SSSBB HW 1

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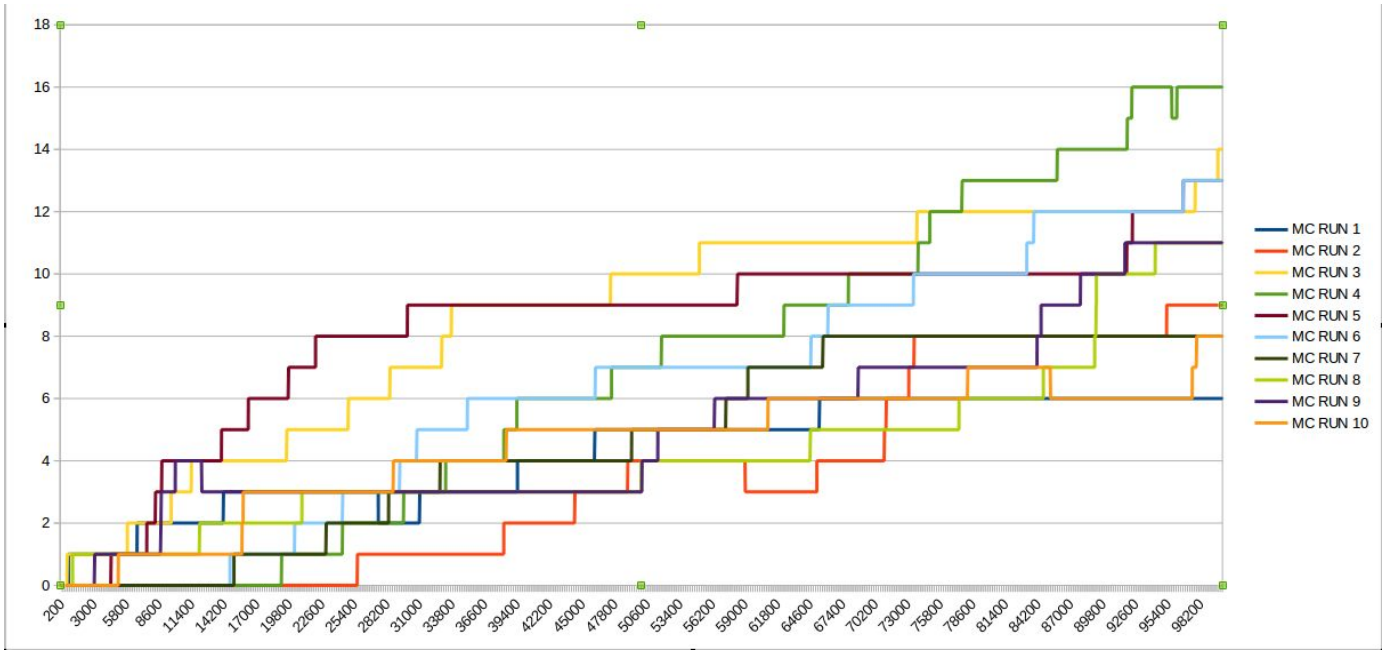
Ans 1)

Graph of Number of apoptosomes V/S MC steps for all the 10 runs



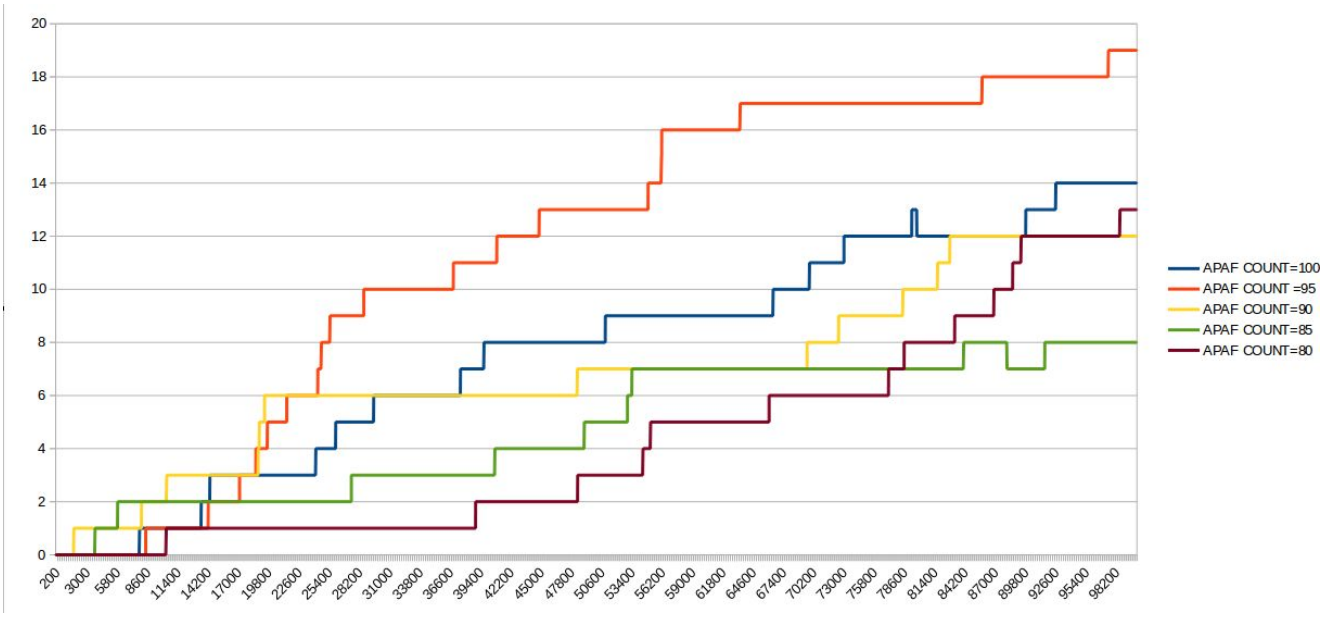
Here t= time to apoptosome formation for first 2 apoptosomes

MC RUN 1: t=6643
MC RUN 2: t=38180
MC RUN 3: t=5796
MC RUN 4: t= 24310
MC RUN 5: t= 7473
MC RUN 6: t= 20198
MC RUN 7: t= 22906
MC RUN 8: t= 12022
MC RUN 9: t= 8685
MC RUN 10: t= 15669

Standard deviation of ‘time to apoptosome formation’= 9796.9301

Average value of ‘time to apoptosome formation’=16188.200001

Effect of Apaf level variation on apoptosome variation

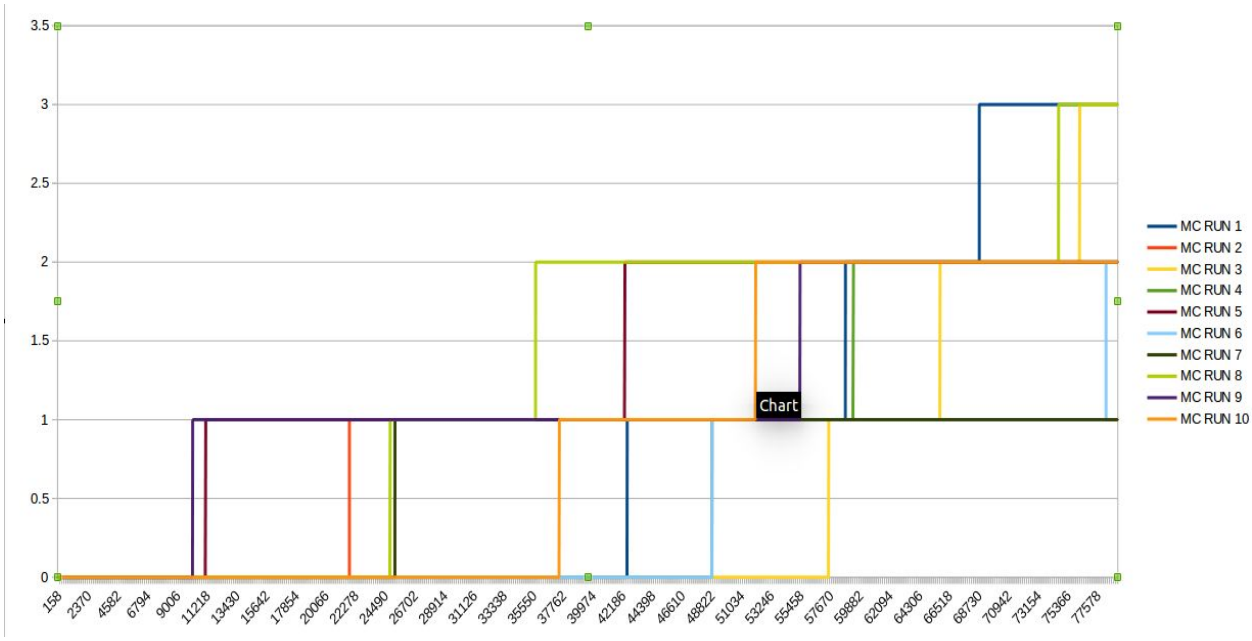


As we decrease the number of molecules of apaf, the number of apoptosomes formed at saturation decreases. Also the time to apoptosome formation gets delayed.

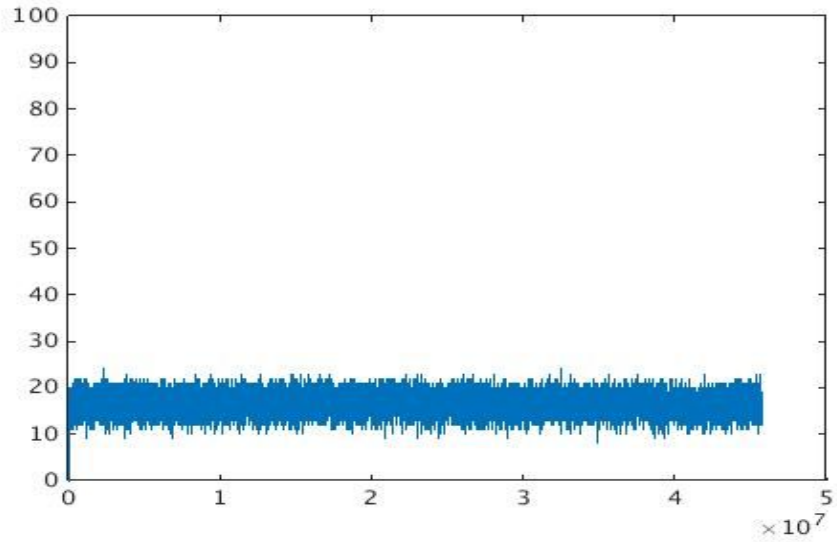
Ans 2)

Dimer model simulation

a)



b) Apoptosome formation for 1 MC run (10^7 MC steps)



From the figure a), we observe that the average time to apoptosome formation is 48,000 =4.8 * 10 ^4 which is greater than the time to apoptosome formation in the first part. Hence time to apoptosome formation has increased. Also from b) we see that the fluctuations have increased. The number of apoptosomes formed have also reduced since now the apoptosomes are dimers of cytoc-apaf complexes.

Ans 3) i)

Through the analysis of our kinetic monte carlo simulations , we observed that low apaf levels leads to slow apoptosome formation.Initially when the number of apaf molecules were 50, the time to first apoptosome formation is less as compared to when the number of apaf molecules were lesser. As we decrease apaf molecules, slow type 1 activation frequently replaces type 2 activation and the time to first apoptosome formation increases. Since the time to first apoptosome formation increases, some cells escape death so lesser cells are dying.One of the aims of our kinetic monte carlo simulations was to decrease the cell to cell variability so that the same methodology can be applied to a larger number of cells which leads to apoptosis .

Ans 3 ii)

Cytoc → Cyctoc * (degraded form of cytoc)

As in the above reaction , the degradation of cytoc results in the formation of cytoc*.This is not a reversible reaction so due to this reaction the number of cytoc molecules decreases. Therefore, less number of cytoc molecules will react with apaf to form apoptosomes. Hence less number of apoptosomes will be formed and more fraction of cells will survive.

Ans 4)

In the presence of environmental pollutants, the DNA of neural cells may get damaged.Also, direct exposure of particulate matter activates toxic neurological effects. Due to this, the genes responsible for making proteins(such as Bid protein which is involved in Apoptosis) get mutated, leading to increase in production of Bid. This leads to increase in activation of Bax, due to which cytoc is released in large amounts. This further enhances apoptosis leading to neurodegenerative diseases. Our Kinetic MC results can help us by implying an increase in the number of apoptosomes formed and hence indicating the presence of neurodegenerative diseases.
Hence to cure this disease, we need to kill these damaged DNA cells.

Ans 5)

For treating neurodegenerative disorders we want to decrease apoptosome formation and also increase cell to cell variability.In case of cancer , we know that we need a BCL2 inhibitor which decreases the apoptosis resistance of cancer cells.Such BCL2 inhibitor or also called a chemotherapeutic agent is a key step in designing successful anti cancer therapy as it induces selective apoptotic death of cancer cells. But in case of degenerative disorders like Alzheimer's disease , our aim is to decrease apoptosome formation. One of the strategies for the same is caspase 6 inhibition which switches the activation from type 1 to type 2 and increases cell to cell variability thereby increasing apoptosome formation.Through genomic data information , we can extract all necessary protein data and use the same for plotting apoptosome formation with respect to MC runs.