Modelling substantia-nigra neurons to quantify the effects of alpha-synuclein in Parkinson's Disease

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Modelling electrical properties of neurons – in particular the membrane-voltage time course – is a mature discipline. The dynamics of different classes of neuron in the brain can be modelled accurately using the Hodgkin-Huxley formalism - high-dimensional non-linear coupled differential equations representing the various transmembrane ionic currents. Though this approach provides a quantitative description, a large number of parameters needs to be fixed experimentally and, importantly, the models are not tractable mathematically and can only be simulated on a computer. At the other end of the spectrum are "reduced" neuron models that capture the neuronal dynamics as well as possible while still remaining solvable. Such models are either proposed theoretically or can be extracted directly from experiment using dimensional-reduction techniques. One of the more successful models is called the Exponential Integrate-and-Fire model. This model has been shown (Harrison et al 2015) to provide an excellent reproduction of the voltage and firing patterns of neocortical neurons. Recently, with Emily Hill and Mark Wall, we have been examining the effect of alpha synuclein (one of the toxic species implicated in Parkinson's Disease) on neurons in the substantia nigra. During these analyses we saw that the usual dimensional-reduction techniques did not work well for these cells and that the Exponential Integrate-and-Fire model provides a bad fit. Quantitative and mathematically tractable models of neurons are, however, crucial for understanding cellular pathologies in Parkinson's Disease. The goal of this project then is to develop extensions and improvements of the dimensional-reduction technique to develop experimentally verified models of substantia-nigra neurons. For this project we are in the fortunate position to have a significant amount of experimental data which can be used to evaluate the models. The starting point of the project will be extending the Dynamic I-V curve method (see Badel et al 2008 and Harrison et al 2015). One obvious avenue for research will be to combine this a-priori modelling method with data-driven machine-learning techniques to develop hybrid improved models. The following references provide some background for the research.

Hill et al (2020) eNeuro, 10.1523/ENEURO.0330-20.2020
Harrison et al (2015) PLOS Computational Biology 11: e1004165
Badel et al (2008) Journal of Neurophysiology 99: 656-666