Concretizing Process Hitting models into Biological Regulatory Networks with Thomas' formalism using ASP

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Katsumi INOUE[2], Morgan MAGNIN[1], Olivier ROUX[1]

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[3] AMIB team / LIX / École Polytechnique (Palaiseau, France)
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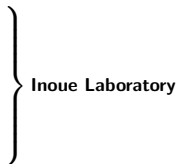
A multi-team topic

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

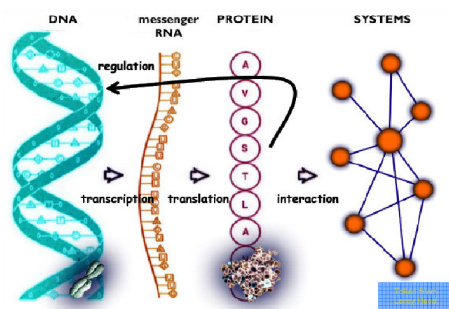**Morgan MAGNIN**
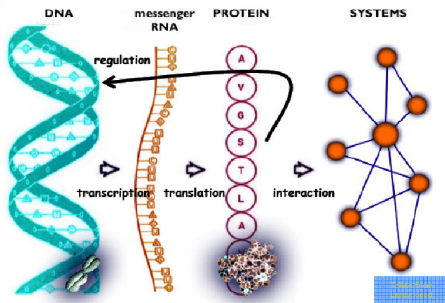Associate professor

Maxime FOLSCHETTE
1st year PhD student

MeForBio

Algebraic modeling to study complex dynamical biological systems:
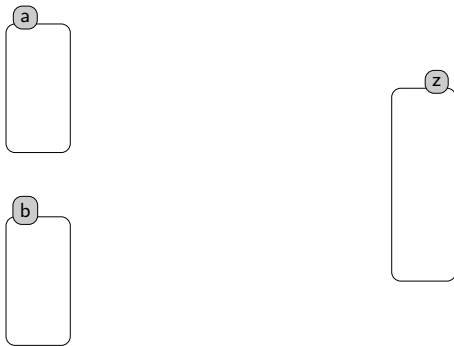
Algebraic modeling to study complex dynamical biological systems:

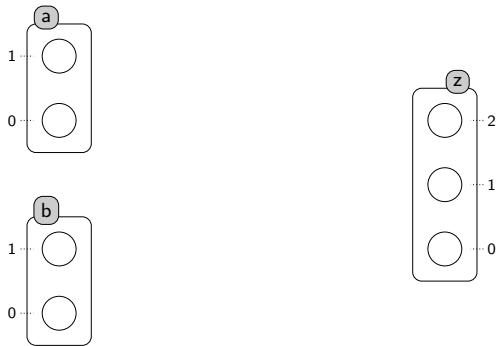- Historical model: Biological Regulatory Network (René Thomas)
- New developed model: Process Hitting
$\rightarrow$ Allow efficient translation from Process Hitting to BRN

The Process Hitting modeling
[PMR12-MSCS]

Sorts: components a, b, z

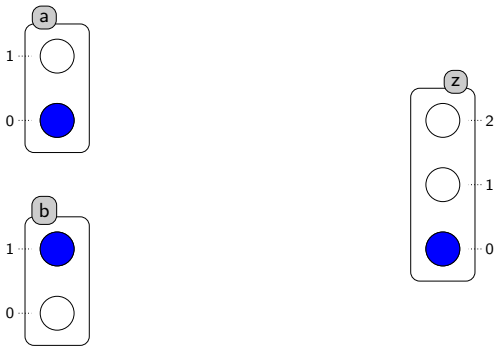The Process Hitting modeling

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Processes: local states / levels of expression z_0, z_1, z_2

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States: sets of active processes $\langle a_0, b_1, z_0 \rangle$

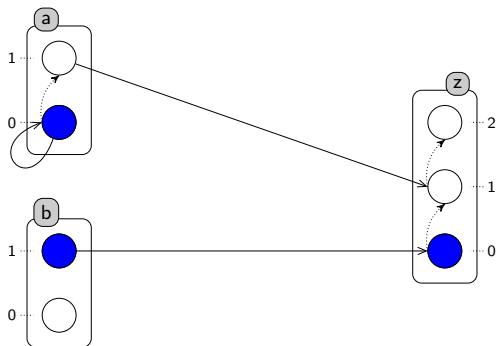## The Process Hitting modeling
[PMR12-MSCS]

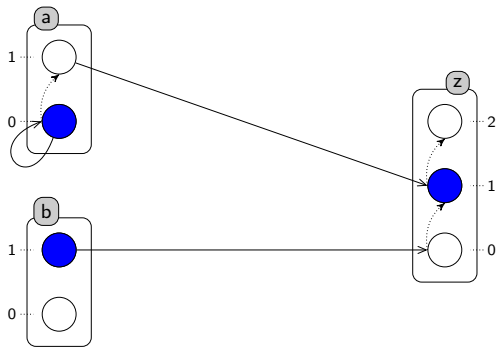**Sorts**: components a, b, z

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Actions: dynamics $b_1 \to z_0 \uparrow z_1$, $a_0 \to a_0 \uparrow a_1$, $a_1 \to z_1 \uparrow z_2$

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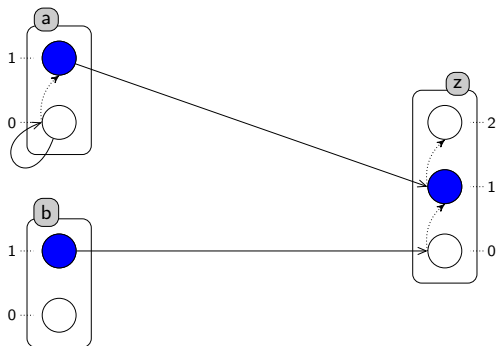
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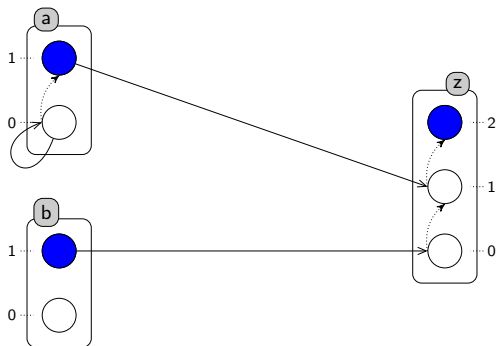
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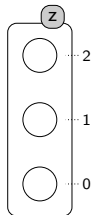
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[PMR12-MSCS]

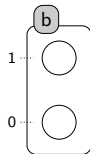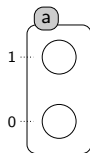How to introduce some **cooperation** between sorts?

The Process Hitting modeling
[PMR12-MSCS]

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Solution: a **cooperative sort** ab

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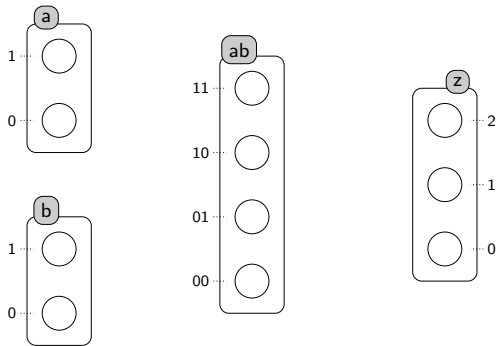Solution: a **cooperative sort** ab

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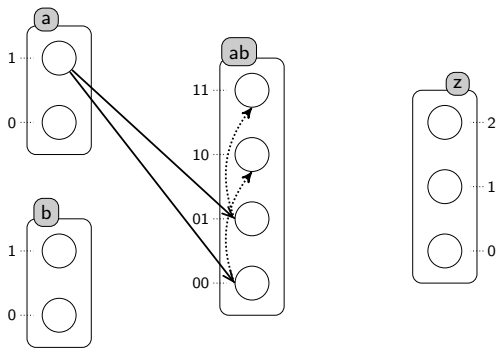
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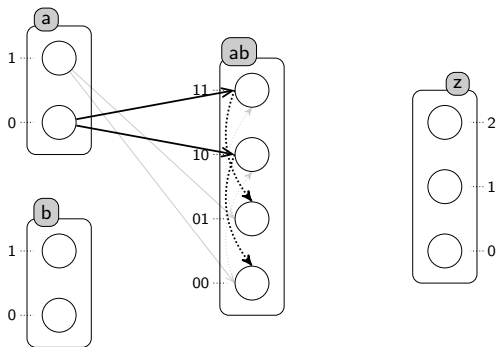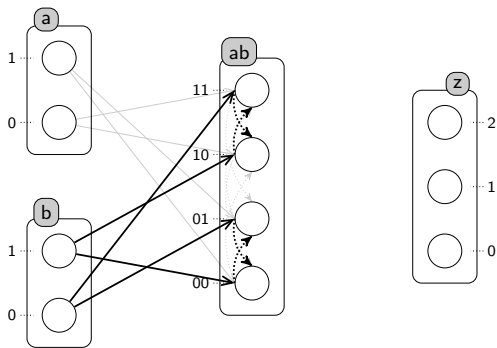

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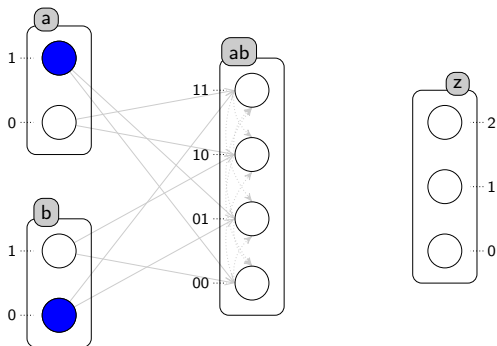[PMR12-MSCS]

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The Process Hitting modeling
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How to introduce some **cooperation** between sorts? $\quad a_1 \wedge b_0 \rightarrow z_1 \overset{\curvearrowright}{} z_2$

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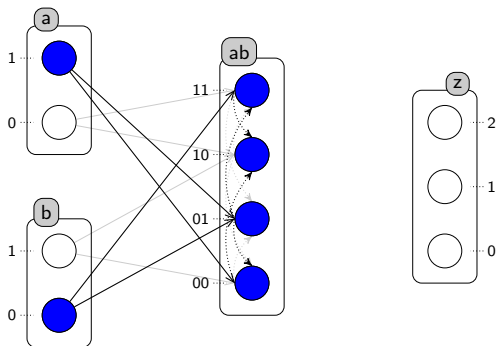
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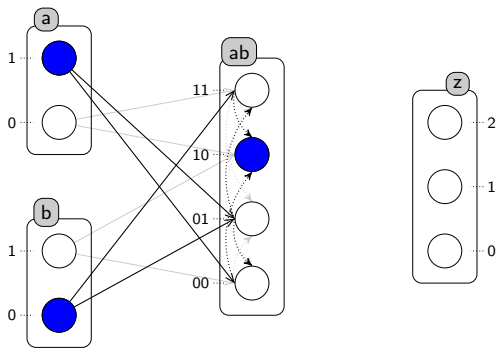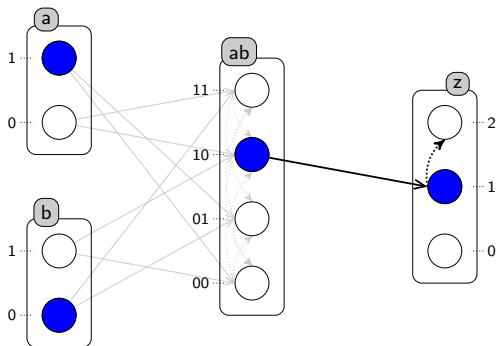

How to introduce some **cooperation** between sorts? $a_1 \wedge b_0 \rightarrow z_1 \uparrow z_2$

Solution: a **cooperative sort** ab to express $a_1 \wedge b_0$, $a_1 \oplus b_1$

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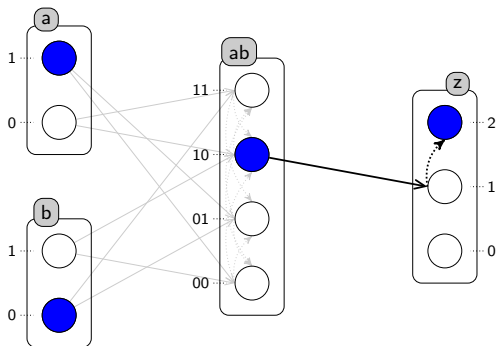
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Advantage: regular sort; drawbacks: complexity, temporal shift

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[PMR12-MSCS]
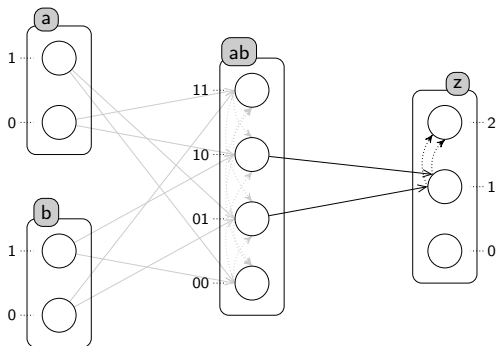
The Process Hitting framework:

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

Biological Regulatory Network

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

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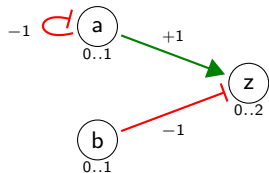
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Historical bio-informatics model for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

Biological Regulatory Network
[RCB08]

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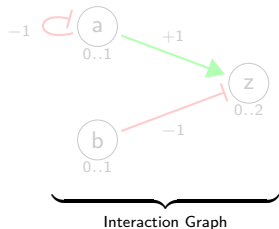
Interaction Graph

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

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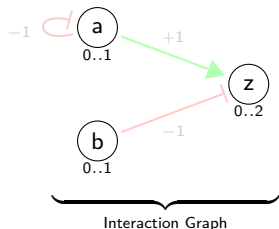
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Nodes: genes
  $\rightarrow$ Name a, b, z
  $\rightarrow$ Possible values (levels of expression)   0..1, 0..2

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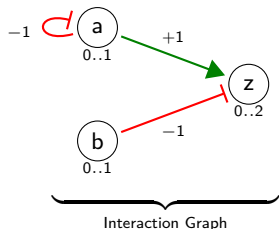
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Edges: interactions
- $\rightarrow$ Type (activation or inhibition) $+ / -$
- $\rightarrow$ Threshold   1

Biological Regulatory Network
[RCB08]
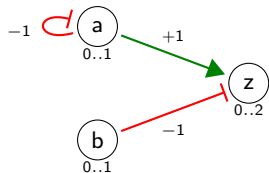
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Parametrization

Parametrization: strength of the influences (evolution tendencies)

Biological Regulatory Network
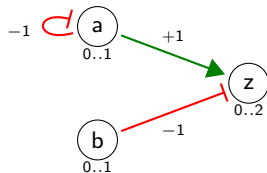
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Maps of tendencies for each gene
- $\rightarrow$ To any **set of predecessors** $\quad \omega$
- $\rightarrow$ Corresponds a **parameter** $\quad k_{x,\omega}$

Biological Regulatory Network

[RCB08]

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Parametrization

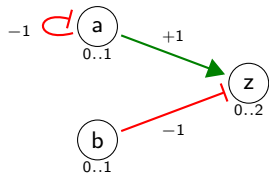**Parametrization**: strength of the influences (evolution tendencies)

Maps of tendencies for each gene
  $\rightarrow$ To any **set of predecessors** ω
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"$k_{z,\{a\}} = 2$"   means: "z tends to 2 when $a \geq 1$ and $b < 1$"

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[RCB08]

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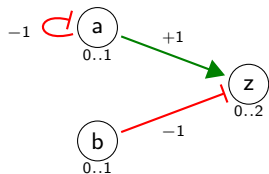 $\rightarrow$ To any **set of predecessors** ω
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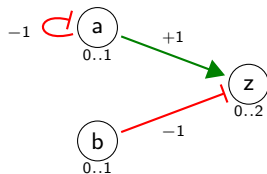- $\rightarrow$ To any **set of predecessors** ω
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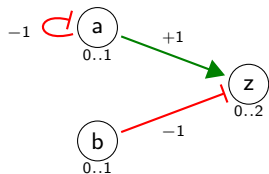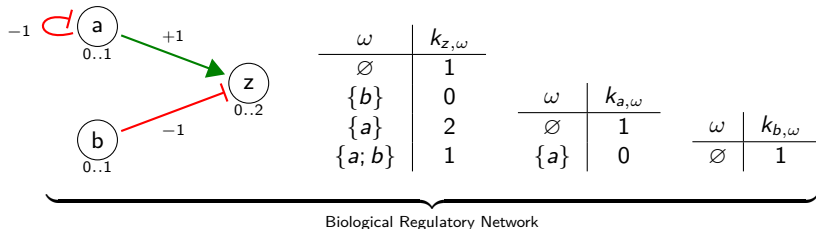 $\rightarrow$ To any **set of predecessors** ω
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Biological Regulatory Network

$\rightarrow$ All needed information to run the model or study its dynamics:
- Build the State Graph
- Find reachability properties, fixed points, attractors
- Other properties...

$\rightarrow$ **Strengths**: well adapted for the study of biological systems
$\rightarrow$ **Drawbacks**: inherent complexity; needs the full specification of cooperations
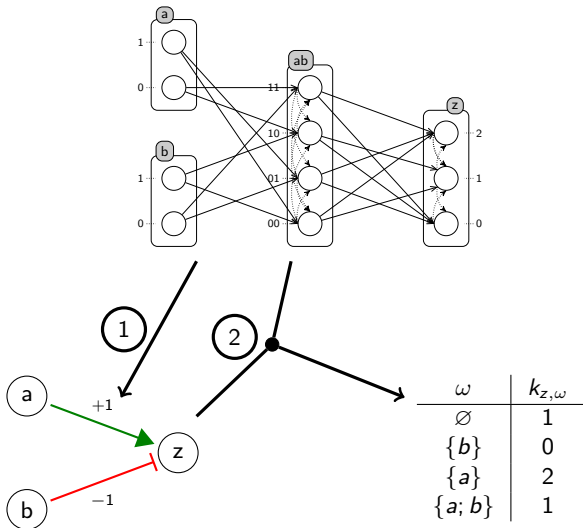
Inferring a BRN with Thomas' parameters
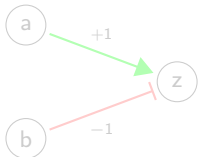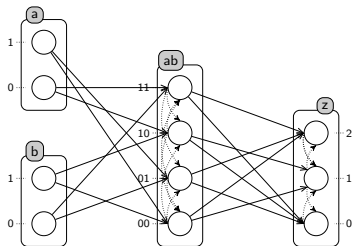
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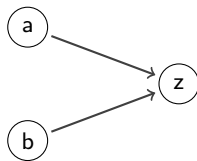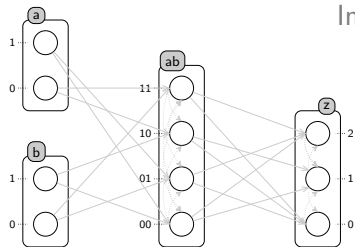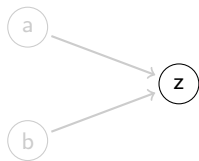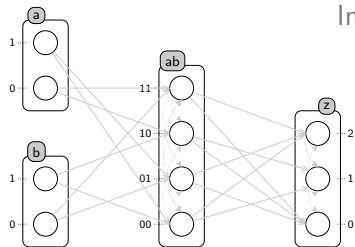| ω	$k_{z,\omega}$
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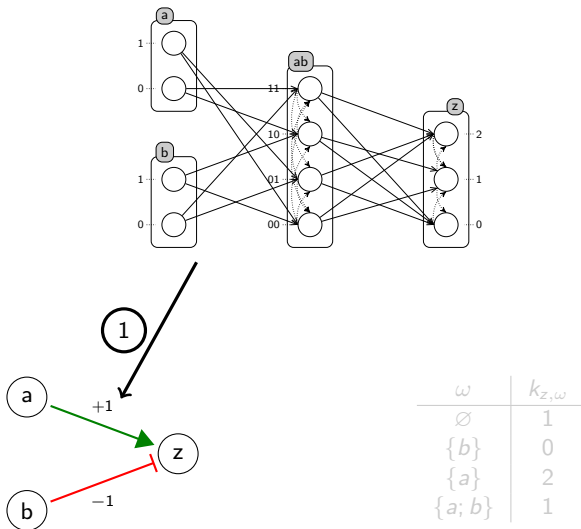
Inferring the Interaction Graph
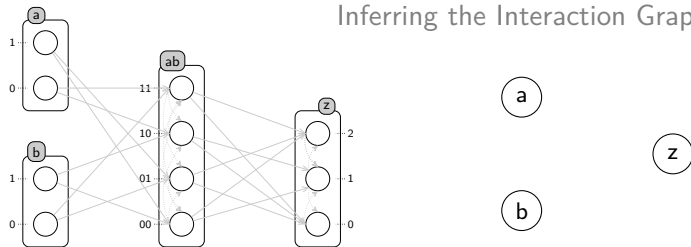
- **Inputs:** a Process Hitting model
- **Output:** An interaction graph with all information:
    $\rightarrow$ edges, signs and thresholds

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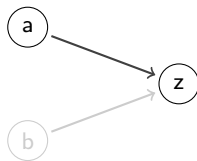- **Idea:** Exhaustive search in all possible configurations

Inferring the Interaction Graph

Inferring the Interaction Graph

- For each gene [z]

Inferring the Interaction Graph
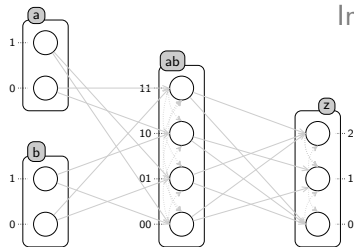
- For each gene [z], consider one possible regulator [a]

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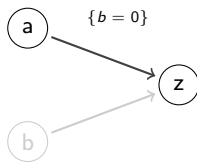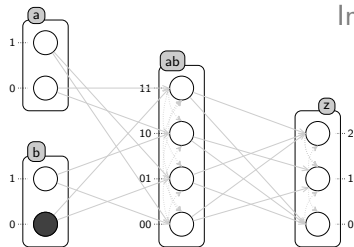
- For each gene [z], consider one possible regulator [a]
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Inferring the Interaction Graph

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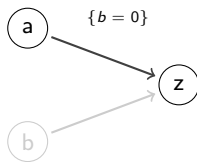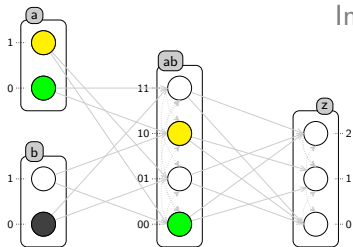
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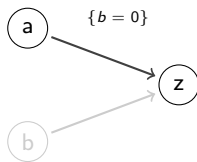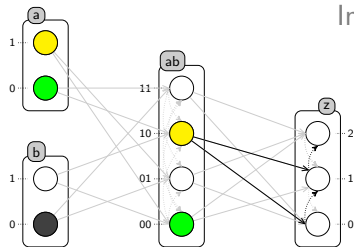
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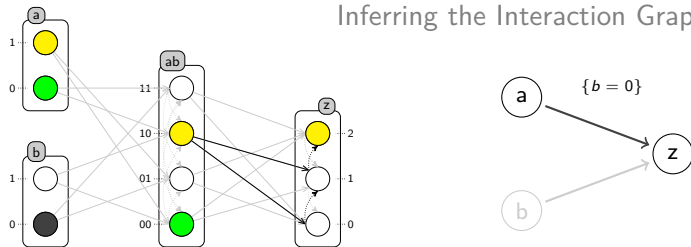
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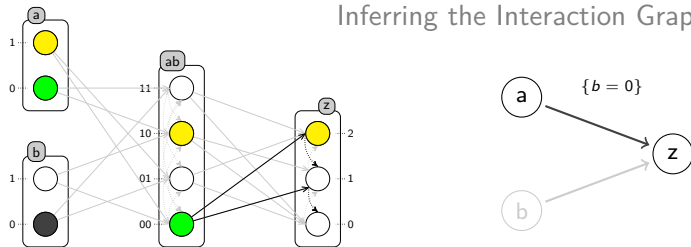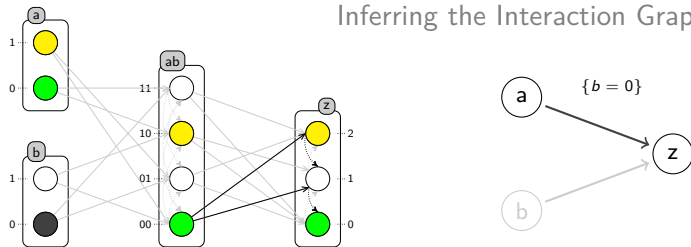Inferring the Interaction Graph

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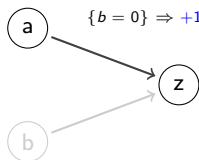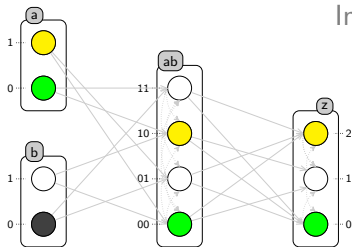## Inferring the Interaction Graph

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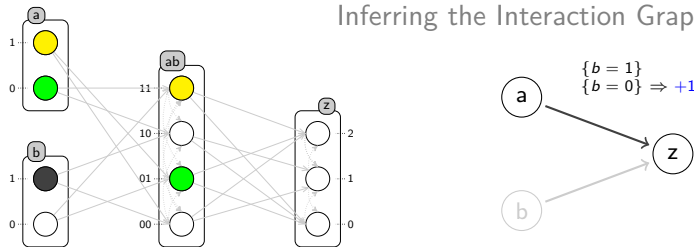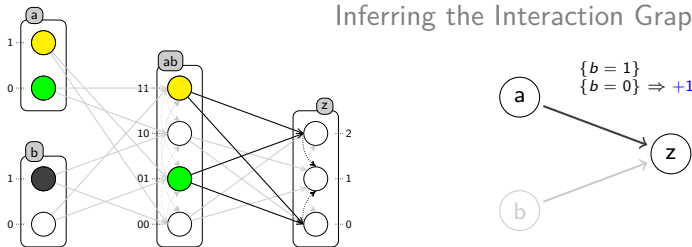
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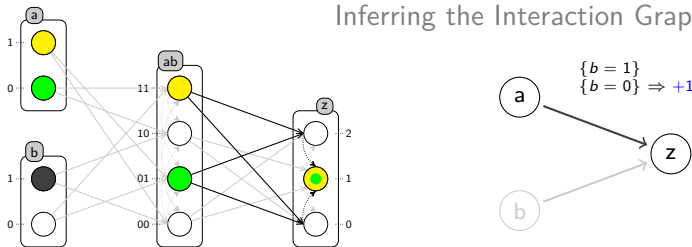
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Inferring the Interaction Graph

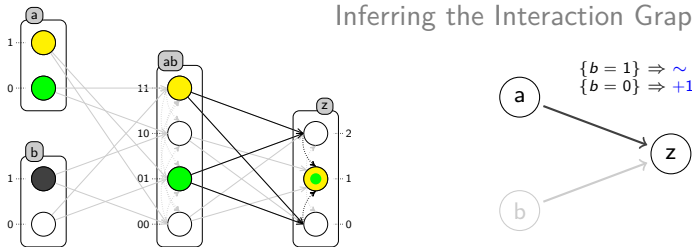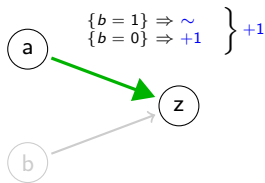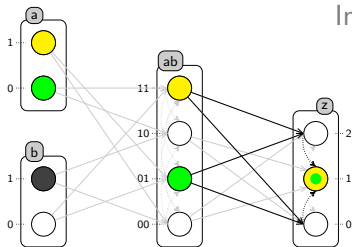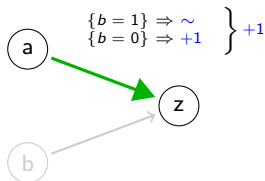$$\left.\begin{array}{l} \{b=1\} \Rightarrow \sim \\ \{b=0\} \Rightarrow +1 \end{array}\right\} +1$$

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    $\{b=0\} \rightarrow a_0 < a_1$ and $\{z_0\} \preccurlyeq \{z_2\} \Rightarrow$ activation ($+$) & threshold $= 1$
    $\{b=1\} \rightarrow a_0 < a_1$ and $\{z_1\} = \{z_1\} \Rightarrow$ inconclusive ($\sim$)

  - If possible, determine the general influence of a on z

Problematic cases:

$$\left.\begin{array}{l} \rightarrow \text{ No focal processes (cycle)} \\ \rightarrow \text{ Opposite influences } (+ \ \& \ -) \end{array}\right\} \Rightarrow \text{ Unsigned edge}$$

Inferring the Interaction Graph

Implementation & Results

Programming in ASP:

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

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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

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- **Clingo** to solve the description with the adequate program

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

- $<$ 1s for 20 & 40 genes models
- $\simeq$ 13s for a 94 genes model
- $\simeq$ 4min for a 104 genes model

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

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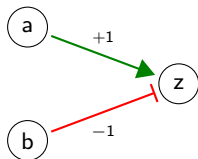
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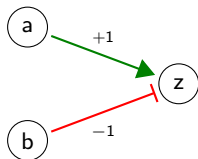| ω	$k_{z,\omega}$
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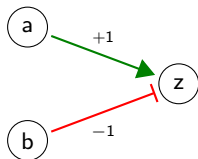
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$\{a\}$	
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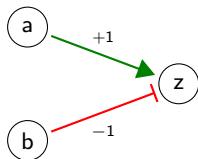**Inputs:** The Process Hitting model and the related Interaction Graph
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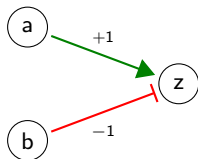- For each gene [z] and each **configuration** of resources [$\omega = \{a; b\}$]
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Problematic cases:

$\rightarrow$ Behavior cannot be represented as a BRN

$\rightarrow$ Lack of cooperation (no focal processes)

Enumerating admissible Parametrizations
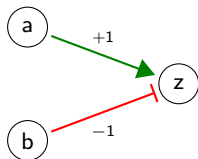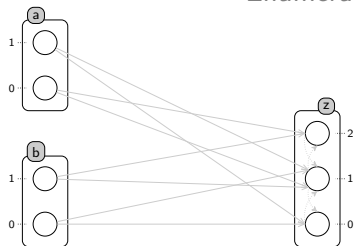
ω	$k_{z,\omega}$
$\varnothing$	?
$\{b\}$	0
$\{a\}$	2
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Inputs: The Process Hitting, the related Interaction Graph
   and the partially inferred Parametrization

Output: All admissible Parametrizations observing the dynamics

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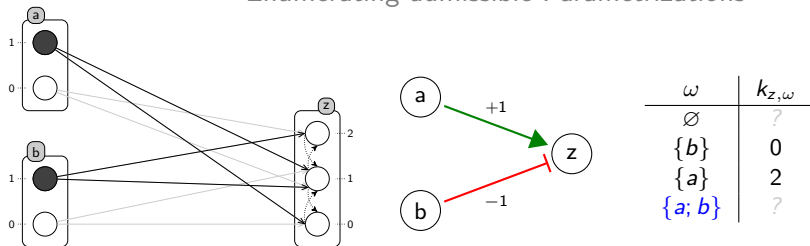
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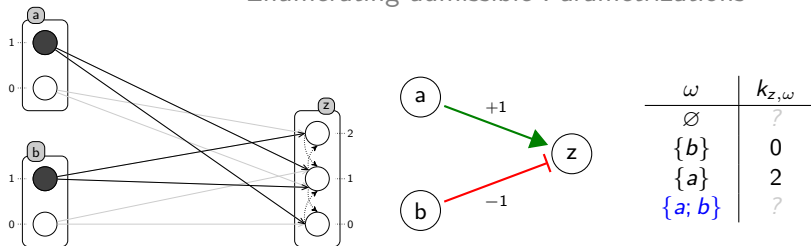
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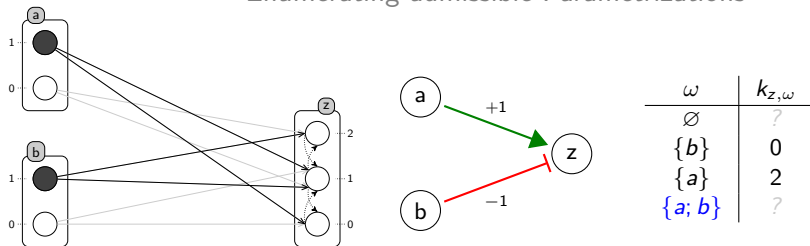
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$\rightarrow$ Enumeration regarding:

- Biological constraints
- The dynamics of the Process Hitting

Enumerating admissible Parametrizations

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

Enumerating admissible Parametrizations

Implementation & Results

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

Results:

- Very fast execution for parameters inference
    - < 1s for 20 & 40 genes models
- Efficient Parametrizations enumeration
    - After one cooperation removal:
        - $\simeq$ 4s to find all 42 Parametrizations (40 genes model)
        - $\simeq$ 20s to find all 129 Parametrizations (20 genes model)

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

Summary & Future work

- Inference of the **complete Interaction Graph**
    - $\rightarrow$ Exhaustive approach to find the mutual influences
- Inference of the **possibly partial Parametrization**
    - $\rightarrow$ Exhaustive approach to find the necessary parameters
- Enumerate all full & **admissible Parametrizations**
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- Complexity: linear in the number of genes,
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- Complexity: linear in the number of genes,
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- Concretize into more expressive BRN representations
    - $\rightarrow$ Tackle with **unsigned edges** (problematic cases)
    - $\rightarrow$ Use multiplexes to decrease the size of Parametrizations
- Use **projections** to remove cooperative sorts
    - $\rightarrow$ Make actions independent
    - $\rightarrow$ 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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Thank you

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