Information Processing in Microtubules

STUART R. HAMEROFF
Department of Anesthesiology, University of Arizona,
Health Sciences Center, Tucson, Arizona 85724, U.S.A.

AND

RICHARD C. WATT
Department of Electrical Engineering, University of Arizona,
Tucson, Arizona 85724, U.S.A.

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Biological information processing, storage, and transmission are theorized to occur by "computer-like" transfer and storage among subunits of polymerized cytoskeletal proteins: microtubules. Biological information functions (cellular and organismal control, axoplasmic transport, consciousness awareness) could be explained by comparing microtubule structure and activities to Boolean switching matrices, parallel computers, and such technologies as monolithic circuits, magnetic bubble memory, charge transfer devices, surface acoustic wave resonators, and/or holography.

Introduction

Microtubules (MT) are cylindrical, grid-like polymers which comprise cilia, flagella and the structural skeletal of living cells. Their functions include cellular orientation, structure, and guidance of membrane and cytoplasmic movement. Evidence has linked neuronal MT to trophic and differentiation (Cohn & Runak, 1969; Faulkes & McClellan, 1974; Singer, 1974; Bray & Gilbert, 1981) as well as to conscious perception, behavior, and intellect (Steile, Miel & Vullier-Luciani, 1973; Croxley-Dillon, Carden & Burka, 1974; Croxley-Dillon & Perry, 1976; Perry & Croxley-Dillon, 1978; Joegensen & Meyer, 1979). Theorized processes which could explain these apparent information functions occurring within MT include cooperative resonance among spatially arrayed proteins (Frohlich, 1975; Goodsky, 1976; Kaiser, 1978; Adey, 1981) and propagated conformational changes along MT protofilaments (Attna, 1973). Propagated changes along helical row axes as well as longitudinal protofilaments would imply that polymer subunits within cylindrical grid-like MT structure, connecting proteins, and...
intracellular tubular networks (Porter & Tucker, 1981) could provide programmable switching matrices for information transfer via Boolean logic. Calcium-dependent conformation states coupled to charge or energy quanta could be a medium of information transfer among the few nanometer (nm) slid 4,000 dalton MT subunits (tubulin), with programming by genetic or environmental effects. Transduction of information signals by ATPase mechanical proteins would result in temporal and spatial control of protein mechanical functions and cellular activity. In the nervous system, parallel computing in neural MT arrays may be coupled to action potentials or calcium ion (Ca\(^{++}\)) flux. Such coupling could result in cooperative resources, field excitations, and interference patterns which might comprise conscious awareness functions within the brain.

**Microtubules**

MTs are ubiquitous structures which shape and direct cellular movement, growth, structure, and function (Porter, 1986; Wilson, 1970; Baker & Ames, 1978). Multiple complexes of MT and interconnecting proteins such as cilia, mitotic spindles and centrioles perform specific functions in which they guide, signal, or direct cellular constituents through time and space. These include cilium, flagella, and axonemal movement, stereocilia, phagocytosis, axoplasmic transport, mitosis, growth and differentiation (Dustin, 1978).

Most microtubules are assemblies of thirteen longitudinal protomodules which are each a series of polar, tubule dimers (Fig. 3). A dimer consists of two slightly different 55,000 molecular weight monomers α and β tubulins which are each 4 nm in diameter (Borisy & Taylor, 1967; Denser et al., 1974; Lee & Timasheff, 1977). Leftward helices of α and β tubulin interfaces in three, five, and eight-start pattern have been observed (Bayne, 1972; Aris & Klap, 1974; Burns, 1978). MT outer diameters are 25-30 nm and inner diameters of the MT cavities are 14-15 nm (Timney, 1977). Functional MT lengths may apparently range from hundreds of nm to micrometers and perhaps even within some mammalian neurons (Alliston & Numa, 1986, Atuma, 1975). Tubulin dimer subunits are synthesized by DNA/RNA regulated ribosomes and subsequently self-polymered or are assembled into MT on patterned organizing structures (Tucker, 1977). Variability in the array of MT subunits' primary structures due to ribosomal genetic influences has been observed (Borchke & Forer, 1967; Bryan & Wilson, 1971). At least 17 isoforms of brain tubulin have been detected (Field, 1983). Potential non-genetic modifications of assembled MT structures include calmodulin (Means & Dedman, 1983), GTP (Bryan, 1972).
Fig. 1. Microtubule (MT), 25 nanometers thick in actual diameter, shown with attached functional ultraform proteins engaged in axoplasmic transport via "sliding filament." Spherical subunits in MT structure are 55,000 daltons. 8 nanometer proteins, "preparable on-off" conformational coupling to change or energy transfer may regulate biological functions through MT and APase microtubule protein activities.

- Glutamyl binding (Bhattacharyya & Wolff, 1974; Bryan, 1972), glycosylation (Behnke, 1975), and enzymatic addition of tyrosine to the C-terminal end of α-tubulin (Agarana et al., 1977). GTP binds at two different sites per tubulin dimer: a tightly bound site and a freely exchangeable Mg2+ dependent site coupled to tubulin conformational changes (Bryan, 1972). Low concentrations of calcium ion (Ca2+) stimulate and fortify MT assembly but millimolar Ca2+ prevents polymerization. Calmodulin, a 17,000 dalton protein may mediate Ca2+ effects on MT (Means & Dedman, 1980).

- In neurons MT assembly in the cell body and grow outward at 1 mm/day through axons and dendrites. Small filamentous and contractile polymers proteins including neurofilaments interconnect with MT to form intracellular skeletal networks (Pulay, 1956; Porter & Tucker, 1981; Bray & Gilbert, 1983). Neuretransmitter secretion and membrane excitability function are linked to MT structural integrity (Matsunoto & Sakai, 1979). In both myelinated and unmyelinated cat neurons, action potential frequency has been correlated with intraneuronal MT polymerization and density (Alvarez, 1979; Alvarez & Ramirez, 1979). Morphological maintenance
by proximal and retrograde axoplasmic transport (1–400 mm/day) of specific substances including synaptic receptors (Young, Wamsley, Zarbin & Kohler, 1980) that locally regulates neuronal membrane composition, as well as glial and postsynaptic cells (Paulson & McClure, 1974). Movement of filamentous contractile ATPase proteins attached to or regulated by MT surfaces appears to account for axoplasmic transport and many other facets of MT function (Haga, 1974). Major transmitters, neurotransmitters, and general and local anesthetics bind to intraneuronal MT and at high doses may inhibit axoplasmic flow, depolymerize MT or disconnect filamentous attachments between MT and membrane proteins (Allison & Nunn, 1966; Heschke, Byers & Tink, 1974; Caan & Hinman, 1975; Edelmann et al., 1975; MacKinney, Vyas & Walker, 1978).

Several types of MT-associated proteins (MAPs) bind to MT surfaces, often at regularly spaced intervals in a spiral whose pitch differs from the inherent MT three, five, and eight start helices (Tilney, 1971; Burn, 1978). Among these proteins are filamentous bridges which extend laterally and often contact other MTs (McElroy, 1974), contractile ATPases such as dynein which perform orchestrated mechanical work, and a variety of 10,000 to 400,000 dalton proteins (Sandoval & Chaitcus, 1976; Vallee & Borisy, 1981). Filamentous bridges among MTs are seen in complex geometric arrays of multiple MT throughout biology (Connolly et al., 1977; Vallee & Borisy, 1981). One type of array, layers of MT sheets with alternating 90 degree orientations polymerize in nuclei of rat sympathetic neurons within minutes following stimulation of those neurons (Szent-Gyorgyi et al., 1973). Evidence for gross MT involvement in memory, recognition, and consciousness include correlation of brain tubulin content with chronic sensory input in rats (Jorgensen & Moer, 1979) and cdc54 codes for known to disrupt MT-induced (use of experimental memory function in goldfish (Cohon-Dillon & Perry, 1976). Tubulin synthesis coincides with the period of critical functional development in visual cortex (Perry & Cohon-Dillon, 1978). Correlation of intraneuronal MT polymerization density with nerve stimulation and action potential frequency implies possible possible conditioning and information storage. Documented MT functions include cellular skeletal support, motility, transport, and memory (Porter & Tucker, 1981).

Models of Regulatory Charge/Energy Transfer in Proteins
Various models of regulatory charge/energy transfer in proteins have been proposed, and will be considered in the context of MT. Charge and energy transfer, resonance, and long-range coherent interactions within proteins have been described theoretically (Szent-Gyorgyi, 1960; Froehlich,
1968). Oxidation/reduction electron movement within proteins spatially fixed in an organelle or membrane has been compared to solid state electronics (Cope, 1974; Rosenburg & Postow, 1973) although intraprotein energy gaps may exceed available thermal energy. Specific protein conductivities among spatially arrayed aromatic amino acid resonance orhtols (Szejt-Gyorgy, 1960) have been linked to semiconducting protein functions in membranes, mitochondria, and intercellular gap junctions (Gutman & Lyons, 1969; Papas, Asada & Bennett, 1971; Pulitoff, 1977).

Intracellular electron dipole oscillations may be coupled to mechanical conformational changes and necessary for enzyme function (Frohlich, 1975). Functional long-range coherent transitions among spatially arrayed charge sites in membrane or other matrix may be cooperatively coupled (Adel, 1977). Cooperative processes involving phase transitions, hysteresis, and avalanche effects in subcellular systems have also been described (Frohlich, 1970; Kaiser, 1978; Adel, 1981). Electron superconductivity (Cope, 1974) and intermolecular quantum mechanical tunneling over several nm (Miller, 1971) are suggested to occur widely in biological systems.

Functional transfer of biological energy quanta has been described for packets of protein lattice conformational energy ("phonons", "excitons", conformational) (Avery & Pavlidou, 1974; Shohet & Reish, 1974). Cooperativity in a rigidly ordered biological lattice has been likened to a quantum amplification device with long-range phase changes ("Einstein-Bose condensation") (Frohlich, 1975; Grodsky, 1976; Adel, 1977).

Solitary, non-dissipative waves which could propagate in protein systems (Carter, 1980), have been theoretically coupled to neuronal systems (Tuckwell, 1979). Spatio-temporal conformational wave patterns in protein systems have been linked to nervous system function (Drond-Naunin, 1973).

Transfer of excited electron resonance energy has been demonstrated between MT and membrane proteins by fluorescent labelling (Becker & Oliver, 1975). Communicative photon perception by MT and other protein structures has also been described (Carlton & Stephens, 1974; Langford & Inoue, 1979). These examples and theoretical models, if they exist, could operate in the grid-like structural matrix of MT and other cytoskeletal proteins.

Organized Transfer Model in Neuronal Microtubules

Conformationally coupled information transfer along MT protofilament subunits in sensory cilia has been proposed (Atienza, 1973). By generalizing directional axes of such transfer to include helical rows, the repetitive
geometric lattice array of MT subunits may serve as a matrix of directional transfer and transduction of biochemical, conformational, or electromagnetic quantum energy and charge with implications for information processing. Based on pre-programmed genetic and environmental memory and an "execute" function (ion flow, charge gradient, action potential), transferable "on-off" states within each MT subunit could provide for Boolean logic and transductive information processing. Several "on-off" functions linked to Ca"2+ binding could suffice:

1. Ca"2+ concentration changes could alter conformational states of certain tubulin subunits which may be pre-programmed (GTP, glycolysis, transcription, posttranslational, primary protein structure, etc.) to undergo conformational changes in the presence of Ca"2+.

2. Ca"2+ effects on tubulin (possibly via calmodulin) could facilitate charge and/or energy transfer in a manner analogous to acceptor impurities in semiconductors (Fig. 2). Ca"2+ could pull an electron from its resonance orbital in a hydrophobic region, creating an electron "hole" and unpaired spinmate. Thus, transfer of an electron from one packet of conformational...

![Diagram](image-url)
www.energy (phonons, solitons, etc.) to an adjacent subunit could be facilitated.

MT structure can be viewed as a cylindrical, leftward spiral grid (Fig. 3). With assumption of Ca⁺⁺ linked "on-off" states in tubulin subunits and the following arbitrary conditions, the continuous grids of intraneuronal MT could function as programmable switching matrices capable of information processing and transfer via Boolean logic. Within nerve cells, transfer of MT conformational status or energy state could be "driven" (execute function) by traveling nerve action potentials and/or associated transmembrane Ca⁺⁺ flux. Velocities of action potentials and accompanying Ca⁺⁺ flux (0 to 100 meters/sec) would result in time intervals for 4 nm tubulin subunit transfers of about 10⁻¹⁰ sec, and thus be consistent with observed nanosecond-range protein conformational oscillations (Bakowskie, 1987).

Fig. 3. Unwrapped membrane (MT) grid as programmable switching matrix. Gradually "on"-permitting adjustable subunit border (on-off) states allows Ca⁺⁺ related conformational status coupled to charge on energy quanta. "Left" and "right" tubulin protein subunit states (leftward 3, up 1.5) represent electronic microsecond evidence of MT membrane potential attachment (Bakowskie, 1987). Leftward MT could be driven by potential state of experimental programming matrix. Charge transfers can be driven, nerve mediated by Ca⁺⁺ flux or cytoskeletal energetic attachments.
& Weber, 1973). Based on approximations of intracellular MT density, fraction of brain which is neuronal, and average neuronal MT length, parallel computing in MT coupled to action potentials could approach 10^16 transfers/sec ("bits") in the human brain. The following arbitrary set of assumptions describes one particular, possible mechanism for parallel computing and information processing in neuronal MT.

1. At time t, each tubulin subunit is one of two possible states which may correspond with a particular conformation and/or excited state coupled to Ca^2+ binding.

2. With each nerve action potential, tubulin states advance one subunit in the direction of the action potential.

3. In the direction of the action potential, each state change has two possible directions: straight ahead along one of the microtubules or leftward along the three structural helical rows.

4. Switching mechanisms exist at each subunit which direct propagation of tubulin state either straight or leftward. Possible substrates for such switching mechanisms might include genetically programmed alterations in primary protein structure, posttranslational modification, or changes due to environmental interactions. Tubulin binding to GTP, cation, tyrosine phosphorylation, glycosylation, or other factors could induce conformational and energy states such that "straight ahead" transfer from the preomote is inhibited and "leftward" transfer promoted. Alternatively, pre-programming factors may determine which subunit line will respond to Ca^2+.

5. Chaperoned MAPs bind at sites of charge/energy/Ca^2+ abundance ("sink proteins"); charge, conformational energy, ion (acceptor) or charge/energy qualified ("source proteins"); charge, energy ions supplied. Switching charge/energy transfers through sink-source relations may control movement and function of MAPs which may extend laterally as contractile filaments which contact other MT in the geodesic cellular skeleton, transport cytoplasmic organelles, or regulate membrane function. Sequential, oxidized MAP activities such as axonotrophic transport may not be controlled by pulsed MT transfers (Fig. 4).

Functional mechanical movements of MAPs including APlus scaffold protein such as dynein could be regulated by transfer patterns over time. A specific model of axonotrophic transportation on MT programmed scaffold protein activities is shown in Fig. 4. Unidirectional, specific transport of synaptic thick endosomes or precursors via a sliding filament is represented as a function of "on-off" states of the scaffold protein's anchoring MT subunits. Each scaffold is shown anchored to two subunits, two rows apart ("sink-source pairs"). If either row subunit is occupied ("on") and the other row subunit is not occupied ("off") the scaffold contractile protein contracts...
Fig. 4. "Comparative" MT model of axoplasmic transport. A single column of MAP "polymers" forms a "bucket brigade" model of axoplasmic transport of a single filament, connecting pools in front of or proximal to interfilamentous. Each MAP is anchored to microtubules, two rows apart, so the polymer chains form "channels" between microtubules. Motility and multidomain MAP movement and transfer are also programmed, thus organizing and regularizing cellular transport, cellular growth and movement, and other biological functions may be similarly viewed.
To illustrate MT-computer analogies, switching decisions based on left switch programming and neural pulsed transfer are represented in a flowchart in Fig. 5. MT programming could channel charge/energy/Ca"" such that specifically arrayed subunits, M(2), M(5, 2), etc., would maintain particular conformational and receptor states. Thus, in addition to "real-time" MAP regulation, location of MAPs, sink-source protein pairs, and their functional activities may be programmed by genetic or environmental modes. Left switch sites sufficient to explain one particular "defensive 3, up 1" observed pattern of NAP attachments (Burns, 1978) is expressed in Table 1 as a Fortran program.

MT signaling could occur by modulated, pulsed traffic through associated proteins or by low intensity radiant field effects of nanosecond fluctuations in electromagnetic vectors. Such signaling could be perceived by other MT or various structures which may respond via cooperative phase transitions, conformational changes, or other reactions. Dynamic electrical fields have been detected oriented to microspines, coupled to embryonic neural growth axes, and theoretically linked to organization patterns of cellular growth and functions (Burt & Nelson, 1946). MT spatial regularity
of 6 ms intervals could possibly promote coherence and resonance among MT subunit extended states. In the nervous system, action potentials traveling through parallel MT arrays could induce cascades of excited states and resultant wave field patterns similar to optical parallel computing (Kosmanay & Anoma, 1987; Maitchadin, 1962; Roger, 1977). Interference patterns within the coherent wave fields (possibly vortex, electric, magnetic, photon, biochemical, ionic, mechanical, sol-gel, solution, etc) could reconstruct image type information as in holography (Gabriel, 1968; Westlake, 1979; Hinterolf, 1974, Pichard, 1974). Such patterning could regulate cytoskeletal polymerization, cell growth, differentiation and membrane protein arrangement. Excited state resonance among spatially arrayed tubulin subunits could be similar to quantum optical mode locking of coherent laser light, superconductivity, and supermagnitization which manifest second order phase transition phenomena as maximal resonances are approached (Vagager, 1973). Resonant phase transitions in level of awareness of specific personal information sets (“consciousness”) might depend on MT density, MAP level, charge/energy conformalional states and occurrence of pattern altering action potentials within neuronal groups. Thought, awareness, imagery, and recall could thus represent continuous tuning and detuning of various subsets of MT subunit field. Other macromolecular grid-like structures (vimentin–myosin microfilaments, myelin lamellae, etc) could utilize similar information processing and regulation.

Table 1

<table>
<thead>
<tr>
<th>FOR X = -1, +1</th>
<th>FOR M = +1</th>
<th>NEXT M</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOR Y = -1, +1</td>
<td>FOR M = +1</td>
<td>NEXT N</td>
</tr>
<tr>
<td>NEXT X</td>
<td>Y = +N</td>
<td>N + 1</td>
</tr>
<tr>
<td>NEXT X</td>
<td>Y = +N</td>
<td>N + 1</td>
</tr>
</tbody>
</table>

In a 2-dimensional array M, X, Y = -1 or +1 are updated.

Conclusion

Intracellular biological communication, regulation, information processing, and neural thought processes are postulated to occur via computer-
like” and resonant functions in the matrix grid of microtubule (MT) subunits and associated proteins.

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