Synaptic travelling waves

Abstract

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. I propose to address this issue by developing a novel mathematical analysis of the dynamics of synaptically interacting neural systems and by establishing a framework for comparison with experimental measures of neural activity. The focus of the study will be on travelling waves and spatially structured activity observed in cortex during epileptic seizures, the travelling spindle waves observed in thalamus at the onset of sleep or drowsiness and waves of activity in animal motor systems. The understanding of the mechanisms for such a wide range of both pathological and naturally occuring phenomena is directly relevant to both improved clinical treatments and the understanding of the role of dynamics in neurobiological function. Since neuronal rhythmic activity also manifests itself in various aspects of normal brain function, that include synchronisation and waves of excitation observed in cortex during sensory processing, the work will have broad application in the neurosciences.

Apart from the application of the tools of nonlinear dynamical systems theory to systems of synaptically interacting model neurons the work will 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 continuation of integral equations.

Background

Travelling waves in neurobiology are receiving increased attention by experimentalists, in part due to their ability to visualise them with multi-electrode recordings and imaging methods. In particular it is possible to electrically stimulate slices of pharmacologically treated tissue taken from the cortex [1], hippocampus [2] and thalamus [3] and also living spinal preparations of simple vertebrates [4]. Under a variety of circumstances this results in the propagation of electrical activity in the form of a travelling wave. In brain slices these waves can take the form of spindle waves seen at the onset of sleep, the propagation of synchronous discharge during an epileptic seizure [5] and waves of excitation associated with sensory processing [6]. In vertebrates the waves of activity observed in the spinal cord are generators for locomotor patterns.

Such waves are a consequence of synaptic interactions and the intrinsic behaviour of local neuronal circuitry. Many cells in nature are excitable in the sense that a sufficiently strong stimulus will induce the membrane potential of the cell to undergo a large excursion, known as an action potential, before coming back to rest. Action potentials generated at the axon hillock travel along axons, via the regenerative movement of ions across the cell membrane, and terminate at synapses on postsynaptic dendrites. Here they produce potentials that accumulate to trigger (or inhibit) further action potentials. The class of computational models that are believed to support synaptic waves differ radically from classic models of waves in excitable systems. Most importantly, synaptic interactions are non-local (in space), involve communication (space-dependent) delays (arising from the finite propagation velocity of an action potential) and distributed delays (arising from neurotransmitter release and dendritic processing). Moreover, there has long been evidence that nonlinear membrane properties are not confined to the axon hillock, but are spread throughout the dendritic tree [7]. In contrast many studies of excitable waves assume that the underlying mechanism for wave propagation is diffusive in nature, as exemplified by an action potential travelling along an axon.

The strong and growing body of experimental data relating to the anatomy, electro-physiology and pharmacology of brain slice preparations has encouraged the development of detailed biophysical models. Numerical simulations of these models have shown that the broad features associated with wave propagation have been captured. For thalamic slice models these include the generation of both spontaneous and evoked spindle episodes, the high degree of synchrony between neuronal sub-populations and the observation of travelling fronts with speeds around 1 mm/s (60-90 mm/s for cortical slices). An inherent problem with this approach is the analytically intractable nature of such detailed models and that large scale network simulations are computationally expensive with many adjustable parameters.

In the light of these observations the pursuit of minimal models consistent with biology and subsequent mathematical analysis is an important challenge for applied mathematics.

Programme and methodology

The proposed research will investigate a variety of wave-like phenomena associated with neural systems using, and establishing links between, appropriate areas of applied mathematics, physics and biology. More specifically the focus will be on the study of recently observed dendritic electrical waves in distal dendrites, waves of synaptically mediated activity in vertebrate preparations and the waves of excitation and inhibition commonly observed in brain slices. Each of these phenomena requires distinct levels of biophysical description. I wish to pursue the use of tools from nonlinear dynamical systems theory to provide a firm framework for the understanding of seemingly diverse types of neural wave. The ultimate use of such theories is in testing ideas for the neurobiological function of such dynamical systems using the language of mathematics.

The project involves a number of biophysical models, each of which provides a different level of description and requires different branches of mathematics for analysis. The systematic use of mathematical reduction will highlight relations between these levels of description and show how techniques from one discipline may complement those of another. The main points of this proposal are as follows.

Waves of spiking events in synaptically coupled networks

The leading edge of travelling synaptic waves can often be described by specifying the time of action potential generation at the front. A minimal biophysical model, therefore, has to incorporate a mechanism for the generation of *spiking* events. The generation of electrical spikes is commonly described by systems of the form

$$C\frac{dv}{dt} = -\sum_k g_k m_k^{p_k} h_k^{q_k}(v - v_k) + u,$$

where v is the membrane voltage, C the membrane capacitance, $p_k, q_k \in \mathbb{Z}$, m_k and h_k are gating variables that satisfy differential equations, v_k is the constant reversal potential of the kth ion channel, g_k are a set of constants, and u is an applied current. When the gating variables are described by the Hodgkin-Huxley model (HH) [8], positive feedback may result in the generation of an action potential. Appropriate choices for the number and type of conductance channels and their associated gating variable can lead to other types of neural firing patterns such as bursting of the type observed in thalamic and cortical neurons [9] . The observation that both real neurons and model systems have a well defined *threshold* for spike initiation has led to the study of the much simpler integrate-and-fire (IF) model, which lacks any gating variables, but retains the notion of a voltage threshold. In this model the cell potential obeys an ordinary differential equation (describing the cell membrane properties and external input) until it reaches some threshold where it is discontinuously reset to some reset level and considered to have fired an action potential. In fact it may be shown that the IF oscillator can be obtained as a reduction of the full HH system of equations so that all parameters in the IF model have a biological interpretation [10]. Firstly, I propose an analysis of a one-dimensional continuum of spiking IF neurons with synaptic input at position x given by

$$u(x,t) = \int_{-\infty}^{\infty} w(x-y)\int_0^{\infty}\eta(s)\sum_{m\in\mathbb{Z}}\delta(s-t+T^m(y))dyds. \qquad (1)$$

This models the effect of an idealised action potential (delta-Dirac function) arriving at a synapse and initiating a postsynaptic current $\eta(t-T^m)$ at time T^m. The convolution over space takes into account the connectivity pattern of the synapses between neurons, described by the function $w(x)$. The simplicity of the IF model will allow a systematic study of solitary pulses with firing times given by $T^m(x) = x/c$. An examination of the conditions for reaching threshold will be used to determine the velocity of a pulse in a self-consistent manner.

An important, and often ignored contribution, to synaptic currents is the effect of dendritic processing on synaptic stimuli. Dendrites are large branched structures upon which incoming fibres make connections and, at the very least, act as a spatio-temporal filter for patterns of incoming synaptic activity. The use of Green's function techniques [SC:10]

will allow a systematic analysis of the effects of a passive dendritic tree on wave propagation (with the generalisation $w(x)\eta(t) \to G(x,y,t)$ reflecting more accurately the distribution of axo-dendritic connections in neural tissue and y being a co-ordinate label on the dendritic tree). This approach may also be extended to cover the so-called quasi-active membrane (linearised HH kinetics) that is thought relevant to understanding experimentally observed sub-threshold voltage oscillations associated with voltage-dependent ionic channels distributed along the dendritic tree. In contrast to the purely passive model of a dendritic tree the Green's function of the model tree will have an oscillatory component reflecting more closely the band-pass nature of real dendritic tissue. The inclusion of recently observed excitable channels capable of generating action potentials [11] is a further challenge. As dendrites form the predominant elements in neurons, so dendritic spines form the dominant component of many types of dendritic trees. They are small mushroom like appendages with a bulbous head (with surface area of order $1\mu m^2$) and a tenuous stem (of length around $1\mu m$) and may be found in their hundreds of thousands on the dendritic tree of a single cortical pyramidal cell. In the cerebral cortex approximately 80 percent of all excitatory synapses are made onto dendritic spines. Theoretical explorations for both IF and HH models of excitable spine head tissue coupled to a passive dendritic segment have shown that travelling waves may arise from a succession of local all-or-none events at the spine heads [SC:22,25,26]. The effects of these single neuron waves on network dynamics is a fascinating open question that can be systematically explored within this part of the programme. This will also involve studying the effects of wave scattering on a branched dendritic tree using boundary conditions (Kirchoff's laws) at branch points on a graph of dendritic links, as well as using techniques from homogenisation and perturbation theory to cope with the fact that spines are located at distinct points on a dendritic tree.

A simple generalisation of the IF travelling pulse analysis to cover Δ-periodic waves would assume firing times of the form $T^m(x) = x/c + m\Delta$. However, physically inconsistent results are likely to emerge for small Δ where the lack of a refractory variable in the IF model is likely to lead to inconsistencies with biology (namely divergent wave-speeds). To address this issue I will pursue generalisations of the IF model that include a dead time, modelling an absolute refractory time-scale, and an adapting threshold, for modelling the relative refractory period of a neuron. A subsequent self-consistent analysis of the periodic wave ansatz will give the dispersion curve, $c = c(\Delta)$. In many excitable systems the dispersion curve forms the basis of a kinematic model. In this framework a set of ODEs describes the evolution of firing times within a spike train (and all biophysical detail is subsumed within the shape of the dispersion curve). Although built up from knowledge of periodic behaviour, it is actually a theory of more general irregular waves and can be used to investigate the stability and bifurcation of travelling wave solutions. A kinematic theory is also ideal for exploring the dependence of dynamics on initial conditions in a system that is likely to support multiple forms of discharge pattern.

The extension of this work to cover systems with currents that support bursting behaviour, such as thalamic neuronal networks, is also important. As they stand IF models do not caricature the so-called *rebound* currents (associated with low-threshold T-type calcium fluxes) that give rise to *bursts* of action potentials upon release from inhibition. Recent work by Greg Smith [12] has shown that there is a natural extension of the IF model that reproduces the salient features of experimentally observed thalamocortical relay neuron response. Interestingly, the periodic behaviour of this single neuron integrate-and-fire-or-burst model (IFB) can be exactly analysed using the language of impact oscillators [SC:28]. By including the extra ionic currents of the IFB model one may then analyse the *bursting waves* of thalamic systems, with connectivities and types of synapse taken directly from the known two layer structure of interacting thalamocortical and reticular cells. It has also been conjectured that bursting patterns observed from cortical pyramidal cells play a major role in epileptogenesis [5]. The problem of epileptogenesis can be divided into two distinct but related components: the initiation of synchronous discharge, and its subsequent propagation. This division reflects clinical studies which suggest that a partial seizure originates in a localised area of cortex, involving several thousand neurons that act as pacemaker cells, and either remains there or spreads to new areas. In contrast to the synchronisation properties of regular spiking model neurons, very little is known about how networks of synaptically coupled bursters synchronise their activity. The analytical tractability of synaptically coupled IFB neurons should allow a thorough investigation of both synchronous bursting and travelling waves via a firing time ansatz similar to that used for the study of periodic waves. Interestingly, detailed biophysical continuum models have been shown to support both smoothly propagating waves and lurching (or saltatory) waves [13]. An analysis of the IFB firing time map will be used to uncover the mechanisms for wave

destabilisation associated with lurching waves.

Undoubtedly there will be some instances in which the use of an IF or related model is inappropriate. One important property of a single excitable neuron that an IF model neglects is the ability to fire upon release from inhibition via anode break excitation (without the use of rebound currents, such as the T-current). A more obvious shortfall is its lack of a recovery variable to mimic refractoriness. Both these related aspects of single neuron behaviour are likely to have a significant influence on systems with reciprocal inhibitory connections. This suggests a treatment of more biophysically realistic models with HH type kinetics. Unfortunately, not only would the equations for a network be very high dimensional, but they would also be inherently nonlinear for all times. This motivates the application of techniques such as invariant manifold theory, geometric singular perturbation methods and averaging theory to reduce the network dynamics to a system in which the relative phase between oscillatory sub-populations is the important dynamical variable. With this in mind I turn to the McKean model of a single neuron [14], which is a planar relaxation oscillator. One may regard it as either a caricature of the HH system or a generalisation of the integrate-and-fire model to incorporate a state-dependent threshold and a representation of a spike. In either case it is an analytically tractable single neuron model that has been shown to produce the type of responses observed in recent experiments of forced single neurons [SC:23]. Initial progress in studying networks of weakly interacting McKean oscillators has been made, although in some singular limit [SC:27]. That results may be applied to the non-singular limit is expected by the Fenichel persistence theorem. Direct numerical explorations (of both McKean and HH models) will be used to test the validity of the theory far away from the singular limit and to uncover those dynamic behaviours associated purely with strong coupling. A major challenge is to make analytic progress without recourse to the assumption of *fast* relaxation (the singular limit) and *weak* coupling. Guided by exact results for the IF networks (valid in the strong coupling regime) I plan to develop such a theory based around my recent work on the McKean model and ideas of Yoshinaga *et al.* for the numerical study of HH networks with synaptic interactions [15]. Ultimately the program of research for IF, IFB and McKean networks will be extended beyond the one dimensional continuum model to cover lattice models and two dimensional continuum models.

Waves of firing rate activity

The theory of synchronicity and periodic waves in tonic spiking neural networks provides a foundation for understanding the travelling electrical waves that are observed in olfactory, visual, and visuomotor areas of cortex in a variety of species [16]. However, when viewed from the perspective of firing rate activity such behaviours are merely uniform states. Of course this is not the case for networks of bursting neurons, where a range of interspike-intervals are expected. To study the coarse grained features of networks with bursting it is natural to adopt the language of firing rates.

In many continuum models for the propagation of electrical activity in neural tissue it is assumed that the synaptic input current is a function of the pre-synaptic firing rate function [17]. If the synaptic response is on some slow time scale (compared to the intrinsic ones of the model neuron) then it is natural to replace a spike train with a (smooth) function of synaptic activity. This firing rate function, $f(u)$, may also be prescribed purely in terms of the properties of the biophysical single neuron model. This gives rise to integral models of neuronal tissue of the type proposed by Wilson and Cowan [17]:

$$u(x,t) = \int_{-\infty}^{\infty} w(x-y) \int_{0}^{\infty} \eta(s) f(u(y, t-s-|x-y|/v)) ds dy,$$

where space-dependent delays arising from finite conduction velocities v are included. Simulations, with sigmoidal f, show that the system supports unattenuated travelling waves as a result of localised input. The model has been analysed by Amari [18] in the context of pattern formation and by Ermentrout and Cowan in two dimensions as a model of drug induced hallucinations in layer one of visual cortex [19]. The simplicity of the model over that of the spiking equivalent will allow an analysis of space-dependent delays and extensions to cover anisotropic and inhomogeneous connectivities. Necessarily this will involve some choice of the firing rate function which I propose to obtain numerically for biophysical models and to derive for the IF, IFB and McKean models. In more detail, I will consider the realistic case that the synaptic response $\eta(t)$ is the Green's function of some linear differential operator Q: $Q\eta(t) = \delta(t)$. With the inclusion of a dendritic tree one would have to consider a more general space-time differential operator, but the essential technique

remains unchanged. After applying Q to the Wilson-Cowan equations one would have that $Qu(x,t) = \psi(x,t)$, where

$$\psi(x,t) = \int_{-\infty}^{\infty} dy \int_{-\infty}^{\infty} G(x-y, t-s) f(u((y,s))ds, \qquad G(x,t) = w(x)\delta(t-|x|/v).$$

If the two dimensional Fourier transform of the Green's function $G(x,t)$ is a rational function, i.e. $G(k,w) = P(k,w)/R(k,w)$ for Fourier parameters k and w, then it is possible to obtain a partial differential equation for ψ as $\widehat{P}\psi(x,t) = \widehat{R}f(u(x,t))$ where $\widehat{P}$ and $\widehat{R}$ are linear space-time differential operators associated with the functions P and R (by inverse Fourier transforms). The study of travelling waves is then accomplished by moving to a travelling wave frame to generate a set of ODEs for the wave profile. Importantly, one may then bring to bear many standard techniques for ODEs (such as the study of global connections) to investigate wave speed, wave profile and stability . Interestingly for synaptic kernels $w(x)$ with compact support the operator $\widehat{R}$ also has a *shift* property so that source terms may be both advanced and retarded in space and retarded in time. The analysis of mixed functional differential equations is extremely complicated and even the basic existence-uniqueness theory has not been established. This highlights the fact that in general the basic model is non-local and that general choices of synaptic kernel may not lead to an equivalent PDE representation. Rather one must tackle the issue of travelling waves in the original integral framework head on. Exact solutions are not expected to be forthcoming, except in the special case that the firing rate function is a threshold function (so that ψ depends only the value of the threshold and not the shape of u). I propose to develop the numerical analysis suitable for studying the integral Wilson-Cowan type equations in a travelling wave frame. Necessarily this will require the development of numerical schemes for integral equations to tackle, for example, the numerical *shooting* of integral equations, the construction of homoclinic and heteroclinic orbits and the solution of periodic boundary value problems. For global connections this will involve solving the travelling wave problem on a fixed (large) interval. Any numerical scheme will require data from outside of this interval, so that some asymptotic approximation to the true solution is useful. A set of appropriate boundary conditions (the analogue of *projection boundary conditions* for ODE systems) for well-posed problems will be constructed by linearising around the fixed points and using perturbation theory to generate a self-consistent hierarchy of solution approximations. A numerical implementation of pseudo-arclength continuation will be used to generate solution branches in parameter space starting from the analytical solution for the pure threshold model (regarded as the high gain limit of a sigmoid). To tackle the issue of wave stability I shall compute travelling wave solutions in the spatially discretised integral equation directly, using both a Newton method based on a pseudospectral discretisation, and a Newton-Picard method based on a finite difference discretisation. Details about the eigenspectrum of the linearisation about a wave are then naturally available.

In real cortical tissues there are an abundance of metabolic processes whose combined effect is to modulate neuronal response. It is convenient to think of these processes in terms of local feedback mechanisms that modulate synaptic currents. Such feedback may be used to modify behaviour in the wake of a travelling front so as to bring activity back down to some resting level. I will consider simple models of so-called *spike frequency adaptation* (i.e. the addition of a current that activates in the presence of high activity) that should lead to the generation of pulses for network connectivities that would otherwise only support travelling fronts.

From a mathematical perspective, travelling front and pulse solutions are not structurally stable so that the introduction of even small inhomogeneities in the connectivity pattern may lead to propagation failure. Motivated by the anisotropic and inhomogeneous nature of many cortical areas I shall use averaging and homogenisation theory to uncover the role of the periodic microstructure of cortex in front and pulse propagation and its failure, along the lines developed in [20]. Furthermore, it is important to remember that in specific brain regions, such as mammalian neocortex, connectivity patterns follow a laminar arrangement, with strong vertical coupling between layers. Consequently cortical activity is considered as occuring on a two-dimensional plane, with the coupling between layers ensuring near instantaneous vertical propagation. The study of truly two dimensional spiral waves and target patterns in neural fields, arising from space-dependent delays, dendrites, adaptive and rebound currents is an important motivation for this work, that will be explored with a mixture of analysis and direct numerical simulations.

The success of these complementary mathematical studies will be judged in part by comparisons with experimental data from the literature on synaptic waves and comparison with simulations of detailed biophysical models. Building on an ongoing collaboration with Professor Alan Roberts (Biological Sciences, Bristol University) a direct application of this work will be to the waves of synaptic activity observed in the spinal cord of the Xenopus tadpole during swimming.

The work will be disseminated through published papers in academic journals (Physical Review, SIAM Journal on Applied Mathematics, Physica D, Journal of Neurophysiology), talks at scientific conferences (SIAM Dynamical Systems, Gordon Conference on Mathematical Biology, Neuroscience, Society for Mathematical Biology Annual Meeting) and personal contacts with relevant research groups: Greg Smith (Arizona) on IFB dynamics, Paul Bressloff (Utah) on propagation failure in inhomogeneous neural networks, Gabriel Lord (Heriot-Watt) on the numerical analysis of travelling waves in biophysical neural network models and Alan Roberts (Bristol) on models of locomotion in the Xenopus tadpole.

Publications with an SC prefix are those for S Coombes as listed on the attached publications list.

References

[1] D Golomb and Y Amitai. Propagating neuronal discharges in neocortical slices: Computational and experimental study. *Journal of Neurophysiology*, 78:1199–1211, 1997.

[2] R Miles, R D Traub, and R K S Wong. Spread of synchronous firing in longitudinal slices from the CA3 region of hippocampus. *Journal of Neurophysiology*, 60:1481–1496, 1995.

[3] U Kim, T Bal, and D A McCormick. Spindle waves are propagating synchronized oscillations in the ferret LGNd *in vitro*. *Journal of Neurophysiology*, 74:1301–1323, 1995.

[4] Alan Roberts. How does a nervous system produce behaviour? A case study in neurobiology. *Science Progress Oxford*, 74:31–51, 1990.

[5] B W Connors and Y Amitai. *Epilepsy: Models, Mechanisms and Concepts*, Generation of epileptiform discharges by local circuits in neocortex, pages 388–424. Cambridge University Press, 1993.

[6] C M Gray. Synchronous oscillations in neuronal systems: mechanisms and functions. *Journal of Computational Neuroscience*, 1:11–38, 1992.

[7] C Li and H H Jasper. Microelectrode studies of the electrical activity of the cerebral cortex in the cat. *Journal of Physiology*, 121:117–140, 1953.

[8] A L Hodgkin and A F Huxley. A quantitative description of membrane and its application to conduction and excitation in nerve. *Journal of Physiology*, 117:500–544, 1952.

[9] J Huguenard and D A McCormick. *Electrophysiology of the Neuron*. Oxford University Press, 1996.

[10] L F Abbott and T B Kepler. Model neurons: From Hodgkin–Huxley to Hopfield. In L Garrido, editor, *Statistical Mechanics of Neural Networks*, pages 5–18. Springer–Verlag, 1990.

[11] I Segev and W Rall. Excitable dendrites and spines: earlier theoretical insights elucidate recent direct observations. *Trends in Neuroscience*, 21(11):453–460, 1998.

[12] G D Smith, C L Cox, S M Sherman, and J Rinzel. Fourier analysis of sinusoidally driven Thalamocortical relay neurons and a minimal integrate-and-fire-or-burst model. *Journal of Neurophysiology*, 83:588–610, 2000.

[13] D Golomb, X J Wang, and J Rinzel. Propagation of spindle waves in a thalamic slice model. *Journal of Neurophysiology*, 75:750–769, 1996.

[14] H P McKean. Nagumo's equation. *Advances in Mathematics*, 4:209–223, 1970.

[15] T Yoshinaga, Y Sano, and H Kawakami. A method to calculate bifurcations in synaptically coupled Hodgkin-Huxley equations. *International Journal of Bifurcation and Chaos*, 9:1451–1458, 1999.

[16] G B Ermentrout and D Kleinfeld. Traveling electrical waves in cortex: insights from phase dynamics and speculation on a computational role. *Neuron*, 29:33–44, 2001.

[17] H R Wilson and J D Cowan. A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue. *Kybernetik*, 13:55–80, 1973.

[18] S Amari. Dynamics of pattern formation in lateral-inhibition type neural fields. *Biological Cybernetics*, 27:77–87, 1977.

[19] G B Ermentrout and J D Cowan. A mathematical theory of visual hallucination patterns. *Biological Cybernetics*, 34:136–150, 1979.

[20] P C Bressloff. Traveling fronts and wave propagation failure in an inhomogeneous neural network. *Physica D*, 155:83–100, 2001.