

– journée bioSTIC de l’I3S –

Modélisation Discrète de Réseaux de Régulation Biologiques

Gilles Bernot – pôle MDSC

Laboratoire I3S



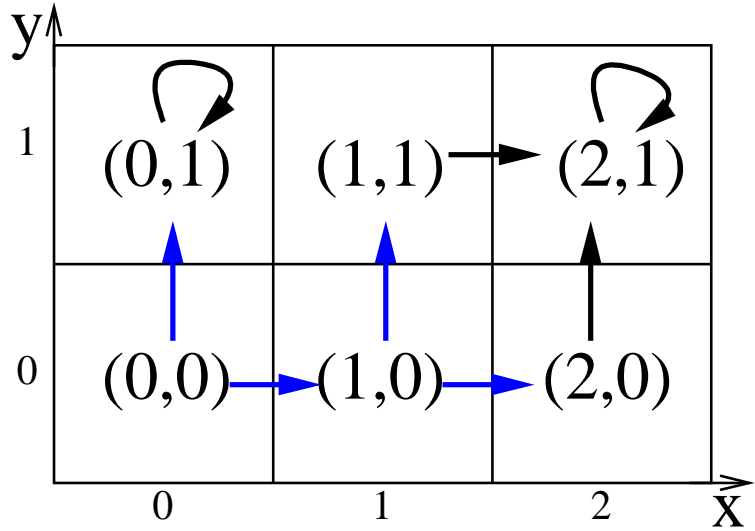
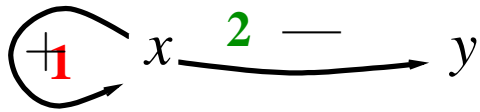
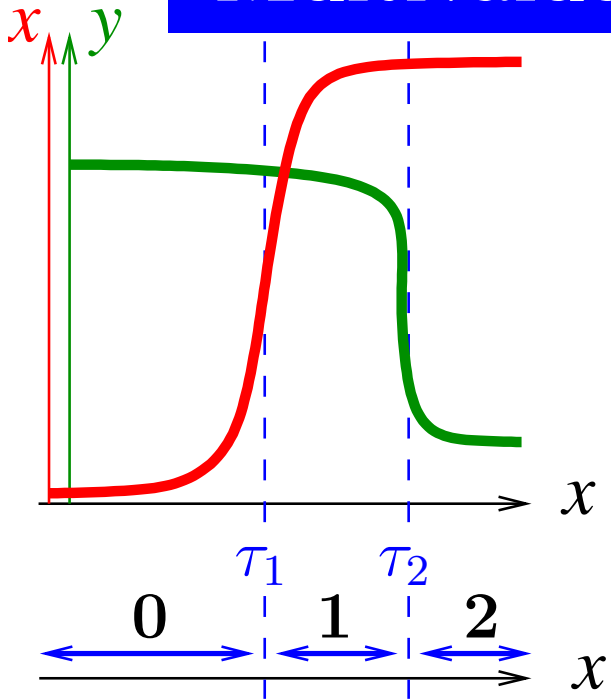
The power of formal logic

“Brute force” simulations are not the only way to use a computer. We can offer computer aided environments which help:

- to choose an appropriate abstraction level, avoiding models that can be “tuned” *ad libitum*
- to automatically deduce model parameters from known behaviours
- to characterise the possible behaviours from the model shape
- to define only models that could be experimentally refuted
- to prove refutability w.r.t. experimental capabilities
- to validate models with a reasonable number of experiments

Multivalued Regulatory Graphs

René Thomas (seventies)



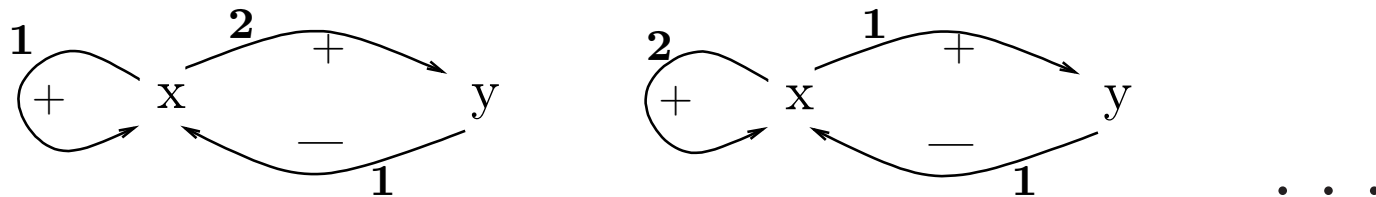
Computer Aided Elaboration of Models

From biological knowledge and/or biological hypotheses, it comes:

- **properties Φ :**

“If gene x has its basal expression level, it remains at this level.”

- **model shapes \mathcal{M} :**



1. **Is it possible that Φ and \mathcal{M} ? Consistency** of knowledge and hypotheses. ($\exists? M \in \mathcal{M} \mid M \models \varphi$)
2. **If so, is it true *in vivo* that Φ and \mathcal{M} ?** Propose experiments to **refute** the selected model(s).

→ Computer aided *proofs* and *validations*

CTL = Computation Tree Logic

Atoms = comparisons : $(x=2)$ $(y>0)$...

Logical connectives: $(\varphi_1 \wedge \varphi_2)$ $(\varphi_1 \implies \varphi_2)$...

Temporal connectives: made of 2 characters

<u>first character</u>	<u>second character</u>
A = for A ll path choices	X = ne X t state
E = there E xist a choice	F = some F uture state
	G = all future states (G lobally)
	U = U ntil

$AX(y = 1)$: the concentration level of y belongs to the interval 1 in all states directly following the considered initial state.

$EG(x = 0)$: there exists at least one path from the considered initial state where x always belongs to its lower interval.

CTL to encode Biological Properties

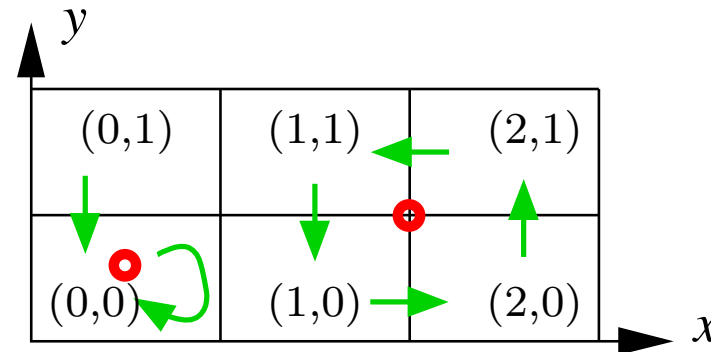
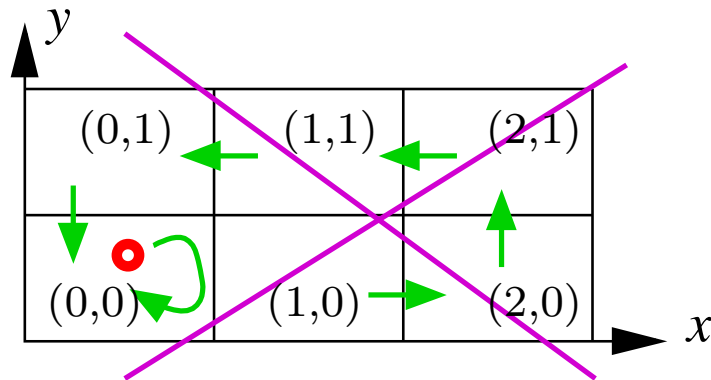
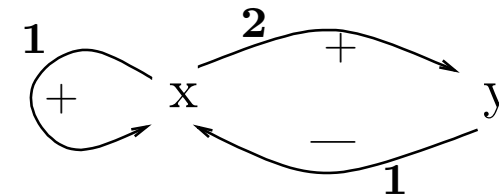
Common properties:

“functionality” of a sub-graph

Special role of “feedback loops”

– positive: *multistationnarity* (even number of —)

– negative: *homeostasis* (odd number of —)



Characteristic properties: $\left\{ \begin{array}{l} (x = 2) \implies AG(\neg(x = 0)) \\ (x = 0) \implies AG(\neg(x = 2)) \end{array} \right.$

Model Checking *solves the consistency question: SMBioNet*

Theoretical Models \leftrightarrow Experiments

CTL formulae are satisfied (or refuted) w.r.t. a set of paths from a given initial state

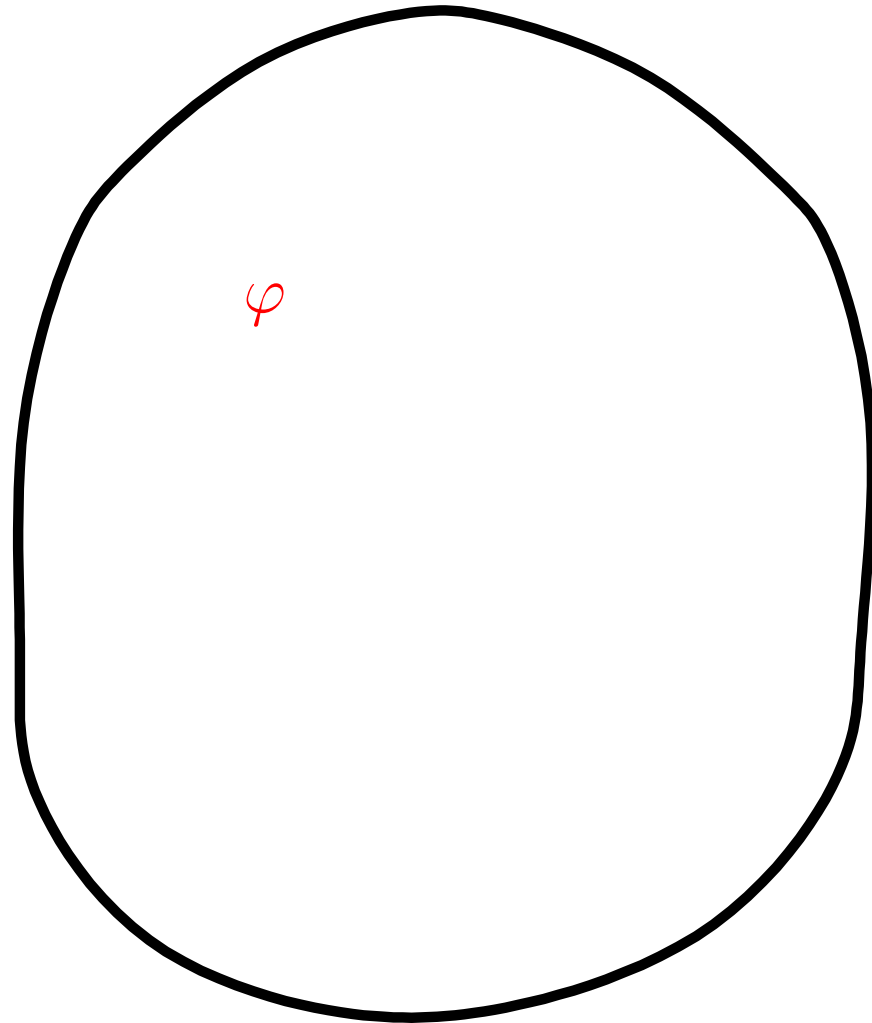
- They can be tested against the possible paths of the theoretical models ($M \models_{Model\ Checking} \varphi$)
- They can be tested against the biological experiments ($Biological_Object \models_{Experiment} \varphi$)

CTL formulae link theoretical models and biological objects together

Generation of biological experiments (1)

Set of all the formulae:

φ = hypothesis

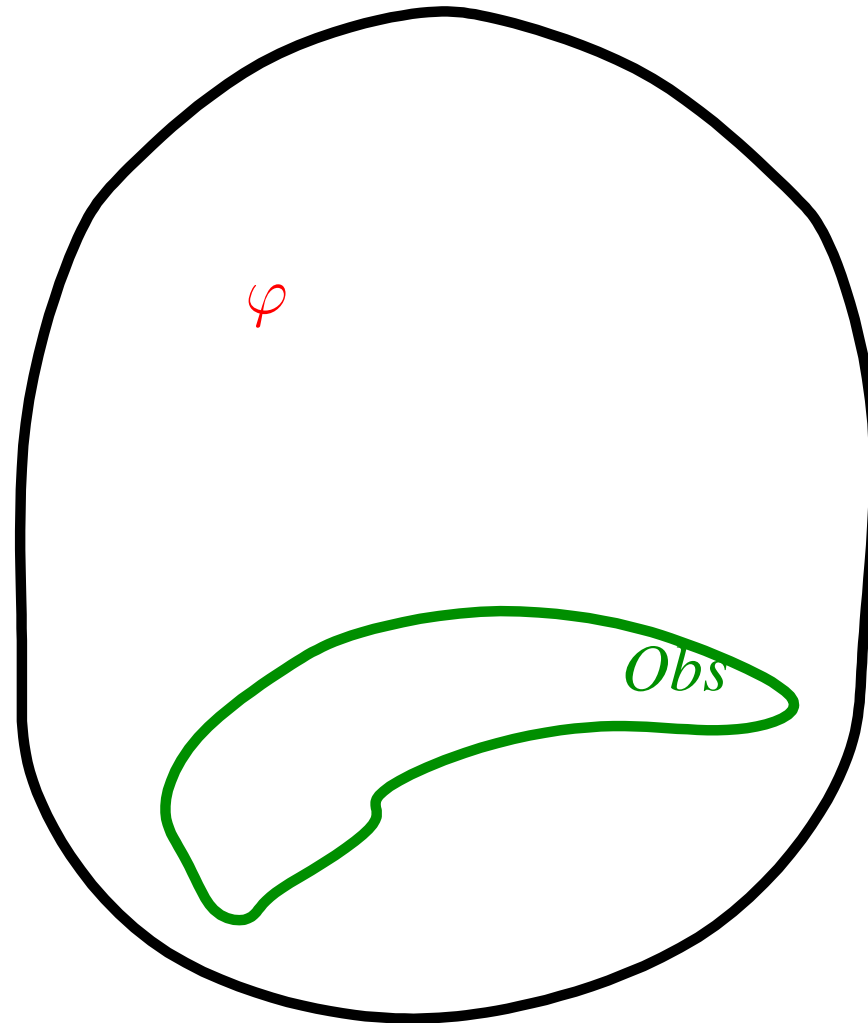


Generation of biological experiments (2)

Set of all the formulae:

φ = hypothesis

Obs = possible experiments



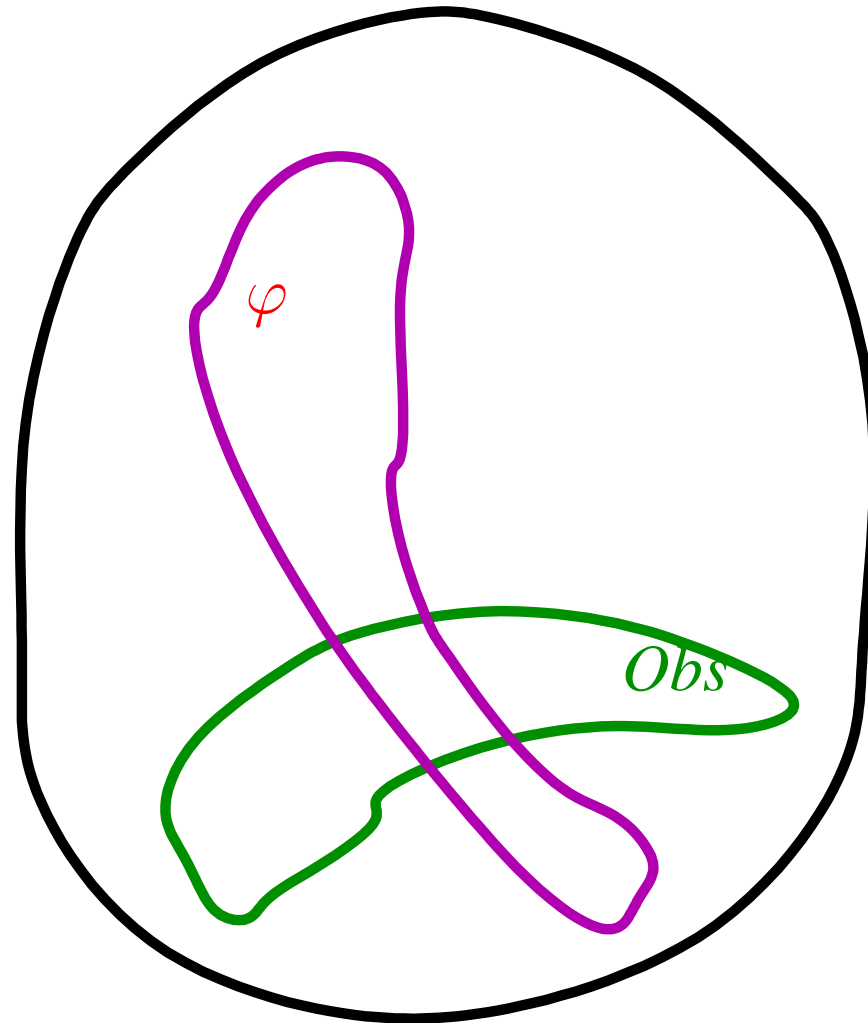
Generation of biological experiments (3)

Set of all the formulae:

φ = hypothesis

Obs = possible experiments

$Th(\varphi)$ = φ inferences



Generation of biological experiments (4)

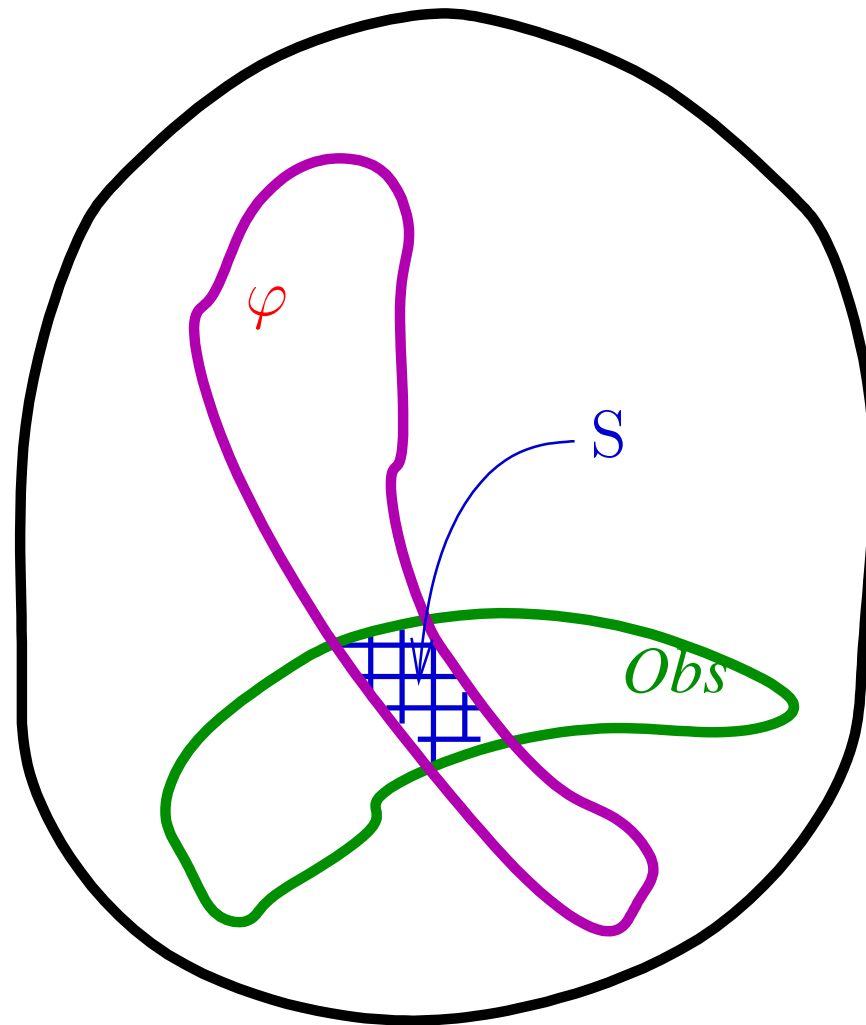
Set of all the formulae:

φ = hypothesis

Obs = possible experiments

$Th(\varphi)$ = φ inferences

S = sensible experiments



Generation of biological experiments (5)

Set of all the formulae:

φ = hypothesis

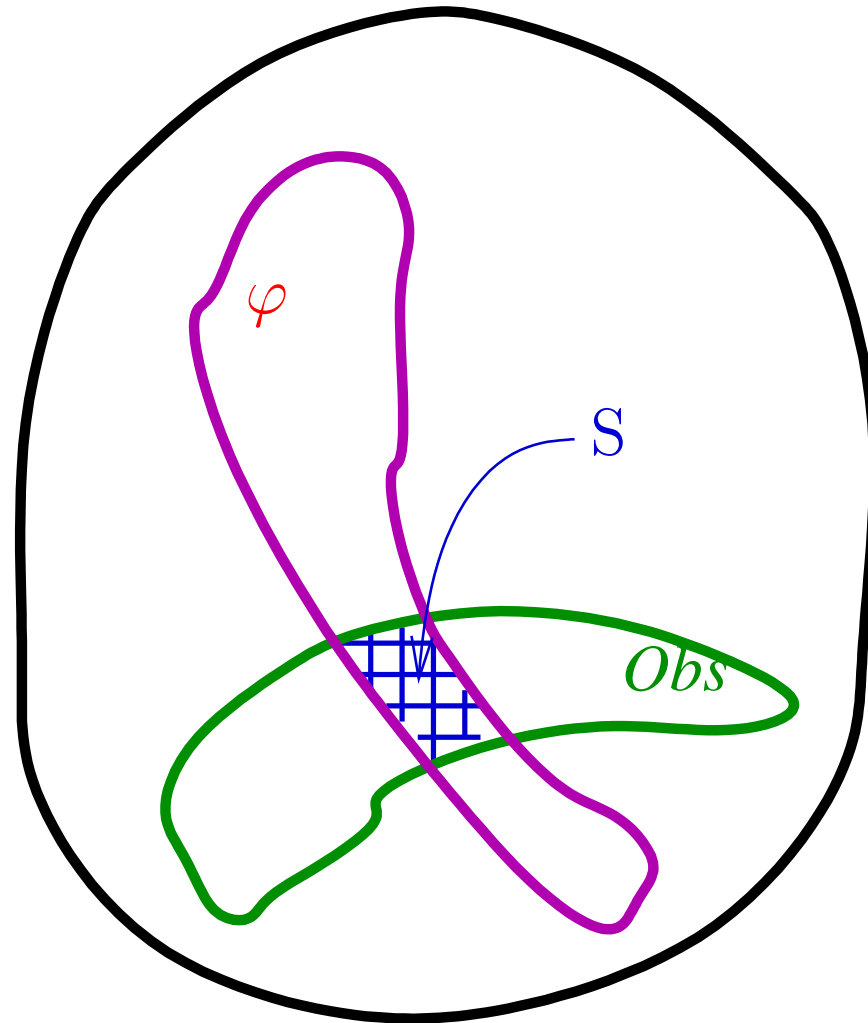
Obs = possible experiments

$Th(\varphi)$ = φ inferences

S = sensible experiments

Refutability:

$$S \implies \varphi ?$$



Generation of biological experiments

Set of all the formulae:

φ = hypothesis

Obs = possible experiments

$Th(\varphi)$ = φ inferences

S = sensible experiments

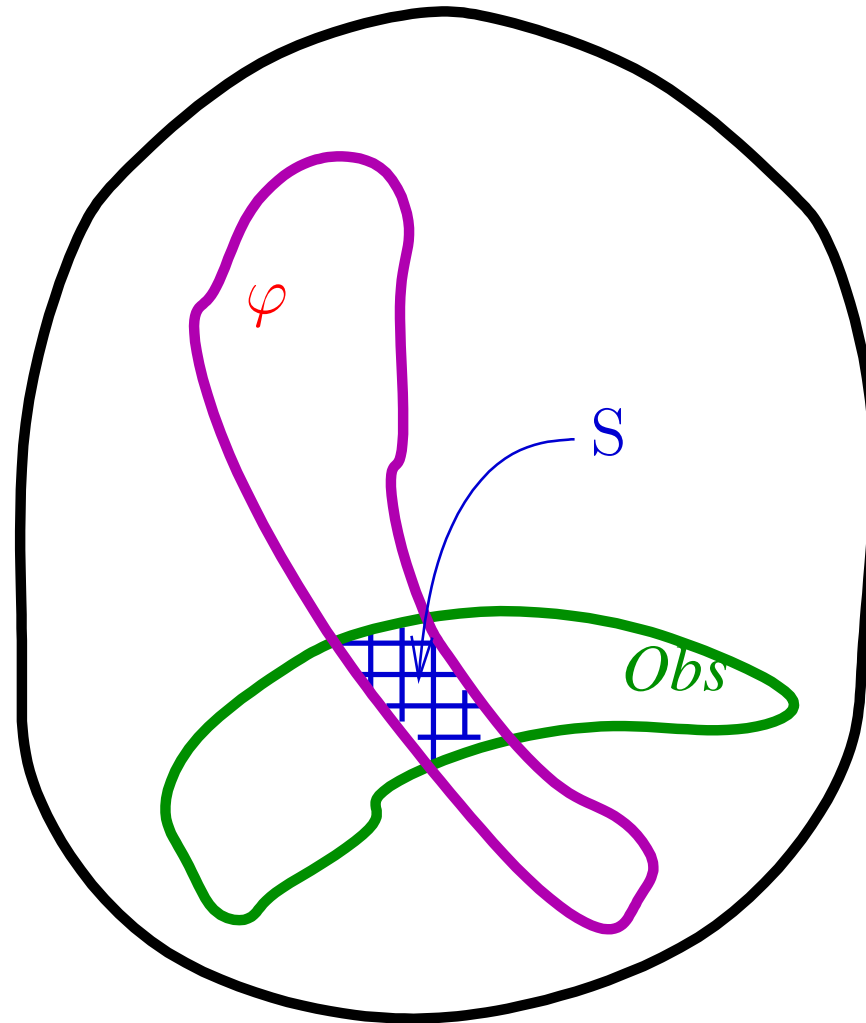
Refutability:

$$S \implies \varphi ?$$

Best refutations:

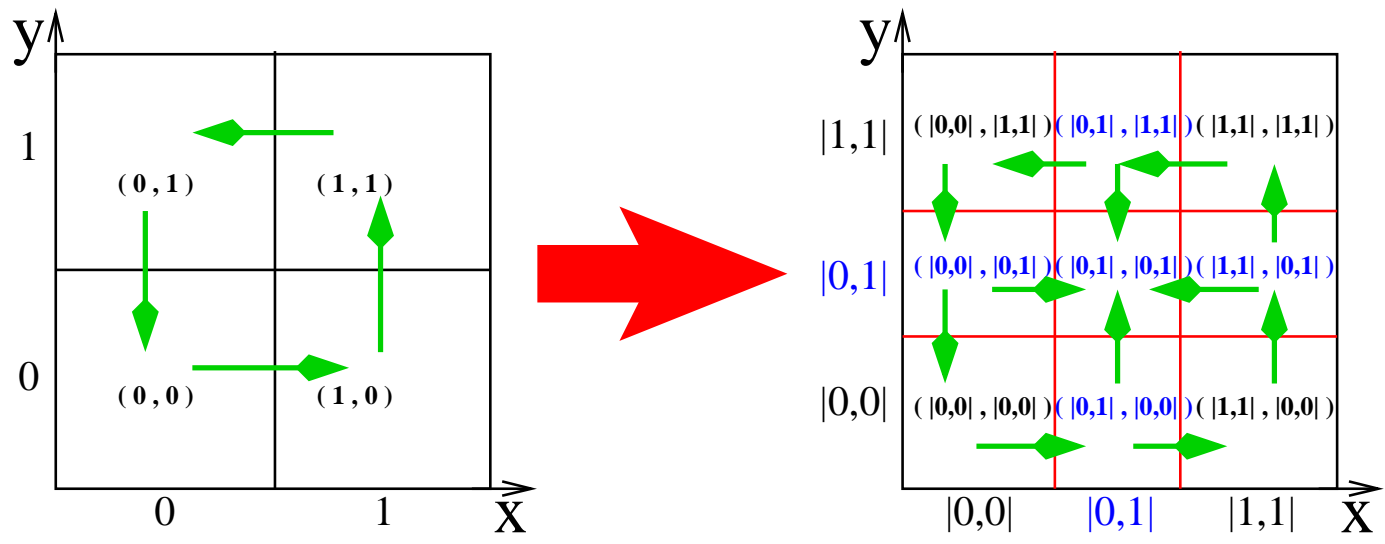
Choice of experiments in S ?

... optimisations



Research topics (1)

Explicit singular states:

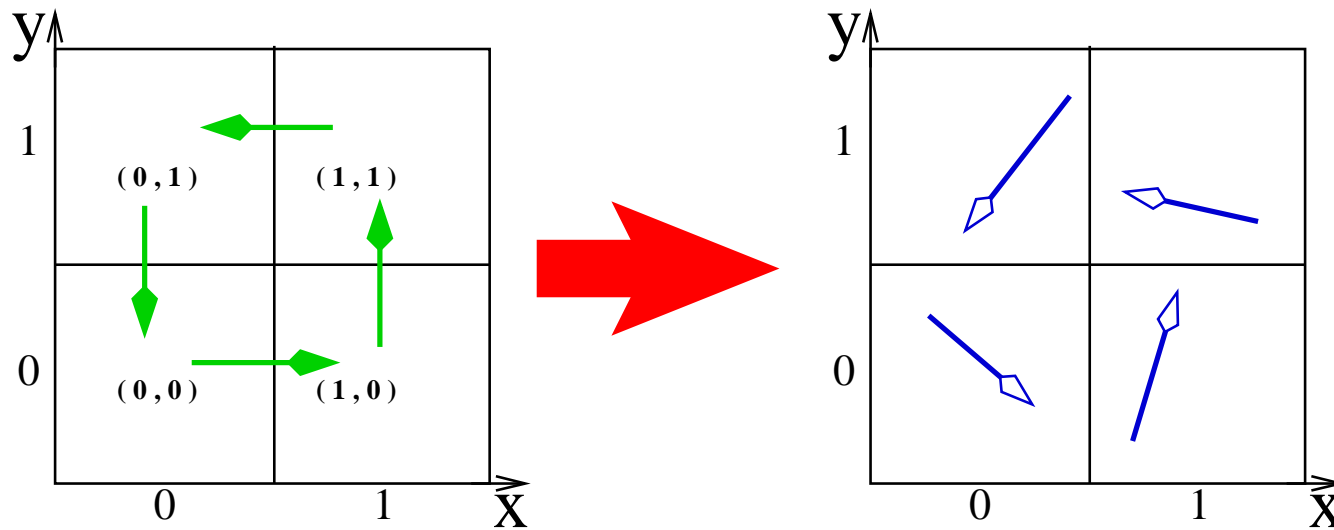


e.g. to distinguish stable states from limit cycles

Research topics (2)

Hybrid approaches:

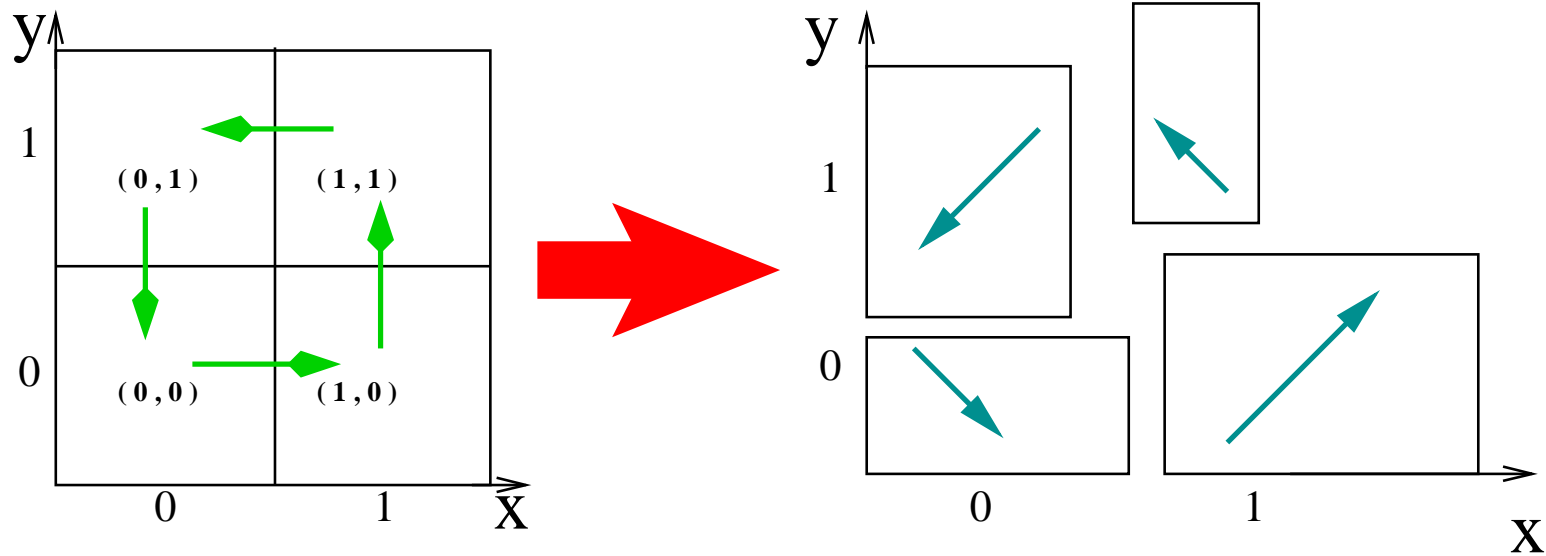
simplified trajectories which locally approximate differential equations



(e.g. linear)

Research topics (3)

Time delays:

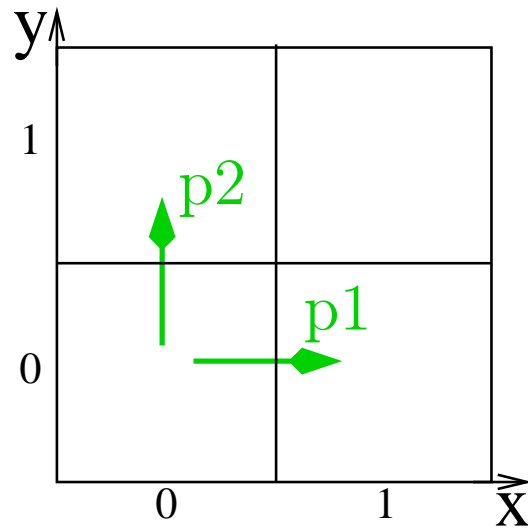


(size of rectangular areas = delays)

Requires constraint solving

Research topics (4)

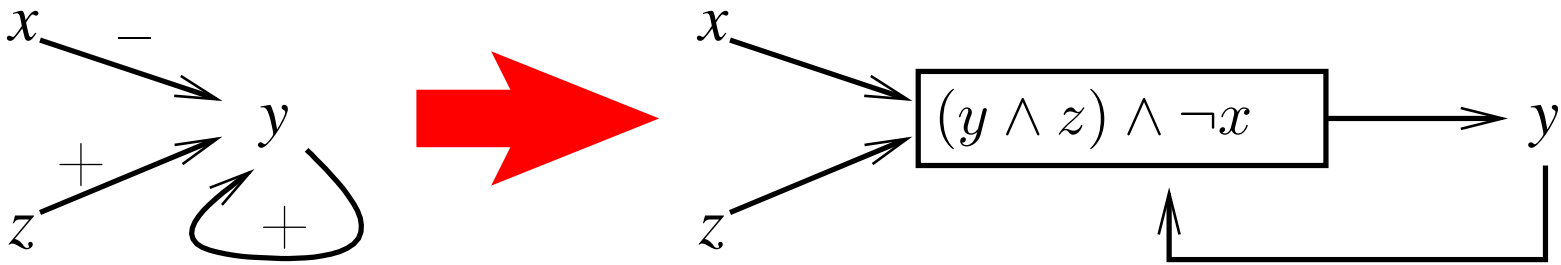
Stochastic approaches:



More or less dual to delays

Research topics (5)

Networks with multiplexes:



Explicit encoding of knowledge on cooperations

Research topics (6)

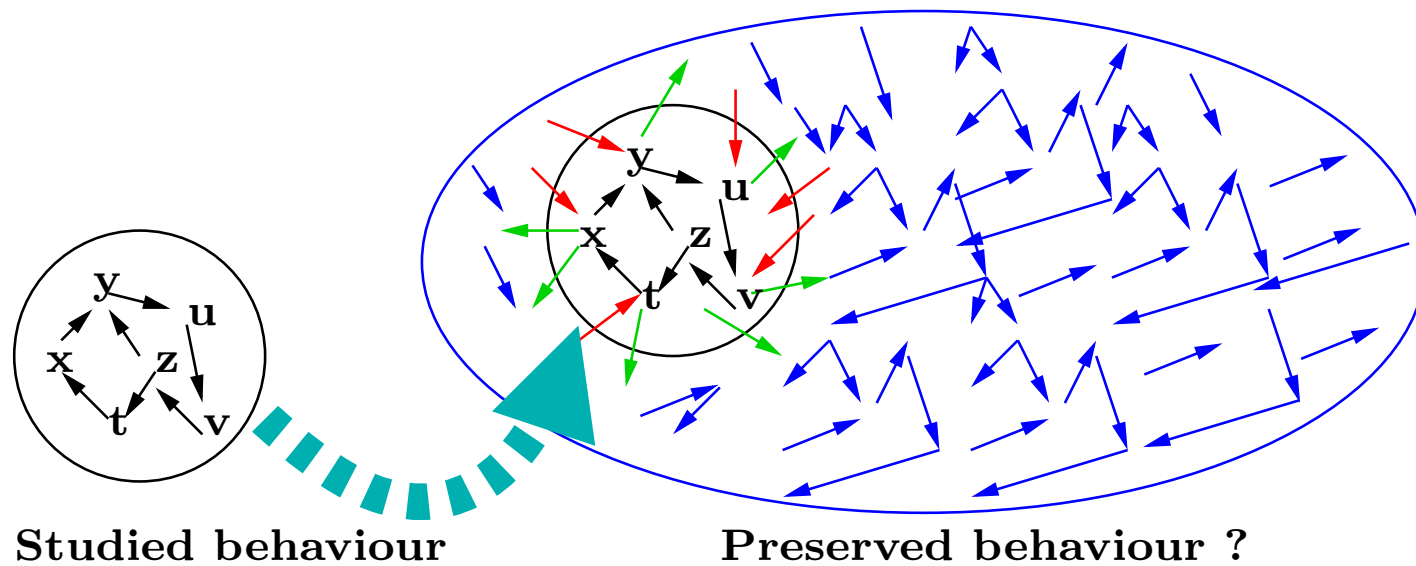
From static shapes to properties on dynamics:

- positive/negative cycles and epigenesis/homeostasis
- maximum number of attraction basins
- ...

Mathematical proofs similar to the ones for cellular automaton

Research topics (7)

Embeddings of Regulatory Networks:



Necessary and sufficient condition on the *local* dynamics of the “input frontier”

Offers a methodology to identify interesting sub-networks

Concluding Comments

Models to encode already elucidated biological models *v.s.*
modelling methods to help discovery in biology...

Behavioural *properties* (Φ) are as much important as *models* (\mathcal{M})

Modelling is significant only with respect to the considered
experimental *reachability* and *observability* (*Obs*)

Formal proofs can suggest wet experiments