www.systemsbiology.ie

Science Foundation Ireland Research Professor
Award 03/RP1/I382

Annual Report 2006 – 2007

Peter Wellstead
Science Foundation Ireland Research Professor
Hamilton Institute

www.systemsbiology.ie

Contents

Contents

Preface

Introduction

Review of the Year

Photo Gallery

Project Overviews

The Systems Biology Group

Visits by Team Members

External Talks by Team Members

Visiting Scientists

Visitor Seminars

Partnerships

Publications

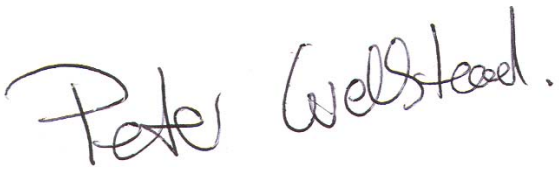
Scientific Advisory Panel

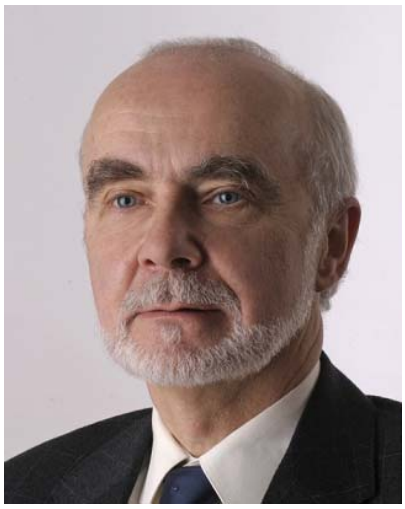
www.systemsbiology.ie

Preface

This is the third report on work conducted as part of the research professor award SFI Research Professorship award 03/RP1/I382. The report covers the period July 2006 to June 2007 and, as in the previous reports, the aim is to acquaint other researchers with our activities and those of our collaborators. We also hope that it will be informative and generate the groundwork for further collaboration. Beyond this it is intended to supplement the formal progress report required under the terms of the Research Professor Award by Science Foundation Ireland.

For more information on our work and soft 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.





Peter E. Wellstead
Science Foundation Ireland Research Professor
Hamilton Institute
NUI Maynooth
Maynooth
Co. Kildare
Ireland

Introduction

Background

The first two years of work were driven by our objectives to: (a) establish a systems biology awareness in the country, (b) establish the Hamilton Institute systems biology research activities and (c) build links to local and international partners in systems biology research. With these objectives successfully completed, we have reduced our general outreach activities and in this third year focussed on our own research activities and collaborations. In this respect, we are pleased to be part of the proposed National Bio-Photonic Imaging Programme that was submitted under the Higher Education Authority strategic planning programme (PRTLI). We are also invited partners in two potential systems biology programmes under Framework 7 of the EU research directorate.

Notable events during the reporting period included the group's organisation of an International Workshop on Systems Biology at NUIM and our successful passage through a detailed scientific review of our programme by an international peer review panel appointed by Science Foundation Ireland. More will be said of this later. Also this year we were able to welcome a number of distinguished scientists as visitors to the Hamilton Institute. Some stayed only a brief time, but others were here longer. In particular, Dr. Phil Hodgkin, Head of Immunology, at the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia (www.wehi.edu.au) joined us for six months as an E.T.S. Walton Visitor. His visit was initiated by the Dean of Science at NUIM, Bernard Mahon, and was jointly hosted by the Hamilton Institute and the Institute of Immunology NUIM. A complete listing of visitors is given in the corresponding section of this report.

In addition to receiving many visitors, members of the systems biology team have also travelled both nationally and internationally. Most of these trips were visits to our international collaborators, but we have also travelled to other international Systems Biology groups and to relevant life science laboratories. In this context, it is important to note that the Hamilton Institute Systems Biology team is part of a larger community of researchers that makes up the Hamilton Institute. The support of, and interaction with, other members of the Hamilton Institute is an important component of any success that we might have in our studies of the systems of nature.

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

The Programme Plan

The general objective of the author's Research Professor programme is to establish a Systems Biology research team that achieves international standards of research competence via high quality projects that are relevant to the needs of science. 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. Our first step was to raise national awareness by visits to Irish universities and through a public lecture, entitled 'Schrödinger's Legacy', in April 2005 at the Royal Irish Academy (RIA).

Schrödinger's Legacy was prepared for an audience of scientists. A second lecture 'On the Industrialisation of Biology' and aimed at research strategists, was used in 2006 to help industry and government plan its future investments. The further component of raising national awareness was our organisation of two national Systems Biology Workshops on behalf of the Science Foundation Ireland. Both these events took place in 2005 at NUIM and were hosted by the Hamilton Institute. As a result of these activities the interest in a systems approach to biology is growing in Ireland and SFI is now developing its national systems biology programme.

In this context, we advocated that SFI create a programme in which the specialist systems theory was focussed in a central 'dry' systems biology laboratory (based upon its existing systems biology investments at the Hamilton Institute), but with computational biological modellers sited in a selection of biology laboratories across the university system. The aim of this would be to use the concentration of specialised mathematical/systems skills to support and coordinate the mathematical modelling activities in the biology laboratories. In this way the cultural and scientific change associated with systems biology would be propagated to life science departments nationally and to the benefit of all. However, SFI have instead elected to develop a centralised national institute of systems biology with partial funding from industrial partners. Our previous experience with this funding model lead us to doubt its appropriateness at this stage in the development of systems biology. Despite this difference in approaches, we wish SFI success with its strategy and will continue to support their plans.

With the development aspect of our mission complete we are now exclusively focussed upon the main component of the programme plan – namely our own activities and collaborations. While our own research projects (outlined later in this report) lie at the heart of our activities, this is augmented by a wider interest in the application of systems theory to the life sciences. In this context, our plan includes hosting visits by researchers from other research institutes and the organisation and hosting of international events. The first of these – an International Systems Biology Workshop – is described later in this report. Based on the success of this event, the Hamilton Institute Systems Biology group is currently organising the second such international workshop. This will be held in Maynooth in July 2008 (for details see www.hamilton.ie/systemsbiology/Workshop2008/index.html). Contingent upon the successful outcome of the 2008 workshop, there is an intention that it will become a regular bi-annual event. In the same spirit, members of the Hamilton Institute Systems Biology group have made, and will continue to make, regular visits to other institutes for discussions and presentation of our work.

At NUI Maynooth generally, the development activity over the first two years of our project are beginning to show results. Specifically, interest in a systems approach to biology has developing firm roots and colleagues in the Department of Chemistry and

the Institute of Immunology are now orienting their research in new ways. We look forward to further growth in our collaborations with these excellent life science partners.

Within the Hamilton Institute, our position remains that we are a predominantly 'dry' Systems Biology laboratory, performing *in-silico* analysis and modelling of biological problems, and developing novel signal processing methods for recovering information from bio-sensors and biological measurements. Thus the research programme addresses Systems Biology from the viewpoint of: **Mathematical Modelling and Analysis** and **Bio-Sensor Signal Processing** as follows:

Systems Biology: Mathematical Modelling and Analysis

Motivation

In the nineteenth and twentieth century, with the visible world largely explained, science turned its attention to less tangible challenges - electricity and the structure of the atom. Since then science has relied more and more upon hypothetical models that in turn stimulate focussed experiments (for example Millikan's experiment to test Einstein's 1905 quantum model). In this way, the construction of mathematical models of dynamical systems became central to our understanding of the physical world. In considering the problems in Systems Biology, we conclude that the same pattern will be repeated in the biological world as we attempt to unravel the mysteries that rule the mechanisms of life. Thus we believe that in the twenty-first century, mathematical modelling and the analysis of the associated dynamical system models will be indispensable components of life sciences research.

Programme

The mathematical modelling and analysis activities that were established in the first two years continue to develop in the ways outlined in the previous annual reports[1]. Our focus remains on research into the systems theory and applied mathematics that underlie dynamical mechanisms in biology, disease and healthcare. Essential components in this are methods to build mathematical models appropriate for biological systems. Added to this, our aim is to develop 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 emphasis of Hamilton Institute can play some useful part.

More technically, we hope to contribute to an understanding of biological behaviour associated with the nonlinear dynamics and organisational complexity that determine the nature and performance of living organisms. There is a compelling need for mathematical methods that describe biological behaviour in ways that make sense out of organism complexity and allow inference and prediction of organism dynamics. In addition, we need methods for determining suitable model structures, estimating their parameters, and analysing their performance in a way that increases our understanding of the underlying biology. As hinted above, it is only by use of such models can we (a) extrapolate beyond what can be directly measured experimentally in the 'wet' laboratory, and (b) suggest new hypotheses that can be tested in new experiments.

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

Systems Biology: Bio-Sensor Signal Processing

Motivation

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 accurate measurement.

Programme

Our aim is to contribute to the development of theoretically sound and technically appropriate signal 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 component of the programme, since without reliable and biologically meaningful information from biosensors it is not possible to setup comprehensive and credible mathematical models of the associated biological processes. This was our rationale for engaging in the National Bio-Photonics Programme in the ways described earlier – a rationale based on our conviction that signal-processing methods must be especially designed to extract information which is truly relevant for building meaningful mathematical models.

There are currently three parts to the sensor signal processing work. The first builds on our previous research in developing compact, portable Near Infrared (NIR) sensing devices, and explores their use as a non-invasive, real-time, bio-sensor. This line of work is based upon previous research by the author on active control and optimisation methods for two beam interferometers. The significance of this development is that it allows an important class of indirect sensors of organic compounds to be made much smaller and more robust than was previously possible. The implications of these sensors for bio–sensing are that we may be able to develop non-intrusive measurement techniques for real-time on-line measurement of certain bio-molecules. Together with special signal processing methods that we intend to develop, this will enable us to extract quantitative information on bio-molecules from noisy sensor data. It is important to note that there already exists a strong national research activity in NIR sensing, and we intend to collaborate with these groups.

The second biosensor signal processing work concerns 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 neuropharmacolgist Dr William O'Connor of the University of Limerick (formerly UCD). This and other projects are explained in more detail in the Project Overviews.

Thirdly, we report new activities in extracting quantitative information from imaged based biological data. This new development comes from the Systems Biology team's recognition that control and signal processing ideas from technological image processing can be equally applied to images from microscopes. This work is described more fully later in the report.

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

Overall Research Policy

The Systems Biology team at the Hamilton Institute will develop in a way that supports the general areas outlined in the preceding paragraphs. Specifically, we are focused on building our expertise in certain generic research areas that reflect our conviction that issues of ***dynamics*** and ***complexity*** are crucial. Specifically:

(a) Modelling and analysis techniques for inter and intra-cellular dynamics.

(b) The analytical techniques required to model and analyze the highly complex networks of dynamical and stochastic interactions that take place in a living organism and between sets of organisms.

(c) The sensor signal processing and analysis methods required to obtain biologically meaningful information from sensing modalities for biology and medicine.

Working in collaboration with biologists, chemists and others, we will use these generic systems skills in specific biological ***application*** studies to provide an analytical basis of observed biological information, and give guidance for new laboratory investigations. As our motivating objective, and without being prescriptive about research opportunities, we will use our systems perspective to work especially on problems that relate to the ***mechanisms of neurodegeneration***.

Finally, and to be absolutely explicit, there is a long-term scientific objective – to add usefully to the understanding of neurodegeneration. This objective is supported by a plan to develop appropriate generic systems skills and employ them in collaborative applications with experimental experts in relevant biological areas.

The Hamilton Institute Systems Biology group: 2006 – 2007

(Not shown: Steffen Borcher, Thomas Eißing, Andrés Peters, Eoin Mullholland,

Tim Rutjes, Monica Schlieman, Thomas Schröck)

Review of the Year

General

This third year has been one of focus on our own programmes and joint work with collaborators. The theoretical aspects of our programmes is flourishing, and the signal processing component of our bio-sensing activity has also progressed well, but will further benefit from investment from the proposed National Bio-Photonics Platform. The NIR hardware aspects of our plan have been under invested over the first half of the five-year plan. We will remedy this by either winning further research funding for our NIR bio-sensor developments, or subsuming this area into our component of the National Biophotonic Imaging Platform.

Within the Hamilton Institute, two new faculty members (Wilhelm Huisinga and Rick Middleton) with an interest in Systems Biology have been appointed. Wilhelm Huisinga joined the faculty in 2006 from the Matheon in Berlin, and his arrival has brought a new computational physiology dimension to the Hamilton Institute's research portfolio.

Rick Middleton was awarded an SFI Research Professorship and joined the faculty in the first quarter of 2007. Rick is an internationally renowned systems theorist who also has an interest in Systems Biology. In this connection, he collaborated with members of the System Biology Group members during his sabbatical visit in 2006. These two very welcome additions to the faculty will widen and strengthen the Hamilton Institute research into 'the systems of nature'. In practical terms, the arrival of Rick and Wilhelm means that the web site http://www.systemsbiology.ie/ has grown and now references more activities than those uniquely associated with this award (03/RP1/I382).

Within NUIM, the Systems Biology Forum mentioned in the previous report, has developed into a research discussion group that is now more tightly focussed on electro-chemical sensing in systems biology (with the Department of Biology) and mathematical modelling in immunological systems (with the Institute of Immunology). From a teaching perspective the first systems biology teaching modules to biology students where delivered over the reporting session and we have designed Systems Biology modules for a national PhD training platform within the National Biophotonic Imaging Platform.

Externally we continue our support for research and research 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 BIOMAX Institute of the National University of Seoul.

In the community, Eric Bullinger has been elected to the UK BBSRC Panel for Mathematical Networks in Systems Biology and Peter Wellstead the Canadian NERC Review Panel with special reference to systems biology grants.

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 NUIM (Bernard Mahon) and jointly hosted by the Institute of Immunology and the Hamilton Institute. He worked with us on the mathematical and systems aspects of a probabilistic model of cell fate that Dr Hodgkin termed the Cyton model. This involved a close collaboration with Hamilton Institute colleagues Ken Duffy and Vijay Subramanian on probabilistic models of the 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 the experimental methodologies, and in doing so did much to draw together the Hamilton Institute and the Institute of Immunology at NUIM.

Events

First International Workshop on Systems Biology

In July 2006, we hosted the First International Workshop on Systems Biology. The three-day event was organised by the Hamilton Institute Systems Biology Group and held in the John Hume building of NUI Maynooth. The Workshop consisted of a series of plenary talks by world authorities in systems biology and medicine, with additional poster sessions, discussion groups and breakout sessions led by plenary speakers. The aim of this event was twofold:

1. To present an authoritative overview of the area as seen by leading thinkers in the field.
2. To give postgraduate and postdoctoral researchers the opportunity to present their work in poster sessions.

By holding the workshop in the handsome surroundings of St. Patrick's College and the John Hume Building, the organisers were able to create an informal atmosphere that allowed research students to mix with expert researchers in an informal environment that stimulated interaction and discussion. In this spirit, the event was designed to be small scale, with approximately 100 delegates representing 13 nationalities.

Plenary Speakers included:

Dr. Neil Benson, Pfizer, UK

Prof. Hamid Bolouri, University of British Colombia, Vancouver, Canada

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

Dr. Heinrich Huber, Siemens, Ireland

Prof. Brian Ingalls, Department of Applied Mathematics, University of Waterloo, Canada

Prof. Elling W. Jacobsen, Automatic Control Lab, KTH Stockholm, Sweden

Prof. Roy Kishony, Bauer Center for Genomics Research, Harvard University, Cambridge, MA, USA

Pierre De Meyts, Novo Nordisk, Denmark

Prof. Lucila Ohno-Machado, Harvard Medical School, Cambridge, MA Brigham and Women's Hospital, Boston, MA, USA

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

Prof. Corrado Priami, President and CEO of The Microsoft Research - University of Trento, Centre for Computational and Systems Biology, Italy

Prof. Ilya Shmulevich, Institute for Systems Biology, Seattle, WA, USA

Dr. Michael Stumpf, Centre for Bioinformatics, Imperial College, UK

Prof. Hans Westerhoff, Manchester Centre for Integrative Systems Biology, UK

For more details of the First International Workshop on Systems Biology see the web page http://www.hamilton.ie/sysbioworkshop2006 and the photo-gallery in this report.

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. However, Science Foundation Ireland has now begun to support the Challenge by supplementation of PI grants in the Hamilton Institute. With support from SFI the future of the Maynooth Mathematics Challenge is assured for the next three years. Under the new funding mechanism, Oliver Mason coordinates the Challenge with support from Mark Verwoerd and many other Hamilton Institute staff. More details of this activity are to be found on the Hamilton Institute website.

New Initiatives

We are pleased to be part of the proposed National Bio-Photonic Imaging Programme submitted under the Higher Education Authority strategic planning programme (PRTLI) in May 2007. This pan-university programme is a coordinated research and infrastructure plan for non-invasive bio-medical imaging using a wide range imaging modalities. The Hamilton Institute Systems Biology Group organised and will coordinate the ‘image to mathematical model transition’ core of the proposed Bio-Photonic Programme. We are also partners in two systems biology collaborations under the EU Framework 7 programme.

Systems Biology RP Grant: Site Visit and Review

In August 2006, Science Foundation Ireland conducted its mid-term review of our programme. This comprised a detail written submission from the Systems Biology Group, followed by a site review by a panel of international experts. The team’s efforts were rewarded with a ‘very good’ assessment from the panel, accompanied by supportive comments and constructive suggestions for further improving our programme. We express our appreciation to the panel of expert reviewers for the time, care and professionalism that they gave to the task of assessing our programme.

External Talks and Visits

Members of the group have visited numerous other institutes over the year and a full list of such visits in given in later in this report. Among these visits some deserve especial mention. First, we were privileged in September 2006 to be a guest of the Rector of the University of the University of Guadalajara, Mexico and speak as part of their 'Catedra Neal R. Amundson' lecture series. These lectures, given annually, are in celebration of the scientific contribution of one of the university's most important scientific mentors and benefactors – Neal Amundson.

This was followed in Spring 2007 by our participation at a special INIRA/NSF Workshop on Systems Biology held in Toulouse. Eric Bullinger represented the Systems Biology Group at this meeting and the Springer Verlag volume of the lecture texts has appeared from Springer-Verlag. Eric Bullinger and Peter Wellstead were also invited speakers on systems biology at the UK Research Council Postgraduate Summer School in the autumn of 2006.

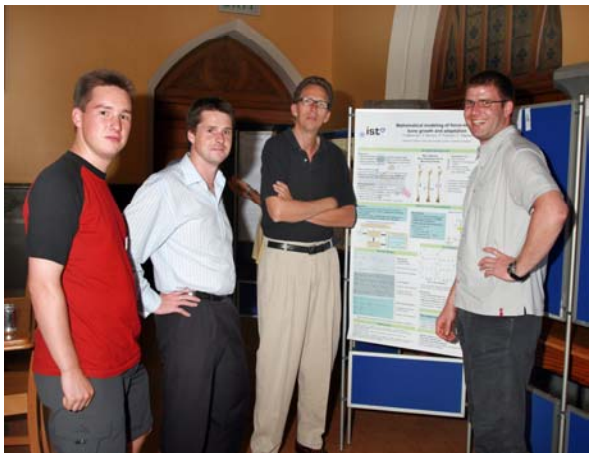
Finally, we gave two plenary talks on systems biology, with special emphasis of the work of our group at (a) CONCIBE 2006 and (b) an audience made up from the delegates to the International Federation for Automatic Control (IFAC) Symposia DYCON 2007 and CAB 2007. The text of this last talk, entitled 'The Role of Control and System Theory in Systems Biology', completes the cycle of general lectures and articles that started with Schrödinger's Legacy. Printed versions of this text are available from the Hamilton Institute Administrative Office or electronically as detailed below under 'Web Resources'.

Web Resources

Over time our Systems Biology Group web masters have assembled a range of useful systems biology resources on our group 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 scope of systems biology at the Hamilton Institute is spreading beyond that funded by this grant, as this happens we will add links to other related activity at the Hamilton Institute.

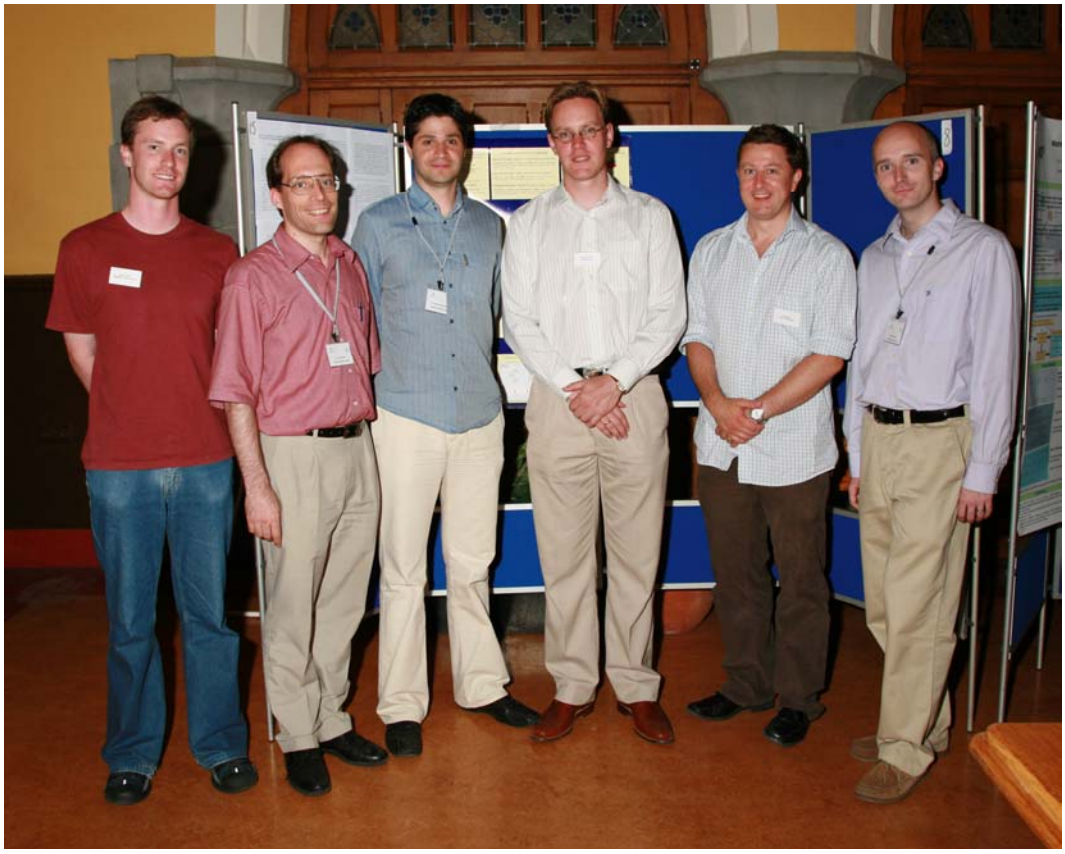
Photo Gallery

Saint Patrick's College, Maynooth, Location for the First International Workshop on Systems Biology, NUI Maynooth, July 2006



At the Workshop Poster Session in the Pugin Hall of St Patrick's College

Plenary Speakers at the Workshop outside St Patrick's College
(From left to right, Brian Ingalls, Micheal Stumpf, Roy Kishony, Hamid Bolouri, Elling Jacobsen, Lucila Ohno-Machado, Neil Benson, Hans Westerhoff with Peter Wellstead)



The Workshop organising committee with industrial speaker Neil Benson
(From left to right, Stuart Butler, Eric Bullinger, Dimitris Kalamatianos, Mark Verwoerd, Neil Benson and Oliver Mason)

Catedra Admundsun, Rectory Building, University of Guadalajara

The Rectory Building, University of Guadalajara

With the Rector of the University of Guadalajara

Project Overviews

As described elsewhere in the report, the work of the Systems Biology Group at the Hamilton Institute falls into three themes:

(i) Modelling and Analysis of Cell Signalling,
(ii) Dynamics and Networks in Biology and
(iii) Bio-Sensor Signal Processing.

These thematic areas overlap significantly and have an underlying a wish to illuminate the mechanisms of neurodegeneration. 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.

Theme 1: Modelling and Analysis of Cell Signalling

The aim of this project is the design of mathematical models for specific biological systems as well as the development of general methodologies that can compactly describe the characteristic dynamical behaviour of inter and intra-cellular signalling. Signalling is often highly complex due to large numbers of involved components as well as the importance of quantitative and dynamic effects.

Mathematical modelling requires close collaboration with experimentalists. The resulting models allow testing of the consistency of biological hypotheses with each other and with experimental data. Particular biological systems under study are the pathways leading to, or preventing, apoptosis, the control of the metabolism in the neuron-glia-symbiosis and the regulation of the contraction of sponges.

Project Overview: The modelling of caspase dynamics during apoptosis

Apoptosis is a form of programmed cell death, and its correct regulation is essential for healthy organisms as mis-regulation can lead to severe pathologies. For example, up-regulation of apoptosis is present in neurodegenerative diseases while cancer reduces the rate of cell deaths.

The process of apoptosis is irreversibly started when a sufficient number of active effector caspases is present in a cell. After a pro-apoptotic stimulus, for example using the cytokine TNFα as extra-cellular signal, the number of active caspases slowly increases in a cell population, but quickly within individual cells. We are currently expanding the model to include other pro-apoptotic pathways as well as anti-apoptotic pathways and validating it with experimental data obtained by Monica Schliemann of the University of Stuttgart (Peter Scheurich).

Project Overview: Cell population modelling

Unsynchronised cells are common in biological application. Modelling the biochemical reaction describes a single cell, which can be qualitatively much different from the average cell. Information on a single cell level can help generating a family of single cell models that reflects both the behaviour of

individual as well as of the whole population. In collaboration with Prof. Mohamed Al-Rubeai (UCD) we develop models of Chinese hamster ovary (CHO) cell cultures combining single cell metabolism, cell cycle information via flow cytometry and extracellular concentrations. This project is unconnected with UCD's proposals for a centre for systems biology research.

Project Overview: System identification

Signalling pathways are often complex and contain many different components. The system behaviour is not only defined by the structure of the system, but also by the values of the system parameters. These parameters are usually hard to obtain directly from experiments. We are currently developing system theoretical approaches for estimating parameters of biochemical reaction networks taking explicitly into account the mathematical peculiarities of these networks.

Theme 2: Dynamics and Networks in Biology

Introduction

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 mathematical models for such 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.

Theme 2a: Analysis of biological interaction networks

At the time of the previous annual report, we had completed a comprehensive survey of graph theoretical methods in Biology. The resulting paper 'Graph Theory and Networks in Biology' has now been published in the journal IET Systems Biology.

In the latter half of last year, we carried out an analysis of the growth properties of a class of Duplication-Divergence network models for proteome evolution. This work combined mathematical analysis and computational simulation, and was carried out in collaboration with a visiting student, Tim Rutjes. Much of the work pertains to the existence and evolution of a 'giant' component in protein-protein

interaction networks. The results of these investigations have been accepted for publication at the FOSBE conference in Stuttgart in September 2007.

To date, we have focussed on the simple model of Vazquez and co-authors[3]. In the future, we hope to develop this line of work by extending our results to more complex and realistic models. In particular, we would like to study the evolution of a giant component in models that allow for the addition of new links as well as the removal of existing ones during the evolution of the network. We shall continue to focus on the evolution of a giant component for such models and to investigate the connection between local clustering properties, the existence of certain small subgraphs and cliques and the evolution of a giant component.

Recently, in collaboration with Professor R. Middleton and a visiting student, Andres Peters, we have begun to investigate the role that different cyclic structures in interaction networks play in the emergence of dynamical behaviours such as multistability and oscillations. In particular, we are currently developing algorithms to automatically search such networks for structures likely to be associated with these behaviours.

Theme 2b: Network topology and dynamics

The second strand of this research theme, as outlined in the Annual Reports for 2004-2005 and 2005-2006, concerns the study of network dynamics, with a view to applications in the modeling of intercellular communication. We have investigated the emergence of synchronisation in systems of coupled oscillators, and (as reported in the Publications section) have derived a number of novel results. The novelty of these contributions pertains to the problem setting: as opposed to the vast majority of papers in the existing literature, we start from a finite-dimensional system description; that is, we focus on systems with finitely many oscillators.

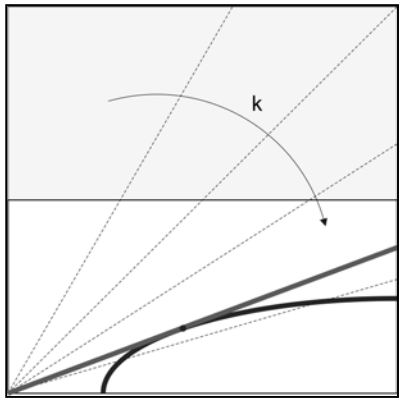


Figure 1 The critical coupling is the smallest coupling for which the curves have at least one point of intersection

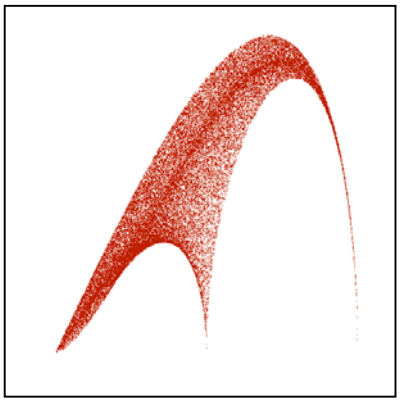


Figure 2 Diagram for assessing stability in a 4-oscillator system

There are a number of well-established mathematical models of synchronisation, the properties of which have been studied for many cases. Surprisingly however, most of the results reported to date pertain to a setting wherein the size of the population is assumed to be infinite (or tending to infinity – the so called thermodynamic limit). As a result, finite-size effects are still relatively poorly understood.

Given that biological systems are necessarily finite, there is a clear need for a finite-dimensional theory of synchronisation, if only to understand the limitations of the mean-field theory associated with the continuum approach. It is our aim to contribute to such a theory. So far our focus has been on deriving conditions for the existence of so called global phase-locked solutions (GPLS). We have shown, for all finite networks in a given class, there exists a criticial value for the coupling strength, such that, when the coupling strength is greater than this critical value, the system

[3] Vazquez, A. et al. Modeling of protein interaction networks. ComPlexUs:38–46, 2003

has at least one GPLS, while no GPLS exists when the coupling strength is less than this critical value. We have derived theoretical lower and upper bounds on this critical coupling, and we have shown that the critical coupling can be found numerically by finding the solution of a particular scalar equation, which, as we have shown, can be done very efficiently. incidently, we have also gained insight in the dynamics of synchronisation, specifically in the rate at which trajectories converge to a phase-locked state. More precisely, we have shown that, for a system of identical oscillators, the evolution of the magnitude of the order parameter is upper bounded by the solution of a particular scalar differential equation.

Our plan for the next year is to extend this work and apply it in the following ways:

1. *Investigate the dependence of the critical coupling on the shape of the distribution of oscillator frequencies*. We have derived bounds on the critical coupling in terms of simple population statistics like maximum absolute deviation from the mean and sample standard deviation, among others. Using the scalar equation referred to above, we can derive many other, and potentially more meaningful, bounds in term of higher-order moments of the frequency distribution.
2. *Study the statistical properties of the critical coupling as a function of different distributions and different population sizes*. For a given distribution of compact support, we can compute or approximate the expected value of the critical coupling, in some cases even analytically. In addition, we can derive bounds on the second- and higher-order moments in terms of the number of oscillators. In particular, we can show that the critical coupling converges in probability to its expected value as the number of oscillators tends to infinity.
3. *Relax the assumption of all-to-all coupling to allow for arbitrary weighted connections*. Preliminary results have been obtained for rings and complete bi-partite graphs.
4. *Replace the current one-dimensional model with more realistic dynamic models of biological oscillators*. Our focus will be on models of glycolytic oscillators in yeast. Under particular experimental conditions, dense suspensions of yeast cells exhibit synchronized oscillatory behaviour. The literature on this phenomena contains a wealth of experimental data, both qualitative and quantitative, as well as a variety of mathematical models describing the same. This case study will help us determine how well our theory of synchronisation applies to real biological phenomena. Interestingly, in a typical experimental setting, the coupling between yeast cells can be assumed to be homogenous, which suggests that the results obtained in previous work can indeed be usefully applied here.

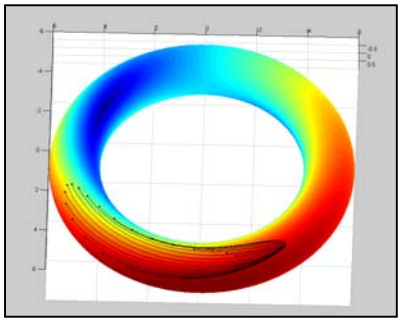


Figure 3 Converging trajectories on the 2-torus

In general, our aim is to adapt the formal framework we have developed over the past year in such a way as to make it more applicable to real biological systems. As said, we shall focus our attention on the mathematical analysis of glycolytic oscillations in yeast.

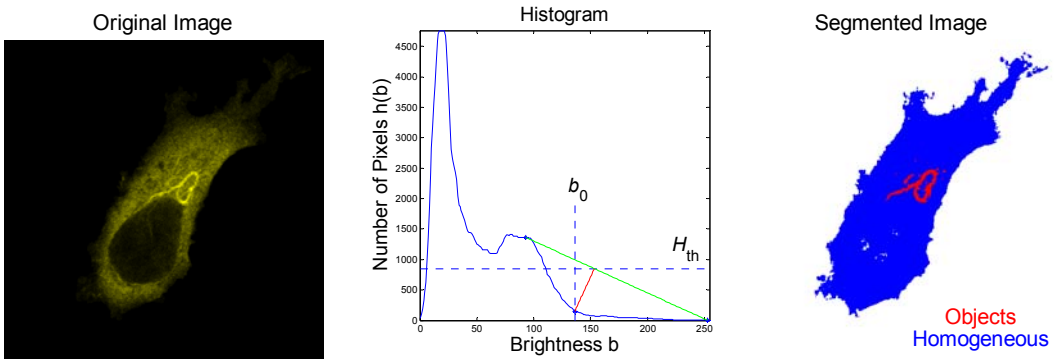
Theme 3: Bio-Sensor Signal Processing

Project Overview

This project focuses on bio-medical signal processing, the robust extraction of information from diverse data sources, and mathematical modelling and estimation. Current research thrusts include:

High-throughput image processing

High-throughput image analysis is a powerful tool for the analysis of large cell-based screens for different subcellular localization patterns of transfected fluorescently labelled fusion proteins. We have developed a software approach for the automated analysis of imaging data obtained from a Filament Interaction Trap (FIT) assay and classify the various types of molecular interaction by fluorescence pattern classification. Our approach is divided in three steps. First, the boundaries of the individual cells are identified and the image is segmented accordingly. We use whole cell staining and a pyramid linking approach on the analysis side to find the cell boundaries by expanding an initial contour from the nucleus. The second step consists of detecting subcellular objects by using a modified triangle algorithm to detect the intensity limit of the background in the intensity histogram of the image (see image below). The last step groups neighbouring pixels and classifies the cells using characteristic properties such as average intensity, number of large groups and their size, etc. Then, supervised or unsupervised classification techniques, e.g., hierarchical clustering or linear discriminant analysis, can be applied to the cell characteristics, to classify the cells into different categories according to their properties.



Non-invasive blood analysis

In order to support non-intrusive measurement techniques for real-time and on-line measurement of certain bio-molecules, special signal processing methods are required. This will enable us to extract quantitative information on bio-molecules from noisy non-contact sensing data. To this end, we use multivariate statistical methods; both supervised and unsupervised, for the analysis of near-infrared spectroscopic data from blood substitutes, such as creatinine, urea and glucose. Emphasis has been given on the use of discriminant analysis and feed-forward ANN's, specifically radial-basis functions neural networks.

Image processing and mathematical modelling for time series data from heterogeneous bio-imaging sources

Normally, images are processed and enhanced one-by-one, whereas many bio-photonic measurement modalities produce image sequences or movies. This task will produce equivalent time/space series data from movie/image sequences that

can be used for dynamical/spatial model identification. The challenges here include optimal information extraction and noise rejection. Combining different quantitative and qualitative images and movies into a common framework is possible with mathematical modelling. We aim to develop both prior models of shape and geometry in scenes and to use these models for statistical inference, reasoning, and estimation. This project fits with the needs of the proposed National Bio-Photonics and Imaging Platform, as described earlier in this report.

General 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. He is now completing his assessment with the neuro-pharmacology teams and preparing to submit his PhD thesis in the autumn of 2007.

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

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 results of this work are currently in the process of publication and, in collaboration with Cameron Wellard of WEHI, is presently being developed further to encompass predictions of cell differentiation during proliferation.

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

This project aims to uncover optimality principles that can describe the performance and structure of metabolic networks and their associated dynamics. Specifically, metabolic networks consist of interconnected biochemical reactions catalyzed by a set of enzymes. 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.

In this framework, a natural fusion between biology and control and systems theory arises. The concept of optimizing dynamical systems is well known in the control theory community and well established techniques have been developed throughout the years, leading to landmark results in a broad range technological applications. The use of these control theoretic techniques in biology may lead to new interesting results, or perhaps stimulate the development of new theoretical concepts. In either case, establishing optimality principles would provide valuable insights into kinetic and structural properties of metabolic networks and provide a framework for generalisation of results.

Project Description: Parameter estimation in biochemical reaction networks (contact: Dirk Fey)

A vital part of mathematical modelling is the accurate and reliable estimation of the model parameters. In biology, the required parameters are particularly difficult to measure because of either weaknesses in the measurement technology or a lack of direct measurements. In the latter case, parameters must be estimated from indirect measurements, usually in the form of time-series data, which are themselves sparse and noisy. The objective of this project is to address this problem by developing novel estimation methods that are particularly tailored to biological models consisting of nonlinear ordinary differential equations. Approaches taken in this project assume specific types of nonlinearities, such as generalized mass action, Michaelis Menten and Hill kinetics, and then use a suitable model extension that decouples the estimation of non-measured states from the parameters. This allows a two-step approach: (1) reconstruction of all extended states; (2) estimation of the parameters using these reconstructed states. An important advantage of the proposed method is that it allows us to identify suitable measurements and/or model structures for which the parameters can be estimated. In addition, it is generally applicable to models of metabolic networks, signal transduction and gene regulation.

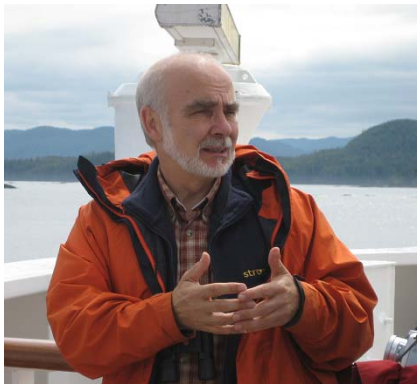
The Systems Biology Group

Core Team Members

Peter Wellstead

SFI Research Professor

peter.wellstead@nuim.ie



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

SFI Postdoctoral Researcher

eric.bullinger@nuim.ie

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.

In January 2005, he joined the Systems Biology Group at the Hamilton Institute. Currently, 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. Eric is a tenured faculty member at NUIM.

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. Exemplarily, Eric is developing novel system identification algorithms with Dirk Fey and modelling pro-and anti-apoptotic signalling pathways with Monica Schliemann (University of Stuttgart) and Steffen Borchers.

Dimitrios Kalamatianos

SFI Postdoctoral Researcher

dimitris.kalamatianos@nuim.ie

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.

Oliver Mason

SFI Postdoctoral Researcher

oliver.mason@nuim.ie

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. Since June 2004, he has been a member of the Systems Biology Group at the Hamilton Institute. 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.

Mark Verwoerd

SFI Postdoctoral Researcher

mark.verwoerd@nuim.ie

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

stuart.butler@nuim.ie

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.

Dirk Fey

Research Assistant

Dirk.fey@nuim.ie

Dirk Fey joined the Hamilton Institute in January 2007 as a PhD student, after graduating from the University of Stuttgart in engineering cybernetics. Under the supervision of Eric Bullinger he is developing parameter estimation algorithms for biochemical reaction networks.

Diego Oyarzun

Research Assistant

diego.oyarzun@nuim.ie

Diego joined the Hamilton Institute in 2006 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.

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, his developing the mathematical aspects of his the hypothesis that lymphocytes behave as if composed of separate independent 'machines' with stochastic features that govern times to divide and times to die and the rate of differentiation in association with division number with Hamilton Institute colleagues Ken Duffy and Vijay Subramanian, and a generic cell model for cell fate processes with Mark Verwoerd and Eoin Mulholland.

Steffen Borchers

Population modelling of apoptotic signalling pathways

steffen.borchers@web.de

Steffen Borchers is a visiting student at the Hamilton Institute since March 2007. Under the supervision of Eric Bullinger and Monica Schliemann, he carries out the final project (Diplomarbeit) of his studies in engineering cybernetics for the University of Stuttgart. His topic is the modelling and analysis of biochemical reaction models based on heterogeneous cell population data as obtained for example from Monica.

Thomas Eißing

A Systems Science View on Cell Death Signalling

eissing@ist.uni-stuttgart.de

Thomas Eißing studied technical biology at the University of Stuttgart and is currently a PhD student in the Institute for Systems Theory and Automatic Control of the University of Stuttgart, supervised by Eric Bullinger. Thomas came to the Hamilton Institute twice, in July 2006 and April 2007 to work on joint publications as well as on his PhD thesis, which he submitted in June 2007.

Eoin Mulholland

Visiting Research Student

eoinmul@gmail.com

Eoin Mulholland is a visiting student from the University of Cambridge) at the Hamilton Institute between May and August 2007. Under the supervision of Mark Verwoerd he is working 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 is 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.

Tim Rutjes

Visiting Research Student

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Tim.rutjes@nuim.ie

Tim Rutjes visited the Hamilton Institute from August to December 2006 as an intern student from the Eindhoven University of Technology. Tim's work was concerned with the mathematical properties of random growing network models for the evolution of protein interaction networks. In particular, he combined theoretical and numerical techniques to study the growth of giant components in duplication-divergence models, and also analysed certain key statistical parameters of such models, including degree distributions and betweenness centralities. The work of Tim's project will be published in the proceedings of the 2007 conference 'Foundations of Systems Biology in Engineering' (FOSBE).

Monica Schliemann

TNFα-induced pro- and anti-apoptosis signalling: modelling and experimental validation

monica.schliemann@izi.uni-stuttgart.de

Monica Schliemann visited the Hamilton Institute in August/September 2006. In the final project (Diplomarbeit) of her studies in technical biology at the University of Stuttgart, she developed a mathematical model of the TNFα-induced pro- and anti-apoptosis signalling, co-supervised by Eric Bullinger. She is currently a PhD student in the Institute of Cell Biology and Immunology, University of Stuttgart, in the group of Prof. Peter Scheurich. In collaboration with Eric Bullinger, she is currently enhancing the model as well as validating it by performing quantitative time-series experiments.

Thomas Schröck

Visiting Research Student

Thomas.schroeck@nuim.ie

Thomas Schröck is a visiting student at the Hamilton Institute between June and December 2006. Under the supervision of Eric Bullinger he carried out the final project (Diplomarbeit) of his studies in technical cybernetics for the University of Stuttgart. In his project, Thomas developed mathematical models of Chinese hamster ovary (CHO) cell cultures. His mathematical models aimed at fusing data from the different measurement sources and the checking of whether the data are compatible with biological hypotheses. This project is part of a collaboration between Prof. Mohamed Al-Rubeai of UCD Dublin and Eric Bullinger.

Gerd Simon Schmidt

Finite Time Lyapunov Exponents in Systems Biology

schmidtg@ist.uni-stuttgart.de

Gerd Simon Schmidt was a visiting student at the Hamilton Institute from September 2006 to March 2007. Under the supervision of Eric Bullinger he carried out the final project (Diplomarbeit) of his studies in technical cybernetics for the University of Stuttgart. Gerd analysed the suitability of the newly developed Finite Time Lyapunov Exponents for analysing the sensitivity of mathematical models in systems biology.

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 2006

Institute of Systems Biology, Seattle, USA, August 2006

Strathclyde University, Glasgow, UK, August 2006

University of Guadalajara, Mexico, UK, September 2006

Systems Biology Centre, University of Rostock, Germany, September 2006

Bio-Systems Signal Processing Laboratory, City University of London, UK, November 2006.

Free University of Berlin, November 2006

Imperial College, London, UK, January 2007

Technical University of Berlin, January 2007

University College London, UK, March 2007

Royal College of Medicine, London, UK, May 2007

External Talks by Team Members

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

Current trends in systems biology, **P. Wellstead**, Faculty of Engineering and Mathematics, City University, London, October 2006.

Control theoretical challenges in systems biology, **E. Bullinger**, Faculty of Earth and Bio-Sciences, University of Stuttgart, November 2006.

Control theoretical challenges in systems biology, **E. Bullinger**. Control research group, University of Leicester, 22 November 2006.

Lyapunov stability of time-varying positive linear systems, **O. Mason,** Free University of Berlin, November 2006.

Control theory challenges in biology & medicine, **E. Bullinger,** Faculty of Bioscience, Katholieke Universiteit Leuven, March 2007.

Systems biology: The academic perspective, **P. Wellstead,** INFOTECH for Pharma and Biotech, London, (http://www.infotechpharma-biotech.com/) March 2007.

A systems biology perspective of apoptosis signalling, **E. Bullinger,** UCD Conway Lecture and Seminar Series (CLASS), University College Dublin, May 2007.

Switched Systems and Positivity, **O. Mason,** Technical University of Berlin, January 2007.

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:

Dr. Niko Beerenwinkel, Harvard University

Dr. Neil Benson, Pfizer, UK

Prof. Hamid Bolouri, University of British Colombia, Vancouver, Canada

Prof. Frank Doyle, University of California, Santa Barbara, USA

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

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

Prof. Brian Ingalls, Department of Applied Mathematics, University of Waterloo, Canada

Prof. Elling W. Jacobsen, Automatic Control Lab, KTH Stockholm, Sweden

Prof. Roy Kishony, Bauer Center for Genomics Research, Harvard University, Cambridge, MA, USA

Pierre De Meyts, Novo Nordisk,

Prof. Lucila Ohno-Machado, Harvard Medical School, Cambridge, MA Brigham and Women's Hospital, Boston, MA, USA

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

Dr. Fernando Ortega, School of Biosciences, University of Birmingham

Prof. Michel Perrier, Ecole Polytechnique, Montreal, Canada.

Prof. Corrado Priami, President and CEO of The Microsoft Research - University of Trento, Centre for Computational and Systems Biology, Italy

Dr. Andrea Rocco, Department of Statistics, University of Oxford

Prof. Ilya Shmulevich, Institute for Systems Biology, Seattle, WA, USA

Dr. Michael Stumpf, Centre for Bioinformatics, Imperial College, UK

Prof. Hans Westerhoff, Manchester Centre for Integrative Systems Biology, UK

Dr Henning Schmidt, Fraunhofer Chalmers Center, Gothenburg, Sweden

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:

Noam Shoresh, Systems Biology, Harvard Medical School. *An Equivalence Principle for the Incorporation of Favorable Mutations in Asexual Populations*. July 20, 2006.

Prof. Frank Doyle, Chemical Engineering/Biomolecular Science & Engineering/ Institute for Collaborative Biotechnologies, University of California, Santa Barbara, USA. *Systems Approaches to Robustness Analysis of Circadian Oscillators*. August 22, 2006.

Dr. Michael Nickel, Department of Zoology, Biological Institute, Stuttgart University. *Systems Biology of Sponges – Understanding the evolution of integration in animals – new input from systems biology?* November 23, 2006.

Tim Rutjes. Eindhoven University of Technology. *Duplication-Divergence and Proteome Evolution*. December 6, 2006.

Thomas Schröck, Stuttgart University. *Modelling Mammalian Cell Culture Proliferation*. December 6, 2006.

Prof. Stephen McLaughlin, Signals and Systems Group, School of Engineering and Electronics, University of Edinburgh. *An Investigation of the Empirical Mode Decomposition Based on Genetic Algorithm Optimization Schemes*. December 13, 2006.

Dr. Wilhelm Huisinga, Free University of Berlin. *Metastability of Markovian Systems*. January 18, 2007.

Dr. Andrea Rocco, Department of Statistics, University of Oxford, UK. *Modelling Environmental Fluctuations in Biochemical Systems*. February 21, 2007.

Dr. Fernando Ortega, School of Biosciences, University of Birmingham, UK. *Analysis of Metabolic Responses*. March 21, 2007.

Dr. Phil Hodgkin, Head, Immunology Division, The Walter and Eliza Hall Institute of Medical Research, Victoria, Australia. *Modelling the Immune Response using Probabilistic Concepts.* March 22, 2007.

Dr. Niko Beerenwinkel. Harvard University, *Program for Evolutionary Dynamics. Evolutionary Escape on Fitness Landscapes*. April 25, 2007.

Dr. Phil Hodgkin, Head, Immunology Division, The Walter and Eliza Hall Institute of Medical Research, Victoria, Australia. *Differentiation and Integration by cells: The Cellular Calculus*. May 9, 2007.

Dr. John Moriarty, UCC. *Applications of Probability in Genetics, Ecology and Population Genetics*. May 15, 2007.

Dr. Henning Schmidt, Fraunhofer Chalmers Research Centre (FCC), Gothenburg, Sweden. *Systems Biology at FCC - From Theory to Application.* May 30, 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

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

Information and Biomedical Engineering Centre, City University, London, & Acimetrics Ltd, Manchester University Science Park, UK.

- A novel dual-modality optical and electrical non-invasive system for nerve conduction studies with application to neural degenerative diseases
- Non-Invasive Blood and Tissue Diagnostics using novel digital signal processing methods with a portable, real time, NIR sensor.

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

- 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.

Departments of Experimental Physics & Biology, NUIM, Ireland.

- Optical monitoring of cellular structure during implantation of various DNA material.

Department of Chemistry NUIM, Ireland & Solvay Pharmaceuticals, Weesp, The Netherlands.

- 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:

- Modeling and analysis of Tumor Necrosis Factor signaling 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

UCD School of Chemical & Bioprocess Engineering, Ireland.

Prof. Mohamed Al-Rubeia

- Modelling and optimal control of heterogeneous cell cultures

LaVision BioTec GmbH, Bielefeld, Germany.

Dr. Olaf Selchow

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

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

O Wolkenhauer, M Mesarovic and **P. Wellstead.** *A Plea for More Theory in Molecular Biology*, In P. Bringmann, E.C. Butcher, G. Parry and B. Weiss, editors, *Systems Biology: Applications and Perspectives*, Ernst Schering Research Foundation Workshop 61, pages 117-138, Springer-Verlag 2007.

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.

Journals

T. Eißing, S. Waldherr, F. Allgöwer, P. Scheurich and **E. Bullinger,** *Response to bistability in apoptosis: Roles of Bax, Bcl-2, and mitochondrial permeability transition pores*, Biophys. J., 92, 9, pp3332–3334, 2007

T. Millat**, E. Bullinger,** J. Rohwer and O. Wolkenhauer. *Approximations and their consequences for dynamic modelling of signal transduction pathways*, Math Bioscience, 1, pp40-57, 2007

M. Nickel, **E. Bullinger** and F. Beckmann, *Functional morphology of Tethya species (porifera): 2. Three-dimensional morphometrics on spicules and skeleton superstructures of T. minuta,* Zoomorphology, 125, 4, pp225–239, 2007

J. Vera, E. Balsa-Canto, **P. Wellstead,** J.R. Banga and O. Wolkenhauer, *Power-Law models of signal transduction pathways*, Cellular Signalling, 19, pp1531-1541, 2007

M. Verwoerd and **O. Mason,** *Discussion on Multi-Layer Switching Control using Generalized Sampled-Data Hold Functions*, European Journal of Control, 12, 5, 2007

O. Mason and **M. Verwoerd,** *Graph Theory and Networks in Biology*, IET Journal of Systems Biology, 1, 2, pp89-119, 2007

M. Verwoerd and **O**. **Mason,** *Global Phase-locking in a finite population of phase-coupled oscillators*, Siam Journal of Dynamical Systems, (to appear 2007)

M. **Verwoerd,** G. Meinsma and T. de Vries, *On equivalent feedback: Youla parameterization in Iterative Learning Control*, Automatica, 42, 12, 2006

E. Zeheb, **O. Mason**, S. Solmaz and R. Shorten, *Some results on quadratic stability of switched systems with interval uncertainty*, International Journal of Control, 80, 6, pp825-831, 2006

O. Mason, R. Shorten and S. Solmaz, *On the Kalman-Yakubovich-Popov lemma and common Lyapunov solutions for matrices with regular inertia,* Linear Algebra and its Applications, 420, pp183-197, 2007

L. Gurvits, R. Shorten and **O. Mason,** *On the stability of switched positive linear systems*, IEEE Transactions on Automatic Control, 52, 6, pp1099–1103, 2007

O. Mason and R. Shorten, *On linear copositive lyapunov functions and the stability of switched positive linear systems*, IEEE Transactions on Automatic Control, 52, 7, pp1346–1349, 2006

Conferences and Workshop Proceedings

S. Streif, R. Findeisen, E. **Bullinger.** *Relating cross Gramians and sensitivity analysis in systems biology.* Proc. Int. Symposium on Mathematical Theory of Networks and Systems, pp437-442, 24-28 July, 2006

M. Schliemann, T. Sauter, **E. Bullinger**, T. Eißing, F. Allgöwer, O. Sawodny and P. Scheurich. *Mathematical modelling of TNF induced apoptotic and anti-apoptotic crosstalk in mammalian cells*. In Conference on Systems Biology of Mammalian Cells SBMC 2006, Heidelberg, Germany, 12-14 July, 2006

P. **Wellstead** (invited speaker), *Control theoretical challenges in systems biology*, EPSRC/UKACC Postgraduate Workshop, Glasgow, 24-29 August, 2006

E. **Bullinger** (invited speaker), *Systems Biology*, EPSRC/UKACC Postgraduate Workshop, Glasgow, 24-29 August, 2006

P. Wellstead (invited speaker), *Schroedinger's Legacy and the Industrialisation of Biology*. Catedra Neal R Anderson, University of Guadalajara, 25 September, 2006

P. Wellstead (plenary speaker), *Systems Problems in Cell Biology and Bio-Medicine*. Congresso de Control Aplicado a las Ciencias Biomedicas, 28 September, 2006

P. Wellstead (plenary speaker), *The Role of Control in Systems Biology*. IFAC Symposium on Computer Applications in Biotechnology, and the IFAC Symposium on Dynamics and Control of Process Systems, 4-8 June, 2007

T. Eißing, S. Waldherr, C. Gondro, **E. Bullinger**, O. Sawodny, F. Allgöwer, P. Scheurich and T. Sauter. *Sensitivity analysis of programmed cell death and*

implications for crosstalk phenomena during Tumor Necrosis Factor stimulation, IEEE Conference on Control Applications, 4-6 October, 2006

M. Farina, R. Findeisen**, E. Bullinger**, S. Bittanti, F. Allgöwer and **P. Wellstead,** *Results towards identifiability properties of biochemical reaction networks,* 45th IEEE Conf. on Decision and Control, San Diego, USA, 13-15 December, 2006

M. Verwoerd, *Fixed-Point Analysis of a Finite System of Kuramoto Oscillators*, Fourth Irish Conference on the Mathematical Foundations of Computer Science and Information Technology, 1-5 August, 2006

D. Kalamatianos, P. Liatsis and **P.E. Wellstead,** *Near-infrared spectroscopic measurements of blood analytes using multi-layer perceptron neural networks*, 28th International Conference of the IEEE EMBS, 30 August-3 September, 2006

D. Kalamatianos, **P.E. Wellstead**, P. Liatsis and R.J. Houston, *Control and data analysis tool for a novel FT-NIR spectrometer*, IET International Control Conference, 30 August-1 September, 2006

D. Kalamatianos, *Novel FT-NIR instrumentation for real-time blood monitoring*, Annual Meeting of the Association of Physical Scientists in Medicine, 11-12 May, 2007

E. Bullinger, R. Findeisen, **D. Kalamatianos** and P. Wellstead, *System and control theory allows to further understanding of biological signal transduction*, Proc. CNRS-NSF Workshop Biology and control theory: Current challenges, Toulouse, France, 2006

F. Kämper, O. Selchow, **D. Kalamatianos**, H. Wajant, K. Pfizenmaier, E. Bullinger, *High-throughput image analysis for the classification of subcellular localization patterns of fluorescently labelled proteins*, Proc. International Conference on Systems Biology, Yokohama, Japan, 9-13 October, 2006

O. Mason and **M. Verwoerd**, *Graph Theory and Networks in Biology*, International Conference on Systems Biology, Yokohama, Japan, 9-13 October, 2006

F. Knorn and **O. Mason**, *Protein Interaction Networks, Essentiality and Sensitivity*, Computational Methods in Systems Biology, Trento, 2006

S. Butler, **P. Wellstead**, R.G. Reilly and W.T. O'Connor, *Visualisation and Modelling Neural Transmission in Conscious Brain using an Integrated Workbench*, SFN 2006 - 36th Annual Meeting (Society for Neuroscience), Atlanta, Georgia, U.S.A, 14-18 October, 2006

Scientific Advisory Panel

Professor Peter J. Hunter
Director Bioengineering Institute
University of Auckland
Level 6, 70 Symonds Street
Auckland
NEW ZEALAND
Tel: +64 9 373 7599 x88395
Fax: +64 9 367 7157

Professor Denis Noble CBE FRS
University Laboratory of Physiology
Parks Road
Oxford OX1 3PT
ENGLAND
Tel: +44 1865 272528
Fax: +44 1865 272554

Professor Dr. H.V. Westerhoff
Professor of Microbial Physiology, Free University Amsterdam and Professor of Systems Biology, University of Manchester
CRBCS
FALW
Free University
De Boelelaan 1087
NL-1081 HV Amsterdam
THE NETHERLANDS
Phone: +31 20 5987230
FAX: +31 20 5987229

Professor Olaf Wolkenhauer
Chair in Systems Biology & Bioinformatics
University of Rostock
Albert Einstein Str. 21
18051 Rostock
GERMANY
Tel./Fax: +49 (0)381 498 75 70/72

www.systemsbiology.ie

Hamilton Institute
National University of Ireland Maynooth
Maynooth
Co. Kildare
Ireland

Tel: +353 (0)1 7086100
Fax: +353 (0)1 7086269
Web Site: www.hamilton.ie