

# Identifying System Dynamics with Machine Learning

Tony Ribeiro

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Inoue Laboratory, NII, Tokyo

Nantes, April 9th 2018

# Outline

## 1 Who is this guy?

## 2 Background

- Machine Learning
- Logic Programming
- Inductive Logic Programming

## 3 PhD work

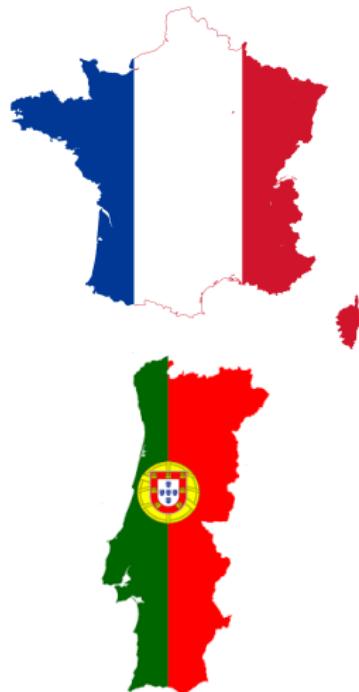
- Memoryless Systems
- Systems with Memory
- Non-Deterministic Systems

## 4 Postdoc Projects

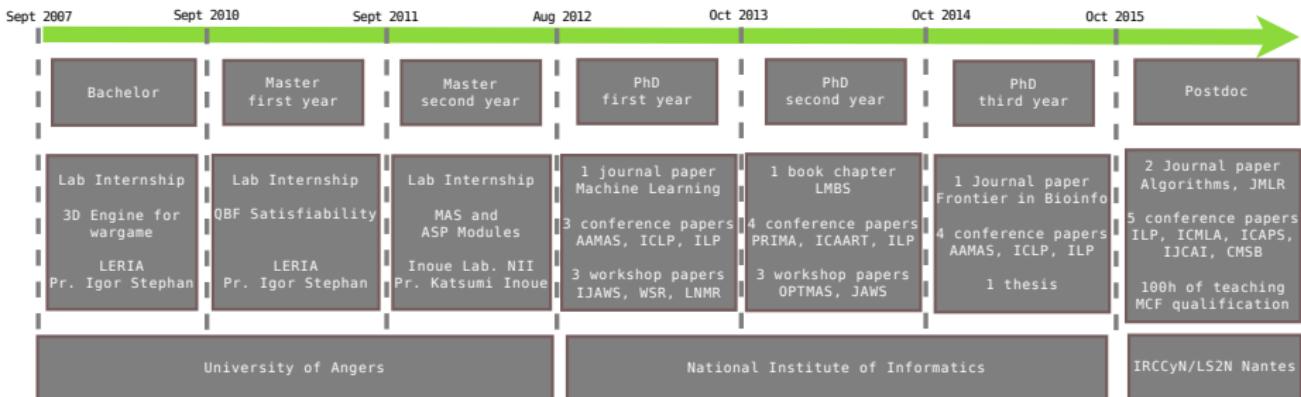
- Hyclock
- DREAM Challenge 11
- Biology institute of Valrose

## 5 Conclusion

# About Me



# Study



## Thesis:

Studies on Learning Dynamics of Systems from State Transitions

# Inoue Lab

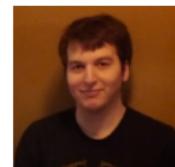


Morgan Magnin



Prof. Katsumi Inoue  
Main Research Topics

- Machine Learning
- Multi-agent System
- Multi-objective Optimization
- System Resilience



Maxime Clément



Kotaro Okazaki



Nicolas Schwind



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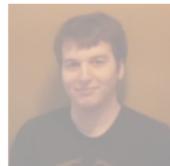


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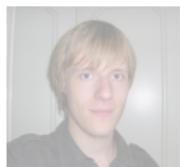
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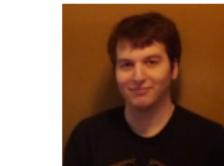


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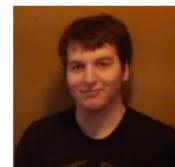


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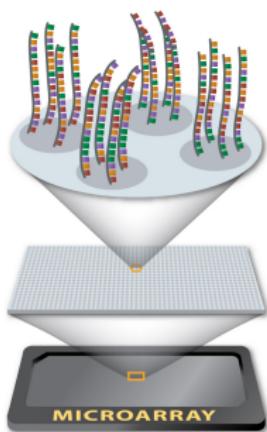
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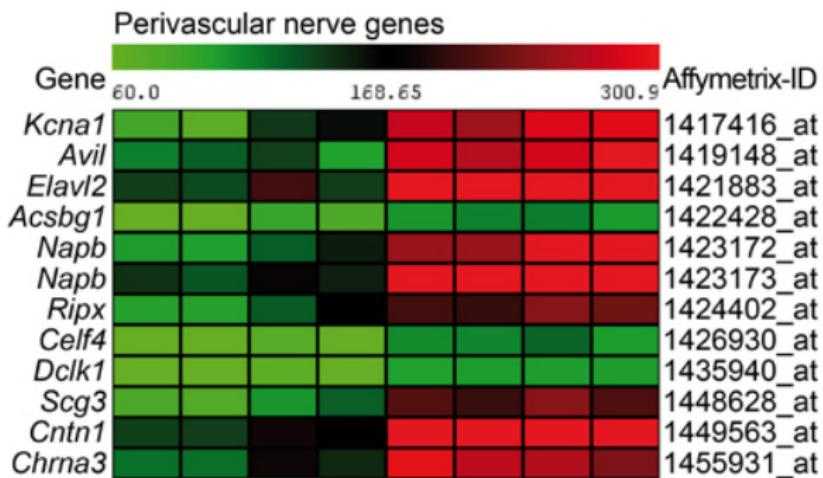
# Motivations

With the development of new measurement technologies a large amount of time series data is now produced every day.



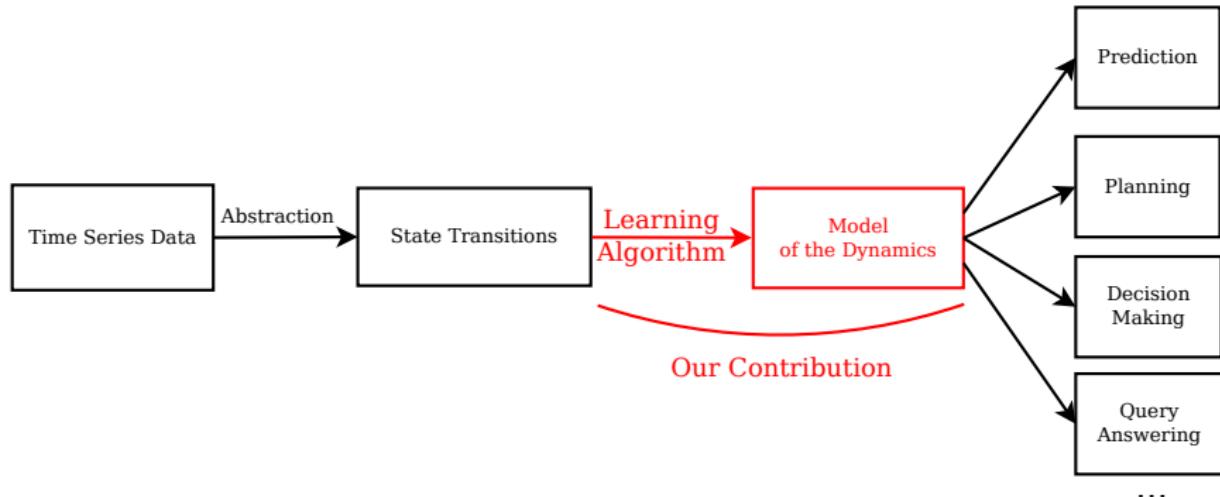
# Motivations

But data alone may be not sufficient: we need readability, usability.



Microarray data from Perivascular nerve genes (*Abd Alla et al. 2013*)

# Motivations



Problem:

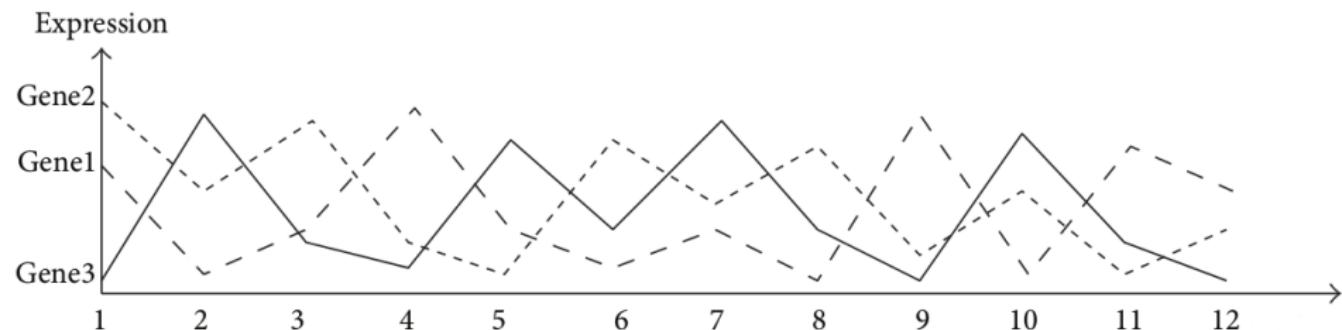
- Time series data alone are not sufficient, we need models.

Goal:

- Automated modeling of systems dynamics from these data.

# Abstraction: From Time Series Data to State Transitions

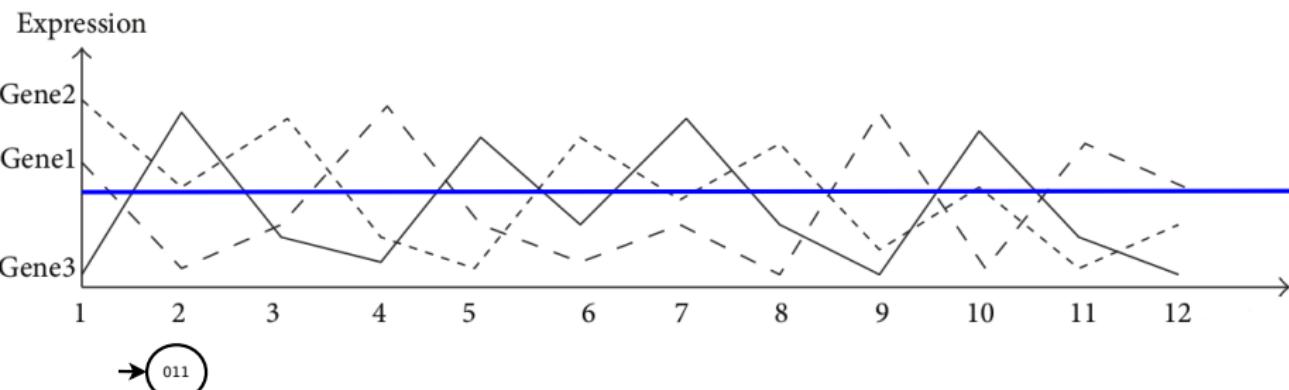
Time series data can be abstracted in many ways. It depends of what we know and what we want to learn about the system.



Time series data of gene expression (*Nakajima and Akutsu 2014*).

## Abstraction: From Time Series Data to State Transitions

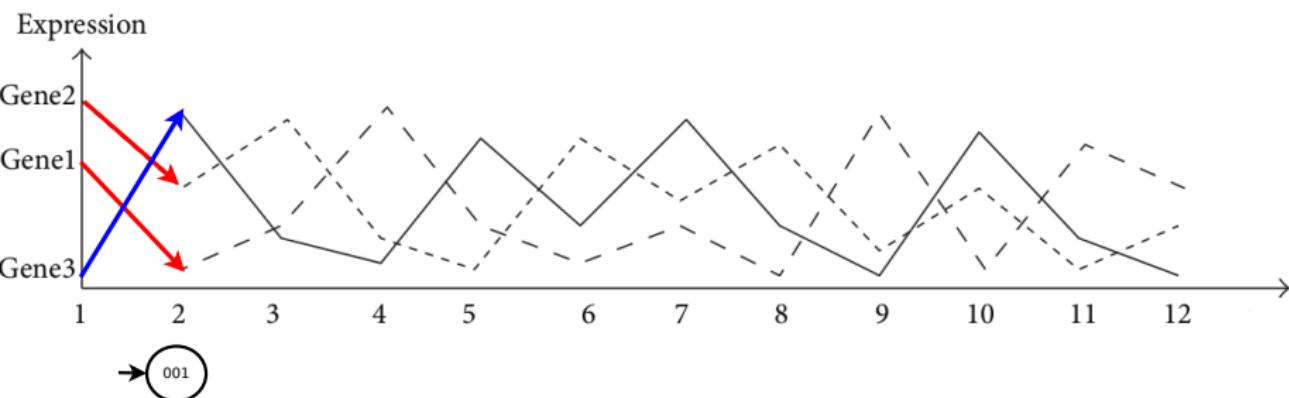
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We can set thresholds to discretize the level of expression of genes.

## Abstraction: From Time Series Data to State Transitions

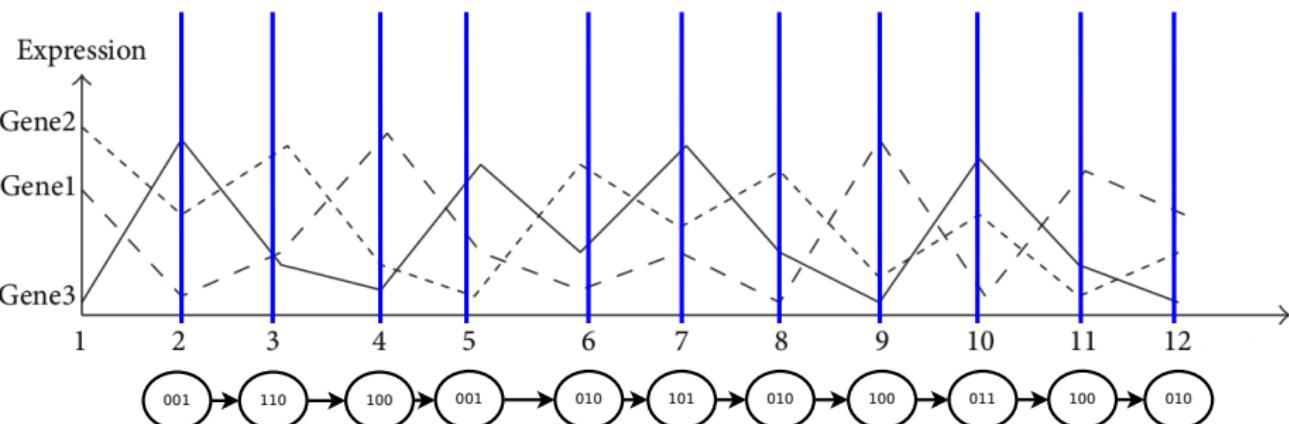
Time series data can be abstracted in many ways. It depends of what we know and what we want to learn about the system.



We can consider the concentration behavior (increase/decrease).

# Abstraction: From Time Series Data to State Transitions

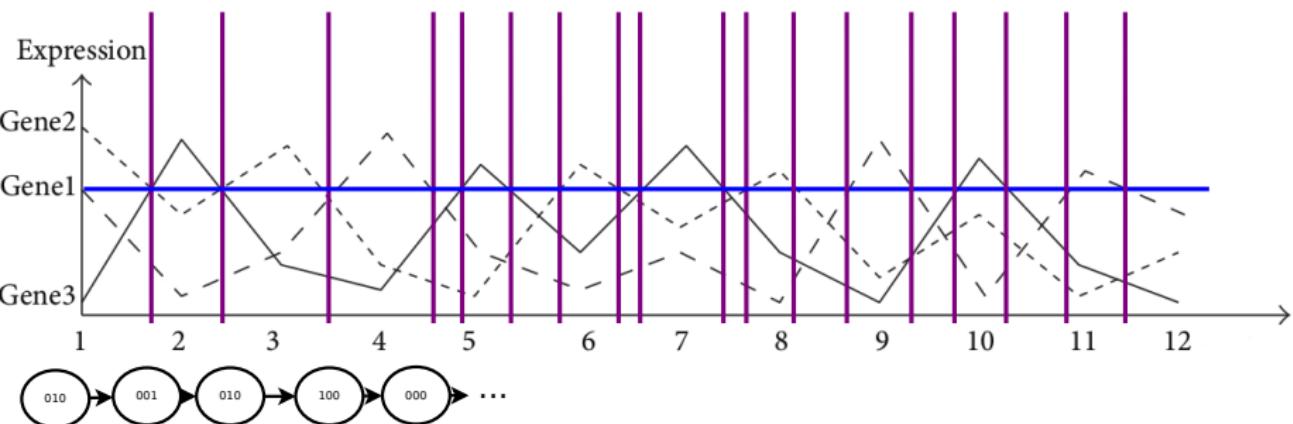
Time series data can be abstracted in many ways. It depends of what we know and what we want to learn about the system.



Transitions can be **time-based**: a state for each time unit.

# Abstraction: From Time Series Data to State Transitions

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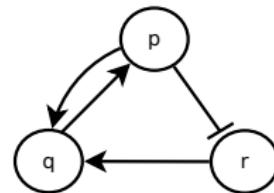
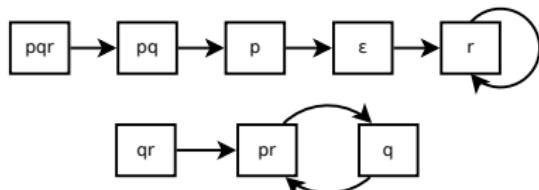
Transitions can be **event**-based: a state for each change.

# Learning From Interpretation Transitions (LFIT)

A framework for learning system dynamics from state transitions.

- Basic Idea:

- Learn a logic program by observing the behavior of a system.
- This logic program represents the dynamics of the system.



**Input:** Behavior of the system

**Output:** Dynamics of the system

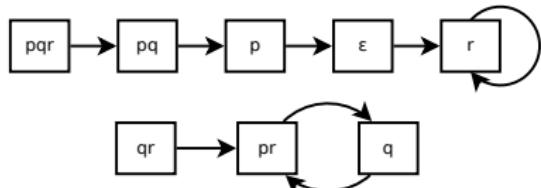
$$\begin{aligned}p(t+1) &\leftarrow q(t). \\q(t+1) &\leftarrow p(t) \wedge r(t). \\r(t+1) &\leftarrow \neg p(t).\end{aligned}$$

**Representation:** Logic Program

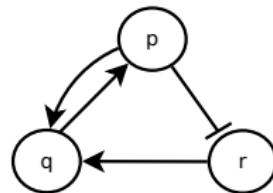
# Learning From Interpretation Transitions (LFIT)

# A framework for learning system dynamics from state transitions.

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## What happens



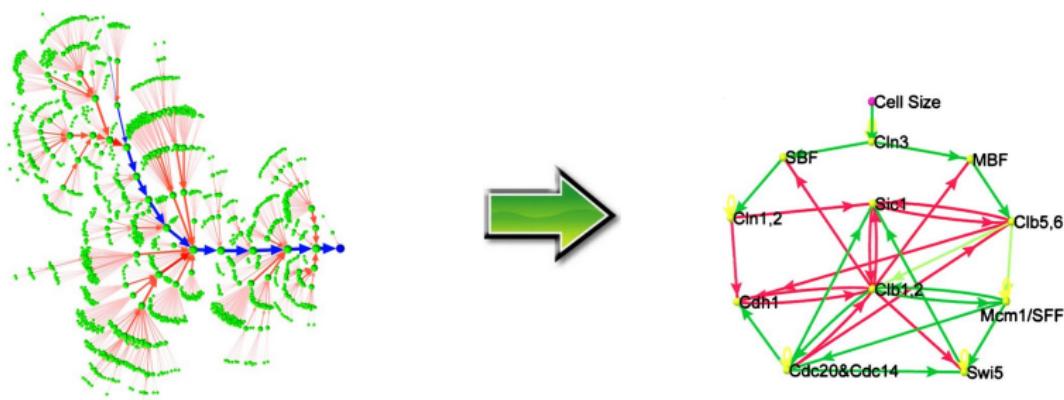
## Why it happens

$$\begin{aligned} p(t+1) &\leftarrow q(t). \\ q(t+1) &\leftarrow p(t) \wedge r(t). \\ r(t+1) &\leftarrow \neg p(t). \end{aligned}$$

## Representation: Logic Progam

# Applications in Bioinformatics

Construction of gene regulatory networks.



A state transition diagram (left) and the Boolean network of the *budding yeast* (right) (Li et al. 2004).

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## Background: Machine Learning

*Arthur Samuel, 1959:* “Field of study that gives computers the ability to learn without being explicitly programmed.”

The learning algorithms can be categorized according to the learning style they use:

## Supervised learning



Example: given a set of samples we want to learn what is a cat.

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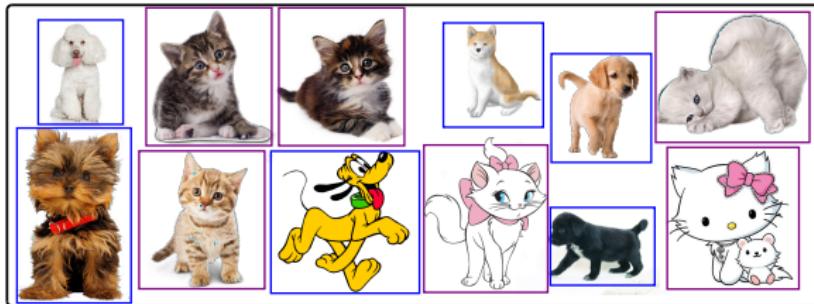
## Unsupervised learning



Example: given a set of samples, classify them into two groups.

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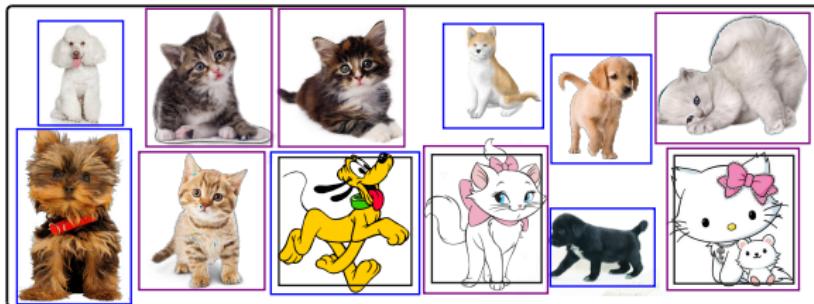
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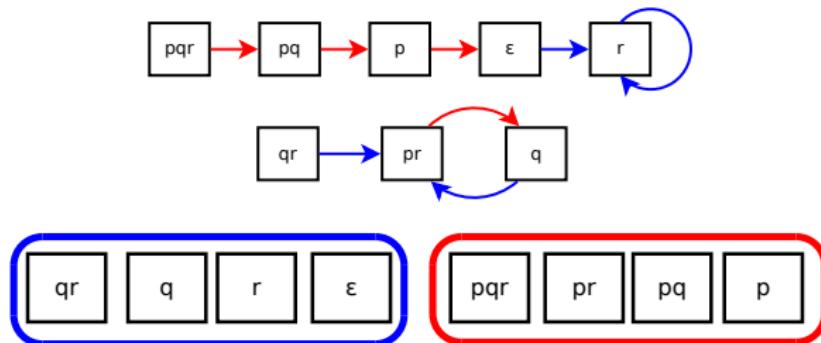
## Unsupervised learning



Example: given a set of samples, classify them.

## Example

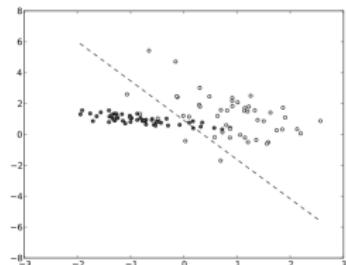
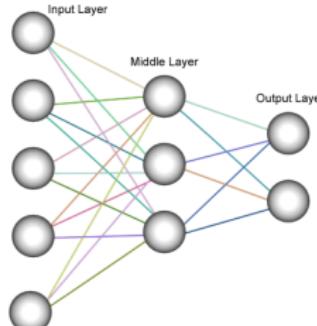
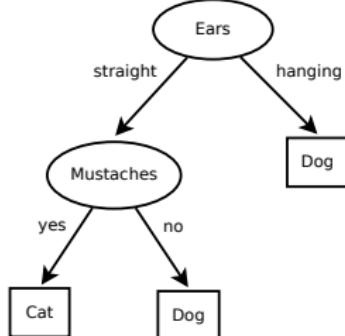
Our algorithms belong to supervised learning: samples are states labeled according to a variable value in next state:



The states where  $r$  is in next state and the ones where  $r$  is not.

## Example

From the samples, a machine learning algorithm learns a model:



There exists several model representations: decision tree, neural network, support vector machine...

# Example

From the samples, a machine learning algorithm learns a model:

## **Logic rules**

Cats if ears=straight and whiskers=yes.  
Dogs if ears=hanging or whiskers=no.

Example: rules which define cats and dogs.

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## Background: Logic Programming

Logic Programming is a form of programming, where a program is defined by a set of elementary facts and logic rules associating these facts with their (more or less) direct consequences.

```
cat ← ears_straight ∧ whiskers.  
dog ← ears_hanging.  
dog ← ¬whiskers.
```

Example: a logic program that defines what is *cat* and *dog*.

We consider a propositional *logic program*  $P$  as a set of *rules*  $R$  of the form

$$R := p \leftarrow p_1 \wedge \cdots \wedge p_m \wedge \neg p_{m+1} \wedge \dots \wedge \neg p_n \quad (1)$$

where  $p$  and  $p_i$ 's are atoms ( $n > m \geq 0$ ).

### Definition (Herbrand base)

The Herbrand base of a logic program  $P$ , denoted by  $\mathcal{B}$ , is the set of all ground atoms in the language of  $P$ .

### Example

- $R_1 = \text{cat} \leftarrow \text{ears\_straight} \wedge \text{whiskers}$
- $R_2 = \text{dog} \leftarrow \text{ears\_hanging}$
- $R_3 = \text{dog} \leftarrow \neg \text{whiskers}$
- $P = \{R_1, R_2, R_3\}$  is a logic program
- The Herbrand base of  $P$  is  
$$\mathcal{B} = \{\text{cat}, \text{dog}, \text{ears\_straight}, \text{ears\_hanging}, \text{whiskers}\}$$

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$$R := \textcolor{blue}{p} \leftarrow p_1 \wedge \cdots \wedge p_m \wedge \neg p_{m+1} \wedge \dots \wedge \neg p_n \quad (1)$$

- left part of  $\leftarrow$  is the *head* denoted  $h(R)$
- the conjunction to the right of  $\leftarrow$  is the *body* denoted  $b(R)$
- the positive part of the body is  $b^+(R)$
- the negative part of the body is  $b^-(R)$

### Definition (Interpretation)

Let  $\mathcal{B}$  be the Herbrand base of a logic program  $P$ . An *interpretation* is a subset of  $\mathcal{B}$ .

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### Definition ( $T_P$ Operator)

For a logic program  $P$  and an interpretation  $I$ , the *immediate consequence operator* (or  $T_P$  operator) is the mapping  
 $T_P : 2^{\mathcal{B}} \rightarrow 2^{\mathcal{B}}$ :

$$T_P(I) = \{ h(R) \mid R \in P, b^+(R) \subseteq I, b^-(R) \cap I = \emptyset \}. \quad (2)$$

The state transitions of a logic program  $P$  can be represented as a set of pairs of interpretations  $(I, T_P(I))$ .

In our methods, we represent and learn the **dynamics** of a system:  
**when** things happen, in which circumstances a variable takes which value. Using the  $T_P$  operator we can reproduce the state transitions.

$$\begin{aligned} p(t+1) &\leftarrow q(t). \\ q(t+1) &\leftarrow p(t) \wedge r(t). \\ r(t+1) &\leftarrow \neg p(t). \end{aligned}$$

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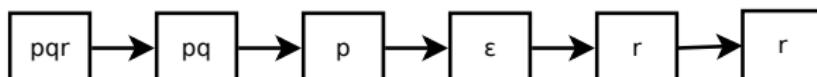
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## Example

- $T_P(\{p, q, r\}) = \{p, q\}$
- $T_P(\{p, q\}) = \{p\}$
- $T_P(\{p\}) = \emptyset$
- $T_P(\emptyset) = \{r\}$
- $T_P(\{r\}) = \{r\}$



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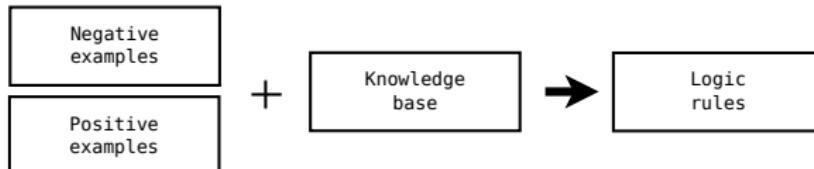
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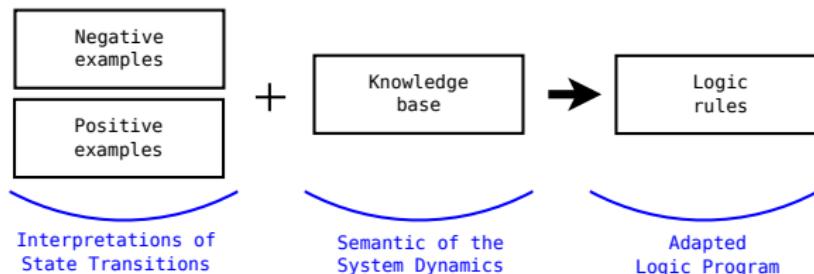
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What we do is a form of **Inductive Logic Programming** (ILP). From a base of positive and negative examples, an ILP system tries to deduce a logic program which confirms the positive examples and refutes the negative ones.



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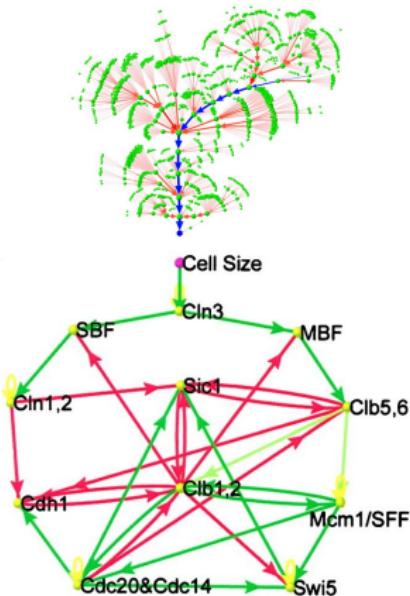
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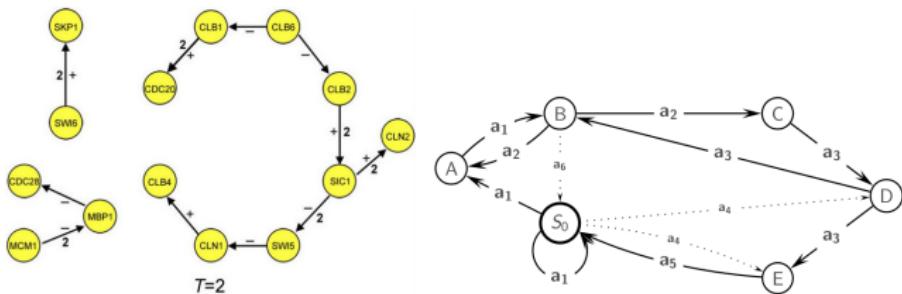
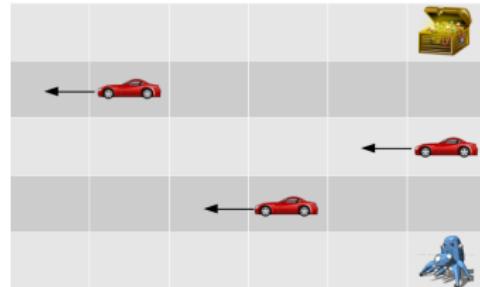
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# Contribution

We propose several algorithms that capture different types of dynamics.

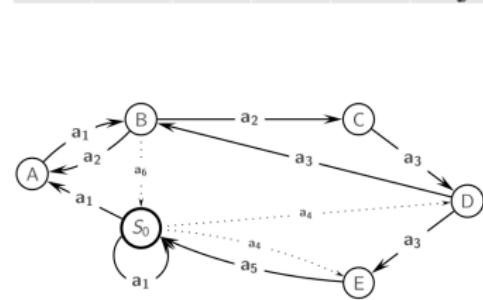
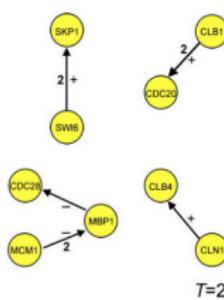
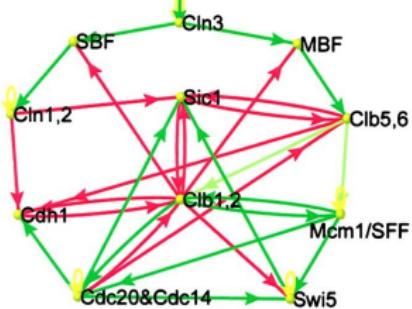
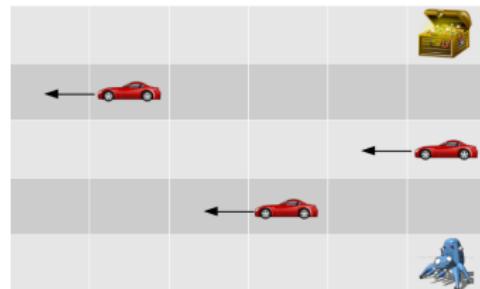
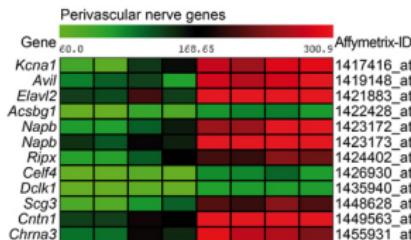
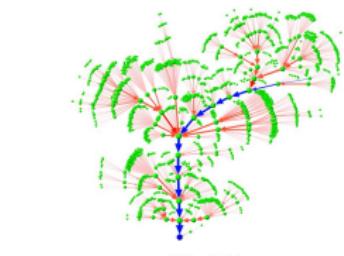


Perivascular nerve genes		
Gene	Affymetrix-ID	
Kcnai	1417416_at	
Avil	1419148_at	
Elavl2	1421883_at	
Acsgbg1	1422428_at	
Napb	1423172_at	
Napb	1423173_at	
Ripk	1424402_at	
Celf4	1426930_at	
Dolk1	1435940_at	
Scg3	1448628_at	
Cntn1	1449563_at	
Chrna3	1455931_at	



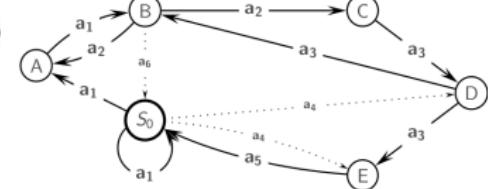
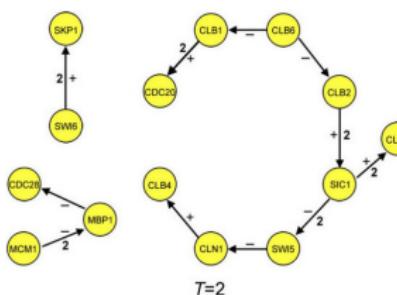
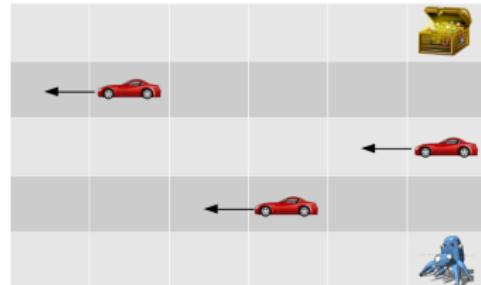
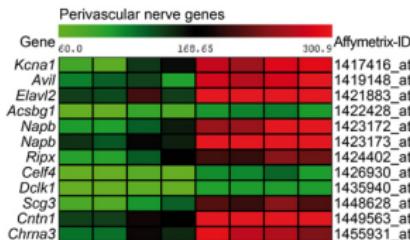
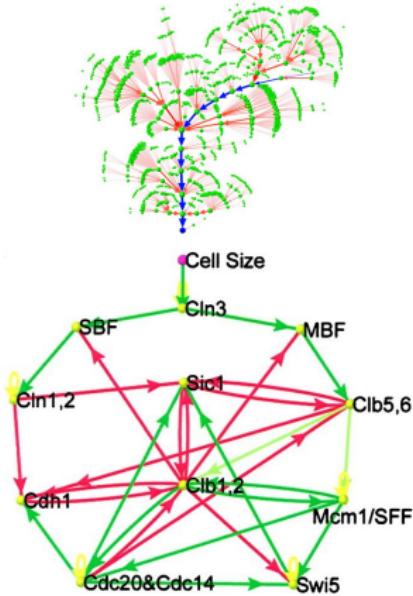
# Contribution

Memory-less models: Boolean network, gene regulatory network, neural network and Petri net.



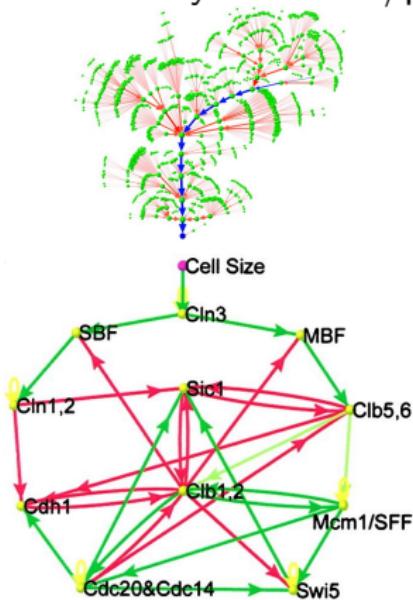
# Contribution

Dynamics with duration, accumulation, i.e. delays. Delayed models: timed Boolean network, timed Petri net.

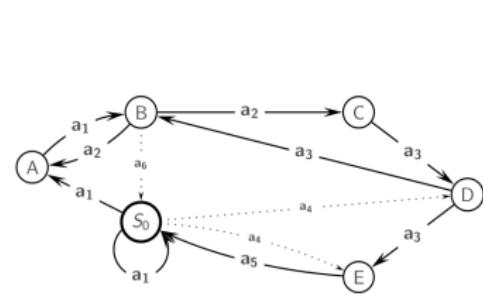
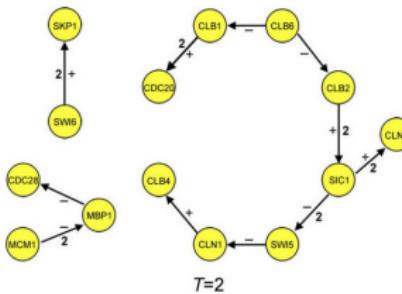
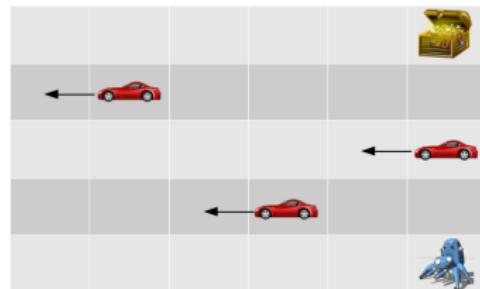


# Contribution

From one state, multiple futures. Non-deterministic models:  
 asynchronous/probabilistic Boolean network, action model.



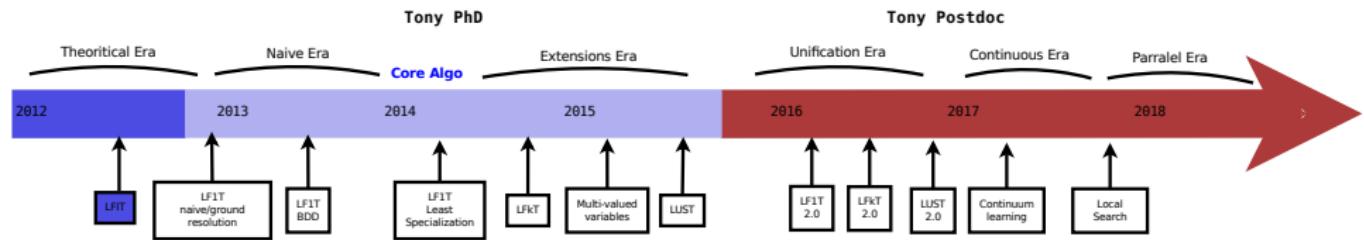
Perivascular nerve genes				
Gene	60,0	168,65	300,5	Affymetrix-ID
Kcnal1				1417416_at
Avil				1419148_at
Elavl2				1421883_at
Acsgb1				1422428_at
Napb				1423172_at
Napb				1423173_at
Ripx				1424402_at
Celf4				1426930_at
Ddk1				1435940_at
Scg3				1448628_at
Cntr1				1449563_at
Chrna3				1455931_at



# Outline

- 1 Who is this guy?
- 2 Background
  - Machine Learning
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  - Inductive Logic Programming
- 3 PhD work
  - Memoryless Systems
  - Systems with Memory
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  - DREAM Challenge 11
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- 5 Conclusion

# LFIT Chronology



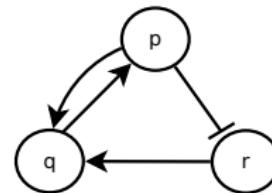
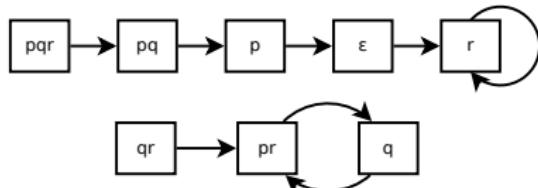
Short paper ILP 2012.

# Learning From Interpretation Transitions (LFIT)

A framework for learning system dynamics from state transitions.

- Basic Idea:

- Learn a logic program by observing the behavior of a system.
- This logic program represents the dynamics of the system.



**Input:** Behavior of the system

**Output:** Dynamics of the system

$$\begin{aligned}p(t+1) &\leftarrow q(t). \\q(t+1) &\leftarrow p(t) \wedge r(t). \\r(t+1) &\leftarrow \neg p(t).\end{aligned}$$

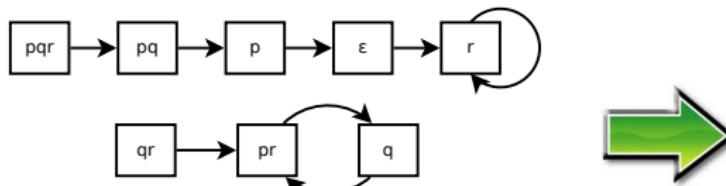
**Representation:** Logic Program

# Learning From Interpretation Transitions (LFIT)

A framework for learning system dynamics from state transitions.

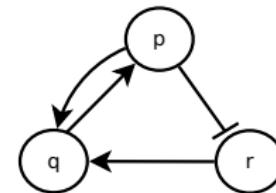
- Basic Idea:

- Learn a logic program by observing the behavior of a system.
- This logic program represents the dynamics of the system.



**What** happens

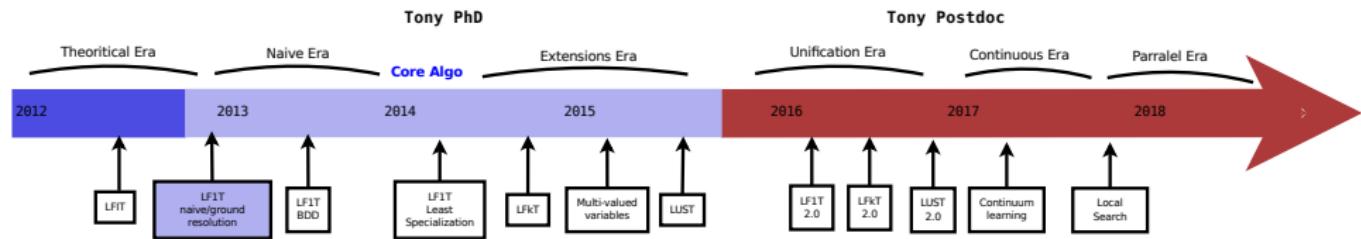
$$\begin{aligned} p(t+1) &\leftarrow q(t). \\ q(t+1) &\leftarrow p(t) \wedge r(t). \\ r(t+1) &\leftarrow \neg p(t). \end{aligned}$$



**Why** it happens

**Representation:** Logic Program

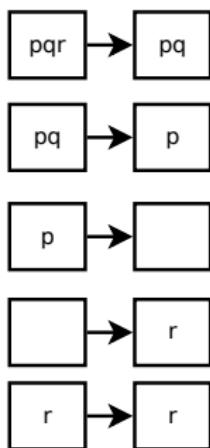
# LFIT Chronology



Long paper ILP 2013/2014, journal MLJ 2014.

# LF1T: Learning From 1-step Transitions (memory-less systems)

INPUT:  
A set of pairs of interpretations



OUTPUT:  
A normal logic program

$$\begin{aligned} p(t+1) &\leftarrow q(t). \\ q(t+1) &\leftarrow p(t) \wedge r(t). \\ r(t+1) &\leftarrow \neg p(t). \end{aligned}$$

# Learning from 1-step transition (LF1T) (*Inoue et al. MLJ 2013*)

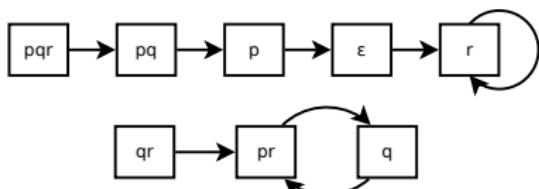
Input:

- The variables of the systems (pqr)
- A set  $E$  of state transitions (trace of executions)

Output:

- A set of rules  $P$  which represents the dynamics of the system

State Transitions



LF1T Input

$$E = \{ (pqr, pq), (pq, p), (p, \emptyset), (\emptyset, r), (r, r), (qr, pr), (pr, q), (q, pr) \}$$

# Learning from 1 step transition (*Inoue et al. MLJ 2013*)

Let  $(I, J) \in E$ , for each  $A \in J$  we can infer a **positive** rule  $R_A^I$ :

$$R_A^I := (A \leftarrow \bigwedge_{B_i \in I} B_i \wedge \bigwedge_{C_j \in \beta \setminus I} \neg C_j)$$

## Example

From the state transition  $(pqr, pq)$  we can infer 2 rules:

- $p \leftarrow p \wedge q \wedge r.$
- $q \leftarrow p \wedge q \wedge r.$

## Learning from 1 step transition (*Inoue et al. MLJ 2013*)

Let  $(I, J) \in E$ , for each  $A \in J$  we can infer a **positive** rule  $R_A^I$ :

$$R_A^I := (A \leftarrow \bigwedge_{B_i \in I} B_i \wedge \bigwedge_{C_j \in \beta \setminus I} \neg C_j)$$

### Example

From the next transition  $(pq, p)$  we can infer 1 logic rule:

- $p \leftarrow p \wedge q \wedge \neg r.$

# Generalization Techniques

Generalize knowledge to learn the real relationship.

- $p \leftarrow p \wedge q \wedge r.$
- $p \leftarrow p \wedge q \wedge \neg r.$

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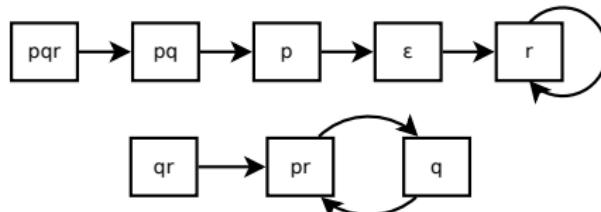
# Generalization Techniques

Generalize knowledge to learn the real relationship.

- $p \leftarrow p \wedge q.$
- $p \leftarrow \neg p \wedge q.$
- $p \leftarrow q.$

# Running Example

## Input State Transitions

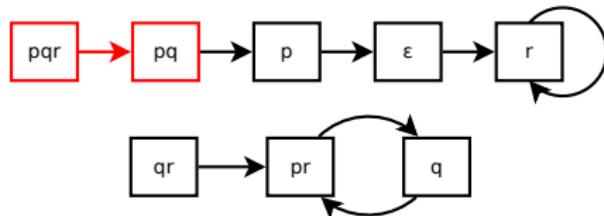


Learned Rules:  
 $\emptyset$

Knowledge Base:  
 $\emptyset$

# Running Example

## Input State Transitions



Learned Rules:

$$p \leftarrow p \wedge q \wedge r.$$

$$q \leftarrow p \wedge q \wedge r.$$

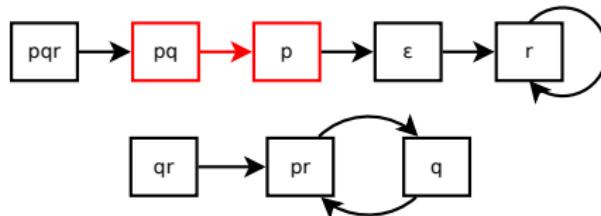
Knowledge Base:

$$p \leftarrow p \wedge q \wedge r.$$

$$q \leftarrow p \wedge q \wedge r.$$

# Running Example

## Input State Transitions



Learned Rules:

$$p \leftarrow p \wedge q \wedge \neg r.$$

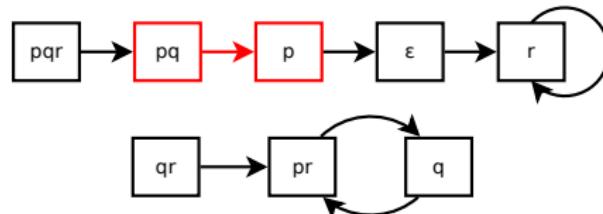
Knowledge Base:

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$$q \leftarrow p \wedge q \wedge r.$$

# Running Example

## Input State Transitions



Learned Rules:

$$p \leftarrow p \wedge q \wedge \neg r.$$

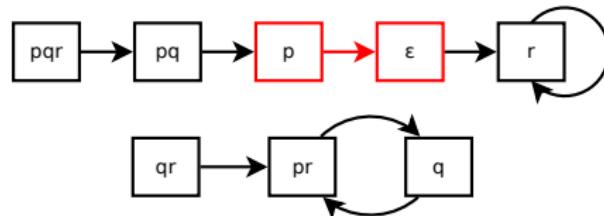
Knowledge Base:

$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

# Running Example

## Input State Transitions

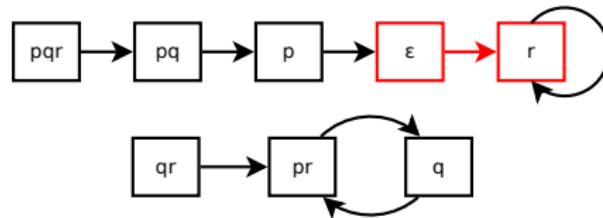


Learned Rules:  
 $\emptyset$

Knowledge Base:  
 $p \leftarrow p \wedge q.$   
 $q \leftarrow p \wedge q \wedge r.$

# Running Example

## Input State Transitions



Learned Rules:

$$r \leftarrow \neg p \wedge \neg q \wedge \neg r.$$

Knowledge Base:

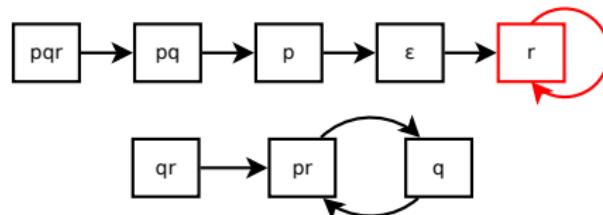
$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

$$r \leftarrow \neg p \wedge \neg q \wedge \neg r.$$

# Running Example

## Input State Transitions



Learned Rules:

$$r \leftarrow \neg p \wedge \neg q \wedge r.$$

Knowledge Base:

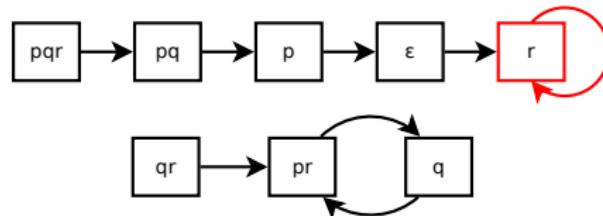
$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

$$r \leftarrow \neg p \wedge \neg q \wedge \neg r.$$

# Running Example

## Input State Transitions



Learned Rules:

$$r \leftarrow \neg p \wedge \neg q \wedge r.$$

Knowledge Base:

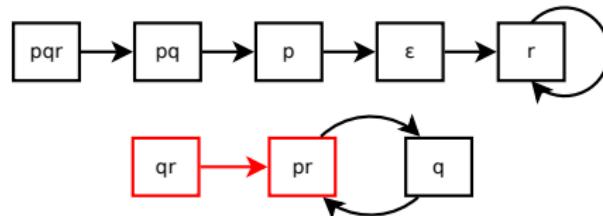
$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

$$r \leftarrow \neg p \wedge \neg q.$$

# Running Example

## Input State Transitions



Learned Rules:

$$p \leftarrow \neg p \wedge q \wedge r.$$

$$r \leftarrow \neg p \wedge \textcolor{red}{q} \wedge r.$$

Knowledge Base:

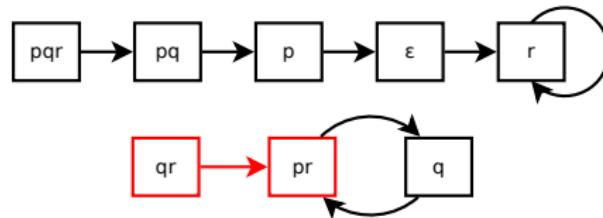
$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

$$r \leftarrow \neg p \wedge \neg q.$$

# Running Example

## Input State Transitions



Learned Rules:

$$p \leftarrow \neg p \wedge q \wedge r.$$

$$r \leftarrow \neg p \wedge q \wedge r.$$

Knowledge Base:

$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

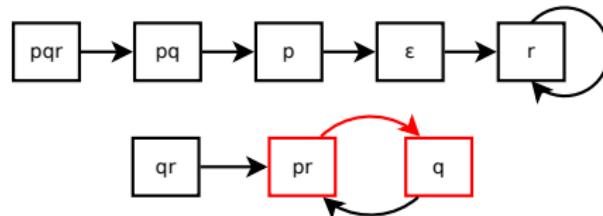
$$r \leftarrow \neg p \wedge \neg q.$$

$$p \leftarrow q \wedge r.$$

$$r \leftarrow \neg p \wedge r.$$

# Running Example

## Input State Transitions



Learned Rules:

$$q \leftarrow p \wedge \neg q \wedge r.$$

Knowledge Base:

$$p \leftarrow p \wedge q.$$

$$q \leftarrow p \wedge q \wedge r.$$

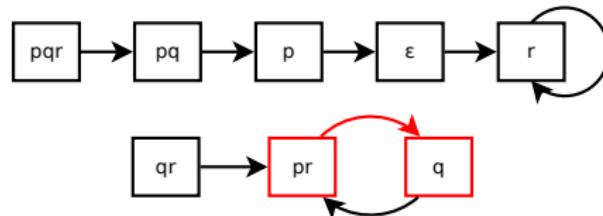
$$r \leftarrow \neg p \wedge \neg q.$$

$$p \leftarrow q \wedge r.$$

$$r \leftarrow \neg p \wedge r.$$

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## Input State Transitions



Learned Rules:

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Knowledge Base:

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$$q \leftarrow p \wedge r.$$

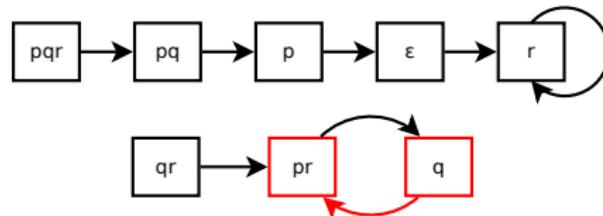
$$r \leftarrow \neg p \wedge \neg q.$$

$$p \leftarrow q \wedge r.$$

$$r \leftarrow \neg p \wedge r.$$

# Running Example

## Input State Transitions



Learned Rules:

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$$r \leftarrow \neg p \wedge \textcolor{red}{q} \wedge \neg r.$$

Knowledge Base:

$$p \leftarrow p \wedge q.$$

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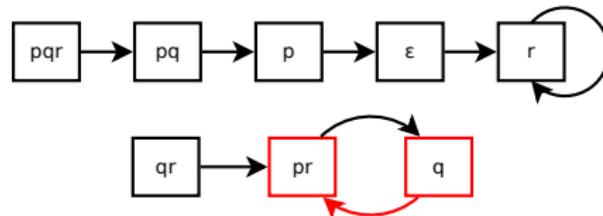
$$r \leftarrow \neg p \wedge \textcolor{red}{q}.$$

$$p \leftarrow q \wedge r.$$

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## Input State Transitions



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$$p \leftarrow q \wedge \neg r.$$

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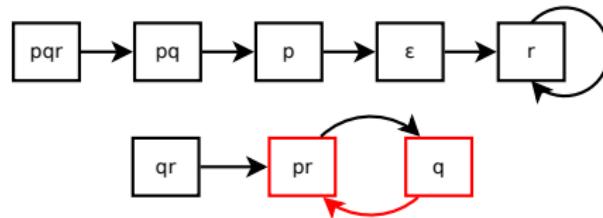
$$r \leftarrow \neg p \wedge \neg q.$$

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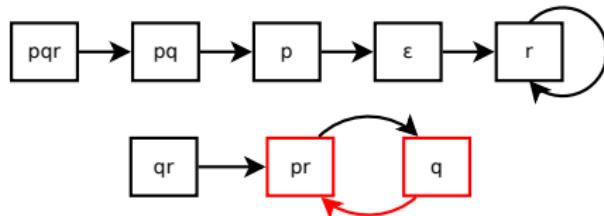
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# Running Example

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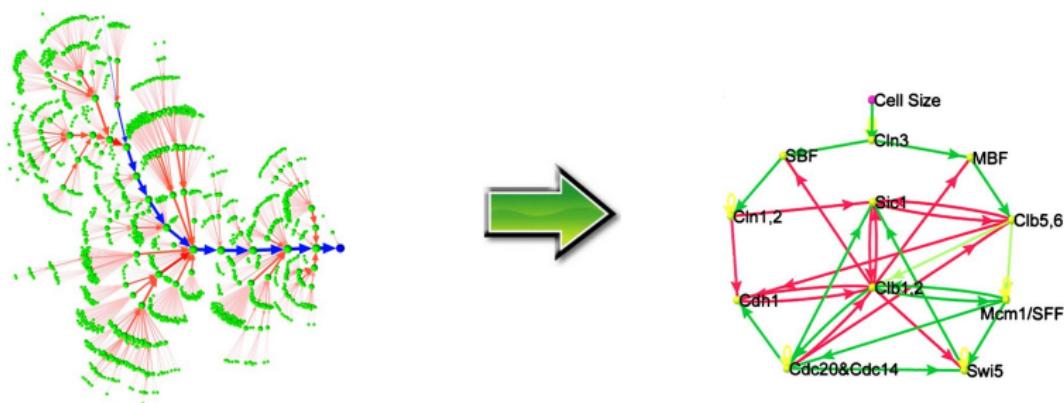
$$q \leftarrow p \wedge r.$$

$$p \leftarrow q.$$

$$r \leftarrow \neg p.$$

# Applications in Bioinformatics

Given the state transitions of the *budding yeast* we can learn its gene regulatory networks.



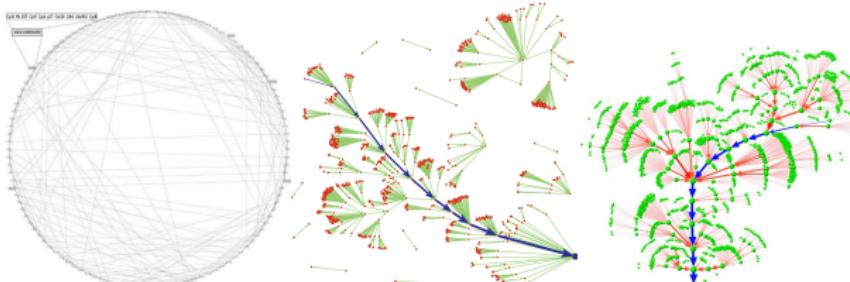
A state transition diagram (left) and the Boolean network of the *budding yeast* (right) (Li et al. 2004).

# Evaluation

Memory use and learning time of **LF1T** for Boolean networks benchmarks up to 23 nodes

Algorithm	Mammalian (10)	Fission (10)	Budding (12)	Arabidopsis (16)	T helper (23)
Naïve	142 118/4.62s	126 237/3.65s	1 147 124/523s	T.O.	T.O.
Ground	1036/ <b>0.04s</b>	1218/ <b>0.05s</b>	21 470/0.26s	271 288/4.25s	T.O.
Ground-BDD	<b>180</b> /0.24s	<b>147</b> /0.24s	<b>541</b> / <b>0.19s</b>	<b>779</b> / <b>2.8s</b>	<b>611</b> / <b>3360s</b>
Full Naïve	377 539/29.25s	345587/24.03s	T.O.	T.O.	T.O.
Full Ground	1066/0.24s	1178/0.23s	23 738/4.04s	399 469/111s	T.O.
Least Specialization	<b>375</b> / <b>0.06s</b>	<b>377</b> / <b>0.08s</b>	<b>641</b> / <b>0.35s</b>	<b>2270</b> / <b>5.28s</b>	<b>3134</b> / <b>5263s</b>

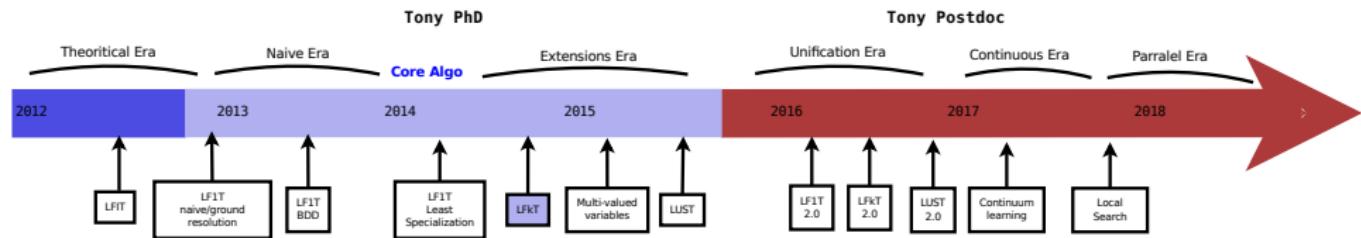
Memory use and learning time of **LF1T** for Boolean networks benchmarks up to 23 nodes



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# LFIT Chronology



Short paper **ILP 2014/2015**, journal **Frontiers 2015**, long paper **ICMLA 2015**.

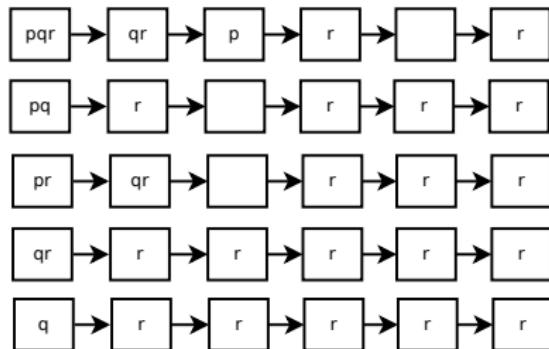
# LFkT: Learning From k-step Transitions (markov( $k$ ) systems)

INPUT:

A set of **sequences** of interpretations

OUTPUT:

A normal logic program with **delay**



$p(t) \leftarrow q(t-1) \wedge q(t-2).$   
 $q(t) \leftarrow p(t-1) \wedge r(t-1).$   
 $r(t) \leftarrow \neg p(t-2).$

# Formalization: Markov( $k$ ) into Logic Program

## Definition (Timed Herbrand base)

Let  $\mathcal{B}$  be the Herbrand base of a program  $P$  and  $k$  be a natural number. The timed Herbrand base of  $P$  (with period  $k$ ) denoted by  $\mathcal{B}_k$ , is as follows:

$$\mathcal{B}_k = \bigcup_{i=1}^k \{v_{t-i} \mid v \in \mathcal{B}\}$$

Where  $t$  is a constant term which represents the current time step.

## Example

If the Herbrand base of a program  $P$  is  $\mathcal{B} = \{a, b, c\}$  then

- $\mathcal{B}_1 = \{a_{t-1}, b_{t-1}, c_{t-1}\}$
- $\mathcal{B}_2 = \{a_{t-1}, b_{t-1}, c_{t-1}, a_{t-2}, b_{t-2}, c_{t-2}\}$

# Markov( $k$ ) Systems

A Markov( $k$ ) system can be interpreted as a logic program.

## Definition (Markov( $k$ ) system)

Let  $P$  be a logic program,  $\mathcal{B}$  be the Herbrand base of  $P$  and  $\mathcal{B}_k$  be the timed Herbrand base of  $P$  with period  $k$ . A Markov( $k$ ) system  $S$  with respect to  $P$  is a logic program where for all rules  $R \in S$ ,  $h(R) \in \mathcal{B}$  and all atoms appearing in  $b(R)$  belong to  $\mathcal{B}_k$ .

## Example

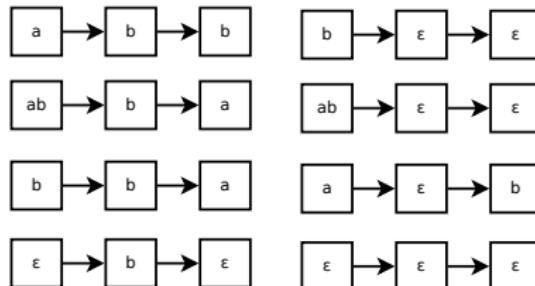
If the Herbrand base of a program  $P$  is  $\mathcal{B} = \{a, b\}$  then

- $\mathcal{B}_2 = \{a_{t-1}, b_{t-1}, a_{t-2}, b_{t-2}\}$ .
- Let  $R_1 = a \leftarrow b_{t-1}, b_{t-2}$  and  $R_2 = b \leftarrow a_{t-2}, \neg b_{t-2}$ .
- $S = \{R_1, R_2\}$  is a Markov(2) system.

# Example

Let  $S$  be a  $\text{Markov}(k)$  system as follows:

$$S = \{(a \leftarrow b_{t-1}, b_{t-2}), (b \leftarrow a_{t-2}, \neg b_{t-2})\}$$



Eight traces of executions of the system  $S$

# Running Example

Initialization		$a \rightarrow b \rightarrow b$	$ab \rightarrow b \rightarrow a$
2-step program	1-step program		
<i>a.</i> <i>b.</i>	<i>a.</i> <i>b.</i>		

# Running Example

Initialization		$a \rightarrow b \rightarrow b$	$ab \rightarrow b \rightarrow a$
2-step program	1-step program	( $a_2 b_1, b$ )	
$a.$ $b.$	$a.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $b.$	

# Running Example

Initialization		$a \rightarrow b \rightarrow b$	$ab \rightarrow b \rightarrow a$
2-step program	1-step program	( $a_2 b_1, b$ )	( $a_1, b$ )
$a.$ $b.$	$a.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $b.$	$a \leftarrow \neg a_1.$ $a \leftarrow b_1.$ $b.$

# Running Example

Initialization		$a \rightarrow b \rightarrow b$		$ab \rightarrow b \rightarrow a$	
2-step program	1-step program	$(a_2 b_1, b)$	$(a_1, b)$		
$a.$ $b.$	$a.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $b.$	$a \leftarrow \neg a_1.$ $a \leftarrow b_1.$ $b.$ $(a_2 b_1, b)$		
			$a \leftarrow \neg a_1, \neg b_1.$ $a \leftarrow a_1, b_1.$ $b.$		

# Running Example

Initialization		$a \rightarrow b \rightarrow b$		$ab \rightarrow b \rightarrow a$	
2-step program	1-step program	( $a_2 b_1$ , $b$ )	( $a_1$ , $b$ )	( $a_2 b_2 b_1$ , $a$ )	
$a.$ $b.$	$a.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $b.$	$a \leftarrow \neg a_1.$ $a \leftarrow b_1.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $a \leftarrow \neg a_1, \neg b_1.$ $a \leftarrow a_1, b_1.$ $b.$	
				$a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	

# Running Example

Initialization		$a \rightarrow b \rightarrow b$		$ab \rightarrow b \rightarrow a$	
2-step program	1-step program	( $a_2 b_1$ , $b$ )	( $a_1$ , $b$ )	( $a_2 b_2 b_1$ , $a$ )	( $a_1 b_1$ , $b$ )
$a.$ $b.$	$a.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $b.$	$a \leftarrow \neg a_1.$ $a \leftarrow b_1.$ $b.$  ( $a_2 b_1$ , $b$ ) $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $a \leftarrow \neg a_1, \neg b_1.$ $a \leftarrow a_1, b_1.$ $b \leftarrow \neg a_2.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $a \leftarrow a_1, b_1.$ $b.$

# Running Example

Initialization		$a \rightarrow b \rightarrow b$		$ab \rightarrow b \rightarrow a$	
2-step program	1-step program	( $a_2 b_1$ , $b$ )	( $a_1$ , $b$ )	( $a_2 b_2 b_1$ , $a$ )	( $a_1 b_1$ , $b$ )
$a.$ $b.$	$a.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $b.$	$a \leftarrow \neg a_1.$ $a \leftarrow b_1.$ $b.$	$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $a \leftarrow \neg a_1, \neg b_1.$ $a \leftarrow a_1, b_1.$ $b.$	$a \leftarrow \neg b_1.$ $a \leftarrow a_1, \neg b_1.$ $a \leftarrow a_1, b_1.$ $b \leftarrow \neg a_1.$ $b \leftarrow \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$
		( $a_2 b_1$ , $b$ )		( $a_2 b_2 b_1$ , $a$ )	

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
$(b_2 b_1, a)$		
$a \leftarrow \neg a_2.$		
$a \leftarrow b_2.$		
$a \leftarrow \neg a_1.$		
$a \leftarrow \neg b_1.$		
$b \leftarrow \neg a_2, \neg b_2.$		
$b \leftarrow \neg a_2, a_1.$		
$b \leftarrow \neg a_2, \neg b_1.$		
$b \leftarrow \neg b_2.$		
$b \leftarrow a_1.$		
$b \leftarrow \neg b_1.$		

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
( $b_2 b_1, a$ )	( $b_1, b$ )	
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
( $b_2 b_1, a$ )	( $b_1, b$ )	
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$ (b $_2 b_1, a$ )	

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
( $b_2 b_1, a$ )	( $b_1, b$ )	( $\epsilon, \epsilon$ )
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$  $(b_2 b_1, a)$ $a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_2, \neg b_2.$ $a \leftarrow \neg a_2, a_1.$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_1.$ $a \leftarrow b_2, \neg b_1.$ $a \leftarrow a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, a_1.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_1.$ $b \leftarrow b_2, \neg b_1.$ $b \leftarrow a_1, \neg b_1.$

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
( $b_2 b_1, a$ )	( $b_1, b$ )	( $\epsilon, \epsilon$ )
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$  $(b_2 b_1, a)$ $a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_2, b_2.$ $a \leftarrow \neg a_2, a_1.$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_1.$ $a \leftarrow b_2, \neg b_1.$ $a \leftarrow a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, a_1.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_1.$ $b \leftarrow b_2, \neg b_1.$ $b \leftarrow a_1, \neg b_1.$
		( $\epsilon, \epsilon$ )
		$a \leftarrow \neg a_1, \neg b_1.$
		$b \leftarrow a_1.$
		$b \leftarrow \neg b_1.$

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
( $b_2 b_1, a$ )	( $b_1, b$ )	( $\epsilon, \epsilon$ )
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$  ( $b_2 b_1, a$ )	$a \leftarrow \neg a_2, b_2.$ $a \leftarrow \neg a_2, a_1.$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2.$ $a \leftarrow a_1.$ $a \leftarrow \neg b_1.$ $a \leftarrow \neg b_2, \neg b_1.$ $a \leftarrow a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, a_1.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_1.$ $b \leftarrow b_2, \neg b_1.$ $b \leftarrow a_1, \neg b_1.$
		( $\epsilon, \epsilon$ )
		$b \leftarrow a_1.$

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
( $b_2 b_1, a$ )	( $b_1, b$ )	( $b_2, \epsilon$ )
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$ $(b_2 b_1, a)$ $a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2.$ $a \leftarrow b_2, a_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_1.$ $a \leftarrow b_2, \neg b_1.$ $a \leftarrow a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow \neg b_2, \neg b_1.$ $b \leftarrow a_2, \neg b_1.$ $b \leftarrow a_2, b_2, \neg b_1.$ $b \leftarrow b_2, \neg b_1, a_1.$
	( $\epsilon, \epsilon$ )	( $\epsilon, \epsilon$ )

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
$(b_2 b_1, a)$	$(\epsilon, \epsilon)$	$(b_2, \epsilon)$
$(b_1, b)$	$(\epsilon, \epsilon)$	$(b_1, \epsilon)$
$a \leftarrow \neg a_2.$ $a \leftarrow b_2.$ $a \leftarrow \neg a_1.$ $a \leftarrow \neg b_1.$ $b \leftarrow \neg a_2, \neg b_2.$ $b \leftarrow \neg a_2, a_1.$ $b \leftarrow \neg a_2, \neg b_1.$ $b \leftarrow \neg b_2.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$	$a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$ $(b_2 b_1, a)$ $a \leftarrow \neg a_1, \neg b_1.$ $b \leftarrow a_1.$ $b \leftarrow \neg b_1.$ $a \leftarrow a_2, \neg b_1.$ $a \leftarrow \neg b_2, \neg b_1.$ $a \leftarrow a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, a_1.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_1.$ $b \leftarrow b_2, \neg b_1.$ $b \leftarrow a_1, \neg b_1.$	$a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2.$ $a \leftarrow b_2, a_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_1.$ $b \leftarrow a_2, b_2, \neg b_1.$ $b \leftarrow b_2, \neg b_1, a_1.$

# Running Example

$b \rightarrow b \rightarrow a$	$\epsilon \rightarrow \epsilon \rightarrow \epsilon$	$b \rightarrow \epsilon \rightarrow \epsilon$
$(b_2 b_1, a)$	$(\epsilon, \epsilon)$	$(b_2, \epsilon)$
$a \leftarrow \neg a_2.$	$a \leftarrow \neg a_1, \neg b_1.$	$a \leftarrow \neg a_2, b_1.$
$a \leftarrow b_2.$	$b \leftarrow a_1.$	$a \leftarrow a_2, b_2.$
$a \leftarrow \neg a_1.$	$b \leftarrow \neg b_1.$	$a \leftarrow b_2, a_1.$
$a \leftarrow \neg b_1.$		$a \leftarrow b_2, b_1.$
$b \leftarrow \neg a_2, \neg b_2.$		$a \leftarrow a_1.$
$b \leftarrow \neg a_2, a_1.$		$a \leftarrow a_2, \neg b_1.$
$b \leftarrow \neg a_2, \neg b_1.$		$b \leftarrow a_2, \neg b_2.$
$b \leftarrow \neg b_2.$		$b \leftarrow \neg b_2, b_1.$
$b \leftarrow a_1.$		$b \leftarrow a_1.$
$b \leftarrow \neg b_1.$		$b \leftarrow a_2, \neg b_1.$
		$b \leftarrow a_2, b_2, \neg b_1.$
		$b \leftarrow b_2, \neg b_1, a_1.$

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$
$(a_2 b_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, a_1.$ $a \leftarrow a_2, b_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, a_1, \neg b_1.$		

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$
( $a_2 b_2$ , $\epsilon$ )	( $a_1 b_1$ , $\epsilon$ )	
$a \leftarrow \neg a_2, b_1.$	$b \leftarrow a_1, \neg b_1.$	
$a \leftarrow a_2, b_2, \neg a_1.$		
$a \leftarrow a_2, b_2, \neg b_1.$		
$a \leftarrow b_2, b_1.$		
$a \leftarrow a_1.$		
$a \leftarrow a_2, \neg b_2, \neg b_1.$		
$a \leftarrow a_2, \neg a_1, \neg b_1.$		
$b \leftarrow a_2, \neg b_2.$		
$b \leftarrow \neg b_2, b_1.$		
$b \leftarrow a_1.$		
$b \leftarrow a_2, \neg b_2, \neg b_1.$		
$b \leftarrow a_2, a_1, \neg b_1.$		

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$
$(a_2 b_2, \epsilon)$	$(a_1 b_1, \epsilon)$	
$a \leftarrow \neg a_2, b_1.$	$b \leftarrow a_1, \neg b_1.$	
$a \leftarrow a_2, b_2, a_1.$		
$a \leftarrow a_2, b_2, b_1.$	$(\epsilon, \epsilon)$	
$a \leftarrow b_2, b_1.$		
$a \leftarrow a_1.$		
$a \leftarrow a_2, \neg b_2, \neg b_1.$		
$a \leftarrow a_2, \neg a_1, \neg b_1.$		
$b \leftarrow a_2, \neg b_2.$		
$b \leftarrow \neg b_2, b_1.$		
$b \leftarrow a_1.$		
$b \leftarrow a_2, \neg b_2, \neg b_1.$		
$b \leftarrow a_2, a_1, \neg b_1.$		

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$
$(a_2 b_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, \mathbf{a}_1.$ $a \leftarrow a_2, b_2, \mathbf{b}_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, \mathbf{a}_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, \mathbf{a}_1, \neg b_1.$	$(a_1 b_1, \epsilon)$ $b \leftarrow a_1, \neg \mathbf{b}_1.$ $(\epsilon, \epsilon)$ $b \leftarrow a_1, \neg b_1.$	$(a_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \mathbf{a}_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$	
( $a_2 b_2, \epsilon$ )	( $a_1 b_1, \epsilon$ )	( $a_2, \epsilon$ )	
$a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, a_1.$ $a \leftarrow a_2, b_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, a_1, \neg b_1.$	$b \leftarrow a_1, \neg b_1.$ $(\epsilon, \epsilon)$	$a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$	

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$
$(a_2 b_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, a_1.$ $a \leftarrow a_2, b_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, a_1, \neg b_1.$	$(a_1 b_1, \epsilon)$ $b \leftarrow a_1, \neg b_1.$ $(\epsilon, \epsilon)$ $b \leftarrow a_1, \neg b_1.$	$(a_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $(a_1, \epsilon)$ $b \leftarrow a_1, \neg b_1.$ $a \leftarrow a_2, \neg b_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $(\epsilon, b)$ $\emptyset$

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$			
$(a_2 b_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, a_1.$ $a \leftarrow a_2, b_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, a_1, \neg b_1.$	$(a_1 b_1, \epsilon)$ $b \leftarrow a_1, \neg b_1.$ $(\epsilon, \epsilon)$ $b \leftarrow a_1, \neg b_1.$	$(a_2, \epsilon)$ $a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $\emptyset$	$(a_1, \epsilon)$ $b \leftarrow a_1, \neg b_1.$ $(\epsilon, b)$ $b \leftarrow a_1.$	$(b_1, \epsilon)$ $a \leftarrow \neg a_2, b_2 b_1.$ $a \leftarrow \neg a_2, a_1 b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow a_2, \neg b_2, b_1.$ $b \leftarrow \neg b_2, a_1, b_1.$ $b \leftarrow a_1.$	

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$			
$(a_2 b_2, \epsilon)$	$(a_2, \epsilon)$	$(b_1, \epsilon)$			
$a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, a_1.$ $a \leftarrow a_2, b_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, a_1, \neg b_1.$	$b \leftarrow a_1, \neg b_1.$  $(\epsilon, \epsilon)$	$a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$	$b \leftarrow a_1, \neg b_1.$  $(\epsilon, b)$	$a \leftarrow \neg a_2, b_2 b_1.$ $a \leftarrow \neg a_2, a_1 b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow a_2, \neg b_2, b_1.$ $b \leftarrow \neg b_2, a_1, b_1.$ $b \leftarrow a_1.$	$\emptyset$
$(a_1 b_1, \epsilon)$	$(a_1, \epsilon)$	$(\epsilon, b)$			

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$			
$(a_2 b_2, \epsilon)$	$(a_2, \epsilon)$	$(b_1, \epsilon)$			
$a \leftarrow \neg a_2, b_1.$ $a \leftarrow a_2, b_2, a_1.$ $a \leftarrow a_2, b_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ $a \leftarrow a_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ $b \leftarrow a_2, a_1, \neg b_1.$	$b \leftarrow a_1, \neg b_1.$  $(\epsilon, \epsilon)$  $b \leftarrow a_1, \neg b_1.$	$a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, a_1, \neg b_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$	$b \leftarrow a_1, \neg b_1.$  $(\epsilon, b)$  $\emptyset$	$a \leftarrow \neg a_2, b_2 b_1.$ $a \leftarrow \neg a_2, a_1 b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow a_2, \neg b_2, b_1.$ $b \leftarrow \neg b_2, a_1, b_1.$ $b \leftarrow a_1.$	$\emptyset$  $(b_1, \epsilon)$  $\emptyset$

# Running Example

$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$			
$(a_2 b_2, \epsilon)$	$(a_2, \epsilon)$	$(b_1, \epsilon)$			
$a \leftarrow \neg a_2, b_1.$ <del><math>a \leftarrow a_2, b_2, a_1.</math></del> <del><math>a \leftarrow a_2, b_2, b_1.</math></del> $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $a \leftarrow a_2, \neg b_2, \neg b_1.$ <del><math>a \leftarrow a_2, a_1, \neg b_1.</math></del> $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2, \neg b_1.$ <del><math>b \leftarrow a_2, a_1, \neg b_1.</math></del>	$b \leftarrow a_1, \neg b_1.$ $(\epsilon, \epsilon)$ $b \leftarrow a_1, \neg b_1.$	$a \leftarrow \neg a_2, b_1.$ $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ <del><math>a \leftarrow a_2, \neg b_2, a_1 \neg b_1.</math></del> $b \leftarrow a_2, \neg b_2.$ $b \leftarrow \neg b_2, b_1.$ $b \leftarrow a_1.$	$b \leftarrow a_1, \neg b_1.$ $(\epsilon, b)$ $\emptyset$	$a \leftarrow \neg a_2, b_2 b_1.$ <del><math>a \leftarrow a_2, a_1 b_1.</math></del> $a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2.$ <del><math>b \leftarrow a_2, \neg b_2, b_1.</math></del> <del><math>b \leftarrow \neg b_2, a_1, b_1.</math></del> $b \leftarrow a_1.$	$(\epsilon, b)$ $\emptyset$

Merging of the programs	OUTPUT
$a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow a_1.$	

# Running Example

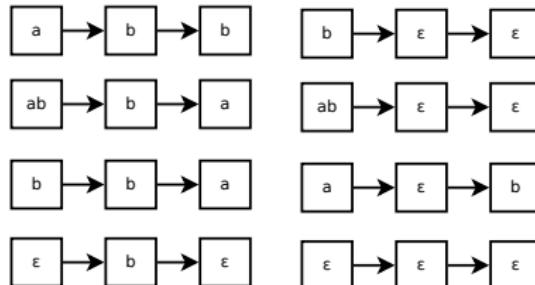
$ab \rightarrow \epsilon \rightarrow \epsilon$	$a \rightarrow \epsilon \rightarrow b$	$\epsilon \rightarrow b \rightarrow \epsilon$			
$(a_2 b_2, \epsilon)$	$(a_2, \epsilon)$	$(b_1, \epsilon)$			
$(a_1 b_1, \epsilon)$	$(a_1, \epsilon)$	$(\epsilon, b)$			
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Merging of the programs	OUTPUT
$a \leftarrow b_2, b_1.$ $a \leftarrow a_1.$ $b \leftarrow a_2, \neg b_2.$ $b \leftarrow a_1.$	$a \leftarrow b_2, b_1.$ $b \leftarrow a_2, \neg b_2.$

# How to know the Delay?

Let  $S$  be a  $\text{Markov}(k)$  system as follows:

$$S = \{(a \leftarrow b_{t-1}, b_{t-2}), (b \leftarrow a_{t-2}, \neg b_{t-2})\}$$

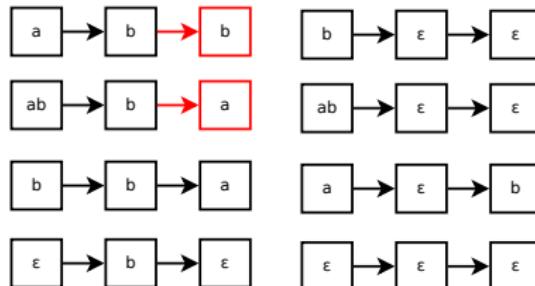


Eight traces of executions of the system  $S$

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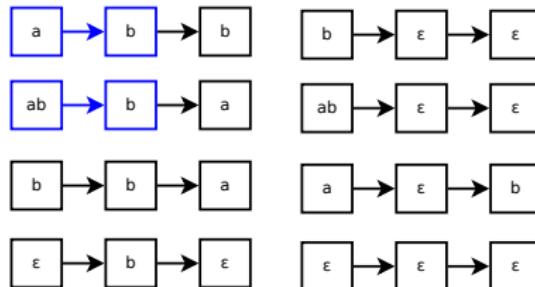


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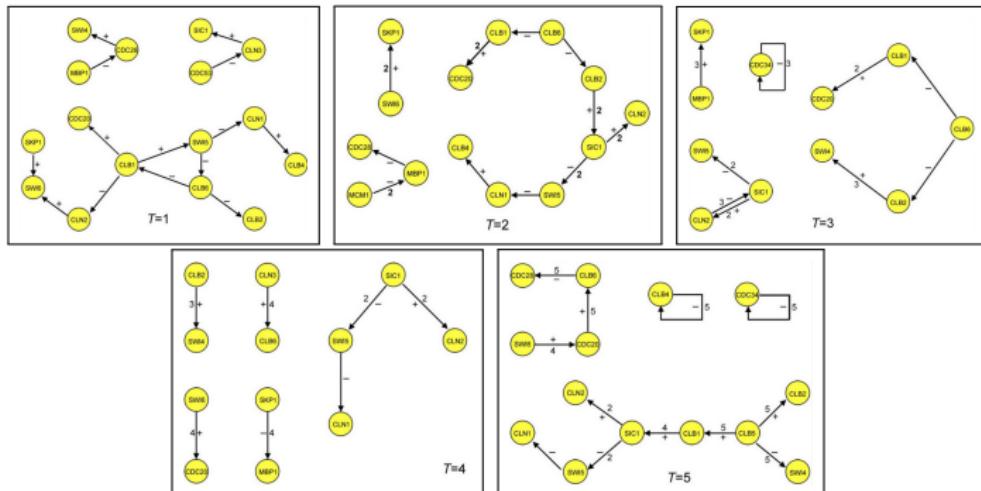


Eight traces of executions of the system  $S$

# Experiments

We evaluated LFkT on learning 5 real biological benchmarks.

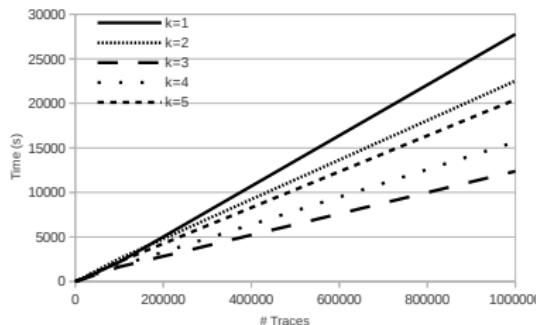
- Benchmark are Markov(1) to Markov(5) systems
- LFkT input goes from 10 to 1 million traces



The time-delayed gene regulatory networks of the human HeLa cell cycling (Li et. al 2006).

# Evaluation

# Traces	Run time (# of seconds)					
	k=1	k=2	k=3	k=4	k=5	k=7
10	0.23s	0.27s	<b>0.16s</b>	0.28s	0.31s	2.8s
100	1.87s	2.49s	<b>1.63s</b>	2.37s	2.84s	27s
1,000	15.3s	18.5s	<b>13.3s</b>	20.1s	23.8s	249s
10,000	<b>146s</b>	218s	147s	201s	234s	3,621s
100,000	2,177s	2,577s	<b>1,643s</b>	1,764s	2,243s	39,973s
1,000,000	27,768s	22,517s	12,384s	15,670s	20,413s	327,480s



LFkT Run time varying the input size (number of traces)

# Evaluation

Runtime and output size of **LFkT** on learning the benchmark from (*Dubrova and Teslenko 2011*), with regard to different delays.

Delay	Runtime (in seconds)/Output size (# of rules)			
	Mammalian (10)	Fission (10)	Budding (12)	Arabidopsis (15)
k=1	0.06s / 23	0.07s / 24	0.42s / 54	5.87s / 28
k=2	6.92s / 3,922	2.5s / 2,003	213s / 10,551	6,902s / 4,981
k=3	752s / 54,692	49.39s / 11,312	20,970s / 60,568	T.O.
k=4	12,448s / 293,020	302s / 32,581	T.O.	T.O.
k=5	T.O.	1,197s / 70,322	T.O.	T.O.
k=6	T.O.	3,585s / 129,603	T.O.	T.O.
k=7	T.O.	9,401s / 216,212	T.O.	T.O.

The complexity of learning a markov( $k$ ) system  $S$  from a set of observations  $O$  with **LFkT** is respectively:

$O(2^{nk})$  for memory and  $O(\sum_{T \in O} |T| \cdot n2^{nk})$  for runtime.

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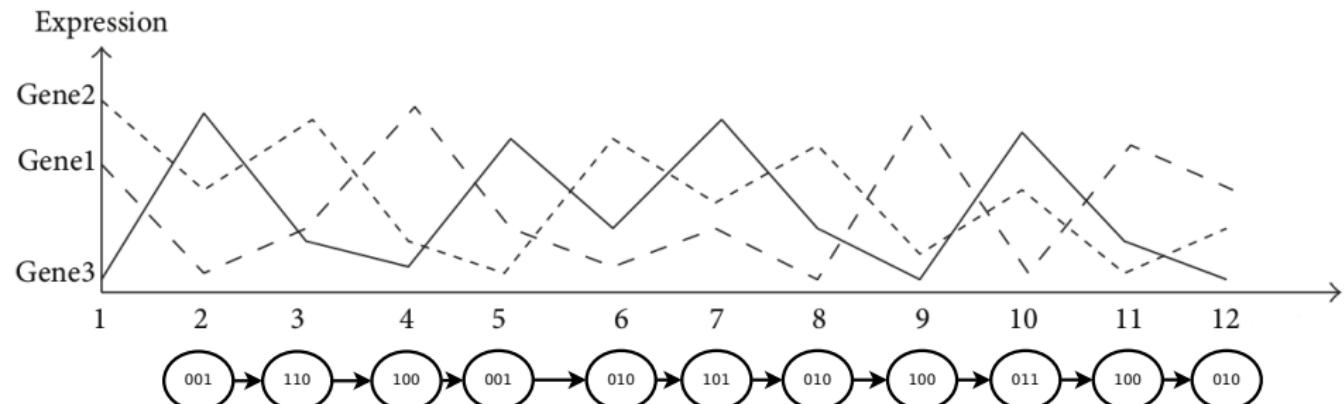
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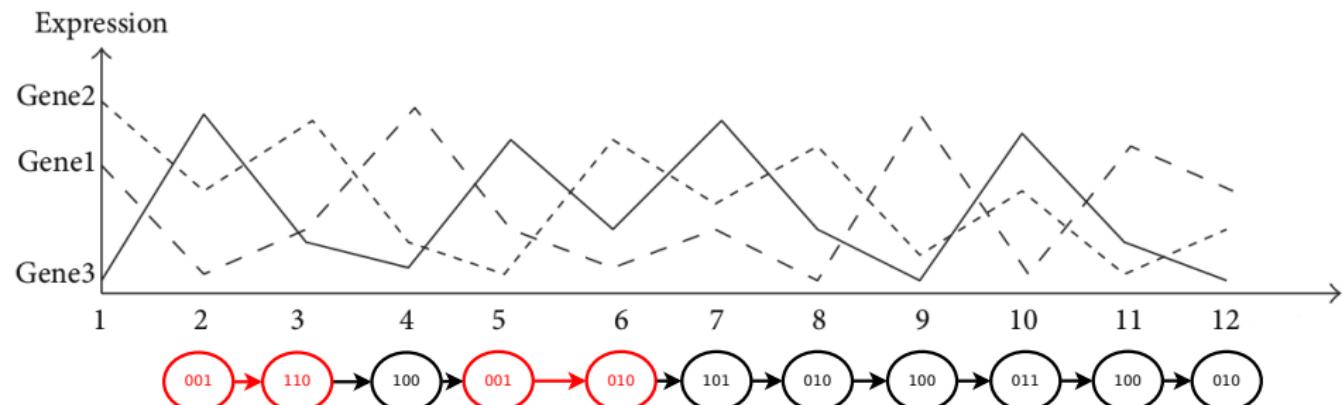
# Construction of Temporal Boolean networks with LFkT

Represent the time series as a sequence of state transitions.



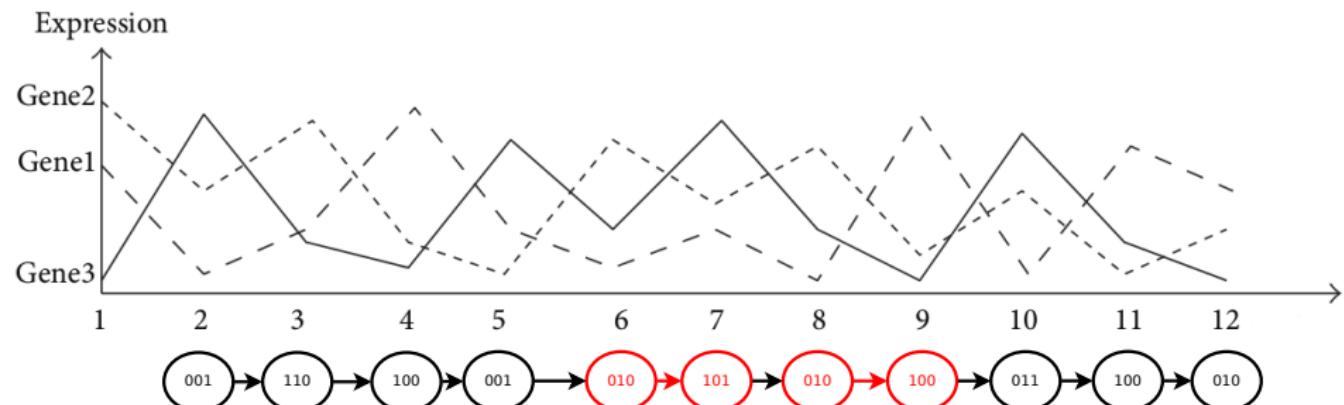
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The algorithm explains inconsistency by using delays.



# Construction of Temporal Boolean networks with LFkT

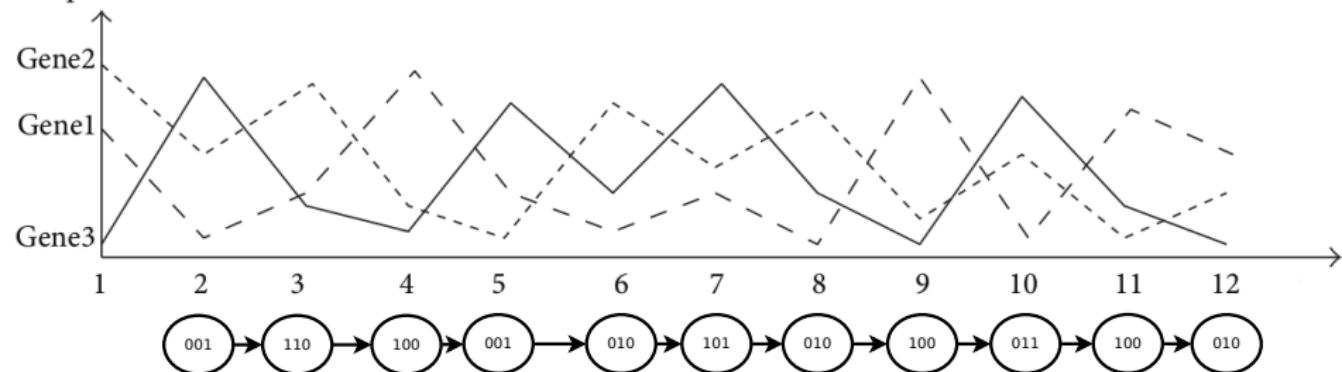
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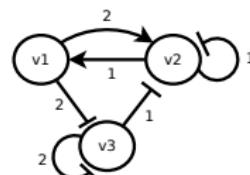
# Construction of Temporal Boolean networks with LFkT

Construct **one** logic program with LFkT that explains the **entire trace** and compute the corresponding **Timed Boolean network**.

Expression



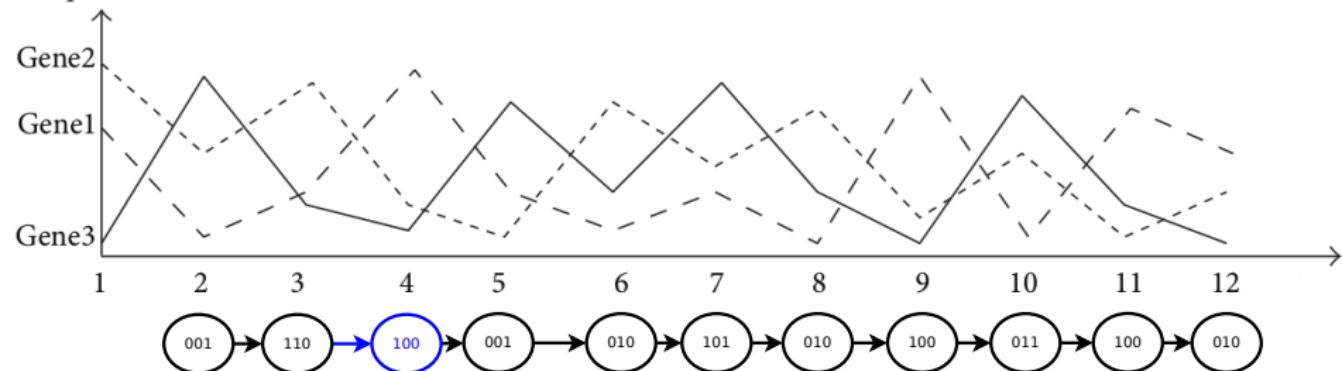
$v1(t) :- v2(t-1).$   
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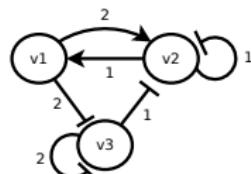
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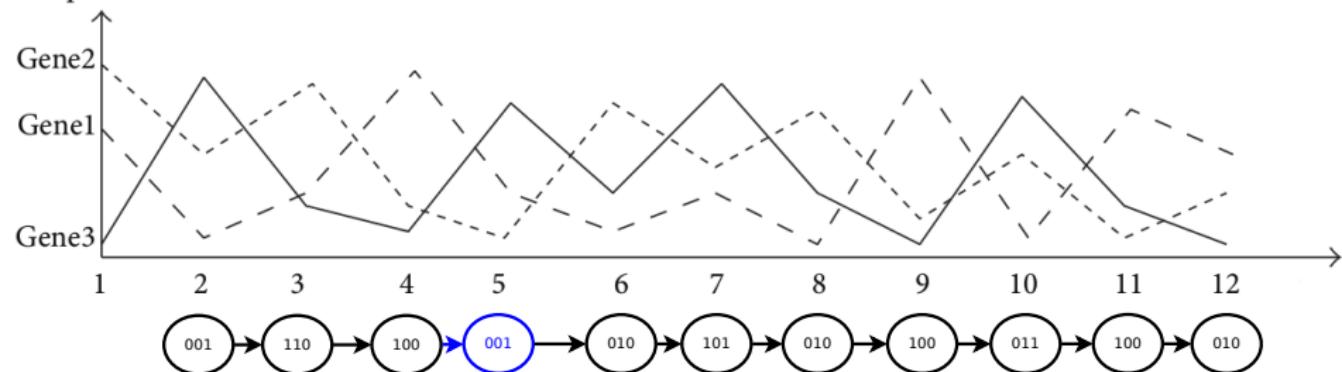
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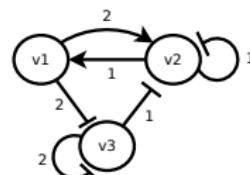
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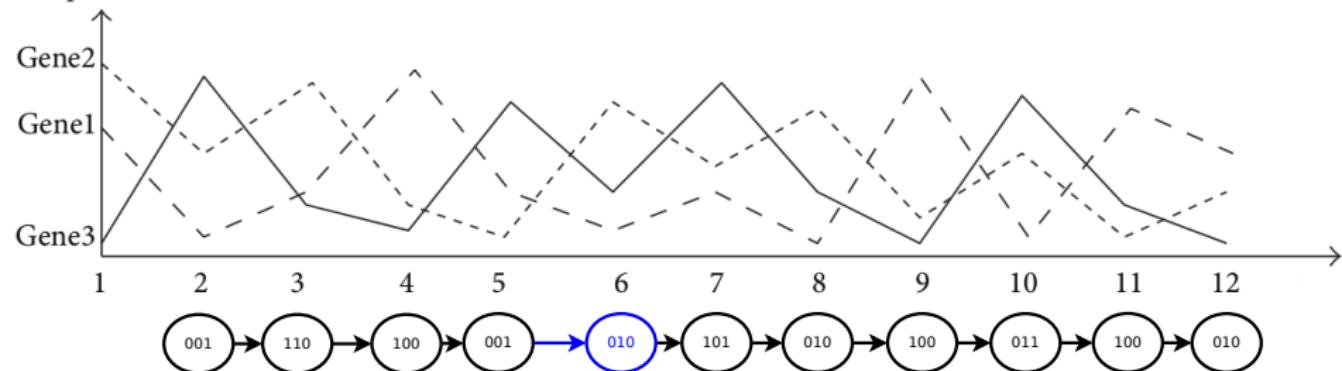
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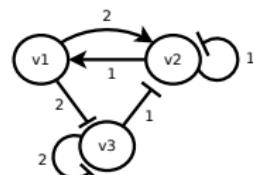
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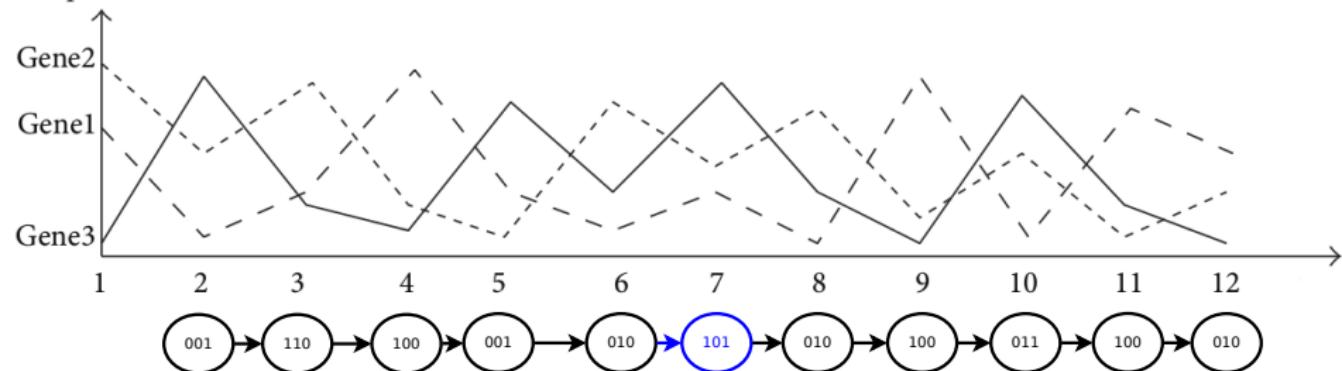
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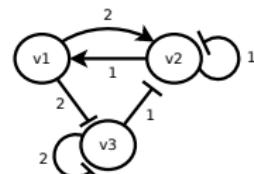
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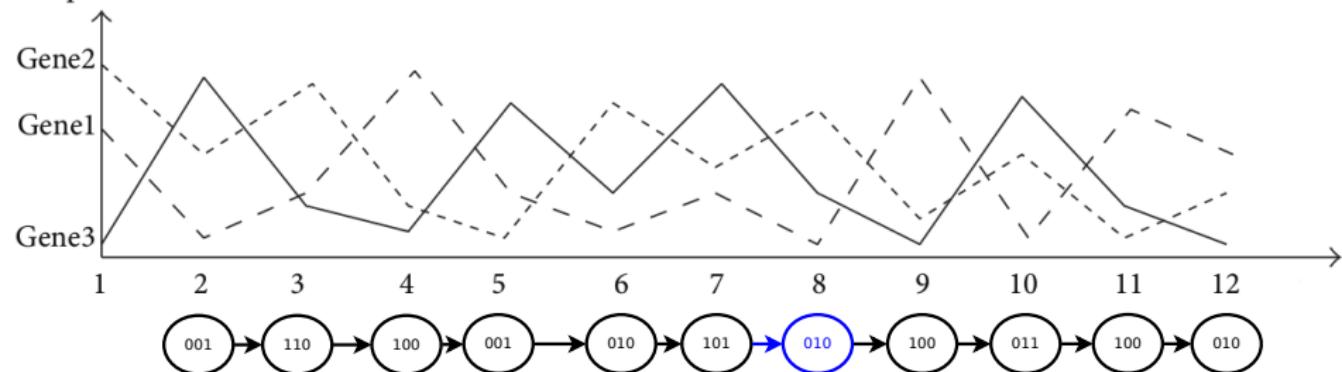
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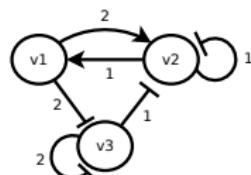
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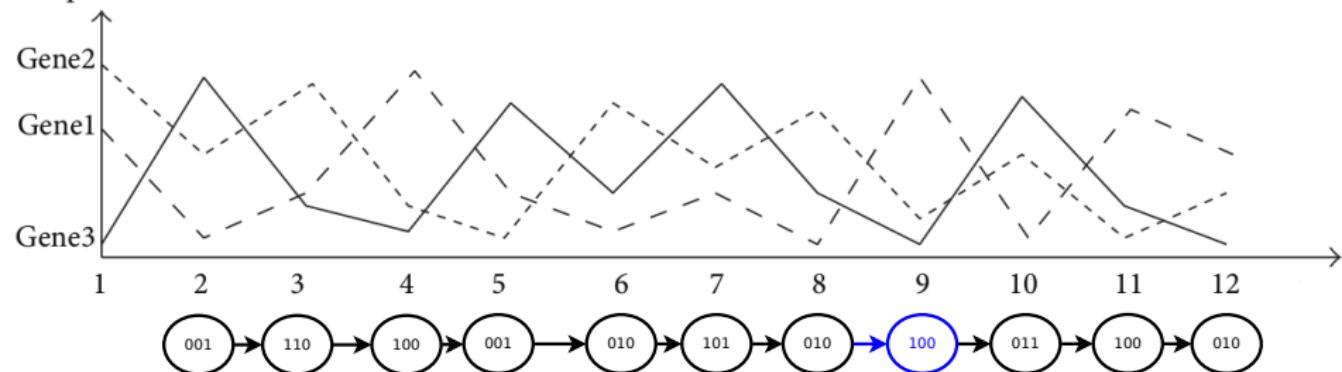
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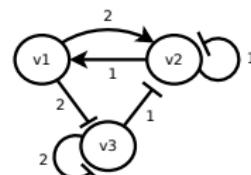
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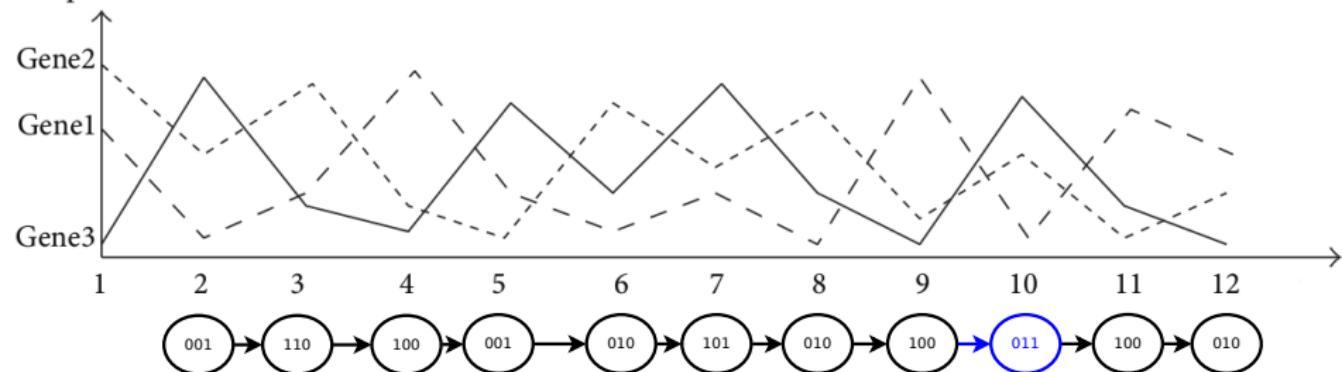
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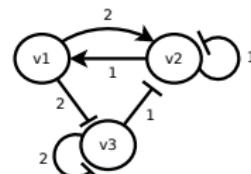
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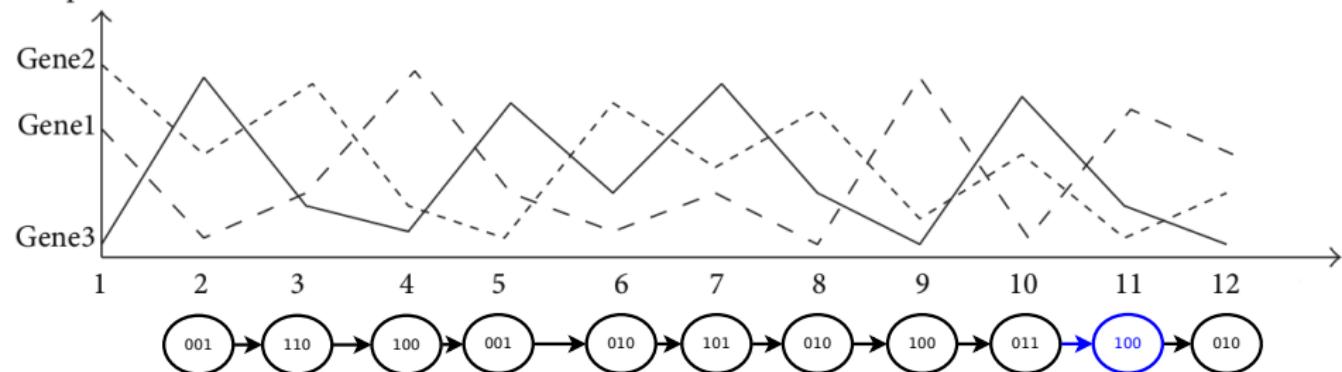
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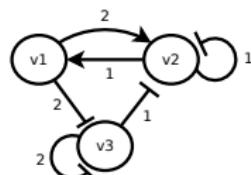
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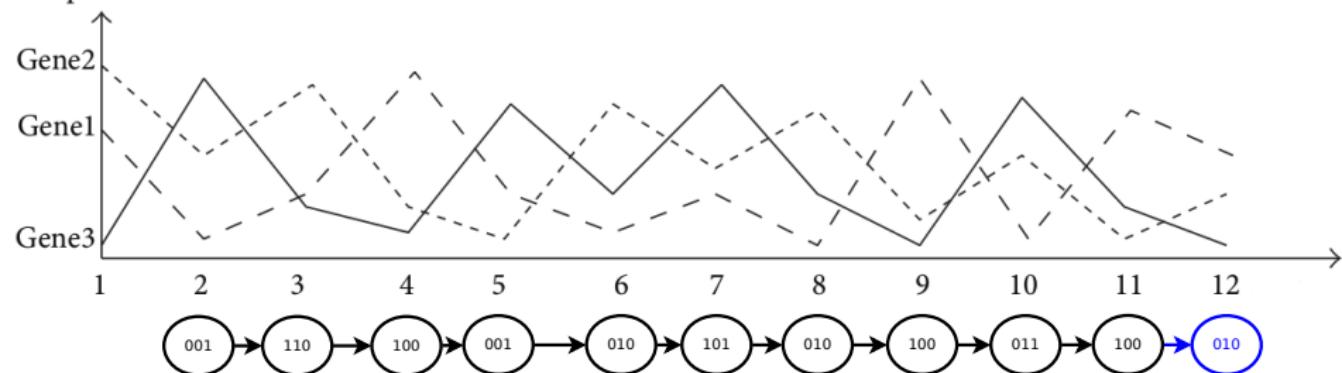
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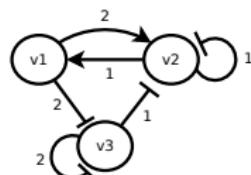
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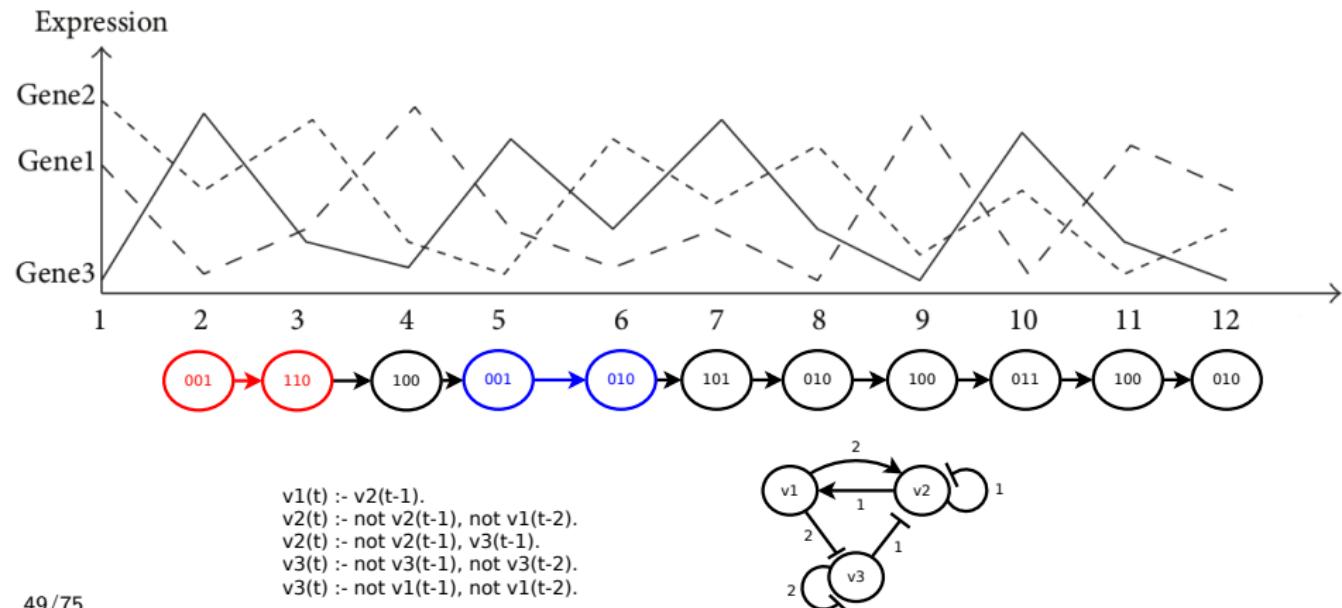


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# Construction of Temporal Boolean networks with LFkT

But the beginning of the trace could not be captured by the model because of the delay.

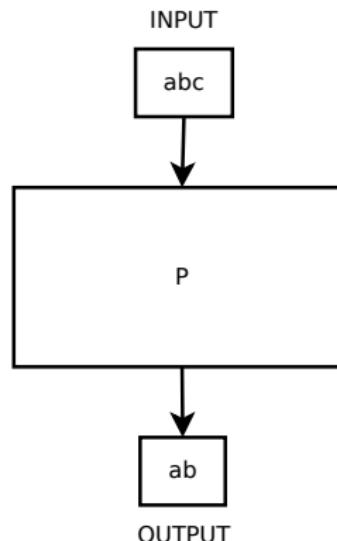


# Outline

- 1 Who is this guy?
- 2 Background
  - Machine Learning
  - Logic Programming
  - Inductive Logic Programming
- 3 PhD work
  - Memoryless Systems
  - Systems with Memory
  - Non-Deterministics Systems
- 4 Postdoc Projects
  - Hyclock
  - DREAM Challenge 11
  - Biology institute of Valrose
- 5 Conclusion

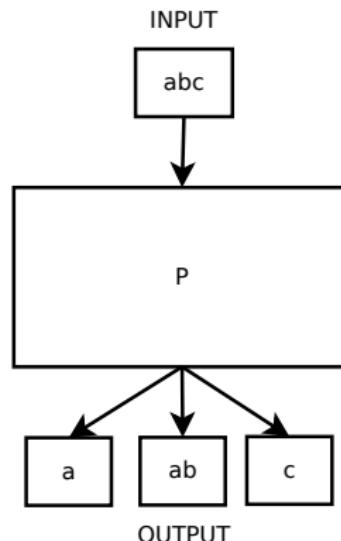
# Non-deterministic System

Deterministic system: from the same input we always have the same output.



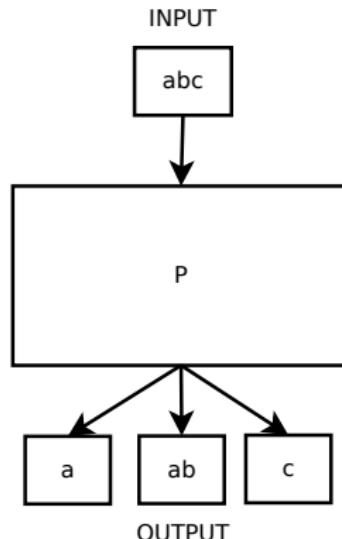
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Non-deterministic system: from the same input we can have a different output.



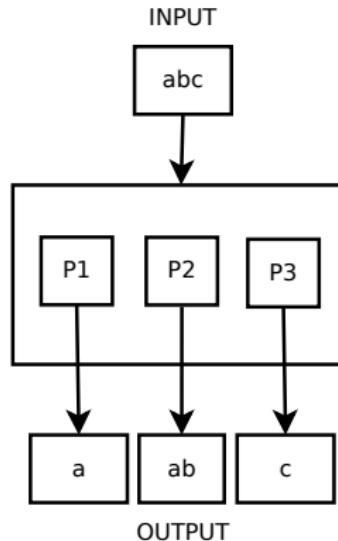
# Non-deterministic System

We represent non-deterministic system by a set of logic programs.  
For an input state, each program provides one possible next state.

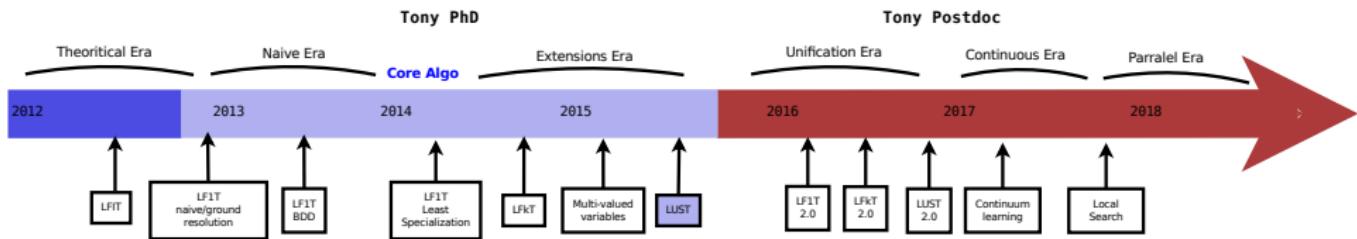


# Non-deterministic System

We represent non-deterministic system by a set of logic programs.  
For an input state, each program provides one possible next state.



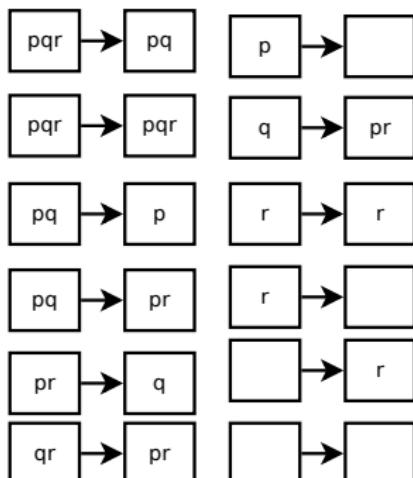
# LFIT Chronology



Tech. com ICLP 2015, long paper ICAPS 2016, journal JMLR 2017.

# LUST: Learning from Uncertain State Transitions (non-deterministic systems)

INPUT:  
A set of pairs of interpretations



OUTPUT:  
A **set** of normal logic programs

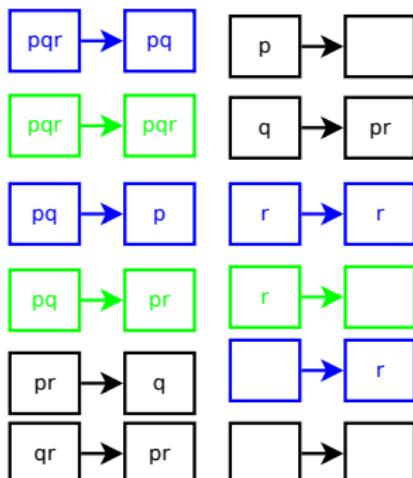
$p(t) \leftarrow q(t - 1).$   
 $q(t) \leftarrow p(t - 1) \wedge r(t - 1).$   
 $r(t) \leftarrow \neg p(t - 1).$

$\oplus$

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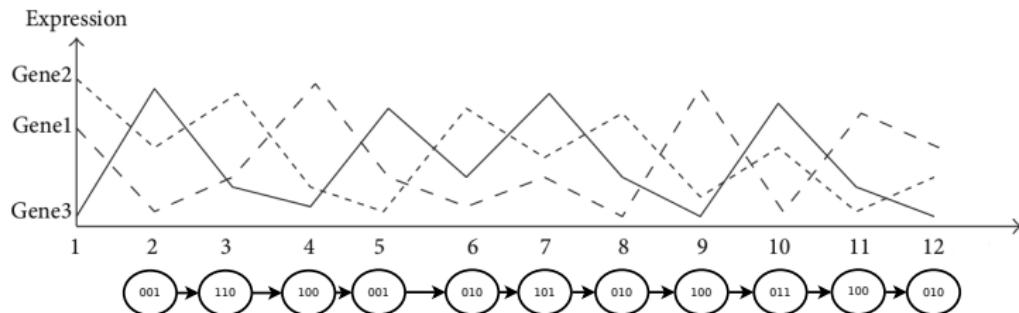
$$\begin{aligned} p(t) &\leftarrow q(t-1). \\ q(t) &\leftarrow p(t-1) \wedge r(t-1). \\ r(t) &\leftarrow \neg p(t-1). \end{aligned}$$

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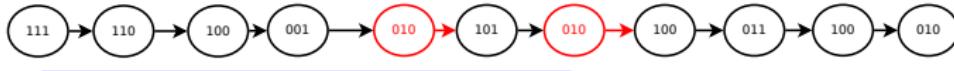
# LUST: Learning From Uncertain State Transition

How to learn this set of logic programs from uncertain state transitions ?



# LUST: Learning From Uncertain State Transition

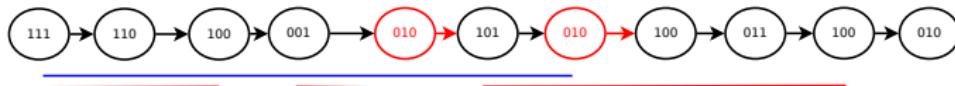
The algorithm starts by learning one program until non-determinism is encountered.



```
v1 :- v2.  
v2 :- not v2, v3.  
v2 :- v1, v3.  
v3 :- not v1, not v3.  
v3 :- not v2, not v3.
```

# LUST: Learning From Uncertain State Transition

The first program is copied and rules are added to the copy to realize the new transition.

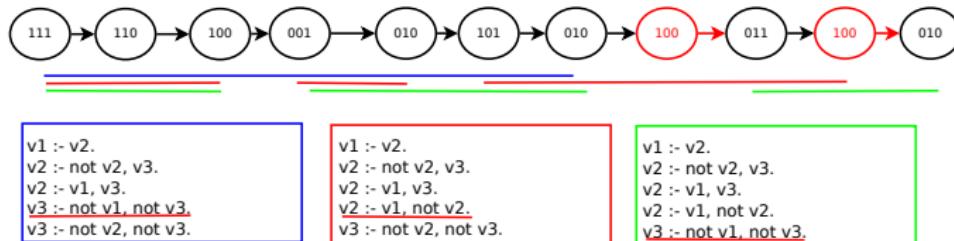


v1 :- v2.  
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v3 :- not v2, not v3.

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v2 :- v1, v3.  
v2 :- v1, not v2.  
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# LUST: Learning From Uncertain State Transition

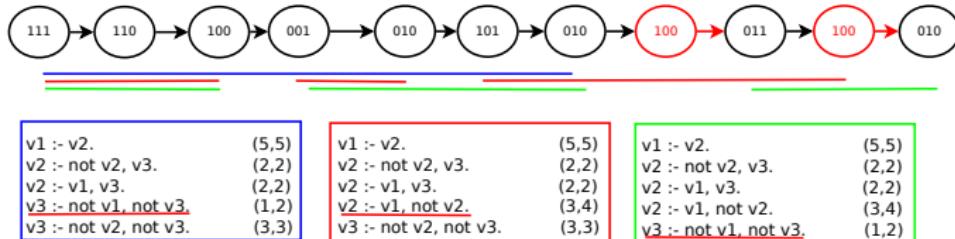
For each transition that is not realized by any program, the same process is performed.



Complexity:  $O(\textcolor{red}{d} \cdot \sum_{T \in O} |T| \cdot n2^n)$  for run time and  $O(\textcolor{red}{d} \cdot 2^n)$  for memory, with  $\textcolor{red}{d}$  the maximal out-degree of an observed state.

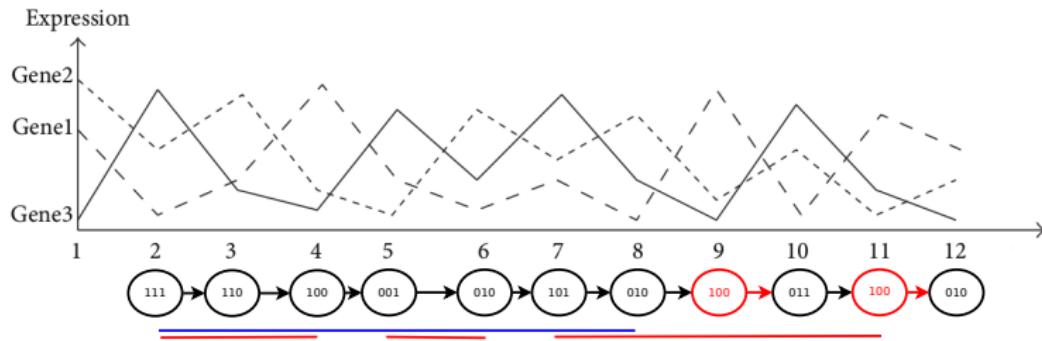
# LUST: Learning From Uncertain State Transition

Counting the number of times a rule matches correctly provides its probability.



# LUST: Learning From Uncertain State Transition

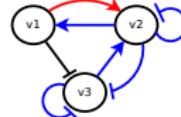
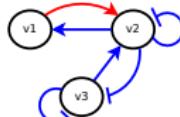
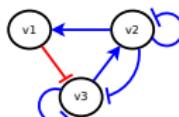
Application: model gene regulatory network from **noisy** data.



$v1 \leftarrow v2.$  (5,5)  
 $v2 \leftarrow \text{not } v2, v3.$  (2,2)  
 $v2 \leftarrow v1, v3.$  (2,2)  
 $\boxed{v3 \leftarrow \text{not } v1, \text{not } v3}$  (1,2)  
 $v3 \leftarrow \text{not } v2, \text{not } v3.$  (3,3)

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# Outline

## 1 Who is this guy?

## 2 Background

- Machine Learning
- Logic Programming
- Inductive Logic Programming

## 3 PhD work

- Memoryless Systems
- Systems with Memory
- Non-Deterministic Systems

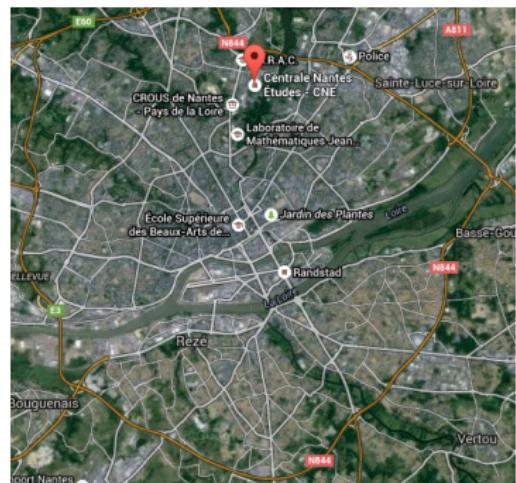
## 4 Postdoc Projects

- Hyclock
- DREAM Challenge 11
- Biology institute of Valrose

## 5 Conclusion

# Laboratory

2 years and 3 months of Postdoc in the MeForBio team of  
IRCCyN/LS2N at École Centrale de Nantes.



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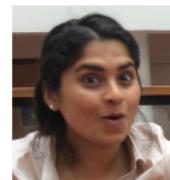
# Team MeForBio of IRCCyN



1 Professor: Olivier Roux



2 Associate Professors: Morgan Magnin and Carito Guziolowski



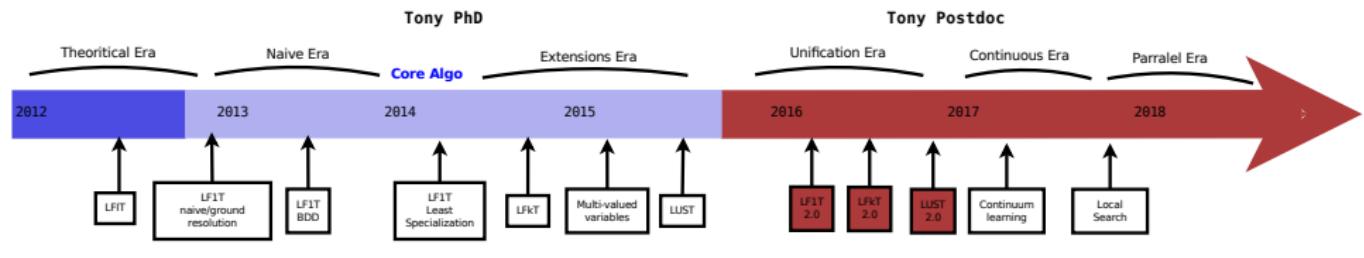
4 PhD: Louis Fippo Fitime, Bertrand Miannay, Emna Ben Abdallah, Misbah Razzak

# Motivation: biological system modeling

## Projects

- Hyclock: influences modeling
- DREAM Challenge 11: predictions
- Biology Institute of Valrose: gene level of expression

# LFIT Chronology



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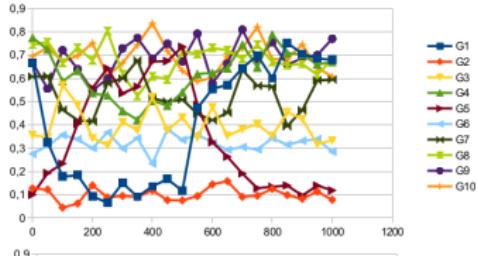
## 5 Conclusion

# Hyclock project: modeling the mammalian circadian clock

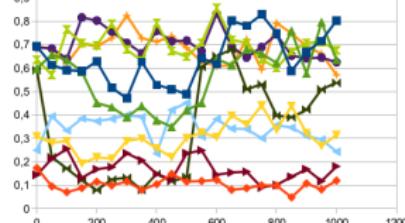
## Data

- 45,000 variables
- 2 time series of 30h
- 1 data point per hour for each variable

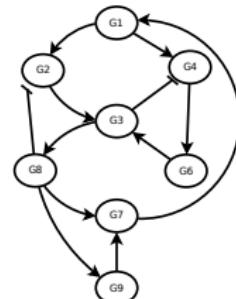
Goal: extract gene influences



G1  
G2  
G3  
G4  
G5  
G6  
G7  
G8  
G9  
G10



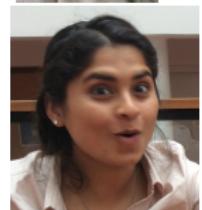
G1  
G2  
G3  
G4  
G5  
G6  
G7  
G8  
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# Team Neo Naoned



3 Professors: Olivier Roux, Paco Chinesta, Katsumi Inoue

2 Associate Professors: Morgan Magnin and Carito Guziolowski

2 Postdocs: Tony Ribeiro and Domenico Borzachiello

3 PhD: Bertrand Miannay, Emna Ben Abdallah, Misbah Razzak

# DREAM Challenge 11: prediction

## Data

- 120 patients, 7 viruses
- Time series over 22 000 variables (gene probes)
- Meta data: shedding, symptomatic and symptoms

## Specificities

- Irregular time points over 240h
- Different sizes of the series

## Challenge

- 25 test patients
- Subchallenge 1: predict probability of shedding
- Subchallenge 2: predict probability of symptomatic
- Subchallenge 3: predict logsymptoms

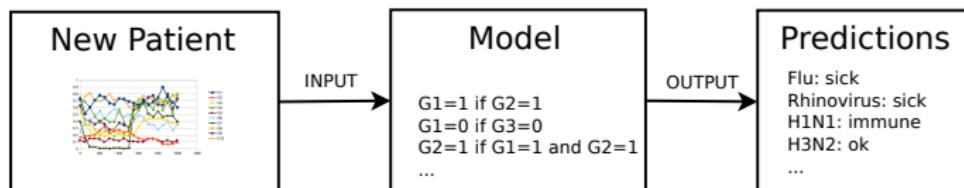
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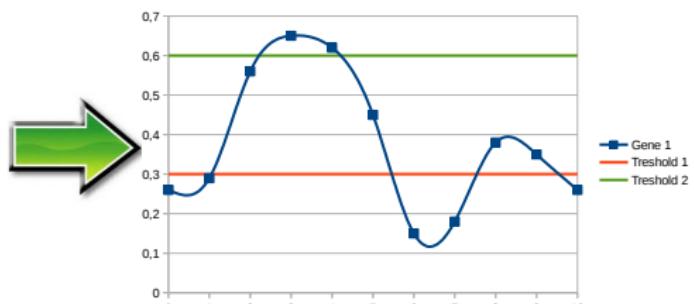
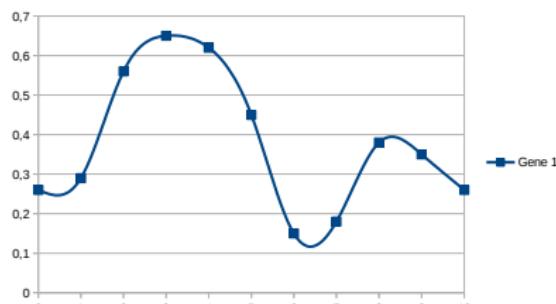
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# Identification of gene level of expression

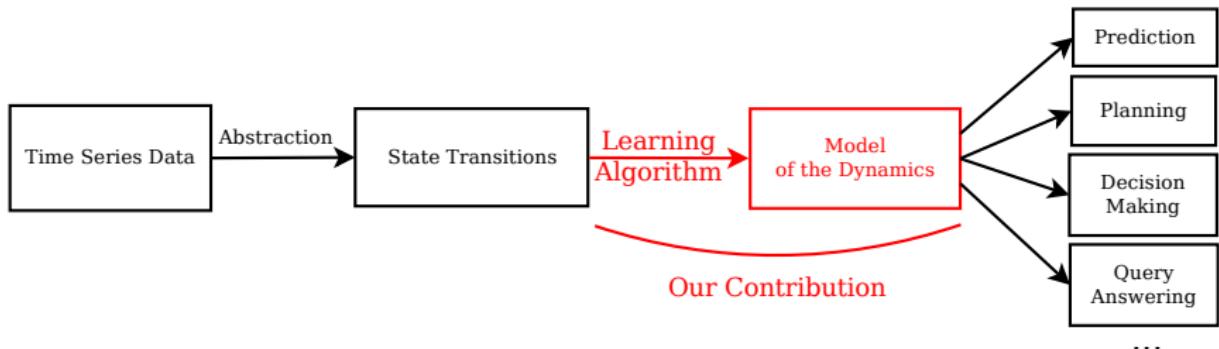
## Data

- 2 genes
- time series **on demand**
- precision **on demand**

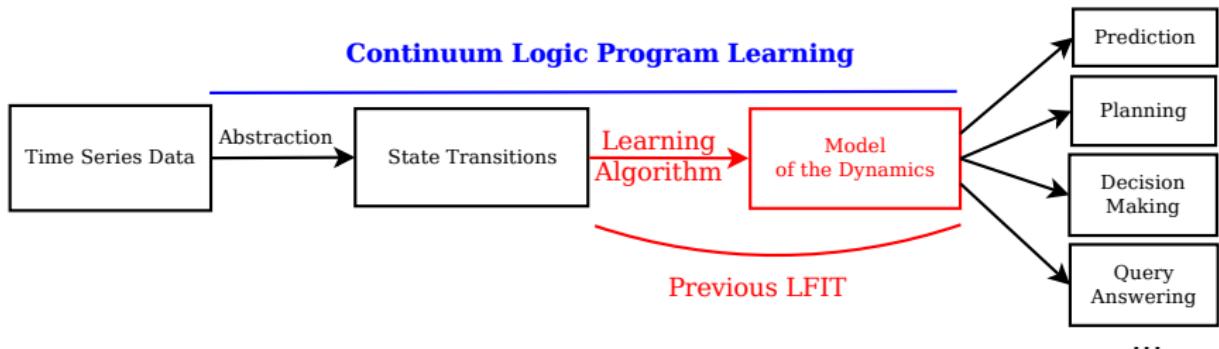
Goal: extract the **levels of expression** of both gene



# LFIT process



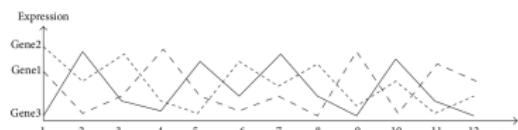
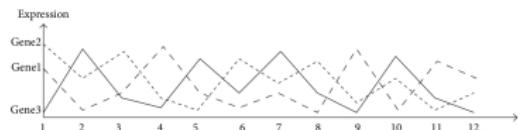
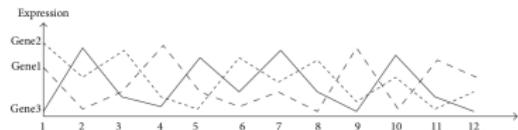
# LFIT process



# Continuum Logic Program

INPUT:

A set of **time series data**



OUTPUT:

A **continuum logic program**

$p([0, 0.5], t) \leftarrow q([0, 0.5], t - 1).$

$p([0.5, 1], t) \leftarrow q([0.5, 1], t - 1).$

$q([0, 0.5], t) \leftarrow p([0, 0.5], t - 1) \wedge r([0.5, 1], t - 1).$

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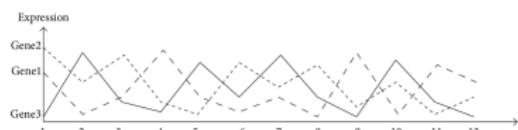
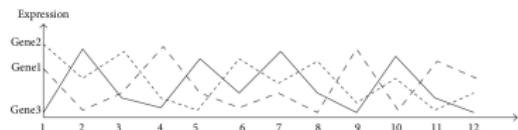
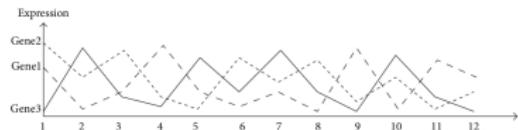
$r([0, 0.5], t) \leftarrow p([0.5, 1], t - 1).$

$r([0.5, 1], t) \leftarrow p([0, 0.5], t - 1).$

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OUTPUT:

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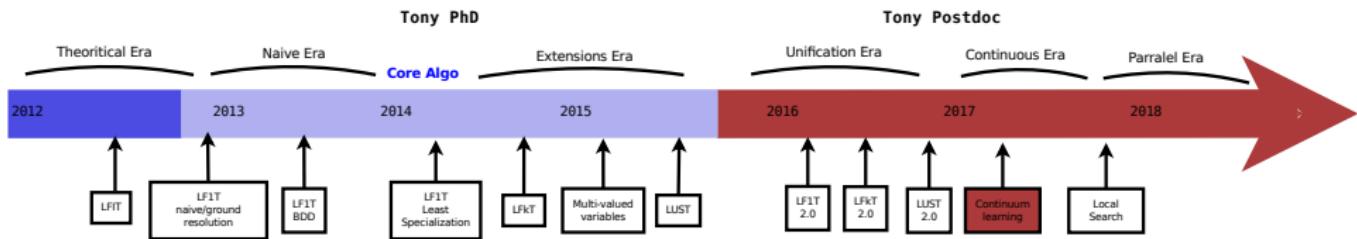
$q([0, 0.5], t) \leftarrow p([0, 0.5], t - 1) \wedge r([0.32, 1], t - 1).$

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# LFIT Chronology



Long paper ILP 2017.

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# Conclusion

## LFIT contribution summary

- Genes influences (LF1T, LFkT, LUST)
- Gene's level of expression (ACEDIA)
- Prediction (NN-LFIT)

## Ongoing

- Local search LFIT
- Temporal logic constraints / Continuous Time Learning
- Learning asynchronous/general semantics

# Conclusion

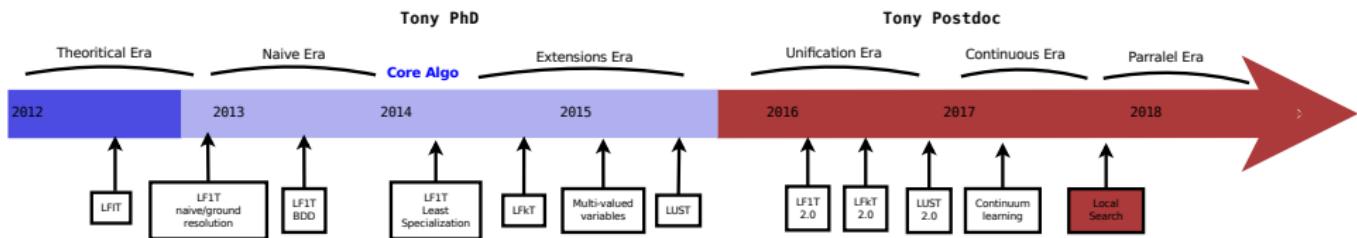
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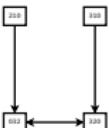
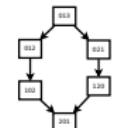
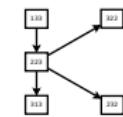
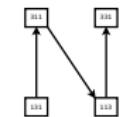
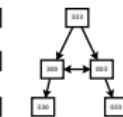
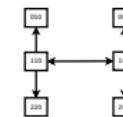
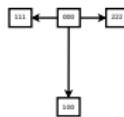
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# LFIT Chronology



Submitted Journal MLJ 2018.



Who is this guy?  
Background  
PhD work  
Postdoc Projects  
Conclusion

# Questions?

