

Highlights 2010-2011

Postdoctoral researchers. The first two rounds of recruited postdocs have started to produce interdisciplinary publications, including papers in PNAS and Nature Communications. (see pages 2-6)

Phd Students Four PhD students (three based in Maths, one in BMC) started during the autumn term.

Complex Systems working lunch seminars. Regular seminar series, with wide range of subject areas and good attendance. Guests often stay for longer visits and talk to multiple groups. Several larger meetings. Including a climate modelling workshop, have taken place. All information about the centre is to be found at www.math.uu.se/cim.

Mathematical and Computational Consultation Regular meetings, wide variety of cases. Informal coffee every week.

Positive KoF report. “novel vehicle”; “continuity and security” while being an “informal focal point and platform for easy and successful interdisciplinary research”; “a new type of researcher will be formed which will be very important for a modern and technology oriented society”. (see page 7).

Challenges 2012-

Broadening involvement in other departments.

Focus on particular areas? For example, biology?

Permanent staff, relationship to mathematics department.

Andreas Grönlund

Computational and analytical models of intracellular regulation (2008-2011)

The aim of the project is to develop models of intracellular regulation to obtain a quantitative picture of how cells control molecule copy numbers. More specifically, the cells need to keep the molecule number at a desired level in the presence of perturbations like chemical (intrinsic) noise, gene replication, cell growth and cell division. To a large extent such perturbations are ignored when modelling intracellular regulation and frequently the calculations are performed in the limit of a large number of molecules. However the most common regulatory feedback loop, and the simplest one, is the auto-repressor, which is found to be present in more than half of all the transcription factors in *E. coli*. Still little is known of the constraints and limitations of such feedback and at what time scales it needs to operate on to be efficient. To improve the knowledge of such regulation, stochastic models of intracellular regulation that incorporates at least the most basic perturbations need to be analyzed in depth.

Progress. We have carried out calculations, starting from the chemical master equation, to analyse how homeostatic control cope with delays in the feedback. Feedback delays typically arise as a consequence of having a number of synthesis steps for making the feedback molecule. We have performed calculations on the efficiency of such delayed feedback by two methods, the first one from an interpolation scheme, where the noise properties directly can be calculated from a matrix equation that describes the fluctuation dissipation properties of the system. In the study we could quantify the need for accompanying transcriptional repression with direct enzymatic inhibition and the efficiency of product formation in the presence of feedback delays.

In a second study, we calculated the efficiency of such feedback by modelling each molecular reaction step leading to the feedback delay. In the study we re-discovered the interpolation scheme and in addition could demonstrate an increase of fluctuations from delay-induced bursts in synthesis of new molecules.

Publications (*co-authored interdisciplinary work)

*A. Grönlund, P. Lötstedt P and J. Elf, *Delay-induced anomalous fluctuations in intracellular regulation*, Nature Communications 2 419 (2011)

*A. Grönlund, P. Lötstedt P and J. Elf, *Costs and constraints from time-delayed feedback in small gene regulatory motifs*, PNAS 2010 107 (18) 8171-8176

A. Grönlund, B. Eliasson and M. Marklund, *Evolution of rogue waves in interacting wave systems*, Europhysics Letters 86, (2009) 24001

Planned research. We are currently investigating the implications of replication, cell growth and cell division for the homeostatic properties of the cell. There is some work in this direction, eg. By Otto Berg, but little is known of how accurate feedback control may take care of these perturbations. We are currently performing mathematical modelling, computer simulations in conjunction with experimental data to quantify the constraints and benefits of such feedback control when considering the different aspects of the cell cycle.

Peter Gennemark

Optimal Design in Population Kinetic Experiments by Set-Valued Methods (2008-2010, 50%)

The aim of the was project was to develop set-valued methods for experimental design, with special emphasis on pharmacometrics.

Progress. We have developed a new method for optimal experimental design of population pharmacometric experiments based on global search methods using interval analysis; all variables and parameters are represented as intervals rather than real numbers. The evaluation of a specific design is based on multiple simulations and parameter estimations. The method requires no prior point estimates for the parameters, since the parameters can incorporate any level of uncertainty. In this respect, it is similar to robust optimal design. Representing sampling times and covariates like doses by intervals gives a direct way of optimizing with rigorous sampling and dose intervals that can be useful in clinical practice. Furthermore, the method works on underdetermined problems for which traditional methods typically fail.

Publications (*co-authored interdisciplinary work)

* Peter Gennemark, Alexander Danis, Joakim Nyberg, Andrew C. Hooker and Warwick Tucker, (2011) Optimal Design in Population Kinetic Experiments by Set-Valued Methods, *The AAPS Journal*, <http://dx.doi.org/10.1208/s12248-011-9291-8>

Kattas, GD, Gennemark, P. and Wedelin, D. Structural identification of GMA models: algorithm and model comparison. Accepted paper for Computational methods in systems biology, Trento, Italy. (2010)
Kühn C., Prasad K.V.S., Klipp E., Gennemark P. 2010. Formal representation of the High Osmolarity Glycerol pathway. *Genome informatics* 22:69-83

Gennemark, P. and Wedelin, D. 2009. Improved Parameter Estimation for Completely Observed Ordinary Differential Equations with Application to Biological Systems. In *Computational methods in systems biology*, LNCS 5688, 205-217. ISBN 978-3-642-03844-0.

Gennemark P. and Wedelin D. 2009. D. Benchmarks for identification of ordinary differential equations from time series data. *Bioinformatics* 25(6):780-6.

Planned future research

Gennemark now works for Astra Zeneca, and continued collaboration between BMC (Hooker), and Maths (Tucker) on experimental design is planned.

Richard Mann

Inferring the rules of motion in animal groups (2010-)

The aim of the project is to identify the behavioural rules, particularly those relating to motion, that individual animals follow within groups, and which lead to emergent properties of collective motion, such as schooling and flocking. To do this we primarily use data in the form of the recorded motions of individuals within groups to learn how they react to the movements and behaviour of the other animals around them. We deploy methods from machine-learning and Bayesian inference to effectively identify the rules from data, comparing a variety of possible models for the observed movements and selecting which measurable aspects of the environment, including physical, social and internal cues, are responsible for determining future behaviour.

Progress. I began by developing and studying a framework for performing parameter estimation and model selection in the context of self-propelled particle models of collective motion and recorded movement data (Mann, 2011). These techniques were then applied to match the data on the movement of prawns in an annular ring. Basic models prove insufficient to capture both the fine-scale and large-scale behaviour of the individual prawns and the group simultaneously. As a result we have developed an extension to these models, incorporating previously unexplored 'memory effects' that allow the prawns to integrate their experiences over time (Mann et al., submitted). In a separate project on fish, I used a function-fitting based on neural-networks that allowed the movements of the fish to be decomposed into constituent responses to different physical and social cues (Herbert-Read et al., accepted).

Aside from the main CIM project I have carried out and am continuing work on models of economic development, optimal information search strategies in networks and graphs, and sexual ornamentation.

Publications (*co-authored interdisciplinary work)

R. P. Mann: Bayesian inference for identifying behavioural rules in moving animal groups, *PLoS ONE* (2011)

* J. E. Herbert-Read, A. Perna, R. P. Mann, T. Schaerf, D. J. T. Sumpter & A. J. W. Ward: Inferring the rules of interaction of shoaling fish, *PNAS* (in press)

* R. P. Mann, A. Perna, D. Strömbom, R. Garnett, J. E. Herbert-Read, D. J. T. Sumpter & A. J. W. Ward: Multi-scale inference of interaction rules in animal groups using Bayesian model selection, *PLoS Computational Biology* (under revision).

* N.Kolm, M. Amcoff, R. P. Mann & G. Arnqvist : Fishing for females: diversification of a food-mimicking male ornament via sensory drive

R. Freeman, R. Mann, T. Guilford & D. Biro: Group decisions and individual differences: route fidelity predicts flight leadership in homing pigeons (*Columba livia*), *Biol. Lett.* (online 2010, print 2011)

S. Reece, R. Mann, I. Rezek & S. J. Roberts: Gaussian process segmentation of co-moving animals, Proc. Workshop on Bayesian Inference and Maximum Entropy Methods in Science and Engineering (2010)

R. Garnett, Y. Krishnamurthy, D. Wang, J. Schneider & R. P. Mann: Bayesian Optimal Active Search on Graphs, Proc. Workshop on Mining and Learning with Graphs (2011)

R. P. Mann: Waypoint Detection, To appear in Encyclopedia of Nanotechnology (Springer) (due 2012)

Jonas Theis

Numerical methods for fluid dynamics with climate applications (2011-)

Aims: My main line of research is to develop robust numerical linear algebra for fluid dynamical problems, and to develop software and custom algorithms for climate applications on parallel computers. On the numerical aspects, I collaborate with Per Lotstedt and Maya Neytcheva (TDB, UU), and with Fred Wubs (Groningen). For the climate applications I work together with Henk Dijkstra (Utrecht, oceanography) and Nina Kirchner (SU, glaciology).

Publications

J. Thies and F.W. Wubs: "Design of a parallel hybrid direct/iterative solver for CFD problems", conference contribution, 8 pages, accepted for presentation at the "7th IEEE International e-Science Conference", Stockholm, Dec 2011.

F.W. Wubs and J. Thies: "A robust two-level incomplete factorization for (Navier-)Stokes saddle point matrices", 32 pages, accepted for publication in SIAM J. Matrix Anal. and Appl., Sept. 2011.

Hanna Härdin

Development of computational methods for analyzing slow dynamics in biochemical systems with focus on understanding the molecular interactions underlying atherosclerosis (2010-)

Aims: Biochemical systems typically exhibit a wide range of timescales and hence it is of interest to study their dynamics on the slow timescale—in which they reside most of their time—to improve the understanding of their dynamics. The aim of this project is to develop computational methods for this. The biochemical models that we consider consist of ordinary differential equations and we analyze their slow dynamics by studying invariant manifolds in the state space on which the dynamics is slow. The models we study describe a variety of different biochemical processes in living cells such as metabolic and signaling systems. In particular, we focus the analysis on the system of molecular interactions involved in the development of atherosclerosis in order to achieve a better understanding of this disease.

Progress. We have implemented an algorithm, in C++, for computing approximations of slow invariant manifolds. In order to get an accurate estimate of the manifold, it is advantageous to be able to compute as high order derivatives as possible. In our algorithm we make use of automatic differentiation to enable this. The algorithm has been tested on a variety of biochemical models and for these it can compute slow invariant manifolds of arbitrary accuracy. The algorithm is now applied to a model of atherosclerosis that is developed by coworkers at the Karolinska Institutet. In particular, we investigate whether the slow dynamics differs for different values of the model parameters and we seek to relate this with pathological versus healthy dynamics of the system.

As a side project has been initiated with Allan Willms, University of Guelph, Canada we are looking at a reduction method based on observations about a type of simple behavior on the slow invariant manifolds of certain biochemical system.

Work submitted/in preparation

Härdin HM, Zagaris A & Westerhoff HV Relaxation behavior in reactive protein networks as instantiated in the phosphotransferase system. submitted.

HM Härdin and W Tucker, An algorithm for computing slow manifolds. In prep.

HM Härdin and A Willms, Linearly-consistent slow manifolds. In prep.

HM Härdin J Tegner and D Gomez-Cabrero, In prep.

4. Centre for Interdisciplinary Mathematics, CIM

- **General assessment**

CIM is a novel vehicle to carry out multidisciplinary research, both with other sciences and industry. An organisation of this kind was recommended by KoF07, though under a different name, and the Panel was very happy to see that the university has taken here a successful, decisive action.

CIM is formally part of the Department of Mathematics but is in practice a joint effort with the Department of Information Technology, in particular with the Division of Scientific Computing.

Although the budget is only about 4 MSEK annually, a lot of cooperation has been created and the format seems to give on one hand continuity and security for the people (as them being employed by departments) and on the other hand an almost informal focal point and platform for easy and successful interdisciplinary research.

It is too early to do a comprehensive evaluation at this point. However, to make a fair assessment one needs to first increase the funding to a level that achieves a steady state where each year a group of new PhD's can be hired. The panel has already positively noted that with the present leadership, interaction with CS and UU in general is growing, and with the start of the graduate school, a new type of researcher will be formed which will be very important for a modern and technology oriented society.

The quality of the research and ambition and enthusiasms of the people associated with the Institute are high and this type of approach not only removes barriers between mathematics and other sciences on problems where it is already well known that mathematical modeling and scientific computing is a necessity, but it also activates mathematicians to observe the intellectual challenges in new application areas.

- **Other issues**

A graduate school has been initiated. The Panel considered it important that the students which have their regular working places at their primary institutions, would have a "physical home place" to share experiences with each other. There is a great and long lasting added value in networking the PhD students from different fields together.