Simulation and synthesis of formal models of biological systems

Athénaïs Vaginay
Post-doc in MTV (dep. M2F), with Loïc Paulevé

Sémidoc @ LaBRI, Bdx — 2024 July 19

Outline

1. My curriculum :)))
2. A light intro to systems biology and formal models in general
3. Formal methods for the simulation of reaction networks
4. Formal methods for the simulation of Boolean networks
5. Formal methods for the synthesis of Boolean networks
6. Conclusion

Curriculum

Me and my background

Currently (for two more weeks): post-doc in MTV, under the supervision of Loïc Paulevé.

- Medical studies, 1 year
- Biology, licence
- Bio-info, master + "ingénieure d'études" a few months
- Theoretical systems biology ($\sim$ computer science), PhD, postdoc, ...

Reach out: room B353, `athenais.vaginay@labri.fr`

My first time in this amphi: in 2021 (CMSB conference).

Introduction

Systems biology

Formal modelling and reasoning about biological systems

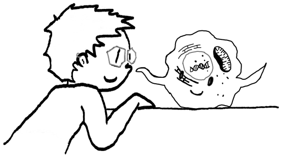
A model = an abstract representation (abbreviated and convenient) of the reality (more complex and detailed)

A set species of species of interest genes, proteins, cells, animals. . .

Questions

How does the system evolve?

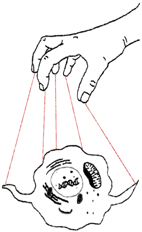
Is the population of some cell type stable over time?



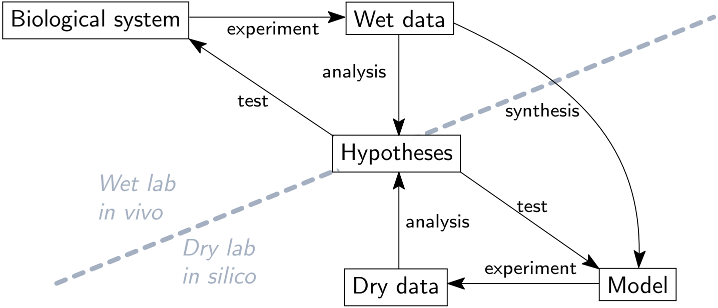
How to control the system?

Cure a pathological system

Produce more of some species of interest



The workflow of system biology [Kohl et al., 2010]



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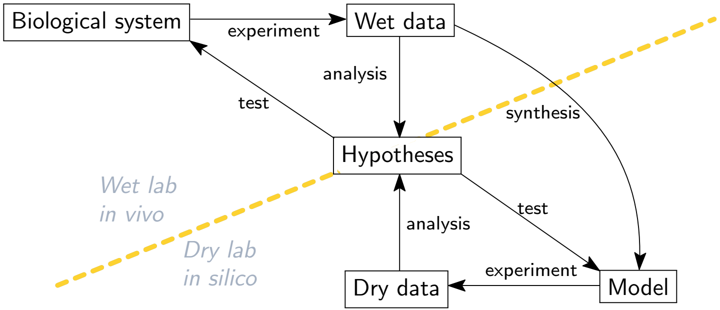

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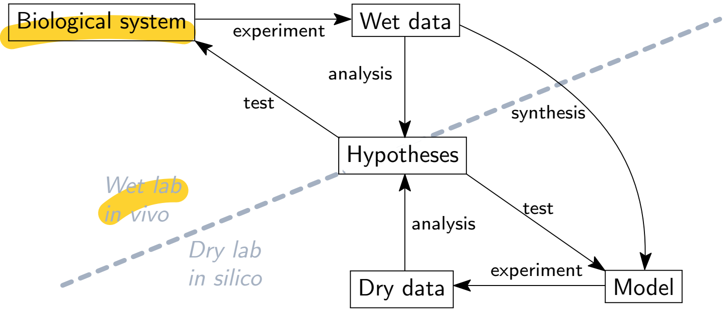

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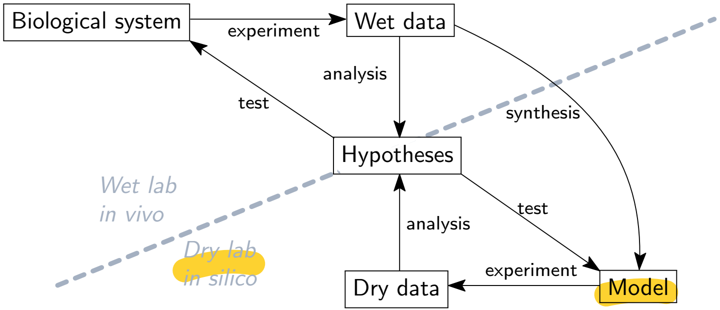

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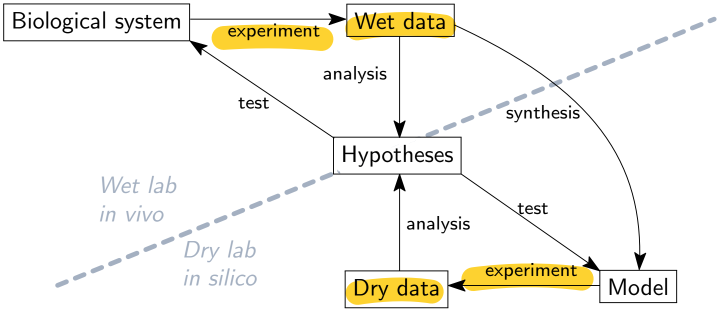

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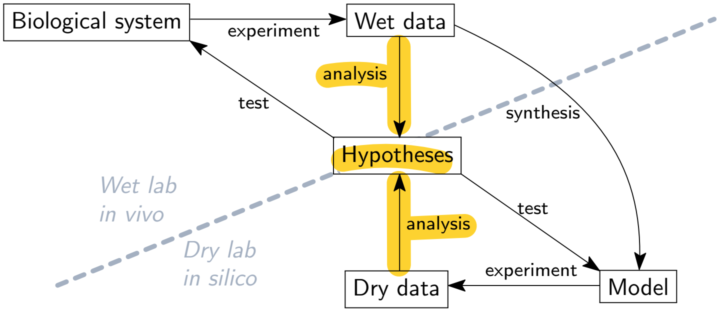

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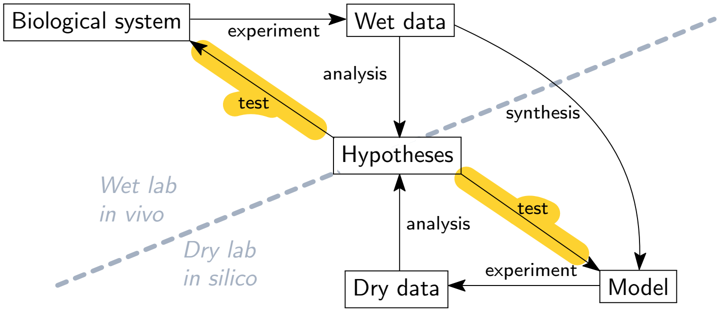

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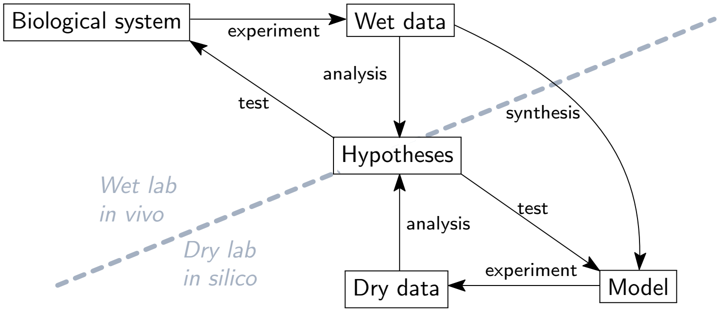

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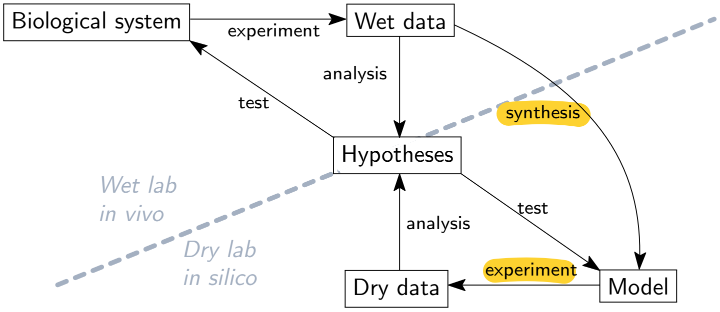


Synthesis:

- from available knowledge and data about the structure and the dynamics
- parameter fitting task find models that optimise some criteria

Experiment: e.g. simulation = execution of the model

A zoo of modelling approaches

Reaction network

continuous time Markov chain

ODEs

statistical models

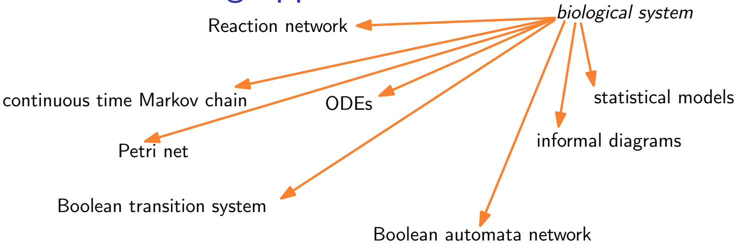
informal diagrams

Petri net

Boolean transition system

Boolean automata network

A zoo of modelling approaches



informal **abstractions**

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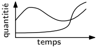
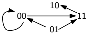
Model = rules A → B

Reaction networks	**Boolean networks**
Transformation of reactants into products	Influence of regulators on regulees
Differential equations	Boolean functions (propositional logics)
$\dot{B} = f(A)$	$B = f(A)$
	
Time series	Transition graph
Continuous time and values	Discrete time, boolean values

Formal methods for the simulation of reaction networks

Static analysis of a reaction network

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

reaction, reactants, products, kinetics

Example

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

$$\mathcal{R}_1 : \mathsf{A} + \mathsf{B} \xrightarrow{e_1} 2 \times \mathsf{C}$$

$$\mathcal{R}_2 : \mathsf{C} \xrightarrow{e_2} \mathsf{B}$$

Static analysis = derive correct conclusions about the dynamics without having to actually simulate the model.

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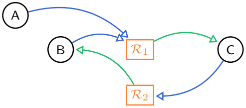
Reaction graph

$(\mathcal{S} \cup \mathcal{R}, E \subseteq (\mathcal{S} \times \mathcal{R}) \cup (\mathcal{R} \times \mathcal{S}))$



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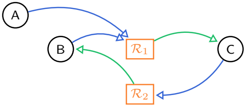

$\rightsquigarrow$ A can only decrease

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Abstract simulation of a reaction network

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Ordinary Differential Equations

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Boolean transition system

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continuous time, continuous values

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

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continuous time, discrete values

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

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A- -; B- -; C+=2

Boolean transition system

discrete time, boolean values

A, B `in` $\{0,1\}$; C `in` $\{1\}$

$$\begin{tikzcd}[row sep=tiny]
 & 101 \\
110 \arrow[ur] \arrow[r] \arrow[dr] \arrow[ddr] & 011 \\
 & 111 \\
 & 001
\end{tikzcd}$$

Abstract simulation of a reaction network

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$110 \to 101$, $110 \to 011$, $110 \to 111$, $110 \to 001$

Formal abstraction between two **semantics**

Abstract simulation = derive correct conclusions using a simpler simu. of the model [Cousot, Cousot, 1977], [Fages, Soliman, 2008a]

Formal methods for the simulation of Boolean networks

The dynamics of a Boolean network using a SAT solveur

A BN f is a function $\mathbb{B}^n \to \mathbb{B}^n$ usually expressed in propositional logics.

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Example

$$x_1' = (x_1 \wedge x_2 \wedge x_3) \wedge x_2' = (x_1 \vee x_3) \wedge x_3' = ((x_2 \wedge x_3) \vee (x_1 \wedge x_2 \wedge x_3) \vee (x_1 \wedge x_2 \wedge x_3))$$

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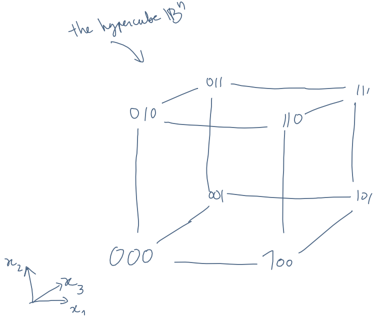

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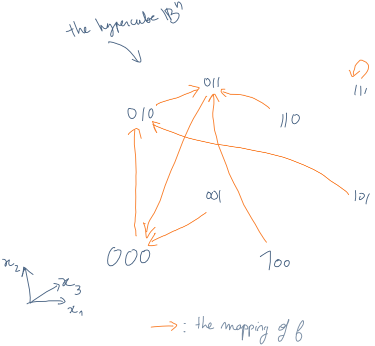

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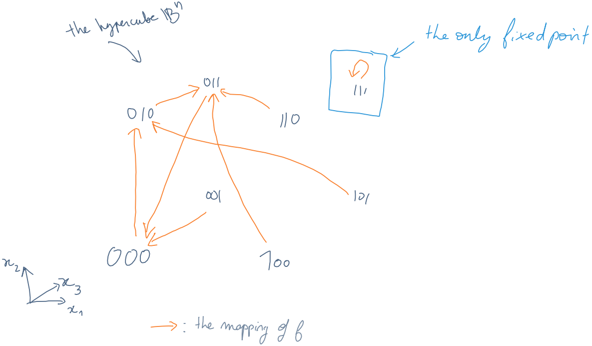

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Trapspace: a subcube t of $\mathbb{B}^n$ such that $\forall x \in t : f(x) \in t$

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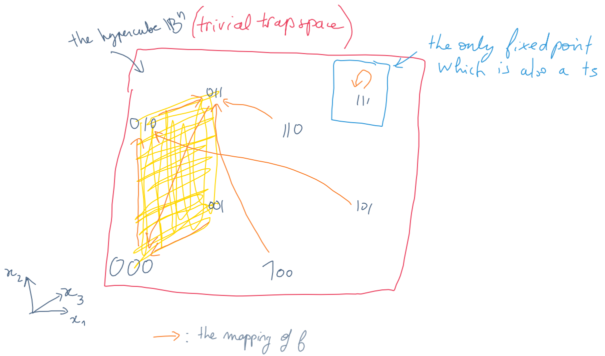

Boolean networks as concurent systems

The impact of updates

A Boolean network is a function $f : \mathbb{B}^n \to \mathbb{B}^n$.
Alternatively, f consists of n local functions $\mathbb{B}^n \to \mathbb{B}$ (one per species in $\mathcal{S}$).

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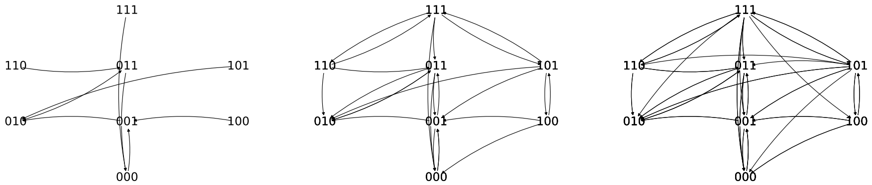
synchronous: $\{\{A, B, C\}\}$ async.: $\{\{A\}, \{B\}, \{C\}\}$ general async.: $\mathcal{P}(\mathcal{S}) \setminus \emptyset$



Strongly impacts the dynamics $\to$ adapt your SAT constraints accordingly

Formal methods for the synthesis of Boolean networks

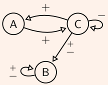
Formal synthesis of Boolean networks

Boolean network

$$\left\{ f_X : \mathbb{B}^{|\mathcal{S}|} \rightarrow \mathbb{B} \mid X \in \mathcal{S} \right\}$$

influence graph ? transition graph

Formal synthesis of Boolean networks



influences
specifications

100 is a fixpoint

$000 \longrightarrow 011 \longrightarrow 111 \longrightarrow 110$

dynamics
specifications

Boolean network

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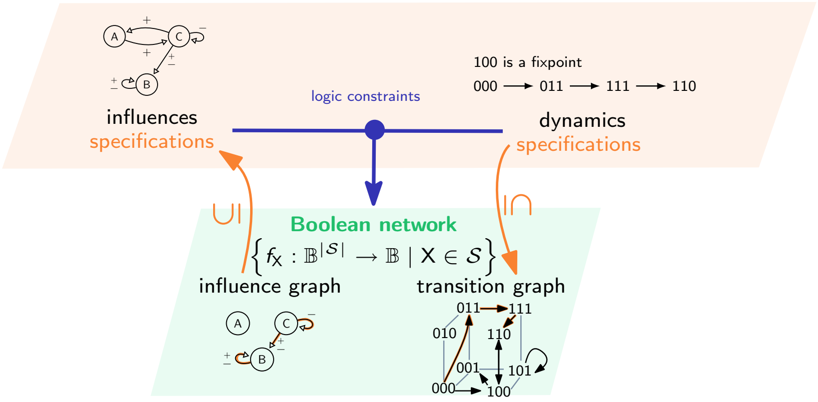
influence graph

?

transition graph

Formal synthesis of Boolean networks



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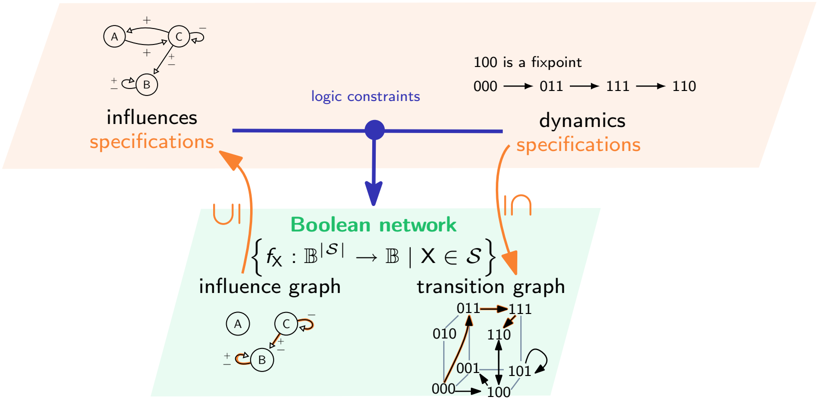


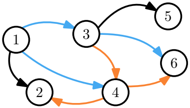
Tool: ASP (Answer set programming) provides an expressive modeling language + fast solvers

Check `BoNesis` from Loïc Paulevé and co.!

`https://bnediction.github.io/bonesis/`

Propose fix if UNSAT

- A Boolean network f consists of n local functions $\mathbb{B}^n \to \mathbb{B}$ (one per species in $\mathcal{S}$).
- BN synthesis may be UNSAT because of conflicting dynamics specifications.



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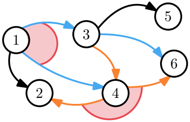

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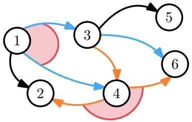
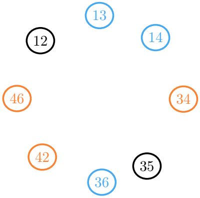
- To remove as few conflicting specifications as possible, find maximum independent sets in the conflict graph.





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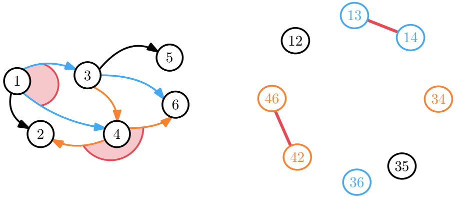

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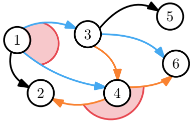

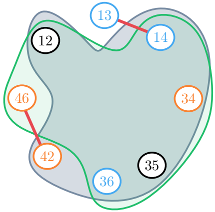

Conclusion and perspectives

To sum up

Biological system
xp / simulation
in vivo
synthesis
in silico
Models

To sum up

Biological system

xp / simulation

synthesis

in vivo

in silico

Models

Reaction networks

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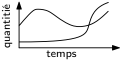
reaction, reactants, products, kinetics

$\mathcal{R} : \mathsf{A} + \mathsf{B} \xrightarrow{e} 2 * \mathsf{C}$

(mostly) time series from diff. eq.



$\rightarrow$ continuous time and values

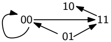
Boolean networks

$$\mathcal{B} = \left\{ f_\mathsf{X} : \mathbb{B}^{|\mathcal{S}|} \rightarrow \mathbb{B} \mid \mathsf{X} \in \mathcal{S} \right\}$$

local update function

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

Transition graph



$\rightarrow$ discrete time, boolean values

Various other formalisms

My research questions

Biological system

xp / simulation

synthesis

in vivo

in silico

Models

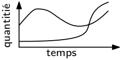
Reaction networks

$\mathcal{R} = \left\{ \mathcal{R}_i : R_i \xrightarrow{e_i} P_i \mid i = 1 \ldots m \right\}$

reaction, reactants, products, kinetics

$\mathcal{R} : A + B \xrightarrow{e} 2 * C$

(mostly) time series from diff. eq.



→ continuous time and values

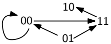
Boolean networks

$\mathcal{B} = \left\{ f_X : \mathbb{B}^{|\mathcal{S}|} \rightarrow \mathbb{B} \mid X \in \mathcal{S} \right\}$

local update function

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

Transition graph



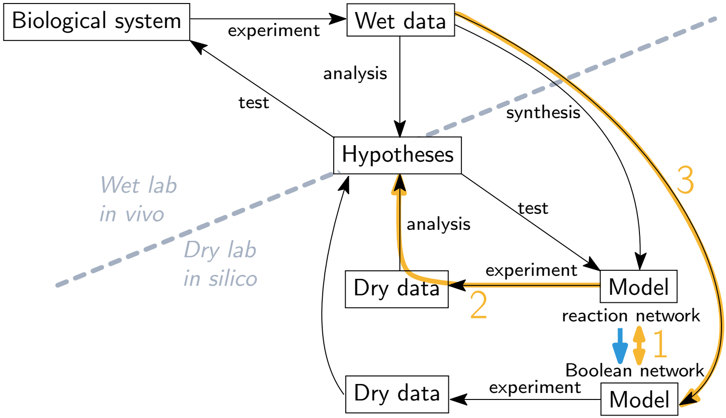
→ discrete time, boolean values

Various other formalisms

Improve synthesis and analysis of models, study abstraction relationship between the formalisms.

Thank you for your attention.

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

Perspectives

1. Formalize the relationship between RN and BN
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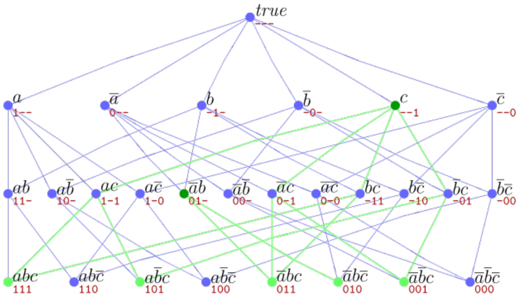
Minimal DNF

Given a set S of inputs for which a function f eval. to 1, each minimal-by-inclusion set of nodes that covers exactly S forms a (subset-)minimal DNF of f.
f might have several (subset-)minimal DNFs.

Example: $S = \{abc, a\bar{b}c, \bar{a}bc, \bar{a}b\bar{c}, \bar{a}\bar{b}c\}$ (light green) $\rightsquigarrow \{\bar{a}b, c\}$ (dark green)



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