Assignment 9

for lecture "Bioinformatics III" WS 08/09

Return by email to p.walter@bioinformatik.uni-saarland.de until **Feb. 1**. This assignment will be discussed in the tutorial on Feb. 2, 2009, room15, building E1 3

Dynamic simulations of networks

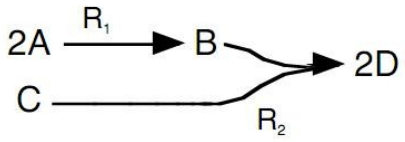
A static analysis of a (metabolic) network can reveal its steady state properties like the most important flux modes or identify seemingly redundant reactions. However, as life is not always static, a network can exhibit a different or unexpected behaviour, when subjected to time dependent concentration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

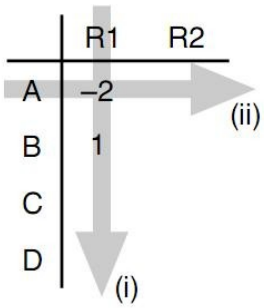
For these dynamic simulations, two major approaches exist: for large densities of the relevant molecules, the network can be treated by a set of differential equations that describe the time evolution of the densities, while for small densities, where the dynamics are governed by the binding and unbinding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

This assignment introduces you to the basic simulation techniques with a simple four-species network.

1. A simple reaction network (100 pts)

For this part, consider the network displayed below: two molecules of A associate to create one B, which is converted into D, when it encounters one molecule of C.





$$\text{(i)}\quad \frac{dR_1}{dt} = k_1 A^2$$

$$\text{(ii)}\quad \frac{dA}{dt} = -2\,\frac{dR_1}{dt}$$

(a) **Preflight preparations** **(20)**

A convenient recipe to compile the (sometimes complicated) set of differential equations that describe a system is to start from the stoichiometric matrix. To do so, first set up the stoichiometric matrix for the above example network. (i) Then walk through the columns to derive the rates dR1/dt and dR2/dt for the reactions R1 and R2, respectively, from the entries with a negative sign (which are the educts for the corresponding reaction). (ii) Via the columns you can then figure out, which reactions con-tribute to the time evolution of a given molecule. This recipe is explained for R1 and dA/dt in the figure on the top (note that the stoichiometric matrix is not complete …).

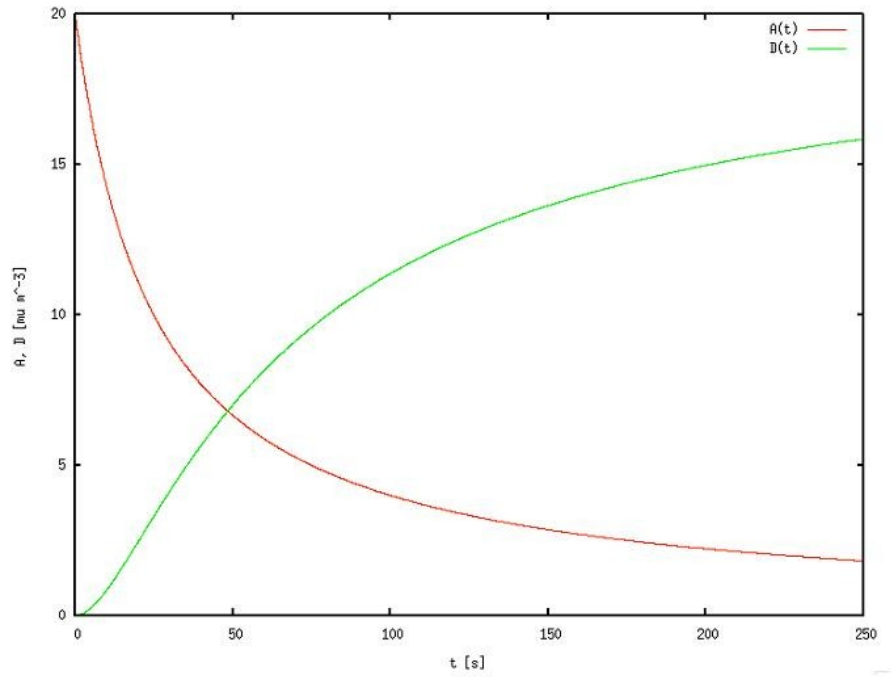
Complete the stoichiometric matrix, give dR1/dt and dR2/dt explicitly and list the rates for the changes of A, B, C, and D in terms of the rates for R1 and R2.

Finally, for the simulation we need the changes of the metabolites during a time step Δt, which are given as $\Delta A = \Delta t\, dA/dt$, …

Note: the amounts of metabolites — A, B, C, and D — are given as densities with units

of particles per volume (for example: 1/nm3, mol/l, …). Consequently, the actual size of the system (test tube) is neglected in this description.

(b) **Implementation with rate equations** **(30)**



With the differences per time step ΔA, ΔB, ΔC, and ΔD implement a differential equation model of the above network. Use a time step Δt of 0.1 s and a final time of 250 s. At t = 0 start from A = 20 μm^{-3}, C = 10 μm^{-3}, and B = D = 0. Set the reaction constants to k1 = 10^{-3} µm3/s and k2 = 3 * 10^{-3} $\mu m^3/s$.
Hint: First calculate the increments, before you add them to the densities of the molecules.
Plot the time traces of A(t), B(t), C(t) and D(t) into a single plot, describe them and explain from their behaviour the dynamics of the network. For comparison, the traces of A and D should look as give here. Then, run the simulation until t = 100 s and give the final values of A, B, C, and D.

(c) **Stochastic implementation** **(35)**

Now implement the same reactions using the Gillespie method as explained in lecture 15, pages 14–15. Give the formulas for the probabilities P1 and P2 for the two reactions. In the above continuous description you directly worked with the densities of the metabolites. Now use the particle numbers! The possible reactions are obviously the two reactions R1 and R2 from above. For the probability table you need, at each time step, the respective probabilities P1 and P2 for reactions R1 and R2, given the current state (= particle numbers of A, B, C, and D). You can determine them as follows from the rates dR1/dt and dR2/dt:
The rate dR1/dt describes how the densities of the metabolites A and B change with time. Its units are [particles per (volume and time)]. N_A is the number of molecules A, and V is the system volume.

$$\frac{dR_1}{dt} = -\frac{1}{2V}\frac{dN_A}{dt} = k_1 A^2 = k_1 \frac{N_A}{V}\frac{N_A}{V}$$

For the Gillespie algorithm you need the probability per time, i.e., in units of [particles per time]

$$P_1 = -\frac{1}{2}\frac{dN_A}{dt} = \frac{k_1}{V}N_A^2 = V\frac{dR_1}{dt}$$

Note that for a reaction of first order, e.g., a dissociation reaction AB –> A + B, the rate dAB/dt already has the correct dimensions of a (decay) probability.

With P1 and P2 you can then determine the probability table and the total probability Plot and from these — via the two independent random numbers r1 and r2 — the next time-step and which reaction will take place.
As a last step you have to update the particle numbers. When, e.g., reaction R1 takes place, N_A is decreased by two and N_B increased by one.
Note that the Gillespie method is similar in spirit to the preferential attachment in the Barabási–Albert algorithm for scale–free networks.
After each time step print out the densities of the molecules, i.e., NA/V, etc, even though the simulation uses the particle numbers. Set the volume to 5 μm^3 and 2 μm^3, respectively, and use the same rate constants and initial densities as above.

Hint: how many particles A do you need to have an initial density of 5 μm^{-3} at the given volumes?

For each of the volumes create a plot of the time traces A(t), B(t), … for $t \leq 250$ s as from the continuous model and compare the three plots. Which differences do you observe? What do you observe, when you repeat the stochastic simulations a few times? Explain your observations.

(d) **Stochastic uncertainties** **(15)**

As a rule of thumb one can expect statistical fluctuations on the order of N1/2 for N particles. To check this rule, run the stochastic simulations 50 times until t = 100 s for both of the volumes of 5 µm3 and 2 µm3. Determine the average numbers of A, B, C, and D and their standard deviations σA, σB, σC, and σD (give their values). For each molecule check whether σN–1/2 yields the same number at both volumes.

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