Bioinformatics III

Prof. Dr. Volkhard Helms   Saarland University
Daria Gaidar, Maryam Nazarieh, Duy Nguyen, Thorsten Will   Department of Computational Biology
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Tutorial 9
Due: January 8, 13:15

Submit your solutions on paper, hand-written or printed, at the beginning of the lecture or in the building E2.1, Room 3.09. Alternatively you may send an email with a single PDF attachment of the solution paper to daria.gaidar@bioinformatik.uni-saarland.de. If requested in the assignment, please forward your source code via mail, too.

Dynamic Simulations of Networks

A static analysis of a (metabolic) network can reveal its steady state properties like the most important flux modes or identify seamingly redundant reactions. However, as life is not always static, a network can exhibit a different or unexpected behavior, when subjected to time dependent concentration changes of the metabolites. This is where dynamic network simulations come into play.

For these dynamic simulations, two major approaches exist: for large densities of the relevant molecules, the network can be treated by a set of differential equations that describe the time evolution of the densities, while for small densities, where the dynamics are governed by the binding and unbinding events of individual molecules, stochastic approaches like the Gillespie algorithm are more appropriate.

When proceeding through this assignment you will build a solid understandign of the underlying theory and then get to model the circadian clock of Drosophila.

Exercise 9.1: Theoretical drill (50 points)

(a) **Define Stochastic and Deterministic reaction kinetics.** (5)

(b) **Poissonian process. Master equations.** Go through sections 1 - 3 in the tutorial of F. Hayot and C. Jayaprakash (1). And at least 4.1.1. from the link (2) to get accustomed to the differences in notations and get the point.

    (1) Give 3 (three) examples of two-state system. (3)

    (2) Why, on your opinion, does the probability density function for successive time intervals in Poisson distribution is a decaying exponential? (7)

    (3) Write down the probability P1(t + dt) that the particle is in state 1 at time t + dt using the rules of conditional probability. Progress to the formulation of the Master equations using the definition of reaction rate. Mention the Markov assumption about the transition rate at some appropriate point. (7)

    (4) What is the Master equation? (7)

(c) **Gillespie algorithm (i).** (7)

"Gillespie at ___ showed the ___ algorithm to be equivalent to solving the ___ equation of a system of ___ reactions in a well stirred container. The crux of the algorithm is the drawing of two ___ numbers at each time step, one to _____, the second one to _____."
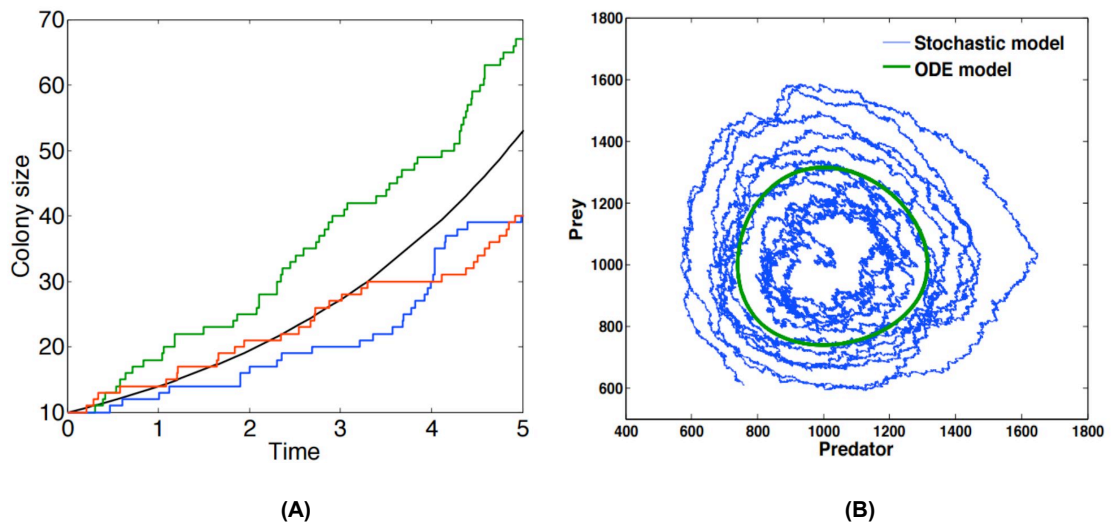
Figure 1: (A) - plot of the solution of the deterministic system versus three different realizations of the stochastic system; (B) - simulation of Lotka-Volterra Two Species Model. (borrowed from here)

(d) **Gillespie algorithm (ii). Write down the steps of Gillespie algorithm in the easy pseudocode version.** (7)

(e) **Elaborate on the behaviour of the Stochastic and Deterministic models plotted on the Figure 1.** Mention the effect that the noise has on the model. Also talk about the quality of the predictions that models generate. (7)

Oscillating Reactions: *Circadian Clock*

Exercise 9.2: Deterministic versus stochastic models for circadian rythms. (50 points)
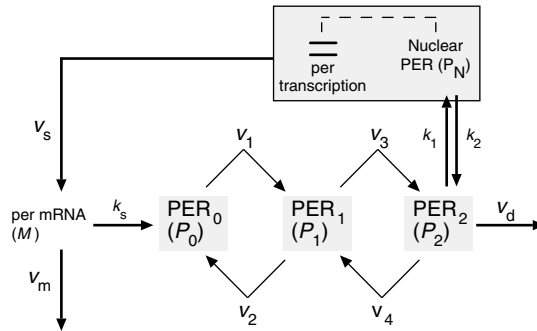
Figure 2: Reaction schematic

Figure 2 shows a model for *circadian oscillations* in Drosophila based on negative autoregulation of the per gene by its protein product PER3. The model incorporates gene transcription into per mRNA, transport of per mRNA into the cytosol as well as mRNA degradation, synthesis of the PER protein at a rate proportional to the per mRNA level, reversible phosphorylation and degradation of PER, as well as transport of PER into the nucleus where it represses the transcription of the per gene. For details please refer to (3) and (4).

(a) **Provide the *deterministic* version of a five-variable molecular model for circadian oscillations (Figure 2). Rate equations.** (15)

(b) **Describe the reaction steps as *stochastic* birth and death processes.** (10)

(c) **Implement the *deterministic* model.** (15)

Start with the following parameter set:

$v_s = 0.76$ μM/h, $v_m = 0.65$ μM/h, $v_d = 0.95$ μM/h,

$k_s = 0.38$ h^{-1}, $k_1 = 1.9$ h^{-1}, $k_2 = 1.3$ h^{-1},

$V_1 = 3.2$ μM/h, $V_2 = 1.58$ μM/h, $V_3 = 5$ μM/h, $V_4 = 2.5$ μM/h,

$K_1 = K_2 = K_3 = K_4 = 2$ μM, $K_I = 1\mu$M, $K_{m1} = 0.5$ μM, $K_d = 0.2$ μM.

(d) **Plot the protein and mRNA concentrations as functions of time. Describe your findings.** (5)

(e) **What happens if you modify the PER-degradation rate v_d? Verify your finding plotting the period of oscillation as a function of v_d.** (5)

References

[1] F. Hayot and C. Jayaprakash. "A tutorial on cellular stochasticity and Gillespies algorithm", https://www.cs.princeton.edu/picasso/mats/matlab/princeton_spring06.pdf.

[2] R. Toral and P. Colet. "Stochastic Numerical Methods: An Introduction for Students and Scientists", Willey, 2014, http://ifisc.uib-csic.es/raul/CURSOS/SP/Introduction_to_master_equations.pdf.

[3] Goldbeter, Albert. "A model for circadian oscillations in the Drosophila period protein (PER)." Proceedings of the Royal Society of London B: Biological Sciences 261.1362 (1995): 319-324.

[4] Goldbeter, Albert. "Computational approaches to cellular rhythms." Nature 420.6912 (2002): 238-245.