Stochastic simulations
Application to circadian clocks

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Circadian rhythms
Circadian rhythms allow living organisms to live in phase with the alternance of day and night...

Molecular mechanism of circadian clocks
Core mechanism: negative feedback loop

Expression of per gene

Circadian rhythms in Drosophila

Locomotor activity


Mammals

Neurospora

Core mechanism: negative feedback loop

Drosophila per (period), tim (timeless)
Mammals mper1-3 (period homologs)
Neurospora freq (frequency)
Deterministic models for circadian rhythms

Goldbeter's 5-variable model


\[
\frac{dM_p}{dt} = v_5 \frac{K_p^m}{K_p^m + P_N^m} - v_m \frac{M_p}{K_m + M_p}
\]

\[
\frac{dP_0}{dt} = k_4 M_p - v_1 \frac{P_1}{K_1 + P_0} + v_2 \frac{P_2}{K_2 + P_1}
\]

\[
\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}
\]

\[
\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_3 \frac{P_2}{K_3 + P_2} - k_1 P_1 + k_2 P_N
\]

\[
\frac{dP_N}{dt} = k_1 P_2 - k_2 P_N
\]
Goldbeter’s 5-variable model

Dynamics of per mRNA (MP): degradation
\[
\frac{d\text{MP}}{dt} = v_5 \frac{K_i^n}{K_i^n + P_N} \text{MP} - v_m \text{MP} / (K_m + \text{MP})
\]

Degradation: Michaelis-Menten

Degradation rate:

\[
v_m = k_2 \text{E}_{\text{tot}}
\]

\[
E \ll M, \quad k_1, k_2 \gg k_2
\]

\[
K_M = (k_1 + k_2) / k_1
\]

Goldbeter’s 5-variable model

Dynamics of PER protein (P0, P1, P2, PN)
\[
\frac{dP_0}{dt} = k_4 \text{MP} - v_1 \frac{P_0}{K_1 + P_0} + v_2 \frac{P_1}{K_2 + P_1}
\]

PER synthesis: proportional to mRNA

\[
\frac{dP_1}{dt} = v_1 \frac{P_0}{K_1 + P_0} - v_2 \frac{P_1}{K_2 + P_1} - v_3 \frac{P_1}{K_3 + P_1} + v_4 \frac{P_2}{K_4 + P_2}
\]

\[
\frac{dP_2}{dt} = v_3 \frac{P_1}{K_3 + P_1} - v_4 \frac{P_2}{K_4 + P_2} - v_5 \frac{P_2}{K_d + P_2} - k_1 P_2 + k_2 P_N
\]

\[
\frac{dP_N}{dt} = k_1 P_2 - k_2 P_N
\]
Goldbeter's 5-variable model

Dynamics of PER protein (P₀, P₁, P₂, Pₙ)

\[
\frac{dP₀}{dt} = k₁Mₚ - \frac{P₀}{K₁ + P₀} + \frac{P₁}{K₂ + P₁}
\]

\[
\frac{dP₁}{dt} = v₁\frac{P₀}{K₁ + P₀} - \frac{P₁}{K₂ + P₁} - \frac{P₂}{K₃ + P₂} + \frac{P₄}{K₄ + P₄}
\]

\[
\frac{dP₂}{dt} = v₃\frac{P₂}{K₄ + P₂} - \frac{k₃P₂}{K₅ + P₅} - k₄P₄
\]

\[
\frac{dPₙ}{dt} = k₅P₅ - k₆P₆
\]

PER nuclear transport: linear

Limit-cycle oscillations

- Mutants (long-period, short-period, arrhythmic)
- Entrainment by light-dark cycles
- Phase shift induced by light pulses
- Suppression of oscillations by a light pulse
- Temperature compensation
- ...

Molecular mechanism of circadian clocks

interlocked positive and negative feedback loops

Clock gene | Activator | Effect of light
---|---|---
Drosophila | per, tim | clk, cyc
Mammals | mper1-3, cry1,2 | clock, bmal1
Neurospora | frq | wc-1, wc-2


Model for the mammalian circadian clock


16-variable model including per, cry, bmal1, rev-erbα

Circadian clocks limited by noise?

Circadian clocks limited by noise

Goldbeter’s 5-variable model

Stochastic simulations

Fluctuations are due the limited number of molecules (molecular noise). They can be assessed thanks to stochastic simulations.

Such an approach requires a description in term of the number of molecules (instead of concentrations).

Here, we will focus on several robustness factors:

- Number of molecules
- Degree of cooperativity
- Periodic forcing (LD cycle)
- Proximity of a bifurcation point
- Coupling between cells

Gillespie algorithm

A reaction rate $w_i$ is associated to each reaction step. These probabilities are related to the kinetics constants.

Initial number of molecules of each species are specified.

The time interval is computed stochastically according the reaction rates.

At each time interval, the reaction that occurs is chosen randomly according to the probabilities $w_i$ and both the number of molecules and the reaction rates are updated.


Detailed reaction scheme

Successive binding of 4 $P_N$ molecules to the gene $G$

Transcription

Degradation of mRNA

Translation

Two reversible phosphorylation steps

Degradation of protein

Translocation of protein

Stochastic description of the model

<table>
<thead>
<tr>
<th>Reaction step</th>
<th>Reaction step</th>
<th>Probability of reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$G + P_N \rightarrow GP_N$</td>
<td>$\nu \times \frac{1}{4}$</td>
</tr>
<tr>
<td>2</td>
<td>$GP_N + P_N \rightarrow GP_{2N}$</td>
<td>$\nu \times \frac{1}{2}$</td>
</tr>
<tr>
<td>3</td>
<td>$GP_{N2} + P_N \rightarrow GP_{3N}$</td>
<td>$\nu \times \frac{1}{4}$</td>
</tr>
<tr>
<td>4</td>
<td>$GP_{N3} + P_N \rightarrow GP_{4N}$</td>
<td>$\nu \times \frac{1}{2}$</td>
</tr>
<tr>
<td>5</td>
<td>$P_h + E_1 \rightarrow C_1 \rightarrow P_1 + E_1$</td>
<td>$\nu \times \frac{1}{4}$</td>
</tr>
<tr>
<td>6</td>
<td>$P_h + E_2 \rightarrow C_2 \rightarrow P_2 + E_2$</td>
<td>$\nu \times \frac{1}{2}$</td>
</tr>
<tr>
<td>7</td>
<td>$P_h + E_3 \rightarrow C_3 \rightarrow P_3 + E_3$</td>
<td>$\nu \times \frac{1}{4}$</td>
</tr>
<tr>
<td>8</td>
<td>$P_h + E_4 \rightarrow C_4 \rightarrow P_4 + E_4$</td>
<td>$\nu \times \frac{1}{2}$</td>
</tr>
<tr>
<td>9</td>
<td>$P_h + E_3 \rightarrow C_3 \rightarrow P_3 + E_3$</td>
<td>$\nu \times \frac{1}{4}$</td>
</tr>
<tr>
<td>10</td>
<td>$P_h + E_4 \rightarrow C_4 \rightarrow P_4 + E_4$</td>
<td>$\nu \times \frac{1}{2}$</td>
</tr>
</tbody>
</table>

Successive binding of 4 $P_N$ molecules to the gene $G$

Transcription

Degradation of mRNA

Translation

Two reversible phosphorylation steps

Degradation of protein

Translocation of protein
Stochastic oscillations and limit cycle

Deterministic

Stochastic


Developed vs non-developed model


Effect of the number of molecules, $\Omega$

$\Omega=1000$

$\Omega=100$

$\Omega=10$

Effect of the degree of cooperativity, $n$

$n=4$

$n=1$

Quantification of the effect of noise

Effect of the number of molecules, $\Omega$

Effect of the degree of cooperativity, $n$

Auto-correlation function

Effect of a periodic forcing (LD cycle)

Light-dark cycle
LD 12:12
light induces PER protein degradation, $v_d$

Effect of the proximity of a bifurcation point

Cooperative protein-DNA binding

We define $\gamma$:

$$a_i \rightarrow a_i / \gamma \quad (i = 1,...,4)$$

$$d_i \rightarrow d_i / \gamma \quad (i = 1,...,4)$$

Developed deterministic model

$$\frac{dP_{G}}{dt} = -\alpha G P_{G} + \beta P_{G}$$

$$\frac{dP_{X}}{dt} = \alpha G P_{G} - \delta P_{X} - \gamma (P_{X} - P_{X}) P_{G}$$

$$\frac{dP_{Y}}{dt} = \delta P_{X}$$

$$\frac{dP_{Z}}{dt} = -\delta P_{Y} + \epsilon P_{Z}$$

$$\frac{dP_{P}}{dt} = -\epsilon P_{Z} + \delta P_{P}$$

Deterministic model: bifurcation diagram

Influence of the protein-DNA binding rate

$\gamma = 100$

$\gamma = 1000$

Developed deterministic model: excitability

\[ \gamma = 1000 \]

\[ \gamma = 100 \]

\[ \gamma = 1 \]

Mechanisms of noise-resistance

Mechanisms of noise-resistance in genetic oscillators


Mutation and robustness to noise

Stochastic simulation of the mammalian circadian clock


Stochastic resonance in circadian clock?

Internal noise stochastic resonance in a circadian clock system


Light-noise induced supra-threshold circadian oscillations and coherent resonance in Drosophila

Coupling circadian oscillators

Mammals: SCN

Neurospora crassa

Neurospora: molecular mechanism

Neurospora crassa: Molecular mechanism of the circadian clock


Neurospora crassa

Coupling circadian oscillators: Neurospora

Neurospora crassa syncitium

Neurospora crassa circadian clock: single-cell model

\[
\begin{align*}
\frac{dM}{dt} &= \lambda v_m - \frac{M}{K_m + M} - v_n M \\
\frac{dF_n}{dt} &= k_2 M - v_d \frac{F_n}{K_f + F_n} - k_1 F_n + k_2 F_n \\
\frac{dF_c}{dt} &= k_1 F_c - k_2 F_n
\end{align*}
\]
**Robust circadian oscillations** are observed for a limited number of molecules, i.e., some tens mRNA molecules and hundreds of proteins molecules.

- **Cooperativity** increases the robustness of the oscillations.

- The **periodic forcing** of the oscillations (LD cycle) increases the robustness by stabilizing the phase of the oscillations.

- The proximity of a **bifurcation point** decreases the robustness of the oscillations. In particular, near an excitable steady state, highly irregular oscillations are observed.

- **Coupling** between cells increases the robustness of the oscillations.

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