Learning Biological Regulatory Networks from Time Series with LFIT and Application to Phytoplankton

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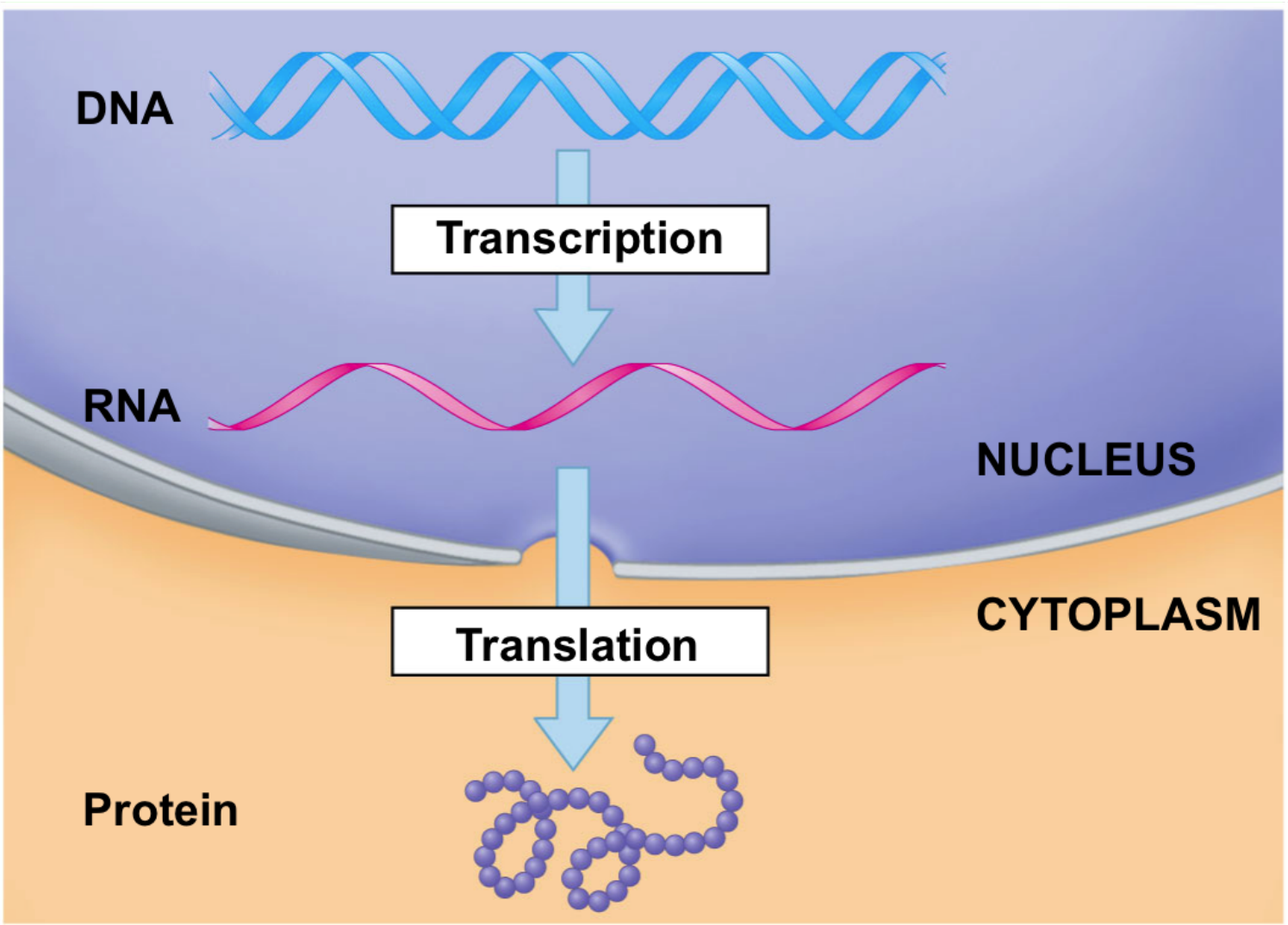
MIAT Seminar

Joint work with: Tony Ribeiro (Centrale Nantes), Morgan Magnin (Centrale Nantes), Katsumi Inoue (NII, Japan), Madeleine Eyraud (CNRS), Sébastien Lefebvre (Univ. Lille), Cédric Lhoussaine (Univ. Lille)

Outline

- Biological regulatory networks
- LFIT: an approach to learn a discrete model from its stage graph
- Heuristic for noisy/incomplete data
- Application to phytoplankton monitoring

Preliminary Abstraction



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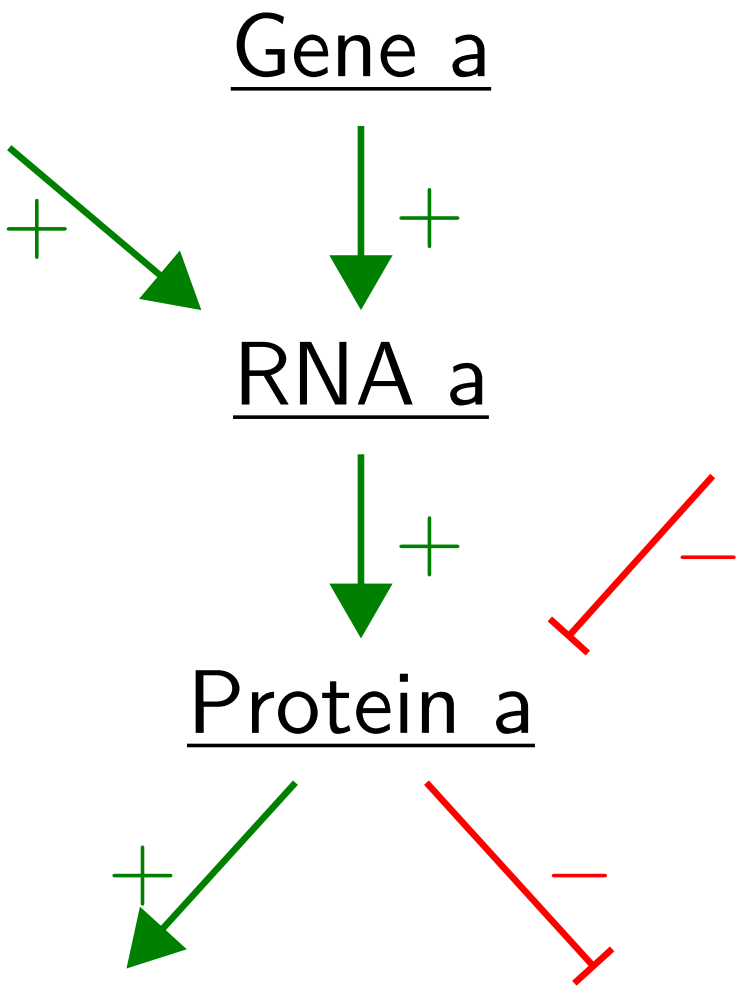

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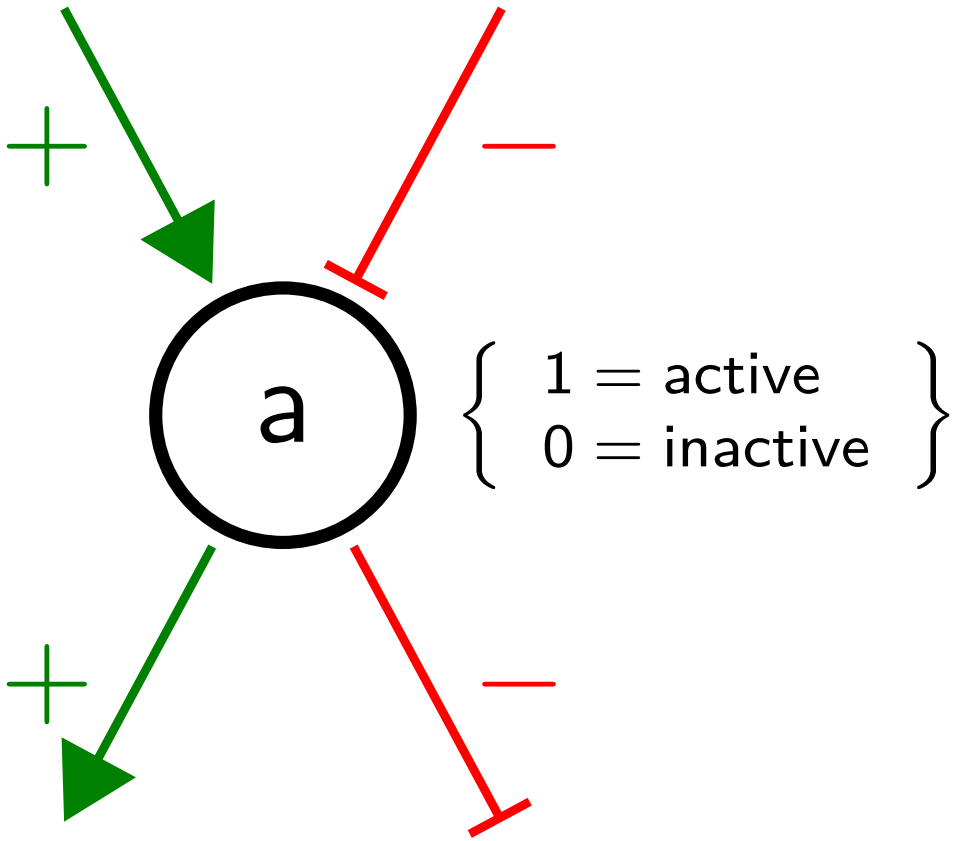
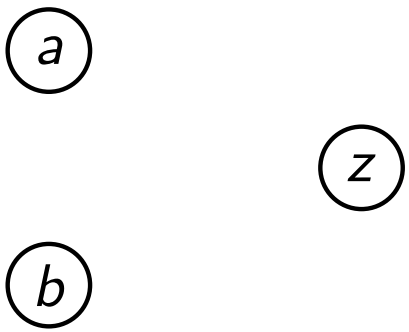


Biological Regulatory Networks

Discrete Networks / Thomas Modeling

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

- A set of components $N = \{a, b, z\}$



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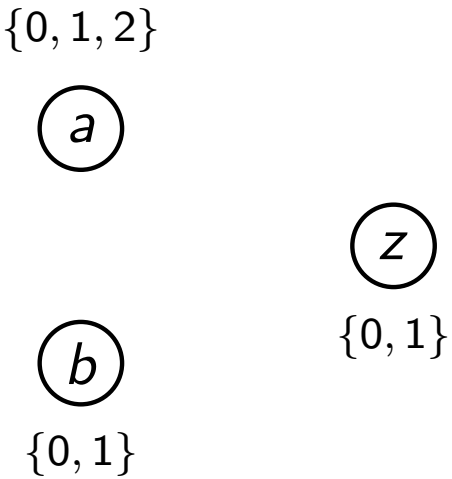

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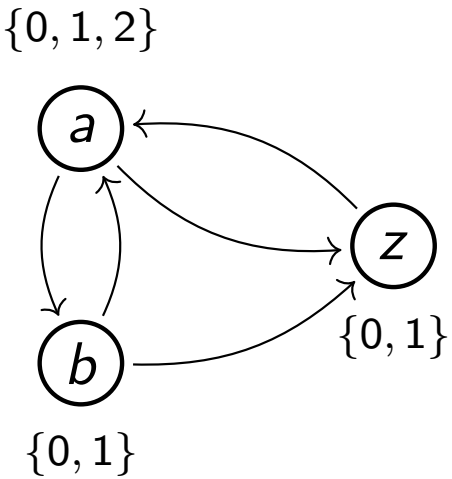
- Discrete parameters / evolution functions $f_a : \mathcal{S} \to \mathrm{dom}(a)$



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
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

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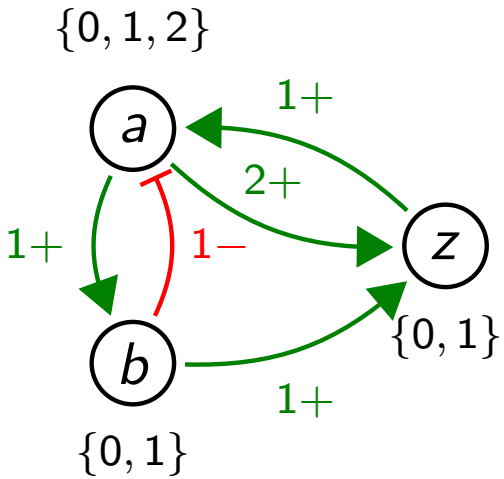
- A discrete domain for each component $\mathrm{dom}(a) = \{0, 1, 2\}$
- Discrete parameters / evolution functions $f_a : \mathcal{S} \to \mathrm{dom}(a)$
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



a	f_b
0	**0**
1	**1**
2	**1**

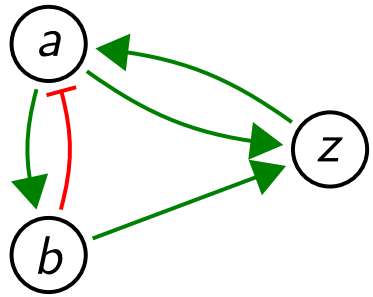
z	b	f_a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	f_z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

State Graph

The state graph depicts explicitly the whole dynamics

abz			
000	010	001	011
100	110	101	111
200	210	201	211



$+ f_a, f_b, f_c$

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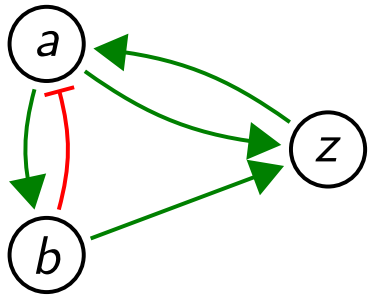

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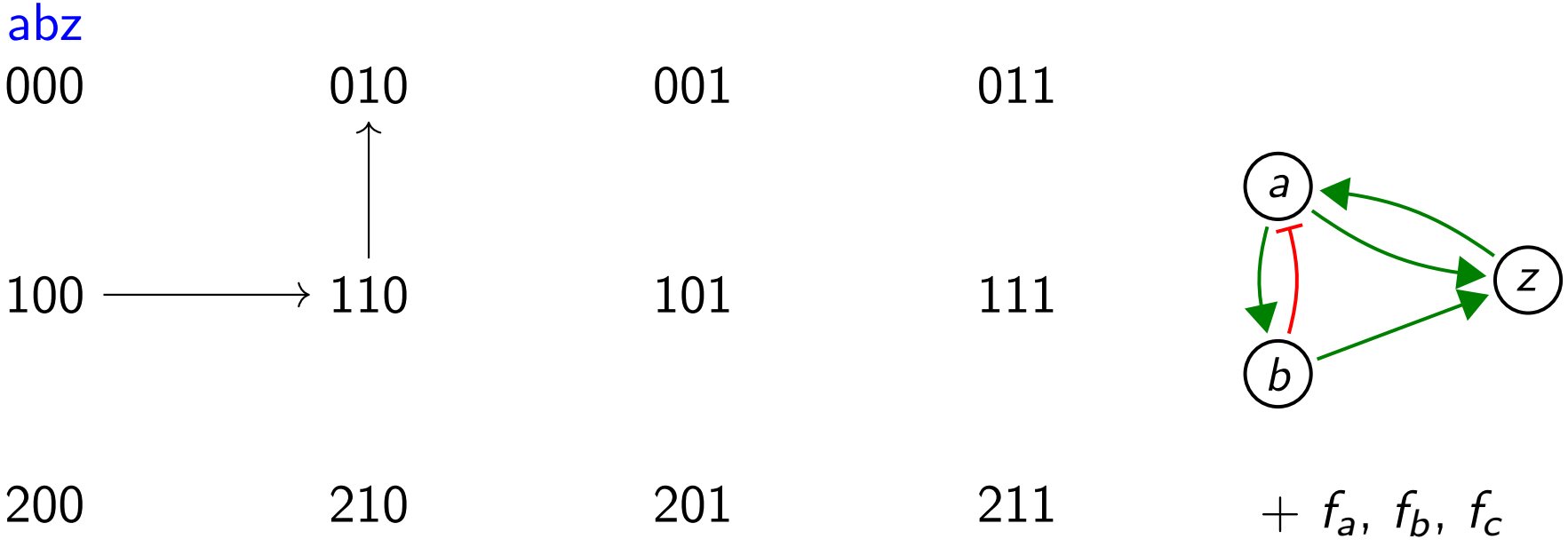

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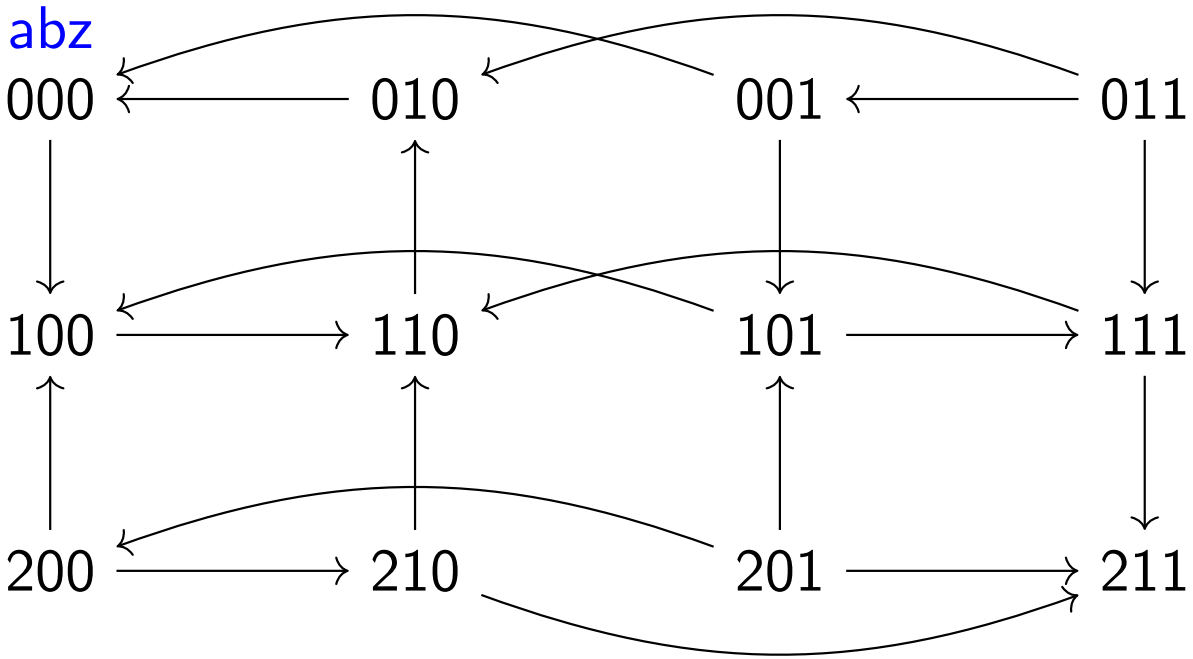

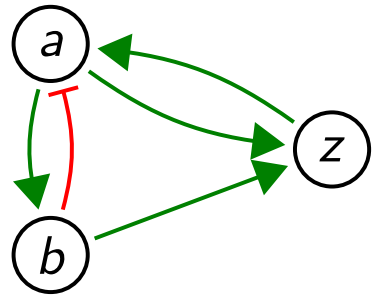

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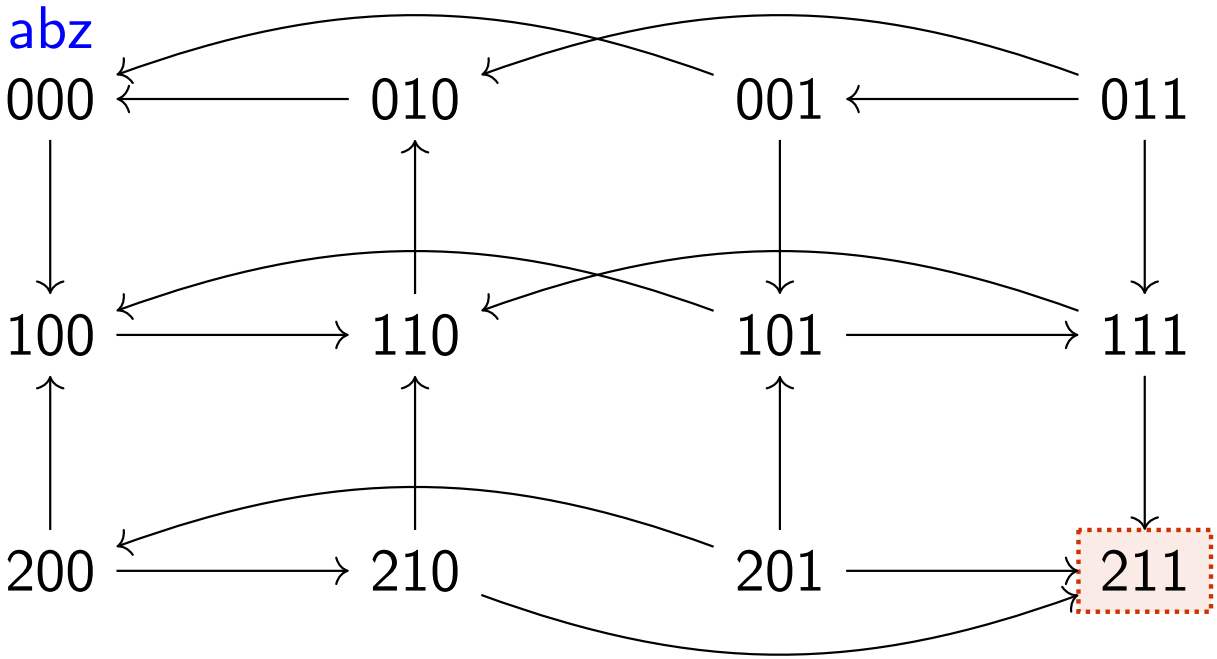

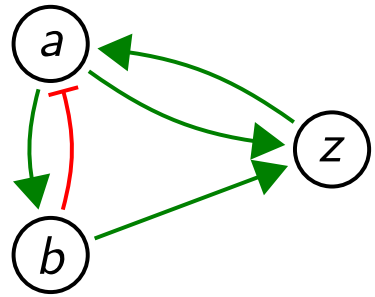

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- **Stable state** = state with no successors

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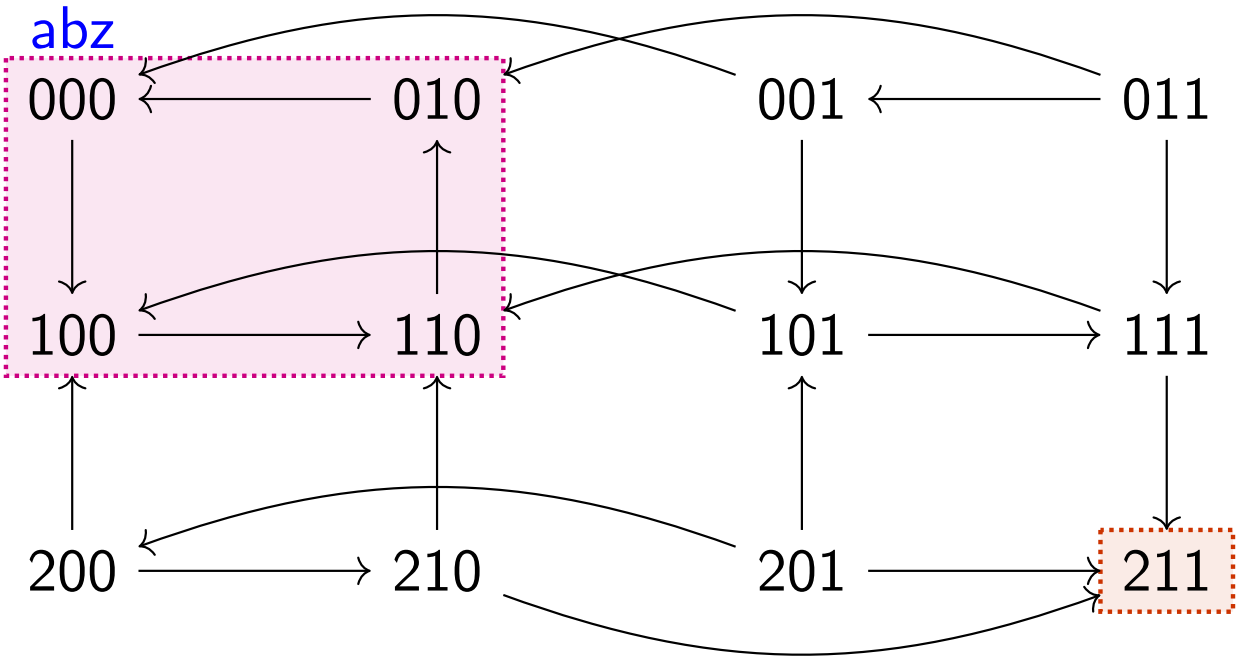

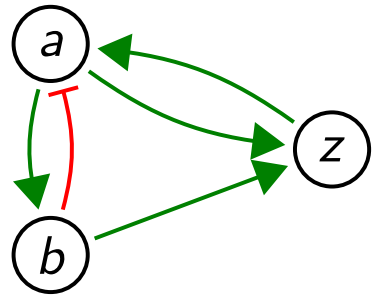

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- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape

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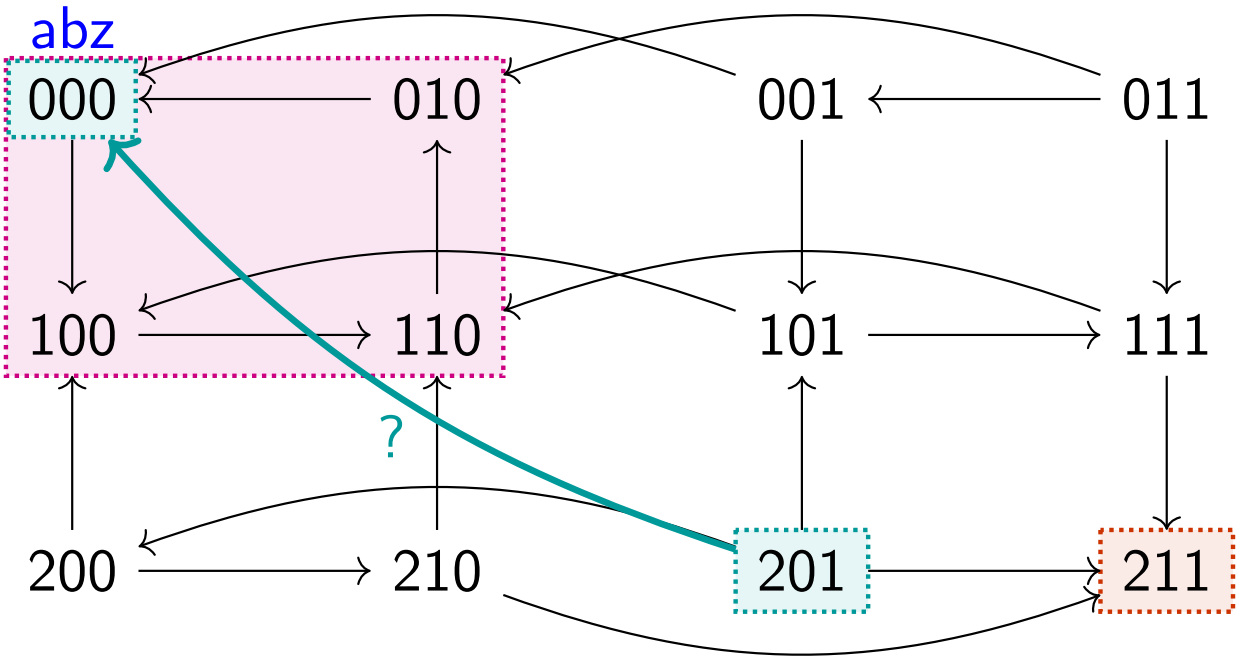

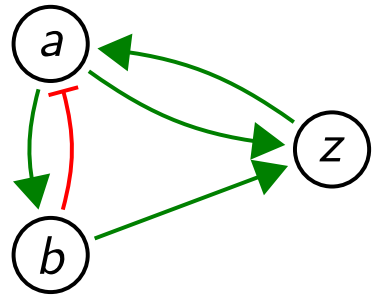

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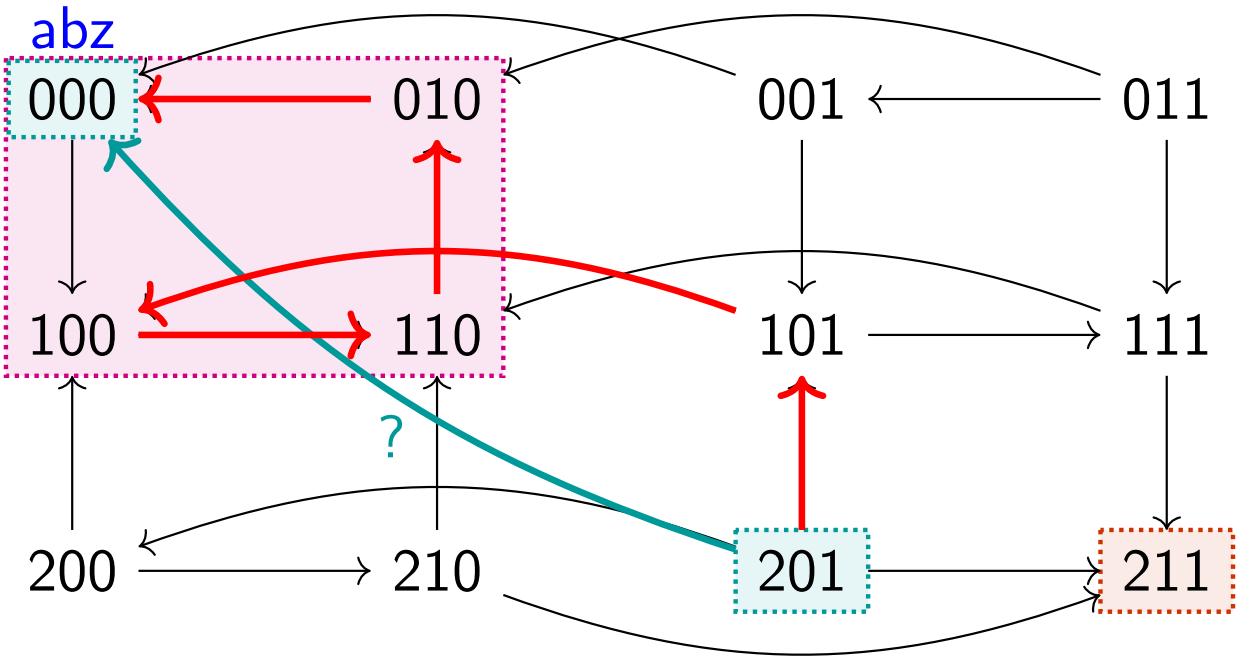

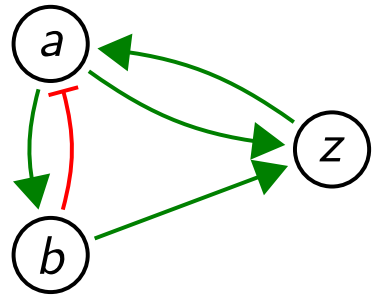

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Semantics

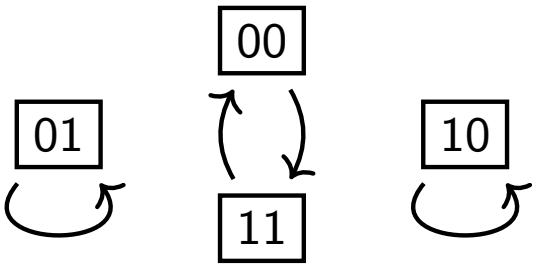
$f_a = \neg b$

b	f_a
0	1
1	0

$f_b = \neg a$

a	f_b
0	1
1	0

State transitions differ according to the update semantics used:



Synchronous

- **Synchronous**: all variables are updated

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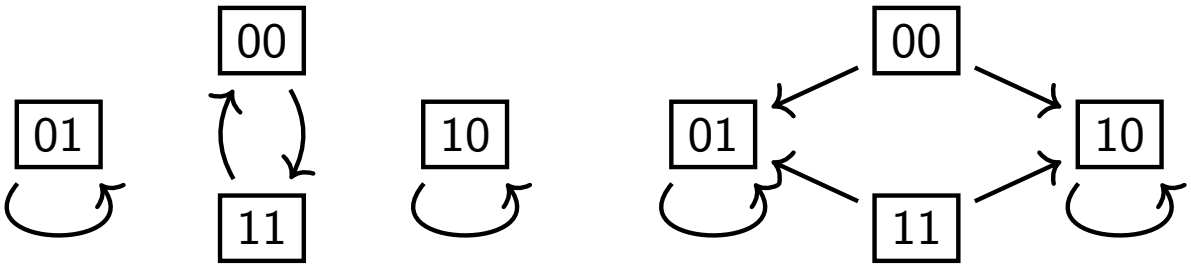

Synchronous **Asynchronous**

- **Synchronous**: all variables are updated
- **Asynchronous**: only one variable is updated

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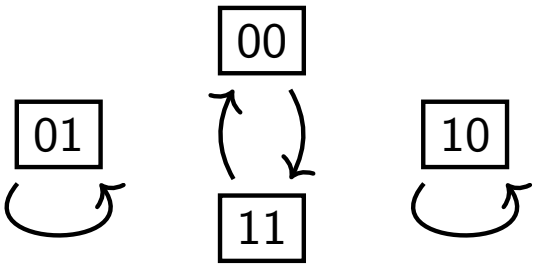
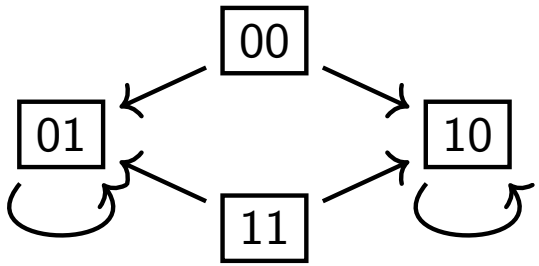
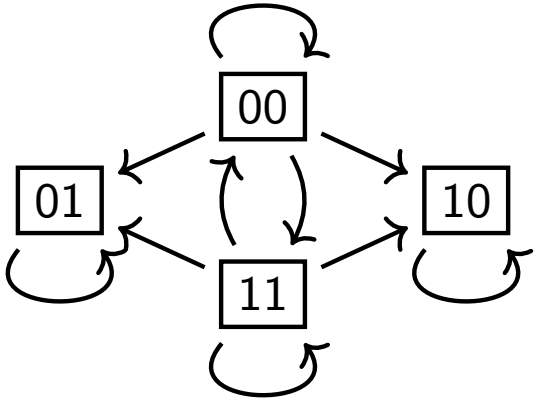


Synchronous



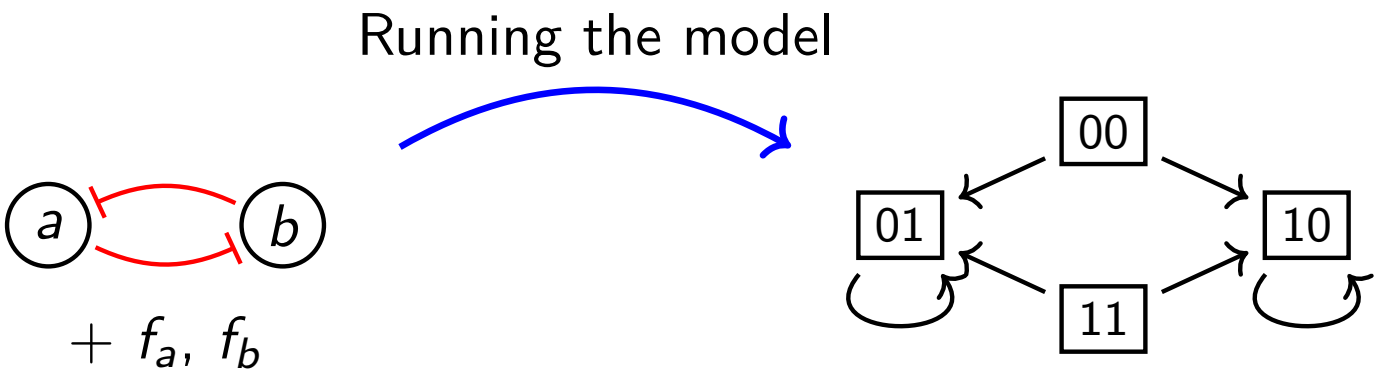
Asynchronous



General

- **Synchronous**: all variables are updated
- **Asynchronous**: only one variable is updated
- **General**: any number of variables can be updated

Learning from the State Graph



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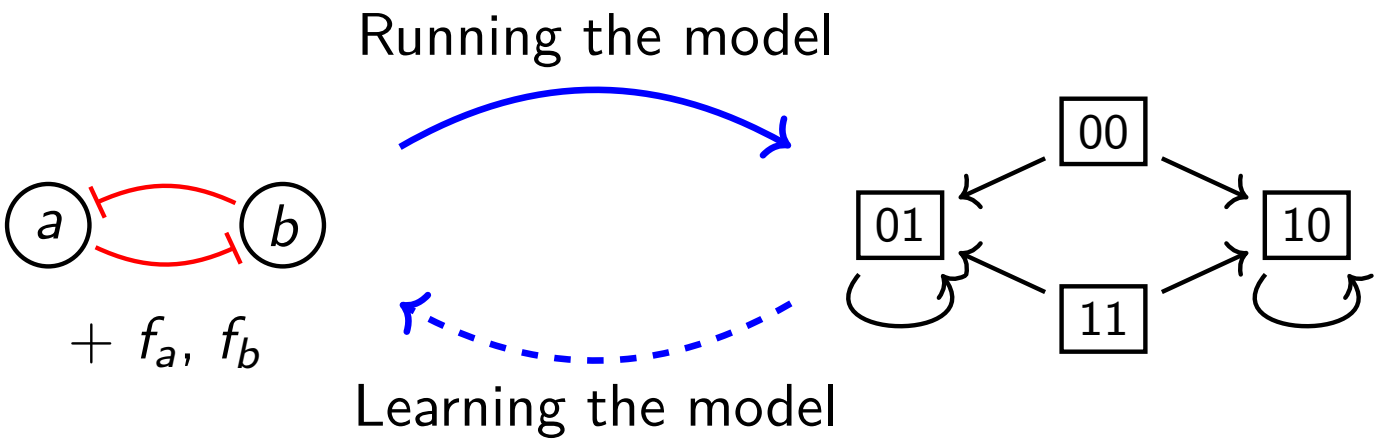

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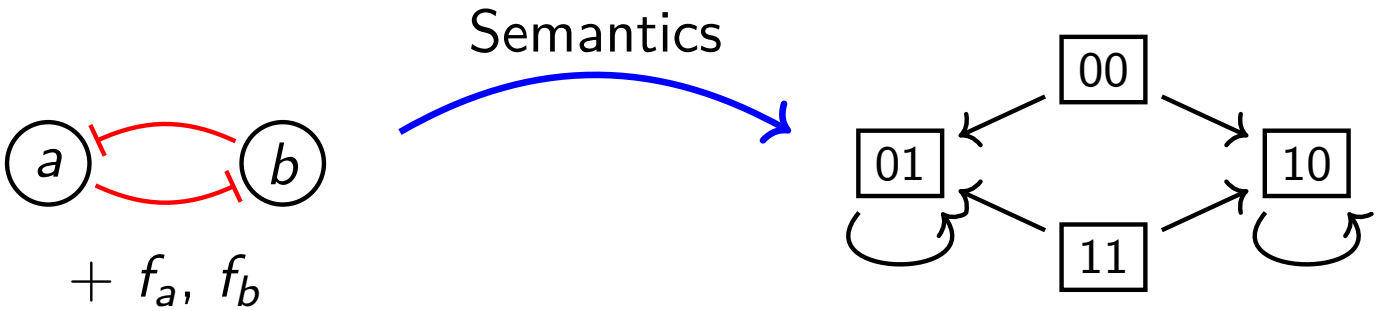

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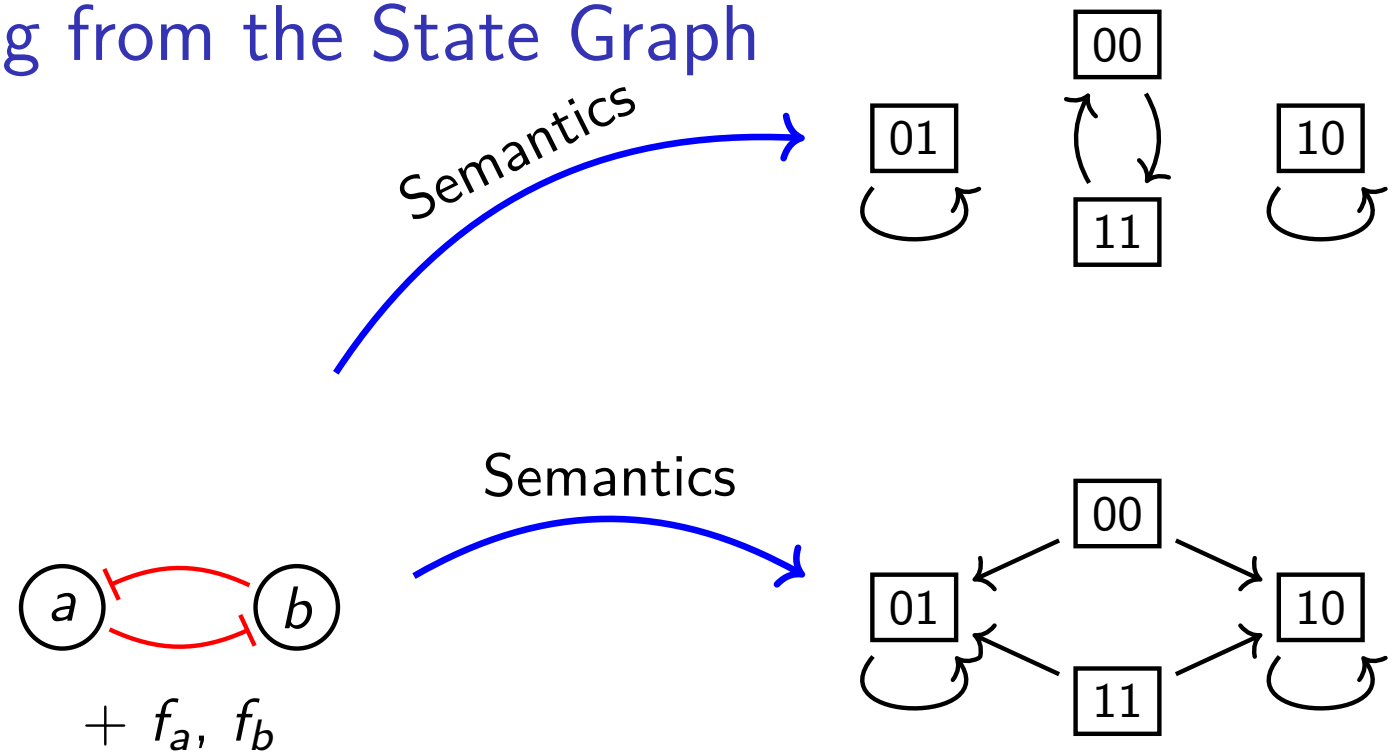

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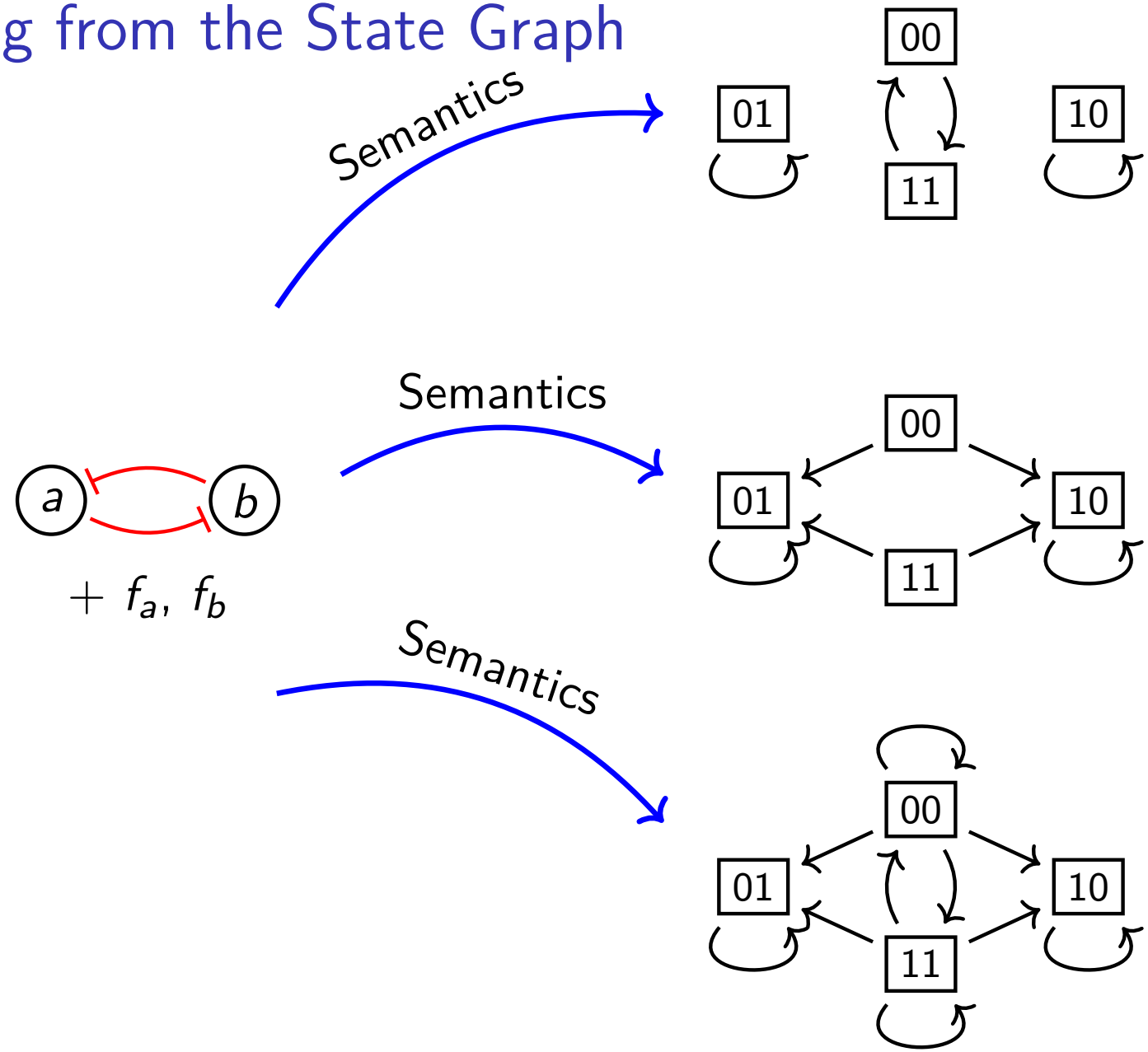

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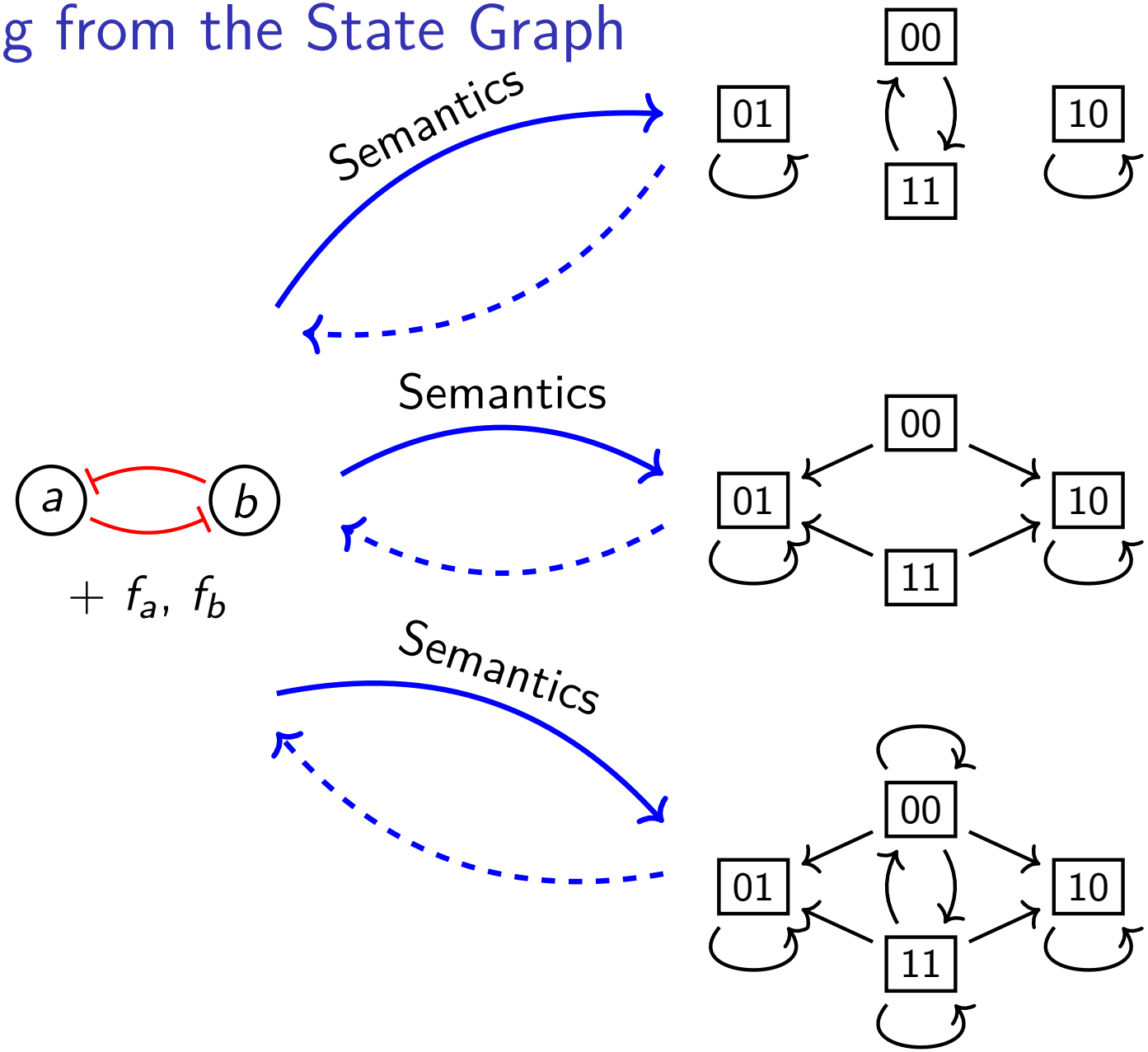

Logic Rules

A logic program is a set of logic rules.
It is an alternative representation of biological networks.

$$a_1 \leftarrow a_0, b_0, c_2.$$

If a and b are at level 0 and c is at level 2, then a can change its value to 1.

$$a_1 \leftarrow c_2.$$

Whenever c is at level 2, a can change its value to 1.

$$a_1 \leftarrow .$$

a can change its value to 1 anytime.

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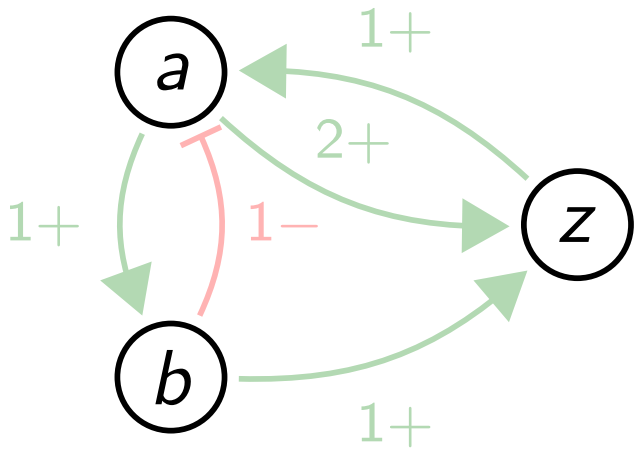
The same notion of **semantics** applies.

Discrete Models as Logic Programs

Discrete model:



Logic program:

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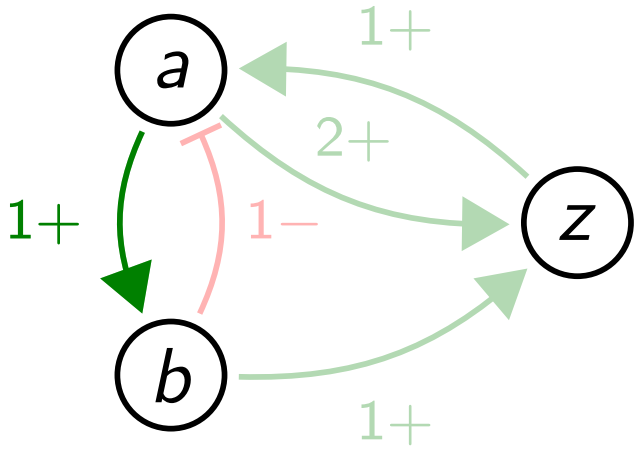

Logic program:

$$b_1 \leftarrow a_1.$$
$$b_1 \leftarrow a_2.$$
$$b_0 \leftarrow a_0.$$

Discrete Models as Logic Programs

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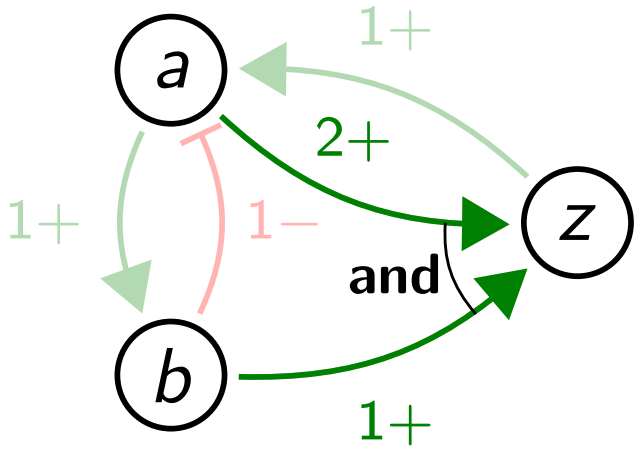

Logic program:

$b_1 \leftarrow a_1.$
$b_1 \leftarrow a_2.$
$b_0 \leftarrow a_0.$

$z_1 \leftarrow a_2 \wedge b_1.$
$z_0 \leftarrow a_0.$
$z_0 \leftarrow a_1.$
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Discrete Models as Logic Programs

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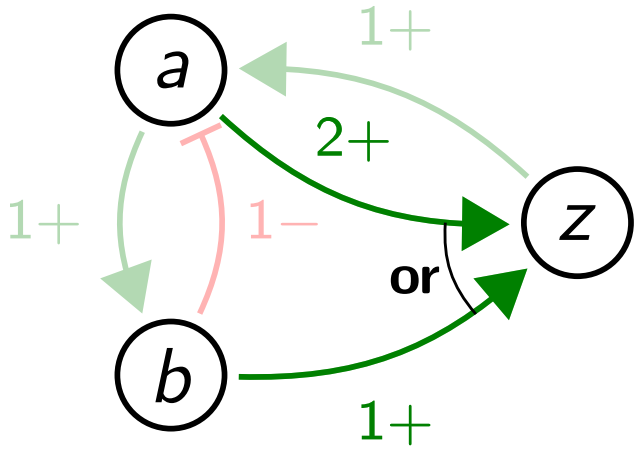

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Discrete Models as Logic Programs

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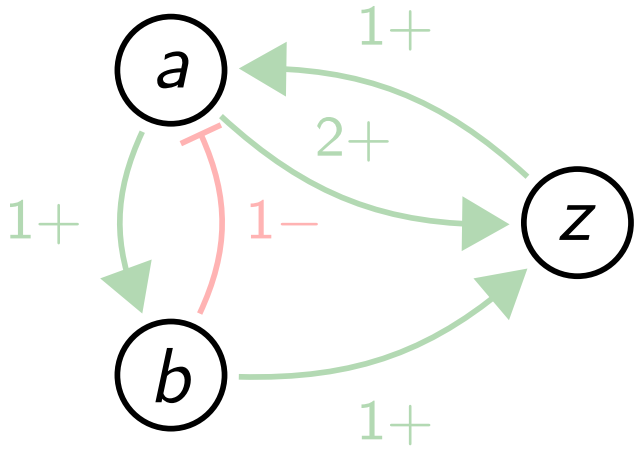

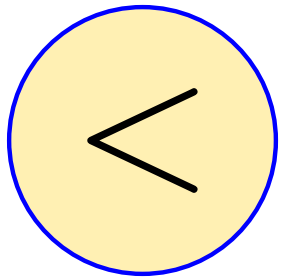

Expressivity

Logic program:

$b_1 \leftarrow a_1.$
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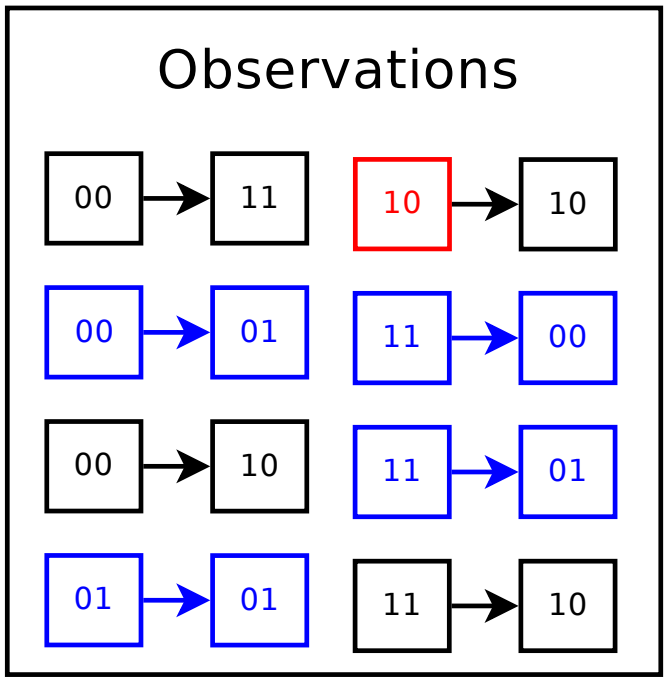
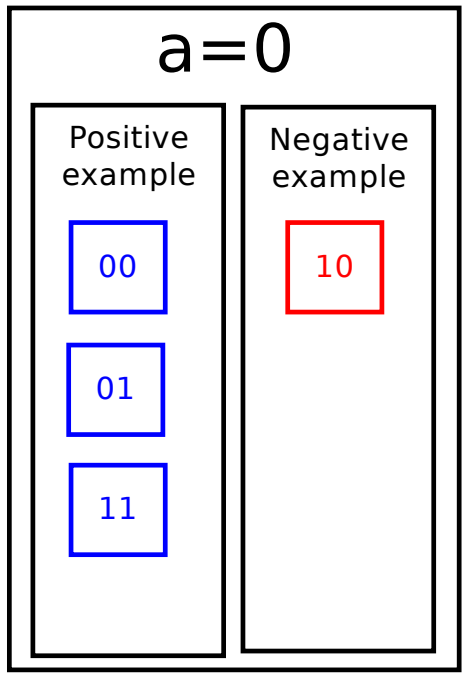
$z_1 \leftarrow a_2.$
$z_1 \leftarrow b_1.$
$z_0 \leftarrow a_1 \wedge b_0.$
$z_0 \leftarrow a_0 \wedge b_0.$

Learning From Interpretation Transition (LFIT)

Learning Algorithm Intuition: Classification Problem

Learn applicable rules: conditions so that a variable **can** take a certain value in next state.





Equivalent to a **classification problem**: What is a typical state where a can take value 0 in the next state ? Here: when a_0 or b_1 is present.

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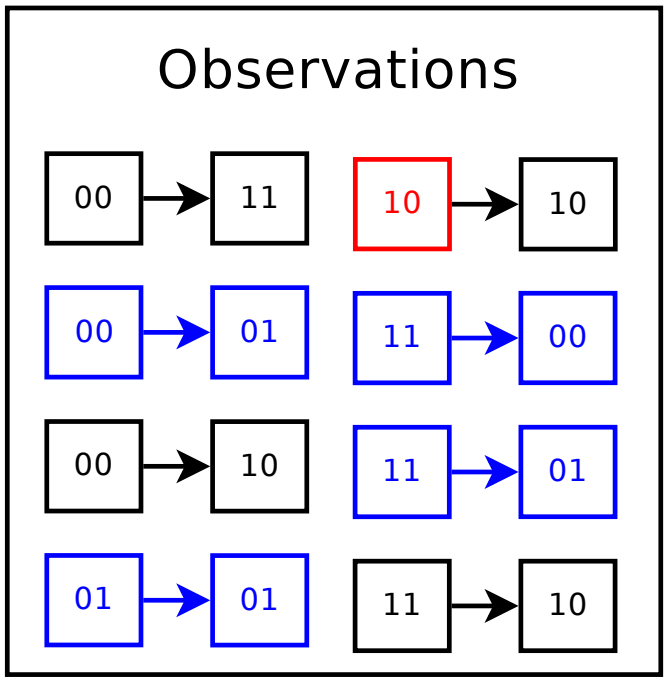

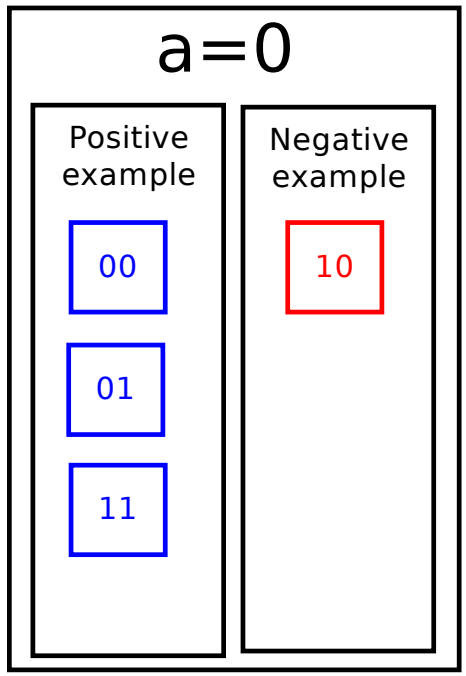

Equivalent to a **classification problem**: What is a typical state where a can take value 0 in the next state ? Here: when a_0 or b_1 is present.

That is: $a_0 \leftarrow a_0.$ $a_0 \leftarrow b_1.$

Presentation of GULA

GULA = General Usage LFIT Algorithm

Input: a set of transitions $(s_1 \rightarrow s_2)$

Output: a logic program that reproduces the input

Principle: minimal refinements of the rules

Compatible with the synchronous, asynchronous and general semantics (and any semantics without memory or hard-coded behaviors)

GULA: Initial Logic Program

Suppose:

- a and b have two levels $\{0, 1\}$ and c has three levels $\{0, 1, 2\}$

GULA starts with the most general program:

$$a_0 \leftarrow . \qquad b_0 \leftarrow . \qquad c_0 \leftarrow .$$
$$a_1 \leftarrow . \qquad b_1 \leftarrow . \qquad c_1 \leftarrow .$$
$$c_2 \leftarrow .$$

With this program, everything is always possible

At each step, some rules can be **refined** by adding atoms to their body

GULA: One Step of Minimal Refinements

Suppose:

- a and b have two levels $\{0, 1\}$ and c has three levels $\{0, 1, 2\}$
- the current program contains the following rules regarding a_1:

$$a_1 \leftarrow c_2. \qquad\qquad a_1 \leftarrow b_1.$$

- from state $\langle a_1, b_0, c_2 \rangle$, a_1 is never observed in the next states.

However, the first rule allows this; it is then necessary to make **minimal refinements** in order to make this rule inapplicable:

GULA: One Step of Minimal Refinements

Suppose:

- a and b have two levels $\{0, 1\}$ and c has three levels $\{0, 1, 2\}$
- the current program contains the following rules regarding a_1:

$$a_1 \leftarrow c_2. \qquad a_1 \leftarrow b_1.$$

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However, the first rule allows this; it is then necessary to make **minimal refinements** in order to make this rule inapplicable:

$$a_1 \leftarrow a_0, c_2.$$
$$a_1 \leftarrow b_1, c_2.$$
$$a_1 \leftarrow c_2, c_0.$$
$$a_1 \leftarrow c_2, c_1.$$

$$a_1 \leftarrow b_1.$$
(No change)

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$$a_1 \leftarrow b_1.$$
(More general)

GULA: One Step of Minimal Refinements

Suppose:

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- the current program contains the following rules regarding a_1:

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However, the first rule allows this; it is then necessary to make **minimal refinements** in order to make this rule inapplicable:

$$a_1 \leftarrow a_0, c_2. \qquad a_1 \leftarrow b_1.$$

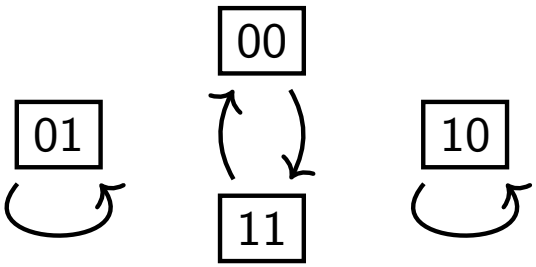
Example: Synchronous Semantics

$f_a = \neg b$

b	f_a
0	1
1	0

$f_b = \neg a$

a	f_b
0	1
1	0



Synchronous

// $f_a = \neg b$

$a_0 \leftarrow b_1$

$a_1 \leftarrow b_0$

// $f_b := \neg a$

$b_0 \leftarrow a_1$

$b_1 \leftarrow a_0$

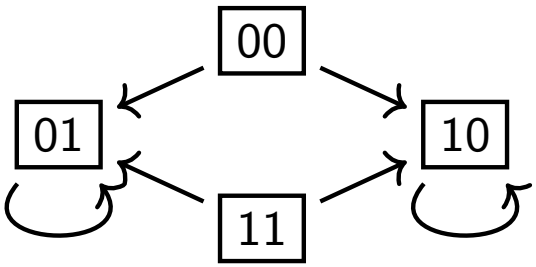
Example: Asynchronous Semantics

$f_a = \neg b$

b	f_a
0	1
1	0

$f_b = \neg a$

a	f_b
0	1
1	0



Asynchronous

// $f_a = \neg b$

$a_0 \leftarrow b_1$

$a_1 \leftarrow b_0$

// $f_b = \neg a$

$b_0 \leftarrow a_1$

$b_1 \leftarrow a_0$

// Default rules

$a_0 \leftarrow a_0$

$a_1 \leftarrow a_1$

$b_0 \leftarrow b_0$

$b_1 \leftarrow b_1$

GULA: Good Properties

The output of GULA respects some good properties:

- **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 conditions)

Results

GULA: an algorithm to learn a biological regulatory network

- From the state graph
- In order to recover the structure of the model
- Applicable to a widespread class of semantics

Limitations:

- Exponential complexity
  - **PRIDE**: a greedy polynomial version of **GULA**
- What if the data is **incomplete** or **noisy**?
  - Heuristic to avoid overfitting

Heuristic: Weighted Likeliness/Unlikeliness Rules

- Use the algorithm twice to learn two logic programs:
  - likeliness rules: what is possible
  - unlikeliness rules: what is impossible
- Weight each rule by the number of observations it matches

Likeliness rules

$(3, a_0 \leftarrow b_1)$

$(15, a_1 \leftarrow b_0)$

$\vdots$

Unlikeliness rules

$(30, a_0 \leftarrow c_1)$

$(5, a_1 \leftarrow c_0)$

$\vdots$

Heuristic: Using Weighted Likeliness/Unlikeliness Rules

Explainable predictions:

- Compare weights of applicable likeliness/unlikeliness rules
- Ratio of highest weights $\Rightarrow$ **probability** P
- Rules with highest weights $\Rightarrow$ **explanation** E

$$\text{predict} : (atom, state) \mapsto (P, E)$$

Likeliness rules	**Unlikeliness rules**
$(3, a_0 \leftarrow b_1)$	$(30, a_0 \leftarrow c_1)$
$(15, a_1 \leftarrow b_0)$	$(5, a_1 \leftarrow c_0)$

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Likeliness rules	**Unlikeliness rules**
$(3, a_0 \leftarrow b_1)$	$(30, a_0 \leftarrow c_1)$
$(15, a_1 \leftarrow b_0)$	$(5, a_1 \leftarrow c_0)$

$$\text{predict}(a_1, \langle a_1, b_0, c_0 \rangle) = (0.75, ((15, a_1 \leftarrow b_0), (5, a_1 \leftarrow c_0))) \Rightarrow \text{Likely}$$

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Explainable predictions:

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- Rules with highest weights $\Rightarrow$ **explanation** E

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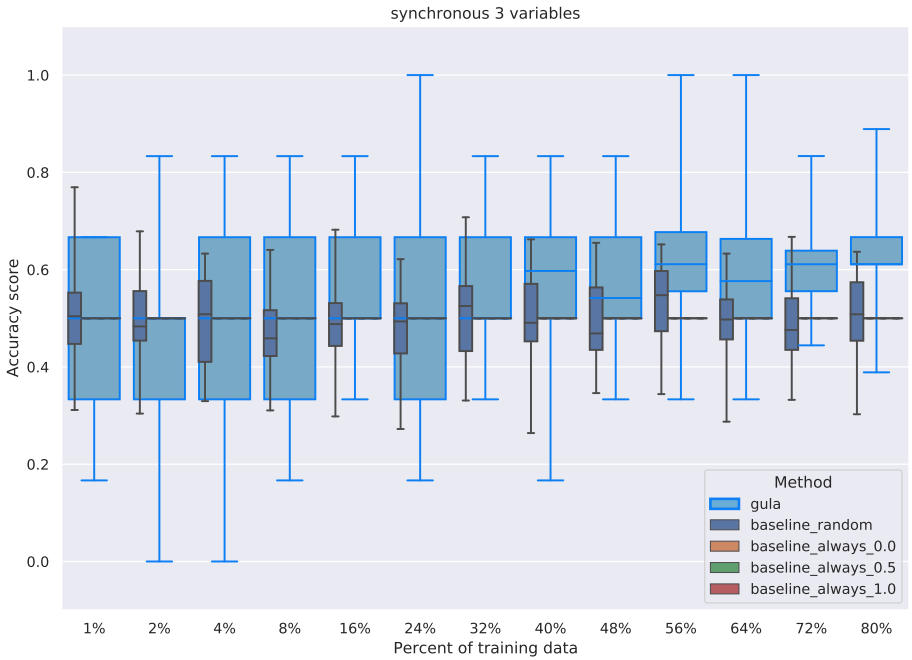
Likeliness rules	**Unlikeliness rules**
$(3, a_0 \leftarrow b_1)$	$(30, a_0 \leftarrow c_1)$
$(15, a_1 \leftarrow b_0)$	$(5, a_1 \leftarrow c_0)$

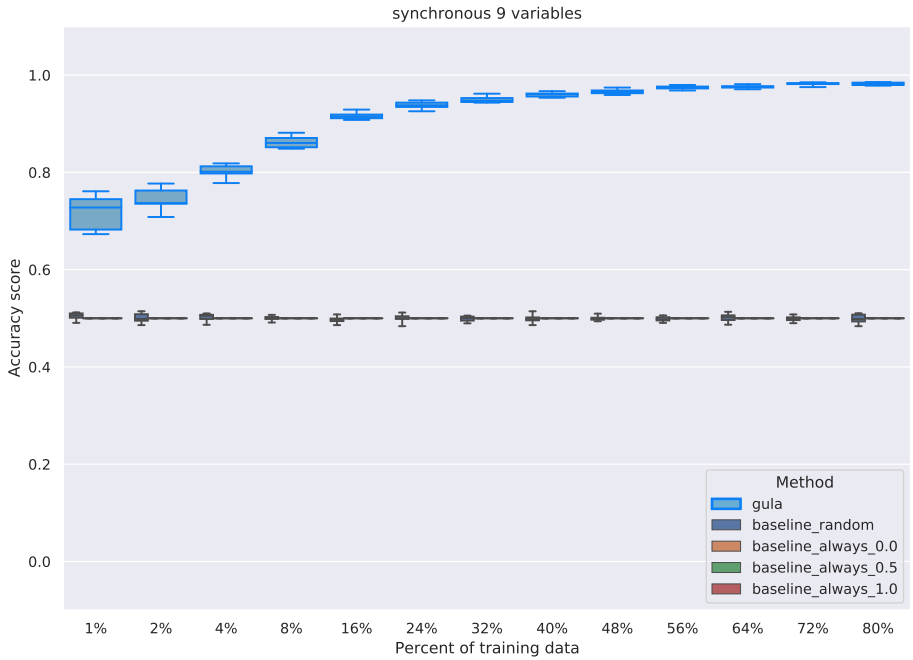
$\text{predict}(a_1, \langle a_1, b_0, c_0 \rangle) = (0.75, ((15, a_1 \leftarrow b_0), (5, a_1 \leftarrow c_0))) \Rightarrow$ Likely

$\text{predict}(a_0, \langle a_1, b_1, c_1 \rangle) = (0.09, ((3, a_0 \leftarrow b_1), (30, a_0 \leftarrow c_1))) \Rightarrow$ Unlikely

Prediction power



3 variables



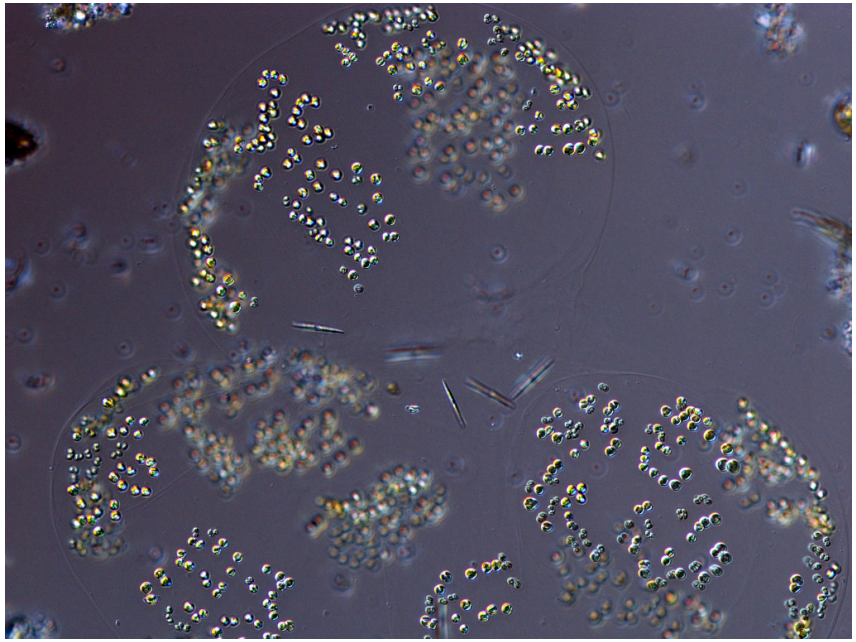
9 variables

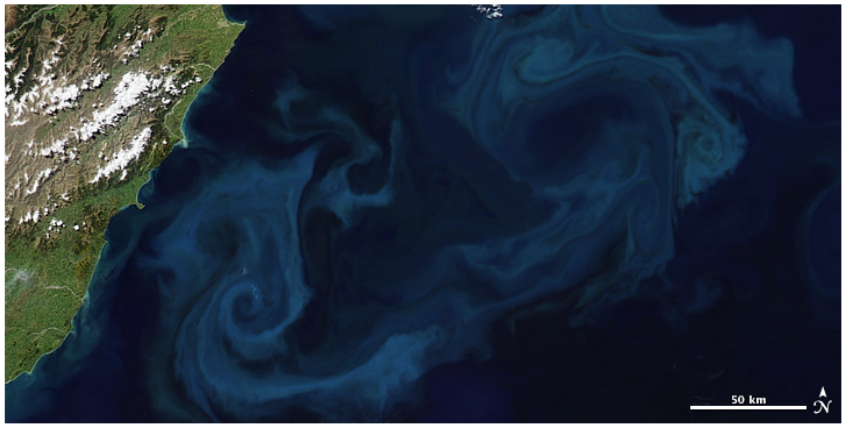
Training data = X% of transitions

Tested against unseen states (not in the training data)

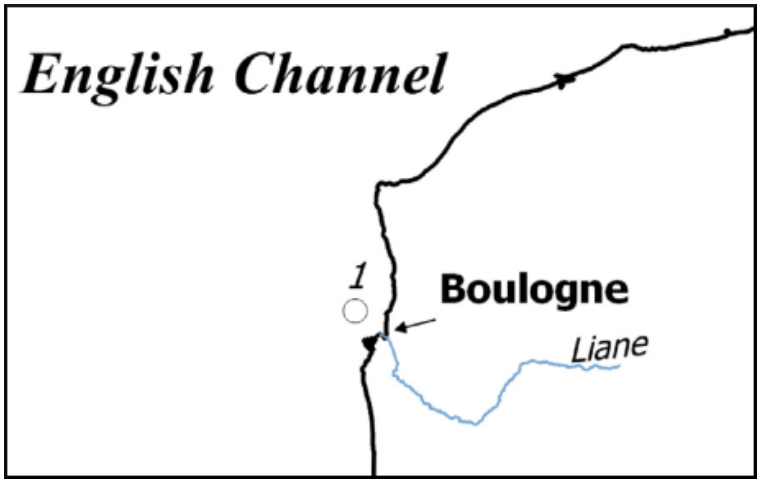
Application: Dynamics of Marine Phytoplankton

Phytoplankton Blooms





SRN Dataset



https://www.seanoe.org/data/00397/50832/

Sampling location	Sampling date	Taxon/Measurment	Value	Sampling depth
001-P-015	1992-05-18	CHLOROA	6.0	Surface (0-1m)
006-P-001	2019-12-02	Chaetoceros	1000.0	Surface (0-1m)
002-P-007	1994-05-25	Pleurosigma	100.0	Surface (0-1m)
002-P-030	2005-10-19	SALI	34.83	Surface (0-1m)
006-P-007	2015-09-28	Guinardia delicatula	11400.0	Surface (0-1m)

Environmental variables (7) Phytoplankton species (12)

Applying LFIT

Expectations

- Find known **abiotic** influences (of environment on phytoplankton)
- Find new **biotic** influences (of phytoplankton species on others)

Input

- 12 species and 11 environmental variables
- Data interpolation: 1 data point / month

Output

- Run time = 1h (5 runs of **PRIDE**)
- 20'000 rules
- Model accuracy: **0.86**

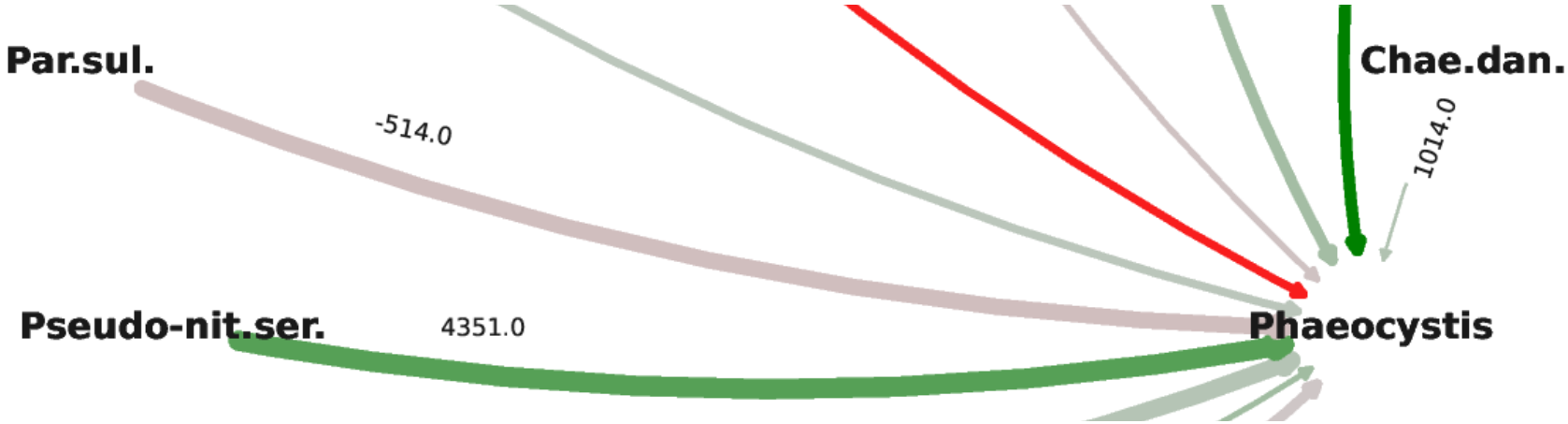
Global Influences

Process: Search and count patterns in rules that characterize an activation/inhibition

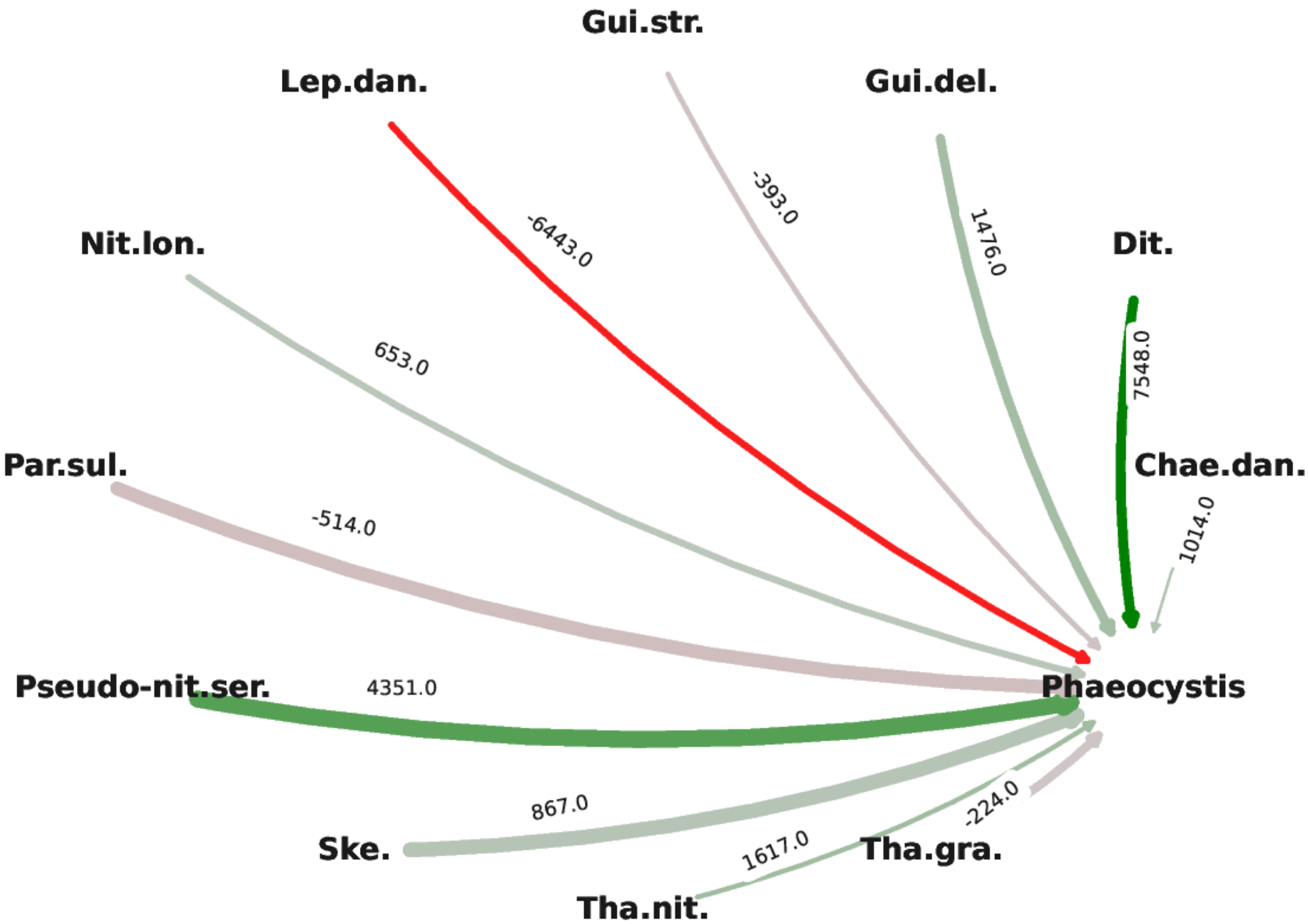
$$a_1 \leftarrow a_0, b_0, c_1.$$

Extracted patterns: $a \xrightarrow{-} a$, $b \xrightarrow{-} a$, $c \xrightarrow{+} a$

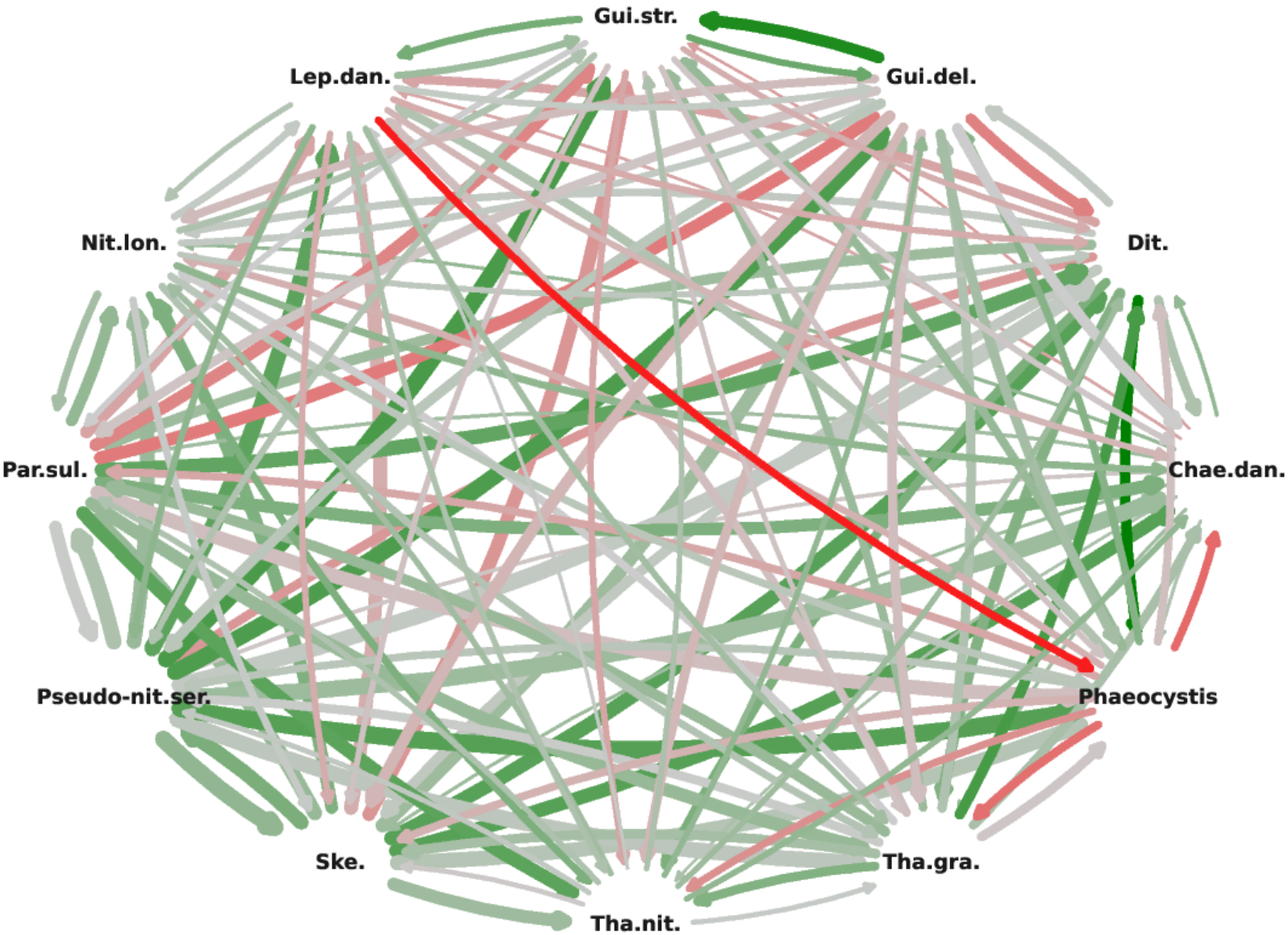
Result: Scores characterizing weight and sign for each pair



Results: Phaeocystis



Results: All Species



Conclusion

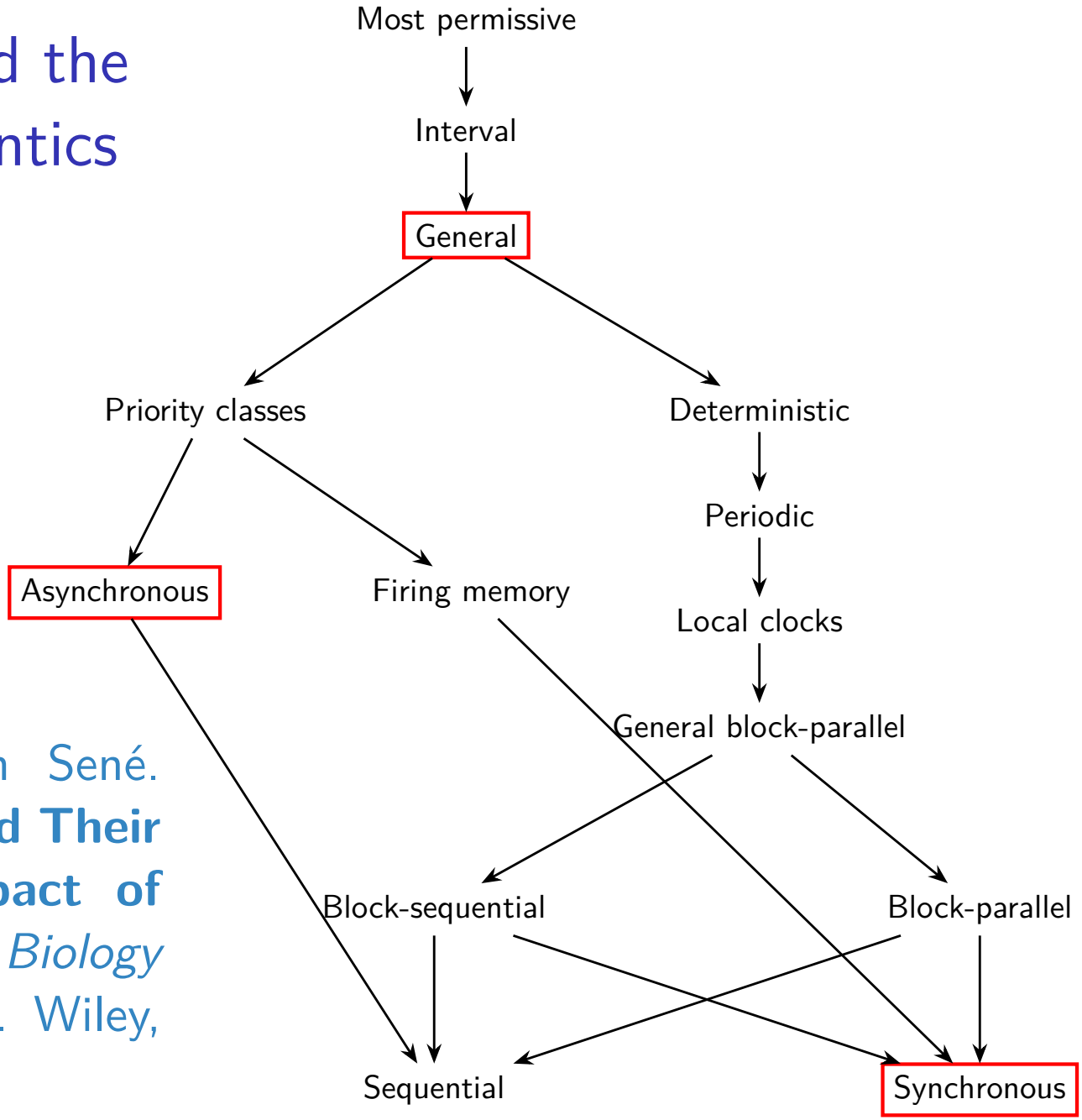
Conclusion

- **Learn** biological regulatory networks with LFIT
- **Heuristics** to tackle real data
  - Good results with 10% of the transitions
- **Application** to phytoplankton
- You can try LFIT at home:
  `https://github.com/Tony-sama/pylfit`

Outlooks:

- Use **GULA** instead of **PRIDE** to get a complete picture
- Improve pre-processing to focus on biotic interactions
- Make LFIT applicable to other semantics

Ongoing: LFIT and the Hierarchy of Semantics



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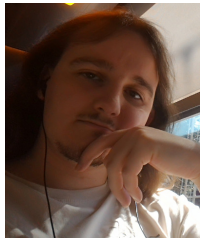
Thanks



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