World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:14, No:12, 2020

# Constraint-Based Computational Modelling of Bioenergetic Pathway Switching in Synaptic Mitochondria from Parkinson's Disease Patients

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**Abstract :** Degeneration of substantia nigra pars compacta dopaminergic neurons is one of the hallmarks of Parkinson's disease. These neurons have a highly complex axonal arborisation and a high energy demand, so any reduction in ATP synthesis could lead to an imbalance between supply and demand, thereby impeding normal neuronal bioenergetic requirements. Synaptic mitochondria exhibit increased vulnerability to dysfunction in Parkinson's disease. After biogenesis in and transport from the cell body, synaptic mitochondria become highly dependent upon oxidative phosphorylation. We applied a systems biochemistry approach to identify the metabolic pathways used by neuronal mitochondria for energy generation. The mitochondrial component of an existing manual reconstruction of human metabolism was extended with manual curation of the biochemical literature and specialised using omics data from Parkinson's disease patients and controls, to generate reconstructions of synaptic and somal mitochondrial metabolism. These reconstructions were converted into stoichiometrically- and fluxconsistent constraint-based computational models. These models predict that Parkinson's disease is accompanied by an increase in the rate of glycolysis and a decrease in the rate of oxidative phosphorylation within synaptic mitochondria. This is consistent with independent experimental reports of a compensatory switching of bioenergetic pathways in the putamen of post-mortem Parkinson's disease patients. Ongoing work, in the context of the SysMedPD project is aimed at computational prediction of mitochondrial drug targets to slow the progression of neurodegeneration in the subset of Parkinson's disease patients with overt mitochondrial dysfunction.

**Keywords :** bioenergetics, mitochondria, Parkinson's disease, systems biochemistry
**Conference Title :** ICSRD 2020 : International Conference on Scientific Research and Development
**Conference Location :** Chicago, United States
**Conference Dates :** December 12-13, 2020