Bioinformatics III

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Exercise Sheet 10

Dynamics Simulation of Networks

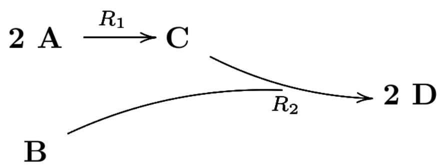
Due: January 23, 2020 14:15

Submit your solutions on paper, hand-written or printed at the beginning of the lecture or in building E2.1, Room 3.01. Alternatively, you can send an email with a single PDF attachment to pratiti.bhadra@bioinformatik.uni-saarland.de. Additionally, send your source code via email. Please document your Python source code. Only Python code will be accepted. Either add documentation comments in your source code or provide a README file. Your source code should be executed without any error. Subject of the email should be in the following format: Assignment10-"your name".

Please feel free to contact me for any clarifications either via email or you can reach me in building E2.1, Room 3.01 (preferably between 3 pm and 4 pm).

Q1 Mass Action Kinetics(*25 points*)

A simple network



Two molecules of A associate to create one C, which is converted into D, when it encounters one molecule of B.

(a) Deterministic Model (*10 points*)

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

i. Set up the stoichiometrix matrix.

ii. Derive the rates $\frac{dR_1}{dt}$ and $\frac{dR_2}{dt}$.

iii. List the rates for the changes of **A**, **B**, **C** and **D** in terms of the rates of R_1 and R_2.

iv. List the changes of the metabolites during a time step Δt.

(b) Deterministic Implementation and Interpretation (*15 points*)

Implement a differential equation model of the above network using the simple Euler-Forward Integrator.

Use: $\Delta t = 0.05$ s, $t_{final} = 500$,

$A_{t=0} = 10\ \mu\text{m}^{-3}$, $B_{t=0} = 5\ \mu\text{m}^{-3}$, $C_{t=0} = D_{t=0} = 0\ \mu\text{m}^{-3}$,

$k_{R_1} = 10^{\ -3}\ \frac{\mu m^{-3}}{s}$ and $k_{R_2} = 3 * 10^{\ -3}\ \frac{\mu m^{-3}}{s}$.

i. Plot the time traces of $A(t)$, $B(t)$, $C(t)$ and $D(t)$ into a single plot and describe the time traces and explain their behavior.

ii. Then, run the simulation until $t = 200s$ and give the final values of the metabolites.

Q2 Stochastic Model(*40 points*)

$\mathbf{2\ A + B \xrightarrow{R_1} 3\ A}$	$\emptyset \xrightarrow{R_2} \mathbf{A}$	$\emptyset \xleftarrow{R_3} \mathbf{A}$	$\emptyset \xrightarrow{R_4} \mathbf{B}$
$k_1 = 4 \cdot 10^{-5}\ \mathrm{s}^{-1}$	$k_2 = 50\ \mathrm{s}^{-1}$	$k_3 = 10\ \mathrm{s}^{-1}$	$k_4 = 25\ \mathrm{s}^{-1}$

(a) Rate Equations (10)
Set up the rate equations for the reactions and the metabolites. Calculate A and B at the steady state.

(b) Implement the network using the Gillespie method. Plot the number of molecules of A and B, respectively, vs time. Use A(0) = 10, B(0) = 10, $t_{initial} = 0$ and $t_{final} = 80$ minutes. The number of molecules should be given on a logarithmic scale in the plot. (*30 points*)
Hints: Lecture V22, Slide no 36 "Gillespie Algorithm"

Q3 Enzyme kinetics (*35 points*)

(a) Derive an equation for $\frac{1}{V}$ from the Michaelis Menten Kinetic equation as a function of $\frac{1}{S}$ in form of a straight line equation ($y = a.x + b => \frac{1}{V} = a.\frac{1}{S} + b$) (*1*0 points)

Michaelis Menten Kinetic equation: $V = \frac{V_{max}S}{K_M + S}$ *where* V *is the initial rate,* V_{max} *is the maximum rate of the reaction with substrate saturation,* S *is the substrate concentration at the start of the reaction.*

(b) The reaction between nicotineamide mononucleotide and ATP to form nicotineamideadenine dinucleotide and pyrophosphate is catalyzed by the enzyme nicotinamide mononucleotide adenylyltransferase. The following table provides typical data obtained at a pH of 4.95. The substrate, S, is nicotinamide mononucleotide and the initial rate, v, is the mol of nicotinamideadenine dinucleotide formed in a 3-min reaction period. Determine the value of V_{max} and K_M. (*1*0 points)

S (mM)	V (μmol)
0.138	0.148
0.220	0.171
0.291	0.234
0.560	0.324
0.766	0.390
1.460	0.493

Hint:

- *The equation of* $\frac{1}{V}$ *which has been derived by you as answer of Q3(a).*
- *Plot* $\frac{1}{V}$ *Vs* $\frac{1}{S}$

(c) Does the equation of $\frac{1}{V}$ have any advantage over Michaelis Kinetic equation? Justify your answer. (*5* points)

(d) An solution initially contains a catalytic amount of an enzyme with $K_M = 1.5$ mM, 0.25 M of substrate, and no product. After 45 seconds, the solution contains 25 M of product. Find V_{max} and the concentration of product after 2.0 minutes. (*Hint:* $S >> K_M$) (*10* points)