

Boolean Network Identification from Multiplex Time Series Data

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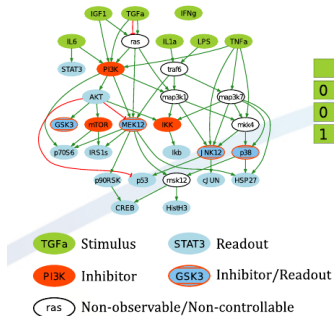
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Challenge

Refine a model with respect to **time series (partial) observations**

Challenge

Phosphoproteomics



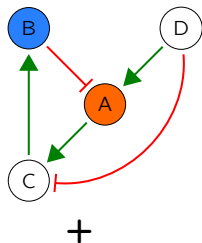
Stimuli	Inhibitors	Readouts
0 0 0 1 0 0 0	0 0 0 0 0 0 0	0.12 0.95 0.02 0.21 0.10
0 0 0 0 0 1 0	0 0 0 0 0 0 1	0.32 0.01 0.25 0.05 0.92
1 0 0 0 0 0 0	0 1 0 0 0 0 0	0.09 0.17 0.86 0.43 0.78
⋮	⋮	⋮
Combinatorial perturbations		Phosphorylation activity in [0,1]

Typical approach:

- Early-response hypothesis: 2 points are considered.
 - Pseudo steady-state approach: *cannot infer cycles*.
 - Difficult to predict *dynamical models* that can reproduce the data.
- ⇒ move to *more general challenge* of learning model from *time-series data*.

Challenge

Prior Knowledge Network (topology)



+

⇒

Dynamical models

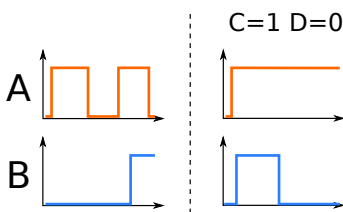
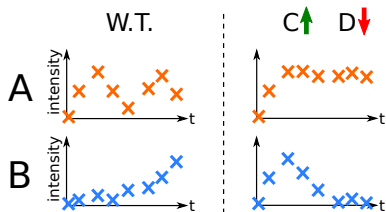
(Boolean networks)

$$A' = D \wedge \neg B$$

$$B' = C$$

$$C' = A \wedge \neg D ; C' = A \vee \neg D$$

Multiplex Time Series Data



Our contribution

We want **all models** (Boolean Networks)

- 1 **compatible with the prior** knowledge network (topology);
- 2 that **can reproduce** the time series data.

Necessary conditions for reproducing time series data

- Quickly invalidate models.
- **No false negative.**
- False positives can be filtered out *a posteriori* using model-checking.

Distance between Boolean Networks and time series data

- When no valid models exist, find close ones (optimization).

Implementation using Answer-Set Programming (ASP)

- Declarative approach.
- **Efficient solver for solution enumeration** and optimization.

Boolean Networks

Definition

Specification: $F = (f_1, \dots, f_n)$

where each $f_i : \mathbb{B}^n \rightarrow \mathbb{B}$, $i \in \{1, \dots, n\}$:

- associates the **next value of node i** to each global state;
- typically depends on a few other nodes.

Semantics: **general updating** mode.

$$\forall x, x' \in \mathbb{B}^n, x \neq x', \quad x \rightarrow x' \stackrel{\Delta}{\Leftrightarrow} \forall i \in \{1, \dots, n\}, x_i \neq x'_i \Rightarrow x'_i = f_i(x)$$

Example

$$\begin{aligned} f_1(x) &= \neg x_2 \vee x_3 \\ f_2(x) &= x_1 \\ f_3(x) &= \neg x_2 \vee x_3 \end{aligned} \quad \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}$$

Remarks: **non-deterministic dynamics**; no chronometry.

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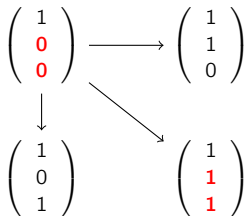
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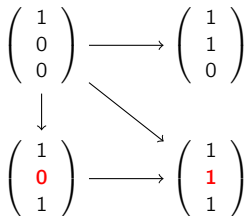
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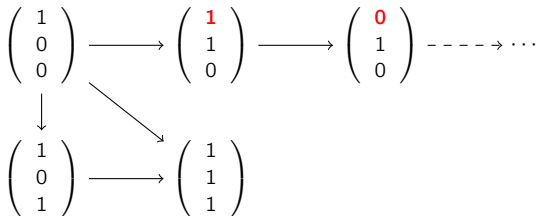
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Boolean Networks

Interaction graph and admissible models



$$\Leftrightarrow \exists x \in \mathbb{B}^n : f_2 \begin{pmatrix} 0 \\ x_2 \\ \vdots \end{pmatrix} < f_2 \begin{pmatrix} 1 \\ x_2 \\ \vdots \end{pmatrix}$$



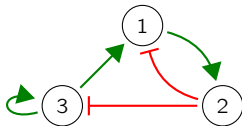
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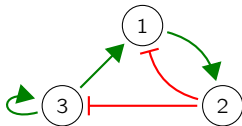
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A Boolean Network is **compatible with a Prior Knowledge Network (PKN)** iff

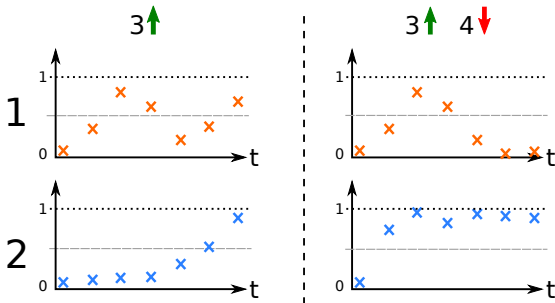
- its interaction graph is **included in the PKN**;
- its interaction graph is **simple** (no double-signed relations).

(we used DNF representations generated from the PKN)

Multiplex Time Series Data

Phosphoproteomics data

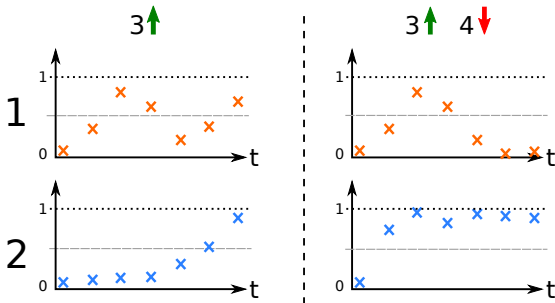
- Different experimental settings
- Partial observations
- Normalized intensities



Multiplex Time Series Data

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Binarization with 0.5 threshold

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A necessary condition for reachability

Verifying if $x \rightarrow^* x'$ is hard (exact model-checking; NP-complete)
 \Rightarrow check a **weaker condition** first.

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Meta-states

- Each node has its value in $\mathbb{M} \triangleq \{\boxed{0}, \boxed{1}, \boxed{0\ 1}\}$.
- If $u \in \mathbb{M}^n$, $S(u) \triangleq \{x \in \mathbb{B}^n \mid \forall i \in \{1, \dots, n\}, x_i \in u_i\}$:

$$u = \begin{pmatrix} \boxed{0} \\ \boxed{0\ 1} \\ \boxed{1} \\ \boxed{0\ 1} \end{pmatrix} \quad S(u) = \left\{ \begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ 1 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ 1 \\ 1 \end{pmatrix} \right\}$$

$$(\boxed{0\ 0} \equiv \boxed{0}; \boxed{1\ 1} \equiv \boxed{1}; \boxed{1\ 0} \equiv \boxed{0\ 1})$$

A necessary condition for reachability

Meta-states semantics ($u \Rightarrow v$ with $u, v \in \mathbb{M}^n$)

- $g_i(u) = u_i \cup \{f_i(x) \mid x \in S(u)\}$;
- Asynchronous updating: only one node value changes.

$$\begin{pmatrix} u_{1..i-1} \\ \boxed{a} \\ u_{i+1..n} \end{pmatrix} \Rightarrow \begin{pmatrix} u_{1..i-1} \\ \boxed{0} \quad \boxed{1} \\ u_{i+1..n} \end{pmatrix} \quad \text{if } \exists x \in u : f_i(x) \neq a$$

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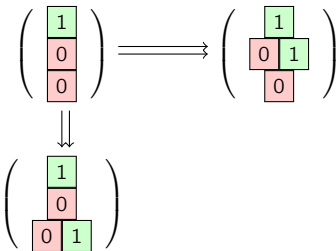
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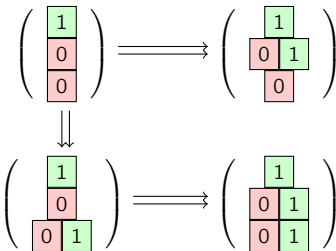
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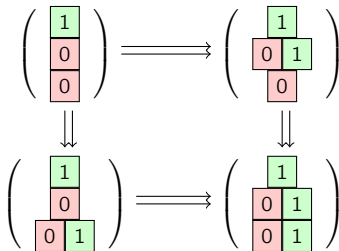
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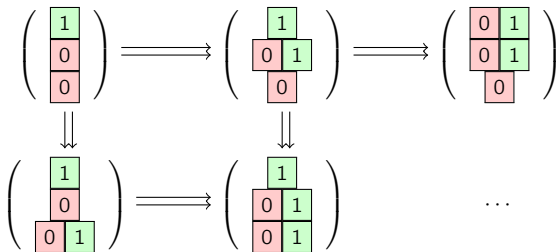
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Theorem

$$\begin{pmatrix} x_1 \\ \vdots \\ x_n \end{pmatrix} \rightarrow^* \begin{pmatrix} y_1 \\ \vdots \\ y_n \end{pmatrix} \text{ only if } \exists \begin{pmatrix} \boxed{x_1} \\ \vdots \\ \boxed{x_n} \end{pmatrix} \Rightarrow^* \begin{pmatrix} \boxed{y_1} \quad \boxed{} \\ \vdots \\ \boxed{y_n} \quad \boxed{} \end{pmatrix} = v$$

where if $x_i = y_i$ with $\boxed{y_i} \quad \boxed{} = \boxed{0} \quad \boxed{1}$, $\exists x' \in S(v) : f_i(x') = x_i$.

Verifying $u \Rightarrow^* v$ is easier than $x \rightarrow^* y$:

- \Rightarrow is strictly monotonous ($S(u) \subsetneq S(v)$);
- no cycles;
- traces have at most n steps (until fixed point).

But is it discriminative enough?

\Rightarrow check false positive rate.

Overview & Implementation

Basic scheme

Input: Data + Prior Knowledge Network (PKN)

0: Binarized Data

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1. Find all BNs compatible with the PKN that satisfy

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(initial value of non-observed nodes is the same across all experiments)

2. (optional) Filter out false positives using model-checking

⇒ No false negatives!

Overview & Implementation

Optimization scheme

When no admissible Boolean Network can reproduce the data...

⇒ find all BNs with the minimum errors.

- Allow mis-matches with the binarized data;
- Minimize the mean square error w.r.t. continuous data.

But we are over-approximating the satisfaction criteria (optimistic):

- returned $\widehat{\text{mse}}$ is smaller than the true minimum mse;
- $\widehat{\text{mse}} = \text{mse}$ if there is at least one true positive (w.r.t. errors).

Implementation

- Answer-Set Programming (declarative approach);
- Gringo+Clasp¹: efficient solver with solutions optimization and enumeration.

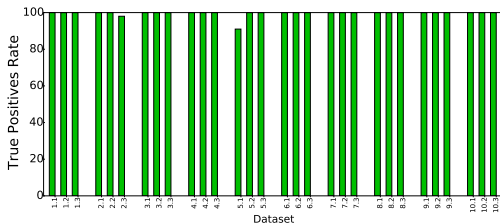
¹: <http://potassco.sourceforge.net>

Evaluation

True positives rate

Synthetic data

- 10 PKNs random subset of a master PKN;
- PKNs gather between 13 and 17 nodes;
- 3 BNs/PKN; 6 observed nodes; 16 time points; 10 experimental settings.



Results

- Time for enumeration: < 2s;
- Results: 12-2,640 BNs (subset-minimal specs.); up to 54,000 for all.
- Posterior model-checking: 1-300s/BN.

Evaluation

Other benchmarks

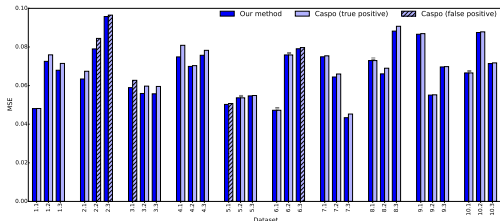
Comparison with [MacNamara Phys. Biol. 2012]

- Same data, recover the predicted BN, and others.
- Faster by **several orders of magnitude**;
- **Exhaustive** identification.

Comparison with **2-points inference methods** using Caspo

[Guziolowski et al., Bioinformatics 2013]

- Advantage of taking into account the dynamics (more accurate predictions);
- Can infer **feedback loops**.



Summary

- Boolean Networks compatible with a PKN that can reproduce time series data.
- Two stages: (1) **quick over-approximation** of resulting set; (2) filter out.
- Declarative implementation.

Features

- **Exhaustive** identification.
- **No false negatives** for exact matching.
- **Optimization** in case of (necessary) errors (MSE under-estimated)
⇒ towards scoring PKNs.

Future work

- Adaptive and multiple discretization thresholds.
- Address larger and real networks (≥ 100 nodes).

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