— CMSB'2012 —

The 10th Conference on Computational Methods in Systems Biology

Concretizing the Process Hitting into Biological Regulatory Networks

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[2] Inoue Laboratory / NII / Sokendai University (Tokyo, Japan)
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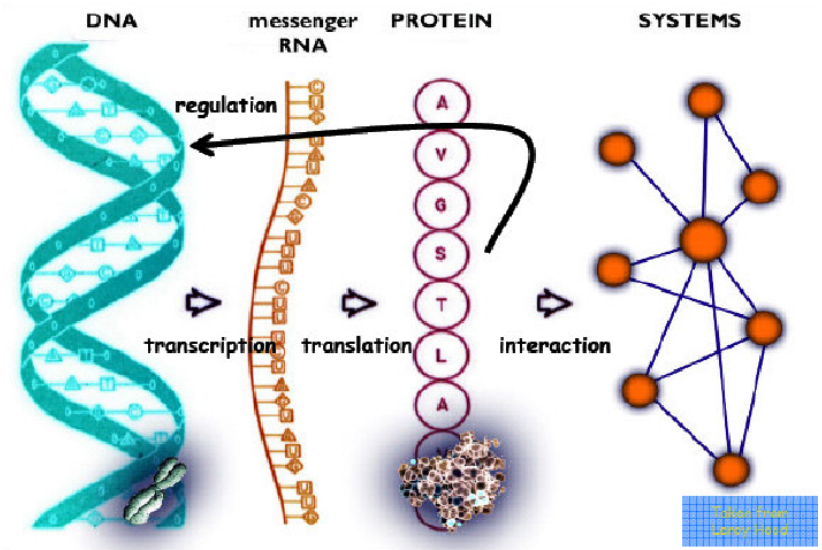
AtlanSTIC sojourn financed by NII & Centrale Initiatives

Context and Aims

Algebraic modeling to study complex dynamical biological systems:



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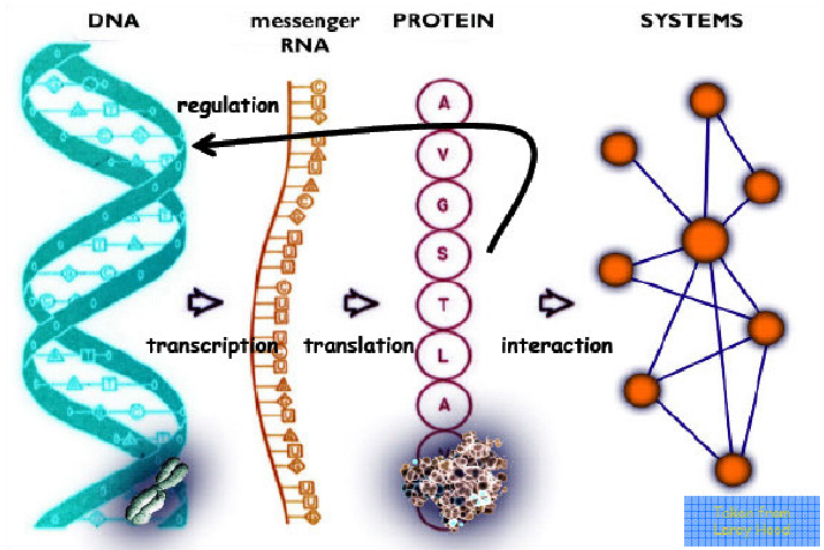
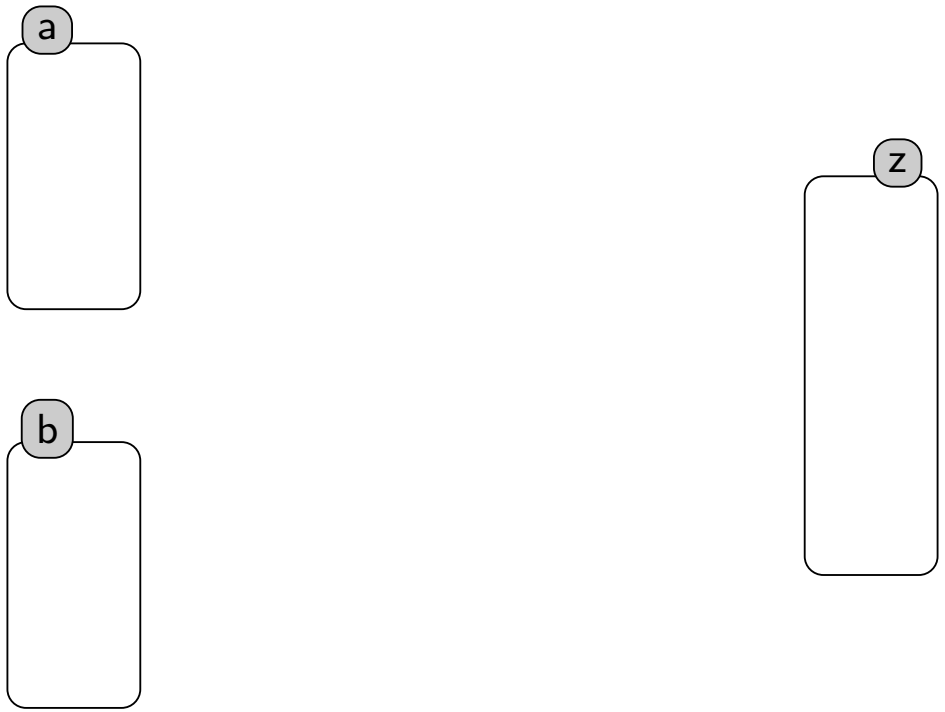


- Historical model: Biological Regulatory Network (René Thomas)
- New developed model: Process Hitting

$\Rightarrow$ **Allow efficient translation from Process Hitting to BRN** $\Leftarrow$

The Process Hitting modeling

[PMR12-MSCS]



Sorts: components a, b, z

The Process Hitting modeling

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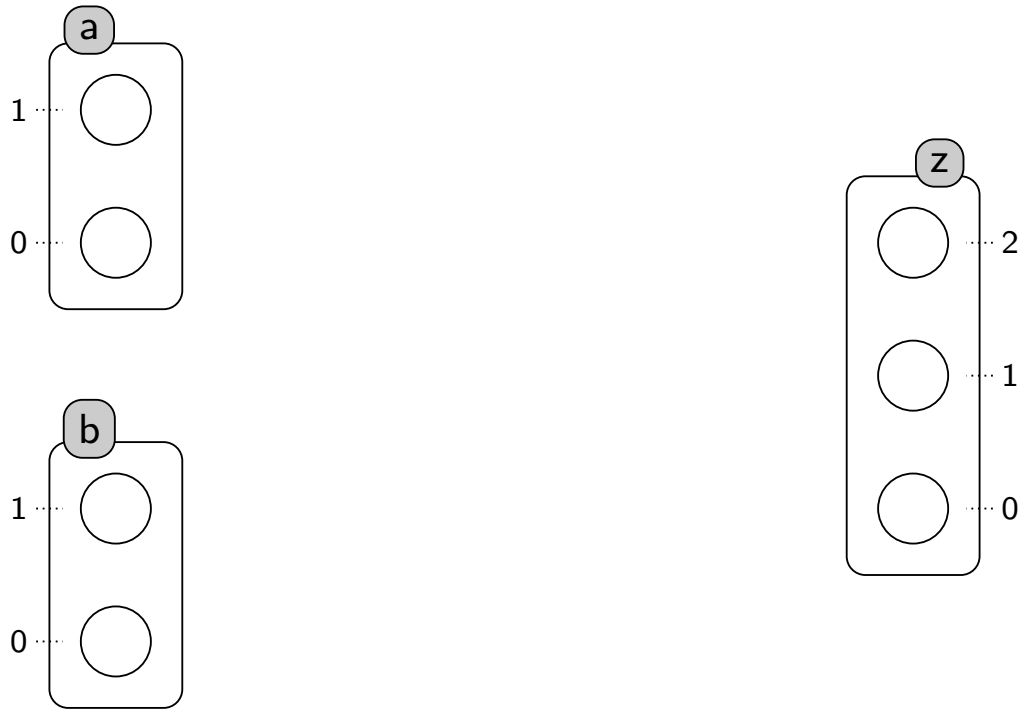

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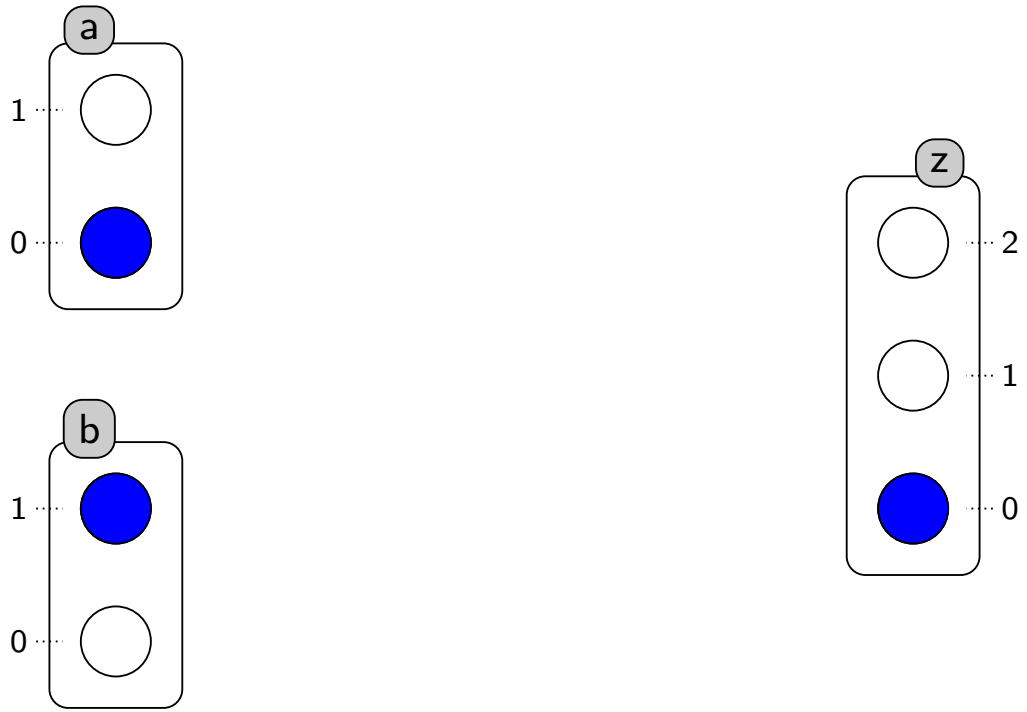

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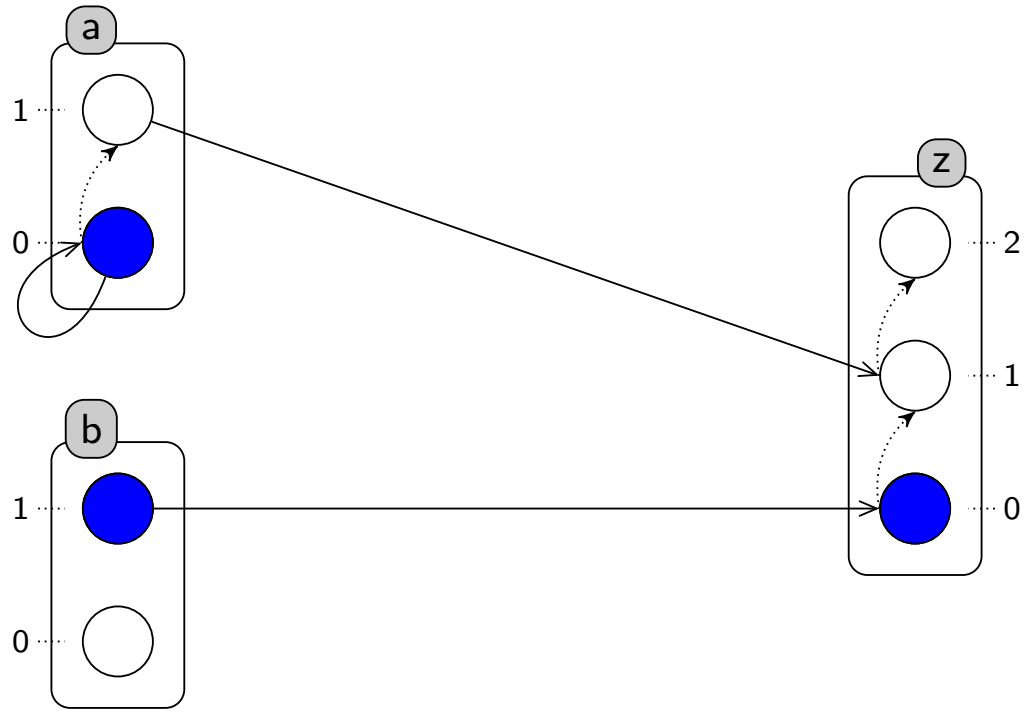

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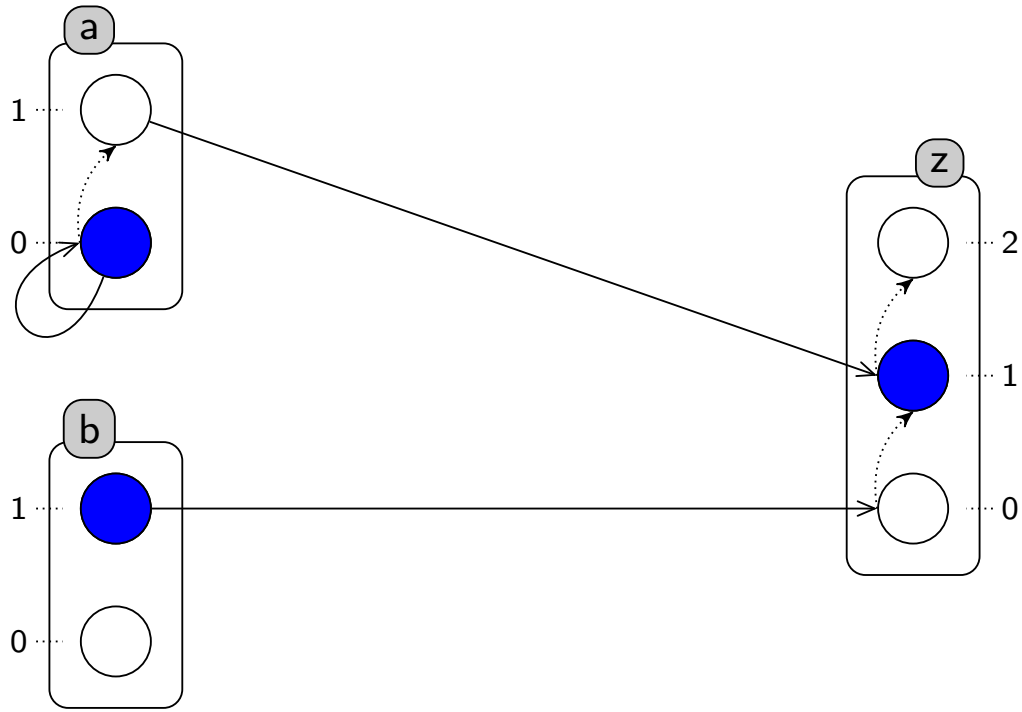

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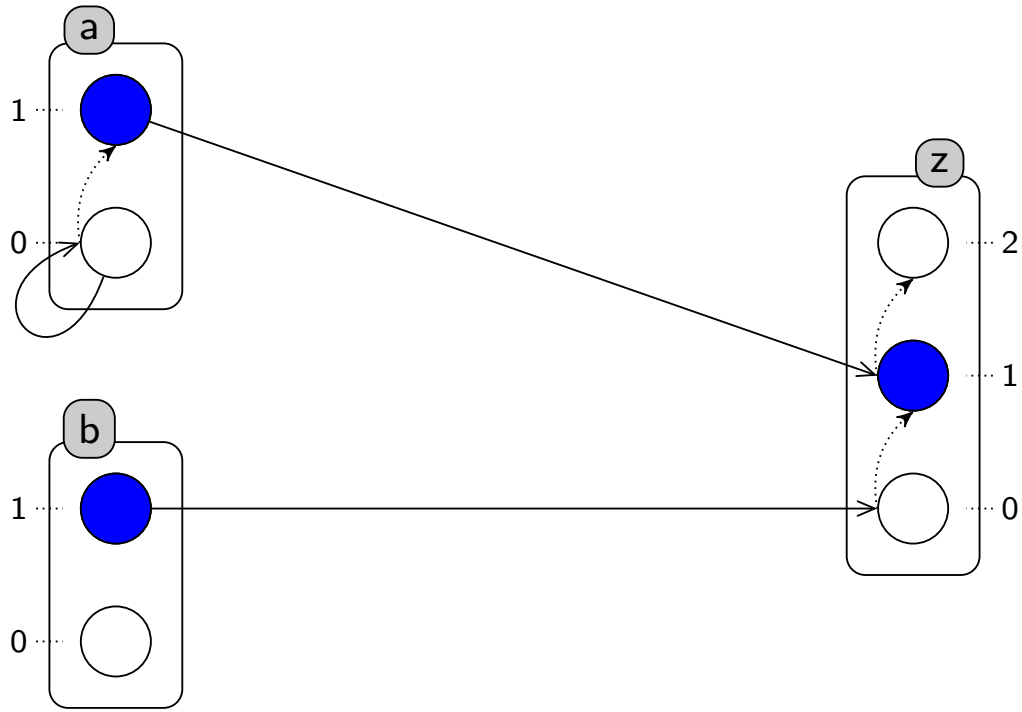

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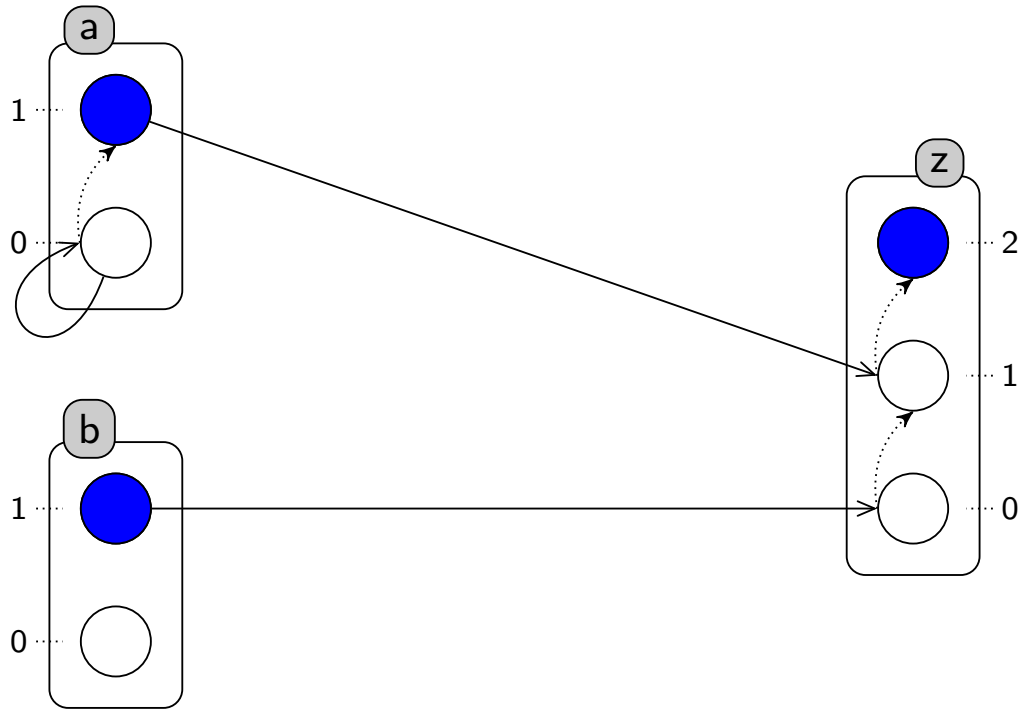

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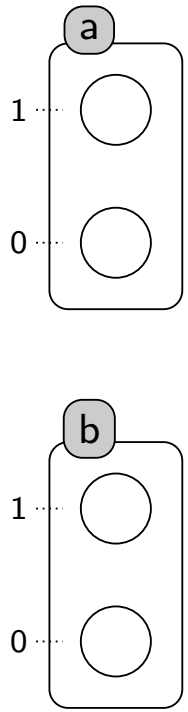

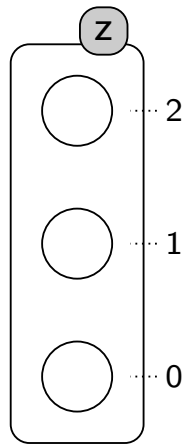

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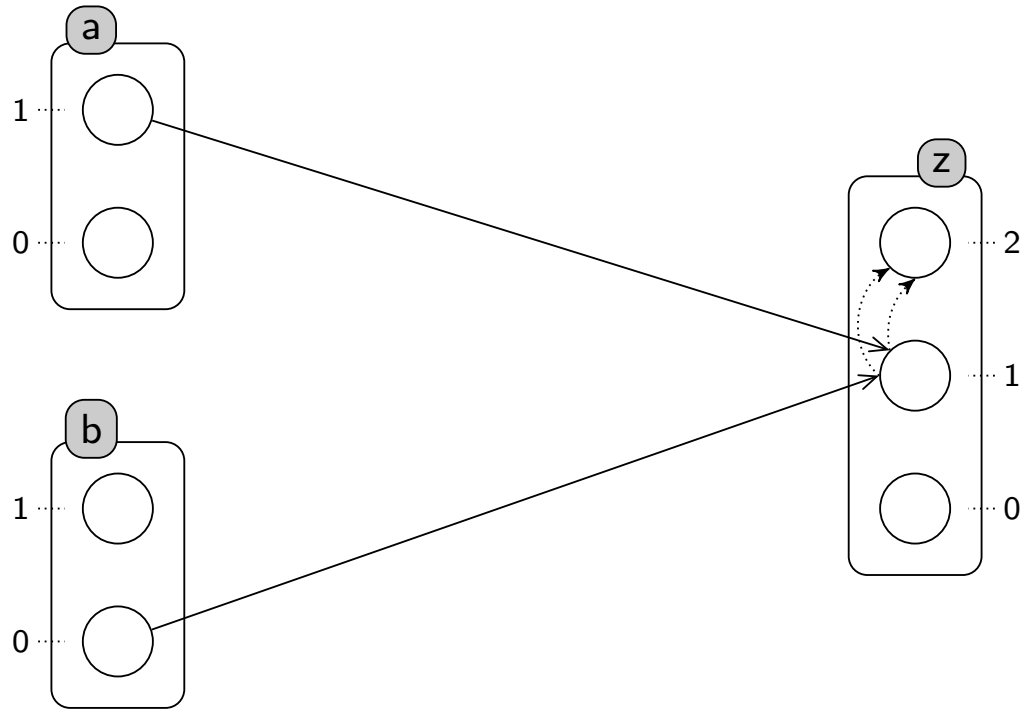

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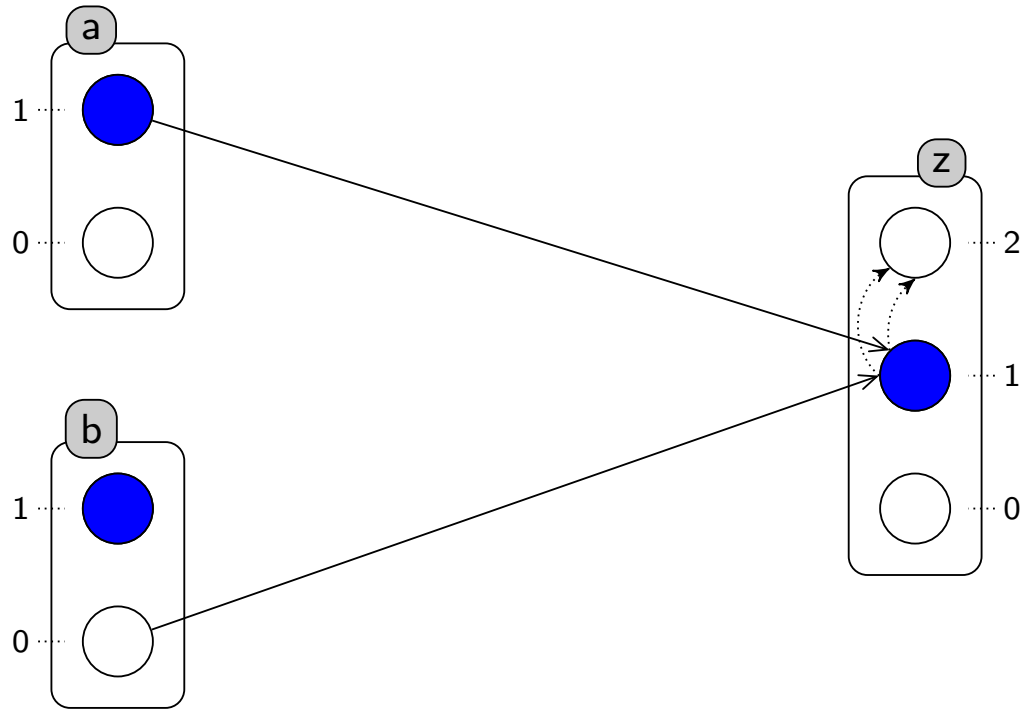

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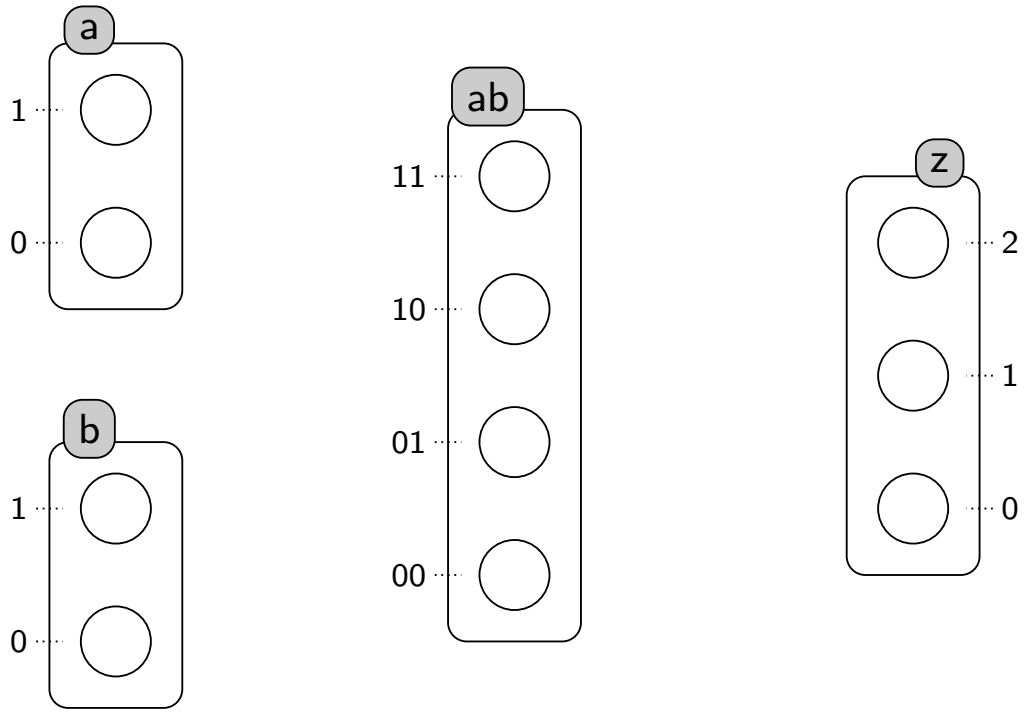

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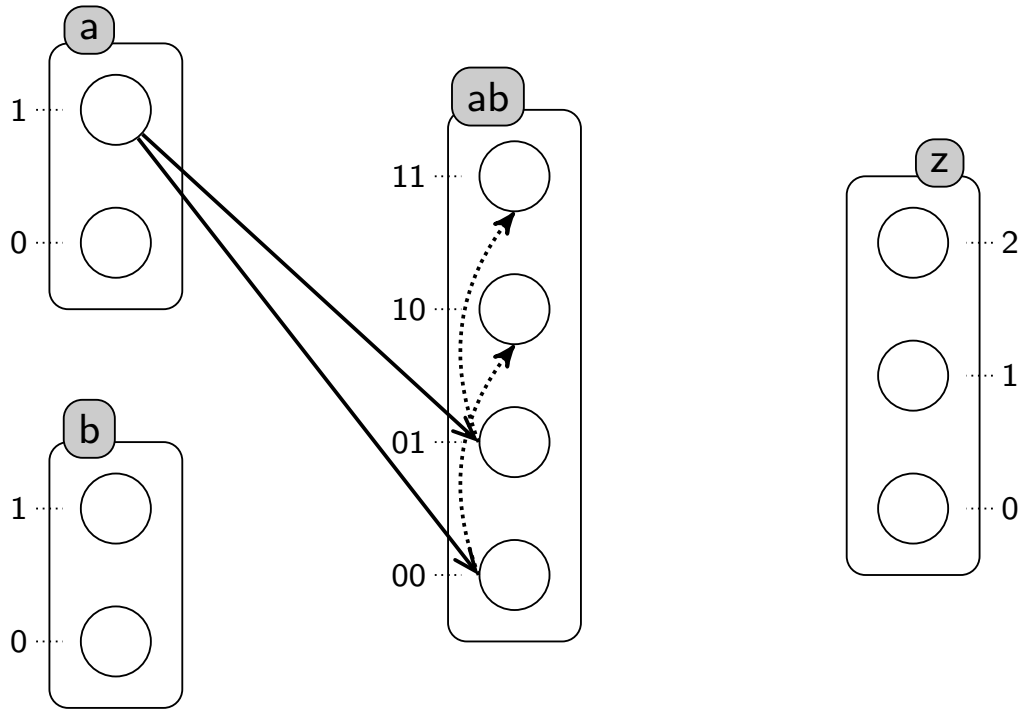

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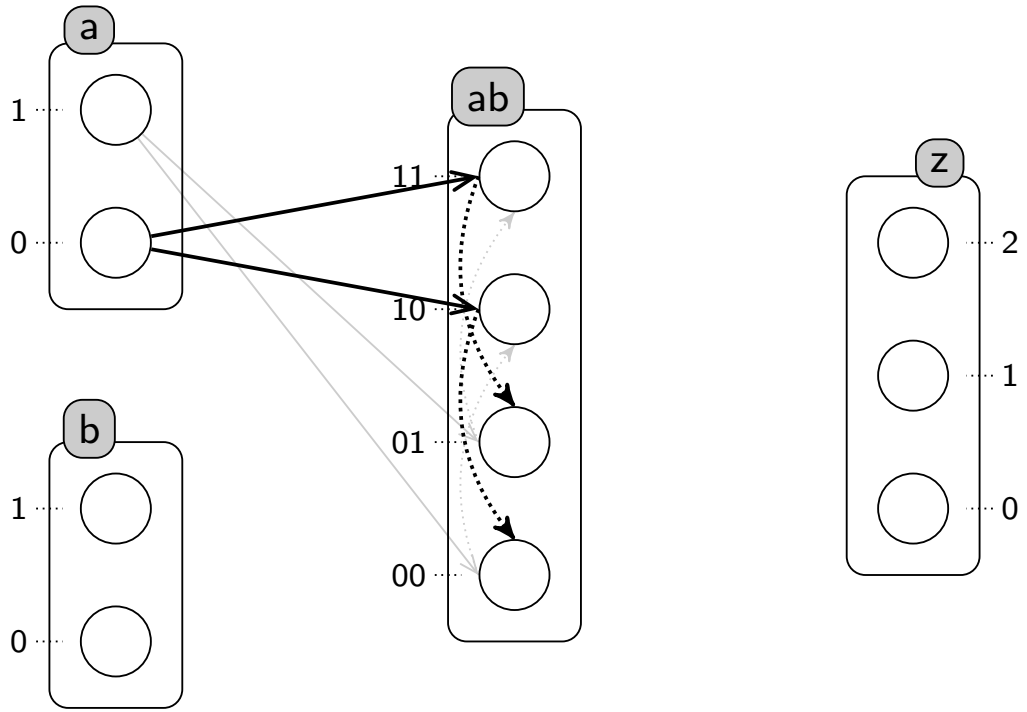

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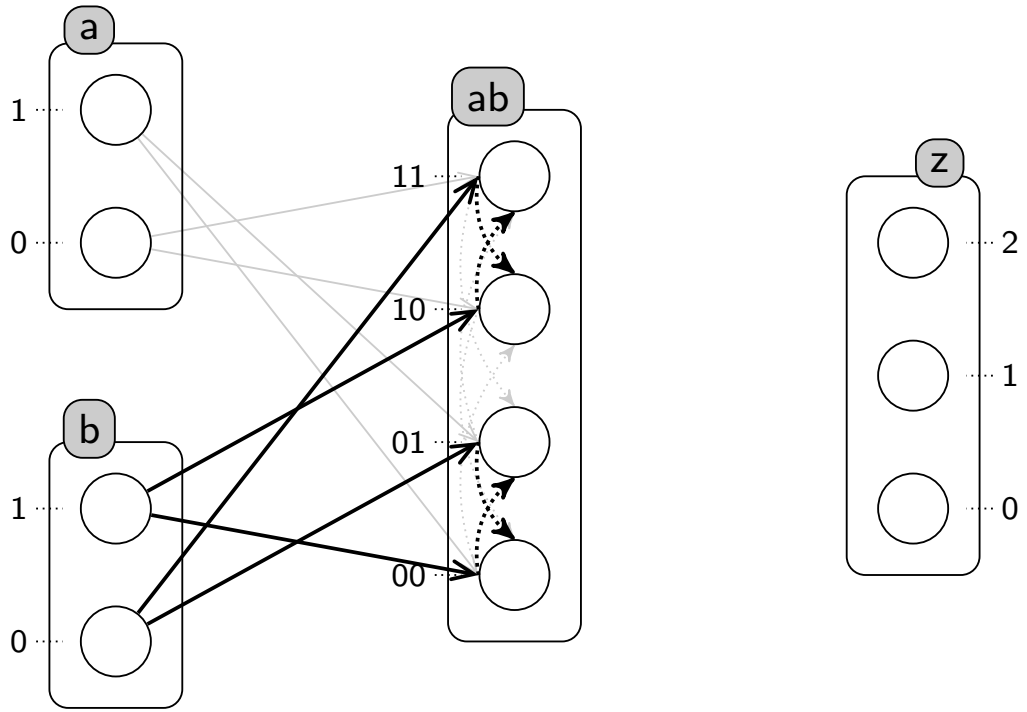

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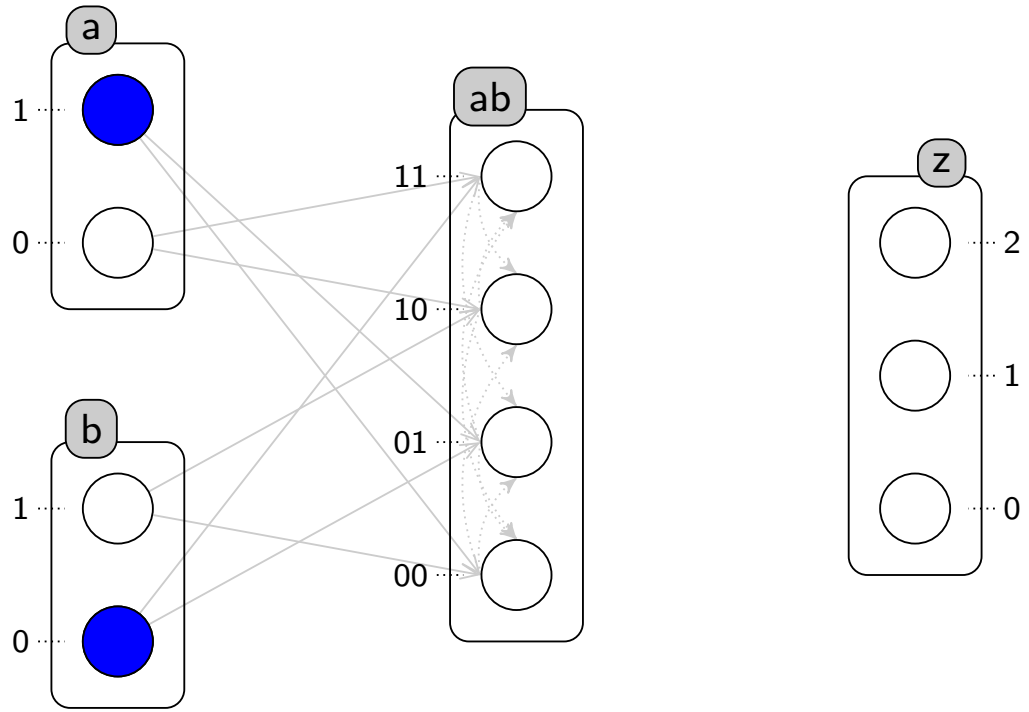

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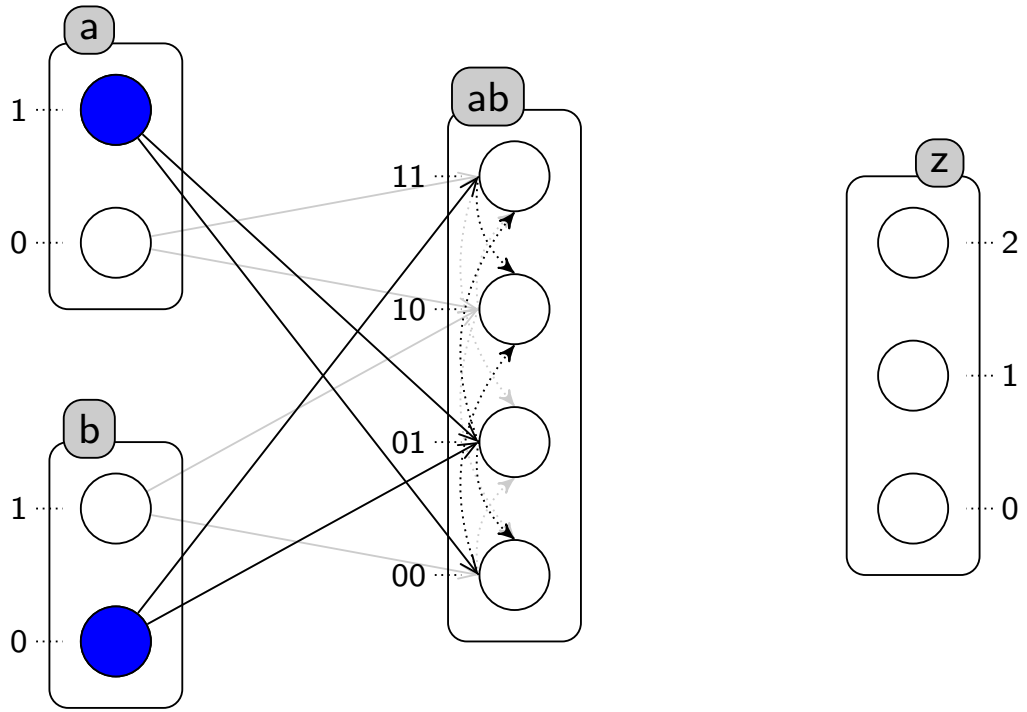

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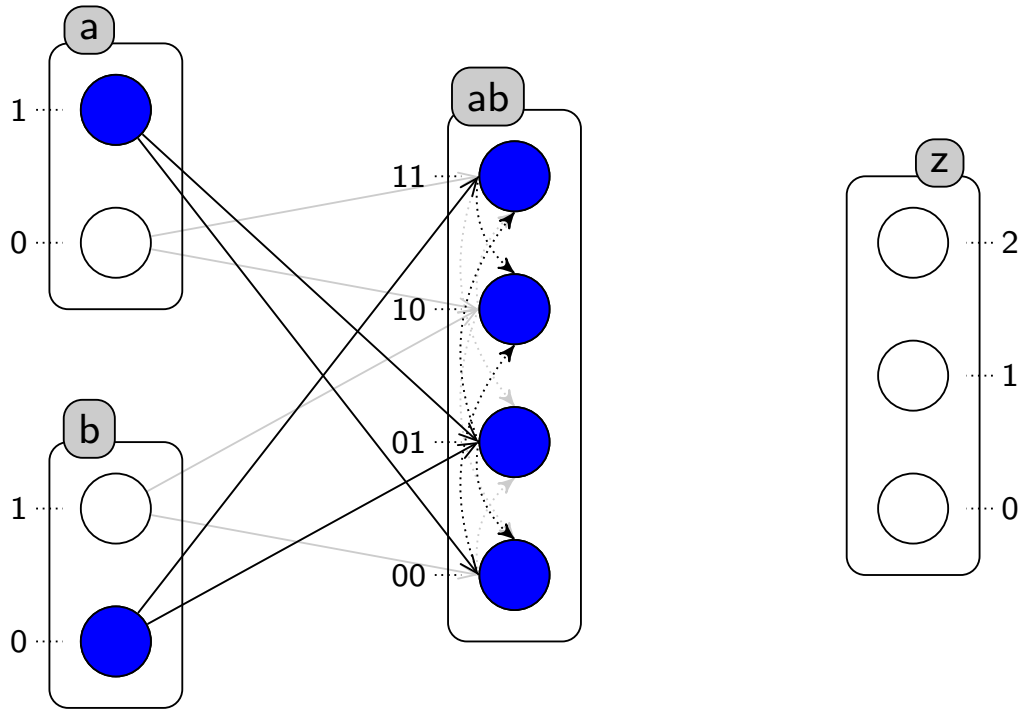

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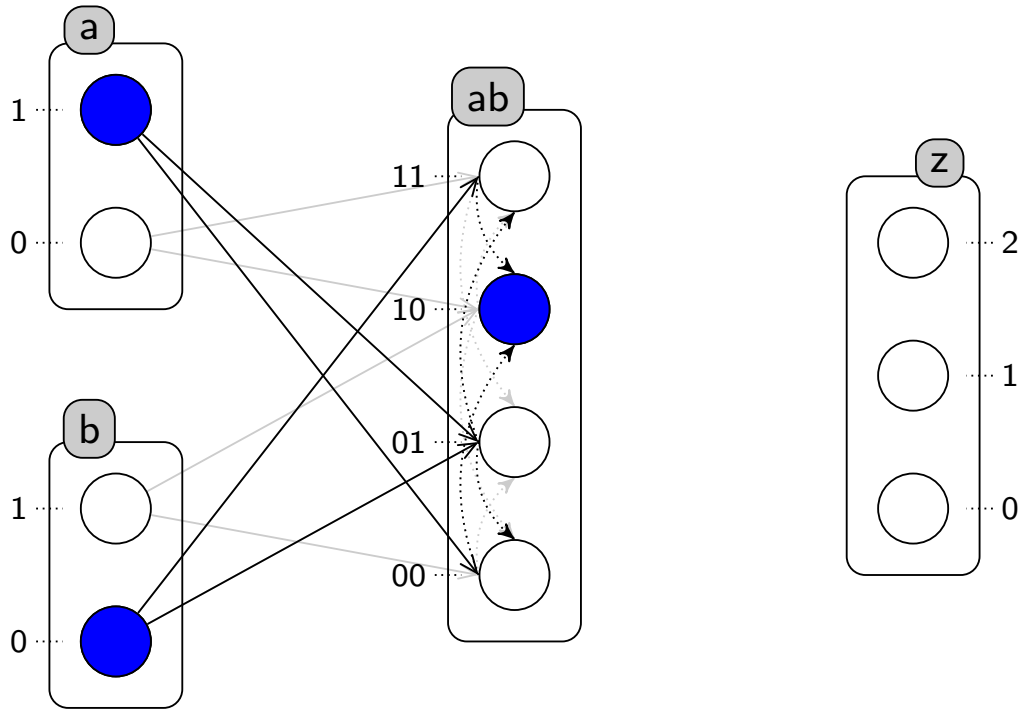

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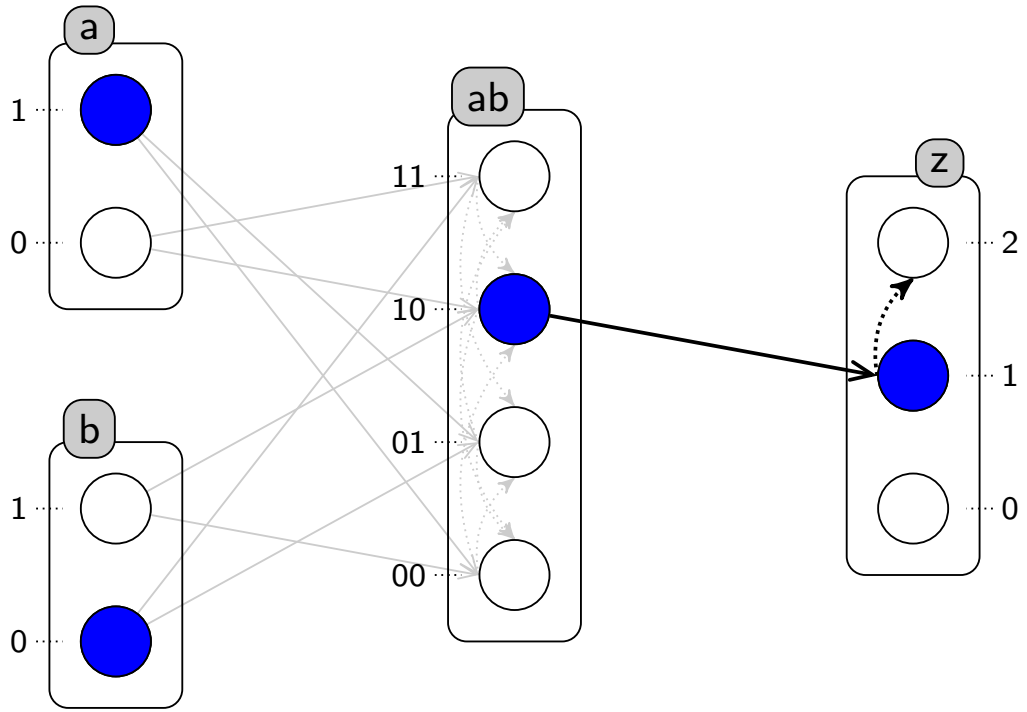

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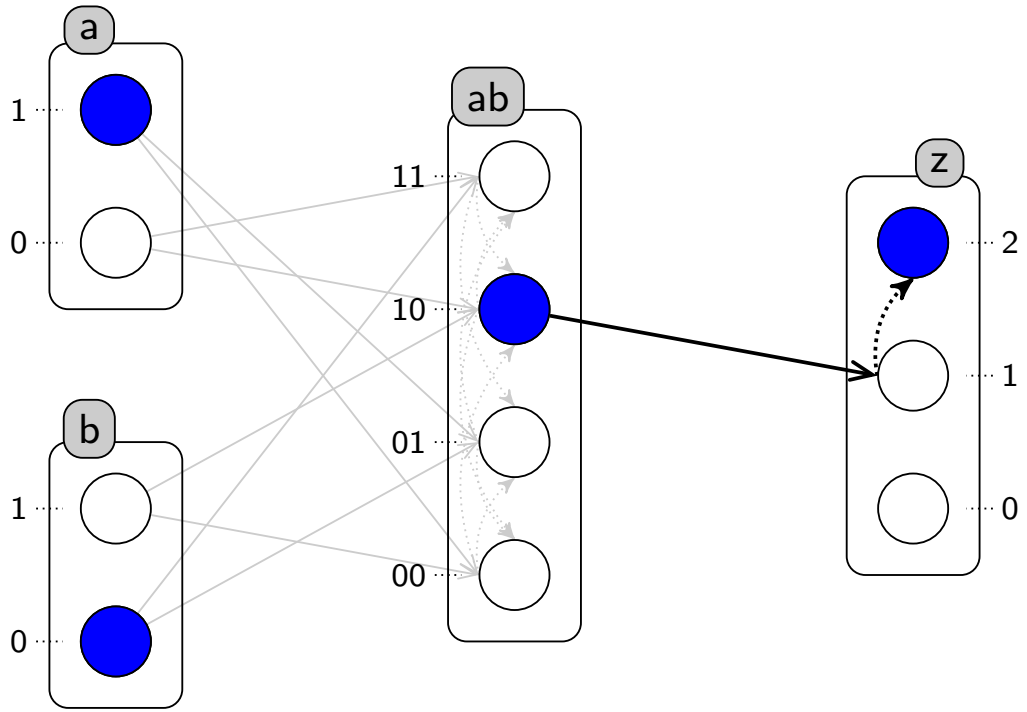

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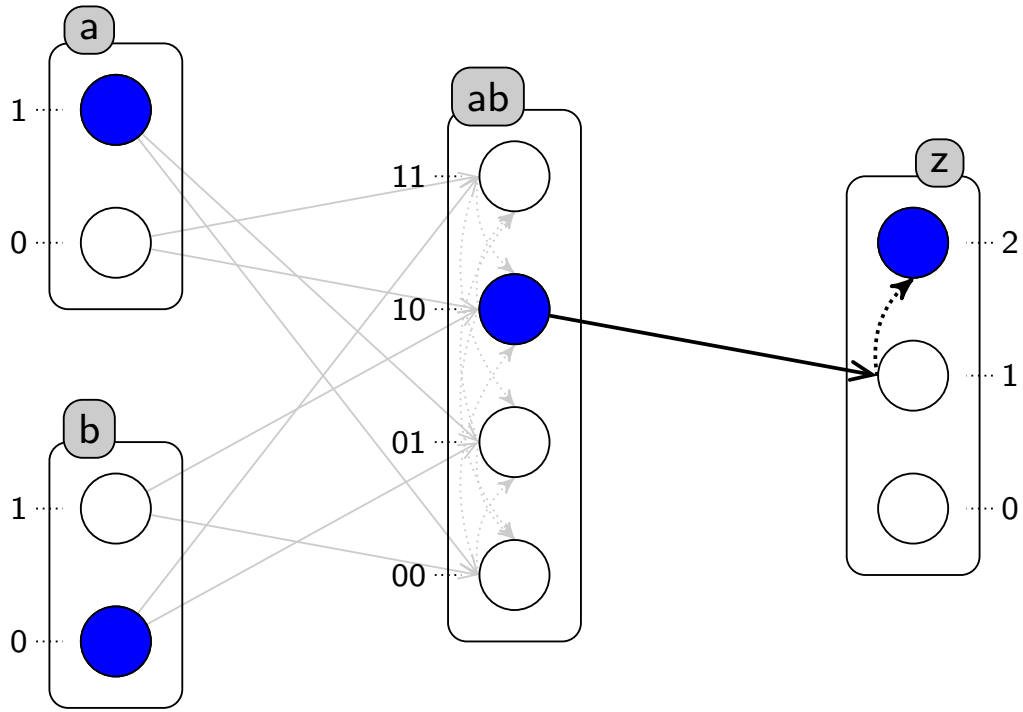

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Advantage: regular sort; drawbacks: complexity, temporal shift

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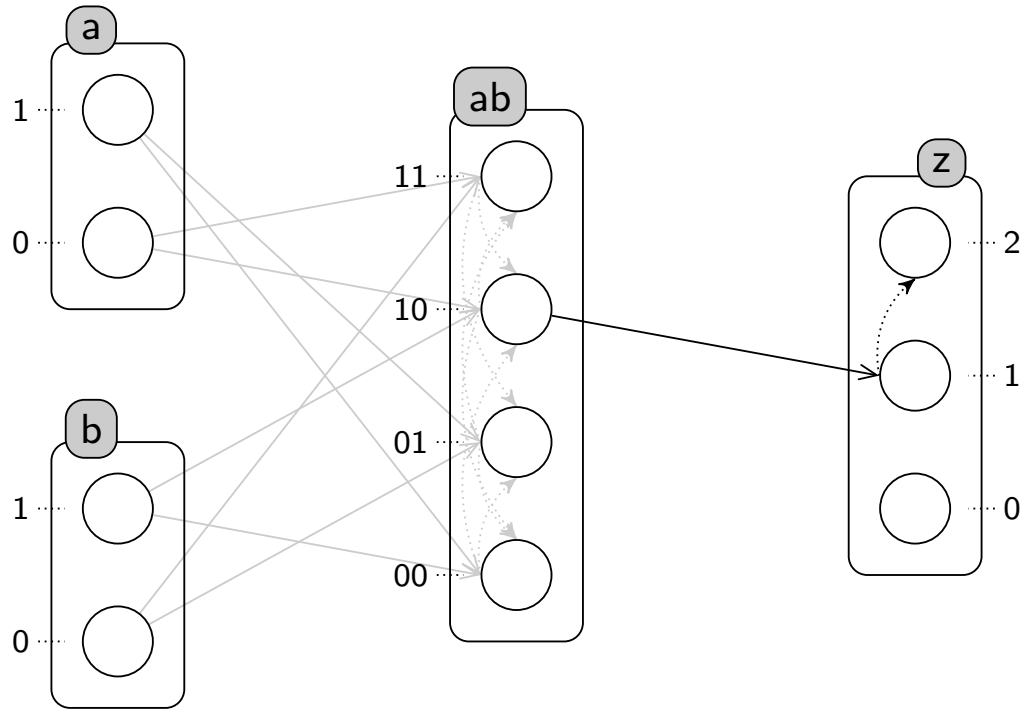
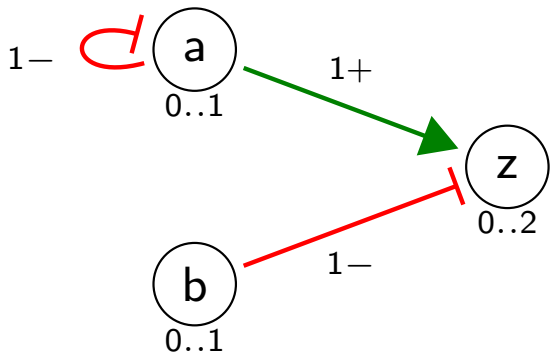


The Process Hitting framework:

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

Biological Regulatory Network

[RCB08]



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Historical bio-informatics model for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

Biological Regulatory Network

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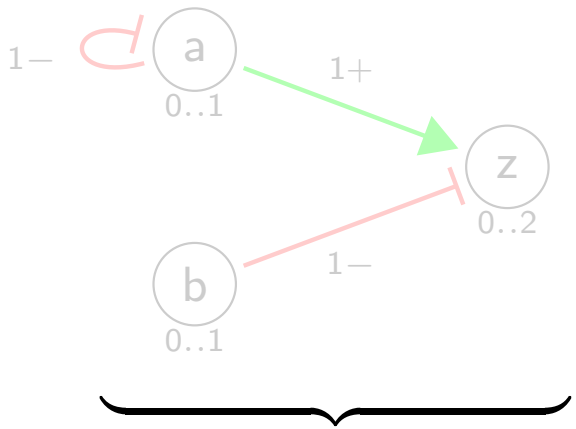

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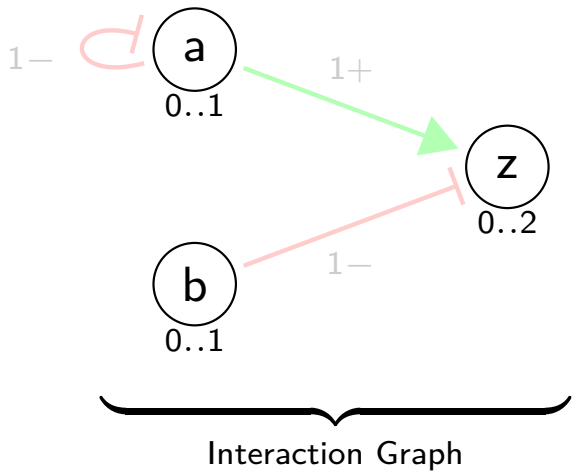
Interaction Graph: structure of the system (genes & interactions)

Biological Regulatory Network

[RCB08]



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

Nodes: genes

→ Name *a*, *b*, *z*

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

Biological Regulatory Network

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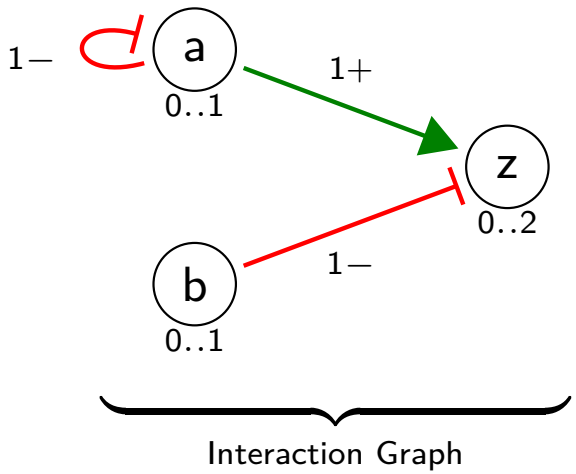

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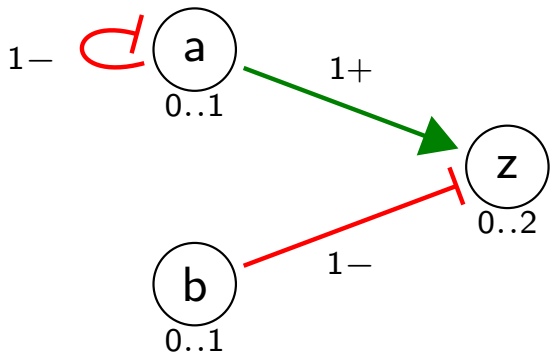
Edges: interactions

→ Threshold 1

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

Biological Regulatory Network

[RCB08]



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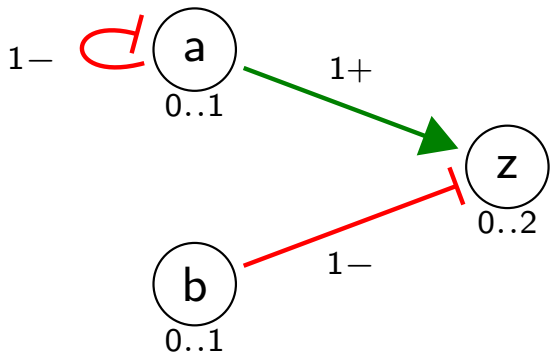
Parametrization

Parametrization: strength of the influences (evolution tendencies)

Biological Regulatory Network

[RCB08]



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Parametrization: strength of the influences (evolution tendencies)

Maps of tendencies for each gene

→ To any **set of predecessors** ω

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

Biological Regulatory Network

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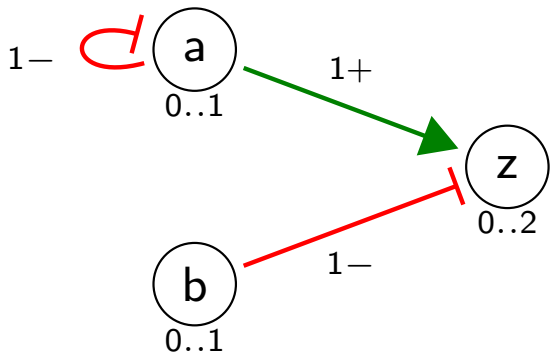

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Biological Regulatory Network

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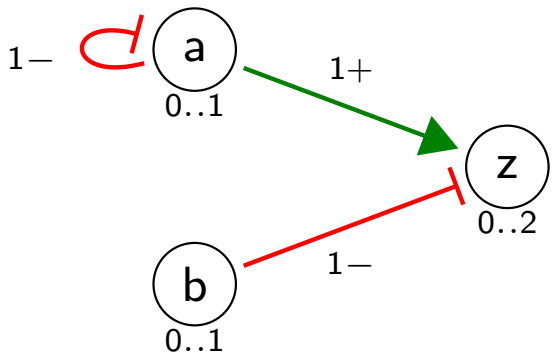

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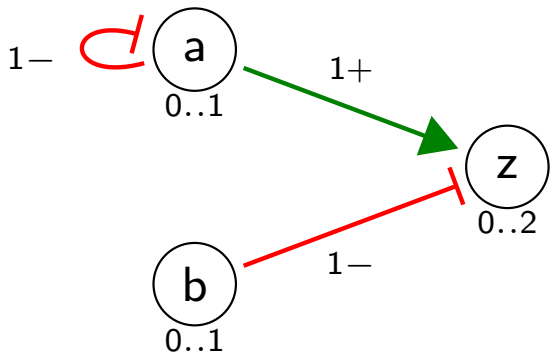

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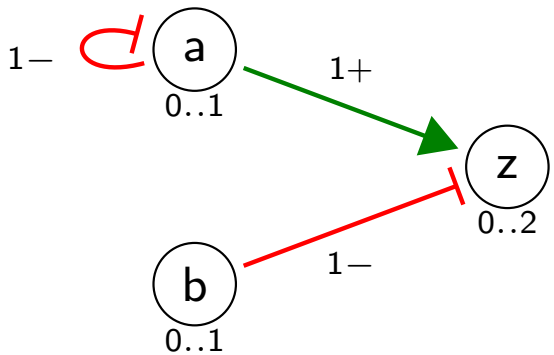
→ Corresponds a **parameter** $k_{x,\omega}$

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

Biological Regulatory Network

[RCB08]



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

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

ω	$k_{b,\omega}$
$\varnothing$	$[0;1]$

Parametrization

Parametrization: strength of the influences (evolution tendencies)

Maps of tendencies for each gene

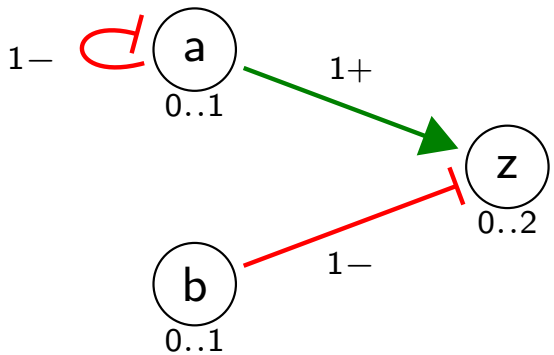
→ To any **set of predecessors** ω

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

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

Biological Regulatory Network

[RCB08]



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

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

ω	$k_{b,\omega}$
$\varnothing$	$[0;1]$

Biological Regulatory Network

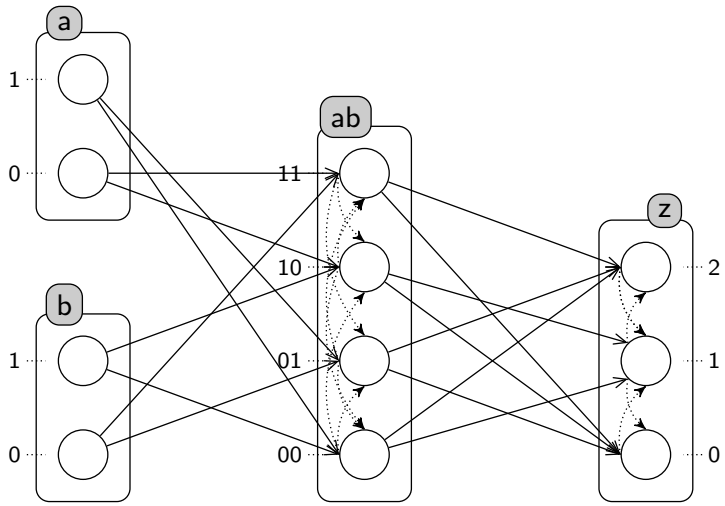
→ All needed information to run the model or study its dynamics:

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

→ **Strengths**: well adapted for the study of biological systems

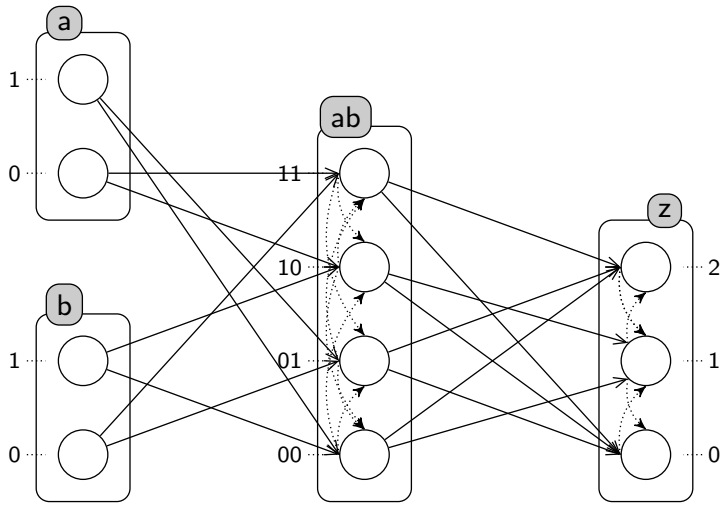
→ **Drawbacks**: inherent complexity; needs the full specification of cooperations

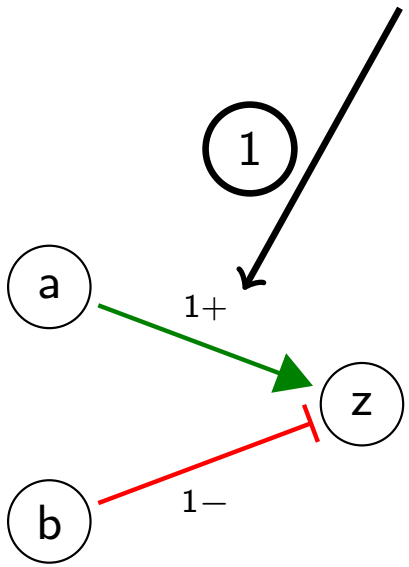
Inferring a BRN with Thomas' parameters



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

Inferring a BRN with Thomas' parameters





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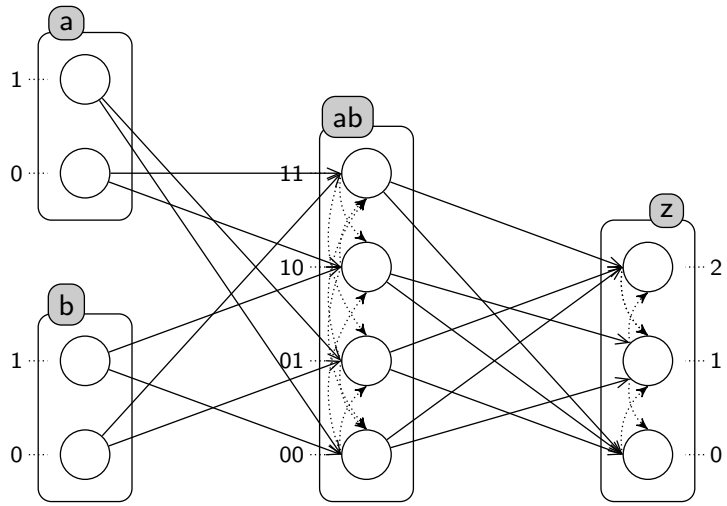
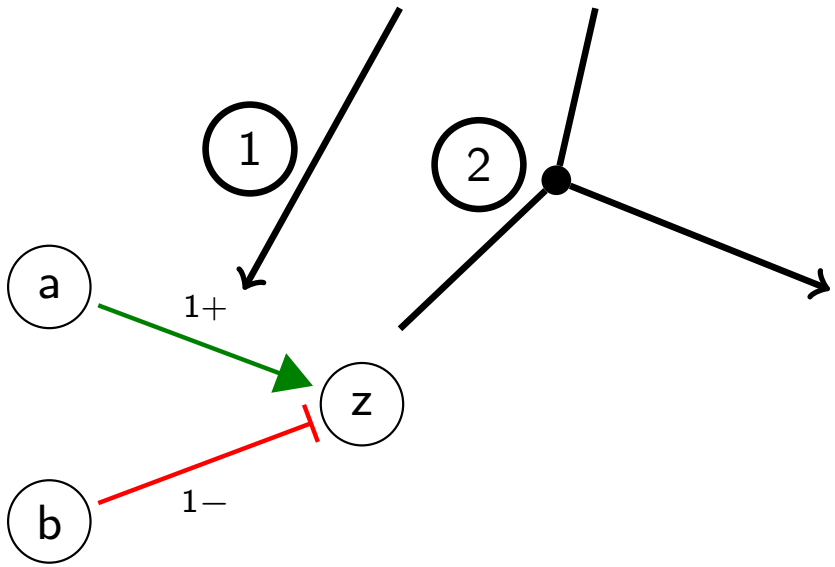
Inferring a BRN with Thomas' parameters





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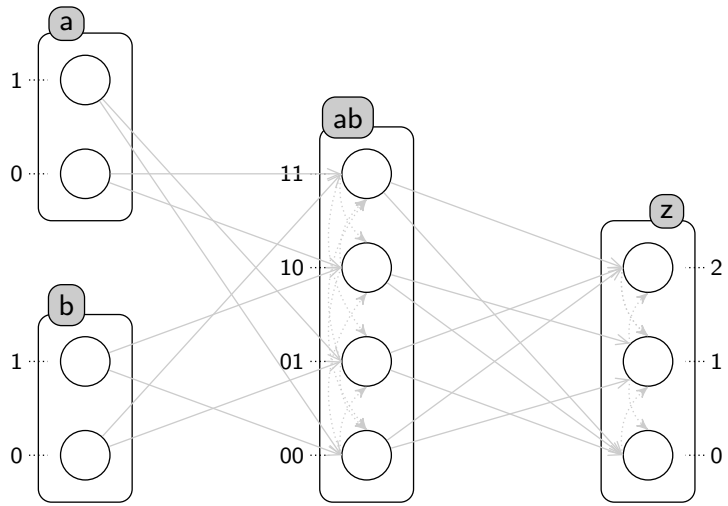
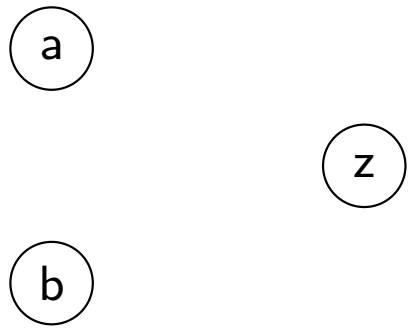
Inferring the Interaction Graph

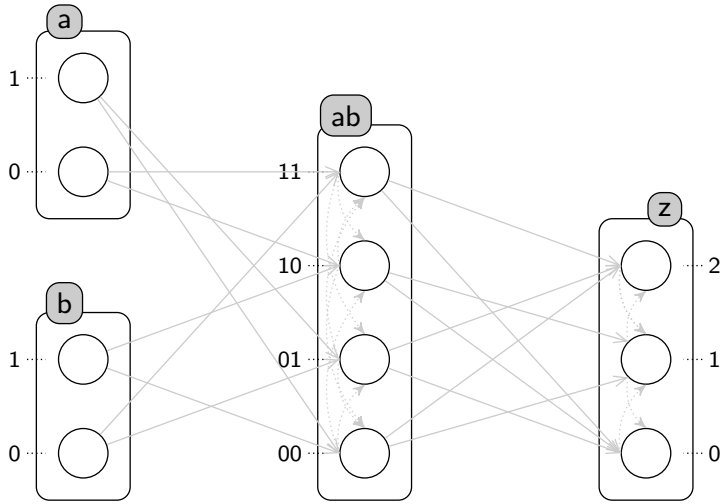


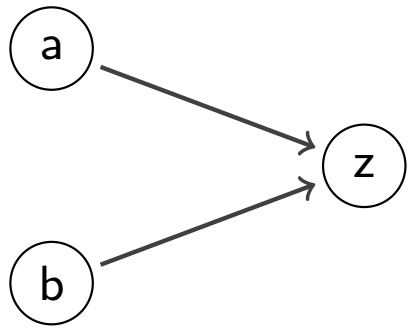


- **Inputs:** a Process Hitting model
- **Output:** An interaction graph with all information:
  $\rightarrow$ edges, signs and thresholds

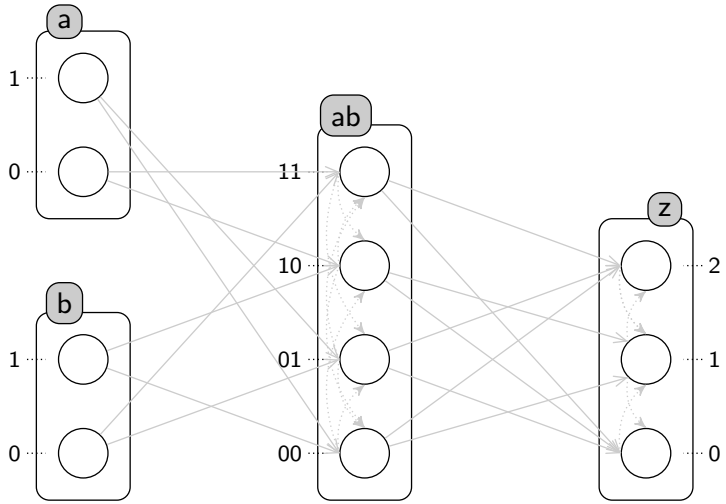
- **Difficulties:** Process Hitting is more atomistic than BRNs
- **Idea:** Exhaustive search in all possible configurations

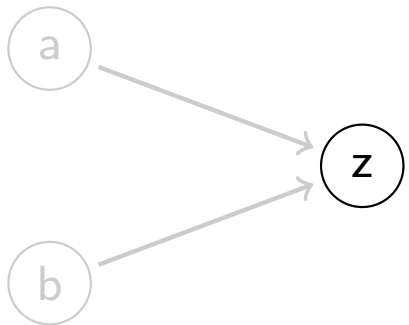
Inferring the Interaction Graph





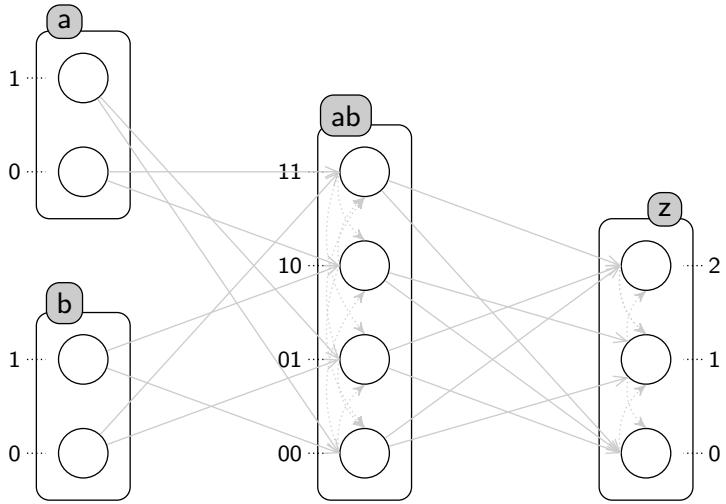
Inferring the Interaction Graph

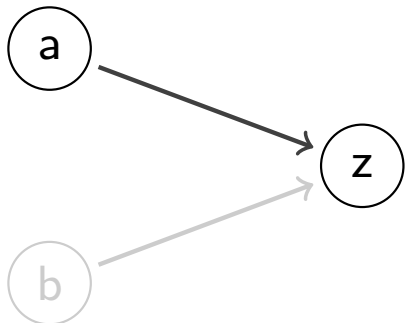




- For each gene $[z]$

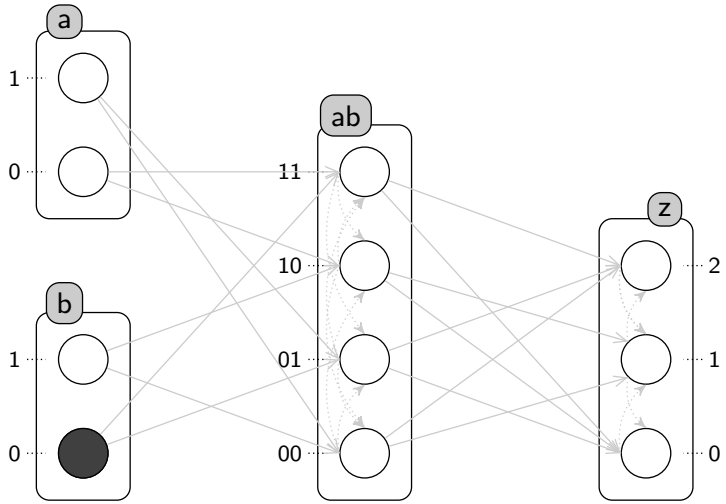
Inferring the Interaction Graph

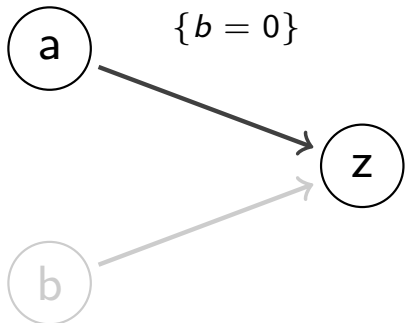




- For each gene [z], consider one possible regulator [a]

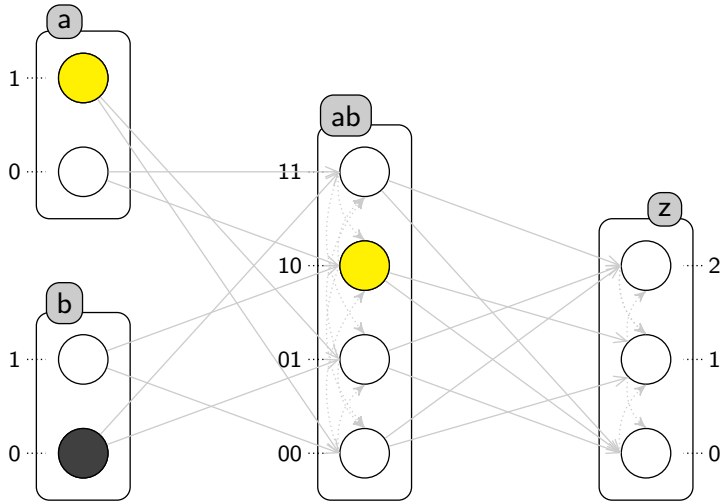
Inferring the Interaction Graph

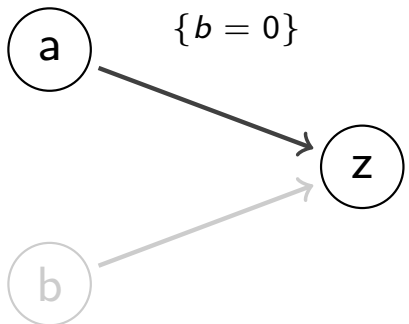




- For each gene [z], consider one possible regulator [a]
- Consider a **configuration** of all other regulators [$\{b = 0\}$]

Inferring the Interaction Graph





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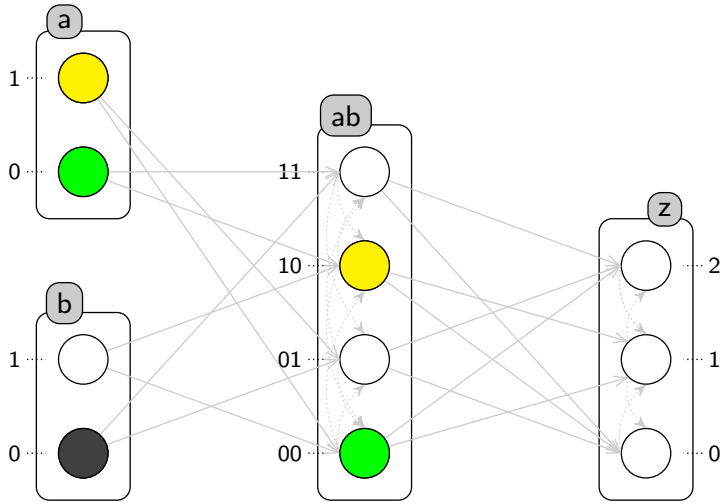
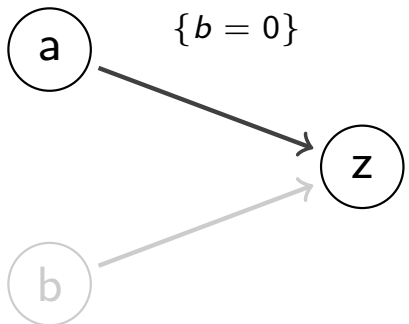
Inferring the Interaction Graph





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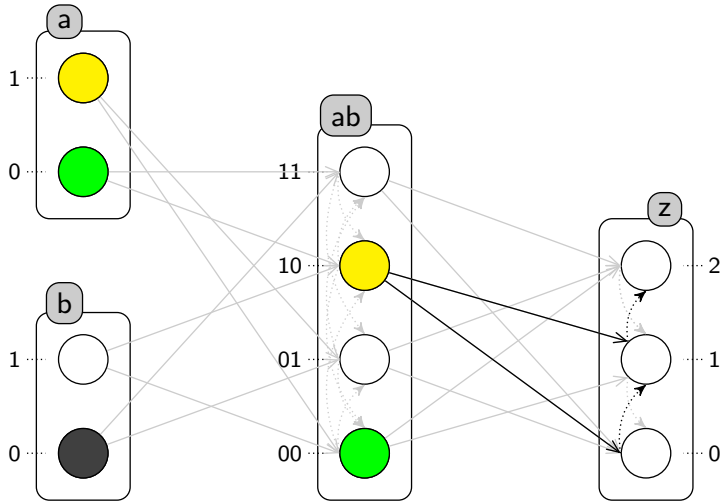

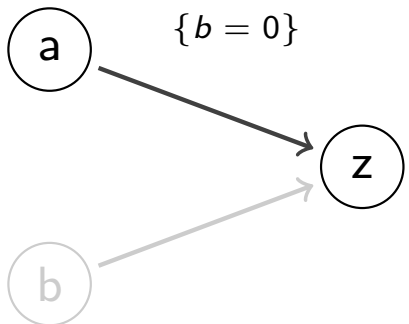

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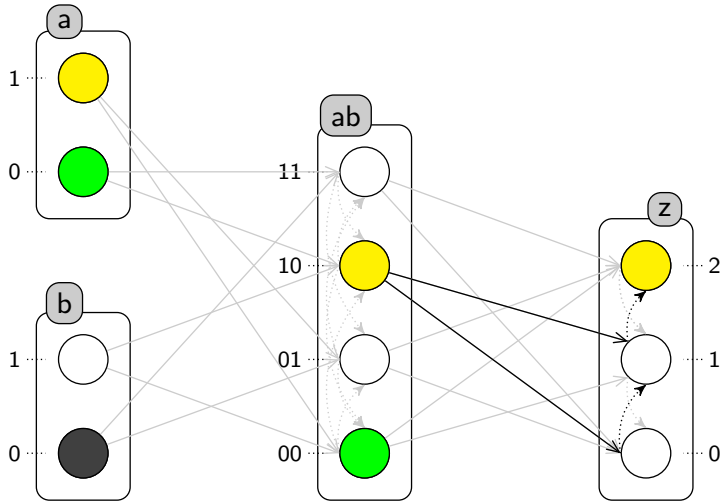

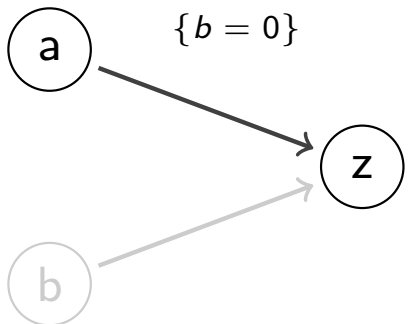

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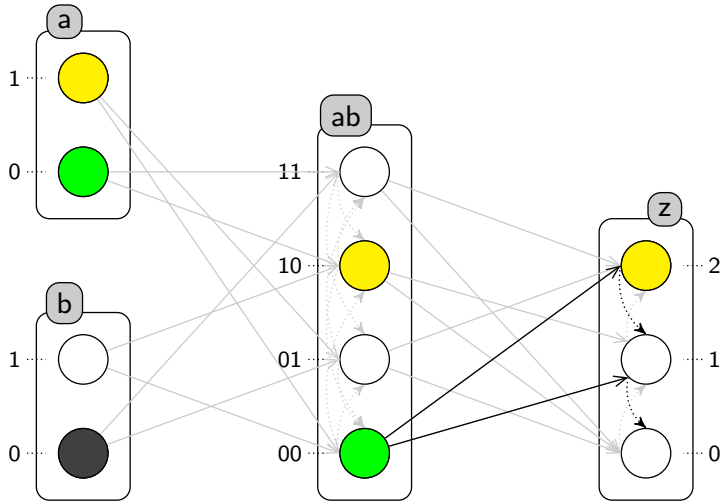

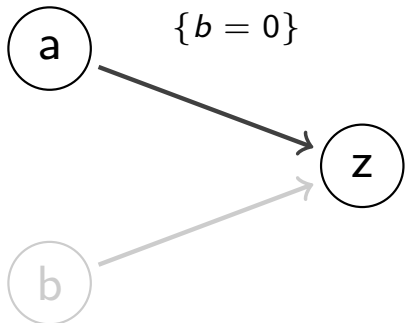

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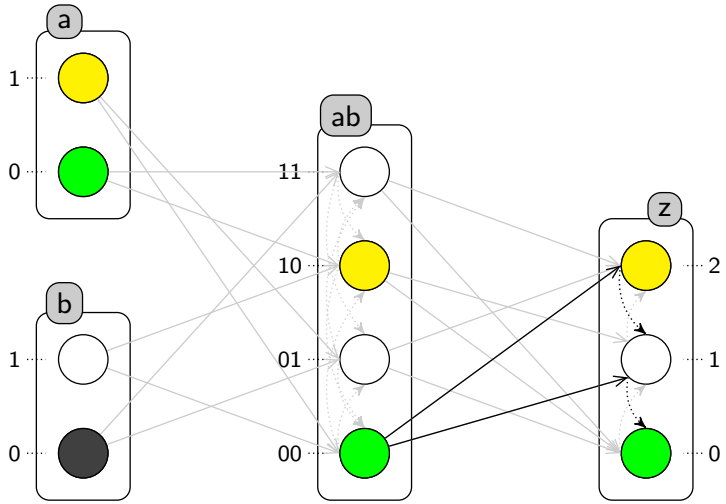

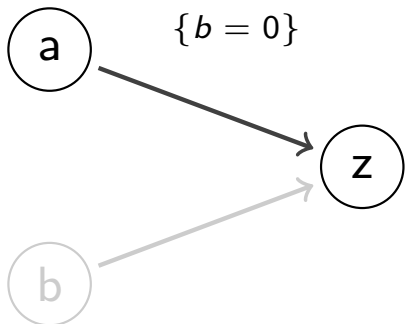

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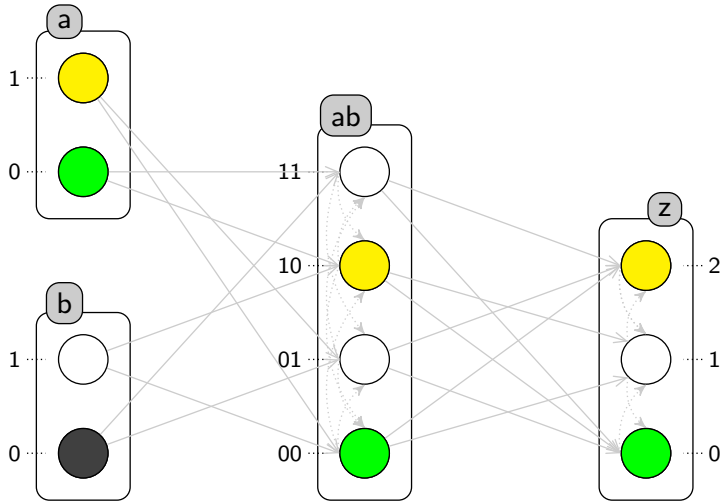

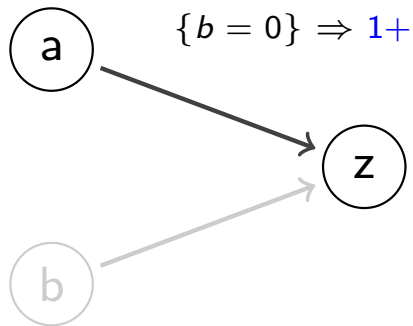

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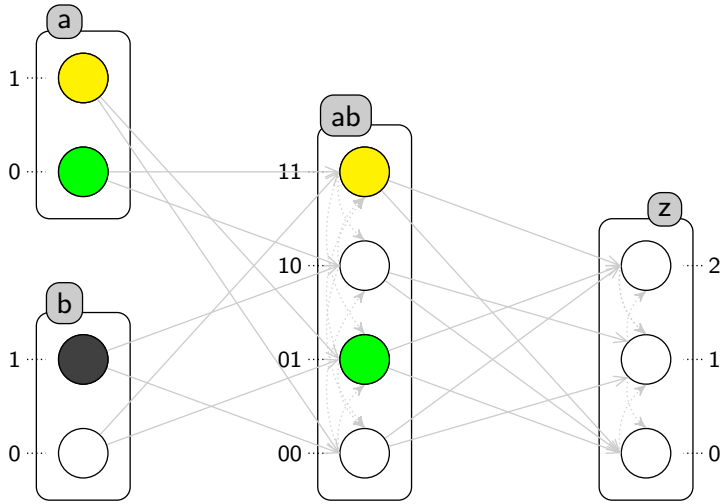
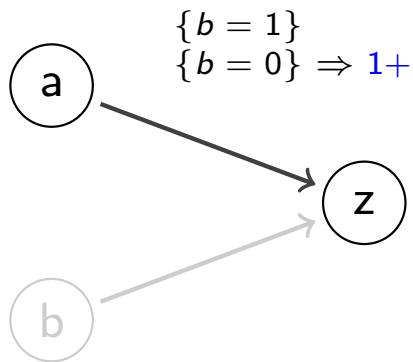
  - Comparing the sets of focal processes gives the influence

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

Inferring the Interaction Graph





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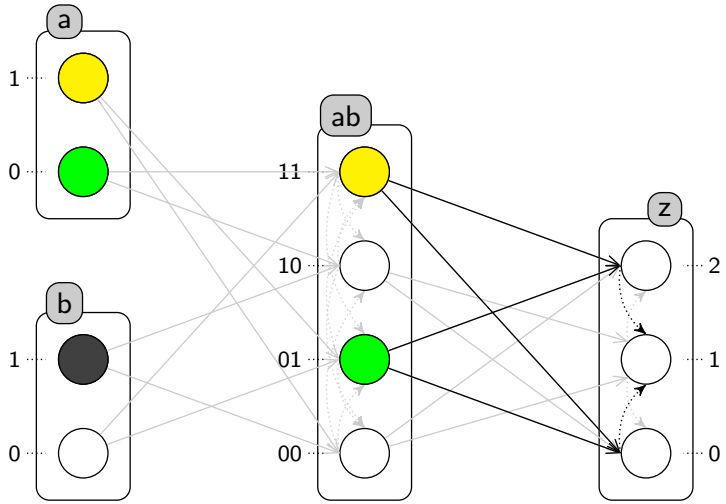

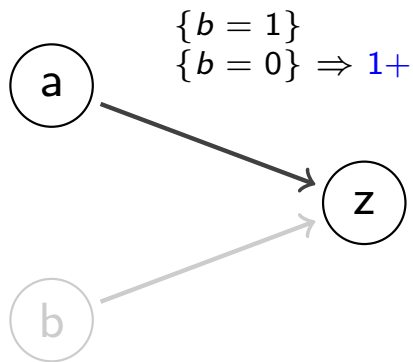

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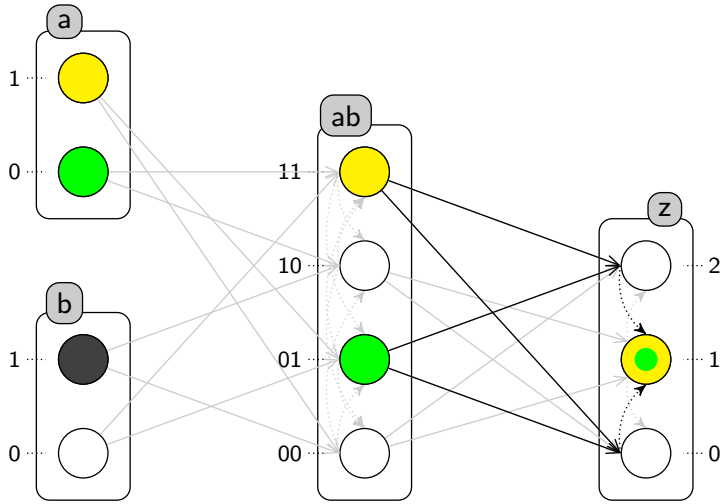

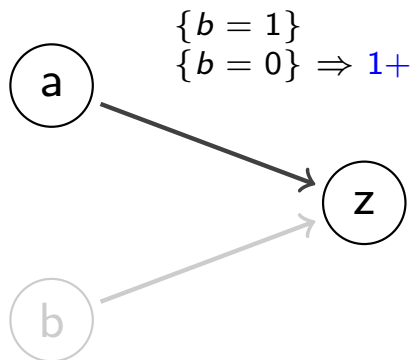

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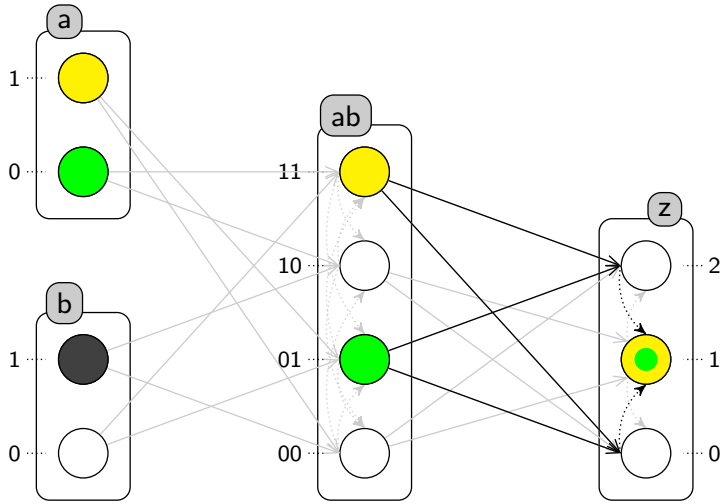

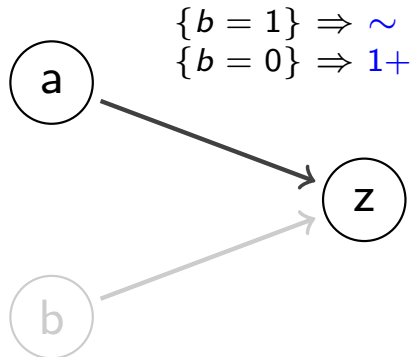

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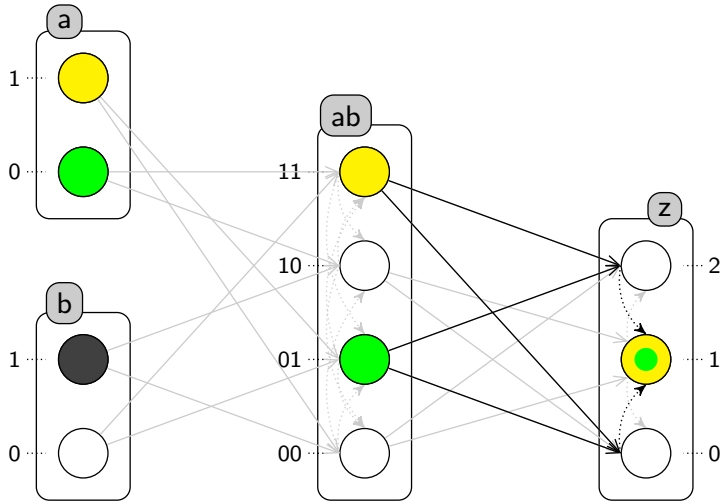
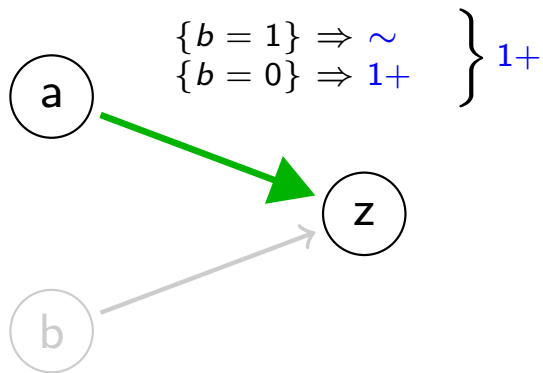
Inferring the Interaction Graph





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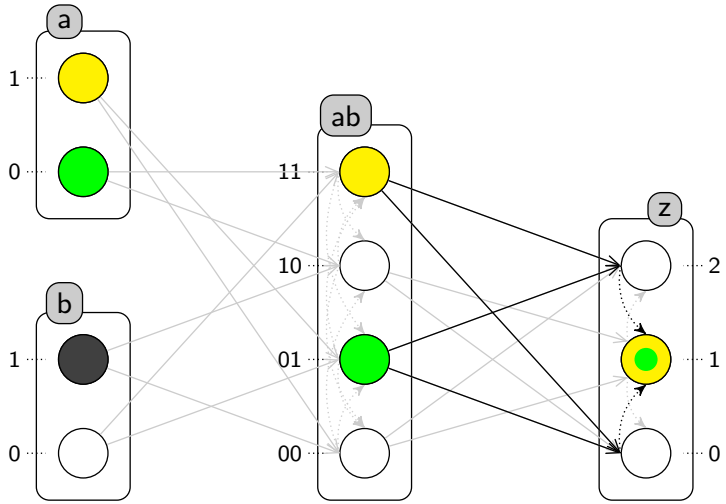
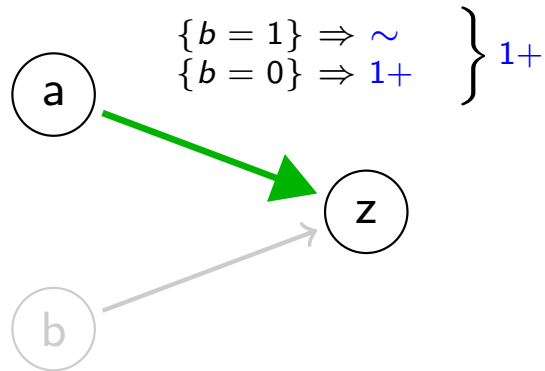
Inferring the Interaction Graph





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Problematic cases:

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

$\Rightarrow$ Unsigned edge

Interaction Graph Inference

Implementation

Programming in ASP:

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

Interaction Graph Inference

Implementation

Programming in ASP:

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Calling ASP:

- **Pint** (existing OCaml library) to read Process Hitting models
  Free library + examples: http://processhitting.wordpress.com/
- **OCaml** to translate these models to an ASP description
  and parse the results
- **Clingo** to solve the description with the adequate program

Interaction Graph Inference

Results

Results: Very fast execution (personal laptop, 1.83GHz dual-core)

$<$ **1s** for 20 & 40 genes models **[EGFR20 & TCRSIG40]**
$\simeq$ **13s** for a 94 genes model **[TCRSIG94]**
$\simeq$ **4min** for a 104 genes model **[EGFR104]**

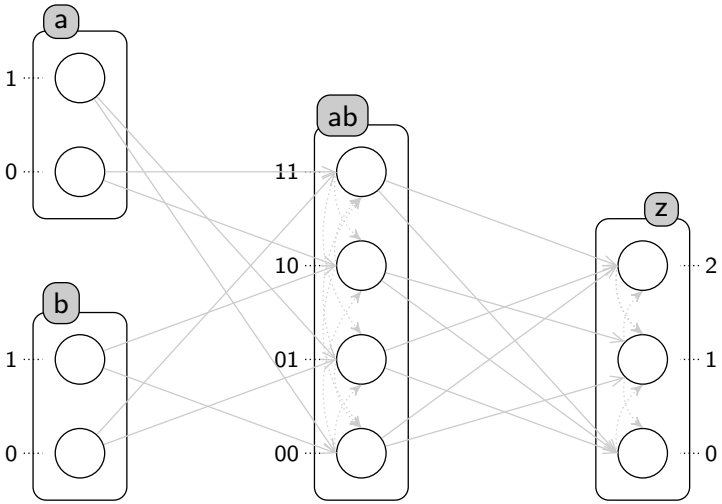
Model name	Model specifications				IG inference	
	Sorts	CS*	Processes	Actions	Time	Edges
[EGFR20]	20	22	152	399	$<$ **1s**	50
[TCRSIG40]	40	14	156	301	$<$ **1s**	54
[TCRSIG94]	94	39	448	1124	$\simeq$ **13s**	169
[EGFR104]	104	89	748	2356	$\simeq$ **4min**	241

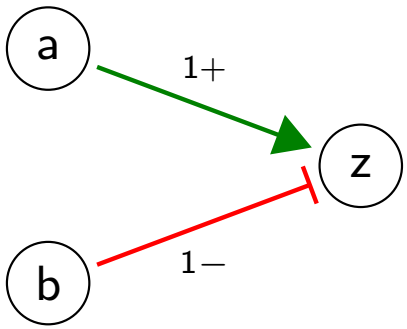
*CS = Cooperative sorts

- **[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.

Inferring Parameters

[PMR10-TCSB]



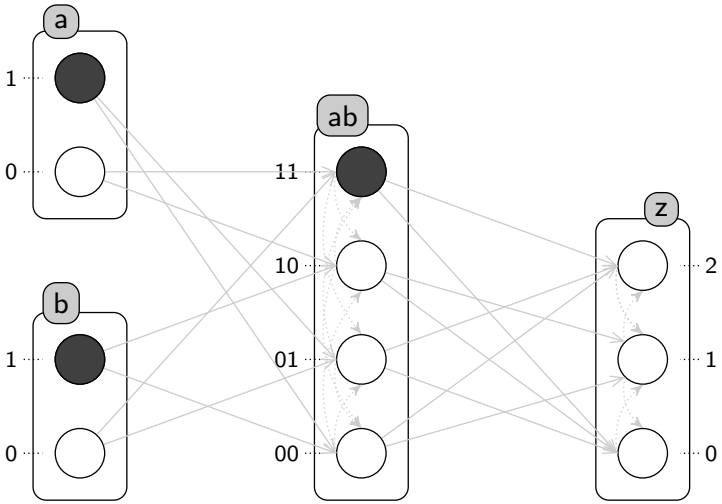


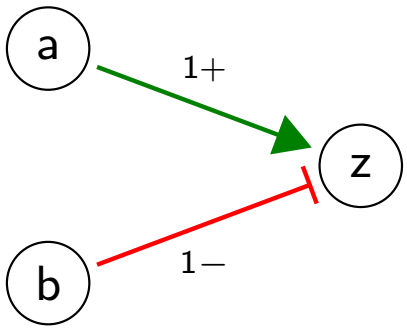
ω	$k_{z,\omega}$
$\varnothing$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	

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

Inferring Parameters

[PMR10-TCSB]





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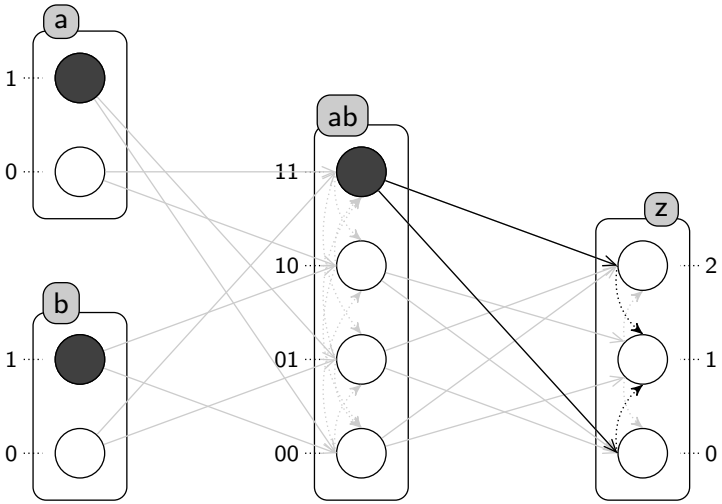

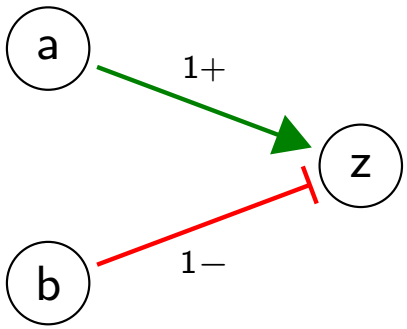

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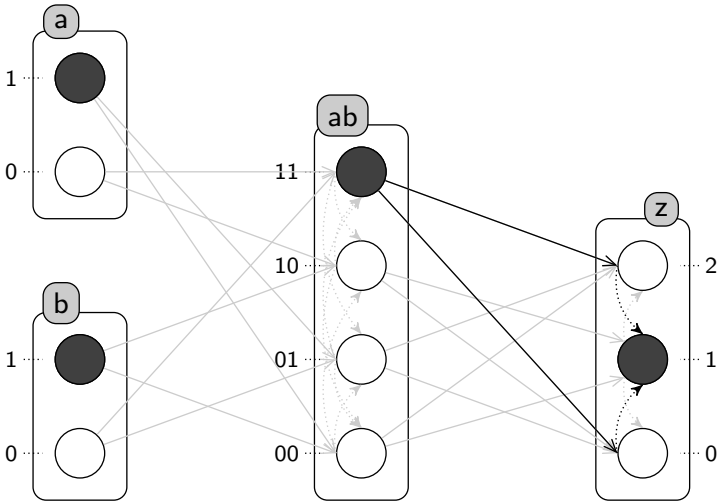
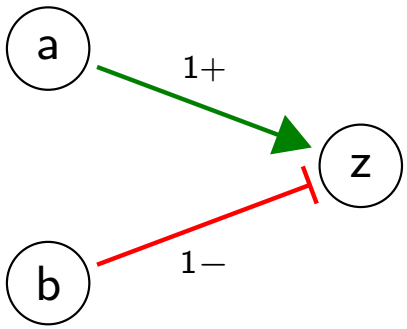
Inferring Parameters

[PMR10-TCSB]





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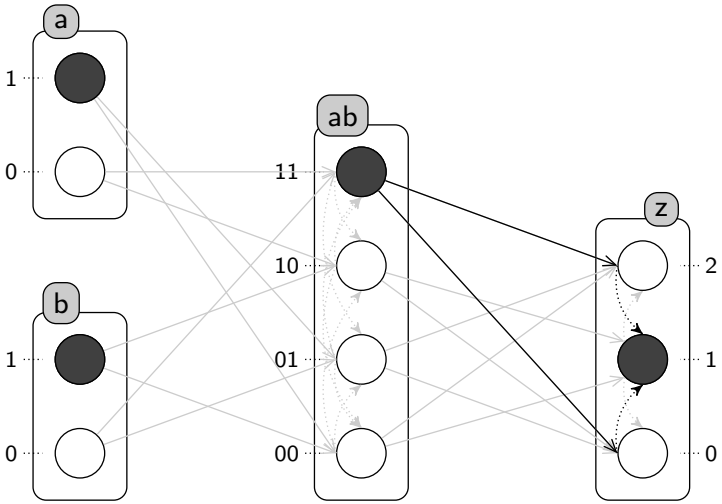
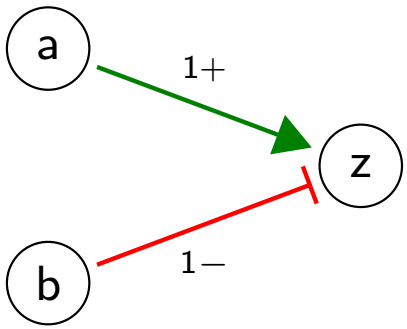
[PMR10-TCSB]





ω	$k_{z,\omega}$
$\emptyset$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	$[1; 1]$

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- For each gene $[z]$ and each **configuration** of resources $[\omega = \{a; b\}]$
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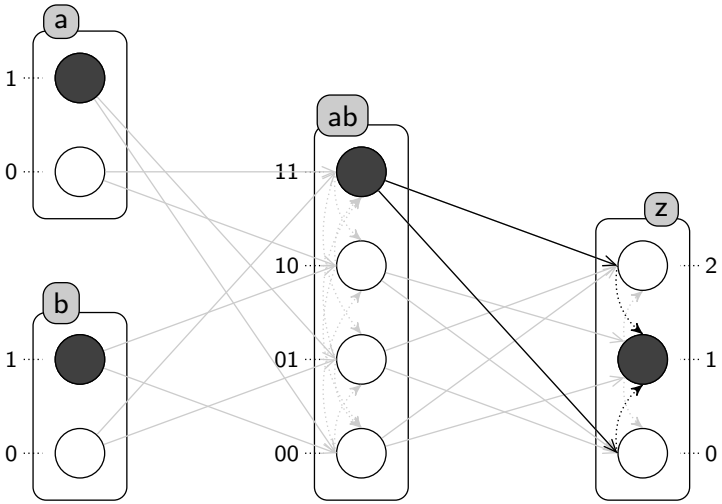
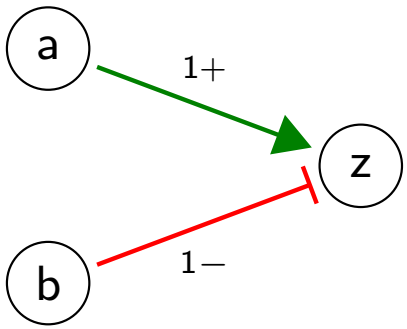
Inferring Parameters

[PMR10-TCSB]





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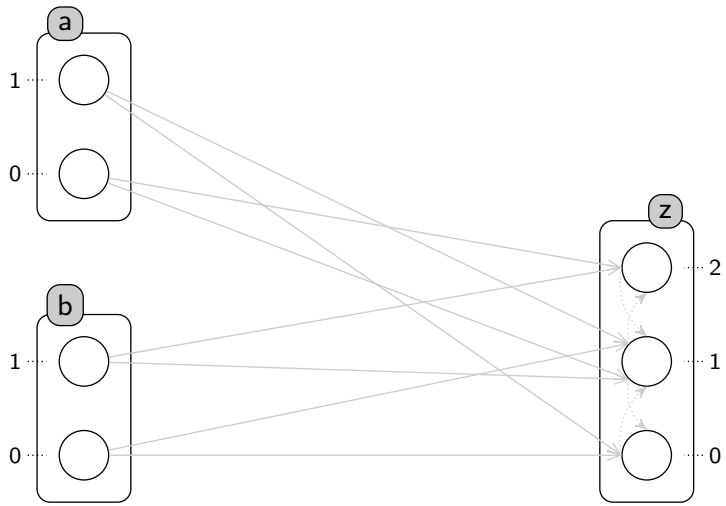
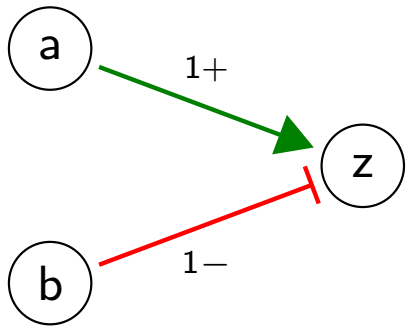
Problematic cases:

→ Behavior cannot be represented as a BRN

→ Lack of cooperation (no focal processes)

Enumerating admissible Parametrizations



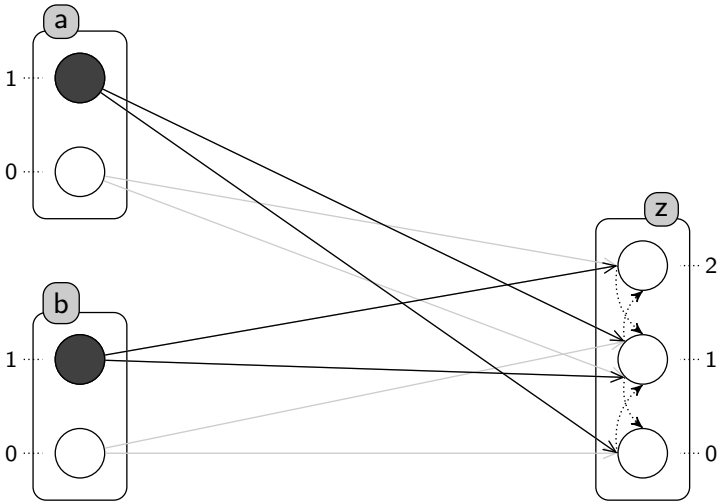


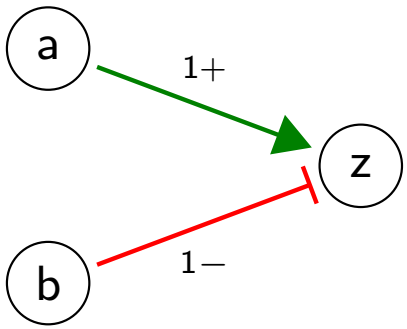
ω	$k_{z,\omega}$
$\varnothing$	?
$\{b\}$	$[0;0]$
$\{a\}$	$[2;2]$
$\{a;b\}$	?

Inputs: The Process Hitting, the related Interaction Graph and the partially inferred Parametrization

Output: All admissible Parametrizations observing the dynamics

Enumerating admissible Parametrizations





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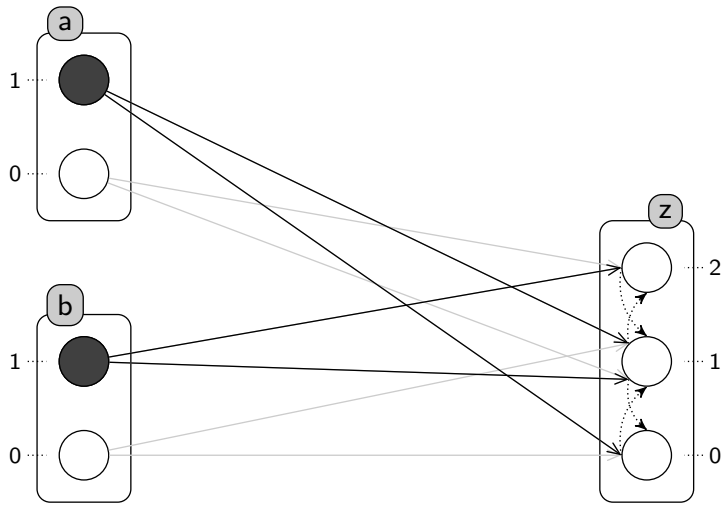

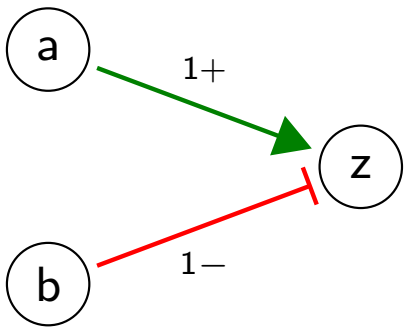

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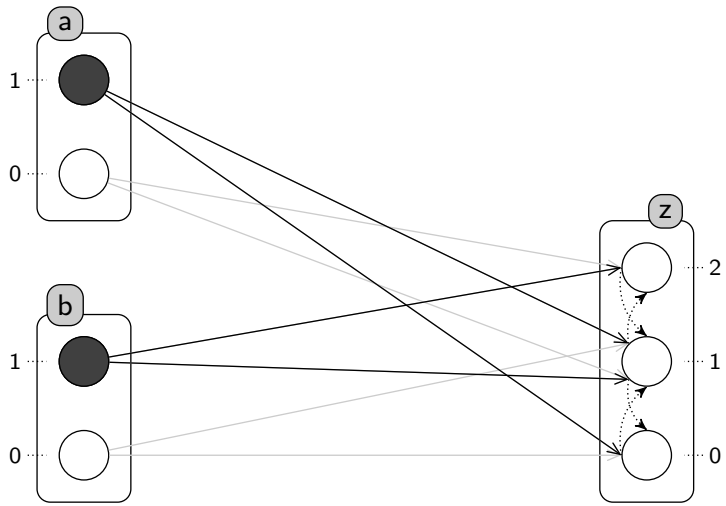
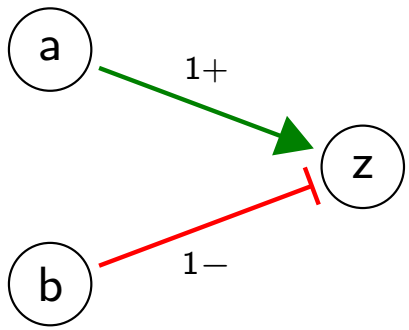
$[k_{z,\{a,b\}} = [0;0]?\ [0;1]?\ [1;1]?\ [1;2]?\ [2;2]?\ [0;2]?]$

Enumerating admissible Parametrizations





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$$[k_{z,\{a,b\}} = [0;0]?\ [0;1]?\ [1;1]?\ [1;2]?\ [2;2]?\ [0;2]?]$$

→ Enumeration regarding:

- Biological constraints
- The dynamics of the Process Hitting

Parametrization Inference

Results

Two steps:

- Parameters inference (partial)
- Admissible Parametrizations enumeration (total)

Parametrization Inference

Results

Two steps:

- Parameters inference (partial)
- Admissible Parametrizations enumeration (total)

Results:

- Very fast execution for parameters inference
  - $<$ **1s** for the 20 & 40 genes models **[EGFR20 & TCRSIG40]**
  - $\simeq$ **1min 30s** for the 104 genes models **[EGFR104]**
- Admissible Parametrizations enumeration

  After one cooperation removal:
  - $\simeq$ **4s** to find 42 admissible Parametrizations **[TCRSIG40]**
  - $\simeq$ **20s** to find 129 admissible Parametrizations **[EGFR20]**

ASP is convenient to handle enumeration (**cardinalities**)
and filter only admissible answers (**constraints**)

Summary & Future work

- 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
- Enumerate all full & **admissible Parametrizations**
  → Exhaustive approach to find only relevant answers

- Complexity: linear in the number of genes,
  exponential in the number of regulators of one gene

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- Enumerate all full & **admissible Parametrizations**
  → Exhaustive approach to find only relevant answers

- Complexity: linear in the number of genes,
  exponential in the number of regulators of one gene

- Concretize into more expressive BRN representations
  → Tackle with **unsigned edges** (problematic cases)
  → Use multiplexes to decrease the size of Parametrizations
- Use **projections** to remove cooperative sorts
  → Make actions independent
  → Drop inference 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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New translation: Process Hitting $\rightsquigarrow$ René Thomas

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

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

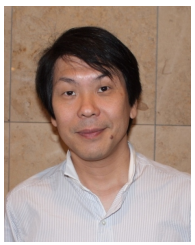
Using ASP

$\rightarrow$ Tackles with complexity/combinatorial explosion

$\rightarrow$ Allows efficient **exhaustive** search & enumeration

A multi-team topic

Inoue Laboratory (NII, Sokendai): 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

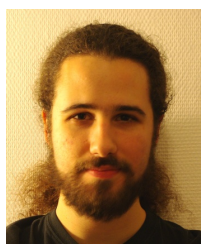
Inoue Laboratory

Loïc PAULEVÉ
Post-doc

AMIB

Olivier ROUX
Professor & team leader

Morgan MAGNIN
Associate professor



Maxime FOLSCHETTE
$\simeq 2^{nd}$ year PhD student

MeForBio

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Thank you