In search of memory

Storage and recall of ultrametric patterns in a realistic neural network of hippocampus
«The Brain — is wider than the Skys»

Emily Dickinson, *Complete Poems*, 1924
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<tbody>
<tr>
<td>AAC</td>
<td>axo-axonic cell</td>
</tr>
<tr>
<td>ACPD</td>
<td>trans-(1S,3R)-1-amino-1,3-cyclopentanedicarboxylic acid</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxalonepropionic acid</td>
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<tr>
<td>ANN</td>
<td>artificial neural network</td>
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<tr>
<td>AP</td>
<td>action potential</td>
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<tr>
<td>APV</td>
<td>2-amino-5-phosphonovaleric acid</td>
</tr>
<tr>
<td>BC</td>
<td>basket cell</td>
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<tr>
<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
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<tr>
<td>BPAP</td>
<td>backpropagating action potential</td>
</tr>
<tr>
<td>BSC</td>
<td>bistratified cell</td>
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<tr>
<td>CA</td>
<td>cornu ammonis</td>
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<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CB</td>
<td>calbindin</td>
</tr>
<tr>
<td>CCK</td>
<td>cholecystokinin</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CREB</td>
<td>cAMP response element binding protein</td>
</tr>
<tr>
<td>DG</td>
<td>dentate gyrus</td>
</tr>
<tr>
<td>EC</td>
<td>entorhinal cortex</td>
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<tr>
<td>EPSC</td>
<td>excitatory postsynaptic current</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>EPSP</td>
<td>excitatory postsynaptic potential</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminobutyric acid</td>
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<tr>
<td>GC</td>
<td>granule cell</td>
</tr>
<tr>
<td>GHK</td>
<td>Goldman–Hodgkin–Katz equation</td>
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<tr>
<td>HF</td>
<td>hippocampal formation</td>
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<tr>
<td>HH</td>
<td>Hodgkin-Huxley model</td>
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<tr>
<td>IPSC</td>
<td>inhibitory postsynaptic current</td>
</tr>
<tr>
<td>IPSP</td>
<td>inhibitory postsynaptic potential</td>
</tr>
<tr>
<td>LEC</td>
<td>lateral entorhinal cortex</td>
</tr>
<tr>
<td>LTD</td>
<td>long-term depression</td>
</tr>
<tr>
<td>LTP</td>
<td>long-term potentiation</td>
</tr>
<tr>
<td>MAP</td>
<td>mitogen-activated protein</td>
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<tr>
<td>MEC</td>
<td>medial entorhinal cortex</td>
</tr>
<tr>
<td>MF</td>
<td>mossy fibre</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger RNA</td>
</tr>
<tr>
<td>MS</td>
<td>medial septum</td>
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<tr>
<td>MST</td>
<td>minimum spanning tree</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartic acid</td>
</tr>
<tr>
<td>NPY</td>
<td>neuropeptide Y</td>
</tr>
<tr>
<td>OLM</td>
<td>oriens lacunosum moleculare</td>
</tr>
<tr>
<td>PC</td>
<td>pyramidal cell</td>
</tr>
<tr>
<td>PER</td>
<td>perirhinal cortex</td>
</tr>
<tr>
<td>PKA</td>
<td>protein kinase A <em>also known as</em> cAMP-dependent protein kinase</td>
</tr>
<tr>
<td>POR</td>
<td>postrhinal cortex</td>
</tr>
<tr>
<td>PV</td>
<td>parvalbumin</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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viii
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>SK</td>
<td>Sherrington–Kirkpatrick spin-glass</td>
</tr>
<tr>
<td>SOM</td>
<td>somatostatin</td>
</tr>
<tr>
<td>STDP</td>
<td>spike-timing-dependent plasticity</td>
</tr>
<tr>
<td>Sub</td>
<td>subiculum</td>
</tr>
<tr>
<td>VIP</td>
<td>vasoactive intestinale peptide</td>
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The process of memory formation, storage and recall is a central, and to a large extent not understood, task carried out by the brain. Getting a better grasp of it may be crucial for the devise of effective therapies for memory-related pathologies, the most famous of which being Alzheimer’s disease. An important, but difficult, task in this context is to integrate the discoveries made at the level of the molecular alterations that are found to occur in single neurons during memory formation (e.g. activity dependent activation of specific transcription factors and resulting gene alterations) into the higher order, system-level organization of the neuronal networks that encode memory.

As the encoding of facts and events (declarative memory) first takes place in the *hippocampus*, this structure (and especially the CA3-CA1 pyramidal neurons connection) has been intensively studied by all types of researchers interested in memory. The molecular alterations of CA1 pyramidal neurons that result from experience- or learning-dependent synaptic activation are complex and still not fully identified. It is now clear, however, that during memory formation occurs a robust activation of CA1 synaptic inputs by CA3 axonal stimulation, leading to long-term potentiation (LTP) of the AMPA receptor current at these synapses (Whitlock et al., 2006). This robust activation of CA1 inputs results in calcium entry in the post-synaptic neuron and activates a variety of transcription factors, the most studied of which is the cAMP Response Element Binding protein (CREB). This suggests that CREB-dependent transcription of specific genes must, at least in part, drive memory encoding (Kandel, 2001).

Recent works led to the characterization of CREB-dependent neuronal alterations. In particular, CREB-activated neurons display a higher number of synapses containing only NMDA receptors (silent synapses), more spines, a higher magnitude of LTP, and increased excitability (Marie et al., 2005; Huang et al., 2008; de Armentia et al., 2007; Dong et al., 2006). Furthermore, it has recently been shown that increasing CREB activity in the CA1
or dentate gyrus of the hippocampus enhances memory formation in rodents (Restivo et al., 2009). We must therefore conclude that the neuronal adaptations mediated by CREB-dependent gene transcription are at the basis of memory formation and that, by boosting these adaptations, one could improve memory processes in cases where they are impaired.

The problem of how CREB-dependent neuronal alterations (in synaptic strength, excitability and LTP, which have been observed at a single neuron level using biological tools) can improve the formation of memory by a complex neuronal network has so far escaped detailed investigation. We have created a small realistic hippocampal network in order to verify whether the single cell properties altered by increased CREB-dependent transcription may actually contribute to improving memory formation.

Furthermore, a realistic model of long-term memory should include the concept of category. In Artificial Neural Network (ANN) models, words or patterns to be stored have to be encoded in approximately orthogonal vectors, that is just exactly the opposite of the way human memory works. It is part of our every day experience that when we try to memorize new information we look for all the possible relationships with previously stored words. If we can classify the new pattern, that is, place it in a hierarchical tree of categories, we do it with so much eagerness that sometimes we just censor the data so as to eliminate some exceptional features. However, if the word is really orthogonal to all the previously stored ones we have reluctantly to initiate a new category.

This problem will be solved if we could modify the model in such a way that the patterns to be memorized fall into a hierarchical tree. This type of organization is called ultrametricity. Therefore, an interesting question that arises is if such an organization could be implemented in a network of realistic neurons.

Our network reconstruction and its operation are based on the ideas discussed in several papers, originating with the work by Hasselmo et al. (2002) and recently implemented, using several important experimental constrains, by Cutsuridis et al. (2010). The model consists of 100 pyramidal (P) cells, 2 basket cells (BC), 1 bistratified (BS) cell, 1 axo-axonic (AA) cell, and 1 oriens lacunosum moleculare (OLM) cell. Simplified morphologies including the soma, apical and basal dendrites and a portion of axon, were used for each cell type. The biophysical properties of each cell were adapted from cell types reported in the literature (Poirazi et al., 2003a,b). The network stores and retrieves patterns by modifying the synaptic connections through Spike Time Dependent Plasticity (STDP). All simulations were performed within the NEURON environment (Hines and Carnevale, 1997).
Part I

In search of memory: a neuroscientific approach
Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant. [...] It is the same thing which makes us mad or delirious, inspires us with dread and fear, whether by night or by day, brings sleeplessness, inopportune mistakes, aimless anxieties, absent-mindedness, and acts that are contrary to habit. These things that we suffer all come from the brain, when it is not healthy, but becomes abnormally hot, cold, moist, or dry, or suffers any other unnatural affection to which it was not accustomed. Madness comes from its moistness. When the brain is abnormally moist, of necessity it moves, and when it moves neither sight nor hearing are still, but we see or hear now one thing and now another, and the tongue speaks in accordance with the things seen and heard on any occasion. But when the brain is still, a man can think properly.

attributed to Hippocrates  
V Century, B.C.\(^1\)

The last frontier of the biological sciences – their ultimate challenge – is to understand the biological basis of consciousness and the mental processes by which we perceive, act, learn, and remember.

Such a comprehensive approach depends on the view that all behaviour is the result of brain function. What we commonly call the mind is a set of operations carried out by the brain.

The task of neural science is to explain behaviour in terms of the activities of the brain. How does the brain marshal its millions of individual nerve cells to produce behaviour, and how are these cells influenced by the environment, which includes the actions of other people?

To answer these questions, we necessarily focus on the cerebral cortex, the part of the brain concerned with the most evolved human behaviours. Here we see how the brain is organized into regions or brain compartments, each made up of large groups of neurons, and how highly complex behaviours can be traced to specific regions of the brain and understood in terms of the functioning of groups of neurons.

1.1 A brief historical excursus

Our current views about nerve cells, the brain, and behaviour have emerged over the last century from a convergence of five experimental traditions: anatomy, embryology, physiology, pharmacology, and psychology.

Nervous tissue did not become the subject of a special science until the late 1800s, when the first detailed descriptions of nerve cells were undertaken by Camillo Golgi and Santiago Ramón y Cajal.

Golgi developed a way of staining neurons with silver salts that revealed their entire structure under the microscope. He could see clearly that neurons had cell bodies and two major types of projections or processes: branching dendrites at one end and a long cable-like axon at the other. Using Golgi’s technique, Ramón y Cajal was able to stain individual cells, thus showing that nervous tissue is not one continuous web but a network of discrete cells. In the course of this work, Ramón y Cajal developed some of the key concepts and much of the early evidence for the neuron doctrine – the principle that individual neurons are the elementary signaling elements of the nervous system.

Physiological investigation of the nervous system began in the late 1700s when the Italian physician and physicist Luigi Galvani discovered that living excitable muscle and nerve cells produce electricity. Modern electrophysiology grew out of work in the nineteenth century by the German physiologist Hermann von Helmholtz who was able to show that the electrical activity of one nerve cell affects the activity of an adjacent cell in predictable ways.

By as early as the end of the eighteenth century the first attempts had been made to bring together biological and psychological concepts in the
study of behaviour. Franz Joseph Gall, a German physician and neuroanatomist, proposed three radical new ideas. First, he advocated that all behaviour emanated from the brain. Second, he argued that particular regions of the cerebral cortex controlled specific functions. Third, Gall proposed that the center for each mental function grew with use, much as a muscle bulks up with exercise. As each center grew, it purportedly caused the overlying skull to bulge, creating a pattern of bumps and ridges on the skull that indicated which brain regions were most developed (Figure 1.1). His psychology, based on the distribution of bumps on the outside of the head, became known as *phrenology*.

Figure 1.1 – According to the nineteenth-century doctrine of phrenology, complex traits such as combativeness, spirituality and hope are controlled by specific areas in the brain, which expand as the traits develop. This enlargement of local areas of the brain was thought to produce characteristic bumps and ridges on the overlying skull, from which an individual’s character could be determined. This map, taken from a drawing of the early 1800s, purports to show 35 intellectual and emotional faculties in distinct areas of the skull and the cerebral cortex underneath.

These studies were later refined by the German neurologist Karl Wernicke and the English physiologist Charles Sherrington into a view of brain function called *cellular connectionism*. According to this view, individual neurons are the signaling units of the brain; they are generally arranged in functional groups and connected to one another in a precise fashion. Wernicke’s work in particular showed that different behaviours are produced by different brain regions interconnected by specific neural pathways.
1.2 Introducing the cerebral cortex

The brain operations responsible for our cognitive abilities occur primarily in the cerebral cortex – the furrowed gray matter covering the cerebral hemispheres. In each of the brain’s two hemispheres the overlying cortex is divided into four anatomically distinct lobes: frontal, parietal, temporal, and occipital (Figure 1.2). These lobes have specialized functions. The frontal lobe is largely concerned with planning future action and with the control of movement; the parietal lobe with somatic sensation; the occipital lobe with vision; the temporal lobe with hearing, and through its deep structures – the hippocampus and the amygdaloid nuclei – with aspects of learning, memory and emotion. Each lobe has several characteristic deep infoldings (a favored evolutionary strategy for packing in more cells in a limited space). The crests of these convolutions are called gyri, while the intervening grooves are called sulci or fissures.

Figure 1.2 – The four lobes of the cerebral cortex.

The organization of the cerebral cortex is characterized by two important features. First, each hemisphere is concerned primarily with sensory and motor processes on the contralateral (opposite) side of the body. Second, although the hemispheres are similar in appearance, they are not completely symmetrical in structure nor equivalent in function.

1.3 Nerve cells and behaviour

The remarkable range of human behaviour depends on a sophisticated array of sensory receptors connected to a highly flexible neural machine – a brain – that is able to discriminate an enormous variety of events in the environment. The continuous stream of information from these receptors is organized by the brain into perceptions (some of which are stored in memory for future reference) and then into appropriate behavioural responses. All
of this is accomplished by the brain using nerve cells and the connections between them.

Individual nerve cells, the basic units of the brain, are relatively simple in their morphology. Although the human brain contains an extraordinary number of these cells (on the order of $10^{11}$ neurons), which can be classified into at least a thousand different types, all nerve cells share the same basic architecture. The complexity of human behaviour depends less on the specialization of individual nerve cells and more on the fact that a great many of these cells form precise anatomical circuits. One of the key organizational principles of the brain, therefore, is that nerve cells with basically similar properties can nevertheless produce quite different actions because of the way they are connected with each other and with sensory receptors and muscle.

Since relatively few principles of organization give rise to considerable complexity, it is possible to learn a great deal about how the nervous system produces behaviour by focusing on four basic features of the nervous system:

- the mechanisms by which neurons produce signals;
- the patterns of connections between nerve cells;
- the relationship of different patterns of interconnection to different types of behaviour;
- the means by which neurons and their connections are modified by experience.

**Structure of a neuron**

A typical neuron has four morphologically defined regions: the cell body, dendrites, the axon, and presynaptic terminals (Figure 1.3).
Most neurons in the vertebrate nervous system have several main features in common. The cell body contains the nucleus, the storehouse of genetic information, and gives rise to two types of cell processes, axons and dendrites. Axons, the transmitting element of neurons, can vary greatly in length; some can extend more than 3 m within the body. Most axons in the central nervous system are very thin (between 0.2 and 20 µm in diameter) compared with the diameter of the cell body (50 µm or more). Many axons are insulated by a fatty sheath of myelin that is interrupted at regular intervals by the nodes of Ranvier. The action potential, the cell’s conducting signal, is initiated either at the axon hillock, the initial segment of the axon, or in some cases slightly farther down the axon at the first node of Ranvier. Branches of the axon of one neuron (the presynaptic neuron) transmit signals to another neuron (the postsynaptic cell) at a site called the synapse. The branches of a single axon may form synapses with as many as 1000 other neurons. Whereas the axon is the output element of the neuron, the dendrites (apical and basal) are input elements of the neuron. Together with the cell body, they receive synaptic contacts from other neurons.

The cell body (soma) is the metabolic center of the cell. It contains the nucleus, which stores the genes of the cell, as well as the endoplasmic reticulum, an extension of the nucleus where the cell’s proteins are synthesized. The cell body usually gives rise to two kinds of processes: several short dendrites and one, long, tubular axon. Dendrites branch out in tree-like fashion and are the main apparatus for receiving incoming signals from other nerve cells. In contrast, the axon extends away from the cell body and is the main conducting unit for carrying signals to other neurons. An axon can convey electrical signals along distances ranging from 0.1 mm to 3 m. These electrical signals, called action potentials (or spikes), are rapid, transient, all-or-none nerve impulses, with an amplitude of 100 mV and a duration of about 1 ms (Figure 1.4). Action potentials (APs) are initiated at a specialized trigger region at the origin of the axon called the axon hillock (or initial segment of the axon); from there they are conducted down the axon without failure or distortion at rates of 1–100 m per second. The amplitude of an action potential traveling down the axon remains constant because the action potential is an all-or-none impulse that is regenerated at regular intervals along the axon.

This historic tracing is the first published intracellular recording of an action potential. It was obtained in 1939 by Hodgkin and Huxley from the squid giant axon, using glass capillary electrodes filled with sea water. Time marker is 500 Hz. The vertical scale indicates the potential of the internal electrode in mV, the sea water outside being taken as zero potential. (From Hodgkin and Huxley (1939)).
Action potentials constitute the signals by which the brain receives, analyzes, and conveys information. These signals are highly stereotyped throughout the nervous system. The information conveyed by an action potential is determined not by the form of the signal but by the pathway the signal travels in the brain. The brain analyzes and interprets patterns of incoming electrical signals and in this way creates our everyday sensations of sight, touch, taste, smell, and sound.

To increase the speed by which action potentials are conducted, large axons are wrapped in a fatty, insulating sheath of myelin. The sheath is interrupted at regular intervals by the nodes of Ranvier. It is at these uninsulated spots on the axon that the action potential becomes regenerated.

Near its end, the tubular axon divides into fine branches that form communication sites with other neurons. The point at which two neurons communicate is known as a synapse. The nerve cell transmitting a signal is called the presynaptic cell. The cell receiving the signal is the postsynaptic cell. However, a presynaptic cell does not actually touch or communicate anatomically with the postsynaptic cell since the two cells are separated by a space, the synaptic cleft. Most presynaptic terminals end on the postsynaptic neuron’s dendrites, but the terminals may also end on the cell body or, less often, at the beginning or end of the axon of the receiving cell.

As we saw, Ramón y Cajal provided much of the early evidence for the now basic understanding that neurons are the signaling units of the nervous system and that each neuron is a discrete cell with distinctive processes arising from its cell body (the neuron doctrine). By examining the structure of neurons in almost every region of the nervous system and tracing the contacts they made with one another, Ramón y Cajal grasped, in addition to the neuron doctrine, another principle of neural organization that would prove particularly valuable in studying communication in the nervous system.

The principle of connectional specificity, states that nerve cells do not connect indiscriminately with one another to form random networks; rather each cell makes specific connections – at particular contact points – with certain postsynaptic target cells but not with others. Taken together, these two principles form the cellular basis of the modern connectionist approach to the brain.

A morphological survey

Ramón y Cajal was also among the first to realize that the feature that most distinguishes one neuron from another is shape – specifically, the number and form of the processes arising from the cell body. On the basis of
shape, neurons are classified into three large groups: unipolar, bipolar, and multipolar.

Unipolar neurons are the simplest nerve cells because they have a single primary process, which usually gives rise to many branches. One branch serves as the axon; other branches function as dendritic receiving structures (Figure 1.5a). These cells predominate in the nervous systems of invertebrates; in vertebrates they occur in the autonomic nervous system.

Bipolar neurons have an oval-shaped soma that gives rise to two processes: a dendrite that conveys information from the periphery of the body, and an axon that carries information toward the central nervous system (Figure 1.5b). Many sensory cells are bipolar cells, including those in the retina of the eye and in the olfactory epithelium of the nose. The mechanoreceptors that convey touch, pressure, and pain to the spinal cord are variants of bipolar cells called pseudo-unipolar cells. These cells develop initially as bipolar cells; later the two cell processes fuse to form one axon that emerges from the cell body. The axon then splits into two; one branch runs to the periphery (to sensory receptors in the skin, joints, and muscle), the other to the spinal cord (Figure 1.5c).

Multipolar neurons predominate in the nervous system of vertebrates. They have a single axon and, typically, many dendrites emerging from various points around the cell body (Figure 1.5d). Usually the number and extent of their dendrites correlate with the number of synaptic contacts that other neurons make onto them. A spinal motor cell with a relatively modest number of dendrites receives about 10000 contacts – 2000 on its cell body and 8000 on its dendrites. The dendritic tree of a Purkinje cell in the cerebellum is much larger and bushier, as well it might be – it receives approximately 150000 contacts.

Neurons are also commonly classified into three major functional groups: sensory, motor, and interneuronal. Sensory neurons carry information from the body’s periphery into the nervous system for the purpose of both perception and motor coordination. Motor neurons carry commands from the brain or spinal cord to muscles and glands. Interneurons constitute by far the largest class, consisting of all nerve cells that are not specifically sensory or motor.

Electrophysiology

The different types of signals used by a neuron are determined in part by the electrical properties of the cell membrane. At rest, all cells, including neurons, maintain a difference in the electrical potential on either side of the plasma (external) membrane. This is called the resting membrane potential.
Neurons can be classified as unipolar, bipolar, or multipolar according to the number of processes that originate from the cell body. A. Unipolar cells have a single process, with different segments serving as receptive surfaces or releasing terminals. Unipolar cells are characteristic of the invertebrate nervous system. B. Bipolar cells have two processes that are functionally specialized: the dendrite carries information to the cell, and the axon transmits information to other cells. C. Certain neurons that carry sensory information to the spinal cord belong to a subclass of bipolar cells designated as pseudo-unipolar. As such cells develop, the two processes of the embryonic bipolar cell become fused and emerge from the cell body as a single process. D. Multipolar cells have an axon and many dendrites. They are the most common type of neuron in the mammalian nervous system. Three examples illustrate the large diversity of these cells. Spinal motor neurons (left) innervate skeletal muscle fibers. Pyramidal cells (middle) have a roughly triangular cell body; dendrites emerge from both the apex (the apical dendrite) and the base (the basal dendrites). Pyramidal cells are found in the hippocampus and throughout the cerebral cortex. Purkinje cells of the cerebellum (right) are characterized by the rich and extensive dendritic tree in one plane. Such a structure permits enormous synaptic input. (Adapted from Ramón y Cajal (1933)).
The brain and behaviour

In a typical resting neuron the electrical potential difference is about 65 mV. Because the net charge outside of the membrane is arbitrarily defined as zero, we say the resting membrane potential is −65 mV (in different nerve cells it may range from about −40 to −80 mV). The difference in electrical potential when the cell is at rest results from two factors:

1. the unequal distribution of electrically charged ions, in particular, the positively charged Na\(^+\) and K\(^+\) ions and the negatively charged amino acids and proteins on either side of the cell membrane;

2. the selective permeability of the membrane to just one of these ions, K\(^+\).

The unequal distribution of positively charged ions on either side of the cell membrane is maintained by a membrane protein that pumps Na\(^+\) out of the cell and K\(^+\) back into it. This Na\(^+\)-K\(^+\) pump keeps the Na\(^+\) ion concentration in the cell low (about 10 times lower than that outside the cell) and the K\(^+\) ion concentration high (about 20 times higher than that outside).

At the same time, the cell membrane is selectively permeable to K\(^+\) because the otherwise impermeable membrane contains ion channels, pore-like structures that span the membrane and are highly permeable to K\(^+\) but considerably less permeable to Na\(^+\). When the cell is at rest, these channels are open and K\(^+\) ions tend to leak out. As K\(^+\) ions leak from the cell, they leave behind a cloud of unneutralized negative charge on the inner surface of the membrane, so that the net charge inside the membrane is more negative than on the outside.

Excitable cells, such as nerve and muscle cells, differ from other cells in that their membrane potential can be significantly and quickly altered; this change can serve as a signaling mechanism. Reducing the membrane potential by say 10 mV (from −65 mV to −55 mV) makes the membrane much more permeable to Na\(^+\) than to K\(^+\). This influx of positively charged Na\(^+\) ions tends to neutralize the negative charge inside the cell and results in an even greater reduction in membrane potential – the action potential. The action potential is conducted down the cell’s axon to the axon’s terminals which end on other cells (neurons or muscle), where the action potential initiates communication with the other cells. As noted earlier, the action potential is an all-or-none impulse that is actively propagated along the axon, so that its amplitude is not diminished by the time it reaches the axon terminal. Typically, an action potential lasts about one millisecond, after which the membrane returns to its resting state, with its normal separation of charges and higher permeability to K\(^+\) than to Na\(^+\).
In addition to the long-range signal of the action potential, nerve cells also produce local signals, such as synaptic potentials, that are not actively propagated and therefore typically decay within just a few millimeters. Both long-range and local signals result from changes in the membrane potential, either a decrease or increase from the resting potential. A reduction in membrane potential (e.g., from $-65 \text{ mV}$ to $-55 \text{ mV}$) is called \textit{depolarization}. Because depolarization enhances a cell's ability to generate an action potential, it is \textit{excitatory}. In contrast, an increase in membrane potential (e.g., from about $-65 \text{ mV}$ to $-75 \text{ mV}$) is called \textit{hyperpolarization}. Hyperpolarization makes a cell less likely to generate an action potential and is therefore \textit{inhibitory}.

As we will see in the next section, when an action potential reaches the synaptic terminal, the cell releases a chemical signal (a neurotransmitter) across the synaptic cleft. The transmitter binds to receptor proteins, and the resulting reaction transduces the potential chemical energy of the transmitter into electrical energy. This in turn alters the membrane potential of the postsynaptic neuron, a change called the \textit{synaptic potential}.

The amplitude of the synaptic potential depends on how much chemical transmitter is released, and its duration on how long the transmitter is active. The synaptic potential can be either depolarizing or hyperpolarizing, depending on the type of receptor molecule that is activated. Synaptic potentials are local changes in membrane potential that spread passively along the neuron (Figure 1.6a).

Action potentials are generated by a sudden influx of Na$^+$ ions through voltage-sensitive channels in the cell membrane. When an input signal (a synaptic potential) depolarizes the cell membrane, the change in membrane potential opens the Na$^+$ ion channels, allowing Na$^+$ to flow down its concentration gradient, from outside the cell where the Na$^+$ concentration is high to inside the cell where it is low. These voltage-sensitive Na$^+$ channels are concentrated at the initial segment of the axon, an uninsulated portion of the axon just beyond the neuron’s input region. In sensory neurons the highest density of Na$^+$ channels occurs at the myelinated axon’s first node of Ranvier; in interneurons and motor neurons the highest density occurs at the axon hillock, where the axon emerges from the cell body.

Because it has the highest density of voltage-sensitive Na$^+$ channels, the initial segment of the axon has the lowest threshold for generating an action potential. Thus, an input signal spreading passively along the cell membrane is more likely to give rise to an action potential at the initial segment of the axon than at other sites in the cell. This part of the axon is therefore known as the impulse initiation zone, or \textit{trigger zone}. It is here that the activity of all receptor (or synaptic) potentials is summed and where, if the size of the input signal reaches threshold, the neuron fires an action potential.
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(Figure 1.6b).

The action potential, the conducting signal of the neuron, is all-or-none. This means that while stimuli below the threshold will not produce a signal, all stimuli above the threshold produce the same signal. The action potential does not decay as it travels along the axon to its target – a distance that can measure 3 m in length – because it is periodically regenerated. This conducting signal can travel at rates as fast as 100 meters per second.

Figure 1.6 – A sensory neuron transforms a physical stimulus (in our example, a stretch) into electrical activity in the cell. A The input signal (a synaptic potential) is graded in amplitude and duration, proportional to the amplitude and duration of the stimulus. B The trigger zone integrates the input signal into a trigger action that produces action potentials that will be propagated along the axon. An action potential is generated only if the input signal is greater than a certain spike threshold. Once the input signal surpasses this threshold, any further increase in amplitude of the input signal increases the frequency with which the action potentials are generated, not their amplitude. The duration of the input signal determines the number of action potentials. Thus, the graded nature of input signals is translated into a frequency code of action potentials at the trigger zone. C Action potentials are all-or-none. Every action potential has the same amplitude and duration, and thus the same wave form on an oscilloscope. Since action potentials are conducted without fail along the full length of the axon to the synaptic terminals, the information in the signal is represented only by the frequency and number of spikes, not by the amplitude. D When the action potential reaches the synaptic terminal, the cell releases a chemical neurotransmitter that serves as the output signal. The total number of action potentials in a given period of time determines exactly how much neurotransmitter will be released by the cell.

Only two features of the conducting signal convey information: the number of action potentials and the time intervals between them (Figure 1.6c).
What determines the intensity of sensation or speed of movement is not the magnitude or duration of individual action potentials, but their frequency. Likewise, the duration of a sensation or movement is determined by the period over which action potentials are generated.

When an action potential reaches a neuron’s terminal it stimulates the release of a chemical transmitter from the cell (Figure 1.6d). Transmitters can be small molecules, such as L-glutamate and acetylcholine, or they can be peptides like enkephalin.

The release of chemical transmitter serves as a neuron’s output signal. Like the input signal, the output signal is graded. The amount of transmitter released is determined by the number and frequency of the action potentials in the presynaptic terminals. Whether the synaptic potential has an excitatory or inhibitory effect will depend on the type of receptors in the postsynaptic cell, not on the particular neurotransmitter.

### 1.4 Synaptic transmission

What gives nerve cells their special ability to communicate with one another so rapidly, over such great distances, and with such tremendous precision? We have already seen how signals are propagated within a neuron, from its dendrites and cell body to its axonal terminal. We now consider the cellular mechanisms for signaling between neurons. The point at which one neuron communicates with another is called a synapse, and synaptic transmission is fundamental to many of the processes we will consider later, such as learning and memory.

The average neuron forms about 1000 synaptic connections and receives even more, perhaps as many as 10000 connections. The Purkinje cell of the cerebellum receives up to 100000 inputs. Although many of these connections are highly specialized, all neurons make use of one of two basic forms of synaptic transmission: electrical or chemical. Moreover, the strength of both forms of synaptic transmission can be enhanced or diminished by cellular activity. This plasticity in nerve cells is crucial to memory and other higher brain functions.

In the brain, electrical synaptic transmission is rapid and rather stereotyped. Electrical synapses are used primarily to send simple depolarizing signals; they do not lend themselves to producing inhibitory actions or making long-lasting changes in the electrical properties of postsynaptic cells. In contrast, chemical synapses are capable of more variable signaling and thus can produce more complex behaviours. They can mediate either excitatory or inhibitory actions in postsynaptic cells and produce electrical changes in the postsynaptic cell that last from milliseconds to many minutes. Chem-
ical synapses also serve to amplify neuronal signals, so that even a small
presynaptic nerve terminal can alter the response of a large postsynaptic
cell.

**Electrical synapses**

At electrical synapses the current that depolarizes the postsynaptic cell is
generated directly by the voltage-gated ion channels of the presynaptic cell.
Thus these channels not only have to depolarize the presynaptic cell above
the threshold for an action potential, they must also generate sufficient ionic
current to produce a change in potential in the postsynaptic cell.

Electrical transmission takes place at a specialized region of contact be-
tween two neurons termed the gap junction. At electrical synapses the
separation between two neurons is much less (3.5 nm) than the normal, non-
synaptic space between neurons (20 nm). This narrow gap is bridged by the
gap-junction channels, specialized protein structures that conduct the flow
of ionic current from the presynaptic to the postsynaptic cell.

Why is it useful to have electrical synapses? Transmission across elec-
trical synapses is extremely rapid because it results from the direct flow of
current from the presynaptic neuron to the postsynaptic cell. And speed is
important for certain escape responses. For example, the tail-flip response
of goldfish is mediated by a giant neuron (known as Mauthner’s cell) in the
brain stem, which receives input from sensory neurons at electrical synap-
ses. These electrical synapses rapidly depolarize the Mauthner’s cell, which
in turn activates the motor neurons of the tail, allowing the fish to escape
quickly from danger.

In addition to providing speed in neuronal signaling, electrical synapses
also may transmit *metabolic signals* between cells. Because gap-junction
channels are relatively large and nonselective, they readily allow inorganic
cations and anions to flow through. In fact, gap-junction channels are large
enough to allow moderate-sized organic compounds (less than 1000 molecu-
lar weight) – such as the second messenger cAMP, and even small peptides
– to pass from one cell to the next.

**Chemical synapses**

In contrast to the situation at electrical synapses, there is no structural
continuity between pre- and postsynaptic neurons at chemical synapses. In
fact, at chemical synapses the region separating the pre- and postsynap-
tic cells – the synaptic cleft – is usually slightly wider (20–40 nm), some-
times substantially wider, than the adjacent nonsynaptic intercellular space
(20 nm). As a result, chemical synaptic transmission depends on the release of a neurotransmitter from the presynaptic neuron. A neurotransmitter is a chemical substance that will bind to specific receptors in the postsynaptic cell membrane. At most chemical synapses, transmitter release occurs from presynaptic terminals, specialized swellings of the axon. The presynaptic terminals contain discrete collections of synaptic vesicles, each of which is filled with several thousand molecules of a specific transmitter.

Figure 1.7 – Synaptic transmission at chemical synapses involves several steps. An action potential arriving at the terminal of a presynaptic axon causes voltage-gated Ca\(^{2+}\) channels at the active zone to open. The influx of Ca\(^{2+}\) produces a high concentration of Ca\(^{2+}\) near the active zone, which in turn causes vesicles containing neurotransmitter to fuse with the presynaptic cell membrane and release their contents into the synaptic cleft. The released neurotransmitter molecules then diffuse across the synaptic cleft and bind to specific receptors on the post-synaptic membrane. These receptors cause ion channels to open (or close), thereby changing the membrane conductance and membrane potential of the postsynaptic cell. The complex process of chemical synaptic transmission is responsible for the delay between action potentials in the pre- and post-synaptic cells compared with the virtually instantaneous transmission of signals at electrical synapses.

The synaptic vesicles cluster at regions of the membrane specialized for releasing transmitter called active zones. During discharge of a presynaptic action potential, Ca\(^{2+}\) enters the presynaptic terminal through voltage-gated Ca\(^{2+}\) channels at the active zone. The rise in intracellular Ca\(^{2+}\) concentration causes the vesicles to fuse with the presynaptic membrane and thereby release their neurotransmitter into the synaptic cleft, a process termed exocytosis.

The transmitter molecules then diffuse across the synaptic cleft and bind to their receptors on the postsynaptic cell membrane. This in turn activates the receptors, leading to the opening or closing of ion channels. The resulting
ionic flux alters the membrane conductance and potential of the postsynaptic cell (Figure 1.7).

These several steps account for the synaptic delay at chemical synapses, a delay that often lasts several milliseconds or longer. Although chemical transmission lacks the speed of electrical synapses, it has the important property of amplification. With the discharge of just one synaptic vesicle, several thousand molecules of transmitter stored in that vesicle are released. Typically, only two molecules of transmitter are required to open a single postsynaptic ion channel. Consequently, the action of one synaptic vesicle can open thousands of ion channels in the postsynaptic cell. In this way a small presynaptic nerve terminal, which generates only a weak electrical current, can release thousands of transmitter molecules that can depolarize even a large postsynaptic cell.

1.5 Synaptic integration

The first insight into synapses in the central nervous system mediated by ionotropic receptors came from experiments by John Eccles and his colleagues in the 1950s on the synaptic mechanisms of the spinal motor neurons that control the stretch reflex. The spinal motor neurons remain particularly useful for examining central synaptic mechanisms because they have large, accessible cell bodies and, most important, they receive both excitatory and inhibitory connections and therefore allow us to study the integrative action of the nervous system on the cellular level.

To analyze the synapses that mediate the stretch reflex, Eccles activated a large population of axons of the sensory cells that innervate the stretch receptor organs in the quadriceps muscle. Passing sufficient current through a microelectrode into the cell body of a stretch-receptor neuron generates an action potential in the sensory cell. This in turn produces a small excitatory postsynaptic potential (EPSP) in the motor neuron innervating the same muscle monitored by the sensory neuron (Figure 1.8). The EPSP produced by the one sensory cell depolarizes the motor neuron by less than 1 mV, often only 0.2–0.4 mV, far below the threshold for generating an action potential (typically, a depolarization of 10 mV or more is required to reach threshold).

Stimulating a stretch-receptor neuron that innervates the biceps (hamstrings), a muscle group antagonistic to the quadriceps, produces a small inhibitory postsynaptic potential (IPSP) in the motor neuron of the quadriceps (Figure 1.8). This hyperpolarizing action is mediated by an inhibitory interneuron, which receives excitatory input from the sensory neurons of the biceps and in turn connects with the quadriceps motor neurons.

Although a single EPSP in the motor neuron is not nearly large enough
Figure 1.8 – This idealized experimental setup shows the approaches to studying the inhibition and excitation of an extensor motor neuron. Top Two alternatives for eliciting excitatory potentials in the extensor motor neuron. (1) The whole afferent nerve from the quadriceps can be stimulated electrically with extracellular electrodes, or (2) single axons can be stimulated with an intracellular current-passing electrode inserted into the sensory neuron cell body. An action potential stimulated in the afferent neuron from the quadriceps triggers an excitatory (depolarizing) postsynaptic potential, or EPSP, in the extensor motor neuron. Bottom The setup for eliciting and measuring inhibitory potentials in the flexor motor neuron. The inhibitory interneurons receiving input from the quadriceps pathway are stimulated intracellularly. An action potential stimulated in the inhibitory interneuron in the quadriceps (extensor) pathway causes an inhibitory (hyperpolarizing) postsynaptic potential, or IPSP, in the flexor motor neuron. (Adapted from Eccles (1964)).

to elicit an action potential, the convergence of many excitatory synaptic potentials from many afferent fibers can be integrated by the neuron to initiate an action potential. At the same time, inhibitory synaptic potentials, if strong enough, can counteract the sum of the excitatory actions and prevent the membrane potential from reaching threshold.

In addition to counteracting synaptic excitation, synaptic inhibition can exert powerful control over spontaneously active nerve cells. By suppressing the spontaneous generation of action potentials in these cells, synaptic inhibition can shape the pattern of firing in a cell.

As we learned before, the effect of a synaptic potential – whether it is excitatory or inhibitory – is determined not by the type of transmitter released from the presynaptic neuron but by the type of ion channels gated by the transmitter in the postsynaptic cell. Although most transmitters are recognized by types of receptors that mediate either excitatory or inhibitory potentials, some act predominantly on receptors that are of one or another sign. For example, in the vertebrate brain neurons that release glutamate typically act on receptors that produce excitation; neurons that release γ-
aminobutyric acid (GABA) or glycine act on ionotropic inhibitory receptors.

**Excitatory synapses**

The excitatory transmitter released from the stretch-receptor neurons is the amino acid L-glutamate, the major excitatory transmitter in the brain and spinal cord. Eccles and his colleagues discovered that the excitatory postsynaptic potential in spinal motor cells results from the opening of glutamate-gated channels permeable to both Na\(^+\) and K\(^+\).

The glutamate receptors can be divided into two broad categories: the ionotropic receptors that directly gate channels (Figure 1.9) and the metabotropic receptors that indirectly gate channels through second messengers. There are three major subtypes of ionotropic glutamate receptors: AMPA, kainate, and NMDA, named according to the types of synthetic agonists that activate them (\(\alpha\)-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, kainate, and N-methyl-D-aspartate, respectively). The NMDA glutamate receptor is selectively blocked by the drug APV (2-amino-5-phosphonovaleric acid). The AMPA and kainate receptors are not affected by APV, thus they are sometimes referred to together as the non-NMDA receptors. The action of glutamate on the ionotropic receptors is always excitatory, while activation of the metabotropic receptors can produce either excitation or inhibition.

![Glutamate receptors regulate excitatory synaptic actions in neurons in the spinal cord and brain](image)

The motor neuron has both non-NMDA and NMDA receptors. At the normal resting potential the non-NMDA ionotropic receptors generate the
large early component of the EPSP in motor neurons (as well as in most other central neurons) in response to stimulation of the primary afferent sensory fibers. These receptors gate cation channels with relatively low conductances (<< 20 pS) that are permeable to both Na\(^+\) and K\(^+\) but are usually not permeable to Ca\(^{2+}\).

The NMDA receptor-channel, which contributes to the late component of the EPSP, has three exceptional properties. First, the receptor controls a cation channel of high conductance (50 pS) that is permeable to Ca\(^{2+}\) as well as to Na\(^+\) and K\(^+\). Second, opening of the channel requires extracellular glycine as a cofactor. Third, its opening depends on membrane voltage as well as a chemical transmitter.

In the NMDA-activated channels an extrinsic blocking particle, extracellular Mg\(^{2+}\), binds to a site in the pore of the open channel and acts like a plug, blocking current flow. At the resting membrane potential (−65 mV) Mg\(^{2+}\) binds tightly to the channel. But when the membrane is depolarized (for example, by the action of glutamate on the non-NMDA receptors), Mg\(^{2+}\) is expelled from the channel by electrostatic repulsion, allowing Na\(^+\) and Ca\(^{2+}\) to enter.

Most cells have both NMDA and non-NMDA glutamate receptors. However, because Mg\(^{2+}\) is present in the NMDA receptor-channel at the resting membrane potential, this channel does not normally contribute significantly to the EPSP. Thus the EPSP generated at the resting level depends largely on the activation of the non-NMDA receptors. As the depolarization of the neuron increases, Mg\(^{2+}\) is driven out of the mouth of the NMDA receptor-channels, more NMDA-type channels are opened, and more current flows through these channels.

The NMDA-type channel has a further characteristic property: it opens and closes relatively slowly in response to glutamate and thus contributes to the late phase of the EPSP (Figure 1.10). This late phase of the EPSP is normally small after a single presynaptic action potential, because of Mg\(^{2+}\) blockade of the channel. However, when the presynaptic neuron fires repeatedly so that the EPSPs summate to depolarize the postsynaptic cell by 20 mV or more, the NMDA receptor gives rise to a much larger current. This current is carried, to an important degree, by Ca\(^{2+}\). Thus activation of the NMDA receptor leads to the activation of calcium-dependent enzymes and certain second messenger-dependent protein kinases in the postsynaptic cell. These biochemical reactions are important for triggering signal transduction pathways that contribute to certain long-lasting modifications in the synapse that are thought to be important for learning and memory (Chapter 3). Because the NMDA receptors require a significant level of presynaptic activity before they can function maximally, long-term synaptic modification mediated by the NMDA receptor is often referred to as activity-dependent
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Figure 1.10 – The NMDA-type glutamate receptor-channel contributes only a small late component to the normal excitatory postsynaptic current. These records are from a cell in the hippocampus. Similar receptor-channels are present in motor neurons and throughout the brain. The contribution of the NMDA receptor-channel to the excitatory postsynaptic current is revealed by the drug APV, which selectively binds to and blocks the NMDA receptor. The records show the excitatory postsynaptic current before and during application of 50 µM APV at three different membrane potentials. The difference between the traces (blue region) represents the APV-sensitive current, which yields the NMDA receptor-channel contribution. The current that remains in the presence of APV is the non-NMDA receptor-channel contribution to the synaptic current. At $-80 \text{ mV}$ there is no current through the NMDA receptor-channels because of pronounced Mg$^{2+}$ block. At $-40 \text{ mV}$ a small late inward current is evident. At $20 \text{ mV}$ the late component is more prominent and has reversed to become an outward current (Hestrin et al., 1990).

synaptic modification.

Inhibitory synapses

Inhibitory postsynaptic potentials in spinal motor neurons and most central neurons are generated by the inhibitory amino acid neurotransmitters GABA and glycine. GABA is a major inhibitory transmitter in the brain and spinal cord. It acts on two receptors, GABA$_A$ and GABA$_B$. The GABA$_A$ receptor is an ionotropic receptor that gates a Cl$^-$ channel. The GABA$_B$ receptor is a metabotropic receptor that activates a second-messenger cascade, which often activates a K$^+$ channel. Glycine, a less common inhibitory transmitter, also activates ionotropic receptors that gate to Cl$^-$ channels.
The unitary currents through single GABA and glycine receptor-channels have been measured using the patch-clamp technique. Both transmitters activate Cl\(^{-}\) channels that show all-or-none step-like openings, similar to the glutamate-activated current.

The inhibitory action upon the opening of these Cl\(^{-}\) channels can be easily demonstrated. In a typical neuron the resting potential \((-65\, \text{mV})\) is slightly more positive than the equilibrium potential for Cl\(^{-}\), \(E_{\text{Cl}} = -70\, \text{mV}\). Thus, at the resting potential the electrochemical driving force on Cl\(^{-}\) (given by \(V_{\text{m}} - E_{\text{Cl}}\)) will be positive. As a result, the opening of Cl\(^{-}\) channels leads to a positive (outward) current. In the case of the IPSP, the charge carrier is actually the negatively charged Cl\(^{-}\) ion. Thus, the positive current corresponds to an influx of Cl\(^{-}\) down its electrochemical gradient. This causes a net increase in the total negative charge on the inside of the membrane’s capacitance so the membrane hyperpolarizes.

In some cells, such as those with GABA\(_B\) receptors, inhibition is associated with the opening of K\(^{+}\) channels. Since the K\(^{+}\) equilibrium potential of neurons is always more negative than the resting potential \((E_{\text{K}} = -80\, \text{mV})\), the opening of K\(^{+}\) channels will inhibit the postsynaptic cell even more profoundly than the opening of Cl\(^{-}\) channels (assuming a similar-size postsynaptic conductance).

### 1.6 The integrative action of the nervous system

Each neuron in the central nervous system, whether in the spinal cord or in the brain, is constantly bombarded by synaptic input from other neurons. A single motor neuron, for example, may be innervated by as many as 10,000 different presynaptic endings. Some are excitatory, others inhibitory; some inputs contact the motor cell on the tips of its apical dendrites, others on proximal dendrites, some on the dendritic shaft, others on dendritic spines.

The synaptic potentials produced by a single pre-synaptic neuron typically are small and are not capable of exciting a postsynaptic cell sufficiently to reach the threshold for an action potential. The net effect of the inputs at any individual excitatory or inhibitory synapse will therefore depend on several factors: the location, size, and shape of the synapse, and the proximity and relative strength of other synergistic or antagonistic synapses.

These competing inputs are integrated in the postsynaptic neuron by a process called neuronal integration. Neuronal integration reflects at the level of the cell the task that confronts the nervous system as a whole: decision making.

Because neuronal integration involves the summation of synaptic potentials that spread passively to the trigger zone, it is critically affected by two
passive membrane properties of the neuron. First, the time constant helps to determine the time course of the synaptic potential and thereby affects temporal summation, the process by which consecutive synaptic potentials at the same site are added together in the post-synaptic cell. Neurons with a large time constant have a greater capacity for temporal summation than do neurons with a smaller time constant.

Second, the length constant of the cell determines the degree to which a depolarizing current decreases as it spreads passively. In cells with a larger length constant, signals spread to the trigger zone with minimal decrement; in cells with a small length constant the signals decay rapidly with distance. Since the depolarization produced at one synapse is almost never sufficient to trigger an action potential at the trigger zone, the inputs from many presynaptic neurons acting at different sites on the postsynaptic neuron must be added together (spatial summation).

Originally, propagation of signals down dendrites was thought to be purely passive. However, we now know that the dendrites of most neurons contain voltage-gated Na\(^+\), K\(^+\), and Ca\(^{2+}\) channels that amplify the small EPSP. In some neurons there are sufficient concentrations of voltage-gated channels in the dendrites to serve as a local trigger zone. This can further amplify weak excitatory input that arrives at remote parts of the dendrite. When a cell has several dendritic trigger zones, each one sums the local excitation and inhibition produced by nearby synaptic inputs and, if the net input is above threshold, an action potential may be generated, usually by voltage-dependent Ca\(^{2+}\) channels.

The dendritic voltage-gated channels also permit action potentials generated at the axon hillock to propagate backwards into the dendritic tree. These back-propagating action potentials are largely generated by dendritic voltage-gated Na\(^+\) channels. Although the precise role of back-propagating action potentials is not clear, they may provide a temporally precise mechanism for regulating current flow through the NMDA receptor by the depolarization-dependent relief of Mg\(^{2+}\) block.
LEARNING AND MEMORY

In humans the most important mechanisms by which the environment alters behaviour are learning and memory. Learning is the process by which we acquire knowledge about the world, while memory is the process by which that knowledge is encoded, stored, and later retrieved.

Many important behaviours are learned. Indeed, we are who we are largely because of what we learn and what we remember. We learn the motor skills that allow us to master our environment, and we learn languages that enable us to communicate what we have learned, thereby transmitting cultures that can be maintained over generations.

In the study of learning and memory we are interested in several questions. What are the major forms of learning? What types of information about the environment are learned most easily? Do different types of learning give rise to different memory processes? How is memory stored and retrieved?

2.1 Implicit and explicit memory

As early as 1861 Pierre Paul Broca had discovered that damage to the posterior portion of the left frontal lobe (Broca’s area) produces a specific deficit in language. Soon thereafter it became clear that other mental functions, such as perception and voluntary movement, can be related to the operation of discrete neural circuits in the brain. The successes of efforts to localize brain functions led to the question: are there also discrete systems in the brain concerned with memory? If so, are all memory processes located in one region, or are they distributed throughout the brain?
In contrast to the prevalent view about the localized operation of other cognitive functions, many experts of learning doubted that memory functions could be localized. In fact, until the middle of the twentieth century many psychologists doubted that memory was a discrete function, independent of perception, language, or movement. One reason for the persistent doubt is that memory storage does indeed involve many different regions of the brain. We now appreciate, however, that these regions are not equally important. There are several fundamentally different types of memory storage, and certain regions of the brain are much more important for some types of storage than for others.

The first person to obtain evidence that memory processes might be localized to specific regions of the human brain was the neurosurgeon Wilder Penfield. By the 1940s Penfield had begun to apply electrical stimulation to map the motor, sensory, and language functions in the cerebral cortex of patients undergoing brain surgery for the relief of focal epilepsy. Since the brain itself does not have pain receptors, brain surgery is painless and can be carried out under local anesthesia in patients that are fully awake. Thus, patients undergoing brain surgery are able to describe what they experience in response to electrical stimuli applied to different cortical areas.

Penfield explored the cortical surface in more than a thousand patients. On rare occasions he found that electrical stimulation of the temporal lobes produced what he called an *experiential response* – a coherent recollection of an earlier experience. More convincing evidence that the temporal lobes are important in memory emerged in the mid 1950s from the study of patients who had undergone bilateral removal of the hippocampus and neighboring regions in the temporal lobe as treatment for epilepsy.

The first and best-studied case of the effects on memory of bilateral removal of portions of the temporal lobes was the patient called H.M., studied by Brenda Milner (Milner, 1966), a colleague of Penfield and the surgeon William Scoville. H.M., a 27-year-old man, had suffered for over 10 years from untreatable bilateral temporal lobe seizures as a consequence of brain damage sustained at age 9 when he was hit and knocked over by someone riding a bicycle. As an adult he was unable to work or lead a normal life. At surgery the hippocampal formation, the amygdala, and parts of the multimodal association area of the temporal cortex were removed bilaterally (Figure 2.1).

H.M.’s seizures were much better controlled after surgery, but the removal of the medial temporal lobes left him with a devastating memory deficit. This memory deficit (or *amnesia*) was quite specific. H.M. still had normal short-term memory, over seconds or minutes. Moreover, he had a perfectly good long-term memory for events that had occurred before the operation. He remembered his name and the job he held, and he
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Figure 2.1 – The medial temporal lobe and memory storage. 

A The longitudinal extent of the temporal lobe lesion in the patient known as H.M. in a ventral view of the brain. 

B Cross sections showing the estimated extent of surgical removal of areas of the brain in the patient H.M. 

C Magnetic resonance image (MRI) scan of a parasagittal section from the left side of H.M.’s brain. The calibration bar on the right side of the panel has 1 cm increments. The resected portion of the anterior temporal lobes is indicated with an asterisk. The remaining portion of the intraventricular portion of the hippocampal formation is indicated with an open arrow. Approximately 2 cm of preserved hippocampal formation is visible bilaterally. (Kandel et al., 2000)

vividly remembered childhood events. He retained a perfectly good command of language, including his normally varied vocabulary, and his IQ remained unchanged in the range of bright-normal.

What H.M. now lacked, and lacked dramatically, was the ability to transfer new short-term memory into long-term memory. He was unable to retain for more than a minute information about people, places, or objects. Asked to remember a number such as 8414317, H.M. could repeat it immediately for many minutes, because of his good short-term memory. But when distracted, even briefly, he forgot the number. Thus, H.M. could not recognize people he met after surgery, even when he met them again and again.

Milner originally thought that the memory deficit after bilateral medial temporal lobe lesions affects all forms of memory equally. But this proved not to be so. The spared component of memory was first revealed when Milner discovered that H.M. could learn new motor skills at a normal rate. For example, he learned to draw the outlines of a star while looking at his
hand and the star in a mirror (Figure 2.2). Like normal subjects learning this task, H.M. initially made many mistakes, but after several days of training his performance was error-free and indistinguishable from that of normal subjects.

Figure 2.2 – The patient H.M. showed definite improvement in any task involving learning skilled movements. He was taught to trace between two outlines of a star while viewing his hand in a mirror. He improved considerably with each fresh test, although he had no recollection that he had ever done the task before. The graph plots the number of times, in each trial, that he strayed outside the outlines as he drew the star. (Kandel et al., 2000)

Later work by Larry Squire and others has made it clear that the memory capacities of H.M. and other patients with bilateral medial temporal lobe lesions are not limited to motor skills. Rather, these patients are capable of various forms of simple reflexive learning, including habituation, sensitization, classical conditioning, and operant conditioning.

The memory capability that is spared in patients with bilateral lesions of the temporal lobe typically involves learned tasks that have two things in common. First, the tasks tend to be reflexive rather than reflective in nature and involve habits and motor or perceptual skills. Second, they do not require conscious awareness or complex cognitive processes, such as comparison and evaluation. The patient only responds to a stimulus or cue, and need not to try to remember anything. Thus, when given a highly complex mechanical puzzle to solve the patient may learn it as quickly and as well as a normal person, but will not consciously remember having worked on it previously. When asked why the performance of a task is much better after several days of practice than on the first day, the patient may respond, «What are you talking about? I’ve never done this task before.»

Although these two fundamentally different forms of memory – for skills and for knowledge – have been demonstrated in detail in amnesia patients with lesions of the temporal lobe, they are not unique amnesiacs. Cognitive psychologists had previously distinguished these two types of memory in normal subjects. They refer to information about how to perform something as implicit memory (also referred to as nondeclarative memory), a memory that is recalled unconsciously. Implicit memory is typically involved in training
reflexive motor or perceptual skills. Factual knowledge of people, places, and things, and what these facts mean, is referred to as *explicit memory* (or *declarative memory*). This is recalled by a deliberate, conscious effort (Figure 2.3). Explicit memory is highly flexible and involves the association of multiple bits and pieces of information. In contrast, implicit memory is more rigid and tightly connected to the original stimulus conditions under which the learning occurred.

![Two forms of memory diagram](image)

**Figure 2.3** – Various forms of memory can be classified as either explicit (declarative) or implicit (nondeclarative).

The psychologist Endel Tulving first developed the idea that explicit memory can be further classified as episodic (a memory for events and personal experience) or semantic (a memory for facts). We use episodic memory when we recall that we saw the first flowers of spring yesterday or that we heard Beethoven’s *Moonlight Sonata* several months ago. We use semantic memory to store and recall objective knowledge, the kind of knowledge we learn in school and from books. Nevertheless, all explicit memories can be concisely expressed in declarative statements, such as «Last summer I visited my grandmother at her country house» (episodic knowledge) or «Lead is heavier than water» (semantic knowledge).

**Animal studies help to understand memory**

The surgical lesion of H.M.’s temporal lobe encompassed a number of regions, including the temporal pole, the ventral and medial temporal cortex, the amygdala, and the hippocampal formation (which includes the hippocampus proper, the subiculum, and the dentate gyrus) as well as the surrounding entorhinal, perirhinal, and parahippocampal cortices. Since lesions restricted to any one of these several sectors of the medial temporal lobe are rare in humans, experimental lesion studies in monkeys have helped
define the contribution of the different parts of the temporal lobe to memory formation.

Mortimer Mishkin and Squire produced lesions in monkeys identical to those reported for H.M. and found defects in explicit memory for places and objects similar to those observed in H.M. Damage to the amygdala alone had no effect on explicit memory. Although the amygdala stores components of memory concerned with emotion, it does not store factual information. In contrast, selective damage to the hippocampus or the polymodal association areas in the temporal cortex with which the hippocampus connects – the perirhinal and parahippocampal cortices – produces clear impairment of explicit memory.

Thus, studies with human patients and with experimental animals suggest that knowledge stored as explicit memory is first acquired through processing in one or more of the three polymodal association cortices (the prefrontal, limbic, and parieto-occipital-temporal cortices) that synthesize visual, auditory, and somatic information. From there the information is conveyed in series to the parahippocampal and perirhinal cortices, then the entorhinal cortex, the dentate gyrus, the hippocampus, the subiculum, and finally back to the entorhinal cortex. From the entorhinal cortex the information is sent back to the parahippocampal and perirhinal cortices and finally back to the polymodal association areas of the neocortex (Figure 2.4).

Thus, in processing information for explicit memory storage the entorhinal cortex has dual functions. First, it is the main input to the hippocampus. The entorhinal cortex projects to the dentate gyrus via the perforant pathway and by this means provides the critical input pathway through which the polymodal information from the association cortices reaches the hippocampus (Figure 2.4b). Second, the entorhinal cortex is also the major output of the hippocampus. The information coming to the hippocampus from the polymodal association cortices and that coming from the hippocampus to the association cortices converge in the entorhinal cortex. It is therefore understandable why the memory impairments associated with damage to the entorhinal cortex are particularly severe and why this damage affects not simply one but all sensory modalities. In fact, the earliest pathological changes in Alzheimer disease, the major degenerative disease that affects explicit memory storage, occurs in the entorhinal cortex.

2.2 Explicit memory and the association cortices

Lesions of the medial temporal lobe in patients such as H.M. interfere only with the long-term storage of new memories. These patients retain a reasonably good memory of earlier events.
Figure 2.4 – **The anatomical organization of the hippocampal formation.** A The key components of the medial temporal lobe important for memory storage can be seen in the medial (left) and ventral (right) surface of the cerebral hemisphere. B The input and output pathways of the hippocampal formation.
The fact that patients with amnesia are able to remember their childhood, the lives they have led, and the factual knowledge they acquired before damage to the hippocampus suggests that the hippocampus is only a temporary way station for long-term memory. If so, long-term storage of episodic and semantic knowledge would occur in the unimodal or multimodal association areas of the cerebral cortex that initially process the sensory information.

Viewed in this way the hippocampal system would mediate the initial steps of long-term storage. It would then slowly transfer information into the neocortical storage system. The relatively slow addition of information to the neocortex would permit new data to be stored in a way that does not disrupt existing information. If the association areas are the ultimate repositories for explicit memory, then damage to association cortex should destroy or impair recall of explicit knowledge that is acquired before the damage. This is in fact what happens. Patients with lesions in association areas have difficulty in recognizing faces, objects, and places in their familiar world. Indeed, lesions in different association areas give rise to specific defects in either semantic or episodic memory.

**Semantic knowledge**

As we have seen, semantic memory is that type of long-term memory that embraces knowledge of objects, facts, and concepts as well as words and their meaning. It includes the naming of objects, the definitions of spoken words, and verbal fluency.

How is semantic knowledge built up? How is it stored in the cortex? The organization and flexibility of semantic knowledge is both remarkable and surprising. Consider a complex visual image such as a photograph of an elephant. Through experience this visual image becomes associated with other forms of knowledge about elephants. The more associations we have made to the image of the elephant, the better we encode that image, and the better we can recall the features of an elephant at a future time. Furthermore, these associations fall into different categories. For example, we commonly know that an elephant is a living rather than a nonliving thing, that it is an animal rather than a plant, that it lives in a particular environment, and that it has unique physical features and behaviour patterns and emits a distinctive set of sounds. The word *elephant* is associated with all of these pieces of information, and any one bit of information can open access to all of our knowledge about elephants.

As this example illustrates, we build up semantic knowledge through associations over time. The ability to recall and use knowledge – our cognitive efficiency – is thought to depend on how well these associations have orga-
nized the information we retain. When we recall a concept it comes to mind in one smooth and continuous operation. However, studies of patients with damage to the association cortices have shown that different representations of an object—say, different aspects of elephants—are stored separately. These studies have made clear that our experience of knowledge as a seamless, orderly, and cross-referenced database is the product of integration of multiple representations in the brain at many distinct anatomical sites, each concerned with only one aspect of the concept that came to mind. Thus, there is no general semantic memory store; semantic knowledge is not stored in a single region. Rather, each time knowledge about anything is recalled, the recall is built up from distinct bits of information, each of which is stored in dedicated memory stores. As a result, damage to a specific cortical area can lead to loss of specific information and therefore a fragmentation of knowledge.

Episodic knowledge

Whereas some lesions to multimodal association areas interfere with semantic knowledge, others interfere with the capacity to recall any episodic event experienced more than a few minutes previously, including dramatic personal events such as accidents and deaths in the family that occurred before the trauma.

The areas of the neocortex that seem to be specialized for long-term storage of episodic knowledge are the association areas of the frontal lobes. These prefrontal areas work with other areas of the neocortex to allow recollection of when and where a past event occurred.

Explicit knowledge

We have learned three important things about episodic and semantic knowledge. First, there is not a single, all-purpose memory store. Second, any item of knowledge has multiple representations in the brain, each of which corresponds to a different meaning and can be accessed independently (by visual, verbal, or other sensory clues). Third, both semantic and episodic knowledge are the result of at least four related but distinct types of processing: encoding, consolidation, storage, and retrieval.

Encoding refers to the processes by which newly learned information is attended to and processed when first encountered. The extent and nature of this encoding are critically important for determining how well the learned material will be remembered at later times. For a memory to persist and be well remembered, the incoming information must be encoded thoroughly
and deeply. This is accomplished by attending to the information and associating it meaningfully and systematically with knowledge that is already well established in memory so as to allow one to integrate the new information with what one already knows.

Consolidation refers to those processes that alter the newly stored and still labile information so as to make it more stable for long-term storage. As we shall learn in the next chapter, consolidation involves the expression of genes and the synthesis of new proteins, giving rise to structural changes that store memory stably over time.

Storage refers to the mechanism and sites by which memory is retained over time. One of the remarkable features about long-term storage is that it seems to have an almost unlimited capacity.

Finally, retrieval refers to those processes that permit the recall and use of the stored information. Retrieval involves bringing different kinds of information together that are stored separately in different storage sites.

2.3 An overall view

The neurobiological study of memory has yielded three generalizations: memory has stages, long-term memory is represented in multiple regions throughout the nervous system, and explicit and implicit memories involve different neuronal circuits.

Different types of memory processes involve different regions and combinations of regions in the brain. Explicit memory underlies the learning of facts and experiences – knowledge that is flexible can be recalled by conscious effort and can be reported verbally. Implicit memory processes include forms of perceptual and motor memory – knowledge that is stimulus-bound, is expressed in the performance of tasks without conscious effort, and is not easily expressed verbally. Implicit memory flows automatically in the doing of things, while explicit memory must be retrieved deliberately.

Long-term storage of explicit memory requires the temporal lobe system. Implicit memory involves the cerebellum and amygdala and the specific sensory and motor systems recruited for the task being learned. Moreover, the memory processes for many types of learning involve several brain structures.

This parallel processing may explain in part why a limited lesion often does not eliminate a specific memory, even a simple implicit memory. Another important factor that may account for the failure of small lesions to adversely affect a specific memory may reside in the very nature of learning. As we shall see in the next chapter, memory involves both functional
and structural changes at synapses in the circuits participating in a learning task. Although such changes are likely to occur only in particular types of neurons, the complex nature of many tasks makes it likely that these neurons are widely distributed within the pathways that mediate the response. Therefore some components of the stored information (i.e., some of the synaptic changes) could remain undisturbed by a small lesion. Furthermore, the brain can take even the limited store of remaining information and construct a good representation of the original, just as the brain normally constructs conscious memory.
CHAPTER
THREE

CELLULAR MECHANISMS OF LEARNING

All behaviour is a function of the brain and malfunctions of the brain give rise to characteristic disturbances of behaviour. Behaviour, in turn, is shaped by learning. How does learning act on the brain to change behaviour? How is new information acquired and, once acquired, how is it retained? In the preceding chapter we saw that memory – the outcome of learning – is not a single process but has at least two forms. Implicit memory is unconscious memory for perceptual and motor skills, whereas explicit memory is a memory for people, places, and objects that requires conscious recall.

In this chapter we examine the cellular and molecular mechanisms that contribute to the explicit memory by exploring the mechanisms that underlie the complex explicit forms of memory storage in vertebrates. We shall see that the molecular mechanisms of memory storage are highly conserved throughout evolution, and that the more complex forms of learning and memory depend on many of the same molecular mechanisms used in the simplest forms.

3.1 Explicit memory in mammals

What mechanisms are used to store explicit memory – information about people, places, and objects? One important component of the medial temporal system of higher vertebrates involved in the storage of explicit memory is the hippocampus. As first shown by Per Andersen, the hippocampus has three major pathways: (1) the perforant pathway, which projects from the entorhinal cortex to the granule cells of the dentate gyrus; (2) the mossy
fiber pathway, which contains the axons of the granule cells and runs to the pyramidal cells in the CA3 region of the hippocampus; and (3) the Schaffer collateral pathway, which consists of the excitatory collaterals of the pyramidal cells in the CA3 region and ends on the pyramidal cells in the CA1 region (Figure 3.1).

Figure 3.1 – The three major afferent pathways in the hippocampus. (Arrows denote the direction of impulse flow.) The perforant fiber pathway from the entorhinal cortex forms excitatory connections with the granule cells of the dentate gyrus. The granule cells give rise to axons that form the mossy fiber pathway, which connects with the pyramidal cells in area CA3 of the hippocampus. The pyramidal cells of the CA3 region project to the pyramidal cells in CA1 by means of the Schaffer collateral pathway. Long-term potentiation (LTP) is nonassociative in the mossy fiber pathway and associative in the other two pathways.

In 1973 Bliss and Lomø discovered that each of these pathways is remarkably sensitive to the history of previous activity. A brief high-frequency train of stimuli to any of the three major synaptic pathways increases the amplitude of the excitatory postsynaptic potentials in the target hippocampal neurons. This facilitation is called long-term potentiation (LTP). The mechanisms underlying LTP are not the same in all three pathways. LTP can be studied in the intact animal, where it can last for days and even weeks. It can also be examined in slices of hippocampus and in cell culture for several hours.
3.2 LTP in the Schaffer collateral pathway

The Schaffer collateral pathway connects the pyramidal cells of the CA3 region of the hippocampus with those of the CA1 region (Figure 3.1 and 3.2a). The terminals of the Schaffer collaterals use glutamate as transmitter, and LTP in the Schaffer collateral pathway requires activation of the NMDA-type of glutamate receptor.

LTP in the Schaffer collateral pathway typically requires activation of several afferent axons together, a feature called cooperativity. This feature derives from the fact that the NMDA receptor-channel becomes functional and conducts Ca^{2+} only when two conditions are met: glutamate must bind...
to the postsynaptic NMDA receptor and the membrane potential of the postsynaptic cell must be sufficiently depolarized by the cooperative firing of several afferent axons to expel Mg$^{2+}$ from the mouth of the channel (Figure 3.3). Only when Mg$^{2+}$ is expelled can Ca$^{2+}$ influx into the postsynaptic cell occur. Calcium influx initiates the persistent enhancement of synaptic transmission by activating two calcium-dependent protein kinases – the Ca$^{2+}$/calmodulin-dependent protein kinase and protein kinase C – as well as PKA and the tyrosine protein kinase fyn.

LTP in the Schaffer collateral pathway requires concomitant activity in both the presynaptic and postsynaptic cells to adequately depolarize the post-synaptic cell, a feature called **associativity**. As we have seen, to initiate the Ca$^{2+}$ influx into the postsynaptic cell, a strong presynaptic input sufficient to fire the postsynaptic cell is required.

The finding that LTP in the Schaffer collateral pathway requires simultaneous firing in both the postsynaptic and presynaptic neurons provides direct evidence for **Hebb’s rule**, proposed in 1949 by the psychologist Donald Hebb (Hebb, 1949): «When an axon of cell A [. . .] excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A’s efficiency as one of the cells firing B is increased.»

The induction of LTP in the CA1 region of the hippocampus depends on four postsynaptic factors: postsynaptic depolarization, activation of NMDA receptors, influx of Ca$^{2+}$, and activation by Ca$^{2+}$ of several second-messenger systems in the postsynaptic cell. The mechanisms for the expression of this LTP, on the other hand, is still uncertain. It is thought to involve not only an increase in the sensitivity and number of the postsynaptic non-NMDA (AMPA) receptors to glutamate as a result of being phosphorylated by the Ca$^{2+}$/calmodulin-dependent protein kinase, but also an increase in transmitter release from the presynaptic terminals of the CA3 neuron. Indeed, biochemical studies suggest that the release of glutamate is enhanced during LTP.

Since induction of LTP requires events only in the postsynaptic cell (Ca$^{2+}$ influx through NMDA channels), whereas expression of LTP is due in part to a subsequent event in the presynaptic cells (increase in transmitter release), the presynaptic cells must somehow receive information that LTP has been induced. There is now evidence that calcium-activated second messengers, or perhaps Ca$^{2+}$ itself, causes the postsynaptic cell to release one or more retrograde messengers from its active dendritic spines.

These studies of the Schaffer collateral pathway indicate that LTP in CA1 uses two associative mechanisms in series: a Hebbian mechanism (simultaneous firing in both the pre- and postsynaptic cells) and activity-dependent presynaptic facilitation.
Figure 3.3 – A model for the induction of the early phase of long-term potentiation. A During normal synaptic transmission glutamate (Glu) is released from the presynaptic terminal and acts on both the NMDA and non-NMDA receptors. The non-NMDA receptors here are the AMPA type. Na\(^+\) and K\(^+\) flow through the AMPA channels but not through the NMDA channels, owing to Mg\(^{2+}\) blockage of this channel at the resting level of membrane potential. B When the postsynaptic membrane is depolarized by the actions of the AMPA receptor-channels, as occurs during a high-frequency train of stimuli that induces LTP, the depolarization relieves the Mg\(^{2+}\) blockage of the NMDA channel. This allows Ca\(^{2+}\) to flow through the NMDA channel and triggers calcium-dependent kinases and the tyrosine kinase Fyn that together induce LTP. In addition, once LTP is induced, the postsynaptic cell is thought to release a set of retrograde messengers, that act on protein kinases in the presynaptic terminal to initiate an enhancement of transmitter release that contributes to LTP.
3.3 Consolidated late phase of LTP

As with memory storage, LTP has phases. One stimulus train produces a short-term phase of LTP (called early LTP) lasting 1-3 hours; this component does not require new protein synthesis. Four or more trains induce a more persistent phase of LTP (called late LTP) that lasts for at least 24 hours and requires new protein and RNA synthesis.

What are the properties of this late phase of LTP? Cellular-physiological studies (Bolshakov et al., 1997) suggest that the late phase of LTP involves the activation, perhaps the growth, of additional presynaptic machinery for transmitter release and the insertion of new clusters of postsynaptic receptors.

Vadim Bolshakov and his colleagues have examined LTP by stimulating a single presynaptic CA3 neuron and recording from a single CA1 postsynaptic cell. They observed that a single CA3 neuron makes only a single functional synaptic contact on a CA1 neuron. This single synaptic contact appears to have only one active zone from which the transmitter content of only a single vesicle is released, in an all-or-none way, by a presynaptic action potential.

What happens during the early phase of LTP? It produces no change in the number of synapses, the number of active zones, or the maximal number of vesicles released with each action potential. Thus the early phase of LTP represents a functional change – an increase in the probability of transmitter release – without structural changes. An action potential still releases only one vesicle of transmitter from a single release site, but now it does so more reliably.

During the late phase of LTP a single action potential in a single CA3 cell releases several vesicles of transmitter onto the CA1 neuron. Such an increase in the number of vesicles released would seem to entail growth of new pre-synaptic release sites as well as new clusters of post-synaptic receptors. Consistent with this idea, and with the properties of the late phase of LTP, the generation of these new distributions requires new protein synthesis (Figure 3.4).

How do genes and proteins operate in the consolidation of long-term changes? Studies of long-term sensitization of the gill-withdrawal reflex indicate that with repeated application of serotonin the catalytic subunit of the cAMP-dependent protein kinase (PKA) recruits another second messenger kinase, the mitogen-activated protein (MAP) kinase, a kinase commonly associated with cellular growth. Together the two kinases translocate to the nucleus of the sensory neurons, where they activate a genetic switch. Specifically, the catalytic subunit phosphorylates and thereby activates a transcrip-
Cellular mechanisms of learning

Figure 3.4 – A model for the early and late phase of LTP. A single train of action potentials leads to early LTP by activating NMDA receptors, Ca$^{2+}$ influx into the postsynaptic cell, and a set of second messengers. With repeated trains the Ca$^{2+}$ influx also recruits an adenylyl cyclase, which activates the cAMP-dependent protein kinase (cAMP kinase) leading to its translocation to the nucleus, where it phosphorylates the CREB protein. CREB in turn activates targets that are thought to lead to structural changes. Mutations in mice that block PKA or CREB reduce or eliminate the late phase of LTP. The adenylyl cyclase can also be modulated by dopaminergic and perhaps other modulatory inputs. BDNF = brain-derived neurotrophic factor; C/EBP = transcription factor; P = phosphate; R(AB) = dominant negative PKA; tPA = tissue plasminogen activator.
tion factor called CREB-1 (cAMP response element binding protein). This transcriptional activator, when phosphorylated, binds to a promoter element called CRE (the cAMP response element). By means of the MAP kinase the catalytic subunit of PKA also acts indirectly to relieve the inhibitory actions of CREB-2, a repressor of transcription.

The presence of both a repressor (CREB-2) and an activator (CREB-1) of transcription at the very first step in long-term facilitation suggests that the threshold for putting information into long-term memory is highly regulated. Indeed, we can see in everyday life that the ease with which short-term memory is transferred into long-term memory varies greatly depending on attention, mood, and social context. In fact, when the repressive action of CREB-2 is relieved (by injecting, for example, a specific antibody to CREB-2), a single pulse of serotonin, which normally produces only short-term facilitation lasting minutes, is able to produce long-term facilitation, the cellular homolog of long-term memory.

The more enduring consequence of the activation of CREB-1 is a cascade of gene activation that leads to the growth of new synaptic connections. It is this growth process that provides the stable, self-maintained state of long-term memory.

The ongoing modification of synapses throughout life means that all behaviour of an individual is produced by genetic and developmental mechanisms acting on the brain – that everything the brain produces, from the most private thoughts to the most public acts, should be understood as a biological process. Environmental factors and learning bring out specific capabilities by altering either the effectiveness or the anatomical connections of existing pathways.
Part II

Methods in neuronal modelling
As we saw in the previous chapters, to understand the nervous system of even the simplest of animals requires an understanding of the nervous system at many different levels, over a wide range of both spatial and temporal scales. We need to know at least the properties of the nerve cell itself, of its specialist structures such as synapses, and how nerve cells become connected together and what the properties of networks of nerve cells are.

The complexity of nervous systems make it very difficult to theorise cogently about how such systems are put together and how they function. To aid our thought processes we can represent our theory as a computational model, in the form of a set of mathematical equations. The variables of the equations represent specific neurobiological quantities, such as the rate at which impulses are propagated along an axon or the frequency of opening of a specific type of ion channel. The equations themselves represent how these quantities interact according to the theory being expressed in the model. Solving these equations by analytical or simulation techniques enables us to show the behaviour of the model under the given circumstances and thus addresses the questions that the theory was designed to answer. Models of this type can be used as explanatory or predictive tools.

Most attempts to analyse computational models of the nervous system involve using the powerful computers now available to find numerical solutions to the complex sets of equations needed to construct an appropriate model.

To develop a computational model in neuroscience the researcher has to decide how to construct and apply a model that will link the neurobiological
reality with a more abstract formulation that is analytical or computationally tractable. Guided by the neurobiology, decisions have to be taken about the level at which the model should be constructed, the nature and properties of the elements in the model and their number, and the ways in which these elements interact.

4.1 The basis of electrical activity in the neuron

All living cells have an electrical voltage, or potential difference, between their inside and outside. Since the cell’s membrane is what separates the inside from the outside, this potential difference is referred to as the membrane potential. In mathematical terms, the membrane potential $V_M$ is defined as

$$V_M = V_{in} - V_{out} \tag{4.1}$$

where $V_{in}$ is the potential on the inside of the cell and $V_{out}$ is the potential on the outside. This will change during an action potential, for example.

The resting potential refers to the potential across the membrane when the cell is at rest. A typical neuron has a resting potential of about $-65$ mV. An inward current corresponds to a positively charged ion, such as $\text{Na}^+$, entering the cell. This raises the membrane potential; that is, it brings the membrane potential closer to zero. In this case, the cell is said to be depolarized. An outward current corresponds to a positively charged ion, such as $\text{K}^+$, leaving the cell or a negatively charged ion, such as $\text{Cl}^-$, entering the cell. In this case, the cell becomes hyperpolarized.

As we have briefly shown in Section 1.3, the potential difference arises from differences in the concentrations of various ions within and outside the cell. The maintenance of the potential difference also involves the transport of ions across the cell membrane and the selective permeability of the membrane to these ions. The principal ions found on either side of the cell membrane are $\text{Na}^+$, $\text{K}^+$, and $\text{Cl}^-$. The concentration of $\text{K}^+$ ions inside a cell is about 10 times that in the extracellular fluid, whereas the concentrations of $\text{Na}^+$ and $\text{Cl}^-$ are much higher outside the cell than inside.

The lipid bilayer of the cell membrane is a poor conductor of ionic current because it is not permeable to ions. However, the membrane does contain channel proteins that allow for the ions to move through it. There are two types of ion channels in the membrane: gated and nongated. Nongated channels are always open, whereas gated channels can open and close and the probability of opening often depends on the membrane potential; these are referred to as voltage-gated channels. Gated channels are typically selective for a single ion. The permeability of the membrane to a particular ion depends on the number of open channels selective for that ion. Most gated
channels are closed at rest; hence, the nongated ion channels are primarily responsible for establishing the resting potential. An action potential is generated when gated channels open allowing for the flux of ions across the cell membrane.

Because of concentration differences, when the appropriate channels are open, Na\(^+\) and Cl\(^-\) ions tend to diffuse into the cell, whereas K\(^+\) ions tend to diffuse outward. Note that ions do not simply diffuse in or out of an open channel until the concentration of that ion on either side of the cell is zero. This is because of the electric field created by separation of positive and negative charges across the cell membrane.

![Figure 4.1](image)

**Figure 4.1**—The K\(^+\) flux is determined by both the K\(^+\) concentration gradient and the electrical potential across the membrane.  
A For a cell that is permeable only to K\(^+\), the concentration gradient of K\(^+\) moves K\(^+\) ions out of the cell.  
B The continued efflux of K\(^+\) builds up an excess of positive charge on the outside and an excess of negative charge on the inside. At equilibrium, the electrical and chemical driving forces are equal and opposite.

Suppose, for example, the cell is permeable only to K\(^+\). The concentration gradient of K\(^+\) moves K\(^+\) ions out of the cell. However, the continued efflux of K\(^+\) builds up an excess of positive charge on the outside of the cell and leaves behind an excess of negative charge on the inside. The negative charge consists mostly of impermeable organic anions A\(^-\). This buildup of charge acts to impede the further efflux of K\(^+\), so eventually an equilibrium is reached. At this equilibrium, the electrical and chemical driving forces are equal and opposite (Figure 4.1). The membrane potential at which K\(^+\) ions are in equilibrium across the membrane is called the K\(^+\) Nernst, equilibrium, or reversal potential.

In the next section, we shall derive the following expression for the K\(^+\) Nernst potential:

\[
E_K = \frac{-RT}{zF} \ln \frac{[K^+]_{\text{in}}}{[K^+]_{\text{out}}}
\]

where \(R\) is the gas constant, \(T\) is the absolute temperature in kelvin, \(z\) is
the valence of $K^+$, $F$ is Faraday’s constant, and $[K^+]_{\text{out}}$ and $[K^+]_{\text{in}}$ are the concentrations of $K^+$ ions outside and inside the cell. A similar formula holds for the Na$^+$ and Cl$^-$ Nernst potentials.

Neurons at rest are permeable to Na$^+$ and Cl$^-$ in addition to $K^+$. Because of their concentration differences, Na$^+$ and Cl$^-$ ions move into the cell and $K^+$ ions move outward. The influx of Na$^+$ ions tends to depolarize the cell, whereas the efflux of $K^+$ and the influx of Cl$^-$ have the opposite effect. The resting potential of the cell is the potential at which there is a balance between these fluxes.

In the following sections, we shall derive the Goldman–Hodgkin–Katz (GHK) equation, which gives an explicit expression for how the resting potential depends on the concentrations, both inside and outside, of ions and the permeabilities of the membrane to the ions.

### 4.2 The Nernst equation

Here we derive the Nernst equation and, in Section 4.3 we derive the GHK equation. Recall that if the membrane is permeable to only one ion, then that ion’s Nernst potential is the resting potential at which the electrical and chemical driving forces balance. The GHK equation is, in some sense, a generalization of the Nernst equation in which we assume the membrane is permeable to more than just one ion. The GHK equation determines the resting potential at which the electrical and chemical forces, generated by each of these ions, balance each other.

In what follows, let $[C](x)$ be the concentration of some ion and $V(x)$ the potential at the point $x$ across the membrane. Then, Fick’s law of diffusion says that the diffusive flux, $J_{\text{diff}}$, is given by

$$J_{\text{diff}} = -D \frac{\partial[C]}{\partial x} \quad (4.2)$$

The diffusion constant $D$ (empirically measured) depends on the size of the molecule and the medium in which it is diffusing. A typical value for ions such as $K^+$, Cl$^-$, and Na$^+$ is $2.5 \times 10^{-6} \text{ cm}^2/\text{s}$. Calcium ion has a diffusion constant about an order of magnitude less. The direction of movement is from high concentrations to low concentrations.

The other physical force that is responsible for the passive movement of ions is the electrical drift described by the microscopic version of Ohm’s law:

$$J_{\text{drift}} = -\mu z [C] \frac{\partial V}{\partial x} \quad (4.3)$$

where $z$ is the valence of the ion ($\pm 1$, $\pm 2$, etc.) and $\mu$ its mobility. The higher the concentration, the greater the drift.
The total flux across the membrane is given by the sum of the diffusive flux and the electrical drift:

\[ J_{\text{total}} = -D \frac{\partial [C]}{\partial x} - \mu z [C] \frac{\partial V}{\partial x} \]  \hspace{1cm} (4.4)

Einstein’s relation connects the mobility with the diffusion coefficient:

\[ D = \frac{\mu kT}{q} \]  \hspace{1cm} (4.5)

where \( k \) is Boltzmann’s constant, \( T \) is the absolute temperature, and \( q \) is the charge. Thus, we can write the total flux as

\[ J_{\text{total}} = -\frac{\mu kT}{q} \frac{\partial [C]}{\partial x} - \mu z [C] \frac{\partial V}{\partial x} \]  \hspace{1cm} (4.6)

It is convenient to convert this equation, which is in terms of the number of individual molecules, into its molar equivalent, by dividing by Avogadro’s number. It is also convenient to introduce \( RT/F \), where \( R \) is the ideal gas constant and \( F \) is Faraday’s constant, instead of \( kT/q \). This will yield the flux per mole. Multiplying this flux by the Faraday’s constant yields a current flux

\[ I = - \left( \frac{uRT}{F} \frac{\partial [C]}{\partial x} + uz [C] \frac{\partial V}{\partial x} \right) \]  \hspace{1cm} (4.7)

measured in A/cm². The quantity \( u \) is the molar mobility, \( u = \mu / N_A \). This equation is the Nernst–Planck equation.

The Nernst equation is obtained by setting the current equal to zero. That is, for a given ionic species, at equilibrium, the diffusion and electric effects balance:

\[ I = - \left( \frac{uRT}{F} \frac{\partial [C]}{\partial x} + uz [C] \frac{\partial V}{\partial x} \right) = 0 \]  \hspace{1cm} (4.8)

Integrating we obtain the Nernst equation:

\[ V_{\text{eq}} = V_{\text{in}} - V_{\text{out}} = -\frac{RT}{zF} \ln \frac{[C]_{\text{in}}}{[C]_{\text{out}}} \]  \hspace{1cm} (4.9)

That is, the equilibrium (or Nernst) potential, which occurs when all the fluxes balance, depends on the logarithm of the ratio of the concentrations of the ions inside and outside the cell.

In Table 4.1 we illustrate how to use the Nernst equation to compute the equilibrium potential in the squid axon.
### Table 4.1 – The concentrations of various ions in the squid giant axon and outside the axon, in the animal’s blood. Equilibrium potentials are derived from these values using the Nernst equation 4.9, assuming a temperature of 6.3°C. For calcium, the amount of free intracellular calcium is shown. There is actually a much greater total concentration of intracellular calcium (0.4 mM), but the vast bulk of it is bound to other molecules. From Hodgkin (1964).

<table>
<thead>
<tr>
<th>Ion</th>
<th>K⁺</th>
<th>Na⁺</th>
<th>Cl⁻</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration inside [mM]</td>
<td>400</td>
<td>50</td>
<td>40</td>
<td>10⁻⁴</td>
</tr>
<tr>
<td>Concentration outside [mM]</td>
<td>20</td>
<td>440</td>
<td>560</td>
<td>10</td>
</tr>
<tr>
<td>Equilibrium potential [mV]</td>
<td>−72</td>
<td>52</td>
<td>−64</td>
<td>139</td>
</tr>
</tbody>
</table>

#### 4.3 The Goldman–Hodgkin–Katz equation

The Nernst–Planck equation describes the movement of charged ions in aqueous media. However, the cell membrane has thickness and there may be energy barriers or blocking sites within the channel. In this case, the ions flowing through the open channel may not obey the Nernst–Planck equation and we must model the complex behaviour within the membrane to get a true picture of the flux across the cell.

Goldman, Hodgkin and Katz came up with a simplified model called the constant-field equation. They assumed that 1) the electric field across the lipid membrane is constant, 2) the Nernst–Planck equation holds within the membrane, and 3) the ions all move independently.

Let \( V_M \) be the total potential across a membrane of width \( l \). Since the electric field is constant, \( E = -V_M/l \). This implies that \( dV/dx = V_M/l \). The mobility of ions within the membrane will be different from that in the aqueous solution; denote this mobility by \( u^* \). Finally, let \( \beta \) be the ratio of the ion solubility within the membrane to the ion solubility in the aqueous solution. Thus, if \( [C] \) is the aqueous concentration, then \( \beta \cdot [C] \) is the membrane concentration. With these assumptions, the Nernst–Planck equation for current across the membrane is

\[
I = -u^*z^2F\beta \cdot [C] \frac{V_M}{l} - u^*zRT \beta \frac{d[C]}{dx} \quad 0 < x < l \tag{4.10}
\]

By solving the first-order linear ordinary differential equation for \([C]\) with the boundary conditions \([C](0) = [C]_{\text{in}}, \quad [C](l) = [C]_{\text{out}}\) we obtain

\[
I = \frac{u^*z^2FV_M\beta}{l} \left( \frac{[C]_{\text{out}}e^{-\xi} - [C]_{\text{in}}}{e^{-\xi} - 1} \right) \tag{4.11}
\]

where

\[
\xi = \frac{zV_MF}{RT} \tag{4.12}
\]
This expression is often written in terms of the permeability,

$$P \equiv \frac{\beta u^* RT}{lF}$$

that is,

$$I = PzF \xi \left( \frac{[C]_{\text{out}}e^{-\xi} - [C]_{\text{in}}}{e^\xi - 1} \right)$$

The permeability has dimensions of cm/s. Thus, the dimensions are in terms of current per unit area. Equation 4.14 is called the constant-field equation.

This is the current due to a single ionic species. The current vanishes at the equilibrium or Nernst potential of the ionic species.

Given several ionic species, the total current is just a sum of the individual currents. This is a consequence of assumption 3), which says that the ions do not interact. Suppose there are three permeable ions, $K^+$, $Na^+$, and $Cl^-$ with corresponding currents, $I_K$, $I_{Na}$, and $I_{Cl}$. At equilibrium, the total current, $I = I_K + I_{Na} + I_{Cl}$, vanishes; that is, $I = 0$. The potential at which this occurs is

$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{\text{out}} + P_{Na}[Na^+]_{\text{out}} + P_{Cl}[Cl^-]_{\text{in}}}{P_K[K^+]_{\text{in}} + P_{Na}[Na^+]_{\text{in}} + P_{Cl}[Cl^-]_{\text{out}}}$$

where the $P_i$'s are the permeabilities of each of the three ionic species. This is a generalization of the Nernst equilibrium discussed above and is called the Goldman–Hodgkin–Katz (GHK) equation. With one species, the equation reduces to the Nernst potential.

### 4.4 Equivalent circuits: the electrical analogue

We saw in Section 4.3 that the electrical properties of cells are determined by the ionic species that move through the membrane. Currents flow according to the permeabilities of ion channels and concentration gradients across the cell membrane. However, all of our discussion so far has been in a steady-state environment. The GHK equation does not determine how the membrane potential changes in response to changes in the permeabilities. For this reason, it cannot be used to understand how these changes in permeabilities may generate an action potential. A very useful way to describe the behaviour of the membrane potential is in terms of electrical circuits; this is commonly called the equivalent circuit model. The circuit consists of three components: 1) conductors or resistors, representing the ion channels; 2) batteries, representing the concentration gradients of the ions; and 3) capacitors, representing the ability of the membrane to store charge.
We first consider a membrane that is only permeable to potassium. The equivalent circuit is shown in Figure 4.2. The lipid bilayer that constitutes the cell membrane has dielectric properties and as such behaves in much the same manner as a capacitor. The relationship between the charge stored and the potential is given by

\[ q = C_M \cdot V_M \]  \hspace{1cm} (4.16)

that is, the total charge \( q \) is proportional to the potential \( V_M \) with a proportionality constant \( C_M \) called the membrane capacitance. Note that the total capacitance depends on the total area of the dielectric; thus, larger neurons have a larger total capacitance than smaller ones. The capacitance per square centimeter is called the specific membrane capacitance and will be denoted as \( c_M \). Hence, the total membrane capacitance \( C_M \) is the specific membrane capacitance \( c_M \) times the total surface area of the cell. In general, the specific membrane capacitance may depend on the potential; however, for most cell membranes, the specific membrane capacitance is very close to \( 1 \, \mu\text{F/cm}^2 \).

Since current is the time derivative of charge, we can differentiate 4.16, divide by the cell’s area, and obtain an expression for the specific capacitance current:

\[ i_{\text{cap}} = c_M \frac{dV_M}{dt} \]  \hspace{1cm} (4.17)

This gives the capacitance current per unit area. We will denote the total capacitance current as \( I_{\text{cap}} \).

In the equivalent circuit, K\(^+\) channels are represented as a conductor in series with a battery. If \( \hat{g}_K \) is the conductance of a single K\(^+\) channel, then, using Ohm’s law, the ionic current through this channel is

\[ \hat{I}_K = \hat{g}_K (V_M - E_K) \]  \hspace{1cm} (4.18)
Now suppose there are $N_K$ K$^+$ channels in a unit area of membrane. These can all be combined into the single equivalent circuit shown in Figure 4.2. The conductance per unit area, or specific membrane conductance ($S/cm^2$), is given by $g_K = N_K \times \hat{g}_K$. Since the Nernst potential depends only on the concentration gradient of K$^+$, and not on the number of K$^+$ channels, it follows that the K$^+$ current, per unit area, is given by

$$I_K = g_K(V_M - E_K) \quad (4.19)$$

Kirchhoff’s current law states that the total current into the cell must sum to zero. Together with the equivalent circuit representation, this leads to a differential equation for the membrane potential:

$$0 = i_{cap} + I_K = c_M \frac{dV_M}{dt} + g_K(V_M - E_K) \quad (4.20)$$

or

$$c_M \frac{dV_M}{dt} = -g_K(V_M - E_K) \quad (4.21)$$

Figure 4.3 shows an equivalent circuit with three parallel conductances and a current source, $I(t)$. Here the capacitance current must be equal to the sum of the ionic currents and the current source. As before, the capacitance current, per unit area, is given by 4.17 and the ionic current, per unit area, is given by

$$i_{ion} = -g_{Cl}(V_M - E_{Cl}) - g_K(V_M - E_K) - g_{Na}(V_M - E_{Na}) \quad (4.22)$$

The current source is not typically expressed as current per unit area, so we must divide $I(t)$ by the total surface area of the neuron, $A$. It then follows that

$$c_M \frac{dV_M}{dt} = -g_{Cl}(V_M - E_{Cl}) - g_K(V_M - E_K) - g_{Na}(V_M - E_{Na}) + I(t)/A \quad (4.23)$$

For a passive membrane in which the conductances and currents are all constant, $V_M$ will reach a steady state:

$$V_{ss} = \frac{g_{Cl}E_{Cl} + g_KE_K + g_{Na}E_{Na} + I/A}{g_{Cl} + g_K + g_{Na}} \quad (4.24)$$

In the absence of the applied current, the steady-state potential is a weighted sum of the equilibrium potentials of the three currents. This is similar to the GHK equation 4.15, in which the contribution to the resting potential by each ion is weighted in proportion to the permeability of the membrane to that particular ion. Note, however, that in the equivalent circuit model, the equilibrium is a linear weighted sum of the equilibrium potentials, whereas in the GHK equation, the sum is nonlinear.
4.5 The cable equation

We have, so far, considered the passive properties of an isopotential cell. This analysis may be used to describe signaling within the cell body, which can be approximated by a sphere. However, it is clearly not appropriate for studying electrical properties of the axon or dendrites. These are better approximated by cylinders that are not isopotential. A subthreshold voltage signal that is initiated at one point along the axon or dendrite will decrease in amplitude with distance from the point of initiation. It is important to understand how the geometry of the cell affects the spread of the signal. The signal may, for example, correspond to synaptic input from another neuron. Understanding how geometry affects the spread of the signal will help determine whether the synaptic input will cause the cell to fire an action potential. Here, we assume the membrane is passive, so the analysis is more applicable to dendrites than to axons.

We consider a cell that is shaped as a long cylinder, or cable, of radius $a$. We assume the current flow is along a single spatial dimension, $x$, the distance along the cable. In particular, the membrane potential depends only on the $x$ variable, not on the radial or angular components.

The cable equation is a partial differential equation that describes how the membrane potential $V_M(x, t)$ depends on currents entering, leaving, and flowing within the neuron. The equivalent circuit is shown in Figure 4.4. In what follows, we will assume $R_e = 0$, so that the extracellular space is isopotential. This assumption is justified if the cable is in a bath with large cross-sectional area.

We first consider the axial current flowing along the neuron due to voltage gradients. Note that the total resistance of the cytoplasm grows in proportion to the length of the cable and is inversely proportional to the cross-sectional area of the cable. The specific intracellular resistivity, which
we denote as $r_L$, is the constant of proportionality. Hence, a cable of radius $a$ and length $\Delta x$ has a total resistance of

$$R_L = \frac{\Delta x}{\pi a^2} r_L \quad (4.25)$$

It follows from Ohm’s law that at any point $x$, the decrease in $V_M$ with distance is equal to the current times the resistance. That is,

$$V_M(x + \Delta x, t) - V_M(x, t) = -I_{\text{long}}(x, t) \cdot R_L = -I_{\text{long}}(x, t) \frac{\Delta x}{\pi a^2} r_L \quad (4.26)$$

There is a minus sign because of the convention that positive current is a flow of positive charges from left to right. If voltage decreases with increasing $x$, then the current is positive. In the limit $\Delta x \to 0$,

$$I_{\text{long}}(x, t) = -\frac{\pi a^2}{r_L} \frac{\partial}{\partial x} V_M(x, t) \quad (4.27)$$

Let $i_{\text{ion}}$ be the current per unit area due to ions flowing into and out of the cell. Then the total ionic current that flows across a membrane of radius $a$ and length $\Delta x$ is given by $I_{\text{ion}} = (2\pi a\Delta x)i_{\text{ion}}$.

The total capacitance of a membrane is equal to the specific membrane capacitance $C_M$ multiplied by the total surface area of the membrane. Hence, for a cable of radius $a$ and length $\Delta x$, the total capacitance is given by $C_M = (2\pi a\Delta x)c_M$ and the amount of current needed to change the membrane potential at a rate $\partial V_M/\partial t$ is

$$I_{\text{cap}}(x, t) = (2\pi a\Delta x)c_M \frac{\partial V_M}{\partial t} \quad (4.28)$$

From Kirchhoff’s law, the change in intracellular axial current is equal to the amount of current that flows across the membrane. Hence,

$$I_{\text{cap}}(x, t) + I_{\text{ion}}(x, t) = -I_{\text{long}}(x + \Delta x, t) + I_{\text{long}}(x, t) \quad (4.29)$$
from which it follows that

\[(2\pi a\Delta x)c_M \frac{\partial V_M}{\partial t} + (2\pi a\Delta x)i_{\text{ion}} = \frac{\pi a^2}{r_L} \left[ \frac{\partial}{\partial x} V_M(x + \Delta x, t) - \frac{\partial}{\partial x} V_M(x, t) \right] \]

We divide both sides of this equation by \(2\pi a\Delta x\) and let \(\Delta x \to 0\) to obtain the cable equation:

\[c_M \frac{\partial V_M}{\partial t} = \frac{a}{2r_L} \frac{\partial^2 V_M}{\partial x^2} - i_{\text{ion}} \quad \text{(4.30)}\]

For a passive cable, in which the resting potential is assumed to be zero,

\[i_{\text{ion}} = \frac{V_M(x, t)}{r_M} \quad \text{(4.31)}\]

where \(r_M\) is the specific membrane resistance. Then 4.30 becomes

\[c_M \frac{\partial V_M}{\partial t} = \frac{a}{2r_L} \frac{\partial^2 V_M}{\partial x^2} - \frac{V_M}{r_M} \quad \text{(4.32)}\]

We can rewrite this equation as

\[\tau_M \frac{\partial V_M}{\partial t} = \lambda^2 \frac{\partial^2 V_M}{\partial x^2} - V_M \quad \text{(4.33)}\]

where

\[\lambda = \sqrt{\frac{a r_M}{2r_L}} \quad \text{and} \quad \tau_M = c_M r_M \quad \text{(4.34)}\]

are the space or length constant and the membrane time constant, respectively. Note that the space constant depends on the geometry of the cable, that is, the cable’s diameter; however, the time constant does not.

For now, it is instructive to consider steady-state solutions. Suppose, for example, we consider a semi-infinite cable (defined for \(x > 0\)) and we inject a step of current, \(I_0\), at \(x = 0\). As \(t \to \infty\), the solution \(V_M(x, t)\) approaches a steady-state solution \(V_{ss}(x)\) that does not depend on time. Setting \(\frac{\partial V_M}{\partial t} = 0\) in 4.33, we find that \(V_{ss}\) satisfies

\[\lambda^2 \frac{\partial^2 V_{ss}}{\partial x^2} - V_{ss} = 0 \quad \text{(4.35)}\]

To solve this equation, we need boundary conditions. Recall from 4.27 that

\[I_0 = -\pi a^2 r_L \frac{\partial V_M}{\partial x} \quad \text{(4.36)}\]

It follows that \(V_{ss}\) must satisfy the boundary condition

\[\frac{d}{dx} V(0) = -\frac{r_L}{\pi a^2} I_0 \quad \text{(4.37)}\]
The solution of 4.35 and 4.37 is

\[ V_{ss}(x) = \frac{\lambda r_L}{\pi a^2} I_0 e^{-x/\lambda} \]  

(4.38)

Note that the membrane potential decays exponentially. The distance at which the potential has decayed to \(1/e\) is the space constant \(\lambda\). Since the space constant is proportional to the square root of the cable’s radius, we conclude that thicker axons or dendrites have larger space constants than narrower processes. That is, thicker processes transmit signals for greater distances. This is important because it influences the ability of the neuron to spatially summate incoming synaptic potentials. Moreover, the electrotonic, or passive, conductance plays an important role in the propagation of the action potential. Thicker cells with a larger space constant are more easily excited and are able to generate faster action potentials.

### 4.6 The squid action potential

We have so far viewed the membrane as a passive cable. However, linear cables cannot transmit information over long distances unless the cable has an enormous diameter. For example, the squid axon is more than 5 cm long, has a diameter of about 0.5 mm, a resting membrane resistance of \(r_M = 700 \Omega \text{cm}^2\), and a transmembrane resistance of \(r_L = 30 \Omega \text{cm}\). Thus, the space constant for the squid axon is \(\lambda = 5.4 \text{mm}\). This is an order of magnitude smaller than the length. If the potential at one end of the axon is held at 120 mV above rest, then the potential at the other end is about 10 µV above the rest, a 10 000-fold decrement. For neural signals to reach any distance, there must be another way to carry them so that they do not degrade.

Nature has solved this problem by inserting voltage-gated channels into the membranes of many cell types. These channels are proteins which selectively let different ionic species into the cell. Furthermore, the permeability of the channels depends on the local environment near the channel. In particular, for voltage-gated channels, whether the channel is open or closed depends on the local potential near the channel. It is the opening and closing of voltage-gated channels that is responsible for the generation of the action potential that propagates along the axon.

Hodgkin and Huxley (1952) were the first to provide a comprehensive, quantitative description of the regenerative currents generating the action potential (AP). The choice of the squid axon was fortuitous since the electrical properties rely primarily on Na\(^+\) and K\(^+\) ions. Consider the equivalent circuit shown in Figure 4.5 and assume the cell is isopotential. Then the
membrane potential satisfies
\[ \frac{dV}{dt} = c_M (V - E_{Na}) - g_K (V - E_K) - g_L (V - E_L) \] (4.39)

Here, we write \( V \) instead of \( V_M \) and \( I_L \equiv g_L (V - E_L) \) is called the *leak current*. It corresponds to passive flow of ions through nongated channels. The leak conductance, \( g_L \), is constant. Since most nongated channels are permeable to \( K^+ \) ions, \( E_L \) is close to \( E_K \). The conductances \( g_{Na} \) and \( g_K \) may change with time since these correspond to the opening and closing of \( Na^+ \) and \( K^+ \) channels, respectively. At rest, \( g_K \) is about 30-fold bigger than \( g_{Na} \), so the resting state is near \( E_K \) at about \(-65 \text{ mV}\). Suppose we could increase the conductance of \( g_{Na} \) 100-fold, then the resting potential would be much closer to the Nernst potential of \( Na^+ \), which is about 55 mV. Thus, the amplification of the potential, such as during an action potential, involves changes in the relative conductances of the dominant ionic species. Hodgkin and Huxley’s insight was that voltage-gated channels provide the substrate for this dynamic regulation of the conductances.

The basic mechanisms underlying action potentials are the following (Figure 4.6). At rest, most of the \( Na^+ \) channels are closed, so the membrane potential is determined primarily by the \( K^+ \) Nernst potential. If the cell is depolarized above some threshold, then \( Na^+ \) channels open and this further depolarizes the cell. This allows even more \( Na^+ \) channels to open, allowing more \( Na^+ \) ions to enter the cell and forcing the cell toward the \( Na^+ \) Nernst potential. This is the upstroke of the action potential. The \( Na^+ \) channel is transient, so even when they are depolarized, the \( Na^+ \) channels eventually shut down. In the meantime, the depolarization opens \( K^+ \) channels and \( K^+ \) ions exit the cell. This hyperpolarizes the cell as the membrane potential moves toward the \( K^+ \) equilibrium potential. Until the voltage-gated \( K^+ \) channels close up again, the membrane is refractory. During this time, pumps exchange excess \( Na^+ \) ions inside the cell with excess \( K^+ \) ions outside the cell.
Figure 4.6 – The action potential (AP). During the upstroke, Na\(^+\) channels open and the membrane potential approaches the Na\(^+\) Nernst potential. During the downstroke, Na\(^+\) channels are closed, K\(^+\) channels are open, and the membrane potential approaches the K\(^+\) Nernst potential.

4.7 Voltage-gated channels

In the Hodgkin–Huxley (HH) model, each channel is viewed as a transmembrane protein that forms a pore through which ions can diffuse down their concentration gradients. The pores have gates that can be either open or closed; the probability that a gate is open or closed depends on the membrane potential. The gate model can be summarized by the diagram

\[
\begin{array}{c}
C \\
\alpha(V) \\
\beta(V) \\
O
\end{array} \quad \begin{array}{c}
\Rightarrow \\
\Leftrightarrow
\end{array} \quad \begin{array}{c}
C \\
\alpha(V) \\
\beta(V) \\
O
\end{array}
\]

where \(C\) and \(O\) correspond to the closed and open states, respectively, and \(\alpha(V)\) and \(\beta(V)\) are the voltage-dependent rate constants at which a gate goes from the closed to the open and vice-versa, respectively. If we let \(m\) be the fraction of open gates, then \(1 - m\) is the fraction of closed gates and, from the law of mass action,

\[
\frac{dm}{dt} = \alpha(V)(1 - m) - \beta(V) \cdot m = \frac{m_\infty(V) - m}{\tau(V)} \quad (4.40)
\]

where

\[
m_\infty(V) = \frac{\alpha(V)}{\alpha(V) + \beta(V)} \quad \text{and} \quad \tau(V) = \frac{1}{\alpha(V) + \beta(V)} \quad (4.41)
\]
It is easy to solve this equation if $V$ is constant. The solution starting at $m(0)$ is

$$m(t) = m_\infty(V) + (m(0) - m_\infty(V)) e^{-t/\tau(V)} \quad (4.42)$$

Note that the solution approaches the steady-state $m_\infty(V)$ at a rate determined by the time constant $\tau(V)$.

One must obtain expressions for the voltage-dependent rate constants $\alpha$ and $\beta$. In the Hodgkin–Huxley model, these functions were derived by fitting the data.

### 4.8 Hodgkin–Huxley model

We are now ready to derive the Hodgkin–Huxley model for the propagation of an action potential along the squid’s giant axon. We view the axon as a cylinder of fixed radius, $a$, so the membrane potential depends on the spatial variable $x$ and time $t$. Here, we assume there are voltage-gated $K^+$ and $Na^+$ channels and a leak current. Then balancing currents, as in 4.29, we have

$$I_L = I_{\text{cap}} + I_{\text{ion}} \quad (4.43)$$

or, using 4.17 and 4.30,

$$\frac{a}{2r_L} \frac{\partial^2 V_M}{\partial x^2} = c_M \frac{\partial V_M}{\partial t} + I_K + I_{Na} + I_L \quad (4.44)$$

If each ionic current is ohmic, then this can be written as

$$c_M \frac{\partial V_M}{\partial t} = \frac{a}{2r_L} \frac{\partial^2 V_M}{\partial x^2} - g_K(V_M - E_K) - g_{Na}(V_M - E_{Na}) - g_L(V_M - E_L) \quad (4.45)$$

To complete the model, we need to describe how one computes the membrane conductances $g_K$, $g_{Na}$ and $g_L$. Note that the voltage-gated conductances $g_K$ and $g_{Na}$ change with time during an action potential.

Hodgkin and Huxley used two experimental methods to separate the ionic currents and compute how the $K^+$ and $Na^+$ conductances depend on voltage. The first was a simple feedback circuit called the voltage clamp that allows the experimenter to hold the membrane potential at a constant or holding level $V_C$. The voltage clamp does so by injecting a current into the axon that is equal and opposite to the current flowing through the voltage-gated channels. Note that the voltage clamp separates the total membrane current into its ionic and capacitive components. Recall that from 4.17, if the membrane potential is fixed at some constant, then the capacitive current must be zero. Moreover, the total current can be made spatially uniform by inserting a highly conductive axial wire inside the fiber; the axon is then
said to be *space-clamped*. In this case, \( \partial^2 V_M / \partial x^2 = 0 \). It then follows that any changes in current must be due to either the leak or the opening and closing of voltage-gated membrane channels.

We first consider how the voltage clamp can be used to determine the leak conductance, \( g_L \). Note that most of the voltage-gated channels are closed at rest. Moreover, if we hyperpolarize the cell, then we may assume all of the voltage-gated channels are closed. It follows that if the membrane potential is clamped at some sufficiently strong hyperpolarized level, then the total current is given by the leak; that is,

\[
I_M \approx g_L (V_C - E_L)
\]

From this equation, we can easily solve for \( g_L \).

Figure 4.7 – **Numerically computed voltage-clamp experiment.** A The membrane potential is stepped from rest to 0 mV. This results in an inward current followed by an outward current. The separate K\(^+\) and Na\(^+\) currents are also shown. B The membrane potential is stepped to different values and the resulting K\(^+\) and Na\(^+\) conductances are computed.

Figure 4.7a shows the results of a (numerically computed) voltage-clamp experiment when the membrane potential is clamped at 0 mV. Note that there is an inward current followed by an outward current. This result suggests the depolarizing voltage step turns on two voltage-gated channels. The inward current is due to the influx of Na\(^+\) ions, whereas the outward current is due to the outward flow of K\(^+\) ions. It is not clear, however, how these two separate ions contribute to the total membrane current. For this it is necessary to isolate the two voltage-gated currents.

Hodgkin and Huxley were able to isolate the K\(^+\) current by replacing Na\(^+\) ions in the external bathing solution with a larger, impermeant cation. This eliminated the inward Na\(^+\) current. Once Na\(^+\) has been removed, the voltage clamp can be used to determine how \( I_K \) depends on the membrane potential. That is, one holds the membrane potential at various levels and
determines the time course of the total membrane current $I_M$. If $Na^+$ is removed, then the $K^+$ current is computed by subtracting the leak current from $I_M$.

It is also now possible to block $K^+$ channels using the drug tetraethylammonium. This was not available to Hodgkin and Huxley; however, if $I_K$ and $I_L$ are known, then one computes $I_{Na}$ simply by subtracting $I_K$ and $I_L$ from $I_M$. Once these currents have been determined, we can calculate the $I_K$ and $I_{Na}$ conductances using Ohm’s law. That is,

$$g_K(t) = \frac{I_K(t)}{V_M - E_K} \quad \text{and} \quad g_{Na}(t) = \frac{I_{Na}(t)}{V_M - E_{Na}}$$

Figure 4.7b shows the $I_K$ and $I_{Na}$ conductances for different levels of the holding potential. Note than $g_{Na}$ turns on more rapidly than $g_K$. Moreover, the $Na^+$ channels begin to close before the depolarization is turned off, whereas the $K^+$ channels remain open as long as the membrane is depolarized. This suggests the $Na^+$ channel can exist in three states: resting, activated, and inactivated. When the cell is depolarized, the $Na^+$ channels switch from the resting (closed) to the activated (open) state. If the depolarization is maintained, then the channel switches to the inactivated (closed) state.

Using the voltage-clamp data, Hodgkin and Huxley derived expressions for the $K^+$ and $Na^+$ conductances. They proposed that

$$g_K = \overline{g}_K n^4 \quad \text{and} \quad g_{Na} = \overline{g}_{Na} m^3 h$$

where $\overline{g}_K$ and $\overline{g}_{Na}$ are maximum conductances and $n$, $m$, and $h$ are gating variables that take values between 0 and 1. Hence, $n^4$ represents the probability that a $K^+$ channel is open: the $K^+$ channel has four independent components, all of which are identical. The probability that the sodium activation gate is open is $m^3$ and the probability that the sodium inactivation gate is open is $h$. Each of the gating variables satisfies a first-order differential equation of the form 4.40. That is, they satisfy equations of the form

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V) \cdot n = \frac{n_\infty(V) - n}{\tau_n(V)}$$
$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V) \cdot m = \frac{m_\infty(V) - m}{\tau_m(V)}$$
$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V) \cdot h = \frac{h_\infty(V) - h}{\tau_h(V)}$$

If $X = n$, $m$ or $h$, then

$$X_\infty(V) = \frac{\alpha_X(V)}{\alpha_X(V) + \beta_X(V)} \quad \text{and} \quad \tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}$$
To match the data, Hodgkin and Huxley chose the following parameters and gating functions: \( g_{Na} = 120 \text{mS/cm}^2 \), \( g_K = 36 \text{mS/cm}^2 \), \( g_L = 0.3 \text{mS/cm}^2 \), \( E_{Na} = 50 \text{mV} \), \( E_K = -77 \text{mV} \), \( E_K = -54.4 \text{mV} \),

\[
\begin{align*}
\alpha_n (V) &= \frac{0.01 (V + 55)}{1 - e^{-(V+55)/10}} \\
\beta_n (V) &= 0.125 e^{-(V+65)/80} \\
\alpha_m (V) &= \frac{0.1 (V + 40)}{1 - e^{-(V+40)/10}} \\
\beta_m (V) &= 4 e^{-(V+65)/18} \\
\alpha_h (V) &= 0.07 e^{-(V+65)/20} \\
\beta_h (V) &= \frac{1}{1 + e^{-(V+35)/10}}
\end{align*}
\]  

In Figure 4.8 we plot the activation curves \( n_\infty (V) \), \( m_\infty (V) \) and \( h_\infty (V) \) along with \( \tau_n (V) \), \( \tau_m (V) \) and \( \tau_h (V) \). Note that \( n_\infty (V) \) and \( m_\infty (V) \) are increasing functions that approach 0 for hyperpolarizing currents and approach 1 for depolarizing currents. Hence, \( n \) and \( m \) become activated when the membrane is depolarized. On the other hand, \( h_\infty (V) \) is a decreasing function, so the Na\(^+\) channels inactivate when the membrane is depolarized. It is also important to note that \( \tau_m (V) \) is considerably smaller than \( \tau_n \) or \( \tau_h \). Hence, Na\(^+\) channels activate much faster than they inactivate or K\(^+\) channels open. In Figure 4.9, we show the response of \( m \), \( h \), and \( n \) to a step in voltage.

### 4.9 The action potential revisited

In summary, the Hodgkin–Huxley model is a system of four differential equations; there is one equation for the membrane potential and three
equations for channel gating variables. In the case of a space-clamped squid axon, we write these equations as

\[ c_M \frac{dV}{dt} = -g_{Na}m^3h(V - E_{Na}) - g_K n^4(V - E_K) - g_L(V - E_L) \]  \hspace{1cm} (4.60)

\[ \frac{dn}{dt} = \phi [\alpha_n(V)(1 - n) - \beta_n(V) \cdot n] \]  \hspace{1cm} (4.61)

\[ \frac{dm}{dt} = \phi [\alpha_m(V)(1 - m) - \beta_m(V) \cdot m] \]  \hspace{1cm} (4.62)

\[ \frac{dh}{dt} = \phi [\alpha_h(V)(1 - h) - \beta_h(V) \cdot h] \]  \hspace{1cm} (4.63)

Here, we added a parameter \( \phi \); this is the temperature factor. It is important to realize that the temperature at which an experiment is done can be very important. Since channels are stochastic in nature, they are sensitive to the temperature, so the rates of switching states depend exponentially on the temperature. Higher temperatures cause faster switching. Thus, there is a factor

\[ \phi = Q_{10}^{(T - T_{base})/10} \]  \hspace{1cm} (4.64)

\( Q_{10} \) is the ratio of the rates for an increase in temperature of 10°C. For the squid giant axon, \( T_{base} = 6.3^\circ C \) and \( Q_{10} = 3 \).

Figure 4.10 shows solutions of these equations in response to different levels of steps in currents. Note that there is “all-or-none” behaviour: when the applied current is below some threshold, the membrane potential returns quickly to the rest; when the current is above some threshold, there is an action potential. If the applied current is sufficiently large and held for a sufficiently long time, then the model generates a periodic response.
In Section 4.6, we described the events underlying the action potential in terms of the inward and outward flow of Na\(^+\) and K\(^+\) ions. Here, we give a more ‘mathematical’ explanation in terms of the behaviour of the dependent variables in the differential equations (Figure 4.11).

When we depolarize the cell, we change the values of the activation curves: \(n_\infty(V)\) and \(m_\infty(V)\) increase, whereas \(h_\infty(V)\) decreases. Since \(n, m,\) and \(h\) tend toward their activation curves, it follows that \(n\) and \(m\) initially increase, whereas \(h\) decreases. That is, K\(^+\) channels open, whereas Na\(^+\) channels both activate and inactivate. However, \(\tau_m\) is much smaller than both \(\tau_h\) and \(\tau_n\). It follows that the Na\(^+\) channels activate much faster than they inactivate or K\(^+\) channels open. Therefore, the Na\(^+\) conductance, \(g_{Na} = g_{Na} m^3 h\), increases faster than \(g_K = g_K n^4\).

The increase in the Na\(^+\) conductance leads to a large increase in the Na\(^+\) current, \(I_{Na} = g_{Na}(V - E_{Na})\). As long as the cell is near rest, the driving force \(V - E_{Na}\) is large (recall that \(E_{Na} \approx 55\) mV). Hence, the Na\(^+\) current will dominate the equation for the membrane potential and \(V\) will increase toward the Na\(^+\) Nernst potential. As \(V\) increases, \(m_\infty(V)\) increases further, leading to further increase in Na\(^+\) activation.

As \(V\) increases toward \(E_{Na}\), Na\(^+\) channels inactivate. This is because \(h \rightarrow h_\infty(V) \approx 0\). Moreover, the Na\(^+\) driving force \(V - E_{Na}\) decreases. For both reasons, the Na\(^+\) current turns off. Meanwhile, the K\(^+\) channel activates because \(n \rightarrow n_\infty(V) \approx 1\). Moreover, the K\(^+\) driving force \(V - E_K\) becomes very large.

It follows that eventually, the K\(^+\) current dominates and the membrane potential must fall back toward the K\(^+\) Nernst potential. This corresponds to the downstroke of the action potential.

After the action potential, the cell is hyperpolarized with \(m_\infty \approx 0, n_\infty \approx 71\).
0 and $h_\infty \approx h$. After some time, $m$, $n$, and $h$ approach their steady-state values and the cell returns to rest.
CHAPTER

FIVE

THE ULTRAMETRIC ORGANIZATION
OF MEMORIES

5.1 Hopfield model in a nutshell

Neural networks have been proposed as associative memories to model the behaviour of human long term memory (Hopfield, 1982). A neural network is essentially an amorphous aggregate of neurons that, in this context, are idealized as physical two-state devices (McCulloch and Pitts, 1943) coupled through a symmetrical matrix $J_{ij}$ that represents the synapses.

Here we summarize the basic assumptions and definitions of such a simple model.

- The all-or-none firing of a neuron is represented by a spin that can take two values: $S_i = +1$ (firing), $S_i = -1$ (rest).

- A pattern of activity, $\mu$, of a network of $N$ neurons is represented by a spin configuration $\{\xi_i^\mu\}$, $i = 1, \ldots, N$, that lies at one of the corners of a hypercube in $N$-dimensional configuration space.

- Two patterns of activity, $\mu$ and $\nu$, may be compared through their overlap:

$$\langle \mu|\nu \rangle = \frac{1}{N} \sum_{i=1}^{N} \xi_i^\mu \xi_i^\nu$$  \hspace{1cm} (5.1)

- An energy function can be written as

$$E = -\frac{1}{2} \sum_{i \neq j} J_{ij} S_i S_j$$  \hspace{1cm} (5.2)
The dynamics of a neuron is a stochastic threshold dynamics:

\[ S_i = \text{sgn} h_i \]

\[ h_i = \sum_{j, j \neq i}^N J_{ij} S_j \quad (5.3) \]

The neuron dynamics is such that each spin tends to decrease its energy. A stable configuration is therefore a local minimum of the energy \( E \).

During learning the \( J_{ij} \) are modified by the environment. A set of \( p \) patterns \( \{\xi_i^\mu\}, i = 1, \ldots, N, \mu = 1, \ldots, p \), is embedded in the \( J_{ij} \)'s, via the Hebbian learning rule

\[ J_{ij} = \frac{1}{N} \sum_{\mu=1}^p \xi_i^\mu \xi_j^\mu \quad (5.4) \]

The patterns are memorized in the sense that every one of the network configurations

\[ S_i = \xi_i^\mu \quad i = 1, \ldots, N \quad (5.5) \]

for every one of the \( p \) pattern labelled by \( \mu \), is a fixed point of the dynamics (attractor).

We also define the capacity of the network as \( \alpha = p/N \).

The first question to ask about the storage prescription 5.4 is: does it actually stabilize the inscribed patterns, \( \xi_i^\mu \)? Would a network in a state that is a stored pattern, \( S_i = \xi_i^1 \), be dynamically stable? The condition that a certain network state \( \{S_i\} \) be dynamically stable is

\[ S_i h_i > 0 \quad i = 1, \ldots, N \quad (5.6) \]

namely the local field must be of the same sign as the local value of the spin.

With Eq. 5.4, the local field at neuron \( i \) is

\[ h_i \{S\} = \sum_{j, j \neq i} J_{ij} S_j = \frac{1}{N} \sum_{j, j \neq i} \sum_{\mu=1}^p \xi_i^\mu \xi_j^\mu S_j \quad (5.7) \]

Next, \( S_i \) is replaced by \( \{\xi_i^1\} \), where the choice of the pattern is arbitrary since the patterns enter the synaptic matrix symmetrically. The condition for the stability of bit number 1 becomes

\[ \xi_i^1 h_1 = \frac{N-1}{N} + \frac{1}{N} \sum_{j, j \neq i}^p \sum_{\mu=2}^p \xi_i^1 \xi_j^\mu \xi_j^\mu > 0 \quad (5.8) \]

where the sum over \( \mu \) has been separated into two parts.
The ultrametric organization of memories

- A *signal* term, the term with $\mu = 1$, corresponding to the pattern whose stability is being investigated.

- A *noise* term which includes the contribution of all the remaining stored patterns to the PSP.

In a large system (as $N \to \infty$), the signal term is equal to unity. The noise term contains a sum of $(N - 1)(p - 1) \approx Np$ bits of +1 and −1. Since the bits of different patterns at the same site and the bits of the same pattern at different site are uncorrelated, the sum of the $Np$ bits in the noise term is a one dimensional random walk of $Np$ steps of size unity. In such a walk, steps are taken both forward and backward. The sum will fluctuate about zero and its mean square displacement from the origin is $Np$. Taking into account that the sum is divided by $N$, one can estimate the noise term by $\sqrt{p/N}$. The local field at a typical neuron can now be written as

$$\xi_i^1 h_i = 1 + R$$

with

$$|R| \approx \sqrt{\frac{p}{N}}$$

The conclusion is that if $p$ is kept fixed as $N$ is made very large, the noise becomes negligible in comparison with the signal. Since the sign of the field is equal to the sign of the spin, the subsequent state of the network will be identical to the present state. This, in turn, implies that every pattern is a fixed point.

In fact, the patterns are very stable fixed points. Suppose that a finite fraction, $d$, of spins is flipped away from one of the patterns, randomly, then the expression for the signal will become $1 - 2d$ and the noise will remain unchanged. The local fields will be

$$h_i = m_0 + R$$

with

$$m_0 = 1 - 2d$$

The noise, being of order $N^{-1/2}$ is still negligible compared to the signal which is of order unity. As a consequence, the network will immediately align itself with the pattern, even if it was rather far off to start with. In other words, the patterns have very large basins of attraction.

**Pros and cons**

So defined, the model has the following properties:
i) it stores a certain amount of information. If $N$ is the number of neurons, one can store $\approx 0.15 N$ words of $N$ bits (Hopfield, 1982; Amit et al., 1985b);

ii) the retrieval of the information is such that from a partial, deteriorated, knowledge of one word the system is able to reconstruct the full word (the number of bits that can be so reconstructed decrease as we try to store more words);

iii) after storing $P$ words the system — requested to retrieve a particular pattern — may, generically, answer with a “spurious” word, i.e. one that has not been originally stored. The number of spurious words increases at least exponentially with $P$ (Amit et al., 1985a);

iv) the storage prescription adopted in e.g. Hopfield (1982) works best if the words are at least approximately orthogonal.

The type of organization of a neural network is natural for biological system. From the neural sciences point of view, such a model has the drawback of assuming symmetric synapses. Modifying it with an asymmetric matrix $J_{ij}$ leads us outside the well-known domain of statistical mechanics into the realms of cellular automata where must less is known.

The major testable predictions of these models fall in the realm of cognitive psychology: we should confront the behaviour of a neural network with what we know about human memory. Comparisons of this type have already been discussed in the literature. For instance the spurious words have been seen as a proof that these models are not just repetitive but have the ability to imagine new representations (Anderson, 1983). The storage capability (Hopfield, 1982) has also been discussed in this context.

From this point of view, we notice as a serious flaw in the model that words or patterns to be stored have to be encoded in approximately orthogonal vectors, just exactly the opposite of the way human memory works. It is part of our every day experience that when we try to memorize new information we look for all the possible relationships with previously stored words. If we can classify the new pattern, that is, place it in a hierarchical tree of categories, we do it with so much eagerness that sometimes we just censor the data so as to eliminate some exceptional features. However, if the word is really orthogonal to all the previously stored ones we have reluctantly to initiate a new category.

Another problem of the model, closely related to the previous one, is that when errors in retrieval occur, either because of spurious states or because of the limits in capacity, there is no way to control the quality of these errors. On the other hand, biosystems cannot afford certain errors more than once.
The ultrametric organization of memories in a lifetime. A hierarchy among errors is therefore mandatory. This can be automatically implemented if we have classified the patterns in a hierarchical tree of categories. An unimportant error will be to confuse individuals inside a category while a more serious one will be to confuse categories (incidentally it follows that this type of categorization must occur very early in the evolutionary tree: distinguishing between prey and predators is more vital than distinguishing among varieties of predators).

Both problems above will be solved if we could modify the model in such a way that the patterns to be memorized instead of being orthogonal fall into a hierarchical tree. This type of organization (ultrametricity) appears spontaneously in the equilibrium states of a Sherrington–Kirkpatrick (SK) spin-glass, a limiting case of a Hopfield model (Mézard et al., 1984).

Due to the similarity between the SK spin glass and a neural network there is an exciting possibility that the type of architecture of the network leads spontaneously to categorization.

5.2 Ultrametricity in mathematics

A metric space is a space endowed with a distance. A distance, in general, obeys the triangular inequality

\[ d(A, C) \leq d(A, B) + d(B, C) \]  \hspace{1cm} (5.13)

where \( A, B, C \) are any three points of the space.

The ultrametric inequality is a stronger inequality:

\[ d(A, C) \leq \max \{ d(A, B), d(B, C) \} \]  \hspace{1cm} (5.14)

A distance that satisfies the ultrametric inequality is called an ultrametric distance. A space endowed with an ultrametric distance is called an ultrametric space.

\( p \)-adic numbers

Let us consider the formal sums

\[ \pm \sum_{i=0}^{\infty} a_i p^i \ \text{with} \ 0 \leq a_i \leq p - 1 \]  \hspace{1cm} (5.15)

where the number \( p \) and the coefficients \( a_i \) are natural integers. Such a sum represents an integer \( x \) if

\[ x \equiv a_0 + a_1 p + \cdots + a_i p^i \pmod{p^{i+1}} \ \text{for all} \ i \]  \hspace{1cm} (5.16)
Actually it can be verified that any integer, positive or negative, can be represented by a sum \( \sum_{i=0}^{\infty} a_i p^i \), with \( 0 \leq a_i \leq p - 1 \).

With the inclusion of negative exponents, one could represent not only integers, but also rational numbers. Thus a rational number can be represented as a formal sum

\[
\sum_{i=r}^{\infty} a_i p^i \quad \text{with} \quad 0 \leq a_i \leq p - 1, \quad a_r \neq 0
\]

where \( r \) is a relative integer (positive, negative, or zero); such a representation is unique. The set of all formal sums is denoted \( \mathbb{Q}_p \) and is called the field of \( p \)-adic numbers; it contains \( \mathbb{Q} \), the usual field of rational numbers, but is distinct from it.

At the beginning of the century, the notations of topology were spreading and, in 1906, M. Frechet introduced the general notion of metric space. A metric space \( E \) is a space for which a distance function \( d(x, y) \) is defined for any pair of elements \((x, y)\) belonging to \( E \). The distance function takes non-negative values and satisfies three properties (obeyed by the usual Euclidean distance),

\[
\begin{align*}
(\text{i}) & \quad d(x, y) = 0 \iff x = y \\
(\text{ii}) & \quad d(y, x) = d(x, y) \\
(\text{iii}) & \quad d(x, z) \leq d(x, y) + d(y, z)
\end{align*}
\]

this last property is the triangular inequality 5.13.

An example of such a distance is the \( p \)-adic distance on the field \( \mathbb{Q} \) of rational numbers. Given a fixed prime number \( p \), for any relative integer \( x \), \( x \neq 0 \), let

\[
|x|_p = p^{-r}
\]

where \( p^r \) is the highest power of \( p \) dividing \( x \).

Let us recall that an absolute value on a field \( K \) is a function \( \varphi \), with non-negative values, such that

\[
\begin{align*}
(\text{i}) & \quad \varphi(x) = 0 \iff x = 0 \\
(\text{ii}) & \quad \varphi(xy) = \varphi(x)\varphi(y) \\
(\text{iii}) & \quad \varphi(x + y) \leq \varphi(x) + \varphi(y)
\end{align*}
\]

One sees by conditions (i) and (ii) that if some absolute value on \( \mathbb{Q} \) is such that \( \varphi(x) = |x|_p \), whenever \( x \) is a nonzero integer, it is unique. Then one shows that this \( \varphi \) also satisfies condition (iii): it is called the \( p \)-adic absolute value \(|x|_p\).
In the case of the classical absolute value $|x| = \max (x, -x)$, one has $|x + x| > |x|$ if $x \neq 0$, which constitutes the principle of Archimedes. With the definition of the $p$-adic absolute value, one has

$$|x + y|_p \leq \max \{|x|_p, |y|_p\} \quad (5.21)$$

which is a more stringent inequality than (iii) above. More strikingly,

$$|x + x|_p \leq |x|_p \quad (5.22)$$

which violates the principle of Archimedes. For this reason, the $p$-adic absolute value is said to be non-Archimedean (or ultrametric).

Through the $p$-adic absolute value $|x|_p$, the $p$-adic distance $d_p(x, y)$ is defined by

$$d_p(x, y) = |x - y|_p \quad (5.23)$$

As a consequence of this definition, two rational numbers are $p$-adically close if their difference is divisible by a high power of $p$. Let us consider an example, $p = 5$. Two numbers are 5-adically close if their difference is divisible by a high power of 5. Thus 6 is closer to 1 than it is to 7. Equidistant to 1, 11, 16, 21, or 26, 6 is closer to 31 and even closer to 131, closer still to 631. If, for example, one considers the triangle formed by the three numbers 1, 6, 7, one observes that it is an isosceles triangle with 7 equidistant to 1 and 6.

The natural geometrical ordering of $p$-adic numbers is thus not along the real line but on a hierarchical generating tree.

Coinage of the word ultrametric is due to Marc Krasner (1912–1985). In a note presented at the French Academy of Sciences on October 23, 1944, entitled “Nombres semi-réels et espaces ultramétriques”, he elucidated the topological generality of ultrametric spaces, beyond the algebraic context in which the notion had appeared.

Thus, as he noticed, in an ultrametric space, every point inside a ball (that is, every point $B$ such that $d(A, B) \leq r$) is itself at the center of the ball, and the diameter of a ball is equal to its radius. Each ball is both open and closed. Two balls are either disjoint or contained one within the other. In equivalent terms, the ultrametric inequality 5.14 implies that, in an ultrametric space, all triangles are either equilateral or isosceles with a small base (third side shorter than the two equal ones).

### 5.3 Hierarchy in an ANN

We shall start by describing the storage and retrieval of a very simple tree of states, composed by a single parent and one generation of descendants (see Figure 5.1).
The parent is an unbiased pattern $\xi$ of $\pm 1$’s, hence

$$\langle \langle \xi \rangle \rangle = 0$$

We then generate the offspring stochastically as a set of $p$ patterns $\{\xi^\mu\}$, each bit of each pattern chosen, independently, to be either equal or minus the corresponding bit in the parent, according to a given probability distribution (Virasoro, 1986). This can be expressed as

$$\xi^\mu_i = \xi_i \eta_i^\mu$$ (5.24)

with

$$\Pr(\eta = \pm 1) = \frac{1}{2}(1 \pm a)$$ (5.25)

As a consequence, the overlap of two different descendants is

$$\langle \mu | \nu \rangle = \frac{1}{N} \sum_{i=1}^{N} \xi^\mu_i \xi^\nu_i = \frac{1}{N} \sum_{i=1}^{N} \eta^\mu_i \eta^\nu_i = a^2$$ (5.26)

i.e. they are all equidistant.

To store parent and descendants, the synaptic matrix could be

$$T_{ij} = \frac{1}{N} \xi_i \xi_j \left( 1 + \frac{1}{\Delta} \sum_{\mu=1}^{p} (\eta^\mu_i - a)(\eta^\mu_j - a) \right)$$ (5.27)

that is essentially a slight modification of the Hebb rule for biased patterns. The main differences are that a ‘ferromagnetic’ term $\xi_i \xi_j$ has been added to the matrix storing the $p$ patterns, and a coefficient $1/\Delta$ has been introduced. The stability of the memorized patterns is verified by a calculation of the local fields produced in the states $\xi$ and $\xi^1$, for the choice $\Delta = 1 - a^2$. The first is

$$h_i(\xi) = \xi_i \left( 1 + \frac{1}{(1-a^2)N} \sum_{\mu=1}^{p} \sum_{j \neq i}^{N} (\eta^\mu_i - a)(\eta^\mu_j - a) \right)$$ (5.28)
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The signal is 1. The noise vanishes and has an RMS of \( \alpha \). Hence, the parent is stable if \( \alpha \ll 1 \). For the descendants,

\[
h_i(\xi_i^1) = \xi_i \left( a + \frac{1}{(1-a^2)N} \sum_{\mu=1}^{p} \sum_{j,i \neq i} (\eta_i^\mu - a)(\eta_j^\mu - a)\eta_j^i \right)
\]

(5.29)

In the second term on the right-hand side we separate the \( \mu = 1 \) contribution from the rest, which is noise with vanishing mean and RMS of \( \alpha \). The signal is just

\[
S = \xi_i \left( a + \frac{1}{(1-a^2)N} \sum_{j,j \neq i} (\eta_i^1 - a)(\eta_j^1 - a)\eta_j^i \right) = \xi_i \eta_i^1 = \xi_i
\]

(5.30)

which shows that the descendants are also stable for small \( \alpha \).

Two further conclusions follow:

- With the particular choice of \( \Delta = 1 - a^2 \), parent and descendants have a signal of the same magnitude, and hence the same energy.

- The calculation of the noise indicates that the storage capacity for the retrieval of all \( p + 1 \) memories is the same as for the usual, unbiased patterns.

The degeneracy between the parent and the descendants is lifted when the value of \( \Delta \) is changed. In fact, this parameter can vary in the interval

\[
1 - a^2 \leq \Delta < \frac{(1-a^2)(1+a)}{a}
\]

(5.31)

and still have all the stored patterns stable. Consequently,

- The parent is the absolute energy minimum and the descendants are \( p \) satellite meta-stable states (Feigelman and Ioffe, 1987).

- When the degeneracy is lifted, there are two values of the storage capacity, \( \alpha_1 \) and \( \alpha_2 \). Above the first there are no retrieval states; between the two only the parent is an attractor and below \( \alpha_2 \) both parent and descendants are retrievable. For \( \Delta = 1 - a^2 \) the two values coincide. The two storage capacities are plotted in Figure 5.2 as a function of \( \Delta \).
Multi-ancestors and two levels

Instead of the single ancestor $\xi$, we now take $p$ patterns $\{\xi^{\mu}\}$ with $\mu = 1, \ldots, p$. Each of these will have $q$ descendants $\{\xi^{\mu,\nu}\}$. In general, the branching ratio can vary from parent to parent, i.e. $q = q_\mu$. Moreover, the stochastic process generating the branching at each ancestor can vary with the ancestor, namely the probability (bias $a$) for transmitting the structure of the ancestor to its descendant may depend on $\mu$, i.e. $a = a_\mu$. See, e.g., Figure 5.3.

![Figure 5.2](image)

**Figure 5.2** – The storage capacities of parent ($\alpha_1$) and descendants ($\alpha_2$) vs the relative synaptic strength parameter $\Delta$. (Feigelman and Ioffe, 1987).

![Figure 5.3](image)

**Figure 5.3** – A two level tree with different ancestors.

The generalization of the stochastic construction, Eq. 5.24 and 5.25, is just

$$\xi^{\mu,\nu}_i = \xi^{\mu}_i \eta^{\mu,\nu}_i$$

(5.32)

with

$$\Pr(\eta^{\mu,\nu} = \pm 1) = \frac{1}{2}(1 \pm a_\mu)$$

(5.33)

Now the overlap of two different descendants can have two values: if
they belong to the same bunch (same parent \(\mu\)), then

\[
\langle \mu, \nu | \mu, \lambda \rangle \equiv \frac{1}{N} \sum_{i=1}^{N} \xi_{\mu}^{\mu_i} \xi_{\nu}^{\mu_i} = \frac{1}{N} \sum_{i=1}^{N} \eta_{\mu}^{\mu_i} \eta_{\nu}^{\mu_i} = a_{\mu}^2
\]

(5.34)

i.e. they are all equidistant. If they belong to two different groups and the parents are uncorrelated, then

\[
\langle \mu, \nu | \rho, \lambda \rangle = 0
\]

(5.35)

At this stage we have ultrametricity. If we choose any three states which are either in one bunch or in three separate bunches, then they are equidistant. If two are in one bunch and the third is in a separate one, then two distances are maximal (= 1) and one distance is less than 1.

The synaptic matrix is now

\[
T_{ij} = \frac{1}{N} \sum_{\mu=1}^{p} \xi_{\mu}^{\mu} \xi_{\nu}^{\mu} \left( 1 + \frac{1}{\Delta} \sum_{\nu=1}^{q_{\mu}} (\eta_{\mu}^{\nu} - a_{\mu})(\eta_{\nu}^{\nu} - a_{\mu}) \right)
\]

(5.36)

The properties of this network can be directly deduced from those of the simpler one described in the previous section.

- When \(\Delta = 1 - a^2\), the degeneracy between parents and descendants sets in. The storage capacity is the familiar \(\alpha \approx 0.15\), where \(\alpha\) refers to the total number of memorized pattern, i.e.

\[
\alpha N = p + \sum_{\mu=1}^{p} q_{\mu}
\]

(5.37)

All these states become attractors.

- If \(\Delta > 1 - a^2\) the degeneracy is lifted and the parents become lower in energy than the descendants.

- The total storage capacity remains the same, but the ancestors appear first, at higher loading levels, and then the detailed descendants become retrieval states at lower loading levels.

### 5.4 Deviations from ultrametricity

So far, we introduced sequences of pattern with an ultrametric structure as a result of a Markov process, inspired by the work of Parga and Virasoro (1986). However we can identify at least other two methods in constructing...
ultrametric spaces. The first one, which we will investigate here, is deduced from the paper of Rammal et al. (1986) and is based on the concept of indexed hierarchy. The second one, more general, is the construction made by Lerman (1981), which is based on a lattice of partitions of a set with finite number of elements. We will examine this approach in Section 5.5.

The goal of this section is threefold. First, we shall introduce some precise definitions relative to various concepts discussed in this section. Second, the notion of the subdominant ultrametric $d^*$ will be introduced and a simple method for its construction given. A measure of the deviation from exact ultrametricity is implied from the definition of $d^*$. The end of the section is devoted to illustrative examples.

**Basic definitions**

Let $E$ be a finite set. A hierarchy $\hat{H}$ on $E$ is a special set of partitions of $E$, $\hat{H}(E)$, such that

i) $E \in \hat{H}(E)$;

ii) each single element $a \in E$ belongs to $\hat{H}(E)$, i.e. the atoms of the partitions can be also single elements, (singleton);

iii) for each pair of partitions $r, r' \in \hat{H}$, such that $r \cap r' \neq 0 \Rightarrow r \subset r'$ or $r' \subset r$.

An indexed hierarchy on $E$ is a pair $\{\hat{H}, f\}$ where $\hat{H}$ is a given hierarchy on $E$ and $f$ is a positive function satisfying the following conditions

i) $f(a) = 0$ if and only if $a$ is a single element of $E$ (a singleton);

ii) if $a \subset a'$ then $f(a) < f(a')$.

$f$ corresponds to the index of the levels of the hierarchies introduced in the Markov chain approach.

In order to build up a hierarchy on a given set $E$, it is useful to introduce a dissimilarity index or aggregation index $\delta$, between the elements of $E$. For each pair of elements $(a, b)$ of $E$, $\delta(a, b)$ is a positive real number $\delta(a, b) \geq 0$ such that $\delta(a, b) = \delta(b, a)$. If $E$ is a metric space with a distance $d$, the index $\delta$ can be defined as the Hausdorff distance between two parts $a$ and $b$ in $E$:

$$\delta(a, b) = \min\{d(x, y) \mid x \in a, y \in b\} \quad (5.38)$$

In general, given $E$ and an aggregation index $\delta$, the construction of the corresponding hierarchy can be carried out through the search of a sequence
of partitions of $E$, starting with the finest partition and ending with the class $E$ containing all elements of the set $E$.

Hierarchies and ultrametrics

Note first that any given partition of the set $E : E = \bigcup_i E_i$ induces a large number of trivial ultrametrics: $d(x, x) = 0$, $d(x, y) = 1$ if $x \in E_i$, $y \in E_j$ ($i \neq j$), and $d(x, y) = a$ if $i = j$, $0 < a < 1$. The general connection between indexed hierarchies and ultrametrics, which is clearly visible on the classification trees, was rigorously proven by Benzécri (1980). This result states that there is a one-to-one correspondence between indexed hierarchies and ultrametrics both defined on the same set. Indeed, associated with each indexed hierarchy $\{\hat{H}(E), f\}$ on $E$ is the following ultrametric:

$$\sigma(x, y) = \min_{a \in \hat{H}(E)} \{f(a) \mid x \in a, y \in a\}$$

(5.39)

This means that the distance $\sigma(x, y)$ between two elements $x$ and $y$ in $E$ is given by the index of the smallest element in $\hat{H}(E)$, which contains both $x$ and $y$ (rule of the closest common ancestor).

The previous equivalence between the set $\mathcal{H}$ of indexed hierarchies and the set $\mathcal{U}$ of ultrametrics on $E$ leads to the natural question of how we find the best hierarchy on $E$. The answer is to optimize $\Delta(d, \delta)$ over the set $\mathcal{U}$ of ultrametrics where $\delta \in \mathcal{U}$ and $d$ is a given metric on $E$. Here $\Delta$ refers to a measure of adequacy between $d$ and $\delta$. Such an optimization problem is actually not very well defined, because of two intrinsic difficulties. The first originates in the choice of the adequacy measure $\Delta(d, \delta)$ and the second is that of the unicity of the optimized hierarchy. Among various proximity measures between two metrics $d$ and $\delta$, we choose the following

$$\Delta_0(d, \delta) = \max_{x, y \in E} |d(x, y) - \delta(x, y)|$$

(5.40)

Given a proximity measure $\Delta$, there is in general the possibility of two or more optimal hierarchies. Remarkably, a simple though partial solution to this degeneracy problem is provided by the notion of the subdominant ultrametric.

Subdominant ultrametric

Instead of considering the whole set $\mathcal{U}$ of ultrametrics on $E$, one limits the search for $\delta$ to

$$\mathcal{U}^s = \{\delta \in \mathcal{U} \mid \delta \leq d\}$$

(5.41)
which is the set of ultrametrics on $E$ which are lower than $d$ (i.e., $\delta$ is lower than $d$ if $\delta(x, y) \leq d(x, y)$ for all pairs $x, y$). The subdominant ultrametric $d^s$ is defined as the upper limit of $\mathcal{U}^s$. This is the maximal element in $\mathcal{U}^s$, and by definition

$$d^s(x, y) = \max \{ \delta(x, y) | \delta \in \mathcal{U}, \delta \leq d \} \quad (5.42)$$

This somewhat abstract definition of $d^s$ becomes clearer in terms of the associated optimization problem. If $\Delta(d, \delta)$ denotes a proximity measure, such as $\Delta_0$, then $d^s$ is the only solution that realizes the minimum of $\Delta(d, \delta)$. More precisely,

$$\Delta(d, d^s) = \min \{ \Delta(\delta, d) | \delta \in \mathcal{U}, \delta \leq d \} \quad (5.43)$$

In addition to its simplicity and remarkable properties, the subdominant ultrametric $d^s$ is actually very easy to obtain. Usually (Benzécri, 1980), the hierarchy $(\hat{H}(E), f)$ is constructed first and then $d^s$ is deduced from $\hat{H}$. For the sake of simplicity, we shall describe another equivalent method, giving directly the output $d^s$ from the input $d$. This is the minimum-spanning-tree construction method (Murtagh, 1983).

Because of the transparent interpretation of this method we shall outline the basic steps in this construction. The minimum-spanning-tree (MST) method can be readily described in graph theoretic terms. Associated with the metric space $(E, d)$, with a finite number of elements, is a simple, non-directed graph, with the elements of $E$ as vertices. The edge $(x, y)$ has a length equal to $d(x, y)$, and we will assume it as the “cost” of the edge. The main step in obtaining $d^s$ is the construction of a minimum spanning tree on the connected graph so obtained. Recall that the MST is a tree $A$, having the same vertices as $E$, but of minimal total length. We used the Prim’s algorithm (Prim, 1957) for contracting the MST. Prim’s algorithm works by attaching a new edge to a single growing tree at each step: start with any vertex as a single-vertex tree; then add the edges to it, always taking next the minimum-weight edge that connects a vertex on the tree to a vertex not yet on the tree. It is possible to see examples of this construction on Youtube [http://www.youtube.com/watch?v=YyLaRffCdk4](http://www.youtube.com/watch?v=YyLaRffCdk4), where the Prim’s algorithm is described visually. Note that $A$ is not uniquely defined, and more than one MST can be constructed on $E$. Despite this nonunicity of $A$, $d^s$ as obtained is unique. When there is a MST on $E$, the distance $d^s(x, y)$ between two elements $x$ and $y$ in $E$ is given by

$$d^s(x, y) = \max \{ d(w_i, w_{i+1}), i = 1, \ldots, n - 1 \} \quad (5.44)$$

where $\{(w_1, w_2), (w_2, w_3), \ldots, (w_{n-1}, w_n)\}$ denotes the unique chain in $A$, between $x$ and $y$ ($w_1 = x, w_n = y$). An illustrative example is shown in Figure 5.4 for a set $E$ of five elements.
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Figure 5.4 – An illustrative example of the construction of the subdominant ultrametric \( d^s \) (bottom) on the metric space \((E, d)\) of five elements, using the method of the minimum-spanning tree (MST).

Examples

As was shown before, given a finite metric space \((E, d)\), we can obtain from the subdominant ultrametric \( d^s \) a simple solution of the optimization problem posed in Section 5.4. Furthermore, \( d^s \) can readily provide clear information on the degree of ultrametricity of \((E, d)\). In particular, \( d^s \) provides an answer to the following question: how far is \( d \) from being an ultrametric? In other words, what is the “minimal distortion” of \( d \) in order to become an ultrametric? A possible answer is given by the comparison of \( d \) with \( d^s \). A measure of the proximity between \( d \) and \( d^s \) will be given by

\[
D = 1 - \frac{\sum_{x,y \in E} d^s(x, y)}{\sum_{x,y \in E} d(x, y)}
\]

where \( d \) denotes the input metric on \( E \), and \( d^s \) is the associated subdominant ultrametric. In general, \( 0 \leq D \leq 1 \), vanishes if \( d \) is already an ultrametric (i.e., \( d^s = d \)) and provides a quantitative measure of ultrametricity. Small values of \( D \) would indicate that \( d \) is not very far from being an ultrametric and inversely.

Example 1. A simple example where the MST construction is a trivial task is provided by \( E = \{x_1, \ldots, x_n\} \), where \( E \) denotes \( n \) points on the real line, and \( d(x_i, x_j) = |x_i - x_j| \) is the usual Euclidean metric. In the case where the points are the integers \( x_i = i \), then the MST is simply the set of edges going from \( x_i \) to \( x_{i+1} \) and it is easy to see that the subdominant ultrametric \( d^s \)
Chapter 5

reduces to the trivial ultrametric \( d^s(x_i, x_j) = 1 \): all triangles are equilateral. It can be shown that for large \( n \)

\[
D \simeq 1 - \frac{3}{n + 1} \sim 1
\]

(5.46)
in agreement with the simple intuition that Euclidean spaces are far from being ultrametric spaces.

**Example 2.** A less trivial example is given by the case where \( E \) is a set of \( P \) binary words, taken randomly from among the \( 2^N \) possible words, of \( N \) bits each. This is a subset of the \( N \)-dimensional hypercube, and the distance between two words

\[
\xi^1 = (\xi^1_1, \ldots, \xi^1_N), \quad \xi^2 = (\xi^2_1, \ldots, \xi^2_N)
\]

can be defined by the Hamming metric

\[
d(\xi^1, \xi^2) = \sum_{i=1}^{N} |\xi^1_i - \xi^2_i|
\]

(5.47)

It is clear that for \( P = 2^N \), \( d^s \) reduces to the trivial ultrametric and \( D_N(x = 1) = 1 - 2/N \sim 1 \) at large \( N \). Here \( x = P/2^N \) refers to the filling factor of the hypercube of all the configurations \( \{0, 1\}^N \). For fixed but large \( N \) numerical calculations show that \( D_N \) approaches zero as \( x \) goes to zero. This means that ultrametricity is actually a natural property of large spaces (if the hypercube of patterns is not filled, i.e. for sparse coding).

### 5.5 Space of partitions as an ultrametric space

In this section we will introduce a more general approach to the creation of ultrametric spaces, following the construction made by Lerman (1981). First, we will introduce the concept of lattice of partitions and then show how it is possible to construct an ultrametric space on it. This approach is more general than the construction of hierarchies described in Section 5.4.

**Basic definitions**

**Definition 1.** Let \( E \) be a finite set. A **partition** of \( E \) is a set of disjoint subsets of \( E \) such that their union is \( E \), the classes of the partition being the subsets.

Let us consider an example:

\[
E = \{a, b, c, d, e, f, g\}
\]
A partition of $E$ is
\[ \left\{ \{a, b, c, d\}, \{e, f\}, \{g\} \right\} \]
while the classes of the partitions are
\[ \{a, b, c, d\}, \{e, f\}, \{g\} \]

We will indicate with $\hat{P}(E)$ the set of the partitions of $E$, $P$ being a
 generic partition.

It is possible to define an equivalence relation in $E$ using the concept of
partition.

**Definition 2.** Two elements of $E$ are *equivalent* if they belong to the same
class of the partition $P$.

The graph of an equivalence relation induced by $P$ (Figure 5.5) is indicated with $\text{Gr}(P)$,
\[ \text{Gr}(P) = \{(x, y) \mid x \in E, y \in E \text{ and } xPy\} \quad (5.48) \]

$\text{Gr}(P)$ is a subset of $E \times E$. This inclusion allow us to define an ordering in
$\hat{P}$.

![Figure 5.5 – A simple example of a graph of the partition $\left\{ \{a, b, c, d\}, \{e, f\}, \{g\} \right\}$](image)

**Definition 3.** $P < P'$ if $\text{Gr}(P) < \text{Gr}(P')$ or if, $\forall x, y \in E$, $xPy \implies xP'y$.

For example the partition
\[ \left\{ \{a, b, c, d\}, \{e, f\}, \{g\} \right\} \]
is smaller than the partition
\[ \{\{a, b, c, d\}, \{e, f, g\}\} \]

In this way \( \hat{P}(E) \) is an ordered set with the structure of a lattice in the sense that for any pair of partitions there is a “greatest smaller” partition \( P \land P' \) and a “smallest greater” partition \( P \lor P' \).

The partition \( P \land P' \) is defined by its graph
\[ \text{Gr}(P \land P') = \text{Gr}(P) \land \text{Gr}(P') \quad (5.49) \]
x\( (P \land P')y \) if and only if \( xPy \) and \( xP'y \). On the other hand, \( \text{Gr}(P \lor P') \) is the smallest graph containing the set \( \text{Gr}(P) \) or \( \text{Gr}(P') \).

**Example 3.** Consider the same partition \( P \) introduced before and a new one \( P' \):

\[ P = \{\{a, b, c, d\}, \{e, f\}, \{g\}\} \]
\[ P' = \{\{a\}, \{c, d\}, \{e, f, g\}\} \]
\[ P \land P' = \{\{a\}, \{c, d\}, \{e, f\}, \{g\}\} \]
\[ P \lor P' = \{\{a, b, c, d\}, \{e, f, g\}\} \]

The lattice \( \hat{P}(E) \) depends only on the number \( n \) of elements of \( E \) and for sake of simplicity in what follows we will denote it with \( \hat{P} \). In this example the classes of the smallest partition of \( \hat{P} \) are the single elements of \( E \), the largest is the set \( \{a, b, c, d\} \). We show in Figure 5.6 the example of lattice constructed starting from this set of four elements.

**Chain of partitions and ultrametric spaces**

**Definition 4.** Let \((E, d)\) be a metric space with a finite number of elements. A divisor of \( E \) is an equivalence relation \( D \) in \( E \) such that
\[ \forall a, b, x, y \in E \quad aDb \quad \text{and} \quad d(x, y) \leq d(a, b) \Rightarrow xDy \quad (5.50) \]

We can associate to each sequence of increasing lattices of partitions of \( E, \hat{P}(E) \), an ultrametric space. That is, if we consider a finite sequence of partitions of \( E, P_i \), with \( P_i < P_{i+1} \), these partitions decrease their fineness as \( i \) increase.

We define the distance function \( d(x, y) : E \times E \to I \subset \mathbb{N} \) as the smallest \( i \) such that \( x, y \) belong to the same class \( P_i \). \( I \) is a finite set of integers. Thus defined, \( d \) has the following property.
Proposition 1. $d$ is an ultrametric distance on $E$ such that the divisors are the $P_i$. The inverse also holds.

The relations among the various classes of the partitions and the elements of these classes are described in general terms which we have to define for the sake of clarity. For any two objects in the finite space $E$ we have defined a distance among them. Based on this definition, we introduce some general binary relations among the pairs.

i) a binary relation on $E$ is a preorder if it is reflexive and transitive;

ii) a binary relation on $E$ is an equivalence relation if it is reflexive, transitive and symmetric;

iii) a binary relation on $E$ is an order if it is reflexive, transitive and anti-symmetric;

iv) a binary relation is called total if it holds for all the pairs $(i, j) \in E \times E$, or partial otherwise.

A preorder can be associated to a set of partitions organized in a lattice $\hat{P}(E)$. Let $F$ be the set of all pairs of elements in $E$. The distance $d$ defines a total preorder in $F$:

$$\forall \{(x, y), (z, t)\} \in F : (x, y) \leq (z, t) \iff d(x, y) \leq d(z, t) \quad (5.51)$$

The preorder is indicated with $\omega$. Two distances on a given set $E$ are equivalent if the preorderings associated with each of them on $E$ are identical. A total preorder is equivalent to a partition which defines an equivalence relation on $F$, and to a total order on the set of classes.
Definition 5. A preorder $\omega$ is called ultrametric if

$$\forall x, y, z \in E: \rho(x, y) \leq r, \rho(y, z) \leq r \implies \rho(x, z) \leq r$$

$\rho(x, y)$ is the rank of the pair, for $\omega$ defined by the non-decreasing values of the distance $d$ in $E$.

We have the following link among the ultrametric preordering, which in turn is connected with the sequence of partitions, and the ultrametricity of the distance $d$.

Proposition 2. A necessary and sufficient condition for a distance $d$ to be ultrametric is that the associated preordering is ultrametric.

Difference between preorder and ultrametric preorder

Given a metric space $(E, d)$ a natural question arises, that is if this space is also ultrametric. In general the answer is no, but what is interesting to know is how much such a metric space differs from an ultrametric space. We recall that a necessary and sufficient condition for a distance $d$, defined on $E$, to be ultrametric is that all the triangles are isosceles, the basis being the smallest side. This condition can be reformulated by means of the above definition of the preordering $\omega$. We say that $\omega$ is ultrametric if for any three elements $(x, y, z)$ of $E$ such that

$$(x, y) \leq (y, z) \leq (x, z)$$

it happens that

$$(x, z) \leq (y, z)$$

in other terms, if $(x, z)$ and $(y, z)$ are in the same class of the preorder $\omega$.

It is possible to introduce a quantity which measures the degree of ultrametricity starting from these definitions. Let $J$ be the set of all the triplets $(x, y, z)$ of elements of $E$. Consider the application $\tau$ of $J$ in $F$ that, given $(x, y, z)$ and the preorder $\omega$, associates to them the open interval $[M(x, y, z), S(x, y, z)]$, which are respectively the median and the maximum among the three couples $(x, y), (y, z)$ and $(z, x)$.

We just say that a triplet $(x, y, z)$ for which $(x, y) \leq (y, z) \leq (x, z)$, given the preordering $\omega$, is such that the interval $[(y, z), (x, z)]$ is empty if $\omega$ is ultrametric. Considering such a triplet, the preorder $\omega$ is less and less ultrametric as the cardinality of $[(y, z), (x, z)]$ becomes bigger. To take into account the set $J$ of all the triplets, we may adopt as a measure of the discrepancy between $\omega$ and an ultrametric preorder:

$$HC(\omega) = \sum_J ||M(x, y, z), S(x, y, z)|| = \sum_J \Lambda(x, y, z) \quad (5.52)$$

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where \( \Lambda(x, y, z) \) is the cardinality of \( |M(x, y, z), S(x, y, z)| \). To make the statistic of \( H(\omega) \) independent from the cardinality of \( E \), we normalize it with number of the triples \( |J| \) and with the number of the pairs \( |F| \). So the measure of the discrepancy becomes

\[
H(\omega) = \frac{HC(\omega)}{|F||J|} = \frac{1}{|J|} \sum_{J} \frac{|M(x, y, z), S(x, y, z)|}{|F|}
\]

(5.53)

**Example 4.** Let \( E = \{a, b, c, d, e\} \), and \( \omega \) the preorder on \( E \)

\[
\{a, d\} < \{a, c\} < \{a, e\} < \{b, d\} = \{c, d\} < \{b, c\} < \{d, e\} < \{a, b\} < \{b, e\}
\]

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Table 5.1 – Calculating the Lerman index \( H(\omega) \) in the case of Example 4. On each row, a “•” indicates the pairs contained in the triple and a “×” the pairs which are strictly between the median and the maximum.

In Table 5.1 we reported on the rows the set of the triples \( J \) and on the columns the set of the pairs \( F \). On each row, a “•” indicates the pairs contained in the triple and a “×” the pairs which are strictly between the median and the maximum. If there are no crosses the median and the maximum are in the same class and the preordering is ultrametric, hence \( H(\omega) = 0 \). Summing the number of crosses for the pairs which are strictly included between some median and maximum one obtains a quantitative measure of the deviation of \((E, \omega)\) from the ultrametric preordering.

\( H(\omega) \) is a more reliable measure of the deviation from ultrametricity than the distortion index of the subdominant metric introduced in Section 5.4 because the subdominant metric can be very different from the metric \( d \).

To sum up, we introduced \( H(\omega) \) as a measure on the space \( F \), counting the number of pairs in \( F \) which are strictly included in the interval \( |M(x, y, z), S(x, y, z)| \). Given any pair \( p \in F \), we define the subset \( J_p \) of \( J \)
such that, for any triple \( \{x, y, z\} \in J_p \), \( p \) is strictly included in the interval \( ]M(x, y, z), S(x, y, z) [ \):

\[
M(x, y, z) < p < S(x, y, z)
\]

It is then possible to define a measure \( m_p \) on the space of pairs \( F \) such that for any \( p \in F \)

\[
m_p = \frac{|J_p|}{|J|}
\]

(5.54)

For any preorder \( \omega \) we can then define the vector \( D(\omega) \) as the set of \( m_p, p \in F \). If the preorder is ultrametric this vector has all the components equal to 0. Thus the number of components of \( D(\omega) \) which are different from zero (and also the values of these components) are a measure of the deviation from ultrametricity. Regarding the Example 4, we have that

\[
H(\omega) = \frac{13}{10 \times 10}
\]

\[
D(\omega) = (0.3, 0.3, 0.2, 0.2, 0.1, 0.1, 0.1, 0, 0, \ldots)
\]

For large \( n \), the number of elements of \( E \), and for a large sample \( Q \) of sets of triples \( J \) (obtained by generating the triples with uniform probability), we have that \( H(\omega) \) has a gaussian distribution since is the sum of independent, uniformly distributed random variables:

\[
H'(\omega) = \frac{1}{|Q|} \sum_{\{x,y,z\} \in Q} \Lambda(x, y, z)
\]

(5.55)

For the sake of clarity, consider a further example, this time based on patterns constructed with the Markov process described in Section 5.3. We will show a direct comparison of the two methods of calculating the deviation from ultrametricity, the one described in Section 5.4 (the Rammal index) and the one of Section 5.5, \( H(\omega) \).

Consider a set of 6 patterns, organized in a tree with 2 ancestors and 2 descendants for each ancestor. We construct a graph in which each vertex is a pattern, the edge between the vertices being the Hamming distance between the patterns. We then choose at random a starting vertex, and construct the minimum-spanning tree with the Prim’s algorithm.

We define the subdominant ultrametric with Eq. 5.44, and by a comparison between it and the standard metric (Eq. 5.45) we calculate the Rammal index.

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Minimum-spanning-tree

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Deviation from ultrametricity (Rammal index): 0.00788955

We then construct the preorder, based on the the distances of the MST. In Table 5.2 we show the results of this calculation. As we can see, there are no values that are strictly included in the interval \([M(x, y, z), S(x, y, z)]\) (there are no crosses in the table). Thus, \(H(\omega) = 0\), i.e. the space is already ultrametric.

Preorder \(\omega\)

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Deviation from ultrametricity (Lerman’s \(H(\omega)\)): 0
Table 5.2 – Calculating $H$ in the neuronal case. We indicate with a “–” the lack of values in the interval $[(x, y, z)]$. (z = H(x, y, z))

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$\text{Interval } [(x, y, z)]$
Part III

An associative memory model of hippocampus
The hippocampal regions CA3 and CA1 have long been proposed to be auto- and heteroassociative memories, respectively (Treves and Rolls, 1994), for the storage of declarative information. An autoassociative memory is formed when a set of neurons are recurrently connected by modifiable synapses, whereas a heteroassociative memory is formed through modifiable connections from an input layer of neurons to an output layer. Associative memory storage simply requires a Hebbian strengthening of connections between neurons that are coactive (Amit, 1989; Hopfield, 1982). Recall proceeds from a cue activity pattern across neurons that is a partial or noisy version of a previously stored pattern. A suitable firing threshold on each neuron that receives input from already active neurons ensures that neural activity evolves towards the stored pattern. This may happen with only one or two updates of each neuron’s activity. Accurate recall is obtainable provided not too many patterns have been stored, otherwise recall is poor, or even impossible.

Network models of spiking neurons can be used to explore the dynamics of storage and recall in such memory networks. Here we introduce a feedforward network model for CA1 area. Cells are simplified compartmental models with complex ion channel dynamics. In addition to pyramidal cells, one or more types of interneuron are present. We investigate, in particular, the roles of these interneurons in setting the appropriate threshold for memory recall.
6.1 Associative memory and the hippocampus

Pyramidal cells within CA3 form sufficient recurrent connections between themselves that they can putatively operate as an associative memory network. Patterns of pyramidal cell (PC) activity may largely be determined by mossy fibre inputs from the dentate gyrus (Figure 6.1). Such patterns are stored autoassociatively by Hebbian modification of recurrent connections between CA3 PCs (Treves and Rolls, 1994). Patterns of CA1 PC activity may be determined by direct afferent input from the entorhinal cortex (Figure 6.1). Temporal correspondence between these patterns and patterns of activity in CA3 PCs results in their heteroassociation in CA1 by modification of CA3 Schaffer collateral synapses onto active CA1 PCs (Hasselmo et al., 2002a).

Figure 6.1 – Associative memory in the hippocampus. Mossy fibre (MF) inputs from the dentate gyrus create pyramidal cell (PC) activity in CA3 that is stored autoassociatively by Hebbian modification of recurrent collateral synapses between coactive PCs. Patterns of activity in layer II of entorhinal cortex (EC II) may be heteroassociated with these CA3 patterns. At the same time, CA1 PCs receiving input both from layer III of entorhinal cortex and from CA3 PCs form a heterassociation with the active CA3 PCs through Hebbian modification of the Schaffer collateral synapses.

Gamma frequency rhythms (30–100 Hz) are assumed to constitute a basic clock cycle such that patterns of activity for storage and recall correspond to PCs that are active in a particular gamma cycle. The slower theta rhythm (4–10 Hz) is assumed to modulate episodes of storage of new information and recall of old information in its half cycles (Hasselmo et al., 2002a,b). During exploration an animal is likely to encounter both familiar and novel situations. Storage of new episodes with minimal interference from already encoded episodes takes place most efficiently if storage and recall are temporally separated in the encoding neural networks (Wallenstein and Hasselmo, 1997). Waxing and waning of GABA-mediated inhibition from the medial septum lead alternately to disinhibition and inhibition of PCs during a theta cycle, corresponding to ideal conditions for pattern recall and pattern storage, respectively.
6.2 The CA1 network

The principal excitatory cells of the CA1 region are pyramidal cells. These cells are driven by excitatory inputs from layer III of the entorhinal cortex and the CA3 Schaffer collaterals and an inhibitory input from the medial septum. Recurrent connectivity between pyramidal cells is negligible in CA1 (less than 1%). We construct a feedforward neural network model consisting of 100 pyramidal cells (PC) and four types of inhibitory interneurons: 2 basket cells (BC), 1 bistratified cell (BSC), 1 axo-axonic cell (AAC) and 1 oriens lacunosum-moleculare (OLM) cell (see Figure 6.2).

All cell morphologies included a soma, apical and basal dendrites and a portion of axon. The biophysical properties of each cell were adapted from cell types reported in literature (Bianchi et al., 2012; Poirazi et al., 2003a,b; Saraga et al., 2003; Santhakumar et al., 2005). The complete mathematical formalism of the model is described in Appendix A.

Each kind of interneuron has a specific function in modulating not only the overall network functions, but also the I/O properties of the principal neurons (the CA1 pyramidal neurons) and, especially, the synaptic plasticity.
processes leading to memory storage. For the OLM, BC, BSC and AAC the models defined for the networks of Cutsuridis et al. (2010) are employed. The CA1 model employed, instead, has the same morphology of the CA1 template used by Cutsuridis et al. but different distributions of the ionic currents (Bianchi et al., 2012). A schematic representation of the model cells is depicted in Figure 6.3.

The relative cell proportions and connectivity of the network is consistent with previous implementation of similar networks (Hasselmo et al., 2002a; Cutsuridis et al., 2010).

All simulations were performed using NEURON (version 7.3, Hines and Carnevale (1997)) running on a cluster of 8 nodes with MPI (Message Passing Interface).

Figure 6.3 - Compartmental structure models for the different cell types. LM-t: lacunosum moleculare thin compartment; LM-M: lacunosum moleculare medium compartment; LM-T: lacunosum moleculare thick compartment; OriProx: oriens-proximal compartment; OriMed: oriens medial compartment; OriDist: oriens distal compartment; RadProx: radiatum proximal compartment; RadMed: radiatum medial compartment; RadDist: radiatum distal compartment; Dend: basal OLM cell compartment.

Synaptic properties

In the model, AMPA, NMDA, GABA\textsubscript{A} and GABA\textsubscript{B} synapses are considered. GABA\textsubscript{A} is present in all strata, whereas GABA\textsubscript{B} is present in medium and distal SR and SLM dendrites. AMPA synapses are present in strata LM (EC connections) and radiatum (CA3 connections), whereas NMDA are present only in stratum radiatum (CA3 connections).

Model inputs

Inputs to the CA1 model come from the medial septum (MS), entorhinal cortex (EC) and CA3 Schaffer collaterals. The EC input is modelled as
the firing of 20 entorhinal cortical cells at an average gamma frequency of 40 Hz (spike trains only modelled and not the explicit cells), and the CA3 input is modelled with the same gamma frequency spiking of 20 out of 100 CA3 pyramidal cells (see Appendix A for details). PCs, BCs, AACs, BSCs received CA3 input in their medial SR dendrites, whereas PCs, BCs and AACs received also the EC layer III input in their apical LM dendrites. EC inputs preceded CA3 inputs by 9 ms on average, in accord with experimental data showing that the conduction latency of the EC-layer III input to CA1 LM dendrites is less than 9 ms (ranging between 5 and 8 ms), whereas the conduction latency of EC-layer II input to CA1 radiatum dendrites via the di/tri-synaptic path is greater than 9 ms (ranging between 12 and 18 ms) (Soleng et al., 2003). MS input, which is modelled as the rhythmic firing of 10 septal cells (see Appendix A for details), provides GABA_A inhibition to all interneurons in the model (strongest to BC and AAC; Freund and Antal (1988)). MS input is phasic at theta rhythm and is on for 125 ms during the retrieval phase.

**Presynaptic GABA_B inhibition**

It has been shown that the strengths of the synaptic inputs from the EC perforant path and the CA3 Schaffer collaterals wax and wane according to the extracellular theta rhythm and 180° out of phase from each other (Wyble et al., 2000). These cyclical theta changes are likely due to the presynaptic GABA_B inhibition to CA3 Schaffer collateral input to CA1 PCs’ synapses, which is active during the storage cycle and inactive during recall (Molyneaux and Hasselmo, 2002). This is modelled simply as a reductive scaling during storage of the CA3-AMPA synaptic conductance, so that the effective conductance \( g' \) is

\[
g' = g_s \cdot g
\]

where \( g_s \) is the scaling factor (set to 0.4 in the presented simulations). During recall, \( g' \) is simply equal to \( g \) (the AMPA conductance determined by the connectivity weight matrix).

**6.3 Neurons architecture**

**Pyramidal cells**

Each P cell had 15 compartments, each containing a transient Na\(^+\) current, potassium K-DR, K\(_A\), and K\(_M\) currents, non-specific I\(_h\) current, three main types of calcium currents (CaT, CaN, and CaL), their related slow and fast Ca\(^{2+}\)-dependent K\(^+\) currents (K\(_{AHP}\) and K\(_C\)), and a calcium extrusion mechanism. The K-DR and Na\(^+\) currents are modeled, following the results
of Bianchi et al. (2012), to reproduce the depolarization block. The calcium currents are distributed according to the experimental findings Magee and Johnston (1995), the $K_A$ and $I_h$ increase linearly with distance from the soma (Hoffman et al., 1997; Magee, 1998) and the $K_{AHP}$ and $K_C$ currents are equally distributed. The peak conductances of the ionic currents were adjusted to qualitatively reproduce specific experimental findings on control and increased CREB conditions.

Each P cell’s soma rested in the stratum pyramidale (SP), while its dendrites extended across the strata from stratum oriens (SO) to striatum radiatum (SR) and stratum lacunosum-moleculare (SLM). Each pyramidal cell received somatic synaptic inhibition from the basket cells, mid-dendritic excitation from CA3, distal apical excitation from the entorhinal cortex (EC), proximal excitation from around 1% of other pyramidal cells in the network (recurrent collaterals) (Amaral and Lavenex, 2007; Andersen et al., 2007), axonic inhibition from the axoaxonic cell, spatially-distributed (six contacts) mid-dendritic synaptic inhibition from the bistratified cells population, and distal synaptic inhibition on each SLM dendritic branch from the OLM cell.

Axo-axonic cells

Each AA cell had 17 compartments, which included a leak conductance, a sodium current, a fast delayed rectifier $K^+$ current, an A-type $K^+$ current, L- and N-type $Ca^{2+}$ currents, a $Ca^{2+}$-dependent $K^+$ current and a $Ca^{2+}$- and voltage-dependent $K^+$ current (Santhakumar et al., 2005). As with the P cells in the network, each AA’s cell body rested primarily in the SP, while its dendrites extended across the strata from SO to SR and SLM.

Axo-axonic cells received excitatory inputs from the EC perforant path to their SLM dendrites and excitatory inputs from the CA3 Schaffer collateral to their SR dendrites. In addition, the axo-axonic cells received inputs from active CA1 pyramidal cells in their SR medium and thick dendritic compartments as well as inhibitory input from the septum in their SO thick dendritic compartments (Andersen et al., 2007).

Basket cells

Each B cell had 17 compartments, containing a leak conductance, a sodium current, a fast delayed rectifier $K^+$ current, an A-type $K^+$ current, L- and N-type $Ca^{2+}$ currents, a $Ca^{2+}$-dependent $K^+$ current and a $Ca^{2+}$- and voltage-dependent $K^+$ current. As before, all B cells’ somas rested in SP, whereas their dendrites extended from SO to SLM.
Introducing the model

All B cells received excitatory connections from the EC to their distal SLM dendrites, from the CA3 Schaffer collaterals to their medium SR dendrites and from active pyramidal cells to their medium and thick SR dendritic compartments and inhibitory connections from neighboring B and BS cells in their soma (Freund and Buzsáki, 1996) and from the medial septum in their SO thick dendritic compartments.

Bistratified cells

Each BS cell had 13 compartments, which included the same ionic currents as the B and AA cells. All BS cells’ somas rested in the SR, whereas their dendrites extended from SO to SR.

All BS cells received excitatory connections from the CA3 Schaffer collaterals in their medium SR dendritic compartments and from the active pyramidal cells in their thick SO dendritic compartments and inhibitory connections from the medial septum in their thick SO dendritic compartments and from neighboring B cells in their somas.

OLM cells

Each OLM cell had four compartments, which included a sodium (Na+) current, a delayed rectifier K+ current, an A-type K+ current, and an h-current (Saraga et al., 2003). Each OLM cell’s soma and basal dendrites rested in SP, whereas its axon extended from SP to SLM.

Each OLM cell received excitatory connections from the active pyramidal cells in their basal dendrites as well as inhibitory connections from the medial septum in their soma.

6.4 Synaptic plasticity

In this work, the synaptic weights evolve with a Spike-Timing-Dependent Plasticity (STDP) rule, according to which long-term synaptic plasticity critically depends on the relative timing of pre- and postsynaptic activity in the millisecond range. In principle, all kinds of synapses should follow specific synaptic plasticity rules, undergoing LTP or long term depression (LTD) according to the local pre- and post-synaptic activity. However, there is not enough experimental evidence to constrain the plasticity rules for all types of synapses used in the network. We have thus initially implemented synaptic plasticity only for the CA3 inputs on CA1, fixing all the other peak synaptic conductances to values consistent with experimental observations.
Interestingly, the rules for STDP vary widely within brain region, cell, and synapse type. During storage we have applied a STDP learning rule specific for hippocampus, based on the experimental findings by Nishiyama et al. (2000). Therefore, the induction of LTP or LTD (i.e. the change of the peak synaptic conductance) is determined by the correlation of the pre- and post-synaptic activation as follows:

\[ g_p(t) = g_p^0 + A(t) \]  \hspace{1cm} (6.2)

with

\[ A(t) = \begin{cases} 
A(t-1) \left(1 - d \frac{e^{-(\Delta t - M)^2/2V^2}}{\sqrt{2\pi}} \right) & \text{if } \Delta t < 0 \\
A(t-1) + (\overline{g}_p - g_p^0 - A(t-1)) e^{-\Delta t/\tau} & \text{if } \Delta t > 0 
\end{cases} \]  \hspace{1cm} (6.3)

where \( \Delta t = t_{\text{post}} - t_{\text{pre}} \). \( A \) is always \( \geq 0 \) and represents the degree of potentiation. The constants \( M = -22 \text{ ms} \), \( V = 5 \text{ ms} \), \( \tau = 10 \text{ ms} \) reproduce the critical time window found by Nishiyama et al. (2000). \( g_p^0 \) denotes the initial peak conductance and \( \overline{g}_p \) its maximum value. The parameters \( p \) and \( d \) are chosen in such way that, during a time span of 16 s, the potentiated and depressed values for the peak synaptic conductance are consistent with experimental findings (Nishiyama et al., 2000).

6.5 Storage and recall mechanism

Hasselmo et al. (2002a,b) have hypothesized that the hippocampal theta rhythm (4–7 Hz) can contribute to memory formation by separating encoding and retrieval of memories into different functional half-cycles. Recent experimental evidence has shown that different types of inhibitory interneurons fire at different phases of the theta rhythm (Klausberger et al., 2004; Somogyi and Klausberger, 2005; Klausberger and Somogyi, 2008).

Storage cycle

During the storage cycle of the theta (Figure 6.4a), we propose the following: an EC input pattern arrives at the apical SLM dendrites of the B, AA and P cells at time \( t_i \), whereas an indirect CA3 input pattern via the di/trisynaptic loop arrives at the medium SR dendrites of the B, AA, BS and P cells at time \( t_i + \Delta t \) (mean \( \Delta t = 9 \text{ ms} \)). In the B and AA cells, the EC input is strong enough to induce an action potential in their soma. Furthermore, the GABAergic cell population of the medial septum is minimally active and therefore transmits the least amount of inhibition to the CA1 inhibitory interneurons. These active CA1 inhibitory cells are free to do
Introducing the model

Figure 6.4 – Active network pathways during (A) storage cycle and (B) recall cycle. Only black solid lined cells and pathways are active in each cycle. Numbers above and next to pathways indicate the temporal order of information processing during each cycle.
several things. First, the axo-axonic and basket cells exert tight inhibitory control on the axons and somas of the pyramidal cells, thus, preventing them from firing during the storage cycle. Second, the basket cells exert powerful inhibitory control to neighboring basket cells and bistratified cells, which prevents the latter from firing during the storage cycle. The bistratified cells are thus 180° out-of-phase with the basket and axo-axonic cells.

Since place cells in CA1 were found to be maintained solely by direct input from EC and CA, we infer that the CA3 input to P cells provides the contextual information (e.g., familiarity of environment), whereas the EC input to P cells provides the sensory information (e.g., current location). Since there is no topography in CA1 (Amaral and Lavenex, 2007), during the storage cycle, 20% of the P cells in the network are randomly selected to receive the EC input pattern in their apical SLM dendrites. The summed postsynaptic potentials (PSP) generated in the SLM dendrites are attenuated on their way to the soma and axon, but if coinciding with CA3 input, provide a sufficient depolarized potential in the SR dendrites to drive STDP (Stuart and Spruston, 1998).

The B and AA cell mediated inhibition prevents the PSP from causing P cell firing. This inhibition also hyperpolarizes the P cell soma, axon and proximal dendrites of those P cells that do not receive the EC input, preventing them from participating in STDP.

In contrast to the EC input, all P cells in the network are activated by the CA3 input in their medial SR dendrites. The relative timing between the incoming CA3 Schaffer collateral spike and the EC PSP in the SR dendrites will induce LTP or LTD via a local STDP rule (see Section 6.4). The amplitude of the CA3 input is reduced (putatively by presynaptic GABA_B inhibition), hence, P cells not receiving EC input should not exhibit CA3 synaptic plasticity as no depolarizing postsynaptic signal is generated.

**Recall cycle**

The recall cycle (Figure 6.4b) begins as the presynaptic GABA_B inhibition to CA3 Schaffer collateral input to P cell synapses declines and GABAergic cells of the septum approach maximum activity. Because of this septal input, the basket and axo-axonic cells are now inhibited, releasing pyramidal cells, bistratified cells and OLM cells from inhibition. Pyramidal cells may now fire more easily, thus, allowing previously learned patterns to be recalled.

During the recall cycle, the CA3 Schaffer collateral input plays the role of a cueing mechanism. If the CA3 input excited a pyramidal cell during this time, any synapses that were strengthened during the storage cycle will
be activated, recalling the memory. Because the CA3 input is directed to all P cells, which potentially activates unwanted P cells and hence spurious memories are recalled, the role of the bistratified cells is to ensure that these spurious cells will be silenced by broadcasting a nonspecific inhibitory signal to all P cells in the network.

As it has been suggested by Hasselmo et al. (2002a), during recall the entorhinal cortical input provides a weak background excitation to the CA1 region that aids the recall process, causing depolarized cells to fire. However, this excitation can potentially give rise to unwanted or similar memories.

In our model, P cells, after being released by the basket and axo-axonic cell inhibition, excite the OLM cells. This excitation was assumed strong enough to overcome the OLM septal inhibition. In return, the OLM cells strongly inhibit the distal SLM dendrites of the P cells (Freund and Buzsáki, 1996), where the direct entorhinal input arrives, thus, preventing unwanted memories from being recalled.

### 6.6 Recall quality

The input and output patterns are binary sequences indicating the state of activity (firing/quiescent) of each neuron. After supplying an input pattern with $nP$ active neurons for storage, the quality of the recall (ranging from 0 to 1) is measured by its correlation with the output pattern, calculated as the normalized dot product:

$$q(P, P') = \frac{\sum_{i=1}^{N} P_i \cdot P'_i}{\sqrt{\sum_{i=1}^{N} \sum_{j=1}^{N} P_i \cdot P'_j}}$$  \hspace{1cm} (6.4)

where $P$ is the input pattern, $P'$ the output pattern and $N$ the total number of CA1 neurons.

In general, a higher quality reflects a better recall. To be more precise, $q = 1$ indicates that the input and output patterns are the same, while $q = 0$ indicates either that the output has no active CA1s in common with the input, or that all cell are quiescent. A pattern was considered correctly recalled if its recall quality $q$ was above a threshold $Th$. This value corresponds to the quality of the recall of an output pattern in which all neurons are active. For our network ($N = 100, nP = 20$), $Th = \frac{20}{\sqrt{20 \times 100}} = 0.4472$. 

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7.1 Storage and recall performance

Now, we consider the storage and recall of new patterns via the STDP learning rule. In the model, storage and recall of memories is separated into two functional subcycles of each theta cycle. The duration of a theta cycle was set to 250 ms (125 ms for storage and 125 ms for recall). Pattern presentation occurs at gamma frequency throughout theta, as described above.

The EC and CA3 inputs correspond to the output and input patterns, respectively, that are associated by modifying the CA3 AMPA synapses on the SR dendrites of CA1 PCs. EC input to PCs summing with CA3 input, provides the postsynaptic signal which is compared with the presynaptic spike times of CA3 inputs in the SR dendrites to drive the STDP learning rule. If the postsynaptic signal occurs a suitably short time after a presynaptic spike, the corresponding synapse is strengthened. If the signal is just before the presynaptic spike, the synapse is weakened.

To test pure recall by the CA3 input cue, in the following results the EC input is disconnected from the CA1 PCs.

The recall of one pattern in a set of five is shown in Figure 7.1. Figure 7.1a shows a raster plot of the spiking of the septal (top 10 rows), EC (next 20 rows) and CA3 (next 100 rows) inputs. The firing of the interneurons (bottom 5 rows) is also shown. The CA1 PCs spiking activity (Figure 7.1b) could be compared to stored pattern (depicted in red). Ten recall cycles are shown, following an initialization period of 100 ms.

Recall performance is calculated by measuring the CA1 PC spiking activity during a sliding 5 ms time window. For each window a binary vector
Chapter 7

(a) Input spikes

(b) Pyramidal cell spikes

(c) Recall quality

Figure 7.1  Example of pattern recall in CA1. The CA3 input is cueing a pattern (in red) in a stored set of five. EC input is present to drive the inhibitory interneurons, but is disconnected from the CA1 PCs, so that recall is purely due to the CA3 input cue. Ten 125 ms recall half-cycles are shown (the light blue areas), starting at 100 ms (interspersed with 125 ms storage half-cycles, but STDP is turned off). A Raster plot showing the septal (top 10), EC (next 20), CA3 (next 100) and interneurons (bottom 5) spikes. B Raster plot showing CA1 PC activity – virtually the only active cells are those belonging to the stored pattern. C Recall quality.

of length 100 is formed, with entries having a value of 1 if the corresponding PC spikes in the window. The correlation (normalized dot product, Eq. 6.4) of this vector with the expected pattern vector is calculated to give a measure of recall quality between 0 and 1, with 1 corresponding to perfect recall. Figure 7.1c shows recall quality over time.

When CA1 PC spiking occurs, always the first PCs to fire are the ones belonging to the stored pattern, and quality goes to one. This is sometimes quickly followed by the firing of a few spurious PCs and the quality drops (see the recall event at 1663 ms). Most recall events in this example are perfect and the recall quality averages at 0.95. Figure 7.2 shows voltage traces from a CA1 PC that belongs to the pattern, plus each of the four classes of interneuron. The phase relationships of the interneuron firing can be seen.
The effects of increased CREB activity on the processes of pattern storage and retrieval in a hippocampal CA1 neuron network have already been investigated by Bianchi et al. (2013), and for this work we adopted their model. Experimentally, it has been shown that CA1 neurons become more excitable when higher CREB levels are present (de Armentia et al., 2007; Dong et al., 2006). Among other results, they found that the over-expression of a constitutively active form of CREB increased neuronal excitability and inhibited slow and medium potassium currents responsible for after-hyperpolarization currents. The effect of CREB was modeled by decreasing the peak conductance of after-hyperpolarizing currents by the same proportion found by de Armentia et al. (2007), i.e. 52% for mAHP current and 64% for sAHP current.

The effect of CREB involves not only the excitability of the neuron but also the magnitude of LTP. Actually, Marie et al. have found out that increasing CREB function leads to both an enhancement of NMDA receptor-mediated synaptic responses and to an increase in the magnitude of AMPA receptor-mediated LTP, compared to the control neurons. More specifically, the increase in the AMPA receptor-mediated Excitatory Post-Synaptic Currents (EPSCs) after LTP induction were larger after CREB activation than in control neurons (by 266% in CREB case, by 164% in control case). We therefore also took into account this result in our model. In summary, dur-
ing a storage cycle we simulate the control case by setting $g_p = 1.64 \cdot g_p^0$, while the CREB case is obtained with

- decreasing the peak conductances of mAHP and sAHP currents by 52% and by 64%, respectively;
- setting $g_p = 2.66 \cdot g_p^0$.

In all simulations, we used $g_p^0 = 0.45 \text{ nS}$. This value was chosen in such a way as not to have spurious spikes during the random background activity.

Bianchi et al. showed that 25 seconds of simulation time, i.e. 100 theta cycles, was enough to allow the synaptic weights to reach an equilibrium value. In Figure 7.3, we show typical results for a few synaptic weights during a simulation. In about 16s, the conductance peaks reach a maximum value (as in the experimental protocol of Nishiyama et al. (2000)) and, for the remaining time, they oscillate within the same range. Although the qualitative time course of the weights is the same under control and CREB conditions, the higher neuronal excitability and LTP magnitude under CREB results in the weights reaching a higher value (Figure 7.3, right).

![Plasticity of synaptic weights](image)

**Figure 7.3 – Plasticity of synaptic weights.** Time course for the peak conductance of selected CA3 active synapses (7 out of 100), targeting one of the CA1 neurons involved in a pattern presented during a simulation (100 theta-cycles of storage/recall); **(left)** control, **(right)** under CREB conditions. Synaptic activation times were identical in both conditions. (From Bianchi et al. (2013)).

Due to the lack of computational resources available for this work, in the attempt to economize the computational cost of the simulations and without losing biological detail, we set the simulation time to 20s, i.e. 80 theta cycles.

In Figure 7.4, we show a typical result during 5 theta cycles of simulation, after weights equilibration, under control (Figure 7.4a) and CREB (Figure 7.4b) conditions. The somatic membrane potential of one of the CA1 neurons belonging to the input pattern (middle plots) shows that CA1 cells are more active in the increased CREB case with respect to control.
RESULTS

However, in both cases, their spiking activity very closely matches the input pattern, resulting in a very high quality of the recall (bottom plots). These results suggest that increased CREB activity does not generate much difference from the control case in terms of the overall quality of the recall, although the higher cell excitability, as Bianchi et al. suggested, may lead to a better robustness of the output during pathological conditions.

![Diagram showing spiking activity and quality](image)

Figure 7.4 – Typical example of an input/output activity during a simulation. In both cases (A, Control and B, CREB) the raster plot (above) shows the spiking times during a 1.25 s simulation segment, for, up to down, the septum (10 inputs), EC (20 inputs), CA3 (100 inputs), the 5 interneurons, and the 100 CA1 neurons. The highlighted areas indicate the time windows for the expected CA1 output (recall phase). The somatic membrane voltage for one of the CA1 pyramidal cells belonging to the input pattern is shown in the middle panel. At the bottom, the recall quality for this particular simulation segment is shown.

7.3 Storage and recall of random patterns

Next, we tested the recall quality of an increasing number of random patterns. This corresponds to an increasing average number of overlapping active neurons.

Again, due to the limited computational resources, our analysis is far from being statistical accurate, but as we will see our preliminary results are in agreement with those present in literature (Bianchi et al., 2013).

Figure 7.5 shows the quality obtained as a function of the number of stored patterns. The recall quality decreases with the number of stored
patterns, the reason being easily explained by considering that random patterns may have one or more active neurons in common. Thus, each time a new pattern is stored, the synaptic configuration of the previously stored patterns may be altered. In particular, with 20% of active neurons, any two patterns will have, on average, four active neurons in common. The storage of each new pattern will thus tend to modify previously active synapses, influencing the recall quality of previously encoded patterns. The effects cumulate each time a new pattern is stored. As shown in Figure 7.5, in all cases the quality was surprisingly above $Th$ for the entire range, that for computational causes we limited to 20 patterns. The neuron’s higher excitability and increased LTP underCREB did not significantly change this result.

![Figure 7.5 – Increasing CREB function does not significantly improve the recall quality of random patterns. Recall quality under control (blue circles) and CREB (red triangles) conditions as a function of the number of stored random patterns. The dotted line represents the threshold, $Th$, for the acceptable quality level.](image)

7.4 Ultrametricity of the patterns

At the end of Section 5.5 we already examined an example of application of the definitions of ultrametricity to the patterns used in the simulations. In that case, we start from a hierarchy (in the sense explained in Section 5.3). As a matter of fact, we can effortlessly apply those arguments to any random pattern, since we are in the case of *sparse coding*.

Given a set of 6 random patterns, we construct the minimum-spanning-
Results

tree starting from the Hamming distances between each pattern.

<table>
<thead>
<tr>
<th>Minimum-spanning-tree</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 -&gt; 0 : 32</td>
</tr>
<tr>
<td>0 -&gt; 3 : 30</td>
</tr>
<tr>
<td>3 -&gt; 2 : 36</td>
</tr>
<tr>
<td>2 -&gt; 4 : 31</td>
</tr>
<tr>
<td>4 -&gt; 1 : 31</td>
</tr>
</tbody>
</table>

We can now build a tree of categories by means of the subdominant ultrametric (Figure 7.6). In this case, calculating the Rammal index for the deviation from the ultrametricity gives as a result 0.02, while the calculation of the Lerman index gives again 0, as in the example of Table 5.2.

An interesting question that arises is therefore whether the recall quality depends on the degree of ultrametricity of the patterns to be stored. We manually constructed pseudo-random pattern in order to obtain a range of values for the Rammal index. Figure 7.7 shows the quality of the recall obtained as a function of the deviation from ultrametricity of the stored patterns (in the case under examination, we fixed the number of patterns at \( p = 6 \)). As we can see, a greater deviation from ultrametricity seems to cause an impairment of the recall.

Figure 7.6 – An example of the construction of the subdominant ultrametric \( d' \) starting from 6 random patterns, using the method of the minimum-spanning tree (MST).
A greater deviation from ultrametricity seems to cause an impairment of the recall. Recall quality under control (blue circles) conditions as a function of degree of ultrametricity of the stored patterns.
The hypothesis of associative memory function in the subsystems of the hippocampus cannot yet be tested by direct experiments. It is technically not possible to instantiate specific patterns of neural activity for either storage or subsequent recall. That such a process does take place is based on the suitability of the network architecture and evidence from tissue slice experiments of the Hebbian induction of long-lasting changes in synaptic strength at the relevant connections (Bliss et al., 2007). Behavioural experiments in mammals, including humans, implicate the hippocampus in the intermediate-term storage of episodic memories. Thus we must rely on computational models to assess the recall and storage abilities of the neural subnetworks of the hippocampus. The model presented here is devised to address the specific issue of whether network inhibition provides suitable control of pyramidal cell activity to allow the successful recall of previously stored patterns.

A detailed biophysical model of the hippocampal CA1 microcircuitry has been presented, which demonstrates the biological feasibility of the separation of storage and recall processes into separate theta subcycles. The model simulated the timing of firing of different hippocampal cell types relative to the theta rhythm in anesthetized animals (Klausberger et al., 2004; Somogyi and Klausberger, 2005). The model also proposed functional roles for different classes of inhibitory interneurons in encoding and retrieval of information. We propose that in our CA1 microcircuit model the basket and axo-axonic cells prevent pyramidal cells from firing during the encoding process, but also set the stage for learning to occur. During the retrieval process, bistratified cells set the threshold for pyramidal neurons so that those that had not learnt the pattern were silent, whereas those that had to be able to reliably recall it were active. OLM cells helped prevent errors and facilitate disambiguation during the retrieval. The firing phases of all neurons in our model were modulated by the $\theta$-driven inhibition from the septal region. As others before (Kunec et al., 2005), our model emphasized
the cooperation of extra-hippocampal inputs for the proper memory storage and recall.

Most of the models present in literature relied on Hebbian synaptic plasticity. In our model, encoding occurred based on a local STDP learning rule in P cell SR dendrites between the EC and CA3 inputs. As in (Kunec et al., 2005), for our plasticity to occur, the postsynaptic neuron did not have to produce an action potential, but simply needed a depolarized dendritic membrane potential to elicit the strengthening process (Golding et al., 2002).

Because of CREB’s role in memory formation, the concept of CREB-based memory enhancers, i.e. drugs that would boost memory by CREB activation, has emerged. However, not much is known about how CREB-dependent neuronal alterations in synaptic strength, excitability, and LTP, which have been observed at the single neuron level using biological tools, can boost memory formation in the complex architecture of a neuronal network. To this purpose, we extended the model of Cutsuridis et al. (2010) to allow storage/recall of more than one pattern, using a specific STDP learning rule (Nishiyama et al., 2000) and a CA1 model able to reproduce many experimentally observed features of these neurons under control (e.g. the depolarization block (Bianchi et al., 2012)) and under CREB activity (de Armentia et al., 2007).

One of the main results of the model is that under control conditions, the larger excitability and LTP magnitude caused by enhanced CREB function does not appear to significantly improve the number of patterns that can be recalled with an acceptable quality. This is consistent with the experimental findings of Barco et al. (2002) suggesting that, while expression of VP16-CREB facilitates the establishment of hippocampal LTP, training the transgenic mice (expressing the VP16-CREB) in a spatial learning task might cause too many synapses to become strongly and irreversibly potentiated, preventing the storage of new information.

Finally, the analysis of the ultrametric structure of the patterns to be stored is an unusual and promising approach that leaves a great number of questions unanswered. With a more conspicuous amount of computational resources it will possibly improve our understanding of the subject.
Appendix
A.1 Pyramidal cell model

The geometry of the pyramidal cell, and for the other cell models for CA1, is given in Table A.1. Passive parameters and reversal potential values for all compartments of pyramidal cells are listed in Table A.2.

The reduced model adopted here (derived from the one of Bianchi et al. (2012)) includes the following 15 types of ionic channels, most of them distributed non-uniformly along the somatodendritic region. More precisely,

**Soma** : a leak current, a transient sodium ($NaT$) current, a delay-rectifier potassium ($K_{DR}$) current, an A-type potassium current ($K_A$), a M-type potassium current ($K_M$), a mixed conductance hyper-polarization activated h-current, three types of voltage dependent calcium currents (namely $LVA$ T-type current, a $HVA$ R-type current, a $HVA$ L-type current), two types of calcium dependent potassium currents (a slow $AHP$ current and a medium-fast $AHP$ current);

**Axon** : a $NaT$ current, a $K_{DR}$ current, a leak current, a $K_A$ current and $K_M$ current;

**Basal dendrites and apical trunk** : all currents included in the soma with the exception of $K_M$ current (the $HVA$ R- and L-type are different from those in soma);

**Distal dendrites** : all currents included in the apical trunk except the $HVA$ L-type current.
Appendix A

Table A.1 – Structure of CA1 model cells.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Soma</th>
<th>Axon</th>
<th>Oriens</th>
<th>Radiatum</th>
<th>LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_m$ [pF/cm$^2$]</td>
<td>1</td>
<td>1</td>
<td>1.12</td>
<td>1.12</td>
<td>1.12</td>
</tr>
<tr>
<td>$R_m$ [Ohm$^2$cm$^2$]</td>
<td>28,000</td>
<td>28,000</td>
<td>25,000</td>
<td>25,000</td>
<td>25,000</td>
</tr>
<tr>
<td>$R_e$ [Ohm$\Omega$cm$^2$]</td>
<td>150</td>
<td>50</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Reversal potentials [mV]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_L$</td>
<td>$-70$</td>
<td>$-70$</td>
<td>$-70$</td>
<td>$-70$</td>
<td>$-70$</td>
</tr>
<tr>
<td>$E_{Na}$</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>$E_{K}$</td>
<td>$-10$</td>
<td>$-10$</td>
<td>$-10$</td>
<td>$-10$</td>
<td>$-10$</td>
</tr>
<tr>
<td>$E_{Ca}$</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>$E_{K}$</td>
<td>$-80$</td>
<td>$-80$</td>
<td>$-80$</td>
<td>$-80$</td>
<td>$-80$</td>
</tr>
</tbody>
</table>

Table A.2 – Passive parameters for all compartments of pyramidal model cells.

Ionic currents were modeled following a Hodgkin-Huxley-like formalism as follows:

$$I_{ion,j} = g_{ion,j} m^a_j h^b_j (V - E_{ion,j})$$  \hspace{1cm} (A.1)

where $g_{ion,j}$ represents the maximal ionic conductance, $\{m, h\}_j$ and $\{a, b\}_j$ are the gating variables for activation and inactivation and their exponents, respectively, and $E_{ion,j}$ is the reversal potential associated with the particular ion or ions that make up the current. The dynamics of the gating
variables \((m_j, h_j)\) is governed by an ODE of the form

\[
\frac{d\chi}{dt} = \frac{\chi_\infty - \chi}{\tau_\chi}
\]  
(A.2)

where the activation and inactivation steady-state functions \(\chi_\infty\) are given alternately by

\[
\chi_\infty = \frac{\alpha_\chi(V)}{\alpha_\chi(V) + \beta_\chi(V)} \quad \text{or} \quad \chi_\infty = \frac{1}{1 + e^{(V-V_1/2)/k_\chi}} 
\]  
(A.3a)

(A.3b)

while their time constant \(\tau_\chi\) by

\[
\tau_\chi = \frac{Q}{\alpha_\chi(V) + \beta_\chi(V)} \quad \text{or} \quad \tau_\chi = \tau_\chi^0 + \frac{\tau_\chi}{G_\chi \left[e^{\gamma_\chi(V-V_1/2)/k_\chi} + e^{(\gamma_\chi-1)(V-V_1/2)/k_\chi}\right]} 
\]  
(A.4a)

(A.4b)

**Transient NaT current**

The NaT current was implemented according to Shah et al. (2008), so (A.1) becomes:

\[
I_{NaT} = g_{NaT} m_{NaT}^3 h_{NaT} (V - 50) 
\]  
(A.5)

with \(g_{NaT} = 18\) mS/cm².

The dynamics of the gating variable \(m_{NaT}\) is described by (A.2), (A.3a) and (A.4a) as follows

\[
\alpha_{m_{NaT}} = \begin{cases} 
0.4 \frac{(V-V_{m_{NaT}}^{1/2})}{1 - \exp[-(V-V_{m_{NaT}}^{1/2})/k_{m_{NaT}}]} & |V - V_{m_{NaT}}^{1/2}| > 10^{-6} \text{ mV} \\
0.4 k_{m_{NaT}} & \text{otherwise}
\end{cases}
\]

\[
\beta_{m_{NaT}} = \begin{cases} 
-0.124 \frac{(V-V_{m_{NaT}}^{1/2})}{1 - \exp[(V-V_{m_{NaT}}^{1/2})/k_{m_{NaT}}]} & |V_{m_{NaT}}^{1/2} - V| > 10^{-6} \text{ mV} \\
0.124 k_{m_{NaT}} & \text{otherwise}
\end{cases}
\]

\[
\tau_{m_{NaT}} = \begin{cases} 
\frac{1}{\alpha_{m_{NaT}}(V) + \beta_{m_{NaT}}(V)} & \alpha_{m_{NaT}}(V) + \beta_{m_{NaT}}(V) > 0.02 \text{ ms} \\
0.02 \text{ ms} & \text{otherwise}
\end{cases}
\]

The dynamics of the gating variable \(h_{NaT}\) is described by (A.2), (A.3b),
and (A.4a), i.e.

\[
(h_{NaT})_\infty = \frac{1}{1 + \exp\left(\frac{V - V_{hNaT}^{1/2}}{k_{hNaT}}\right)}
\]

\[
\alpha_{hNaT} = \begin{cases} 
\frac{0.03 (V+45)}{1-\exp[-(V+45)/1.5]}, & |V - V_{hNaT}^{1/2}| > 10^{-6} \text{ mV} \\
0.045, & \text{otherwise}
\end{cases}
\]

\[
\beta_{hNaT} = \begin{cases} 
\frac{-0.01 (V+45)}{1-\exp(V+45)/1.5)}, & |V_{hNaT}^{1/2} - V| > 10^{-6} \text{ mV} \\
0.015, & \text{otherwise}
\end{cases}
\]

with: \(V_{mNaT}^{1/2} = -28 \text{ mV}\) for every section except in the axon whose value is \(-30 \text{ mV}\), \(k_{mNaT} = 7.2 \text{ mV}\) everywhere except in the axon whose value is \(7.5 \text{ mV}\). \(V_{hNaT}^{1/2} = -50 \text{ mV}, k_{hNaT} = 2 \text{ mV}\).

**Delayed rectifier K\(^+\) current**

The delayed rectifier \(K^+\) current \((I_{KDR})\), taken from Shah et al. (2008), is given by:

\[I_{KDR} = \overline{g}_{KDR} m_{KDR} (V + 77)\]  \hspace{1cm} (A.6)

with \(\overline{g}_{KDR} = 10 \text{ mS/cm}^2\).

The dynamics of \(m_{KDR}\) is described by (A.2), (A.3b) and (A.4b), with \(V_{mKDR}^{1/2} = 13 \text{ mV}, k_{KDR} = -8.824 \text{ mV}, \tau_{mKDR}^0 = 0 \text{ ms}, \gamma_{mKDR} = 0.8, G_{KDR} = 1, \tau_{mKDR} = 50 \text{ ms}, \bar{k}_{NaT} = 8.824 \text{ mV}, \) and a minimum value for \(\tau_{mKDR}\) of 2 ms.

**Potassium M-type current**

The M current \((I_{K_M})\) was modeled according to Shah et al. (2008), namely

\[I_{K_M} = \overline{g}_{K_M} m_{K_M} (V + 77)\]  \hspace{1cm} (A.7)

with \(\overline{g}_{K_M} = 1 \text{ mS/cm}^2\).

The dynamics of the gating variable \(m_{K_M}\) is described by (A.2), (A.4b) and (A.3b) with the following formula:

\[
(m_{K_M})_\infty = \frac{1}{1 + \exp\left(\frac{V - V_{mK_M}^{1/2}}{(k_{mK_M})}\right)}
\]  \hspace{1cm} (A.8)

where: \(V_{mK_M}^{1/2} = -42 \text{ mV}, k_{mK_M} = -4 \text{ mV}, \tau_{mK_M}^0 = \frac{1}{0.03} \text{ ms}, \bar{k}_{mK_M} = -1 \text{ mV}, \gamma_{mK_M} = 0.7, \gamma_{mK_M}^0 = 60 \text{ ms}, G_{mK_M} = 1\).
**Ca$^{2+}$-dependent K$^+$ currents: slow and medium AHP**

The Ca$^{2+}$-dependent slow and medium AHP potassium channels (along with a calcium pump/buffering mechanism) are distributed uniformly along the neuron, but they are not inserted in the axon. The conductance values are: $g_{sAHP} = 15 \text{ mS/cm}^2$ and $g_{mAHP} = 100 \text{ mS/cm}^2$. The corresponding somatic values for medium AHP potassium current is two times higher than elsewhere.

The channel kinetics for $I_{sAHP}$ are taken with no modifications from Destexhe et al. (1994):

$$I_{sAHP} = g_{sAHP} m_{sAHP}^3 (V + 80) \quad (A.9)$$

The kinetics equations are given by (A.2) and (A.3b) with the following formula:

$$(m_{sAHP})_\infty = \frac{Cac}{1 + Cac} \quad (A.10)$$

where $Cac = ([Ca^{2+}]_m/0.025)^2 \text{ [mM]}^2$ and $[Ca^{2+}]_m$ is the internal calcium concentration.

For what concerns $\tau_{mAHP}$ the formula is:

$$\tau_{mAHP} = \max \left( \frac{1}{0.003 \text{ [1/ ms]} \cdot (1 + Cac) \cdot 3(\deg \circ ^{-22})/10}, 0.5 \right) \quad (A.11)$$

The medium AHP current $I_{mAHP}$, from Moczydlowski and Latorre (1983), is given by

$$I_{mAHP} = g_{mAHP} m_{mAHP} (V + 77) \quad (A.12)$$

The dynamics of the gating variable $m_{mAHP}$ is described by (A.2), (A.3a) and (A.4a). The $\alpha_m$ and $\beta_m$ are given by:

$$\alpha_{mAHP} = \frac{0.48}{1 + \frac{0.18}{[Ca^{2+}]_m} \exp[-2d_1 V - 37.775]} \quad (A.13)$$

$$\beta_{mAHP} = \frac{0.28}{1 + \frac{0.011}{[Ca^{2+}]_m} \exp[-2d_2 V - 37.775]} \quad (A.14)$$

with $d_1(m_{AHP}) = 1$, $d_2(m_{AHP}) = 1.5$.

**Hyperpolarization h current**

The h current ($I_h$) was modeled according to Magee (1998), namely

$$I_h = g_h m_h (V + 10) \quad (A.15)$$
Appendix A

The dynamics of the gating variable $m_h$ is described by (A.2), (A.4b) and (A.3b) with the following formula:

$$m_{h,\infty} = \frac{1}{1 + \exp\left(\frac{(V - V_{m_h}^{1/2})}{k_{m_h}}\right)}$$  \hspace{1cm} (A.16)

with $V_{m_h}^{1/2} = -73 \text{ mV}$ if the channel is distant less than 100 $\mu$m, otherwise $V_{m_h}^{1/2} = -81 \text{ mV}$. $k_{m_h} = -8 \text{ mV}$. The others are set as follows: $\tau_{m_h}^0 = 0 \text{ ms}$, $\tau_{m_h} = 78.21 \text{ ms}$, $G_{m_h} = 1$, $\gamma_{m_h} = 0.4$, $\hat{k}_{m_h} = -12.02 \text{ mV}$. For the formula (A.4b): $V_{m_h}^{1/2} = -75 \text{ mV}$.

Moreover, the hyperpolarization-activated $h$-current is known to be differentially distributed along the dendritic arbour of CA1 neurons with increasing channel density from the soma to the distal trunk sections. The elevated dendritic conductance has been shown to have a location-dependent impact in the basic membrane properties and the propagation of voltage traces (Magee, 1998). In order to fit these empirical data, the $I_h$ mechanism in our model cell is distributed in a sigmoidally increasing manner from the soma to the main apical trunk:

$$g_h(x) = g_{h,\text{soma}} + \frac{g_{h,\text{end}} - g_{h,\text{soma}}}{1.0 + \exp\left(\frac{(d_{\text{half}} - d_x)}{\text{steep}}\right)}$$ \hspace{1cm} (A.17)

where

$$g_{h,\text{soma}} = 0.04 \text{ mS/cm}^2, \quad g_{h,\text{end}} = 7 \cdot g_{h,\text{soma}}, \quad d_{\text{half}} = 280 \mu\text{m}, \quad \text{steep} = 50 \mu\text{m}.$$

**Fast inactivating potassium current $I_A$**

A-type potassium channels are known to be distributed in high densities in the dendrites of CA1 pyramidal neurons while channel kinetics are different between proximal and distal populations (Hoffman et al., 1997; Migliore et al., 1999). Based on these findings, a linear increase in $I_A$ channel conductance was implemented along the apical trunk, with different channel kinetics for proximal ($I_{A,\text{prox}}$) and distal ($I_{A,\text{dist}}$) compartments. The current equations for both channels are given by

$$I_A = g_A \cdot m_{K_A} \cdot h_{K_A} \cdot (V + 80)$$ \hspace{1cm} (A.18)

The dynamics of the gating variable $m_{K_A}$ is described by (A.2), (A.4b) and (A.3b) with the following formula:

$$m_{K_A,\infty} = \frac{1}{1 + \exp\left(\frac{(V - V_{m_{K_A}}^{1/2})}{k_{m_{K_A}}}\right)}$$ \hspace{1cm} (A.19)
The dynamics of the gating variable \( h_{K_A} \) is described by (A.2) and (A.3b) with the following formula:

\[
h_{K_A} = \frac{1}{1 + \exp[(V - V^{1/2}_{h_{K_A}})/k_{h_{K_A}}]} \tag{A.20}
\]

For what concerns \( \tau_{h_{K_A}} \) the formula is:

\[
\tau_{h_{K_A}} = 0.26 \text{ ms/mV} (V + 50) \tag{A.21}
\]

The parameters for \( I_{A_{\text{prox}}} \) are:

\[
V^{1/2}_{m_{K_A}} = 11 \text{ mV}, \ V^{1/2}_{h_{K_A}} = -56 \text{ mV}, \ k_{h_{K_A}} = 8.70 \times 10^5, \ k_{m_{K_A}} = 2.61 \times 10^6, \ Z(V) \text{ mV and } Z(V) = -1.5 + \frac{1}{1 + \exp[(V + 40)/50]}.
\]

\[
\tau_{m_{K_A}} = 0 \text{ ms}, \ \tau_{m_{K_A}} = 0.01 \text{ ms}, \ G_{m_{K_A}} = 1, \ \gamma_{m_{K_A}} = 0.55, \ \tilde{k}_{m_{K_A}} = -k_{m_{K_A}}.
\]

The parameters for \( I_{A_{\text{dist}}} \) are:

\[
V^{1/2}_{m_{K_A}} = -1 \text{ mV}, \ V^{1/2}_{h_{K_A}} = -56 \text{ mV}, \ k_{h_{K_A}} = 8.70 \times 10^5, \ k_{m_{K_A}} = 2.61 \times 10^6, \ Z(V) \text{ mV and } Z(V) = -1.8 + \frac{1}{1 + \exp[(V + 40)/50]}.
\]

\[
\tau_{m_{K_A}} = 0 \text{ ms}, \ \tau_{m_{K_A}} = 2 \text{ ms}, \ G_{m_{K_A}} = 1, \ \gamma_{m_{K_A}} = 0.39, \ \tilde{k}_{m_{K_A}} = -k_{m_{K_A}}.
\]

For both currents a minimum value for \( \tau_{m_{K_A}} \) is fixed to 0.1 ms, for \( \tau_{h_{K_A}} \) to 2 ms.

The maximal conductance values for both channel types vary as a function of distance from the cell body according to the following equations:

\[
\mathcal{g}_{A_{\text{prox}}}(x) = \begin{cases} 
\mathcal{g}_{A_{\text{init}}} \cdot (1 + \mathcal{g}_{A_{\text{factor}}} \cdot \frac{d_x}{100 \mu m}) & \text{if } d_x \leq 100 \mu m \\
0 & \text{if } d_x > 100 \mu m \end{cases} \tag{A.22}
\]

\[
\mathcal{g}_{A_{\text{dist}}}(x) = \begin{cases} 
0 & \text{if } d_x \leq 100 \mu m \\
\mathcal{g}_{A_{\text{init}}} \cdot (1 + \mathcal{g}_{A_{\text{factor}}} \cdot \frac{d_x}{100 \mu m}) & \text{if } d_x > 100 \mu m \end{cases} \tag{A.23}
\]

where the initial conductance value \( \mathcal{g}_{A_{\text{init}}} = 7 \text{ mS/cm}^2 \) and the maximum dendritic factor \( \mathcal{g}_{A_{\text{factor}}} = 3 \).

Voltage-dependent calcium currents

Calcium channel kinetic equations and density distributions are adapted from Magee and Johnston (1995).

LVA (T-type) \( \text{Ca}^{2+} \) channel

The LVA (T-type) \( \text{Ca}^{2+} \) current is given by The kinetics are given by

\[
I_{CaT} = \mathcal{g}_{CaT} m_{CaT}^a h_{CaT} \ \frac{0.001 \text{ mM}}{0.001 \text{ mM} + [\text{Ca}^{2+}]_{\text{in}}} g_{hk}(V) \tag{A.24}
\]
with

$$ghk(V) = -x \left( 1 - \frac{[Ca^{2+}]_{in}}{[Ca^{2+}]_{out}} e^{\frac{x}{2}} \right) f\left( \frac{V}{x} \right)$$  \hspace{1cm} (A.25)

$$x = \frac{0.0853 \cdot (T + deg \, C)}{2}$$  \hspace{1cm} (A.26)

$$f(z) = \begin{cases} 1 - \frac{z}{e^{z-1}} & \text{if } |z| < 10^4 \\ \frac{z}{e^{z-1}} & \text{otherwise} \end{cases} \hspace{1cm} (A.27)$$

$[Ca^{2+}]_{in}$ and $[Ca^{2+}]_{out}$ are the internal and external calcium concentrations.

The dynamics of the gating variable $m_{CaT}$ and $h_{CaT}$ are described by (A.2), (A.3a) and (A.4a) with:

$$\alpha_{m_{CaT}} = -0.196 \cdot \frac{V - 19.88}{e^{(V - 19.88)/10}}$$  \hspace{1cm} (A.28)

$$\beta_{m_{CaT}} = 0.046 \cdot e^{V/22.73}$$  \hspace{1cm} (A.29)

$$\alpha_{h_{CaT}} = 0.00016 \cdot e^{-(V+57)/19}$$  \hspace{1cm} (A.30)

$$\beta_{h_{CaT}} = \frac{1}{e^{-(V-19)/10} + 1}$$  \hspace{1cm} (A.31)

$$Q_{\tau m_{CaT}} = 1$$  \hspace{1cm} (A.32)

$$Q_{\tau h_{CaT}} = \frac{1}{0.68}$$  \hspace{1cm} (A.33)

LVA (T-type) Ca$^{2+}$ channels are distributed along the main trunk, starting from the proximal dendrites to the distal tuft, with linearly increasing conductance as shown by

$$\overline{g}_{CaT}(x) = \begin{cases} \overline{g}_{CaT_{soma}} \cdot \left( 1 + \overline{g}_{CaT_{factor}} \cdot \frac{d_x}{60 \mu m} \right) & \text{if } d_x \leq 300 \mu m \\ \overline{g}_{CaT_{soma}} \cdot 6 & \text{if } d_x > 300 \mu m \end{cases}$$  \hspace{1cm} (A.34)

where $\overline{g}_{CaT_{soma}} = 0.5 \, mS/cm^2$ and $\overline{g}_{CaT_{factor}} = 1$. LVA (T-type) Ca$^{2+}$ channels are also inserted at the soma and basal dendrites with a conductance value of $g_{CaT} = 0.5 \, mS/cm^2$. The corresponding distal conductance is three times higher than the somatic value.

HVAm (R-type) Ca$^{2+}$ channels

The dendritic HVAm (R-type) Ca$^{2+}$ channels are distributed in a uniform way along the apical trunk and basal dendrites, with a small conductance value of $\overline{g}_{CaR} = 0.1 \, mS/cm^2$. The corresponding somatic conductance is five times higher than the apical trunk value, $\overline{g}_{CaR}^s = 0.5 \, mS/cm^2$. The distal conductance is the half of the apical trunk value.
The HVAm (R-type) Ca\textsuperscript{2+} current is given by

\[ I_{CaR} = g_{CaR} m_{CaR}^3 h_{CaR} (V - 140) \]  

(A.35)

The dynamics of the gating variable \( m_{CaR} \) and \( h_{CaR} \) are described by (A.2), (A.3b). The difference between somatic and dendritic CaR currents lies in the \( m_{CaR\infty} \), \( h_{CaR\infty} \) and \( \tau_{CaR} \) parameter values. For the somatic current, \( \tau_{m_{CaR}} = 100 \) ms and \( \tau_{h_{CaR}} = 5 \) ms while for the dendritic current \( \tau_m = 50 \) ms and \( \tau_h = 5 \) ms.

The \( m_{CaR\infty} \) and \( h_{CaR\infty} \) equations for dendritic CaR channels are

\[ m_{CaR\infty} = \frac{1}{1 + e^{-(V+48.5)/3}}, \quad h_{CaR\infty} = \frac{1}{1 + e^{V+53}} \]  

(A.36)

while for the somatic CaR channels

\[ m_{CaR\infty} = \frac{1}{1 + e^{-(V+60)/3}}, \quad h_{CaR\infty} = \frac{1}{1 + e^{V+62}} \]  

(A.37)

**HVA (L-type) Ca\textsuperscript{2+} channels**

Most of the kinetic equations for somatic HVA (L-type) channels are the same as the equations for T-type channels. Equations that are different between the two mechanisms are given by

\[ I_{CaL}^s = g_{CaL}^s m_{CaL}^0 0.001 \text{mM} [Ca^{2+}]_{in} ghk(V) \]  

(A.38)

\[ \alpha_{m_{CaL}} = -0.055 \cdot \frac{V + 27.01}{e^{-(V+27.01)/3.8} - 1} \]  

(A.39)

\[ \beta_{m_{CaL}} = 0.94 \cdot e^{-(V+63.01)/17} \]  

(A.40)

\[ Q_{\tau_{m_{CaL}}} = \frac{1}{5} \]  

(A.41)

where \( g_{CaL}^s = 7 \text{mS/cm}^2 \).

Dendritic L-type calcium channels have different kinetics. The current is given by

\[ I_{CaL}^d = g_{CaL}^d m_{CaL}^3 h_{CaL} (V - 140) \]  

(A.42)

The dynamics of the dendritic gating variable \( m_{CaL} \) and \( h_{CaL} \) are described by (A.2), (A.3b):

\[ m_{CaL\infty} = \alpha(V) = \frac{1}{1 + e^{-(V+37)}}, \quad h_{CaL\infty} = \frac{1}{1 + e^{(V+41)/0.5}} \]  

(A.43)

Time constants are equal to \( \tau_{m_{CaL}} = 3.6 \) ms and \( \tau_{h_{CaL}} = 29 \) ms.
The dendritic HVA (L-type) channels are distributed in a nonuniform way along the apical trunk:

\[
\mathcal{g}_{\text{CaL}}^d(x) = \begin{cases} 
\mathcal{g}_{\text{CaL,init}} (1 - \mathcal{g}_{\text{CaL,factor}} \cdot \frac{d_x}{200 \mu m}) & \text{if } d_x < 200 \mu m \\
0 & \text{if } d_x \geq 200 \mu m 
\end{cases} \tag{A.44}
\]

where \( \mathcal{g}_{\text{CaL,init}} = 1 \text{ mS/cm}^2 \).

The basal conductance is ten times lower than the apical trunk value. No HVA (L-type) channels are inserted in distal dendrites.

**Calcium pumping/buffering**

A calcium pump/buffering mechanism is also inserted at the cell body and along the apical trunk. The mechanism is taken from Destexhe et al. (1994) and was modified to replicate the sharp Ca\(^{2+}\) spike repolarization observed in Golding et al. (1999). The factor for Ca\(^{2+}\) entry was changed from \( f_e = 10000 \) to \( f_e = 10000/18 \) and the rate of calcium removal was made seven times faster. The kinetic equations are given by

\[
d\text{Ca}_d/dt = \text{drive}_\text{ch} + \frac{10^{-4} \text{ [mM]} - \text{Ca}}{7 \cdot 200 \text{ [ms]}} \tag{A.46}
\]

\[
d\text{drive}_\text{ch} = \begin{cases} 
-f_e \cdot \frac{I_{\text{Ca}}}{\text{FARADAY}} & \text{if drive}_\text{ch} > 0 \text{ mM/ ms} \\
0 & \text{otherwise} \tag{A.45}
\end{cases}
\]

**A.2 Axo-axonic, Basket and Bistratified cell models**

Active properties of these cells are derived from the interneuron model of Santhakumar et al. (2005). All compartments obey the following current balance equation:

\[
C_m \frac{dV}{dt} = I_{\text{ext}} - I_L - I_{\text{Na}} - I_{\text{K-DR,fast}} - I_A - I_{\text{CaL}} - I_{\text{CaN}} - I_{\text{AHP}} - I_C - I_{\text{syn}} \tag{A.47}
\]

where \( C_m \) is the membrane capacitance, \( V \) is the membrane potential, \( I_L \) is the leak current, \( I_{\text{Na}} \) is the sodium current, \( I_{\text{K-DR,fast}} \) is the fast delayed rectifier K\(^+\) current, \( I_A \) is the A-type K\(^+\) current, \( I_M \) is the M-type K\(^+\) current, \( I_h \) is a hyperpolarizing h-type current, \( I_{\text{CaL}} \) is the L-type Ca\(^{2+}\) current, \( I_{\text{CaN}} \) is the N-type Ca\(^{2+}\) current, \( I_{\text{AHP}} \) is the Ca\(^{2+}\)-dependent K\(^+\) current, \( I_C \) is the Ca\(^{2+}\) and voltage-dependent K\(^+\) (BK) current and \( I_{\text{syn}} \) is the synaptic current. The conductance and reversal potential values of all ionic currents are listed in Table A.3.
CA1 microcircuit model in detail

Table A.3 – Passive parameters and active ionic conductances of channels for all compartments of axo-axonic (AAC), basket (BC) and bistratified (BSC) model cells.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>AAC</th>
<th>BC</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_m ) [( \mu F/cm^2 )]</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>( R_a ) [( \Omega cm )]</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Leak conductance [( S/cm^2 )]</td>
<td>( 1.8 \times 10^{-4} )</td>
<td>( 1.8 \times 10^{-4} )</td>
<td>( 1.8 \times 10^{-4} )</td>
</tr>
<tr>
<td>Sodium cond. [( S/cm^2 )]</td>
<td>0.15</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Delayed rectifier K(^+) cond. [( S/cm^2 )]</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>A-type ( \text{Ca}^{2+} ) cond. [( S/cm^2 )]</td>
<td>( 1.5 \times 10^{-4} )</td>
<td>( 1.5 \times 10^{-4} )</td>
<td>( 1.5 \times 10^{-4} )</td>
</tr>
<tr>
<td>L-type ( \text{Ca}^{2+} ) cond. [( S/cm^2 )]</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>N-type ( \text{Ca}^{2+} )-dep K(^+) cond. [( S/cm^2 )]</td>
<td>( 2.0 \times 10^{-6} )</td>
<td>( 2.0 \times 10^{-6} )</td>
<td>( 2.0 \times 10^{-6} )</td>
</tr>
<tr>
<td>( \text{Ca}^{2+} )- and voltage-dep K(^+) cond. [( S/cm^2 )]</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>Decay constant of intracellular ( \text{Ca}^{2+} ) [( \text{ms} )]</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Steady-state intracellular ( \text{Ca}^{2+} ) conc. [( \mu M )]</td>
<td>( 5.0 \times 10^{-6} )</td>
<td>( 5.0 \times 10^{-6} )</td>
<td>( 5.0 \times 10^{-6} )</td>
</tr>
<tr>
<td>( E_{Na} ) [mV]</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>( E_{K} ) [mV]</td>
<td>( -90 )</td>
<td>( -90 )</td>
<td>( -90 )</td>
</tr>
<tr>
<td>( E_{Ca} ) [mV]</td>
<td>130</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>( E_L ) [mV]</td>
<td>( -60 )</td>
<td>( -60 )</td>
<td>( -60 )</td>
</tr>
<tr>
<td>( [\text{Ca}^{2+}]_0 ) [( \mu M )]</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

The sodium current and its kinetics are described by

\[ I_{Na} = g_{Na} m^3 h (V - E_{Na}) \] \hspace{1cm} (A.48)

\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \] \hspace{1cm} (A.49)

\[ \alpha_m = \frac{-0.3 (V - 25)}{1 - e^{-(V - 25)/5}}, \quad \beta_m = \frac{0.3 (V - 53)}{1 - e^{-(V - 53)/5}} \] \hspace{1cm} (A.50)

\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \] \hspace{1cm} (A.51)

\[ \alpha_h = \frac{0.23}{e^{(V-3)/20}}, \quad \beta_h = \frac{3.33}{1 + e^{-(V-55.5)/10}} \] \hspace{1cm} (A.52)

The fast delayed rectifier K\(^+\) current, \( I_{K,\text{DR,fast}} \), is given by

\[ I_{Na} = g_{K,\text{DR,fast}} n_f^4 (V - E_{K}) \] \hspace{1cm} (A.53)

\[ \frac{dn_f}{dt} = \alpha_{n_f} (1 - n_f) - \beta_{n_f} n_f \] \hspace{1cm} (A.54)

\[ \alpha_{n_f} = \frac{-0.07 (V - 47)}{1 - e^{-(V - 47)/6}}, \quad \beta_{n_f} = 0.264 e^{(V-22)/4} \] \hspace{1cm} (A.55)

The N-type \( \text{Ca}^{2+} \) current, \( I_{CaN} \), is given by

\[ I_{CaN} = g_{CaN} c^2 d (V - E_{Ca}) \] \hspace{1cm} (A.56)

\[ \frac{dc}{dt} = \alpha_c (1 - c) - \beta_c c \] \hspace{1cm} (A.57)
\[ \alpha_c = \frac{0.19 (19.88 - V)}{e^{(19.88 - V)/10} - 1}, \quad \beta_c = 0.046 e^{-V/20.73} \quad (A.58) \]

\[ \frac{dd}{dt} = \alpha_d (1 - d) - \beta_d d \quad (A.59) \]

\[ \alpha_d = 1.6 \times 10^{-4} \cdot e^{-V/48.4}, \quad \beta_d = \frac{1}{1 + e^{(39-V)/10}} \quad (A.60) \]

The Ca\(^{2+}\)-dependent K\(^+\) (SK) current, \(I_{AHP}\), is described by

\[ I_{AHP} = \bar{g}_{AHP} q^2 (V - E_K) \quad (A.61) \]

\[ \frac{dq}{dt} = \alpha_q (1 - q) - \beta_q q \quad (A.62) \]

\[ \alpha_q = \frac{0.00246}{e^{-12 \log_{10}([Ca^{2+}]) + 28.48}/4.5}, \quad \beta_q = \frac{0.006}{e^{(12 \log_{10}([Ca^{2+}]) + 60.4)/35}} \quad (A.63) \]

\[ \frac{d[Ca^{2+}]_i}{dt} = B \sum_{T,N,L} I_{Ca} - \frac{[Ca^{2+}]_i - [Ca^{2+}]_0}{\tau} \quad (A.64) \]

where \( B = 5.2 \times 10^{-6}/(A \cdot d) \) in units of M/(C m\(^3\)) for a shell of surface area \( A \) and thickness \( d \) (0.2 \( \mu \)m), and \( \tau = 10 \) ms was the calcium removal rate. \([Ca^{2+}]_0 = 5 \) \( \mu \)M was the resting calcium concentration.

The Ca\(^{2+}\) and voltage-dependent K\(^+\) (BK) current, \(I_C\), is

\[ I_C = \bar{g}_C \cdot o (V - E_K) \quad (A.65) \]

where \( o \) is the activation variable (Migliore et al., 1995).

The A-type K\(^+\) current, \(I_A\), is described by

\[ I_A = \bar{g}_A a b (V - E_K) \quad (A.66) \]

\[ \frac{da}{dt} = \alpha_a (1 - a) - \beta_a a \quad (A.67) \]

\[ \alpha_a = \frac{0.02 (13.1 - V)}{e^{(13.1 - V)/10} - 1}, \quad \beta_a = \frac{0.0175 (V - 40.1)}{e^{(V - 40.1)/10} - 1} \quad (A.68) \]

\[ \frac{db}{dt} = \alpha_b (1 - b) - \beta_b b \quad (A.69) \]

\[ \alpha_b = 0.0016 e^{-(V+13)/18}, \quad \beta_b = \frac{0.05}{1 + e^{(10.1-V)/5}} \quad (A.70) \]

The L-type Ca\(^{2+}\) current, \(I_{CaL}\), is described by

\[ I_{CaL} = \bar{g}_{CaL} s^2_\infty V \frac{1 - [Ca^{2+}]_i}{[Ca^{2+}]_0} \frac{e^{2FV/kT}}{1 - e^{2FV/kT}} \quad (A.71) \]
where $s_{\infty}$ is the steady-state activation variable, $F$ is Faraday’s constant, $T$ is the temperature, $k$ is Boltzmann’s constant, $[\text{Ca}^{2+}]_0$ is the equilibrium calcium concentration and $[\text{Ca}^{2+}]_i$ is described above. The activation variable, $s_{\infty}$, is then

$$s_{\infty} = \frac{\alpha_s}{\alpha_s + \beta_s}, \quad \alpha_s = \frac{15.69(81.5 - V)}{e^{(81.5 - V)/10} - 1}, \quad \beta_s = 0.29e^{-V/10.86} \quad (A.72)$$

### A.3 OLM cell model

Active properties are derived from the model of Saraga et al. (2003). The somatic (s), axonic (a) and dendritic (d) compartments of each OLM cell obeyed the following current balance equations:

$$C_m \frac{dV}{dt} = I_{\text{ext}} - I_L - I_{\text{Na,s}} - I_{\text{K,s}} - I_A - I_{\text{syn}} \quad (A.73)$$

$$C_m \frac{dV}{dt} = I_{\text{ext}} - I_L - I_{\text{Na,d}} - I_{\text{K,d}} - I_A - I_{\text{syn}} \quad (A.74)$$

$$C_m \frac{dV}{dt} = I_{\text{ext}} - I_L - I_{\text{Na,a}} - I_{\text{K,a}} \quad (A.75)$$

The conductance and reversal potential values per compartment are listed in Table A.4.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Soma</th>
<th>Dendrite</th>
<th>Axon</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_m \quad \mu\text{F/cm}^2$</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>$R_a \quad \Omega\text{cm}$</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Leak conductance [S/cm^2]</td>
<td>$5.0 \times 10^{-5}$</td>
<td>$5.0 \times 10^{-5}$</td>
<td>$5.0 \times 10^{-5}$</td>
</tr>
<tr>
<td>$E_L \quad \text{mV}$</td>
<td>-70</td>
<td>-70</td>
<td>-70</td>
</tr>
<tr>
<td>Sodium cond. [S/cm^2]</td>
<td>0.0107</td>
<td>0.0234</td>
<td>0.01712</td>
</tr>
<tr>
<td>$E_{\text{Na}} \quad \text{mV}$</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Delayed rectifier K(^+) cond. [S/cm^2]</td>
<td>0.0319</td>
<td>0.046</td>
<td>0.05104</td>
</tr>
<tr>
<td>$E_K \quad \text{mV}$</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>A-type K(^+) cond. [S/cm^2]</td>
<td>0.0165</td>
<td>0.004</td>
<td>-</td>
</tr>
<tr>
<td>$E_A \quad \text{mV}$</td>
<td>-100</td>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>$I_h$ cond. [S/cm^2]</td>
<td>0.0005</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$E_h \quad \text{mV}$</td>
<td>-32.9</td>
<td>-32.9</td>
<td>-32.9</td>
</tr>
</tbody>
</table>

Table A.4 – Passive parameters and active ionic conductances of channels for all compartments of OLM model cells.

The sodium current is described by

$$I_{\text{Na}} = g_{\text{Na}} m^3 h (V - E_{\text{Na}}) \quad (A.76)$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \quad (A.77)$$
\[
\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h
\]  
(A.78)

where \(m\) and \(h\) are the activation and inactivation variables, respectively. The forward and backward rate constants are described by

\[
\begin{align*}
\alpha_{m, \text{soma/axon}} &= -0.1 \frac{(V + 38)}{e^{-\frac{(V+38)/10}{10}} - 1}, \\
\beta_{m, \text{soma/axon}} &= 4 e^{-\frac{(V+63)/18}{18}} \\
\alpha_{h, \text{soma/axon}} &= 0.07 e^{-\frac{(V+63)/20}{20}}, \\
\beta_{h, \text{soma/axon}} &= \frac{1}{1 + e^{-\frac{(V+33)/10}{10}}} \\
\alpha_{m, \text{dend}} &= -0.1 \frac{(V + 45)}{e^{-\frac{(V+45)/10}{10}} - 1}, \\
\beta_{m, \text{dend}} &= 4 e^{-\frac{(V+70)/18}{18}} \\
\alpha_{h, \text{dend}} &= 0.07 e^{-\frac{(V+70)/20}{20}}, \\
\beta_{h, \text{dend}} &= \frac{1}{1 + e^{-\frac{(V+40)/10}{10}}}
\end{align*}
\]  
(A.79 - A.82)

The potassium current, \(I_K\), is described by

\[
I_K = \mathcal{g}_K n^4 (V - E_K)
\]  
(A.83)

\[
\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n
\]  
(A.84)

where \(n\) is the activation variable for this channel. The forward and backward constants are described by

\[
\begin{align*}
\alpha_{n, \text{soma/axon}} &= -0.018 \frac{(V - 25)}{e^{-\frac{(V-25)/25}{25}} - 1}, \\
\beta_{n, \text{soma/axon}} &= \frac{0.0036 (V - 35)}{e^{\frac{(V-35)/12}{12}} - 1} \\
\alpha_{m, \text{dend}} &= -0.018 \frac{(V - 20)}{e^{-\frac{(V-20)/21}{21}} - 1}, \\
\beta_{m, \text{dend}} &= \frac{0.0036 (V - 30)}{e^{\frac{(V-30)/12}{12}} - 1}
\end{align*}
\]  
(A.85 - A.86)

The transient potassium current, \(I_A\), is described by

\[
I_A = \mathcal{g}_A \ a b (V - E_K)
\]  
(A.87)

\[
\begin{align*}
\frac{da}{dt} &= \frac{a_a - a}{\tau_a}, \\
\frac{db}{dt} &= \frac{b_a - b}{\tau_b}, \\
a_a &= \frac{1}{1 + e^{-\frac{(V+14)/16.6}{16.6}}}, \\
b_a &= \frac{1}{1 + e^{-\frac{(V+71)/7.3}{7.3}}}, \\
\tau_a &= 5 \text{ ms} \\
\tau_b &= \frac{1}{\alpha_b - \beta_b}
\end{align*}
\]  
(A.88 - A.89)

where \(a\) and \(b\) are the activation and inactivation variables, respectively. The rate constants are given by

\[
\begin{align*}
\alpha_b &= \frac{0.000009}{e^{\frac{(V-26)/18.5}{18.5}}}, \\
\beta_b &= \frac{0.014}{0.2 + e^{-\frac{(V+70)/11}{11}}}
\end{align*}
\]  
(A.90)

The non-specific cation channel, \(I_h\), is described by

\[
I_h = \mathcal{g}_h r (V - E_r)
\]  
(A.91)

\[
\frac{dr}{dt} = \frac{r_a - r}{\tau_r}
\]  
(A.92)
where $r$ is the activation variable for this channel. The steady-state activation curve and time constant are given by

$$r_{\infty} = \frac{1}{1 + e^{(V+84)/10.2}}, \quad \tau_r = \frac{1}{e^{-(17.9+0.11 \cdot V)} + e^{0.09 \cdot V-1.84} + 100} \quad (A.93)$$

### A.4 Network input spike trains

**Septal cells**

Septal cell output was modelled as bursts of action potentials using a presynaptic spike generator. A spike train consisted of bursts of action potentials at a mean frequency of 50 Hz for a half-theta cycle (125 ms; corresponding to a recall period) followed by a half-theta cycle of silence. Due to 40% noise in the interspike intervals, the 10 spike trains in the septal population were asynchronous.

**Entorhinal cells (EC)**

EC cells were also modelled as noisy spike trains, using a presynaptic spike generator. A spike train consisted of spikes at an average gamma frequency of 40 Hz, but with individual spike times Gaussian-distributed around the regular ISI of 25 ms, with a standard deviation of 0.2. The population of EC inputs fired asynchronously.

**CA3 pyramidal cells**

CA3 pyramidal cells were modelled as spike trains of the same form and with the same characteristics (mean frequency and noise level) as the EC cells. Onset of CA3 firing was delayed by 9 ms relative to the EC trains to model the respective conduction delays of direct and trisynaptic loop inputs to CA1.

### A.5 Synaptic currents

In addition to the above channel mechanisms, AMPA, NMDA, GABA_A and GABA_B synaptic mechanisms are implemented in the model.

All synaptic currents were modeled using dual exponential conductance waveforms. The parameters for the synaptic currents used are listed in Table A.5. All connection strengths (maximum conductances) of the different pathways are listed in Table A.6.
### Appendix A

#### Table A.5 – Synaptic parameters.

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<tr>
<th>Mechanism</th>
<th>AMPA</th>
<th>NMDA</th>
<th>GABA&lt;sub&gt;A&lt;/sub&gt;</th>
<th>GABA&lt;sub&gt;B&lt;/sub&gt;</th>
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<td>Fall [ms]</td>
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<td>Reversal potential [mV]</td>
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<th>Sep</th>
<th>Pyr</th>
<th>AAC</th>
<th>BC</th>
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Table A.6 – Synaptic conductance parameters (in µS). Text in parenthesis signifies the type of postsynaptic receptor.

#### Pyramidal cell

Axonic (a) and somatic (s) compartments receive GABA<sub>A</sub> inhibition from axo-axonic and basket cells, respectively. The radiatum-proximal (Rad-Prox) compartment receives recurrent excitation via AMPA synapses from its neighboring P cells, whereas the radiatum-medium (RadMed) compartment receives both AMPA and NMDA excitation from the CA3 Schaffer collateral input and GABA<sub>A</sub> and GABA<sub>B</sub> inhibition from the bistratified cells. The RadMed AMPA synapse is plastic and changes according to the Eq. (6.1)-(6.3). The lacunosum-moleculare thick (LM-T) compartment receives AMPA excitation from the EC perforant path and GABA<sub>A</sub> and GABA<sub>B</sub> inhibition from the OLM cells.
CA1 microcircuit model in detail

**Axo-axonic cell**

Radiatum-thick (Rad-T) and radiatum-medium (Rad-M) compartments received AMPA excitation from the CA3 Schaffer collateral input. LM-medium (LM-M) compartment received AMPA excitation from the EC perforant path input, whereas the Ori-T compartment received AMPA excitation from the P cell feedback excitation and GABA-mediated inhibition from the septum.

**Basket cell**

Radiatum-thick (Rad-T) and radiatum-medium (Rad-M) compartments received AMPA excitation from the CA3 Schaffer collateral input. LM-medium (LM-M) compartment received AMPA excitation from the EC perforant path input, whereas the Ori-T compartment received AMPA-mediated excitation from the P cell feedback excitation and GABA-mediated inhibition from the septum. The somatic compartment received $\text{GABA}_A$ synaptic inhibition from neighboring basket and bistratified cells.

**Bistratified cell**

The radiatum-thick (Rad-T) and radiatum-medium (Rad-M) compartments received AMPA synaptic excitation from the CA3 Schaffer collateral input. The somatic compartment received $\text{GABA}_A$ inhibition from neighboring bistratified cells. The Ori-T compartment received AMPA excitation from the P cell feedback excitation and GABA-mediated synaptic inhibition from the septum.

**OLM cell**

Each OLM cell received AMPA excitation in their dendrites from the P cells and GABA-mediated inhibition from the septum.
Bibliography
REFERENCES FOR INTRODUCTION


REFERENCES FOR CHAPTER 1


REFERENCES FOR CHAPTER 2


REFERENCES FOR CHAPTER 3


REFERENCES FOR CHAPTER 4


REFERENCES FOR CHAPTER 5


REFERENCES FOR CHAPTER 6


REFERENCES FOR CHAPTER 7


REFERENCES FOR CONCLUSIONS


REFERENCES FOR APPENDIX A


