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Science Foundation Ireland Research Professor Award 03/RP1/I382

Annual Report 2005 – 2006

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Hamilton Institute

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Preface

This is the second in a series of reports describing the contributions of the author and co-workers (colleagues, students and visitors) funded under SFI Research Professorship award 03/RP1/I383. As in the previous report, the key aim of the report is to acquaint other researchers with our activities and those of our collaborators. We also hope that it will 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. The report covers the period from July 2005 to June 2006.

For more information on our work, 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 are given in the biography section of this report.

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Introduction

Background

In this second year of the Research Professor Programme, our aims have been to consolidate our first year's efforts, further develop our research activities and lay the foundations for expansion with additional funding mechanisms. In this respect we are pleased to be part of the proposed National Bio-Photonic Imaging Programme. This pan-university programme is a coordinated research and infrastructure plan for non-invasive bio-medical imaging using a wide range of imaging modalities. We coordinate the NUI Maynooth contribution via a project for 'real-time quantitative NIR bio-imaging'. If successful, this will join the unique real-time biochemical sensing technologies of Professor John Lowry of the Chemistry Department with the signal processing and NIR sensing technology of the Hamilton Institute. In a similar spirit, we also organised the 'image to mathematical model transition' core of the proposed Bio-Photonic Programme. This core will be a partnership between the Hamilton Institute, the Royal College of Surgeons Ireland and the Boole Centre for Research in Informatics, UCC. It has the aim of developing the algorithms and methods needed to take data from a range of bio-imaging modalities and transform them into quantitative mathematical models. The models will be such that they have biological meaning and corresponding analytical diagnostic and predictive properties needed in a systems approach to biology.

Also this year we were able to welcome a number of distinguished scientists as visitors to the Hamilton Institute. Some, like Sir Alistair MacFarlane, Professors Bernhard O. Palsson and Olaf Wolkenhauer stayed only a brief time. Others were here longer. In particular Professor Richard Middleton of the University of Newcastle, was with us for six months during which time he added greatly to the intellectual (and sporting) life of the Hamilton Institute. A complete listing of visitors is given in the corresponding section of this report.

In addition to receiving many visitors, we have also travelled more, both nationally and internationally. Many of these trips were visits to collaborating groups, but we have also travelled to promote Systems Biology in general, and to make the work of the Hamilton Institute better known internationally and with research planners[1]. In this context it is important to add that the Systems Biology team is just one part of the 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.

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.

[1] The lecture 'On the Industrialisation of Biology' distributed with this report, was a part of our international and industry lectures during the year.

The Programme Plan

The general objective of the author's Research Professor programme is to establish a Systems Biology research programme 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), an emerging discipline with no presence in Ireland. We are pleased to report that the growth of Systems Biology in Ireland is now under way. Our first step was to raise national awareness through a public lecture in April 2005 at the Royal Irish Academy. The lecture, 'Schrödinger's Legacy', has since been used extensively elsewhere and an edited video of the lecture has been made available for downloading by the Higher Education Authority at their web site www.hea.ie. The second stage in raising national awareness was the SFI Systems Biology Workshop, (June 2005), with further reinforcement in the shape of a second Systems Biology Workshop (reported later in this document), in September 2005. Both these events were hosted by the Hamilton Institute Systems Biology group and took place in Maynooth.

The Hamilton Institute Systems Biology group do not work alone, and it is a pleasure to acknowledge that a decisive factor in developing Systems Biology has been SFI's strong and proactive support throughout the year. We anticipate that, with the planned Science Foundation Ireland's Systems Biology initiative, interest will continue to grow nationally and be further cemented by the International Systems Biology Workshop that the author's group is organising for July 2006. We now consider our national awareness campaign to be complete and have accordingly refocused our efforts on the Hamilton Institute programme and our work with international collaborators.

At the Hamilton Institute, we remain a predominantly 'dry' Systems Biology laboratory, performs *in-silico* analysis and modelling of biological problems, and developing novel signal processing methods for recovering information from bio-sensors. 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 year continue to develop in the ways outlined in the first annual report[2]. Our focus remains on research into the systems theory and applied mathematics that underlie dynamical mechanisms in biology, disease and healthcare. Essential components in

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

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 the use of such models that we can (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.

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[3] 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 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 set up 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.

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

The second aspect of the 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 University College Dublin. This and other projects are explained in more detail in the Project Overviews.

Thirdly, we report new activities in extracting quantitative information from image 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.

Feedback Medicine: Implications for Personalised Medicine

The concept of a personalised, predictive and preventative approach to medicine is seductive. However, from a science viewpoint, we recall that the human body is an intricate set of feedback systems held in balance by a series of homeostatic regulators. Thus when we begin to think about the implications of personalised medicine, we see potentially harmful scope for the external feedback loops imposed by clinicians to 'fight' the internal homeostatic loops. We must therefore combine sound feedback control design methods with personalised medicine – we call this feedback medicine. For example, the idea that we can apply forecasting tools to the time histories of relevant personal bio-indicator data and potentially prevent the onset of disease by 'closing the loop' around a patient is a wonderful thing. However, this has implications for conflict between internal homeostatic regulators and the external regulation applied by the clinician. This kind of feature has been observed during the application of composite treatments, particularly in intensive care. In this spirit, this sub-project aims to add value to the predictive medicine concept by considering the control theoretic implications of multiple interventions both in intensive treatment (using regular sampled data theory) and in normal consulting (using batch-to-batch control ideas). This is a joint project with Professor Rick Middleton of the University of Newcastle, Australia.

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 Systems Biology group at the Hamilton Institute (with special guests Rick Middleton, Chris Kellett and Thomas Schrock): 2005 – 2006

Review of the Year

General

This second year has been one of consolidation and development. A large part of this has been working to grow the activities with biologists that we need as a 'dry' laboratory. In this context, we have seen two team members make their own applications for grant funding, and a concerted effort to develop our bio-sensing activity by becoming part of the proposed National Bio-Photonics Platform. This will see us collaborating with experts on real-time biochemical sensing (Professor John Lowry of the Chemistry Department), NIR sensing and neuropharmacology (Professor Jeff Glennon).

Within NUIM we have formed a Systems Biology Forum as a place to develop systems activities in life science at Maynooth, and coordinate cross-departmental collaboration. As part of this we will be teaching Systems Biology modules to biology students in the coming session, and the Department of Biology has created a new departmental position in Systems Biology to help in this respect.

Externally we have provided indications of our support to research and research training initiatives elsewhere in Europe, including, the Manchester University Doctoral Training Programme in Systems Biology, and as well as support to initiatives in the Systems Biology and Bioinformatics Group at the University of Rostock and the Case Centre for Complex Systems Biology, at Case Western University.

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.

Events

External Talks

Following its use in 2004 at the Royal Irish Academy, the 'Schrödinger's Legacy' talk has been used to stimulate interest in Systems Biology nationally by locally given seminars and internationally to create an awareness of Systems Biology activities at the Hamilton Institute. Nationally, the lecture was suggested to the Presidents of all universities as a way of focussing ideas in their institutes. Although most Presidents accepted the offer with enthusiasm, only two Irish universities pursued the offer. These two talks were however useful and established collaborative links and discussions for local interdisciplinary activity. Internationally, we have presented the talk at the following venues: Imperial College London, the Institute of Information Theory of the Czech Academy of Science, the Engineering Department of Cambridge University, City University London, Max-Planck-Institut Dynamik komplexer technischer Systeme, Magdeburg, Germany, Case Western Reserve University, École Polytechnique de Montreal (via Institut Gerad and jointly with McGill University and Université de Montreal).

A limited number of further international invitations have been accepted for the first half of the third year of the project. The lecture will then be phased out and replaced by research talks plus a lecture for a general audience that follows on from the Schrödinger talk by couching the argument for applying mathematics, physics and technology to biology in an historical context[4]. As part of our outreach and education responsibility a video of the Schrödinger lecture will remain on the HEA web site (http://www.hea.ie), and the texts of all public talks will be held at http://www.systemsbiology.ie on the reports and downloads page.

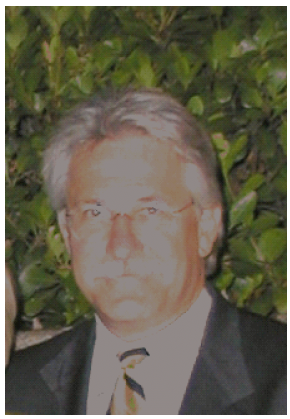
Maynooth Mathematics Challenge

As a further contribution to education and outreach, Oliver Mason joined a team of NUIM staff, led by Professor Robert Shorten, in organising a Mathematics Competition for secondary schools in the area. The competition was spread over several months and was a resounding success. It is anticipated that the Science Foundation Ireland will support future versions of the Maynooth Mathematics Challenge under the direction of Dr. Mason.

Second Systems Biology Workshop

On the 1st and 2nd September 2005, we hosted the second SFI sponsored workshop on Systems Biology. The event was organised and hosted by the Hamilton Institute Systems Biology Team and held in the John Hume building of NUI Maynooth. The aim of this event was to build on the momentum established by previous Systems Biology events organised by the Hamilton Institute in 2005. Keynote speakers for this event were Professor Olaf Wolkenhauer and Louis Coffman, the Operations Director of the Institute of Systems Biology, Seattle.

Professor Olaf Wolkenhauer: Key Note Speaker at Second Systems Biology Workshop



Louis Coffman: Key Note Speaker at Second Systems Biology Workshop

The event was structured to give an overview of the various areas and disciplines that make up Systems Biology. In addition, a cross spectrum of industry speakers described the potential of Systems Biology in their sectors. Over 70 delegates, mainly from Irish universities and industry, attended the event and opportunities were provided in the programme for networking between delegates and matching researchers with potential collaborators.

[4] *On the Industrialisation of Biology*

Project Overviews

As hinted elsewhere in the report, the work of the Systems Biology team 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 aim of helping illuminate the mechanisms of neurodegeneration. However, for clarity the three areas are described here under separate headings.

Theme 1: Modelling and Analysis of Cell Signalling

The aim of this project is the design of mathematical models for specific biological systems, in close collaboration with experimentalists, 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 models allow the consistency of biological hypotheses to be tested 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 have developed a nonlinear, dynamical model that, in a qualitative manner, reproduces this behaviour if an inhibitor is included - a characteristic that was previously unknown. The main system property of the model is bistability: “life” and “death” each correspond to a stable steady-state. These are connected by a slow manifold along which the trajectories of the concentrations evolve over time. 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.

At present, the model is being expanded to include other pro-apoptotic pathways as well as anti-apoptotic pathways. It is being 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 in collaboration with the Systems Biology group at the University of Stuttgart (Peter Scheurich & Frank Allgöwer) and the Department of Physiology at the Royal College of Surgeons in Ireland (Jochen Prehn).

Project Overview: Properties of signalling modules.

Signalling pathways are often complex and contain many different components. In many cases, specific core modules are responsible for the system's behaviour. With this in mind, we have analysed simple proteolytic feedback loops for their ability to achieve bistable behaviour. Positive feedback combined with cooperativitiy, zero-order ultra sensitivity or inhibition all allow for bistability in a suitably chosen range of parameters. The robustness of each set-up is similar, though cooperativitiy is most sensitive to zymogeneity.

An important, but often neglected aspect of mathematical modelling is the type of kinetics, for example whether mass action or Monod kinetics is employed. We have shown that of two identical models with different kinetics only one model might oscillate. Therefore, care has to be taken if the transient is essential to biological function, as it seems to be in many signalling pathways. This project is a joint work with the Systems Biology and Bioinformatics group at the University of Rostock (Olaf Wolkenhauer) and the Systems Biology group at the University of Stuttgart (Peter Scheurich & Frank Allgöwer).

Theme 2: Dynamics and Networks in Biology

Introduction

The past decade has witnessed phenomenal advances in measurement techniques in the biological sciences. As a direct result of this, there is now an unprecedented volume of data available on the bio-molecular networks underpinning key biological processes. These developments have naturally generated a need for more systematic methods for the analysis of the complicated networks whose structure is beginning to emerge.

This research theme is concerned with developing the study of networks and dynamical processes in Biology. As such, a major aspect of this research theme is to gain a thorough understanding of the topological and structural properties of static biological network models such as protein-protein interaction networks, and to develop a suite of theoretical results for mathematical models of such networks. 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. In addition to this

work, we are also interested in studying the stability properties of positive dynamical systems, which are of particular relevance to biological applications.

Theme 2a: Analysis of biological interaction networks

As announced in last year's annual report, we have completed a survey of the various mathematical methods applied to biological networks to have emerged in the recent past. The corresponding paper, with the title 'Graph Theory and Networks in Biology' has been provisionally accepted for publication in IEE Proceedings, Systems Biology and is expected to appear in early 2007. A poster of the same title will be presented at the International Conference on Systems Biology, in October 2006.

Work on investigating the properties of a family of Duplication-Divergence network models has been initiated and some preliminary results have been obtained, which will be submitted for presentation at an international conference early next year. This work has been carried out in collaboration with a visiting intern student and has involved a combination of numerical simulation and theoretical analysis of network models for proteome evolution. To date, the topics studied have included the impact of an initial network's topology on the evolution of the network, and the relationship between the local clustering properties of the network and its propensity to remain connected or to split into several components of similar size. In particular, much of the work pertains to the existence and evolution of a 'giant' component in protein-protein interaction networks.

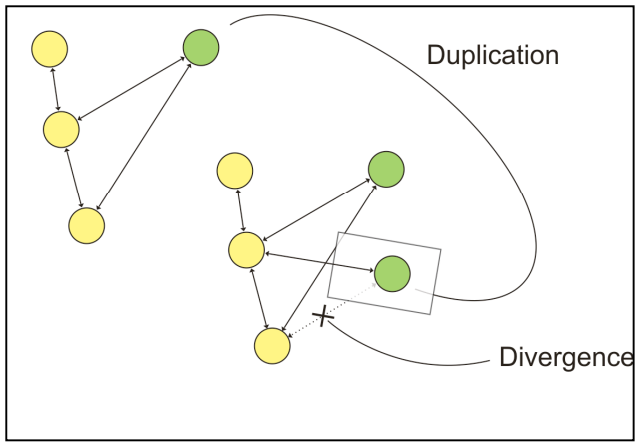


Figure 1: Duplication Divergence Network Models

To date, we have focussed on the simple model of Vazquez and co-authors[5]. 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.

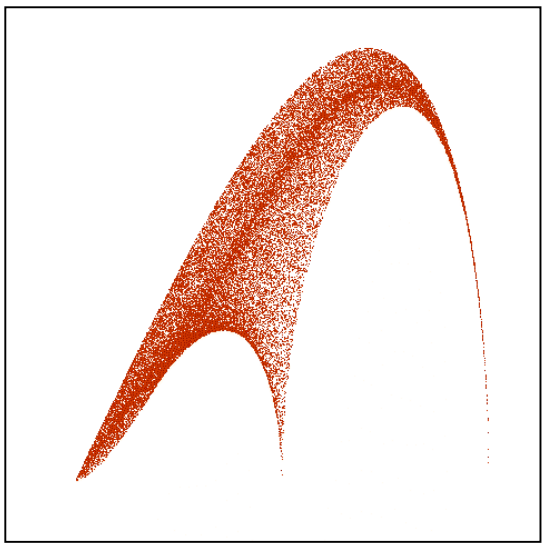


Figure 2 Diagram for assessing stability in a 4-oscillator system

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

Theme 2b: Network topology and dynamics

The second strand of this research theme, as outlined in the Annual Report 2004-2005, concerns the interaction between the topology of a network and dynamical processes that take place on it. 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 problem of synchronisation has been studied for many decades and the literature is vast. 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) and finite-size effects are still 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 fixed points (states of the system wherein every oscillator phase locks to every other) in a system with finitely many oscillators. We have shown that there exists a criticial value for the coupling strength, such that, when the coupling strength is greater than this critical value, the system has at least one fixed point, while no fixed point exists when the coupling strength is less than the critical value. We have derived theoretical lower and upper bounds on this critical coupling; incidently, we have also gained insight in the dynamics of synchronisation, specifically in the rate at which trajectories converge to a phase-locked state. Lastly, we have developed an efficient computational procedure that allows us to compute the critical coupling with arbitrary precision.

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

1. Investigate the dependence of the critical coupling on the shape of the distribution of oscillator frequencies;
2. Study the statistical properties of the critical coupling as a function of different distributions and different population sizes;
3. Relax the assumption of all-to-all coupling to allow for arbitrary weighted connections;
4. Replace the current kinematic model with more realistic dynamic models of biological oscillators, in particular circadian clock oscillators;
5. Investigate the possibility of extending the current one-parameter model to a simple two-parameter model, with a view to capturing variations in cycle length, which are known to occur in free-running circadian clocks.

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. We shall focus our attention on the mathematical analysis of circadian clock models.

We have also continued the line of research concerned with the stability analysis of positive dynamical systems, which was described in last year's report. In fact, we have obtained several novel results in the past year concerning the existence of copositive Lyapunov functions for time-varying positive linear systems and more general results on stability conditions for this class of systems. In the future, it is hoped to extend these results to more realistic system classes incorporating parameter uncertainty and non-linear effects.

Theme 3: Bio-Sensor Signal Processing

Project Overview

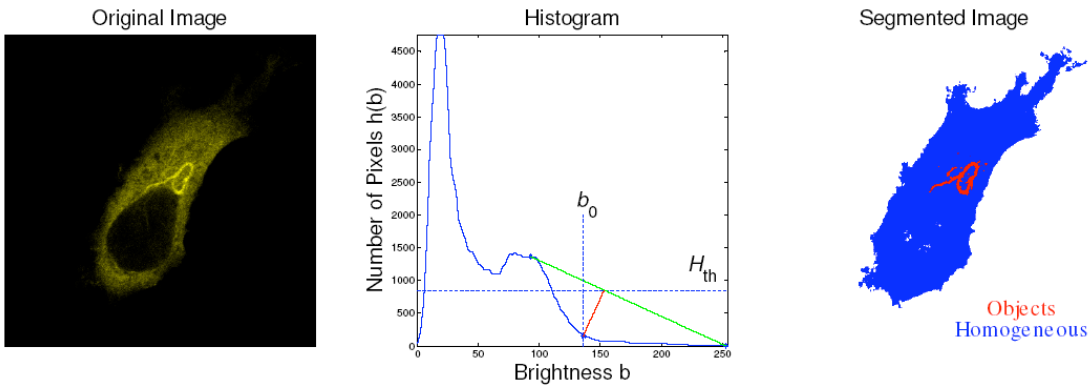
This project focuses on multidimensional signal processing in the presence of uncertainty, the robust extraction of information from diverse data sources, and decision making in the face of noise. The main research topics covered by this project are the following:

- Bio-medical signal and image processing.
- Mathematical modelling and estimation.
- Bio-sensing and life science measurements.

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 classified 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 placed on the use of discriminant analysis and feed-forward ANN's, specifically radial-basis function 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.

Project Description: The visualisation of neurotransmitter concentrations from microdialysis sensors

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. 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. As reported last year, Stuart Butler has built a neuroinformatic visualisation tool with which neuro-pharmacologists can review and study the dynamical variations in neurotransmitter levels. This is now undergoing assessment with the neuro-pharmacology teams and further refinement by Stuart.

Project Description: Feedback Medicine

This project is in collaboration with Professor Rick Middleton of the University of Newcastle, and concerns the interactions between personalised medicine and internal homeostatic loops. Generally, our objective is to expose a potential role for feedback control theory in personalised medicine and combinatorial intervention. In particular, we formulate a feedback control interpretation for the administration of medicine as envisaged by the personalised approach, and explore its implications in the light of homeostatis and interactions between treatments. There are two reasons for doing this. First, personalised medicine is distinctly different from the normal process of general practice medicine, which is based upon a diagnostic consultation, with possible follow up by irregular and occasional monitoring consultation. The personalised medicine approach is closer to a regular feedback control regime with a similar regularity of measurement, analysis and treatment that closely mirrors the processes within a feedback control system. Second, the notions of combinatorial action in treatment clearly indicate that the processes of medicine are multivariable and coordinated in nature. It is shown that in simplified models of disease states that personalised treatments may disturb internal homeostatic states in a detrimental manner.

The Systems Biology Team

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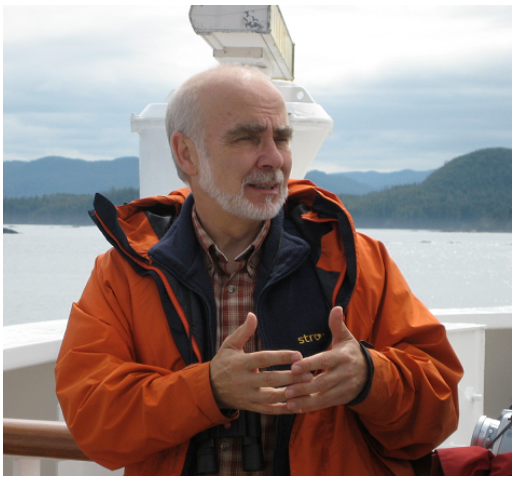

Peter Wellstead is a Science Foundation Ireland Professor at the Hamilton Institute NUIM. Prior to his current appointment in 2004, he was an E.T.S. Walton Visitor at the Hamilton Institute and before that Professor of Control Engineering at the Control Systems Centre, University of Manchester Institute 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.

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. 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 research 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 faculty member at NUIM.

Stuart Butler

Postgraduate Student

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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.

Dimitrios Kalamatianos

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 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 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 PhD 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. Oliver is a faculty member at NUIM.

Mark Verwoerd

SFI Postdoctoral Researcher

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

Visiting Team Members and Students

Rick Middleton

Visiting Research Professor

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Rick Middleton visited the Hamilton Institute between August 2005 and February 2006 as Visiting Research Professor and worked on the control theoretic implications of predictive medicine and personalised therapy. He collaborated with Wellstead and Wolkenhauer on the concepts of Feedback Medicine, and developed the feedback control implications of multiple feedback loops in medical interventions. In addition, and in keeping of the multidisciplinary nature of the Hamilton Institute, he also contributed to Professor Robert Shorten's research programme into the analysis and design of TCP for the Internet and Professor Doug Leith's wireless systems research programme.

Rick is one of Australia's most distinguished control systems experts with an international reputation for his contributions to theory and practice. He was the 2004 recipient of the MA Sargent Medal, awarded by Engineers Australia each year for distinguished contributions to electrical engineering. He is currently Director of the ARC Centre for Complex Dynamic Systems and Control at the University of Newcastle.

Florian Knorn

Visiting Project Student

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Florian Knorn was a visiting student (from the Otto–von–Guericke–Universität Magdeburg) at the Hamilton Institute from March to September 2005. He worked with Dr. Oliver Mason on the properties of ranking schemes for complex networks, leading to a studienarbeit thesis that was successfully submitted in October 2005. His thesis was entitled "Ranking and Importance in Complex Networks". In particular, he investigated the impact of false or missing data on the performance of various measures of network importance, including the PageRank algorithm and Kleinberg's HITS algorithm. And then studied the performance of such ranking schemes as indicators of essentiality within protein interaction networks and on the impact of false positive and false negative data on the same.

Thomas Schröck
Visiting Research Student

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Thomas Schröck is a visiting student at the Hamilton Institute between June and December 2006. Under the supervision of Eric Bullinger he will carry out the final project (Diplomarbeit) of his studies in technical cybernetics for the University of Stuttgart. In his project, Thomas is developing mathematical models of Chinese hamster ovary (CHO) cell cultures. His mathematical models will allow the data fusion 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 Dr. Eric Bullinger of the Hamilton Institute.

Visits by Team Members

In addition to regular exchanges with local research collaborators, members of the Hamilton Institute Systems Biology team paid visits to the following Institutes and laboratories:

School of Engineering, **Imperial College,** London, UK. (Contact: Richard Vinter)

School of Engineering and Mathematics, **City University,** London. UK. (Contact: Panos Liatsis)

Department of Engineering, **Cambridge University** (Contact: Keith Glover)

Department of Engineering, **Oxford University,** UK (Contact: Stephen Duncan).

Department of Physiology**, Oxford University**, UK (Contact: Marianne Fillenz)

Institute of Information Theory, **The Czech Academy of Science,** Prague, Czech Republic (Contact: Mirek Karny)

Max Planck Institute – Magdeburg, Germany (Contact: Jörg Raisch)

Centre for Complex Systems Biology, **Case Western Reserve University –** Cleveland, Ohio, USA. (Contact: Sree Sreenath)

Ecole Polytechnique and Institut Gerad – Montreal, Quebec, Canada. (Contact: Michel Perrier)

University of Patras and Patras Science Park, Greece. (Contact: Petros Groumpos)

University of Santa Barbara, California, USA. (Contact: Duncan Mellichamp)

University of Stuttgart, Germany. (Contact: Frank Allgöwer)

External Talks by Team Members

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

Oliver Mason, *On the quadratic stability of switched interval systems: preliminary results*, Mediterranean Control Conference, Cyprus, June 2005

Eric Bullinger, *A systems biology approach to apoptosis*. Department of Physiology, RCSI, Dublin, 20 July 2005.

Peter Wellstead, *Strategic Directions in Systems Biology* – Second Systems Biology Workshop at NUI Maynooth, September 2005

Eric Bullinger, *Modelling of cellular dynamics*. 2nd Systems Biology Workshop, NUI Maynooth, 1 September 2005.

Oliver Mason, *Theory and Analysis of Interaction Networks* – Second Systems Biology Workshop at NUI Maynooth, September 2005

Dimitris Kalamatianos, *Classification of urea data from a novel near-infrared spectrometer*, Photonics in Medicine, Sep. 12-14, 2005, Toronto, Canada

Peter Wellstead, *Schroedinger's Legacy*, University College Cork, October, 2005.

Oliver Mason, *Switched linear systems and common quadratic Lyapunov functions*, Seminar Series of the Mathematics Department, University of Limerick, October 2005.

Eric Bullinger, *Dynamic modelling, simulation & analysis - useful for understanding biology?* Biochemistry, NUI Galway, 11 November 2005.

Peter Wellstead, *Schroedinger's Legacy*, Department of Engineering University of Cambridge, 11 November, 2005.

Oliver Mason, *Analysis of biological interaction networks: some recent results and open problems* – Workshop on Data, Algorithms and Decision-making, Institute of Information Theory and Automation, Czech Academy of Sciences, Prague, December 2005

Peter Wellstead, *Schroedinger's Legacy* – Workshop on Data, Algorithms and

Decision-making, Institute of Information Theory and Automation,

Czech Academy of Sciences, Prague, December 2005

Eric Bullinger, *Dynamic modelling, simulation & analysis - useful for understanding biology?* Second International Symposium of the Austrian Proteomics Platform, Seefeld im Tirol, 19 January 2006.

Peter Wellstead, *Schroedinger's Legacy*, Institute for Complex Systems, Max Planck Institute, Magdeburg, 26 January, 2006.

Peter Wellstead, *Schroedinger's Legacy*, City University, London, 22 February, 2006.

Peter Wellstead, *Schroedinger's Legacy*, Imperial College, London 23 February, 2006.

Peter Wellstead, *Schroedinger's Legacy and The Industrialisation of Biology*, Centre for Complex Systems Biology, Case Western University, Cleveland, 28-30th March, 2006.

Peter Wellstead, *Schroedinger's Legacy and The Industrialisation of Biology*, Institute Gerad (Ecole Polytechnique, McGill University, Universite Montreal), 16-18th May, 2006.

Eric Bullinger, *Control theoretical challenges in systems biology*. Control and Power Research Group, Imperial College London, 24 May 2006.

Eric Bullinger, *Control theoretical challenges in systems biology*. Control Group, Cambridge, UK, 26 May 2006.

Eric Bullinger, Control theoretical challenges in systems biology. Case Western Reserve University, 12 June 2006.

Eric Bullinger, *Controllability, observability and sensitivity analysis in biological systems*. Special Session: Biological Control Systems: Endogeneous and Exogeneous Analysis and Design, American Control Conference, Minneapolis, 14 June 2006.

Visitors

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. Visitors for this reporting period included:

Professor Tulay Adali, Department of CSEE, University of Maryland.

Dr. A. Anastasiadis, School of Computer Science and Information Systems, Birkbeck, University of London, UK.

Dr. John Appleby, Dublin City University.

Dr. Neil Benson, Pfizer, UK.

Louis Coffman, Institute of Systems Biology, Seattle.

Ayalvadi Ganesh, Microsoft Research Cambridge, Cambridge.

Dr. Phil Hodgkin, University of Melbourne.

Dr. Wilhelm Huisinga, DFG Research Center MATHEON & Free University of Berlin.

Professor Roy Kishony, Department of Systems Biology, Harvard Medical School.

Dr. Peter Latham, Gatsby Computational Neuroscience Unit, University College London.

Prof. John P. Lowry. The Conway Institute, University College Dublin.

Prof. Sir Alistair MacFarlane. The Millenium Institute, Edinburgh.

Prof. Richard Middleton, The University of Newcastle, Australia.

Professor Bernhard O. Palsson, Department of Bioengineering, UCSD.

Professor Jan H. van Schuppen, CWI, Amsterdam.

Professor Jens Timmer, Universitat Freiberg.

Professor Olaf Wolkenhauer, Universitat Rostock.

Visitor Seminars

As part of the overall Hamilton Institute activity, we have an active seminar programme. Hamilton Institute seminars are deliberately multidisciplinary, and for this reporting period only those seminars with a Systems Biology theme are included:

Prof. Sir Alistair MacFarlane. The Millenium Institute, Edinburgh, *The Future of Machines*. 8 September, 2005

Prof. John P. Lowry. The Conway Institute, University College Dublin, *In Vivo Voltammetry: Real-Time Analysis of Neuronal Signalling, Drug Actions, and Behaviour*, 14 September, 2005

Dr. Peter Latham, Gatsby Computational Neuroscience Unit, University College London. *Requiem for the Spike.* 30 September, 2005

Dr. John Appleby, Dublin City University. *Oscillation and periodicity in stochastic systems.* 30 November 2005

Professor Tulay Adali, Department of CSEE, University of Maryland. *Independent Component Analysis of functional MRI and Complex-valued Data.* 14 December, 2005

Professor Roy Kishony, Department of Systems Biology, Harvard Medical School. Biological functionality in gene and drug networks. 3 March, 2006

Professor Bernhard O. Palsson, Department of Bioengineering, UCSD.
New 'Dimensions' in Genome Annotation, 24 March, 2006

Ayalvadi Ganesh, Microsoft Research Cambridge, Cambridge, UK.
Epidemics on Networks. 31 May, 2006

Professor Jan H. van Schuppen, CWI, Amsterdam.
Control and system theory for biochemical reaction networks, 7 June, 2006

Dr. Wilhelm Huisinga, DFG Research Center MATHEON & Free University of Berlin. *Adaptive approach for non-linear sensitivity analysis of dynamical systems with application to systems pharmacokinetics*, 13 June, 2006

Prof. Richard Middleton, The University of Newcastle, Australia.
Control, Systems Biology & Communication Networks, 21 June, 2006

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 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, Chair in Systems Biology

- 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

Department of Chemistry, NUIM, Ireland and Solvay Pharmaceuticals, Weesp, The Netherlands,

- In-vivo electro-chemical sensing for Systems Biology

Systems Biology Group, University of Stuttgart, Germany

Prof. Frank Allgöwer, Thomas Eißing, Dr. Rolf Findeisen, Stefan Waldherr

- 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

Institute of Cell Biology and Immunology, University of Stuttgart, Germany.

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

Prof. Dr. D. Oesterhelt and Stefan Streif

- Sensitivity analysis of biochemical reaction networks

Department of Electrical and 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.

Prof. Dr. 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 literature produced in the reporting year. Please visit our website www.systemsbiology.ie, for a list of downloadable reports and papers. Visit the personal websites of the team members, for past research records and further downloadable papers.

Chapters in Books

O. Wolkenhauer, M. Mesarovic and **P. Wellstead**, "A Pleas for More Theory in Molecular Biology", In *Systems Biology - Applications and Perspective*. E.Butcher, P.Bringmann, B.Weiss (eds.), Springer-Verlag, In press, 2006

O. Wolkenhauer, M. Mesarovic, S. Sreenath, **P. Wellstead** and A. Rolfs, "From Regulation, Control and Adaption to the Coordination of Cell Function. In *Regulation*. M.Laubichler, H.-J.Rheinsberger, P.Hammerstein (eds.), for publication in Vienna Series of Theoretical Biology, MIT Press. In press., 2006

Journals

S. Duncan, P. Jones and **P. Wellstead**. "A Frequency Domain Approach to Determining the Path Separation for Spray Coating". IEEE Trans ASE, 2, 3, pp 233-239, 2005

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

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

E. Bullinger and F. Allgöwer. Adaptive lambda-tracking for nonlinear higher relative degree systems. Automatica, 41(7):1191–2000, 2005

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". FEBS Letters, 579, pp4520-4528, 2005

T. Eißing, F. Allgöwer and **E. Bullinger**. "Robustness properties of apoptosis models with respect to parameter variations and intrinsic noise". IEE Sys.Biol., 152(4):221–228, 2005

Oliver Mason and **Mark H.A. Verwoerd**, "Graph Theory and Networks in Biology", Journal of Systems Biology, submitted, 2005

D. Kalamatianos, J. Edmunds and **P. Wellstead,** "Active Alignment for Two-Beam Interferometers", *Review of Scientific Instruments*, vol. 77, 2006

Mark H.A. Verwoerd, Gjerrit Meinsma, and Theo J.A. de Vries "Youla Parameterization in Iterative Learning Control", *Automatica*, to appear, 2006

O. Mason and R. Shorten *On the simultaneous diagonal stability of a pair of positive linear systems*, - Linear Algebra and its Applications, 413, pp 13-23, 2006

O. Mason, R. Shorten and S. Solmaz. *On the Kalman-Yakubovich-Popov lemma and common Lyapunov solutions for matrices with regular inertia*, submitted to Linear Algebra and its Applications, 2006

R. N. Shorten, F. Wirth, **O. Mason**, K. Wulff, C. King *Stability Criteria for switched and hybrid systems*, - Invited paper for SIAM Review, currently under review - version available at www.hamilton.ie

E. Zeheb, **O. Mason**, S. Solmaz and R. Shorten, *Some results on quadratic stability of switched systems with interval uncertainty*, submitted to International Journal of Control, 2006

L. Gurvits, R. Shorten and **O. Mason**, *On the stability of switched positive linear systems*, submitted to IEEE Transactions on Automatic Control, 2006

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, 2006. in press

R.J. Middleton, and **P. Wellstead**, "On Intervention in Feedback Loops with Integral Control: Implications for Feedback Medicine", submitted, Journal of Systems Biology, 2006

Conferences and Workshop Proceedings

O. Mason, E. Zeheb, S. Solmaz and R. Shorten "On the quadratic stability of switched interval systems: preliminary results", Mediterranean Control Conference, June 2005

D. Kalamatianos, P. Liatsis and **P. Wellstead**, "Classification of Urea Data from a Novel Near-Infrared Spectrometer", In W.C. Chan, K. Yu, U.J. Krull, R.I. Hornsey, B.C. Wilson, and R.A. Weersink, editors, *Proc. SPIE*, vol. 5969, pp. 379–387, 2005

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

C. Cimatoribus, T. Eißing, 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, pages 197–200, 2005

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

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

Stuart Butler, Mark H.A. Verwoerd, William T. O'Connor, Ronan G. Reilly, and **Peter Wellstead**, "Dynamic Visualization and Modelling of Neurotransmitter Data", International Conference on Systems Biology, Boston, October 19-24, 2005

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

E. Bullinger. System analysis of a programmed cell death model. In Proc. of the 44th IEEE Conf. on Decision and Control and European Control Conference, ECC'05, Seville, Spain, pages 7994–7999, 2005

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

T. Sauter, M. Schliemann, T. Eißing, **E. Bullinger**, E.D. Gilles, F. Allgöwer and P. Scheurich. Mathematical modelling of TNF induced apoptosis and anti-apoptotic crosstalk in mammalian cells. 6th International Conference on Systems Biology ICSB 2005, October 19-24, Boston, MA, USA, 2005

S. Butler, **P. Wellstead**, R.G. Reilly and W.T. O'Connor, "An Integrated Software Toolkit for the Visualisation of Microdialysis Data", SFN 2005 - 35th Annual Meeting (Society for Neuroscience) Washington D.C., U.S.A, November 12-16, 2005

E. Bullinger, R. Findeisen, **D. Kalamatianos** and P. Wellstead, "System and control theory allows to further understanding of biological signal transduction", In *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", In *Proc. International Conference on Systems Biology*, Yokohama, Japan, 2006

D. Kalamatianos, P. Liatsis and **P. Wellstead**, "Near-infrared spectroscopic measurements of blood analytes using multi-layer perceptron neural networks", In *Proc. IEEE Engineering in Medicine and Biology Conference*, New York, US, 2006

D. Kalamatianos, **P. Wellstead**, P. Liatsis and R. Houston, "Control and data analysis tool for a novel FT-NIR Spectrometer", In *Proc. Control 2006 Conference*, Glasgow, UK, 2006

Oliver Mason and **Mark H.A. Verwoerd**, “Graph Theory and Networks in Biology”, International Conference on Systems Biology, October 9-13, Yokohama, Japan, 2006

Mark H.A. Verwoerd, “Fixed Point Analysis of a Finite System of Kuramoto Oscillators”, Proceedings of the Conference on the Mathematical Foundations of Computer Science and Information Technology, August 1-5, Cork, Ireland, 2006

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

S. Butler, **P. Wellstead**, R.G. Reilly and W.T. O’ Connor, “An Integrated Environment for the Visualisation and Analysis of Microdialysis Data”, Monitoring Molecules in Neuroscience - 11th International Conference on In Vivo methods, Cagliari, Italy May 19- 22, 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, October 14-18, 2006

M. Farina**,** R. Findeisen, **E. Bullinger**, S. Bittani, F. Algower and **P. Wellstead**. Results toward Identifiability Properties of Biochemical Reaction Networks. CDC, 2006

E. Bullinger, R. Findeisen and S. Streif. Relating cross gramians and sensitivity analysis in systems biology. In Proc. Int. Symposium on Mathematical Theory of Networks and Systems, 2006. in press

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. In Proc. IEEE Conference on Control Applications, 2006. in press

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