Bayesian modelling of mtDNA deletions in subatantia nigra neurons

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Mutations in mitochondrial DNA (mtDNA) have been observed to accumulate with age in a variety of tissues. They have recently been shown to accumulate with age to high levels in the substantia nigra region of the brain, with deletion levels observed in Parkinson's disease (PD) patients being higher than in controls. Neuronal loss in this region of the brain causes the major symptoms of PD. The role that these mtDNA deletions play in neuronal loss is still to be established. Understanding how mtDNA deletions accumulate is important for testing hypotheses about the link between deletion accumulation and cell death. Ultimately, a mechanistic model of cell death in the substantia nigra would allow us to estimate the effect of interventions designed to halt or reverse the decline in neurons associated with PD. It would also allow us to predict any change of incidence of PD in ageing populations.

We have constructed a stochastic kinetic model of mtDNA population dynamics which describes the accumulation of deletions in a population of substantia nigra neurons via random genetic drift, and the removal of cells from that population which have a high mutation load. The current version of the model has several parameters whose values are unknown. In order to estimate these parameters and thus calibrate the kinetic model, we have gathered quantitative data on the accumulation with age of mtDNA deletions in substantia nigra neurons. We adopt a Bayesian approach to inference which allows us to incorporate detailed prior information about the values of the unknown parameters. Our Bayesian model links the experimental data to the output of the simulation model through a measurement error model.

Markov chain Monte Carlo (MCMC) can be used to sample from the posterior distribution of the model parameters. This requires exact simulation from the kinetic model by using, for example, Gillespie's algorithm. However, this is impractical as exact simulation is too slow: one set of replicate data takes approximately two minutes to generate. Instead we fit a Gaussian process-based regression model to output from the kinetic model and use the fitted model to emulate the kinetic model in the MCMC calibration scheme.

Our stochastic kinetic model fits the deletion accumulation data well, but it predicts neuron survival with age less well, though still adequately. It may be that random genetic drift in intracellular mtDNA populations is not sufficient to describe these data. We are currently developing models including selection of mutant mtDNA for synthesis or degradation, and will repeat this analysis for these models.