Assignment 4: Monte Carlo methods
Genetic oscillator

Computational Methods for Scientific Applications, 2023

Background

This assignment is a continuation of the previous one. It is based on the same research paper (Vilar, Kueh, Barkai, Leibler)[1] but here we concentrate on the stochastic model of the "circadian clock".

Assignment

In the previous assignment the circadian rhythm was modeled with an ODE. An alternative model is to describe it with a stochastic model:

$$
\left.\begin{array}{rcl} D'_a & \xrightarrow{\theta_a D'_a} & D_a \\ D_a + A & \xrightarrow{\gamma_a D_a A} & D'_a \\ D'_r & \xrightarrow{\theta_r D'_r} & D_r \\ D_r + A & \xrightarrow{\gamma_r D_r A} & D'_r \end{array}\right\}
\quad
\left.\begin{array}{rcl} \emptyset & \xrightarrow{\alpha'_a D'_a} & M_a \\ \emptyset & \xrightarrow{\alpha_a D_a} & M_a \\ M_a & \xrightarrow{\delta_{ma} M_a} & \emptyset \end{array}\right\}
\quad
\left.\begin{array}{rcl} \emptyset & \xrightarrow{\beta_a M_a} & A \\ \emptyset & \xrightarrow{\theta_a D'_a} & A \\ \emptyset & \xrightarrow{\theta_r D'_r} & A \\ A & \xrightarrow{\delta_a A} & \emptyset \\ A + R & \xrightarrow{\gamma_c A R} & C \end{array}\right\}
$$

$$
\left.\begin{array}{rcl} \emptyset & \xrightarrow{\alpha'_r D'_r} & M_r \\ \emptyset & \xrightarrow{\alpha_r D_r} & M_r \\ M_r & \xrightarrow{\delta_{mr} M_r} & \emptyset \end{array}\right\}
\quad
\left.\begin{array}{rcl} \emptyset & \xrightarrow{\beta_r M_r} & R \\ R & \xrightarrow{\delta_r R} & \emptyset \\ C & \xrightarrow{\delta_a C} & R \end{array}\right\}
\qquad (1)
$$

This is a discrete Markov process and it can be simulated numerically with the Gillespies algorithm, also called Stochastic Simulation Algorithm (SSA). To solve the problems, you can either download `gillespie.py` from Studium or you can use the SSA-function from the lab (it is the same code).

[1] *José M. G. Vilar, Hao Yuan Kueh, Naama Barkai, Stanislas Leibler : Mechanisms of noice-resistance in genetic oscillators*, PNAS April 30, 2002 vol. 99 no. 9 page 5988-5992. The article is available in Studium.

To do

a) Reproduce the results in Fig 2, c and d in the article, i.e. simulate the circadian rhythm using the stochastic description and study how the proteins A and R vary during 400 hours. Use the same parameter values as in the ODE-assignment.
What happens when you run the simulation several times? Does the solution agree with the ODE-solution in previous assignment, and does it exactly agree with the solution in Fig 2 c and d? If not, why?

b) The article was one of the first in systems biology to point out that the deterministic reaction rate equations (the ODE model) not gave a good enough description of the biochemical reactions. The authors of the article point out that the presence of random white noice in the stochastic model sometimes can lead to qualitative differences in comparison with the deterministic model. One illustration of this is shown in Fig. 5, and your task here is to reproduce the result in Fig 5 (also reproduce the ODE-solution for this case). What is the difference between the deterministic and the stochastic solution in this particular case?

c) To think about before the feedback session...
You don't need to answer anything here but an interesting question to think about here is the choice of mathematical model, i.e. a deterministic (an ODE here) vs. stochastic model. When do you think the deterministic model is a better description of reality, and when is a stochastic model to prefer? Can you find any clues in the article? Read the article, especially the beginning and the summary in the end. We will have a short discussion about this on the feedback session.