

— CMSB'2012 —

The 10th Conference on Computational Methods in Systems Biology

Concretizing the Process Hitting into Biological Regulatory Networks

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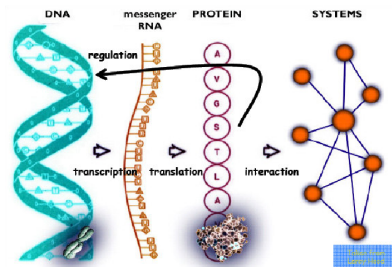
³ AMIB / LIX / École Polytechnique (Palaiseau, France)

pauleve@lix.polytechnique.fr

AtlanSTIC sojourn financed by NII & Centrale Initiatives

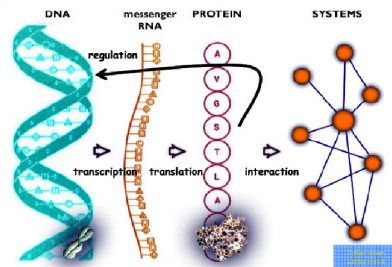
Context and Aims

Algebraic modeling to study complex dynamical biological systems:



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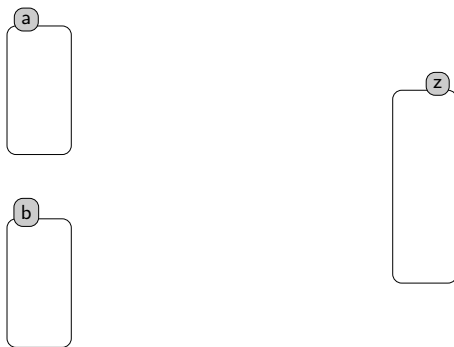


- Historical model: Biological Regulatory Network (René Thomas)
- New developed model: Process Hitting

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

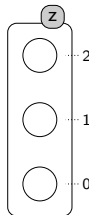
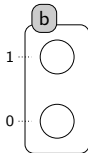
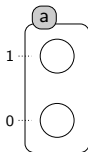
The Process Hitting modeling

[PMR12-MSCS]



Sorts: components *a, b, z*

The Process Hitting modeling [PMR12-MSCS]

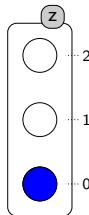
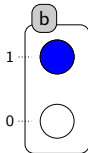
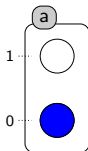


Sorts: components *a, b, z*

Processes: local states / levels of expression *z₀, z₁, z₂*

The Process Hitting modeling

[PMR12-MSCS]

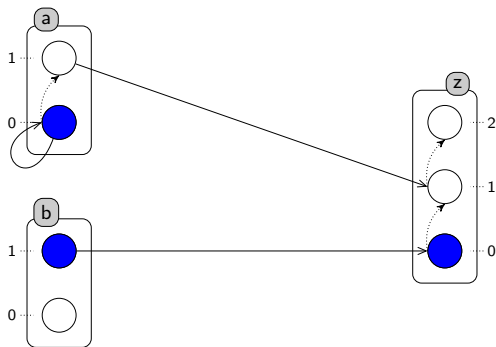


Sorts: components a, b, z

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

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

The Process Hitting modeling [PMR12-MSCS]



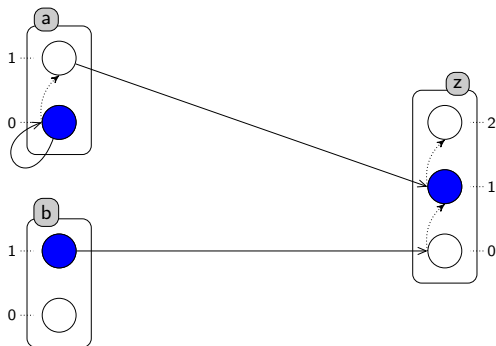
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Actions: dynamics $\underline{b_1 \rightarrow z_0} \uparrow z_1, \underline{a_0 \rightarrow a_0} \uparrow a_1, a_1 \rightarrow z_1 \uparrow z_2$

The Process Hitting modeling [PMR12-MSCS]



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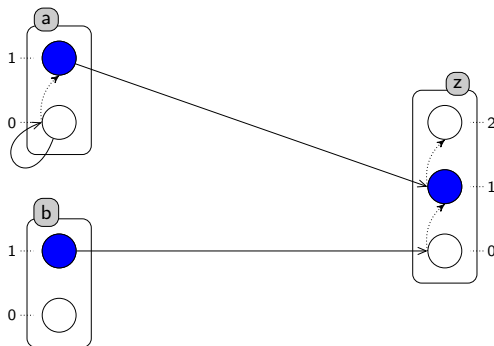
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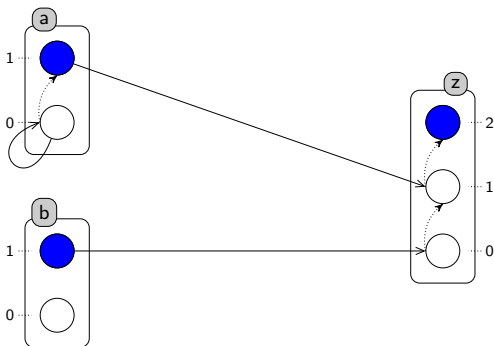
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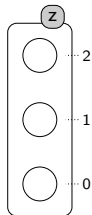
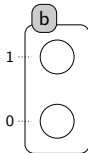
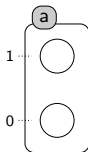
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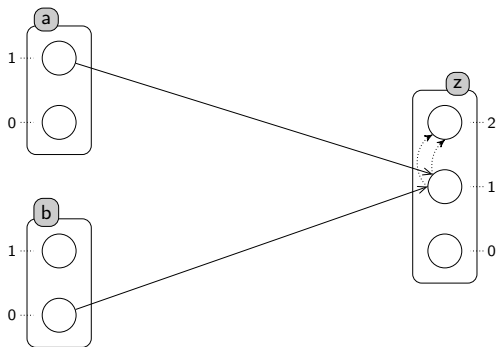


How to introduce some **cooperation** between sorts?

$$a_1 \wedge b_0 \rightarrow z_1 \uparrow z_2$$

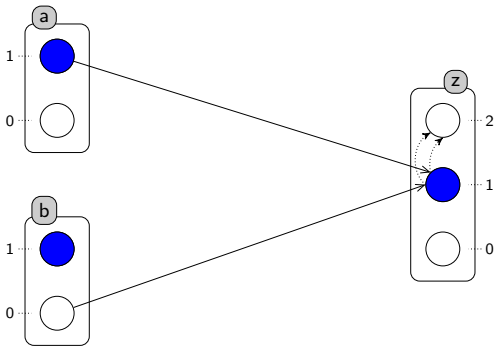
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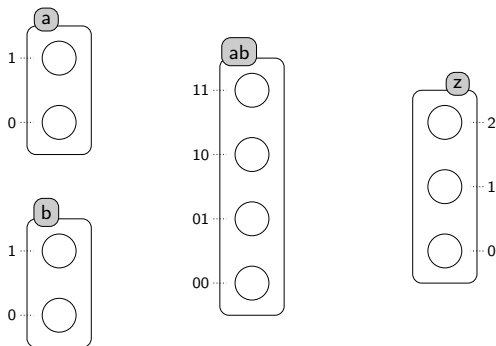
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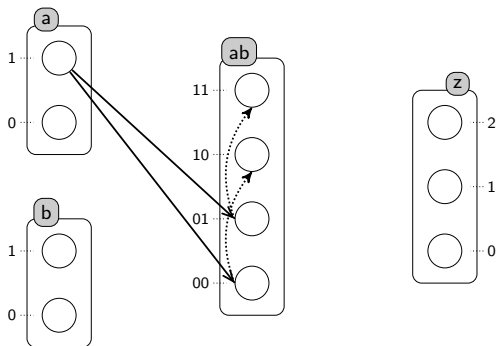


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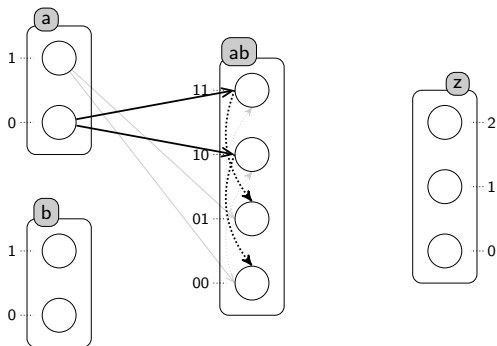


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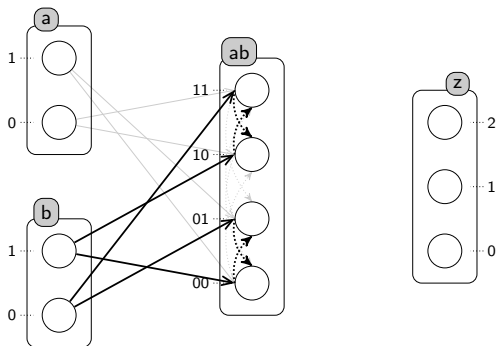


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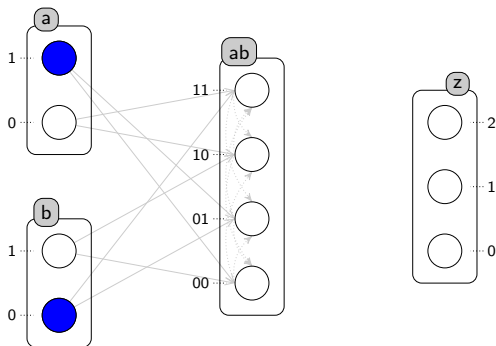


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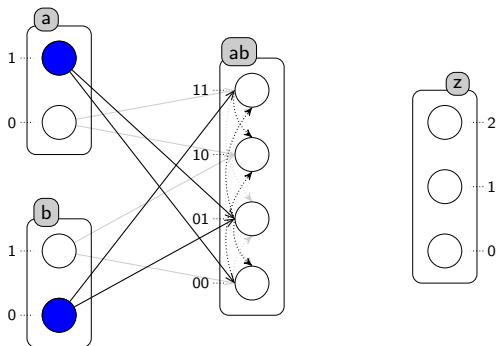


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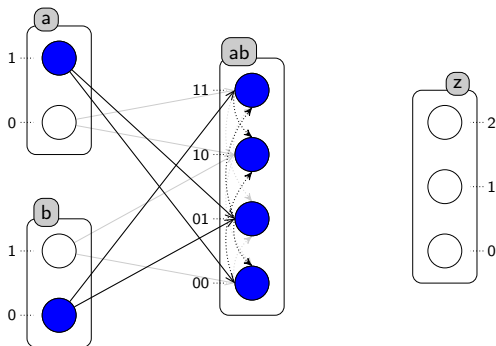


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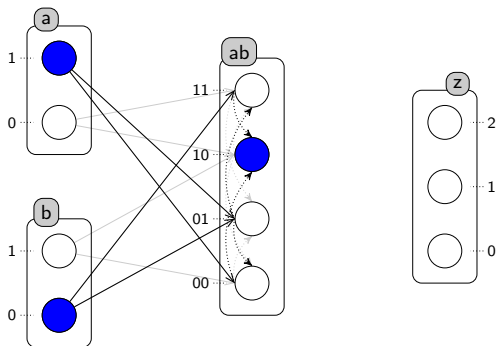


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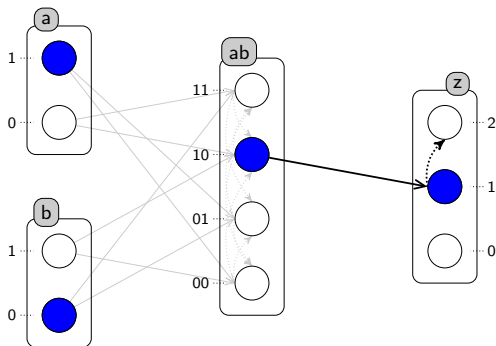
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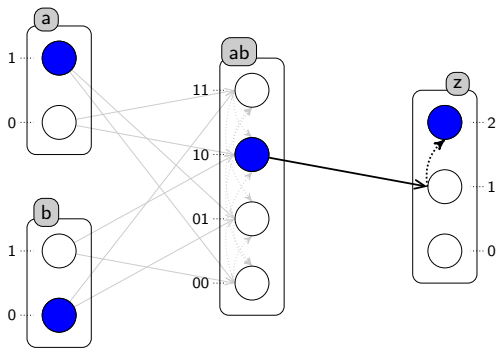


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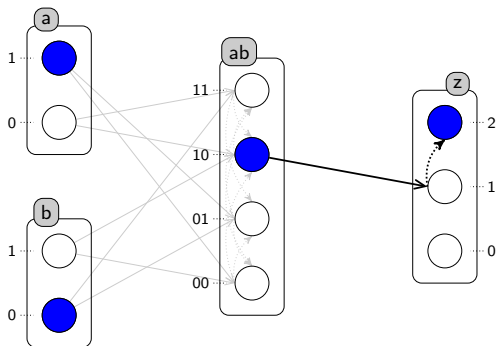


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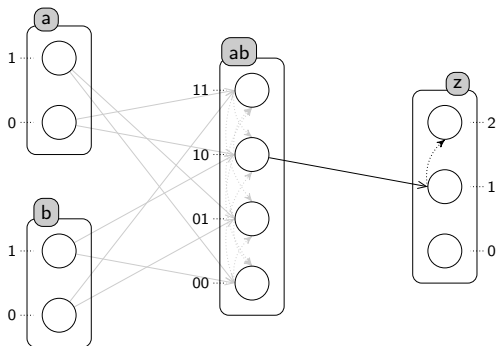
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Advantage: regular sort; drawbacks: complexity, temporal shift

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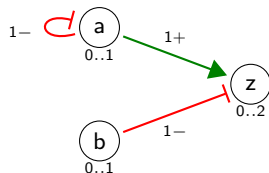


The Process Hitting framework:

- **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]



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

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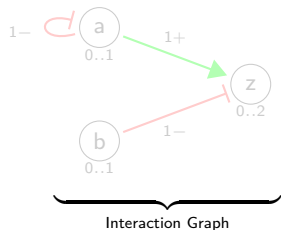
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Historical bio-informatics model for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

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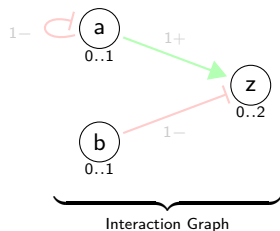
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Interaction Graph: structure of the system (genes & interactions)

Biological Regulatory Network

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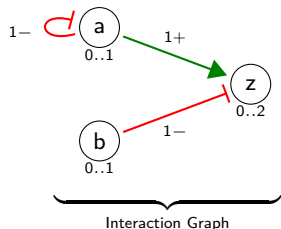
Nodes: genes

→ Name a, b, z

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

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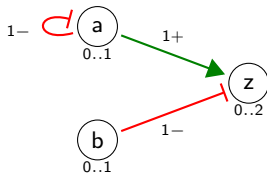
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Edges: interactions

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

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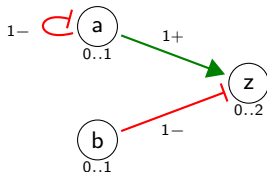
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Parametrization

Parametrization: strength of the influences (evolution tendencies)

Biological Regulatory Network

[RCB08]



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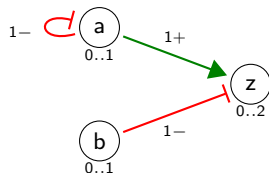
Parametrization: strength of the influences (evolution tendencies)

Maps of tendencies for each gene

- To any **set of predecessors** ω
- Corresponds a **parameter** $k_{x,\omega}$

Biological Regulatory Network

[RCB08]



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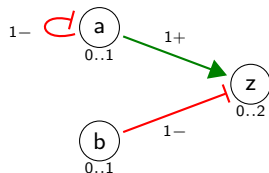
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" $k_{z,\{a\}} = [2; 2]$ " means: "z tends to $[2; 2]$ when $a \geq 1$ and $b < 1$ "

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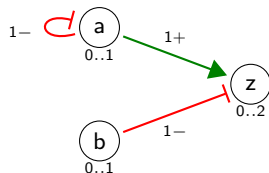
→ To any **set of predecessors** ω

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Biological Regulatory Network

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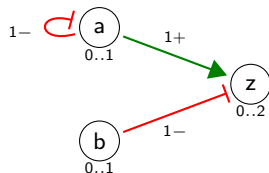
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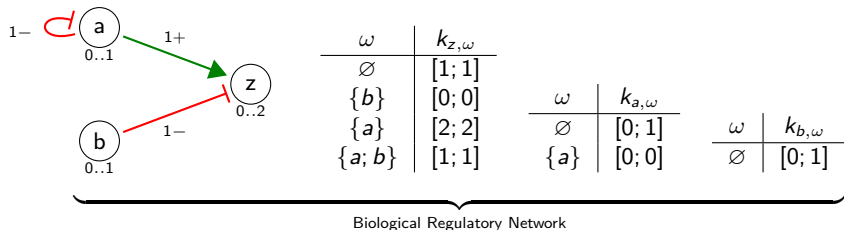
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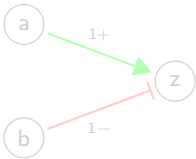
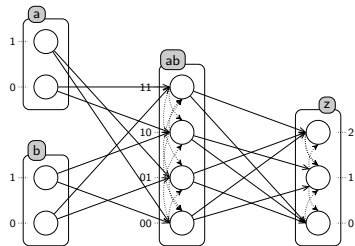
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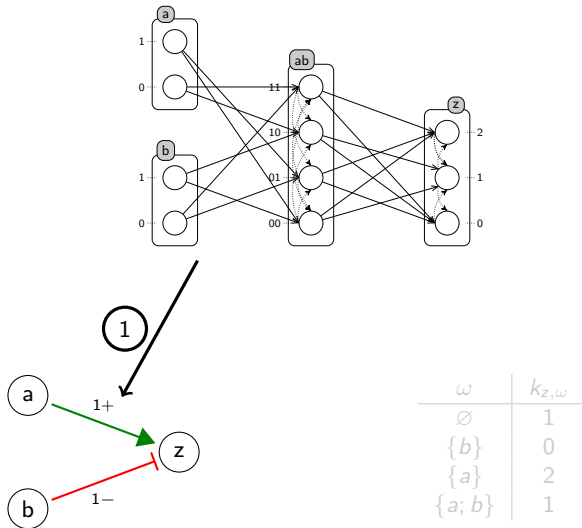
- All needed information to run the model or study its dynamics:
 - Build the State Graph
 - Find reachability properties, fixed points, attractors
 - Other properties...
- **Strengths:** well adapted for the study of biological systems
- **Drawbacks:** inherent complexity; needs the full specification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

Infering a BRN with Thomas' parameters

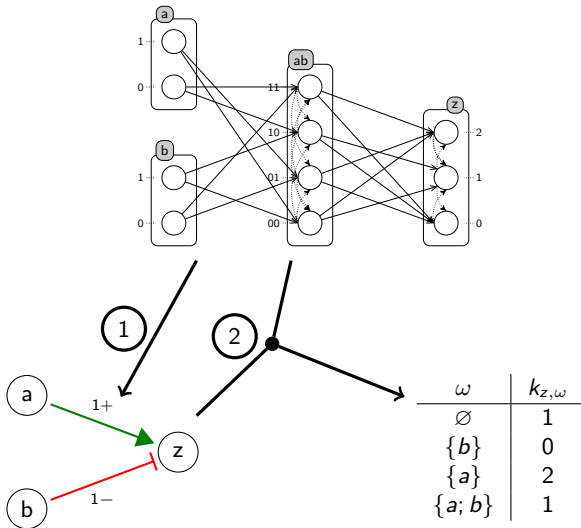


ω	$k_{z,\omega}$
\emptyset	1
$\{b\}$	0
$\{a\}$	2
$\{a; b\}$	1

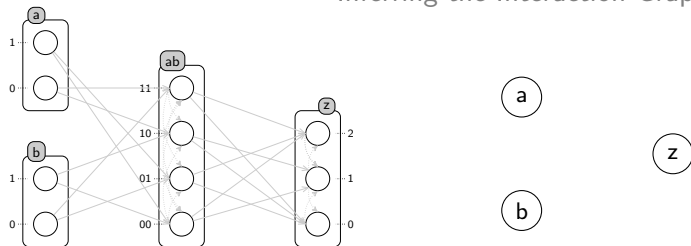
Inferring a BRN with Thomas' parameters



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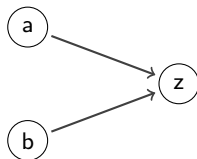
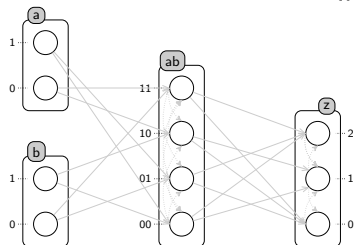


Inferring the Interaction Graph

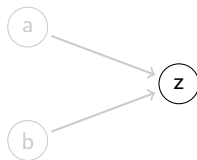
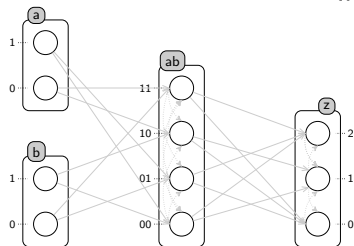


- **Inputs:** a Process Hitting model
- **Output:** An interaction graph with all information:
→ edges, signs and thresholds
- **Difficulties:** Process Hitting is more atomistic than BRNs
- **Idea:** Exhaustive search in all possible configurations

Inferring the Interaction Graph

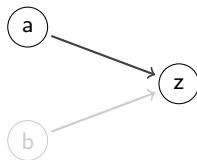
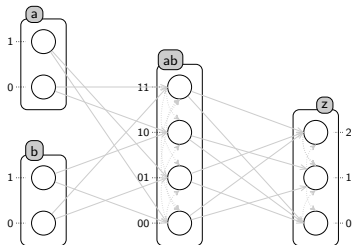


Inferring the Interaction Graph



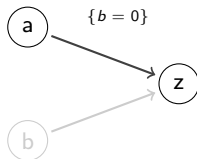
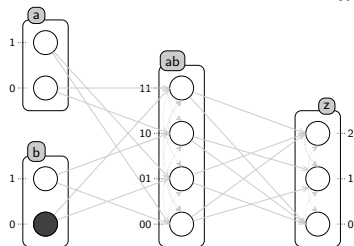
- For each gene **[z]**

Inferring the Interaction Graph



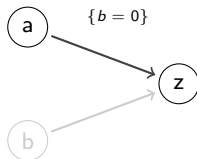
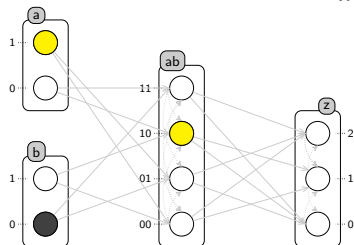
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Inferring the Interaction Graph



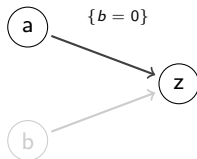
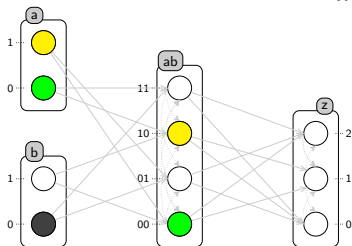
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Inferring the Interaction Graph



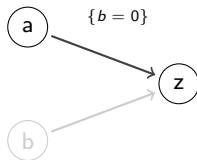
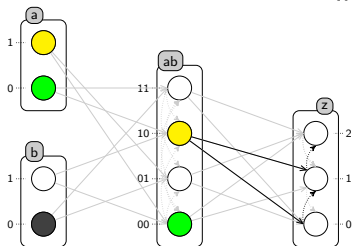
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Inferring the Interaction Graph



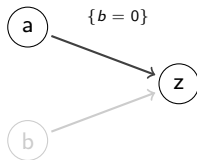
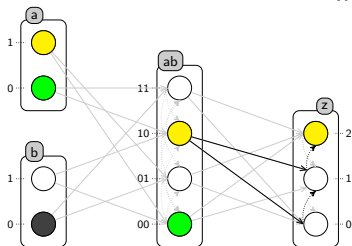
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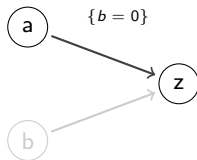
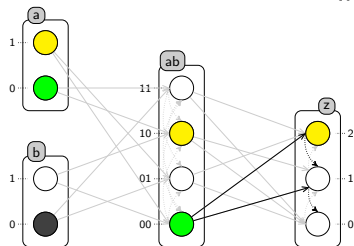
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Inferring the Interaction Graph



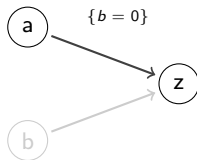
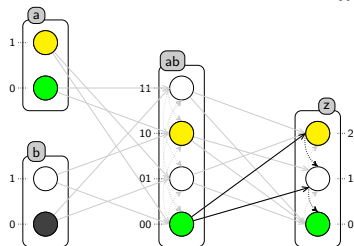
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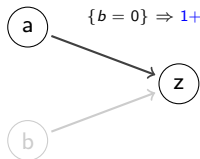
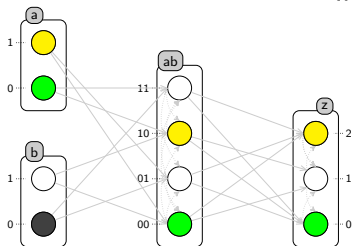
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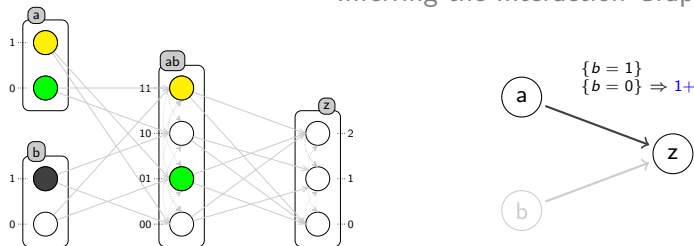
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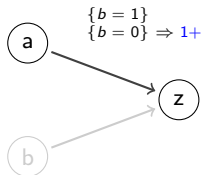
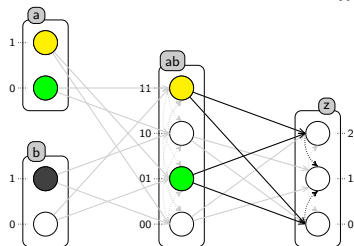
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Inferring the Interaction Graph



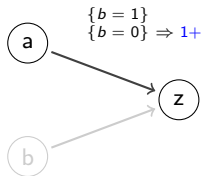
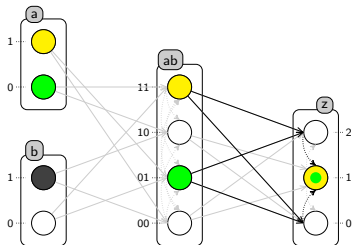
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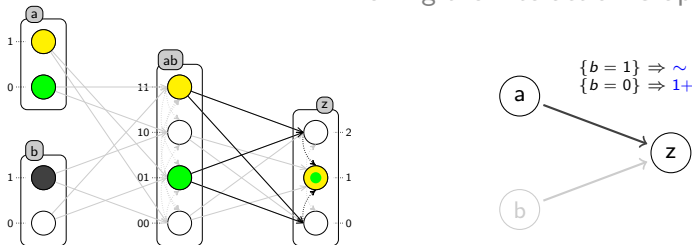
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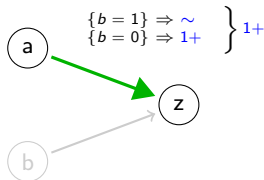
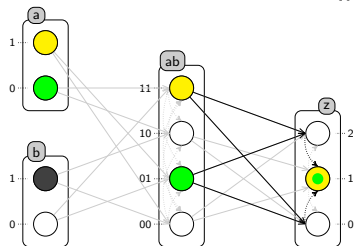
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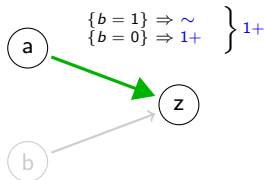
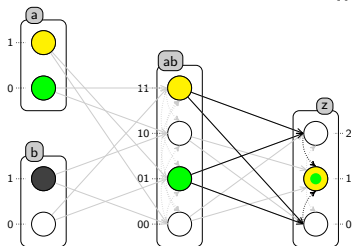
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Problematic cases:

- \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)

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

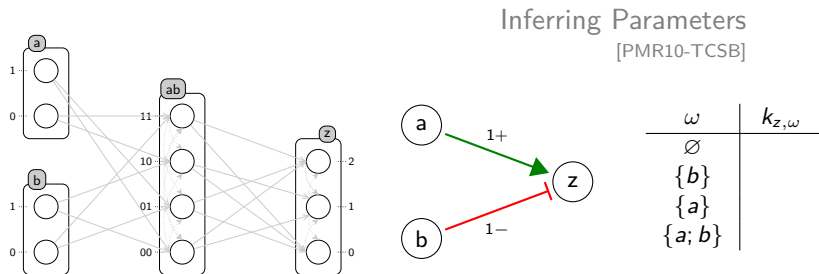
Results

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

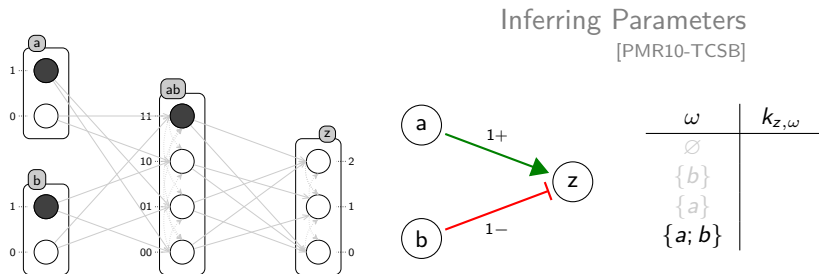
*CS = Cooperative sorts

- [\[EGFR20\]](#): 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.



Inputs: The Process Hitting model and the related Interaction Graph

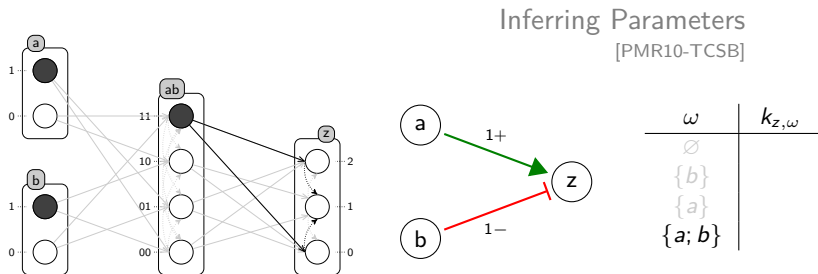
Output: The Parametrization related to the Interaction Graph



Inputs: The Process Hitting model and the related Interaction Graph

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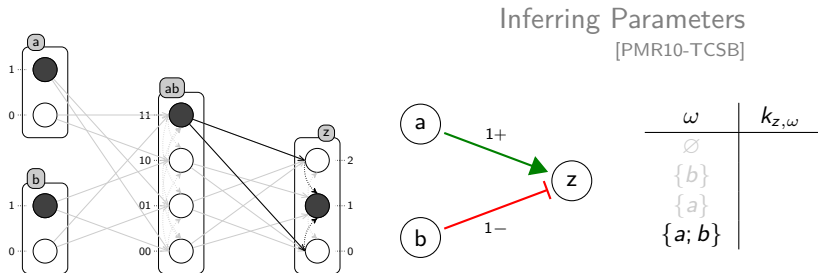
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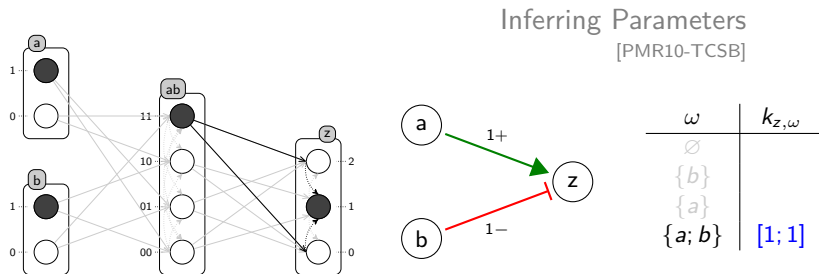
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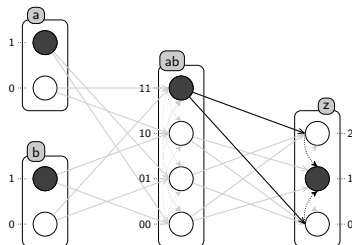
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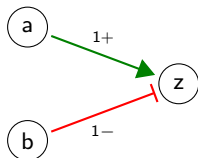
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- For each gene $[z]$ and each **configuration** of resources $[\omega = \{a; b\}]$
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- Under some conditions, this set is the parameter: $k_{z,\{a,b\}} = [1; 1]$



Inferring Parameters

[PMR10-TCSB]



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

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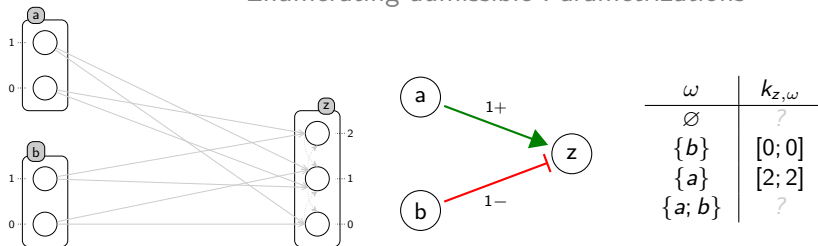
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Problematic cases:

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

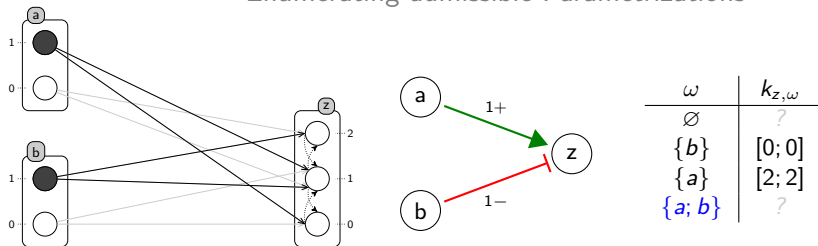
Enumerating admissible Parametrizations



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

Output: All admissible Parametrizations observing the dynamics

Enumerating admissible Parametrizations

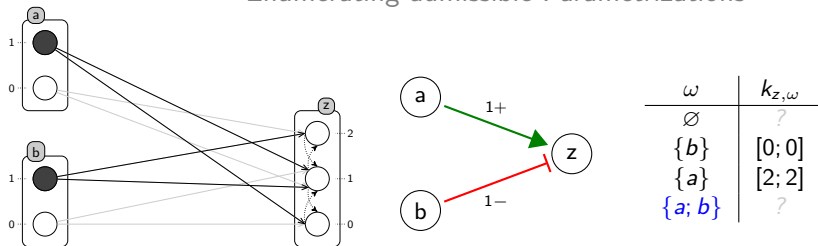


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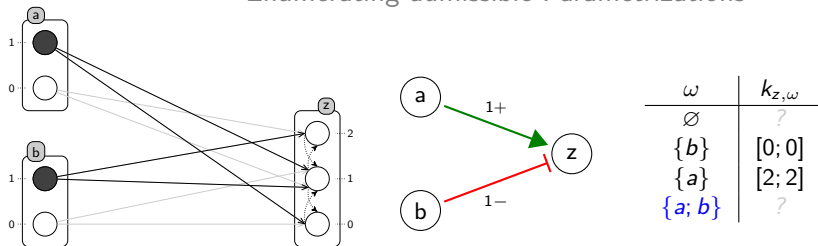


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→ Enumeration regarding:

- 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]
 - ≈ **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**
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- Complexity: linear in the number of genes,
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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

- 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



Katsumi INOUE
Professor & team leader

} **Inoue Laboratory**



Loïc PAULEVÉ
Post-doc

} **AMIB**



Olivier ROUX
Professor & team leader



Morgan MAGNIN
Associate professor



Maxime FOLSCHETTE
 \simeq 2nd year PhD student

} **MeForBio**

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Thank you