Learning Biological Regulatory Networks from Time Series with LFIT: Theory and Practice

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Workshop on network and model inference (CIRM)

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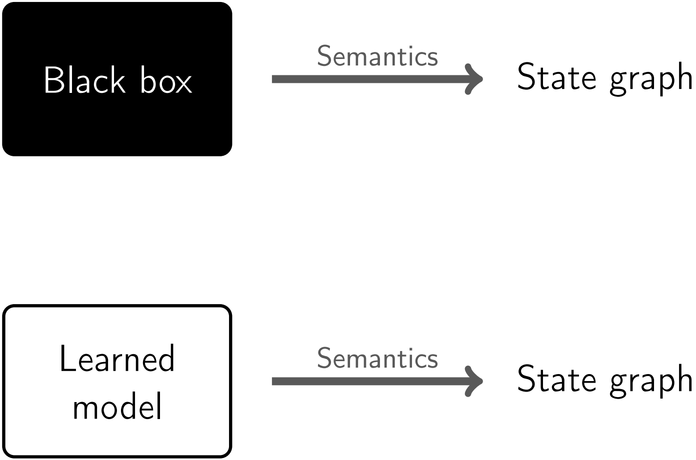
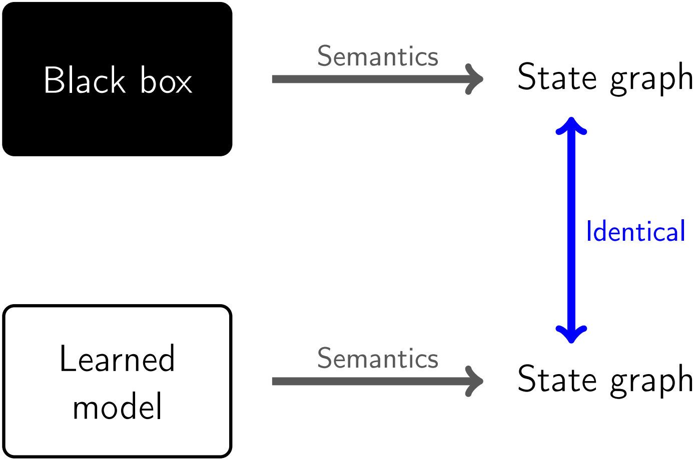
Morgan Magnin (Centrale Nantes, France),
Katsumi Inoue (NII, Tokyo, Japan)

Outline

Introduction



Introduction



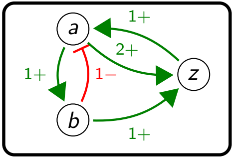
Introduction

Black box

Semantics

State graph

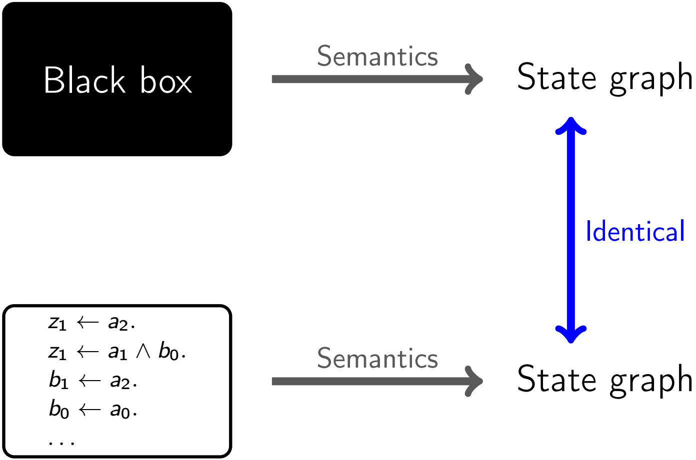
Identical



Semantics

State graph

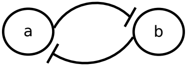
Introduction



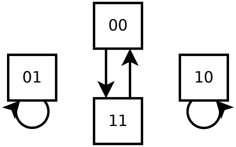
General Definitions

Dynamical Semantics

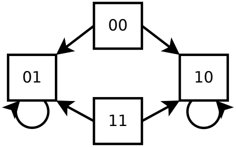
A Boolean network is a (syntactical) structure.
It must be interpreted with a semantics to run.



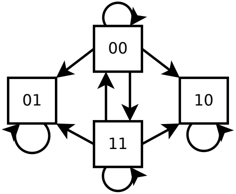
f(a) := not b.
f(b) := not a.



Synchronous



Asynchronous

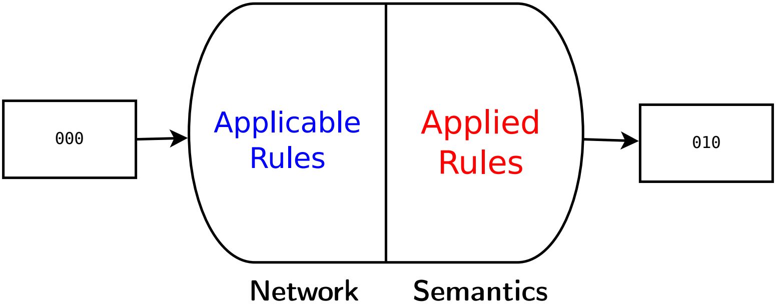


General

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

Definition of Semantics

In a given state, among the possible changes permited by the network (structure), the semantics select which ones to apply and how to combine them.



Logic Rules

LFIT learns a logic program, which is a set of logic rules.
It is an alternative representation of biological networks.

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

The network states that 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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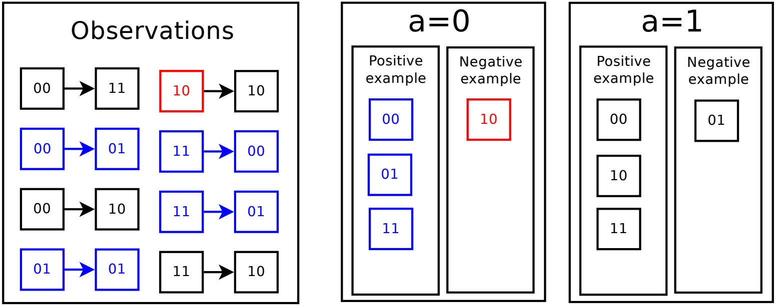
a **can** change its value to 1 anytime.

When **will** a take value 1? This depends on the semantics

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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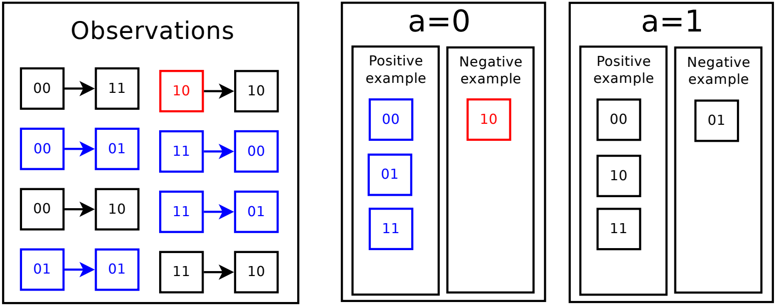

Equivalent to a **classification problem**: What is a typical state where a can take value 0 in the next state ? Here: when a_0 or b_1 is present.

$$a_0 \leftarrow a_0. \qquad a_0 \leftarrow b_1.$$

Presentation of GULA

GULA = General Usage LFIT Algorithm

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

Output: a logic program that 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 conditions)

Method: start from most general rules and **specialize** iteratively.

Minimal refinements

Suppose: $\text{dom}(a) = \text{dom}(b) = \{0, 1\}$ and $\text{dom}(c) = \{0, 1, 2\}$
and 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.

Minimal refinement to make the rules inapplicable in this state:

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

$a_1 \leftarrow b_1.$
(No change)

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(More general)

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Results

Tony Ribeiro, Maxime Folschette, Morgan Magnin and Katsumi Inoue. **Learning any memory-less discrete semantics for dynamical systems represented by logic programs**. *Machine Learning* 111, Springer. November 2021. `https://doi.org/10.1007/s10994-021-06105-4`

- **Allows to learn the network** (structure of the model)
- **Independent of the semantics**
  (characterization of applicable memoryless semantics)

Nice in theory, but in practice?

- **Exponential complexity** $\rightarrow$ How to handle big datasets?
  (many transitions, many variables)
- **Exact learning** $\rightarrow$ How to handle noise?

Two Heuristic on LFIT

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

Statistical overlay $\Rightarrow$ usable on **noisy datasets**

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

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

$(3, a_0 \leftarrow b_1)$

$(15, a_1 \leftarrow b_0)$

Unlikeliness rules

$(30, a_0 \leftarrow c_1)$

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

$\text{predict}(a_1, \langle a_1, b_1, c_0\rangle) = (0.75, ((15, a_1 \leftarrow b_0), (5, a_1 \leftarrow c_0)))$ ⇒ Likely

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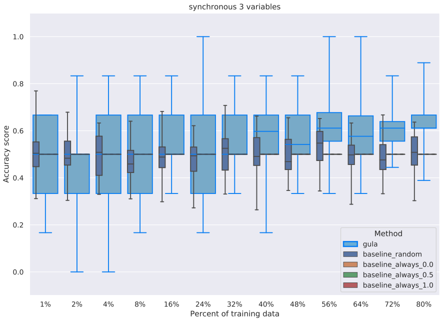
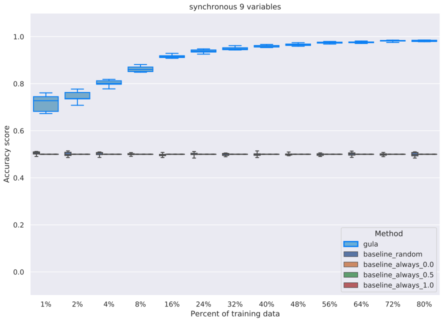
$\text{predict}(a_0, \langle a_1, b_1, c_0 \rangle) = (0.09, ((3, a_0 \leftarrow b_1), (30, a_0 \leftarrow c_1)))$ ⇒ Unlikely

Prediction power



3 variables



9 variables

Training data = X% of transitions
Tested against unseen states (not in the training data)

PRIDE: Polynomial Alternative to GULA

GULA: **Exponential complexity** in the number of variables

PRIDE: Greedy version of **GULA** that only keeps the first compatible minimal refinement ⇒ subset of rules

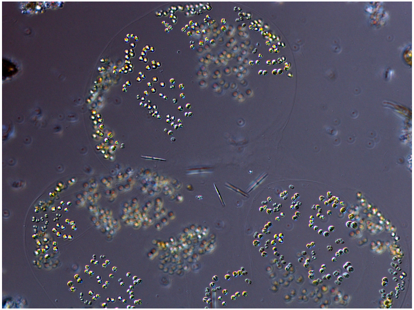
- **Consistency**: the program allows no negative examples
- **Realization**: the program covers all positive examples
- ~~**Completeness**: the program covers all the state space~~
- **Minimality** of the rules (most general conditions)

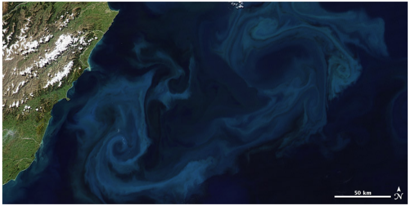
...And the results depends on the ordering of variables

Polynomial complexity ⇒ usable on **large datasets**

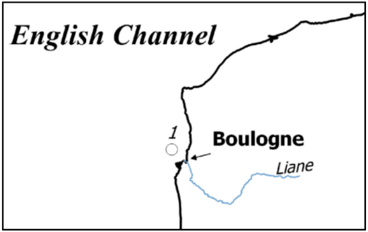
Application: Dynamics of Marine Phytoplankton

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
- 253 training transitions
- 53 testing transitions

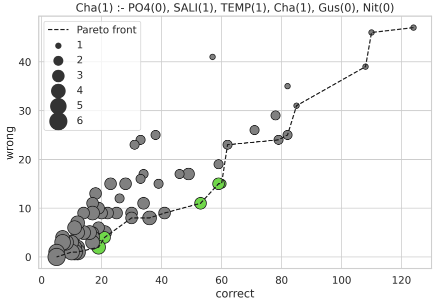
Output

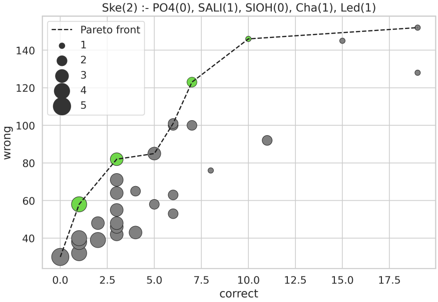
- Run time = 2.35s (**PRIDE**)
- 1683 likeliness rules
- 1981 unlikeliness rules
- Model accuracy: **0.670**

Model Improvement

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**

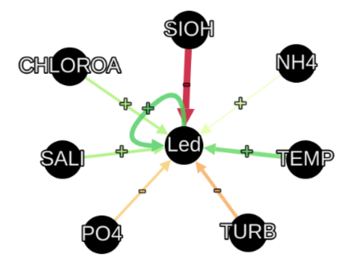
Unlikeliness rules: 1981 → **1405**

Global Influences

Process: Search and count patterns in rules that characterize an activation/inhibition
Hypotheses: Monotonous influences & same threshold for all variables
Result: Score $[-1; +1]$ between each pair of variables (no threshold)

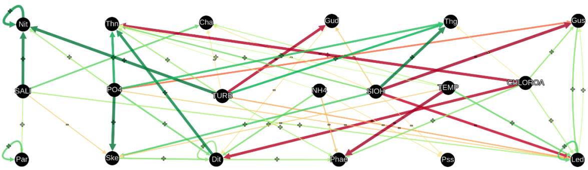
Influences on phytoplankton specie Led:

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

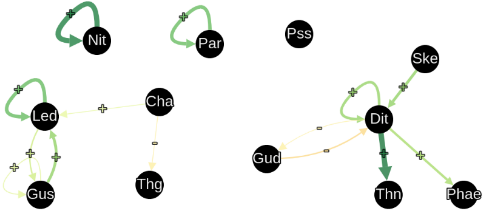


$$\text{global\_influence}(\texttt{PO4} \rightarrow \texttt{Led}) = \frac{+0 + (-58)}{161} = -0.36$$

Results



Global influence graph (biotic and abiotic interactions)



Biotic interactions (between phytoplankton only)

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

Conclusion

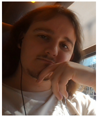
Conclusion

- **Learn** the network with LFIT (theory)
- **Heuristics** to tackle real data (practice)
- **Application** to phytoplankton

Outlooks:

- Quatify how many rules are “missed” by PRIDE
- Integrate biological knowledge to improve learning
- Improve the Biological network inference
- ...

Thanks



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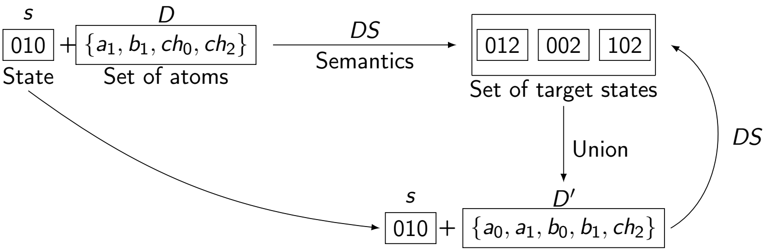
Bibliography

- About GULA: Tony Ribeiro, Maxime Folschette, Morgan Magnin and Katsumi Inoue. **Learning any memory-less discrete semantics for dynamical systems represented by logic programs**. *Machine Learning* 111, Springer. November 2021. `https://doi.org/10.1007/s10994-021-06105-4`
- pyLFIT Python library: `https://github.com/Tony-sama/pylfit`
- About PRIDE: Tony Ribeiro, Maxime Folschette, Morgan Magnin and Katsumi Inoue. **Polynomial Algorithm For Learning From Interpretation Transition**. Poster at the *1st International Joint Conference on Learning & Reasoning*. October 2021, Online. `https://hal.science/hal-03347026v1`
- About the application: Omar Iken, Maxime Folschette and Tony Ribeiro. **Automatic Modeling of Dynamical Interactions Within Marine Ecosystems**. Poster in the *1st International Joint Conference on Learning & Reasoning*. October 2021, Online. `https://hal.science/hal-03347033v1`

Pseudo-idempotent semantics

GULA can model observations from any pseudo-idempotent semantics.



$$\longrightarrow DS(s, D) = DS\Big(s, \bigcup_{s' \in DS(s,D)} s'\Big)$$

where DS is the dynamical semantics, and D is set of heads of rules of a multi-valued logic program that match the sate s.