Réunion finale BioTempo

Introducing time parameters into Process Hitting with classes of priorities

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Joint work with:
Loïc PAULEVÉ, Morgan MAGNIN, Olivier ROUX

Context and Aims

MeForBio team: Algebraic modeling to study large dynamical biological systems

→ Contribution: the **Process Hitting** framework
[Paulevé *et al.* in Transactions on Computational Systems Biology, 2011]
[Paulevé *et al.* in Mathematical Structures in Computer Science, 2012]

- A restriction of synchronous automata networks
- Special form for the actions ⇒ more atomistic than Interaction Graphs
- Efficient reachability analysis

→ Introduction of temporal features:

1) Stochastic parameters
   [Paulevé *et al.* in Transactions on Computational Systems Biology, 2011]
2) Priorities
   [Folschette *et al.* in Workshop on Interactions between Computer Science and Biology, 2013]
3) Neutralizing edges

The Process Hitting modeling

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

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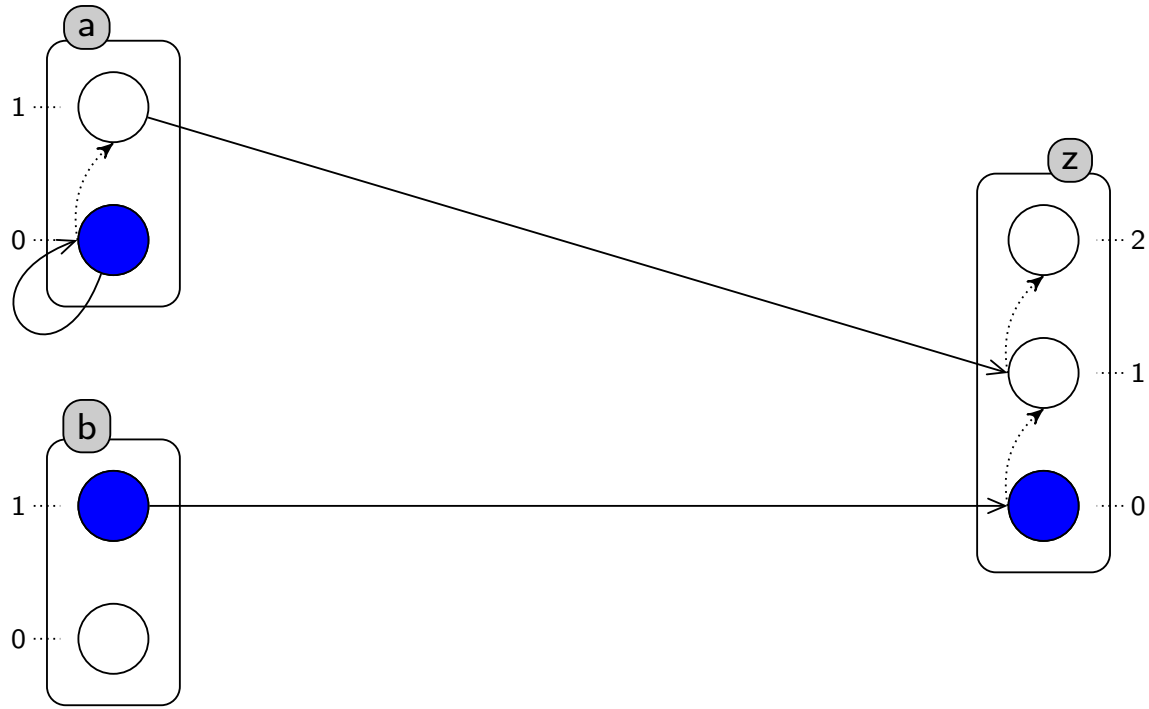

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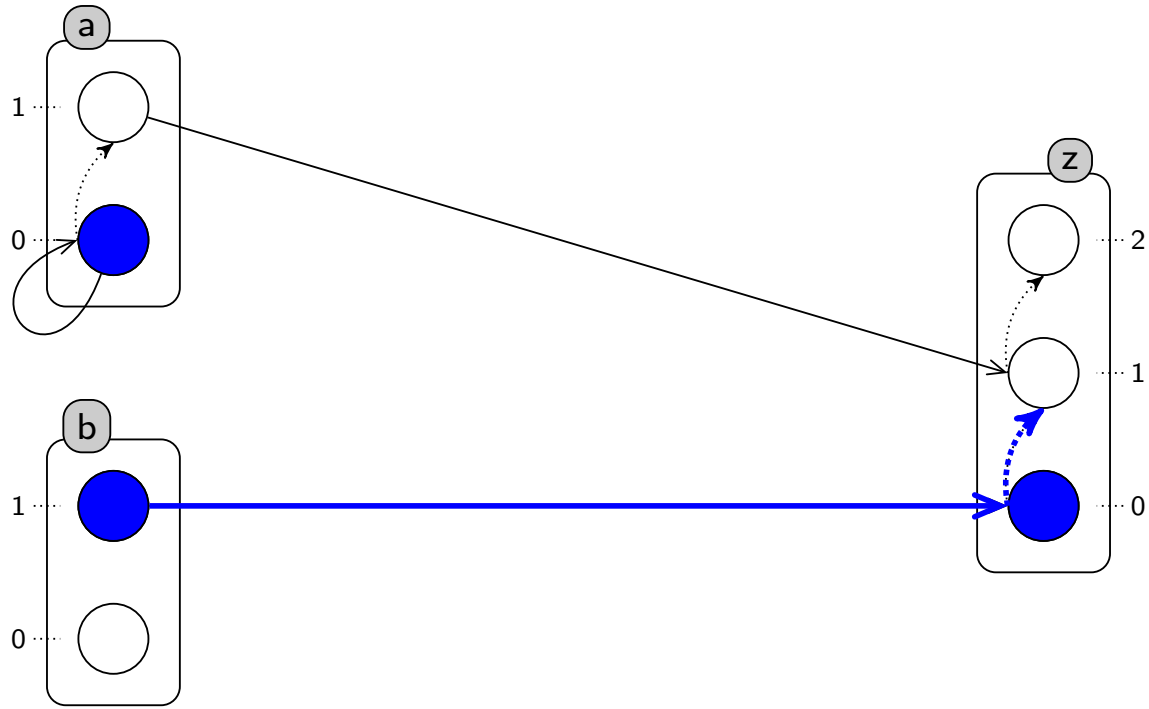

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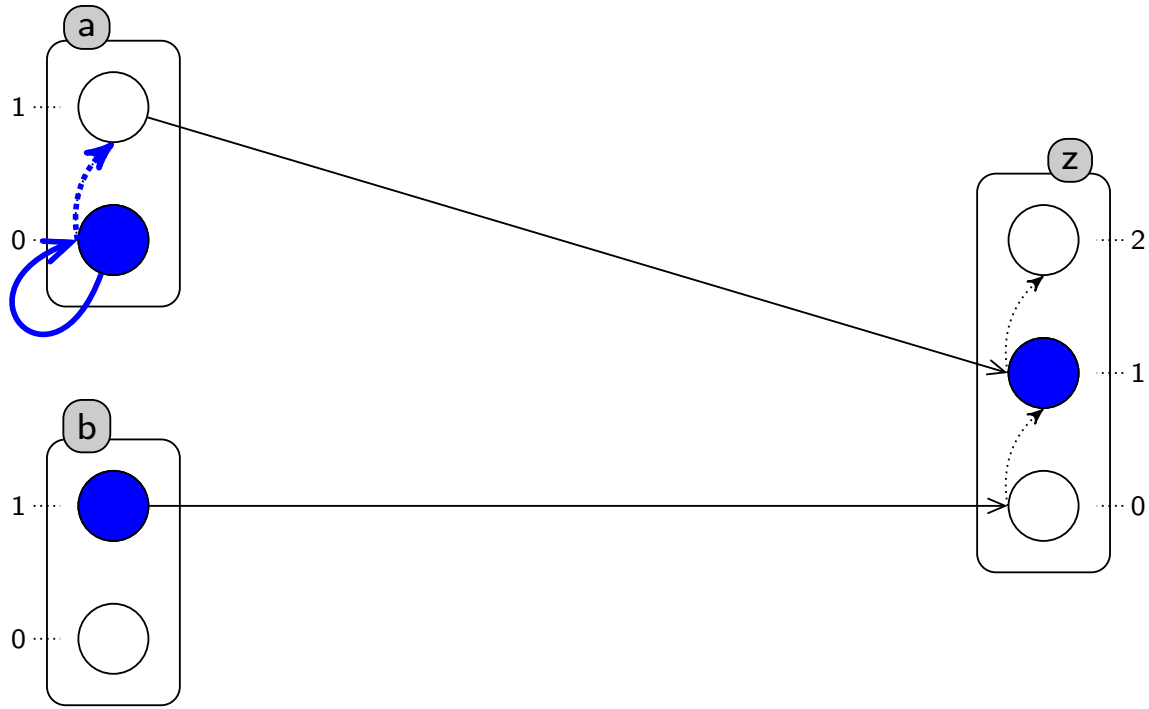

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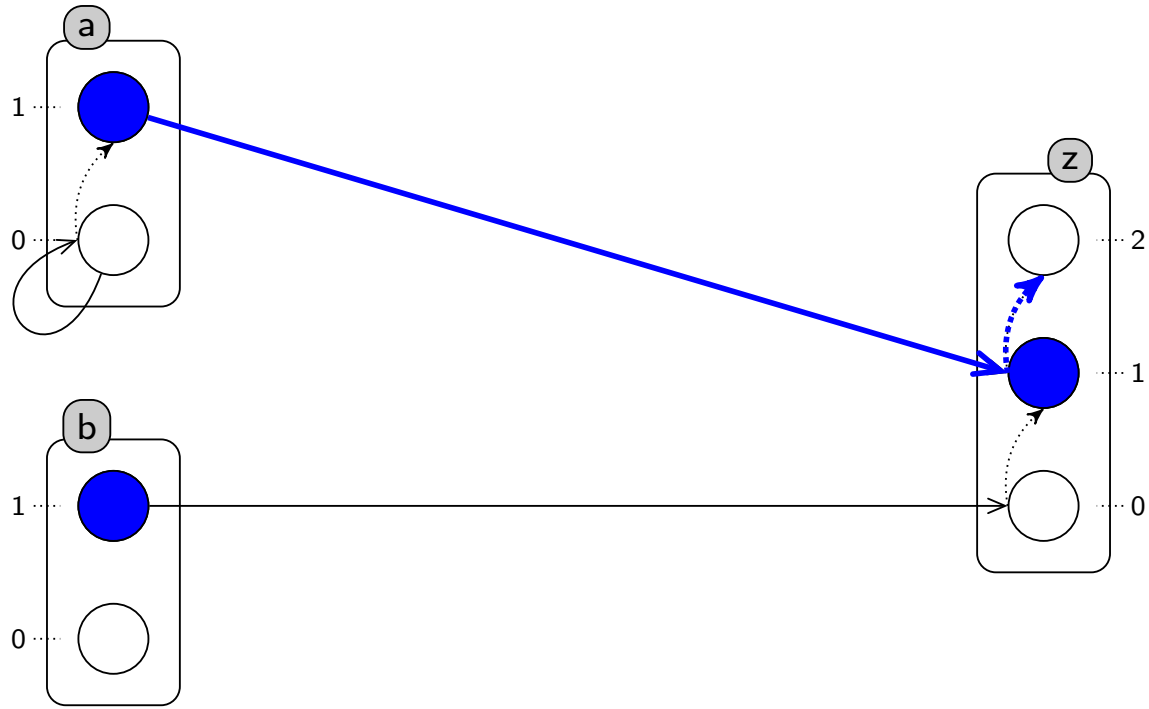

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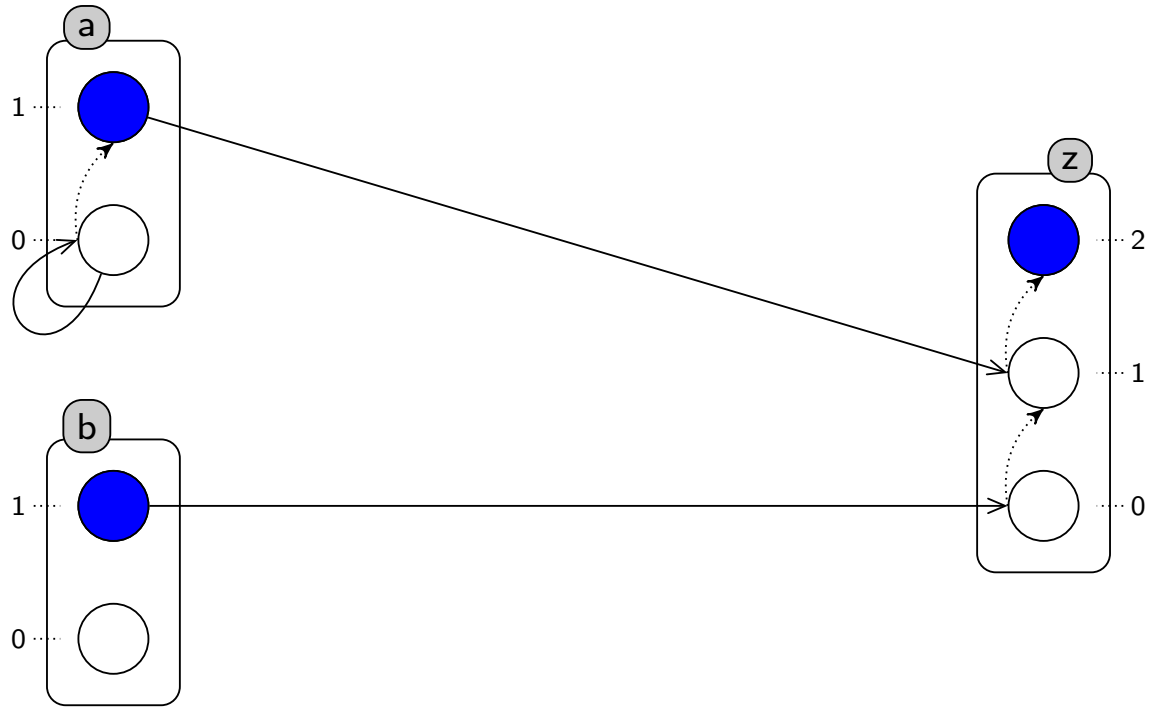

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Adding cooperations

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

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

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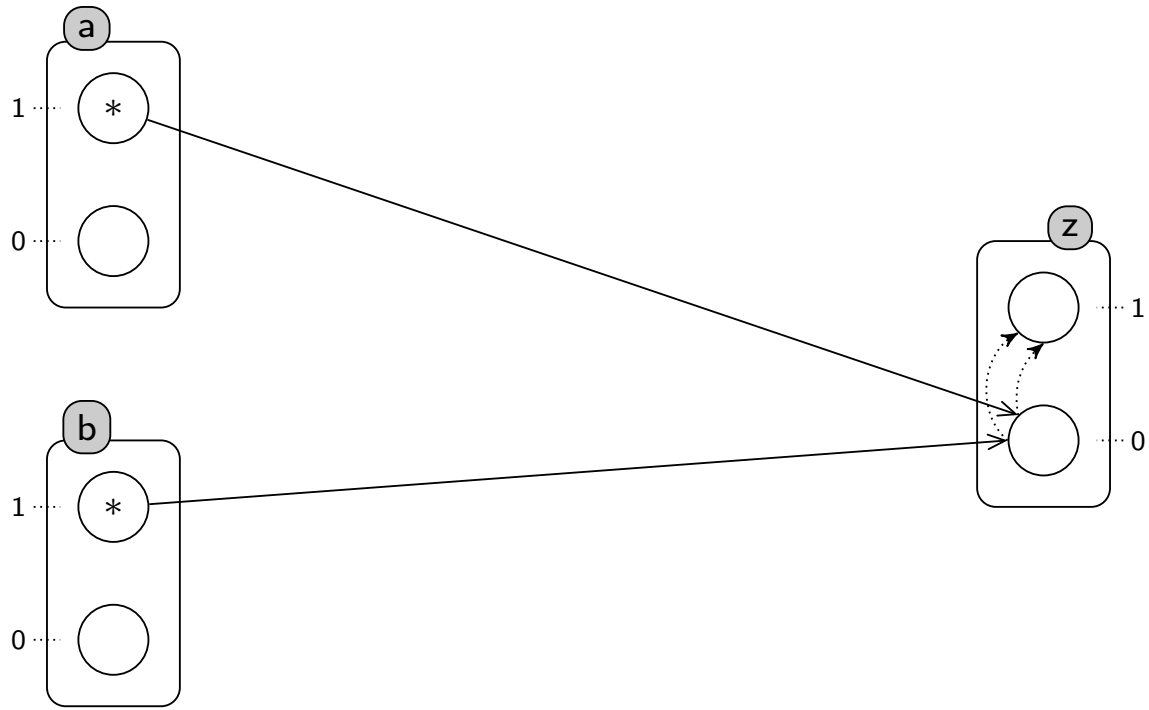

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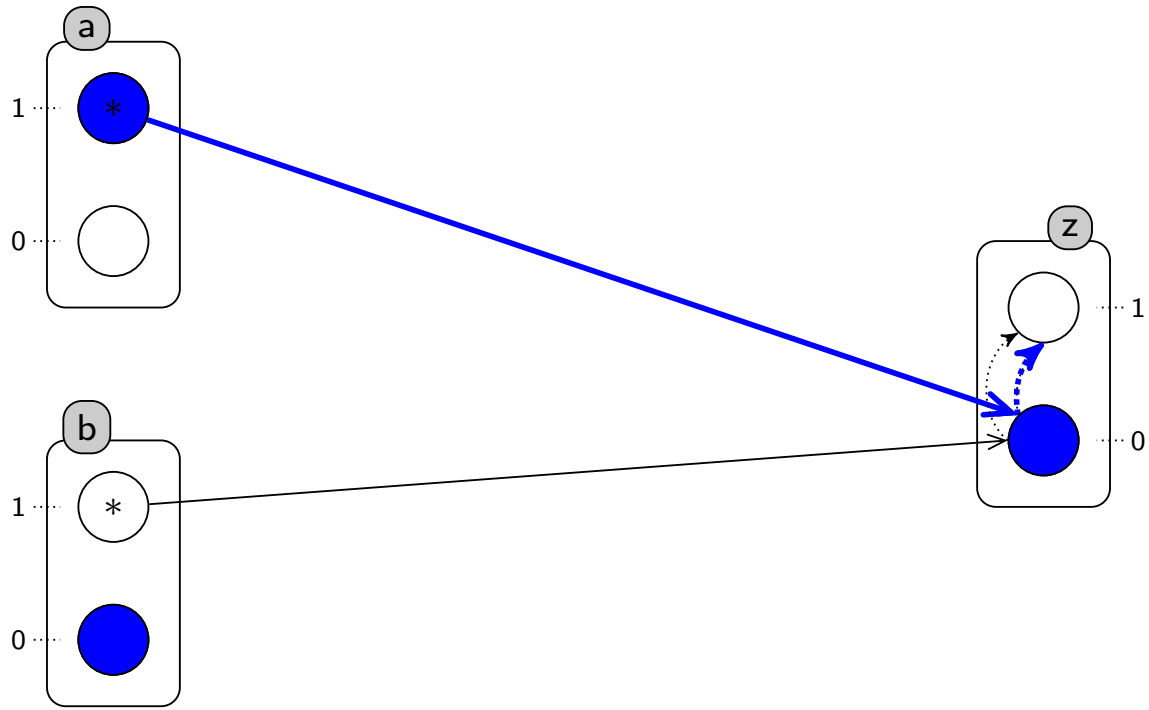

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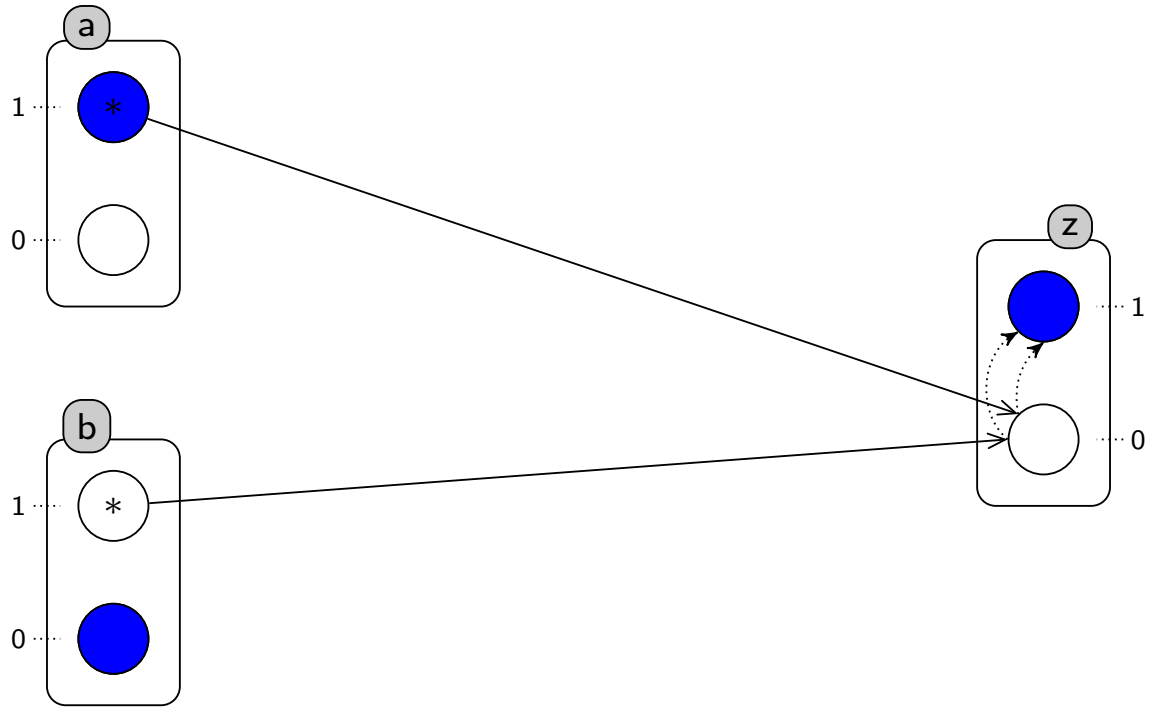

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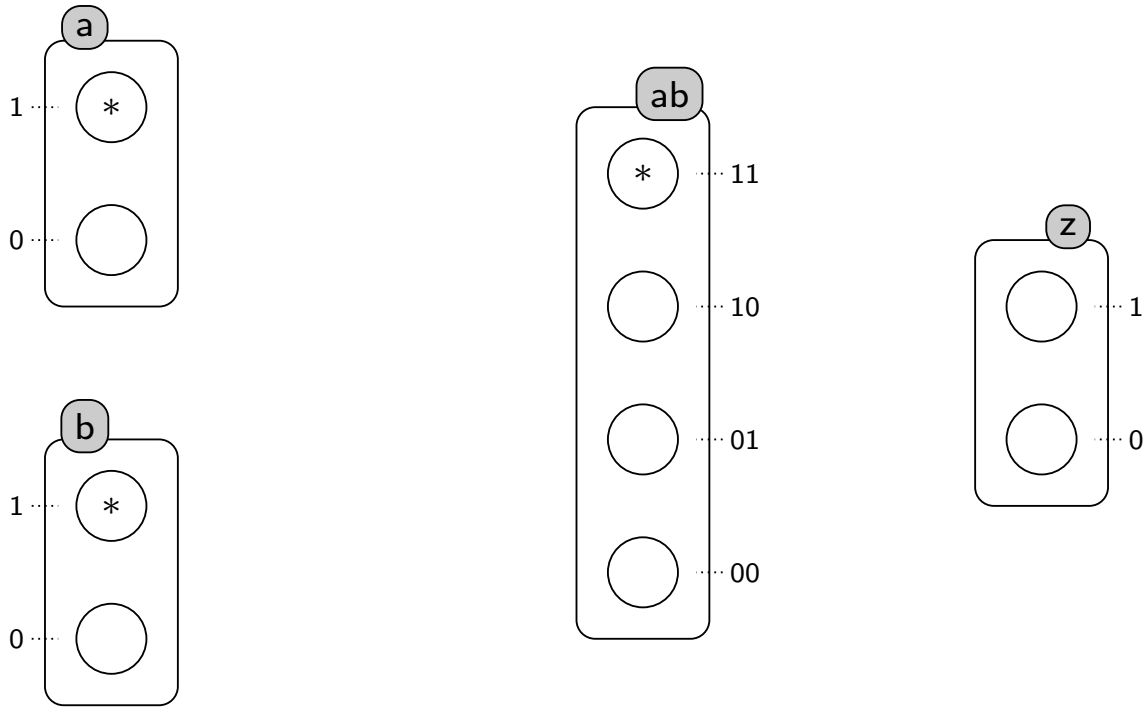

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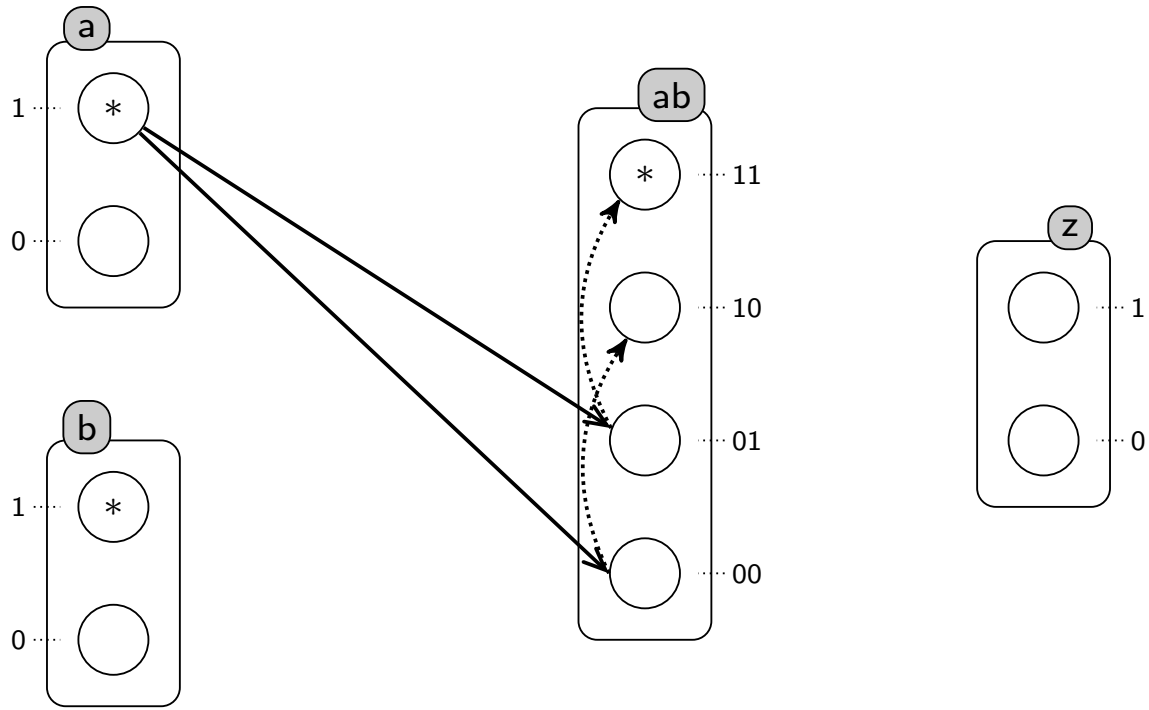

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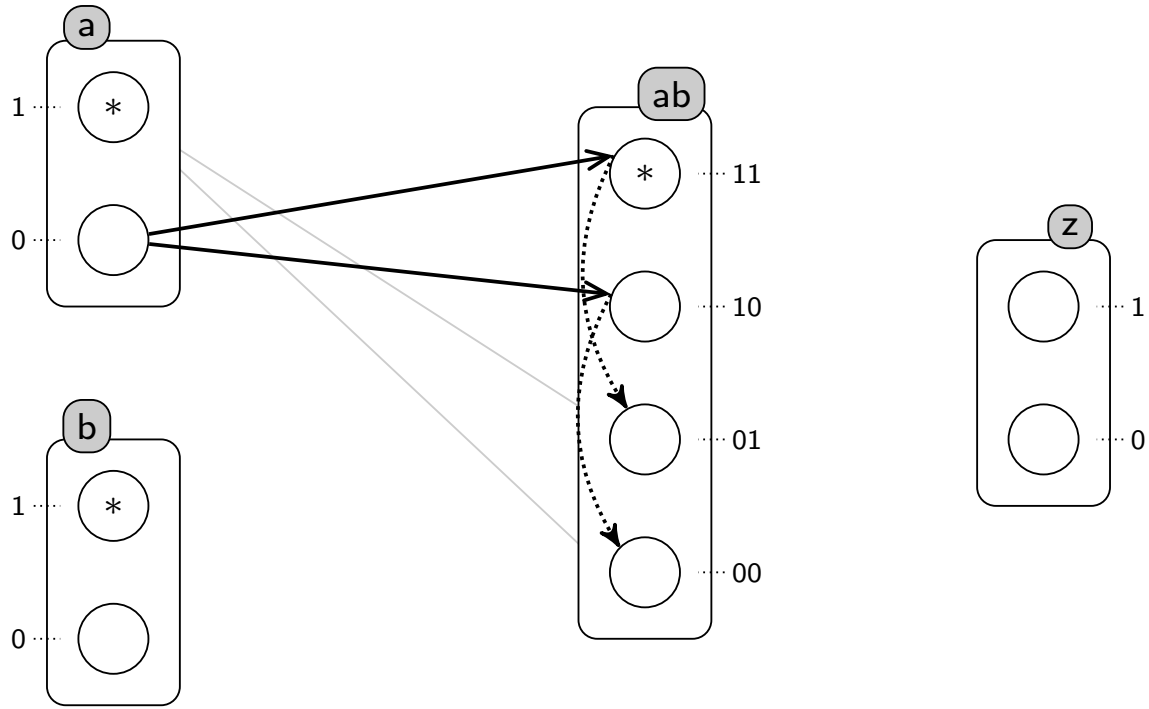

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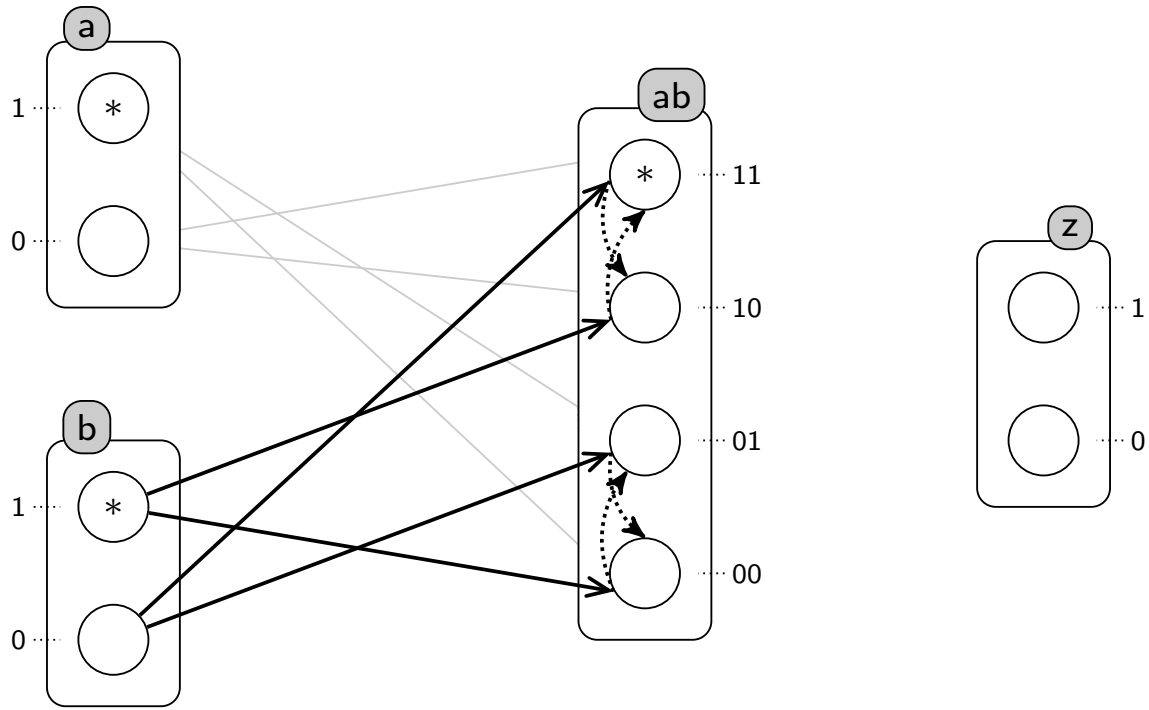

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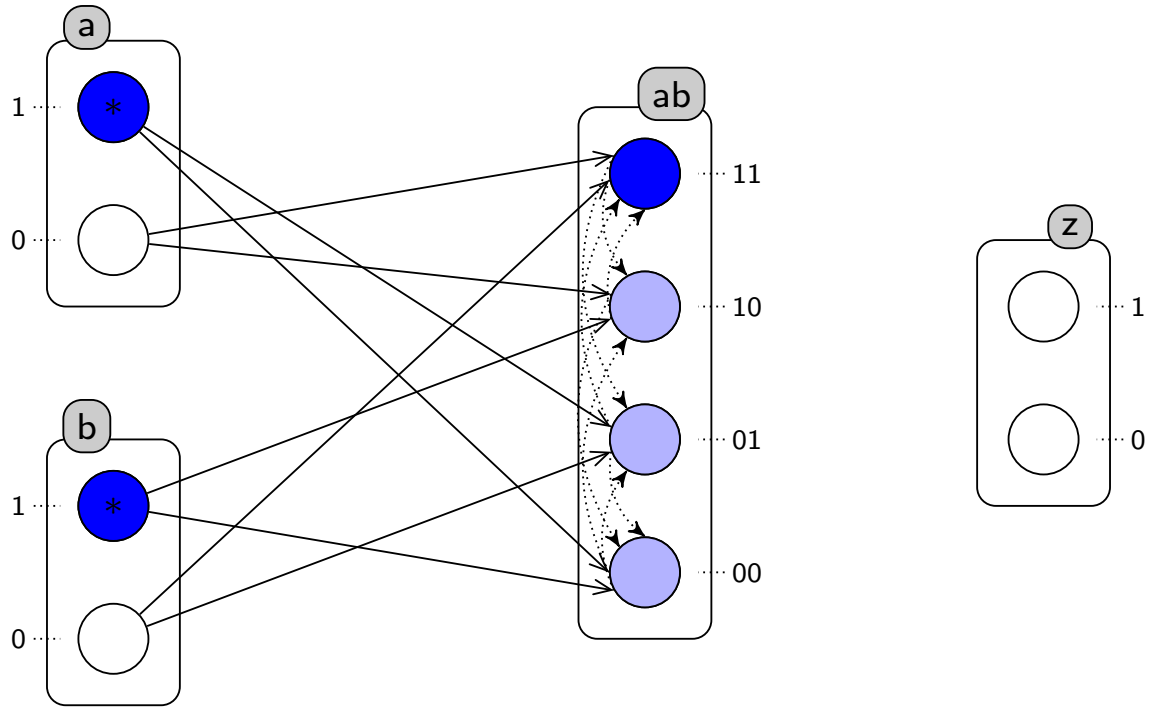

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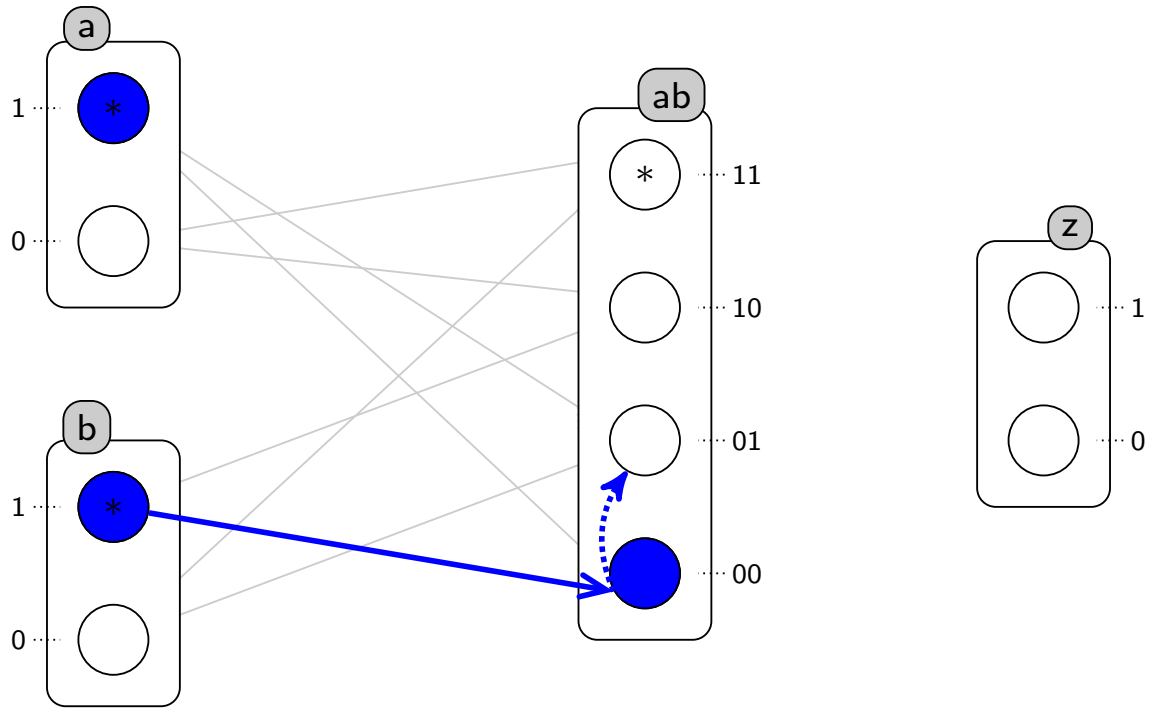

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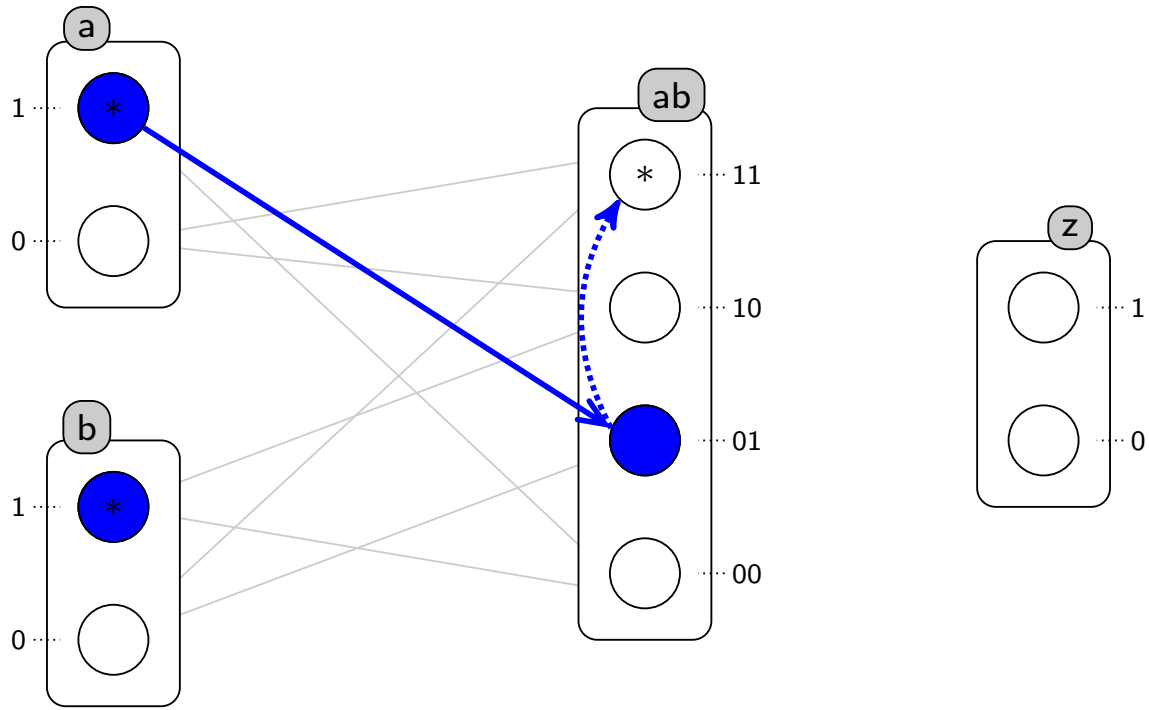

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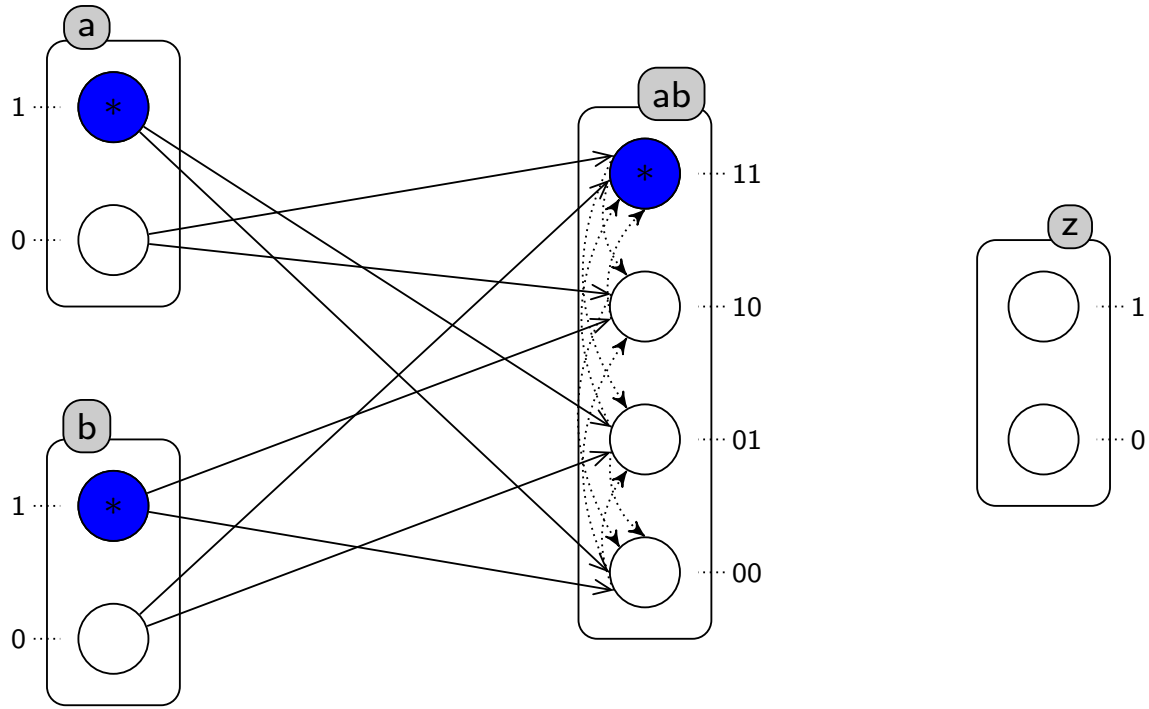

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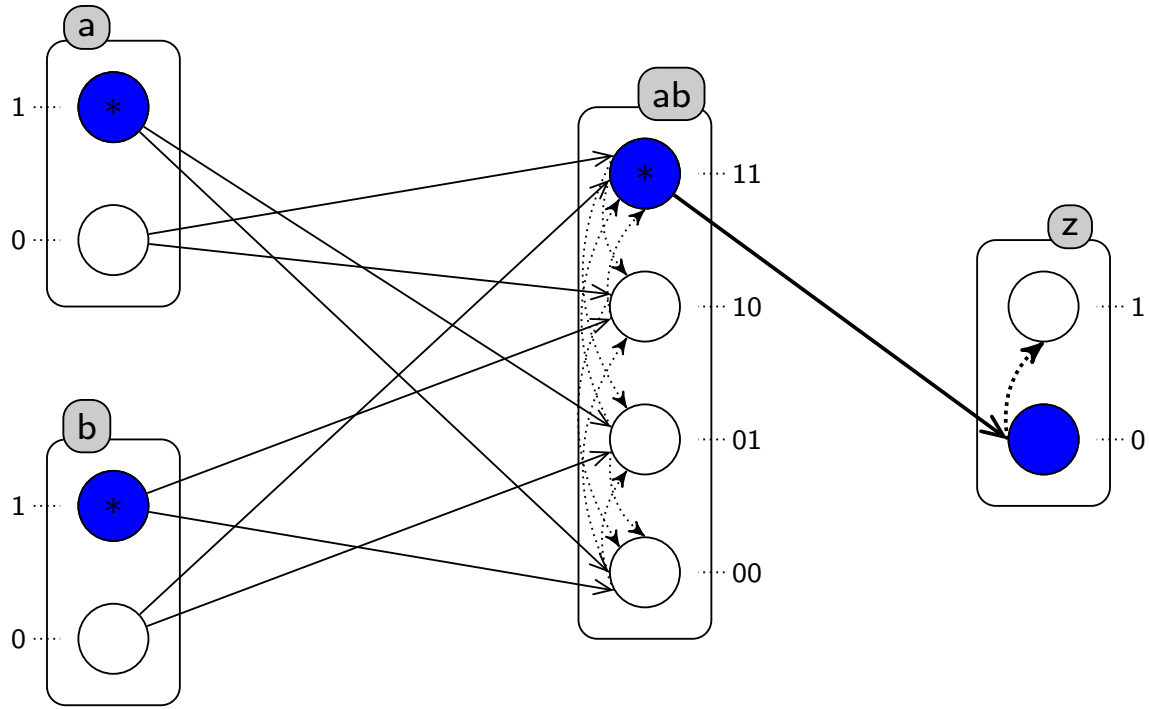

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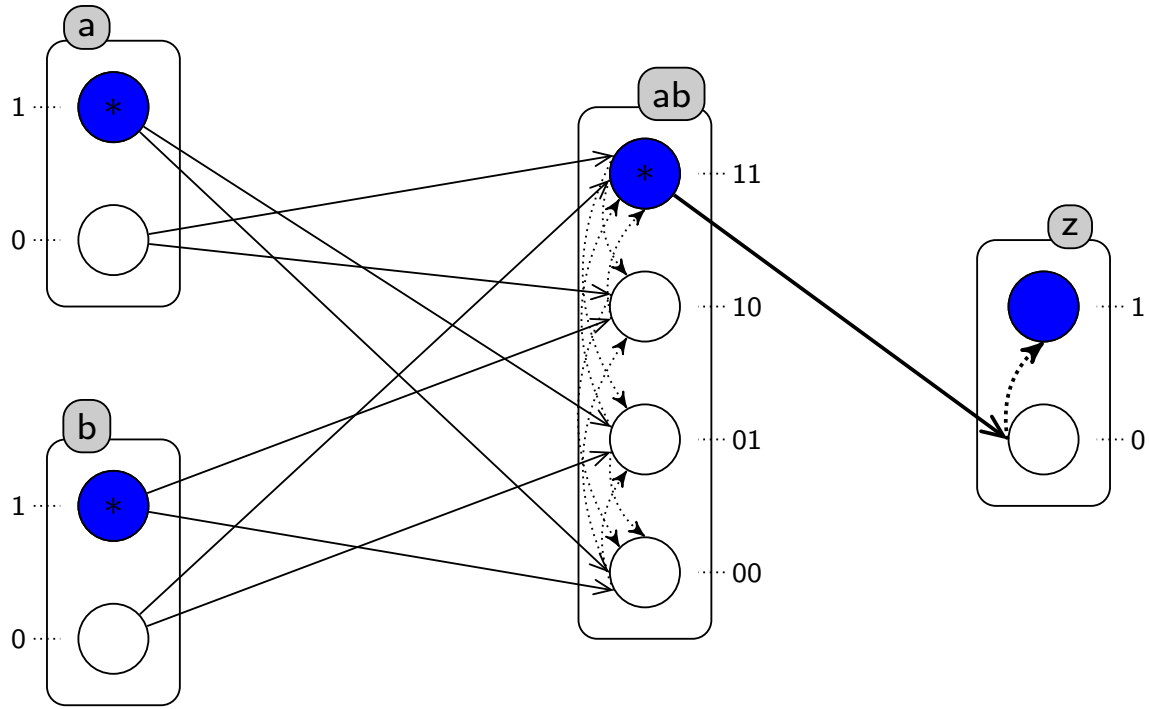

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[Paulevé *et al.* in Mathematical Structures in Computer Science, 2012]

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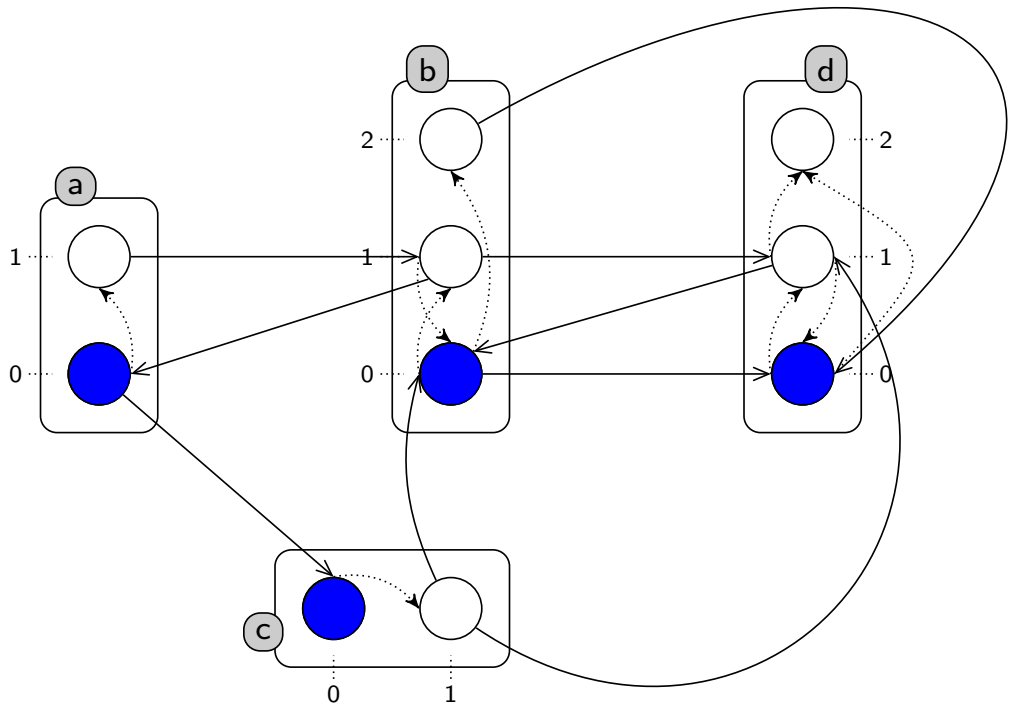

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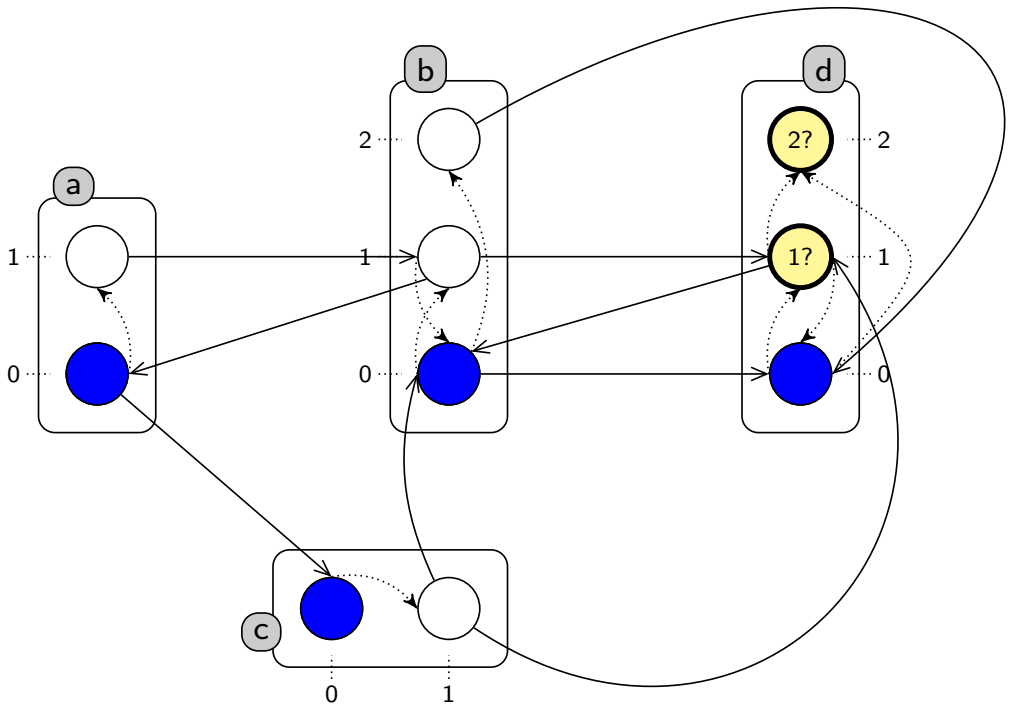

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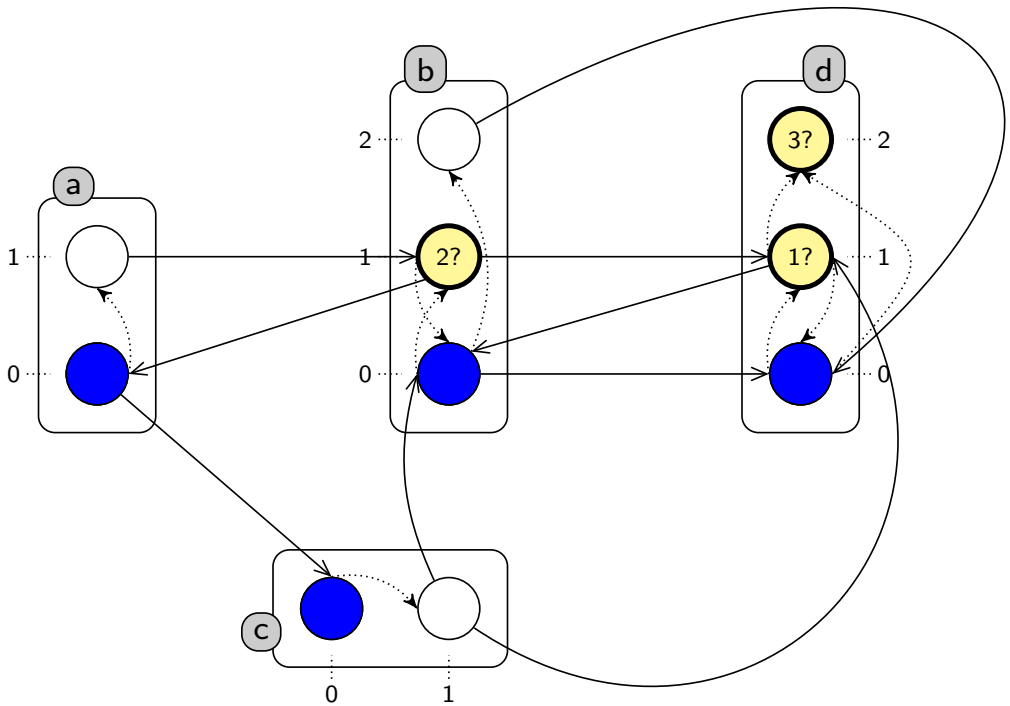

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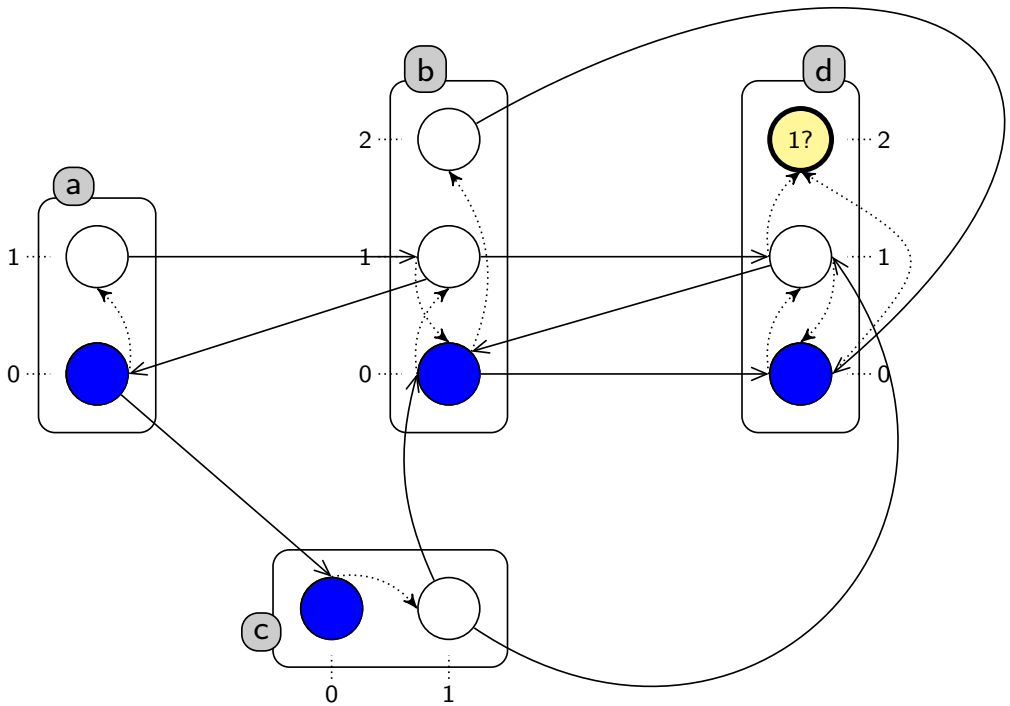

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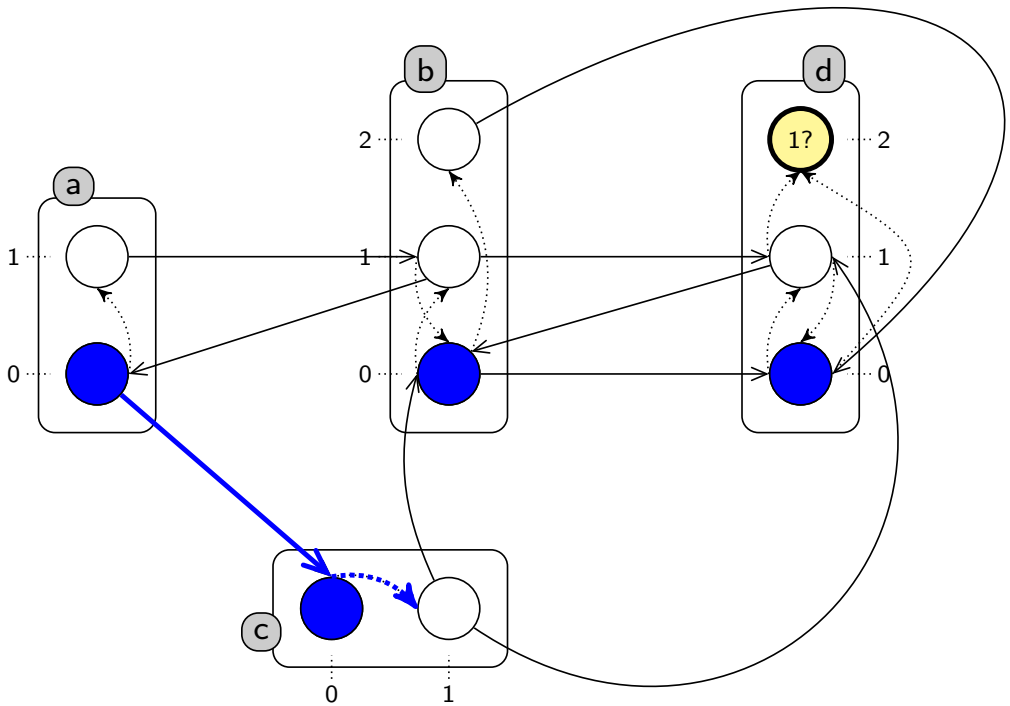

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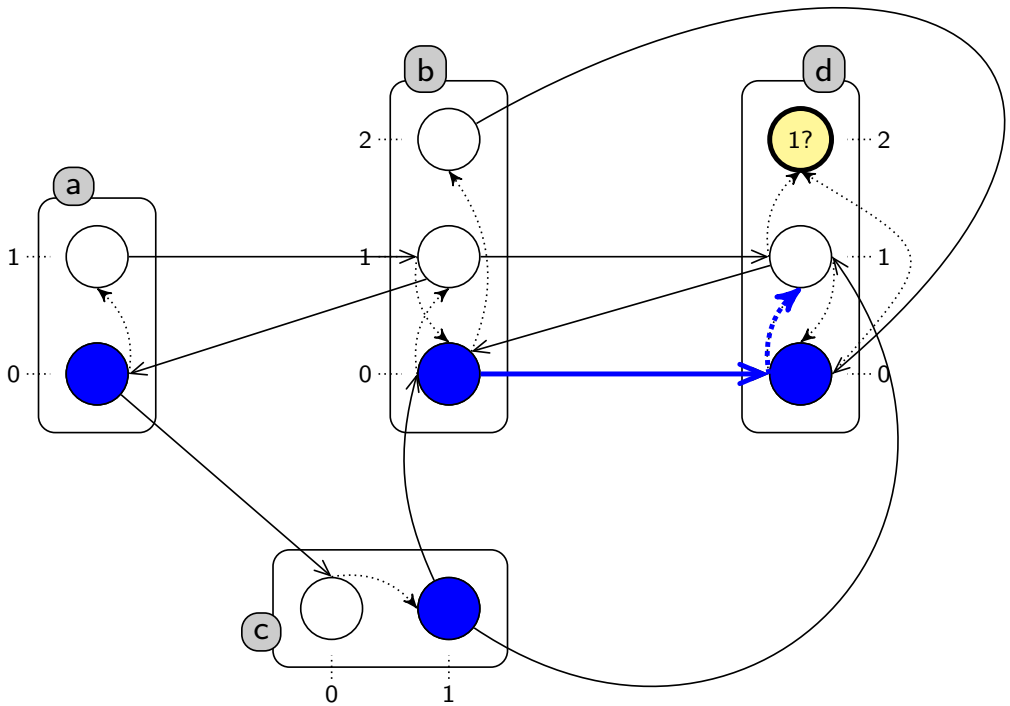

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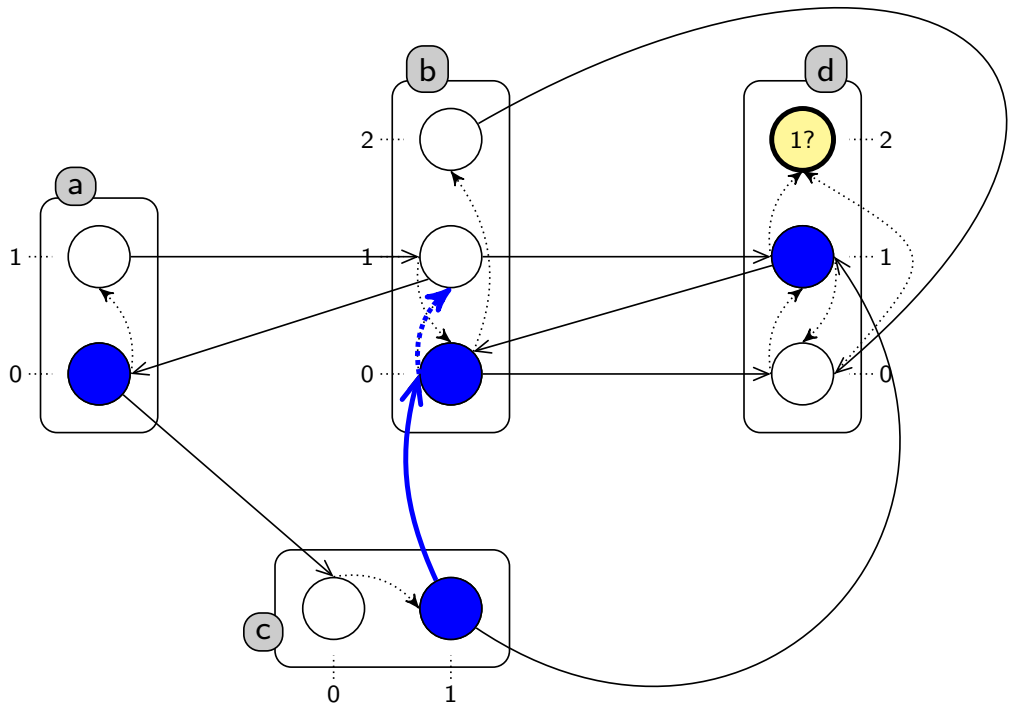

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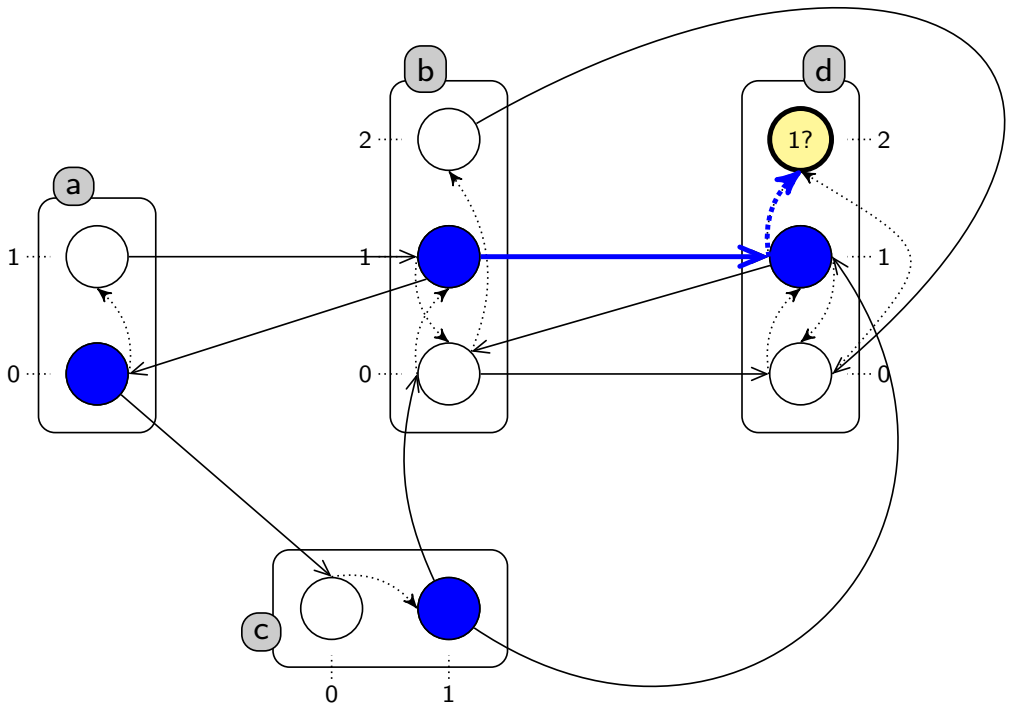

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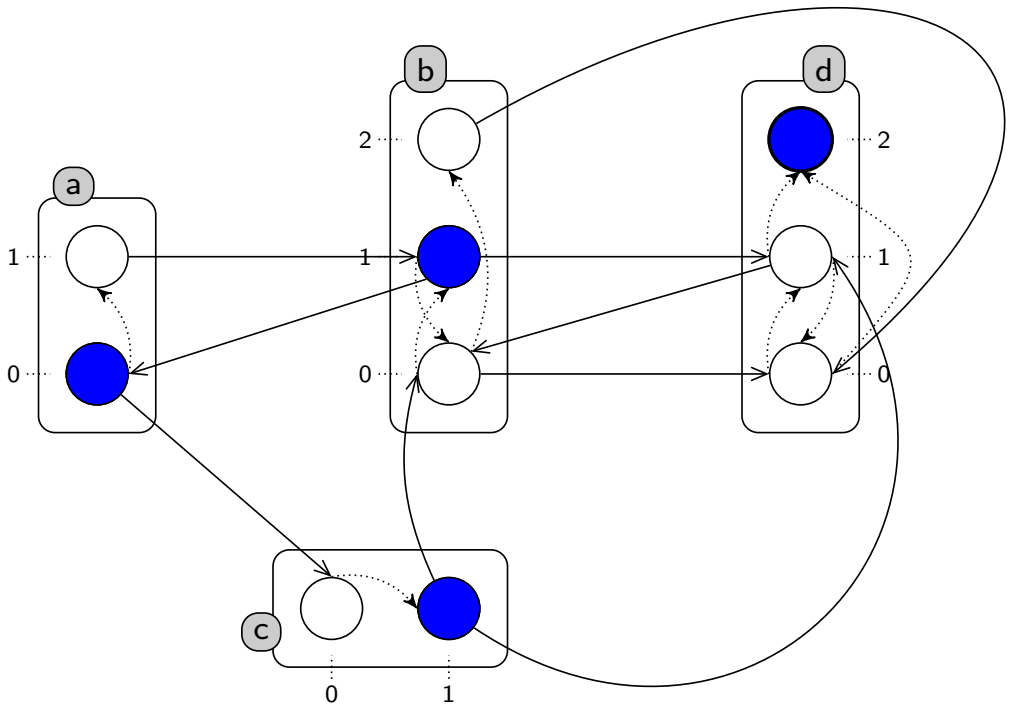

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Over- and Under-approximations

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

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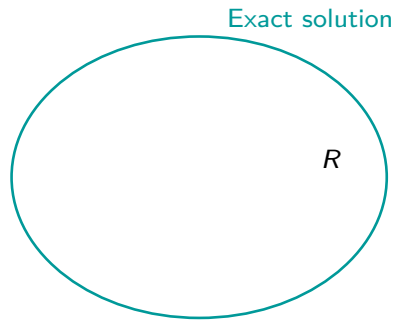

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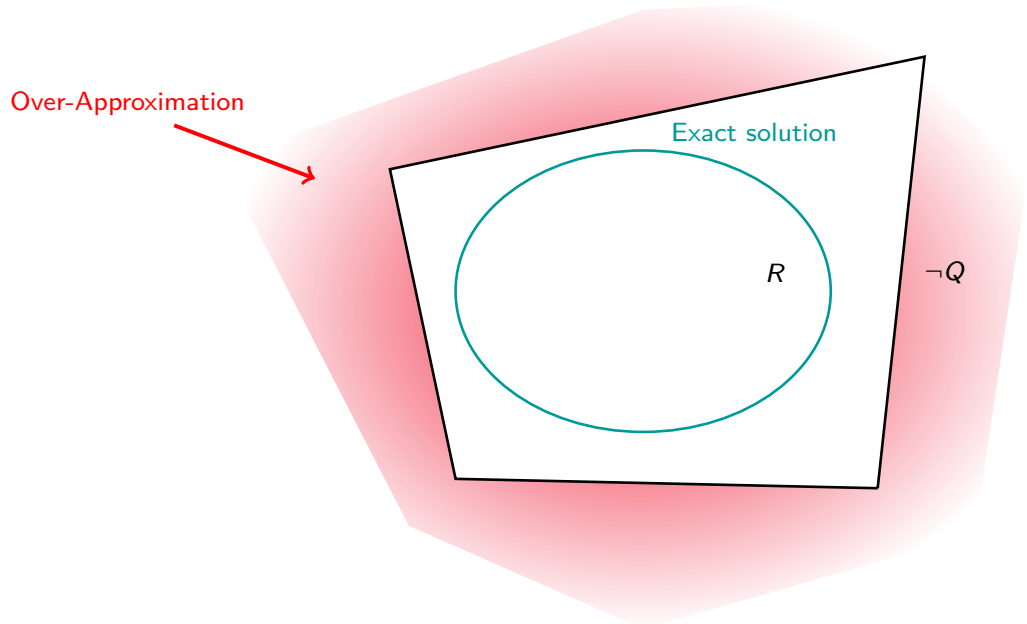

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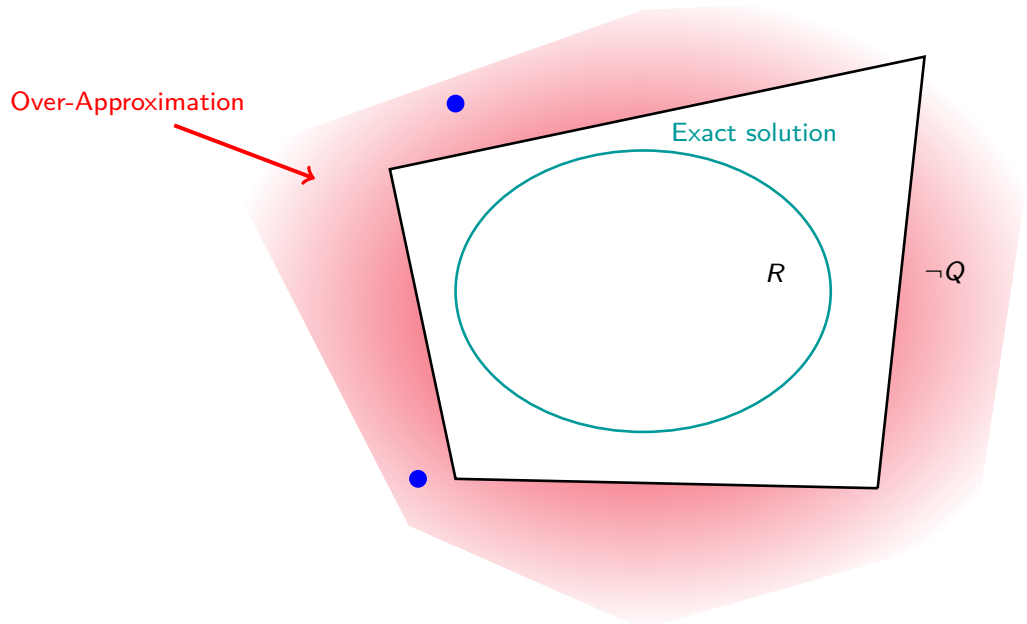

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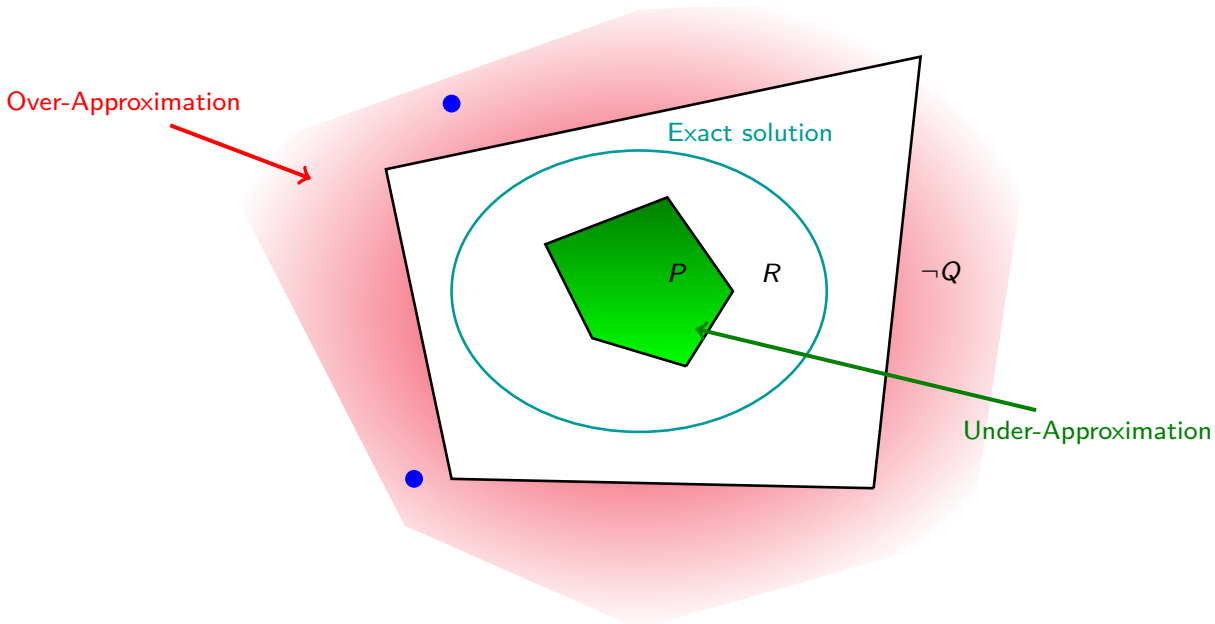

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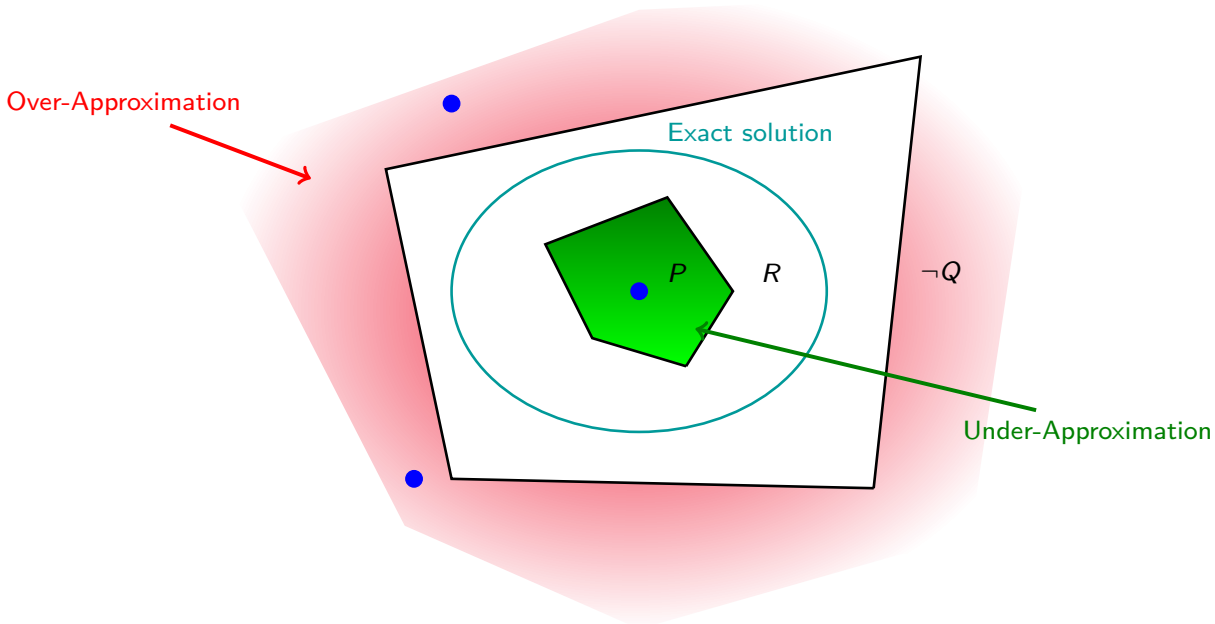

Over- and Under-approximations

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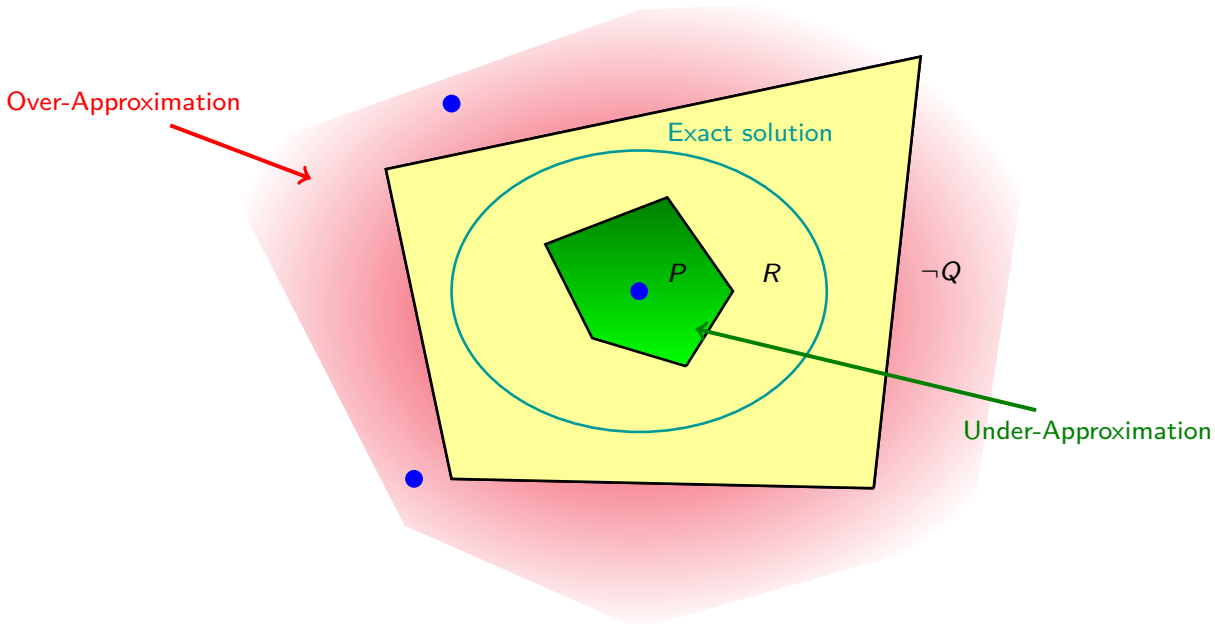

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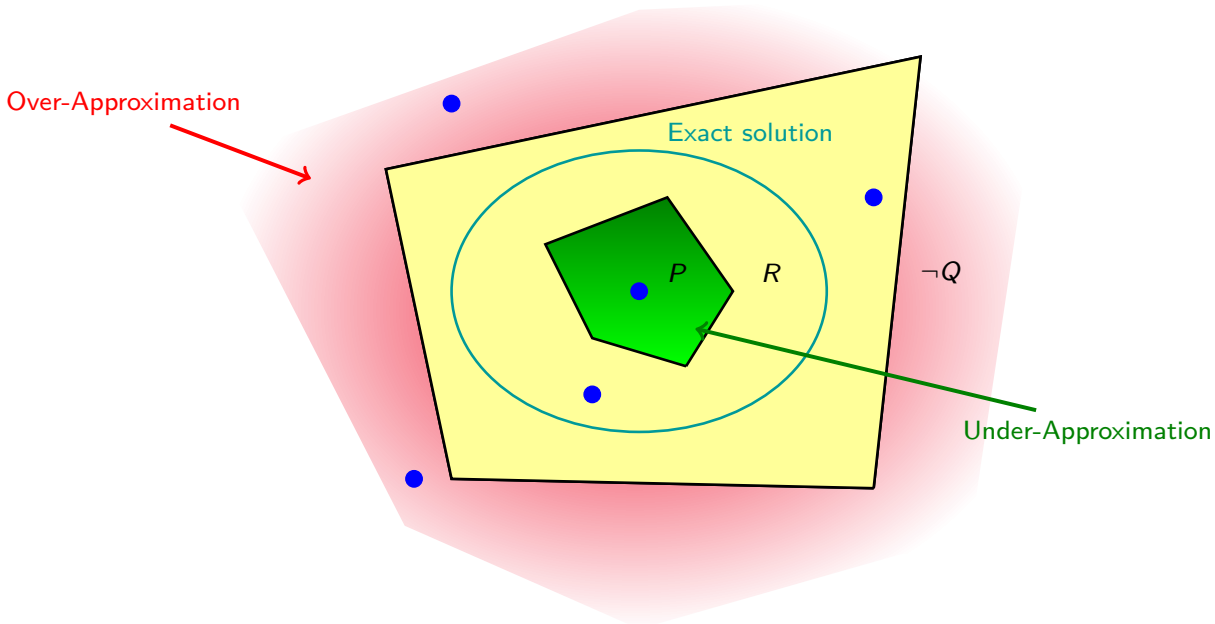

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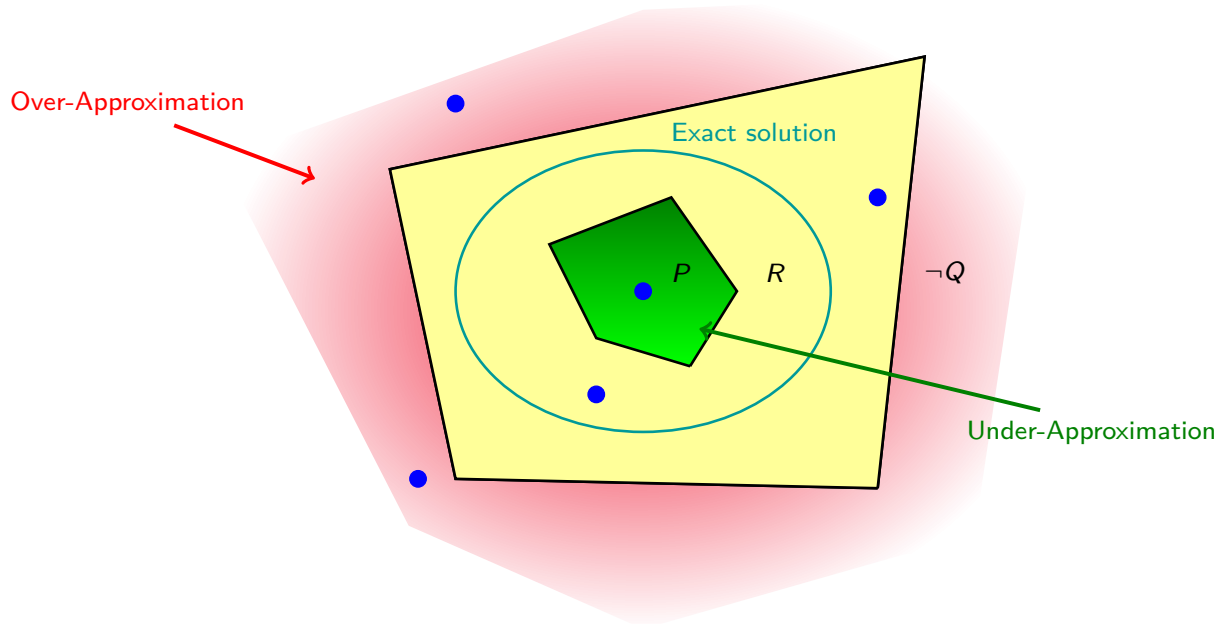
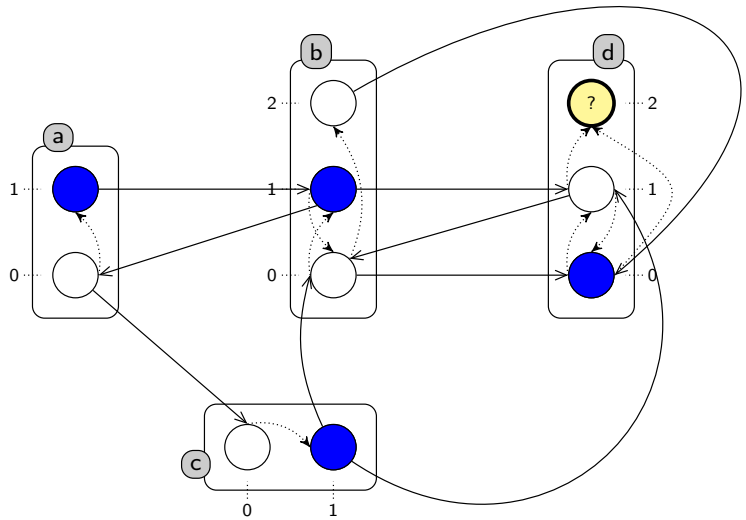


Polynomial w.r.t. the number of sorts and
exponential w.r.t. the number of processes in each sort

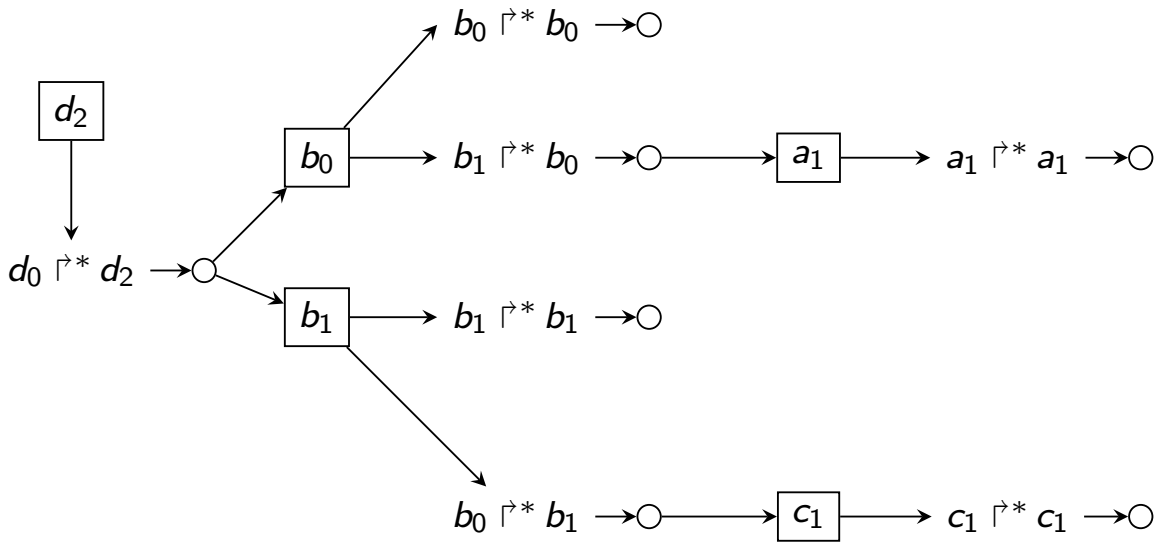
→ Efficient for big models with few levels of expression

Under-approximation



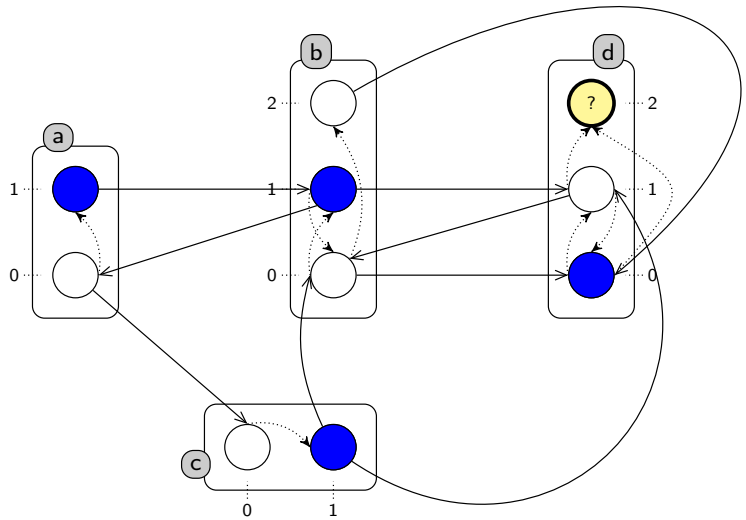
Sufficient condition:

- no cycle
- each objective has a solution



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

Under-approximation



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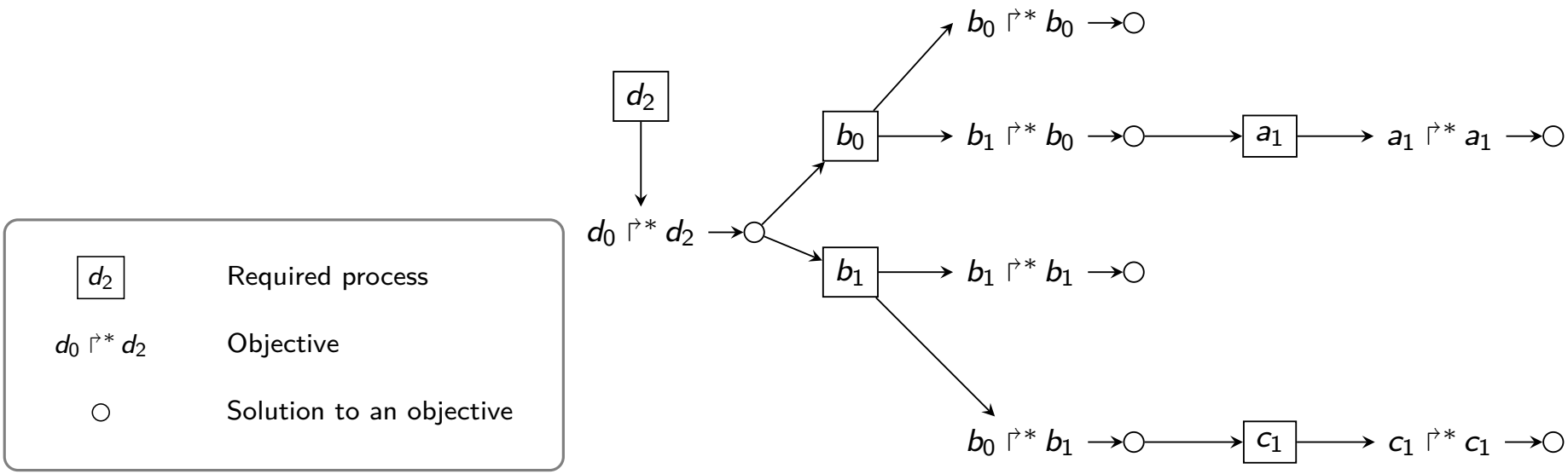
R is **true**



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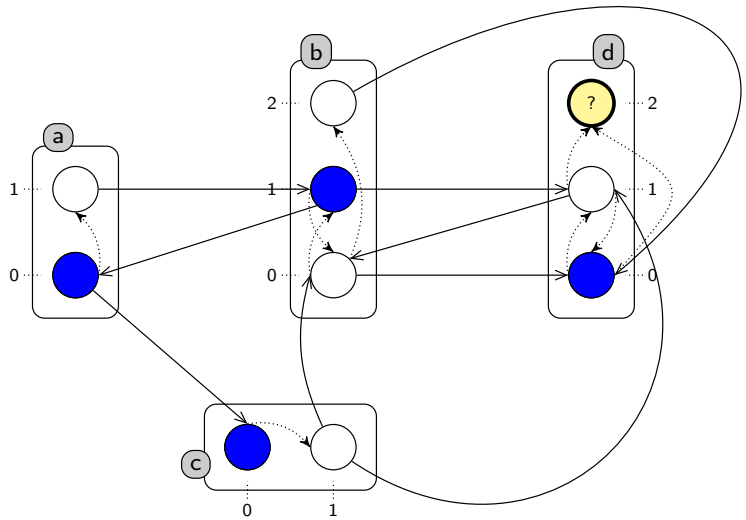

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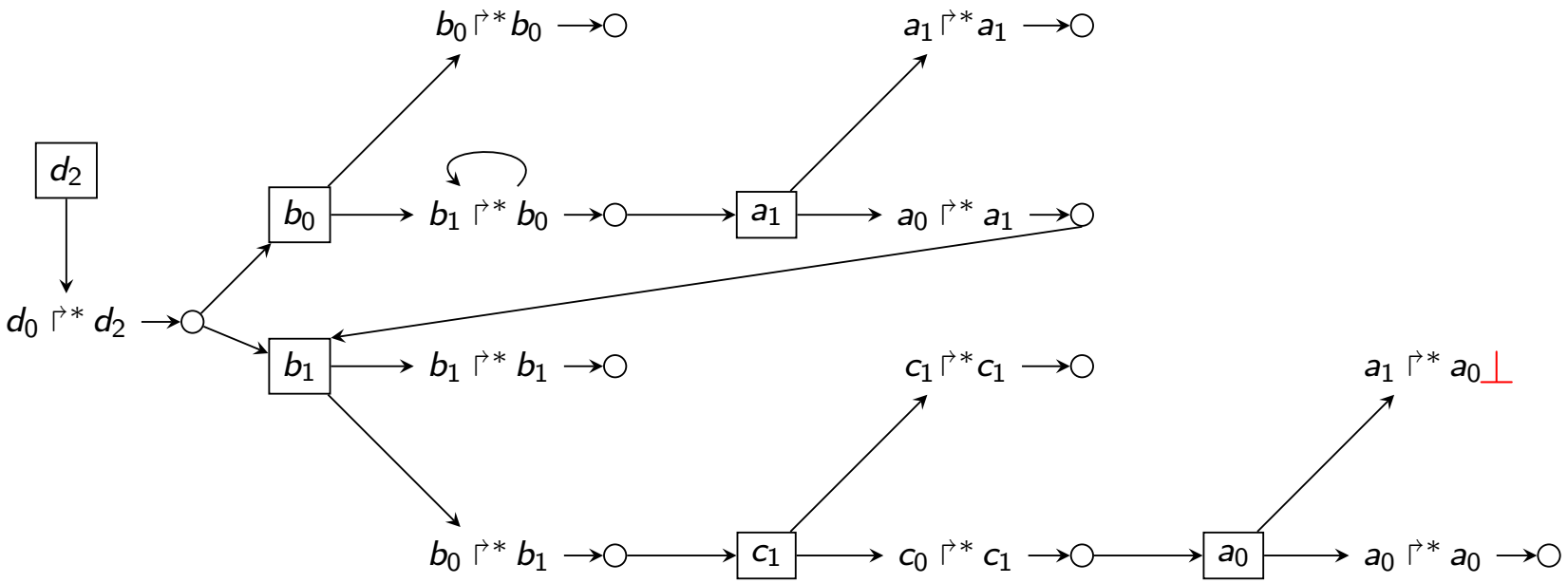

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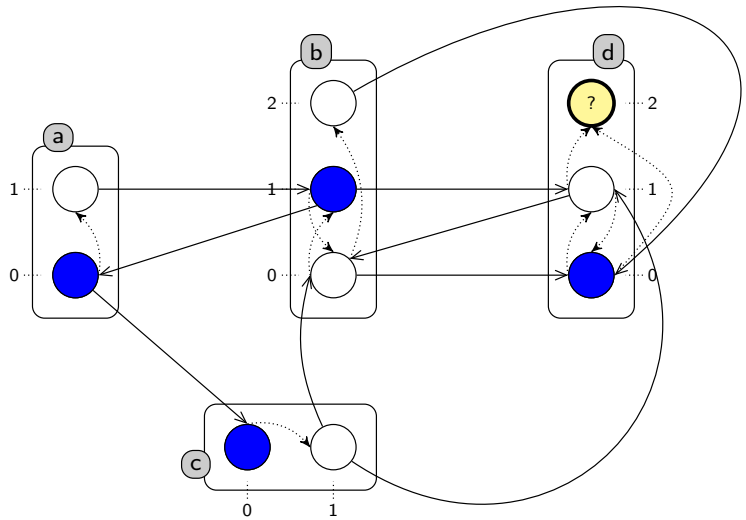

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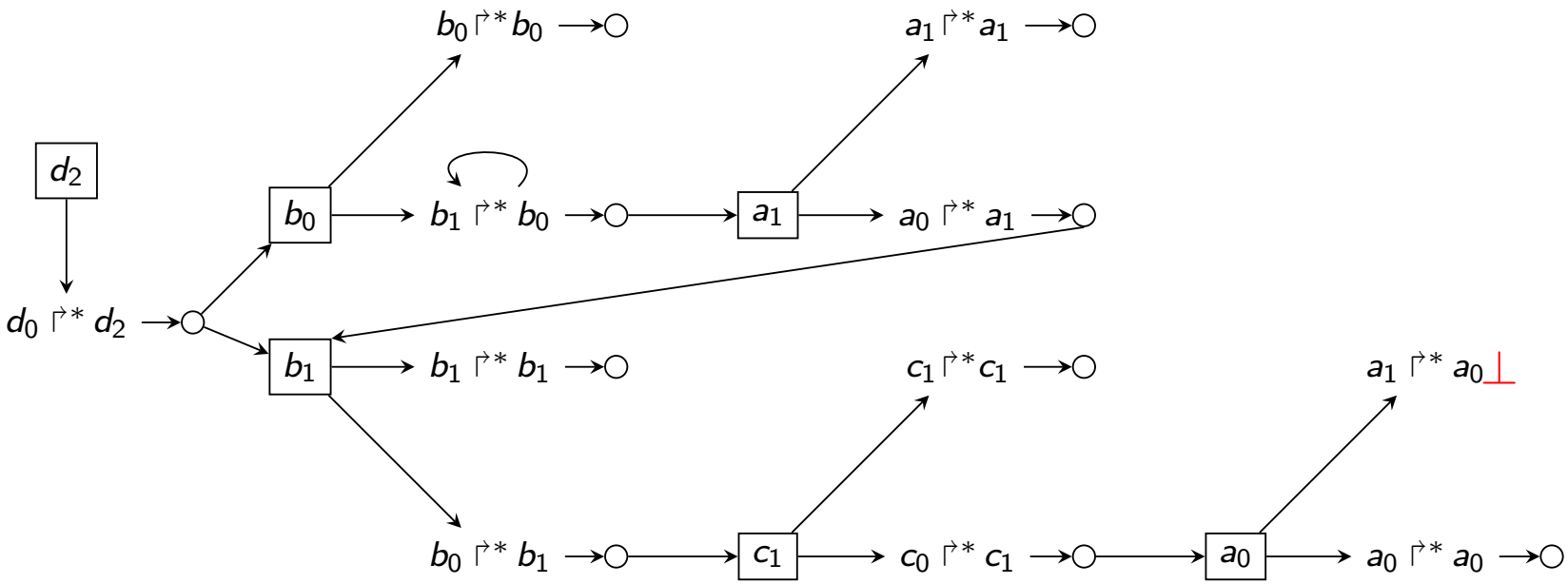
Inconclusive



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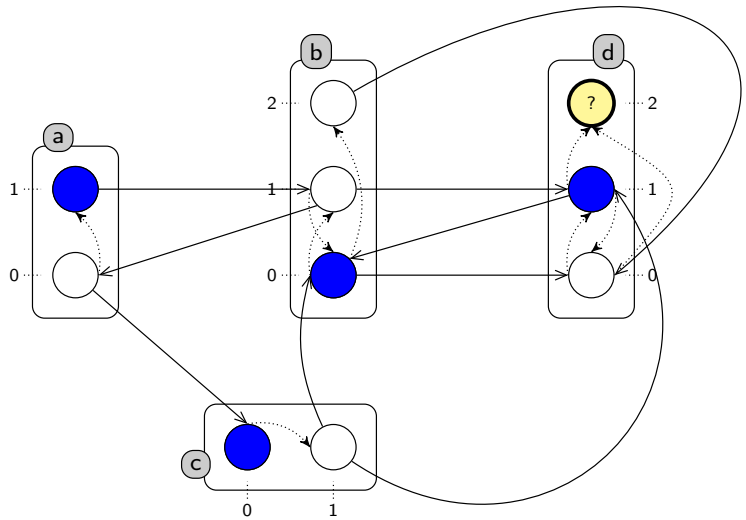

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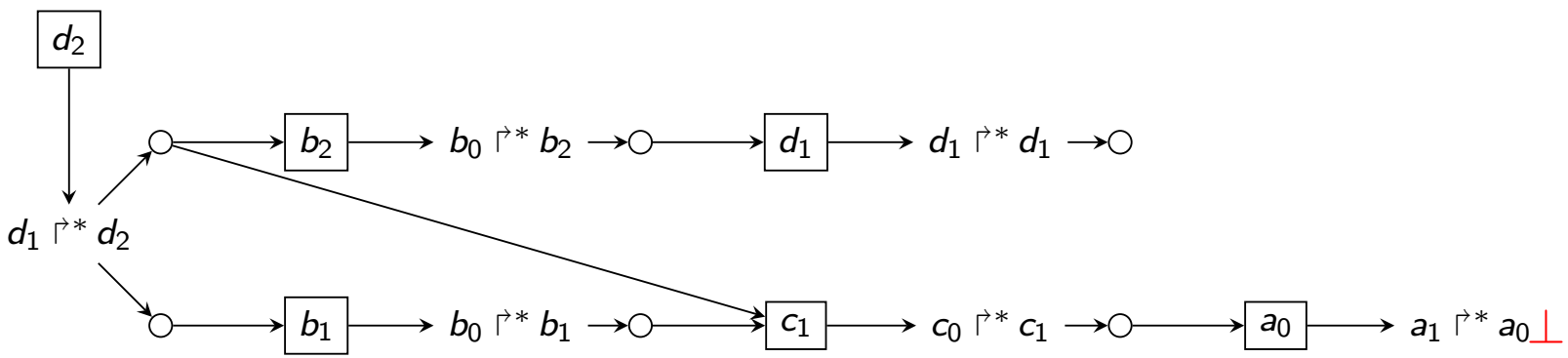

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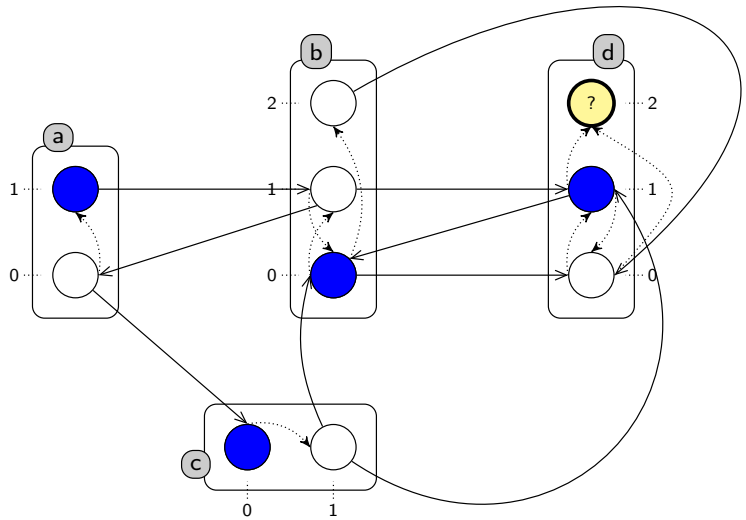

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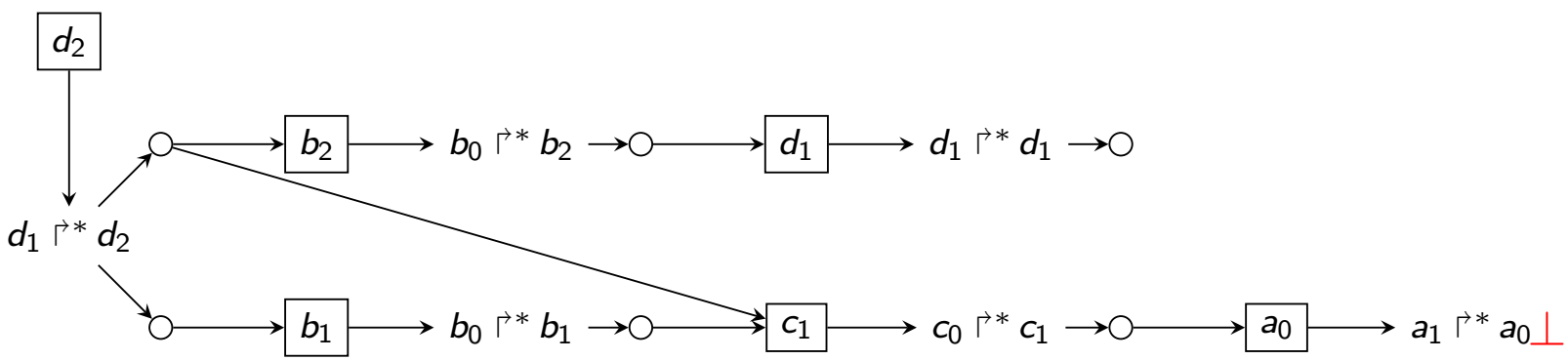

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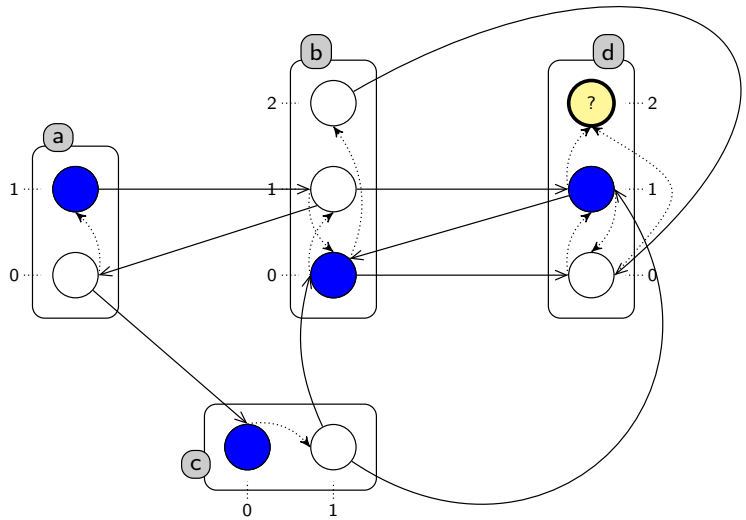

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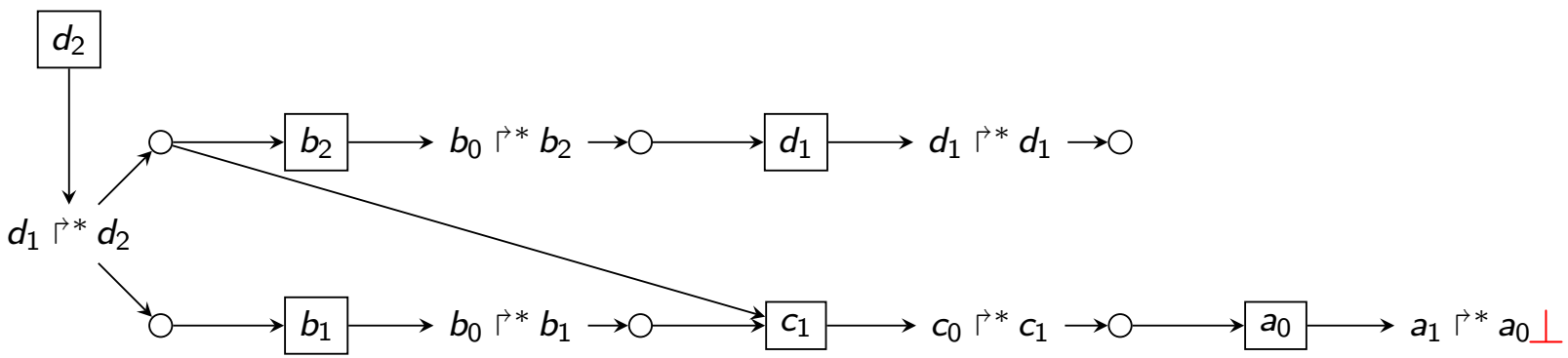

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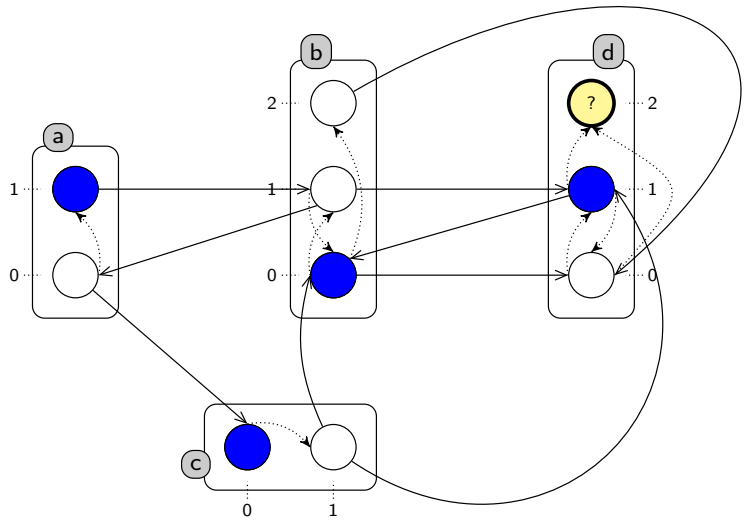

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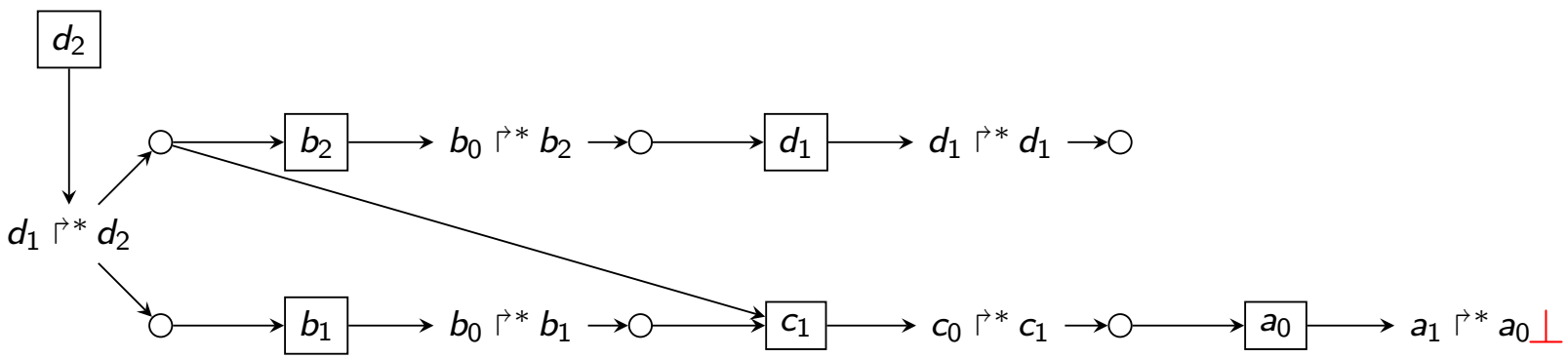
R is **false**



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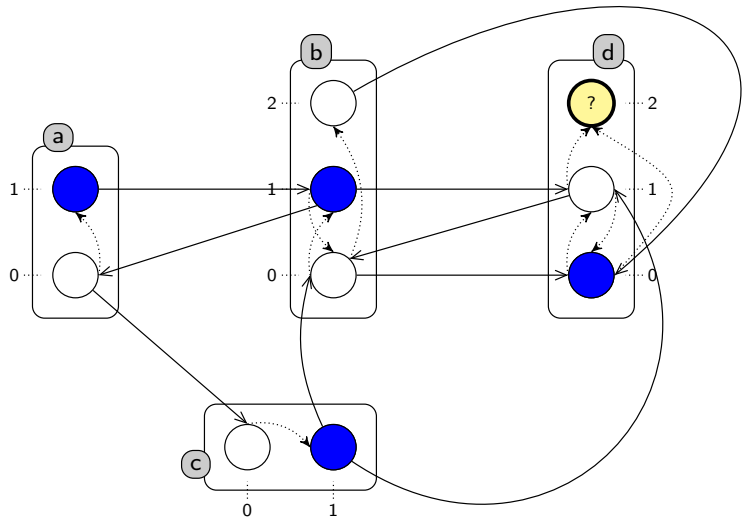

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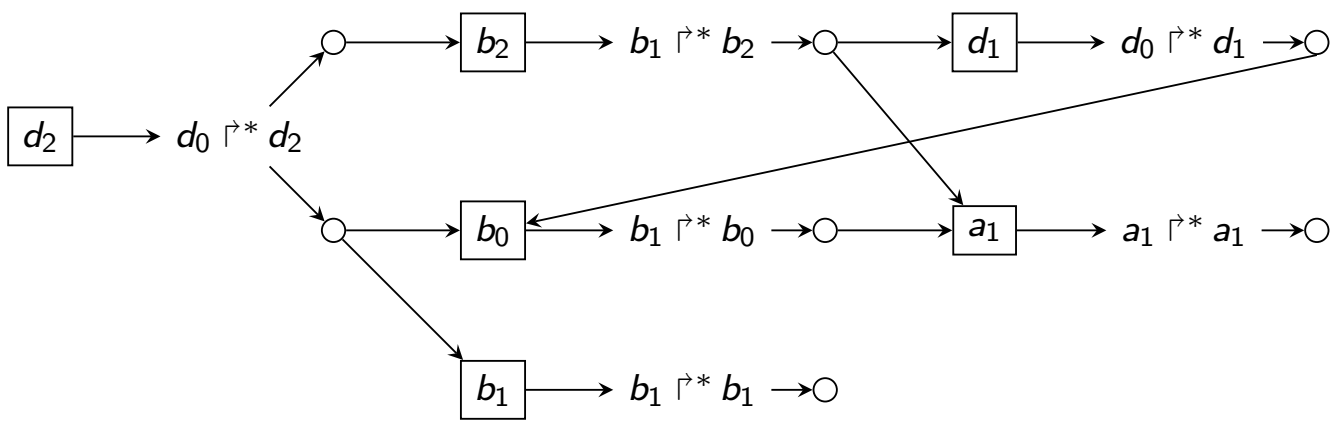

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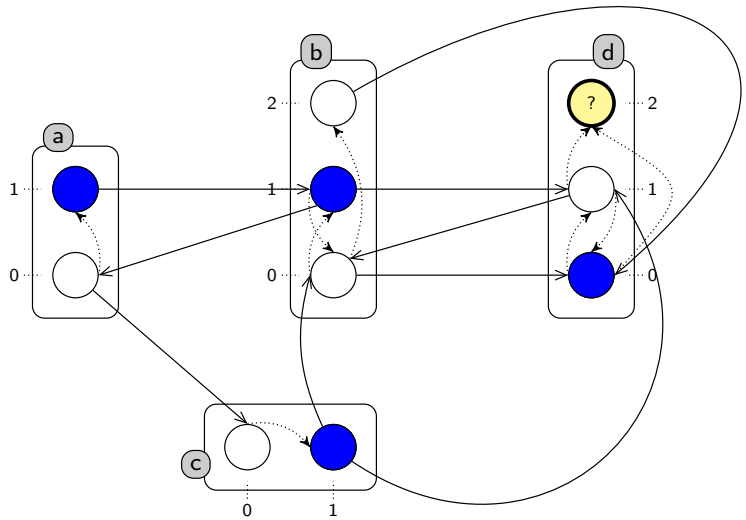

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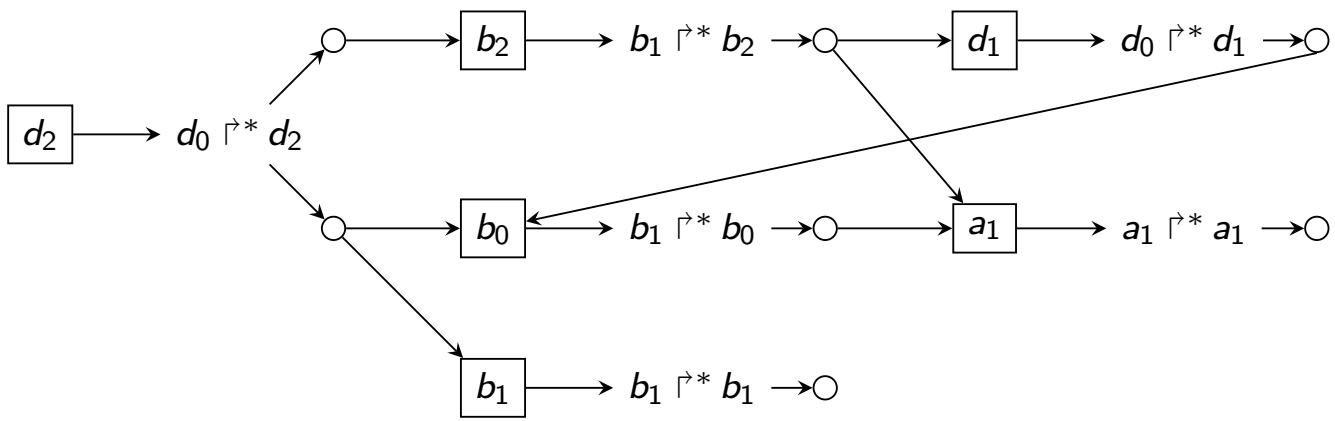


The Process Hitting modeling

- **Dynamic** modeling with an **atomistic** point of view
  - → Independent actions
  - → Cooperation modeled with cooperative sorts
- Efficient **static analysis**
  - → Reachability of a process can be computed in **polynomial time** in the number of sorts
  - → Useful for the study of **large biological models** (up to hundreds of sorts)
- Results:

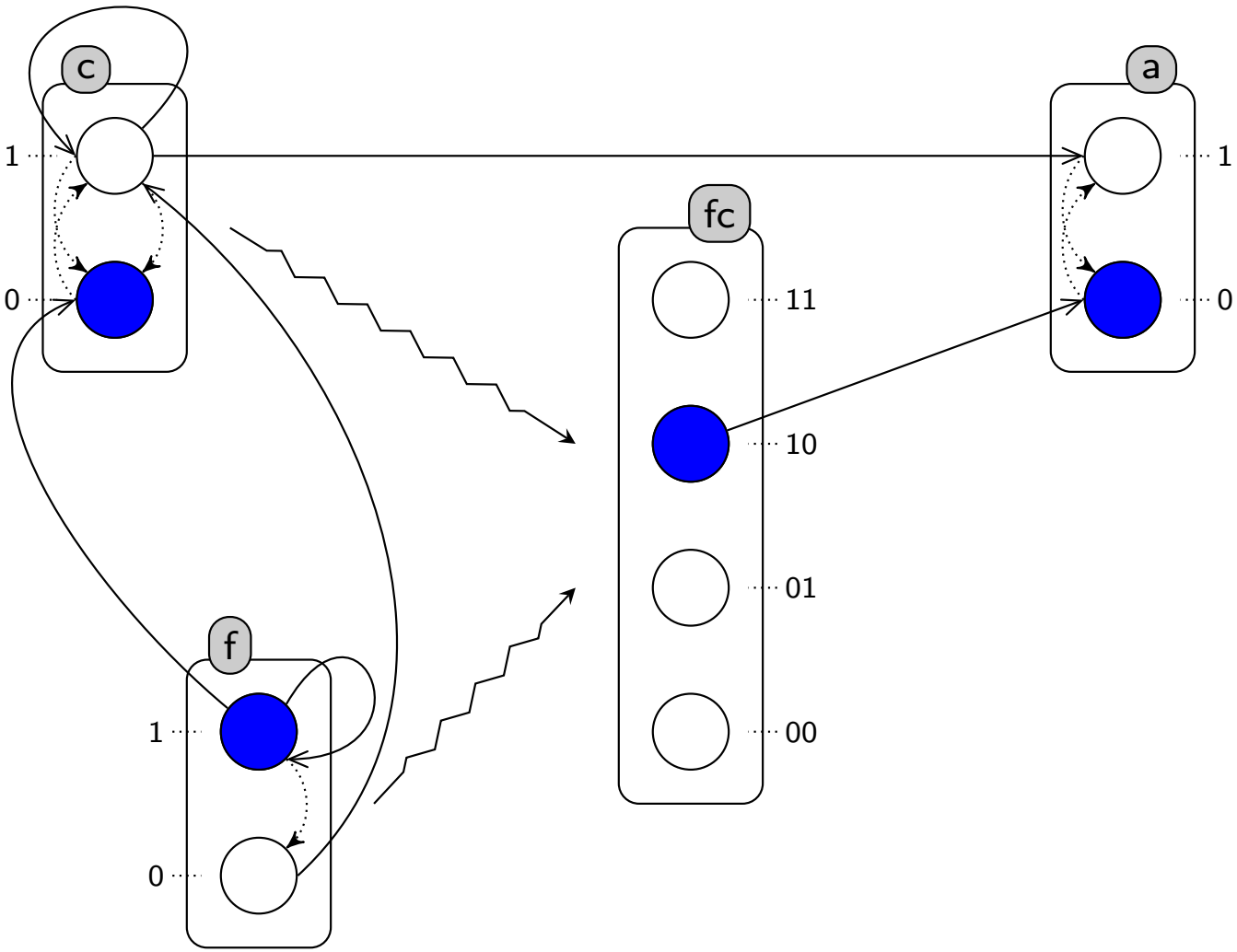
Model	Sorts	Procs	Actions	States	Biocham[1]	libddd[2]	PINT
egfr20	35	196	670	2^{64}	[3s–∞]	[1s–150s]	**0.007s**
tcrsig40	54	156	301	2^{73}	[1s–∞]	[0.6s–∞]	**0.004s**
tcrsig94	133	448	1124	2^{194}	∞	∞	**0.030s**
egfr104	193	748	2356	2^{320}	∞	∞	**0.050s**

[1] Inria Paris-Rocquencourt/Contraintes
[2] LIP6/Move

egfr20: [Epidermal Growth Factor Receptor, by Özgür Sahin *et al.*]
egfr104: [Epidermal Growth Factor Receptor, by Regina Samaga *et al.*]
tcrsig40: [T-Cell Receptor Signaling, by Steffen Klamt *et al.*]
tcrsig94: [T-Cell Receptor Signaling, by Julio Saez-Rodriguez *et al.*]

The Metazoan Segmentation Model

[François *et al.* in Molecular Systems Biology, 2007]



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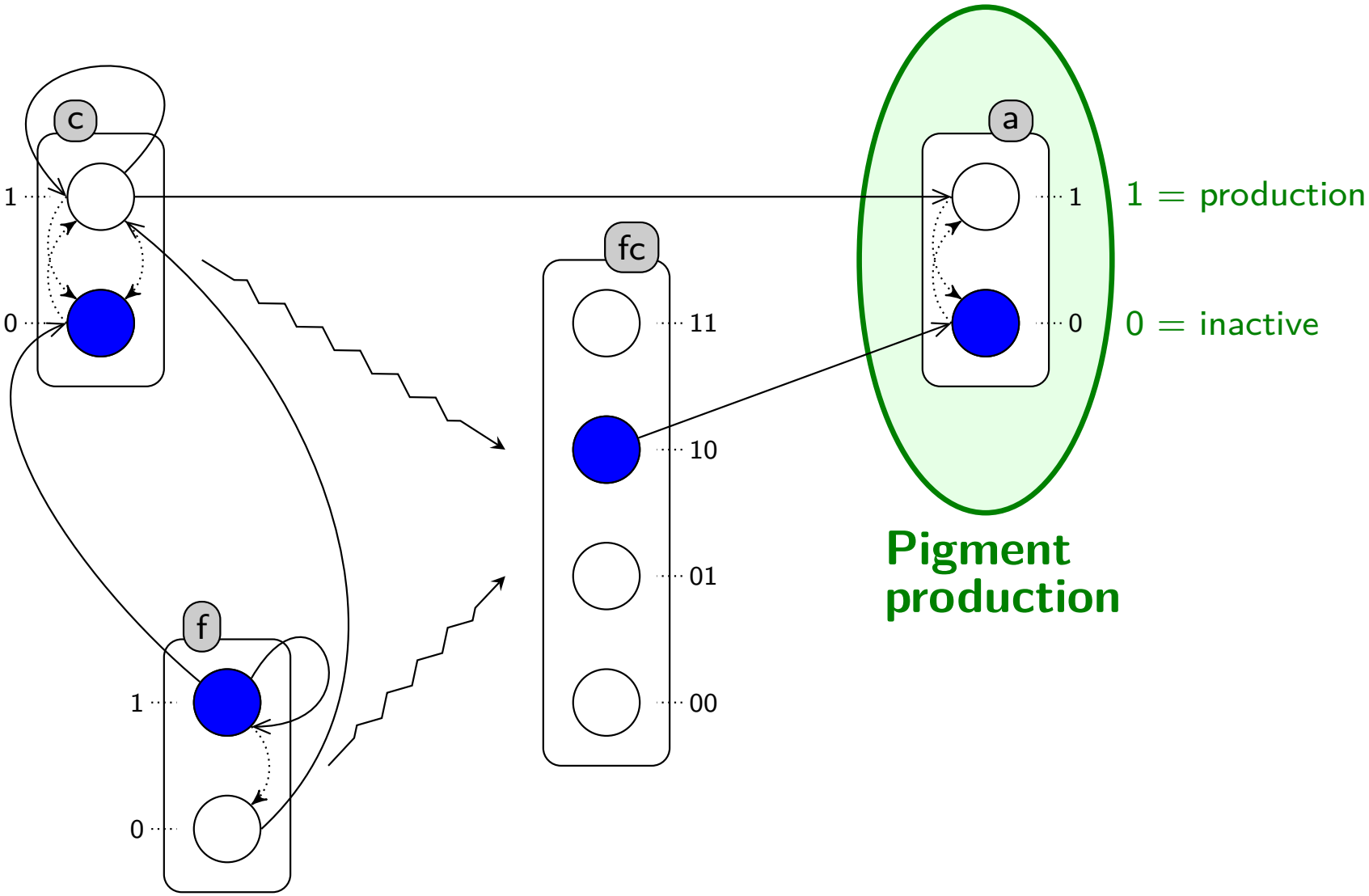

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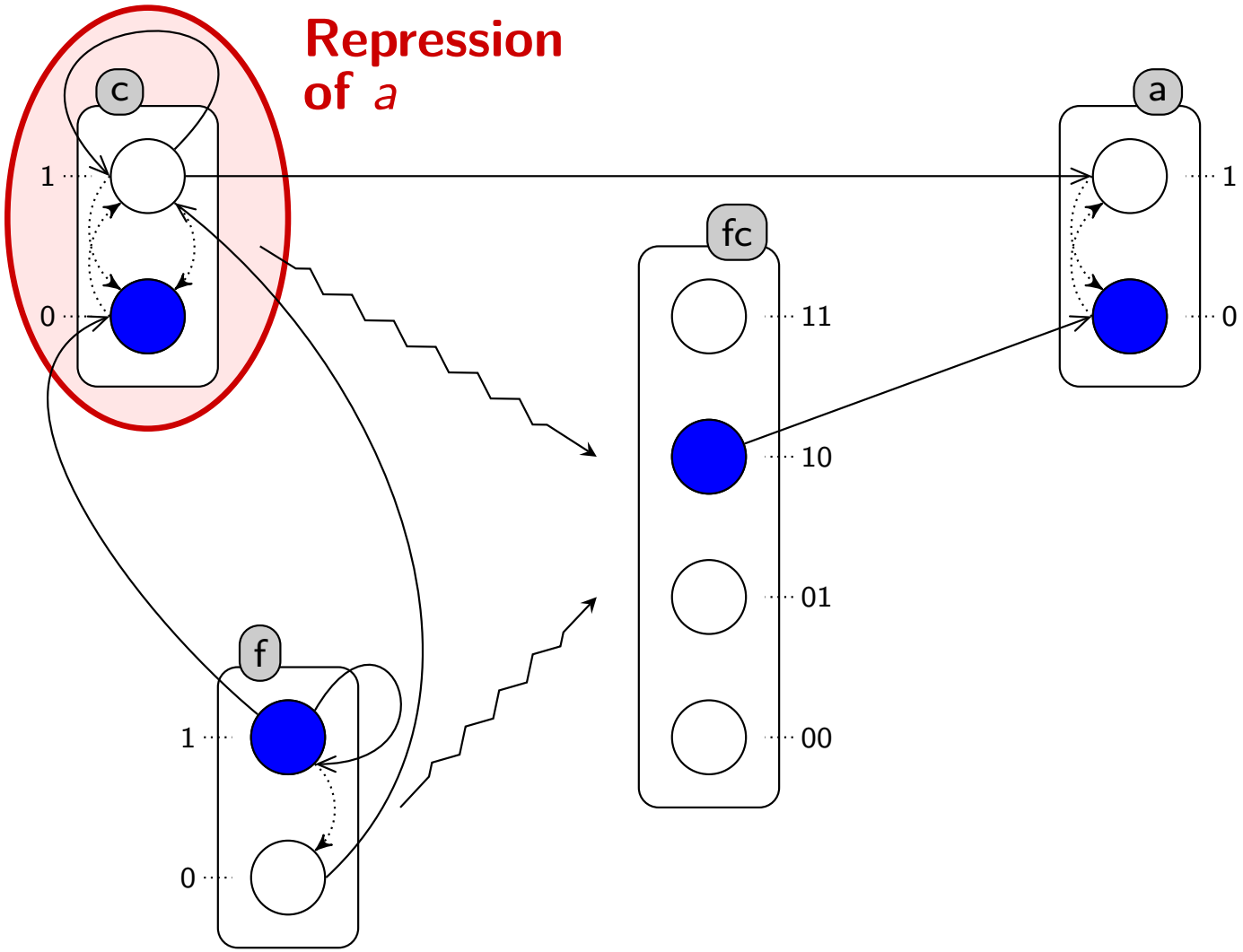

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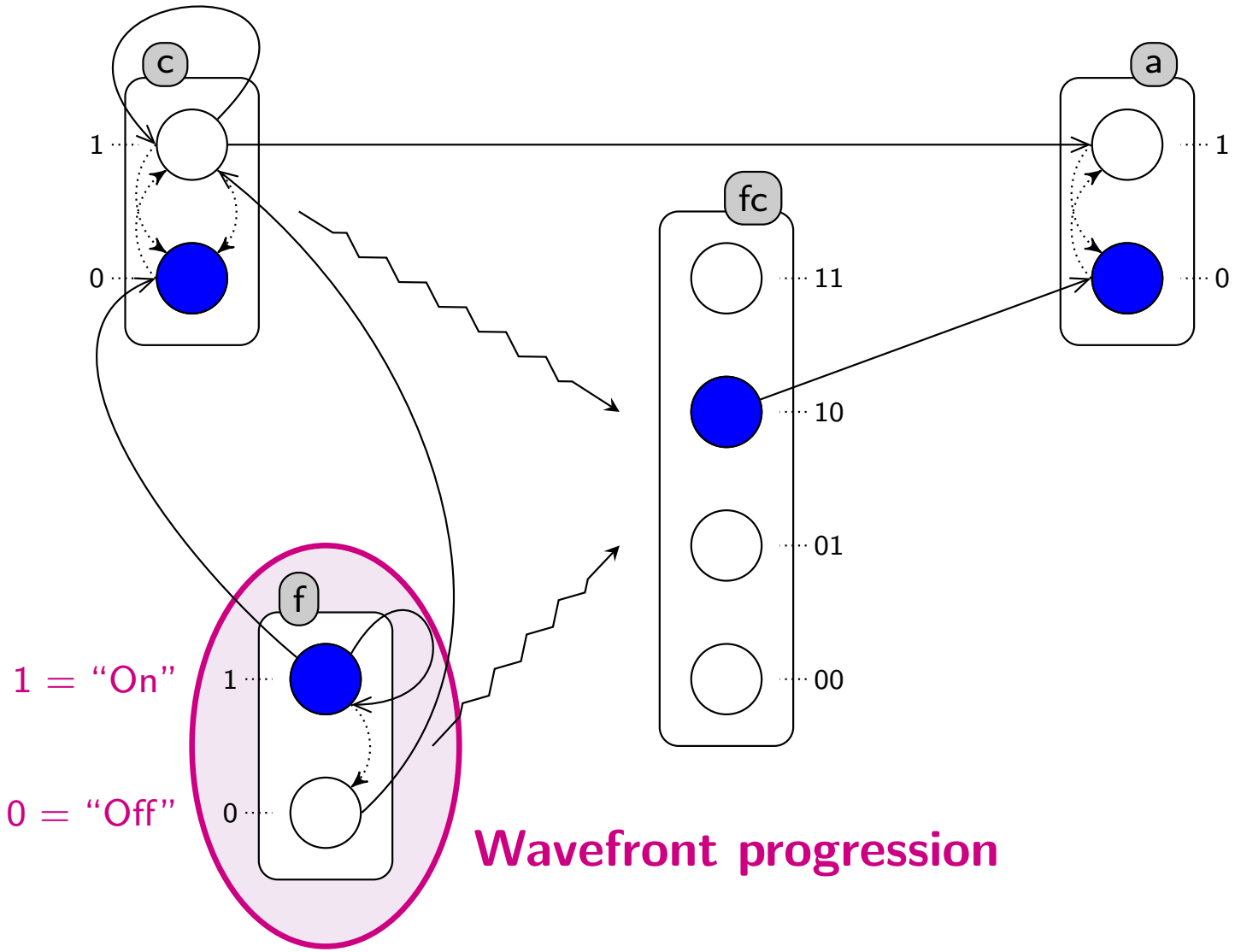

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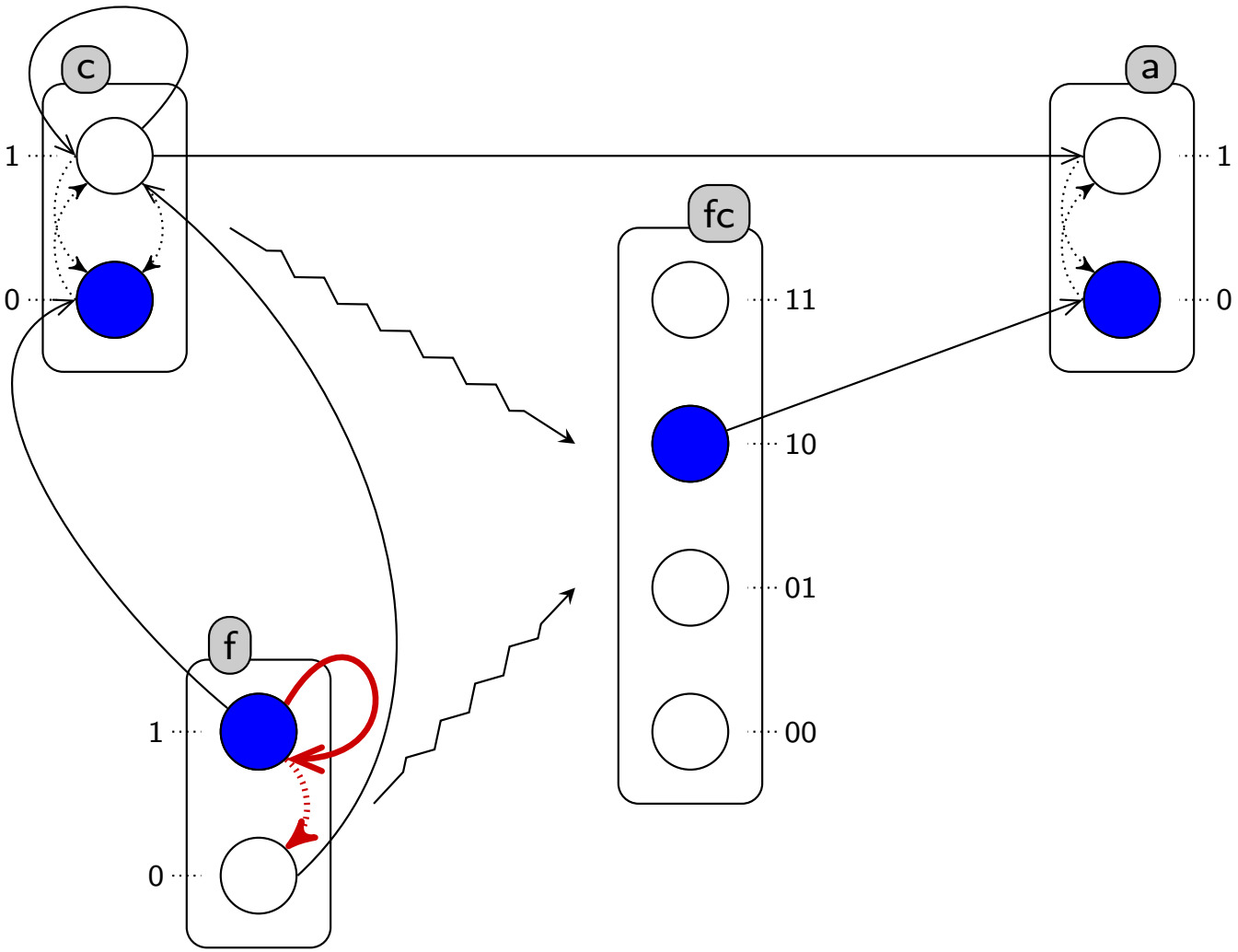

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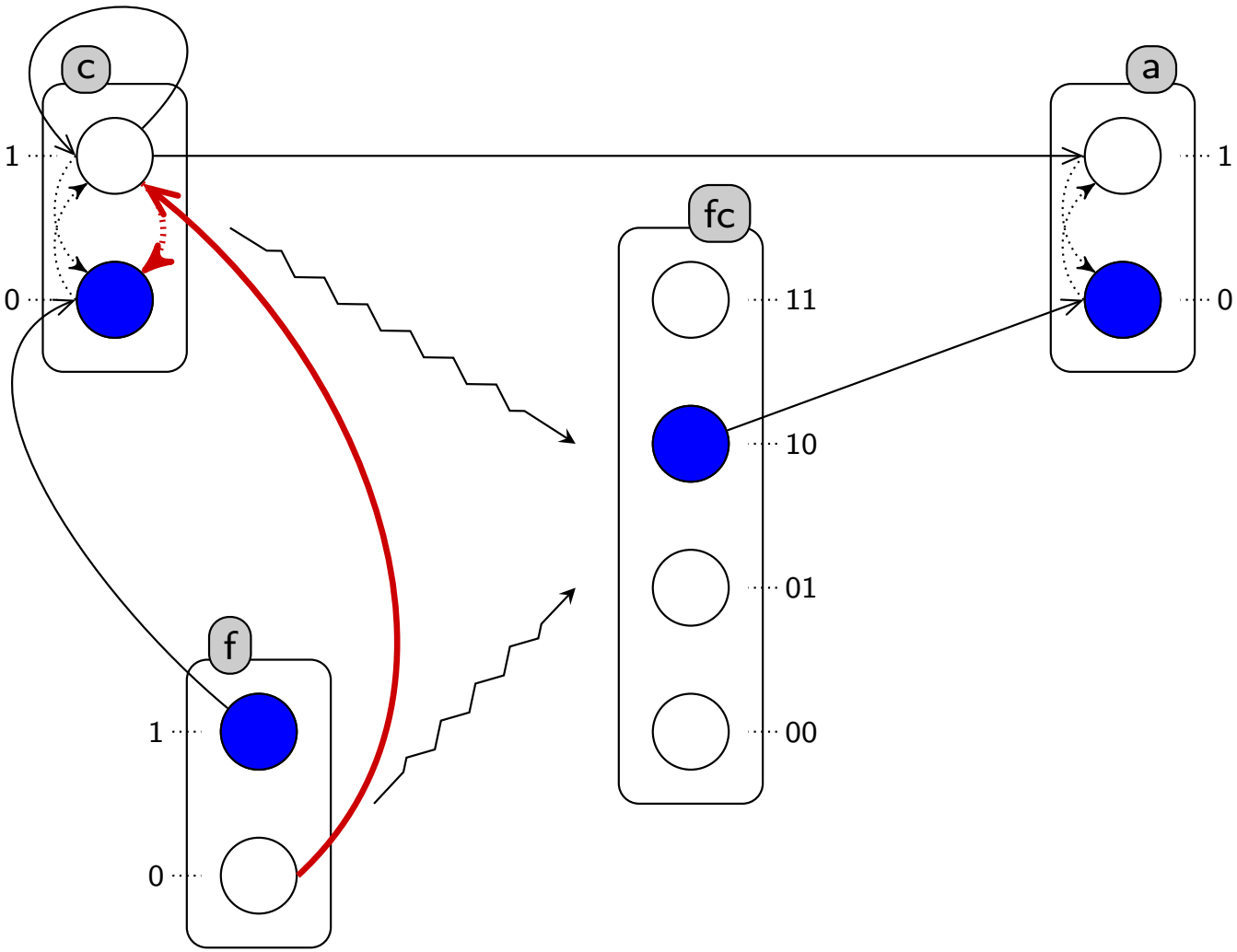

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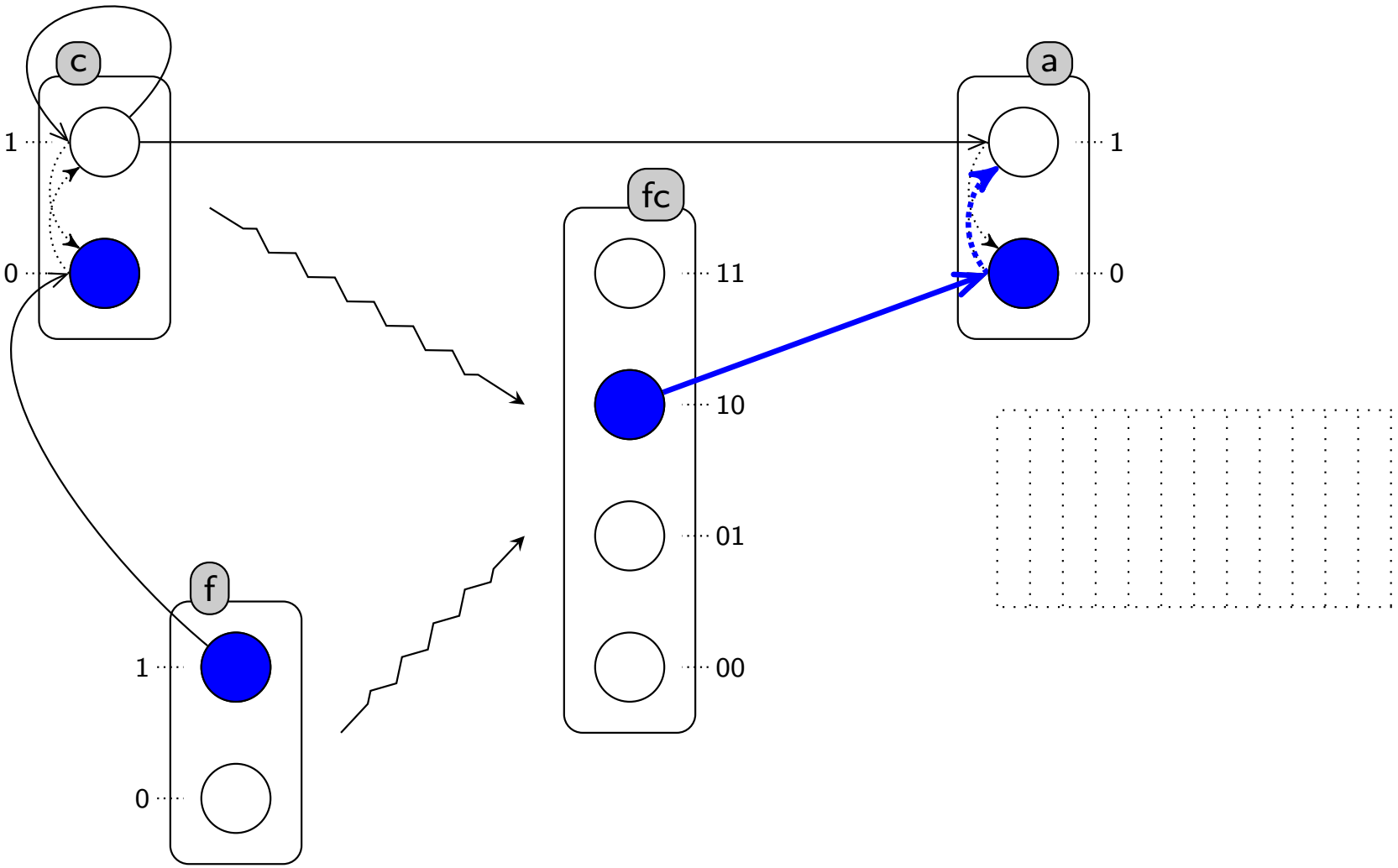

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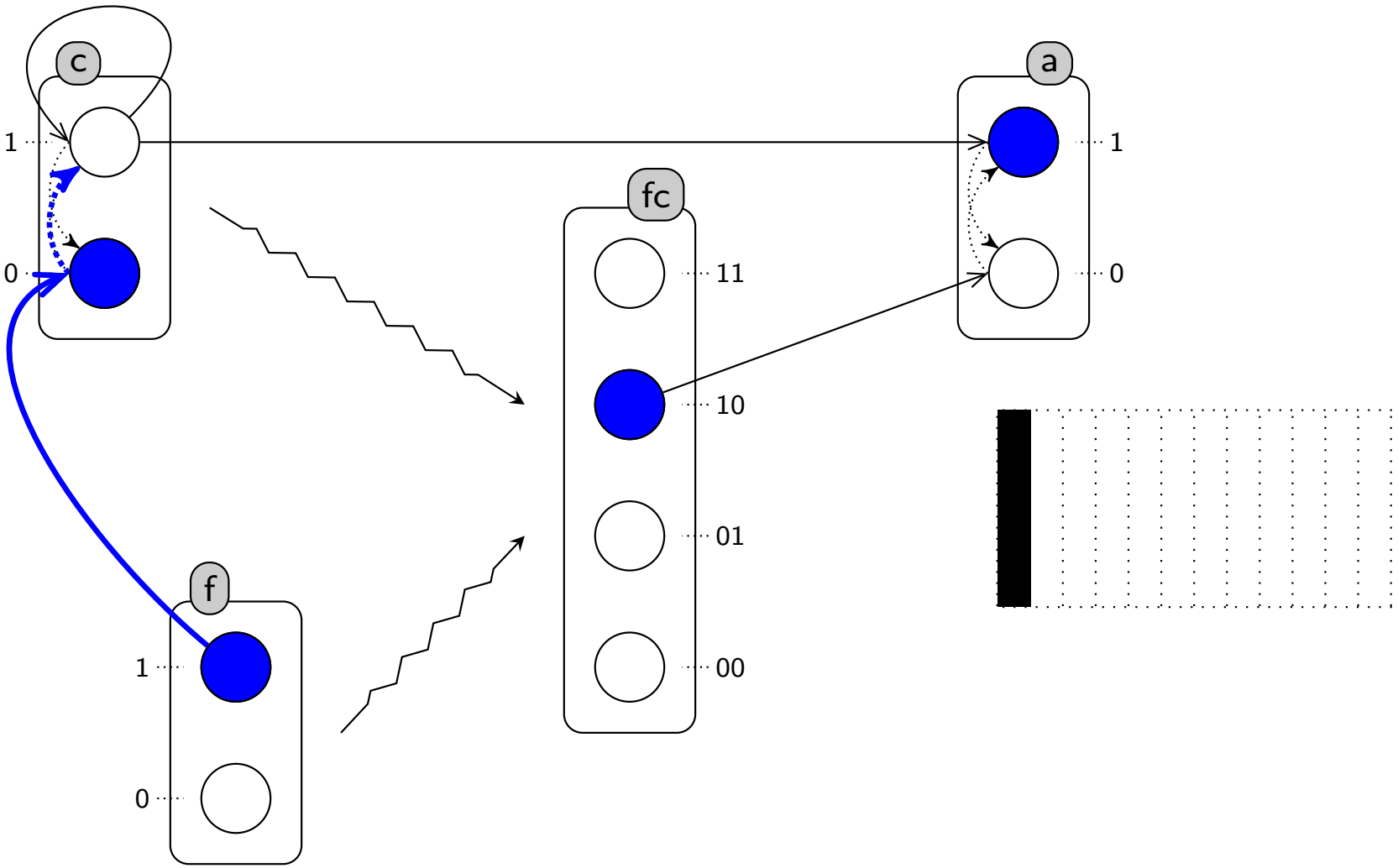

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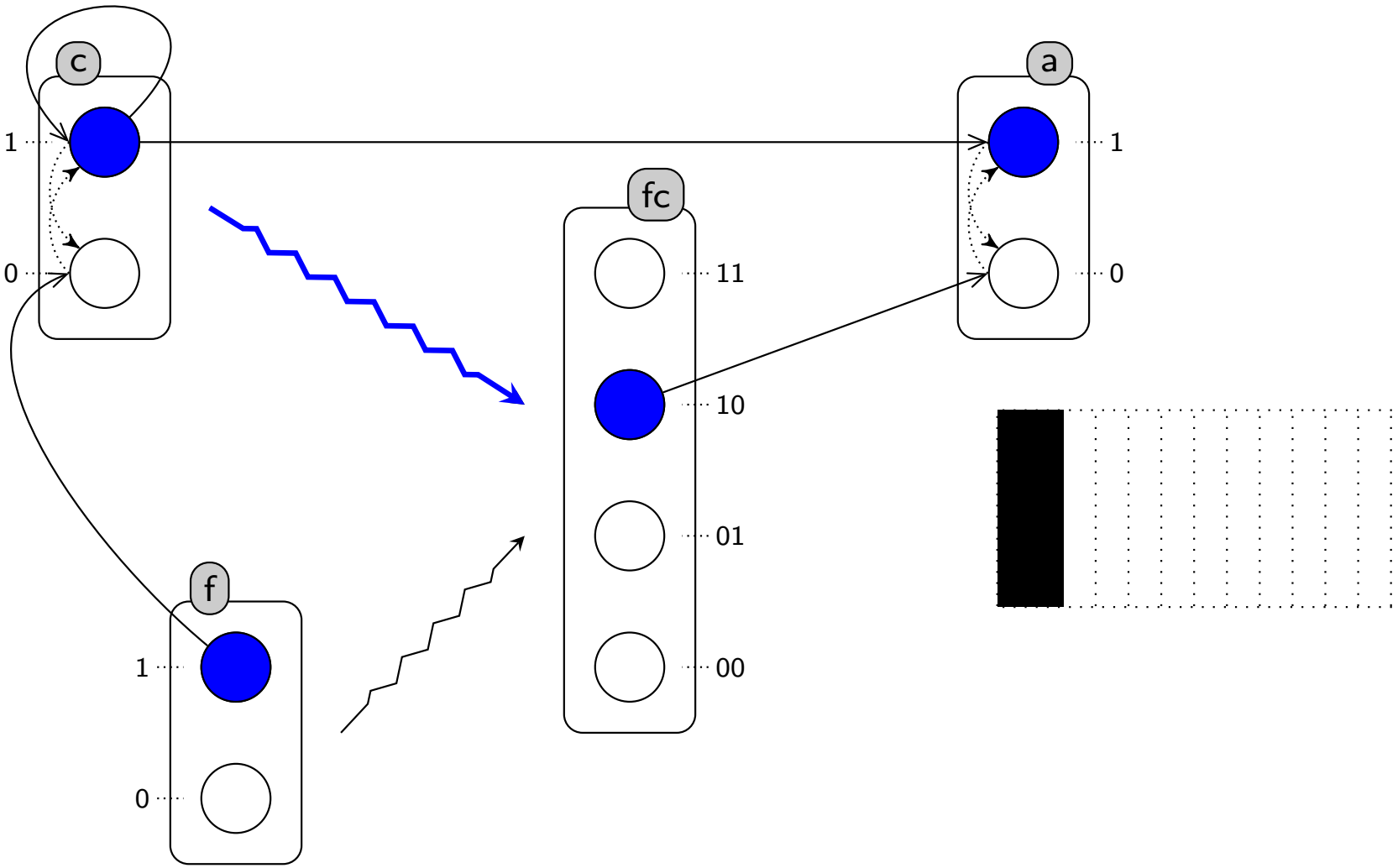

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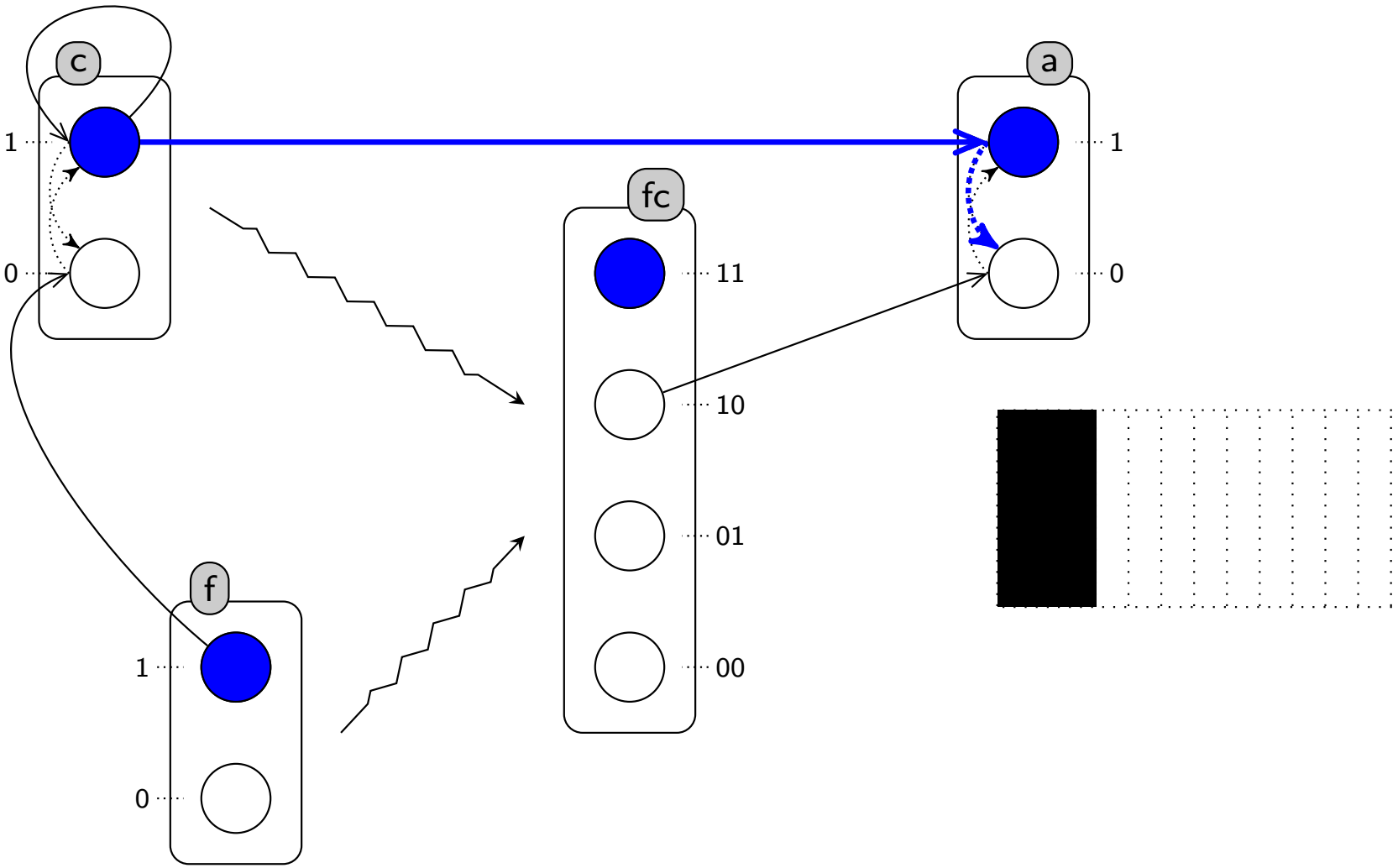

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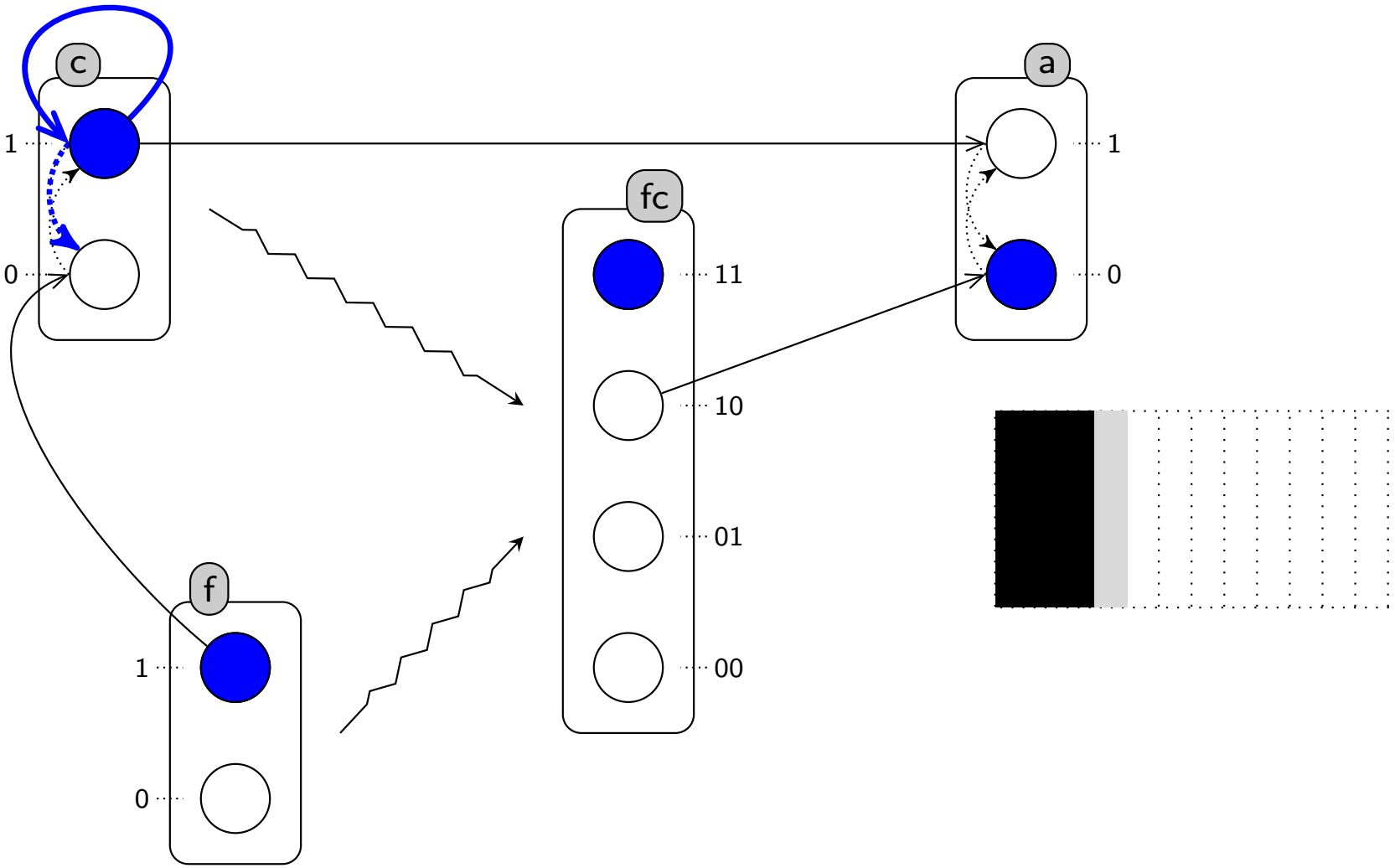

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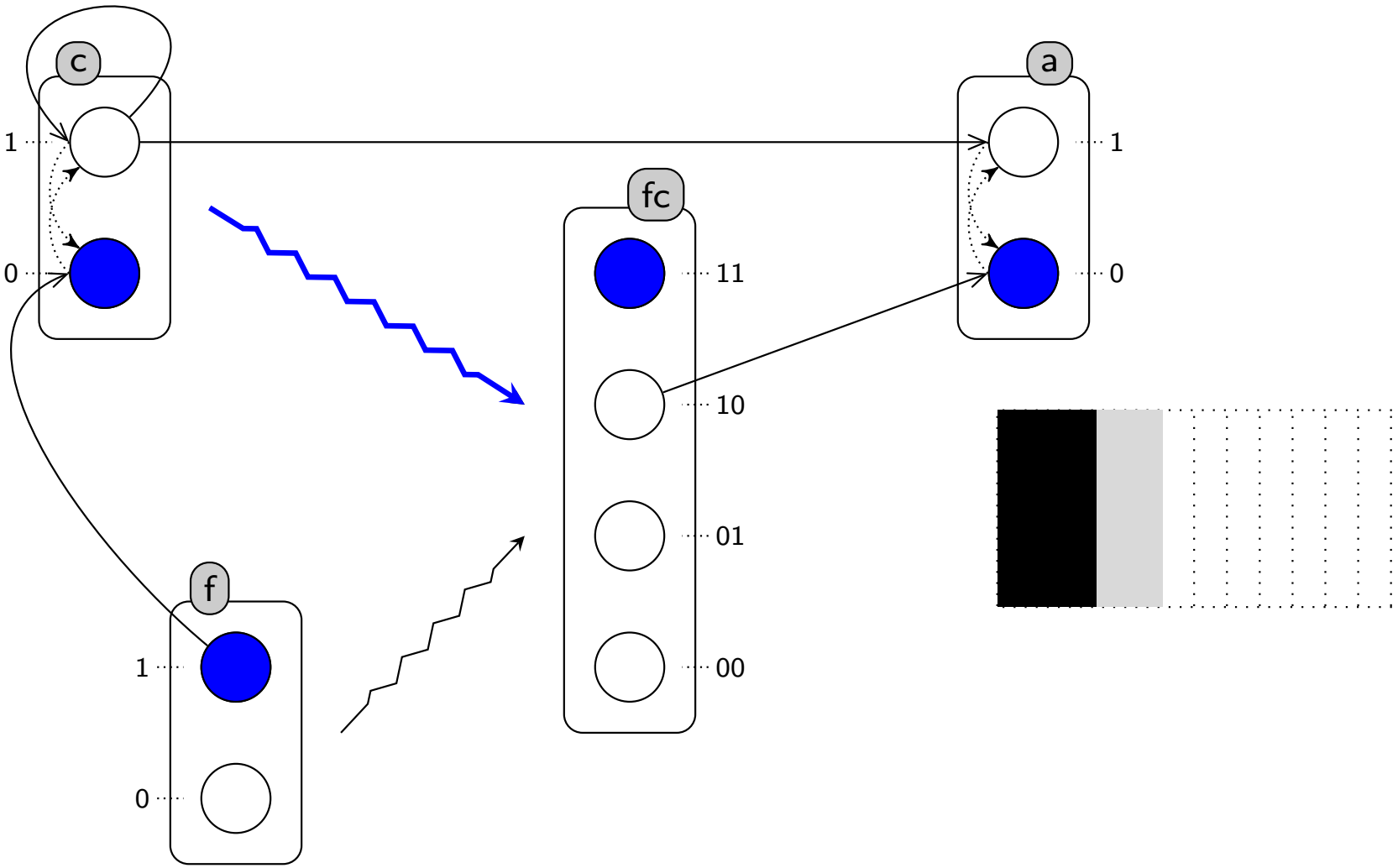

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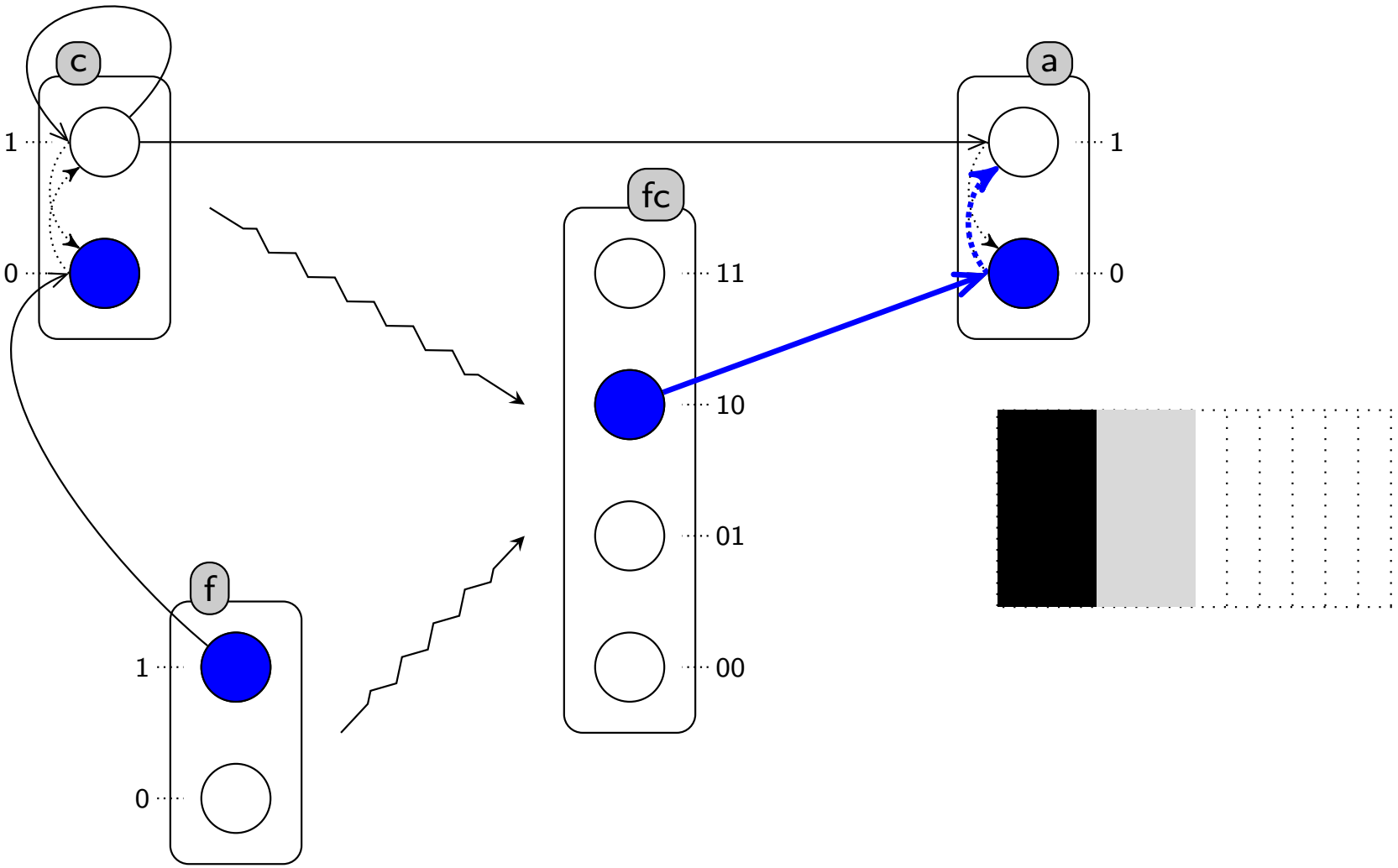

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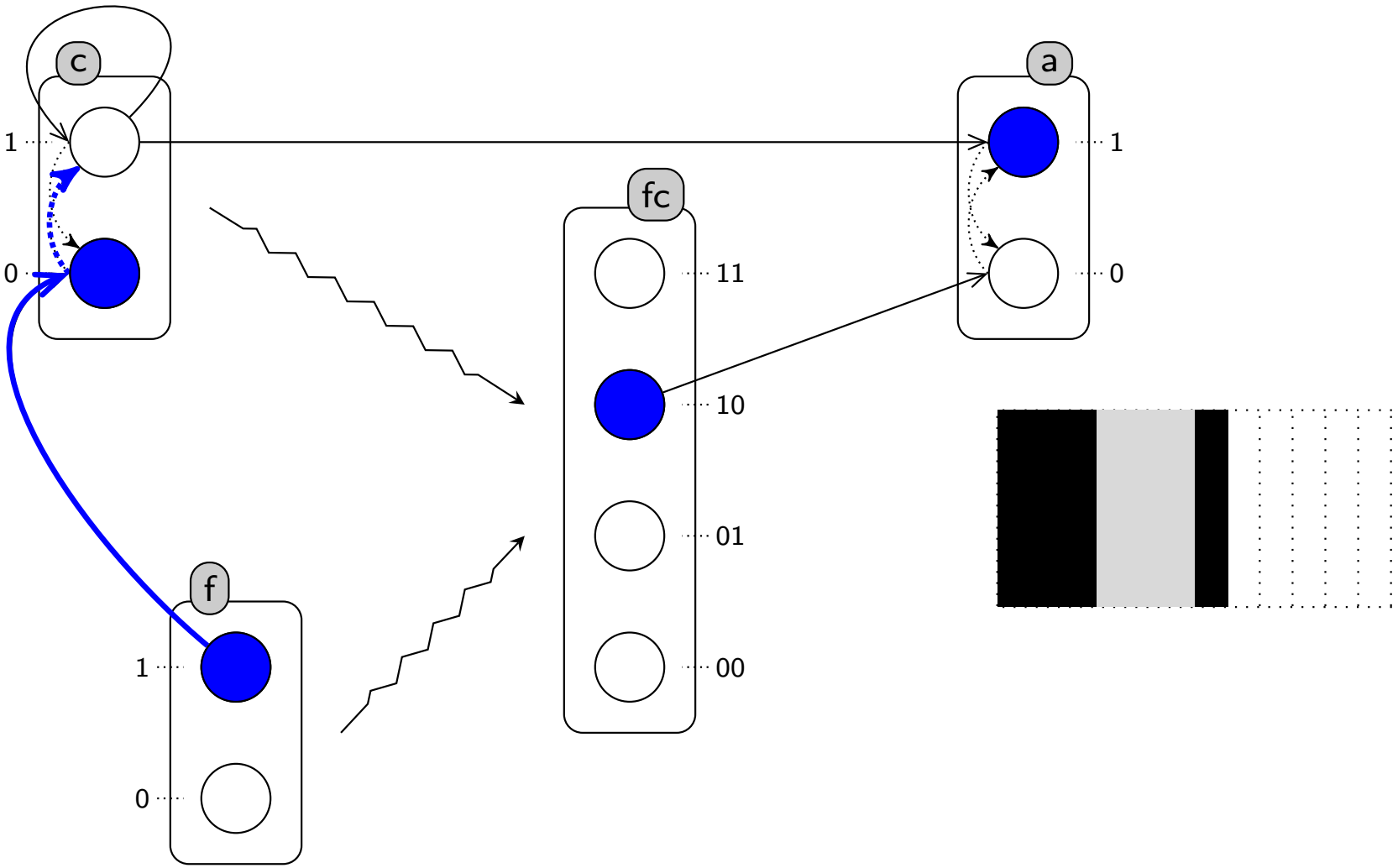

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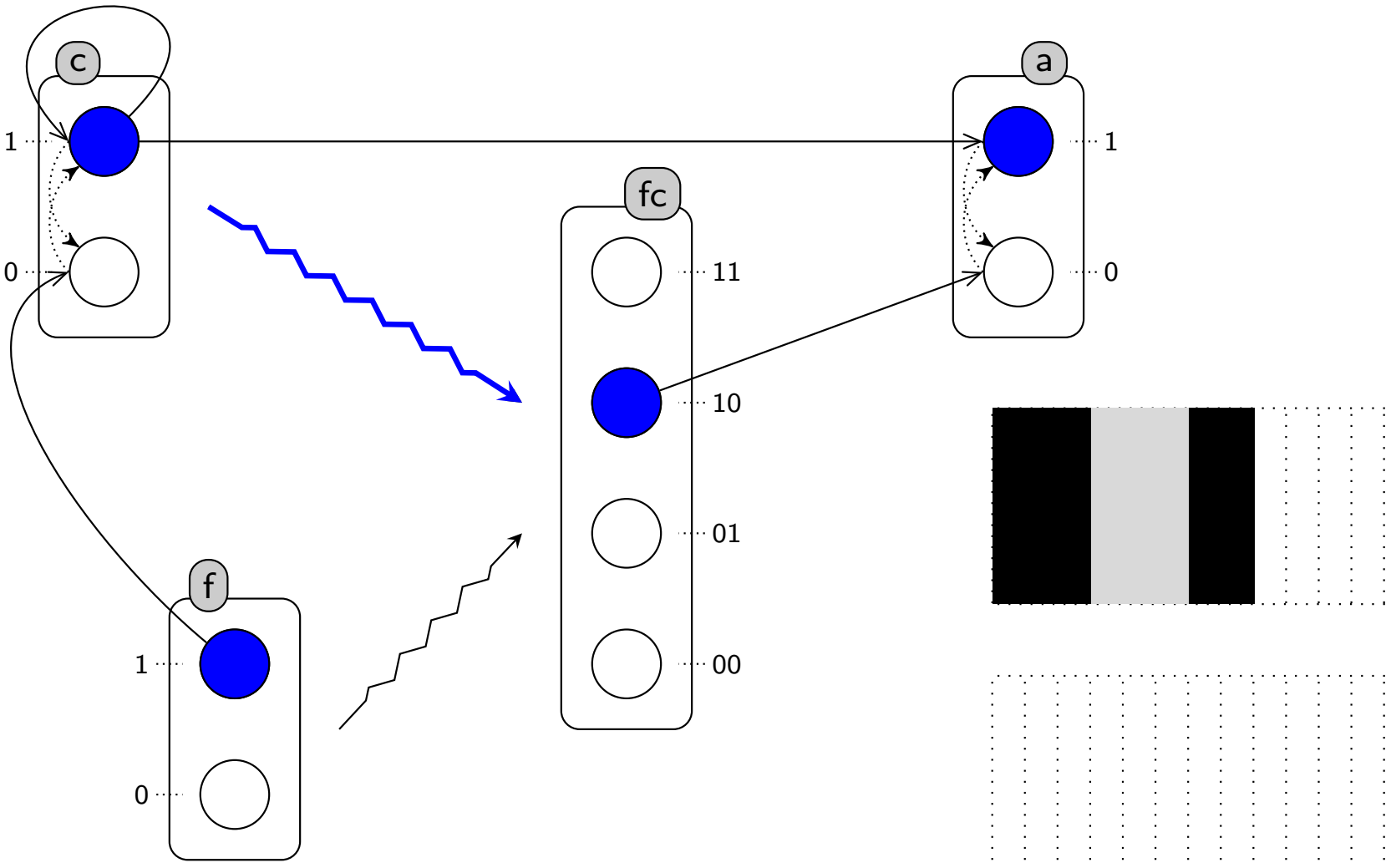

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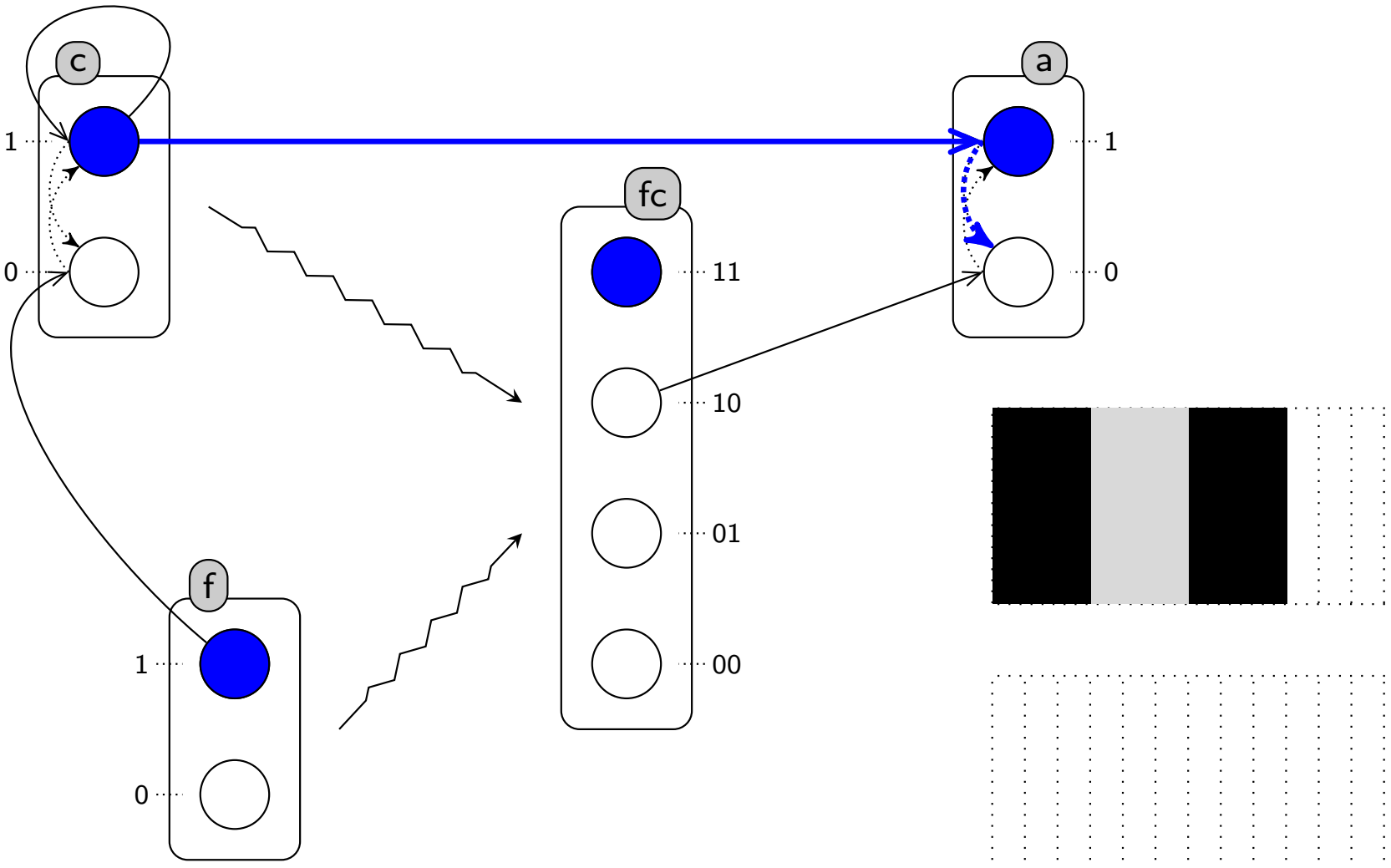

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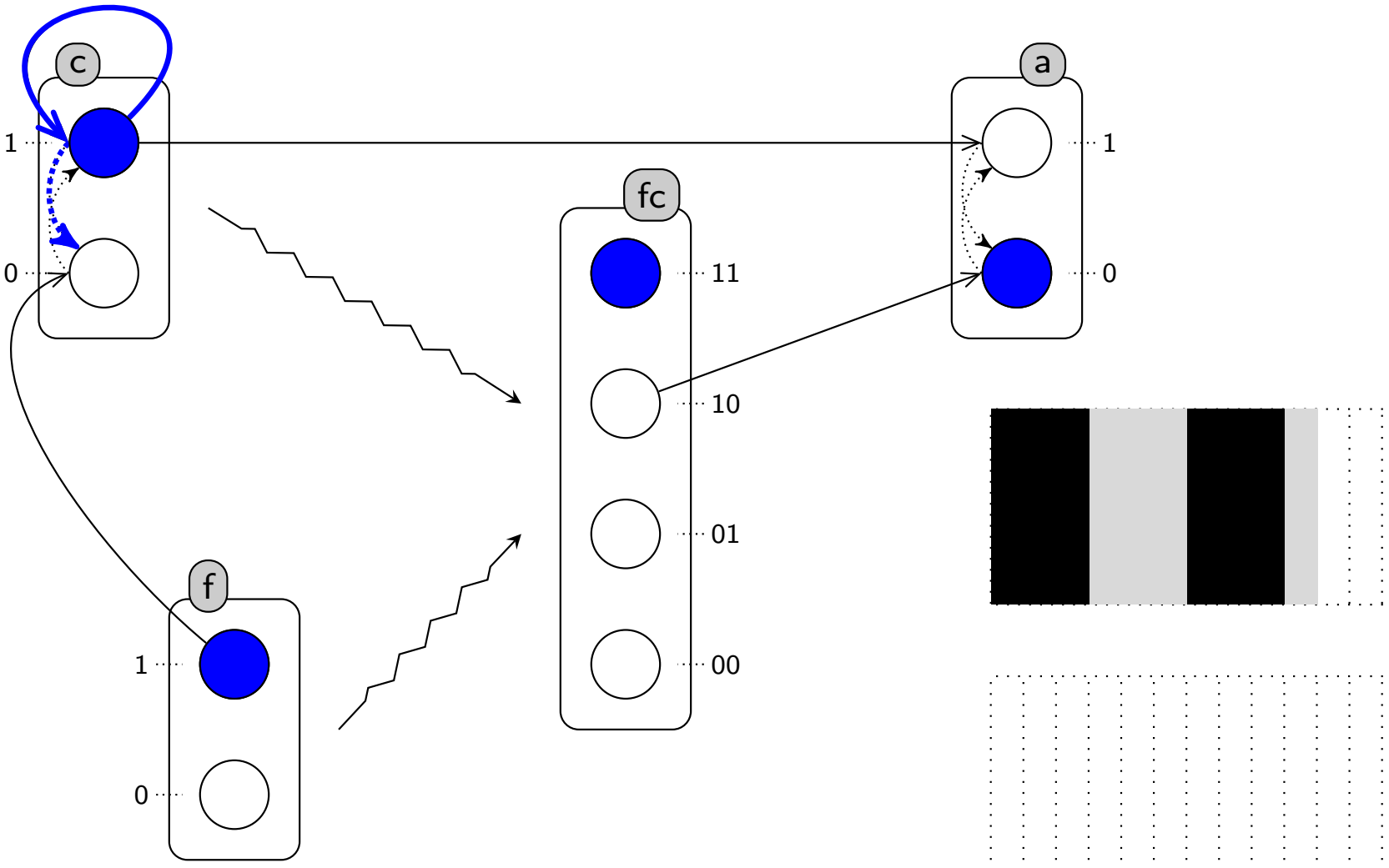

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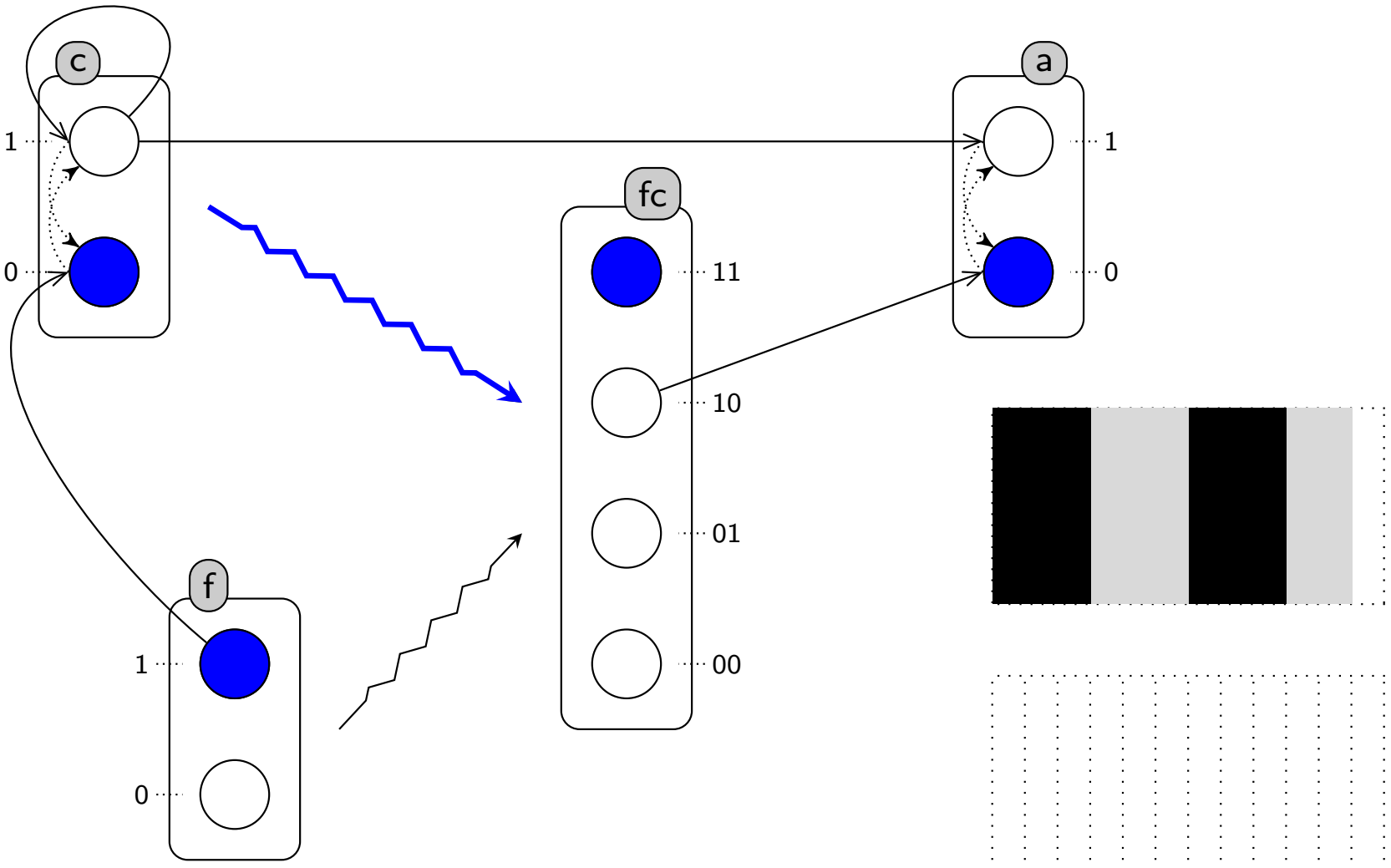

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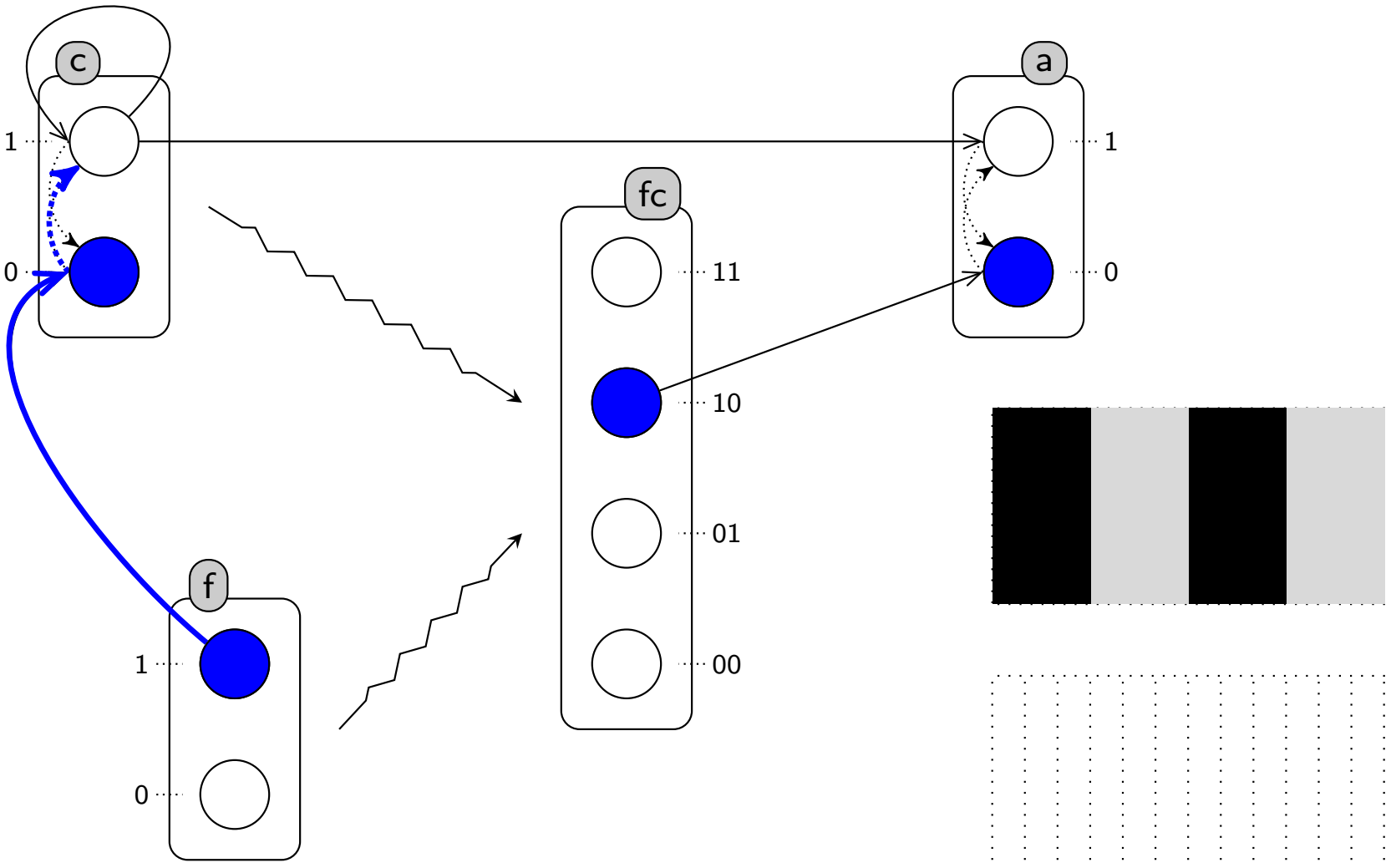

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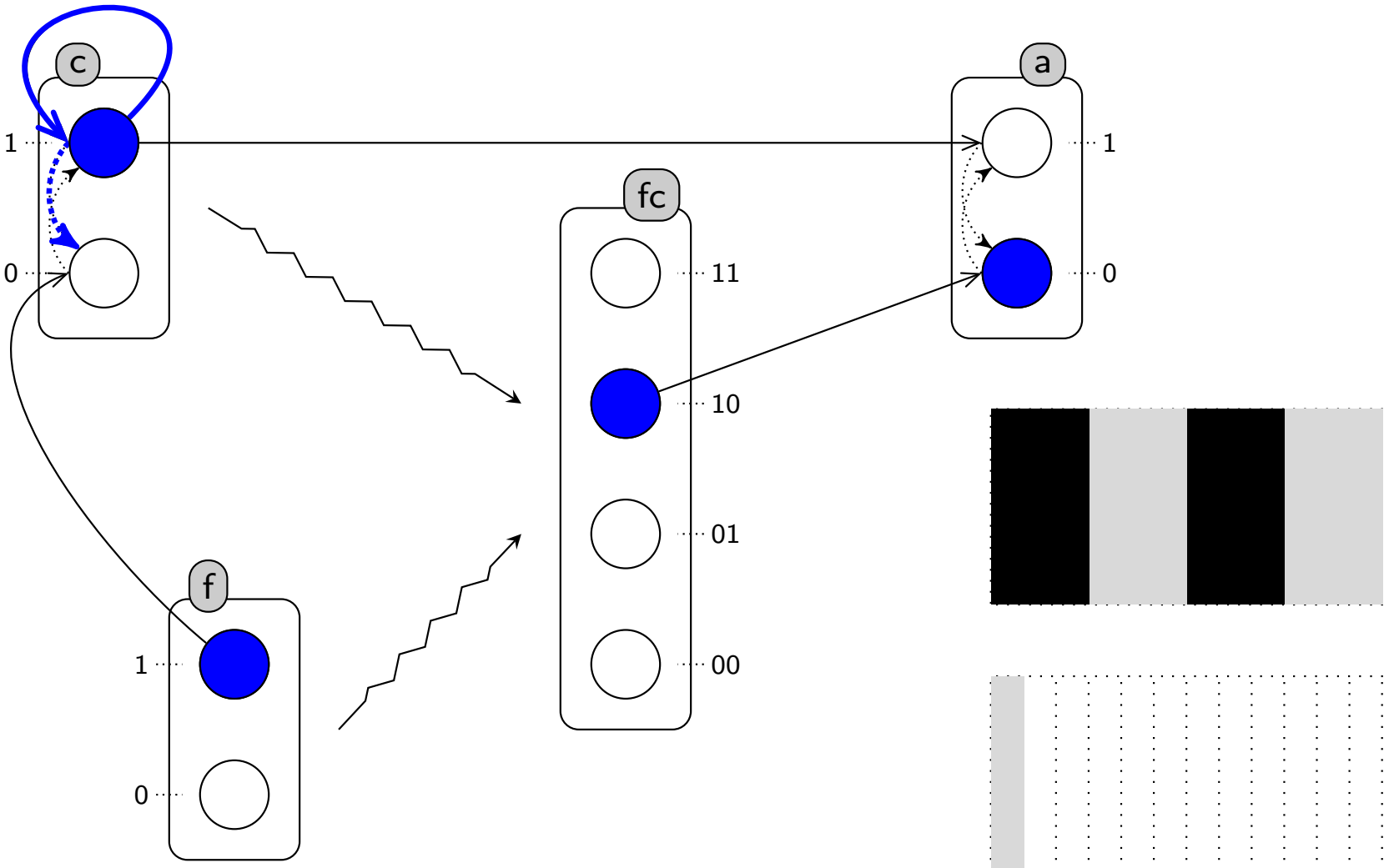

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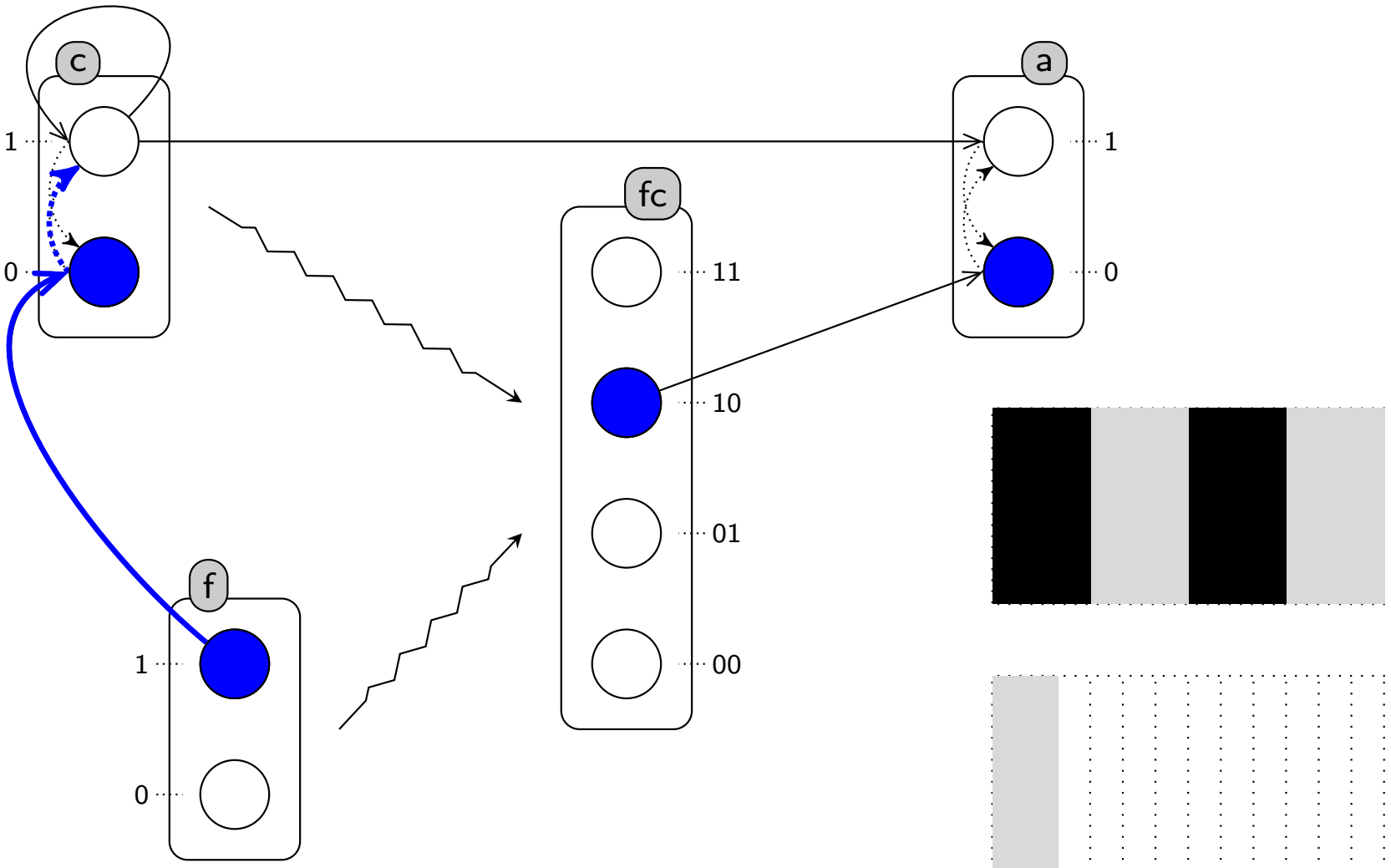

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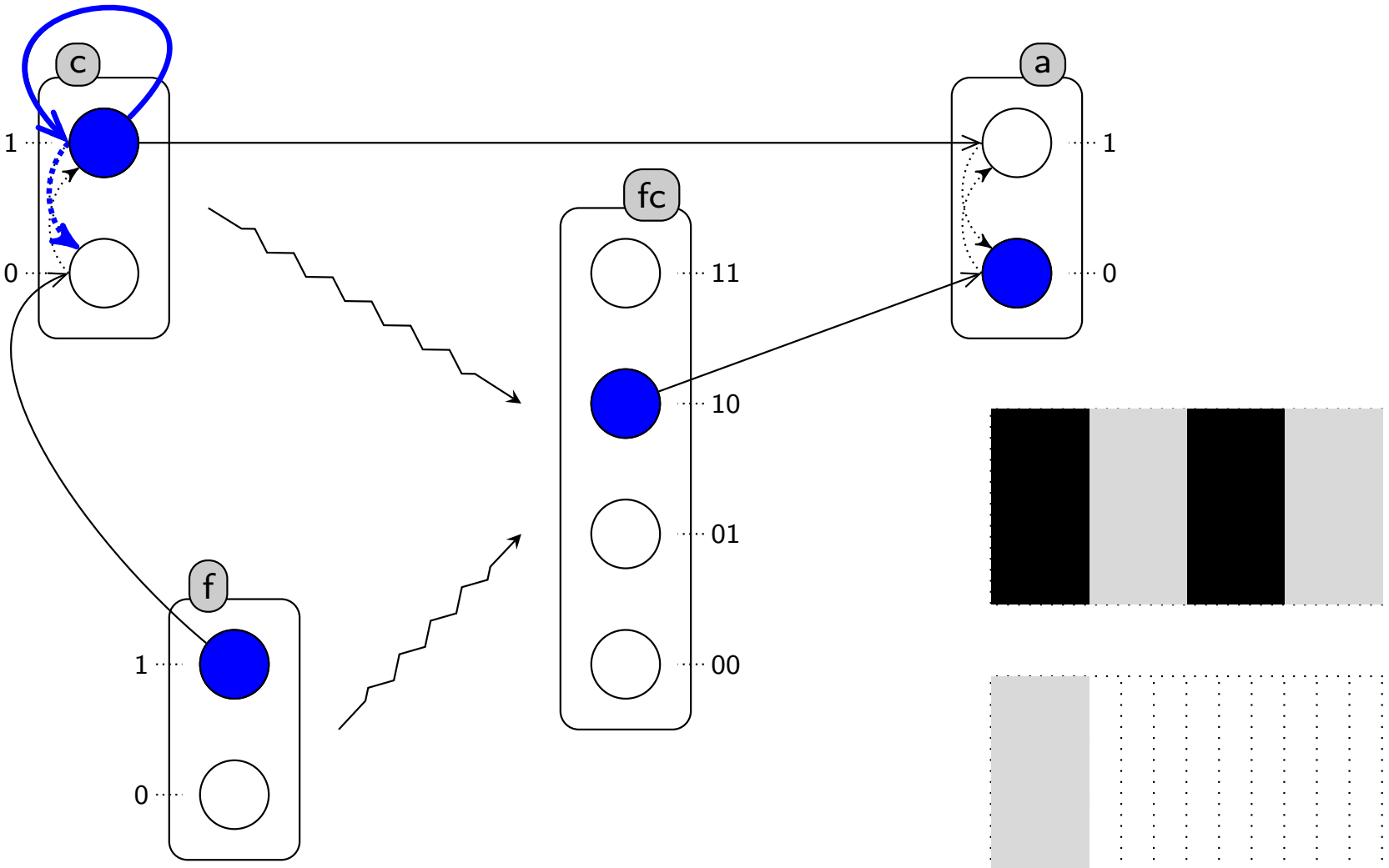

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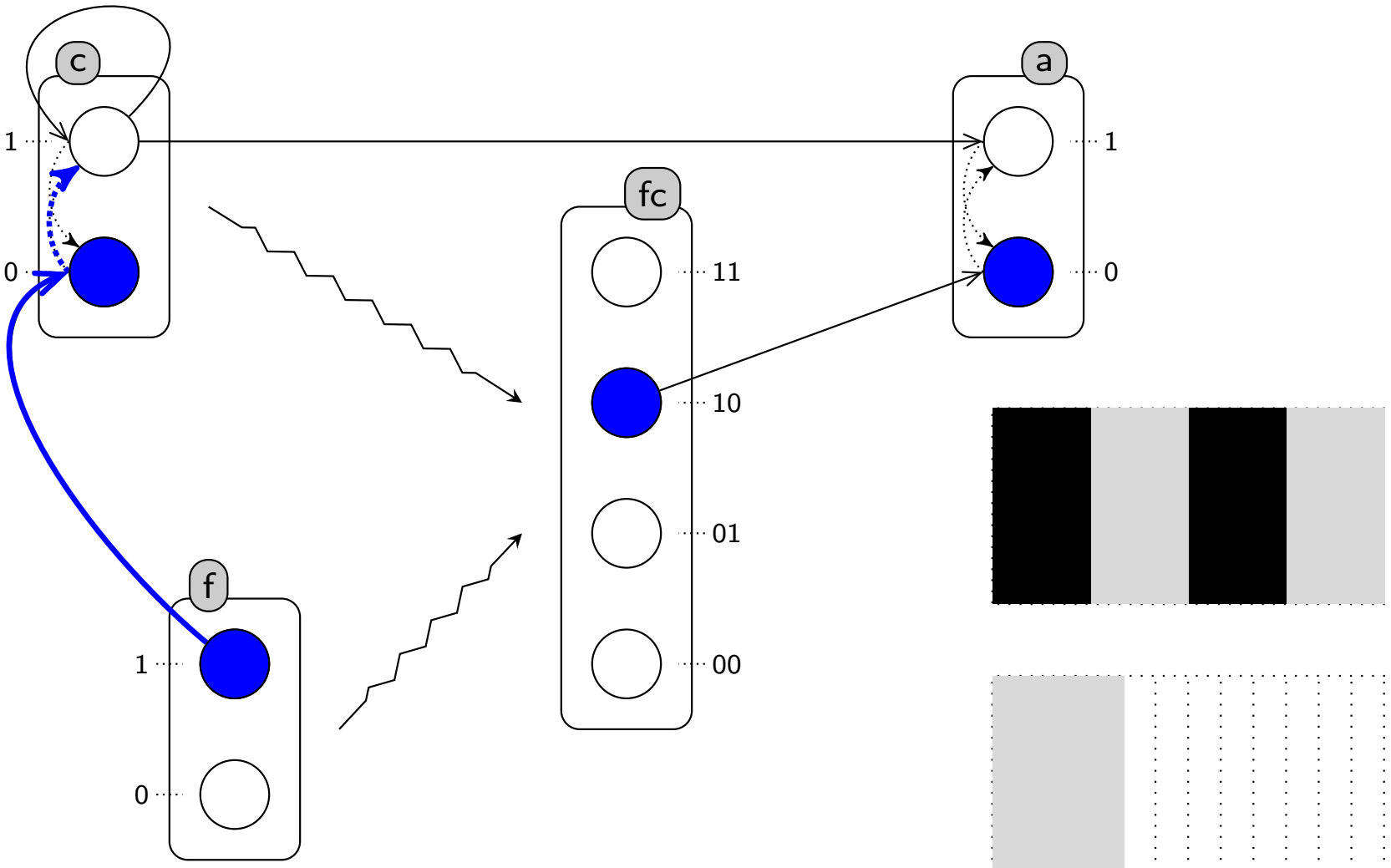

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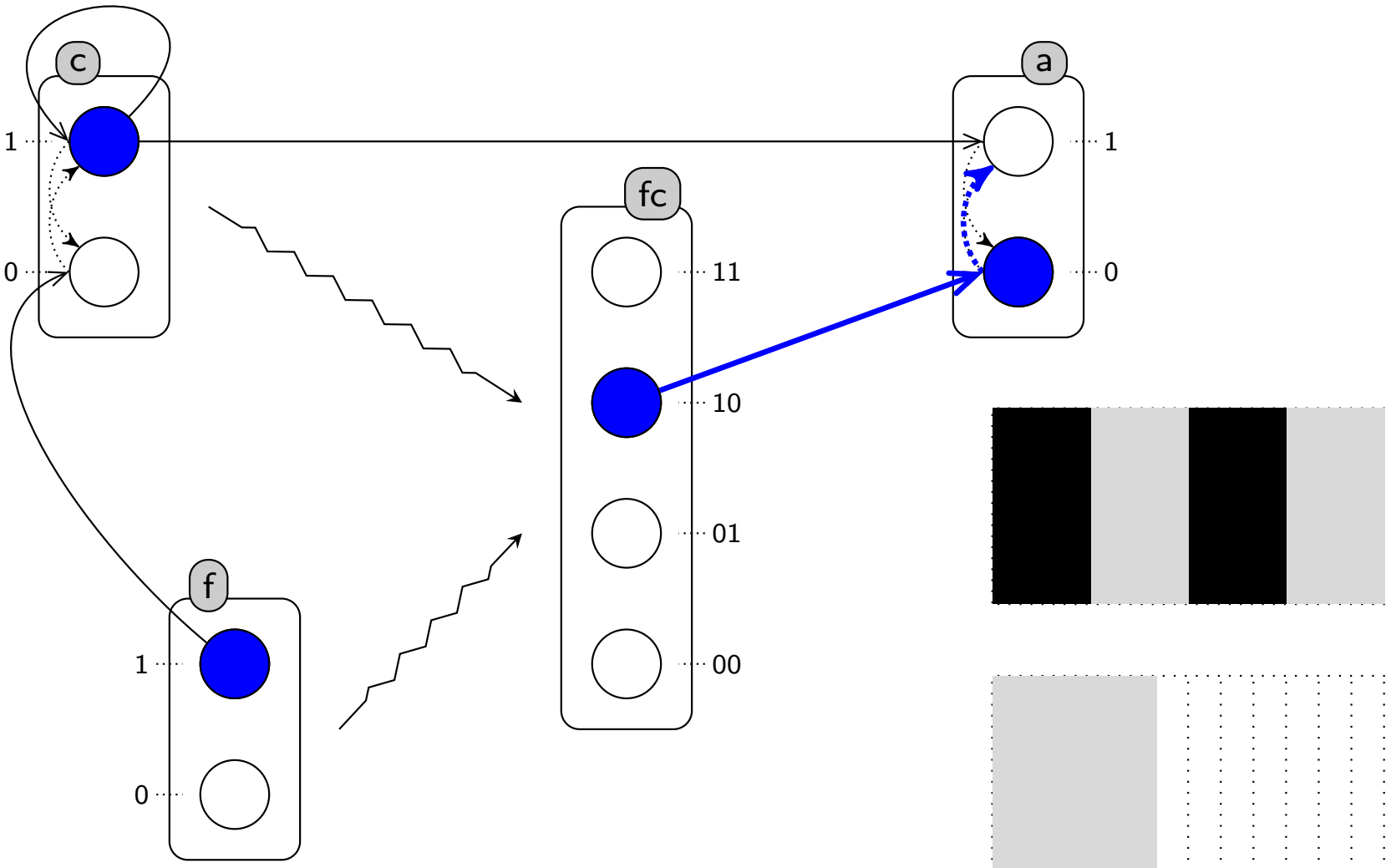

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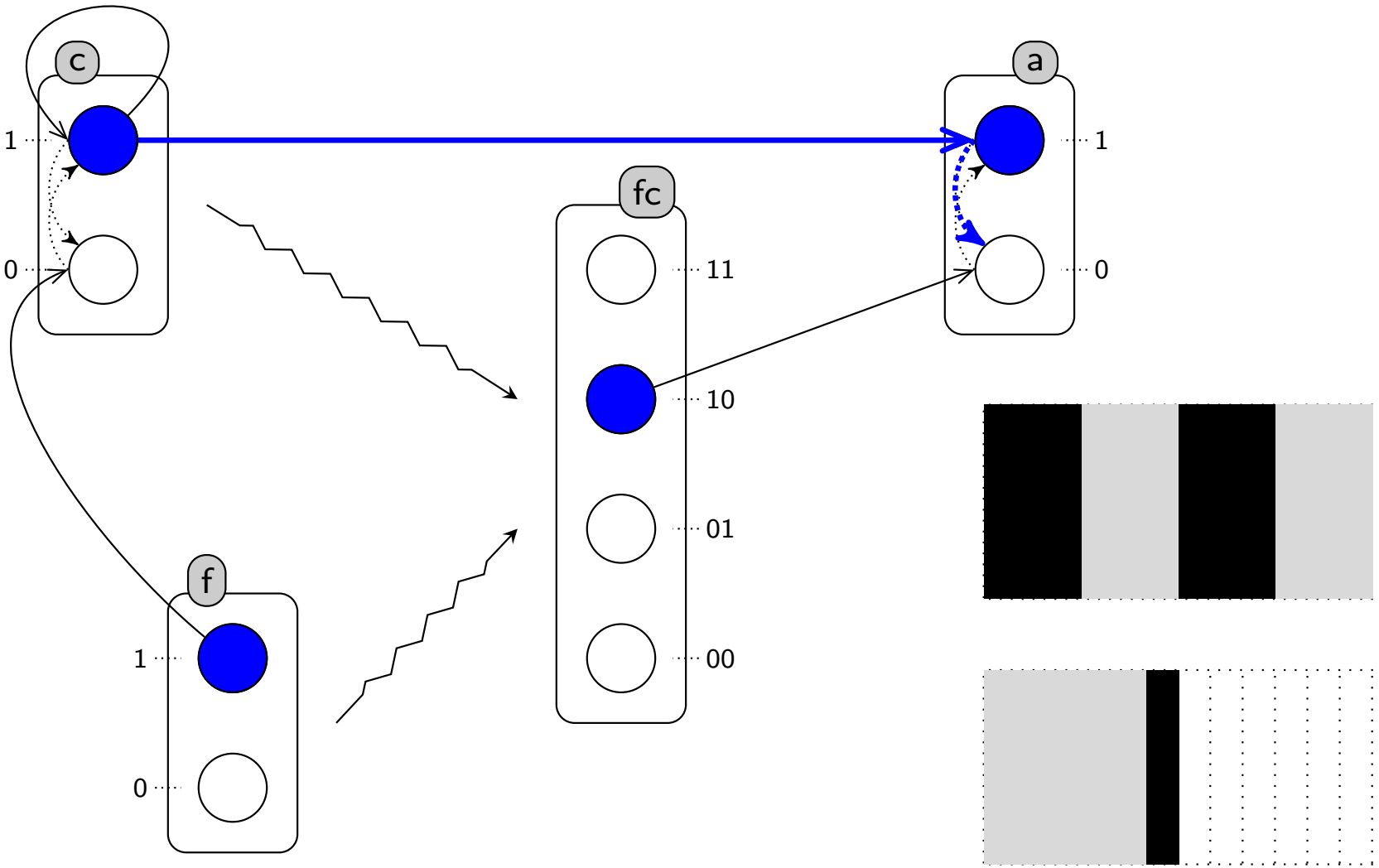

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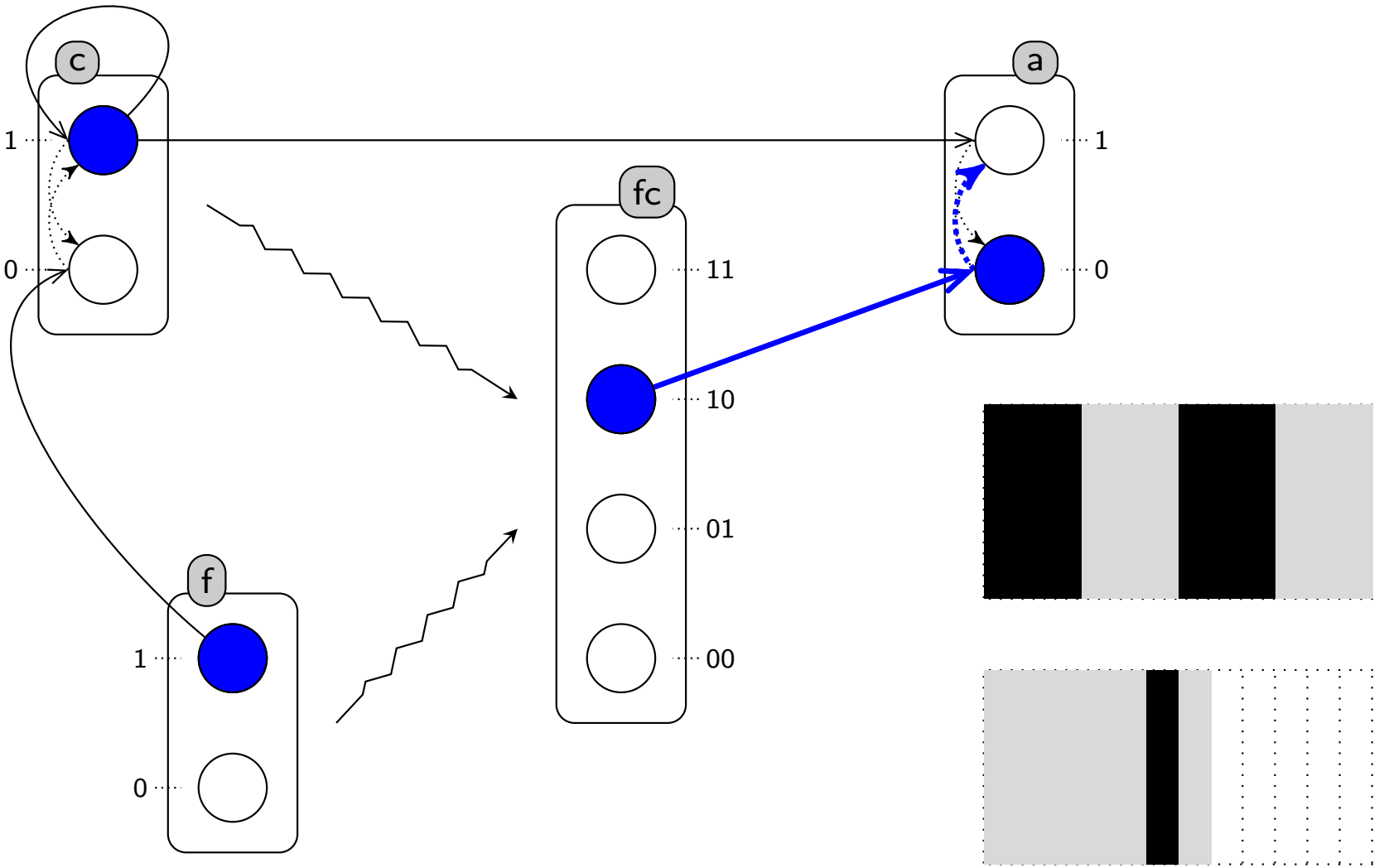

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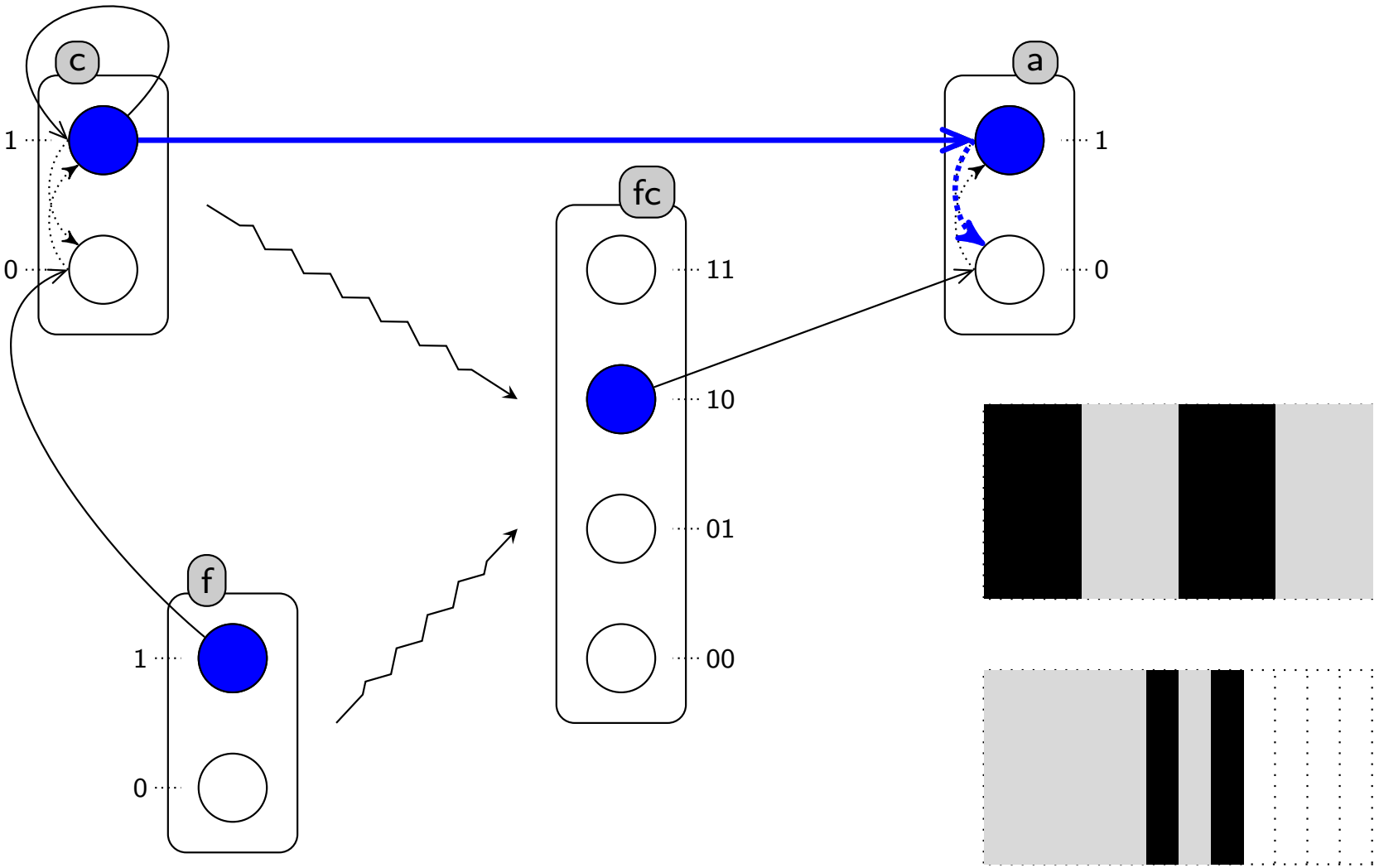

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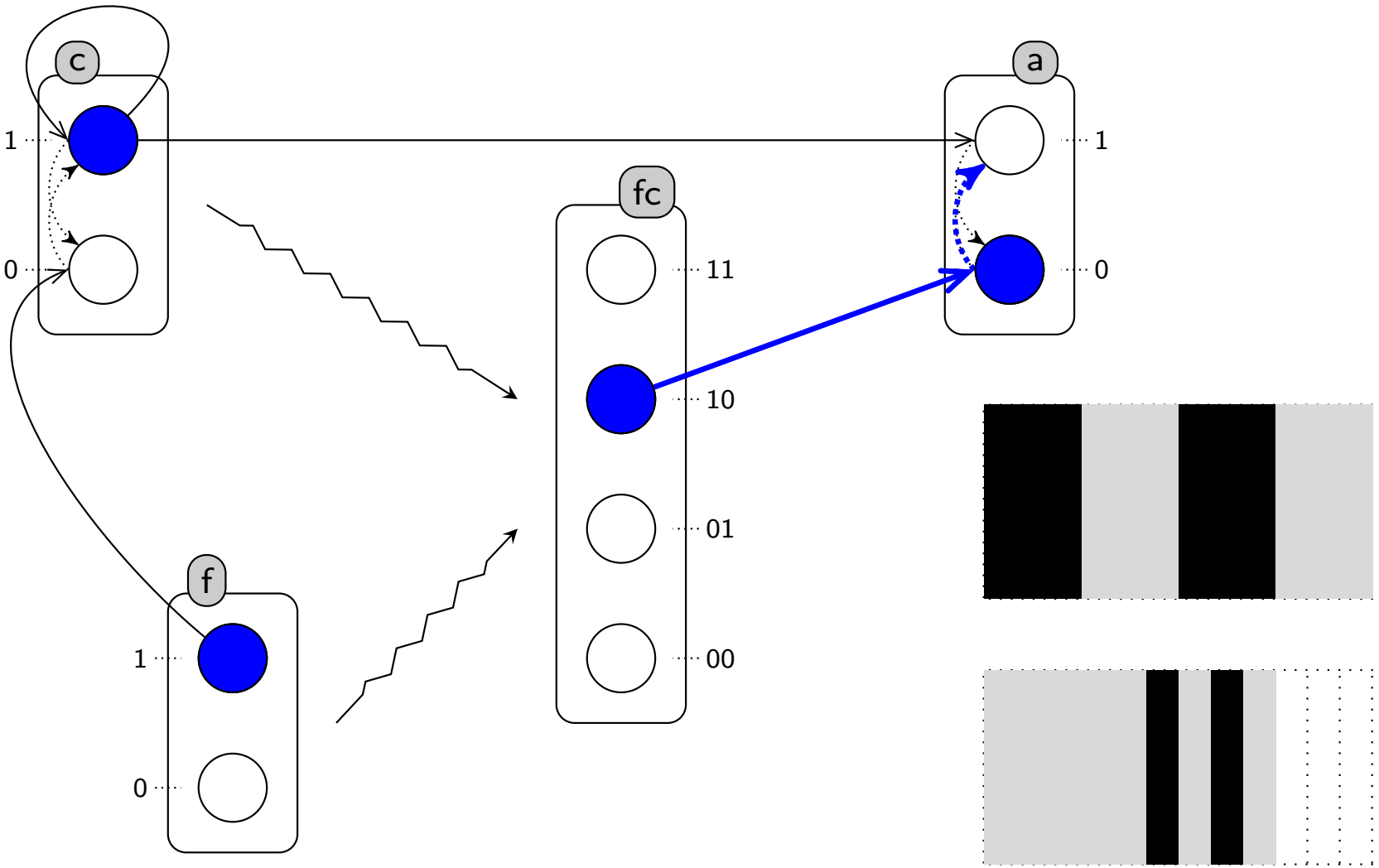

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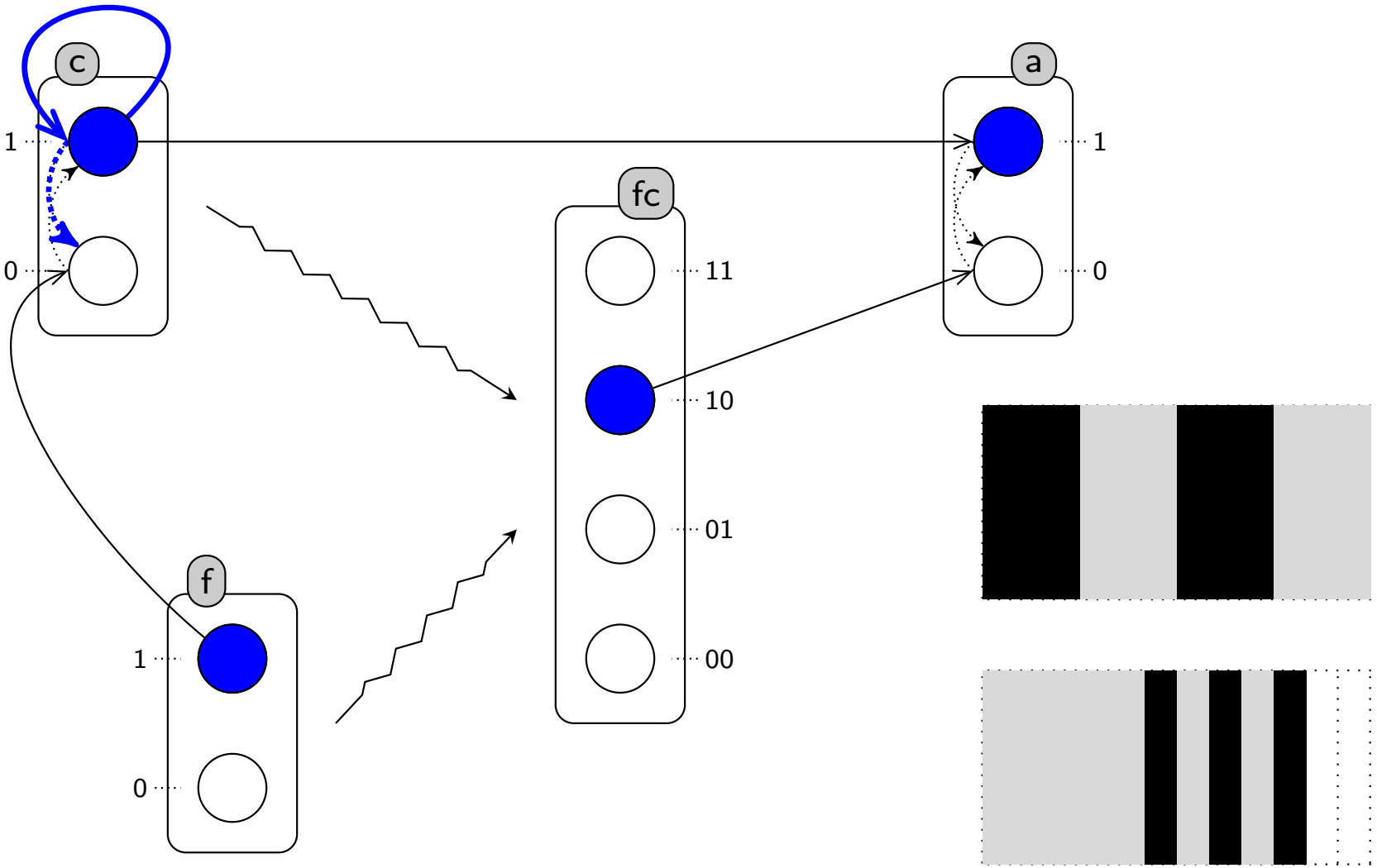

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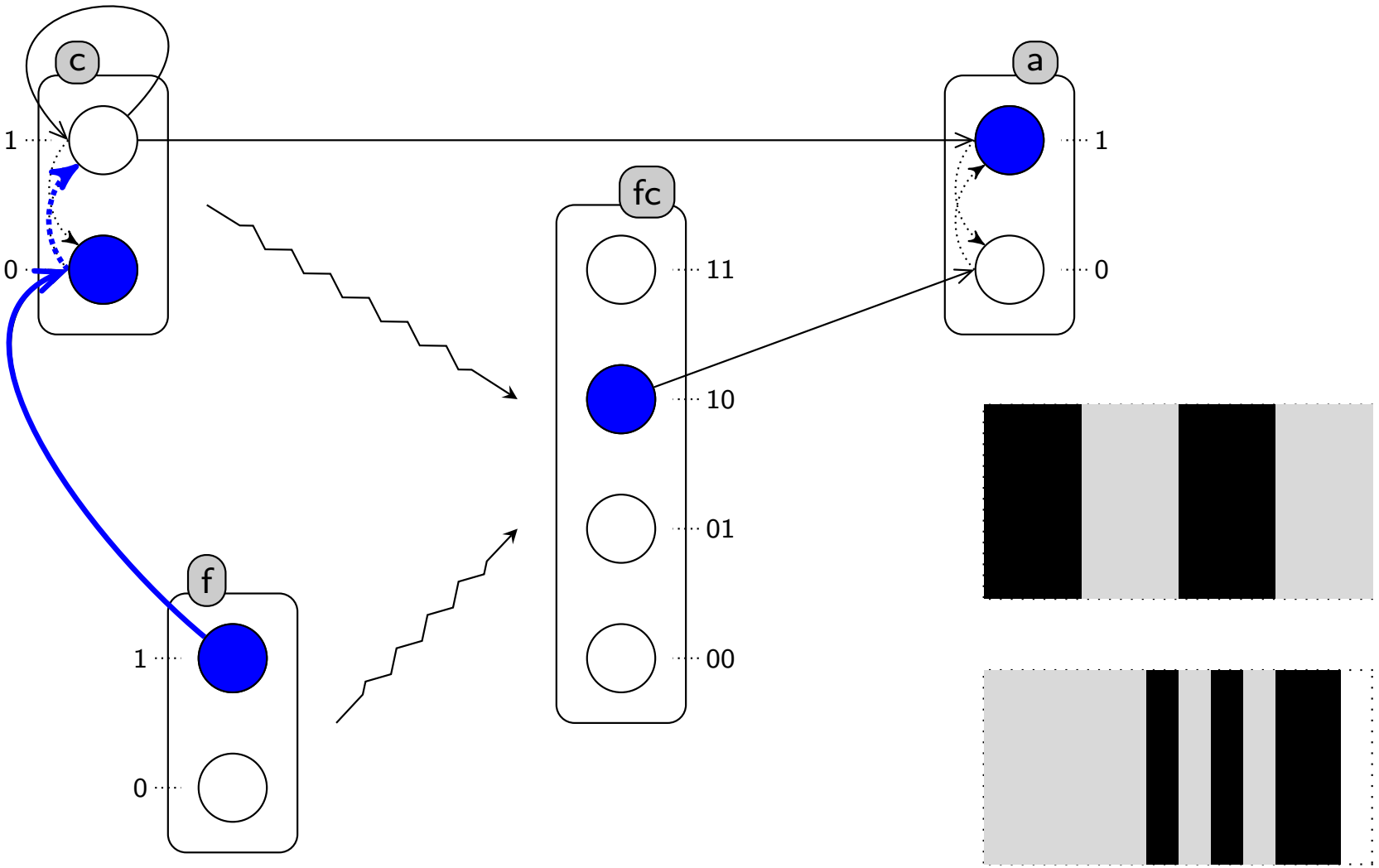

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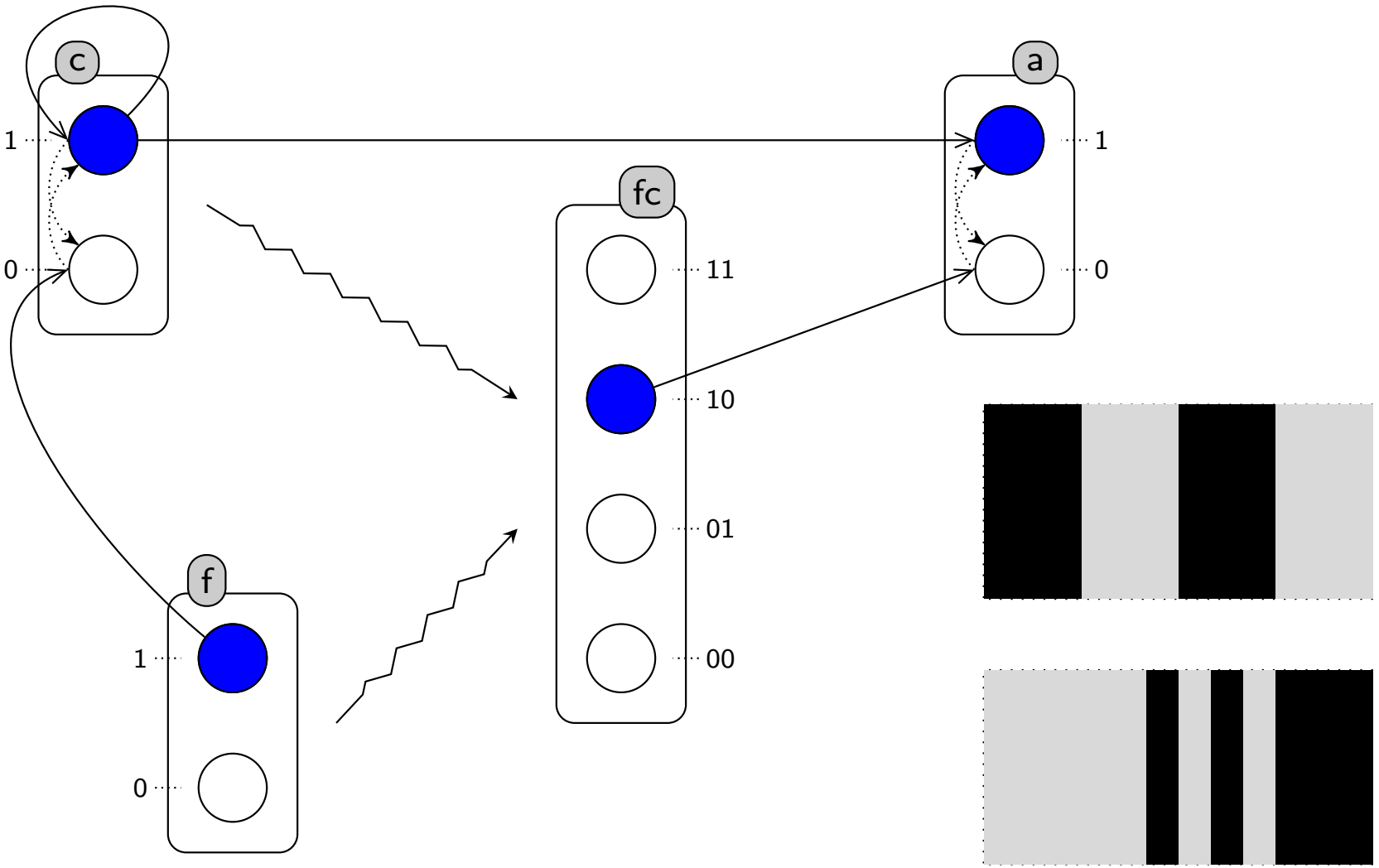
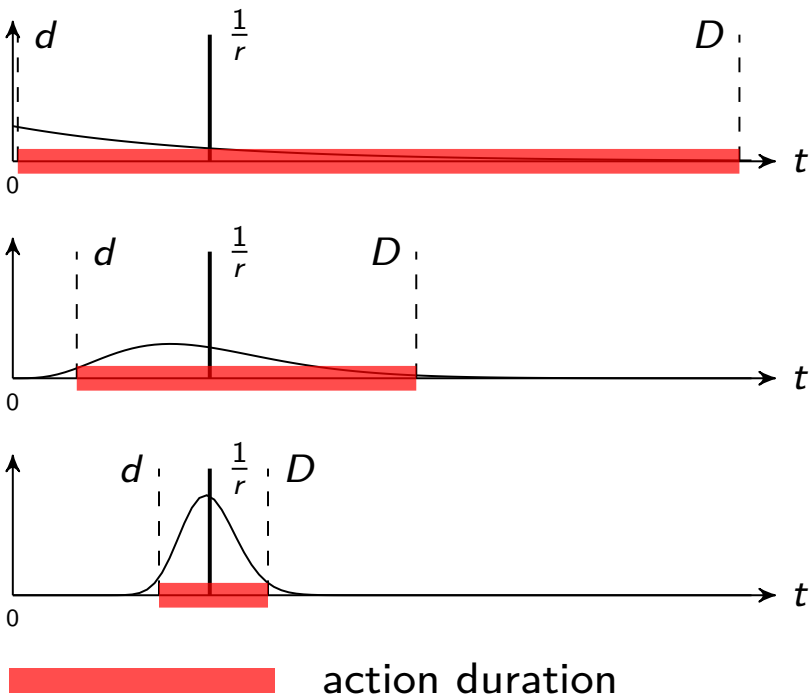


Stochastic Features

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

- Introduces time features
- Parameters: either (r, sa), or the **firing interval** $[d; D]$.



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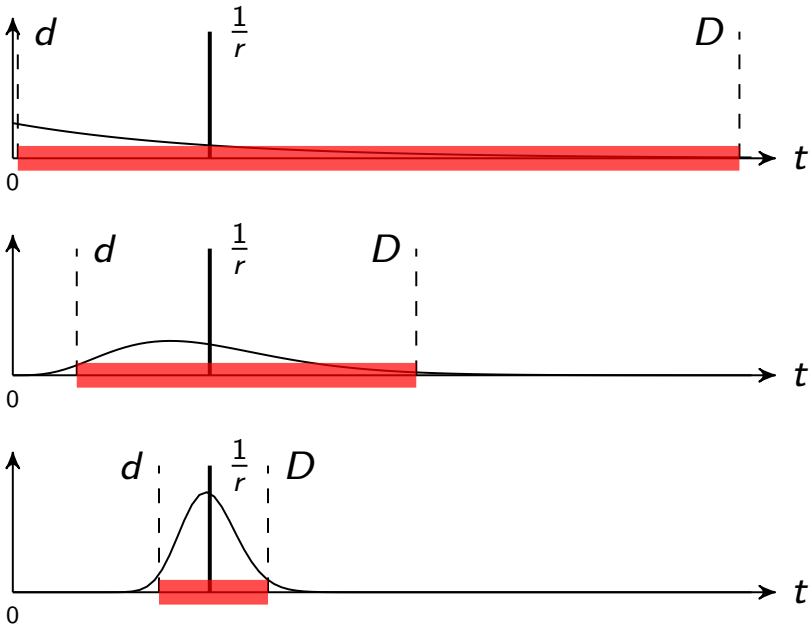
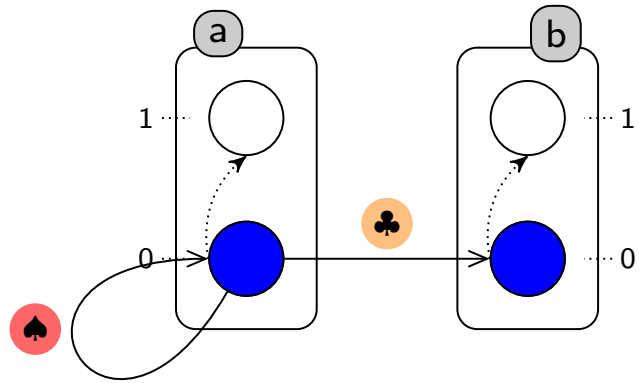
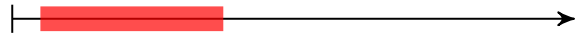


action duration



$a_0 \rightarrow b_0 \Rsh b_1$ (♣)

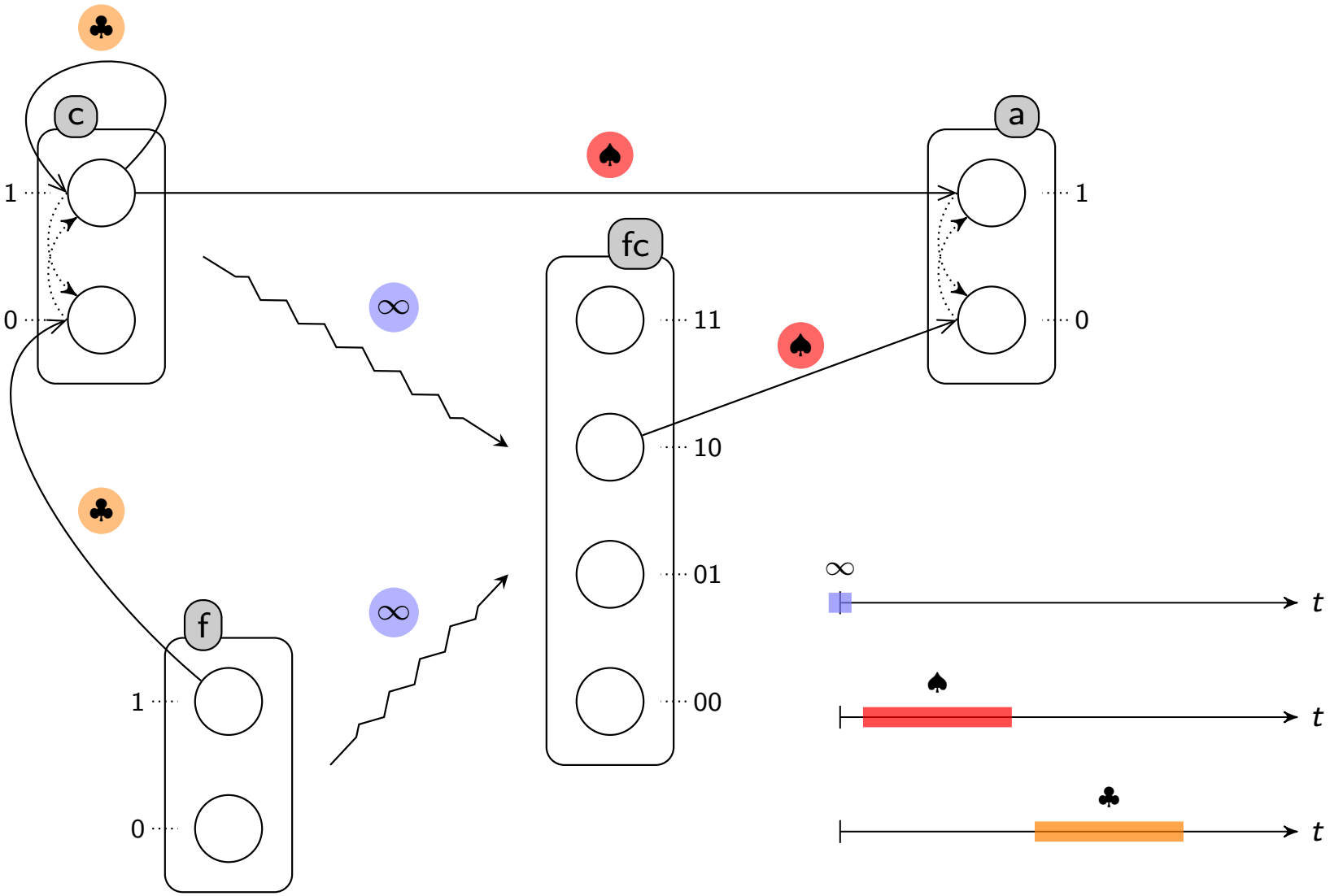
$a_0 \rightarrow a_0 \Rsh a_1$ (♠)



$\rightarrow$ b_1 reached with a **very low probability**.

Metazoan Segmentation with Stochastic Parameters

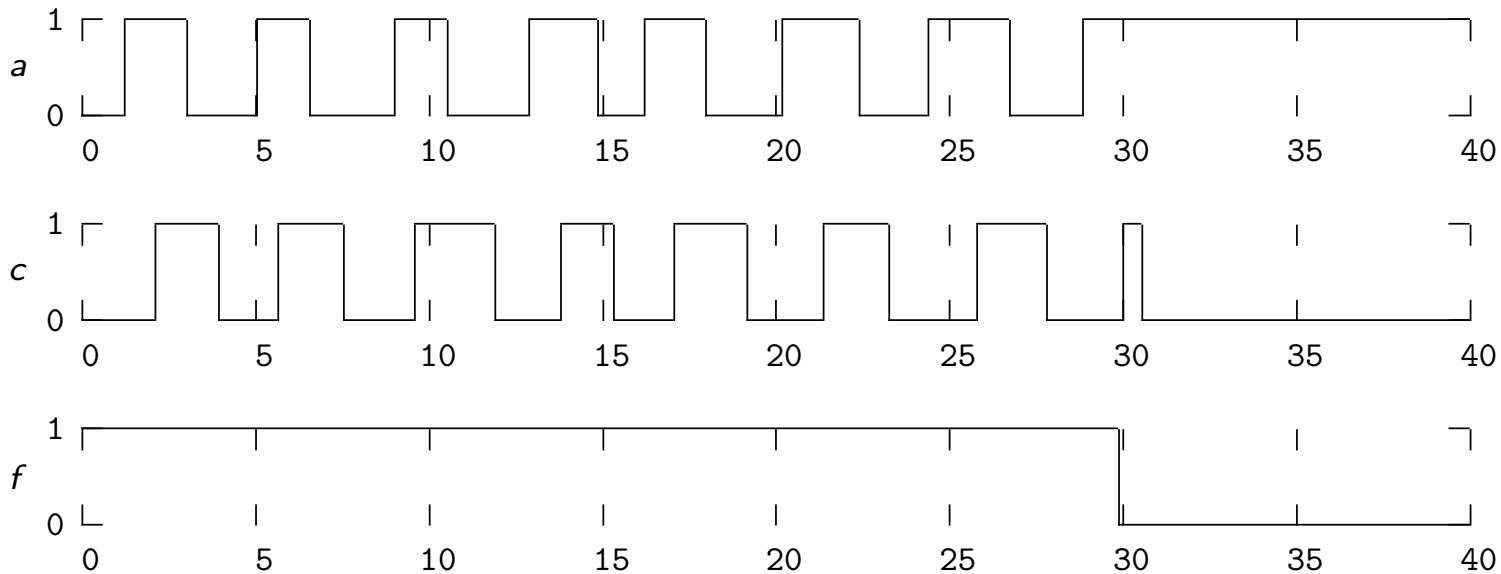
[Paulevé *et al.* in Transactions on Computational Systems Biology, 2011]



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

Pros and Cons of Stochastic Parameters

Pros:

- Introduction of temporal features
- Simulation in continuous time

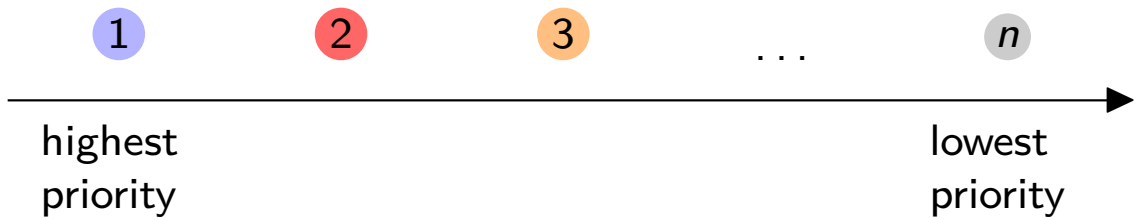
Cons:

- Very hard to analyze
  - Either multiple runs (statistics)
  - Or model checkers (PRISM) but combinatorial explosion

Introduction of Classes of Priorities

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

- Each action is associated to a class of priority.
- An action cannot be played if another action of higher priority is playable.



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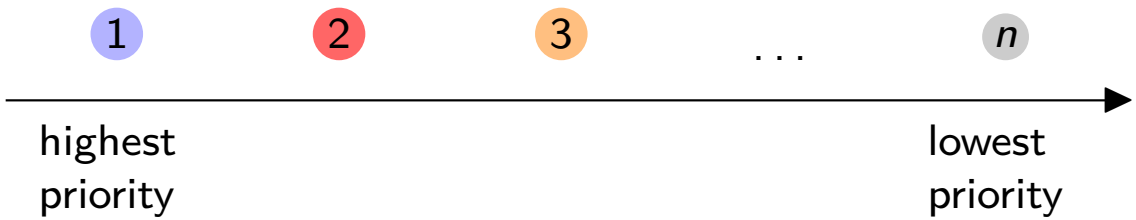

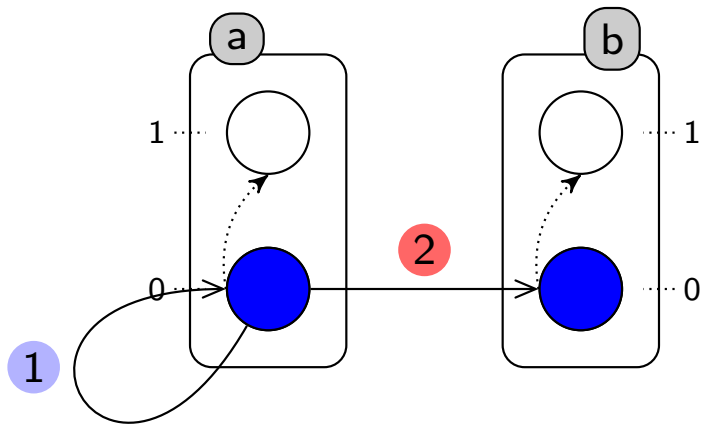

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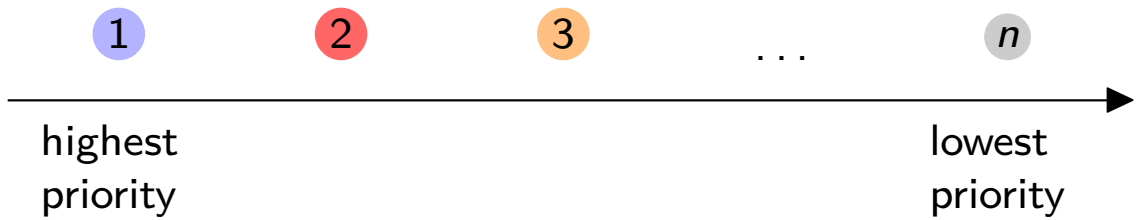

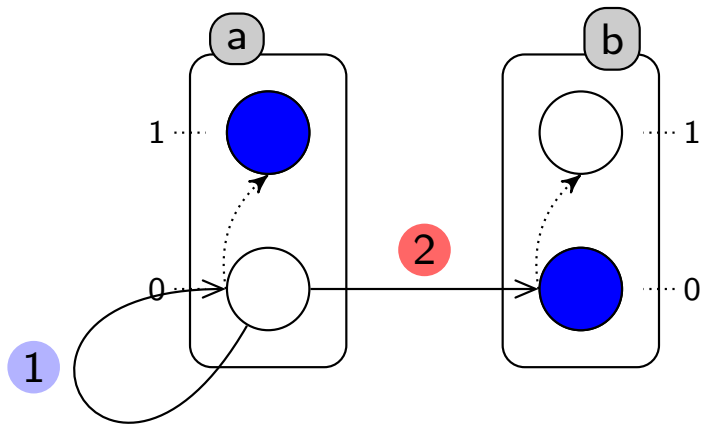

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Metazoan Segmentation with Priorities

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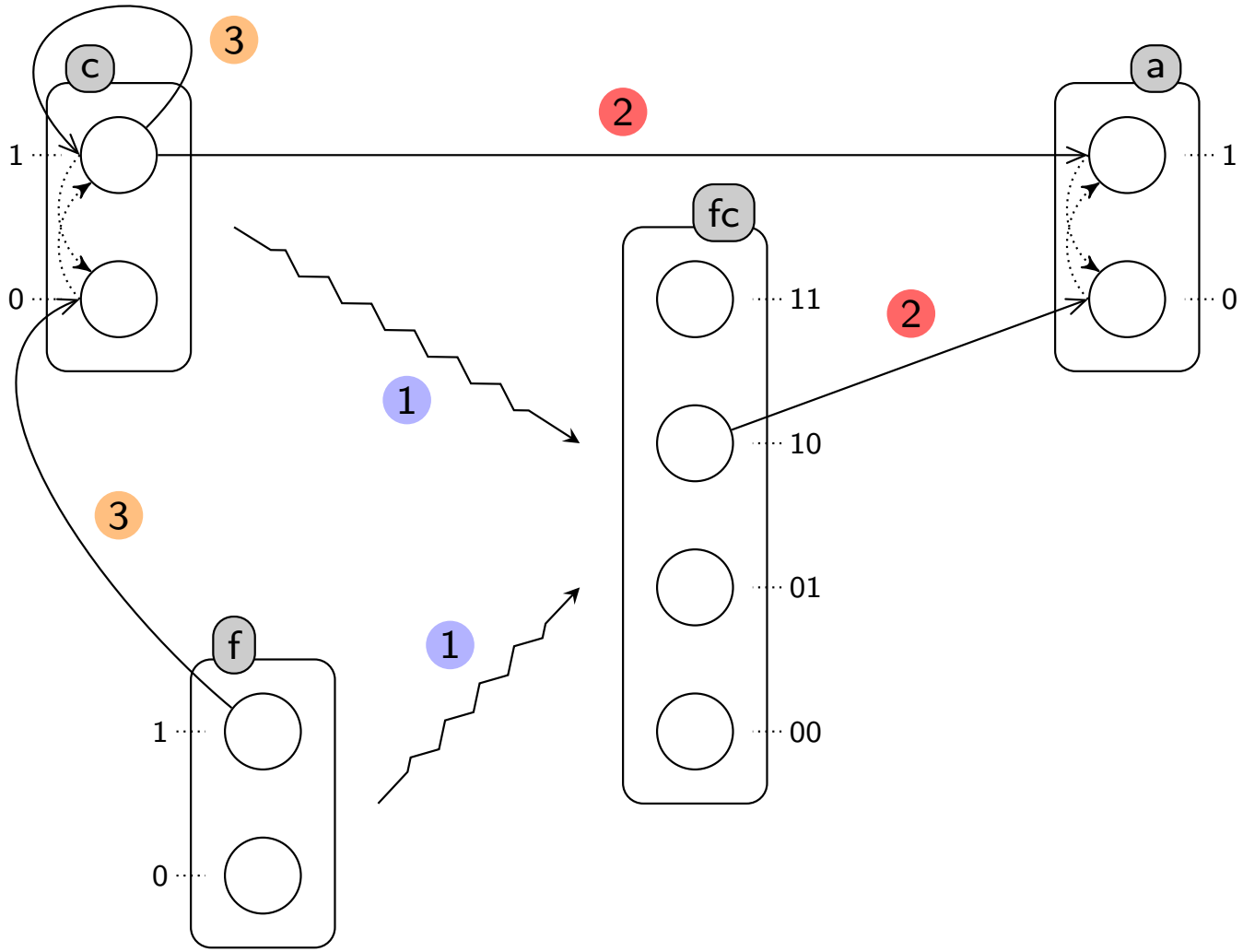

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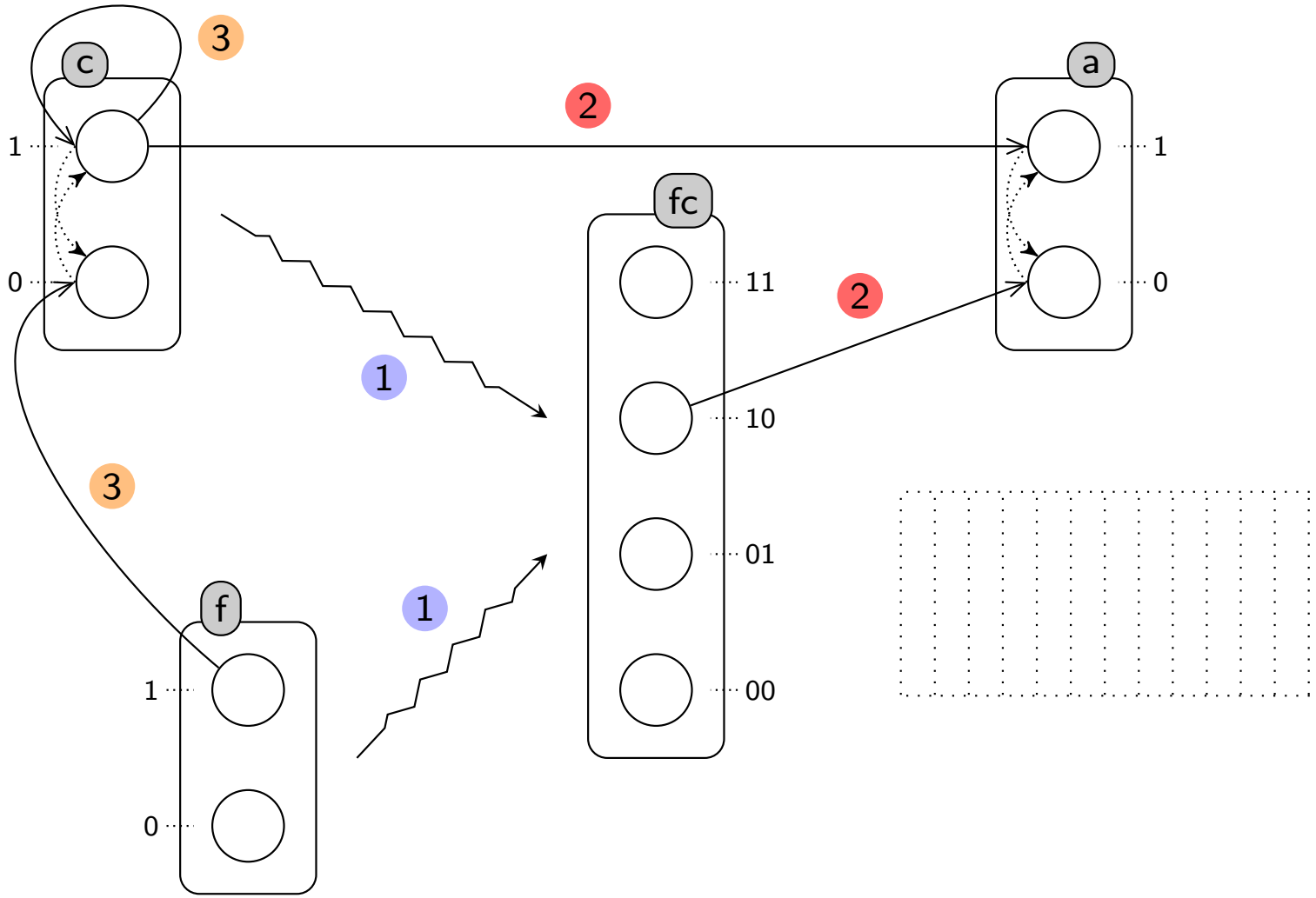

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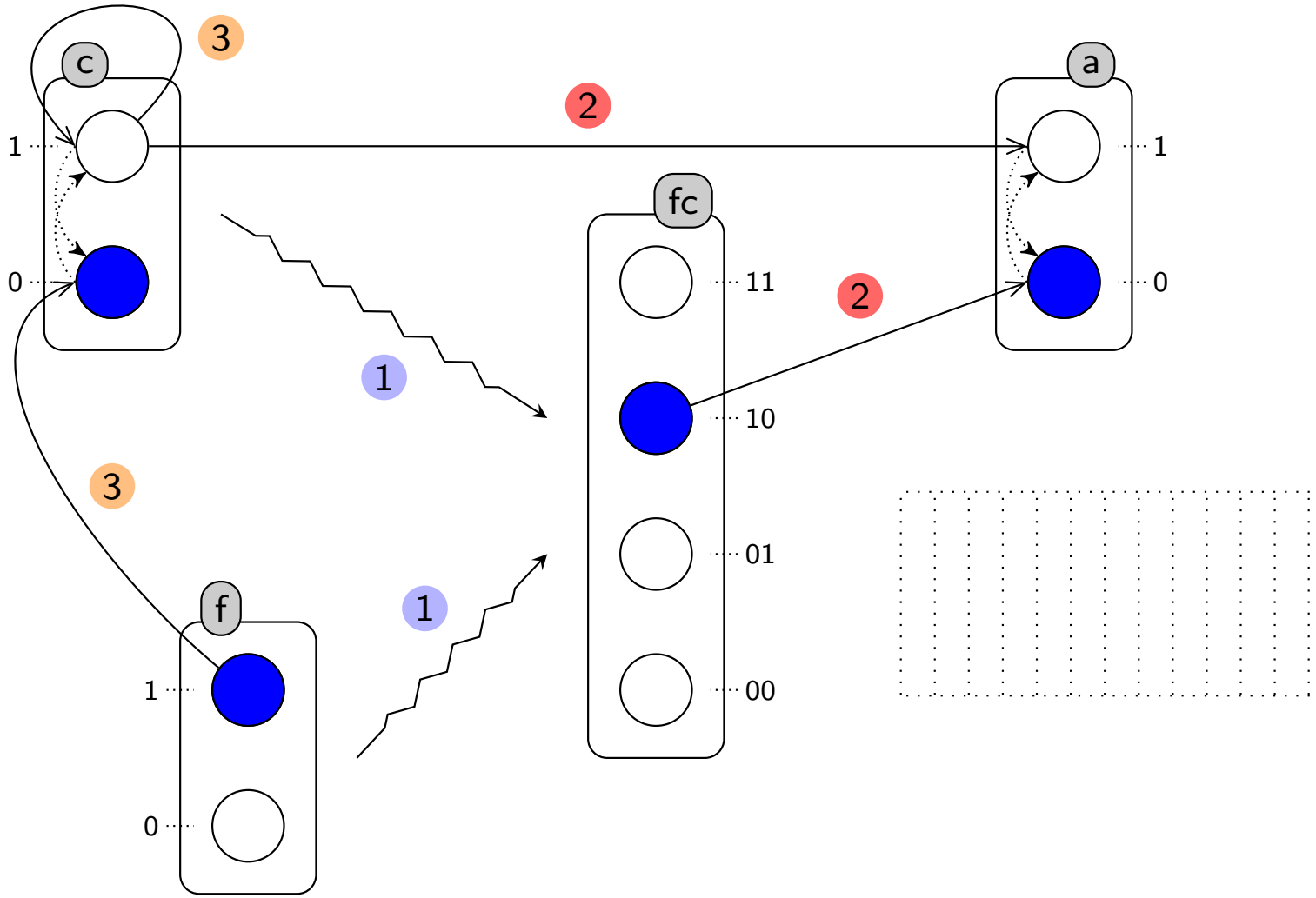

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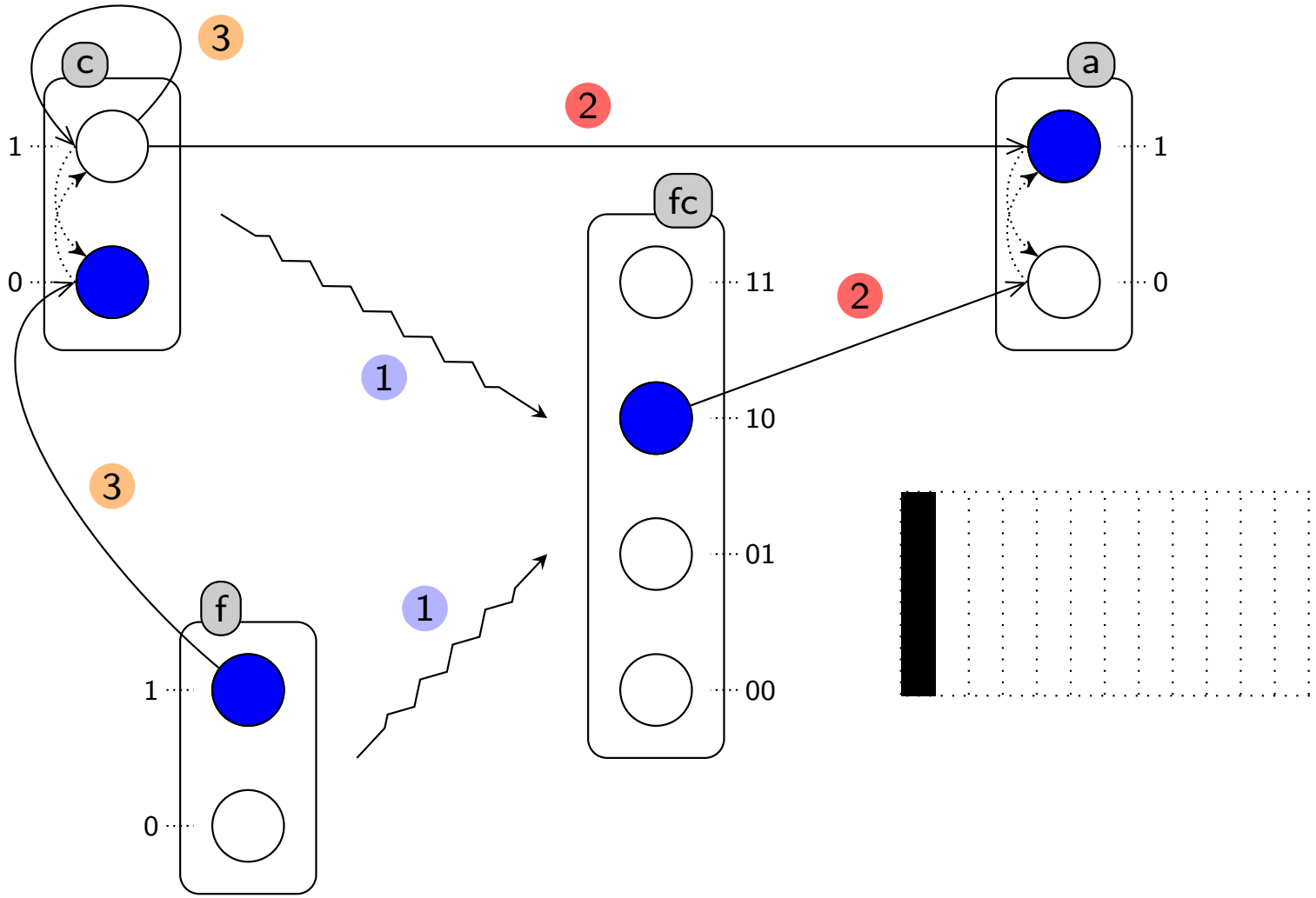

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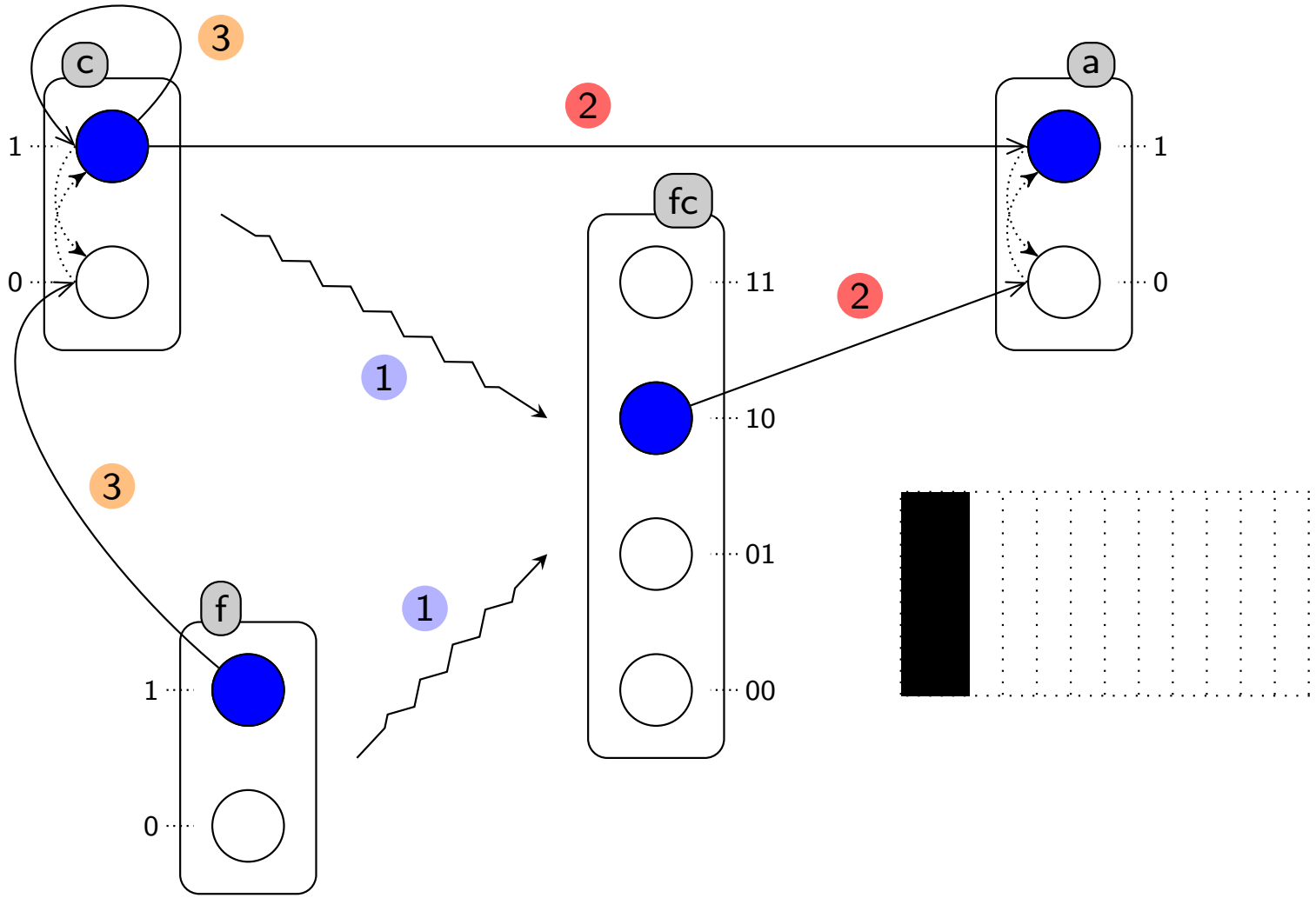

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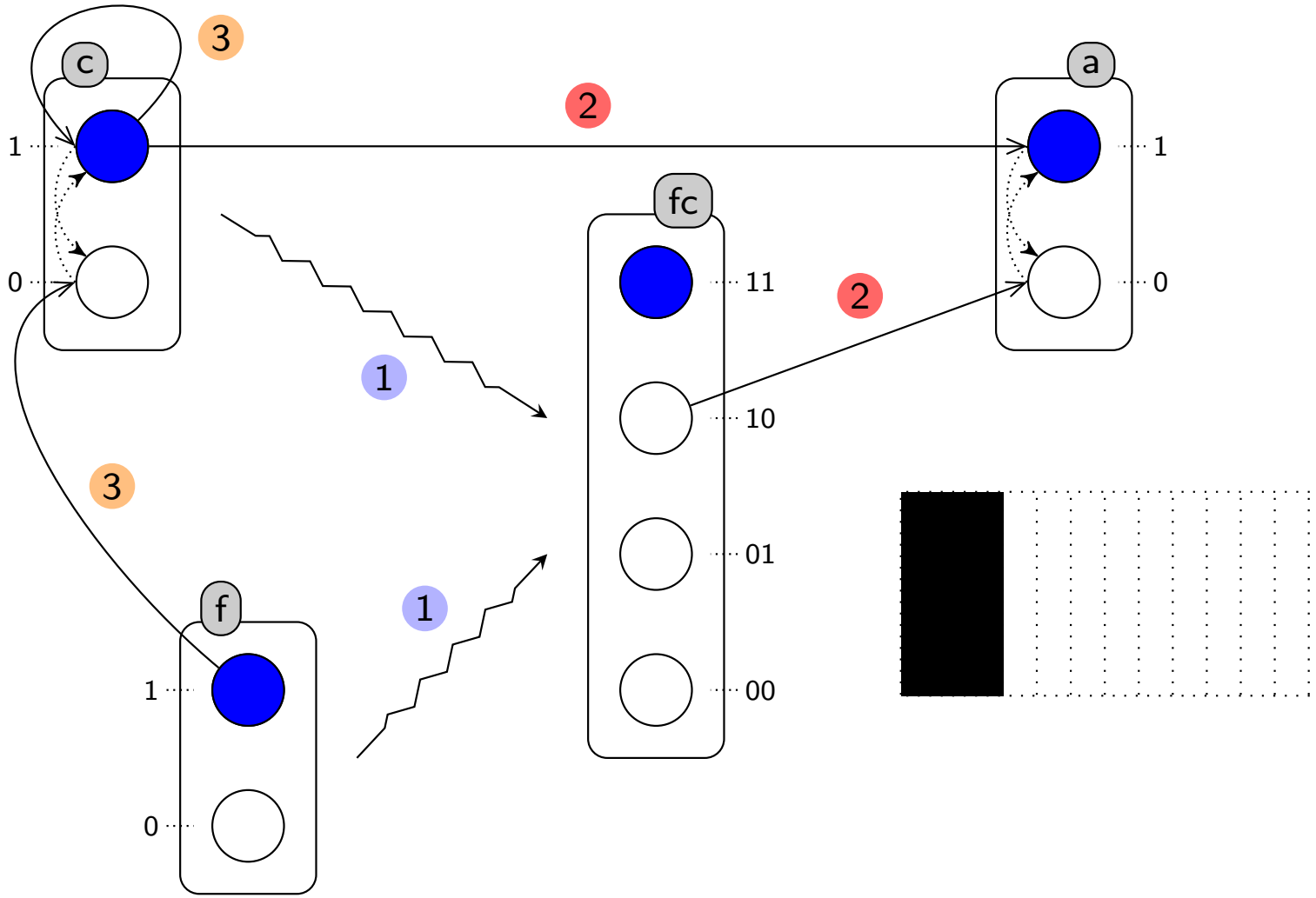

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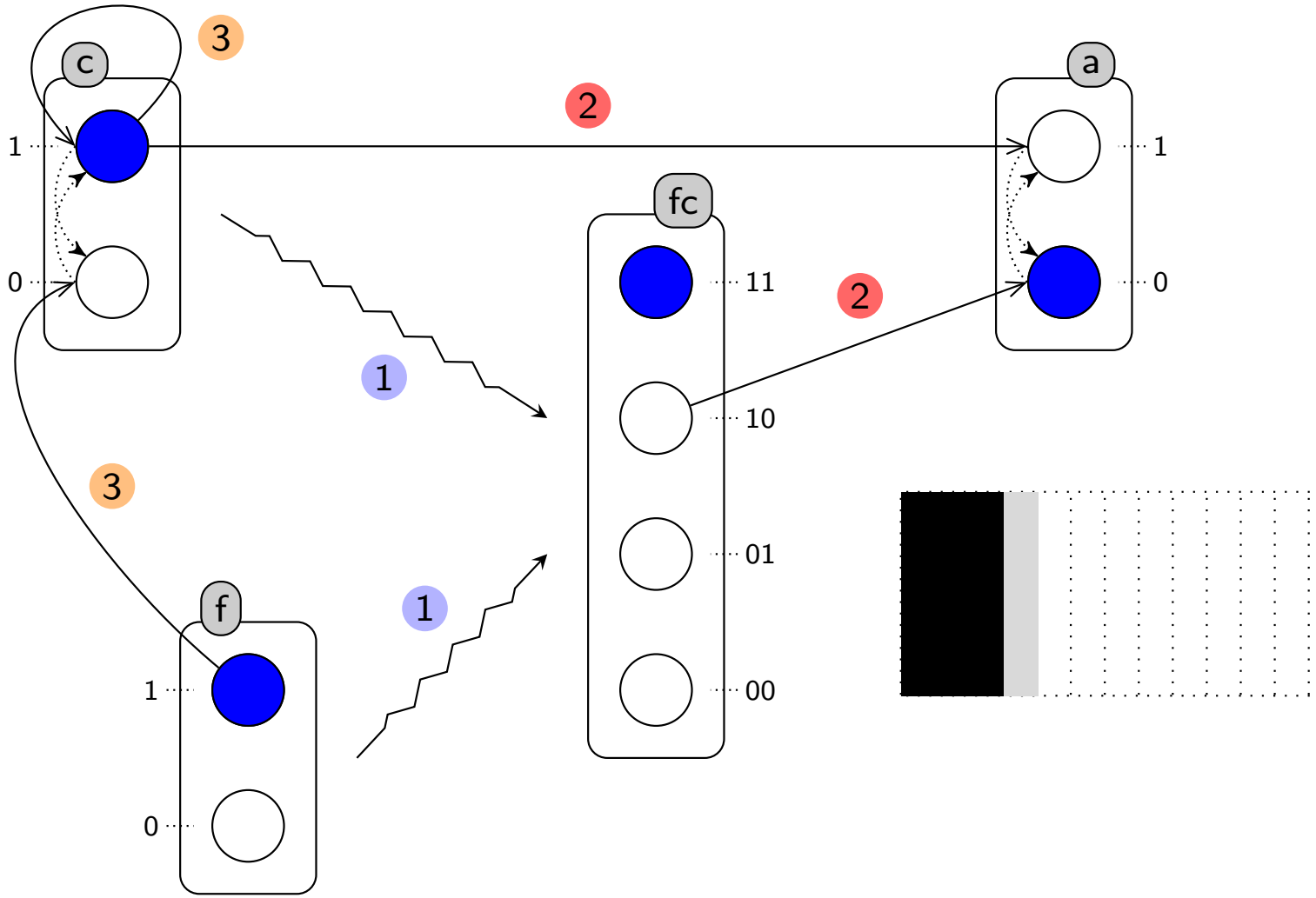

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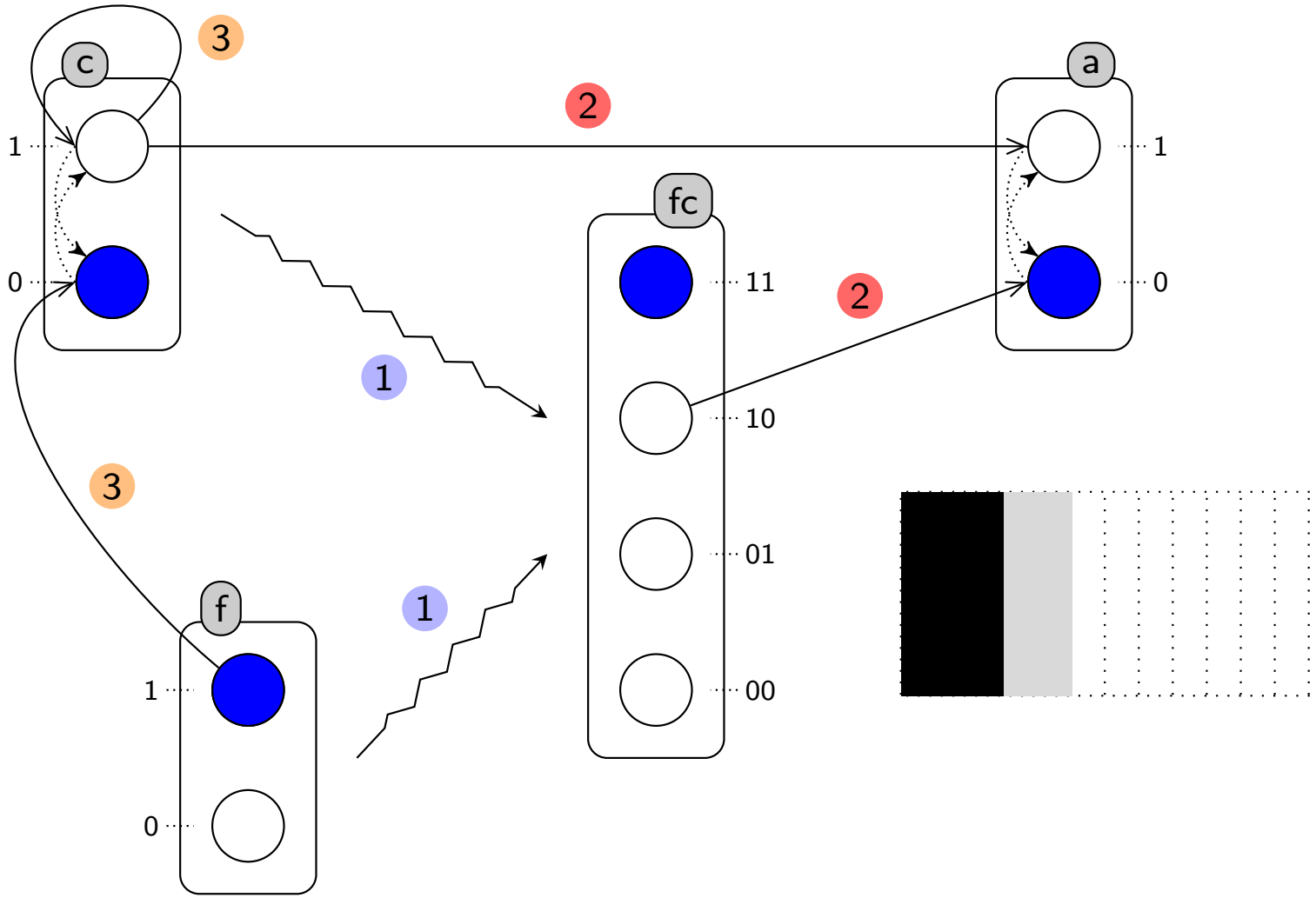

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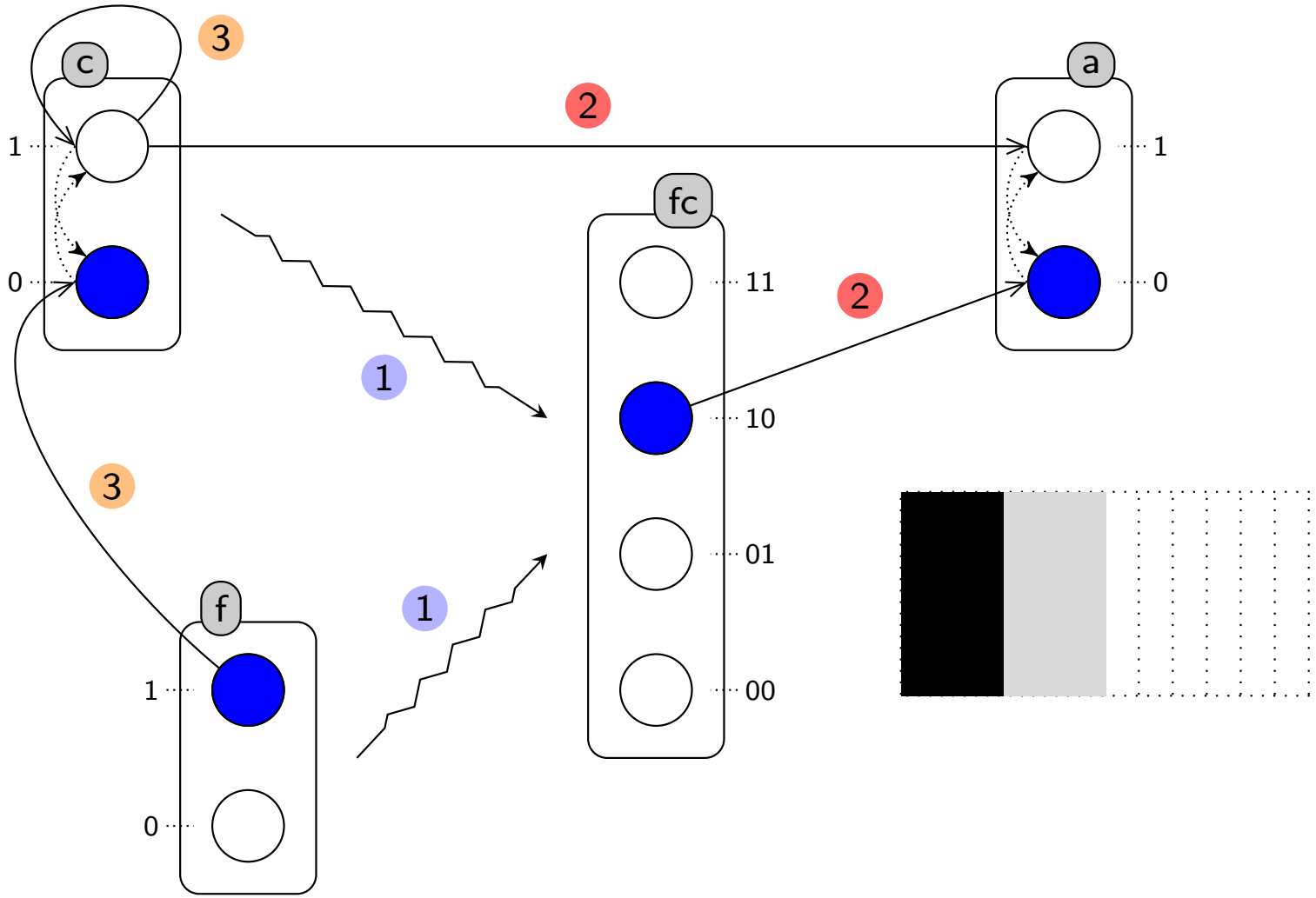

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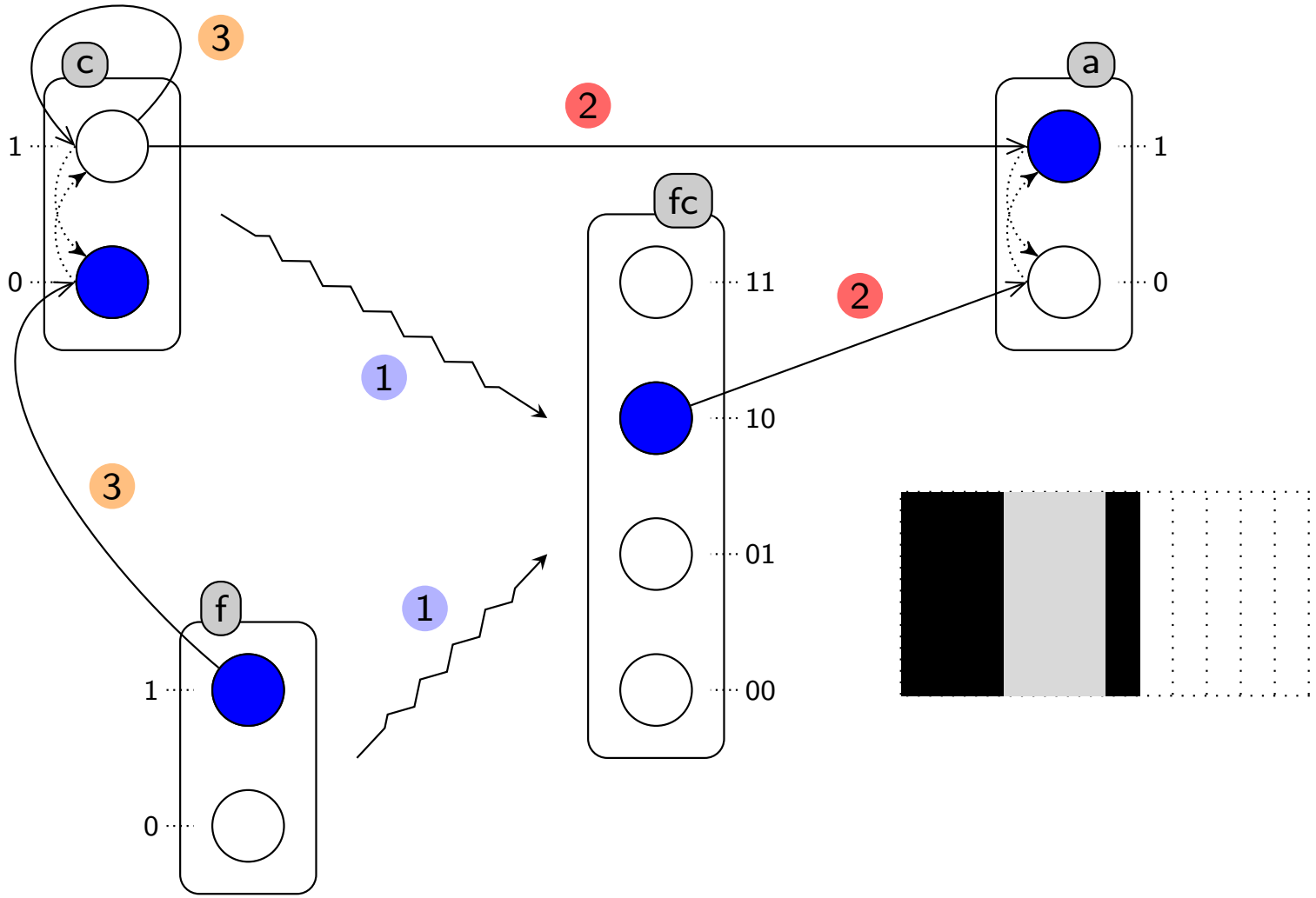

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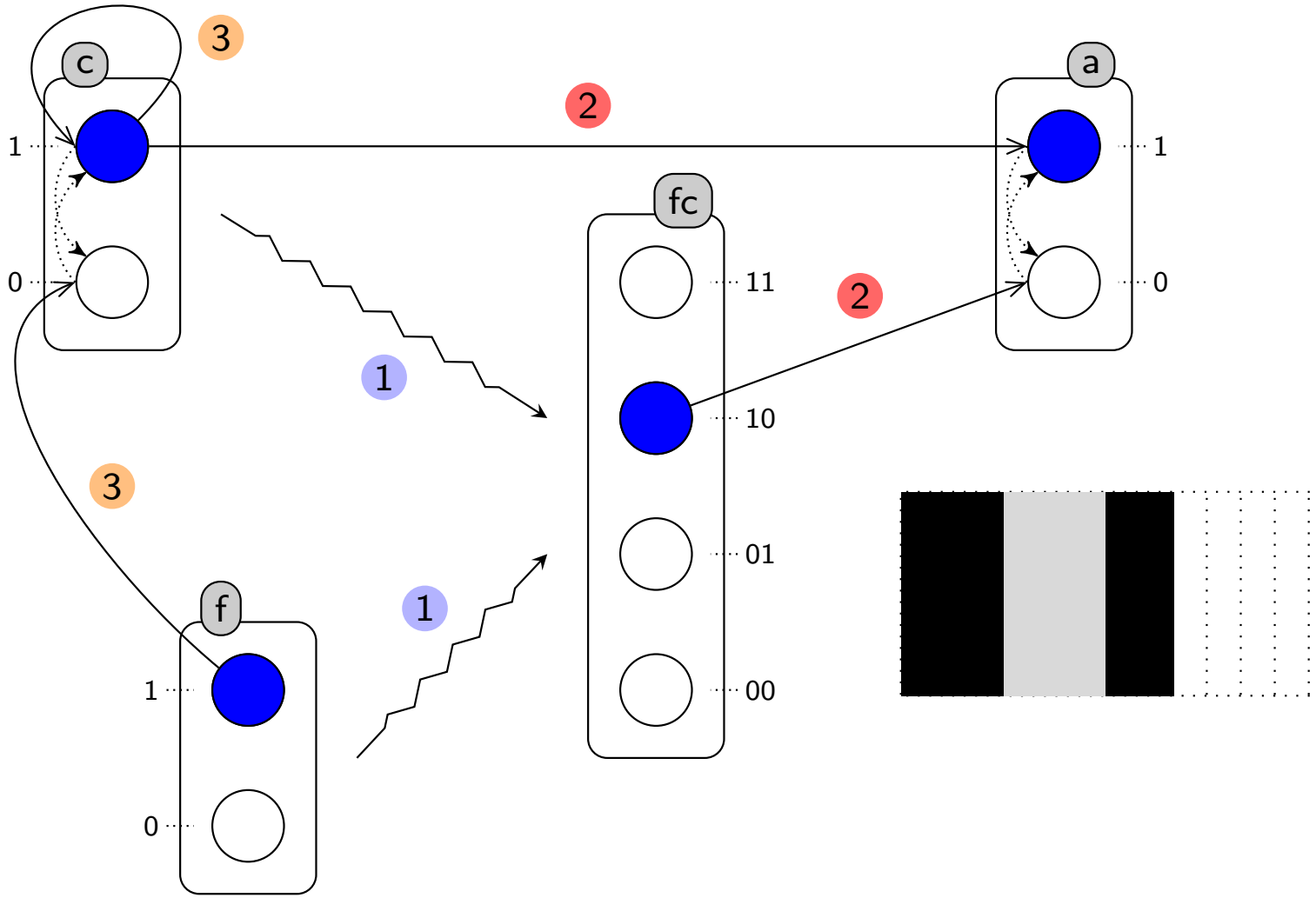

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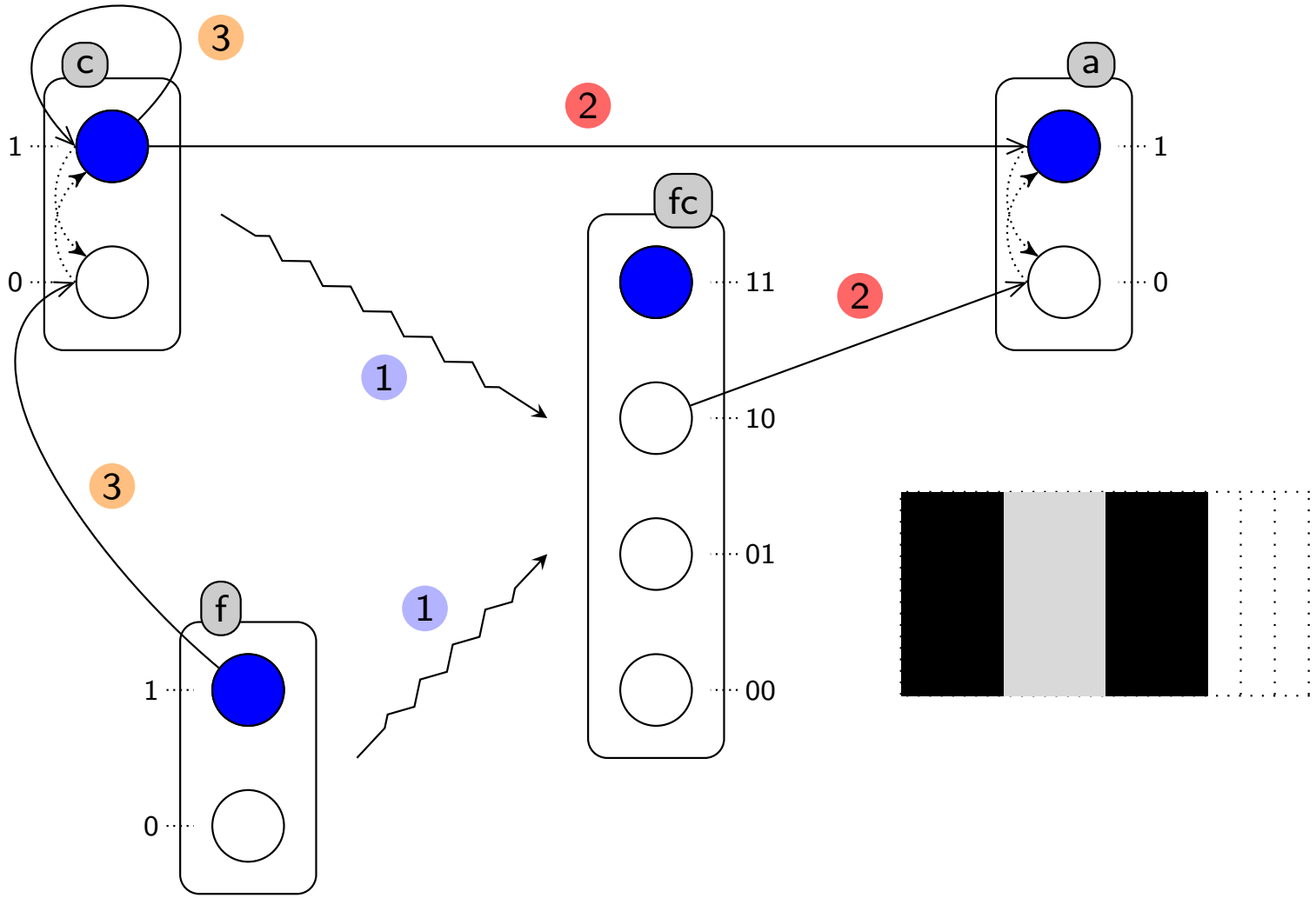

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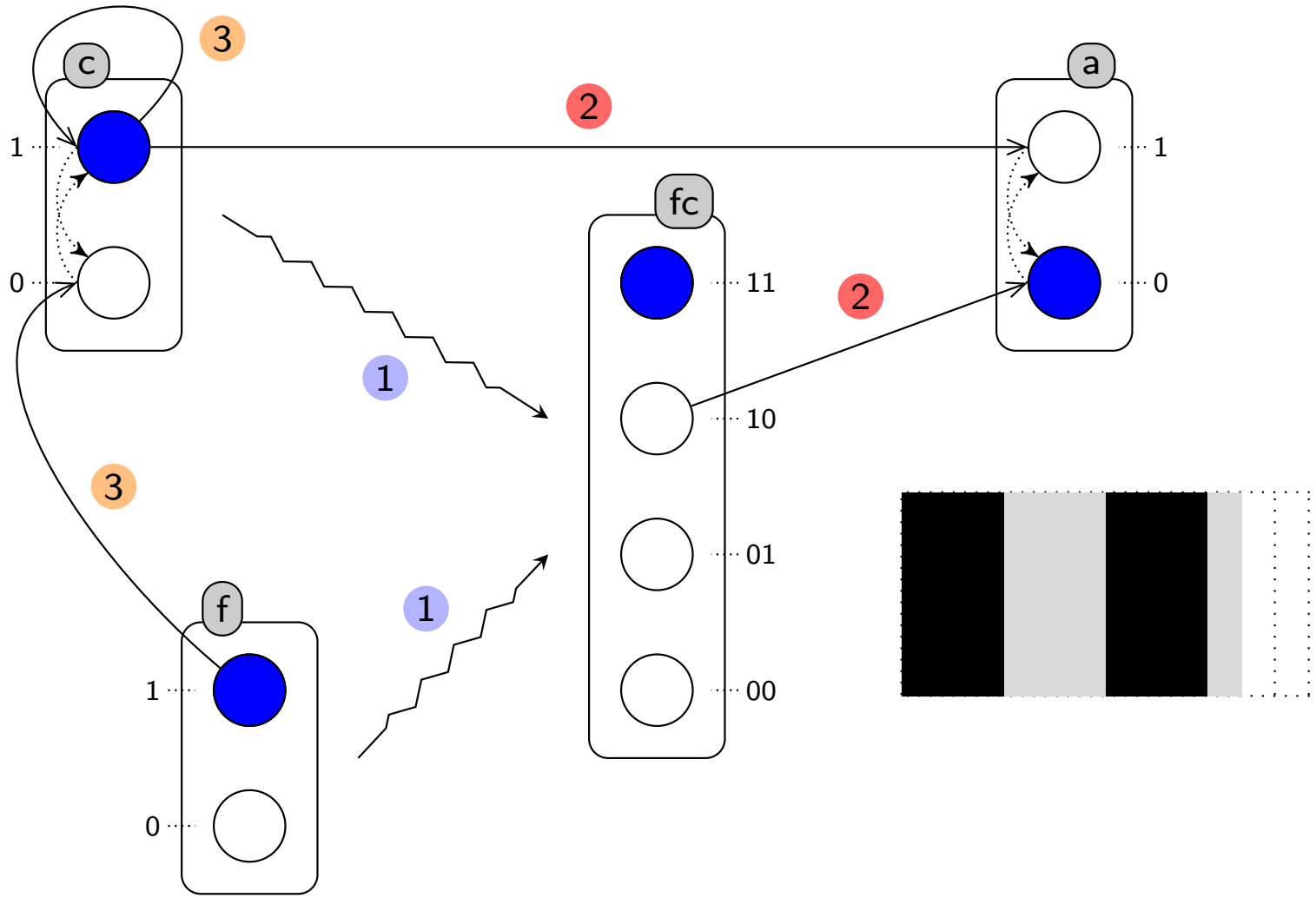

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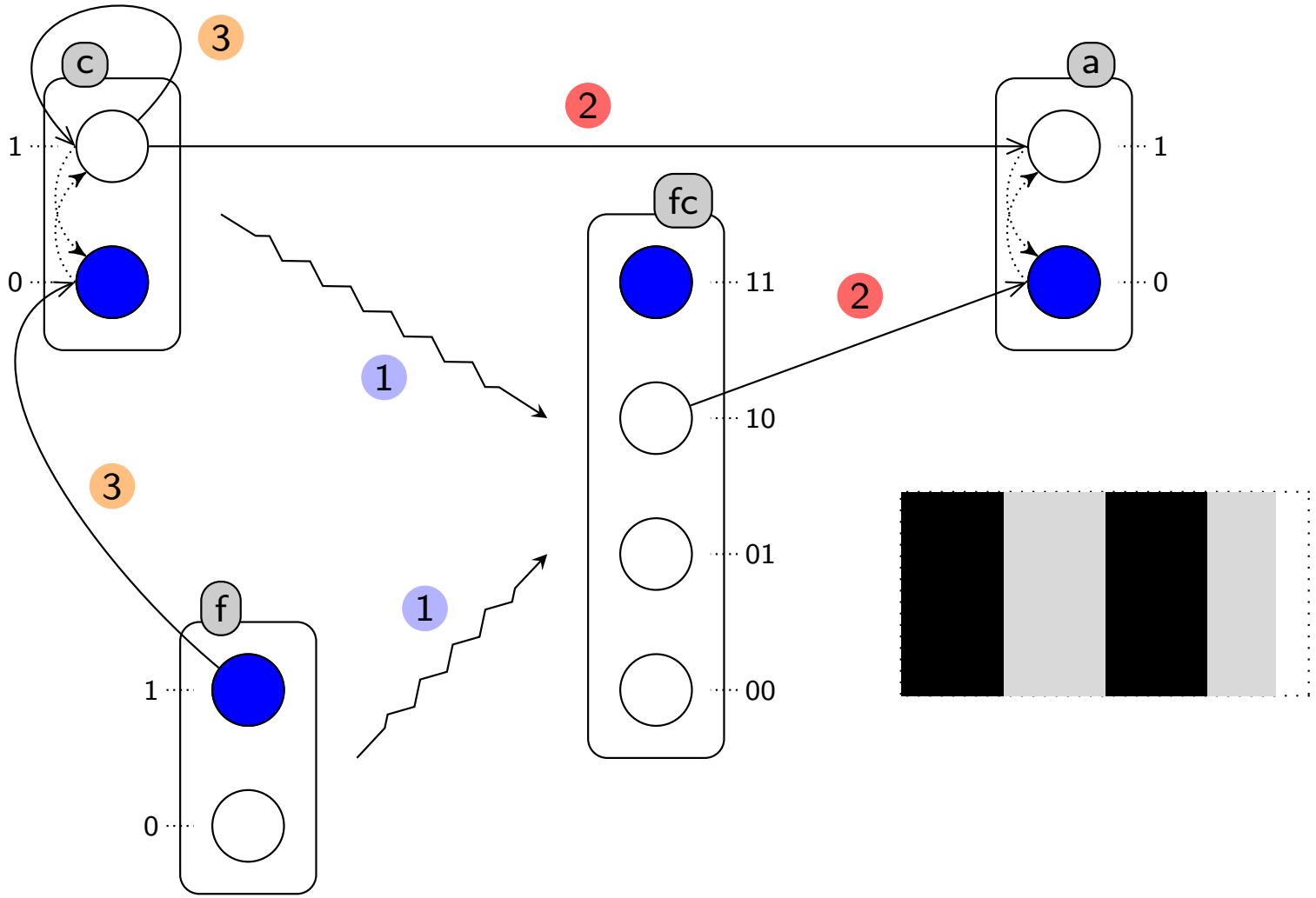

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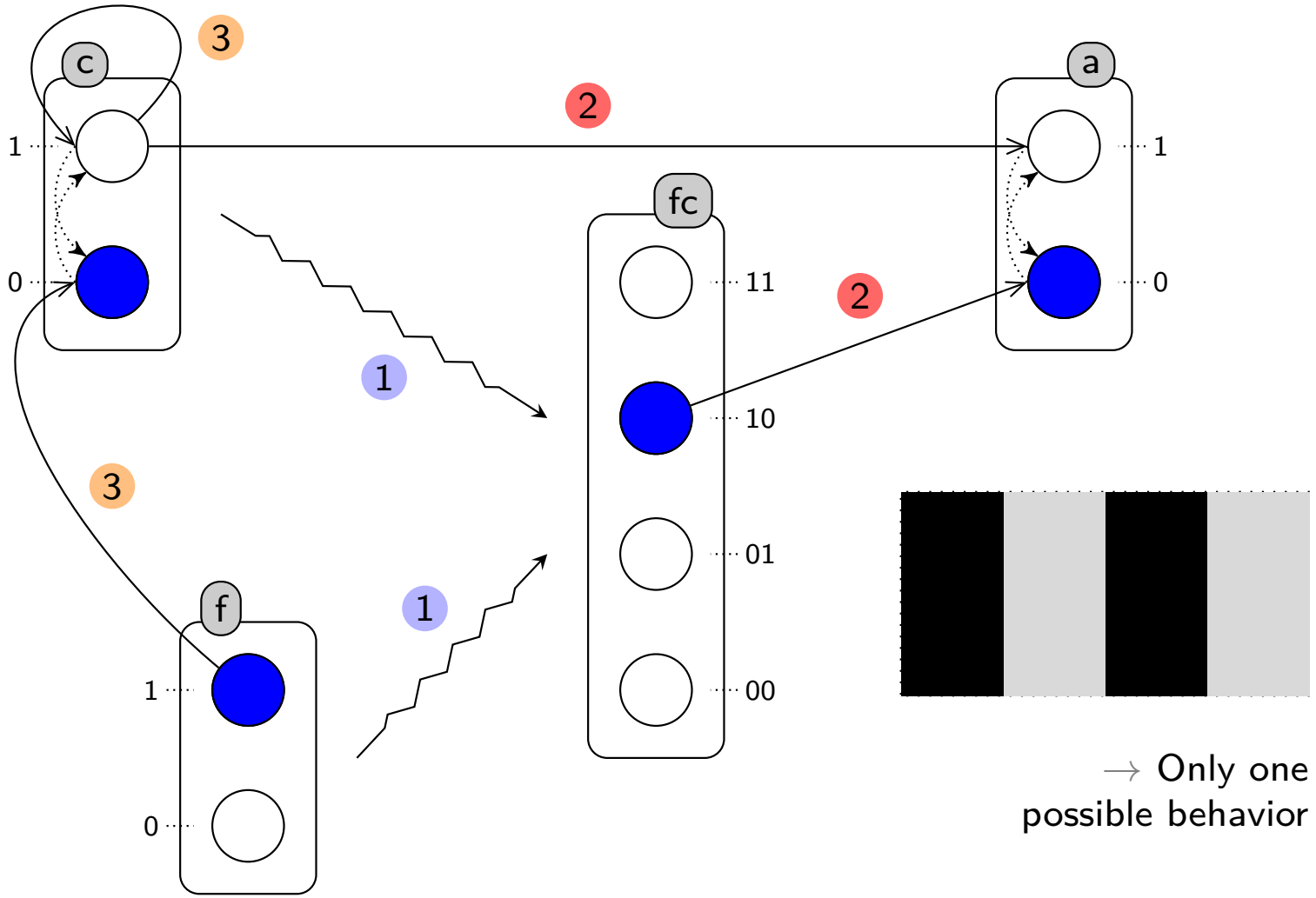
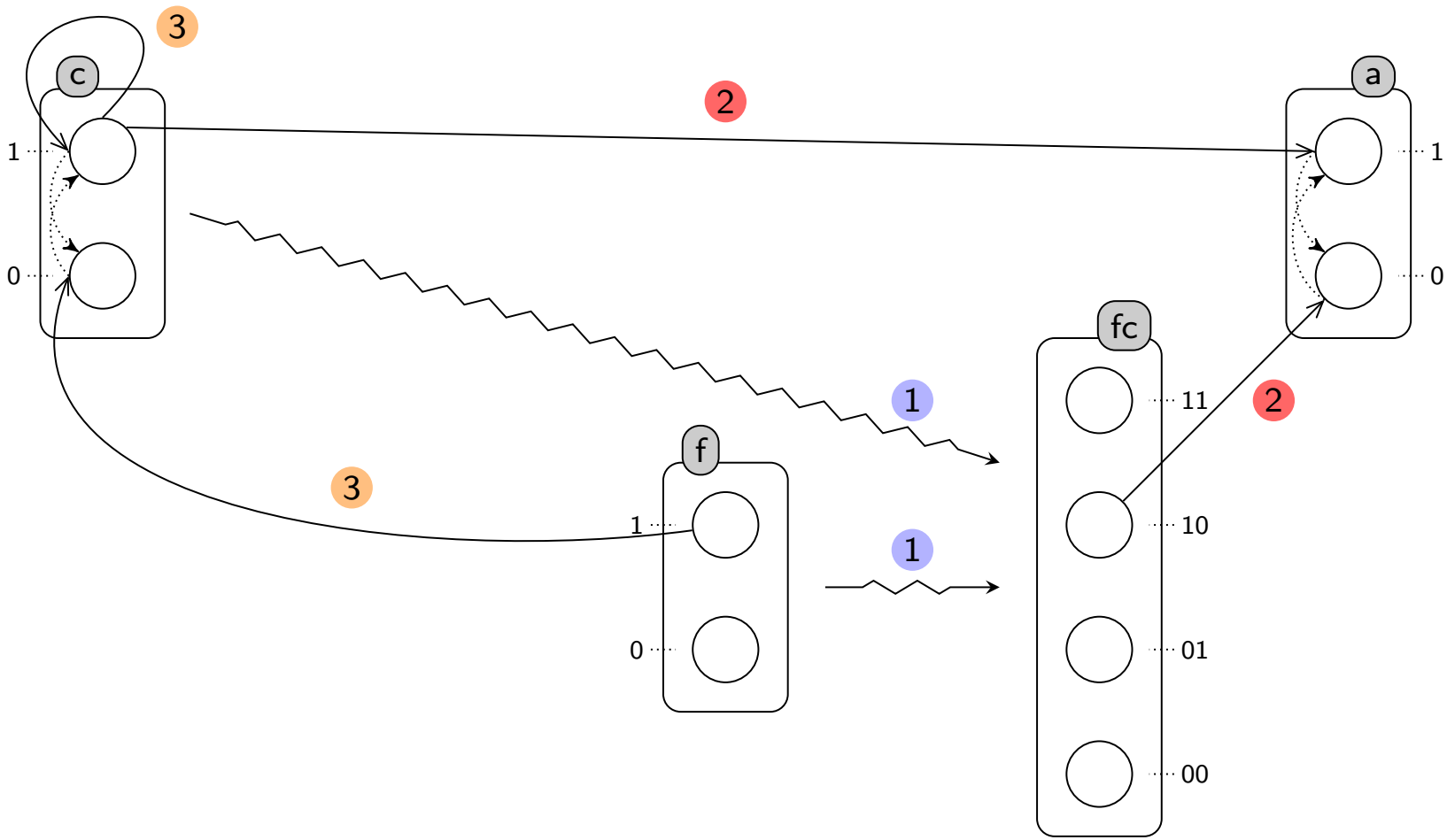


→ Only one possible behavior

Metazoan Segmentation in Canonical Form



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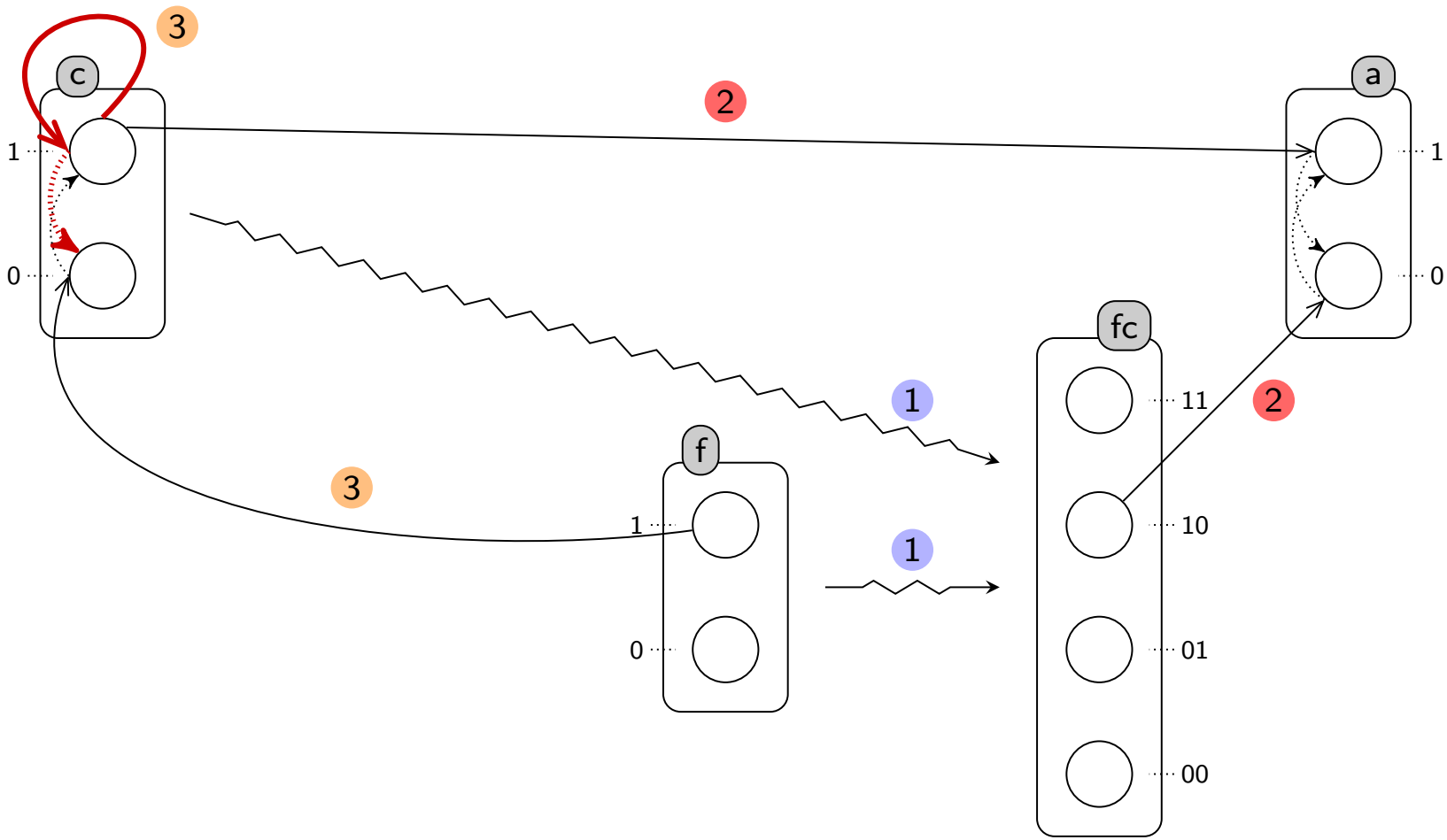

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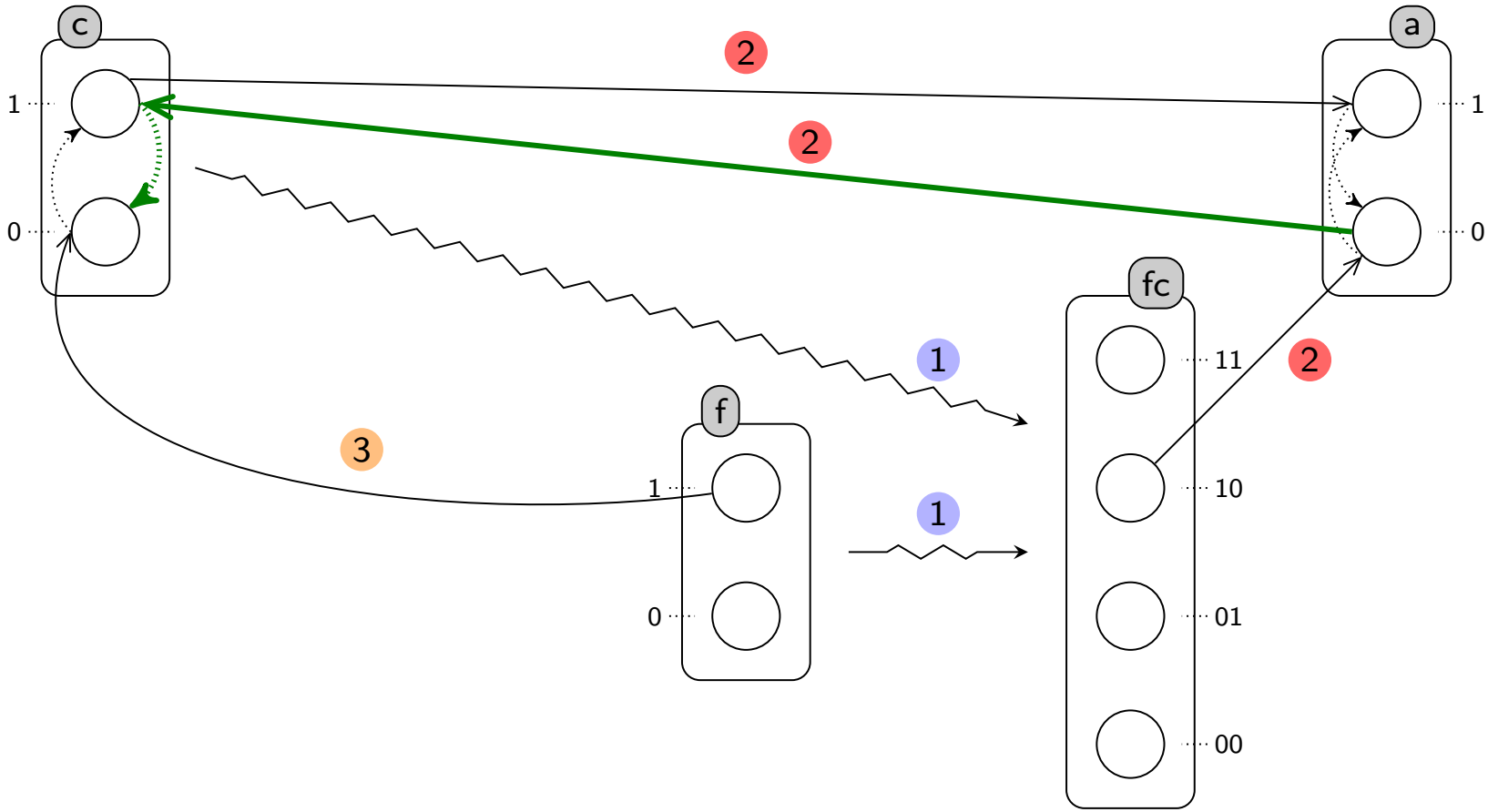

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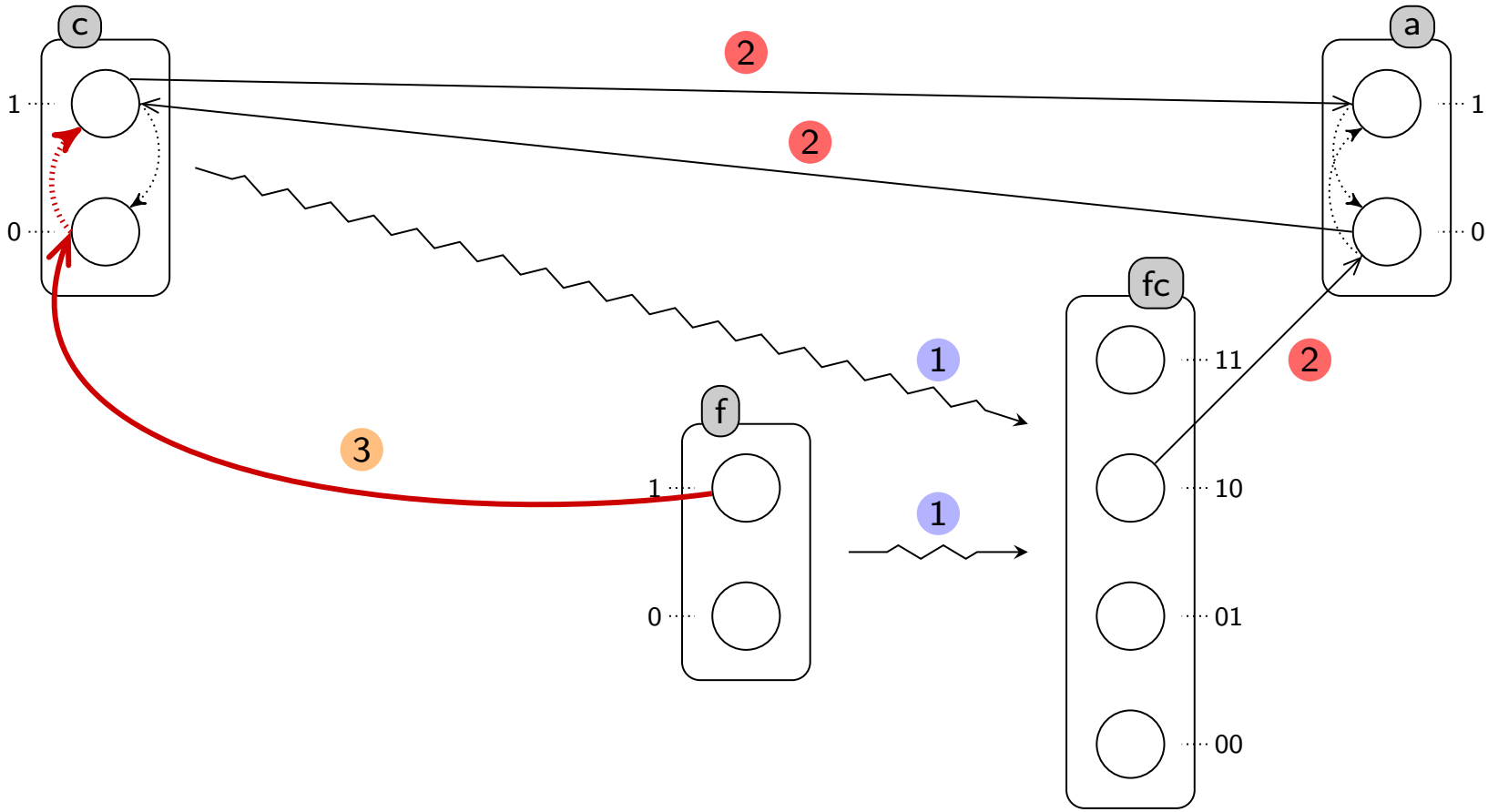

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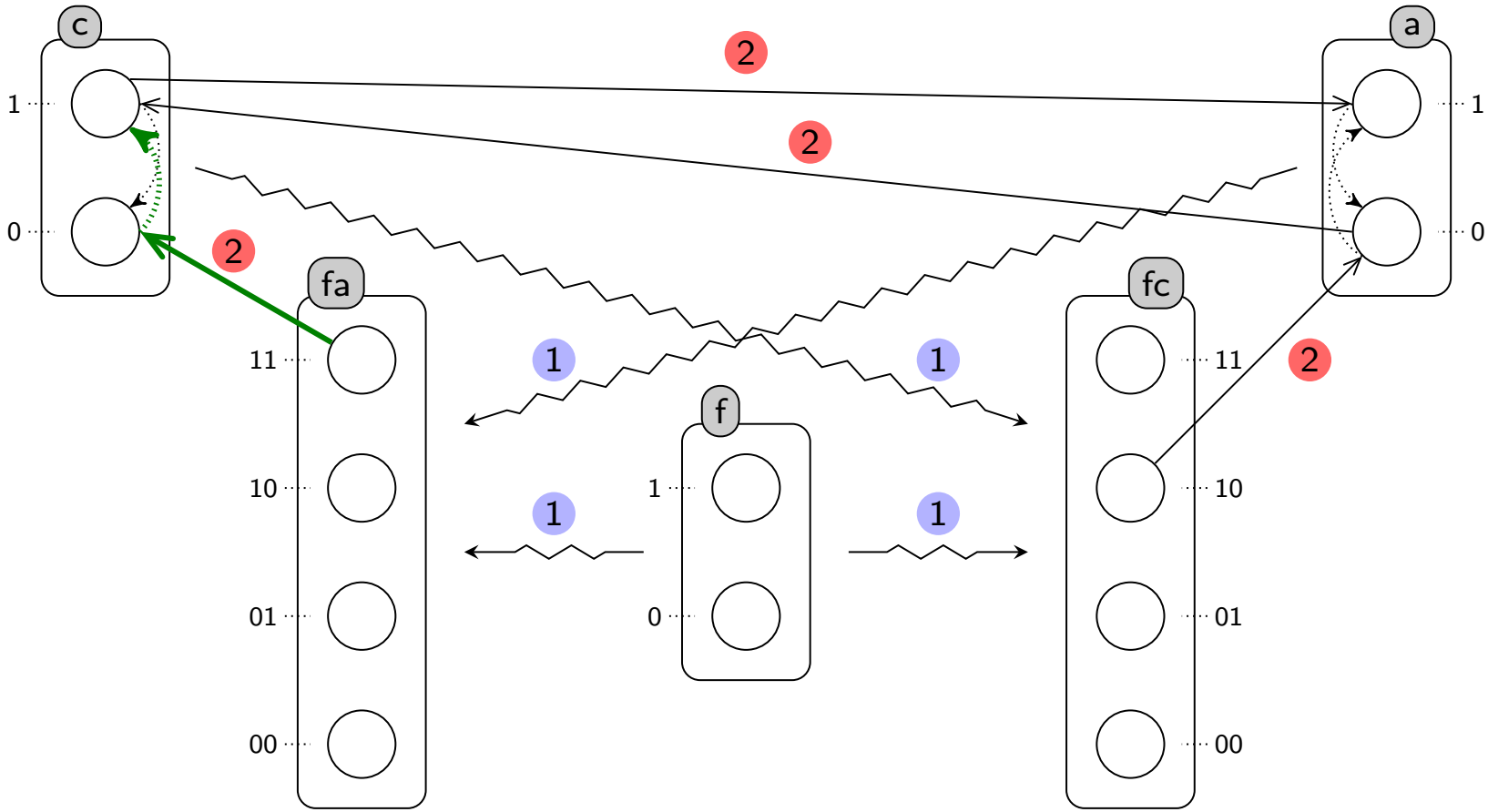

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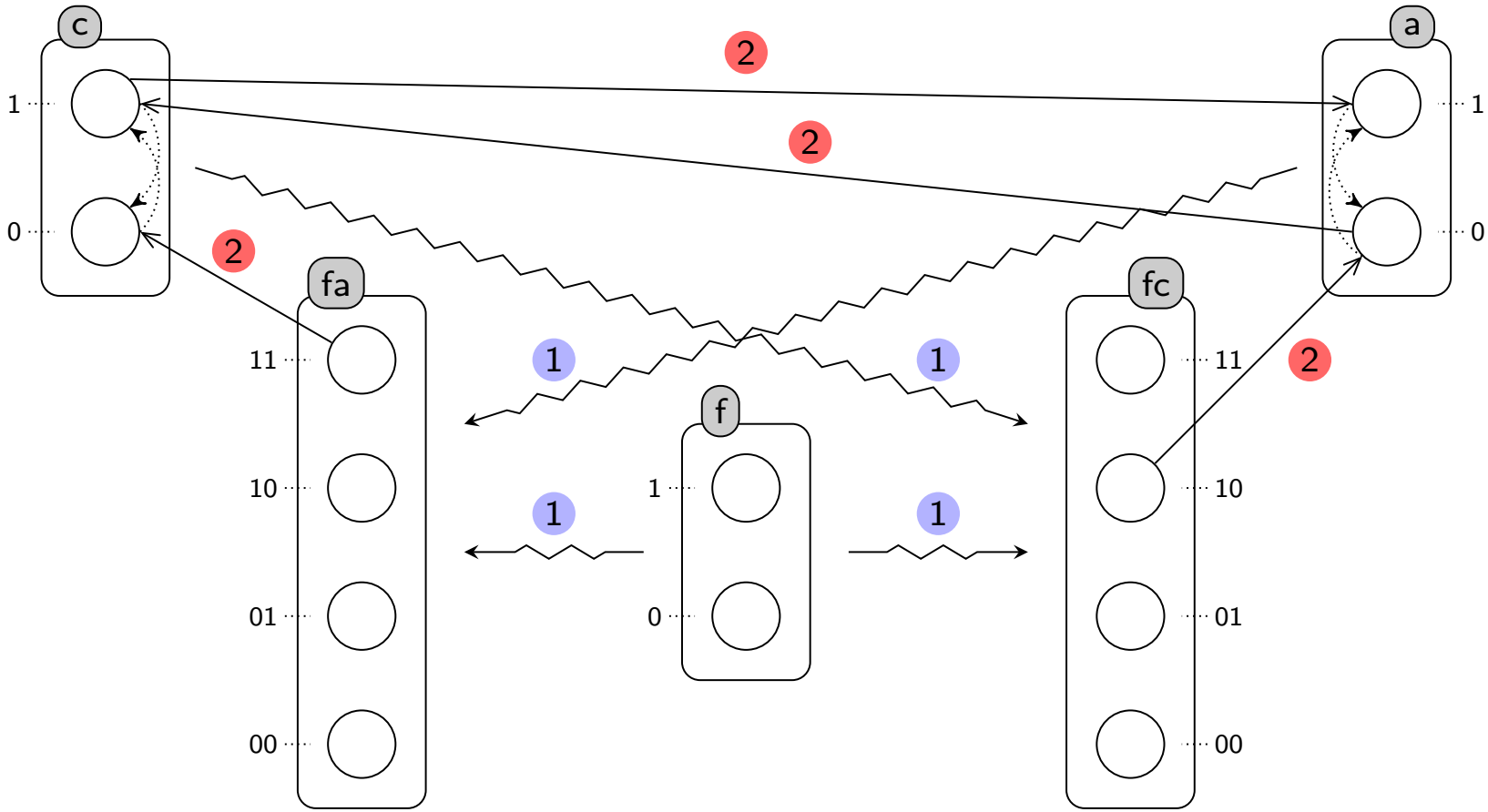


→ Same dynamics but only 2 priorities
→ Priority 1 is only for cooperative sorts

Pros and Cons of Classes of Priorities

Pros:

- Better expressivity (same as Boolean Networks!)
- Efficient static analysis

Model	Sorts	Procs	Actions	States	libddd[1]	PINT
tcrsig94	133	448	1124	2^{194}	∞	**0.008s – 0.060s**

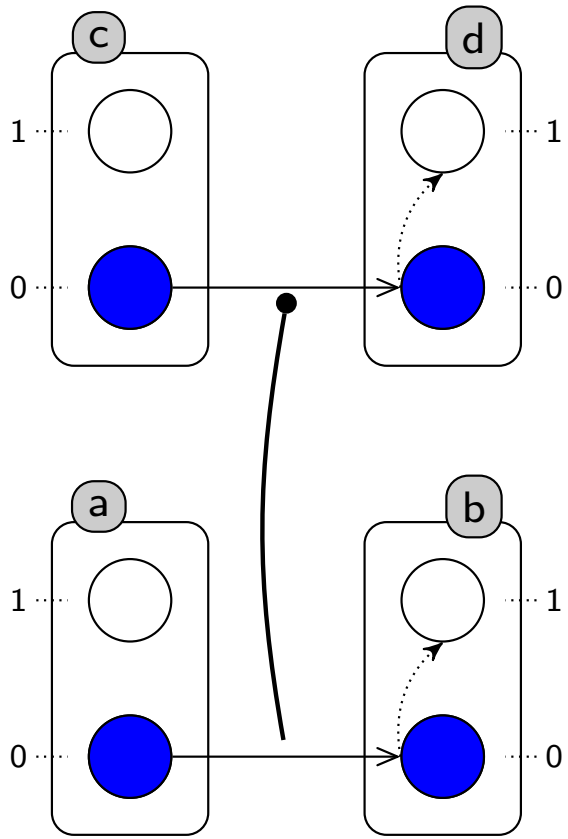
[1] LIP6/Move

tcrsig94: [T-Cell Receptor Signaling, by Julio Saez-Rodriguez *et al.*]
(Here with prioritized cooperative sorts)

Cons:

- No accumulation phenomenons
  Contrary to stochastic simulation
- Translation to canonical form is exponential
  → For each action of priority n, exponential in the number of actions of priority $[\![2; n-1]\!]$

Neutralizing Edges

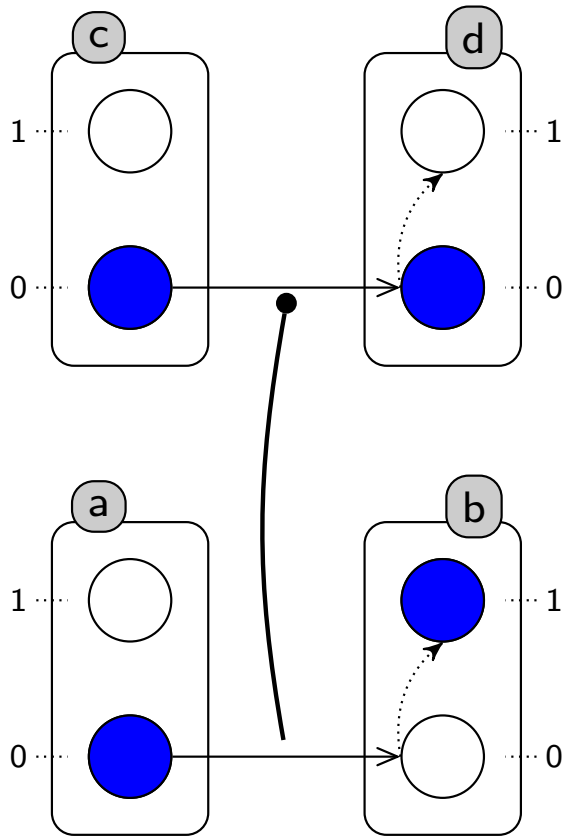


$c_0 \rightarrow d_0 \nearrow d_1$ cannot be played **while**

$a_0 \rightarrow b_0 \nearrow b_1$ is playable

$\rightarrow$ Here, only one possible behavior

Neutralizing Edges



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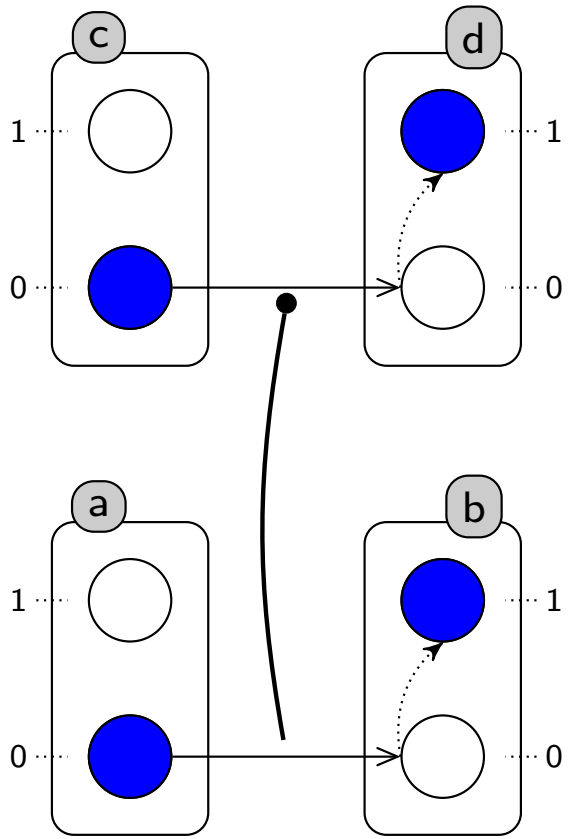

$c_0 \rightarrow d_0 \Rsh d_1$ cannot be played **while**

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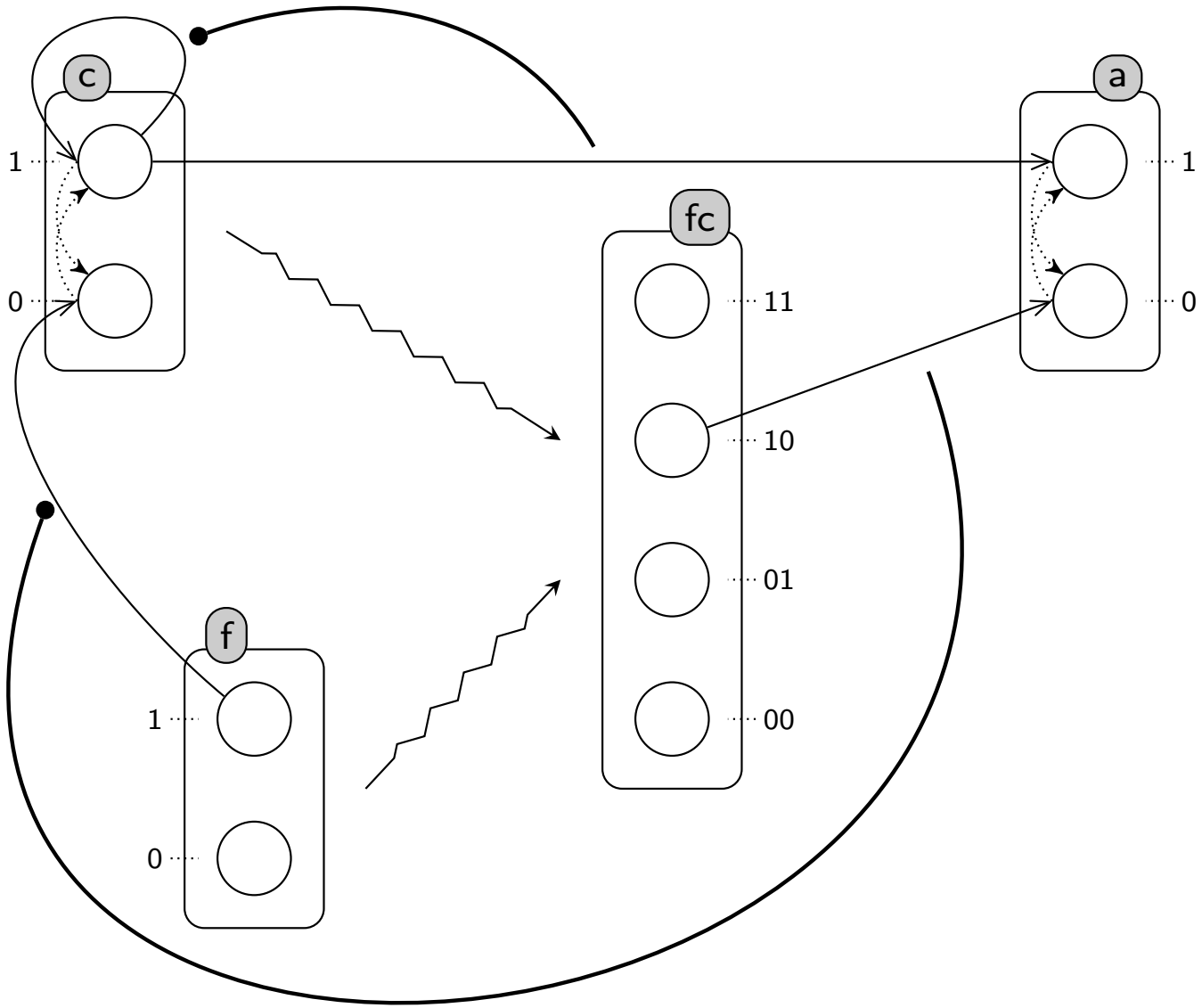
Metazoan Segmentation with Neutralizing Edges



Pros and Cons of Neutralizing Edges

Pros:

- Same expressivity than Priorities
  - → Can be translated to the canonical form
- Finer preemption relations
  - → Easier modeling in some cases
- Sparser constraints
  - → More efficient translation to canonical form

Summary & Conclusion

Process Hitting: an atomistic modeling with powerful static analysis

1. Stochastic parameters:
   - To model systems with chronometric features
   - **Continuous time**
   - But **hard to analyze**
2. Classes of priorities:
   - Allows to reproduce the same behaviors
   - Efficient **static analysis**
   - But the translation to canonical form faces **combinatorial explosion**
3. Neutralizing edges:
   - Alternative to priorities
   - Closer to reality in some cases
   - **Lighter translation** to canonical form

Thank you

Bibliography

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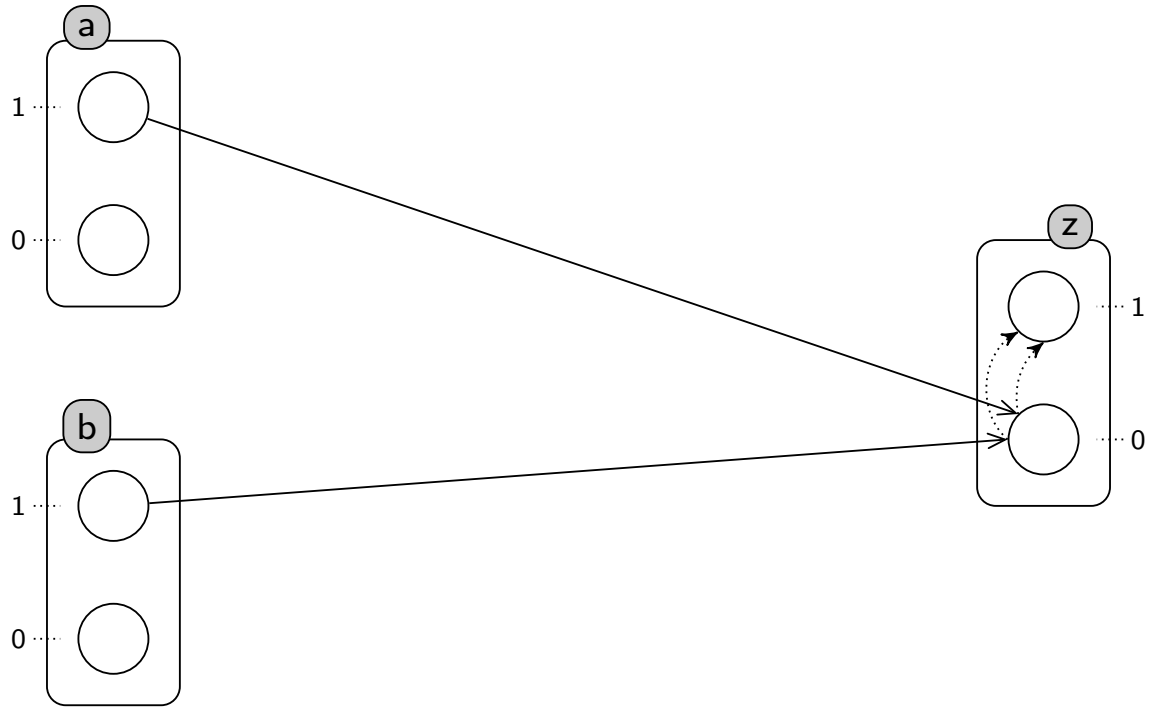
Adding cooperations

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

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

Adding cooperations

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



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

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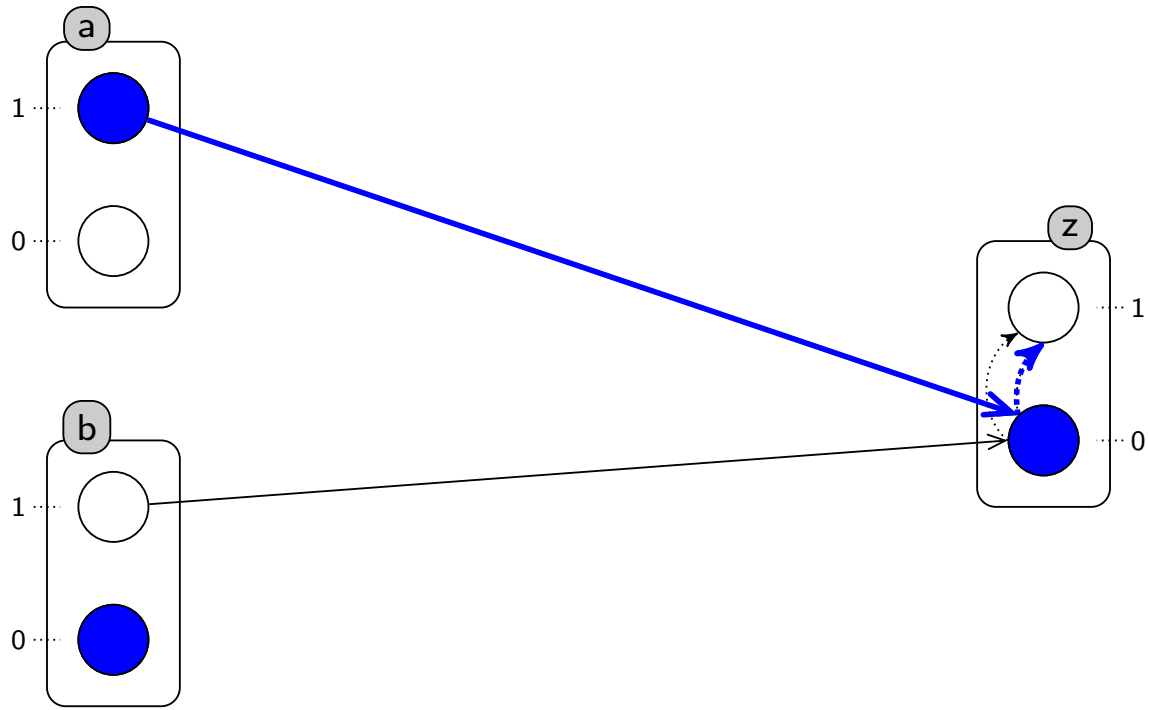

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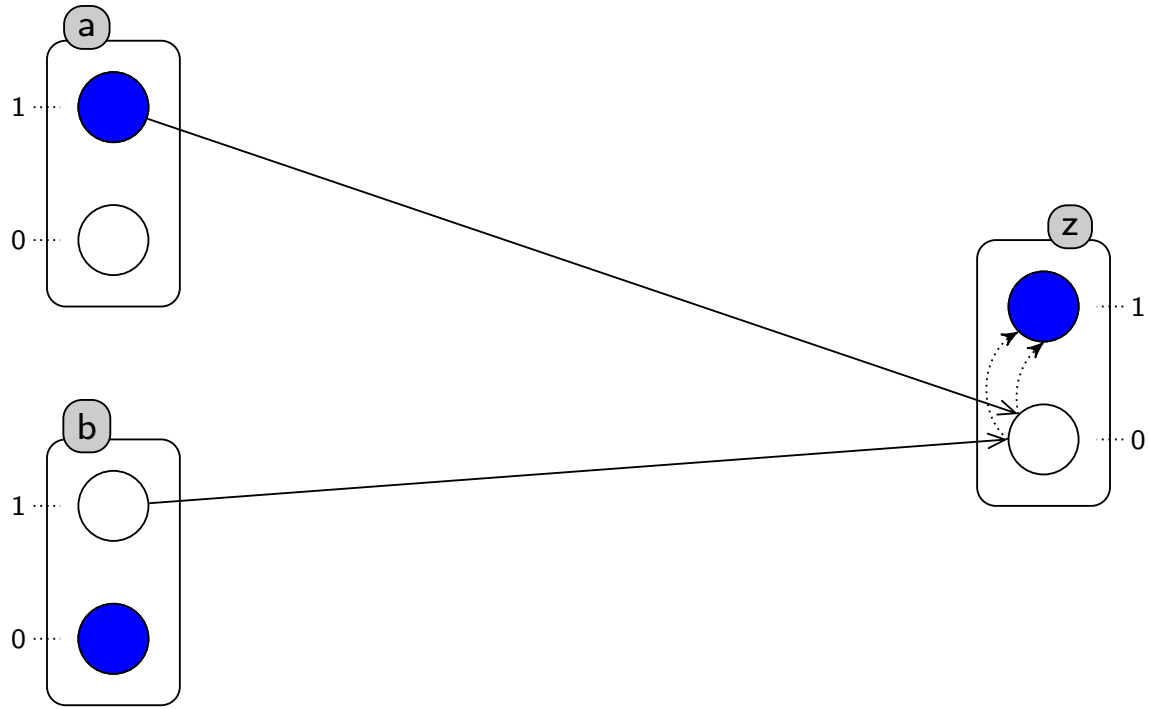

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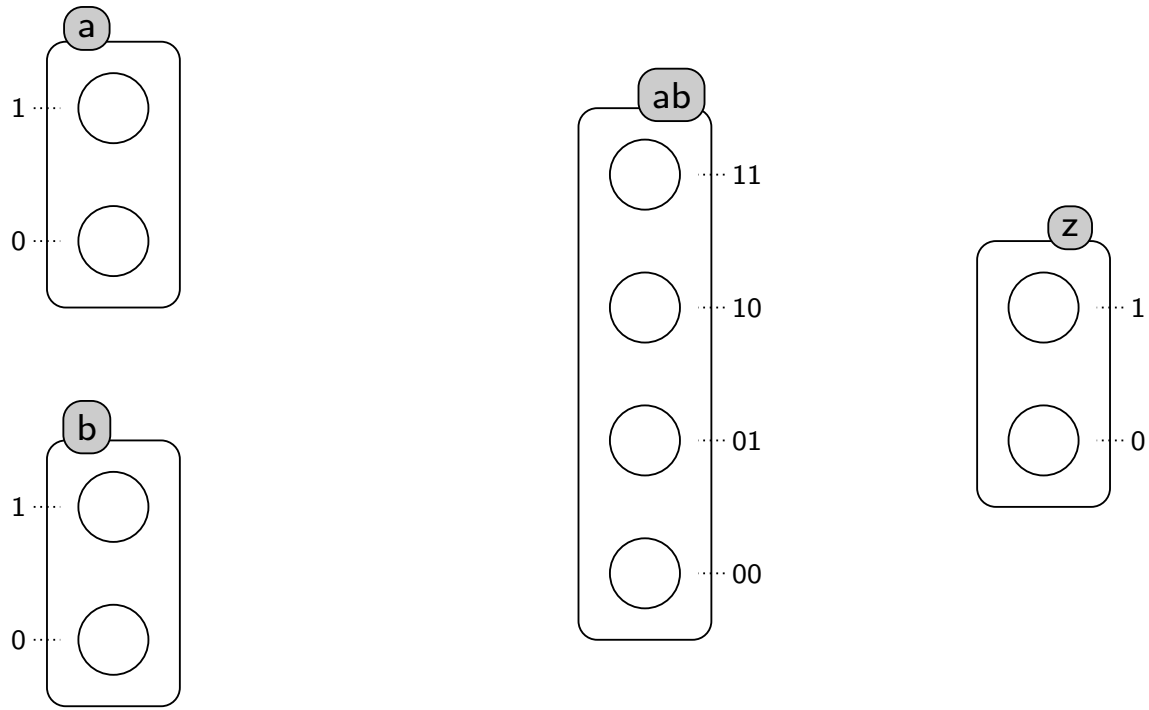
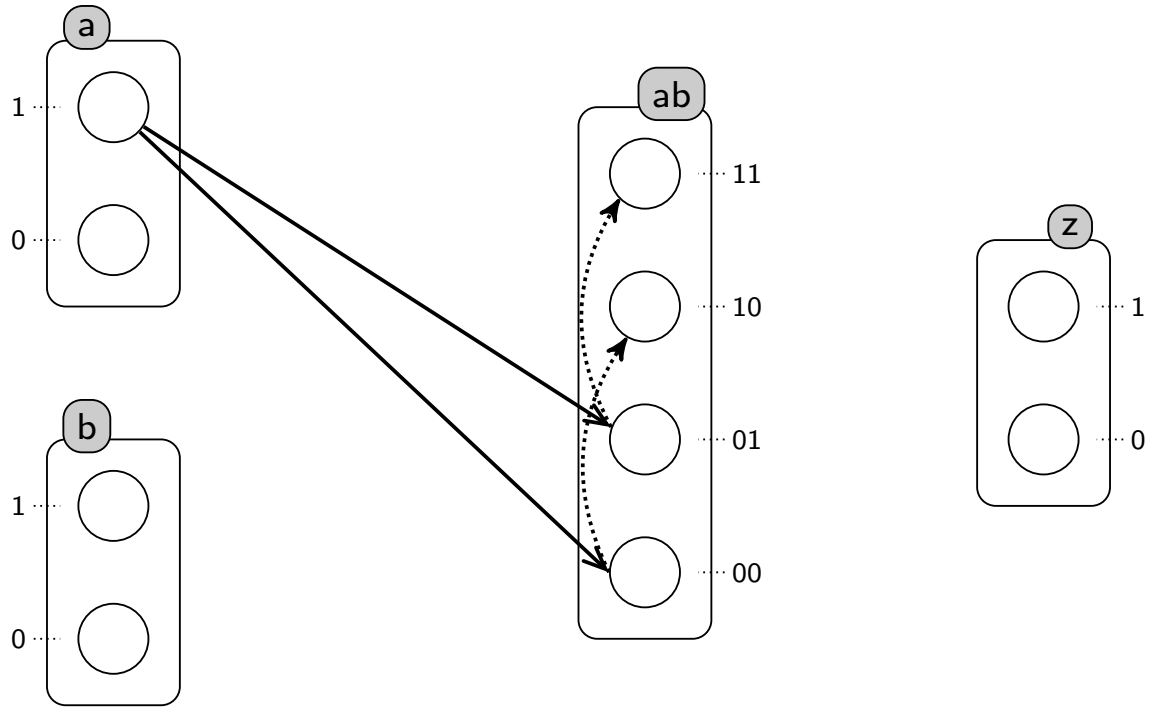


Cooperation between a_1 and b_1: $\underline{a_1 \wedge b_1} \rightarrow z_0 \Rsh z_1$

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

Adding cooperations

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



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

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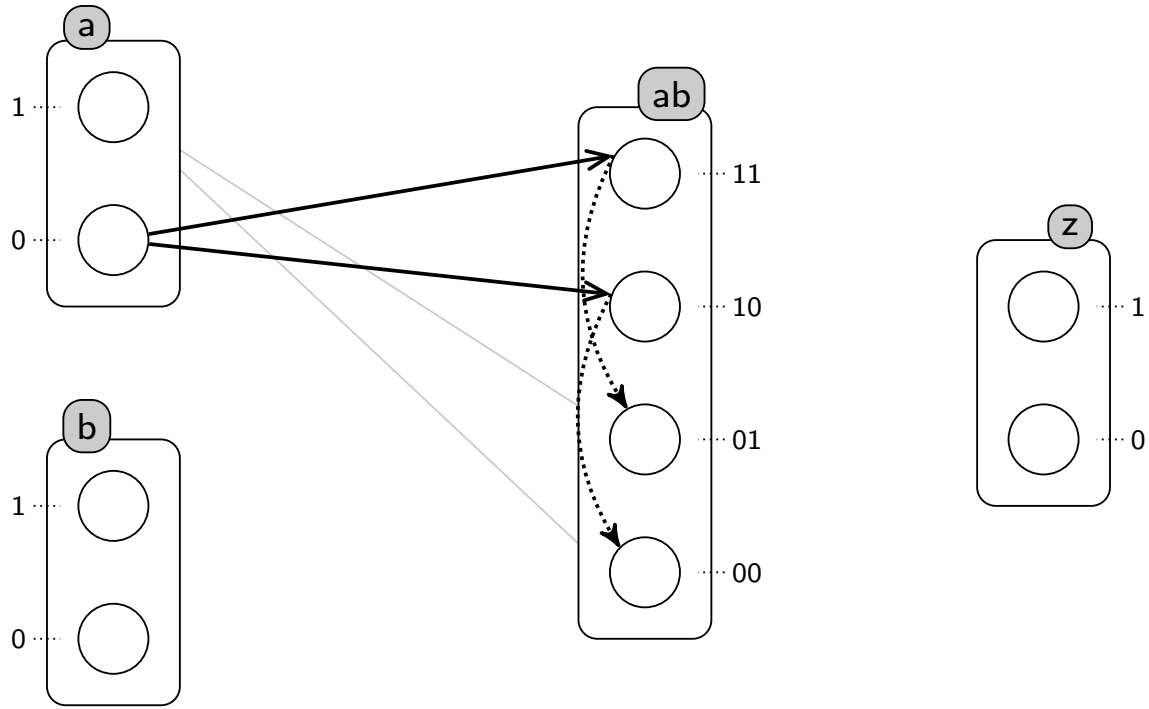

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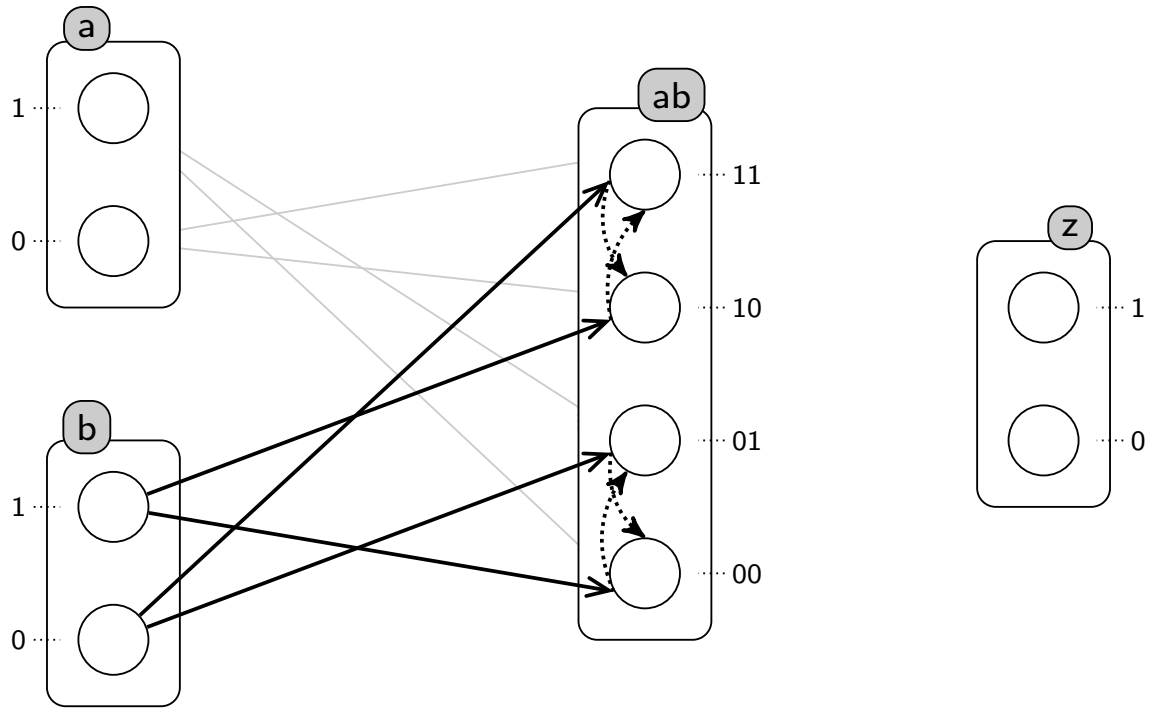

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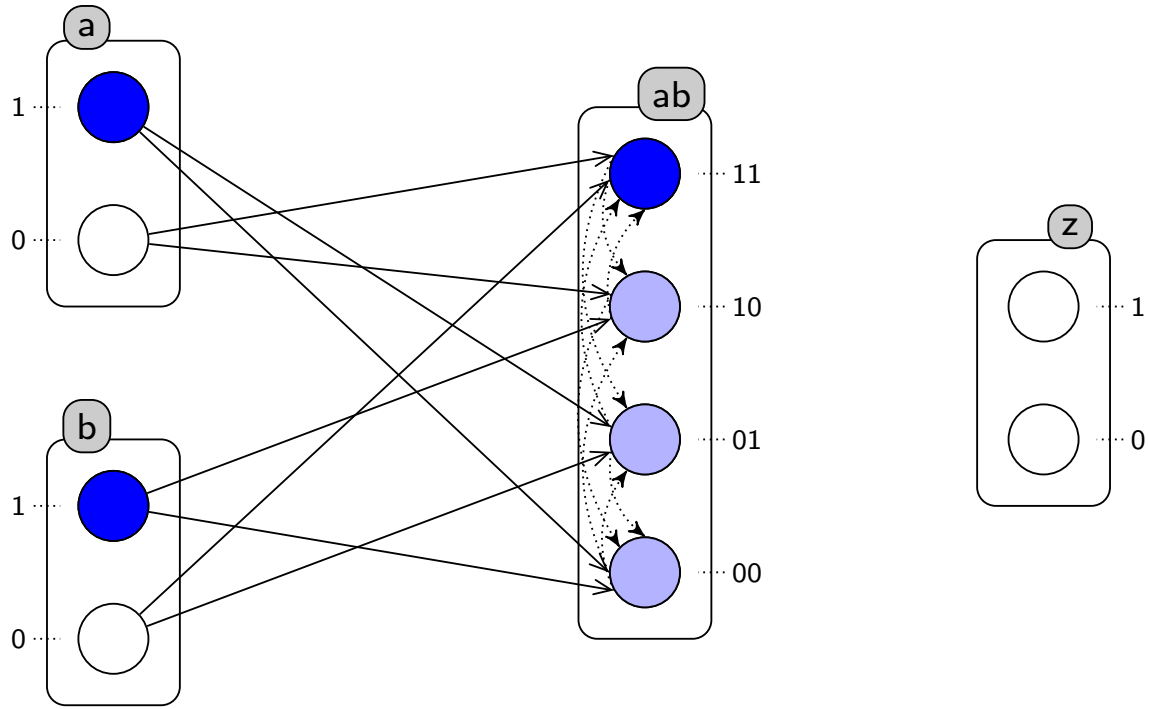

Cooperation between a_1 and b_1: $\underline{a_1 \wedge b_1} \rightarrow z_0 \Rsh z_1$

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

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

Adding cooperations

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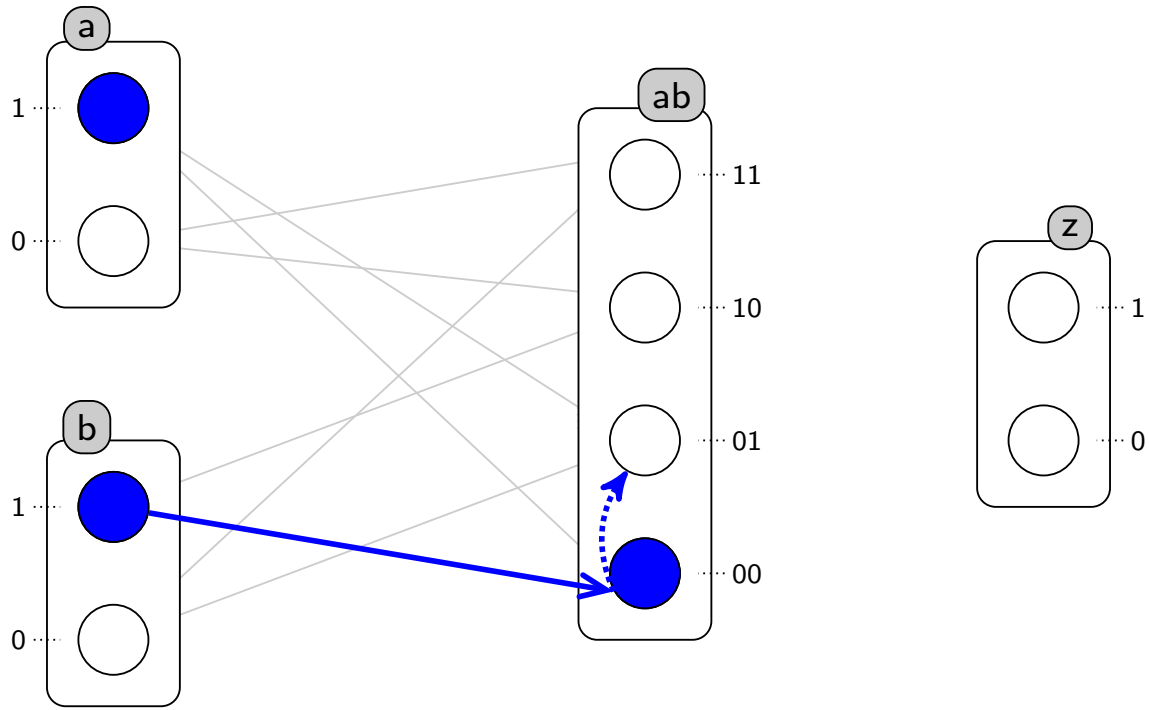

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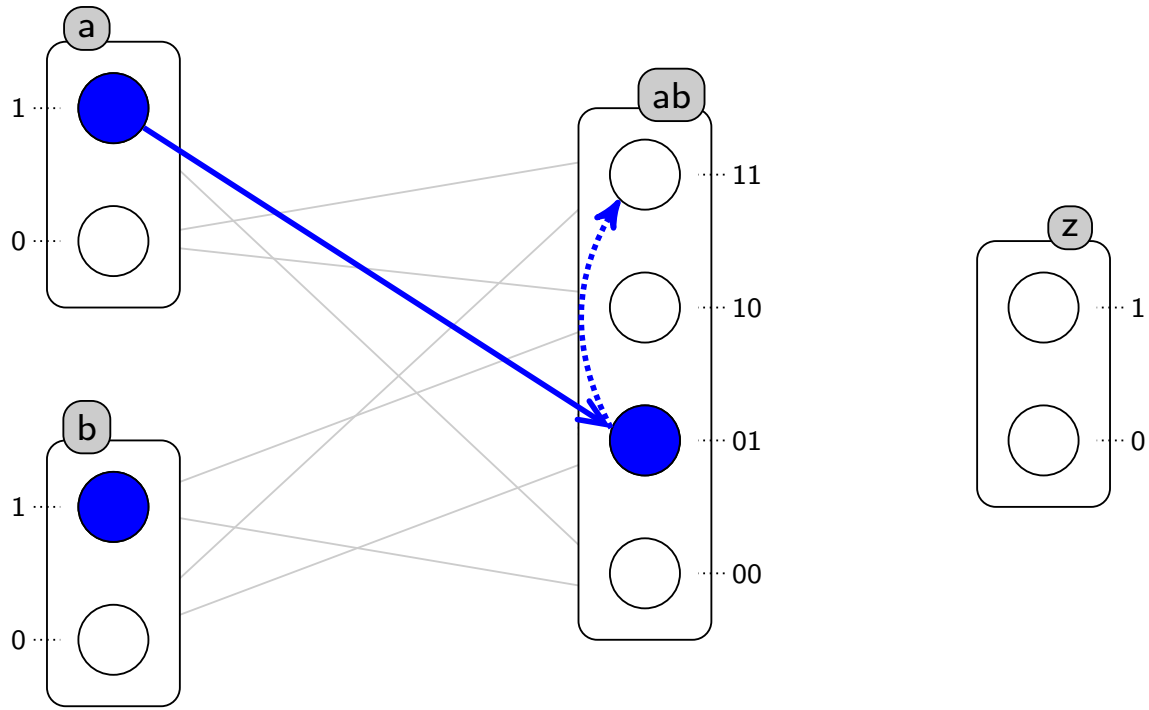

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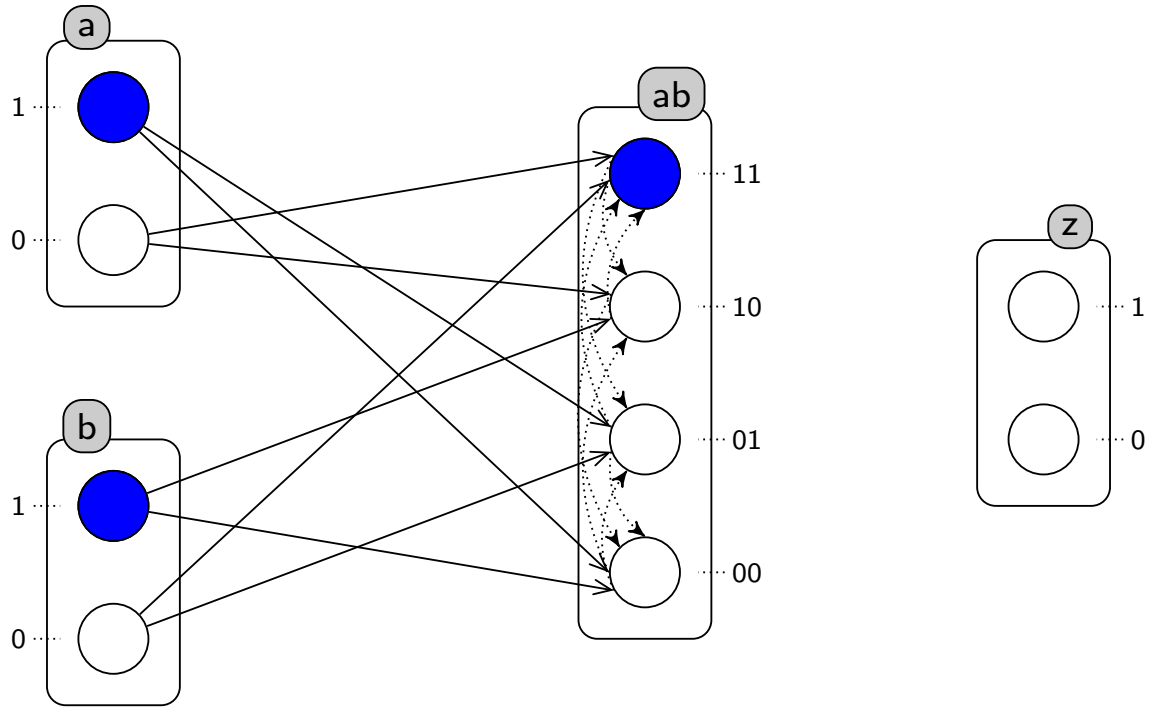

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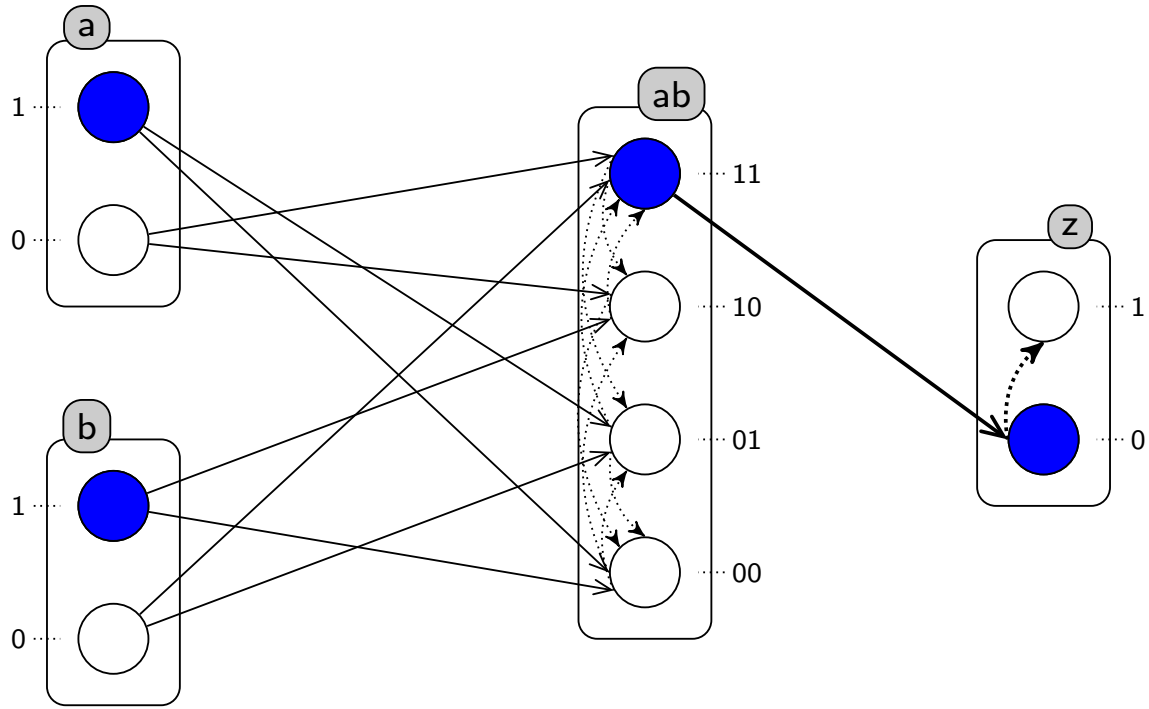

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Adding cooperations

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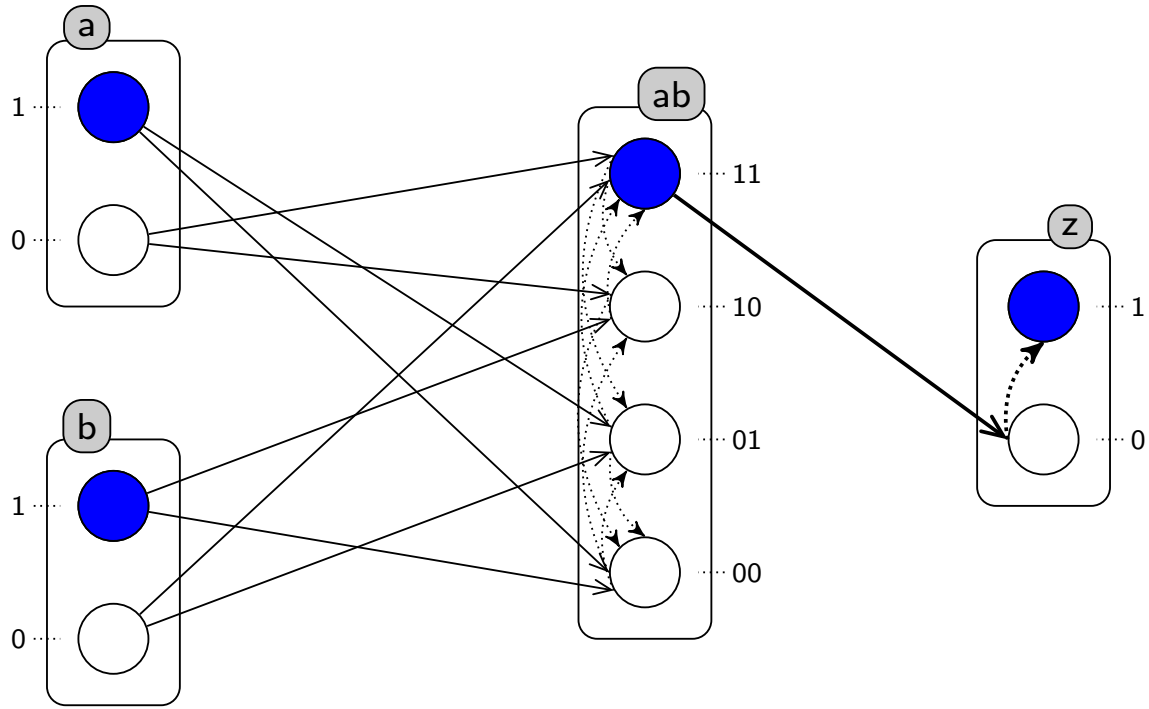

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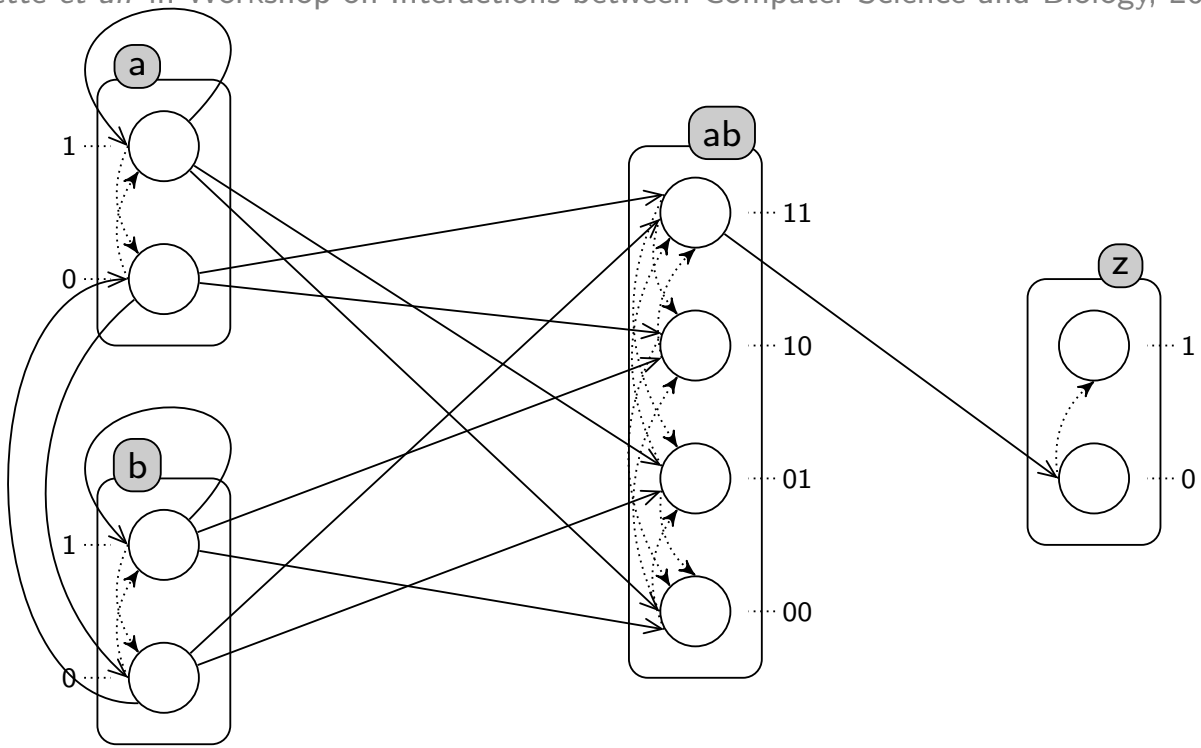
Adapting the expressivity of PH

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



Drawback: Cooperations are too "loose" to be as expressive as ADN.

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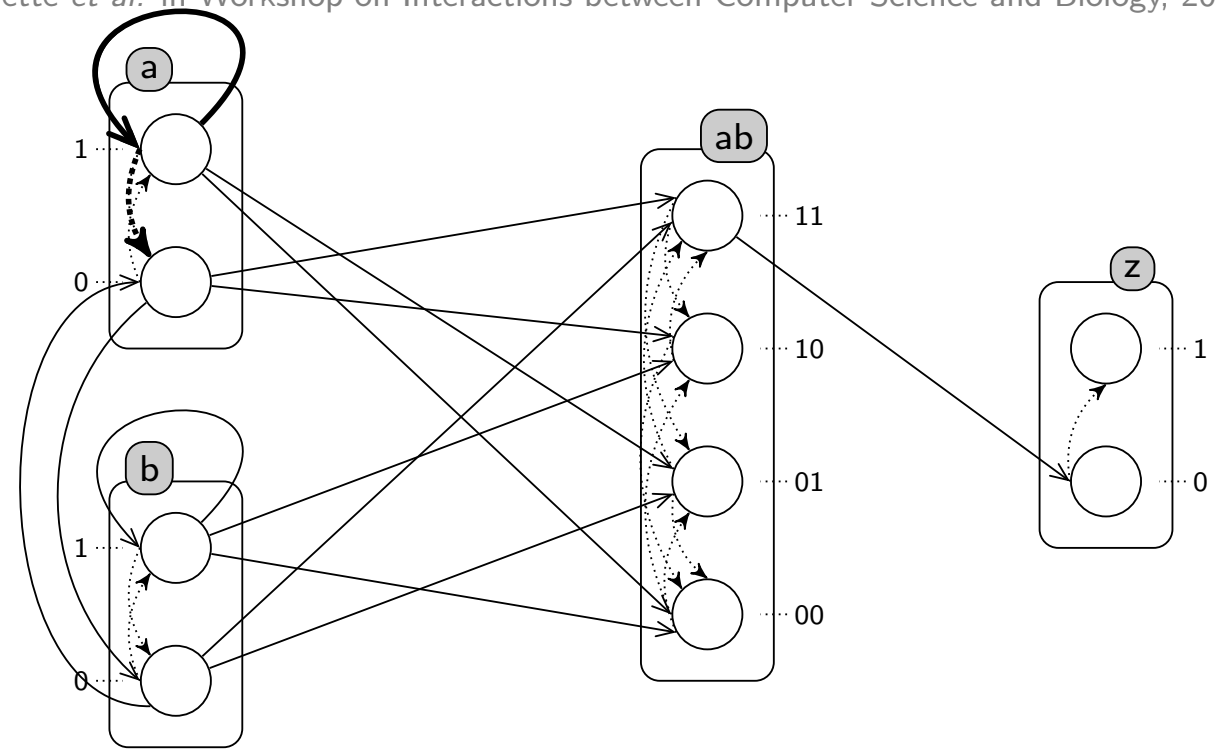

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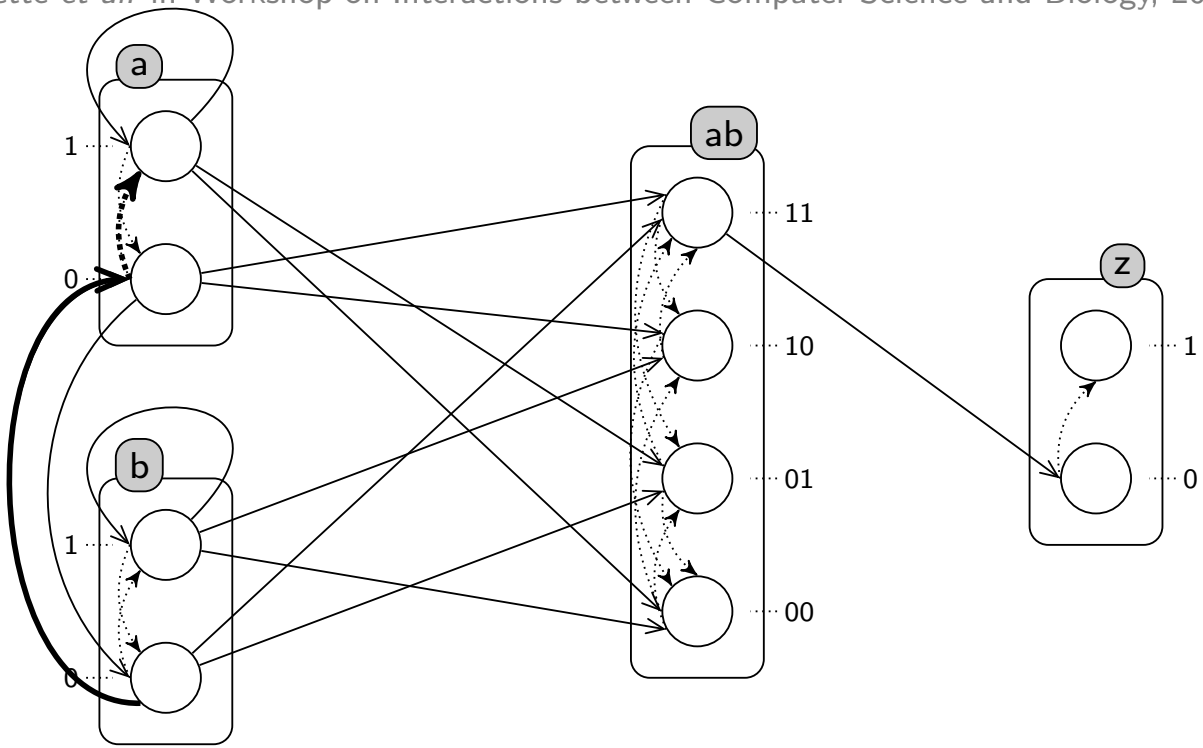

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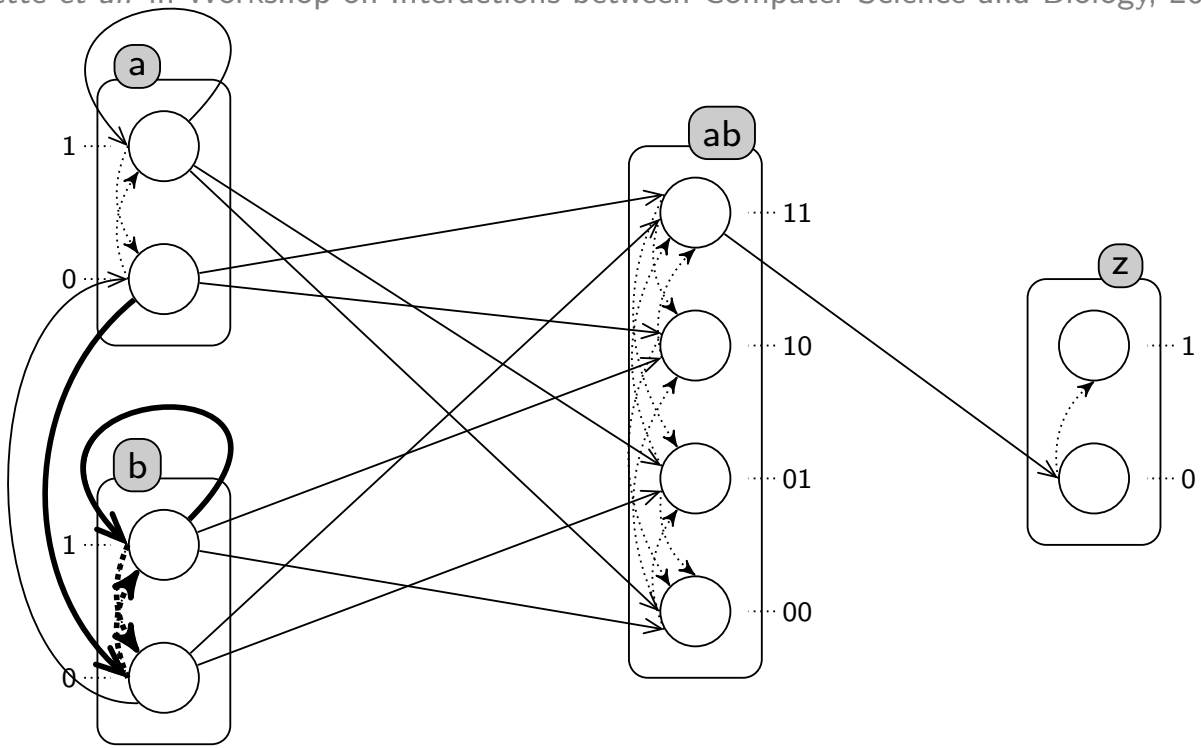

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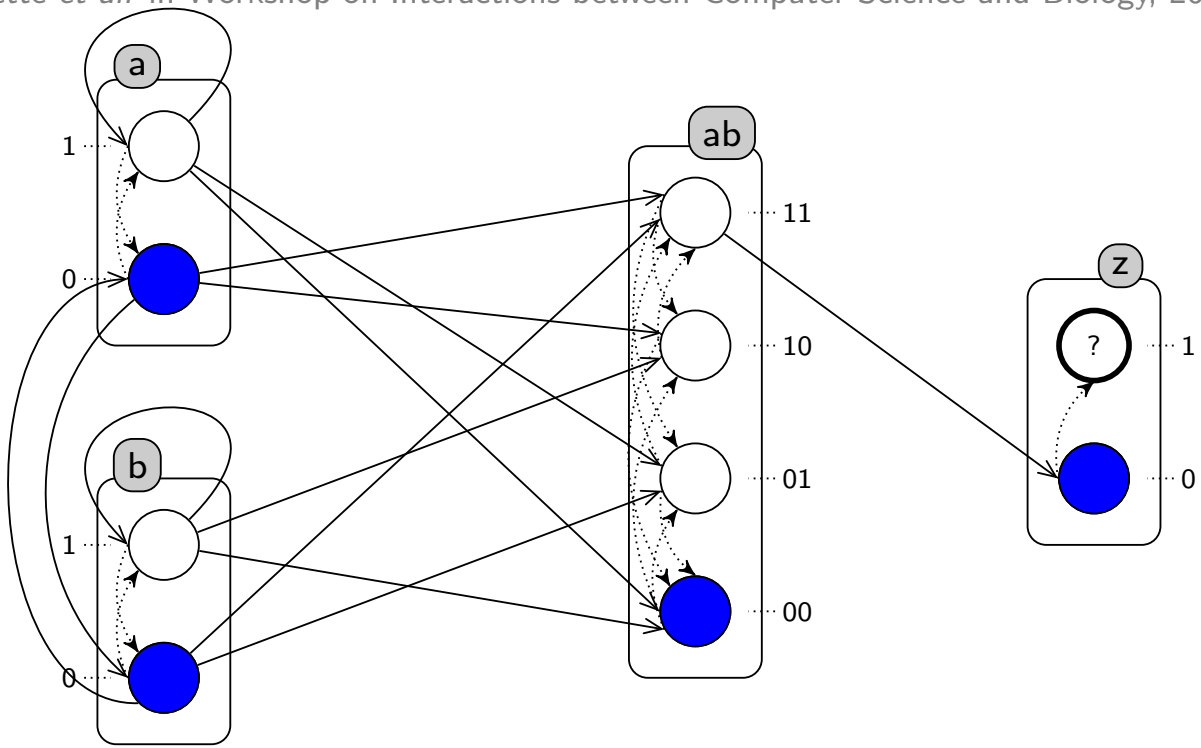

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$\langle a_0, b_0, ab_{00}, z_0 \rangle$

Adapting the expressivity of PH

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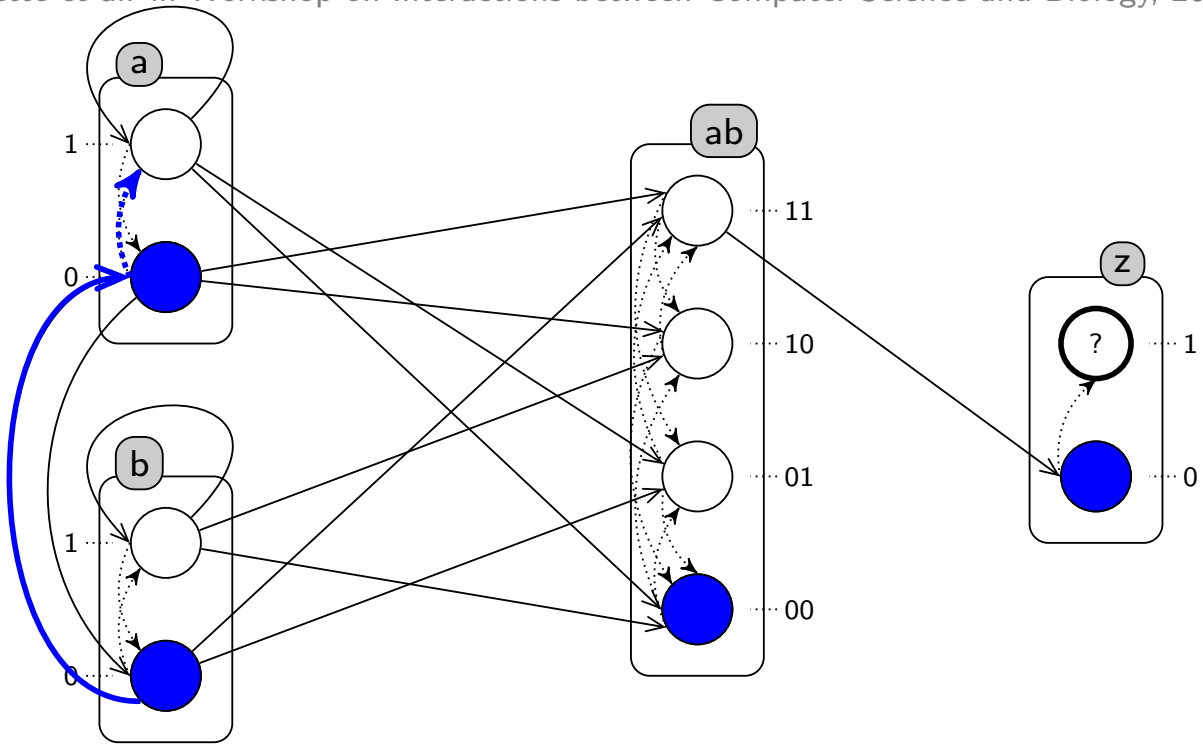

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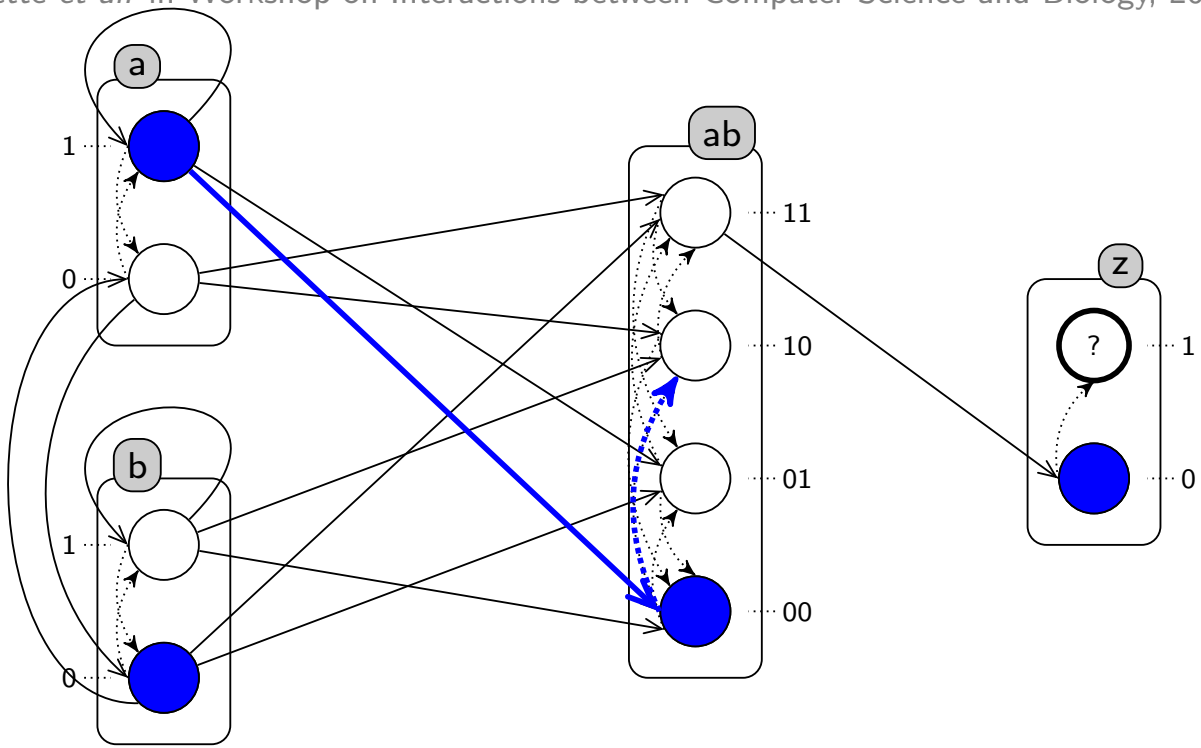

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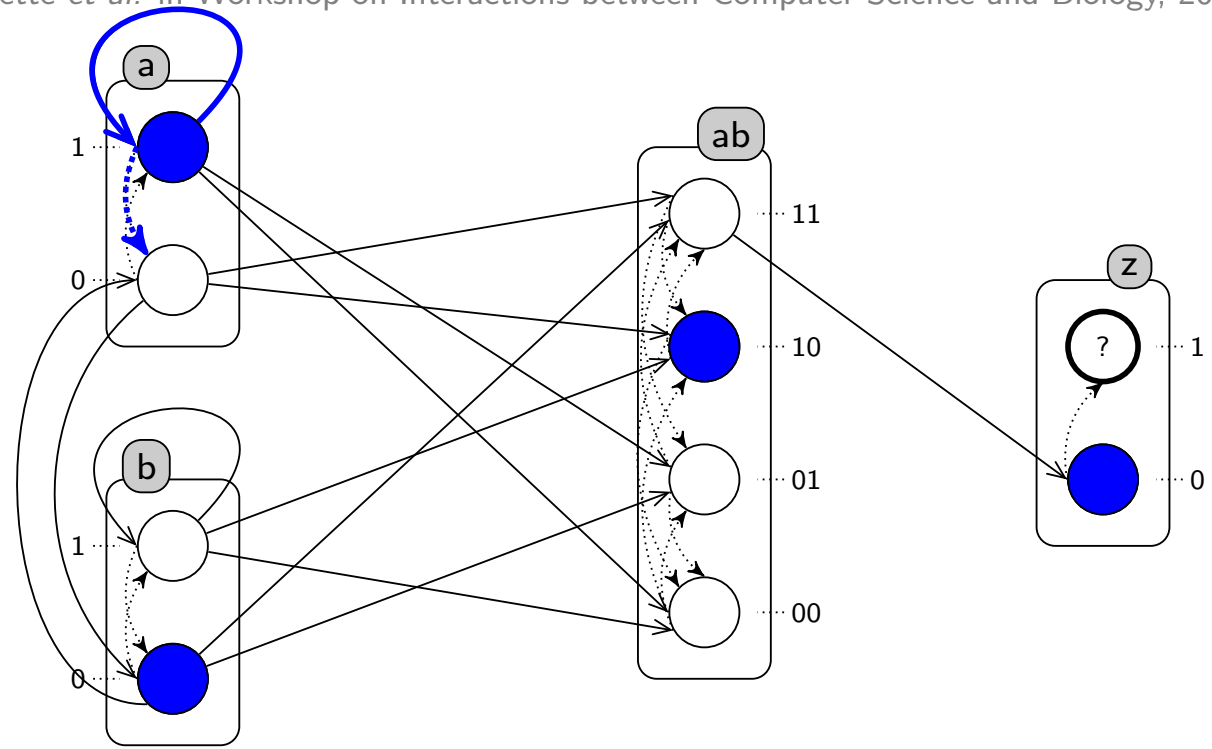

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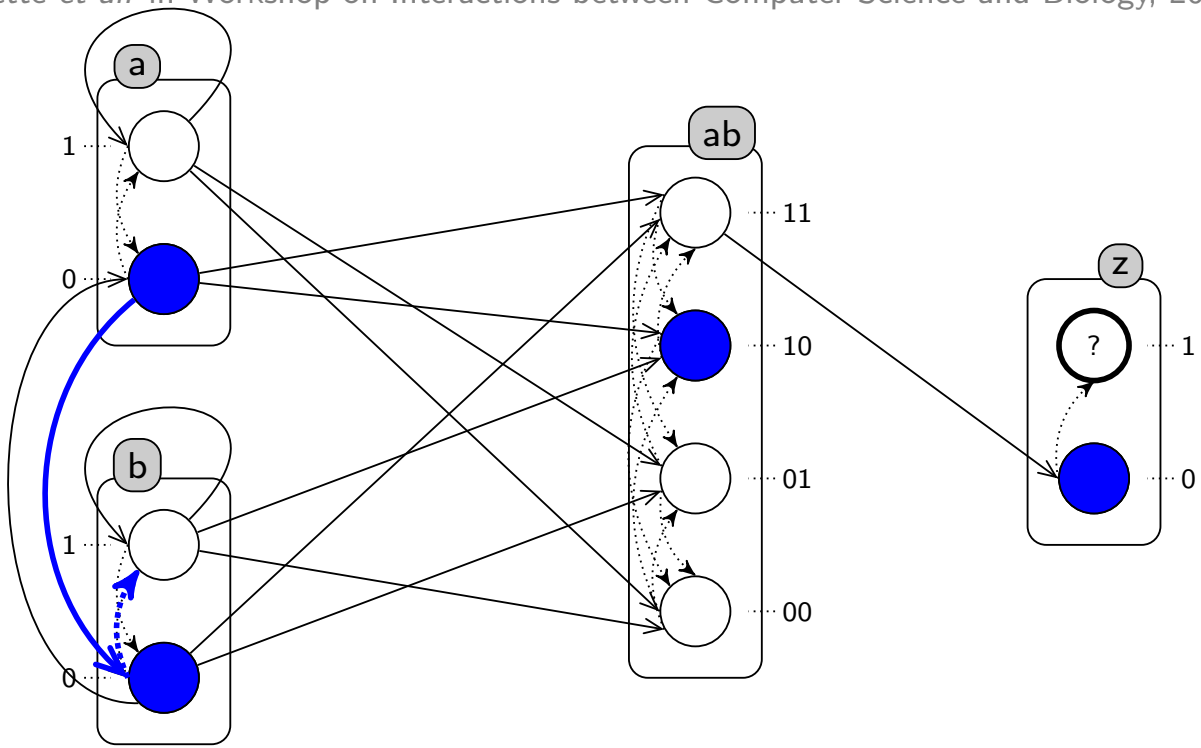

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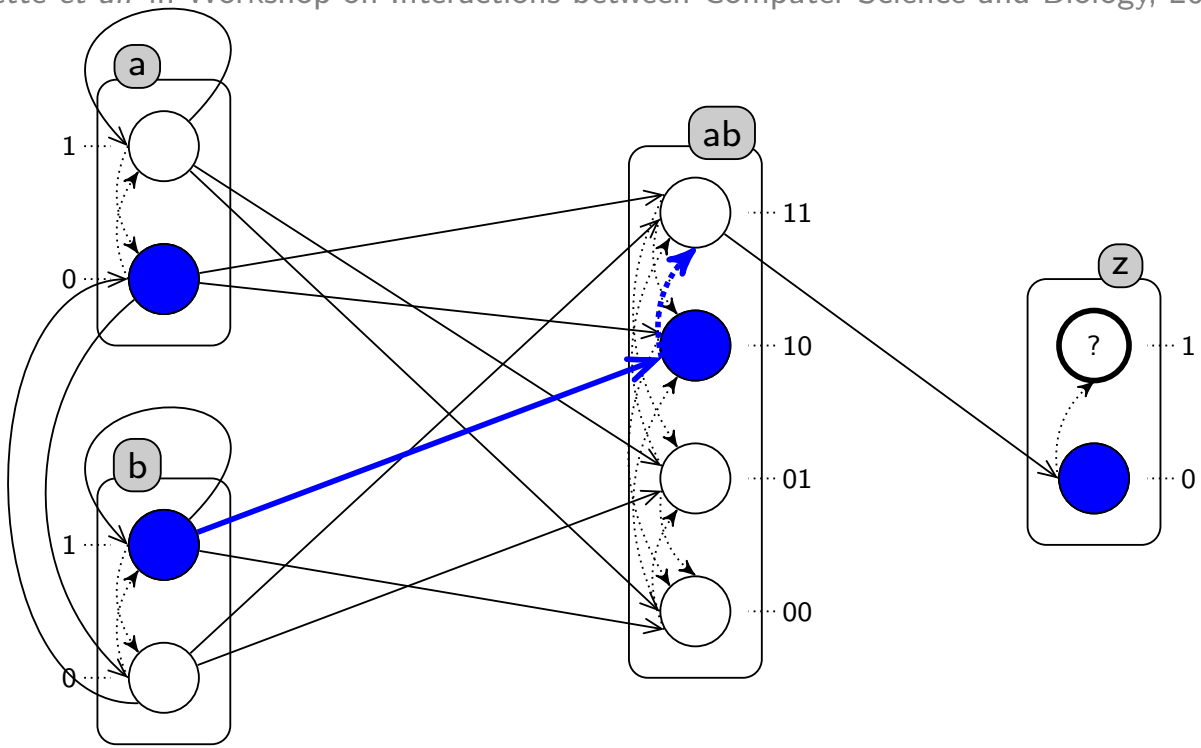

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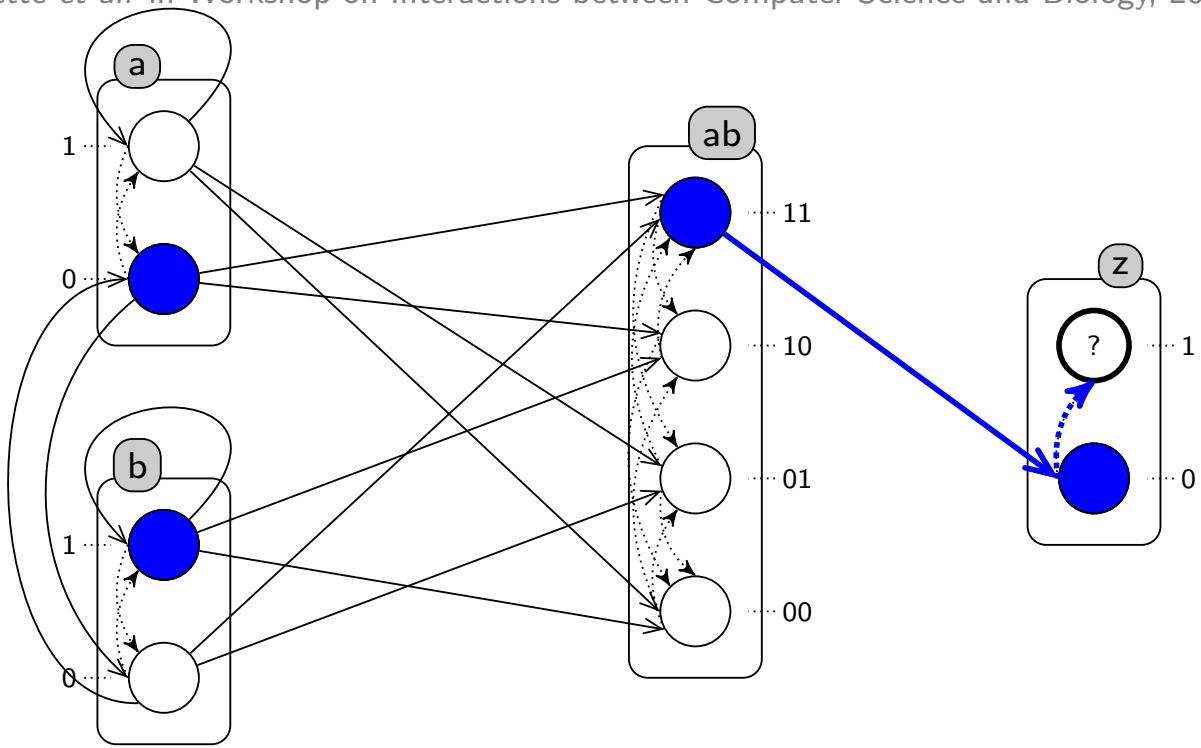

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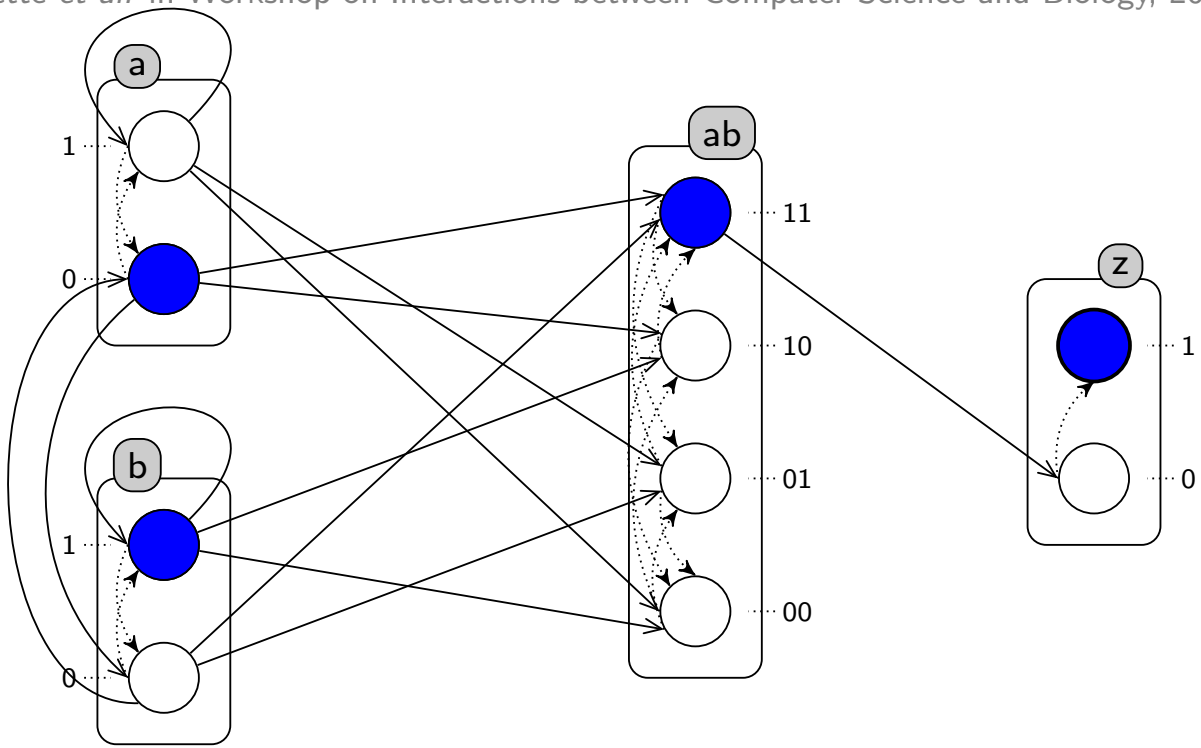

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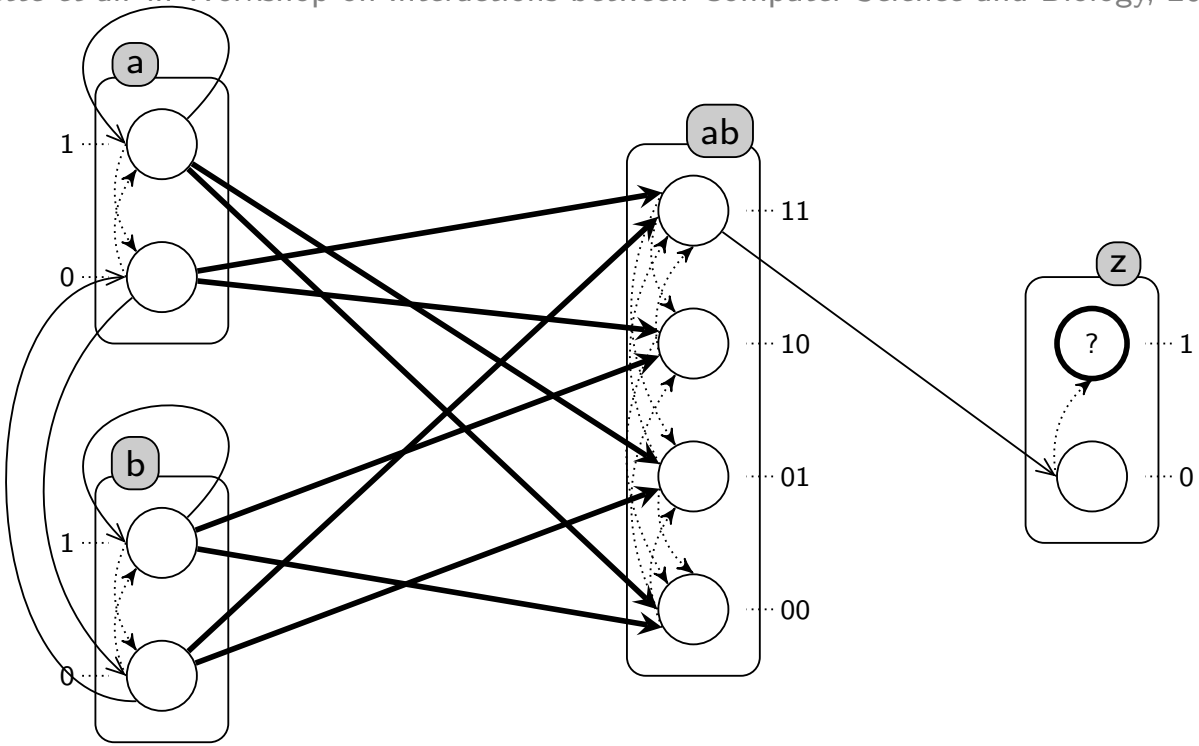
The cooperativity should be: $a_1 \wedge b_1$ **simultaneously** *i.e.* "in the same state"

but the model behaves like: $\mathbf{P}(a_1) \wedge \mathbf{P}(b_1)$ with $\mathbf{P}$ = "previously"

Adapting the expressivity of PH

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



- Prioritise actions updating cooperative sorts (non-biological actions)
- All other actions remain unprioritised (evolutions with delays)

Adapting the expressivity of PH

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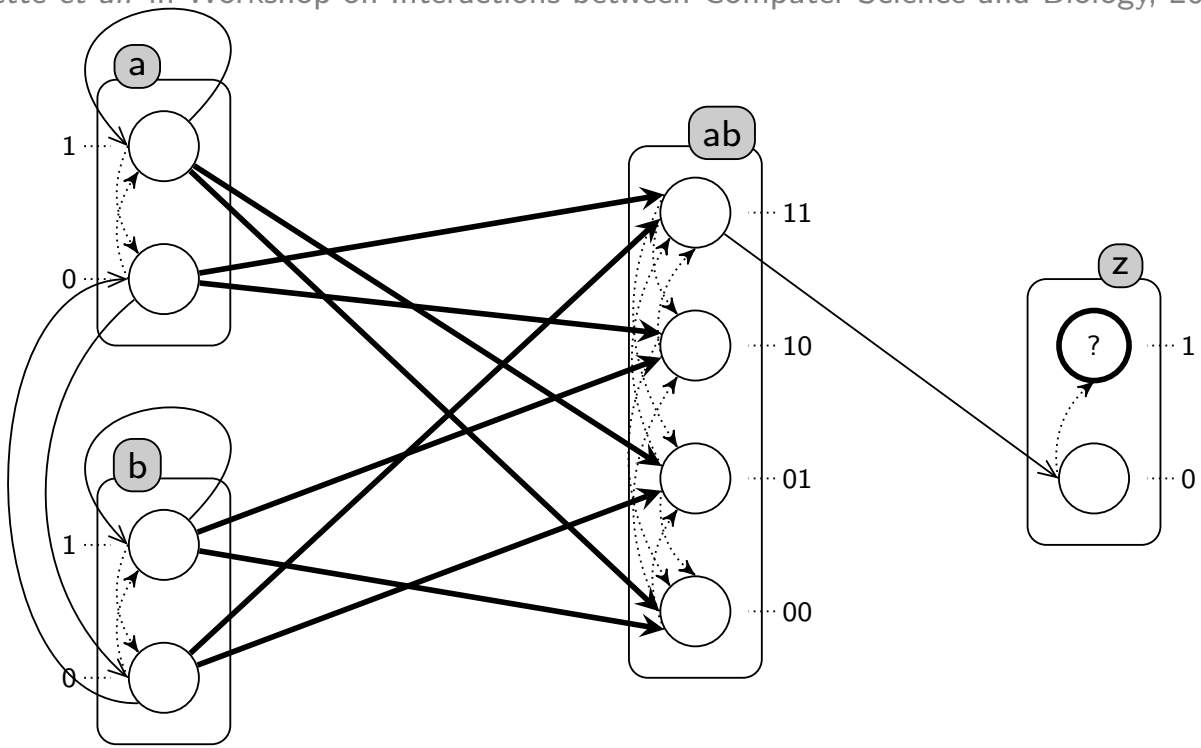

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Adapting the expressivity of PH

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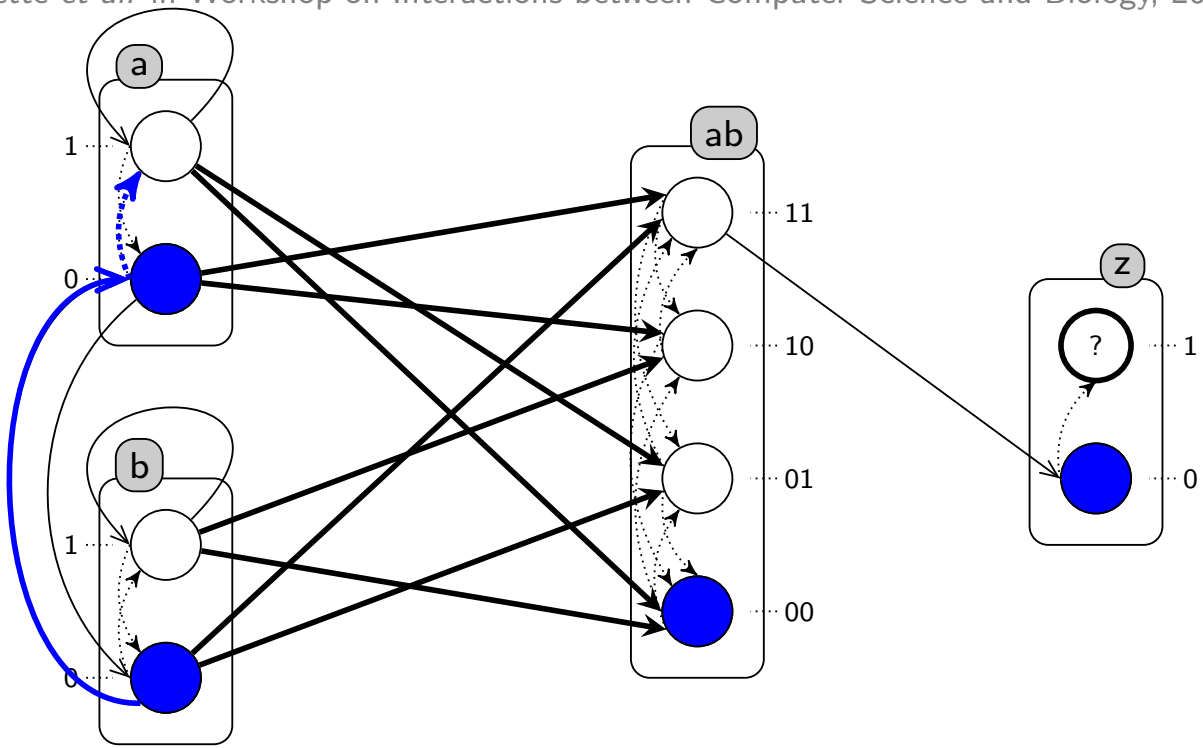

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Adapting the expressivity of PH

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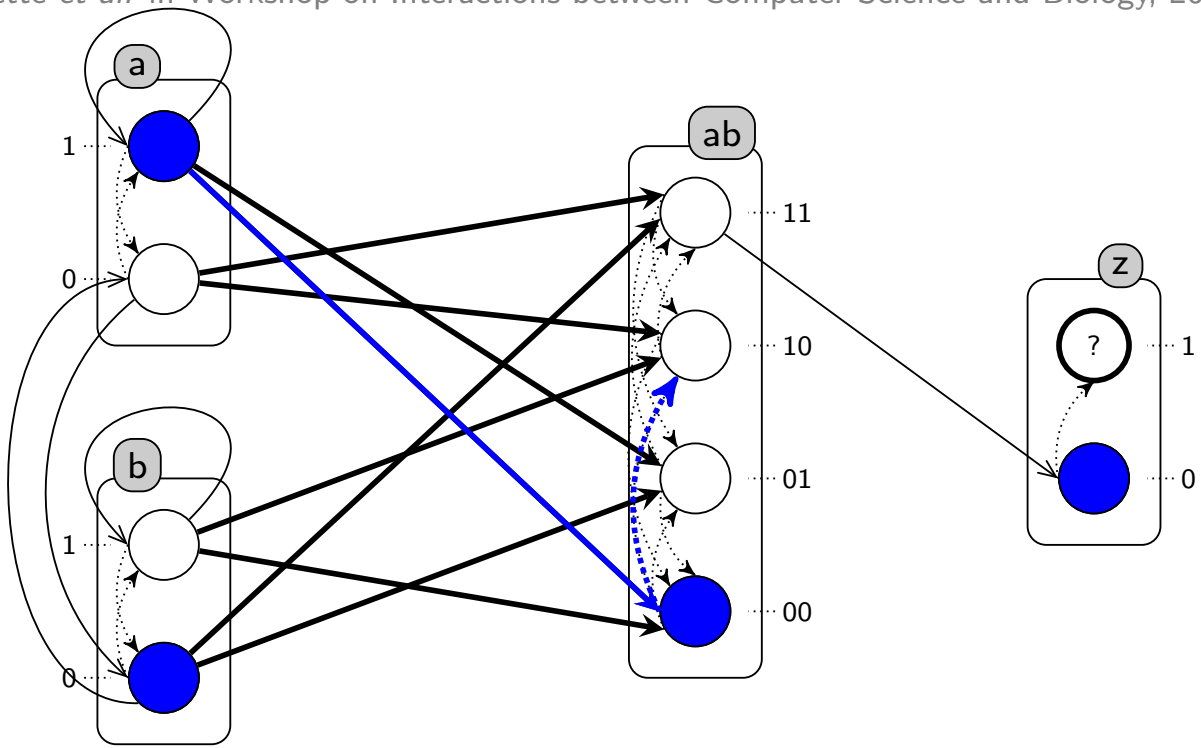

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Adapting the expressivity of PH

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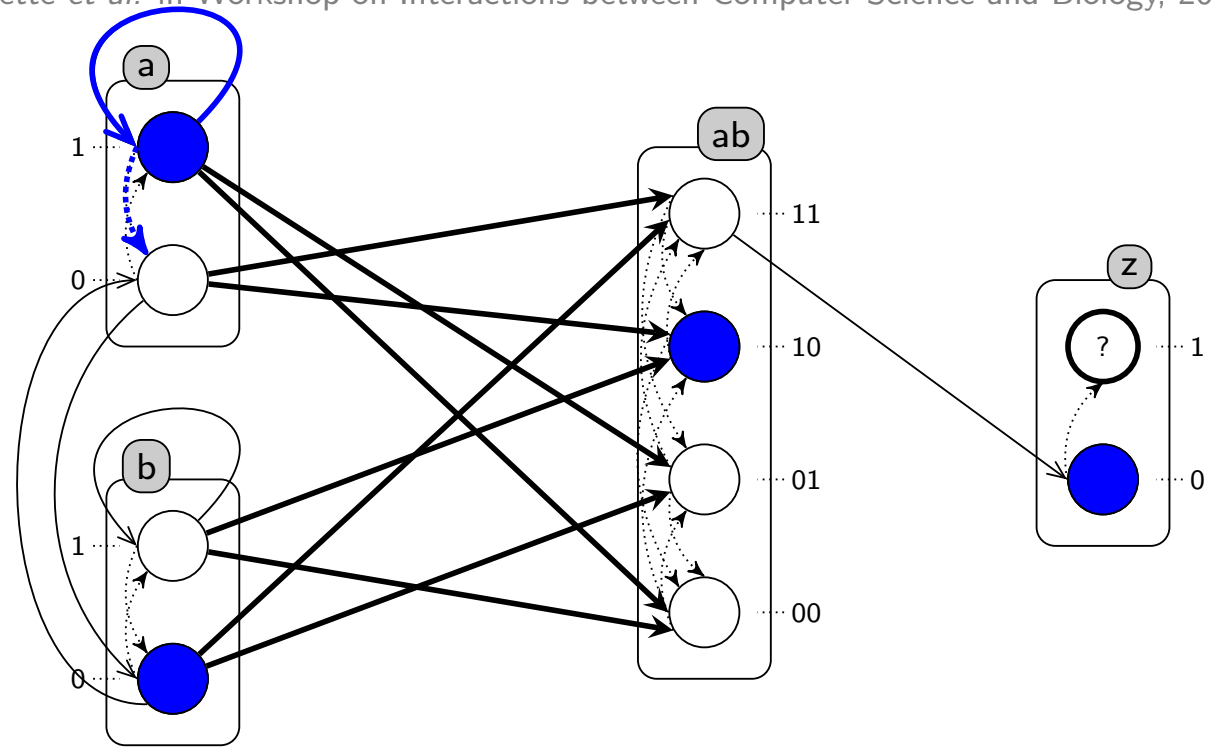

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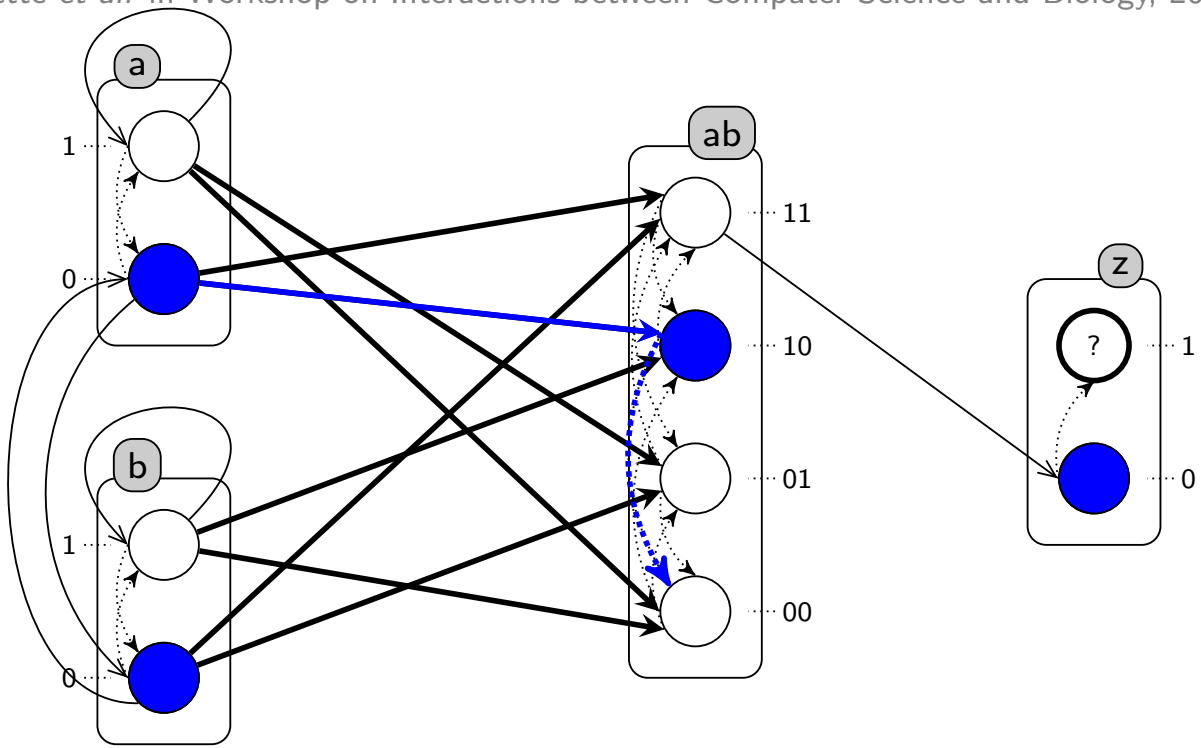

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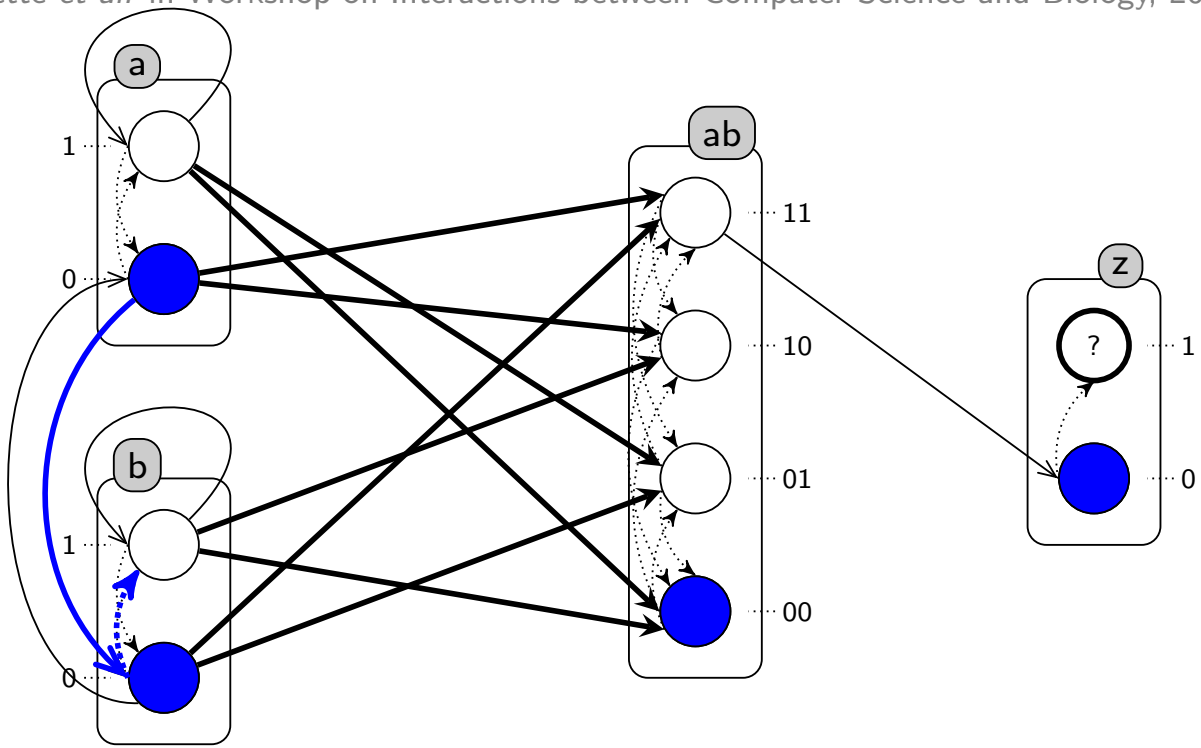

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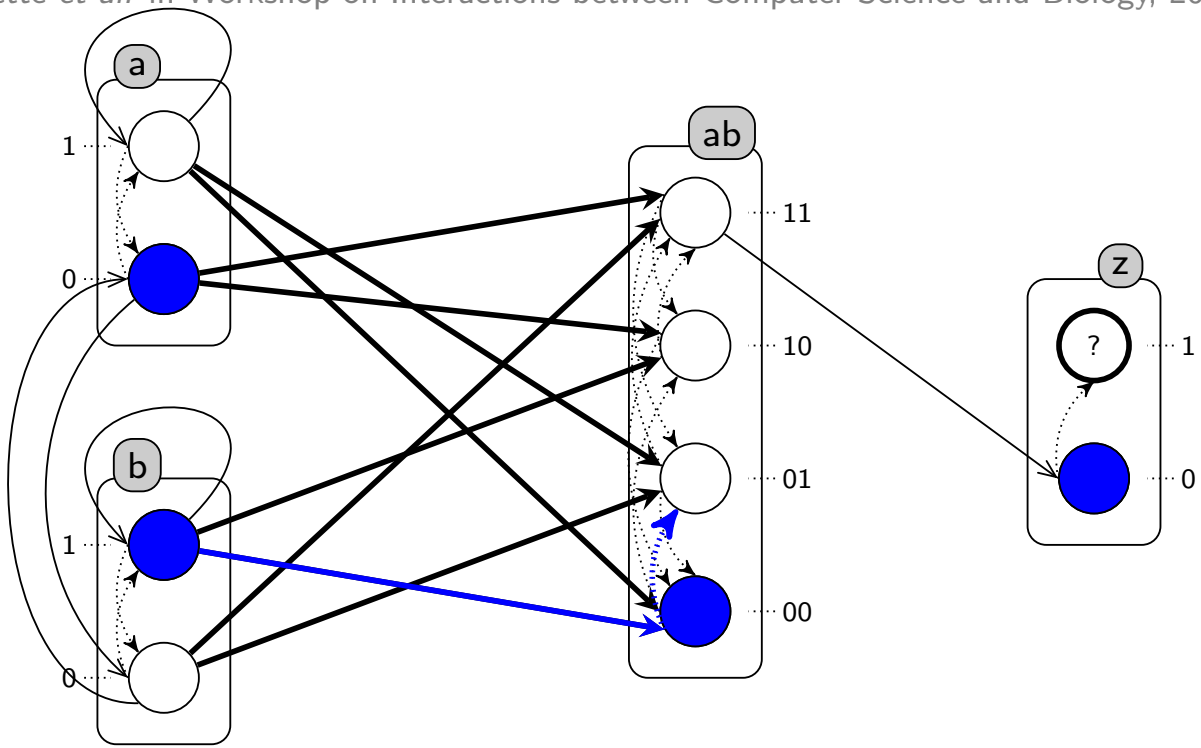

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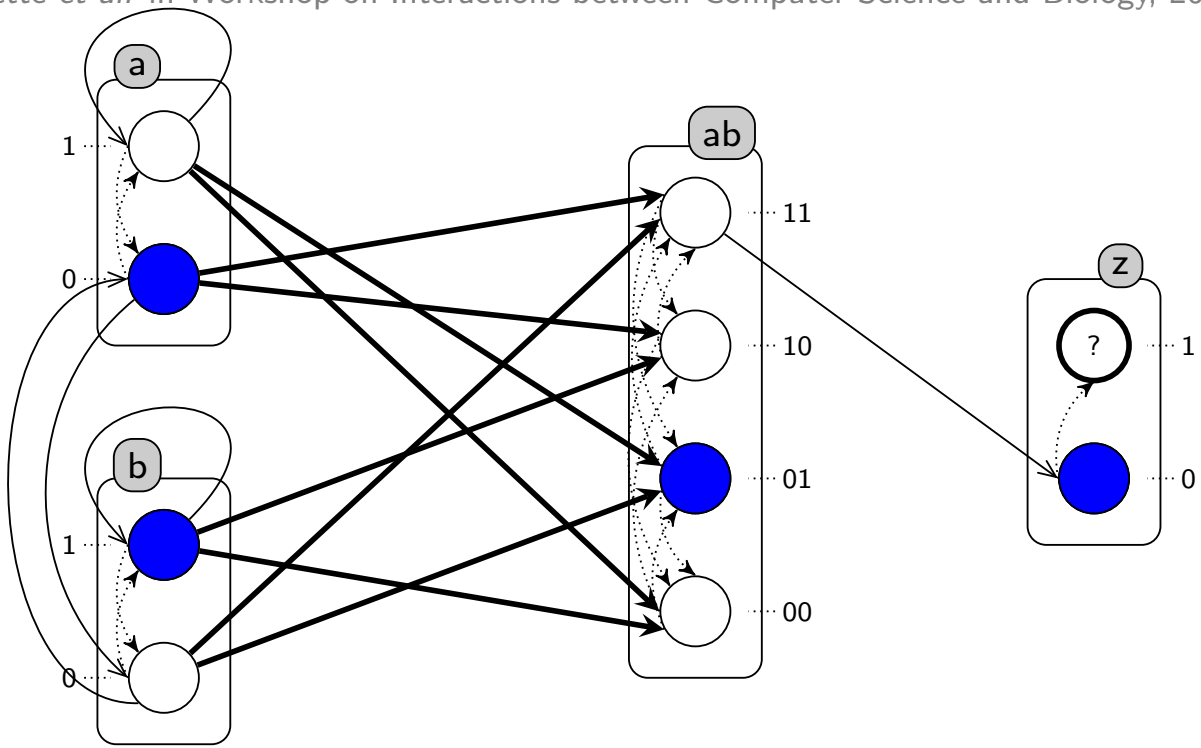

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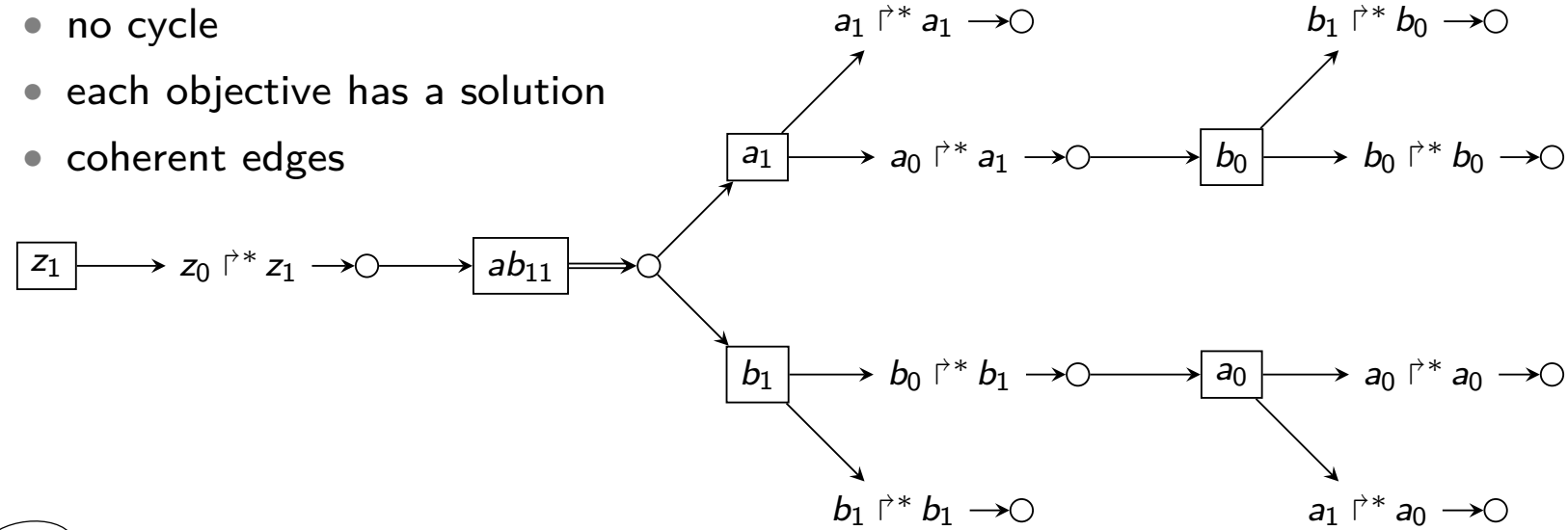
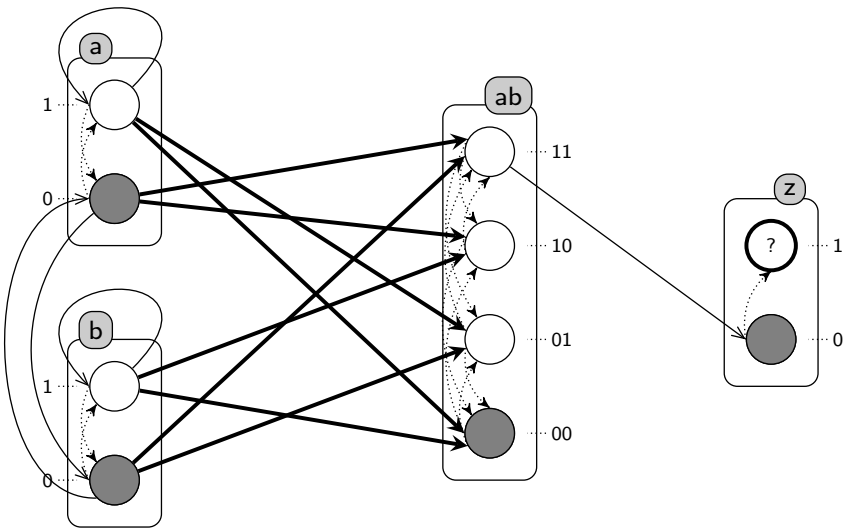
Static analysis with prioritised actions

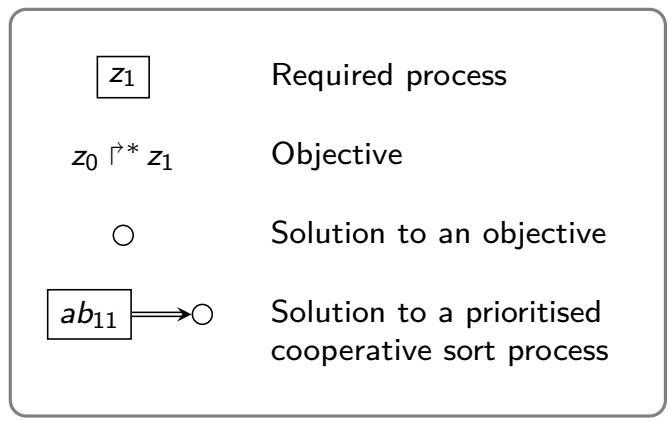
[Folschette *et al.* in Workshop on Interactions between Computer Science and Biology, 2013]

Sufficient condition:

- no cycle
- each objective has a solution
- coherent edges







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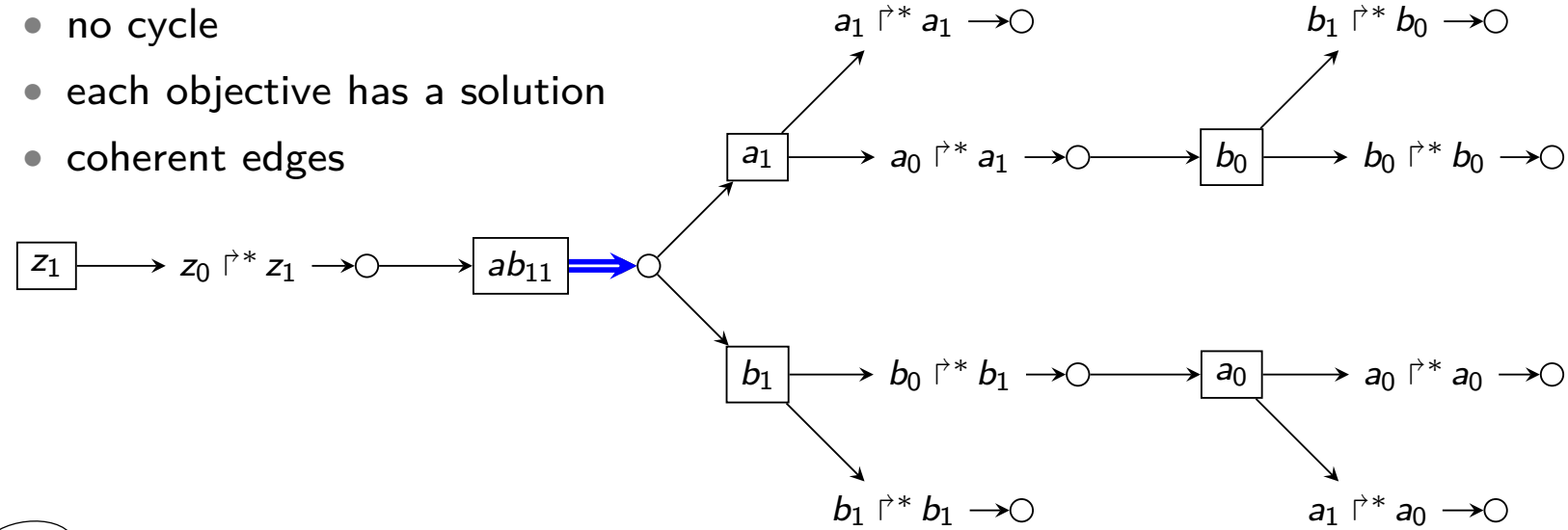
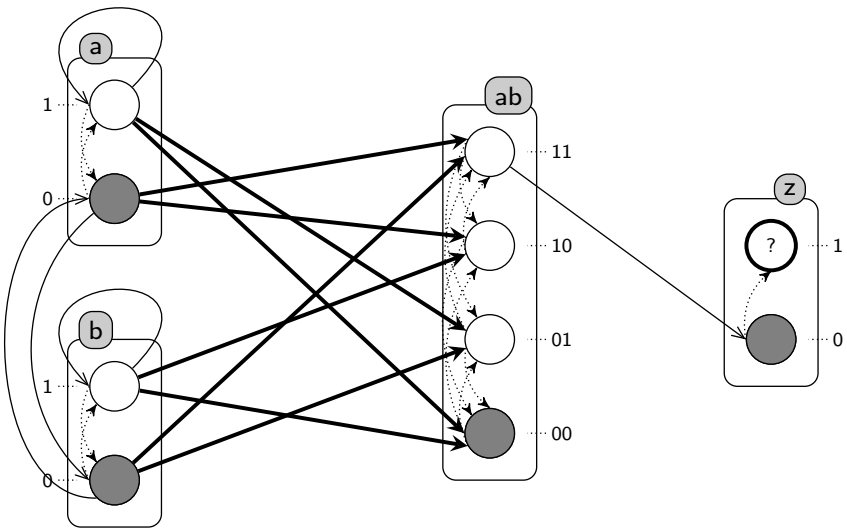
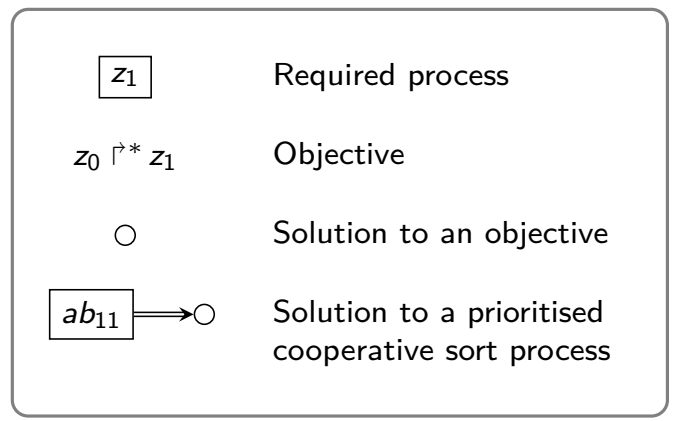




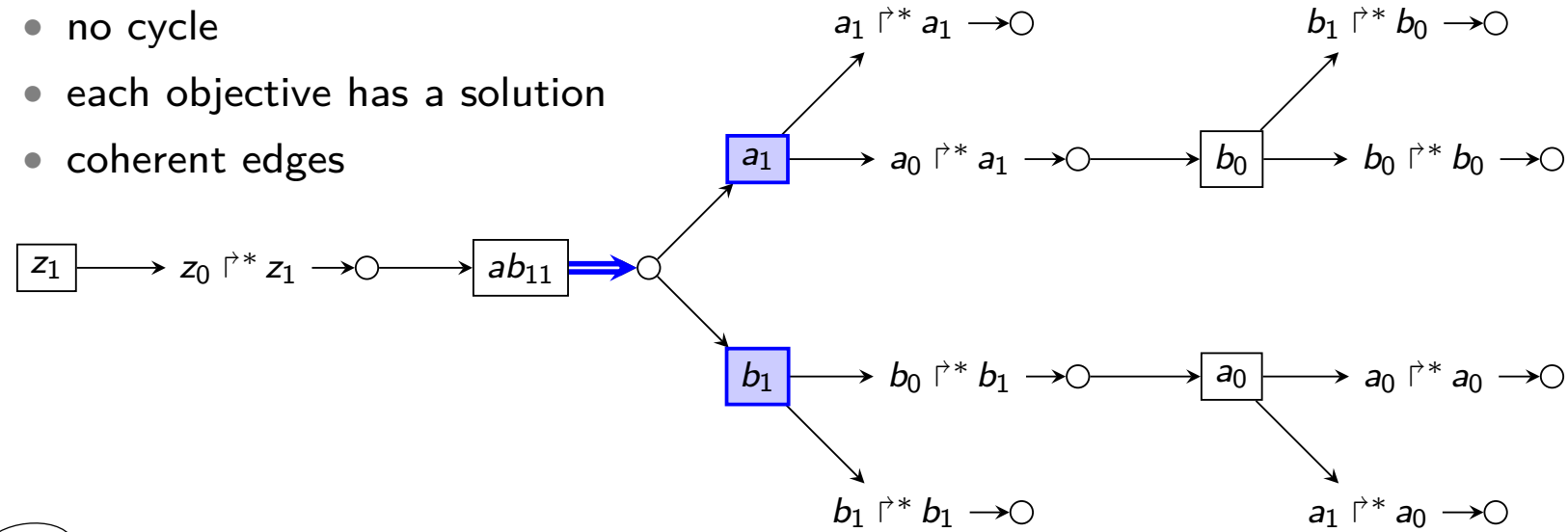


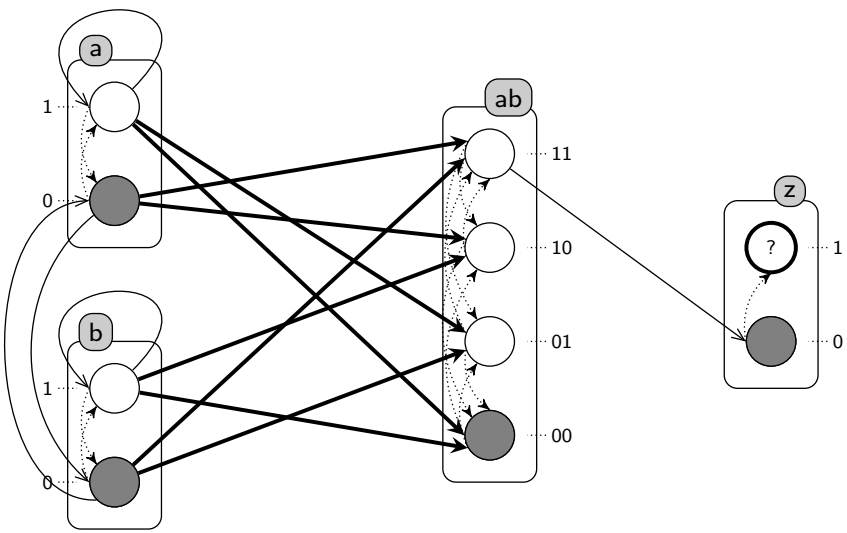
Static analysis with prioritised actions

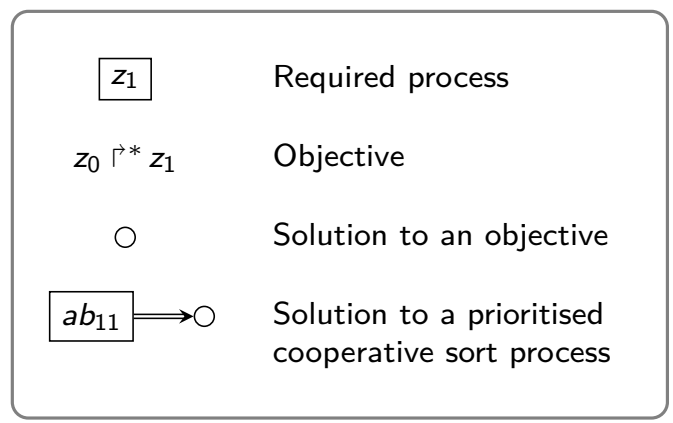
[Folschette *et al.* in Workshop on Interactions between Computer Science and Biology, 2013]

Sufficient condition:

- no cycle
- each objective has a solution
- coherent edges







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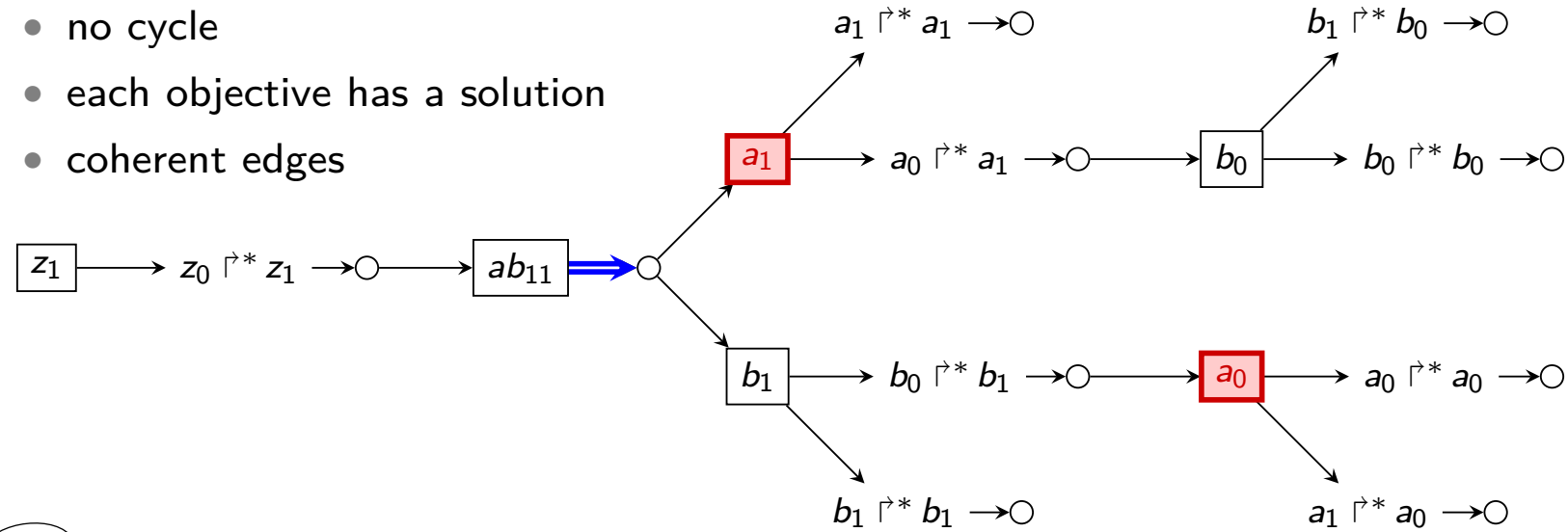

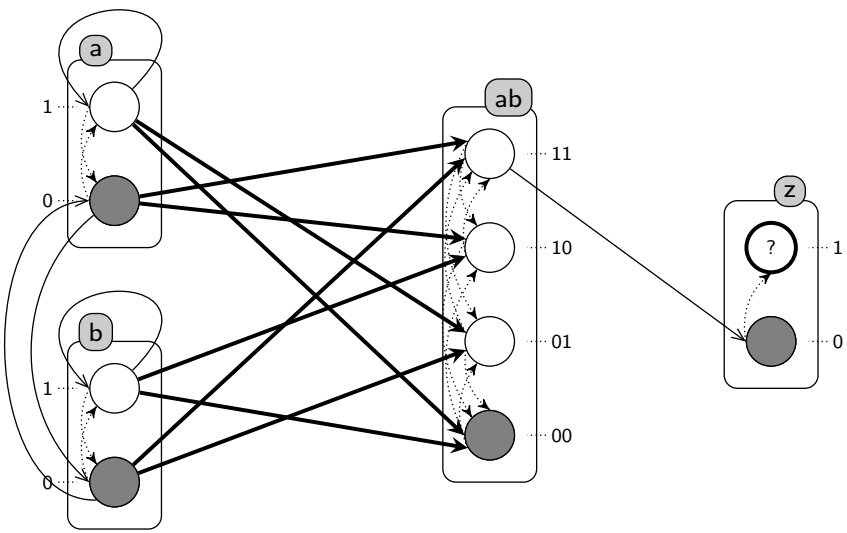

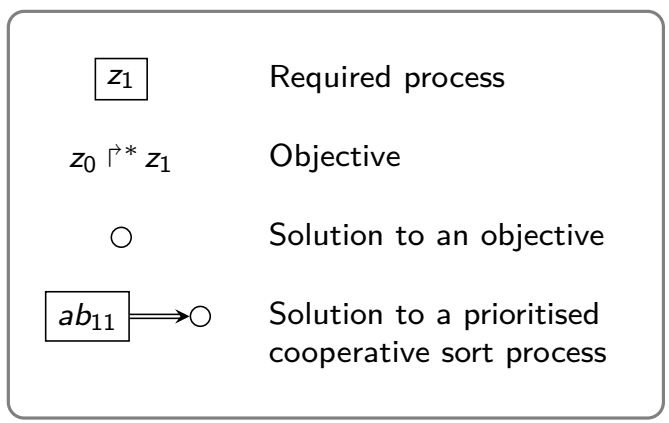

Static analysis with prioritised actions

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

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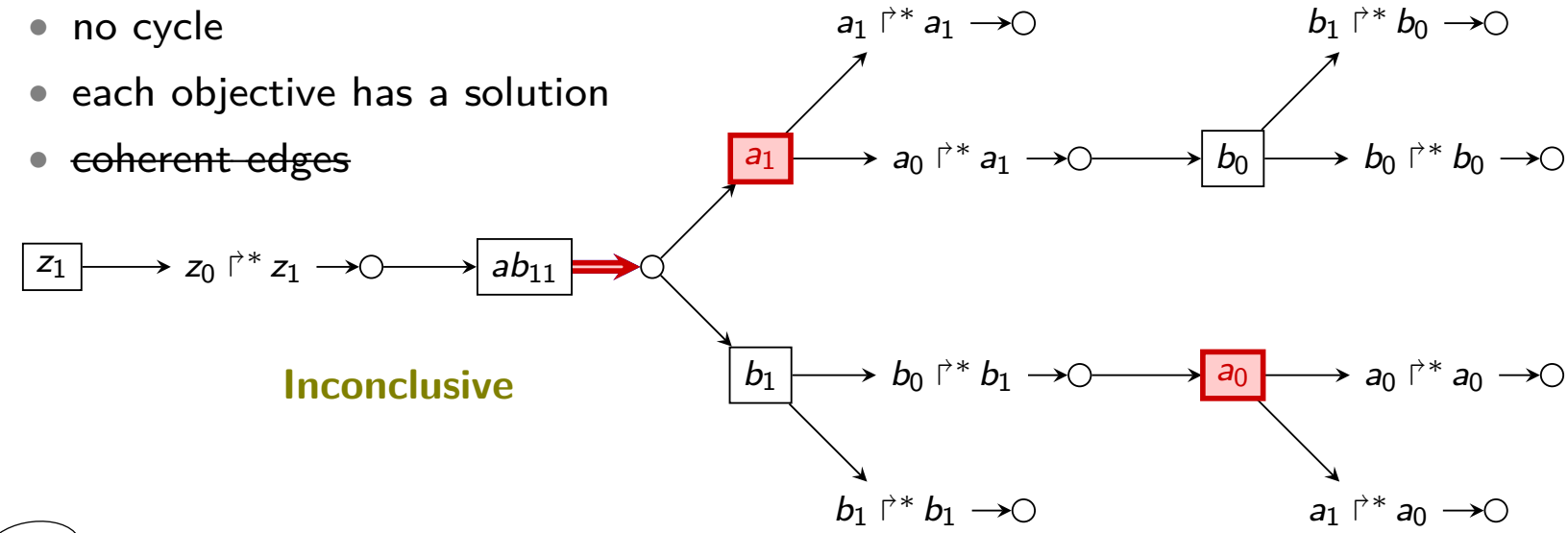

Inconclusive