MODELLING PROTEIN AND OXIDATIVE STRESS PATHWAYS IN PARKINSON'S DISEASE:
IDENTIFICATION OF A POSITIVE FEEDBACK MOTIF AS A POTENTIAL ETIOLOGICAL TRIGGER

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Except for a small percentage of genetic cases, the causes of Parkinson's disease (PD) are unknown and aging remains the major risk factor. However, the apparition and progress of the disease have been linked to a number of biological mechanisms. We study two such mechanisms - the accumulation of reactive oxygen species (ROS) and misfolded a-synuclein (aSYN). Despite their association with the disease, the causal contributions of ROS and aSYN remain poorly understood. Using a mathematical modelling framework, we integrate the known feedback interactions between ROS/aSYN pathways. By reducing the model down to its essential components, we are able to identify a positive feedback loop that interlinks changes in ROS and misfolded aSYN concentrations. This feedback system exhibits bistability for a wide range of physiological conditions, with one stable state at high ROS and misfolded aSYN concentrations. This indicates a highly plausible mechanism to explain the dynamic and irreversible progression of Parkinson's disease. The physiological cues of aging, such as reduction in metabolism and increase in oxidative stress have been used to probe the stability of the healthy steady-state and the findings are coherent with current knowledge.