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Computational model of mutant ARPP protein aggregation and diffusion and its impact on calcium dynamics and stress responses using NEURON.

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Amyotrophic lateral sclerosis (ALS) is a typically late-onset neurodegenerative disease characterized by a breakdown in the signalling of motor neurons. Many cases of ALS are of unknown etiology, but there are many proposed genetic and pathophysiological mechanisms by which motor neurons malfunction. Two such proposed disease mechanisms of ALS are; neuronal excitotoxicity, and the accumulation of pathogenic proteins. These mechanisms may be linked by the novel ALS-related gene *ARPP-21*, also known as *RCS* (Regulator of Calmodulin Signalling). The ARPP-21 protein is known to bind with CaM proteins, and to aggregate when mutated. Aberrant aggregation and protein binding could thus hypothetically alter Ca^{2+} availability in the cell, altering the viability of neuronal signalling. We were interested in investigating the reciprocal effect of pathogenic aggregation of *ARPP-21* and neuronal excitotoxicity on synaptic firing and aimed to model this *in-silico* using the modelling package NEURON.

We use the NEURON package to model diffusion and aggregation of CaM proteins and non-mutant and mutant ARPP-21 proteins and explore several parameter ranges for the binding of these proteins with each other and vary protein diffusion speeds and aggregation sizes. We utilize reaction-diffusion equations to describe the diffusion of these proteins through the motor neuron and simulate and measure input spikes and neuronal response. We observe the resultant change in signalling patterns in each of these scenarios. In this way we computationally test hypotheses for the mechanisms by which ARPP-21 aggregation may impact motor neuron signalling. We compare our simulation results with those obtained from live fluorescence imaging of mouse embryonic stem cell-derived motor neurons engineered to express tagged versions of either the wildtype *ARPP-21* gene and mutant *ARPP-21* gene. The fluorescent images of the stimulated motor neuron and tagged ARPP-21 proteins were collected and analysed using Imagej.