Parkinson's disease: the future

John Fleming discusses his PhD research on Parkinson's disease and how he is utilising computational modelling to improve our understanding of how the disease develops

What is the problem and what needs to be done to improve things?

My PhD research investigates changes in brain network dynamics which occur in Parkinson's disease. Parkinson's disease is a neurodegenerative disease caused by the death of dopamine producing cells in a region of the brain known as the substantia nigra pars compacta. This area is part of the basal ganglia network which is located under the cortex, deep within the brain. The basal ganglia is associated with a variety of functions including cognition, emotion, learning and control of voluntary movements. In Parkinson's disease the level of dopamine in the basal ganglia network is reduced. This change in dopamine level is thought to increase the strength connections between different interconnected regions of the basal ganglia network which subsequently leads to changes in dynamics of the network, and thus the manifestation of disease symptoms. The most well-known triad of symptoms affecting patients with Parkinson's disease are rest tremor, bradykinesia and akinesia, which are a slowness in movements and a difficultly initiating movement, respectively. Patients usually present varying degrees of severity of these symptoms, which also usually change as the disease progresses. At present, the exact architecture of the basal ganglia and the mechanisms which result in disease symptoms manifesting are currently unknown. However, it is thought that connectivity changes in the architecture of the basal ganglia may lead to changes in the network's dynamics, which results in the development of symptoms.

How does your research go about improving it?

My current research utilises computational modelling to study the underlying architecture of the basal ganglia network, and subsequent network connectivity changes which lead to Parkinson's disease. I analyse the network using complex network theory. In network theory, a complex network is a network with features that do not occur in simple networks, such as lattices or random graphs, but often occur in graphs which model real systems. Complex networks are composed of interconnected dynamical units. To capture the global properties of these systems they are modelled as graphs whose nodes represent the dynamical units, and whose links stand for the interactions between them. In my research, the dynamical units represent neurons in the basal ganglia network and the network links represent synaptic connections which connect

these neurons. This allows me to vary connectivity patterns, and the strength of connections in the network to investigate the effects of these properties on the dynamics of the basal ganglia network. By comparing the dynamics resulting from different network topologies with those observed in experimental studies I aim to identify the most likely connectivity patterns for the basal ganglia using this computational model. With this topology identified I can simulate dopamine depletion by increasing the strength of connections in the network, allowing me to subsequently examine changes in basal ganglia network dynamics during Parkinson's disease.

How did you get started and what was the aim?

The overall aim of my PhD research is to improve how deep brain stimulation (DBS) is controlled in Parkinson's disease. Medication, such as Levodopa, a synthetic form of naturally occurring dopamine, is the most common treatment for Parkinson's disease. However, medication can become ineffective for patients over time. When this occurs, DBS may be proposed as an alternative treatment method for improving disease symptoms. Although DBS can help alleviate patient symptoms the exact mechanism of how it works is at present unknown. The current process for setting stimulation parameters in Parkinson's disease involves a skilled clinician adjusting stimulation parameters over a period of up to several months. The clinician's aim is to find an optimal combination of stimulation pulse amplitude, duration and frequency, which will minimize the symptoms of the disease and any side effects which can result from the stimulation. Side effects can be obvious, such as a worsening of tremor, or more subtle changes, such as a change in mood. The timescales at which these side effects present themselves can also vary greatly. An increase in tremor may appear very quickly as the clinician changes parameters. However, a change in mood, such as depression, may evolve over several weeks. Thus, parameters which may initially seem optimal in improving a patient's condition may be suboptimal in the long run. Another complicating factor is that Parkinson's disease is a dynamic disease. This means that the severity of a patient's symptoms can vary throughout the day, and also as the disease progresses. Thus, it is a challenging and time-consuming process to try to identify optimal stimulation parameters for treating the condition. To overcome these issues, we aim to develop a 'closed-loop' or adaptive control system, which would ideally, be able to sense the severity of a patient's symptoms and any stimulation-induced side-effects, and automatically adjust stimulation parameters to minimize both. To do this, we need to be able to quantify the severity of a patient's symptoms. It is known that in Parkinson' s disease there is an increase in the level of synchronisation and oscillatory activity of neurons within the basal ganglia network. The strength of these neural oscillations have been shown to be correlated with the symptoms of tremor, akinesia and bradykinesia. Utilising this, recent research has been aimed at reducing this oscillatory activity to improve disease symptoms. This oscillatory activity has been proposed as a possible 'biomarker'. Biomarkers refer to measurable indicators of some biological state or condition. Thus, to improve stimulation techniques in Parkinson's disease we need to identify suitable biomarkers which can indicate the severity of the disease symptoms. If we can monitor these biomarkers, we can then monitor the effects of stimulation on them. This has the potential to speed-up the process of stimulation parameter tuning as the clinician would be able to automatically identify optimal stimulation settings. We can then work towards developing a stimulation system that monitors patient symptoms and side-effects, adjusting parameter settings automatically when necessary to minimize both disease symptoms and stimulation side-effects. Although there is much research looking at the behaviour of the basal ganglia network, there is still no clear definition of the connections within the network. In particular, the number of connections between, and within, populations is still unclear. This is what lead me to my current research investigating the architecture of the network in my computational model. My aim is to use insight gained from the architecture to design new stimulation techniques which take advantage of the basal ganglia architecture for optimal deep brain stimulation.

Did you hit any glitches and how were these overcome?

I initially set about modelling the network using computationally efficient neuron models which can reproduce a wide variety of spiking patterns observed experimentally. I was interested in the dynamics that result from the interaction of neurons in a network rather than the individual dynamical units which make up the network. I originally worked on setting up a network of these neurons with the aim to then tune their parameters to mimic the dynamics of those observed from the corresponding neurons of the basal ganglia network. However, these neuron models are phenomenological and their dynamics are not representative of the underlying dynamics in the actual neurons that I am interested in. The firing of neurons are the result of a combination of gating dynamics where ions traverse the membrane of a given neuron. By using phenomenological models rather than more physiologically-based neuron models it may be difficult to determine whether the modelled network dynamics are truly representative of the interaction of the underlying dynamical units or if they are simply due to artefacts resulting from the model used. Because my research is currently interested in understanding the effects of differing topologies on the dynamics of the basal ganglia network I decided to use less computationally efficient models of neurons, which are more biophysically realistic of the underlying neuron dynamics. For this reason, I now model the neurons in my network using neuron models which are more representative of the intrinsic dynamic processes of neurons in the basal ganglia network. This allows me to investigate the effects of network topology and connectivity on the basal ganglia network dynamics with more confidence that the behaviour I see is due to topology and connectivity changes, and are not simply modelling artefacts due to the dynamical units used in the network model.

Any plans going forward for continued development/research/awards, etc?

In 2018 I plan to travel to France to collaborate with the Signals and Systems lab in Centrale Supélec, Paris under the supervision of Professor Antoine Chaillet. Professor Chaillet's lab is doing very interesting research exploring methods to suppress pathological frequencies present in the basal ganglia network during Parkinson's disease, while leaving other 'healthy' frequencies in the network untouched. Their research focuses on an alternative modelling approach where they model the average population activity of neuron populations in the basal ganglia. My motivation for going there is to adapt and implement their control technique so that it can be used in my model and, thus, help validate their control technique as a robust technique for pathological frequency suppression that can be used for treating Parkinson's disease.
Next June, my research group, the UCD Neuromuscular Systems lab, are hosting the International Society of Electrophysiology and Kinesiology conference here in Dublin (https://isek.org/2018-welcome/). The conference brings together researchers from a range of multidisciplinary backgrounds specialising in human movement and the neuromuscular system. The conference is a great opportunity to present my research and hear different perspectives from researchers interested in these areas, with different research backgrounds to my own.
In the future, my plan is to work as a researcher in the US. Deep brain stimulation is also being investigated as a treatment for other neurological and psychiatric conditions, including epilepsy and depression. Electrical stimulation is also widely used in neuroprosthetic devices which are used to substitute a motor, sensory or cognitive function that may have been damaged due to injury or disease. Cochlear implants are established examples of these devices; however researchers are now looking to develop visual, and even memory prosthetics. I think the area of neuroprosthetics is a fascinating field, which will only become more interesting as we continue to learn more about how the brain works and how we can interact with it in a beneficial manner.