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Developing a continuous time Markov chain to simulate the effectiveness of an intracellular therapeutic against Alzheimer's disease (AD)

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As the sixth-leading cause of death in the United States, Alzheimer's disease (AD) has received significant attention as a neurodegenerative disease that needs an effective treatment option. In particular, oxidative stress has gained prominence for its emergence during the aging process and ability to activate inflammatory pathways. In order to simulate signaling pathway behavior accurately, a continuous time Markov chain (CTMC) is developed to include stochasticity of pathway behavior. Using the PRISM model checker, the c-Jun/JNK pathway is developed with oxidative stress as the input stimuli, and multiple transition routes within the pathway were added to include stochastic effects. Along with the signaling pathway, gene expression was also coded by developing modules for BACE1 transcription and protein production. Relating oxidative species concentration to kinase phosphorylation was achieved by using a variation of Michaelis-Menten kinetics; at extremely high concentrations of oxidative species, the concentration of phosphorylated kinases reaches a limiting value corresponding to the maximum number of kinases available for phosphorylation. After running the simulation for 650 seconds, several observations were made: at lower levels of oxidative stress for activating the pathway, because of the effects of the stochasticity, most of the results for varying inputs of oxidative stress stimuli resulted in a relatively same range of BACE1 mRNA transcripts and amyloid beta protein concentration. However, in the short run, higher amounts of oxidative species caused a more rapid phosphorylation of the signaling pathway, resulting in a faster increase of amyloid beta before steady state is reached.

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Enhanced and cell selective drug delivery of gold nanoparticles functionalized with cell penetrating peptide derived from maurocalcine animal toxin

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Cell penetrating peptides (CPPs) have been developed as vectors for molecular delivery into various cells for use in drug delivery, gene therapy and cancer treatment by their property transporting various molecules into cytoplasm. CPPs with high internalization, cell specificity, and low cytotoxicity have been considered to increase the applicability for cell engineering. Gold nanoparticles (GNPs) are a useful tool for molecular imaging, because they are non-cytotoxic and have high solubility, ease of synthesis and excellent light scattering property. Here, we investigated the cell penetrability of TAT-C and MCaUF1-9(Ala)-C peptides conjugated to using of dark field imaging and atomic absorption spectroscopy. Depending on the peptide sequence had the different cell penetrating (CP) activity for three kinds of cell lines, Hela, A431, and MDA-MB-231. Peptide conjugated GNP showed low cytotoxicity and high selectivity against three cell types respect to net charge difference between peptide. $MCa_{UF1-9(Ala)}$-C-GNP and TAT-C-GNP displayed higher affinity for MDA-MB-231 (24.2%) and A431 (17.6%) cells, respectively. We studied the cytotoxic activity of an anti-cancer drug doxorubicin (DOX) conjugated to the peptide conjugated GNP. They showed different cytotoxicity against the three cell lines, depending on the peptide sequence, with a higher efficiency than free DOX at the same concentration. The cytotoxicity by DOX was correlated with the CP activity of the peptides against the three cell lines. DOX-$MCa_{UF1-9(Ala)}$-C-GNP induced the highest cytotoxicity in MDA-MB-231 cells (30%). These results demonstrated that peptide conjugated GNP would be a useful tool for the development of a new cell-selective drug delivery system.

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