Synaptic travelling waves: Final report

Background/Context

Neural field models of firing rate activity have had a major impact in helping to develop an understanding of the dynamics seen in brain slice preparations. These models typically take the form of integro-differential equations. Their non-local nature has led to the development of a set of analytical and numerical tools for the study of waves, bumps and patterns, based around natural extensions of those used for local differential equation models. My own work in this area has opened up the way for future studies of neural fields in both one and two dimensions that can incorporate realistic forms of axo-dendritic interactions and the slow intrinsic currents that underlie bursting behaviour in single neurones. Moving beyond applications to brain slices this work is directly relevant to understanding the generation of EEG rhythms, mechanisms for short term working memory, motion perception, representations in the head-direction system, and feature selectivity in the visual cortex.

Executive Summary

An important goal of neuroscience is to establish a series of direct links between the abstract nature of biophysical model equations and their interpretation in terms of experimental findings in biological neural networks. The objective of my proposal was to address this by developing a novel mathematical analysis of the dynamics of synaptically interacting neural systems and to promote its use in experimental neuroscience. The main focus of the work was to be on travelling waves and spatially structured activity in cortical and thalamic neural tissue. Apart from the application of the tools of nonlinear dynamical systems theory to systems of synaptically interacting model neurones this would require the development of new mathematics for analysing strongly interacting relaxation oscillators, the synchronicity of coupled bursting oscillators, the effects of space-dependent delays and the numerical analysis of integral equations.

My research over the last five years has been dictated by the above objectives. The academic freedom afforded to me by the award of an Advanced Research Fellowship has allowed me the opportunity to make significant inroads into all of my original goals. To illustrate this I will revisit each of the specific milestones described in the original proposal, and briefly describe how they have been met.

Key Advances and Supporting Methodology

Passive and quasi-active dendritic waves. By developing a kinematic approach in [7] I was able to study not only the properties of periodic waves in the dendrites of single neurones, but also irregular waves (arising via a period doubling). More recently I have developed the techniques for studying arbitrary branched geometries (using a "sum-over-trips" formalism) in [28], and will shortly complete an invited *Prospects* article for Biological Cybernetics on this topic.

Rebound currents, synchronised bursting & transition to travelling waves. In [2] I develop a minimal neural field theory for thalamic networks possessing a slow T-type (rebound) calcium current. By considering slow synaptic interactions I show how a tissue level dynamics can be described with a smooth firing rate model. Moreover, I show how one may mathematically analyse so-called lurching waves (which travel with constant speed, but non-constant profile), and demonstrate that a network of purely inhibitory thalamo-cortical (TC) relay cells supports a slowly propagating lurching pulse (with a corresponding unstable branch of fast solutions). I also develop descriptions for reticular (RE) cells and analyse the synchronised bursting that can emerge in RE-TC networks. Related work on clustering appeared in [10].

Axo-dendritic interactions on active spines. My work on passive dendrites was used to seed a study of dendrites with active processes. Initial work focused on the numerical analysis of a detailed biophysical model [1], and moved on to develop analytically tractable threshold models. This resulted in several papers on the so-called spike-diffuse-spike model [3, 23, 24], and indeed follow on funding from EPSRC (for a post-doc and student). This work also lead to funding from the DTI to work with a group of like-minded mathematicians and experimentalists in Texas.

Strongly coupled relaxation oscillators. To move beyond my pre-Fellowhip work in this area, which was done in some singular limit, has proved very rewarding and will now seed alot of further work on networks with gap junction coupling. The presence of gap junction coupling among inhibitory neurons of the neocortex has been appreciated for some time now. In recent years there has been an upsurge of interest from the mathematical community in understanding the contribution of these direct electrical connections between cells to large-scale brain rhythms. In [26] I focus on a class of exactly soluble single neuron (relaxation) models, capable of producing realistic action potential shapes, that can be used as the basis for understanding dynamics at the network level. Under constant current injection periodic responses are obtained in closed form, as indeed is the phase response curve, and conditions for stability (using Floquet theory). For large networks with global connectivity I develop a theory of strong coupling instabilities of the splay state. In this case an increase in the strength of gap junction coupling is shown to lead to large amplitude bursting oscillations in the mean membrane potential.

PDE versions of space-delayed integral model. In [4] myself and collaborators consider a firing rate model of a neuronal network continuum that incorporates axo-dendritic synaptic processing and the finite conduction velocity of the action potential. We develop formal reductions of the non-local system description to equivalent partial differential equation (PDE) models (making extensive use of integral transforms). We investigate travelling wave solutions in a comoving frame by numerically computing global connections for sigmoidal firing rate functions. We also calculate exact solutions for the Heaviside firing rate function. The same techniques are readily adapted for the study of spatially localised solutions and we are able to show that localised multi-bumps are lost (in favour of global patterns) when a stable N-bump and an unstable (N+2)-bump coalesce.

Adaptive processes and pulses. This work continues the theme above, but with a focus on avoiding PDE equivalent models in favour of truly non-local models described by integral equations. In [12] we show how to construct the Evans function for travelling wave solutions of integral neural field equations when the firing rate function is a Heaviside. The zeros of the Evans function determine the location of the point spectrum and can be used to determine solution stability (the essential spectrum being confined to the left-hand complex plane). Using this approach we establish the stability of coexisting travelling fronts beyond a front bifurcation and consider parameter regimes that support two stable travelling fronts of different speed. Such fronts may be connected and depending on their relative speed the resulting region of activity can widen or contract. The conditions for the contracting case to lead to a pulse solution are established. The stability of pulses is obtained for a variety of examples, in each case confirming a previously conjectured stability result.

In [15, 27] we include a local phenomenological model of threshold accommodation (spike frequency adaptation) into a standard neural field model and consider the effect on network dynamics. Focusing on spatially localised states we use our Evans function techniques to show that bumps may undergo instabilities leading to the emergence of both breathers and travelling waves. A similar analysis for travelling pulses leads to the conditions necessary to observe a stable travelling breather. Direct numerical simulations both confirm our theoretical predictions and illustrate the rich dynamic behaviour of this model, including the appearance of self-replicating bumps and spatio-temporal chaos. Moreover, travelling pulses in this model exhibit particle like properties, and behave as dispersive solitons. To our knowledge this is the first time that such a plethora of exotic solutions has been found in a homogeneous neural field model.

An invited review [14] summarises much of my work on neural fields up to 2005, with a more general overview appearing on Scholarpedia [20].

Numerical continuation of global connections and periodic waves. This has been a theme throughout my work on travelling waves in both neural fields and dendrites. In my work on threshold models I have been able to calculate such solutions exactly. For more general (and biophysically detailed) problems I have been fortunate enough to collaborate with Dr Gabriel Lord to pursue numerical continuation of not only periodics, but homoclinic and heteroclinic connections, as well as connections between periodic orbits [1].

Numerical techniques for integral models. The direct simulations of neural field models has been underpinned by a number of numerical schemes, developed in collaboration with Dr Markus Owen. It has been necessary to develop such tools since the computational overheads in evolving a non-local model in one or two space and one-time dimension with a further space-dependent delay are considerable. In one spatial dimension a number of numerical techniques have been developed including using a "delayed-grid" technique [4], and exploiting a convolution structure with the introduction of an auxiliary dimension [15, 27]. The former is more a brute-force approach whilst the latter allows the use of spectral methods (in any spatial dimension).

Comparison of dendritic and axonal delays. For weakly coupled spiking networks this was first analysed in [6]. A systematic comparison of these distinct signalling delays in neural field models was performed later in [33]. Here we also develop the weakly nonlinear analysis of such models and derive the "amplitude" equations for travelling periodic patterns, building on work in [14].

Effects of anisotropy and inhomogeneity. It is now known that the neocortex has a crystalline microstructure at the millimetre length scale, so that the assumption of isotropic connectivity has to be revised. In [29] we treat "patchy" connections, whereby a homogeneous and isotropic system is modulated in a spatially periodic fashion. In this case the emergence of a "lattice-directed" travelling wave predicted by a linear instability analysis is confirmed by numerical simulation. I am currently organising a minisymposium for SIAM Life Sciences 2008 (Montreal) on this topic.

Comparison with experimental data and detailed biophysical models. Work on wave initiation, termination and propagation for swimming and struggling in the Xenopus tadpole was pursued jointly with a PhD student, Matthew Denman-Johnson, and forms a large part of his thesis [39]. Work related to epilepsy (with Paul Bressloff) is presented in [36]. My current research is done under the umbrella of the Nottingham Institute of Neuroscience, which comprises clinicians, biologists, psychologists, physicists and mathematicians, all pursuing highly multi-disciplinary work on brain dynamics. One of my current projects involves collaboration with Dr Rob Mason from the School of Biomedical Sciences, exploring the role of cannabinoids in the modulation of brain rhythms. Cannabinoids – the active ingredient of marijuana – are a potential trigger for schizophrenia; my concern is with the use of mathematical models to explain the effect of cannabinoids on brain states. I am also working closely with Dr Chris Sumner of the Institute of Hearing Research on a Marie-Curie funded project building neural models of auditory processing. Another collaboration with Professor Dorothee Auer from the Academic Radiology Group involves the development of tissue-level models of the brain, which can be used to better understand EEG and fMRI recordings. Such interactions are tremendously important to my work. Using locally collected data I have been working on the development of biophysically detailed models for these collaborations as well as pursuing the analysis of mathematically reduced models. In illustration of this I point to the hippocampal modelling that has been developed with the Mason Lab [35, 34], with papers in preparation with the Sumner Lab (on mode-locked responses of auditory chopper cells), and an invited presentation for the work with the Auer Lab at the upcoming Human Brain Mapping conference in 2008 (Melbourne).

Two dimensional studies. The analysis of localised states (bumps and rings) was treated in [30] for neural fields in 2D. Importantly we show (again using Evans function techniques) that angular perturbations can destabilise spatially localised solutions. Moreover, beyond the instability our simulations demonstrate the emergence of multi-bump and labyrinthine patterns. With the addition of spike-frequency adaptation, numerical simulations of the resulting vector model show that it is possible for structures without rotational symmetry, and in particular multi-bumps, to undergo an instability to a rotating wave. We use a general argument, valid for smooth firing rate functions, to establish the conditions necessary to generate such a rotational instability. For models with threshold dynamics we further show that travelling spot solutions in 2D can have highly non-trivial dynamics, and indeed can scatter as auto-solitons [27]. With the inclusion of space-dependent delays we show in [29] how to approximate the full non-local model by a set of coupled nonlinear wave equations, thus facilitating further numerical study.

Other work on neural systems. Work not directly forecast in the original fellowship proposal, but obviously related, includes that on general mechanisms for neural synchronisation [36], mode-locking [16], the role of distributions of axonal delays in neural field dynamics [22], spatially localised states in spiking networks [19], a "Visions" article for Phil. Trans. Roy. Soc. A [21], a study of "equipotent" synapses [32], two editorials [18, 25], and publishing an edited book [37].

Other work on cellular calcium signalling. I have also been able to do some completely separate work on the dynamics of intracellular calcium signalling, and secured independent funding from EPSRC for this work. This work has primarily evolved around travelling wave analysis in both deterministic and stochastic settings [8, 5, 9, 11, 13, 31], though more recently has expanded to include the development of computationally cheap, yet biophysically realistic, models of atrial myocytes [17, 38].

Research Plan Review

There were no changes to the original plan.

Research Impact and Benefits to Society

My work has generated a number of collaborations, which in turn has led to work in related areas. Locally at Nottingham I am now well recognised within the Institute of Neuroscience as someone with the relevant expertise to help experimentalist who wish to expand their work to include modelling. On top of the established collaborations I have already mentioned I am currently pursuing grant applications with Dr Noah Russell (Biophysics) on understanding spiking correlation structures seen in cultured neuronal networks [Leverhulme Trust], and Dr Jon Peirce (Psychology) on developing feature based models of visual cortex (specifically v4) [Wellcome Trust]. Outside of Nottingham, I have national collaborators that include Dr Gabriel Lord (Heriot-Watt) and Dr Rasmus Petersen (Manchester). In the former case Gabriel has pursued independent work on the numerical *continuation* of integral equations as a result of our joint work on neural fields, and in the latter case Rasmus has recognised that some of his data collected from the mechanoreceptors of rat vibrissa can be explained using ideas I developed for the mode-locking of spiking neurons. At the international level I now have collaborations with people in Texas (Drs Steve Cox, Kresimir Josic and Costa Colbert), New Zealand (Dr Carlo Laing) and Australia (Dr David Liley), which will persist for some foreseeable future.

My research activities have impacted in other areas to the extent that I have now been asked (and given) two plenary talks at conferences with a broad remit – namely one in Bristol on "Successes and Failures of Continuous Models for Discrete Systems", (September 2005) and another in Memphis on "Fluids and Waves: Recent Trends in Applied Analysis" (March 2006).

I am currently the PI of an EPSRC funded UK Mathematical Neuroscience Network (2008-2011), whose remit is to bring together experimental neuroscientists and mathematicians to tackle outstanding challenges in the neurosciences. It is in this link to clinicians where the impact to society may be most keenly felt. Improved treatments for neuropathologies, such as epilepsy and Parkinson's disease are already benefiting from a deeper understanding of such treatments as deep brain stimulation (currently in use in around 40,000 patients), and there is hope for further success stories based on collaborations seeded by our Network activities.

Explanation of Expenditure

The Fellowship covered my salary, as well as a stipend for research expenses. There was no variation from the original spending plan. The stipend was primarily spent on attending meetings/conferences and short collaborative visits. The majority of these were in N. America (with 4-5 trips per year of 1-3 weeks duration), with one to Australia/New Zealand, and a much smaller number (over the five years) in mainland Europe. Funds were also spent on computing equipment (two Mac Desktops and two Mac laptops), and a number of specialist research text books. Some of my stipend was also spent on covering partial costs of bringing collaborators to the UK (including Dr LieJune Shiau from Texas, Dr Carlo Laing from New Zealand, and Dr David Liley from Australia).

On top of the N. American collaborators already named, the N. American trips included visits to Dr Brent Doiron (NYU), Dr Greg Smith (Virginia), Dr Carson Chow (NIH, Maryland), Prof Paul Bressloff (Utah), all of which resulted in publications.

I attended one EPSRC Fellows workshop in Nottingham (2002) as well as a College Launch Day (2002).

Outcomes

The *added value* of the Fellowship to my career has been enormous. I am now a full professor (in applied mathematics) with a thriving research group (currently one post-doc and five PhD students), and have follow on funding (from EPSRC, BBSRC, DTI, Nuffield). The paragraphs above hopefully give a clear picture of the number of new international collaborations I have developed as well the fact that I am now heavily involved in the activities of experimental groups at Nottingham.

Although not required to teach I voluntarily ran some lecture courses throughout my Fellowship. Two of these are now part of the curriculum (B12412: Computational Neuroscience and Neuroinformatics, G14TNS: Theoretical Neuroscience).

The first year of my Fellowship was held at Loughborough University (where I was a senior lecturer). The Fellowship was no doubt a factor in the willingness of Nottingham to offer me a readership in 2003.

Support of Employing Organisation

I have been awarded all the usual support associated with a full academic appointment at Nottingham, including office space, computing support, library, secretarial support, staff development courses, etc.

Dissemination Activities and Further Research

As well as the usual mechanism of publications and oral presentations I have co-organised a number of meetings, which at some level have helped to promote my work:

1. Modelling of Neuronal Dendritic Trees, Friday June 18th 2004: ICMS, 14 India St, Edinburgh. [with G J Lord]
2. Mathematical Neuroscience, 21 March to 23 March 2005, Edinburgh. [with G J Lord]
3. Leverhulme Trust Theoretical Neuroscience Network Annual Meeting, 21st -23rd September 2005, Loughborough. [with J Terry]
4. Theory and Applications of Coupled Cell Networks, 26 - 30 September 2005, Cambridge. [with P C Matthews, P Ashwin, J Dawes and M Golubitsky)]
5. Nottingham Neurodynamics Meeting, Wed 22 February 2006, Nottingham.
6. Gordon Research Conference on Theoretical Biology and Biomathematics, 4-9 June 2006, Tilton, New Hampshire, USA. [with P Bressloff]
7. Mathematical Neuroscience, 16 - 19 September 2007, Centre de Recherches Mathématiques, Université de Montréal, Montréal, Québec. [with A Longtin and J Rubin]

I am currently organising meetings associated with the UK Mathematical Neuroscience Network in Warwick (Dec 17-18 2007) and Edinburgh (Mar 17-19 2008).

I am also proud to have put together a book on Neural Bursting. This gathers together internationally recognised leading experts to provide a detailed overview of the current state-of-the-art in the mathematical and computational modelling of neural bursting [37]. [MathSciNet Review at http://www.ams.org/mathscinet-getitem?mr=2210821].

Building on my Fellowship work on synaptic travelling waves I expect to work in the area of mathematical neuroscience for the rest of my academic career.

Public Awareness Activities

In this regard I have written a Scholarpedia article on neural fields in terms understandable to non-experts [20]. My student, Nikola Venkov, has also presented aspects of our joint work at two public science events:

1. A "Scientists on the Sofa" discussion on the ethics and social impact of Neuroscience, Science Oxford centre, Oxford (2007).
2. Perspectives 2007 (EPSRC funded) "How does the human brain tick? . . . Do we really want to know?" BA Festival of Science, York (2007).

I would be happy to assist EPSRC in relevant future promotional activity.

Scheme Effectiveness

To my mind the Fellowship has met the objectives of the scheme. Not only has my personal research flourished, this award has allowed me the time to build up UK activities in the exciting new field of Mathematical Neuroscience. I strongly recommend that EPSRC support Fellowships of this type as part of their basic remit.

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