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Information Processing in Microtubules

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Biological information processing, storage, and transduction are theorized to occur by "computer-like" transfer and resonance among subunits of polymerized cytoskeletal proteins: microtubules. Biological information functions (ciliary and flagellar control, axoplasmic transport, conscious awareness) could be explained by comparing microtubule structure and activities to Boolean switching matrices, parallel computers, and such technologies as transistor 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 skeleton of living cells. Their functions include cellular orientation, structure, and guidance of membrane and cytoplasmic movement. Evidence has linked neuronal MT to trophism and differentiation (Ochs & Ranish, 1969; Paulson & McClure, 1974; Singer, 1974; Bray & Gilbert, 1981) as well as to conscious perception, behavior, and intellect (Seite, Mei & Vuillet-Luciani, 1973; Cronley-Dillon, Carden & Birks, 1974; Cronley-Dillon & Perry, 1976; Perry & Cronley-Dillon, 1978; Jorgensen & Meier, 1979). Theorized processes which could explain these apparent information functions occurring within MT include cooperative resonance among spatially arrayed proteins (Frohlich, 1975; Grodsky, 1976; Kaiser, 1978; Adey, 1981), and propagated conformational changes along MT protofilaments (Atema, 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

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intracellular trabecular 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 four nanometer (nm), 55 000 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 neuronal MT arrays may be coupled to action potentials or calcium ion (Ca^{2+}) flux. Such coupling could result in cooperative resonances, field fluctuations, and interference patterns which might comprise conscious awareness functions within the brain.

Microtubules

MT are ubiquitous structures which shape and direct cellular movement, growth, structure, and function (Porter, 1966; Wilson, 1970; Baker & Amos, 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 ciliary, flagellar and ameboid movement, secretion, phagocytosis, axoplasmic transport, mitosis, growth and differentiation (Dustin, 1978).

Most microtubules are assemblies of thirteen longitudinal protofilaments which are each a series of polar, tubulin dimers (Fig. 1). A dimer consists of two slightly different 55 000 molecular weight monomers (α and β tubulin) which are each 4 nm in diameter (Borisy & Taylor, 1967; Dentler *et al.*, 1974; Lee & Timasheff, 1977). Leftward helices of α and β tubulin interfaces in three, five, and eight start patterns have been observed (Bryan, 1972; Amos & Klug, 1974, Burns, 1978). MT outer diameters are 25–30 nm and inner diameters of the MT cavities are 14–15 nm (Tilney, 1971). Functional MT lengths may apparently range from hundreds of nm to micrometers and perhaps meters within some mammalian neurons (Allison & Nunn, 1968; Atema, 1975). Tubulin dimer subunits are synthesized by DNA/RNA regulated ribosomes and subsequently self-polymerize 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 (Behnke & Forer, 1967; Bryan & Wilson, 1971). At least 17 isozymes of brain tubulin have been detected (Field, 1982). Potential nongenetic modifications of assembled MT structure include calmodulin (Means & Dedman, 1980), GTP (Bryan, 1972),

FIG. 1. Microtubule (MT), 25 nanometers (nm) in actual diameter, shown with attached functional sidearm proteins engaged in axoplasmic transport via "sliding filament." Spherical subunits (α or β tubulin) are 55 000 dalton, 4 nm diameter proteins. Programmable "on–off" conformational coupling to charge or energy transfer may regulate biological functions through MT and ATPase sidearm protein activities.

cation binding (Bhattacharyya & Wolff, 1974; Bryan, 1972), glycosylation (Behnke, 1975), and enzymatic addition of tyrosine to the C-terminal end of α tubulin (Argarana *et al.*, 1977). GTP binds at two different sites per tubulin dimer: a tightly bound site and a freely exchangeable Mg^{2+} dependent site coupled to tubulin conformational changes (Bryan, 1972). Low concentrations of calcium ion (Ca^{2+}) stimulate and fortify MT assembly but millimolar Ca^{2+} prevents polymerization. Calmodulin, a 17 000 dalton protein may mediate Ca^{2+} effects on MT (Means & Dedman, 1980).

In neurons MT assemble in the cell body and grow outward at 1 mm/day through axons and dendrites. Small filamentous and contractile polymer proteins including neurofilaments interconnect with MT to form intracellular skeletal networks (Palay, 1956; Porter & Tucker, 1981; Bray & Gilbert, 1981). Neurotransmitter secretion and membrane excitability function are linked to MT structural integrity (Matsumoto & 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 & Kuhar, 1980) trophically 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 apparently account for axoplasmic transport and many other facets of MT function (Ochs, 1974). Major tranquilizers, anticonvulsants, 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, 1968; Haschke, Byers & Fink, 1974; Cann & Hinman, 1975; Edstrom *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; Burns, 1978). Among these proteins are filamentous bridges which extend laterally and often contact other MT (McIntosh, 1974), contractile ATPases such as dynein which perform orchestrated mechanical work, and a variety of 100 000 to 400 000 dalton proteins (Sandoval & Cuatrecasas, 1976; Vallee & Borisy, 1978). Filamentous bridges among MT are seen in complex geometric arrays of multiple MT throughout biology (Connolly *et al.*, 1977; Vallee & Borisy, 1977). One type of array, layers of MT sheets with alternating 90 degree orientations polymerize in nuclei of cat sympathetic neurons within minutes following stimulation of those neurons (Seite *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 (Jorgenson & Meier, 1979) and colchicine (drug known to disrupt MT) induced loss of experimental memory function in goldfish (Cronley-Dillon & Perry, 1976). Tubulin synthesis coincides with the period of critical functional development in visual cortex (Perry & Cronley-Dillon, 1978). Correlation of intraneuronal MT polymerization density with nerve stimulation and action potential frequency implies 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; Frohlich,

1968). Oxidation/reduction electron movement within proteins spatially fixed in an organelle or membrane has been compared to solid state electronics (Cope, 1974; Rosenberg & Postow, 1973) although intra-protein energy gaps may exceed available thermal energy. Specific protein conductivities among spatially arrayed aromatic amino acid resonance orbitals (Szent-Gyorgyi, 1960) have been linked to semiconductive protein functions in membranes, mitochondria, and intercellular gap junctions (Gutman & Lyons, 1969; Pappas, Asada & Bennett, 1971; Politoff, 1977). Intraprotein 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 (Adey, 1977). Cooperative processes involving phase transitions, hysteresis, and avalanche effects in subcellular systems have also been described (Frohlich, 1970; Kaiser, 1978; Adey, 1981). Electron superconductivity (Cope, 1974) and intermolecular quantum mechanical tunneling over several nm (Miller, 1975) 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", "conformons") (Avery & Pavlidou, 1974; Shohet & Reible, 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; Adey, 1977). Solitons, non-dissipative waves which could propagate in protein systems (Carter, 1980), have been theoretically coupled to neuronal systems (Tuckwell, 1979). Spatially locked conformational wave patterns in protein systems have been linked to nervous system function (Drost-Nausen, 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 (Carlson & Stephens, 1974; Langford & Inouie, 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 (Atema, 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 quantal energy and charge with implications for information processing. Based on pre-programming (genetic and environmental memory) and an "execute" function (ion flux, 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, glycosylation, tyrosylation, 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*, or packet of conformational

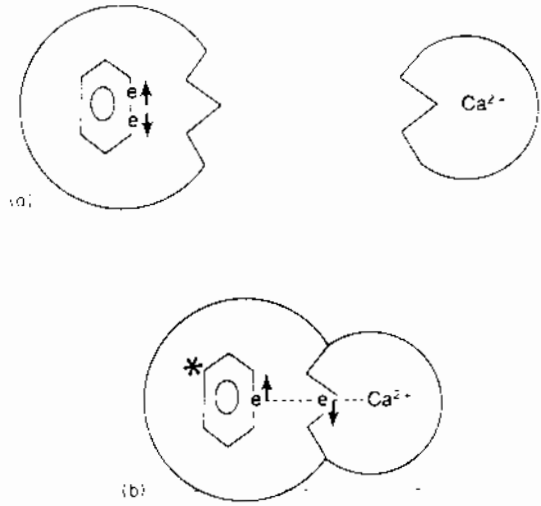

FIG. 2. Calcium-calmodulin complex acting to facilitate charge/energy transfer in tubulin subunits. In (a), a tubulin subunit is shown schematically with an aromatic amino acid ring having paired electrons within a hydrophobic pocket. A calcium ion-calmodulin complex is represented with a tubulin specific binding site. In (b) the calcium-calmodulin complex is bound to the tubulin. The charged calcium ion has delocalized an electron from its orbital spinmate resulting in an unstable electron "hole". Thus transfer of charge *from* an adjacent subunit, or transfer of energy *to* an adjacent subunit could be enhanced. This process may be analogous to acceptor impurities in semiconductors.

or wave 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^{2+} 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 transduction via Boolean logic. Within nerve cells, transfer of MT conformational, charge, or energy state could be "driven" ("execute function") by travelling nerve action potentials and/or associated transmembrane Ca^{2+} flux. Velocities of action potentials and accompanying Ca^{2+} flux (10 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 (Lakowicz

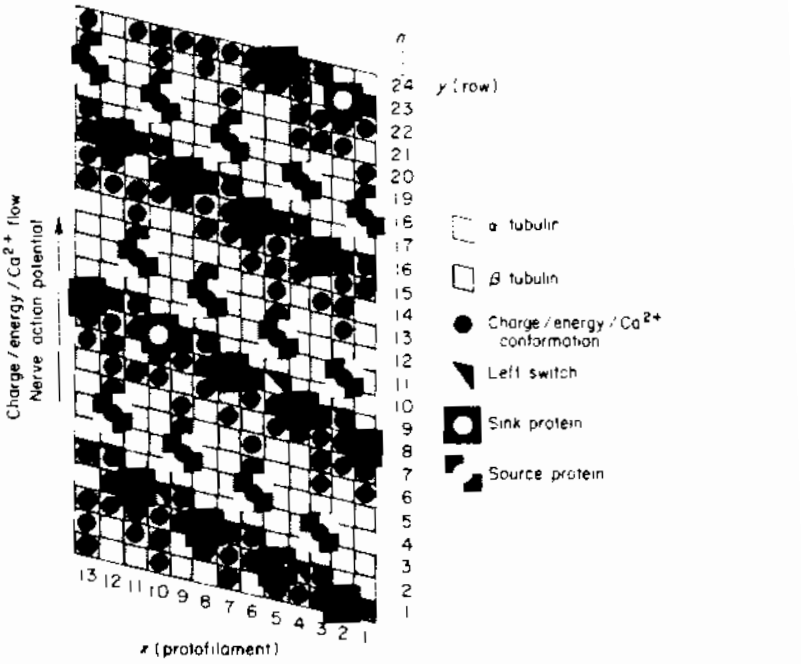

FIG. 3. Unwrapped microtubule (MT) grid as programmable switching matrix. Grid-like ray permits addressable tubulin subunits. "On–off" states may be Ca^{2+} related conformational states coupled to charge or energy quanta. "Sink" and "source" sidearm protein achment patterns ("leftward 3, up 1") represent electron microscopic evidence of MT ociated protein attachment (Burns, 1978). Left switch loci could be determined by various netic or experiential programming modes. Charge/energy/Ca^{2+} transfers may be driven nerve action potentials coupled by Ca^{2+} flux or cytoskeletal membrane attachments.

& Weber, 1973). Based on approximations of intraneuronal MT density fraction of brain which is neuronal, and average neuronal firing rates parallel computing in MT coupled to action potentials could approach 10^7 transfers/sec ("bits") in the human brain. The following arbitrary set of assumptive conditions describes one particular, possible mechanism for parallel computing and information processing in neuronal MT.

(1) At time (t) each tubulin subunit is in 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 protofilaments, or leftward along the three start helical row.

(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, polymerization effects, or changes due to environmental interactions. Tubulin binding to GTP, cations, tyrosylation, glycosylation, or other factors could induce conformational and energy states such that "straight ahead" transfer from the monomer is inhibited and "leftward" transfer promoted.) Alternately, pre-programming factors may determine which subunit loci will respond to Ca^{2+}.

(5) Charged MAPs bind at sites of charge/energy/Ca^{2+} abundance ("sink proteins"; charge, conformational energy, ions accepted) or charge/energy paucity ("source proteins": charge, energy, ions supplied). Shunting charge/energy transfers through sink-source circuits may control movement and function of MAP's which may extend laterally as contractile filamentous bridges which contact other MT in the geodesic cellular skeleton, transport cytoplasm and organelles, or regulate membrane function. Sequential, coordinated MAP activities such as axoplasmic transport may thus be controlled by pulsed MT transfers (Fig. 4).

Functional mechanical movement of MAPs including ATPase sidearm proteins such as dynein could be regulated by transfer patterns over time. A specific model of axoplasmic transport based on MT programmed sidearm protein activities is shown in Fig. 4. Unidirectional, specific transport of synaptic bound enzymes or precursors via a sliding filament is represented as a function of "on-off" states of the sidearms' anchoring MT subunits. Each sidearm is shown anchored to two subunits, two rows apart ("sink-source pair"). If either row subunit is occupied ("on") and the other row subunit is not occupied ("off") the sidearm contractile protein conforma-

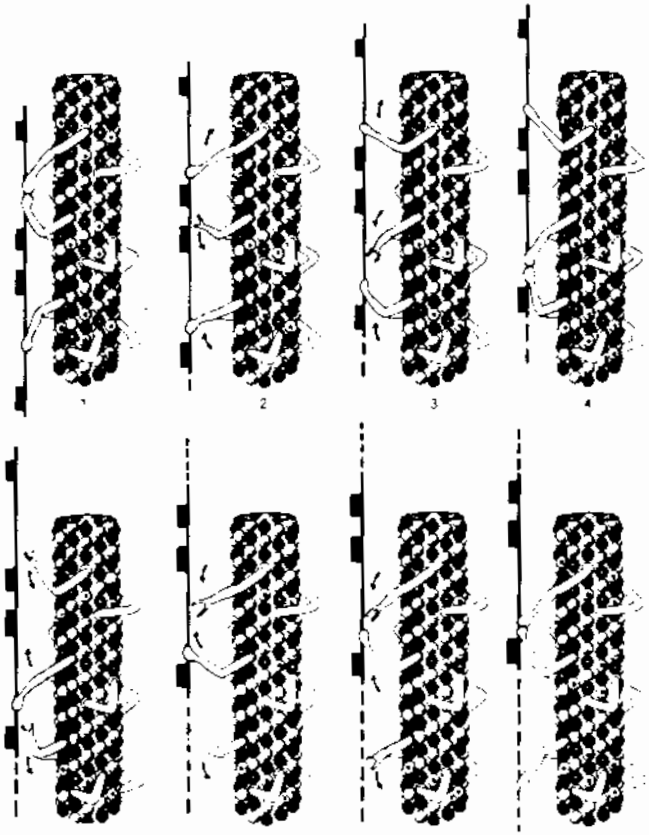

FIG. 4. "Computer-like" MT model of axoplasmic transport. A single column of MAP "sidearm" protein in a "bucket brigade" model of axoplasmic transport of a sliding filament carrying specific enzymes or precursors is portrayed. Each sidearm is anchored to two subunits, two rows apart. In this particular model, sidearms point towards an unopposed "on" subunit. Rotational and multidirectional MAP movements and transfer are also programmable. Ciliary and flagellar bending, cellular growth and movement, and other biological functions may be similarly viewed.

tionally points toward the "on" row. Thus, unidirectional axoplasmic transport may be regulated. Mechanical or biochemical "sensory" perturbations (Atema, 1973) of laterally projecting MAPs could also modulate MT function via feedback loops. Sink-source protein pairs and leftward switches could then be viewed as variable transistor or logic circuits programmable by electronic, biochemical, or mechanical interactions. Other possibly analogous technological functions occur in charge coupled devices, acoustic

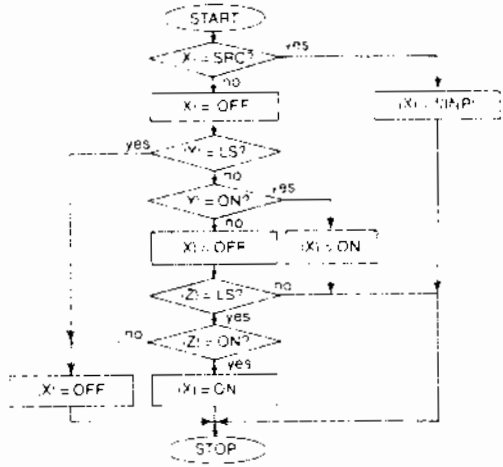

FIG. 5. Flow chart describing a decision process for MT quantal pulsed transfer and switching. Nerve action potential can drive MT transfers and "left switch" sites may be determined by genetic or experiential modes. (X) = condition of a given tubulin subunit (Y) = condition of a subunit directly below X; (Z) = condition of a subunit to adjacent right of X; SRC = source protein; LS = left switch protein; INP = factors affecting source charge

surface wave resonators, magnetic bubble memories, and Boolean switching matrices.

To illustrate MT-computer analogies, switching decisions based on left switch programming and neural pulsed transfer are represented in a flow chart in Fig. 5. MT programming could channel charge/energy/Ca^{2+} such that specifically arrayed subunits, $M(2, 1)$ $M(5, 2)$, 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 "leftward 3, up 1" observed pattern of MAP attachments (Burns, 1978) is expressed in Table 1 as a Fortran subprogram.

MT signalling could occur by modulated, pulsed traffic through associated proteins or by low intensity radiant field effects of nanosecond fluctuations in electromagnetic vectors. Such signalling 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 mitotic spindles, coupled to embryonic neural growth axes, and theoretically linked to organization patterns of cellular growth and functions (Burr & Nelson, 1946). MT spatial regularity

TABLE 1

Fortran subprogram plotting left switch sites to channel charge/energy/ions through MT loci known to bind functional proteins (Burns, 1978)

In a 2-dimension array $M(X, Y)$ is 0 or 1 (left or straight).

```
FOR Y = 1, 24          FOR N = 0, 23          100 M(X, Y) = 0
FOR X = 1, 13          FOR M = 1, 3           NEXT M
M(X, Y) = 1            X = X + M              NEXT N
NEXT X                 Y = Y + N
NEXT Y                 IF X = 14 GO TO 100
X = 2                  X = 1
Y = 2                  Y = Y + 3
```

of 4 nm intervals could possibly promote coherence and resonance among MT subunit excited 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 (Kovasznay & Arman, 1957; Maclachlan, 1962; Rogers, 1977). Interference patterns within the coherent wave fields (possible vectors: electric, magnetic, photon, biochemical, ionic, mechanical, sol-gel, soliton, etc) could reconstruct image type information as in holography (Gabor, 1968; Westlake, 1970; Hameroff, 1974, Pribram, 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 supermagnetism which manifest second order phase transitions as maximal resonance is approached (Sargent, 1973). Resonant phase transitions in level of awareness of specific neuronal information sets ("consciousness") might depend on MT density, MAP loci, charge/energy conformational 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 loci. Other macromolecular grid-like structures (actin-myosin, neurofilaments, myelin lamellae etc) could utilize similar information processing and regulation.

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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