Linear Time Logic Specifications for Systems Biology

Illustration with a Coupled Model of the Cell Cycle and the Circadian Clock

Junior Seminar

16th June 2015

Pauline Traynard

Lifeware Team

- Led by **François Fages**

- **Constraint programming methods** for optimization problems
  « The Holy Grail of Programming » - what not how

- Developing formal methods for understanding the cell machinery
  Use of **concepts and tools from computer science to master the complexity of cell processes**
  Reason about biochemical reaction networks at **different levels of abstraction**, in the **stochastic, differential, discrete, logical and hybrid semantics** of the reactions

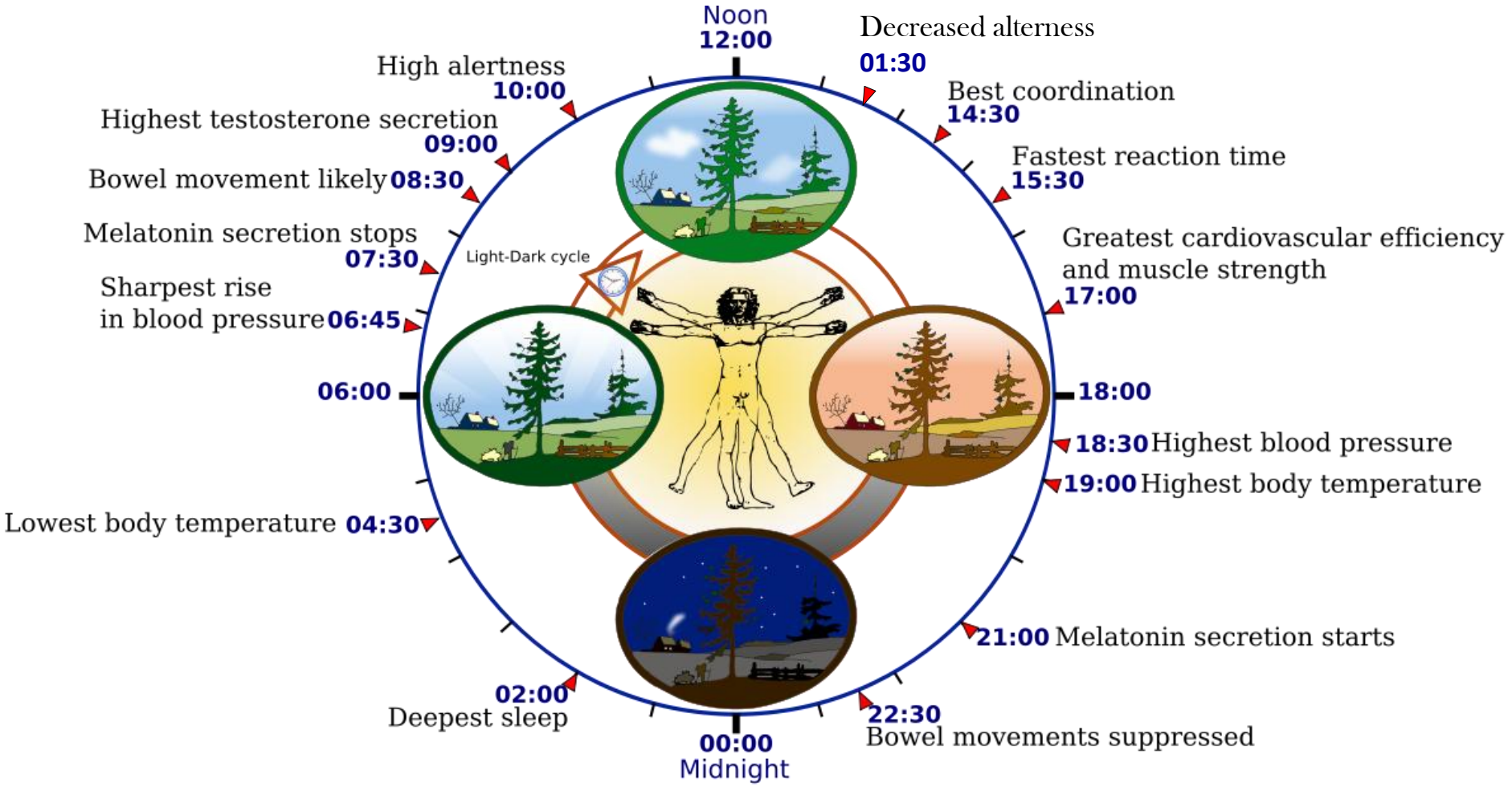
IBENS
Institut de Biologie de l'Ecole Normale Supérieure

- Software: **BIOCHAM**
  The Biochemical Abstract Machine: modeling and analysis platform
  http://lifeware.inria.fr/Biocham/

- Closed-loop control of intracellular processes

Chronobiology

- **Circadian clocks** regulate the **physiology** of many organisms



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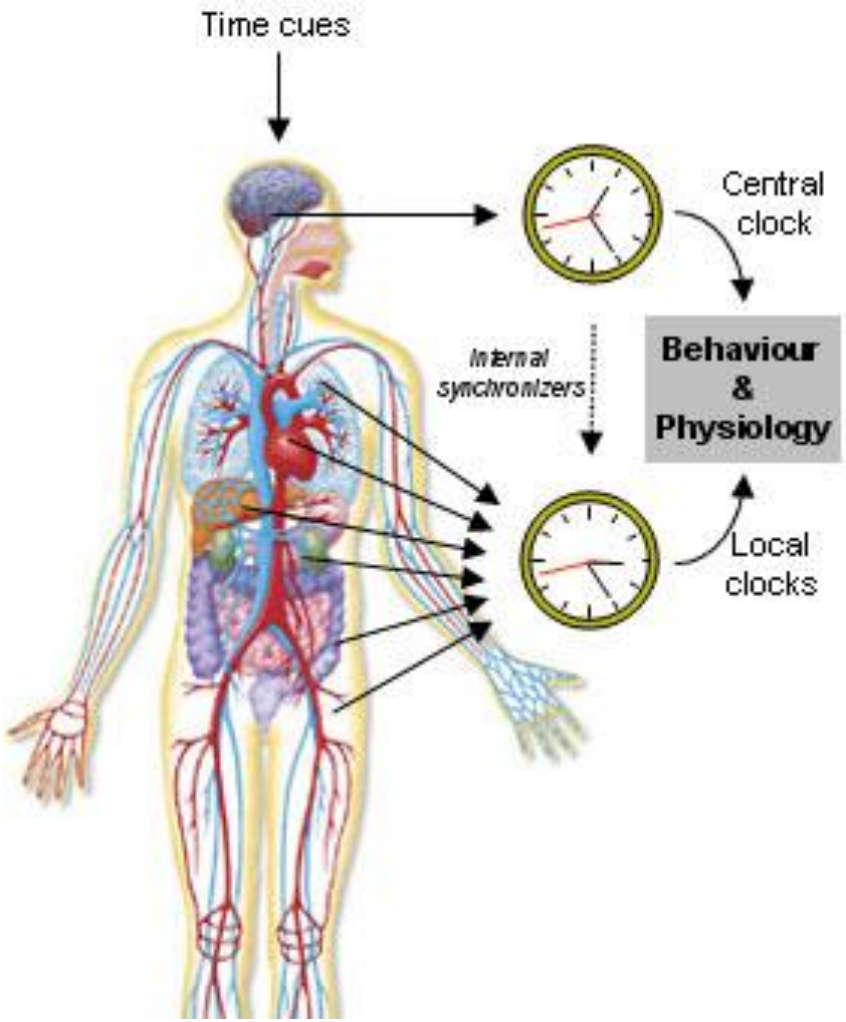
- **Local clocks** are present in most cells and synchronised by the **central clock**



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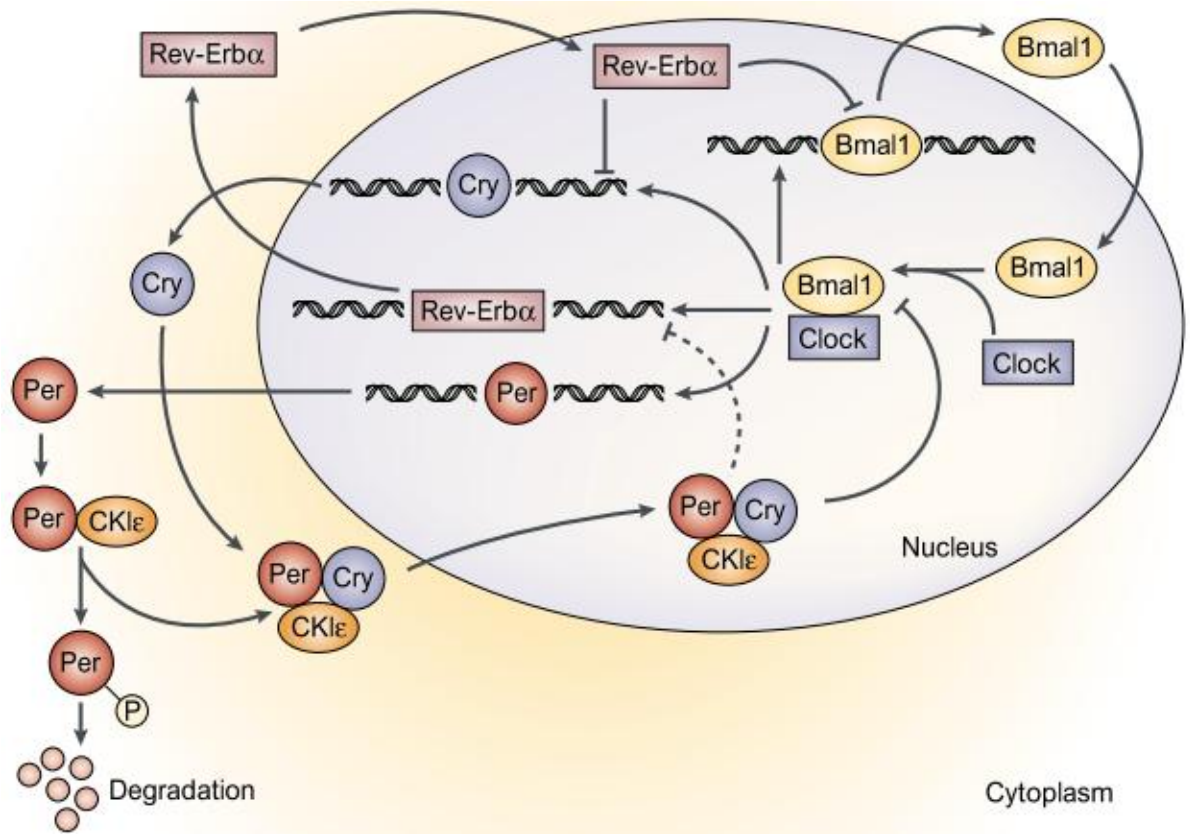
- The mamalian clock: a **set of genes** that interact in a complex network with intertwined **transcriptional and post-translational feedback loops**.



[Fu and Lee, Nature 2003]

Chronobiology

- **Circadian clocks** regulate the **physiology** of many organisms

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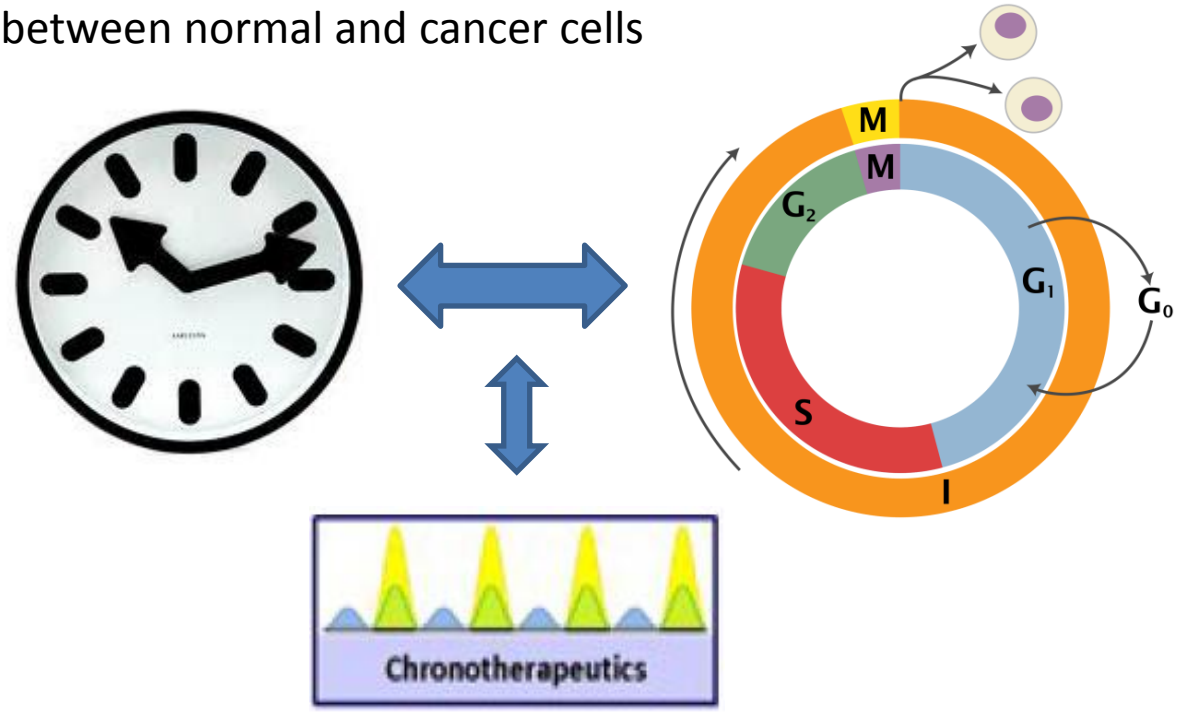
- Links with the cell cyle:
  - -The circadian clock influences **cell proliferation** and cell suicide
  - -**Disruption** of the circadian clock has been associated with **cancer**
  - -**Asynchrony** between normal and cancer cells



Modeling the coupling between the cell cycle and the circadian clock

Question: What are the links between the circadian clock and the cell divisions, especially regarding cancer ?

Experimental observations suggest bidirectional influence between cell divisions and the cellular circadian clock

Model building assisted with formal methods (model calibration)

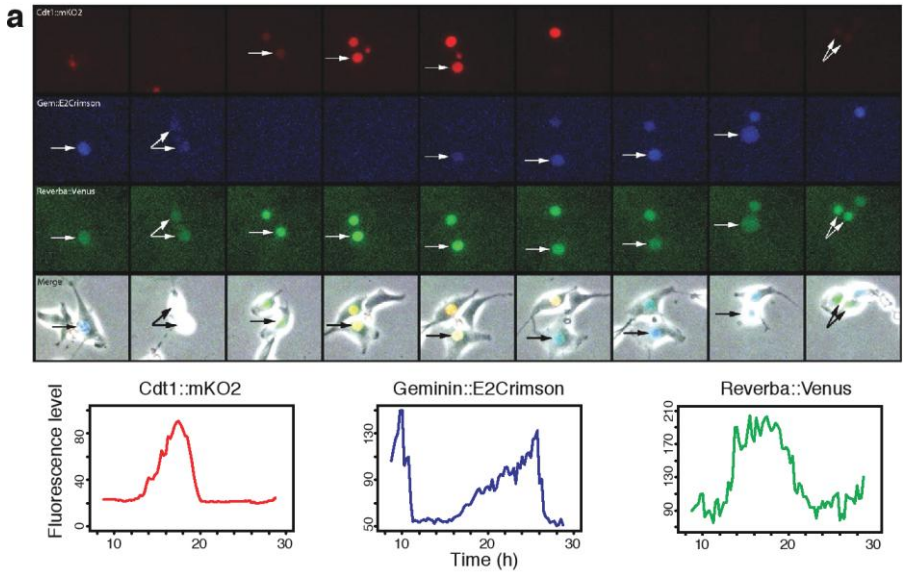
Predictions: mechanisms and perturbations, optimization

Bidirectional coupled model of the cell cycle and the circadian clock
Mechanistic differential model: set of ODEs

Experimental data:

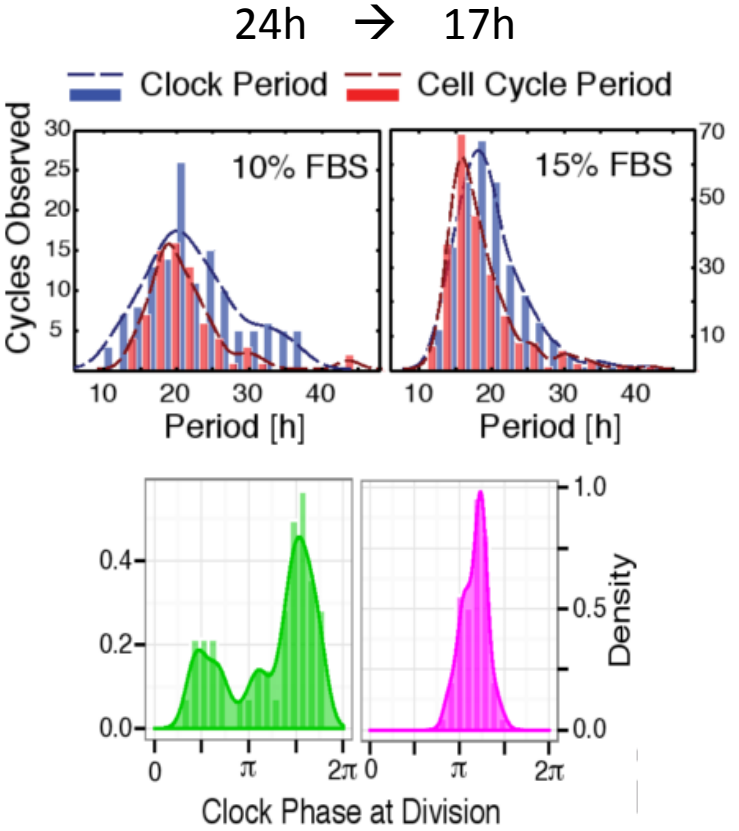
Experiments

- Fluorescent markers of the cell cycle and the circadian clock
- Time series in individual mouse cells
- Medium with various concentrations of serum to modulate cell cycle length



Observations:

- Acceleration of the circadian clock in fastly dividing cells (not in confluent cells)
- Different modes of phase-locking

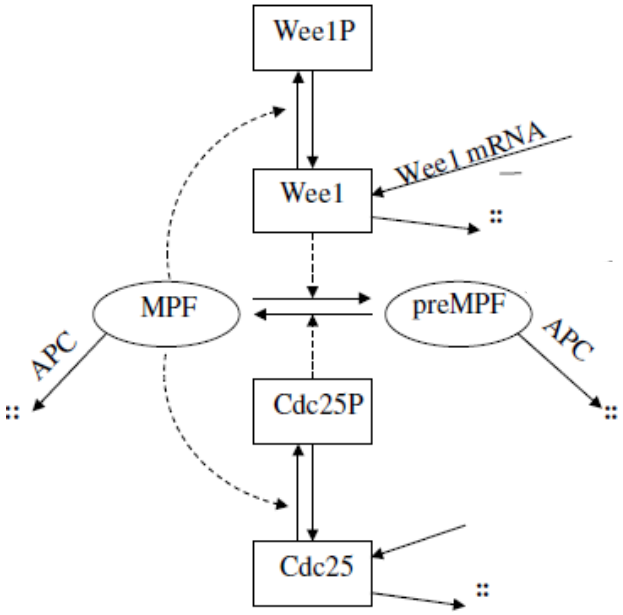


Data on the periods and phases of the two oscillators

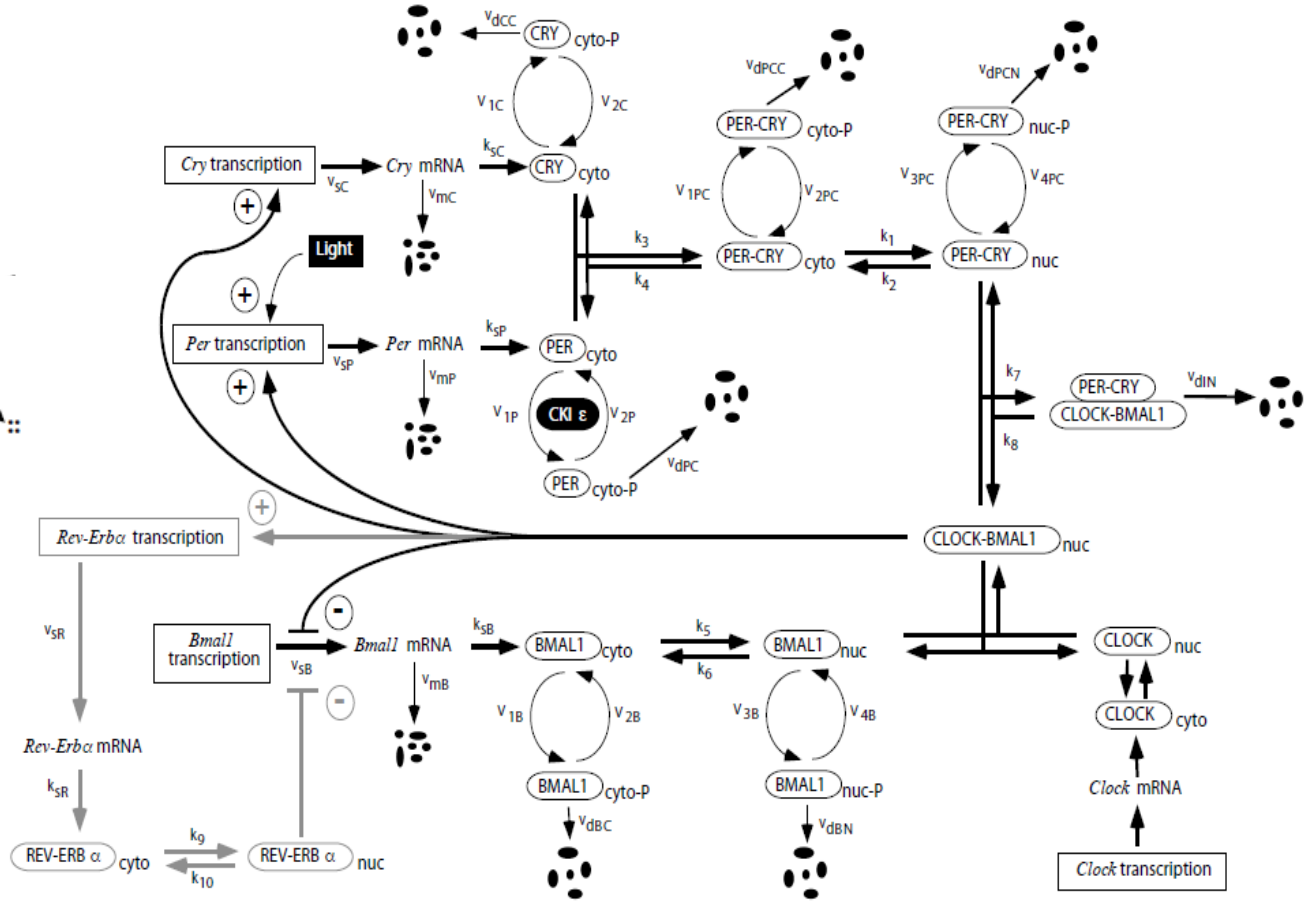
[Feillet-Krusche-Tamanini 2014]

Differential models

Cell cycle : G2/M transitions
10 equations, 30 parameters
[Qu, McLellan, Weiss 2003]



Circadian clock
19 equations, 70 parameters
[Leloup, Goldbeter 2003]

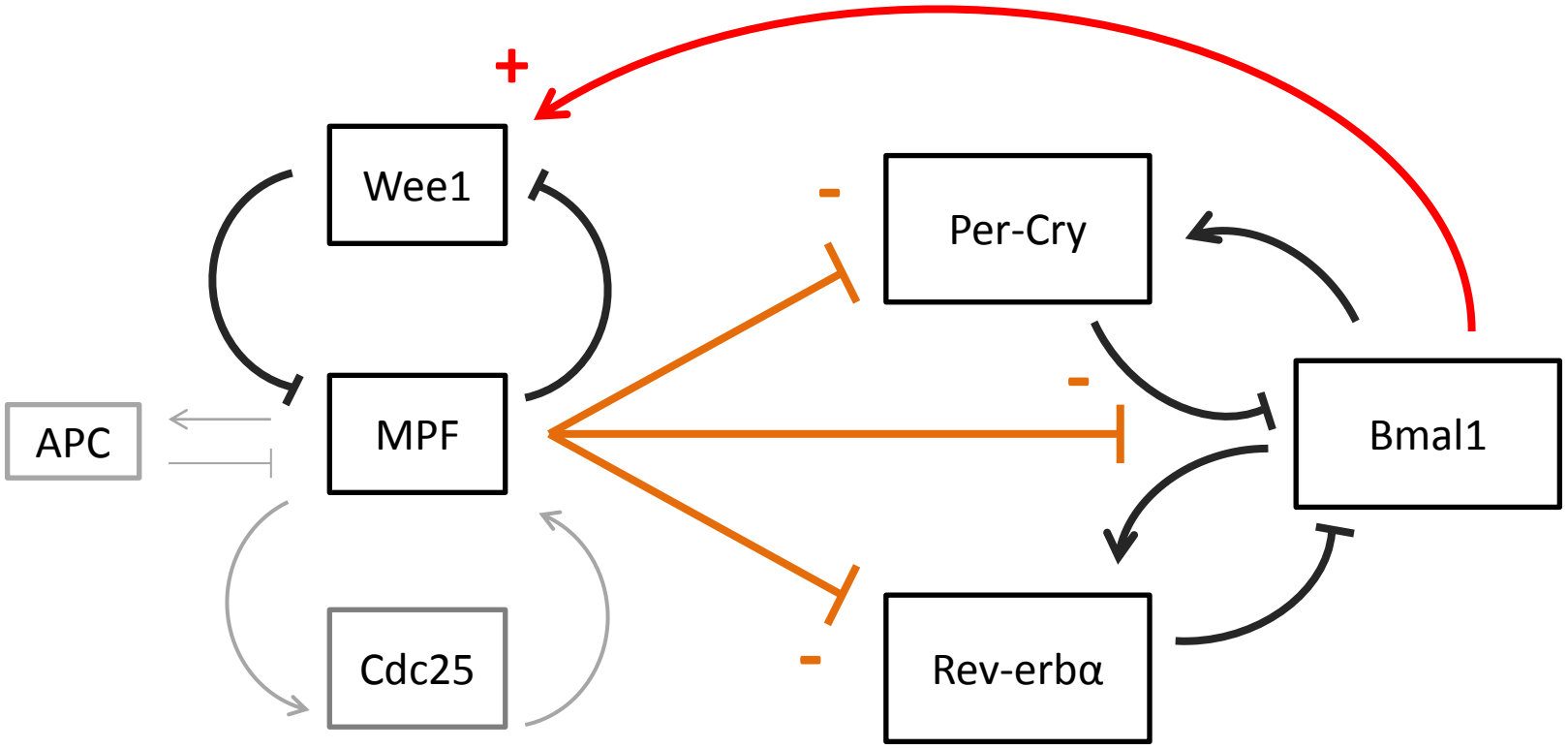


Bidirectional coupled model

Modelling the bi-directional coupling between the cell cycle and the circadian clock :

- division gating through Wee1

- inhibition of the transcription during division

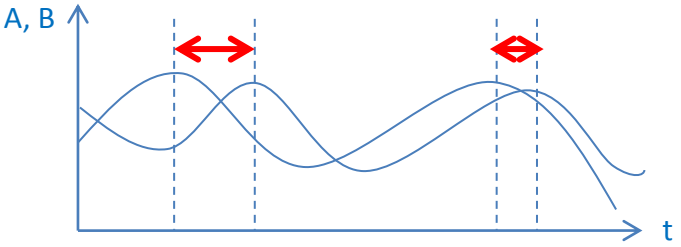


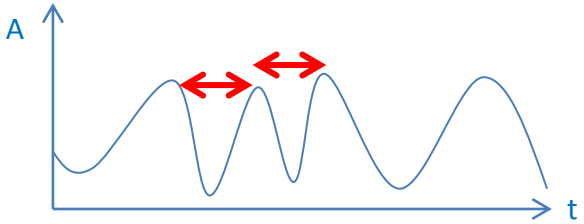
How do these new regulations affect:

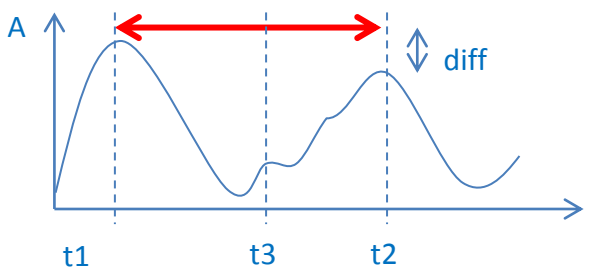
– The amplitude
– The period
– The regularity of the oscillations
– The phases

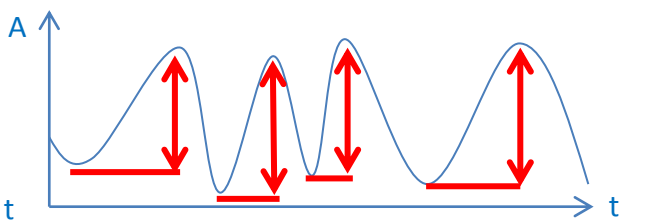
Linear Time Logic

- **Dynamical behaviors for oscillatory systems:**
  - period, amplitude, phase
  - oscillations regularity









- **Formalised in temporal logic LTL(R):**

  Syntax: temporal operators **F, G, X, U**

  Ex: <u>period</u> $\phi = \exists(t1, t2) \mid p = t_2 - t_1 \wedge t_1 < t_2$

$$\wedge \mathbf{F}(\frac{dA}{dt} > 0 \wedge \mathbf{X}(\frac{dA}{dt} \leq 0 \wedge Time = t1))$$

$$\wedge \mathbf{F}(\frac{dA}{dt} > 0 \wedge \mathbf{X}(\frac{dA}{dt} \leq 0 \wedge Time = t2))$$

<u>Result:</u>

- Validity domain: p = 23 | p=24.5
- Satisfaction degree (with objective p=24): 0.95

- **Applications:**
  - **Data analysis**: extracting meaningful information from a trace
  - **Model checking**: verifying that a model satisfies some constraints
  - **Model analysis**: comparing how the properties of a model evolve when some parameters vary
  - **Parameter inference:** continuous score for some properties

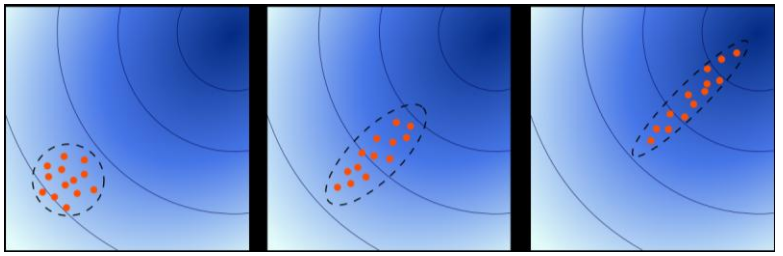
Linear Time Logic for model calibration

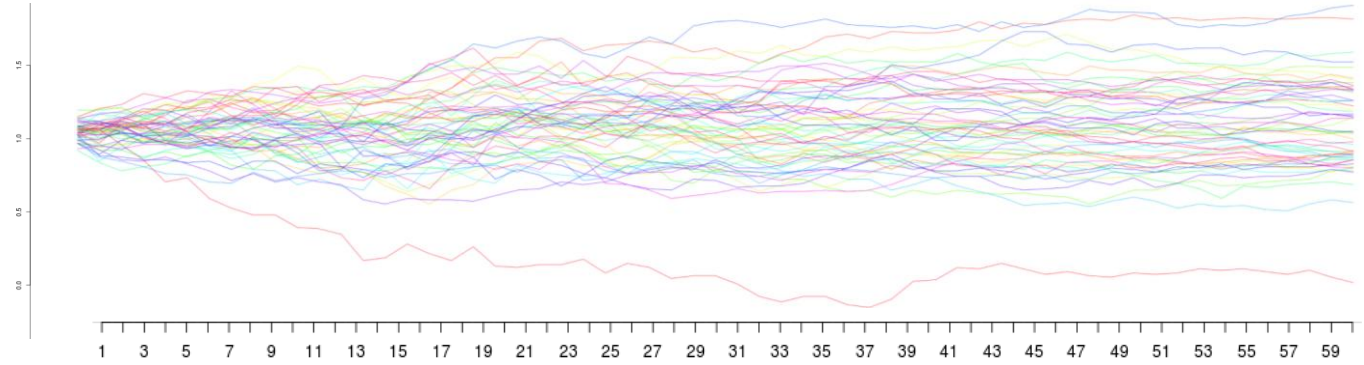
CMA-ES optimization strategy implemented in BIOCHAM

- Stochastic method for parameter optimization

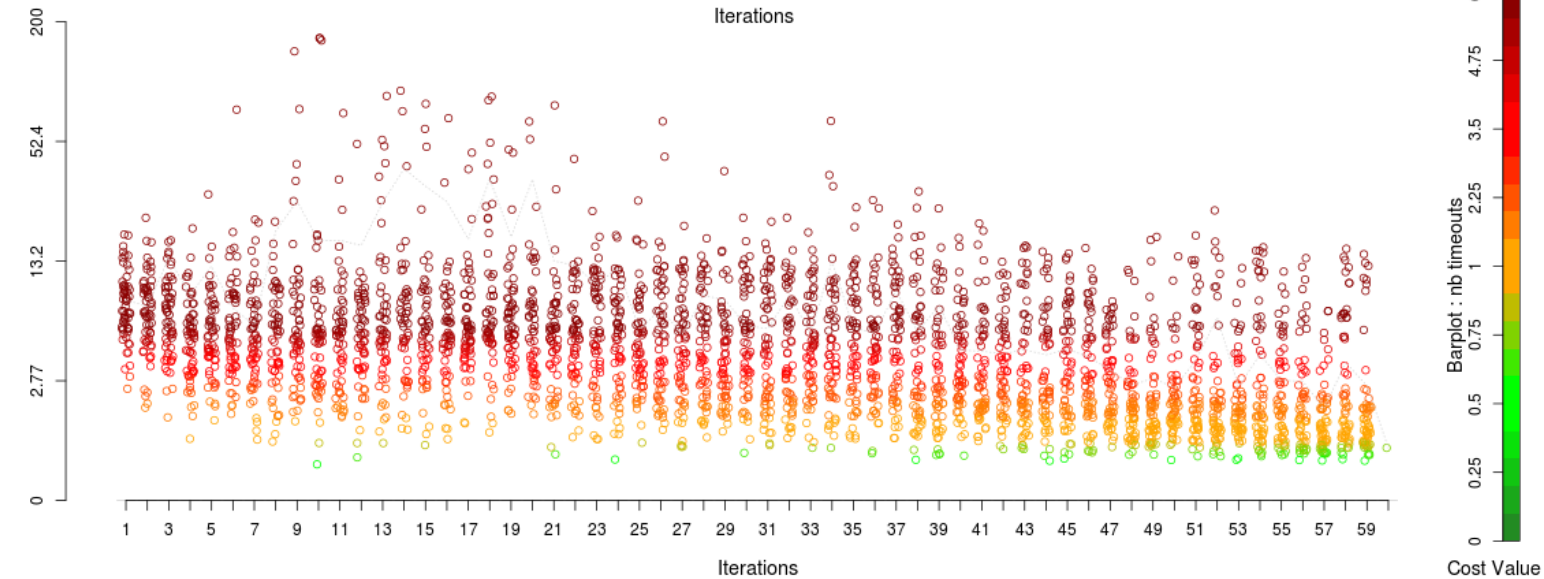
Covariance Matrix Adaptation Evolution Strategy

- **Search space:** kinetic parameters
- **Optimization function** to orient the search: satisfaction degree of a logical specification





Parameter search

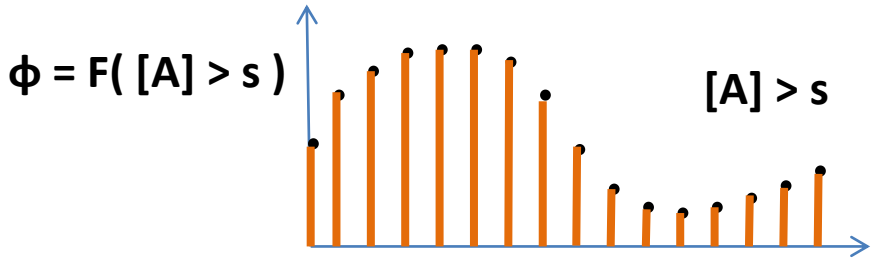


Satisfaction degree of the temporal specification

Efficient processing of a LTL formula

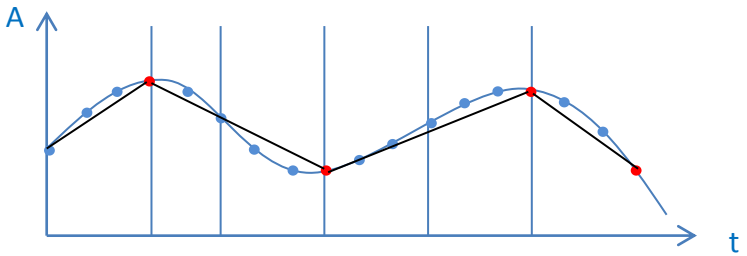
Generic algorithm

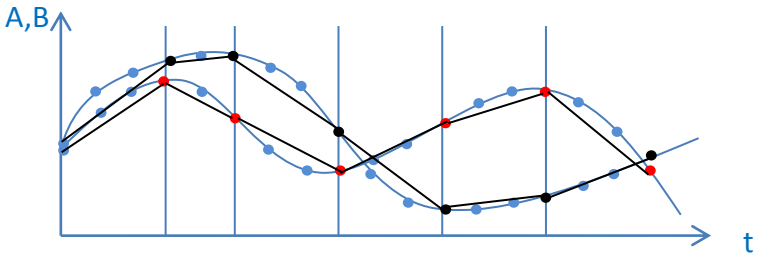
- Combination of the validity domains of the sub-formulae on each point of the trace



Trace simplification

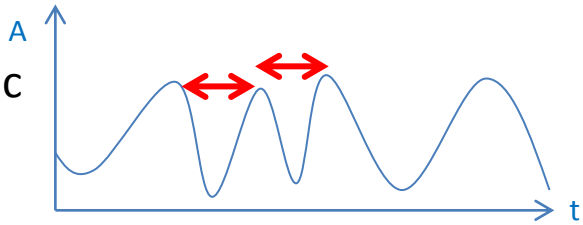
- **Under some conditions on the constraints** we can consider only the subtrace of extrema points without changing the result (theorems)





Dedicated solvers

- Function corresponding to a LTL(R) pattern formula for a specific dynamical behavior
- Direct computing of the validity domain on the trace



distanceSuccPeaks(A,p)

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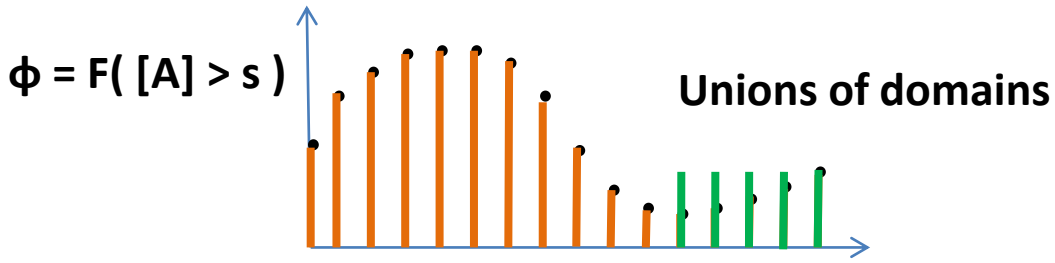

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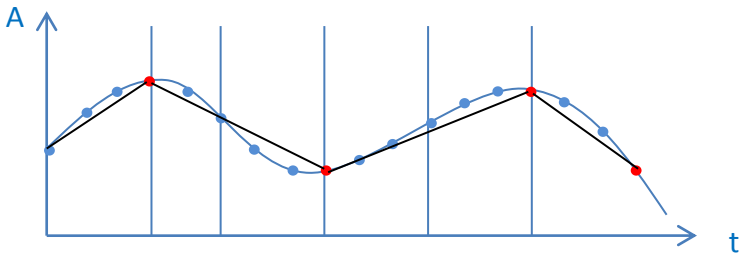

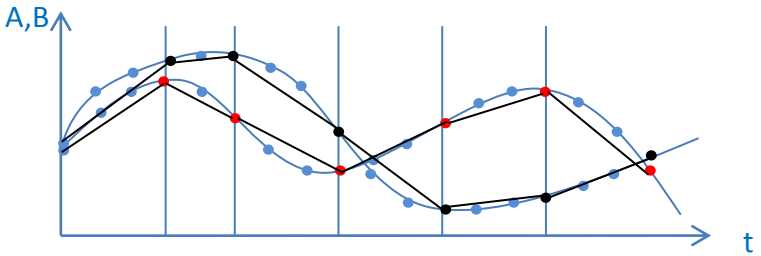

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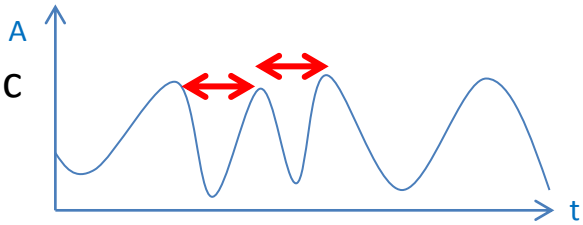

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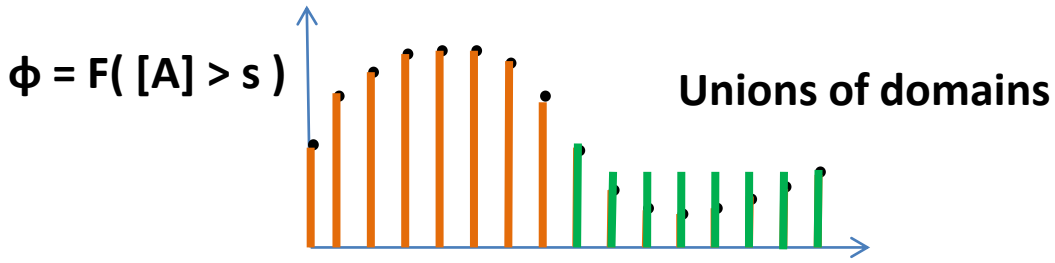

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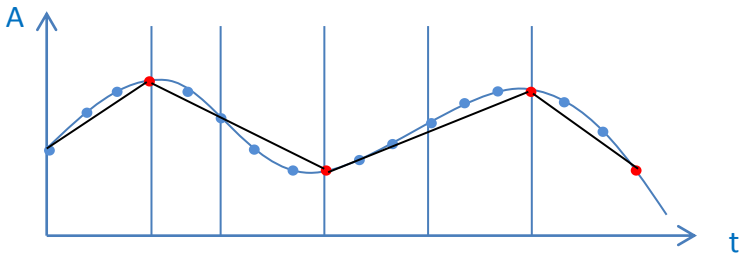

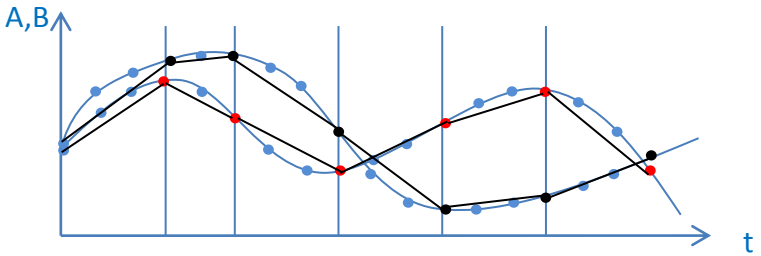

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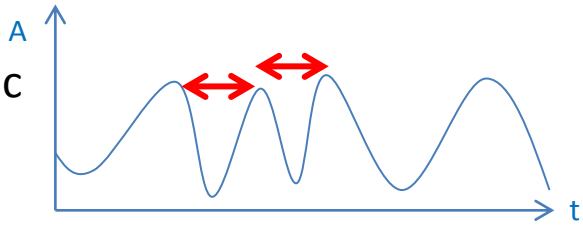

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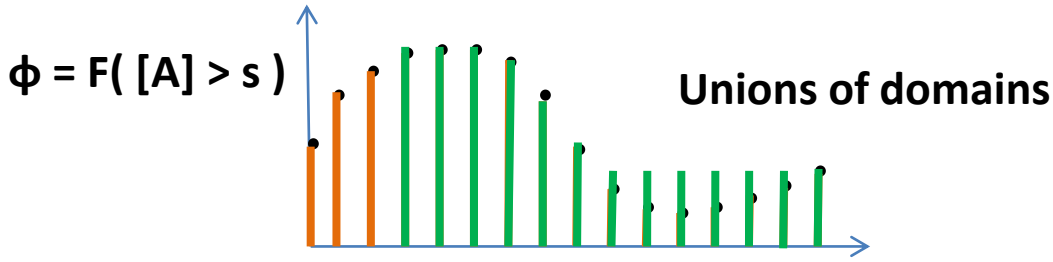

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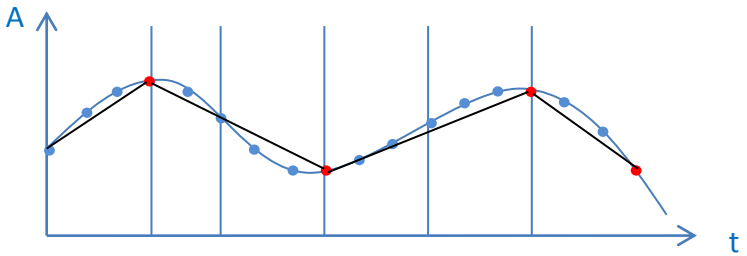

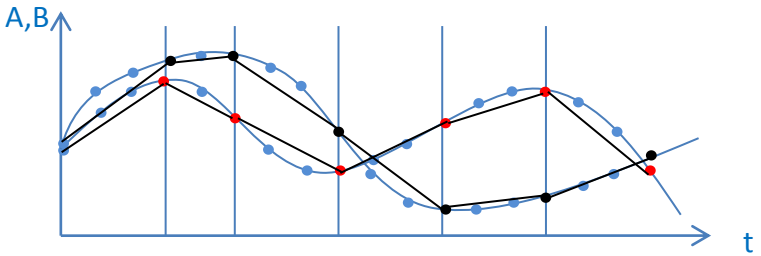

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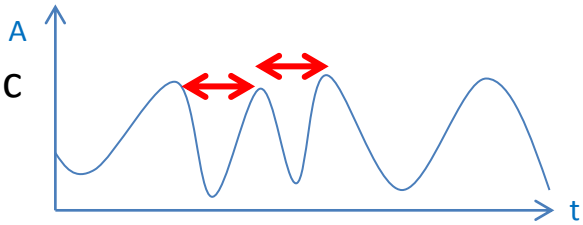

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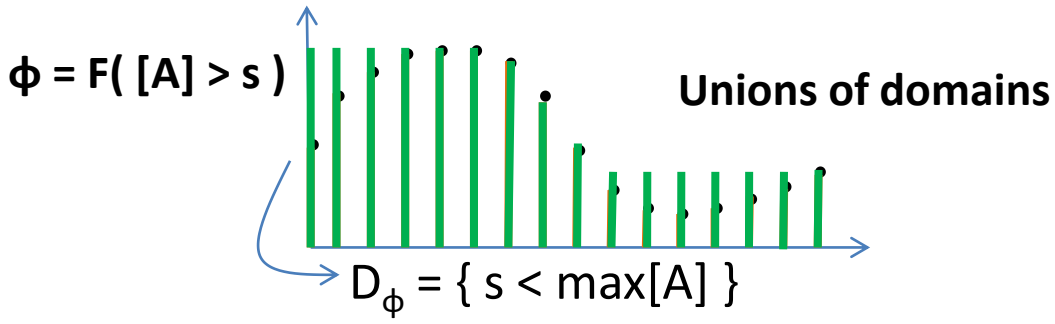

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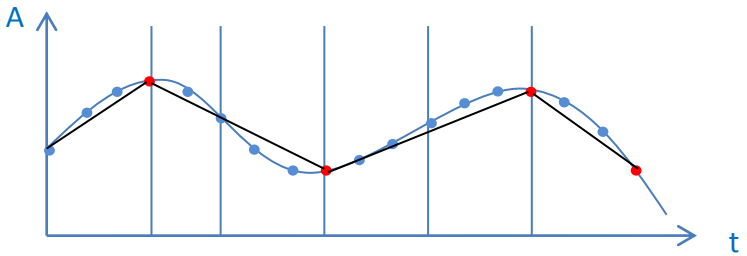

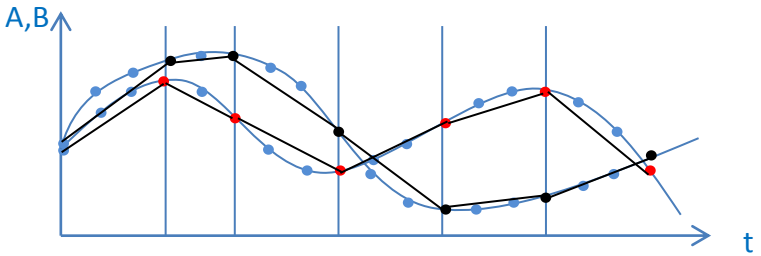

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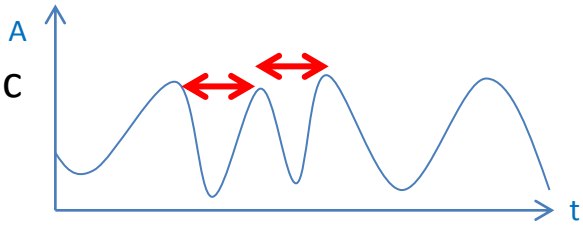
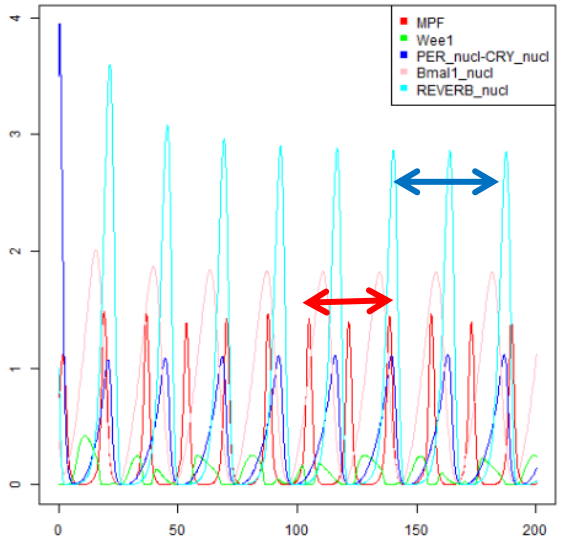


distanceSuccPeaks(A,p)

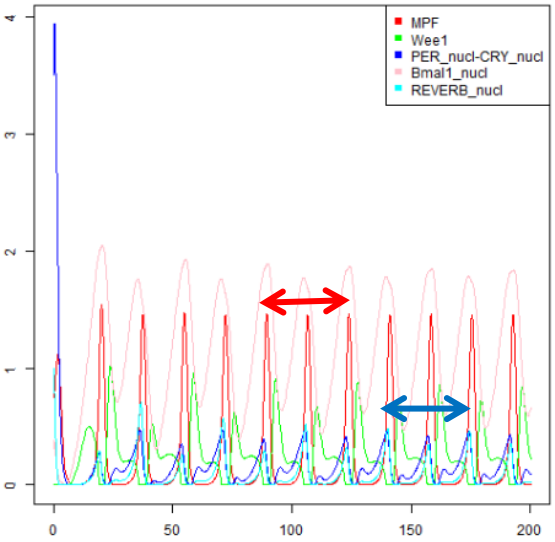
Bidirectional entrainments: results

Entrainment of the clock found after **parameter search with BIOCHAM temporal logic :**

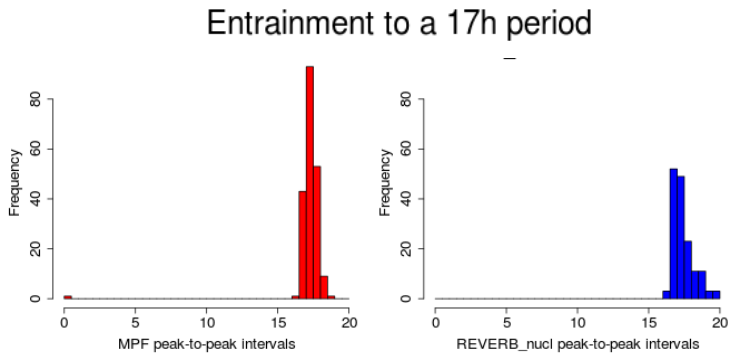
Free clock :
Clock period = 23,7h
Cycle period = 16,5h



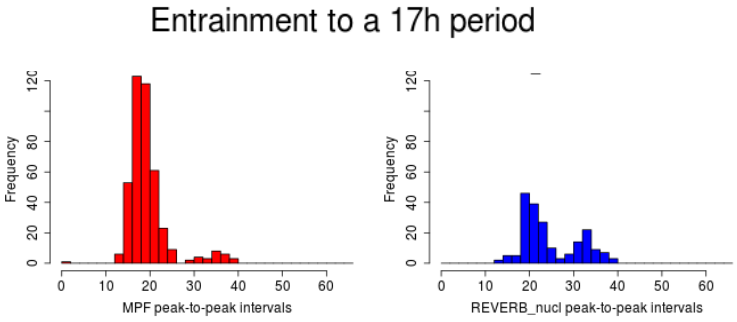
Bi-directional coupling :
Clock period = 17,23h
Cycle period = 17h



Sets of parameters with a **robust entrainment**



A set of parameters with a **tendency to period doubling**

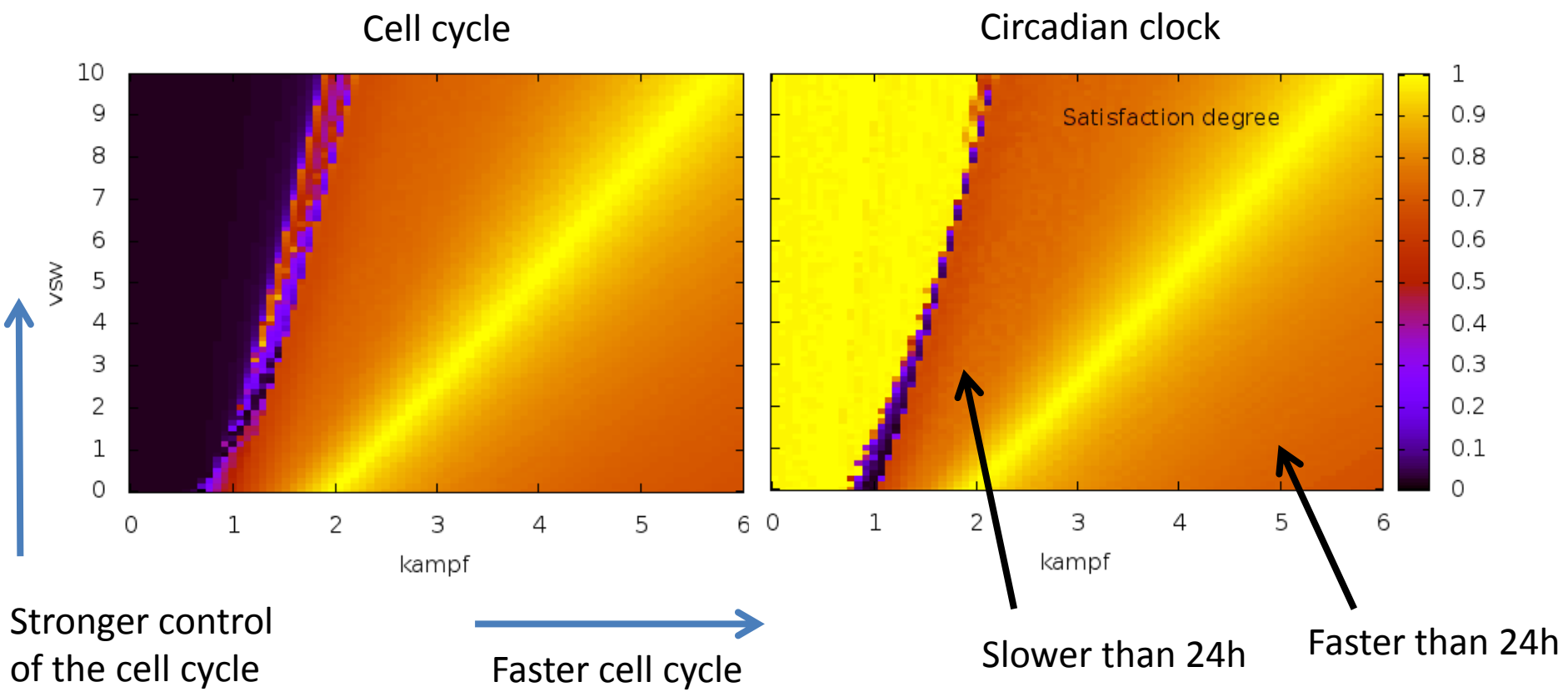


- The coupling hypothesis are compatible with the experimental observations
- Several sets of parameters possible for the same result
- Different robustness

Bidirectional entrainments: results

Score for :

- an **objective of 24h for the period**
- additional **penalties** on the irregularity of the period and the amplitude



Conclusion

- We **use Linear Time Logic** specifications in BIOCHAM with applications to **model checking** and **model calibration**

- We reproduce the **acceleration of the circadian clock** by a fast cell cycle

- We still need to understand the cause of the different phases for division and test other coupling hypotheses

- **Predictions** from the model: perturbations, new behaviors

- Temporal Logic is also used for model-checking boolean models

Acknowledgements

• **Lifeware Team**
François Fages
Sylvain Soliman
Grégory Batt
Thierry Martinez
François-Marie Floch
François Bertaux
Denis Thieffry

• **Collaborations**
C5Sys (ERASysBio)
ANR HyClock

• **GENCI cluster**
Public high performance computing resources

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