Peter Érdi
Anna Esposito
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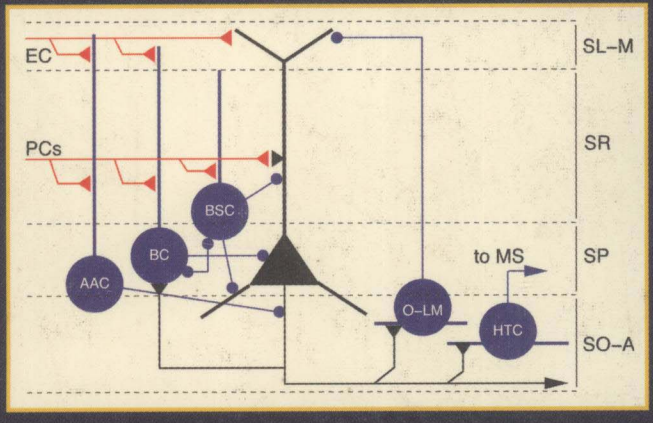
Computational Neuroscience: Cortical Dynamics

**8th International Summer School on Neural Nets
Erice, Italy, October/November 2003
Revised Lectures**



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Preface

This volume contains invited and contributed papers presented at the eighth edition of the International Summer School on Neural Networks, dedicated to Prof. Eduardo R. Caianiello. The school was established in 1996 by Prof. Antonio Zichichi, director of the Ettore Maiorana Centre for Scientific Culture in Erice (Sicily), and Prof. Maria Marinaro, director of the International Institute for Advanced Scientific Studies in Vietri sul Mare, in Italy. The school is held each year, alternating between Erice and Vietri, proposing surveys on several research fields related to cybernetics studies and human-machine interaction. The eighth edition of the school was on cortical dynamics and was held in Erice.

The contributions collected in this book are aimed at providing primarily high-level tutorial coverage of the fields related to cortical dynamics, reporting recent experimental and theoretical results investigating the processing, the transmission, and the imprinting of information in the brain, and important functions of the cortical area such as cortical rhythms, cortical neural plasticity, and their structural basis and functional significance.

Height surveys, reporting the most recent original results, are offered by specialists in the field. Consequently, the volume may be used as a reference book on models of cortical dynamics from neuroscience and physics. To this aim the volume is divided into two sections: fundamentals of cortical dynamics, and mathematical models of cortical dynamics.

Fundamentals of cortical dynamics deals with problems related to the functioning of the brain in complex biological systems, their organization and the existence of hierarchies and multiple-scale networks at several levels of miniaturization and information processing. Fundamental and innovative ideas in neuroscience are covered. This section contains three tutorial papers. The first tutorial, authored by Bruce P. Graham, discusses underlying dynamic signal processing within hippocampal pyramidal cells, their properties and their functioning as associative memories. The second, by Luigi Agnati and colleagues, describes and accounts for various basic features and functions of the central nervous system (CNS), suggesting that the understanding of its functioning is better explained by hypothesizing nested hierarchical structures of computational devices that process incoming input signals at different computational levels of miniaturization and then integrate both spatial and temporal relationships among informational elements and computations, exhibiting emergent behaviors. Finally, the tutorial by Alessandro Treves reports on the physiological changes that may have occurred during the evolutionary process in the neuronal circuitry and may have contributed to the development of a fundamental neuronal mechanism such as the firing rate adaptation.

Mathematical models of cortical dynamics deals with the mathematical modeling and computer simulation of the brain's functions. Inspired by the recent discoveries on the chaotic behavior of neuronal cells and supported by the need

to find solutions for approximating the probability distributions of the cortical cell's dynamics, this research aims to describe brain dynamics using theoretical neural networks models. To this aim it appears that mean field theory (MFT) and chaotic theory offer realistic interpretations. The first paper in this section, authored by John Hertz and colleagues, shows how mean field theory is able to model appropriately the dynamics of dense, randomly connected cortical circuits, their firing statistics and the correlations among them. The second paper, by Fortunato Tito Arecchi, describes the process of "feature binding", i.e., the capacity of the brain to combine external data with internal memories into coherent patterns of meaning, and its modeling through homoclinic chaos (HC). The following three papers demonstrate how several characteristics observed in the dynamic activity of the brain can be mathematically modeled in terms of the information theory of chaos. The first paper of this series, authored by Ichiro Tsuda and Hiroshi Fujii, provides a mathematical model that accounts for the instability and the nonstationary features of the cortical activity through the theory of chaotic itinerancy (CI). The second, authored by Ichiro Tsuda and Shigeru Kuroda, proposes a computational model for the formation of episodic memory based on cantor coding theory. Finally, the last paper of the series, authored by Hiroshi Fujii and Ichiro Tsuda, shows how the behavior of some interneuron systems in the neocortex generates a variety of synchronous inhibitory rhythms that could be mathematically described by an expression of chaotic itinerancy between pseudoattractors.

The editors would like to thank the University of Salerno, the Regione Campania, the Ettore Majorana Center for Scientific Studies, the Italian Neural Network Society, the Italian Ministry for Education and Scientific Reserarch (MIUR), and the International Institute for Advanced Scientific Studies "E.R. Caianiello", for their support in sponsoring, financing, and organizing the school. In addition, the editors are grateful to the contributors of this volume whose work stimulated an extremely interesting interaction with the attendees, who in turn shall not be forgotten for being so highly motivated and bright. This book is dedicated to the memory of Prof. Eduardo Renato Caianiello, who disappeared 10 years ago from the scientific scene. His work and his dedication to research in cybernetics is still alive in all of us and continue to stimulate our research work.

Peter Erdi, Anna Esposito, Maria Marinaro, Silvia Scarpetta

Organization

The eighth edition of the International School on Neural Nets "E.R. Caianiello", titled *Computational Neuroscience: Cortical Dynamics*, was held from October 31 to November 7, 2003, at the Center for Scientific Culture EMFCSC in Erice in Italy.

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Table of Contents

Section 1 – Fundamentals of Cortical Dynamics

Section 2 – Mathematical Models of Cortical Dynamics

Dynamics of Storage and Recall in Hippocampal Associative Memory Networks

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Abstract. A major challenge to understanding cortical function is the complexity found both at the single cell and microcircuit levels. This review covers theoretical studies aimed at elucidating dynamic signal processing within hippocampal pyramidal cells. This processing involves both the intrinsic pyramidal cell properties as well as the microcircuit of inhibitory interneurons that synapse onto the cell. These factors are considered within the framework of associative memory function in areas CA1 and CA3 of the mammalian hippocampus.

1 Introduction

Considerable detail is now known about the individual neuronal cell types found in the cortex, and the circuits they form. However, mathematical models and computer simulations typically concentrate on a particular level of detail, either the single cell, or networks with simplified cellular descriptions. It is both possible and desirable to try to formulate functional models of cortical networks that include known details of all cell types and their detailed microcircuitry. This review considers theoretical modelling studies that cover aspects of the function of the mammalian hippocampus. Firstly, details of the microcircuitry formed by pyramidal cells and the variety of inhibitory interneurons in regions CA3 and CA1 of the hippocampus are given. Then single cell studies of hippocampal pyramidal cells are introduced. Finally, certain network-level models that treat these hippocampal areas as associative memories are described. Only models that attempt to include biophysical details of the cell types and realistic microcircuitry are included here. The emphasis is on providing an overview of a breadth of work that is not usually considered together, at the expense of depth in any particular aspect.

Associative memory is one of the oldest artificial neural network (ANN) paradigms. More than any other ANN, it is also plausibly a model of how certain brain regions may operate. Of particular interest here is the mammalian hippocampus, in which regions CA3 and CA1 have been proposed to be auto- and heteroassociative memories, respectively [80]. This has led to the formulation of biophysically realistic network models of associative memory based on

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the architecture and operation of these hippocampal areas [55, 82]. A number of factors must be considered when moving from an ANN model to a biophysical model, including:

- how are patterns of information coded by neuronal spikes?
- what, if anything, constitutes a rhythmic clock cycle?
- how are storage and recall modes separated in space and time?
- what roles do the different neuronal types play?

The work described here makes the premise that gamma frequency rhythms (30-80Hz) may constitute a basic clock cycle [9, 45, 55]. A slower theta frequency rhythm (5-12Hz) is superimposed on this clock cycle and controls phasing of storage and recall [23, 26, 82]. This is based on the hippocampal activity seen in rats exploring a novel environment, absorbing and storing new spatial information [60]. These models do not attempt to include all behavioural states in rats, such as associated with sharp waves [7], nor necessarily any states found in other animals, particularly primates. Nonetheless, they provide explicit biophysical formulations of associative memory operation and provide an excellent viewpoint from which to try to understand neuronal cellular and microcircuit functioning in a broader context.

2 The Hippocampal Microcircuit

The dominant cell type in many areas of neocortex and hippocampus is the pyramidal cell (PC). The outputs from these cells are excitatory and the networks they form are likely to be the principal information processing structures in these brain regions. When ANNs are considered as models of the brain they are typically being equated with networks of PCs. Pyramidal cells, both in hippocampus and in neocortex, are surrounded by a variety of inhibitory interneurons (INs). These INs differ in morphology, pharmacology and connectivity [17, 46, 52]. Understanding their functional roles is a great challenge. ANN models usually contain only a single cell type (PCs) within a simple network architecture. Many of the details of the microcircuitry involving pyramidal cells and these interneurons is now known for the CA1 and CA3 regions of the hippocampus [17]. The basic hippocampal microcircuit is shown in Figure 1.

The first feature to note is the spatial segregation of excitatory input from different pathways onto a PC [34]. In CA1, the Schaffer collateral input from CA3 PCs is largely to stratum radiatum (SR), constituting the proximal region of the apical dendritic tree. Recurrent collaterals from other CA1 PCs synapse on the basal dendritic tree (stratum oriens: SO). Perforant path input from layer III of entorhinal cortex (EC) reaches the distal part of the apical dendritic tree (stratum lacunosum-moleculare: SL-M). In region CA3, input to stratum radiatum and stratum oriens is largely from other CA3 PCs. Input to the distal apical tree comes from layer II of entorhinal cortex. A third excitatory input in CA3 comes from granule cells of the hippocampal dentate gyrus which form the mossy fibre synapses in the very proximal region of the apical tree.

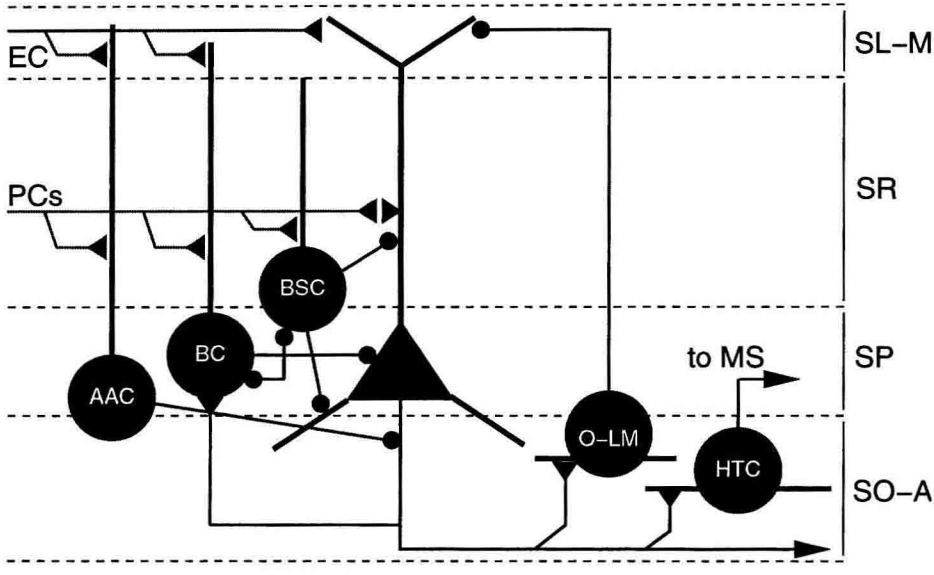

Fig. 1. Microcircuit architecture of INs surrounding a PC in the CA1 or CA3 region of the hippocampus. Small triangles are excitatory synapses and small circles are inhibitory synapses. Adapted from Paulsen and Moser [62]. See text for details.

Though a complete catalogue of interneuronal types remains to be determined, several classes can be distinguished on anatomical and pharmacological grounds [17, 46, 52]. These include basket cells (BC), bistratified cells (BSC), axo-axonic (chandelier) cells (AAC) and oriens lacunosum-moleculare (horizontal) cells(O-LM). These INs are all inhibitory GABAergic cells. As illustrated in Fig. 1, like excitatory afferents, different IN types target specific spatial regions on PCs. They also receive excitatory input from particular pathways and may form synaptic (inhibitory) and gap junction (excitatory) connections with other INs. Other cell classes include horizontal and radial trilaminar cells and INs that only synapse onto other INs [17]. A subclass of horizontal trilaminar cells (HTC) send axon collaterals out of the hippocampus to the medial septum (MS). There may also be inhibitory projections between hippocampal subfields (CA1 to CA3).

In addition to targetting specific dendritic localities on PCs, different classes of IN also exhibit a specific spread in their network connectivity across cells. Typically, an IN makes synaptic connections within a defined local area, unlike PCs that make widespread connections. Total IN numbers may be only 10% of the total cell population, with a single PC innervating hundreds of INs and an IN innervating several thousand PCs [17]. The spread of IN connections may be highly focussed. For example, a single O-LM cell makes connections in the distal dendritic tree of PCs with a spread that exactly matches the spread of excitatory input from a single entorhinal cell onto the same PC dendritic location [17].

The nature of the inhibitory connections also differs with IN class. Basket and axo-axonic cells make several powerful connections onto the perisomatic and axon initial segment regions of a single PC, respectively, indicating the ability to strongly influence spike generation and output in the PC. In contrast, bistratified cells make more diffuse connections, with no more than one connection on a particular dendritic branch [17].

There is not a one-to-one correspondence between morphology, pharmacology and electrical activity in INs, making classification very difficult [17, 46, 52]. Basket cells, in particular, include at least two types that are distinguishable on pharmacological grounds and appear to have distinct functional roles within the hippcampal microcircuit [16]. In the associative memory models to be described later in this paper, the basket cells are likely the parvalbumin (PV)-containing cells. Recent data indicates that certain cell types may be distinguished by their firing patterns in different brain states [41].

What does the microcircuit do? Most well studied, both experimentally and with mathematical modelling, is the contribution of the microcircuit to generating and stabilising oscillatory activity at different frequencies [78]. Though the mechanisms that produce oscillations are not the focus here, two different oscillations, the theta and gamma rhythms, play an important part in certain models of associative memory function in the hippocampus. The precise mechanisms underlying theta (5-12Hz) are complex and include extra- and intrahippocampal sources [8, 61]. Gamma (30-80Hz) is strongly determined by the intrinsic cellular and synaptic properties of the hippocampal microcircuit [83] and may be controlled by external inputs to the hippocampus [13]. Here we are concerned with the possible functioning of the microcircuit as an *information processing* construct. In the final sections of this paper we will consider the possible role of this microcircuit in controlling storage and recall within associative memory networks.

3 Signal Processing in Neurons

Neurons integrate synaptic input from other neurons for the end purpose of producing their own output signals for propagation to receiving neurons. The synaptic input also results in signals that are internal and localised within a neuron and determine synaptic plasticity. The integration of synaptic input involves the spatial and temporal summation of signals from different synapses and the interaction of these summed signals with the intrinsic membrane properties of the neuron. These properties are determined by the typically heterogeneous distribution of different types of ion channels throughout the dendritic tree.

3.1 Intrinsic Properties of Pyramidal Cells

Increasingly detailed knowledge is being obtained about the spatial distribution of ion channels in different neuronal types, as recently reviewed in Migliore and Shepherd [59]. CA1 pyramidal cells are amongst the most well characterised in this regard. Sodium and calcium channels maintain a relatively uniform density

out into the apical dendritic tree, though sodium channel characteristics and the type of calcium channel may change with distance [38, 50]. The fast A-type potassium channel and the mixed cation H channel increase in density roughly 6-fold over several hundred micrometers distally in the apical tree [30, 47].

Voltage-activated ion channels are characterised by the membrane voltage range over which they open (activate), and the time course of their opening and closing. Certain channel types will remain open while the membrane voltage is within the appropriate range. Other channels inactivate with a certain time course, that is they will close some time after they have opened, even though the membrane voltage may still be within the range at which these channels first open. Many ion channels activate when a cell is depolarised, that is, when the membrane potential moves towards zero from rest. Such channels include sodium, calcium, delayed rectifier (DR) and A-type (A) potassium, and the mixed cation M channels. Other types, such as the H channel are activated at hyperpolarised potentials. Sodium, calcium and the DR and A potassium channels activate quickly with millisecond kinetics. The M and H channels activate with time courses in the tens of milliseconds. These channel types will be more extensively discussed than others in what follows. Slower channels, such as the calcium-activated slow-after-hyperpolarizing-potential potassium channel (AHP), have activation dynamics in the range of hundreds of milliseconds to seconds, and contribute to spike frequency adaptation.

Functionally, these voltage-activated ion channels may be classified as *amplifiers* or *suppressors* of changes in membrane voltage. Ion channels whose reversal potential and activation range are in the same direction as a change in membrane potential away from rest act as amplifiers. The current generated by the opening of these channels will move the voltage further from rest. Sodium and calcium channels are amplifiers. In contrast, various potassium and mixed cation (M and H) channels are suppressors of voltage change. Movement of the membrane potential away from rest into the activation range of these channels is in the opposite direction to their reversal potential. Consequently the current generated by the opening of these channels will tend to nullify the original change in potential. The action potential (AP) is the classic example of the interaction of amplification by sodium channels and suppression by potassium channels. Fast channels such as these, with dynamics in the millisecond range, are responsible both for generating action potentials and shaping synaptic voltage responses (EPSPs) as they travel through the dendritic tree to the soma. Slightly slower channels, such as M and H, that are suppressors of voltage change, act as high pass filters and contribute to electrical resonance in neurons, as will be described below.

A detailed exposition of the different ion channel types found in hippocampal pyramidal cells and their dynamic characteristics is given by Borg-Graham [6].

3.2 Signal Integration

The dynamic characteristics of different ion channels and their spatial distribution within dendritic trees gives them specific functional roles for synaptic signal

integration. Ion channels contribute to the time course and summation of synaptic input. Here we consider work that addresses how excitatory inputs that are widely distibuted across the apical dendritic tree of PCs summate to affect cell output in the soma. Do such inputs sum linearly? Will distant inputs have as much influence on cell output as those close to the cell body?

Synaptic Scaling. One consequence of synapses being spatially distributed across a dendritic tree is that those synapses that are more distant from the cell body may have less impact on the voltage response at the soma than more proximal synapses, due to membrane current leakage as signals travel through the dendrites. Either distal synapses need to produce larger local EPSPs or signals need to be amplified as they travel along the dendrites to overcome this disadvantage. There is experimental evidence that the synaptic AMPA conductance does increase with the distance of the synapse from the soma in the apical dendrites of CA1 pyramidal cells [2, 49].

Temporal Summation. The rising density with distance from the soma of A and H channels in the apical dendritic tree of CA1 PCs may in part determine the temporal summation of synaptic inputs. In a series of experimental and modelling studies, Magee [47, 48] has demonstrated that deactivation of the H current may act to shorten the time course of distal EPSPs. This has the effect that the temporal summation of trains of EPSPs is independent of their spatial location within the dendritic tree.

In a modelling study, Migliore [57] has demonstrated that activation of the A current and deactivation of the H current are instrumental in restricting the temporal integration of distal and proximal inputs to a time window of around 20msecs within which the distal input precedes the proximal input.

Spatial Summation. For a pyramidal cell to produce an output it typically needs to receive a number of contemporaneous inputs. These inputs are likely to be spatially distributed across a portion of the dendritic tree. Their spatial locations, in combination with the local membrane characteristics, will determine how the different inputs summate.

Various functional scenarios depend on the mathematical form of input summation. In a study of pattern recognition by CA1 PCs, Graham [19] considered a situation in which a pyramidal cell needed to be able to accurately distinguish the number of simultaneous excitatory inputs arriving at random locations within the *stratum radiatum* portion of the apical dendritic tree. The amplitude of the voltage response in the soma was used as the criterion for measuring the number of inputs. Different spatial distributions of the same number of inputs produced slightly different voltage amplitudes, introducing noise into the measurement that limited the discrimination that could be made.

Different characteristics of the synaptic input and the membrane properties of the dendritic tree were explored. The basic case consisted of all inputs (in the form of single APs) arriving at exactly the same time onto a dendritic tree containing only a leak conductance (passive membrane). A comparison was made

between the distributions of voltage amplitudes for 200 compared with 100 inputs to synapses at different random spatial locations. Amplifying mechanisms at each synapse and in the dendritic membrane that boosted distal inputs all acted to improve the signal-to-noise ratio between the amplitude distributions of 200 and 100 inputs. This equates with an improvement in the cell's discrimination of the number of simultaneuous inputs reaching its dendritic tree. The amplifying mechanisms included (1) scaling of the synaptic AMPA conductance so that the EPSP amplitude at the soma of a single input was independent of synaptic location, (2) an NMDA component of the synaptic EPSP, (3) a uniform distribution of persistent (noninactivating) sodium channels in the dendritic membrane, and (4) a uniform distribution of low-voltage-activated calcium channels. These mechanisms improved input discrimination when included individually and in combination.

Two extra sources of noise were included. Firstly, rather than the APs arriving synchronously at all the synapses, the arrival times were uniformly distributed across a short interval of 20msecs. Secondly, a random variation in the maximum synaptic conductance was added to each synapse to simulate quantal variance. As might be expected, discrimination ability was reduced by quantal variance. Intriguingly, the temporal variance of arrival times actually increased discrimination ability. This was presumably due to a reduction in nonlinear summation at nearby synapses and a randomisation of EPSP arrival times at the soma.

Linear and Nonlinear Summation. Using a very detailed model of a CA1 pyramidal cell, Poirazi et al. [64, 65] investigated the impact of the relative spatial location of synapses on the summation of their EPSPs. They considered the cellular response to active synapses clustered locally on a dendritic branch, with a number of clusters on different branches. The computer simulations demonstrated that the clustered inputs on a single branch summed nonlinearly due to amplification by NMDA, sodium and calcium currents. The peak voltage output from a dendritic branch was a sigmoidal function of the number of active inputs on that branch. However, the voltage signals propagating from separate branches summed linearly in the trunk of the apical dendritic tree due to rectification by the A current. Thus they characterised the pyramidal cell as a two-layer network in which the input at the soma consisted of the linear sum of a set of sigmoidal units, corresponding to the dendritic branches.

3.3 Resonance

The dynamics of neuronal membrane and ion channels causes electrical resonance in neurons. The membrane capacitance and resistance (or leak conductance) provide low-pass filtering of electrical signals. This is most clearly seen if a neuron is driven by a subthreshold oscillatory current. The amplitude of the voltage response gradually decreases as the current frequency increases, for the same current amplitude. In contrast, relatively slowly activating ion channels that act as suppressors of voltage change provide high-pass filtering. These channels do