~~Benzo[a]pyrene detox~~

Property Driven Models: Experimental Validations and Simplifications

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cnrs dépasser les frontières

Menu

1. Models and Formal Logic
2. Gene Networks and Temporal Logic
3. Extracting Experiments from Models
4. Model Simplifications
5. Circadian Circle, Seasons and Jet-lag

Mathematical models: what for ?

- Models as "Data Base" to store biological knowledge
- Models as design tools
- Models as logical analysis of causality chains
- Models as guidelines for the choice of experiments

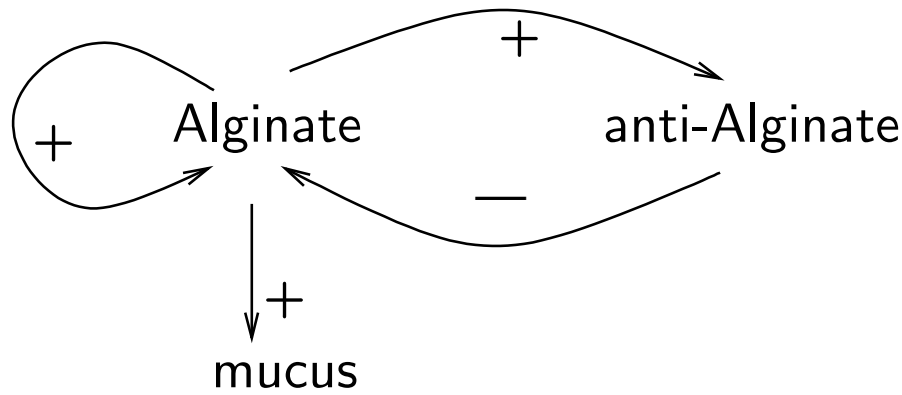
For the 2 last purposes, models can deviate far from biological descriptions but remain very useful: "Kleenex" models !

Static Graph *v.s.* Dynamic Behaviour

Difficulty to predict the result of combined regulations

Difficulty to measure the strength of a given regulation

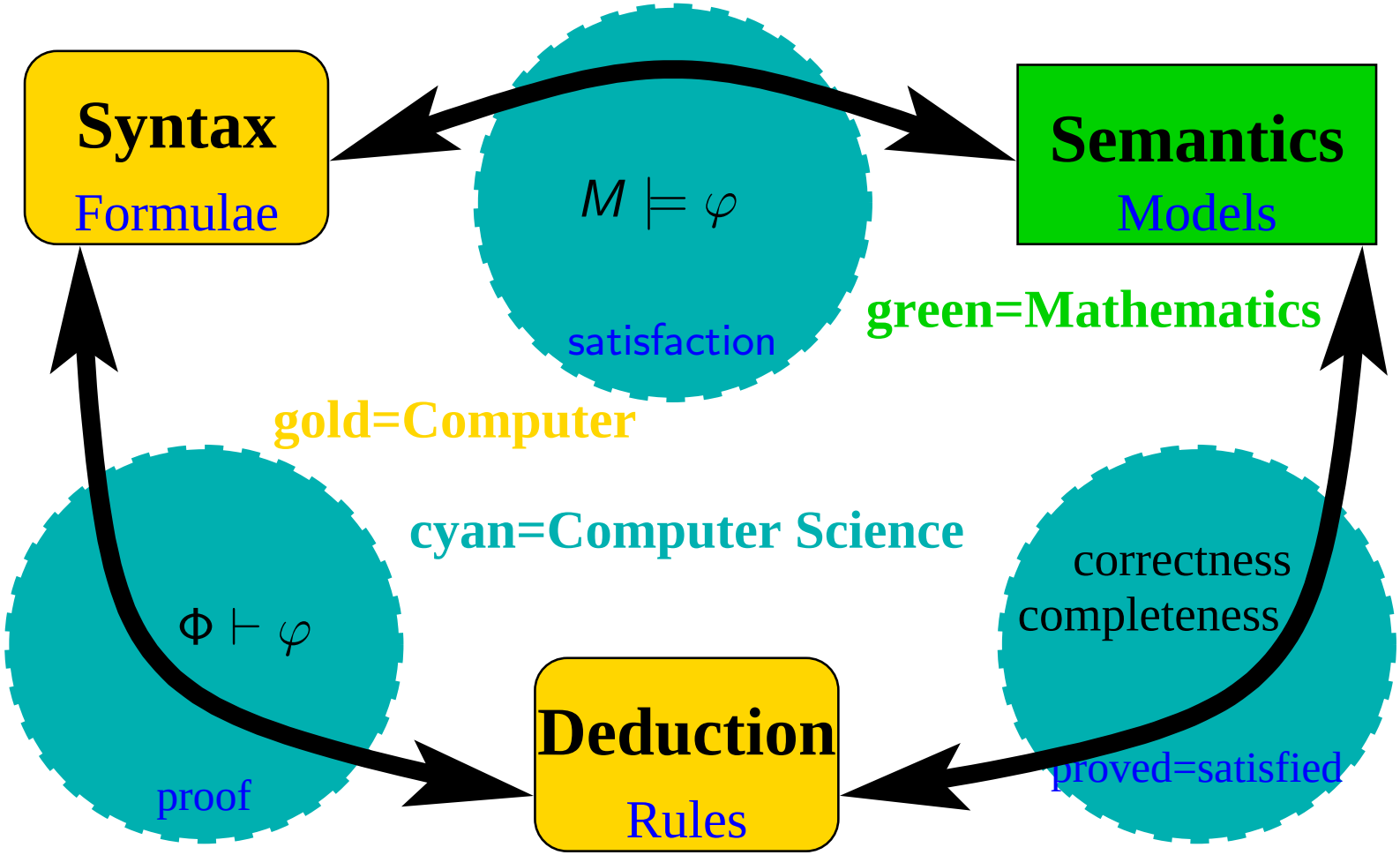
Example of "competitor" circuits



Multistationarity ?
Homeostasy ?

Many underlying models $\approx$ *700 qualitative behaviours*

Formal Logic: syntax/semantics/deduction



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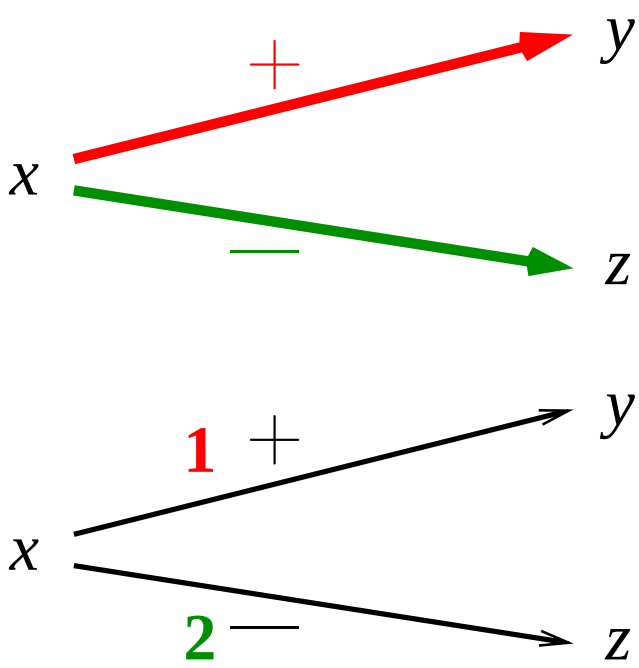
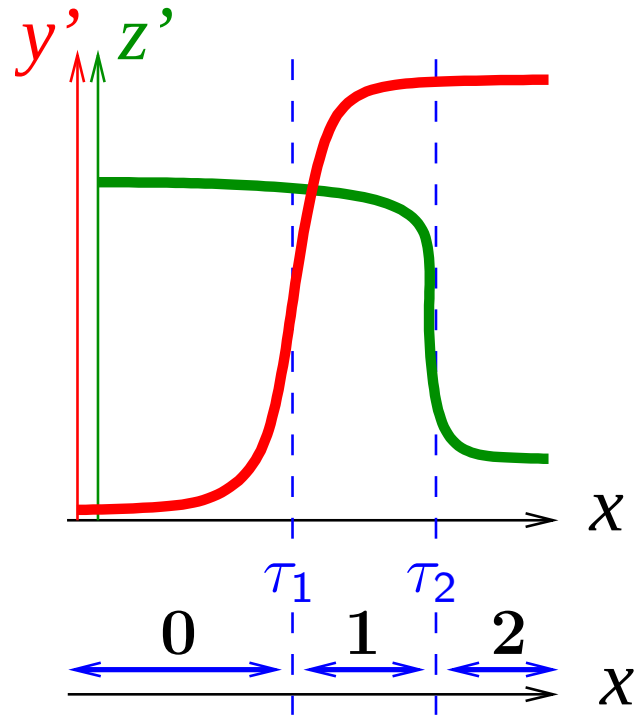
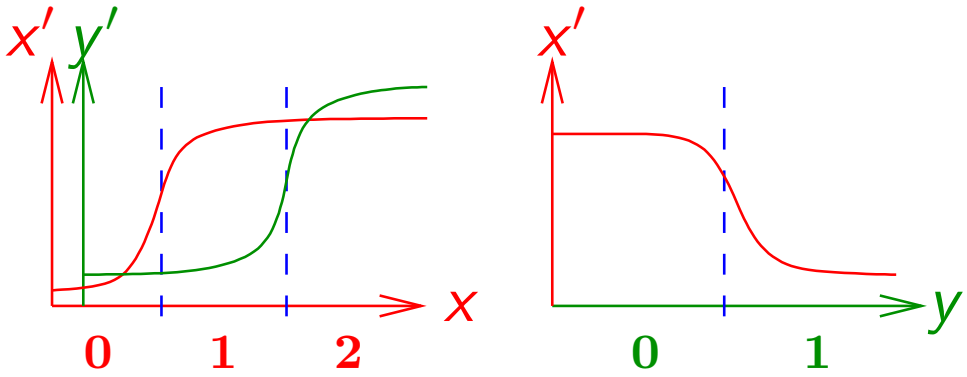
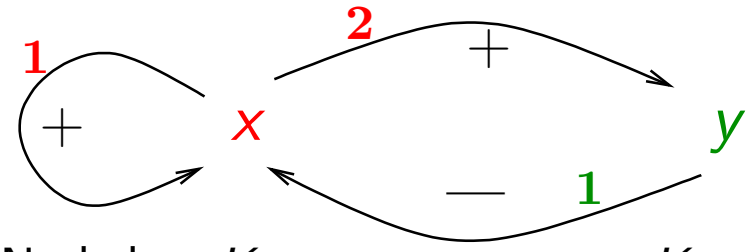
Multivalued Regulatory Graphs





Regulatory Networks (R. Thomas)





No help : K_x K_y

x helps : $K_{x,x}$ $K_{y,x}$

Absent y helps : $K_{x,\overline{y}}$

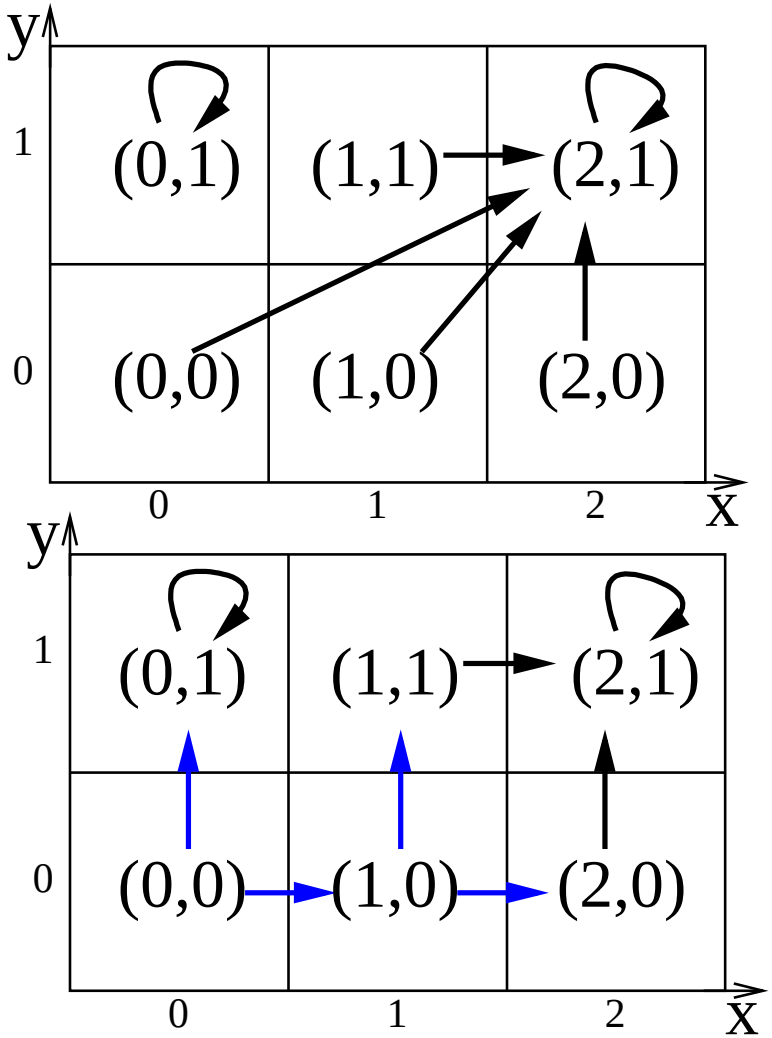
Both : $K_{x,x\overline{y}}$

(x,y)	*Focal Point*
(0,0)	$(K_{x,\overline{y}}, K_y)$
(0,1)	(K_x, K_y)
(1,0)	$(K_{x,x\overline{y}}, K_y)$
(1,1)	$(K_{x,x}, K_y)$
(2,0)	$(K_{x,x\overline{y}}, K_{y,x})$
(2,1)	$(K_{x,x}, K_{y,x})$

State Graphs

(x,y)	*Focal Point*
(0,0)	$(K_{x,\overline{y}}, K_y)=(2,1)$
(0,1)	$(K_x, K_y)=(0,1)$
(1,0)	$(K_{x,x\overline{y}}, K_y)=(2,1)$
(1,1)	$(K_{x,x}, K_y)=(2,1)$
(2,0)	$(K_{x,x\overline{y}}, K_{y,x})=(2,1)$
(2,1)	$(K_{x,x}, K_{y,x})=(2,1)$

"desynchronization" $\longrightarrow$
by units of Manhattan distance



CTL = Computation Tree Logic

Atoms = comparaisons : (x=2) (y>0) ...

Logical connectives: $(\varphi_1 \wedge \varphi_2)$ $(\varphi_1 \Longrightarrow \varphi_2)$ $\cdots$

Temporal modalities: made of 2 characters

first character	second character
A = for **A**ll path choices	X = ne**X**t state
	F = for some **F**uture state
E = there **E**xist a choice	G = for 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

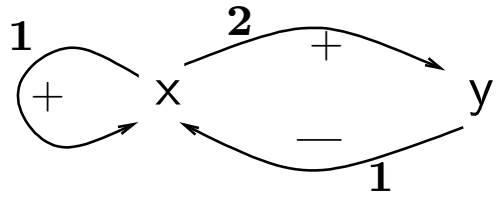
Common properties:

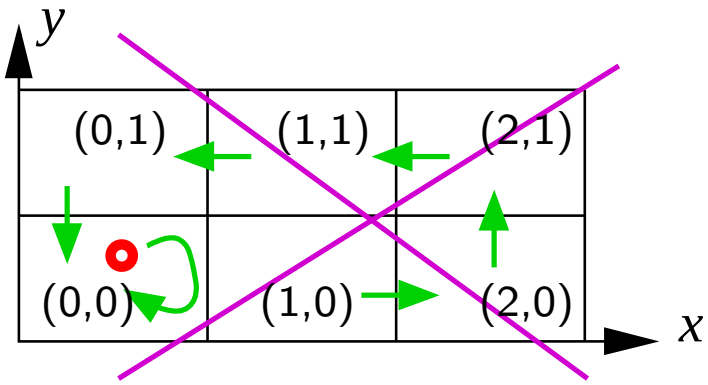
"functionality" of a sub-graph

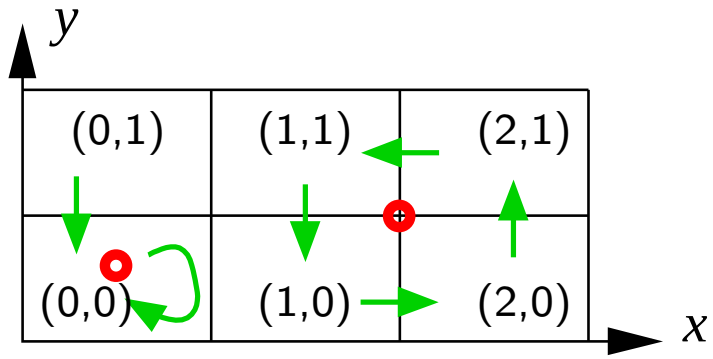
Special role of "feedback loops"

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

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







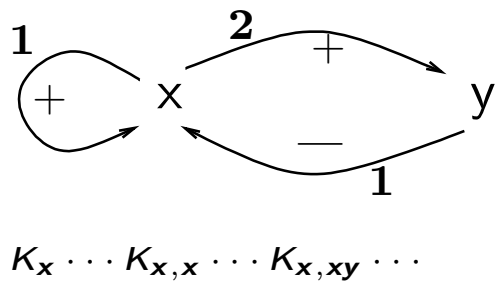
Characteristic properties: $\begin{cases} (x = 2) \Longrightarrow AG(\neg(x = 0)) \\ (x = 0) \Longrightarrow AG(\neg(x = 2)) \end{cases}$

They express *"the positive feedback loop is functional"*

(satisfaction of these formulae relies on the parameters $K_{...}$)

The Two Questions

$\Phi = \{\varphi_1, \varphi_2, \cdots, \varphi_n, H\}$ and $\mathcal{M} =$



. . .

1. Is it possible that Φ and $\mathcal{M}$?
   Consistency of knowledge and hypotheses. Means to select models belonging to the schemas that satisfy Φ.
   $(\exists ?\ M \in \mathcal{M} \ \mid \ M \models \Phi)$
2. If so, is it true *in vivo* that Φ and $\mathcal{M}$?
   Compatibility of one of the selected models with the biological object. Require to propose experiments to **validate** or **refute** the selected model(s).

$\rightarrow$ Computer aided *proofs* and *validations*

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 is a bridge between theoretical models and biological objects

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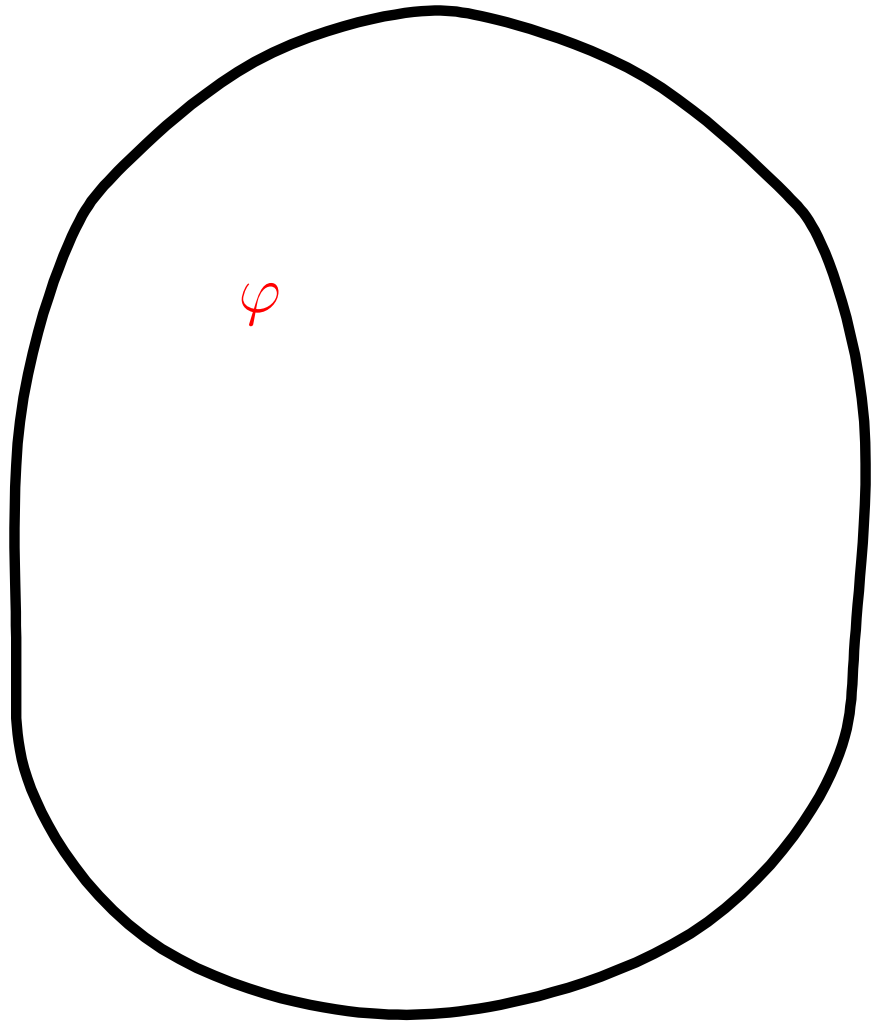
Generation of biological experiments (1)

Set of all the formulae:

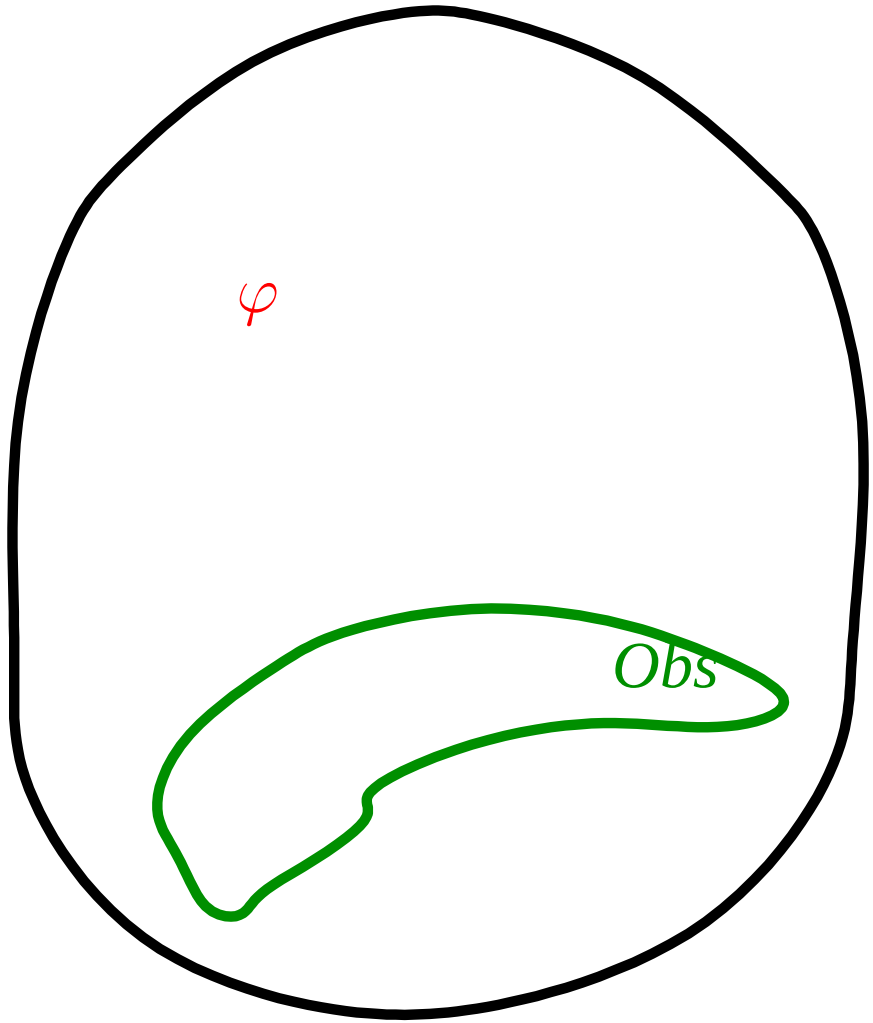
φ = hypothesis



Generation of biological experiments (2)

Set of all the formulae:

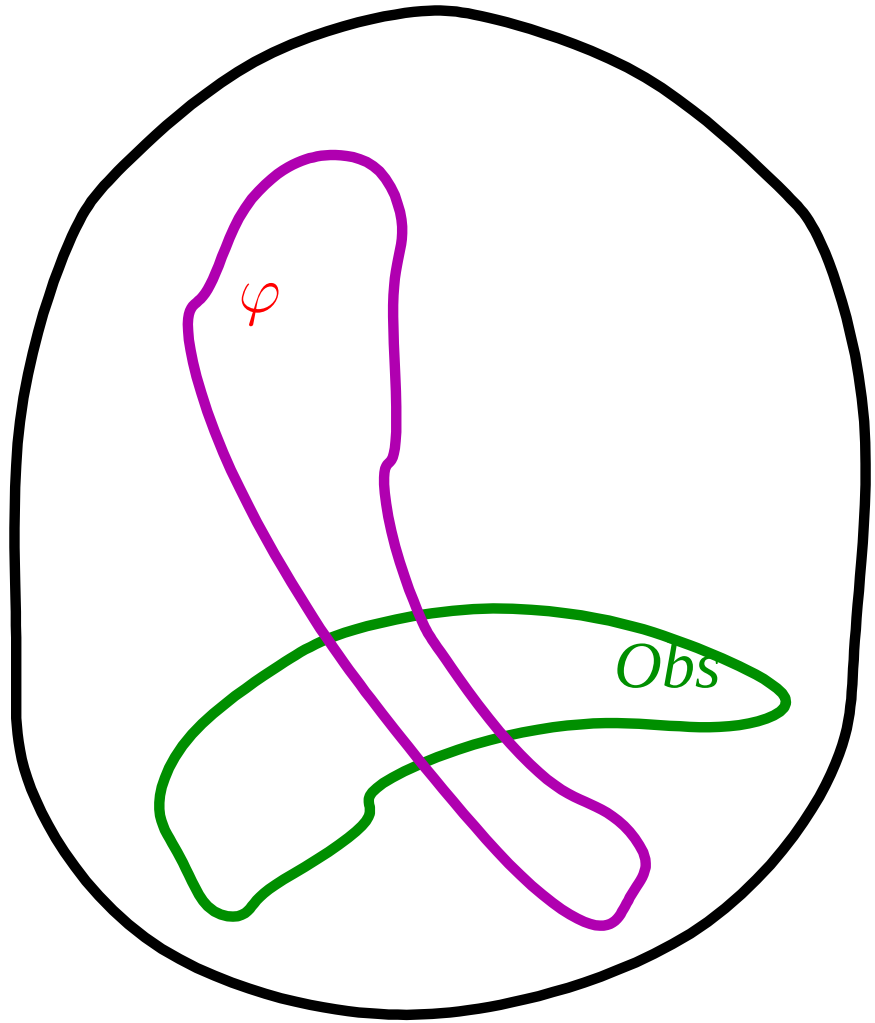
φ = hypothesis
Obs = possible experiments



Generation of biological experiments (3)

Set of all the formulae:

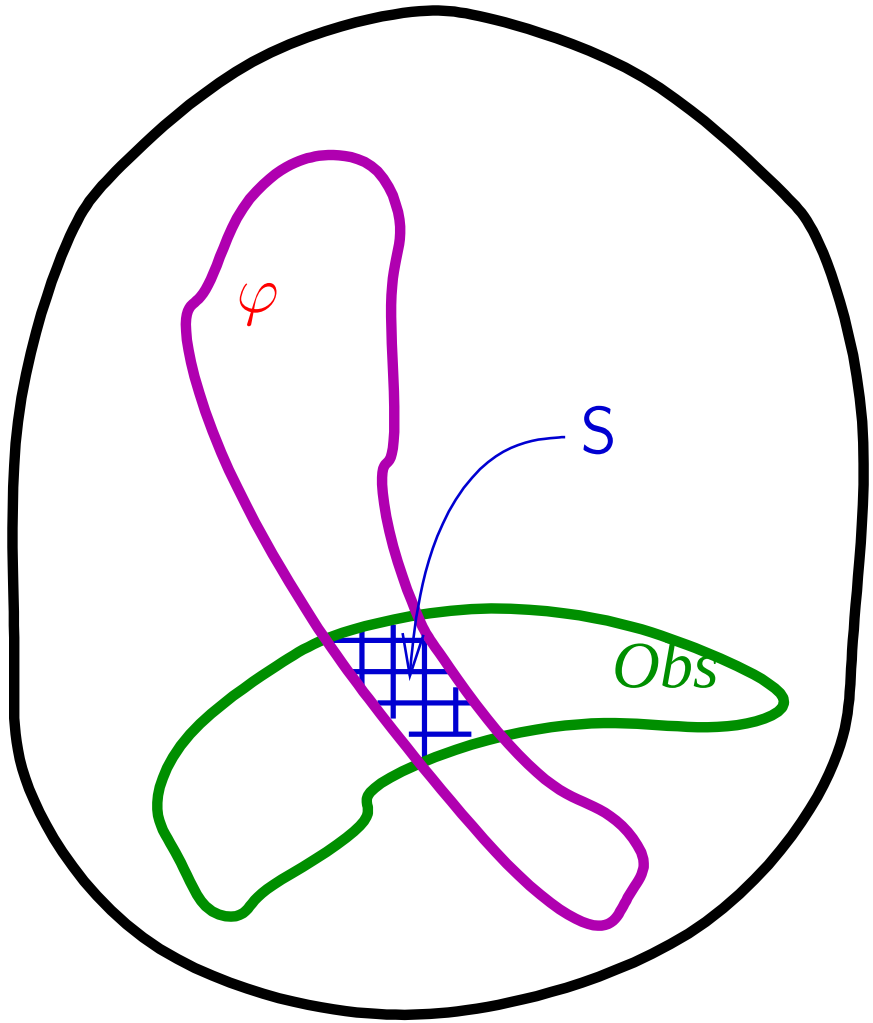
φ = hypothesis
Obs = possible experiments
$Th(\varphi)$ = φ inferences



Generation of biological experiments (4)

Set of all the formulae:

φ = hypothesis
Obs = possible experiments
$Th(\varphi)$ = φ inferences
S = sensible experiments



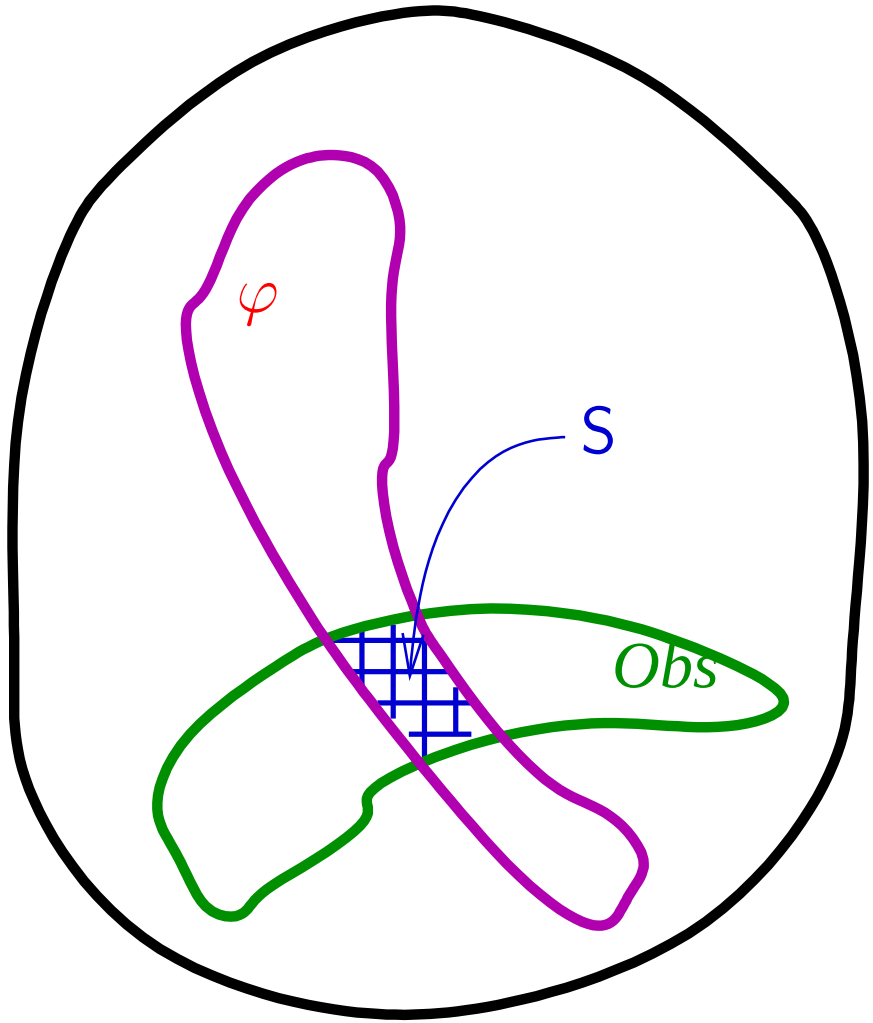
Generation of biological experiments (5)

Set of all the formulae:

φ = hypothesis
Obs = possible experiments
$Th(\varphi)$ = φ inferences
S = sensible experiments

Refutability:

$$S \Longrightarrow \varphi \ ?$$



Generation of biological experiments

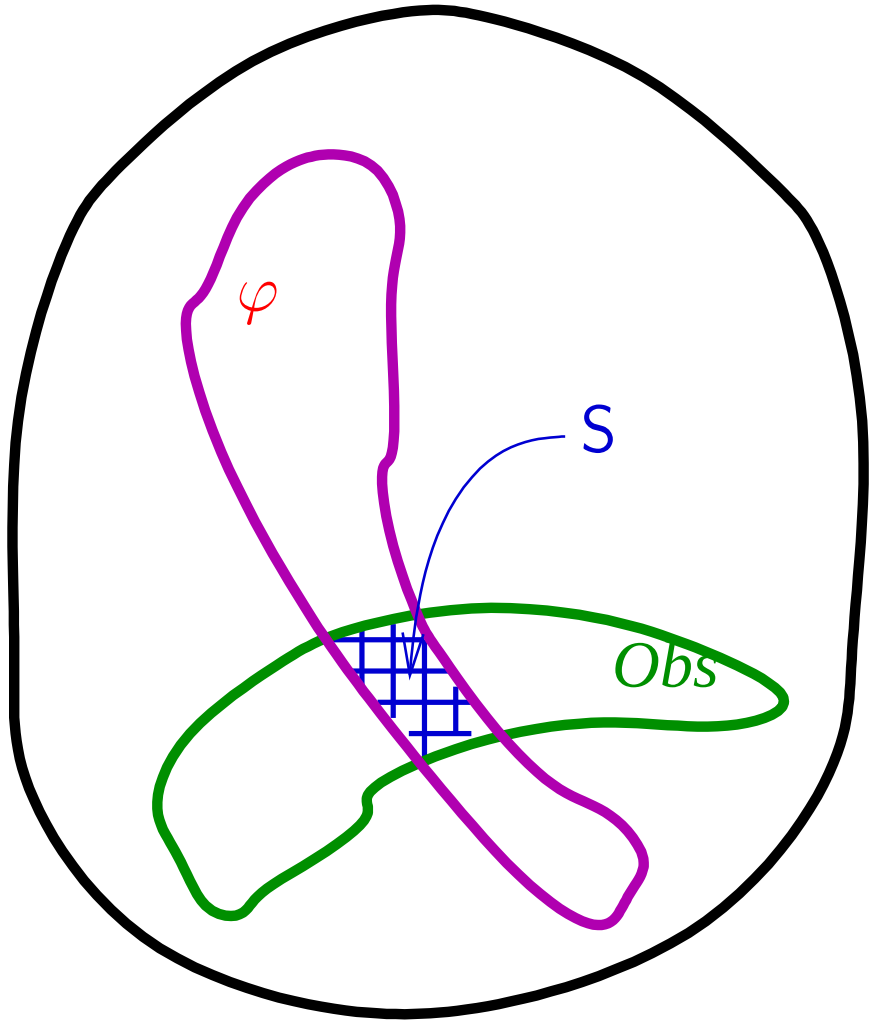
Set of all the formulae:

φ = hypothesis
Obs = possible experiments
$Th(\varphi)$ = φ inferences
S = sensible experiments

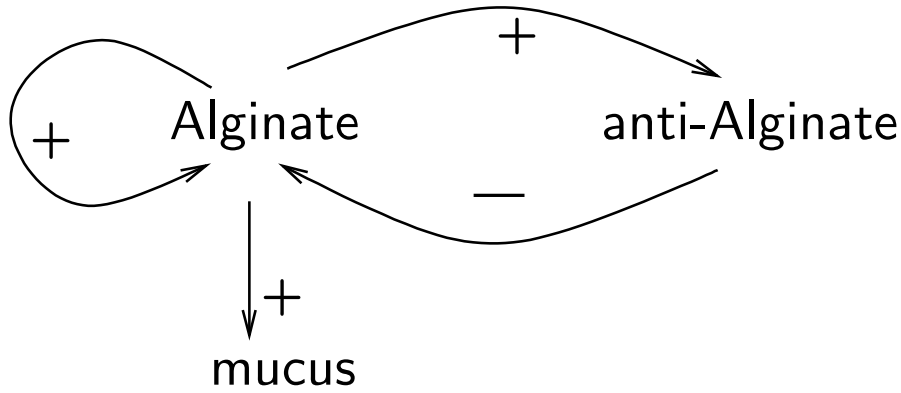
Refutability:

$$S \Longrightarrow \varphi \ ?$$

Best refutations:
Choice of experiments in S ?
. . . optimisations



How to validate a multistationnarity



Hypotheses: $\begin{cases} (Alginate = 2) \Longrightarrow AG(Alginate = 2) \\ (Alginate = 0) \Longrightarrow AG(Alginate < 2) \end{cases}$

Assume that only *mucus* can be observed:

Lemma: $AG(Alginate = 2) \Longleftrightarrow AFAG(mucus = 1)$

(. . . formal proof by computer . . .)

$\rightarrow$ To validate: $(Alginate = 2) \Longrightarrow AXAG(mucus = 1)$

$(Alginate = 2) \Longrightarrow AXAG(mucus = 1)$

$A \Longrightarrow B$	*true*	*false*
true	true	false
false	true	true

Karl Popper:

to validate = to try to refute

thus A=false is useless

experiments must begin with a pulse

The pulse forces the bacteria to reach the initial state $Alginate = 2$.
If the state is not directly controlable we need to prove lemmas:

$$(something\ reachable) \Longrightarrow (Alginate = 2)$$

General form of a test:

$$(something\ \underline{reachable}) \Longrightarrow (something\ \underline{observable})$$

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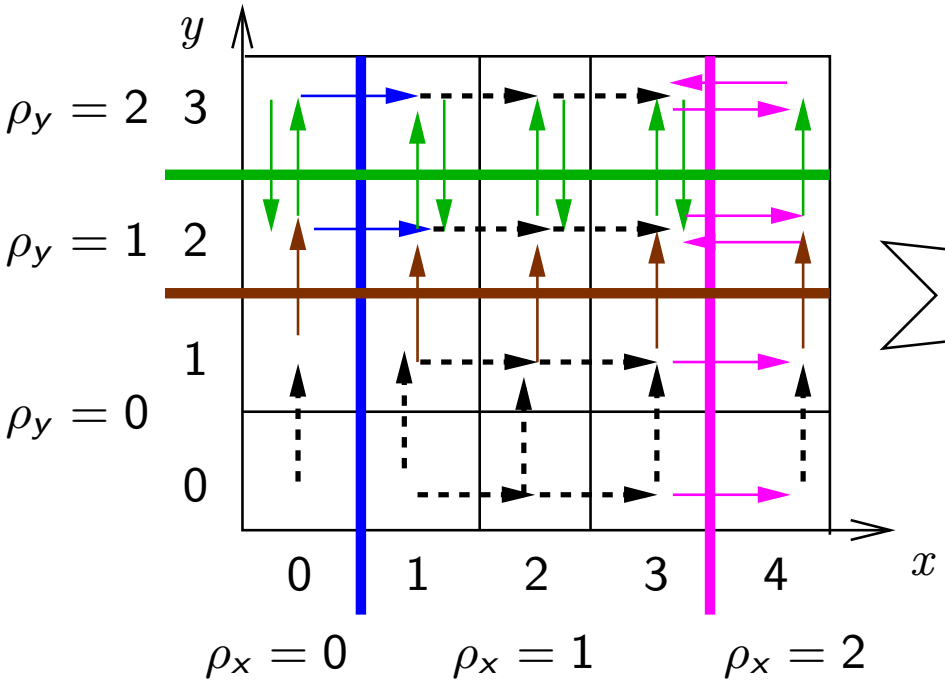
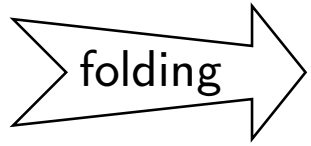
Hypothesis driven model simplifications

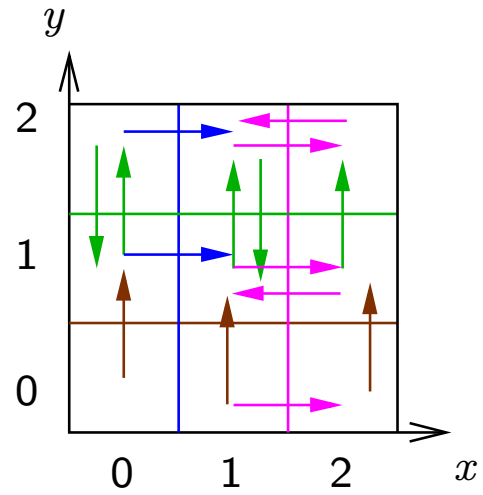
Successive simplified views of the studied biological object:

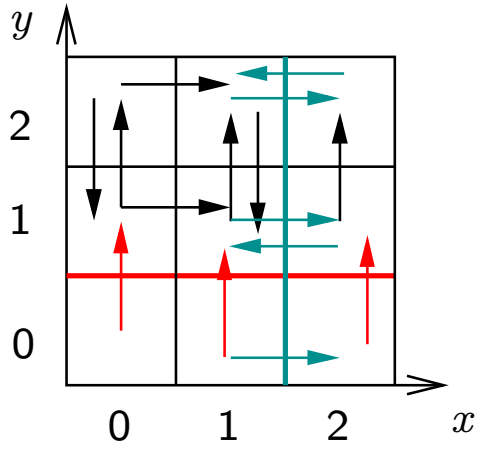
$$\begin{array}{ccccccc} \text{Model} & & \text{Model} & & \text{Model} & & \\ M_1 & \Longleftrightarrow & M_2 & \Longleftrightarrow & M_3 & \Longleftrightarrow & \ldots \\ \text{satisfies} & & \text{satisfies} & & \text{satisfies} & & \\ \varphi_1 & & \varphi_2 & & \varphi_3 & & \end{array}$$

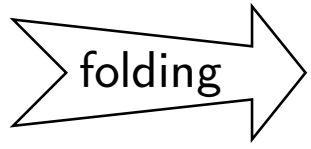
Simplifications *via* level folding

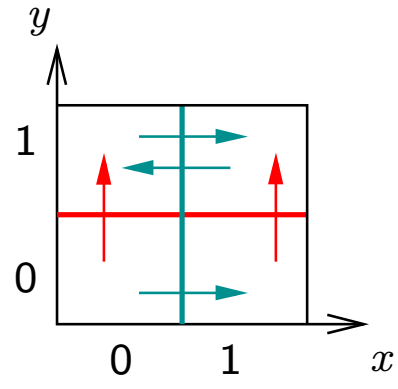






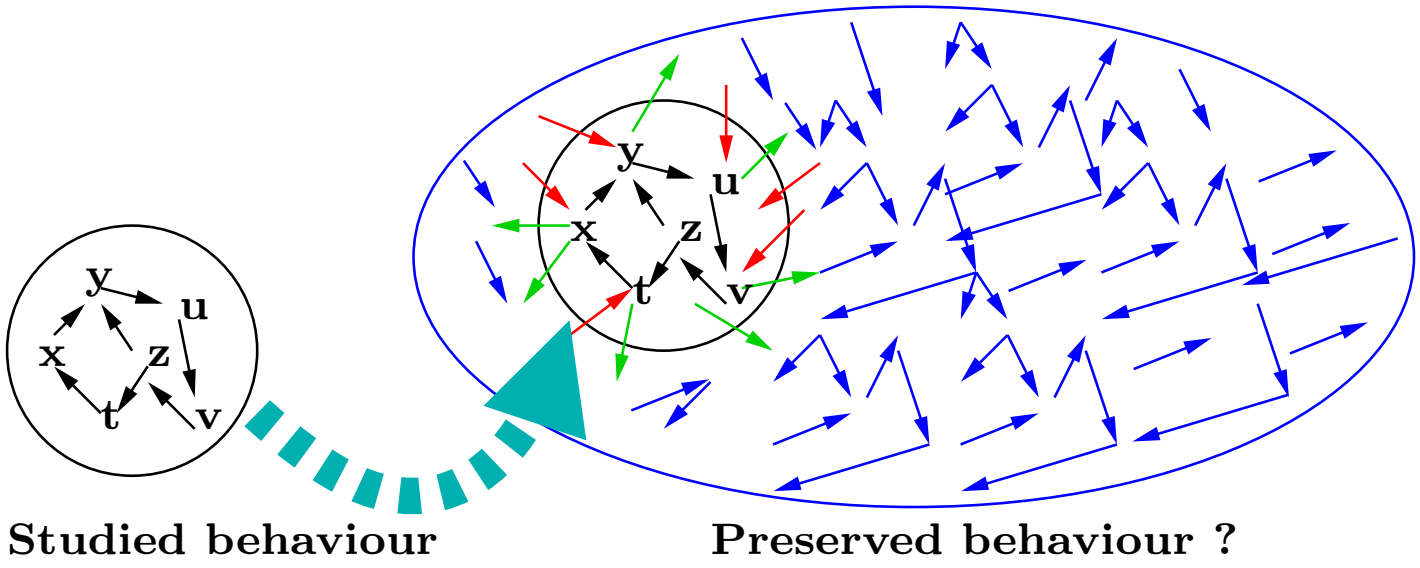






Simplifications *via* subgraphs

Embeddings of Regulatory Networks:



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

. . . *Also* fusion of genes, *etc.*

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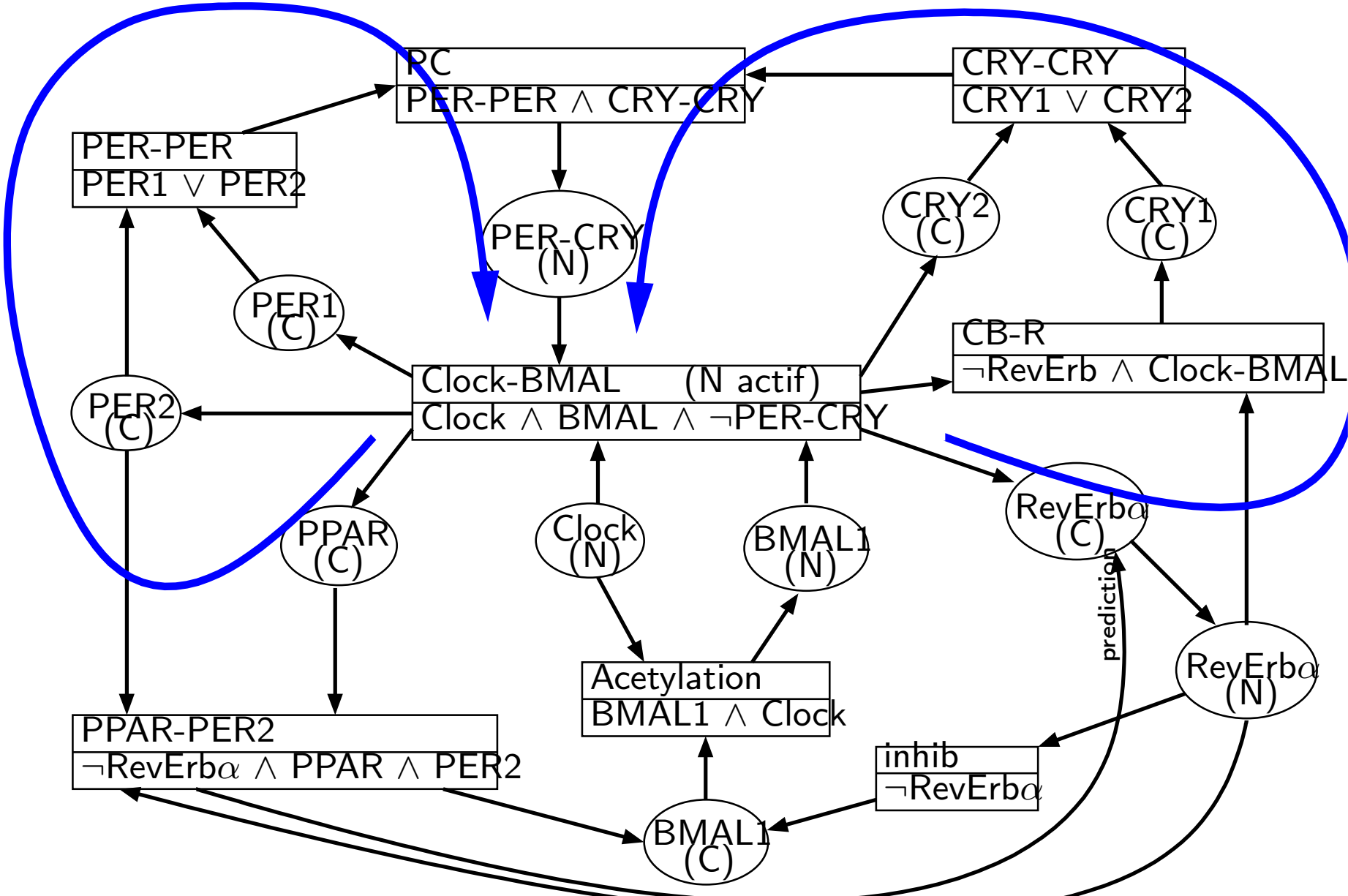
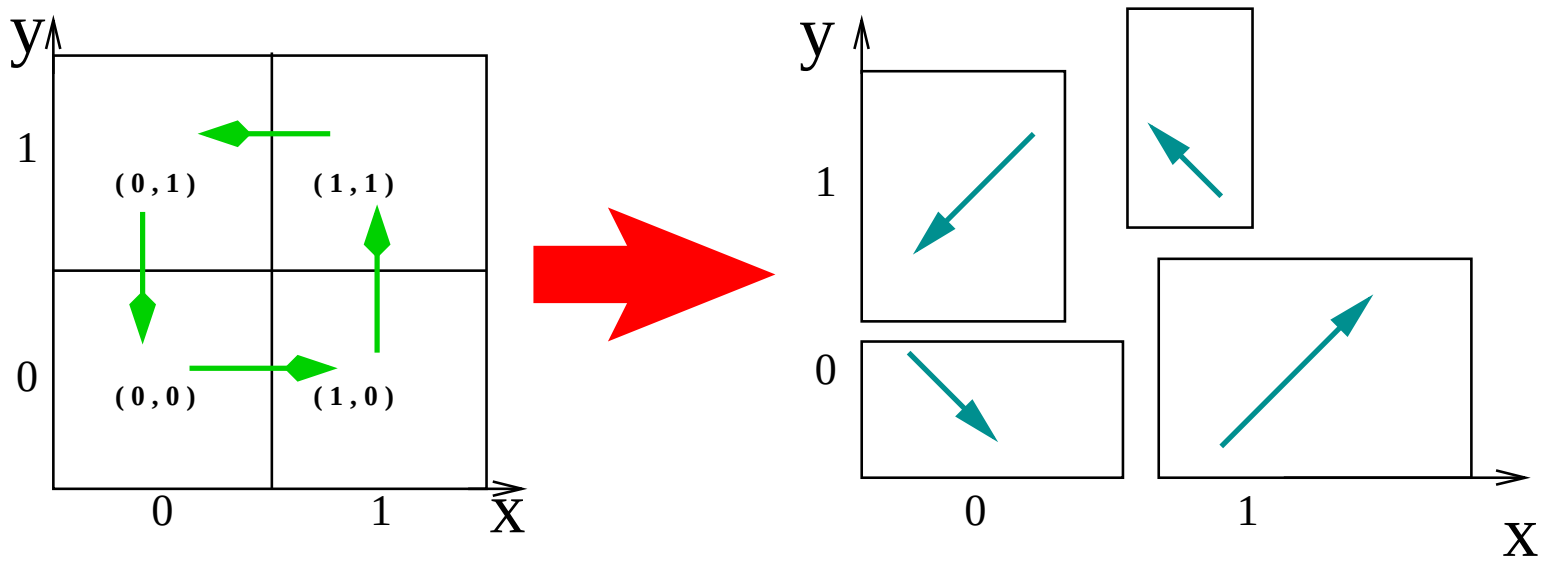
"Data Base" interaction graph



The target question

Impact of the day length on the persistence of the circadian circle ?

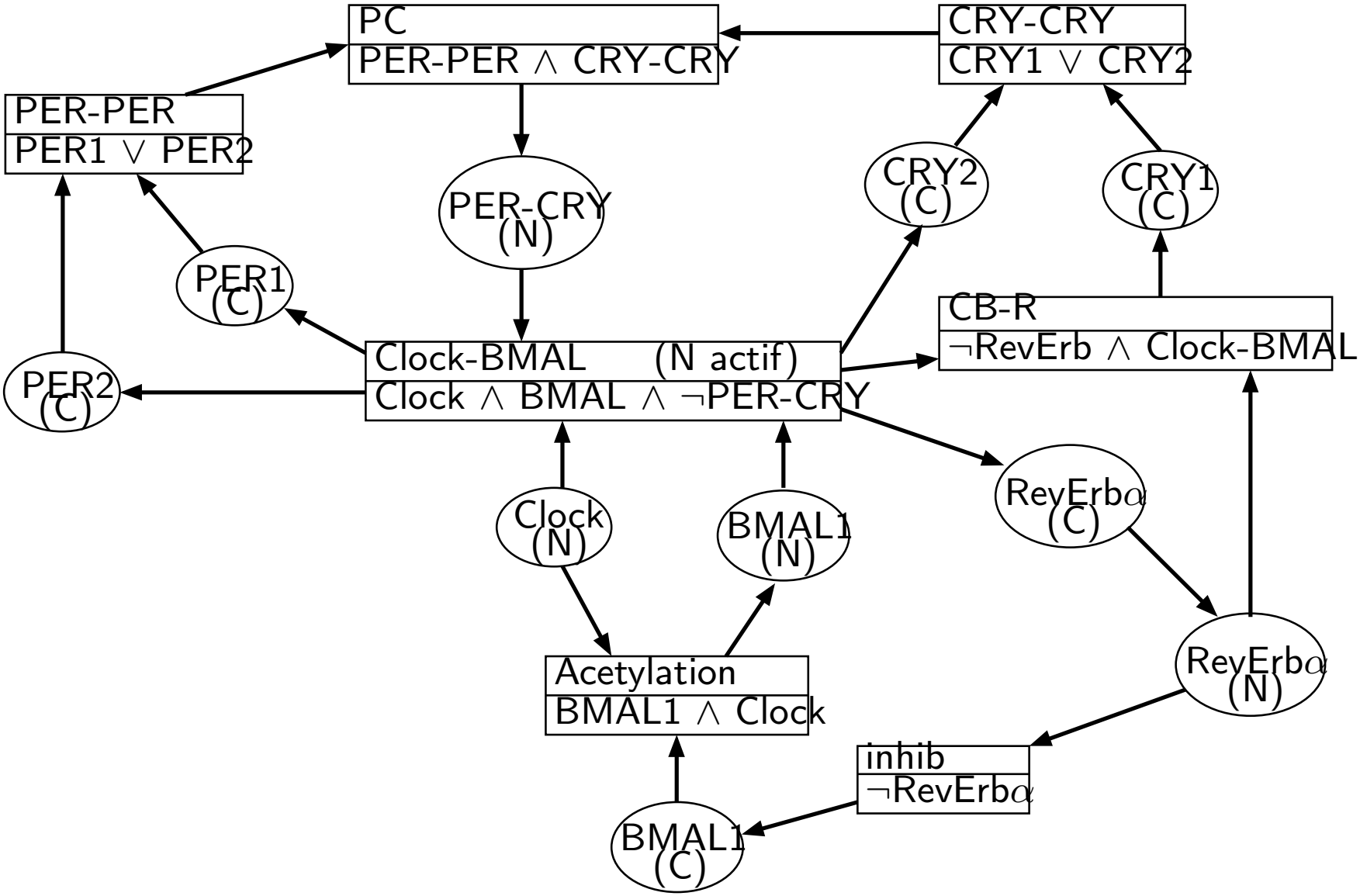
$\Longrightarrow$ framework with time delays:



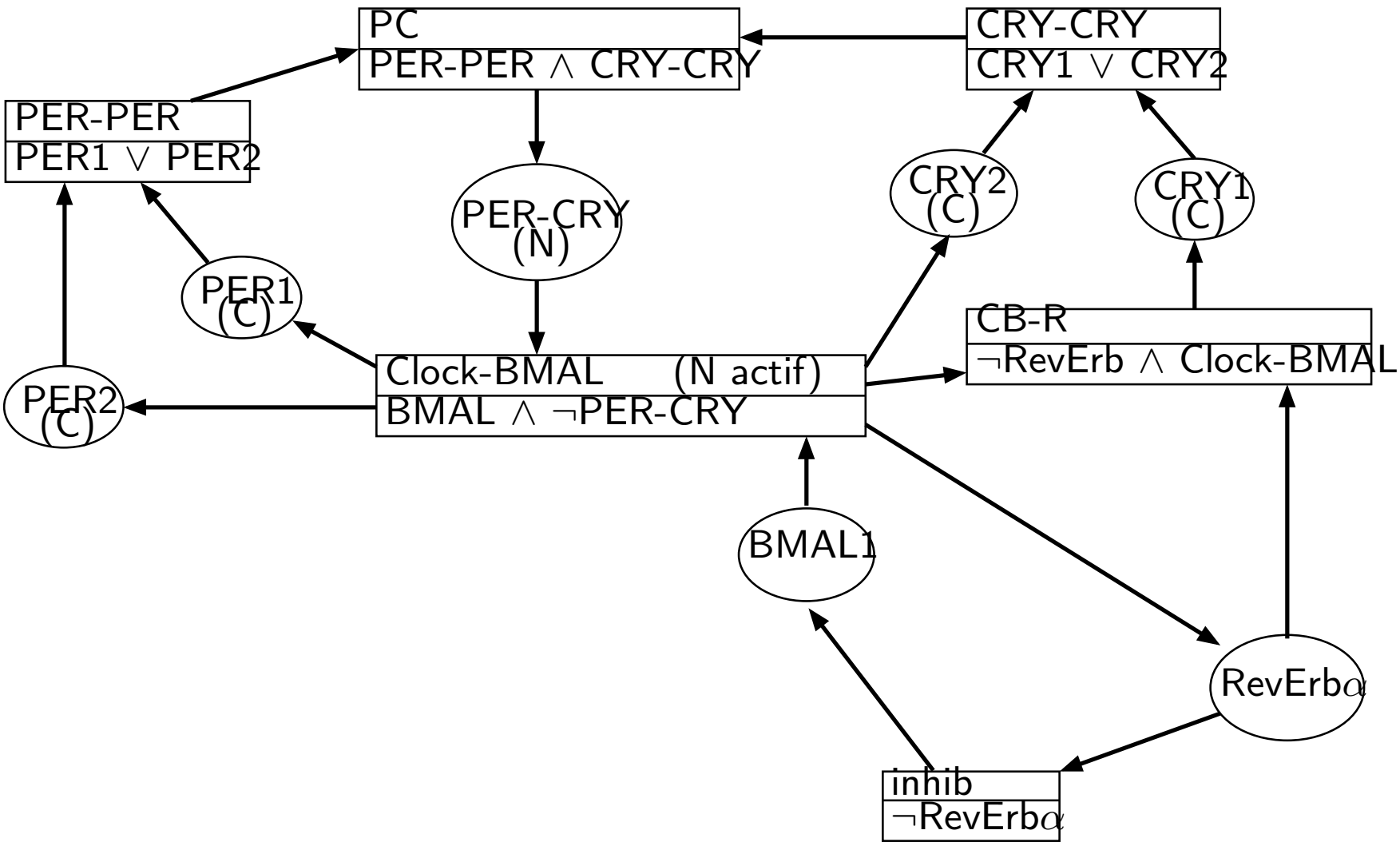
(size of rectangular areas = delays)

+ extension of temporal logic with delays. . .

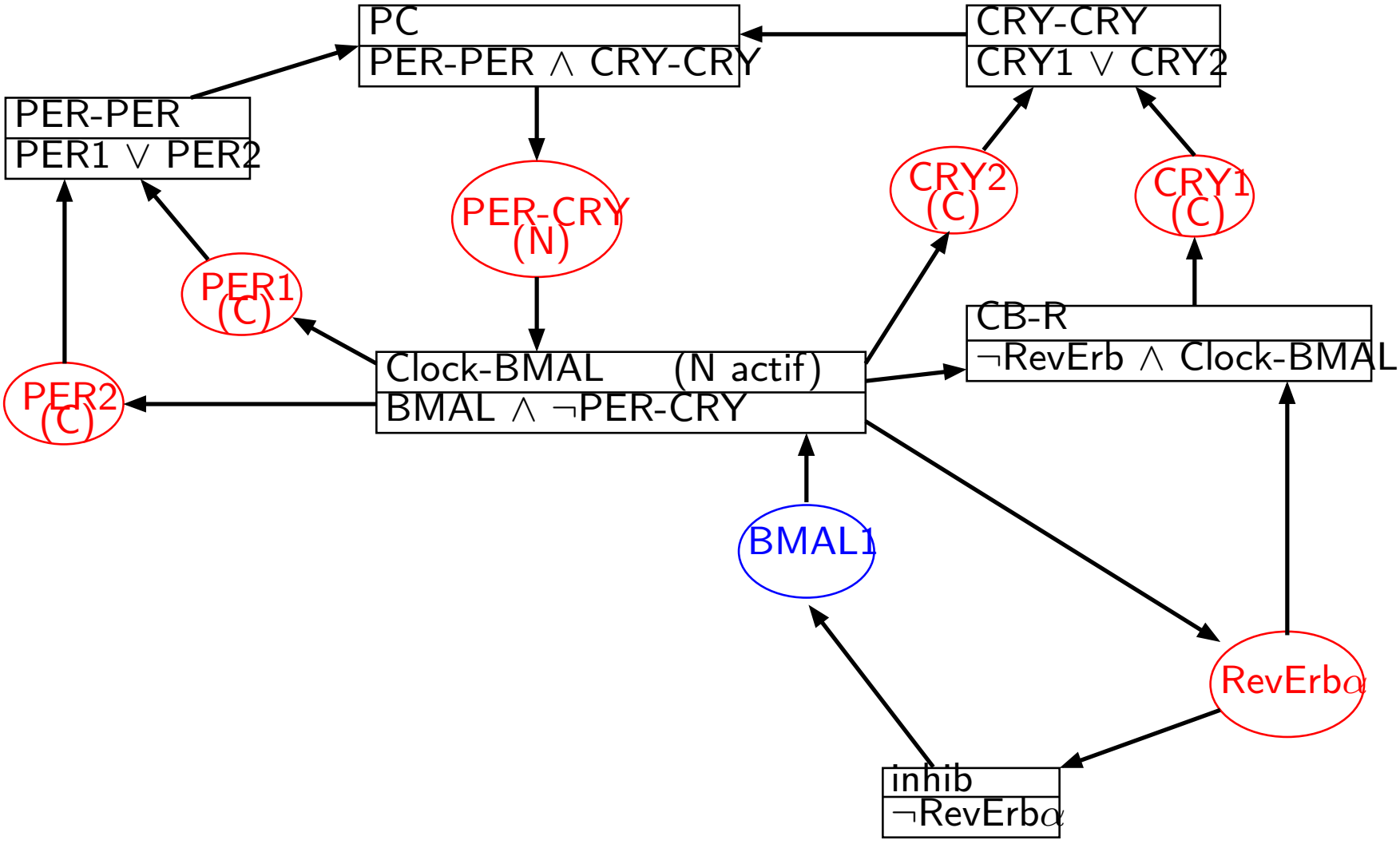
Fold levels and remove PPAR



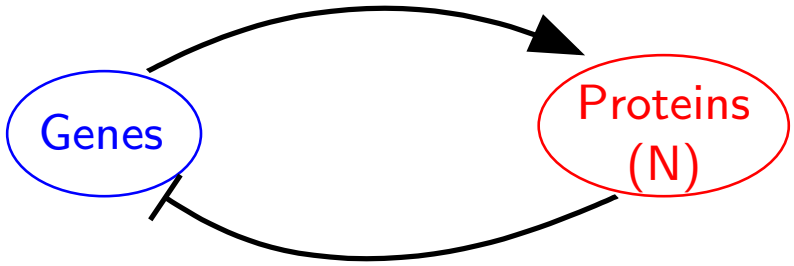
Remove Clock and "tunnel" pathways



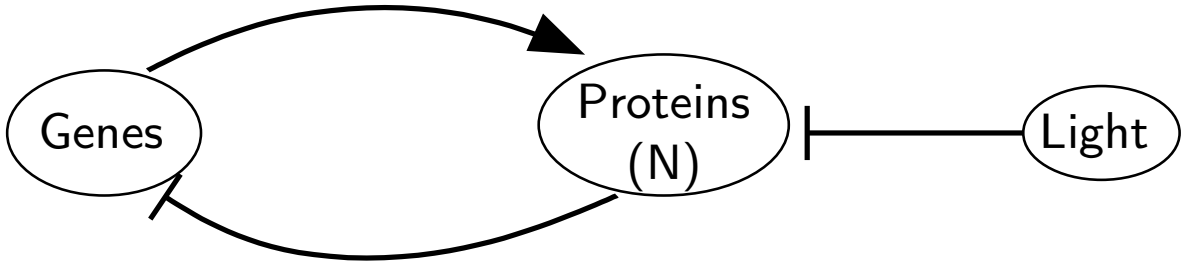
Separate inhibitors/activators of Clock-BMAL



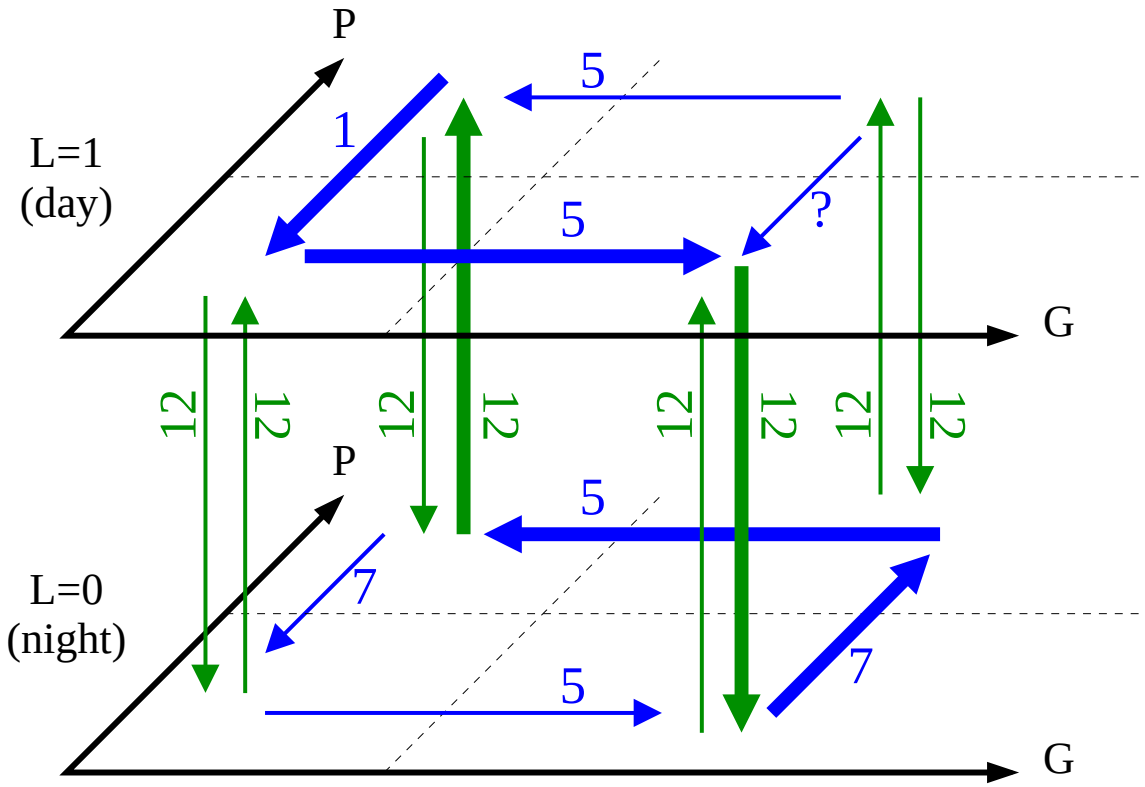
Fusion of all inhibitors



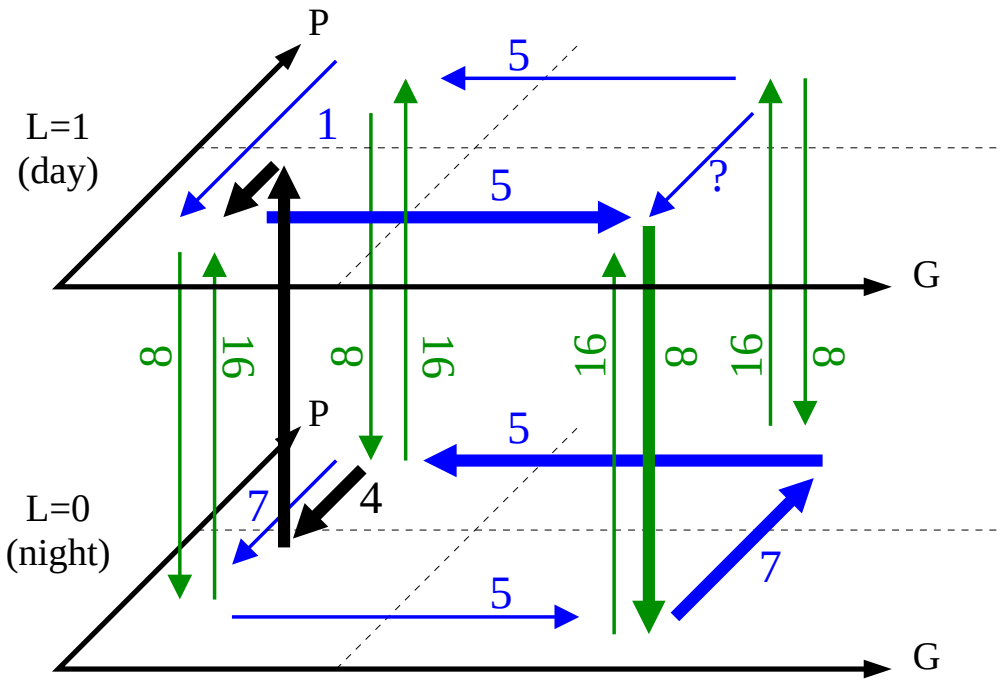
and Light prevents PER-CRY to enter the nucleus:



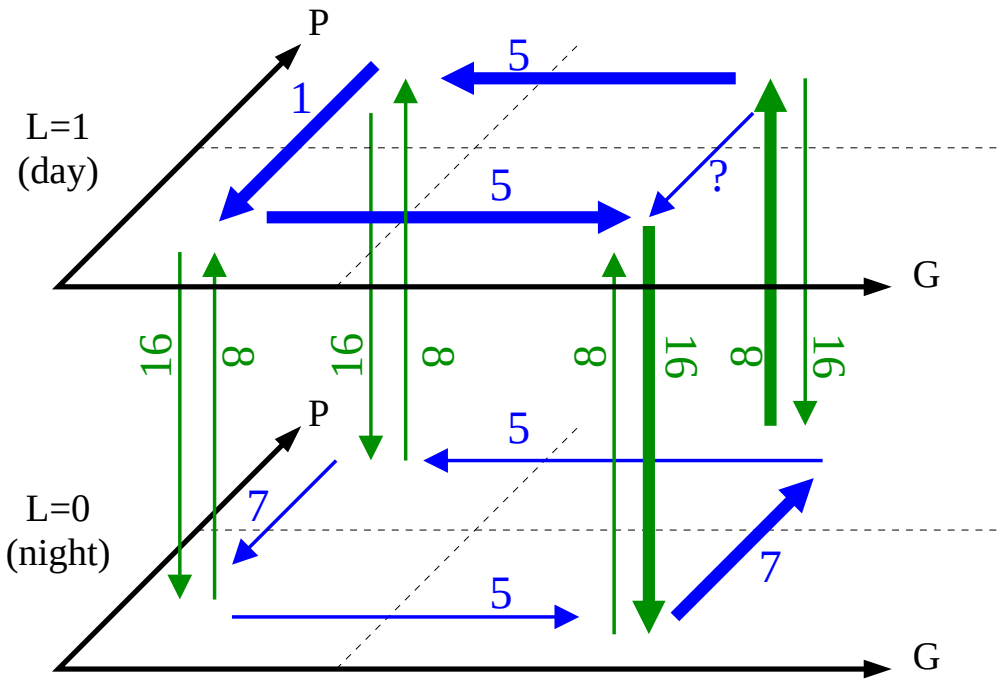
12 hours model



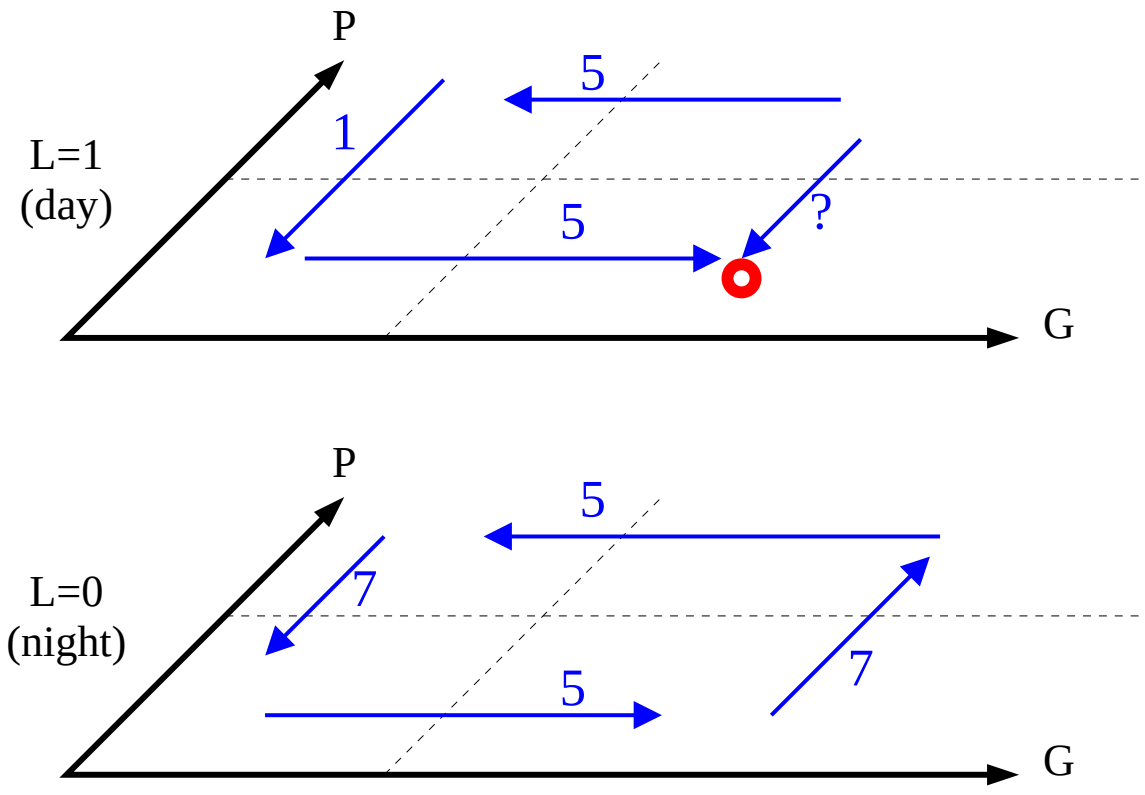
Winter model



Summer model



Jet lag + training



Yet far from automatic simplifications but...

Abstract interpretation at 

Model reduction at 

Acknowledgements

- *Observability Group*, Epigenomics Project (Genopole®)
- Janine Guespin (Rouen)
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- Amélie Cessieux (Polytech, BIMB)

Polytech Option BIMB en Génie Biologique

Take Home Messages

Make explicit the hypotheses that motivate your research

A far as possible formalize them to get a computer aided approach

Behavioural *properties* are as much important as *models*

Mathematical models are not reality: let's use this freedom !
(several views of a same biological object)

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

Formal proofs can suggest wet experiments

"Kleenex" models help understanding main behaviours