Systems and models in chronobiology

Modeling and analysis of the circadian rhythm

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Outline

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Definition and origin

Biological rhythms

Periodic variation of a measurable biological quantity (protein concentration, mRNA concentration, number of cells...)

Origin

Regulation and interaction phenomena (either positive or negative) at different levels:

- enzyms (activation, inhibition)
- receptors (desensibilization)
- ionic channels (inactivation)
- transport
- genes (induction, repression)

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Main biological rhythms

Rhythm	**Period τ**
Neural rhythms*	$0.001s - 10s$ (and more?)
Cardiac rhythms*	$1s$
Calcium oscillations*	$1s - 1min$
Mitotic cycle*	$10min - 15h$
Biochemical oscillations*	$1min - 20min$
Hormonal rhythms*,+	$10min - 5h$
Circadian rhythms*	$24h$
Ovarian cycle+	28 days
Annual rhythms+	1 year
Epidemiology and ecological oscillation	years

* Cellular rhytms

+ Poorly known rhythms

Circadian rhythms (1)
Definition and roles

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

Favorite organisms
Neurospora, drosophilia, cyanobacteria, Chlamydomonas, hamsters and mices.

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

Historical flags

"Prehistory"

Jean-Jacques d'Ortous de Mairan (1729), *Lotka-Volterra* (1920-1925), *Hodgkin-Huxley* (1952)

"Middle-age"

- *Winfree* (1960-1990): qualitative description
  First emphasis on interconnection and synchronisation
- *Goodwin* (1965): first biochemical model
  Coupling (2 oscillators)

"Modern age"

Developments of genetics and technology (microarrays...)
Goldbeter (1996): one of the first quantitative biochemical model

Goals

Goals

Using **mathematical models** coupled with **experimental data** (intuition is not enough) to

- analyze *principles* and *mechanisms* (unification, key parameters, links with other phenomena)
- make *quantitative prediction* on the system (sometimes inacessible to experiments)

$\longrightarrow$ possibility to drive **future experiments**

But...

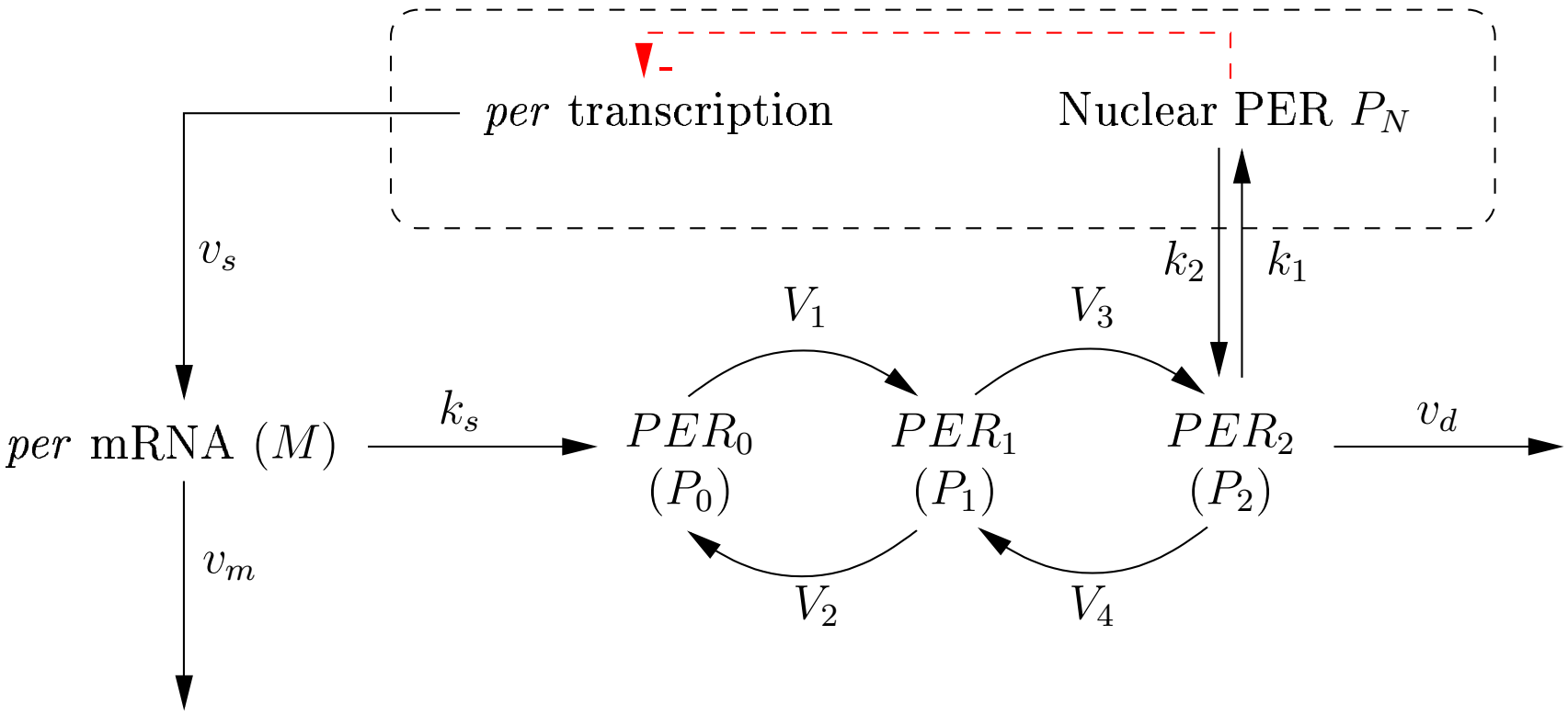
Most biologists are still suspicious about mathematical modelling because

- most biological process at the cellular level should be regarded as **stochastic processes (molecular noise)**
- very often, few information is known about real **parameter values** or even range
- real curves are always **less smooth**, and less reproductible

HOWEVER these models don't claim to represent the reality but are just tools we can use to better *understand* the phenomena and make some *predictions*.

Simple model

Biochemical principle



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

Simple model

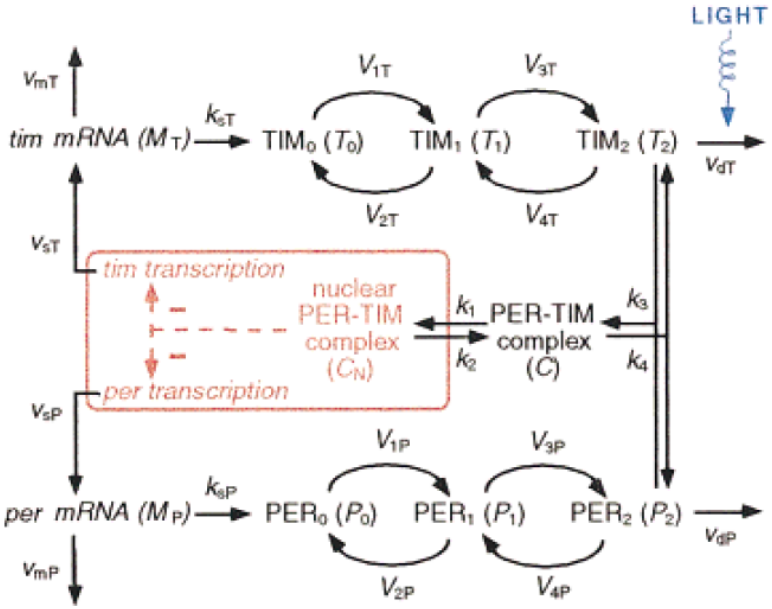
Equations

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

- 5 nonlinear ODEs
- 17 parameters

Evolutions of the model

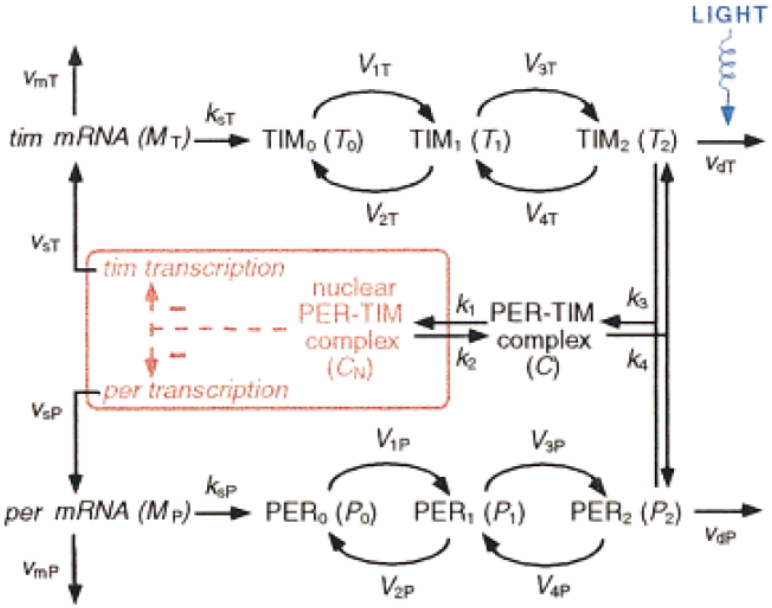
Drosophilia



- 10 nonlinear ODEs
- 34 parameters

Evolutions of the model

Drosophilia



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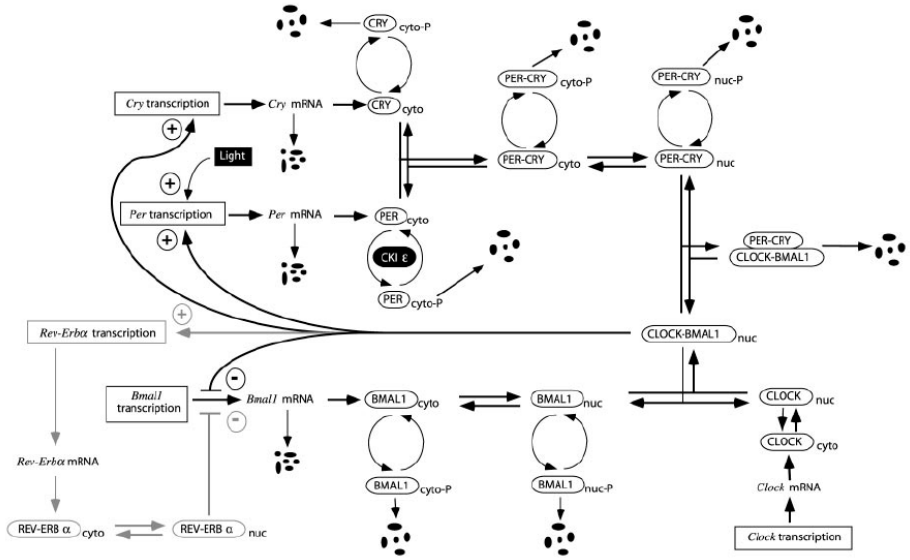
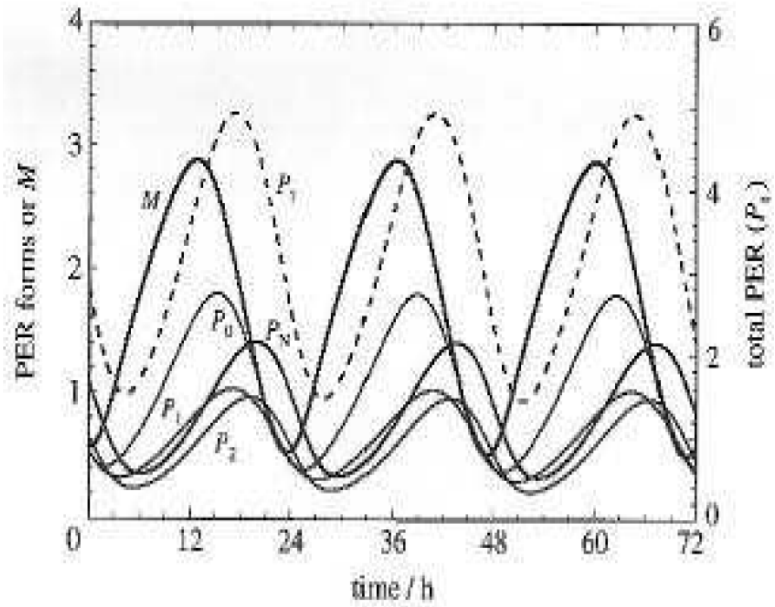
Mammals



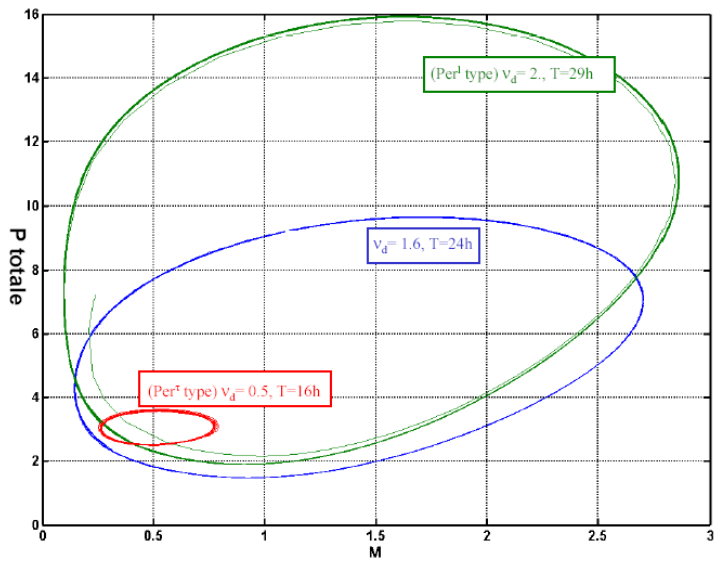
- 19 nonlinear ODEs
- 59 parameters

Results (1)
Oscillations and limit cycle

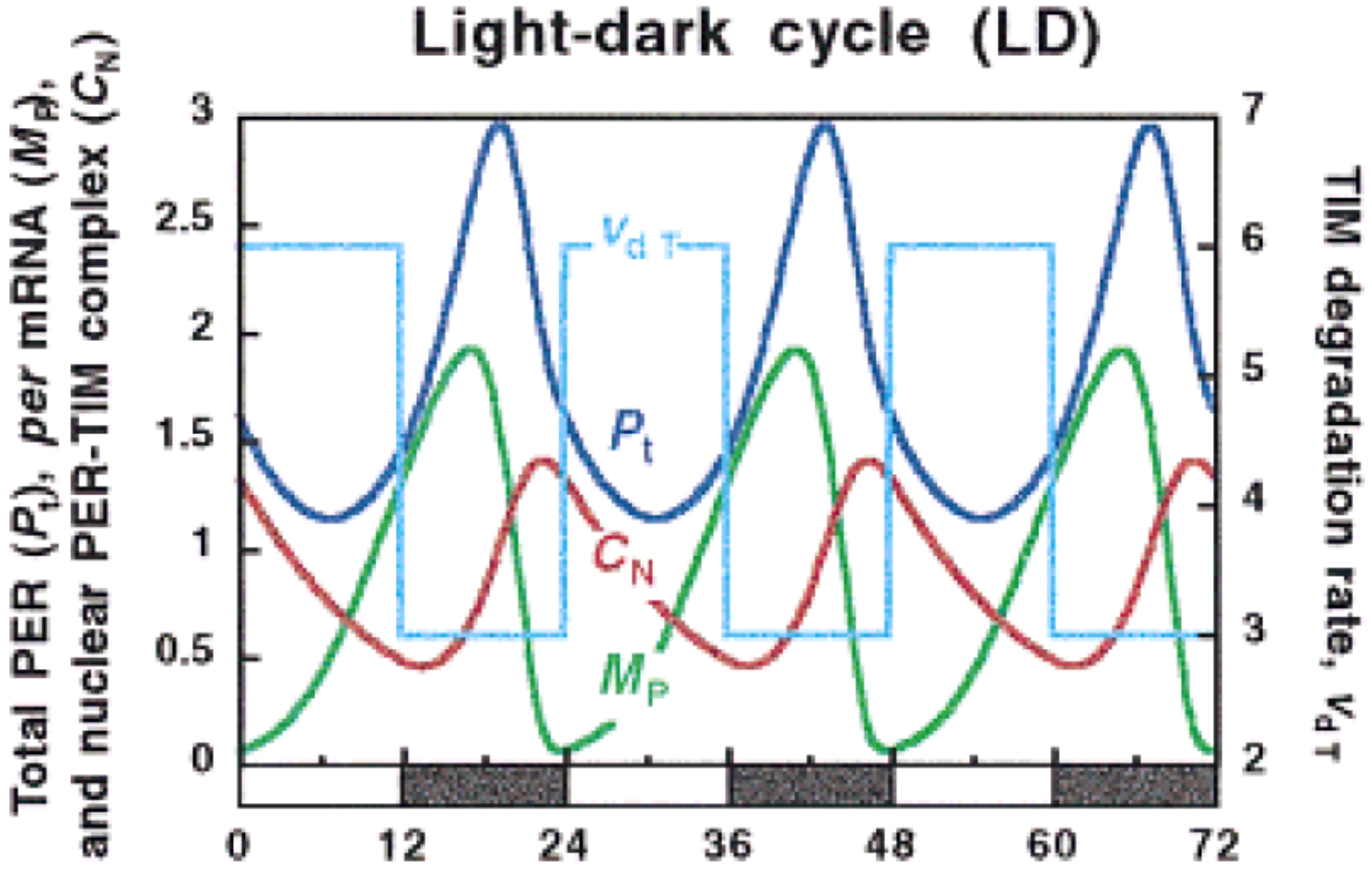
Oscillations



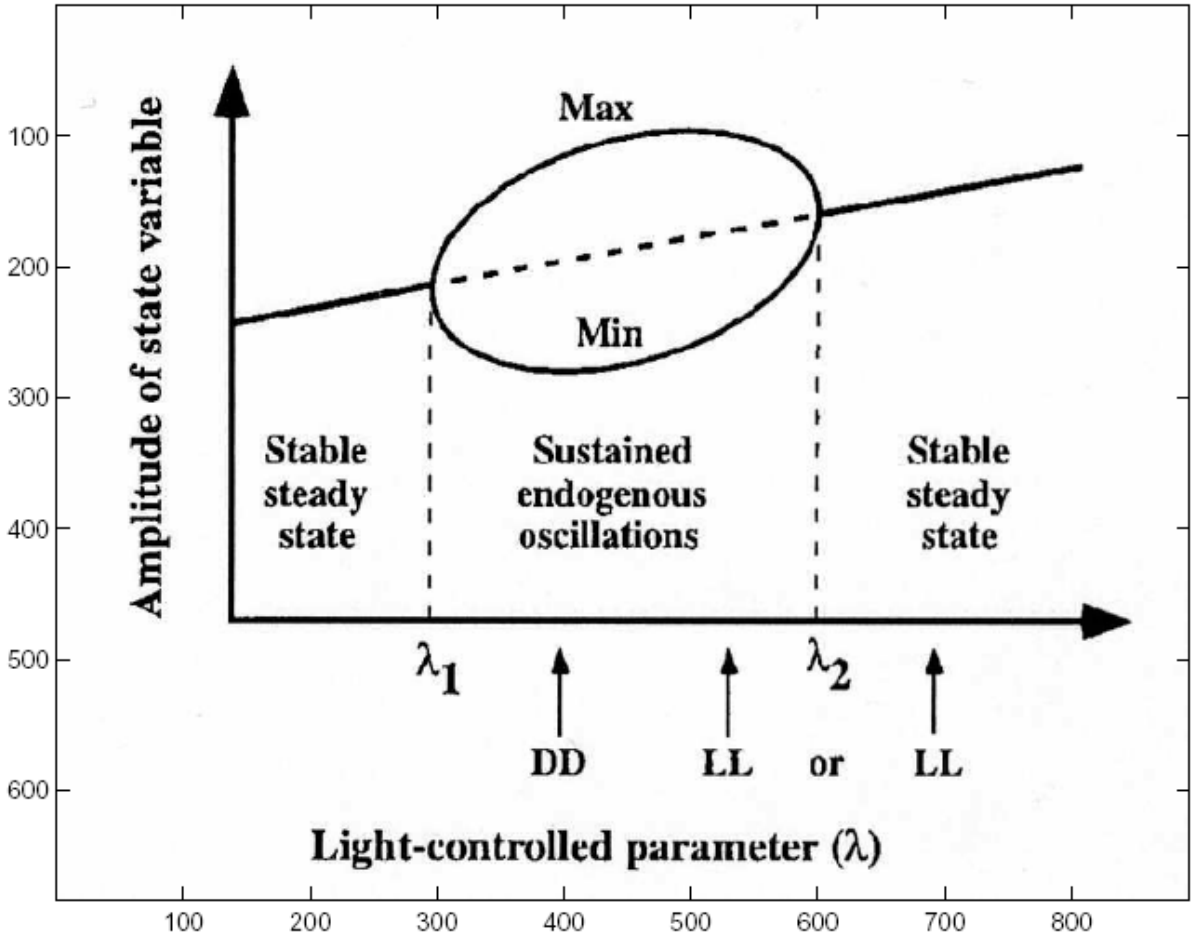
Limit Cycle



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 computally) 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 particulary 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 synchronisation in networks of oscillators? What kind of synchronized behaviour may we expect given a particular network configuration?

System approach
Necessity of research

Objective: make a link between *natural properties* and *mathematical structure*

However, those questions are still **open question** for oscillators

There is thus a strong need for research in that field!

System approach
Sontag's remarks

- Not sufficient to merely apply existing theories because, at closer look, biological problems are quite **different of standard system problems**
  $\longrightarrow$ necessity to develop *dedicated tools* for biological modelling
- Analysis of the **very efficient robustness** of biological system can also influence new development of control theory

First approach: application of existing theories
Classical methods

Classical methods for the analysis of limit cycle

There exist various tools for the (global) analysis of limit cycles:

- phase plane methods
- Poincarré-Bendixon theorem
- Poincaré maps

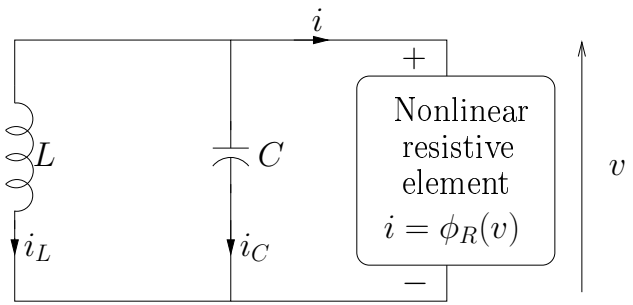
Limitations: either useless in high dimension (and so for interconnections) or unable to handle global treatment

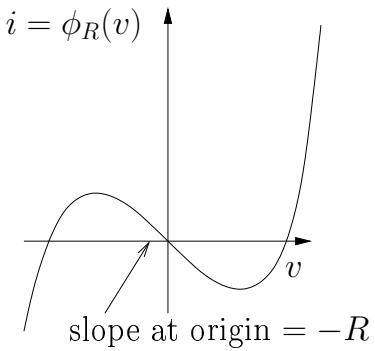
Second approach: abstract models

Using well-known (abstract) oscillating models manipulated so that $\tau \sim 24h$ to modelize circadian rhythm

Example

The Van der Pol oscillator





Second approach: abstract models

The Van der Pol oscillator

$$\begin{aligned} \dot{x} &= y + \epsilon(x - \frac{1}{3}x^3) \\ \dot{y} &= -x \end{aligned} \quad \rightarrow \quad \begin{aligned} \frac{12}{\pi}\dot{x} &= y + \epsilon(x - \frac{4}{3}x^3) + B \\ \frac{12}{\pi}\dot{y} &= -\left(\frac{24}{\tau}\right)^2 x + By \end{aligned}$$

Very basic low dimensionnal model

Mostly used to analyse interconnection of oscillators (robustness, stability...)

Limitations

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

Third approach: development of new methods

A few examples:

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

Third approach: development of new methods

Dissipative systems

This theory was developed in the control group at the University of Liège.
It relies on the dissipativity (passivity) theory to analyse

- **global stability** of limit cycles
- global stability of oscillations and synchronization in **interconnections**

$\longrightarrow$ first analysis of an oscillatory *mechanism*
Not applicable to Goldbeter's model
My personnal research is the continuation of this work, but for another kind of mechanism valid on Goldbeter's model.

Outline

Conclusion

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

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