Systems and models in chronobiology

A delay model for the circadian rhythm

M. Dechesne
R. Sepulchre

Department of Electrical Engineering and Computer Science
Montefiore Institute
University of Liège

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Outline

Introduction

State of the art in mathematical modeling of the circadian rhythm
  Biological modeling for the circadian oscillator
Results

Systems viewpoint: Why is it useful?

Application to the analysis of the circadian rhythm

Conclusion
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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

<table>
<thead>
<tr>
<th>Property</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ubiquitous</td>
<td>All eukaryotes and some prokaryotes</td>
</tr>
<tr>
<td>Entrainment</td>
<td>Zeitgeber=light/temperature cycles</td>
</tr>
<tr>
<td>Genetic mechanisms</td>
<td>Single-gene clock mutants isolated</td>
</tr>
<tr>
<td>Precision</td>
<td>$\Delta \tau &lt; 0.1%$</td>
</tr>
<tr>
<td>Robustness</td>
<td>$T^\circ, IC...$</td>
</tr>
<tr>
<td>Cellular nature</td>
<td>A cell-autonomous circadian oscillator mechanism exists and appears to be a fundamental unit even among multicellular organisms</td>
</tr>
</tbody>
</table>
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Simple model
Biochemical principle

Simple model
Equations

\[
\begin{align*}
\dot{M} &= v_s \frac{K^n}{K^n + P_n^N} - v_m \frac{M}{k_m + M} \\
\dot{P}_0 &= k_s M - V_1 \frac{P_0}{K_1 + P_0} + V_2 \frac{P_1}{K_2 + P_1} \\
\dot{P}_1 &= V_1 \frac{P_0}{K_1 + P_0} - V_2 \frac{P_1}{K_2 + P_1} - V_3 \frac{P_1}{K_3 + P_1} + V_4 \frac{P_2}{K_4 + P_2} \\
\dot{P}_2 &= V_3 \frac{P_1}{K_3 + P_1} - V_4 \frac{P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - v_d \frac{P_2}{k_d + P_2} \\
\dot{P}_N &= k_1 P_2 - k_2 P_N
\end{align*}
\]

- 5 nonlinear ODEs
- 17 parameters
Evolutions of the model

Drosophila

- 10 nonlinear ODEs
- 34 parameters
Evolutions of the model

**Drosophila**
- 10 nonlinear ODEs
- 34 parameters

**Mammals**
- 19 nonlinear ODEs
- 59 parameters
Results (1)
Oscillations and limit cycle

Oscillations

Limit Cycle
Results (2)

Entrainment
Results (3)
Bifurcation diagram
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Limitations of current mathematical modeling

- Very complicated systems (strongly nonlinear, several variables and parameters)
  → 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)
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 ($T^\circ$, 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?
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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
Recent approaches

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Variation on Goldbeter’s model: 2 variables

\[
\dot{M} = v_s \frac{K_l^n}{K_l^n + P^n} - v_m M
\]
\[
\dot{P} = v_P M(t - \tau)^m - v_d P
\]

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

This model is equivalent to the famous Mackey and Glass’ model for Red Blood Cell regulation.
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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 tempted 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... :-)