A First-Order Axiomatization for Transition Learning with Rich Constraints

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Problem overview

- Reminder - a Boolean network:
  - is essentially a function: $BN : \text{Bool}^n \rightarrow \text{Bool}^n$,
  - iterated from a state eventually reaches an attractor,
  - can be represented by $n$ propositional formulas.
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- Our task: Learn a Boolean network model given:
  - Observed data (List of $\text{Bool}^n \times \text{Bool}^n$)
  - Constraints on attractor behaviour.
  - Constraint on the type of formulas representing the BN.
Considerations for applications in bioinformatics

- Observed data – scarce.
- Attractor constraints – may be known.
  - e.g.: Cell eventually reaches homeostasis, dies etc.
- Formula constraints – reasonable assumptions normally hold in practical models.
  - e.g.: Both Mammalian Cell Cycle \( (n=9)^1 \) and Fanconi Anemia \( (n=28)^2 \) models can be represented by 4-term DNFs.

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2 Alfredo Rodríguez et al. “A Boolean network model of the FA/BRCA pathway”. In: Bioinformatics 28.6 (2012).
Why constraint the model?

- Theorem: To learn a unique, correct BN from data only, we need to know transitions from all possible states.\(^3\)
  - No free lunch for BN learning.
- We show that adding the constraints reduces the need for data.

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Example
Given observations

000 → 001
100  101
↑      ↑
110  ← 111
010    011
Example

$2^n$ possible transitions from each unseen state. Which one to choose?
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With constraints

- When we use the following constraints, there is a unique admissible model:
  - Exactly 2 attractors; one of period 2 and one fixed point.
  - Formula for each variable is a conjunction of literals.

\[
p(t + 1) = q(t) \\
q(t + 1) = p(t) \land r(t) \\
r(t + 1) = \neg p(t)
\]
Identifying the solutions
A provisional algorithm

- Transform the constraints and data to axioms of a FOL theory.
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- Transform the constraints and data to axioms of a FOL theory.
- Use a model-checking technique to find its model(s).\(^4\)
- Transition formulas can be read directly from the model.

Identifying the solutions
A possible formalization as a theory in FOL with equality

- Axiom for transition observation (example 000 → 001):
  \[ p(f, f, f) = f \land q(f, f, f) = f \land r(f, f, f) = t \]
- We must explicitly state that: \( \neg(f = t) \)
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- **We must explicitly state that:** \( \neg (f = t) \)

- **Define semantics of propositional conjunction:**

  \[
  \forall P_p, P_q, P_r, N_p, N_q, N_r, l_p, l_q, l_r. \ \conj(P_p, P_q, P_r, N_p, N_q, N_r, l_p, l_q, l_r) = t \iff \\
  \bigwedge_{i \in \{p, q, r\}} (P_i = t \rightarrow l_i = t) \land (N_i = t \rightarrow l_i = f)
  \]

- **Constraint expressivity of** \( p \) **to conjunction**:

  \[
  \exists P_p, P_q, P_r, N_p, N_q, N_r. \ \forall l_p, l_q, l_r. \ p(l_p, l_q, l_r) = \conj(P_p, P_q, P_r, N_p, N_q, N_r, l_p, l_q, l_r)
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  - **Formulas can be read from Skolem constants in a model.**
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- Constraint “There is a fixed-point attractor”:

  \[
  \exists l_p, l_q, l_r. \ p(l_p, l_q, l_r) = l_p \land q(l_p, l_q, l_r) = l_q \land r(l_p, l_q, l_r) = l_r
  \]

- To require higher order attractors, iterate the transition function or use a reachability predicate.

- To restrict other attractors, use also uniqueness quantification.
Experimental results

On the above model with conjunction expressivity constraint

- exactly 2 attractors with lengths 1 and 2
- no constraint
- exactly 2 diff. attractors, unspec. lengths
- exactly 1 attractor with length 1
- exactly 1 attractor with length 2

- number of known transitions
- mean number of smallest models

Note: Without the conjunction constraint, the number of admissible models would be far higher: \(8^{8-|data|}\).

With the strongest constraints, \(\frac{5}{8} = 62.5\%\) data was usually enough to unambiguously identify the single correct model.

Conclusion: Knowledge about attractors can help us reduce the need for data in BN learning.


Thank you for attention!