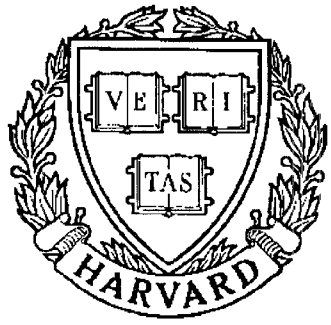
TECHNICAL RESEARCH REPORT

SYSTEMS RESEARCH CENTER



Supported by the National Science Foundation Engineering Research Center Program (NSFD CD 8803012), Industry and the University

Biological Plausibility of Back-Error Propagation through Microtubules

by J. Dayhoff, S. Hameroff, C.E. Swenberg, and R. Lahoz-Beltra

TR 92-17

BIOLOGICAL PLAUSIBILITY OF BACK-ERROR PROPAGATION THROUGH MICROTUBULES

Judith Dayhoff
Systems Research Center, University of Maryland
College Park, MD 20742

-

Stuart Hameroff
Advanced Biotechnology Laboratory
Dept Anesthesiology, University of Arizona
College of Medicine, Tucson, AZ 85724

-

Charles E. Swenberg
Armed Forces Radiobiology Research Institute
Bethesda, MD 20889-5145

-

Rafael Lahoz-Beltra
Advanced Biotechnology Laboratory
Dept Anesthesiology, University of Arizona
College of Medicine, Tucson, AZ 85724

-

Corresponding author: Judith Dayhoff

January 2, 1992

Abstract

We propose a plausible model for learning by back-error propagation in biological neurons. Forwards propagation occurs as action potentials propagate signals along branching axons and transmit those signals across axo-dendritic synapses, whereupon post-synaptic neurons sum their incoming signals. In our model, back-error propagation is proposed to occur via signals within intraneuronal cytoskeletal microtubules. These signals modify the effective strengths of synapses during learning. Differences between network output and desired (target) outputs are computed at synapses or by synaptic complexes. Biophysical mechanisms are suggested for the summing of errors and the propagation of errors backwards through microtubules within each neuron of the network. We discuss issues and assumptions of the model, alternative candidate mechanisms, and the degree of biological plausibility.

1 Introduction

A fundamental challenge today is to explain the possible mechanisms for learning in the brain and in nerve cell assemblies. A variety of learning models have been proposed, including those of "artificial neural networks", which employ processing units that are inspired by biological neurons but are greatly simplified. The leading paradigm in artificial neural networks is back-error propagation, which has led to a large number of applications. Back-propagation has been shown to have powerful mathematical properties with respect to approximation of arbitrary functions and discerning of arbitrary differences among input patterns (Hornik et al, 1990).

Prior studies regarding biological back-error propagation have assumed that error feedback must be provided by action potentials and axodendritic synapses (Stork, 1989; Hecht-Nielsen, 1989, Churchland and Sejnowski, 1989). This assumption requires a heavy density of bidirectionally connected cells, in which many pairs of cells must be connected in both directions via axodendritic synapses. For each forwards connection to a target neuron, there was assumed to be a backwards connection from the target neuron to the original neuron, to send error difference signals backwards through the network. Because of the lack of evidence for the occurrence of such arrangements, the biological plausibility of back-error propagation has been considered extremely unlikely. Here we take a radically different approach to the biological plausibility of back-error propagation. We utilize the internal complexity of

the neuron to construct a model in which back-error signals are propagated within a nerve cell through the cell cytoskeleton, the cell's structural support system, which is comprised mostly of microtubules (MTs).

Biological neurons are extremely complex and employ a wide variety of anatomical and biophysical structures and mechanisms to perform their dynamic roles in neural information processing. Complex anatomy and physiology include the spatial arrangement of axons and dendrites, their branching topologies, the location of cell bodies and the interconnection configuration among cells. Field interactions, molecular-level structures such as membrane channels, receptors, voltage and time dependent channel conductances, membrane resistance and capacitance, receptor binding and conformational changes, and ionic diffusion also play roles in neural processing. The chemical synapse formed between neurons has been identified as the primary neuronal structure associated with learning and memory. The synapse responds in a complex dynamical manner to not only its primary neurotransmitter but also to a host of neuromodulators. Each synapse is a vast electrochemical factory that exhibits a history-dependent plasticity. Because of this, each synapse has tremendous potential for computational activity. Synapses also interact with internal processes within the cell, including the cell cytoskeleton.

Recent models have suggested that the cytoskeleton - the structural support system within cells - might be capable of transmitting signals and could do so internally within a nerve cell (Rasmussen et al, 1990). In this paper we propose a model in which back-error propagation occurs via signals trav-

eling from axon to dendrite within intraneuronal cytoskeletal microtubules, and in which these signals modify the effective strengths of synapses during learning via the biophysical interaction between cytoskeletal microtubules and nerve cell membranes. This model argues for the biological plausibility of back-error propagation.

The cytoskeleton is a rich structural network which includes microtubules (MT), centrioles, actin and intermediate filaments, membrane coupling proteins such as fodrin, and microtubule associated proteins (MAPs) which crosslink MTs and other structures. Microtubules are found in virtually all living cells, and they provide physical and structural support to the cell. (See Figure 1.) In addition, they provide a communication and transport channel between remote cell parts. In most cells, the MTs connect the cell center (centriole) to the cell periphery in a radial pattern. In nerve cells the MTs have evolved a striking adaptation in that the microtubular lattice extends into the extremities of the axons and the dendrites, and some MTs may bypass the cell center. These internal highly ordered structures allow not only for the mechanical transport of material particles, but possibly the transmission of information coded in MT conformational patterns. A variety of candidate mechanisms have been proposed for microtubule signal propagation, including particle transport and traveling conformational changes (Hameroff, 1987; Hameroff et al, 1989; Rasmussen et al, 1990).

The assumption of microtubular signaling alleviates the need for bidirectional connections among cells, used in previous arguments for biological

plausibility of back-error propagation. Furthermore, the model proposed here fits strikingly with a variety of experimental evidence from studies of the cytoskeleton and its associated biochemistry. This evidence is included in Section 2. Previous authors have suggested that MTs are indeed involved in back-error propagation (Werbos, 1990; Werbos, 1992; Hameroff et al, 1989; Rasmussen et al, 1990) or in neuronal learning (Grossberg 1969), but did not develop a description of the underlying biophysics or suggest anatomical sites at which each of the necessary computations take place. Specific sites and biophysical mechanisms are suggested in this paper as candidate mechanisms for the proposed model.

The model proposed in this paper was constructed with the following approach:

1. Forwards propagation is accomplished via membrane phenomena such as the propagation of action potentials, the summing of incoming signals via post-synaptic potentials, and the propagation of these potentials across dendrites and cell bodies. Action potentials, axo-dendritic synapses and dendritic summing are utilized. Dendrites act as receivers of information, and axons act as output channels for information signals.

2. Learning is accomplished through the adjustment of synapses. Biophysical parameters that impact synaptic strengths or sensitivities are adjusted during learning.

3. Error feedback signals are carried inside the cells by MTs, in a direction opposite from the propagation of action potentials. The MT signals originate in axons, at pre-synaptic sites, and are carried internally within the neuron to its dendrites, to post-synaptic sites; these signals then influence or control the changes in synaptic efficacies during learning. In some cases, chemicals propagate backwards across the synapses and thereby initiate signals in the presynaptic neuronal MTs. (We do not require that the MTs themselves perform adaptive computing paradigms, as in earlier studies (e.g. Rasmussen et al, 1990); here we model the participation of microtubules to be merely through signaling and averaging of adjacent signals.)

In this paper we attempt to document and validate the model by associating biophysical processes with known biological structures. A few parts of the model require postulated structures or processes that currently have not been identified in biological neural systems, but arguments are given to suggest that these additional hypothetical entities are highly plausible. Other aspects of the model are based on previous simulation modeling studies for which experimental evidence is not yet available, largely because of the present lack of suitable nanoscale experimental technologies (e.g. techniques that probe the nanometer / nanosecond ranges). No theoretical models are ever complete and hence we expect that future research findings will necessitate model refinements of some aspects of the proposed mechanisms.

This paper is organized as follows. Section 2 describes the structure and properties of MTs, reviews experimental evidence for their participation in

neural computation, and describes previous modeling results of signal propagation in MTs. Section 3 breaks down the back-propagation learning rules into separate equations that govern the artificial neural network paradigm. Section 4 proposes a specific biophysical site at which each of the computations could take place, and proposes plausible biophysical mechanisms that could perform each individual computational process at the suggested site. In addition we discuss alternative biophysical structures that might accomplish the same or similar computations. Section 5 discusses the generality of the proposed model and its potential impact.

2 Microtubules

2.1 Microtubule structure

Interiors of neurons and other eukaryotic cells contain a lattice-like network of protein polymers collectively termed the cytoskeleton. Primary organizing elements of the cytoskeleton are called microtubules (MTs), which are arrayed in parallel and inter-connected by microtubule associated proteins (MAPs). Other interconnecting networks of smaller filamentous proteins (actin, intermediate filaments, etc.) intersperse with MTs to form a dynamic gel whose activities in all types of cells are essential to the living state. The cytoskeleton participates in activities such as mitosis, growth and differentiation, locomo-

tion, food ingestion or phagocytosis, synapse modification, dendritic spine formation, cytoplasmic formation, and neurotransmitter release (Burgoyne, 1991).

MTs are hollow cylinders, 25 nanometers (10^{-9} meters) in diameter, whose lengths may span meters in some mammalian neurons. MT cylinder walls are assemblies of 13 longitudinal protofilaments that are each a series of subunit proteins known as tubulin. (See Figure 2.) Each tubulin subunit is a polar dimer, measuring 8 nm (nanometers) in length, that consists of two slightly different classes of 4 nm monomers known as α and β tubulin (Amos and Klug, 1974). The tubulin dimer subunits within MTs are arranged in a hexagonal lattice that is slightly twisted, resulting in differing neighbor relationships among each subunit and its six nearest neighbors.

Interconnected by MAPs, MTs form a lattice network configuration within cells that provides structural support. In cells such as neurons they interconnect the cell membrane with cell organelles, and play a role in material transport and possibly in signaling that promotes protein synthesis. MTs generally radiate from a MT organizing center (the centriole) located near, but outside, the cell nucleus, although in neurons some MTs may bypass the centriole. Cytoskeletal elements apparently play a role in gene expression and cell shape changes, and may allow the environment of the cell to trigger protein synthesis (Ben Ze'ev, 1991). Distal ends of MTs typically connect via anchoring proteins (such as fodrin) with membrane proteins, including receptors and ion channels.

MTs are polar; the tubulin dimer is oriented with a negatively charged alpha chain at one end and a positively charged beta chain at the other end. The entire MT as well as individual subunits have the same polarity, thus, MTs are predicted to behave as "electret polymers" which have piezoelectric properties (Mascarenhas, 1974 ; Athenstaedt, 1974). This polar nature of MTs introduces an asymmetry into their orientation within the cells. For MTs in axons, almost all have been reported to be oriented with their beta (+) end towards the axon terminus and their alpha (-) end towards the cell body (Burton and Paige, 1981; Heidemann et al, 1981). MTs in the dendritic part of the cell are mixed with approximately half oriented with their plus ends away from the cell body (Burton, 1988).

MTs undergo dynamic assembly and disassembly processes, in which MTs either grow or shrink, and may oscillate between these two processes (Kirc-shner and Mitchison, 1986). MT assembly and disassembly are complex processes that depend on various factors including temperature, calcium ion concentration and the availability of GTP, a high-energy phosphory-lated molecule similar to ATP. GTP-tubulin is required for assembly, and the hydrolysis of GTP-tubulin to GDP-tubulin occurs in the assembled MT. (Utilization of GTP hydrolysis energy by assembled MTs in theory could pump conformational excitations involved in cytoskeletal signaling.) MTs can quickly change from depolymerization to reassembly in another direc-tion (DeBrabander 1982). The resulting MT polymerization plays a role in the dynamic architecture and form of cells, including the formation and structural support of axonal and dendritic spatial branching structures, and

possibly the formation and modification of synapses. A centralized "orientation" is maintained by centrioles, pairs of cylindrical super-assemblies comprised of nine MT triplets.

Microtubule associated proteins (MAPs) attach to MTs at specific dimer sites, and MAP attachments can result in either irregular, or various superhelical, periodic patterns of the MT surface lattice (Kim et al, 1986). Figure 3 shows such experimentally observed patterns, which can be simulated by calculation of coherent phonon mode maxima in MT (Samsonovich et al, 1992). Coherent phonons have been proposed as a candidate mechanism for signaling along MTs although experimentally not verified.

Some MAPs form bridges that laterally connect specific subunits on parallel-arrayed MT as well as neurofilaments, membrane proteins, and organelles. Other MAPs, such as dynein and kinesin, are contractile and use biochemical energy from ATP or GTP hydrolysis for mechanical movement such as axoplasmic transport. Axoplasmic transport moves molecules and particles from the cell body along axons and dendrites to synapses.

Neurons are distinguished from other cells by their highly elongated processes (axons and dendrites) and must maintain their nutrient competence by a flow of material from regions near the soma to their elongated extremities. Since most cellular biosynthesis occurs in the region of the cell body, enzymes, receptors, neurotransmitter, and other substances must be transported. The transport of material away from the cell body towards axonal and dendritic

extremities is called anterograde transport whereas transport towards the soma is termed retrograde transport. Retrograde transport may recycle some material or provide feedback information. Axonal anterograde transport is generally classified by the rates at which transport of material occurs. There are different, distinct forms of fast anterograde transport with rates of 100-400 mm/day, 20-70 mm/day, and 3-20 mm/day (Vallee and Bloom, 1991), and rates of 400-2000 mm/day have also been reported (Ochs 1982). They are in all likelihood mediated by different mechanisms and involve the transport of different material particles, possibly different sizes of polypeptides. (Grafstein and Forman, 1980). The two forms of slow anterograde transport have transport rates on the order of 0.1-4 mm/day and presumably involve "treadmill-like" movement of the cytoskeleton and its membrane connections (Brady and Lasek, 1981). Our knowledge of retrograde material transport is not as extensive as anterograde transport although reputed rates are generally of the same order of magnitude, about 300 mm/day (Grafstein and Forman, 1980).

The polar nature of MTs noted previously offers directionality to the transport motor which somehow allows for the coupling and uncoupling of selective carrier proteins. Kinesin and cytoplasmic dynein proteins appear to have a role in fast anterograde and retrograde axonal transport respectively whereas dynein has been implicated in slow transport. However, lacking detailed evidence to the contrary, it is reasonable to assume MT play a role in transporting material from the cell body to the dendritic terminals. Thus axonal retrograde transport and dendritic anterograde material transport

allows for an effective coupling between axon terminals and the dendrites.

Axonal and dendritic transport, important for synaptic maintenance and modulation, depend on contractile MAPs which hydrolyze ATP for energy. Two types of mechanisms have been proposed: in one, transported materials bind to contractile MAP proteins, kinesin, cytoplasmic dynein and/or dynamin which then, as a complex, interacts transiently with the MT structure like trains on a track (Pfister et al, 1989; Brady et al, 1990). Alternatively, contractile "sidearm" MAPs, attached at specific MT sites, pass materials in a cooperative "bucket brigade". The MAPs consume ATP hydrolysis energy in the process, however the mechanism for orchestration and sequential signaling within MTs is unknown. In either type of mechanism, material can travel in opposite directions along a single microtubule.

Other cytoskeletal activities involve the molecular machinery of cell division, growth, differentiation, formation of synapses and dendritic spines (Burgoyne, 1991; Hirokawa, 1991). Formation of synapses including dendritic spines involves "neurite" and growth cone extension by polymerization of MT, actin, and other cytoskeletal proteins. Once established, synapses are maintained and modulated by axoplasmic transport and other mechanisms. In single cell organisms like amoeba and paramecium, which do not have synapses or brains to explain their adaptive behaviors, relatively complex behaviors are controlled by or involve the cytoskeleton.

2.2 Cytoskeleton and Computation

Experimental evidence suggests that the cytoskeleton may be directly involved in neural information processing, cognition, and learning. For example, Mileusnic et al. (1980) correlated production of MT subunit protein ("tubulin") and microtubule activities with peak learning, memory, and experience in baby chick brain. Cronly-Dillon et. al. (1974) showed that when baby rats begin their critical learning phase for the visual system (when they first open their eyes), neurons in the visual cortex begin producing vast quantities of tubulin. Tubulin production is drastically reduced when the critical learning phase is over (when the rats are 35 days old). In gerbils exposed to cerebral ischemia (lack of brain blood flow), Kudo et al (1990) correlated the amount of reduction in MAP2 levels with the degree of cognitive impairment. Bensimon and Chermat (1991) found that selective disruption of brain MTs by the drug colchicine caused cognitive defects in learning and memory which mimic the clinical symptoms of Alzheimer's disease. One of the neuronal MAPs is axon-specific "tau protein", the major constituent of the neuropathological correlate of Alzheimer's disease (Matsuyama and Jarvik, 1989).

Conventional wisdom generally links cognitive functions including learning with synaptic plasticity, and evidence linking synaptic plasticity to the cytoskeleton includes the following. Lynch and Baudry (1987) have studied synaptic changes in hippocampal neurons. They have examined long-term

potentiation (LTP) of synaptic efficacy in glutamate-NMDA hippocampal neurons, a correlative model of learning. They find, as does Friedrich (1990), that LTP depends on rearrangement of the subsynaptic cytoskeleton. Other studies have suggested that cytoskeletal proteins directly link to nerve membrane ion channels and receptors and that the intra-neuronal cytoskeleton is linked to nerve membrane excitability and synaptic transmission (Matsumoto and Sakai, 1979; Hirokawa, 1991).

Desmond and Levy (1988) have studied dendritic spine structural changes during a synaptic learning paradigm. They find mechanical shape changes in spines mediated by cytoskeletal actin connected to microtubules in dendrites. Kwak and Matus (1988) and Aoki and Siekowitz (1989) have shown that in neurons deprived of input, the cytoskeleton depolymerizes. The latter authors have also found that signaling and regulation for dendrite spine synapse function depends on phosphorylation of a cytoskeletal protein: the dendrite - specific MAP, called MAP-2. Halpain and Greengard (1990) have shown that activation of glutamate-NMDA receptors induces rapid dephosphorylation of MAP-2. MAP-2 is responsible for the consumption of a significant portion of brain biochemical energy. MAP-2 phosphorylation and dephosphorylation are regulated by cyclic AMP-dependent protein kinase and calcium-calmodulin protein kinase, second messenger systems activated by neurotransmitter-receptor binding. Theurkauf and Vallee (1983) have found MAP-2 to be "the major substrate for endogenous cyclic AMP-dependent phosphorylation in cytosolic brain tissue", and they concluded that MAP-2 phosphorylation "may be an important reaction in response to neurotrans-

mitter stimulation". Schulman and Lou (1989) and Aszodi et al (1991) have shown that membrane receptor initiated second messengers (e.g. Ca^{++}, cyclic AMP) converge on protein kinase A and/or Ca++/calmodulin dependent protein kinases which respond by prolonged phosphorylation of intracellular proteins including MAPs, MTs and neurofilaments (Vallano et al, 1986). These authors suggest that such prolonged phosphorylation, which supplies biochemical energy, also participates in learning. Bigot and Hunt (1990) showed that glutamate and NMDA stimulation of cultured neurons cause a redistribution of tau and MAP2. Other couplings between the cytoskeleton and membrane / synaptic function include second messenger systems such as G-proteins (Rasenick et al, 1990), calcium ion fluxes, and direct links via fodrin, synapsin, or other proteins to ion channel mediated membrane excitability and synaptic transmission (Matsumoto and Sakai, 1979; Hirokawa, 1991).

2.3 Signal Transmission in Microtubules

The study of possible modes of signal transmission in microtubules provides candidate mechanisms for backwards signaling in neurons. Direct evidence for signal propagation in MTs has been generated by Vassiliev et al. (1985) who suspended parallel, excitable membranes in ionic solution containing unpolymerized tubulin. Only when tubulin was assembled and the two membranes were connected by MTs did excitation in one membrane induce ex-

citation in the other. These authors suggested that similar communication signals occurred routinely within the cytoskeleton.

Signals propagated by microtubules have been studied both experimentally and through models of candidate mechanisms. Cytoskeletal signals could be propagated through axoplasmic transport, for which much experimental evidence exists. Because "axoplasmic" (and "dendritoplasmic") transport is bidirectional and includes a component from axon to dendrite, the transported material itself is one possible mediator of neuronal learning signals. Such transport is relatively slow (in the range of about 400 mm/day). However, more rapid signaling in MTs may regulate the sequence of contraction of mechanical MAP sidearms in axoplasmic transport as well as provide a more general medium of information processing dynamics.

Candidate mechanisms for more rapid MT signals include the propagation of tubulin conformational changes along the MT (Hameroff and Watt, 1982). Proteins exhibit conformational alterations over a wide range of time scales, and very rapid (10^{-15} sec) changes occur in protein side chains or local regions. Collective conformational transitions involving the protein globally generally occur in the nanosecond to 10 picosecond (10^{-11} sec) range (Frauenfelder et al, 1988; Karplus and McCammon, 1983). These global coordinated changes are linked to protein functions and in the case of tubulin, can represent discrete states suitable for information representation. Models which relate tubulin conformational states within MTs to signaling and information processing include propagating tubulin conformational changes

mediating sensory transduction in ciliary MT (Atema, 1973), conformational gradients (representing information) among tubulin subunits (Roth and Pihlaja, 1977), changes in MT-tubulin lattice symmetry (Koruga, 1984), memory storage in neurofilaments (Barnett, 1987) and automata-behavior in MT (Hameroff et al, 1989; Rasmussen et al, 1990). Propagation of tubulin conformational changes within MTs resulting in waves and patterns capable of information transmission would require cooperative interactions and energy pumping. Such cooperative interactions have been described as coherent excitations, acousto-conformational transitions ("phonons") and/or solitons.

Frohlich (1970,1975, 1986) proposed that protein conformational states are coupled to charge redistributions such as dipole oscillations within specific regions of proteins. His model also predicted that proteins which have an interconnected lattice structure, are joined within a common voltage field, and are "pumped" with biochemical energy (e.g. protein phosphorylation, GTP or ATP hydrolysis) will display long-range coherent excitations in the range from 10^{-9} to 10^{-11} seconds. Such excitations may also be described as acousto-conformational transitions ("phonons") in the GHz to microwave frequency range. Experimental evidence for such coherent excitations includes observation of GHz-range phonon excitations in proteins (Genberg et al, 1991), sharp-resonant, non-thermal effects of microwave irradiation on living cells (Grundler and Keilman, 1983), GHz induced activation of MT pinocytosis in rat brain (Neubauer et al, 1990) and long-range regularities in cytoskeletal structures, such as the super-lattice attachment pattern of MAPs on MT (Kim et al, 1986). Models that predict MAP attachment sites

are based on phonon excitations (Samsonovich et al, 1992).

Traveling conformational waves which propagate without changing form and maintain localized shape are called "solitary waves". In special cases where they can pass through each other without change of form and with only a slight change in phase, the solitary waves are called "solitons". Initially observed by John Scott Russell in 1934 in the movement of water waves on the surface of a canal, solitons were introduced into the biological literature by Davydov (1973) as a means of temporarily storing the dephosphated energy of ATP within a protein and conveying it to active sites such as in actin-myosin muscle contraction. According to Davydov, the hydrolysis of ATP (about 0.49 eV/molecule) injects energy into the protein alpha-helical chains. Due to nonlinear coupling of the energies of dispersion and stretching, stable, pulse-like waves would move within the protein (Scott, 1982). Although presently unproven experimentally in proteins, DNA has been conjectured to support solitons and solitons have been used to explain the hydrogen-deuterium exchange reaction of double-helical-polynucleotides (Nakanishi and Tsubooi, 1978; Teitelbaum and Englander, 1975). In this system the soliton is viewed as a configuration formed by the localized partial unwinding of the DNA helix over a few base pairs. Using model Hamiltonian parameters, Yamosa (1984) demonstrated the non-local character of this excited mode: it extends over 10 base pairs, and moves with a velocity of about $8x10^3$ cm/s, a value significantly less than the velocity of sound in DNA (Hakim et al, 1984; Swenberg and Miller, 1989). On a microscopic scale, however, this is a fast mode of transport compared to material trans-

port discussed above. In addition to alpha-helical solitons, DNA solitons, and membrane solitons, lattice solitons appropriate for cytoskeletal structures have been proposed. Sataric et al (1992) and Manka and Ogrodnik (1992) have proposed lattice soliton models in MTs as mechanisms of signaling and information transport.

Coherent excitations, phonons, solitons, or any propagated conformational changes may mediate signaling and information processing in MT/MAP networks in the context of molecular automata. Automata are computational systems described by Von Neumann (1966) ("cellular automata"). The idea of cellular automata models within neurons as a basis for intracellular information processing related to cognition was introduced by Conrad and coworkers (1973). Automata models require a lattice with subunits that can exist in two or more states at discrete time steps ("clocking frequency") governed by transition rules between states. Transition rules depend on neighboring subunits in the lattice. Depending on the pattern of initial states and transition rules, patterns can propagate, interact, compute and store information, often in exceedingly complex ways (Wolfram, 1984a,b). Von Neumann (1966) proved mathematically that automata are capable of universal computation. Cooperative coupling among neighboring tubulin conformational states, for the coherent phonon models, has been utilized to demonstrate that MT automata models are capable of nanosecond pattern generation, storage and processing, shown in Figure 4a-g (Rasmussen et al, 1990; Hameroff et al, 1989; Hameroff, 1987). Models of MT automata networks linked by MAPs are capable of adaptive learning and association as well as bidirectional in-

formation propagation. The velocity of pattern propagation in MT/MAP phonon automata is predicted to be 8 nm per excitation time (10^{-9} to 10^{-11} sec), yielding a velocity of 8 or more meters per second - similar to the velocity of traveling membrane potentials. Thus cytoskeletal information may propagate in concert with action potentials, as well as in the reverse direction. Such signals would have the required properties for back-propagation signaling from axons to dendrites through the MT structure.

3 Back-Error Propagation Paradigm

In this section we describe a back-error propagation paradigm that appears frequently in artificial neural network applications studies. It is powerful computationally and has considerable capabilities in the learning of arbitrary nonlinear functions and pattern classification tasks (Hornik et al, 1990). Back-propagation networks are non-linear mappers, capable of drawing non-linear boundaries to divide patterns. They were first proposed by Werbos (1974), in his thesis, appropriately entitled "Beyond Regression". Here we follow a specific back-propagating algorithm summarized by Rumelhart, Hinton, and Williams (1986).

We restrict this section to a back-error propagation paradigm for a three-layer feed-forward network. We assume that processing units are organized into layers and that the network is fully interconnected - e.g., the units in each

layer send interconnections to all of the units in the next layer. Back-error propagation is not, however, limited to this configuration. This is an important point since biological systems do not have this restricted interconnection configuration. Thus the greater flexibility in interconnection topologies found in biology does not preclude the use of back propagation during biological learning. The model proposed here could potentially be extended to apply to more flexible interconnection topologies.

Each back-propagation iteration during learning consists of a forwards propagation step and a backwards propagation step. In the forwards step, the network is presented with an input pattern (a vector), and produces an output pattern. In the backwards propagation step, the network compares its answer to that of a target answer, and backwards propagates error computations that are used to adjust weight values. Weights are adjusted incrementally to eventually learn the pattern-mapping task at hand (if convergence is successful). A tutorial level explanation of back-error propagation is available elsewhere (Dayhoff, 1990).

Typically, training a network requires many iterations of pattern presentations. Each iteration consists of presentation of a set of patterns known as the "training set". Weights are adjusted after each pattern in the training set ("pattern learning"), or may be adjusted after the entire training set has been presented ("batch learning"). The training set consists of a list of pattern (vector) pairs, with each pair being an input pattern and a target output pattern. This supervised training method is plausible biologically

because learning tasks frequently involve the recall of one pattern given the presentation of another; both the initial pattern and the pattern to be recalled (the "input" and "target" patterns) would be present during training. An example would be in teaching a child the letters of the alphabet; a written "A" (input pattern) would be presented at the same time as a verbal "A" (target pattern).

The notation and equations for the algorithm are as follows. Let n_h be the number of processing units in layer h. Each unit has an activation level, which is a real number. Let $a_{i,h}$ be the activation level of unit i in layer h. Each interconnection has a weight, also a real number. Let $w_{ji,h}$ be the weight to unit j (layer h+1) from unit i (layer h). Note that each interconnection weight can be thought of as a synaptic weight.

In forwards propagation, a vector pattern is presented to the network, and the values of the vector entries are taken on by the input units.

$a_{1,1}, a_{2,1}, ..., a_{n_1,1}$

Then the hidden layer calculates its activation levels as follows:

$$a_{j,2} = f(\sum_{i=1}^{n_1} a_{i,1} w_{ji,1}) \tag{1}$$

where f is a "squashing" function. In most applications of back propagation, the squashing function is chosen to be a sigmoid function:

$$f(x) = 1/(1 + e^{-x}) \tag{2}$$

However, any semilinear function will enable gradient-descent learning (Rumelhart et al, 1986).

An alternative squashing function that deserves mention is the ramp function:

$$g(x) = \begin{cases} 0 & \text{if } x \leq 0 \\ sx & \text{if } 0 < x < c \\ b & \text{if } c \leq x \end{cases}$$

The derivative of the squashing function arises in the weight adjustment equations given below. For sigmoids

$$f'(x) = f(x)(f(x) - 1)$$

For ramp functions

$$g'(x) = \begin{cases} s & \text{if } 0 < x < c \\ 0 & \text{if } x \leq 0 \text{ or } x \geq c \end{cases}$$

Note that the derivative defines an operational range in each case, and multiplication by the derivative corresponds to windowing the operational range. Figure 5 shows these squashing functions and their derivatives.

For a three-layer network the output layer activation is:

$$a_{j,3} = \sum_{i=1}^{n_2} a_{i,2} w_{ji,2} \tag{3}$$

assuming that no squashing function is used by the output units. A three-layer network has powerful and general mathematical mapping properties even when the squashing function is eliminated from the output layer units as above (Hornik et al, 1990). If a squashing function is used at the output units, then the output units activations are instead

$$a_{j,3} = f(\sum_{i=1}^{n_2} a_{i,2} w_{ji,2}) \tag{4}$$

In back-error propagation calculations, error values are computed for each processing unit and then error values are used subsequently to adjust the interconnection weights. These delta values are first computed for the output layer, then for the hidden layer.

Let $\delta_{j,h}$ be the delta value for unit j, layer h. For the output layer, the

delta value is

$$\delta_{j,3} = (t_j - a_{j,3}) \tag{5}$$

assuming that the output layer does not utilize a squashing function, otherwise

$$\delta_{j,3} = (t_j - a_{j,3}) f'(S_{j,3}) \tag{6}$$

where f' is the derivative of the squashing function, and $S_{j,h}$ denotes the incoming sum to unit j, layer h:

$S_{j,h} = \sum_{i=1}^{n_{h-1}} a_{i,h-1} w_{ji,h-1}$

Weights associated with interconnections that go to the output layer are changed as follows:

$$\Delta w_{ji,2} = \eta \delta_{j,3} a_{i,2} \tag{7}$$

where η is the learning rate. The value of η is typically set by the user during artificial neural network experiments, and may vary during training.

For the hidden layer, the delta values are

$$\delta_{j,2} = (\sum_{k=1}^{n_3} w_{kj,2}\delta_{k,3}) f'(S_{j,2}) \tag{8}$$

and the corresponding weights to the hidden layer are changed by the amount:

$$\Delta w_{ji,1} = \eta \delta_{j,2} a_{i,1} \tag{9}$$

Equation (8) must be refined into greater detail for the biological model because multiplication of weights times delta values occurs at one site whereas summation occurs elsewhere.

The above description assumes a rigid architectural configuration of units - layered and fully interconnected. It is convenient to use a layered fully interconnected configuration to explain the neuronal model in this paper. However, more flexible and irregular configurations are possible, both in artificial neural networks and in our biological model. For example, neurons need not be organized into layers, and furthermore they may be sparsely interconnected instead of being fully interconnected layered configurations (Werbos, 1988). In addition, learning need not be restricted to pattern or batch learning, but could involve something in between (e.g., where the Δw's

are added over a time window before changes are made). Further generalities of the back-propagation network and of the biological model proposed here are possible.

4 Biological Model

In this section we describe a general biological model that utilizes back-error propagation. We propose particular sites where computations are performed and suggest physiological and biophysical mechanisms for their occurrence. In some cases we postulate the existence of second messengers or other mechanisms that are biologically plausible but postulated substrates. We argue that it is plausible that a back- error propagation paradigm is computed in the various biophysical forms that we describe. Note that the model(s) proposed here are candidate models that must be subjected to experimental verification at a later date.

Figure 6 shows a neuron drawn schematically to make the important structures obvious. Dendritic trunks are drawn without the arborizations, for visual clarity. Axons are drawn exceedingly wide to show the highly organized nature of their microtubules, and axons may have branches.

Figure 7 shows the interconnection structure for a layered feed-forward network model. Neurons are interconnected via axodendritic connections.

This particular configuration has three layers and is fully interconnected. As in artificial neural network terminology, we will refer to the layers as the input, hidden, and output layers. Our model for back-error propagation through the microtubules will be illustrated for this network, although the model is not limited to layered, fully-interconnected networks, and back-propagation has no such limitation.

4.1 Forwards Propagation

Consider the forwards propagation mode for the network illustrated in Figure 7. The neurons depicted follow typical biological mechanisms, with propagation of signals forwards through the network via action potentials. Axo-dendritic synapses send signals from one layer to the next. Neurons do summation in the dendrites, and propagate membrane potentials to the spike initiation zone where a fire-at-threshold mechanism occurs.

During training, the network is presented with an input pattern. In artificial neural networks, the input pattern is a vector with the length of the vector equal to the number of input units. For a biologically plausible model, we can assume frequency coding of the input vector. Thus, the input pattern $(x_1, x_2, ..., x_n)$ would be modeled as a firing frequency x_i for each input unit i. It is assumed that an external stimulus causes the firing frequency to occur in the input layer neurons. The external stimulus would arise from a

particular pattern, such as seeing the written letter "A".

The hidden and output layers sum arriving impulses via normal biological mechanisms, based on post-synaptic potentials, membrane conductances, and spatial locations and changes in membrane potentials. The network's output is "read off" the output layer and is a vector with length equal to the number of output units. Again the simplest biological model is to assume frequency coding. Thus, y_i would be the firing rate of output neuron i, with output vector $(y_1, y_2, ..., y_m)$. The goal of training is to have the output vector of the trained network match a target vector $(t_1, t_2, ..., t_m)$ for the entire training set.

For an artificial neural network the synaptic weights are scalars, either positive, negative, or zero. Biological synapses are complex with many different spatial locations and configurations. In addition there are many different biophysical mechanisms for weighting a synapse. One possibility is to take the synaptic weight equal to the initial height of the post-synaptic potential. This model assumes that the synaptic weight is proportional to the number of post-synaptic receptor molecules.

Such a model is adequate to produce the general pattern-mapping ability of artificial feed-forward networks. This capability has been shown specifically in pulsed networks that are layered and that utilize a post-synaptic potential height as the weight, with a fire-at-threshold mechanism that returns the post-synaptic potential to resting level after a refractory period.

General pattern mapping ability has been found with this network, and, in fact, it is mathematically equivalent to a feed-forward network with a ramp squashing function (Dayhoff, 1991).

4.1.1 Alternative Models

More complex temporal structure in nerve impulse trains might be utilized biologically instead of a firing frequency code (Perkel and Bullock, 1972; Dayhoff and Gerstein, 1983a). Although there is considerable biological evidence for the existence of frequency coding, there are also alternative models for neural representation and coding. Alternative neural coding could involve the use of bursts, synchronous firing, temporal patterns, or simultaneously active groups. The mathematical processing of a feed-forward network could probably be duplicated with any of these coding schemes, at least as an approximation. Temporal patterns do appear to be of importance in biological systems from data analysis studies (Dayhoff and Gerstein, 1983b; Abeles and Gerstein, 1988; Frostig et al, 1990; Optican and Richmond, 1987). Our use of firing frequencies does not preclude the use of more complex temporal patterning in alternative models that incorporate the same biologically plausible mechanisms presented in this paper.

Synaptic weights, in addition to or instead of using the number of postsynaptic receptors, could employ the following processes or structures: (1) the

area of the synapse and/or density of the post-synaptic receptors, as they influence the overall efficacy of the receptor molecules, (2) the number of synapses, (3) the type of transmitter, (4) the presence of neuromodulators (compounds that influence the transmitter efficacy), (5) the amount of presynaptic transmitter released from each impulse, (6) the spatial effects, such as axon and dendritic branching, whereby synapses at different dendritic locations have different degrees of influence on the cell soma, (7) effects of the dendritic spine (its size and shape), (8) the curvature of the synapse, and (9) density and complexity of the synaptic cytoskeleton (Friedrich, 1990).

4.2 Error Computation for Output Units

In this section, three models that could accomplish the computation of equations (5) or (6) for the back-propagating model are described. These models are shown schematically in Figure 8 (a-c). Figure 3a is based on a reciprocal synapse, whereas Figure 8b assumes the existence of an intermediate neuron. Figure 8c is the most speculative of the models and assumes feedback within a single synapse. The target neurons play the role of transmitting a 'desired' response to the network. For each output neuron there is a corresponding target neuron, whose firing frequency represents the target frequency for the output neuron. Each target neuron corresponds to an entry in the target vector $(t_1, t_2, ..., t_n)$. Then t_i is the firing frequency of the i^{th} target neuron. Equations 5 and 6 become computations of differences between output and

target cell firing rates.

The difference between equations (5) and (6) is that (6) contains an additional factor, the derivative of the squashing function. Figure 5d shows the derivative of the ramp function, which is a windowing function that multiplies by a constant in a certain range and by zero elsewhere. This could be imposed by the MT being able to transmit signals only in a given range, corresponding to the window, and that otherwise no signals occur. Figure 5b shows a "soft" windowing effect. A windowing of allowable signal values could correspond to actual biophysical constraints for transport of the signal.

MODEL 1 (See Figure 8a.)

This case corresponds to a reciprocal synapse, here depicted as a pair of axo-axonal synapses, a type of synapse that is not uncommon in the nervous system (Bodian, 1972). G is an output neuron from the network configuration of Figure 7 and H is the corresponding target neuron. The goal of the back-propagation algorithm is for training to bring the firing rate of G to the firing rate of H. G's firing rate is reflected by the post-synaptic activation at H in the region of the forwards synapse. H's firing rate is reflected by the post-synaptic activation of G, in the region of the reciprocal synapse. To implement back-propagation, the difference between these rates must be computed. A signal that is proportional to this difference is assumed to be initiated in G at the MT end and to propagate internally through the MT of cell G.

We assume that the signal value is increased by an increased firing rate of unit H, which causes increased activation at the post-synaptic site of the reciprocal synapse. We assume that the firing rate of G decreases the signal that goes along the MT. For example, the synapse from G to H could be inhibitory or in some way inhibit the release of neurotransmitter across the reciprocal synapse.

A general expression for this type of process is as follows:

$$D = f_1(R_G, R_H, M_{G1}, M_{G2}, M_{H1}, M_{H2}, S_{GH}, S_{HG}, A_G, L)$$

where D is the signal initiated at the MT of cell G, R_X is the firing rate of unit X, M_{Xi} is the set of parameters that govern the membrane parameters and biophysical activities for unit X, synapse i, S_{XY} is the set of synaptic parameters and biophysical activities for the synapse from X to Y, A_G is the set of parameters and biophysical activities that govern the anchoring proteins at unit G as well as signal initiation at the MT, and L stands for any additional parameters of other biophysical processes.

A first-order approximation to the above could plausibly be the following equation:

$$D = \alpha_1(R_H - R_G) + d_1 \tag{10}$$

where d_1 is a baseline value (it is possible for d_1 to be zero). The magnitude of D is thus proportional to the strength of the signal along the MT. The parameter α_1 results from structural factors and relationships that depend on the actual underlying mechanisms. Plausible biophysical mechanisms for the initiation of the MT signal are covered in Section 4.3.1. Equation (10) implements equation (5), as needed.

MODEL 2 (See Figure 8b.)

Instead of assuming a reciprocal synapse, error computation could be modeled by postulating an intermediate neuron I. Neuron I receives excitatory input from H and inhibitory input from G. The firing rate of I (R_I) then reflects the difference in rates between H and G ($R_H - R_G$), which represents the error difference as given by equation (5).

To initiate a signal within the MT of cell G, there is also an axo-axonic synapse postulated (labelled J in Figure 8b). The post-synaptic membrane activation at J is taken as proportional to the average firing rate of I. In this model a signal is initiated along the MT whose end abuts the post-synaptic membrane at synapse J, and the magnitude of this signal is modulated by the average post-synaptic membrane potential at J. As in the case of the model in Figure 8a, the strength of the signal initiated at the MTs of cell G is proportional to the frequency differences between the excitatory and inhibitory inputs of cell I.

A general expression that reflects this type of error difference may be expressed as follows:

$$R_I = f_1(R_G, R_H, S_{GI}, S_{HI}, M_I, M_G, M_H, L) \tag{11}$$

$$D = f_1(R_I, M_G, , M_I, S_{IG}, A_G, L) \tag{12}$$

where D is the signal along the MT of cell G, starting at synapse J.

A plausible first-order approximation is the following:

$R_I = \alpha_2(R_H - R_G) + d_2$

and

$D = \alpha_3 R_I$

where α_2 is a constant, d_2 is a constant indicating the minimum rate of R_I due to an external source (a possible value for d_2 is zero), and α_3 is another constant. The values of α_2 and α_3 rely on the underlying biophysical mechanisms and parameters.

MODEL 3 (See Figure 8c.)

Another candidate model is shown in Figure 3c, representing a synapse from neuron G to neuron H. The synapse here might be axo-somatic or perhaps axo-axonic located above neuron H's spike initiation zone. The firing rate of G is reflected by the post-synaptic activation of H at the synapse. In addition, the post-synaptic membrane at H reflects the firing rate of H prior to firing because it receives travelling post synaptic potentials (PSPs) that sum to cause spike generation at the spike initiation zone of H. Thus the post-synaptic membrane tends to be activated when the firing rate of H is high. We assume in this model that the two effects tend to subtract from one another, and that the synapse from G to H is probably inhibitory.

In addition to a neurotransmitter that traverses the synaptic cleft from G to H, across the synapse in a forwards direction, there may also be a reverse intermediary, such as arachadonic acid (AA) or nitric oxide (Barinaga, 1991). The reverse intermediary is transmitted from the post-synaptic site to the pre-synaptic site (Williams et al, 1989). In this case, its amount or effectiveness is modeled to be proportional to the difference $R_H - R_G$. This model involves only one single synapse and bears a strong relationship to models recently proposed for long-term potentiation (LTP) in hippocampal neurons (Bliss et al, 1990; Malinow, 1991).

LTP is a relatively long-lasting use-dependent form of synaptic enhancement that can be induced by brief periods of suitable presynaptic activity.

LTP is currently throught to underlie some forms of learning and memory (Bliss and Lynch, 1988; Kennedy, 1989; Madison et al, 1991). Although LTP refers to enhancement in the postsynaptic membrane potential, the actual mechanism of LTP is currently still disputed. Both presynaptic mechanisms, either through an increase in the quantal probability of synaptic release or an increase in the actual number of presynaptic releasing sites and postsynaptic mechanisms, such as an increase in the efficacy of the receptor sensitivity, have been suggested (Bekkers and Stevens, 1990). As indicated in Figure 8c one possible mechanism for neuronal signaling of postsynaptic activity to the presynaptic membrane is through receptor-mediated release of "second messengers" that target presynaptic sites. In studies of Aplysia sensory cells (Piomelli et al, 1987) inhibitory synaptic actions of the neuroactive peptide FMRFamide are mediated by lipoxygenase metabolites of arachadonic acid. Thus Figure 8c includes a reverse intermediary which could be AA or nitric oxide (NO), or possibly another chemical (Schuman and Madison, 1991). Since LTP is monotonically related to the number of NMDA receptors activated, it is reasonable to postulate that the amount of the intermediate chemical is similarly related to the membrane potential.

Although higher pre-synaptic activation could increase the amount of the reverse intermediary, this alone does not necessarily imply an increase in the effectiveness of the reverse intermediary at presynaptic sites. In fact, an increased firing rate of G could actually decrease the number of available presynaptic sites at which the reverse intermediary could interact. Then the input signal to cell G's MTs could be proportional to the difference in neurons

G and H firing rates. This corresponds to a realization of the model that assumes an excitatory synapse, as is usually observed in LTP experiments in the hippocampus. If we were to assume an inhibitory synapse, then the firing of G would decrease activation at the post-synaptic site and hence decrease the release of the reverse intermediary.

A general expression in this case can be written as:

$$D = f_2(R_G, R_H, S_{GH}, M_G, M_H, A_G, L)$$

where D is the amount or effectiveness of the reverse intermediary in initiating a MT signal in cell G.

We postulate that for a plausible approximation this case can be modeled as:

$$D = \alpha_4(R_H - R_G) + d_3$$

where d_3 is ambient background and allows for negatives to be "coded" as small values (possibly $d_3 = 0$), and α_4 is a constant that is a function of the underlying biophysics.

Here we postulate that the amount or effectiveness of the intermediary is proportional to the activation level of H (e.g. the average firing rate of H) minus the average firing rate of G. Thus, for example, a higher post-synaptic

activation raises the effectiveness or amount of intermediary. A higher pre-synaptic activation lowers the amount of intermediary or its effectiveness. We assume this relationship is approximated by first order differences, as above.

4.3 Microtubule backwards signals

Since forwards propagation takes place via cell membranes and synapses in this model, using widely known mechanisms, no further explanation is required for the medium of signal propagation. Backwards error signals, however, are propagated inside the cell via MTs, which is a novelty of our proposed model, and thus requires explanation for both signal initiation and signal propagation. We suggest candidate biophysical mechanisms for signal initiation at MT ends and for signal propagation.

4.3.1 Signal Initiation

Candidate mechanisms for the initiation of MT signals in axon terminals are as follows:

1. Material transport. Molecules and particles that can be transported by MTs and the cell cytoskeleton are present at the end of the axons. Their

presence and subsequent transport could constitute a signal that carries information to the cell body, and then to the dendrites. Their concentration could perhaps determine the magnitude of the signal. Such molecules would be transported via well-known mechanisms for MT transport, described earlier (e.g., retrograde axonal transport and anterograde dendritoplasmic transport).

2. Phosphorylation / dephosphorylation of MAPs. Since MAPs are bound to MTs, a phosphorylation-induced conformational change could initiate MT signals. For example, protein kinase C (activated by membrane events, such as binding of NMDA and glutamate to receptors) phosphorylates MAP-2 in dendrites, and similar events could occur with other MAPs in axons.

3. Calcium - initiated events. Calcium is well-known to be released during synaptic activity, and is capable of binding to calmodulin. Since calmodulin is bound to MTs and MAPs, this coupling could in turn cause conformational or other changes in the MTs which initiate a signal up the MT. Calcium might also directly bind to MTs, initiating tubulin conformational changes.

4. A specialized protein or molecule might bind at the end of the MT, to a MAP, an anchoring protein, or to the MT itself. Binding would then cause a conformational change that initiates a MT signal. Particular proteins might even be responsible for initiating different particular signal patterns. Furthermore, such a molecule might be a compound such as AA or NO,

that diffuses in a retrograde fashion across synapses, or another compound that is activated by such a retrograde messenger. This mechanism is highly speculative but deserves mentioning.

5. Fodrin and other anchoring proteins might initiate signals at the axonal end of a MT, because they are known to form bridges from the MTs to the synaptic membrane. In this case the signal might be initiated by the membrane potential, membrane proteins, second messengers, or other activity at the membrane, or by modulations in the distance between the membrane and the MT.

6. Other chemical messengers might interact with MTs, MAPs, or anchoring proteins to effect a signal initiation at the microtubular end. Ben Ze-ev (1991) reviews possibilities that involve a receptor bonding to an intermediary which in turn interacts with the cytoskeleton.

4.3.2 Signal Propagation in MTs

Candidate mechanisms for signal propagation along MTs are as follows:

1. MTs, together with associated proteins, bring about particle transfer. This transfer could go in both directions, and a variety of specific rates have been observed. Rates of 400 mm/day and even 2000 mm/day have been

reported (Ochs 1982).

2. A propagated conformational change along the MT constitutes another general type of signal propagation. Propagation of tubulin conformational states are implicated in ciliary MT (Atema, 1973) and by Cianci et al (1986), who claim that MTs are capable of ATP-induced "gelation-contraction" which presumably results from all tubulin subunits assuming shorter conformational states. Sequential shortening of subunits would propagate a wave. In a propagated conformational change, individual tubulin molecules would alter their conformational state in response to neighboring tubulin molecules, causing a signal to propagate down the MT. Energy pumping would be required to counteract energy dissipation, perhaps by GTP hydrolysis and MAP dephosphorylation. Hameroff et al (1989) and Rasmussen et al (1990) considered conformational states (alpha, beta) in each tubulin dimer characterized by a negative charge redistribution towards either the alpha or beta monomer. Dipole coupling among neighboring tubulins and energy pumping via GTP hydrolysis were modeled and resulted in traveling patterns of tubulin conformational state changes. Such traveling conformational patterns are suitable for internal neuronal signaling, and are consistent with models of coherent phonons, solitons, Frohlich depolarization waves or acousto - conformational transitions.

The back propagation algorithm imposes the requirement that the signal must carry both a magnitude and a polarity. One possibility is the following model. Tubulin can be modeled as having two conformational states, α and

β. The simplest signal would be a traveling cluster of one state (foreground) on a background of another state. For example, a positive polarity could be a signal in state β on a background of state α , and a negative polarity would be a signal in state α on a background of state β. In this case the size of the foreground cluster would correspond to the signal's magnitude. Alternatively, the signal could be a traveling segment that has some percent of the foreground configuration on the background configuration. The percent could then be proportional to the signal magnitude. An alternative way to encode the polarity is to simply have a "baseline" signal size b such that a signal of size D is interpreted as D-b. This would allow us to encode negative numbers with a signal that has only a magnitude.

In the MT molecular automata models developed by Hameroff et al (1989) and Rasmussen et al (1990), specific types of patterns (e.g. "bus gliders") propagate as tubulin conformational changes. They are modeled as cellular automata. Such propagating patterns could represent signals of different polarities and magnitudes. Since the patterns would be discrete entities, each different pattern could stand for a different discrete magnitude being signaled. Quantized magnitudes would be sufficient for learning.

3. Ion transfer. The MT might transfer an ion from one end of the tubule to the other, either inside or outside the MT. This is within the realm of possibilities but has not been experimentally observed. A likely candidate ion is Ca^{++}, which is an important ion that participates in synaptic activity. Quantity, patterns of release or of ion types (e.g., Ca^{++}, Mg^{++}) might be

employed as signaling mechanisms.

4. The actual movement of a MT is a possibility, in a direction towards one of its terminals. This movement alone could be initiated by appropriate anchoring proteins that connect the MTs to the synapse. MTs may be under tension because of the anchoring proteins; thus the cytoskeleton may be a "tensegrity net" (Joshi et al, 1985) capable of end-to-end movements or end-to-end pressure. An alternative form of movement is slow axoplasmic transport in which MTs "grow" by polymerizing at one end and depolymerizing at the other end (1 -3 mm/day) (Kirschner and Michison, 1986).

4.4 Correction of Synaptic Sensitivities / Weights

4.4.1 Models for Synaptic Weights

In artificial neural networks, the weight of an interconnection is presumed to be a simplification for the strength of a biological synapse. In biological systems many factors could influence the strength or sensitivity of a synapse. Potential factors include the spatial locations of synapses, their size, the types of receptors and transmitters, the effectiveness of the transmitters, the number of synapses, etc. We consider first the number of post-synaptic receptors as a model for synaptic strength.

Weight adjustment in back propagation obeys equation (7), which includes the factors of pre-synaptic activation level (firing rate) and the delta (error) value for the target (post-synaptic) neuron. For the network in Figure 7, weight adjustments must be made at the synapses that send signals to the dendrites of the hidden and output layer neurons. In our model, a signal D travels up the MTs to arrive at the dendrites. The arriving microtubule signal needs to be a factor in determining the amount of weight adjustment to take place. We postulate that the MT signal D is proportional to δ_j, the post-synaptic neuron's error delta value from the back propagation equation (7). This value of D must then be multiplied by R_i, the firing rate of the pre-synaptic neuron, to determine the amount of weight change. A constant factor (η) known as the learning rate parameter is also involved. Note that over time, the average post-synaptic membrane potential can be modeled to be approximately proportional to the firing rate of the pre-synaptic neuron.

Suppose that δ_j is positive, as computed by (5), (6), or (8). Then its effect on the number of post-synaptic receptors should be to increase their number. This increase must be in proportion to δ_j times the post-synaptic membrane activation (on average). For simplicity, we assume that D can implement increased synaptic strength by increasing the number of post-synaptic receptors; alternatively, their sensitivity could be enhanced by altering their conformational states. D may increase the number of active receptor molecules by augmenting transport of nutrients to the axonal terminal. D might also stimulate new synthesis of receptors, because the signal from the axonal end passes through the cell body and the MT lattice connects to the nucleolus

where protein synthesis is controlled. D could thereby trigger an increase in synthesis of post-synaptic receptor molecules. For example, a large amount of positive signals, with a high average magnitude, would trigger synthesis near the nucleus. This would make more receptor molecules available to increase the synaptic strength. The positive signal D thereby increases the number of membrane receptors at the post-synaptic site.

D may also act by influencing receptor conformational states. For example, receptor / ion channel complexes (e.g. acetylcholine receptor, NMDA receptor, etc.) involve numerous proteins connected on the cytoplasmic side to fodrin or other anchoring proteins of MTs. There is experimental evidence that anchoring proteins connect to MTs and fasten the receptor molecules in place (Hirokawa, 1991). Different states of these complexes might occur in response to different signals (e.g., polarity and magnitude) arriving via cytoskeletal MTs. Friedrich (1990) has proposed that, in learning, sub-synaptic cytoskeletal receptor complexes become fortified and increase in complexity.

If the arriving signal D is negative, then the number of post-synaptic receptors would need to decrease. This might happen possibly by degradation of fodrin and other anchoring proteins which connect the MTs to the synapse. On the post-synaptic membrane, degradation of fodrin might serve to release these receptor molecules thereby decreasing the number of active receptor molecules available at the post-synaptic site. Instead of degradation it is possible that a deactivation or conformational change in the anchoring proteins could bring about a decrease in the number of active receptor

molecules. Receptor molecules are known to constantly "turn over"; thus non-replacement would lead to a dwindling of numbers. Degradation of fodrin has been observed experimentally (Siman et al 1984).

A general expression for this model can be written as:

$$\Delta W = f(P, D, L)$$

where P is the post-synaptic activation level, D is the arriving MT signal, and L denotes other biophysical parameters.

An approximate first-order effect could plausibly be the following

$$\Delta W = \alpha_5 D R_I$$

where R_I is the firing rate of the pre-synaptic neuron, D is the magnitude of the signal arriving up the MT, and α_5 is a parameter that reflects the underlying biophysical processes. Assume

$$P = \alpha_6 R_I$$

approximately represents the relationship that the post-synaptic activation level reflects the pre-synaptic firing rate, with α_6 another parameter that reflects the actual molecular mechanisms.

4.4.2 Additional Candidate Mechanisms for Synaptic Strength

There are obviously many alternative candidate mechanisms for synaptic strength, and the modulation of synaptic strength, which could be factored into a more detailed biological model for back-error propagation. These include: the amount of pre-synaptic transmitter or amount released for a fixed input stimulus; conformational and spatial changes in the postsynaptic dendritic spines (these have been implicated in LTP in the hippocampus) (Desmond and Levy, 1988); curvature and other spatial properties of the synapse; changes in the quantal release probability (this form of presynaptic potentiation has been suggested by Bekkers and Stevens (1990) for LTP; efficacy of receptor molecules (e.g. conductances); possible intermediaries between MTs and membrane, other than anchoring proteins; the amount of neurotransmitter per vesicle; distance between the MT and cell membrane; pre-synaptic enhancement of neurotransmitter release; binding affinity of receptors for neurotransmitter; metabolism and clearance of transmitters; presence of modulators; kinetics of state transitions for channels or receptors; number of synapses; area of synapses, number of receptors; phosphorylation of Ca^{++}/calmodulin dependent protein kinase C (Schulman and Lou, 1989); influences of the anchoring proteins, and density and architecture of the synaptic cytoskeleton (Friedrich, 1990). One of the most interesting of these possibilities is the change in the curvature of the synapse and the shape of the dendritic spines. Anchoring proteins such as actin form bridges between MT ends and synaptic membranes. Actin may contract dendritic spines and

thereby influence the synaptic strength; the actin is in an ideal location to receive a MT signal that might initiate such a contraction. Weight adjustment at synapses might also be accomplished with backwards transmission at the synapse, such as with arachadonic acid, nitric oxide, or other reverse intermediaries, which would then cause alterations on the pre-synaptic side that could in turn influence the synaptic strengths.

4.5 Sending the Error Back to the Previous Layer

This section addresses the issue of how the hidden neuron receives the error information it needs to compute its own error value. (See equation (8)). Let the hidden unit j have error value $\delta_{j,2}$ according to back propagation. From our biological model, the signal arriving through the MT from the output unit k is $D_{k,3}$ where $D_{k,3}$ is proportional to $\delta_{k,3}$ (in equation (8)). For each synapse from each axon branch in the hidden unit, a signal $D_{k,3}$ is received at the post-synaptic MT end. According to equation (8), a multiplication

$$D_{k,3}w_{kj,2} \tag{13}$$

must take place; in our model the site for this multiplication is the synapse from the hidden unit to the output unit. (See Figure 9.) Later, the summation in equation (8) is modeled to occur within the hidden unit.

After the multiplication of (13) takes place, a signal is initiated up the MTs at the hidden unit's pre-synaptic site. Again, for simplicity, we assume that the synaptic strength is the number of post-synaptic receptor molecules. It is not difficult then to imagine the underlying biophysics for such a computation. Suppose that the value $D_{k,3}$ arrives, and via fodrin is communicated to the post-synaptic membrane. If we assume that the amount of fodrin present is proportional to the number of active receptors, then it is also proportional to the synaptic weight. We presume then that the signal arriving from the MT to the post-synaptic membrane will be proportional to $D_{k,3}$ times the amount of fodrin. A reverse intermediary such as AA or NO would then go backwards towards the pre-synaptic membrane, thereby transmitting this signal, with the value in (13). Thus the concentration or effectiveness of the reverse intermediary is the value transmitted.

We assume that a reverse intermediary (e.g., AA or NO) binds to pre-synaptic receptors which then interact with fodrin to initiate a signal within the hidden unit's MT. (This is shown at site K in Figure 9.) The microtubules transmit this signal back to the dendrites of the hidden neurons, where additional weight adjustment takes place.

An alternative model is to assume that the synaptic strength arises from the number of receptor molecules in a particular conformational state. In this case, $D_{k,3}$ would influence, via MT-fodrin interactions, changes in receptor conformational states which in turn effect the release of retrograde transmitters (e.g. AA or NO)

4.6 Summing of microtubule signals

In our model, summing of microtubule signals occurs within the axon. This summation is included in equation (8) in the back-propagation paradigm. There are two factors in (8), the first being a sum of weighted error values from the output layer of neurons.

$$\sum_{k=1}^{n_3} w_{kj,2}\delta_{k,3} \tag{14}$$

Multiplication of $\delta_{k,3}$ times the weight $w_{kj,2}$ occurs at the synapse between the hidden unit j and output unit k. Thus, the signal d_k, that goes up the k^{th} axonal branch of hidden unit j, represents the product $w_{kj,2}\delta_{k,3}$. Assume

$$d_k = \alpha_7 w_{kj,2}\delta_{k,3} \tag{15}$$

where α_7 is a constant dependent on the underlying biophysics. We propose a possible explanation in this section of how the summation of these individual terms d_k might occur in the hidden units.

Note that the second factor in equation (8) is $f'(S_{j,k})$, which is the derivative of the squashing function. For a ramp squashing function, this is zero everywhere except for an interval. (See figure 5d.) Its effect is to filter the

operating range, and produces 0 for parameter values too large or too small. This corresponds to a biophysical mechanism that works only within a given range of signal values, a plausible assumption for this model.

Figure 10 illustrates a schematic neuron with MTs drawn within each axonal branch. This Figure illustrates a single bundle of MT within the axonal trunk (before branching), with crossbridge MAPs connecting the individual MTs. The bundle divides into smaller bundles with each going into an axonal branch. In the cell body, the lattice-like network of MT is simplified as a converging of specific MT bundles, from the axon and from each dendritic trunk. The MTs are taken to be interconnected via MAPs within each bundle.

In this model, each signal d_k is transmitted to the axonal trunk via MT bundles. The signals are summed in the axonal trunk because the MT bundles gather together in the trunk, and as a result the signal strengths are integrated. Then, the total amount of signal going along the axonal trunk is the sum of the signals along each branch.

A concern arises because the reading mechanism for this sum may be sensitive to variations in the different MT signal values. It is preferable then to have each MT carry the same approximate value signal upon its arrival at the cell body. Such an operation could be accomplished via "probabilistic bus-MAPs", a (postulated) MAP protein that transfers activation among the MTs. These postulated proteins need only transfer activation some of

the time (probabilistically, such as 20 percent of the time). The net result would be that when the signals arrive at the cell body, each MT would be carrying a signal equal to the average of all of the original signals within each microtubule. The average of these signals could then conveniently contribute to compute the sum of the signals by simply multiplying n, the number of branches, by the average signal. The sum would then be

$$S = D_{j,2} = \sum_{k=1}^{n_3} d_k \tag{16}$$

How might the appropriate signal then be transferred back to the dendrites? We propose a model whereby each dendritic trunk has a bundle of MTs that pick up the signal from the axon originating in the cell body. Figure 10 shows a central position where this might occur, but in fact the signal transfer need not necessarily occur at a single position. Furthermore, since each MT filament from the axonal trunk carries the same (average) signal, the dendritic MTs might accept the signals at different locations within the interconnected MT lattice. The resulting signal would then have the value S for each dendritic trunk. Obviously, a variety of detailed models could be constructed depending on specific lattice configurations, based on these general ideas.

The dendritic MTs would then transmit the signal S to the terminal ends of the dendrites. In our model, the entire bundle transmits this signal to

each incoming synapse at the dendrite. In contrast to this simplified model, in living cells there is an intertwined lattice of MTs around the centriole which occupies a considerable part of the cell soma area. MTs support each dendritic branch, and thus we assume that the signal reaches each incoming synapse.

The probabilistic bus-MAP is a concept similar to the bus-MAPs proposed in Rasmussen et al (1990). More complex boolean operations in MAPs have been proposed in MAP crossbridges among MTs [Lahoz-Beltra et al, 1992]. In fact, these MAP models can be theoretically constructed to perform BCN (binary-coded decimal) operations such as binary addition and subtraction. Although biological plausibility is not evident for this scheme, it appears to be a powerful construct for future molecular computing engineering designs, and it is inspired by the signal summation model here for MTs.

5 Discussion

This paper demonstrates the biological plausibility of back-error propagation through intraneuronal microtubules (MTs). We have identified specific sites and biophysical mechanisms that could implement each of the calculations of neuronal back-propagation. Forwards propagation is accomplished through traditional mechanisms, with action potentials and axo-dendritic synapses.

Back-error propagation is accomplished through the calculation of error differences (between target and output) at specialized synapses, the backwards propagation of these signals through MTs of the cytoskeletal lattice from the axons to the dendrites, the adaptation of synapses in response to MT arriving signals, and the transport of a MT signal from an output unit to a hidden unit. Biophysical plausibility arguments are given for each step in this process, and for how the biophysical mechanisms might implement the needed computations. The model proposed here should be considered a baseline model; we expect that refinements will be needed as additional experimental and theoretical results become available.

The model covered in this paper is far more general than the layered, fully-interconnected configuration used here (shown in Figure 7). This interconnection configuration was chosen because it would provide a clear explanation. Back-error propagation, however, is not limited to layered configurations, nor to full interconnectivity. Back-error propagation can also incorporate recurrent loops, feedback loops, and time delays in both layered and non-layered configurations (Werbos, 1988; Waibel et al, 1989). The principles used in the model proposed here can be applied to any of these more general configurations. Furthermore, back-propagation is also not limited to the minimization of RMS, as a different performance measure could be optimized by a back-propagating network.

The model here could be extended further through incorporating additional biological complexities, such as multiple synapses between two neu-

rons, different numbers of MTs in each branch of an axon or dendrite, different numbers of MTs arriving at each synaptic site, different lattice and cross-bridge structures for MTs, and more detailed biochemistry. The model could also be extended to incorporate neural assemblies (groups) in place of any of the neurons in Figure 7. Learning does not have to be limited to pattern or batch learning, but updates of weights could be integrated or delayed over time, which seems more plausible biologically. Alternative conduction mechanisms might be employed through neurofilaments instead of MTs, as neurofilaments are also an integral part of the cytoskeleton. Barnett (1988) has even proposed that neurofilaments serve as memory elements, with parallel arrays that are laterally interconnected to MT processing elements.

Biological systems must have maximal weight strengths, as does any physical implementation of a neural network. The magnitude of a transmitted error signal would also have a maximal value possible. Furthermore, biological systems are expected to have a recruitment capability, whereby additional connections are spawned between two neurons, or additional neurons are recruited to participate in a particular network circuit. The cytoskeleton is integrally involved with the formation of new branches, as it supports physically these new spatial structures and defines their spatial configuration. According to the back-error model in this paper, error signals that traverse the cytoskeleton provide information appropriate to a decision to spawn a new axonal or dendritic branch. Suppose that a large error signal in a MT actually triggers the production of a new branch, and that this branch would be initiated by cytoskeletal mechanisms. Then the new branch could target

to synapse on a neuron within the network or a new neuron. In the first case, there is a new synapse that would probably alleviate the need for such a large error difference. In the latter case, a new neuron would be recruited, which might also alleviate the need for such a large error difference to be transmitted. Thus during training, if a weight or signal gets too high, the MT might respond by spawning a new branch for new interconnections, and this would provide advantages in training the network. In the model proposed here, the information for such a capability is in the appropriate place - the MT.

There are models of learning other than back-error propagation in which MT signaling within neurons would provide a missing link to help develop biologically plausible models. One such model is Edelman's selectionist "population approach", which invokes heterosynaptic inputs – other dendrites on the same neuron communicating and modifying a given dendritic synapse. The same intra-neuronal cytoskeletal communication we suggest for back-propagation could accomplish the information transmission needed along dendrites for heterosynaptic modification. Another neural learning model that could plausibly utilize MTs is Adaptive Resonance Theory (Carpenter and Grossberg, 1987; Carpenter and Grossberg, 1988; Grossberg, 1976) in which each connection from the input to the output layer has a reciprocal connection with its own weight. Resonance, or reinforcement of signals, is obtained between the forwards and backwards connections during learning. The forwards connections might be implemented with action potentials and axo-dendritic synapses, and the backwards connections might be implemented with MTs. The pi-sigma architecture (Shin and Ghosh, 1991;

Rumelhart et al, 1986), which also utilizes backwards propagation of errors, might also be modeled with MTs. Pribram's cytoskeletal dendritic microprocessing could also be subserved by conformational dynamics and signaling in the cytoskeleton (Pribram, 1991). There are even more possibilities for biological models of other neural network paradigms, in which MTs would be assumed to provide internal signals.

MTs certainly have a justified existence without their transmission of signals involved in neuronal learning: they mechanically support the extensive branching structure in both axons and dendrites. These special structures are uniquely complex in neurons, as neurons have extensive development of the cell cytoskeleton. Furthermore, the cytoskeleton anchors synaptic membrane proteins; this is sufficient to explain the relationship of MTs to synapses. Thus one might question the rationale for postulating yet another function for the neuronal cytoskeleton.

On the other hand, the cell cytoskeleton has developed (evolved) more than one role that is critical to the functioning of a nerve cell. Transport of nutrients is critical and is accomplished by MTs and MAPs. Structural support for spatial branching of axons and dendrites is critical to the cell, and depends on cytoskeletal structure and the assembly and disassembly of MTs. Since these different vital functions have evolved for MTs, why not another function, namely, to participate in neural learning? The cytoskeleton already participates in synaptic processes by attaching to proteins that anchor postsynaptic receptors in place, and therefore might influence synaptic strength

through a variety of candidate mechanisms.

Clearly the cytoskeleton is in a key anatomical position to participate in neuronal learning through the transmission of signals. The cytoskeletal lattice extends without interruption from axons to dendrites. When passing near the nucleus, synthesis of new protein molecules, such as receptors, could be triggered by cytoskeletal signals. The new receptors could then increase synaptic strengths. MTs anchor to synapses and receptor molecules through anchoring proteins such as fodrin and actin, and so a convenient anatomical pathway exists to influence synapses by MT signals. If the MTs signal delta error values, then they are strategically placed to signal information available that could appropriately trigger the formation of new branches and hence new synapses. Thus there is much circumstantial evidence for the plausibility of cytoskeletal signals contributing to neuronal learning.

To study biological systems is to catch evolution in the act. The process of evolution has put mechanisms in place that could plausibly implement back-error propagation and internal signaling for neuronal learning. Further experimental evidence is needed to determine whether Nature is actually using these mechanisms. If not, perhaps a new step in evolution is about to take place.

6 Acknowledgements

Dr. Judith Dayhoff was supported by the Naval Surface Warfare Center Focussed Technology Program on Molecular Computing, headed by Ann Tate. She received an ONR Visiting Summer Faculty Program appointment through ASEE for her work at the NSWC. She was also supported by the Systems Research Center at the University of Maryland.

Dr. Stuart Hameroff was supported by the University of Arizona Department of Anesthesiology.

Dr. Charles E. Swenberg acknowledges support of the Armed Forces Radiobiology Research Institute under work unit 00145.

Dr. Rafael Lahoz-Beltra was supported by the Ministerio de Educacion y Ciencia (Spain) under a Fulbright Scholarship.

7 References

M. Abeles and G. L. Gerstein (1988). Detecting spatiotemporal firing patterns among simultaneously recorded single neurons. J. Neurophys. 60 (3): 909-924.

J. Alvarez and B. J. Ramirez (1979). Axonal microtubules: Their regulation by the electrical activity of the nerve. Neuroscience Letters, 15: 19-22.

L. A. Amos and A. Klug (1974). Arrangement of subunits in flagellar microtubules. J. Cell Sci., 14: 523-550.

A. Aszodi, U. Muller, P. Friedrich, and H-C. Spatz (1991). Signal convergence on protein kinase A as a molecular correlate of learning. Proc. Natl. Acad. Sci. USA 88: 5832-5836.

C. Aoki and Siekowitz (1989). Plasticity in brain development. Sci. Am., 34-42, December.

J. Atema (1973). Microtubule theory of sensory transduction. J. Theor. Biol. 38: 181-190.

H. Athenstaedt (1974). Pyroelectric and peizoelectric properties of vertebrates. Ann. NY Acad. Sci. 238: 68-93.

M. Barinaga, (1991). Is nitric oxide the retrograde messenger. Science 254: 1296-1297.

M. P. Barnett (1987). Molecular systems to process analog and digital data associatively, in: Proceedings of Third International Symposium of Molecular Electronic Devices, Oct. 6-8, 1986, Arlington, Virginia. Eds: F.

L. Carter, R. E. Siatkowski and H. Wohltjen. Amsterdam: Elsevier-North Holland, 229-244.

J. S. Becker, J. M. Oliver and R. D. Berlin (1975). Fluorescence techniques for following interactions of microtubule subunits and membranes. Nature, 254: 152-154.

A. Ben-Ze'ev (1991). Animal cell shape changes and gene expression. BioEssays 13 (5): 207-212.

J. M. Bekkers and C. F. Stevens (1990). Presynaptic mechanism for long-term potentiation in the hippocampus. Nature 346: 724-729.

G. Bensimon and R. Chermat (1991). Microtubule disruption and cognitive defects: effect of colchicine on learning behavior in rats. Pharmacol. Biochem. Behavior 38: 141-145.

D. Bigot and S. P. Hunt (1990). Effect of excitatory amino acids on microtubule-associated proteins in cultured cortical and spinal neurones. Neuroscience Letters 111: 275-254.

T. V. P. Bliss, M. P. Clements, M. L. Errington, M. A. Lynch, J. H. Williams (1990). Presynaptic changes associated with long-term potentiation in the dentate gyrus. The Neurosciences 2: 345-354.

T. V. P. Bliss and M. A. Lynch (1988). Long term potentiation of synaptic transmission in the hippocampus: Properties and mechanisms. In Long-term Potentiation: From Biophysics to Behavior, ed. P. Landfield and S. A. Deadwyler, New York: Liss.

D. Bodian, (1972). Neuron junctions: A revolutionary decade. Anat. Rec. 174: 73-82.

S. T. Brady, and R. J. Lasek (1981). Nerve specific enolase and creatine phosphokinase in axonal transport: soluble proteins and axoplasmic matrix. Cell 23: 515-523.

S. T. Brady, K. K. Pfister, and G. S. Bloom (1990). A monoclonal antibody to the heavy chain of kinesin inhibits anterograde and retrograde axonal transport in isolated squid axoplasm. Proc. Natl. Acad. Sci. USA 87: 1061-1065.

R. D. Burgoyne (1991). Cytoskeleton is a major neuronal organelle. In: The Neuronal Cytoskeleton, ed. R. D.Burgoyne, New York: Wiley-Liss, 1-3.

R. G. Burns (1978). Spatial organization of the microtubule-associated proteins of reassembled brain microtubules. J. Ultrastruct. Res. 65: 73-82.

P. R. Burton (1988). Dendrites of mitral cell neurons contain microtubules of opposite polarity. Brain Res. 473: 107-115.

P. R. Burton and J. L. Paige (1981). Polarity of axoplasmic microtubules in the olfactory nerve of the frog. Proc. Natl. Acad. Sci., U.S.A. 78: 3269-3273.

G. Carpenter and S. Grossberg (1987). ART 2: Self-organization of stable category recognition codes for analog input patterns. Applied Optics 4919-4930.

G. Carpenter and S. Grossberg (1988). The ART of adaptive pattern recognition by a self-organizing neural network. Computer, March, 77-88.

P. S. Churchland and T. J. Sejnowski (1989). Neural representation and neural computation. In Neural Connections, Mental Computation, eds. L. Nadel, L. A. Cooper, P. Culicover, and R. M. Harnish. Cambridge, Massachusetts: A Bradford Book, MIT Press, 15-48.

C. Cianci, D. Graff, B. Gao, and R. C. Weisenberg (1986). ATP-dependent gelation contraction of microtubules in vitro. Ann. N. Y. Acad. Sci. 466: 656-659.

M. Conrad, W. Guttinger, and M. Dal Cin (1973). Lecture Notes in Biomathematics, Vol. 4, Physics and Mathematics of the Nervous System, Proc. of a Summer School Organized by the Int'l Center for Theoretical Physics, Trieste, and the Inst. for Info. Sciences, Univ. Tubingen.

J. Cronly-Dillon, D. Carden and C. Birks (1974). The possible involvement of brain microtubule in memory fixation. J. Exp. Biol., 61: 443-454.

A. S. Davydov (1973). The theory of contraction of proteins under their excitation. J. of Theoretical Biology 38: 559-569.

J. E. Dayhoff, (1990). Neural Network Architectures: An Introduction. New York: Van Nostrand Reinhold.

J. E. Dayhoff (1991). Pattern Mapping in Pulse Transmission Neural Networks. Analsis of Neural Network Applications (ANNA) Conference Proceedings (ACM Press), 146-159.

J. E. Dayhoff and G. L. Gerstein (1983a). Favored patterns in nerve spike trains. I. Detection. J. Neurophys. 49: 1334-1348.

J. E. Dayhoff and G. L. Gerstein (1983b). Favored patterns in nerve spike trains. II. Application. J. Neurophys. 49: 1349-1363.

M. DeBrabander (1982). A model for the microtubule organizing activity of the centrosomes and kinetochores in mammalian cells. Cell. Biol. Int'l Reports, 6 (10): 901-915.

M. DeBrabander, R. Nuydens, G. Geuens, M. Moermans, and J. DeMay (1986). The use of submicroscopic particles combined with video contrast

enhancement as a simple molecular probe for the living cell. In: Cell Motility in the Cytoskeleton 6: 105-113.

N. L. Desmond and W. B. Levy (1988). Anatomy of associative long-term synaptic modification, in: Long-Term Potentiation: From Biophysics to Behavior. eds. P. W. Landfield and S. A. Deadwyler.

L. Finkel, G. Reeke, and G. Edelman (1989). A population approach to the neural basis of perceptual categorization. In: Neural Connections, Mental Computation, Eds. L. Nadel, L. A. Cooper, P. Culicover, and R. M. Harnish. Cambridge, Massachusetts: A Bradford Book, MIT Press, 146-179.

H. Frauenfelder, F. Parak, and R. D. Young (1988). Conformational substates in proteins, Ann. Rev. Biophys. Biophys. Chem. 17: 451-479.

P. Friedrich (1990). Protein structure: the primary substrate for memory. Neuroscience 35 (1): 1-7.

H. Frohlich (1970). Long range coherence and the actions of enzymes. Nature 228: 1093.

H. Frohlich (1975). The extraordinary dielectric properties of biological materials and the action of enzymes. Proc. Natl. Acad. Sci. 72: 4211-4215.

H. Frohlich (1986). Coherent excitations in active biological systems, in:

Modern Bioelectrochemistry, eds. F. Gutmann and H. Keyzer New York: Plenum Press, 241-261.

R. D. Frostig, Z. Frostig, and R. M. Harper (1990). Recurring discharge patterns in multiple spike trains. Biol Cyber. 62: 487-493.

L. Genberg, L. Richare, G. McLendon, R. J. Dwayne Miller (1991). Direct observation of global protein motion in hemoglobin and myoglobin on picosecond time scales. Science 251: 1051-1054.

B. Grafstein and D. S. Forman, 1980. Intracellular transport in neurons. Physiol. Rev. 60: 1167-1283.

S. Grossberg (1969). On the production and release of chemical transmitters and related topics in cellular control. J. Theor. Biol 22: 325-364.

S. Grossberg (1976). Adaptive pattern classification and universal recoding: I. Parallel development and coding of neural feature detectors. Biological Cybernetics (23): 121-134.

W. Grundler and F. Keilman (1983). Sharp resonances in yeast growth prove nonthermal sensitivity to microwaves. Phys. Rev. Lett. 51: 1214-1216.

F. Gutmann (1986). Some aspects of charge transfer in biological systems.

In R. Gutmann and H. Keyzer (Eds.), Modern Bioelectrochemistry (pp. 177-197). New York: Plenum Press.

M. B. Hakim, S. M. Lindsey, and J. Powell (1984). The speed of sound in DNA. Biopolymers 23: 1185-1192.

S. Halpain and P. Greengard (1990). Activation of NMDA receptors induces rapid dephosphorylation of the cytoskeletal protein MAP2. Neuron 5: 237-246.

S. R. Hameroff (1987). Ultimate Computing: Biomolecular Consciousness and Nanotechnology Amsterdam: Elsevier-North Holland.

S. R. Hameroff and R. C. Watt (1982). Information processing in microtubules. J. Theor. Biol. 98: 549-561.

S. R. Hameroff, S. Rasmussen, and B. Mansson (1989). Molecular automata in microtubules: basic computational logic of the living state? In C. Langton (Ed.), Artificial Life, Santa Fe Institute Studies in the Sciences of Complexity, Vol. VI (pp. 521-553). Reading, Massachusetts: Addison-Wesley.

R. Hecht-Nielsen (1989). Theory of the backpropagation neural network. IJCNN Washington D. C. June 1989. I: 593-605.

S. R. Heidemann, J. M. Landers, M. A. Hamburg, 1981. Polarity orientation of axonal microtubules. J. Cell. Biol. 91: 661-665.

N. Hirokawa (1991). Molecular architectures and dynamics of the neuronal cytoskeleton. In The Neuronal Cytoskeleton, ed. R. D. Burgoyne, New York: Wiley-Liss, 5-74.

K. Hornik, M. Stinchcombe, and H. White (1990). Universal approximation of an unknown mapping and its derivatives using multilayer feedforward networks. Neural Networks 3 (5): 551-560.

H. C. Joshi, D. Chu, R. E. Buxbaum, and S. R. Heidemann (1985). Tension and compression in the cytoskeleton of PC12 neurites. J. Cell. Biol. 101: 697-705.

M. B. Kennedy (1989). Regulation of synaptic transmission in the central nervous system: Long-term potentiation. Cell 59: 777-787.

M. Karplus and J. A. McCammon (1983). Protein ion channels, gates, receptor. In: Dynamics of Proteins: Elements and Function., ed. J. King. Menlo Park, California: Benjamin Cummings. Annual Rev. Biochem. 53: 263-300.

H. Kim, C. G. Jensen and L. I. Rebhund (1986). The binding of MAP-2 and tau on brain microtubules in vitro. Dynamic aspects of Microtubule

Biology (D. Soifer, ed.) 218-239.

M. Kirschner and T. Michison (1986). Beyond self-assembly: from microtubules to morphogenesis. Cell 45: 329-342.

D. L. Koruga (1984). Microtubules screw symmetry: packing of spheres as a latent bioinformation code. In D. Soifer (Ed.), Dynamic Aspects of Microtubule Biology, Annals of the NY Acad. Sci. 466: 953-955.

T. Kudo, K. Tada, M. Takeda, and T. Nishimura (1990). Learning impairment and microtubule-associated protein 2 (MAP-2) decrease in gerbils under chronic cerebral hypoperfusion. Stroke 21: 1205-1209.

S. Kwak, and A. Matus (1988). Denervation induces long-lasting changes in the distribution of microtubule proteins in hippocampal neurons. J. Neurocytology 17: 189-195.

R. Lahoz-Beltra, S. R. Hameroff, and J. E. Dayhoff (1992). Cytoskeletal Logic: A model for molecular computing via boolean operations in microtubules and microtubule-associated proteins. Manuscript in preparation.

R. W. Linck and L. A. Amos (1974). The hands of helical lattices in flagellar doublet microtubules. J. Cell. Sci. 14: 551-559.

G. Lynch and M. Baudry (1984). The biochemistry of memory: A new

and specific hypothesis. Science 224: 1057-1063.

G. Lynch and M. Baudry (1987). Brain spectrin, calpain and long term changes in synaptic efficacy. Brain Res. Bull., 18: 809-815.

D. V. Madison, R. C. Malenka, and R. A. Nicoll (1991). Mechanisms underlying long-term potentiation of synaptic transmission. Ann. Rev. Neurosci. 14: 379-397.

R. Malinow (1991). Transmission between pairs of hippocampal slice neurons: Quantal levels, oscillations, and LTP. Science 252: 722-724.

E. M. Mandelkow, R. Shultheiss, R. Rapp, M. Muller, and E. Mandelkow (1986). On the surface lattice of microtubules. J. Cell. Biol. 102: 1067-1073.

R. Manka and B. Ogrodnik (1992). Soliton model of transport along microtubules. J. Biol. Physics, in press.

S. Mascarenhas (1974). The electret effect in bone and biopolymers and the bound water problem. Ann. N. Y. Acad. Sci. 238: 36-52.

G. Matsumoto and H. Sakai (1979). Microtubules inside the plasma membrane of squid giant axons and their possible physiological function. J. Membr. Biol. 50: 1-14.

S. S. Matsuyama and L. F. Jarvik (1989). Hypothesis: Microtubules, a key to Alzheimer's disease. Proc. Nat. Acad. Sci., 86: 8152-8156.

R. Mileusnic, S. P. Rose and P. Tillson (1980). Passive avoidance learning results in region specific changes in concentrations of, and incorporation into, colchine binding proteins in the chick forebrain. Neur. Chem. 34: 1007-1015.

M. Nakanishi and M. Tsuboi (1978). Two channels of hydrogen exchange in a double-helical nucleic acid. J. Molecular Biol. 124: 61-71.

C. Neubauer, A. M. Phelan, H. Keus, D. G. Lange (1990). Microwave irradiation of rats at 2.45 GHz activates pinocytotic-like uptake of tracer by capillary endothelial cells of cerebral cortex. Bioelectromagnetics 11: 261-268.

S. Ochs (1982). Axoplasmic Transport and its Relation to Other Nerve Functions. Wiley-Interscience, N. Y.

L. M. Optican and B. Richmond (1987). Temporal encoding of two-dimensional patterns by single units in primate inferior temporal cortex. II. Information theoretic analysis. J. Neurophysiol. 57: 162-178.

D. E. Parker, (1988). A comparison of algorithms for neuron-like cells, in J. Denker (ed), Proc. Second Annual Conference on Neural Networks for Computing, Proc. Vol. 151, 327-332, Amer. Inst. of Phys, New York.

D. H. Perkel and T. H. Bullock (1968). Neural coding. Neurosci. Res. Program Bulletin 6 (3).

K. K. Pfister, M. C. Wager, D. L. Sternoven, S. L. Brady, and G. S. Bloom (1989). Monoclonal antibodies to kinesin heavy and light chain stain vesicle-like structures, but not microtubules in cultured cells. J. Cell. Biol. 108: 1453-63.

D. Piomelli, A. Volterra, N. Dale, S. A. Siegelbaum, E. R. Kandel, J. H. Schwartz, and F. Belardetti (1987). Lipoxygenase metabolites of arachidonic acid as second messengers for presynaptic inhibition of Aplysia sensory cells. Nature 328: 38-43.

K. H. Pribram (1991). Brain and Perception: Holonomy and Structure in Figural Processing. Hillsdale, N.J.: Lawrence Erlbaum.

M. M. Rasenick, N. Wang and K. Yan (1990). Specific associations between tubulin and G proteins: participation of cytoskeletal elements in cellular signal transduction, in The Biology and Medicine of Signal Transduction, ec. Y. Nichizuka, et al, Raven Press, New York, 381-386.

S. Rasmussen, H. Karampurwala, R. Vaidyanath, K.S. Jensen, and S. R. Hameroff (1990). Computational connectionism with neurons: A model of cytoskeletal automata subserving neural networks, Physica D 42: 428-429.

L. E. Roth and D. J. Pihlaja (1977). Gradionation: hypothesis for positioning and patterning. J. Protozoology 24: 2-9.

D. E. Rumelhart, G. E. Hinton and R. J. Williams (1986). Learning internal representations by error propagation. In Parallel Distributed Processing, eds. D. E. Rumelhart and J. L. McClelland. Cambridge, Massachusetts: MIT Press.

A. Samsonovich, A. Scott, S. R. Hameroff (1992). Acousto-conformational transitions in cytoskeletal microtubules: implications for neuro-like protein array devices. Nanobiology, in press.

M. V. Sataric, R. B. Zakula, and J. A. Tuszynski (1992). A model of the energy transfer mechanisms in microtubules involving a single soliton. Nanobiology, in press.

E. M. Schuman and D. V. Madison (1991). A requirement for the intercellular messenger nitric oxide in long term potentiation. Science 254: 1503-1506.

A. C. Scott (1982). Dynamics of Davydov solitons. Phys. Rev. A 26: 578-595.

Y. Shin and J. Ghosh (1991). The pi-sigma network: An efficient higher-order neural network for pattern classification and function approximation.

Proc. Int'l. Joint Conf. Neural Networks, I:13-18.

R. Siman, M. Baudry, and G. Lynch (1984). Brain fodrin: Substrate for calpain I, an endogenous calcium-activated protease. Proc. Natl. Acad. Sci. 81: 3572-3576.

Siman and Lynch (1985). (Regulation of glutamate binding by fodrin.) Nature 313: 225-228, 1985.

H. Schulman and L. L. Lou (1989). Multifunctional Ca^{++} / calmodulin - dependent protein kinase: domain structure and regulation. Trends Biochem. 14: 62-66.

H. Stebbings and C. Hunt (1982). The nature of the clear zone around microtubules. Cell Tissues Res. 227: 609-617.

D. Stork (1989). Is back-propagation biologically plausible. IJCNN Washington D. C. II: 241-246.

C. E. Swenberg and J. Miller (1989). Response to 'Are solitons responsible for energy transfer in oriented DNA' Intl. J. Radiat. Biol. 56 (3): 383-386.

H. Teitelbaum and S. W. Englander (1975). Open states in native polynucleotides. I. Hydrogen-exchange studies of adenine-containing double helices. Open states in nature polynucleotides. II. Hydrogen - exchange study of

cystosine-containing double helices. J. Molecular Biology 92: 55-92.

W. E. Theurkauf and R. B. Vallee (1983). Extensive cAMP-dependent and cAMP- independent phosphorylations of microtubule associated protein 2. J. Biol. Chem., 285: 7883-7886.

R. Vale (1987). Intracellular transport using microtubule-based motors. Ann. Rev. Cell Biol. 3: 347-378.

M. L. Vallano, J. R. Goldenring, R. S. Lasher, and R. J. DeLorenzo (1986). Association of calcium / calmodulin-dependent kinase with cytoskeletal preparations: phosphorylation of tubulin, neurofilament, and microtubule-associated proteins. Ann. N. Y. Acad. Sci. 466: 357-374.

R. B. Vallee and G. S. Bloom (1991). Mechanisms of fast and slow axonal transport. Annu. Rev. Neurosci. 14: 59-92.

P. Vassiliev, M. Kanazirska and H. T. Tien (1985). Intermembrane linkage by tubulin. Biochem. Biophys. Res. Comm., 126 (1): 559-565.

J. Von Neumann (1966). Theory of self-reproducing automata. ed. A. W. Burks, Urbana: University of Illinois Press.

A. Waibel, T. Hanazawa, G. Hinton, K. Schikano, and K. Lang (1989). Phoneme recognition using time-delay neural networks. IEEE Trans. Acous-

tics, Speeck, and Signal Processing 37: 328-339.

P. J. Werbos (1974). Beyond Regression: New tools for prediction and analysis in the behavioral sciences. Ph.D thesis, Harvard University. thesis.

P. J. Werbos (1988). Back-propagation through time: What it does and how to do it. Proc. of the IEEE 78 (10): 1550-1560.

P. J. Werbos (1990). A menu of designs for reinforcement learning over time. Chapter 3 in Neural Networks for Control ed. W. T. Miller III, R. S. Sutton, and P. J. Werbos. MIT Press, Cambridge, Ma. 67-95.

P. J. Werbos (1992). The cytoskeleton: Why it may be crucial to human learning and to neuro-control. In press.

J. H. Williams, M. L. Errington, M. A. Lynch, and T. V. P. Bliss (1989). Arachidonic acid induces a long-term activity-dependent enhancement of synaptic transmission in the hippocampus. Nature 341: 739-742.

S. Wolfram (1984a). Cellular automata as models of complexity. Nature 311: 419-424.

S. Wolfram (1984b). Universality and complexity in cellular automata. Physica 10D: 1-35.

S. Yamosa (1984). Solitary excitations in deoxyrybonucleic acid (DNA) doublehelices. Physical Review. A30: 474-480.

C. Zhu and R. Skalak (1988). A continuum model of protrusion of pseudopod in leukocytes. Biophys. J. 54: 1115-1137.

8 Figures

1. (a) Cell cytoskeleton shown in two cells shortly after division. Immunostaining allows MTs to be seen. Nuclei appear as circles, nearby to dense MT lattice areas. Reprinted from DeBrabander et al (1986). (b) Electronmicrograph of MTs, MAPs. Quick-freeze deep-etched pellets of MTs were polymerized with MAPs and tau. Reprinted with permission from Hirokawa (1991).

2. MTs are comprised of 13 protofilaments in parallel to form a tubular structure. Protofilaments are each a string of tubulin dimers consisting of α and β tubulin monomers. Dimers are 8 nm long. By Fred Anderson; reprinted from Hameroff (1987).

3. (a-h): Experimentally observed patterns of MAP attachment sites on MTs (Burns, 1978; Kim et al, 1986). Blackened elements indicate tubulin dimers that are binding sites for MAPs; unfilled elements indicate unbound

tubulin dimers. (i-t): Theoretically calculated patterns of MT phonon mode maxima (Samsonovich et al, 1992). Experimental patterns match the theoretically predicted patterns, with either an exact or approximate match.

4. MT pattern signaling, predicted by computations of MT automata models (Rasmussen et al, 1990). Black elements are tubulin dimers in the β conformational state; white elements are background α conformational states. (a) Left: Three successive time frames for four objects ("dot glider", "spider glider", "triangle glider", "diamond blinker"), moving leftward, leaving "wakes" which result in traveling wave patterns. Right: Three successive time frames for a "dot glider" and three other gliders. Simulated with different automata threshold parameters (lower coupling forces). The gliders travel leftwards without a wake. (b) Eight successive time frames for β states on α background (at low coupling force). Pattern at right is a β pattern that expands bidirectionally, and organizes into a bus glider of fixed length moving leftward. At top left is a dot glider that moves leftward without changing. At bottom left, another pattern evolves into a bus glider that moves leftwards and re-emerges on the far right because in this simulation the MT is toroidal.

5. Squashing functions and their derivatives. (a) Sigmoid (b) Derivative of sigmoid (c) Ramp function (d) Derivative of ramp.

6. A schematic neuron. Cell nucleus is shown along with a schematic representation of the cytoskeleton. Axonal widths and branches are exaggerated in size to show internal MT structure; dendritic tree has been abbreviated

but is also supported by the MT lattice.

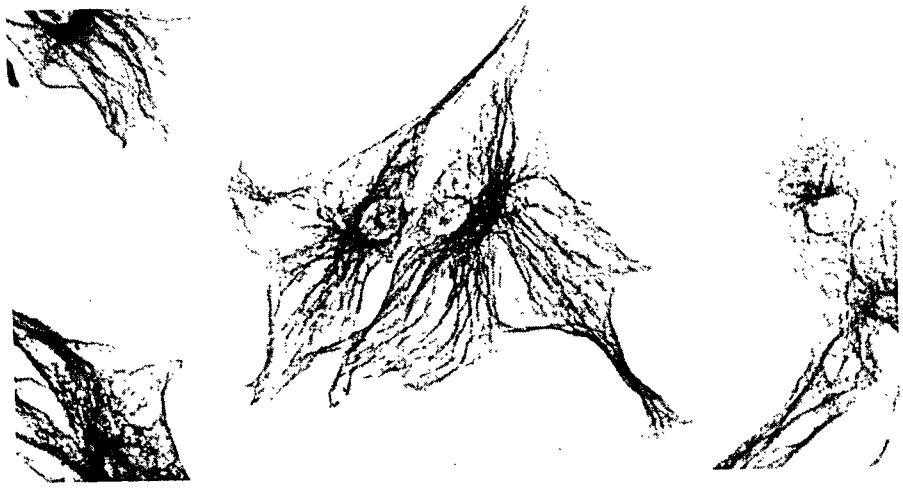
7. Layered feed-forward network, fully interconnected, consisting of an input layer, a hidden layer, and an output layer.

8. Three models for error-differencing computations. (a) Reciprocal synapse. (b) Intermediate neuron. (c) Feedback within a single synapse.

9. Sending the error back to the previous layer. When MT signal D arrives at the synapse, from cell G, a signal proportional to Dw is initiated up the axon of cell E. The parameter w represents the synaptic weight, as implemented by the biological synapse.

10. Summation of delta signal values in the MT lattice. Signals d_i propagate along axon branches to the axon trunk. The axonal fiber between the soma and branches is postulated to average and sum signals to perform $S = \sum d_i$. Signals S then propagate up dendritic trunks.

(a)



(b)

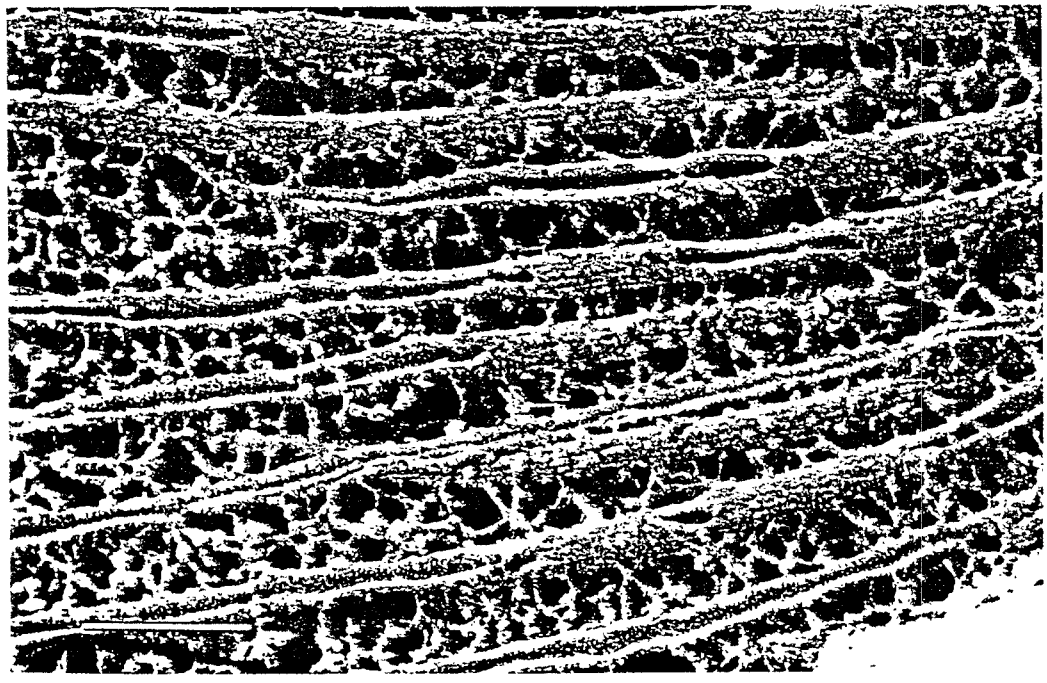


Figure 1

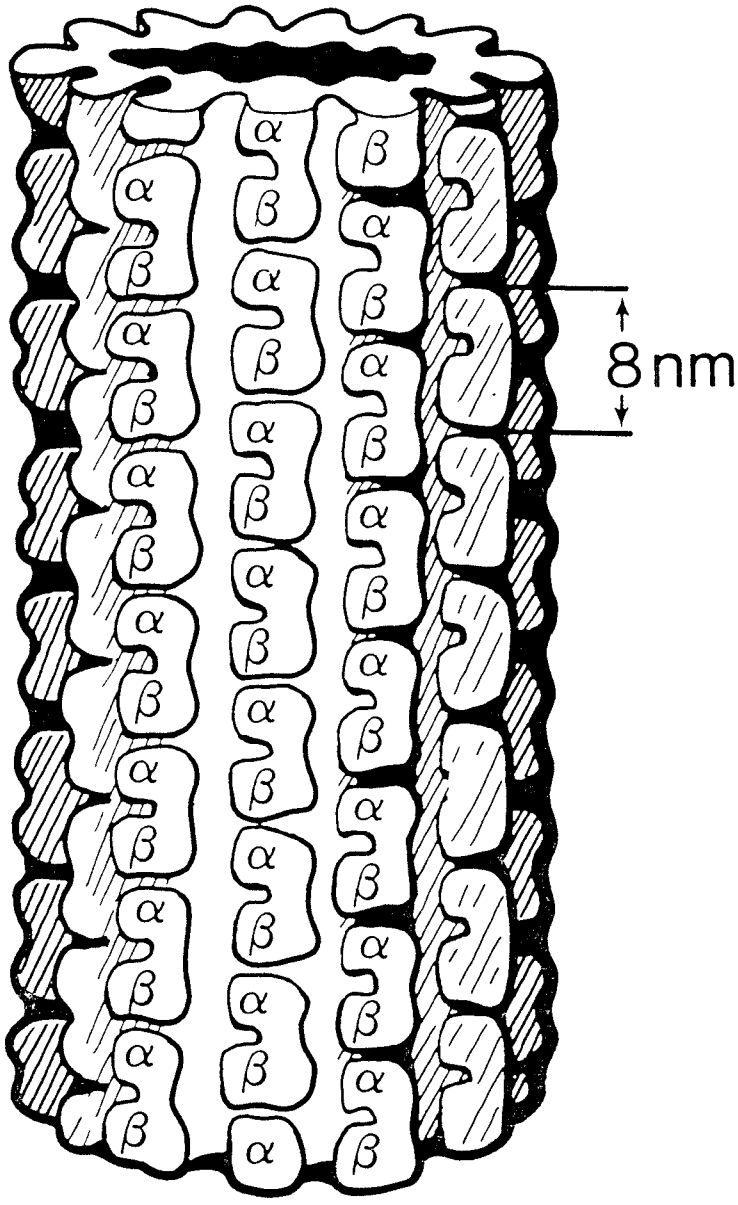


Figure 2

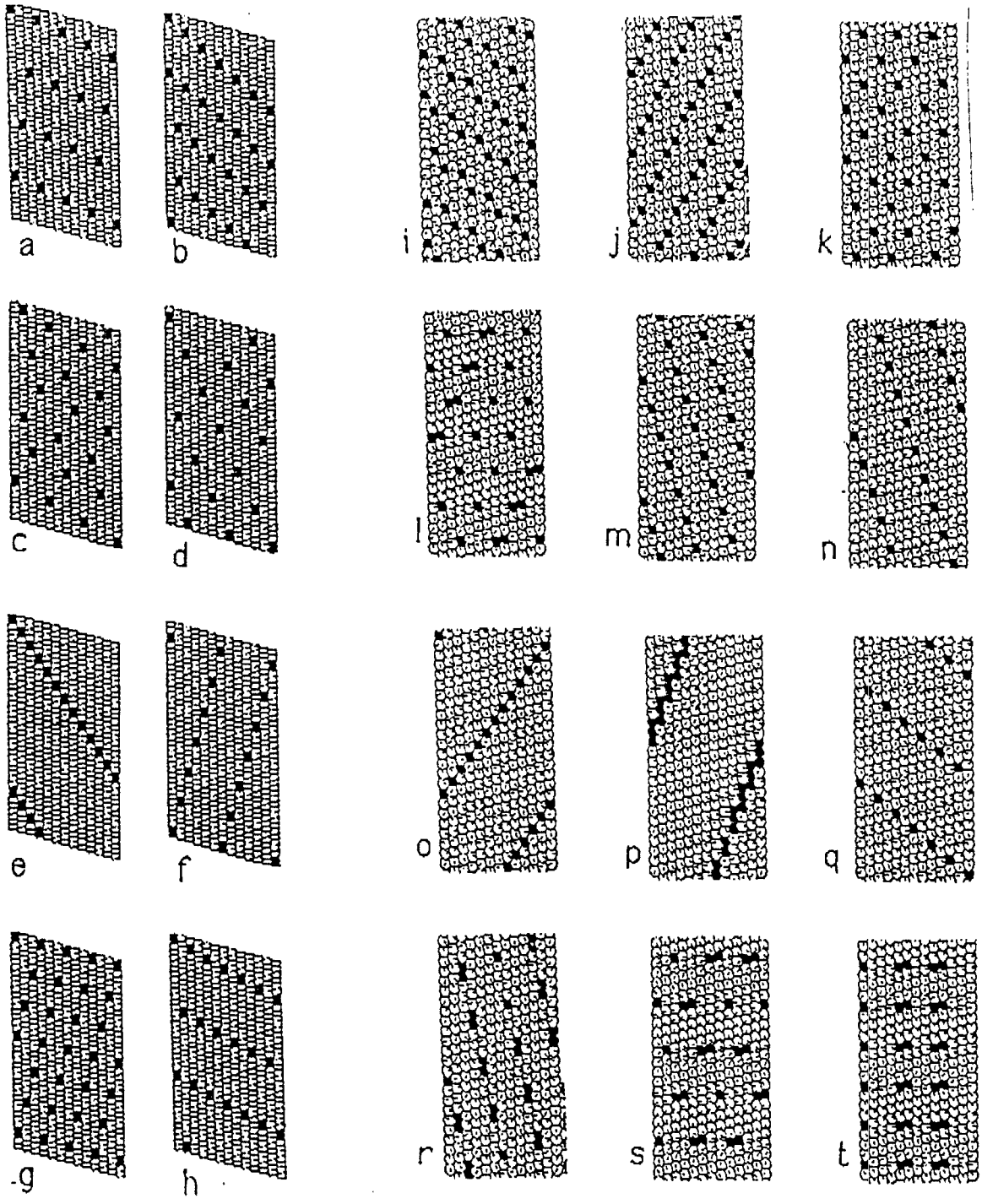
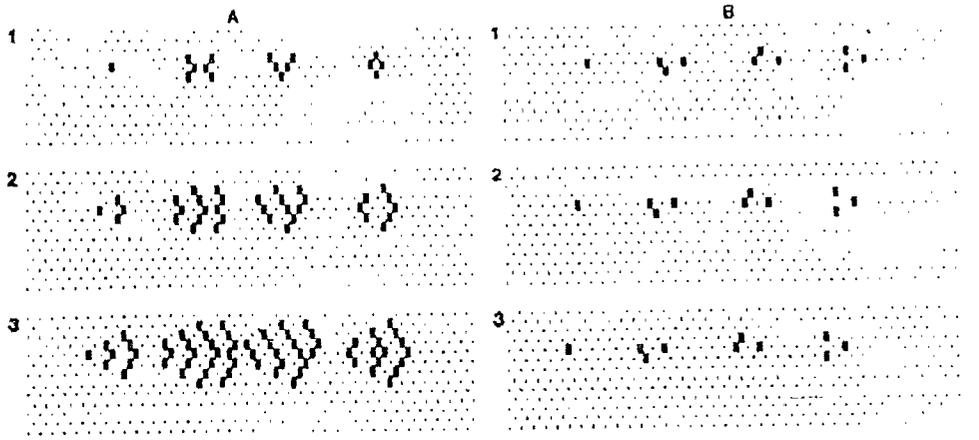


Figure 3

(a)



(b)

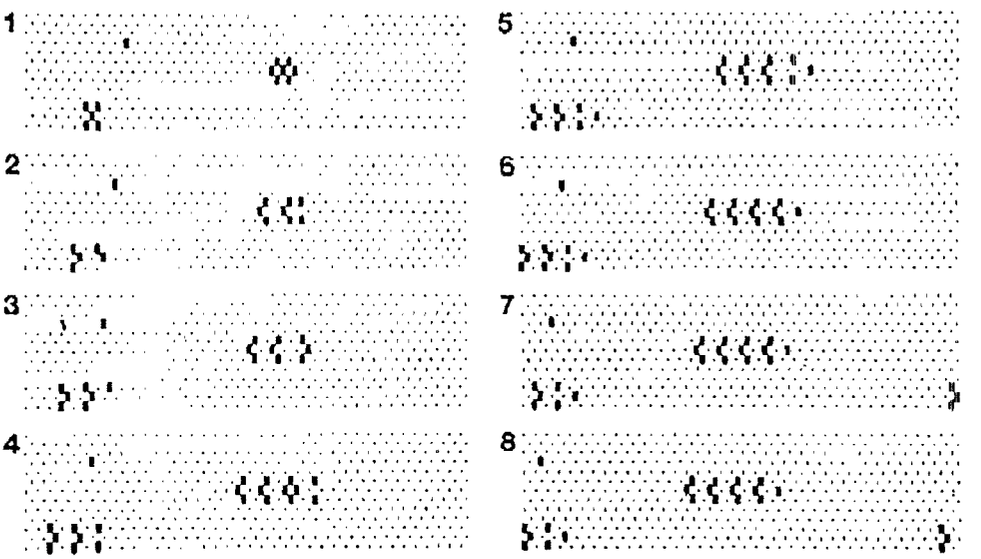
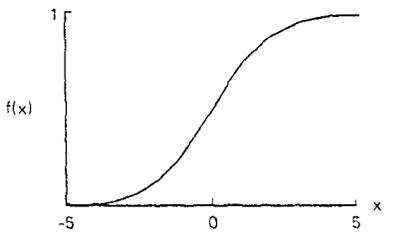
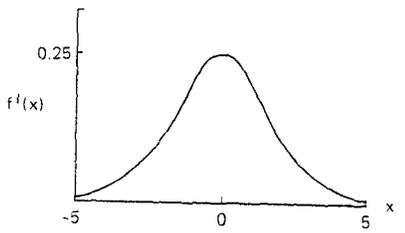


Figure 4

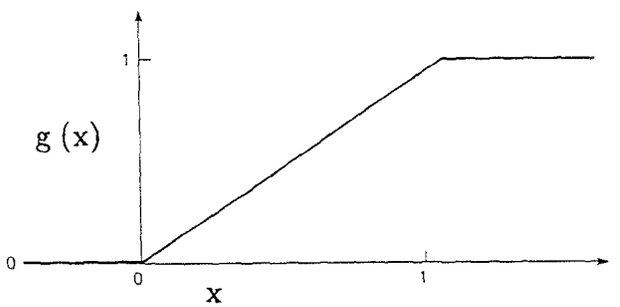
(a)



(b)



(c)



(d)

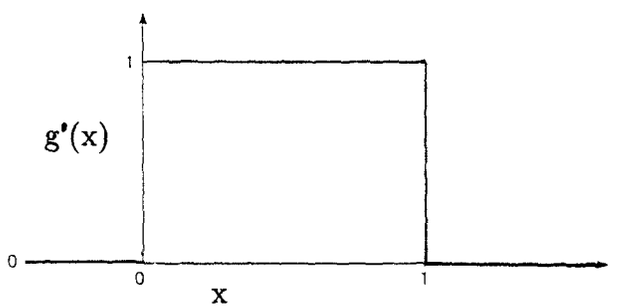


Figure 5

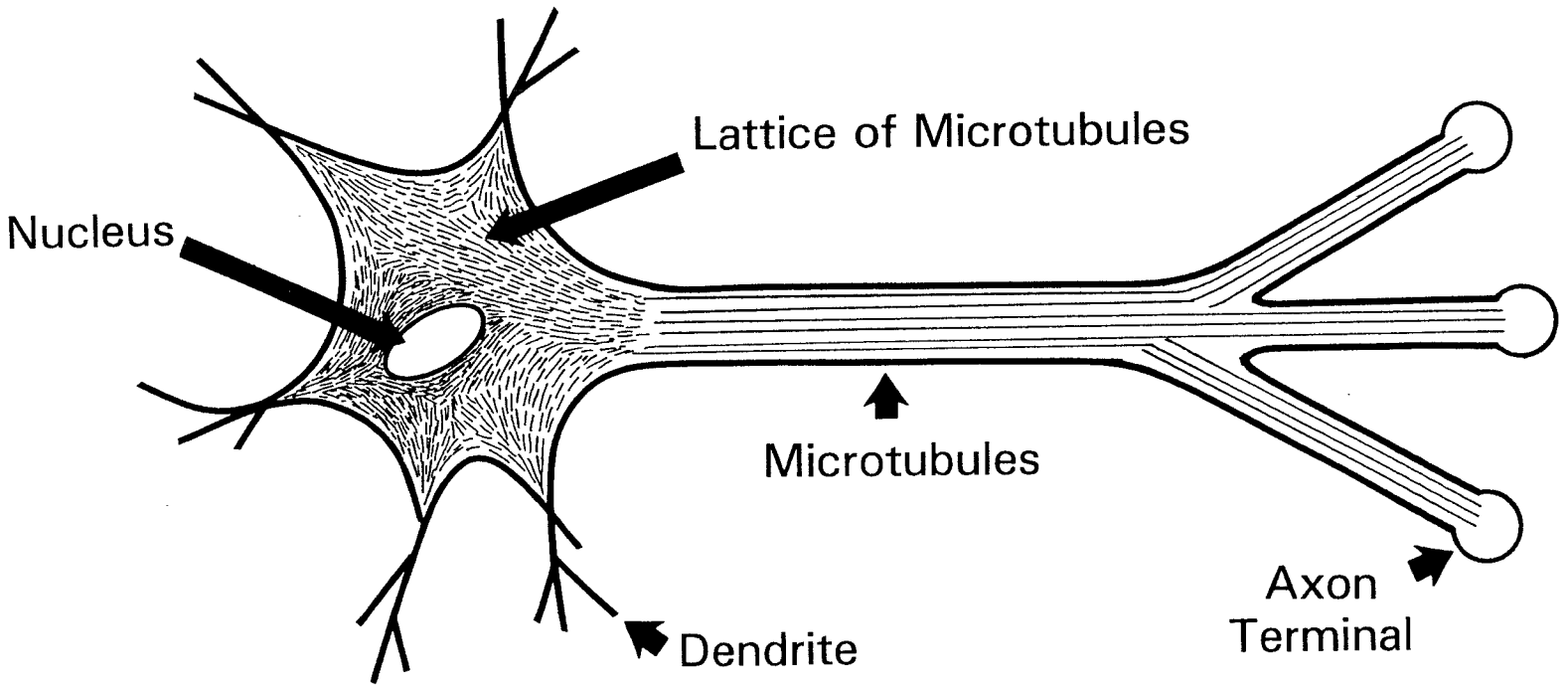

Lattice of Microtubules
Nucleus
Microtubules
Axon
Terminal
Dendrite

Figure 6

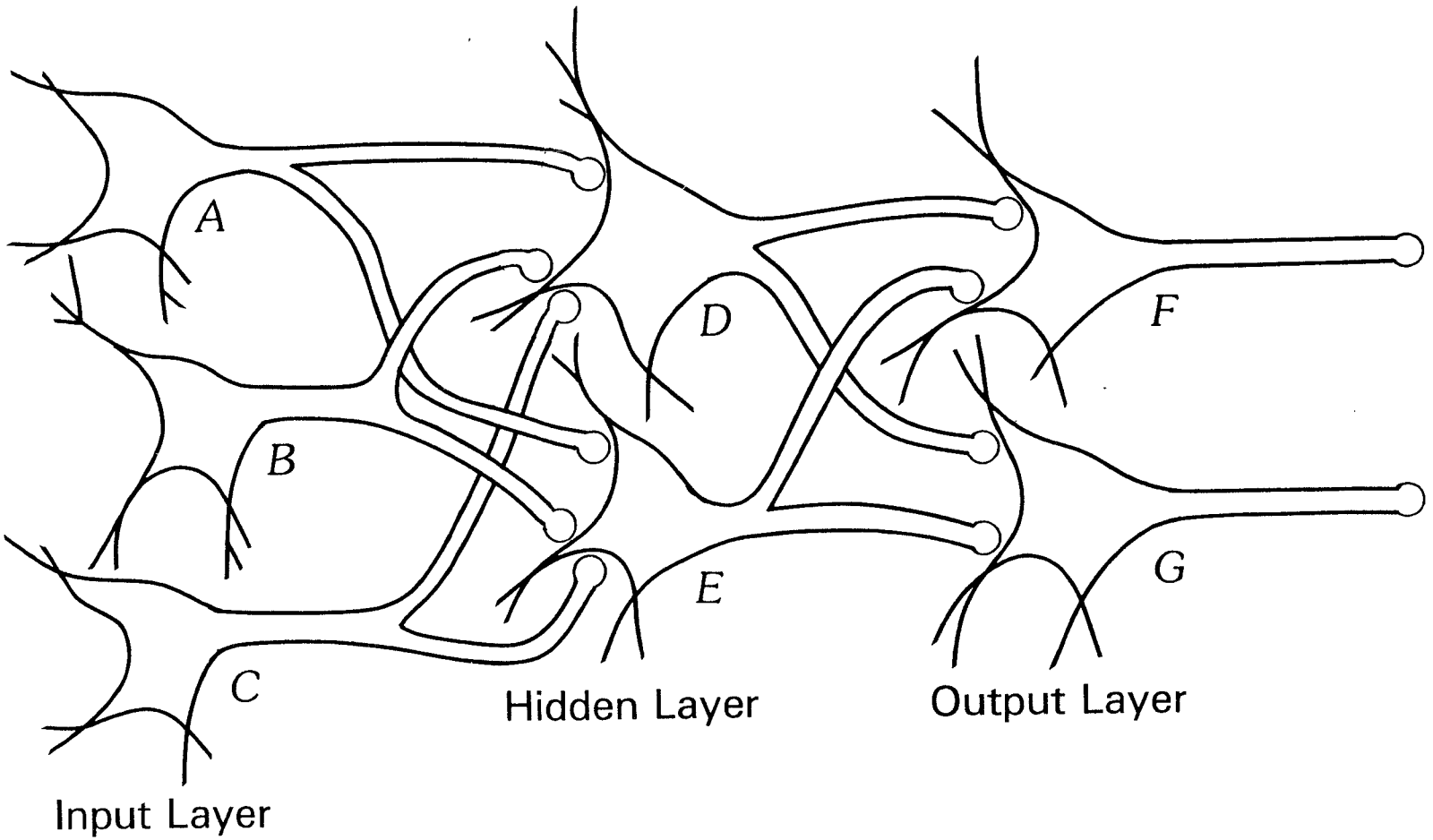


Figure 7

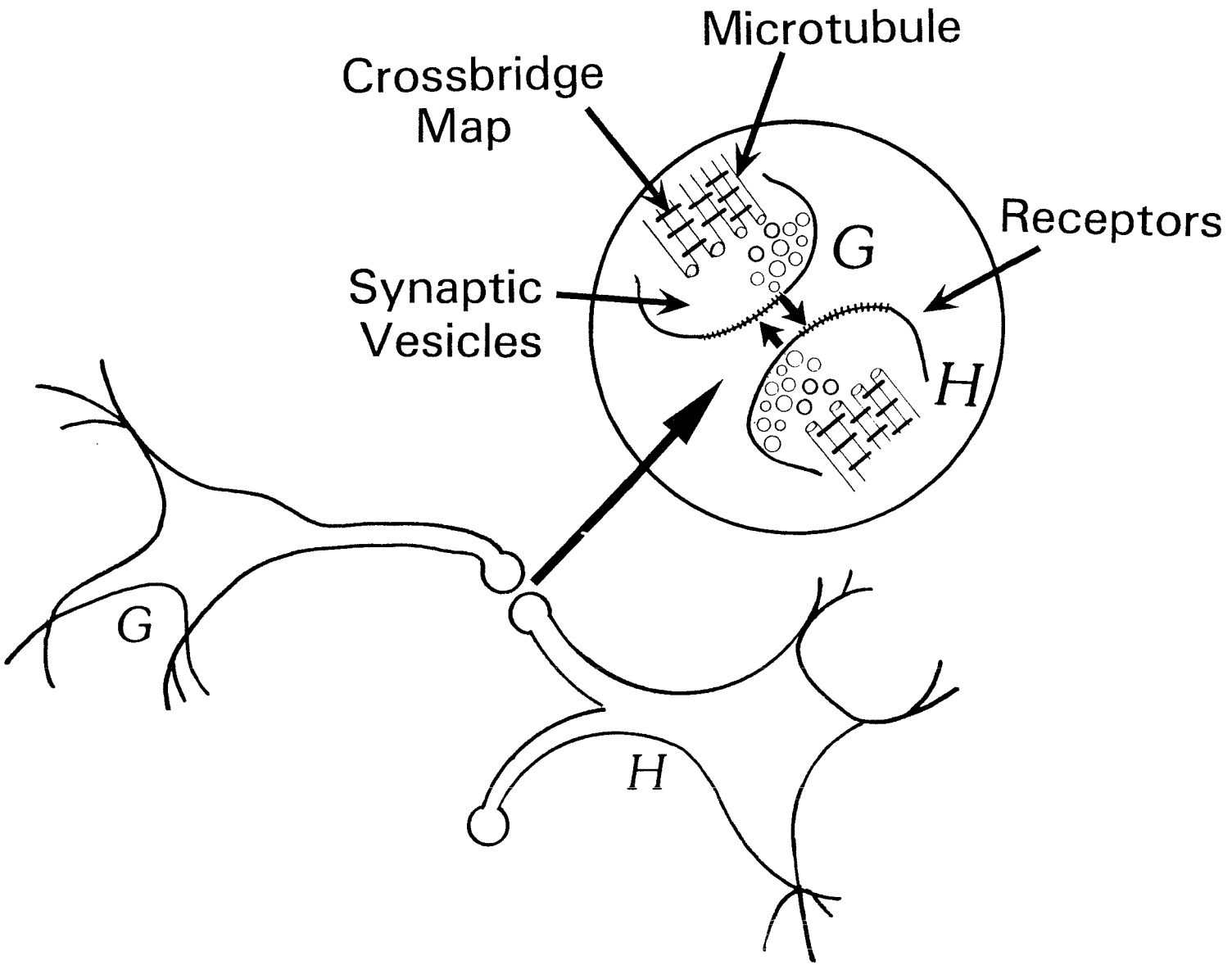

Microtubule
Crossbridge Map
Receptors
G
Synaptic Vesicles
H
G
H

Figure 8 (a)

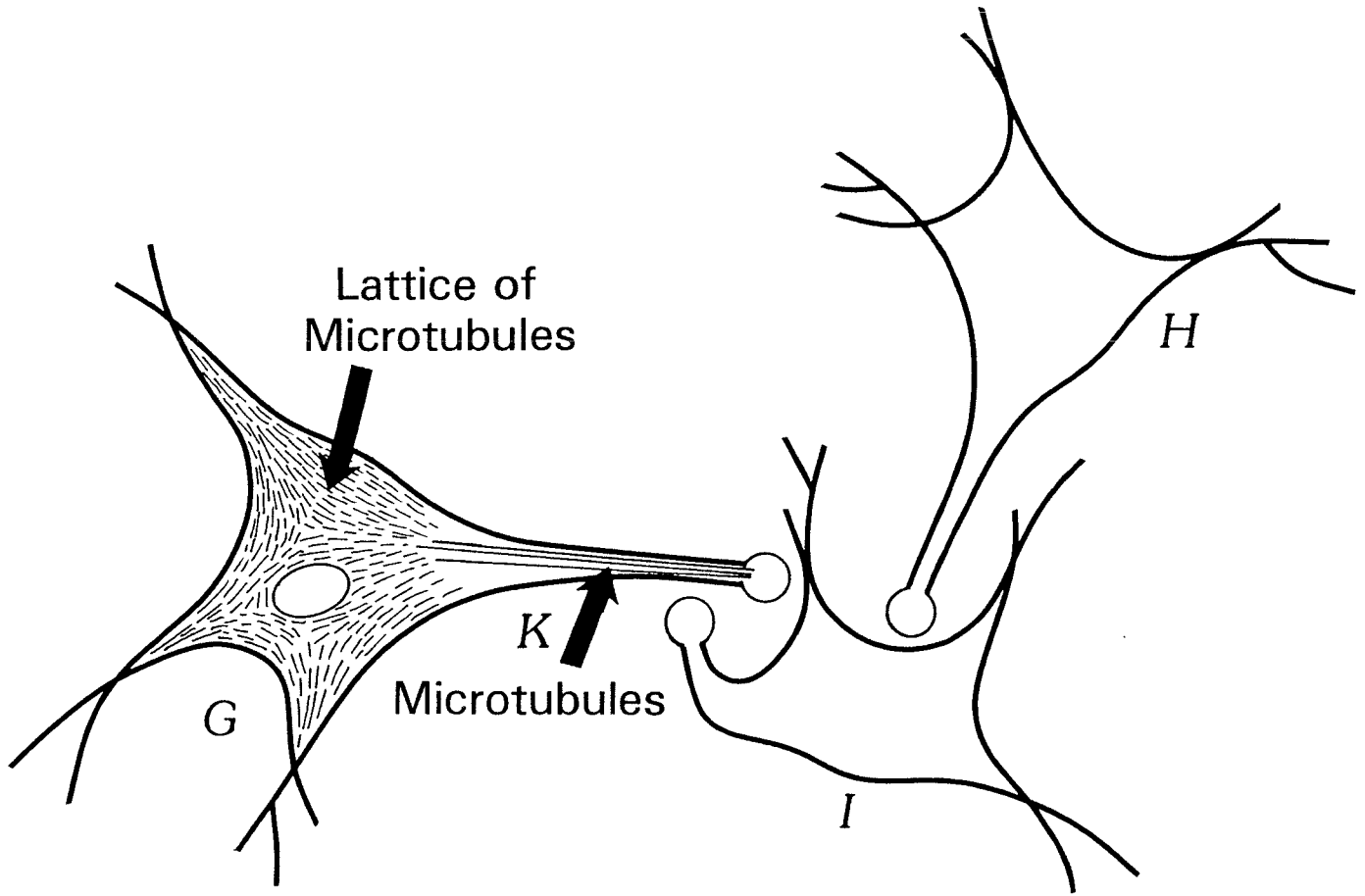


Figure 8 (b)

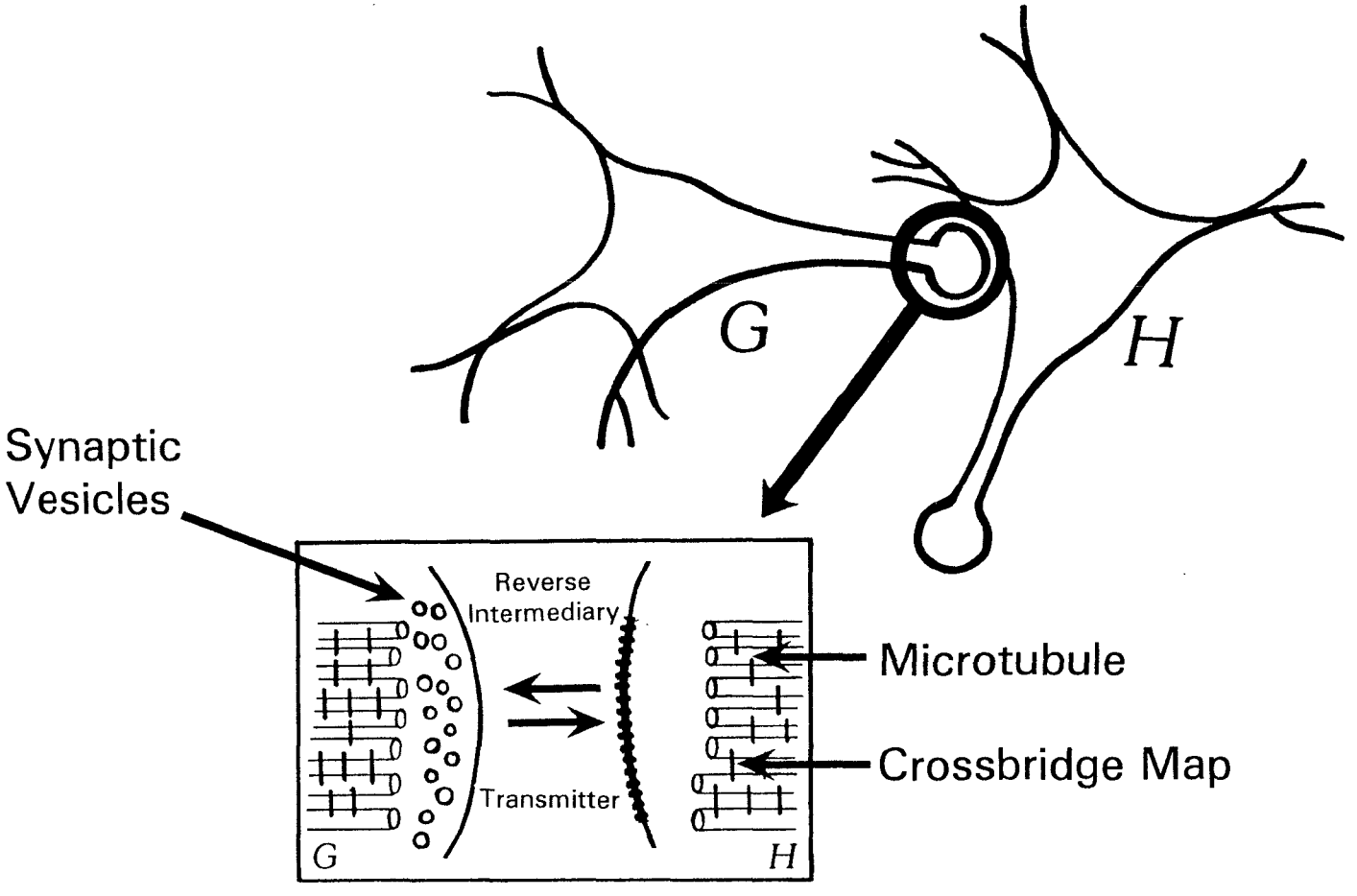

G
H
Synaptic
Vesicles
Reverse
Intermediary
Transmitter
Microtubule
Crossbridge Map
G
H

Figure 8 (c)

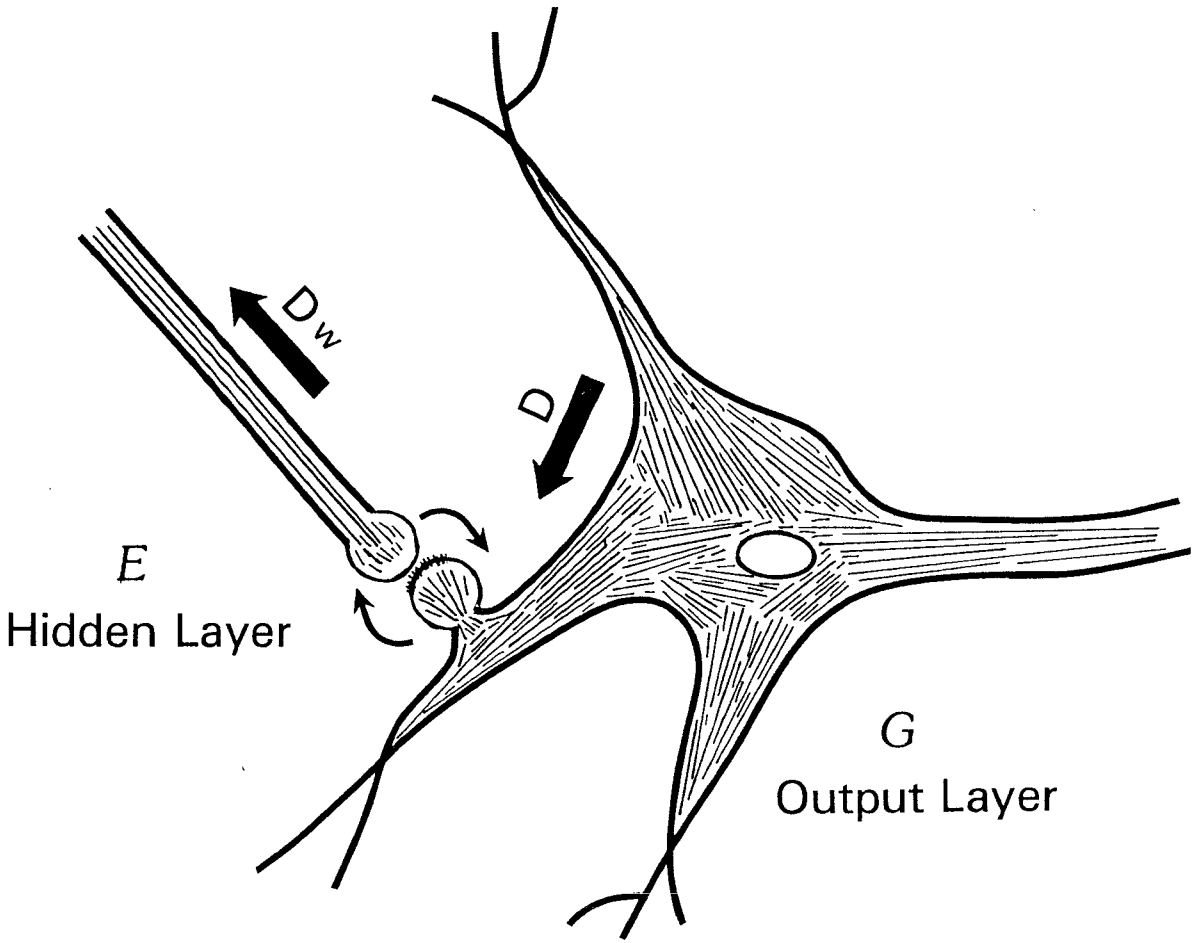


Figure 9

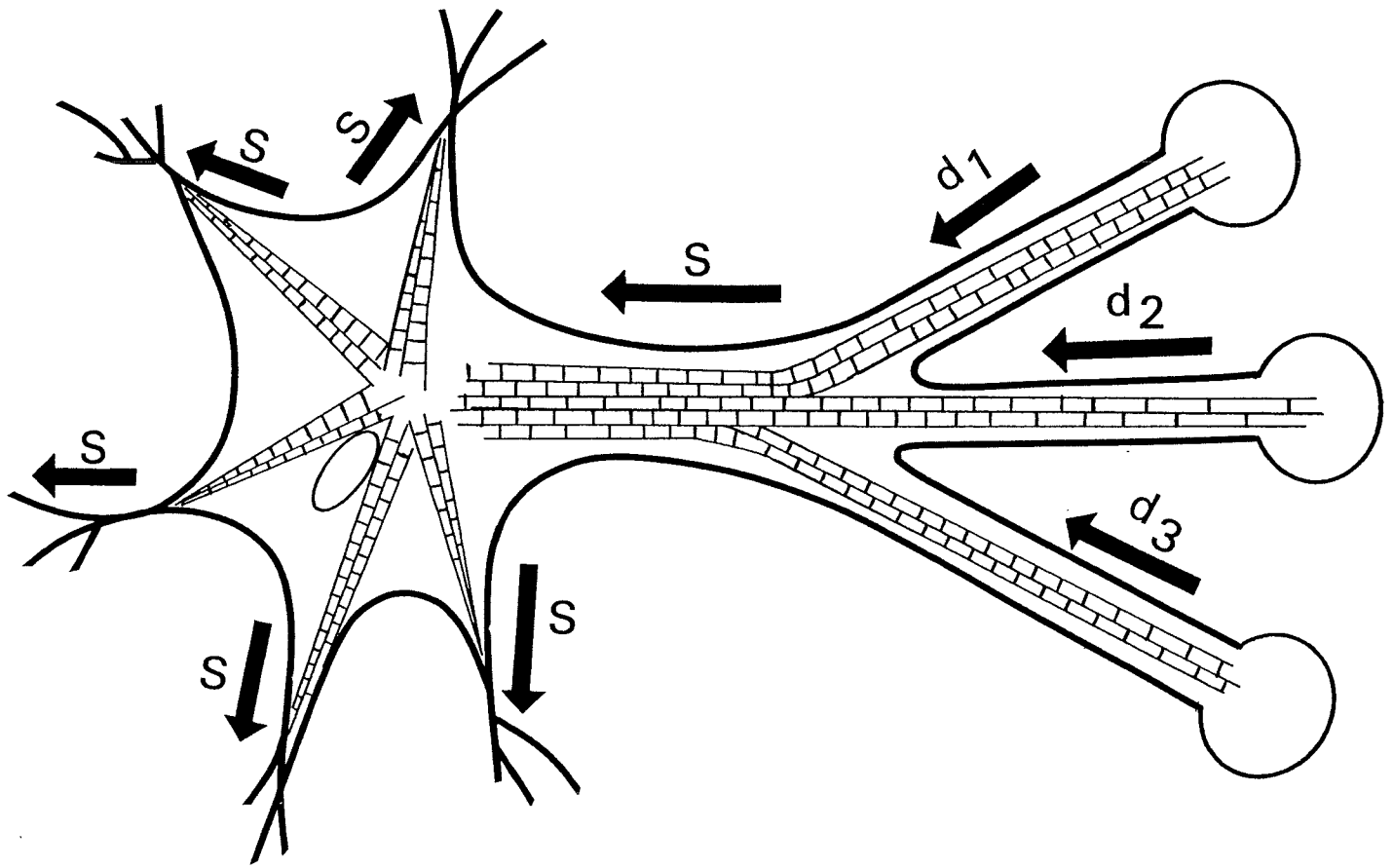


Figure 10