Journées annuelles 2018 du GT Bioss

GULA: Semantics-Free Learning of a Biological Regulatory Networks from a Synchronous, Asynchronous or Generalized State Graph

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Introduction

Learn interaction rules from the dynamical transitions

- LFIT: synchronous, deterministic (Boolean)
  [Inoue, Ribeiro, Sakama, *Machine Learning Jour.*, 2014]
- LFkT: synchronous, with memory (Boolean)
  [Ribeiro, Magnin, Inoue, Sakama, *Frontiers in Bioeng. and Biotech.*, 2015]
- LUST: synchronous, non-deterministic
  [Martinez, Ribeiro, Inoue, Alenya, Torras, *ICLP*, 2015.]
- ACEDIA: synchronous, continuous domains
  [Ribeiro, Tourret, Folschette, +5, *ILP*, 2017]

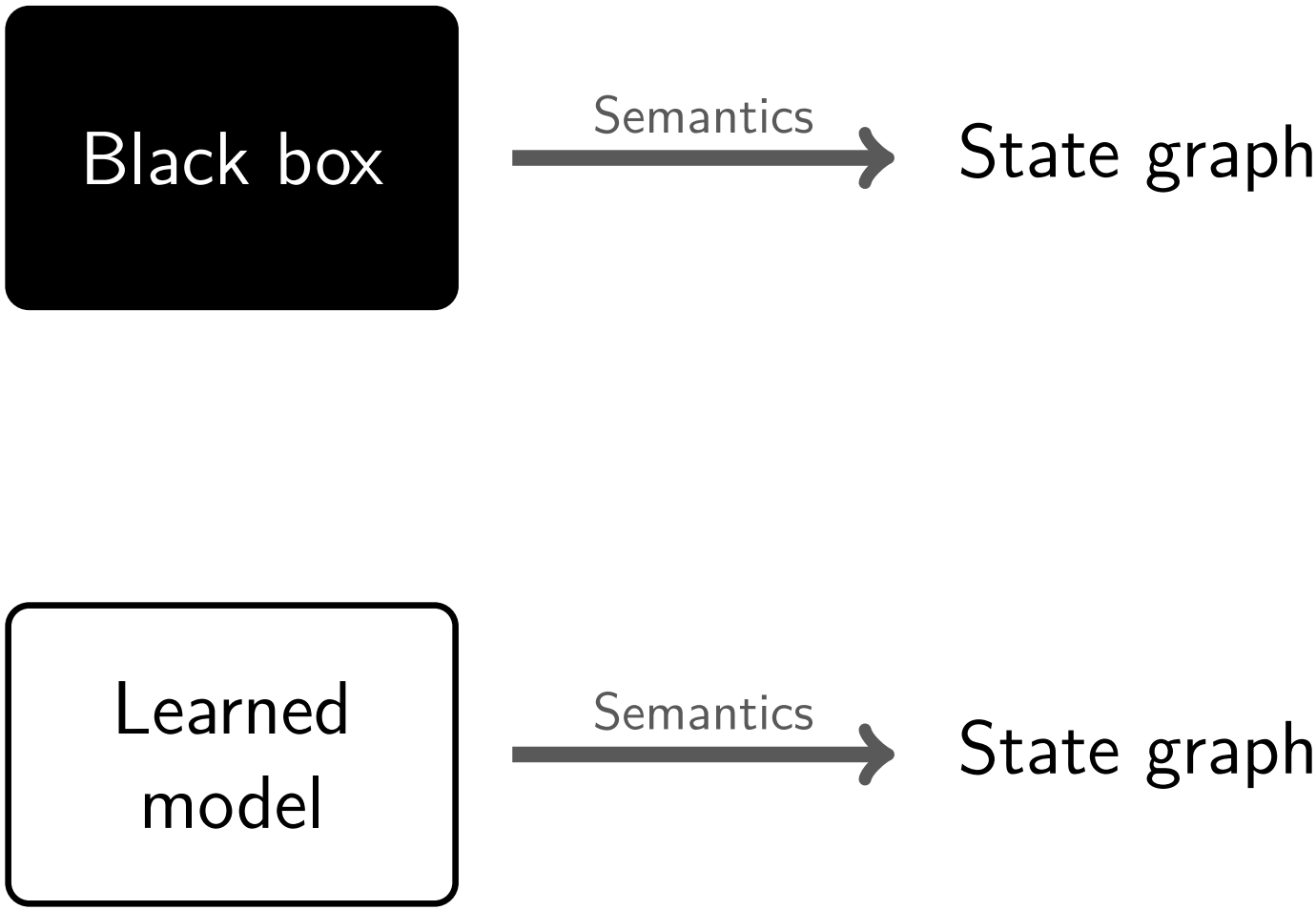
...But all are semantics-specific

What if the semantics is unknown?

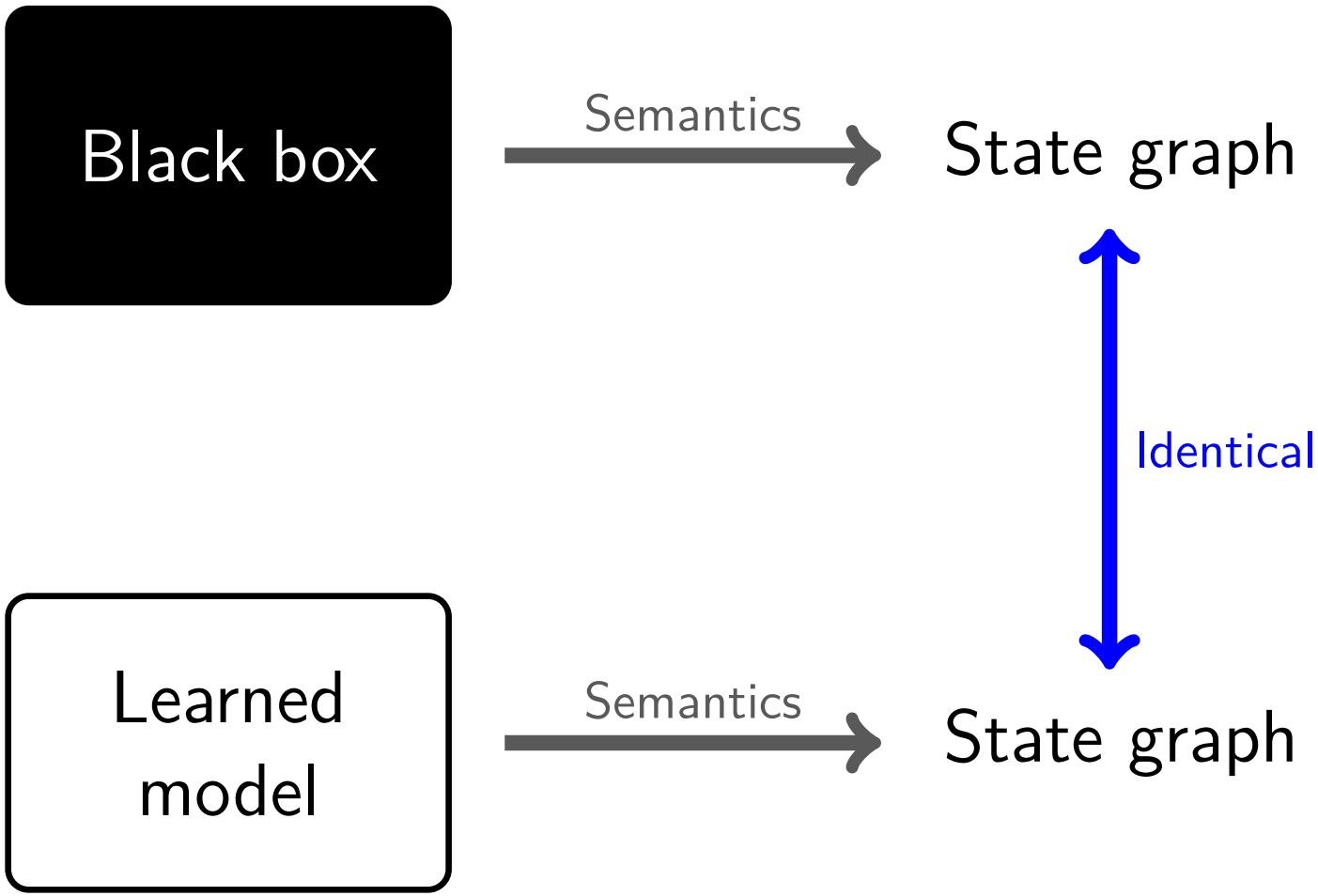
→ Learn general rules without foreseeing the semantics

→ Properties to characterize the semantics

Introduction



Introduction



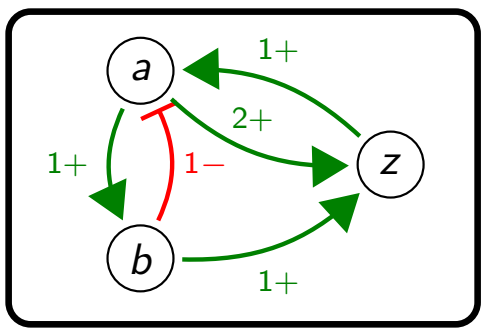
Introduction

Black box

Semantics

State graph

Identical

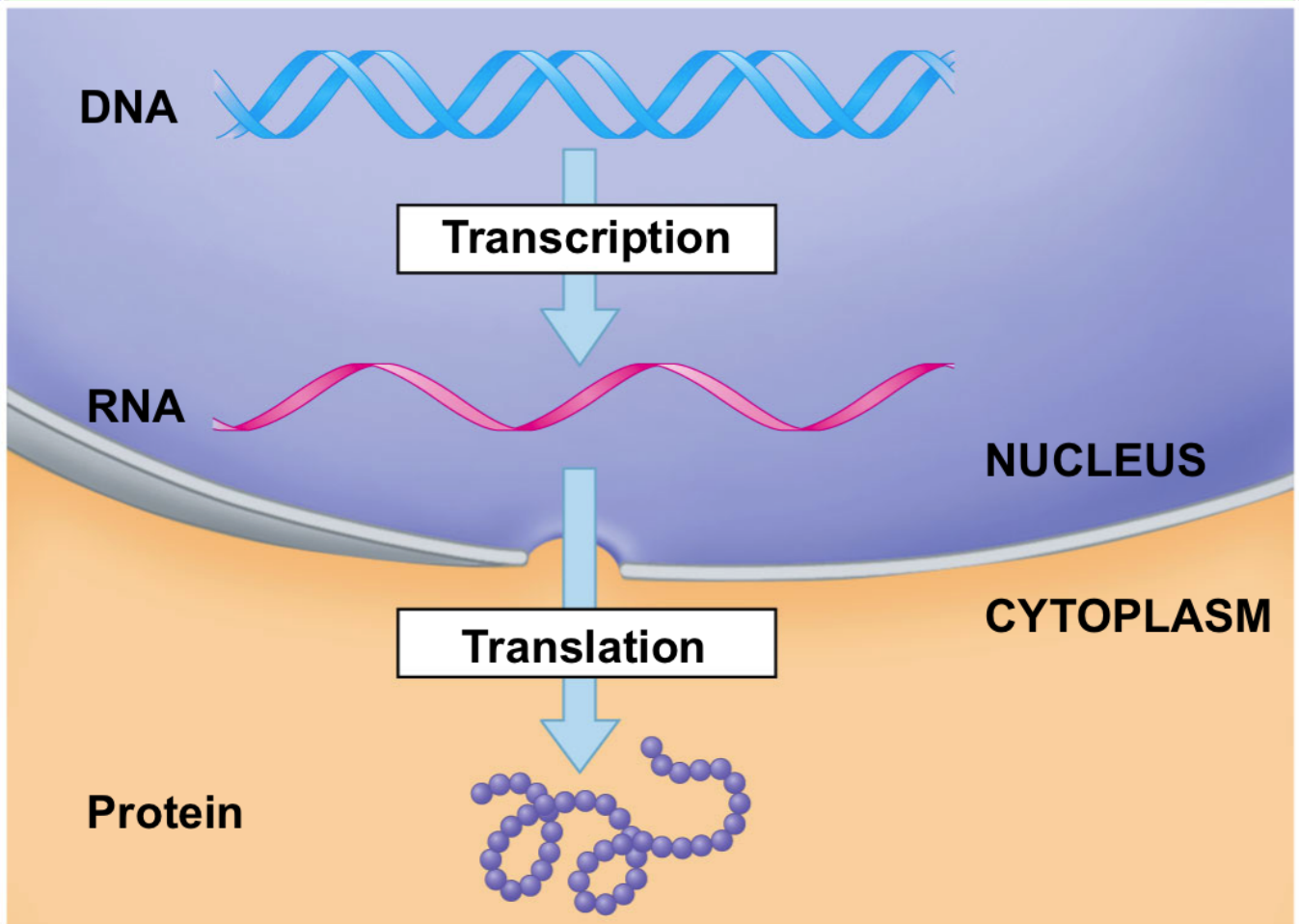


Semantics

State graph

Discrete Networks

Preliminary Abstraction



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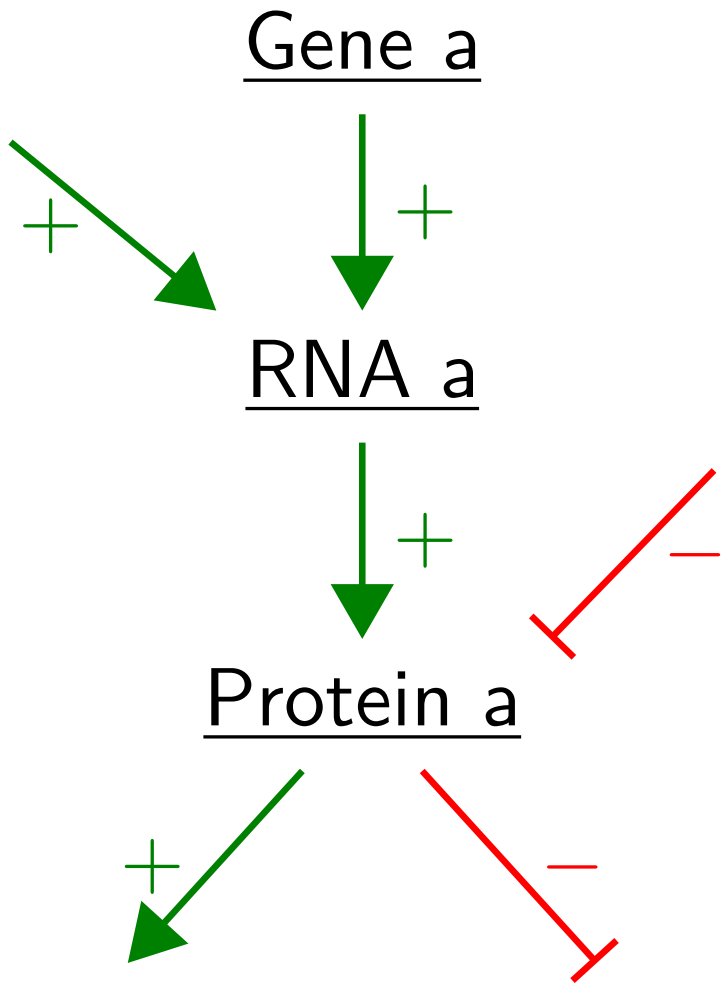

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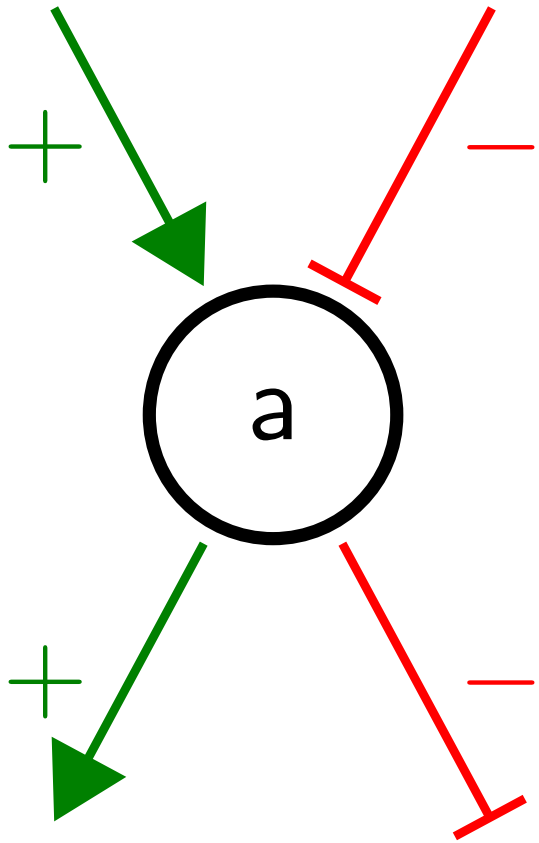

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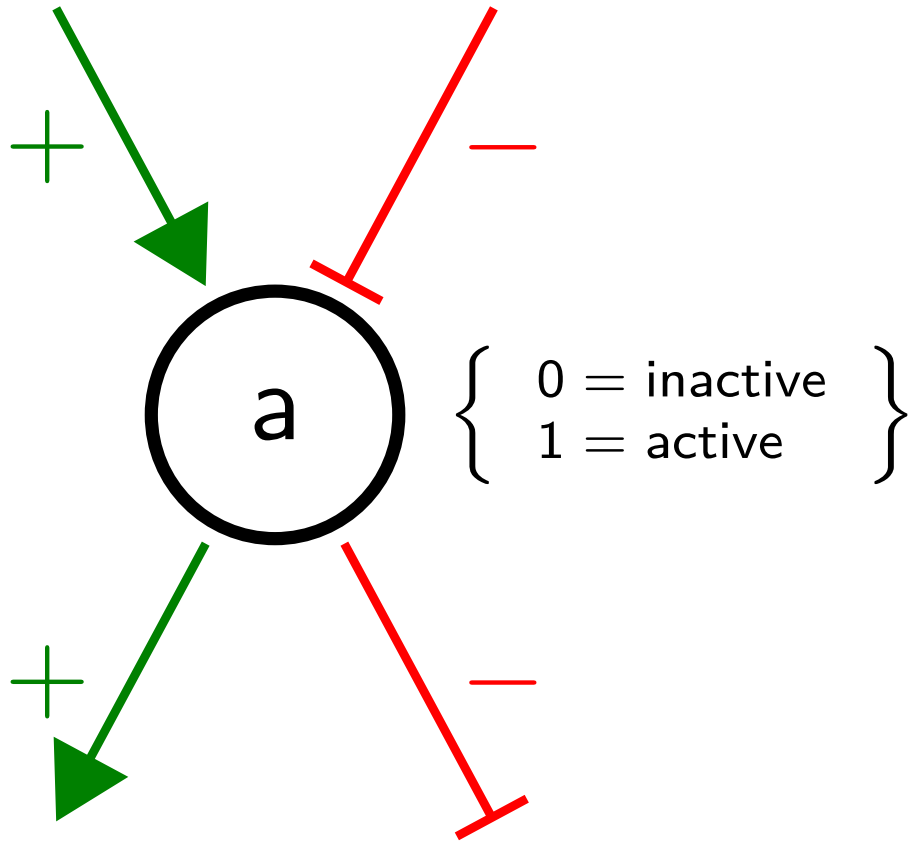

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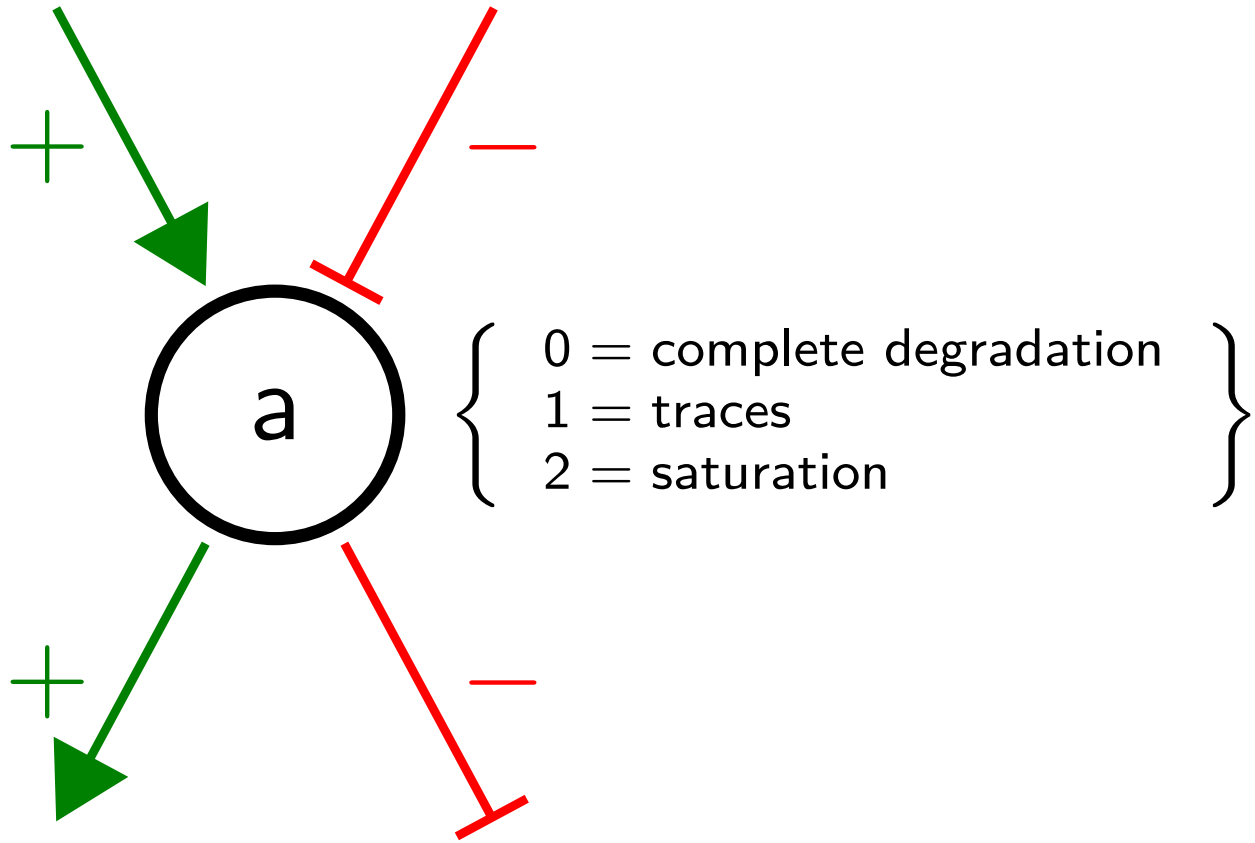
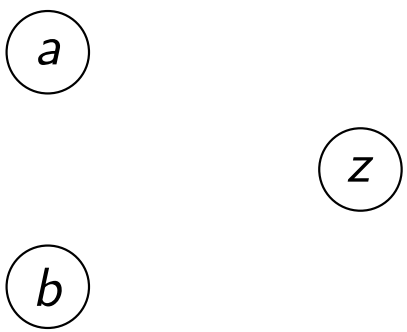


Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
[Thomas, *Journal of Theoretical Biology*, 1973]

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$
- Discrete parameters / evolution functions $f^a : \mathcal{S} \to \mathrm{dom}(a)$
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



a	f^b
0	**0**
1	**1**
2	**1**

z	b	f^a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	f^z
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0	1	**0**
1	0	**0**
1	1	**0**
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Semantics = From this information, what are the next possible state(s)?

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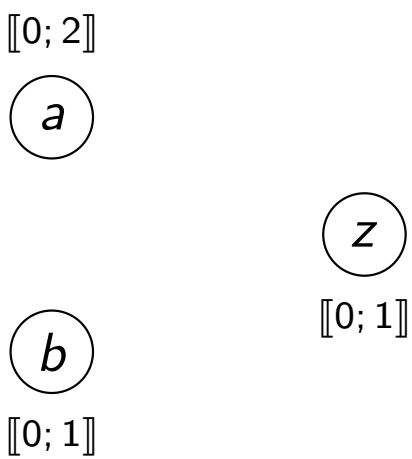

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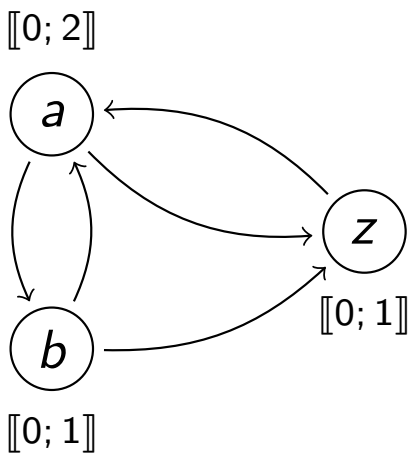

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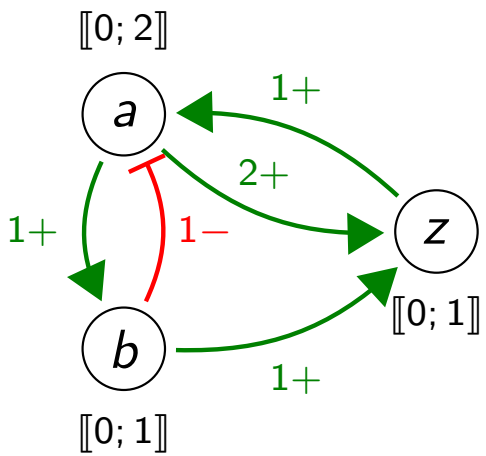

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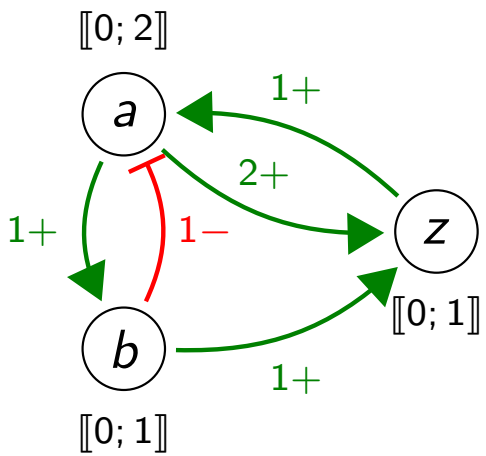

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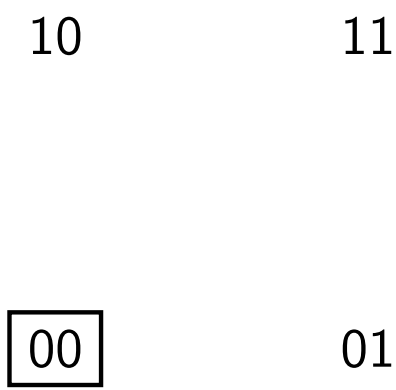
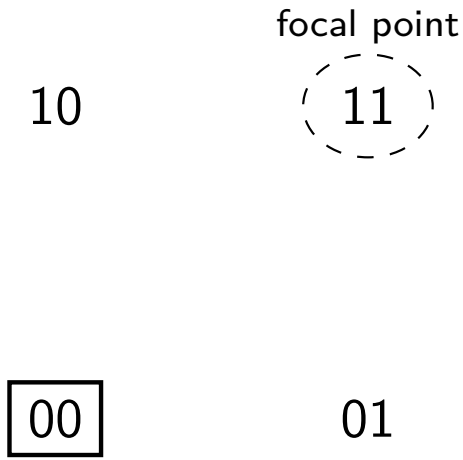


Synchronous **Asynchronous** **Generalized**

Other semantics:

- Round-robin
- With memory
- With priorities
- ...

Semantics



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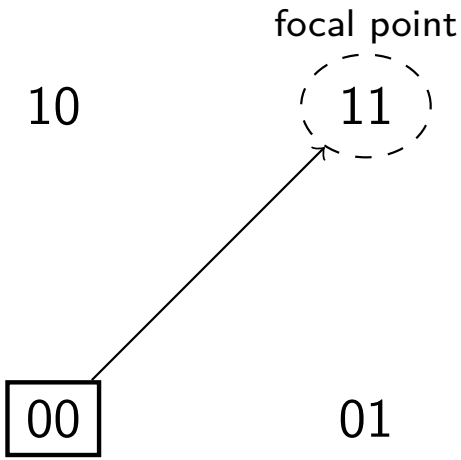

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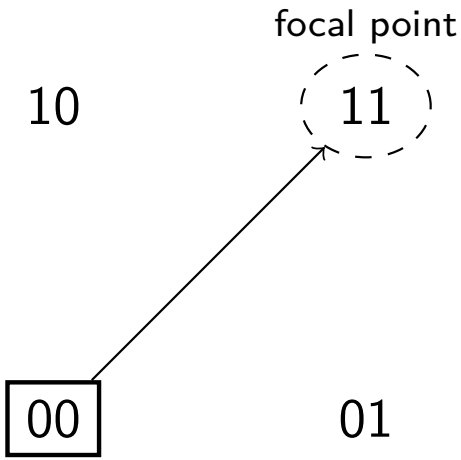

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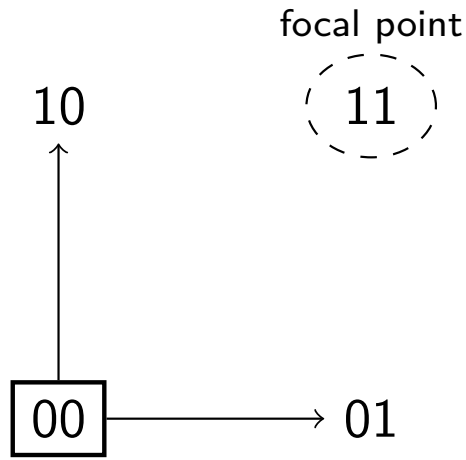

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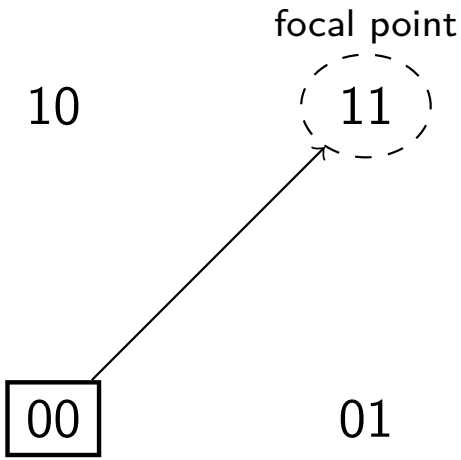

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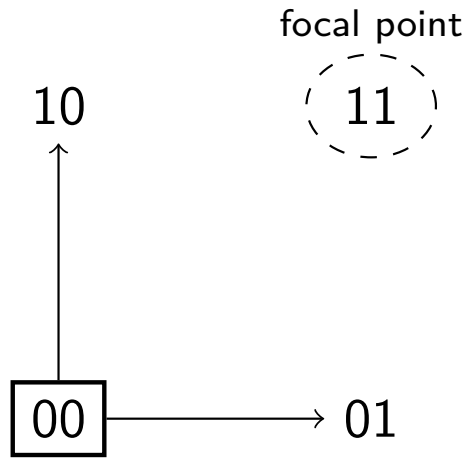

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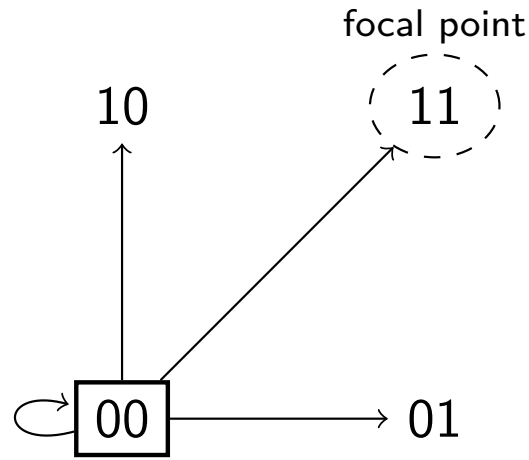

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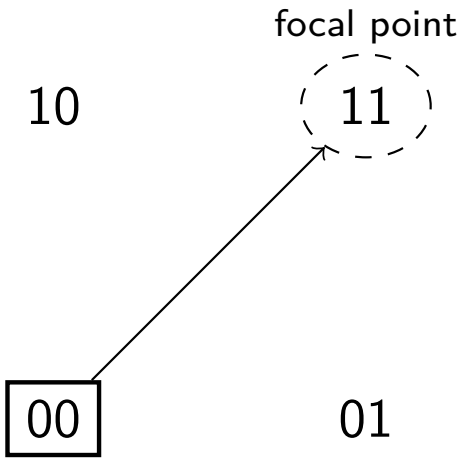

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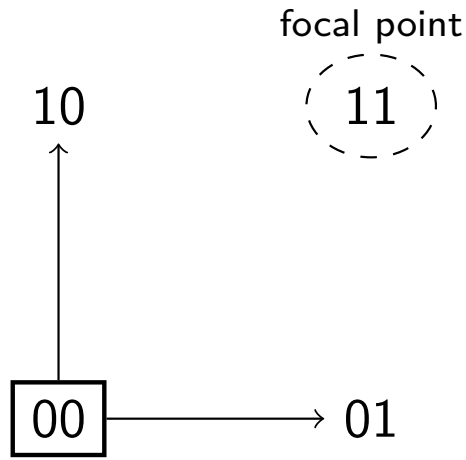

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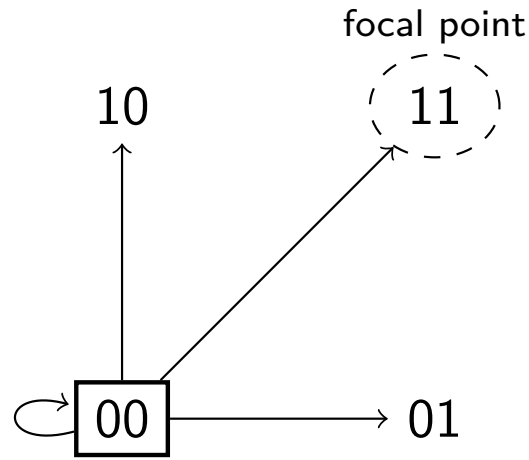

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Logic Programs

Logic Rule

$$\underbrace{x_0^{val_0}(t)}_{head} \leftarrow \underbrace{x_1^{val_1}(t-1) \wedge x_2^{val_2}(t-1) \wedge \ldots \wedge x_n^{val_n}(t-1)}_{body}.$$

- x_0, x_1, x_2, …, x_n: variables a, b, z
  No duplicates in x_1, x_2, …, x_n in the *body*
- val_0, val_1, val_2, …, val_n: values $0, 1, 2, \ldots$
  With $val_i \in \mathrm{dom}(x_i)$
- t: time step
  Always t in the *head* and $t-1$ in the *body*
- All atoms in the *body* are in conjunction
- $\leftarrow$ is the (reverse) implication

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Logic Rule

Set interpretation:

$$\underbrace{x_0^{val_0}(t)}_{head} \leftarrow \underbrace{\{\, x_1^{val_1}(t-1),\ x_2^{val_2}(t-1),\ \ldots,\ x_n^{val_n}(t-1)\,\}}_{body}.$$

→ When *body* is true, *head* is a potential outcome

Examples: $\left.\begin{array}{l} a^1 \leftarrow \{a^2, b^0, c^1\}. \\ b^1 \leftarrow \{c^1\}. \\ c^0 \leftarrow \emptyset. \end{array}\right\}$ all **match** $\langle a^2, b^0, c^1\rangle$

A rule R **matches** a state s iff $body \subseteq s$

→ For all state s, if the rule **matches** s then there exists a state s' so that $s \to s'$ and $x_0^{val_0} \in s'$

Semantics: same as for discrete networks

Logic Rule

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Semantics: same as for discrete networks

Logic Rule

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$$\underbrace{x_0^{val_0}}_{head} \leftarrow \underbrace{\{ x_1^{val_1}, x_2^{val_2}, \ldots, x_n^{val_n} \}}_{body}.$$

$\rightarrow$ When *body* is true, *head* **may be** a potential outcome

Examples: $\left.\begin{array}{l} a^1 \leftarrow \{a^2, b^0, c^1\}. \\ b^1 \leftarrow \{c^1\}. \\ c^0 \leftarrow \emptyset. \end{array}\right\}$ all **match** $\langle a^2, b^0, c^1 \rangle$

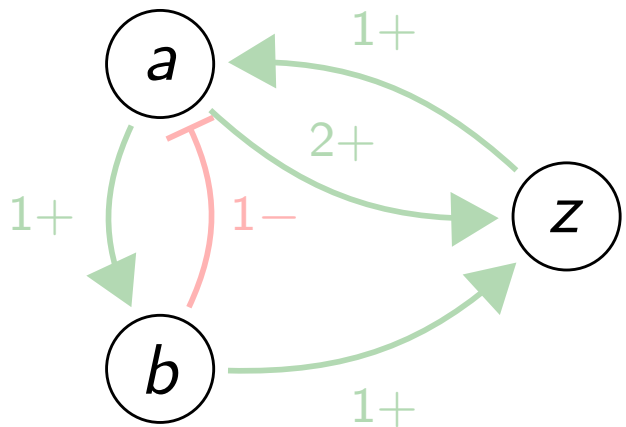
A rule R **matches** a state s iff $body \subseteq s$

$\rightarrow$ For all state s, if the rule **matches** s then
there **should exist** a state s' so that $s \rightarrow s'$ and $x_0^{val_0} \in s'$

Semantics: same as for discrete networks

Model as a Logic Program

Discrete model:



\+ Table of parameters
or logic gates

Logic program:

$$b(1,t) \leftarrow a(1,t-1).$$
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etc...

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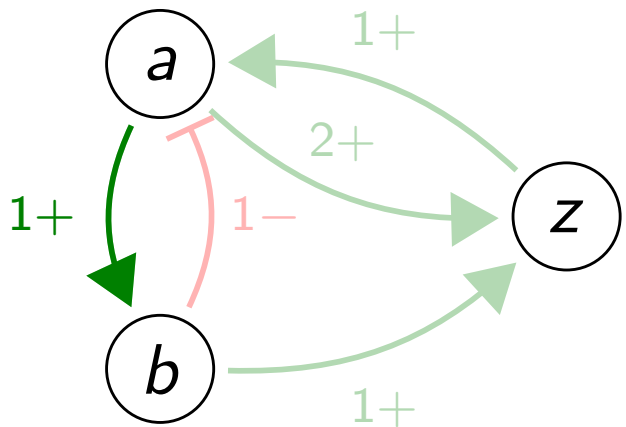

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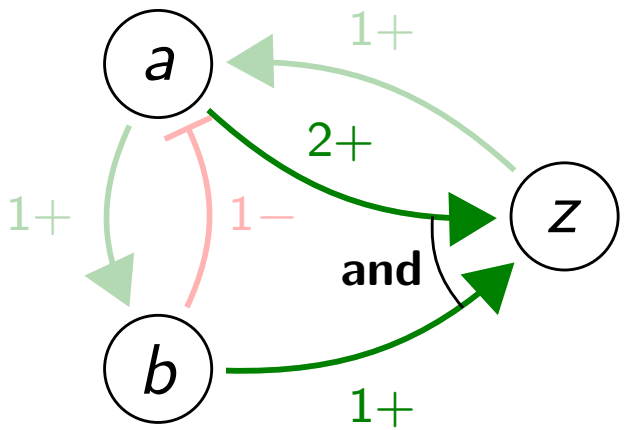

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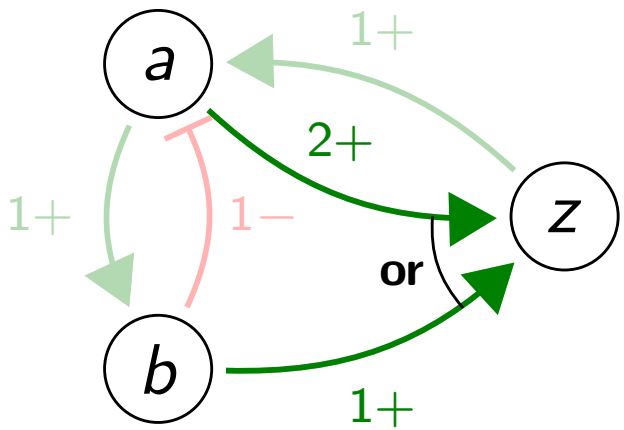

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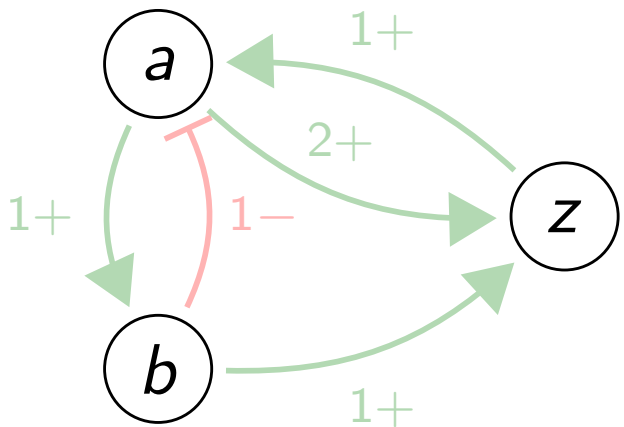

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Learning

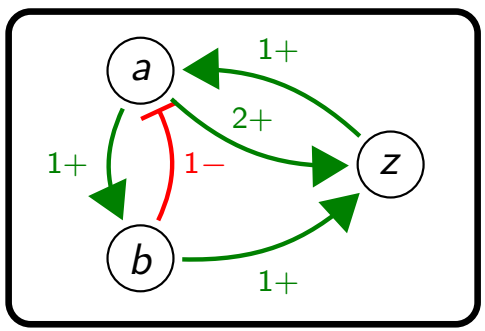
Principle of the Learning

Black box

Semantics

State graph

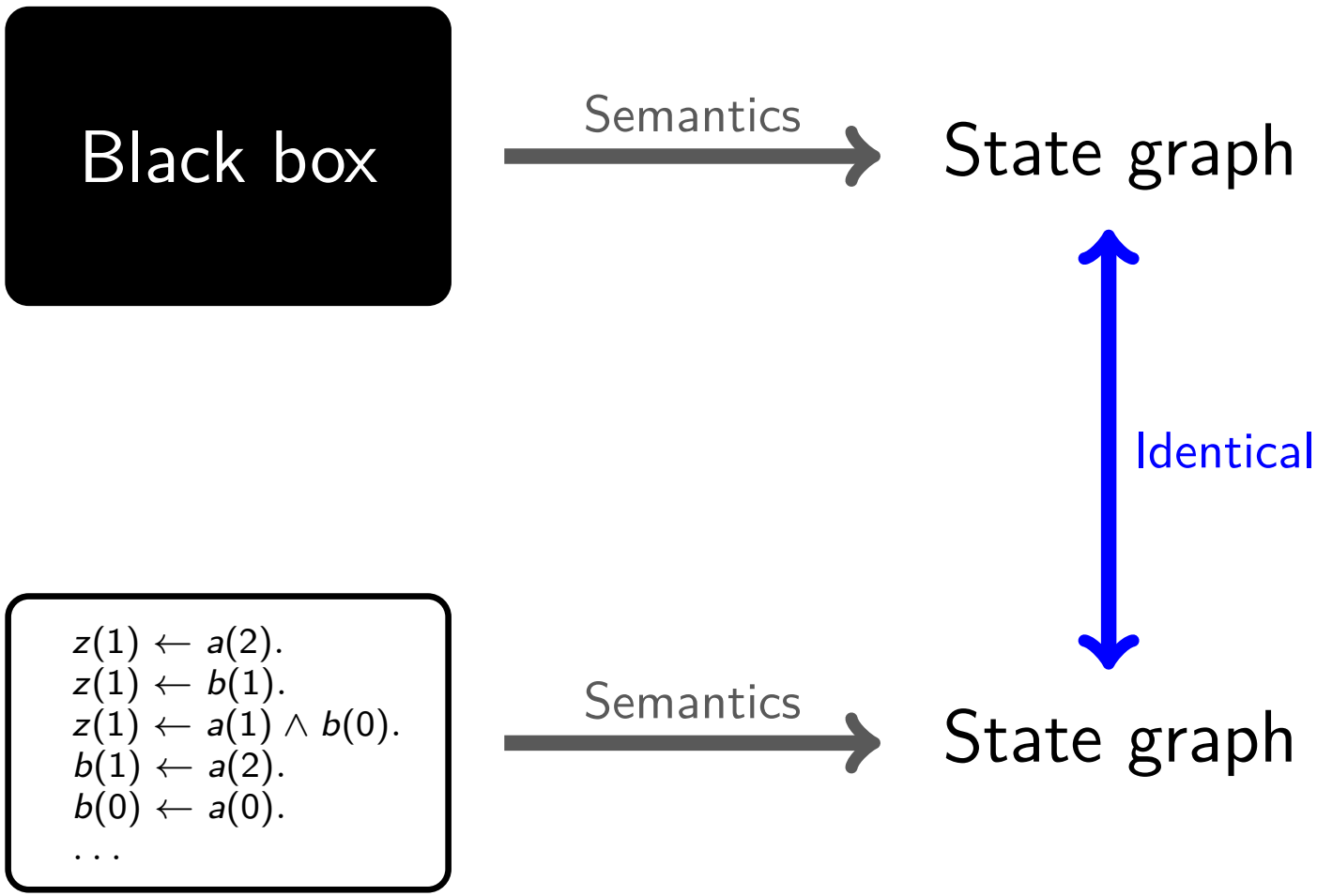
Identical



Semantics

State graph

Principle of the Learning



GULA

GULA = General Usage LFIT Algorithm

Input: a set of transitions (elements of $\mathcal{S} \times \mathcal{S}$)

Output: a program that respects:

- **Consistency**: The program allows no negative examples
- **Realization**: The program covers all positive examples
- **Completeness**: The program covers all the state space
- **Minimality** of the rules (most general bodies)

Algorithm

- Start from the most general program:

$$P := \{x^{val} \leftarrow \emptyset. \mid x \in V \wedge val \in \mathrm{dom}(x)\}$$

- For each state s:
  - consider all transitions that start from s
  - make minimal revisions on the program with these transitions
- Remove all dominated rules (that are not the most general)

where R dominates R' iff $\mathit{head}(R) = \mathit{head}(R')$ and $\mathit{body}(R) \subseteq \mathit{body}(R')$

This learning is independent from the semantics! (but...)

Formally proved: Compatible with transitions generated in **synchronous**, **asynchronous** and **generalized** semantics

Expectation: Compatible with a wider class of "learnable" semantics

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Semantics

Definition of a Semantics

Formally, a semantics is an element of:

$$\{\text{Set of } \textbf{complete programs}\} \rightarrow (\mathcal{S} \rightarrow \wp(\mathcal{S}) \setminus \emptyset)$$

Complete program = for all state s and all variable x, there exists a rule that matches s and whose head is about x

That is, a function that, to each complete program, associates a set of transitions so that each state has at least one successor.

- Non-determinism is the general case
  Because each state can have several successors
- Stable rules (not changing the state) can be included or not
  Depends on the chosen semantics
- No dead-ends, only fixed points as self-loops
  Because the state graph must also be complete

Examples of Semantics

Synchronous semantics

$$P \mapsto (s \mapsto \{\{\mathit{head}(R) \mid R \in P \wedge R \text{ matches } s\} \subseteq \mathcal{S}\})$$

Update all variables at each step using *head*s of on matching rules

Asynchronous semantics

$$P \mapsto (s \mapsto \{s \backslash\backslash \mathit{head}(R) \mid R \in P \wedge R \text{ matches } s \wedge \mathit{head}(R) \notin s\} \cup \{s \mid \text{if } s \to s \text{ is the only outcome}\})$$

where: $s \backslash\backslash x^{val} :=$ s in which the value of x is replaced by val

Update one variable at each step, avoid self-loops if possible

\+ **Generalized semantics**
\+ **Characterizations** of each semantics

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Limits of the Semantics

Limit of this definition:

$$P \mapsto (s \mapsto \{\langle 00...0 \rangle\})$$

is a valid semantics, that doesn't allow to learn the interactions

The learned program will always be: $\{x^0 \leftarrow \emptyset. \mid x \in V\}$ whatever the original program P used to generate the dynamics

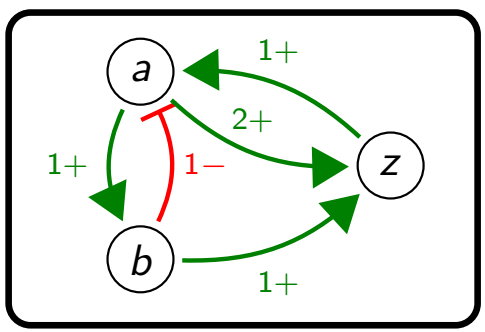
$\Rightarrow$ An "interesting" (learnable) semantics takes into account the *head*s of the rules in P

Other limitations?

Learning Time Series

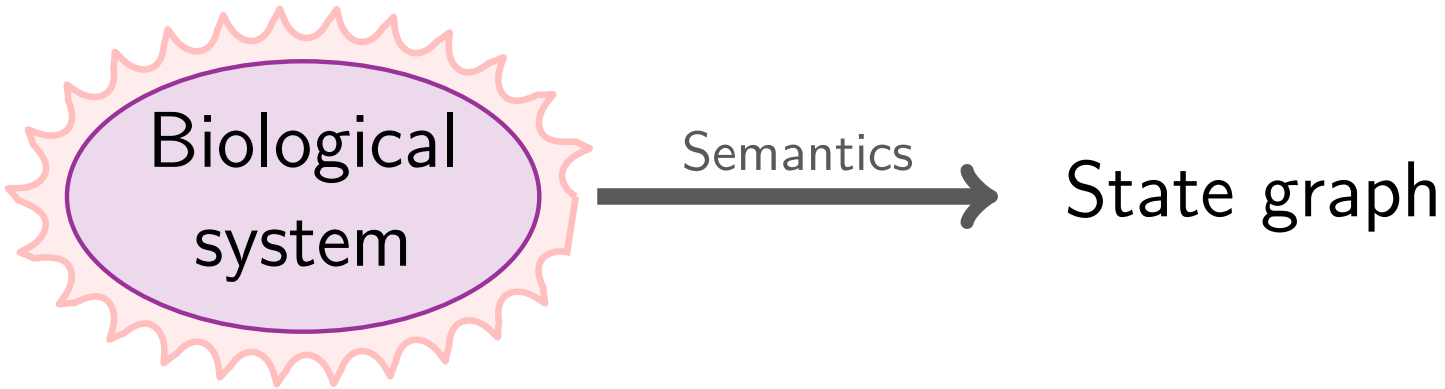
Potential Usage

Black box → Semantics → State graph



→ Semantics → State graph

Potential Usage



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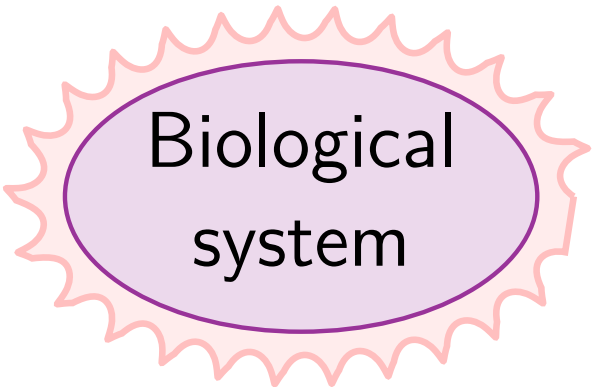
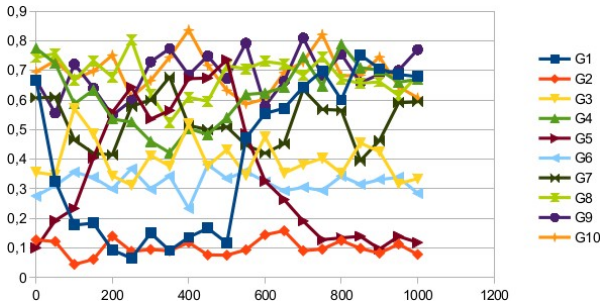
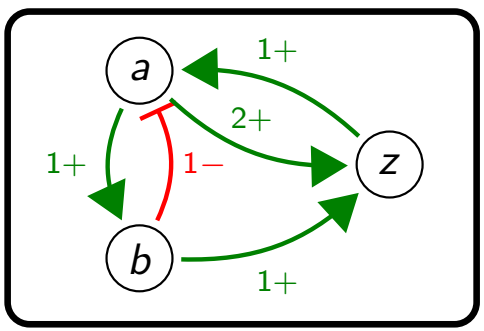


Behavior





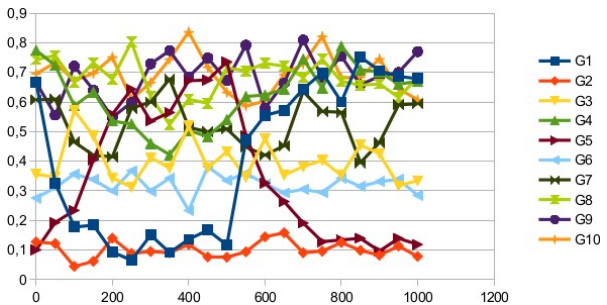
Semantics

State graph

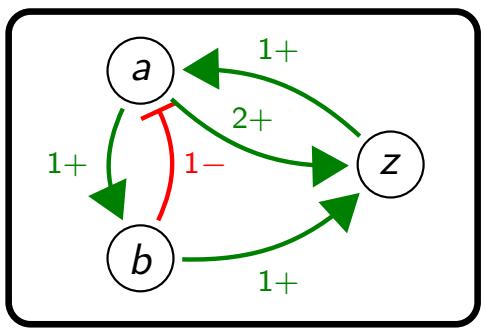
Potential Usage

Biological system

Behavior



Discretization



Semantics

State graph

Potential Usage

Towards the automation of learning time series

Challenges:

- Discretization → ACEDIA
  A different discretization gives a different result
- Partial data → LUST
  Predict parts of the system
- Noise
  Try not to over-learn
- Changing or heterogeneous "semantics"
  Over time or between components

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Conclusion

Logic rules $\Leftrightarrow$ networks interactions $\Leftrightarrow$ automata transitions

Learning of the structure of a model 1-step learning algorithm by successive refinements

Independent of the semantics
Proved for synchronous, asynchronous, generalized semantics

Outlooks

- Definition of what can be learned / what is interesting in a semantics
- Automatic learning of time series data (noise, discretization, ...)
- Learning the semantics alongside the structure
- Optimizations (parallelization, approximations)

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Learning Process

The algorithm successively takes into account groups of transitions and performs **minimal modifications** on the program learned so far

Let R a rule in conflict with the current transitions, that is: there exists a state s so that R **matches** s, but $\forall s' \in \mathcal{S}$ so that $s \to s'$, $head(R) \notin s'$
That is: R expresses a potential outcome for a variable which never happens in s

Least specialization of R by s:

$$R := head \leftarrow body$$

$$L_{spe}(R, s) := \{head \leftarrow body \cup \{x^{val}\} \mid x^{val} \notin s \wedge \forall val' \in \mathbb{N}, x^{val'} \notin body\}$$

Least revision of P by a set of transitions T:

$$L_{rev}(P, T) := (P \setminus R_P) \cup \bigcup_{R \in R_P} L_{spe}(R, s)$$