SYSTEMS BIOLOGY
Hamilton Institute

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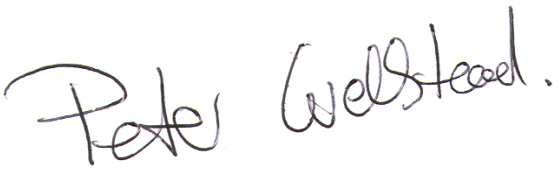
Preface

This is the fifth and final report for the SFI Research Professorship Award 03/RP1/I382. The report covers the period July 2008 to December 2009 and is a supplement to the formal progress and financial report submitted to Science Foundation Ireland under the terms of the Award.

For more information on our work, and electronic copies of past reports, please visit www.systemsbiology.ie and go to publications and reports. For background on the Hamilton Institute generally go to www.hamilton.ie. The individual contact points for the Systems Biology team and visiting co-workers are given in the relevant sections of this report and our website. The reader is also invited to visit www.systemsofparkinsons.org. This website is a forum for sharing information and research associated with our theme project of systems approaches to Parkinson's disease.



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Review of the Programme Outputs

Initially, this Research Professor programme had two objectives: (i) a medium term objective to develop Near Infrared (NIR) signal processing methods for bio-signal analysis and use with a novel two-beam interferometer in medical diagnostic applications, and (ii) a more ambitious goal to develop the area of systems biology in Ireland and in the Hamilton Institute.
The novel hardware associated with the first objective did not live up its promise and this part of the project subsequently became the Image to Mathematical Modelling Transformation part of the National Biophotonics Imaging Platform. The systems biology objective thus became the focus of the RP programme with the following specific aims:

(a) To establish an awareness of systems biology in Ireland.
(b) To build a systems biology research group of critical mass in the Hamilton Institute.
(c) To perform original research into systems approaches to neurodegenerative disease – in particular Parkinson's disease.

Over the duration of the programme we believe that we have made the following contributions toward these objectives:

Awareness of Systems Biology in Ireland

At the time of our arrival in Ireland there was no systems biology activity of visible significance in the country. On behalf of SFI, we conducted a campaign to raise awareness of the area. In 2004/5 we (a) gave a series of lectures on systems biology to a number of life science departments in Irish universities and held numerous awareness meetings with biologists and life science groups, (b) organised two SFI sponsored national one-day workshops on systems biology, (c) presented the E.T.S. Walton lecture entitled *Schrödinger's Legacy* on systems biology at the Royal Irish Academy[1] and (d) developed briefing documents for research policy and planners on the strategic implications of systems biology[2]. In addition, the Hamilton Institute systems biology group organised two highly successful international workshops on systems biology (in 2006 and 2008). The third such workshop is in the final stages of organisation and is scheduled for August 2010. This awareness and engagement campaign has encouraged the growth of systems biology research in Ireland and provided motivation for SFI planning of a dedicated Institute of Systems Biology.

Systems Biology at the Hamilton Institute

Starting in 2004 with an initial group of four researchers, the SFI Research Professor Award stimulated the growth and diversification of systems biology interests within the Institute. The current size of the Hamilton Institute systems biology activity is now much larger with a critical mass supported by four Principal Investigators, plus a range of international visitors and collaborators.

The unique feature of systems biology at the Hamilton Institute lies in its strong foundations in applied mathematics, mathematical modelling, and dynamical systems theory. While the Hamilton Institute systems biology group is now a diverse bunch, its focus is on systems approaches to the causes of diseases and their treatment.

[1] An edited video of the lecture is available via HEAnet and the lecture text is available from our group website.

[2] On the industrialisation of biology, AI & Society, 2009. doi: 10.1007/s00146-009-0232-3

Claimed Original Research Outputs

The post doctoral/doctoral research team have focussed upon (a) conducting research into the theoretical aspects of systems biology and (b) developing a systems approach to Parkinson's disease. The main claimed research outputs in these areas are:

Theory of Systems Biology

We have an interest in developing theoretical methods and analysis that can underpin a systems approach to biology and in particular to disease. In this context, we have worked on general properties of metabolic systems, biological networks and coupled networks of oscillators. Specifically:

- Oscillations and the synchronisation of families of coupled oscillators are important issues in biological systems. For example, many biological processes in living systems rely upon synchronised periodic activity. For various network types, we have studied synchronization and phase-locking in the context of the Kuramoto model of weakly coupled nonlinear oscillators. Our contributions to this area are the development of new methods for computing bounds on the critical coupling coefficient, and results on the behaviour of the critical coupling coefficient as the number of oscillators tends to infinity. We believe that this is the first convergence result for Kuramoto type systems. (*See references – published papers*).
- Motivated by observations of apparent sequential action in metabolic processes, we have analyzed linear metabolic networks from a control theoretic viewpoint. The result is that they can be interpreted as an optimal control system which minimizes the cost/benefit relation between the transition to a target steady state and the genetic "effort"' required by enzyme synthesis. (*See references – published papers*)
- Motivated by our research into Parkinson's disease, we have conducted a detailed systems analysis of control mechanisms and structures that regulate cellular energy metabolism. This analysis allowed the assignment of specific functional roles to regulatory mechanisms for cell energy trafficking, in a way that we believe may have a wider implication in the analysis of disease. (*See references – published papers*).
- We have combined results from the brain energy metabolism model that we developed for Parkinson's disease (PD) research with control systems insights to explain the energetic role of astrocytes as a dynamical feedforward mechanism for energy regulation. This has relevance in our energy systems theory for PD etiology (see below), and has the potential to resolve a controversy that has divided brain metabolism researchers for over 10 years. (*Paper under review*).

Parkinson's Disease - Modelling and Analysis of Causal Mechanisms

In terms of potential impact on medicine I believe that our work on Parkinson's disease has been the most fruitful. Specifically, by proposing and developing a systems approach to neurodegeneration, we have opened up a new way of thinking about and researching the causes of Parkinson's disease. Using the tools of mathematical modelling, dynamical systems analysis and control theory we have been able to pose and investigate questions concerning the etiopathogenesis of PD in a systematic and modular way, thus clearing the way for contributions from a new type of PD researcher from the fields of dynamical systems analysis and control engineering. In more detail:

- We have developed an integrative mathematical model of brain energy metabolism as a framework for studying age-related neurodegenerative diseases such as PD and AD. The modelling framework is readily expandable, such that

sub-models of cellular processes implicated in a disease can be added in a modular fashion, and their interaction with other factors examined, (*see references – published journal papers*).

- We have used the brain energy metabolism model to develop and provide *in-silico* evidence that supports the idea that energy has a role in the etiology of Parkinson's disease. According to the energy theory of PD, a compromised brain energy metabolism (caused by advanced age, head trauma or toxins) would allow the cumulative impact over a lifetime of transient energy insults to form an etiological trigger for pathogenic mechanisms, (*paper under review*).
- We have developed a mathematical model of alpha-synuclein metabolism in Parkinson's disease, attached it to the framework provided by our brain energy metabolism model and analyzed *in-silico* the possible pathogenic consequences of certain etiological mechanisms – including compromised energy metabolism (both age-related and head trauma) and external toxins, (*see references – conference papers/posters*). This is a first step in developing the set of sub-models of processes implicated in Parkinson's disease, and referred to earlier.

As work in progress:

- We have identified (and are in the process of elucidating) certain regulatory and structural mechanisms that form a feedback motif for the etiopathogenesis of Parkinson's disease. Our current results suggest this will clarify the causality of two important pathological factors in a manner that is coherent with observations of disease progress, and offer a systems structure for the study of the etiopathogenesis of PD.
- We have proposed a new model for the oscillatory circuits within the basal ganglia, and which exhibits new synchronising-desynchronising properties that may have relevance to Deep Brain Stimulation (DBS). Current work is aimed at a more accurate characterisation of neuronal spiking in the basal ganglia.
- We have proposed a novel explanation of DBS's quenching of Parkinson-type tremor based upon selective blockading of axonal transmission by antidromic activity. Current work aims to extend the explanation to the point at which theoretical predictions can be made and tested experimentally.

Acknowledgements

It is a great pleasure to acknowledge for the final time the contributions of the Scientific Advisory Panel who help guide our programme over its five-year span. The names and affiliations of the current panel members are listed at the end of this report. They each have my personal appreciation for their inputs over the five years of this Research Professor (RP) programme. In the same spirit, I thank all the members (past and present) of my RP research team. It was a great pleasure to have worked with them, a pleasure that will continue as we go on in our joint research into the causes of PD. In the same spirit, I thank the administrative and scientific staff of the Hamilton Institute for the chance to work with them over the period of this RP award. The Hamilton Institute is a remarkable scientific community and a great scientific asset to Ireland.

I also thank the officers and staff of Science Foundation Ireland. The plan for a campaign to develop systems biology in Ireland came out of my initial meetings with the first SFI Director, Bill Harris and his colleague Rich Hirsch, in 2003. This Research Professor programme in systems biology was the result of those discussions, and any successes that have emerged from the programme are in significant part due to their courage in making the award and their unfailing support during their tenure at SFI. Funding an engineer to study Parkinson's disease was an act of faith on their part – I hope that our work comes some way to justifying that faith.

Introduction

Background

While our own research projects (outlined later in this report) in systems approaches to neurodegeneration lie at the heart of our research, this is augmented by a wider interest in the application of systems theory to the life sciences. In addition to our own theoretical research efforts, our programme also includes hosting visits by researchers from other research institutes, plus the organisation and hosting of international events. In this spirit, and in addition to receiving scientific visitors, such as those who spoke at the 2008 Workshop, we have continued to engage with the Walton Fellowship programme. The most recent Walton Visitor – Professor Richard Abadi - joined the Hamilton Institute in November 2008 to pursue his innovative research on the classification of visual hallucinations.

Also over the reporting period, members of the systems biology team have continued to travel to present seminars and lectures at systems biology events. Many of these trips were combined with visits to our international collaborators. In this connection, we have continued development of the Systems of Parkinson's community, both through the web site, www.systemsofparkinsons.org, through collaborations and our own research outputs (detailed later in this report).

Within the Hamilton Institute, we note that the systems biology activity has expanded significantly over the five years of this programme. In fact, the research team supported by this grant is now only one part of a larger community of systems biology researchers at the Hamilton Institute. To reflect this wider activity, we have expanded the web site (www.systemsbiology.ie) to cover, or link to, all related Hamilton Institute life science interests. From a personal perspective, this growth of systems biology at the Institute from small beginnings to a substantial and diverse activity is a particularly rewarding outcome.

Outreach and Collaboration

The science outreach highlight of this reporting period was the Second International Workshop on Systems Biology (IWSB). This was held in August 2008 at Maynooth with a distinguished group of speakers and a very lively set of delegates. The event was a scientific and networking success. So much so that the Hamilton Institute systems biology group will run the event again. The 3rd IWSB will take place in 2010 with a similar format and an equally outstanding group of speakers (full details posted at www.hamilton.ie). A further gratifying sequel to this Research Professor programme is that there is now a healthy and diverse community of systems biology researchers in a number of Irish universities. The 3rd IWSB will reflect this with a national organising committee that involves members from these research groups.

Within Ireland, specific collaborations continue and have born fruit. At NUI Maynooth, our work on the energy metabolism of the brain with Professor Lowry's neurochemical sensor laboratory in the Department of Chemistry is particularly important. The use of his unique neurochemical sensing capability is crucial to our mathematical modelling of brain energy metabolism, and we are grateful for his open spirited collaboration. Nationally, the Hamilton Institute IMMT team (www.hamilton.ie/systemsbiology/immt), who spun out of this RP award, are funded by the Higher Education Authority (HEA) and collaborate with the Royal College of Surgeons in Ireland (RCSI), and University College Cork (UCC). We congratulate them on their recent successes with RCSI colleagues on an intelligent microscope patent, and their innovative Image to Mathematical Modelling Software

Workbench project with UCC. The results of these developments were featured at the Festival of Science held in Dublin in December 2008 and were the National Biophotonic Imaging Platform (www.nbipireland.com) contribution to the Festival.

Internationally, we continue to work with colleagues in the University of Rostock, the Brain Laboratory of KAIST, Korea, and the Systems Biology Initiative in Case Western Reserve University. In specific scientific areas, the Systems of Parkinson's team are working with collaborators in Montreal and at Georgia Tech on modelling metabolic pathways of pathologies associated with Parkinson's disease. Also, and resulting from a DBS Workshop held at the Hamilton Institute in 2008, the Deep Brain Stimulation part of the Systems of Parkinson's group is collaborating with other European researchers in a EU call for systems biology proposals.

Research Strategy and Motivation

Over the last two years the research of the Research Professorship team has focussed on our core interests - the theoretical aspects of systems biology and a systems approach to Parkinson's disease. The motivation for choosing these two broad areas is clarified below.

Theory of Systems Biology

Cybernetics and Control Theory … this branch of science which most completely describes the complex activity of all living things. (J. E. Lovelock)

We use Lovelock's words to again emphasis the role of control systems science, since they capture in a forceful way the importance of control and cybernetics as a central pillar of a systems approach to biology. In fact, Lovelock was writing about his Gaia concept of the planet as a complex set of integrated feedback control systems, but he could equally well have been referring to metabolism or cell biology. The control, modelling and dynamical analysis activities performed in previous years are outlined in the annual reports[3]. In keeping with this previous activity, our focus remains on developing mathematical methods for the analysis of biological processes and using them to understand the control mechanisms that regulate life and disease. More technically, we are working on nonlinear dynamics and organisational complexity in biology. In particular, we are looking at the issues of interconnectivity in biological systems, the role of groups of coupled oscillatory processes and the role of feedback mechanisms. Essential to this is the development of methods with which to understand and analyse the dynamics and complexity of such models. This is the area where the applied mathematics emphasis of the Hamilton Institute plays its part.

A Systems Approach to Parkinson's

As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him for a moment; even when exhausted nature seizes a small portion of sleep… The power of articulation is lost… and at the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release...

Thus did James Parkinson describe the last protracted stages of the disease that now bears his name. Parkinson's seminal essay on the Shaking Palsy was published in 1817 and was the first detailed characterisation of the condition in the Western world. Two hundred years later, and despite the best efforts of life science researchers, we still do not know what causes Parkinson's diseases, nor can we halt its progress. Yet this, and other neurodegenerative diseases, will soon come to dominate healthcare in the developed

[3] Past Annual Reports are downloadable in pdf form from www.systemsbiology.ie

world. The human, social and economic cost of neurodegenerative disorders is already large – and with the prediction that average life spans will continue to increase[4] – the costs will spiral, eventually overwhelming the capacity of healthcare systems. At a human level, our grandchildren (in addition to their other problems) will live in a world where many of the population are elderly and wanting of support. In such a world, the mechanisms that drive western societies will falter.

This is a problem with catastrophic potential and requires urgent responses. However, as yet (speaking now of Parkinson's disease), we know little of the mechanisms that initiate and drive the progress the disease. Our only treatments are palliatives that offer temporary relief while the disease progresses slowly toward its inevitable conclusion and the "wished-for release" referred to earlier.

Our reason for entering the area of systems biology was frustration at the glacial rate of progress of research into the causes of PD. After careful deliberation we came to believe that the lack of progress is a question of scientific methodology. In particular, life sciences are essentially qualitative forms of science, with experimental methods that are unsuited to problems of great physiological and biological complexity, and which involve many dynamically interacting factors. And yet the development of Parkinson's disease is acknowledged to be a multi-factorial process, potentially involving many pathogenic players and with dynamics that unfold over timescales that range from minutes to a lifetime.

This mix of multi-factorial complexity and dynamics demands that a new approach be added to the research repertoire. As an engineer, I believe that this new approach should be based upon a quantitative mathematical framework that can systematically handle complexity between dynamically interacting factors. Of course, there are also the facts that Parkinson's disease develops over a lifetime and only in the human brain. So we have no true animal models of the disease – only ourselves.

Following from the above issues, an aim in the Systems of Parkinson's project is to use mathematical modelling and systems analysis tools to build a virtual Parkinson's disease model that will allow the study of lifetime disease progression in a comprehensive computational framework. In the same spirit, we aim to use dynamical analysis of the mathematical model in an attempt to understand the complexity and interactions that underlie the etiopathogenesis of the disease, and to help explain how new therapies (e.g. Deep Brain Stimulation) work.

[4] Ageing populations: the challenges ahead, in The Lancet, October 3, 2009

Review

General

This fifth year has mainly been one of preoccupation with our research programmes in the causes of neurodegeneration. In addition, however, the theoretical part of our research has also flourished, as has our co-funded work on modelling and analysis of cell death. These co-funded projects are jointly run with the IMMT team mentioned earlier and are led by Dimitris Kalamatianos. The IMMT team are the Hamilton Institute component of the National Biophotonic Imaging Platform.

Also within the Hamilton Institute, two other faculty members (Wilhelm Huisinga and Rick Middleton) continue to develop their systems biology research portfolios. Rick in particular, is a partner in the Systems of Parkinson's project. In addition, Hamilton Institute faculty member, Ken Duffy, has just returned from Australia where he continued his collaboration with former E.T.S. Walton Visitor Prof Phil Hodgkin of the Walter and Eliza Institute (www.wehi.edu.au). Also, Barak Perlmutter (computational neuroscience) continues his collaboration with the DBS group, as well as sponsoring our current E.T.S. Walton Visitor. With these and other developments underway, the Hamilton Institute systems biology web site (http://www.systemsbiology.ie/) has expanded and now references many more activities than just those funded by the award reported here. We anticipate that, with a major redesign in spring 2010, the site will further mature to cross-reference other systems biology activities in Ireland.

Within NUIM, the Systems Biology Forum mentioned in previous reports has ended its work. Results of the Forum's work from previous years are: active research collaborations with the Department of Chemistry in systems biology; systems biology teaching modules in the Institute of Immunology, and delivered by our colleague Wilhelm Huisinga; and a systems biology and image processing module to engineering students from Dimitris Kalamatianos and Perrine Paul. Dimitris and Perrine are also collaborating with RCSI colleagues on a systems biology post graduate training module for the National Biophotonic Imaging Platform.

Externally we continue our support for research and training initiatives nationally and as well as working with colleagues in the University of Rostock, Georgia Tech, the École Polytechnique de Montréal, the Case Centre for Complex Systems Biology, at Case Western University, the Department of Bio and Brain Engineering, Korean Advanced Institute of Science and Technology (KAIST). Also, from January 2010, a PhD researcher funded by the RP award, Diego Oyarzún, will take up a Marie Curie Fellowship to work with Madelena Chaves of the systems biology group at Sophia Antipolis (INRIA), France. We expect collaborations to grow from this Fellowship visit.

Visitor Programme

We have maintained our visitor programme through the year with a series of external speakers and collaborators spending time with us. We have already mentioned E.T.S. Walton Visitor Professor Richard Abadi who joined the Institute in the autumn of 2008 to work on mathematical modelling of visual hallucinations, collaborating with our colleague Professor Barak Pearlmutter and the Department of Psychology at NUIM. Hallucinations can be an early stage indicator of neurological and neurodegenerative disorders and are therefore of great interest to the systems biology group. Other visitors are all named separately in the appropriate sections of the report.

Events

Second International Systems Biology Workshop

In July 2008, the Hamilton Institute systems biology group held the second International Workshop on Systems Biology. The event took place over three days, and drew approximately 90 delegates from 12 countries. The structure of the event was a series of keynote and plenary talks from distinguished speakers, with poster sessions, discussion groups and breakout events that enabled the many young researchers at the workshop to meet and interact with more experienced researchers.

Talks covering the areas: (i) modelling spatial and temporal signals, (ii) dynamics in physiology and biology, (iii) and biological oscillations, with the speakers invited according to their contributions to these topics. They included: David Angeli, Pierre de Metz, Frank Doyle, Johan Elf, Mark Girolami, Albert Goldbeter, Peter Hunter, Frank Jülicher, Eda Klipp, Andreas Reichel and Mike White. The event was financed by Science Foundation Ireland, Novo Nordisk, IET and Unilever Ltd. More details are at www.hamilton.ie/SystemsBiology/Workshop2008, with visuals in the Photo Gallery of this report.

Deep Brain Stimulation Workshop

Immediately following the Systems Biology Workshop, the Systems of Parkinson's team held a one-day symposium on mathematical approaches to the analysis of Deep Brain Stimulation. The aim of the meeting was to identify analytical methods that could explain how and why DBS works, and to form an international DBS working group with delegates from Italy, France, Canada, UK and Ireland. The joint working group has recently expanded and transformed into a DBS research consortium seeking funding from the current EU Framework Programme. Rick Middleton and Miriam Garcia will lead this activity locally.

E.T.S Walton Lecture

On the 12th November 2009, Richard Abadi gave his E.T.S. Walton Visitor Lecture as part of the National Science Week at NUIM. His talk entitled *It ain't what you see – it's the way that you see it* described his work on visual hallucinations and their nature.

External Talks and Visits

Members of the group have visited a number of other institutes over the year and a full list of visits is given later in this report. However, as a policy we have reduced the number of outside talks in order to focus upon research delivery and the development of continuity and transition schemes for the close of the RP programme at the end of 2009.

Maynooth Mathematics Challenge

The Maynooth Mathematics Challenge is a three month long competition for second level schools aimed at raising the profile of mathematics among school pupils. The Challenge is currently funded by Science Foundation Ireland by supplementation of PI project grants (including this RP award) in the Hamilton Institute. During the reporting period Oliver Mason coordinated the Challenge with support from other Hamilton Institute staff including Mark Verwoerd. More details of this activity are to be found on the Hamilton Institute website.

Web Resources

Over time our group web master (Diego Oyarzún) has assembled a range of useful systems biology resources on our web site www.systemsbiology.ie. In addition to a full description of the group's activities and publications, there are useful links to other relevant sites and forthcoming events in the field. We also archive reports and general lecture texts, together with past annual reports. To maintain a clear external face for systems biology at the Hamilton Institute, we list all Hamilton Institute staff who have projects in systems biology, or related areas, in the website. Where they are affiliated staff, or staff not directly funded by this grant, their group web site is given alongside their names. The web site will undergo a major redesign in Spring 2010 to reflect the widened interests in systems biology at the Hamilton Institute, and the growth of systems biology in Ireland.

The Systems of Parkinson's project (described later in this report) is documented at www.systemsofparkinsons.org. The site is intended to form a meeting point for work on systems approaches to PD. While the Systems of Parkinson's project has grown since its launch in 2008, the website has been relatively static and awaits a redesign in spring 2010.

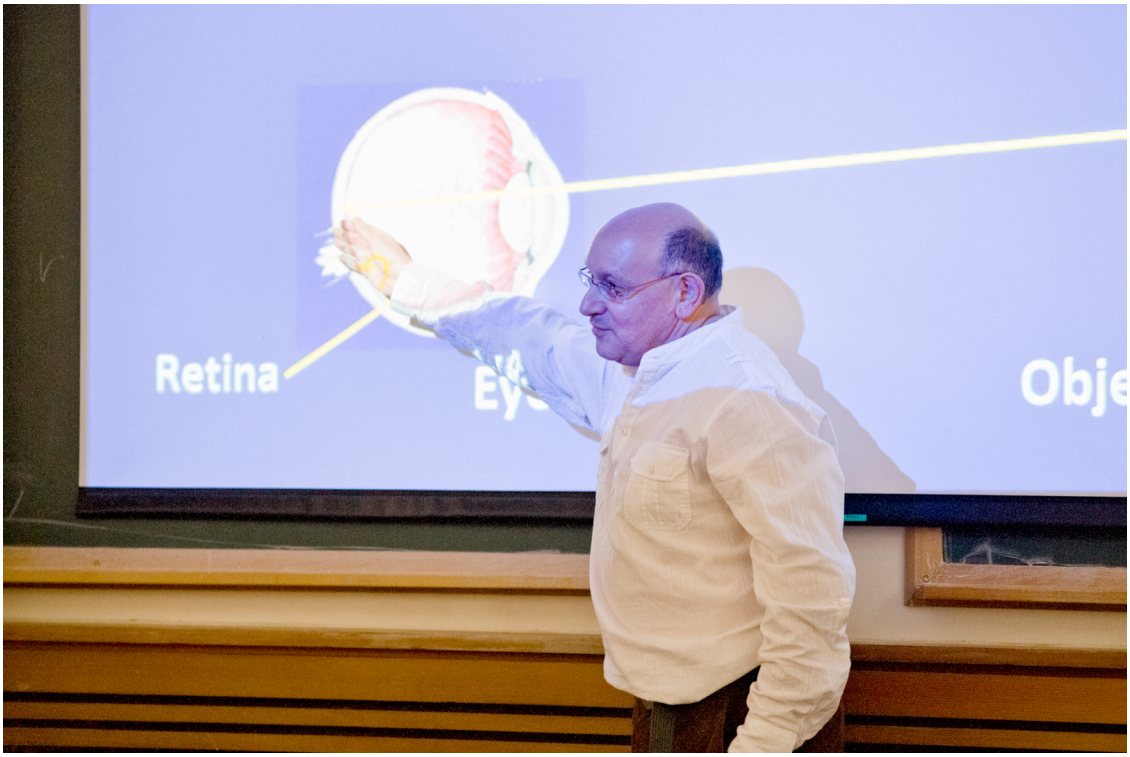
Photo Gallery[5]

Systems Biology at the Hamilton Institute 2008-2009

At the Second International Workshop on Systems Biology (July 2008)

[5] All photographs by Florian Knorn

At the Second International Workshop on Systems Biology (July 2008)



Richard Abadi – E.T.S. Walton Lecture (November 2009)

Project Overviews

As described elsewhere in the report, the research work of the systems biology group funded under this Research Professor Award addresses theoretical and application areas relevant to neurodegeneration under the banners:

(i) Theory of Systems Biology
(ii) The Systems of Parkinson's Disease

For clarity, the areas are described here under separate headings and with the name of the relevant research team members in parenthesis. The work of research visitors and intern students is discussed separately.

Theory of Systems Biology: Mathematical Modelling and Analysis of Biological Systems

The design of mathematical models for biological systems has emerged as a necessary precursor to a systems approach to biology. As evoked in Figure 1, mathematical models, calibrated using system identification techniques applied to biological data, provide the basis for the dynamical and structural analysis of biological processes. In turn, we use the results from modelling and theoretical analysis to help guide our collaborators in the design of laboratory experimentation and measurement strategies.

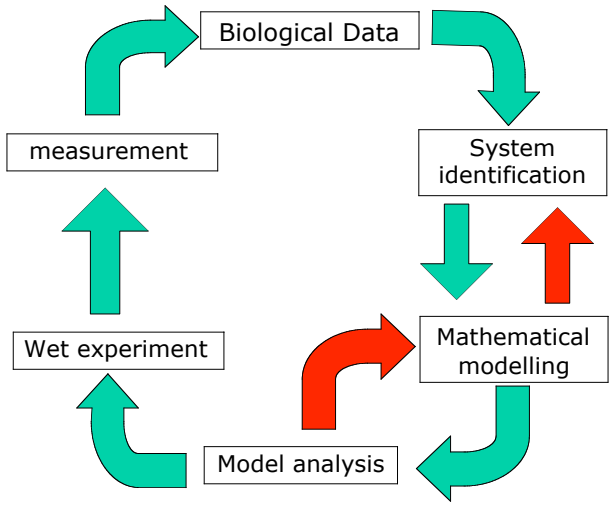


Figure 1. Illustrating the systems approach to biological process investigation

In our programme we have modelling projects that cover brain energy metabolism, alpha-synuclein metabolism and co-funded work on the signalling pathways involved in apoptosis and autophagy.

Mathematical Modelling: Brain Metabolism

Mathematical modelling of brain energy metabolism (Mathieu Cloutier)

A peculiarity of cerebral tissue is that it is composed of two interacting cellular species: neurons and astrocytic cells. The exact role of astrocytes became a subject for debated in

the literature after the traditional view of exclusive glucose oxidation in neurons was challenged. Instead, it was suggested that astrocytic metabolism is coupled to neuronal activation by a mechanism that allows lactate transfer from astrocytes to neurons during high activity periods. We have developed a mathematical model of brain energy metabolism that incorporates the role of astrocytes. A sketch of the model is given in figure 2, showing (a) the main compartments – neuron – astrocyte – capilliaries - extracellular space, and (b) the main biochemical flux paths. The model implementation and documentation has been placed in the CellML project models database[6].

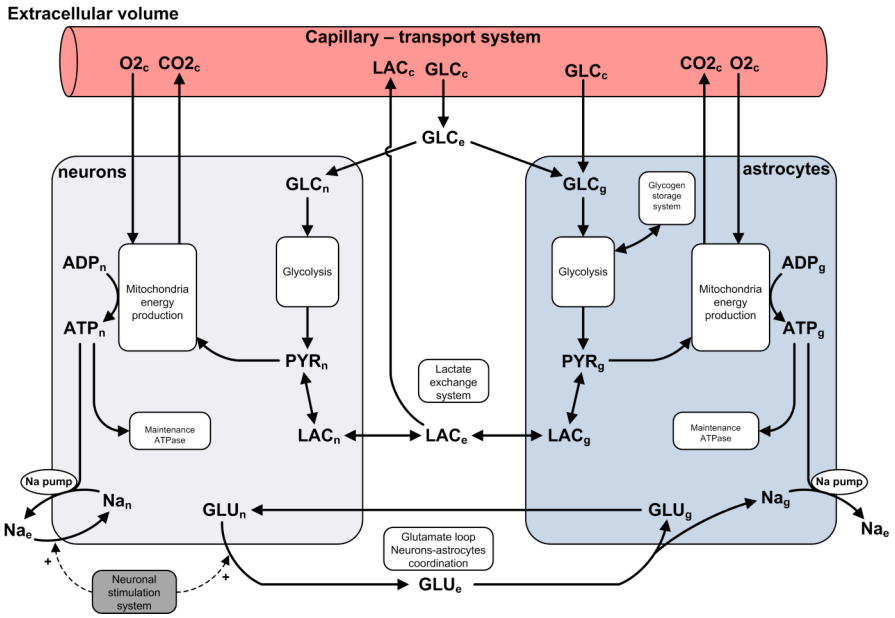


Figure 2. Structure of the brain energy metabolism model

In collaboration with John Lowry at the Department of Chemistry (NUIM), quantitative *in vivo* time profiles of cerebral energy substrates obtained from freely moving animals were used to calibrate the model of figure 2. The results were impressive, and we are now in the process of adding further to the accuracy of the model, through collaboration with the École Polytechnique in Montréal (Canada) where neuron-astrocyte cultures will be used to quantify the energetic response to perturbations using *in vitro* NMR spectroscopy. This will allow us to improve the model further with the aim of a realistic, physiological representation of energy and metabolic 'trafficking' in the cerebral environment. This said, the model is already in use as a tool for systems analysis of energy regulation and its implications in neurodegeneration, as described later in the section on the Systems of Parkinson's project.

<u>Mathematical modelling of α-synuclein metabolism in Parkinson's disease (Mathieu Cloutier, Pierre-Olivier Poliquin)</u>

One of the cellular mechanisms thought to be associated with the idiopathic form of PD, is the accumulation of mis-folded proteins in neurons most affected by the disease. The protein α-synuclein is a major component of these accumulations, and mutations in the corresponding family of genes have been implicated in familial forms of PD. There is also evidence to suggest that the mis-folding of α-synuclein is implicated in idiopathic PD.

Alpha-synuclein protein accumulations can form specific neuronal inclusions called Lewy bodies (LB), although there is controversy as to whether LBs are a neuro-protective mechanism or part of the PD pathology. Thus, considering it's implication in PD processes (See Systems of Parkinson's section), the metabolism of α-synuclein is a strong candidate for mathematical modelling as a potential pathogenic mechanism.

[6] http://models.cellml.org/

A schematic diagram of our current α-synuclein metabolism model is shown in Figure 3. The schema shows the main processes involved, with the 'connecting points' to the energy metabolism model in red as the 'inputs' of ATP. In the model framework, these would be supplied as part of the 'maintenance ATP-phase modules' – shown in both neuronal and astrocytic compartments of Figure 2.

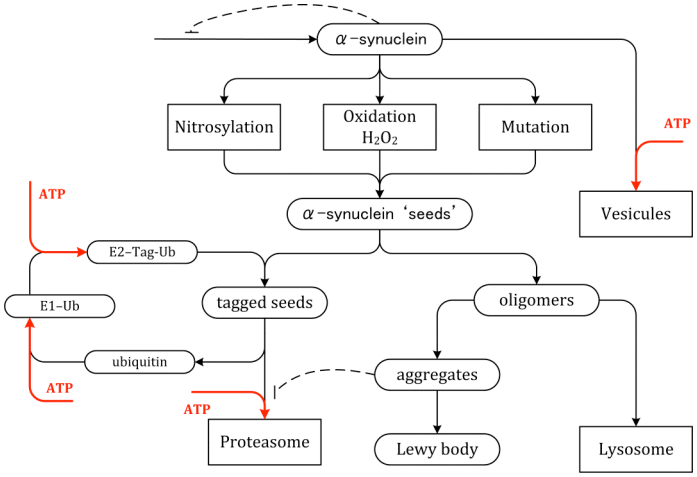


Figure 3. Structure of the α-synuclein metabolism mathematical model, with links to the energy metabolism by the consumption of ATP indicated in red

Model Analysis: Control Principles

Elucidation of the Astrocyte Neuron Lactate Shuttle (Mathieu Cloutier)

Although considerable work and results are found in the literature on brain physiology and brain energy metabolism, there is still no systems framework within which to rationally analyze rival hypotheses concerning the role of astrocytes (i.e. are neurons using lactate as an energy substrate?) in a way that is integrated with quantitative data. Our goal with this work was to put forward a systems view of the energy management in the brain by using dynamic and descriptive metabolic modelling tools and control theory. Our model of the brain energy metabolism incorporates both neuronal and astrocytic compartments. However, while it is well established that neurons are the functional 'units' for neurotransmission, the exact role of astrocytes is still debated in the literature.

As noted previously, the traditional view of exclusive glucose oxidation in neurons has been challenged by the proposition that astrocytic metabolism is coupled to neuronal activation, a mechanism that allows lactate transfer from astrocytes to neurons during high activity periods. In control theory terms this is an example of a feedforward mechanism of the type that is commonly used in technological control systems in order to maintain regulatory effectiveness of a control loop where there are rapid changes in load demand. This corresponds closely to the situation found in neurons, where rapid transient increases in ATP demands are made during neuronal stimulation. This led us to test the astrocyte neuron lactate shuttle (ANLS) as a feedforward structure by comparing the hypothesis to experimental data obtained from direct *in-vivo* electrochemical measurement and *in vitro* measurements of NADH. Our results (as yet unpublished) support the theory that astrocytes offer dynamical feedforward regulation during neuronal excitation.

Control systems structures in energy metabolism (Mathieu Cloutier)

The *in-silico* support for the ANLS theory as a feedforward control structure led to an investigation of control of energy metabolism in general. This research revealed other control structures (feedback, feedforward, minor loop feedback) and mechanisms (proportional, derivative and integral control) in cellular energy metabolism. As evoked in Figure 4 we found that all these control mechanisms and structures are present in cellular energy metabolism at one level or another. This interesting observation has stimulated further research with our collaborators in Montreal into the general implications of a compromised energy metabolism in disease etiology.

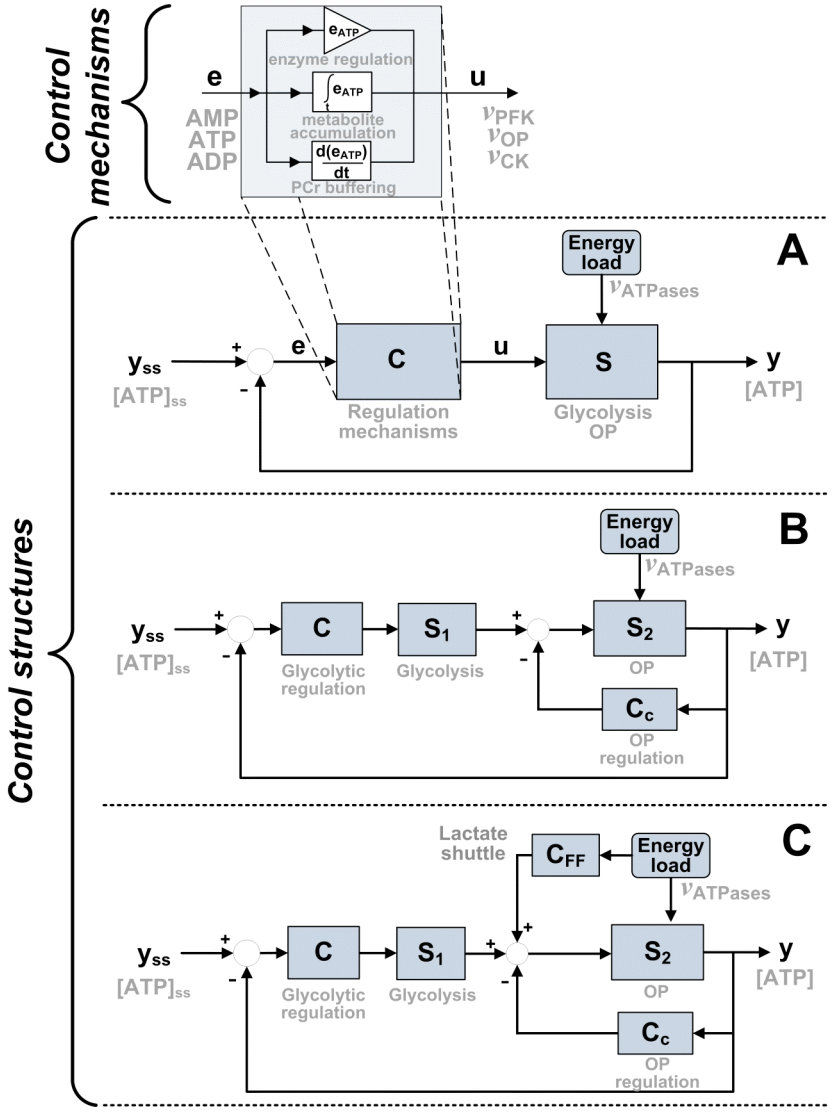


Figure 4. Overview of control mechanisms and structures in energy metabolism

Optimal control principles in metabolic regulation (Diego Oyarzún)

Metabolic regulation improves cellular robustness under changing environmental conditions, and the characterization of general control principles that underpin metabolic dynamics is an important part of systems analysis in biology. In this context, it has long been argued that many biological regulatory mechanisms have evolved so as to optimize cellular adaptation in response to external stimuli. In this project we explore the role of optimisation principles in metabolic networks by using tools from optimal control theory to solve optimization problems associated with metabolic dynamics.

Traditional approaches to metabolic regulation consider enzymatic concentrations as fixed parameters of the individual reactions, thus considering regulation only at a metabolic level (e.g. via biochemical interactions such as allostery or product inhibition). However, enzyme dynamics can also play an important role in metabolic regulation. In the first stage of this project we considered the optimization of networks by time-dependent enzyme concentrations, assuming that enzymes can be immediately available. A more realistic approach must account for the fact that enzyme dynamics operate at a much slower time-scale. We thus consider integrated models composed of a metabolic network with nonlinear dynamics coupled with a linear model for enzyme expression/degradation (Fig. 5). In this setup the enzymatic expression rates (*r*) are regarded as control inputs that drive the network between different metabolic steady states.

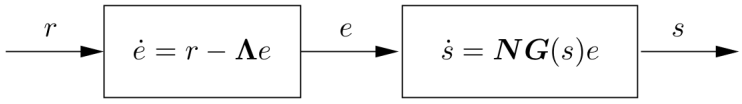


Figure 5. Block diagram of a metabolic network coupled with enzyme synthesis dynamics.

We consider the minimization of the cost/benefit relation between the transition to a target steady state and the genetic "effort"' required by enzyme synthesis. This is quantified by an integral functional that measures the deviation of the metabolites (*s*), enzymes (*e*) and their expression rates with respect to their target values, together with the rate of change of the expression rates. The quadratic form of the cost function can be exploited to obtain suboptimal solutions of the nonlinear optimal control problem (Fig. 6). The problem is recast as an iterative sequence of finite horizon Linear-Quadratic (LQ) problems that can be readily solved with classical theory. The iterative scheme can be shown to converge for a broad range of metabolic networks, provided that the time horizon is sufficiently small.

A special form of this problem arises if we force the metabolites to remain constant in the optimization interval. In this case the formulation is simpler and can be recast as an infinite horizon LQ problem for a linear differential-algebraic dynamical system. The algebraic part arises from the steady state stoichiometric constraint imposed upon the enzyme concentrations and expression rates. An explicit solution to this constrained problem can be obtained by exploiting the structure of the system matrices.

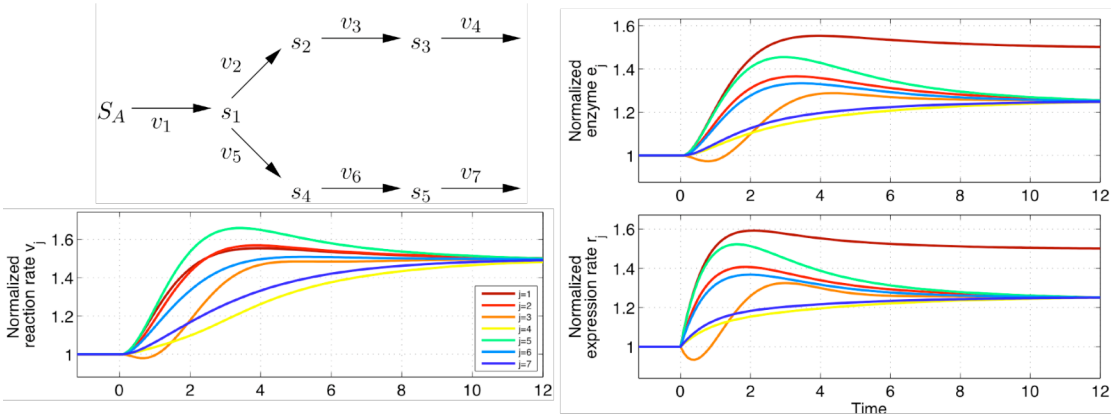


Figure 6. Suboptimal expression rates and species concentrations in a branched network with Michaelis-Menten kinetics. The objective is to increase the fluxes and metabolites by 50%.

Theory of Systems Biology: Dynamics and networks

Theoretical studies

The past decade has witnessed an explosion in the volume of data available for bio-molecular networks. There is a hope that analysis of these networks will add to our understanding of disease, and yield systematic approaches for the analysis of complicated biological networks whose structural properties are only just beginning to emerge. The first major aspect of our contributions in this area focused on the topological and structural properties of static biological network models such as protein-protein interaction networks. Specifically, we investigated the structure of such networks and how it relates to biological properties. We are also interested in analysing mathematical models for biochemical reaction networks, using a combination of analytical and computational approaches. Work of this nature is required if such network models are to be reliably used to gain insights into the evolutionary mechanisms behind proteome development.

The above line of work is mainly concerned with static properties of biological networks. However, as hinted previously, a core issue in the analysis and modelling of biological systems is the interplay between dynamics and network structure. In particular, the role that network structure plays in enhancing the onset of synchronised behaviour is of considerable relevance and importance for a number of biological applications ranging from the study of circadian rhythms to neural communication within the brain and pathologies such as Parkinson's disease and schizophrenia. The second aspect of this theme is largely concerned with the question of synchronisation, and the role of network topology in the emergence of this and other dynamical phenomena of biological relevance.

Analysis of biological interaction networks (Mark Verwoerd and Oliver Mason)
We have built on our earlier survey of biological network analysis and studies of simple duplication-divergence models for the evolution of protein-protein interaction networks. Specifically, we have concentrated on the link between a protein's position within an interaction network and the biological functions of the protein. This has allowed us to develop a formal theoretical framework for the problem of algorithmically predicting protein function based on network topology. This result allows many of the previously suggested methods for protein function prediction to be fitted within a common framework. We have also identified key issues with existing approaches that need to be addressed before real progress can be made, and have conducted an extensive survey and comparison of such methods. This work will appear in a forthcoming book.

Network topology and dynamics (Mark Verwoerd)
This research strand concerns the study of network dynamics. The overall objective of this work is to develop computational methods for the analysis of intercellular communication with a view to applications in Parkinson's disease and Deep Brain Stimulation. In previous work, we have looked at synchronization and phase-locking in the context of the Kuramoto model of weakly coupled nonlinear oscillators. Our main contribution to this area has been the development of new methods for computing bounds on the critical coupling coefficient. This coefficient is an important characteristic of the model and is associated with the onset of completely coherent behaviour. Among the networks we have studied are the complete graph and the complete bipartite graph.

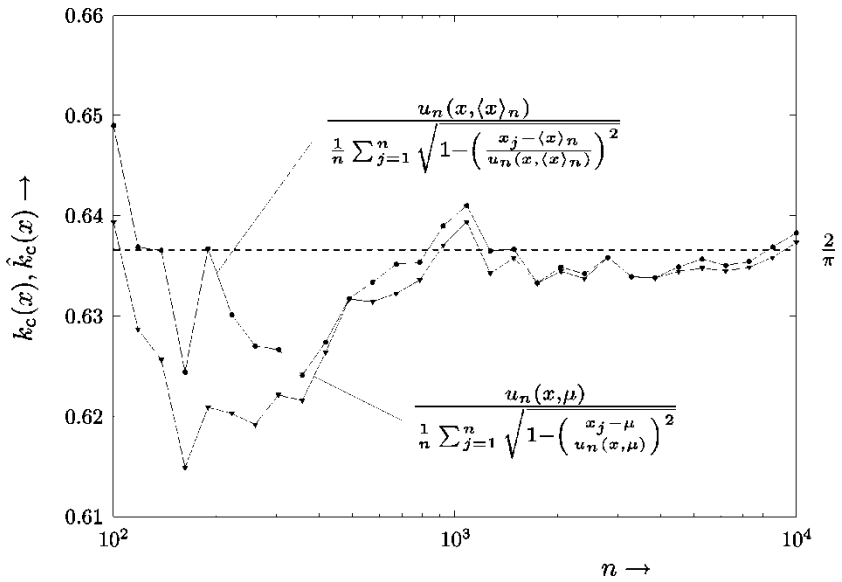


Figure 7. The critical coupling coefficient converges in probability as the number of oscillators tends to infinity

In particular, we have been able to prove a number of results on the behaviour of the critical coupling coefficient in the limit as the number of oscillators tends to infinity (see Figure 7). Specifically, we have shown that the critical coupling strength converges in probability as the number of oscillators tends to infinity.To the best of our knowledge this is the first convergence result for the classical Kuramoto model. Our objective with this work is to contribute to the resolution of a long-standing open problem in the theory of the Kuramoto model, which is concerned with so-called finite-n fluctuations. The current lack of understanding of these fluctuations highlights the gap that exists between the theory for the classical finite-dimensional Kuramoto model and concurrent theories based on an infinite-dimensional versions of the same. We are confident that our results will contribute to a better understanding of the subtleties of the model's asymptotic behaviour and thereby help close the said gap.

Application to dynamics of coupled oscillators in the brain

In recent years there has been a general agreement that oscillatory synchronization constitutes a fundamental mechanism for coordinating communication between spatially distributed local networks in the brain. Abnormal synchronization processes have been associated with several neurological disorders including epilepsy, schizophrenia, dementia, and including disorders concerning the motor systems, such as Parkinson's disease.

Based upon experimental successes, electrical stimulation of the deep brain is now accepted as a therapeutic procedure for motor disorders. Although significant advances have been made in the understanding of this technique, named Deep Brain Stimulation (DBS), fundamental questions about its basic mechanisms still remain open. In the context of this project, we are studying the hypothesis that DBS acts via stimulation-induced modulation of the pathological network activity. In addition, we feel that this could offer the opportunity for some useful theoretical and simulation questions that can be posed in a systems biology framework. In particular, we study the synchronisation hypothesis in two relevant and different cases: DBS for Parkinson's disease and for minimally conscious brains.

A computational model of desynchronisation in the basal ganglia (Mark Verwoerd & Miriam Garcia)

In parallel with the more theoretical work described previously, we have begun developing a simple computational model for desynchronization of neural activity in the basal ganglia of parkinsonian patients. This research is motivated by the idea that Deep Brain Stimulation works by desynchronizing pathologically synchronized neural activity. When a person develops Parkinson's disease, the autonomous oscillations characteristic of the normal brain give way to patterns of low-frequency rhythmic bursting. In addition, there is an increased tendency for neuronal elements in these nuclei to synchronize their activities at frequencies around 20-35Hz. Most therapies, including DBS, appear to act by suppressing pathological patterns of activity. We seek to offer insight into how this might work, and thereby suggest candidate stimulation regimes that may improve the effectiveness and reliability of DBS

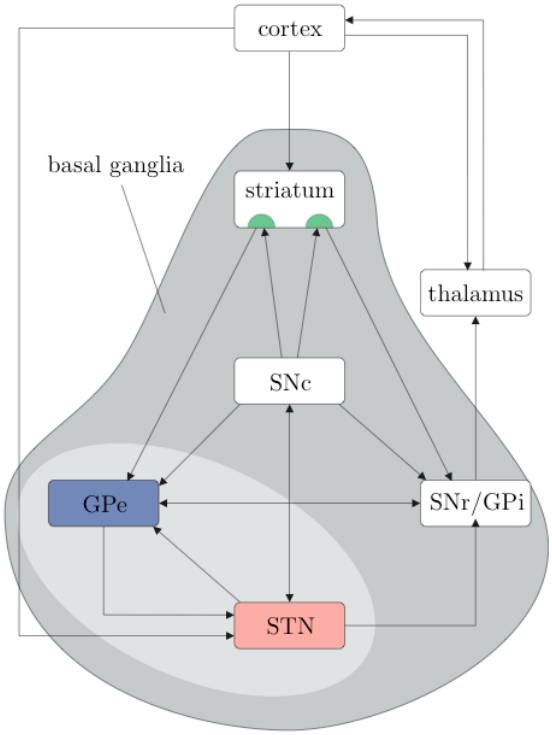


Figure 8. The basal ganglia: illustrating the neural circuits involved in Parkinsonian motor circuit dysfunction

In this, the first strand of our modelling work, we have focused our attention on a subnetwork of the basal ganglia (BG) formed by two key nuclei (see Figure 8): the globus pallidus pars externa (GPe) and the subthalamic nucleus (STN). The STN and the GPe form a reciprocal network of connections which can be described mathematically as a bipartite graph.

Our model describes the dynamics of a system of pulse-coupled neuronal oscillators on a directed graph. Central to the model is the concept of a clock neuron. We define a clock neuron as a pair (i,c_i), where i is a positive integer corresponding to a neuron number and c_i is a clock. The purpose of the clock is to 'keep track' of the spike times of individual neurons. In the absence of other spiking events, the clock value c_i(t) denotes the time difference between the instance when neuron i next generates a spike and the

present time, t. If and when c_i reaches zero, its value is reset to a default value. In case a spiking event occurs before c_i reaches zero, all clock values are adjusted according to a certain update rule, with the clock value being increased if the nature of the event is inhibitory and decreased if it is excitatory. The concept of a clock neuron is motivated by the idea that, at a level of abstraction appropriate for the questions to be addressed in this framework, it is rather more useful to know *when* individual spikes are generated than to know *how* they are generated. All clock neurons in our model are autonomous oscillators. Nominally every neuron generates 1 spike per unit of time. However, when subjected to input from other neurons, a neuron may decrease or increase its firing rate depending on the nature of the input it receives, which can be either inhibitory (GPe to STN), excitatory (STN to GPe), or a combination of both. Along with the concept of a clock neuron, we have introduced the notion of the s-measure. The s-measure is an indication of the level of synchrony for a system of clock neurons on a directed graph.

We have obtained some preliminary results for the case of a system of clock neurons on a complete bipartite graph (which approximates the rather more involved interconnection structure that exists between the GPe and the STN). One of the situations that we considered (see Figure 9) was a scenario in which the neurons of the GPe (blue) were nominally synchronized (low value of the s-measure) and the neurons of the STN (red) were oscillating out of phase (high value of the s-measure). Interestingly, following stimulation of the GPe with a high-frequency pulsatile signal, (the second (shaded) half of the plot in Figure 9), the synchrony of the system shifted from the GPe to the STN. This would suggest that the complete bipartite structure of the network facilitates a form of complementary synchrony between the GPe and the STN. To the best of our knowledge, this is a new finding. There are many questions that remain to be answered as we work toward a more complete understanding of this interesting 'synchrony shift' phenomenon.

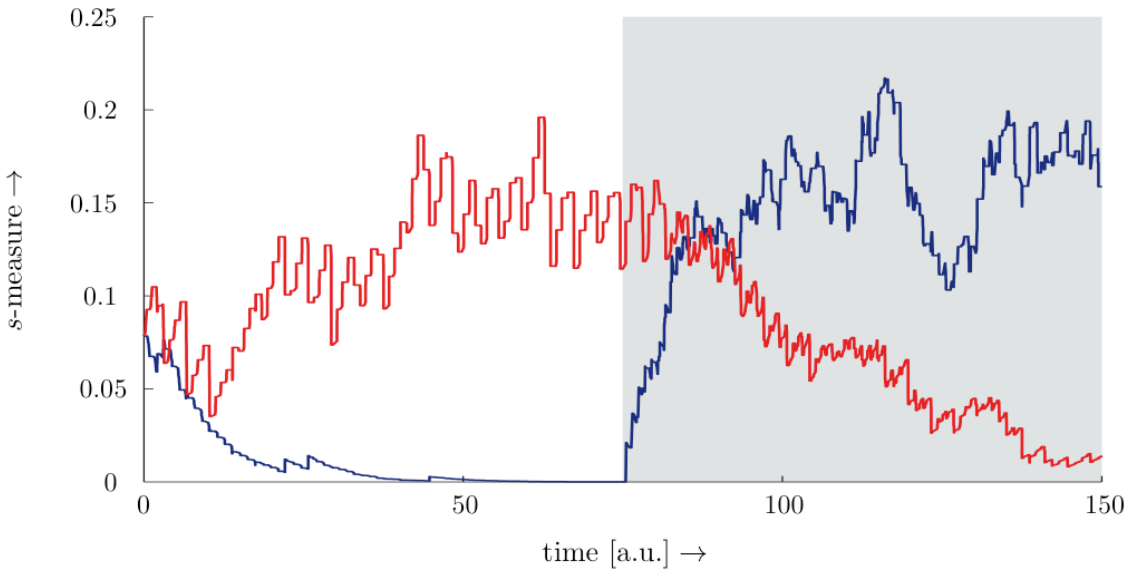


Figure 9. Deep Brain Stimulation induces a synchrony shift in the STN-GPe network. The red s-measure decrease indicates synchrony increasing in the STN, and vice-versa for the blue (Gpe) plot. The grey region of the plot indicates the period of external stimulation.

A computational model of axonal excitation in DBS (Miriam R. Garcia and Mark Verwoerd)

In a second strand of our DBS modelling work, we consider the involvement of axonal stimulation. Specifically, new experimental evidence suggests that DBS acts by stimulating the axons connecting the cortex with the thalamus-basal ganglia circuit. One of

the key points of this new perspective is that the spikes induced by the external stimulation travel in the opposite direction to that which is usual in the brain, i.e., from the axon to the soma.

Earlier work in our research group focussed in understanding how the external stimulus activates the axons and how the spikes propagate along axonal bundles. Since axonal bundles are not homogeneous, the axonal conduction velocities will differ even in the same pathway, thus causing different communication delays in the transmission between cerebral nuclei. Closed-loop control systems can often be made unstable or oscillatory by the introduction of time delays, and we hypothesize that deep brain stimulation (DBS) may work in this way. E.g. DBS ameliorates essential and Parkinsonian tremor by reducing time delays in the feedback paths of the motor control system, thus stabilizing the system. The mechanism we posit for this reduction in feedback delay is a partial blockade of axonal pathways by antidromic activation, with the blockade being less complete for axons with higher propagation velocities.

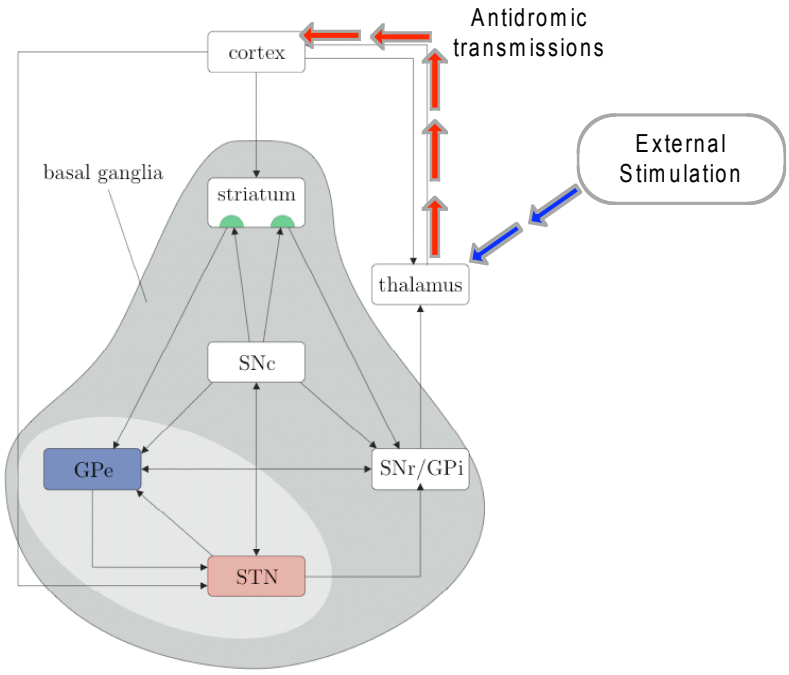


Figure 10. DBS may work by antidromic stimulation the projections from the cortex to the thalamus-basal ganglia circuit.

The plausibility of the hypothesis has been studied by means of a simple biomechanical model of the forearm. The model shows how the postural tremor appears, and even increases, when the communication delays are large. It also shows how the tremor is suppressed by the blockade of the slower axons (and hence of the largest contributors to the delay of the signal), thus replicating the effect observed with DBS. In addition, this partial blockade hypothesis explains aspects related to the target and frequency of stimulation and the tremor response to DBS. It also predicts testable experiments that, if confirmed, may help to improve the treatment considerably.

A computational model of spiking patterns in the subthalmic nucleus (Nicola Mulroony, Miriam R. Garcia, Mark Verwoed)

The subthalamic nucleus (STN) has an important role in motor circuit malfunction in Parkinson's disease. As a result, we are in the process of developing a computational model of the STN neuron that accurately represents its firing properties. In particular, we aim to characterise the intrinsic features that allow the STN neuron to fire in self-sustained trains of bursts. The ability of STN neurons to be able to switch their pattern of behaviour from (i) spontaneous single spiking (pace-making) to (ii) trains of burst spikes, has been reported in the literature. This modelling work is intended to recreate these phenomena in a computational model, which will subsequently be used in our studies of DBS.

We have explored the possible pacemaker currents that allow the STN neuron to fire in the absence of an additional input. The sub-threshold persistent sodium current, I_{NaP}, appeared to be the most likely mechanism for pace-making. Further research has indicated its exact role in maintaining constant membrane oscillations by depolarisation of the membrane as far as the sodium current threshold between each action potential spike, thus enabling the STN neuron's unique spontaneous spiking to occur. The hyperpolarization-activated cation current appears to be implicated in subthreshold pace-making. This current is activated at hyperpolarisation levels stronger than -60mV and is inactivated upon depolarisation, but appears to have a less significant role than I_{NaP}.

Investigation into the bursting potentials of STN neurons moves us away from sodium currents and into the realm of calcium and calcium-activated currents; T type, L type and calcium-activated potassium currents to be more exact. The L type current has the responsibility of driving depolarisation and maintaining spiking, T type currents are essential for each individual spike, while calcium activated potassium currents have the essential role of repolarising the membrane at the inter-burst level.

Figure 11 illustrates the two different activity patterns exhibited by our model: the pace-making and bursting activity. Our next goal is to create a similar computational model of the external globus pallidus (GPe). Once trains of burst spiking have been recorded from both, the aim would be to investigate the synchronized behaviour that exists between them. We hope that these investigations will shed light on the mechanism by which burst spiking might contribute to the resting tremor symptoms in Parkinson's disease.

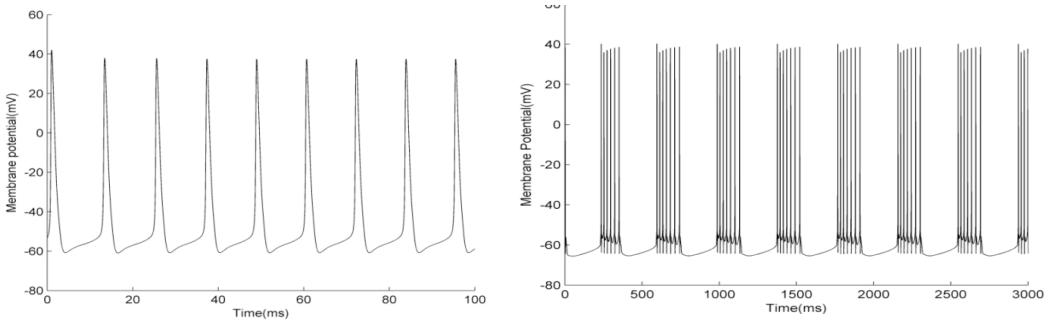


Figure 11. Pace-making activity (left) and bursting behaviour (right), as exhibited by the computational model of the STN

Co-projects with IMMT

Our co-funding of research with IMMT covers research projects into apoptosis and autophagy. These are dynamical systems that maintain cellular homeostasis. Failure of these systems is implicated in many diseases including Parkinson's disease, however their precise function and role remains ill-understood. Our approach to understanding their role is to remodel them as feedback systems in way in that provides insight into how they interact with each other and other cellular functions. Mark Readman co-supervises these PhD projects in collaboration with the IMMT project team and our Visiting Senior Lecturer – Eric Bullinger.

Systems analysis of caspase activation apoptosis models

Apoptosis maintains the natural balance between cell production and cell death. Using ideas from systems and control theory a dynamical model of apoptosis can be remodelled as a feedback system. In this scenario inhibitors are controls modulating active caspases to control cell death. Viewed in this way the machinery of systems and control is used to analyse dynamic models of apoptosis and to gain insight into this important biochemical pathway. Ultimately it is hoped that, using systems and control ideas, it will be possible to predict and control cell death in a therapeutic arena; for example in Parkinson's disease and colorectal cancer. This project is in collaboration with the University of Liege and the Department of Physiology and Medical Physics at RCSI.

Mathematical modelling of autophagy

Autophagy is a catabolic process that degrades long-lived proteins into amino acids via lysosomes for recycling into the cytoplasm and is also responsible for removing bacteria and toxins. Autophagy is essential for maintenance of cellular homeostasis and is implicated in many neurodegenerative diseases. For example, in Parkinson's disease where autophagy failure may allows toxins to accumulate in neurons, thus impairing their function. The initial aim is to obtain a calibrated mathematical model of the molecular dynamics that control autophagy. This combines ideas from systems modelling, identification and biochemistry. This research project is in collaboration with the University of Liege and the Department of Physiology and Medical Physics at RCSI.

The Systems of Parkinsons Disease

As previously emphasized, our aim in the Research Professor programme is to contribute to the understanding of neuro-degenerative diseases, with particular reference to Parkinson's disease. We do this by mathematically modelling the processes that drive the disease and use dynamical systems theory to analyse the factors implicated in disease causation and development. The individual research projects that constitute our steps toward this goal have been described in the previous sections – here we place these individual research contributions in the context of the disease.

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Background

Parkinson's disease is an example of a multi-factorial condition that involves numerous interacting physiological and intracellular systems. Specifically, although the causes of Parkinson's disease are unknown, evidence suggests that it is caused by a combination of various interacting factors in different cellular and metabolic sub-systems. These biological interactions combine to produce the observed symptoms of the disease - in particular, the death of SN neurons, and the disturbed motor circuits of the basal ganglia, as explained in the previous section on oscillations in the brain.

The multi-factorial aspect of Parkinson's disease is typical of the many important systemic diseases that involve highly complex interdependencies between biological processes. Such complex diseases will require a systems approach that fully exploits topics in mathematics, systems dynamics and control theory, as well as innovations in measurement. We believe that it is only by the integrated application of such topics that we can hope to understand the complex interactions and dynamics that drive systemic disease.

In the case of Parkinson's disease we classify some of the factors that may be involved as shown in Figure 12.

The figure shows just some of the wide range of factors that are potentially implicated in Parkinson's disease. They are classified according to:

A. Inherited contributions
B. Life course contributions
C. Cellular and physiological mechanisms implicated in the disease

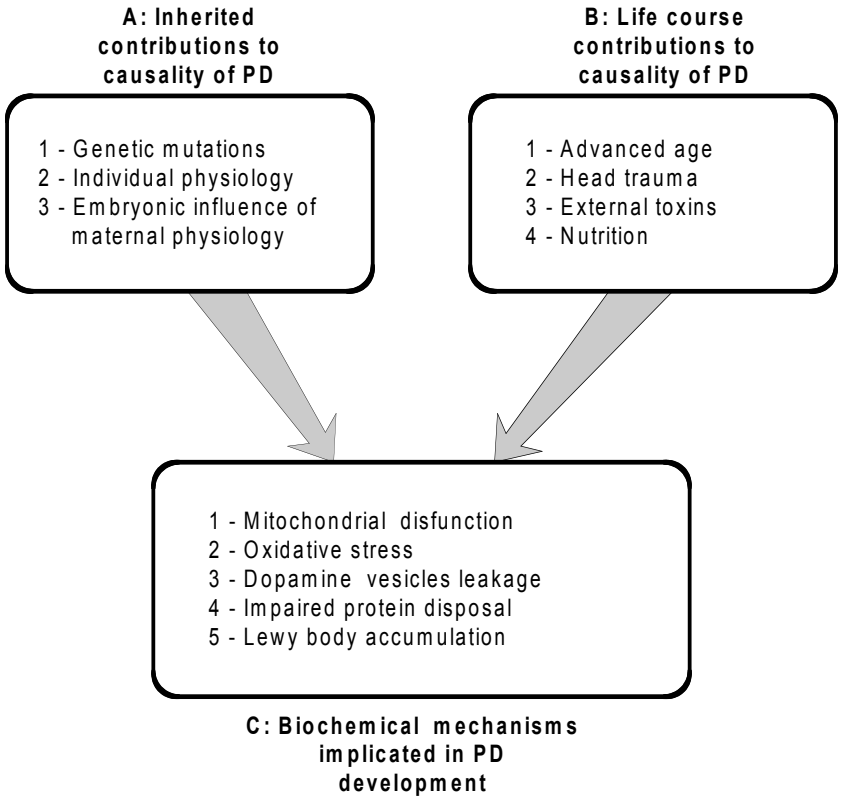

Figure 12. The multi-factorial nature of Parkinson's disease

Relating this classification to terminology used in disease research, A and B are concerned with the trigger mechanisms (eitology) for disease. The items in C are related to possible pathogenic factors that are thought to drive the progression of Parkinson's disease, and leading to the disease trademarks:

- The loss of dopaminergic neurons in the substantia nigra
- The accumulation of alpha-synuclein in neurons (Lewy Bodies)

The first of these trademarks causes failure of the motor circuits and the key visible symptoms of the disease. A dementia associated with Lewy Body deposits frequently follows the onset of motor symptoms. The results of motor circuit failure are alleviated by drugs which attempt to compensate for loss of dopaminergic neurons, or by electrical stimulation of the deep brain (Deep Brain Stimulation) which (it is thought) influences the synchrony of transmissions in the basal ganglia.

This is a simplified explanation of a highly complex situation. For example, only a small percentage of instances of PD are familial (e.g. genetic), but genomic research has indicated that mutations in a number of genes are associated with the disease. Likewise, PD sufferers may not develop Lewy Bodies, and instances exist of alpha-synuclein accumulation without failure of the motor circuits. There is also a staging theory of PD that suggests that alpha-synuclein agglomerations spread through the brain according to a predictable pattern.

Strategy

By taking a systems approach to Parkinson's disease we have set ourselves an ambitious target that will be difficult for one group with limited resources to achieve. We have therefore decided upon a strategy of community research whereby we share the outputs of our research via the web site www.systemsofparkinsons.org. In this way we hope to

build interest and activity in systems and control methods applied to Parkinson's disease. In this spirit, and where appropriate, the code for our models and our theoretical analyses will be made available for download and use by other groups. For example, the implementation of the brain energy metabolism model (described earlier) is already available via the CellML project (http://models.cellml.org/).

Modelling and Analysis of Parkinson's Disease

The energy systems framework

Initially it was not easy to see what form a systems approach to the causes of neurodegeneration should take. After long deliberation and some false starts, we eventually decided that it would be logical to construct a mathematical framework based upon the energetic processes that fuel cerebral tissue and maintain cellular activity. This energy systems approach was the motivation for the mathematical modelling of brain energy metabolism described earlier in the report.

Energy is the thing that drives all biological function, so a mathematical model of the brain energy metabolism forms a computational modelling framework to which we can attach mathematical models of any cellular process that might be implicated in the disease. Although the energy metabolism model framework was conceived initially for Parkinson's disease, we believe that by attaching different sub-models to the framework, it can be used for a systems approach to other neurodegenerative conditions – in particular Alzheimer's disease.

The energy systems modelling framework is illustrated in Figure 13, which shows some of the cellular and physiological processes implicated in neurodegeneration. These processes are 'attached' to the brain energy metabolism framework via the energy flux (ATP) that drives cellular and physiological functions.

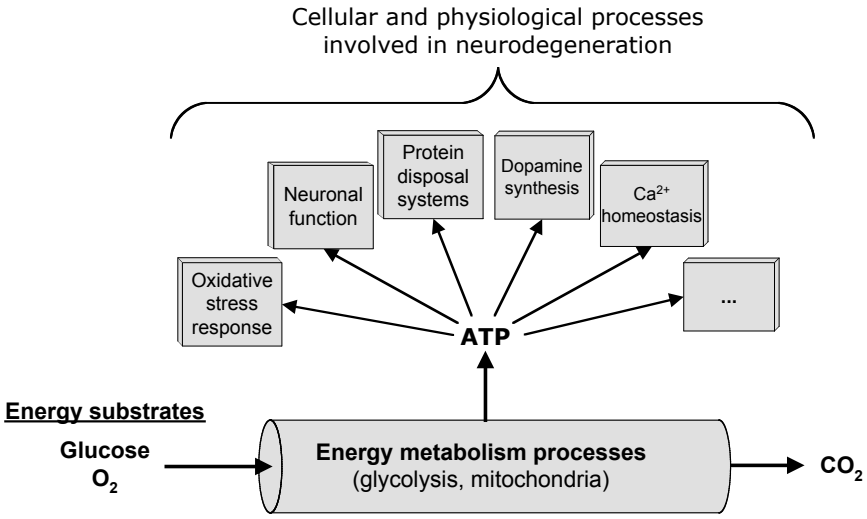

Figure 13. Showing the brain energy metabolism as a modelling framework, to which cellular and physiological processes, as they relate to a particular neurodegenerative disease, can be added

Energy and neurodegeneration

In additional to its organisational role of providing a computational and analytical framework, there was also a scientific reason for considering the brain energy metabolism as the basis for a systems approach to neurodegenerative disease. Specifically, we believe that flaws in the brain energy metabolism associated with advancing age or brain trauma may be a contributory factor to the degeneration of neuronal function.

As remarked earlier, there is usually no one cause for Parkinson's disease. On the contrary, PD seems to be multi-factorial, involving a complex combination of interactions between various possible pathogenic mechanisms. However there should be some initial phenomena that triggers the various factors involved in the disease progression – and advanced age is the only common factor found in all sufferers of idiopathic Parkinson's disease. With advanced age the efficiency in the energy metabolism is known to decline significantly, (the figure of a 50% decline at the age of 60 has been given). In view of this, and the linkage between PD and age, we suggest that a compromised energy metabolism could be an etiological trigger deriving from such life-course processes as shown in figure 12.

This claim is made more plausible by (as yet unpublished) results in which *in-silico* tests suggesting that transient insults to the brain occur during stimulation of a compromised energy metabolism. Neurons that have the largest energy requirements are preferentially damaged in PD; that is neurons with unmyelinated axons, with exceptionally long axons, or exceptionally large numbers of synapses. Neurons are among the hardest working cells in the body and the most sensitive to defects in the energy metabolism. Interestingly, our estimates from published calculations of the energy budgets in the brain suggest that substantia nigral (SN) neurons have energy budgets that are hugely greater than other neurons –two orders of magnitude greater. Coincidentally, it is neurons in parts of the SN that are the most susceptible to Parkinson's disease damage.

Modelling and diseases of age

There is also a powerful common sense reason for building a mathematical model of neurodegenerative diseases (like PD). As noted earlier, AD and PD are diseases of the elderly. Moreover, they are (as far as we know) unique to human brains, and are only manifested in the elderly. Thus, *in-vivo* investigation of the causes of neurodegeneration in human subjects is practically impossible. However, with a computational (*in-silico*) modelling framework we can rapidly and systematically perform as many multi-factorial simulations as might be required to investigate potential etiopathogenic mechanisms. Moreover, these *in-silico* tests are precisely repeatable – thus overcoming the variability that occurs in practical experiments by different investigators and in different laboratories.

Toward a virtual Parkinson's disease model

Following from the above remarks about diseases of age, we believe that there is a urgent need to create computer-based simulations of disease systems that can be used to either replace or complement animal models and cellular homologues. This is particularly important in PD, since existing animal models only reproduce certain symptoms. They are therefore of use in research into therapies which alleviate symptoms, but of less value in understanding causal mechanisms. Likewise, we note that investigations of cellular pathways in animal neuronal milieus do not necessarily transfer to the human case.

Motivated by this, we note that the modelling structure of Figure 13 is not only a structure in which to investigate etiopathogenic factors. By the gradual addition of the cellular and physiological mechanisms that are implicated in PD, it can also form the master structure for an *in-silico* approach to PD modelling. In this context, the successfully connection (described earlier) of an alpha-synuclein metabolism model to the brain energy metabolism model demonstrates the principle that the energy metabolism modelling framework has the potential for extension into a comprehensive *in-silico* model of PD - a virtual PD model in fact.

A virtual PD model would provide a quantitative means with which to conduct research rapidly and in a repeatable form ready for immediate dissemination and challenge in other laboratories. *In-silico* models have limitations. However, there is flexibility with *in-silico* models, and since their limitations are associated with known approximations used in the model, they are extendable and can be improved as better modelling information becomes available.

Analysis of Therapeutic Mechanisms

Deep Brain Stimulation

We are interested in understanding the electrical therapy known as Deep Brain Stimulation (DBS). As described elsewhere in the report, DBS is a treatment, whereby probes are placed in the subthalmic nucleus (STN) and repetitive low intensity electrical pulses are applied. In a favourable percentage of cases this procedure has been successful in reducing Parkinsonian tremors and other manifestations of the disease. Also, unlike chemical or surgical lesioning of the brain, DBS is reversible. However, the mechanisms by which DBS works are unknown and it this aspect of the technique that we are researching.

For some years, and as discussed previously in this report, we have been studying the mathematical properties of groups of oscillators. More recently we have added a more applied element to this theoretical research. Specifically, we are examining how ideas from synchronisation and desynchronisation of oscillator groups might be used to understand the mechanisms that make DBS an effective therapy. In a parallel research line, we are examining the possibility that a selective blockade of axonal transmission may be associated with the success of DBS. The hope is that a plausible theoretical model of the desynchronisation/synchronisation process, together with the axonal transmission ideas, will be of assistance in understanding DBS and how this important therapeutic instrument may be improved.

The Systems Biology Group

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Visiting Senior Lecturer Hamilton Institute

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Eric Bullinger studied electrical engineering at ETH Zurich. He graduated in 1995, obtaining the ETH medal. He then took up a position as a research and teaching assistant at the Automatic Control Laboratory, ETH Zurich, later moving to Stuttgart University. He was a member of the Systems Biology Group at the Hamilton Institute from 2005 to 2007, before joining the staff of Strathclyde University to help build their systems biology activities. He is currently Francqui Assistant Professor at Institut Montefiore, Université de Liège. His major research interests are the development of mathematical models of signal transduction networks, in particular the development of systems identification and sensitivity analysis methods. His current interest is the development of system theoretical tools for modelling and analysis of biological system models as well as the application of modelling to specific biological questions.

Mathieu Cloutier

Postdoctoral Researcher

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Mathieu Cloutier studied chemical engineering at the Ecole Polytechnique, Montreal. He graduated in 2002, and then his postgraduate studies in the laboratory of Mario Jolicoeur at the Polytechnique. In January 2008, he joined the Systems Biology Group at the Hamilton Institute. His research interests are the development of mathematical models and analysis of the brain energy metabolism as part of the Systems of Parkinson's Disease project. With the end of the Research Professor programme, Mathieu recently returned to Montreal, but continues to work on Parkinson's disease through his collaboration with Ecole Polytechnique and the Hamilton Institute.

Miriam Garcia

SFI Postdoctoral Researcher

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Miriam obtained her M.Sc. degree in chemistry (2001) and her Ph.D. degree in applied mathematics (2008) from the University of Vigo, Spain. All the research work before and during her Ph.D. was developed in the Process Engineering Group belonging to the Spanish Council for Scientific Research (IIM-CSIC) inside the framework of three national and one European project. She joined the Hamilton Institute in March 2008, where she works upon coupled oscillators, synchronisation and desynchronisation. Her applications focus is the mechanisms that underlie Deep Brain Simulation as part of the Systems of Parkinson's project.

Mark Readman

Research Fellow

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Mark Readman studied Applied Sciences at the University of Sussex, UK obtaining a B.Sc. in Automatic Control. He obtained his M.Sc. in Control Systems Theory and Practice from Manchester University UK (UMIST). For his Ph.D. in Electrical Engineering he studied at McGill University, Montreal, Canada; a book based on his Ph.D. was published by CRC press. At the Hamilton Institute he works with the IMMT team of Dr Kalamatianos assisting in the co-funded projects on modelling of apoptosis and autophagy.

Mark Verwoerd

SFI Postdoctoral Researcher

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Mark Verwoerd obtained his M.Sc. (honours) and Ph.D. degree from the department of Electrical Engineering, University of Twente, the Netherlands, in 2000 and 2005 respectively. His Ph.D. thesis is a critical study into the relative merits of a class of learning control algorithms. He joined the Systems Biology Group in March 2005. Currently, his main interest is in the dynamics of (biological) networks (e.g. neural networks, gene regulatory networks, protein interaction networks, etc.), particularly the interaction between network structure (topology) and function. With the end of the Research Professor programme Mark has recently taken up an industrial position in the Netherlands.

Research Students

Diego Oyarzun
Research Assistant

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Diego joined the Hamilton Institute in 2007 as a Ph.D. student, after graduating in 2006 as Civil Electronic Engineer with B.Sc. and M.Sc. in Electronic Engineering from Universidad Técnica Federico Santa María in Valparaíso, Chile. Diego is researching concepts of optimality in metabolic systems and corresponding links to control theoretic results. During the year he was presented with the awards, 'Roberto Ovalle Aguirre' by the Chilean Institute of Engineers and 'Aida Valenzeula' by University Federico Santa María, Valparaiso, Chile. Diego was recently awarded a Marie Curie Fellowship, and from the beginning of 2010 he will work with systems biology researchers in France – collaborating with the Hamilton Institute.

Visiting Research Students

Rachael Dunne
Intern Student

rachael.dunne@nuim.ie

Rachael was an intern research student working on the modelling, control and stability of apoptotic pathways. She was under the supervision of Mark Readman and Peter Wellstead as a part of a co-funded IMMT project. Rachael is a graduate of the Mathematics Department, NUIM

Helen O'Gorman
Intern Student

Helen.ogorman@nuim.ie

Helen was a visiting student at the Hamilton Institute from June 2008 to September 2008. Under the supervision of Peter Wellstead she worked on the social and economic arguments for national investment in neurodegeneration research. Helen is a graduate of the Mathematics Department of NUIM.

Pierre-Olivier Poliquin
Intern Student

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Pierre was a visiting research student at the Hamilton Institute from June 2008 to September 2008. Under the supervision of Mathieu Cloutier he worked on the mathematical modelling of alpha-synuclein metabolism. Pierre is a graduate of the Ecole Polytechnique, Montreal, Canada, where he has returned to complete his masters degree. He is currently working with our collaborator Mario Jolicouer on the brain metabolism model to design and implement biological experiments that will further validate and calibrate the model.

Maria Secrier
Intern Student

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Maria was a visiting student in the Hamilton Institute between June and August 2009. Under the supervision of Dimitris Kalamatianos she worked on a co-fund project for the modelling of neuronal migration. This important and yet largely unknown area has potentially deep implications for the etiology of neurological conditions.

Nicola Mulrooney
Intern Student

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Nicola was an intern student and about to enter her fourth year of neuroscience at University College Dublin. During her intern period she worked with Mark Verwoerd and Miriam Garcia on the modelling of neurons in one of the usual targets for Deep Brain Stimulation - the subthalamic nucleus.

Visits by Team Members

In addition to regular exchanges with established research collaborators (listed elsewhere), members of the Systems Biology Group paid visits to the following Institutes and laboratories:

Bio-Systems Signal Processing Laboratory, City University of London, UK, November 2008, (visiting Professorship duties)

Freiburg Initiative for Systems Biology (FRISYS), University of Freiburg, Germany, October 2008 (Scientific Advisory Board Meeting)

Royal College of Medicine, London, UK, May 2009, (SPRING, Parkinson's Disease Research Meeting)

Luton and Area Parkinson's Disease Group, Luton, UK, July 2009, (Outreach talk to PD group)

University of Aas, and University Hospital of Oslo, Norway, September 2009, (Research visit and short course)

Oxford University, Oxford, UK, October 2009, (seminar and research discussions)

Université de Liège, Belgium, December 2009, (seminar and research discussions)

External Talks by Team Members

The following talks were given by group members as part of visits to other Institutes and Universities:

Brain energy metabolism (Invited talk). Summer School on Systems Biology for Medical Applications, Tenerife, October 2008

A systems approach to Parkinson's disease, (Invited talk), Scottish Biosystems modelling network, Dundee, February 2009

Dynamic optimization of metabolic pathways (Invited talk), 3rd Conference of Young Chilean Scientists, Göttingen, Germany, February 2009

Optimal metabolic pathway activation (Contributed talk) at the 17th IFAC World Congress, Seoul, Korea, October 2008

Energy systems in Parkinson's disease (seminar), Oxford University, 26th October 2009

An energy systems approach to Parkinson's disease (seminar) Université de Liège, 2nd December 2009

Visiting Scientists and Seminars

As part of the overall Hamilton Institute activity, we have an active seminar programme and visitor programme in systems biology. Hamilton Institute seminars are deliberately multidisciplinary and a full listing is given on the web site www.hamilton.ie. Internal seminars which are similarly listed at www.systemsbiology.ie .

Spatial mapping of the Earth beneath the ocean - systems of a different kind Peter Simpkin, IKB Technology. September 24th, 2008

A systems approach to the modelling of visual hallucinations Richard Abadi, Manchester University, E.T.S. Walton Visitor, November 12th, 2008

Exploring Multistability in Biochemical Networks Antonio A. Alonso, GEPRO, IIM-CSIC, Vigo, Spain. December 10th, 2008

Modelling the synapse: from numbers to networks Eduardo Mendoza, Ludwig-Maximilian Universität, München. January 14th, 2009

Extracellular Potassium Dynamics and Epileptogenesis Maxim Bazhenov, University of California, Riverside CA. USA. January 21st, 2009

Kinetic Modelling of Metabolism Professor David Fell, Oxford Brookes University, Oxford, UK. January 28th, 2009

Analysis of dynamical systems with steep sigmoidal response functions Erik Plathe, Norwegian Centre for Integrative Genomics, Aas, Norway, March 4th, 2009

Model-Based Functional Brain Imaging and the Neurobiological Basis of Human Reinforcement-Learning John P. O'Doherty, Trinity College Institute of Neuroscience, Trinity College Dublin, March 10th, 2009

Value of Pharmacokinetic and Pharmacodynamic Modelling for Tumour Patients Charlotte Kloft, Martin-Luther-Universität Halle-Wittenberg. Germany, March 12th, 2009

Multivariate Time Series Analysis in Neurology Björn Schelter, Freiburg Center for Data Analysis and Modelling. May 6th, 2009

How to understand the cell by breaking it - computational inference of cellular networks from gene perturbation screens Florian Markowetz, Cancer Research UK, Cambridge Research Institute. June 10th, 2009

A systems biology approach to apoptosis signalling Dr. Eric Bullinger, Institut Montefiore, Université de Liège, Belgium. June 17th, 2009

Can't move to the rhythm? Inappropriate neuronal synchrony and oscillations in Parkinson's disease Peter Magill, MRC Anatomical Neuropharmacology Unit, University of Oxford. July 15th, 2009

Partnerships

Interaction with other research centres is important and we continue to build a national and international network of partners and collaborators with whom we can exchange ideas, staff and students. The full list of centres with whom we interacted over the reporting period is given below:

Université de Liège, Belgium

Professor Eric Bullinger

- Modelling and analysis of apoptosis and autophagy

Ecole Polytechnique de Montreal, Canada

Professor Mario Jolicoeur

- The Systems of Parkinson's

Middlesex University, UK

Professor Richard Bayford

- The Systems of Parkinson's

Systems Biology and Bioinformatics, University of Rostock, **Germany**

Professor Olaf Wolkenhauer, Chair of Systems Biology and Bioinformatics

- Systems Theoretic Issues in Biology
- The Systems of Parkinson's

Case Complex Systems Biology Center, Case Western Reserve University, Cleveland, Ohio, USA

Professor Sree Sreenath, Chair in Systems Biology

- Systems Theoretic Issues in Biology

Department of Chemistry NUIM, Ireland

Professor John Lowry

- *In-vivo* electro-chemical sensing for systems biology

University of Stuttgart, Germany

Institute for Systems Theory and Automatic Control

Professor Frank Allgöwer, Thomas Eißing, Dr Rolf Findeisen, Stefan Waldherr:

- Modelling and analysis of Tumour Necrosis Factor signalling and apoptosis

Institute of Cell Biology and Immunology

Professor Dr. Peter Scheurich, Monica Schliemann:

- Modelling TNF-induced pro- and anti-apoptotic pathways and experimental validation of the models

Professor Dr. Klaus Pfizenmaier

- High-throughput image analysis for the classification of sub-cellular localization patterns of fluorescently labelled proteins

Politecnico di Milano, Italy

Professor Dr. Sergio Bittanti and Marcello Farina

- System Identification in Biological Applications

Max Planck Institute of Biochemistry, Martinsried, Germany

Professor Dr. D. Oesterhelt and Stefan Streif

- Sensitivity analysis of biochemical reaction networks

Department of Applied Mathematics, University of Waterloo

Professor Brian Ingalls

- Optimal control concepts in metabolism

Publications

This lists publications produced in the reporting year. For a full list of reports and past publications, please visit our website www.systemsbiology.ie. A further sources of past research records and downloadable papers are the personal websites of the team members.

Chapters in Books

Fey, R. Findeisen and **E. Bullinger**, Identification of biochemical reaction networks using a parameter-free coordinate system. In P. A. Iglesias and B. Ingalls, editors, *Control-Theoretic Approaches in Systems Biology*, pages 293–310. MIT Press, 2009

H. Huber, **E. Bullinger** and M. Rehm, Systems biology approaches to the study of apoptosis. In X.-M. Yin and Z. Dong, editors, *Essentials of Apoptosis*, pages 283–297. Humana Press, second edition, 2009

Mason, O., and **Verwoerd, M.H.A.**, Inference of Protein Function from the Structure of Interaction Networks, In *Structural Analysis of Complex Networks: Theory and Applications*. (Editor: Matthias Dehmer), Birkhauser, New York, 2010

Wellstead, P, Sreenath, S, Cho, K-H and Wolkenhauer, O. Systems and Control Theory for Medical Systems Biology, *Handbook of Research on Systems Biology Applications in Medicine*, (Editor: Andriani Daskalaki), Medical Information Science, New York, 2009

Published papers

M. Cloutier and **P**. **Wellstead,** The control systems structures of energy metabolism, Journal of the Royal Society Interface, 2009

doi: 10.1098/rsif.2009.0371

M. **Cloutier**, F.B. Bolger, J.P. Lowry and **P**. **Wellstead,** An integrative dynamic model of brain energy metabolism using in-vivo neurochemical measurements. Journal of Computational Neuroscience: Volume 27, Issue 3 (2009), Page 391**,** 2009

doi 10.1007/s10827-009-0152-8

D.A. Oyarzún, B. P. Ingalls, R.H. Middleton and D. Kalamatianos, Sequential activation of metabolic pathways: a dynamic optimization approach. *Bulletin of Mathematical Biology*, 71, 8, 1851-1872, 2009

doi: 10.1007/s11538-009-9427-5

M. Verwoerd and O. Mason, On Computing the Critical Coupling Coefficient for the Kuramoto Model on a Complete Bipartite Graph, SIAM Journal of Applied Dynamical Systems, 8, 1, 417-453, 2009

M. Verwoerd and O. Mason, Observations on the stability properties of cooperative systems, Systems and Control Letters, 58, 6, 416-467, 2009

P. Wellstead, On the industrialisation of biology, AI & Society, 2009
doi: 10.1007/s00146-009-0232-3

P. Wellstead, Systems Biology and the Spirit of Tustin, IEEE Control Systems Magazine, February, 2010, (in press)

Conference proceedings/posters

Fey, R. Findeisen and **E. Bullinger**, Parameter estimation in kinetic reaction models using nonlinear observers facilitated by model extensions. In *Proceedings of the 17th IFAC World Congress*, Seoul, Korea, pages 313–318, 2008

D. A. Oyarzún, B. Ingalls, R. Middleton, and D. Kalamatianos, Optimal metabolic pathway activation. In *Proceedings of the 17th IFAC World Congress*, Seoul, Korea, pages 12587-12592, Jul. 2008

M. Cloutier, P.O. Poliquin, M. Jolicoeur and **P. Wellstead**. An integrative modelling approach for the implications of energy metabolism in neurodegeneration. In *Foundations of Systems Biology in Engineering (FOSBE*), Denver, USA, Aug. 2009

M.R. García, C. Vilas, E. Balsa-Canto and A.A. Alonso, Analytic Real Time Optimisation for thermal processes. In *Proceedings of the European Control Conference* 2009 - Budapest, Hungary, pages 2039-2044, Aug. 2009

B.-F. Krippendorff, **D.A. Oyarzún** and W. Huisinga, Ligand accumulation counteracts therapeutic inhibition of receptor systems. In *3rd Foundations of Systems Biology & Engineering (FOSBE)*, Denver, USA, Aug. 2009

M. Peters, **D.A. Oyarzún**, E. Silva and M. Salgado, Analytic characterization of a stabilizing feedback for LTI plants. In *10th European Control Conference*, Budapest, Hungary, Aug. 2009

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