Learning Multi-Valued Biological Models with Delayed Influence from Time-Series Observations

Tony Ribeiro
Morgan Magnin, Katsumi Inoue, Chiaki Sakama

Department of Informatics
The Graduate University for Advanced Studies, Japan

National Institute of Informatics, Japan

Wakayama University, Japan

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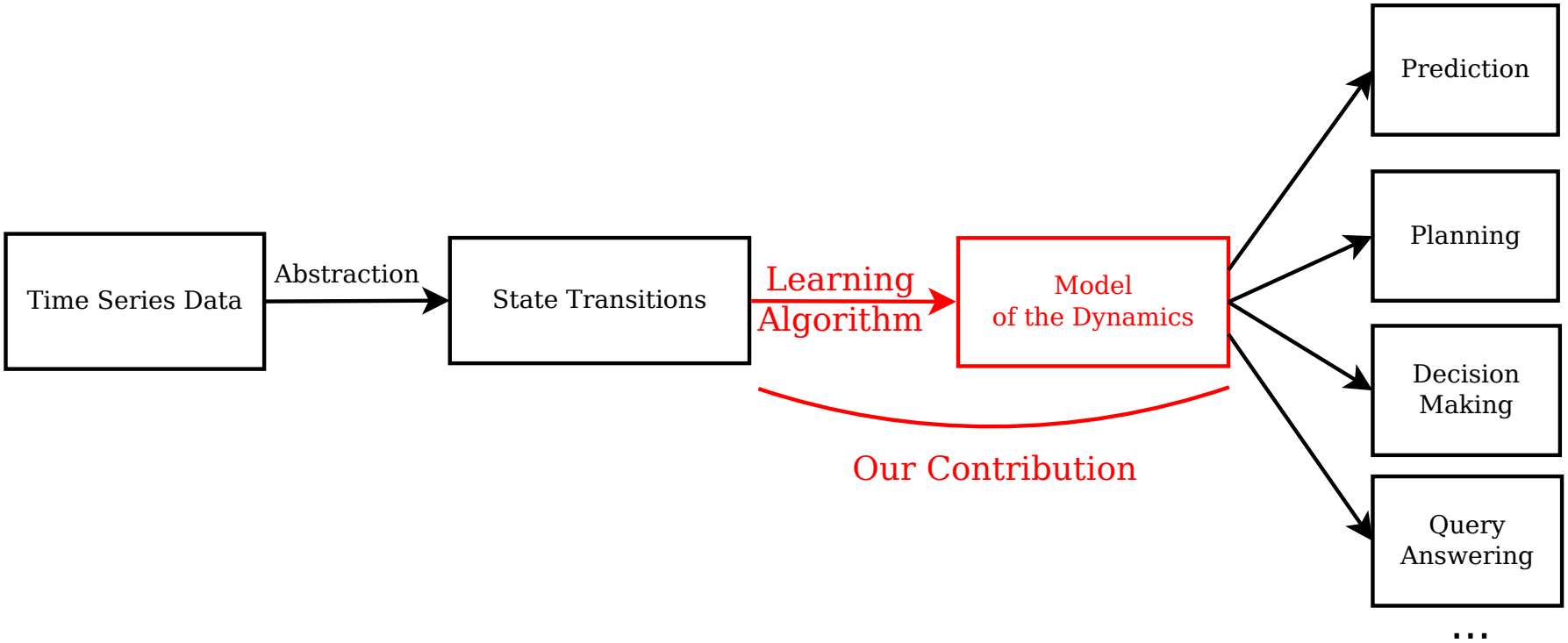
Motivations



Problem:

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

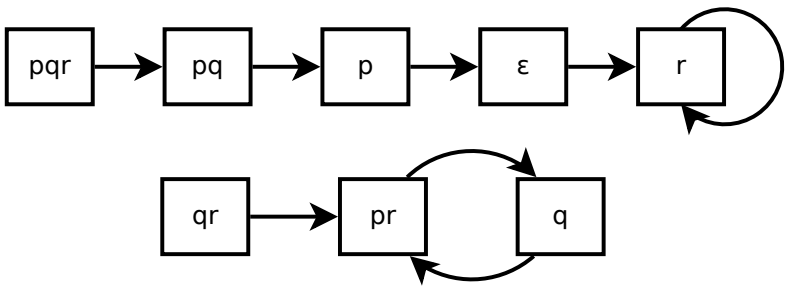
Goal:

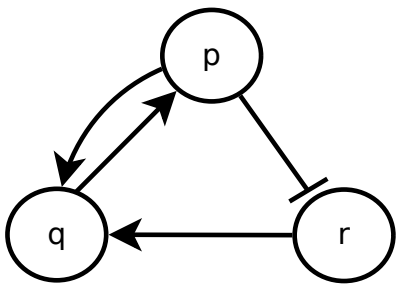
- Automated modeling of systems dynamics from these data.

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

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

Representation: Logic Progam

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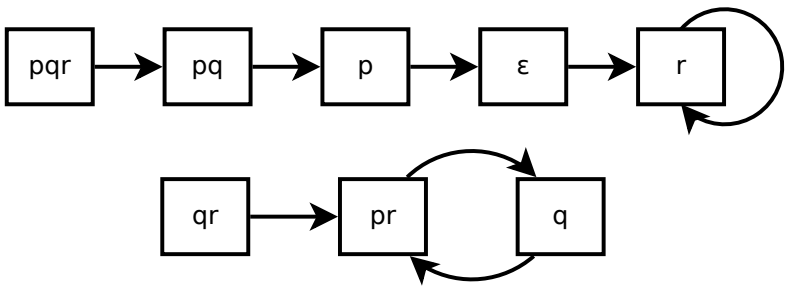
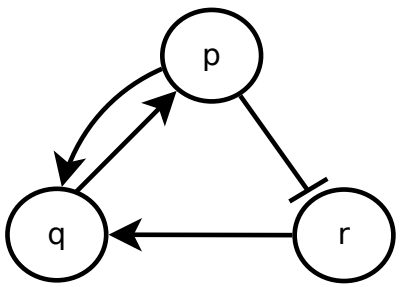


What happens



Why it happens

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

Representation: Logic Progam

Learning From k-Step Transitions (LFkT)

Motivation

- Learn Systems with delayed influences: Markov(k) systems.
- Extract causality from observations, why things happen.
- Predict consequences of new observations, what will happen.

What is new?

- **Automatic** computation of delays
- **Multi-valued** variables
- **Real** benchmark evaluation

Outline

Logic Program

We consider a *logic program* as a set of *rules* of the form

$$p \leftarrow p_1 \wedge \cdots \wedge p_m \wedge \neg p_{m+1} \wedge \ldots \wedge \neg p_n \quad (1)$$

where p and p_i's are atoms ($n \geq m \geq 1$).

Definition (Herbrand Base)

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

Example

- $R_1 = a \leftarrow b \wedge c$
- $R_2 = b \leftarrow a \wedge c$
- $P = \{R_1, R_2\}$ is a logic program
- The Herbrand Base of P is $\mathcal{B} = \{a, b, c\}$

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:

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

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

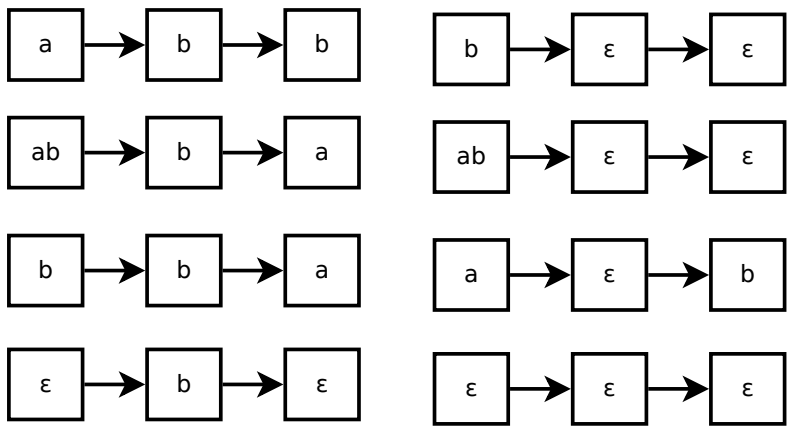
If the Herbrand base of a program P is $\mathcal{B} = \{a, b\}$ then

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

Outline

Example: Detection of the Delay

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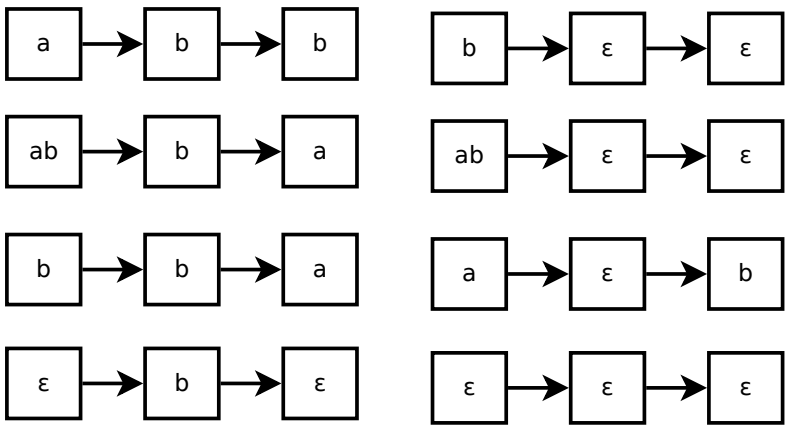

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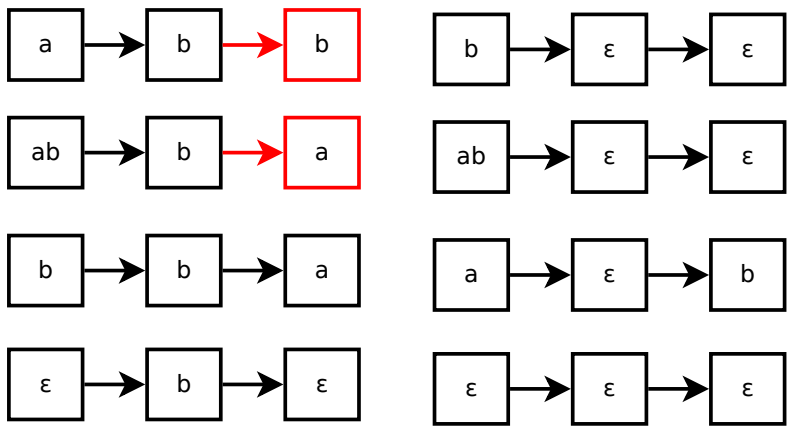

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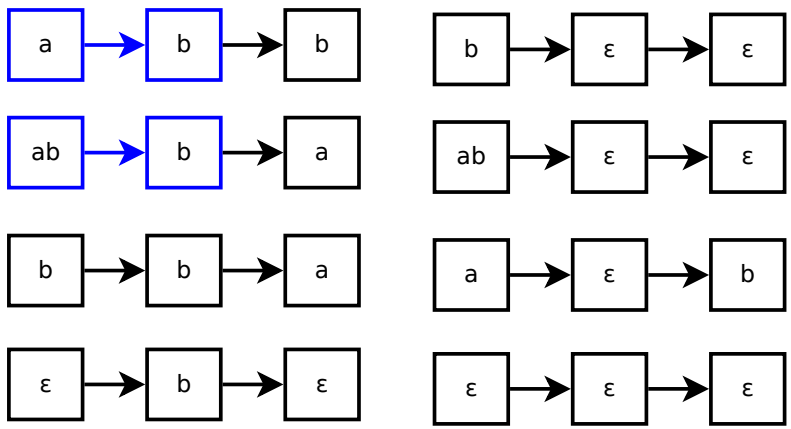


Eight traces of executions of the system S

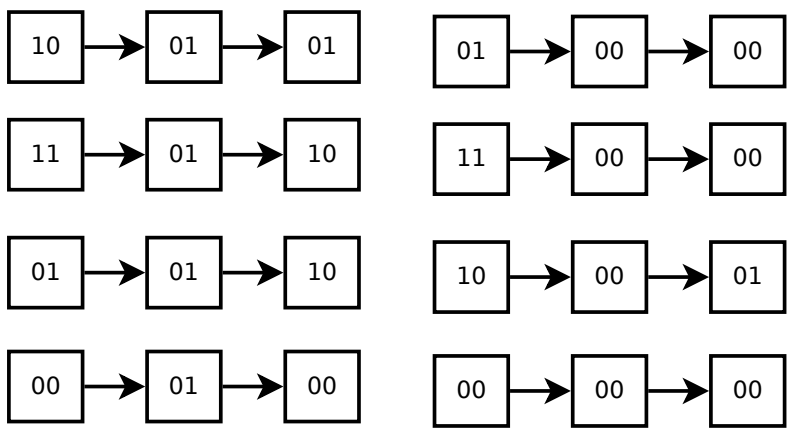
Multivalued Variables

In order to represent multi-valued variables, we now restrict all atoms of a logic program to the form var^{val}. We consider a *multi-valued logic program* as a set of *rules* of the form

$$var^{val} \leftarrow var_1^{val_1} \wedge \cdots \wedge var_n^{val_n} \tag{2}$$

where var^{val} and $var_i^{val_i}$ are atoms ($n \geq 0$).

$$S = \{(a^1 \leftarrow b^1_{t-1}, b^1_{t-2}), (b^1 \leftarrow a^1_{t-2}, b^0_{t-2})\}$$



Outline

DREAM4 input data

- Case studies:
  - 5 different systems each composed of 10 genes
  - 5 different systems composed of 100 genes
  - All come from E. coli and yeast networks
- Data sets available for each system of 10 genes (resp. 100):
  - 5 (resp. 10) time series data with 21 time points
  - Steady state at wild type, i.e. 1 steady state
  - Steady state after knocking out each gene, i.e. 10 steady states (resp. 100)
  - Steady state after knocking down each gene (transcription rate at 50%), i.e. 10 steady states (resp. 100)
  - Steady states after some random multifactorial perturbations, i.e. 10 steady states

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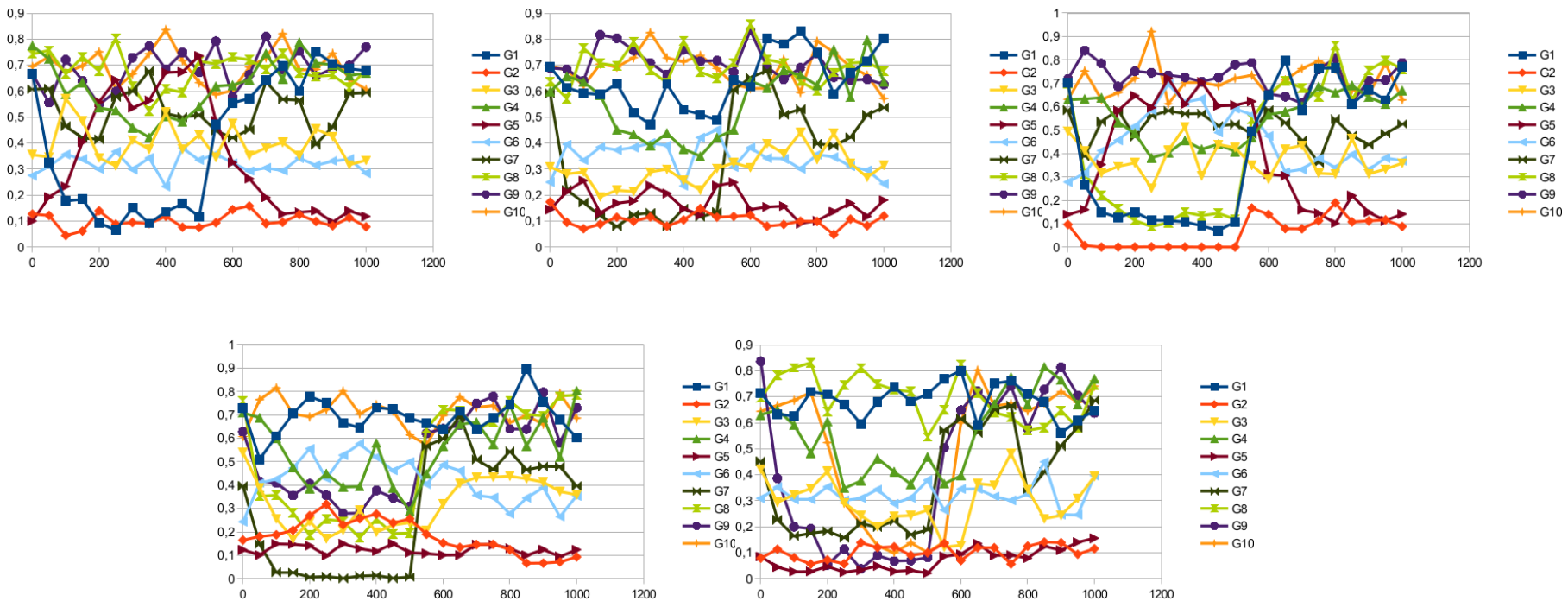
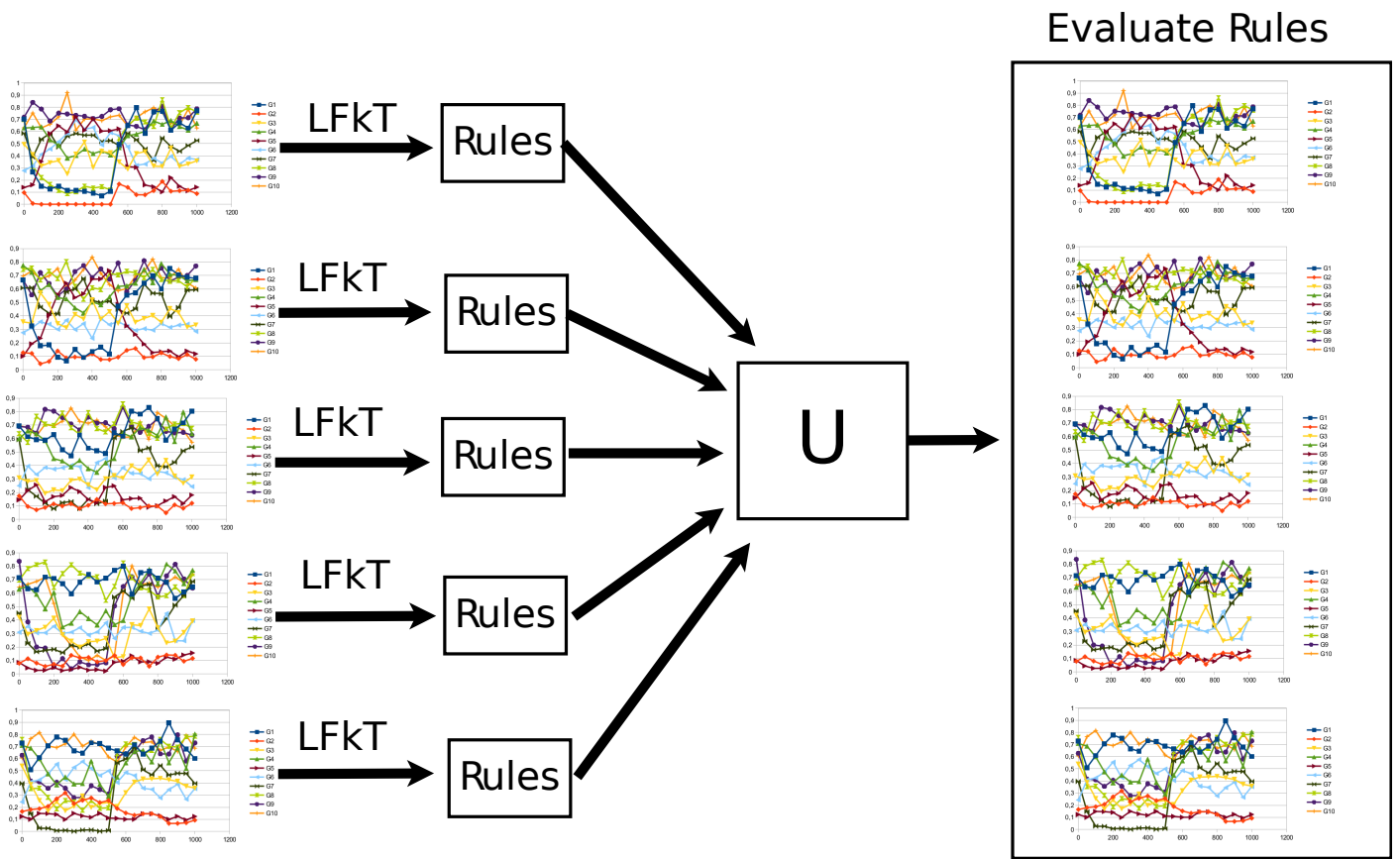
DREAM4 Challenge

- DATA: 5 different time series of genes expression.
- GOAL:
  - Predict the directed unsigned interaction graph
  - Predict steady states from dual knockouts



Learning phase

- INPUT: 5 series of 20 transitions with different perturbations.
- Approach:
  - Learn independently each series with LFkT.
  - Evaluate rules on all series (full cross-validation).



Prediction

Evaluation

- INPUT:
  - An initial state
  - 5 different conditions of dual genes to be knockout simultaneously
- GOAL:
  - Predict the point attractor

Benchmark	run time	raw output	final output	Mean squared error
insilico_size10_1	28s	118,834	359	0.073
insilico_size10_2	2m5s	401,923	462	0.064
insilico_size10_3	44s	151,021	480	0.019
insilico_size10_4	22s	90,904	387	0.031
insilico_size10_5	1m04s	297,364	326	0.091

Evaluation: precision is evaluated as the mean squared error of the difference between predicted/expected values.

Outline

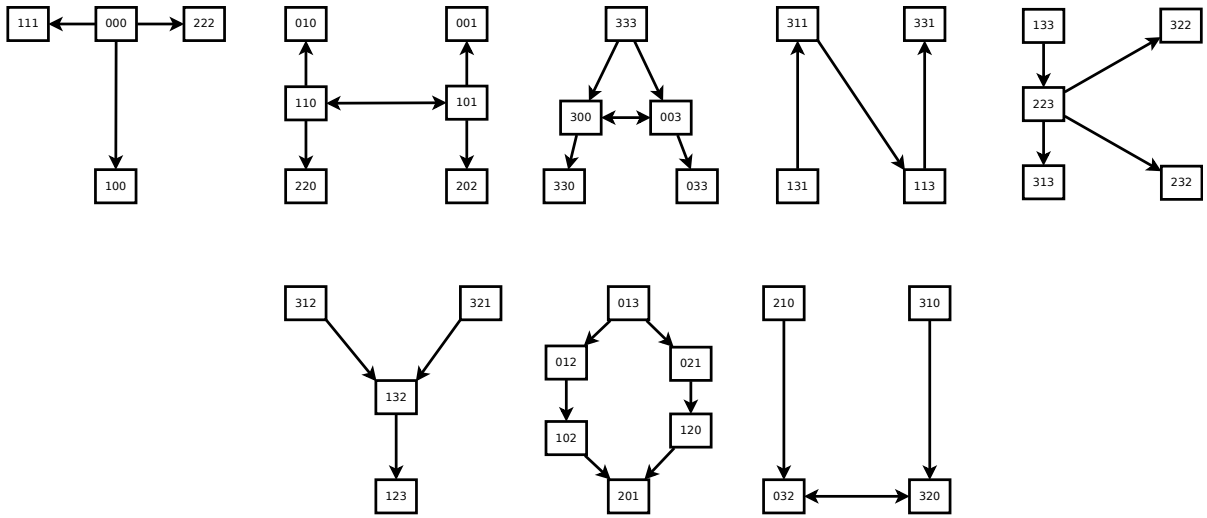
Conclusion

Contribution

- Extension of the LFkT algorithm
  - Detect delay dynamically
  - Handle multivalued variable
- Practical methods
  - Automatic discretization of time series (pre-processing)
  - Heuristic for model simplification (post-processing)

Current & Future works

- Improve performances to tackle big network (DREAM4 100)
- Design method to extract the real influences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