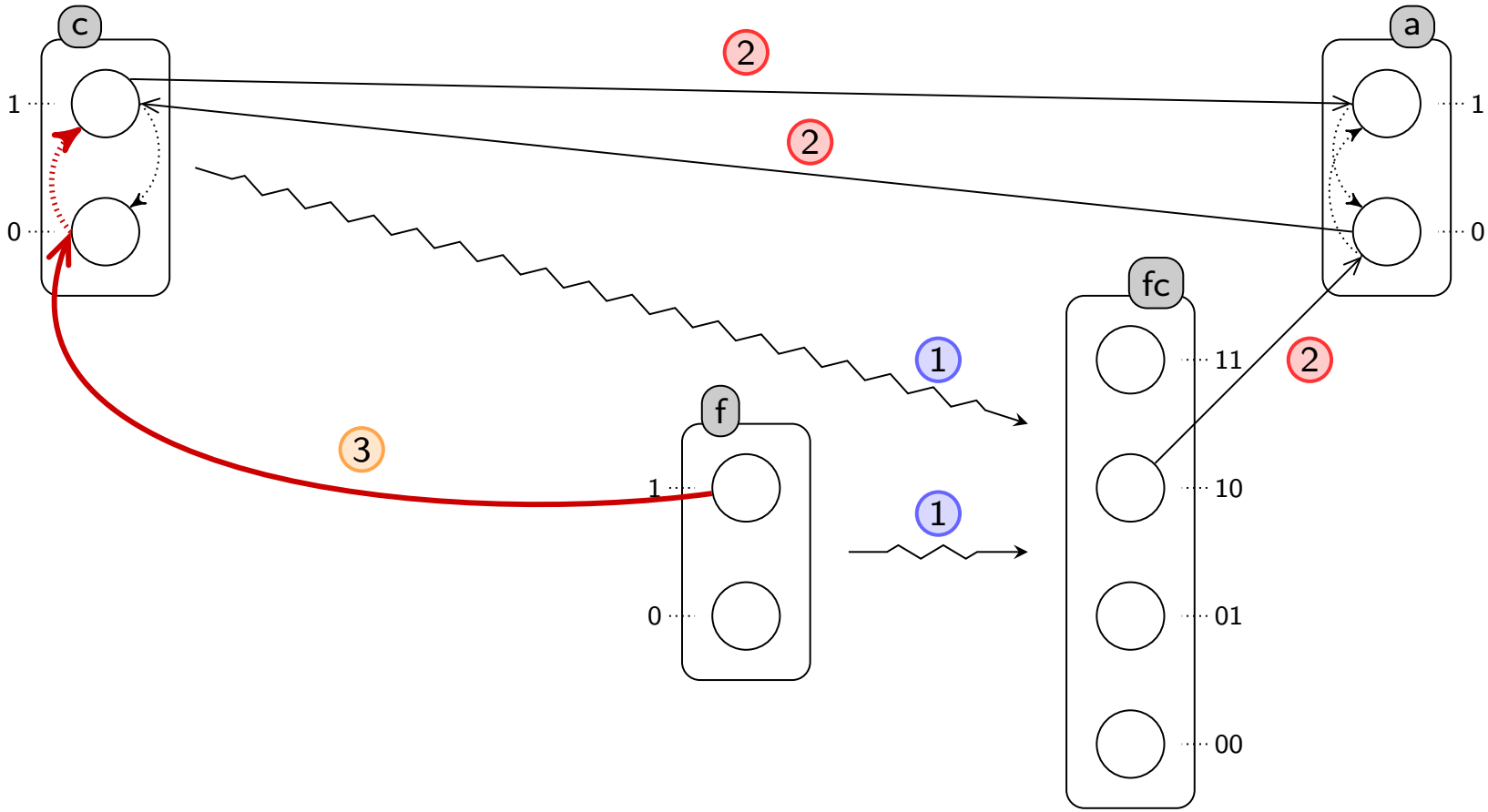

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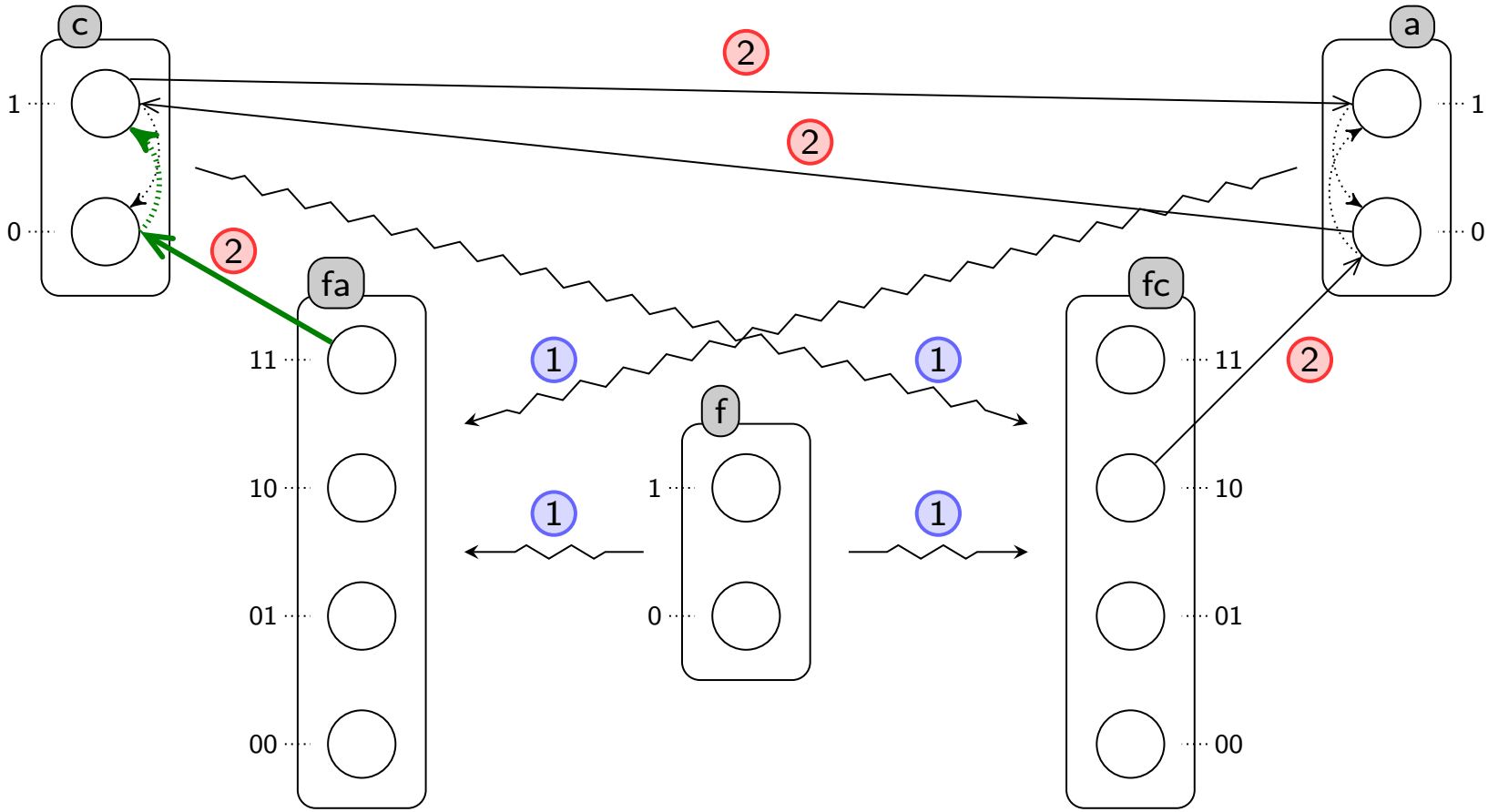

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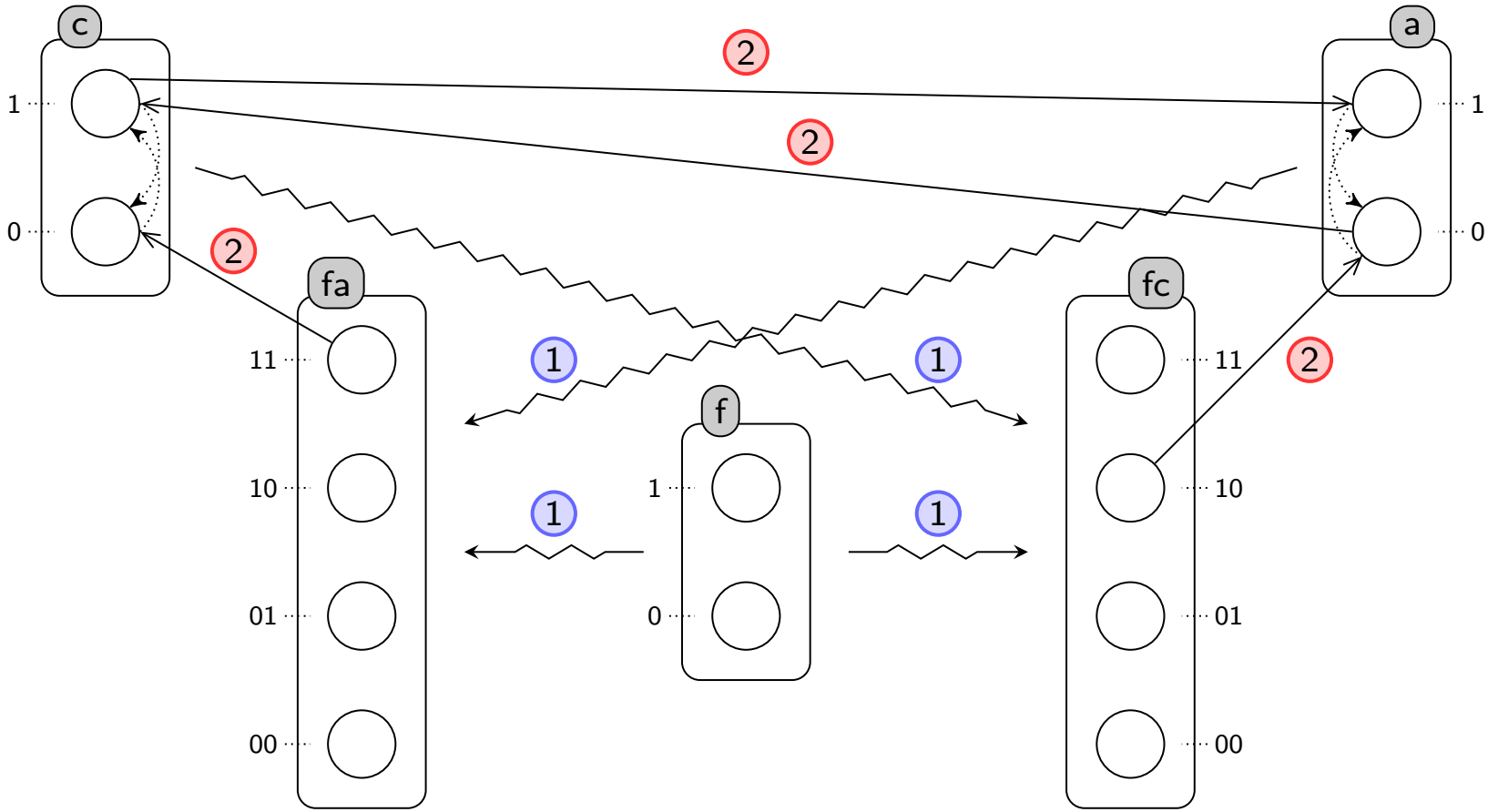
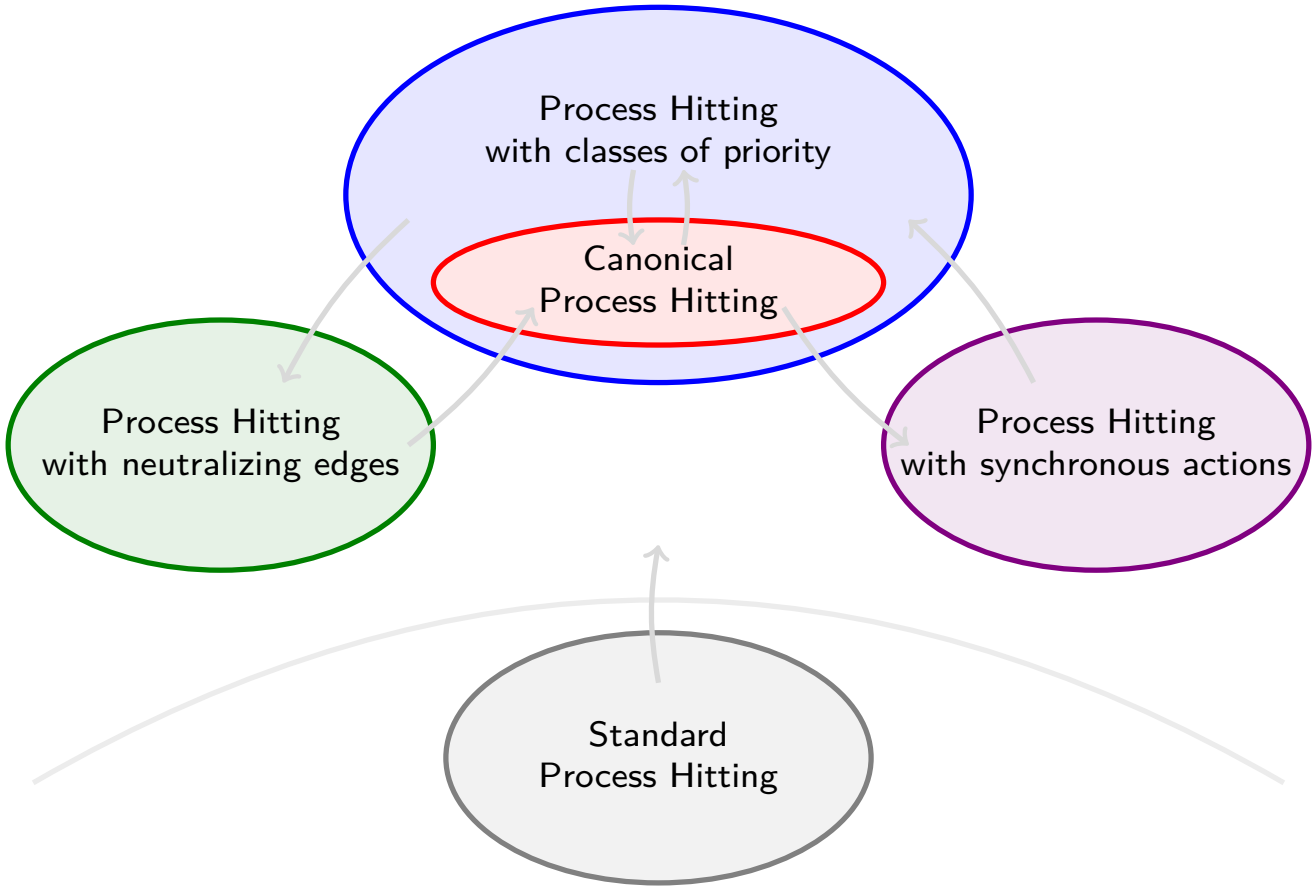


→ Same dynamics (with supplemental cooperative sorts)

→ 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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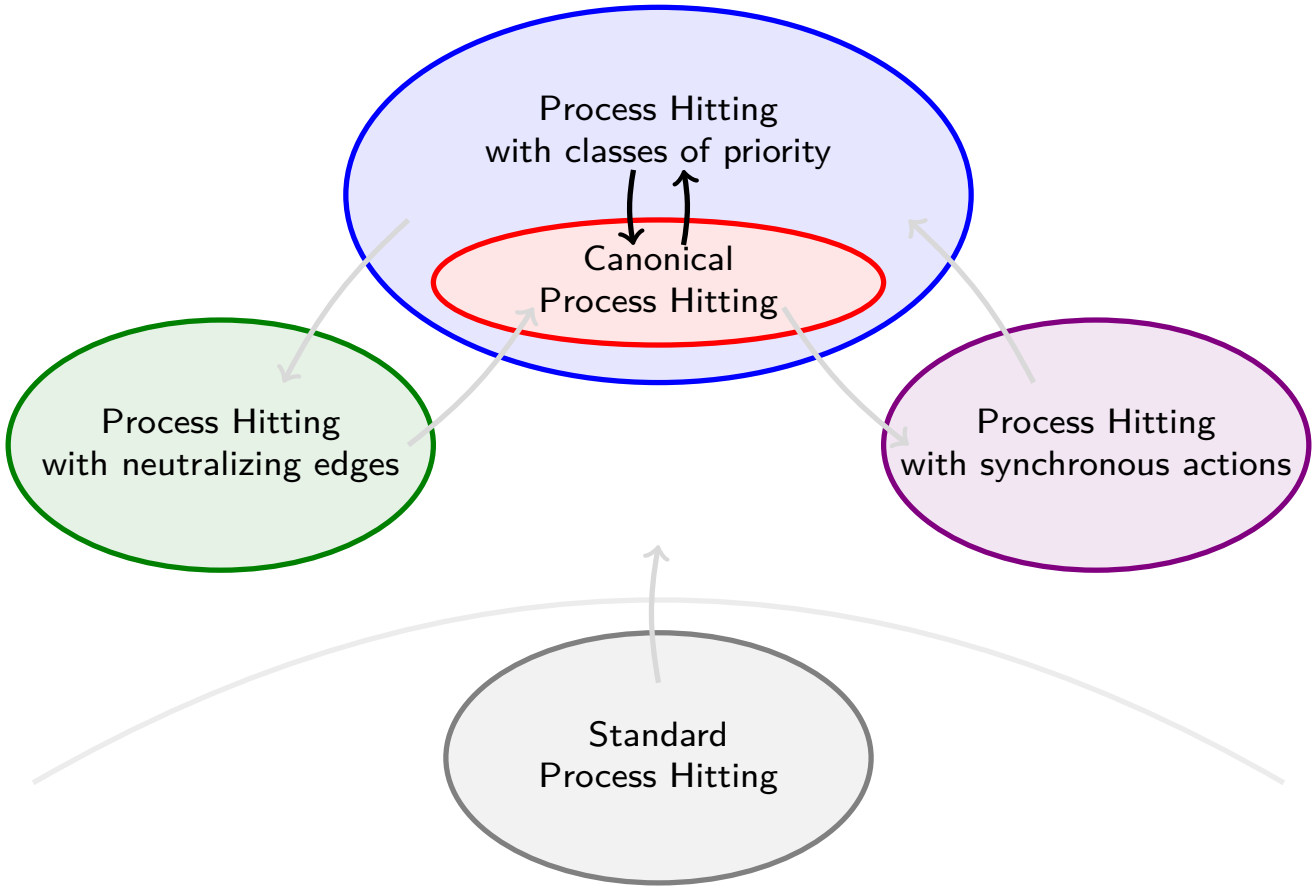

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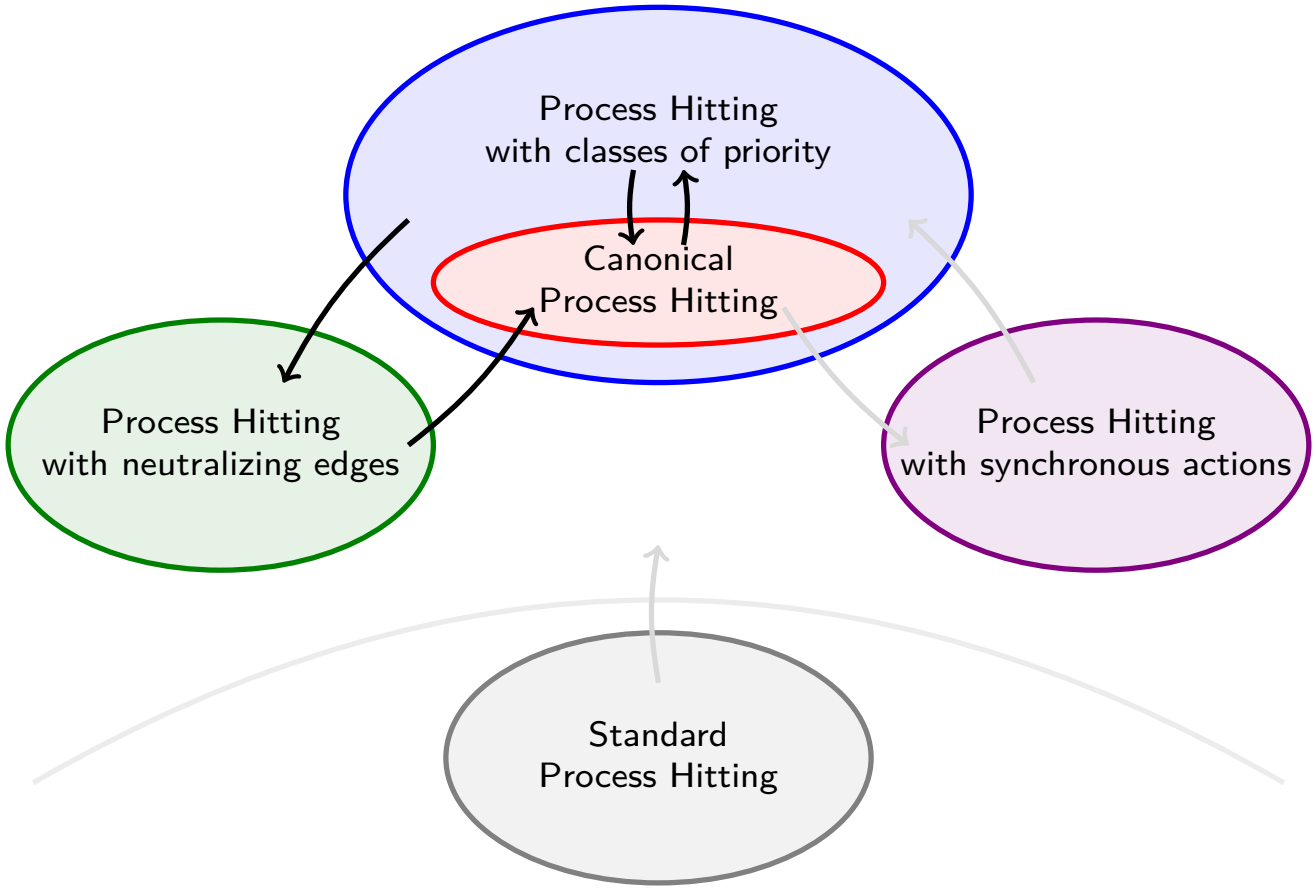

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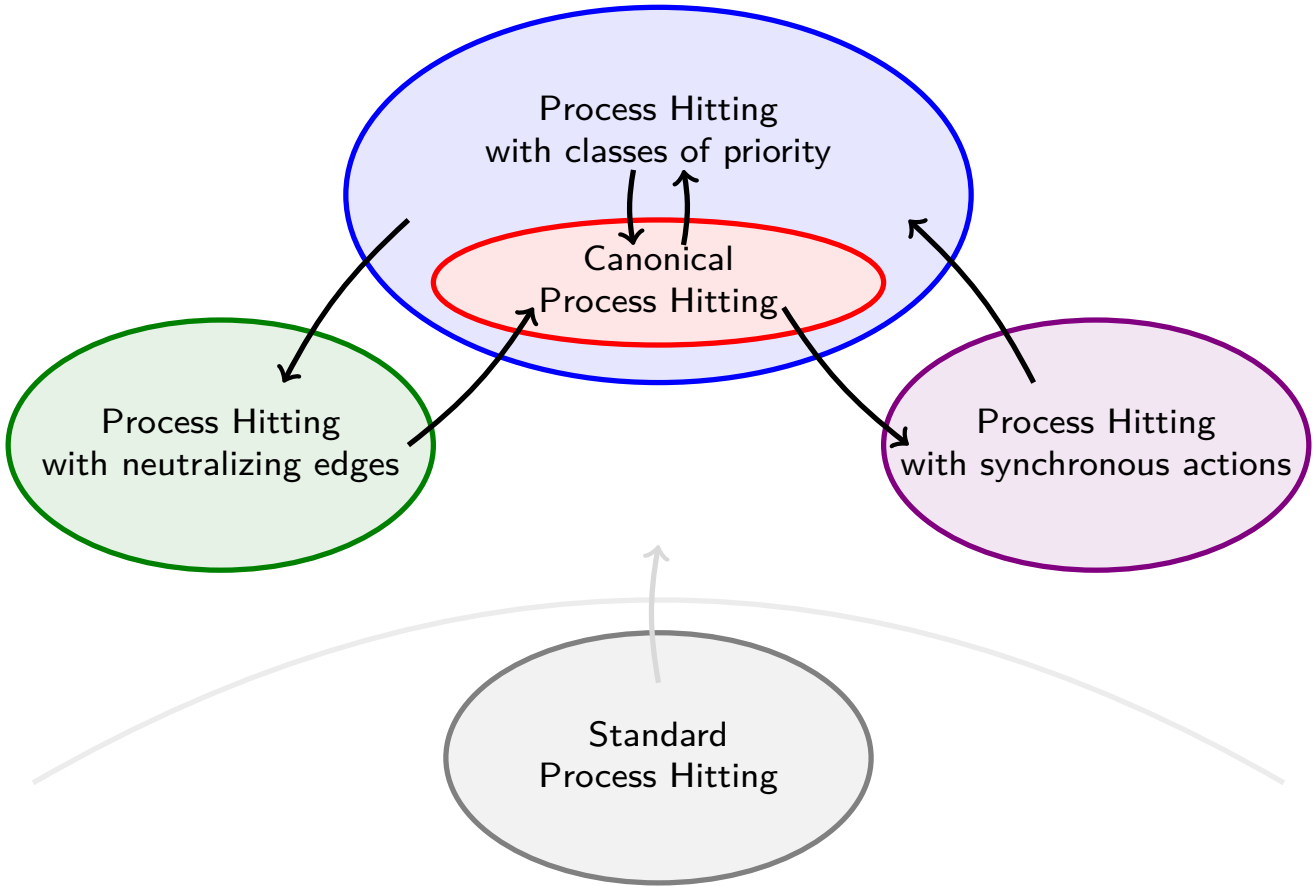

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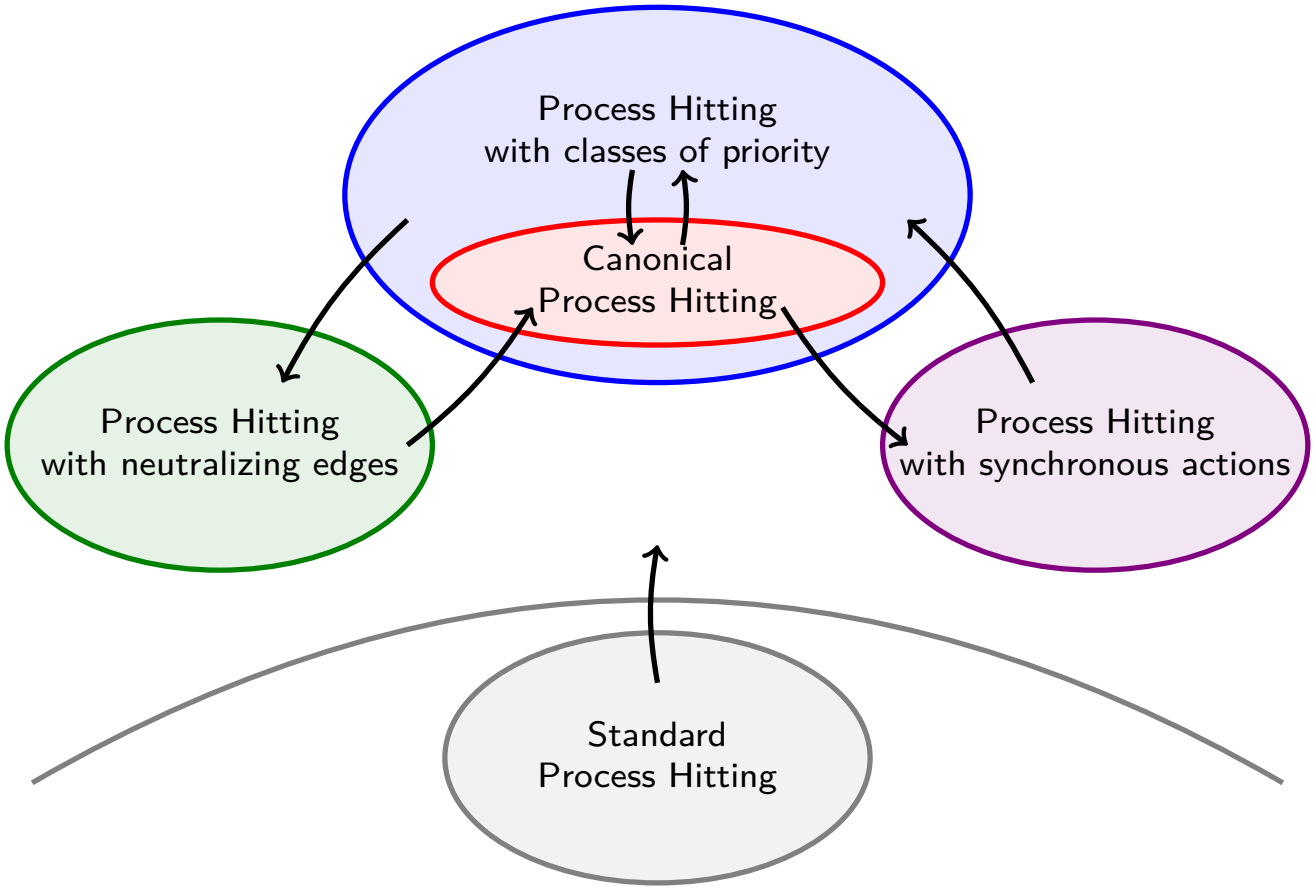

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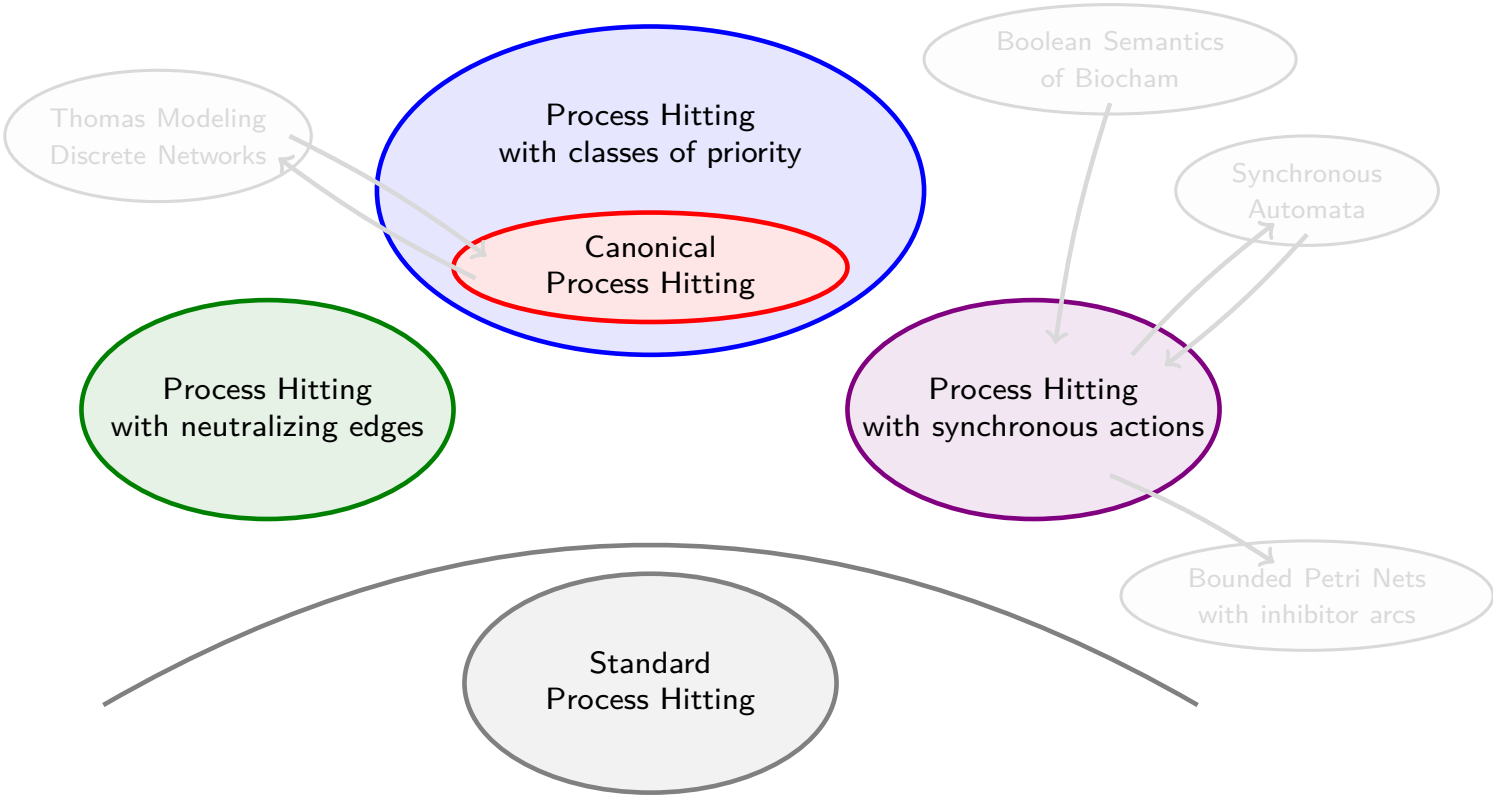
Translation From and To Other Discrete Models



- Equivalence with discrete networks / Thomas modeling
- Equivalence with synchronous automata networks
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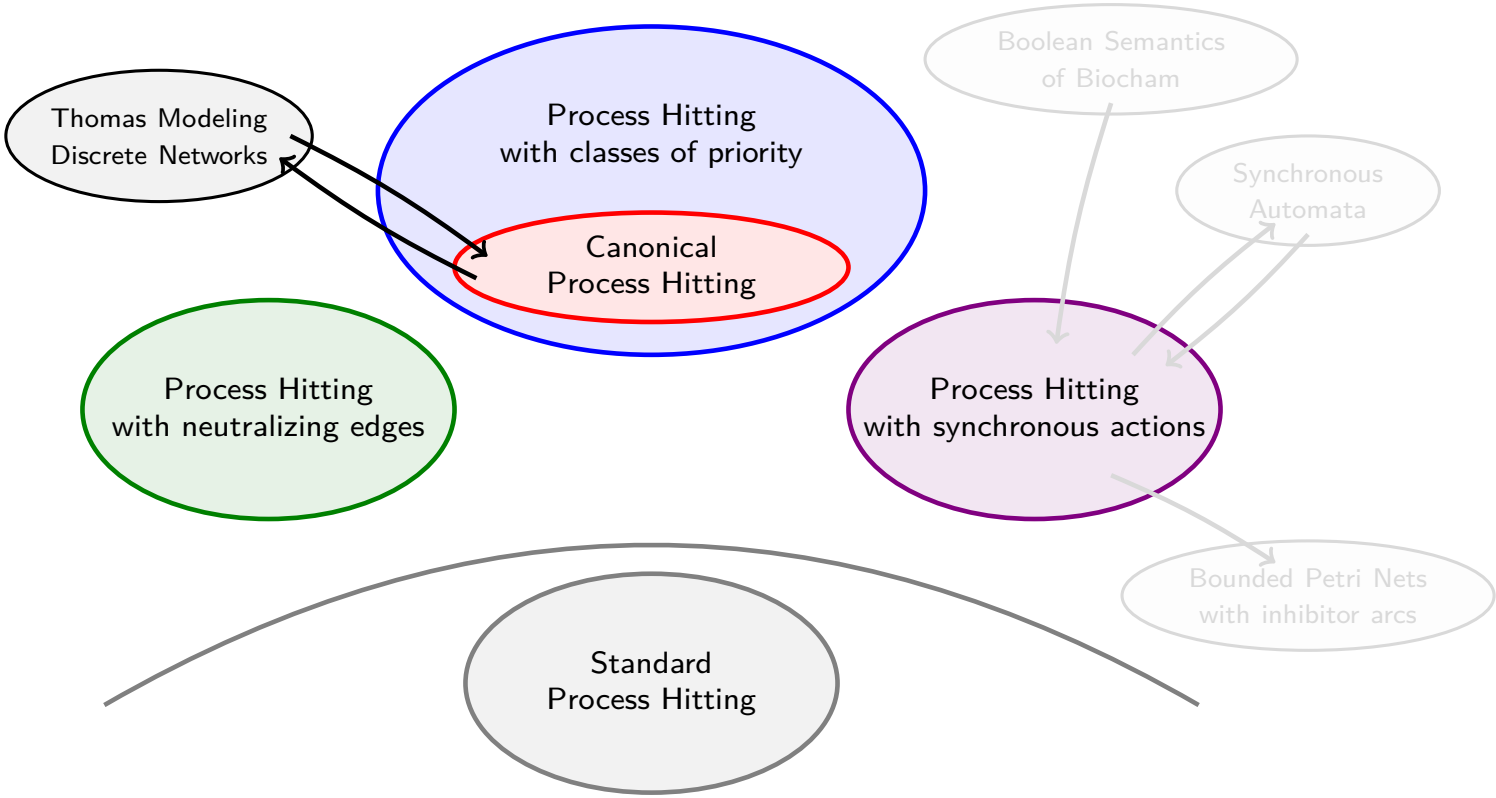

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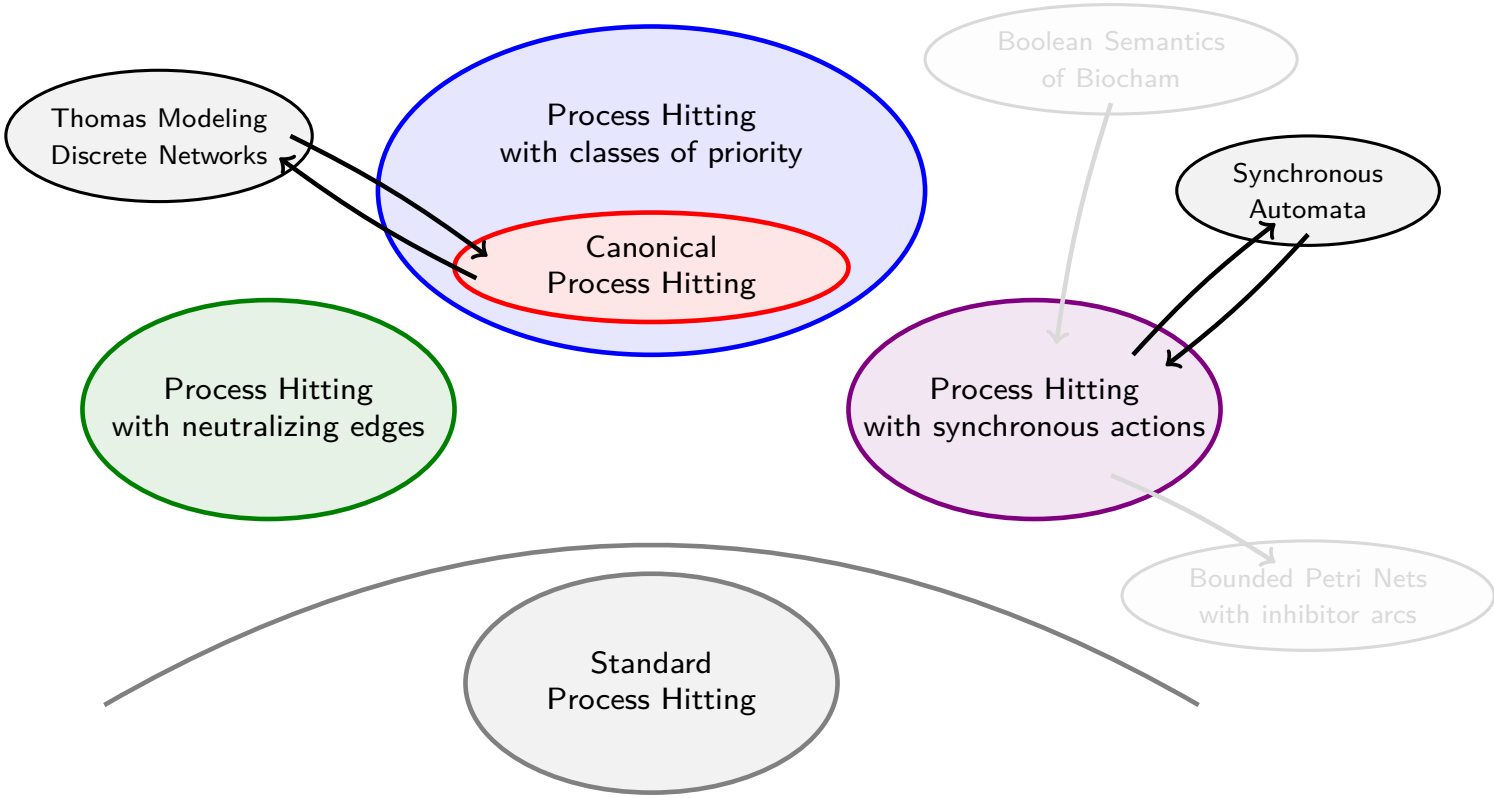

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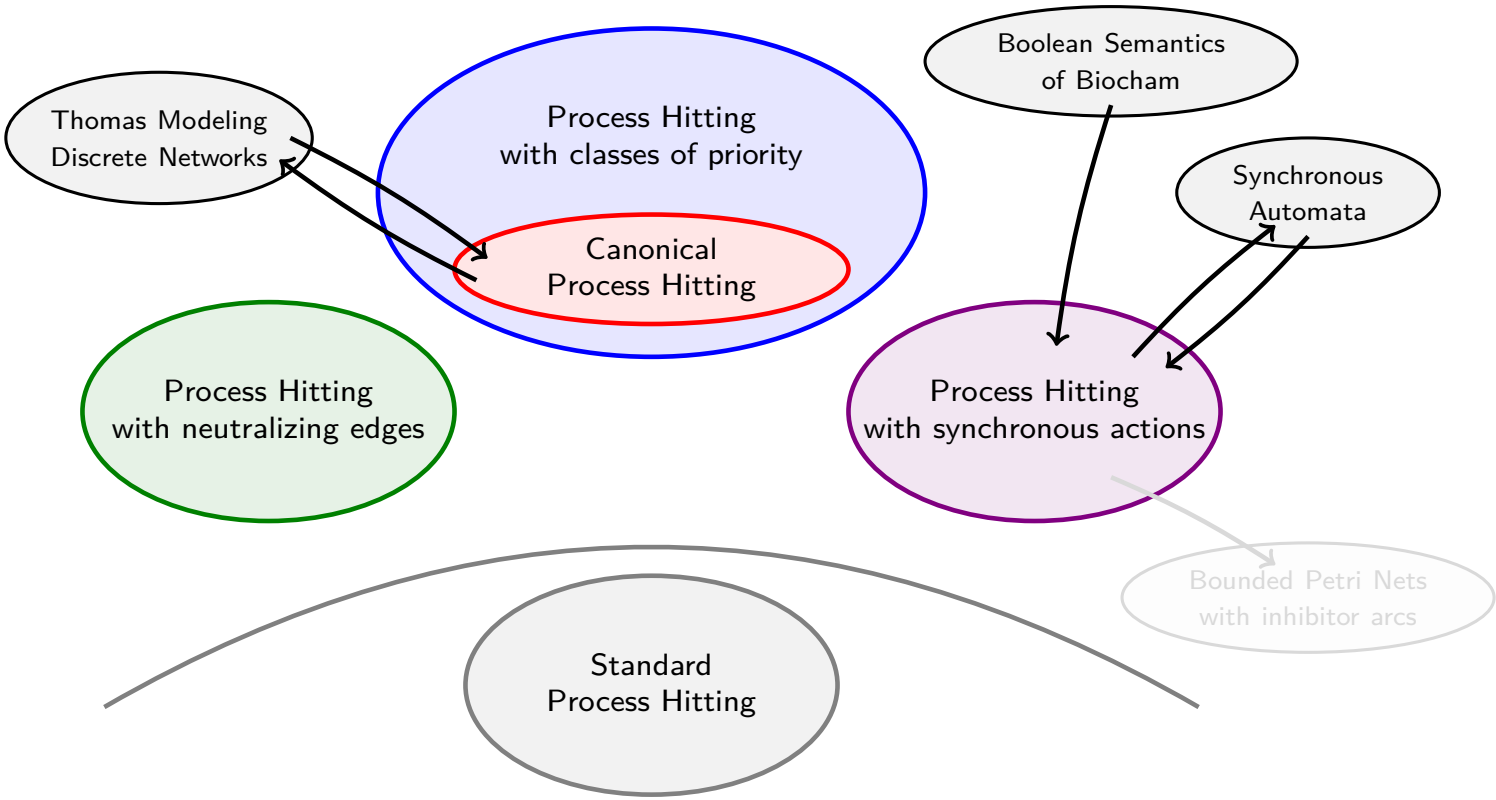

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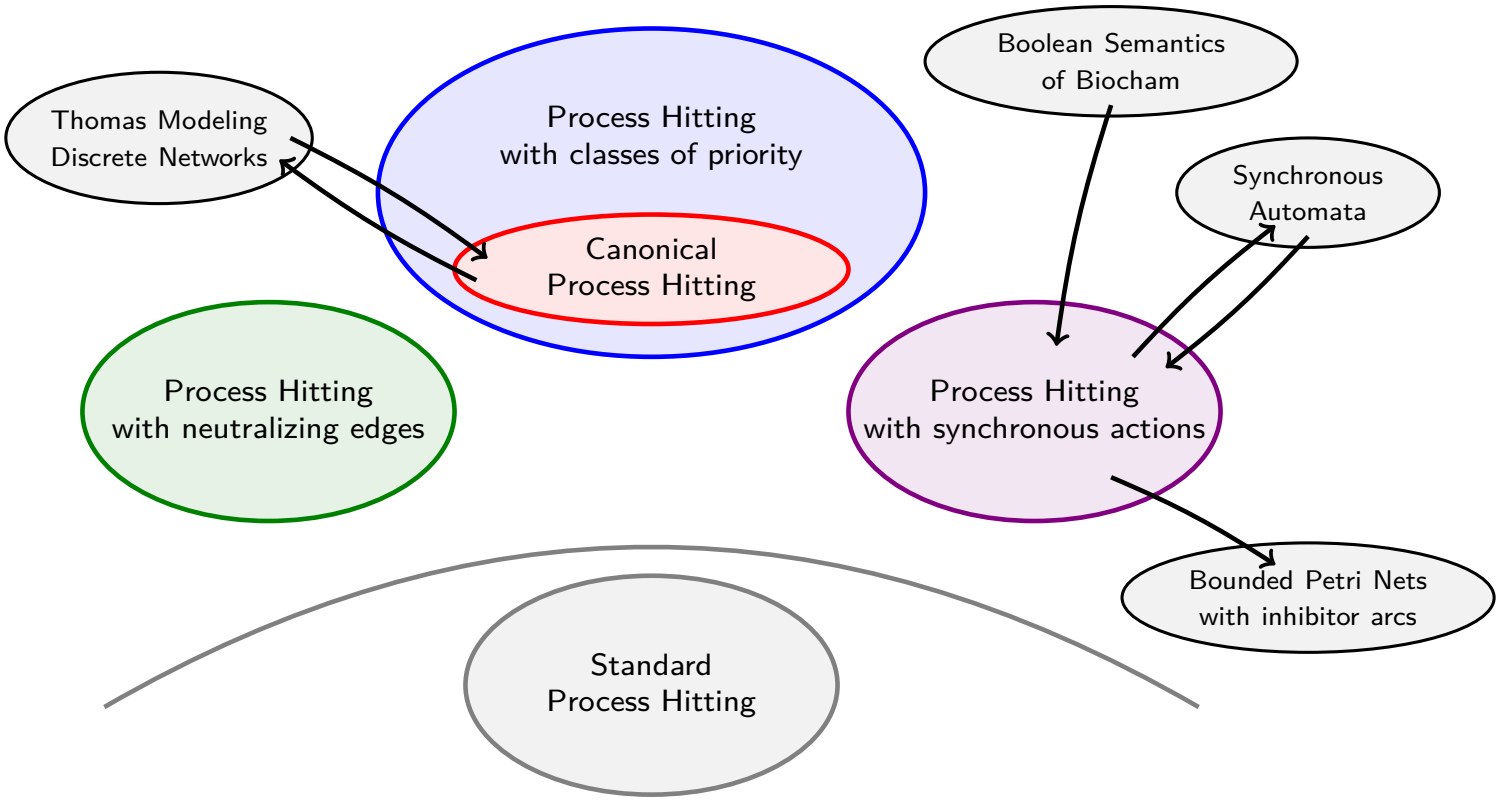

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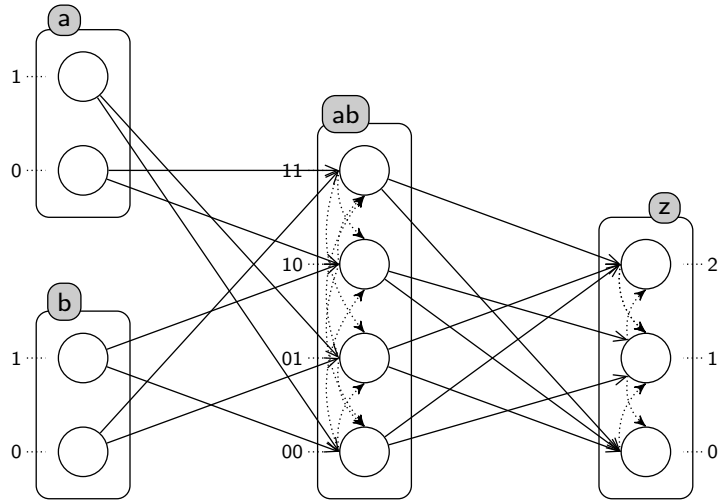
Inferring a BRN with Thomas' parameters



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

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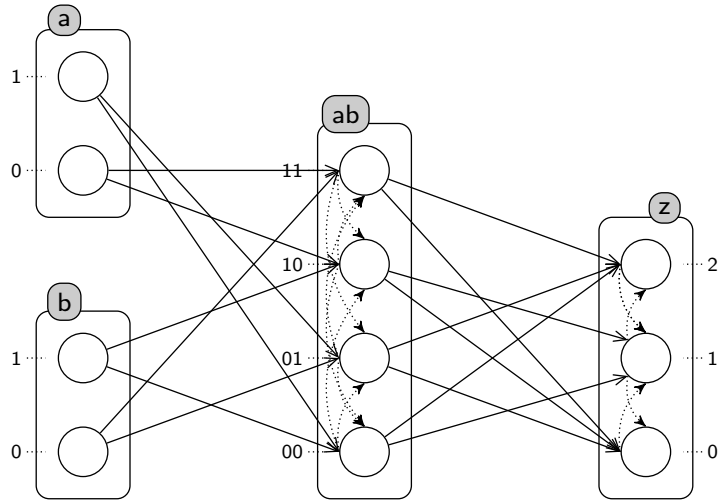

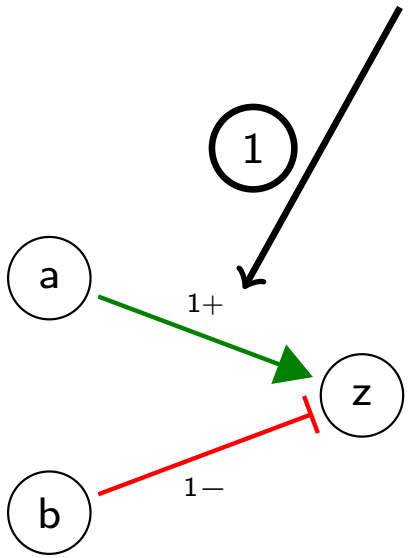

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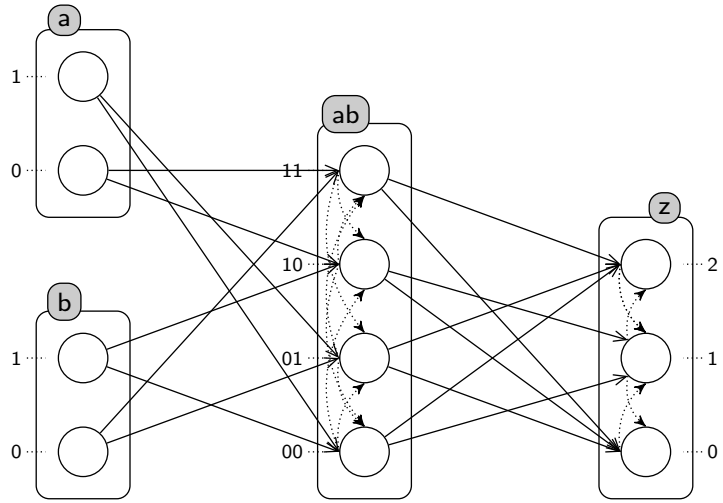

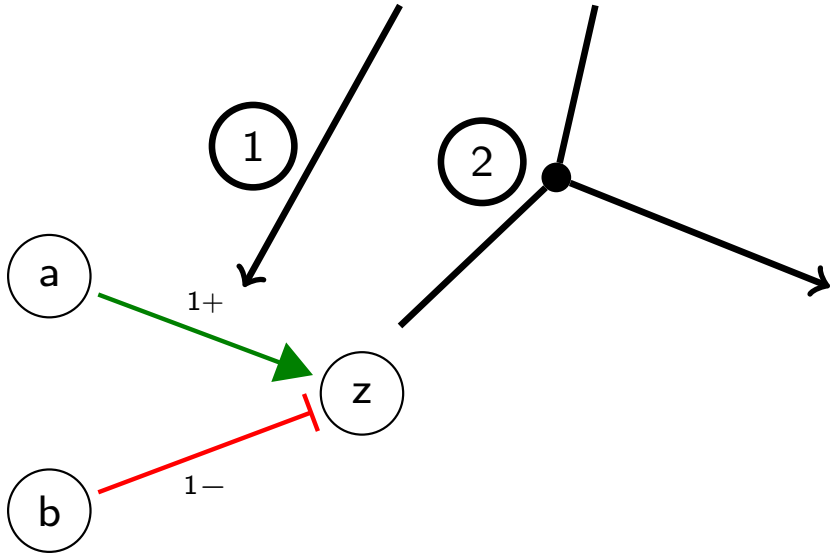

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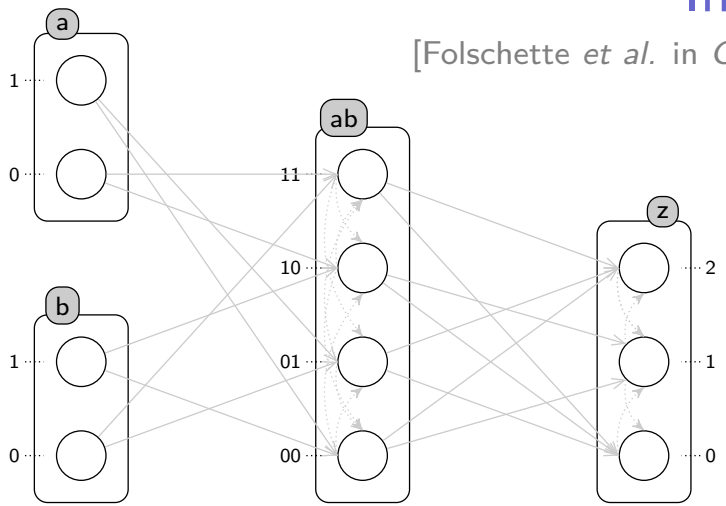
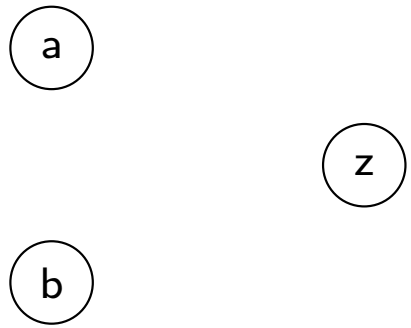
Inferring the Interaction Graph

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





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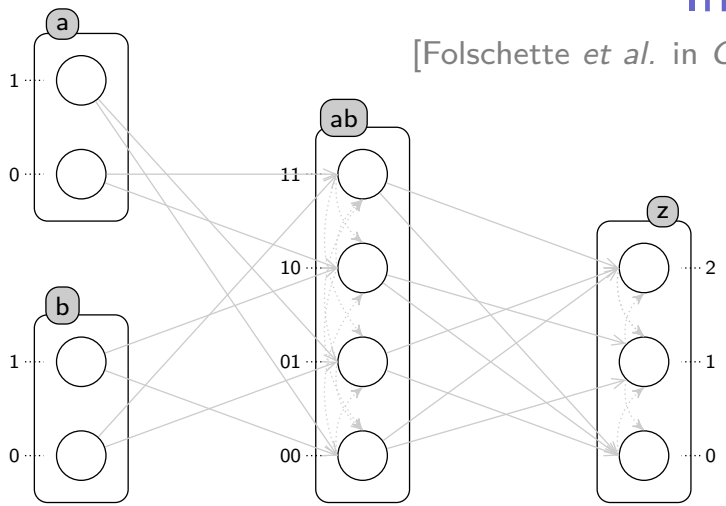

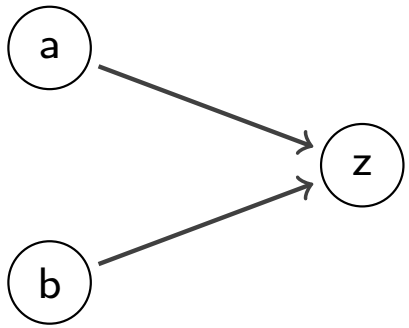

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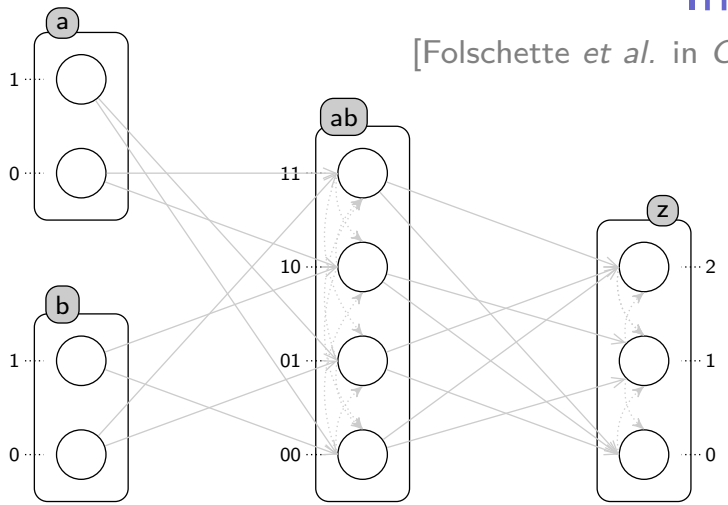

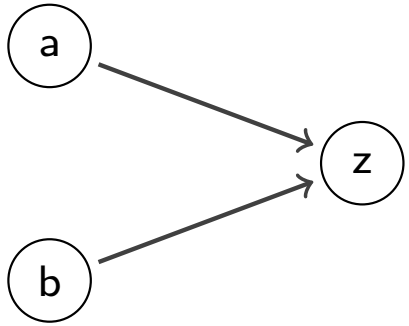

→ **Exhaustive search in all possible configurations**

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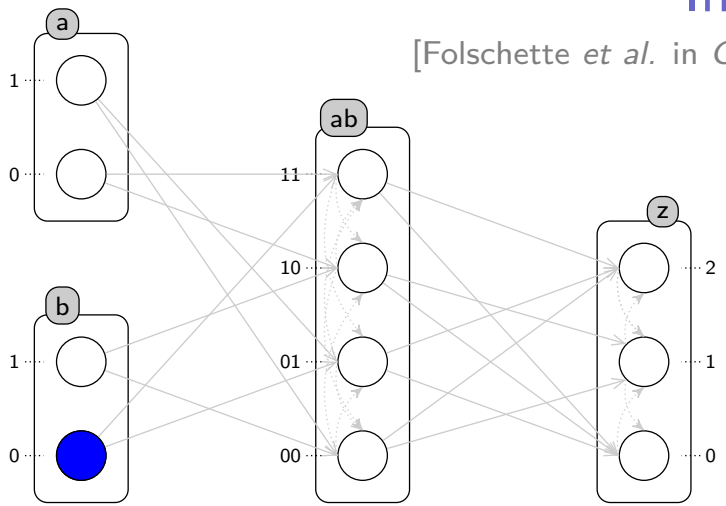

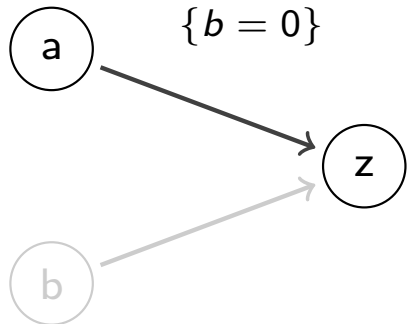

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1. Pick one regulator [a], and choose an active process for all the others [b_0].

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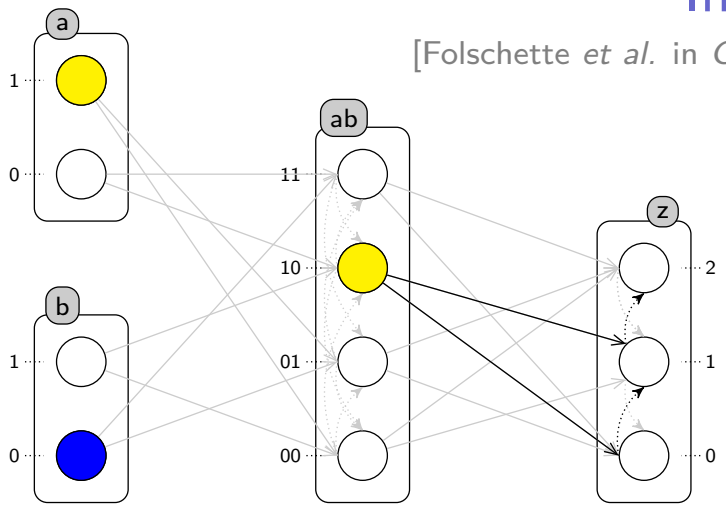
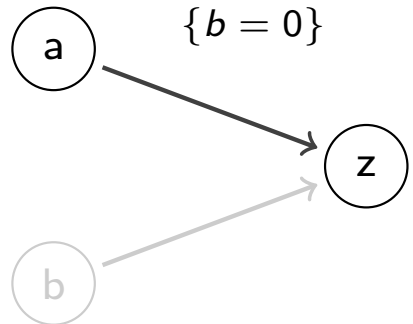


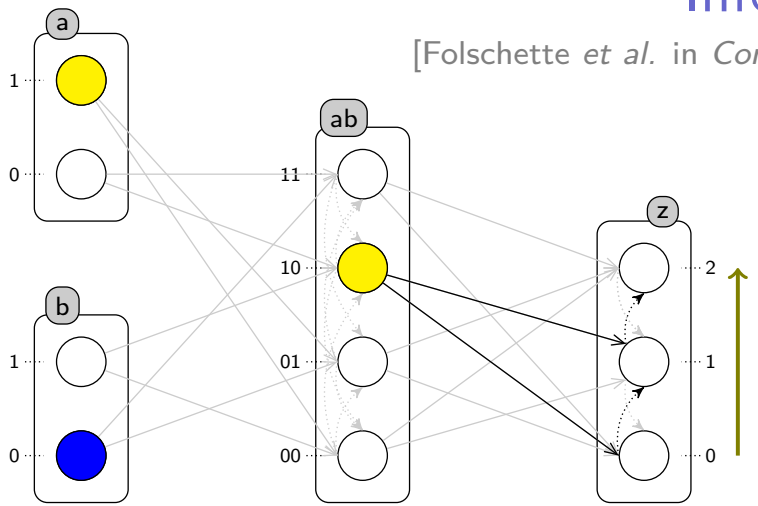


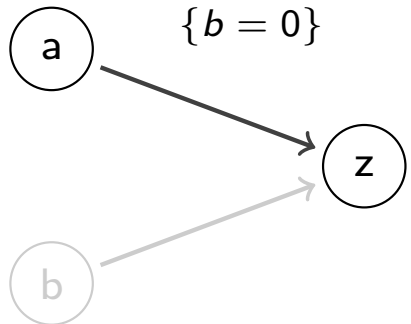
→ **Exhaustive search in all possible configurations**

1. Pick one regulator [a], and choose an active process for all the others [b_0].
2. Change the active process of the regulator [a_0, a_1] and watch the **evolution**.

Inferring the Interaction Graph

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





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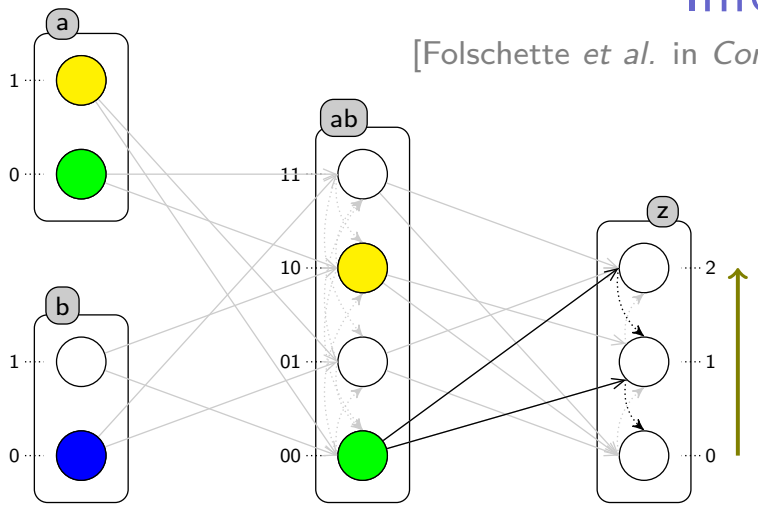

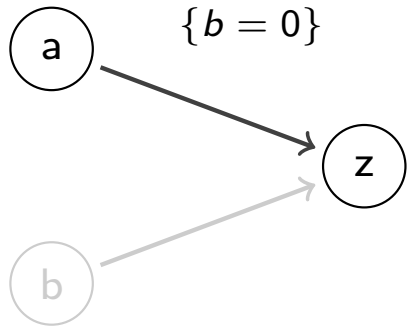

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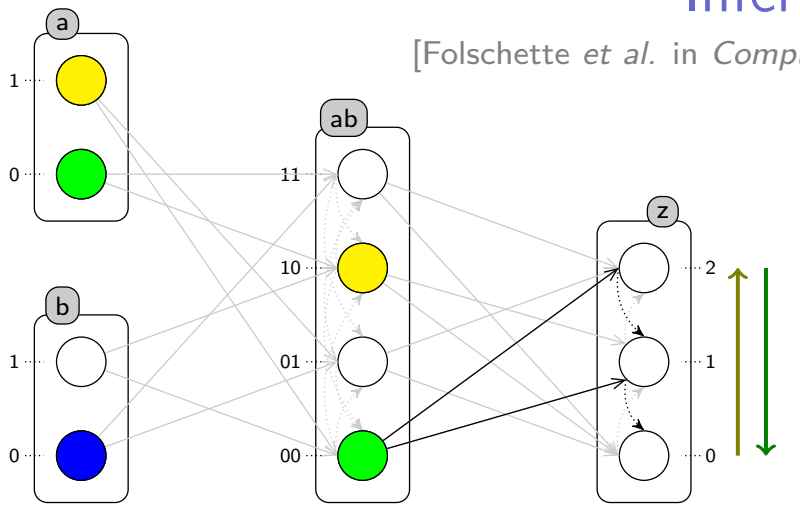

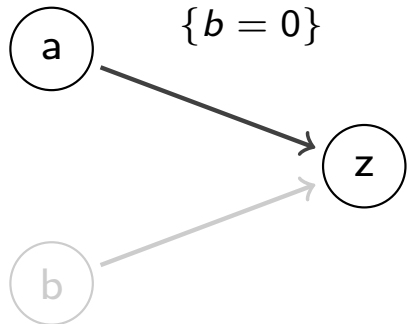

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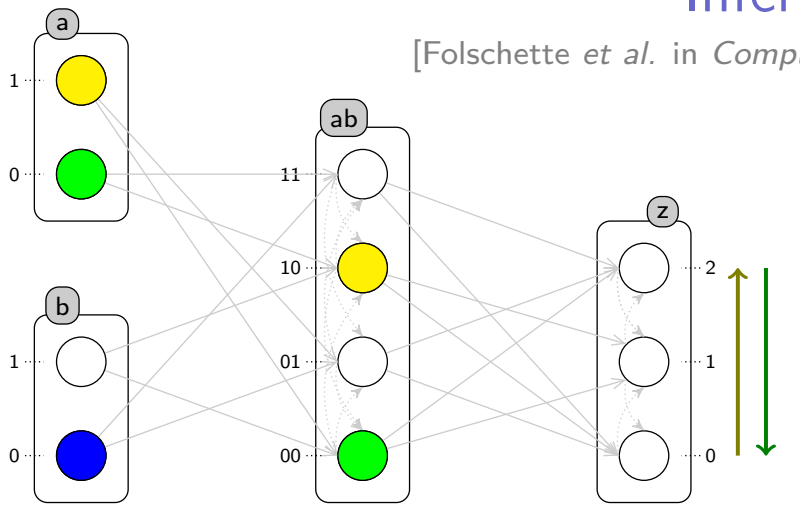

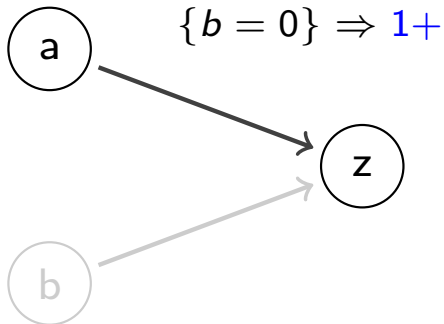

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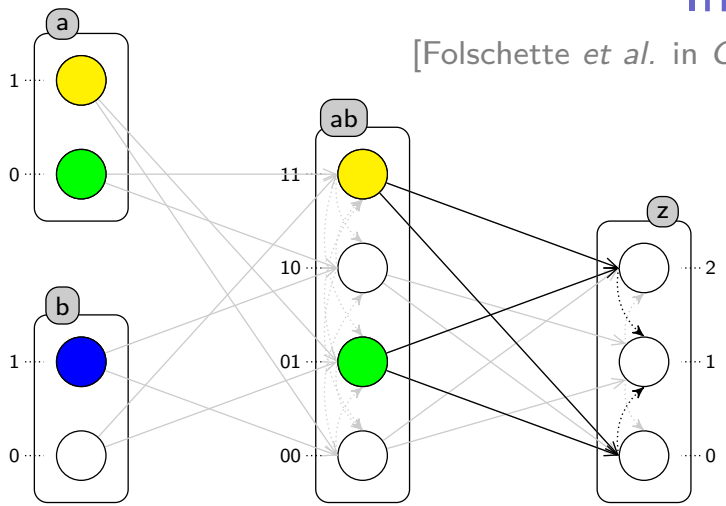

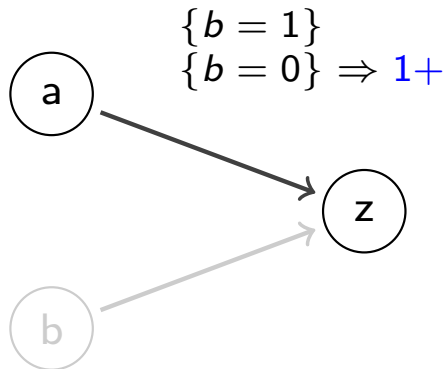

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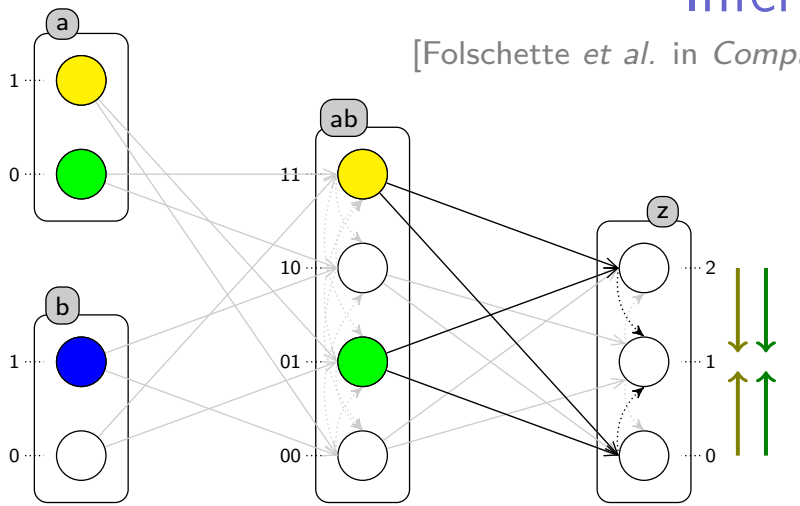

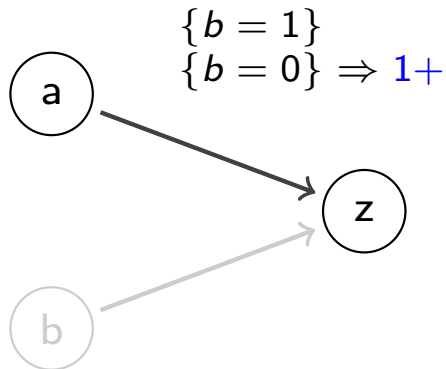

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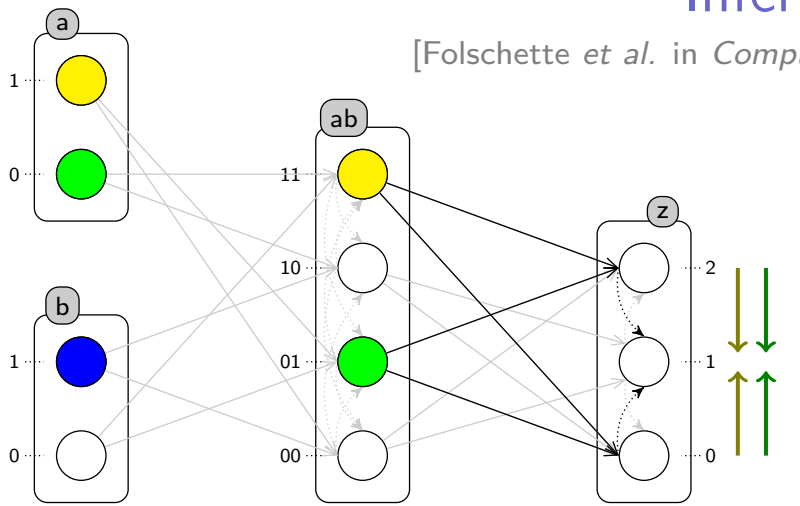

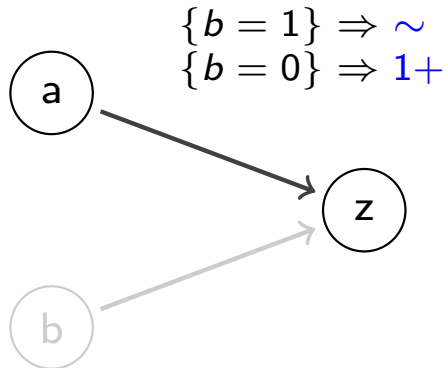

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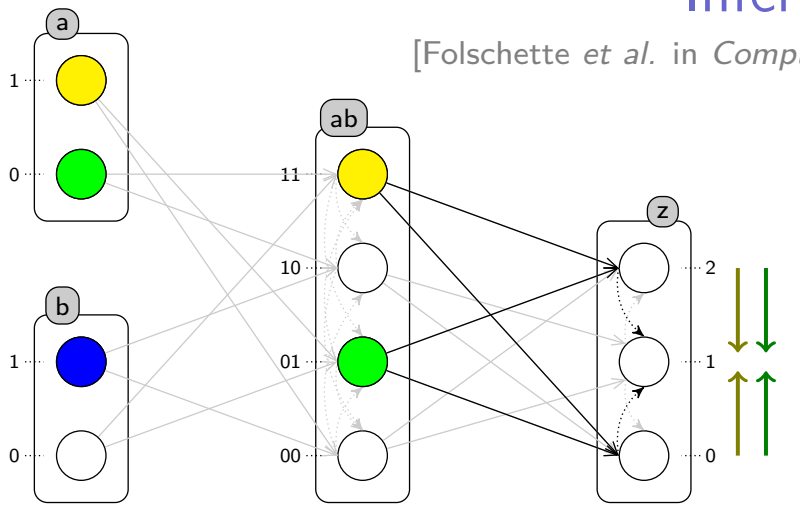

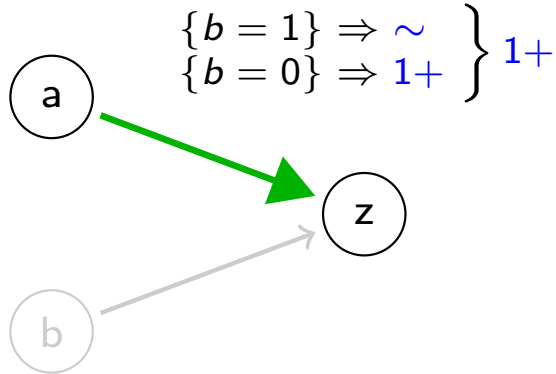

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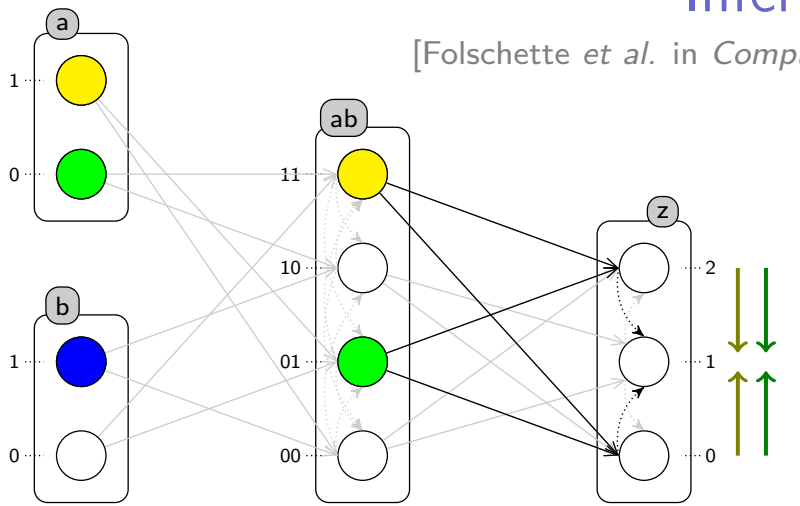

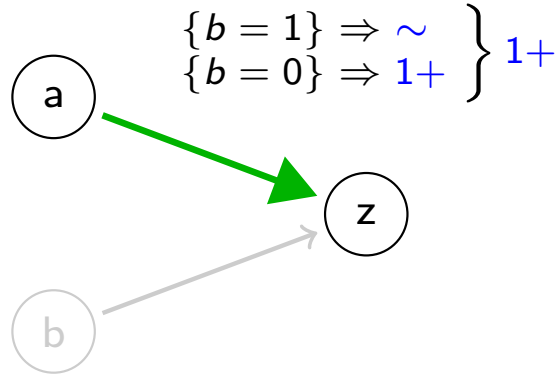

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4. Iterate and conclude globally.

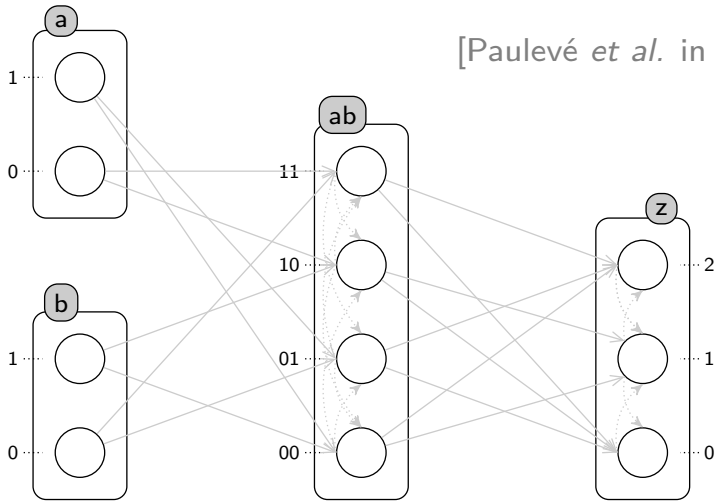
Problematic cases:

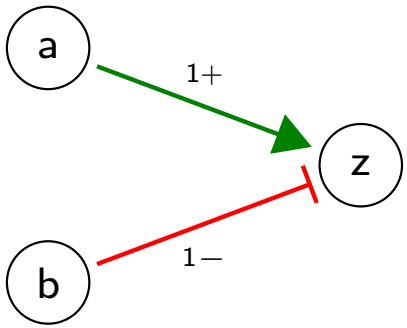
→ No focal processes (cycle)
→ Opposite influences ($+$ & $-$)

$\Rightarrow$ Unsigned edge

Inferring Parameters

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

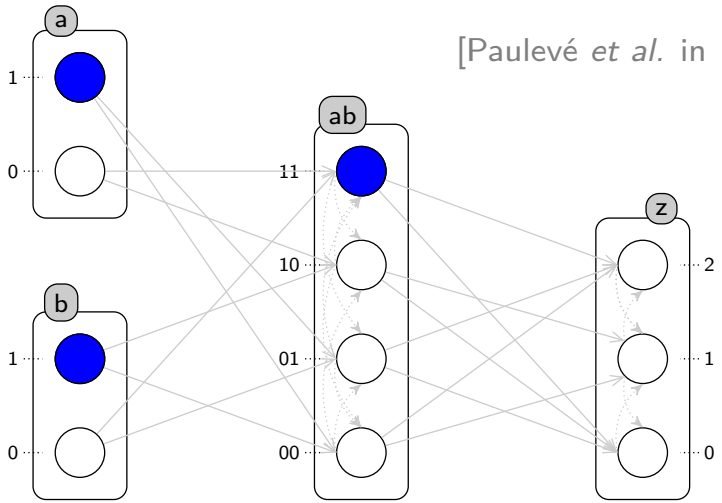


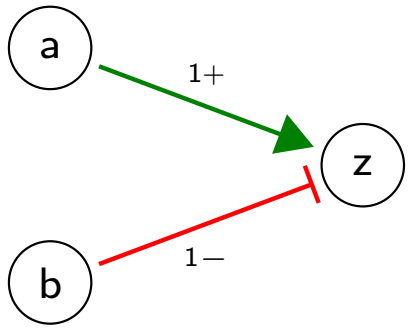


ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	

Inferring Parameters

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





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

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

Inferring Parameters

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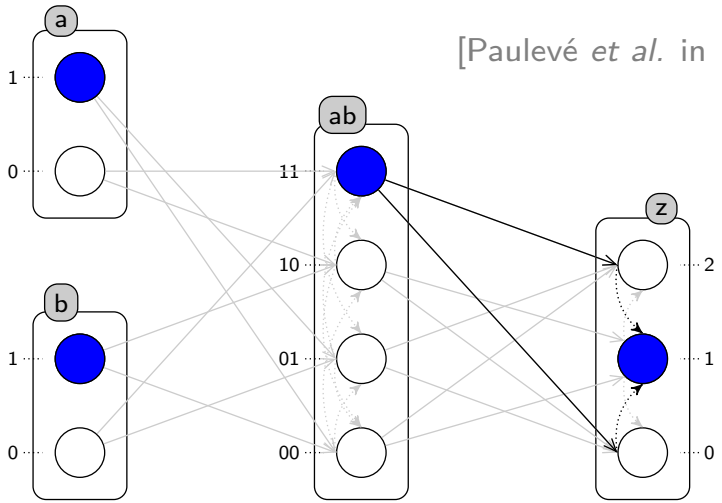

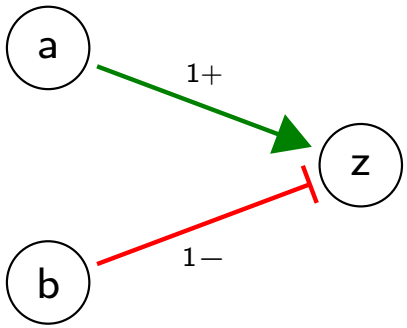

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	

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

Inferring Parameters

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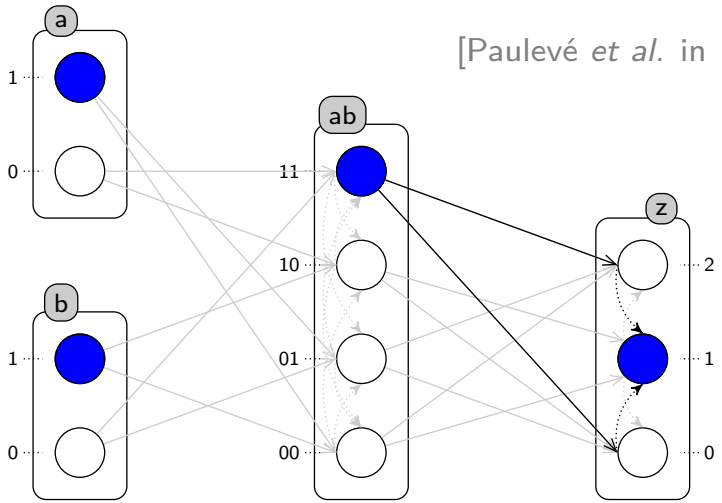

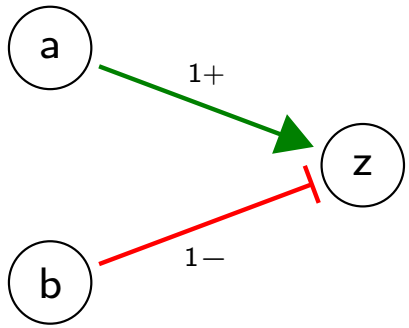

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	1

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

Inferring Parameters

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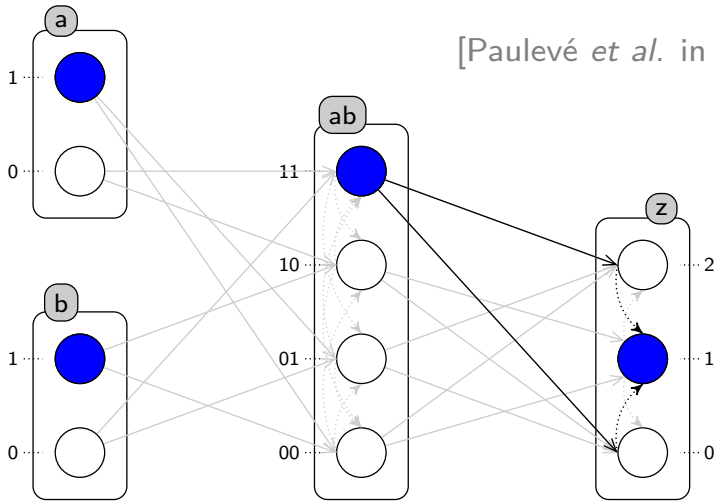

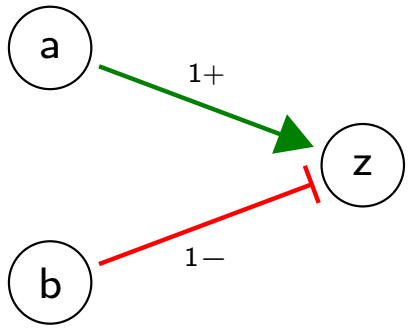

ω		$k_{z,\omega}$
a	b	
−	+	
−	−	
+	+	
+	−	1

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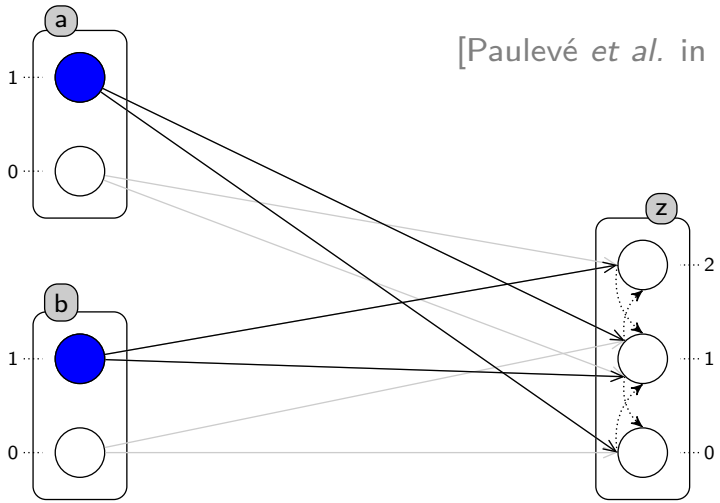

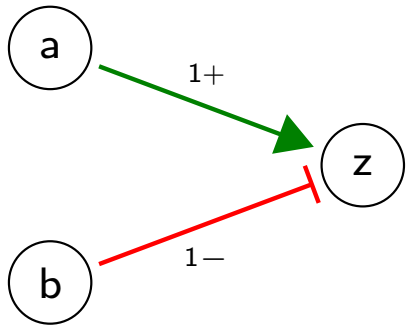

ω		$k_{z,\omega}$
a	b	
−	+	?
−	−	0
+	+	2
+	−	?

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

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

2. If some parameters could not be inferred, enumerate all admissible parametrizations, regarding:
   - Biological constraints [Bernot *et al.* in *Concurrent Models in Molecular Biology*, 2007]
   - The dynamics of the Process Hitting

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

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	42	152	399	**1s**	51	**1s**	192
tcrsig40	54	156	305	**1s**	55	**1s**	143
tcrsig94	133	448	1082	**100s**	197	**1s**	578
egfr104	193	744	2304	**200s**	280	**3s**	27'496

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

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 $\longrightarrow$ 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**:

- Abstraction of temporal parameters: find properties to avoid Zeno behavior
- Dynamical classes of priorities
- Guarded actions or complex logic gates
- New model checking tools (Hoare logic, ...)

Thank you for your attention

Personal Contributions

Book chapter:

- Loïc Paulevé, Courtney Chancellor, Maxime Folschette, Morgan Magnin, Olivier Roux. Analyzing Large Network Dynamics with Process Hitting, In Luis Farinas del Cerro and Katsumi Inoue, editors: *Logical Modeling of Biological Systems*, 2014.

Journal article:

- Maxime Folschette, Loïc Paulevé, Katsumi Inoue, Morgan Magnin, Olivier Roux. Constructing Biological Regulatory Networks from Process Hitting models, *Theoretical Computer Science*, Vol. 586, 2015.

Conference:

- Maxime Folschette, Loïc Paulevé, Morgan Magnin, Olivier Roux. Under-approximation of reachability in multivalued asynchronous networks, CS2Bio'13, *Electronic Notes in Theoretical Computer Science*, Vol. 299, 2013.

Workshops:

- Maxime Folschette, Loïc Paulevé, Katsumi Inoue, Morgan Magnin, Olivier Roux. Concretizing the process hitting into biological regulatory networks, CMSB'12, *Lecture Notes in Computer Science*, 2012.
- Maxime Folschette, Loïc Paulevé, Katsumi Inoue, Morgan Magnin, Olivier Roux. Abducing Biological Regulatory Networks from Process Hitting models, *ECML-PKDD'12 / LDSSB'12*, 2012.

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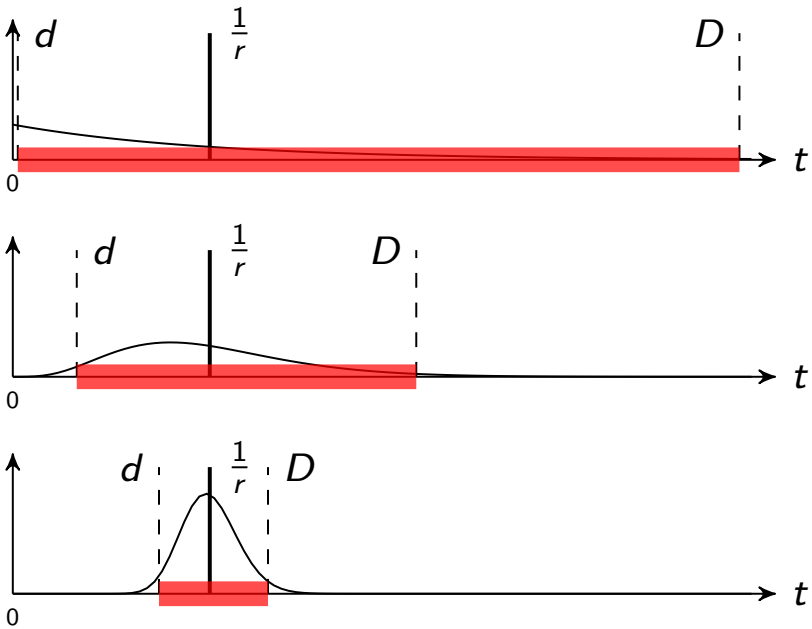
Stochastic Parameters

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

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

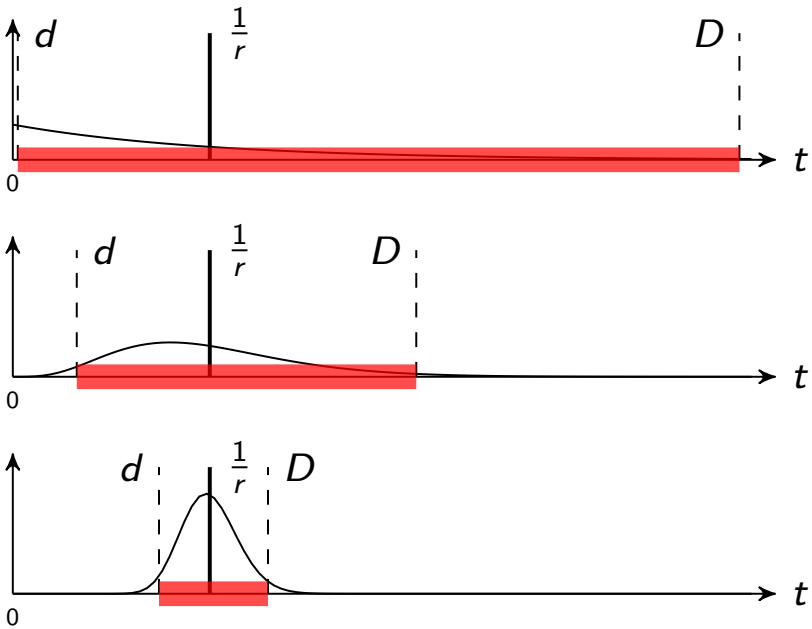


Intervalle de tir

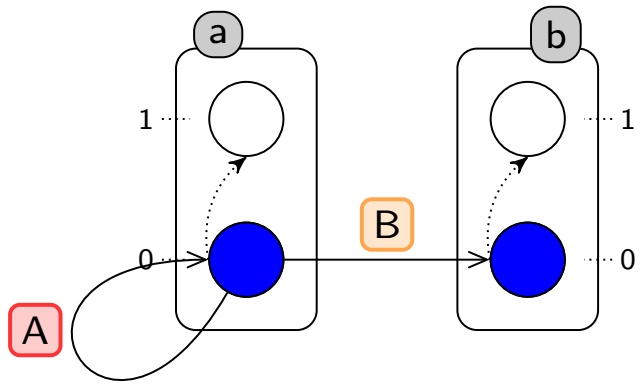
Stochastic Parameters

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

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

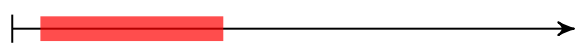


Intervalle de tir



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

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

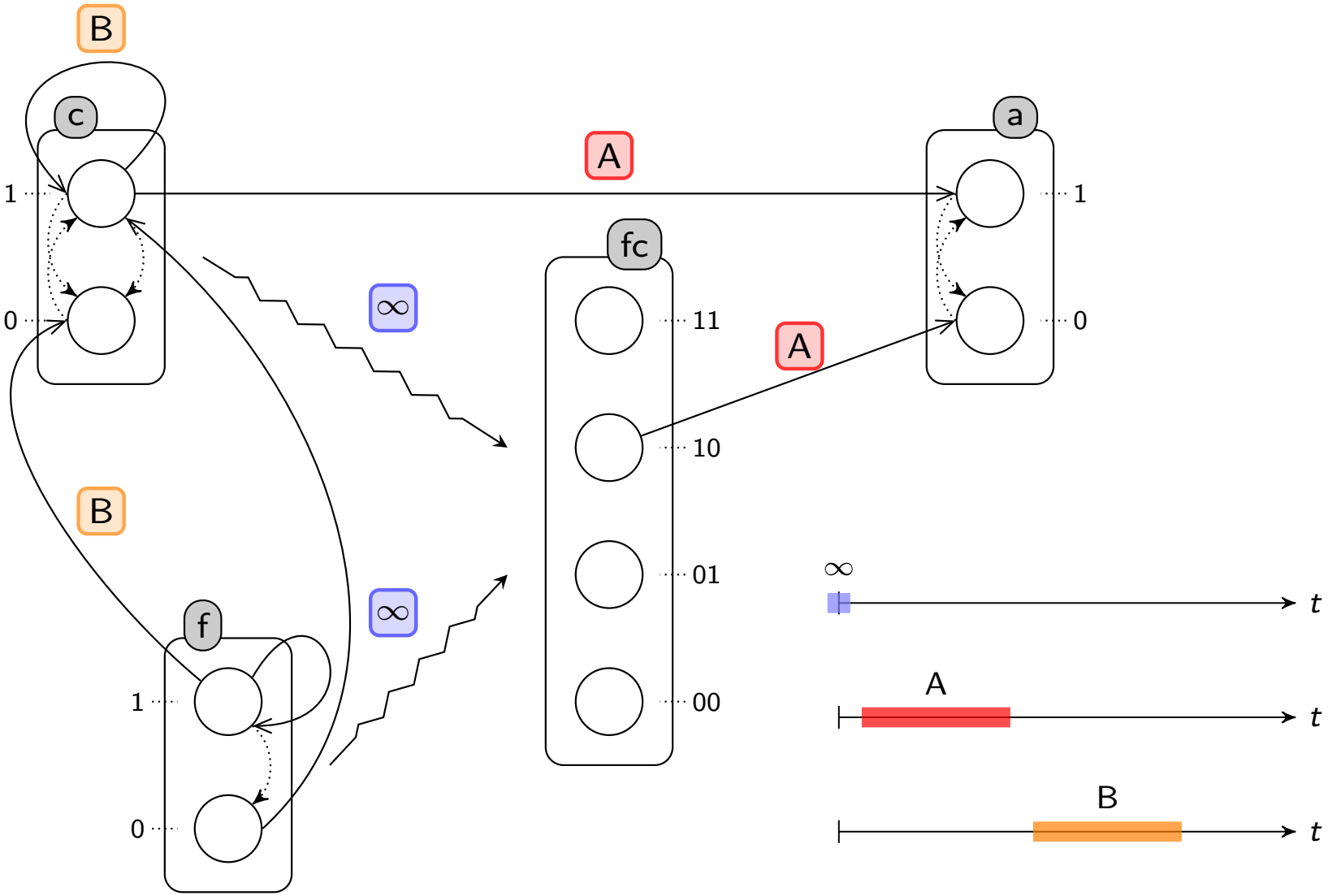


$\rightarrow$ **Very low probability** to reach b_1

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

Use of Stochastic Parameters

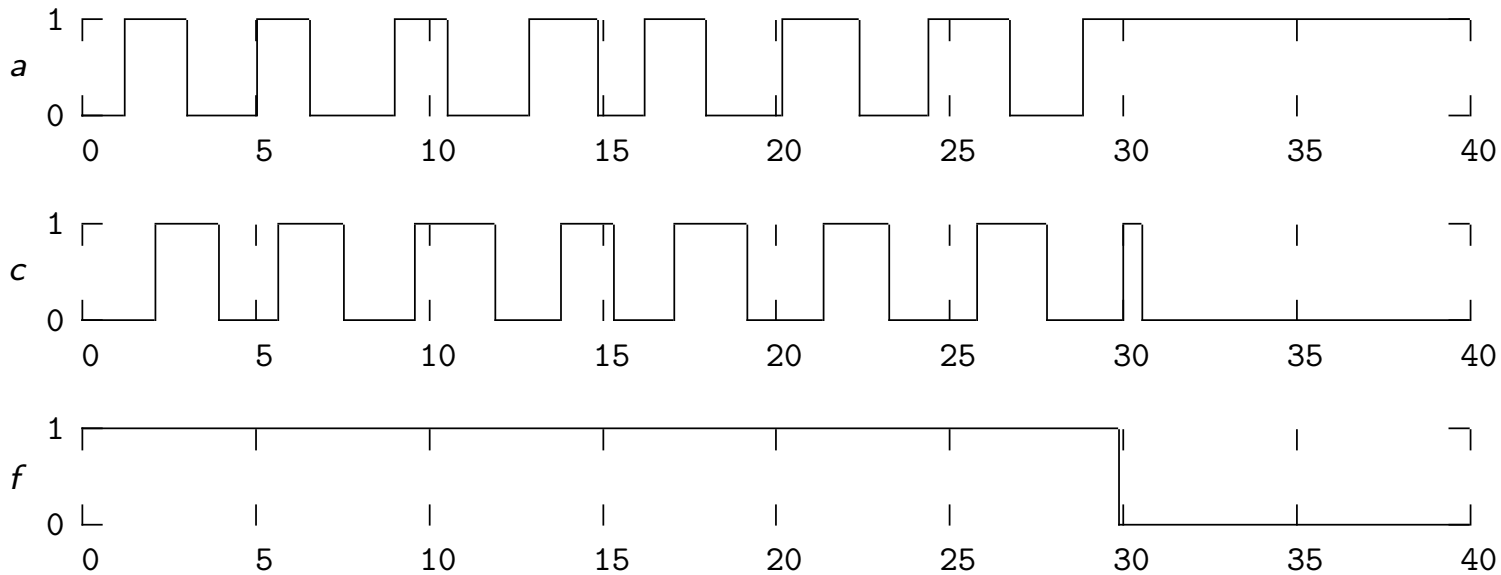
[Paulevé *et al.* in *Transactions on Computational Systems Biology*, 2011]



Temporal Simulation

[Paulevé (PhD thesis), 2011]

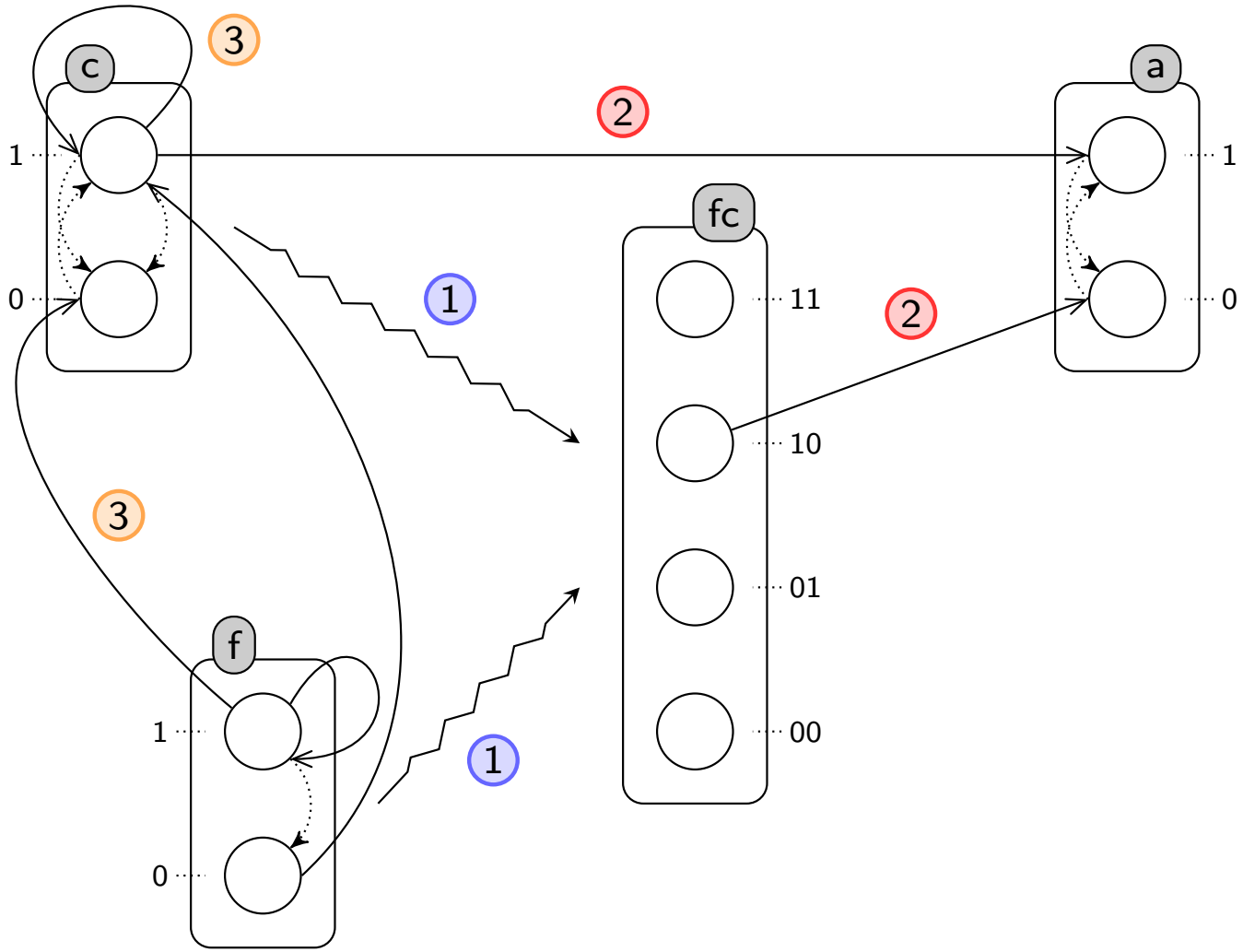
- Simulation with stochastic parameters:



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

Use of the Classes of Priorities

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



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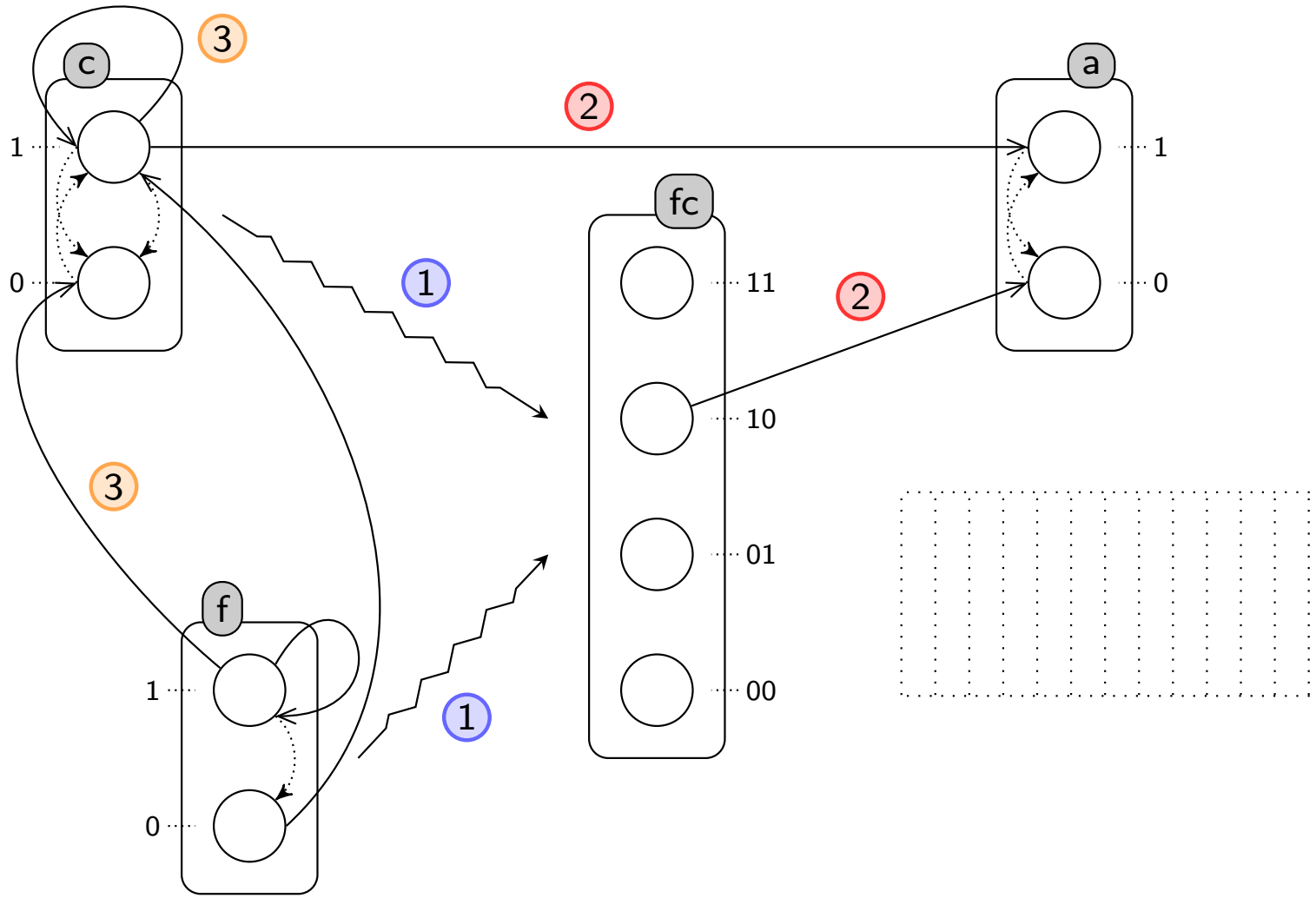

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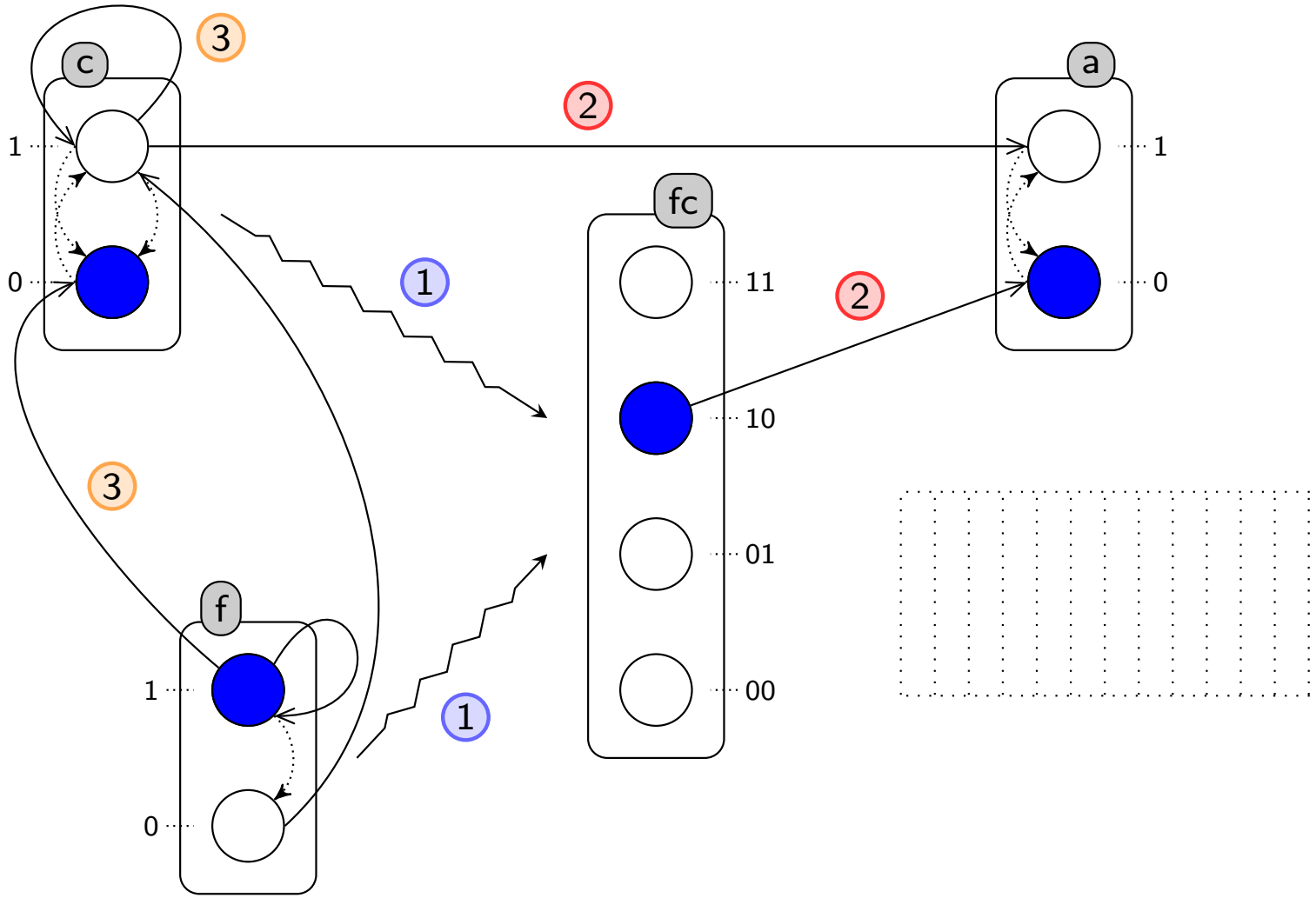

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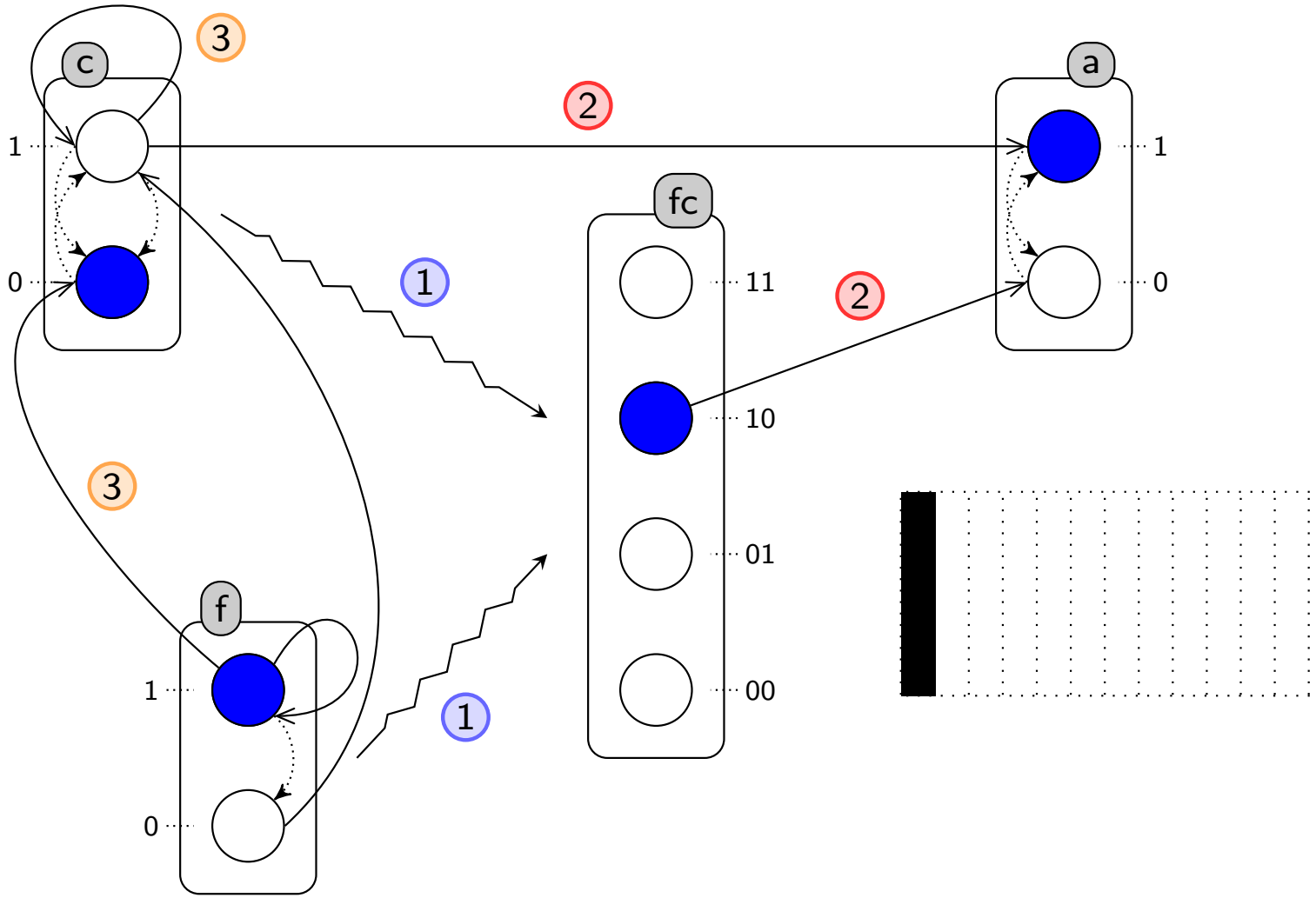

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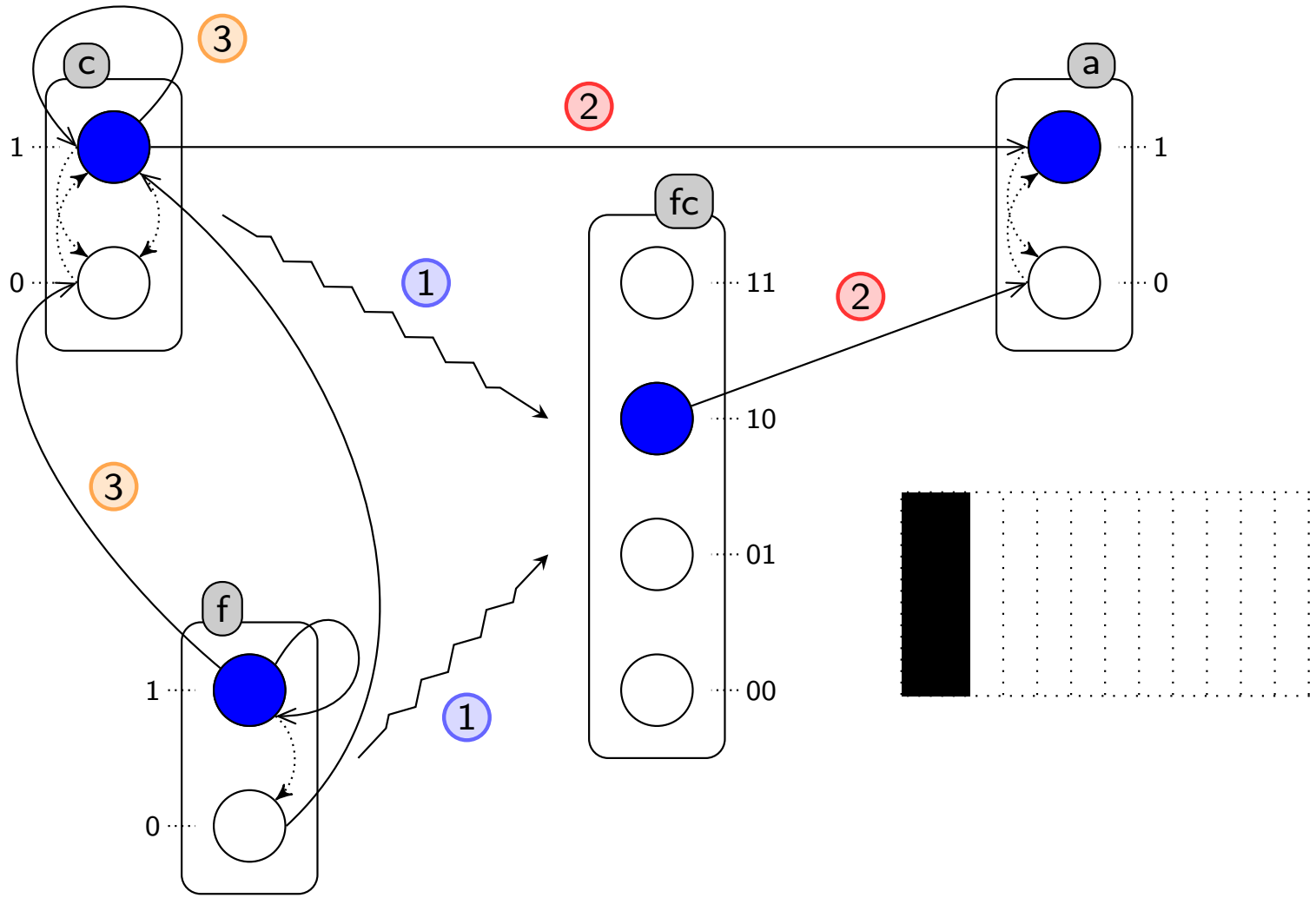
[Folschette *et al.* in *Workshop on Interactions between Computer Science and Biology*, 2013]



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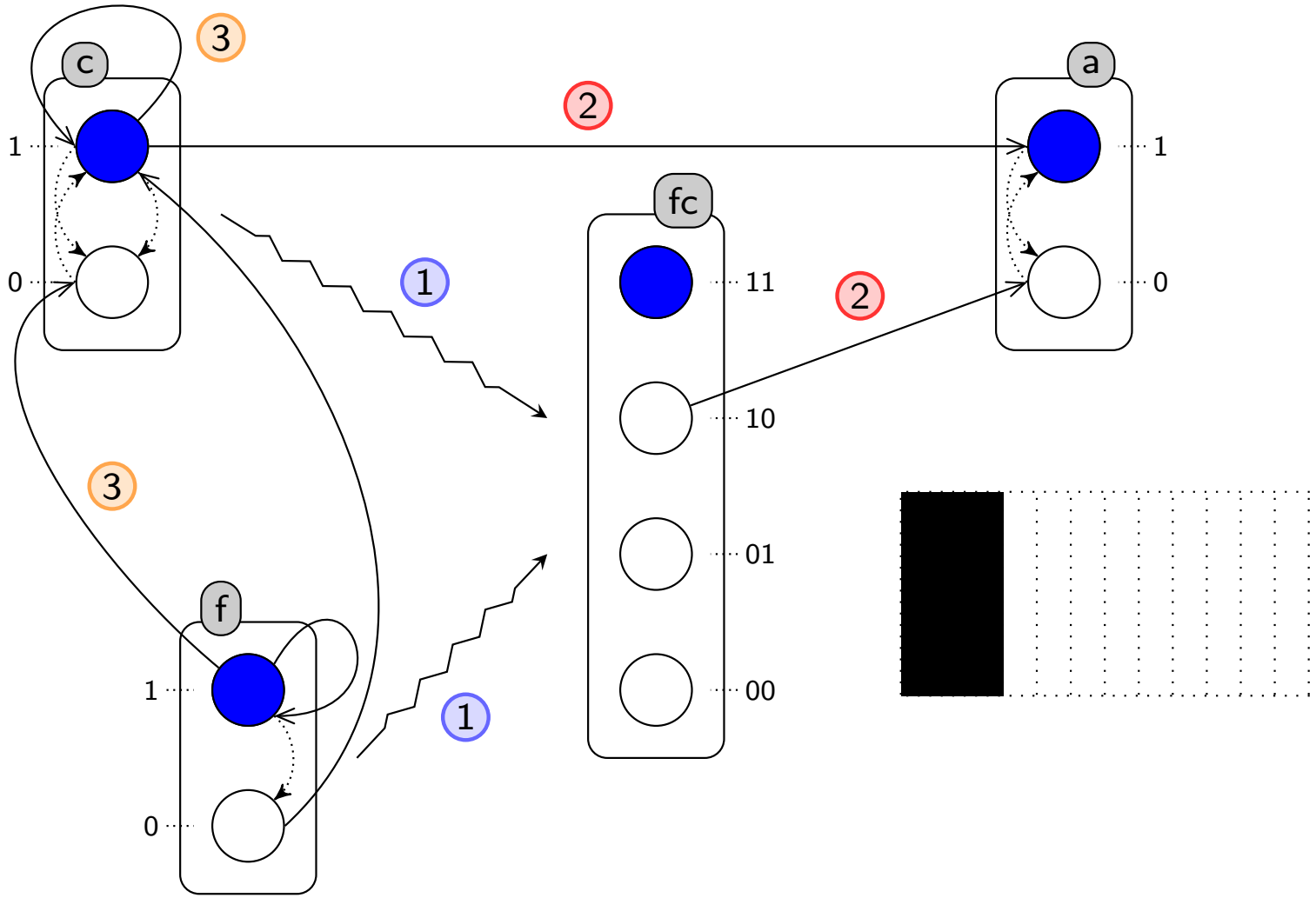

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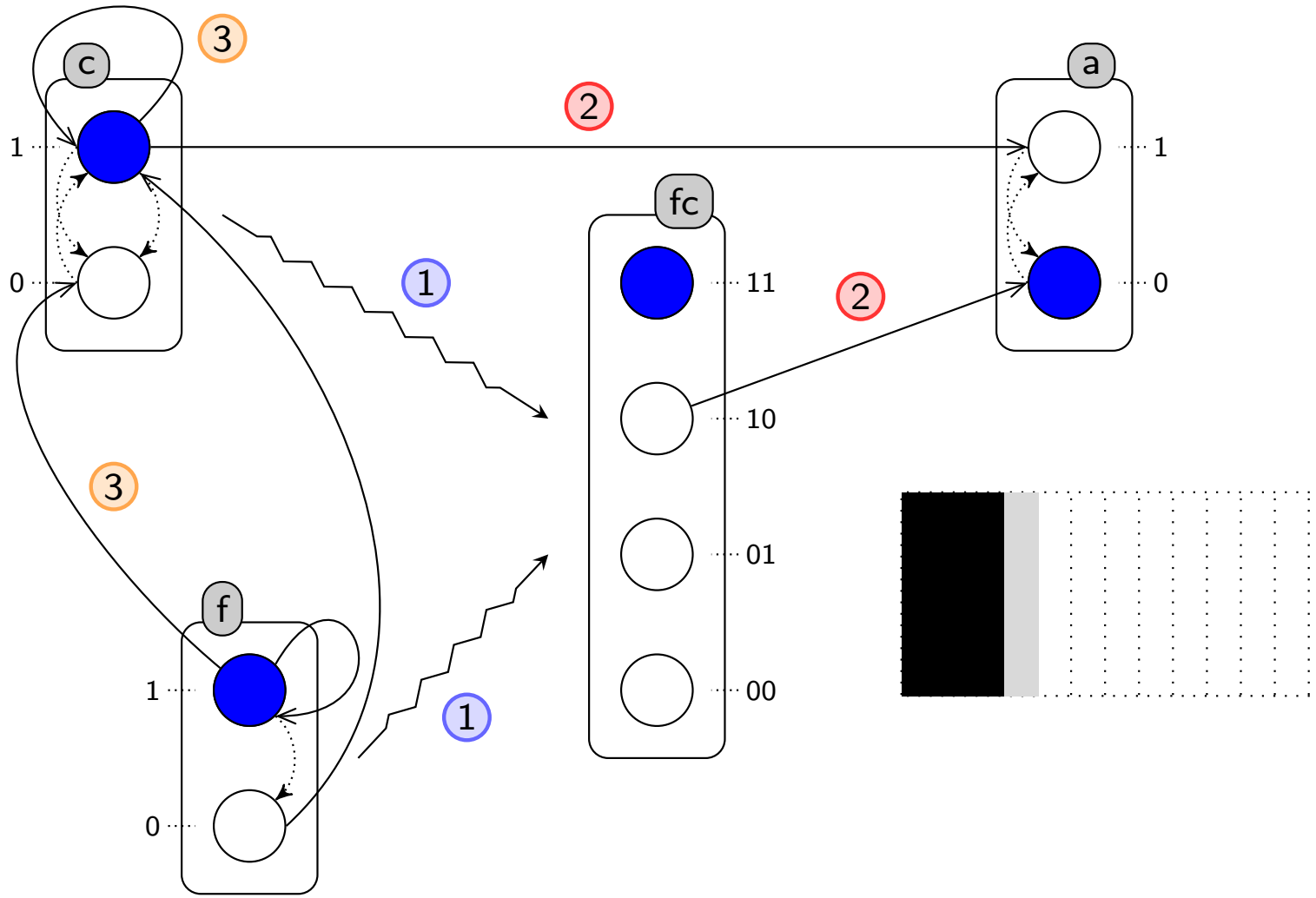

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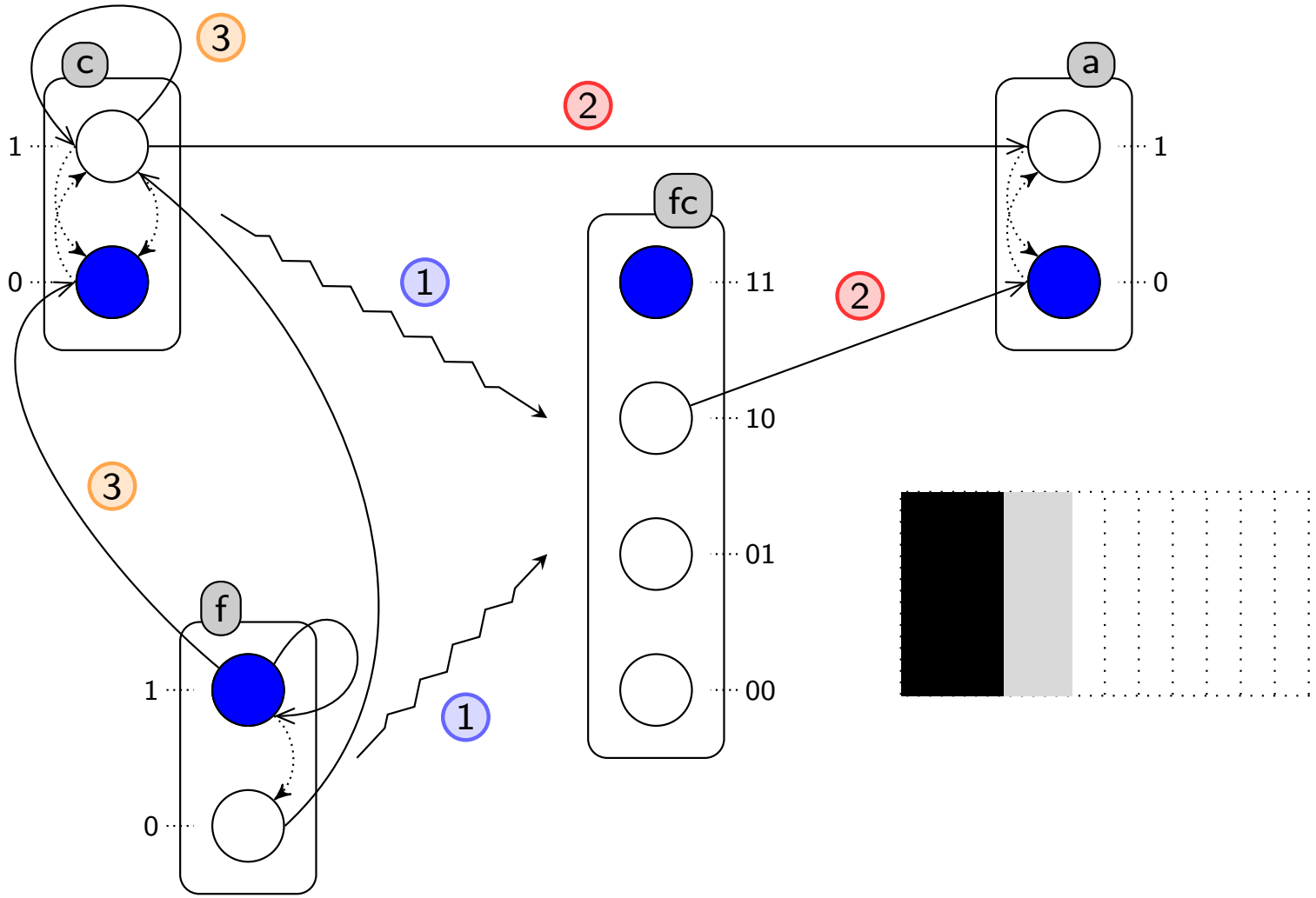

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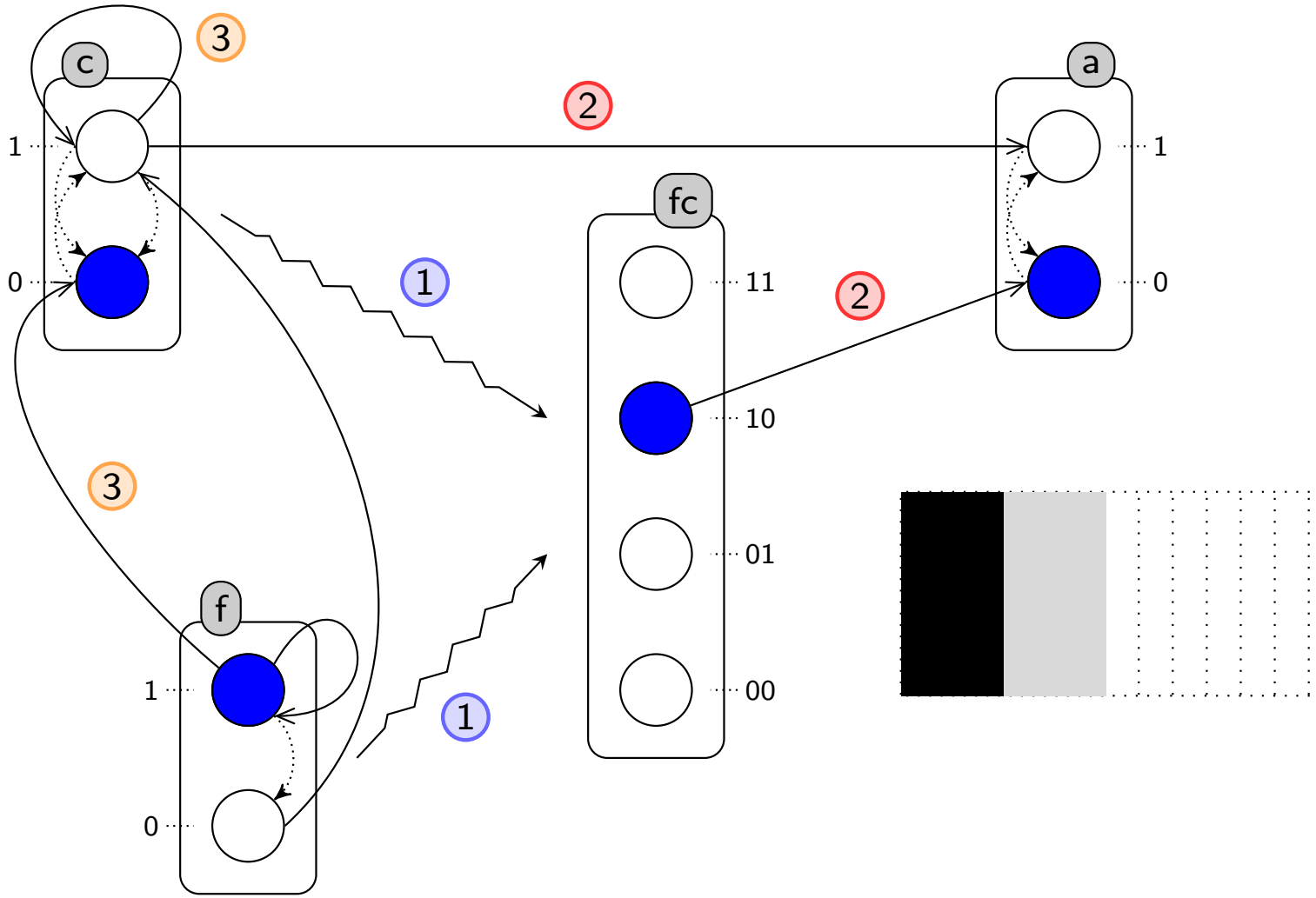

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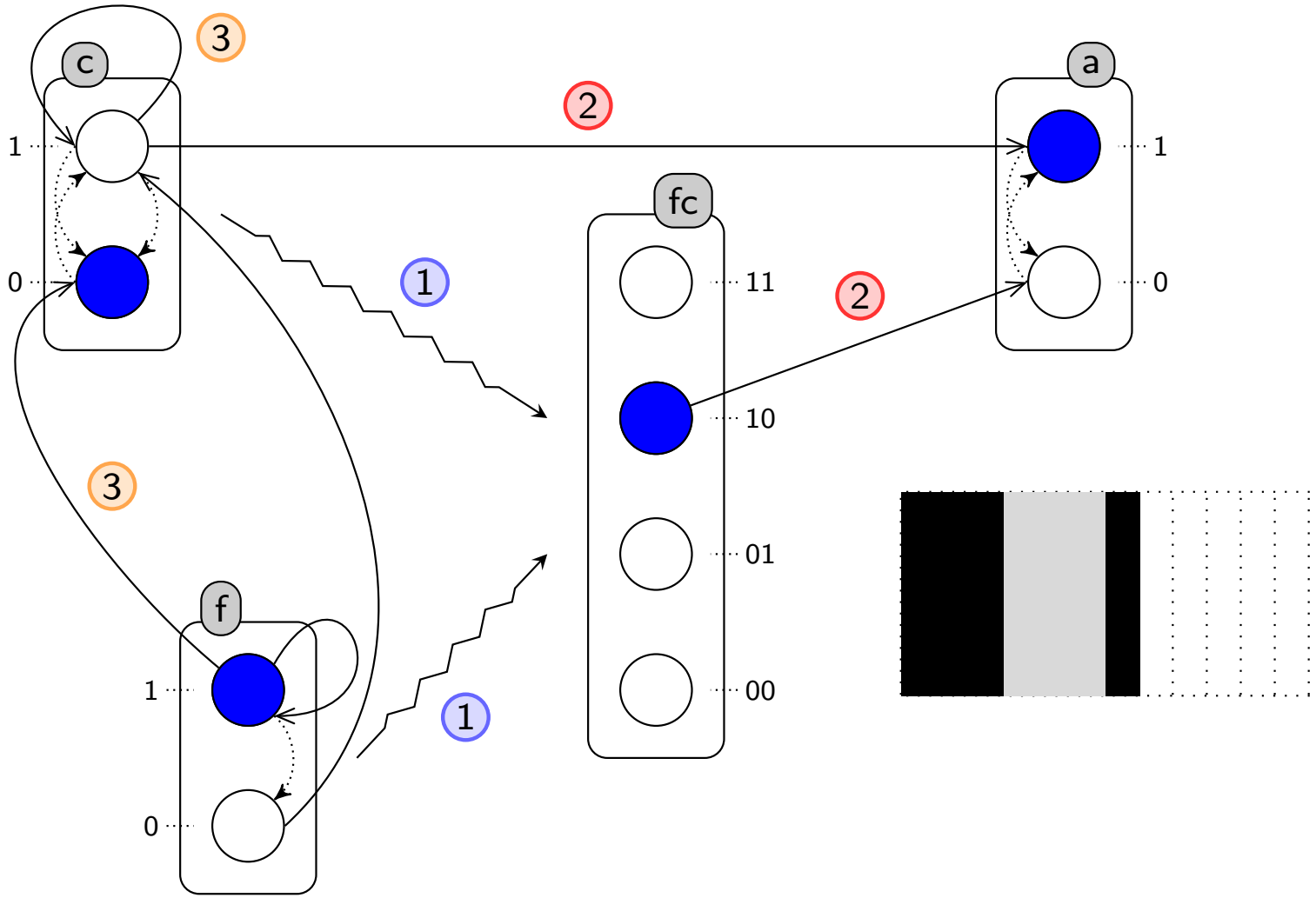

Use of the Classes of Priorities

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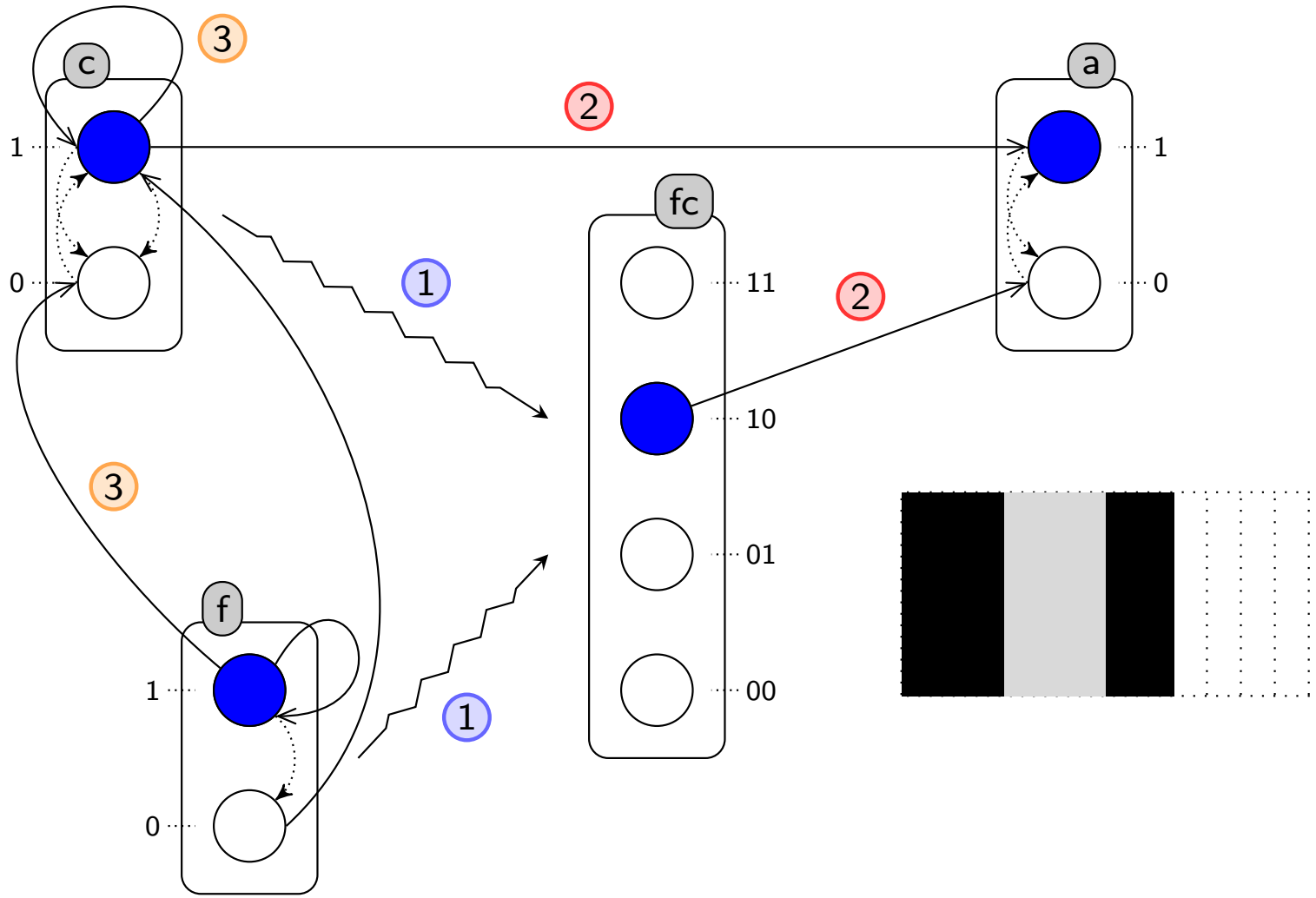

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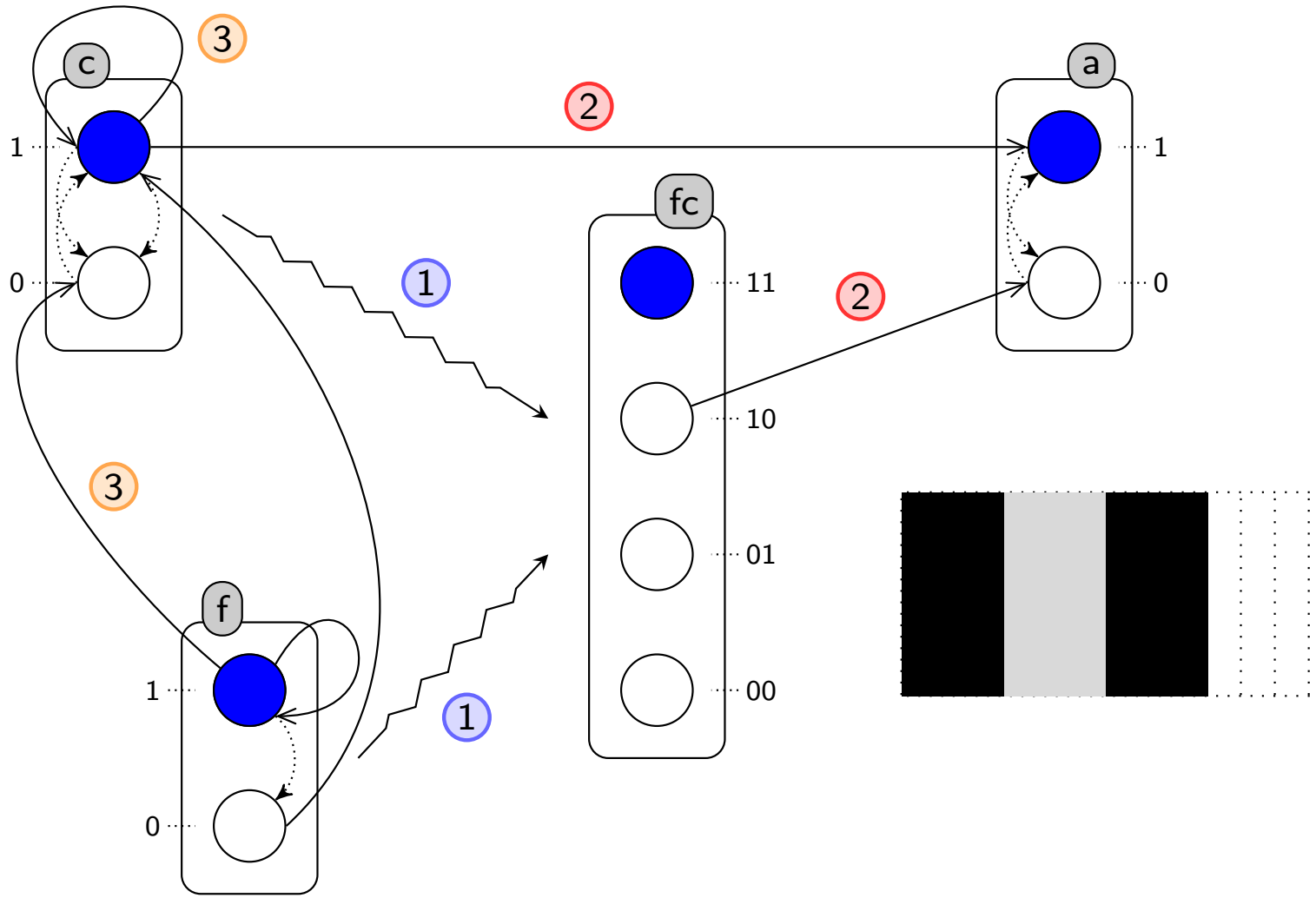

Use of the Classes of Priorities

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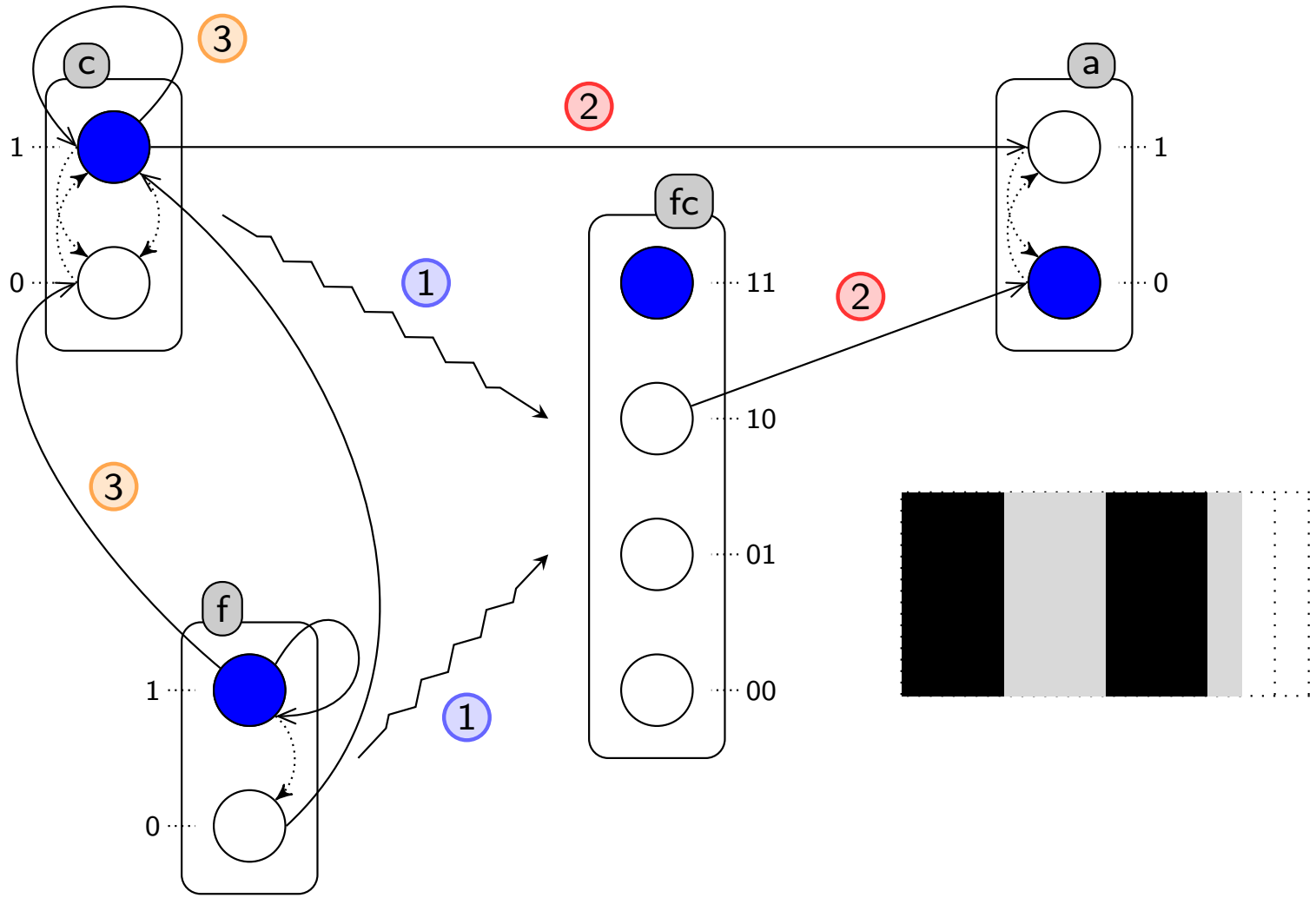

Use of the Classes of Priorities

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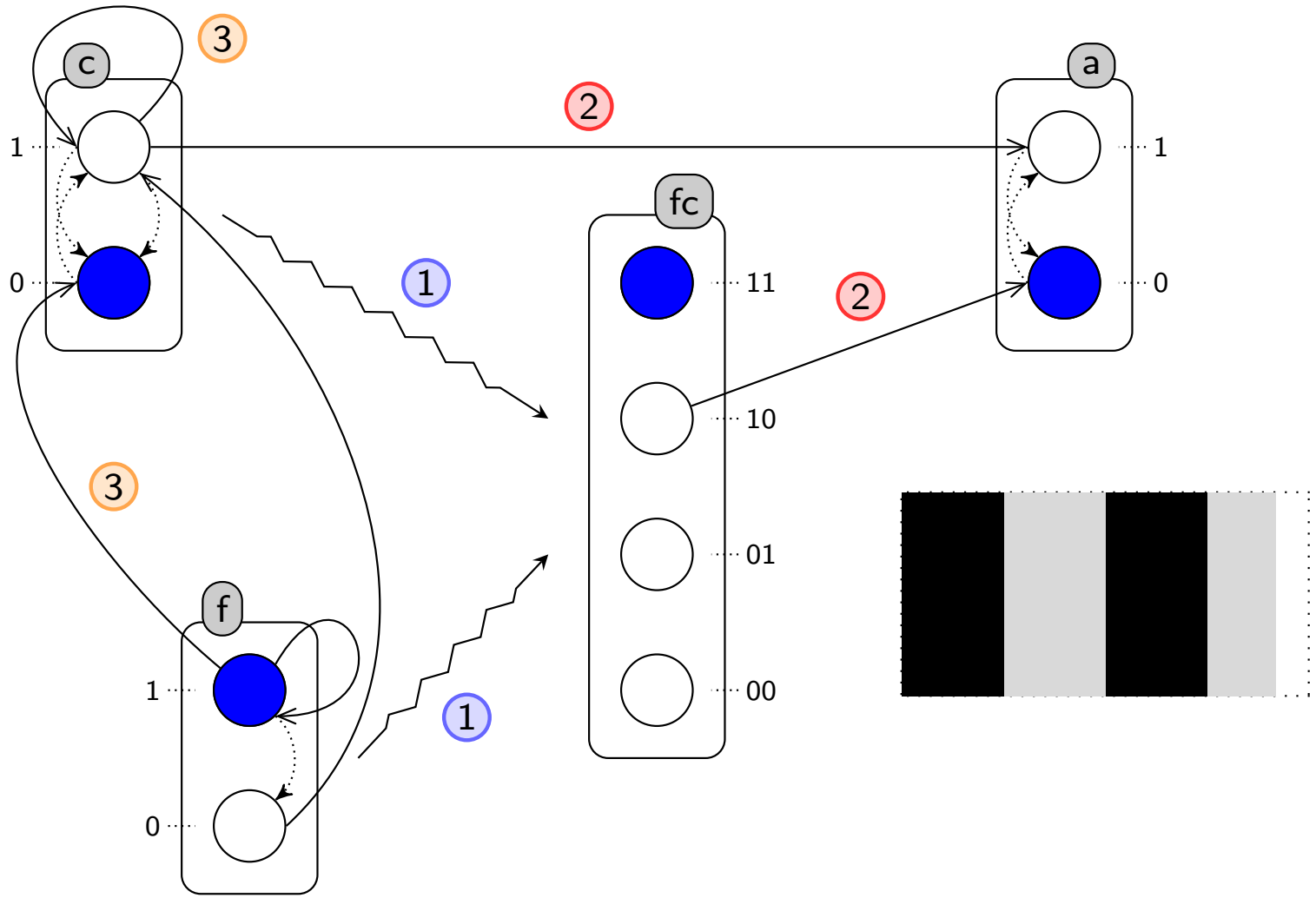

Use of the Classes of Priorities

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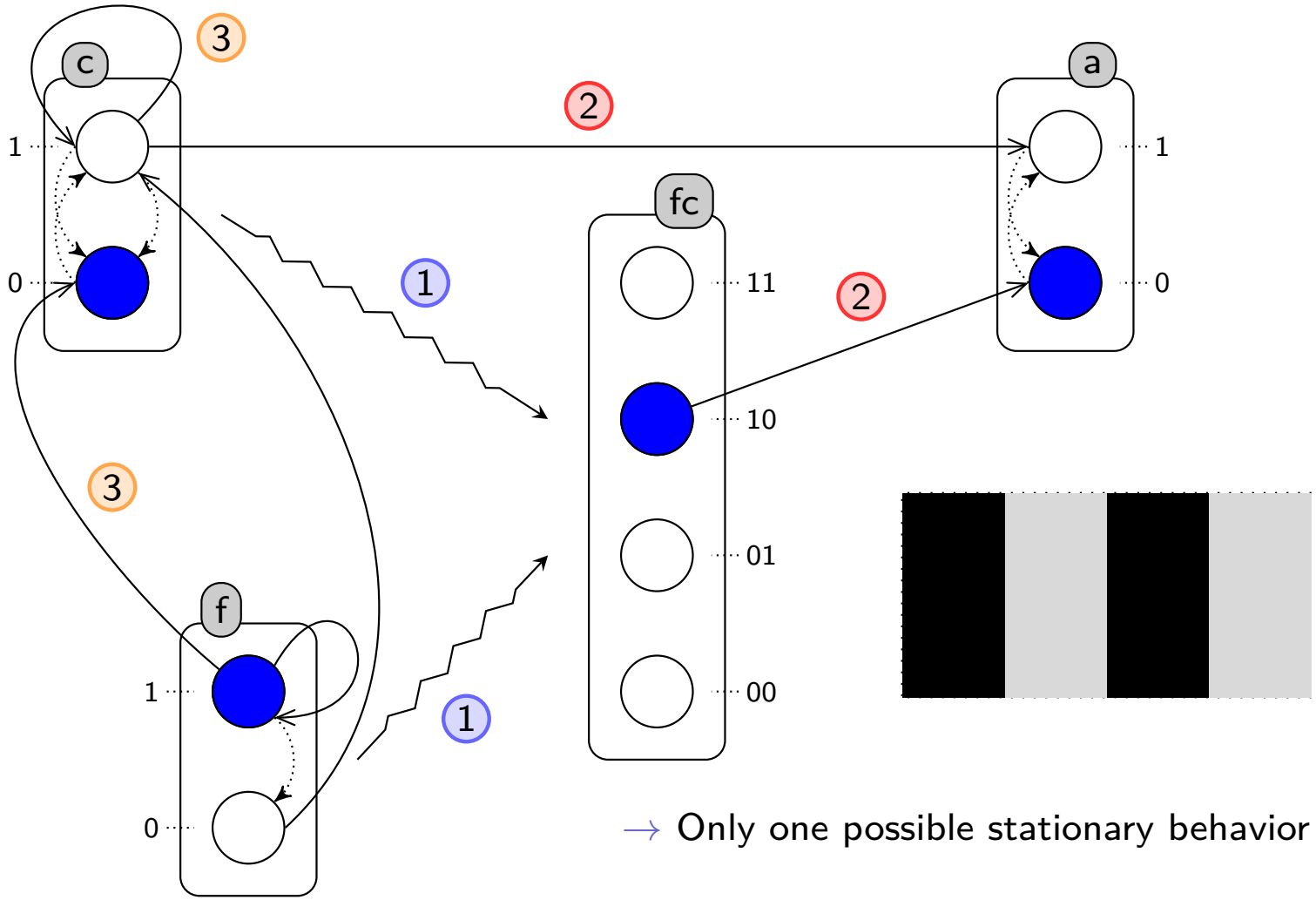
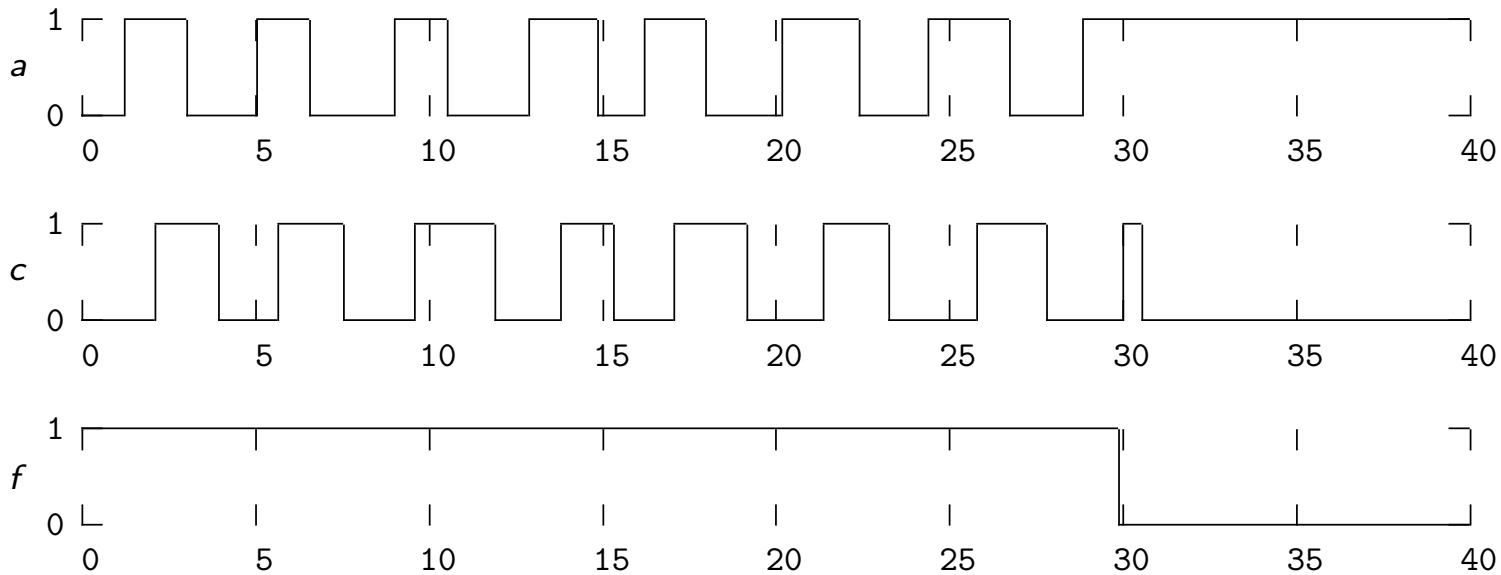


→ Only one possible stationary behavior

Abstraction of Temporal Parameters

[Paulevé (PhD thesis), 2011]

- Simulation with stochastic parameters:

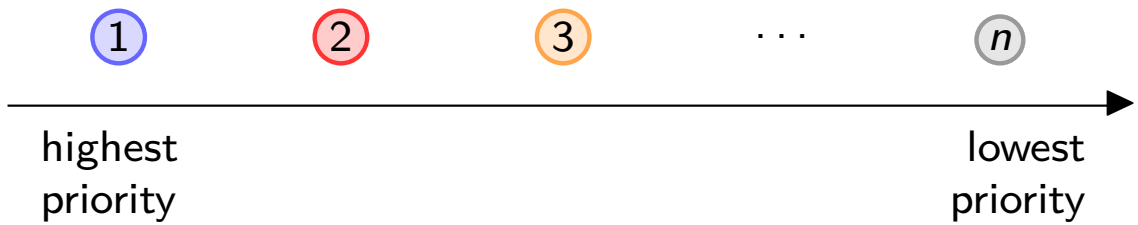


- Other possible analysis: stochastic model checkers (PRISM)
  → But combinatoric explosion: PRISM fails for more than 5 components

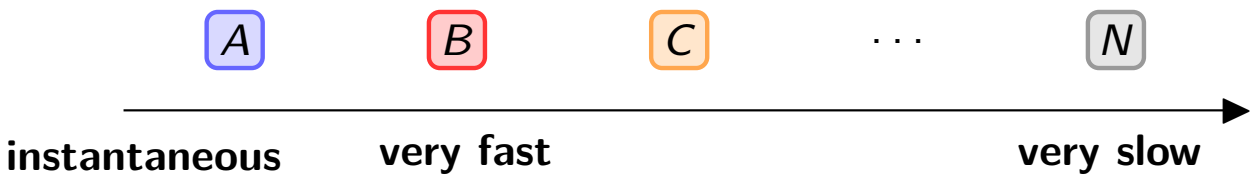
Addition of classes of priorities

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

- Each action is associated to a discrete priority
- An action is playable only if no other action with higher priority is playable

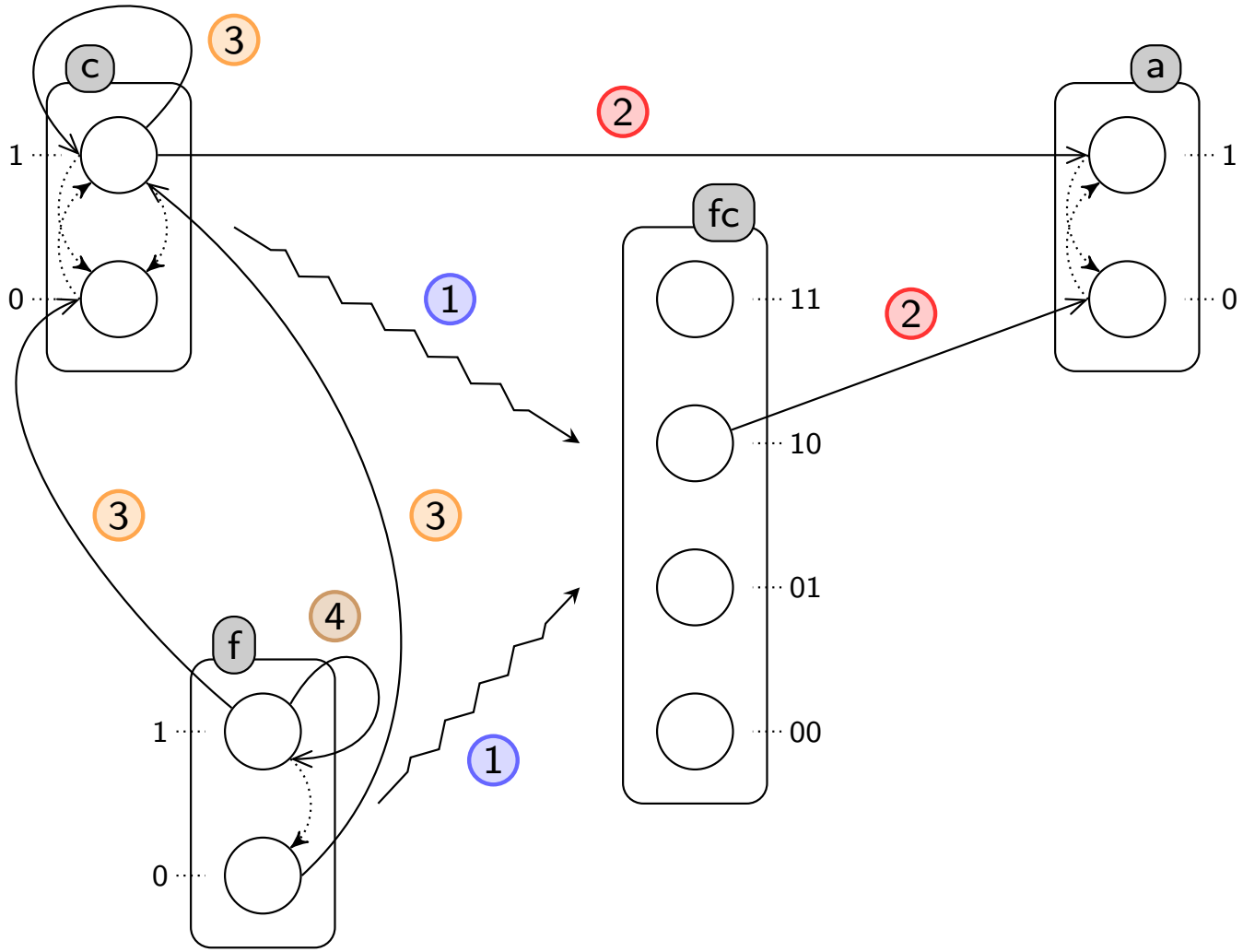


- Allow to model classes of actions with similar speeds or temporal parameters



Limitation of the Classes of Priorities

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



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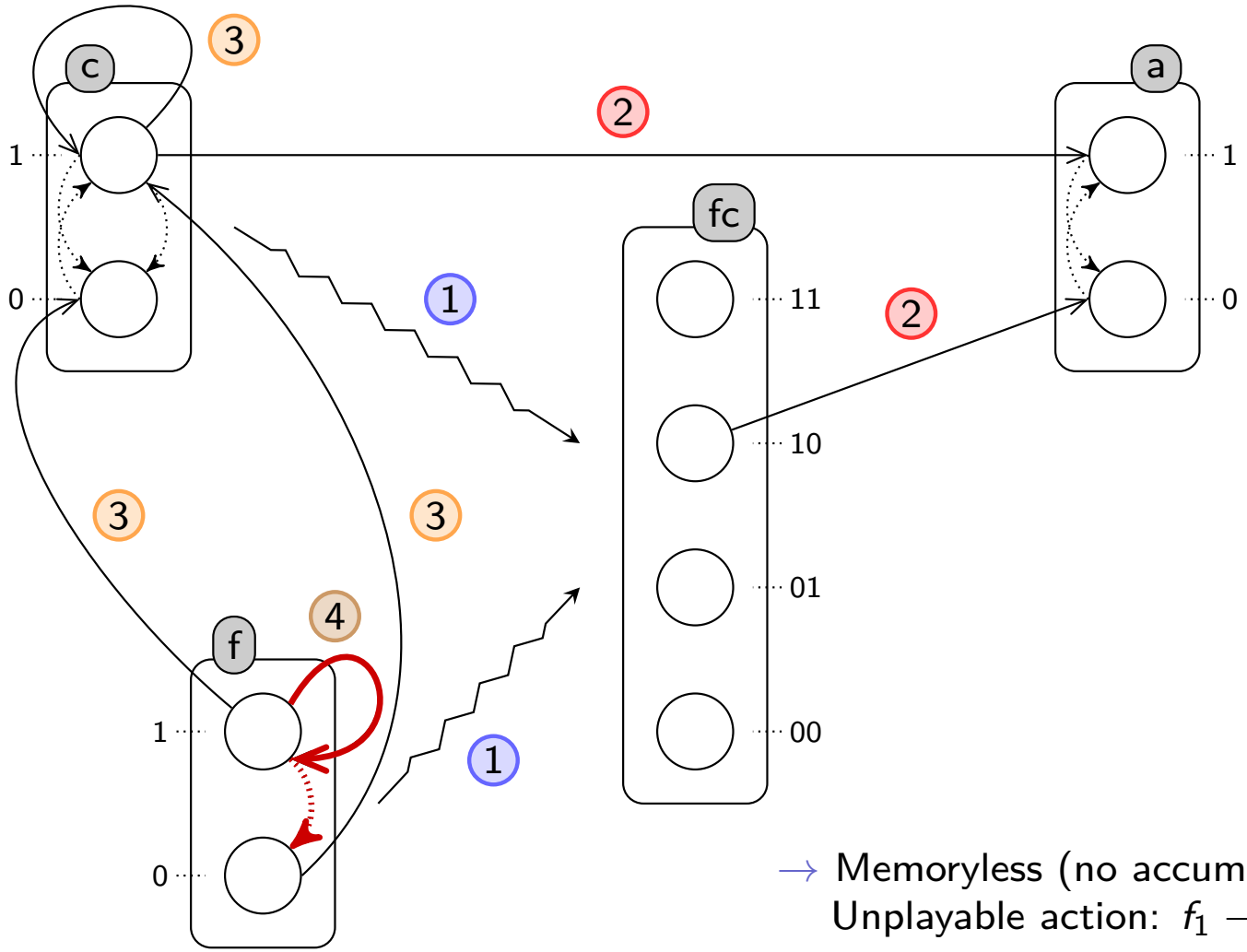
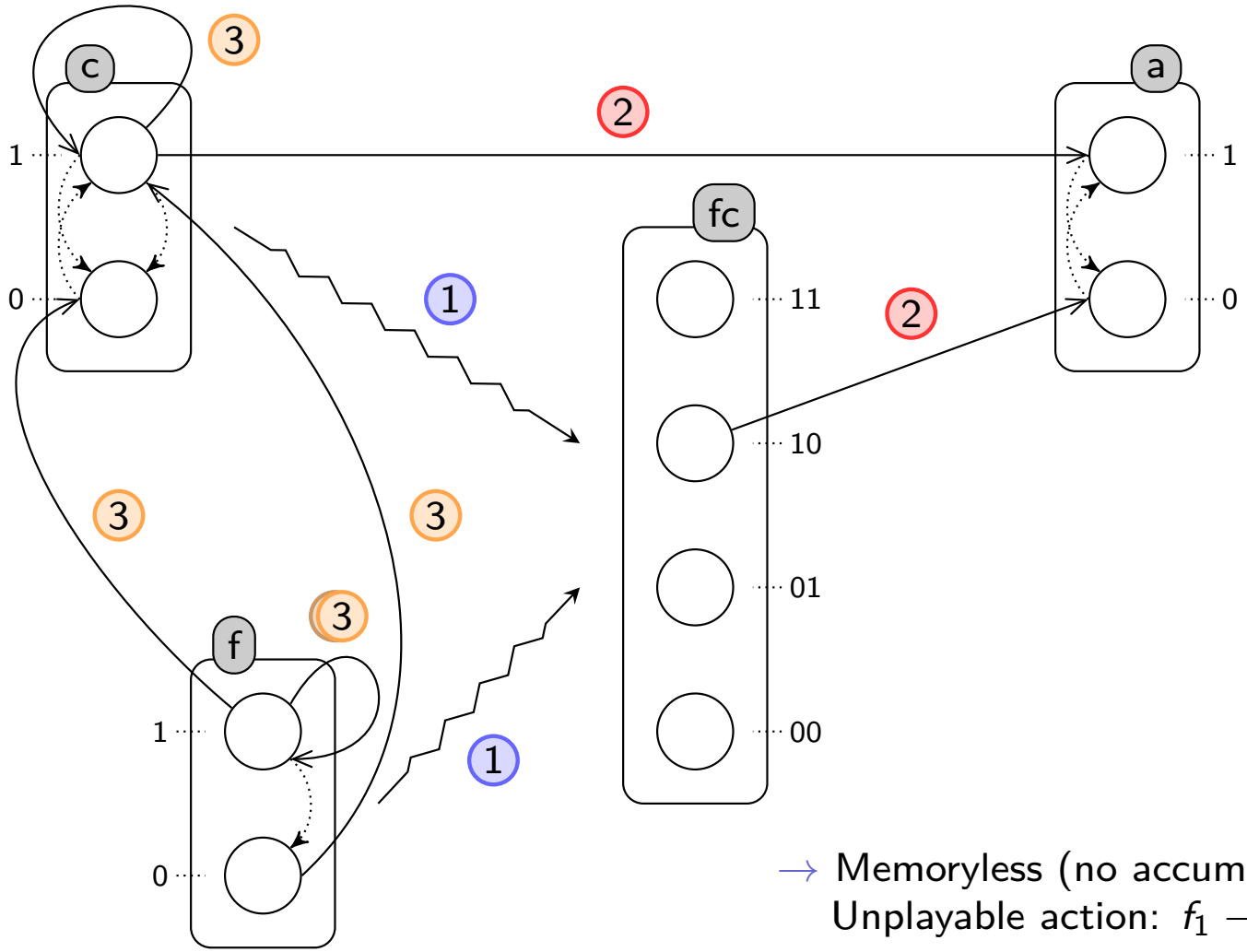


→ Memoryless (no accumulation)
Unplayable action: $f_1 \rightarrow f_1 \not\vdash f_0$

Limitation of the Classes of Priorities

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

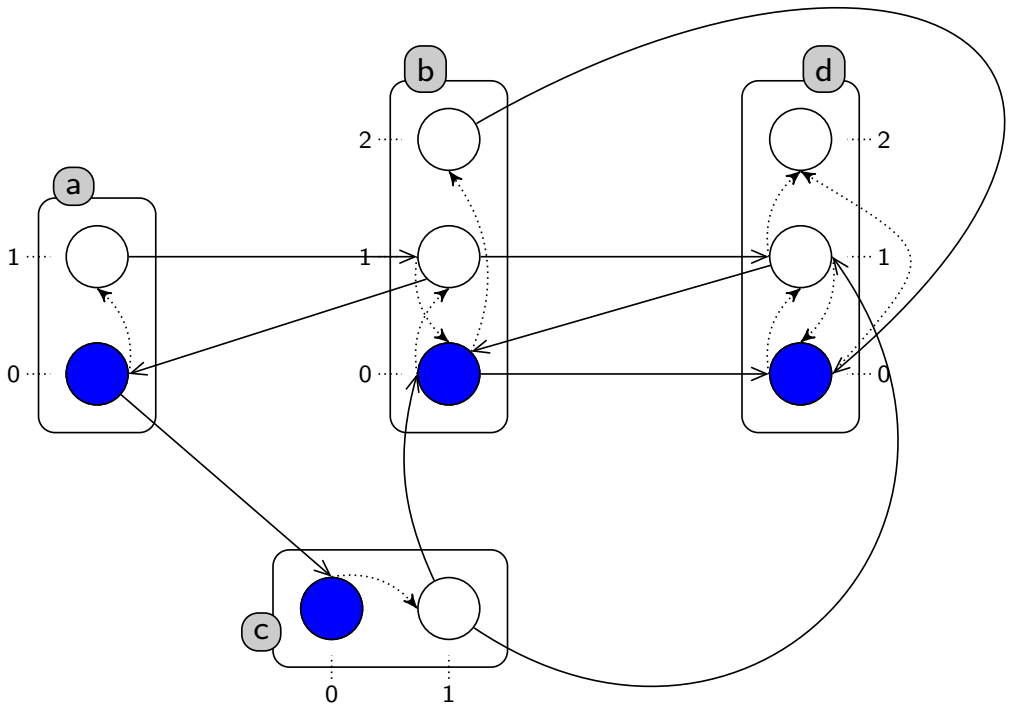


→ Memoryless (no accumulation)
Unplayable action: $f_1 \rightarrow f_1 \not\vdash f_0$

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]

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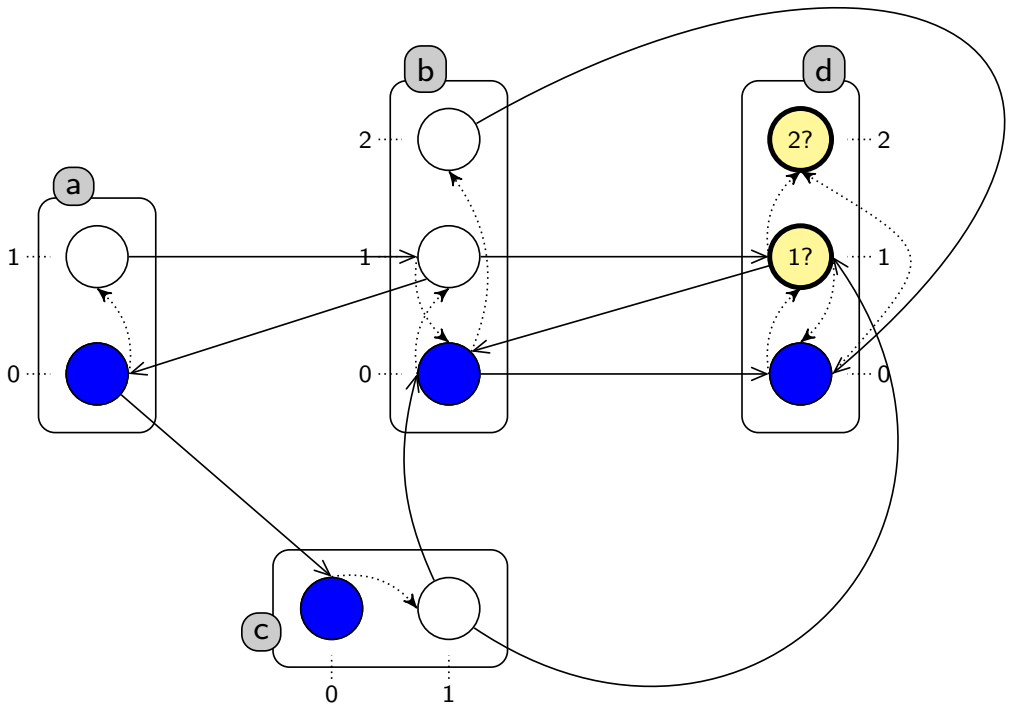
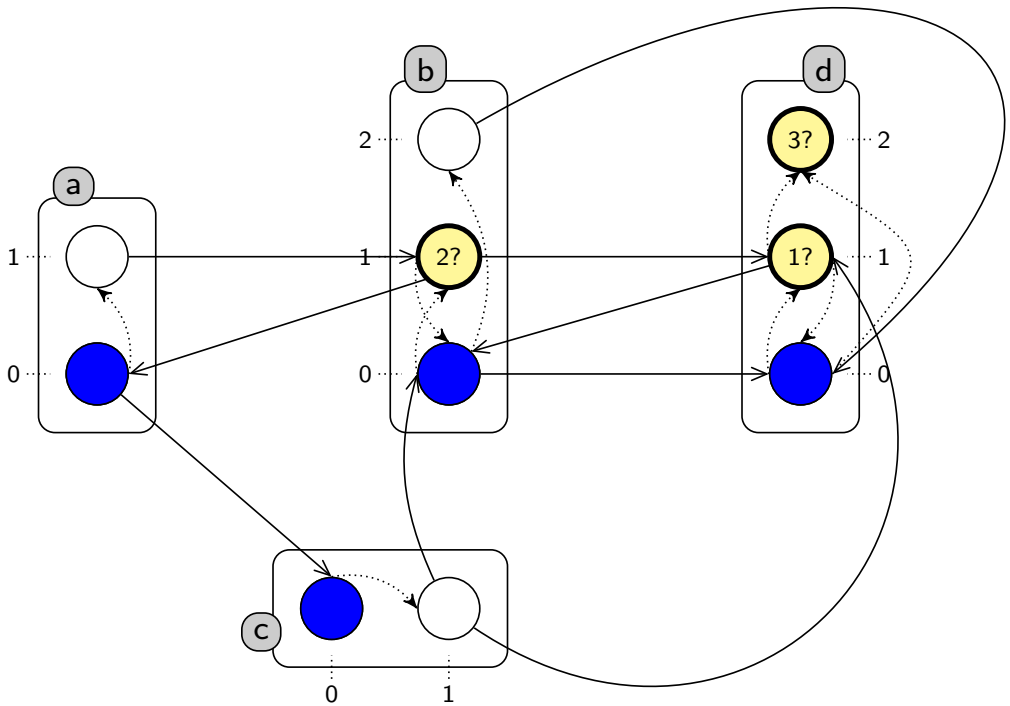


- Initial state $\langle a_1, b_0, c_0, d_0 \rangle$
- Objectives $[\ \Rsh d_1 \ :: \Rsh d_2\ ]$

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

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

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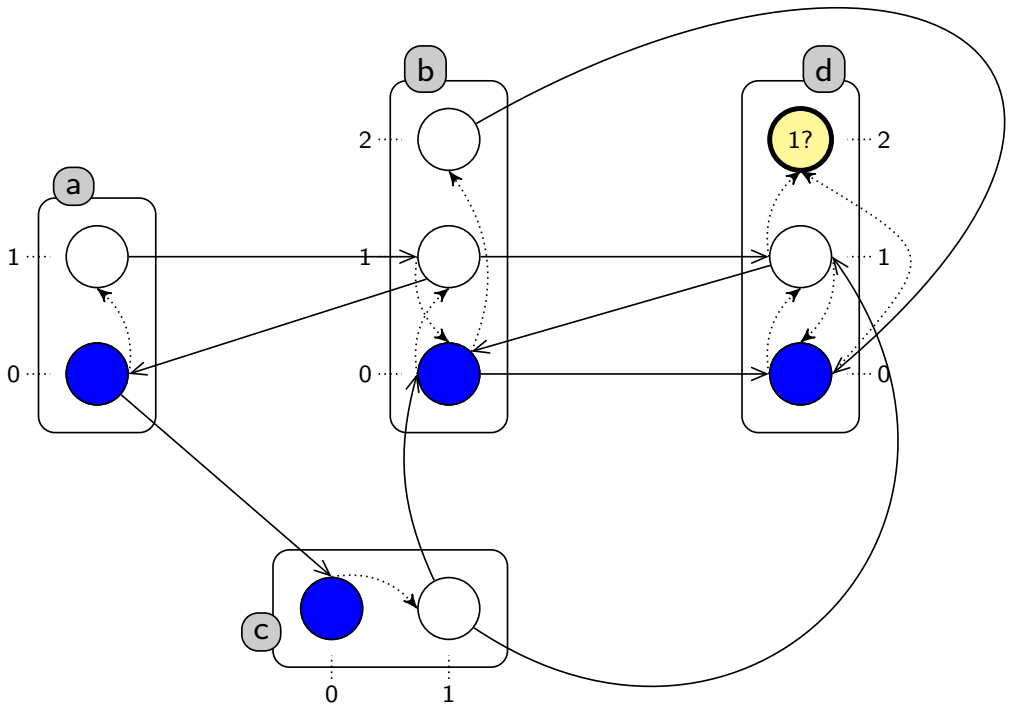

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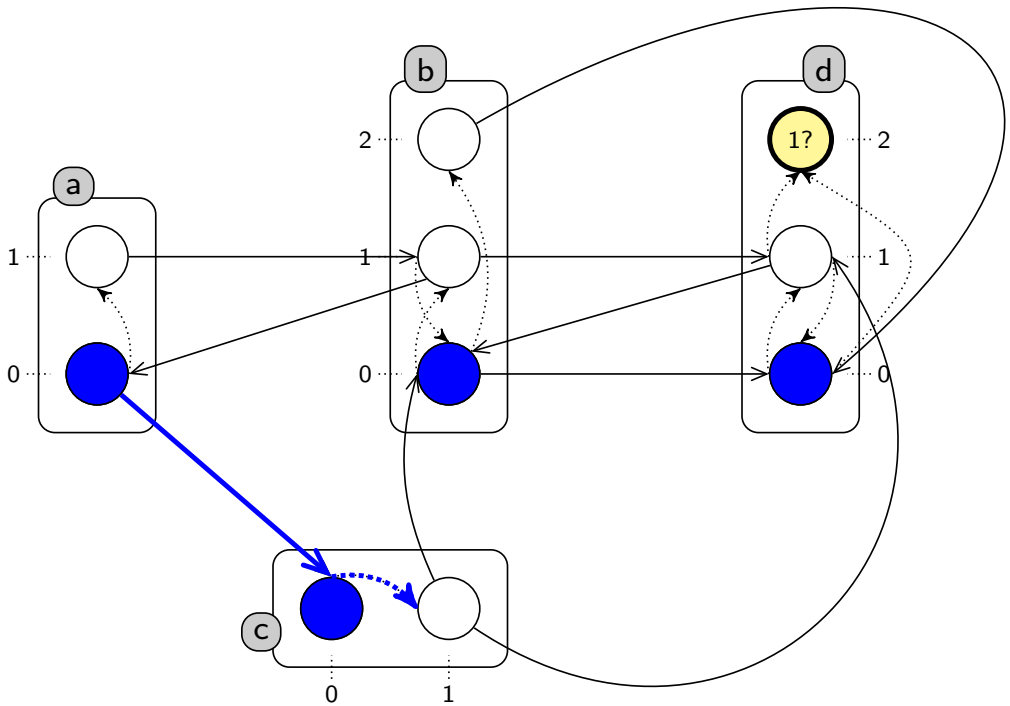

- Initial state

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

- Objectives

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

$\rightarrow$ Concretization of the objective = scenario

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

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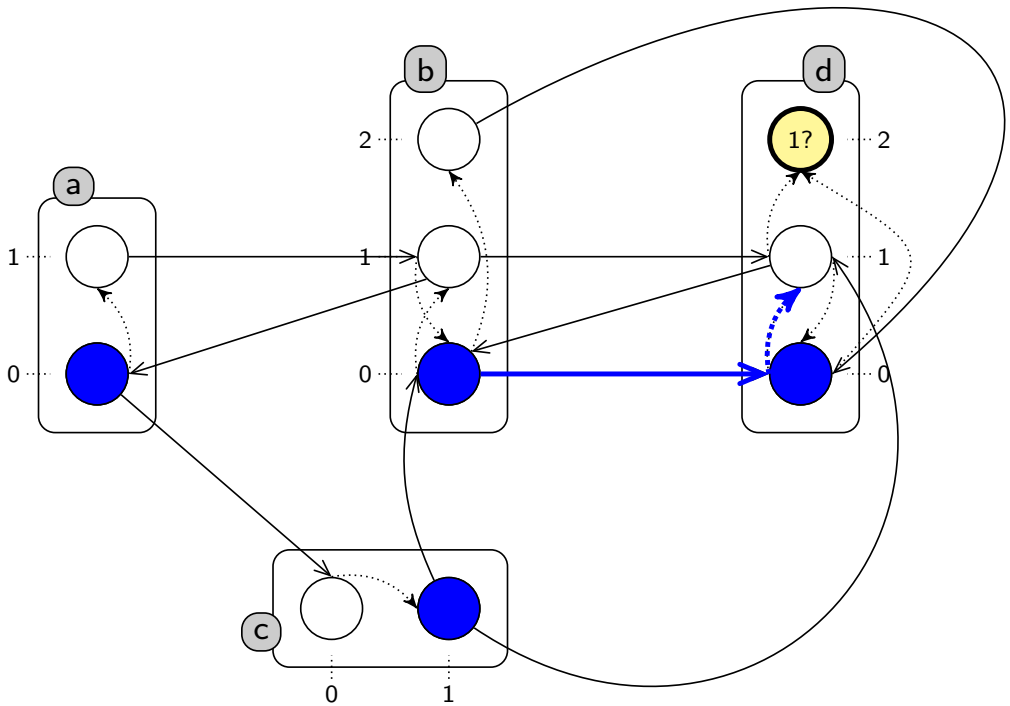

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$$[\ \Rsh\ d_1 \ :: \Rsh\ d_2\ ]$$
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$$[\ \Rsh\ d_2\ ]$$

$\rightarrow$ Concretization of the objective = scenario

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

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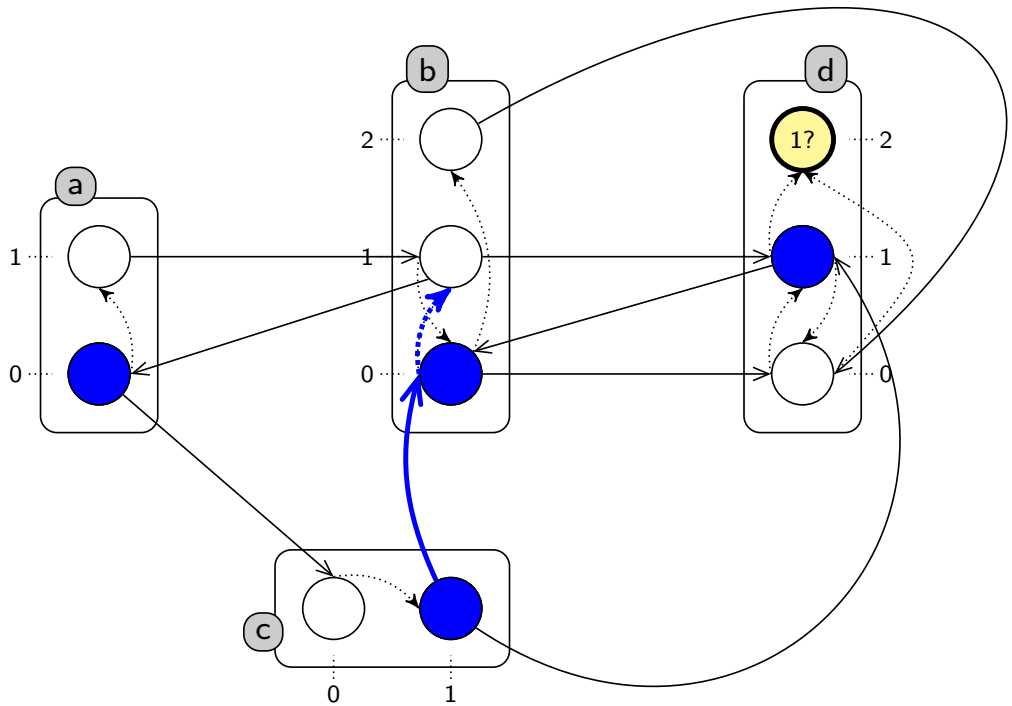

- Initial state

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

- Objectives

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

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

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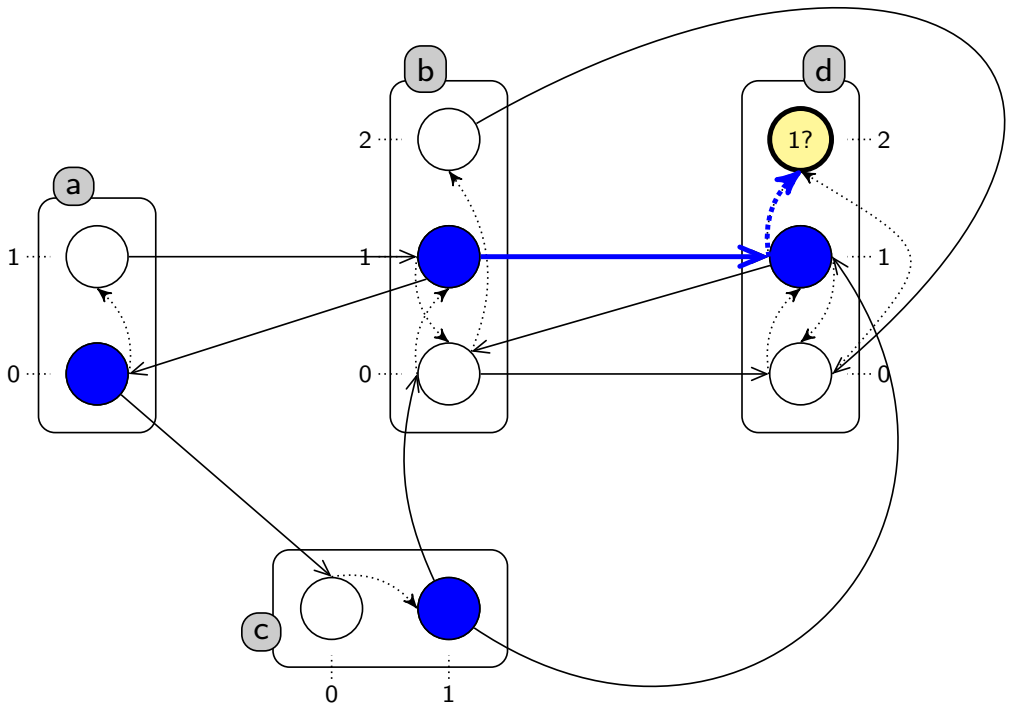
Successive reachability of processes:



- Initial state

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- Objectives

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

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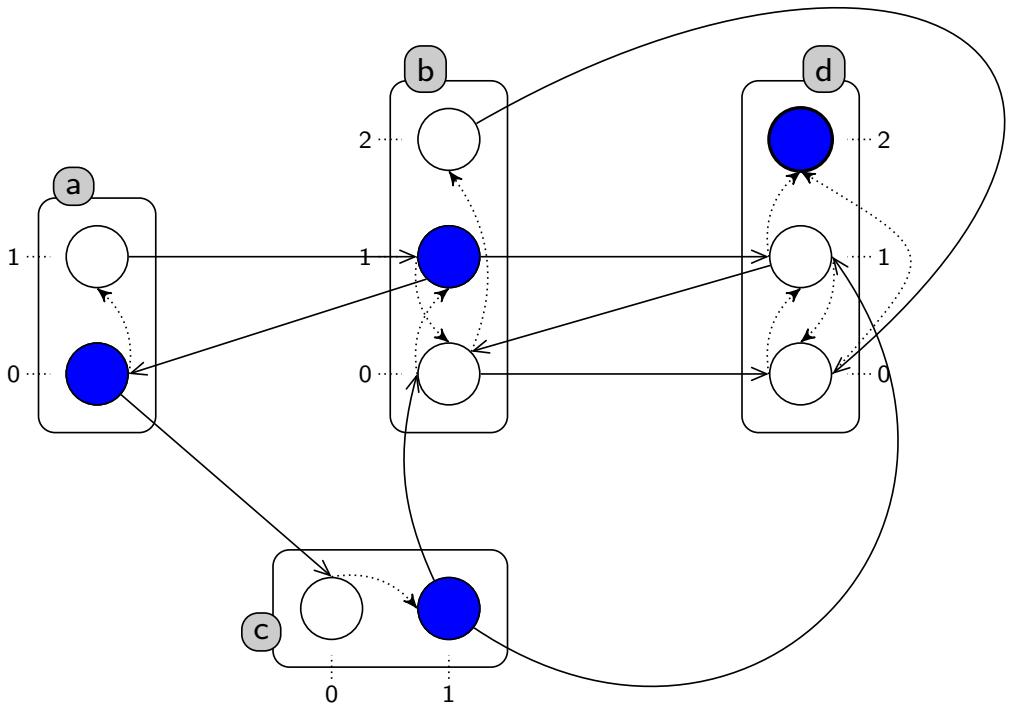
Successive reachability of processes:



- Initial state

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

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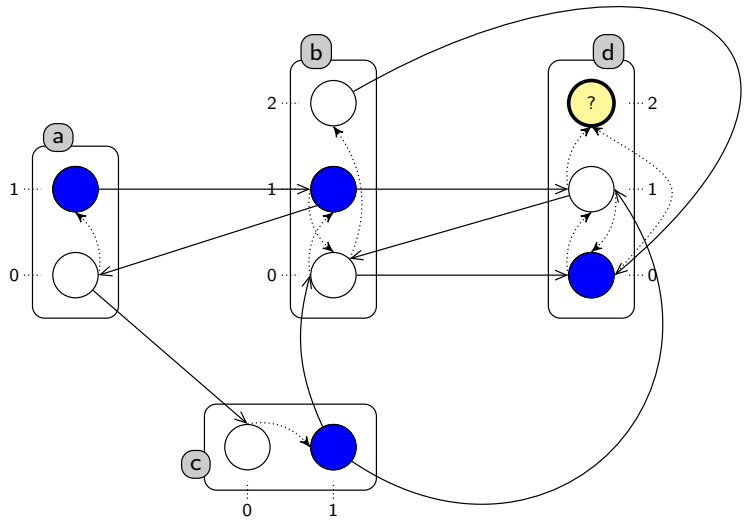
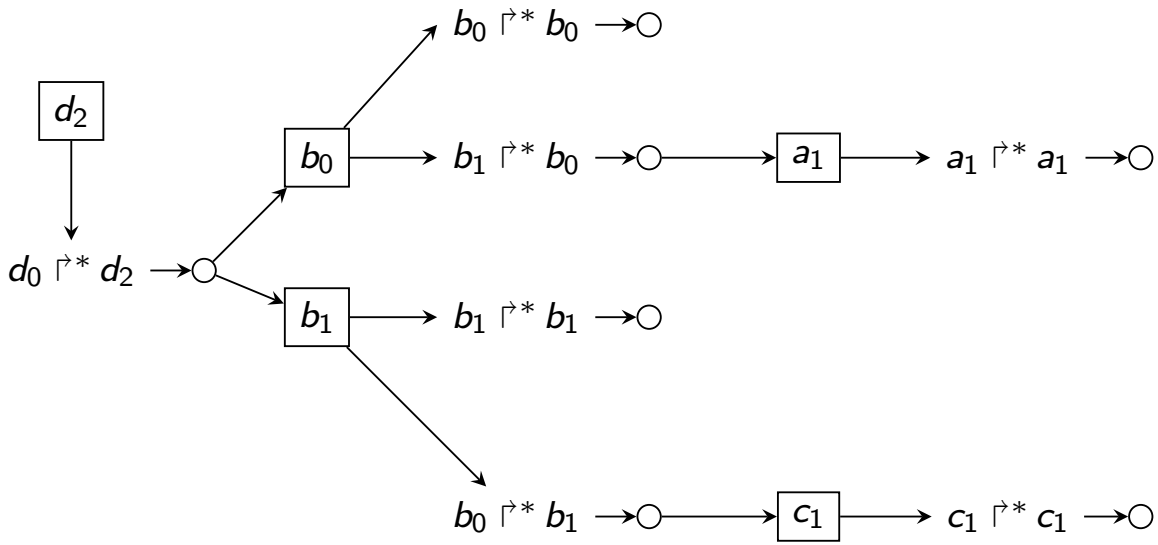
$$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow d_0 \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$$

Under-approximation



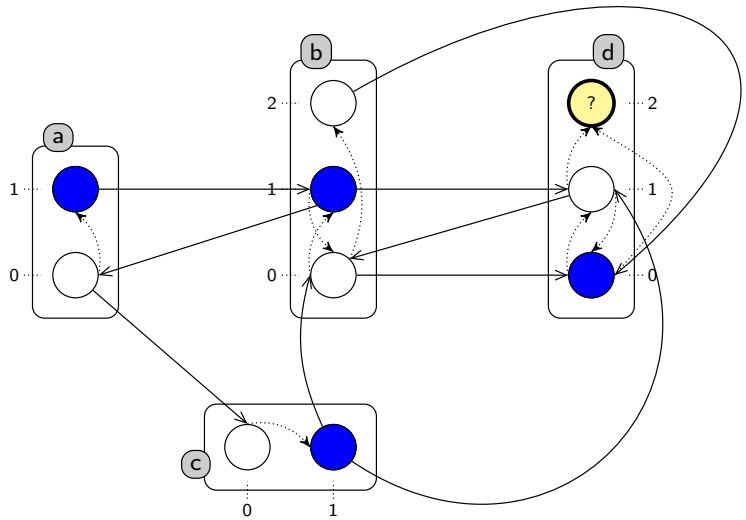
Sufficient condition:

- 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
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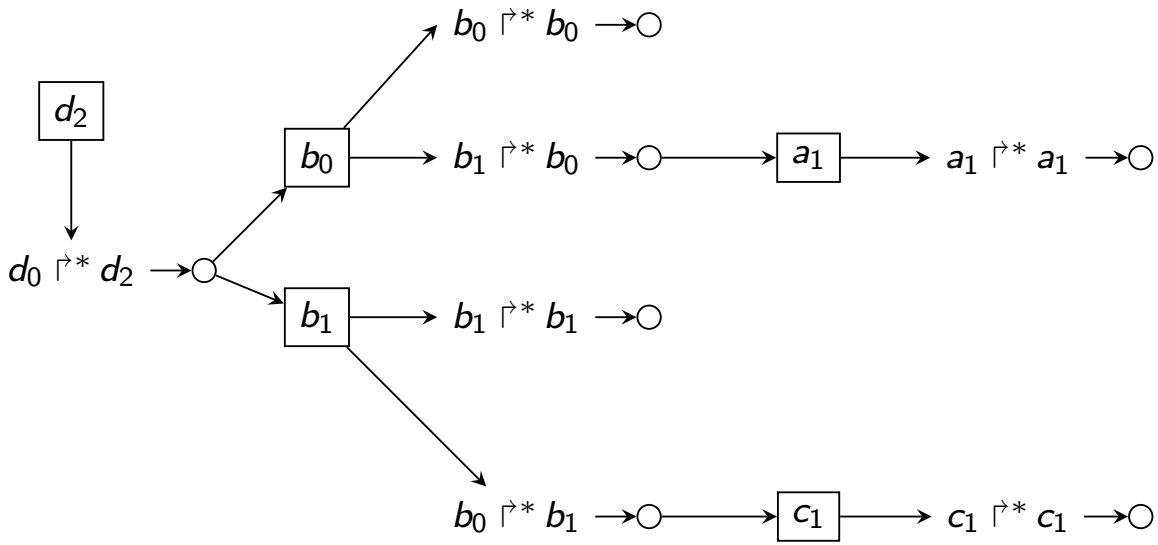
R is **true**



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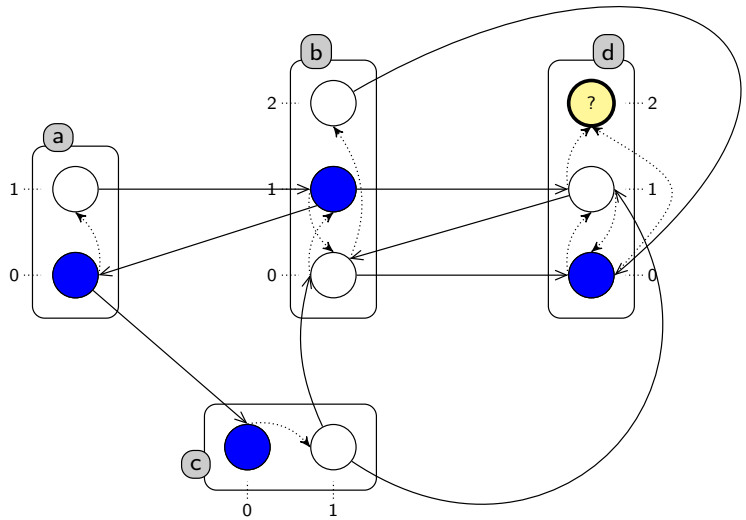
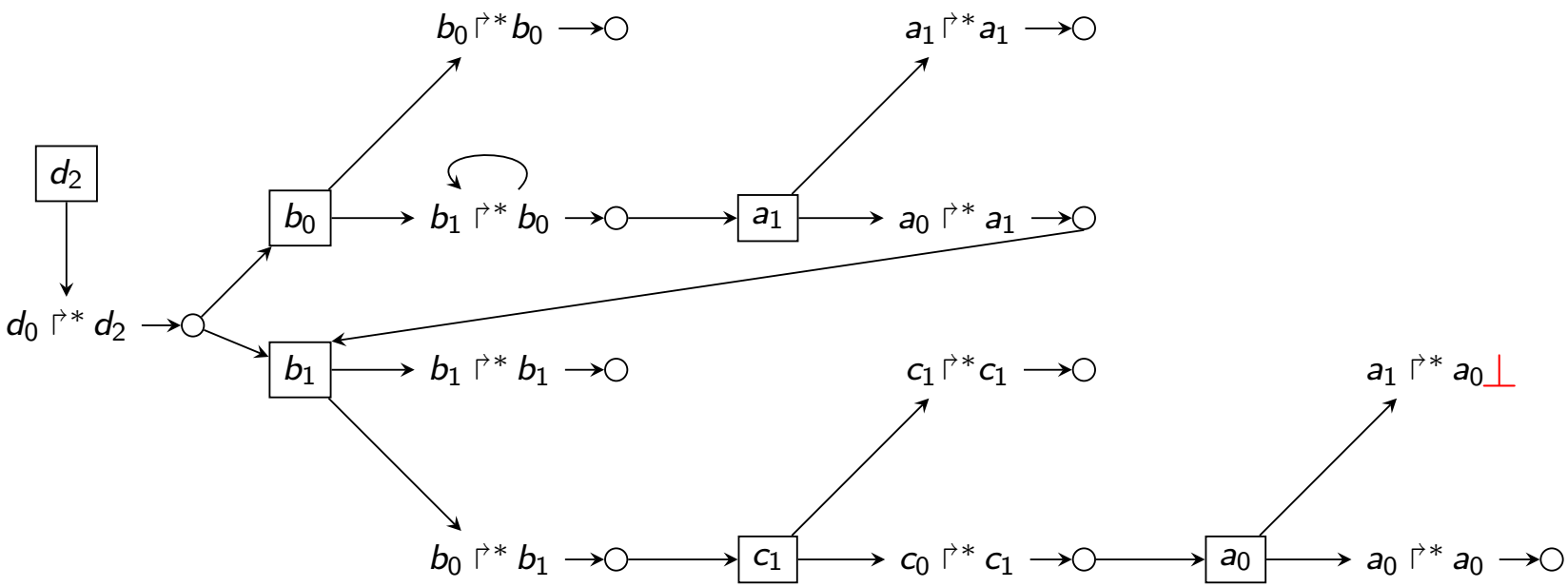
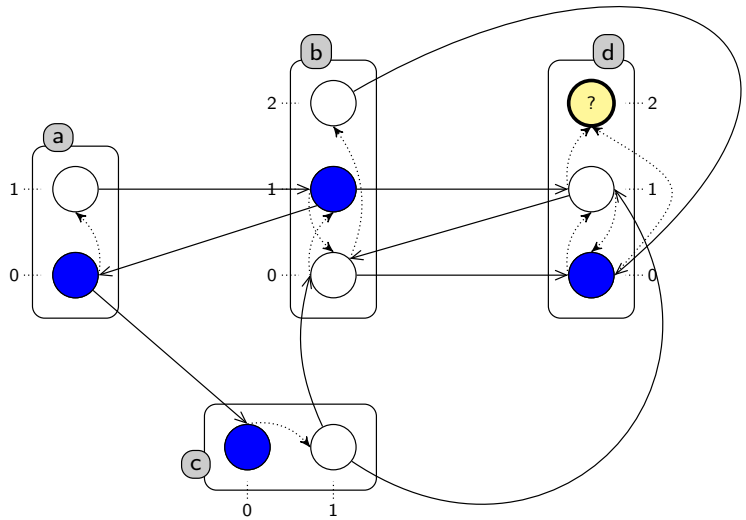


Sufficient condition:

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



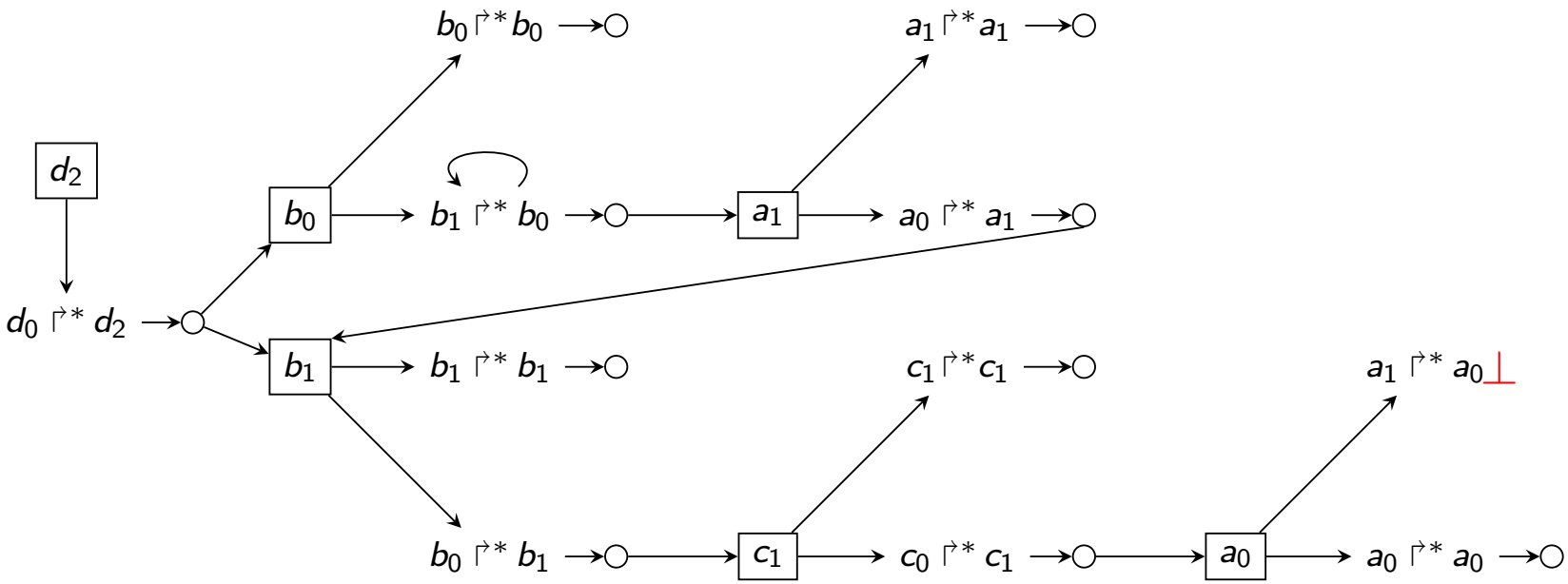
Under-approximation



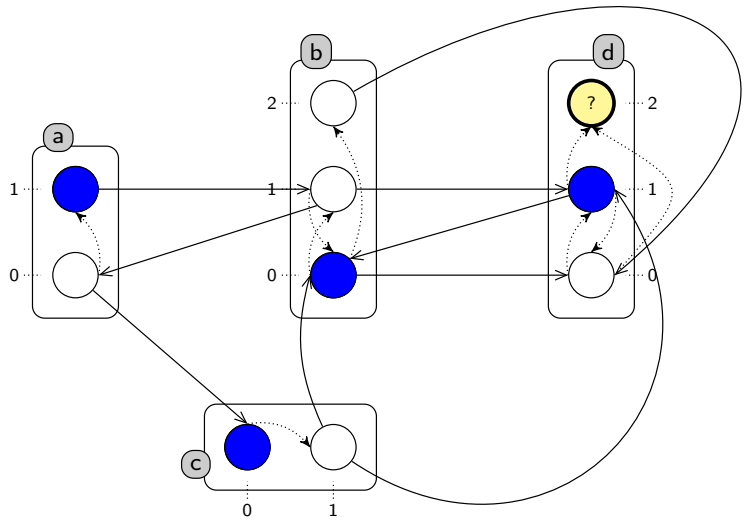
Sufficient condition:

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

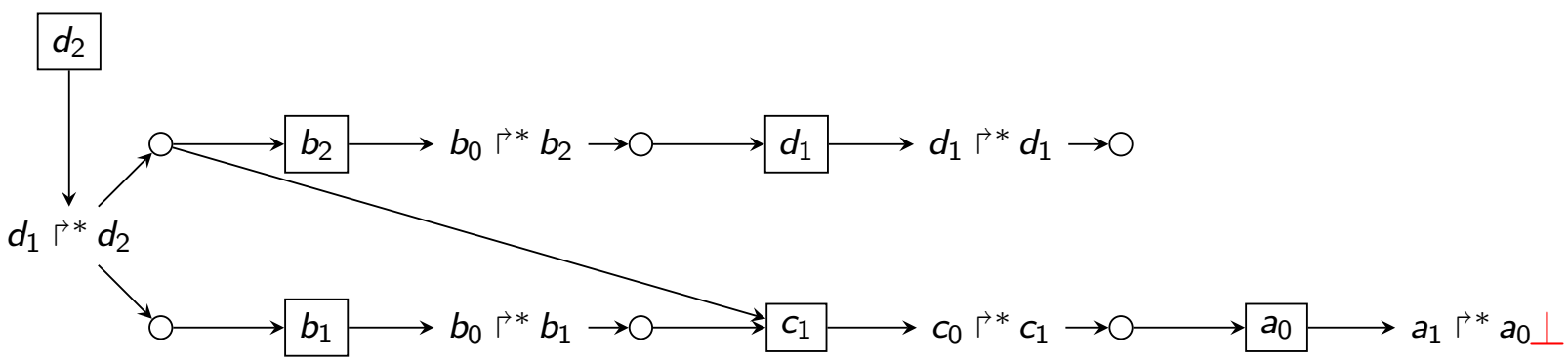
Inconclusive



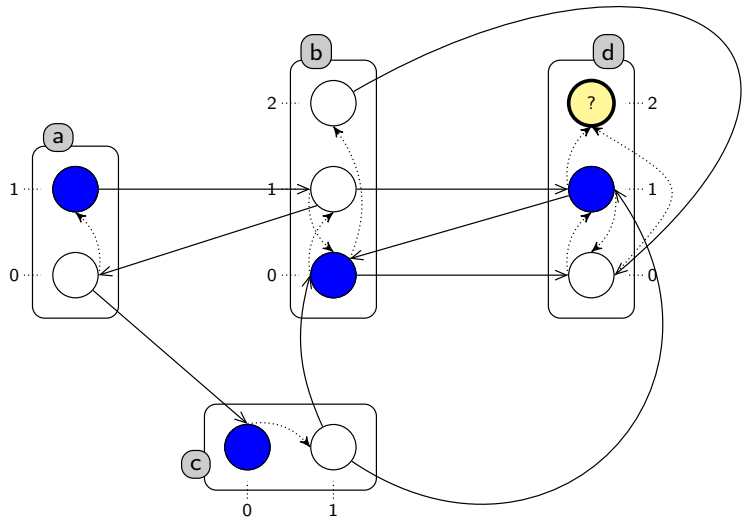
Over-approximation



Necessary condition:



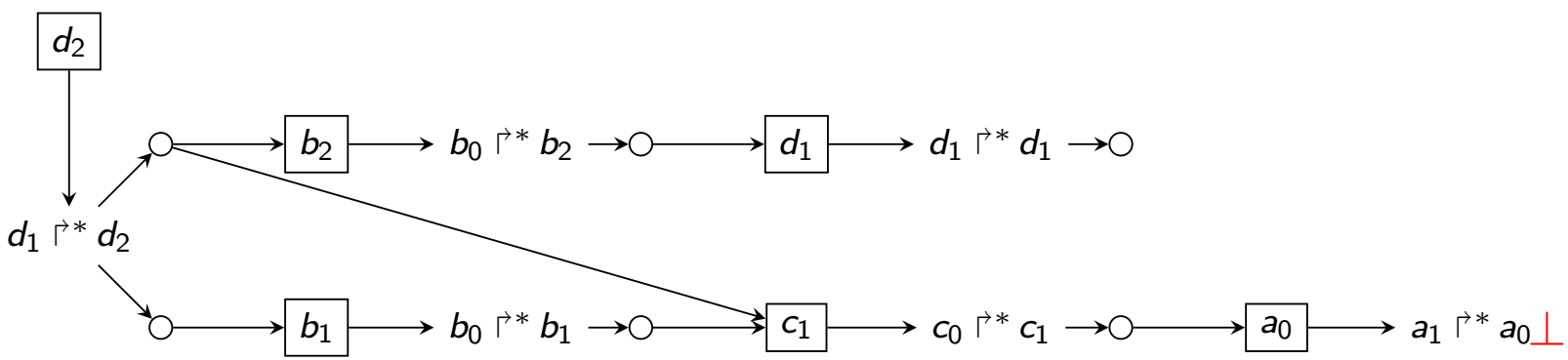
Over-approximation



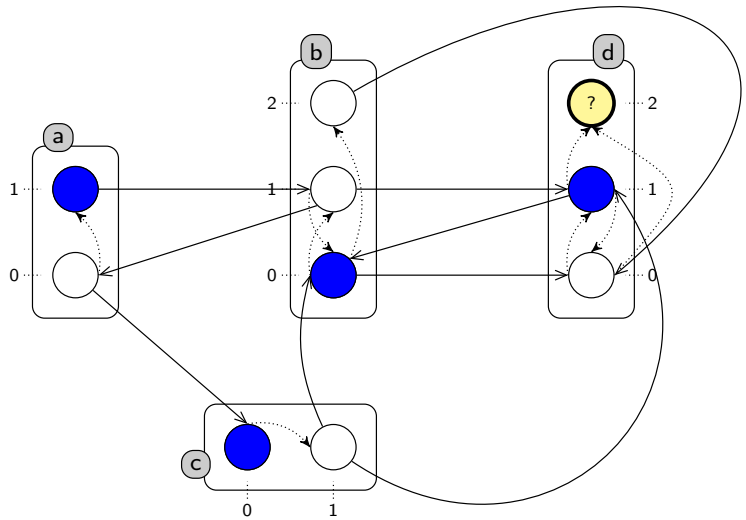
Necessary condition:

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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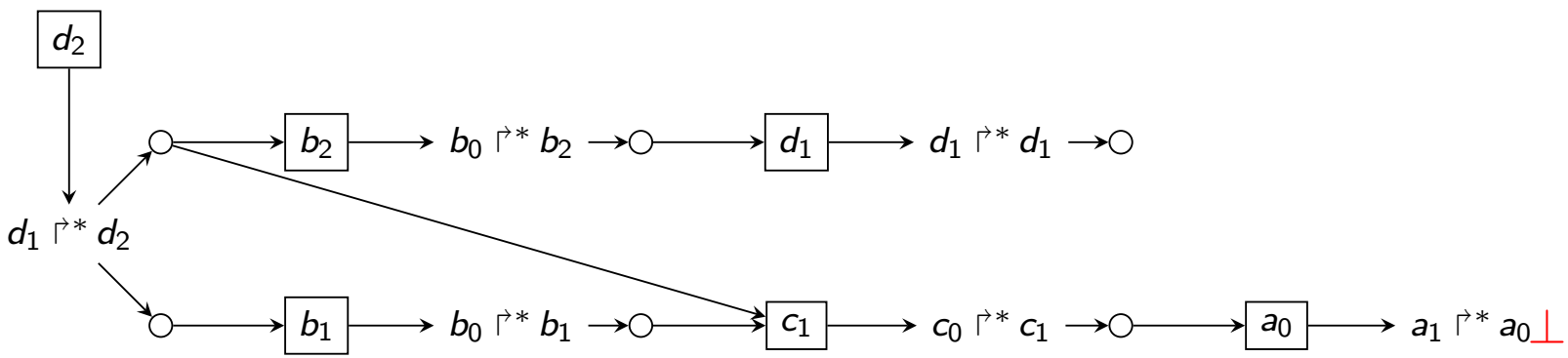
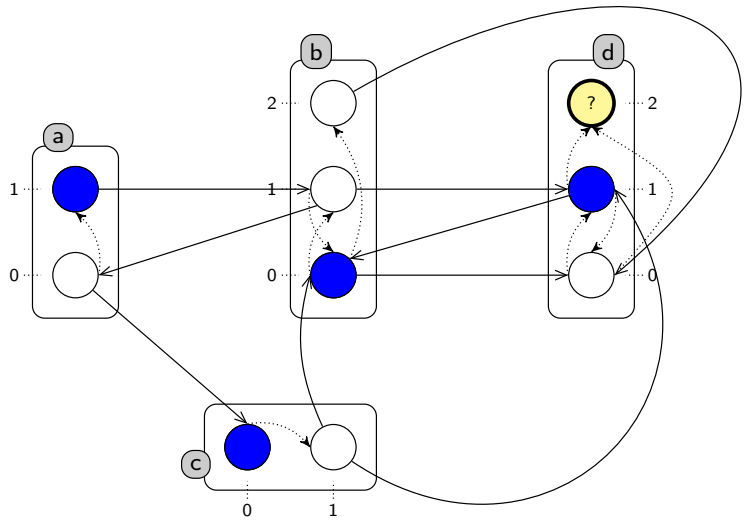


Over-approximation



Necessary condition:

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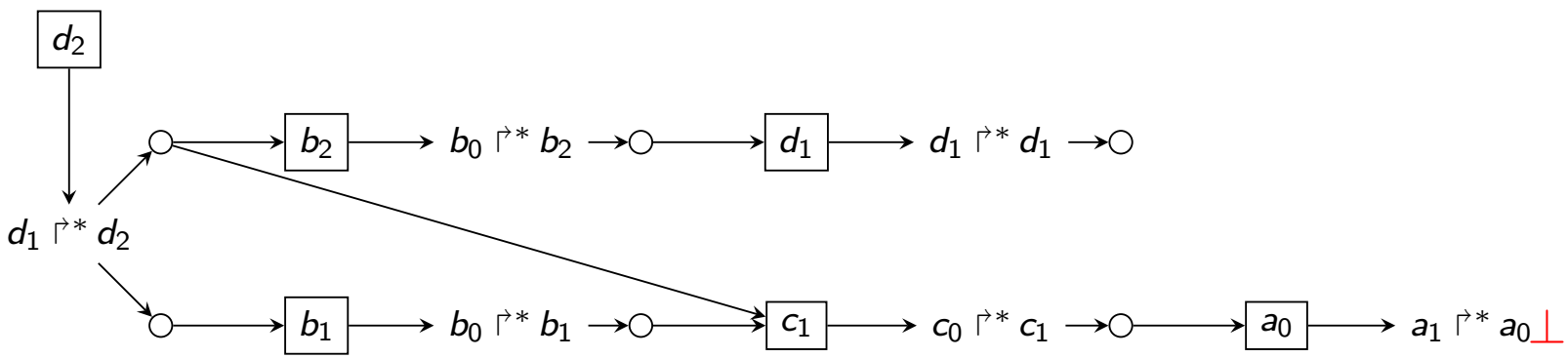
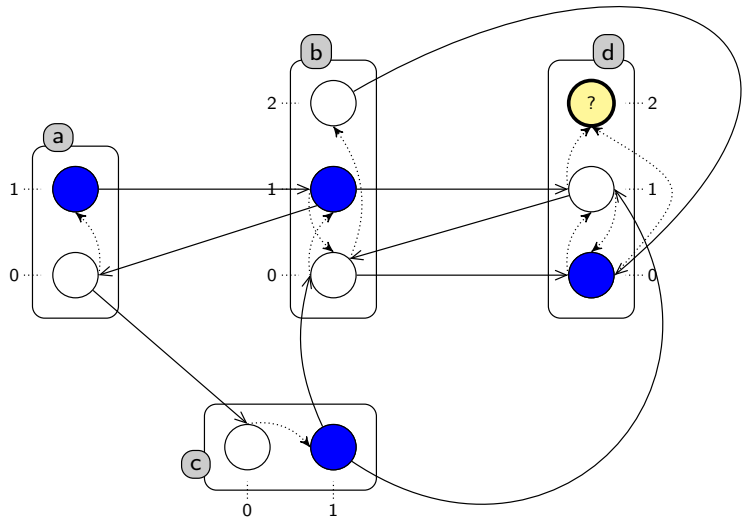
- process → follow all objectives

R is **false**



Over-approximation



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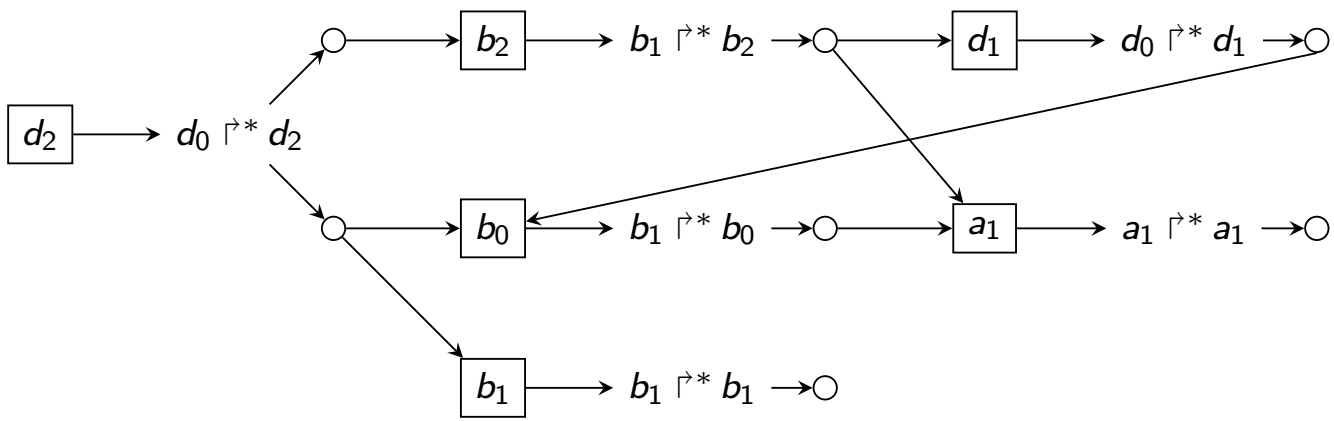
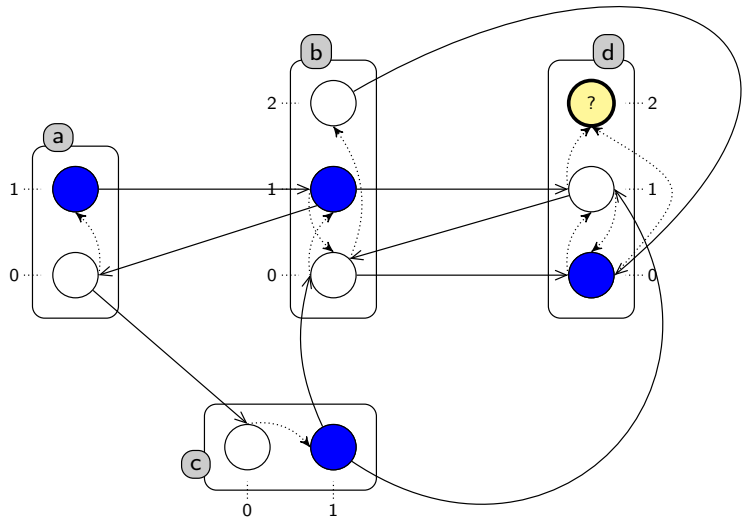


Over-approximation



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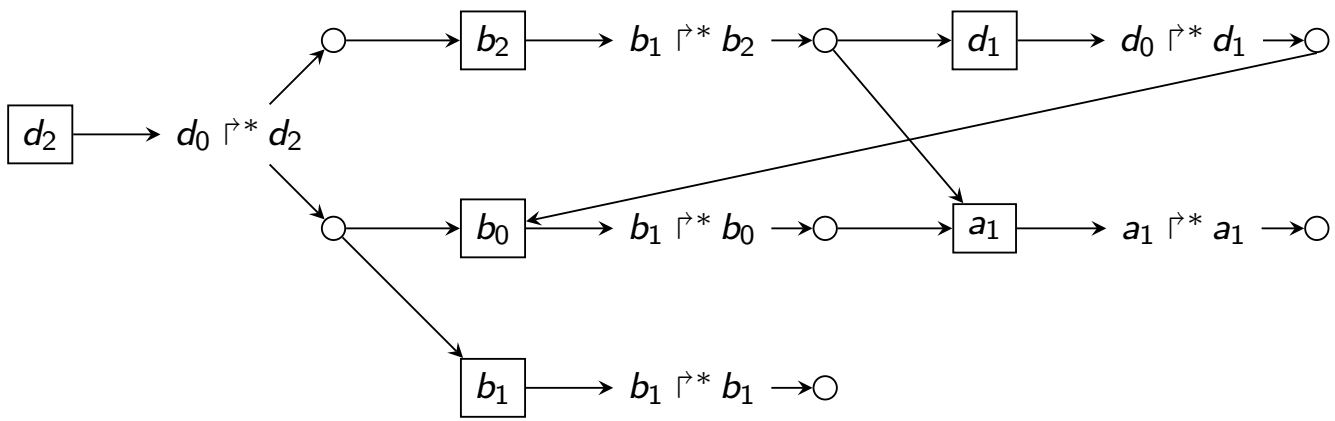
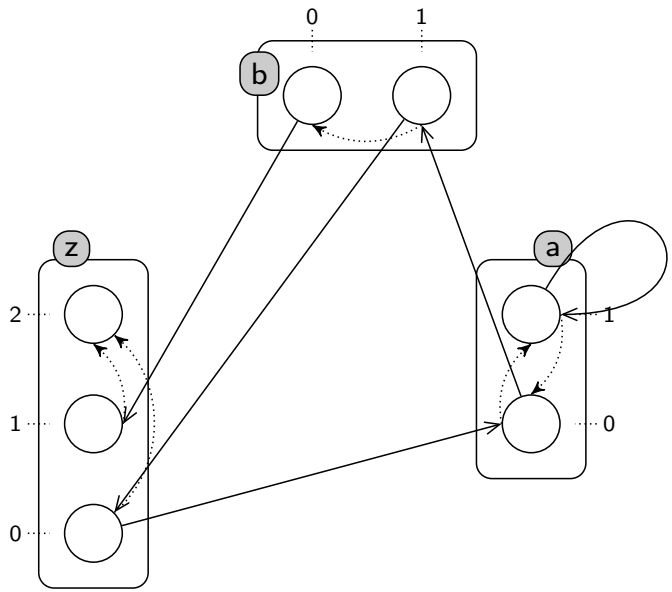


Static Analysis: Fixed Points

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

Fixed point = state where no action can be fired

→ avoid couples of processes bounded by an action



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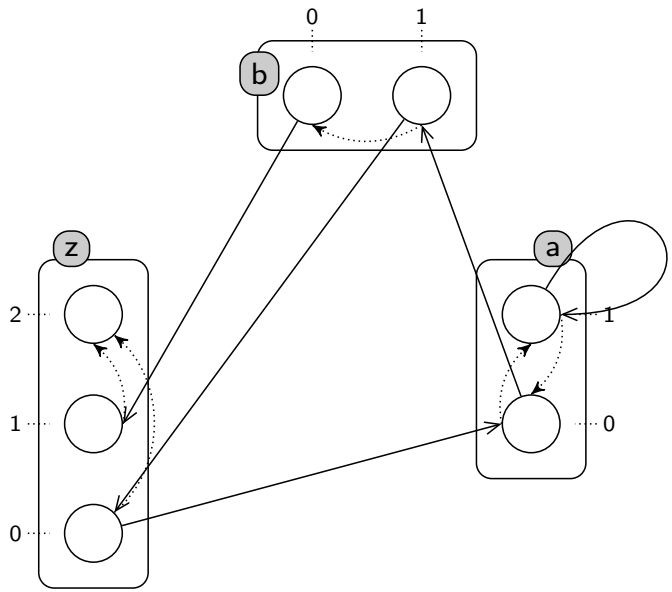
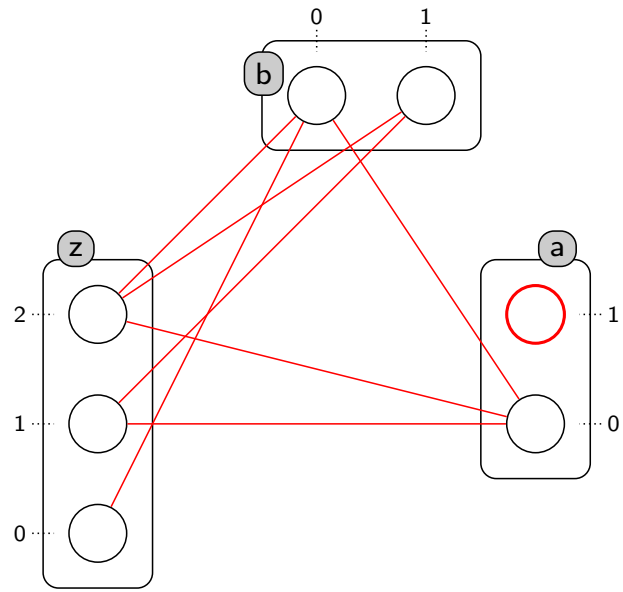
→ Hitless Graph





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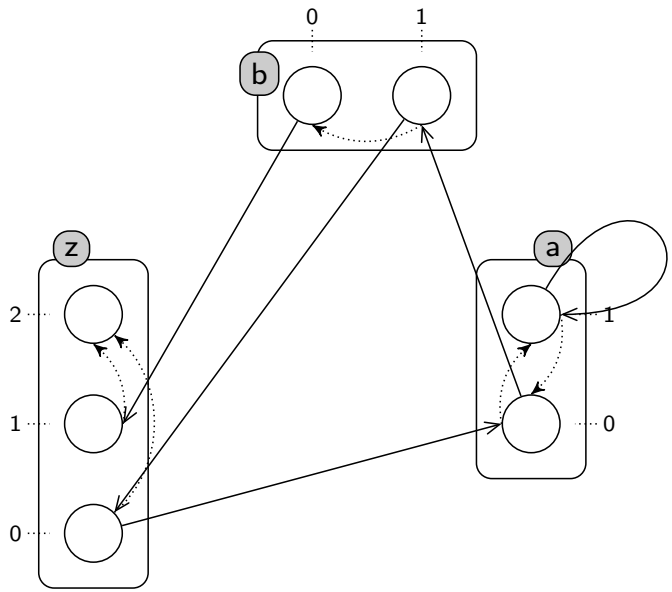

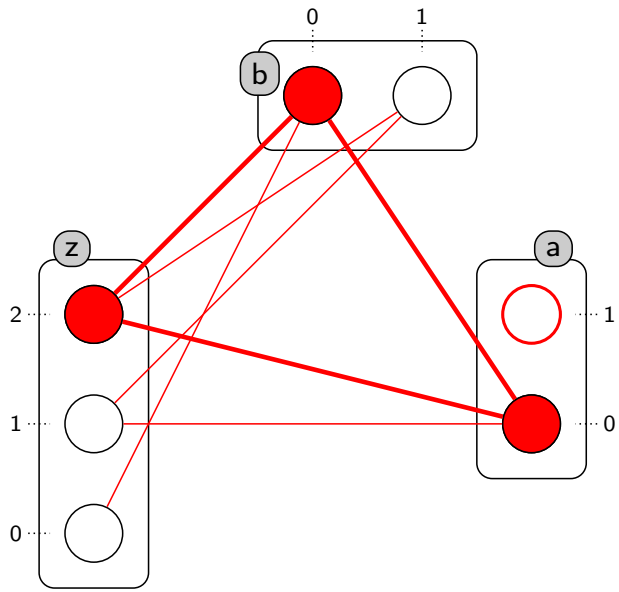

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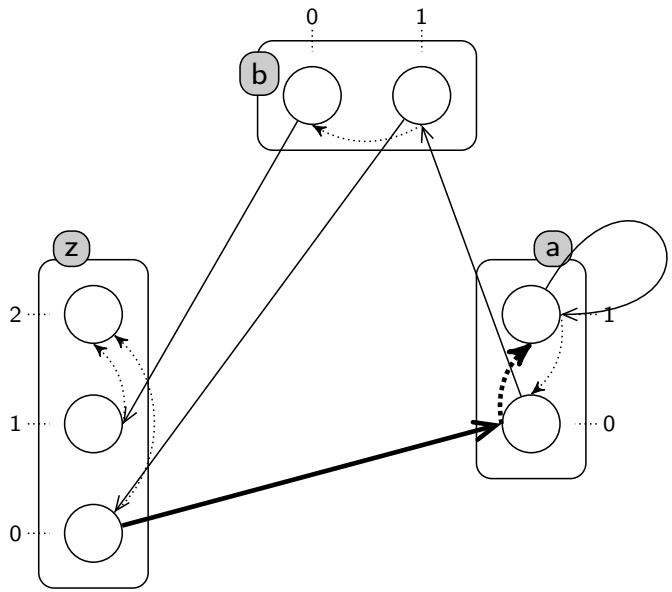

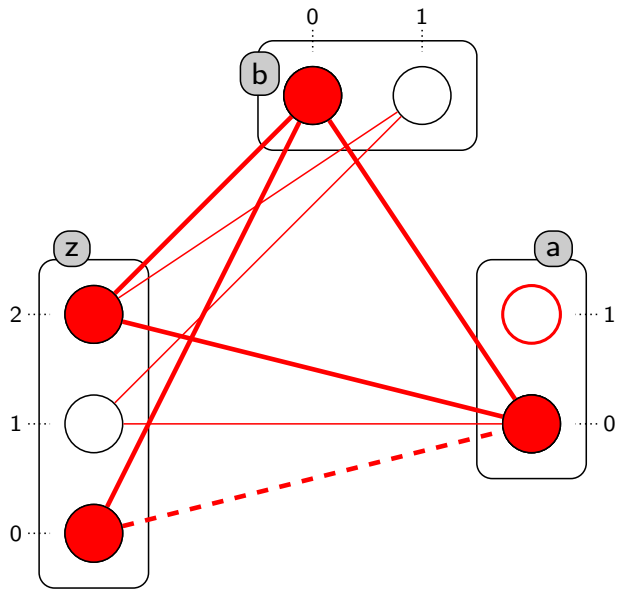

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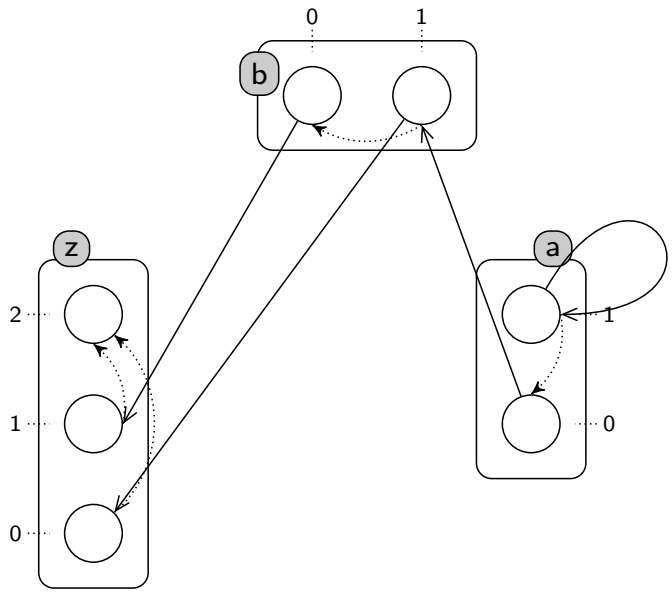

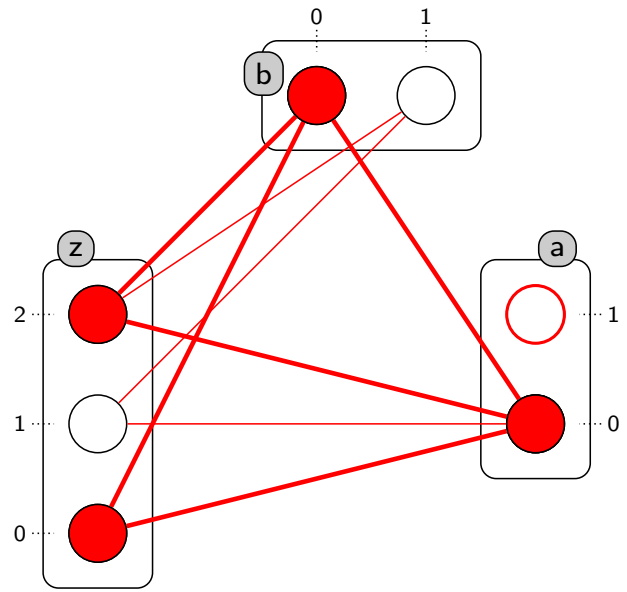

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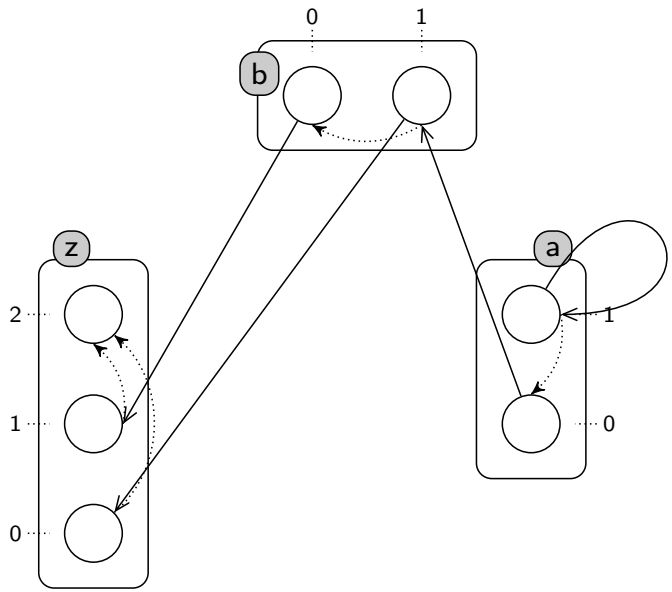

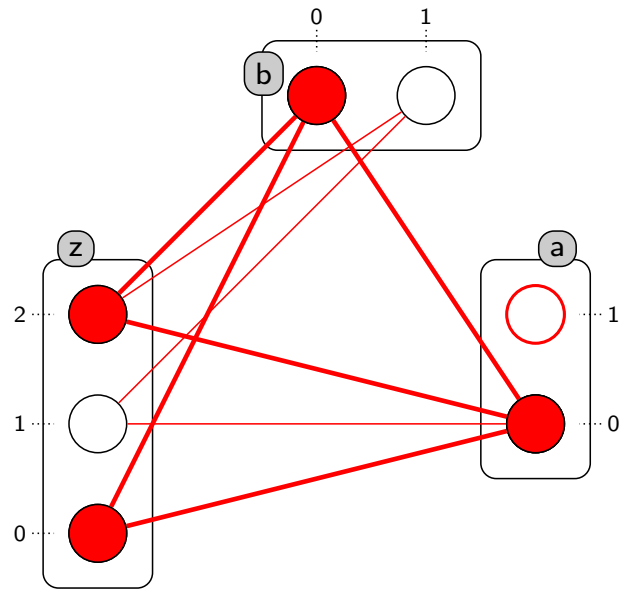

Exponential complexity w.r.t. the number of sorts