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Science Foundation Ireland Research Professor Award 03/RP1/I382

Annual Report 2007 – 2008

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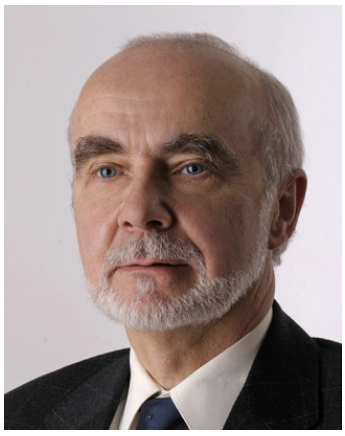
Preface

This is the fourth report for the SFI Research Professorship award 03/RP1/I382. The report covers the period July 2007 to June 2008 and is a supplement to the formal progress and financial report submitted to Science Foundation Ireland under the terms of the Research Professor Award.

For more information on our work, and electronic copies of past reports, please visit www.systemsbiology.ie. 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 the recently launched website – www.systemsofparkinsons.org. This website is a community forum for systems scientists who are applying a systems approach to Parkinson's Disease. A systems approach to disease is the applications theme of our work and the Systems of Parkinson's project is our main project in this area.



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Introduction

Background

The first years of the Research Professor project were driven by two objectives: (a) to establish a systems biology awareness in the country, and (b) to build a systems biology research group of critical mass in the Hamilton Institute. With these objectives completed, and from year three onward, the Hamilton Institute systems biology team has focussed its efforts upon its own research activities and collaborations. This fourth year report describes our progress in, and consolidation of, this process.

A specific collaborative outcome was the success of our application for HEA funding as a partner in the National Biophotonic Imaging Platform (NBIP). Specifically, the Hamilton Institute is now funded to run the Image to Mathematical Modelling Transition (IMMT) facility of the NBIP. Together with our partners at the Royal College of Surgeons in Ireland and University College Cork, the Hamilton Institute IMMT team are working on methods to extract mathematical models directly from bio-images – in still and video form. A review of this research is given later in this report.

In addition to receiving scientific visitors 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 other systems biology groups. An outcome of this work was the development of a web site, www.systemsofparkinsons.org, designed to link systems biologists, mathematicians and control engineers working on the systems aspects of this disease. More locally, it is important to note that the Hamilton Institute systems biology team is part of a larger community of interdisciplinary researchers that are studying the systems of life and disease in the Hamilton Institute. Interaction with these colleagues is an important component of any success that we might have in our research.

New funding opportunities have allowed us to align our work specifically toward a systems approach to neurodegenerative disease and the underpinning systems theory. In particular, we welcomed two new postdoctoral research fellows – Miriam Garcia and Mathieu Cloutier - to work on the systems aspects of Parkinson's Disease. Their work is discussed later in this report.

Last, but by no means least, it is a great pleasure to again acknowledge the contributions of the Scientific Advisory Panel who guide our programme. The names and affiliations of the current panel members are listed at the end of this report. As ever, they have my personal thanks for their inputs over the year.

The Programme Plan

The main objective of this Research Professor programme is to establish a systems biology research team that reaches international standards of research competence via projects that are relevant to the needs of science and society. At a broader level, our aim is to assist in the development of a national competence in what was, (at the time of our initial discussions with SFI in early 2003), an emerging discipline with no representation in Ireland. How we set about that initial mission, and its outcome for Ireland, are fully described in previous annual reports. Here we report exclusively on our own activities.

Outreach and Collaboration

With the national strategic and developmental aspects of our mission completed by the end of year two, we have for some time been focussed upon our own research and collaborations. While our own research projects (outlined later in this report) lie at the heart of our work, this is augmented by a wider interest in the application of systems theory to the life sciences. In this context, our programme includes hosting visits by researchers from other research institutes, plus the organisation and hosting of international events. The first of these – an International Systems Biology Workshop – was held in the summer of 2006 and was described in last year's annual report. Based on the success of this event, the Hamilton Institute systems biology group decided to organise a second workshop. This was held in Maynooth in July 2008 and thus falls within in the scope of next year's annual report. However, as a sneak preview (see also the material on our website), I can report that it was a popular success. A set of distinguished systems biologists gave two and a half days of their time to present their work in a range of keynote and plenary addresses, and to discuss science with the young researchers who attended. From my perspective as honorary chair, it was among the most fruitful events that I have ever attended – gratifyingly, the delegates felt the same way. We hope that a third International Workshop on Systems Biology (IWSB) will be held in 2010 – the arrangements for this are a matter of current discussion.

Within Ireland, specific collaborations are now firmly established and producing research outputs. At NUI Maynooth, we work with Professor Lowry's neurochemical sensor laboratory in the Department of Chemistry on the energy metabolism of the brain. Nationally, the IMMT team are collaborating with Professor Prehn's laboratory in the Royal College of Surgeons in Ireland, and Professor Morrisson's laboratory at University College Cork. 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, we are developing the Systems of Parkinsons community and a discussion group on the systems and theoretical aspects of Deep Brain Stimulation.

Research Strategy

The external review panel for this project endorsed our research programme with a 'very good' grading. However, they also suggested that we focus more upon the pure systems biology aspects, rather than a mix of systems biology and bio-imaging. In response to this suggestion additional funding was sought through non-SFI sources to allow the bio-imaging and signal processing elements of the project to develop its activities. As a result our work is now focussed on systems biology research that performs *in-silico* analysis and modelling of biological problems. The signal processing research for recovering information from bio-sensors and biological measurements, which was originally a significant component of the project reported here, is now funded as the IMMT project of NBIP. In this new position, and under the leadership of Dr. Dimitris Kalamatianos, the bio-image processing group maintains its work on mathematical modelling for systems biology analysis and thus still interacts closely with the project reported here. Indeed we review its activities briefly within this report. In a similar vein, Dr. Oliver Mason shifted from the author's grant programme to the new HEA funded Network Mathematics project and won independent funding for his research. Since these transfers of staff and research funding occurred in this reporting period, we also include a review of the relevant activities of Dimitris Kalamatianos and Oliver Mason in this report.

As previously noted, two new postdoctoral research fellows have joined the systems biology team to work on a systems approach to neurodegeneration. This is our core application with a specific focus on Parkinson's Disease. The Systems of Parkinson's project mentioned previously is described in detail later in this report.

In this realigned format the research programme addresses two generic areas: **The Theory of Systems Biology** and **Quantitative Bio-Imaging and Model Analysis**, with the second of these the responsibility of the IMMT team. The application focus of our work is the **Systems of Parkinsons** with the practical aim of understanding the causal mechanisms and developing an *in-silico* test bed for the study of this neurodegenerative disease. These areas are discussed below.

The 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)

Since the mid twentieth century, physical science has relied more and more upon mathematical models to stimulate and support experiments. In the field of engineering, the construction of mathematical models of dynamical systems has become central to the development of new technologies and innovative products. We maintain that a similar pattern will be repeated in the life sciences. Indeed this is already happening, with many groups working on mathematical modelling of cellular and metabolic pathways. However, a model is only of use when it has purpose and is understood as part of an overall system. This in turn requires a control systems analysis that is able to cope with the dynamical nature of living processes and the complexity of their interactions. It is our belief that dynamical systems analysis and control theory are the appropriate tools for this task – hence our use of Lovelock's words at the beginning of this description. Lovelock was writing about his Gaia concept of the planet as a complex, tightly integrated, set of feedback control systems, but he could equally well have been referring to cell biology.

The mathematical modelling and analysis activities that were established in the first three years continue in the manner outlined in the previous annual reports[1]. Our focus remains on developing mathematical methods for the analysis of biological processes and using them to understand the mechanisms by which diseases work. Essential and complementary 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 we feel sure that the applied mathematics and control theoretic emphasis of the Hamilton Institute can play a part.

More technically, we hope to contribute to an understanding of behaviour associated with the nonlinear dynamics and organisational complexity in biology. In particular, we are looking at the problem of interpreting large-scale interconnectivity in biological systems and the role of large groups of coupled oscillatory processes. The mechanisms of life are determined by periodically varying signals that interact in special ways. We hope to help in the understanding of these using analysis based on network mathematics and coupled oscillator theory.

Quantitative Bio-Imaging and Model Analysis

What is more important than human genius is the development of technology, and it is no surprise that the start of the scientific revolution coincides with the development of the telescope and the microscope…

Thus wrote John Gribben[2] when describing the history of science between 1543 and 2001. His words are equally applicable to the development of a systems approach to biology – it is unlikely that significant breakthroughs will be made without new and

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

[2] Science – a History, Penguin Books, London, 2003.

accurate measurement techniques. In this context, our aim is to contribute to the development of theoretically sound and technically appropriate signal/image processing methods with which to extract dynamic information from the wide diversity of sensing modalities that are being used and developed by various international groups. Close collaboration with sensing groups is vital to the modelling and analysis components of the programme, since without reliable and biologically meaningful experimental information it is not possible to set up comprehensive and credible mathematical models of the associated biological processes. This was our rationale for engaging in the National Biophotonics Imaging Platform (www.nbipireland.ie) – a rationale based on our conviction that signal and image-processing methods must be especially designed to extract quantitative and dynamic information that can be used to build appropriate mathematical models. Thus from October 2007 our work on quantitative bio-imaging and the associated image processing has become part of the Image to Mathematical Model Transition (IMMT) facility of the National Biophotonic Imaging Platform. This national platform is funded by HEA and the author coordinates the IMMT component of the platform, while the Hamilton Institute part of IMMT is led by Dimitris Kalamatianos. Because this is a transition year between funding bodies, we report on the IMMT activities later in this report.

A further aspect of the second biosensor signal processing work continues to concern the interpretation of signals from electrical and microdialysis probes used to measure neurotransmitter concentrations in the brain. The first part of this project – a neuro-informatic workbench for visualising microdialysis data – is well advanced and the researcher responsible (Stuart Butler) is currently refining this visualisation tool in collaboration with the neuropharmacologist Dr William O'Connor of the University of Limerick. This and other projects are explained in more detail in the Project Overviews.

The Systems of Parkinsons

The systems biology team at the Hamilton Institute has developed by building our expertise in certain generic research areas that reflect our conviction that issues of dynamics, control and complexity are crucial in biology. Working in collaboration with biologists and chemists, we are now applying our systems skills in specific biological application studies, with the aim of providing an analytical basis for observed biological behaviour and guiding new laboratory investigations. In particular, we work on problems that relate to the mechanisms of neurodegeneration, with Parkinson's Disease as the target application.

Parkinson's disease is usually associated with its most evident symptoms – a shaking action of the body, difficulty in moving, loss of facial expression and dementia. Medically it is associated with protein agglomerations in neurons and the loss of dopaminergic neurons in the substantia nigra of the basal ganglia. However, the causes of Parkinson's Disease are unknown, although there is evidence for the involvement of genetic mutations, toxins and possibly pathogens. The therapies for Parkinson's Disease are usually pharmaceutical, however a recent electrical therapy – Deep Brain Stimulation – has shown impressive results in relieving the physical symptoms of the disease.

Our research into the systems associated with Parkinson's Disease is in two parts:

(i) Mathematical modelling and analysis of the implicated biological processes and
(ii) Mathematical analysis of electrical therapies.

The first of these is an attempt to understand possible causal mechanisms by constructing mathematical models of the corresponding biochemical processes. We

have started with the energy metabolism of the brain since we believe that flaws in the brain energy metabolism may be a causal factor. In fact, there is (except in a small percentage of familial cases) probably no one cause for the disease. On the contrary, Parkinson's disease (PD) seems to be a complex combination of conditions that are caused by interactions between several potential mechanisms. It is therefore a systems disease, and thus a candidate for a systems approach. We base our systems approach upon the development of an *in-silico* mathematical model that can potentially embody all possible implicated cellular and metabolic systems, but (as explained elsewhere in this report) starting with the brain energy metabolism as the core of the model.

The second part of our work addresses the theoretical background to Deep Brain Stimulation. This technique is based upon the repetitive electrical stimulation of key sites in the basal ganglia in a way that reorganises the neural signalling in the motor circuit of the brain. There is evidence to suggest that the therapy is associated with the de-synchronisation of neural circuits by independent external oscillations. Thus the studies of coupled oscillators reported in previous reports and elsewhere in this document are relevant. This and other studies are reported below, and collected in the web site www.systemsofparkinsons.org.

Review of the Year

General

This fourth year has been one of focus on our own programmes and joint work with collaborators. The theoretical and applications aspects of our programmes are flourishing, and the signal processing component of our bio-sensing activity has been subsumed into our component of the National Biophotonic Imaging Platform. Also two systems biology team members (Oliver Mason and Dimitris Kalamatianos) are now separately funded for their work. Oliver has become part of the newly funded Network Mathematics project at the Hamilton and has his own Research Frontiers grant from SFI to study positive systems – an area that is of significant relevance to theoretical studies of biology. In the same spirit, Dimitris is now funded by the IMMT project at the Hamilton and leads a team on bio-image processing and modelling of apoptosis. Within the Hamilton Institute, two other faculty members (Wilhelm Huisinga and Rick Middleton) with an interest in systems biology continue to grow their own research portfolio. With these and other developments underway, the web site http://www.systemsbiology.ie/ has expanded and now references many more activities than those funded only by the award reported here.

Within NUIM, the Systems Biology Forum mentioned in previous reports is now focussed on using the unique electro-chemical sensing skills of the Department of Chemistry in systems biology. Mathematical modelling in immunological systems (with the Institute of Immunology) is now associated with our Hamilton Institute colleague Wilhelm Huisinga. In teaching, Wilhelm gave the second set of systems biology teaching modules to biology students over the reporting session and we will give systems biology modules for the PhD training platform within the National Biophotonic Imaging Platform and locally at NUIM. As systems biology matures, we anticipate developing more courses in this area at both the graduate and undergraduate level.

Externally we continue our support for research and training initiatives nationally and as well as working with colleagues in the Systems Biology and Bioinformatics Group at the University of Rostock, the Case Centre for Complex Systems Biology, at Case Western University and the Department of Bio and Brain Engineering, Korean Advanced Institute of Science and Technology (KAIST).

Visitor Programme

We have maintained our visitor programme through the year with a series of external speakers and collaborators spending time with us. Our visitors are all named separately in the appropriate sections of the report. However, it is appropriate that we make special mention of Phil Hodgkin of the Walter and Eliza Hall Institute for Medical Research, Melbourne, Australia. Dr Hodgkin was an E. T. S. Walton Visitor invited by the Dean of the NUIM Science Faculty (Bernard Mahon) and jointly hosted by the Institute of Immunology and the Hamilton Institute. He worked with Hamilton Institute colleagues Ken Duffy and Vijay Subramanian on probabilistic models of his Cyton model and with the Systems Biology group on the generic cellular mechanisms that could give rise to the variations. Phil Hodgkin also worked intensively in the Institute of Immunology on experimental methodologies, and in doing so did much to draw together the Hamilton Institute and the Institute of Immunology at NUIM.

Looking ahead, we will welcome another E.T.S. Walton Visitor in 2008. Professor Richard Abadi will join us in the autumn of 2008 to work on mathematical modelling of

visual hallucinations, collaborating with our colleague Professor Barak Pearlmutter. Hallucinations can be an early stage indicator of neurological and neurodegenerative disorders and are therefore of great interest to the systems biology team.

Events

New Initiatives

Image to Mathematical Model Transition

As reported last year, we were part of the National Bio-Photonic Imaging Project that was submitted under the Higher Education Authority strategic planning programme (PRTLI) in May 2007. Fortunately, the submission was successful with start date in October 2007. This pan-university programme is a coordinated research and infrastructure plan for non-invasive bio-medical imaging using a wide range of imaging modalities. The author organised and now coordinates the 'image to mathematical model transition' (IMMT) facility of NBIP. This project is a three-institute partnership that links the Hamilton Institute, (NUIM) with the biological skills of the Royal College of Surgeons and the computer science skills of University College Cork. See www.hamilton.ie/SystemsBiology/immt.

The Systems of Parkinsons Community Website

After a lot of hard work involving Mathieu Cloutier, Diego Oyarzún, Miriam Garcia and a number other Hamilton Institute researchers, the community website http://www.systemsofparkinsons.org/ was launched at the end of this reporting period. The aim of this site is to act as a forum for systems researchers (as opposed to life scientists) who are applying a systems biology approach to Parkinson's disease. We have made it specific to researchers from outside life science because we want to avoid potential duplication of existing medical biological research programmes. In particular, we offer a systems approach to the various metabolic and cellular sub-systems that may be implicated in Parkinson's disease. We are working toward the ambitious goal of an *in-silico* model for research into the causal factors of Parkinson's Disease.

As a secondary issue, we also intend our work to be a 'technology demonstrator' for control systems engineers, chemical engineers and applied mathematicians who are interested in life science problems but are uncertain how to get started. The idea of a technology demonstrator is quite particular to engineering, so I will explain its meaning. In industrial research and development it is important to be able to show that a new concept or product idea is feasible before anyone will invest time or money in it. Similar factors apply in university research now; in order to maintain funding (and employment) researchers need to show scientific productivity each year. This makes it hard for researchers to move out of their established areas and develop new research directions. We hope that the Systems of Parkinson's website will indicate how methods from engineering and physical sciences can be readily applied to life science research. It is important to add that this is not a new idea, and there are already a number of outstanding examples of this method of transfer of ideas in the Physiome Project.

E.T.S Walton Lecture

On the 25th July 2007, Phil Hodgkin gave his E.T.S. Walton Visitor Lecture at the Royal Irish Academy, Dublin. His visit to Ireland was jointly hosted by the Department of Immunology NUIM and the systems biology group of the Hamilton Institute. Entitled *Divide and conquer: The remarkable story of our immune defence system* the lecture built on the fact that fifty years ago Macfarlane Burnet published a two page manuscript that came to be seen as one of the most important scientific papers of the 20th Century. In this paper Burnet outlined the principles for understanding immunity - the remarkable ability of our bodies to detect and eliminate a vast range of potential disease causing organisms. Burnet's idea solved a centuries old problem and precipitated a sequence of experimental investigations into the detailed operation of the immune system that continues to this day and has had a major impact on human health.

External Talks and Visits

Members of the group have visited a number of other institutes over the year and a full list of visits in given in later in this report. Among these some deserve especial mention. First, it was a privilege to be the 2008 presenter of the Tustin Lecture. Arnold Tustin was a distinguished control engineer and polymath who made fundamental contributions to the control of electrical machines early in his professional life. This was followed by a career in which he showed how control theory is fundamental to many scientific areas including economics and biology. The lecture, given in May 2008 at Savoy Place London, was entitled, *Systems Biology and the Spirit of Tustin*, and honoured Tustin's pioneering work on a systems approach to biology. Printed versions of the text of this lecture are available from the Hamilton Institute Administrative Office or electronically as detailed below under 'Web Resources'.

Other plenary talks on systems biology, in this period include workshops in Vigo (Spanish Council for Scientific Research) and London, (Institute of Chemical Engineers). Also throughout the year members of the systems biology team presented lectures at conferences and invited seminars in Europe and the Americas. We were represented at the Foundations of Systems Biology in Engineering conference, the International Conference on Systems Biology and the International Federation of Automatic Control three yearly gathering in South Korea.

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. Previously this was organised and funded from internal Hamilton Institute funds. It is currently funded by Science Foundation Ireland by supplementation of PI grants in the Hamilton Institute. During the reporting period Oliver Mason coordinated the Challenge with support from Mark Verwoerd and other Hamilton Institute staff. 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. The web site also reflects how the scope of systems biology research at the Hamilton Institute has spread well beyond that funded by this grant. Thus, 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 not directly funded by this grant, their group web site is given alongside their names.

Staff Changes

From the 1st January 2008 Oliver Mason moved to be funded by the Hamilton Institute Network Mathematics project, and to coordinate the Network Mathematics postgraduate programme. He was also successful in winning SFI support under the Research Frontiers Programme for his research into the stability properties of positive dynamical systems. In October 2007 Dimitris Kalamatianos moved to be head of the NUIM IMMT group at the Hamilton Institute. Because of the overlap in reporting periods, Oliver and Dimitris's work is discussed in this document with the caveat that they were only partially supported by this grant during the reporting period.

In February 2008 Mathieu Cloutier joined the systems biology team to work on the metabolic and cell signalling modelling aspects Systems of Parkinsons project, and in March 2008 Miriam Garcia joined the team to work on the synchronisation of oscillator families with particular reference to Deep Brain Stimulation in Parkinson's Disease.

Book Launch

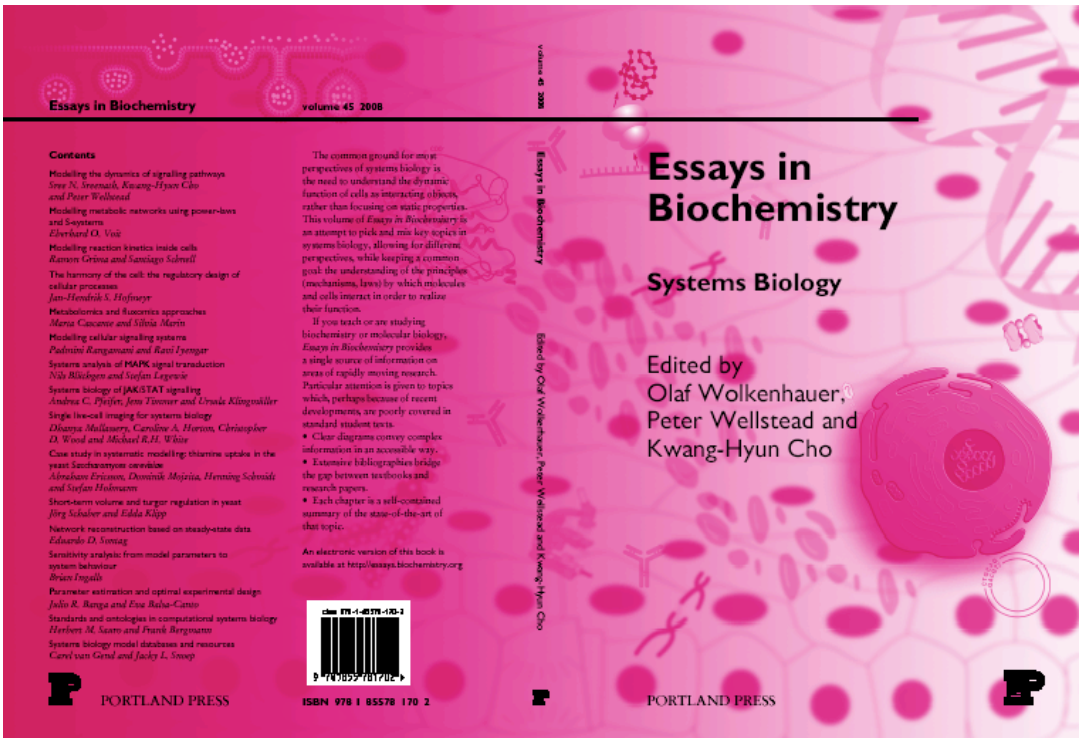
In addition to publishing generally in the scientific literature, we were also invited by our collaborator Olaf Wolkenhauer to join him as co-editor of a new collection of essays on systems biology. The collection, entitled Essays in Biochemistry: Systems Biology, was recently launched by Portland Press (see Photo Gallery).

Photo Gallery

Systems Biology at the Hamilton Institute 2007-2008

The Australian Ambassador introducing Professor Phil Hodgkin's E.T.S. Walton Lecture at the Royal Irish Academy.

The 2008 Tustin Lecture 'Systems Biology and the Spirit of Tustin.



Essays in Biochemistry: Systems Biology

Project Overviews

As described elsewhere in the report, the work of the systems biology group at the Hamilton Institute has two generic areas and one application area:

(i) Theory of Systems Biology
(ii) Image to Mathematical Modelling Transition
(iii) The Systems of Parkinson's Disease

For clarity, the three areas are described here under separate headings. In the same spirit, the work of research visitors and intern students has touched upon other related areas. Where appropriate, these are discussed separately at the end of this section and after the thematic areas.

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

The design of mathematical models for biological systems has emerged as a basic component in 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. These in turn should guide the design of laboratory experimentation and measurement strategies.

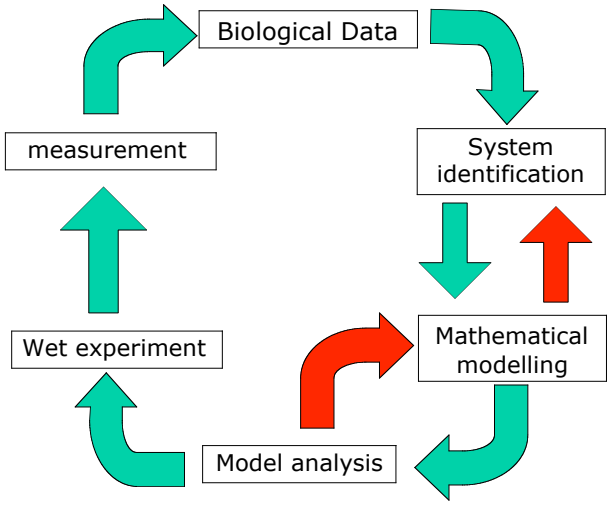


Figure 1. Illustrating the systems approach to biological process investigation

In our programme we have modelling projects that cover brain energy metabolism, alpha-synuclein metabolism and the signalling pathways involved in apoptosis. The last of these is discussed in the IMMT section, while modelling of energy metabolism is covered in the following section. Analysis of the model properties can reveal important underlying features that may have more general biological application and relevance. Our work on this concerns optimisation principles in metabolic regulation, and is also described below.

The modelling and analysis of brain energy metabolism (Mathieu Cloutier)

All living tissues require energy in order to fuel their proper functioning. As regards energy management, the brain is particular in that it requires roughly 10 times more

energy than the other tissues in the body. This energy is required by neurons in order to maintain functional neurotransmission capacity. Another particularity is that the cerebral tissue is composed of two interacting cellular species: neurons and astrocytes. While it is well established that neurons are the functional 'units' for neurotransmission, the exact role of astrocytes is still debated in the literature. Pellerin and Magistretti[3] challenged the traditional view of exclusive glucose oxidation in neurons by proposing that astrocytic metabolism is coupled to neuronal activation, a mechanism that allows lactate transfer from astrocytes to neurons during high activity periods. This is exemplified in Figure 2, where different hypotheses (blue, green or red highlight) are considered for energy management in neurons.

The different mechanisms for energy control are shown in Figure 2. Glycolytic enzymes can be activated to process more glucose (blue 'valve'), mitochondria can be activated as well to quickly produce energy (green 'valve') and finally, we can consider the possibility of using lactate as an additional energy substrate (red 'valve'). By integrating different hypotheses about energy substrates trafficking in the cerebral tissue, it is possible to rationally identify the functional properties of brain energy metabolism.

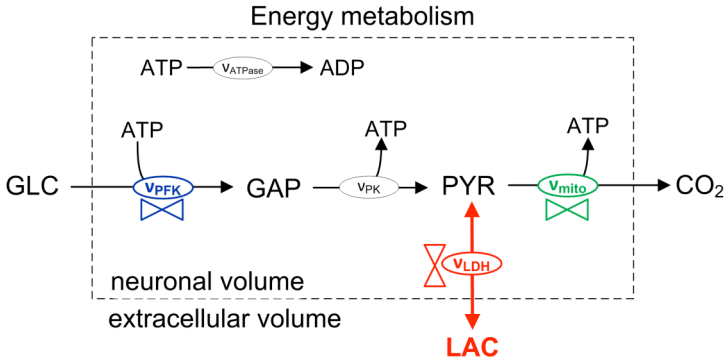


Figure 2. Model for neuron energy metabolism and hypotheses about internal regulation mechanisms and lactate utilization

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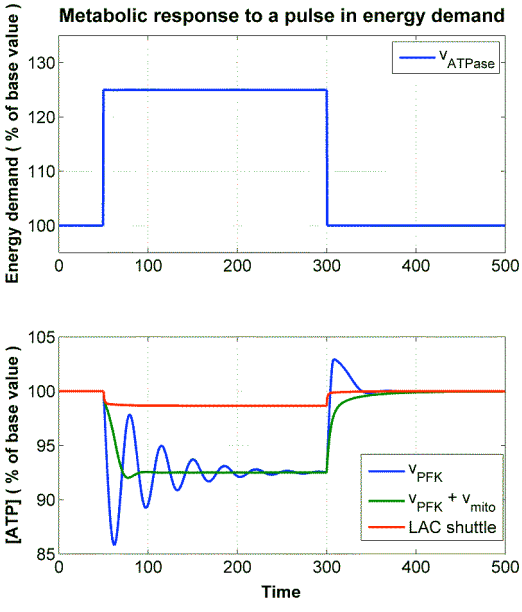
Figure 3. Simulation output showing the effect of a perturbation on energy metabolism with different control mechanisms



The control properties induced by the different mechanisms are shown in Figure 3. Although considerable work and results are found in the literature on brain physiology and brain energy metabolism, there is still no systems framework to rationally analyze hypotheses (i.e. are neurons using lactate as an energy substrate?) and integrate quantitative data. Our goal with this project on brain energy metabolism is to put forward a systems view of the energy management in the brain by using dynamic and descriptive metabolic modelling tools and control theory.

In collaboration with Prof. John Lowry at the Department of Chemistry (NUIM), quantitative *in vivo* time profiles of cerebral energy substrates obtained from freely

[3] Pellerin, L. and Magistretti, P. Glutamate uptake into astrocytes stimulates aerobic glycolysis. PNAS 91:10625-10629, 1994.

moving animals are used to calibrate our model. This data set will be complemented through collaboration with the École Polytechnique in Montréal (Canada) where neurons cultures will be used to quantify the energetic response to perturbations in *in vivo* NMR spectroscopy. This will allow us to build a realistic, physiological model of energy and metabolic 'trafficking' in the cerebral environment. This model will then be used as a tool for a systems understanding of energy control and its implications in neurodegeneration, as described in the section on the Systems of Parkinson's disease project.

Optimisation principles in metabolic regulation (Diego Oyarzun)

The search for general control principles that underlie a range of biological functions is an important part of systems analysis in biology. A particular topic of interest is the role of optimisation principles in the sequences of biochemical reactions that make up metabolic networks. Biochemical reactions are enabled by enzymes that convert substrate molecules into chemical products. Traditional approaches to metabolic regulation consider enzymatic concentrations as fixed parameters of the individual reactions, thus considering the regulation only at a metabolic level (implemented via biochemical interactions such as allosteric or product inhibition). However, as shown by Alon and coworkers[4], enzymatic synthesis can also play a key role in metabolic regulation and therefore, integration of enzyme dynamics and metabolic dynamics becomes necessary. Alon showed that a specific temporal program in enzymatic expression appears in the activation of aminoacid biosynthetic pathways. This temporal program consists of a sequential expression of each enzyme according to the position where they act in the pathway. Mathematical analysis suggests that this expression program is optimal for the control objective of rapidly reaching a production goal with minimal enzyme production.

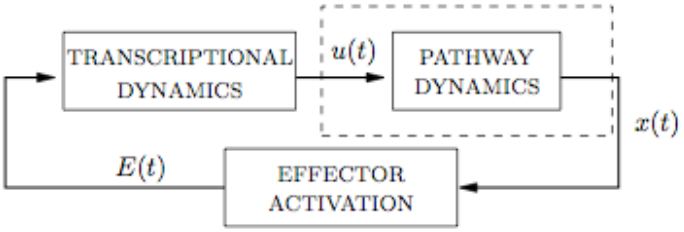


Figure 4. Feedback regulation of enzyme synthesis

Our approach is to explore the aforementioned ideas for more general metabolic networks. Using the theory of dynamic optimization, we seek realistic tools for the analysis of optimal behaviour in such networks. As seen in Figure 4, enzyme synthesis can be regulated by the metabolites in the network, which generates a regulatory feedback loop that couples metabolic and transcriptional networks. The dynamics of these feedback loops are highly nonlinear and therefore the analysis must be done on a case-by-case basis. As a first step, we dealt with the time-optimal activation of a general unbranched network under constraints in total enzyme abundance. The solution of this optimal control problem leads to a sequential activation pattern (Figure 5) that qualitatively resembles the results of Alon et al.

In the next stage we aim at developing a method for the systematic computation of the optimal response of metabolic networks under genetic regulation. One of its most promising applications is gaining insight into the function of regulatory structures that are commonly seen in nature, such as the "single-input module" structures.

[4] Zaslaver et al., "Just-in-time transcription program in metabolic pathways," *Nature Genetics*, 36(5), pp. 486-491, 2004.

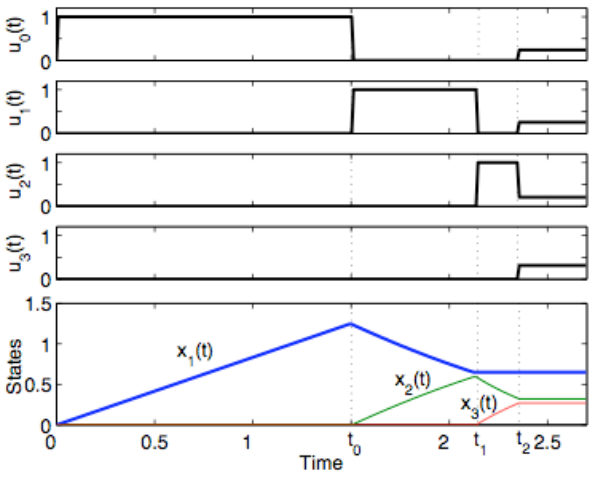


Figure 5. Optimal sequential enzyme activation

Theory of Systems Biology: Dynamics and networks

The past decade has witnessed phenomenal advances in measurement techniques in the biological sciences leading to an explosion in the volume of data available on bio-molecular networks. In order to make the best use of these advances, there is a pressing need for more systematic approaches to the analysis of the complicated networks whose structure is beginning to emerge.

In this section of the overall work programme, we are concerned with developing the study of networks and dynamical processes in biology. The first major aspect of this research focuses on the topological and structural properties of static biological network models such as protein-protein interaction networks. Specifically, we investigate the structure of such networks and how this 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, one of the core issues 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 (Oliver Mason and Mark Verwoerd)

Earlier work had focussed on surveying the major topics of current interest in biological network analysis, and on studying simple duplication-divergence models for the evolution of protein-protein interaction networks. In the past year, we have developed this line of research, concentrating on the link between a protein's position within an interaction network and the biological functions of the protein.

More specifically, we have developed a formal theoretical framework for the problem of algorithmically predicting protein function based on network topology, and shown how many of the previously suggested methods for protein function prediction can be fitted within this 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. The results of this line of work were reported in an invited book chapter to appear in "Structural Analysis of Complex Networks: Theory and Applications", which will be published by Birkhauser in the coming year.

Network topology and dynamics (Oliver Mason and Mark Verwoerd)

The second strand of this research theme, as outlined in previous Annual Reports, concerns the study of network dynamics, with a view to applications in the modeling of intercellular communication. So far, our work has focused on the study of synchronization in the framework of the Kuramoto model of weakly coupled nonlinear oscillators.

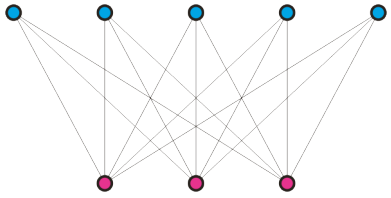
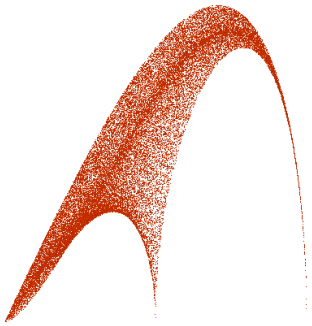


Figure 6. An example of a complete bipartite graph

Specifically, we have developed novel tools for computing the critical coupling associated with the onset of synchronized behaviour for a relatively simple but important class of network topologies (this class includes the complete graph and the complete bipartite graph). These tools enable us to systematically investigate the dependence of the critical coupling on the distribution of frequencies and the topology of the network. For instance, using these tools we were able to compare the critical coupling of a complete bipartite graph with the critical coupling of the associated complete graph for networks with large numbers of nodes (oscillators). After renormalization of the coupling strength, we found that the critical coupling of the complete graph is significantly smaller than that of the bipartite graph. We also found that the critical coupling of the appropriately renormalized bipartite graph tends to a limit as the number of oscillators tends to infinity.

Figure 7. Diagram for assessing the stability in a 4-oscillator system



Most importantly perhaps, our approach has opened up ways of proving new convergence results for the case when the number of oscillators tend to infinity (the case originally considered by Kuramoto). In fact, based on the work described above we have recently submitted an article in which we show that, under certain mild conditions, the critical coupling of a system of coupled oscillators on a complete graph converges in probability to a constant depending only on the properties of the

distribution of intrinsic frequencies. We expect to be able to derive a similar result for the case of a complete bipartite graph. This work is a first step towards a new and rigorous interpretation of Kuramoto's classical work on the onset of coherent behaviour.

On the applications side, we have recently started collaborating with Dr. Miriam Garcia on a theory of desynchronization for Deep Brain Stimulation (see the next section for more details).

Dynamics of coupled oscillators in the brain (Miriam Garcia)

Project Overview

In recent years there has been large agreement about the assumption that oscillatory synchronization constitutes a fundamental mechanism for coordinating communication between spatially distributed local networks in the brain. In fact, abnormal synchronization processes have been associated with several neurological disorders including epilepsy, schizophrenia, dementia, and especially, disorders concerning the motor systems such as tremor or 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), some 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/simulation questions that can be posed in a systems biology framework. Particularly, the plan for the next year is to study the synchronisation hypothesis in two relevant and different cases: DBS for Parkinson's Disease and for minimally conscious brains.

DBS in Parkinson's Disease

Currently, we are focussed on Parkinson's Disease where the pathological behaviour is a consequence of the reduction of the dopamine supply to the striatum reducing the inhibition of the indirect circuit and, therefore, causing the pathway to be highly excited. According to the stimulation-induced modulation hypothesis, DBS would modulate this pathological activity by interfering with the interneuronal communication, specifically by breaking the abnormal patterns of synchrony. Until now the efforts have been addressed in two directions:

(i) Some computational exercises and mathematical transformations have been implemented in order to select a model combining relevant neuronal network behaviour in Parkinson's disease with a suitable structure for mathematical analysis.
(ii) In addition, experts in the area with different backgrounds were recently our guests at a DBS workshop in the Hamilton Institute in Maynooth. Currently, the workshop attendees are iteratively elaborating a document in order to explore the possibility of interchanging knowledge and experimental data.

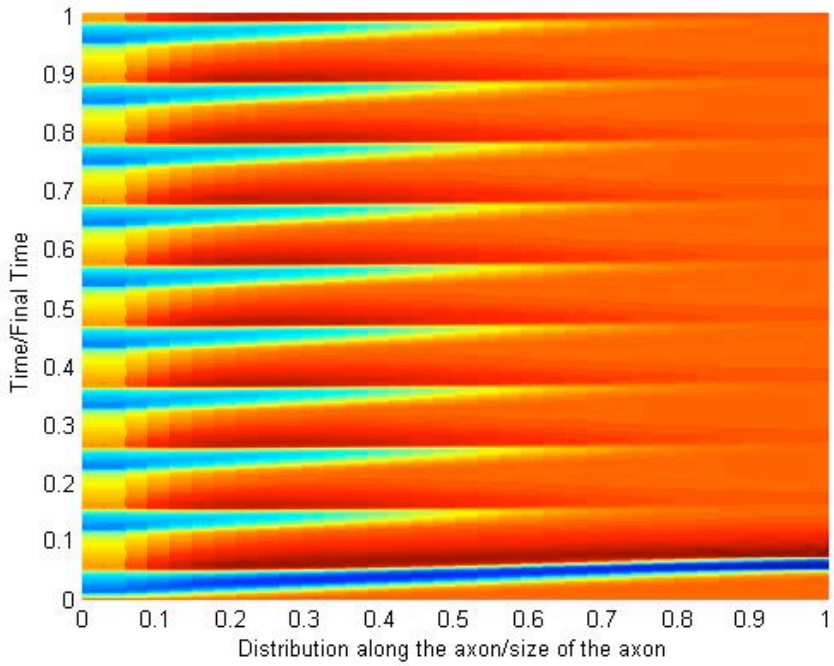


Figure 8. Spatial and time propagation of spikes along the axon when the soma is spiking. In this case, the soma is spiking with low amplitude and only the first spike is able to reach the end of the axon.

DBS in minimally conscious brains

As the complementary problem to DBS in Parkinson's Disease, we want to consider the hypothesis that in minimally conscious brains DBS works by synchronising the affected area of the brain and thus has an 'arousal', or reorganising, role. In the arousal or re-synchronisation hypothesis we propose that in a diseased brain the signalling along the bundles axons that connect various parts of the brain becomes disorganised and desynchronised due to reduced inter-axon coupling within the bundles. The role of DBS in this hypothesis is to provide a strong external oscillator that is capable of providing a signal capable of restoring synchronisation, (and hence organisation) to the axonal bundles that connect one brain region to another.

Image to Mathematical Model Transition (Dimitris Kalamatianos)

Project Overview

This project focuses on bio-medical signal processing, the robust extraction of information from diverse data sources, and mathematical modelling and estimation. The Image to Mathematical Model Transition group is lead by Dr. Dimitris Kalamatianos and its members are: Dr. Mark Readman, Dr. Perrine Paul and Fernando Caamal-Lopez. Current research thrusts include:

Image Processing for Live Cell Imaging Systems

This project is part of the Imaging Technology Core of the NBIP and focuses on the development of a novel automated monitoring system for live cell imaging based on real time evaluation. Our scope is to develop a robust real-time image analysis and modelling solution along with its associated development environment. Both the algorithms and associated software will be made available to all NBIP partners via a software workbench. The Image Analysis Software should accomplish the following

tasks: cell segmentation, cell tracking, signal loss detection, cell morphology changes, generation of time series and events. Below we present an example of the prototype segmentation tool (Figure 9) and the real-time time-series generation (Figure 10), both developed by Dr. Perrine Paul of the Hamilton Institute IMMT team.

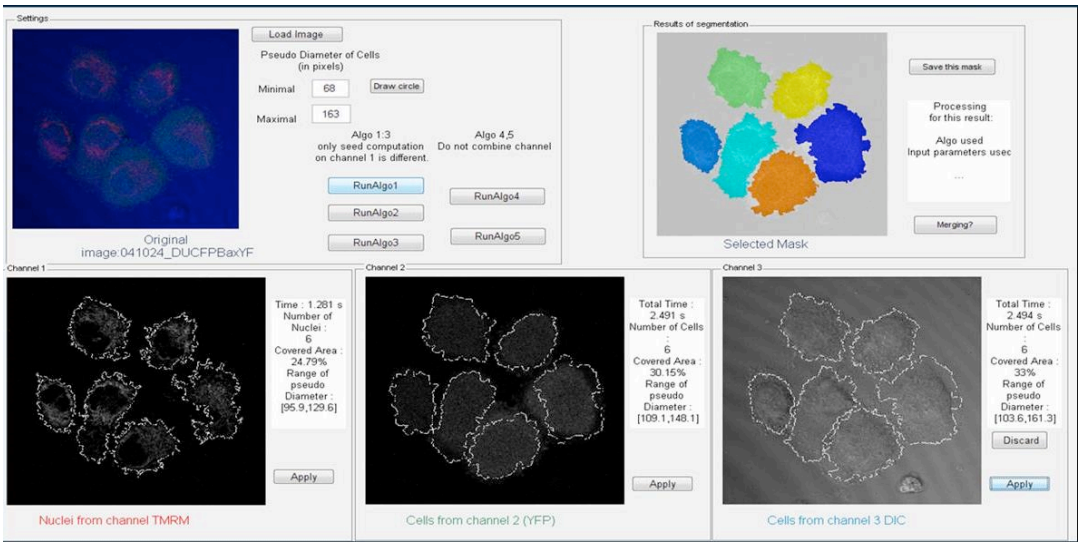


Figure 9. An example of the segmentation GUI

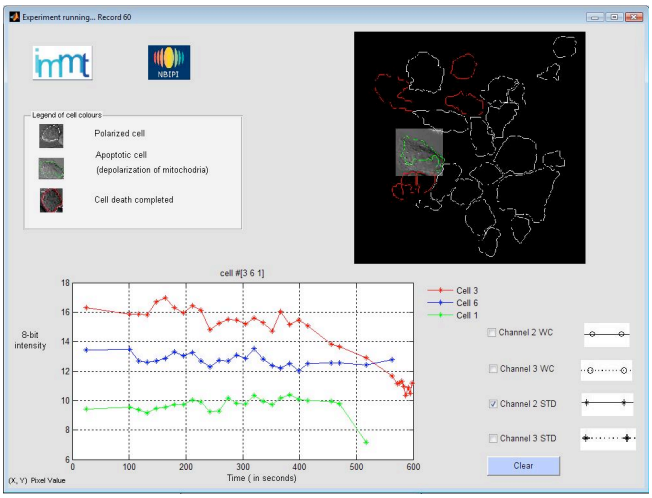


Figure 10. Real time cell analysis and time series generation

This project partners research programmes in the following cores of the NBIP: Molecular and Cellular Imaging Core (RCSI), Compute Node (UCC) and elements within the Imaging Technology Core (RCSI, NUIM).

Systems Analysis of Caspase Activation Apoptosis Models

Apoptosis is a form of programmed cell death, removing unwanted cells within multicellular organisms to maintain a proper balance between cell reproduction and death. This project uses engineering methods from systems and control theory to analyse different robustness aspects for models of the direct signal transduction pathway of receptor-induced apoptosis. It is a collaborative research project with the Department of Physiology and Medical Physics at RCSI.

Mathematical Modelling of the Mechanisms of Cell Death

This project compares apoptotic and alternative cell death signalling pathways by comprehensive systems modelling. It aims at identifying the molecular control mechanisms regulating cell death and survival in human cancer cells. Furthermore, it will provide experimentally testable hypotheses on the protein dynamics of the intracellular signalling networks. This project is carried out in collaboration with Dr. Markus Rehm at the Department of Physiology and Medical Physics, RCSI.

The Systems of Parkinsons Disease

Background

This is our main application project. It was chosen because it is representative of the neurodegenerative diseases that provided the initial orientation and motivation for our Research Professor programme. From a strategic perspective, Parkinson's Disease is an instance of how a systems approach to biology and physiology can be useful, because it represents an example of a 'systems disease'. Specifically, the cause for Parkinson's disease is unknown. Indeed there is strong evidence that it there is no one single cause, but rather a number of weaknesses or defects in different cellular and metabolic sub-systems that combine to produce the observed symptoms of the disease.

The multi-system aspect of Parkinson's Disease is typical of the many important unsolved 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. These are the topics that put the word systems in 'systems biology'. It is only by the integrated application of such topics that we can hope to understand the complex cellular and metabolic interactions that drive many diseases. In the case of Parkinson's disease we can illustrate the various systems that may be involved diagrammatically as in Figure 11.

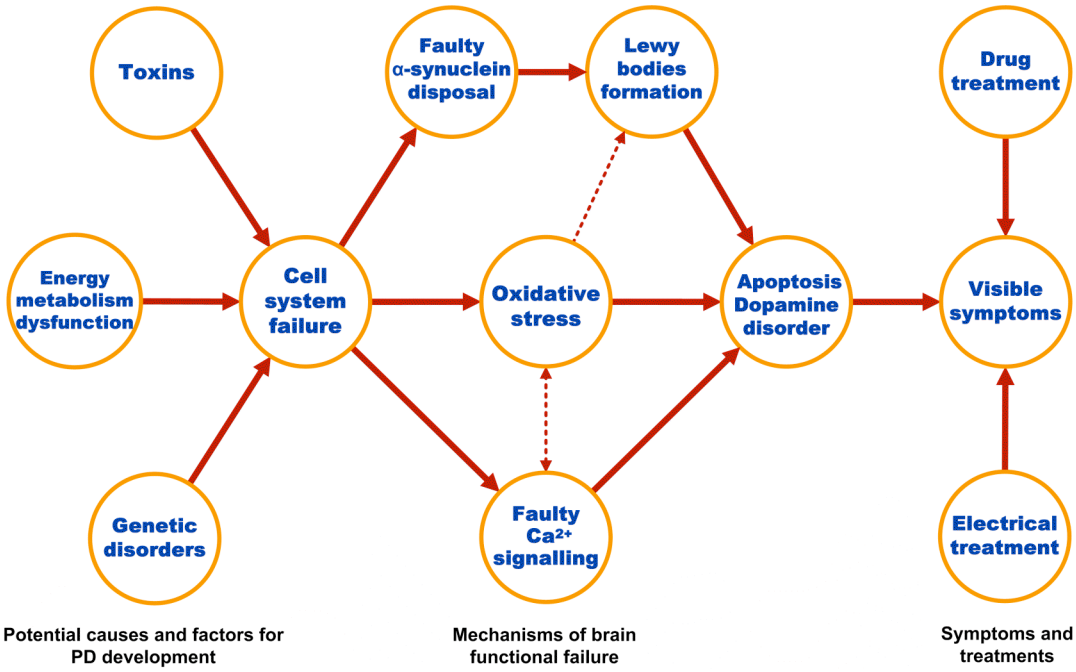


Figure 11. Systems of Parkinson's disease

The figure shows the mix of factors that are potentially implicated in damage to cellular function. They include:

- Faulty energy metabolism
- Exogenous or endogenous toxicity
- Genetic disorders

These factors are thought to be associated with factors including oxidative stress, damage to the cellular disposal system for proteins (alpha-synuclein) and calcium signalling that, together or separately, lead to the key features of PD. Namely,

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

A combination of these issues then results in the key visible symptoms of the disease:

- Failure of the motor circuits
- Lewy Body dementia

The first of these symptoms can be treated with drugs which attempt to compensate for loss of dopamine generating drugs, or by electrical stimulation of the deep brain – as indicated in the figure.

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 shown that mutations in the alpha synuclein gene 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 a progressive build up of alpha synuclein in the brain, starting at the brain stem.

Analysis of Causal Mechanisms

Brain Energy Metabolism

From a systems analysis perspective our starting point in studying PD is the brain energy metabolism. Specifically, it is those cells that have a large energy requirement that are preferentially damaged in PD. Thus neurons with a weak myelin protective sheath to their axons, or neurons with exceptionally long axons, are particularly susceptible. In the same spirit, neurons are among the hardest working cells in the body and thus the most sensitive to defects in the energy metabolism. A chemical biomarker for Parkinson's Disease is the accumulation of alpha-synuclein protein in the neurons. The normal protein disposal mechanisms in the neuron make significant energy demands, and may be among the cellular duties neglected during times of high utilisation of energy in a brain with an inefficient energy metabolism. In other cells such a failure can be compensated for by the mother cell's sequestration of unwanted protein products prior to cell division.

In the first instance a mathematical model of the brain energy metabolism allows us to analyze the dynamic and organisational features of brain energy transactions. However, it can also play a central role in the investigation of disease. Specifically, energy is the quantity that links all cellular processes, thus a mathematical model of brain energy metabolism can act as a 'master model' to which models of other cellular systems can be attached.

An overview of the brain energy metabolism model is given in Figure 12. Also shown (Figure 13) is a model of the alpha-synuclein metabolism as a subsystem that can be installed within the master model structure provided by the brain energy metabolism model.

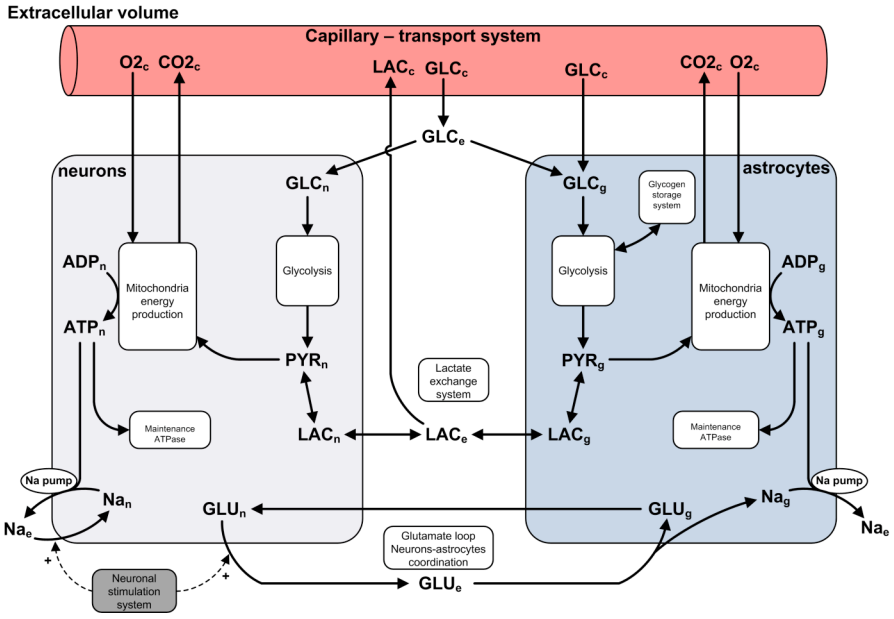


Figure 12. Model for brain energy and physiology

The modelling and analysis work for PD is not exclusive to the systems biology group at the Hamilton Institute. We are also collaborating with Professor Rick Middleton's team in the Hamilton Institute who are working in the modelling and analysis of calcium dynamics in spiking neurons. This modelling work should fit into the master model structure provided by the brain energy metabolism model and form an important bridge project between the modelling work with the DBS research reported below.

Neural apoptosis is responsible for the loss of dopaminergic neurons in PD sufferers. We hope therefore that the apoptosis work mentioned elsewhere in this report will also be installed within the master model structure at some stage.

Toward an *In-Silico* Model of Parkinson's Disease

The demonstration that the cellular processes associated with alpha-synuclein disposal can be connected to the master model of the energy metabolism has a more general significance. Specifically, we believe that there is a 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. Thus they are of use in research into therapies, but of limited use in understanding causal mechanisms. Likewise, investigations of cellular pathways in animal neurons do necessarily transfer to the human case.

The advantage of an *in-silico* approach to disease modelling is that it provides a quantitative means with which to conduct research rapidly and in a repeatable form ready for immediate dissemination and challenge in other laboratories. Like animal models or cellular analogues, *in-silico* models are of limited scope. However, there is flexibility with *in-silico* models, since their limitations are associated with the approximations used in the model. As a result *in-silico* disease models are extendable, since when limitations are revealed, they can be corrected by further modelling.

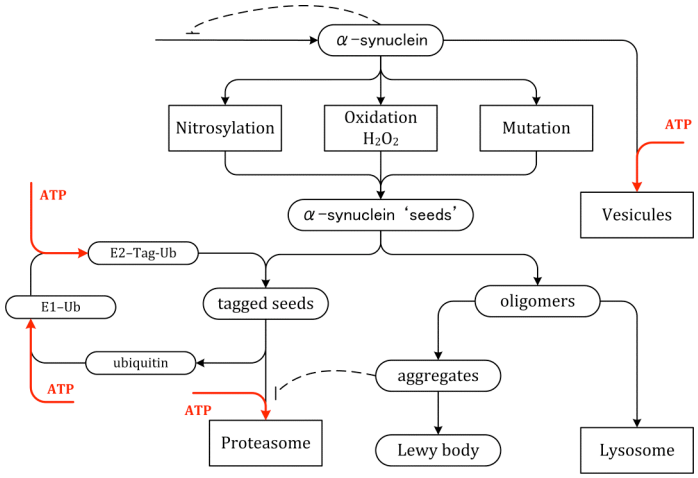


Figure 13. A model for the Parkinson's disease pathway, showing that alpha-synuclein links with energy metabolism by the consumption of ATP (indicated in red).

By implementing the mathematical model of the brain energy metabolism in a standard scientific computing environment (Matlab and the Systems Biology Toolbox), we have the basis of an *in-silico* model of Parkinson's disease. As a demonstration that the energy metabolism model is an extendable platform for *in-silico* disease modelling, the mathematical model of the alpha-synuclein metabolism (referred to elsewhere in this report and illustrated in Figure 13) has been embedded into the master model.

Analysis of Therapeutic Mechanisms

The right hand side of Figure 11 indicates the two therapeutic approaches to PD as pharmaceutical and electrical. We treat these two areas separately below.

Pharmaceutical Therapy: Modelling of Neurotransmitter Variations

Since the beginning of our work at the Hamilton Institute, we have been interested in the dynamical variations in neurotransmitter levels in healthy and Parkinsonian brains. In this connection we have collaborated with the neuropharmacology laboratory of Professor W. O'Connor. In this project Stuart Butler has been working on the collection and analysis of neurotransmitter time course data from micro-dialysis probes. Stuart's work, which is described below in more detail, is primarily concerned with the organisation of the data and its visualisation.

Electrical Therapy: Deep Brain Stimulation

We are interested in the electrical therapy known as Deep Brain Stimulation (DBS). DBS is a treatment, whereby probes are placed in the subthalmic nucleus (STN) and repetitive electrical pulses are applied. In a high percentage of cases this procedure has been successful in reducing Parkinsonian tremors and other physical manifestations of the disease. Also, unlike chemical or surgical lesioning of the brain, DBS is reversible. DBS is a very useful technique for mitigating the symptoms of PD for (possibly) years. However, the mechanisms by which it works are unknown and it this aspect of the technique that we are researching.

For some years, and as discussed previously in this report, Mark Verwoerd and Oliver Mason have been researching the mathematical properties of groups of oscillators. With the arrival of Miriam Garcia, we have been able to add 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. The hope is that a plausible theoretical model of the desynchronisation/synchronisation process will be of assistance in understanding how DBS works and how it may be improved.

Strategy

A systems approach to Parkinson's Disease has ambitious aims that will be impossible 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. This is a slightly different approach to research than that which we are used to, and we are feeling our way in terms of how best it can work. Nonetheless, in due course the code for our models and our theoretical analyses will be made available on the site for download and use by other groups.

Visitor and PhD Projects

The following descriptions cover projects undertaken by our PhD research assistants and visiting researchers.

Project Description: The visualisation of neurotransmitter concentrations from microdialysis sensors (contacts: Stuart Butler and Ronan Riley)

This project is an inter-university collaboration between the Hamilton Institute, the Department of Computer Science, NUI Maynooth, and Professor William O'Connor of the University of Limerick. In it we consider the variations in neurotransmitter levels that occur in particular parts of the brain associated with Parkinson's Disease and Schizophrenia. Currently we are researching the bioinformatic and visualisation issues that occur in merging data from disparate neurological bio-sensors. Stuart Butler has built a neuroinformatic visualisation tool with which neuro-pharmacologists can review and study the dynamical variations in neurotransmitter levels. It is a measure of the potential value of Stuart's work in neuro-pharmacology, that his studentship and project have been extended to 2008. He is now completing his work with the neuro-pharmacology teams and preparing to submit his PhD thesis in the autumn of 2008.

Project Description: Determining the expected variability in immune response (contacts: Phil Hodgkin, Vijay Subramanian and Ken Duffy)

This project is a collaboration between Phil Hodgkin and Dr Ken Duffy and Dr Vijay Subramanian of the Hamilton Institute. In this work we develop modifications to the mathematical theory of branching processes in order to analyse a recently proposed model of the immune response to a mitogenic signal. In an advance on earlier studies, these newly developed techniques enable us to deduce large-scale stability in lymphocyte population size, despite small-scale variability. The model-based predictions have shown to be accurate when compared with data taken from *in vitro* and *in vivo* experiments. The first results of this work have been published and further work is in press.

Project Description: Optimality principles in metabolic networks (contact: Diego Oyarzún)

Metabolic networks consist of interconnected biochemical reactions catalyzed by a set of enzymes. This project aims to uncover optimality principles that can describe the

performance and structure of metabolic networks and their associated dynamics. The dynamics of the overall network depends critically on both the network topology and the enzyme kinetic properties. The project is based on the premise that evolutionary processes have, over time, optimized the design of these networks such that certain properties important to cellular function are maintained. In this spirit, the optimization may account for different objectives such as: (a) ensuring that certain key functions of the cell are not disrupted under changing environmental conditions or, (b) the speed taken building up biomolecules is sufficient to meet urgent requirements in other pathways.

The Systems Biology Group

Core Team Members

Peter Wellstead
SFI Research Professor

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Peter Wellstead is a Science Foundation Professor at the Hamilton Institute NUIM. Prior to his current appointment in 2004, he was an E.T.S. Walton Visitor at the Hamilton Institute and before that Professor of Control Engineering at the Control Systems Centre, University of Manchester Institute of Science and Technology. His current interest is in the application of systems ideas and methods in biology and medicine – with particular emphasis upon the mechanisms of neurodegeneration in Parkinson's Disease.

Eric Bullinger
Visiting Senior Lecturer

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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. 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

SFI 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. Currently, 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.

Miriam Garcia

SFI Postdoctoral Researcher

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Miriam obtained her M.Sc. degree in chemistry (2001) and her PhD. degree in applied mathematics (2008) from the University of Vigo, Spain. All the research work before and during her PhD 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.

Dimitrios Kalamatianos

Research Fellow

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Dimitrios Kalamatianos studied electrical and computer engineering at the University of Patras, Greece, and was awarded a first class honours degree in 2001 and received a prestigious scholarship from the I. Liatsis Institution. In October 2001, he started his Ph.D. in Electrical and Electronic Engineering at the University of Manchester Institute of Science and Technology (UMIST), UK. His research involved the development of a novel near-infrared spectrometer for non-contact measurement. Since October 2004, he has been a member of the Systems Biology Group at the Hamilton Institute, National University of Ireland, Maynooth. In 2007, Dimitris received a Distinguished Scientist Deferral of Military Service, awarded by the Greek Ministry of Defence. His major research interests are in the development of statistical pattern analysis methods for spectroscopic data and the development of measurement techniques for cell imaging using near-infrared sensors. He is now head of the NUIM IMMT group at the Hamilton Institute.

Oliver Mason

Research Fellow

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Oliver Mason studied mathematics at Trinity College Dublin, and was awarded a first class honours degree and a gold medal in his final examinations in 1995. He won several prizes as an undergraduate, including the Townsend Exhibition, Rowe Prize, Minchin Prize, the Lloyd Exhibition and was elected a foundation scholar of the college in 1993. He obtained an M.Sc. degree in mathematics by research in 1998 and in 2004 a PhD on the stability of switched linear systems. Currently, his major research interests are in the use of graph-theoretic methods in Biology and the stability of positive dynamical systems. In particular, he is working on the development and theory of methods to identify important nodes and functional modules within biological networks and on the properties of various random graph models of protein interaction networks and other bio-molecular networks. Oliver is a tenured faculty member at NUIM and is now a member of the Network Mathematics project and responsible for its postgraduate training programme.

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.

Research Students

Stuart Butler

Research Assistant

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Stuart Butler graduated from the National University of Ireland, Maynooth in 2003 with a first class honours degree in Computer Science and Software Engineering. He returned to the Department of Computer Science in November 2004 to undertake a Ph.D. degree under the joint supervision of Professor Ronan Reilly of the Computer Science Department, NUIM, Professor Peter Wellstead of the Hamilton Institute, NUIM, and Dr William O'Connor of the University of Limerick. His Ph.D. is concerned with the development of a neuroinformatic system aimed at the visualisation, analysis, and modelling of neurotransmitter data generated from *in-vivo* experiments.

Diego Oyarzun
Research Assistant

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Diego joined the Hamilton Institute in 2007 as a PhD 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.

Visiting Researchers and Research Students

Philip Hodgkin
E.T.S. Walton Visitor

Hodgkin@wehi.edu.au

During his visit, Phil Hodgkin pursued the systems biology aspects of his research into a probabilistic modelling of proliferation, survival and differentiation decisions in lymphocytes. Specifically, he is developing the mathematical aspects of the hypothesis that lymphocytes behave as if composed of separate independent 'machines' that have stochastic features that govern times to divide and times to die. In this area he is collaborating with Hamilton Institute colleagues Ken Duffy and Vijay Subramanian, and a generic cell model for cell fate processes with Mark Verwoerd and Eoin Mulholland.

Helen O'Gorman
Intern Student

helenogorman@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 O. Poliquin
Intern Student

pierre-olivier.poliquin@polymtl.ca

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 will work with our collaborator Mario Jolicouer on the alpha –synuclein to design and implement biological experiments that will validate and calibrate the model. Alpha-synuclein is a protein that is a bio-marker for Parkinson's Disease.

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 the IMMT project. Rachael is a graduate of the Mathematics Department, NUIM

Eoin Mulholland
Intern Student

eoinmul@gmail.com

Eoin Mulholland was a visiting student from the University of Cambridge) at the Hamilton Institute between May and August 2007. Under the supervision of Mark Verwoerd he worked on a generic cellular model in a form that can be used to show which cellular signalling mechanisms and dynamics determines the probabilistic variations observed by Phil Hodgkin (Visiting Research Scientist – see above).

Andrés Peters
Visiting Research Student

apeters@elo.utfsm.cl

Andrés Peters was visiting the Hamilton Institute as visiting researcher 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. He is working on methods to identify dynamical sub-elements of biological networks under the supervision of Oliver Mason and Rick Middleton.

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:

University of Manchester, UK, July 2007

University of Gronningen, July 2007

Systems Biology Centre, University of Rostock, Germany, September 2007

University of Stuttgart, September 2007

University of Bristol, October 2007

University of Cambridge, November 2007

Bio-Systems Signal Processing Laboratory, City University of London, UK, November 2007

U. Federico Santa María, Valparaíso, Chile December, 2007

Department of Applied Mathematics, University of Waterloo, Canada, May 2008

Department of Chemical Engineering, Ecole Polytechnique de Montreal, Canada, May and April, 2008

Imperial College, London, UK, June 2008

University of Oxford, June 2008

External Talks by Team Members

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

A systems biology perspective of apoptosis signalling. (Invited talk). Workshop Proteomics and Phos-phoproteomics of RTK Signaling Networks Hinxton Hall, Cambridge, July 2007.

Topics in systems biology, (Seminar), Faculty of Engineering and Mathematics, City University, London, October 2007.

Cells, Signals and Synchronisation. (Invited talk). Bristol Centre for Complexity Sciences, Bristol, October 2007.

System Identification and Modelling of Biochemical Systems. (Invited talk). Workshop on Control Theory for Systems Biology, Groningen, The Netherlands, November 2007.

A Systems Approach to Disease. (Invited talk). EU Workshop on Systems Biology, Rostock, Germany, November 2007.

Optimal control and metabolic regulation. (Seminar). University Santa María, Valparaíso, Chile, December 2007.

Systems Biology in the Hamilton Institute. (Seminar). University Santa María, Valparaíso, Chile, December 2007.

Integrative modelling of brain energy metabolism. (Seminar), Ecole Polytechnique de Montreal, Canada, April 2008.

Optimal regulation of metabolic activation, (Invited talk), University of Waterloo, Canada, May 2008.

Optimal regulation of metabolic activation, (Invited talk), Ecole Polytechnique de Montreal, Canada, May 2008.

Systems Biology and the Spirit of Tustin, (Tustin Lecture 2008), Savoy Place, London, May, 2008.

Systems Biology – systems and disease, (Invited talk), Systems Biology in Spain: Opportunities and Challenges, *Spanish Council for Scientific Research*, Vigo, May, 2008.

A Systems Approach to Disease, (Invited talk), Institute of Chemical Engineers Meeting on Systems Biology with an Industrial Focus, *Imperial College*, London, June, 2008.

Visiting Scientists

As part of the overall Hamilton Institute activity, we have an active visitor programme in systems biology. With the programme we aim to bring both established and younger international researchers to the Hamilton Institute to discuss topics of mutual interest or significant topicality. International visitors for this reporting period included:

Prof. Richard Abadi, University of Manchester

Prof. Julio Banga, CSIC Spanish Council for Scientific Research, Vigo, Spain

Dr. Guy-Bart Stan, Cambridge University, UK

Prof. Ricard Bayford, Middlesex University, UK

Daniel Baum, Zuse-Institut Berlin

R. Fleming, Palsson Systems Biology Research Group, UCSD, San Diego, USA

Dr. Jeffrey Glennon, Director of In Vivo Neuropharmacology, Solvay Pharmaceuticals, The Netherlands

Prof Luigi Glielmo, Universita del Sannio, Benevento, Italy

Prof. Phil Hodgkin, Head, Immunology Division, The Walter and Eliza Hall Institute of Medical Research, Victoria, Australia

Prof. Mario Jolicoeur, Ecole Polytechnique, Montreal, Canada.

Dr. Ingeborg M.M. van Leeuwen, University of Dundee, Scotland

Prof. Michael C. Mackey, McGill University

Dr. Brendan O'Malley, Systems Biology of Lipid Metabolism Project, Corporate Research - Biosciences Unilever R & D, UK

Julio Vera, University of Rostock

Visitor Seminars

As part of the overall Hamilton Institute activity, we have an active seminar programme. Hamilton Institute seminars are deliberately multidisciplinary and a full listing is given on the web site www.hamilton.ie. Likewise, the Systems Biology Group hold internal seminars which are similarly listed at www.systemsbiology.ie Here we list only those seminars with a systems biology theme and presented by visiting scientists:

Global Analysis and Synthesis of Networks of Oscillators: A dissipativity approach, Dr Guy-Bart Stan, University of Cambridge, June 25th 2008

Experiences in Plant Metabolic Measurement. Prof Mario Jolicouer, Ecole Polytechnique de Montreal, Canada, June 24th 2008

An Integrative Computational Model of Colorectal Carcinogenesis. Dr. Ingeborg M.M. van Leeuwen, University of Dundee, Scotland. May 14th 2008

Identification and Feedback Control in Deep Brain Stimulation. Prof Luige Glielmo, Universita del Sannio, Benevento, Italy. May 7th 2008

Dark Energy, Vacuum Fluctuations and Microscopic Irreversibility. Prof. Michael C. Mackey, McGill University

Structural Modelling of the Whole Head for Electrical Impedance Imaging and Deep Brain Stimulation. Prof. Richard Bayford, Middlesex University and Imperial College. April 8th 2008

Optimization and Optimality in Systems Biology. Prof. Julio Banga, CSIC Spanish Council for Scientific Research, Vigo, Spain. April 22nd 2008

Integrated stoichiometric, thermodynamic and kinetic modelling of steady state metabolism, R. Fleming Visiting scholar, Palsson Systems Biology Research Group, UCSD, San Diego, USA. February 6th 2008

A Point-Based Algorithm for Multiple 3D Surface Alignment of Drug-Sized Molecules Daniel Baum, Zuse-Institut Berlin. August 28th 2007

Stochastic modelling of the immune response Ken Duffy and Vijay Subramanian, Hamilton Institute, NUIM. September 27th 2007

Mathematical modelling of cell signalling pathways: a useful tool for data integration and validation of hypothesis Julio Vera, University of Rostock. October 3rd 2007

Seeing more than meets the eye, Richard Abadi, University of Manchester. November 14th 2007

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. Some of these collaborations (such as those with Rostock and Bio-Max, NUIM Chemistry, Engineering and Biology) are close, others less so. Nonetheless we value them all. The full list of centres with whom we interacted over the reporting period is given below:

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

Prof. Olaf Wolkenhauer, Chair of Systems Biology and Bioinformatics

- □ Systems Theoretic Issues in Biology
- □ The Systems of Parkinsons

Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology, Republic of Korea

Prof. K-H Cho, Chair in Systems Biology

- □ Systems Theoretic Issues in Biology

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

Prof. Sree Sreenath, Chair in Systems Biology

- Systems Theoretic Issues in Biology

The University of Limerick & Department of Computer Science, NUIM, **Ireland**.

Prof. William O'Connor, Chair in Biology

- Visualisation, modelling and analysis of neural pathways using microdialysis sensors

Department of Electronic Engineering, NUIM, Ireland

- Optical monitoring of cellular structure during implantation of various DNA material
- A novel dual-modality optical and electrical non-invasive system for nerve conduction studies with application to neural degenerative diseases.

Department of Chemistry NUIM, Ireland

Prof John Lowry

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

University of Stuttgart, Germany.

Institute for Systems Theory and Automatic Control

Prof. 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

Prof. Dr. Peter Scheurich, Monica Schliemann:

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

  Prof. Dr. Klaus Pfizenmaier
- High-throughput image analysis for the classification of sub-cellular localization patterns of fluorescently labelled proteins

Politecnico di Milano, Italy.

Prof. Dr. Sergio Bittanti and Marcello Farina

- System Identification in Biological Applications

Max Planck Institute of Biochemistry, Martinsried, Germany.

Prof. Dr. D. Oesterhelt and Stefan Streif

- Sensitivity analysis of biochemical reaction networks

Department of Electrical & Computer Engineering, University of Patras, and Patras Science Park, Greece.

Prof. Petros Groumpos and Dr. A. Anastadiadis

- Systems Theory and Neural Networks in Bioinformatics

University College Cork.

Professor John Morrisson

- Software workbench for the Image to Mathematical Model Transition project of NBIP

Royal College of Surgeons in Ireland, Dublin.

Professor Jochen Prehn, Heinrich Huber

- Software workbench for the Image to Mathematical Model Transition project of NBIP

Ecole Polytechnique de Montreal, Canada

Professor Mario Jolicoeur

- The Systems of Parkinsons (energy metabolism)

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

E. Bullinger, R. Findeisen, **D. Kalamatianos** and **P. Wellstead**. *System and control theory furthers the understanding of biological signal transduction*. In I. Queinnec, S. Tarbouriech, G. Garcia and S-I. Niculescu, editors, *Biology and Control Theory: Current Challenges*, volume 357 of Lecture Notes in Control and Information Sciences, pages 123–135. Springer-Verlag 2007.

S. N. Sreenath, K-H. Cho and **P. Wellstead**. *Modelling the dynamics of signalling pathways*. In O. Wolkenhauer, P. Wellstead and K-H Cho, editors, *Essays in Biochemistry: Systems Biology*, volume 357 of Lecture Notes in Control and Information Sciences, pages 1–15. Portland Press 2008.

Journals

M. Verwoerd and **O. Mason**, *Global phase-locking in finite populations of phase-coupled oscillators*, SIAM Journal of Applied Dynamical Systems, 7, 1, pp134–160, 2007.

E. Bullinger, D. Fey, M. Farina & R. Findeisen, *Identifikation biochemischer Reaktionsnetzwerke: Ein beobachterbasierter Ansatz*, AT-Automatisierungstechnik, 56, 5, pp269–279, 2007.

P Wellstead, E Bullinger, D. Kalamatianos, O. Mason and **M. Verwoerd**, *The rôle of control and system theory in systems biology*, Annual Reviews of Control, 32, 1, pp33–47, 2008.

P Wellstead and E. Ragnoli, *Sistemi e vita*, Xla Tangente, May, pp16–22, 2008.

Conferences and Workshop Proceedings

D. Oyarzún, B. Ingalls, **D. Kalamatianos.** *Optimal metabolic regulation by time variation of enzyme activities: a control theoretic approach.* Proc.2nd Foundations of Systems Biology in Engineering FOSBE 2007, 9–12 September, Stuttgart

M. Farina, **E. Bullinger**, R. Findeisen and S. Bittanti*. An observer based strategy for parameter identification in systems biology.* Proc.2nd Foundations of Systems Biology in Engineering FOSBE 2007, 9–12 September, Stuttgart

M. Schliemann, T. Eißing, P. Scheurich and **E. Bullinger**. *Mathematical modelling of TNF-α induced anti-apoptotic signalling pathways in mammalian cells.* Proc. 2nd Foundations of Systems Biology in Engineering FOSBE 2007, 9–12 September, Stuttgart

S. Streif, R. Findeisen & **E. Bullinger**. *Nonlinear sensitivity analysis of biochemical reaction network.* Proc.2nd Foundations of Systems Biology in Engineering FOSBE 2007, 9–12 September, Stuttgart

M. Verwoerd. *I1-Optimal Robust Iterative Learning Controller Design.* Proc. American Control Conference 2008, 11-13 June, Seattle, USA.

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