## Series Foreword

Computational neuroscience is an approach to understanding the information content of neural signals by modeling the nervous system at many different structural scales, including the biophysical, the circuit, and the systems levels. Computer simulations of neurons and neural networks are complementary to traditional techniques in neuroscience. This book series welcomes contributions that link theoretical studies with experimental approaches to understanding information processing in the nervous system. Areas and topics of particular interest include biophysical mechanisms for computation in neurons, computer simulations of neural circuits, models of learning, representation of sensory information in neural networks, systems models of sensory-motor integration, and computational analysis of problems in biological sensing, motor control, and perception.

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# Preface

The present book is a continuation of an earlier monograph, *Neuronal Networks of the Hippocampus* (Traub and Miles 1991). The theme of the earlier work concerned the interaction between intrinsic cellular properties, synaptic organization, and network properties in the hippocampus. Our thinking was influenced by research analyzing invertebrate central pattern generating circuits (Marder and Calabrese 1996), but the approach in mammalian brain was of necessity modified, owing to the large number of neurons in mammals and to the absence therein of neurons with specific identities. In consequence, the connectivity in large networks of mammalian neurons can only be described in statistical terms rather than by specifying which particular neurons connects to which particular other neuron.

The scientific questions considered in the earlier monograph had to do with in vitro models of epilepsy, for epileptiform events represented the type of network phenomenon most readily induced experimentally in brain slices. The epilepsy model studied in most detail was the model obtained by blockade—either complete or partial—of $GABA_A$ receptor-mediated inhibition, with resultant ''epileptic'' events that consisted of one or more synchronized bursts. A burst is a series of three or more action potentials, usually riding on a depolarizing wave.

The approach in the previous monograph—as in the present one—was to analyze the behavior of large networks of neurons,

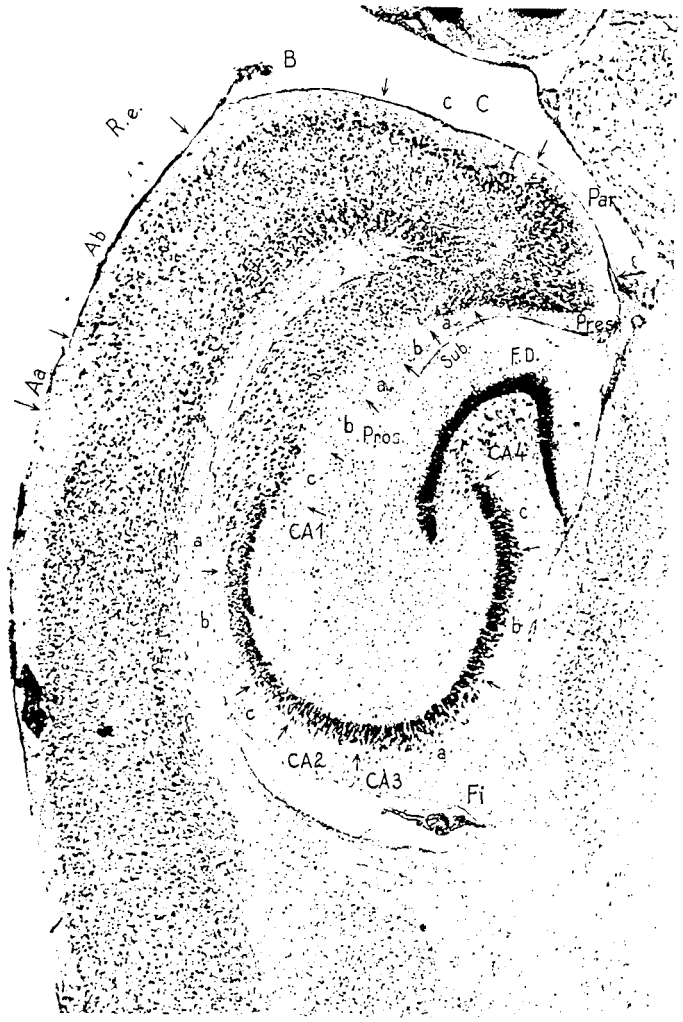


**Figure P.1**
Hippocampus and related structures: horizontal section of mouse brain. The tissue was prepared with Nissl stain, which reveals neuronal somata. CA1, CA2, CA3, and CA4 (hilus) are portions of the hippocampus. Other symbols are *F.D.*., fascia dentata (dentate gyrus); *R.e.*, regio entorhinalis (entorhinal cortex); *Par*., parasubiculum; *Sub.*, subiculum; *Pres*., presubiculum; *Pros*., prosubiculum; *Fi*, fimbria. (From Lorente de Nó, 1934.)

using a combination of electrophysiological and computer modeling techniques. In order to understand synchronization of bursting, it was necessary to analyze:

1. How excitation spreads through recurrently connected networks of intrinsically bursting neurons. Intrinsically bursting implies that the neuron possesses such a repertoire of membrane conductances that allow it to burst in response to a brief current pulse alone without a requirement for sustained synaptic excitation. Intrinsic bursting is characteristic of CA3 pyramidal cells when the membrane potential is in an appropriate range.

2. How the extent of synchrony (on a time scale of tens of ms) is regulated by synaptic inhibition.

3. How partial blockade of inhibition leads to interesting population phenomena, such as oscillation of the population as a whole but without oscillation of individual cells, and in which the cellular composition of individual population waves is random.

The mathematical concepts that influenced our thinking came in part from percolation theory (Fisher 1961), although the language used to express our ideas was mostly biological. We showed that a small number of principles on intrinsic bursting and on the ability of bursting in one neuron to induce bursting in another could explain interictal spikes but not sustained epileptic afterdischarges. An interictal spike is a brief—tens of ms—EEG event, which at the cellular level consists of synchronized bursting among a population of neurons. Our results raised the question that an inaccurate model of individual cells might be one reason why the network model could not replicate afterdischarges, another reason perhaps being the failure to include excitatory synaptic actions lasting tens of ms or more.

Several advances in the past seven years have motivated the writing of a new monograph. Below is a list of some of these advances, omitting for now details and citations to the literature:

1. Patch clamp techniques, applied both to acutely isolated neurons and to neurons in slices, have led to a more accurate kinetic description of membrane voltage-dependent currents, including calcium currents. Patch clamp techniques applied to dendrites have also extended earlier observations based on dendritic recordings with sharp electrodes and have allowed better definition of the spatial distribution of ionic conductances over the cell membrane.

2. These data in turn allow one to model single pyramidal cells more accurately. Once a model had been developed in which repetitive dendritic calcium spikes could be generated, as in real pyramidal cells, it became possible to understand in vitro afterdischarges produced by blockade of synaptic inhibition. Subsequently, progress has been made in understanding certain other experimental epilepsies as well and in understanding some of the underlying principles common to the epilepsies.

3. It was demonstrated that pharmacologically isolated networks of interneurons could produce synchronized bursts, resembling in form interictal spikes. These data suggested that interneuron networks might also generate interesting population phenomena under more physiological conditions.

4. It was shown that pharmacologically isolated interneuron networks could produce gamma-frequency ($>$ 30 Hz but often simply called 40 Hz) oscillations in vitro, and this behavior could be explained using physical ideas of Wang and Rinzel and of Destexhe and Babloyantz. The discovery of gamma oscillations in slices implied that in vitro methods could be useful in elucidating cellular mechanisms of a phenomenon that many (including these authors) believe is important for perception and cognition.

5. It next became possible to induce 40 Hz oscillations in slices by tetanic stimulation so that both pyramidal cells, as well as interneurons, fired. Furthermore, such oscillations could synchronize over distances of several mm. Such in vitro oscillations not only share a

number of phenomenological features with in vivo oscillations, such as long latency to onset, but in slices, it was possible to analyze cellular mechanisms with electrophysiological and computer modeling techniques. In this way, one could account for long-range synchrony, even if inhibitory synaptic connectivity is localized and axon conduction is slow; the fast and reliable synaptic communication between pyramidal cells and interneurons plays a crucial role in this long-range synchrony.

6. Finally, it has been shown that 40 Hz oscillations themselves can induce synaptic plasticity, and the resultant plastic changes in turn influence the oscillations, as well as leading to a different sort of oscillation: beta (10–25 Hz). If 40 Hz oscillations are indeed relevant to perception, then these data suggest a connection between perception and memory.

The above-listed advances, their background and ramifications, and the in vivo context into which they fit, all make up the content of the present monograph. There is, of course, great interest in gamma oscillations among in vivo neurophysiologists because the manner in which such oscillations are induced by sensory stimulation—including global features of the stimulus—suggests some connection of the phenomenon with perception or cognition. Furthermore, it seems likely that gamma oscillations are produced by the brain for some fundamental, if still elusive, reasons. Oscillations are found in phylogenetically old parts of the brain (the olfactory system) and in the visual cortex of ancient types of vertebrates, for instance, reptiles (Prechtl 1994). Oscillations are also found in the olfactory systems of invertebrates (Laurent and Davidowitz 1994). One particular set of ramifications to be considered includes the mechanism of action of general anesthetics and the means by which opiates induce cognitive dysfunction.

Why include epileptic events and gamma oscillations as part of the same story, apart from the authors' having worked on both phe-