Systems modelling of mitochondrial bioenergetics enables exploration of molecular defects contributing to Parkinson's pathogenesis

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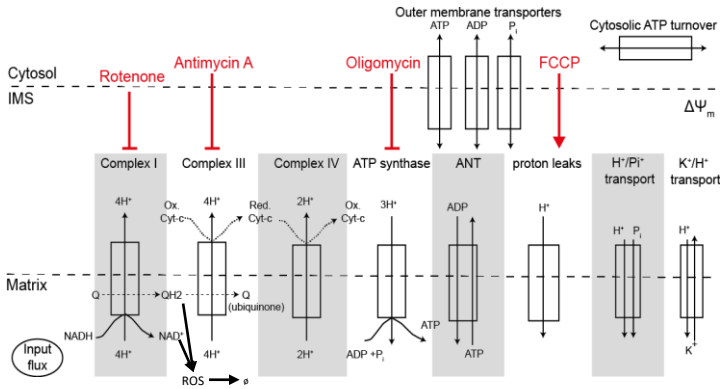
Introduction & Objectives

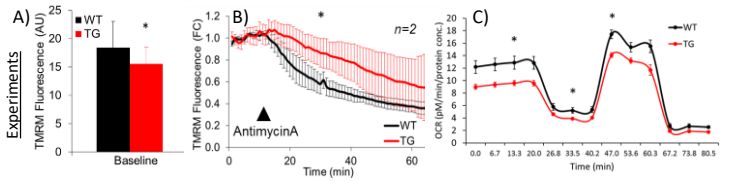
Mitochondrial bioenergetic dysfunction is known to play a key role in Parkinson's pathogenesis. The PD-MitoQUANT project (www.pdmitoquant.eu) is investigating mitochondrial dysfunction in Parkinson's and its interplay with α-synuclein toxicity. Here, we combined a systems model of mitochondrial bioenergetics with biochemical studies to pinpoint and explore bioenergetic molecular dysfunctions in Parkinson's.

Computational model of mitochondrial respiratory chain

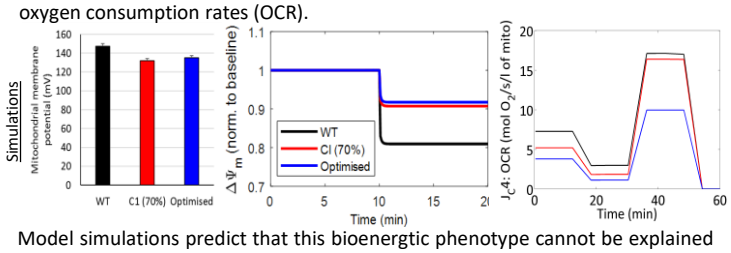


This computational model of the mitochondrial respiratory chain is implemented in MATLAB. It was originally developed in [1] and calibrated to primary neurons in [2]. As respiratory oxygen species (ROS) may contribute to differential susceptibility of specific cell types in Parkinson's, we first expanded the model to include generation and detoxification of ROS.

Pink-1 KO neurons: simulations predict that combined mitochondrial impairments contribute to bioenergetic defects

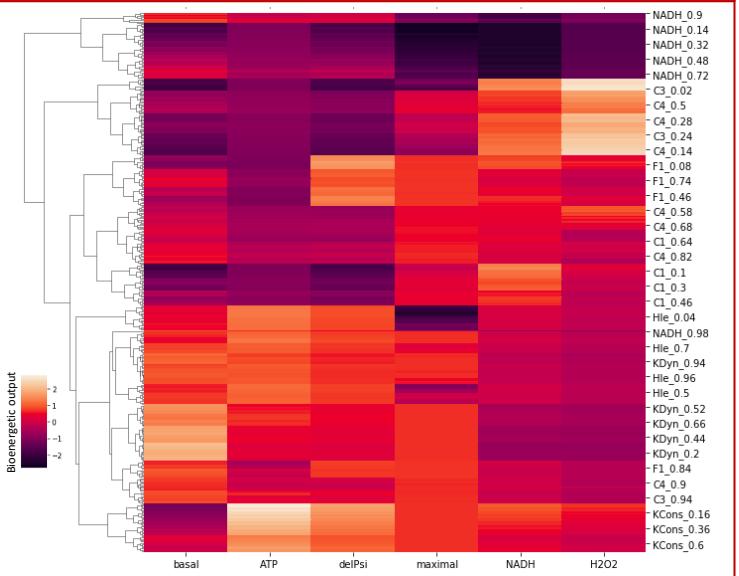


In primary cortical neurons from Pink-1 knockout mice, we measured (A) reduced mitochondrial membrane potential (TMRM), (B) decreased sensitivity to Complex III inhibition (Antimycin A), and (C) reduced basal and maximal oxygen consumption rates (OCR).



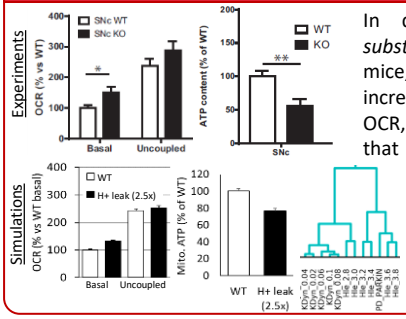
Model simulations predict that this bioenergtic phenotype cannot be explained by a Complex I defect alone, but may be due to combined defects in Complex I, proton leak, and/or ATP consumption ('Optimised').

Sensitivity analysis clusters similar impairments



To thoroughly investigate the effects of respiratory chain impairments, we sequentially simulated defects in several model components and clustered these based on their impact on key bioenergetic parameters. Large defects in complex III and IV (C3, C4) clustered together (and away from defects in C1), and are primarily characterised by increased ROS (H2O2). These analyses enable hypothesis generation and inform experimental design. For instance, we propose that measurements of mitochondrial ATP should be deprioritised as they cannot easily distinguish between different defects.

Parkin KO neurons: simulations verify that bioenergetic phenotype can be explained by partial uncoupling



In dopaminergic neurons from the *substantia nigra* (SNc) of Parkin knockout mice, Giguere *at al* [3] measured increased basal OCR, unchanged maximal OCR, and reduced ATP, and hypothesised that this may be due to mitochondrial uncoupling.

Our model simulations and cluster analysis verified that this phenotype can be reproduced by increased proton leak (uncoupling).

Conclusions

- We here expanded a systems model tool to pinpoint &explore putative bioenergetic molecular defects contributing to Parkinson's pathology.
- Different phenotypes observed in Parkinson's disease animal models may be explained by heterogeneity in bioenergetic impairments.
- Our sensitivity analysis provides an in-depth resource detailing the effects of respiratory chain defects on key bioenergetic parameters.
- As part of the PD-MitoQUANT project (www.pdmitoquant.eu), these techniques will now be used to investigate the effect of α-synuclein on mitochondrial bioenergetics.

References

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