Aim: To create a mathematical simulation that provides an environment for making and testing predictions relating to the pathological accumulation of iron in the human brain, in Neurodegeneration with Brain Iron Accumulation (NBIA).

What is NBIA? "Neurodegeneration with Brain Iron Accumulation (NBIA) is a group of rare, genetic neurological disorders characterized by abnormal accumulation of iron in the basal ganglia. The basal ganglia are structures deep within the base of the brain that assist in regulating movements. The exact relationship between iron accumulation and the symptoms of NBIA is not fully understood. Although we all normally have iron in this area, people with NBIA have extra iron that can be seen on MRI (magnetic resonance imaging). Certain MRI views (T2-weighted images) show the iron as dark regions in the brain. High brain iron is most often seen in the part of the basal ganglia called the globus pallidus. It is also often seen in another part called the substantia nigra. NBIA is progressive and, at this time, there is no cure." *www.nbiadisorders.org/about-nbia/overview-of-nbia-disorders*

Objectives:

1. Identify the key changes to brain iron metabolism in a rare human disease (Neurodegeneration with Brain Iron Accumulation, NBIA), compared to normal healthy individuals.
2. Extend an existing compartmental systems model of the healthy brain to then describe brain iron uptake in NBIA.
3. Develop a preliminary model of iron exchange between key regions of the brain: globus pallidus, substantia nigra, caudate nucleus, putamen, white matter.
4. Determine whether the experimentally-observed selective iron-loading of the globus pallidus in NBIA can be achieved through altered regulation of iron metabolism in the model.
5. Use the model predictions to design experiments that can be used in future to refine the model and, in due course, to verify the predictions.

Introduction: Research into common neurodegenerative disorders such as Alzheimer's has arguably been underfunded compared to other high-incidence diseases such as cancer and heart disease. This will hopefully change, as dementia (an umbrella term including Alzheimer's and related disorders) has become highly visible on the political agenda in developed nations over the past 12-18 months. Despite this optimism, there remain a number of rare and devastating neurodegenerative diseases that are barely known, let alone receive research funding, yet progress in understanding and treating these illnesses is essential to offer a reasonable life span or meaningful quality of life for the children, teenagers, and adults who are affected. A common factor in many of these rare, or 'orphan' diseases, is altered metal-ion metabolism – including changes to regulation of the transition metals iron, copper, and zinc. Systems models of the kind to be developed in this project have great scope for impact, as this research field – spanning neuroscience and metallomics – is limited by the complexity of the underlying biological systems to being primarily descriptive. It can be shown experimentally where the concentration of a particular metal or metal-binding protein changes in a given compartment (e.g. a cell type, brain region, or pathological inclusion), but describing the mechanism by which this change occurred, the timescales involved, the anticipated impact, and the scope to modify or correct the disrupted metabolism with drug treatments (e.g. metal binding drugs - chelators) requires robust models to handle these highly complex systems. The outputs have the potential to support future research in both the academic and pharmaceutical industry sectors, and to support healthcare providers and patients in due course.

Summary of Background and Techniques: There is a significant gap in understanding the processes that control iron levels in different brain regions, so that evaluation of brain iron as a diagnostic marker is constrained by the limited availability of post-mortem data, and there is an analytical constraint on understanding mechanisms of brain iron chelation, as the target for chelation is primarily an extremely low concentration of labile or loosely-bound iron which is likely impossible to detect non-invasively by clinical methods. The systems model of brain iron that we are currently developing (**Figure 1,** below) will provide a powerful tool to address both these challenges.

The proposed MSc project will focus specifically on NBIA, building from the existing model that uses ordinary differential equations and has been created in collaboration with Dr Simon Mitchell at UCLA. The present brain iron model (**Figure 1**), from which the NBIA model will be developed, is available in Systems Biology Markup Language and has been created in COPASI (open-source). It incorporates compartments for the brain capillary epithelial cells, interstitial and cerebrospinal fluids, and the epithelial cells between the cerebrospinal fluid and the blood. New compartments representing the primary anatomical brain regions affected in NBIA will be incorporated into the model, to describe iron trafficking within the brain, so that potential drivers for unexplained but clinically observed region-specific accumulation of iron in NBIA [*Dezortova 2012, DOI: 10.1002/cmmi.1482*] can be explored.

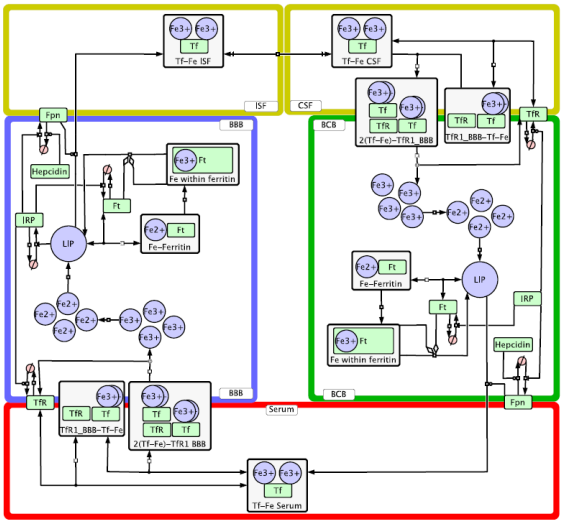

Figure 1: Model of iron uptake into the brain. Mitchell et al, manuscript in preparation

Timeliness: A powerful systems model of liver iron metabolism was developed by our colleague Dr Simon Mitchell with some results now public domain [*Mitchell 2013, DOI: 10.1371/journal.pcbi.1003299*]. Subsequently we have collaborated with Simon to develop a model of iron uptake into the brain. Vindy Tjendana Tjhin, a first year PhD student in our group, is refining this model and will be extending it to consider scenarios where iron is dysregulated in disease, including aspects of Alzheimer's and Parkinson's disease pathology. Recent advances in the field, including important experimental results and preliminary models of uptake [*Simpson 2014, doi:10.1038/jcbfm.2014.168*], and clinical data indicating the efficacy of an iron chelating drug in modifying iron loading in certain neurodegenerative disorders, makes this project an opportunity to deliver tangible impact.

Subsequent Phd Project: There are several natural extensions to develop this into a full PhD project, including:

i) Developing and refining the model to more fully describe Neurodegeneration with Brain Iron Accumulation, taking into account variants such as panthotenate-kinase-associated neurodegeneration (PKAN) which underpins the MSc project described here, and neuroferritinopathy which leads to massive brain iron accumulation due to a defect in a gene required for the iron storage protein ferritin.

ii) Incorporating copper metabolism into the iron model, where it is known that iron and copper metabolism are inter-dependent, and where this extension will allow diseases involving copper accumulation (such as Wilson disease), and aceruloplasminemia (disrupted iron metabolism as a result of a failure in the copper-carrying protein caeruloplasmin), to be modelled.

Supervisors: We have delivered international impact in trace metals in medicine (Dr Collingwood) and pharmacokinetic modelling (Dr Chappell), and are increasingly bringing these specialisms together to tackle fundamental challenges in the field of neurodegenerative disorders. We have successfully co-supervised MSc and PhD students, and have highly complementary expertise spanning experimental and computational methods.

Dr Joanna Collingwood
School of Engineering
J.F.Collingwood@warwick.ac.uk