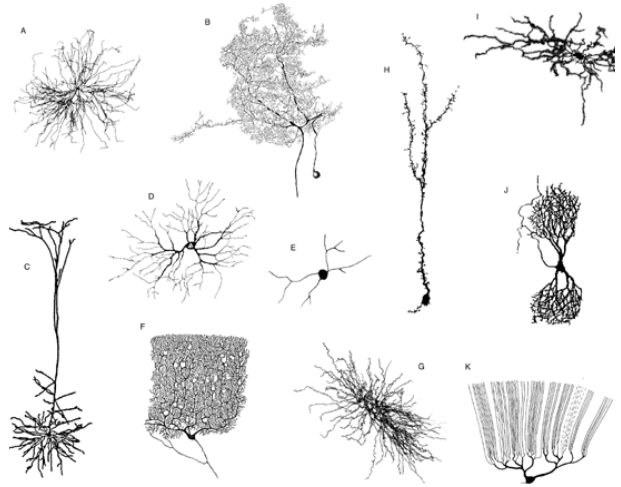


Branching dendrites with active spines

Background

Dendrites form the major components of neurons. They are complex, branching structures that receive and process thousands of synaptic inputs from other neurons. There are many different types of dendritic tree structure (see right [1]), each believed to subservise a different functional process. Unfortunately, many of the current mathematical approaches used in systems neuroscience are built upon a core set of assumptions that exclude the notion of the neuron as a spatially extended object with nonlinear processing capability. Although at odds with the evidence that has been amassed using sharp electrode recordings beginning in the late 1940's, simple spiking or firing rate models of point neurons continue to dominate the mathematical neuroscience literature (the simplicity of these point models has meant that it is feasible to consider large networks both analytically and numerically). Against this, Rall [2], and more recently Koch [3], have developed cable and compartmental models of spatially extended dendritic neurons of increasing sophistication. As evidence that the neuroscience community is ready to address the serious need for a renewed theoretical attack on the active properties of branched neurons we draw attention to comments from Segev and London [4] calling for a strengthening of the dialogue between models and experimentalists. They emphasize that insight into dendritic function has already been enriched by the theoretical work of Rall. Similar comments can be found in the work of Shepherd [5] and are a subtext of the first book devoted exclusively to dendrites by Stuart, Spruston and Häusser [6]. However, the gap between theory and experiment is in danger of growing even further with evidence that the dendrites of many neurons are equipped with excitable channels located in so-called *dendritic spines* that can support an all-or-nothing action potential response to an excitatory synaptic input.



As dendrites form the predominant elements in neurons, so dendritic spines form the dominant component of many types of dendritic tree. They are small mushroom like appendages with a bulbous head and a tenuous stem (of length around $1\mu\text{m}$) and may be found in their hundreds of thousands on the dendritic tree of a single cortical pyramidal cell (see right from Synapse Web, Boston University, <http://synapses.bu.edu>). These extensions of the dendritic tree provide junction points for the axons of other neurons (i.e., provide surface area for synapses), and thus serve as loci for receiving inputs. In the cerebral cortex approximately 80% of all excitatory synapses are made onto dendritic spines. Since the biophysical properties of spines can be modified by experience in response to patterns of chemical and electrical activity, morphological and electro-chemical changes in populations of dendritic spines are thought to provide a basic mechanism for Hebbian learning in the nervous system. In fact the properties of spines have also been linked with the implementation of logical computations [7] coincidence detection [8] orientation tuning in complex cells of visual cortex [9] and the amplification of distal synaptic inputs [10]. The implication of excitable channels in the spine head membrane for amplification of excitatory synaptic inputs was first discussed by Jack *et al.* [11]. However, it is only relatively recently that confocal and two-photon microscopy observations have confirmed the generation of action potentials in the dendrites. Since dendritic spines possess excitable membrane, the spread of current from one spine along the dendrites may bring adjacent spines to threshold for impulse generation, resulting in a saltatory propagating wave in the distal dendritic branches [12].



The first step towards the development of a spiny dendritic tissue model that might be used to explore these issues can be attributed to Baer and Rinzel [13] who considered a passive uniform unbranched dendritic tree coupled to a population

of excitable dendritic spines. In this *continuum* model the active spine-head dynamics is modeled with Hodgkin-Huxley (HH) kinetics whilst the (distal) dendritic tissue is modeled with the cable equation. The spine-head is coupled to the cable via a spine-stem resistance that delivers a current proportional to the number of spines at the contact point. There is no direct coupling between neighboring spines; voltage spread along the cable is the only way for spines to interact. Although the numerical studies of [13] show travelling wave solutions the underlying continuous nature of the model precludes the possibility that these waves are truly saltatory. The saltatory nature of a propagating wave in a spiny neuron may be directly attributed to the fact that active spines are physically separated. Although we can numerically simulate the nonlinear and nonuniform properties of biologically realistic dendritic trees with discrete and clustered distributions of spines, based around natural extensions of the Baer-Rinzel (BR) model, there is a lack of analytical tools for dealing with such systems.

However, recent work by Coombes, Bressloff and Lord [14, 15, 16] has shown that the active membrane dynamics of spines can be treated using an analytically tractable integrate-and-fire (IF) process. The resulting model has been termed the Spike-Diffuse-Spike (SDS) model since spine head dynamics is an all-or-nothing action potential response, whilst dendritic cable is passive. To date this work has only considered unbranched structures and a continuous distribution of spines. In this proposal we identify new mathematical approaches for the study of discrete spines in dendrites. When combined with the analytical techniques developed by Bressloff [17] for studying branched passive dendritic structures and the numerical expertise of Lord in working with BR and SDS type models we are in an ideal position to develop the analysis of spiking spiny branched dendritic trees.

Saltatory wave propagation and wave scattering amongst the branches are fascinating dynamical phenomenon that may be analysed in the SDS framework. Moreover, the model is computationally inexpensive and ideally suited for the study of neural response to complicated spatio-temporal patterns of synaptic input that typically occur in cortical neurons. Importantly, since the SDS model preserves the notions of spine density and spine-stem conductance it will be possible to use variations of existing biophysically motivated Hebbian learning schemes to study learning in the dendritic tree.

Aims and Objectives. The overall aim of this work is to develop a biophysically realistic model of branched dendritic tissue with active spines that is both computationally inexpensive and mathematically tractable. Our two major objectives are to i) develop an understanding of saltatory wave propagation and scattering using a mixture of analysis and efficient numerical simulations and ii) to explore the effects of Hebbian learning schemes on spine distributions and neuronal response to patterned synaptic input.

Programme and Methodology

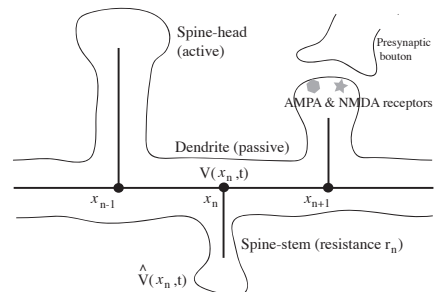
The methodology we propose to employ draws upon a number of established principles from different scientific disciplines, but is predominantly from those of nonlinear dynamics, numerical analysis of stochastic and deterministic systems, computational neuroscience and computational learning theory. We now provide more details of the methods and dual aspect of our proposed programme of research.

I: Dynamics. We consider a hierarchy of models of spines in a dendritic continuum of the form

$$V_t = -V/\tau + DV_{xx} + \rho(x)[\hat{V} - V], \quad (1)$$

where $V(x, t)$ denotes the voltage at position x at time t and the function $\hat{V}(x, t)$ describes the spine-head voltage. The function $\rho(x)$ describes a distribution of spines that can be estimated from experimental data. The membrane time constant of the cable and the diffusion coefficient are τ and D respectively. First consider an extension of the SDS model ($\rho(x) \neq \text{const}$) where that consists of an array of point-source spines embedded in a dendritic continuum (see right). The function $\rho(x) \equiv \sum_n \delta(x - x_n)/\tau_n$ describes a distribution of spines embedded at the sites where $x = x_n$ and the parameters τ_n are proportional to the spine stem resistance at those sites.

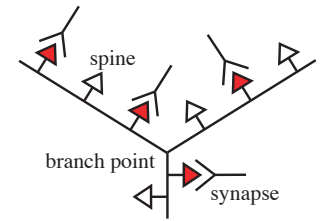
Active membrane in the spine-head underlies the generation of action-potentials at well defined instants of time so that it is natural to consider $\hat{V}(x_n, t) = \sum_m \eta(t - t_n^m)$. The times t_n^m indicate the m th firing of the spine head at position x_n . The shape of the action potential is specified by the (fixed) function η (which can be fitted to the universal shape of



an action potential). In the SDS model firing events are determined by the implicit solution to a threshold process such that if the solution to $U_t = -U + [V - U]/\tau_n$ crosses a firing threshold, h , then $t_n^m = T$ where $U(x_n, t_n^m) = h$ (and U is discontinuously reset, i.e., $U(x_n, T^+) = 0$). In contrast to the original formulation of the SDS model the spine density function considered here lacks translation symmetry, so that travelling waves of constant profile are not expected (but saltatory ones are). Although we have broken translation symmetry (so that many of the standard techniques for travelling wave analysis no longer apply) the linearity of the model means that it may be solved with Green's functions where the full (time-asymmetric) Green's function may be expressed solely in terms of the well known time-translation invariant Green's function of (1) (without spines) via a Dyson like equation (a recursive technique commonly used in quantum field theory).

In the hierarchy of models based on (1), one possibility is to smooth the density $\rho(x)$ of the point spine heads, in which case convergence results may be sought. The mollified version may be physically interesting as the effect of overlapping interaction of spines can be investigated. Results can also be compared to constant, uniformly varying and heterogeneous densities $\rho(x)$ using techniques from homogenization theory (described in [28]). A further model in the hierarchy is to keep HH dynamics for generation of the function η . We shall also explore whether numerical and analytical stability analysis developed for the study of saltatory waves in combustion theory [29] may be transferable to the problem at hand.

To cope with BRANCHED STRUCTURES (see right; triangles denote spine-heads) we observe that an arbitrary dendritic tree may be construed as a set of branching nodes linked by finite length pieces of nerve cable. In a sense, the fundamental building blocks of a dendritic tree are single branching nodes and compartmental chains plus incumbent boundary conditions (so that transmembrane potential is continuous and takes a value that ensures conservation of axial current at the branch point). One can then exploit reflection arguments from the theory of random walks [17] to express the Green's function



of the tree in terms of the solution to the unbranched problem (which we have just outlined how to obtain). Hence there is a concrete formal setting in which to analyse saltatory travelling wave solutions to (1) and to explore how waves may scatter at branch points and spines on an inhomogeneous tree with varying thicknesses, electrical properties and spine densities. For example, in an unbranched uniform dendrite with a regular spacing of spines a distance d apart a saltatory pulse is a solution of the form $t_n^1 = n\Delta$ with a dispersion relation $\Delta = \Delta(d)$ determined by the firing condition $\lim_{N \rightarrow \infty} U(Nd, N\Delta) = h$. To aid in the development of a more general theory that incorporates boundary conditions at branching nodes (where impedance mismatches will lead to scattering) simulations of the model will be performed. This in itself raises interesting numerical issues. We will initially proceed by combining recent techniques described by Lindsay *et al.* [18] for passive trees with those already used and developed by us for the unbranched case (e.g. [16]). This is preferred over using existing software such as GENESIS, NEURON and SURF-HIPPO because of the discontinuous nature of the IF dynamics in the spine-head and the need for accurate determination of threshold crossings (defining spiking events). Initially we will probe conditions for the initiation and propagation of a wave. This combination of analysis and numerics will be used to explore experimental findings suggesting that i) in an excitable dendritic tree with uniform ion channel densities, the propagation of an action potential is more secure towards distal branches and is usually blocked proximally, ii) the threshold for initiating an action potential in distal arbors and spines depends crucially on the spatial distribution of the excitatory input (i.e, on the input conditions in the tree discussed in more detail in II: Learning), iii) the timing of action potential initiation, and the spatial extent of active spread in excitable dendrites depends, with non-linear sensitivity, on the timing and location of the excitatory and inhibitory inputs in the dendritic tree and iv) a backward-forward *ping-pong* interaction between the axon and the excitable channels in branched dendrites shapes the output pattern of spikes firing in the axon [19]. Neuronal geometries are increasingly available through online databases [20] and will provide test-cases for our modelling studies. Graph theory techniques, described in [20], will be used to characterise average measures of connectivity, similarity of connection patterns and cluster indices so that the role of dendritic geometry in influencing firing patterns may be systematically investigated.

Models of dendrites are typically formulated using deterministic equations, thereby ignoring the different noise sources encountered by the input signals that impinge on dendrites. These noise sources include stochastic ion-channel noise and

massive spontaneous background synaptic activity. To quantify the ability of the SDS model to transmit information in the presence of noise we shall use recent numerical techniques developed for the study of stochastic PDEs [21]. This will allow a comparison of the relative contributions of both external and internal noise sources to neuronal processing. External noise that is white in time and either spatially smooth or white in space will be added to the equations of motion as a simple model of background activity. Internal noise will be modelled either considering multiplicative noise or by treating the threshold for firing as a random variable drawn from a distribution that is naturally derived from models of ion channel kinetics [22].

II: Learning.

The dominant theory of learning and memory in neurons is based upon the idea of Hebb: *when an axon of cell A is near enough to excite cell B or consistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.* Hebbian mechanisms of learning are most well studied in the hippocampus and in particular at excitatory synapses on spine heads. Long term potentiation (LTP), whereby Hebbian learning results in an enhancement of excitatory post synaptic potentials, has been shown to be associated with a dramatic increase in peak spinal calcium concentrations. In fact two-photon microscopy has shown that spines are calcium compartments that can undergo activity-dependent morphological changes. By activity we mean synaptic current associated with glutamate triggered AMPA and NMDA channels. These currents are naturally included in the SDS framework by considering an additive current to the IF process in the spine head which we denote as $I_{\text{syn}} = I_{\text{AMPA}} + I_{\text{NMDA}}$. After triggering I_{AMPA} has a simple form like an alpha function $\alpha(t) = \alpha^2 t e^{-\alpha t}$, whilst the NMDA receptor only fully opens for large spine potential (sufficient to remove a magnesium block) and is better described by a form such as $\alpha(t)/(1 + [\text{Mg}^{2+}]e^{-\beta \hat{V}})$. The NMDA current is known to influence intracellular spinal calcium levels and as such is highly important for synaptic plasticity. Moreover, since elevated spinal calcium is currently believed to activate a spine's actin network, which eventually results in a division of the spine it is reasonable to treat spine density as an adjustable *synaptic weight*, indirectly controlled by pre-synaptic events and elevated spine potentials. The invasion of a back-propagating dendritic action potential is one cause of increased spine potential and is expected to play a key role in any Hebbian model of synaptic adaptation at the spine head [23]. We propose to develop a minimal model of LTP based around these ideas that avoids the need for a detailed model of intracellular calcium dynamics. We shall focus on simple Hebbian learning schemes for the density of spines in the SDS model which we write *symbolically*

$$\rho_t = \text{Hebb}(\rho, T_{\text{pre}}, \hat{V}) + \text{Transport}(\rho). \quad (2)$$

Here $T_{\text{pre/post}}$ is the time of a pre/post synaptic event and rather than use T_{post} as an argument to the Hebbian learning scheme we emphasize its dependence on the spine head voltage which is expected to be significant when a back-propagating dendritic wave invades the spine head. A number of Hebbian schemes for synapses have been proposed that may be used for the choice of the Hebb function. In particular many of the rules developed within the context of spike-time dependent plasticity are appropriate since they clearly distinguish between pre and post-synaptic events and are local and asymmetric in time [24]. The Transport term describes spine motility [25], which we shall initially treat as a diffusive process but may modify to accommodate future experimental findings.

By coupling the branched SDS model with active spines to a regional Hebbian learning rule we have a means to explore the role of spine reorganisation in the filtering of sensory information. In particular we wish to investigate the findings of Rose and Fortune who have shown a positive correlation between spine density and low-pass temporal filtering in the midbrain of certain electric fish [26]. By *training* the SDS model on natural patterns of sensory input we hope to establish how filters that pass biologically relevant information and reject inappropriate information (for selective behavioral responses) can be learnt, maintained and adjusted in the dendrites. Rose and Fortune have also examined the response of these neuronal filters to periodic current injection. The mathematical simplicity of the SDS model means that for a learnt distribution of spines it should also be possible to calculate response to such current injection (using techniques from [27]), allowing further interesting comparisons to be made. In fact, in this part of the proposed research we shall also explore, within the SDS framework, the effect of known spine distributions on neuronal response to patterned synaptic input.

We will also investigate the idea that nonlinear integration of visual inputs to the dendrites of single pyramidal cells can contribute to complex-cell receptive field structure [9]. In particular we are interested in establishing how branching and active spines can influence spatial phase-invariant orientation tuning using excitatory inputs from overlapping on and off center visual (thalamic) subfields. This classic property of a complex cell is traditionally thought to arise by from the pooling of output from so-called simple cells. Within the SDS framework we shall investigate how simple-cell (sensitive to orientation *and* spatial phase) computations might be performed directly within the dendrites of complex cells.

Justification of methods. The methods we propose are based on a mixture of well established techniques from different disciplines. Mathematics already has a track record of providing useful insights into dendritic systems [2], and the use of modern numerical methods is appropriate for gaining insight into the dynamics of biologically realistic branching structures.

Timeliness and novelty. This work is timely because dendrites and their spines are just beginning to surrender to the sophisticated optical and electrical techniques that have been developed in the last decade. Importantly we are currently in a position to build upon the theoretical insights gained from early models of spiny dendritic tissue to tackle the effects of branching and active spines on dynamics and learning. The novel theoretical framework we have proposed will help to unravel some of the design principles by which dendritic machinery is used for information processing in these fundamental building blocks of the nervous system.

Management and milestones. Activity will be coordinated by Dr Coombes.

The PDRA will spend the first 1.5 years in Heriot-Watt. During this period numerical routines for investigating the SDS model and related models will be developed by Dr Lord and the PDRA. User specified branching patterns and spine distributions will then be introduced. The theory of wave propagation and scattering will be developed in parallel by Dr Coombes using feedback from numerical experiments to guide analysis. The PDRA will then move to Loughborough for a further 1.5 years to develop Hebbian learning rules with Dr Coombes that may be used in training SDS networks for sensory information processing.

The research student will be based at Loughborough and initially work on the problem of wave propagation in the presence of a discrete distribution of spines for simple geometries and uniform distributions of spines, then work with the PDRA on scattering, and finally progress to the calculation of network response to current injection.

Relevance to beneficiaries. This work will help establish a theoretical underpinning for a new theory of information processing in branched dendritic trees with active membrane and will have its highest impact in the field of computational neuroscience. It will also encourage a cross-fertilisation of ideas between the research areas of deterministic and stochastic numerical analysis of dynamical systems and cell neurophysiology. While key insights may be gained from numerical exploration of excitable dendrites, experience from cable theory tells us that a comprehensive understanding eventually comes from analytical approaches. The type of mathematical neuroscience that we propose to undertake is ideal for developing an understanding of behavioural processes in terms of single-neuron properties, and will constitute a step towards a functional proteomics of nerve cells relevant to the larger neuroscience community. In particular, the UK Neuroscience community will benefit from the seeding of a new generation of researchers, equipped with powerful mathematical and numerical tools, ready to delve into the fascinating properties of dendrites, spines, active membrane and their role at the heart of neural information processing.

Dissemination and exploitation. We intend to raise the awareness of the benefits of this UK based multi-disciplinary collaboration with conference presentations at the Annual Society for Neuroscience conference, the Annual Society for Mathematical Biology meeting and the SIAM conferences on Life Sciences and Dynamical Systems as well as smaller Computational Neuroscience meetings in Europe. Papers will be submitted to multi-disciplinary journals such as the J. of Computational Neuroscience, Neural Computation, J. of Neuroscience and Physica D. Code will be made freely available on the internet and linked to via the Neuroinformatics web site (www.neuroinf.org).

Justification of resources. Funding is requested for a 3 year PDRA (1.5 years at Heriot-Watt, then 1.5 years at Loughborough) and one project student. The multi-disciplinary nature of the project requires the appointment of a

PDRA with experience in at least one of the areas of numerics of dynamical systems or computational neuroscience. Aspects of the project form an ideal basis to train a PhD student in this cross-disciplinary field and are also sufficiently open ended to allow a student to do new and independent research in their own right. Funding is also requested for essential computing equipment and software, for attendance at international and European conferences/workshops and for meetings between the groups at Heriot-Watt and Loughborough.

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