SSSBB Winter 2017
HW Assignment 1
(Group Project Work)

1. In the type 2 cell death pathway, apoptotic stress induces release of cytochrome c from mitochondria and activation of the downstream signaling module. In Alzheimer's disease, for example, Aβ oligomers are known to cause mitochindrial cytochrome c release in certain neural cells. Post-mitochondrial regulation of the type 2 pathway is mediated through cyto c-ATP-apaf complex (also called apoptosome) formation and activation of an initiator caspase (caspase 9) needed for signal amplification and effector caspase activation.

   (10 pts) Develop a simplified kinetic Monte Carlo model of apoptosome formation. Simuate the above described post-mitochondrial regulation of apoptosis mediated through cyto c and Apaf. Cyto c molecules (surrogate for cyto c-ATP complex) bind to apaf and this leads to cyto c-apaf complex formation. Several such cyto c-apaf complexes can form higher order oligomers (apoptotsome).

   Challenge question: Simulate formation of pro caspase 9 dimer molecules (bound to apoptosome) and activation of caspase 9.

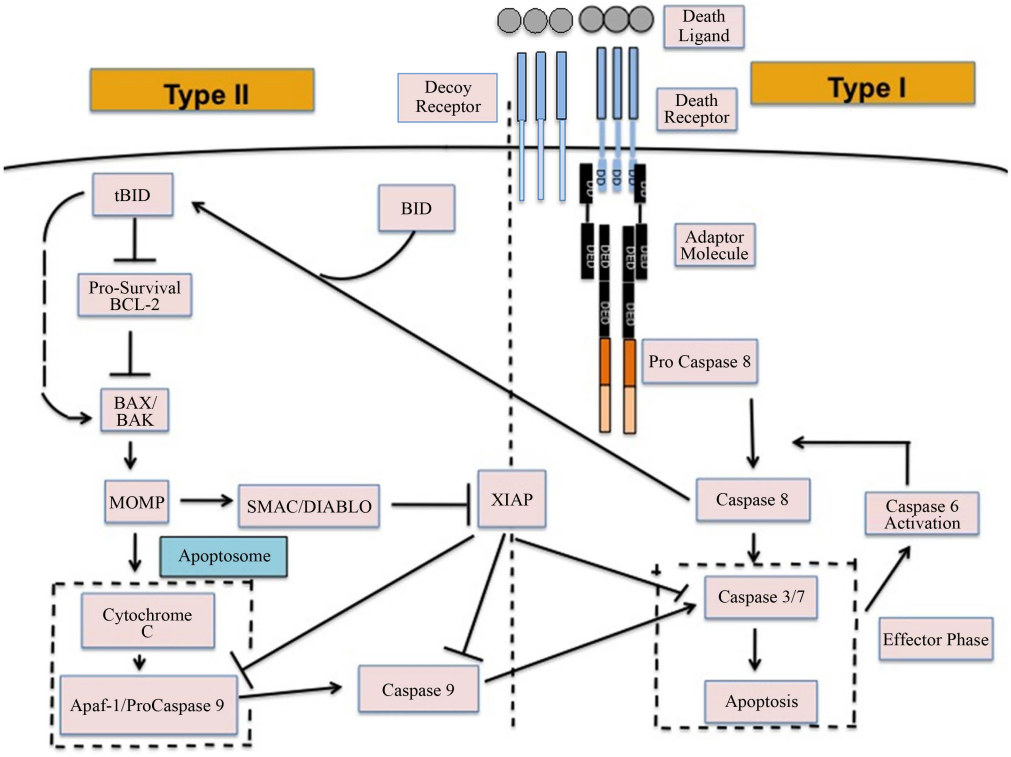


**Figure 1.** A schematic for the apoptotic death signaling network showing membrane proximal signaling module and type 1/type 2 pathways.

(i) (4 pts) Determine the time-to-apoptosome formation for each Monte Carlo run and estimate average and standard deviation (as a measure of fluctuation) from many runs of simulation (at least 10 MC runs). Study the effect of apaf level variation on time-to-apoptosome formation.

(ii) (4 pts) Now simulate the oligomeric (cyto-apaf) apoptotosme formation (dimer model) and show that the average time-to-apoptosome and fluctuations in T_apop increase. (Challenge question: simulation of trimeric apoptosome formation).

(iii) (3 pts) Discuss how slow cell death (as apaf level is decreased) may lead to bifurcation in cell fate (survival / death) for a population of cells. Also discuss the role of cell-to-cell variability in Apaf levels on bistable response in a population of cells.

(iv) (4 pts) Apoptotic cell death can be considered as an inherent immune mechansim for eliminating damaged cells (such as DNA damaged cells). DNA damaged cells frequently activate the type 2 apoptotic cell death pathway. Discuss the implication of your kinetic MC simulation results for neural apoptosis in the context of neurodegeneration under enviornmental pollutants (such as due to high particulate matter 2.5 levels).

(v) (5 pts) Consider application of stochastic modeling (kinetic MC simulations) in designing effective chemotherapeutic strategies for neural degenerative disorders such as Alzheimer's disease. Think how bioinformatic data (such as genomic data) analysis can be combined with kinetic MC based studies.

You may use:

(i) A simulation volume of $60 \times 60 \times 60$ (assuming lattice spacing d $\sim$ 20 nm).

(ii) Total simulation time up to $T = 10^8$ MC steps with $\Delta T = 10^{-4}$ sec.

(iii) Assume cytochrome c = 100 molecules (100 nM), apaf = 50 molecules (50 nM) when developing the initial kinetic MC model. Try to estimate cytochrome c and apaf levels (in neural cells) based on data provided in databases and published papers (some links are provided with assignment).

(iv) Kinetic rate constants and corresponding MC probabilities can be found in the following reference: Cells 2:361-392 (posted on backpack). $P_{diff}$ for oligomeric cyto c-apaf complexes can be taken to be zero.

Challenge problems:

1) Simulate the effect of neuroglobin (is known to bind cytochrome c with low affinity) on apoptosome formation in neural cells.

   Ref: Apoptosis 15:401-411 (2010)