ASKeD-BN: Automatic Synthesis of Boolean Networks from Biological Knowledge and Data

Athénaïs Vaginay, Taha Boukhobza, Malika Smaïl-Tabbone

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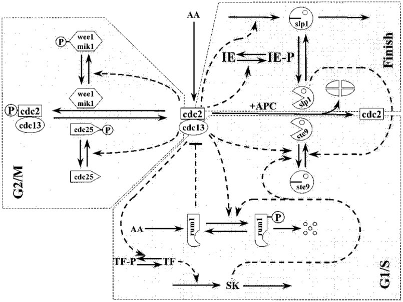
Modeling Biological Systems with Boolean Networks

Boolean Networks (BN) are:

- qualitative formalism, well-suited for biological systems
- built from experimental data and knowledge from literature
- the **automatic** synthesis of BNs from biological data and knowledge is still a challenge



from Novak et al. 2001

Boolean Networks – Generalities

$$\mathscr{B} = \begin{cases} f_{\mathsf{A}} : a_{t+1} &= c_t \\ f_{\mathsf{B}} : b_{t+1} &= b_t \wedge \neg c_t \\ f_{\mathsf{C}} : c_{t+1} &= \neg c_t \end{cases}$$

in the Boolean world: $\mathbb{B} = \{0, 1\}$

n Boolean **components**

BN = set of n **update functions**

negation: $\neg$ disjunction: $\vee$ conjunction: $\wedge$

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"C activates A"

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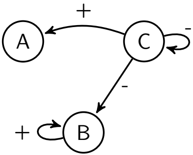

Interaction Graph (IG)

nodes: components of the BN

edges: influences + polarity

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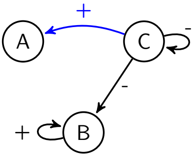

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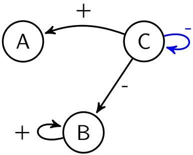

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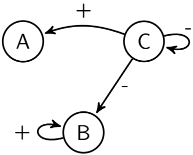

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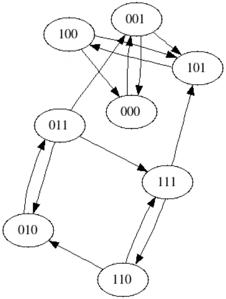
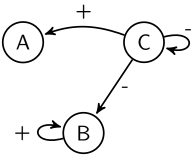


State Transition Graph (STG)

nodes: configurations of the BN (vector $\in \mathbb{B}^n$)
e.g. 001, 010, 111, ...

edge from c to c' if c' = f(c)

Boolean Networks – Synthesis from Knowledge and Data



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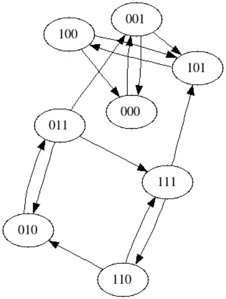

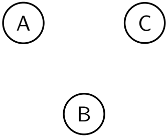

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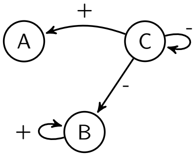

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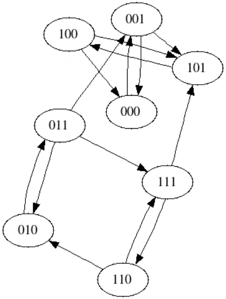

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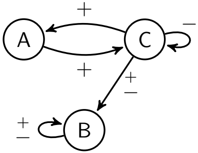

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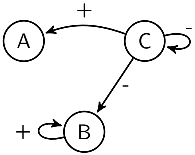

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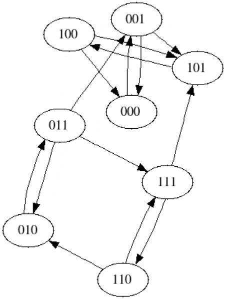

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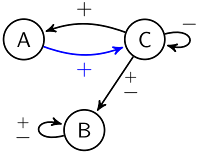

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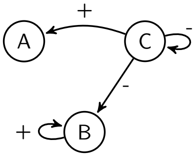

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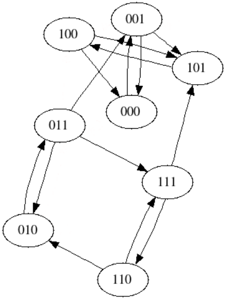

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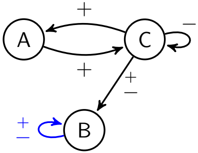

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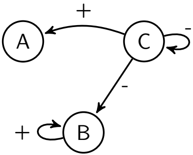

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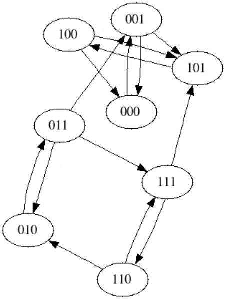

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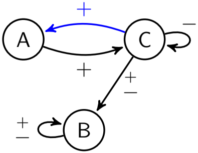

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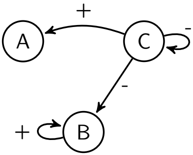

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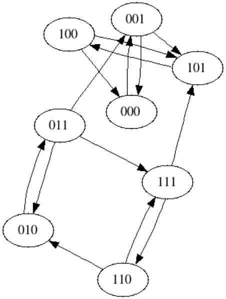

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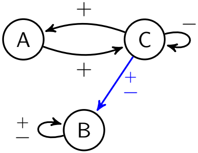

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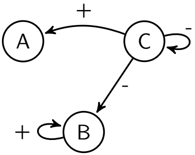

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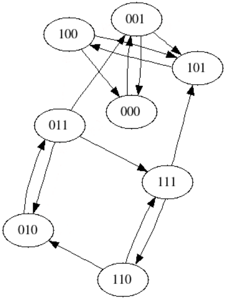

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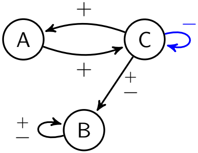

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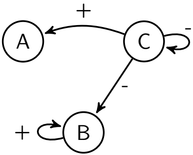

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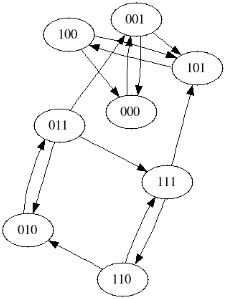

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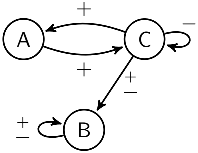

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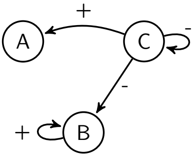

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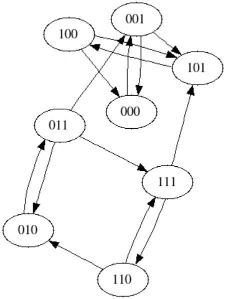

Prior Knowledge Network (PKN)

Super-set of influences allowed

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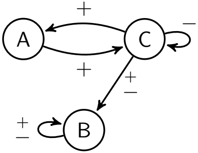

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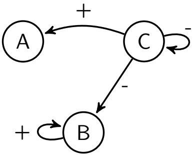

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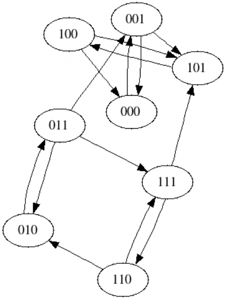

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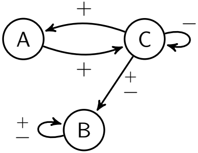

Multivariate Time Series (TS)

Concentrations of the components over time

t	1	2	3	4	5	6	7	8	9	10	11	12	13	...
A	0	3	7	13	20	30	49	61	100	63	36	25	2	...
B	100	86	64	57	54	53	51	49	45	37	33	28	22	...
C	0	27	36	42	60	75	54	44	38	48	60	72	88	...

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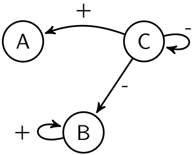

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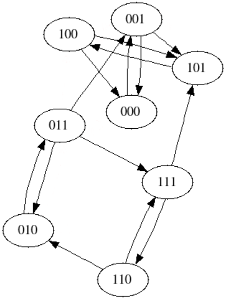

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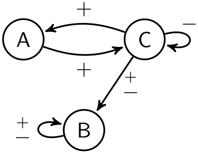

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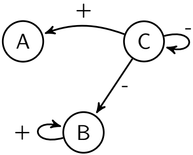

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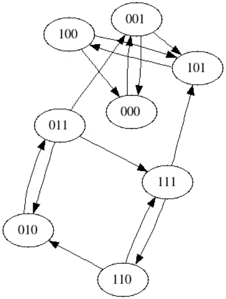

Prior Knowledge Network (PKN)

Super-set of influences allowed

"A activates C"
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"C activates A"
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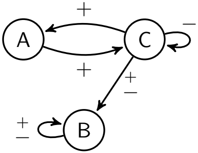
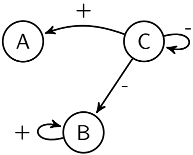


Multivariate Time Series (TS)

Concentrations of the components over time

t	1	2	3	4	5	6	7	8	9	10	11	12	13	...
A	0	3	7	13	20	30	49	61	100	63	36	25	2	...
B	100	86	64	57	54	53	51	49	45	37	33	28	22	...
C	0	27	36	42	60	75	54	44	38	48	60	72	88	...

Boolean Networks – Synthesis from Knowledge and Data



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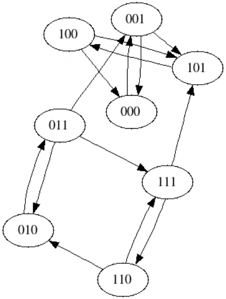

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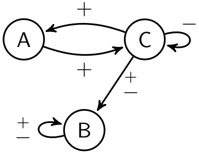

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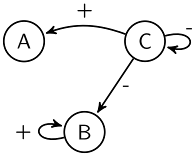

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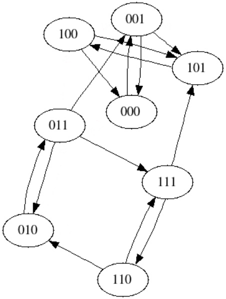

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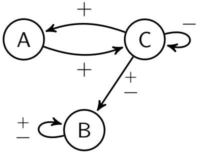

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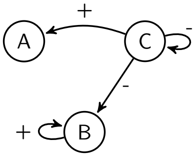
t	1	2	3	4	5	6	7	8	9	10	11	12	13	...
A	🟥 0	🟥 3	🟥 7	🟥 13	🟥 20	🟥 30	🟥 49	🟩 61	🟩 100	🟩 63	🟥 36	🟥 25	🟥 2	...
B	🟩 100	🟩 86	🟩 64	🟩 57	🟩 54	🟩 53	🟩 51	🟥 49	🟥 45	🟥 37	🟥 33	🟥 28	🟥 22	...
C	🟥 0	🟥 27	🟥 36	🟥 42	🟩 60	🟩 75	🟩 54	🟥 44	🟥 38	🟥 48	🟩 60	🟩 72	🟩 88	...

Boolean Networks – Synthesis from Knowledge and Data



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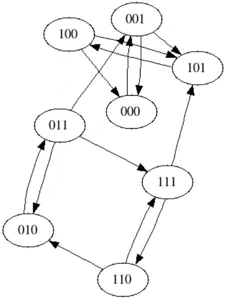

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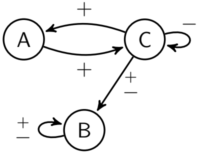

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t	1	2	3	4	5	6	7	8	9	10	11	12	13	. . .
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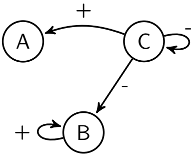
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	🟥	. . .
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	🟩	. . .

Boolean Networks – Synthesis from Knowledge and Data



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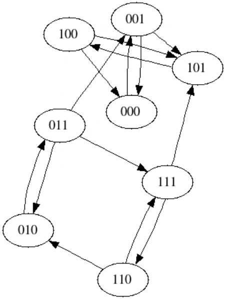

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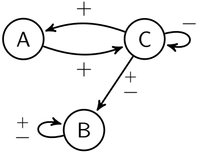

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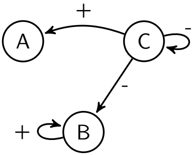
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	. . .
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	🟥	. . .
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	🟩	. . .

Boolean Networks – Synthesis from Knowledge and Data



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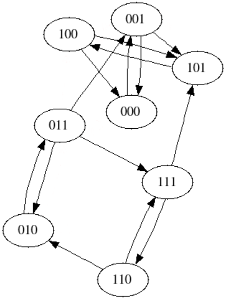

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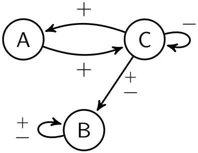

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		010		→	011		→	100		→	001		
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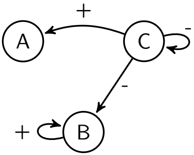
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	🟩	. . .

Boolean Networks – Synthesis from Knowledge and Data



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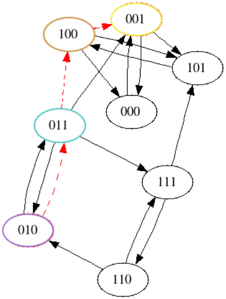

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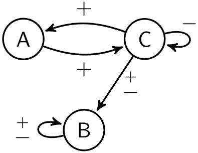

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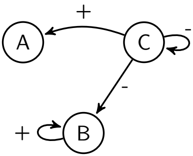
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	🟩	. . .

Boolean Networks – Synthesis from Knowledge and Data



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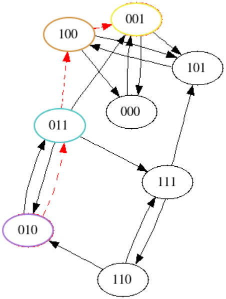

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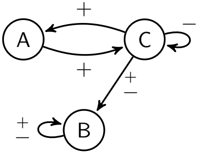

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Get the best coverage possible

Existing tools

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Automatic synthesis of BNs from a Prior Knowledge Network (PKN)
and a multivariate Time Series (TS)
= hard problem (combinatorial explosion)

`REVEAL`
`Best-Fit`
`caspo-TS`

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	PKN	TS	assumptions
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Similar principles:

1. delimitation of the search space using the PKN as constraint
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1. delimitation of the search space using the PKN as constraint
2. optimization of a criteria which measure the adequacy of the synthesized BNs with the TS (coverage)

Multiple optimal solutions are all returned

ASKeD-BN

ASKeD-BN

Formulation the BN synthesis problem as a logic program with the Answer Set Programming (ASP) framework

ASKeD-BN

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Main parts of the logic program:

1. generates all the possible candidate functions
2. removes the ones that do not respect the PKN
3. acts like an exhaustive evaluation of all the candidates and returns the *parsimonious* candidates which explain best the *binarized* observations from the given time series

ASKeD-BN

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ASP solvers are designed to solve hard combinatorial satisfaction problem. They prune the search space *efficiently* (heuristic from SAT solvers).

Evaluation Procedure

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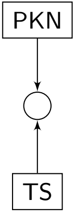

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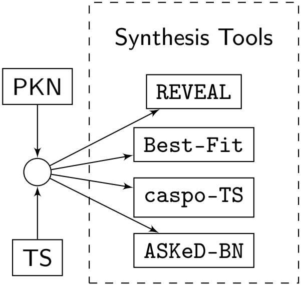

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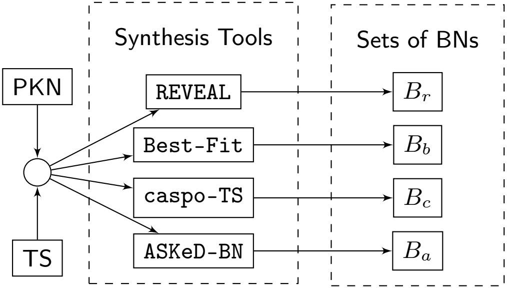

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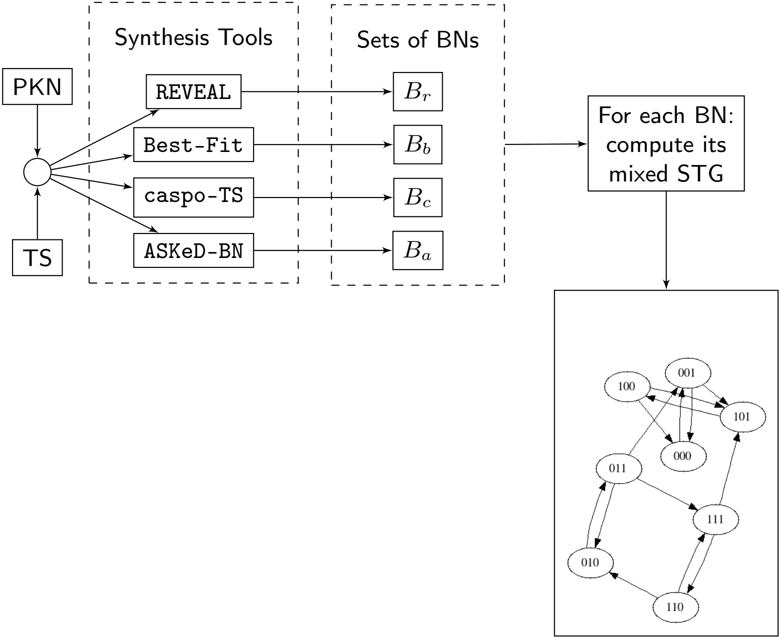

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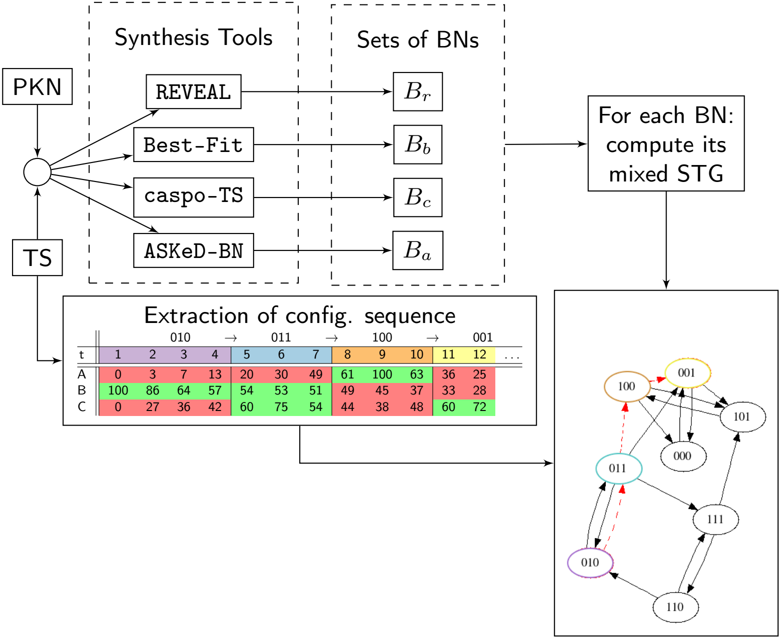

Synthesis Tools

Sets of BNs

PKN

TS

REVEAL

Best-Fit

caspo-TS

ASKeD-BN

B_r

B_b

B_c

B_a

For each BN: compute its mixed STG

Extraction of config. sequence

		010		→		011	→		100	→		001	
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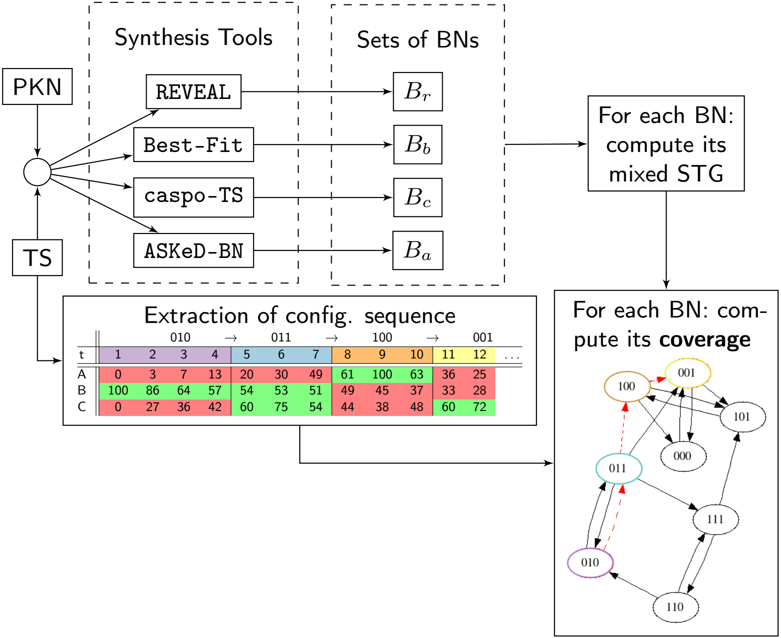

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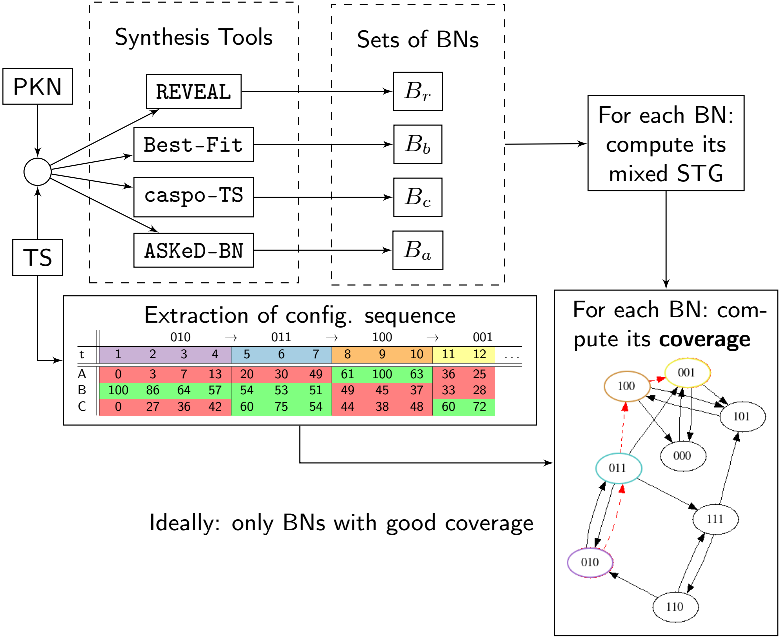

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Ideally: only BNs with good coverage

Datasets for Evaluation

2 real datasets:

System	PKN		TS	
	# nodes	# edges	# time steps	# transitions
yeast (cell cycle)	4	28	14	6
A. thaliana (circadian clock)	5	8	50	11

6 synthetic datasets:

Various complexity: from 3 to 10 nodes.
Various conditions: synch. or async. update scheme, with or without repetition, with or without noise

336 experiments at total including 42 with the ARN setting.

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Evaluation – Quality of the Synthesised BNs

REVEAL

Best-Fit

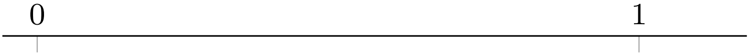
caspo-TS

ASKeD-BN

Evaluation – Quality of the Synthesised BNs

`REVEAL` `Best-Fit` `caspo-TS` `ASKeD-BN`

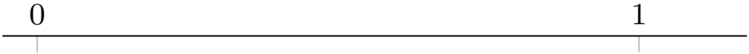
schematic representation of the coverage ratio
of BNs synthesized for a given (PKN + TS).
Points are jittered



Evaluation – Quality of the Synthesised BNs

REVEAL   Best-Fit   caspo-TS   ASKeD-BN

schematic representation of the coverage ratio
of BNs synthesized for a given (PKN + TS).
Points are jittered

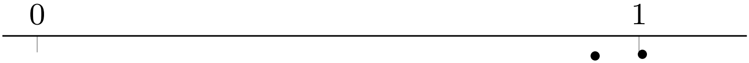


coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

REVEAL Best-Fit caspo-TS ASKeD-BN

schematic representation of the coverage ratio
of BNs synthesized for a given (PKN + TS).
Points are jittered



coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	...
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

`REVEAL` `Best-Fit` `caspo-TS` `ASKeD-BN`

schematic representation of the coverage ratio
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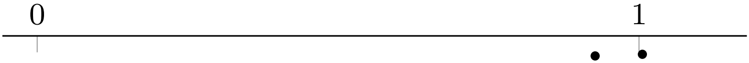
Points are jittered



`REVEAL` coverage	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

REVEAL Best-Fit caspo-TS ASKeD-BN

schematic representation of the coverage ratio
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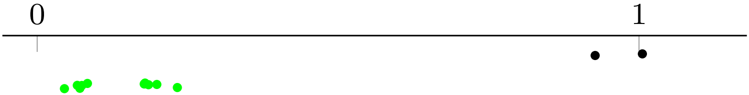
Points are jittered

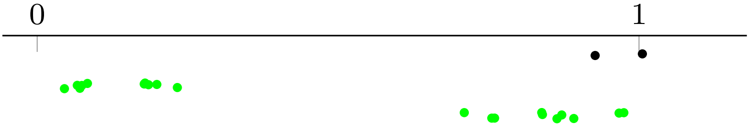


REVEAL	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

REVEAL Best-Fit caspo-TS ASKeD-BN

schematic representation of the coverage ratio
of BNs synthesized for a given (PKN + TS).
Points are jittered



REVEAL	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

REVEAL Best-Fit caspo-TS ASKeD-BN

schematic representation of the coverage ratio
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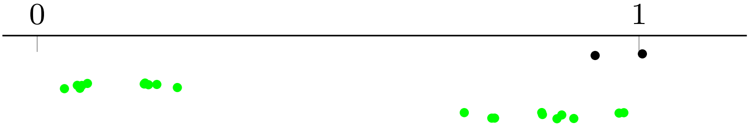
Points are jittered



REVEAL & Best-Fit	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

`REVEAL` `Best-Fit` `caspo-TS` `ASKeD-BN`

schematic representation of the coverage ratio
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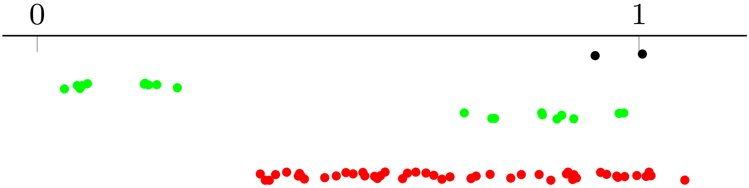
Points are jittered

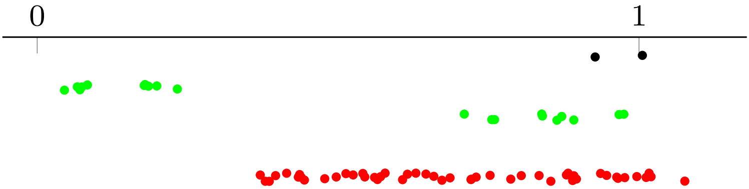


`REVEAL` & `Best-Fit`	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

REVEAL   Best-Fit   caspo-TS   ASKeD-BN

schematic representation of the coverage ratio
of BNs synthesized for a given (PKN + TS).
Points are jittered



caspo-TS	010	→	*	→	011	→	* →	100		→ *	→	001	
REVEAL & Best-Fit	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

REVEAL   Best-Fit   caspo-TS   ASKeD-BN

schematic representation of the coverage ratio
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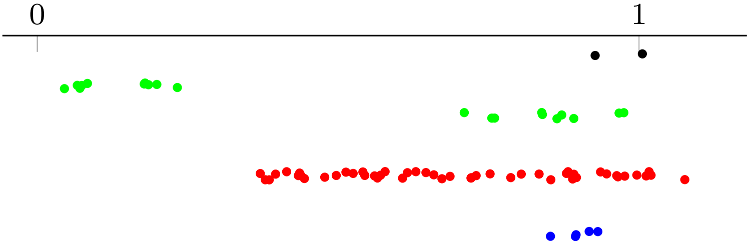


caspo-TS: 010 → * → 011 → * → 100 → * → 001

REVEAL & Best-Fit: 010→010→010→010→011→011→011→100→100→100→001→001→

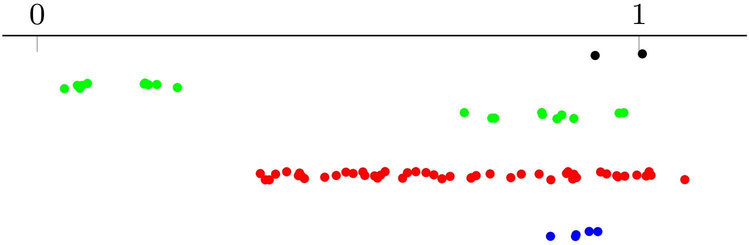
coverage: 010 → 011 → 100 → 001

t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	🟥	🟩	🟩	

Evaluation – Quality of the Synthesised BNs

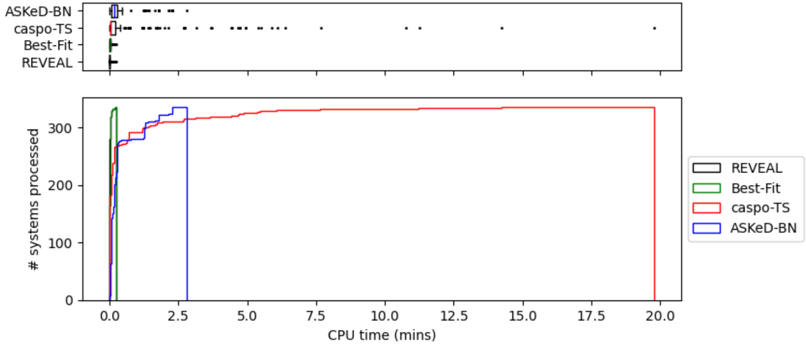
REVEAL   Best-Fit   caspo-TS   ASKeD-BN 🏆

schematic representation of the coverage ratio
of BNs synthesized for a given (PKN + TS).
Points are jittered



caspo-TS	010	→	*	→	011	→	* →		100	→ *	→	001	
REVEAL & Best-Fit	010→	010→	010→	010→	011→	011→	011→	100→	100→	100→	001→	001→	
coverage			010	→		011	→		100	→		001	
t	1	2	3	4	5	6	7	8	9	10	11	12	. . .
A	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟥	🟥	
B	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	
C	🟥	🟥	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	

Evaluation - Comparison Runtime



336 experiments at total

# fails

`REVEAL`: 240, `Best-Fit`: 64, `caspo-TS`: 20, `ASKeD-BN`: 0

Conclusion

Contribution:

- `ASKeD-BN`: Automatic Synthesis of Boolean Networks constrained in their structure (PKN knowledge) and their dynamics (TS data)
- Approach free of strong / restraining assumptions
- Formulation as a logic program (Answer-Set Programming)
- `ASKeD-BN` gives good results

All data + code available at:
`https://gitlab.inria.fr/avaginay/OLA2021`

Work in progress:

- Apply `ASKeD-BN` on PKN and TS directly extracted from existing biological models (ODE-like)

The end. Any question?

Automatic Synthesis of Boolean Networks
from Biological Knowledge and Data

Athénaïs Vaginay, Taha Boukhobza, and Malika Smaïl-Tabbone

International Conference on Optimization and Learning

ola 2021

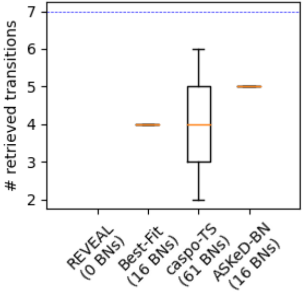
21-23 June 2021, Catania, Italia

`https://ola2021.sciencesconf.org/data/pages/book_ola2021_en.pdf`

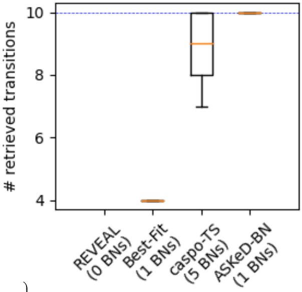
Annexe

Evaluation on Real Datasets

yeast
4 components, 7 transitions



A. thaliana
5 components, 10 transitions



- `REVEAL` fails
- `Best-Fit` lacks consistency
- `caspo-TS` and `ASKeD-BN` find good BNs
- `caspo-TS` returns more BNs, some of them with poor coverage

} confirmed on synthetic datasets

→ `ASKeD-BN` returns a small number of BN, with good coverage and low variance ✓

Synthetic Data – Complexity

system	# node	# edges	# hyperedges (caspo-TS)
raf	3	8	17
randomnet_n7k3	7	35	125
xiao_wnt5a	7	12	19
arellano_rootstem	9	18	60
davidich_yeast	10	27	117
faure_cellcycle	10	35	194

Synthetic Data – Comparison of the # of BN Returned

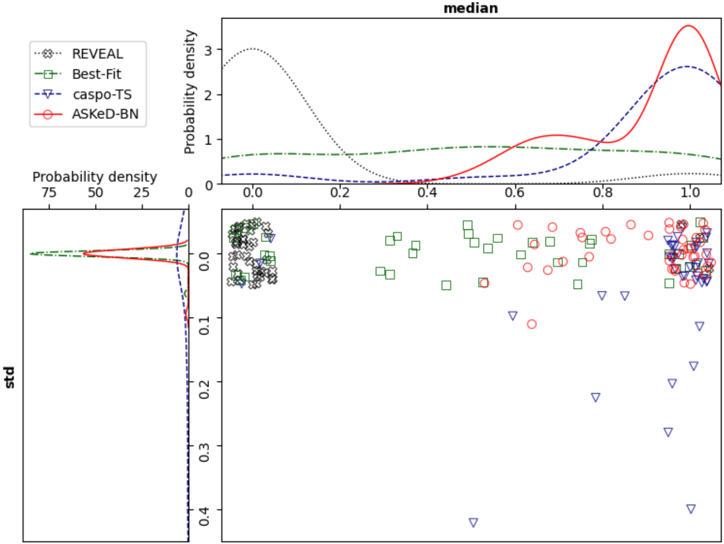
336 experiments at total including 42 with the ARN* setting.

		REVEAL		Best-Fit		caspo-TS	ASKeD-BN
	setting	before filter	after filter	before filter	after filter		
# failing xp	all	230	240	0	64	20	0
# total returned BNs	all	100 677 500	406	100 678 198	724	8481	1210
# total returned BNs	ARN	3	3	51	35	720	85

- REVEAL often fails
- REVEAL and Best-Fit return a lots of BNs which are not respecting the PKN
- caspo-TS returns in average between 5 and 7 times more BNs than ASKeD-BN (depending on the setting)

*: ARN = Asyn. update scheme, with repetition and noise

Synthetic data, ARN setting – Quality of the BNs



Evaluation - Comparison time and RAM

yest

method	running time (s)	cputime (s)	max_rss (MB)
REVEAL	1.0095	0.55	72.97
Best-Fit	1.4069	1.10	92.77
caspo-TS	24.6545	12.91	183.08
ASKeD-BN	5.4209	4.90	186.80

A. thaliana

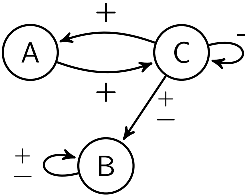
method	running time (s)	cputime (s)	max_rss (MB)
caspo-TS	7.0394	1.85	139.93
ASKeD-BN	8.5820	8.19	163.38

observed in general:

- ASKeD-BN faster in general, but does not scale
- caspo-TS is using less RAM

ASKeD-BN: Hard Constraints

"A activates C"
"B interacts with itself"
"C activates A"
"C interacts with B"
"C inhibits itself"



ASKeD-BN: Hard Constraints

"A activates C"
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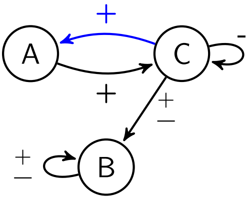


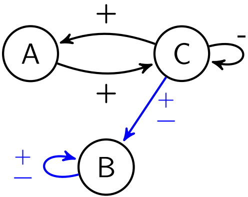
For A:

3 choices:
A := C
A := 0
A := 1

but not:
A := B
A := ¬C

ASKeD-BN: Hard Constraints

"A activates C"
"B interacts with itself"
"C activates A"
"C interacts with B"
"C inhibits itself"



For A:

3 choices:
A := C
A := 0
A := 1

but not:
A := B
A := ¬C

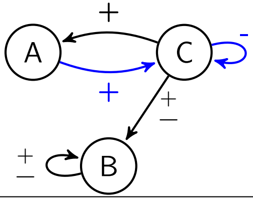
For B:

16 choices:
B := B ∧ ¬C
B := (B ∧ ¬C) ∨ (¬B ∧ C);
. . .
B := 0
B := 1

but not:
B := A

ASKeD-BN: Hard Constraints

"A activates C"
"B interacts with itself"
"C activates A"
"C interacts with B"
"C inhibits itself"



For A:

3 choices:
$A := C$
$A := 0$
$A := 1$

but not:
$A := B$
$A := \neg C$

For B:

16 choices:
$B := B \wedge \neg C$
$B := (B \wedge \neg C) \vee (\neg B \wedge C);$
. . .
$B := 0$
$B := 1$

but not:
$B := A$

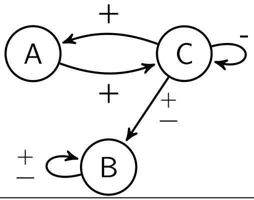
For C:

6 choices:
$C := \neg C$
$C := A$
. . .
$C := 0$
$C := 1$

but not:
$C := A \wedge B$

ASKeD-BN: Hard Constraints

"A activates C"
"B interacts with itself"
"C activates A"
"C interacts with B"
"C inhibits itself"



For A:

3 choices:
$A := C$
$A := 0$
$A := 1$

but not:
$A := B$
$A := \neg C$

For B:

16 choices:
$B := B \wedge \neg C$
$B := (B \wedge \neg C) \vee (\neg B \wedge C)$;
...
$B := 0$
$B := 1$

but not:
$B := A$

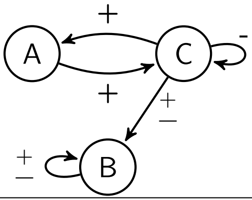
For C:

6 choices:
$C := \neg C$
$C := A$
...
$C := 0$
$C := 1$

but not:
$C := A \wedge B$

ASKeD-BN: Hard Constraints

"A activates C"
"B interacts with itself"
"C activates A"
"C interacts with B"
"C inhibits itself"



For A:

3 choices:
$A := C$
$A := 0$
$A := 1$

but not:
$A := B$
$A := \neg C$

For B:

16 choices:
$B := B \land \neg C$
$B := (B \land \neg C) \lor (\neg B \land C);$
...
$B := 0$
$B := 1$

but not:
$B := A$

For C:

6 choices:
$C := \neg C$
$C := A$
...
$C := 0$
$C := 1$

but not:
$C := A \land B$

ASKeD-BN: Soft constraints — Example 1

	010			→	011		→	100		→	001									
t	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A	0	3	7	13	20	30	49	61	100	63	36	25	2	3	1	1	3	0	0	0
B	100	86	64	57	54	53	51	49	45	37	33	28	22	19	14	12	9	5	2	0
C	0	27	36	42	60	75	54	44	38	48	60	72	88	90	100	100	100	100	100	100

$\mathscr{U}$ set of unexplained timesteps

Mean Absolute Error $\mathsf{MAE}_{\mathsf{X}} = \frac{\sum_{t' \in \mathscr{U}} |\theta_{\mathsf{X}} - x_{t'}|}{T}$

	$a_{t+1} = c_t$	✓	$a_{t+1} = 0$
$\mathscr{U}$	$\emptyset$		$\{8\}$
MAE	0	✓	0.55

ASKeD-BN: Soft constraints — Example 2

	010				→ 011			→ 100			→ 001									
t	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A	0	3	7	13	20	30	49	61	100	63	36	25	2	3	1	1	3	0	0	0
B	100	86	64	57	54	53	51	49	45	37	33	28	22	19	14	12	9	5	2	0
C	0	27	36	42	60	75	54	44	38	48	60	72	88	90	100	100	100	100	100	100

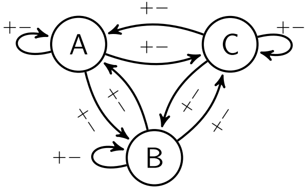
$\mathscr{U}$ set of unexplained timesteps

$$\text{Mean Absolute Error } \mathrm{MAE}_{\mathsf{X}} = \frac{\sum_{t'\in\mathscr{U}} |\theta_{\mathsf{X}} - x_{t'}|}{T}$$

	$b_{t+1} = b_t \wedge \neg \mathsf{c}_t$	✓	$b_{t+1} = (b_t \wedge \neg c_t) \vee (\neg b_t \wedge c_t)$	
$\mathscr{U}$	$\emptyset$		$\emptyset$	
MAE	0	✓	0	✓
# influences	2	✓	4	

How does the PKN help reducing the search space?

Without information



$2^{2^3} = 256$ candidates for each components

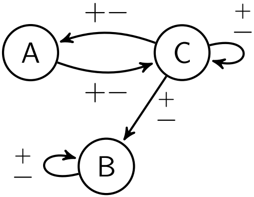
$\rightarrow 256 \times 256 \times 256 = 16777216$ candidate BNs

How does the PKN help reducing the search space?

With PKN

directions only

(REVEAL & Best-Fit)



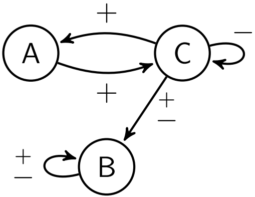
A	B	C
4	16	16

$\rightarrow 4 \times 16 \times 16 = 1024$

candidate BNs

direction + signs

(caspo-TS & ASKeD-BN)



	A	B	C
all	3	16	6
monotonous	3	14	6

$\rightarrow 3 \times 16 \times 6 = 288$

candidate BNs

including 252 locally partial-monotonous.