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Biophysics of Computation: Neurons, Synapses and Membranes

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Synapses, membranes and neurotransmitter play an important role in processing information in the nervous system. We do not know, however, what biophysical mechanisms are critical for neuronal computations, what elementary information processing operations they implement, and which sensory or motor computations they underlie. In this paper, we outline an approach to these problems. We review a number of different biophysical mechanisms, such as synaptic interactions between excitation and inhibition, dendritic spines, non-impulse generating membrane nonlinearities and transmitter-regulated voltage channels. For each one, we discuss the information processing operations that may be implemented. All of these mechanisms act either within a few milliseconds, such as the action potential or synaptic transmission, or over several hundred milliseconds or even seconds, modulating some property of the circuit. In some cases we will suggest specific examples where a biophysical mechanism underlies a given computation. In particlar, we will discuss the neuronal operations, and their implementation, underlying direction selectivity in the vertebrate retina.

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Abstract

Synapses, membranes and transmitters play an important role in processing information in the nervous system. We do not know, however, what biophysical mechanisms are critical for neuronal computations, what elementary information processing operations they implement, and which sensory or motor computations they underlie. In this paper, we outline an approach to these problems. More precisely

(1) we review the mechanisms underlying impulse initiation and conduction, repetitive firing of impulses and the failure of impulses to propagate past axonal branch points, analyzing some of the underlying operations.

(2) We discuss chemical and electrical transduction at the synapse. The operation performed by a chemical synapse is non-linear amplification and is equivalent to a non-reciprocal electrical element. Electrical synapses are equivalent to linear and non-linear resistances, such as diodes.

(3) We introduce postsynaptic interaction between conductance changes. In the specific case of excitation and shunting inhibition, the operation implemented is the analog equivalent of an AND-NOT gate or a veto operation. This mechanism may be the key component in the circuitries computing direction of motion in the retina and depth in cortical cells.

(4) We analyze the function of dendritic spines. Two of the operations that may be implemented by dendritic spines are changing the synaptic weight of a synapse and subserving a very specific interaction between excitation and inhibition. Examples of possible computations are information storage in the cortex and the selective suppression of visual input in the LGN.

(5) We consider the role of quasi-active membranes, i.e., time- and voltage-dependent channels. Short of underlying spiking behavior, they can perform different filtering operations, acting as resonant filters. An example of a specific computation is the tuning of hair cells to acoustic inputs.

(6) Finally we consider transmitter regulation of voltage dependent channels and the action of neurotransmitters at large distances. We discuss how the non-classical action of these neuromodulatory substances may affect the circuitry in a very specific manner over long time-courses.

We will conclude by discussing a possible distinction between biophysical mechanisms acting over short and long time ranges. Finally, we will present a new biophysical model of analog computation which is very different from the model of computation provided by present digital computers and appears to be very suggestive in terms of the nervous system.

0. Introduction

This paper is based on the belief that brains are very sophisticated computing machines, and that one of the ultimate goals of brain science is to understand the computations and information processing they perform. A study of the role of synapses, membranes and cells in information processing tasks is therefore part of this broad enterprise. But this is not the only motivation for such a study. In recent years, computational studies have provided promising — although far from complete — theories of the computations necessary for sensory processing (for partial reviews see Marr, 1982 and Poggio, 1984). Despite their initial success, we have now come to realize that computational theories, even complemented by psychophysical experiments, have inherent limitations in understanding the brain. A given computation, for instance the computation of stereo depth or motion, can in general be performed by several different algorithms. These algorithms depend not only on the nature of the computation itself, but also on the properties and limitations of the hardware in which the algorithm is implemented.

As a consequence, for bridging the gap between the computational theories and the biological data, we must first understand how the elementary computations are performed in neural hardware. Neurobiologists have shown in recent years with such experimental findings as dendrodendritic synapses, gap junctions, dendritic spikes, nonsynaptic release of neural transmitters and a variety of voltage- and transmitter-dependent channels that the complexity of the processing that takes place within a single neuron may be far greater than previously presumed (see Schmitt and Worden (1979) for a thorough review of this developement). An understanding of the role of these biophysical mechanisms in biological information processing is necessary, in order to understand the implementation of specific computations in neuronal hardware.

In Computer Science, work on the *physics of computation* attempts to characterize the physical mechanisms that can be exploited to perform elementary information processing operations in technical systems (Mead and Conway, 1980). These mechanisms constrain in turn the types of operation which can be exploited for computing. A case in point is the so-called metal - oxide - semiconductor (MOS) technology used in integrated circuits. Due to the physics of the MOS transistor, the basic logic circuit is an inverter, whose output is the complement of its input. NAND and NOR logic circuits can be constructed as simple expansions of the basic inverter circuit. Therefore, very large scale integrated (VLSI) systems in MOS technology use NAND and NOR logic (Mead and Conway, 1980). We believe that a *biophysics of computation* is now needed for understanding the role of neurons, synapses and membranes in information processing in biological systems.

Simply stated, the questions that we are asking are: what is the hardware of the brain? Where

are the elementary information processing operations performed? What is the equivalent in nervous systems of transistors and gates? In this paper, we outline our initial approach to these questions. We review briefly some of the biophysical mechanisms, both in synapses and membranes, that may have a role in information processing. For each one, we discuss the information processing operations that may be implemented. In some cases, we will also suggest specific computations, such as the computation of the direction of motion, where the given operation may have an important role. Table 1 gives a list of biophysical mechanisms, of corresponding information processing operations and of specific examples of computations where each mechanism may be used. The list is not intended to be exhaustive.

This paper is speculative. Its main goal is to state the problem — what are the biophysical mechanisms underlying information processing and how are these mechanisms used to perform specific computations — and to stimulate experimental and theoretical research that can lead to its answer. As we will discuss later, many biophysical mechanisms may have only an indirect role in computations in the nervous system and be, so to speak, side effects of cell's properties. The situation is not much different in our present computers: many of the components are dedicated to functions, such as supplying power, that are only indirectly relevant to the elementary information processing operations. Ultimately, only experimental work can answer which biophysical mechanisms are used in information processing, and how. Computational considerations in conjunction with computer simulations can help, however, to direct effectively experimental work.

In this paper we consider several biophysical mechanisms of neuronal membranes and synapses. For each one we discuss the information processing operation that it may implement. For instance, the mechanism leading to action potentials performs a threshold operation similar to the analog-to-digital conversion performed by a Schmitt-trigger. A subset of these operations is sufficient to synthesize a universal computer. All together they provide the nervous system with a powerful set of basic hardware operations in terms of which simple and complex computations and algorithms can be implemented. Whenever possible, we speculate about a specific instance of computation where the biophysical mechanism may play a central role. The best example is probably the computation of the direction of motion in retinal ganglion cells. We suggest that the underlying mechanism is the interaction of excitatory and inhibitory conductance changes of postsynaptic origin.

Section 1 considers the biophysical mechanisms of spike initiation and conduction and the corresponding information processing operations. It also describes a specific example of a computation (for motor control) that exploits the mechanism of differential spike conduction in branching axonal trees. Synapses are discussed in section 2. We first characterize from the point of view of information processing chemical synapses, then electrical synapses

and finally the postsynaptic interactions between synaptic conductance changes. Several examples of computations are suggested. Experiments for testing these hypotheses are also described. Dendritic spines and their possible role in information storage and processing are the subject of section 3. The mechanisms of non-spiking voltage- and time-dependent channels are introduced in section 4.1. As an example of a computation, we describe the resonant tuning of hair cells in the vertebrate cochlea. Transmitter regulation of voltage dependent channels is the subject of section 4.2 and neuropeptides of section 4.3. The final section discusses the distinction between biophysical mechanisms acting in the millisecond range, such as conductance changes or impulse initiation, and the class of mechanisms which modulate the processing of information via these fast mechanisms on a long time scale. We will also briefly allude to a novel model of information processing in analog electrical or chemical networks. Such a model could be easily implemented in neuronal hardware, suggesting a style of neuronal computation very different from threshold models of the McCulloch and Pitts type.

LIST OF SOME NEURONAL OPERATIONS AND THE UNDERLYING BIOPHYSICAL MECHANISMS

Biophysical Mechanism	Neural Operation	Example of Computation
Action potential initiation	analog OR/AND 1-bit analog-to-digital converter	
Repetitive spiking activity	current-to-frequency transducer	
Action potential conduction	impulse transmission	long-distance communication in axons
Conduction failure at axonal branch points	temporal/spatial filtering of impulses	opener muscle in crayfish
Chemically-mediated synaptic transduction	non-reciprocal 2-port "negative" resistance sigmoid "threshold"	
Electrically-mediated synaptic transduction	reciprocal 1-port resistance	coupling of rod photoreceptors to enhance detection of signals
Distributed excitatory synapses in dendritic tree	linear addition	α, β cat retinal ganglion cells bipolar cells
Interaction between excitatory and (shunting) inhibitory conductance inputs	analog AND-NOT, veto operation	directional selective retinal ganglion cells disparity selective cortical cells
Excitatory synapse on dendritic spine with calcium channels	post-synaptic modification in functional connectivity	short- and long-term information storage
Excitatory and inhibitory synapse on dendritic spine	local AND-NOT "presynaptic inhibition"	enabling/disabling retinal input to geniculate X-cells
Quasi-active membranes	electrical resonant filter analog differentiation delay	hair cells in lower vertebrates
Transmitter regulation of voltage-dependent channels (M-current inhibition)	gain control	
Ca^{2+}- sensitivity of cAMP-dependent phosphorylation of K^+-channel protein	functional connectivity	adaptation and associative storage of information in Aplysia
Long-distance action of neurotransmitter	modulating and routing transmission of information	

1. Impulse Initiation and Conduction

Action potential initiation and propagation were among the first biophysical mechanisms that were elucidated. Action potentials and their generation represent such a dominant feature of the nervous system, that for a considerable amount of time it was widely held that they underly all information processing in the nervous system. In the next four sections, we will provide a brief overview of their possible role in information processing.

1.1 Impulse Initiation

1.1.1 Biophysical Mechanism

The first quantitative analysis of the currents underlying the action potential was done on the squid giant axon (Hodgkin and Huxley, 1952; for a summary, consult Katz, 1966; Hodgkin, 1964). The responsible agents are voltage-dependent Na^+channels, described by two variables m and h. The inward current flowing through these channels is given by

$$I_{Na}(t) = \bar{g}_{Na} m^3 h (V(t) - E_{Na}),$$

where $V(t)$ is the voltage across the membrane, E_{Na} is the reversal potential associated with the sodium ions and $\bar{g}_{Na}$ is a constant. The activation variable, m, increases with increasing depolarization, while h, the inactivation variable, decreases. When the membrane is depolarized, the Na^+ conductance begins to increase, depolarizing the membrane further, and so on. This cycle proceeds until the membrane reaches the potential at which there is no more driving potential for the sodium ions, i.e. $V = E_{Na}$, and until voltage-dependent inactivation sets in. In the meantime a counteracting, outward current, mediated by the outflow of potassium, is activated. It it usually described by

$$I_K(t) = \bar{g}_K n^4 (V(t) - E_K),$$

where n is the corresponding activation variable. Concurrent with the activation of the outward potassium current, the inward sodium current begins to inactivate, reducing the voltage to levels slightly below the initial resting level (see figure 1). Action potentials are all-or-none events, and therefore highly non-linear. Below *threshold*, a stimulus elicits only a local, graded response; above threshold, the membrane goes through its stereotyped voltage change independent of the stimulus intensity. Action potentials are all-pervasive, occuring in both vertebrates and invertebrates (Hagiwara, 1983).

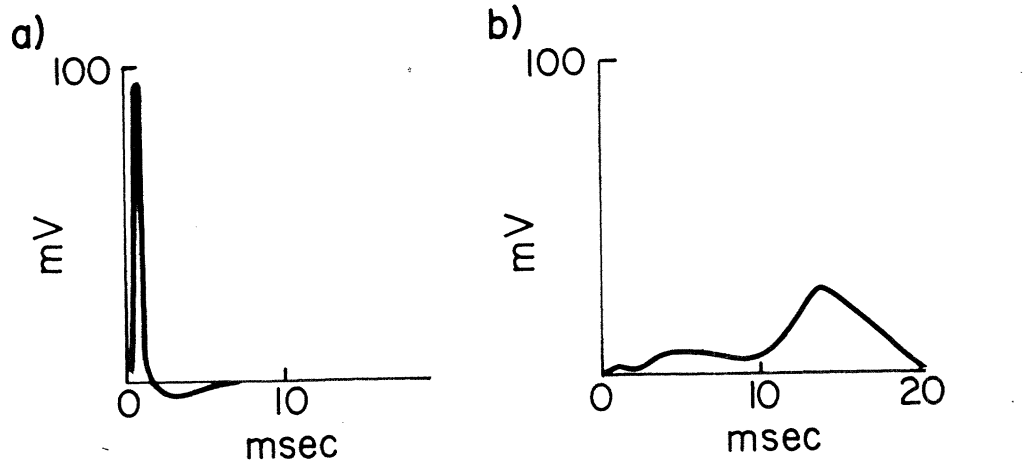

Figure 1. Typical axonal sodium (a) and dendritic calcium (b) action potential. Axonal spikes, in this case from the squid axon, display amplitudes of about $100mV$ and have a pulse width of about $1ms$. Dendritic spikes typically have lower amplitudes and are more "smeared out". Shown is a Purkinje-cell dendritic spike following blockage of sodium current with TTX. Note the humps in the curve that suggest the presence of multiple sites for spike initiation. Adapted from Llinas, 1979.

Calcium currents are also known to trigger all-or-none electrical events (Kleinhaus and Prichard, 1975; Schwartzkroin and Slawsky, 1977; Wong, Prince and Basbaum, 1979; Llinas and Sugimori, 1980; Llinas and Yarom, 1981; Jahnsen and Llinas, 1984). Since most Ca-channels do not inactivate readily, their time course is usually longer than the time course of sodium spikes. Moreover, while the sodium conductances giving rise to spikes are predominately found in cell bodies and axons, high-threshold Ca^{2+} spikes are believed to originate in the dendritic trees of neurons of the vertebrate CNS.

1.1.2 Neuronal Operation

The basic operation implemented by such a threshold mechanism is a digital OR or AND gate. If the threshold is low enough, a single electrical input will be able to surpass the threshold and trigger a spike. For larger threshold values, two or more converging inputs may be required to elicit a spike. The dependance of this scheme on the value of the threshold seems important in light of the observation that the threshold for eliciting spikes is known to depend on the prior spiking history. Thus, the firing threshold in frog sciatic nerve fibers and in cat motoneurons can increase by a factor of two for prolonged spiking activity (Raymond, 1979; Schwindt and Crill, 1982).

The threshold scheme underlies a second operation: converting an analog graded signal, intracellular current or membrane potential, into a digital event, the spike. It is thus similar to a *1-bit analog-to-digital* converter.

1.1.3 An Example of a Computation

The early and influential view of information processing in neurons was expressed well in the threshold neuron model of McCulloch and Pitts (1943). In the most common version of this model, the neuron is considered as the elementary processing unit that receives excitatory and inhibitory inputs leading to depolarizing and hyperpolarizing dendritic potentials. These are subsequently propagated to the soma where they contribute—in a linear fashion—to the somatic potential. If the somatic potential exceeds a given threshold, a spike is initiated and transmitted along the axon. Otherwise the neuron remains silent. It is fairly straightforward to show that a set of these threshold-neurons is *complete*, that is every input-output behavior can be reproduced by appropriate combinations of threshold-neurons (given a fixed input-output coding in some fixed alphabet, like $\{0,1\}$; Kleene, 1956; Palm, 1982).

1.2 Repetitive Spiking Activity

1.2.1 Biophysical Mechanism

One distinguishing characteristic of different types of neurons is their response to prolonged current injections or synaptic input. Responses range from a single burst to tonic, continuous spiking which can increase linearly or non-linearly with increasing stimulus amplitude. If the average firing frequency in response to a constant-current pulse in cat spinal motoneurons is plotted against the injected current strength, the resulting plot, the $f-I$ curve, is best described by two linear segments (figure 2). The steeper linear segment has been termed secondary range and the shallower segment the primary range (Kernell, 1970; Schwindt and Crill, 1982). For cat extraocular motoneurons and frog lumbar motoneurons, the $f-I$ curve is best described by only one linear segment.

The underlying biophysical mechanisms are a slow, outward, calcium-dependent potassium current I_{KS}, a persistent calcium current I_i and the accommodative properties of the axon initial segment which lead to a rise in firing threshold with increasing firing rate (Schwindt and Crill, 1982; Crill and Schwindt, 1983). The potassium current is activated at $10mV$ or greater (relative to the resting potential E_{rest} of the cell) and is partially responsible for the long afterhyperpolarization present in motoneurons. I_i is a steady, inward current activated at voltages traversed by the cell during steady rhythmic firing, showing little evidence of voltage-dependent inactivation. Depolarizing the membrane activates I_i, adding a substantial inward current and increasing the firing rate. I_{KS} and the increase in firing threshold have the converse effect, reducing the $f-I$ slope. Thus, the relative strengths of the tonic inward current and the outward current are the major determinant of the $f-I$ relationship.

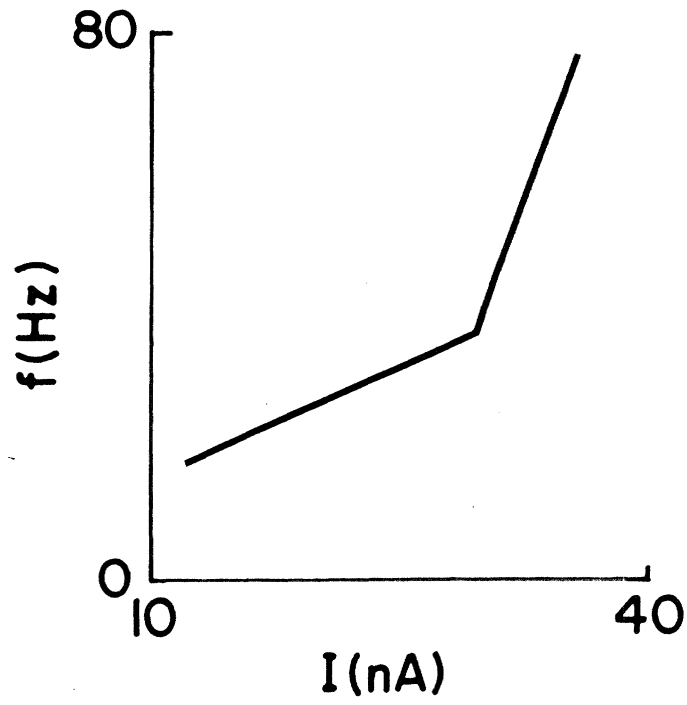

Figure 2. Average steady-state impulse frequency (f) plotted against intensity of injected current (I) in a spinal α motoneuron. There is an approximately linear relation between I and f over a range of lower and higher discharge frequencies (termed "primary" and "secondary" range). Adapted from Kernel, 1970.

It is easy to imagine a calcium current which is already activated near the resting potential and which inactivates for depolarization. Injecting more and more current into the cell causes a "compensatory" decrease in I_i through voltage-dependent inactivation of the calcium currents. The net effect may be a constant firing frequency, relatively independent of the injected current. Calcium channels in egg cell membrane do inactivate for increasing levels of membrane depolarization (Fox, 1981). The inactivation kinetics of the Ca^{2+} current in this case is similar to, but slower, than the kinetics of the Na^{+} channel.

1.2.2 Neuronal Operation

A single action potential carries only 1 bit of information, if its timing is irrelevant. Information is most likely coded in terms of the interval between succesive action potentials. In many instances the nervous system might well use the average spiking frequency as a convenient measure of information. The $f - I$ relationship discussed above would then serve as *current-to-frequency transducer*, converting one sort of graded signal, current, into another, spike frequency. Note that at this level of description, the code used is no longer digital, but analog. The slope of the $f - I$ relationship is primarily governed by two currents, I_{KS}

and I_i. Reducing or enhancing their amplitude, by applying for instance a neurotransmitter or a neuropeptide to the cell, may change the slope of the input-output relationship.

1.3 Impulse Conduction

1.3.1 Biophysical Mechanism

In a cable with a sufficient number of voltage dependent Na^+ and K^+ channels, electrical impulses can propagate in a non-decremental fashion. Once an action potential has been initiated, the initial sodium current will spread to neighboring membrane patches, depolarizing the membrane and going through exactly the same cycle, and so on, down the length of the axon (Katz, 1966; Jack, Noble and Tsien, 1975). Since the shape of the spike remains constant over the whole length of the axon, the conduction is non-decremental. There are two different groups of spike-conducting fibers, myelinated and unmyelinated fibers.

In myelinated axons, only found in vertebrates, conduction does not proceed continuously along the fiber, but jumps, as it were, from node to node. The channels responsible for the regenerative action potential concentrate at these small specialized sites (called nodes of Ranvier). This is known as *saltatory conduction*. The space between the nodes, the internodal segment, is covered by several hundred layers of myelin, what amounts to a high-resistance and low-capacity insulating substance (see, however, Funch and Faber, 1984). While the two dominant currents for non-myelinated axons are sodium and potassium carried, the impulse at the mammalian node of Ranvier is generated almost exclusively by sodium currents (Chiu, Ritchie, Rogart and Stagg, 1979). Potassium channels may however be present below the internodal axonal membrane (Chiu and Ritchie, 1980, 1984; Kocsis and Waxman, 1980). Because ionic currents flow only at the node in myelinated fibers, saltatory conduction is also favorable from a metabolic point of view. Less energy must be expended by the $Na-K$ pump in restoring the Na^+ and K^+ concentration gradients, which tend to run down as a result of prolonged spike activity in small fibers.

Since axons can be up to several tens of centimeters long, the total travel time of the electrical impulses is of crucial importance. In unmyelinated fibers, the conduction times of action potentials is proportional to the square root of the fiber diameter (figure 3). In myelinated fibers, the conduction times are considerably decreased, being directly proportional to the diameter (Rushton, 1951; Pickard, 1969; Ritchie, 1982). Propagation velocity also depends on the number of active channels. If their number drops below a critical value, non-decremental propagation ceases (Sabah and Leibovic, 1972).

1.3.2 Neuronal Operation

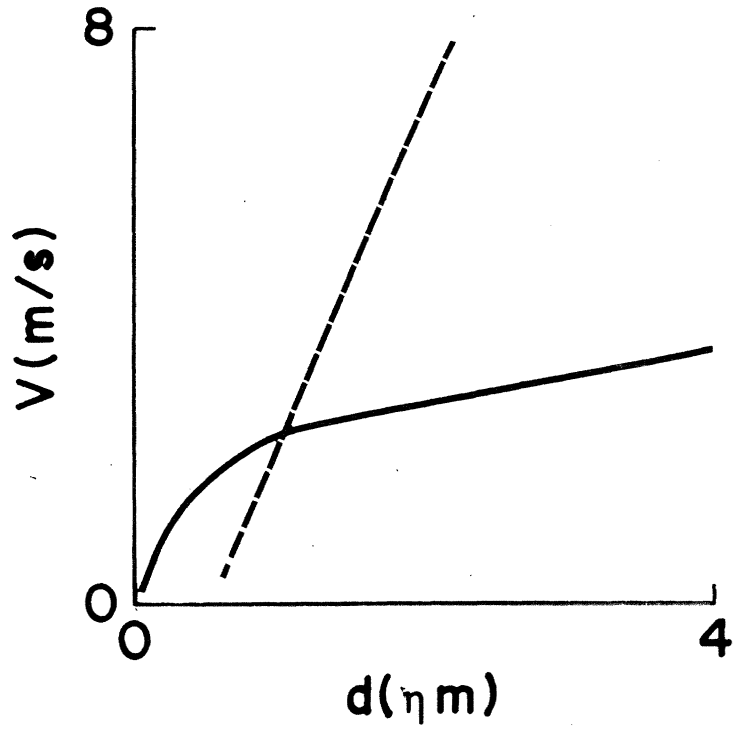

Figure 3. Relation between conduction velocity of action potentials, v, and fiber diameter d for small myelinated and non-myelinated fibers. Adapted from Waxman and Bennett, 1972.

The axon is the equivalent of the wire or interconnect *between* (and not so much within) silicon chips, connecting the different computational devices, neurons, with a high-speed pathway. Thus, its main function is the transmission of impulses, viz. the transmission of information. The reliability of transmission depends on a number of factors, most notable the spike frequency and the specific morphology of the axon (see next section). Axons can have an extensive fan-out, making contact with a multitude of postsynaptic targets, via highly branched axonal trees (for an example in the visual cortex of the cat see Gilbert and Wiesel, 1983).

1.4 Axonal Trees

The all-or-none nature of action potentials has led to the idea that the axon serves mainly as reliable transmission line, connecting two or more information processing devices. The axon itself is assumed to lack any processing function. This view might have to be broadened with the findings that in regions of membrane and geometrical inhomogenities the transmission of action potentials depends on a number of parameters, such as the geometry of the axon and the previous spiking history (for instance Krnjevic and Miledi, 1959; Tauc and Hughes, 1963; Bittner, 1968; Chung, Raymond and Lettvin, 1970; Grossman, Parnas and

Spira, 1979a,b).

1.4.1 Biophysical Mechanism

It has been shown both theoretically and experimentally that action potentials may fail to successfully invade the daughter branches of a bifurcating axon. As the theoretical analysis of Goldstein and Rall (1974) pointed out, the single most important parameter upon which propagation depends is the *geometric ratio*,

$$GR = \frac{d_1^{3/2} + d_2^{3/2}}{d_0^{3/2}},$$

where d_1 and d_2 are the diameters of the daughter branches and d_0 the diameter of the main axon. GR equals the impedance ratio for branches of semi-infinite length. The use of the geometrical ratio assumes that the specific membrane properties are the same in all branches. For $GR = 1$, the action potential does not "see" the branching (i.e. perfect impedance match), and it propagates without perturbation past the branch point. $GR = 1$ essentially captures Rall's equivalent tree concept (Rall, 1964). If $GR < 1$, the action potential behaves as if the axon tapers and it speeds up. The more interesting situation occurs if $GR > 1$, i.e. if the combined load of the daughter branches is larger than the load of the main branch. When $1 < GR < 10$, the action potential is delayed at the branch point and a "reflexion potential" appears (Parnas and Segev, 1979). If $GR = 10$ (e.g. $GR = 10$ if $d_1 = d_2 = 4.6 d_0$), propagation into *both* branches fails simultaneously, since the electrical load of the daughter branches has increased beyond the point where the initiation of the action potential in the daughter branches can be supported. Parnas and Segev (1979) emphasize that for each constant geometric ratio, changes in the diameter ratio of the daughter branches never yield differential conduction into the daughter branches.

In a study of conduction failure in a branching axon of the lobster, Grossman *et al.* (1979a) report that, although the geometrical ratio is close to one, conduction across the branch point fails at stimulation frequencies above $30 Hz$. Moreover, the conduction block appeared first in the *thicker* daughter branch and only later in the *thin* branch, thus calling for an extension of the Goldstein and Rall (1974) model. By increasing the extracellular K^+ concentration, Grossman *et al.* could mimick the block of conduction, suggesting that a differential buildup of extracellular potassium can account for the blockage. For prolonged trains of action potentials, Na^+ accumulates faster in the small diameter daughter branch, triggering the electrogenic Na^+/K^+ pump earlier than in the thick branch. Therefore, the extracellular K^+ accumulation will be reduced faster than for the thick branch, preventing the early onset of conduction block. A further factor known to affect the conduction of action potentials is the average interspike interval (Chung *et al.*, 1970).

1.4.2 Neuronal Operation

Little if anything is known about the possible relevance of action potential conduction failures for information processing. Although it seems possible to control the conduction of action potentials into different branches, such a mechanism may not be robust enough to be widely applied in the nervous system. One could even argue that conduction block is an undesirable property of the system. One possible physiological function could be the protection of the system from over-excitation by limiting the total number of spikes transmitted. One possible role of this phenomenon for information processing could be the following. Virtually all axons, like those in the motor neuron or the geniculo-cortical projection cells, branch frequently before forming their final synaptic processes. In these structures, *filtering* may occur, where the pattern of impulses in the parent axon diverges into different patterns in its daughter branches (Chung *et al.*, 1970; I. Segev, personal communication). The filtering may be *temporal*, where the frequency of the impulses in the daughter branches is different from the parent axon. On the other hand, the filtering could be *spatial*, where temporal patterns are resolved into spatial ones, i.e. different daughter branches show different firing behavior.

1.4.3 Example of a Computation

One instance where such a mechanism might be used to perform a specific function is in the excitatory motor axon innervating the muscle used for opening the claw in the crayfish. This axon branches to different regions of the opener muscle, two of which are called superficial distal and superficial central fibers. When the axon is stimulated at a frequency of $1Hz$ or less, junctional potentials (jp) recorded from the distal fibers are up to 50 times larger than jp's in central fibers. At $80Hz$, central jp's are up to four times larger than those observed in distal fibers. Since equal amounts of depolarization produce equal amounts of tension in both fiber types, it follows that distal fibers produce almost all of the total muscle tension at low frequencies of stimulation. Central fibers add an increasingly greater contribution to the total muscle tension as the corresponding nerve terminals begin to receive acton potentials in response to higher firing frequencies. The mechanism underlying this behavior is thought to be the more efficient invasion of action potentials into distal terminals at low firing frequencies (Bittner, 1968).

2. Synapses

Specialized sites of contact between neurons, called synapses, represent one of the major means of communicating information between cells. In this respect they can be compared to the *pins* on silicon chips, through which information is relayed to and from the chip. There are, of course, several critical differences. Different from today's LSI chips with at most approximately 100 pins (see Blodgett and Barbour, 1982), the dendritic tree of neurons may carry up to 10^5 (morphological) synapses. The synapses themselves not only transmit information from the presynaptic to the postsynaptic neuron, using a chemical or electrical transducing mechanism, but may already process information, i.e. perform some computation. In the following three sections, we will consider the possible role of chemical and electrical synapses in information processing.

2.1 Chemical Synapses

2.1.1 Biophysical Mechanism

We will not attempt to review the literature concerning the biophysical and molecular mechanisms underlying synaptic transmission and release (see Katz, 1966; for a good overview see Shepherd, 1979b). Suffice it to say that the release of a chemical substance, the neurotransmitter, which crosses the cleft between the pre- and postsynaptic membrane, is essentially controlled by the amount of depolarization of the presynaptic terminal. The higher the presynaptic depolarization, the stronger the postsynaptic response, which can be either hyper- or depolarization. The transduction between presynaptic and postsynaptic voltage, V_{pre} and V_{post} is usually described as either an almost linear or a sigmoidal transformation (figure 4).

The neurotransmitter diffusing across the synaptic cleft activates voltage-dependent channels in the postsynaptic membrane, resulting in a change in membrane conductance $g(t)$ in series with the ionic battery E. The conductance change induces in turn a voltage change $V_{post}(t)$ (relative to the resting potential of the cell, E_{rest}). The change in potential is given by the Volterra equation (see for instance Rall, 1967)

$$V_{post}(t) = \{g(t)(E - V_{post}(t))\} * K_{ii}(t)$$

where $K_{ii}(t)$ is the input impedance (Green function) at the postsynaptic location and $*$ represents convolution. For stationary inputs, or when the input changes slowly in comparison with the membrane time constant, this equation reduces to

$$V_{post} = \frac{g\tilde{K}_{ii}(0)E}{1 + g\tilde{K}_{ii}(0)},$$

where $\tilde{K}_{ii}(0)$ is the steady-state real input impedance at location i (essentially, the dc-component of the complex Fourier transform of $K_{ii}(t)$). For a hyperpolarizing synapse, where an increased level of presynaptic potential leads to an increase in the postsynaptic hyperpolarization, the sigmoid relation as illustrated in figure 4 will be inverted (Graubard *et al.*, 1980).

The roll-off at large depolarizations is expected in part from the finite number of receptors in the postsynaptic membrane and partly from the postsynaptic saturation effect, i.e. when the change in voltage V_{post} approaches the synaptic reversal potential E (see for instance figure 12). Subsequent increases in the presynaptic voltage, that is in the conductance $g(t)$, will fail to evoke larger potential responses. Synaptic saturation can be an important factor in limiting the total *dynamic range* of the system. For instance, the dynamic range in insect monopolar cells is $10^1 - 10^2$, in contrast to the range of the presynaptic photoreceptor, 10^5 (Shaw, 1981). One way to avoid having synapses with a low dynamic range is to distribute the synapses in the postsynaptic dendritic tree, thus minimizing synaptic saturation and avoiding the early onset of postsynaptic saturation (see section 2.3.1).

A postsynaptic response graded by the amount of presynaptic depolarization is a crucial property for many synapses. A synapse from an axon terminal is normally activated by an action potential invading the terminal, but a synapse from a dendrite may be activated by the graded depolarization of synaptic potentials within that dendrite (Graubard, 1978). In fact, graded synaptic transmission may even occur between spiking neurons: thus, neurons in the lobster stomatogastric ganglion, in addition to eliciting spike-evoked inhibitory potentials in the postsynaptic cell, also release functionally significant amounts of transmitter below the threshold for action potential (Graubard, Raper and Hartline, 1980 and 1983; see also Llinas, 1979).

One way of characterizing chemical synapses is to measure the synaptic amplification, called *sensitivity* or *dynamic gain*, by recording the change in postsynaptic voltage in response to a small change in the presynaptic voltage, i.e. dV_{post}/dV_{pre} (for a good exposition of this method see Shaw, 1981 or Llinas, 1979). The maximum value of the dynamic gain identifies the most effective operating range at a particular synapse. For the chemical synapse between the photoreceptors and the lamina monopolar cells in the dragonfly retina, the maximum dynamic gain is about 34 at presynaptic depolarizations of only $0.7mV$ (Laughlin, 1973). This system, functioning without action potentials, can optimally signal the potential evoked by a single photon in the photoreceptor. Estimations of the dynamic gain in a homologue system, the rod-to-bipolar synapse in the dogfish, give similar numbers (at

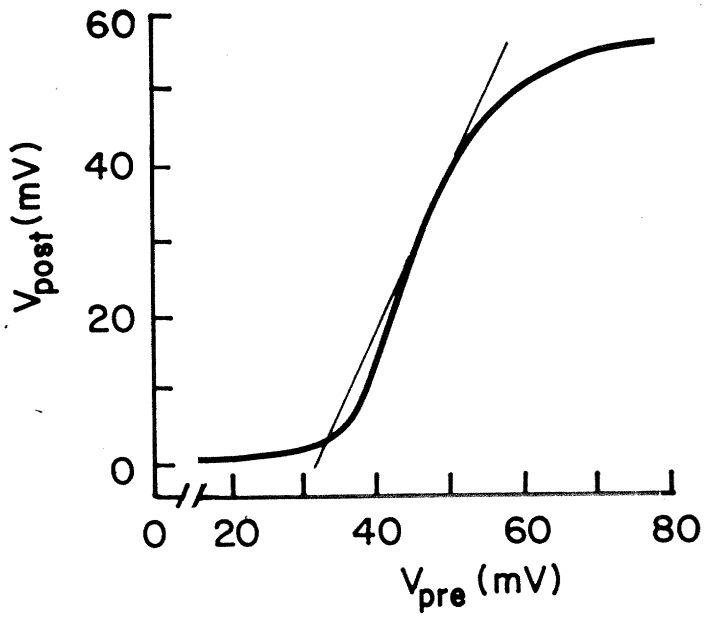

Figure 4. Input-Output relationship for a "typical" synapse from a spiking neuron, in this case the giant synapse in the squid stellate ganglion. The voltages are given with respect to the resting potential. The maximum value of the dynamic gain $dV_{post}/dV_{pre} \approx 3$. Adapted from Katz and Miledi, 1967.

least 50; Ashmore and Falk, 1976 and 1979). By contrast, values for impulse-transmitting, non-sensory synapses are considerably less: 0.3 at a lamprey central synapse (Martin and Ringham, 1975) or approximately 3 at the squid giant synapse (Katz and Miledi, 1967; see figure 4). Both cases are optimized at presynaptic depolarizations of $60 - 80mV$, with little observable transmission taking place below $30mV$. This evidence seems to suggest that in both vertebrates and invertebrates, synapses may be specialized in transmitting either very small voltages with no obvious threshold, i.e. converting one type of an analog signal into another analog signal, or in transmitting unitary impulses in a noise-free manner, i.e. converting a digital signal into an analog signal.

2.1.2 Neuronal Operation

A *chemical synapse* converts V_{pre} into V_{post} (via a chemical process) and corresponds to a *non-reciprocal 2-port* in the sense of Brayton and Moser (1964) or Oster, Perelson and Katchalsky (1971). It can be described as a two-port element, since current and voltage can be varied independently at two sites, pre- and postsynaptically. Chemical synapses are non-reciprocal, since the input and output variables cannot be exchanged. Synapses

decouple neuronal systems from each other, rather like operational amplifiers, since the postsynaptic current can be varied without any change in presynaptic current. *Reciprocal synapses*, like those found between mitral and granule cells in the olfactory bulb (Shepherd, 1979a) or between bipolar and amacrine cells in the vertebrate retina (Dowling and Boycott, 1966; Ellias and Stevens, 1972), may reintroduce reciprocity. Since V_{post} may well be larger in amplitude than V_{pre}, chemical synapses may *amplify*. Moreover, synapses can mimick positive or negative resistances, depending on whether their postsynaptic action is excitatory or inhibitory (Poggio and Koch, 1984).

2.2 Electrical Synapses

2.2.1 Biophysical Mechanism

Interaction between neurons mediated by electrical coupling is a common feature of the nervous system in both invertebrates and vertebrates, including mammals (Bennett, 1977; Korn and Faber, 1979). Effective electrical coupling between cells is achieved through specialized low-resistance connections—the *gap or electrotonic junction*. A gap junction consists of two closely apposed membranes of adjacent cells, with the two membranes separated by a $2-4nm$ space or gap. The junction itself allows the passage of ions or small molecules (of roughly $300-1500$ daltons). Usually, gap junctions can be represented by an electrical resistance, constant over a range of $\pm 25mV$ (Bennett, 1977). Note that due to different values of the input-resistances on the two sides of the junction, this does not necessarily imply symmetrical propagation of impulses. Gap junctions can be strongly unidirectional or *rectifying*. In their study of electrical transmission at the giant motor nerve synapse of the crayfish, Furshpan and Potter (1959) showed that with small potentials across the junction, conductance was rather symmetric, but with potentials exceeding a few millivolts it was markedly nonlinear and asymmetric (figure 5). It has been possible to demonstrate that junctional permeability can be reversibly modulated by intracellular pH (Spray, Harris and Bennett, 1981), voltage across the junction (Harris, Spray and Bennett, 1983) and, possible of great functional consequence, by inhibitory synapses (Spira and Bennett, 1972).

An important difference in comparison to chemically mediated synapses is the lack of a substantial delay between the "presynaptic" depolarization and the "postsynaptic" response, usually averaging at least $0.25ms$ at chemical synapses in warm-blooded animals.

2.2.2 Neuronal Operation

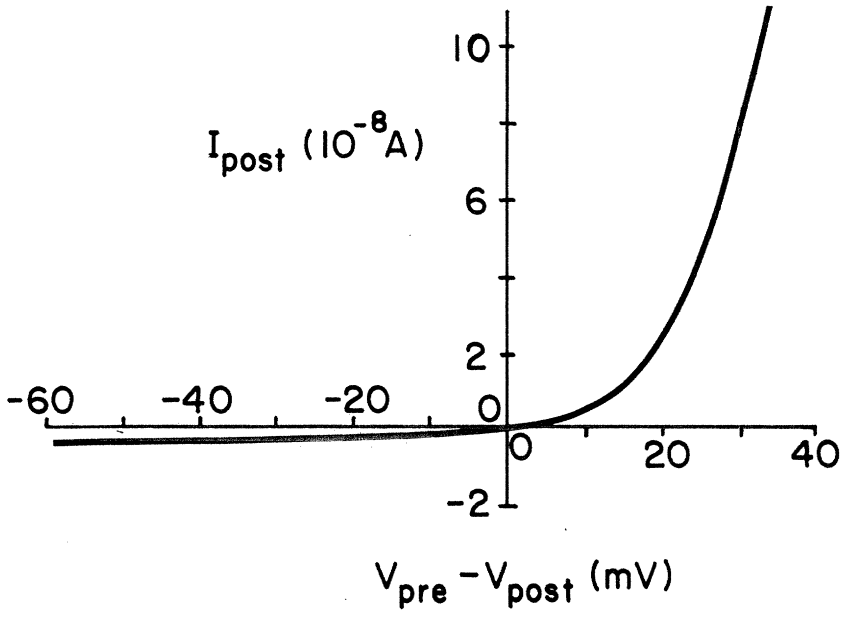

Figure 5. Current-voltage relationship of an electrical-rectifying junction in the crayfish giant motor nerve synapse. Such a synapse mimicks a diode. Adapted from Furshpan and Potter, 1959.

Electrical synapses correspond to *reciprocal 1-ports* in the sense of Brayton and Moser (1964). Varying the potential on one side of an electrical junction leads to a change in the potential at the other side of the junction. Many electrical synapses can be described over a large voltage range by a constant, positive resistance. Thus, different from chemical synapses, they serve to couple cells electrically with little delay. Some electrical synapses behave like a typical rectifier device, implementing the biological analog of a *diode*. Moreover, they serve to synchronize the firing of nearby cells. An instance of such an operation are cardiac muscle cells, which are electrically coupled in an electrical syncytium (Torre, 1976).

2.2.3 An Example of a Computation

In the vertebrate retina, cone photoreceptors of the same spectral sensitivity have been shown to be electrically coupled via non-rectifying gap junctions, as have rods and horizontal cells of teleosts and turtles (Copenhagen and Owen, 1976; Kaneko, 1976; Detwiler and Hodgkin, 1979; Attweil and Wilson, 1980; Torre and Owen, 1983). It can be shown that when the membrane impedance of the photoreceptors can be linearized to a satisfactory approximation, analytical solutions to the network equations can be found that describe the dynamics of the response of any given cell to a variety of one- or two-dimensional

stimuli (Torre, Owen and Sandini, 1983). Such an analysis seems of particular importance when one realizes that under conditions of dark adaptation, for instance at night, the rod response to the absorption of single photons lies well within the linear response range of the cell. As a result of their analysis, Torre *et al.* suggest, following an idea of Hodgkin, that one functional role of coupling is to enhance the detection of signals. In particular, the signal-to-noise ratio decreases for small spots of light, resulting for instance from the random capture of photons, while the ratio increases for diffuse or long narrow patterns of light. Moreover, the coupling may serve to avoid aliasing due to the discrete sampling lattice of the photoreceptors. The Shannon sampling theorem (Shannon and Weaver, 1949) requires the spatial frequencies in the image to be below a critical frequency, in order for perfect reconstruction to occur subsequent to the sampling process. If higher frequencies are present, aliasing occurs, degrading the effective spatial resolution. Since the coupling can be equated with low-pass filtering the image falling upon the retina prior to sampling, it may help to reduce aliasing (Poggio, Nishihara and Nielsen, 1982; Torre *et al.*, 1983).

2.3 Interaction between Synaptic Inputs

When two neighboring regions of a dendritic tree undergo simultaneous conductance changes — induced by synaptic inputs — the resulting postsynaptic potential is in general not the sum of the potentials generated by each synapse alone. The postsynaptic potential induced by one synapse will propagate to the other synaptic site and change the driving potential at that location, i.e. the difference between the present postsynaptic potential and the reversal potential of the synapse. Thus, a different amount of current flows as a result of the "interfering" synapse nearby, allowing for the possibility that synapses situated "close" to each other may interact in a highly nonlinear way. We will briefly examine two different cases: the synaptic interaction between synapses of the same sign and the interaction between excitatory and inhibitory synapses.

2.3.1 Biophysical Mechanism

Nonlinear saturation: Let us consider an excitatory synapse that modulates the conductance g to a particular ion with an associated reversal potential $E > 0$ (relative to E_{rest}). In the steady-state case the change in somatic potential is given by

$$V_s = \frac{g\tilde{K}_{is}(0)E}{1 + g\tilde{K}_{ii}(0)},$$

where $\tilde{K}_{is}(0)$ is the steady-state transfer impedance between the location i and the soma.

For small values of g, V_s is proportional to $g\tilde{K}_{is}(0)E$ and for very large values of g, V_s saturates at $\tilde{K}_{is}(0)E/\tilde{K}_{ii}(0)$. This value therefore represents — under the assumption of a passive membrane — the maximal somatic depolarization evoked by a single synapse. We will now assume that the same synaptic input is spread among N identical synapses (each one with a conductance change g/N). Each one of the synaptic sites has about the same input impedance $\tilde{K}_{ii}$, the same transfer resistance to the soma $\tilde{K}_{is}$ and the same transfer resistance $\tilde{K}_{ij}$ between two synaptic sites i and j. Taking account of the nonlinear interaction between the different synaptic inputs, it can be shown (Koch, Poggio and Torre, 1982) that the combined change in somatic potential is

$$V_s = \frac{g\tilde{K}_{is}E}{1+g\overline{K}_{ii}},$$

where $\overline{K}_{ii} = [\tilde{K}_{ii}+(N-1)\tilde{K}_{ij}]/N$ (in other words, the more the synapses are decoupled, i.e. $\tilde{K}_{ij} \to 0$, the smaller $\overline{K}_{ii}$). In other words, spreading the same conductance change among N at least partially decoupled sites enhances the maximal evoked somatic depolarization by a factor $\tilde{K}_{ii}/\overline{K}_{ii}$ (Koch *et al.*, 1982).

Nonlinear interaction: Let us consider the nonlinear interaction in a passive dendritic tree between an excitatory synapse at location e, with associated conductance change $g_e(t)$ and reversal potential E and an inhibitory synapse at i that increases the membrane conductance by $g_i(t)$ to an ionic species having an equilibrium potential close to the resting potential of the cell, $I = V_{rest} = 0$ (Pogio and Torre, 1978; Torre and Poggio, 1978). γ-amino-butyric acid (GABA), acting via the classical bicuculline sensitive $GABA_A$ postsynaptic receptor and increasing a Cl^- conductance, would be an instance of a shunting inhibition. Activating shunting inhibition is similar to opening a hole in the membrane: its effect is only noticed if excitatory input is present. The resulting somatic potential is given by a system of Volterra integral equations:

$$V_s(t) = \{g_e(t)(E-V_e(t))\} * K_{es}(t) - \{g_i(t)V_i(t)\} * K_{is}(t)$$

$$V_e(t) = \{g_e(t)(E-V_e(t))\} * K_{ee}(t) - \{g_i(t)V_i(t)\} * K_{ie}(t)$$

$$V_i(t) = \{g_e(t)(E-V_e(t))\} * K_{ei}(t) - \{g_i(t)V_i(t)\} * K_{ii}(t),$$

where $K_{ij}(t)$ is the Green function of the system, i.e. the voltage response in time at location j if a δ-pulse of current is injected at i. V_s, V_i and V_e are the values of the membrane potential at the soma, at the excitatory and at the inhibitory synapse, respectively. A simple measure of the effectiveness of shunting inhibition is the ratio (F) between the maximum of somatic depolarization in the absence of inhibition and in the presence of inhibition. For steady-state conductance inputs, it is possible to prove rigorously that for passive and

branched trees without loops the most effective location for inhibition is always on the direct path between the location of the excitatory synapse and the soma (Koch, 1982; Koch, Poggio and Torre, 1982). Rall observed earlier that in a single unbranched cable shunting inhibition effectively vetoes more distal excitation but not more proximal one (Rall, 1964).

Detailed biophysical simulations of highly branched neurons (under the assumption of passive membrane properties) show that this *on-the-path* condition is quite specific: If the amplitude of the inhibitory conductance change is above a critical value ($50nS$ or larger), F values can be quite high ($\approx 2-8$) even when the excitatory inputs are much larger than the inhibitory ones, as long as the inhibition is between the excitatory synapse and the soma (figure 6). Inhibition behind excitation or on a neighboring branch 10 or $20\mu m$ off the direct path, is ineffective in reducing excitation significantly. If the amplitude of the inhibitory conductance change is too small, the strength of the interaction depends mainly on the distance between the two sites, and F values are very low. When the inhibition is not of the shunting type, i.e. $I < V_{rest}$, inhibition at the soma is consistently more efficient (for more details see Koch *et al.*, 1982). This specificity carries over into the temporal domain. Shunting inhibition must be activated shortly preceding or following the onset of excitation, in order to veto excitation effectively (figure 6; Koch, Poggio and Torre, 1983; Segev and Parnas, 1983). In summary, the interaction between excitation and shunting inhibition can be (i) strong, (ii) specific with respect to the relative position of excitation and inhibition and (iii) tuned to their timing.

Our results hold also for the more unusual case of an input that decreases the membrane conductance for ions in equilibrium near the resting potential (see for instance Gerschenfeld and Paupardin-Trisch (1974), who provide evidence for a K^+ decreasing conductance in a molluscan neuron). In this case, the synaptic input *facilitates* the excitatory effect, thus implementing an analog approximation of a logical AND operation instead of the AND-NOT discussed previously (Koch *et al.*, 1983).

2.3.2 Neuronal Operation

One operation implemented by synapses impinging upon the dendritic tree is a form of (nonlinear) *addition*. If the conductance change g is small in comparison with the input impedance $\tilde{K}_{ii}$ at that location ($g\tilde{K}_{ii} < 1$), then the conductance change g can be approximated as current gE and little interaction takes place between different synaptic inputs. This situation may easily occur if the synapse is located onto the soma or a primary dendrite with their low input impedance $\tilde{K}_{ii}$. In these cases the addition will be linear. If the induced conductance change is large, synaptic saturation must be taken into account, and the resulting somatic potential is less than the sum of the individual contributions. The linear, non saturating, operating range can be enhanced, however, by spreading the input

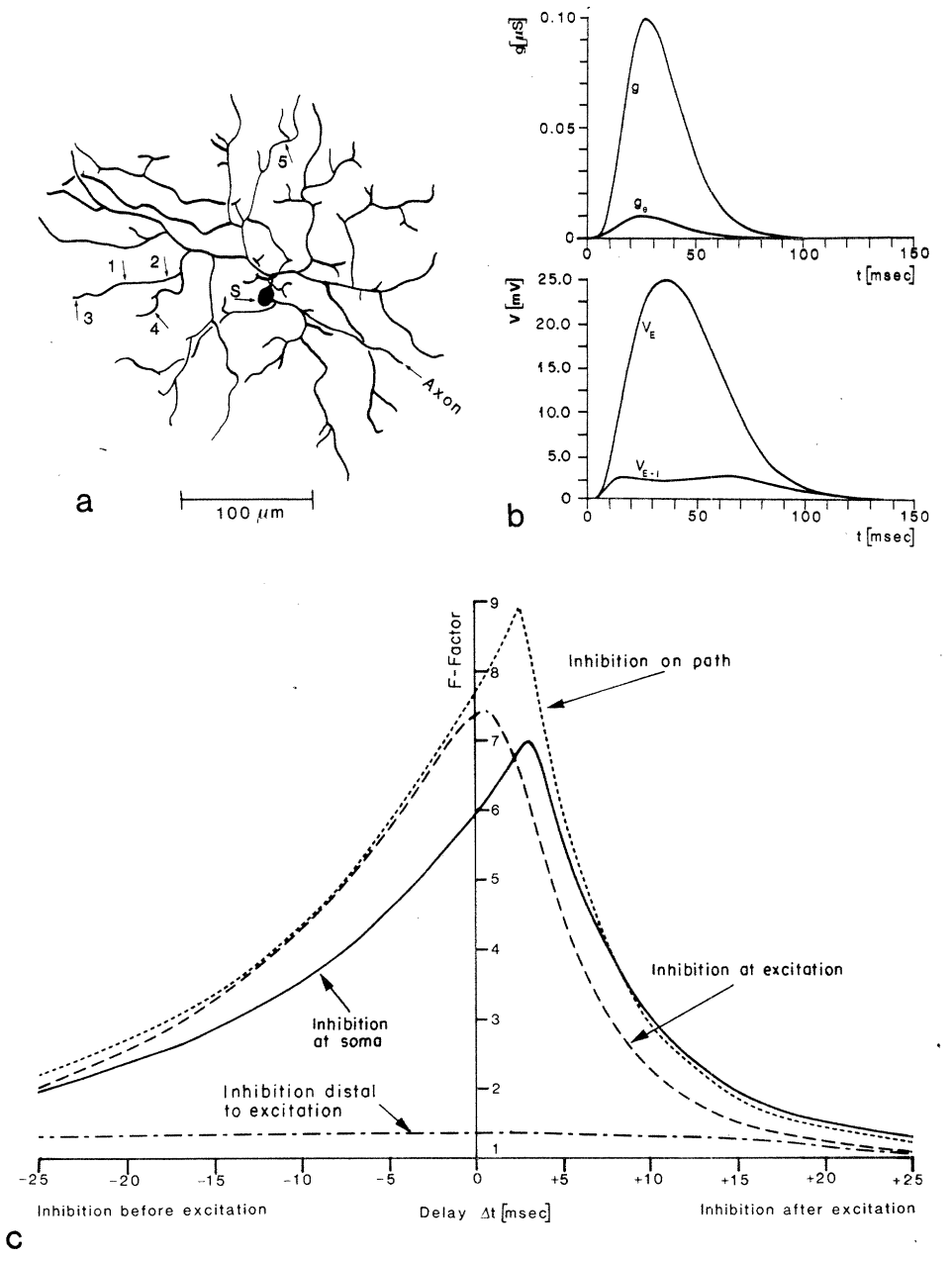

Figure 6. (a) A cat retinal ganglion cell of the δ type (Boycott and Wassle, 1974). (b) The depolarization in the soma of the δ cell for an excitatory conductance input g_e at location 1 and an inhibitory conductance input g_i at location 2. Both inputs have a rise-time of $25ms$ and decay to zero after about $90ms$. Location and timing of inhibition are optimal (i.e. the inhibition is delayed by $2.5ms$). The excitatory battery is $E = 80mV$ and the inhibitory battery $I = 0mV$ (relative to the resting potential). The corresponding somatic depolarization in the absence (V_E) and in the presence (V_{E+I}) of inhibition also shown. Inhibition alone is "invisible" (because $I = 0$); its effect appears only when *simultaneous* excitation takes place, as expected from a multiplication-like interaction. (c) F factor (ratio of the maximum of the somatic depolarization without inhibition to the somatic depolarization with inhibition) for various locations of excitation and inhibition (as indicated in a) as a function of the relative timing. From Koch *et al.*, 1983.

among several, at least partially decoupled sites, such as spines (see section 3). Under these conditions, nonlinear saturation will be substantially reduced. Such linear addition most likely occurs in the morphological α and β cell-classes of the cat retina, corresponding to Y- and X-cells, but not in the γ and δ cells (by exclusion identified with W-cells; Boycott and Wassle, 1974; Koch *et al.*, 1982). It may also be used by bipolar cells to maintain a large dynamic range despite the high synaptic amplification at the photoreceptor synapse (Torre and Poggio, pers. communication).

The nonlinear interaction between an excitatory synapse and a shunting inhibitory synapse implements an analog veto operation, functionally equivalent to a logical AND-NOT gate.[1] Because of the strength and specificity of the veto operation, it may perform characteristic information-processing operations in passive dendritic trees. Since inhibition vetoes more distal excitatory inputs only when it is on the direct path to the soma, a variety of local operations can be synthesized, exploiting the topology of the dendritic tree. Figure 7 shows a highly idealized picture of such "logical" operations implemented within a dendritic tree. Clearly, only certain types of logical operations can be carried out in a given dendritic topology. A cautionary note is in order here: this representation is primarily a convenient way of emphasizing some analogies between neuronal and logical information processing, while neglecting their differences.

This behavior contrasts with the behavior obtained with a hyperpolarizing inhibitory synapse, such as GABA acting onto the bicuculine resistance, baclofen sensitive receptor controlling potassium channels ($GABA_B$ receptor; Newberry and Nicoll, 1984). In this case, the interaction between excitation and inhibition will be linear, that is the inhibitory synapse will reduce the EPSP generated by the excitatory synapse by an amount proportional to the inhibitory conductance change, eventually hyperpolarizing the cell for large enough inhibitory inputs.

In the more unusual case of the postsynaptic conductance decreasing in response to the neurotransmitter, this mechanism implements an analog form of a digital AND gate (for instance Schulman and Weight, 1976).

2.3.3 Three Examples of Computations

Computing the direction of motion in retinal cells: Many neurons in both the retina and the visual cortex, exhibit the property of direction selectivity; they respond maximally to stimuli moving in a particular, the *preferred*, direction and minimally to stimuli moving in the opposite, or *null*, direction (Hassenstein and Reichardt, 1956; Hubel and Wiesel, 1959; Barlow and Levick, 1965; Oyster and Barlow, 1967; Cleland and Levick, 1974; Marchiafava,

[1]Note that AND-NOT is different from NAND.

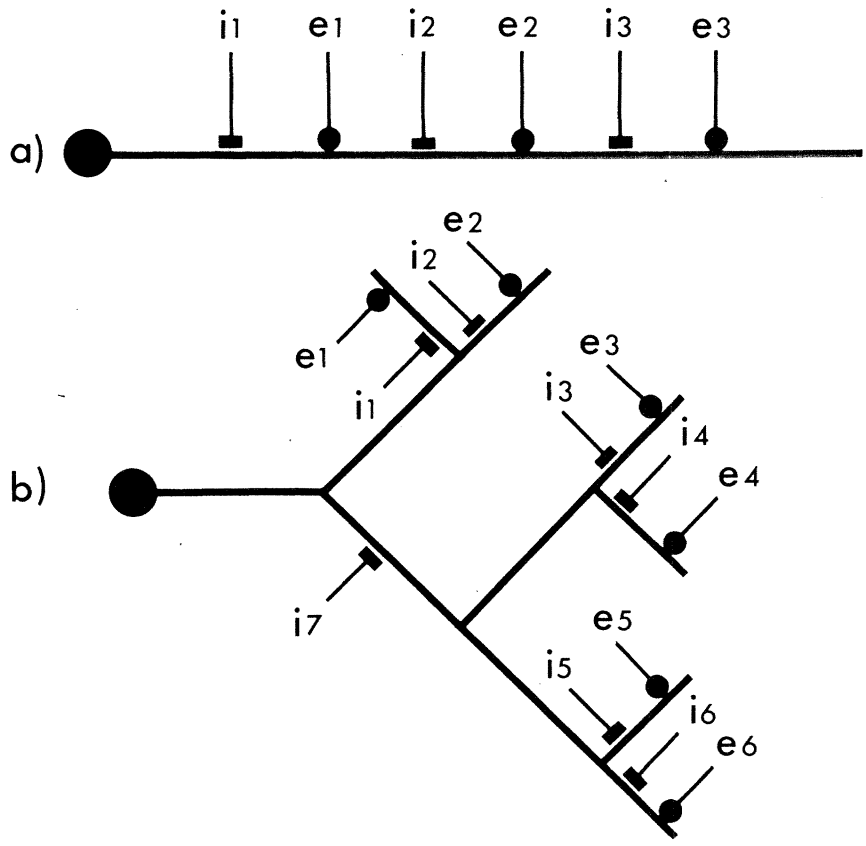

Figure 7. (a) An idealized dendrite of a cat retinal ganglion cell of the γ type (Boycott and Wassle, 1974), receiving excitatory (circles) and inhibitory (rectangles) inputs of the shunting type. Any inhibitory input can effectively veto only more distal excitation and does not affect other inputs more proximal to the soma. If the veto operation is described by an analog form of an digital AND-NOT gate, the operation "implemented" by the cell reads as $[e_3\ AND-NOT\ (i_1\ OR\ i_2\ OR\ i_3)]\ OR\ [e_2\ AND-NOT\ (i_1\ OR\ i_2)\ OR\ (e_1\ AND-NOT\ i_1)]$. (b) An idealized dendrite of a δ cell (see also figure 6a) with excitatory and inhibitory synapses of the shunting type. Each inhibitory input ($i_1 - i_6$) vetoes specifically only the corresponding excitation ($e_1 - e_6$) because it satisfies the on-the-path condition. The operation implemented by this cell is $(e_1\ AND-NOT\ i_1)\ OR\ (e_2\ AND-NOT\ i_2)\ OR\ \{[(e_3\ AND-NOT\ i_3)\ OR\ (e_4\ AND-NOT\ i_4)\ OR\ (e_5\ AND-NOT\ i_5)\ OR\ (e_6\ AND-NOT\ i_6)]\ AND-NOT\ i_7\}$. From Koch *et al.*, 1982.

1979; Jensen and DeVoe, 1983). Preferred and null directions are in general not predictable from the map of the receptive field nor can they be inferred from the global dendritic morphology of the direction selective cell (Amthor, Oyster and Takahashi, 1984). Instead, direction selectivity has been postulated to be generated by asymmetries in the ganglion cell synaptic input (Torre and Poggio, 1978; Koch, Poggio and Torre, 1982).

The seminal work of Barlow and Levick (1965) implied that inhibition is crucial for direction

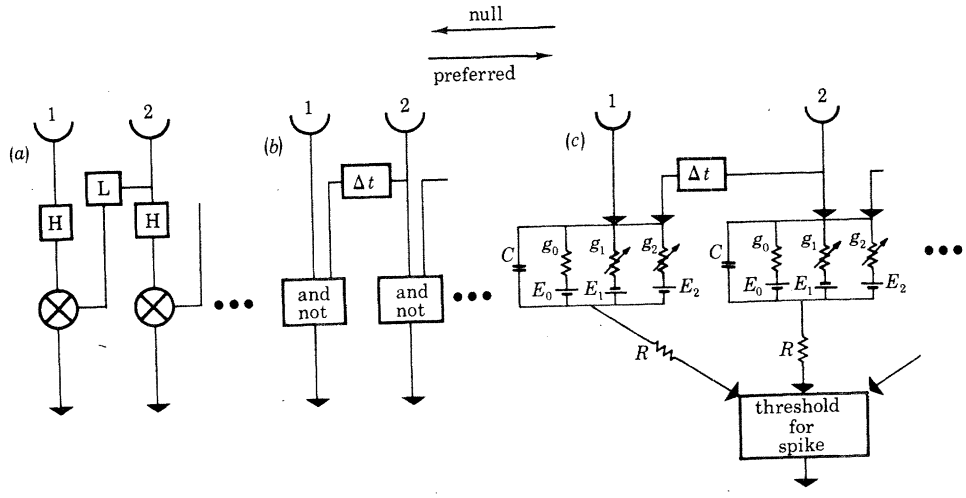

Figure 8. (a) A part of the model of movement detection of Hassenstein and Reichardt (1956). The two inputs are multiplied after low pass filtering with different time constants. If an average operation is made on the output the overall operation is equivalent to cross-correlation of the two inputs. (b) The scheme proposed by Barlow and Levick (1965) to account for direction selectivity of ganglion cells in the rabbit retina. A pure delay Δt is not really necessary: a low pass filtering operation is sufficient (inhibition needs only to last longer than excitation). (c) The equivalent electrical circuit of the synaptic interaction assumed to underly direction selectivity as proposed by Torre and Poggio (1978). The interaction implemented by the circuit is of the type $g_1 - \alpha g_1 g_2$. The ionic battery of the inhibitory input g_2 is assumed to be near the resting potential of the cell. From Torre and Poggio, 1978.

selectivity: for motion in the null direction excitatory inputs are vetoed by inhibitory inputs originating in adjacent regions of the dendritic tree. As shown by Barlow and Levick (figure 8b; see also Wyatt and Daw, 1975), this veto operation must take place within small independent subunits contained within the receptive field which are extensively replicated. Torre and Poggio (see also Torre and Poggio, 1981) proposed that the nonlinear *postsynaptic* interaction between excitation and shunting inhibition underlies this behavior. Direction selectivity is achieved by asymmetric delay (and/or low pass properties) in the excitatory and inhibitory channels from the photoreceptors to the ganglion cell. Since nonlinearity of interaction is an essential requirement of this scheme, Torre and Poggio suggested that the optimal location for excitation and inhibition is on distal fine dendrites where the input impedance $\tilde{K}_{ii}$ is expected to be high (figure 8c).

Among the specific schemes that have been proposed to account for direction selectivity in the retina, two main classes of models have survived so far the experimental evidence,

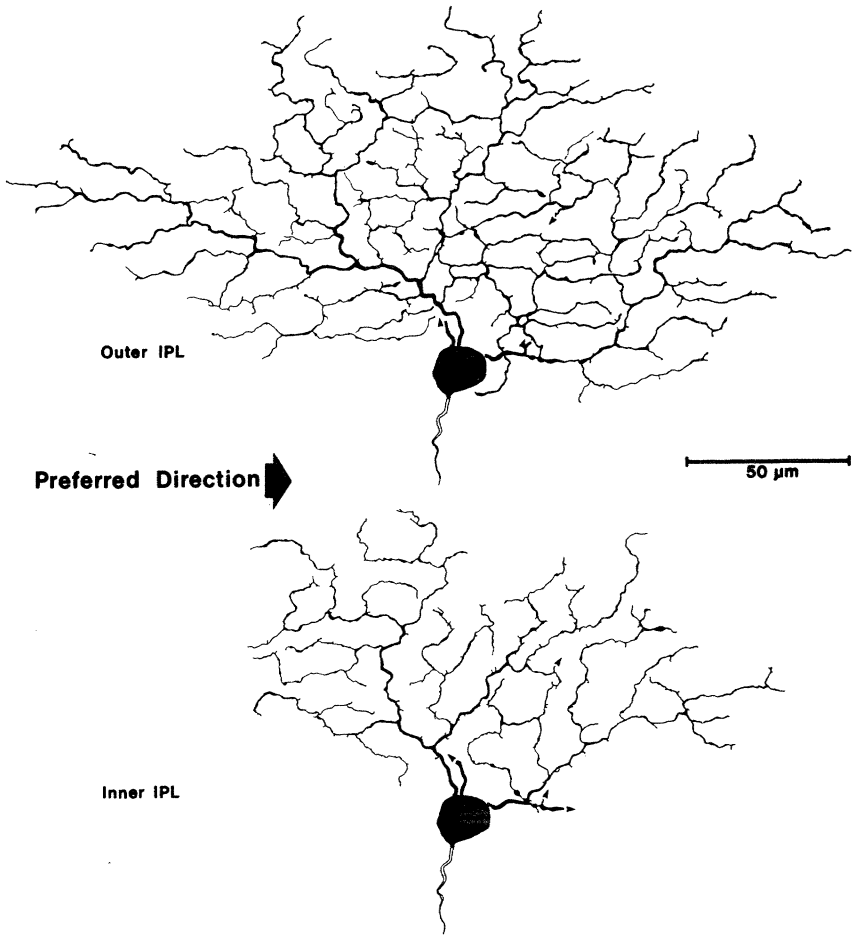

Figure 9. Camera lucida drawing of an HRP-injected on-off direction-selective cell in the visual streak of the rabbit retina. The dendritic fields have been drawn in two parts: "outer" refers to the dendritic layer closest to the inner nuclear layer, while "inner" is the layer closest to the ganglion cell layer. Adapted from Amthor *et al.*, 1984.

based respectively on *postsynaptic* and on *presynaptic inhibition*. We briefly review these models and list their critical predictions.

Postsynaptic models

Detailed biophysical simulations of cat retinal ganglion cells with their highly branched dendritic trees, suggests that the AND-NOT mechanism is compatible with the available data about direction selectivity (Koch, Poggio and Torre, 1982 and 1983; Mistler, Amthor and Koch, 1985). In particular, intracellular recordings from directional selective ganglion cells supports activation of a shunting inhibition in the null direction (Marchiafava, 1979; Ariel and Daw, 1982; Amthor, Oyster and Takahashi, 1983b). This inhibition effectively and specifically shunts excitation as long as it is localized near excitation or between excitation

and the soma. Since such a precise mapping (figure 7) imposes stringent requirement onto the specificity of the positioning of synapses during development, one particular simple rule to follow is that a pair of excitatory and inhibitory inputs always contact the ganglion cell close to each other. Computer simulations show that if excitation and inhibition are located very close to each other (i.e. within a few μm), inhibition will effectively veto excitation (for g_e and $g_i \rightarrow \infty$, $F \rightarrow g_i/g_e + 1$; Koch *et al.*, 1982).

The direction of stimulus motion may thus be computed at many sites in the dendritic tree, independent of the threshold mechanism in the soma. On the basis of its nonlinear behavior and its highly branched dendritic architecture, Koch *et al.* (1982) conjectured that a δ-like cell morphology (in the cat Boycott and Wassle, 1974) represents an ideal substratum for direction selectivity (figure 6a).

Recently, Amthor and his colleagues stained physiologically identified on-off direction-selective cells in the rabbit retina with intracellular injections of HRP (Amthor, Oyster and Takahashi, 1983a; Amthor *et al.*, 1984). Their succesfully stained cells always show a bistratified, quite complex, dendritic tree (figure 9). These cells have extremely thin dendrites which carry spines or spine-like appendages; a rather puzzling feature is the presence of apparent "loops" created by retroflexive branching within the dendritic fields. These loops seem to be a unique feature of direction-selective cells in the visual streak, for cells with such apparent loops have not been reported to occur in the less highly branched bistratified ganglion cells of the same type in the retinal periphery (Famiglietti, 1984. It is therefore doubtful that the loops are actually electrically closed structures. Amthor *et al.* cell's appear to meet the requirement for numerous local non-linear interaction sites, as postulated by Torre and Poggio (1978) and Koch *et al.*, (1983). These distributed AND-NOT-like gates would compute direction selectivity throughout the dendritic tree, prior to somatic integration and impulse generation.

The excitatory input in this model is likely to derive from motion-sensitive cholinergic "starburst" amacrine cells (see below) while inhibition could possibly be mediated by the GABA releasing population of transient on-off amacrine cells (Miller, Dacheux and Frumkes, 1977; Miller, 1979, Dowling, 1979; Vaughn, Famiglietti, Barber, Saito, Roberts and Ribak, 1981).

Presynaptic models

An alternative to the postsynaptic models for direction selectivity in the rabbit is the hypothesis that the necessary computations occurs prior to ganglion cells. Although Werblin (1970) failed to record directional selective responses in any neurons presynaptic to ganglion cells (see also Marchiafava, 1979), this possibility cannot be ruled out, especially if the large number of different amacrine cell classes is taken into consideration (for a recent report of direction selectivity in retinal bipolar cells see Criswell and DeVoe, 1984). Ideal candidates

are "starburst" amacrine cells, believed to provide the cholinergic input to direction selective cells (Masland, 1980; Famiglietti, 1981, 1983b; Masland, Mills and Cassidy, 1984). Masland and his colleagues showed that these cells release ACh transiently at the on- or off-set of light. Starburst amacrine cells (figure 10), thought to be nonspiking, have dendrites that are probably decoupled from each other and the soma (Miller and Bloomfield, 1983). Only the distalmost portion of the dendrites give rise to conventional chemical synaptic output, while the bipolar and amacrine cell input is distributed throughout the cell (Famiglietti, 1983a). Since each dendrite may act essentially as an independent subunit, they could be the morphological basis of Barlow's and Levick's subunits (1965). Moreover, GABA, crucial for direction selectivity (Caldwell, Daw and Wyatt, 1978; Ariel and Daw, 1982), appears to modulate the release of acetylcholine (Massey and Neal, 1979), favoring the scheme whereby an excitatory (bipolar) input in conjunction with the GABAergic input implements an AND-NOT-like gate at the level of the starburst amacrine cell dendrites, whose output would then be directional selective itself. One would then predict that the application of an ACh potentiator should have little effect on the directional selective response of the ganglion cell. Physostigmine, an acetylcholinesterase inhibitor, does however eliminate directional specificity, in favour of the postsynaptic model of Torre and Poggio (Ariel and Daw, 1982). A second class of presynaptic models postulates a hyperpolarizing inhibition vetoing excitation in the null direction. Due to the rectifying properties of the amacrine-ganglion cell synapse, this circuit is functionally also equivalent to an AND-NOT gate. Although both presynaptic models are superficially rather similar, they correspond to very different computations. Thus, it can be shown that for particular stimuli (for instance, sinus gratings of different frequencies), the two models behave very different (Grzywacz and Koch, in preparation).

EM immunocytochemical localization of glutamic acid decarboxylase (GAD) positive synapses in rat retina indicates that there are GABAergic inputs to bipolar, amacrine and ganglion cell processes in descending order of frequency (Vaughn *et al.*, 1981), a result which is consistent with both the pre- and the postsynaptic model.

We emphasize that all models of direction-selectivity relying on the nonlinear interaction between excitation and inhibition to discriminate between different directions, require a precise positioning of the different types of synapses (Swindale, 1983). The partial electron-microscopy reconstruction of a cat α ganglion cell (Freed and Sterling, 1983), supports the notion that such precision is, at least for one type of excitatory input, biological feasible.

Although direction selectivity in the retina will probably represent the first critical test for the AND-NOT scheme, the proposed mechanism might play a role in other neurons of the central nervous system. In fact, the nonlinear synaptic interaction, perhaps augmented by membrane nonlinearities such as dendritic spikes evoked by EPSP's for a stimulus moving

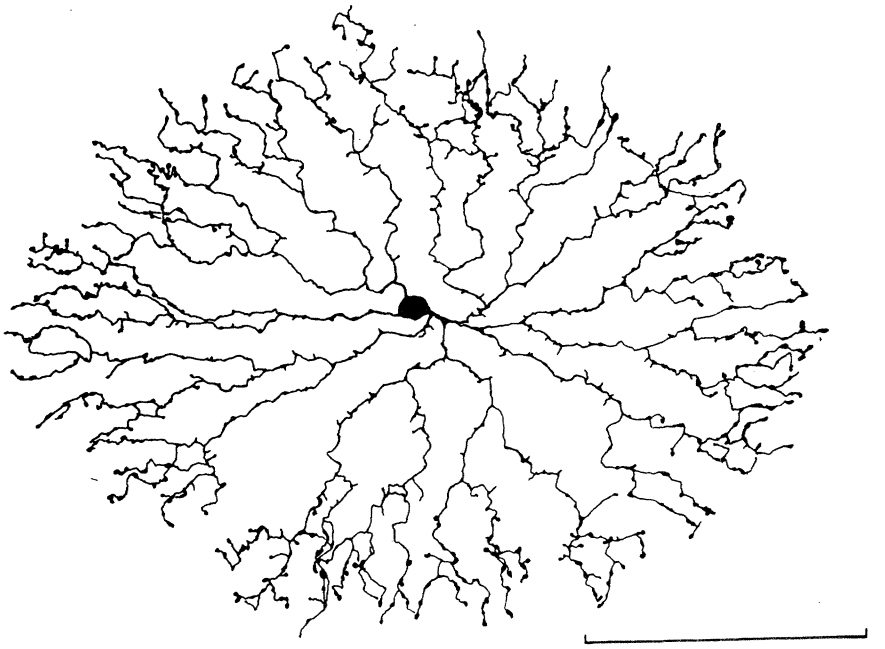

Figure 10. A starburst amacrine cell of the rabbit retina, filled with the fluoroecsent dye Lucifer Yellow. These cells release ACh transiently at the on- or off-set of the light stimulus. The scale bar corresponds to $100\mu m$. Adapted from Tauchi and Masland, 1984.

in the preferred direction, may also be responsible for computing the direction of motion in cortical neurons of the cat and primates as well as underlying orientation selectivity in some cortical neurons (Koch and Poggio, 1984; Emerson, Citron, Felleman and Kaas, 1984).

Computing relative motion in the fly: It has been known for some time that the housefly can discriminate relative movement of an object and its background, even when the two have identical texture (Virsik and Reichardt, 1976). The ability to discriminate objects in front of a distant background in terms of the relative velocity induced by motion is probably of particular importance to fast flying insects that cannot rely on binocular vision. Combining behavioral and electrophysiological experiments, Reichardt and his colleagues analyzed the optomotor response as a function of the spatial extent of motion and the velocity, contrast and spatial structure of the image. They proposed the basic structure of a neuronal circuitry underlying the detection of motion discontinuities, relating it to known properties of cells in the third optic ganglion of the flies (Reichardt and Poggio, 1979; Reichardt, Poggio and Hausen, 1983). A critical component of the model is the *presynaptic* action of shunting inhibition on the output of the individual elementary movement detectors. This circuitry acts as gain control, making the optomotor response independent from the angular extent of the moving or oscillating figure, a well established phenomenon (Reichardt *et al.*, 1983).

Computing disparity in cortical cells: Studies in the alert monkey demonstrated that a large number of neurons in primary visual cortex (area V1) and an even higher proportion in prestriate cortex (area V2) are sensitive to horizontal disparities (Barlow, Blakemore and Pettigrew, 1967). Two main classes of stereoscopic neurons have been recognized (Poggio and Fischer, 1977; Poggio and Talbot, 1981): (1) cells that are selective for a very limited range of disparities, showing excitatory binocular facilitation (tuned excitatory neurons) or, less frequently, inhibitory interaction (tuned inhibitory neurons), and (2) cells that are tuned either to disparities corresponding to objects in front of the fixation plane (NEAR neurons), or those corresponding to objects behind the plane of fixation (FAR neurons). These early studies used isolated line and bar stimuli in the visual field. Thus, there is no possibility of making an incorrect correspondence between elements in the left and the right image. Poggio (1980, 1984) recently showed that roughly one fifth of all the cells whose depth sensitivity was examined responded to isolated lines as well as to random-dot patterns, in which abundant ambiguous matches occur. Interestingly, all of these cells were of the complex type. Thus, these neurons "solve" the *correspondence problem of stereo* (Poggio and Poggio, 1984).

On the basis of the synaptic veto operation, we devised, together with Keith Nishihara, cellular models to account for the different types of disparity selectivity. Figure 11 shows two models for both excitatory and inhibitory neurons tuned for zero disparities and using edges as primitives (Poggio and Poggio, 1984). The synaptic input converging onto one dendritic branch and originating from the two eyes should have very similar receptive fields. The excitatory tuned disparity sensitive cell only responds to an edge if one eye signals ON activity and the other does not signal OFF activity for the same location, while the inhibitory cell always fires except if both eyes signal ON (or OFF) activity. The optimal disparity of these cells can be changed by varying the spatial offset between the receptive fields in the left and the right eye. The processing occurs in many independent subunits throughout the dendritic field of these neurons, using the AND NOT synaptic veto mechanism. This particular model seems consistent with Ferster's "multiplication" data concerning the synergistic interaction between the two eyes (Ferster, 1981). Because ON activity in one eye vetoes the EPSP evoked by OFF activity in the other eye, we predict that in an experiment using the pharmacological agent APB to block the ON channel (Schiller, 1982), the excitatory tuned cell will lose its sensitivity to disparity. On the other hand, the inhibitory tuned disparity cell will continue to react to its tuned disparity in the presence of APB, although the signal-to-noise level will be decreased. Similar models, using AND NOT and AND-like "synaptic logic", can be devised for the NEAR and FAR disparity sensitive neurons.

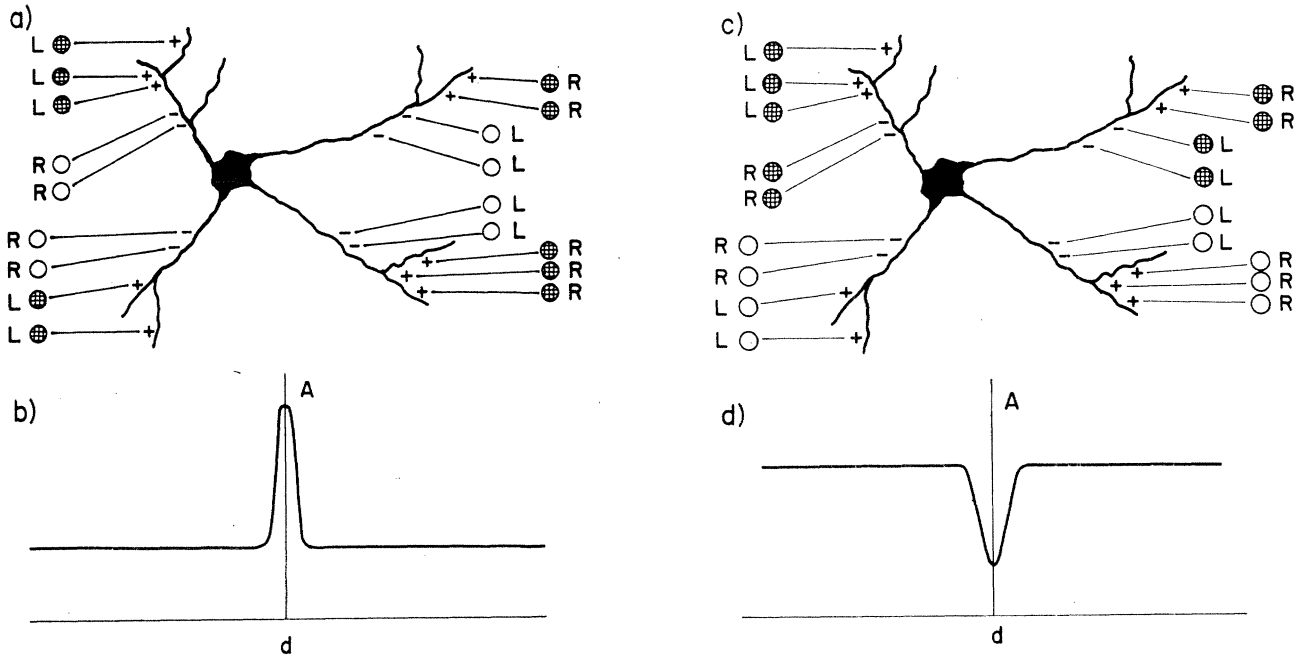

Figure 11. Schematic drawings of two cortical cells excited (a) and inhibited (c) by a given disparity. The excitatory tuned disparity sensitive cell responds only to an edge if one eye signals ON activity (clear circles) while the other eye does not signal OFF activity (hatched circles) for the same location, while the inhibitory tuned cell always fires except when both eyes signal ON (or OFF) activity. The disparity these cells optimal react to can be changed by varying the spatial offset between receptive fields in the left and right eye. (b) and (d) indicate the expected response of the cell to different disparities.

3. Dendritic Spines

Dendritic spines were originally discovered by Ramon y Cajal. Their existence was confirmed by Gray using electron-microscopy (Gray, 1959). A spine usually consists of a thin and slender spine neck and a more bulbous spine head (figure 12). Most important, every spine head has at least one synapse on its surface. These synapses are usually classified as Gray type I and are therefore believed to be excitatory. Most neurons in the CNS can be classified as either spinous or aspinous. In the former case, the majority of excitatory inputs can be seen to be localized on spines. Examples of this cell type are pyramidal and stellate cells in the cortex and purkinje cells in the cerebellum (Shepherd, 1979b).

3.1.1 Biophysical Mechanism

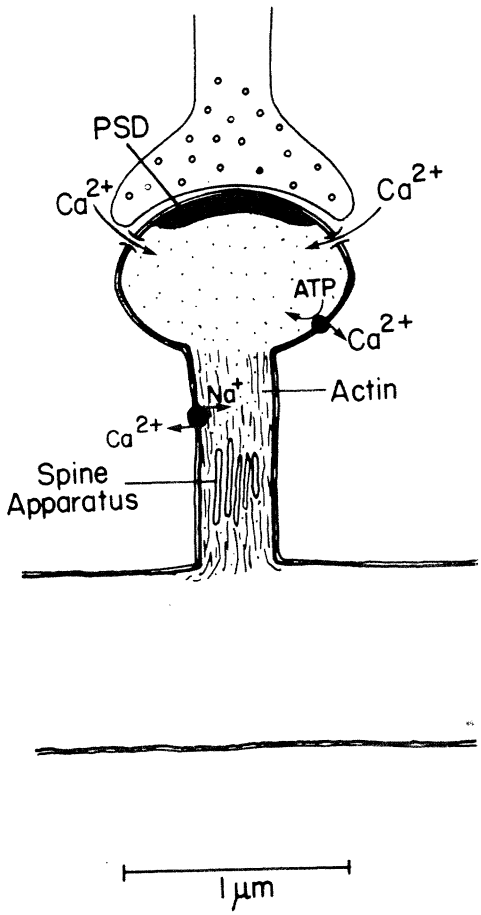

Figure 12. A schematic drawing of a typical dendritic spine in mammalian cortex with some of its constitutive elements. The postsynaptic density (PSD), directly below the presynaptic terminal, is a clump of electron-dense material made up of neurofilaments, actin, fodrin, tubulin, calmodulin, a microtubule-associated protein and other proteins. The spine-apparatus consists of two or three membrane-bound sacs, alternating with thin laminae of dense material. Also shown are the proposed voltage-dependent calcium channels, the sodium-calcium exchange pump and the ATP driven calcium pump. The scale is only approximate. From Robinson and Koch, 1984a.

Dependance of the synaptic weight of a spine on its geometry: Since the synaptically injected current must pass through the relatively thin spine neck in order to reach the soma (Chang, 1952), the synaptic "weight" of the synapse is expected to depend strongly on the geometry of the spine. To study this effect Koch and Poggio (1983a,b) modeled dendritic spines using 1-dimensional cable theory. The spines are described by a thin cylinder of length l and diameter d and a thick and short spine head. The main assumption in this analysis is that the membrane is *passive*. Following the earlier studies of Rall (1974 and 1978) it can be shown that the input resistance of a spine $\tilde{K}_{11}$ as seen by an imaginary electrode in the spine head is the sum of the input resistance in the dendrite just below the spine plus the resistance of the spine neck R_N:

$$\tilde{K}_{11} = \tilde{K}_{22} + R_N.$$

R_N is simply the resistance of a cylinder, i.e. $4R_i l/(\pi d^2)$. Thus, the spine input impedance depends strongly on the geometry of the spine neck. Since $\tilde{K}_{11}$ can be much higher than $\tilde{K}_{22}$ for small spine dimensions, current injected into the spine will produce a much larger *local* depolarization than if injected into the dendritic shaft. It turns out however, that it is irrelevant from the point of view of *somatic depolarization*, whether the current input is in the spine head or directly onto the dendritic stem, next to the spine base. This is easy to understand. Since the membrane surface of the spine is minute ($\approx 1\mu m^2$), essentially no current flows through the spine membrane (see also Koch and Poggio, 1984). Thus all the current injected into the spine head reaches the dendritic stem, or

$$\tilde{K}_{1s} = \tilde{K}_{2s},$$

where $\tilde{K}_{1s}$ (resp. $\tilde{K}_{2s}$) is the transfer impedance between the spine head (resp. dendritic shaft below the spine) and the soma.

Due to their expected high input impedance, spines can show large saturation effects (figure 13). Saturation occurs not only for stationary or slow, but also for very fast conductance changes (Perkel, 1983; Koch and Poggio, 1983a). Figure 14 shows the dependance of the somatic potential on the geometry of the spine neck. If the amplitude of the synaptic input is small with respect to the inverse of the spine neck impedance (i.e. if $R_N g < 1$), synaptic input can be considered as current and little of interest occurs. If, however, the synaptic input is large (i.e. $R_N g > 1$), significant saturation occurs, limiting the inflow of current into the spine. In this case, somatic depolarization induced by the synapse on the spine will depend strongly on spine morphology. The critical parameter determining the function of spines (for passive cable models) is thus the product of the spine neck resistance with the synaptic input rather then the spine input impedance (since both $\tilde{K}_{11}$ and $\tilde{K}_{22}$ can be quite large but R_N small; Turner, 1984). Unfortunately, little experimental data is available to bracket the size of these parameters. Very recently, Kawato, Hamaguchi, Murakami and Tsukahara (1984) estimated a peak conductance change of $43nS$ and a time-to-peak of $0.3ms$ for somatic recorded EPSP's in spiny rubrospinal neurons. Under these conditions, plausible changes in neck length could alter the "weight" of the synapse by a factor of 2 or 3 (Koch and Poggio, 1983b).

Until now we have only considered the case of a passive spine membrane. However, if the number of active, voltage-dependent channels in the spine head membrane is sufficient to trigger all-or-none impulses, the situation changes somewhat. Computer simulations show (Miller, Rall and Rinzel, 1985; Perkel and Perkel, 1985) that active, action potential generating membrane nonlinearities in the spine head can produce amplification rather

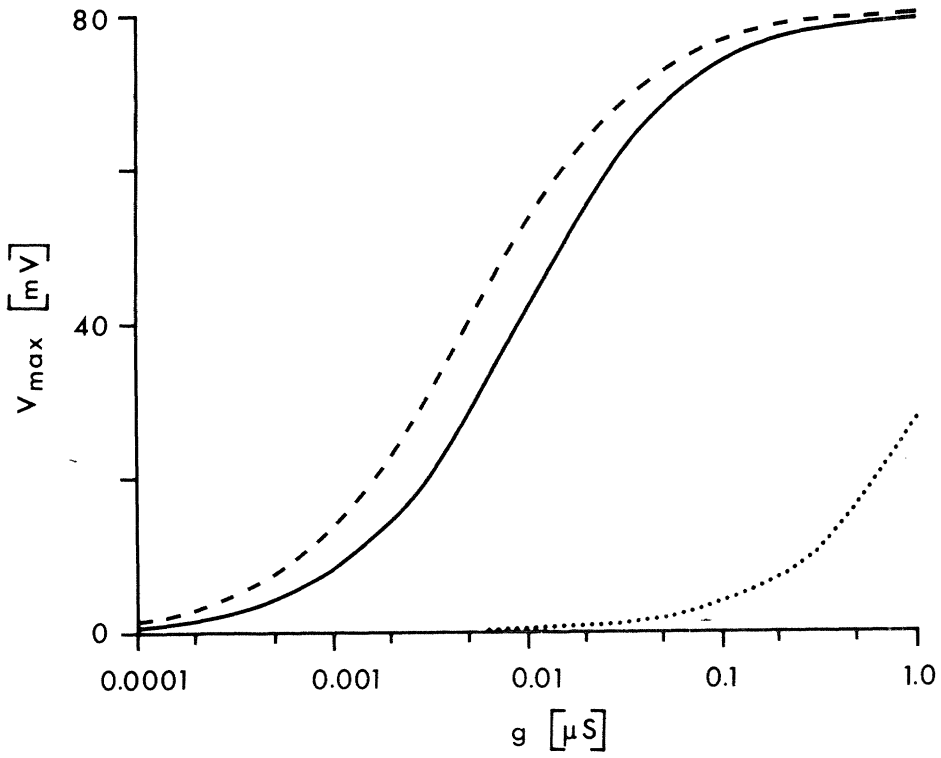

Figure 13. The maximum of the depolarization in the distal apical tree of a cortical pyramidal cell, for a fast transient conductance input of peak amplitude g (with a time-to-peak of $0.25ms$ and total duration of $0.9ms$) of variable amplitude. The solid line indicates the potential at a synapse located within a dendritic spine while the dotted line shows the depolarization for a synapse located just below the spine, directly on the dendritic shaft. The dashed line shows that a steady-state conductance change yields essentially the same depolarization in the spine as the transient input. The membrane time constant is $8ms$. The spine membrane is assumed to be passive. From Koch and Poggio, 1983a.

than attenuation of the postsynaptic potential. The presence and amount of amplification depend on the density of active channels and on the spine-neck resistance. For a given spine head, there is an optimal range of spine neck resistances R_N which will lead to large EPSP's at the base of the spine. Outside of this range, the spine acts as a voltage attenuator.

Interaction between excitation and inhibition: A significant exception to the rule that spines carry only excitatory synapses are spines which show both symmetrical and asymmetrical synaptic profiles, i.e. excitation and inhibition, simultaneously. This situation occurs at about 5 to 15% of all cortical spines (Scheibel and Scheibel, 1968; Jones and Powell, 1969b; Peters and Kaiserman-Abramof, 1969 and 1970; Sloper and Powell, 1979; Somogyi, Kisvarday, Martin and Whitteridge, 1983) and seems to be the rule for the retinal input to X-like relay cells in the lateral geniculate nucleus in the cat (LGN; Famiglietti and Peters, 1972; Friedlander, Lin, Stanford and Sherman, 1981; Hamos, Raczkowski, van Horn

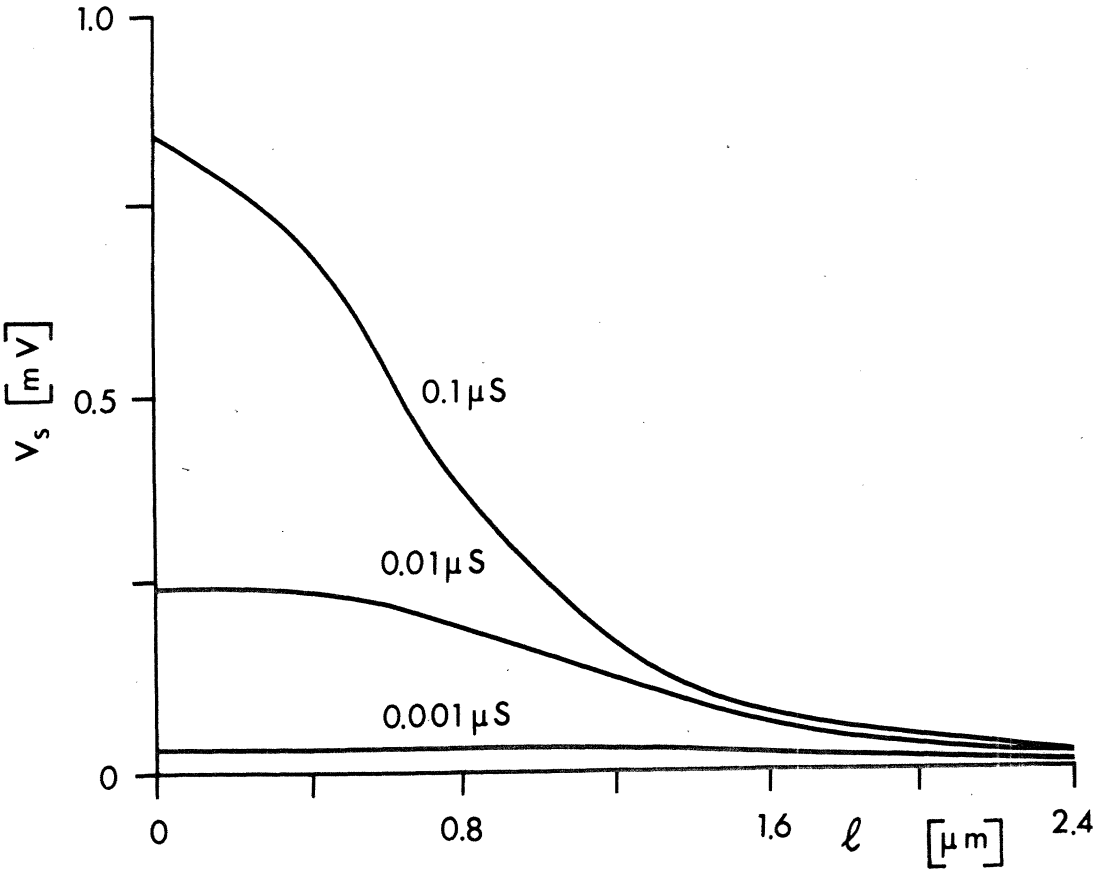

Figure 14. The somatic voltage corresponding to different neck dimensions for small, medium and large steady-state conductance inputs for a synapse located onto a spine in the distal apical tree of a cortical pyramidal cell. Fast, transient inputs yield very similar curves for peak conductance values, except that the somatic depolarization is scaled down by about a factor of 10. The spine neck dimensions were changed in such a way as to leave the total neck surface constant and equal to $dl = 0.1\mu m^2$. Plausible changes in neck length (for instance from 1.0 to $1.7\mu m$ could alter the "weight" of the synapse by a factor 2. From Koch and Poggio, 1983a.

and Sherman, 1983; Hamori, Pasik, Pasik and Szentagothai, 1974).

The nonlinear interaction between an inhibitory conductance change, with a reversal potential close to V_{rest}, and an excitatory conductance change can be quite substantial and very specific, being essentially limited in their effect to the spine (Koch and Poggio, 1983a,b; Koch, 1984b). Thus, if the amplitude of the inhibitory input is large enough ($g_i > 0.05 \cdot 10^{-6} S$ and $g_i > g_e$), the depolarization evoked by the excitatory input is severely curtailed, dropping by a factor of 5 or more. Moreover, the potential at locations outside the spine are little affected by the inhibition. This is in accordance with the on-the-path principle (Koch *et al.*, 1982). When transient inputs are considered, the relative timing between them is an important determinant for the degree of interaction. Figure 15 shows the "tuning curve" of the F factor. As input functions we used fast transients with a time-to-peak of $0.25ms$ and

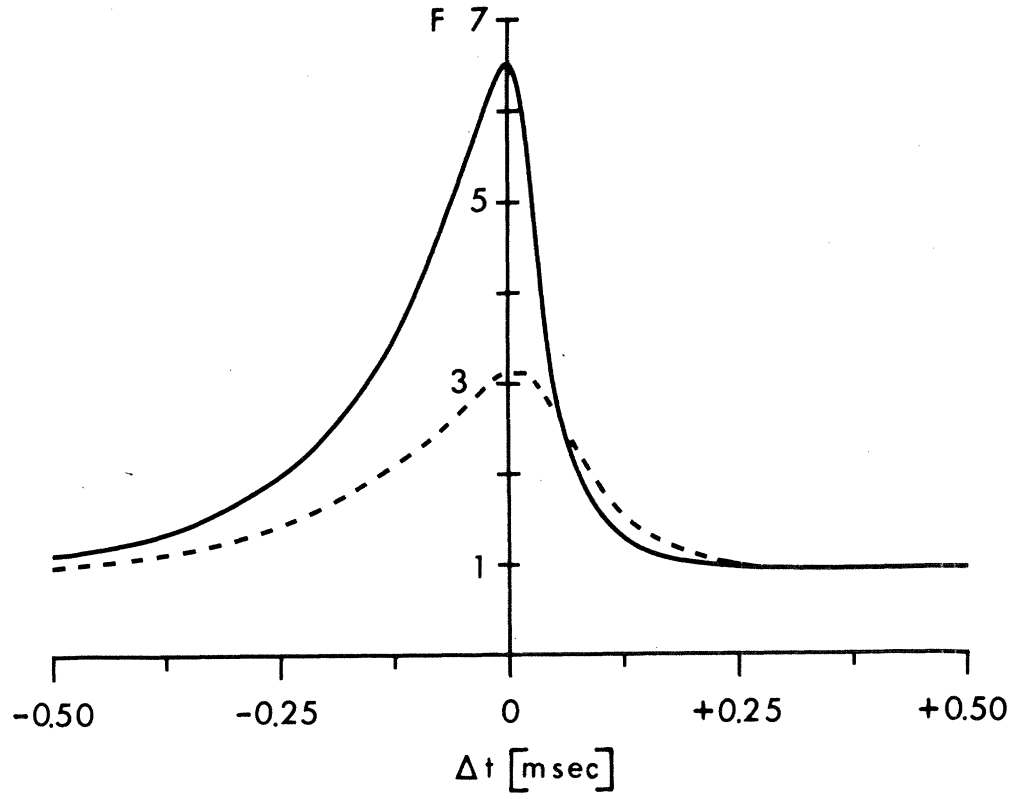

Figure 15. F factor (see figure 6c) for synapses on the spine head (continuous curve) or on the dendritic shaft just below the spine (dashed line) in the distal apical tree of a cortical pyramidal cell. Both input functions have a time-to-peak of $0.25ms$ and decay after $0.9ms$. Inhibition is ten times stronger than excitation (see figure 6b); that is $g_{imax} = 2 \cdot 10^{-7} S$ and $g_{emax} = 10^{-8} S$. Inhibition on a spine is more powerfull and specific than inhibition located on the dendritic shaft. From Koch and Poggio, 1983a.

a total duration of about $1ms$. What is remarkable is that the vetoing effect of inhibition depends very sharply on relative timing beteen the two inputs. Whereas inhibition on the dendritic shaft can effectively veto excitation within a temporal window of the order of $\pm 0.3ms$, inhibition on the spine is stronger and more selective, being effective only in a window of $\pm 0.12ms$ around the onset of excitation.

Activity-dependent change in spine shape: It is well established that the form and shape of dendritic spines can vary following changes in environment and sensory input (see Coss and Globus, 1978 for a study in goldfish; Purpura, 1974 for a study of mentally retarded children; Bradley and Horn, 1979 for a study in chicken; Boycott, 1982 for a study in hibernating ground squirrels; Brandon and Coss, 1982 for a study in bees). Stimulating briefly the afferents to hippocampal cells results in hyperthrophy of the dendritic spines (Van Harreveld and Fifkova, 1975; Fifkova and Anderson, 1981; Fifkova, Anderson, Young and Van Harreveld, 1982). The hippocampus is of particular interest, since it displays a prominent modification of synaptic efficiency, termed long-term potentiation (LTP).

Free intracellular calcium is currently been regarded as one of the key factors underlying certains forms of synaptic plasticity (e.g. in *Aplysia* see Kandel, 1981; in mammalian hippocampus see Baimbridge and Miller, 1981; Turner, Baimbridge and Miller, 1982; Eccles, 1983). Preventing a rise in $[Ca^{2+}]_i$ by injecting a calcium chelating agent such as EGTA (Lynch, Larson, Kelso, Barrionuevo and Schottler, 1983) blocks the establishment of LTP. It is of interest that the spine apparatus, a unique organelle localized in the spine neck and consisting out of two or more flattened sacs or cisternae, as well as the smooth endoplasmic reticulum inside the spine, has been shown to sequester Ca^{2+} at high concentration (Fifkova, Markham and Delay, 1983). Once the concentration of intracellular Ca^{2+} rises to substantial levels, the calcium can trigger a variety of mechanisms leading to a change in synaptic efficiency.

One such mechanism, possibly implementing a transient change in synaptic efficiency, has been proposed by Crick (1982). If contractile proteins, such as myosin and actin, were to be localized in the spine neck, they could lead to a rapid contraction of the neck, possible within a fraction of a second. Functionally, this is equivalent to a rapid enhancement of the synaptic weight. Subsequently, different groups of researchers visualized actin in single neurons. While actin is present at all PSD, it concentrates in dendritic spines where it is either organized in long filaments oriented parallel to the axis of the spine neck or extends throughout the spine head in a lattice-like form (Katsumaru, Murakami and Tsukahara, 1982; Fifkova and Delay, 1982; Matus, Ackermann, Pehling, Byers and Fujiwara, 1983; Fifkova, Markham and Cullen-Dockstader, 1984).

A second mechanism, possibly underlying long-term synaptic modification, is based on calcium-activated enzymes, calpain I and II, present in neuronal membranes (for a summary see Lynch and Baudry, 1984; Eccles, 1983). In the presence of free calcium, this protease breaks up a localized portion of the subcellular fodrin network, irreversibly uncovering glutamate receptors (Siman, Baudry and Lynch, 1983). Since glutamate, or a closely related amino acid, most likely serves as transmitter in several hippocampal pathways, this uncovering will increase the postsynaptic conductance change $g(t)$ and thus the weight of the synapse. We would like to note, however, that for the unmasking of the receptors to increase the synaptic efficiency, two conditions need be meet. First, the factor limiting the size of the postsynaptic conductance change must be the limiting number of postsynaptic receptors and not the amount of transmitter released by the presynaptic terminal. Second, the conductance change prior to the unmasking must be small in relation to the input impedance of the spine. If significant synaptic saturation occurs, increasing $g(t)$ will do little to increase the corresponding EPSP.

On the basis of detailed computer simulations, Robinson and Koch (1984a,b) attempt to model the dynamics of free calcium in dendritic spines. They assume that presynaptic

electrical activity induces, through opening of aspartate or glutamate channels, a large depolarization in the spine head. The EPSP in turn activates voltage-dependent Ca^{2+} channels, resulting in an influx of calcium into the spine (Perkel and Brown, 1982). Such calcium channels are believed to exist in the dendritic arbours of *in vitro* purkinje cells (Llinas and Hess, 1976; Llinas and Sugimori, 1980), olivary neurons (Llinas and Yarom, 1981) and *in vitro* thalamic neurons (Jahnsen and Llinas, 1984). The inflowing calcium will be rapidly bound by high-affinity calcium buffers such as calmodulin and calcineuron, both of which have been localized in substantial amounts in spine cytoplasm and PSD (Grab, Carlin and Siekevitz, 1980; Wood, Wallace, Whitaker and Cheung, 1980; Klee and Haiech, 1980). These buffers, together with the $Na^{+} - Ca^{2+}$ exchange pump, the ATP-driven Ca^{2+} pump and the diffusion of calcium into the dendrites, keep $[Ca^{2+}]_i$ low in response to moderate presynaptic activity. If, however, the presynaptic activity exceeds a critical amount, the calcium buffers will saturate. Since the volume of a dendritic spine is small, very few presynaptic spikes will be sufficient to drive the level of $[Ca^{2+}]_i$ from its resting value around $0.1\mu M$ to values between 10 and $500\mu M$. As Robinson and Koch specifically point out, the optimal strategy to saturate the buffers are very closely timed spikes, i.e. bursts.

The free intracellular calcium can now activate calpain I or II, leading to the irreversible uncovering of the glutamate receptors. Another possibility is the binding of calcium to calmodulin. Once calmoduiin is fully activated, for which all four calcium sites must be occupied, it induces actin-myosin contractions (Klee and Haiech, 1980; Cheung, 1982). The time course of these contractions — and thus of synaptic enhancement — is governed by the rate at which calcium becomes unbound from the calmodulin, which in turn depends on $[Ca^{2+}]_i$. A hypothetical time course of $[Ca^{2+}]_i$ and activated calmodulin for prolonged synaptic inputs is shown in figure 16.
Calmodulin will also interact strongly with another major cytoskeleton protein, fodrin or brain spectrin (Kakiuchi and Sobue, 1983), responsible for giving the neuronal membrane its rigidity. The strong binding of calmodulin directly to fodrin might cause a change in the fodrin-actin network such that loosening of the spine cytoskeleton occurs.

In brief, if calcium channels were to be found at the spine membrane, dendritic spines, due to their special geometry which limits the effects of diffusion and enhances local EPSP's, may implement a calcium-dependent modification in synaptic efficiency spanning different time-scales. This mechanism itself is prone to modification, for instance through voltage, giving rise to possible Hebbian-like interactions between nearby spines. Cooperativity among afferents to CA1 cells in inducing and maintaining LTP has been reported (Lee, 1983).

3.1.2 Neuronal Operation

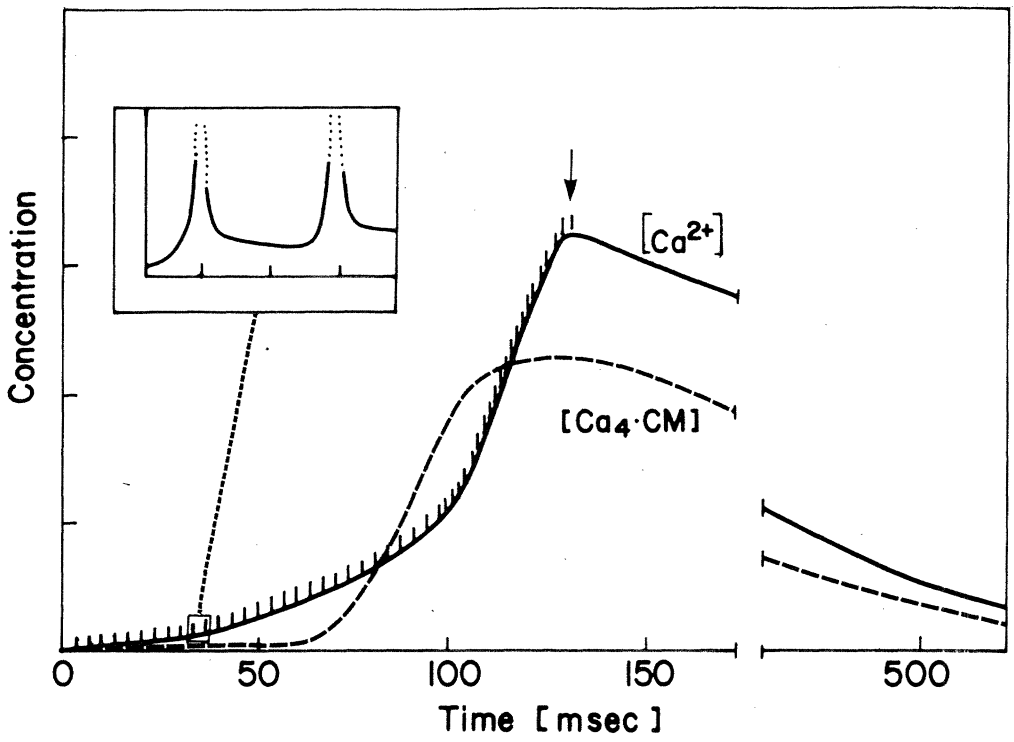

Figure 16. A hypothetical time-course of free intracellular calcium and of activated calmodulin in a dendritic spine during prolonged presynaptic activity (in this case at $300Hz$ for $120ms$). The stimulus-induced influx of Ca^{2+} is buffered within a fraction of a millisecond. Each spike will, however, lead to a small increase in $[Ca^{2+}]_i$ and thus increase the fraction of calcium bound to calmodulin (see inset). Once the presynaptic input ceases, both $[Ca^{2+}]_i$ and the activated calmodulin decay slowly, their time-course being limited by the low off-rate constants of the buffers (Klee and Haiech, 1980). A sudden increase in intracellular calcium during and following repetitive presynaptic stimulation in hippocampal neurons has been reported (Morris, Krnjevic and Ropert, 1983). Detailed computer simulations, describing the time-course of calcium and the various calcium buffers in a 3-compartment model as a function of presynaptic activity, confirm such a behavior (Robinson and Koch, 1984b).

Dendritic spines could be the morphological substrate for at least two different neuronal operations.

First, they could serve as locus for modifying the *functional connectivity* between individual neurons, changing synaptic weights within a fraction of a second (via actin/myosin contractions) to several days or even weeks (via structural changes in the cytoskeleton). It is likely that this synaptic modification is triggered by an activity-dependent calcium influx. These mechanisms are crucially dependent on the potential buffering abilities of the spine cytoplasm. The calcium buffers essentially act to delay the onset of the synaptic enhancement and protect the system from noise induced by spontaneous presynaptic activity. The change in functional connectivity is primarily controlled by the amount and timing of the presynaptic input and secondarily by postsynaptic electrical activity. In particular, if the proposed calcium influx is mediated by voltage-dependent Ca^{2+}-channels,

hyperpolarizing the spine would prevent these channels from opening, thus implementing a kind of Hebbian rule (Hebb, 1948; Palm, 1982).

Second, the synthesis of a circuit consisting of an excitatory and an inhibitory synapse localized onto the same spine, may implement a localized AND-NOT gate. Inhibition vetos excitation very efficiently as long as inhibition is activated in a narrow temporal domain around the onset of excitation. Owing to the particular geometry of the spine, inhibition will do little to influence the electrical activity in the dendritic tree outside the spine. In other words, even though the actual veto operation occurs at a postsynaptic site, it is functionally equivalent to *presynaptic inhibition*.

3.1.3 Two Examples of Computations

Information storage: One obvious function of modifiable spines is information storage over short and long time ranges (Rall, 1974, 1978; Jack, Noble and Tsien, 1975; Koch and Poggio, 1983a,b; Perkel, 1983; see especially Crick, 1982; Eccles, 1983; Lynch and Baudry, 1984). Differing from current digital computers, where the memory resides in specialized hardware — usually kept separate from the logical processor — biological memory would be distributed throughout the information processing machinery, coded in form of the strength of connectivity between the different computational machines. One instance of an experimental well-known paradigm where information could well be "stored" in dendritic spines is LTP in the mammalian hippocampus (for an overview see Chung, 1977 and Swanson, Teyler and Thompson, 1982). It is at the moment still unclear, however, how the actual storage and retrieval of information could take place.

Disabling visual input in the LGN: Recently, electron-microscopic studies of relay cells in the cat LGN have shown that the retinal input of X-cells is associated with a special synaptic circuitry, termed the spine-triad complex (Famiglietti and Peters, 1972; Hamos *et al.*, 1983, 1984; see also Wilson, Friedlander and Sherman, 1984). The retinal afferent makes an asymmetrical synapse with both a dendritic appendage of the X-cell and a geniculate interneuron. The interneuron contacts in turn the same dendritic appendage with a symmetrical synaptic profile. Recent evidence shows that these geniculate interneurons stain for glutamic acid decarboxylase (GAD), the synthesizing enzyme for GABA (Sterling and Davis, 1980; Fitzpatrick, Penny and Schmechel, 1984). The retinal input to geniculate Y-cells is predominately found on dendritic shafts with no triadic arrangement. On the basis of a computer model of an anatomically reconstructed X-relay cell with known somatic input resistance, Koch (1984b) showed that under the assumption that the geniculate interneuron mediates a shunting inhibition, activation of the interneuron by cortical or midbrain inputs can reduce very efficiently the excitatory postsynaptic potential induced by the retinal afferent *without* affecting the electrical activity in the rest of the cell. Since Y-cells lack the

spine-triad structure, inhibition acts globally, reducing and damping the general electrical activity of the cell. Anatomy and electrophysiology indicates that the geniculate interneurons receive an excitatory projection from the visual cortex (Jones and Powell, 1969a; Ahlsen, Grant and Lindstrom, 1982) and inhibition from both the midbrain (Singer, 1977; Foote, Mordes, Colby and Harrison, 1977; Ahlsen, Lindstrom and Lo, 1984) and the thalamic reticular nucleus (Guillery, 1969; Wilson *et al.*, 1984; Hamos *et al.*, 1984). Therefore, Koch proposes that geniculate interneurons selectively gate the flow of visual information into the X-system as a function of the behavioral state of the animal, enhancing the center-surround antagonism and possibly mediating reciprocal lateral inhibition and eye-movement related suppression. Electrophysiological evidence in favor of such a dichotomy between the geniculate X- and Y-system in terms of the action of inhibition can be found in Singer and Bedworth, 1973; Noda, 1975; Tsumoto and Suzuki, 1976; Fukuda and Stone, 1976; Foote *et al.*, 1977; Derrington and Fuchs, 1979; Bullier and Norton, 1979 and Berardi and Morrone, 1984.

4. Membrane Nonlinearities

Ever since Hodgkin and Huxley identified a fast sodium and a delayed rectifying potassium current as the two major currents underlying the generation of action potentials, the total number of currents with widely different dependencies on voltage, time and chemical substances, has multiplied tremendously. What is the function of these currents for information processing? In the next three sections, we will focus on those currents which do not generate all-or-none impulses but modify the electrical behavior of the cell.

4.1 Quasi-Active Membranes

4.1.1 Biophysical Mechanism

Usually, neuronal membranes are classified as either passive, i.e. the voltage decays exponentially to zero, or as active, like for instance the axonal membrane giving rise to action potentials. Between these two extremes, there is a range of membrane behavior we term *quasi-active*. Such a membrane still behaves linearly, i.e. doubling for instance the applied current doubles the voltage response, but it already shows oscillations. We define a membrane to be quasi-active if it shows bandpass-like behavior, i.e. if the membrane impedance has a prominent maximum at some non-zero frequency, called the *resonant frequency*, f_{max}. Such a membrane can always be modeled by an electrical circuit containing an *inductance*.

What are the biophysical mechanisms leading to such a behavior? An electrical component can be described on a phenomenological level by an inductance if its voltage is proportional to the current change. As Detwiler, Hodgkin and McNaughton (1980) pointed out, this situation arises for a time- and voltage-dependent K^+ conductance activated by depolarization and inactivated by hyperpolarization. Examples are the currents mediated by potassium channels in the squid axon (Hodgkin and Huxley, 1952; Mauro, Conti, Dodge and Schor, 1970), or by the calcium-dependent K^+ current in sympathetic neurons and hair cells of the bullfrog (Adams, Constanti, Brown and Clark, 1982; Lewis and Hudspeth, 1983). Alternatively, an inductance can mimick the small-signal behavior of the Na^+ (or Ca^{2+}) conductance inactivated by depolarization and activated by hyperpolarization as for instance the low-threshold calcium mediated current in mammalian CNS neurons (Llinas and Yarom, 1981; Jahnsen and Llinas, 1984b). For small enough excursion of the voltage around a fixed potential $\overline{V}$, these channels can be described by a circuit similar to the one shown in figure 19a.

The presence of an inductance can lead to resonant behavior, i.e. the membrane impedance

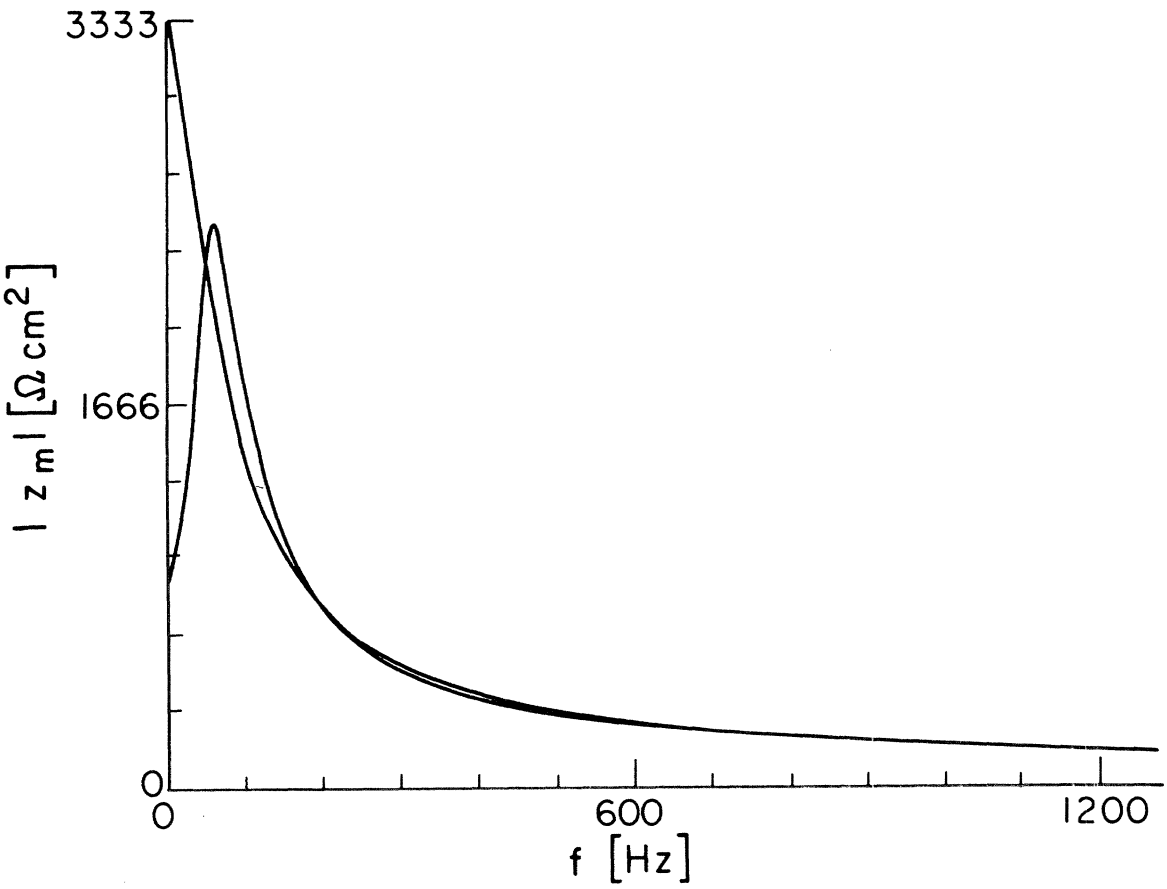

Figure 17. The membrane impedance z_m for two types of membranes as a function of frequency. Calculating the small-signal impedance of a patch of squid axon membrane described by the Hodgkin-Huxley equations gives rise to the bandpass function, which peaks at $67Hz$. Reducing the channel density η to zero, leaving only the passive components, yields the monotonic decaying curve. Note that beyond $200Hz$ both curves coincide. From Koch, 1984a.

shows a maximum at f_{max}. A sinusoidal current of that frequency will therefore decay less than current with lower or higher frequency components, that is, the impedance will show bandpass-like character (figure 17). Thus, excitable membranes are capable of producing subthreshold oscillatory responses near $100Hz$ when K^+ and Na^+ carry the current (Hodgkin and Huxley, 1952; Mauro *et al.*, 1970). The resonant frequency can be modulated by the density η of active channels (Sabah and Leibovic, 1972; Koch, 1984a) and, perhaps less likely, by $[Ca^{2+}]_i$. It can be as low as $1Hz$ as in heart cell membrane (Clapham and DeFelice, 1982) or as high as several hundred Hz as in the frog node of Ranvier (Clapham and DeFelice, 1976). Increasing η increases the degree of membrane excitability and the resonant frequency while decreasing the range of validity of the linear circuit approximation.

4.1.2 Neuronal Operation

Membranes showing quasi-active behavior within a given voltage range can implement at least two different operations. First, such membranes may act as an *electrical resonant filter*, preferentially responding to inputs within a certain frequency range. The value of the resonant frequency can be varied by modulating some of the parameters underlying excitability, like the density of active channels or the level of free, intracellular calcium (Ashmore, 1983; Koch, 1984a).

Second, *quasi-active* membranes may act as *analog, temporal differentiators* (Koch, 1984a). Intuitively, this can be understood by noticing that differentiation is nothing but a high-pass filtering, removing low frequencies. The differentiation of a function $f(t)$ corresponds to the multiplication of the Fourier transformed function with frequency, i.e.

$$\frac{df(t)}{dt} \rightarrow i\omega\tilde{f}(\omega).$$

If the frequency components above the resonant frequency are disregarded, the highpass component of the membrane impedance can be approximated by

$$z_m(\omega) = a + b\omega$$

with a and b positive constants and $b > a$. Injecting a current $I(t)$ containing little or no frequency components above f_{max} into a cable with a quasi-active membrane leads therefore to a change in potential

$$V(t) = aI(t) + b\frac{dI(t)}{dt}.$$

Figure 18 demonstrates such a case. The current $I(t)$ (figure 18a) is injected into an infinite cylinder with a linearized Hodgkin-Huxley membrane (Hodgkin and Huxley, 1952). Figure 18b shows the analytical derivative of $I(t)$, while in figures 18c and 18d the "recorded" voltage change at two different locations in the cable is plotted. Such a situation may possibly occur for instance in the photoreceptor of the fly. Its output process onto a lamina monopolar neuron does not generate spikes under physiological conditions. The visual evoked response in the postsynaptic neuron to a flash or to a step increase of light can be well approximated by the scaled derivative of the response of the photoreceptor as recorded in its soma (Hengstenberg, 1982).

A third operation possibly implemented by quasi-active membranes is *spatio-temporal filtering* in visual neurons (Detwiler *et al.*, 1978 and 1980; Koch, 1984a).

4.1.3 One Example of a Computation

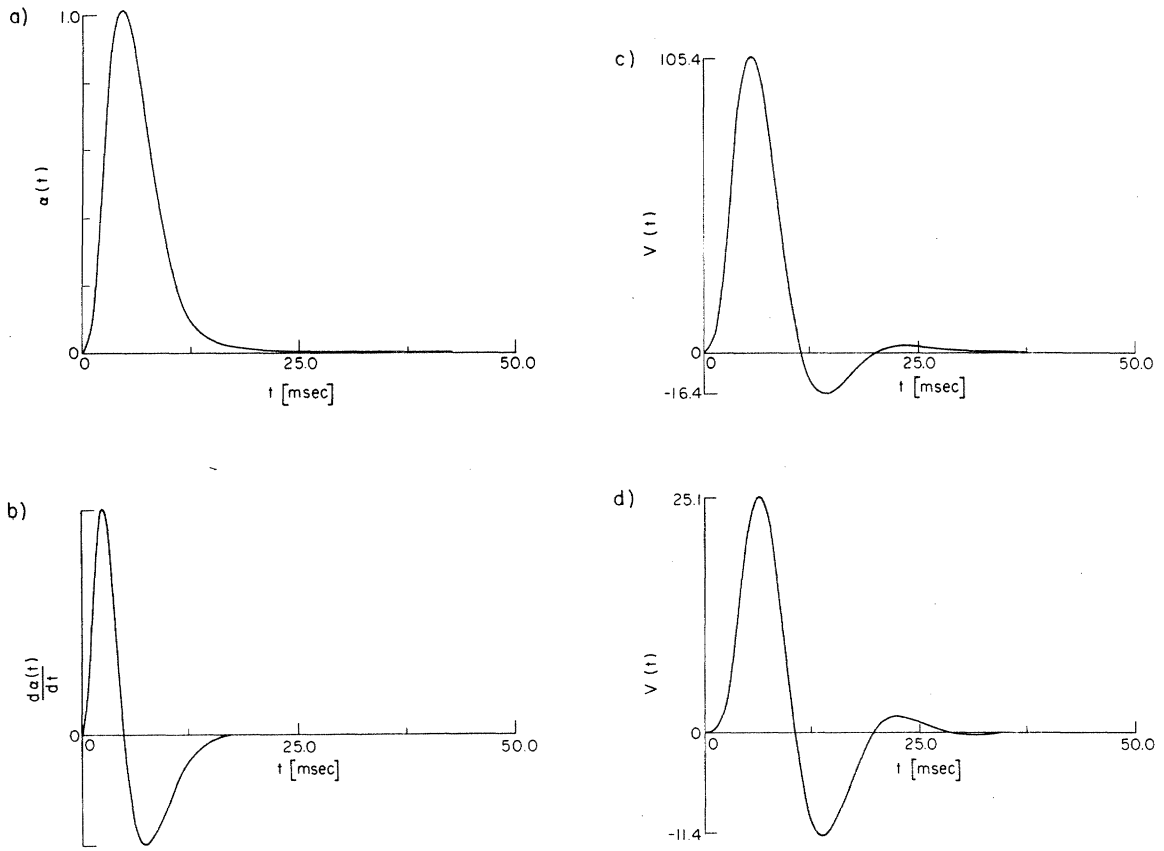

Figure 18. Injecting a subthreshold current, shown in (a), into an infinite cable with a linearized Hodgkin-Huxley membrane. (b) shows the analytic derivative of the injected current. (c) and (d) are plots of the resulting change in potential at the location of the current injection (c) and $350\mu m$ farther away. While the current peaks at $5ms$, the recorded voltages reverses their polarity at 11.3 and $10.5ms$. Note the similarity between the derivative of the current and the recorded voltage. Adapted from Koch, 1984a.

Individual sensory neurons, converting sound pressure or electrical fields into action potentials, have an optimal operating range in terms of the frequency of the input to which they are most sensitive. Such differential receptor tuning has been observed in hair cells of the cochlea in lower vertebrates (Ashmore, 1983; Crawford and Fettiplace, 1980 and 1981a,b; Lewis and Hudspeth, 1983) or in fish electroreceptors thought to derive from hair cells (Hopkins, 1976; Meyer and Zakon, 1982). Hair cells, tonotopically organized along the basilar membrane in the cochlea according to their characteristic frequencies (the frequency of the sound stimuli the cell optimally responds to), reveal their electrical tuning by damped oscillations of the membrane potential induced by current injections. The frequency of the induced oscillations coincides with the characteristic frequency. In mammals the basis of frequency discrimination is believed to be the mechanical travelling wave set up in the inner

ear by the sound wave and first described by von Bekesey (1960). In some lower vertebrates such as the turtle or the bullfrog the tuning effect is believed to be an electrical resonance mechanism located in every hair cell (Crawford and Fettiplace, 1981a) and described by an circuit of the type shown in figure 19a (Crawford and Fettiplace, 1981b). The question of the ionic nature of the underlying mechanism has been investigated recently by Lewis and Hudspeth (1983) using the patch clamp whole-cell technique. They report the presence of three different types of channels (Ca^{2+}-, K^+- and calcium-dependent K^+-conductance), one or several of them being responsible for the tuning effect. In order to explain a) the large range ($70 - 700Hz$) of the characteristic frequency shown by hair cells and b) the systematic variation of this frequency along the basilar membrane, it has been proposed that the nature of the individual channels remains invariant for all cells while the density of channels varies from cell to cell (Crawford and Fettiplace, 1981a; Koch, 1984a). Due to this varying channel density and the concomittant varying degree of electrical excitability, Koch (1984a) predicted a correlation between the characteristic frequency of individual hair cells and their degree of nonlinearity. While this mechanism leads to a fixed, stationary distribution of characteristic frequencies, transient effects might be achieved by a shift in the concentration of some ions like calcium (see Ashmore, 1983), neurotransmitters or even hormones as demonstrated in electric fish (Meyer and Zakon, 1982).

Hair cells seem like ideal candidates for computer simulations, since their role in information processing relies on non-spiking membrane mechanisms which can be modeled using a Hodgkin-Huxley like formalism (for a recent attempt see Lewis, 1984).

4.2 Transmitter Regulation of Voltage Dependent Channels

In the last years the basis of classifying conductances into those which depend only on voltage and those which depend only on the presence of a neurotransmitter (Grundfest, 1957) has gradually been eroded. There are now several examples where a transmitter does not open new ionic channels but modifies a voltage-dependent channel. Examples of such mechanisms include the control of cardiac calcium current by β-adrenergic agents (Reuter, Stevens, Tsien and Yellen, 1982), the action of opiates on neurons of the myenteric plexus and locus coeruleus (North and Williams, 1983), the synaptic inhibition of voltage-sensitive currents in *Aplysia* (Klein and Kandel, 1980) and the muscarinic control of a K^+ conductance in bullfrog sympathetic neurones (Adams and Brown, 1982; Adams, Brown and Constanti, 1982a,b) and in the mammalian hippocampus (Halliwell and Adams, 1982; for a general survey see Siegelbaum and Tsien, 1983). To illustrate this new development and its implications for neuronal computations we will use as a well-characterized example, *M-current inhibition*.

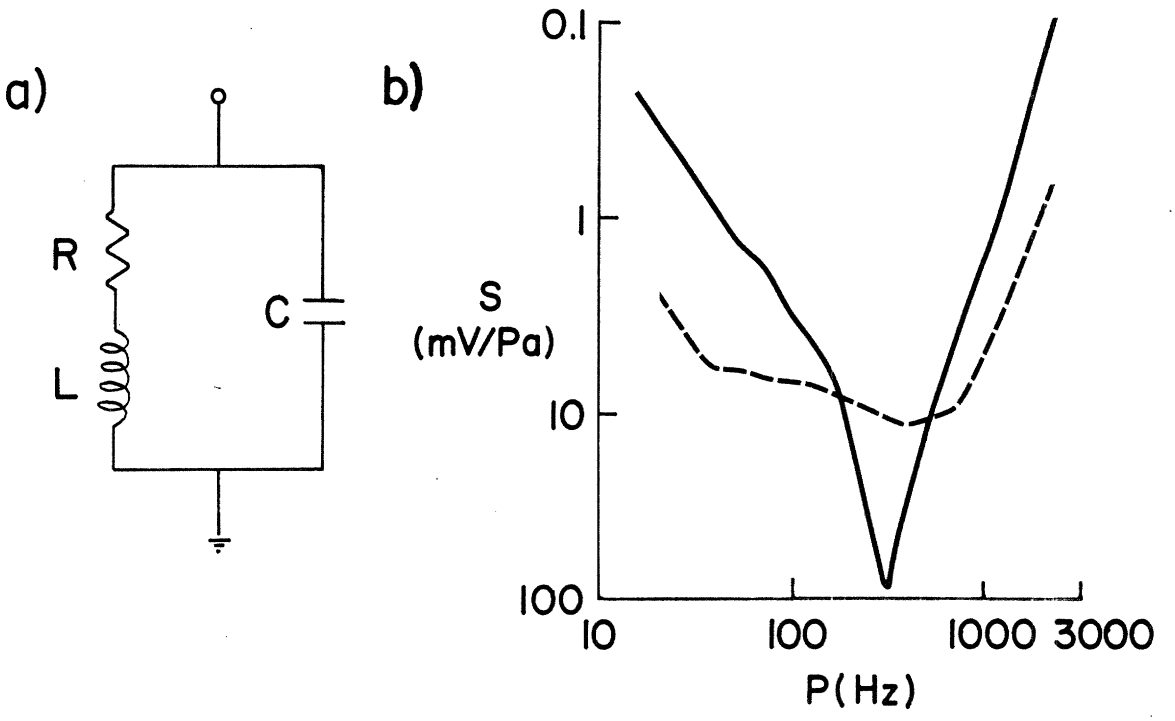

Figure 19. (a) Equivalent RLC circuit used to model the electrical resonance in turtle hair cells. (b) The sensitivity of a hair cell (voltage response normalized to the sound pressure of the tone used) as a function of the frequency of the test tone (P). The cell operates in its linear range. The frequency selectivity derives from a broad bandpass filter common to all hair cells (most likely originating in the middle ear; indicated by the dashed line) and an electrical circuit like the one show in (a) unique to every cell. Adapted from Crawford and Fettiplace, 1981b.

4.2.1 Biophysical Mechanism

Stimulation of cholinergic preganglionic fibers produces two very different excitatory responses in amphibian (B-type) sympathetic neurones: a very fast EPSP with a superimposed spike and a subsequent slow EPSP of small amplitude (figure 20a). The latter begins after a latency of some $200 - 300ms$, peaks at about $2s$ and lasts some $10 - 20s$ (Adams and Brown, 1982; see also Brown, 1983). Both potentials result from the release of ACh from the same preganglionic fibers. The initial fast EPSP, analogous to the "classical" muscle end-plate potential, results from the action of ACh on curare-sensitive *nicotinic* receptors while the slow response is a result of ACh acting on a *muscarinic* receptor. Adams and his colleagues showed that the mechanism underlying the slow EPSP is a selective inhibition of the M-current (I_M), a time- and voltage-dependent K^+-current (Adams *et al.*, 1982a,b). I_M shows no detectable inactivation. It turns on rather slowly, starting at around $-60mV$

and is maximally activated near $-20mV$ (Brown and Adams, 1980). Because it shows no inactivation, it strongly influences the steady-state $I-V$ relation near the resting potential. Under normal conditions the slow EPSP generated by a single preganglionic stimulus closes some $5-10\%$ of the open M-channels; with repeated trains of stimuli up to 50% of the channels can be closed. I_M inhibition usually produces a striking increase in the excitability of the neuron. This usually takes the form of long trains of spikes following the injection of short hyperpolarizing current pulses. Note that the essential action of I_M inhibition is not necessarily the slow EPSP seen, but rather the facilitation of the neurons response to some other excitation.[2] M-current is also sensitive to the neuropeptide LHRH (Adams *et al.*, 1982b; Jan and Jan, 1983; see section 4.3).

4.2.2 Neuronal Operation

The main effect of M-current inhibition is a rise in excitability, while the slow, low-amplitude EPSP may be more of an epiphenomena. The operation implemented by this inhibition has thus the character of *gain control*, i.e. modulating the input-output properties of the cell on a long-lasting time basis. By inhibiting I_M, the neuron has lowered its threshold to synaptic input. Figure 20b graphically demonstrates the possible effect of I_M-current inhibition on the $f-I$ curve of the cell. While the absolute current threshold remains unchanged, the slope of the linear relation between f and I increases.

4.3 Action of "Neurotransmitters" over Long Distances

4.3.1 Biophysical Mechanism

There is good experimental evidence that certain "neuroactive" substances, in particular neuropeptides, are capable of influencing the electrical behavior of neurons "at a distance", i.e. over distances large in comparison with the metric employed for measuring the dimensions between the conventional presynaptic-postsynaptic elements.[3] Examples are the action of a luteinizing-hormone-releasing-hormone (LHRH) like peptide in bullfrog autonomic ganglion (Jan and Jan, 1983), FMRFamide-like and Proctolin-like peptides in the stomatogastric ganglion of crustaceans (Marder and Hooper, 1984; Hooper and Marder, 1984), egg-laying hormone in *Aplysia* (Branton, Mayeri, Brownell and Simon, 1978) and the

[2]Detailed computer simulations of the bullfrog sympathetic neuron, including its seven different currents, calcium and potassium buffers, diffusion and membrane pumps, demonstrate that the slow EPSP and the enhanced susceptibility of the neuron to current inputs is due to the inhibition of two currents, I_M and a smaller, calcium-dependent, non-inactivating current mediating the long hyperpolarization following single spikes, I_{AHP} (Koch and Adams, in preparation).

[3]Schmitt (1984) proposes the generic term *informational substances* to name these and similar chemical mediators.

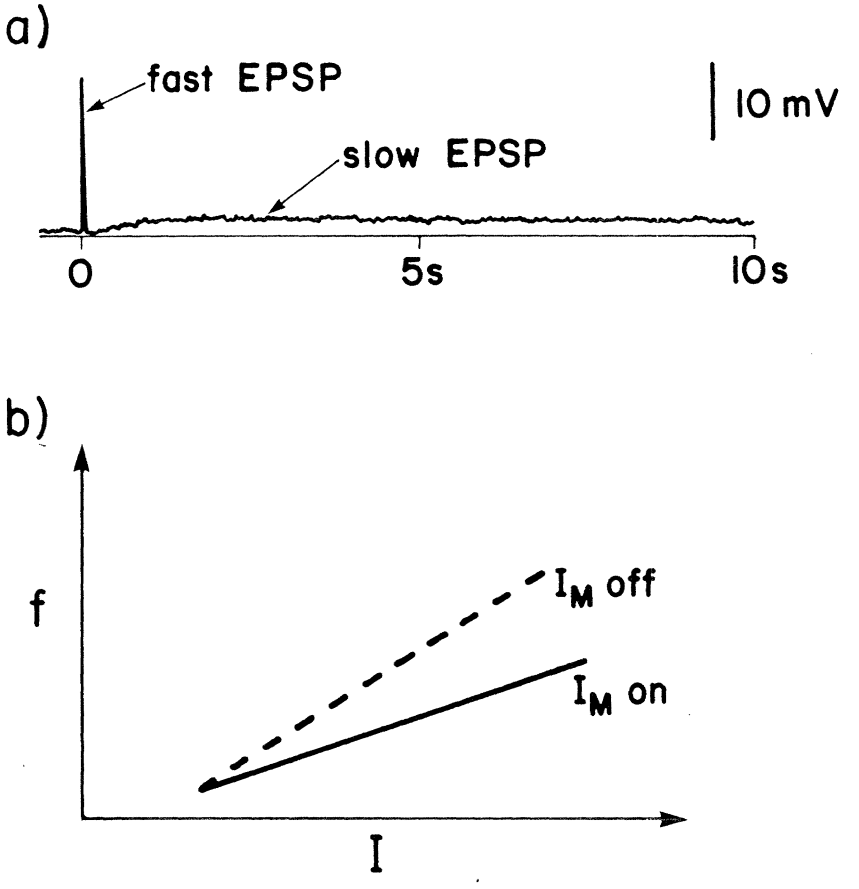

Figure 20. (a) The intracellular potential in a bullfrog sympathetic neuron following a single preganglionic stimulus. The fast EPSP, and the thereby induced action potential, is mediated by a nicotinic ACh receptor while the slow EPSP results from the action of ACh on a muscarinic receptor, inhibiting M-current. Adapted from Adams and Brown, 1982. (b) One possible effect of M-current inhibition on the steady-state firing frequency of a neuron. Note that the current threshold remains unaffected, but that the total response of the cell to synaptic input increases.

proposed nonsynaptic release of norepinephrine and serotonin from the diffusely branching axons originating in the locus coeruleus and the raphe nucleus (Dismukes, 1979; Moore and Bloom, 1978). In order to understand some of the issues involved, we will briefly examine the action of a LHRH-like peptide in the bullfrog.

Stimulation of cholinergic preganglionic fibers in the frog sympathetic ganglion gives rise to three different postsynaptic responses: the fast, nicotinic-mediated EPSP and the slow, muscarinic-mediated EPSP (as discussed in the previous section). A third synaptic potential, termed the late slow potential, lasts for several minutes and is not mediated by ACh (Jan and Jan, 1982 and 1983). Its main action is to increase the excitability of the neuron, similar to M-current inhibition. In fact, the M channel probably is an important component generating the late slow EPSP, although it cannot fully account for all of its ionic basis

(Adams *et al.*, 1982a,b). It is believed that the late slow EPSP is mediated by a peptide structurally very similar to LHRH. This peptide is contained and released from the same preganglionic fiber as ACh. Stimulating a fiber presynaptic to a C neuron gives rise to both the ACh mediated synaptic event and to the late slow EPSP. B cells, though not in any synaptic contact with the fibers presynaptic to C cells, also show the late slow EPSP upon stimulation of the preganglionic C fibers. Thus, the LHRH-like peptide must diffuse for tens of microns from its release site before reaching the surface of B cells. The longevity of the late slow EPSP is not limited by the diffusion time but is a consequence of the long lifetime of the peptide.

Three points are particularly noteworthy in this example and can be generalized to similar cases in other systems. The influence of the peptide on the target cell is of long duration, typically much longer than the millisecond range of action potentials, and contingent upon previous excitation in the target neuron. The last attribute is crucial to the possible modulatory function of peptides (see the discussion by L.L. Iversen in Dismukes, 1979). Thus, M-current inhibition increases the excitability of the neuron without, or only with little, concomittant rise in voltage. Similarly, substance P acts on Renshaw cells in the spinal cord to antagonize the nicotinic actions of ACh, while having no effect when administered alone (Belcher and Ryall, 1977). Lastly, the sphere of influence of these modulatory substances is not confined to the synaptic cleft, but may extend well above the $10\mu m$ range. Their speed of action is usually limited, in the absence of any active transport process, by diffusion, that is distance is proportional to the square (or cubic) root of the elapsed time. It is important then, that these substances are not degraded by enzymes during their diffusion from the release site to the receptor.

Increasing evidence from immunohistochemical studies reveals that neurons may contain one or more neuropeptides in addition to a monomine neurotransmitter such as noradrenaline or ACh (Hoekfelt *et al.*, 1980; for an overview see Lundberg and Hoekfelt, 1983). Concomittantly, iontophoretic experiments demonstrate the presence of more than a single population of receptors on a particular postsynaptic neuron. Cells in the frog sympathetic ganglion respond to ACh, substance P and LHRH (Jan and Jan, 1982) while locus coeruleus neurons bear both opiate and α-adrenoreceptors (Starke, 1981). Since all neuropeptides are made up of amino acids, the total number of possible peptides could be astronomically large, depending on the peptide chain length. Lastly, neuropeptides differ fundamentally from ACh, biogenic amines and amino acids since they are not recycled or reuptaken. Peptidergic neurons rely entirely on the synthesis of the peptide in the cell body and on its axonal transport to the synaptic terminal. This might well have functional consequences under conditions of tonic firing.

4.3.2 Neuronal Operation

We propose that the main action of neuropetides and similar substances is a long-term modulation of cellular excitability without influencing directly neuronal excitability (see figure 20b). Applying the neuropeptide in the absence of any synaptic input will have little effect on the behavior of the neuron. The underlying biophysical mechanisms can be likened to a *gain control*. The major differences to the "conventional" mode of fast and focal chemical interaction is that neuropeptides can activate large areas in the CNS by diffusing throughout the extracellular matrix and that their time-course is typically two to three orders of magnitude larger than the time-course of postsynaptic conductance changes or of impulse initiation. This restricts the use of neuropeptides and similar substances to circumstances where the global properties of a given hardwired circuit need be modified to reflect a different situation requiring a different kind of information processing (see for instance Marder, 1984). Owing to their time-course, it seems unlikely that neuropeptides underly fast computations required for visual perception and motor control.

4.3.3 An Example of a Computation

Recent efforts to plan and build massive parallel computers has led to the growing realization that one major challenge facing the computer architecture designer is the problem of *routing information* efficiently among the individual processors, i.e. with the least amount of time and connections (Hillis, 1981; Poggio, 1984). The cortex, a computational structure comprising roughly 10^{11} individual processors operating in parallel, probably faces a similar problem. How is information routed among neurons without quickly exceeding space by connecting every neuron with every other neuron? One possible mechanism might involve neuropeptides. The basis of the mechanism is illustrated in figure 21. Let us assume that a particular sensory neuron is presynaptic to a large number of neurons, i.e. establishes conventional synapses with them. In the absence of any modulatory input, electrical activity in the sensory neuron evokes some activity in the corresponding postsynaptic elements. In the presence of a particular neuropeptide A, for which only a subset M_A of all neurons have a receptor, the excitability of all neurons in M_A is enhanced. The neuropeptide is released from a local, diffusely branching interneuron. Activity in the sensory neuron will now evoke a much stronger response in the affected neurons than before and the information about the occurance of a specific stimulus has been routed to a certain subset of neurons. If another population of neurons has receptors to a different peptide, the information is routed to a different target. In order for such an *addressing scheme* to work efficiently, a large number of different peptides is required in order to "program" different paths. The number and location of neurons which could be addressed in this way depends critically on the transport mechanism of the neuropeptide, i.e. on diffusion in the extracellular space. Thus, *addressing* works by selectively and temporarily increasing the *gain* of the active membrane

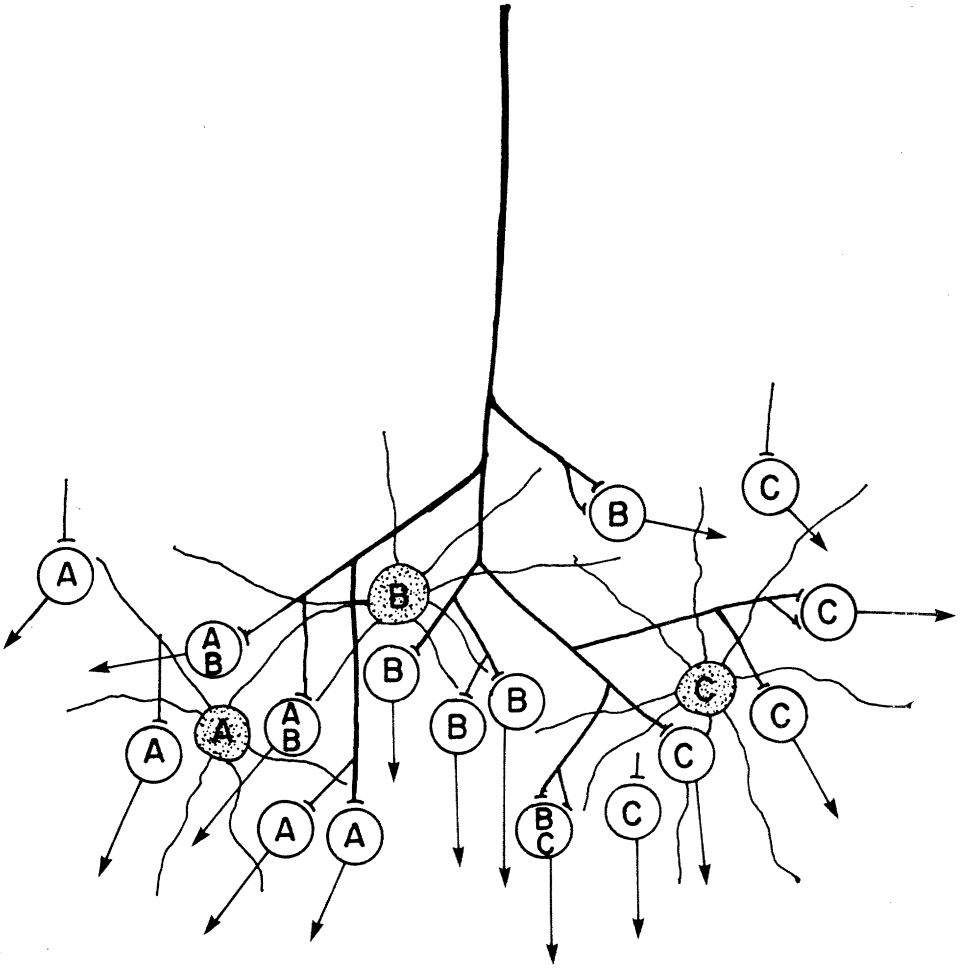

Figure 21. A highly speculative addressing scheme in a closely packed neuronal ganglion. The axon (heavy line) is presynaptic to a variety of cells which project outside the ganglion. Each one of these cells has receptors for one or two different neuromodulators, such as neuropeptides (A, B and C). They are released by local interneurons projecting diffusely throughout parts of the ganglion. Once a specific neuromodulator has been released, it diffuses to its receptor sites, enabling the postsynaptic cell to fire much more vigorously in response to a presynaptic input than before. Thus, information from the axon has been routed to a subset of all its postsynaptic neurons. This mechanism requires a large number of neuropeptides or similar substances, which may diffuse for many microns before binding to a receptor. Moreover, neurons are assumed to have receptors for a few of these substances.

properties of the class of neurons to be addressed, without actually exciting them. This solution to the addressing problem is similar to the traditional telephone system, where connections are made and broken as required for exchanging information. It is conceivable that neuropeptides or other modulators may route information within the branched axonal tree of a single neuron by controlling in a differential way the active membrane properties of the axonal branches.

5. Biophysics of Computation

From the point of view of information processing, an important difference among the biophysical mechanisms we have reviewed above is likely to become increasingly clear. Action potential generation and propagation, synaptic transmission and the interaction between synaptic inputs usually occurs on a timescale of milliseconds, what we term the *primary, logical timescale*. The lower limit on this time-scale is given by the speed of propagation of the electrical potential in axons and other excitable tissues and by the chemical kinetics of the binding of receptors and transmitters. The primary timescale can be likened to the basic *cycle time* of a digital computer. However, some of the newly discovered currents, like for instance the slow, muscarinic-mediated, cholinergic excitation (Brown, 1983) or the effects of neuropeptides on the firing behavior of neurons, take many hundreds of millisecond to be noticeable, and may last many seconds and even minutes. Their use in information processing would be one of modulating the existing, hardwired circuitry, adapting the circuit to different stimuli or to different modes of operation (e.g. Marder, 1983). They act in what we call the *secondary, modulatory timescale*. Biophysical mechanisms operating in the primary time range most likely underly visual perception and the computation required for motor output. Mechanisms acting on the modulatory timescale, on the other hand, may, increase the excitability of a neuronal population following some stimuli alerting the animal to a potential danger, or may mediate sensory aftereffects or habituations. While the biophysical mechanisms in the primary timescale correspond to the physical mechanisms underlying the operation of transistors and gates, there are at present no counterparts to the biophysical mechanisms operating in the modulatory time range.

We still know too little about the computational style used by nervous systems. As a consequence there is a large gap between computational 2theories of vision and motor control and their possible implementation in neural hardware. The model of computation provided by the digital computer is clearly unsatisfactory for the neurobiologist, given the increasing evidence that neurons are complex devices, very different from the simple digital switches suggested by the McCulloch and Pitts (1943) neurons. It is especially difficult to imagine how networks of neurons may solve the equations involved in vision algorithms in a way similar to digital computers.

Recently, Poggio and Koch (1985) have suggested a powerful analog model of computation in electrical or chemical networks for a large class of vision problems, that maps more easily into biologically plausible mechanisms of the type we discuss in this paper. Their suggestion is based on a new theoretical framework for early vision - regularization theory - introduced by Poggio and Torre (1985). Regularization methods solve early vision problems in terms of variational principles of a specific type. Poggio and Koch begin by recognizing

that analog electrical networks are a natural hardware for computing the class of variational principles suggested by regularization analysis. Because of the well-known isomorphism between electrical and chemical networks (see for instance Busse and Hess, 1973 or Eigen, 1974) that derives from the common underlying mathematical structure (i.e. Kirchoff's laws), appropriate sets of chemical reactions can be devised, at least in principle, to "simulate" exactly the electrical circuits (figure 22).

Electrical and chemical systems of this type therefore offer a computational model for early vision that is quite different from the digital computer. Equations are "solved" in an implicit way, exploiting the physical constraints provided by Kirchoff's laws. It is not difficult to imagine how this model of computation could be extended to mixed electrochemical systems by the use of transducers, such as chemical synapses, that can decouple two parts of a system, similarly to operational amplifiers (Poggio and Koch, 1985).

Could neural hardware exploit this model of computation? Several researchers had proposed in the past analog models of computation for the nervous system, most notably Jerry Lettvin. The evidence reviewed in this paper shows that for implementing electrical networks in equivalent neuronal hardware, one can draw upon a large number of elementary circuit elements. Patches of neuronal membrane or cytoplasm can be treated as resistances and capacitances. Voltage sources may be mimicked by synapses on dendritic spines or thin dendrites (Koch and Poggio, 1983b), whereas synapses on large dendrites may act as current sources. Chemical synapses could effectively serve to decouple different parts of a network (see Poggio and Koch, 1985). Chemical processes such as the reactions associated with postsynaptic effects or with neuropeptides could also be thought as part of a complex electrochemical network. Obviously, the analogy cannot be taken too literally. We are convinced, however, that the *style* of computation represented by analog circuits represents a very useful model for neural computations.

In the brief history of computer technology, several different physical effects have been exploited to perform elementary operations, mostly digital. Within a single, very specific technology, however, typically a small number of physical mechanisms and corresponding operations are used, as for instance the inverter and NAND gating in MOS technology. Most of the more complex operations are synthesized starting from these two basic ones.

It would be very surprising if evolution were to choose a very small number of basic mechanisms in the nervous system. This is certainly the "old" view, in which the only operation was a thresholding operation, implemented through the mechanism of spike initiation. The evidence accumulated over the last several years by research on membranes and synapses, has made abundantly clear, however, that several different mechanisms are

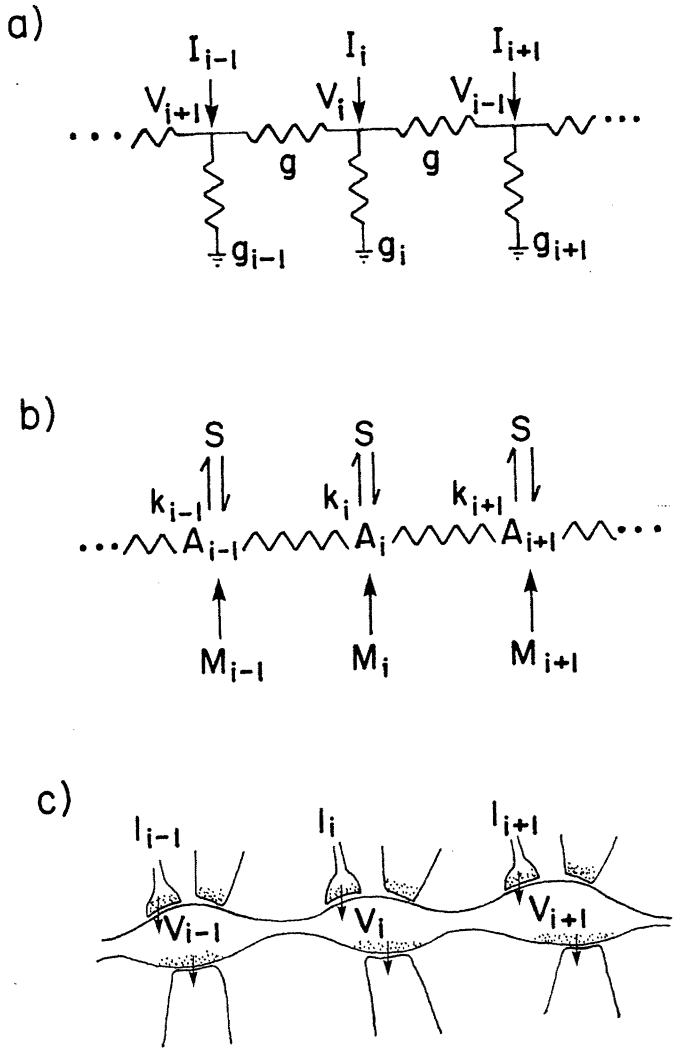

Figure 22. (a) A resistive network solving a particular visual task: computing the smoothest velocity field of a moving contour (Hildreth, 1984). The input data, injected current of amplitude I_i, corresponds to the measured perpendicular velocity component $v_i^{\perp}$. The solution of the network, the voltages V_i, correspond to the unknown normal velocity components $v_i^{\top}$. Sampling the output, i.e. the voltage, between nodes corresponds to linear interpolation between the node values. Notice, that the value of the conductance g_i, varies from location to location. (b) A chemical network which is formally equivalent to the electrical circuit shown in (a). A substance A, the concentration of which corresponds to the desired $v^{\top}$, diffuses along a cable while reacting with an extracellular substance S (first order kinetics). The corresponding On-rate k_i varies from location to location. This could be achieved, for instance, by a differential concentration of an enzyme. The inputs $v_i^{\perp}$ are given by the influxes of substance A. (c) This scheme illustrates an hypothetical neuronal implementation of the electrical and chemical circuit shown above. A dendrite, acting as both pre- and postsynaptic element, has a membrane resistance that can be locally controlled by suitable synaptic input, preferentially from channels with a reversal potential close to the resting potential of the dendrite. The output, the voltage V_i, is sampled by dendro-dendritic synapses. Adapted from Poggio and Koch, 1985.

likely to be exploited by the brain for information processing (Schmitt, 1979; Bullock, 1979). It seems unlikely, on the other hand, that the number of basic mechanisms is much larger than, say a dozen or so. This general class of mechanisms includes

- Voltage-dependent channels
- Neurotransmitter-dependent channels
- Modifications of subcellular components
- Spatio-temporal integration in neuronal structures

Our approach — to identify and characterize some of the basic mechanisms for information processing — may provide powerful constraints for interpreting morphological and physiological data, and for connecting them with computational theories. Clearly, this plan can only be successful if the number of basic biophysical mechanisms in information processing is small.

The final answer to these questions can only be obtained with experimental methods. A case in point is provided by our conjecture about shunting inhibition being a basic mechanism for implementing operations of the analog AND-NOT type. We have isolated a few computations, such as the computation of directional motion, where shunting inhibition may have a critical role. We have shown with theoretical methods and computer simulations based on anatomical data, that the properties of the biophysical mechanisms are consistent with our conjecture in the case of retinal ganglion cells. We have also made specific experimental predictions. Several of them are supported by recent data. If our conjecture turns out to be correct in the case of directional selectivity of retinal ganglion cells, the next task will be to demonstrate that the same mechanism is, or is not, used in other parts of the nervous system for other computations.

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