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

ola 2021

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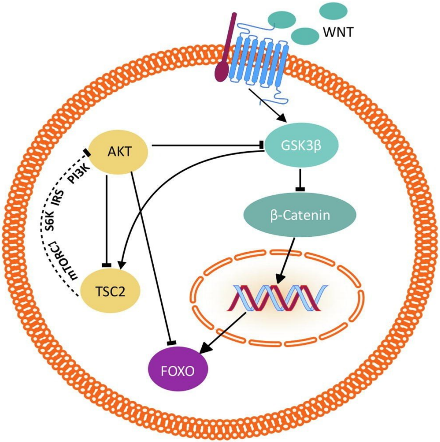
Jun 21-23 2021

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 Schwab et al. 2020.

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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status of child component at $t+1$
= f(status of parents components at t)

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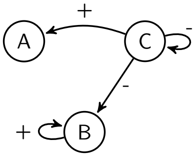

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Interaction Graph (IG)

nodes: components of the BN

edges: influences + polarity

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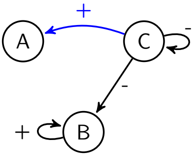

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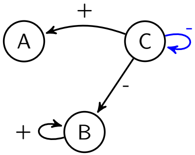

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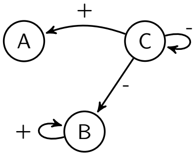

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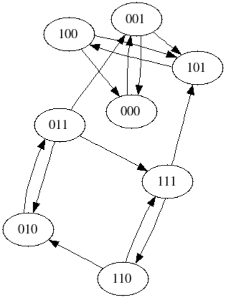
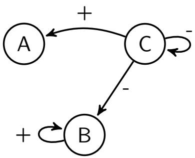


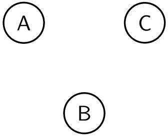
State Transition Graph (STG)

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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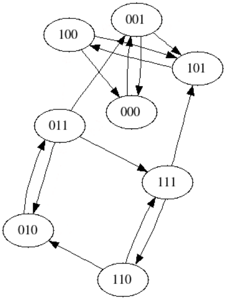

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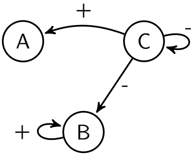

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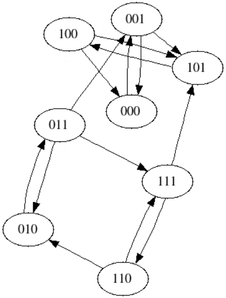

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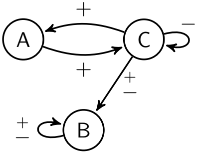

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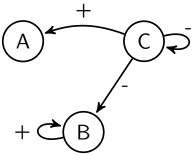

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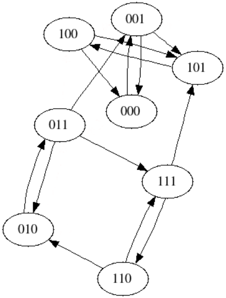

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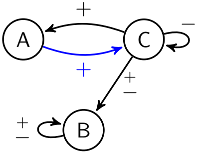

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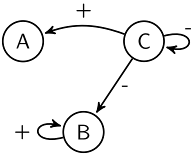

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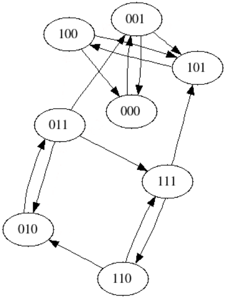

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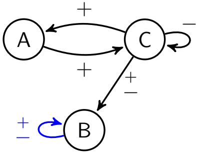

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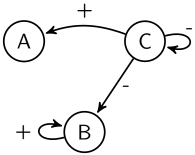

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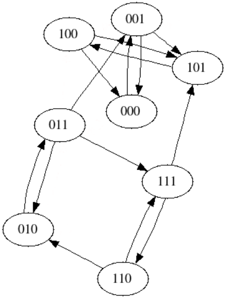

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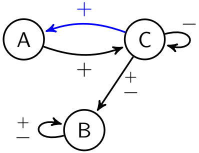

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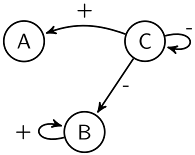

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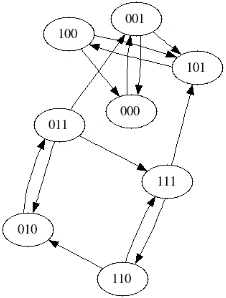

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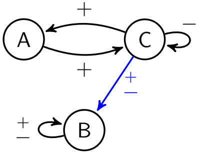

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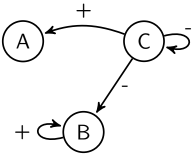

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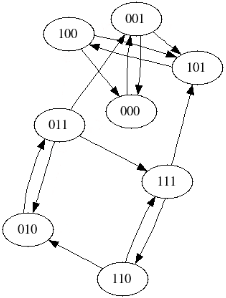

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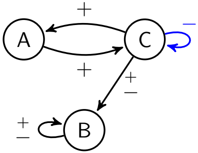

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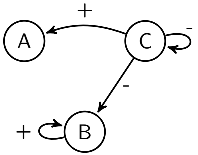

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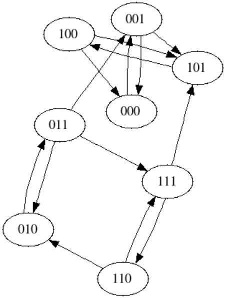

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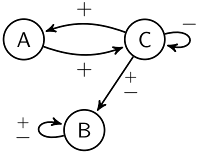

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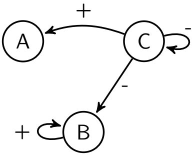

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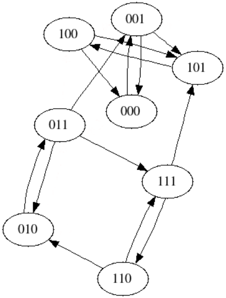

Prior Knowledge Network (PKN)

Super-set of influences allowed

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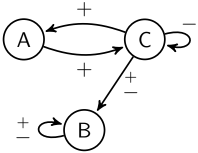

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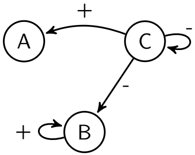

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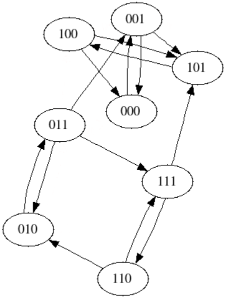

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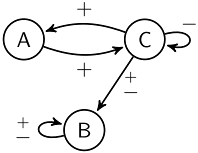

Multivariate Time Series (TS)

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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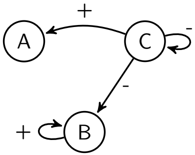

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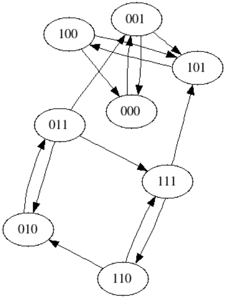

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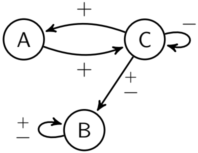

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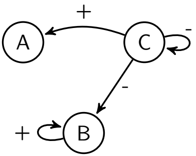

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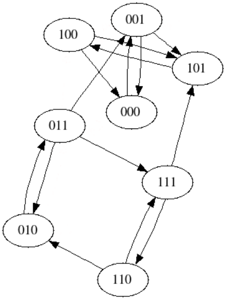

Prior Knowledge Network (PKN)
Super-set of influences allowed

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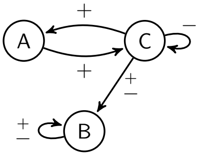

Multivariate Time Series (TS)
Concentrations of the components over time

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	...
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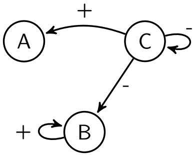
C	0	27	36	42	60	75	54	44	38	48	60	72	88	...

Boolean Networks – Synthesis from Knowledge and Data



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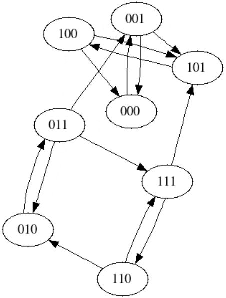

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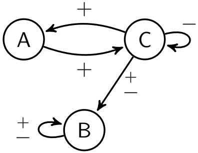

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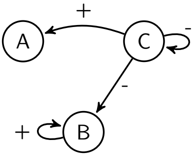

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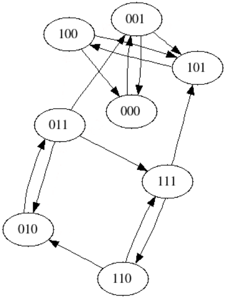

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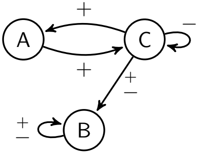

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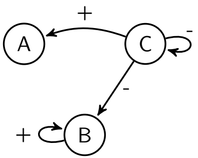

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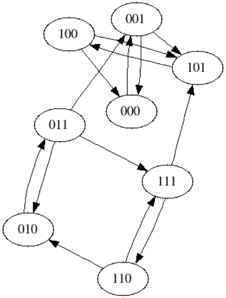

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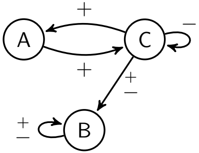

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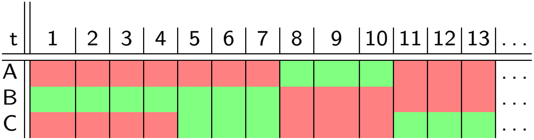

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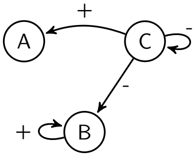

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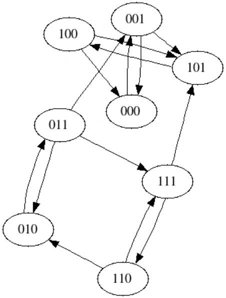

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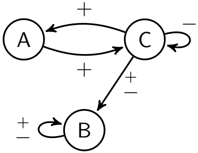

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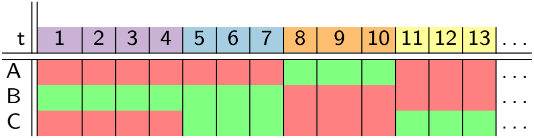

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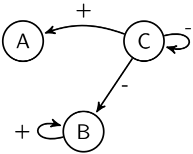

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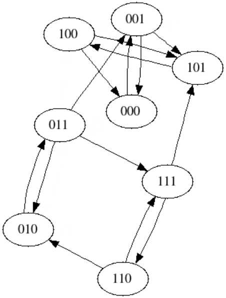

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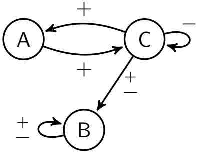

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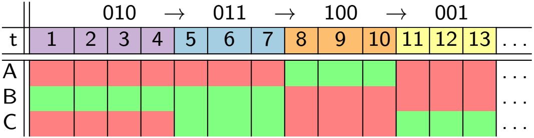
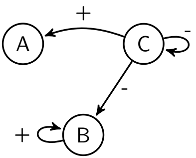


Boolean Networks – Synthesis from Knowledge and Data



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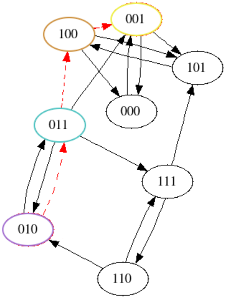

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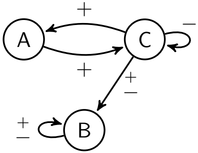

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	010				→ 011			→ 100			→ 001			
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A														...
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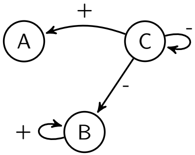
Boolean Networks – Synthesis from Knowledge and Data



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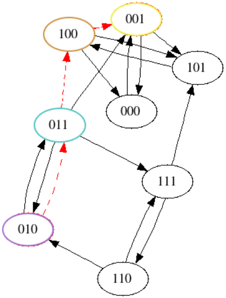

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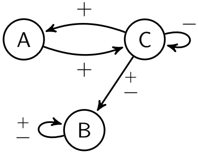

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Get the best coverage possible

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`

Existing tools

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Similar principles:

1. delimitation of the search space using the PKN as constraint
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Multiple optimal solutions are all returned

ASKeD-BN

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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
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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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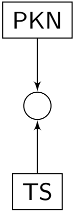

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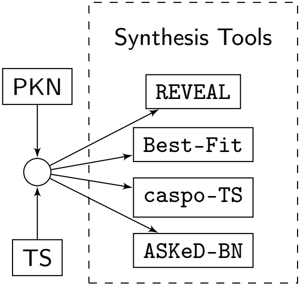

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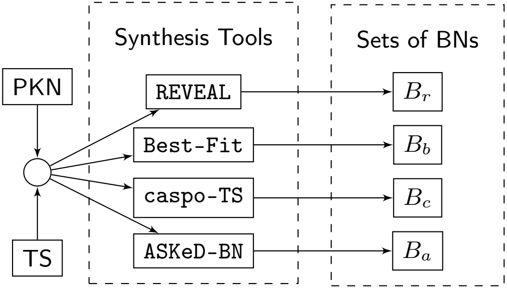

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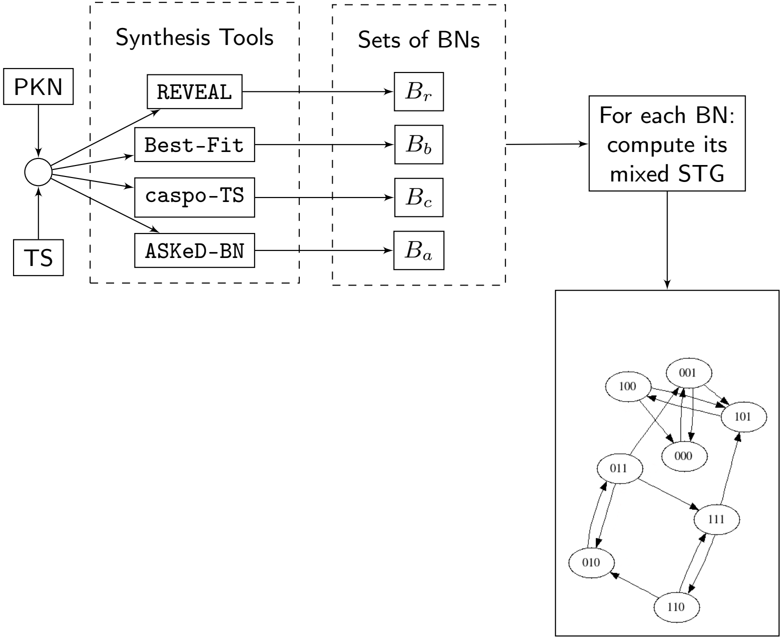

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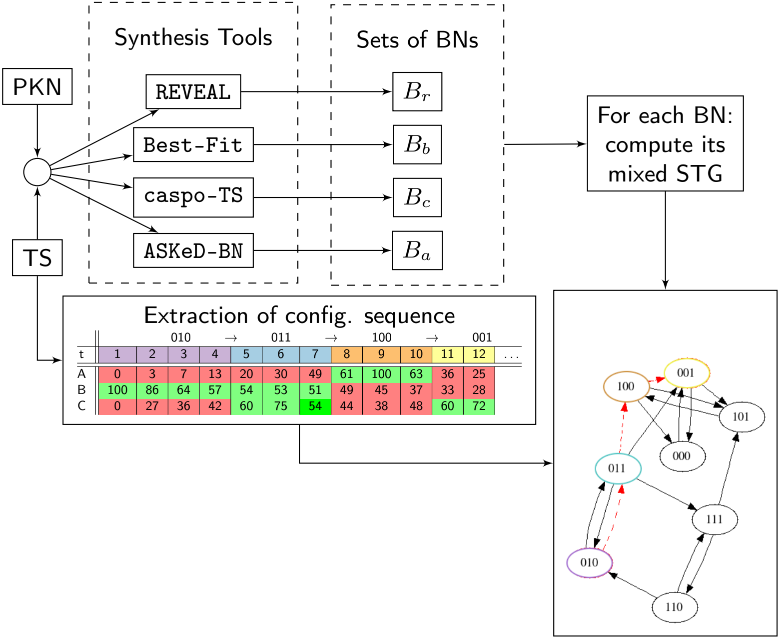

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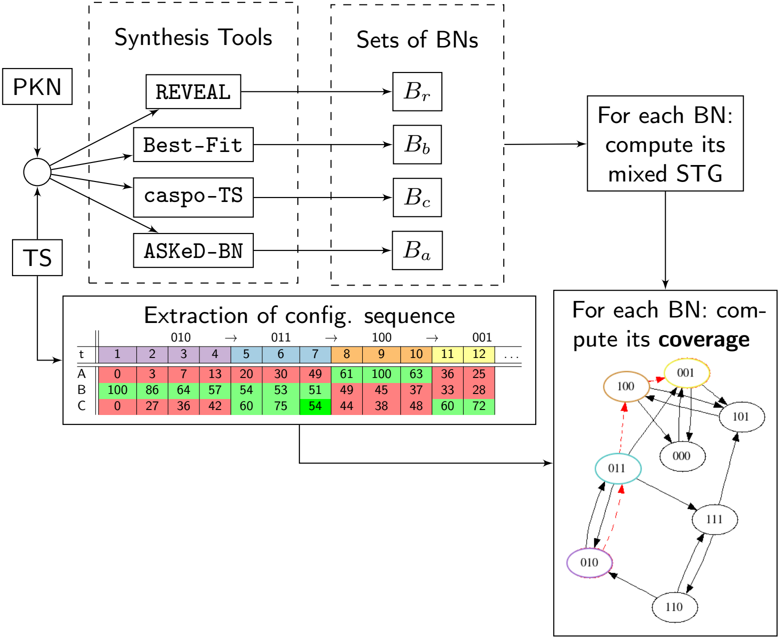

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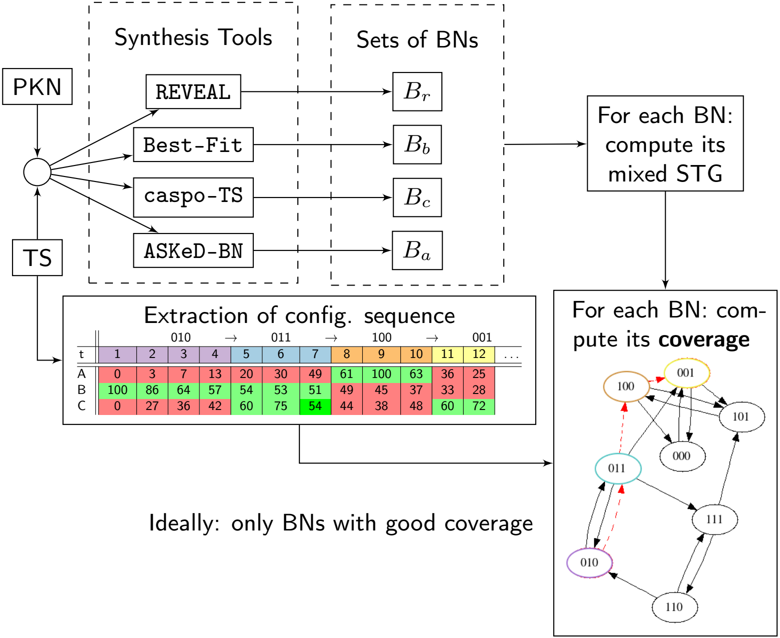

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Evaluation on Real Datasets

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yeast

A. thaliana

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yeast
4 components, 7 transitions

A. thaliana
5 components, 10 transitions

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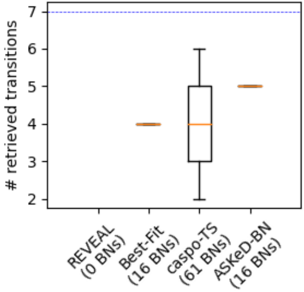

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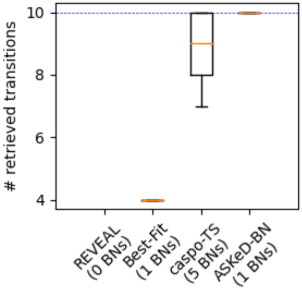

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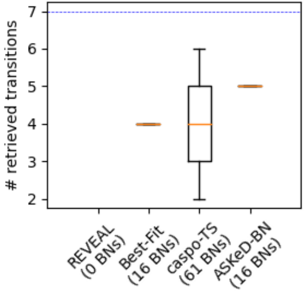

- `REVEAL` fails

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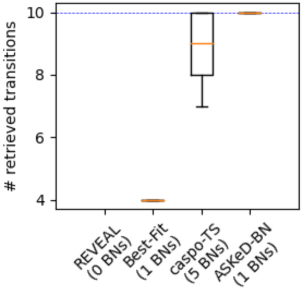

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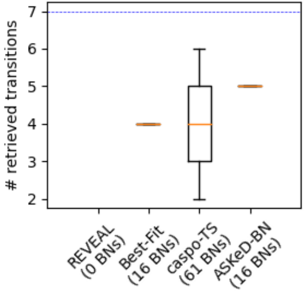

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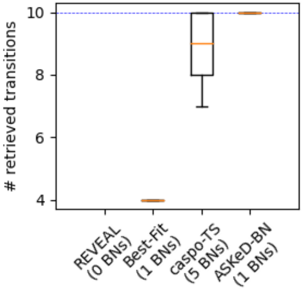

- `REVEAL` fails
- `Best-Fit` lacks consistency

Evaluation on Real Datasets

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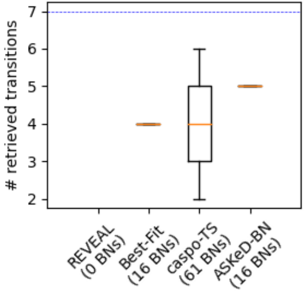

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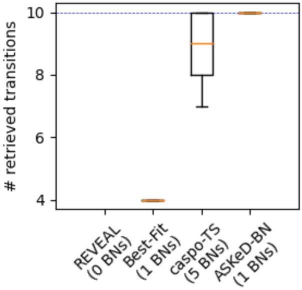

- `REVEAL` fails
- `Best-Fit` lacks consistency
- `caspo-TS` and `ASKeD-BN` find good BNs

Evaluation on Real Datasets

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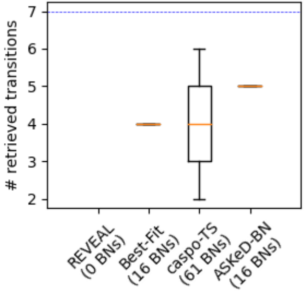

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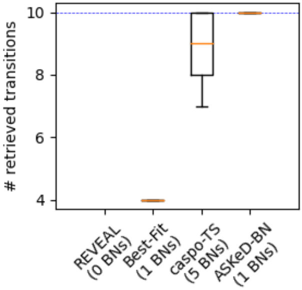

- `REVEAL` fails
- `Best-Fit` lacks consistency
- `caspo-TS` and `ASKeD-BN` find good BNs
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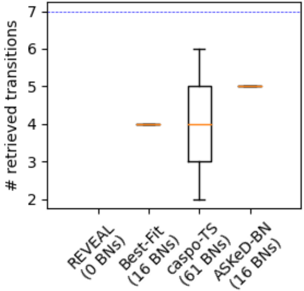
  some of them with poor coverage.

Evaluation on Real Datasets

yeast
4 components, 7 transitions



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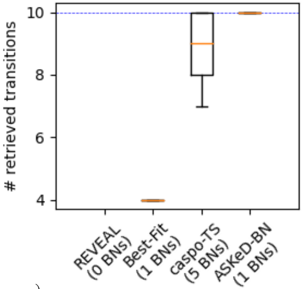

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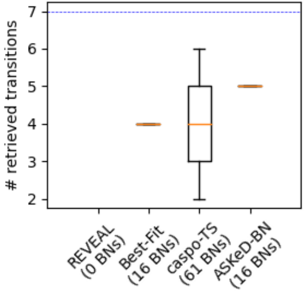

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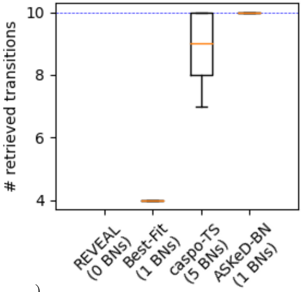

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$\Big\}$ confirmed on synthetic datasets

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

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 questions ?

Annexe

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.

Datasets for Evaluation

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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** (“**ARN**”)

336 experiments at total including 42 with the ARN setting.

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:

- caspo-TS faster and less RAM usage than ASKeD-BN
- but not on some datasets, where ASKeD-BN terminated in less than 100 hours while caspo-TS is still running after more than 300 hours. ← to investigate...

Synthetic Data – Comparison of the Number of BN Returned

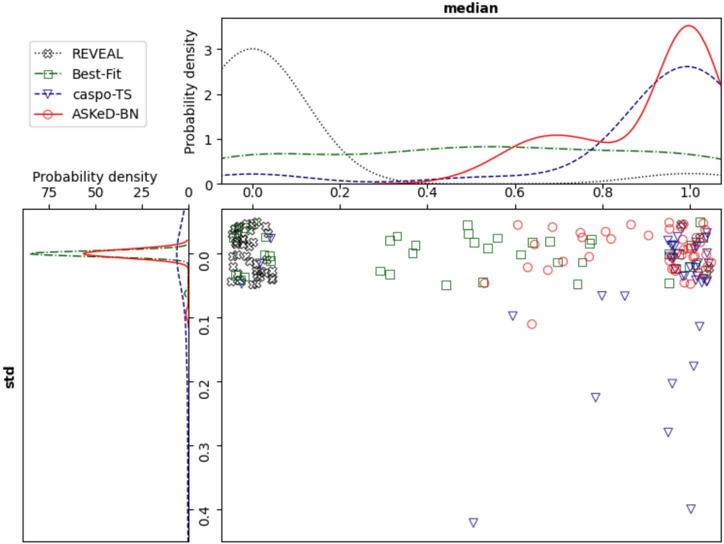
336 experiments at total including 42 with the ARN* setting.

	setting	REVEAL before filter	REVEAL after filter	Best-Fit before filter	Best-Fit after filter	caspo-TS	ASKeD-BN
# 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)

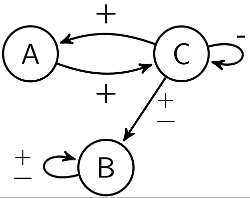
*: ARN = Asyn. update scheme, with repetition and noise

Synthetic data, ARN setting – Quality of the BNs



ASKeD-BN: Hard Constraints

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



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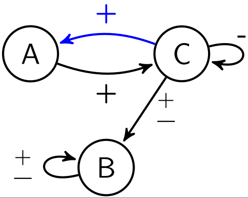

For A:

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

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

ASKeD-BN: Hard Constraints

"A activates C"
"B interacts with itself"
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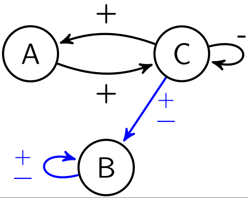

For A:

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

ASKeD-BN: Hard Constraints

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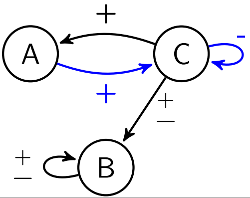

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For B:

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"
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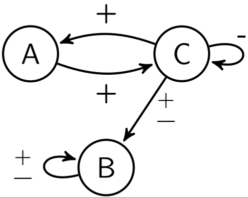

For A:

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

For C:

6 choices:
C := ¬C
C := A
...
C := 0
C := 1

but not:
C := A ∧ B

ASKeD-BN: Hard Constraints

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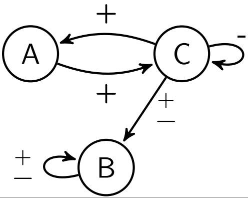

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3 choices:
A $:=$ C
A $:= 0$
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but not:
A $:=$ B
A $:= \neg$C

For B:

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

but not:
B $:=$ A

For C:

6 choices:
$\boxed{\text{C} := \neg\text{C}}$
$\boxed{\text{C} := \text{A}}$
...
C $:= 0$
C $:= 1$

but not:
C $:=$ A $\wedge$ 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 $\mathsf{MAE_X} = \frac{\sum_{t' \in \mathscr{U}} |\theta_{\mathsf{X}} - x_{t'}|}{T}$

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

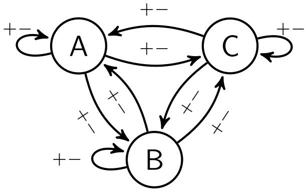
$\mathscr{U}$ set of unexplained timesteps

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

	$b_{t+1} = b_t \wedge \neg \mathsf{c}_t$	✓	$b_{t+1} = (b_t \wedge \neg c_t) \vee (\neg b_t \wedge c_t)$	
$\mathscr{U}$	$\emptyset$		$\emptyset$	
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

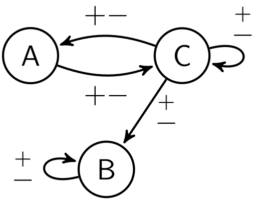
$\rightarrow 256 \times 256 \times 256 = 16777216$ candidate BNs

How does the PKN help reducing the search space?

With PKN

directions only

(`REVEAL` & `Best-Fit`)



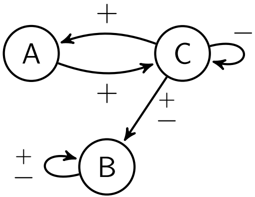
A	B	C
4	16	16

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

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.