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Stochastic modeling of signaling pathways and gene expression mechanisms in Alzheimer's disease using Continuous Time Markov Chains

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As the sixth-largest cause of death in the U.S., Alzheimer's Disease (AD) is one of the most debilitating neurodegenerative disorders that has incited significant research within the scientific community. While researchers have discovered hallmarks of AD such as amyloid beta plaques and tau hyperphosphorylation, the initial molecular events that result in AD still remain unclear. Among current research, a major factor that has been attributed to AD pathogenesis is the presence of oxidative species that enhance expression of amyloid beta-producing enzymes such as BACE1 and impair expression of amyloid beta-clearing enzymes such as neprilysin. Oxidative species affect gene expression through signaling pathways composed of kinases, and this project focuses on the JNK signaling pathway's role in activating BACE1 expression. Using a Continuous Time Markov Chain (CTMC), a method for simulating stochastic processes where events occur independently of the past, the JNK pathway and BACE1 gene expression network are simulated as three different Markov chains that simultaneously execute reactions in distinct regions of the network. In order to portray the intracellular environment pertaining to AD accurately, oxidative species and enzyme denaturation are randomly added to the network, resetting the Markov chains with altered reaction transition intensities that leads the cell toward a state of further chaos and dysfunction. Results have shown that while each individual event occurs probabilistically, oxidative species hyperactivate the JNK pathway, leading to increased amyloid beta production, so such simulations could serve to explore the molecular origins of AD further.

Biography

Sahil Doshi is a rising senior at Upper St. Clair High School who has been researching Alzheimer's Disease and its pathological origins for the past two years. He recently earned honorable mention at the MIT THINK Scholars Program for developing a molecular dynamics simulation and was invited to present at the International Conference for Systems and Synthetic Biology in Munich, Germany for his computational modeling work. Prior to that, he was named America's Top Young Scientist in 2014 for a carbon dioxide battery and presented it to President Obama at the White House Science Fair.

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