BT5240 — Computational Systems Biology

Jan–May 2021
Assignment 3

April 17, 2021

Due date: April 27, 2021 @ 17:00 **Maximum marks: 50**

Instructions: Late assignments will not be accepted. If you need any assistance on computing, feel free to approach me. Evaluation will be based on the code(s), the answers and the methodology. Academic Integrity: You are allowed to discuss the problems verbally with your friends, but copying or looking at codes (either from your friend or the Web) is not permitted. Transgressions are easy to find, and will be reported to the "Sub-committee for the Discipline and Welfare of Students" and will be dealt with very strictly. Mention any collaboration (discussions only!) in your solutions.
Late submission penalties: 1 second–24 h: 20%; 24 – 48 h: 40%; > 48h: 60%
Early submission bonuses: > 24h: 10%, > 48h: 20%
Evaluation: Assignments will be evaluated by the TAs within one weeks of the due date. You can check out your marks and contest them, if needed, for at most one more week postevaluation, i.e. three weeks from the due date of the assignment.
Submission: Since this is a computational assignment, I would also like to look at your codes. Submit your assignment as one zip file by uploading it at http://tinyurl.com/bt5240-submit. Your zip file should be named something like `BTyyBxxx.zip`, based on your roll number. This zip file must contain a single neatly typeset PDF of your solutions (named `BTyyBxxx.pdf`) as well as the codes used for each of problems in a separate folder `codes`.

1 Problem 1

A model of the acetophenone reduction catalyzed by alcohol dehydrogenase from *Thermoanaerobacter* sp. is defined by the kinetic equations detailed below:

1.1 Reactions

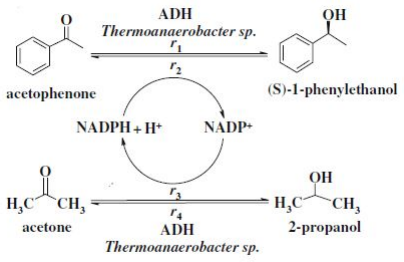

Figure 1: Acetophenone reduction reactions

1.2 Kinetic equations

$$\frac{dc_{acetophenone}}{dt} = -r_1 + r_2$$
$$\frac{dc_{(s)-1-phenylethanol}}{dt} = r_1 - r_2$$
$$\frac{dc_{acetone}}{dt} = -r_3 + r_4$$
$$\frac{dc_{2-propanol}}{dt} = -r_3 - r_4$$
$$\frac{dc_{NADPH}}{dt} = -r_1 + r_2 - r_3 + r_4$$
$$\frac{dc_{NADP+}}{dt} = r_1 - r_2 + r_3 - r_4$$

Kinetic equations

$$r_1 = \frac{V_{m1} \cdot e^{-k_d \cdot t} \cdot c_{acetophenone} \cdot c_{NADPH}}{\left(c_{acetophenone} + K_m^{acetophenone} \cdot \left(1 + \frac{c_{(S)\text{-1-phenylethanol}}}{K_{i1}^{(S)\text{-1-phenylethanol}}} + \frac{c_{acetone}}{K_{i1}^{acetone}} + \frac{c_{2\text{-propanol}}}{K_{i1}^{2\text{-propanol}}}\right) + \frac{c_{acetophenone}^2}{K_{i1}^{acetophenone}}\right) \cdot \left(c_{NADPH} + K_m^{NADPH} \cdot \left(1 + \frac{c_{NADP+}}{K_{i1}^{NADP+}}\right)\right)}$$

$$r_2 = \frac{V_{m2} \cdot e^{-k_d \cdot t} \cdot c_{(S)\text{-1-phenylethanol}} \cdot c_{NADP+}}{\left(c_{(S)\text{-1-phenylethanol}} + K_m^{(S)\text{-1-phenylethanol}} \cdot \left(1 + \frac{c_{acetophenone}}{K_{i2}^{acetophenone}} + \frac{c_{acetone}}{K_{i2}^{acetone}} + \frac{c_{2-propanol}}{K_{i2}^{2-propanol}}\right)\right) \cdot \left(c_{NADP+} + K_m^{NADP+} \cdot \left(1 + \frac{c_{NADPH}}{K_{i2}^{NADPH}}\right)\right)}$$

$$r_3 = \frac{V_{m3} \cdot e^{-k_d \cdot t} \cdot c_{acetone} \cdot c_{NADPH}}{\left(c_{acetone} + K_m^{acetone} \cdot \left(1 + \frac{c_{(S)\text{-1-phenylethanol}}}{K_{i3}^{(S)\text{-1-phenylethanol}}} + \frac{c_{acetophenone}}{K_{i3}^{acetophenone}} + \frac{c_{2\text{-propanol}}}{K_{i3}^{2\text{-propanol}}}\right)\right) \cdot \left(c_{NADPH} + K_m^{NADPH} \cdot \left(1 + \frac{c_{NADP+}}{K_{i3}^{NADP+}}\right)\right)}$$

$$r_4 = \frac{V_{m4} \cdot e^{-k_d \cdot t} \cdot c_{2\text{-proponal}} \cdot c_{NADP+}}{\left(c_{2\text{-proponal}} + K_m^{2\text{-proponal}} \cdot \left(1 + \frac{c_{(S)\text{-1-phenylethanol}}}{K_{i4}^{(S)\text{-1-phenylethanol}}} + \frac{c_{acetone}}{K_{i4}^{acetone}} + \frac{c_{acetophenone}}{K_{i4}^{acetophenone}}\right) + \frac{c_{2\text{-proponal}}^2}{K_{i4}^{2\text{-proponal}}}\right) \cdot \left(c_{NADP+} + K_m^{NADP+} \cdot \left(1 + \frac{c_{NADPH}}{K_{i4}^{NADPH}}\right)\right)}$$

In these equations $c_{acetone}$ means concentration of acetone, and this applies for all other components as well.
Enzyme deactivation is assumed to be zero, $k_d = 0$

1.3 Kinetic parameters and initial conditions

Table 1: Kinetic Parameters.

Parameter	Units	Value
$K_m^{acetophenone}$	mM	0.034
$K_m^{(S)-1-Phenylethanol}$	mM	0.112
$K_m^{acetone}$	mM	1.091
$K_m^{2-propanol}$	mM	0.408
K_m^{NADPH}	mM	0.004
$K_m^{NADP^+}$	mM	0.007
$K_{i1}^{(S)-1-Phenylethanol}$	mM	0.070
$K_{i1}^{acetone}$	mM	0.899
$K_{i1}^{2-propanol}$	mM	10.973
$K_{i1}^{NADP^+}$	mM	0.017
$K_{i1}^{acetophenone}$	mM	6.077
$K_{i2}^{acetophenone}$	mM	0.010
$K_{i2}^{acetone}$	mM	7.576
$K_{i2}^{2-propanol}$	mM	0.079
K_{i2}^{NADPH}	mM	0.006
$K_{i3}^{2-propanol}$	mM	20.303
$K_{i3}^{(S)-1-Phenylethanol}$	mM	0.535
$K_{i3}^{acetophenone}$	mM	1.886
$K_{i3}^{NADP^+}$	mM	0.005
$K_{i4}^{acetone}$	mM	2.242
$K_{i4}^{acetophenone}$	mM	0.348
$K_{i4}^{(S)-1-Phenylethanol}$	mM	29.551
K_{i4}^{NADPH}	mM	0.007
$K_{i4}^{2-propanol}$	mM	288.016

Initial Conditions for ODE simulations:

$c_{acetophenone} = 10mM$, $c_{NADP^+} = 0.75mM$, $c_{2-propanol} = 300mM$, $c_{acetone} = c_{(s)-1-Phenylethanol} = c_{NADPH} = 0mM$

Use **ode23** function for ODE simulations.

Assume that we have experimental data of concentrations of the various species (acetophenone, (s)-1-phenylethanol,acetone, 2-propanol, NADPH, NADP+, in this order itself) at different time points (0 to 20 mins) given as ***data.csv***. Estimate the parameters $V_{m1}, V_{m2}, V_{m3}, V_{m4}$. Use any algorithm discussed in class (e.g. standard minimization algorithm like fminsearch in MATLAB/Simulated annealing) — no need to write your own code (use publicly available libraries).

Start the parameter search from $V_{m1} = 2, V_{m2} = 100, V_{m3} = 2, V_{m4} = 2$

Hint: Use error between the predicted data from ODE simulations and measured data from ***data.csv*** as the objective function. You have to find the parameter set at which the error is least.

2 Problem 2

The kinetics of Glycolysis pathway is represented in ODE equations (given in **odemodel.m**). The parameters and the initial conditions to simulate the kinetics are mentioned below.

Metabolites (Species)	Initial Concentration (mmol/l)
ATP	4.49064
ADP	0.108367
AMP	0.00261149
GLC	0.0112817
F6P	0.65939
FBP	0.00770135
GAP	0.00190919
NAD	3.62057
NADH	0.616118
DPG	0.299109
PEP	0.0021125
PYR	0.00422702
ACA	0.0738334
EtOH	0.33981
P	0

Parameter	Value
V1	0.5
K1GLC	0.1
K1ATP	0.063
V2	1.5
K2	0.002
k2	0.017
K2ATP	0.01
k3f	1
k3b	50
V4	10
K4GAP	1
K4NAD	1
k5f	1
k5b	0.5
V6	10
K6PEP	0.2
K6ADP	0.3
V7	2
K7PYR	0.3
k8f	1
k8b	1.43E-04
k9f	10
k9b	10
k10	0.05
flow	0.011

Figure 2: Kinetic parameters and initial conditions

i Write a code to initialise the variables and perform the time-course simulation, using the ODEs from **odemodel.m**.

ii Change the parameters V4, K4GAP, K8f, K8b individually to 50% and 150% of their original value, and study their effects on NADH concentrations.

All the best!!