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Science Foundation Ireland Research Professor Award 03/RP1/I382

Annual Report 2004 - 2005

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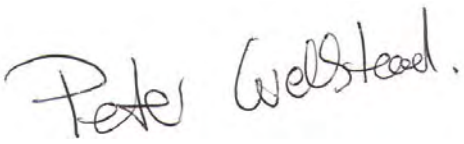
www.systemsbiology.ie

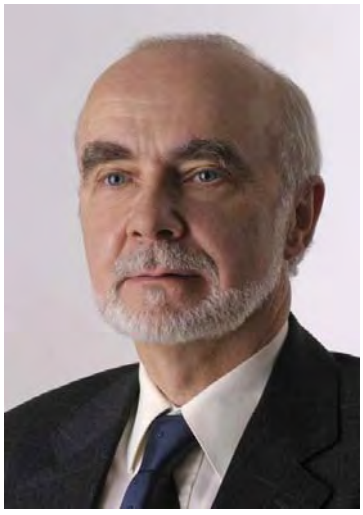
Contents

Preface

This is the first report in a series that describe the contributions of the author and co-workers (colleagues, students and visitors) funded under SFI Research Professorship award 03/RP1/I383. The key aim of the report is to acquaint other researchers with our activities and thus generate the groundwork for collaboration. Beyond this it is intended to supplement the formal progress report required under the terms of the award by Science Foundation Ireland. The report covers the period from July 2004 to June 2005.

For more information on our work, please visit www.systemsbiology.ie. For the Hamilton Institute generally go to www.hamilton.ie. The individual contact points for the Systems Biology team are given in the biography section of this report.





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Introduction

Background

This was the first year of our Science Foundation Ireland (SFI) Research Professor programme, and much of the effort was taken up with recruitment of the research team, working with SFI to build an awareness of Systems Biology in Ireland, and initiating our own research programmes and collaborations in this exciting new area. The field of Systems Biology is new in many respects, but mainly because it represents a different way of thinking about and organising research in the life sciences. It is the author's belief that a systems approach will have profound ramifications for our society - ramifications that will rival those that followed the systematisation of manufacture that was started by the Industrial Revolution. To be specific, in the previous century and before, we developed and refined methods of rapidly and accurately sensing variables. This was complemented by sophisticated methods for processing the signals from the sensors, and using the information derived to analyse the underlying behaviour of physical and technological systems. Using sensing technology, signal processing techniques, and methods invented for the analysis and control of system dynamics, the process of research and development in the physical sciences and industry was greatly enhanced. Not only was the pace of research and development improved, but the systematic techniques that were developed also added to the commercial competitiveness of the developed world. Transposing this 'systems' methodology to the life sciences is the core mission of Systems Biology. This will not be easy, as it involves establishing novel interdisciplinary work patterns that span biology, chemistry, physics, engineering, systems theory, applied mathematics and computation. Nonetheless, it is a prize worth aiming for.

Systems Biology is a new but rapidly growing subject. It has received very large investments internationally, whereas nationally we are just starting in this process. For example, this Research Professor award in July 2004 marked Science Foundation Ireland's first investment in Systems Biology. Since then it has been satisfying to see the speed with which an awareness and interest in Systems Biology has grown in the scientific community, and the effectiveness that SFI have shown in building on this interest.

Lastly, and on a personal note, it is a pleasure to acknowledge the support of Science Foundation Ireland and NUI Maynooth in providing a stimulating, energetic and scientifically excellent research environment for this work in the form of the Hamilton Institute. The Institute is a superb environment in which to do research, and it is a pleasure to be part of the Institute as it strengthens and grows.

The Programme Plan

The overall research programme addresses topics in the area of Systems Biology with two research strands: **Analysis and Modelling** and **Bio-Sensor Signal Processing** as follows:

Systems Biology: Analysis and Modelling

The key objective of the author's Research Professor programme is to establish a Systems Biology research team in the Hamilton Institute that reaches international standards. 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 proposal to SFI in early 2003), considered to be an emerging discipline. Within this context, our plan is for the Hamilton Institute to be a predominantly 'dry' Systems Biology laboratory, performing *in-silico* studies of biological problems and working in collaboration with biologists both nationally and internationally on relevant problems. In this spirit, the Analysis and Modelling for Systems Biology activities that we have established over this first year focus on research into the underlying systems theory and applied mathematics required to understand dynamical mechanisms in biology, disease and healthcare. In the author's view this dynamical systems approach is an essential complement to high throughput 'omic' measurement, and is an area where the Hamilton Institute is strategically placed to play a useful role.

More specifically, and based upon exhaustive measurement and data collection, work in genomics, proteomics and bioinformatics is providing a detailed categorisation of biological behaviour. However, the assembly of purely static data in this way is insufficient to describe the complexity of biological behaviour associated with the nonlinear spatio-temporal dynamics that determine the fate of living organisms. Thus there is a compelling need for mathematical methods that describe biological behaviour in ways that allow inference and prediction of organism dynamics in a biologically informative manner and over a biologically and clinically meaningful time course.

In addition, we need methods for determining suitable model structures and parameters, and analysing their performance in a way that increases our understanding of the underlying biology. Only by use of such models can we extrapolate and infer beyond what can be directly measured in the 'wet' laboratory.

Systems Biology: Bio-Sensor Signal Processing

The second research strand is aimed at developing theoretically sound and technically appropriate signal processing methods with which to extract information from the wide diversity of bio-sensors that are being investigated 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 bio-sensors it is not possible to setup comprehensive and credible mathematical models of the associated biological processes. In the same spirit, signal processing methods must be especially designed to extract information which is truly relevant for mathematical model building.

There are currently two 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[1]. 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 bio-sensor signal processing work is at formative stage of development and concerns the interpretation of signals from electrical and microdialysis probes used to measure neurotransmitter concentrations in the brain. These and other projects are explained in more detail later.

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 relevant ***generic*** research areas:

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

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

(c) The sensor signal processing and analysis methods required to obtain biologically meaningful information from the new forms of bio-sensors currently under development.

Working in collaboration with biologists, bio-chemists and others, we will use these generic systems skills in specific biological ***application*** studies to provide an analytical basis of observed biological behaviour 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 to the understanding of neurodegeneration. This objective is supported by a plan to develop appropriate generic systems skills and employ them in collaborative applications to relevant biological problems.

The Systems Biology group at the Hamilton Institute

1 Real time measurement is crucial for building and parametrising dynamical models. The non-invasive nature of the technique means that measurements can be made non-destructively.

Review of the Year

General

As noted in the introduction, a lot of effort was spent recruiting, setting up our programme and establishing collaborations. Dr. Oliver Mason was recruited on July 1st and took up primary responsibility for developing the graph theoretic aspects of the research programme. Dr. Dimitris Kalamatianos joined the team later in December 2004 and to pursue the area of bio-sensor signal processing. Stuart Butler joined the team in September 2004 as a Ph.D. student jointly supervised by William O'Connor of UCD, Ronan Reilly of Computer Science NUIM, and the author. Stuart is working on visualisation and modelling tools for neuro-transmitter data collected by William O'Connor's neurological bio-sensor team. Dr. Eric Bullinger joined the team in January 2005. He was initially on leave of absence from the Systems Biology group at the University of Stuttgart, but is now a permanent team member with primary responsibility for the inter and intra-cellular dynamics area. He retains a visiting position in Stuttgart and collaborates with the Stuttgart apoptosis research group. Mark Verwoerd joined the team in February 2005. He was previously in the control theory research group at University of Twente, the Netherlands, and at the Hamilton Institute his interests include graph methods, synchronisation in bio-systems, and theoretical issues in pathway modelling related to neurodegeneration.

Setting up collaborations was done at two levels: national and international. At the national level, we have successful established links with the Department of Biology at NUI Maynooth, The Royal College of Surgeons Ireland, and the Conway Institute of Biomolecular and Biomedical Research, UCD. At Maynooth we are in the process of setting up a programme with Dr. Bernard Mahon of the Institute of Immunology on issues in cell signalling dynamics. With the Conway Institute of Biomolecular and Biomedical Research we have established a good working relationship with Dr. Keith Murphy and Dr. William O'Connor. Both Keith and William paid several visits to the Hamilton Institute over the year and gave an introductory series of lectures on issues related to their work in neuropharmacology. In the area of apoptosis research, we are working with the group of Professor Jochen Prehn of the Royal College of Surgeons Ireland.

Internationally, our closest working links are with the Bio-Max Centre in Korea, the University of Rostock and the University of Stuttgart. The later is supported by Eric Bullinger's collaboration with the Institute for System Theory in Engineering on the modelling of apoptosis. Within Ireland generally we have an outreach programme that is currently being driven by a series of workshops, visits to other universities for seminars and facilitation meetings on Systems Biology with various research groups.

Visitor Programme

There were many short-term visitors (see separate list), but three people stayed for a relatively long term. The first two were visiting academics - Professor Kwang-Hyung Cho from the Korea BioMax Centre, Seoul, and Dr. Stephen Duncan of the Engineering Department of Oxford University, England, visited over the late summer of 2004. Professor Cho's special interests are in intracellular signalling, their dynamics and structural estimation. During his stay we worked together on a pathway model for the indirect motor circuit [17], and began a dialogue that subsequently led to joint work with both Wolkenhauer's group, [23,24,26] and

Professor Cho's team at Bio-Max, [26]. In addition, Prof. Cho gave a series of tutorial lectures on kinetics of cellular reactions that were attended by Hamilton Institute staff, colleagues from the Department of Biology NUIM and the Conway Institute of Biomolecular and Biomedical Research, UCD.

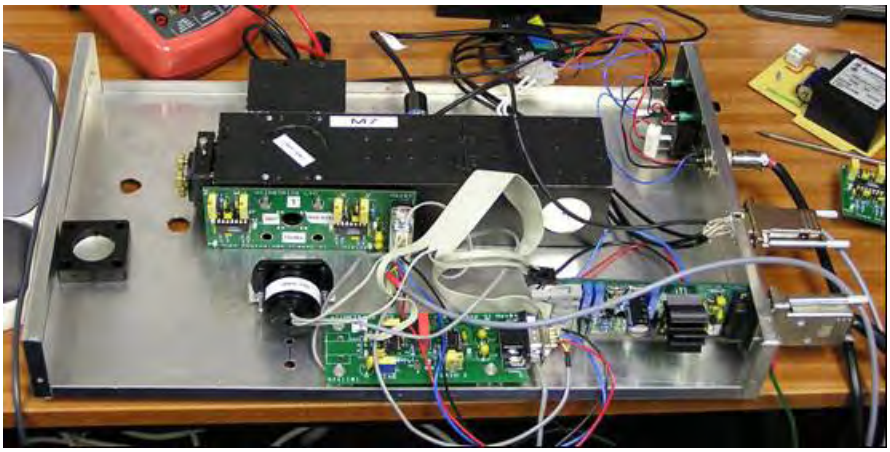
Dr. Duncan's visit was to allow collaboration on biological interaction phenomena and to work on the dynamics of population in epidemics. These are relevant to our interests, since the dynamics of populations are related, be they at the cell or total organism level, to our interests in graph and network methods in biology. The collaborative work with Dr. Duncan is at a formative stage and we expect this to evolve further as our programme evolves.

Last, but not least, an exchange Masters student, Florian Knorn from the University of Magdeberg, worked with Dr. Mason on concepts in interaction networks. Specifically, he carried out numerical studies of the sensitivity of various network centrality measures to missing or inaccurate data. This issue is of considerable importance given the high level of false positives and false negatives present in many biological datasets. In particular, he studied the impact of randomly adding, removing and rewiring edges on a number of classical and recently proposed measures of a node's importance in a network. For the study, real biological data on the protein interaction network in *S.cerevisiae* was used as well as random models of complex networks such as the Barabasi-Albert model.

Events

Elections and Patents

During the reporting period the author was elected as Visiting Professor at the City University of London. In addition, we were informed that our patent application for a novel method for automatic alignment for two beam interferometers passed the PCT investigation stage and had been awarded. This patent is an important enabling tool for the development of small portable two-beam interferometers suitable for bio-sensing based on NIR transmission and backscatter. As described elsewhere, we hope to develop this technology as a non-invasive, non-destructive sensor for on-line real-time measurement of certain bio-molecular concentrations.



Prototype Active Control Michelson Interferometer

Schrödinger's Legacy

As part of the Hamilton Bicentenary Celebration the author presented the E.T.S. Walton lecture 'Schrödinger's Legacy' at the Royal Irish Academy on April 21st, 2005. The lecture was planned and presented as a scientific awareness exercise for Systems Biology. By tracing the origins of Systems Biology back to Erwin Schrödinger's period in Ireland, and in particular his lecture series 'What is Life?', we were able to describe the development of Systems Biology, and provide a guided tour of current research problems and future directions for the systems approach to biology. The lecture text is available at www.systemsbiology.ie and a video of an edited version of the lecture is included in the back fold of this report. Our plan is that this lecture will be updated from time to time, and reused both here and overseas as a public relations tool for our research programme in Systems Biology.

'Schrödinger's Legacy' at the Royal Irish Academy

First Irish Systems Biology Workshop

During the year Science Foundation Ireland began considering further investment in Systems Biology. As part of this process, Leroy Hood and colleagues from the Institute of Systems Biology at Seattle were invited to visit Ireland in June 2005. As part of this visit, and on behalf SFI and IDA, the Hamilton Institute hosted the **First Irish Systems Biology Workshop.** This one-day event was held in the John Hume Building at NUI Maynooth with attendees from biology departments in all the universities. The Workshop's keynote address was given by Dr. Hood, and after general presentations by Dr. Hood's colleagues, each university was given the opportunity to indicate how it's life science research programme might benefit from a systems biology approach. Like the Schrödinger lecture before it, this Workshop had awareness as a key purpose, and in the sequel the **Second Irish Systems Biology Workshop** was announced for September 2005. Our formal report on this has been filed with Science Foundation Ireland, and an informal description will follow in the next annual Research Professor report.

Leroy Hood in conversation with delegates at the first Irish Systems Biology Workshop

Project overviews

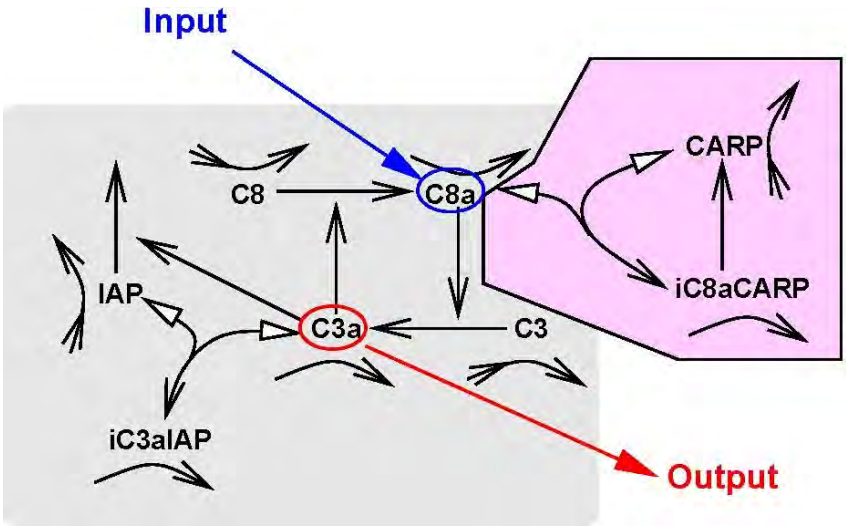
In this section we give a brief review of some of our current projects. The review is not comprehensive, so we apologise to collaborators who's work is not mentioned. The aim is not to give an encyclopaedic cover, but a series of snapshots which show how we are addressing the overall project strategy of building generic knowledge and applying it to particular applications which have a general relevance to our global aim – e.g. a systems understanding of neurodegeneration. Specifically, the research themes outlined below have the potential for general benefit as Systems Biology contributions to the life sciences, but they also have particular relevance to neuro-degeneration. For example, a central feature of degeneration in the brain is the death of neurons. Therefore, a systems understanding of apoptosis (see theme 1) will be of direct value to brain researchers concerned with the reasons for neuronal die-off. Likewise, the analysis of the network properties of organisms and the bio-molecular components (see theme 2) has general application in biology. However, it has particular relevance to the hugely complex and highly interconnected network of cells that is the brain, and how changes in connectivity may be related to degeneration.

Bio-sensing is, we believe, a fundamental enabling technology for Systems Biology. Without the ability to measure the behaviour of cells and organisms in real-time and on-line, then our mathematical analyses must rely upon clever inference and indirect measures of biological behaviour. In theme 3 – Bio-sensor Signal Processing – we describe our work on non-invasive sensing, an area of the highest importance for the study of brain behaviour. The last project described specifically addresses part of our collaboration with Dr. W. O'Connor and Dr. K. Murphy on analysing the concentrations of neurotransmitters in the brains of rats that are subject to neurodegenerative disorders.

Theme 1: Cell Dynamics

The aim here is to develop 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. For checking whether biological hypotheses are consistent with each other and with experimental data, we develop mathematical models of specific signalling pathways. Particular biological systems under study are the pathways leading to or preventing apoptosis, a form of programmed cell death, as well as their interplay. Correct regulation of apoptosis 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.

As the models are nonlinear and themselves complex, simulation studies are not enough to discover the system properties of the models. These can be obtained using system theoretical tools. Besides using standard tools, we develop methods which are particularly suited for the class of models for signalling cascades.



Pathway Model for Caspase Activation

Project Overview: The modelling of caspase dynamics during apoptosis.

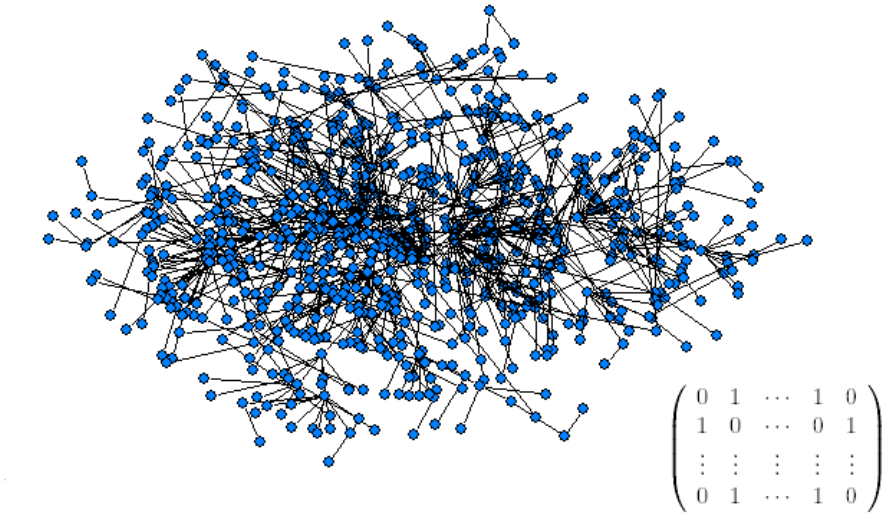
The process of apoptosis is irreversibly started when a sufficient number of active effector caspases is present in a cell. After a pro-apoptotic stimulus, for example using the hormone TNFα as extra-cellular signal, this number slowly increases in a cell population, but quickly within individual cells. We developed a nonlinear, dynamical model that, in a qualitative manner, reproduces this behaviour if an inhibitor is included which was unknown at that time. The main system property of the model is bistability: "life" and "death" each correspond to a stable steady-state. These two are connected by a slow manifold along which the trajectories of the concentrations evolve. Varying initial conditions and strength of the stimulus lead to differences in the length of the lag phase. The actual activation of large numbers of effector caspases is quick in all cases. The influence of intrinsic noise due to the stochasticity of chemical reactions was shown to be negligible, even though during the lag phase very low numbers of active caspases are present. Presently, the model is being expanded to include other pro-apoptotic pathways as well as anti-apoptotic pathways and used to understand how cells achieve a robustness of the balancing between life and death. The expanded model should for example explain why cells start apoptosis only if the stimulation by TNFα lasts long enough, although the anti-apoptotic pathway is already stimulated by a TNFα pulse. This work is a collaboration with the systems biology group at the University of Stuttgart and the group of Jochen Prehn at the Royal College of Surgeons in Ireland.

Theme 2: Graphs and networks and positive dynamical systems

This theme focuses on aspects of network analysis and the theory of dynamical systems that are relevant to key biological questions and particularly to the overall project theme of neurodegeneration. The overall mission is to develop an expertise in these areas that will be of use to the broader biological community in Ireland.

Networks occur in a wide variety of biological contexts, ranging from networks of transcriptional interactions within a cell, through neuronal networks in the brain to networks of interacting individuals within a population. Moreover, in recent years vast quantities of data on bio-molecular and neurological networks have been generated and catalogued. This fact, together with the ubiquity of networks in Biology, has led to a pressing need for analytical tools to make the best use of the data now available on

biological networks. A major aim of this project theme is to develop and extend the current analytical techniques used to study the various networks in Biology. A second important goal is concerned with the analysis of classes of dynamical systems that arise in the biosciences. Arguably the most important such class is that of *positive* systems whose variables are constrained to remain non-negative for all time. The work being done at the Hamilton Institute covers both the general theory of network analysis and dynamics in Biology, as well as topics that are specific to particular biological and medical questions.



Yeast protein – protein interaction map

Project Overview:

Broadly speaking, there are three strands to the work being done at the Hamilton Institute under this theme:

- The development and analysis of algorithms for deriving biological conclusions from the experimentally determined structure of interaction and neurological networks;
- Analysing the interaction between the topology of a network and dynamical processes that take place on it;
- Studying the properties of positive and other dynamical systems that arise in medical and biological applications.

To date, we have mainly focussed on the first and third of the three topics listed above. Firstly, the use of a variety of measures of network centrality for the prediction of gene and protein essentiality has been investigated. In particular, we have applied eigenvector-based measures for ranking nodes within networks, such as are used in modern search engines for the World Wide Web, to publicly available datasets on the protein interaction network of *S.cerevisiae* and the transcriptional regulatory network of *E.coli*. In each case, the correlation between the ranking of a gene or protein and its likelihood to be essential for the survival of the organism was investigated. A paper is currently in preparation in which we will report the results of this and similar work for other centrality measures.

A major effort has gone into a comprehensive review and critique of the various mathematical methods applied to biological networks to have emerged in the recent past. We believe that there is a clear need for such a document in the light of the large amount of papers to have been published in the field in the last four to five years.

Our aim is to produce a review that will be a reference source for researchers interested in biological networks.

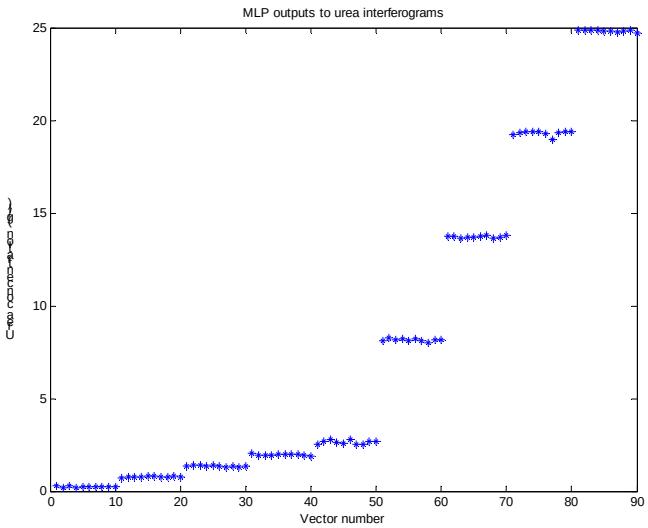
Original theoretical results on the asymptotic behaviour of classes of positive dynamical systems have also been derived and published in journals and at international conferences in the past year. See [6, 7, 9, 10] for some general mathematical results and [17] for a simple example of a positive dynamical system that is of relevance to the issue of neurodegeneration.

Our future research plans include:

- Investigating dynamical systems of direct relevance to neurological disorders and medical applications – specifically models relevant to the parkinsonian tremor and therapy design will be studied;
- Numerical and theoretical studies of the phenomenon of synchronisation on various network structures and its relevance to neurological disease;
- Analysing the impact of different network structures on disease propagation and epidemic dynamics.

Theme 3: Bio-Sensor Signal Processing

Optical methods from the near infrared range, in particular the near-infrared (NIR) spectroscopy, offer a non-invasive real-time technique for monitoring of the blood perfusion and oxygenation in a living tissue. Near-infrared spectrometry is being applied to the solution of problems in many areas of biomedical and pharmaceutical research including cardiovascular radiology, brain imaging, formulation, and has reached the clinical trial stage in some cases. Since near-infrared spectra are typically composed of broad overlapping and, thus, ill-defined absorption bands containing chemical and physical information of all sample components, the analytical information is multivariate in nature and, therefore, hardly selective. To perform qualitative or quantitative NIR analysis, i.e. to relate spectral variables to properties of the analyte, mathematical and statistical methods are required that extract 'relevant' information and reduce 'irrelevant' information, i.e. interfering parameters such as light scattering, path length variations and random noise.



Multi-layer neural network predictions to interferogram data from different urea concentrations.

Project Overview: Non-contact analysis of blood bio-molecules

We use multivariate statistical methods, both supervised and unsupervised, for the analysis of NIR spectroscopic data from blood bio-molecules, such as creatinine, urea and glucose. Emphasis has been given on the use of discriminant analysis and feed-forward ANN's. All of the classification methods can operate either in wavelength space or in dimension-reduced factor space. Results will be compared with other techniques and different set of clinical data.

A novel dual-modality optical and electrical non-invasive system for nerve conduction studies with application to neural degenerative diseases is under consideration (in collaboration with the Department of Electronic Engineering, NUIM, Ireland and Information and Biomedical Engineering Centre, City University, London, UK). The objective of this study is to investigate the feasibility of acquiring fast optical response signals from the peripheral nervous system (PNS) and specifically to obtain knowledge about the state of health of the nerve through comparing electrophysiological responses with those obtained with a novel optical system. Furthermore as a secondary objective clinical tests with subjects suffering from a number of neurodegenerative disorders will be conducted to explore the potential of the technique for diagnostic purposes.

Part of the project includes the development of an optical monitoring system for cellular structure during implantation of various DNA material (in collaboration with the Departments of Electronic Engineering, Experimental Physics and Biology, NUIM, Ireland). This study will investigate the feasibility of automatically discriminating between states of cellular integrity during genetic material implantation studies through optical means. Specifically the aim is to obtain knowledge about the scattering phenomena that may occur during cell illumination with broad-spectrum or near infrared (NIR) light sources. Optical monitoring systems developed by the Biomedical Research Group (NUIM) in combination with signal analysis algorithms developed in the Hamilton Institute could acquire such data reflecting light interaction with cell material.

Application Theme: Systems Understanding of Neurodegeneration

In this diverse area we have begun work with collaborators at the Conway Institute of Biomolecular and Biomedical Research on the variations in neurotransmitter levels that occur in particular parts of the brain associated with Parkinson's Disease and Schizophrenia. These include the modelling of the indirect motor circuit, preliminary results for which are reported in [17], and the data concentration and visualisation issues that occur in merging data from disparate neurological bio-sensors. In this context, the following paragraph describes the work of Stuart Butler in building a neuroinformatic visualisation tool with which neuro-pharmacologists can review and study the dynamical variations in neurotransmitter levels

Project Overview: The visualisation of neurotransmitter concentrations from microdialysis sensors

The aim of this project is to develop a neuroinformatic system to simplify and integrate the visualisation and analysis of neuro-transmitter release in the Motor Circuit from data derived from microdialysis in the basal ganglia of the intact, conscious rat brain.

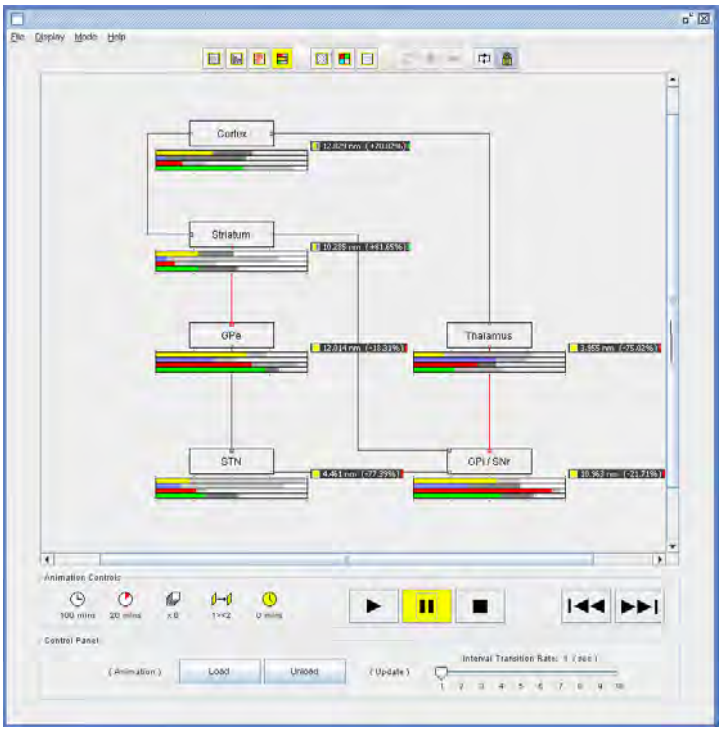
In its current form the system allows the user to:

1. Construct a diagrammatic abstraction of the Motor Circuit of interest;
2. Map experimental datasets to specific brain regions defined in the circuit schematic. Datasets are the results of typical microdialysis experiments,

usually a series of neurotransmitter concentrations from a specific brain region and correlative behavioural and activity data;

3. Create an animation of neurotransmitter fluctuations over time, providing a dynamic and quantitative description of the circuit dynamics;
4. Manipulate, compare and interact with large amounts of complex time-varying information in a coherent, visual context.

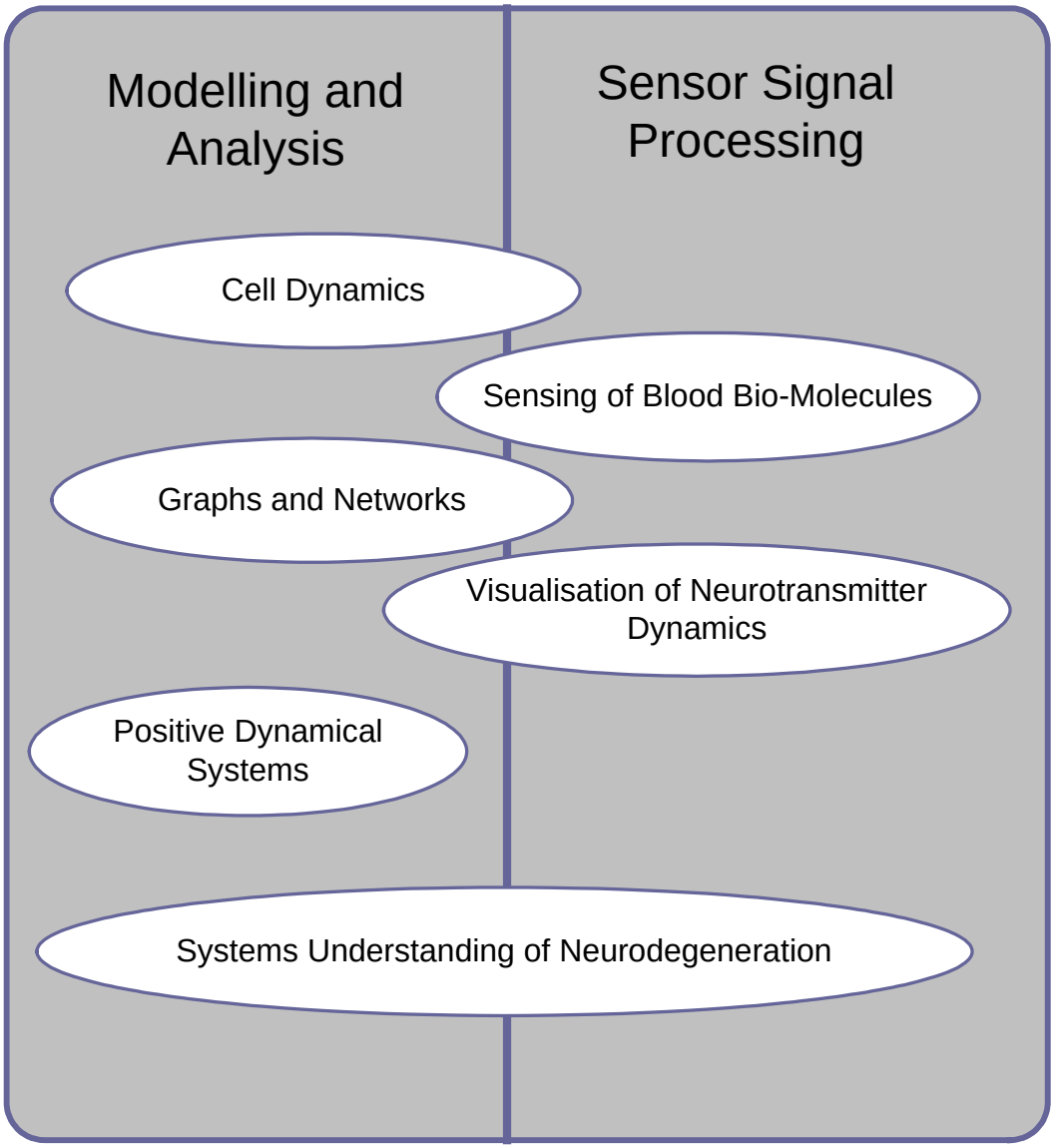
The neuroinformatic system is designed to be extendable, and the next proposed steps will add modelling and identification features for the Motor Circuit and other nerve circuits within the brain. Our goal is to extend the capabilities of the system to support the development and testing of mathematical models of the dynamics of interaction between brain regions, on a time-scale that is roughly that of the microdialysis experiments. This project is an inter-university collaboration between the Hamilton Institute, the Department of Computer Science, NUI Maynooth, and the Conway Institute of Biomolecular and Biomedical Research, University College Dublin.



Screen shot from the Neurotransmitter Visualisation Tool: The figure shows the animation screen for neurotransmitter levels in the indirect motor circuit

Project Overlap and Interdependence

Although the projects have been categorised as either Modelling and Analysis or Bio-Sensor Signal Processing, there is substantial overlap. The project spread figure tries to capture this overlap.



The Systems Biology Team

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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 neurodegenerations.

Eric Bullinger

SFI Postdoctoral Researcher

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Eric Bullinger studied electrical engineering at ETH Zurich. He graduated in 1995, obtaining the ETH medal and his Ph.D. shortly thereafter. He then took up a position as a research and teaching assistant at the Automatic Control Laboratory, ETH Zurich, under the supervision of Professor Frank Allgöwer. Since January 2005, he is a member of the Systems Biology research group at the Hamilton Institute. Currently, his major research interests are the development of mathematical models of signal transduction networks and their mathematical analysis – especially the pathways leading to or preventing apoptosis, the process of programmed cell death.

Stuart Butler

SFI Postgraduate Researcher

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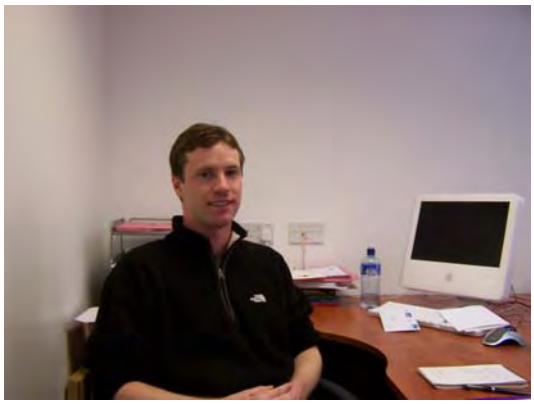

Stuart Butler graduated from the National University of Ireland, Maynooth in 2003 with a first class honours degree in Computer Science and Software Engineering. He returned to the Department of Computer Science in November 2004 to undertake a Ph.D. degree under the joint supervision of Professor Ronan Reilly of the Computer Science Department, NUIM, Professor Peter Wellstead of the Hamilton Institute, NUIM, and Dr. William O'Connor of the Conway Institute, UCD. 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.

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SFI Postdoctoral Researcher

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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 the 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 research group at the Hamilton Institute, National University of Ireland, Maynooth. 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

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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 Ph.D on the stability of switched linear systems. Since June 2004, he has been a member of the Systems Biology research 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.

Mark Verwoerd

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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. At an applied level, he is interested in developing dynamic models of signalling pathways in the brain.

Systems Biology Scientific Advisory Panel

The following panel of distinguished scientists have agreed to advise us in our scientific programme:

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Visits

In addition to regular visits to, and exchanges, with local research collaborators, we made the following visits to other systems biology laboratories:

August 4th – August 8th, 2004: P. Wellstead – Laboratory of Systems Biology, University of Rostock, Germany. For joint research with Professor O. Wolkenhauer on dynamic motifs in biological signalling.

September 2nd – September 7th, 2004: P. Wellstead – Technical University of Vienna, Austria, for discussions and presentations at the IFAC Conference on Control Strategies for Social and Economic Systems.

October 9th - October 13th, 2004: E. Bullinger, O. Mason and P. Wellstead – International Conference on Systems Biology, Heidelberg, Germany, and discussions with international co-workers and scientists.

November 1st – November 27th, 2004: P. Wellstead – Centre for Advanced Control, University of Newcastle, Australia, for joint work with Professor Graham Goodwin, and seminars on Systems Biology.

April 28th – April 29th, 2005: D. Kalamatianos – University of Patras, Greece. For discussion with colleagues on NIR sensing methodologies.

May 1st – June 30th, 2005: E. Bullinger – University of Stuttgart, Germany. For joint research with Professor Allgöwer and colleagues on the modelling of caspase events in apoptosis.

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Academic Visitors

We have established 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 of significant topicality. For this reporting period the visitors included:

Prof. Ali Jadbabaie, Dept. of Electrical and Systems Engineering, University of Pennsylvania, USA. 'Distributed Coordination and Consensus in Mobile Agents: From Bird Flocking and Fish Schooling to Synchronization of Coupled Oscillators'. June 24th, 2005.

Dr. Declan Bates, Department of Engineering, University of Leicester, UK. 'Validation of Biochemical Network Models using Robust Control Theory'. June 17th, 2005.

Leroy Hood, **Hamid Bolouri and Louis Coffman**, Institute of Systems Biology, Seattle, June 14th, 2005.

Alan S. Perelson, Los Alamos National Laboratory, USA. 'An Overview of Computational and Theoretical Immunology'. May 31st, 2005.

Dr. Madalena Chaves, Rutgers University, USA and Sanofi Aventis. 'Some Theoretical Aspects of Cell Signaling: Receptor-ligand Interactions and Signal Amplification Cascades'. Feb. 23rd, 2005.

Prof. Lance Williams, Dept. of Computer Science, University of New Mexico. 'A Computational Theory of Contour Completion in Visual Cortex'. Jan. 12th, 2005.

Prof. Richard Abadi, Faculty of Life Science, University of Manchester, UK. 'How the Brain Keeps the Eyes Still..... and What Happens if it Fails'. Oct. 22nd, 2004.

Prof. David Angeli, Dipartimento di Sistemi e Informatica, Universita degli Studi di Firenze, Italy. 'Monotone Input-Output Systems: Theory and Its Applications to Molecular Biology'. Oct. 8th, 2004.

Prof. Kwang-Hyun Cho, School of Electrical Engineering, University of Ulsan, Korea. 'Systems Biology: Towards Organizing Principles of Cellular Dynamics'. July 21st, 2004.

Prof. Olaf Wolkenhauer, Systems Biology and Bioinformatics Group, Institute for Informatics, University of Rostock, Germany. 'Dynamic Modelling of Signal Transduction Pathways "Simulating what cannot be simulated"'. March 26th, 2004.

Dr. Stephen Duncan, Department of Engineering Science, University of Oxford, UK. 'System Dynamics of Epidemics'. Feb. 20th, 2004.

Prof. Muffy Calder, Department of Computing Science, University of Glasgow, UK. 'Concurrent Models of Biochemical Pathways'. Feb. 5th, 2004.

Partnerships

Interaction with other research centres is important and therefore we have built and will 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 are close (such as those with Rostock and Bio-Max, NUIM Biology and the Conway Institute of Molecular 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

Systems Biology Laboratory (SBL), Bio-Max, Seoul National University, Korea.

Prof. K-H Cho

- Systems Theoretic Issues in Biology

Information and Biomedical Engineering Centre, City University, London, and 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 Conway Institute, UCD, and 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 and Biology, NUIM, Ireland

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

University of Twente, The Netherlands

Prof. Vinod Subramaniam, Professor of Biophysical Engineering

- Correspondences on Systems Biology.

Imperial College, London, **UK.**

Dr. Viswanath Talasila, Control and Power Group, Department of Electrical Engineering

- Systems Biology and Control Theory.

Utah State University, Utah, USA

Prof. Yang Quan Chen, Center for Self-Organizing and Intelligent Systems

- Iterative Learning Control.

Systems Biology Group, University of Stuttgart, Germany

Prof. Frank Allgöwer, Prof. Ernst Dieter Gilles, Prof. Peter Scheurich

- Modeling and analysis of Tumor Necrosis Factor signaling and apoptosis
- Modeling and analysis of the global regulation in *E.coli*
- Modeling and control of glucose level in diabetes.

Max-Planck-Institut Dynamik komplexer technischer Systeme, Magdeburg, Germany

Prof. Ernst Dieter Gilles

- Optimal experiment design for metabolic systems
- Comparison of model reduction algorithms
- Modeling and analysis of the global regulation in *E.coli.*

Physics Department, University of Freiburg, Germany

Prof. Jens Timmer

- Modelling and analysis of Tumor Necrosis Factor signaling and apoptosis.

Chemical Engineering Department, University Politehnica of Bucharest

Dr. Vasile Lavric

- Modelling and analysis of the global regulation in *E.coli.*

Publications

D. **Kalamatianos**, P. Liatsis and **P. Wellstead**, “Near-infrared Technologies for Predictive Medicine”, submitted to Nature Biotechnology, 2005.

2. **D. Kalamatianos**, J. Edmunds and **P. Wellstead**, “Active Alignment for Two-Beam Interferometers”, accepted at Review of Scientific Instruments, 2005.
3. **D. Kalamatianos**, J.M. Edmunds, **P.E. Wellstead**, R.J. Houston, P. Liatsis, S.M. Christie, R.J. Dewhurst, and M.S. Thorniley. “Dynamic alignment system for an FT-NIR Michelson interferometer”. Proceedings of the IEEE International Conference on Virtual Environments, Human-Computer Interfaces and Measurement Systems, pages 120–124, Boston, MA, July 12-14 2004.
4. **M.H.A. Verwoerd**, G. Meinsma, and T.J.A. de Vries. “On the parameterization of all admissible pairs in a class of CCF-ILC algorithms”. Proceedings of the American Control Conference, Boston, Massachusetts, USA, pages 5156-5157, 2004.
5. **M.H.A. Verwoerd**, G. Meinsma, and T.J.A. de Vries. “A class of non-contractive, trial-dependent update rules for iterative learning control”. Proceedings of the American Control Conference, Boston, Massachusetts, USA, pages 5132-5137, 2004.
6. L. Gurvits, R. Shorten and **O. Mason**. “Preliminary results on the stability of switched positive linear systems”. Proceedings of the Mathematical Theory of Networks and Systems (MTNS), Leuven, July 2004.
7. R. Shorten, **O. Mason** and K. Wulff. “Convex cones, Lyapunov functions and the stability of switched linear systems”. Chapter in Switching and Learning in Feedback Systems, Springer LNCS 3355, 2005.
8. M. Vilaplana, **O. Mason**, D. Leith and W. Leithead. “Control of yaw-rate and sideslip in 4-wheel steering cars with actuator constraints”. Chapter in Switching and Learning in Feedback Systems, Springer LNCS 3355, 2005.
9. **O. Mason** and R. Shorten. “The geometry of convex cones associated with the Lyapunov inequality and the common Lyapunov function problem”. Electronic Journal of Linear Algebra, 12:42-63, 2005.
10. **O. Mason** and R. Shorten. “On the simultaneous diagonal stability of a pair of positive linear systems”. To appear in Linear Algebra and its Applications, 2005.
11. H. Conzelmann, J. Saez-Rodriguez, T. Sauter, **E. Bullinger**, F. Allgöwer, and E.D. Gilles. “Reduction of mathematical models of signaltransduction networks: Simulation-based approach applied to EGF receptor signalling”. IEE Systems Biology, 1(1): 159 – 169, 2004.
12. T. Eißing, H. Conzelmann, E.D. Gilles, F. Allgöwer, **E. Bullinger**, and P. Scheurich. “Bistability analyses of a caspase activation model for receptor-induced apoptosis”. J. Biol. Chem., 279(35): 36892–36897, 2004.
13. A. Kremling, S. Fischer, K. Gadkar, F. J. Doyle, T. Sauter, **E. Bullinger**, F. Allgöwer, and E.D. Gilles. “A benchmark for methods in reverse engineering and model discrimination: problem formulation and solutions”. Genome Res., 14(9): 1773–1785, 2004.
14. T. Sauter and **E. Bullinger**. “Detailed mathematical modeling of metabolic and regulatory networks”. BIOforum Europe, 2004(2): 62–64, 2004.
15. T. Eißing, C. Cimatoribus, N. Elvassore, F. Allgöwer, and **E. Bullinger**. “Model discrimination tools in apoptosis”. In Foundations of Systems Biology FOSBE 2005, August 7-10, Santa Barbara, CA, USA, 2005.
16. I.R. Ofiteru, V. Lavric, F. Allgöwer, and **E. Bullinger**. “Sensitivity analysis of Escherichia coli's Tricarboxilic Acid Cycle under anaerobic conditions”. In

Foundations of Systems Biology FOSBE 2005, August 7-10, Santa Barbara, CA, USA, 2005.

17. **P. Wellstead, O. Mason**, W.T. O'Connor, K-H. Cho, **E. Bullinger**, O. Wolkenhauer, and S. Duncan. "Towards a systems understanding of the cerebral motor circuit". In Foundations of Systems Biology FOSBE 2005, August 7-10, Santa Barbara, CA, USA, 2005.
18. **E. Bullinger.** "System Analysis of a Programmed Cell Death Model". Accepted for Proc. of the 44th IEEE Conference on Decision and Control and European Control Conference ECC, Sevilla, Spain 2005.
19. T. Eißing, F. Allgöwer and **E. Bullinger**. "Robustness properties of apoptosis models with respect to parameter variations and intrinsic noise". IEE Syst.Biol., 2005, in press.
20. **E. Bullinger** and F. Allgöwer. "Adaptive lambda -tracking for nonlinear higher relative degree systems". Automatica, 41(7): 1191-2000, 2005.
21. S. Duncan and **P. Wellstead**. "Processing Data form Scanning Gauges on Industrial Web Processes". Automatica, 40, pp 431-437, 2004.
22. R. Shorten, D. Leith, **P. Wellstead**, and R. Stanojevic. "On Queue Provisioning, Network Efficiency and TCP: A framework for adaptive AIMD congestion control". Accepted, Automatica, 2004.
23. O. Wolkenhauer, M. Ullah, **P. Wellstead**, K-H. Cho. "The Dynamic Systems Approach to Control and Regulation of Intracellular Networks". FEBS Letters, 579, pp 1846 – 1853, 2005.
24. O. Wolkenhauer, S.N. Sreenath, **P. Wellstead**, M. Ullah, K-H. Cho. "A Systems and Signal Oriented Approach to Intracellular Dynamics". Biochemical Society Transactions, 33, 3, pp 507 – 515, 2005.
25. S. Duncan, P. Jones and **P. Wellstead**. "A Frequency Domain Approach to Determining the Path Separation for Spray Coating". Accepted, IEEE Trans ASE, 2005.
26. K-H. Cho, S-M. Choo, **P. Wellstead**, and O. Wolkenhauer. "A Unified Framework For Unravelling The Functional Interaction Structure Of A Biomolecular Network Based On Stimulus-Response Experiment Data". Accepted, FEBS Letter 2005.
27. R. Shorten, D. Leith, **P. Wellstead**. "An Adaptive AIMD Congestion Control Protocol for Communication Networks". NETWORKING 2004: pp 699-711.
28. S. Duncan, P. Jones and **P Wellstead**. "Robot Path Planning for Spray Coating: A Frequency Domain Approach". Proceedings of the ACC 2004, Boston, 2004.
29. **S. Butler**, R. Reilly, P. Wellstead and W O'Connor, "Brain-Aid a visulisation tool for microdialysis data", Proceedings Society for Neuroscience (SFN) Washington, 2005
30. **S. Butler**, R. Reilly, P. Wellstead and W. O'Connor, "Visualisation and Harmonisation of data diversity in neuro-pharma sensing", European Brain and Behaviour Society (EBBS) Trinity College, 2005.

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