International Workshop on Systems Biology 2006

Hamilton Institute

National University of Ireland, Maynooth

July 17-19, 2006

SYSTEMS BIOLOGY Hamilton Institute

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Systems Biology
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Welcome

Welcome to the first International Workshop on Systems Biology to be organised and hosted by the Hamilton Institute.

The nascent discipline of Systems Biology has grown at an astonishing rate in recent years. Universities, funding agencies and governments are becoming increasingly aware of the importance of developing activities in the area. As a result an ever-increasing number of initiatives and specialist Systems Biology research centres are appearing around the world. This is all very exciting, but it also makes it difficult for an individual researcher to stay abreast of developments within the field. Thus our aim in designing the programme for this Workshop was to bring together a cross-section of leaders in their field, from both academia and industry, and in a manner that facilitates a free exchange of ideas and discussion.

The Systems Biology group at the Hamilton Institute was formed in 2004 and, since its foundation, has been involved in a number of initiatives aimed at raising the profile of Systems Biology within Ireland and at encouraging constructive engagement between researchers interested in the field. This workshop is the latest part of this programme, but is the first with a specifically international focus. As hinted above, our aim is to provide a forum for researchers in Systems Biology from industry and academia to discuss important recent developments and outstanding issues in the field. The keynote lectures and poster sessions will provide an overview of the major current areas of interest while the break-out sessions and receptions will offer the opportunity to discuss specific items of interest in a less formal setting.

There are a number of people without whose hard work and patient help this workshop would not have been possible. In particular, we would like to thank Stuart Butler for his management of the workshop website and Rosemary Hunt for organising the accommodation and looking after the many other administrative issues that need to be dealt with to ensure the smooth running of an event such as this. The assistance of Thomas Schröck and Kate Moriarty should also be acknowledged here.

We hope that you will find the three days of the workshop both stimulating and informative and that the time you spend here will prove of value to you in your future research and teaching. In closing, we offer you our personal welcome to the home campus of the Hamilton Institute, here at NUI Maynooth, and encourage you to also take some time to admire the beauty of St Patrick's College, its gardens, and of course the hospitality to be found in the town of Maynooth.

The Organising Committee:

Dr. Eric Bullinger;

Dr. Dimitris Kalamatianos;

Dr. Oliver Mason;

Dr. Mark Verwoerd.

Honorary Co-chairs:

Dr. Neil Benson;

Prof. Peter Wellstead;

Prof. Hans Westerhoff.

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Programme

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19:30-21:00 Welcome Reception

Monday, 17 July 2006

Morning Session — Chair: Prof. Peter Wellstead

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9:15-10:00	**Bottom-up Systems Biology** (Part 1) Prof. Hans Westerhoff, *Manchester Centre for Integrative Systems Biology, UK*
10:00-10:05	Break
10:05-10:50	**Computational reconstruction of transcriptional regulatory networks: theory and biological examples** (Part 1) Prof. Hamid Bolouri, *Institute for Systems Biology, USA*
10:50-11:15	Coffee break
11:15-12:00	**Computational reconstruction of transcriptional regulatory networks: theory and biological examples** (Part 2) Prof. Hamid Bolouri, *Institute for Systems Biology, USA*
12:00-12:05	Break
12:05-12:50	**Control theoretic approaches to Systems Biology** (Part 1) Prof. Brian Ingalls, *University of Waterloo, Canada*
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14:00-14:45	**Control theoretic approaches to Systems Biology** (Part 2) Prof. Brian Ingalls, *University of Waterloo, Canada*
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14:50-15:35	**From epistasis information to biological function** (Part 1) Prof. Roy Kishony, *Harvard University, USA*
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11:15-12:00	**Bottom-up Systems Biology** (Part 2) Prof. Hans Westerhoff, *Manchester Centre for Integrative Systems Biology, UK*
12:00-12:05	Break
12:05-12:50	**Statistical and evolutionary inferences from biological networks** (Part 2) Dr. Michael Stumpf, *Imperial College London, UK*
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14:45-14:50	Break
14:50-15:35	**Predictive models in the diagnosis and prognosis of disease** (Part 2) Prof. Lucila Ohno-Machado, *Harvard Medical School, USA*
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11:15-12:00	**Modeling and Inference of genetic networks: Computational and experimental approaches** (Part 1) Prof. Ilya Shmulevich, *Institute for Systems Biology, USA*
12:00-12:05	Break
12:05-12:50	**Modeling and inference of genetic networks: Computational and experimental approaches** (Part 2) Prof. Ilya Shmulevich, *Institute for Systems Biology, USA*
12:50-14:00	Buffet Lunch

Afternoon Session — Chair: Dr. Dimitris Kalamatianos

14:00-14:45	**The role of feedback in intracellular networks** (Part 1) Prof. Elling W. Jacobsen, *KTH Stockholm, Sweden*
14:45-14:50	Break
14:50-15:35	**The role of feedback in intracellular networks** (Part 2) Prof. Elling W. Jacobsen, *KTH Stockholm, Sweden*
15:35-15:45	Closing Remarks Prof. Peter Wellstead, *NUIM, Ireland*
15:45-16:00	Coffee Break
16:00-17:30	Breakout Session 2

Abstracts of Keynote Speakers

Computational reconstruction of transcriptional regulatory networks: Theory & biological examples

Hamid Bolouri

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HBolouri@systemsbiology.org

In the first talk, I will review the theoretical and computational framework for model building and analysis with emphasis on tools and techniques developed by my group. In the second talk, I will take the audience through examples of networks we have constructed in yeast, sea urchin embryos, and mouse macrophages, emphasizing the different needs of different biological systems.

Control theoretic approaches to Systems Biology

Brian Ingalls

Department of Applied Mathematics, University of Waterloo, Canada
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This presentation will introduce aspects of feedback control theory which have proved relevant in the investigation of biochemical networks. These analytic tools, which were developed to aid in the design and analysis of engineered self-regulating systems, provide a valuable framework for the reverse-engineering of networks of regulatory interactions within the cell. Topics covered will include the roles of negative and positive feedback, the special features of integral control, and the analytic framework provided by linearization and the frequency response. These theoretical foundations will be illustrated by specific biological applications.

The role of feedback in intracellular networks

Elling W. Jacobsen

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The presentation will give a control theoretic perspective on the role of feedback in intracellular networks. In the first part I will provide an overview of some general properties of feedback systems, and discuss how these are employed in the cell to generate functions and provide properties such as robustness. In the second part I will introduce tools that can be used to identify and analyze key feedback mechanisms embedded in complex biochemical networks. Relevant biological applications will be used for illustration throughout.

From epistasis information to biological function

Roy Kishony

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Complex biological functions are encoded by networks of interacting genetic components. Epistasis, describing the way multiple perturbations (mutations or drugs) in such networks affect each other's phenotypic consequences, provides essential information for elucidating the network functional architectures. I will describe a combined experimental-theoretical approach to quantify epistatic interactions in bacteria and yeast and for using epistasis information to identify functional gene modules and their system-level organization.

Predictive models in the Diagnosis and prognosis of disease

Lucila Ohno-Machado

Harvard Medical School, Cambridge, MA
and
Brigham and Women's Hospital, Boston, MA, USA
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This presentation will focus on key considerations in building diagnostic and prognostic prediction systems using biomarkers and clinical data. A review of the most commonly used methods for model construction drawn from the statistical and machine learning communities will be followed by a comprehensive exposition on evaluation methods and an overview of deployment strategies. Special emphasis will be given to understanding differences in discrimination and calibration indices and how they impact the use of predictive models.

Modeling and inference of genetic networks: Computational and experimental approaches

Ilya Shmulevich

Institute for Systems Biology, Seattle, WA, USA
and
Department of Bioengineering, University of Washington, Seattle, WA, USA
is@ieee.org

Cellular function and interaction with its microenvironment is governed by the integrated behavior of regulatory networks of interacting biomolecules inside the cell. Revealing the structure of these networks is of paramount importance for understanding the nature of cellular behavior in health and disease. New technologies are now making it possible to measure the activities of thousands of molecular species inside the cell. From these measurements, taken under various conditions and time points, we can make inferences about the structure of the underlying regulatory networks. Combining diverse types of measurements and other data can significantly improve our ability to correctly infer this structure. I will discuss computational and statistical approaches to model, simulate, and infer genetic networks from measurement data. I will present several modeling approaches, along with examples, and discuss the relationships among them.

Statistical and evolutionary inferences from biological networks

Michael Stumpf

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Current protein interaction network data are notoriously noisy and incomplete: for most species – apart from S.cerevisiae – only the interactions among relatively small sets of proteins are known. As a result present network datasets only offer us partial insights into the structure and functional organization of molecular interaction networks in most species. Here we discuss the extent to which such missing information may affect functional and evolutionary inferences in systems biology and statistical tools that allow us to assess the properties of the true network. In particular we will show that it is possible to estimate the size of the true whole-organism interactome from the present partial datasets. We present a powerful, efficient and very reliable estimator and illustrate its performance using several published *S. cerevisae* datasets. We obtain consistent and similar estimates (and associated confidence intervals) for these datasets and estimate that the complete yeast interactome will have approximately 24000-30000 interactions. We then apply the same formalism to different datasets from *P. falciparum*, *D. melanogaster*, *C. elegans* and *H. sapiens* to see if predicted interactome size reflects the complexity of these organisms. We obtain interactome size estimates of approximately 19000, 70000, 230000 and 680000 interactions, respectively, and find good agreement between different datasets for the same species. Thus the human protein interaction network appears to be approximately an order of magnitude larger or more complex than the fruit fly protein interaction network. We show that our approach will yield reliable estimates for most systematic high-throughput experiments. We conclude with a discussion of the implications of these results for comparative and functional analyses in systems biology.

Bottom-up Systems Biology

Hans Westerhoff

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and
Manchester Centre for Integrative Systems Biology, UK
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Systems Biology is the science that aims to lead us from macromolecules to biological function. It is about the dynamic organization of those molecules, the consequent nonlinear interactions and about how these generate properties that are not yet present in the individual molecules. Since Life requires a minimum genome, Systems Biology has to connect ultimately to everything in that genome that affects this emergence of function (www.systembiology.net). Bottom-up Systems Biology starts from a limited set of molecules and examines what new may come from their interactions. Using biology, physical chemistry and mathematics it deduces from known or experimentally determined molecular properties and from known or empirical organization, the functional properties that emerge. In this, bottom-up Systems Biology attempts to discover new laws and principles that govern biological systems. By testing its predictions, it then discovers unknown molecular properties, or verifies the understanding achieved.

Since its focus is on the emergence of new function from already known interactive properties of biological macromolecules, initially new experimentation is not always needed. One may make a replica of the biological system in terms of all its components, their activities and their interactions and then have a computer calculate the emerging behavior. The activities are specified by rate-equations (or equilibrium equations where appropriate) that indicate how processes change when the interactions change. Balance equations specify how component concentrations change due to the activities. The computer merely integrates the equations in time (and space) or solves them for steady state. Such 'computer replica' are being made of an increasing number of pathways in more and more organisms. They are collected in the silicon cell live modelbase, where they are accessible to everyone for direct experimentation in silico through the web. I shall show how one can calculate through the wwweb which may be the best drug target vis-à-vis the sleeping sickness caused by Trypanosomes. This live modelbase is also useful for those wishing to get a feel for the system behavior of various pathways. www.siliconcell.net houses teaching modules to aid in this.

Using the silicon cell one can also do experiments in silico. Thus one may calculate the extent to which each enzyme (or molecular process) in a pathway controls the behavior of the pathway. Metabolic Control Analysis has defined control coefficients in order to quantify this. I shall use this to illustrate how one can discover laws that govern this control vis-à-vis flux, concentrations, electric potentials, and transient times. I shall illustrate this with applications to EGF signaling, anti-tumor drug research, and obesity and type 2 diabetes. Control analysis is also a way to relate the system property of control, to the properties of the components and the topology of the network. Connectivity laws govern these relations. I shall show how the mathematics of the laws of Control Analysis translate into rules of thumb that are close to but sometimes at odds with intuition.

One should expect control of functional processes to reside also at the meta-levels of mRNA metabolism and protein metabolism. And indeed Hierarchical Control Analysis shows that this may miss much of the relevant interactions. The same goes for regulation: when a living organism meets a challenge it often responds by regulating its own functioning. All too often functional genomics studies, though genome-wide, are limited to a single 'layer' of cellular regulation. They presuppose that only transcriptional regulation matters. On the other hand, there is a rich history of studies of metabolic regulation. Are we to suppose that the latter is irrelevant, or the former?

In reality Systems Biology is 'vertical' as well as 'horizontal': it does not so much involve the interactions of mRNAs, in so-called gene networks, as that it involves the interactions between mRNAs, proteins and metabolites involved in the same functional pathway. I shall demonstrate a

method, called 'Hierarchical Regulation Analysis' that enables one to determine quantitatively how much of regulations occurs at the transcription level, how much at the translation level and how much at the metabolic level. The method prescribes a certain type of experimentation, which turns out to be quite feasible and doubly informative thanks to yet another law, now of for regulation rather than control. Illustrating this for yeast starved for nitrogen or carbon, we shall see that the organism employs a rich mixture of regulation strategies: it has certain enzymes biting the bullet by being regulated strongly through gene expression and others following, through weaker metabolic regulation. Sometimes metabolic regulation works against the change in flux; parts of the pathway appear to try to prevent over-regulation by other parts.

Doing bottom-up systems biology of the entire living cells seems an arduous task, knowing that model unicellular organism previously elected because of their simplicity, have thousands of genes and hence thousands of processes. It will be essential therefore to develop a methodology to work on subsystems first and then to combine the results into an understanding of the whole system. Modular kinetic and control analysis are such methodologies and I will demonstrate these for an analysis of the effects of fatty acyl CoA esters on the performance of mitochondria.

All in all, there is now ample methodology for the implementation of bottom-up systems biology, here is no excuse is left for not going the extra mile from functional genomics to the understanding of the basis of biological functioning (and malfunctioning!). For those who want to engage more in this, there is books, advanced courses, training centers (www.systembiology.net), and integrative and coherent systems biology programs such as on the liver cell, yeast, ageing and host parasite interactions (see www.systembiology.net).

Poster Abstracts

A comparative evaluation of protein-protein interaction network clustering methods

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Background Clustering-driven analysis of protein-protein interaction (PPI) networks can lead to the discovery of functional modules (i.e. protein complexes and functional pathways). Clusters may be represented as dense sub-graphs of interacting proteins that are highly connected with each other but that are sparsely linked to other dense sub-graphs. This can also provide insights into how interacting proteins are organized into functional modules and how they participate in common biological processes. Over the past few years relatively more effort has been focused on developing algorithms for PPI networks inference. However, there is a need to assess existing network clustering strategies and propose new approaches for clustering-based visualization.

Methods and Results Representative clustering methods based on graph theoretic approaches: MCODE [1], CFinder [2], [3], Parallel Edge Betweenness Clustering (PEBC) [4], MC^2 [5] were compared on the basis of their clustering outcomes and their relationships to functional modules. We analyzed whether the clusters obtained by each algorithm were biologically meaningful in relation to available functional databases (MIPS and the *Saccharomyces cerevisiae* Genome Database, SGD). Also the Functional Catalog (FunCat) was used to assess the quality of these clusters. Analysis of the enrichment of functional annotations derived from FunCat and SGD was implemented. The FatiGoplus tool was used to determine significant associations between clusters obtained and Gene Ontology (GO) biological process terms. The clusters were matched with known MIPS complexes using a traditional overlapping score [1].

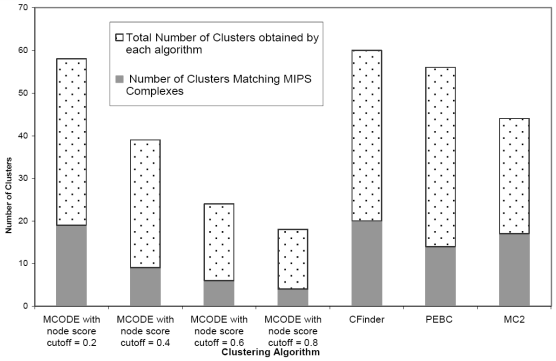

Figure 1: Distribution of the number of predicted clusters that match MIPS complexes (using a class matching score threshold > 0.2).

Overall, MCODE, CFinder and MC^2 generate similar results in terms of their relationships with known complexes (Fig. 1). However, MCODE and PEBC produced higher number of statistical functional classes assessed by GO and FunCat (Fig. 2).

Conclusion The methods assessed are in general capable to detect clusters that may be significantly associated with protein complexes and functional pathways. However, this evaluation provides evidence for a relative high variability of clustering outcomes and a relative lack of robustness using graph theoretic approaches. This motivates the design of alternative knowledge-driven clustering approaches and cluster validity indicators.

References

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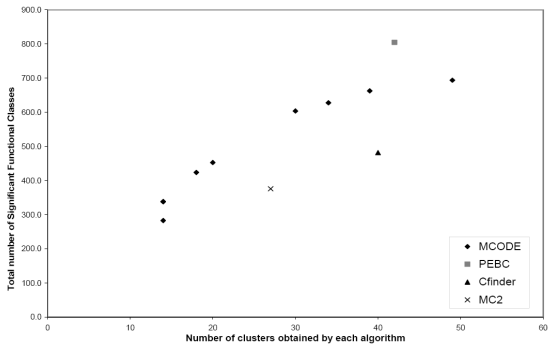

Figure 2: Total number of functional classes significantly associated (as defined by FunCat) with clusters detected by different algorithms. Different partitions can be generated by MCODE [1] for different clustering parameters.

A review of machine and statistical learning models to infer networks of protein-protein interactions in *Saccharomyces cerevisiae*

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Background Protein-protein interactions (PPI) play a key role in many biological systems. An explosion in availability of functional biological data obtained from high-throughput technologies to infer PPI has been observed. However, results obtained from such experiments show high rates of false positives and false negatives predictions as well as systematic predictive bias. Recent research has revealed that several methods applied to integrate relatively weak, diverse sources of large-scale data may provide improved predictive accuracy and coverage of PPI.

Data sources and Gold Standard Diverse sets of relatively strong and weak predictive datasets were integrated to predict PPI in Saccharomyces cerevisiae. Seven genomic datasets obtained from Lu et al. [1] were analysed. These datasets ranged from mRNA co-expression to marginal essentiality. We expanded an existing multi-source dataset from S. cerevisiae by constructing a new set of putative interactions extracted from Gene Ontology-driven annotations in the Saccharomyces Genome Database referred to as GOSEM. To validate PPI computational predictions, a reference dataset (Gold Standard (GSTD)) that contains known positive (proteins that are both in the same complex) and negative (non-interacting) protein pair cases was constructed from the MIPS complex catalogue [2].

Methods Three different computational, integrative methods to predict PPI: Simple Naive Bayesian (SNB), Multilayer Perceptron (MLP) and K-Nearest Neighbors (KNN) were evaluated.

Results The SNB classifier produced the "highest" predictive quality obtaining an area under Receiver Operating Characteristic (ROC) curve (AUC) value of 0.99. The lowest AUC value of 0.90 was obtained by KNN. Fig. 3 displays the predictive performance of each classification method for two data integration schemes 1) "All datasets" which is the integration of all eight datasets and 2) "Strong datasets I" which is the integration of the top 5 datasets. The top datasets are those that obtained the highest AUC values when using these datasets as single predictive sources. As the predictive power of single-source datasets became weaker MLP and SNB tend to perform better than KNN.

This investigation demonstrates the strong predictive power of GO-driven models, which offered predictive performance above 0.90 using the different predictive techniques. The investigation has proven that the dataset GOSEM may improve predictive power when integrated with other large-scale datasets. Integration of weak and stronger datasets may not have significant impact on the predictive performance of all predictive models.

Conclusion SNB and MLP were the best predictive models in terms of AUC values when integrating all datasets. The investigation indicates that predictive saturation could have been reached by the prediction models used in this study. Existing models are limited by predictive bias, incompleteness of existing GSTD and noisy datasets. However, more comprehensive and accurate PPI maps will be produced for S. cerevisiae and beyond with the emergence of large-scale datasets of better predictive quality and the integration of intelligent classification methods.

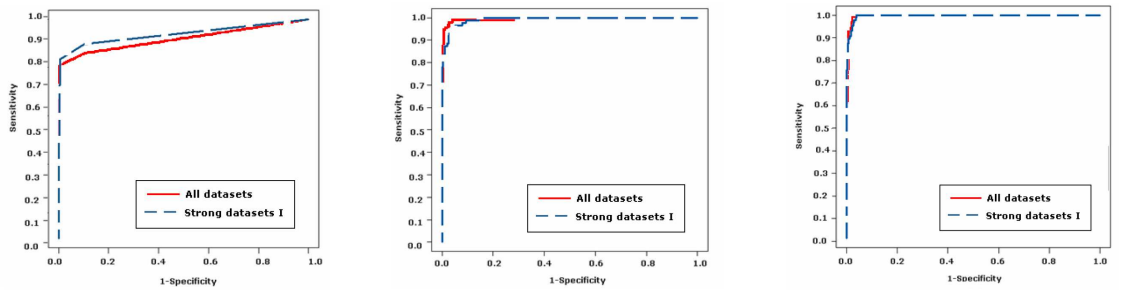

Figure 3: ROC curves obtained from integrating all eight datasets together, compared with integrating only the strongest 5 datasets. Each panel represents a different classifier (a) KNN (b) MLP (c) SNB.

References

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De-noising and stabilization in sampled genomic systems

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Quantitative genomics through microarrays allows researchers to measure the abundance of thousands of mRNA targets simultaneously, and analyze noisy high-dimensional data from measurements of many gene expression changes that are often based on limited experimental conditions, as in the case of time course observations or different experiments. Under such constraints, one of the problems is that of relying on coarse approximations of biological systems. In gene networks, for instance, when the goal is reconstructing from the experimental measurements the gene-gene interactions by identifying the structure of the network and the strength of its connections, an inverse problem has to be solved. In this work, two major aspects of learning from high-dimensional data, i.e. sparsity and intrinsic dimensionality, are considered, together with the contribution of experimental replicates and their influence on the gene selection performance in terms of de-noising and genomic signal stabilization. As the experimental outcomes and the pre-processing steps might be replicate-dependent, a question to address is the sensitivity of the feature learner with respect to within- and between-replicates data. In particular, we show sparsification strategies that stabilize the results with respect to the variability between the replicates variability, and then select estimated gene features with the most informative biological information that help elucidate the underlying regulatory genomic map.

Modelling the G1/S phase transition in liver regeneration

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Hepatic function is maintained even after excessive damage by ingested toxins, as cell death is counterbalanced by compensatory cell division ("regeneration"). During liver regeneration cytokines, which are released from injured sites, stimulate normally quiescent hepatocytes to re-enter the cell division cycle [1]. Using a top down approach we have implemented a first mathematical model that describes cytokine-induced dedifferentiation of hepatocytes and the subsequent initiation of DNA synthesis (G1/S phase transition of the cell cycle). The model accurately reproduces experimentally measured kinetics of various signaling intermediates and that of DNA synthesis in hepatocytes for varying degrees of liver damage, in both wildtype and knockout backgrounds.

We analyze the model in terms of control over signaling times, amplitudes and durations, using recently developed methods from control analysis [2,3]. This analysis enables us to test the robustness of the model. Moreover, control analysis allows us to get insights into the principles that underlie some experimentally observed phenomena. For example, the model accounts for the experimetally observed biphasic response to changing IL6 levels [4]. This dynamics can be related to a hidden feed forward loop in the reaction network [5]. Furthermore, we study the precisely timed regulation of Cyclin D, Cyclin E and their inhibitors [6].

Finally, we discuss extentions of the model beyond the induction of DNA synthesis, and the development of stochastic and spatial models for the size control of the regenerating liver.

References

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Functional evolutionary genomics of orphan genes

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Within all genomes fully sequenced to date, 20-30% of predicted protein coding genes have no recognizable homolog in other species. These genes are considered 'orphans' whose function can only be determined by genetic or biochemical analysis. Our group is investigating how orphan genes arise, evolve and acquire functional roles in model organisms such as Arabidopsis thaliana. In this regard, we are exploring whether rapidly evolving orphan genes may be involved in the evolution of adaptive and reproductive traits, whilst slow-evolving orphan genes may have acquired lineage specific traits.

An approach to evolving cell signaling networks in silico

J. Decraene[†*], G. Mitchell[†], C. Kelly[‡] and B. McMullin[†]

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Cell Signaling Networks(CSN) are complex bio-chemical networks which, through evolution, have become highly efficient for governing critical control processes such as immunological responses, cell cycle control or homeostasis. From a computational point of view, modelling Artificial Cell Signaling Networks (ACSNs) in silico may provide new ways to design computer systems which may have specialized application areas.

To investigate these new opportunities, we review the key issues of modelling ACSNs identified as follows. We first present an analogy between analog and molecular computation. We discuss the application of evolutionary techniques to evolve biochemical networks for computational purposes. The potential roles of crosstalk in CSNs are then examined. Finally we present how artificial CSNs can be used to build robust real-time control systems.

The research we are currently involved in is part of the multi disciplinary EU funded project, ESIGNET, with the central question of the study of the computational properties of CSNs by evolving them using methods from evolutionary computation, and to re-apply this understanding in developing new ways to model and predict real CSNs. This also complements the present requirements of Computational Systems Biology by providing new insights in micro-biology research.

Analysis of gene regulatory elements with information content

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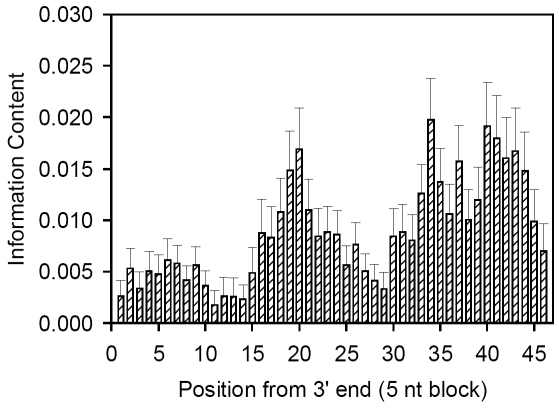
The present study involves three parts. First, we have studied the core promoter region in five sets of promoter sequences (sequences obtained from PlantProm and EPD databases) by calculating the average mutual information content. Here we constructed and applied nucleotide substitution matrices (both neighbor independent and neighbor dependent) for the core promoter region and calculated the information content from these substitution matrices to study the Transcription Start Site (TSS) region, TATA-box, and downstream region. Neighbor independent substitutions will give 4×4 matrix and lack any preferences (this is the standard assumption made in all sequence alignments that the neighboring bases show no preferences). In other words, adjacent bases are considered independent. Next we see the formulae (they will be very similar except the subscripts will now be pairs) for the base pairs taken together, which correspond to a nearest neighbor preference. As we are considering a pair, there will be 16×16 matrix. These matrices include adjacent pair preferences explicitly. The results show that the TSS-region is likely to be 5–10 bases in size. We also notice that both in the case of mouse and humans, both TATA-box and TSS-region are likely to play important roles. However, in case of plant, the results showed the importance of TSS-region for transcriptional initiation (compared to the TATA-box region).

Second, we present a new cluster method to classify Transcription Factor Binding Sites (TFBS). The clustering of TFBS (JASPAR database) with information content suggests that in each group of clustered TFBS with their respective TF-class share any one of TF-class in that clustered TF-class. Thus in JASPAR database, out of the 41 TFBS (in humans), perhaps only 5–10 or so TFs may be actually needed and in case of mouse instead of 13 TFs, we may have actually 5 or so TFs. The experimental data of TFs of specific gene expression from Transcription Regulatory Regions Database (TRRD) is also coincides with our computational results. This gives us a new way to look at the protein classification-not based on their structure or function of TFs but by the nature of their TFBS.

Third, we also analyze the mitochondrial genome sequences for the transcription start sites with the information content. In this study, we concluded that the presence of short-range correlations within the TSS region is species dependent and is not universal. We further noticed that there are other variable regions in the mitochondrial control element (apart from the TSS) that also clearly show up in this study. The information content of the mitochondrial genome near the control element computed as an average for a 5-nucleotide overlapping block shown in the graph (left) the neighbor independent substitution matrix (4×4 matrix). We also note that effective comparisons can only be made on the blocks and single nucleotide comparisons does not give us any detectable signals. We have found that information content may be useful to study the variable functional regions in genome in an efficient manner.



Proposed control of pathway metabolics for geldanamycin synthesis

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The Shikimate and related pathways play a critical role in providing aromatic precursors for microbial biosynthesis of many antibiotics, including geldanamycin, a novel chemotherapeutic agent produced by Streptomyces hygroscopicus var. geldanus in submerged fermentation. The shikimate pathway represents a reaction sequence that proceeds from two precursors of carbohydrate biosynthesis, D-erythrose 4-phosphate (E4P) and phosphoenolpyruvate (PEP), through shikimate to aromatic compounds such as the aromatic amino acids. A by-product of this pathway, 3-Amino-5-hydroxybenzoic acid (AHBA), constitutes an aromatic benzoquinone C7N unit incorporated in the biosynthesis of a wide variety of Streptomyces spp. antibiotics such as rifamycin, mitomycin C, and geldanamycin. Understanding the regulation of the aromatic biosynthetic pathway of this genus is, therefore, of relevance to precursor supply for biosynthesis of a range of clinically and commercially important molecules.

Large scale prediction of protein-protein interaction motifs in yeast

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Short, linear motifs in proteins are fundamental to a wide range of biological processes, including protein-protein interactions (Puntervoll et al. 2003, Neduva et al. 2005, Neduva and Russell 2005). Discovery of such motifs in any given dataset is often hampered by the occurrence of numerous stochastic motifs due to evolutionary relationships between the proteins analysed. We have developed an algorithm, SLiMDisc (Short, Linear Motif Discovery) (Davey et al. 2006), which filters out motifs arising through homology, identifying convergent motifs. Each dataset is run through the TEIRESIAS motif discovery algorithm (Rigoutsos and Floratos 1998) and a BLAST-based algorithm, GABLAM (Edwards and Davey 2006), used to determine sequence similarity. The results from both these programs are then processed by SLiMDisc, which filters out motifs occurring due to shared evolutionary descent.

Large-scale protein-protein interaction datasets present a potential treasure-trove of linear motifs involved in protein-protein interactions. Particularly powerful are genome-wide analyses, such as those performed in yeast (Uetz et al. 2000, Ito et al. 2001, Guldener et al. 2006). Two-hybrid interaction data has come under criticism for containing "false positive" interactions that are not biologically meaningful or reproducible. For motif discovery, however, the distinction between biologically meaningful interactions and spurious interactions caused by proteins coming together outside of their usual biological context is a moot point. The binary nature of two-hybrid interactions reduces the complexity of common mediating interaction partners that other interaction datasets (e.g. TAP-tagging) may suffer from, making them ideal for this kind of motif discovery program.

We have farmed interaction datasets for individual proteins from large-scale yeast two-hybrid experiments and analysed them with SLiMDisc. In addition, datasets based on Gene Ontology (Ashburner et al. 2000) were run through the same motif discovery tool. Results from these two analyses were then compared to identify putative functional motifs involved in protein interactions and/or GO functions.

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Bistability in cell signalling and applications to apoptosis - principles and robustness aspects

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Biological signal transduction is essential to coordinate behaviour. One interesting aspect is that graded input signals can be converted to all-or-non output signals [1], i.e. certain signalling pathways show a bistable behaviour allowing for switching phenomena or memory. We explore simple biochemical mechanisms to generate such a bistable behaviour and study one model in more detail. This model represents the core reaction network of an apoptotic pathway. Apoptosis is a form of programmed cell death present in every cell. The program is essential to remove cells that are old, infected or potentially dangerous. Misregulation is implicated in severe pathological alterations [2]. Using bifurcation (like) studies, we can show minimal requirements for a bistable behaviour of the apoptosis model. Combining this information with reported kinetic values, we can further show that the biological data available is not consistent and that the pathway requires additional regulation. We propose an accordingly extended model, which is now supported by recent experimental findings [3]. The critical role of apoptosis in an uncertain environment with diverse external influences requires a robust performance of the pathway to allow proper biological function. We investigate the robustness of the bistable behaviour with respect to parameter changes and compare the apoptosis models [4] and the additional biochemical mechanisms introduced. We extend these studies to include a special perturbation/influence reported in literature which is so far mostly ignored in mathematical models, i.e. a residual activity of so-called "inactive" components. The different models show surprisingly different behaviours to the perturbations investigated. This has interesting implications for apoptosis and bistability in cell signalling in general.

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Dynamic modelling of the role of gamma-delta T cells in airway inflammation

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Inflammation is a response to infection or immunological insult that has been known since ancient times. Whilst the cardinal signs were known to the Roman Physician, Celsus, the mechanisms underlying that process are complex, dynamic and still to be characterised. Using an infectious model of respiratory challenge and either normal or gene knockout mice, this study probes the temporal events of inflammation in the airways with particular respect to the regulatory role of gdT cells. Time course studies, gene expression arrays, immunohistology and flow cytometry are combined to indicate two mediators which may play a role in the early events of inflammation. The results presented may have significance for neonatal respiratory diseases, and provide testable hypotheses for druggable targets.

Results towards identifiability properties of biochemical reaction networks

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One of the central themes in systems biology is the mathematical modelling, dynamic simulation, and analysis of metabolic and signal transduction pathways. Typically, the modelling based on biochemical reaction networks leads to a high number of states and differential equations, with a large number of parameters describing the reaction kinetics. Examples are models of signalling cascades which have up to several hundred states and even more parameters.

Often, the parameters are either completely unknown, or only rough estimates for them are available. Since the behaviour and dynamics of the network strongly depend on these parameters, estimating them from experimental data is a significant bottleneck in systems biology. Theoretically as well as practically, there are many open questions concerning the parameter identification for biochemical networks, spanning from the rather large measurement errors typically encountered in systems biology, the typical lack of reliable dynamical measurement data, up to the question of parameter identification of continuous time systems.

We consider the problem of parameter identification from a systems perspective. Taking the specific system structure of biochemical reaction networks into account, we derive sufficient conditions for local parameter identifiability based on a suitable system expansion. The presented results should be seen as preliminary results, laying a theoretically sound basis for the development of new identification methodologies for biochemical reaction networks.

Integrated modelling of angiotensin II induced neuronal plasticity in the brain

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The fundamental process underlying all brain function is the ability of the neurons to adapt to external inputs in the context of the neuronal state. The adaptive processes span multiple spatial and temporal scales ranging from millisecond dynamics of the ion channels, seconds to minutes time scale of the signaling pathways, and tens of minutes to hours time scale of the gene regulation and its feedback onto the signaling pathways and electrophysiology. Mathematical modelling and analysis provides appropriate tools to decipher how the signals are integrated in this complex multi-scale system. The present study focuses on integrating two levels of the neuronal adaptation: signaling dynamics elicited by neuropeptide receptors and the consequences on the electrophysiology. The particular system considered is the angiotensin II receptor signaling and electrical activity in the cardiorespiratory neurons in the Nucleus Tractus Solitarius (NTS) in the brainstem. Most of the effects are mediated by the activation of the receptor type I (AT1R) in the NTS neurons. Stimulation of the NTS neurons by AngII has been shown to result in an increase in the electrical activity leading to neuronal adaptation. Pharmacological studies have implicated the signaling kinases, PKC and CaMKII, in modulation of the different ion channels.

To understand the dynamics of the AT1R mediated neuromodulation and the relative contribution of different kinases, we have developed an integrated model of AngII induced neuronal firing behavior. This multi-scale model integrates a Hodgkin-Huxley like model of the electrophysiology (based on Rogers) describing the dynamics of the ion channels and a detailed kinetic reaction model of the AT1R mediated intracellular signaling pathway (based on Mishra and Bhalla). The key aspect of integrating the signaling and electrical models is the change in the conductance of different ion channels upon phosphorylation by the kinases PKC and CaMKII. The exact kinetics of this phosphorylation are not clear and hence different formulations of kinetic behavior were explored in the simulations. Analysis of the model dynamics revealed distinct regulatory properties corresponding to different ion channels and a novel role for the delayed rectifier potassium channel as a dual regulator. In addition, the simulations indicate that the non-voltage-activated transport dynamics lead to transient inhibition in response to AT1R stimulation. However, phosphorylation of the delayed rectifier potassium channel by PKC counteracts this transient inhibition to result in a net increase in the electrical activity, in concordance with the electrophysiological experimental observations.

The current model forms the basis for developing a multi-scale neuronal adaptation model that integrates electrophysiology, signaling and gene regulation.

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Modelling and analysis of force induced bone growth

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Bone is a dynamic living tissue that undergoes continuous adaptation of its mass and structure in response to mechanical and biological environment demands. Studies of bone adaptation have been focused on metabolic stimulus or mechanical stimulus, but mathematical models of bone adaptation considering both, metabolic and mechanical stimulus, are not available by now. In this paper, we propose a mathematical model for the changes on bone adaptation during a remodelling cycle due to mechanical stimulus. The key point in the model is the introduction of osteocytes as mechanotransducer. The achieved results capture the bone adaptation response and the cell interactions during bone remodelling.

Space-temporal modelling of ERKpp/RKIP/Raf-1 dynamics in Ras/Raf/MEK/ERK signal pathway

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It is considered the space-temporal behavior of ERKpp/RKIP/Raf-1 protein complex playing role of a driver of the quasi-stationary behavior of the Ras/Raf/MEK/ERK signaling pathway with a positive feedback mechanism. On the basis of reaction-diffusion model of the process, stable inhomogeneous distributions of ERKpp/RKIP/Raf-1 and other protein concentrations are determined. The reaction-diffusion interaction is interpreted as a possible physical basis of the well-known intracellular compartmentalization.

The investigation, made in this paper is directly related to introduction of reaction-diffusion equation, representing dynamics of ERKpp/RKIP/Raf-1 protein complex in order to analyze its stability. This problem has major biological importance in view of fact that the behaviour of the MEK/ERK pathway near the quasi-stationary state is dependent on the type of dynamical behaviour of this protein complex. By our analysis we show that the stability of this driver is dependent on its initial concentration. In this way, it is firstly proved that at lower initial protein concentration, the corresponding steady state of the driver is stable and near it a spatially inhomogeneous distribution of the protein complex concentration is stable too. Then analogical conclusions are made for the other variables of the Ras/Raf/MEK/ERK pathway. Therefore in terms of spatial modelling, the well-known compartmentalization in the intracellular space can be interpret as stable protein inhomogeneous distributions obtained in the process of reaction-diffusion interaction.

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Combined multi-parameter live cell microscopy and computational modelling identify key players of apoptotic signalling - a Systems Biology approach

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Apoptosis, or programmed cell death, removes superfluous or damaged cells from the body of multi cellular organisms. Enhanced or repressed apoptosis has been shown to contribute to developmental defects, autoimmune diseases, cancer, and neurodegenerative disorders.

Intracellular apoptotic signalling is accompanied by the release of mitochondrial proteins into the cytosol, mitochondrial depolarization, and subsequent activation of proteases of the effector caspase family. In previous studies we established multi-parameter imaging routines to analyse these signalling events spatiotemporally in single living cells using epifluorescence and confocal microscopy: Mitochondrial depolarization was observed by the membrane potential sensitive dye tetramethylrhodamine methyester (TMRM), the release of mitochondrial proteins was detected in cells expressing the fusion proteins cytochrome c-GFP and Smac/DIABLO-YFP. Subsequent caspase activation was detected by an effector caspase specific fluorescence resonance energy transfer (FRET) probe (CFP-DEVD-YFP).

The processes taking place between the mitochondrial release events and the subsequent caspase activation are complex. As naturally experimental set ups are confined to monitor only a limited number of parameters per experiment, quantitatively and temporally little is known about the interactions of the many other proteins within the apoptotic signalling network under physiological conditions. We therefore combined our live cell microscopy experiments with a comprehensive computer model based on the biochemical properties of proteins involved in apoptotic signalling.

With this systems biology approach of live cell imaging and mathematical modelling we were able to characterize the temporal profiles of a multitude of different protein fractions and identified XIAP (X-linked inhibitor of apoptosis protein) as one key regulatory proteins in the signalling network. Hypotheses on the progression of apoptotic signalling upon overexpressing XIAP were subsequently tested by live cell microscopy. We indeed identified a sharp XIAP dependent threshold deciding on the efficient activation of effector caspases at an intracellular concentration range closely resembling the computer model prediction.

Mechanisms of bacterial pathogen - host interaction

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Bacterial infection or pathogenicity relies on successful host interactions and the success of the host immune system in repelling an invasion relies on the disruption of these interactions. There are numerous interactions that take place at various stages during infection e.g. adherence by adhesins, invasion of host cells by invasins, injection of bacterial proteins by injectins etc. Some known bacterial interactions with host cells rely on specific short linear motifs for successful interaction, without which the pathogen looses virulence. In this study we search for important motifs involved in these host-pathogen interactions, and by their identification we hope to shed light on the molecular dynamics of bacterial pathogenicity.

Cellular computation using classifier systems

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The EU FP6 Integrated Project PACE ("Programmable Artificial Cell Evolution") is investigating the creation, de novo, of chemical "protocells". These will be minimal "wetware" chemical systems integrating molecular information carriers, primitive energy conversion (metabolism) and containment (membrane). Ultimately they should be capable of autonomous reproduction, and be "programmable" to realise specific desired function. A key objective of PACE is to explore the application of such protocell technology to build novel nanoscale computational devices. Our contribution to this project is to investigate approaches to adding minimal computational capability to protocells.

We introduce the Molecular Classifier System (MCS) to represent the internal molecular reactions of the protocell. Reactions in the MCS are constrained as follows: The products of the reaction depend on the reactants and the environment in which the reaction took place; The reactions that can happen depend on the physical and chemical structure of the reacting compounds. In our MCS, there are reactants and reaction rules. The rules determine the reactants and the products for a given interaction.

These simple computational processes may also help in understanding the origins of Cell Signaling Networks(CSNs). CSNs are complex bio-chemical networks responsible for coordinating and controlling cellular activities. CSNs can therefore be regarded as computational systems. To understand the evolution of such complex computational systems as found in nature, we will distinguish the minimal computational properties fundamental for the survival of a protocell.

Evolutionary graph theory

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Evolutionary processes may be dramatically amplified or completely suppressed by the effects of spatiotemporal structure. In this talk, we will discuss the Isothermal Theorem and the Structure Theorems of Evolutionary Graph Theory, and introduce the notion of selection amplifiers and suppressors. Using the methods of statistical mechanics, we will derive a first-order theory of neutral strategies in the case of frequency dependent evolution on graphs. Evolution on cascade graphs, computational complexity, and hysteresis will be introduced as time allows.

A 'Shotgun Immunological' approach for the study of complex systems: synthetic anti-terminal cisternae monoclonal antibodies isolated by bacteriophage display.

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Monoclonal antibodies (mAbs) are highly versatile tools for the dissection of complex biological systems, being employed to analyse the structures, functions, locations and macromolecular interactions of their cognate antigens. However, production of mAbs using hybridoma technology is costly, time-consuming, labour-intensive, ethically unfavourable and consumes a large amount of the target biological material for immunisation and screening purposes. The study presented here demonstrates that an array of synthetic single-chain fragment variable (scFv) mAbs recognising sarcoplasmic reticulum proteins can be rapidly isolated using bacteriophage display techniques, using a very small quantity of the target biological material. The panel of scFv mAbs isolated proved useful in a wide range of immunological techniques, including immunoblot, indirect immunofluorescence microscopy and immunoprecipitation. Consequently, such 'shotgun immunological' strategies will prove effective in the characterisation of macromolecular complexes from biological systems.

EATDB: Capturing, analysing and interpreting experimental data in the context of protein structures.

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We present a graphical desktop-based program [EATDB - Enzyme Analysis Tool and DataBase] for analysing datasets of point mutations in proteins or enzymes. EATDB contains functions basic functions for organising and analysing experimental data, and can be used both for predictive and analytical purposes. We present examples of an EAT-based analysis of experimental datasets and show how day-to-day information management in the lab can be handled by EAT. EAT is available from `http://enzyme.ucd.ie`.

Experiment design for systematic excitation of gene regulatory networks

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Excitation, signal directionality and their role in experiment design for identification of gene regulatory networks are here studied from a control theoretic perspective. We limit our consideration to linear dynamic network models for a particular state of the system, e.g. the state of a healthy or disease cell. Rank deficiency of the measurement matrix, containing all measurement samples, constitutes a problem when inferring the "true" system. We have identified three different sources of such deficiency: unidirectionality intrinsic to the system, fast dynamic modes and incomplete excitation of the system. It is conceptually important to distinguish and identify these cases, since they all show up as near singularities in the measurement matrix, but only the latter need to be dealt with through experiment design.

Unidirectionality is caused by moiety conservations, i.e. existence of a strict algebraic relationship between some of the state variables. Dynamics faster than the sampling time also appear as (almost) linearly dependent variables. The near singularity can in the former cases be removed by accounting for the algebraic relationship and lifting out one variable for each algebraic relationship. The same is true for the latter case, unless the fast dynamics are considered important, in which case the sampling frequency needs to be increased.

An experimental setup, i.e. a set of perturbations and measurements, which does not excite all directions of the system will also yield a near singular measurements matrix. This is for example common in gene regulatory networks consisting of weakly connected subsystems. The experiment design must make sure that all output directions are properly excited. The problem of excitation and directionality is here illustrated and studied for small in silico gene regulatory networks, both in the time and the frequency domain, using classical methods like singular value decomposition.

Qualitative modelling inhomogeneous effects in ERK- and STAT- signaling pathways

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A qualitative modelling in terms of theory of dynamical systems is applied to possible inhomogeneous effects in ERK- and STAT- signaling pathways. For this purpose it is taken into account that, concentration variation of the proteins and protein-complexes is a result of two processes: biochemical transformations of the reagents in the reactions and diffusion directed from regions with high concentrations to the low ones. In view of this appropriate partial differential equations are introduced and analyzed with respect to their stability. In this way the question of Turing instability existence (or absence) in both ERK- and STAT- signaling pathways is analyzed to argue the necessity of modelling the interaction of these pathways for revealing their self-organizational behavior. Starting from the verbal description available in the literature of the cross talk between the two pathways, a simple diagram of interaction between ERK and STAT5a proteins is chosen to write corresponding kinetic equations. The dynamics of interaction is modelled in a form of two-dimensional nonlinear dynamical system for ERK- and STAT5a - protein concentrations. In terms of reaction-diffusion scheme the stability and temporal behavior of inhomogeneous distributions of ERK- protein concentrations is analyzed. The stable inhomogeneous distributions are treated as a dynamical basis of the cell compartmentalization. It is shown the effects of molecular crowding, scaffolding and protein density drop and jump propagation could take place in the intracellular space.

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Chemotherapy treatment regimes: developing a mathematical template

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Multidrug treatments are extremely important in medicine – in fact most chemotherapy treatment regimes involve two or more drugs. Like their genetic counterparts, two drugs may have no interaction, or they may interact synergistically or antagonistically to increase or suppress their individual effects. It has recently been shown (Yeh et.al., Nat. Gen. 2006) that a drug interaction network possesses the property that it can be separated into classes of drugs such that any two classes interact either purely synergistically or purely antagonistically (monochromatically). These classes correspond to the cellular functions affected by the drugs. We have curated a database of pairwise drug interactions affecting cancer cells in general, and another of drugs tested specifically on leukemia or lymphoma cells. Based on these data, we have been able to monochromatically separate leukemia and lymphoma drugs into classes, and use this class information to mathematically describe a number of current chemotherapeutic treatment regimes. This mathematical description of the regimes is a basic template for effective treatments that, when refined, can be used to suggest potential new drug combinations for effective treatments.

A bioinformatics platform facilitating robust cross-species comparisons of innate immunity microarray data

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Functional genomics offers the ability to dissect complex biological responses such as innate immunity. However, powerful computational approaches are required in order to make sense of this complexity. We have developed a bioinformatics platform that is tailored towards preparing microarray data sets for cross-species analysis to gain novel insights into innate immunity signaling. This includes: (1) a biomolecular interaction database storing context-rich innate-immunity-specific networks (InnateDB), (2) robust ortholog identification and characterization to improve comparative analyses between human, mouse, cow, chicken and pig species (Ortholuge), (3) a flexible microarray data analysis pipeline that can be operated either via a command-line or web-based interface (ArrayPipe), (4) a database backend storing raw and analysed innate-immunity-specific microarray data sets, (5) accurate linkage of microarray probes to transcripts and genes (ProbeLynx), and (6) development of an intuitive network visualization system to facilitate hypothesis discovery. These resources were originally developed to aid comparative analyses for a large Genome Canada Pathogenomics project (www.pathogenomics.ca) however this platform is now being released as a freely available resource that is open source. Analyses we are performing with this platform are leading to a better fundamental understanding of features of orthologs and should provide insight into the evolution of key pathways which we are studying as therapeutic targets for immune system modulation.

A real-time study of genetic networks using a non-coding RNA reporter system

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The ability to measure transcriptional and translational dynamics in real-time and at the level of a single cell is essential to understanding the function of genetic networks. The relatively slow folding and activation time of green fluorescent protein (GFP) precludes its use as a direct measure of promoter activity on timescales less than 30 minutes, and other attempts to study gene dynamics have used ensemble-averaging techniques that mask the underlying temporal fluctuations. Alternatively, RNA transcripts are excellent probes of promoter activity on fast timescales. I present a new approach to the study of genetic networks using fluorescence correlation spectroscopy (FCS) to track RNA molecules tagged with pre-expressed GFP, in real-time and within a single living *E. coli*.

Relating cross Gramians and sensitivity analysis in systems biology

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One of the key challenges in systems biology is the analysis of often complex biochemical reaction networks which contain many uncertain parameters. Typically, the dynamics of these systems strongly depends on a significant amount of parameters, hampering the analysis significantly as even small changes in the value of parameters can have significant influences on the overall behaviour of the entire network. Thus, one of the key problems in systems biology is to analyse the influence of parameters on the steady state and transient behaviour. In the first part of this work we derive links between first order sensitivity analysis as typically employed in systems biology and the concepts of controllability and observability of systems theory. Specifically we establish a close connection between cross Gramians and the so called response coefficients as used in Metabolic Control Analysis. In a second part we outline an expansion of this approach using empirical cross Gramians, allowing to overcome some of the limitations of first order sensitivity methods such as local validity.

The use of dynamic perturbations to uncover the role of multiple loops in the mammalian circadian clock network

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The circadian clock is a system regulating e.g. sleep, hormonal levels and blood pressure according to the 24 hour rhythm of the day. The clock is composed of a network of dynamically interacting biomolecules. In order to simply generate the desired periodic behavior, interactions between biomolecules corresponding to a single feedback loop would in principle be sufficient. However, the circadian clock network is composed of multiple feedback loops. The advantage primarily suggested for the evolutionary design of multiple loops has been increased robustness, but it has so far not been shown that the observed multiple loop structure indeed leads to robustness (Rand et al. 2004).

Presented here are methods to unravel and analyze feedback structures in biochemical networks using a control theoretic approach. The methods are based on a linear dynamic network representation, with individual components acting as subsystems. At the core of these methods are systematic additions of perturbations to the dynamics of the network. This enables identification of the most critical feedback structures generating the behavior as well as its robustness. Analysis of the mammalian circadian clock model proposed in Leloup and Goldbeter (2004) identifies two important feedback structures. Only one of these is strictly required to generate the circadian rhythm, while the other serves to yield a severalfold increase in the robustness of the periodic behavior. In addition, a third loop in the network is found to be redundant in the sense that it can take over and generate periodic oscillations in case of failure of the first loop. Thus, the results obtained here provide support for the hypothesis that the multiple loop circadian structure has evolved to ensure robustness of the rhythm.

Dynamic visualisation and analysis of neurotransmitter data

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This poster describes a neuro-informatics workbench consisting of two parts. Part (a) simplifies the visualisation of temporally-related neurotransmitter data derived from microdialysis of the intact brains of conscious rats. Part (b) is a parameter estimation and signal processing tool set for constructing mathematical models of neural circuitry, using the data visualised in part (a), to reveal properties of the data not directly visible using the visualisation part of the workbench.

The user constructs diagrams of neural circuits and maps experimental data to specific brain regions defined in the circuit. This mapping of data to the graphical representation allows "animations" of neurotransmitter fluctuations to be created, providing a quantitative description of the circuit dynamics over the time-course of a given experiment. By monitoring neurotransmitter release following the localised administration of a drug, important information is obtained about the dynamical structure and causal nature of a given circuit. The estimation and modelling tools that are built into the workbench allows the user to test the validity of proposed circuit structures and determine the associated dynamics.

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