STOCHASTIC SIMULATIONS IN SYSTEMS BIOLOGY AND BIOPHYSICS
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Homework Assignment 1

Group Members

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Short description of the code

Simulation was done using object oriented programming in java and plots were obtained by reading the created files in MATLAB. A molecule class was created with the following properties -

1. Molecule type : This property refers to the molecule type of the object under consideration.
   1 → Cyto-c
   2 → apaf
   3 → Apoptosome
   4 → Dimer
2. Molecule bonded with : This property refers to the type of molecule that is bonded to the object in consideration.
3. X axis : This property refers to the x coordinate of the object in lattice.
4. Y axis : This property refers to the y coordinate of the object in lattice.
5. Z axis : This property refers to the z coordinate of the object in lattice.
6. Bond direction : This property refers to the direction in which bond was made.
   1 → Right
   2 → Left
   3 → Top
   4 → Down
   5 → Front
   6 → Back

Separate methods were created to ensure separation of concerns with the following identifiers:

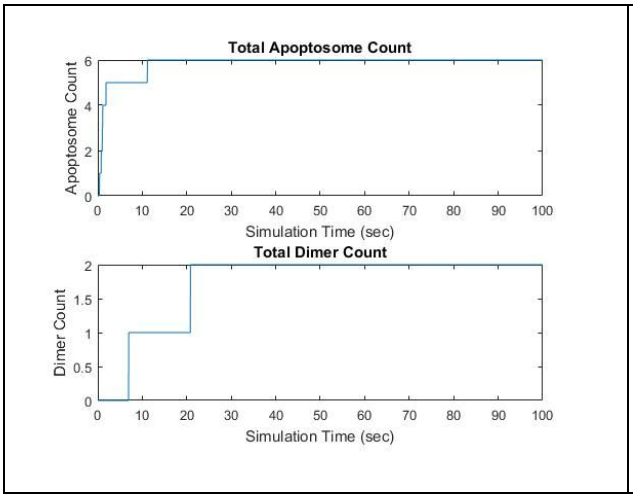
1. Initialization : To initialize lattice and other class variables.
2. Diffusion_cytoc_apaf : To handle 3d random walk of cyto-c and apaf.
3. Diffusion apoptosome : To handle 3d random walk of apoptosome.
4. Bond_formation_by_cytoc_apaf : To handle apoptosome formation.
5. Bond_formation_by_apoptosome : To handle dimer formation.
6. Dissociation_apoptosome : To handle dissociation of apoptosome.

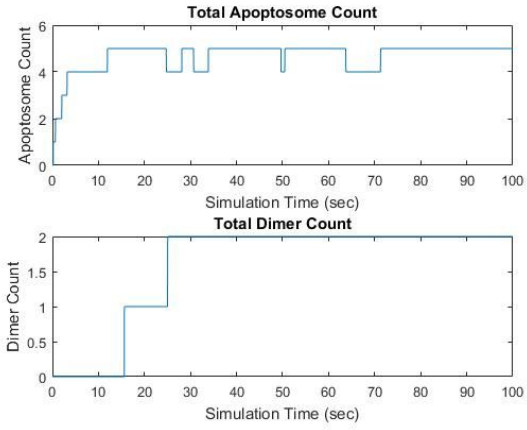
Main was used to make calls to the methods depending upon probabilities. Two files were written as the output and these files were read by MATLAB to generate plots. Another Matlab script was made to compute average and fluctuations in time-to-apoptosome formation and generating plots.
MATLAB scripts has also been provided along with the java code.

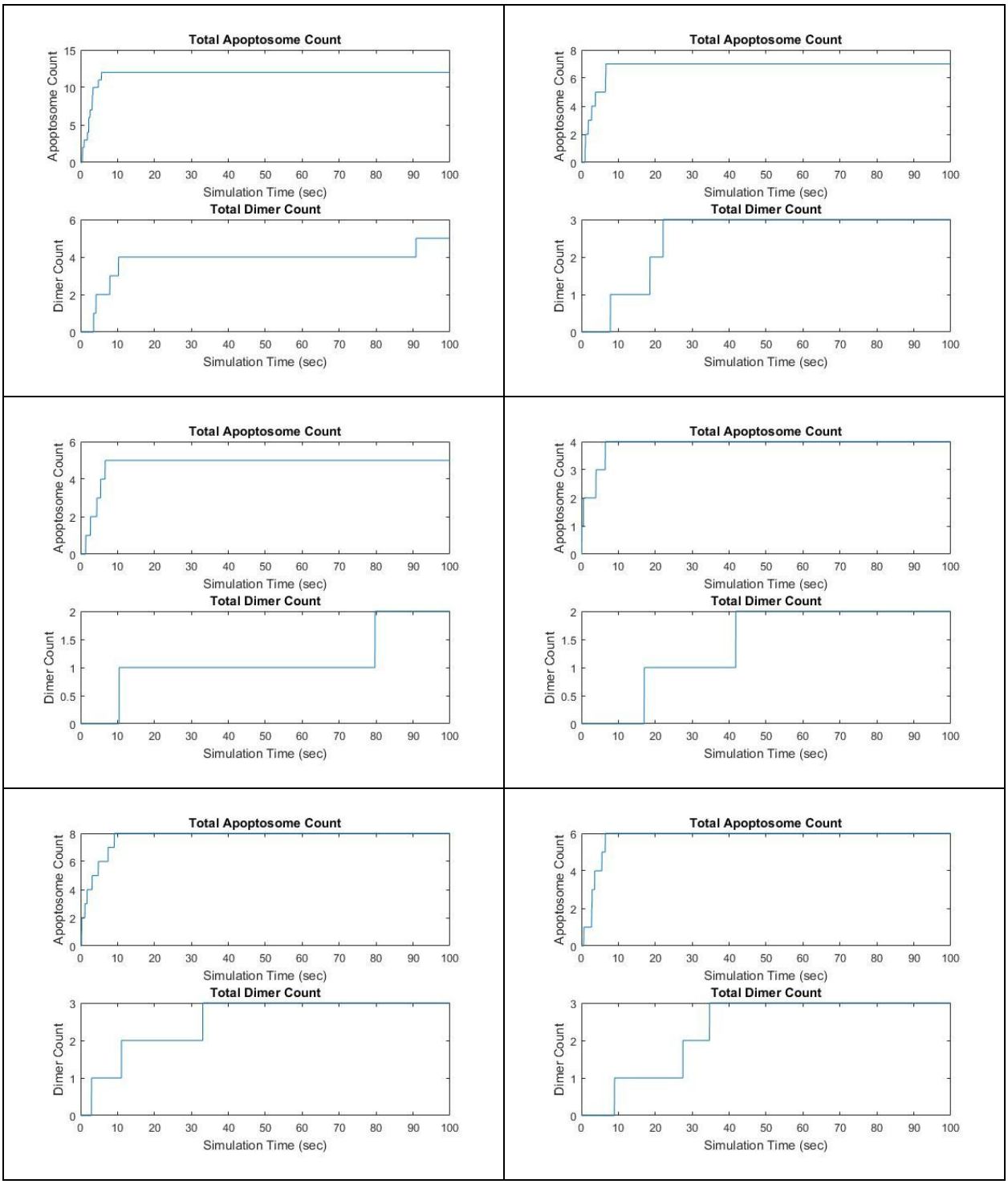
Results

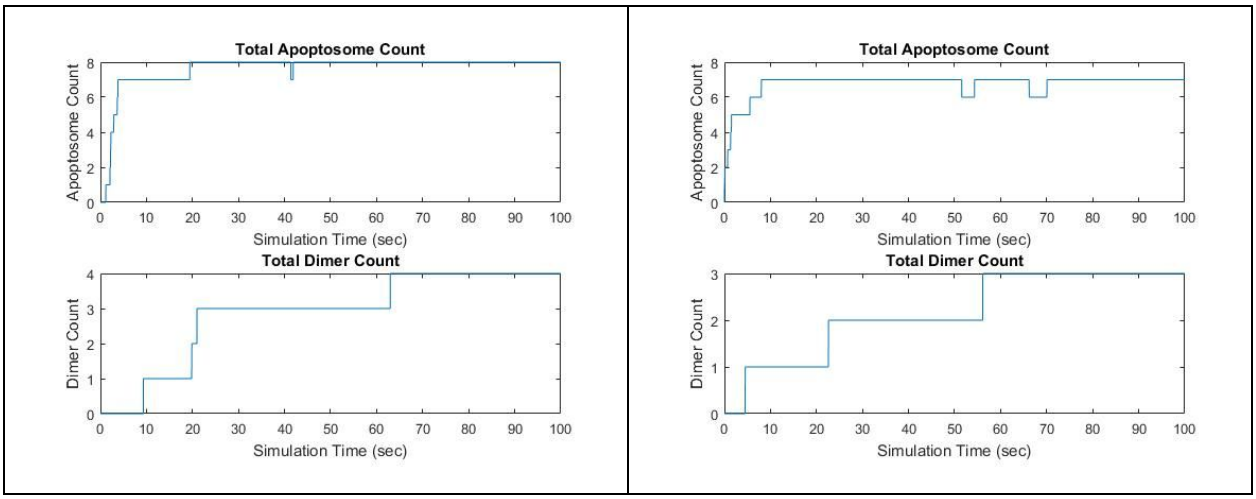
The results for 10 monte carlo runs are shown below. Each results composed of two plots, one for cyto-C - apaf complex and the other for the dimer model. We designed our code such that it captures both the models in a single simulation. The initial values used in these plots are:

Lattice dimension :	60
Monte - Carlo steps:	10^6
Initial Cyto-C molecules:	100
Initial apaf molecules:	50






Total Apoptosome Count
Apoptosome Count
Simulation Time (sec)
Total Dimer Count
Dimer Count
Simulation Time (sec)



Note: Simulations for 10^8 steps were also done, but no further changes in apoptosome or dimer levels were seen.

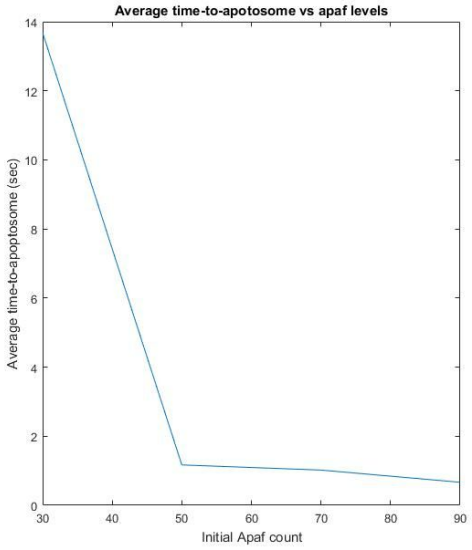
Answer (i)

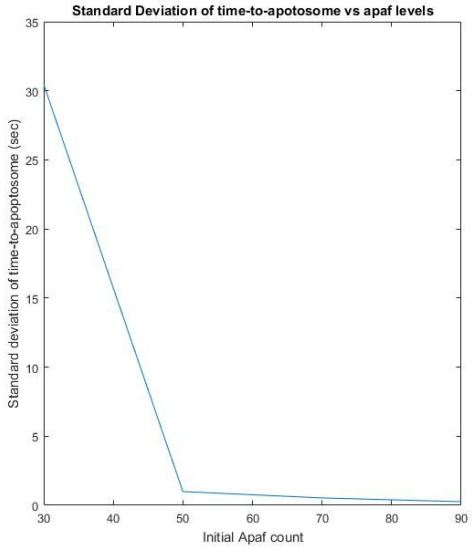
The time-to-apoptosome formation for considered for first two apoptosomes. For each run, the values (in sec) are:

0.7688, 0.6738, 0.5509, 1.1410, 2.6994, 0.5826, 0.2988, 2.7930, 2.0846, 0.0923.

For the above simulation results, mean time-to-apoptosome formation came out to be 1.1685 sec with a standard deviation of 0.9926 sec.

The effect of variation of apaf level within cells to time-to-apoptosome formation was also studied by varying apaf levels to 30, 50, 70 and 90 molecules. The resulting average time to apoptosome is shown in the figure below. Note that for each apaf count, average and standard deviations were computed for 10 monte carlo runs each.





This shows that a higher concentration of apaf within a cell reduces the time of formation of apoptosomes, thereby catalysing apoptosis. This however gets saturated (as seen in graph) and cannot reduce below that. On the contrary, reduced levels of apaf within cells defer its death.

Answer (ii)

As stated above, the dimer model was also considered together with the monomer model. If we consider the dimer model, the time-to-apoptosome (in sec) come out be 20.8217, 25.0456, 4.1934, 18.5861, 79.7145, 41.7918, 11.0671, 27.4836,19.8655, 22.6183. In this case, the mean time-to-apoptosome formation came out to be 27.1188 sec with a standard deviation of 20.9618 sec.

Clearly, in the case, the average time taken is more (around 18 times more), as now we are considering two cyto-C-apaf complexes to fuse together instead of one. This means that two dimers formed is equal to 4 cytochrome-C and 4 apaf molecules coming together, which is an even rare event, thereby taking longer time. The fluctuations also increase by a factor of around 20, thus validating the intuitive results.

Answer (iii)

Cell to cell variability plays a vital role in deciding cell fate and the two prime factors leading to cell to cell variability are (a) variation in apaf and cyto-c levels & (b) Stochasticity in dynamics.

Cyto-c and apaf combine to form apoptosome. Also, two apoptosome complexes combine to form a dimer which is illustrated in the second part of the assignment. As a result of dimer formation, the overall apaf level decreases which in turn leads to slow

cell death as compared to the case when apaf levels were relatively high. It is also evident from the plots that dimer formation leads to slow apoptosome formation. This induces bifurcation in the cell fate for a population of cells. The cells may either survive or die depending upon the cyto-c and apaf levels. The cells in which apoptosome formation is inhibited (due to lack of cyto-c or apaf) would survive and the ones in which apoptosome formation is not inhibited would die.

Additional answer :

Modification/Degradation of cyto-c is explained by the following chemical kinetic equations-

Cyto-c (active) Cyto-c(inactive) kinetic rate constant k1

Cyto-c (active) Cyto-c(degraded) kinetic rate constant k2

As the active cyto-c available for binding with apaf is reduced by rates corresponding to rate constants k1 and k2, therefore this would also slow down the apoptosome formation process. As a result there would be some cells (very few) in which the apoptosome formation would be inhibited due to unavailability of active cyto-c and as a result they would survive.

Answer (iv)

Formation of apoptosome leads to cell death(apoptosis). In the Monte Carlo Simulation it was found that apoptosome count increases and after some time it saturates to a maximum limit .The apoptosome formed are responsible for cell death.

In the context of neurodegeneration under environmental pollutants ,it can be stated that particulate matter has higher level of respirable fraction between 2.5-10 and originate from various environmental factors .They give rise to Neurodegenerative diseases including Alzheimer (AD) and Parkinson (PD). Air Pollution has been found out to be one of the major contributor to neurodegenerative diseases.

We can say that the exposure to lead, manganese, solvents and some pesticides has been related to mitochondrial dysfunction and thus cause release of more amount of Cytochrome-C from mitochondria which binds to apaf and forms more apoptosome and eventually leads to more cell death. In the context of our Monte carlo Simulation ,we can capture the varying level of Cytochrome-C(neurodegeneration) that are released from mitochondria and find the number of apoptosome it forms with apaf and is responsible for cell death.

Answer (v)

Research suggests that neurodegenerative diseases like Huntington's disease, Alzheimer's disease, and Parkinson's disease are mainly characterised by neuronal-cell

death. Moreover, given the fact that central nervous system is not able to regenerate neurons, we mostly rely on artificial chemotherapeutic strategies and simulations to understand and cure such diseases.

Stochastic modelling of cytochrome-C versus apaf can suggest time taken for a neuron to die. This can be applied to a population of healthy and infected cells. Moreover, the cases of cytochrome-C binding with other molecules thereby inhibiting its ability to form apoptosome can also be captured in monte carlo simulations, and a parallel in vivo study of such inhibiting compounds and their binding affinity with cytochrome-C can be fed into the model to predict reliable results about avoiding cell death to some extent.

Also, bioinformatics data can suggest actual quantities of proteins involved in apoptotic pathways in such cells, which can provide inputs to the Monte-Carlo model which we developed. The model then can be used to predict how a population of cells in neurodegenerative diseases with different levels of death inducing proteins react to a foreign chemical. This can model the effectiveness of such a chemical in predicting the time duration for which apoptosis can be deferred.