**Bioinformatics III**

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# Exercise Sheet 8

**Due: January 16, 2015 13:15**

**Submit your solutions on paper, hand-written or printed at the beginning of the lecture or in building E2.1, Room 3.02. 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 nazarieh@mpi-inf.mpg.de.**

## Dynamic Simulations of Networks - Part I

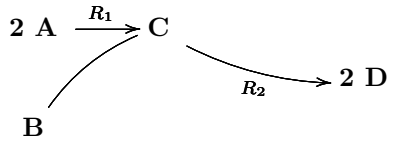
A static analysis of a (metabolic) network can reveal its steady state properties like the most important flux modes or identify seamingly redundant reactions. However, as life is not always static, a network can exhibit a different or unexpected behavior, when subjected to time dependent concentration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

This assignment introduces you to the deterministic simulation technique with a simple four-species network and a larger signaling network, before the next assignment exemplifies the stochastic approaches.

### Exercise 8.1: A simple Reaction Network (25 points)

*Hint: This exercise is required for the next assignment.*




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

(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 $\Delta t$.

(b) **Deterministic Implementation (10)**
With these differences per time step implement a differential equation model of the above

network using the simple Euler-Forward Integrator.
Use: $\Delta t = 0.05$ s, $t_{final} = 500$,
$A_{t=0} = 10\ \mu\text{m}^{-3}$, $B_{t=0} = 5\ \mu\text{m}^{-3}$, $C_{t=0} = D_{t=0} = 0\ \mu\text{m}^{-3}$,
$k_{R_1} = 10^{-3}\ \frac{\mu\text{m}^{-3}}{\text{s}}$ and $k_{R_2} = 3 * 10^{-3}\ \frac{\mu\text{m}^{-3}}{\text{s}}$.

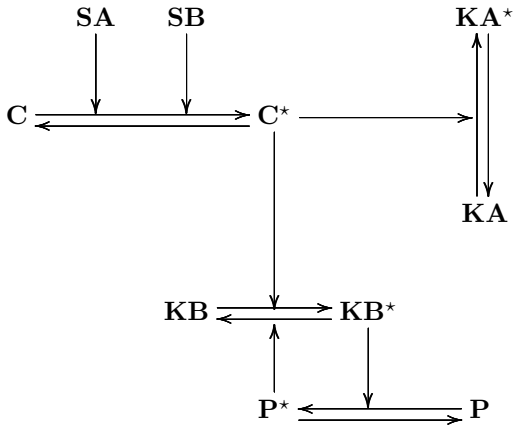
(1) Plot the time traces of $A(t)$, $B(t)$, $C(t)$ and $D(t)$ into a single plot.

(2) Then, run the simulation until $t = 200$ 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: An intracellular Signaling Network (75 points)**

Now, consider the intracellular signaling network displayed to the right.




The system consists of two response pathways, whereby the signaling through these pathways is initiated when the metabolite **C** is activated by binding of the ligands **SA** and **SB** to their receptors. The activated **C** (denoted by **C**$^\star$) activates **KA** or **KB**. The activated **KB** activates the phosphatase **P**, whereby **P**$^\star$ enhances the deactivation of **KB**$^\star$.

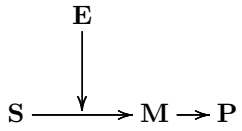
Note, that there is no activation of **KA** and **KB** without **C**$^\star$, but the deactivation of **KB**$^\star$ is also possible without **P**$^\star$. To activate **C** there are two different ways, the first one requires **SA**, the second one **SB**.
**SA**, **SB**, **C**$^\star$ and **P**$^\star$ are enzymes and not used in the reactions.

(a) **Preflight (25)**
Set up the rate equations of the activated components of the signaling network

$$\frac{d[C^\star]}{dt},\ \frac{d[KA^\star]}{dt},\ \frac{d[KB^\star]}{dt},\ \frac{d[P^\star]}{dt}$$

and the corresponding rates of concentration changes ($\Delta[C^\star]$, $\Delta[KA^\star]$, $\Delta[KB^\star]$, $\Delta[P^\star]$).
Use Michaelis-Menten kinetics to model the above activation and deactivation reactions.

*Hint: rate equations using Michaelis-Menten kinetics look like follows:*




$$\frac{d[M]}{dt} = \frac{k_{ME}[E]_0[S]}{K_{ME}+[S]} - \frac{V_M[M]}{K_M+[M]}$$

Additionally, assume that $[A] + [A^\star] = 1$.
Label all required reaction constants in the same way as in the above example.

(b) **Deterministic Model - Implementation (25)**
Implement a differential equation model of the signaling network with the differences per time step. Run the simulation until $t = 90$ s with a timestep of $\Delta t = 0.01$ s. Use the rates

$k_{C^\star SA} = k_{C^\star SB} = 5.0 \cdot 10^{-2}$
$k_{KA^\star C^\star} = 1.5 \cdot 10^{-4}$
$k_{KB^\star C^\star} = 5.0 \cdot 10^{-2}$
$k_{KB^\star P^\star} = 4.0 \cdot 10^{-1}$
$k_{P^\star KB^\star} = 7.5 \cdot 10^{-4}$

$K_{C^\star} = K_{C^\star SA} = K_{C^\star SB} = 10.0$
$K_{KA^\star} = K_{KA^\star C^\star} = 5.0 \cdot 10^{-1}$
$K_{KB^\star} = 1.0 \cdot 10^{-2}$
$K_{KB^\star C^\star} = 5.0 \cdot 10^{-2}$
$K_{KB^\star P^\star} = 2.0 \cdot 10^{-2}$
$K_{P^\star} = K_{P^\star KB^\star} = 1.0$

$V_{C^\star} = 2.5 \cdot 10^{-2}$
$V_{KA^\star} = 5.0 \cdot 10^{-5}$
$V_{KB^\star} = 1.0 \cdot 10^{-3}$
$V_{P^\star} = 6.0 \cdot 10^{-5}$

and let have zero concentrations initially for all activated metabolites.

(c) **Deterministic Model - Interpretation (25)**

(1) Plot the time traces of the concentrations $[C^\star]$, $[KA^\star]$, $[KB^\star]$, and $[P^\star]$ into a single plot. Create two plots, the first one with $[SA]_0 = [SB]_0 = 0.01$ and the second one with $[SA]_0 = [SB]_0 = 0.99$.

(2) Now run the simulation for $[SA]_0 = 0.01$ and $[SB]_0 = 0.01$, 0.02, 0.03, ..., 0.99 and plot the concentration of C, KA and KB at the end of the simulation run vs. the enzyme concentration $[SB]_0$ into a single plot.
Also run the simulation for $[SB]_0 = 0.01$ and $[SA]_0 = 0.01$, 0.02, 0.03, ..., 0.99 and plot the concentration of C, KA and KB at the end of the simulation run vs. the enzyme concentration $[SA]_0$ into a single plot.
Describe and explain the observed response characteristic.

Have fun!