Challenges with the logical modeling of biological systems: learning and analyzing discrete and hybrid models

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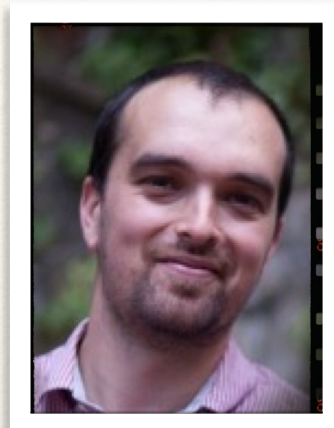
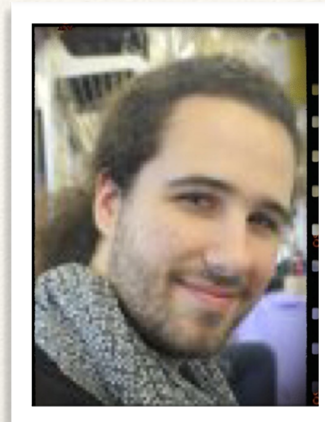


Loïc PAULEVÉ



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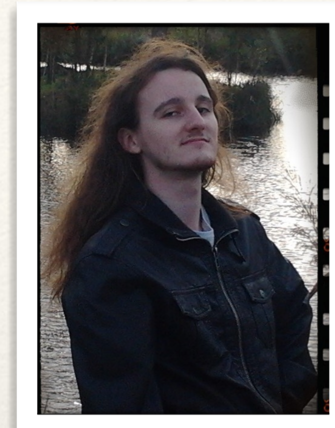

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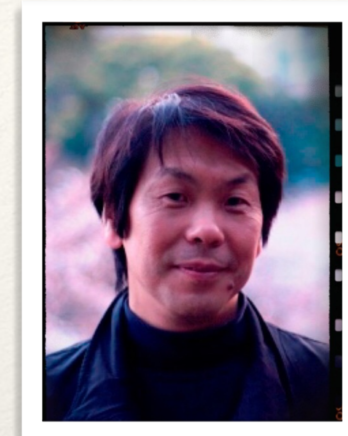

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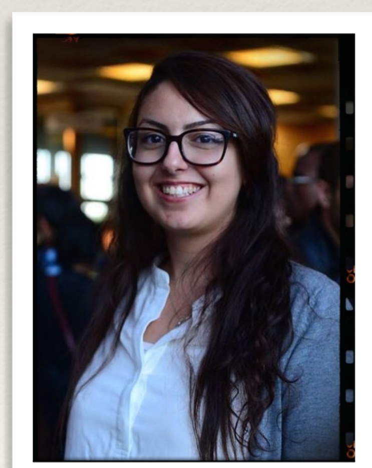
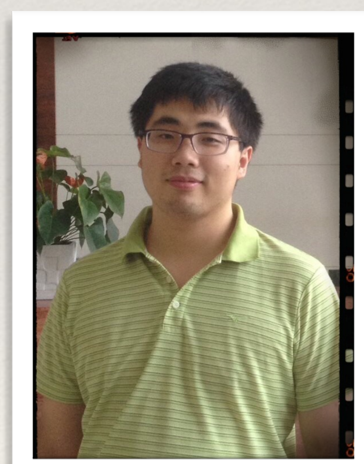
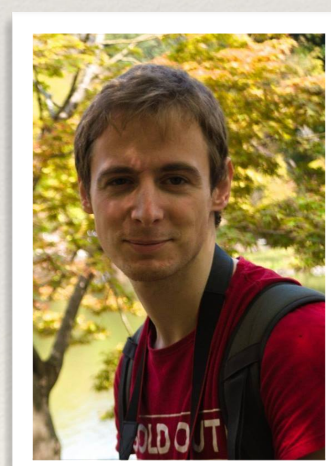


Emna BEN ABDALLAH



Xinwei CHAI



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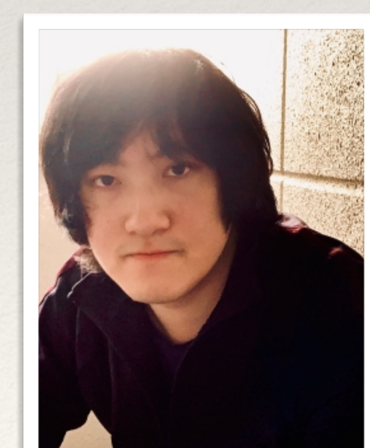
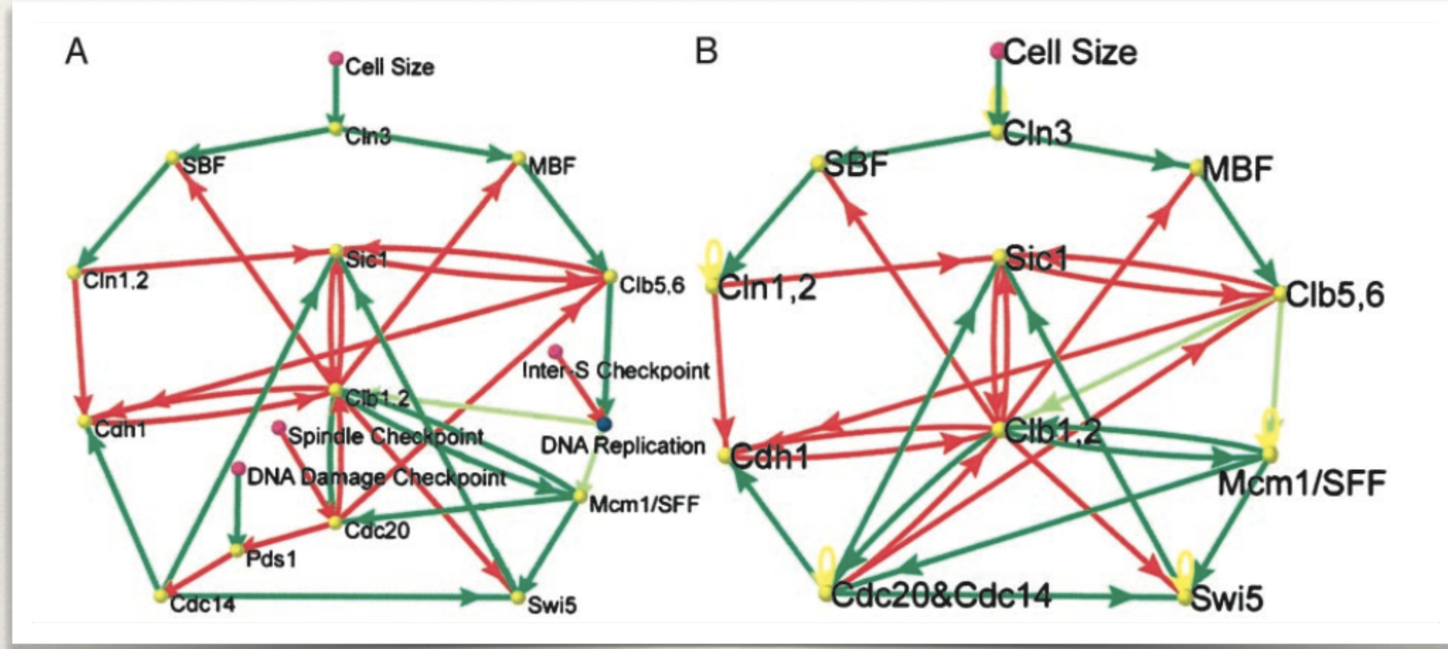


Mitsuhiro ODAKA

Motivations

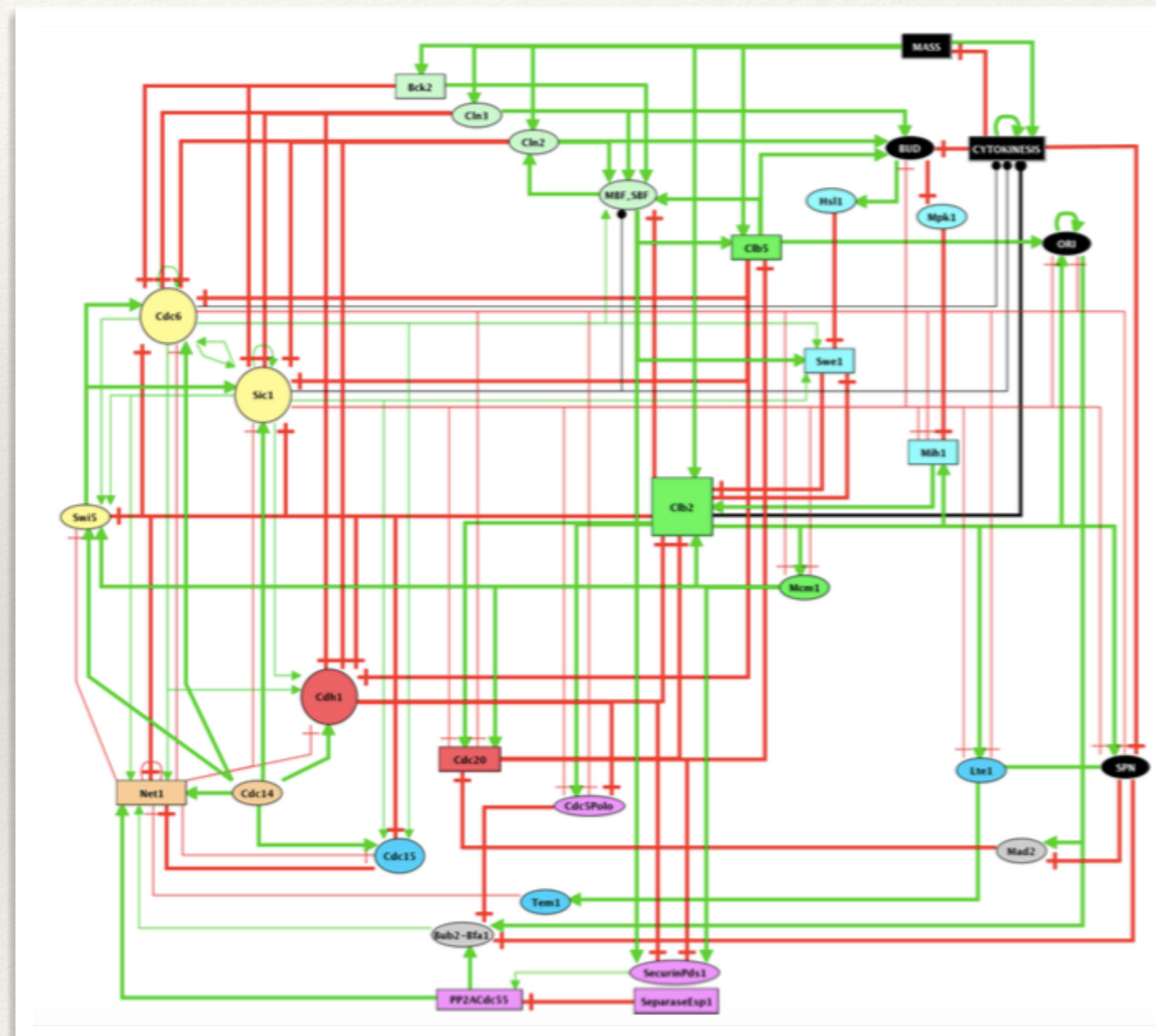
- Goals:
    - Help to the **diagnosis** and **prevention** of diseases
    - Develop new **therapies**
- **Systems biology**
    - Consider a living organism as a system of **interacting networks**
    - Link between physiological functions / **dynamics** of the regulations

Models: why?



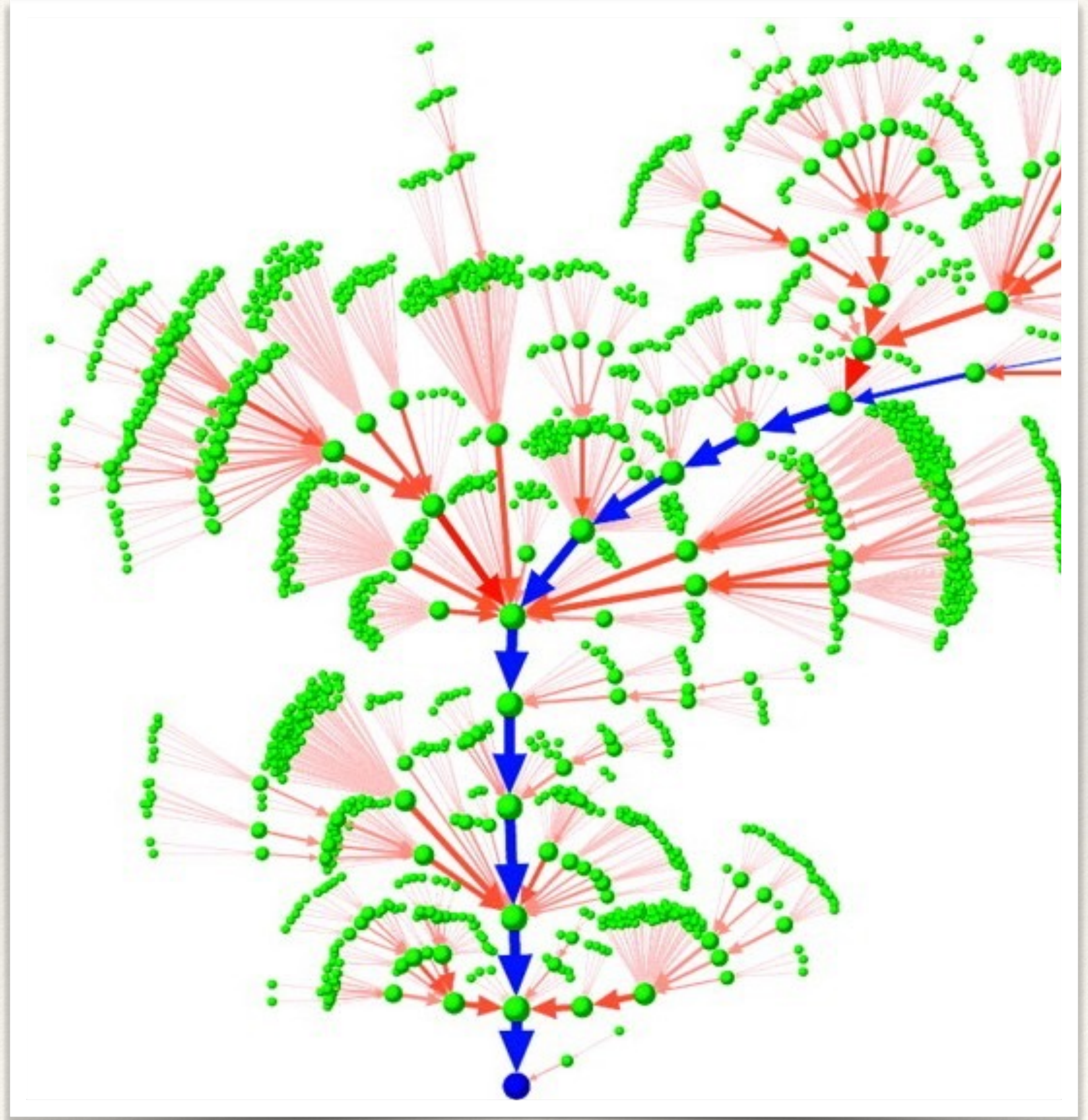
(A) A first model, and (B) a simplified model of the cellular cycle of the budding yeast [LLL+04]

Models: why?



Logical regulatory graph of the budding yeast [FNL+09]

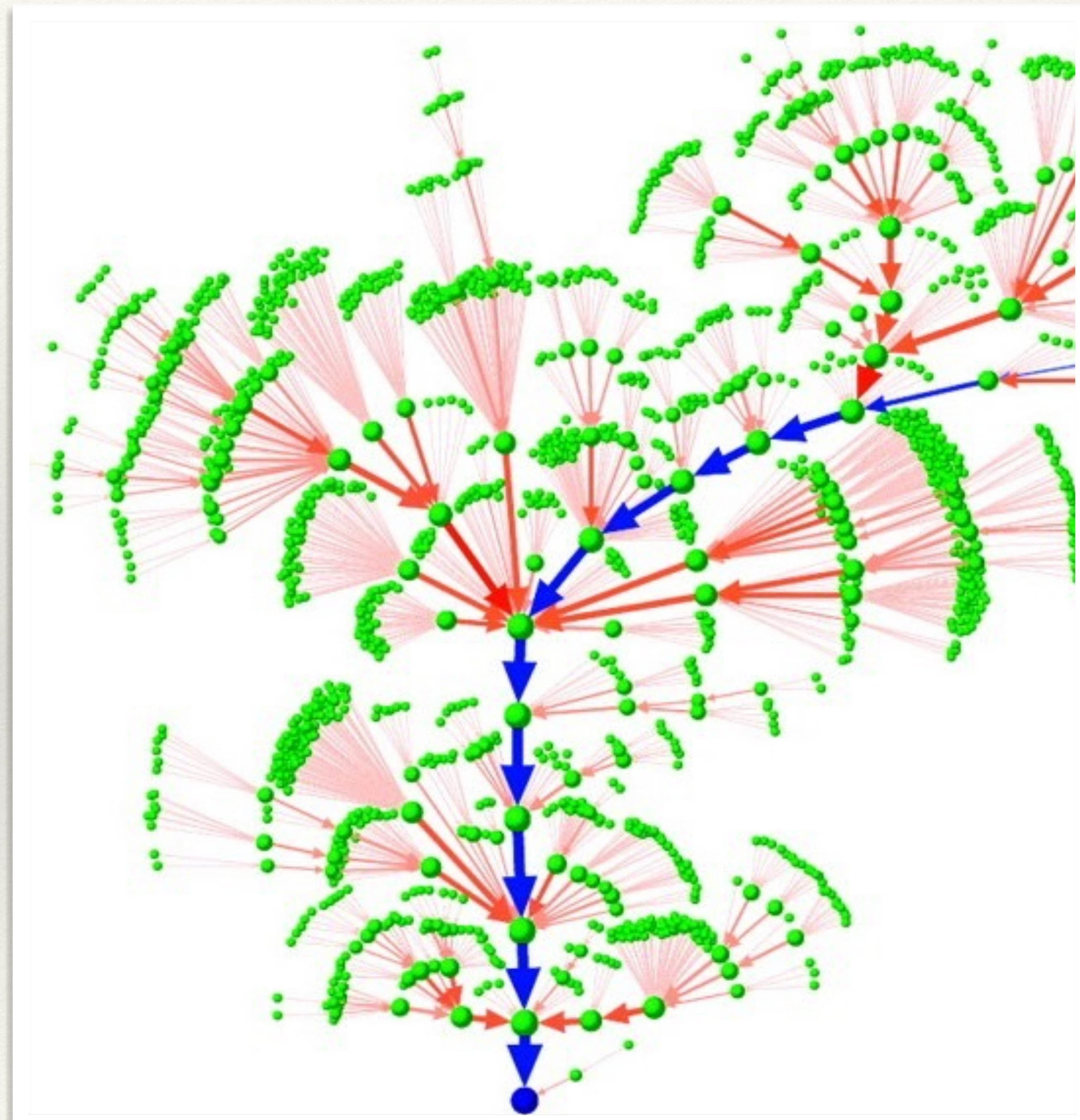
Models: why?



State space of the cellular cycle of the budding yeast [LLL+04]

Models: why?

- Objectives:
  - **Check** whether some expected / unexpected **behaviors** are **possible**
  - Identify **attractors, oscillations,** etc.
  - Understand which are the components **at the origin** of some behaviors
- Problem: how to **circumvent the combinatorial explosion** of the number of behaviors?



State space of the cellular cycle of the budding yeast [LLL+04]

Modeling the dynamics

$t_1\ t_2\ t_3\ t_1\ t_1\ t_5$ ...

Discrete event systems:

- Modeled through transition systems
- Capture the **chronology** (the order) of the events

$(t_1,d_1)\ (t_2,d_2)\ (t_3,d_3)\ (t_1,d_4)\ (t_1,d_5)\ (t_5,d_6)$ ...

Timed systems:

- Modeled through timed transition systems
- Capture the **chronometry** of the events (with their dates)

Scientific challenge

Goals: build **predictive** dynamic **models** from **time series data**

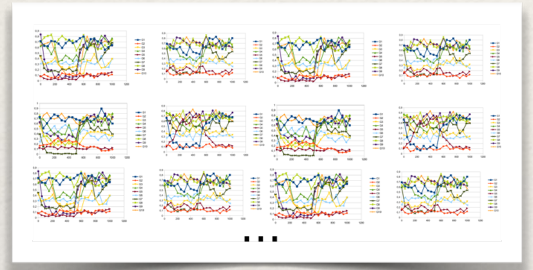
Our motto: **logical modeling** has its own merits w.r.t. continuous approaches (e.g., ODE)

Underlying questions:

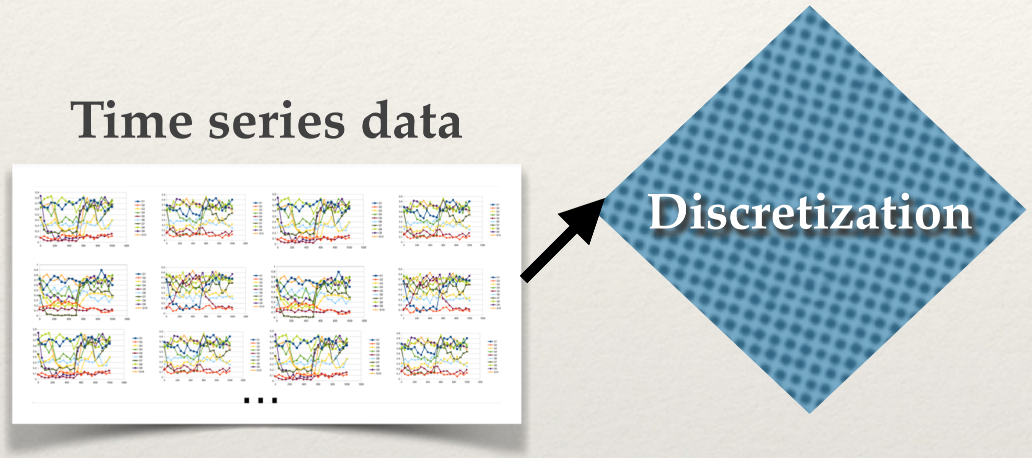
- What are **efficient algorithms** for **discretization** and **learning?**
- What is a *good* predictive model?
- How to validate the **benefits** of our algorithms on "**real-life**" data?

Our scientific challenge

Time series data



Our scientific challenge



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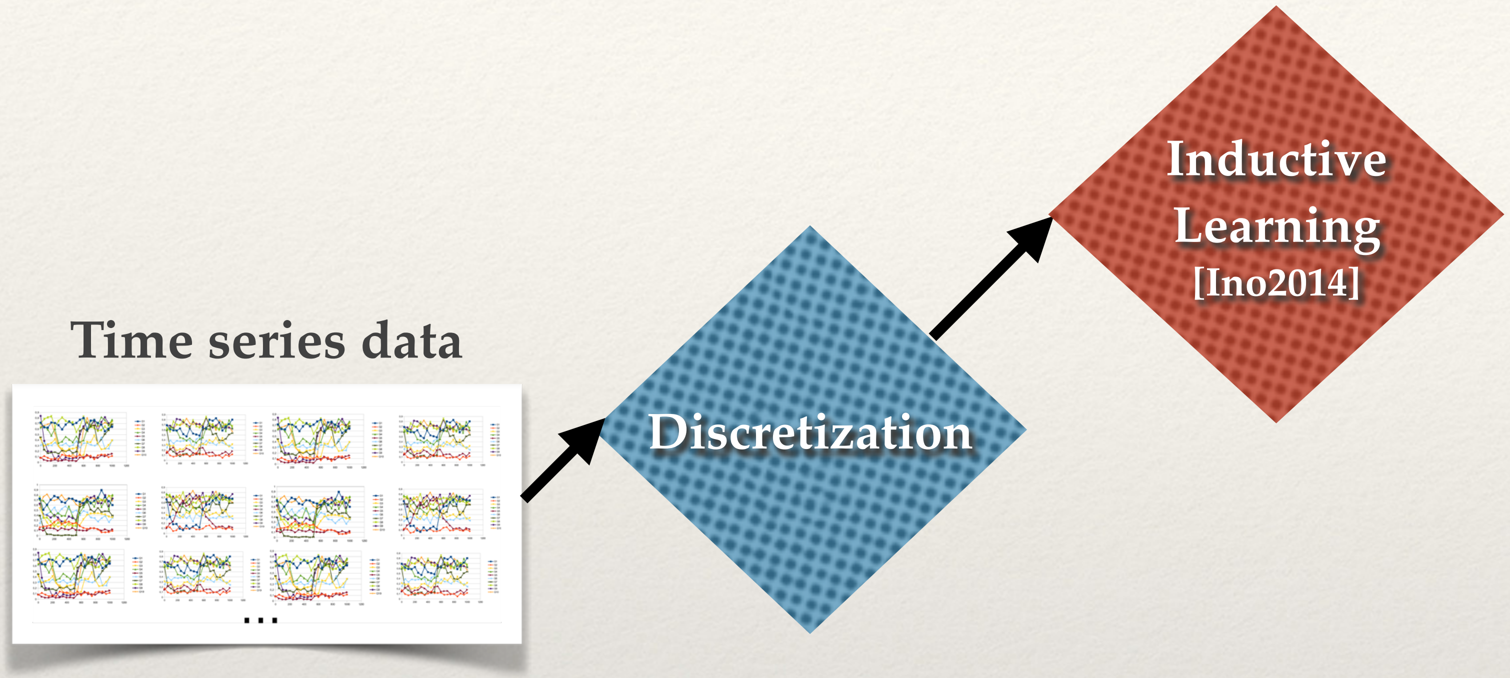
Our scientific challenge



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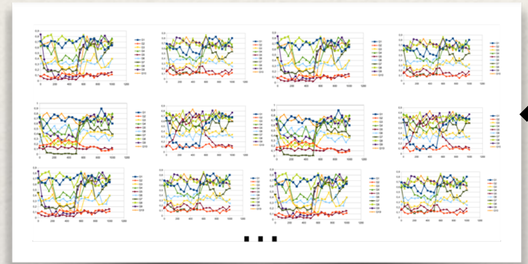
Our scientific challenge

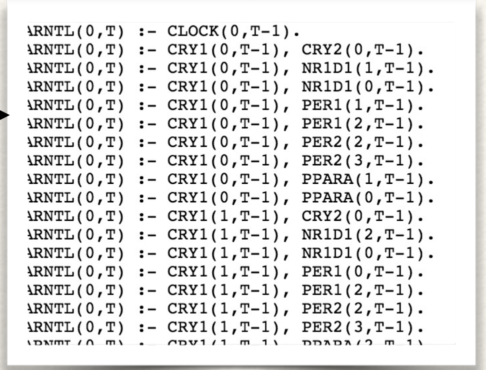
Time series data



Discretization

Inductive Learning [Ino2014]

Dynamical models



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Logic programs

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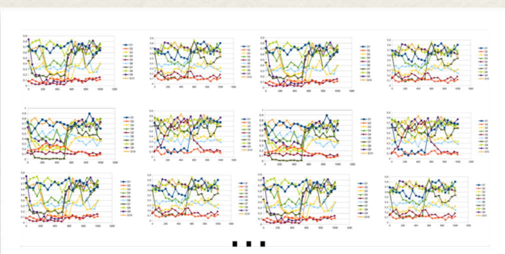
Our scientific challenge

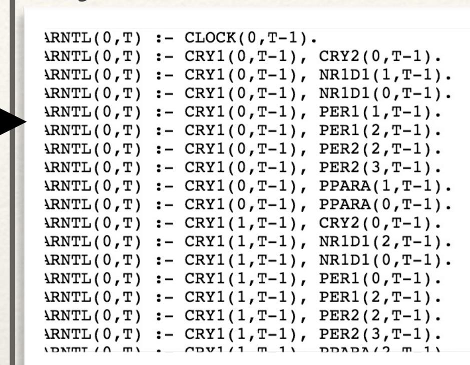
Time series data



Discretization

Inductive Learning [Ino2014]

Dynamical models



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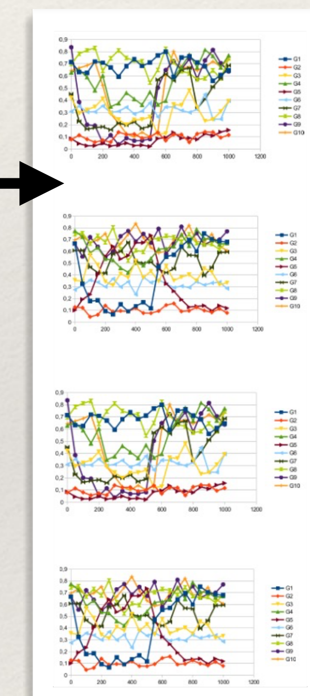
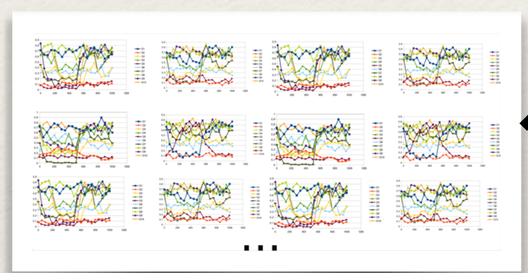
Logic programs

Analysis of dynamic behavior



Our scientific challenge

Time series data



Discretization

Inductive Learning [Ino2014]

Dynamical models

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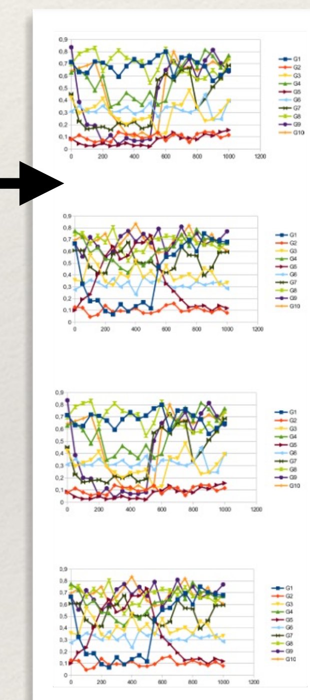
Logic programs

Analysis of dynamic behavior



e.g. fixed points, resilience, bifurcations, …

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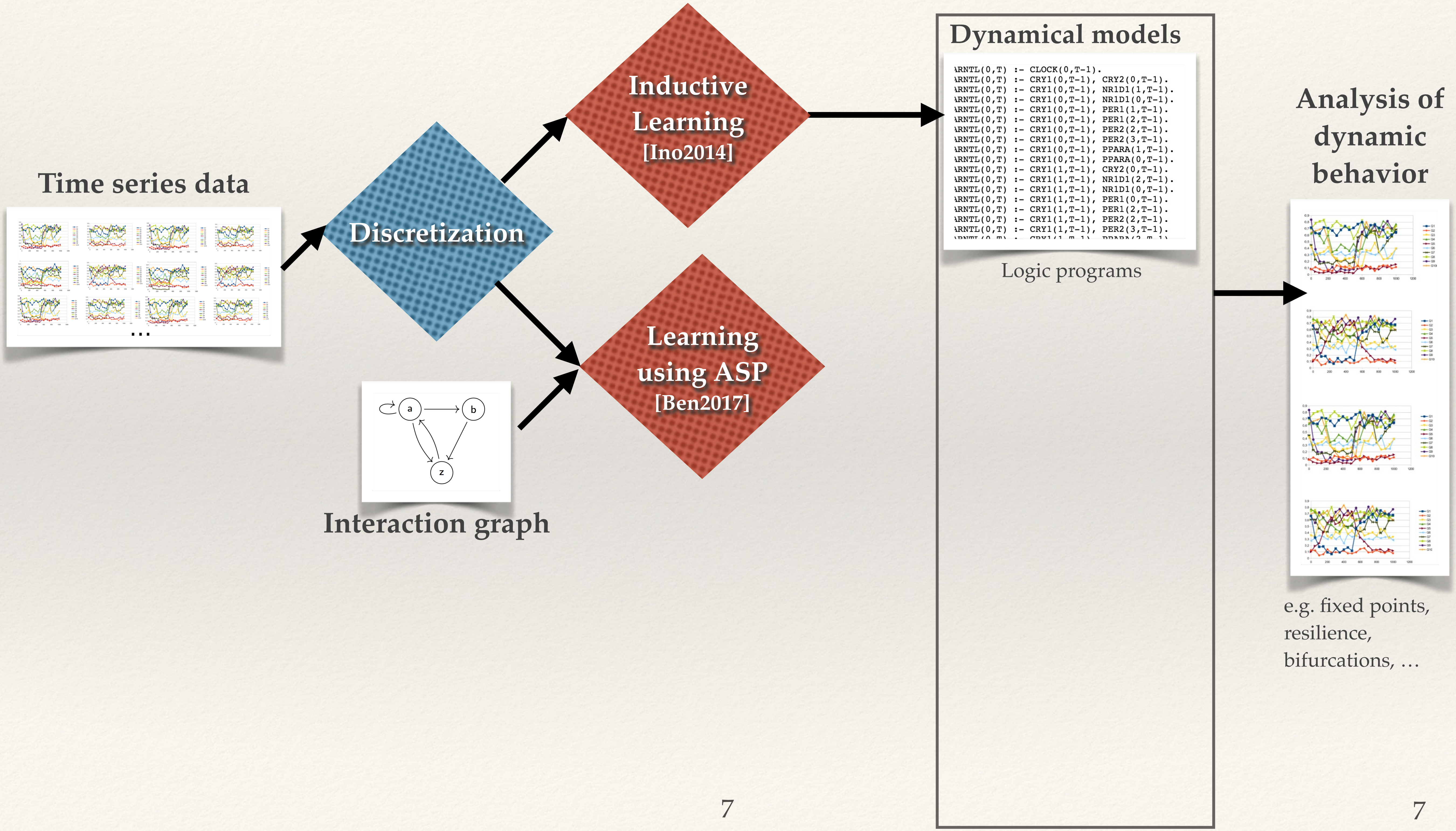
Our scientific challenge



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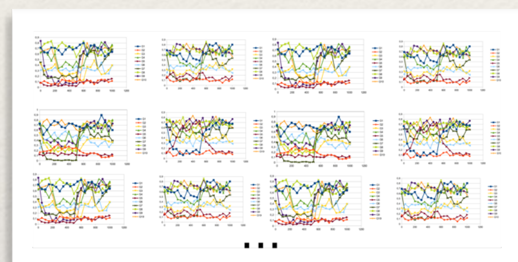
Our scientific challenge

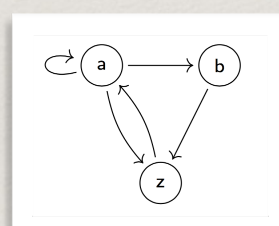
Time series data



Discretization

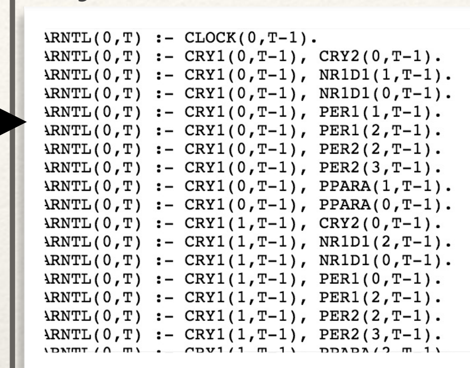
Inductive Learning [Ino2014]

Learning using ASP [Ben2017]



Interaction graph

Dynamical models



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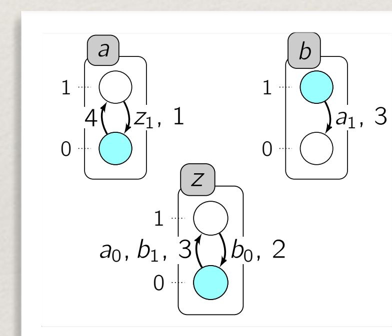
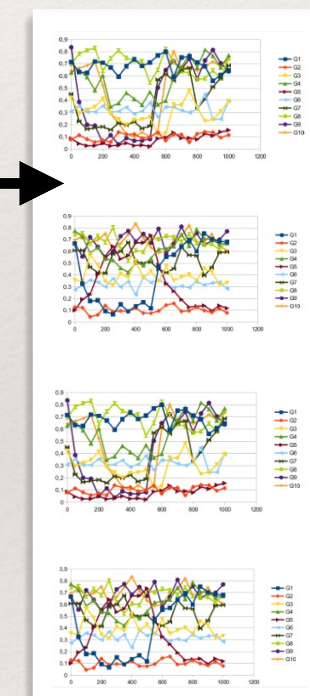
Logic programs



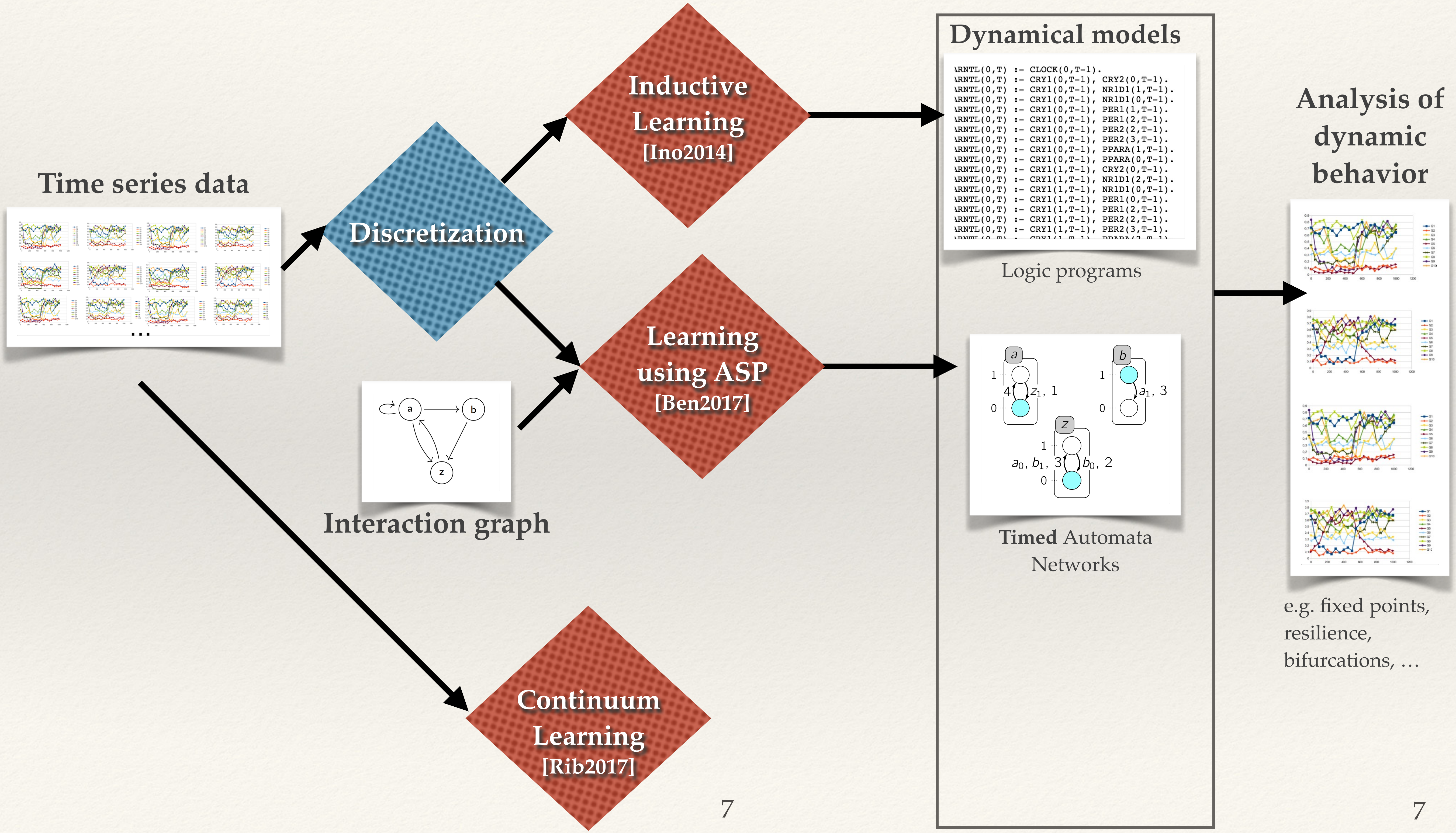
Timed Automata Networks

Analysis of dynamic behavior



e.g. fixed points, resilience, bifurcations, …

Our scientific challenge



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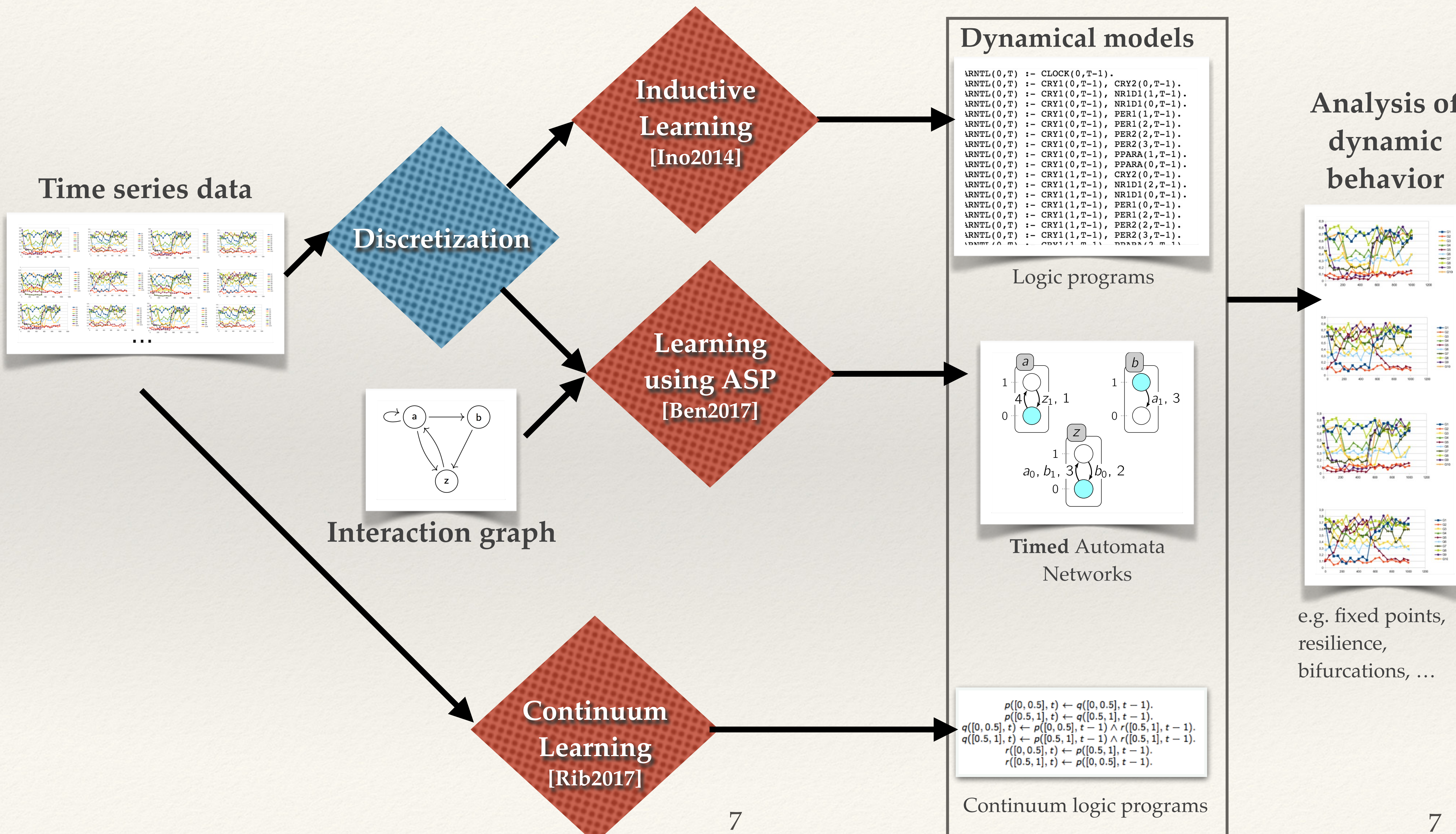

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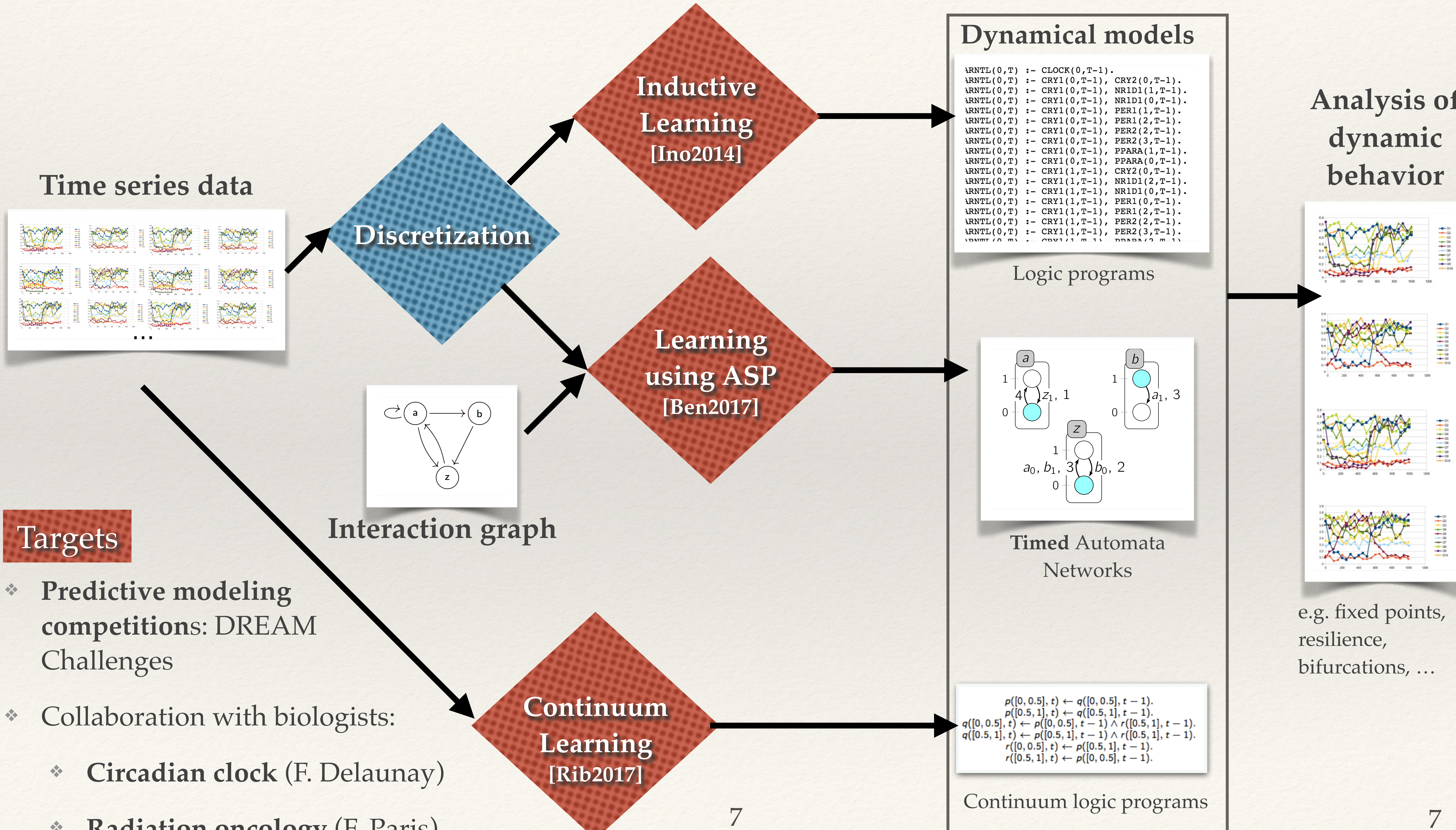

Targets

- **Predictive modeling competitions**: DREAM Challenges
- Collaboration with biologists:
  - **Circadian clock** (F. Delaunay)
  - **Radiation oncology** (F. Paris)

Overview

- Modeling frameworks for dynamical analysis
- Analysis of formal models
- Inference and Learning approaches
- Application to biological case studies

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- **Modeling frameworks for dynamical analysis**
- Analysis of formal models
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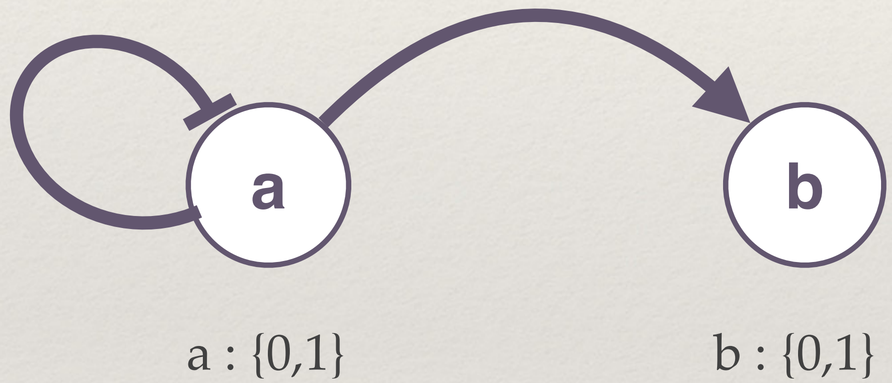
Principles of abstraction



Example of regulatory Boolean network

Abstract:

- Components
- Concentrations
- Interactions
- Time
- Order

Modeling the dynamics

$t_1\ t_2\ t_3\ t_1\ t_1\ t_5$ ...

Discrete event systems:

- Modeled through transition systems
- Capture the **chronology** (the order) of the events

Automata Networks (a.k.a. Process Hitting), **Boolean Networks / Thomas networks**, **Logic Programs**

$(t_1,d_1)\ (t_2,d_2)\ (t_3,d_3)\ (t_1,d_4)\ (t_1,d_5)\ (t_5,d_6)$ ...

Timed systems:

- Modeled through timed transition systems
- Capture the **chronometry** of the events (with their dates)

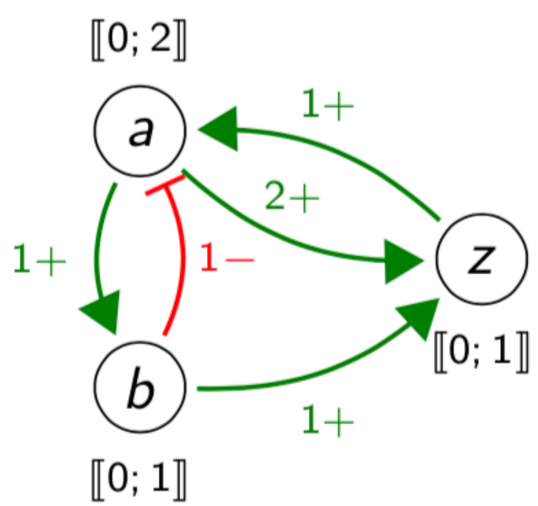
Timed Automata Networks

Different modeling frameworks

Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
[Thomas, *Journal of Theoretical Biology*, 1973]

- A set of components $N = \{a, b, z\}$
- A discrete domain for each component $\mathrm{dom}(a) = [\![0; 2]\!]$
- Discrete parameters / evolution functions $f^a : \mathcal{S} \to \mathrm{dom}(a)$
- Signs & thresholds on the edges (redundant) $a \xrightarrow{2+} z$



a	f^b
0	**0**
1	**1**
2	**1**

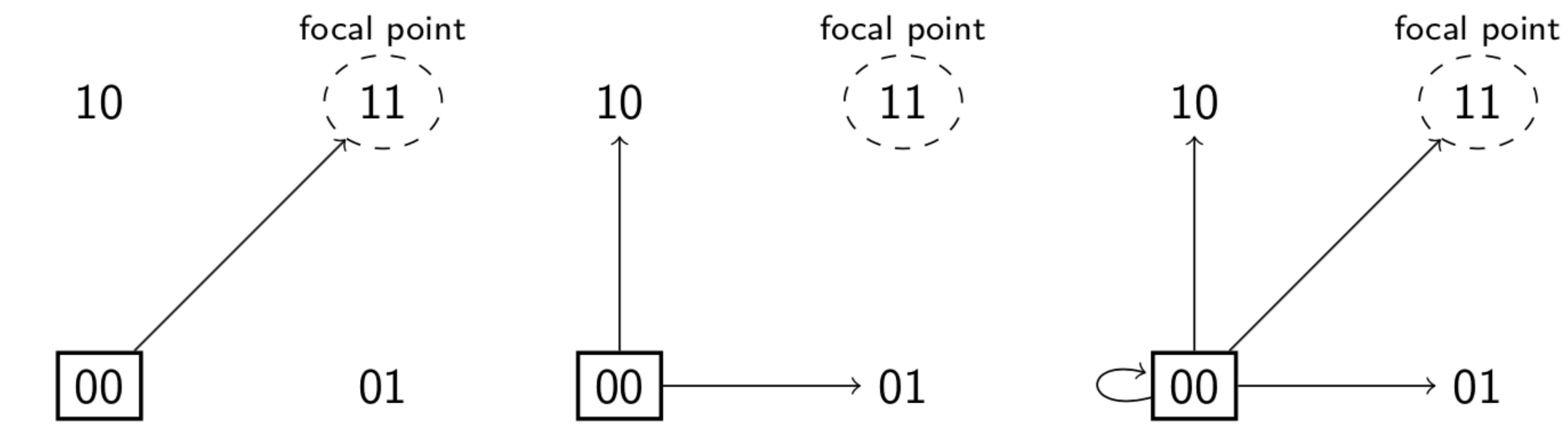
z	b	f^a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	f^z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

Semantics = From this information, what are the next possible state(s)?

Choice of an appropriate semantics

Semantics



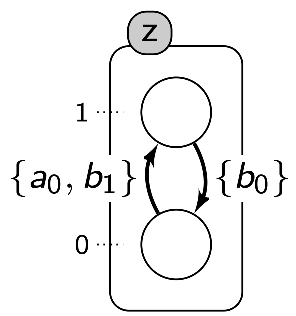
Synchronous **Asynchronous** **Generalized**

Other semantics:

- Round-robin
- With memory
- With priorities
- ...

Different modeling frameworks

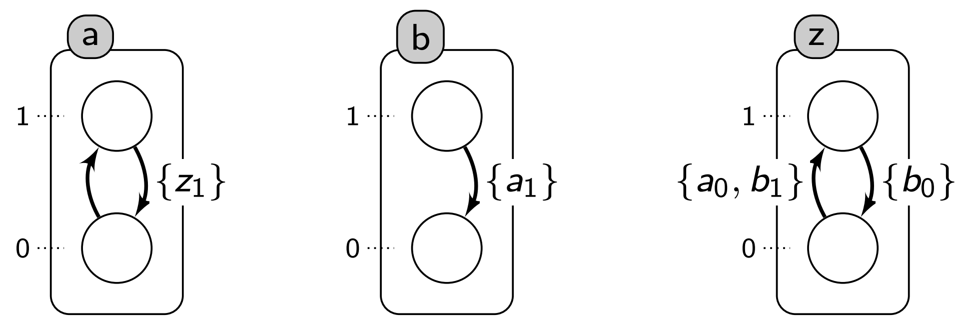
Automata Networks



Automata: components a, b, z

Different modeling frameworks

Automata Networks

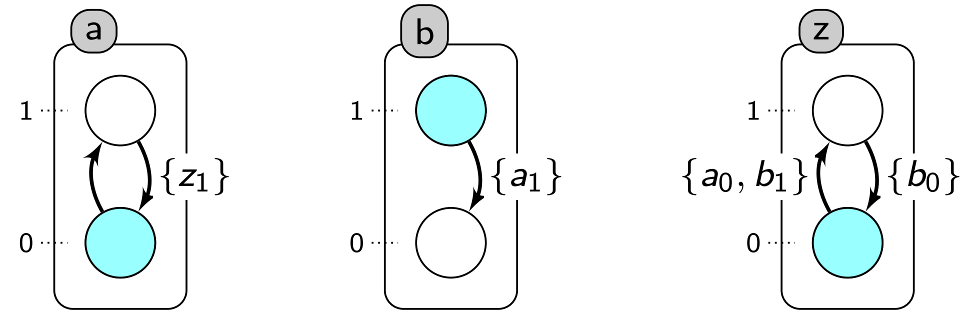


Automata: components a, b, z

Local states: levels of expression $\{a_0, a_1\}$ $\{b_0, b_1\}$ $\{z_0, z_1\}$

Different modeling frameworks

Automata Networks



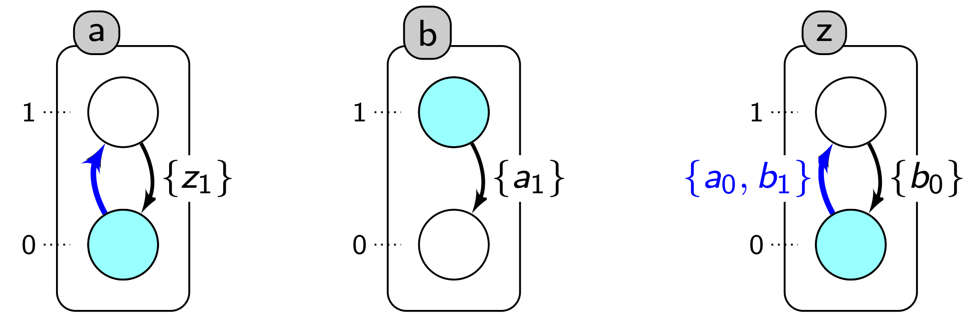
Automata: components $a,\ b,\ z$

Local states: levels of expression $\{a_0,\ a_1\}$ $\{b_0,\ b_1\}$ $\{z_0,\ z_1\}$

State: set of active local states $\langle a_0, b_1, z_0 \rangle \sim$ 010

Different modeling frameworks

Automata Networks



Automata: components $a, \ b, \ z$

Local states: levels of expression $\{a_0, \ a_1\}$ $\{b_0, \ b_1\}$ $\{z_0, \ z_1\}$

State: set of active local states $\langle a_0, b_1, z_0 \rangle \sim$ 010

Local transitions:

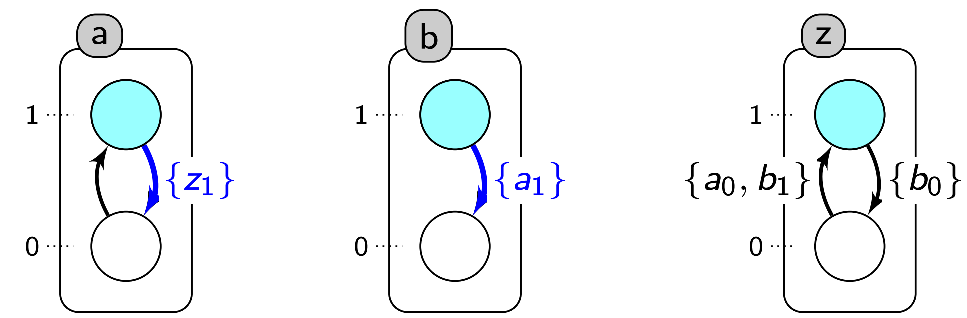
$\tau_1 = a_0 \longrightarrow a_1; \ \tau_3 = a_1 \xrightarrow{\{z_1\}} a_0; \ \tau_4 = b_1 \xrightarrow{\{a_1\}} b_0; \ \tau_2 = z_0 \xrightarrow{\{a_0, b_1\}} z_1; \ \tau_5 = z_1 \xrightarrow{\{b_0\}} z_0;$

Synchronous : [Kauffman, 1969]

010

Different modeling frameworks

Automata Networks



Automata: components a, b, z

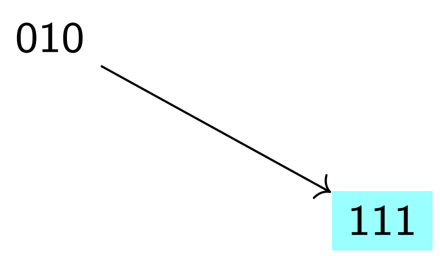
Local states: levels of expression $\{a_0, a_1\}$ $\{b_0, b_1\}$ $\{z_0, z_1\}$

State: set of active local states $\langle a_1, b_1, z_1 \rangle \sim$ 111

Local transitions:

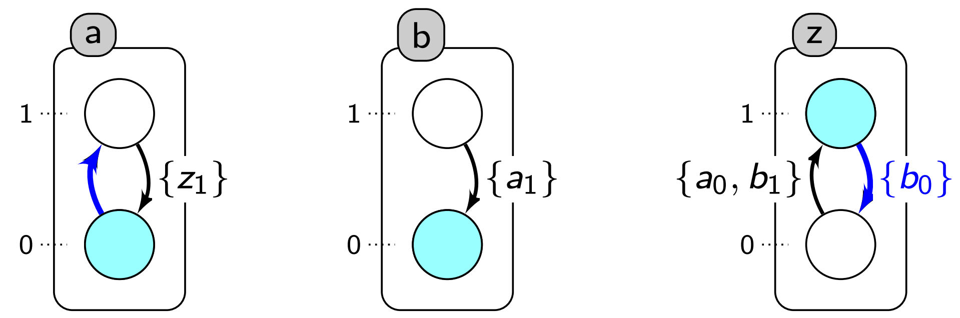
$\tau_1 = a_0 \longrightarrow a_1$; $\tau_3 = a_1 \xrightarrow{\{z_1\}} a_0$; $\tau_4 = b_1 \xrightarrow{\{a_1\}} b_0$; $\tau_2 = z_0 \xrightarrow{\{a_0, b_1\}} z_1$; $\tau_5 = z_1 \xrightarrow{\{b_0\}} z_0$;

Synchronous : [Kauffman, 1969]



Different modeling frameworks

Automata Networks



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Local states: levels of expression $\{a_0, a_1\}$ $\{b_0, b_1\}$ $\{z_0, z_1\}$

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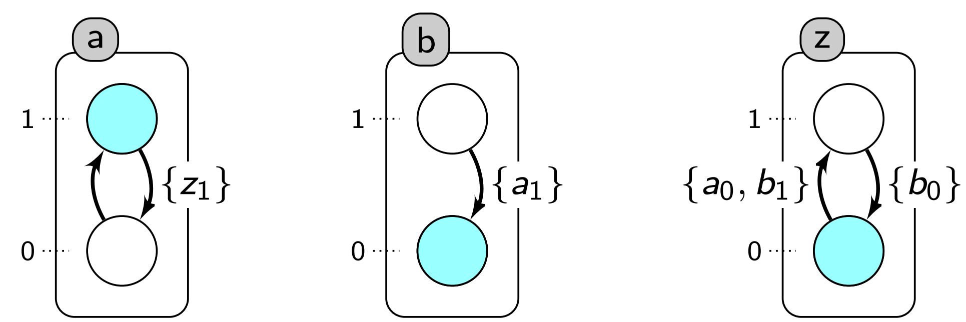
010 $\longrightarrow$ 111 $\longrightarrow$ 001

Different modeling frameworks

Automata Networks



Automata: components $a,\ b,\ z$

Local states: levels of expression $\{a_0,\ a_1\}$ $\{b_0,\ b_1\}$ $\{z_0,\ z_1\}$

State: set of active local states $\langle a_1, b_0, z_0 \rangle \sim$ 100

Local transitions:

$\tau_1 = a_0 \longrightarrow a_1$; $\tau_3 = a_1 \xrightarrow{\{z_1\}} a_0$; $\tau_4 = b_1 \xrightarrow{\{a_1\}} b_0$; $\tau_2 = z_0 \xrightarrow{\{a_0, b_1\}} z_1$; $\tau_5 = z_1 \xrightarrow{\{b_0\}} z_0$;

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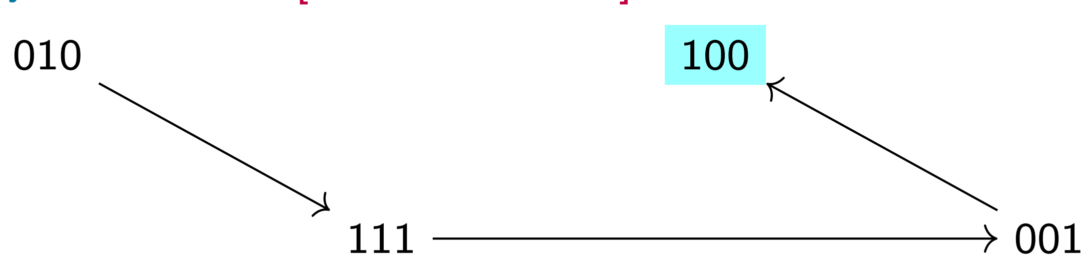
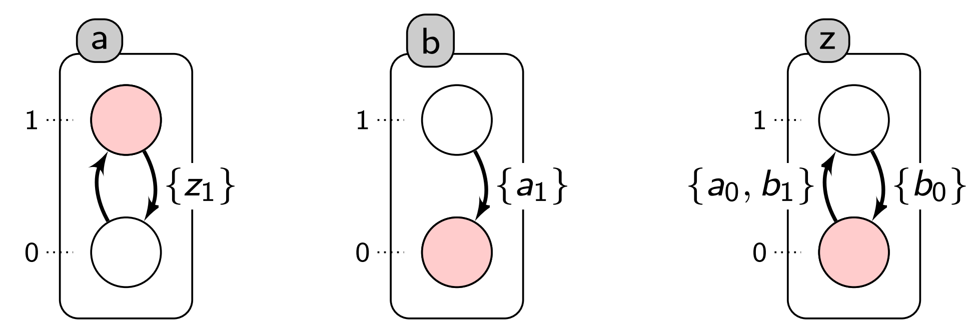


Different modeling frameworks

Automata Networks



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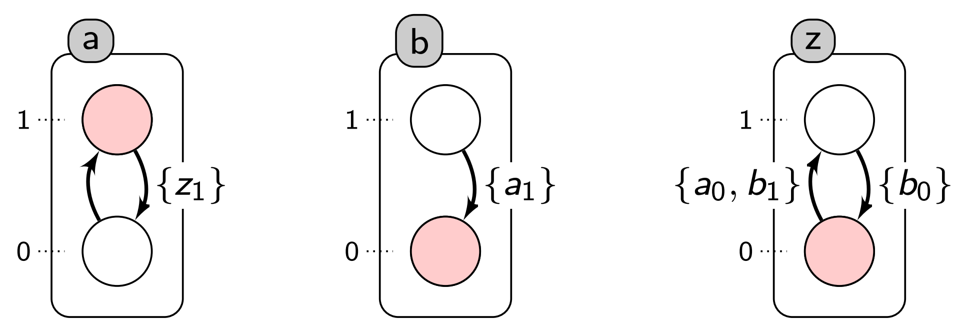
Different modeling frameworks

Automata Networks



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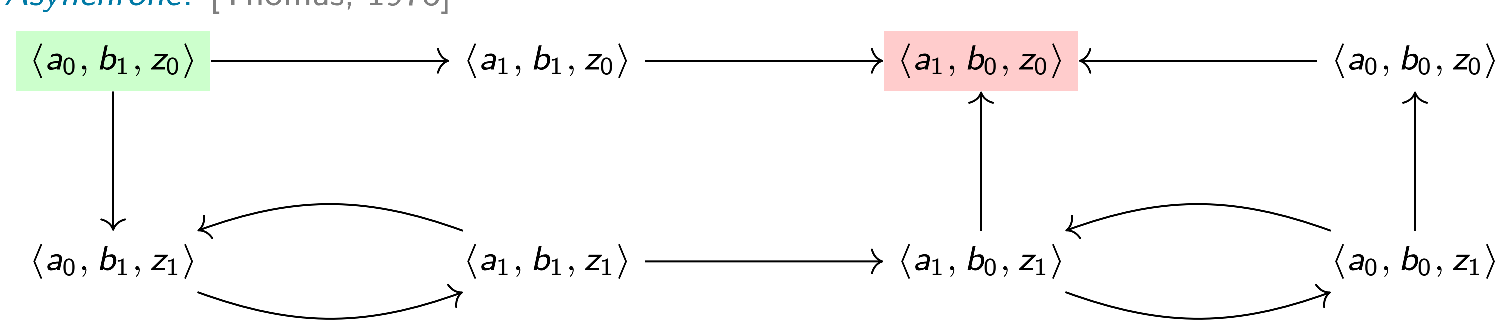
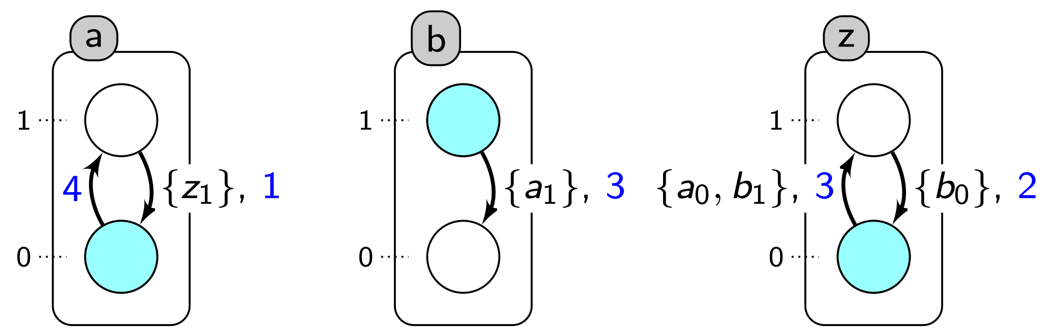
Asynchrone: [Thomas, 1978]



Different modeling frameworks

Timed Automata Networks

Definition



Refinement of th AN dynamics by delays integration : $\delta \in \mathbb{N}$

each delay δ is specific of a local transition τ

and δ represents the necessary time duration of the local transition τ to occur.

Example:

$b_1 \xrightarrow[3]{\{a_1\}} b_0$: 3 represents the time it takes for changing b from the local level 1 to 0.

$\Rightarrow$ How to calculate the states graph of the refined dynamics of a T-AN ?

$\Rightarrow$ What would be the semantics of the dynamics of a T-AN that shows this refinement?

Logic programs

$$\underbrace{x_0^{val_0}(t)}_{head} \leftarrow \underbrace{x_1^{val_1}(t-1) \land x_2^{val_2}(t-1) \land \ldots \land x_n^{val_n}(t-1)}_{body}.$$

Where:

$x_0, x_1, x_2, \ldots, x_n$: Variables

$val_0, val_1, val_2, \ldots, val_n$: Values

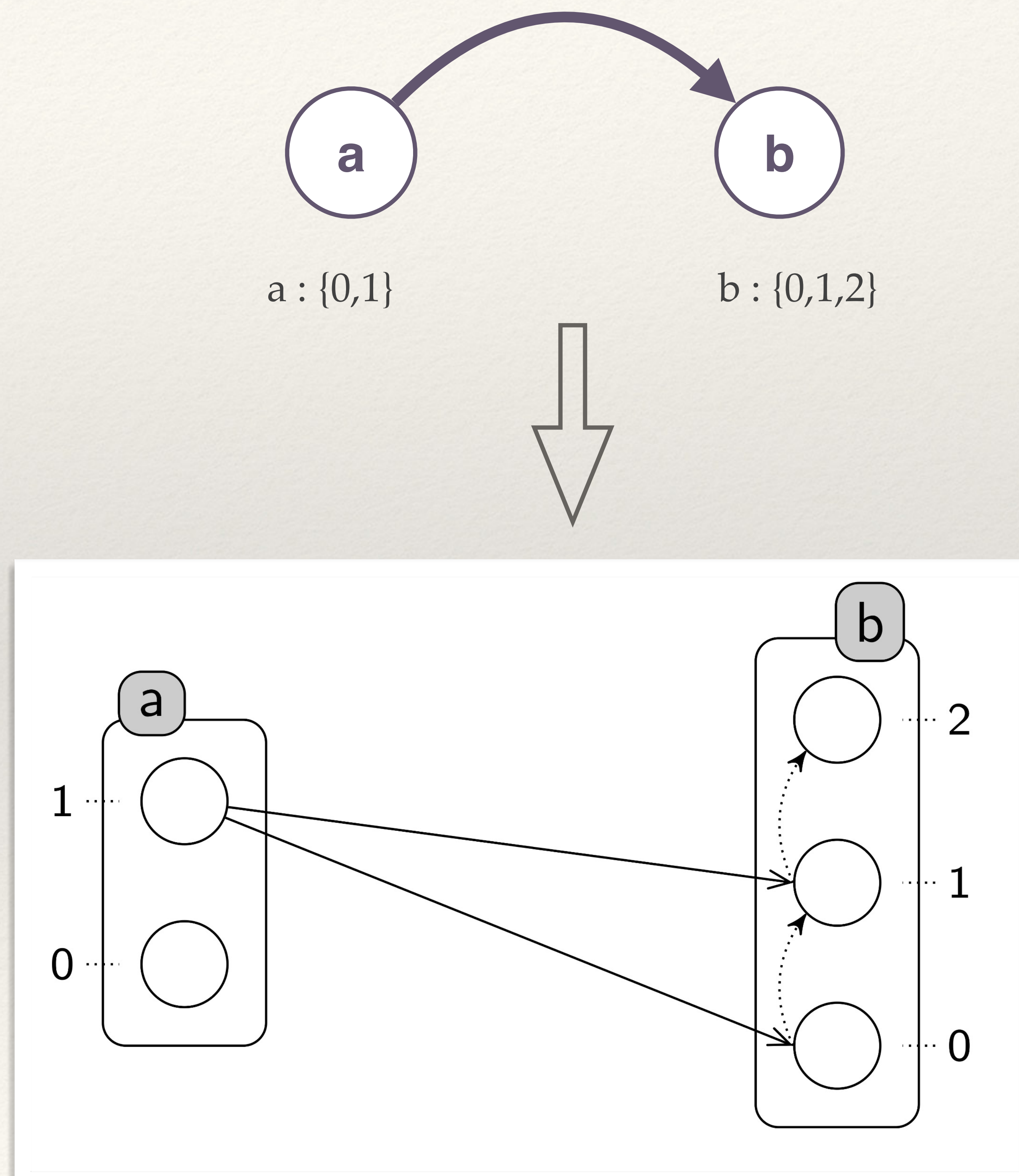
t: Time step

$\leftarrow$ Reverse implication

All atoms in the body are in conjunction

Hypotheses for translation from biology

- Discretization of the **concentration (expression)** of a component: Boolean or multi-valued
- Discretization of **time**: event-bases
- **Unitarian** dynamics
- Semantics: **non-deterministic asynchronous**



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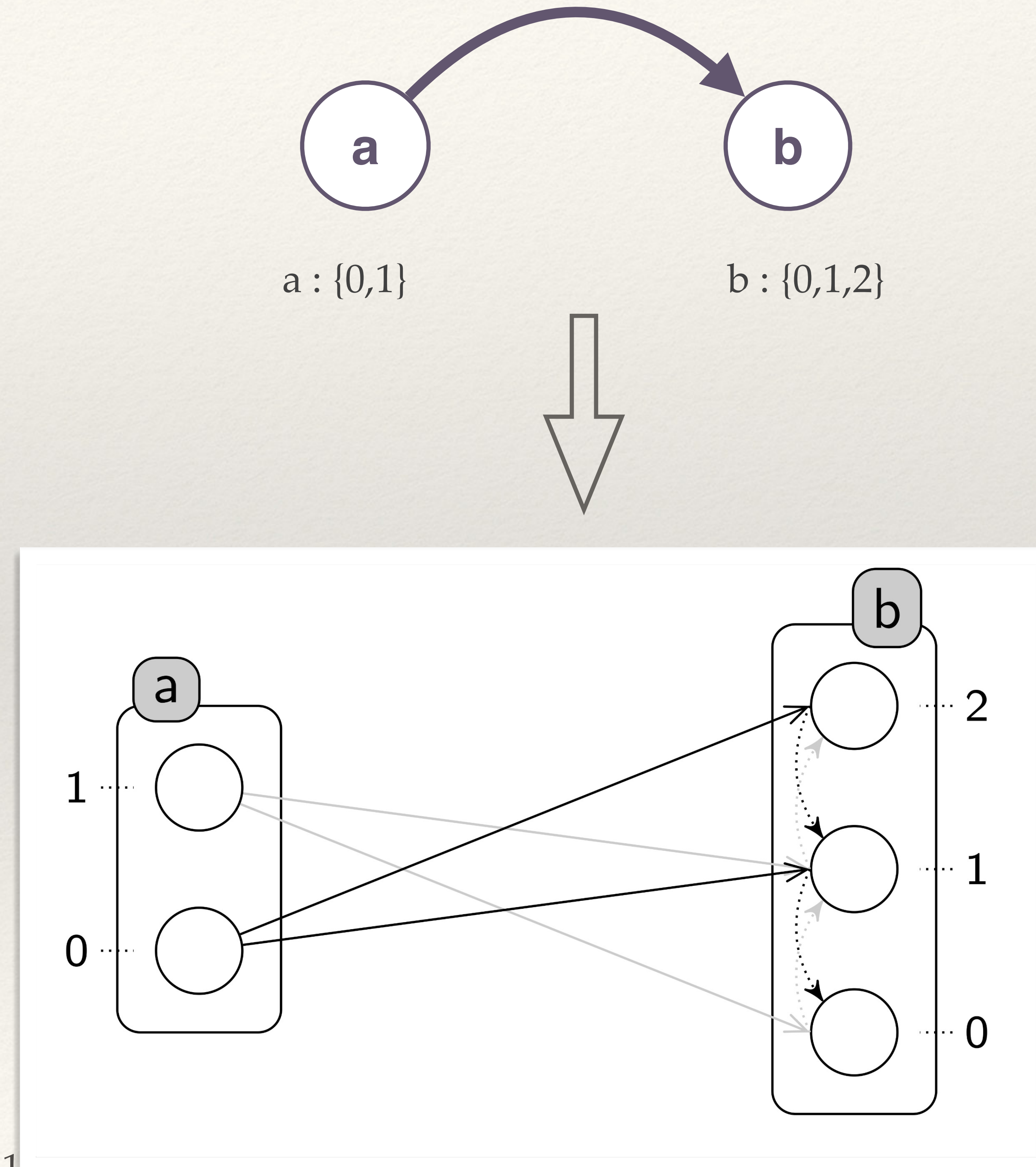

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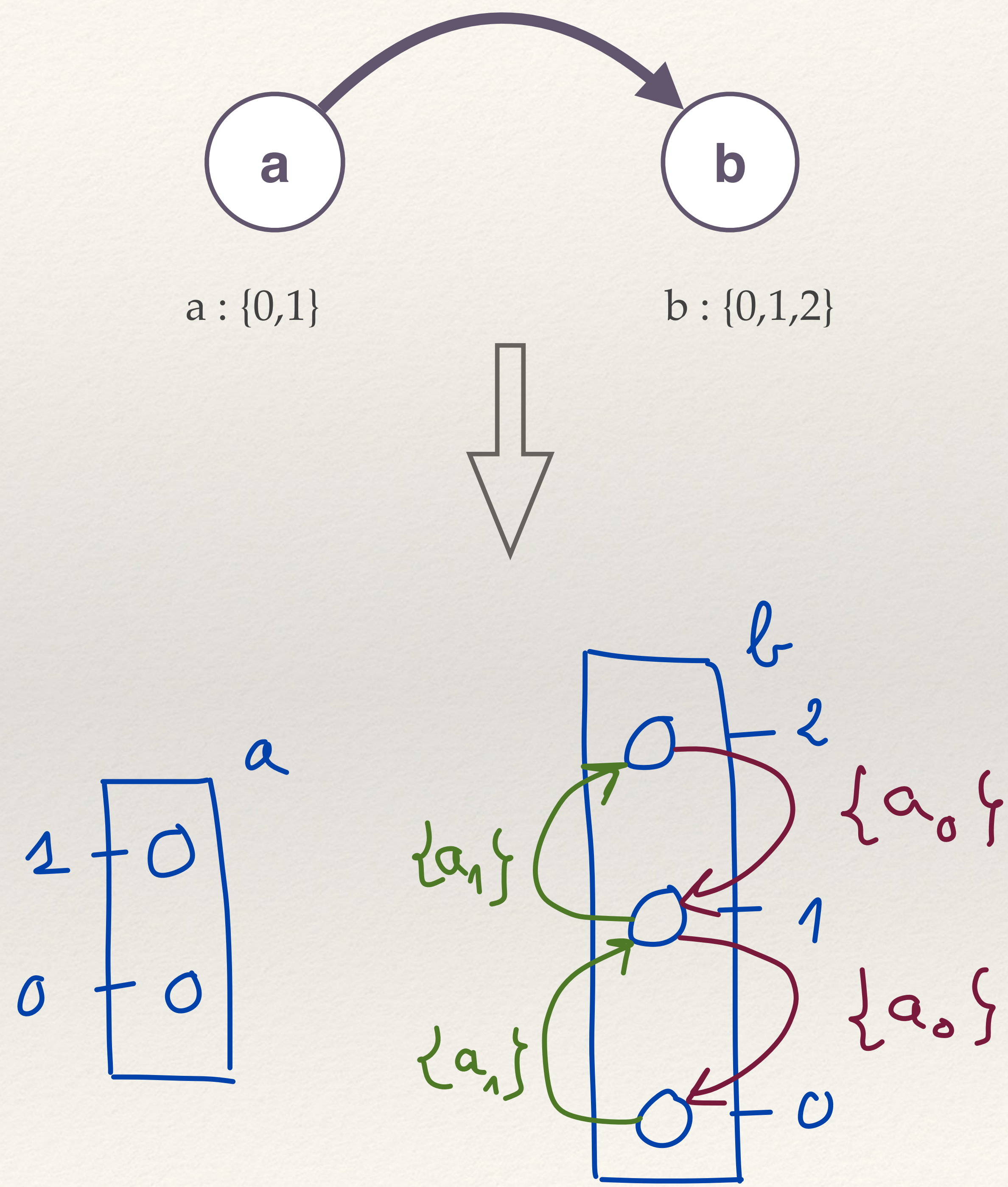
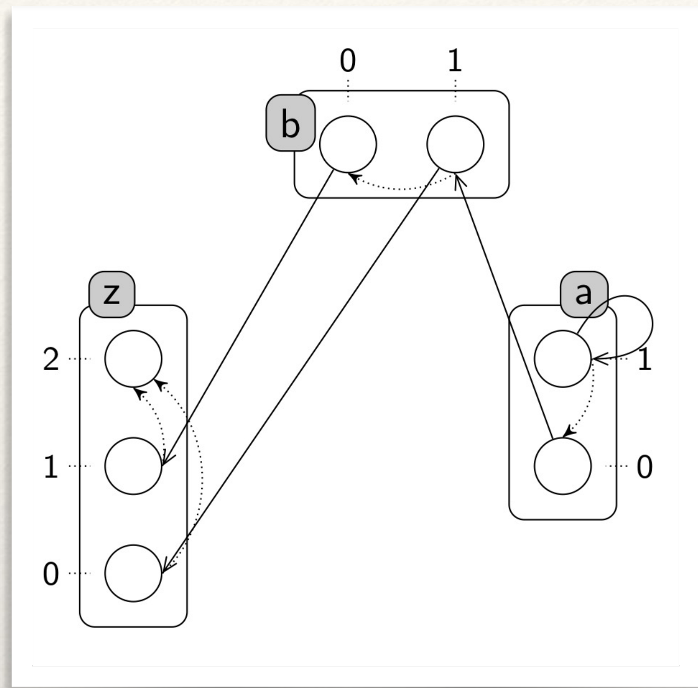


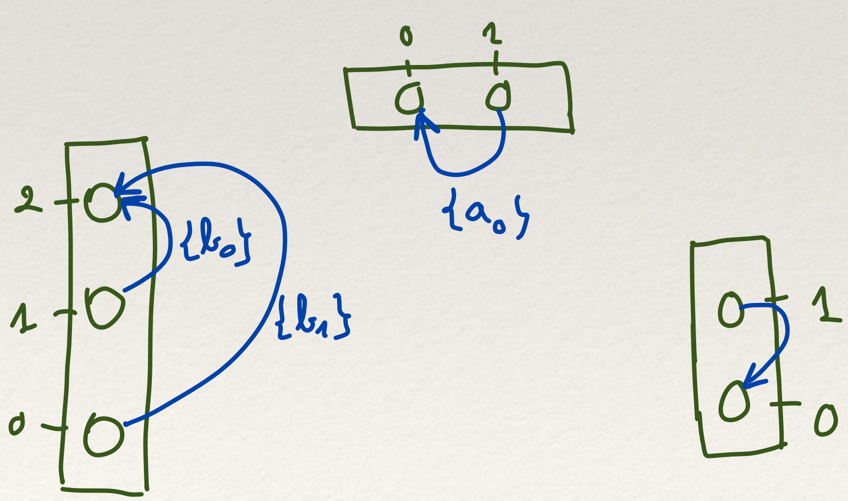
Overview

- Modeling frameworks for dynamical analysis
- **Analysis of formal models**
- Inference and Learning approaches
- Application to biological case studies

An example of static analysis [PMR11a,PCF+14]

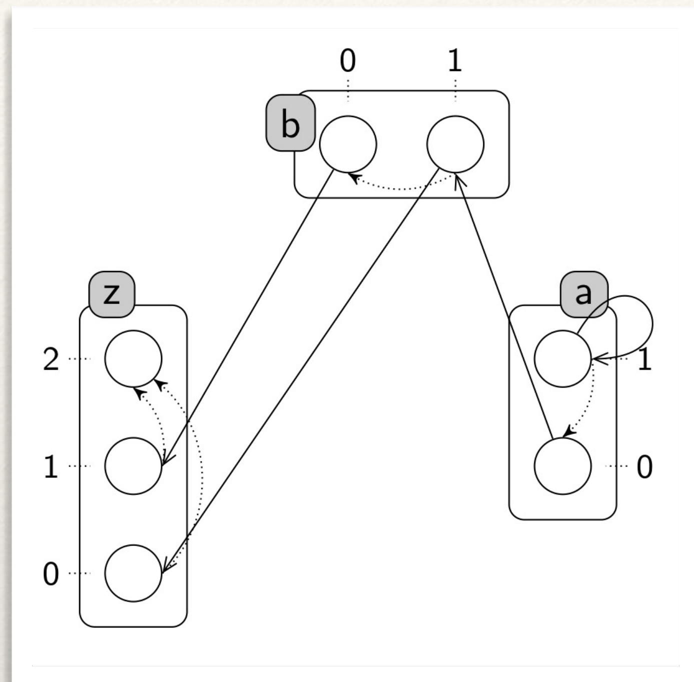


Process Hitting framework



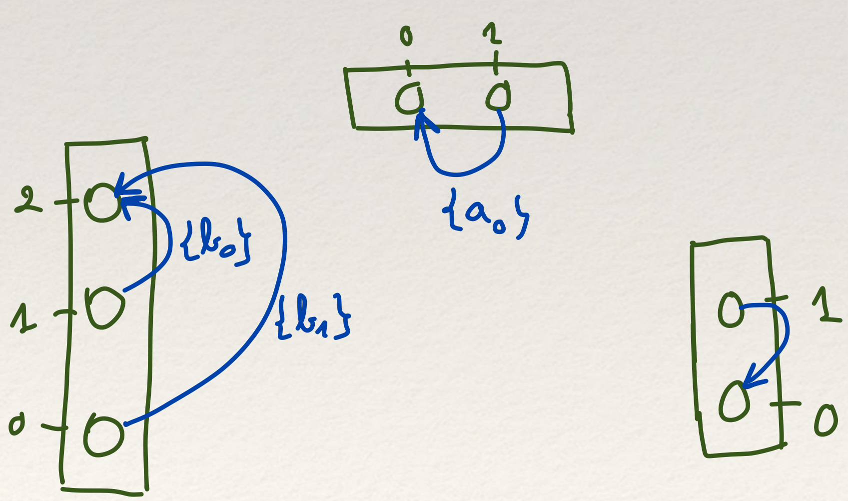
Asynchronous automata network

An example of static analysis [PMR11a,PCF+14]



Process Hitting framework

What are the **fixed points?**



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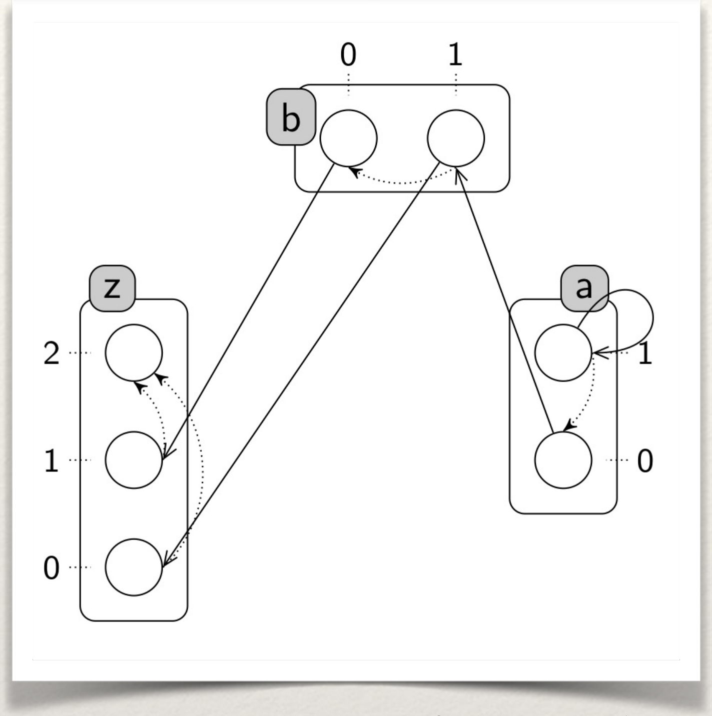

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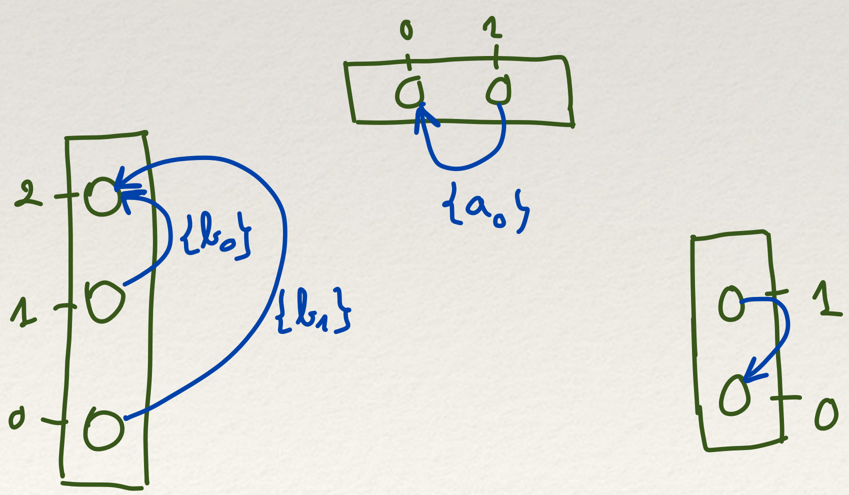
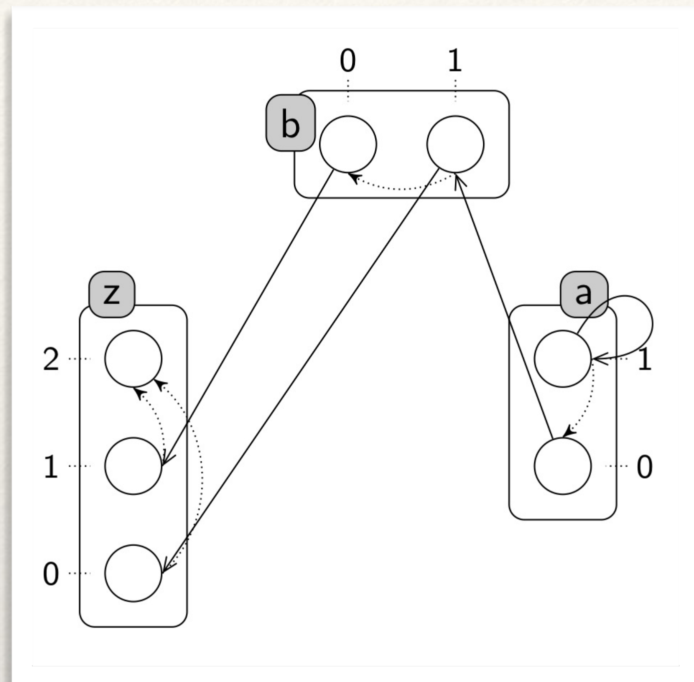


Asynchronous automata network

What are the **fixed points?**

- Naive method: compute all possible scenarios

An example of static analysis [PMR11a,PCF+14]



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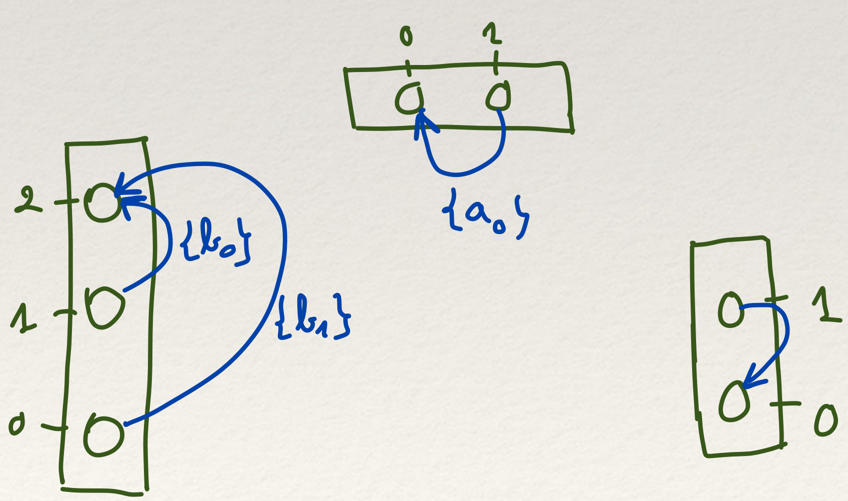


Asynchronous automata network

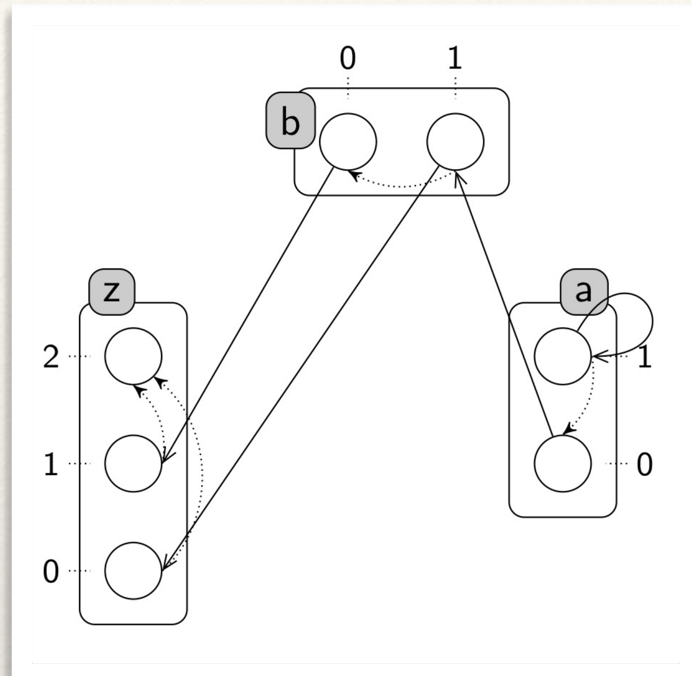
What are the **fixed points?**

- Our proposition: static analysis

An example of static analysis
[PMR11a,PCF+14]

What are the **fixed points?**

- Our proposition: static analysis
  - Compute hitless graph



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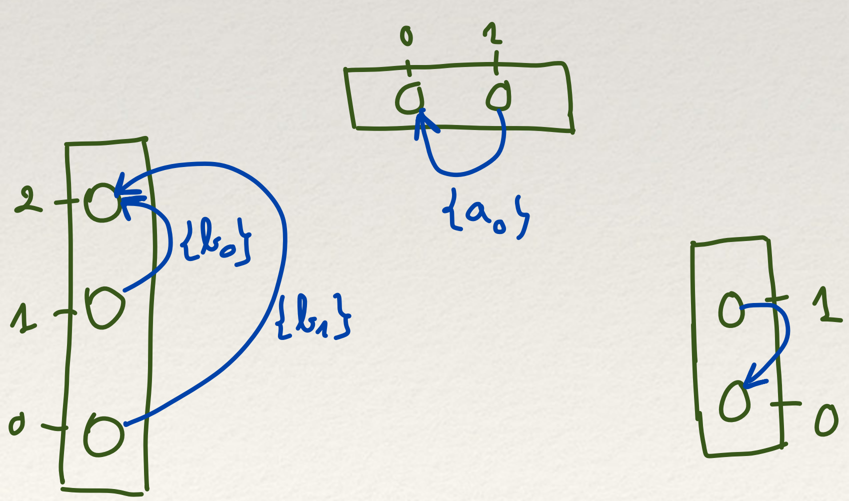

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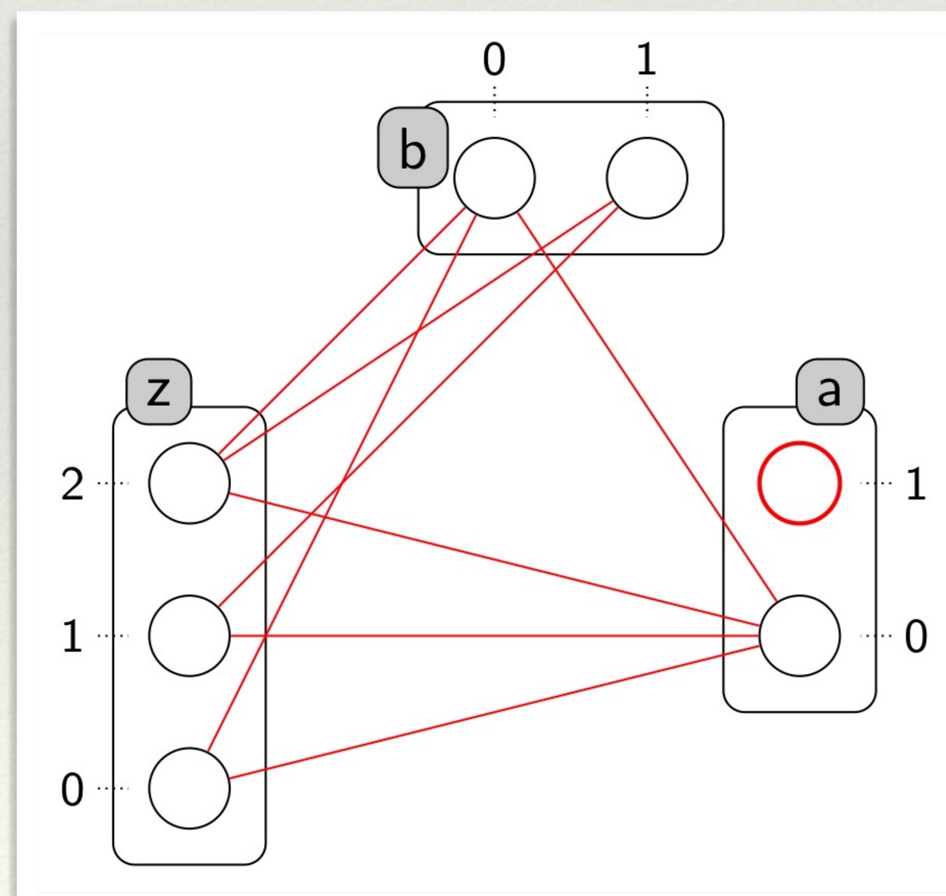
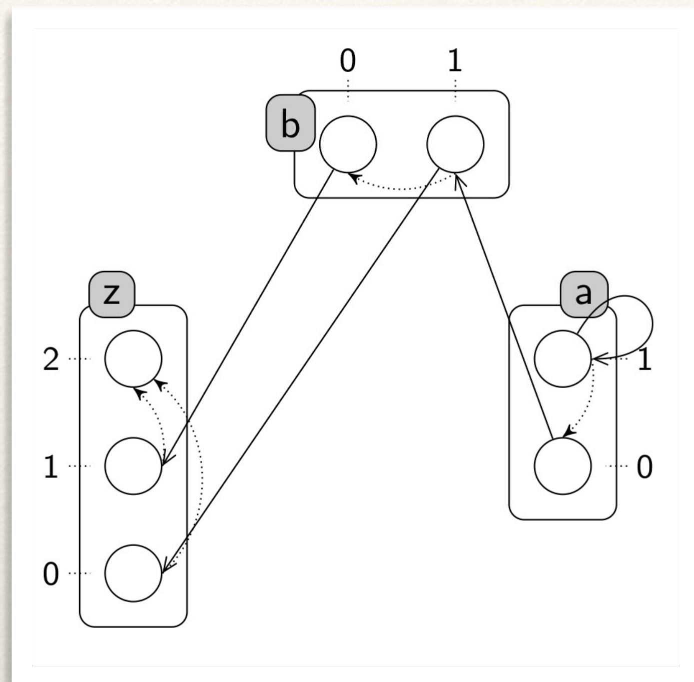


Hitless graph

An example of static analysis
[PMR11a,PCF+14]



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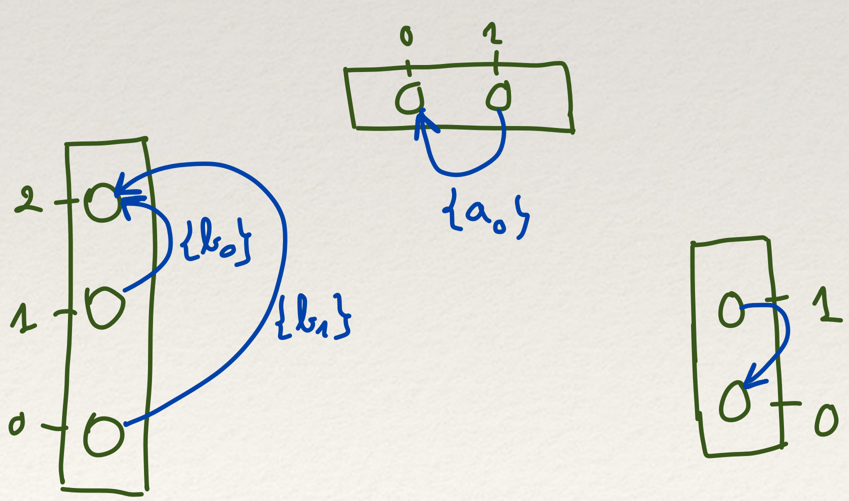
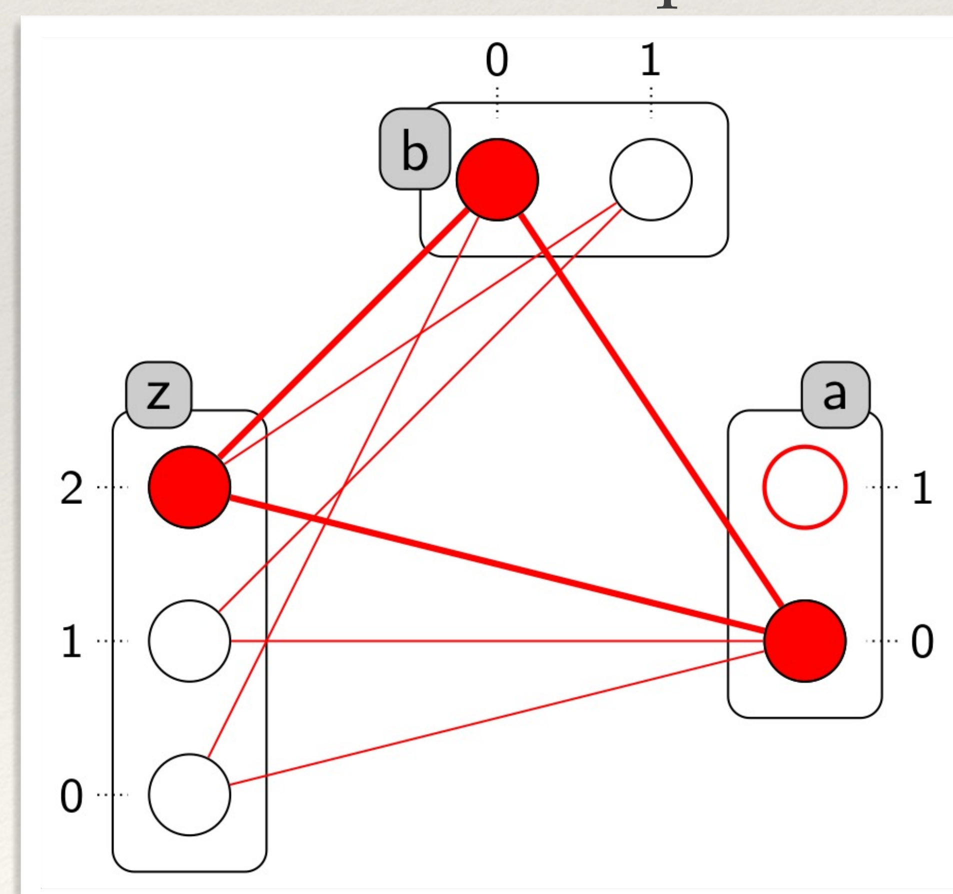


Asynchronous automata network

What are the **fixed points?**

- Our proposition: static analysis
  - Compute hitless graph
  - Enumerate its n-cliques



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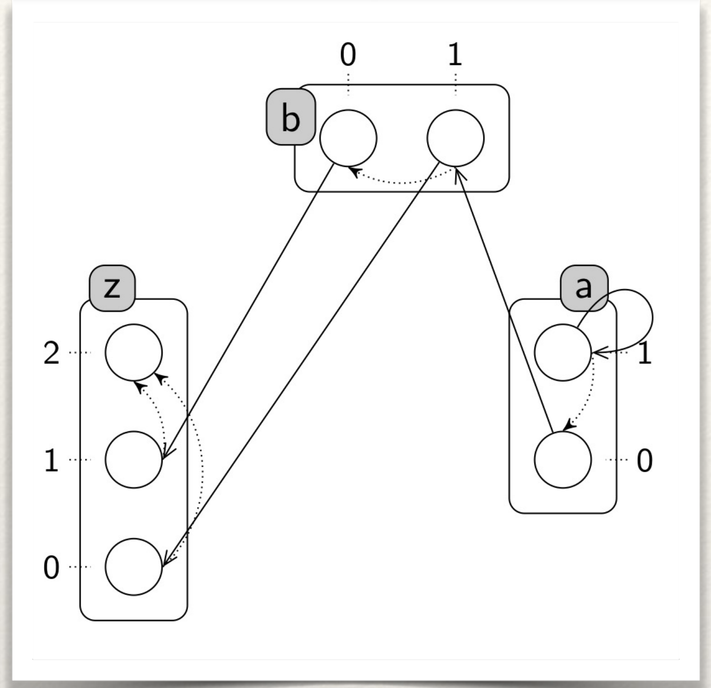

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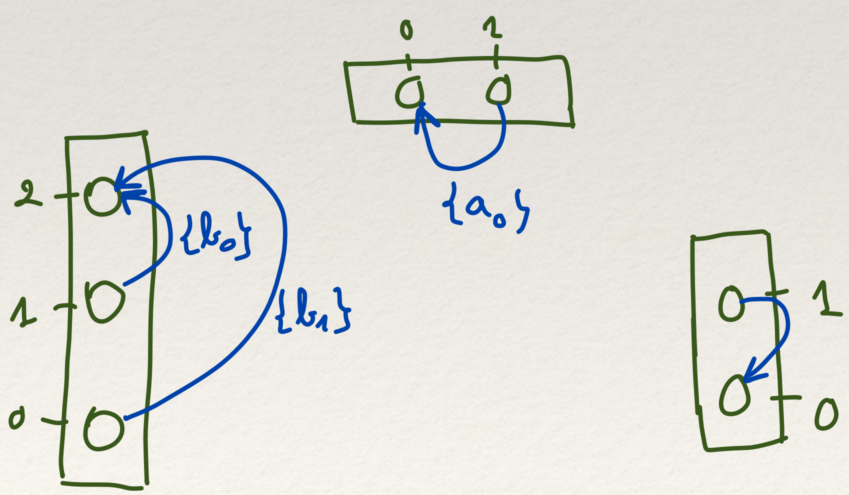

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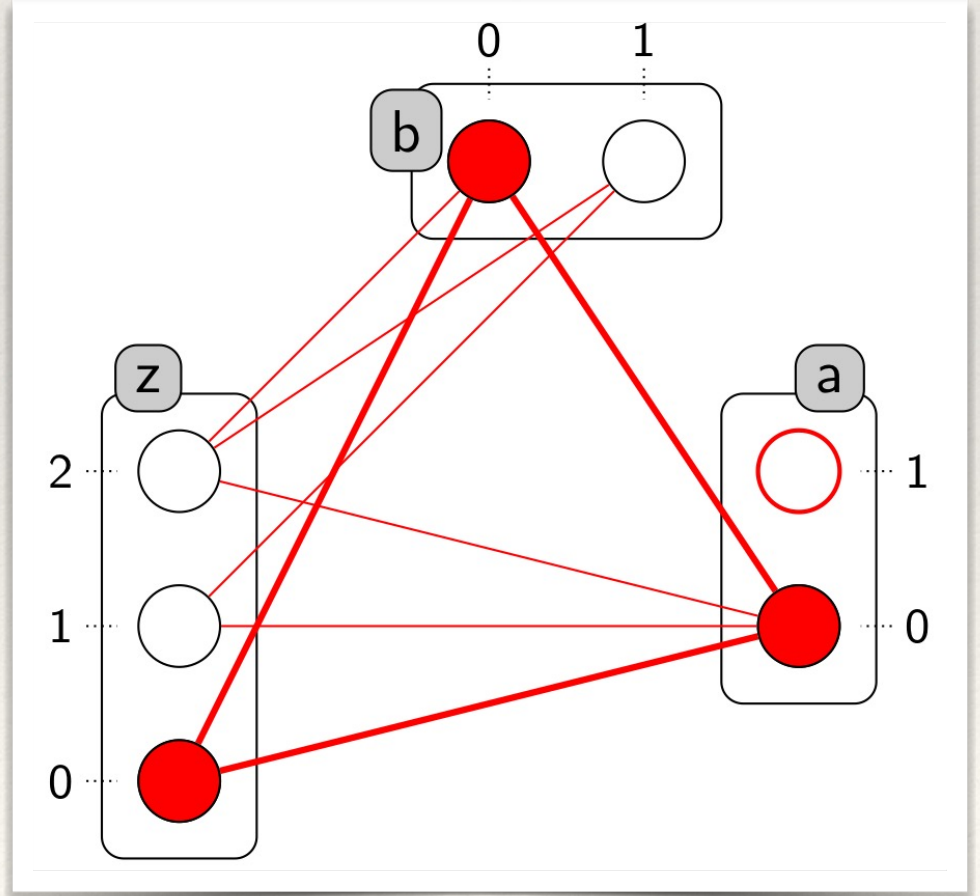
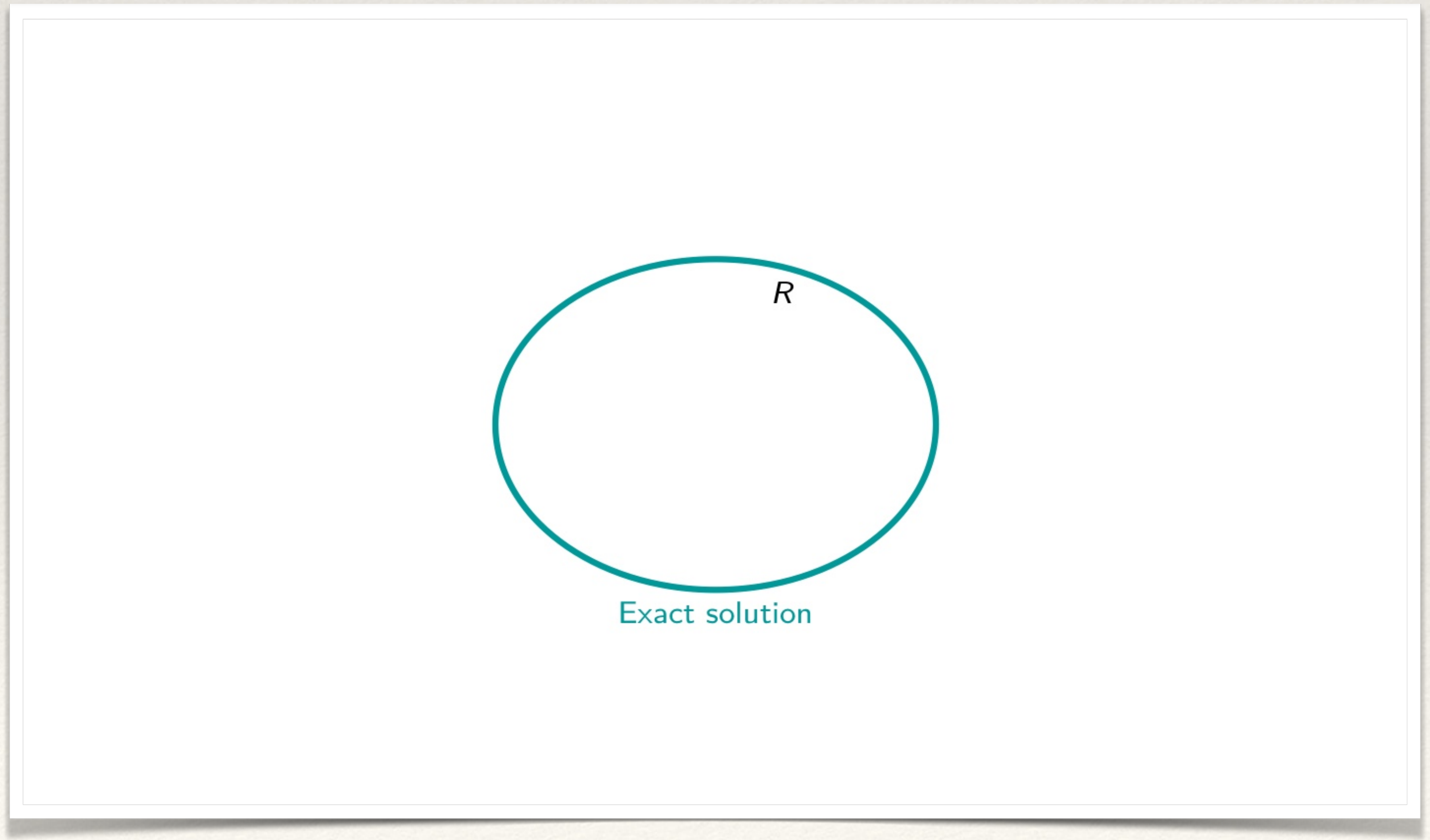


Hitless graph

Reachability analysis [PMR12]

Goal: check properties of the following type
« From an initial state s_0, can we reach a state s_n where a_i is active?»

Our proposition: **under-approximation** P and **over-approximation** Q of the dynamics s.t. $P \Rightarrow R \Rightarrow Q$



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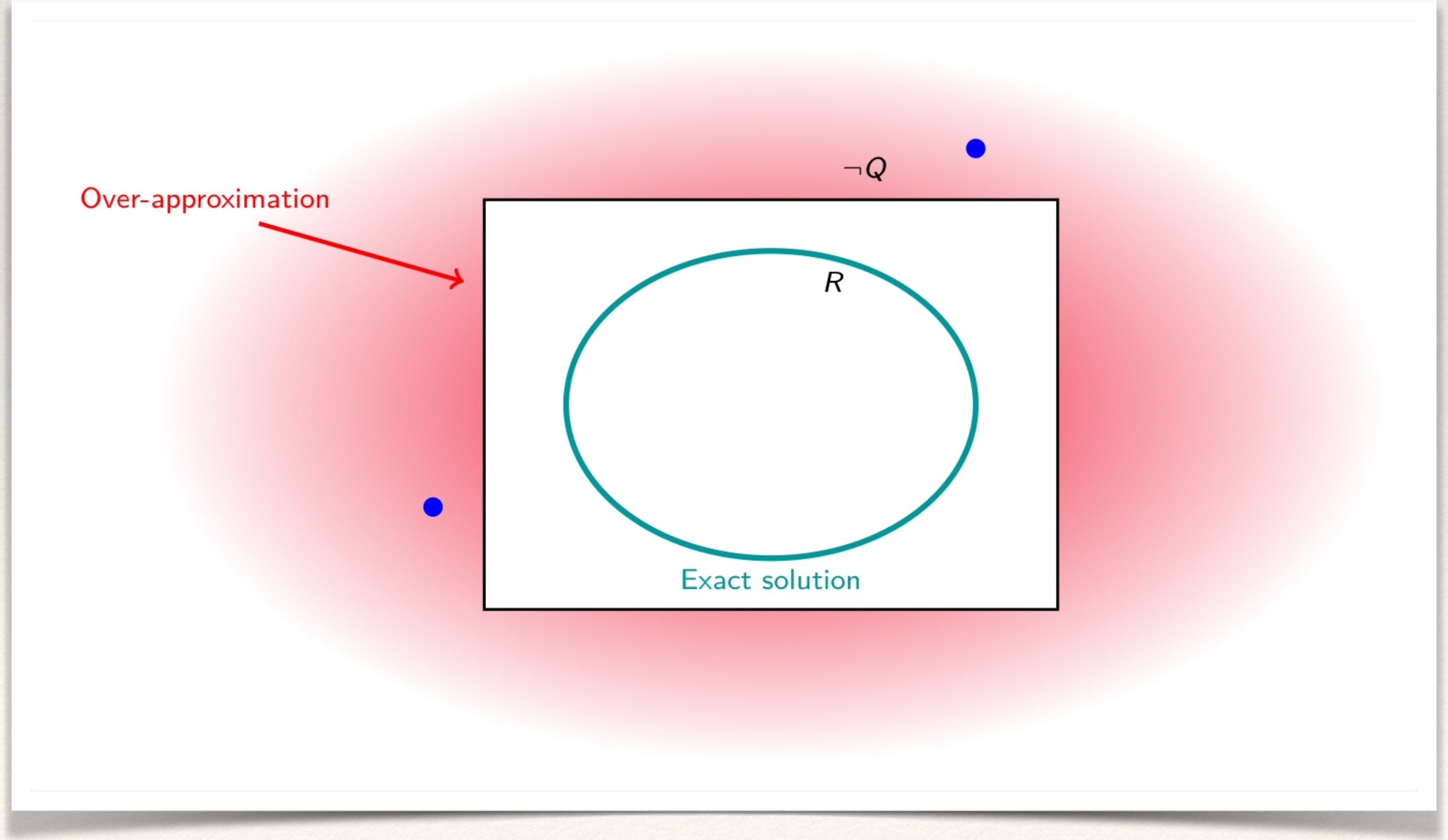

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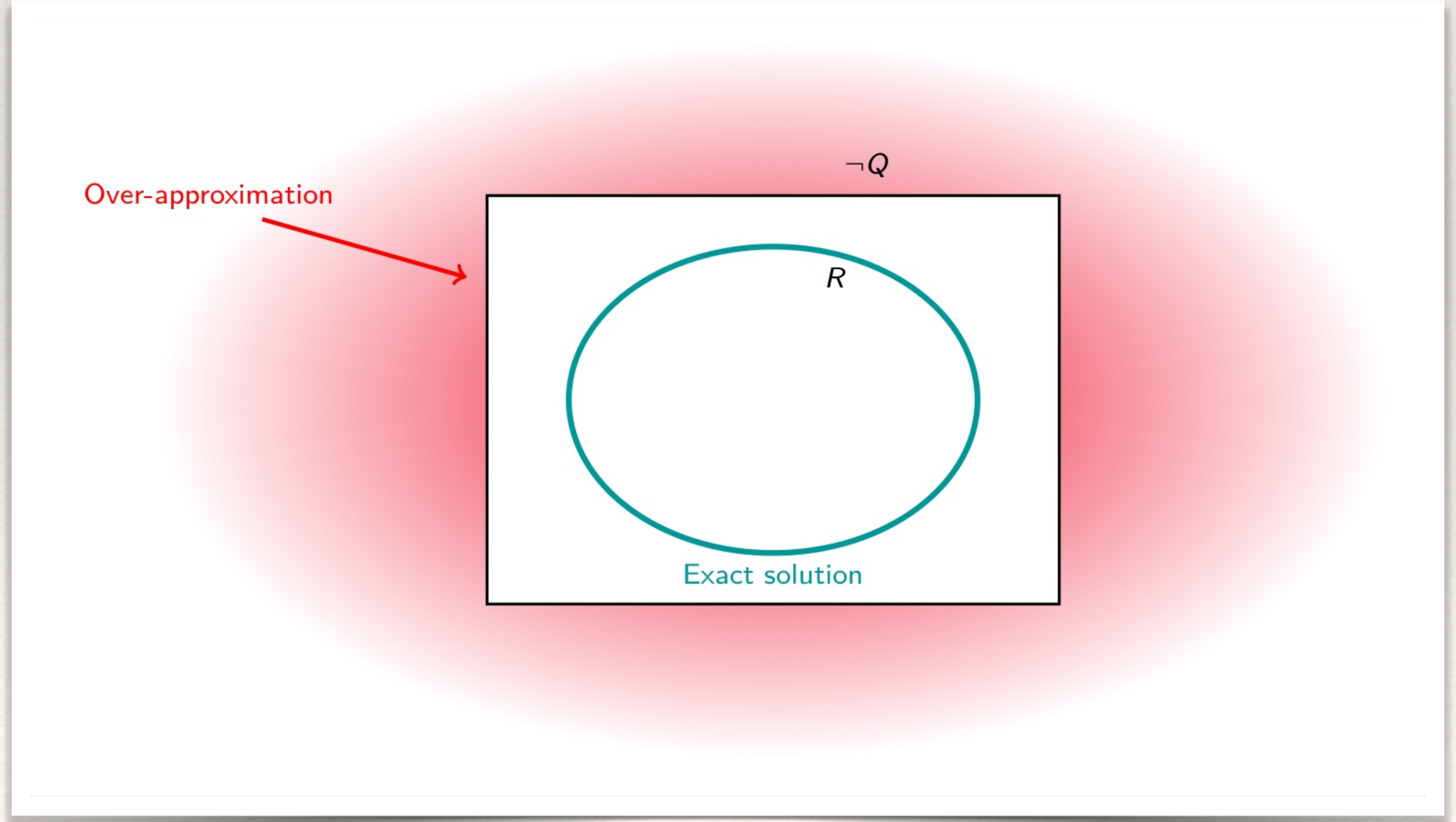

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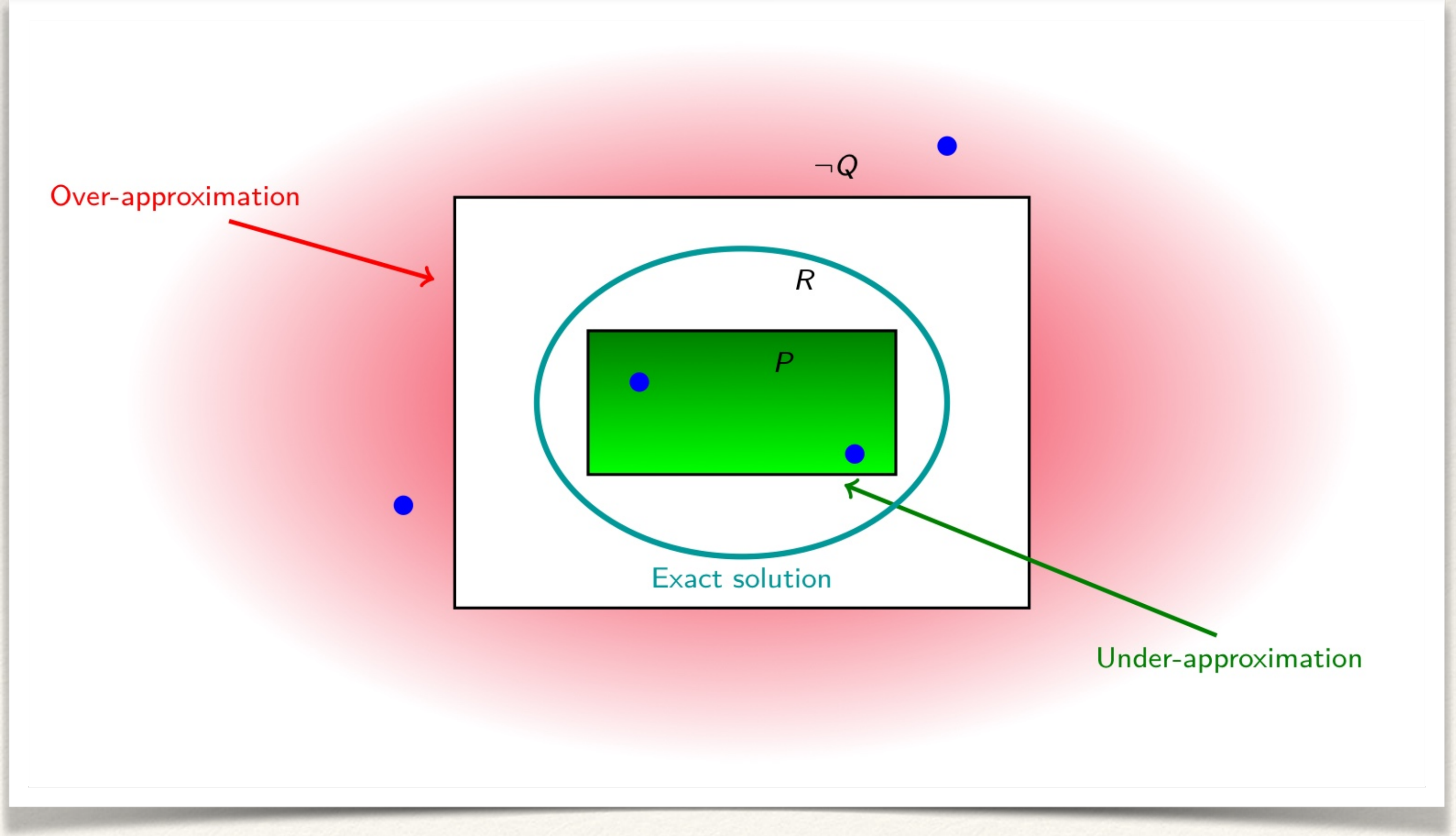

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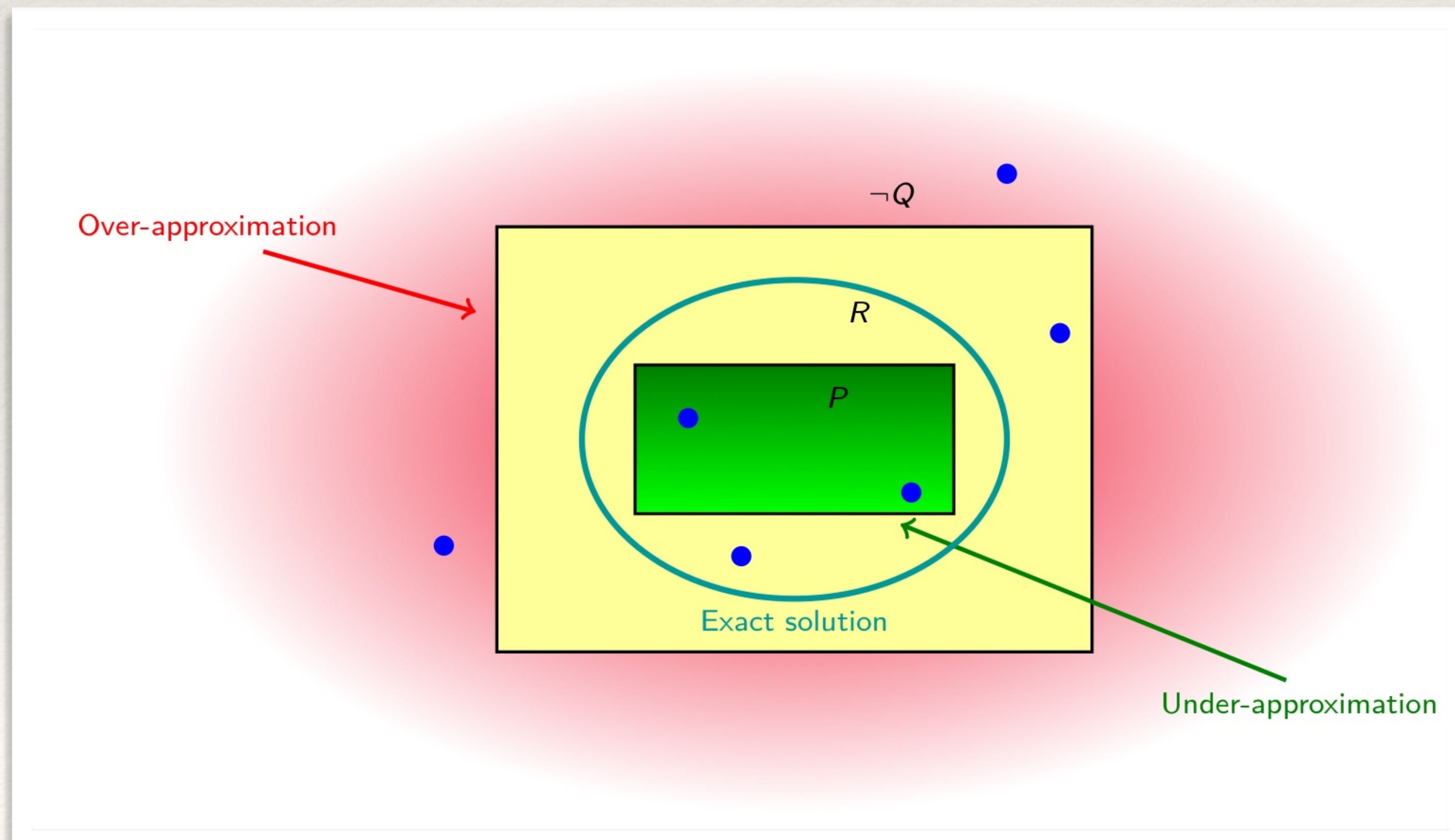

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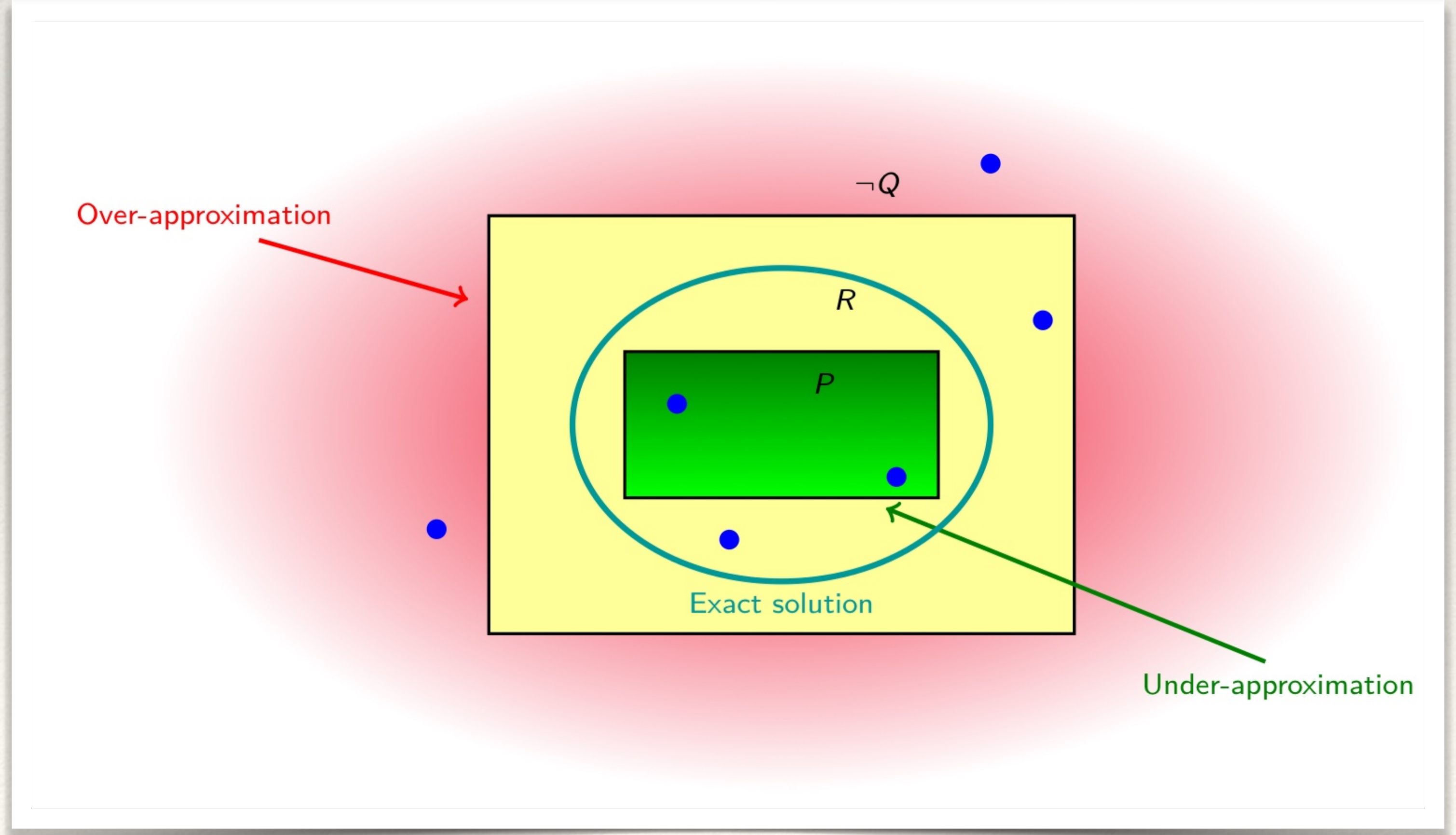


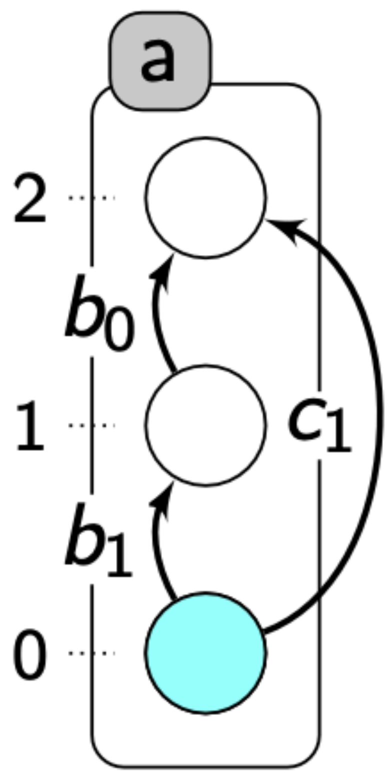
Polynomial in the number of automata

Exponential in the number of local states of each automaton (usually very low, max. 4)

Reachability analysis [PMR12]

- Idea: resolve the reachability of a local state of automata

Example : reachability from a_0 to a_2 : (objective $a_0 \leadsto a_2$)



- 2 local solutions :
  - $a_0 \xrightarrow{c_1} a_2$ (c_1 required)
  - $a_0 \xrightarrow{b_1} a_1$; $a_1 \xrightarrow{b_0} a_2$ (b_0 and b_1 required)

Reachability analysis [PMR12]

- Idea: resolve the reachability of a local state of automata
- **Over-approximation**: **abstraction of the order** in which the required processes are necessary
- **Under-approximation**: all required processes must be activated in all possible orders

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- Idea: resolve the reachability of a local state of automata
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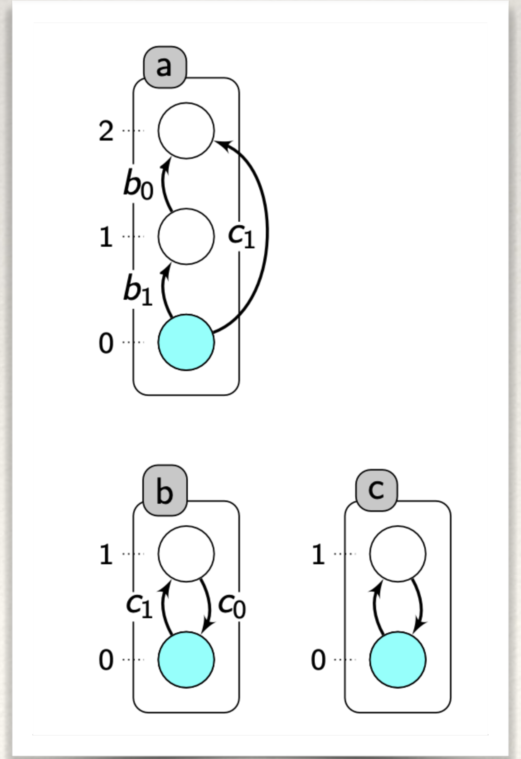
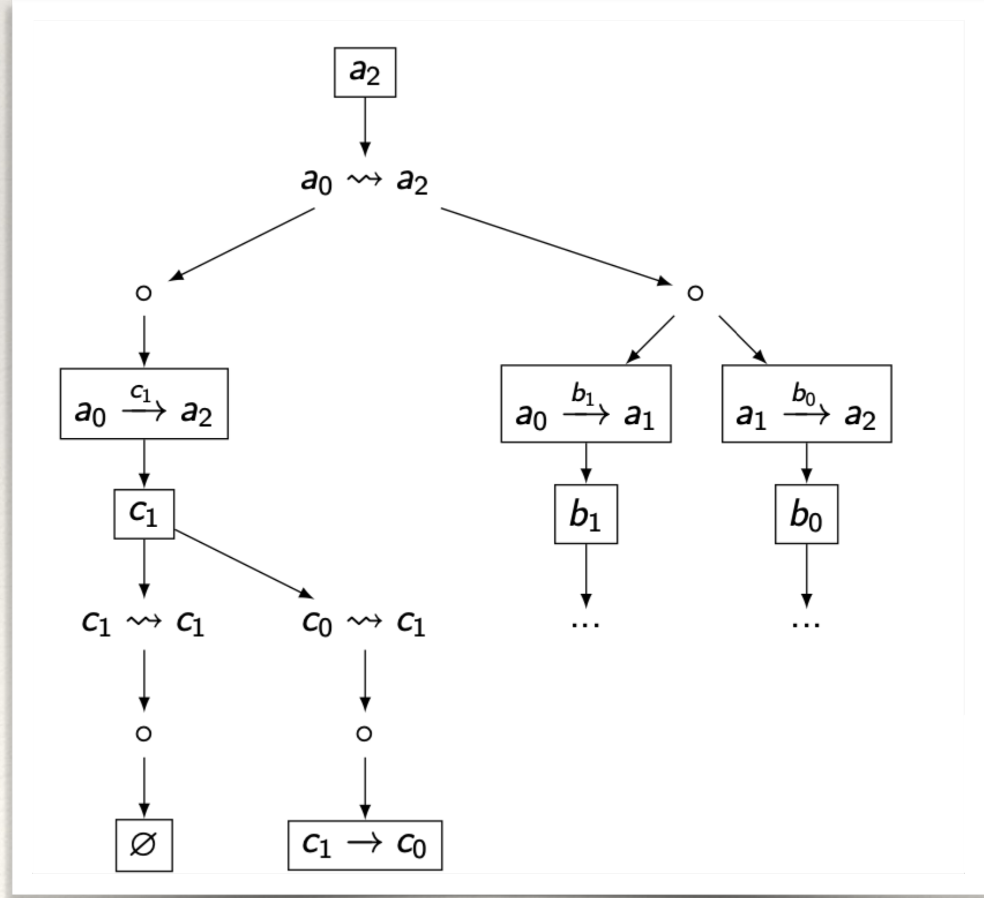
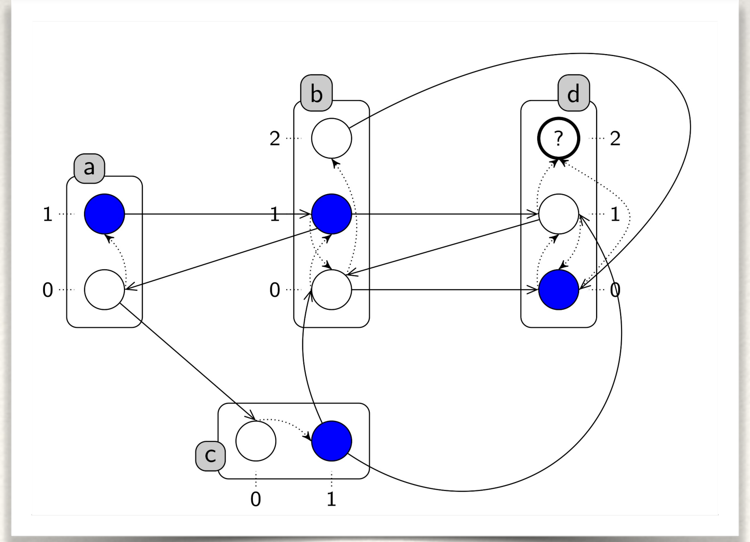
- Construction of **local causality graph**





Implementation of Local Causality Graph [PMR12]

- **Computation** of the local causality graph:
  - **Polynomial** in the number of automata
  - **Exponential** in the number of local states of each automaton (usually low, max. 4)
- **Analysis** of the graph (sufficient condition): **polynomial** in the size of the abstract graph
- **Enumeration** of the subsets of solutions (if needed): **exponential** in the size of the abstract graph



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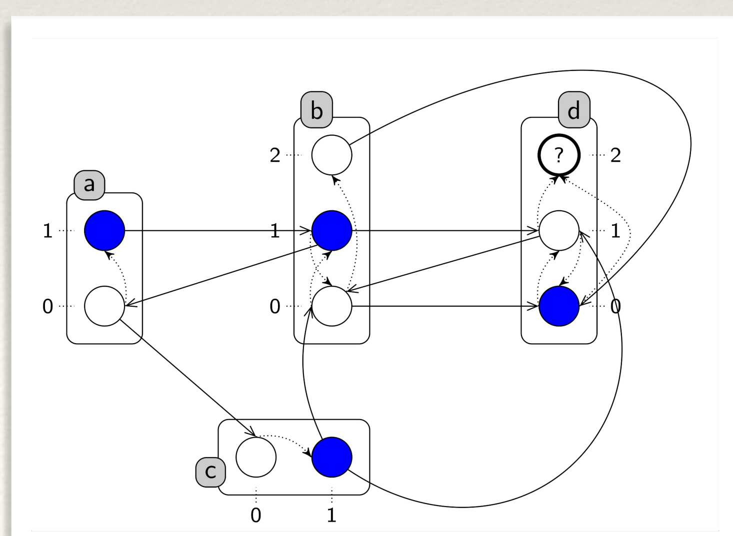
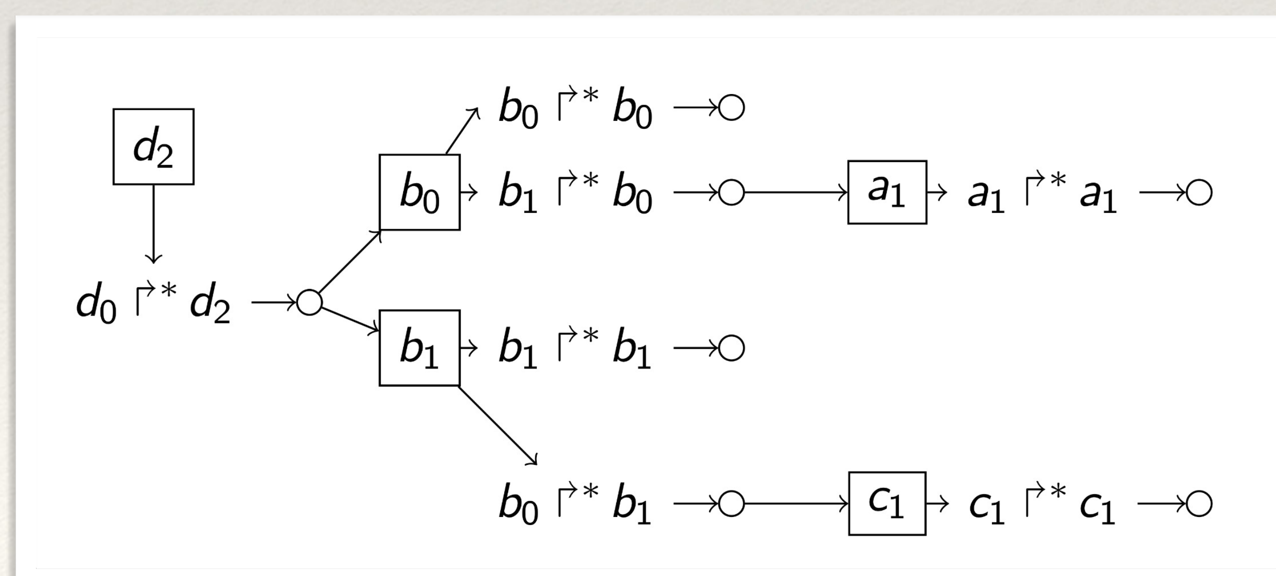


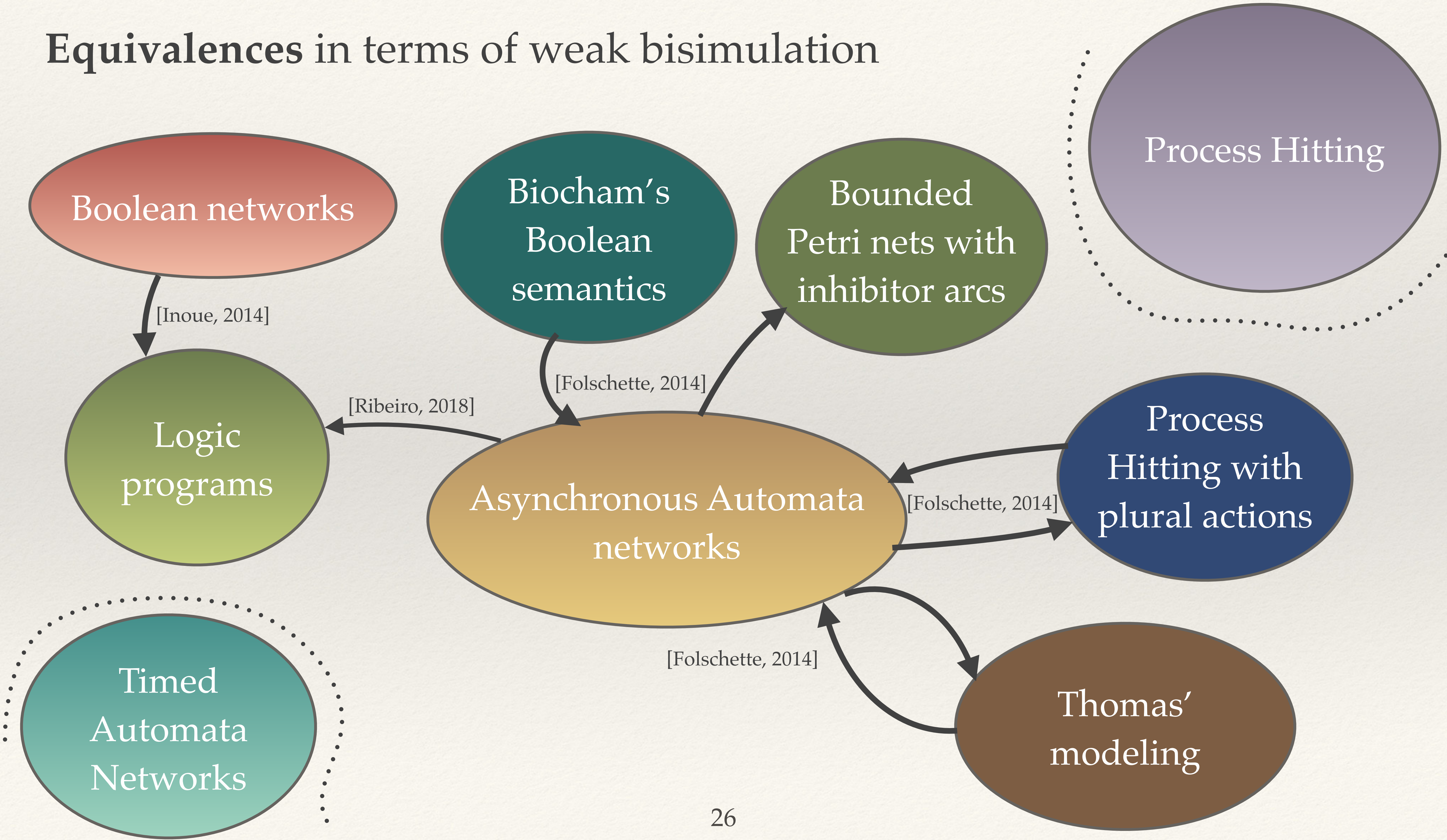


Overview

- Modeling frameworks for dynamical analysis
- Analysis of formal models
- **Inference and Learning approaches**
- Application to biological case studies

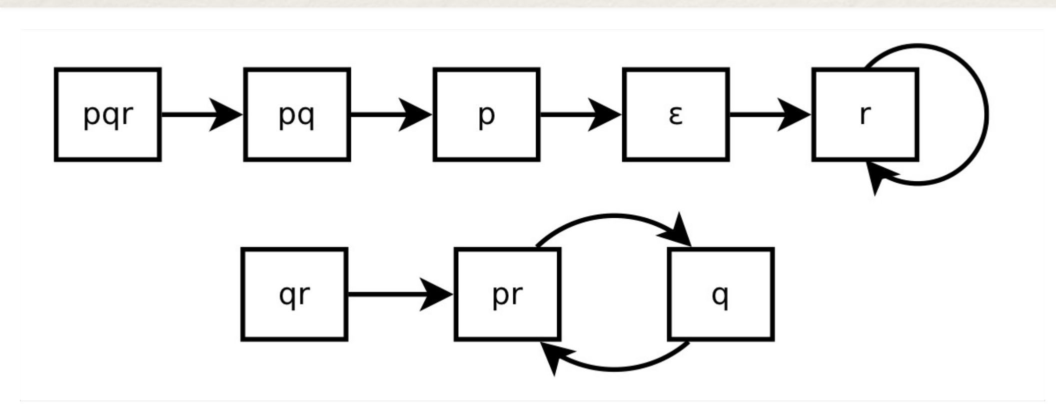
Correspondance between formalisms

Equivalences in terms of weak bisimulation



Learn systems dynamics

Principle of the LFIT framework [IRS14]: learn a **logic program** by observing the behavior of the system expressed as a succession **states-transitions**.



LFIT

$$p(t+1) \leftarrow q(t).$$
$$q(t+1) \leftarrow p(t) \land r(t).$$
$$r(t+1) \leftarrow \neg p(t).$$

Input: observation of the behavior of the system

Output: logic program

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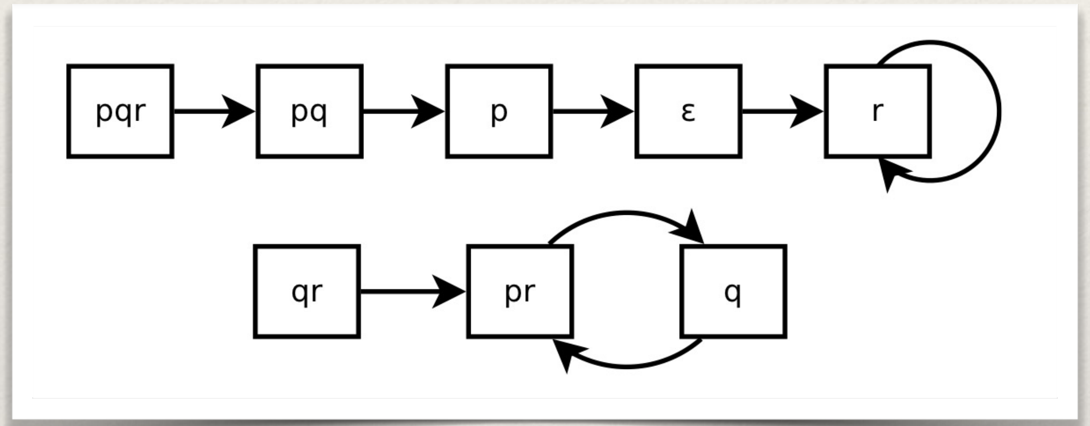

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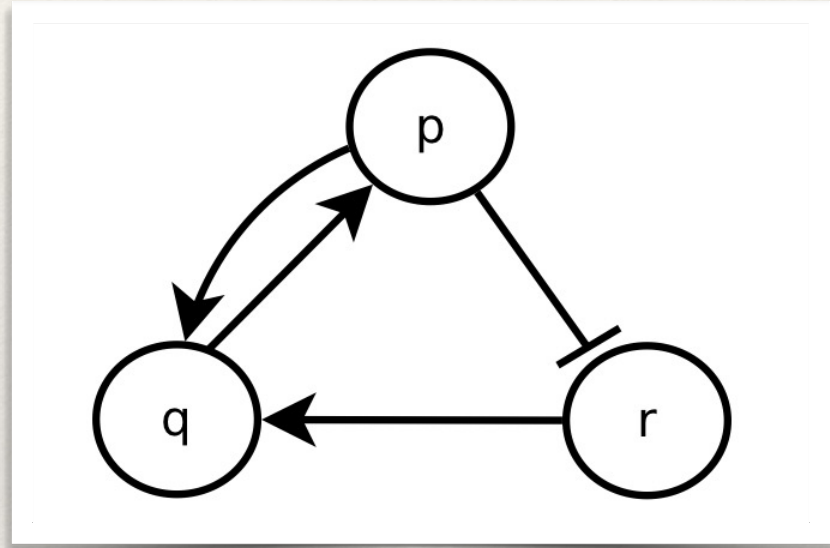

Input: observation of the behavior of the system

Output: Boolean network

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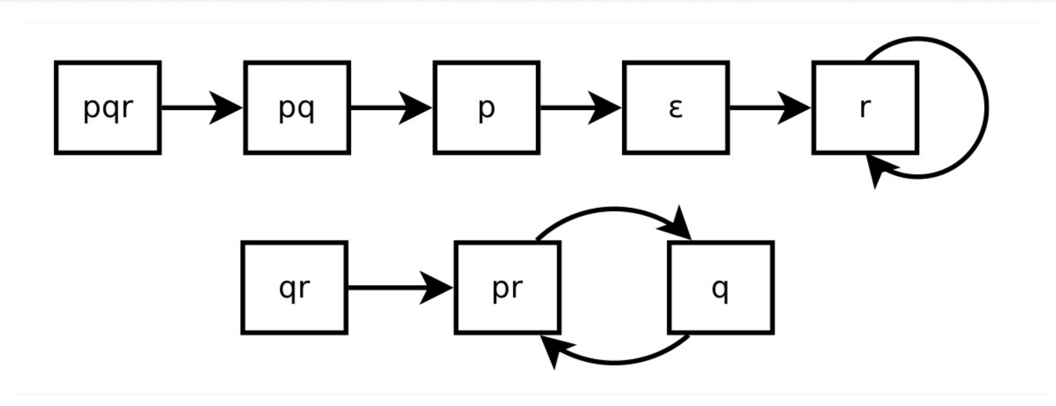

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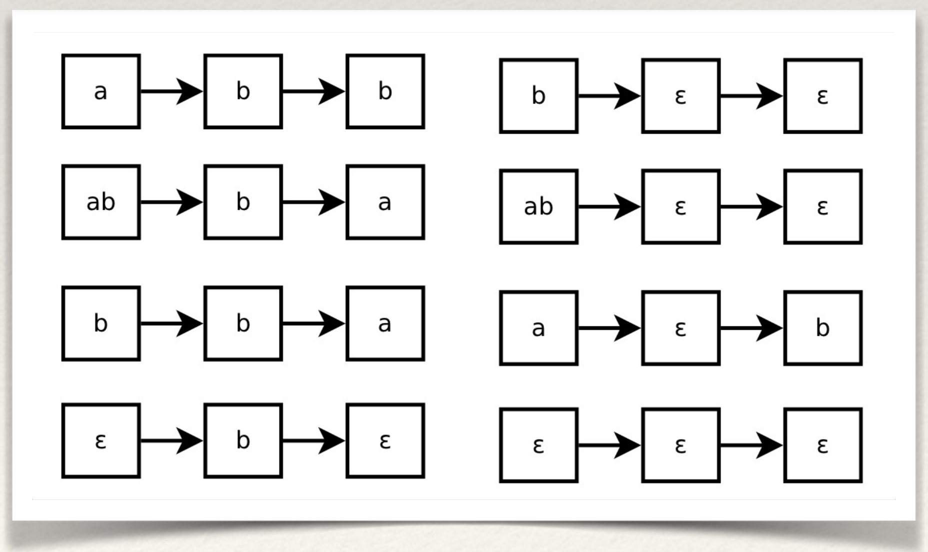
Output: logic program

Boolean variables

Synchronous and **deterministic** dynamics

Apply LFIT to biological systems
[RMI+15a,RMI+15b]

- Successive extensions :
  - **Delayed** influences (models with memory)
  - **Multi-valued** variables
  - **Asynchronous** dynamics
  - **Non-deterministic** semantics



LFkT

a(t) ← b(t−1), b(t−2)
b(t) ← a(t−2), ¬b(t−2)

Input: observation of the system's behavior

Output: logic program

A wide range of possible models (and inference algorithms)

https://github.com/Tony-sama/pylfit

Values	Boolean	Multi-valued	Captured symbolically (e.g. intervals)
Time	Chronological: Event-driven model	Chronometrical: Discrete time	Chronometrical: Dense time
Semantics of discrete transitions	Synchronous	Asynchronous	Generalized
Determinism of discrete transitions	Deterministic	Non-deterministic	Probabilistic
Markov property	With memory	Memoryless	

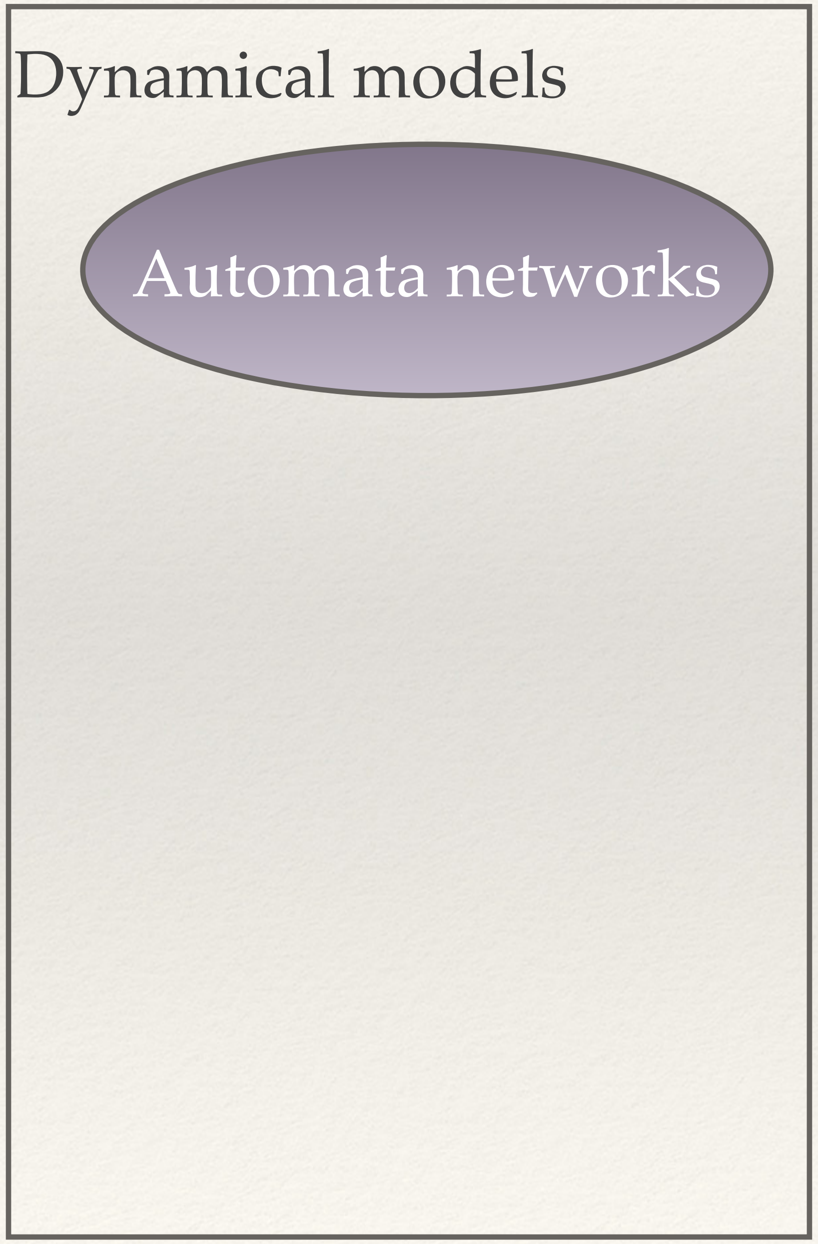
Overview

- Modeling frameworks for dynamical analysis
- Analysis of formal models
- Inference and Learning approaches
- **Application to biological case studies**

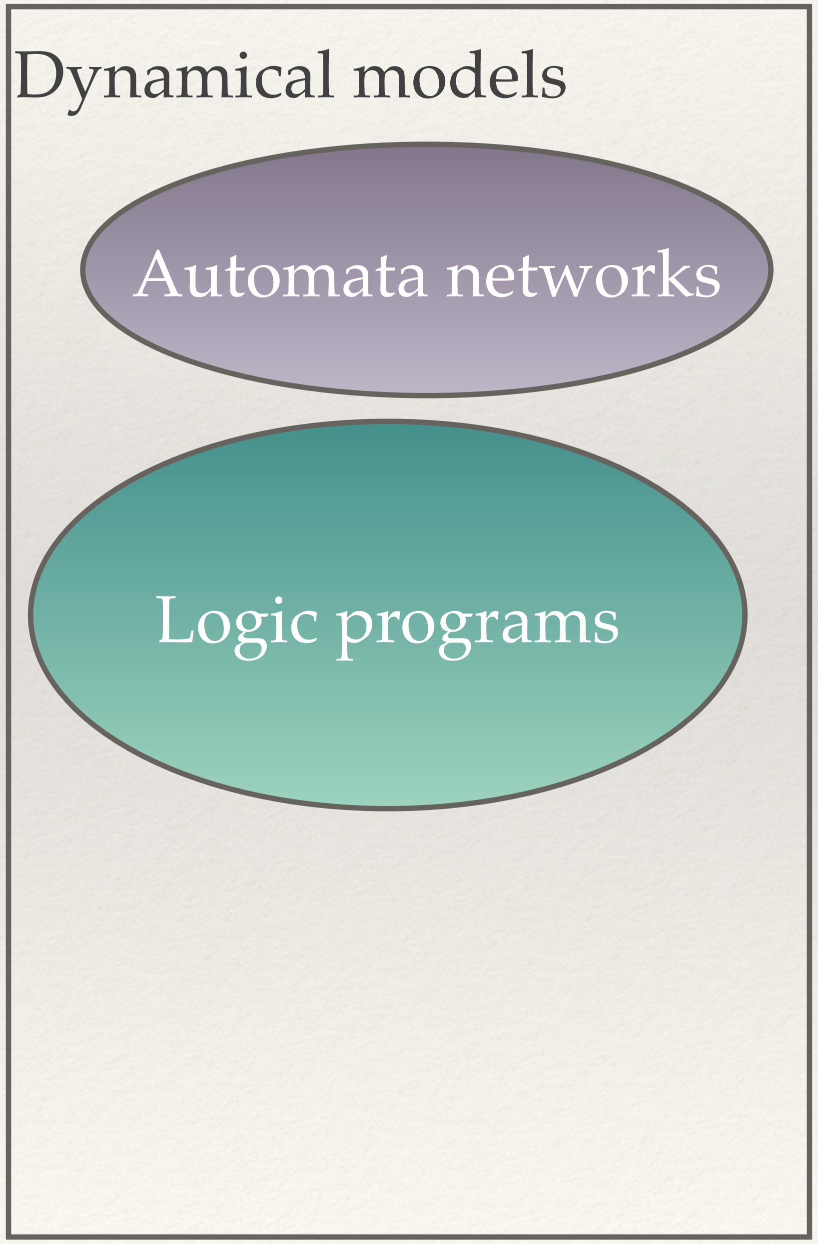
Synthesis of our contributions

Dynamical models

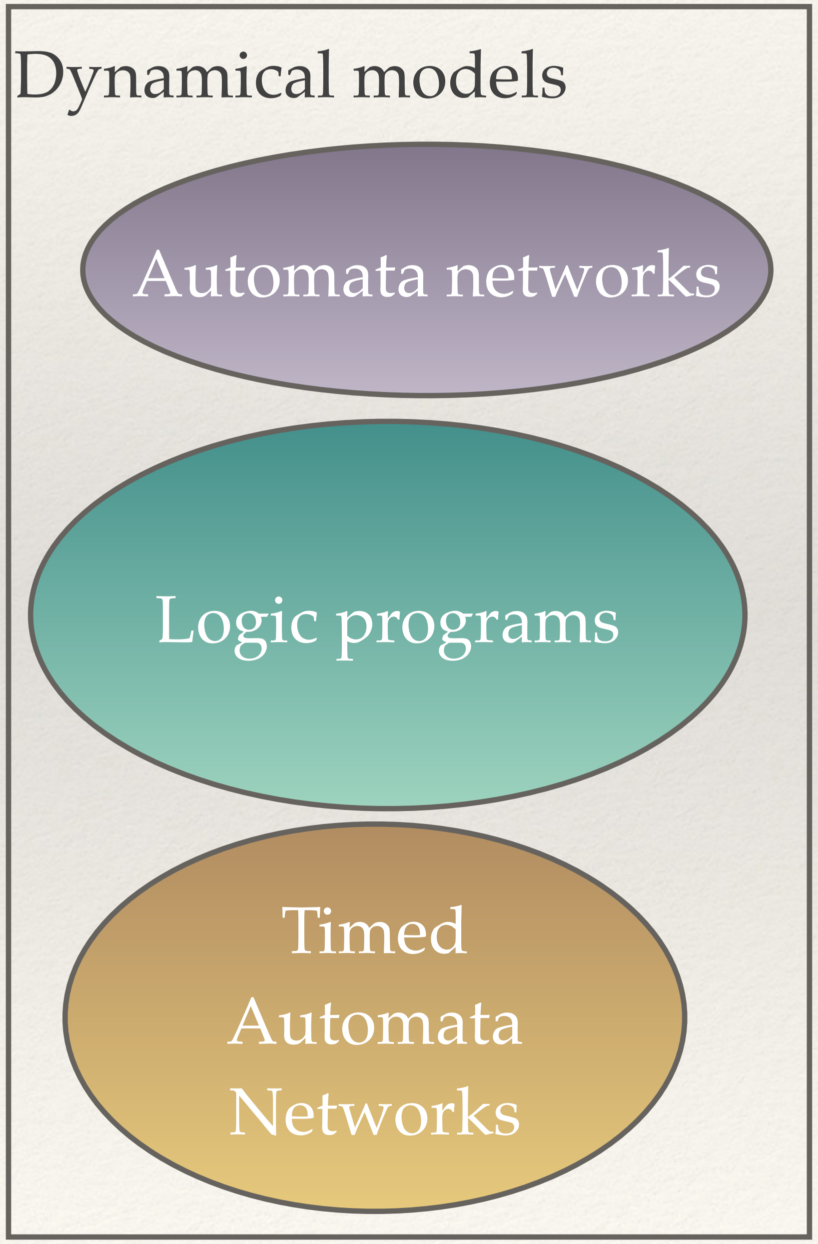
Synthesis of our contributions



Synthesis of our contributions



Synthesis of our contributions



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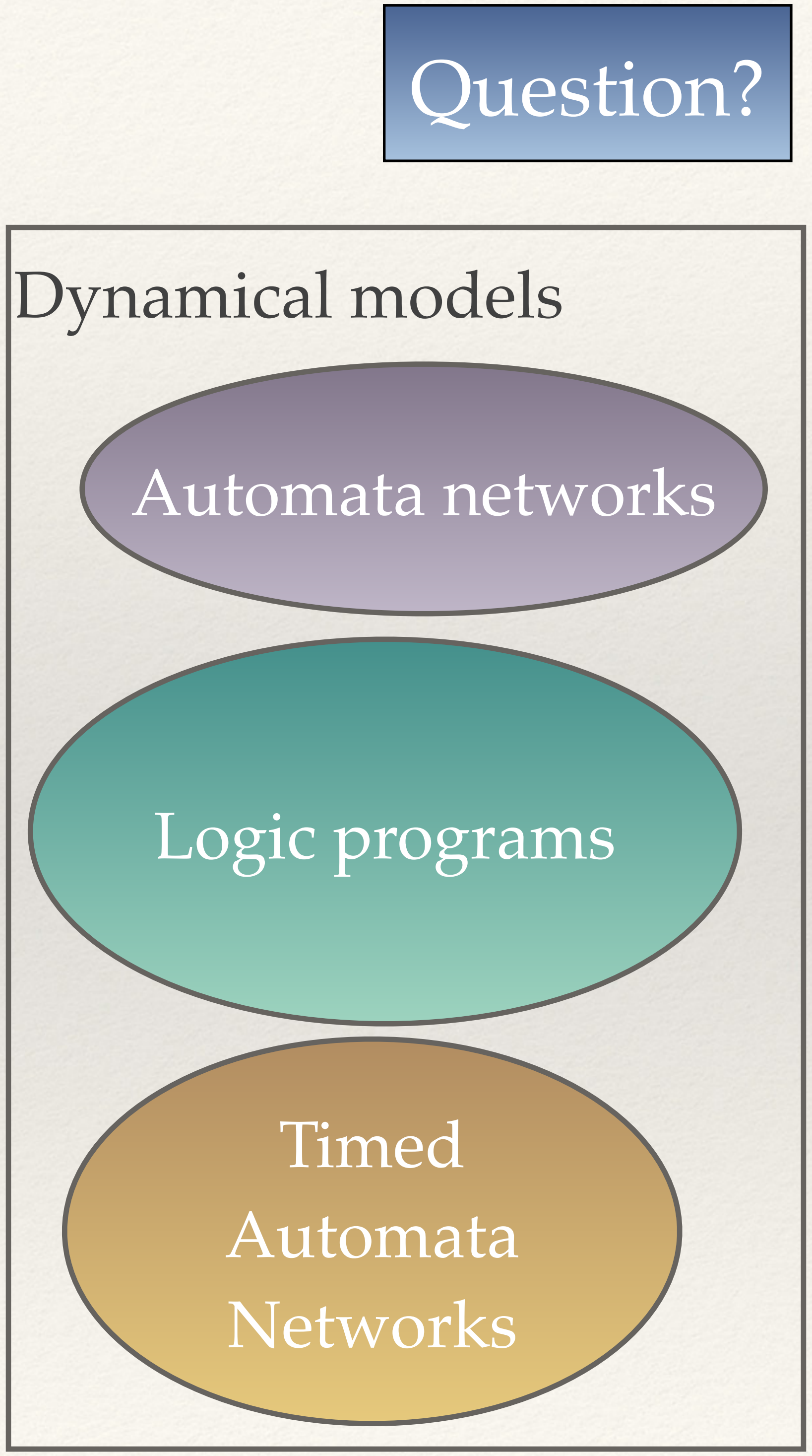

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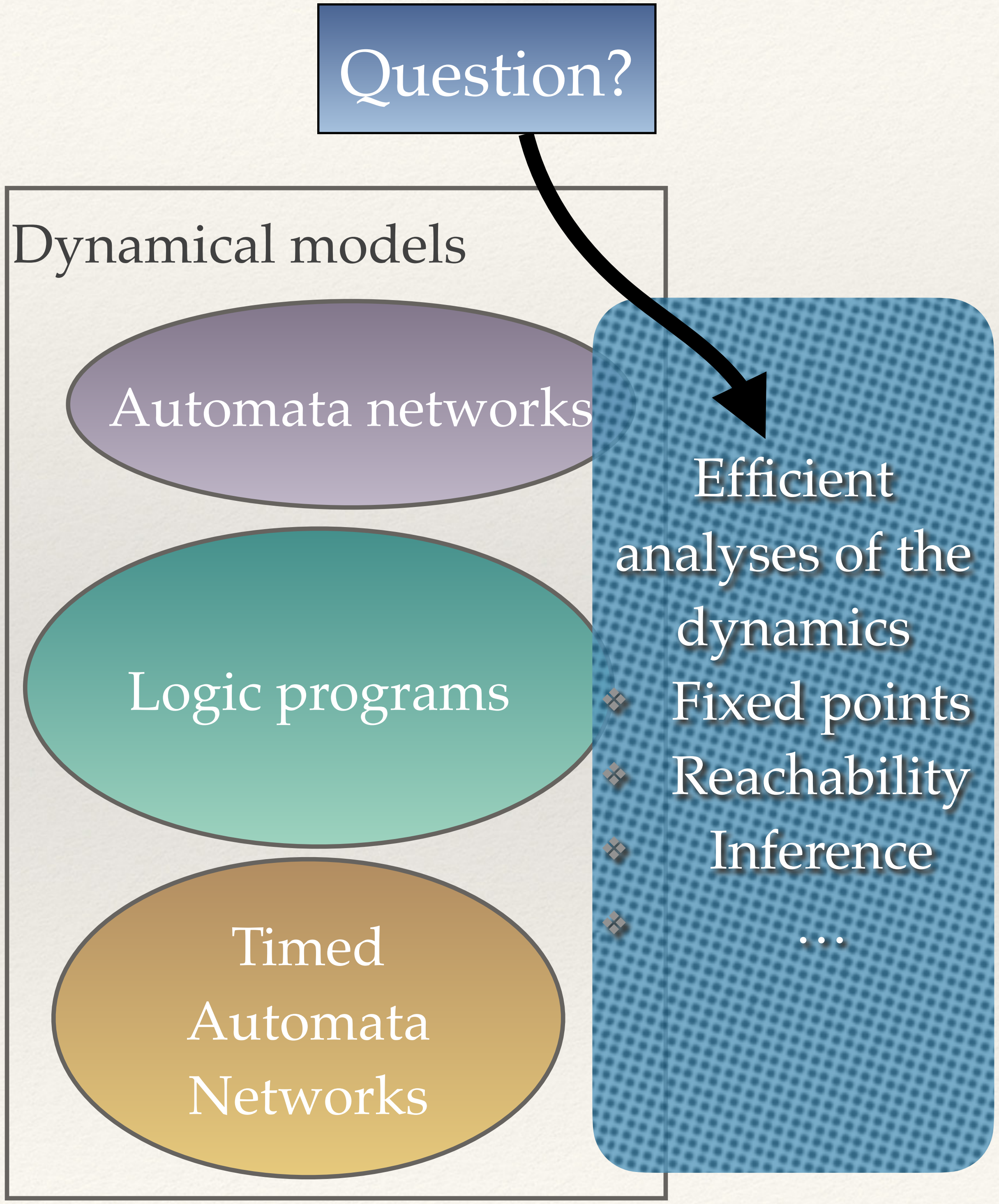


Synthesis of our contributions

Question?

Dynamical models

Automata networks

Logic programs

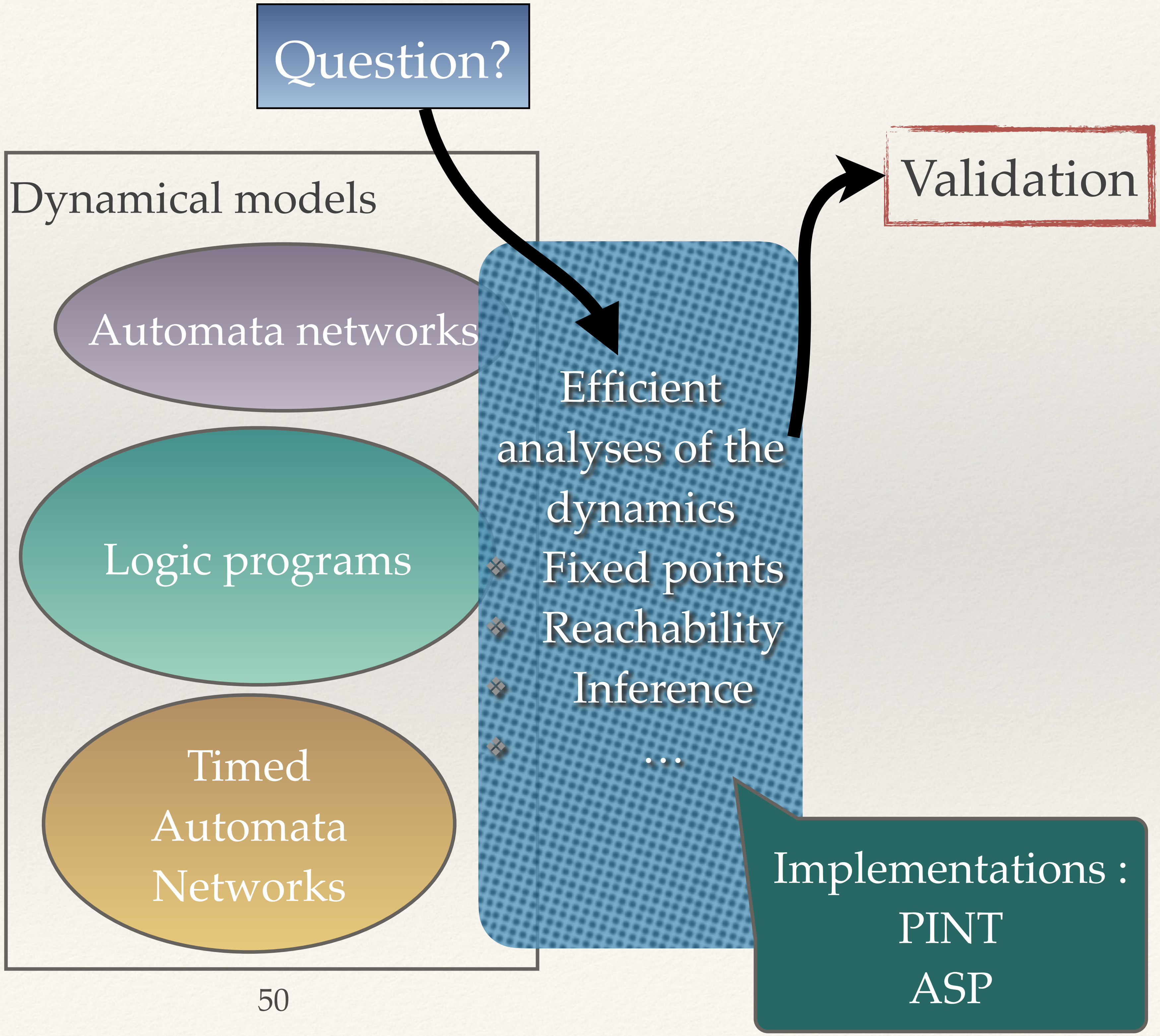
Timed Automata Networks

Efficient analyses of the dynamics

- Fixed points
- Reachability
- Inference
- …

Implementations :
PINT
ASP

Synthesis of our contributions



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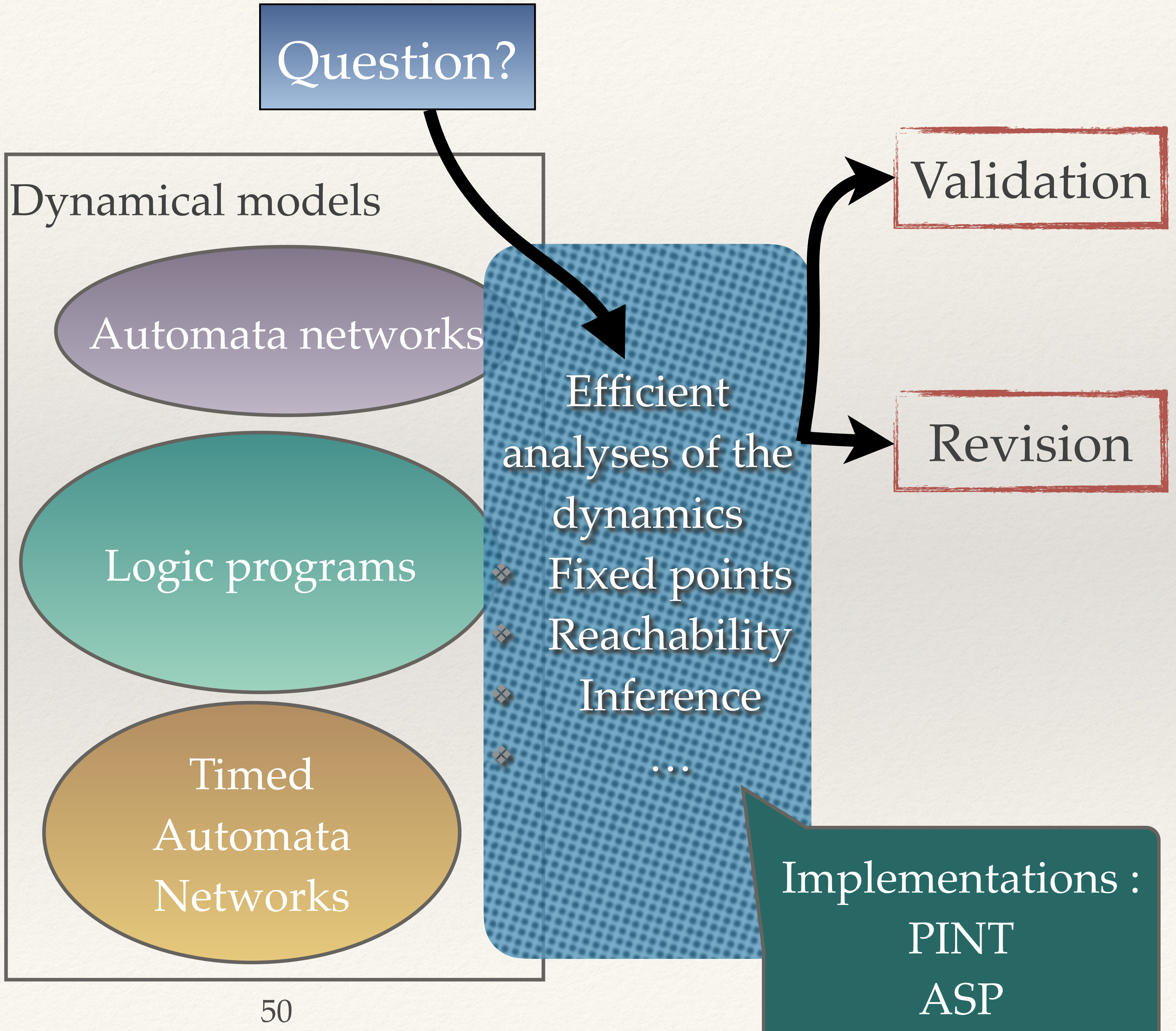

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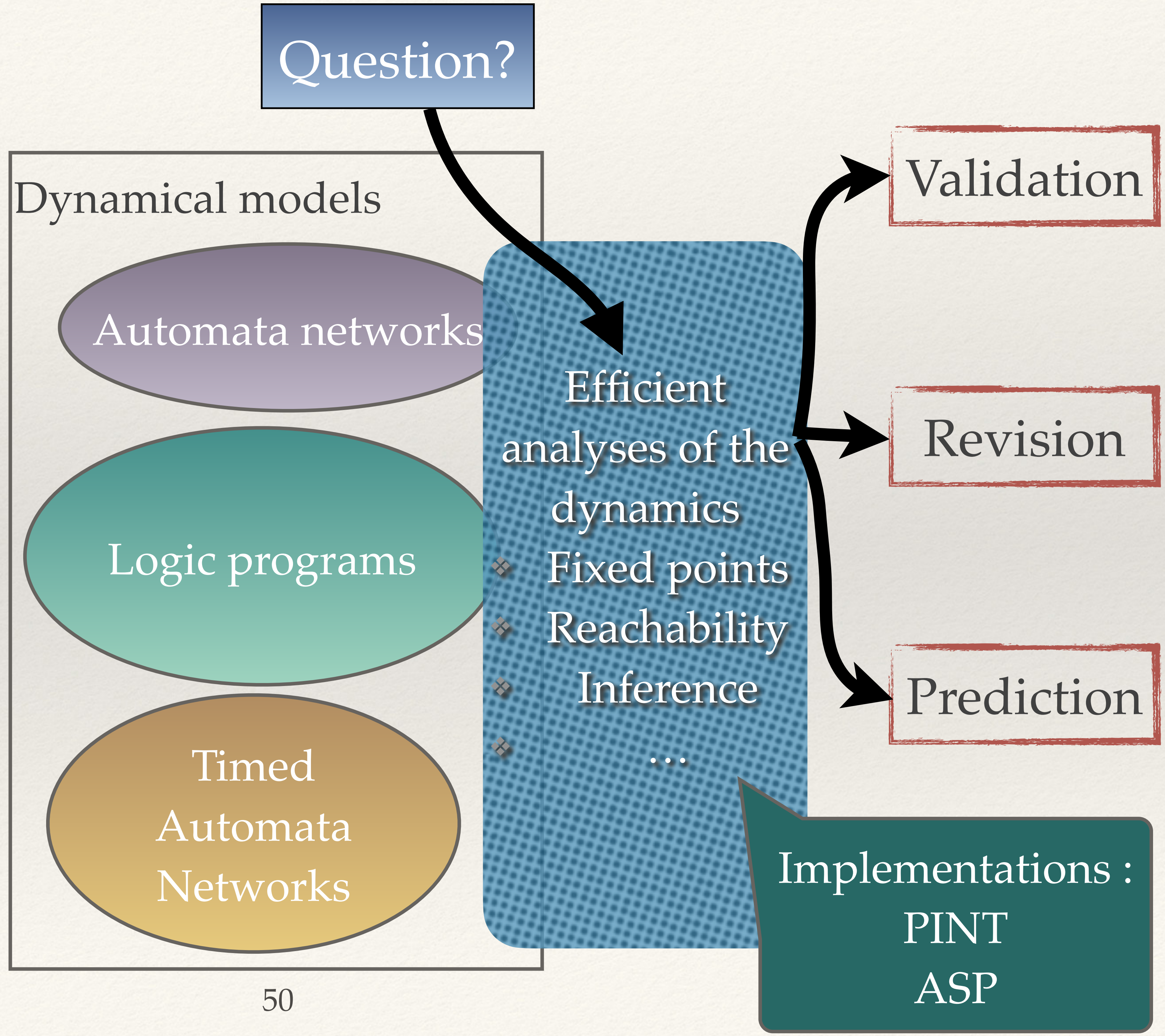

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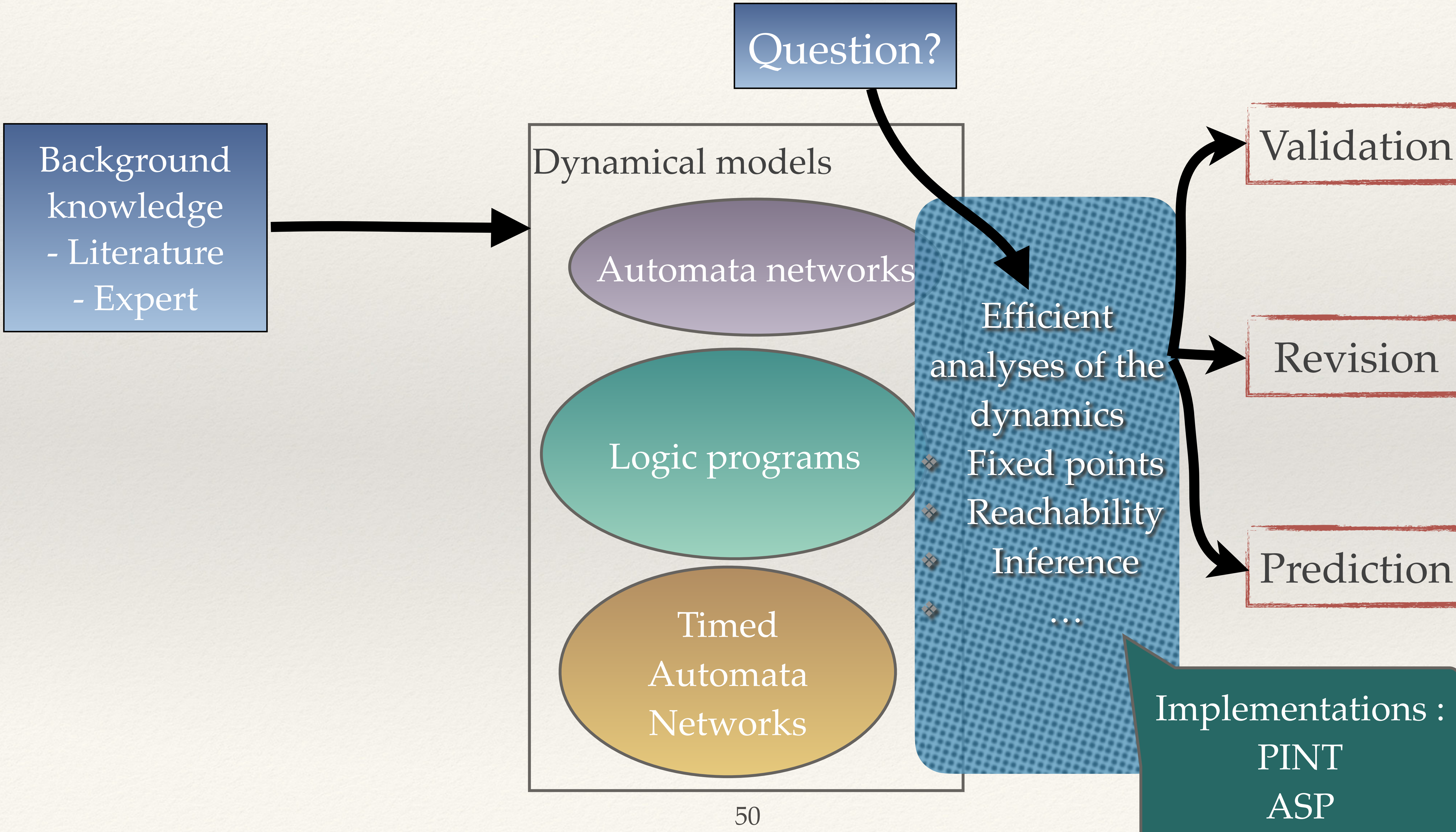
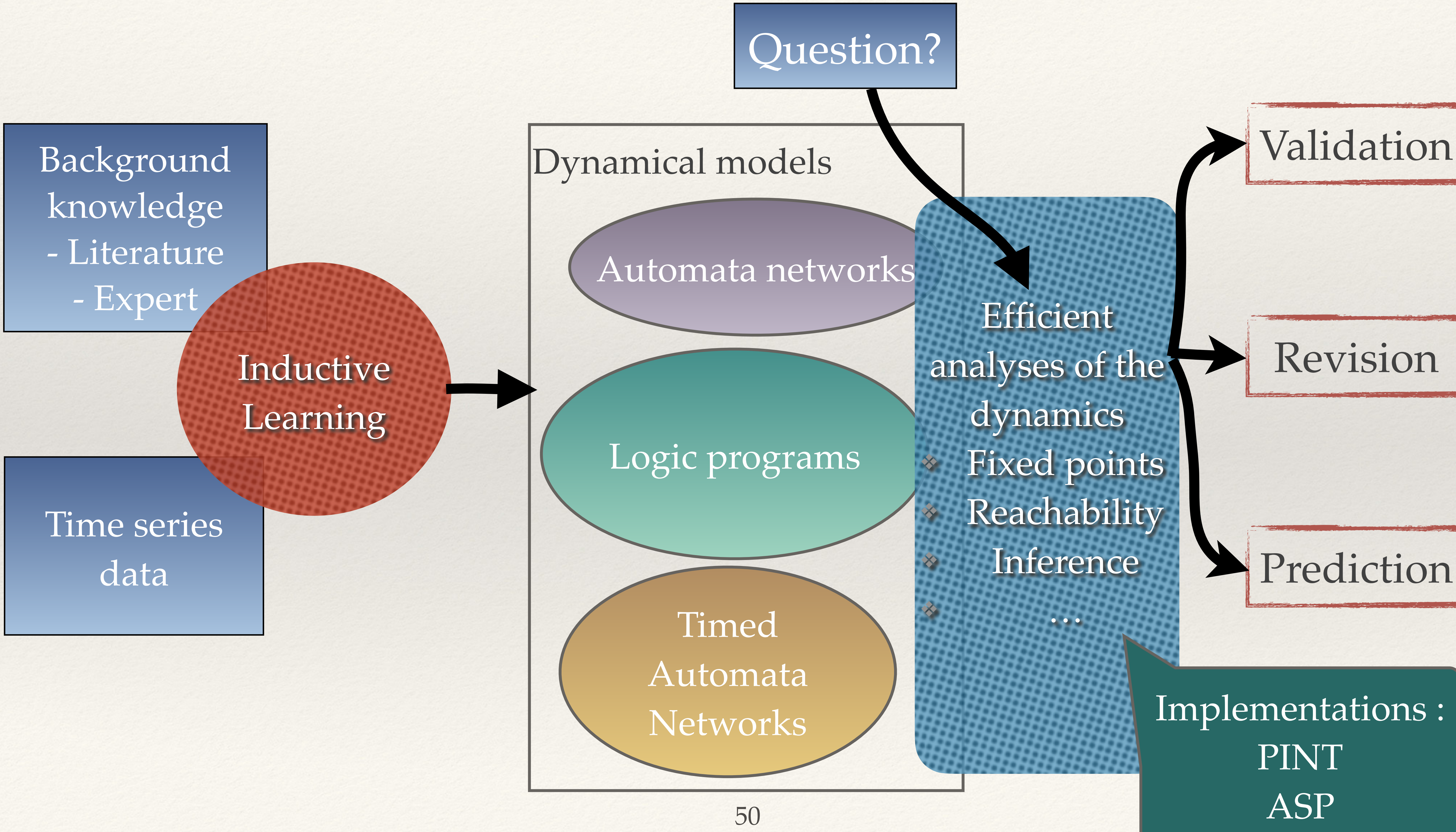


Synthesis of our contributions



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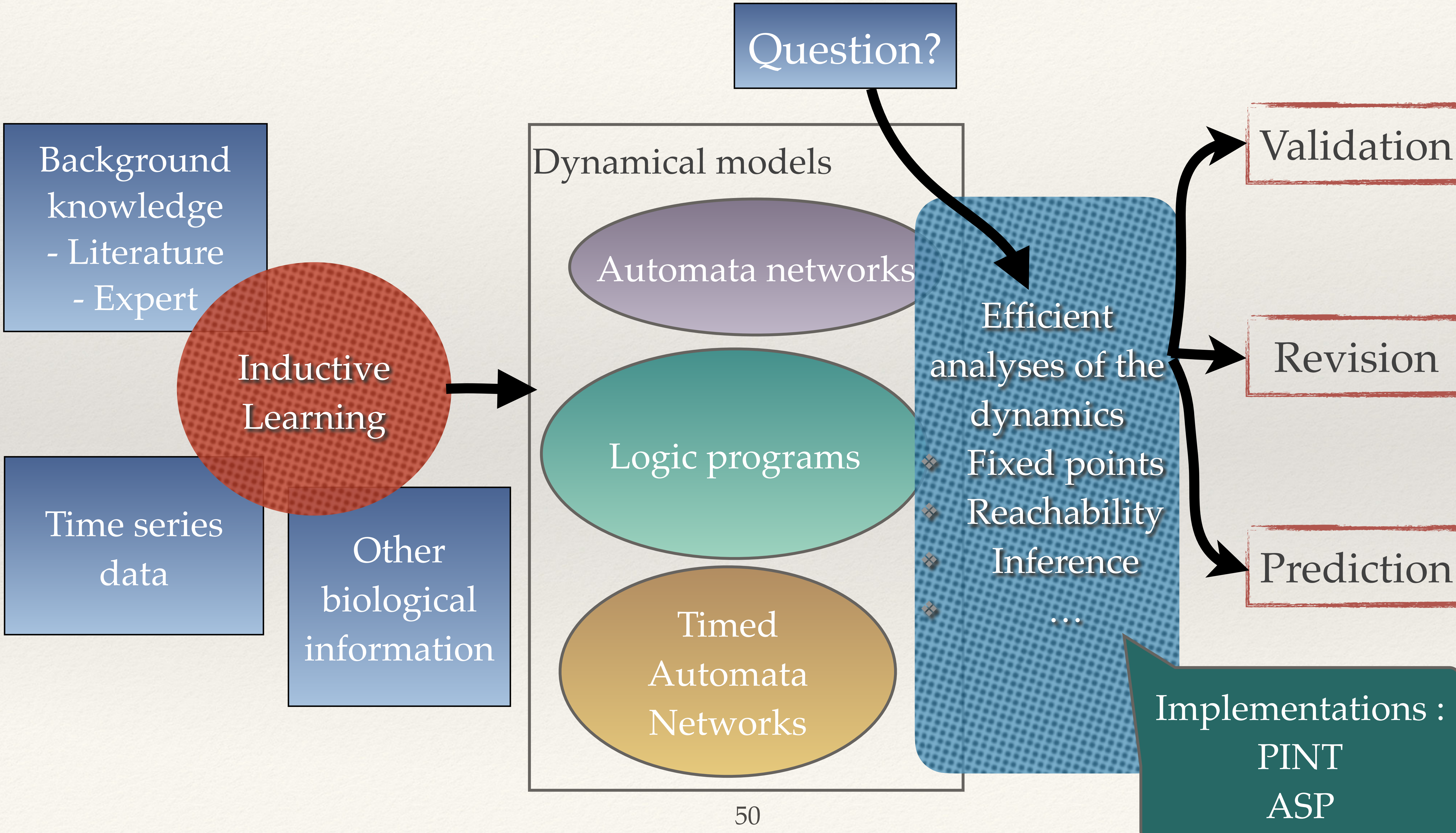
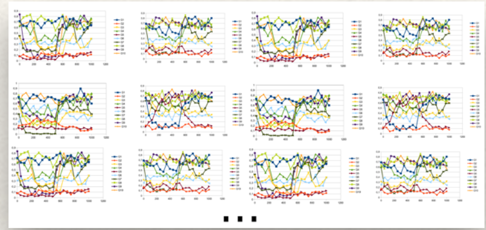


Methodological goals

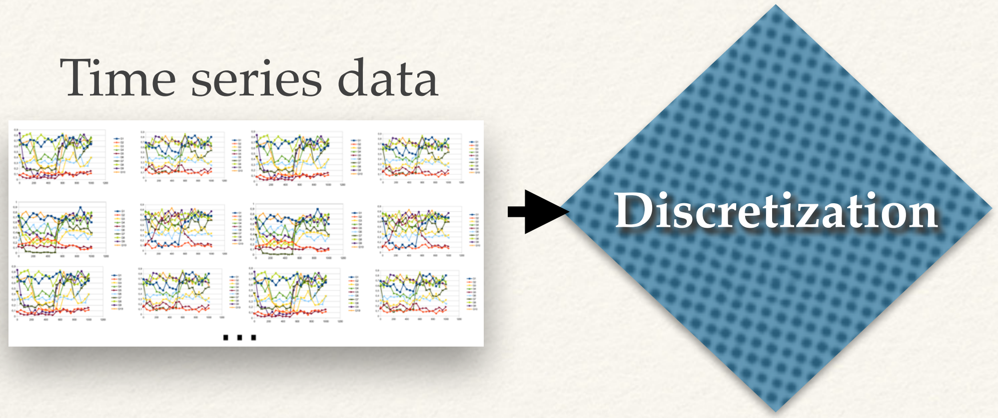
Methodological goals

Time series data



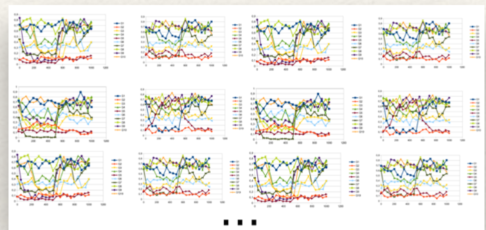
Methodological goals

Time series data



Methodological goals

Time series data

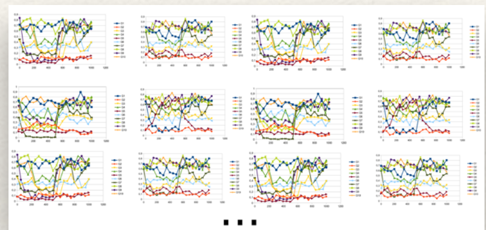


Discretization

Learning

Methodological goals

Time series data



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Discretization

Learning

Dynamical models

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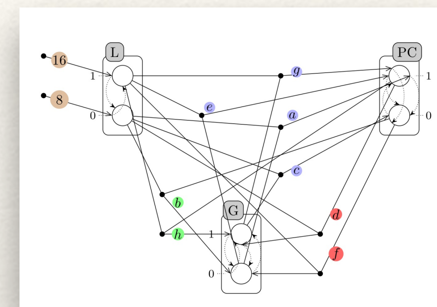
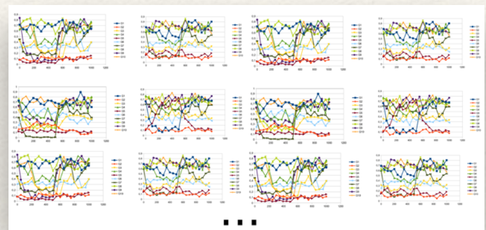
Logic programs



Automata networks

Methodological goals

Time series data



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Discretization

Learning

Goal n°1: improve learning by addressing noisy, incomplete and/or conflicting data

Dynamical models

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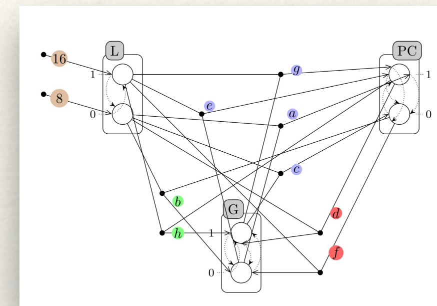
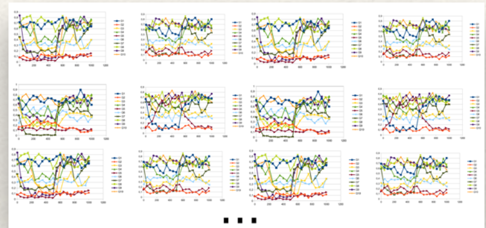
Logic programs



Automata networks

Methodological goals

Time series data



Discretization

Learning

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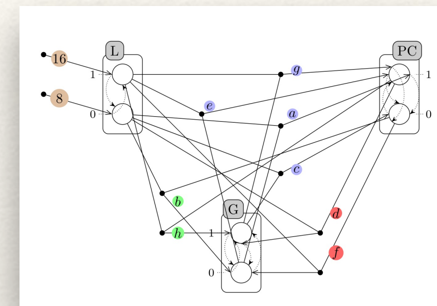
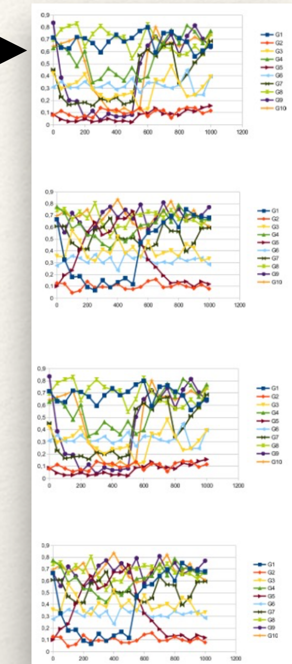
Logic programs



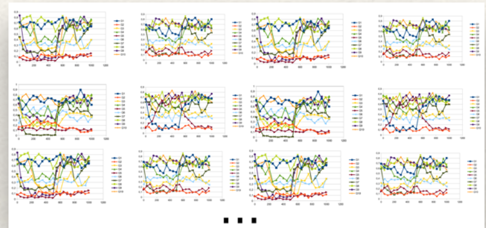
Automata networks

Analysis of dynamic behaviors



Methodological goals

Time series data



Discretization

Learning

Goal n°1: improve learning by addressing noisy, incomplete and/or conflicting data

Dynamical models

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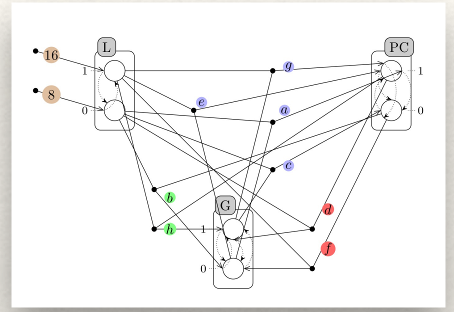
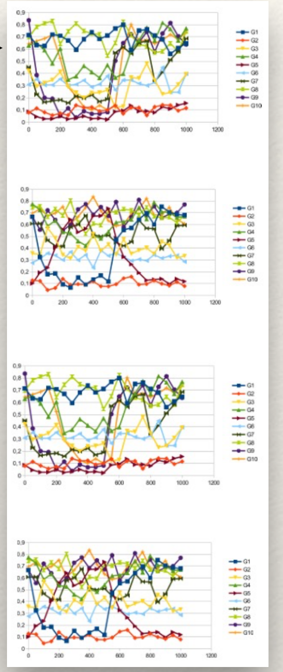
```

Logic programs



Automata networks

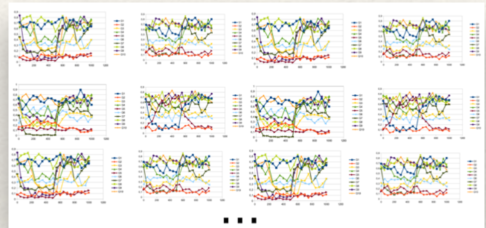
Analysis of dynamic behaviors



Background knowledge on the dynamics

Methodological goals

Time series data



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Discretization

Learning

Goal n°1: improve learning by addressing noisy, incomplete and/or conflicting data

Dynamical models

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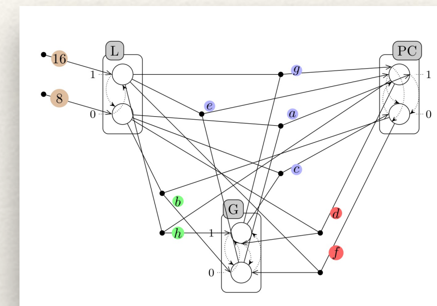
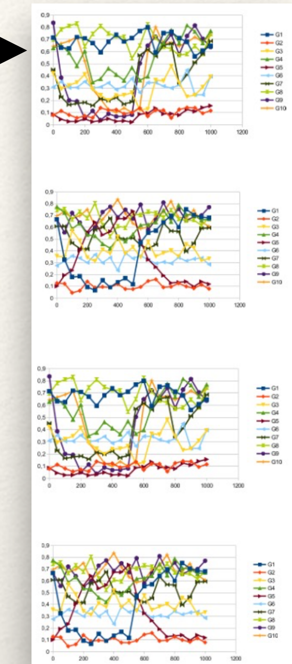
```

Logic programs



Automata networks

Analysis of dynamic behaviors



Background knowledge on the dynamics

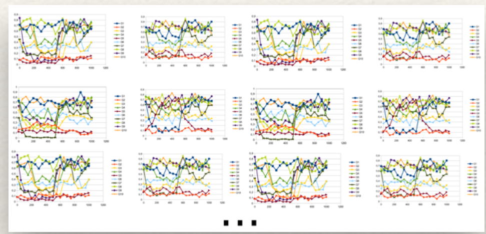
Formalization

Expected properties in temporal logics

$$(M(p_{G0}) = 1 \wedge M(p_{PC0}) = 1) \rightsquigarrow_{[0,\tau_{0,1}]} (M(p_{G1}) = 1)$$

Methodological goals

Time series data



...

Discretization

Learning

Goal n°1: improve learning by addressing noisy, incomplete and/or conflicting data

Dynamical models

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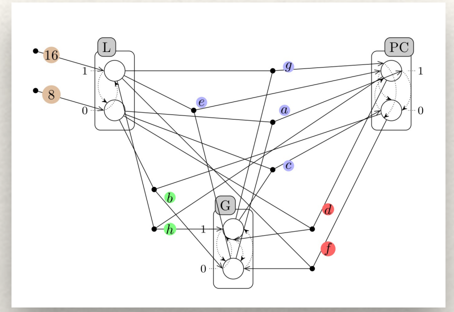
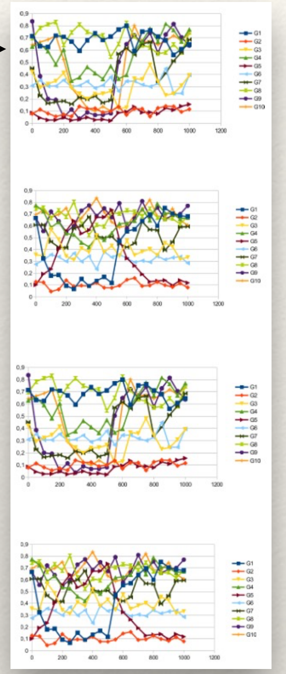
```

Logic programs



Automata networks

Analysis of dynamic behaviors



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Expected properties in temporal logics

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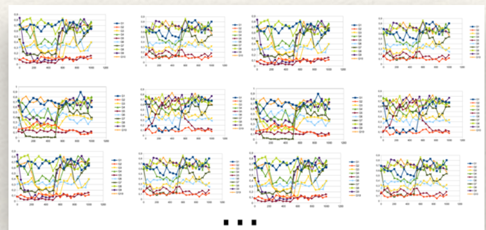
Check properties

Methodological goals

Time series data



Discretization

Learning

Goal n°1: improve learning by addressing noisy, incomplete and/or conflicting data

Dynamical models

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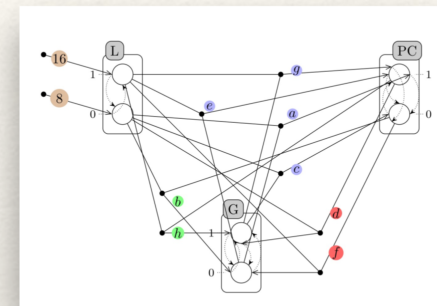
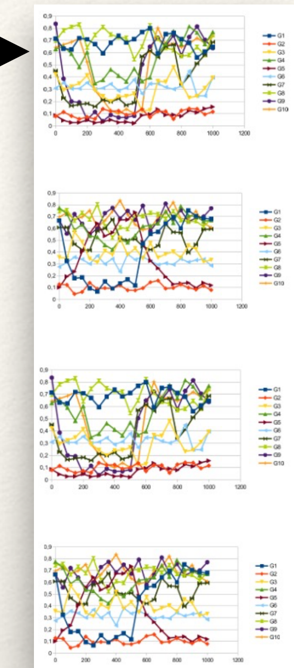
ARNTL(0,T) :- CRY1(1,T-1), PPARA(2,T-1).
```

Logic programs



Automata networks

Analysis of dynamic behaviors



If properties are not verified on the model

Background knowledge on the dynamics

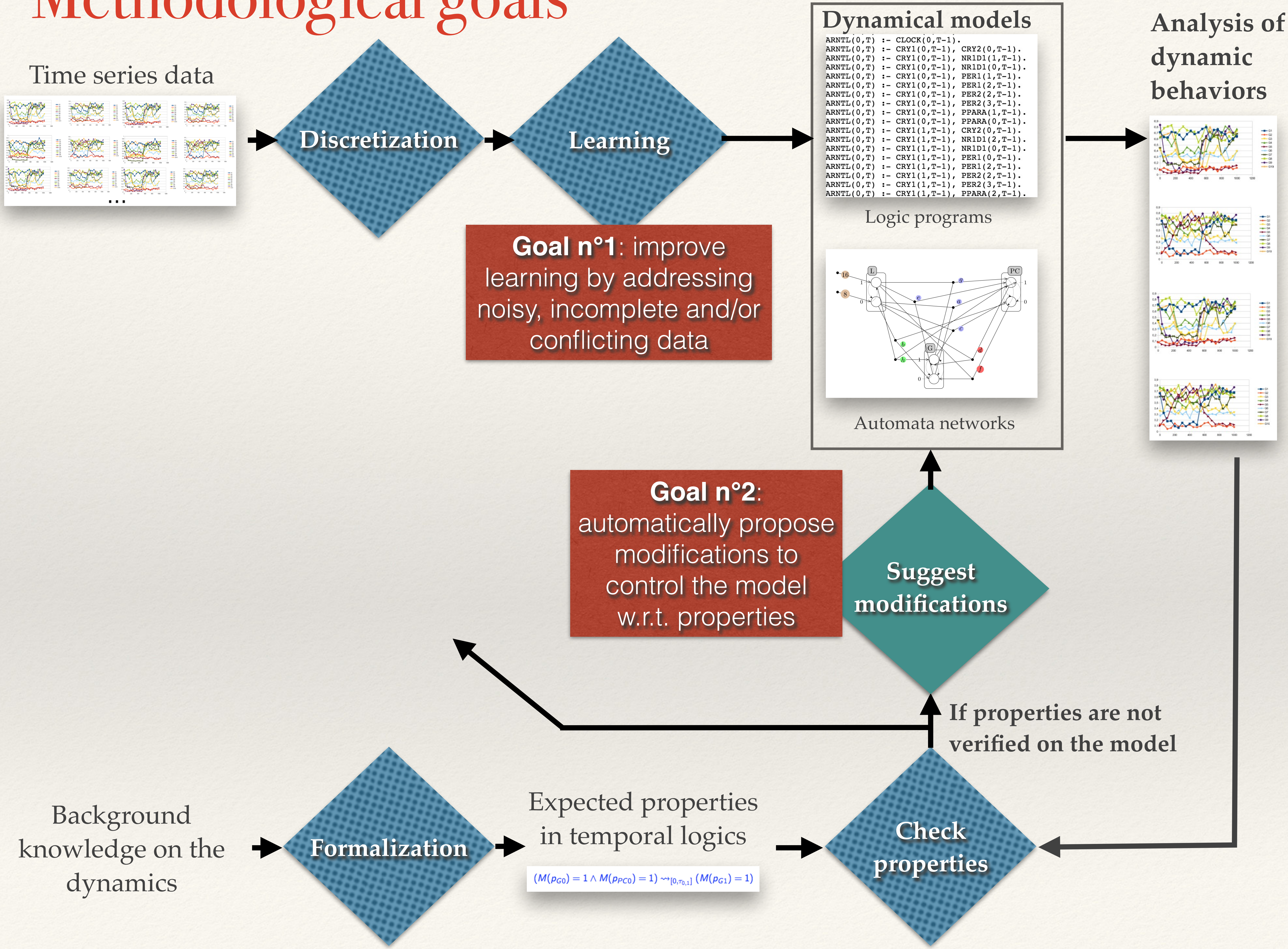
Formalization

Expected properties in temporal logics

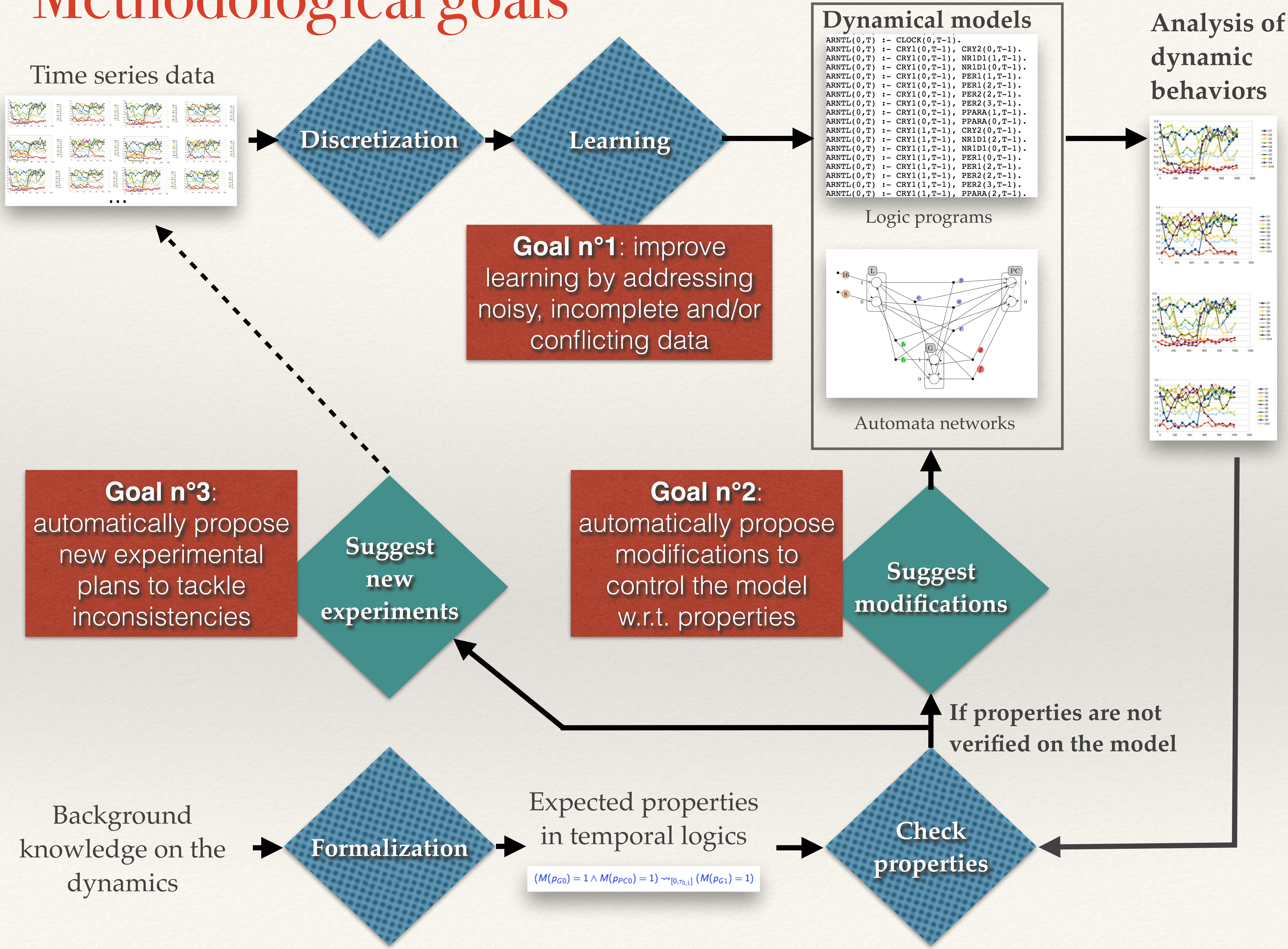
$(M(p_{G0}) = 1 \wedge M(p_{PC0}) = 1) \rightsquigarrow_{[0,\tau_{0,1}]} (M(p_{G1}) = 1)$

Check properties

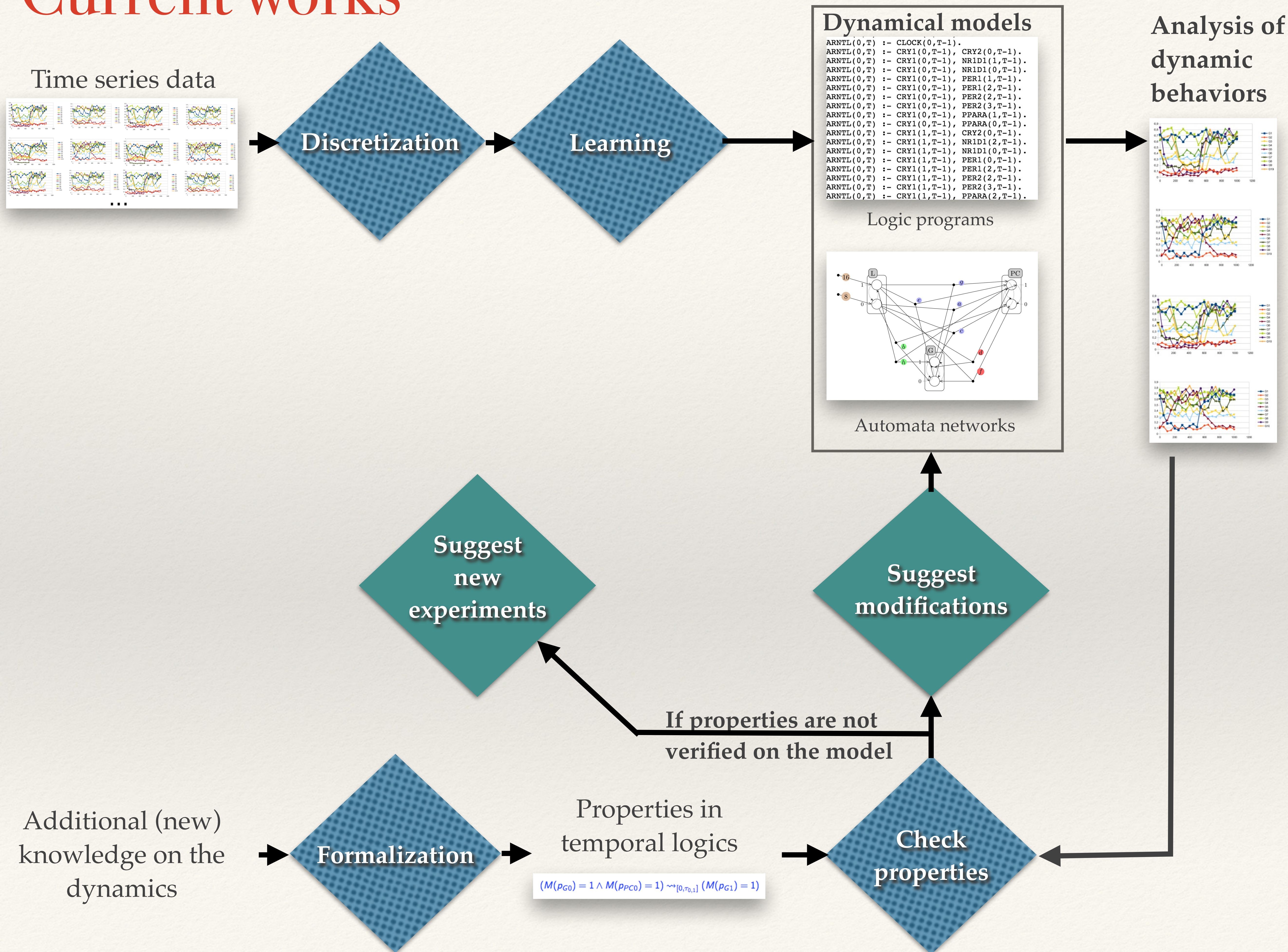
Methodological goals



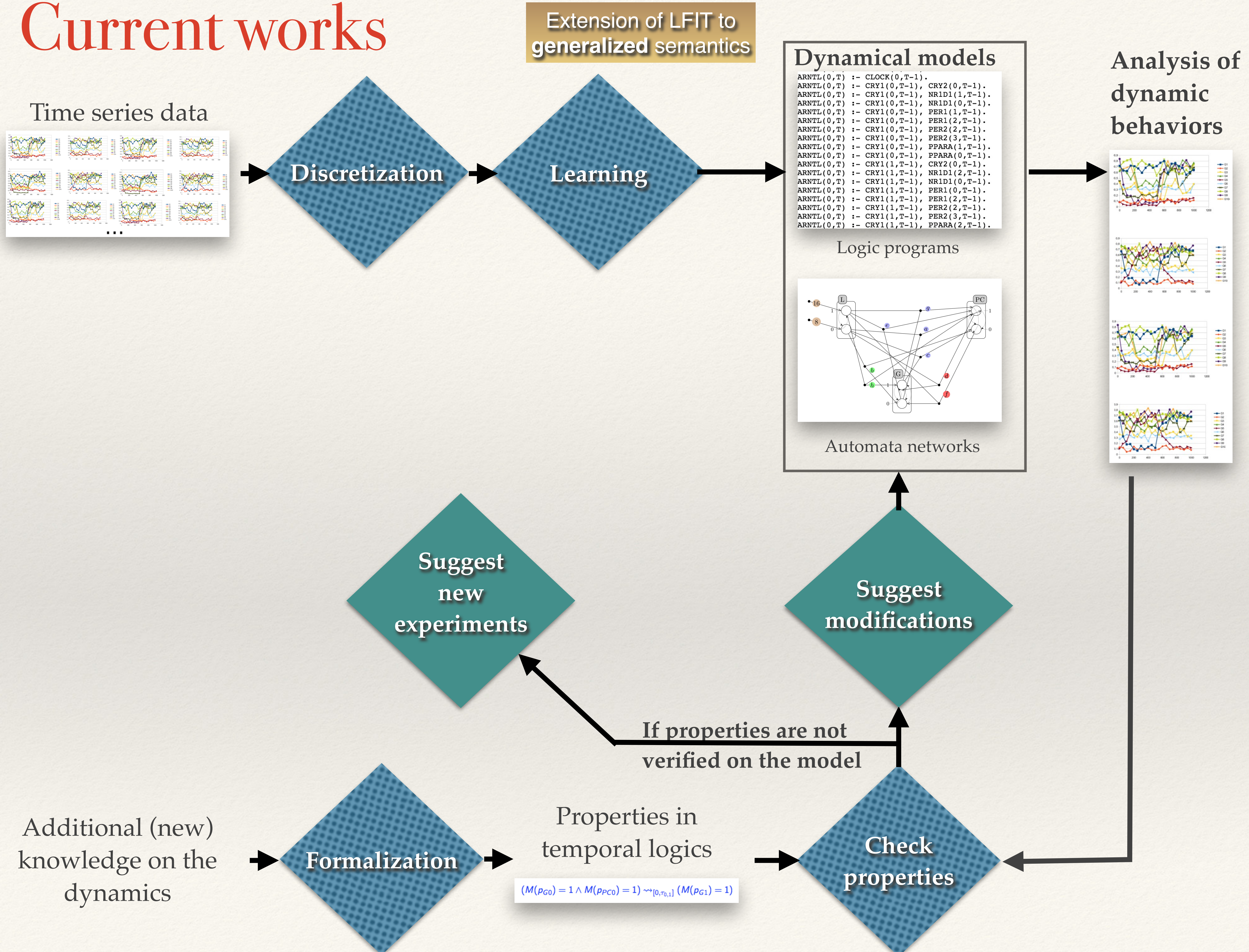
Methodological goals



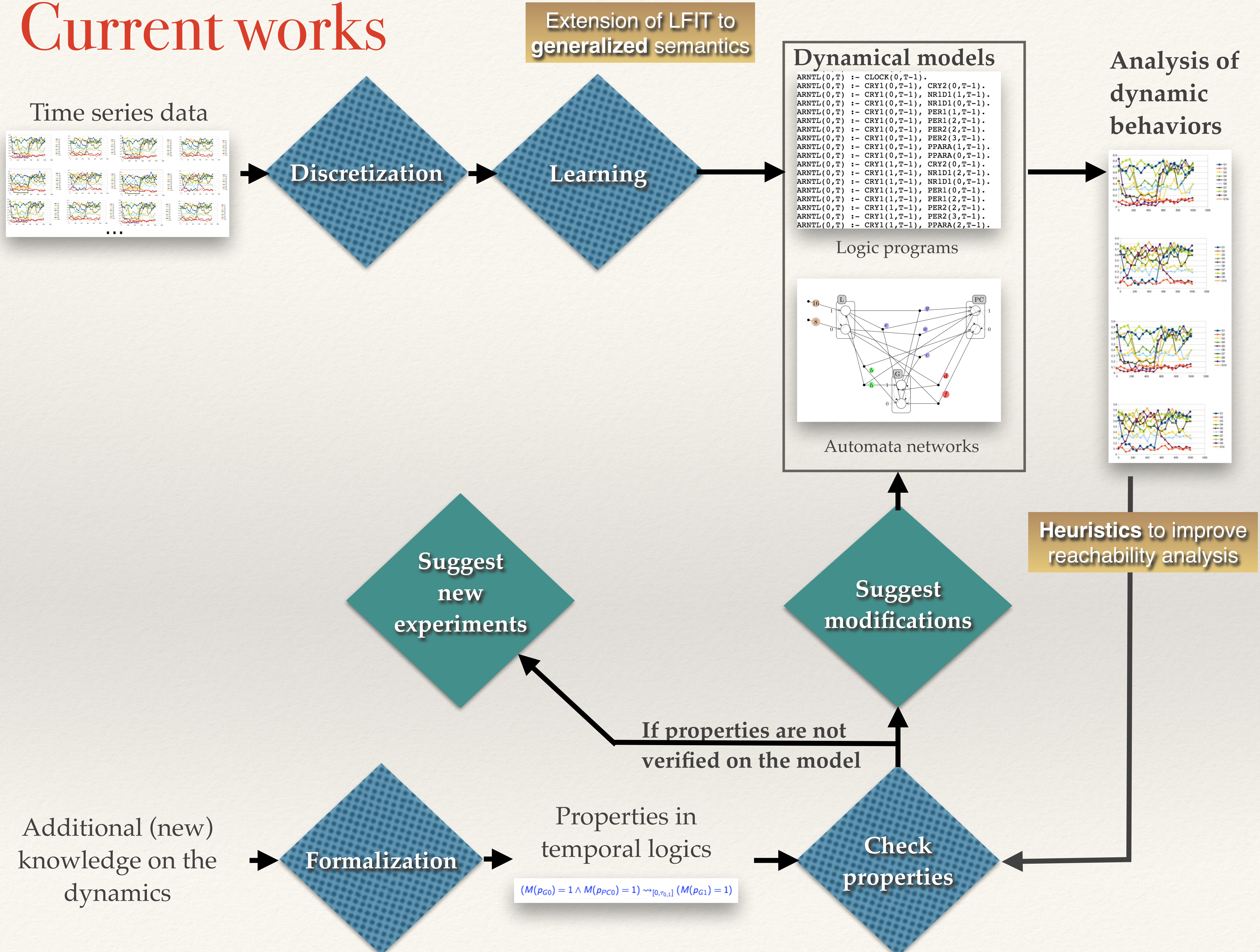
Current works



Current works



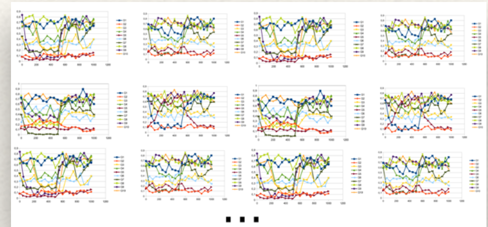
Current works



Current works

Extension of LFIT to **generalized** semantics

Time series data



Discretization

Learning

Dynamical models

```
ARNTL(0,T) :- CLOCK(0,T-1).
ARNTL(0,T) :- CRY1(0,T-1), CRY2(0,T-1).
ARNTL(0,T) :- CRY1(0,T-1), NR1D1(1,T-1).
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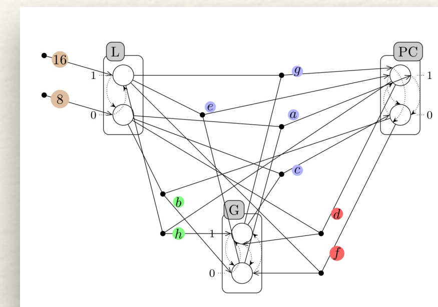
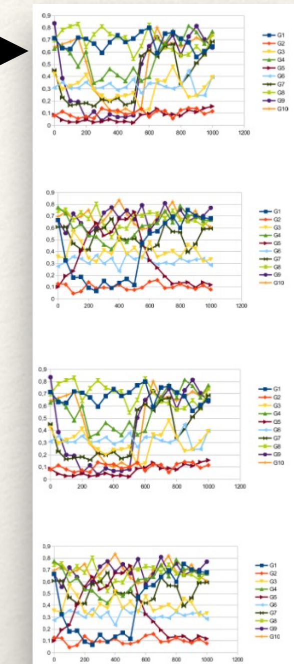
```

Logic programs



Automata networks

Analysis of dynamic behaviors



Heuristics to improve reachability analysis

Use of (i) **ASP** (ii) **SAT-solvers** to analyze reachability

Suggest new experiments

Suggest modifications

If properties are not verified on the model

Additional (new) knowledge on the dynamics

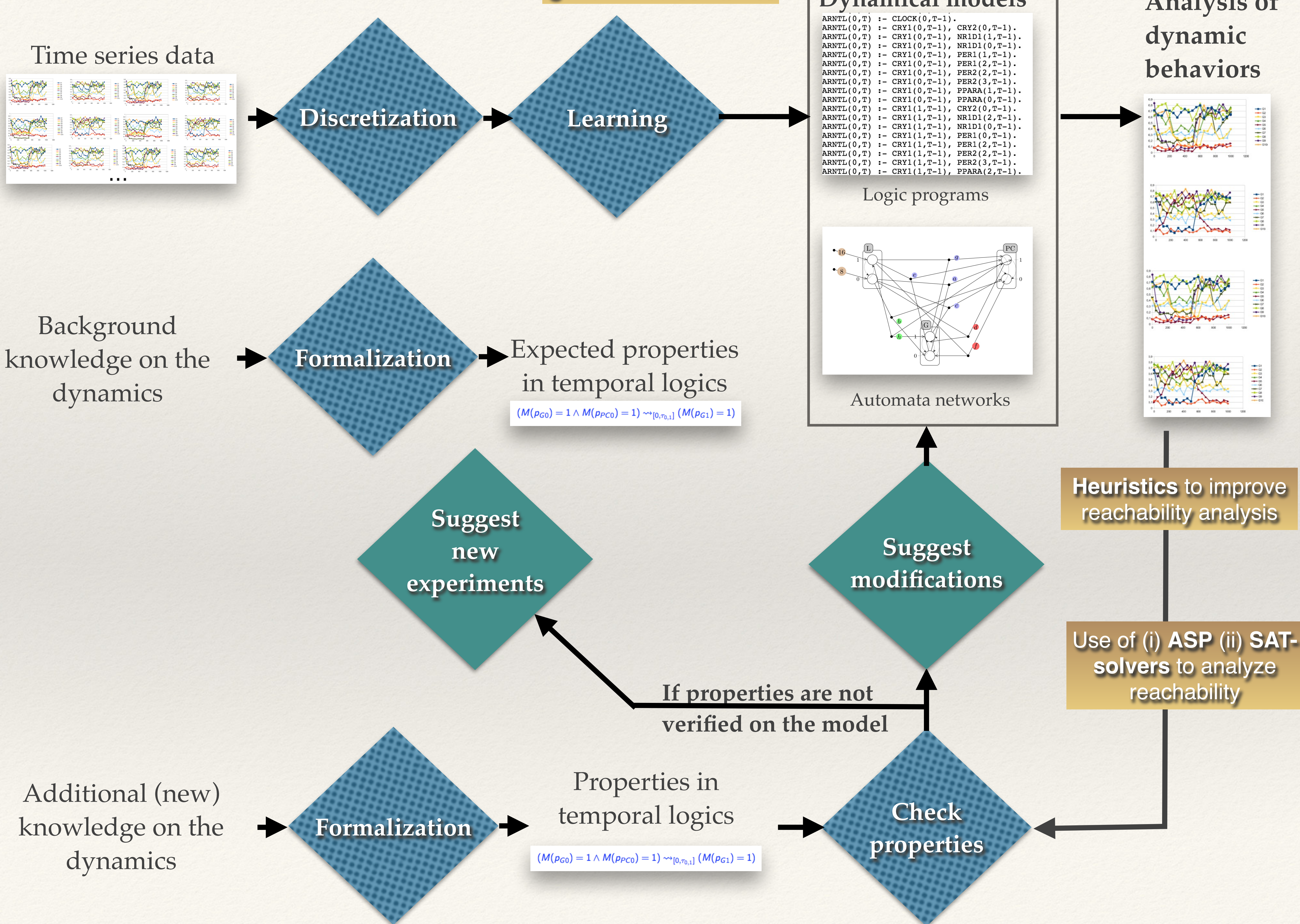
Formalization

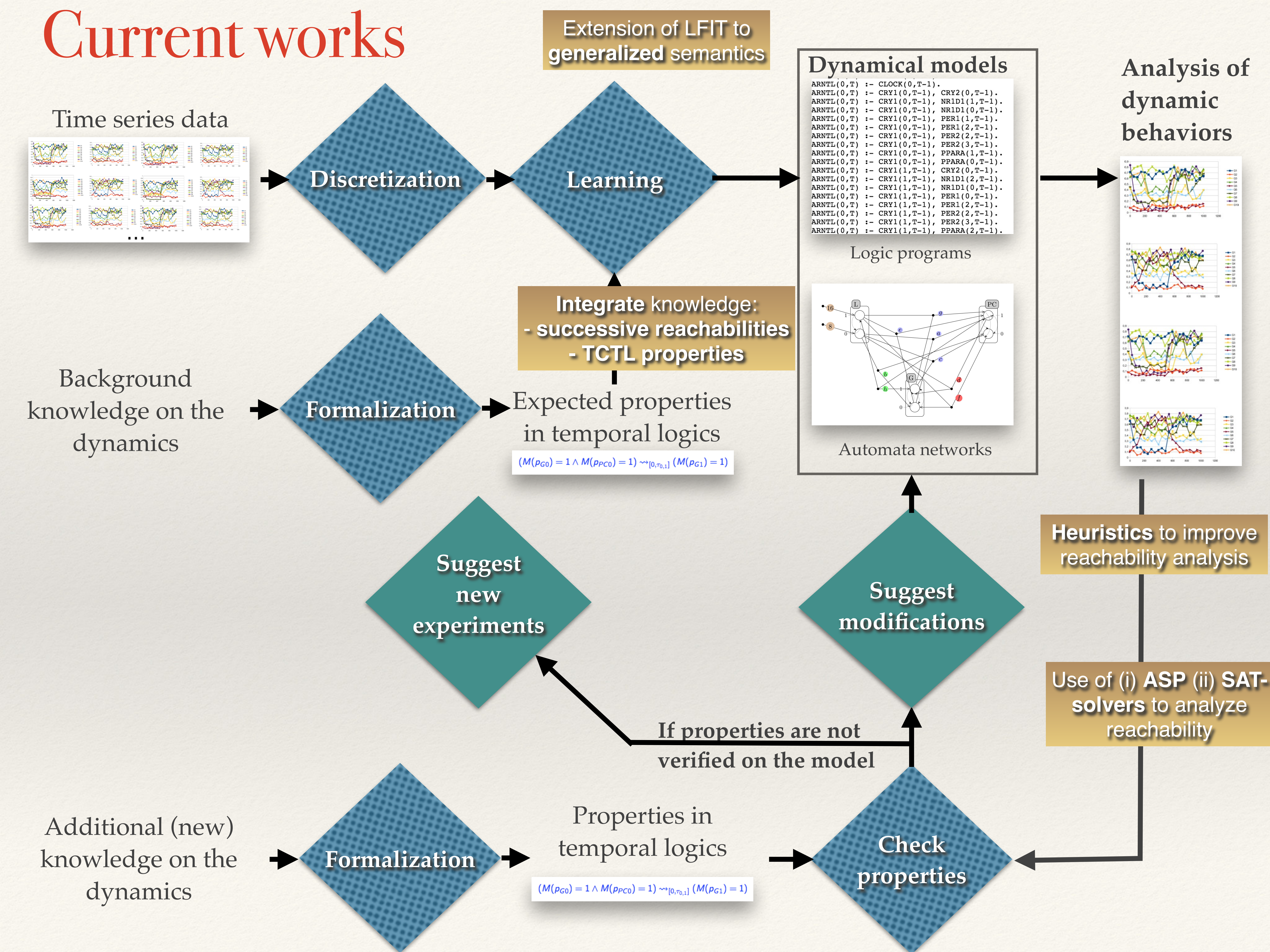
Properties in temporal logics

$(M(p_{G0}) = 1 \wedge M(p_{PC0}) = 1) \rightsquigarrow_{[0,\tau_{0,1}]} (M(p_{G1}) = 1)$

Check properties

Current works




Current works
Extension of LFIT to generalized semantics
Time series data
...
Discretization
Learning
Dynamical models
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ARNTL(0,T) :- CRY1(0,T-1), CRY2(0,T-1).
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ARNTL(0,T) :- CRY1(1,T-1), PPARA(2,T-1).
Logic programs
Automata networks
Analysis of dynamic behaviors
Integrate knowledge:
- successive reachabilities
- TCTL properties
Background knowledge on the dynamics
Formalization
Expected properties in temporal logics
$(M(p_{G0}) = 1 \wedge M(p_{PC0}) = 1) \leadsto_{[0,\tau_{0,1}]} (M(p_{G1}) = 1)$
Heuristics to improve reachability analysis
Suggest new experiments
Suggest modifications
Use of (i) ASP (ii) SAT-solvers to analyze reachability
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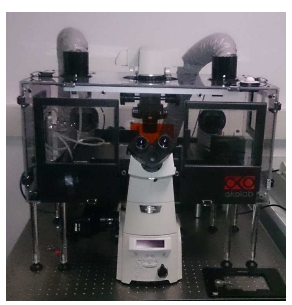
Additional (new) knowledge on the dynamics
Formalization
Properties in temporal logics
$(M(p_{G0}) = 1 \wedge M(p_{PC0}) = 1) \leadsto_{[0,\tau_{0,1}]} (M(p_{G1}) = 1)$
Check properties

With biologists working on radiotherapy

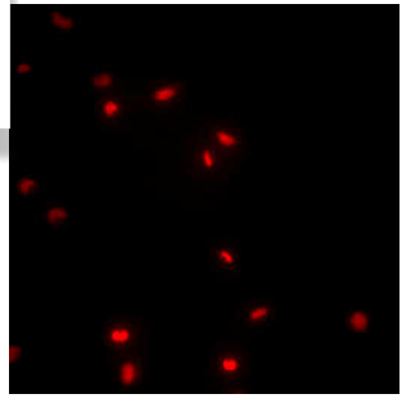
Team of François Paris
(INSERM Nantes)

- Goals:
  - Gain **better knowledge** of the radiobiology in function of the radiation therapy (RT) schemes & time
  - **Assess *in silico* the effects** of new RT protocols, reducing the need of *in vivo* experiments and helping oncologists on their clinical decision allowing personalized treatments

Time lapse



1 image every 10 minutes



1 RT = 1 timelapse

Learning

Each cell has a finite number of states (<10)

Dynamical models

```
ARNTL(0,T) :- CLOCK(0,T-1).
ARNTL(0,T) :- CRY1(0,T-1), CRY2(0,T-1).
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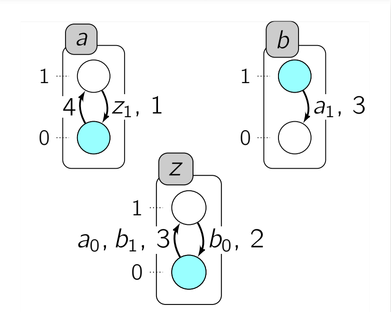
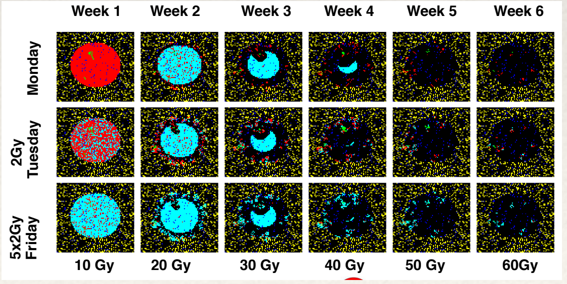
```

Logic program



Automata networks

Simulation of novel radiation protocols

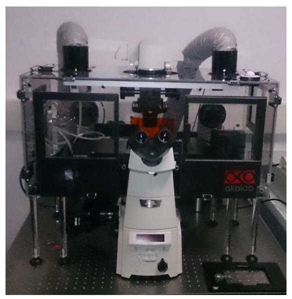


With biologists working on radiotherapy

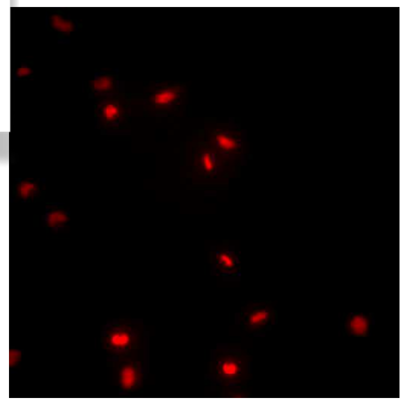
Team of François Paris
(INSERM Nantes)

- New challenges w.r.t. LFIT:
  - Model cell **division** (*mitosis*)
  - Model **spatial interactions** between cells

Time lapse



1 image every
10 minutes



1 RT = 1 timelapse

Learning

Each cell has a
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Dynamical models

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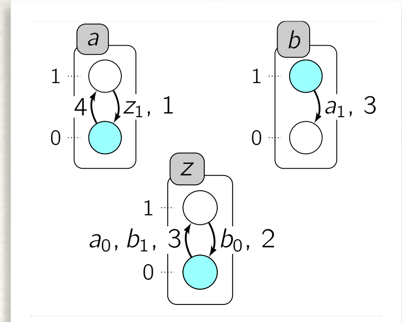
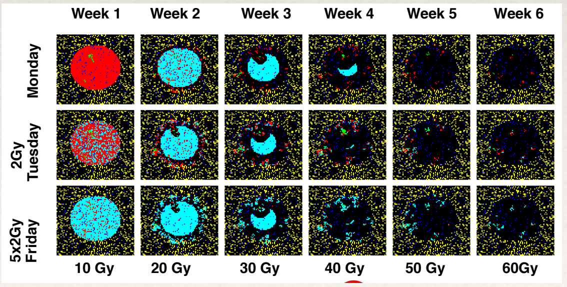
```

Logic program



Automata networks

Simulation of
novel radiation
protocols



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