

Bioengineering 498A: Systems and Synthetic Biology

Feb 09, 2009

Homework Assignment #5

Due: 16th Feb 2009

Points awarded for each question are indicated in square brackets. Return assignment with your name clearly indicated at the top of your answer sheet. [Total points: 100]

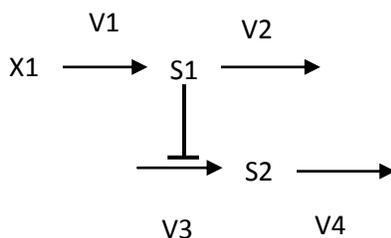
[15] Question 1.

Implement the Gillespie method and use it to simulate the equilibration reaction, $A \rightleftharpoons B$. Try simulating the system with different starting concentrations of A and B. For example:

A	B
10	0
100	0
500	0

Hand in the plots you obtain and a listing of the software you used to implement the Gillespie method.

[30] Question 2. Consider the following simple gene network. Transcription factor S1 is made at a rate V1 and degraded at a rate V2. S1 can inhibit the expression of protein S2. S2 degrades at a rate V4.



The rate laws for this network are (Note the simple inhibition law on v3):

$$v_1 = k_1 x_1$$

$$v_2 = k_2 S_1$$

$$v_3 = \frac{k_3}{K m_1 + S_1}$$

$$v_4 = k_4 S_2$$

Build this network using Jarnac or some other suitable software application. Initialize the parameters to:

$$k_1 = 100; k_2 = 25; k_3 = 10; K m_1 = 0.1; k_4 = 1; X_1 = 1;$$

Initialize $S_1 = 4$ and $S_2 = 5$. These values are roughly at the steady state point.

Run a deterministic simulation of this pathway, record the steady state concentration of S_2 here:

[15] **a)** Steady State Deterministic Concentration of $S_2 =$

Now run a stochastic simulation of this pathway. Because S_2 will fluctuate you will need to compute the mean steady state concentration. You will need to compute the mean concentration of S_2 using the following formula:

$$\text{Mean } S_2 = \sum_{i=1}^{n-1} S_{2i} \frac{(t_{i+1} - t_i)}{t_n}$$

Where t_n = the time at the end of the simulation (as recorded in the result matrix!) and $t_1 = 0$. S_{2i} is the concentration of S_2 at time point i

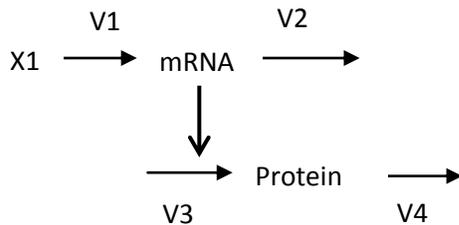
Compute the mean concentration of S_2 using the above formula and record it here:

Mean $S_2 =$

[5] **b)** Explain why it is necessary to use the above formula to compute the mean S_2 rather than simply summing up all the S_2 concentrations and computing the average.

[10] c) Explain why the deterministic and stochastic steady state levels are different?

[30] Question 3. In this question you will investigate a model that mimics protein synthesis.



The rate laws for this model are:

$$v_1 = k_1 x_1$$

$$v_2 = k_2 mRNA$$

$$v_3 = \frac{100 mRNA}{K m_1 + mRNA}$$

$$v_4 = k_4 Protein$$

Carry out two types of simulation on this model, deterministic and stochastic. Protein and mRNA levels can be set to zero at the start of the simulation. Run a simulation for about 200 time units (or whatever is convenient) and plot the graphs for mRNA and Protein.

Investigate the model under two sets of parameters:

1. $k_1 = 80$; $k_2 = 200$; $K m_1 = 10$; $k_4 = 1$;
2. $k_1 = 0.1$; $k_2 = 0.25$; $K m_1 = 10$; $k_4 = 1$;

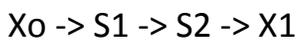
[10] a) What difference do you observe when you carry out stochastic simulations using the two parameter sets?

[20] **b)** Explain in mechanistic terms why the two behaviors are different. To help you answer his question, observe closely the difference in the two parameter sets.

[25] Question 4.

This question is in two stages.

[10] a) Simulate the following model using the Euler integration method (See Algorithm 1 at end of assignment).



Where X_0 and X_1 are fixed species. Each step is governed by a simple irreversible mass-action rate law. Use the rate laws:

$$v_1 = k_1 X_0$$

$$v_2 = k_2 S_1$$

$$v_3 = k_3 S_2$$

Set $k_1 = 0.1$; $k_2 = 0.2$; $k_3 = 0.15$. Initialize $X_0 = 10$ mM and $X_1 = 0$. Simulate for forty time units. Recall that both the Euler and Chemical Langevin methods can work with continuous variables so we do not specify the actual number of molecules but just the concentration.

[15] b) Modify the Euler method you implemented in a) to simulate the same network of three irreversible reaction steps using the Chemical Langevin Method (Look up the algorithm on your class slides).

If you're using Jarnac you can use `stats.gauss (mean, std)` to generate your Gaussian distributed random numbers. If you use Matlab for this question, `randn(1)` will generate Gaussian generated random numbers with mean zero and standard deviation 1. To generate a Gaussian generated random number with a different standard deviation just use: `std*randn(1)` where `std` is your chosen standard deviation.

Algorithm 1 Euler Integration Method

n = Number of State Variables

timeEnd = 10

currentTime = 0

h = stepSize

while $t < \text{timeEnd}$ **do**

for all n **do**

$k_i = f(y_i)$

for all n **do**

$y_i(t + h) = y_i(t) + h k_i$

 currentTime = currentTime + h

end while
