Systems and models in chronobiology

A delay model for the circadian rhythm

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Outline

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Circadian rhythms (1)

Definition and roles

Definition

Biological rhythms with a period $\tau \sim 24$h

Roles

Circadian rhythms control

- Sleep
- Muscular activity and metabolism
- Food ingestion
- ...

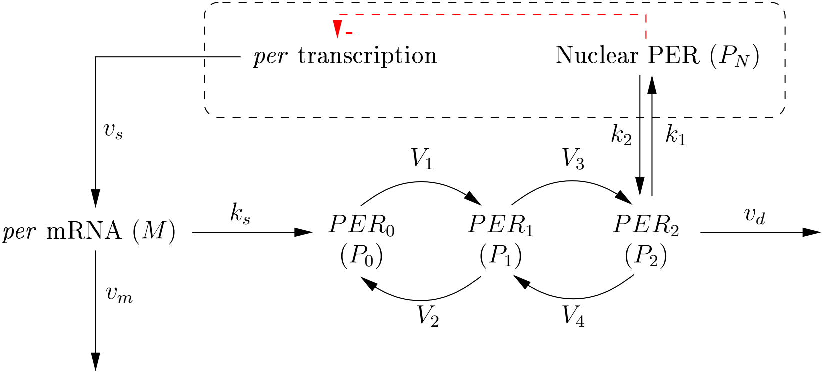
Moreover, there are possible links with various pathologies

Circadian rhythms (2)
Properties

Property	Comment
Ubiquitous	All eukaryotes and some prokaryotes
Entrainment	Zeitgeber=light/temperature cycles
Genetic mechanisms	Single-gene clock mutants isolated
Precision	$\Delta\tau < 0.1\%$
Robustness	T°, IC...
Cellular nature	A cell-autonomous circadian oscillator mechanism exists and appears to be a fundamental unit even among multicellular organisms

Outline

Simple model
Biochemical principle



from Goldbeter, *Biochemical oscillations and cellular rhythms*, Cambridge University Press, 1996

Simple model

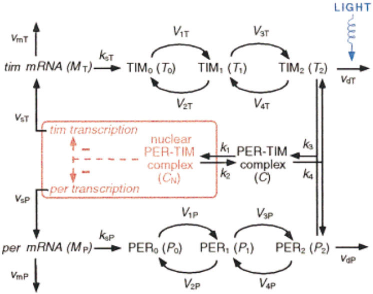
Equations

$$
\begin{aligned}
\dot{M} &= v_s \frac{K_I^n}{K_I^n + P_N^n} - v_m \frac{M}{k_m + M} \\
\dot{P}_0 &= k_s M - V_1 \frac{P_0}{K_1 + P_0} + V_2 \frac{P_1}{K_2 + P_1} \\
\dot{P}_1 &= V_1 \frac{P_0}{K_1 + P_0} - V_2 \frac{P_1}{K_2 + P_1} - V_3 \frac{P_1}{K_3 + P_1} + V_4 \frac{P_2}{K_4 + P_2} \\
\dot{P}_2 &= V_3 \frac{P_1}{K_3 + P_1} - V_4 \frac{P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - v_d \frac{P_2}{k_d + P_2} \\
\dot{P}_N &= k_1 P_2 - k_2 P_N
\end{aligned}
$$

- 5 nonlinear ODEs
- 17 parameters

Evolutions of the model

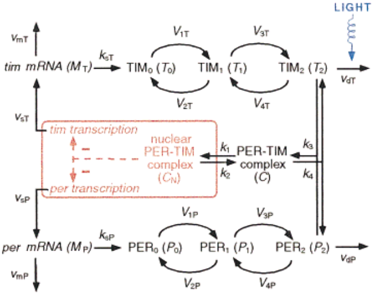
Drosophilia



- 10 nonlinear ODEs
- 34 parameters

Evolutions of the model

Drosophila



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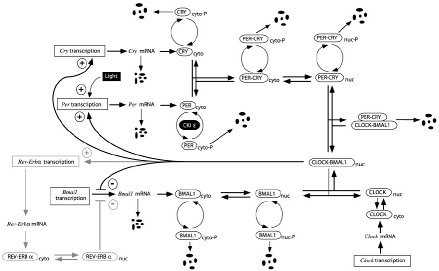
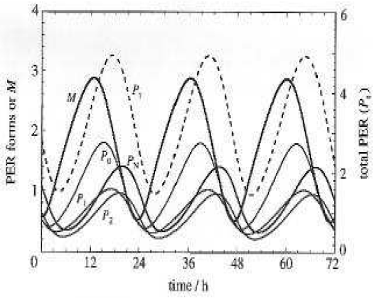
Mammals



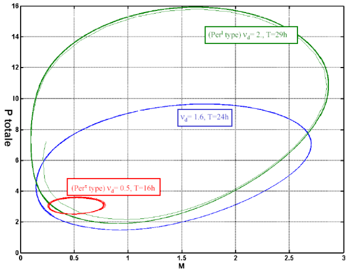
- 19 nonlinear ODEs
- 59 parameters

Results (1)
Oscillations and limit cycle

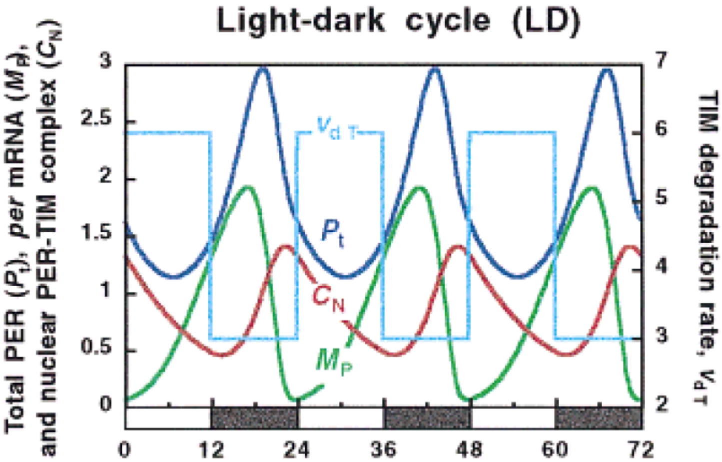
Oscillations



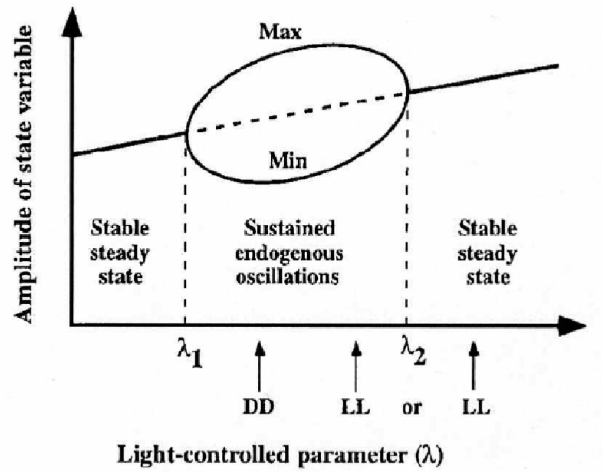
Limit Cycle



Results (2)
Entrainment



Results (3)
Bifurcation diagram



Outline

Limitations of current mathematical modeling

- Very complicated systems (strongly nonlinear, several variables and parameters)
  $\longrightarrow$ restricted to numerical simulations
- Impossible to test all parameter combinations
- Mathematically (and computationally) difficult to study interconnections
- Exhibit some properties, but NOT explain them

System approach
Principle

Developing or using system models and tools for the analysis of biological system (and particularly oscillatory systems)

System approach

Links with system question

By nature, cells are open systems, i.e. with *inputs* and *outputs*
Many unexplained properties are related to fundamental systems questions:

- Why is there an entrainment?
- Why is the system robust to certain parameters variation (T°, initial conditions...)? Why is it robust to molecular noise? And to external disturbance?
- How can we guess from observed properties, the values of unknown parameters?
- Why is there a synchronization in networks of oscillators? What kind of synchronized behaviour may we expect given a particular network configuration?

Outline

Recent approaches

Classical methods for the analysis of limit cycles

Limitations: either useless in high dimension (and so for interconnections) or unable to handle global treatment

Abstract models

Limitations: Acts more as a "black box" i.e. it is possible to obtain qualitative information, but no quantitative one.

Development of new methods

- Monotone Systems (P. de Leenheer, D. Angeli, E. Sontag)
- Piecewise Linear Systems - PLS (J. Goncalves)
- Dissipative Systems (R. Sepulchre, G.B. Stan)

= dedicated I/O approaches

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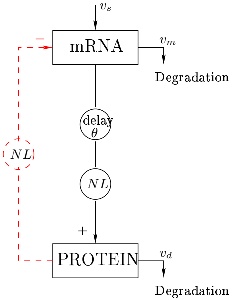
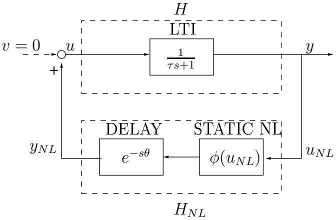
A delay model for the circadian rhythm
Variation on Goldbeter's model: 2 variables

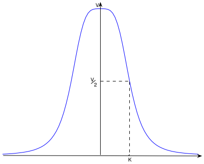


$$\begin{aligned}\dot{M} &= v_s \frac{K_I^n}{K_I^n + P^n} - v_m M\\ \dot{P} &= v_P M(t-\tau)^m - v_d P\end{aligned}$$

from T. olde Scheper and al., *A Mathematical Model for the Intracellular Circadian Rhythm Generator*, J. of Neuroscience, 1999

A delay model for the circadian rhythm
Further simplification : 1 variable





$$\dot{M} = v_s \frac{K_I^n}{K_I^n + M(t-\tau)^n} - v_m M$$

This model is equivalent to the famous **Mackey and Glass' model** for Red Blood Cell regulation

Outline

Conclusion and perspectives

There remains many **unsolved questions** in the exploding field of mathematical biology.
Most of these are **natural** in the framework of **systems modeling**: synchronization, robustness, entrainment...

Our research group currently develops methods based on an input/output approach to answer (some of) those questions and **classify** basic oscillatory mechanisms.

We are tempting to analyze a new mechanism based on a **delay** and a specific **regulatory nonlinearity** in the feedback loop.

Thank you

Thank you for your attention... :-)