Simplified models for the mammalian circadian clock

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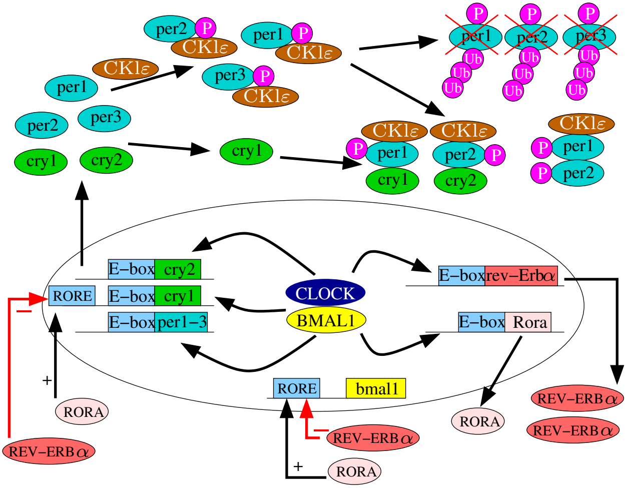
Introduction

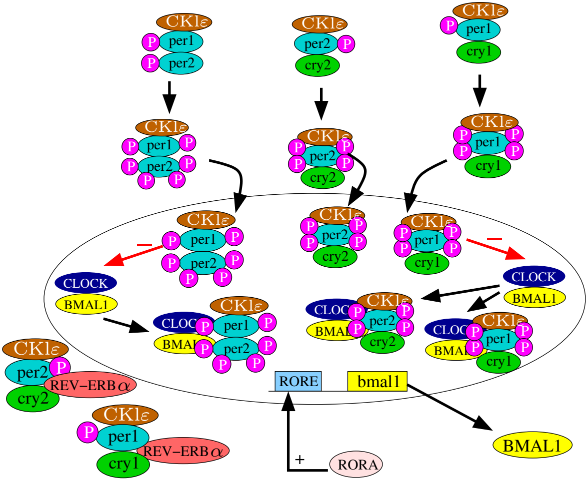
- Interest for circadian clock (jet lag)
  - sleeping, locomotion activities, internal temperature...
  - interactions with other subsystems (cellular cycle, metabolic pathways)
  - drug chronotherapy
- focus on the question of robustness with respect to day length
- different modeling frameworks
  - mathematical differential equations
  - probabilistic approaches
  - discrete and hybrid models (formal methods)
- seminal model : Leloup-Goldbeter
- 4 models compatible with experiments
  - 8 variable differential model
    4 variable differential model
  - purely discrete model
  - hybrid model

Outline

Biological background : during the day

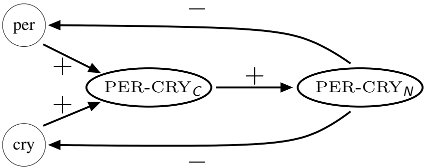


Biological background : during the night

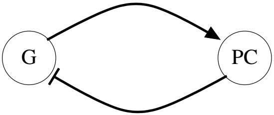


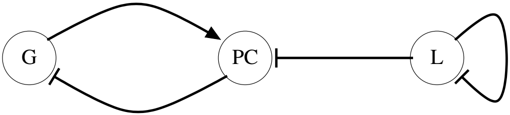
Discrete model

From an abstract point of view :

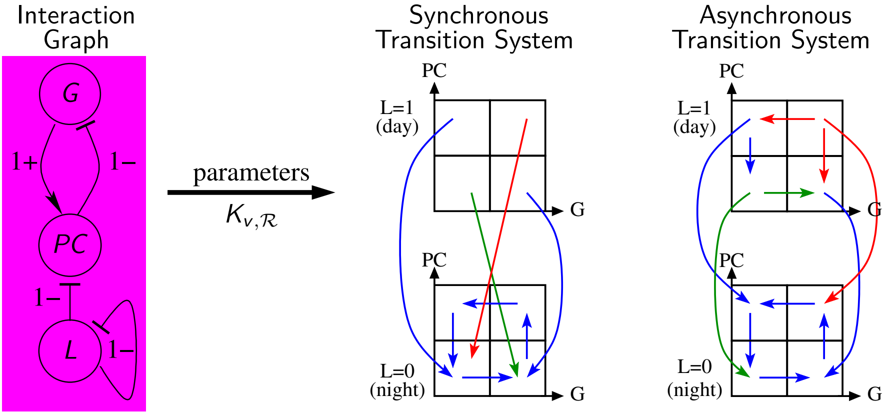


- the 2 negative cycles are known to act roughly in the same time sustaining the circadian oscillation.
- the main role of per and cry is to produce the PER-CRY complex.
- amalgamate per & cry into an abstract "set of genes"
- remove the node PER-CRY$_C$, we get the following model





Thomas' modelling in a nutshell



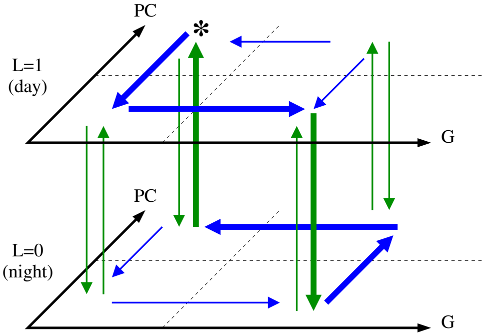
Identifying discrete parameters

- $K_{v,\omega}$: value towards which v is attracted

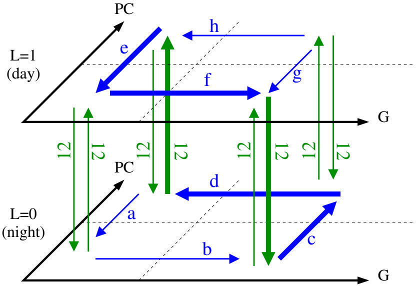
Variable L : $K_{L,\{\}} = 1$ and $K_{L,\{L\}} = 0$
Variable G : $K_{G,\{\}} = 1$ and $K_{G,\{PC\}} = 0$
Variable PC :

1	$G = 0$ and $\mathbf{L = 1}$: no transcription of genes and existing complexes PC_C are kept outside the nucleus	$\Rightarrow$	$\mathbf{K_{PC,\{L\}}} = \mathbf{0}$.
2	$G = 1$ and $\mathbf{L = 1}$: transcription of genes but light prevents complexes to enter the nucleus.	$\Rightarrow$	$\mathbf{K_{PC,\{G,L\}}} = \mathbf{0}$.
3	$G = 0$ and $L = 0$: **no transcription of genes** and PC_C is not synthesized, they do not enter the nucleus.	$\Rightarrow$	$\mathbf{K_{PC,\{\}}} = \mathbf{0}$.
4	$G = 1$ and $L = 0$: then PC complexes accumulate in the cytosol and **they can enter the nucleus**	$\Rightarrow$	$\mathbf{K_{PC,\{G\}}} = \mathbf{1}$.

Qualitative dynamics



Hybrid model : Labelling the state graph with delays



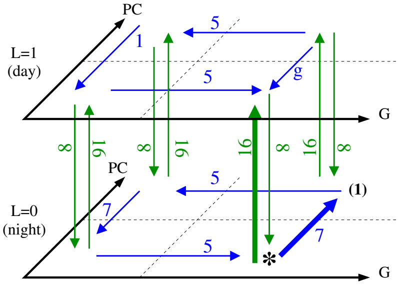
- duration of a transition.
- a clock is associated with each variable

- if a unique outgoing transition : wait and cross the transition when the clock reaches the transition duration
- when several outgoing transitions : wait until the first clock reaches the transition duration
- reset the clocks for which the order has changed

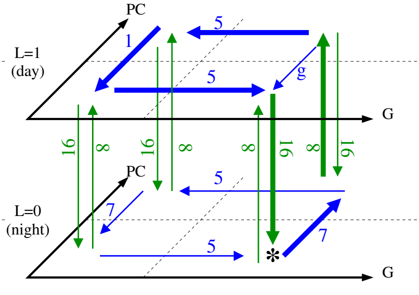
Hybrid model : Identification of delays

Several constraints on delays can be extracted from the biol. knowledge. ⇒ infinity of solutions.

$$
\begin{array}{cccccccccccc}
a & = & 7 & b & = & 5 & c & = & 7 & d & = & 5 \\
e & = & 1 & f & = & 5 & g & = & ? & h & = & 5
\end{array}
$$



During the winter



During the summer

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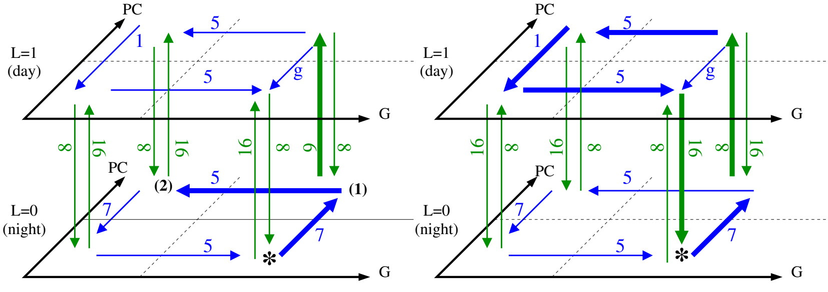

During the winter During the summer

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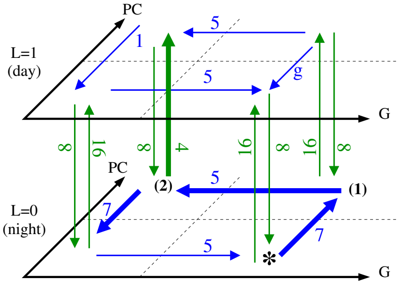

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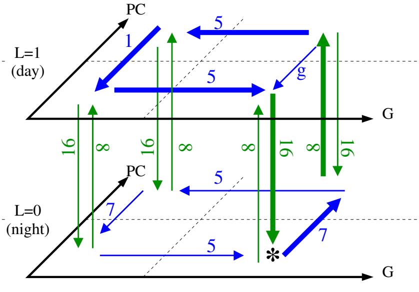

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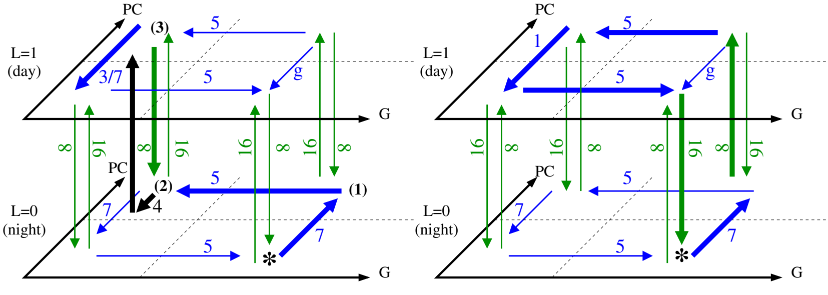

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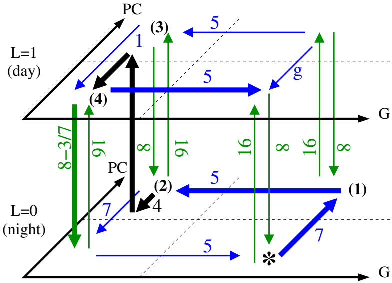

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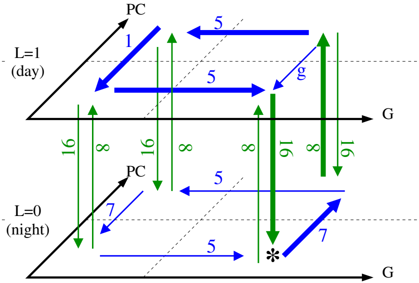

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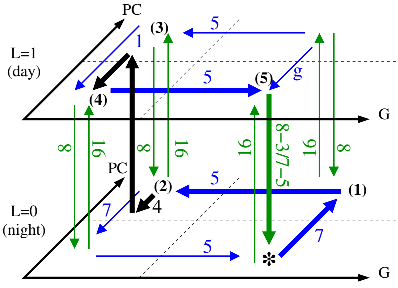

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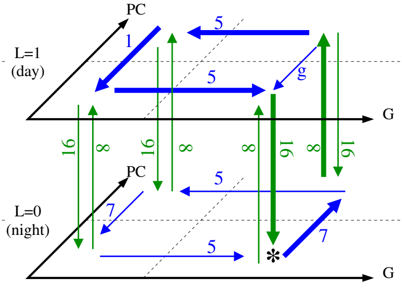


During the summer

Conclusion

- When modeling a biological system, often two options :
  - elaborate a rich model reflecting as much biological knowledge as possible in a consistent way,
  - to design a simplified model dedicated to a given family of questions to study the main causalities at a coarse-grained scale.
- This article was inspired by the second philosophy : the robustness of the model to the day length.

- Future work :
  when focusing on a particular property φ,
  it is possible to transform a model M to a model M' if

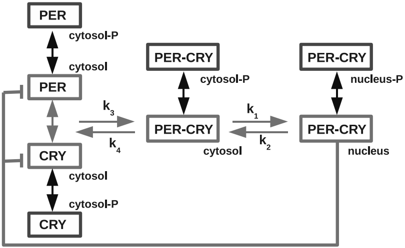
$$M \text{ satisfies } \phi \quad \text{iff} \quad M' \text{ satisfies } \phi'$$

Thank you for your attention

Differential models : the Leloup-Goldbeter model

- 16 variables :
  - mRNA : per, cry, bmal1 — 3
  - (non)phosphorylated proteins in cytosol : PER, CRY — 4
  - (non)phosphorylated complex PER-CRY in cytosol and nucleus — 4
  - (non)phosphorylated protein BMAL1 in cytosol and nucleus — 4
  - complex (PER-CRY)-(CLOCK-BMAL1) — 1
- cyclic behavior with a sensible circadian period
- study of this model in constant darkness and under light-dark alternation (12 hours / 12 hours)
- Correct predictions on several mutants

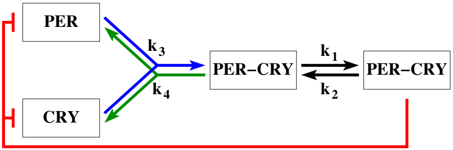
Differential models : A model with 8 variables



- Clock : never a critical resource
- translation + traduction : a unique step
- direct abstract regulation of PER-CRY on PER and CRY (without formation of complex PER-CRY/CLOCK-BMAL1)

- 8 kinetic equations with 28 parameters
- parameter values are chosen similar to those of Leloup and Goldbeter

Differential models : A model with 4 variables



- phosphorylations are removed
- 4 kinetic equations with 12 parameters

$$\frac{dP_C}{dt} = \frac{\mathbf{K^n}}{\mathbf{K^n} + \mathbf{PC_N^n}}\mathbf{v_1} - \mathbf{k_3 P_C C_C} + \mathbf{k_4 PC_C} - kd_1 P_C \quad (1)$$

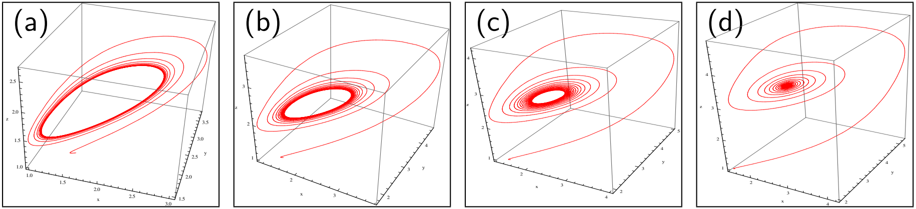
$$\frac{dC_C}{dt} = \frac{\mathbf{K^n}}{\mathbf{K^n} + \mathbf{PC_N^n}}\mathbf{v_2} - \mathbf{k_3 P_C C_C} + \mathbf{k_4 PC_C} - kd_2 C_C \quad (2)$$

$$\frac{dPC_C}{dt} = \mathbf{k_3 P_C C_C} - \mathbf{k_4 PC_C} - \mathbf{k_1 PC_C} + \mathbf{k_2 PC_N} - kd_3 PC_C \quad (3)$$

$$\frac{dPC_N}{dt} = \mathbf{k_1 PC_C} - \mathbf{k_2 PC_N} - kd_4 PC_N \quad (4)$$

Existence of a limit cycle

- the existence of the cycle depends on the degradation rate of PC_N
- Hopf bifurcation for parameter kd_4



$kd_4 = 0.25$ $kd_4 = 0.35$ $kd_4 = 0.42$ $kd_4 = 0.55$

- same bifurcation schema with kd3 (degradation rate of PC_C).