Deterministic and stochastic models of circadian rhythms

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VKBL model of circadian rhythms

Deterministic and stochastic models

- Comparable behaviour for $\delta_R = 0.2$
- Qualitatively different behaviour for $\delta_R = 0.05$

Explanation
VKBL model – parameters

\[ \alpha_A = 50 \text{ h}^{-1} \]
\[ \alpha'_A = 500 \text{ h}^{-1} \]
\[ \alpha_R = 0.01 \text{ h}^{-1} \]
\[ \alpha'_R = 50 \text{ h}^{-1} \]
\[ \beta_A = 50 \text{ h}^{-1} \]
\[ \beta_R = 5 \text{ h}^{-1} \]
\[ \gamma_A = 1 \text{ mol}^{-1} \text{ h}^{-1} \]
\[ \gamma_R = 1 \text{ mol}^{-1} \text{ h}^{-1} \]
\[ \gamma_C = 2 \text{ mol}^{-1} \text{ h}^{-1} \]
\[ \delta_A = 1 \text{ h}^{-1} \]
\[ \delta_R = 0.2 \text{ h}^{-1} \]
\[ \delta_{MA} = 10 \text{ h}^{-1} \]
\[ \delta_{MR} = 0.5 \text{ h}^{-1} \]
\[ \theta_A = 50 \text{ h}^{-1} \]
\[ \theta_R = 100 \text{ h}^{-1} \]

[Vilar, Kueh, Barkai, Leibler, 2002]
Deterministic and stochastic modelling

\[ A \xrightarrow{k} \emptyset \]

\( A(t) \) ... number of molecules in time \( t \), provided \( A(0) = n_0 \)

**Law of mass action:**

\[
\frac{dA(t)}{dt} = -kA(t)
\]

**Gillespie stochastic simulation algorithm:**

\( kA(t)dt \) ... probability that a reaction occurs in \([t, t + dt)\)

(a) \( r \sim U(0, 1) \)

(b) \( \alpha = kA(t), \quad \tau = \frac{1}{\alpha} \ln \frac{1}{r} \)

(c) \( A(t + \tau) = A(t) - 1 \)

(d) \( t := t + \tau, \) go to (a)
VKBL model – law of mass action

\[\begin{align*}
\frac{dD_A}{dt} &= \theta_A D'_A - \gamma_A D_A A \\
\frac{dD'_A}{dt} &= -\theta_A D'_A + \gamma_A D_A A \\
\frac{dD_R}{dt} &= \theta_R D'_R - \gamma_R D_R A \\
\frac{dD'_R}{dt} &= -\theta_R D'_R + \gamma_R D_R A \\
\frac{dM_A}{dt} &= \alpha'_A D'_A + \alpha_A D_A - \delta_{MA} M_A \\
\frac{dM_R}{dt} &= \alpha'_R D'_R + \alpha_R D_R - \delta_{MR} M_R \\
\frac{dA}{dt} &= \beta_A M_A + \theta_A D'_A + \theta_R D'_R \\
&\quad - A(\gamma_A D_A + \gamma_R D_R + \gamma_C R + \delta_A) \\
\frac{dR}{dt} &= \beta_R M_R - \gamma_C A R + \delta_A C - \delta_R R \\
\frac{dC}{dt} &= \gamma_C A R - \delta_A C
\end{align*}\]

Initial conditions:

\[\begin{align*}
D_A &= D_R = 1 \text{ mol} \\
D'_A &= D'_R = M_A = M_R = A = R = C = 0 \text{ mol}
\end{align*}\]
Full system – solution of ODE

\begin{align*}
\text{DA} & \quad \text{DR} \\
\text{MA} & \quad \text{MR} \\
\text{A} & \quad \text{R} \quad \text{C}
\end{align*}

\begin{align*}
time \ [\text{hours}] & \\
0 & \quad 25 \quad 50 \quad 75 \quad 100
\end{align*}
Full system – Gillespie SSA
Full system – comparison

- DA
- stoch DA
- DR
- stoch DR
- MA
- stoch MA
- MR
- stoch MR
- A
- stoch A
- R
- stoch R
Full system – $\delta_R = 0.05$ – solution of ODE
Full system – $\delta_R = 0.05$ – Gillespie SSA
Full system – $\delta_R = 0.05$ – comparison
Full system – phase diagram

\[
\delta R = 0.2
\]

\[
\delta R = 0.05
\]
Simplified system

Quasi-steady state assumptions:

\[
\frac{dR}{dt} = \beta_R \tilde{M}_R^s(R) - \gamma_C \tilde{A}^s(R)R + \delta_A C - \delta_R R \\
\frac{dC}{dt} = \gamma_C \tilde{A}^s(R)R - \delta_A C
\]

\[
\tilde{A}^s(R) = \frac{1}{2}(\alpha'_A \rho(R) - K_d) + \frac{1}{2} \sqrt{(\alpha'_A \rho(R) - K_d)^2 + 4 \alpha_A \rho(R) K_d} \\
\rho(R) = \frac{\beta_A}{\delta_M} \frac{1}{\gamma_C R + \delta_A}, \quad K_d = \frac{\theta_A}{\gamma_A}
\]

\[
\tilde{M}_R^s(R) = \frac{\alpha'_R}{\delta_M} + \frac{\theta_R (\alpha_R - \alpha'_R)}{\delta_M (\theta_R + \gamma_R \tilde{A}^s(R))}
\]

Simplified chemical system:

\[\emptyset \xrightleftharpoons[k_1]{\delta_R} R \xrightleftharpoons[k_2]{\delta_A} C, \quad k_1 = \beta_R \tilde{M}_R^s(R), \quad k_2 = \gamma_C \tilde{A}^s(R)\]
Simplified system – $\delta_R = 0.2$ – two ODE
Simplified system – $\delta_R = 0.2$ – Gillespie SSA
Simplified system – $\delta_R = 0.2$ – comparison

- DA
- stoch DA
- DR
- stoch DR
- MA
- stoch MA
- MR
- stoch MR
- A
- stoch A
- R
- stoch R

Time [hours]
Simplified system – $\delta_R = 0.05$ – two ODE
Simplified system – $\delta_R = 0.05$ – Gillespie SSA
Simplified system – phase diagram

\[ \delta_R = 0.2 \]

\[ \delta_R = 0.05 \]

- **Stochastic**
- **Deterministic**
- **R-nullcline**
- **C-nullcline**

(number of R–molecules vs. number of C–molecules)
Mean period vs. $\delta_R$

![Graph showing the relationship between mean period and $\delta_R$. The graph includes data points for ODE and Gillespie SSA methods, with a downward trend as $\delta_R$ increases.](image)
Mean period – $\delta_R = 0.05$

Stochastic simulations, $\delta=0.05$

Period of deterministic system is infinite.
Conclusion

- Qualitatively different behaviour appears close to a bifurcation point.
- Bifurcation point of stochastic system seems to be around $\delta_R = 0.001$.
- Low copy numbers of a chemical species $\implies$ stochastic effects.
- High copy numbers $\implies$ stochastic and deterministic models agree.
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Thank you for your attention

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