SEARCH FOR QUANTUM AND CLASSICAL MODES OF INFORMATION PROCESSING IN MICROTUBULES: IMPLICATIONS FOR "THE LIVING STATE"

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Abstract
Dynamical activities within living eukaryotic cells are organized by microtubules, main structural components of the cytoskeleton and cylindrical polymers of the protein tubulin. Evidence and theoretical models suggest that states of tubulin may play the role of "bits" in classical microtubule computational automata. The advent of quantum information devices, key roles played by quantum processes in protein dynamics, and coherent ordering in the cell cytoplasm further suggest that microtubules may function as quantum computational devices, and that mesoscopic and macroscopic quantum states are characteristic of living systems. In this paper new results from molecular dynamics simulation based on recently obtained atomic structure of tubulin are presented which provide support for classical and quantum modes of microtubule information processing.

1. Introduction: Cytoplasm, microtubules and information processing

Organisms rely on complex interactions among living cells to enable functional activities of tissues and organs. However individual cells themselves perform quite complicated tasks. For example single cell protozoa like *paramecium* swim around, avoid obstacles and predators, find food and mates and have sex, all involving various activities of their "cytoskeleton". *Within* eukaryotic cells, processes such as mitosis, organelle movement, differentiation, sensory transduction and secretion require dynamical orchestration of cytoskeletal structures 1-3. How are such activities organized? Biochemical studies demonstrate signaling by reaction cascades of soluble molecules, however evidence suggests that the integration of "real time" intracellular activities requires phase transitions in cytoplasmic gels and dynamic activities of the cytoskeleton 4. Could the cytoskeleton/cytoplasmic gel provide a solid state "nervous system" within each cell?

Pondering seemingly intelligent activities of single cell protozoa, famed neuroscientist C.S. Sherrington 5 conjectured in 1951 that "of nerve there is no trace, but the cytoskeleton might serve". The shape and structure of cells is determined by the cytoskeleton, scaffoldings of filamentous protein polymers which include microtubules, actin and intermediate filaments. Traditionally considered as merely "bone-like" structural support, the cytoskeleton is now thought to be involved in intracellular signaling, information processing and cognition 6,7. Rigid microtubules interconnected by microtubule-associated proteins ("MAPs") are bound into a self-supporting dynamic tensegrity network, intertwined by actin filaments. The cytoskeleton also includes microtubule-based organelles called centrioles, membrane-bound microtubule-based cilia which protrude from the cell, and other proteins.

Microtubules, actin and other cytoskeletal proteins form a negatively-charged matrix on which polar cell water molecules are bound and ordered. When actin polymerizes the cytoplasm converts from an aqueous solution ("sol" state) to a solid, gelatinous "gel" state. In the cytoplasmic gel state cytoskeletal surfaces fill cell interiors to the extent that only 5 to 9 layers of water molecules fit between cytoskeletal surfaces, implying that under gel conditions cell water may be completely organized and structured. Ordered water is quite different from disordered bulk water in various properties including the solubility of ions. Thus actin polymerization and cytoskeletal dynamics can cause phase transitions which correspond with ion fluxes and voltage gradients independent of, or in concert with, membrane activities 4.

Among cytoskeletal components, microtubules (MTs) are directly involved in orchestrated cell activities, have the largest diameter (25 nanometers) and appear best suited for information processing. In *paramecium*, a carpet of

protruding MT-based cilia act as both sensory antennae and coherently beating motor oars to guide intelligent movements (and MT-based flagella propel many other cells). In mitosis, MT-based centrioles establish cell polarity, MT mitotic spindles pull chromosomes apart (in conjunction with cytoplasmic gel phase transitions), and MTs and other cytoskeletal structures establish daughter cell shape and function. Cilia and centrioles are also responsible for photodetection in primitive organisms 8, and cilia are found in all retinal rod and cone cells though their function is unclear. In neurons, MTs self-assemble to enable growth of axons and dendrites, serve as tracks on which motor proteins transport materials, maintain and regulate synapses, and have been implicated in cognition and consciousness. Wherever cellular organization and intelligence is required, MTs are present and involved. Many studies have correlated MT activities with higher level information processing in the brain 1-3,6-7, however direct evidence of MT signaling has been difficult. Vassilev et al 9demonstrated signal transmission along chains of MT subunit proteins ("tubulin") formed between excitable membranes, and Maniotis et al 10,11 showed functional signaling from membrane proteins via MTs to the cell nucleus. Albrecht-Buehler 8,12 has shown that cells respond to optical stimulation to redirect their movement via their centrioles, and several studies indicate that microtubules and/or centrioles mediate "delayed luminescence" (or "photon storage") in which optical stimulation results in prolonged (seconds to minutes) optical re-emission 13-15. The role MTs play in dynamical organization, and their "computer-like" lattice structure have suggested information processing capacities to many theorists 1-3,6-7.

MTs are cylindrical polymers of the protein tubulin and are 25 nanometers ("nm" = 10-9 meter) in diameter (Figure 1). MT lengths vary and may be quite long within some nerve structures. MT cylinder walls are comprised of 13 longitudinal protofilaments which are each a series of subunit proteins known as tubulin. Each tubulin subunit is an 8 nm by 4 nm by 5 nm heterodimer which consists of two slightly different classes of 4 nm, 55,000 dalton monomers known as alpha and beta tubulin. The tubulin dimer subunits within MTs are arranged in a hexagonal lattice which is slightly twisted, resulting in differing neighbor relationships among each subunit and its six nearest neighbors, and helical pathways which repeat every 3, 5 and 8 rows. Each tubulin has a dipole, in addition a large negative charge islocalized onthe surface of both monomers 16. Thus MTs can be considered "electrets": oriented assemblies of dipoles which are predicted to havepiezoelectric 17,18 and ferroelectric 7 properties. Biochemical energy is provided to microtubules in several ways: tubulin-bound GTP is hydrolyzed to GDP inMTs, and MAPs which attach to MTs at specific points on the MT lattice are phosphorylated. In addition MTs may possibly utilize nonspecific thermalenergy for "laser-like" coherent pumping, for example in the gigaHz range by a mechanism of "pumped phonons" suggested by Frohlich 19-22. Samsonovich et al 23 simulated coherent phonons in MTs and found phonon maxima corresponded with functional MT-MAP binding sites.

In most cells (neurons are a notable exception), the majority of MTs emanate from a centriole, a pair of cilia-like MT-based cylinders. The negative (alpha tubulin) ends of MTs are anchored at these microtubule organizing centers and the positive (beta tubulin) ends radiate outward toward the cell membrane. In neuronal axons long MTs are similarly arranged with negative ends toward the cell body/axon hillock, and positive ends toward the axon terminal. However in dendrites MTs are short, interrupted and of mixed polarity, arranged in local networks of MTs and MAPs (e.g. the dendrite specific "MAP2" implicated in learning). In primitive organisms MTs may be arranged

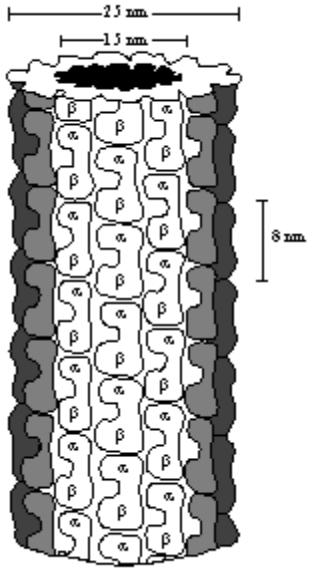

Figure 1. Microtubules are hollow cylindrical polymers of tubulin proteins, each a "dimer" of alpha and beta monomers arranged in a skewed hexagonal lattice.

in complex symmetrical arrays, such as the double spiral MT array found in axonemes of *actinosphaerum*24,25. MTs self-assemble from soluble tubulins under proper biochemical conditions, and the assembly may be somewhat chaotic unless stabilized by cellular factors ("dynamic instability"). MT growth and differentiation determine cell shape and function, however the dynamics of assembled, stable MTs regulate moment-to-moment cellular activities. The "permanent" and dynamical states of individual tubulins within an MT lattice thus become relevant in the context of MT-based information processing.

2. Protein conformational dynamics

Within MTs, individual tubulins may exist in different states which can change on various time scales. Multiple tissue-specific isozymes of tubulin occur, and tubulin may be structurally altered within an MT lattice by "post-translational modifications". Thus each MT may be a more-or-less stable mosaic heteropolymer of slightly different tubulins, with altered properties and functions accordingly. Roth and Pihlaja 26 suggested that stable patterns of tubulins within MTs determine MT function.

Tubulin may also exist in multiple possible dynamical conformational states, switching shapes on a time scale of nanoseconds 27,28. In one example of tubulin conformational change observed in single protofilament chains, one monomer can shift 27 degrees from the dimer's vertical axis 29 with associated changes in the tubulin dipole. Hoenger and Milligan 30 showed a conformational change based in the beta tubulin subunit.

In general, conformational states determine protein function and cellular movement. Individual proteins are synthesized as linear chains of amino acids which "fold" into three-dimensional conformation called the tertiary structure. The precise folding depends on attractive and repellent forces among various amino acid side groups, and a current view is that many possible intermediate conformations precede the final one 31. Predicting final three-dimensional folded shape using computer simulation has proven difficult if not impossible. This conundrum is known as the "protein folding problem" and so far appears to be "NP complete": the answer can be calculated in theory, but the space and time required of any classical computer is prohibitive.

The main driving force in protein folding occurs as uncharged non-polar amino acid groups join together, repelled by solvent water. These "hydrophobic" groups attract each other by van der Waals forces and bury themselves within the protein interior. Intra-protein hydrophobic pockets result, composed of side groups of non-polar (but polarizable) amino acids such as leucine, isoleucine, phenylalanine, tryptophan, tyrosine and valine. Klein-Seetharaman at al 32 have shown that protein folding involves nonlocal (quantum) interactions among tryptophan in hydrophobic pockets. Volumes of the pockets (~400 cubic angstroms, or 0.4 cubic nanometers) are roughly 1/30 to

1/250 the total volume of a single protein, and their physical solvent characteristics most closely resemble olive oil 33. How do weak quantum forces in tiny hydrophobic pockets regulate protein shape and function? As quantum mechanical van der Waals forces in hydrophobic pockets establish protein shape during folding, protein folding may be a quantum computation. Once folded, the same quantum mechanical van der Waals forces regulate dynamic conformational changes. Satinover 34 has emphasized the role of quantum tunneling of electrons in protein folding.

Proteins in a living state are dynamical, with transitions occurring at many scales, however conformational transitions in which proteins move globally and upon which protein function generally depends occur in the microsecond (10^-6 sec) to nanosecond (10^-9 sec) to 10 picosecond (10^-11 sec) time scale 35. Proteins are also only marginally stable. A protein of 100 amino acids is stable against denaturation by only ~40 kiloJoules per mole (kJ mol^-1) whereas thousands of kJ mol^-1 are available in a protein from side group interactions including van der Waals forces. Consequently protein conformation is a "delicate balance among powerful countervailing forces" 36.

The types of forces operating among amino acid side groups within a protein include charged interactions such as ionic forces and hydrogen bonds, as well as interactions between dipoles—separated charges in electrically neutral groups. Dipole-dipole interactions are known as van der Waals forces and include three types:

- Permanent dipole - permanent dipole
- Permanent dipole - induced dipole
- Induced dipole - induced dipole

Type 3 induced dipole - induced dipole interactions are the weakest but most purely non-polar. They are known as London dispersion forces, and although quite delicate (40 times weaker than hydrogen bonds) are numerous and influential. The London force attraction between any two atoms is usually less than a few kiloJoules, however thousands occur in each protein. As other forces cancel out, London forces in hydrophobic pockets can govern protein conformational states.

London forces ensue from the fact that atoms and molecules which are electrically neutral and spherically symmetrical nevertheless have instantaneous electric dipoles due to asymmetry in their electron distribution. The electric field from each fluctuating dipole couples to others in electron clouds of adjacent non-polar amino acid side groups. Due to inherent uncertainty in electron localization, London forces are quantum effects which may couple to "zero point fluctuations" of the quantum vacuum 37,38.

Quantum dipole oscillations within hydrophobic pockets were first proposed by Frohlich 19 to regulate protein conformation and engage in macroscopic coherence. Conrad 39 suggested quantum superposition of various possible protein conformations occur before one is selected. Roitberg et al 40 showed functional protein vibrations which depend on quantum effects centered in two hydrophobic phenylalanine residues, and Tejada et al 41 have evidence to suggest quantum coherent states exist in the protein ferritin. In protein folding, nonlocal quantum interactions among hydrophobic regions guide formation of protein tertiary conformation 32, suggesting protein folding may rely on quantum computation. As quantum effects may provide optimal modes for information processing in technological computers, quantum coherent superposition involving van der Waals London forces in hydrophobic pockets may be important in biological information processing, for example in microtubules. The mechanism of anesthetic gases which reversibly erase consciousness is by interfering with quantum mechanical van der Waals London forces in certain brain proteins (receptors, tubulin etc.)42.

Classical modes of information processing have been proposed in microtubules, and more recently quantum modes have also been suggested. The next section reviews proposed classical modes of microtubule information processing. Conformational changes in tubulins within microtubules may involve either “flexing” of the dimer, or “rocking” at the interface between adjacent dimers along the protofilament 29,30,43. In either case conformational changes may be triggered by/coupled to quantum events in hydrophobic regions acting as a “trigger” or “switch” for the protein. Such conformational changes may propagate along protofilaments, and perhaps along helical pathways within the microtubule lattice.

In filamentous proteins such as actin and MTs, propagating conformational changes can lead to collective changes in charge availability, ordering of water, ionic solubility and phase changes in cytoplasm, for example from a liquid solution ("sol") to a solid state gelationous "gel". In the latter, with actin polymerized, surfaces in cytoplasm may be separated by the equivalent length of 5 to 10 water molecules, meaning that in the gel phase virtually all cell water may be ordered, leading to radically different bulk phase properties. One property may be an environment hospitable to macroscopic quantum states with collective pumping dynamics resulting in laser-like Frohlich coherence, the lack of thermal water effects, and exclusion of ions which would cause decoherence. Quantum events within proteins may be amplified to result in large scale collective changes in biological systems.

3. Models of information processing in microtubules

A number of models have viewed the microtubule lattice as something like a computational matrix in which the states of individual tubulins represented fundamental units of information (e.g. like binary "bits" in a computer). Sherrington 5 raised the idea in a general way in 1951, and Atema 44 conjectured in 1973 that propagating tubulin conformational changes within cilia functioned as signals. Hameroff 45 proposed in 1974 that MTs acted as holographic diffractors, and Hameroff and Watt 46 suggested in 1982 that the MT structure acted as a computer-like switching matrix with input/output via MAPs. Other proposals in the 1990's include the following: Puck and Krystosek 47 suggested waves of phosphorylation/dephosphorylation along MT tubulins conveyed information, and Wang and Ingber 48 described a tensegrity communication structure among MTs and actin filaments. Non-linear soliton waves along MTs have been proposed 49, 50, and Cantiello et al 51 suggested that ion transfer along actin conveyed functional signals, a model that has been extended to ion transfer along MTs 52. Tuszynski et al 2 predicted MT ferroelectric effects and "spin glass" behavior, Albrecht-Buehler 8,12 suggested MTs convey infra-red photons, and Jibu et al 53 proposed MTs as quantum optical waveguides.

Other types of models have more specifically involved the tubulin lattice in computational processing. Hameroff and Watt 46 suggested that the state of each tubulin in the MT lattice functioned as an information "bit" which can exist in two or more conformational states coupled to the tubulin dipole. Subsequently computer simulations of tubulin dipoles coupled to neighbor dipoles modeled "cellular automaton" functions within MTs 54,55.

Cellular automata are lattices of fundamental ("cellular") units, each of which may exist in two or more states. At prescribed time steps, neighbor interactions among the units follow simple rules to determine the state of each "cell" at the subsequent time step. Simple rules among simple units can give rise to complex dynamical patterns. The term "cell" in cellular automata implies the fundamental unit, as traditionally biological cells have been considered fundamental units. Viewing MTs as "cellular automata" implies that the states of tubulin are the fundamental units, therefore we refer to these systems as MT automata, or molecular automata (Rasmussen et al, 55).

MT automata use tubulin conformations and dipoles as "cellular" states, dipole interactions between tubulins as neighbor rules and Frohlich coherent oscillations as time steps. Simulation of such systems produced dynamical patterns which propagate, interact and process information. Simulation of MT automata interconnected by microtubule-associated proteins (MAPs) show MT-MAP networks to be capable of learning .55.

MT automata offer a potentially huge capacity for cellular information processing. Biological cells contain approximately 10^7 tubulins 56, and switching at the Frohlich frequency in the nanosecond regime (10^9/sec) predicts roughly 10^16 operations per second, per cell. This capacity could account for the complex adaptive behaviors of single cell organisms like *paramecium*, and could increase the brain's information processing immensely. Conventional approaches focus on synaptic switching (roughly 10^11 brain neurons, 10^3 synapses/neuron, switching in the millisecond range of 10^3 operations per second) and predict about 10^17 bit states per second for a human brain 57. As the human brain contains about 10^11 neurons, nanosecond microtubule automata offer about 10^27 brain operations per second. But even if microtubule automata do provide the enhanced information processing for which they are capable, information processing *per se* fails to answer fundamental questions about the highest level of brain information processing: consciousness. Accordingly, given the potential for quantum processes in proteins and the advent of quantum information processing, proposals have been put forth for quantum computation in microtubules. This implies quantum coherence in the brain as a prerequisite. Perhaps as suggested in Erwin Schrödinger's famous book "What is Life" 58, quantum coherence is an essential feature of living systems. This possibility will be considered, but first we examine recent findings on relevant properties of tubulin and microtubules.

4. Simulations of tubulin and microtubule properties

Using the atomic resolution structure of tubulin from the Protein Data Bank (PDB) 59 provided by the electron diffraction crystallography of Nogales et al 60, we have determined the electrostatic charge, dipole moment and other characteristics of tubulin. Calculations of the potential energy were done with the aid of the "Tinker" molecular dynamics package 61 which showed that tubulin is quite highly negatively charged at physiological pH and that as much as 40% of the charge is concentrated on the carboxy ("C") -terminus which extends "tail-like" from the globular monomers (see below). First we examine electrostatic properties of tubulin excluding the C-termini (Table 1).

4.1. General properties excluding the C termini

The excess (negative charges) and dipole strengths for the tubulin dimer and alpha monomer were determined excluding the C termini and are shown in Table 1. The x-direction component coincides with the protofilament axis. The y-axis component is oriented radially towards the MT center, and the z-axis direction is tangential to the microtubule surface. The alpha monomer is in the direction of increasing x values relative to the beta monomer.

Table 1. Tubulin's Electrostatic Properties (C terminus tail region excluded)

Tubulin properties	Dimer	Alpha monomer
Electron charges	-10	-5
Overall dipole (Debyes)	1714	566
x component (Debyes)	337	115
y component (Debyes)	-1669	-554
z component (Debyes)	198	-6

4.2. Tubulin surface charge characteristics including C termini

Under "healthy" physiological conditions within cells (i.e. pH 7.2) each tubulin is shaped like a "dimer" of two roughly spherical, 4 nanometer diameter monomers but with linear "tails" extending another 4 to 5 nm outward from the tubulin (and MT outer) surface. These tails are comprised of the carboxy termini ("C termini") of the primary tubulin protein structure and contain 40% of the total (negative) charges on tubulin. Thus in normal conditions there are approximately 8-10 negative charges on each terminus "tail" extending out into the cytoplasm. A titration curve for the charges on tubulin as a function of pH is shown in Figure 2. The negatively charged tails attract positively charged "counterions" creating (with associated ordered water) a "Debye double layer" extending 4 to 5 nm perpendicular to the MT surface. A detailed map of the electric charge distribution on the surface of the tubulin dimer at physiological pH is shown in Figure 3.

At neutral pH, the C terminus negative charges cause it to remain extended due to the electrostatic repulsion within the tail, and between adjacent tails. Under more acidic conditions, the negative charges of the carboxy-termini are neutralized by associated hydrogen ions, allowing the tails to collapse into more compact forms by folding (Figure 4). Although this is probably the largest structural change which occurs due to changes in the cell's pH, other structural variations (genetic isozymes, post-translational modifications, ligand binding etc) may also affect the electrostatics of the tubulin dimer.

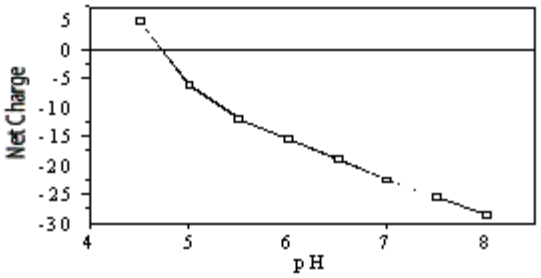

Figure 2. Titration curve for the tubulin alpha\beta heterodimer (including C-termini) as a function of pH; obtained with no salt and no intra-molecular charge compensation. Figure courtesy of D. Sackett 62.

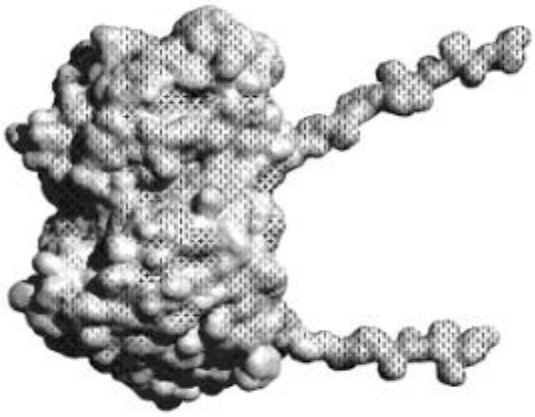

Figure 3. A map of the electric charge distribution on the surface of a tubulin dimer with C-termini tails present. Figure prepared using "MolMol". 63

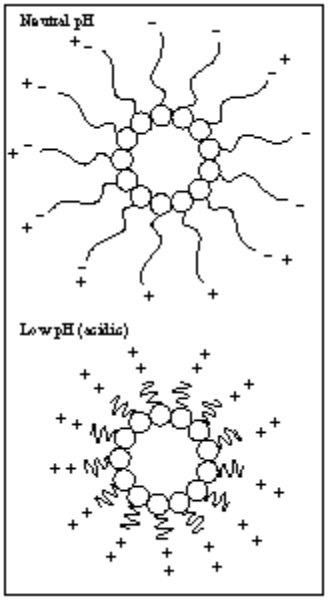

Figure 4. Cross-section of a MT including the carboxy-termini of the tubulin subunits. The folding shown of the carboxy-termini of the tubulin dimer demonstrates the change in the geometry of the molecule with pH. Neutral pH is shown on top, the tail folds at lower pH as the negative charges are neutralized.

4.3. Coulombic forces between adjacent tubulins

When two tubulin dimers are placed in each other's neighborhood and allowed to interact electrostatically, Coulomb forces establish a field of attraction. The brush strokes of Figure 5 represent the direction of the Coulomb force fields of attraction which indicate a hexagonal pattern which matches the microtubule skewed hexagonal lattice 7

4.4. Tubulin dipole moments

The dipole moment of an "isolated" tubulin dipole (as described in Table 1) is shown in Figure 6a. However tubulin dipoles in ionic solution and within a protofilament bring in other factors. For example when two dimers are bound within a protofilament, their positively and negatively charged ends form

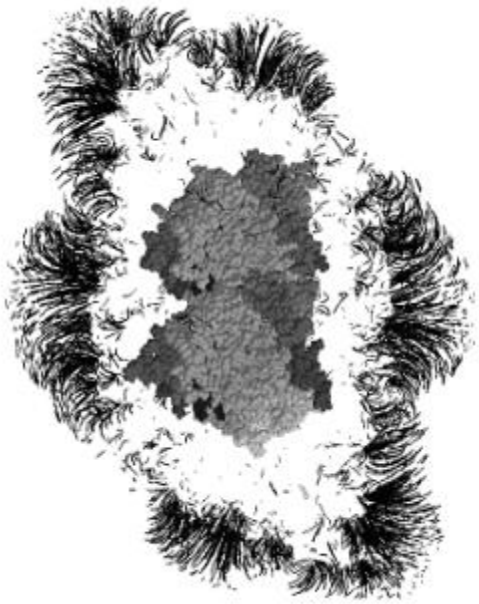

Figure 5. A view of the attractive regions about a tubulin dimer as would be experienced by another dimer. The smallest principal moment of inertia of the dimers is perpendicular to the page, the middle one is aligned vertically, the largest principal moment horizontally. See text for more details. Figure prepared using MolMol 63

a double layer with a net dipole moment along the protofilament axis (Figure 6b). Within each dimer, hydrophobic pocket with delocalizable electrons may develop internal (switchable) dipole moments (see below) due to electronic transitions on a positive background (Figure 6c). Finally, (Figure 6d) the C-termini which are negatively charged are surrounded by counter ions in solution leading to the formation of double layers surrounding the microtubule. However the principal contribution to the dipole moment of a tubulin dimer comes from the location of partial charges on the constituent amino acids. When this is applied to the microtubule structure (Figure 7), an anti-ferroelectric structure is predicted with permanent dipoles placed almost perpendicular to the surface of the MT cylinders, nearly cancelling each other due to rotational symmetry.

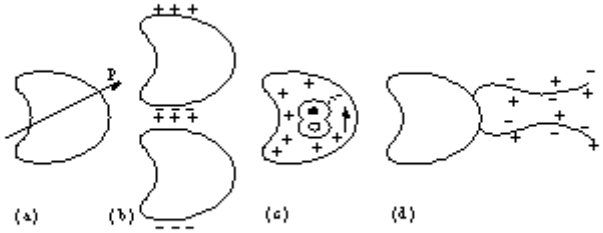

Figure 6. The various contributions to the dipole moment of a tubulin dimer: (a) the intrinsic dipole moment of the globular protein, (b) the double layer formed when two dimers are bound in a protofilament, (c) a possible internal dipole created by electronic transitions in the hydrophobic pocket, and (d) a double layer formed by counter ions surrounding the C-termini tails.

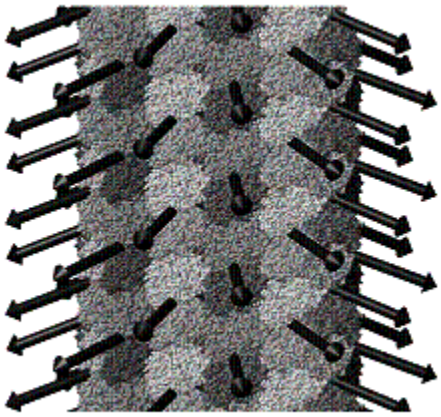

Figure 7. The arrows indicate the orientation of the permanent dipole moments of individual tubulin dimers with respect to the surface of a microtubule. Figure prepared using MolMol 63

4.5. Tubulin internal charge characteristics: a double well potential

Mapping electrostatic partial charges in the interior of tubulin dimer shows a region in the alpha monomer near the neck to the beta monomer of two areas of positive charge in the range of 100-150 meV. These positive potential areas are separated by a negative potential region of about 1.5 nm length. Thus this regions constitutes a double well potential which should enable quantum tunneling of electrons between the two wells since the energy depth is well above thermal fluctuations (kT=25 meV at room temperature). Hence thermal noise is not expected to destroy the tunneling effect. Electrostatic interactions inside the protein should be strong enough to couple the tunneling electrons to other excess electrons in tubulin. The dielectric constant inside tubulin is only 2, compared to roughly 80 in the water environment outside the microtubule,making the quantum electrostatic effects within tubulin 40 times stronger than electrostatic effects in the outside water environment outside the MT. Decoherence by electrostatic effects in the environment upon the quantum double well should thus be negligible (as should thermal effects). Consequently tunneling between the well minima may act as a "quantum switch" inducing quantum transitions of the electrons, and conformational state of the entire protein collectively.

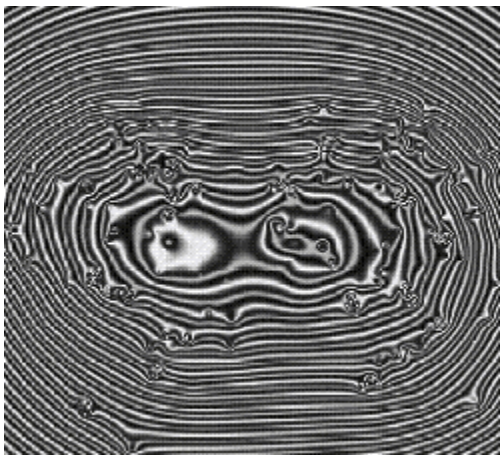

Figure 8. Electrostatic map of a horizontal slice through the alpha monomer near to the "neck" to the beta monomer of tubulin shows a "double well"of positive charge (MolMol63)

4.6. Tryptophan mapping

Within proteins "aromatic" (benzene or indole) electron resonant ring structures in the amino acids tryptophan, tyrosine, histidine and phenylalanine provide regions of delocalizable or polarizable electrons and electronic excited states. Tryptophan has a particular double ring (an "indole ring") which gives tryptophan the greatest electron resonance (and thus most fluorescence) among aromatic amino acids. Becker et al64 showed fluorescent resonance energy transfer (non-radiative photon exchange) between tryptophan and other aromatics in adjacent tubulins in microtubules, and between microtubules and membranes. In addition to fluorescence, indole rings may take part in electron transport (electrons flowing or tunneling between aromatics separated by several nanometers) or exciton hopping (electron excited states jumping between specific locations).

Locations of tryptophan were identified in the tubulin dimer and lines drawn between tryptophans separated by 2 nm or less (Figure 9). The tryptophans are arranged linearly along the long axis of the dimer, with two possible alternate paths connecting sites within 2 nm or less of each other. 65

Conventional wisdom indicates that electron tunneling or exciton hopping in proteins is only possible over distances under 1 nm. This is the “Foerster distance” (maximum length of an excitation to travel). However this pertains to free hopping via an inert medium like an ionic solution. Within proteins electron movements may be facilitated by “through bond hopping” over distances of 2 nm or more. Furthermore if there are sufficient available electrons to fill half or more of the available sites, then conditions can exist within proteins at physiological temperature for (semi)conductivity comparable to silicon or even semi-metals66. With dynamic water ordered at the protein surface, conductivity may be even further enhanced, and proton conduction can also occur. As described earlier, in some enzymes electron hopping between amino acid residues may span 3.5 nm or more67.

Projecting the tryptophan intra-protein pathways onto a microtubule cylindrical lattice reveals a pathway along protofilaments in which tryptophans are within 2 nm of the adjacent tryptophan (Figure 10). In Hameroff et al 65, we also looked at pathways of other aromatic amino acids and found possible pathways around the helical winding patterns intrinsic to the microtubule lattice structure (Figure 11). When the winding patterns are plotted on any given protofilament they are separated by numbers of tubulins which match the Fibonacci series (3, 5, 8, 13, 21…). Intersections of the winding patterns correspond with patterns of attachment of microtubule-associated proteins, which in turn correspond with cytoskeletal and cellular structure and function. Conduction pathways among aromatic rings in tubulin may mediate information processing in microtubules which governs cellular structure and function.

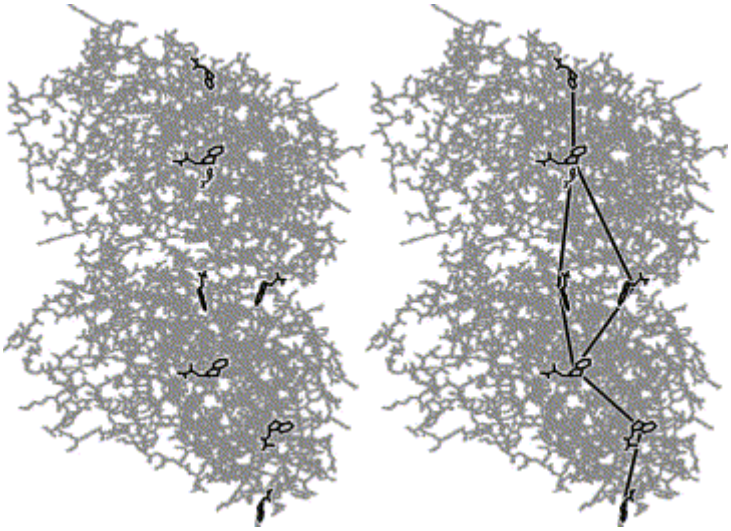

Figure 9.. The tubulin dimer with tryptophans within 2 nm or less of each other connected by lines. There are two possible paths between tryptophans in the two monomers.

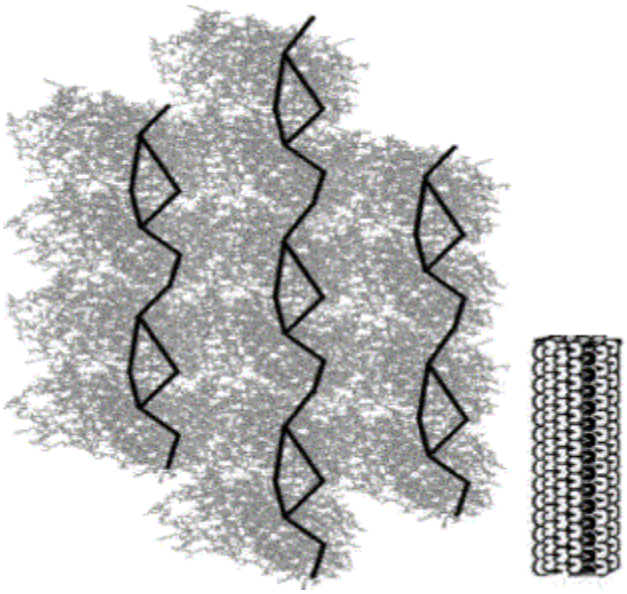

Figure 10. A lattice neighborhood of 7 tubulin dimers showing tryptophan pathways aligning along vertical protofilaments.
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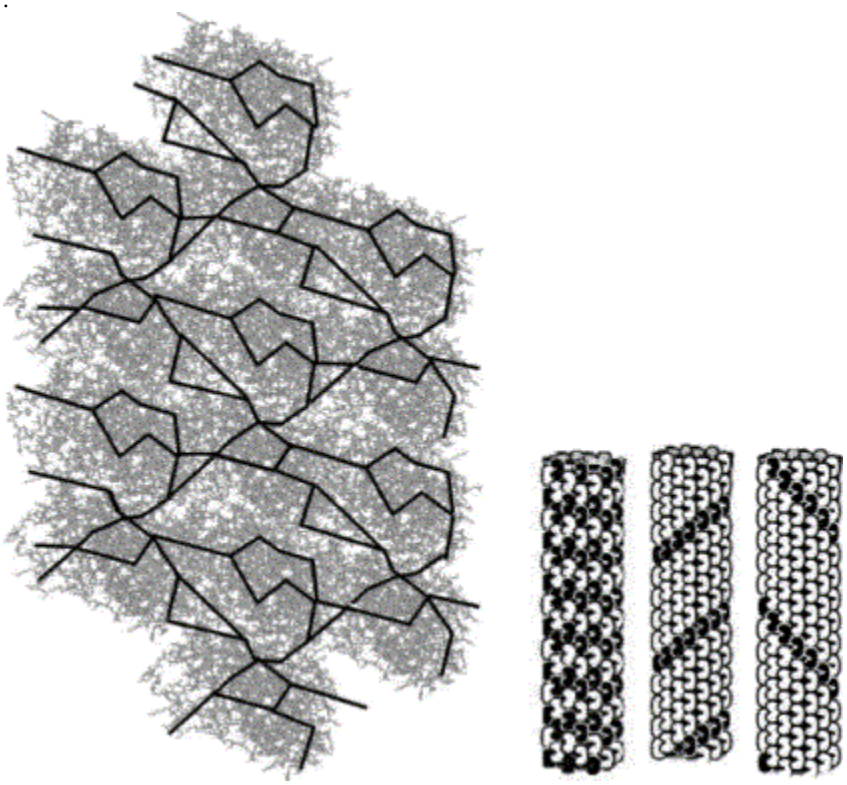

Figure 11. Left: A lattice neighborhood of 7 tubulin dimers with sites of aromatic amino acids phenylalanine and histidine connected. As shown on right, these pathways correspond with 3 additional winding patterns in the microtubule lattice.

5. Quantum information processing

Reality seems to be described by two separate sets of laws. At our everyday large scale classical, or macroscopic world, Newton's laws of motion and Maxwell's equations for electromagnetism are sufficient. However at small scales in the "quantum realm" (and the boundary between the quantum and classical realms remains elusive) objects may exist in two or more states or places simultaneously—more like waves than particles and governed by a "quantum wave function". This property of multiple coexisting possibilities, known as quantum superposition, persists until the superposition is measured, observed or interacts with the classical world or environment. Only then

does the superposition of multiple possibilities "reduce", "collapse", "actualize", "choose" or "decohere" to specific, particular classical states 68,69.
Early experiments seemed to show that even if a machine measured a quantum superposition, the multiple possibilities persisted until the machine's results were observed by a conscious human. This led leading quantum theorists including Bohr, Heisenberg and Wigner to conclude that consciousness caused quantum state reduction, that consciousness "collapsed the wave function" (the "Copenhagen interpretation", reflecting the Danish origin of Niels Bohr, its leading proponent).

To illustrate the apparent absurdity of this conclusion, in the 1930's Schrödinger devised his famous thought experiment now known as Schrödinger's cat. A living cat is placed in a closed box into which poison can be released by a quantum event, e.g., sending a photon through a half-silvered mirror. Being a quantum entity, the (unobserved) photon must be in superposition of both passing through and not passing through the mirror, thus both releasing and not releasing the poison. Consequently, according to the Copenhagen interpretation, until a conscious being were to open the box to observe, the cat is both dead and alive. Schrödinger's point was that this scenario was absurd and that the conscious observer interpretation was incorrect. Modern interpretations would say that any interaction with the environment (i.e. opening the box regardless of whether a conscious observer were present) would "decohere" the quantum superposition. Nonetheless the fate of an isolated quantum superposition, for example an isolated large scale system evolving from, or amplified by, a small scale superposition, remains unknown. Thus events in the quantum realm are not only bizarre, the boundary between the quantum realm and our everyday macroscopic "classical" world remains obscure.

Quantum superpositions and reduction are currently being developed technologically for future use in quantum computers which promise to revolutionize information processing (and perhaps make comparisons between the brain/mind and quantum computers inevitable). First proposed in the early 1980's70, quantum computers are now being developed in a variety of technological implementations (electron spin, photon polarization, nuclear spin, atomic location, magnetic flux in a Josephson junction superconducting loop, etc.). Whereas conventional classical computers represent digital information as "bits" of either 1 or 0, in quantum computers, "quantum information" may be represented as quantum superpositions of both 1 and 0 (quantum bits, or "qubits"). While in superposition, qubits interact with other qubits (by entanglement, see below) allowing computational interactions of enormous speed and near-infinite parallelism. After the computation is performed the qubits are reduced (e.g. by environmental interaction/decoherence) to specific classical states which constitute the solution 71.

Another quantum property is entanglement in which components of a system become unified, governed by one common quantum wave function. If one member of an entangled system is measured or perturbed, other members are instantaneously affected, even over great distances. One example of entanglement is the famous "EPR pairs" (after Einstein, Podolsky and Rosen who posed the problem as a thought experiment in the 1930's). Imagine two members of a quantum system (e.g. two electrons with complementary spin: if one is spin up, the other is spin down, and vice versa). If the paired electrons (each in superposition of both spin up and spin down) are separated by being sent along different wires, say to two different locations miles apart from each other, they each remain in superposition. However when one superpositioned electron is measured by a detector at its destination and reduces/collapses to a particular spin, (say spin up), its entangled twin miles away instantaneously reduces/collapses to the complementary spin down. The experiment has been done repeatedly with electron spin pairs, polarized photons and other quantum systems and always results in instantaneous reduction to the complementary classical state72,73. The instantaneous, faster than light coupling, or "entanglement" (useful in quantum cryptography) remains unexplained, although a potential mechanism holds that quantum information from the collapsed member travels backwards in time to the conjoined origin, then forwards in time to the second pair member 74.

Another form of entanglement occurs in quantum coherent systems such as Bose-Einstein condensates (proposed by Bose and Einstein decades ago but realized in the 1990's). A group of atoms or molecules are brought into a quantum coherent state such that they surrender individual identity and behave like one quantum system, marching in step and governed by one quantum wave function. If one component is perturbed all components "feel" it and react accordingly.

Quantum computing, quantum cryptography and other revolutionary quantum information technologies require isolation from environment to avoid decoherence, and are thus operated at extreme cold to avoid thermal vibrations. At first glance the possibility of significant macroscopic quantum states in biological systems such as microtubules seems unlikely 75, however given the potential evolutionary advantage for quantum information processing biological systems such as microtubules may have evolved mechanisms to deal with decoherence and sustain quantum states 76.

In the next section the molecular dynamics simulations based on recently obtained atomic structure of tubulin and described above are reviewed in terms of features which may avoid decoherence and support quantum modes suitable for quantum information processing.

6. Implications for quantum information processing in microtubules

6.1 "Carboxy termini" antennae

There are several potential implications for quantum and classical modes of information processing of the charged C termini tails and double layer. The tails should be sensitive probes of the environment, acting as "antennae" for MT processes. Moreover they should be quite stiff due to negative charge repulsion, and support high frequency oscillations coupled among the stiff, charged rods on the MT surface in a frequency range (depending on precise stiffness) in the 1010 to 1011 Hz range. This is consistent with the coherent oscillations predicted by Frohlich, and could be coupled to dynamics of the MT "body" and adjacent water.

On the other hand, for example under influence of an influx of positive ions, the C termini may double back onto the tubulin and form a loop or bind lengthwise to the tubulin surface. The charged double layer (C termini tails, counter ions and ordered water) created by the C termini tails, along with the intrinsic tubulin dipole create a spatially organized, periodic structure surrounding MTs along which protons and ions can travel, e.g. as solitons. Such protonic conduction has been demonstrated for actin filaments by Cantiello 51 (c.f. Dreisman 52) and a similar mechanism should occur for MTs whose tubulin components have a larger dipole than do actin monomers (although in both cases the dipole is oriented nearly perpendicular to the long axis of the filament polymer).

Most variations across cells and species in tubulin primary structure occur in the C-termini suggesting the C-termini may be devoted to a specialized function such as signaling rather than purely structural mechanisms. Tubulins without C-termini are little affected by GTP hydrolysis while incorporating C-termini into tubulin leads to huge GTP induced dipole changes, again suggesting signaling, in this case induced by GTP.

The Debye double layer created by the C-termini, counter ions and ordered water may also be important as a screening/isolation mechanism for quantum processes in MTs. Quantum computers require isolation from environmental interactions dues to either electrostatic effects or thermal vibrations which tend to disrupt quantum states due to "decoherence". Beyond the so-called "Debye length" electrostatic effects may be ignored due to screening. This is the dominant length for screening as the "Bjerrum length" (~ 1 nm) which compares electrostatic effects with thermal effects is equal to or larger than the Debye length (~ 1 to 2 nm depending on salt concentration). We expect that thermal interactions as well as electrostatic interactions from ions or other environmental entities, be they charge-charge, charge-dipole, or van der Waal's forces occurring ~1 to 2 nm beyond the Debye double layer (hence 5 to 7 nm above the MT/tubulin surface) are "unfelt" by MTs. Thus under specific conditions quantum processes in MTs may be unperturbed by environmental influences.

A key role for the C termini and associated Debye double layer in communication is suggested by the fact that with increased acidity (e.g. below pH 7.2) or reduced osmolality (below 150 mM) the C termini become less rigid and preferentially collapse back onto the tubulin/MT surface. In these conditions cells do not die but their functions cease. While membrane functions including ion pumps are also impaired by low pH and osmolality, the C termini and Debye layer may be more sensitive and the dominant effect.

6.2 Quantum double well

As described earlier in this paper, mapping electrostatic partial charges in the interior of tubulin dimers shows a region in the alpha monomer near the neck to the beta monomer of two positively charged areas in the range of 100-150 meV. These positively charged areas are separated by a negatively charged region of about 1.5 nm. Thus this regions constitutes a double well potential which should enable quantum tunneling of electrons between the two wells since the energy depth is well above thermal fluctuations (kT=25 meV at room temperature). Hence thermal noise is not expected to destroy the tunneling effect. Electrostatic interactions inside the protein should be strong

enough to couple the tunneling electrons to other excess electrons in tubulin, thus inducing quantum transitions of the electrons (and the entire protein) collectively. The dielectric constant inside tubulin is only 2, compared to roughly 80 in the water environment outside the microtubule, making the quantum electrostatic effects within tubulin 40 times stronger than electrostatic effects in the water environment outside the MT. Decoherence by electrostatic effects in the environment upon the quantum double well should thus be negligible (as should thermal effects). Consequently tunneling between the well minima may act as a "quantum switch" inducing quantum transitions of the electrons, and conformational state of the entire protein collectively.

Outside the double well mobile electrons including surface electrons may be ejected into the conduction band which is expected to begin some 1 to 1.5 eV above the valence band. Thus transition to a conducting state in tubulin and microtubules can arise under the influence of external forces such as membrane potentials that may provide a needed bias. Electron tunneling between the wells would also isolate single, unpaired electrons with implications for the emergence and interactions between magnetic dipoles.

6.3 Spintronics and magnetic dipoles

As demonstrated by Bras 77, microtubules align parallel to strong magnetic fields in the range of 7-30 Tesla. Bras concluded that anisotropic diamagnetism is responsible for MT alignment in these magnetic fields, however the magnetic alignment may instead be due to uncompensated spins in mobile electrons, e.g. those tunneling between potential wells. A single uncompensated electron per tubulin dimer is sufficient to account for the magnetic alignment of MTs provided the spins form an ordered state (weak or induced ferromagnetism). This is consistent with rotational ordering of microtubules due to the torques between the net magnetization and the externally applied magnetic field and with the predicted electronic tunneling between the paired members of the double well.

Moreover, recent work of Binhi et al 78 indicates that unpaired electron spins form networks in protein interiors which are shielded from the environment and lead to functional quantum interactions at physiological temperature. (Macroscopic quantum coherence of nuclear spins has been shown to occur inthe human brain and correlate with conscious processes 79,80). Aligned tubulin electron spins can also oscillate their projection along the MT axis giving rise to spin waves, a phenomenon well-documented in ferromagnetic solids. These should be detectable in spin resonance experiments though the appropriate frequency range and dispersion relations have to be calculated.

6.3 Conformational coupling and quantum superposition

Due to the Mossbauer effect 81, electronic motions in tubulin should be coupled to nuclear motions via a recoil phenomenon, connecting protein conformation to electronic states. The movement would be slight due to the disparity in mass between the single electron and the mass of the protons – a one nanometer shift in location of a single electron would shift the nuclear mass, and hence protein conformation, by only 10-8 nanometers. The charge shift of a single electron is perhaps more likely to exert an effect on conformation.39 Although the quantum character of a single electron tunneling between two wells separated by a nanometer would also result in quantum superposition of nuclear locations, albeit a separation distance of only 10-8 nm. However if the electron coupled to other charges such an effect may be magnified. But even so a miniscule superposition/separation of the location of all nuclei in a tubulin dimer (110,000 dalton) of 10-8nm (or 10-7 nm if 10 electron charges were coupled) would still have consequences. According to Penrose OR such a superposition/separation would lead to objective reduction if enough tubulins were so involved. Consequently, observation of the Mossbauer spectra should demonstrate these transitions, as predicted by Sataric et al 49 assuming isotopic substitutions can be made in the tubulin structure.

6.4 Exciton hopping

Tryptophans in tubulin are aligned in chains in which the individual tryptophans are within 1 to 2 nm of each other. Theory and evidence from delayed luminescence suggests exciton hopping in microtubules 82,83, and the tryptophan pathways may be the route. Such exciton hopping could mediate the observed delayed luminescence which seems to emanate from microtubules.

6.5 Quantum entanglement

C termini tails are candidates for quantum coherent oscillation and entanglement due to resonant dipole coupling effects. If two or more tails are coherently coupled (Frohlich) and a field imparts on them, their quantum states may become entangled. Such entanglement may form the basis of quantum associative memory, particularly if coupled to arrangement of binding of microtubule-associated proteins (MAPs) 84

6.6. Super-radiance and self-induced transparency

Using quantum field theory, Jibu et al 5 have proposed that Frohlich oscillations in microtubules dynamically order water in the hollow microtubule core, leading to quantum optical characteristics known as super-radiance and self-

induced transparency which can mediate macroscopic quantum coherence. The present results indirectly support this possibility by accounting for Frohlich dynamics enhanced by the C termini on microtubule exteriors.

7. Conclusion

Molecular dynamics simulations of tubulin and microtubules based on recently obtained atomic resolution structure reveal several possible mechanisms supporting quantum information processing. In addition to experimental verification, further theory is needed which can integrate these various modes. In the light of vanguard quantum information technology, four billion years of evolution may have endowed microtubules with capabilities beyond our current comprehension.

If microtubules utilize quantum information, cell interiors must be conducive to mesoscopic and macroscopic quantum states, implying that such states are an important and perhaps essential feature of life. The living state is a process generally described in terms of its properties and functions such as self-organization, metabolism (energyutilization), adaptive behavior, reproduction, and evolution. Whether or not this functional description is complete is a matter of contention. Two broad types of approaches have attempted to characterize the essential nature of the life process: (1) functionalism and (2) vitalism85.

Functionalism implies that life is independent of its material substrate. For example, certain types of self-organizing computer programs can exhibit life-like functions, and "artificial life" proponents view such systems as "alive." Functionalists also point out that life's material substrate doesn't distinguish biological matter. Proteins, DNA, carbohydrates, fats, and other biomolecular components are made of the same atoms and elements that make up inanimate substances. Bolstered by the success of genetic engineering, functional/reductive approaches dominate molecular biology. "Life" is ascribed to an emergent property of biochemical processes. Any vitalistic life force or energy field is deemed unnecessary and unacceptable.

Nonetheless, a commonly held contrary viewpoint is that functional descriptions fail to capture an essential self-organizing "unitary oneness" present in living systems. To nineteenth-century biologists this quality was ascribed to a "life force," "elan vital," or energy field. Then, as molecular and cell biology began to reveal the biochemical and physical processes involved in cellular activities, the apparent need for a life force waned, and "vitalists" (or "animists") were vilified. In modern reductionist science the notion of a life force, energy or information field has remained almost taboo.

However, whereas nineteenth-century vitalism was based either completely on electromagnetics or on forces outside the realm of science, a "quantum vitalist" perspective may be taken in which life derives from quantum states in cytoplasm, organized by microtubules and other cytoskeletal structures. This paper proposes several likely candidates in the search for quantum modes and pathways of information transfer and processing at a subcellular level. The living statee may be a state of quantum coherent unity organized in cytoplasm and cytoskeletal proteins.

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