Bioinformatics III

Prof. Dr. Volkhard Helms — Saarland University
Ruslan Akulenko, Mohamed Hamed, Duy Nguyen, Christian Spaniol — Chair of Computational Biology
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Exercise Sheet 8

Due: January 20, 2014 13:15

Submit your solutions on paper, hand-written or printed at the beginning of the lecture or in building E2 1, Room 3.09. Alternatively you may send an email with a single PDF attachment. If possible, please include source code listings. Additionally hand in all source code via mail to s9ruakul@stud.uni-saarland.de.

Dynamic Simulations of Networks

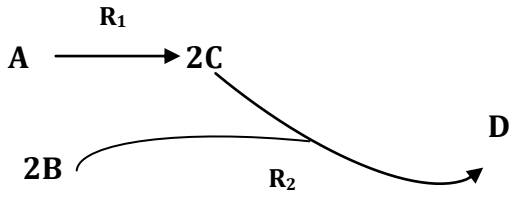
A static analysis of a (metabolic) network can reveal its steady state properties like the most important flux modes or identify seemingly redundant reactions. However, as life is not always static, a network can exhibit a different or unexpected behavior, when subjected to time dependent concentration 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.

This assignment compares the deterministic and the stochastic simulation techniques using a simple four-species network and presents an example in which a stochastic treatment leads to a different dynamic behavior

Exercise 8.1: A simple Reaction Network, part 1 (25 points)

Hint: This exercise is required for the next problem.



Consider the network displayed to the left: one molecule of **A** associates to create two **C**, which is converted into **D**, when it encounters two molecules of **B**.

(a) **Deterministic Model (10)**

A convenient recipe to compile the (sometimes complicated) set of differential equations that describe a system is to start from the stoichiometric matrix.

(1) Set up the stoichiometrix matrix.

(2) Derive the rates $\frac{dR_1}{dt}$ and $\frac{dR_2}{dt}$.

(3) List the rates for the changes of A, B, C and D in terms of the rates of R_1 and R_2.

(4) List the changes of the metabolites during a time step Δt.

(b) **Deterministic Implementation (10)**

With these differences per time step implement a differential equation model of the above network using the simple Euler Integrator.

Use: $\Delta t = 0.02$ s, $t_{final} = 300$, $A_{t=0} = 10\ \mu m^{-3}$, $B_{t=0} = 7\ \mu m^{-3}$, $C_{t=0} = D_{t=0} = 0\ \mu m^{-3}$,

$k_{R1} = 10^{-3}\ \mu m^{-3}/s$ and $k_{R2} = 3*10^{-3}\ \mu m^{-3}/s$.

(1) Plot the time traces of A(t), B(t), C(t) and D(t) into a single plot.

(2) Then, run the simulation until t = 150 s and give the final values of the metabolites.

(c) **Interpretation (5)**

Describe the time traces and explain from their behavior the dynamics of the network.

Exercise 8.2: A simple Reaction Network, part 2 (20 points)

The previous exercise introduced you to the deterministic simulation techniques. Now, this exercise exemplifies the stochastic approaches. Consider the same reactions, rate constants, and initial densities as in Exercise 8.1. In that continuous description you directly worked with the densities of the metabolites. Now use the particle numbers!

(a) **Stochastic Model (5)**

Give the formulas for the probabilities *P1* and *P2* for the two reactions required for the Gillespie method.

(b) **Stochastic Implementation (5)**

Implement the network using the Gillespie method. After each time step print out the densities of the molecules. Run the simulation with volumes of 6 μm^3 and 3 μm^3.

(c) **Interpretation (5)**

For both volumes create a plot of the time traces for $t \leq 500\ s$. Compare the plot with that of the continuous model. Which differences do you observe? What do you observe, when you repeat the stochastic simulations a few times? Explain your observations.

(d) **Stochastic Uncertainties (5)**

As a rule of thumb one can expect statistical fluctuations on the order of $\sqrt{N}$ for N particles.

To check this rule, run the stochastic simulations 40 times until t = 250 s for both volumes.

For each molecule check whether $\frac{\sigma}{\sqrt{N}}$ yields the same number at both volumes whereby σ denotes the standard deviation.

Exercise 8.3: Stochastic Resonance (45 points)

Now consider the following system with the two metabolites A and B.

$A + 2B \xrightarrow{R_1} 2A$	$\emptyset \xrightarrow{R_2} A$	$\emptyset \xleftarrow{R_3} B$	$\emptyset \xrightarrow{R_4} B$
$k_1 = 3 \cdot 10^{-5}\ s^{-1}$	$k_2 = 40\ s^{-1}$	$k_3 = 10\ s^{-1}$	$k_4 = 20\ s^{-1}$

(a) **Model**

(1) Set up the stoichiometric matrix and the rate equations for the reactions and the metabolites (5)

(2) Calculate the steady state (5)

(b) **Implementation**

(1) Deterministic (5):

i. Implement the network using the Euler-Forward Integrator. Run the simulation until convergence.

Use $\Delta t = 5 \cdot 10^{-4}\ s$ as time step.

ii. Show the densities of A(t) and B(t) versus time ([t] = min) using the following initial densities. Plot all results for A into one plot and those for B into another one. (A0, B0) = (10, 10), (2,2000), (100, 2000). Use logarithmic axis

iii. Show the behavior of B(A) in a single plot for the same initial densities.

iv. Try larger time steps for (A0, B0) = (100, 2000), plot the results in a single plot.

(2) Stochastic (15):

i. Implement the network using the Gillespie method.

ii. Plot the number of molecules of A and B, respectively, vs time; whereby [t] = min and the number of molecules should be given on a logarithmic scale.

iii. Present B (A) for (A0, B0) = (10, 10) from the deterministic and stochastic simulations in a single plot.

(c) **Interpretation**

(1) Deterministic (5):

i. Describe and explain the behavior of the network.

ii. Do you recover the steady state calculated above?

iii. What happens if you choose another time step?

(2) Stochastic (10):

i. Describe and explain the behavior of the network.

ii. Compare the deterministic and stochastic curves

iii. Explain from A(t) and B(t) whether the system state evolves clockwise or counterclockwise in the plot of B(A).

Exercise 8.4: Spanning tree search (10 points)

Apply greedy selection of subtrees using algorithm of Kruskal in order to find minimal spanning tree.