Constraint-based Abstraction of Reaction Networks to Boolean Networks

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CLC center, Univ. Iowa, Iowa City, 26th February 2024

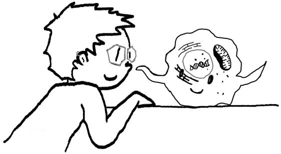
Systems biology

Formal modelling and reasoning about biological systems

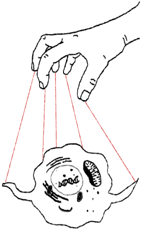
A set of species of interest genes, proteins, cells, animals...
A model = an abstract representation (abbreviated and convenient) of the reality (more complex and detailed).

Questions

How does the system evolve?
Is the population of some cell type stable over time?



How to control the system?
Cure a pathological system
Produce more of some species of interest



A zoo of modelling approaches

Reaction network

continuous time Markov chain

ODEs

statistical models

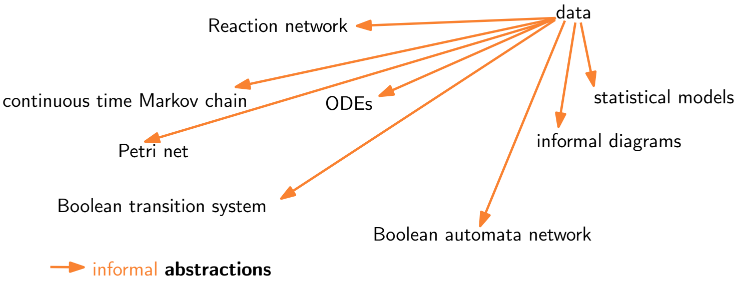
informal diagrams

Petri net

Boolean transition system

Boolean automata network

A zoo of modelling approaches



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Boolean network, structure and dynamics

One transition function per species in $\mathcal{S}$:
$\left\{ f_{\mathsf{X}} : \mathbb{B}^{|\mathcal{S}|} \to \mathbb{B} \right\}_{\mathsf{X} \in \mathcal{S}}$ $\mathbb{B} = \{0, 1\}$

Example

$$\mathcal{S} = \{\mathsf{A}, \mathsf{B}, \mathsf{C}\}$$

$$f_{\mathsf{A}} := 0$$

$$f_{\mathsf{B}} := (\mathsf{B} \wedge \neg \mathsf{C}) \vee (\neg \mathsf{B} \wedge \mathsf{C})$$

$$f_{\mathsf{C}} := \neg \mathsf{C}$$

Boolean network, structure and dynamics

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Influence graph
$IG = (\mathcal{S}, E \subseteq \mathcal{S} \times \mathcal{S}, \sigma : E \to \{+, -, \pm\})$

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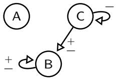

Boolean network, structure and dynamics

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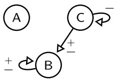
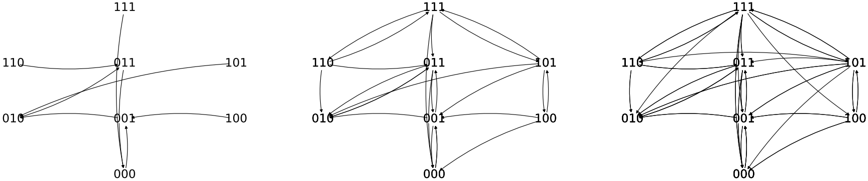


Transition graph $TG = (\mathbb{B}^{|\mathcal{S}|}, E \subseteq \mathbb{B}^{|\mathcal{S}|} \times \mathbb{B}^{|\mathcal{S}|})$, update scheme

synchronous: $\{\{A, B, C\}\}$ $\quad$ async.: $\{\{A\}, \{B\}, \{C\}\}$ $\quad$ general async.: $\mathcal{P}(\mathcal{S}) \setminus \emptyset$



Abstraction relationships between the formalisms

Reaction network

continuous time Markov chain

ODEs

Petri net

Boolean transition system

Boolean automata network
$\boldsymbol{\mathcal{B}} = \left\{ f_X : \mathbb{B}^{|\mathcal{S}|} \to \mathbb{B} \right\}_{X \in \mathcal{S}}$

synchronous → general asynchronous
asynchronous → general asynchronous

Abstraction relationships between the formalisms

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$$\boldsymbol{\mathcal{R}} = \{\mathcal{R}_i : R_i \xrightarrow{e_i} P_i\}_{i=1\dots m}$$

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synchronous asynchronous

general asynchronous

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$\boldsymbol{\mathcal{R}} = \{\mathcal{R}_i : R_i \xrightarrow{e_i} P_i\}_{i=1\ldots m}$

$A + B \xrightarrow{e} 2C$

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continuous time Markov chain

ODEs

$\dot{A} = \dot{B} = -e; \dot{C} = 2e$

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$p(e)$: A- -; B- -; C+=2

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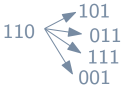

$A = B = 0$ or $1; C = 1$

Boolean automata network

$\boldsymbol{\mathcal{B}} = \left\{ f_X : \mathbb{B}^{|\mathcal{S}|} \to \mathbb{B} \right\}_{X \in \mathcal{S}}$

synchronous asynchronous

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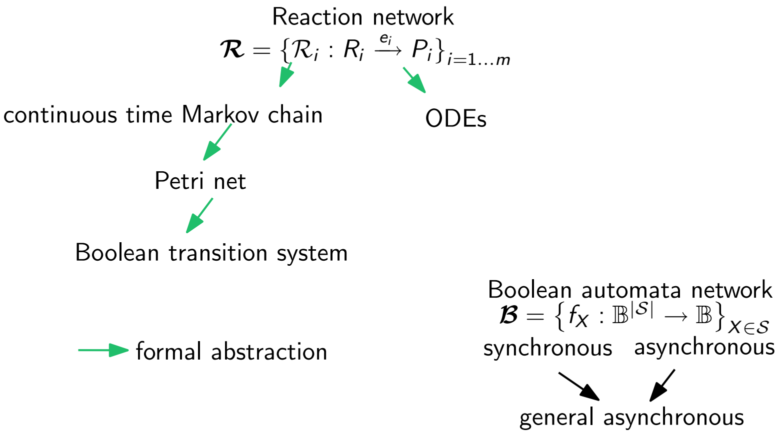
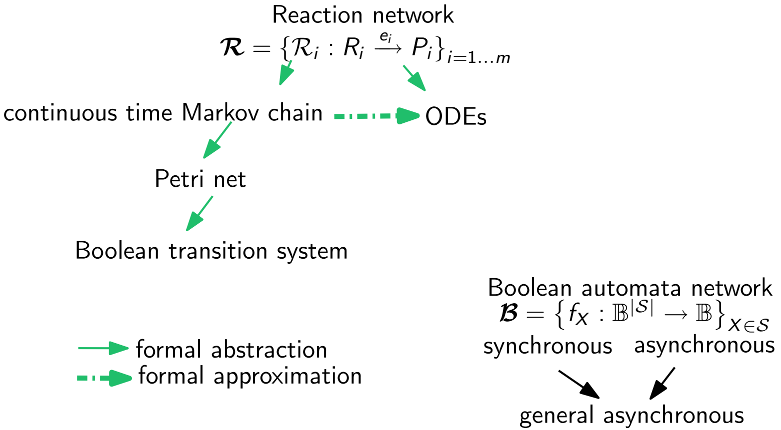


[Fages, Soliman, 2008a]

Abstraction relationships between the formalisms



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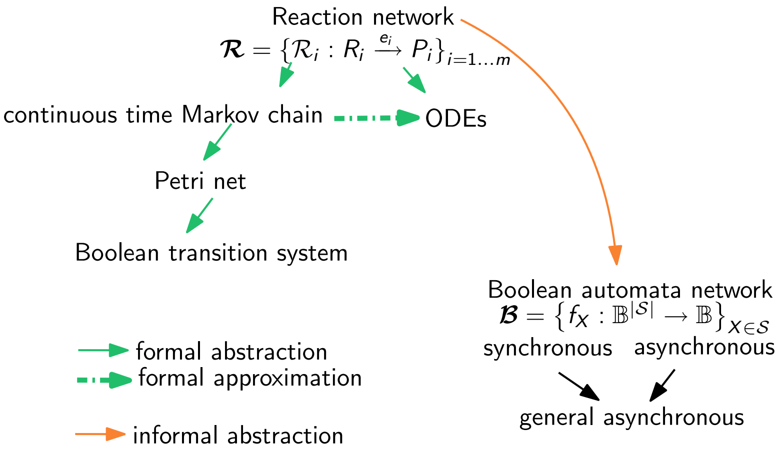

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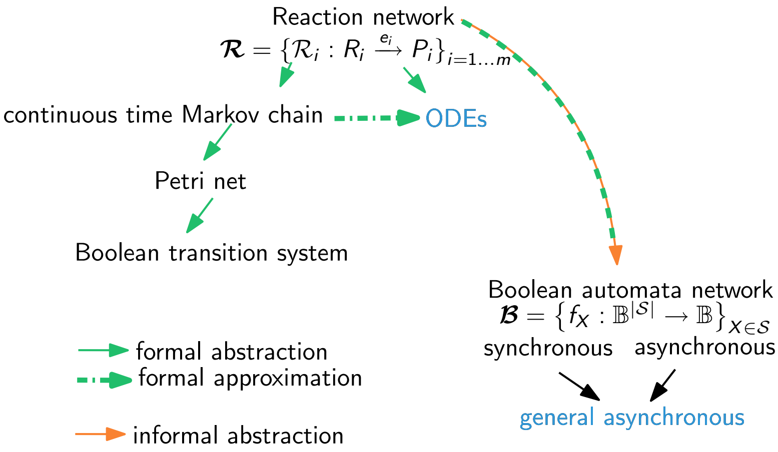

[Fages, Soliman, 2008a]

Problem statement and outline

Automatic transformation (abstraction) of
reaction networks to Boolean networks

1. Introduction and preliminaries
2. The method SBML2BNET and its guarantees
3. Evaluation of the approach
4. Conclusion and perspectives

Outline

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2. The method SBML2BNET and its guarantees
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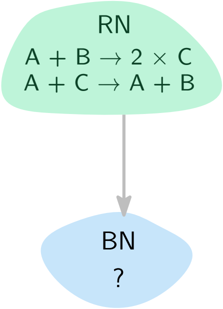
SBML2BNET and its guarantees

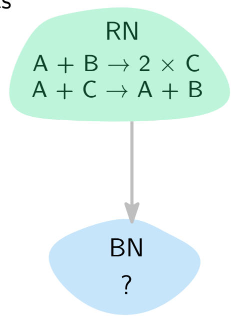
From RN to BN: how?



From RN to BN: how?

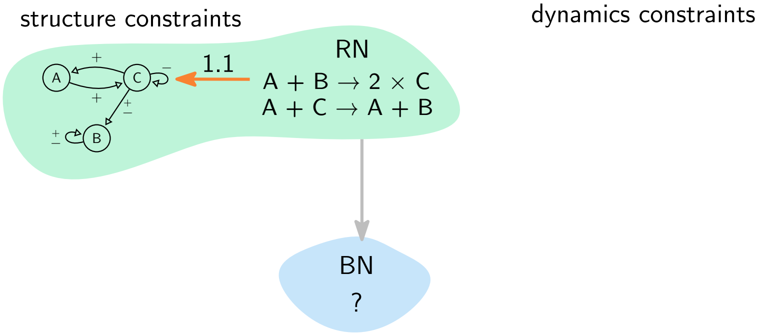
structure constraints

dynamics constraints



STEP 1: Retrieve constraints from the input RN

From RN to BN: how?



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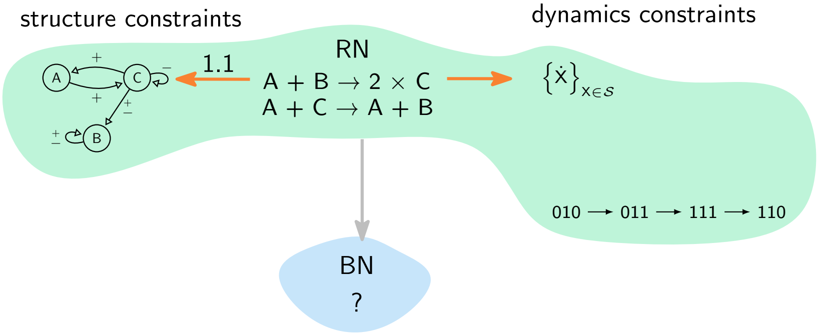
Structure: influence graph

1.1: syntactic parsing of the RN

From RN to BN: how?



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Structure: influence graph **Dynamics**: Boolean transitions

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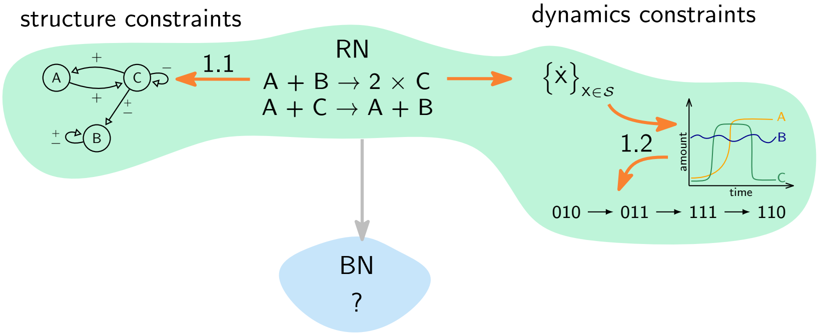

STEP 1: Retrieve constraints from the input RN

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Dynamics: Boolean transitions

1.2: ODEs simulation + binarisation

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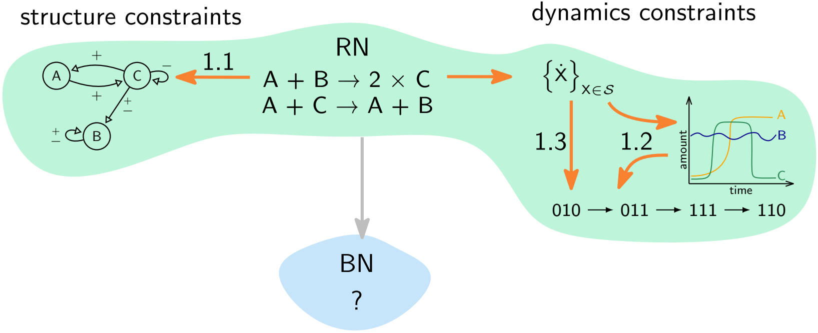

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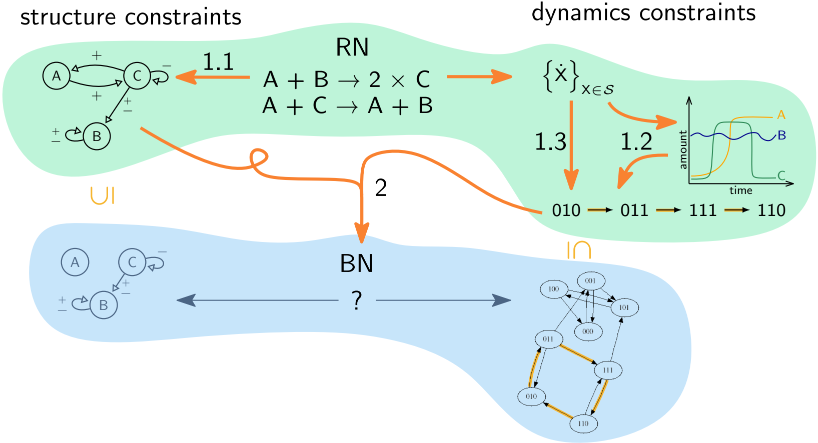

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STEP 2: BN synthesis

Running example $\mathcal{R}_{\text{enz}}$

$$\overbrace{\underbrace{\mathsf{E} + \mathsf{S} \underset{e_{\text{off}}}{\overset{e_{\text{on}}}{\rightleftarrows}} \mathsf{C}}_{\mathcal{R}_{\text{off}}}}^{\mathcal{R}_{\text{on}}} \overbrace{\xrightarrow{e_{\text{cat}}} \mathsf{E} + 2 \times \mathsf{P}}^{\mathcal{R}_{\text{cat}}}$$

Its ODEs (reconstructed)

$$\begin{cases} \dot{\mathsf{S}} = -e_{\text{on}} + e_{\text{off}} \\ \dot{\mathsf{E}} = -e_{\text{on}} + e_{\text{off}} + e_{\text{cat}} \\ \dot{\mathsf{C}} = e_{\text{on}} - e_{\text{off}} + e_{\text{cat}} \\ \dot{\mathsf{P}} = 2 \times e_{\text{cat}} \end{cases}$$

Its parameters (given)

$$e_{\text{on}} = 10^6 \times \mathsf{E} \times \mathsf{S}$$
$$e_{\text{off}} = 0.2 \times \mathsf{C}$$
$$e_{\text{cat}} = 0.1 \times \mathsf{C}$$

Outline

1. Introduction and preliminaries

2. The method SBML2BNET and its guarantees

   STEP 1: Retrieve constraints from the input reaction network
   Structure: influence graph

   - 1.1: syntactic parsing of the reactions

   Dynamics: Boolean transitions

   - 1.2: ODEs simulation + binarisation
   - 1.3: abstract simulation of the ODEs [Niehren et al., 2022]

   STEP 2: BN synthesis with `ASK&D-BN` [Vaginay et al., 2021]

3. Evaluation of the approach

4. Conclusion and perspectives

STEP 1: Retrieve an influence graph and Boolean transitions

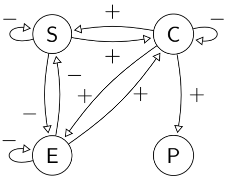
Which contraints to build the influence graph $\mathcal{G}_{\mathcal{R}}$?

Inference of the relationships between the species using **static analysis** of $\mathcal{R}$ [Fages, Soliman, 2008b]

$\mathsf{Y} \xrightarrow{-} \mathsf{X} \in \mathcal{G}_{\mathcal{R}}$ if $\exists \mathcal{R} = R \xrightarrow{e} P$ st $\mathsf{Y} \in R$ and $R(\mathsf{X}) > P(\mathsf{X})$

$\mathsf{Y} \xrightarrow{+} \mathsf{X} \in \mathcal{G}_{\mathcal{R}}$ if $\exists \mathcal{R} = R \xrightarrow{e} P$ st $\mathsf{Y} \in R$ and $R(\mathsf{X}) < P(\mathsf{X})$

$\mathcal{G}_{\mathcal{R}_{\text{enz}}}$



Guarantee: Overapproximates the possible signs of $\frac{\partial \mathsf{X}}{\partial \mathsf{Y}}$
$\rightsquigarrow$ it captures all the **direct influences** between the species ✓

Which constraints to retrieve Boolean transitions from $\mathcal{R}$?

Abstract simulation — Intuition

Joint work with Joachim Niehren and Cristian Versari [Niehren et al., 2022]

Use the rule of signs to reason on the causal relationship between the signs ($\mathbb{S} = \{-1, 0, 1\}$) of the variables values of the ODE system

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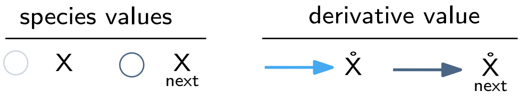

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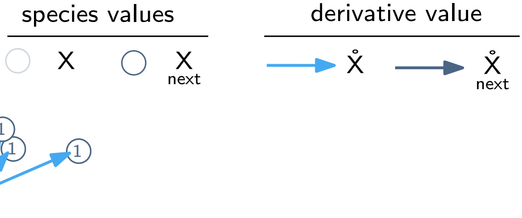

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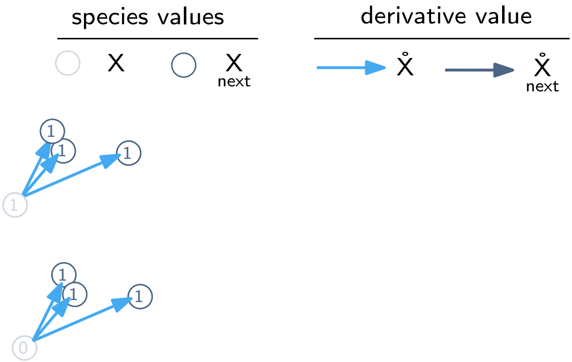

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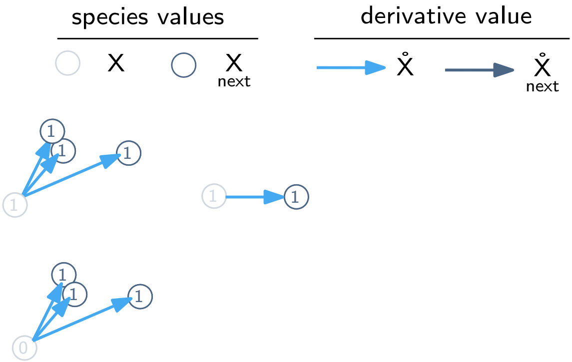

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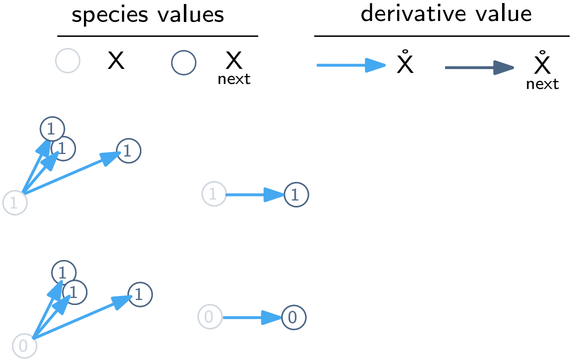

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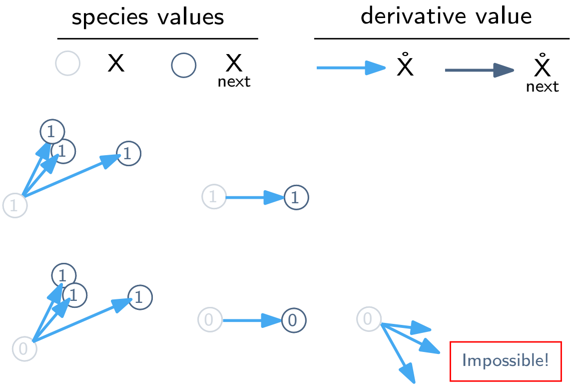

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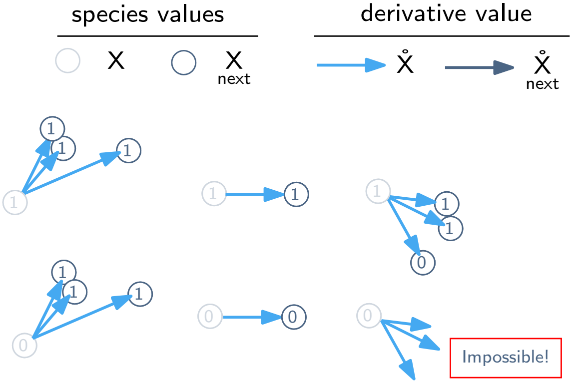

X was above 0 and its derivative was negative

plus $-$ *plus* $=$ *unknown* $\rightsquigarrow$ nondeterminism

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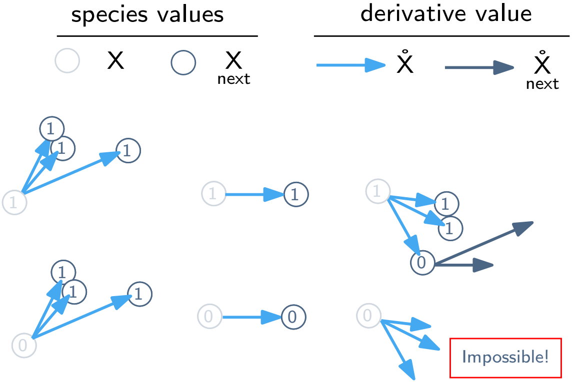

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Which constraints to retrieve Boolean transitions from $\mathcal{R}$?

Abstract simulation — In practice

Contribution

$$\mathcal{V} = \bigcup_{\mathsf{X}\in\mathcal{S}} \left\{\mathsf{X}, \mathring{\mathsf{X}}, \underset{\text{next}}{\mathsf{X}}, \underset{\text{next}}{\mathring{\mathsf{X}}}\right\}$$

- Causal relationships encoded by a first-order logic formula ϕ
- Solve ϕ on $\mathbb{S} = \{-1, 0, 1\}$

$\rightsquigarrow$ relation $\mathbb{B}^{|\mathcal{S}\cup\mathring{\mathcal{S}}|} \times \mathbb{B}^{\left|\underset{\text{next}}{\mathcal{S}} \cup \underset{\text{next}}{\mathring{\mathcal{S}}}\right|}$

- Restrict the solutions on $\mathcal{S} \cup \underset{\text{next}}{\mathcal{S}}$

$\rightsquigarrow$ relation $\mathbb{B}^{|\mathcal{S}|} \times \mathbb{B}^{\left|\underset{\text{next}}{\mathcal{S}}\right|}$

Guarantee

- Keep the causalities of changes
- Proof of correctness: overapproximation of an ideal Euler simulation (perfectly adjusted time step and no computation error)

FOBNN: First-Order Boolean networks with nondeterministic updates

Which constraints to retrieve Boolean transitions from $\mathcal{R}$?

Abstract simulation — Example on $\mathcal{R}_{enz}$

$$
\begin{aligned}
& \mathring{S} = -e_{on} + e_{off} && \wedge\ \underset{next}{\mathring{S}} = -\underset{next}{e_{on}} + \underset{next}{e_{off}} \\
\wedge\ & \mathring{E} = -e_{on} + e_{off} + e_{cat} && \wedge\ \underset{next}{\mathring{E}} = -\underset{next}{e_{on}} + \underset{next}{e_{off}} + \underset{next}{e_{cat}} \\
\wedge\ & \mathring{C} = e_{on} - e_{off} - e_{cat} && \wedge\ \underset{next}{\mathring{C}} = \underset{next}{e_{on}} - \underset{next}{e_{off}} - \underset{next}{e_{cat}} \\
\wedge\ & \mathring{P} = e_{cat} && \wedge\ \underset{next}{\mathring{P}} = \underset{next}{e_{cat}}
\end{aligned}
$$

$$
\begin{aligned}
\wedge\ & \underset{next}{S} = S + \mathring{S} && \wedge\ S \leq \underset{next}{S} \\
\wedge\ & \underset{next}{E} = E + \mathring{E} && \wedge\ E \leq \underset{next}{E} \\
\wedge\ & \underset{next}{C} = C + \mathring{C} && \wedge\ C \leq \underset{next}{C} \\
\wedge\ & \underset{next}{P} = P + \mathring{P} && \wedge\ P \leq \underset{next}{P}
\end{aligned}
$$

with

$$
\begin{aligned}
& e_{on} = 10^6 \times S \times E && e_{off} = 0.2 \times C && e_{cat} = 0.1 \times C \\
& \underset{next}{e_{on}} = 10^6 \times \underset{next}{S} \times \underset{next}{E} && \underset{next}{e_{off}} = 0.2 \times \underset{next}{C} && \underset{next}{e_{cat}} = 0.1 \times \underset{next}{C}
\end{aligned}
$$

Which constraints to retrieve Boolean transitions from $\mathcal{R}$?

$$\underbrace{\overbrace{\mathsf{E} + \mathsf{S} \underset{e_{\text{off}}}{\overset{e_{\text{on}}}{\rightleftarrows}} \mathsf{C}}^{\mathcal{R}_{\text{on}}}}_{\mathcal{R}_{\text{off}}} \overbrace{\xrightarrow{e_{\text{cat}}} \mathsf{E} + 2 \times \mathsf{P}}^{\mathcal{R}_{\text{cat}}}$$

Expected transitions [SECP]:
1100 → **10 → ***1

Which constraints to retrieve Boolean transitions from $\mathcal{R}$?

$$\overbrace{\underbrace{E + S \underset{e_{\text{off}}}{\overset{e_{\text{on}}}{\rightleftarrows}} C}_{\mathcal{R}_{\text{off}}}}^{\mathcal{R}_{\text{on}}} \overbrace{\xrightarrow{e_{\text{cat}}} E + 2 \times P}^{\mathcal{R}_{\text{cat}}}$$

Expected transitions [SECP]:
1100 → **10 → ***1

Which constraints to retrieve Boolean transitions from $\mathcal{R}$?

$$\overbrace{\underbrace{\mathsf{E}+\mathsf{S} \underset{e_{\text{off}}}{\overset{e_{\text{on}}}{\rightleftarrows}} \mathsf{C}}_{\mathcal{R}_{\text{off}}}}^{\mathcal{R}_{\text{on}}} \overbrace{\xrightarrow{e_{\text{cat}}} \mathsf{E} + 2 \times \mathsf{P}}^{\mathcal{R}_{\text{cat}}}$$

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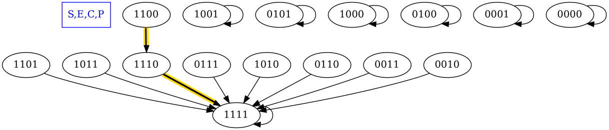
Abstract simulation



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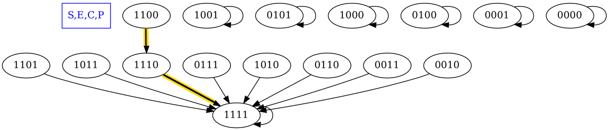
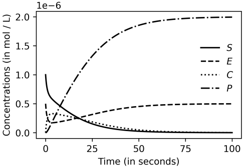
Abstract simulation



Classic ODE simulation + Binarisation



Binarisation	Boolean configuration sequence [SECP]
Midrange	1100 → 1000 → 1010 → 0010 → 0011 → 0101
Median	1100 → 1010 → 0011 → 0101
Mean	1100 → 1010 → 1000 → 0011 → 0101
Above 0	1100 → 1111 → 1011 → 1111 → 0111

Outline

1. Introduction and preliminaries

2. The method SBML2BNET and its guarantees

   STEP 1: Retrieve constraints from the input reaction network
   Structure: influence graph

   - 1.1: syntactic parsing of the reactions

   Dynamics: Boolean transitions

   - 1.2: ODEs simulation + binarisation
   - 1.3: abstract simulation of the ODEs [Niehren et al., 2022]

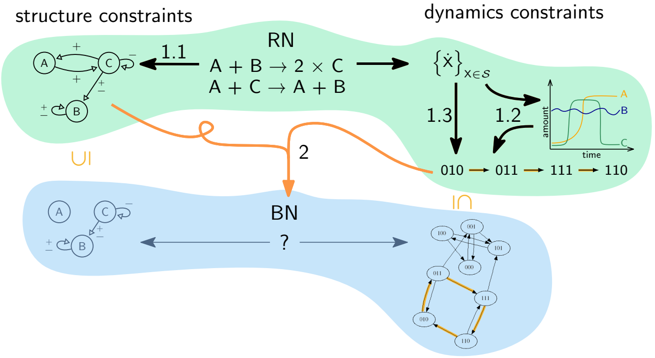
   STEP 2: BN synthesis with `ASK&D-BN` [Vaginay et al., 2021]

3. Evaluation of the approach

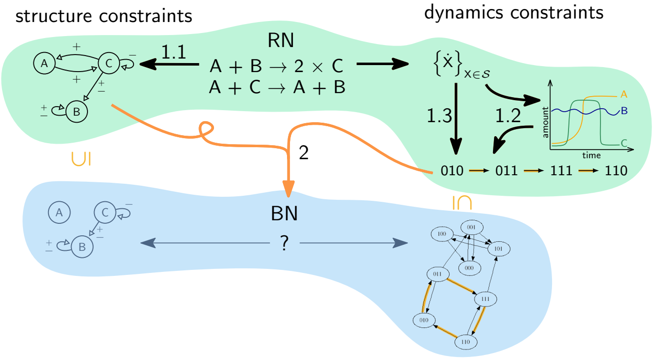
4. Conclusion and perspectives

STEP 2:
Boolean network synthesis with `ASK&D-BN`

ASK&D-BN [Vaginay et al., 2021]



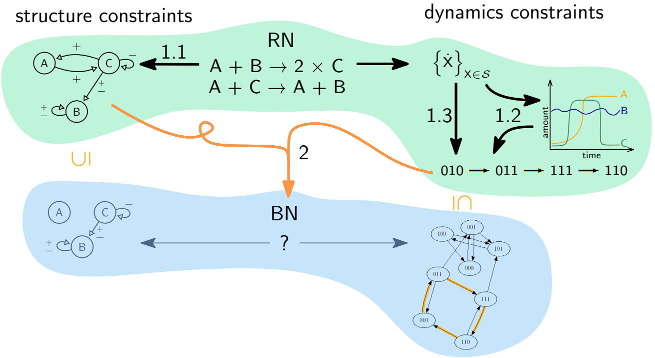
ASK&D-BN [Vaginay et al., 2021]



2.1 **Local search** species-wise synthesis of *all* the transition functions compatible with the given influence graph and time series

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

ASK&D-BN [Vaginay et al., 2021]



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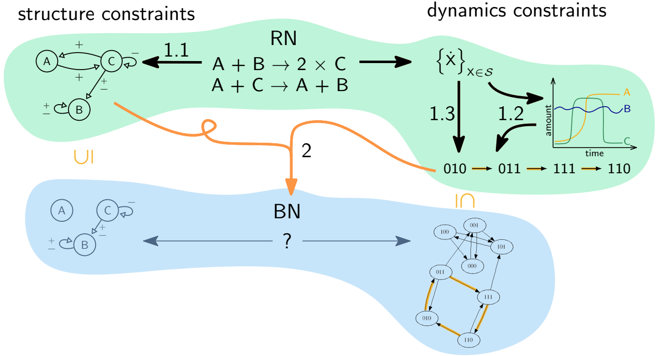
Answer-Set Programming

ASK&D-BN [Vaginay et al., 2021]



2.1 Local search species-wise synthesis of *all* the transition functions compatible with the given influence graph and time series

> Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint
>
> Answer-Set Programming

2.2 Global assembly produce all the possible BNs

ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

Search space: 2^{3^k} non-redundant DNF = non-redundant disjunction of non-redundant conjunctions

ideally: the set of minimal DNF with k inputs.

ASK&D-BN— Local search

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Pick a subset of non-redundant conjunctions
without subsumption and not locally-adjacent

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Pick a subset of non-redundant conjunctions
without subsumption and not locally-adjacent

Examples

invalid candidates:

$(A \wedge \neg B) \vee (A \wedge \neg B) \vee (\neg A \wedge \neg C)$

$(A \wedge A \wedge \neg B) \vee (\neg A \wedge \neg C)$

$(A) \vee (A \wedge B)$

$(A \wedge B) \vee (A \wedge \neg B)$

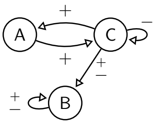
valid candidate:

$(A \wedge \neg B) \vee (\neg A \wedge \neg C)$

ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

influence graph of the Boolean network ⊆ influence graph of the reaction network

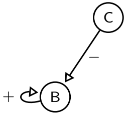


Do not select a conjunction that uses a forbidden literal

Examples

invalid conjunction: $\neg A \wedge \neg C$

valid conjunction: $\neg C \wedge B$



ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

(1) input: Boolean transitions

Build partial truth tables for each species X: what were the values of its putative inputs **when its value changed**? ⇝ Do not assume the underlying update scheme
Compare the truth table of a candidate function to the reconstructed truth table

putative input	output

ASK&D-BN— Local search

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(1) input: Boolean transitions

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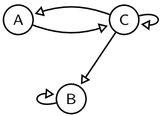
input influence graph (unsigned)



putative input	output
C	A
BC	B
AC	C

ASK&D-BN— Local search

Generate candidates → Structure constraint → **Dynamic constraint** → Minimality constraint

(1) input: Boolean transitions

Build partial truth tables for each species X: what were the values of its putative inputs **when its value changed**? ⇝ Do not assume the underlying update scheme
Compare the truth table of a candidate function to the reconstructed truth table

010 → (1) 011 → (2) 100 → (3) 001

putative input	output
C	A
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Compare the truth table of a candidate function to the reconstructed truth table

$$010 \xrightarrow[(1)]{C} 011 \xrightarrow[(2)]{A,\ B,\ C} 100 \xrightarrow[(3)]{A,\ C} 001$$

putative input	output
C	A
BC	B
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010 $\xrightarrow{C}$ (1) 011 $\xrightarrow{A, B, C}$ (2) 100 $\xrightarrow{A, C}$ (3) 001

putative input	output	
C	A	
1	1	(2)
BC	B	
AC	C	

ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

(1) input: Boolean transitions

Build partial truth tables for each species X: what were the values of its putative inputs **when its value changed**? ⇝ Do not assume the underlying update scheme
Compare the truth table of a candidate function to the reconstructed truth table

010 $\xrightarrow{C}$ (1) 011 $\xrightarrow{A,\,B,\,C}$ (2) 100 $\xrightarrow{A,\,C}$ (3) 001

putative input	output	
C	A	
0	0	(3)
1	1	(2)
BC	B	
AC	C	

ASK&D-BN— Local search

(1) input: Boolean transitions

Build partial truth tables for each species X: what were the values of its putative inputs **when its value changed**? ⇝ Do not assume the underlying update scheme
Compare the truth table of a candidate function to the reconstructed truth table

010 —C (1)→ 011 —A, B, C (2)→ 100 —A, C (3)→ 001

putative input	output	
C	A	
0	0	(3)
1	1	(2)

putative input	output	
BC	B	
11	0	(2)

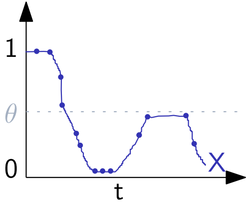
putative input	output	
AC	C	
00	1	(1)
01	0	(2)
10	1	(3)

ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

(2) input: time series

X_t: continuous value of X at time t
θ: binarisation threshold for X



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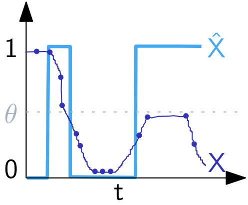

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Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

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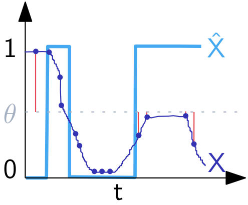
$\mathcal{U}$: set of unexplained time steps

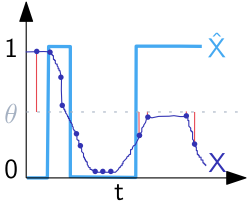


ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

(2) input: time series

X_t: continuous value of X at time t
θ: binarisation threshold for X
$\mathcal{U}$: set of unexplained time steps
$E = \sum_{t \in \mathcal{U}} |\theta - X_t|$ To minimise (ideally 0)



ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

Select candidates with the smallest expressions (subset and/or cardinal minimal) ⇝ most general conditions

putative input	observed output
AB	X
00	
01	0
10	1
11	

ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

Select candidates with the smallest expressions (subset and/or cardinal minimal) ⇝ most general conditions

putative input AB	observed output X	possible completions			
00		0	1	0	1
01	0	0	0	0	0
10	1	1	1	1	1
11		0	0	1	1

ASK&D-BN— Local search

Generate candidates → Structure constraint → Dynamic constraint → Minimality constraint

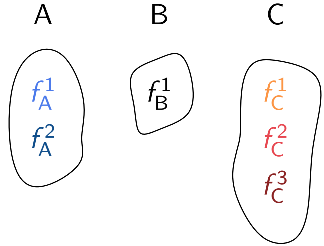
Select candidates with the smallest expressions (subset and/or cardinal minimal) ⇝ most general conditions

putative input AB	observed output X	possible completions			
00		0	1	0	1
01	0	0	0	0	0
10	1	1	1	1	1
11		0	0	1	1
	subset minimal candidates	$A \wedge \neg B$	$\neg B$	A	$A \vee \neg B$
	size	2	1	1	2

card. min. candidates

ASK&D-BN— Global assembly

Cartesian product of the set of transition functions synthesised for each species



$$\mathcal{B}_1 = \{ f_A^1, f_B^1, f_C^1 \}$$
$$\mathcal{B}_2 = \{ f_A^1, f_B^1, f_C^2 \}$$
$$\mathcal{B}_3 = \{ f_A^1, f_B^1, f_C^3 \}$$
$$\mathcal{B}_4 = \{ f_A^2, f_B^1, f_C^1 \}$$
$$\mathcal{B}_5 = \{ f_A^2, f_B^1, f_C^2 \}$$
$$\mathcal{B}_6 = \{ f_A^2, f_B^1, f_C^3 \}$$

Outline

1. Introduction and preliminaries
2. The method SBML2BNET and its guarantees
3. Evaluation of the approach
4. Conclusion and perspectives

Evaluation of the approach

Evaluation of the approach

1. The BN synthesis itself [Vaginay et al., 2021]
   ASK&D-BN versus REVEAL[1], Best-Fit[2] and Caspo-TS[3]

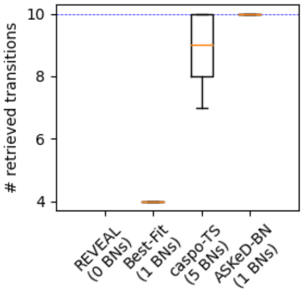
2. One specific variant of the complete approach on real-world reaction networks [Vaginay et al., 2021, Vaginay et al., 2022]
   influence graph + time series and midrange binarisation

3. Several variants of the complete approach on $\mathcal{R}_{enz}$
   compare concrete and abstract simulation

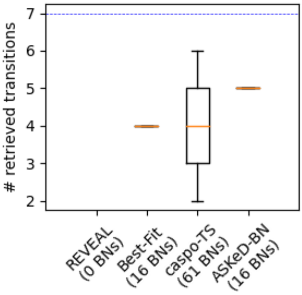
[1] [Liang et al., 1998] [2] [Lähdesmäki et al., 2003] [3] [Ostrowski et al., 2016]

Evaluation of the BN synthesis step

A. thaliana
5 species, 10 transitions



yeast
4 species, 7 transitions



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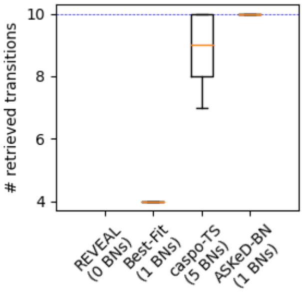

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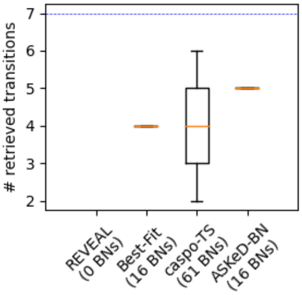

- `REVEAL` fails

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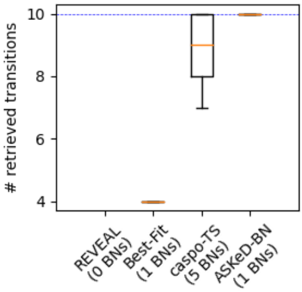

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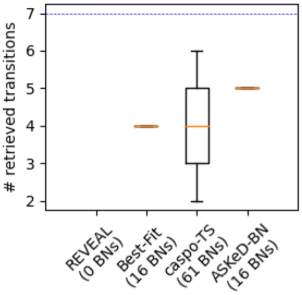

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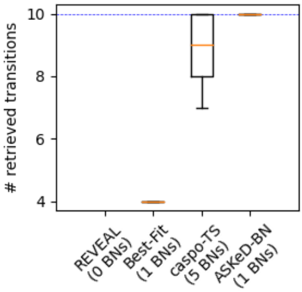

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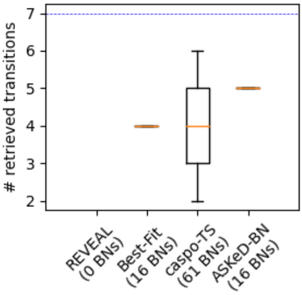

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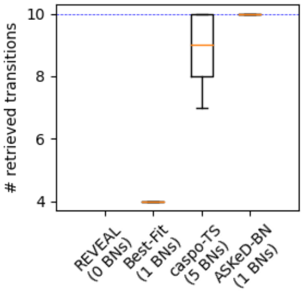

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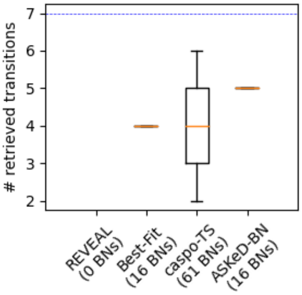

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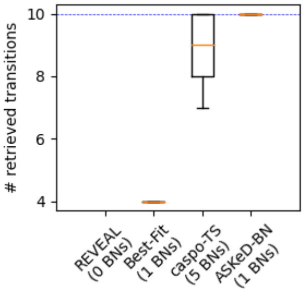

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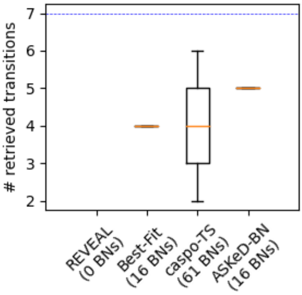

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$\rightsquigarrow$ Confirmed on $>$ 300 datasets generated from existing BNs from the repository of PyBoolNet

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Conclusion and perspectives

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Automatic synthesis of Boolean networks from a given reaction network, with guarantees. ✓

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  Structure: Influence graph from syntactic parsing of the reactions

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  from numerical simulation of the ODEs + binarisation

  - good approximation or the analytical solution
  - but we lose causality

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- Implementation: the SBML2BNET pipeline (+ `ASK&D-BN`)

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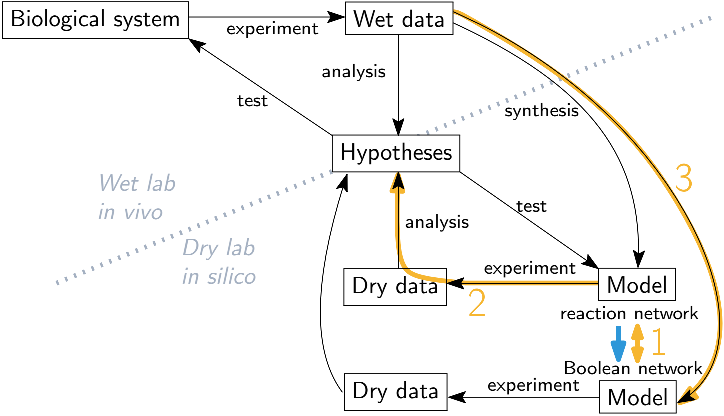
- Evaluation

From RN to BN: the big picture



1. Formalize the relationship between RN and BN
2. Use BNs to facilitate some analyses on RN
3. Improve the BN synthesis methods

Perspectives

1. Formalize the relationship between RN and BN
   Two conjectures to investigate(*), reverse process(*)

2. Facilitate RN analyses
   Make SBML2BNET easy to use, use more evaluation criteria, include more knowledge in the synthesis, analyse FO-BNN themselves (process more RN, compute attractors(*))

3. Improve the BN synthesis methods
   Investigate, in a controled environnement
   - when we can't fullfill the constraints(*)
   - overfitting to *the* sequence of configurations?
   - impact of the choice of the binarisation procedure and error measure

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Thank you for your attention.

Publications

J. Niehren, C. Lhoussaine and **AV**. *Core SBML and its Formal Semantics* CMSB: International Conference on Computational Methods in Systems Biology 2023

Abstract simu. J. Niehren, **AV**, and C. Versari. *Abstract Simulation of Reaction Networks via Boolean Networks* CMSB: International Conference on Computational Methods in Systems Biology 2022

SBML2BNET **AV**, T. Boukhobza, and M. Smaïl-Tabbone. *From Quantitative SBML Models to Boolean Networks* CNA: Complex Networks & Their Applications X 2022

SBML2BNET **AV**, T. Boukhobza, and M. Smaïl-Tabbone. *From Quantitative SBML Models to Boolean Networks* Applied Network Science 2022

ASK&D-BN **AV**, T. Boukhobza, and M. Smaïl-Tabbone. *Automatic Synthesis of Boolean Networks from Biological Knowledge and Data* OLA: Optimization and Learning 2021

A. Hirtz, N. Lebourdais, F. Rech, Y. Bailly, **AV**, M. Smaïl-Tabbone, H. Dubois-Pot-Schneider, and H. Dumond. *GPER Agonist G-1 Disrupts Tubulin Dynamics and Potentiates Temozolomide to Impair Glioblastoma Cell Proliferation* Cells 2021

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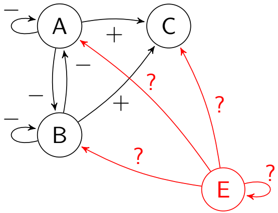
Impact of SBML inconsistencies on structure extraction

Ex. BIOMD n°44: 1 BN generated; coverage=0.55
some kinetics use components not listed in the reactants nor modifiers → incomplete SIG (missing parents)

$$A + B \xrightarrow{f(A,B,E)} C$$



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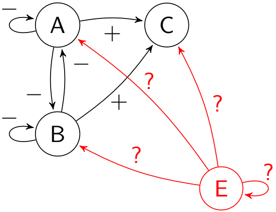


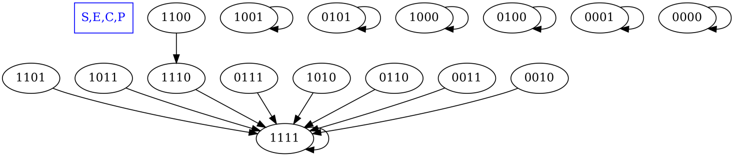
$>$ 60% of SBML models from Biomodels are not "well-formed"[4], but some can be fixed → add a step in the pipeline

[4] [Fages et al. 2012]

FOBNN fixed-points with SAT

Given an FOBNN ϕ with variables $\mathcal{V} = \bigcup_{\mathsf{X}\in\mathcal{S}} \{\mathsf{X}, \mathring{\mathsf{X}}, \underset{\text{next}}{\mathsf{X}}, \underset{\text{next}}{\mathring{\mathsf{X}}}\}$, find the signed assignments $\alpha : \mathcal{V} \to \{1, 0, -1\}$ such that:

$$\forall \mathsf{X} \in \mathcal{S} : \alpha(\mathsf{X}) = \alpha\left(\underset{\text{next}}{\mathsf{X}}\right) \text{ (and no others!)}$$



with Hans-Jörg :)))

Functional dependency for detecting dynamics conflicts

Set of attributes $\mathcal{V}$ (relation scheme)
A set r of tuples that maps each attributes to a value of its domain ($t[X] \in dom(X)$)

A functional dependency (FD) F is an expression of the form $X \rightarrow Y$, where $X, Y \subseteq \mathcal{V}$
F holds in a relation r ($r \models f$) if:

$$\forall t_1, t_2 \in r, t_1[X] = t_2[X] \implies t_1[Y] = t_2[Y]$$

Find counterexamples when it does not hold (work on the conflict-graph).
Find the maximum (biggest) independent sets.

g3-error: minimal proportion of tuples to remove from r to satisfy $F \rightsquigarrow$ coverage measure
Simon Vilmin (AMU) and Pierre Faure--Giovagnoli (LIRIS): relax the equality by using a predicate p instead, study how the complexity of the problems depends on the properties of p (reflexivity, symetry, transitivity, antisymetry)

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t_1	0	0	0	0	0	0	●
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t_3	0	0	0	0	0	1	●

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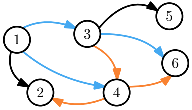

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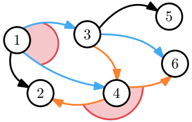

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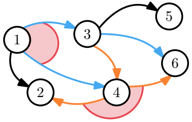

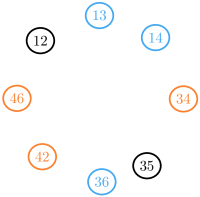

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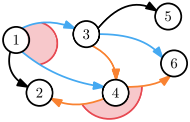

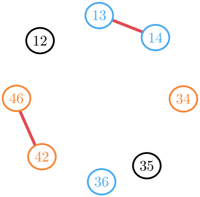

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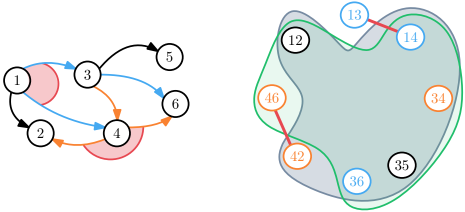

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Our abstraction versus other abstractions

Reaction-thinking

Reaction network

Boolean network

Influence thinking

Our abstraction versus other abstractions

Reaction-thinking

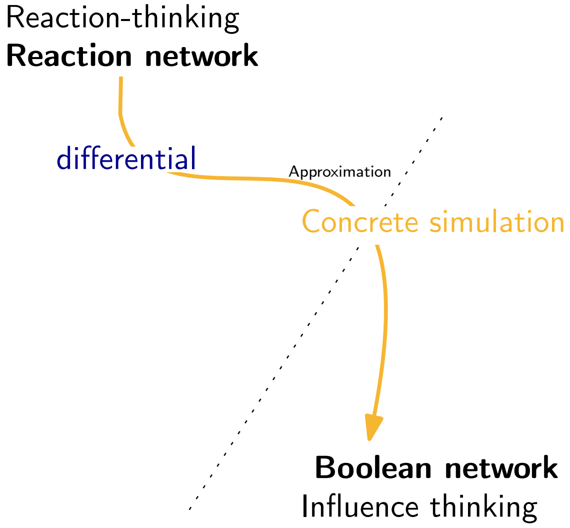
Reaction network

differential

Boolean network

Influence thinking

Our abstraction versus other abstractions



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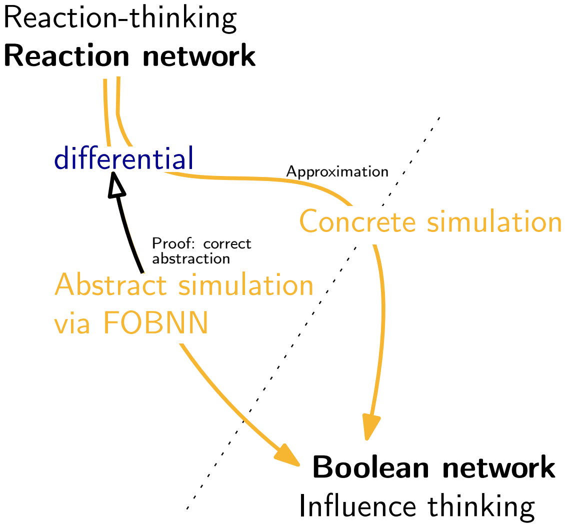

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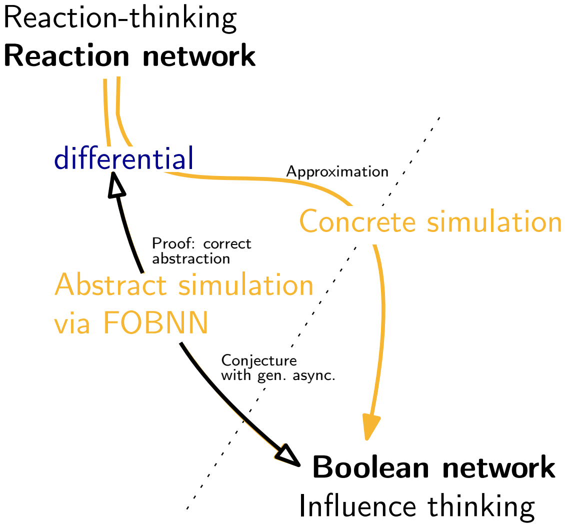

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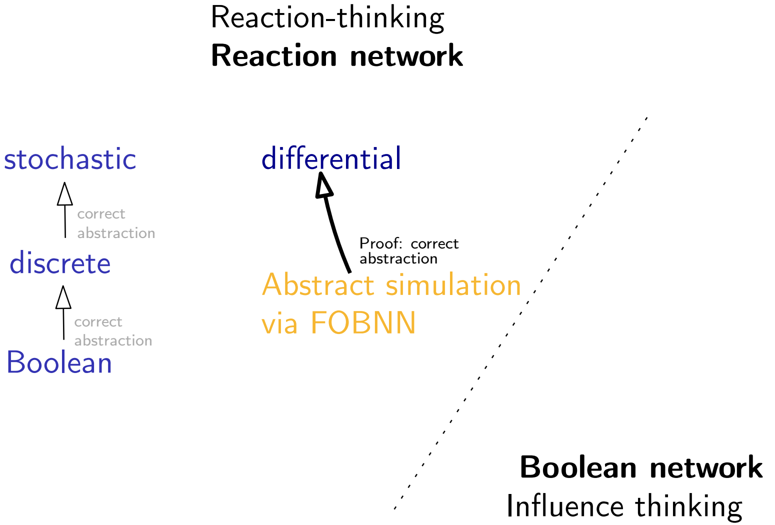

[Fages, Soliman, 2008a]

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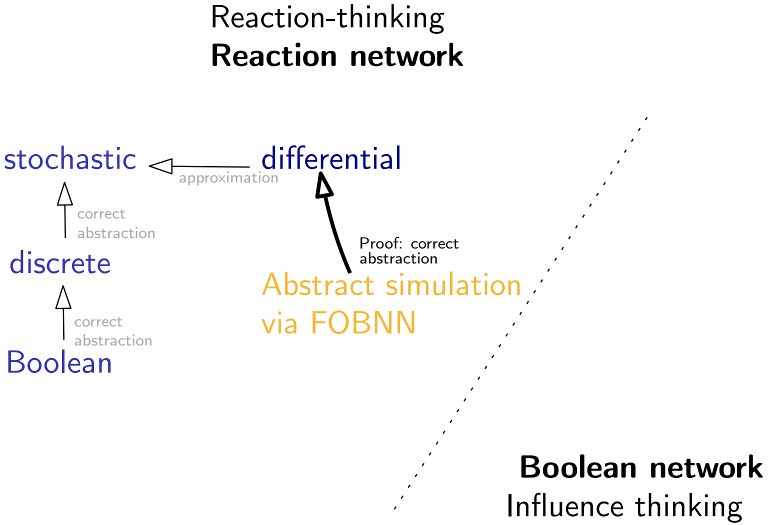

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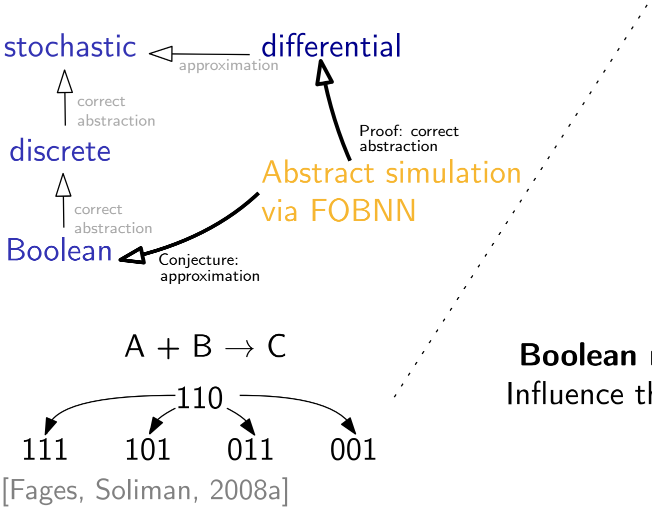
Our abstraction versus other abstractions

Reaction-thinking

Reaction network



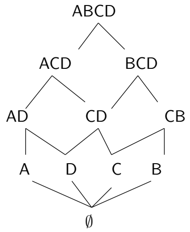
Boolean network

Influence thinking

Learn reaction networks from Boolean transitions

Implication base with variables in $\mathcal{S}$: $\boldsymbol{\mathcal{R}} = \{R_i \to P_i\}_{i=1\ldots m}$
Closed-set: "element of $\mathcal{P}(\mathcal{S})$ such that we cannot derive anything new using $\boldsymbol{\mathcal{R}}$"
Closure system = the set $\mathcal{C}$ of closed-sets of $\boldsymbol{\mathcal{R}}$
$\mathcal{C}$ ordered by $\subseteq \rightsquigarrow$ a lattice

$$
\begin{aligned}
\boldsymbol{\mathcal{R}} = \{ & \\
\mathcal{R}_1 &: \mathrm{A} + \mathrm{B} \to \mathrm{C} + \mathrm{D} \\
\mathcal{R}_2 &: \mathrm{A} + \mathrm{C} \to \mathrm{D} \\
\mathcal{R}_3 &: \mathrm{B} + \mathrm{D} \to \mathrm{C} \\
\} &
\end{aligned}
$$



Simon Vilmin (AMU), Loïc Paulevé? (LABRI)

Learn reaction networks from Boolean transitions

Reaction network with species in $\mathcal{S}$: $\boldsymbol{\mathcal{R}} = \{R_i \to P_i\}_{i=1\dots m}$
Closed-set: "element of $\mathcal{P}(\mathcal{S})$ such that we cannot derive anything new using $\boldsymbol{\mathcal{R}}$"
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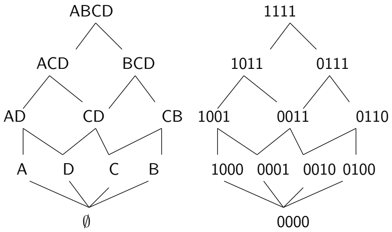
$$\begin{aligned}\boldsymbol{\mathcal{R}} = \{ \\ \mathcal{R}_1 :& A + B \to C + D \\ \mathcal{R}_2 :& A + C \to D \\ \mathcal{R}_3 :& B + D \to C \\ \}\end{aligned}$$



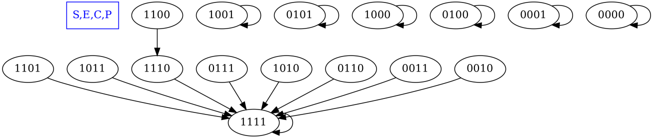
given a closure system, find the implication base(s)
$\stackrel{?}{=}$
given Boolean fixed-points, find the reaction network(s)

Simon Vilmin (AMU), Loïc Paulevé? (LABRI)

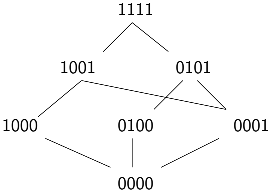
Learn reaction networks from Boolean transitions

$$\overbrace{\underbrace{E + S \underset{e_{\text{off}}}{\overset{e_{\text{on}}}{\rightleftarrows}} C}_{\mathcal{R}_{\text{off}}}}^{\mathcal{R}_{\text{on}}} \overbrace{\xrightarrow{e_{\text{cat}}} E + 2 \times P}^{\mathcal{R}_{\text{cat}}}$$

input state graph:



derived closure system:



derived implication:

$E + S \rightarrow P$ ✓