

— CMSB'2012 —

The 10<sup>th</sup> Conference on Computational Methods in Systems Biology

## Concretizing the Process Hitting into Biological Regulatory Networks

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[ki@nii.ac.jp](mailto:ki@nii.ac.jp)

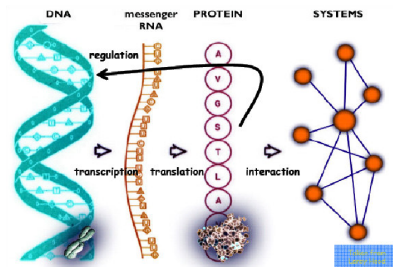
<sup>3</sup> AMIB / LIX / École Polytechnique (Palaiseau, France)

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AtlanSTIC sojourn financed by NII & Centrale Initiatives

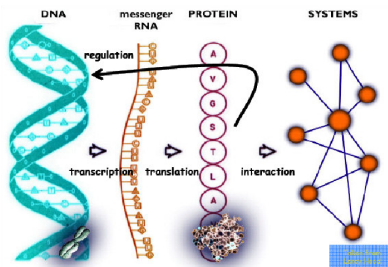
## Context and Aims

Algebraic modeling to study complex dynamical biological systems:



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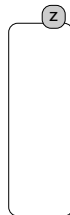


- Historical model: Biological Regulatory Network (René Thomas)
- New developed model: Process Hitting

⇒ **Allow efficient translation from Process Hitting to BRN** ⇐

## The Process Hitting modeling

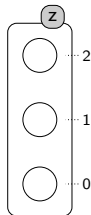
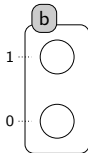
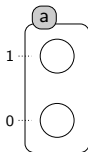
[PMR12-MSCS]



**Sorts:** components    *a, b, z*

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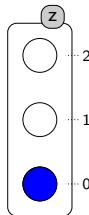
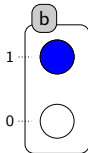
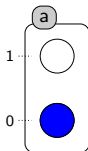


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[PMR12-MSCS]



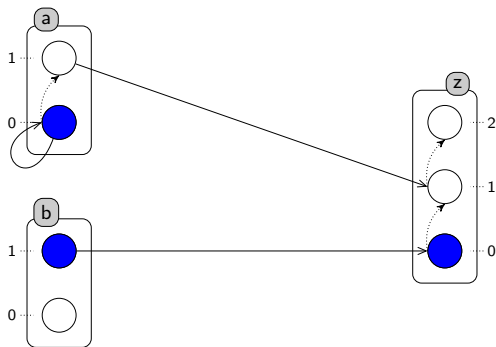
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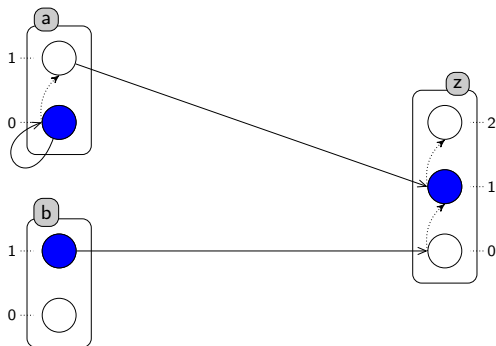
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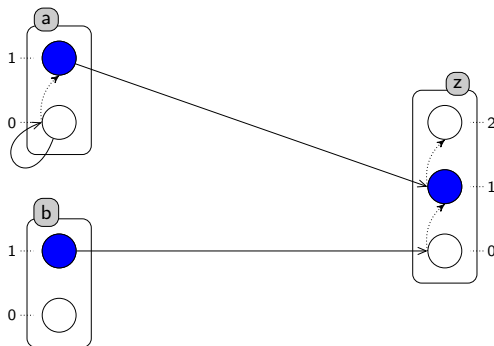
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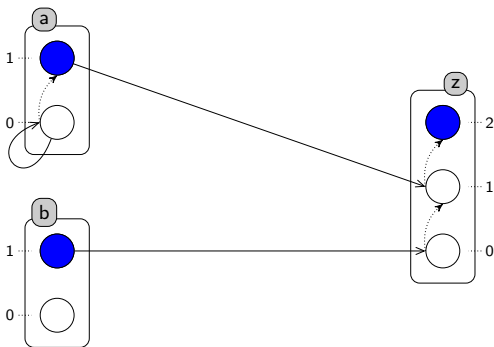
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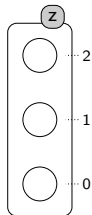
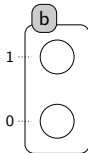
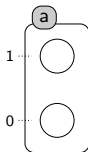
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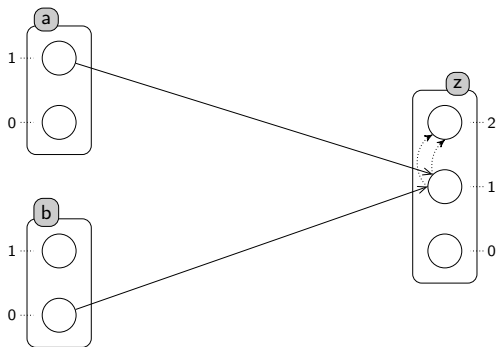


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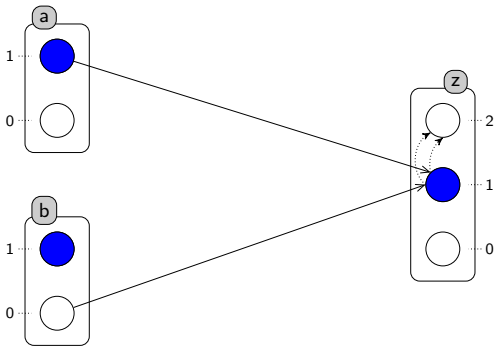
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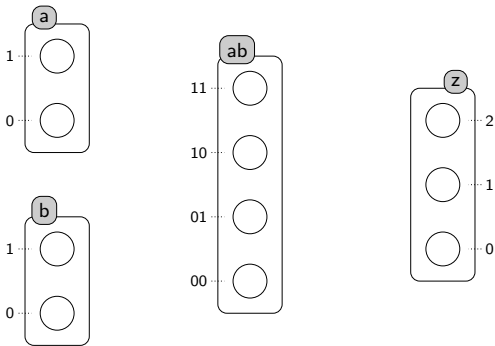
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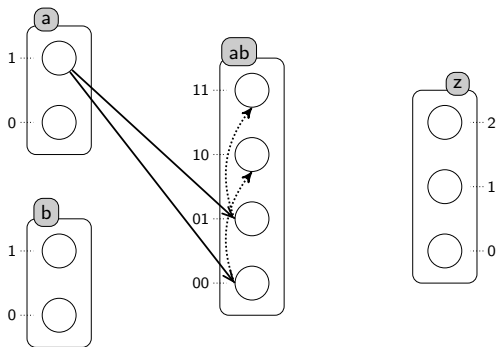


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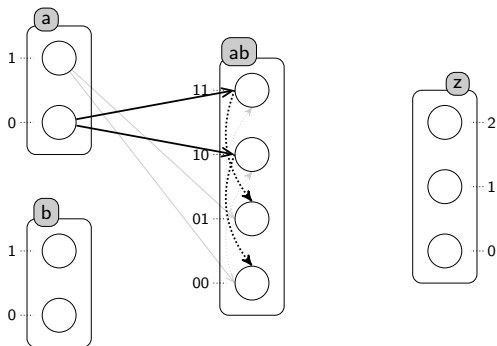


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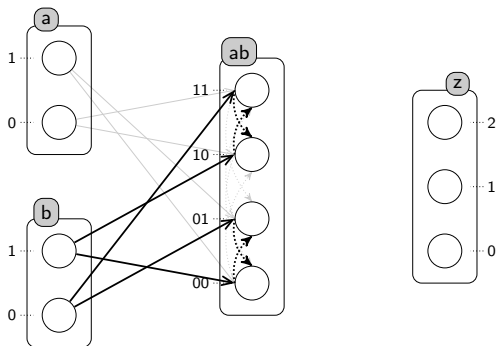
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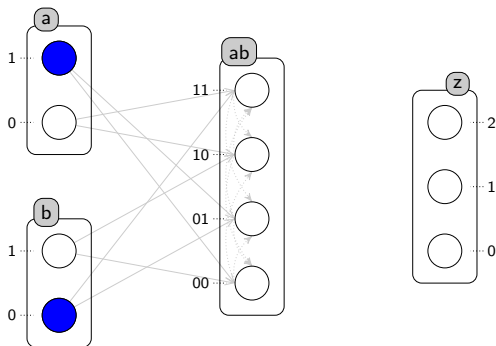


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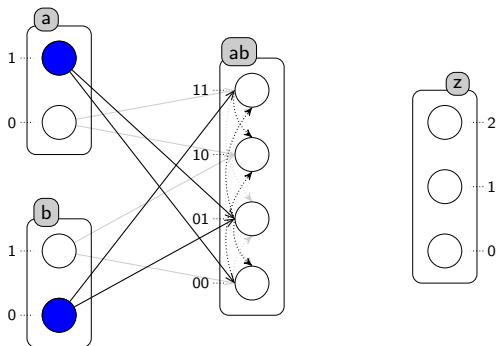


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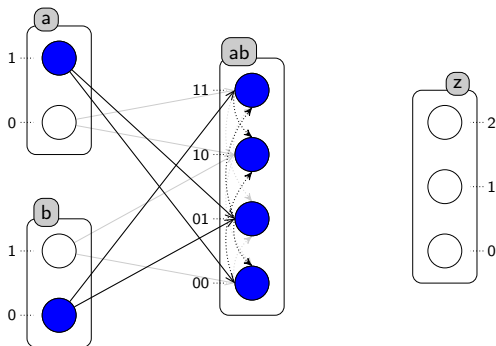


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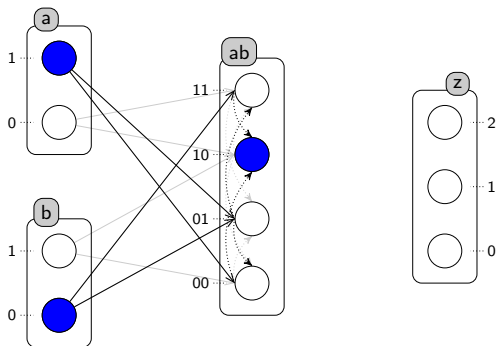


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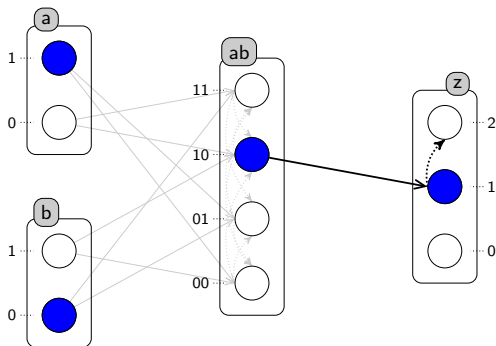


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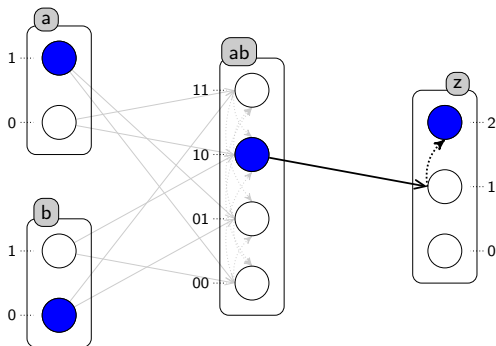


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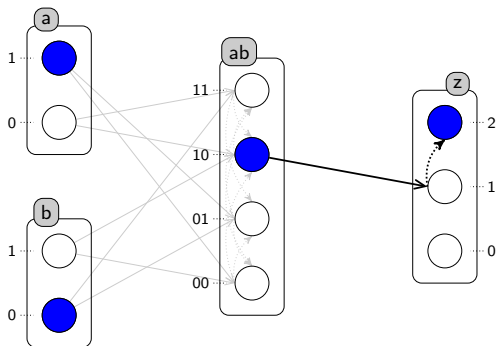


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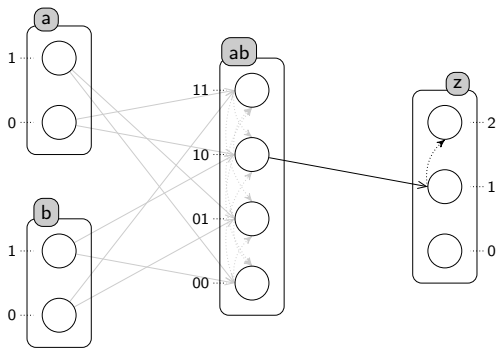
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Advantage: regular sort; drawbacks: complexity, temporal shift



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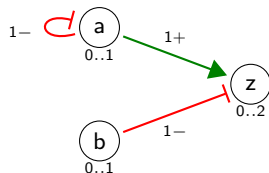


The Process Hitting framework:

- **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]



$\omega$	$k_{z,\omega}$
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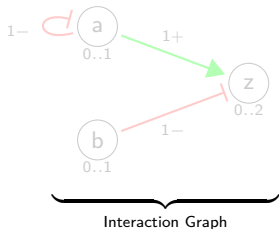
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**Historical bio-informatics model** for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

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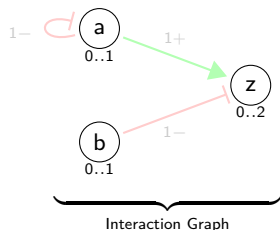
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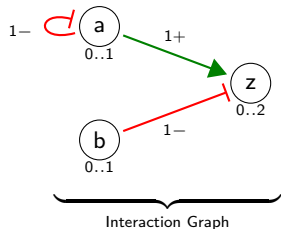
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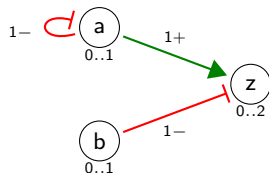
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**Edges:** interactions

- Threshold  $1$
- Type (activation or inhibition)  $+ / -$

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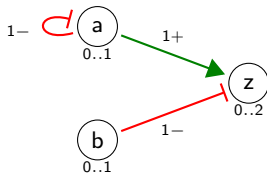
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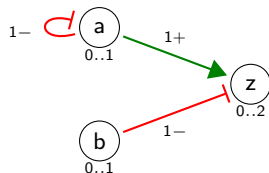
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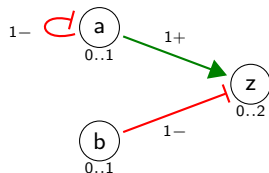
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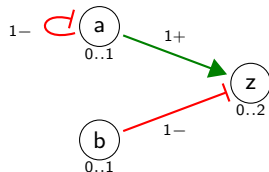
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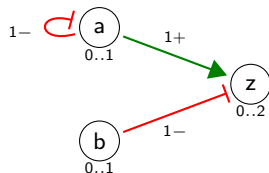
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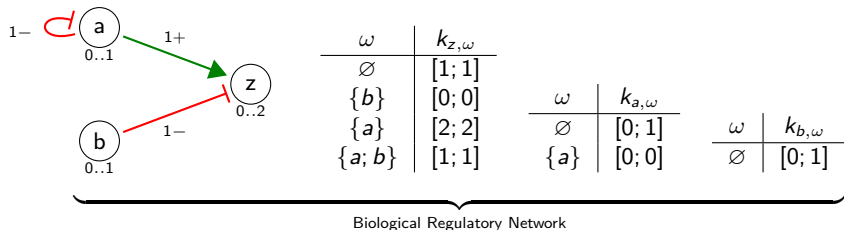
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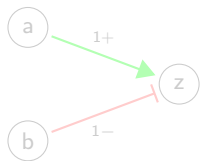
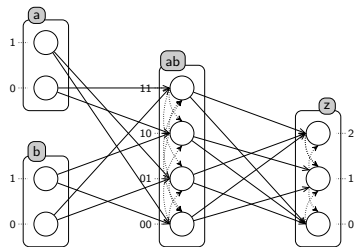
## Biological Regulatory Network

[RCB08]



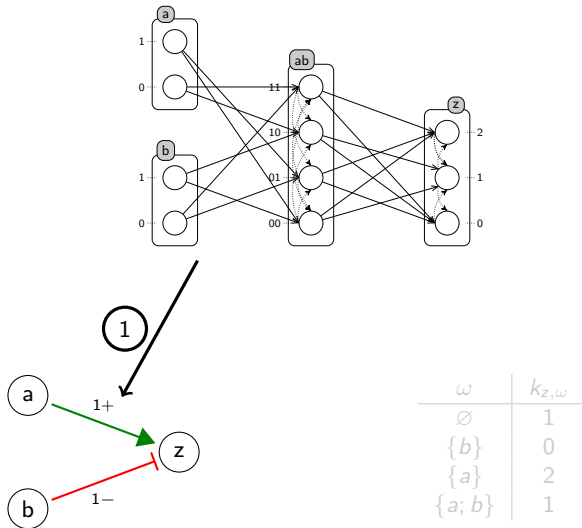
- All needed information to run the model or study its dynamics:
  - Build the State Graph
  - Find reachability properties, fixed points, attractors
  - Other properties...
- **Strengths:** well adapted for the study of biological systems
- **Drawbacks:** inherent complexity; needs the full specification of cooperations

# Inferring a BRN with Thomas' parameters

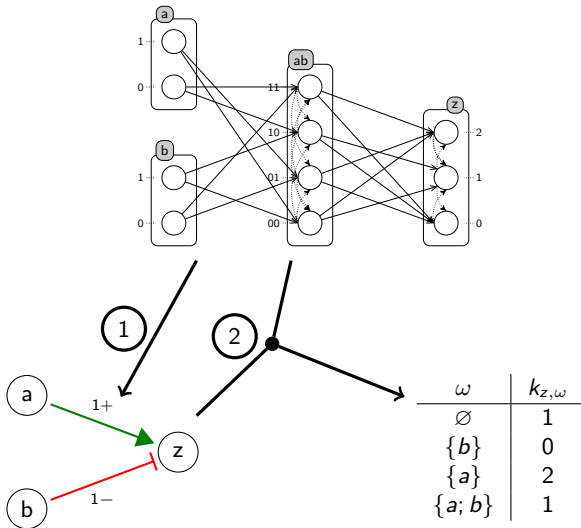


$\omega$	$k_{z,\omega}$
$\emptyset$	1
$\{b\}$	0
$\{a\}$	2
$\{a; b\}$	1

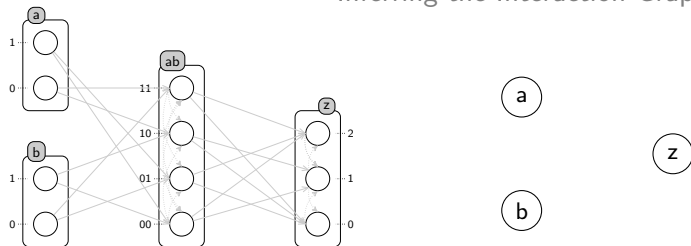
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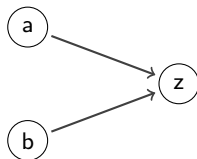
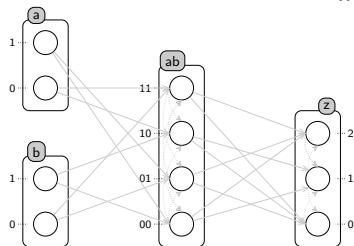
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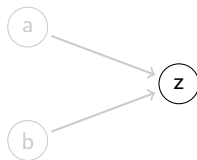
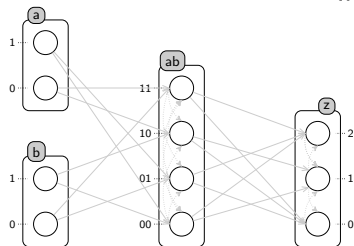
- **Inputs:** a Process Hitting model
- **Output:** An interaction graph with all information:  
→ edges, signs and thresholds
- **Difficulties:** Process Hitting is more atomistic than BRNs
- **Idea:** Exhaustive search in all possible configurations



## Inferring the Interaction Graph

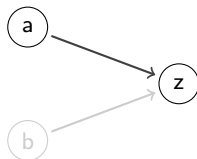
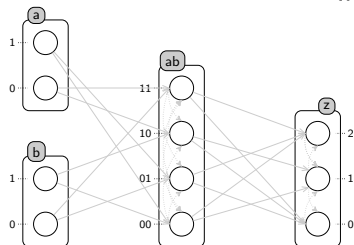


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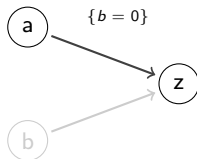
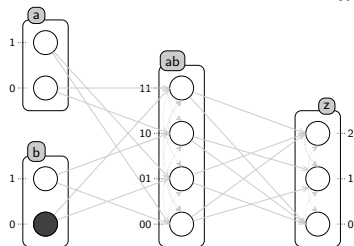
- For each gene  $[z]$

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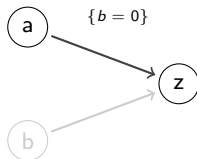
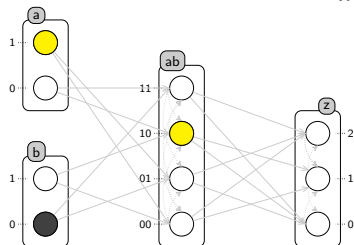
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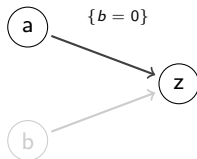
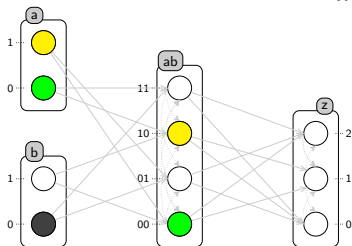
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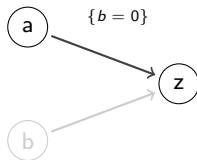
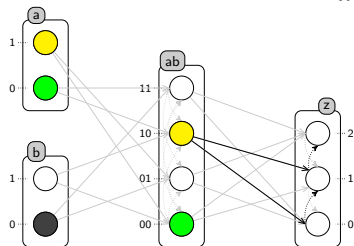
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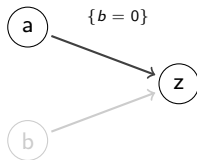
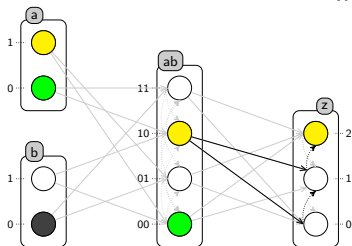
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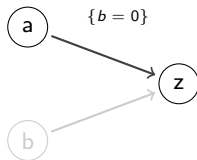
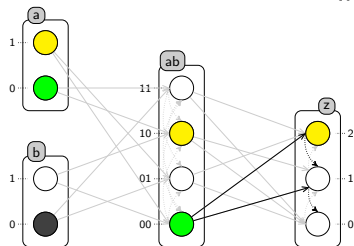
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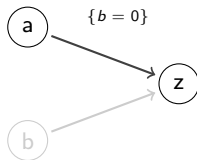
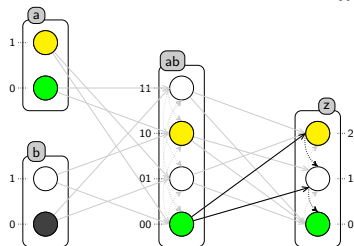


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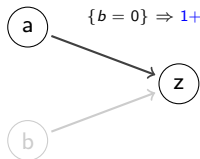
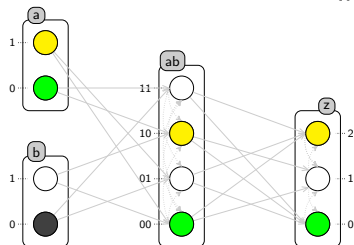
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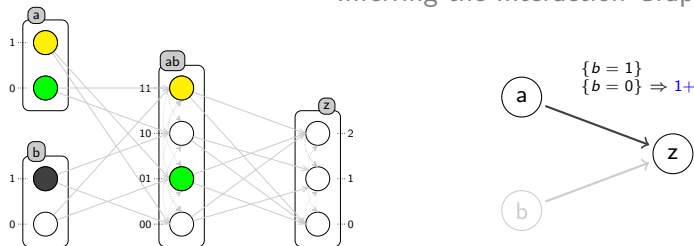
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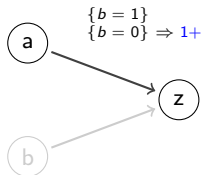
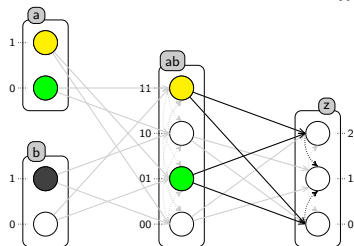
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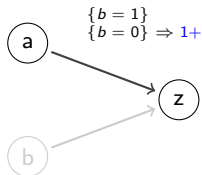
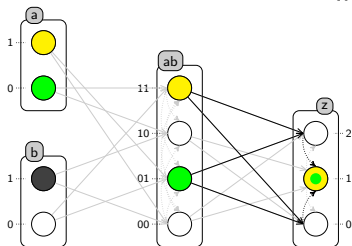
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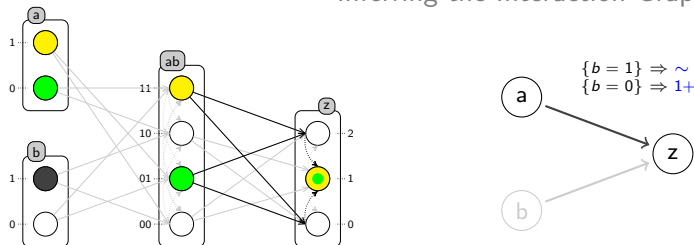
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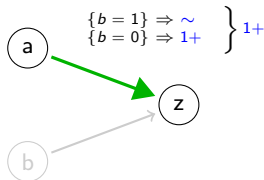
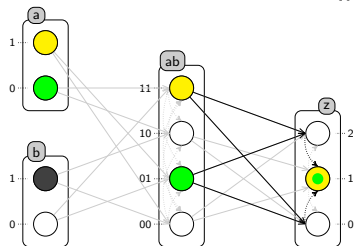
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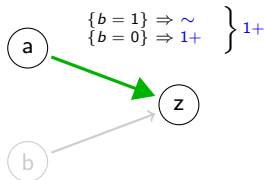
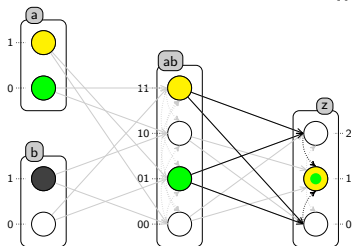
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Problematic cases:

- $\rightarrow$  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)

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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

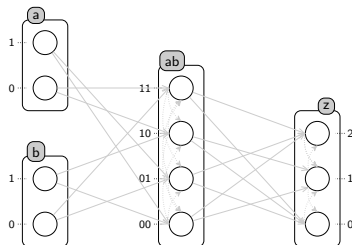
Results

**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 [\[EGFR104\]](#)

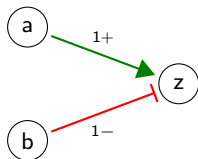
Model name	Model specifications				IG inference	
	Sorts	CS*	Processes	Actions	Time	Edges
<a href="#">[EGFR20]</a>	20	22	152	399	< <b>1s</b>	50
<a href="#">[TCRSIG40]</a>	40	14	156	301	< <b>1s</b>	54
<a href="#">[TCRSIG94]</a>	94	39	448	1124	$\simeq$ <b>13s</b>	169
<a href="#">[EGFR104]</a>	104	89	748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



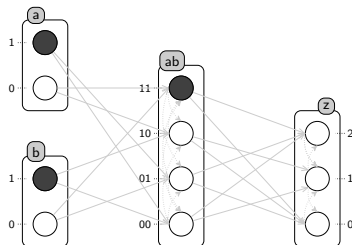
## Inferring Parameters [PMR10-TCSB]



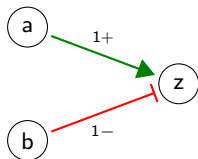
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$\{b\}$	
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**Inputs:** The Process Hitting model and the related Interaction Graph

**Output:** The Parametrization related to the Interaction Graph



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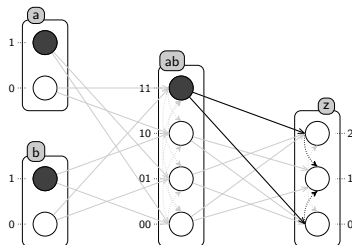


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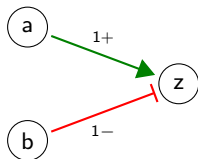
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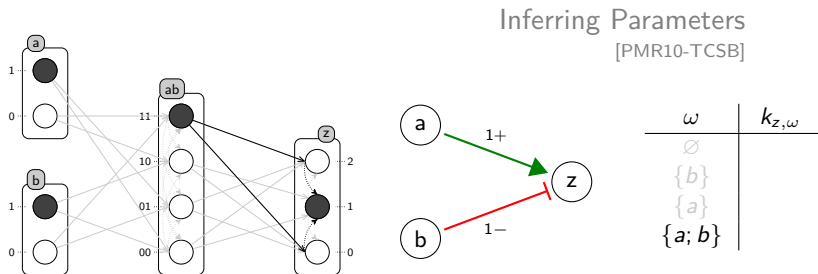


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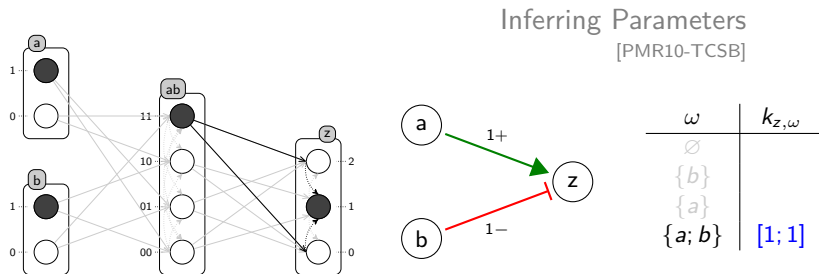


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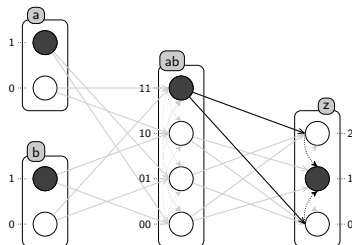




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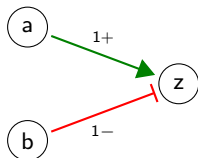
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[PMR10-TCSB]



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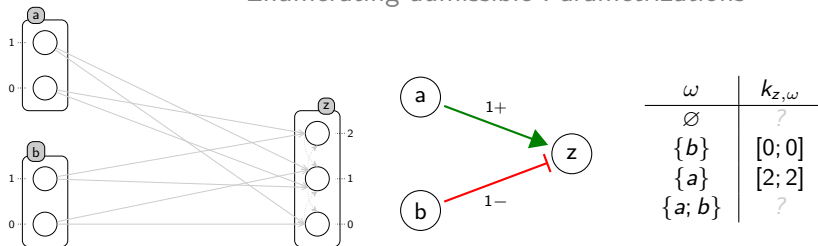
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Problematic cases:

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

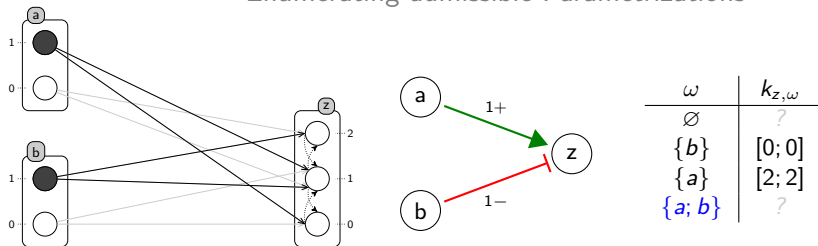
## Enumerating admissible Parametrizations



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

**Output:** All admissible Parametrizations observing the dynamics

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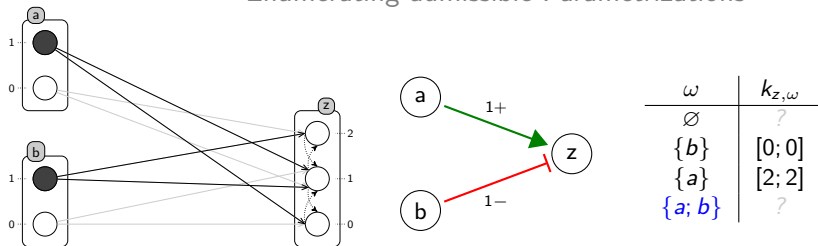


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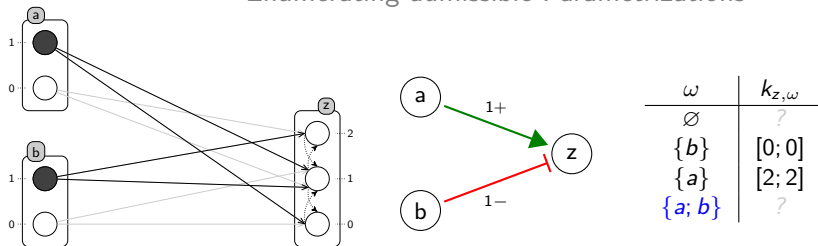


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→ Enumeration regarding:

- Biological constraints
- The dynamics of the Process Hitting

# Parametrization Inference

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Two steps:

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**Results:**

- Very fast execution for parameters inference
  - < **1s** for the 20 & 40 genes models [EGFR20 & TCRSIG40]
  - ≈ **1min 30s** for the 104 genes models [EGFR104]
- Admissible Parametrizations enumeration
  - After one cooperation removal:
    - ≈ **4s** to find 42 admissible Parametrizations [TCRSIG40]
    - ≈ **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

## 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
- 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

- New **formal link** between the two models
- More **visibility** to the Process Hitting

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Using ASP

- Tackles with complexity/combinatorial explosion
- 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



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Associate professor



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} **MeForBio**

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**Thank you**