Teatime capsid:

Constrained Enumeration of Boolean Networks from Biological Data and Knowledge

A paper submission for OLA2021

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OLA2021

International Conference in
Optimization and Learning and their **Application**

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Extended submission deadline : **Feb 05, 2020** (cross your fingers)

`https://ola2021.sciencesconf.org/`

Modeling of biological systems with Boolean Networks

Perfect for systems (even big ones) where the exact reaction times is not of central interest.

Generally built from experimental data and knowledge from the literature either manually or by using programs.

The automatic synthesis of BNs from biological data and knowledge is still a challenge.

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in the Boolean world:

$$\mathbb{B} = \{0, 1\}$$

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1 components $\rightarrow$ 2 configurations:
0; 1

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2 components $\rightarrow$ 4 configurations:
00; 01; 10; 11

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3 components $\rightarrow$ 8 configurations:
000; 001; 010; 011; 100; 101; 110; 111

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4 components $\rightarrow$ 16 configurations:
0000; 0001; 0010; 0011; 0100; 0101; 0110; 0111;
1000; 1001; 1010; 1011; 1100; 1101; 1110; 1111

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- disjunction $a \vee b$: "a or b"
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$=$ disjunction of conjunctions.

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Disjunctive Normal Form (DNF)
= disjunction of conjunctions. $(a \wedge b \wedge c) \vee (a \wedge \neg a \wedge b) \vee a$

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satisfiable conjunction $\rightarrow$ does not contain a variable and its negation.

$$a\text{: OK}$$
$$a \wedge \neg a\text{: not OK}$$
$$(a \wedge \neg a) \vee b\text{: satisfiable } (\equiv b\ ) \text{ but still not OK.}$$

Examples of local update functions

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Examples of local update functions

- "C activates A" $\rightarrow A = f_A(C) = C$
- "C inhibates E" $\rightarrow E = f_E(C) = \neg C$
- "both A and B can activate D"
  $\rightarrow D = f_D(A, B) = A \vee B$

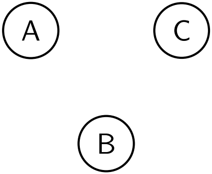
Note: from now on, I will omit the time specifications

Examples of BNs

$$\mathscr{B}_1 = \begin{cases} f_A : A = C \\ f_B : B = B \wedge \neg C \\ f_C : C = \neg C \end{cases}$$

$$\mathscr{B}_2 = \begin{cases} f_A : A = 0 \\ f_B : B = (B \wedge \neg C) \vee (\neg B \wedge C) \\ f_C : C = A \end{cases}$$

Automatic synthesis of BN



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"A activates C"
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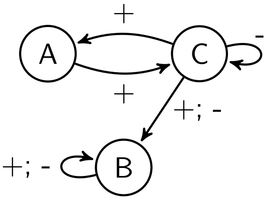

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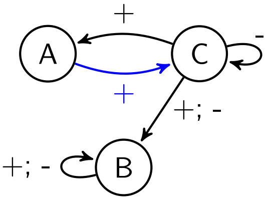

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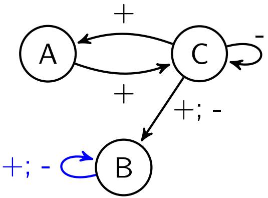

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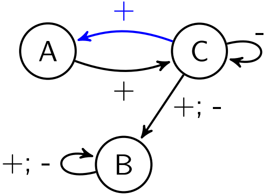

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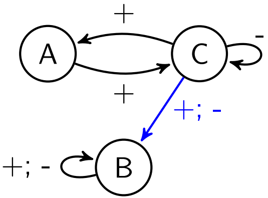

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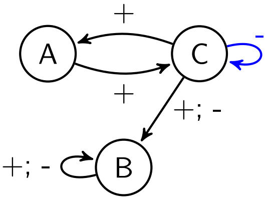

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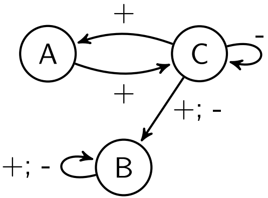

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Prior Knowledge Network (PKN)

Super-set of influences allowed in the synthesized BNs

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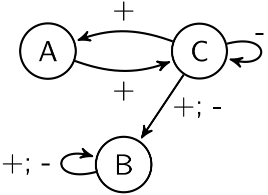

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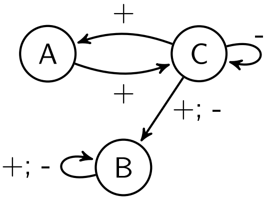

Multivariate Time Series (TS)

Concentrations / activities of the components over time

t	1	2	3	4	5	6	7	8	9	10	13	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

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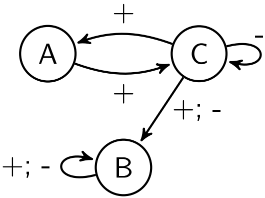

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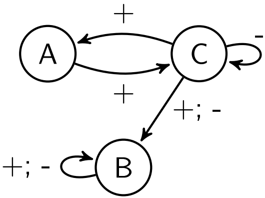

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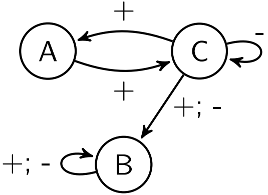

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Automatic approaches

Automatic enumeration of BNs respecting a PKN and a TS.

- `REVEAL`
- `Best-Fit`
- `caspots`
- `our`

Hard constraint: use PKN to delimit the search space

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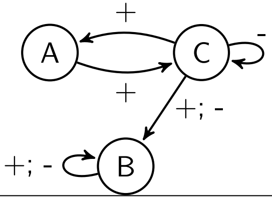

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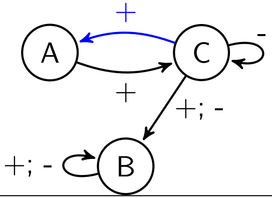

For A:

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

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

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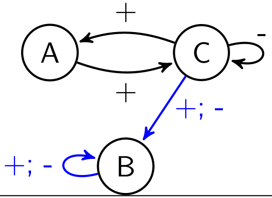

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For B:

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

but not:
$B = A$

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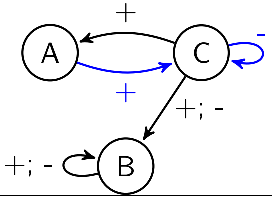

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For C:

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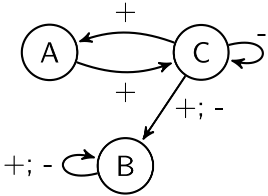
$C = 1$

but not:
$C = A \wedge B$

How did the PKN help reducing the search space?

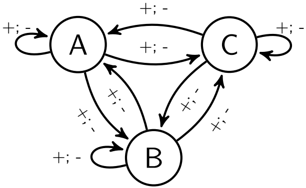
With the PKN



A	B	C
3	16	6

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

Without informations



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

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

Hard constraint: use PKN to delimit the search space

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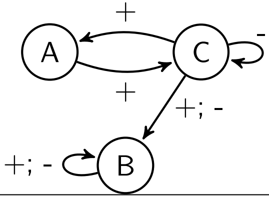

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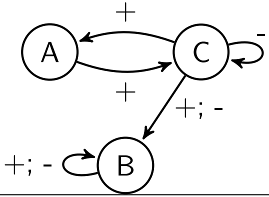
6 choices:
$C = \neg C$;
$C = A$;
...
$C = 0$;
$C = 1$

but not:
$C = A \wedge B$

Hard constraint: use PKN to delimit the search space

Super-set of influences allowed in the synthesized BNs

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



For A:

3 choices:
$\boxed{A = C;}$
$\boxed{A = 0;}$
$A = 1;$

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

For B:

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

but not:
$B = A$

For C:

6 choices:
$\boxed{C = \neg C;}$
$\boxed{C = A;}$
$\ldots$
$C = 0;$
$C = 1$

but not:
$C = A \wedge B$

Soft constraints: adequation with the TS

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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

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t	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
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Binarization of the TS:

$$o'_t = \begin{cases} 1 \text{ if } o_t > \theta_o \\ 0 \text{ otherwise} \end{cases}$$

$$\theta_o = \frac{o_{max} - o_{min}}{2}$$

Soft constraints: adequation with the TS

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
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$$o'_t = \begin{cases} 1 \text{ if } o_t > \theta_o \\ 0 \text{ otherwise} \end{cases}$$

$$\theta_o = \frac{o_{max} - o_{min}}{2}$$

Here :

$\theta_A = \frac{100-0}{2} = 50$ $\theta_B = \frac{100-0}{2} = 50$ $\theta_C = \frac{100-0}{2} = 50$

Soft constraints: adequation with the TS

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
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$$\theta_o = \frac{o_{max} - o_{min}}{2}$$

Here :

$\theta_A = \frac{100-0}{2} = 50$ $\theta_B = \frac{100-0}{2} = 50$ $\theta_C = \frac{100-0}{2} = 50$

Soft constraints: adequation with the TS

t	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
		010																		
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
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	010			$\rightarrow$	011		$\rightarrow$	100		$\rightarrow$	001									
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Which function is best? (for A)

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t	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
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candidates for A	$A = C$	$A = 0$

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Mean Absolute Error

Which function is best? (for A)

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Which function is best? (for A)

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T: number of time steps in the TS

Which function is best? (for A)

		010		$\rightarrow$		011	$\rightarrow$		100	$\rightarrow$		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

candidates for A	$A = C$	$A = 0$
$\mathscr{U}$	$\emptyset$	

Mean Absolute Error $\quad \text{MAE}_X = \frac{\sum_{t' \in \mathscr{U}} |\theta_X - X_{t'}|}{T}$

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MAE	0	0.55

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Which function is best? (for B)

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$$\text{Mean Absolute Error MAE}_X = \frac{\sum_{t' \in \mathscr{U}} |\theta_X - X_{t'}|}{T}$$

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B	100	86	64	57	54	53	51	49	45	37	33	28	22	19	14	12	9	5	2	0
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candidates for B	$B = B \wedge \neg C$	$B = (B \wedge \neg C) \vee (\neg B \wedge C)$

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candidates for B	$B = B \wedge \neg C$	$B = (B \wedge \neg C) \vee (\neg B \wedge C)$
$\mathscr{U}$	$\emptyset$	$\emptyset$
MAE	0 ✓	0 ✓

Mean Absolute Error $\text{MAE}_X = \frac{\sum_{t' \in \mathscr{U}} |\theta_X - X_{t'}|}{T}$

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candidates for B	$B = B \wedge \neg C$		$B = (B \wedge \neg C) \vee (\neg B \wedge C)$	
$\mathscr{U}$	$\emptyset$		$\emptyset$	
MAE	0	✓	0	✓
# of influences	2	✓	4	

$$\text{Mean Absolute Error } \mathrm{MAE}_X = \frac{\sum_{t' \in \mathscr{U}} |\theta_X - X_{t'}|}{T}$$

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$\mathscr{U}$	$\emptyset$		$\emptyset$	
MAE	0	✓	0	✓
# of influences	2	✓	4	

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Which function is best? (for C)

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A	0	3	7	13	20	30	49	61	100	63	36	25	2	3	1	1	3	0	0	0
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Which function is best? (for C)

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candidates for C	$C = \neg C$	$C = A$

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Which function is best? (for C)

010 $\rightarrow$ 011 $\rightarrow$ 100 $\rightarrow$ 001

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candidates for C	$C = \neg C$		$C = A$
$\mathscr{U}$	$\emptyset$		$\{5\}$
MAE	0	✓	0.5

$$\text{Mean Absolute Error } \mathrm{MAE}_X = \frac{\sum_{t' \in \mathscr{U}} |\theta_X - X_{t'}|}{T}$$

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Generated BN

Only one best candidate of each component $\rightarrow$1 BN generated:

$$\mathscr{B}_1 = \begin{cases} f_A : A = C \\ f_B : B = B \wedge \neg C \\ f_C : C = \neg C \end{cases}$$

Summary of our approach

For each component:

- generates the candidate functions
- removes the ones that do not respect the PKN
- acts like an exhaustive evaluation of all the candidates
- returns the ones with the smallest MAE and smallest number of inlfuences

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For each component:

- generates the candidate functions
- removes the ones that do not respect the PKN
- **acts like** an exhaustive evaluation of all the candidates
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The ASP solver is actually able to cut into the search space, and does not need to really evaluate all the candidates to find the best ones.

Other automatic approaches

Other automatic approaches

- `REVEAL`
- `Best-Fit`

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- `Best-Fit`

unsigned PKN

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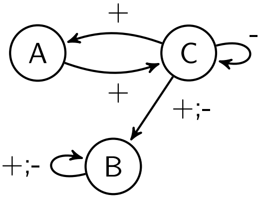
"A activates C"
"B interacts with itself"
"C activates A"
"C interacts with B"
"C inhibits itself"



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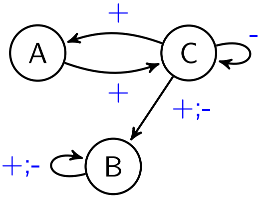

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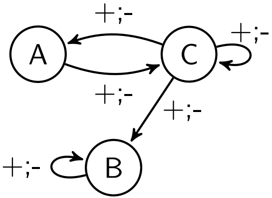

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unsigned PKN $+$ binarized TS.

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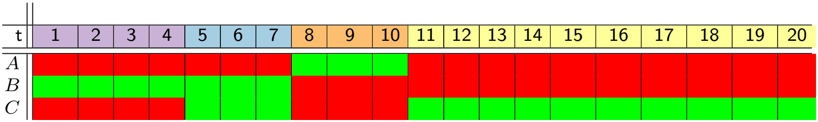

Other automatic approaches

- `REVEAL`
- `Best-Fit`

unsigned PKN + binarized TS.

Tries to explain all / the max # of **time steps**.

t	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
A																				
B																				
C																				

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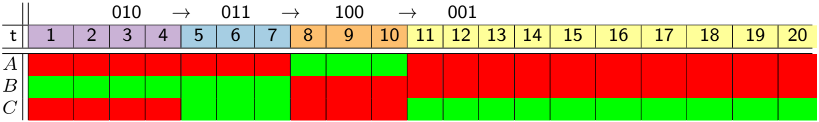

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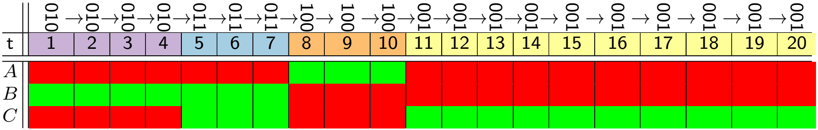

Other automatic approaches

- `REVEAL`
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unsigned PKN + binarized TS.
Tries to explain all / the max # of **time steps**.

- `caspots`

PKN + TS.
Assert **reachability** of the configurations and fit the BN to the TS using MAE (slightly differently than our approach).

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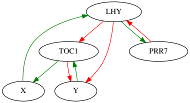
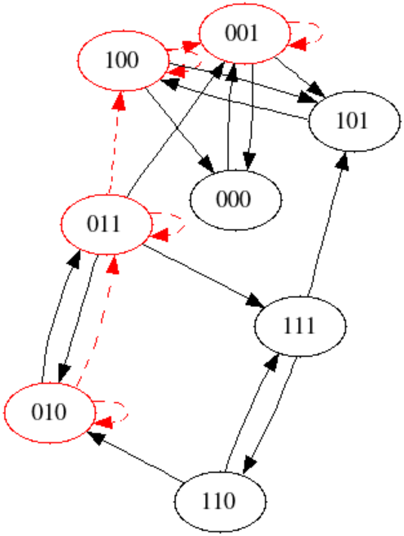
Evaluation on real datasets

System	Genes	PKN	TS	Source
yeast (cell cycle)	Fkh2, Swi5, Sic1 & Clb1	Sic1 does not influence itself nor Fkh2	14 time steps 6 transitions	Spellman 1998
A. thaliana (circadian clock)	LHY, PRR7, TOC1, X & Y		50 time steps 11 transitions	Locke 2006

Evaluation on real datasets

- Give the PKN and TS to REVEAL, Best-Fit, caspots and our method
- For each BN returned, compute its generalized asynchronous STG
- Count the number of configurations transition (extracted from the TS) retrieved.

asynchronous subset $(\{A\},\{B\},\{C\})$ of a generalized asynchronous STG:



Evaluation on real datasets

yeast

6 transitions to retrieve

\# BNs:

`Best-Fit`: 16

`caspots`: 61

`our`: 16

A. thaliana

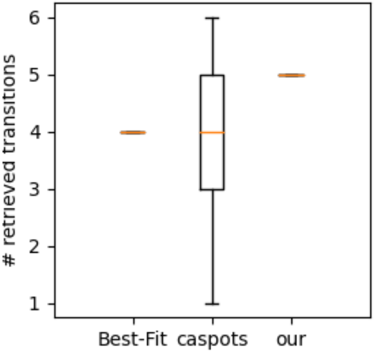
11 transitions to retrieve

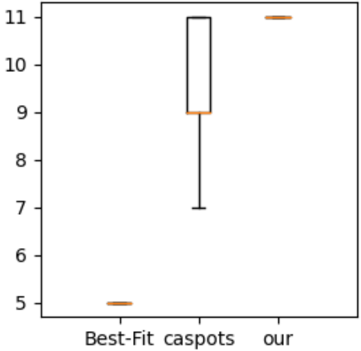
\# BNs:

`Best-Fit`: 1

`caspots`: 5

`our`: 8





Note: `REVEAL` failed because of inconsistencies

Conclusion

The approach we propose is quite simple. Yet, it gaves us interesting results so far.

We are now applying it on more datasets, and then we will use it on PKN and TS directly extracted from SBML models.

The end. Any questions ?

Annexe

About minimal DNF

Minimal DNF: smallest DNF among all the equivalent DNFs.

About minimal DNF

Minimal DNF: **smallest** DNF among all the equivalent DNFs.

Length of a formula: the number of litteral
Example:
$(a \wedge \neg b) \vee (a \wedge c)$: length = 4
$a \wedge a \wedge a \wedge a \wedge a$: length = 5

About minimal DNF

Minimal DNF: **smallest** DNF among all the equivalent DNFs.

Length of a formula: the number of litteral
Example:
$(a \wedge \neg b) \vee (a \wedge c)$: length $= 4$
$a \wedge a \wedge a \wedge a \wedge a$: length $= 5$

Example of min DNF:
a is a minimal DNF, but $a \wedge a$ is not.

Logical operators and their notation

- $\neg a$: "not a" $\rightarrow$ a has to be False
- $a \vee b$: "a or b"
- $a \wedge b$: "a and b"

- $a \Rightarrow b$: "a implies b"
- $a \Leftrightarrow b$: "equivalent"
- True
- False
- $a \oplus b$: "exclusive or", "xor"
- $a \uparrow b$ "nand"
- $a \downarrow b$: "nor"
- ...

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- $a \Rightarrow b \equiv \neg a \vee b$: "$a$ implies b"
- $a \Leftrightarrow b \equiv (\neg a \vee b) \wedge (\neg b \vee a)$: "equivalent"
- True $\equiv a \vee \neg a$
- False $\equiv a \wedge \neg a$
- $a \oplus b \equiv (a \wedge \neg b) \vee (\neg a \wedge b)$: "exclusive or", "xor"
- $a \uparrow b \equiv \neg(a \wedge b)$ "nand"
- $a \downarrow b \equiv \neg(x \vee b)$: "nor"
- ...

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- $\ldots$

Logical operators and their notation

functionally complete:

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Logical operators and their notation

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Automatic approaches

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unsigned PKN + binarized TS.
Tries to explain all the time steps.

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PKN + TS.
Assert reachability of the configurations and fit the BN to the TS using MAE.

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PKN + TS.
Assert reachability of the configurations and fit the BN to the TS using MAE.

- `our`

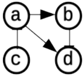
PKN + TS.
Fit the BN to the TS using MAE (but a bit differently than `caspots` ;)).

Boolean Networks (BN): vocabulary

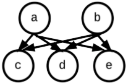
- component
- component's status
- BN's configuration
- influence
- local update functions
- updating scheme
- state transition graph
- reachability

Formalisms for modeling biological systems

Boolean network



Bayesian network

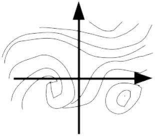


Process algebras

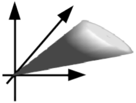
((b(x,de)[E]) || (B(y, dI)[I]))

bh(x, dE) bh(y, dI) (E || I)

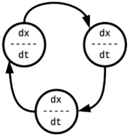
Differential equation



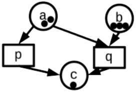
Constraint based model



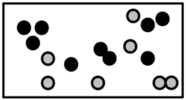
Hybrid systems



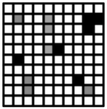
Petri Nets



Agent-based model



Cellular automata



Interacting state machine

Compartment based

Rule based

...

Choice of the formalism

the more abstract the better (do not bother with details) as long as it is sufficient to answer the question