— **ECML-PKDD'2012** —
Workshop on Learning and Discovery in Symbolic Systems Biology

Abducing Biological Regulatory Networks from Process Hitting models

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

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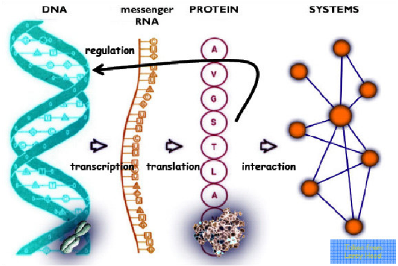
AtlanSTIC sojourn financed by NII & Centrale Initiatives

Context and Aims

Algebraic modeling to study complex dynamical biological systems:



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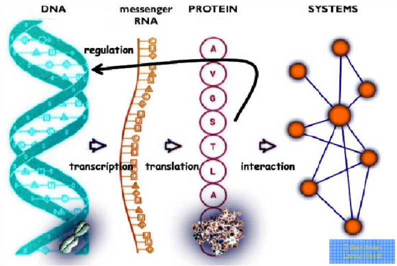
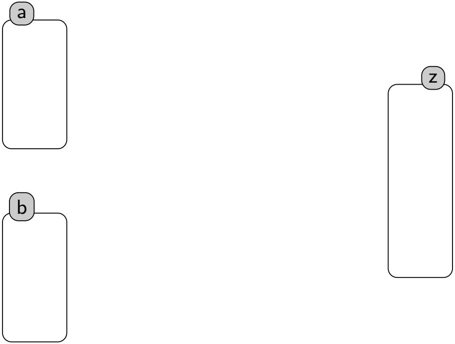


- Historical model: Biological Regulatory Network (René Thomas)
- New developed model: Process Hitting

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

The Process Hitting modeling

[PMR12-MSCS]



Sorts: components a, b, z

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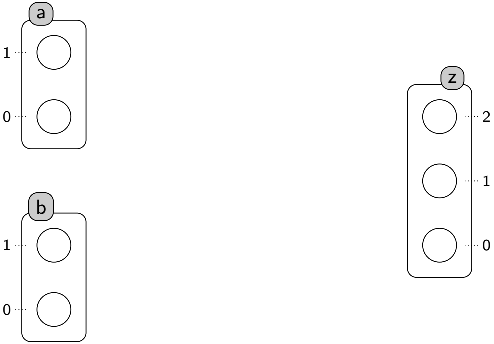

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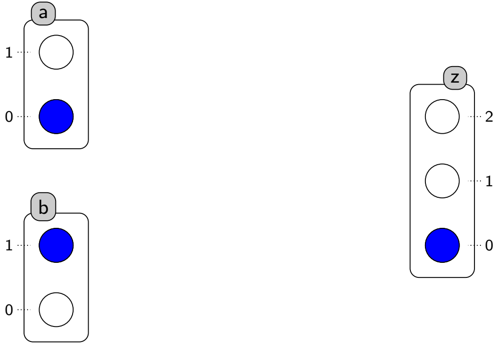

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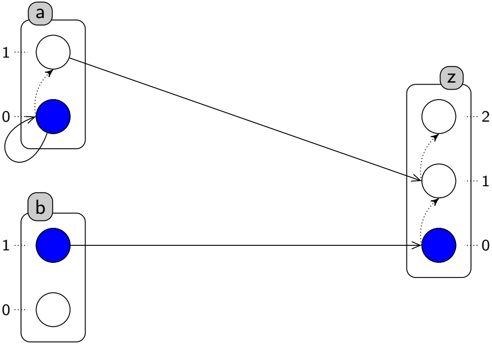

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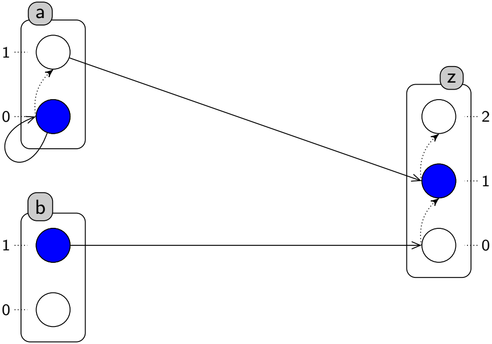

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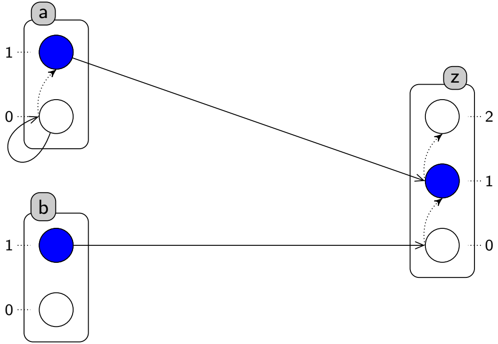

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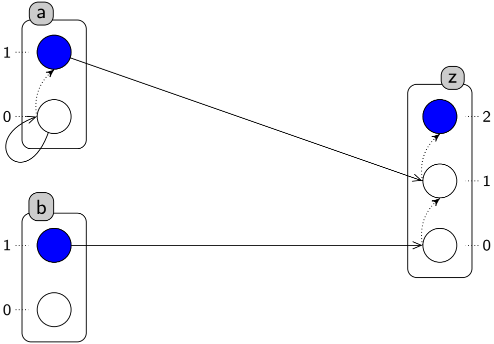

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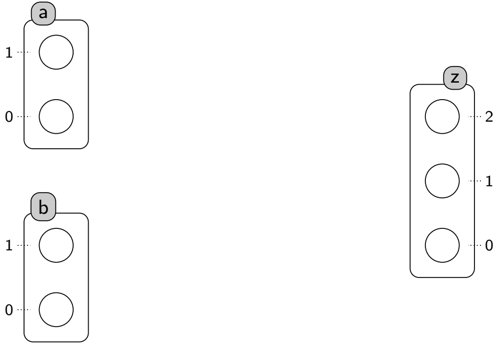

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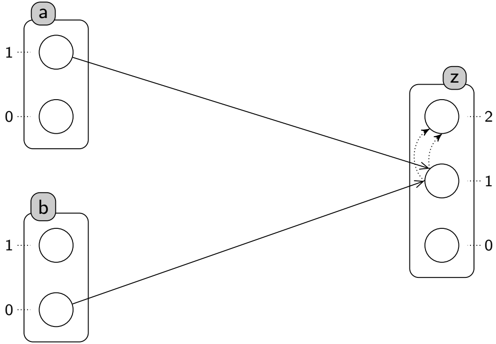

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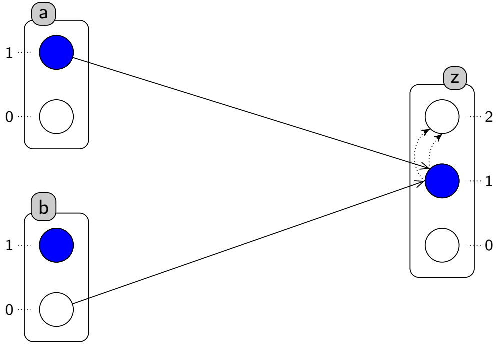

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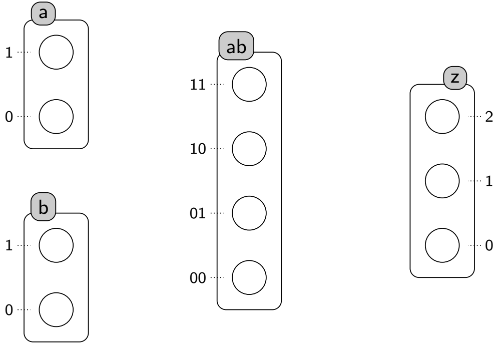

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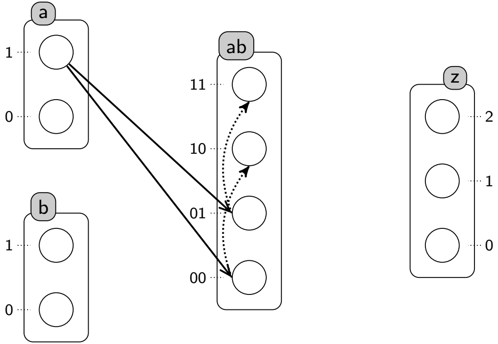

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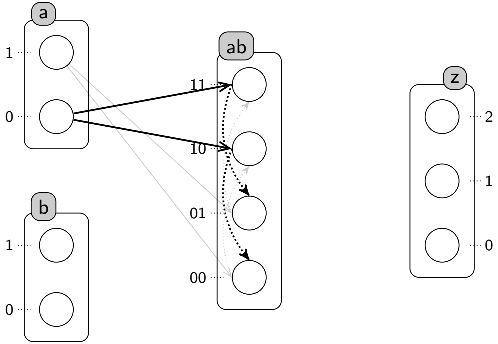

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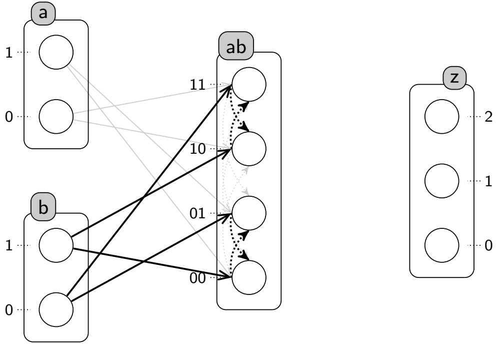

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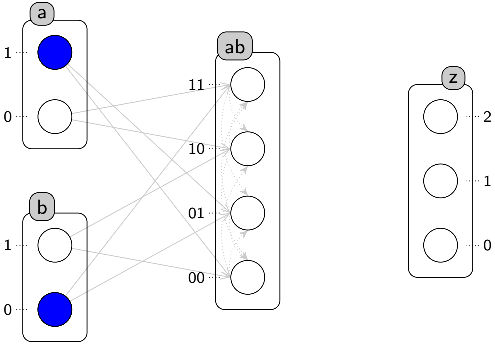

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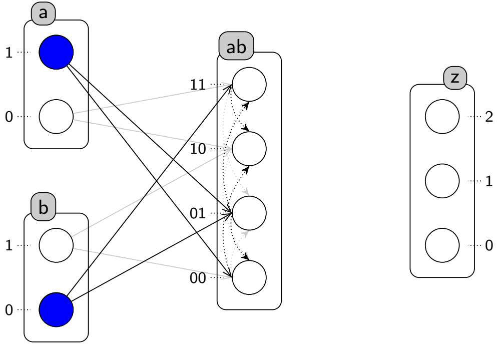

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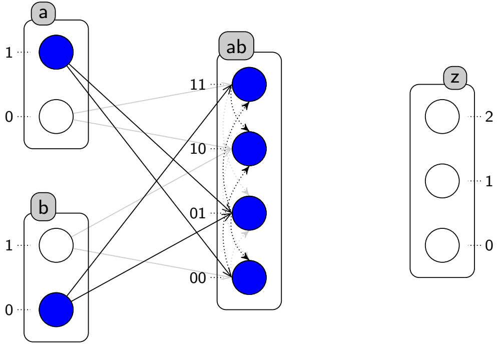

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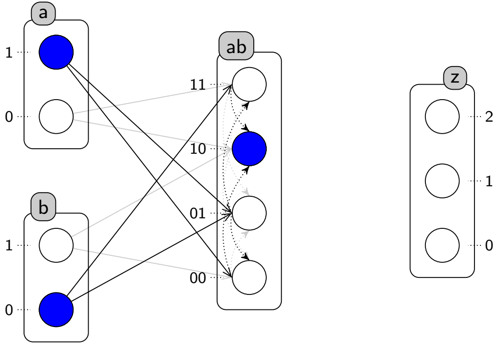

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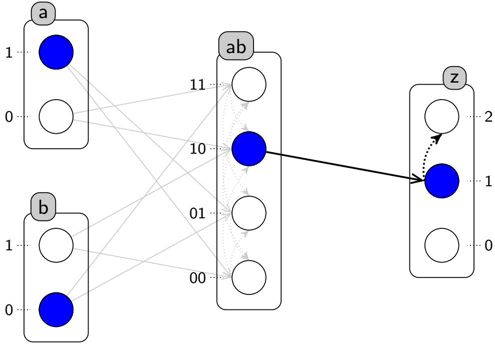

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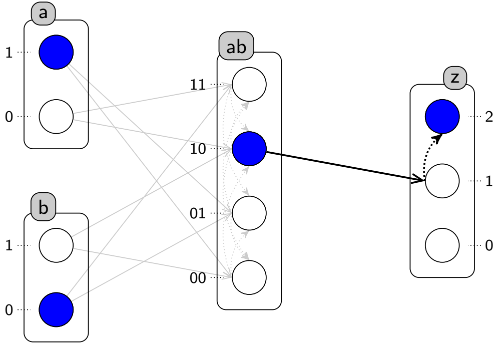

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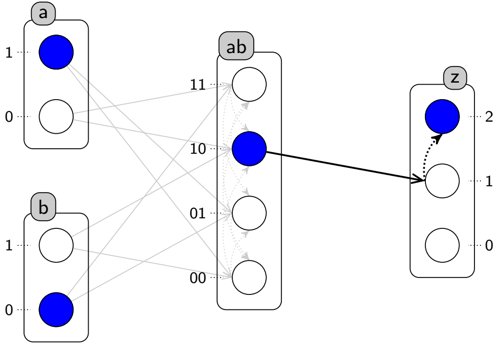

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Advantage: regular sort; drawbacks: complexity, temporal shift

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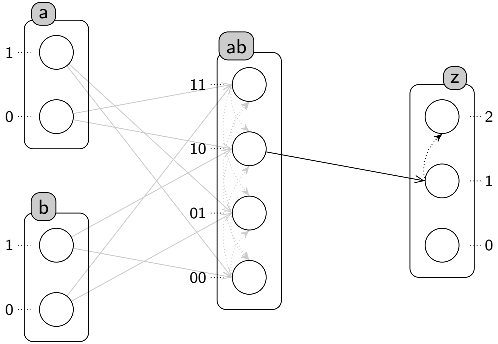
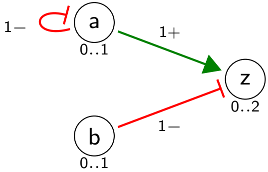


The Process Hitting framework:

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

Biological Regulatory Network

[RCB08]



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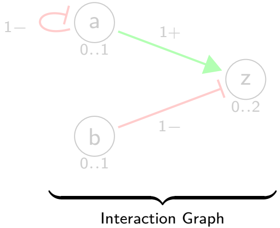
Historical bio-informatics model for studying genes interactions

Widely used and well-adapted to represent dynamic gene systems

Biological Regulatory Network

[RCB08]



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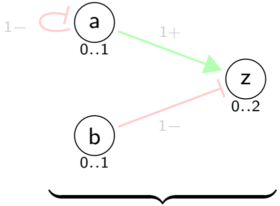
Interaction Graph: structure of the system (genes & interactions)

Biological Regulatory Network

[RCB08]



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

Biological Regulatory Network

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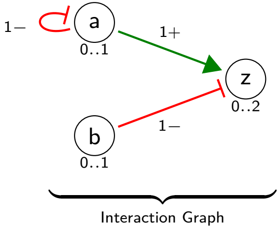

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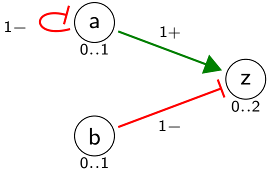
Edges: interactions

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

Biological Regulatory Network

[RCB08]



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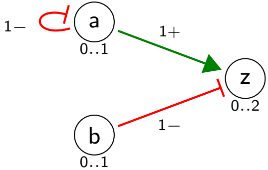
Parametrization

Parametrization: strength of the influences (evolution tendencies)

Biological Regulatory Network

[RCB08]



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Maps of tendencies for each gene

→ To any **set of predecessors** ω

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

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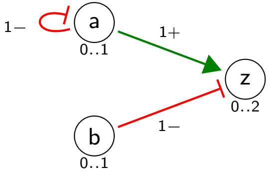

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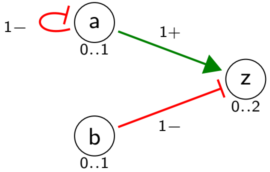

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Biological Regulatory Network

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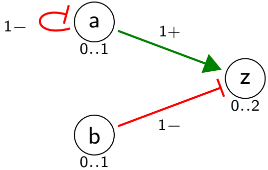

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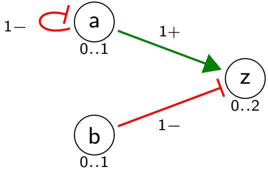

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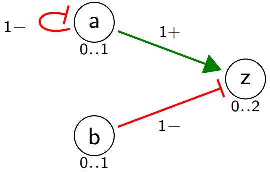

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Biological Regulatory Network

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

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

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

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

ASP Implementation

ASP: Declarative programming

Rule: $head \leftarrow body.$

Fact: $head.$

Constraint: $\leftarrow body.$

Aggregate: $lower\ \{\ atoms\ \}\ upper \leftarrow body.$

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ASP Implementation

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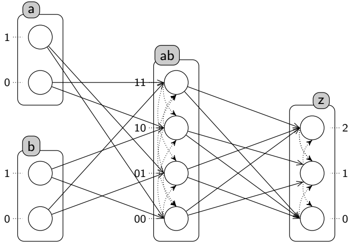
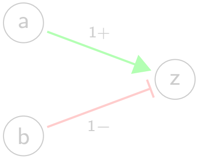
Rule: $head \leftarrow A_1, ..., A_n, \neg A_{n+1}, ..., \neg A_m.$
Fact: $head.$
Constraint: $\leftarrow body.$
Aggregate: $lower \ \{\ atoms\ \}\ upper \leftarrow body.$

Representation of PH / BRNs:
Gene: $component(a, n).$
Action: $action(a, i, b, j, k).$
Cooperation: $cooperation(c, a, i, j).$
Useful rules: $component\_levels(X, 0..M) \leftarrow component(X, M).$

Inferring a BRN with Thomas' parameters

[CMSB12]

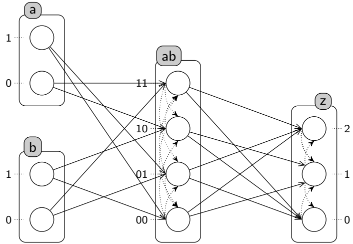


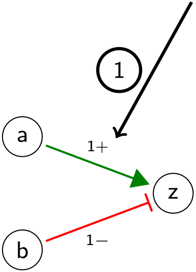


ω	$k_{z,\omega}$
$\emptyset$	1
$\{b\}$	0
$\{a\}$	2
$\{a; b\}$	1

Inferring a BRN with Thomas' parameters

[CMSB12]





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Inferring a BRN with Thomas' parameters

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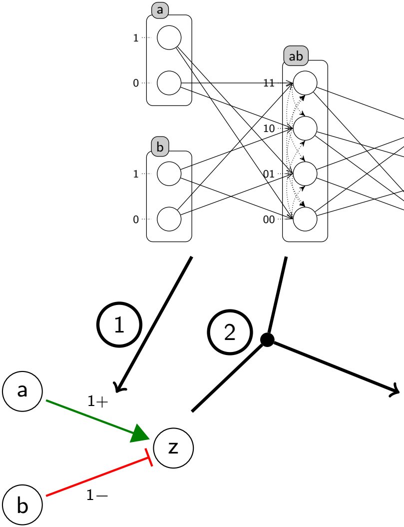

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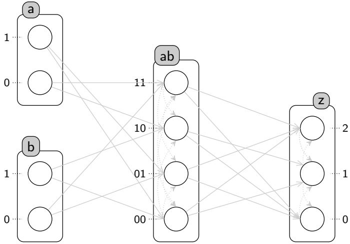
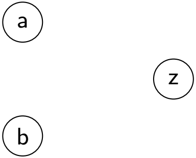
Inferring the Interaction Graph

[CMSB12]



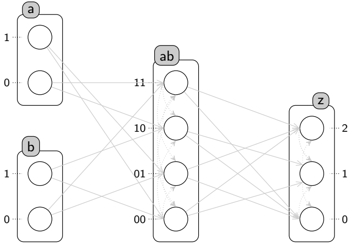


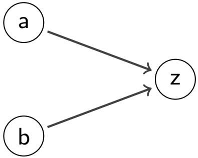
- **Inputs:** a Process Hitting model
- **Output:** An interaction graph with all information:
  $\rightarrow$ edges, signs and thresholds

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

Inferring the Interaction Graph

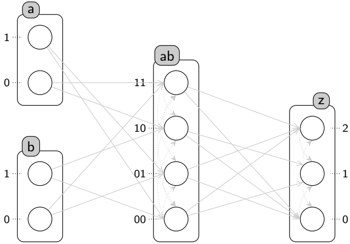
[CMSB12]

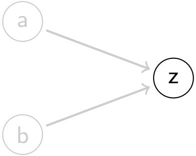




Inferring the Interaction Graph

[CMSB12]

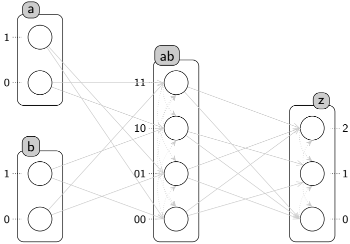


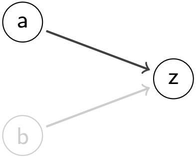


- For each gene [*z*]

Inferring the Interaction Graph

[CMSB12]

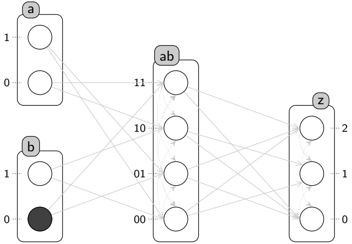


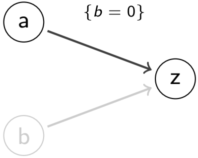


- For each gene [*z*], consider one possible regulator [*a*]

Inferring the Interaction Graph

[CMSB12]

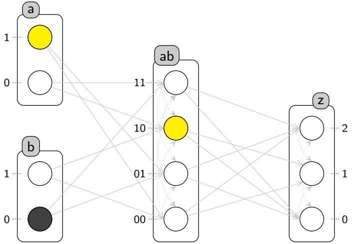


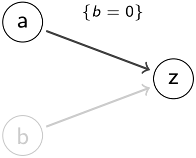


- For each gene [z], consider one possible regulator [a]
- Consider a **configuration** of all other regulators [$\{b = 0\}$]

Inferring the Interaction Graph

[CMSB12]





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Inferring the Interaction Graph

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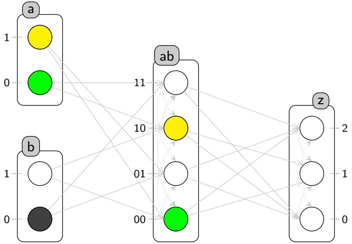

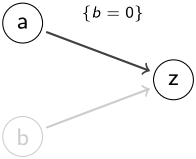

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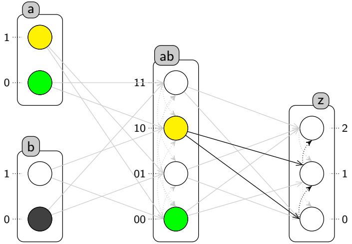

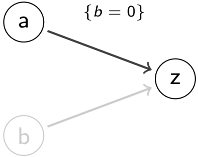

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Inferring the Interaction Graph

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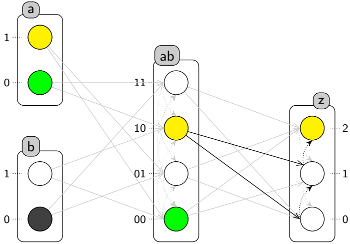

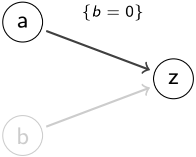

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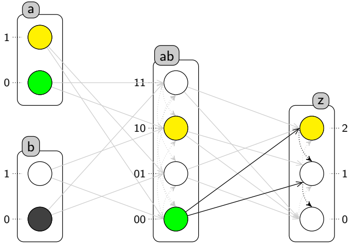

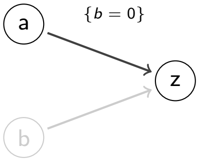

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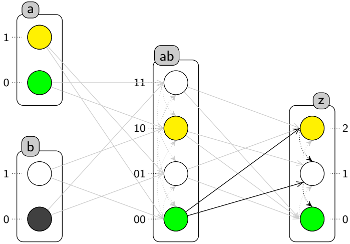

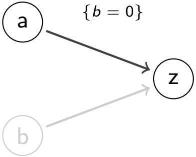

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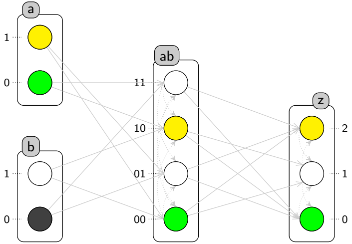

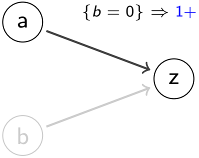

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    $\{b = 0\} \rightarrow a_0 < a_1$ and $\{z_0\} \preccurlyeq \{z_2\} \Rightarrow$ activation $(+)$ & threshold $= 1$

Inferring the Interaction Graph

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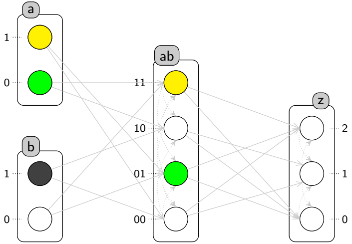

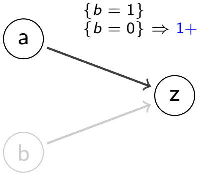

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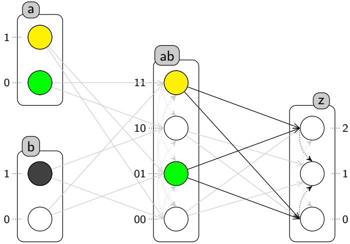

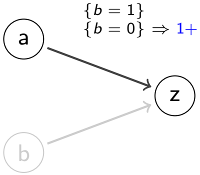

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Inferring the Interaction Graph

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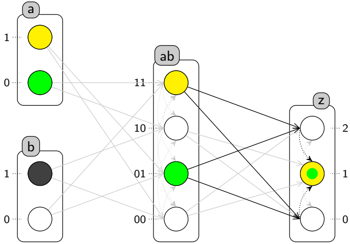

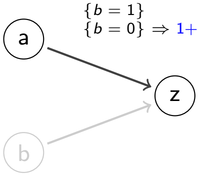

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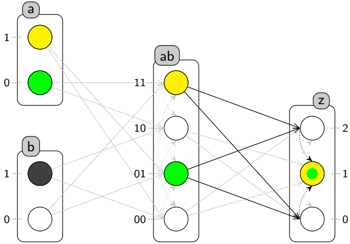

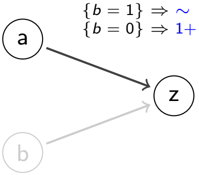

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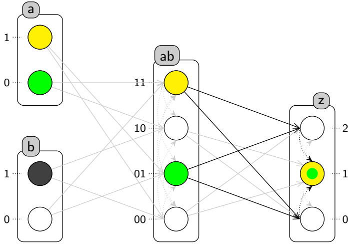
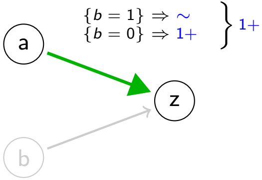
Inferring the Interaction Graph

[CMSB12]





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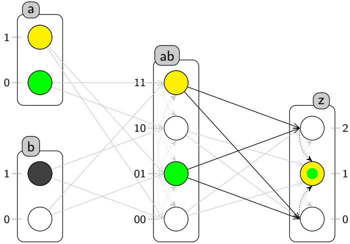
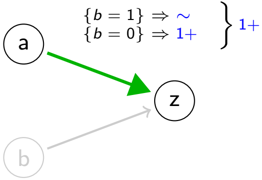
- If possible, determine the general influence of a on z

Inferring the Interaction Graph

[CMSB12]





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

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

Problematic cases:

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

Interaction Graph Inference

Implementation

Programming in ASP:

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

Interaction Graph Inference

Implementation

Programming in ASP:

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

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)

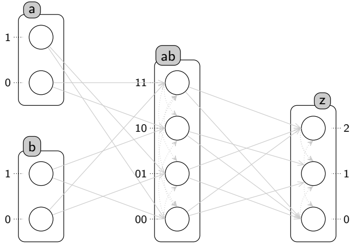
$<$ 1s for 20 & 40 genes models **[EGFR20 & TCRSIG40]**
$\simeq$ 13s for a 94 genes model **[TCRSIG94]**
$\simeq$ 4min for a 104 genes model **[EGFR104]**

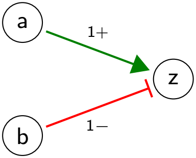
Model name	Sorts	Cooperative sorts	Processes	Actions
[EGFR20]	20	22	152	399
[TCRSIG40]	40	14	156	301
[TCRSIG94]	94	39	448	1124
[EGFR104]	104	89	748	2356

- **[EGFR20]**: Epidermal Growth Factor Receptor, by Özgür Sahin et al.
- **[EGFR104]**: Epidermal Growth Factor Receptor, by Regina Samaga et al.
- **[TCRSIG40]**: T-Cell Receptor Signaling, by Steffen Klamt et al.
- **[TCRSIG94]**: T-Cell Receptor Signaling, by Julio Saez-Rodriguez et al.

Inferring Parameters

[PMR10-TCSB]



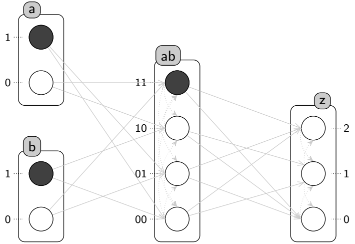


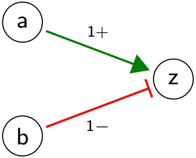
ω	$k_{z,\omega}$
$\varnothing$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	

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

Inferring Parameters

[PMR10-TCSB]





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

Inferring Parameters

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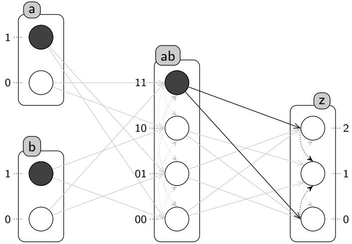

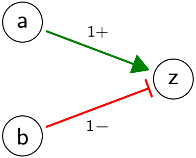

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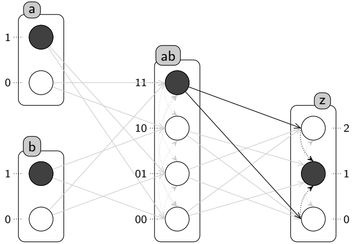
$\emptyset$	
$\{b\}$	
$\{a\}$	
$\{a; b\}$	

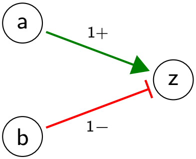
Inputs: The Process Hitting model and the related Interaction Graph
Output: The Parametrization related to the Interaction Graph

- For each gene [z] and each **configuration** of resources [$\omega = \{a; b\}$]
- Find the set of **focal processes** of the gene

Inferring Parameters

[PMR10-TCSB]





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

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

- For each gene [z] and each **configuration** of resources [$\omega = \{a; b\}$]
- Find the set of **focal processes** of the gene [$\{z_1\}$]

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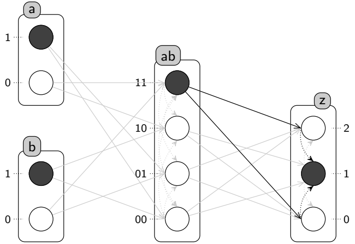

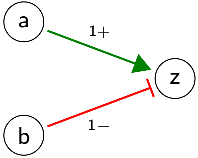

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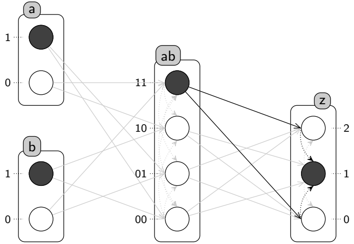

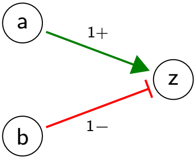

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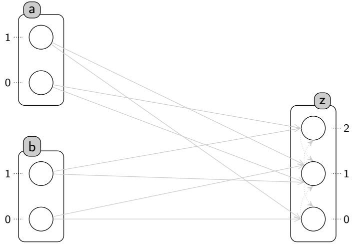
Problematic cases:

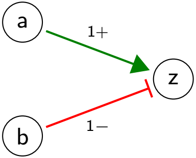
→ Behavior cannot be represented as a BRN

→ Lack of cooperation (no focal processes)

Abducing Parametrizations

[CMSB12]





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

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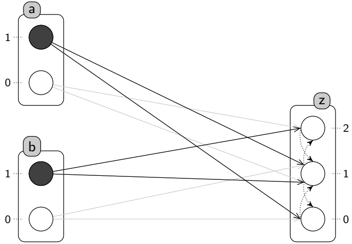

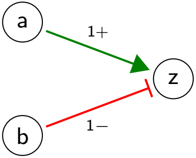

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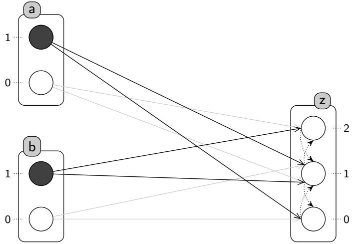

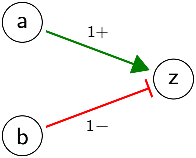

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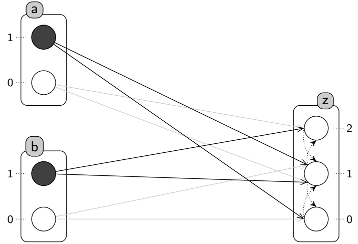

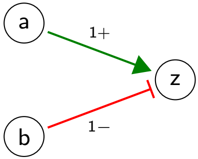

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→ Enumeration regarding:

- Biological constraints
- The dynamics of the Process Hitting

Abducing Parametrizations

Implementation

Parameters definitions:

One identifier for each parameter: *param_label*(a, i)

Useful rules:

less_active$(X, P, Q) \leftarrow K_{X,P}$ has less activators than $K_{X,Q}$

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[X: component; P: parameter label; I: parameter value]

Parametrizations filtering uses constraints:

$\leftarrow less\_active(X, P, Q), \neg param\_inf(X, P, Q).$

[X: component; P, Q: parameter labels]

Parametrization Inference

Results

Two steps:

- Parameters inference (partial)
- Parametrization abduction (total)

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Results:

- Very fast execution for parameters inference
  $<$ 1s for 20 & 40 genes models **[EGFR20 & TCRSIG40]**
- Parametrization abduction
  After one cooperation removal:
  $\simeq$ 4s to find 42 admissible Parametrizations **[TCRSIG40]**
  $\simeq$ 20s to find 129 admissible Parametrizations **[EGFR20]**

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

Summary & Future work

- Inference of the **complete Interaction Graph**
  - → Exhaustive approach to find the mutual influences
- Inference of the **possibly partial Parametrization**
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- Abduce all full & **admissible Parametrizations**
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- 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 ⇝ Process Hitting

New translation: Process Hitting ⇝ René Thomas

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

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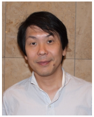
Using ASP

→ 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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Loïc PAULEVÉ
Post-doc

} **AMIB**

Olivier ROUX
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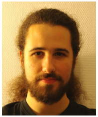
Morgan MAGNIN
Associate professor



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

} **MeForBio**

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Thank you