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Reverse Engineering a Kinetic Model of a Dopaminergic Neuron to Apoptosis

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Reverse Engineering a Kinetic Model of a Dopaminergic Neuron to Apoptosis

Parkinson's Disease affects approximately one million individuals in the United States, with more than 60,000 new cases diagnosed each year. While neurotherapeutics continue to make strides in elucidating the mechanisms by which dopaminergic neurons commit to an apoptosis phenotype, many questions remain. In this work, we have constructed an ordinary differential equation based mathematical model of the intra-cellular signaling pathway of fundamental and key species, including DJ-1, Parkin, and Pink1, involved in the control of cell survival vs apoptosis differentiation. We view the commitment to apoptosis as a biological switch, and utilize our model to identify the subset of kinetic rate values from the parameter space that cause the neuron to toggle to apoptosis. The novelty of our model includes (i) the incorporation of calcium and the IPAS pathway, and (ii) the process of searching the parameter space to "reverse engineer" the kinetics that generate an apoptosis phenotype. We will present our intra-cellular signaling pathway wiring diagram, system of ODEs, approach for traversing the parameter space, and preliminary results that show how only certain combinations of kinetics can produce cell death. We hope that this work will ultimately help identify how existing therapies affect the signaling pathway, and in addition, identify potentially new therapeutic targets based on their impact in the biological switch control system.