

# Report on ICMS Workshop on Mathematical models of development and learning in the nervous system

Edinburgh 21 & 22 July 2006

## Scientific organisers

Chris Williams (PI)	University of Edinburgh	c.k.i.williams@ed.ac.uk
Peter Dayan	Gatsby Computational Neuroscience Unit, UCL	dayan@gatsby.ucl.ac.uk
Andrew Gillies	University of Edinburgh	andrew@anc.ed.ac.uk
David Sterratt	University of Edinburgh	david.c.sterratt@ed.ac.uk

## 1 Deviations from the original proposal

There were no significant deviations from our original proposal to ICMS.

## 2 Short description of the meeting

The formation and modification of connections between nerve cells is of critical importance in understanding the complex and robust computations of the nervous system. Experimental neuroscience provides large quantities of data on the scale of neurons, synapses and molecules as well as on the larger scale of regional brain activity and behaviour. Mathematical models have an important role in formalising the key rules of development and learning that tie together these levels.

A wide variety of mathematical and computational formalisms and techniques were discussed. Although the application of the ideas and methods is more general, some particular neurobiological issues formed the context of the modelling, including:

- the dynamics of how neurons are assembled from proteins and how they follow very noisy molecular gradients to find their target regions;
- the origin of topographic mappings of neurons in one structure (e.g. the retina) to another (e.g. the optic tectum) by molecular gradient matching;
- how the brain can maintain stable memories in the face of constantly changing the representations;
- how cells come to be laid out in semi-regular mosaics in structures such as the retina;
- the role of neuronal activity in self-organisation of neuronal connectivity; and
- how the neurotransmitter dopamine affects learning by gating the plasticity of synapses.

## 3 Comprehensive report of the workshop

Development and learning in the nervous system is a rapidly expanding domain in experimental neuroscience. It incorporates many scales, from genes and molecules to large scale cellular networks. Mathematical models have an important role in establishing the key rules underlying development and function in the nervous system, and provide the primary route to uniting these multiple levels.

The workshop brought together mathematical modellers and key experimentalists in the field of development and learning. The primary objectives of the workshop were to cultivate interaction between mathematical and experimental researchers with the aim of sharing new experimental areas that would benefit from mathematical methods, and identifying new applications of mathematics to modelling problems. The comments in the ICMS feedback testify to the success of the workshop: The meeting provided a platform where an “excellent

combination of theoretical and experimental work was described, showing the clear value of mathematical modelling to the interpretation and understanding of experimental data". There was clear agreement at the workshop that "Mathematical modelling of development has incredible potential as a future growth area, and as such is a key future research area". "what made this was very successful was the highly interdisciplinary character (i.e. the combination of presentations from theoretical and experimental groups) and the high quality of the presentations, which could be a good model for similar workshops in research areas where biology and mathematics interact".

A brief summary of some of the highlights of the workshop is given below. The summary is divided into two, reflecting two of the primary aims of the meeting.

### **3.1 Exposing new experimental techniques and areas which could benefit from mathematical methods**

The early stages of wiring the connectivity among nerve cells depend on sensing molecular cues, such as concentration gradients. Professor Geoff Goodhill presented new experimental techniques developed in his lab that allow the explicit control of molecular gradients in a cell growth medium. This revealed the extreme sensitivity of the special extensions of neurons (called filopodia) to these gradients and a call for a re-evaluation of current theoretical models of gradient detection in cells. In particular, previous work has suggested that an adaptation mechanism is required to cope with widely varying gradients. However, a model that does not incorporate adaptation but that does incorporate temporal and spatial averaging of molecules matches the performance of the experimental axon, suggesting that adaptation is not required to explain the axonal response.

Continuing the theme of developing connectivity among nerve cells, Professor David Price presented new genetic insights into key decision points in the path of axons (in particular axons emitted from cells in the retina must choose which side of the brain to grow to). Axon navigation in the optic nerve is controlled by genes ranging from transcription factors to cell-surface and secreted proteins. This system provides an experimentally accessible example of the complex layers of genetic and proteomic control involved in axon navigation. It is also an archetype for which new theoretical techniques that can combine multiple levels need to be developed.

Dopamine is a neurotransmitter involved or implicated in many neural disorders (e.g. schizophrenia, addiction and Parkinson's disease). Professor Gordon Arbuthnott presented a synthesis of anatomical, pharmacological, physiological, and theoretical approaches leading to a major rethink of the action of dopamine in key target brain areas (such as the striatum). A quantitative analysis of the sub-cellular anatomical arrangements in the striatum together with a formulation of the diffusion and degradation of dopamine in the extracellular medium leads to a radical reevaluation of the dopamine signal. Rather than the traditional synaptic focus for a neurotransmitter, dopamine can act simultaneously in a coordinated manner across large areas of the striatum. This has profound implications for dopamine mediated learning and related disorders. It is a valuable demonstration of using a mathematical framework to tie many experimental domains into a coherent explanation.

### **3.2 Identifying new applications of mathematics to key problems**

The theme of neural development was continued in the presentations of novel applications of mathematical techniques. Professor David Willshaw presented a new theoretical model of the ordered growth of axons emitted from cells in the retina that target the first layers of the brain. The mathematical approach utilised systems of ordinary differential equations and not only yielded a mechanism for ordered map formation between retina and brain, but also provided an extensible framework for predicting the alterations resulting from the new genetic

manipulation approaches. The mechanism that emerged from the system could be responsible for the flexibility with which neurons reorganise their connections during development and the degree of precision in the final map.

Dr Marcus Freaun proposed a complementary formulation of map formation that built on Professor Willshaw's work. Together the approaches provided a powerful demonstration of the mathematical techniques that illuminate the processes underlying the formation of ordered retinal projections.

Professor Christoph von der Malsburg described a model to tackle the problem of matching visual patterns to stored templates via geometrical transformations/warpings. Constraints imposed by the fast object recognition observed in biological systems suggest this requires the storage of these transformational patterns rather than a search process to develop such patterns *ab initio* for each new presentation.

The neural mapping work does not include details about the 3D structure of neurons. In contrast, Dr Bruce Graham presented his work about biophysically realistic mathematical models of neurite outgrowth. In this model, the rate of growth of model is assumed to be controlled by the rate of synthesis and transport of the protein tubulin down the growing axon, and the rates of diffusion and degradation of tubulin. This can be formulated in terms of a PDE with a moving boundary condition. Analysis of the model predicts three different growth regimes. Analysis of the dynamics of outgrowth show that it is usually stable, though oscillations can occur if the tubulin production is not auto-regulated.

Maintaining the usability of memory traces in the brain, given the continuous requirement to store new information and the resulting evolving representations, is an important problem in learning theory. The solution of "replay" in the process of memory consolidation was systematised by Marr in 1971 and later analysed by Willshaw & Buckingham (both of whom attended this meeting). Professor Peter Dayan highlighted that aspects of long term of memory such as the maintenance of access to stored memories and correctly interpreting them have not been thoroughly investigated. His model – a specific version of a Boltzmann machine – suggests that replay of memories in the hippocampus is critical not only for neocortical memory storage but also for maintenance of memories in the neocortex.

### 3.3 Involvement of participants

The two discussion sessions generated a fruitful interplay between the experimentalists and theorists present. The organisers structured the first discussion by posing a number of questions, including what the topic of the next day's discussion should be. The topics addressed in the second day's discussion were then based on the responses from the first day's discussion. Highlights of the issues addressed include:

#### **What experimental facts should the mathematical/modelling community pay attention to?**

Increasing availability of simultaneous multi-electrode recordings from tens of cells will produce large amounts of data to analyse, most probably requiring the development of new statistical techniques. New imaging techniques, for example tracking cell fate through development, will also produce large amounts of data. Here the challenge is how to incorporate this (qualitative) data into models.

Biological systems display considerable (though not limitless) robustness to fluctuations in their environment, achieved through a variety of mechanisms including homeostasis and structural redundancy. Models of the nervous system should exhibit this robustness, and there is considerable scope for investigating models that maintain relatively stable function in the face of changes in the environment or damage to the system.

### **Theoretical or modelling results/predictions that experimentalists should pay attention to**

A general conclusion was that it is not unreasonable for theoreticians to propose things that the brain is not known to do since historically, theory has often preceded experiment. Nevertheless, theoreticians need to understand the slower time course of experiments compared to theory. Also, the timescale for impact of theory can be long.

A number of examples were cited of theoretical models which had affected experimental research: the theoretical interest in the phenomenon of spike timing dependent plasticity has undoubtedly generated further experimental interest and Wickens' model of the basal ganglia and the prediction by Rall and Shepherd of dendro-dendritic synapses. A number of theoretical concepts were cited that have still to be proved, namely synfire chains (Abeles) and rapid synaptic plasticity (von der Malsburg). The theory of "small world" networks has been widely applied to problems in many disciplines, and several participants thought there is much potential for it to be applied to neurobiology.

**What are the mathematical or modelling challenges?** Incorporating better dynamical systems theory into models was felt to be important in understanding the robustness of neuronal systems.

A major challenge is how to map data at more functional levels (e.g. fMRI activity or EEG electrodes) to neuronal activity. A further challenge is to map abstract models of brain function (e.g. Bayesian decision making) to neural systems.

Neural systems are typically modelled as open systems; there is a challenge of models incorporating the complexity of the environment and the feeding the effect of actions changing the environment.

It was felt it would be desirable to have neural simulators that cross scales of organisation, to support "understanding how well-known interactions at neuron level propagate to the network level" (participant comment).

**How can experimentalists and modellers best collaborate?** Some participants felt that we should all be experimentalists. However, others pointed out that being an expert in two mature fields is difficult and time-consuming. It was generally thought to be a good thing for modellers to have had experimental exposure, but as experimental techniques develop very quickly, partnerships between experimentalists and theorists are of crucial importance.

A number of factors that could contribute to successful partnerships were highlighted, including: the need to understand each others motivations (what makes the other "tick"); being clear about the kind of collaboration, for example setting out to solve problem jointly, or discussing parallel paths of research to generate new ideas; and having mutual conceptual frameworks.

It was felt that mutual conceptual frameworks was perhaps the most difficult of these factors to establish. Theorists typically lack biological vocabulary, and experimentalists mathematical skills. More opportunities for discipline hopping would help address these issues, as would perhaps greater links between maths and biology curricula at undergraduate and even high school level (see below). In this context, the Edinburgh Doctoral Training Centre in Neuroinformatics was seen as an example of good practice.

**What should we be teaching our students?** In general, we felt that there should be some overlap between applied mathematics and neuroscience curricula at undergraduate level, so that neuroscientists gain an understanding of how mathematical modelling might help them understand experimental results and so that mathematicians realise that there may be applications in neuroscience. Hopefully this will lead to greater mutual respect between students of either discipline.

We felt that there were possibilities for neuroscience as an application in a maths curriculum, or the application of maths in the neuroscience curriculum even in high school. For example, deducing the firing rate – current curve of integrate and fire neuron models.

Also mentioned in the discussion was the importance of teaching generic skills, in particular how to find the relevant sources of literature, including “pre-web” literature which requires library visits to obtain. Finally, it was noted that the National Research Council of the National Academies of Science report, *BIO2010: Transforming Undergraduate Education for Future Research Biologists* (<http://www.nap.edu/books/0309085357/html/>) “calls for important changes in undergraduate biology training, especially for better preparation in mathematics, physics, and other quantitative sciences” (Mathematical Association of America *Meeting the Challenges* website <http://www.maa.org/mtc/>).

### **3.4 Impact of the workshop: collaborations and new work**

The workshop has led to some new collaborations: “I will embark on a collaboration with one of the attendants”; “a collaboration is planned with other participants on cerebellar Purkinje cell morphologies”; “I had an interesting idea on neuromuscular junction modelling that will very likely lead to renewed collaboration with David Willshaw, and have some thoughts on some of Peter Dayan’s presented work that could lead to interesting student projects (and hence research)”.

Existing collaborations and contacts have been sustained: “certainly helped sustain a direct research contact with Prof Geoff Goodhill (on Bayesian axon guidance)”; “useful for reinforcing my contacts with computational neuroscientists”; and “certainly helped me create new very useful contacts that may result in new collaborations”.

New ideas were generated, which may lead to new work: “Some advice about software that is freely available that will allow us to develop our model of the diffusion of dopamine will make the next version of that idea better”; “I also should be able to supply some experimental data with which to test a model of cell distribution suggested by Stephen Eglon from experiments in retinal development. The retina requires only a 2 dimensional solution but the distribution of chemically specific interneurons in brain will test the three dimensional version of the suggested model for cell distribution.” and “The scientific highlight of the workshop was a number of talks, in particular those by Geoff Goodhill, David Price, David Willshaw, Arjen van Ooyen and Stephen Eglon, that focused on the ontogenesis of the nervous system. . . This is very inspiring for work I am planning to do in the near future.”

## **4 Acknowledgements**

The organisers would like to thank the ICMS and its funders for the financial and organisational support of the meeting, as well as the Institute for Adaptive and Neural Computation and the School of Informatics in the University of Edinburgh for additional financial support.