Modeling and Learning of Biological Regulatory Networks

Maxime Folschette

Univ. Lille, CNRS, Centrale Lille, UMR 9189 CRIStAL, F-59000 Lille, France

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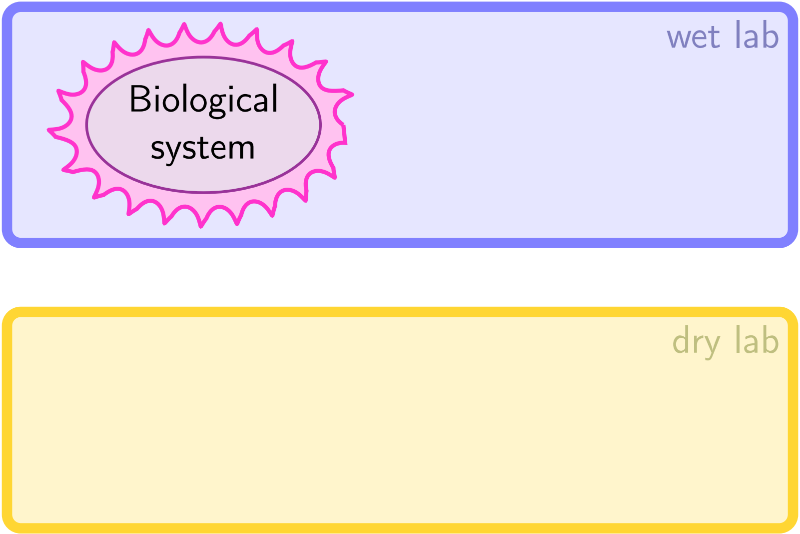
Master Data Science Seminar

Joint work with: Tony Ribeiro (Independant researcher, France),
Omar Ikne (Univ. Lille, France),
Morgan Magnin (Centrale Nantes, France),
Katsumi Inoue (NII, Tokyo, Japan)

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

In Silico Model and Experiments



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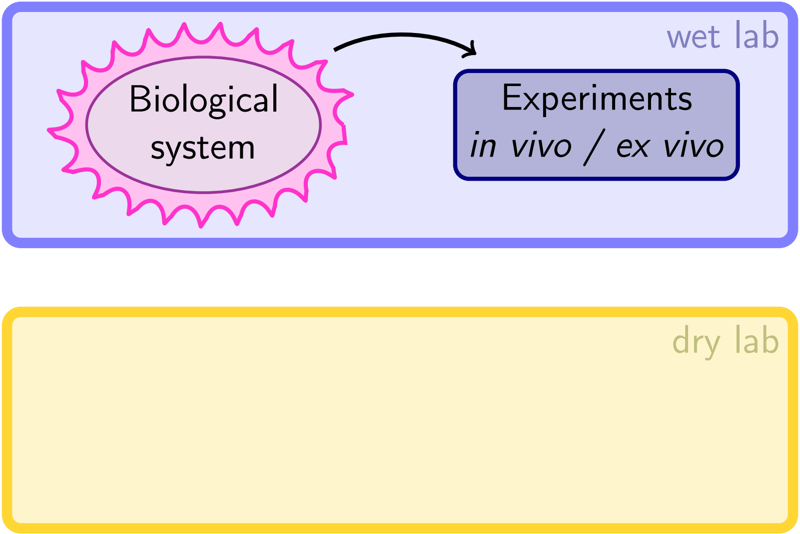

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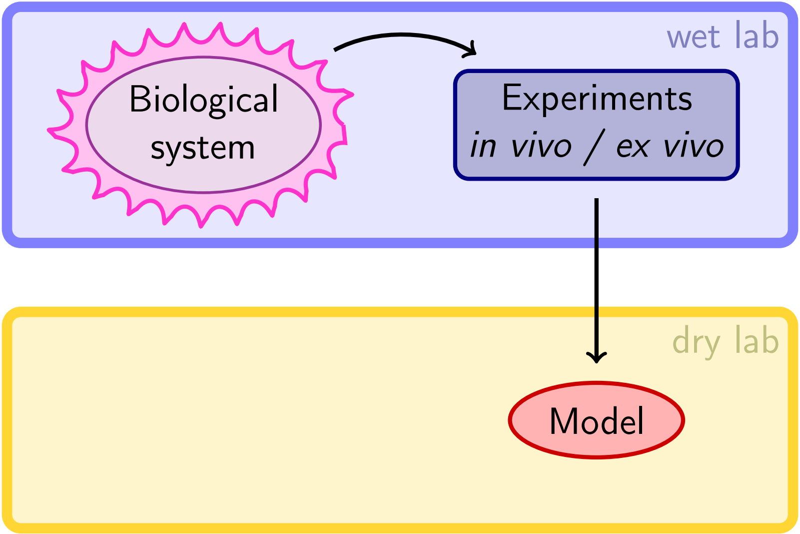

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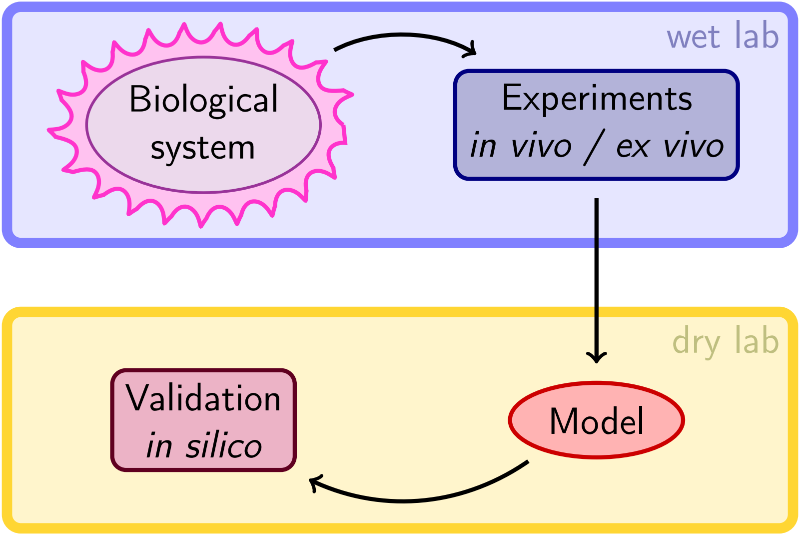

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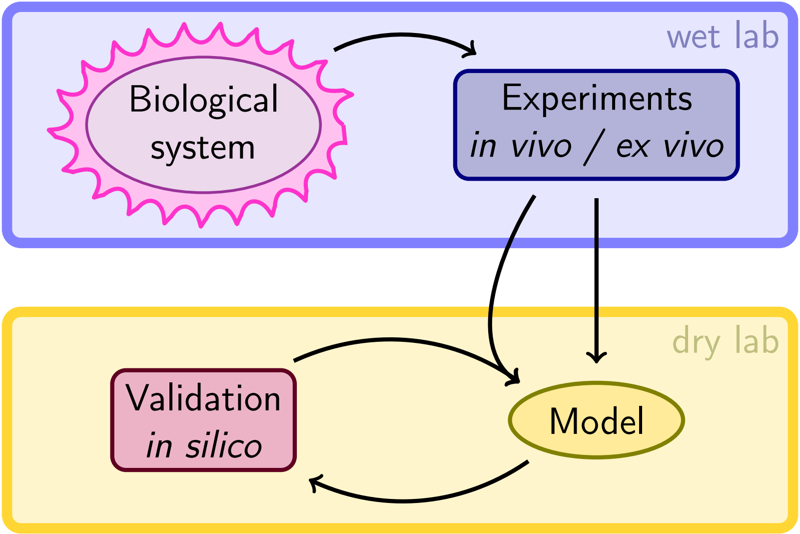

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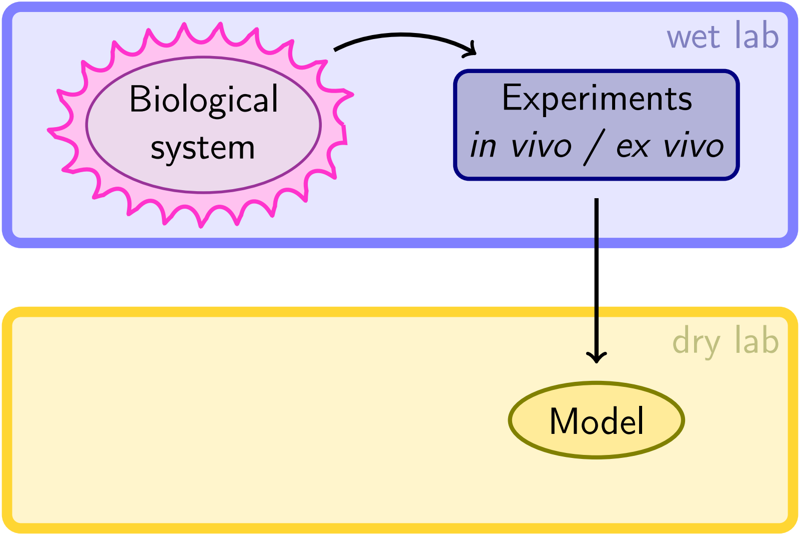

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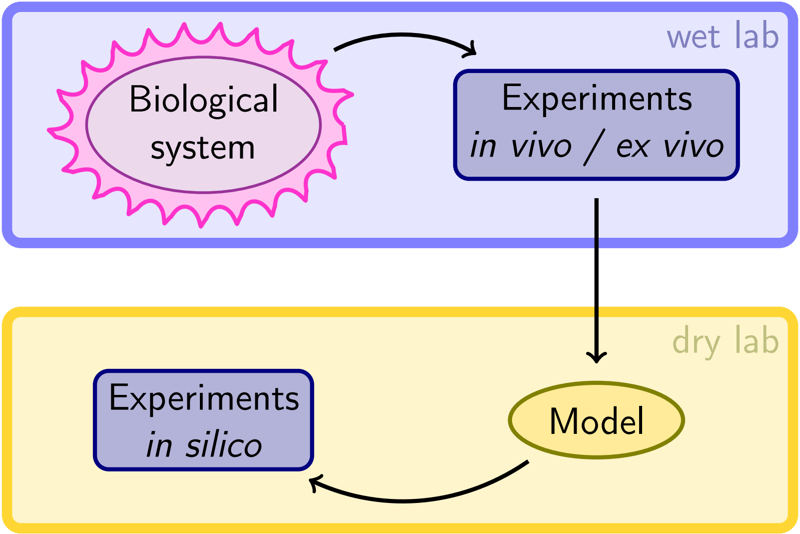

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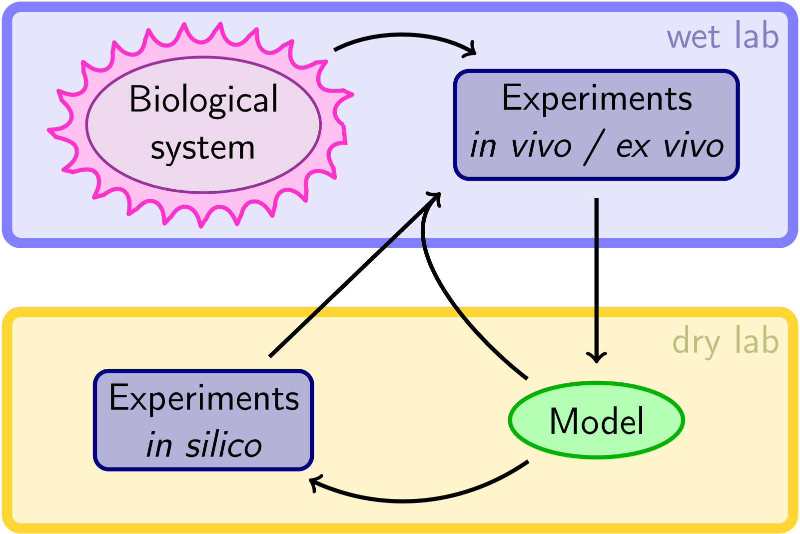

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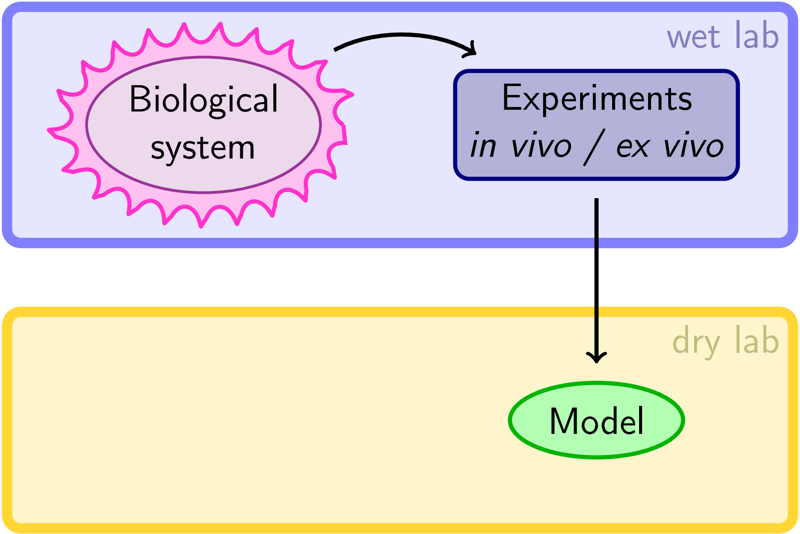

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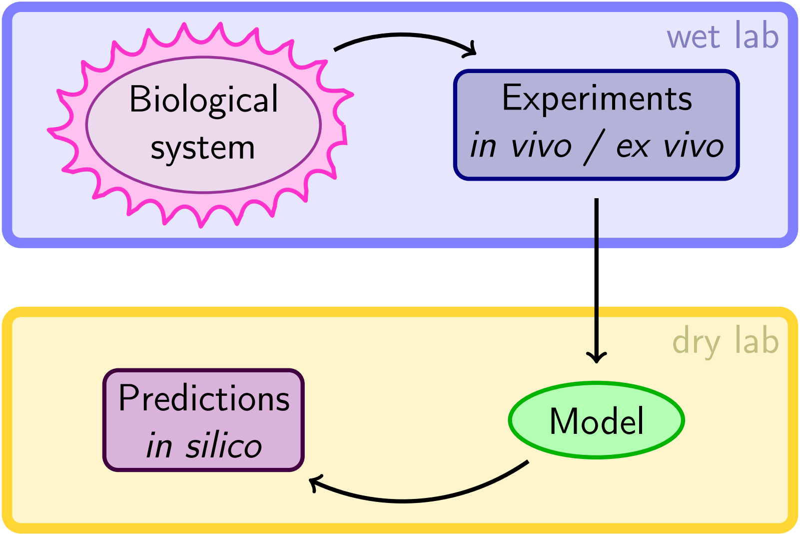

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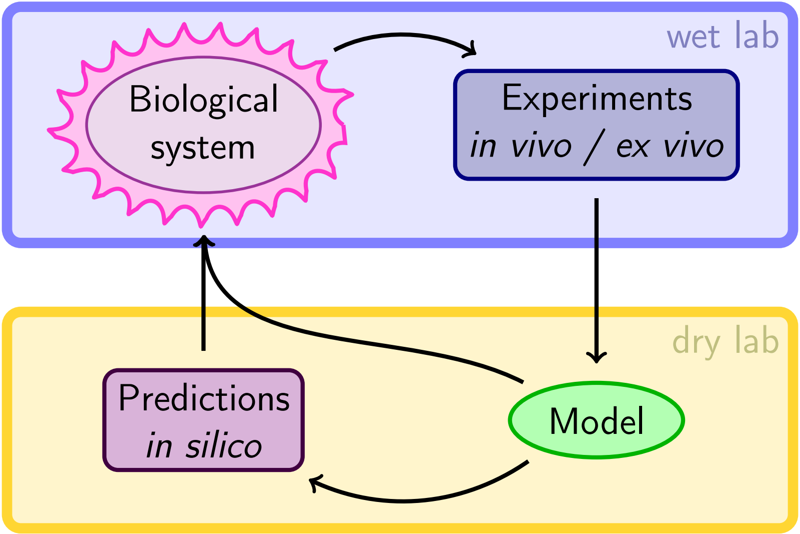
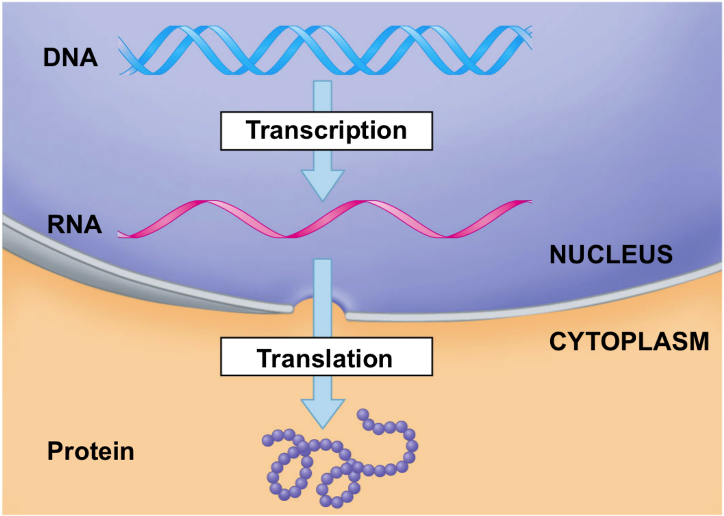


Preliminary Abstraction



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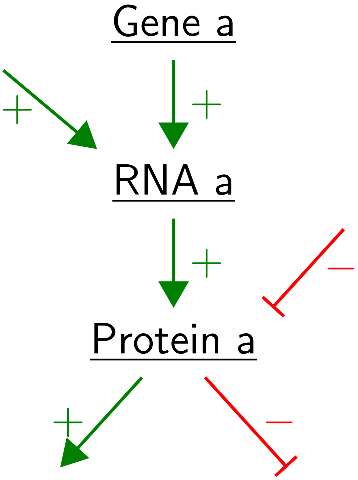

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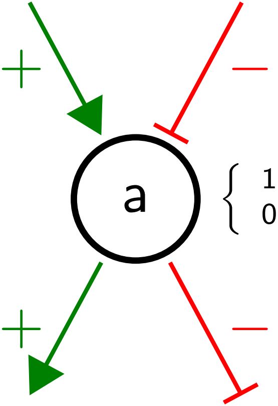


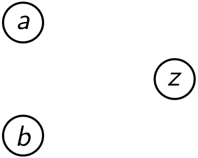
$$\left\{ \begin{array}{l} 1 = \text{active} \\ 0 = \text{inactive} \end{array} \right\}$$

Biological Regulatory Networks

Discrete Networks / Thomas Modeling

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

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



Discrete Networks / Thomas Modeling

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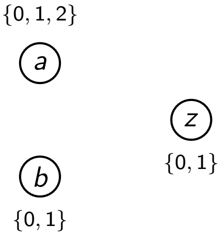

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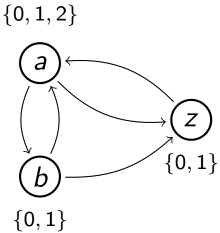
- Discrete parameters / evolution functions $f_a : \mathcal{S} \to \mathrm{dom}(a)$



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

Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
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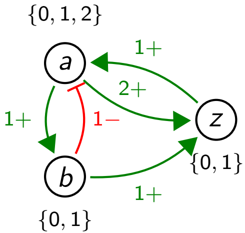
- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = \{0, 1, 2\}$
- Discrete parameters / evolution functions $f_a : \mathcal{S} \to \mathrm{dom}(a)$
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



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

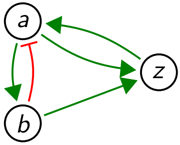
a	b	f_z
0	0	0
0	1	0
1	0	0
1	1	0
2	0	0
2	1	1

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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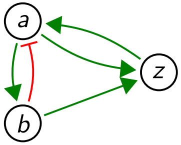
abz

000 010 001 011

100 ⟶ 110 101 111

200 210 201 211



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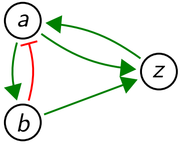
abz

$$\begin{tikzcd}
000 & 010 & 001 & 011 \\
100 \arrow[r] & 110 \arrow[u] & 101 & 111 \\
200 & 210 & 201 & 211
\end{tikzcd}$$



$+ \; f_a, \; f_b, \; f_c$

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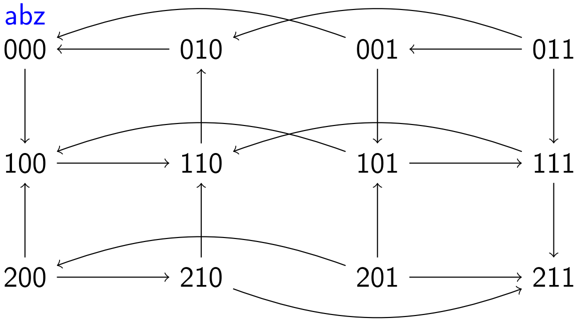

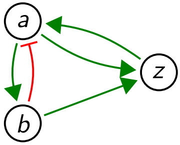

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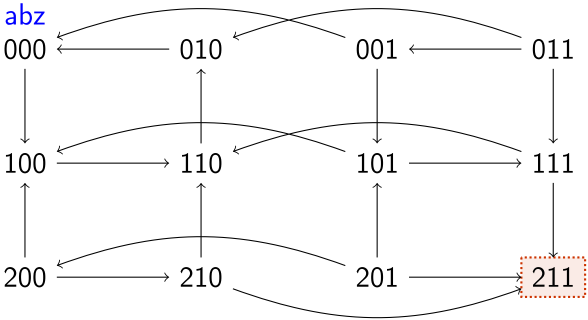

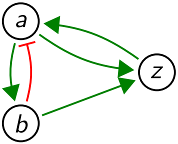

$+ f_a, f_b, f_c$

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

State Graph

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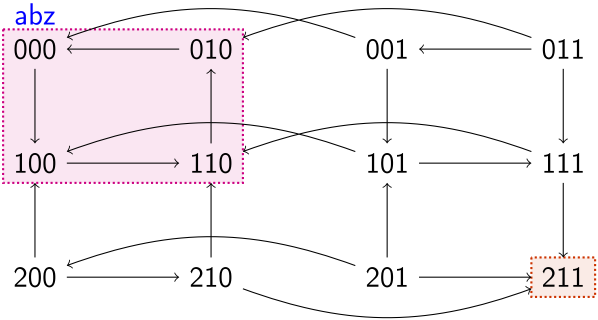

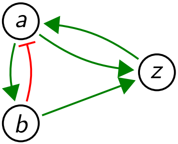

$+ \ f_a, \ f_b, \ f_c$

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

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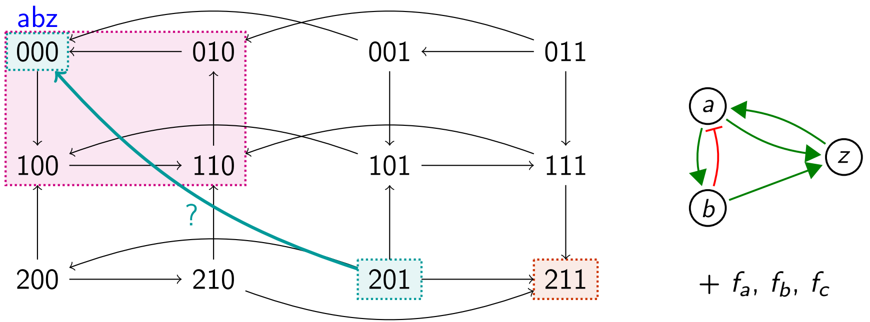

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- **Reachability** = from 201, can I reach 000?

State Graph

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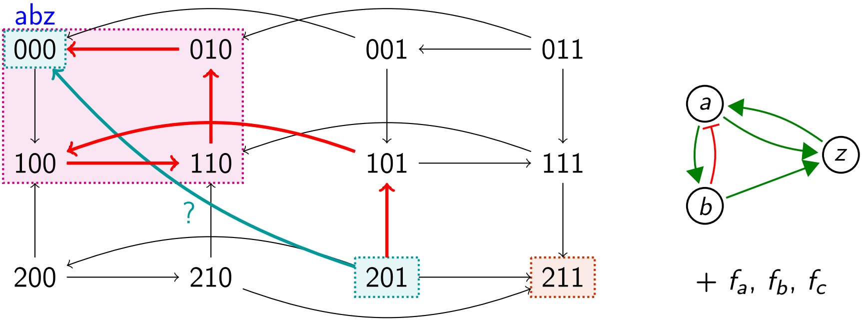


- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from 201, can I reach 000?

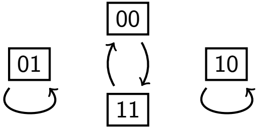
Semantics

$f_a = \neg b \qquad f_b = \neg a$

b	f_a
0	1
1	0

a	f_b
0	1
1	0

State transitions differ according to the update semantics used:



Synchronous

- **Synchronous**: all variables are updated

Semantics

$f_a = \neg b$ $\quad$ $f_b = \neg a$

b	f_a
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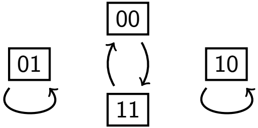
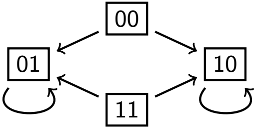


Synchronous



Asynchronous

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

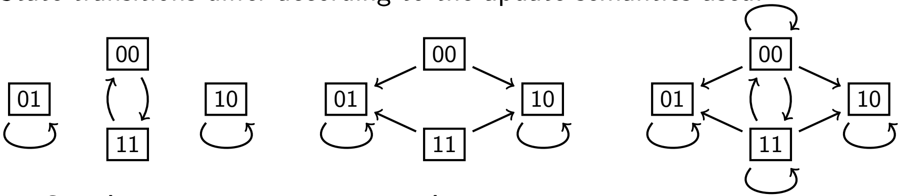
Semantics

$f_a = \neg b$ $\qquad$ $f_b = \neg a$

b	f_a
0	1
1	0

a	f_b
0	1
1	0

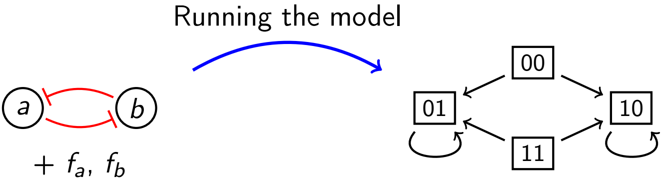
State transitions differ according to the update semantics used:



Synchronous $\qquad$ **Asynchronous** $\qquad$ **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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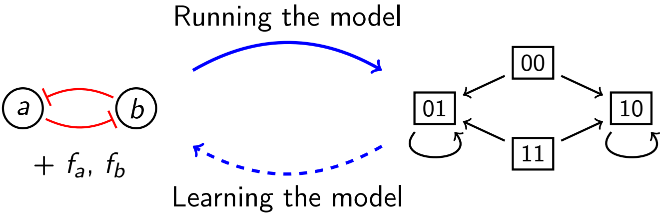

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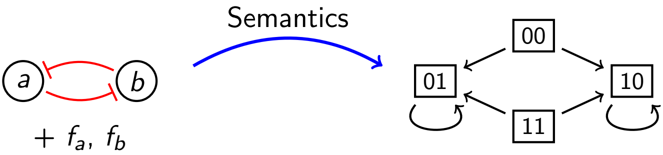

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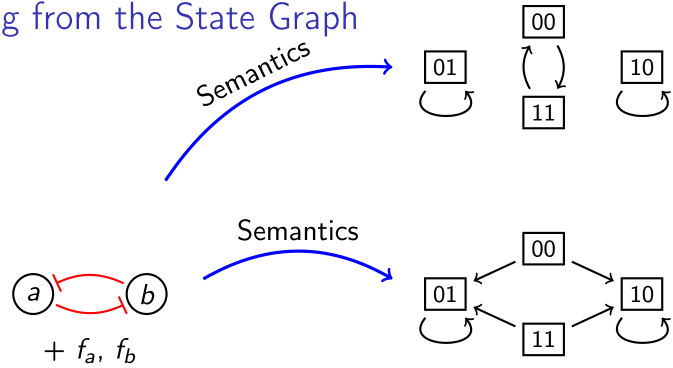

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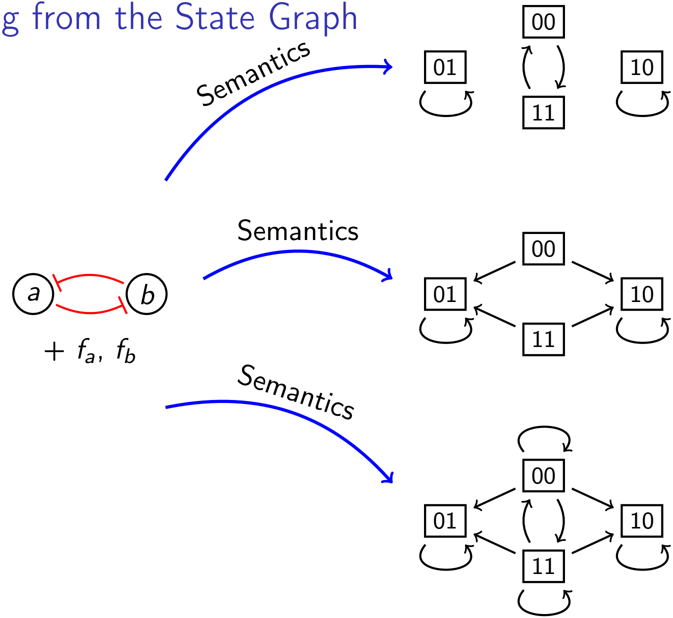

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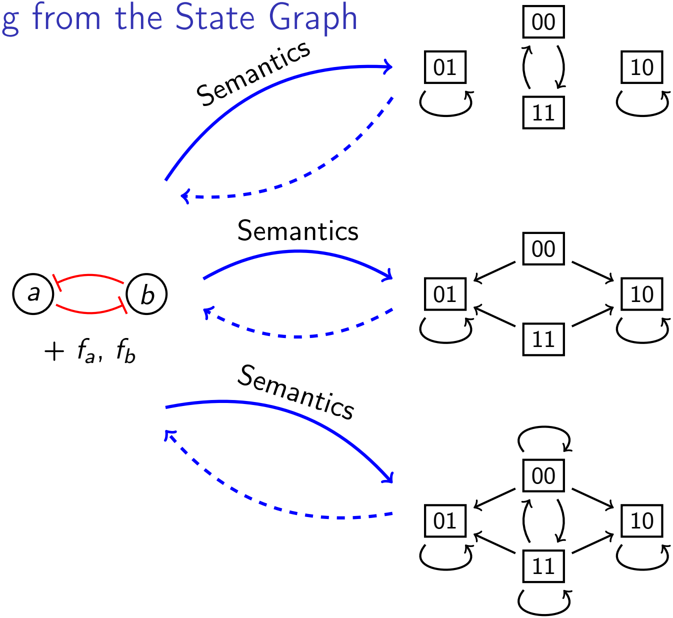
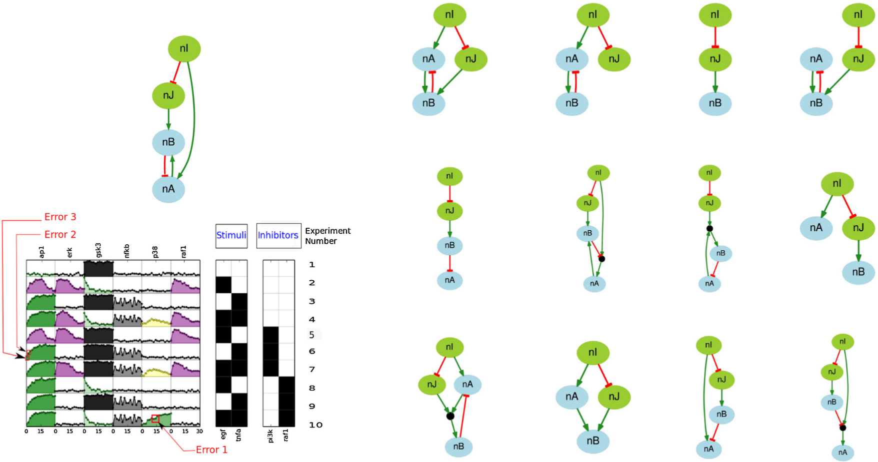


Other Approaches

CaspoTS

[M. Ostrowski, L. Paulevé, T. Schaub, A. Siegel, C. Guziolowski. Boolean network identification from perturbation time series data combining dynamics abstraction and logic programming. Biosystems, Volume 149, 2016, 139–153, ISSN 0303-2647.]



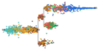
BoNesis

[S. Chevalier, C. Froidevaux, L. Paulevé, A. Zinovyev. Synthesis of Boolean Networks from Biological Dynamical Constraints using Answer-Set Programming. IEEE 31st International Conference on Tools with Artificial Intelligence (ICTAI), Portland, USA, 2019, 34–41, DOI 10.1109/ICTAI.2019.00014.]

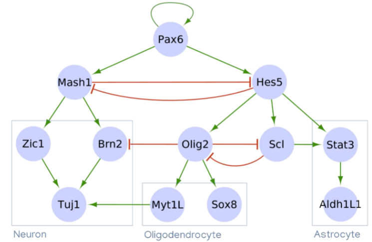
Main lines of the logic program:

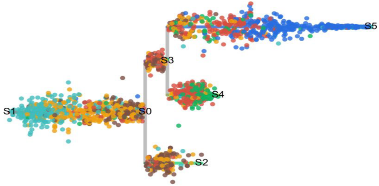
- the description of a BN
- the domain of its functions
  = *PKN*

- the way to compute its dynamic
  = *semantics*
- the properties of its dynamics
  = *observations*



The solver enumerates the solutions
(solutions = BNs compatible with data = models)





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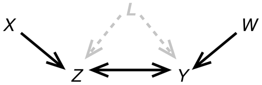
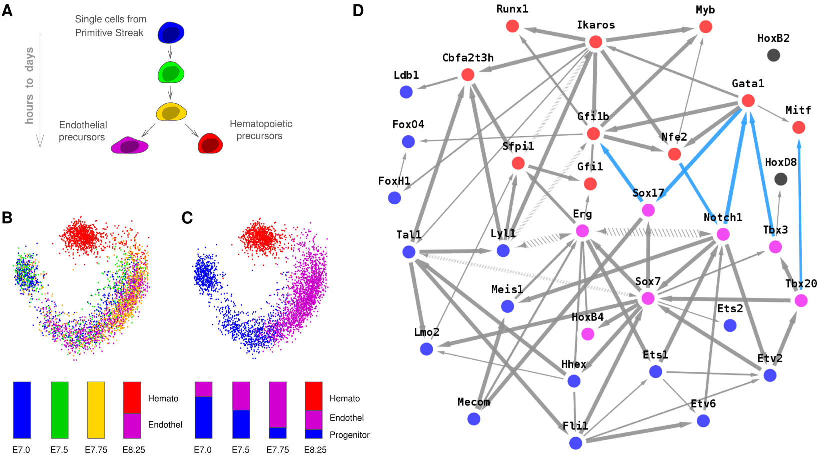
[L. Verny, N. Sella, S. Affeldt, P. P. Singh, H. Isambert. Learning causal networks with latent variables from multivariate information in genomic data. PLoS computational biology, 13(10), 2017, DOI 10.1371/journal.pcbi.1005662.]





Learning From Interpretation Transition (LFIT)

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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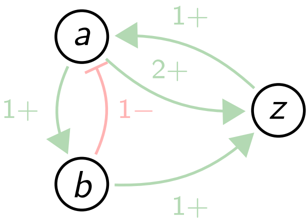
One can run a logic program. The same notion of semantics applies.

Discrete Models as Logic Programs

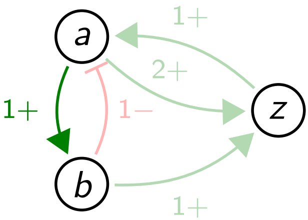
Discrete model:



Logic program:

Discrete Models as Logic Programs

Discrete model:



Logic program:

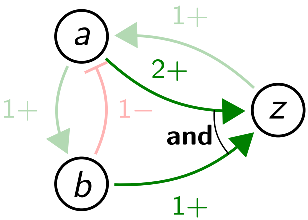
$b_1 \leftarrow a_1.$

$b_1 \leftarrow a_2.$

$b_0 \leftarrow a_0.$

Discrete Models as Logic Programs

Discrete model:



Logic program:

$b_1 \leftarrow a_1.$

$b_1 \leftarrow a_2.$

$b_0 \leftarrow a_0.$

$z_1 \leftarrow a_2, b_1.$

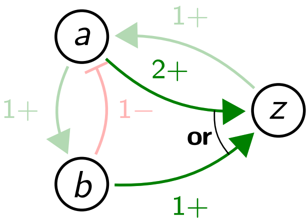
$z_0 \leftarrow a_0.$

$z_0 \leftarrow a_1.$

$z_0 \leftarrow b_0.$

Discrete Models as Logic Programs

Discrete model:



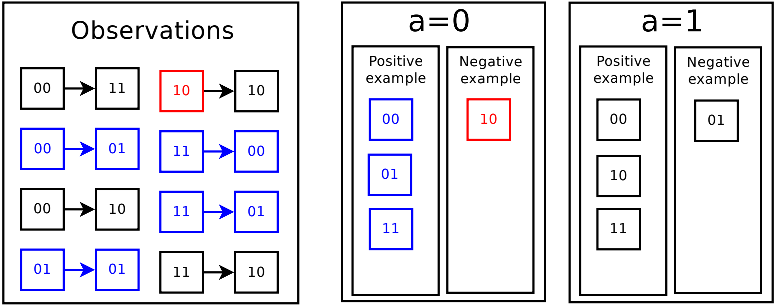
Logic program:

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

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

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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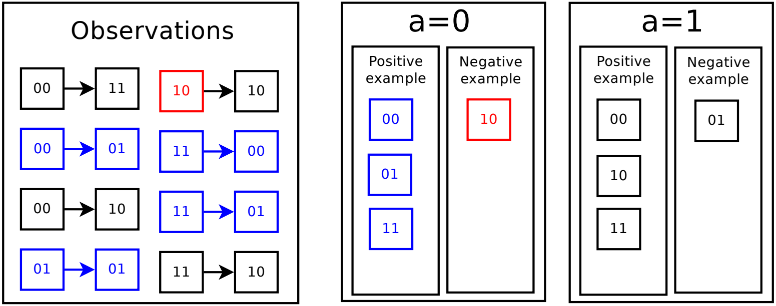

Equivalent to a **classification problem**: What is a typical state where a can take value 0 in the next state ? Here: when a_0 or b_1 is present.

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:

$$
\begin{array}{lll}
a_0 \leftarrow . & b_0 \leftarrow . & c_0 \leftarrow . \\
a_1 \leftarrow . & b_1 \leftarrow . & c_1 \leftarrow . \\
 & & c_2 \leftarrow .
\end{array}
$$

With this program, everything is always possible

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:

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

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

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(More general)

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GULA: Final Result

The output of GULA respects some good properties:

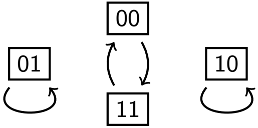
- **Consistency**: the program allows no negative examples
- **Realization**: the program covers all positive examples
- **Completeness**: the program covers all the state space
- **Minimality** of the rules (most general conditions)

Example: Synchronous Semantics

$f_a = \neg b$ $\quad$ $f_b = \neg a$

b	f_a
0	1
1	0

a	f_b
0	1
1	0



Synchronous

$// \ f_a = \neg b$

$a_0 \leftarrow b_1$

$a_1 \leftarrow b_0$

$// \ f_b := \neg a$

$b_0 \leftarrow a_1$

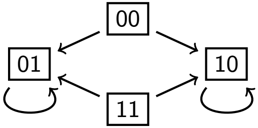
$b_1 \leftarrow a_0$

Example: Asynchronous Semantics

$f_a = \neg b$ $f_b = \neg a$

b	f_a
0	1
1	0

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

$a_0 \leftarrow a_0$

$a_1 \leftarrow a_1$

$b_0 \leftarrow b_0$

$b_1 \leftarrow b_1$

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 ⇒ **probability** P
- Rules with highest weights ⇒ **explanation** E

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

Likeliness rules	**Unlikeliness rules**
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$(15, a_1 \leftarrow b_0)$	$(5, a_1 \leftarrow c_0)$

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

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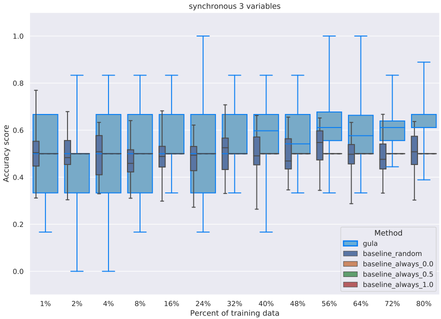
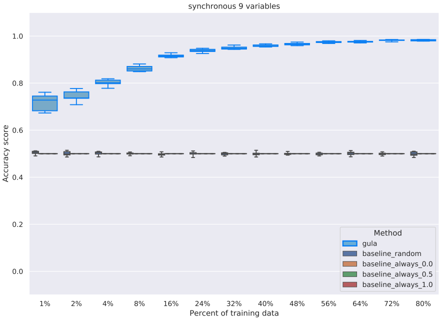
$\text{predict}(a_1, \langle a_1, b_0, c_0\rangle) = (0.75, ((15, a_1 \leftarrow b_0), (5, a_1 \leftarrow c_0))) \Rightarrow$ Likely

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

Prediction power



3 variables



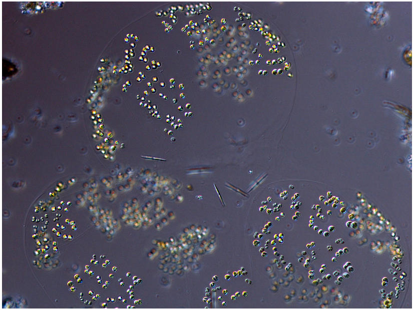
9 variables

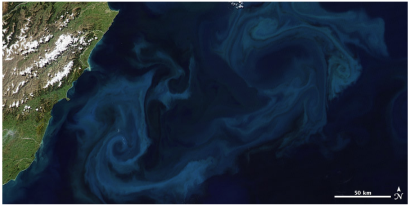
Training data = X% of transitions

Tested against unseen states (not in the training data)

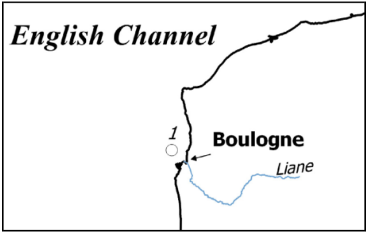
Application: Dynamics of Marine Phytoplankton

Phytoplankton Blooms





SRN Dataset



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

Sampling location	Sampling date	Taxon	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

- Pre-processing: data cleaning + discretization
- Train set: 253 transitions
- Test set: 53 transitions

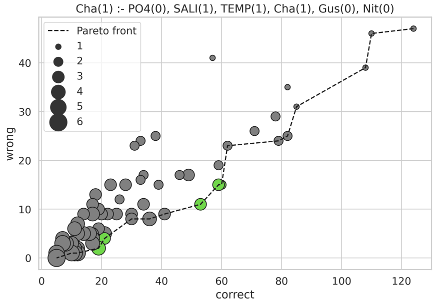
Output

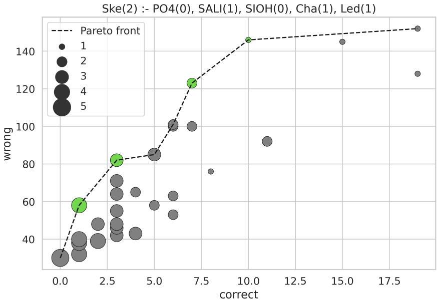
- Run time = 2.35s (**PRIDE**, greedy version of **GULA**)
- **1683** likeliness rules & **1981** unlikeliness rules
- Model accuracy: **0.670**

Model Improvement

Consider rules with subsets of conditions and compute a **Pareto frontier**

- For likeliness rules : maximize correct and minimize wrong weights
- For unlikeliness rules : maximize wrong and minimize correct weights





Accuracy improvement: 0.670 → **0.716**

Likeliness rules: 1683 → **1609**

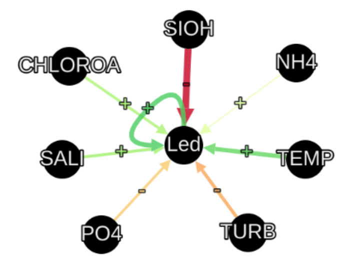
Unlikeliness rules: 1981 → **1405**

Global Influences

Process: Search and count patterns in rules that characterize an activation/inhibition
Result: Score $[-1; +1]$ between each pair of variables

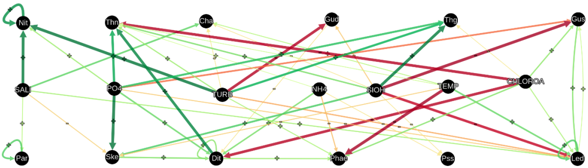
Influences on phytoplankton species `Led`:

Variable	Positive	Negative	Global
`PO4`	$+0$	-58	-0.36
`SALI`	$+71$	-4	$+0.42$
`CHLOROA`	$+84$	-22	$+0.39$
`SIOH`	$+3$	-161	-0.98
`NH4`	$+25$	-5	$+0.12$
`TEMP`	$+106$	-5	$+0.63$
`TURB`	$+10$	-87	-0.48

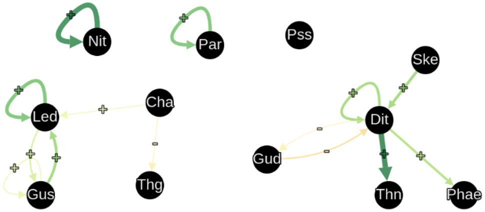


$$\text{global\_influence}(\texttt{PO4} \rightarrow \texttt{Led}) = \frac{+0 + (-58)}{161} = -0.36$$

Results



Global influence graph (biotic and abiotic interactions)



Biotic interactions (between phytoplankton only)

Very few biotic interactions...
Ongoing work: integrate knowledge + validate results

Conclusion

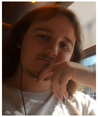
Conclusion

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

Outlooks:

- **PRIDE**: polynomial algorithm that "misses" some explanations
- Improve the application (integrate existing knowledge)
- Improve the biological network inference

Thanks



Tony
RIBEIRO

Omar
IKNE

Morgan
MAGNIN

Katsumi
INOUE

Cédric
LHOUSSAINE

Sébastien
LEFEBVRE

Madeleine
EYRAUD

Bibliography

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