— KUBIC-NII Joint Seminar on Bioinformatics 2012 —

Translating Process Hitting models to Thomas' modeling with ASP

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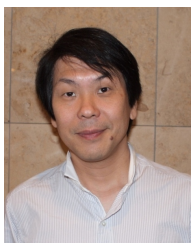
A multi-team topic

Inoue Laboratory (NII): Constraint Programming, Systems Biology
MeForBio (IRCCyN, ÉCN): Formal Methods for Bioinformatics
AMIB (LIX, Polytechnique): Algorithms and Models for Integrative Biology



Katsumi INOUE
Professor & team leader

Inoue Laboratory

Loïc PAULEVÉ
Post-doc

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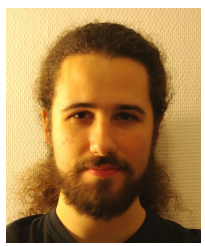
Associate professor

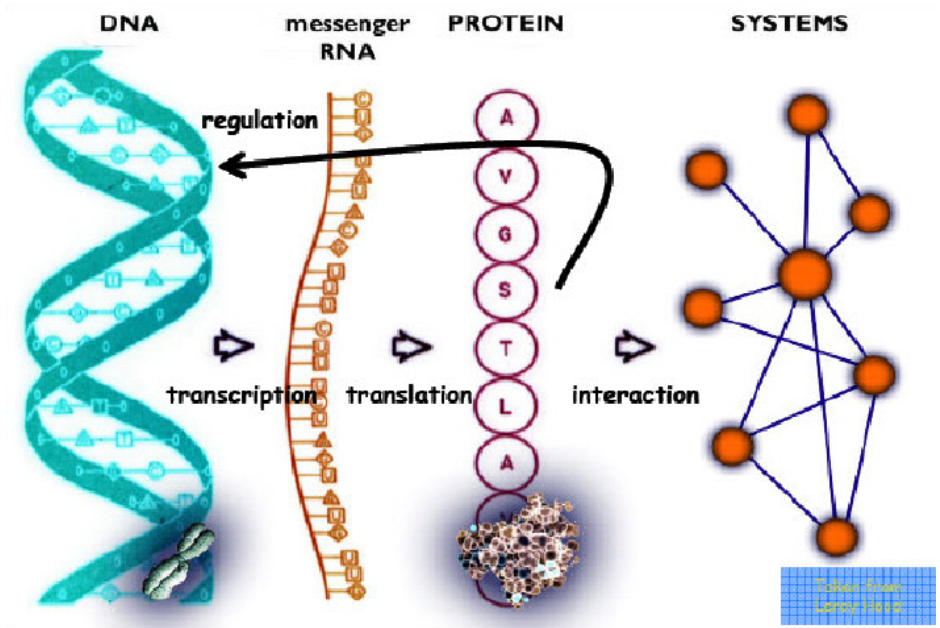


Maxime FOLSCHETTE
1st year PhD student

MeForBio

Context and Aims

Algebraic modeling to study complex dynamical biological systems:

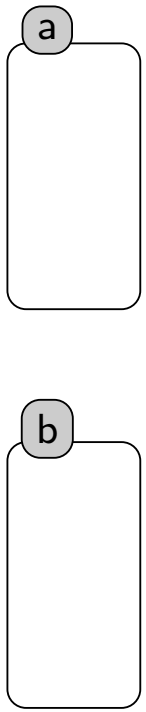


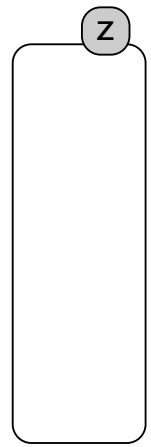
- Historical model: René Thomas' modeling
- New developed model: Process Hitting

→ Allow efficient translation between models

The Process Hitting modeling

[PMR12-MSCS]

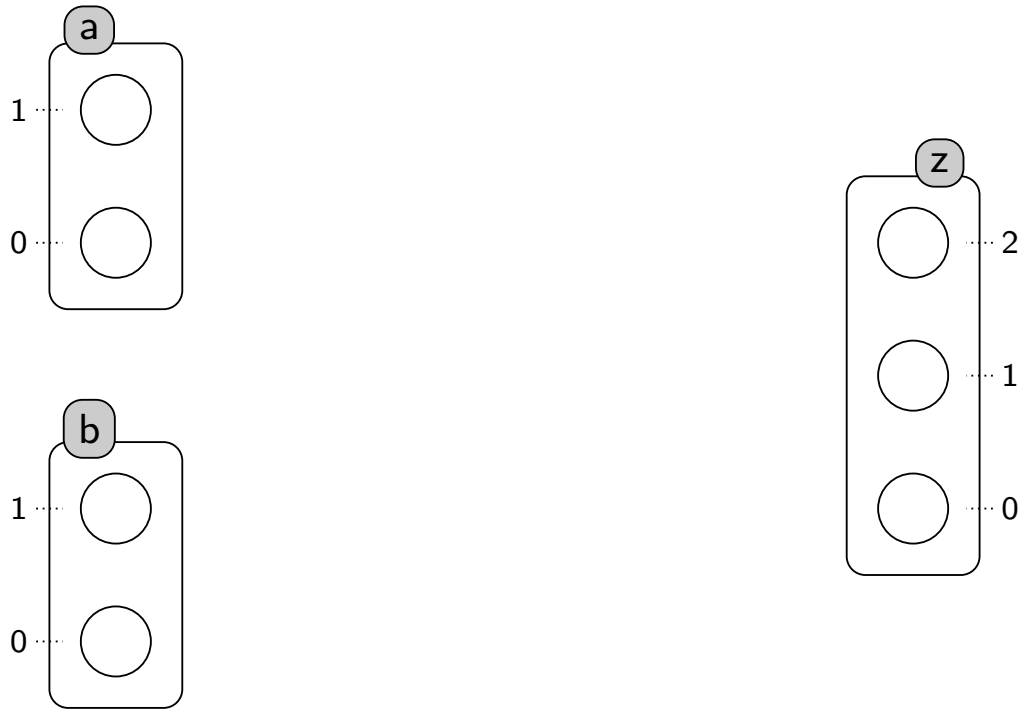




Sorts: components a, b, z

The Process Hitting modeling

[PMR12-MSCS]



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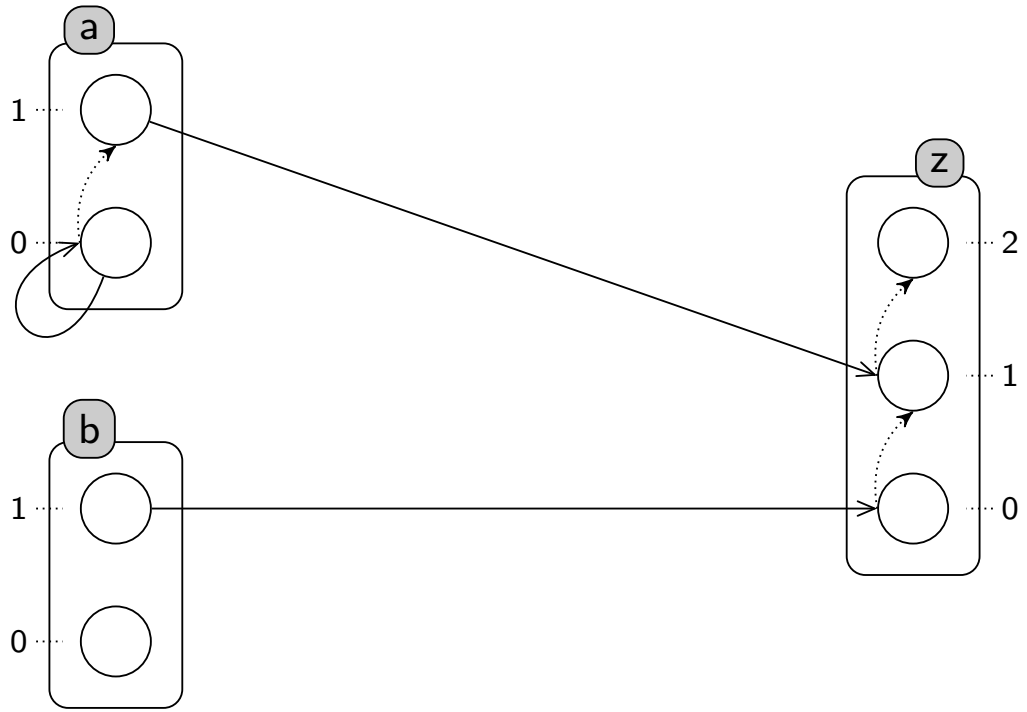

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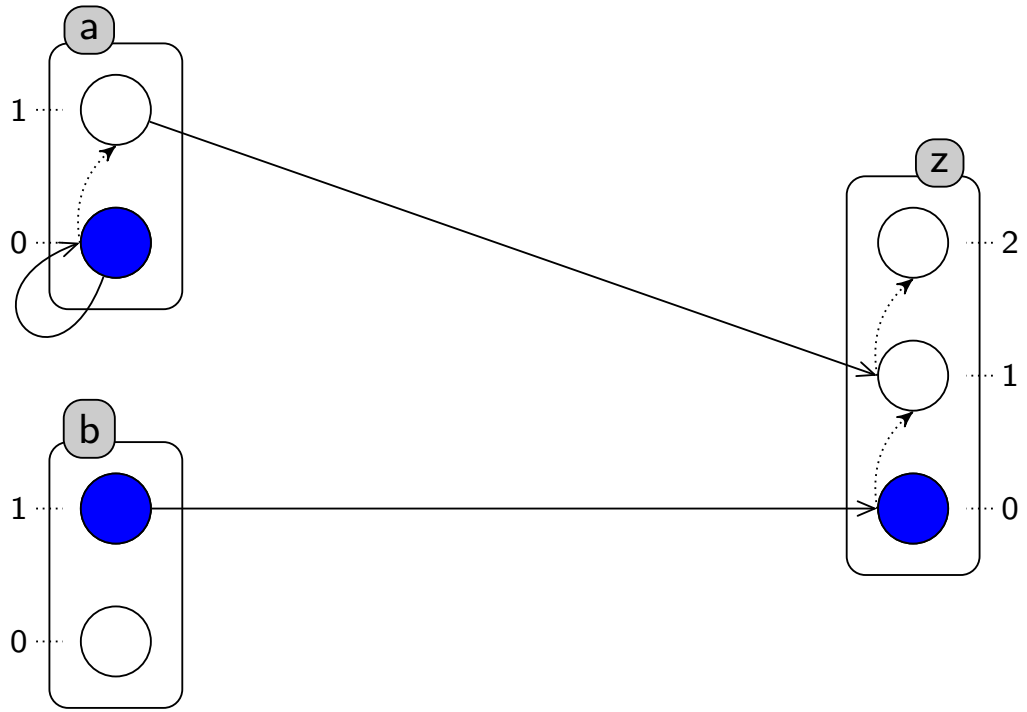

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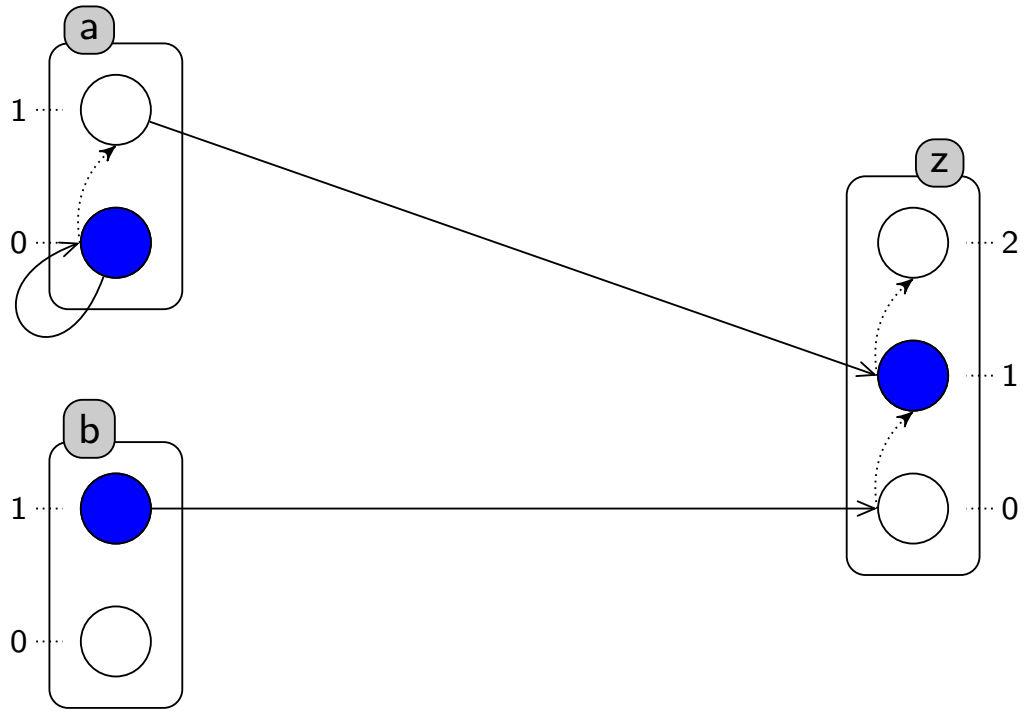

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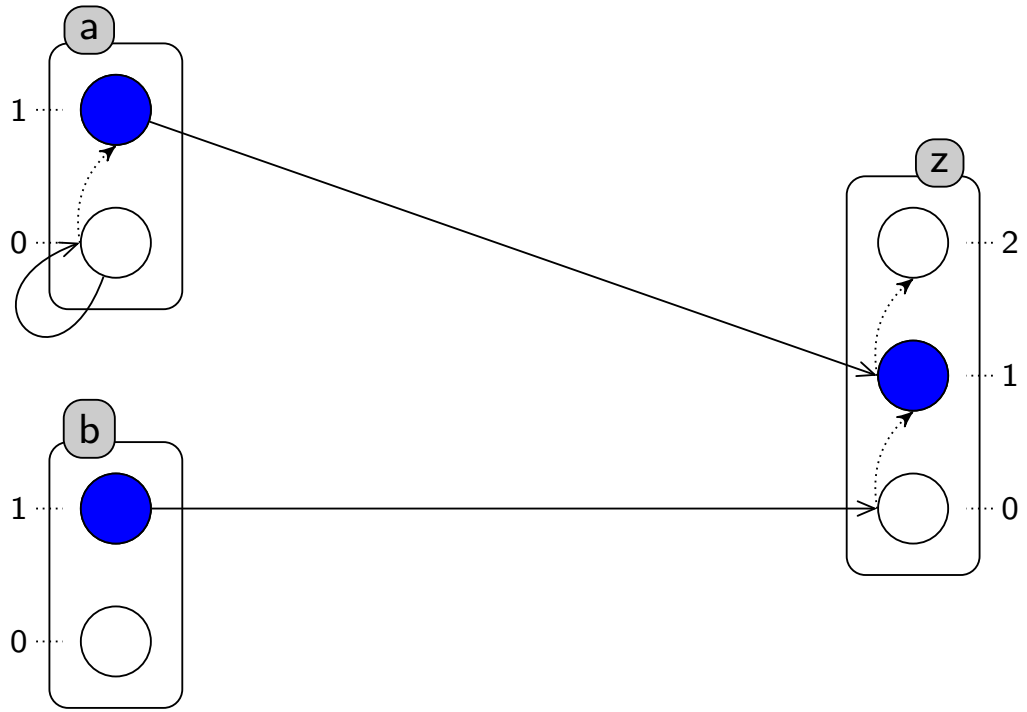

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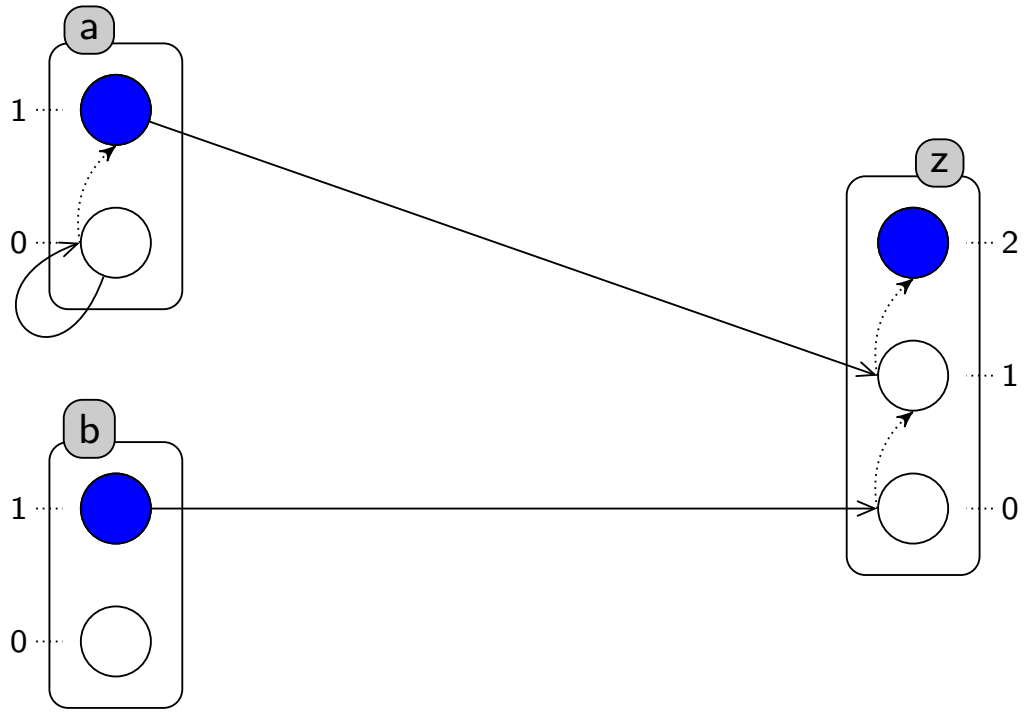

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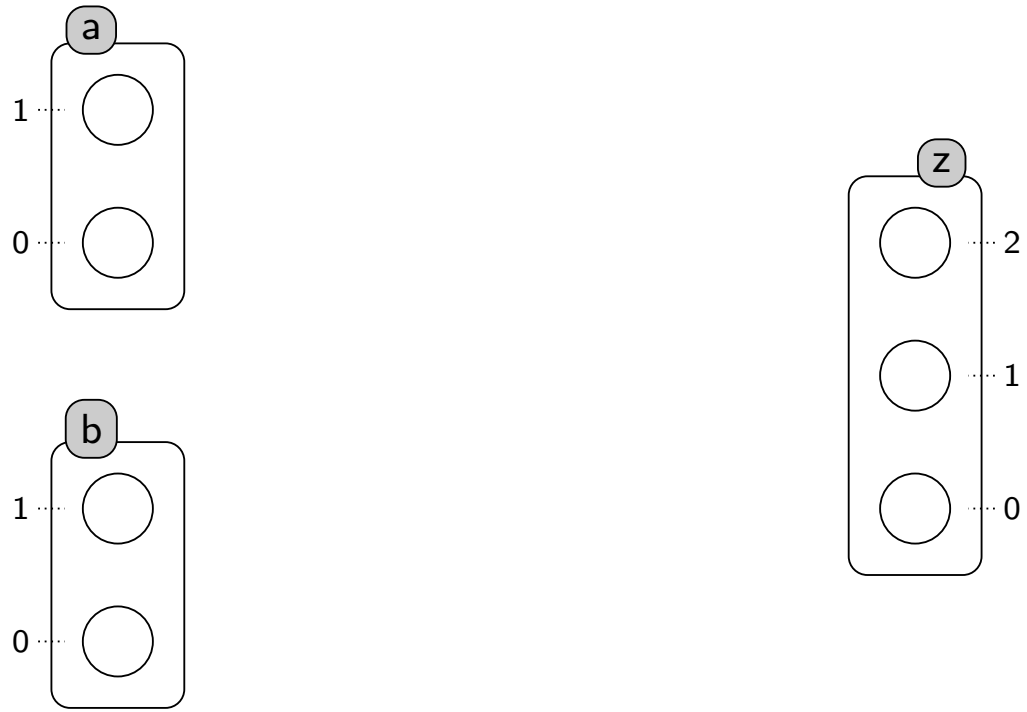

How to introduce some **cooperation** between sorts?

The Process Hitting modeling

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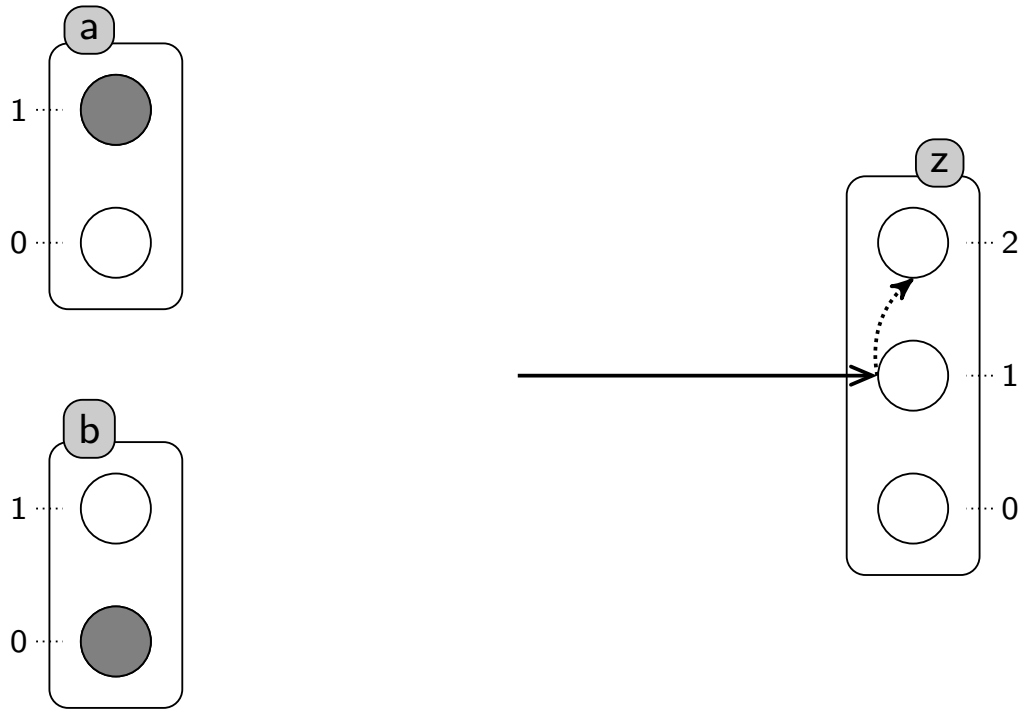

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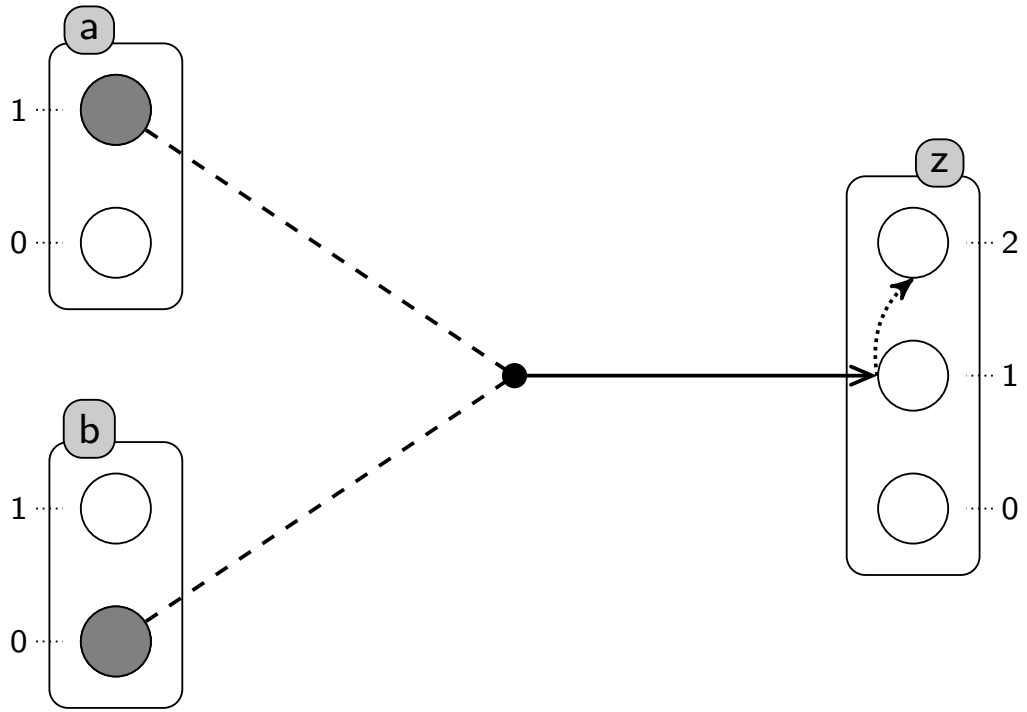

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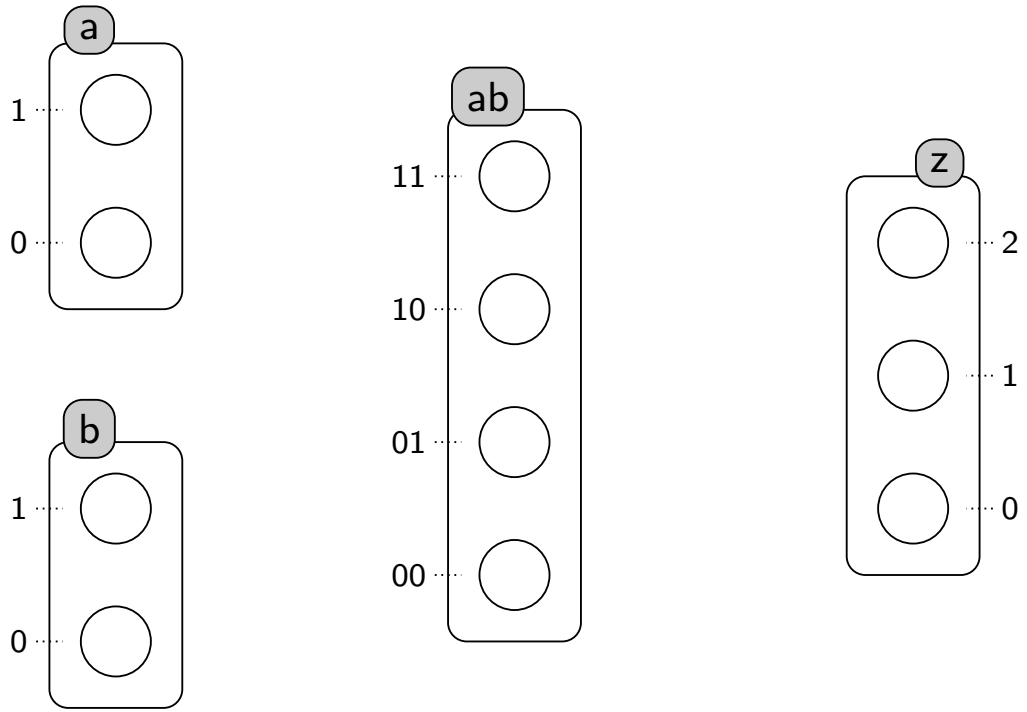

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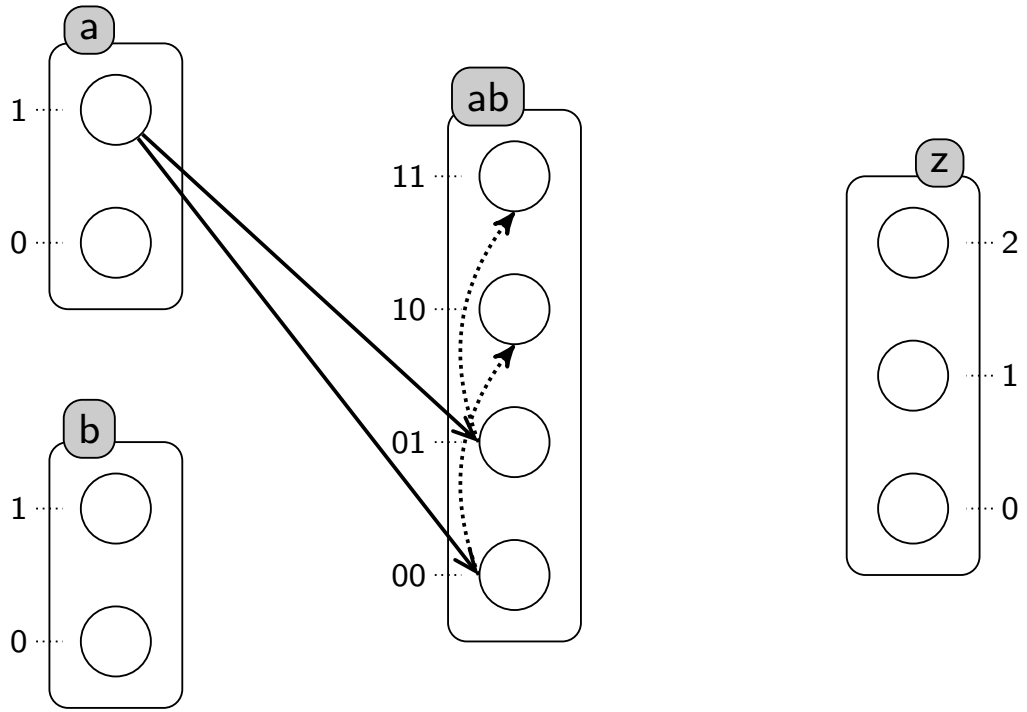

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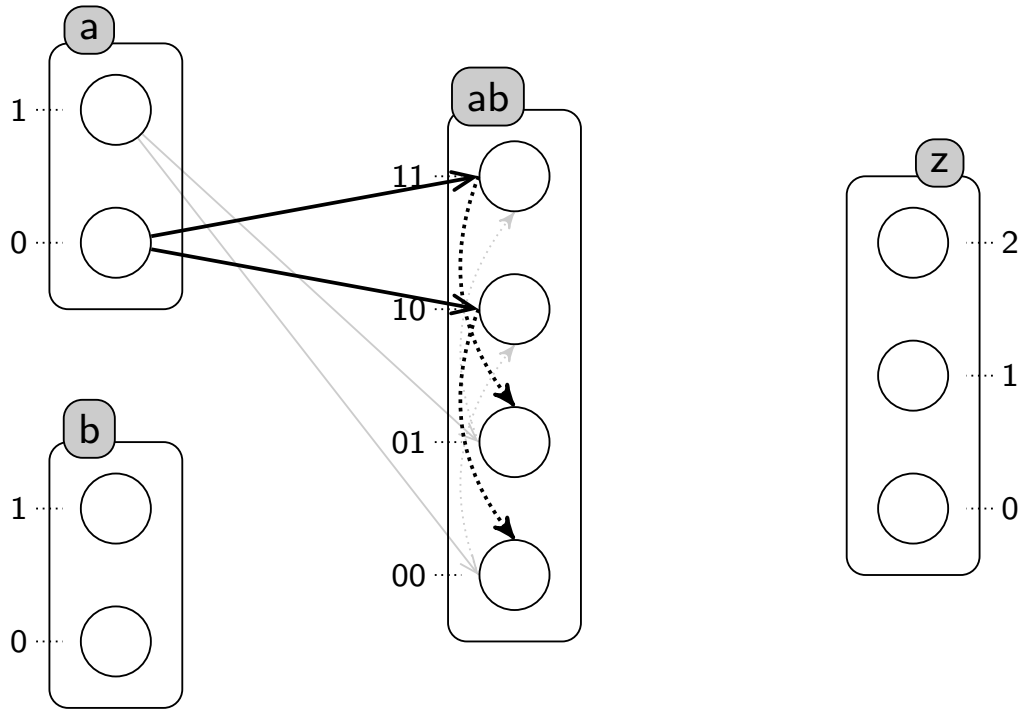

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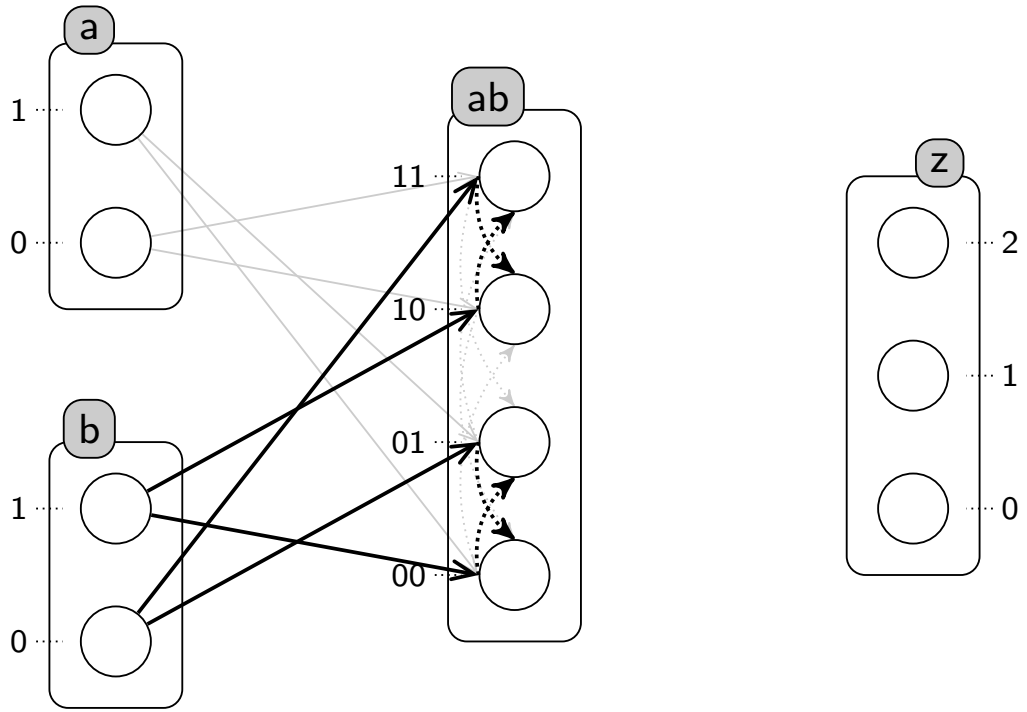

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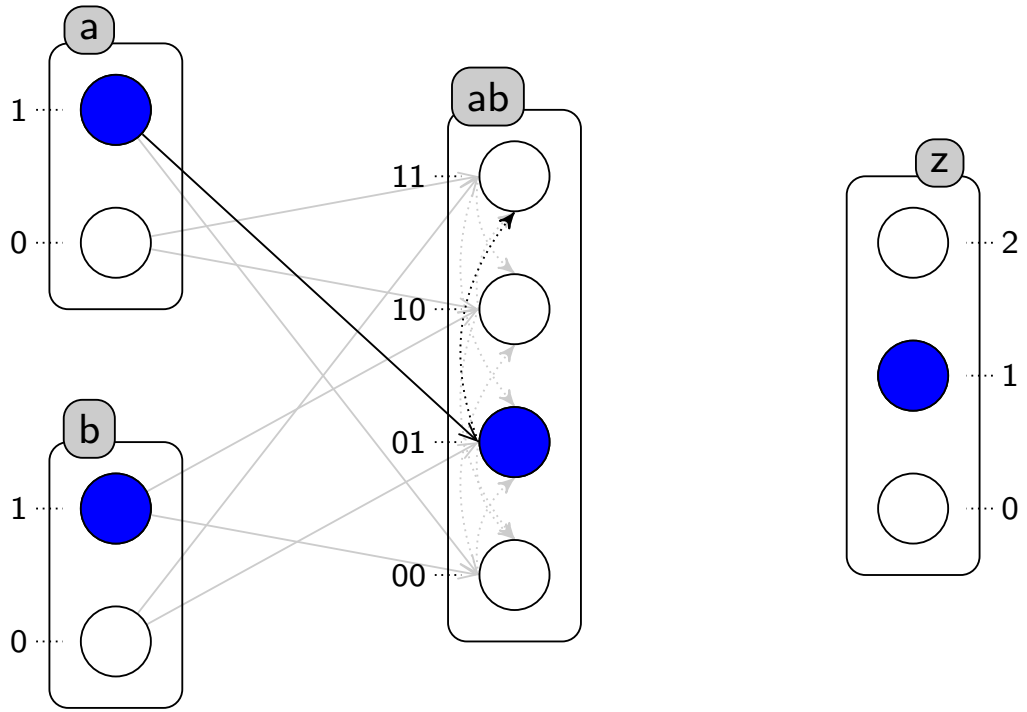

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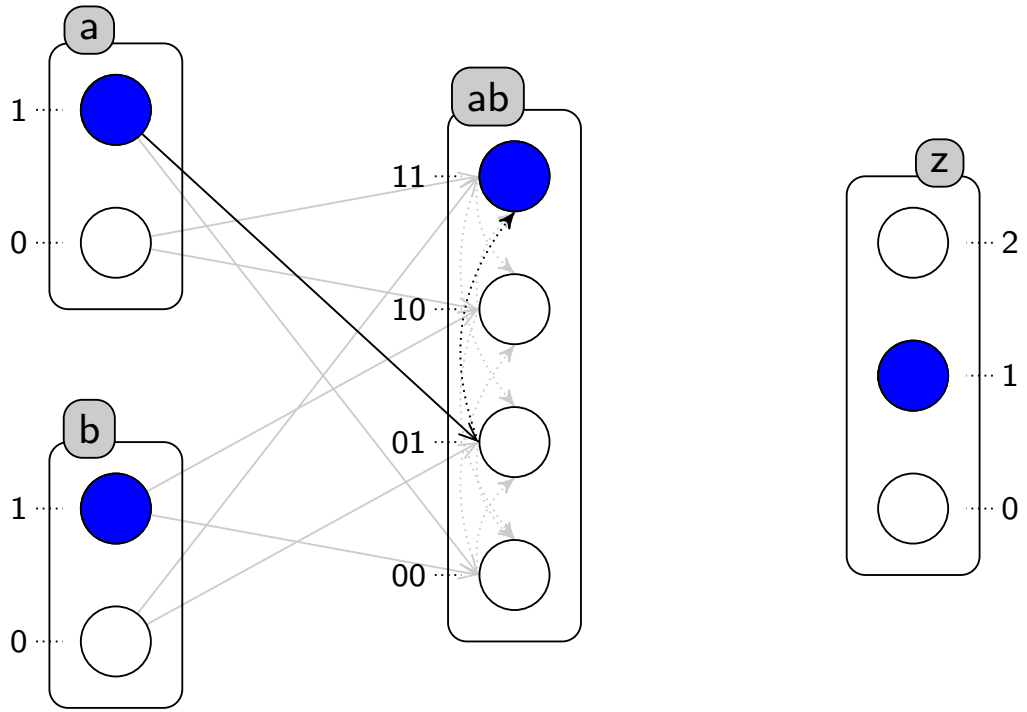

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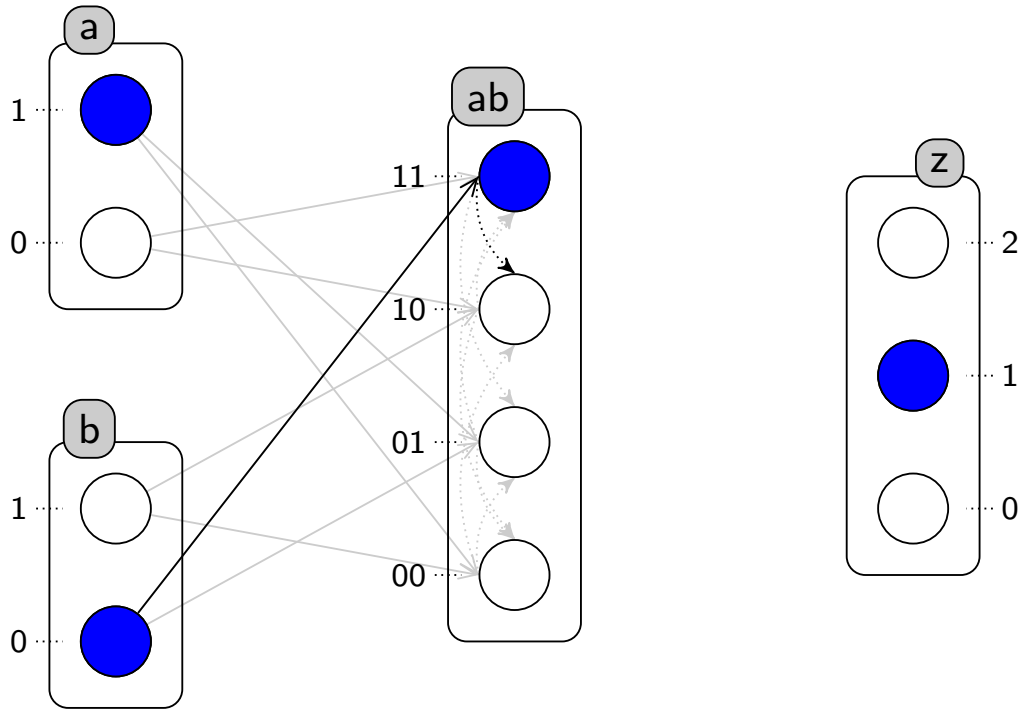

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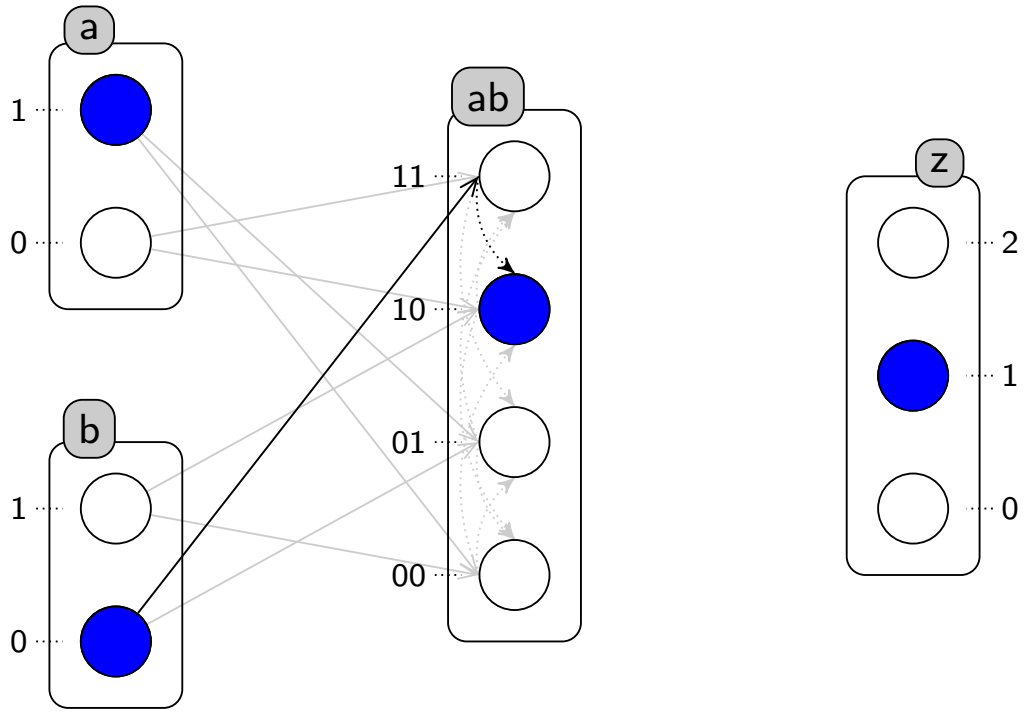

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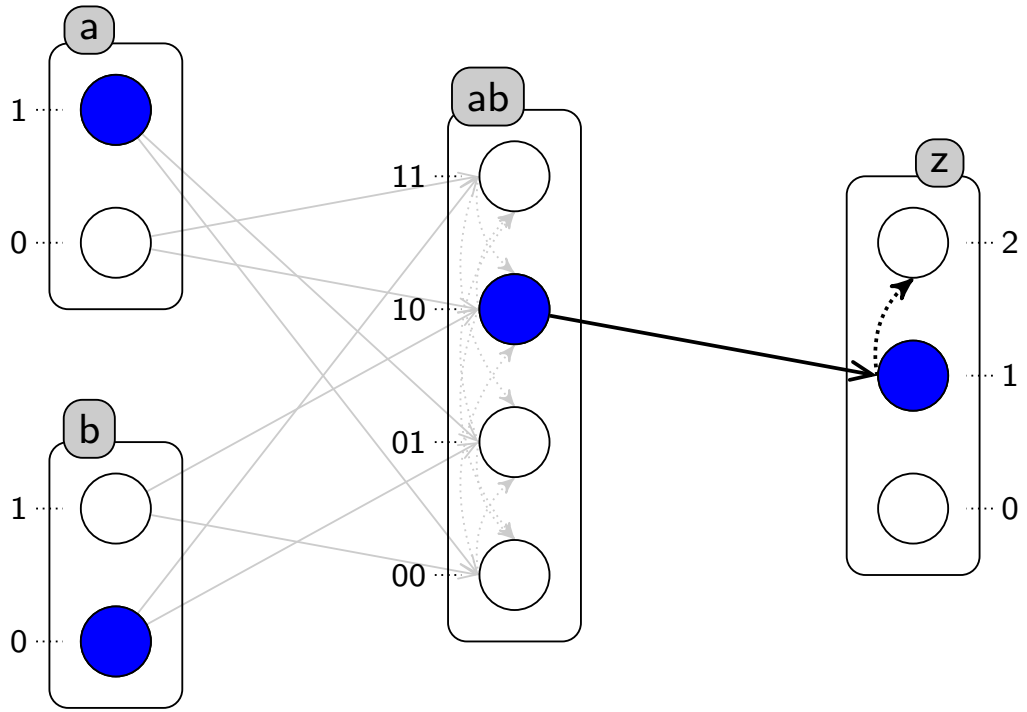

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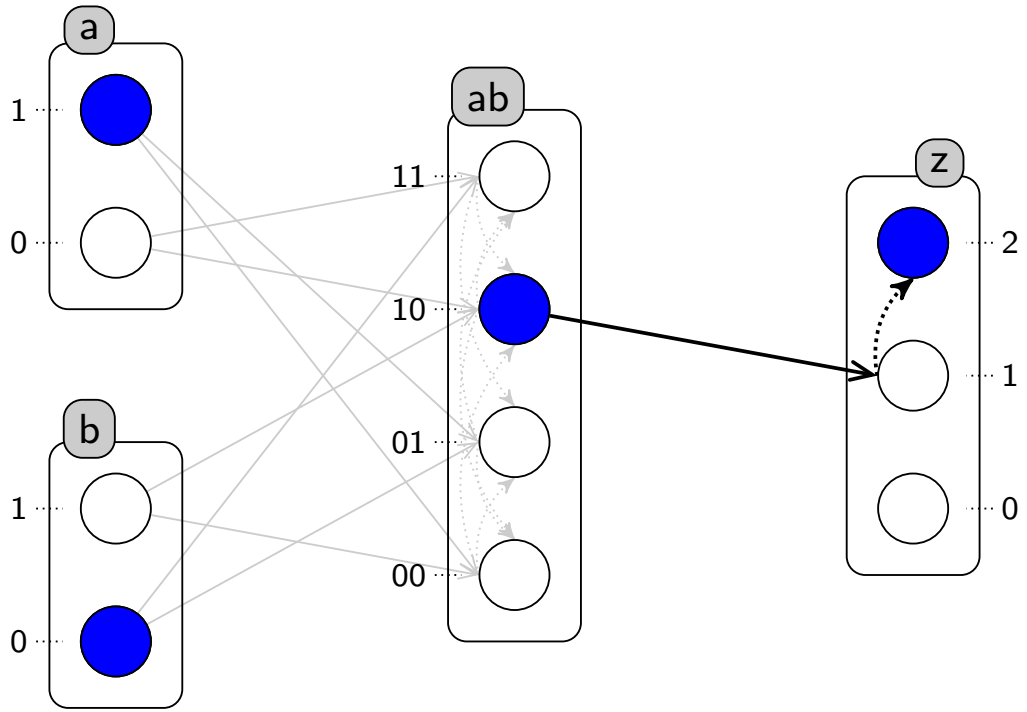

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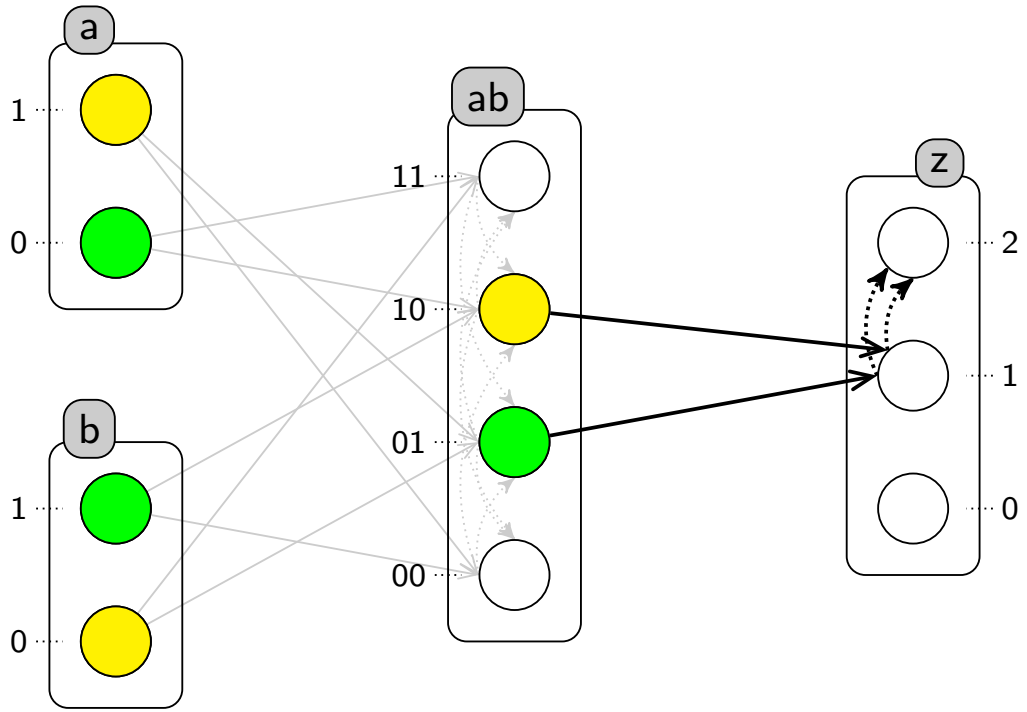

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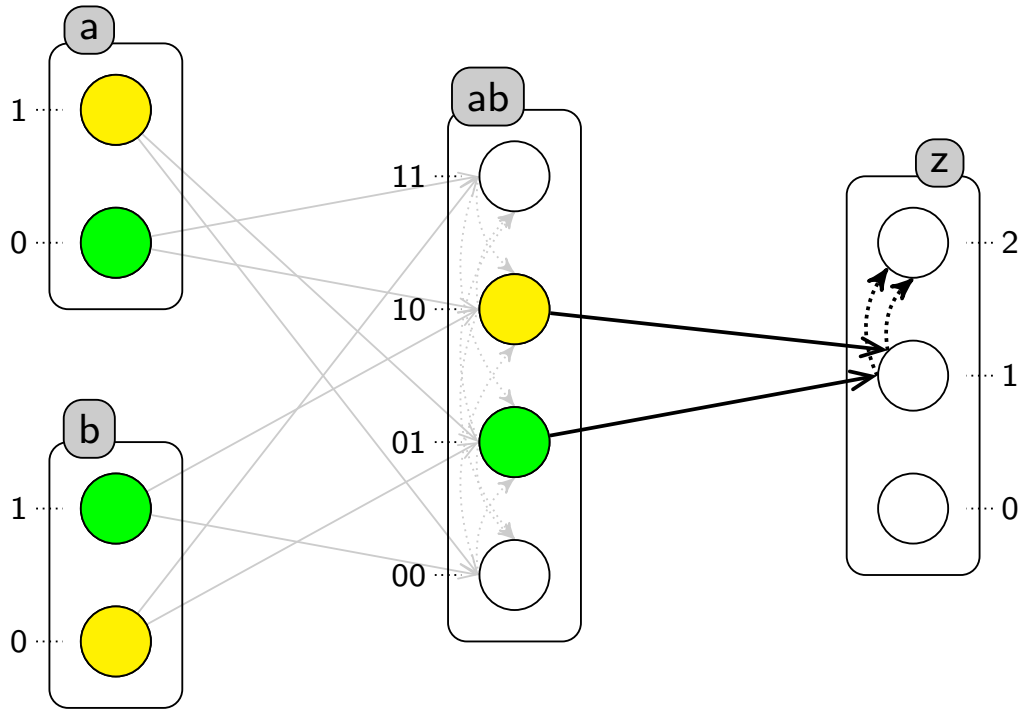

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Drawbacks: complexity, temporal shift

The Process Hitting modeling

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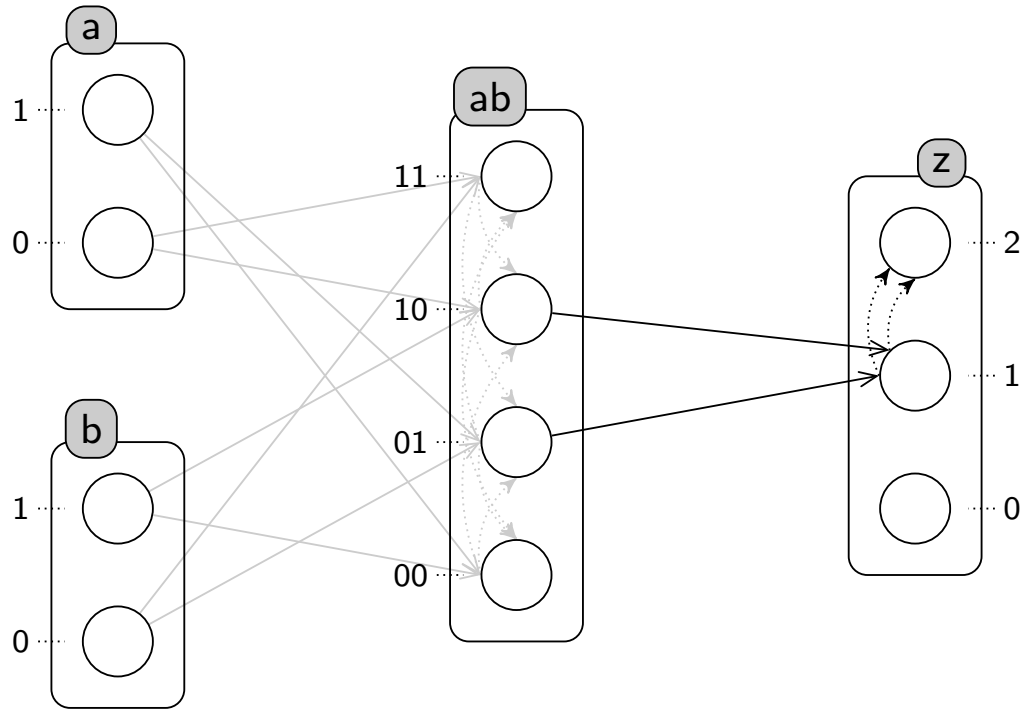
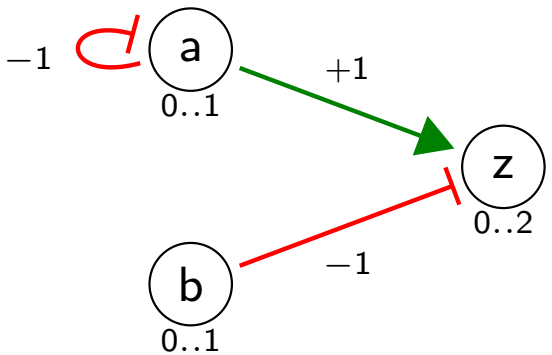


The Process Hitting framework:

- **Dynamic** modeling with an **atomistic** point of view
- Efficient **static analysis** (fixes points, reachability)
- Possible extensions (stochasticity, priorities)
- Useful for the study of **large bioinformatics systems**

René Thomas' Modeling

[RCB08]



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$\varnothing$	1
$\{b\}$	0
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$\{a; b\}$	1

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Historical bio-informatics model for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

René Thomas' Modeling

[RCB08]

Interaction Graph

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Interaction Graph: structure of the system (genes & interactions)

René Thomas' Modeling

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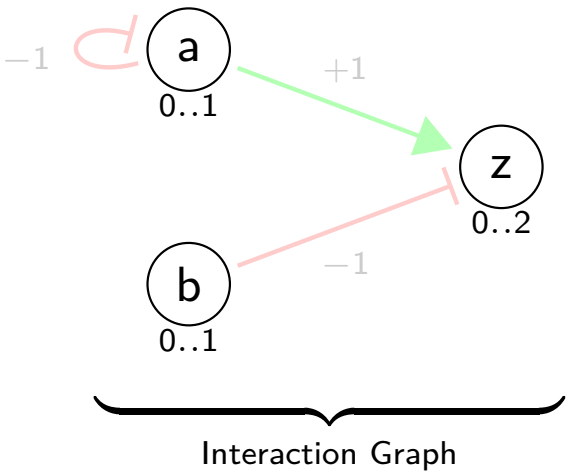

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→ Name a, b, z

→ Possible values (levels of expression) 0..1, 0..2

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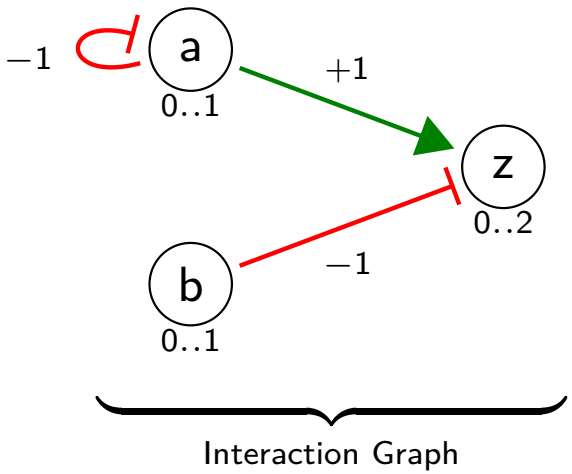

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Edges: interactions

→ Type (activation or inhibition) $+$ / $-$

→ Threshold 1

René Thomas' Modeling

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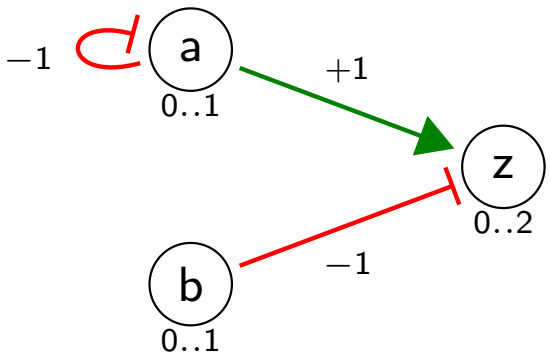

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Parametrization

Parametrization: strength of the influences (evolution tendencies)

René Thomas' Modeling

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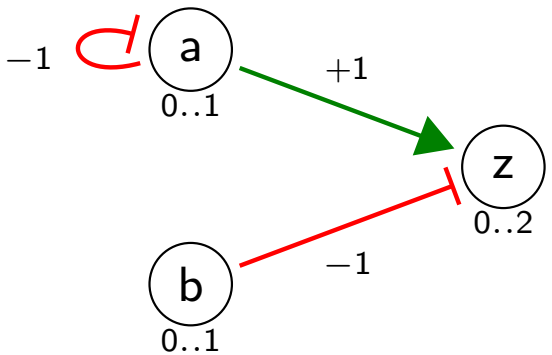

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Maps of tendencies for each gene

→ To any **set of predecessors** ω

→ Corresponds a **parameter** $k_{x,\omega}$

René Thomas' Modeling

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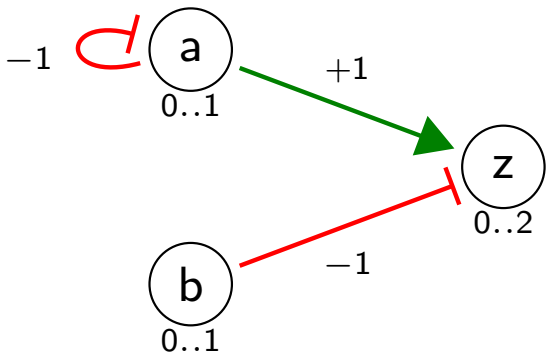

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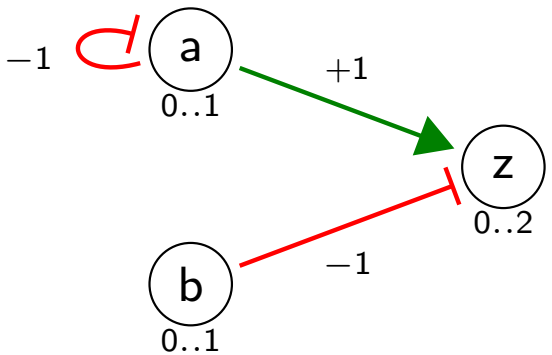

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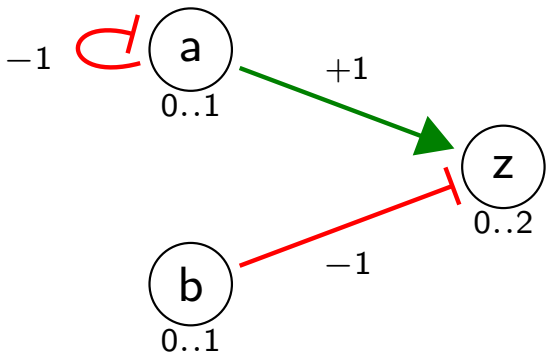

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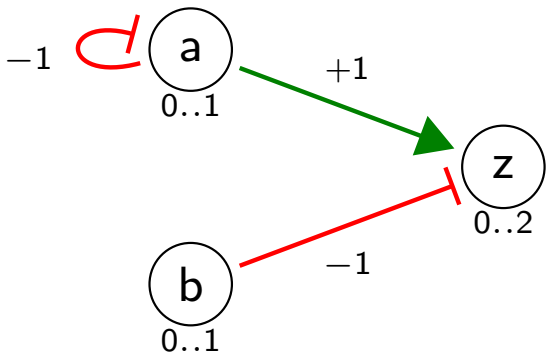

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ω	$k_{a,\omega}$
$\varnothing$	1
$\{a\}$	0

ω	$k_{b,\omega}$
$\varnothing$	1

Parametrization

Parametrization: strength of the influences (evolution tendencies)

Maps of tendencies for each gene

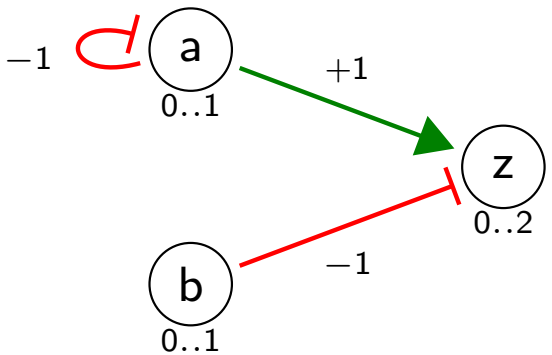
→ To any **set of predecessors** ω

→ Corresponds a **parameter** $k_{x,\omega}$

"$k_{z,\{a\}} = 2$" means: "z tends to 2 when $a = 1$ and $b = 0$"

René Thomas' Modeling

[RCB08]



ω	$k_{z,\omega}$
$\varnothing$	1
$\{b\}$	0
$\{a\}$	2
$\{a; b\}$	1

ω	$k_{a,\omega}$
$\varnothing$	1
$\{a\}$	0

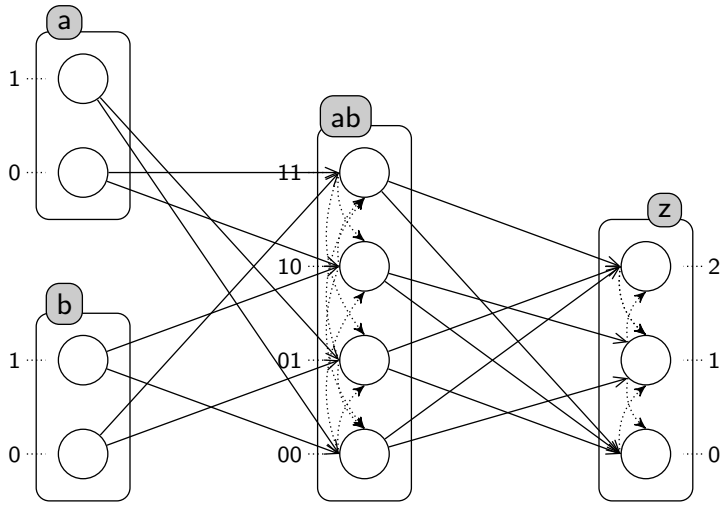
ω	$k_{b,\omega}$
$\varnothing$	1

Biological Regulatory Network

→ All needed information to run the model or study its dynamics:

- Build the State Graph
- Find reachability properties
- Find fixed points or attractors
- Other properties...

Inferring Thomas' Model



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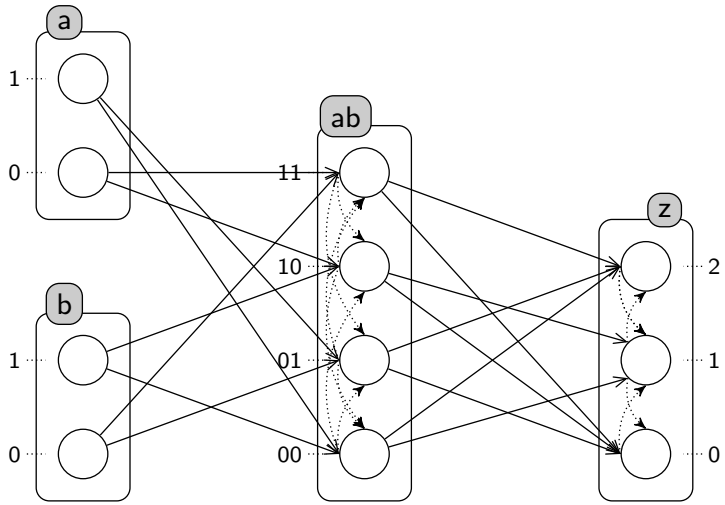
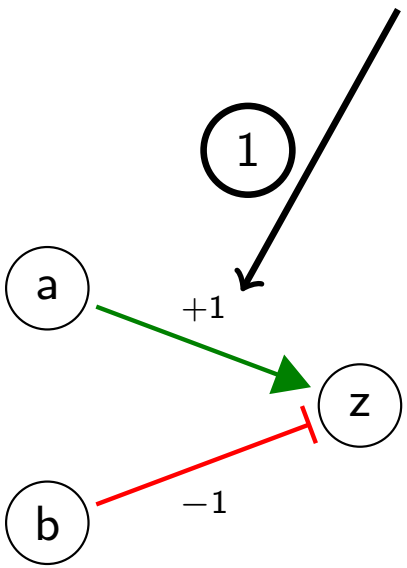
Inferring Thomas' Model





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$\{a\}$	2
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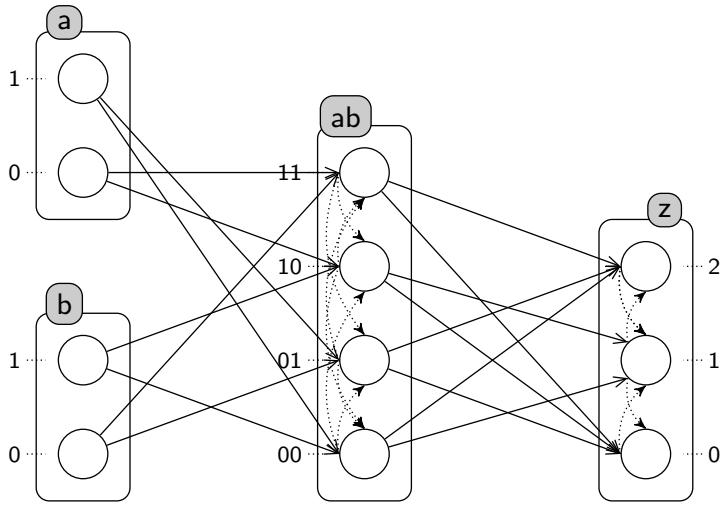

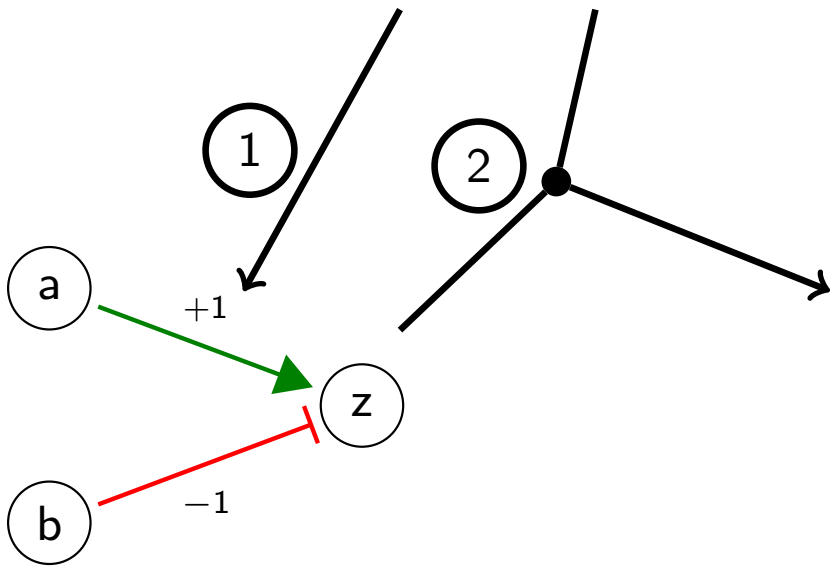

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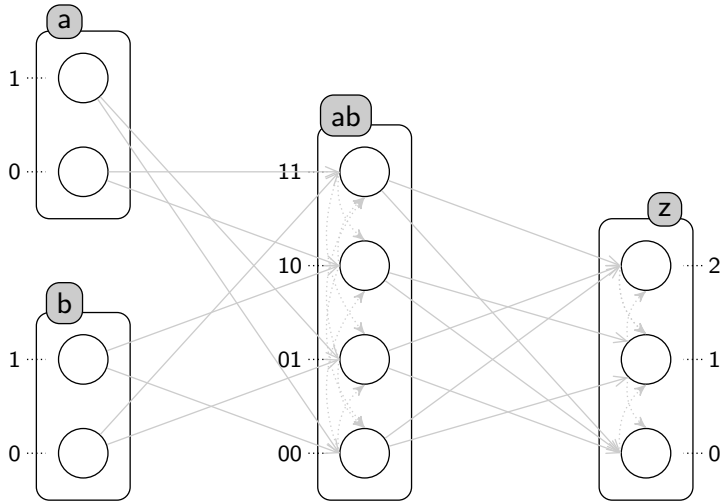
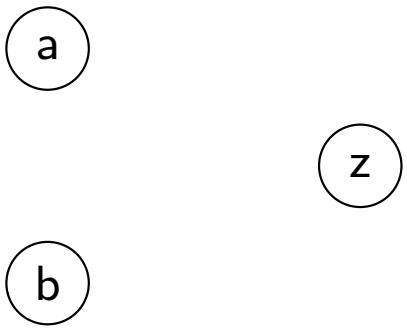
Inferring the Interaction Graph

[Paulevé11]



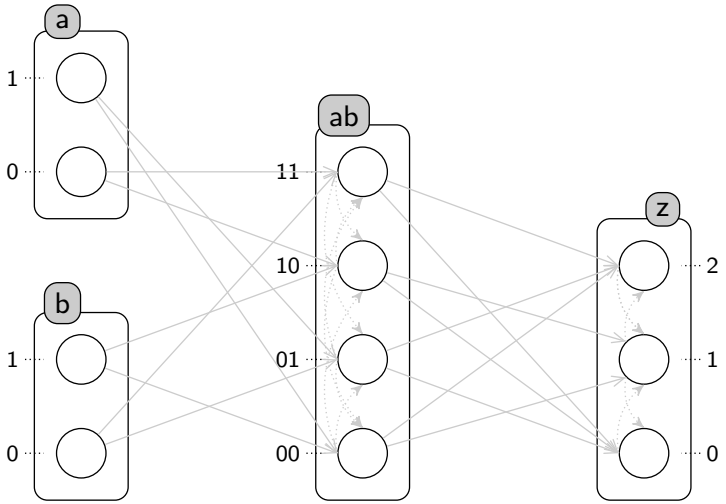


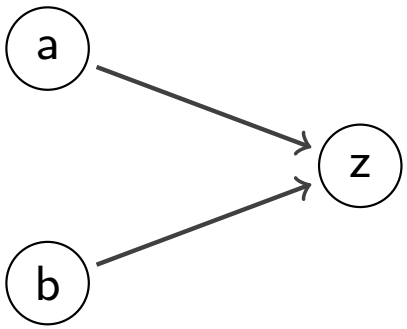
- **Inputs:** a Process Hitting model and a list of genes
  → distinguish cooperative sorts from sorts modeling real genes
- **Output:** An interaction graph with all information:
  → edges, signs and thresholds

- **Difficulties:** The Process Hitting is more atomistic than Thomas' modeling
- **Idea:** Enumeration of the possible configurations

Inferring the Interaction Graph

[Paulevé11]

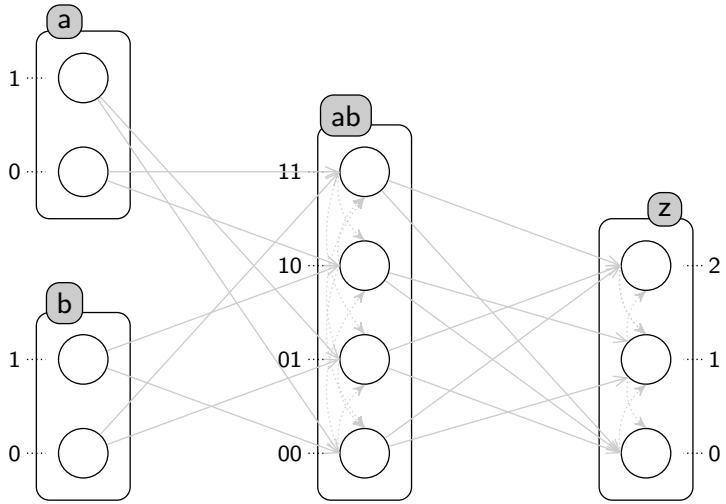


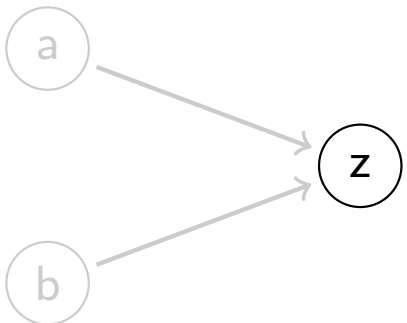


- Determine possible influences ($a \to z$, $b \to z$)

Inferring the Interaction Graph

[Paulevé11]

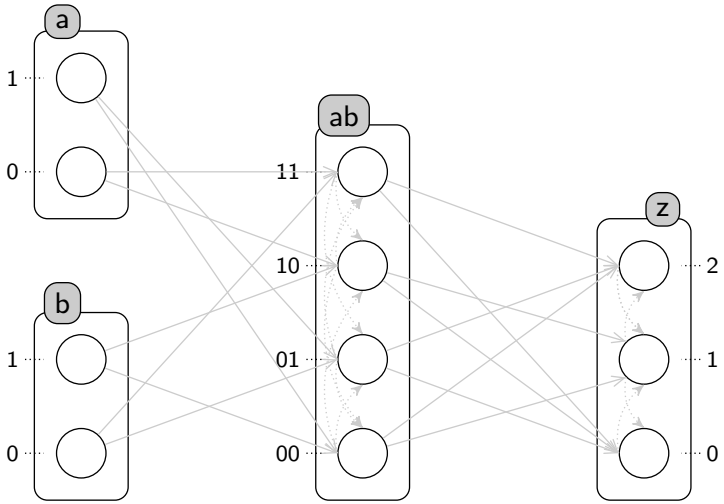


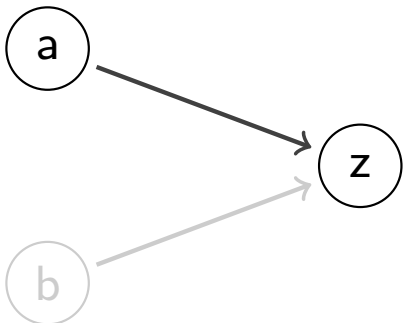


- Determine possible influences ($a \to z$, $b \to z$)
- For each gene $[z]$

Inferring the Interaction Graph

[Paulevé11]





- Determine possible influences ($a \to z$, $b \to z$)
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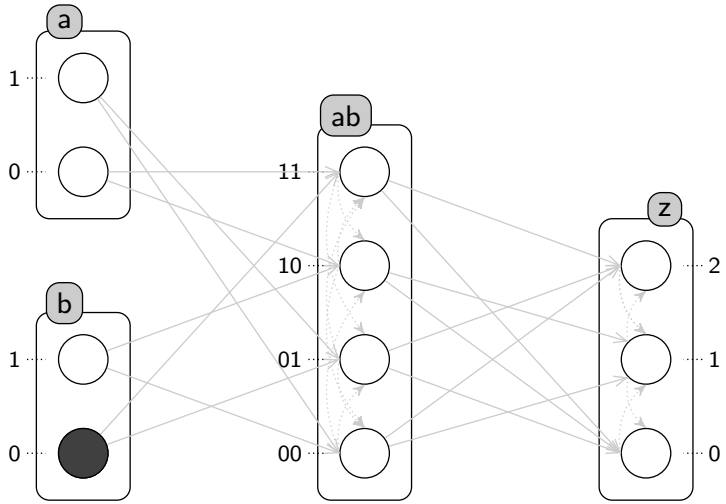
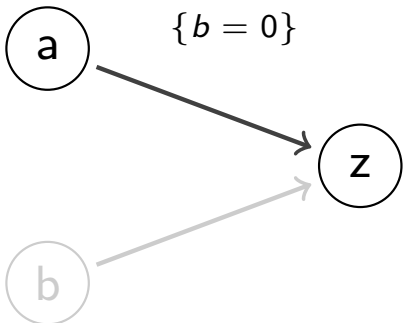
Inferring the Interaction Graph

[Paulevé11]





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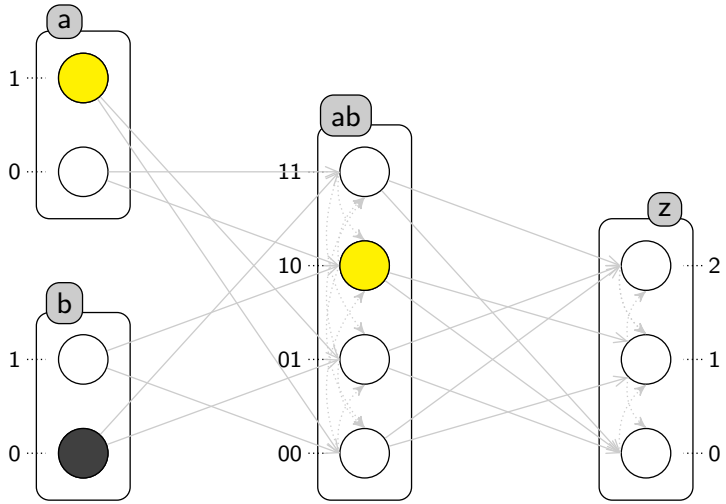
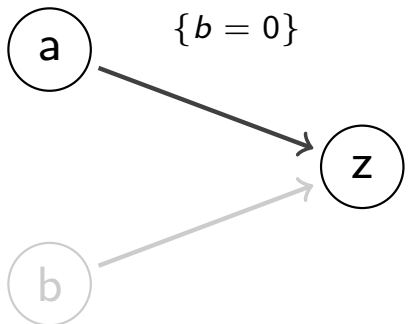
Inferring the Interaction Graph

[Paulevé11]





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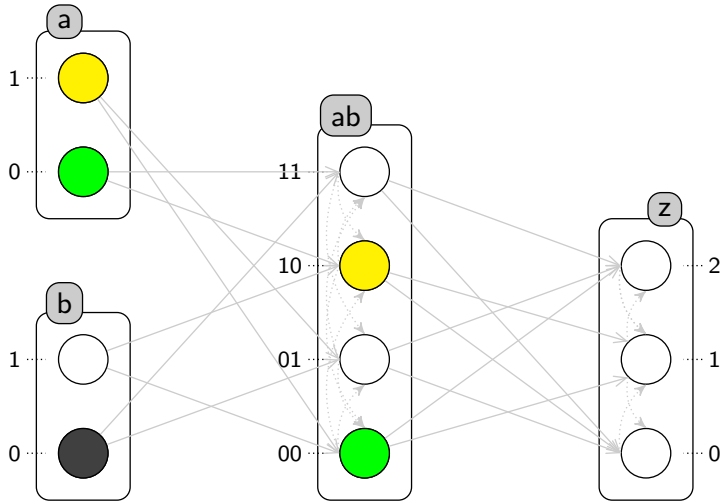
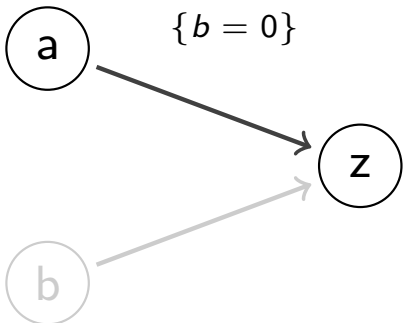
Inferring the Interaction Graph

[Paulevé11]





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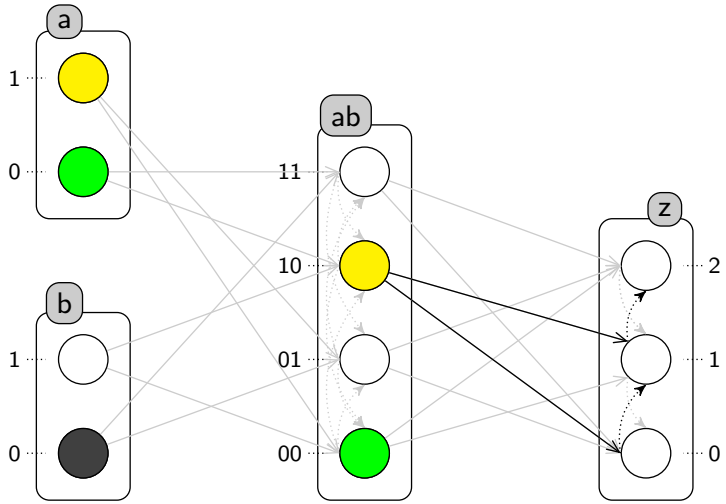

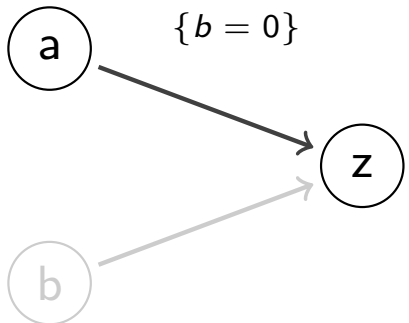

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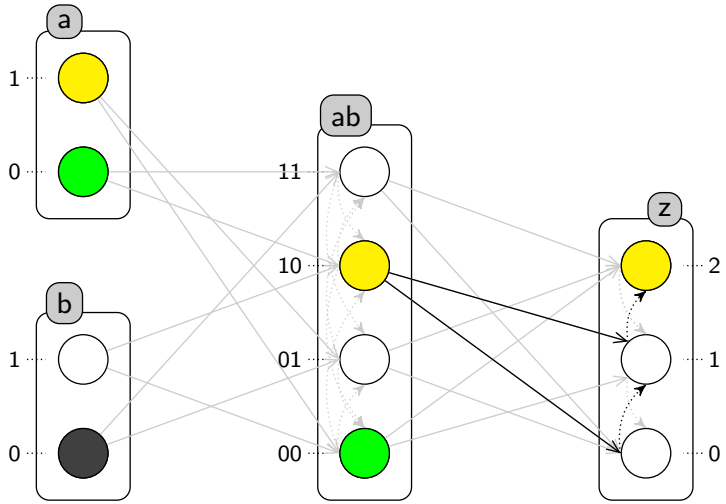

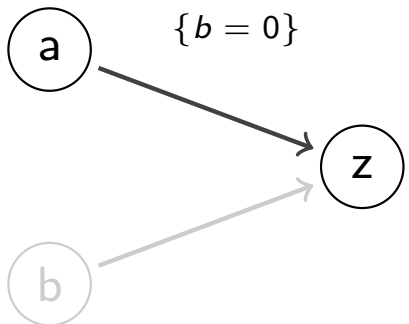

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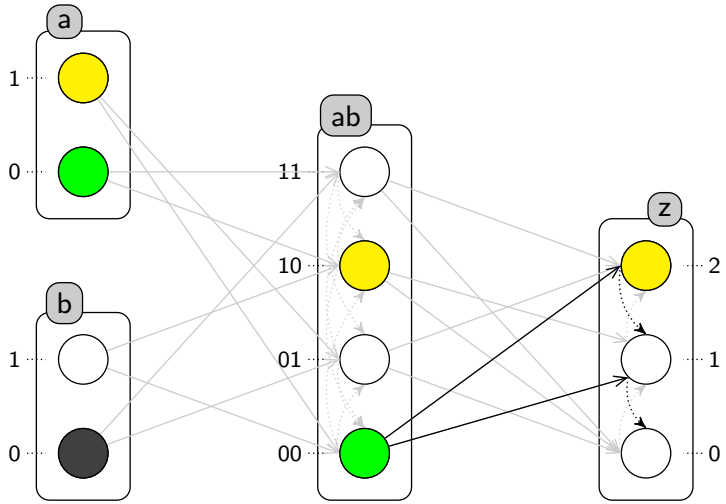

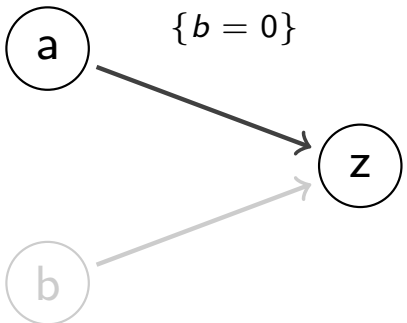

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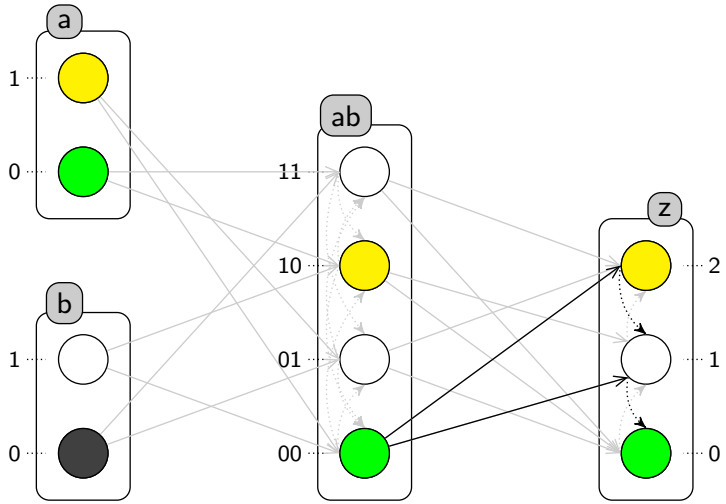

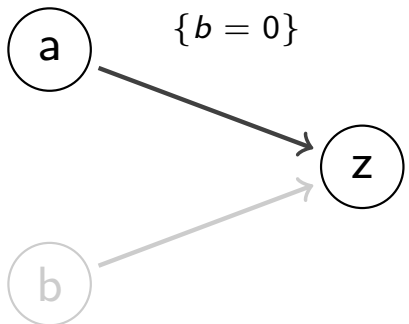

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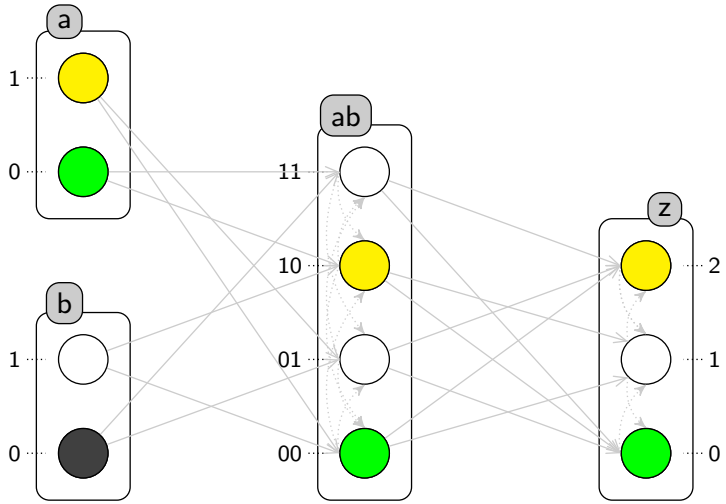

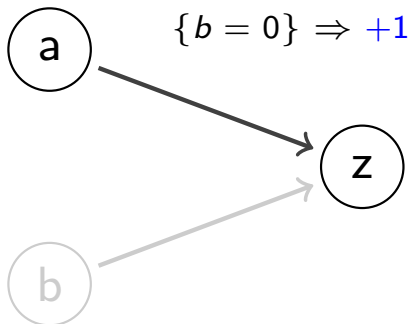

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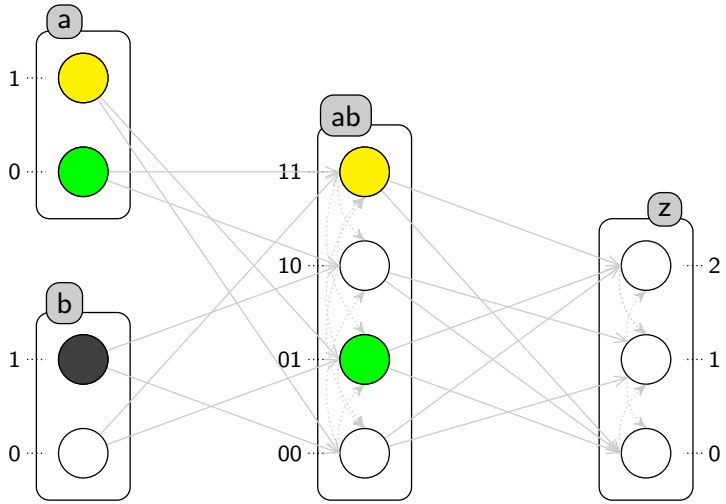
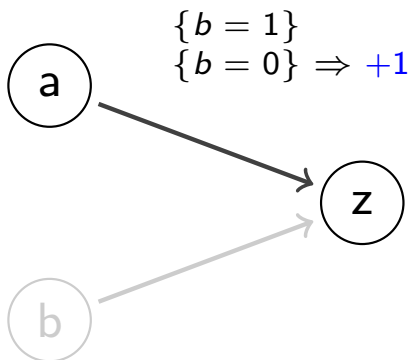
    $\{b = 0\} \to a_0 < a_1$ and $\{z_0\} \preccurlyeq \{z_2\} \Rightarrow$ activation ($+$) & threshold $= 1$

Inferring the Interaction Graph

[Paulevé11]





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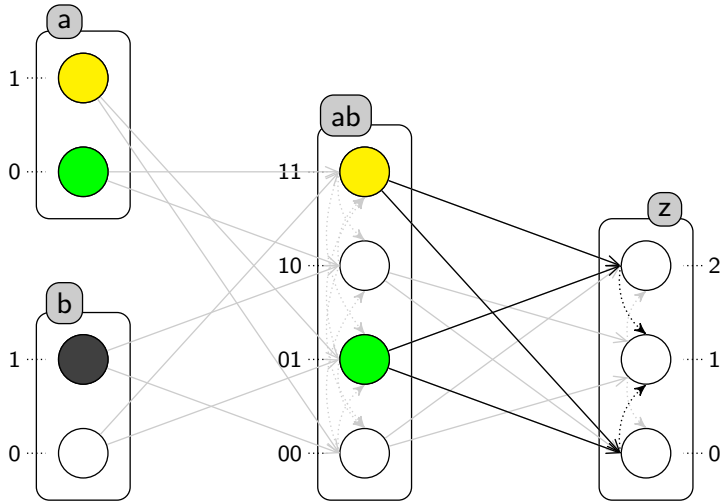

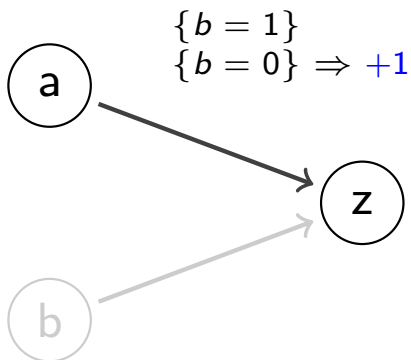

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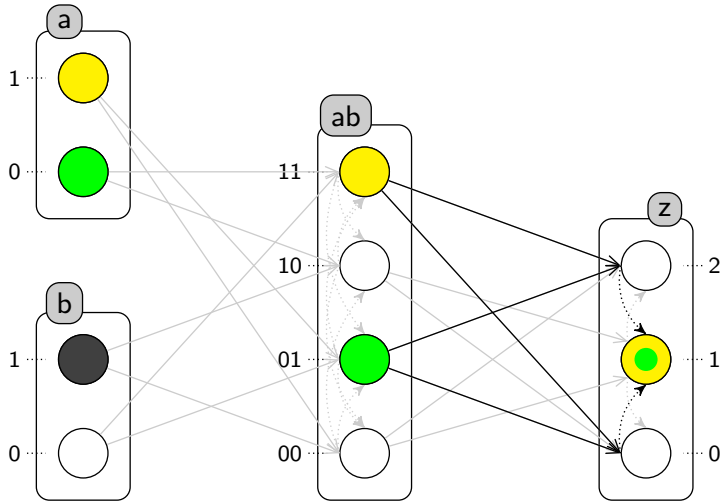

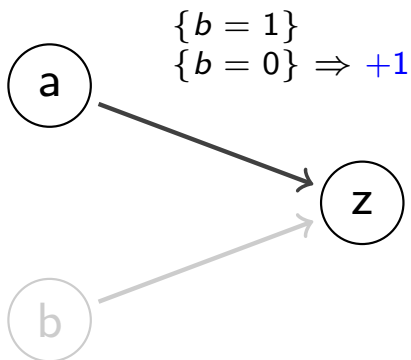

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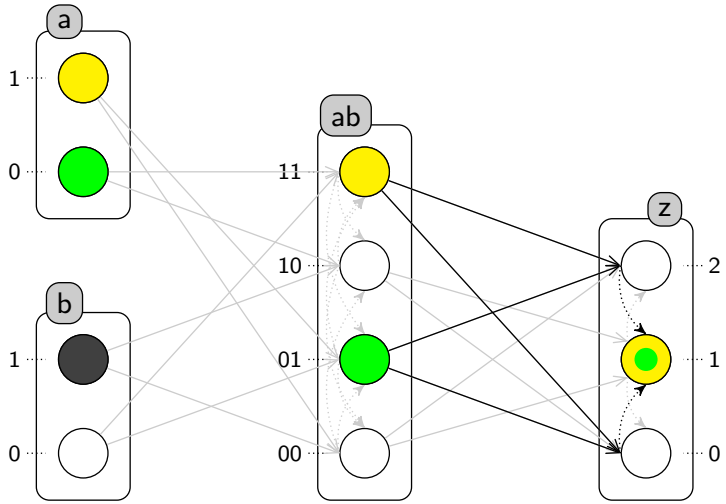

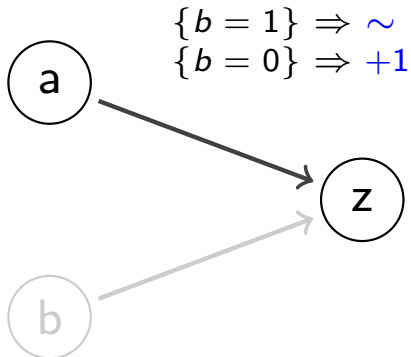

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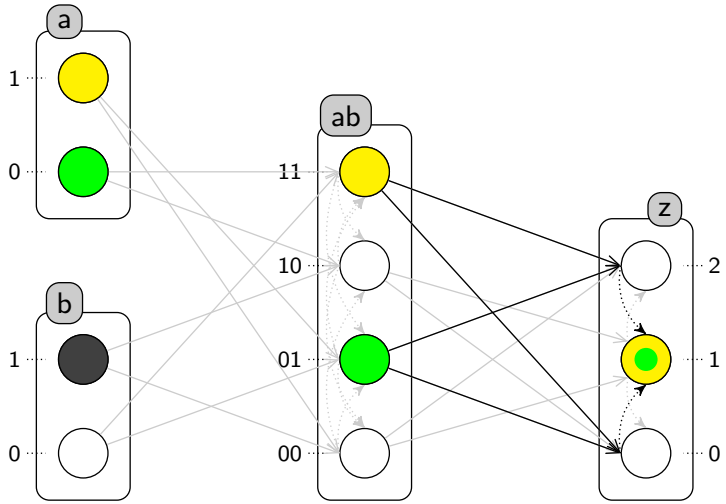

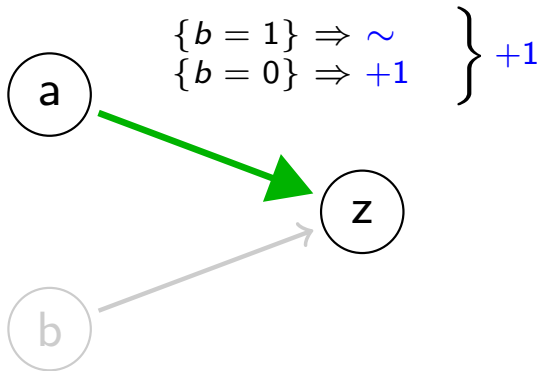

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    $\{b = 0\} \to a_0 < a_1$ and $\{z_0\} \preccurlyeq \{z_2\} \Rightarrow$ activation ($+$) & threshold $= 1$
    $\{b = 1\} \to a_0 < a_1$ and $\{z_1\} = \{z_1\} \Rightarrow$ inconclusive ($\sim$)
- If possible, determine the general influence of a on z

Inferring the Interaction Graph

Implementation & Results

Programming in ASP:

- Formal mathematical definitions $\rightarrow$ ASP
- Use of aggregates (enumeration = 1 active process per sort)

Inferring the Interaction Graph

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Calling ASP:

- Pint (existing OCaml library) to read Process Hitting models

  [http://processhitting.wordpress.com/]
- OCaml to translate these models to an ASP description
- Clingo to solve the description with the adequate program

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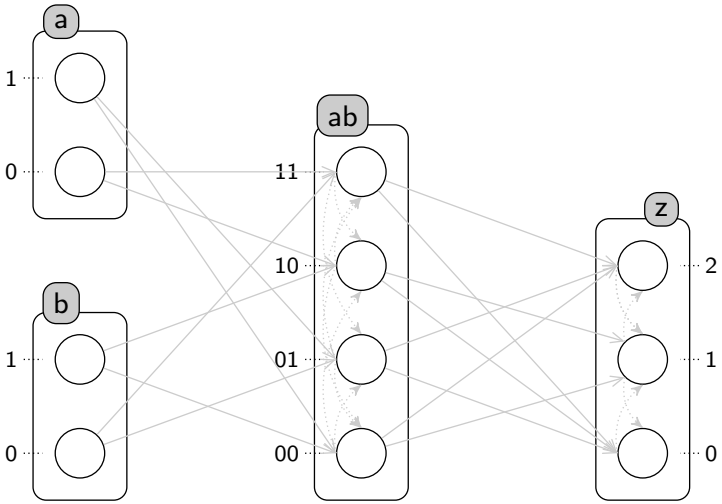
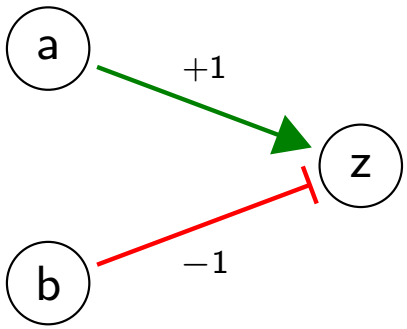
Results:

- Fast execution for "well-shaped" models
  (execution time $<$ 1s for a 40 genes model)
- Very slow execution for "bad-shaped" models
  (with too many predecessors for some genes)

Inferring the Parametrization

[PMR10-TCSB]



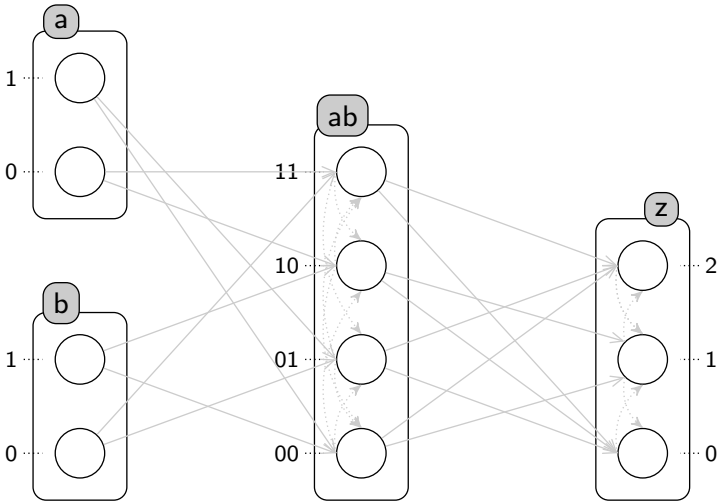


ω	$k_{z,\omega}$
$\varnothing$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	

Inputs: The Process Hitting model and the related Interaction Graph
Output: The Parametrization related to the Interaction Graph

Inferring the Parametrization

[PMR10-TCSB]



ω	$k_{z,\omega}$
$\varnothing$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	

Inputs: The Process Hitting model and the related Interaction Graph
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Similar approach than Interaction Graph Inference (**focal processes**)

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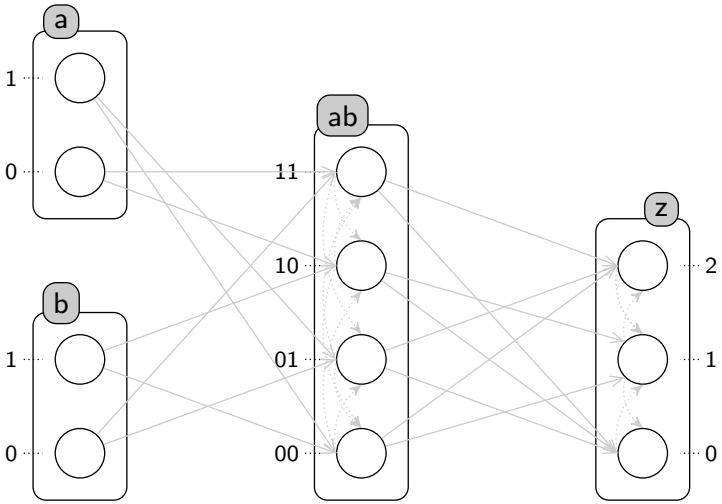

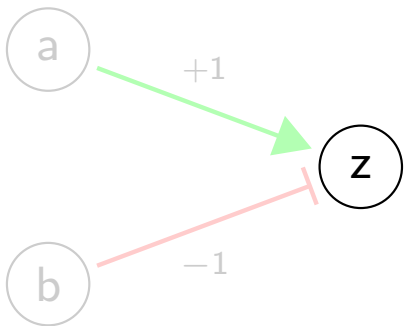

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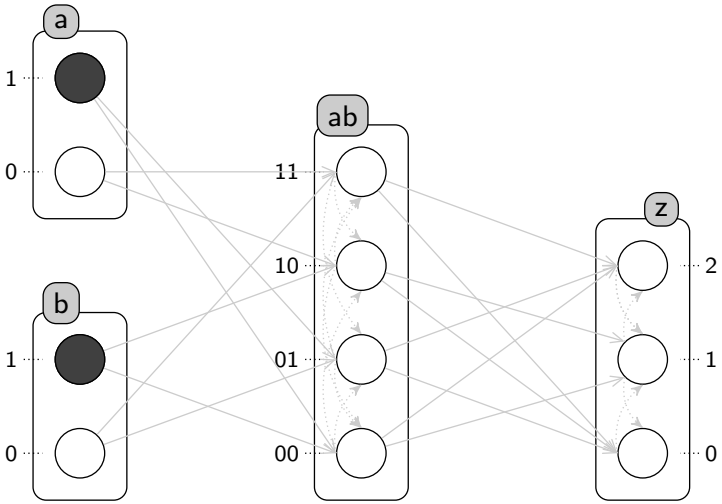

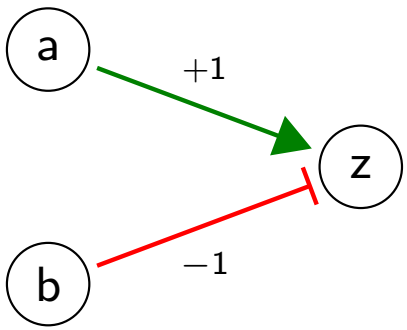

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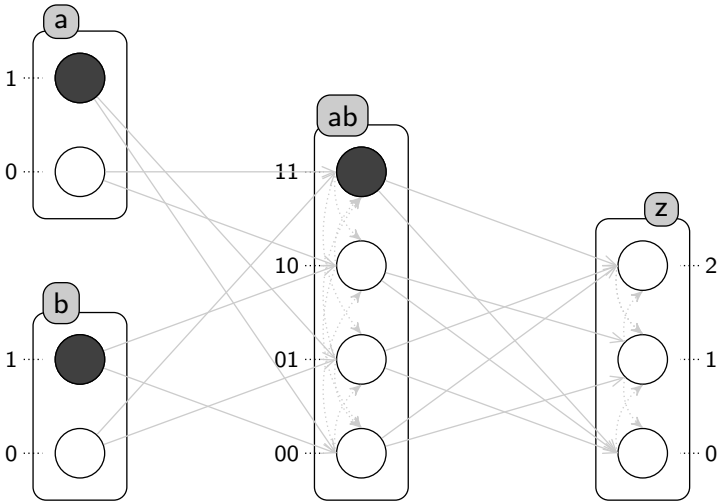

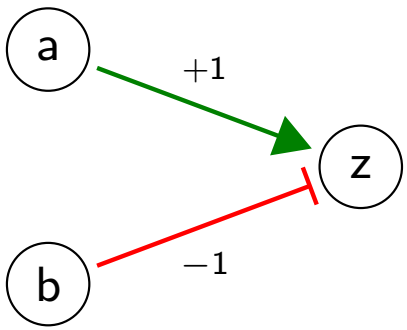

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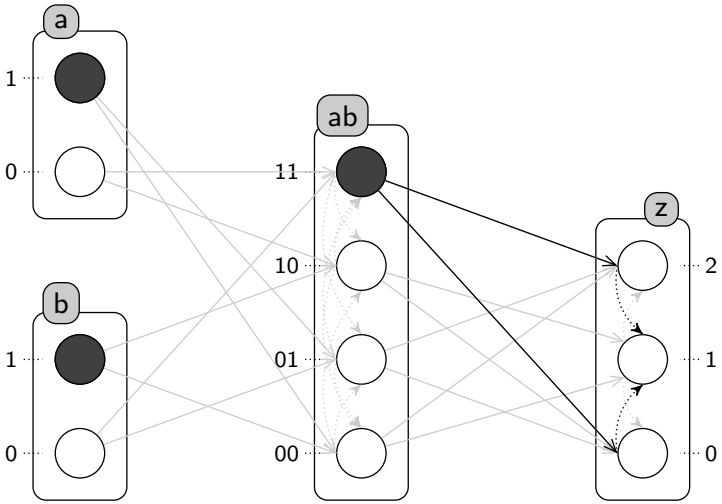

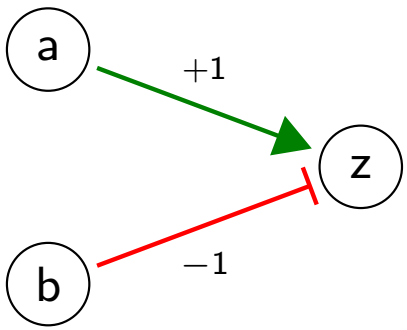

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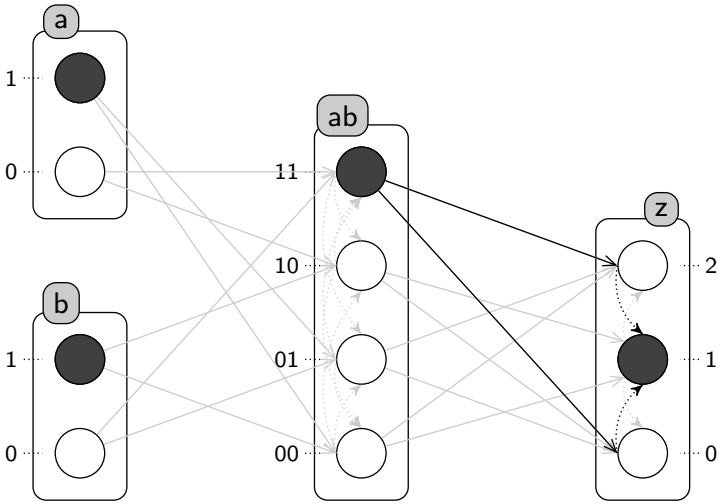
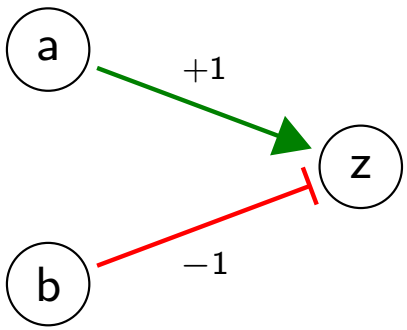
Inferring the Parametrization

[PMR10-TCSB]





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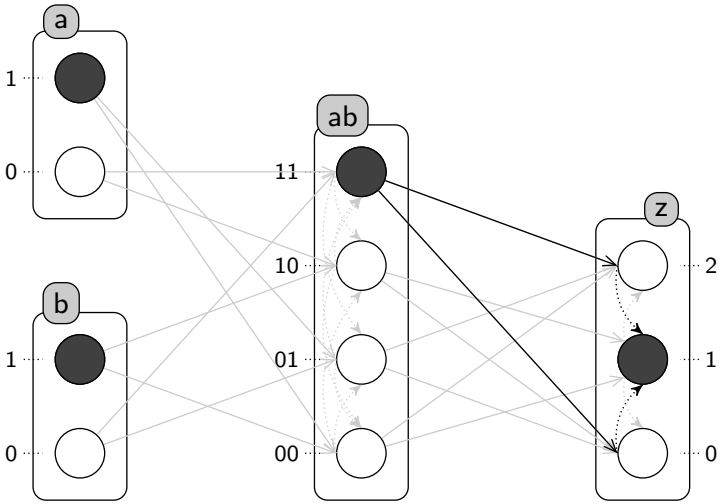

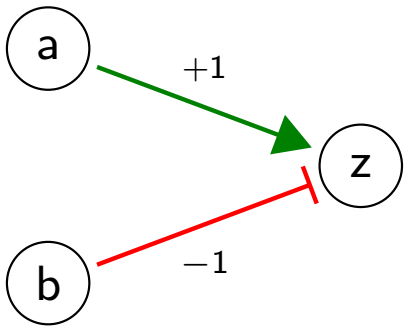

ω	$k_{z,\omega}$
$\varnothing$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	1

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- For each gene $[z]$
- For each configuration of active predecessors $[\omega = \{a; b\}]$
  - Find the set of focal processes of the gene $[\{z_1\}]$
  - If this set respects some conditions (attractor, interval)

    $\rightarrow$ Then we have found the parameter $\Rightarrow k_{z,\{a,b\}} = 1$

Inferring the Parametrization

Implementation & Results

Same implementation scheme than Interaction Graph Inference:
OCaml translation (with Pint) to ASP and ASP execution

Inferring the Parametrization

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Same implementation scheme than Interaction Graph Inference:
OCaml translation (with Pint) to ASP and ASP execution

Results:

- Very fast execution
- May give incomplete results for incomplete models
  $\rightarrow$ Give all possible parametrizations?

Work Summary

- Inference of the **complete Interaction Graph**
  → Exhaustive approach to find the mutual influences
- Inference of the **possibly partial Parametrization**
  → Exhaustive approach to find the necessary parameters
- Rules to auto-detect the cooperative sorts
  → The Process Hitting model is the only input

Future Work

- Work on **complete Parametrizations search**
  - → List all compatible parametrizations given some constraints
- Work on the **Projections Approach**
  - → Idea: model reduction (cooperative sorts removal)
  - → Alternative to the exhaustive approach
  - → Lower complexity?

Conclusion

Existing translation: René Thomas $\rightsquigarrow$ Process Hitting

New translation: Process Hitting $\rightsquigarrow$ René Thomas

$\rightarrow$ New **formal link** between the two models

$\rightarrow$ More **visibility** to the Process Hitting

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Thank you

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