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**A new theory of the origin of cancer:
Quantum coherent entanglement, centrioles, mitosis and differentiation**

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Abstract:

Malignant cells are characterized by abnormal segregation of chromosomes during mitosis (“aneuploidy”), generally considered a *result* of malignancy originating in genetic mutations. However recent evidence supports a century-old concept that maldistribution of chromosomes (and resultant genomic instability) due to abnormalities in mitosis itself is the primary cause of malignancy rather than a mere byproduct. In normal mitosis chromosomes replicate into sister chromatids which are then precisely separated and transported into mirror-like sets by structural protein assemblies called mitotic spindles and centrioles, both composed of microtubules. The elegant yet poorly understood ballet-like movements and geometric organization occurring in mitosis have suggested guidance by some type of organizing field, however neither electromagnetic nor chemical gradient fields have been demonstrated or shown to be sufficient. It is proposed here that normal mirror-like mitosis is organized by quantum coherence and quantum entanglement among microtubule-based centrioles and mitotic spindles which ensure precise, complementary duplication of daughter cell genomes and recognition of daughter cell boundaries.

Evidence and theory supporting organized quantum states in cytoplasm/nucleoplasm (and quantum optical properties of centrioles in particular) at physiological temperature are presented. Impairment of quantum coherence and/or entanglement among microtubule-based mitotic spindles and centrioles can result in abnormal distribution of chromosomes, abnormal differentiation and uncontrolled growth, and account for all aspects of malignancy. New approaches to cancer therapy and stem cell production are suggested via non-thermal laser mediated effects aimed at quantum optical states of centrioles.

Key words: Cancer, centrioles, differentiation, genomic instability, malignancy, microtubules, mitosis, mitotic spindles, neoplasm, quantum coherence, quantum computation, quantum entanglement, quantum theory, stem cells

Theories of the origin of cancer: mutation, aneuploidy, genomic instability

Malignant cells divide and multiply uncontrollably. They evade built-in autodestruct mechanisms, stimulate formation of blood vessels to feed themselves, and can invade other tissues. Proper differentiation – the process by which genetic expression leads to

specific cell types (phenotypes) – is lost. Despite intense efforts and recognition of predisposing factors (e.g. carcinogens, reactive oxidants, genetic/family history) cancer remains an enormous problem.

In the early 20th century German biologist Theodor Boveri observed cell division (“mitosis”) in normal and cancerous cells (Boveri, 1929). Whereas normal cells exhibited symmetrical, bipolar division of chromosomes into two equal mirror-like distributions (Figure 1), Boveri noticed that cancer cells were different. Cancer cells showed imbalanced divisions of chromosomes, with asymmetrical and multipolar unequal (“aneuploid”) distributions (Figure 2 and 3). Boveri suggested that aberrant processes in mitosis itself caused abnormal distribution of chromosomes and genes. He reasoned that most abnormal distributions would be non-viable, but some would lead to viable cells and cancerous differentiation with uncontrollable proliferation. But because no recurrent pattern occurred—the aneuploidy changed from generation to generation (what is now called “genomic instability”)—the majority of scientists assumed the abnormal distribution of chromosomes were effects, rather than causes of malignancy and that cancer originated from intrinsic chromosomal changes. In retrospect, genomic instability is a logical consequence of abnormal mitosis. Nonetheless, the belief that cancer resulted from genetic mutations became the “standard dogma” (Gibbs, 2003).

As DNA and genetics became understood and prominent, the idea that cancer is the result of cumulative mutations became entrenched. Specific alterations in a cell’s DNA, spontaneous or induced by carcinogens, change the particular proteins encoded by cancer-related genes at those spots. Two particular kinds of genes were identified as being potentially relevant to cancer. The first included tumor suppressor genes which normally restrain cells’ tendencies to divide. Presumably mutations affecting these genes disabled them, removing beneficial effects of suppressors. The second group included oncogenes which stimulate growth, or cell division. Mutations leading to cancer were thought to lock oncogenes into a permanently active state.

However in the era of genetic engineering, oncogene/suppressor theory has failed to explain cancer. No consistent set of gene mutations correlate with malignancy; each tumor may be unique in its genetic makeup. In fact tremendous genetic variability occurs within individual tumors, and genomic instability—changes in the genome with subsequent cycles of mitosis—is now seen as the major pathway to malignancy (Marx, 2002).

Some specific DNA factors are indeed related to genomic instability. These include unrepaired DNA damage, stalled DNA replication forks processed inappropriately by recombination enzymes, and defective telomeres which protect ends of chromosomes. But again, inherent DNA mutation and sequelae—the “standard dogma”—don’t explain the entire picture. Other approaches suggest that a combination of DNA defects and other problems are responsible for genomic instability and malignancy.

One approach is called “modified dogma” which revives an idea from 1974 by Lawrence A. Loeb and colleagues (Loeb et al., 1974) who noted that random mutations, on average,

would affect only one gene per cell in a lifetime. Some other factor—carcinogen, reactive oxidants, malfunction in DNA duplication and repair machinery—is proposed to increase the incidence of random mutations (Loeb et al., 2003). Another approach is “early instability” (Nowak et al., 2002) which suggests that master genes are critical to cell division—if they are mutated, mitosis is aberrant. But master genes are still merely proposals.

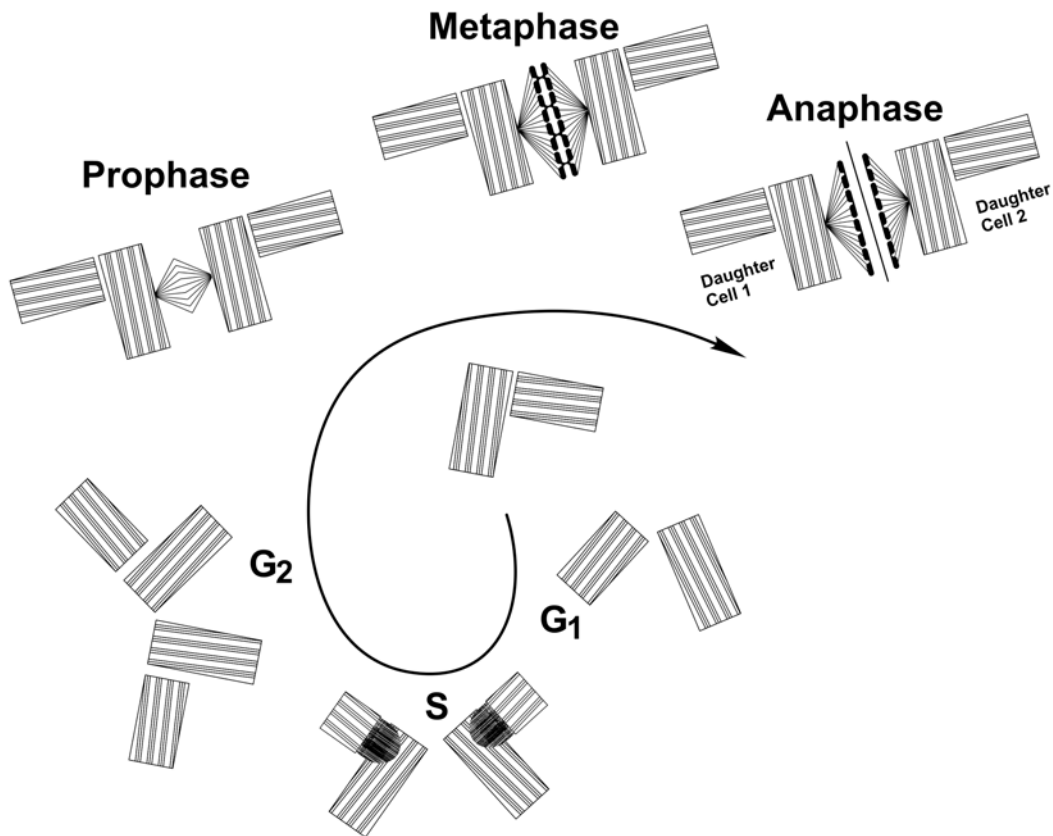


Figure 1. Modifications to the centriole in the normal cell cycle and mitosis (not to scale: centrioles are ~750 nanometers in length and 200 nanometers outer diameter, much smaller than mitotic spindles). Center: centriole as two perpendicular cylinders. Clockwise from center (G1, S and G2 occur during “Interphase” which precedes and follows mitosis): in G1 phase centriole cylinders separate. In S phase centrioles replicate, each cylinder forming a new perpendicular cylinder via connecting filamentous proteins. G2 phase: centrioles separate and begin to migrate. Prophase: centrioles move apart and microtubules form the mitotic spindles between the centrioles. Metaphase: mitotic spindles attach to centromeres/kinetochores on opposite sides of each paired chromosome (only 4 of which are shown). Anaphase: Paired chromosomes separate into sister chromatids and are moved by (and move along) mitotic spindles to newly forming daughter cells. Modified from Hagan et al. (1998) by Dave Cantrell.

Another idea returned to Boveri’s suggestion that the problems lie with the molecular machinery of mitosis which, under normal circumstances, results in precisely equal separation of duplicated chromosomes. The “all-aneuploidy” theory (Duesberg et al.,

2000) proposes that cells become malignant before any mutations or intrinsic genetic aberrancy. With the exception of leukemia, nearly all cancer cells are aneuploid. Thus malignancy is more closely related to maldistribution of chromosomes than to mutations on the genes within those chromosomes. Experiments show that genomic instability correlates with degree of aneuploidy.

What causes aberrant mitosis? Asbestos fibers and other carcinogenic agents are known to disrupt normal mitosis. Certain genes trigger and regulate mitosis, and experimentally induced mutations in these genes result in abnormal mitosis and malignancy. However such mutations in mitosis-regulating genes have not been found in spontaneously occurring cancers. Thus mitosis *itself*, the dynamical, ballet-like mechanical separation of chromosomes into two perfectly equal paired sets, may be at the heart of the problem of cancer. However the organization of mitosis is not understood.

Mitosis and differentiation

Under normal conditions chromosomes replicate into “sister chromatids” which remain attached to each other at a single point via a structure called a centromere/kinetochore. Chromatids are then separated and pulled apart into two identical sets by remarkable molecular machines called mitotic spindles which attach to the chromatid centromere/kinetochore (Hagan et al., 1998). The spindles are composed of microtubules (centromere/kinetochores also contain microtubule fragments). Once separated, sister chromatids are known as daughter chromosomes.

The microtubule spindles pull the daughter chromosomes toward two poles anchored by microtubule organizing centers (MTOCs), or centrosomes (as they are known in animal cells). Centrosomes are composed of structures called centrioles embedded in an electron-dense matrix composed primarily of the protein pericentrin. Each centriole is a pair of barrel-like structures arranged curiously in perpendicular tandem (Figures 4 and 5), and (like mitotic spindles) are comprised of microtubules, self-assembling polymers of the protein tubulin. In centrioles, microtubules are fused longitudinally into triplets; nine triplets are aligned, stabilized by protein struts to form a cylinder which may be slightly skewed (Dustin, 1984). New cylinders self-assemble/replicate perpendicular to existing cylinders, and centriole replication involves self-assembly of two new cylinders from each pre-existing cylinder of the pair which constitutes the centriole (Figure 1-3, G1, S and G2 phases). The two perpendicular pairs then separate resulting in two centrioles.

Centrioles are the specific apparatus within living cells which trigger and guide not only mitosis, but other major reorganizations of cellular structure occurring during growth and differentiation. Somehow centrioles have command of their orientation in space, and convey that information to other cytoskeletal structures. Their navigation and gravity sensation have been suggested to represent a “gyroscopic” function of centrioles (Bornens, 1979). The mystery and aesthetic elegance of centrioles, as well as the fact that in certain instances they appear completely unnecessary, have created an enigmatic aura

“Biologists have long been haunted by the possibility that the primary significance of centrioles has escaped them” (Wheatley, 1982).

The initiation of mitosis (“S” of interphase into prophase) involves centriole replication, separation and migration to form the mitotic poles to which spindles attach (Nasmyth, 2002). The opposite end of each spindle affixes to centromeres/kinetochores on specific

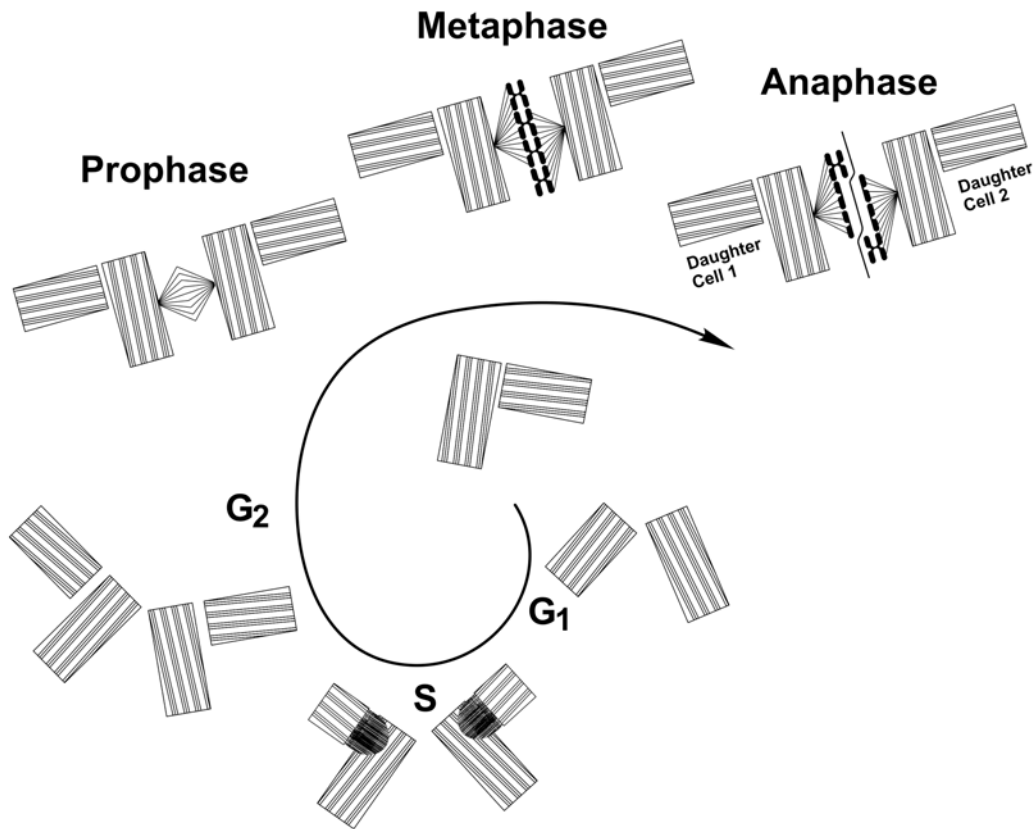


Figure 2. Abnormal centriole activities in mitosis leading to aneuploidy. As in Figure 1 except that during metaphase the centriole/spindle binding of chromatids is defective and asymmetrical leading to maldistribution of chromosomes in the anaphase daughter cells. Each daughter cell is missing an entire chromosome and has an extra chromatid, hence an abnormal genotype. By Dave Cantrell.

chromatids, so that proper separation of centrosomes/centrioles results in separation of chromosomes into equal sets forming the focal point of the two daughter cells (Figure 1).

There are a number of questions regarding mitosis, but one compelling issue is how all the intricate processes are coordinated in space and time by centrioles to generate a geometric structure that maintains itself at steady state. Indeed, the mitotic apparatus resembles a crystalline structure, however it is also a dynamic, dissipative system. A

review in *Science* concluded: “Robustness of spindle assembly must come from guidance of the stochastic behavior of microtubules by a field” (Karsenti, 2001). Without any real evidence some conclude that chromosomes generate some type of field which organizes the centrioles and spindles. However Boveri and later Mazia (1970) believed the opposite, that spindle and centrosome/centriole microtubules generated an organizing field or otherwise regulated the movement of chromosomes and orchestration of mitosis.

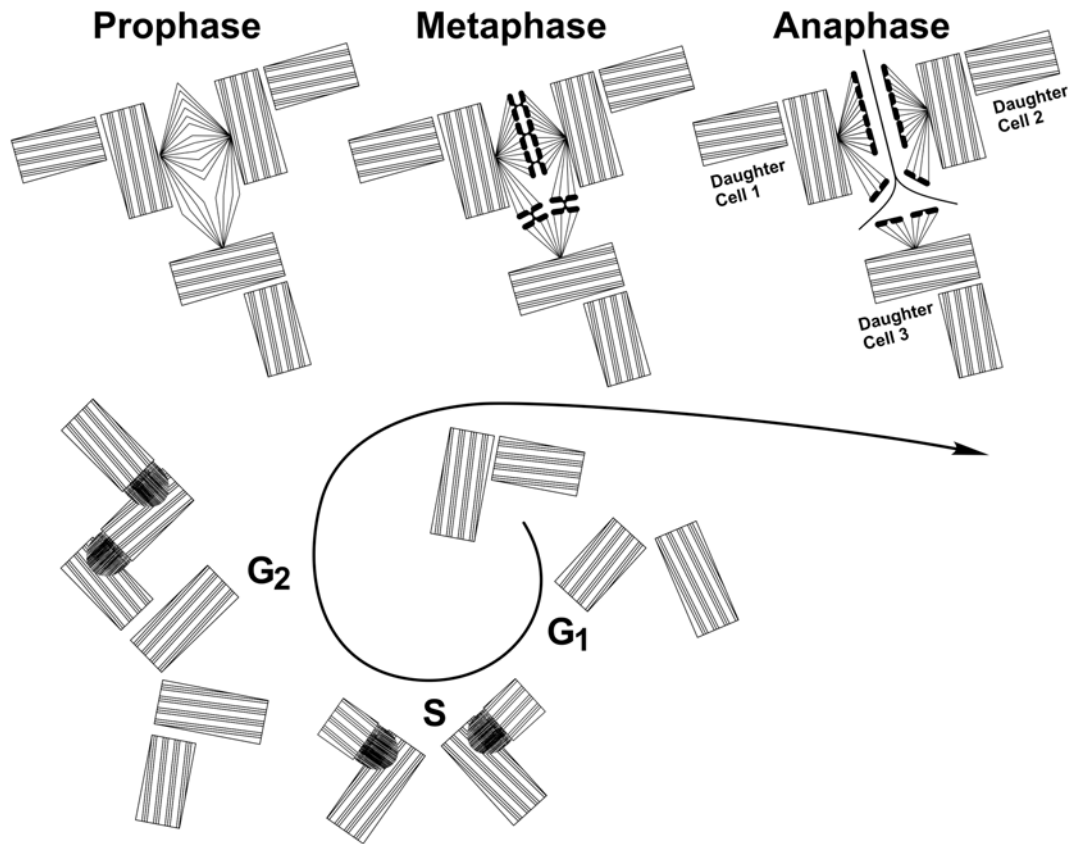


Figure 3. Abnormal centriole activities in mitosis leading to aneuploidy. As in Figures 1 and 2 except that defective centriole replication continues in G2 producing 3 centrioles which form abnormally distributed spindles in prophase and abnormal chromosome distribution/genotypes in metaphase and anaphase. This results in chromosomes maldistributed among 3 daughter cells. By Dave Cantrell.

As centrosomes/centrioles organize the spindles (which anchor in the pericentrin matrix surrounding centrioles), it seems most likely that centrosomes/centrioles are the primary organizers of mitosis.

Cultured cells in which centrosomes are removed by microsurgical techniques, leaving the cell nucleus and cytoplasm, are called karyoplasts. Maniotis and Schliwa (1991) found that karyoplasts reestablish a microtubule organizing center near the nucleus and form mitotic spindles. Karyoplasts can grow but do not undergo cell division/mitosis. Khodjakov et al. (2002) destroyed centrosomes by laser ablation in cultured cells and found that a random number (2 – 14) of new centrosomes formed in clouds of pericentrin.

In any case centrosomes/centrioles are essential to normal mitosis (Marx, 2001; Doxsey, 1998; Hinchcliffe et al., 2001) and impairment of their function can lead to genomic instability and cancer (Szuromi, 2001; Pihan, 1999). Multiple and enlarged centrosomes have been found in cells of human breast cancer and other forms of malignancy (Lingle et al., 1998; 1999; Pihan et al., 2003). Wong and Stearn (2003) showed that centrosome number, hence centriole replication, is controlled by factors intrinsic to the centrosome/centrioles (i.e. rather than genetic control). Referring to the centrosome as the “cell brain”, Kong et al (2002) attributed malignancy to aberrant centrosomal information processing.

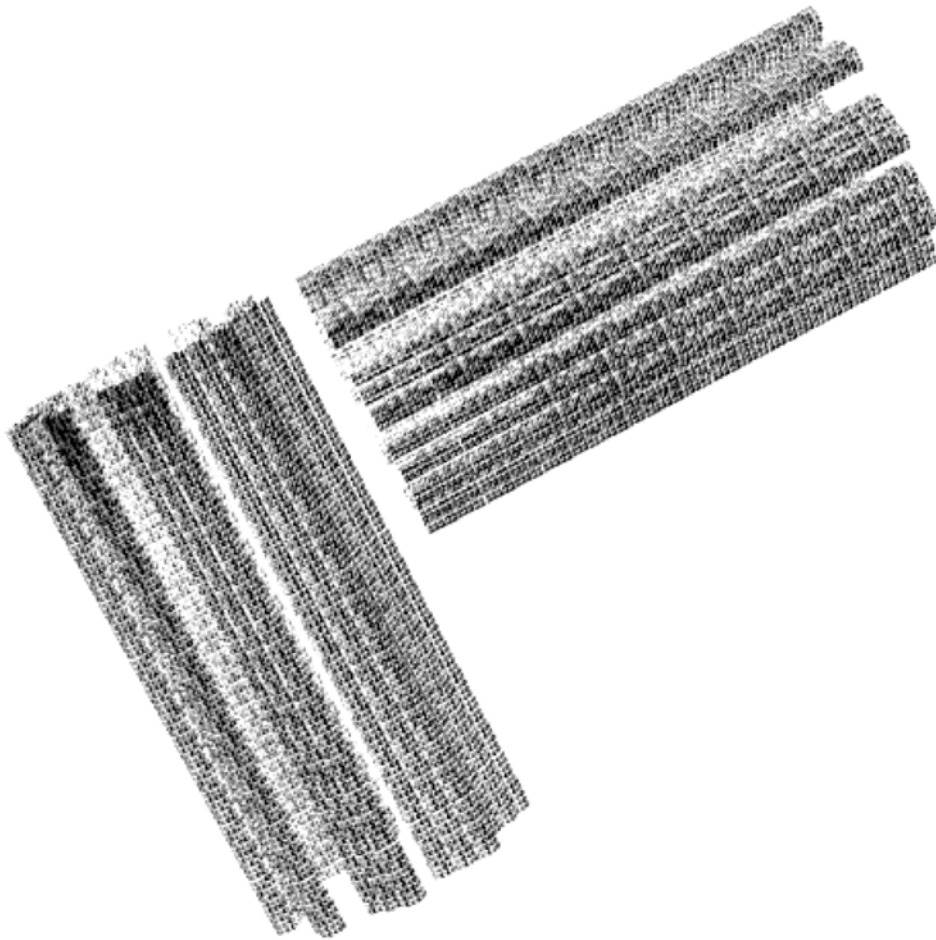


Figure 4. A centriole is comprised of two cylinders (as shown in Figure 5) arranged in perpendicular tandem. Each cylinder is 750 nanometers (0.75 microns) in length. By Dave Cantrell.

In other forms of intracellular movement and organization, microtubules and other cytoskeletal structures are the key players. So it is logical that they also organize mitosis. But something is missing. What type of organizational field, information processing or principle might be occurring in mitosis? Recent attempts to explain higher brain functions have suggested that microtubules within neurons and other cells process information, and may utilize certain *quantum* properties. If so, these same properties could also explain aspects of mitosis and normal cell functions lost in malignancy.

Subsequent to mitosis, embryonic daughter cells develop into particular types of cells (“phenotypes”), e.g. nerve cells, blood cells, intestinal cells etc., a process called differentiation. Each (normal) cell in an organism has precisely the same set of genes. Differentiation involves “expressing” a particular subset of genes to yield a particular phenotype. Neighbor cells and location within a particular tissue somehow convey signals required for proper gene expression and differentiation. For example an undifferentiated “stem cell” placed in a certain tissue will differentiate to the type of cell in the surrounding tissue. However the signaling mechanisms conveyed by surrounding cells to regulate differentiation are unknown.

Cancer cells are often described as poorly differentiated, or undifferentiated – lacking refined properties characteristic of a particular tissue type, and unmatched to the surrounding or nearby normal tissue. Abnormal genotypes (e.g. from aberrant mitosis or mutations) can disrupt normal differentiation, but again the mechanisms of normal differentiation (genotype to phenotype) are unknown.

It seems likely that centrioles play key roles in differentiation. Situated close to the nucleus, centrioles can transduce intra-cellular signals to regulate gene expression (Puck and Krystosek, 1992). As “commander” of the cytoskeleton, centrioles can determine cell shape, orientation and form. And centrioles have the information storage and processing capacity to record the “blueprints” for a vast number of phenotypes, all possible states of differentiation in a specific organism. The key question in differentiation is how signals/communication from neighboring and surrounding tissues mediate gene expression. While chemical messengers and chemical gradients are possible mechanisms (e.g. Niethammer et al., 2004), a more elegant, efficient and practical method may involve nonlocal quantum interactions (e.g. entanglement) among microtubules and centrioles in neighboring and nearby cells.

Microtubules and centrioles

Interiors of eukaryotic cells are structurally organized by the cell cytoskeleton which includes microtubules, actin, intermediate filaments and microtubule-based centrioles, cilia and basal bodies (Dustin, 1984). Rigid microtubules are interconnected by microtubule-associated proteins (“MAPs”) to form a self-supporting, dynamic tensegrity network which, along with actin filaments, comprises a negatively-charged matrix on which polar cell water molecules are bound and ordered (Pollack, 2001).

Microtubules are cylindrical polymers of the protein tubulin and are 25 nanometers ($\text{nm} = 10^{-9}$ meter) in diameter (Figure 6). The cylinder walls of microtubules are comprised of 13 longitudinal protofilaments which are each a series of tubulin subunit proteins (Figure 6). 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 the cylinder wall are arranged in a hexagonal lattice which is slightly twisted, resulting in differing neighbor relationships among each subunit and its six nearest neighbors (Dustin, 1984). Pathways along neighbor tubulins form helices which repeat every 3, 5 and 8 rows (the “Fibonacci series”).

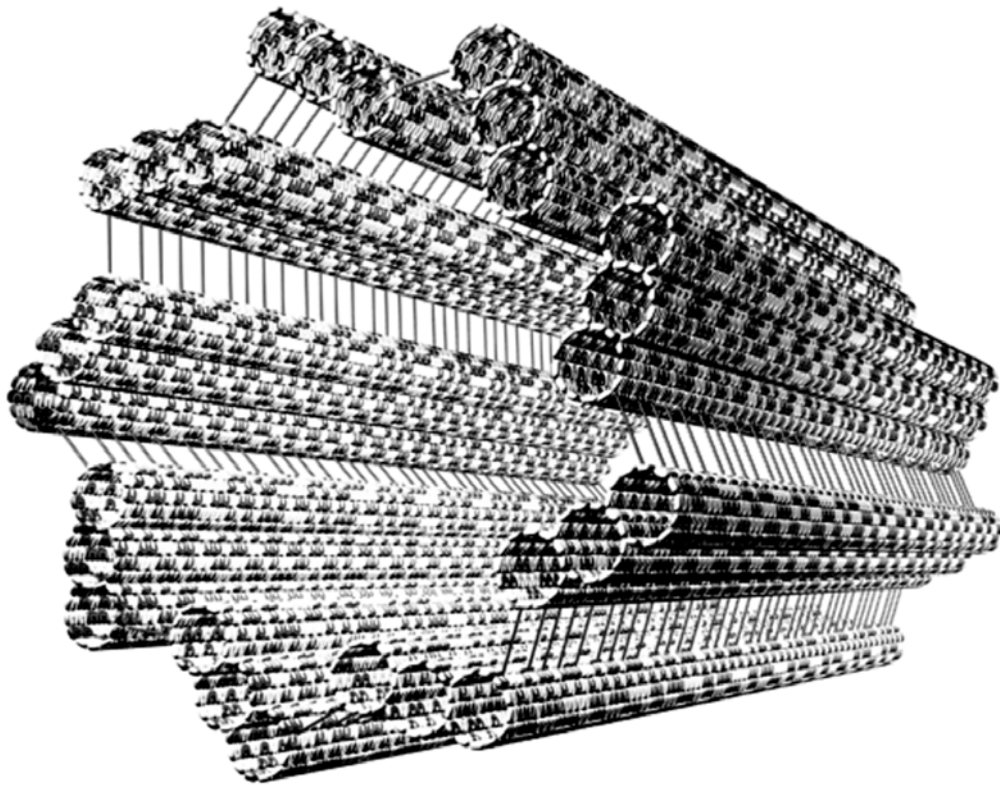


Figure 5. Centriole cylinder (one half of a centriole) is comprised of 9 microtubule triplets in a skewed parallel arrangement. Each microtubule is comprised of tubulin proteins (Figure 6), each of which may be in one or more possible conformational states (illustrated as e.g. black or white). The cylinder inner core is approximately 140 nanometers in diameter and the cylinder is 750 nanometers in length. By Dave Cantrell.

Each tubulin has a surplus of negative surface charges, with a majority on the alpha monomer; thus each tubulin is a dipole (beta plus, alpha minus). Consequently microtubules can be considered “electrets”: oriented assemblies of dipoles which are predicted to have piezoelectric, ferroelectric and spin glass properties (Tuszynski et al., 1995). In addition, negatively charged C-termini “tails” extend outward from each

monomer, attracting positive ions from the cytoplasm and forming a plasma-like “Debye layer” surrounding the microtubule (Hameroff et al., 2002).

Biochemical energy is provided to microtubules in several ways: tubulin-bound GTP is hydrolyzed to GDP in microtubules, and MAPs which attach at specific points on the microtubule lattice are phosphorylated. In addition microtubules may possibly utilize nonspecific thermal energy for “laser-like” coherent pumping, for example in the GigaHz range by a mechanism of “pumped phonons” suggested by Fröhlich (1968; 1970; 1975). Simulation of coherent phonons in microtubules suggest that phonon maxima correspond with functional microtubule-MAP binding sites (Samsonovich et al., 1992).

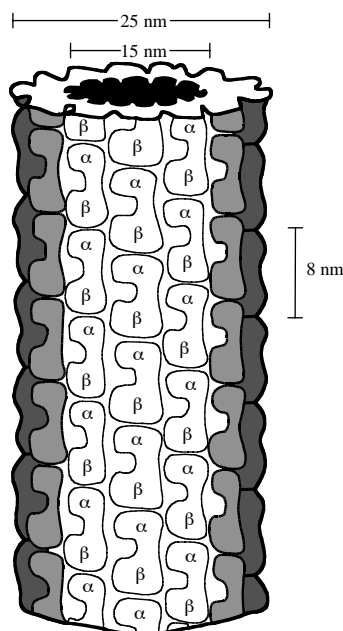


Figure 6. Microtubules are hollow cylindrical polymers of tubulin proteins, each a “dimer” of alpha and beta monomers.

In centrioles (as well as cilia, flagella, basal bodies etc.) microtubules fuse into doublets or triplets. Nine doublets or triplets then form larger barrel-like cylinders (Figure 5) which in some cases have internal structures connecting the doublets/triplets. The nine doublet/triplets are skewed, and centrioles move through cytoplasm by an “Archimedes screw” mechanism.

Albrecht-Buehler (1992) has shown that centrioles act as the cellular “eye”, detecting and directing cell movement in response to infra-red optical signals. (Cilia, whose structure is nearly identical to centrioles, are found in primitive visual systems as well as the rod and cone cells in our retinas.) The inner cylindrical core of centrioles is approximately 140 nanometers in diameter and 750 nanometers in length, and, depending on the refractive

index of the inner core, could act as a waveguide or photonic band gap device able to trap photons (Figure 8). Tong et al (2003) have shown that properly designed structures can act as sub-wavelength waveguides, e.g diameters as small as 50 nanometers can act as waveguides for visible and infrared light.

Historic work by Gurwisch (1922) showed that dividing cells generate photons (“mitogenetic radiation”), and recent research by Liu et al (2000) demonstrates that such biophoton emission is maximal during late S phase of mitosis, corresponding with centriole replication. Van Wijk et al.(1999) showed that laser- stimulated biophoton emission (“delayed luminescence”) emanates from peri-nuclear cytoskeletal structures, e.g. centrioles. Popp et al (2002) have shown that biophoton emission is due to quantum mechanical “squeezed photons”, indicating quantum optical coherence. The skewed helical structure of centrioles may be able to detect polarization or other quantum properties of photons such as orbital momentum.

Unlike centrioles, cilia and flagella bend by means of contractile proteins which bridge between doublets/triplets. The coordination of the contractile bridges are unknown, however Atema (1973) suggested that propagating conformational changes along tubulins in the microtubule doublet/triplets signaled contractile proteins in an orderly sequence. Hameroff and Watt (1982) suggested that microtubules may process information via tubulin conformational dynamics (coupled to dipoles) not only longitudinally (as Atema proposed) but also laterally among neighbor tubulins on the hexagonal microtubule lattice surface, accounting for computer-like capabilities. Rasmussen et al (1990) showed an enormous potential computational capacity of microtubule lattices (and microtubules interconnected by MAPs) via tubulin-tubulin dipole interactions, with the dipole-coupled conformational state of each tubulin representing one “bit” of information. The regulation of protein conformational states is an essential feature of biological systems.

Tubulin conformational states

Within microtubules, individual tubulins may exist in different states which can change on various time scales (Figure 7). Permanent states are determined by genetic scripting of amino acid sequence, and multiple tissue-specific isozymes of tubulin occur (e.g. 22 tubulin isozymes in brain: Lee et al., 1986). Each tubulin isozyme within a microtubule lattice may be structurally altered by “post-translational modifications” such as removal or addition of specific amino acids. Thus each microtubule may be a more-or-less stable mosaic of slightly different tubulins, with altered properties and functions accordingly (Geuens et al., 1986).

Tubulins also change shape dynamically. In one example of tubulin conformational change observed in single protofilament chains, one monomer can shift 27 degrees from the dimer's vertical axis (Melki et al.,1989) with associated changes in the tubulin dipole (“open versus closed” conformational states). Hoenger and Milligan (1997) showed a conformational change based in the beta tubulin subunit. Ravelli et al. (2004)

demonstrated that the open versus closed conformational shift is regulated near the binding site for the drug colchicine. Dynamic conformational changes of particular tubulins may be influenced, or biased, by their primary or post-translational structures.

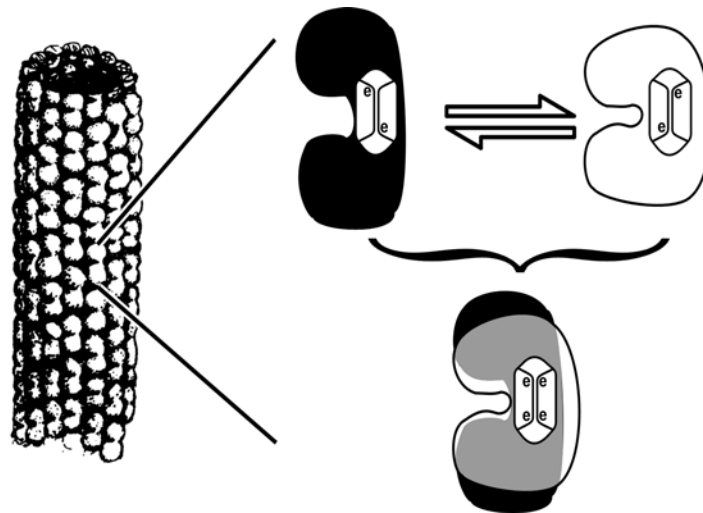


Figure 7. Tubulin protein subunits within a microtubule can switch between two (or more) conformations, coupled to London forces in a hydrophobic pocket in the protein interior. Right (bottom): Each tubulin is proposed to also exist in quantum superposition of both conformational states Penrose and Hameroff (1995; c.f. Hameroff and Penrose 1996a; 1996b).

In general, 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 (Karplus and McCammon, 1983). Proteins are 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 amino acid side group interactions. Consequently protein conformation is a "delicate balance among powerful countervailing forces" (Voet and Voet, 1995).

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:

- 1) Permanent dipole - permanent dipole
- 2) Permanent dipole - induced dipole
- 3) 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 (in some cases) spherically symmetrical, nevertheless have instantaneous electric dipoles due to asymmetry in their electron distribution: electrons in one cloud repel those in the other, forming dipoles in each. 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, the London forces which regulate tubulin states are quantum mechanical and subject to quantum uncertainty.

In addition to electron location, unpaired electron spin may play a key role in regulating tubulin states. Unpaired electron spin is basically a tiny magnet and microtubules are ferromagnetic lattices which align parallel to strong magnetic fields, accounted for by single unpaired electrons per tubulin. Atomic structure of tubulin shows two positively charged areas (~100-150 meV) near the alpha-beta dimer "neck" separated by a negatively charged area of about 1.5 nanometers (Hameroff and Tuszynski, 2003). This region constitutes a double well potential which should enable inter-well quantum tunneling of single electrons and spin states since the energy depth is significantly above thermal fluctuations ($kT=25$ meV at room temperature). The intra-tubulin dielectric constant is only 2, compared to roughly 80 outside the microtubule. Hence neither environmental nor thermal effects should decohere quantum spin states in the double well. Spin states and superposition of unpaired tunneling electrons should couple to excess tubulin electrons and global tubulin conformational states including tubulin quantum superposition states. Tubulin subunits within microtubules may be regulated by quantum effects.

The strange world of quantum reality

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) paradox reigns. 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 "decoheres" via interaction 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. The nature of quantum state reduction—the boundary between the quantum and classical worlds—remains mysterious (Penrose, 1989; 1994).

Another quantum property is entanglement in which components of a system become unified, governed by one common quantum wave function. The quantum states of each component in an entangled system must be described with reference to other components,

though they may be spatially separated. This leads to correlations between observable physical properties of the systems that are stronger than classical correlations. Consequently, measurements performed on one component may be interpreted as “influencing” other components entangled with it.

Because of the implication for non-local, instantaneous (therefore faster than light) influence, Einstein disliked entanglement (and quantum mechanics in general) deriding it as “spooky action at a distance”. Einstein, Podolsky and Rosen (1935) formulated the “EPR paradox”, a thought experiment intended to disprove entanglement. Imagine two members of a quantum system (e.g. two paired electrons with complementary spin: if one is spin up, the other is spin down, and vice versa – Tables 1 and 2, top). If the paired electrons (both in superposition of both spin up and spin down) are separated from each other by being sent along different wires, say to two different locations miles apart from each other, they each remain in superposition of both spin up and spin down. 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 separated twin (according to entanglement) must instantaneously reduce/collapse to the complementary spin down. The experiment was actually performed in 1983 with two detectors separated by meters within a laboratory (Aspect et al., 1982) and showed, incredibly, that complementary instantaneous reduction did occur! Similar experiments have been done repeatedly with not only electron spin pairs, but polarized photons sent along fiber optic cables many miles apart and always results in instantaneous reduction to the complementary classical state (Tittel et al., 1998). The instantaneous, faster than light coupling, or “entanglement” remains unexplained, but is being implemented in quantum cryptography technology (Bennett et al., 1990). (Though information may not be transferred via entanglement, useful correlations and influence may be conveyed.)

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. Bose Einstein condensates (“clouds”) of cesium atoms have been shown to exhibit entanglement among a trillion or so component atoms (Vulsgaard et al., 2001).

There are apparently at least two methods to create entanglement. The first is to have components originally united, such as the EPR electron pairs, and then separated. A second method (“mediated entanglement”) is to begin with spatially separated non-entangled components and make simultaneous quantum measurements coherently, e.g. via laser pulsations which essentially condense components (Bose-Einstein condensation) into a single system though spatially separated. This technique was used in the cesium cloud entanglement experiments and other quantum systems and holds promise for quantum information technology.

Quantum superposition, entanglement and reduction are currently being developed technologically for future use in quantum computers which promise to revolutionize information processing. First proposed in the early 1980's (Benioff, 1982), quantum computers are now being developed in a variety of technological implementations (electron spin, photon polarization, nuclear spin, atomic location, magnetic flux in Josephson junction superconducting loops, 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) 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 (Milburn, 1998).

Are microtubules quantum computers?

Quantum dipole oscillations within proteins were first proposed by Fröhlich (1968; 1970; 1975) to regulate protein conformation and engage in macroscopic coherence. Conrad (1994) suggested quantum superposition of various possible protein conformations occur before one is selected. Roitberg et al (1995) showed functional protein vibrations which depend on quantum effects centered in two hydrophobic phenylalanine residues, and Tejada et al (1996) have evidence to suggest quantum coherent states exist in the protein ferritin. In protein folding, nonlocal quantum electron spin interactions among hydrophobic regions guide formation of protein tertiary conformation (Klein-Seetharaman et al., 2002), suggesting protein folding may rely on spin-mediated quantum computation.

In the context of an explanation for the mechanism of consciousness, Penrose and Hameroff (1995; c.f Hameroff and Penrose 1996a; 1996b; Hameroff 1998) have proposed that microtubules within brain neurons function as quantum computers. The basic idea is that conformational states of tubulins, coupled to quantum van der Waals London forces, exist transiently in quantum superposition of two or more states (i.e. as quantum bits, or "qubits"). Tubulin qubits then interact/compute with other superpositioned tubulins by nonlocal quantum entanglement. After a period of computational entanglement tubulin qubits eventually reduce ("collapse") to particular classical states (e.g. after 25 milliseconds) yielding conscious perceptions and volitional choices which then govern neuronal actions. The specific type of reduction proposed in the Penrose-Hameroff model involves the Penrose proposal for quantum gravity mediated "objective reduction" (Penrose; 1998). Despite being testable and falsifiable, the proposal for quantum computation in neuronal microtubules has generated considerable skepticism, largely because of the apparent fragility of quantum states and sensitivity to disruption by thermal energy in the environment ("decoherence"). Quantum computing technologists work at temperatures near absolute zero to avoid thermal decoherence, so quantum computation at warm physiological temperatures in seemingly liquid media appears at first glance to be extremely unlikely. (Although entanglement experiments are done at room temperature.)

Attempting to disprove the possibility of quantum computation in brain microtubules, University of Pennsylvania physicist Max Tegmark (2000) calculated that microtubule quantum states at physiological temperature would decohere a trillion times too fast for physiological effects, with a calculated decoherence time of 10^{-13} seconds. Neurons generally function in the range of roughly 10 to 100 milliseconds, or 10^{-2} to 10^{-1} seconds.

However Tegmark didn't actually address specifics of the Penrose-Hameroff model, nor any previous theory, but rather proposed his own quantum microtubule model which he did indeed successfully disprove. For example Tegmark assumed quantum superposition of a soliton wave traveling along a microtubule, "separated from itself" by 24 nanometers. The Penrose-Hameroff model actually proposed quantum superposition of tubulin proteins separated from themselves by the diameter of their atomic nuclei. This discrepancy alone accounts for a difference of 7 orders of magnitude in the decoherence calculation. Further corrections in the use of charge versus dipoles and dielectric constant lengthens the decoherence time to 10^{-5} – 10^{-4} seconds. Considering other factors included in the Penrose-Hameroff proposal such as plasma phase screening, actin gel isolation, coherent pumping and quantum error correction topology intrinsic to microtubule geometry extends the microtubule decoherence time to tens to hundreds of milliseconds, within the neurophysiological range. Topological quantum error correction may extend it significantly further. These revised calculations (Hagan et al., 2002) were published in *Physical Reviews E*, the same journal in which Tegmark's original article was published.

The basic premise that quantum states are destroyed by physiological temperature is countered by the possibility of laser-like coherent pumping ("Fröhlich mechanism") suggested to occur in biological systems with periodic structural coherence such as microtubules. Moreover Pollack (2001) has shown that water in cell interiors is largely ordered due to surface charges on cytoskeletal actin, microtubules and other structures. Thus despite being largely water, cell interiors are not "aqueous" but rather a crystal-like structure. Perhaps most importantly, experimental evidence shows that electron quantum spin transfer between quantum dots connected by organic benzene molecules is *more* efficient at room temperature than at absolute zero (Ouyang and Awschalom, 2003). Other experiments have shown quantum wave behavior of biological porphyrin molecules (Hackermüller et al., 2003). In both benzene and porphyrin, and in hydrophobic aromatic amino acid groups in proteins such as tubulin, delocalizable electrons may harness thermal environmental energy to promote, rather than destroy, quantum states.





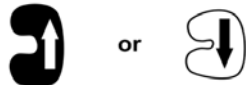

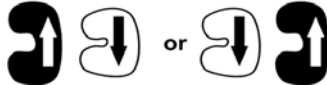

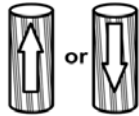

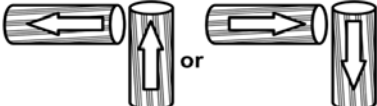
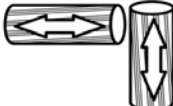
Furthermore, Paul Davies (2004) has suggested that a "post-selection" feature of quantum mechanics put forth by Aharonov et al. (1996) may operate in living systems, making the decoherence issue moot.

Quantum entanglement in mitosis and differentiation?

Centriole replication and subsequent coordinated activities of the mitotic spindles appear to be key factors in forming and maintaining two identical sets of chromosomes, thus

avoiding aneuploidy, genomic instability and cancer. Viewing mitosis as a dissipative, clock-like process which, once set in motion has no adaptive recourse, seems unlikely to account for the necessary precision. Some organizing communication between replicated centrioles and daughter cell spindles seems to be in play (Karsenti, 2001), and would certainly be favored in evolution if feasible. The perpendicular centriole replication scheme has long been enigmatic to biologists. Alternative mechanisms such as longitudinal extension (“budding”), or longitudinal fission with regrowth (akin to DNA

Table 1. Classical and quantum superposition states for electrons/electron pairs (top), tubulins/tubulin pairs (middle), and centriole cylinders/centrioles (bottom).

	Classical State	Quantum Superposition
Single Electron Spin	 Up or Down	 Up and Down
Paired Electrons (Complementary)	 Up, Down or Down, Up	 Up and Down and Down and Up Entangled
Single Tubulin State	 Open or Closed	 Open and Closed
Paired Tubulins (Complementary)	 Open, Closed or Closed, Open	 Open and Closed Entangled
Centriole Cylinder State	 Up or Down	 Up and Down
Paired Cylinder/Centriole (Complementary)	 Horizontal and Vertical or Vertical and Horizontal	 Entangled

replication) would seem to be more straightforward. In DNA replication each component of a base pair is in direct contact so direct binding of the complementary member of the base pair is straightforward. However in centrioles replication by neither extension/budding nor fission would permit direct contact/copying of each component tubulin because of the more complex three dimensional centriole geometry. The enigmatic perpendicular centriole replication provides an opportunity for each tubulin in a mature (“mother”) centriole to be transiently in contact, either directly or via

filamentous proteins, with a counterpart in the immature (“daughter”) centriole. Thus the state of each tubulin (genetic, post-translational, electronic, conformational) may be relayed to its daughter counterpart tubulin in the replicated centriole, resulting in an identical or complementary mosaic of tubulins, and two identical or complementary centrioles. Assuming proteins may exist in quantum superposition of states, transient contact of tubulin twins during centriole replication would enable quantum entanglement so that subsequent states and activities of originally coupled tubulins within the paired centrioles would be unified

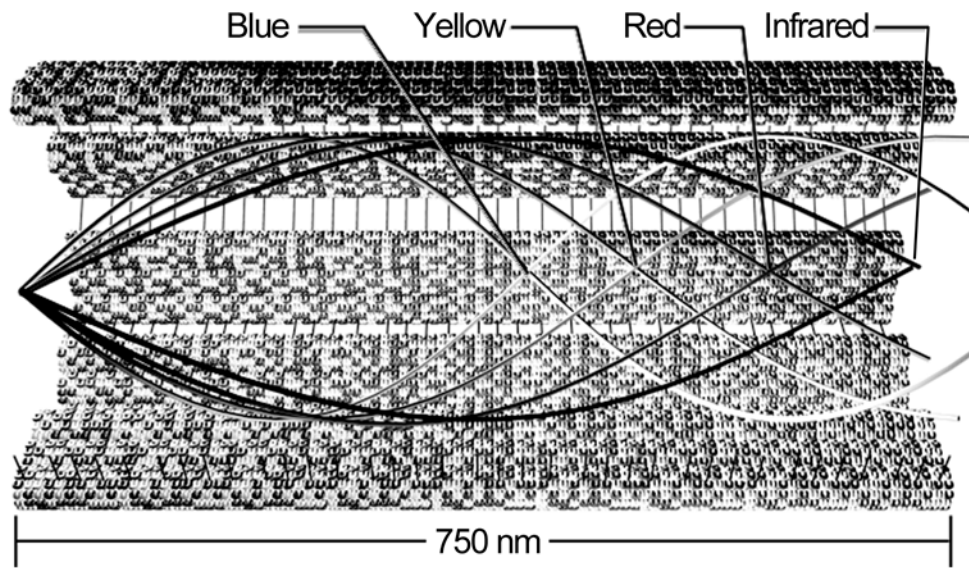


Figure 8. Cutaway view of centriole cylinder showing (to scale) wavelengths of visible and infra-red light suggesting possible waveguide behavior. By Dave Cantrell.

(Tables 1 and 2, middle). Then if a particular tubulin in one centriole cylinder is perturbed (“measured”), or its course or activities altered, its twin tubulin in the paired centriole would “feel” the effect and respond accordingly in a fashion analogous to quantum entangled EPR pairs. Thus activities of replicated centrioles would be mirror-like, precisely what is needed for normal mitosis. In Tables 1 and 2 the state of each centriole is euphemistically represented as either spin up or down (right or left). In actuality the states of each centriole would be far more complex, since each tubulin could be in one particular binary state. There are approximately 30,000 tubulins per centriole cylinder. If each tubulin can be in one of two possible states, each centriole could be in

one of $2^{30,000}$ possible states. Considering variations in isozymes and post-translational modifications, each tubulin may exist in many more than two possible states (e.g. 10), and centrioles may therefore exist in up to $10^{30,000}$ possible states—easily sufficient to represent each and every possible phenotype. But regardless of their specific complexity, replicated centrioles would be in identical (or complementary, i.e. precisely opposite) entangled states.

How could entanglement actually occur? Centrioles are embedded in an electron dense protein matrix (“pericentrin”) to which mitotic spindle microtubules attach; the opposite ends of the spindles bind specific chromatids via centromere/kinetochores. The centriole/pericentrin (“centrosome”) and spindle complex are embedded in protein gel and ordered water so that the entire mitotic complex may (at least transiently) be considered a pumped quantum system (e.g. a Fröhlich Bose Einstein condensate) unified by quantum coherence.

As described previously, quantum optical coherence (laser coupling) can induce entanglement. Although photons generally propagate at the speed of light, recent developments in quantum optics have shown that photons may be slowed, or trapped in “phase coherent materials”, or “phaseonium” (Scully, 2003). In these situations photons are resonant with the materials (which may be at warm temperatures) but not absorbed. Quantum properties of the light can be mapped onto spin states of the material, and later retrieved (“read”) by a laser pulse (or Fröhlich coherence). The dimensions of centrioles are close to the wavelengths of light in the infrared and visible spectrum (Figure 8) such that they may act as phase coherent, resonant waveguides (Albrecht-Buehler, 1992). Fröhlich coherence may then play the role of laser retrieval, coupling/entangling pairs of centrioles. As described previously, experimental evidence shows an association between centriole replication and photon emission (Liu et al., 2000; Van Wijk et al., 1999; Popp et al., 2002).

How would quantum entanglement work in normal mitosis? Binding of a particular chromatid centromere/kinetochore by a spindle connected at its opposite end to a centriole may be considered a quantum measurement of the anchoring centriole, causing reduction/collapse and complementary action in its entangled twin (thus binding the complementary chromatid centromere/kinetochore). Although the action is complementary, and thus in some sense opposite, the operations are identical from an information standpoint (and because centriole orientations are opposite, the actions may be considered equivalent). Consequently, precise complementary mirror-like activities of tubulins in the two entangled centrioles would ensue, and each member of a sister chromatid pair would be captured for each daughter cell. Two precisely equal genomes would result following mitosis.

How would failed quantum entanglement lead to aneuploidy and malignancy? Defects during mitosis can occur in two ways. As shown in Figure 2 spindle attachment to chromatids during metaphase (reflecting entangled information in the centrioles) may go awry, resulting in abnormal separation of chromosomes. This may result from improper communication between the two centrioles (the “right handed centriole doesn’t know

what the left-handed centriole is doing”). Another type of defect may occur in the replication and entanglement as shown in Figure 3, resulting in 3 (or more) centrioles which separate chromosomes into 3 portions rather than 2 precisely equal portions.

Measurement of standard EPR pairs apparently destroys entanglement. Once complementary actions occur, members of separated pairs behave independently. In centrioles, one measurement/operation per tubulin would be useful in mitosis and differentiation, allowing approximately 30,000 measurements/operations per centriole cylinder and ensuring precise division of daughter chromosomes and subsequent differentiation. However an ongoing series of measurement operations (chromatid interactions, movements and binding of other cytoskeletal structures, differentiation etc.) persisting after completion of mitosis could be even more useful.

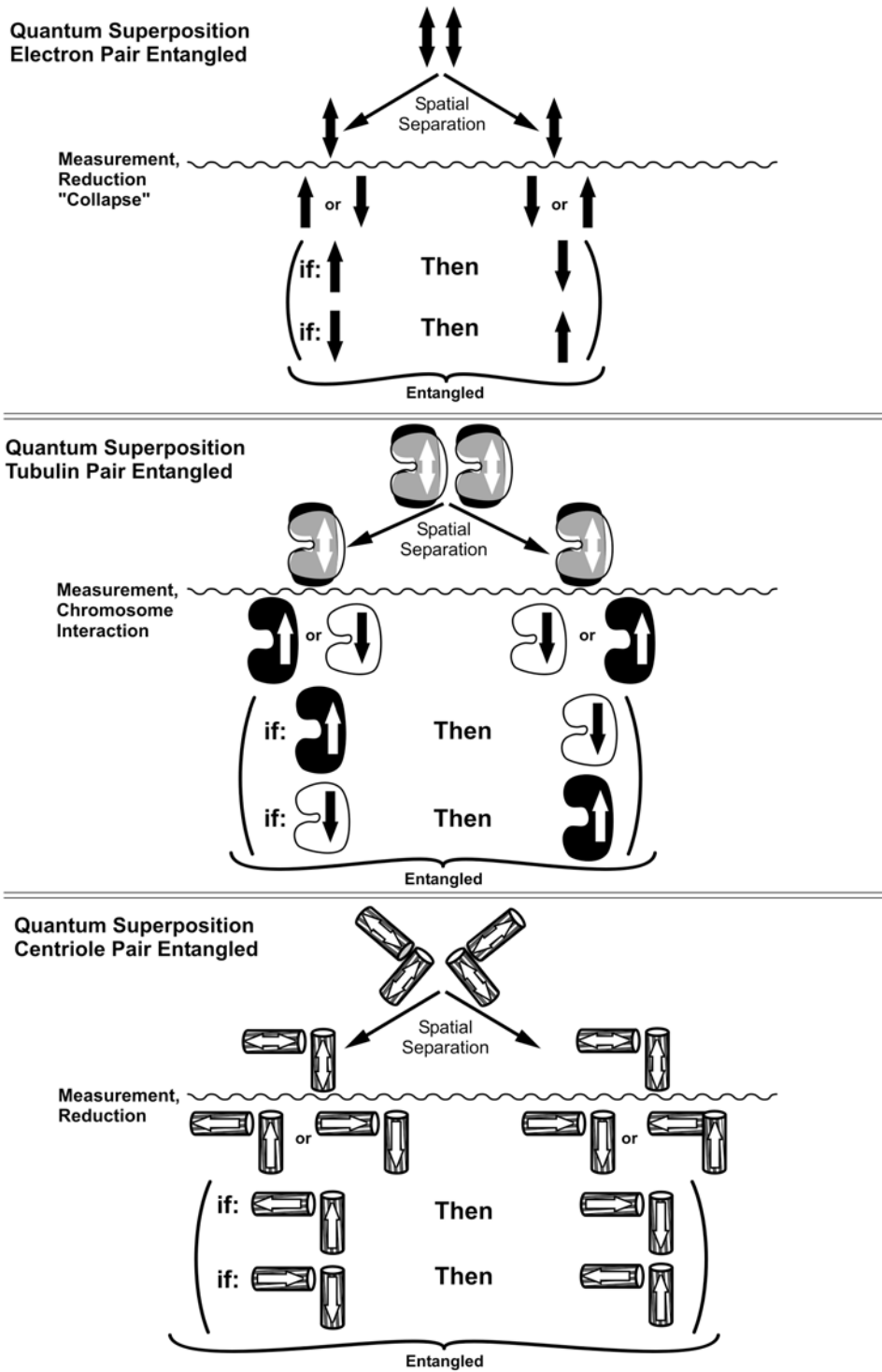
Could persistent entanglement (“re-entanglement”) occur in biological systems? Unlike standard EPR pairs (e.g. electron spin) whose underlying states are random, the conformational state of each member of paired tubulin twins has identical specific tendencies due to genetic and post-translational structure. In the same fashion that laser pulsing mediates entanglement among cesium clouds and other quantum systems, quantum optical (and/or Fröhlich) coherence could mediate ongoing entanglement (“re-entanglement”) among tubulin twins in separated centrioles. Because dynamic conformational states are transient, the quantum state may be transduced to, and stored as, a spin state or other more sustainable parameter. Thus centrioles throughout a tissue or entire organism may remain in a state of quantum entanglement. Impairment or loss of such communicative entanglement may correlate with malignancy.

Implications for cancer therapy

Current therapies for cancer are generally aimed at impairing mitosis and are thus severely toxic. Many cancer drugs (vincristine, taxol etc.) bind to microtubules and prevent their disassembly/assembly required for formation and activities of the mitotic spindles. In addition to generalized toxicity due to impairment of non-mitotic microtubule function, partial disruption of mitosis can cause further aneuploidy (Kitano, 2003). Radiation is also a toxic process with the goal of impairing/destroying highly active malignant cells more than normal cells. Recognizing centrosomes as the key organizing factor in mitosis, Kong et al (2002) proposed disabling centrosomes by cooling/freezing as a cancer therapy.

Low level laser illumination apparently enhances mitosis. Barbosa et al (2002) using 635 and 670 nanometer lasers, and Carnevali et al (2003) using an 830 nanometer laser both showed increased cell division in laser illuminated cell cultures. Using laser interference Rubinov (2003) showed enhanced occurrence of “micronuclei” (aberrant multipolar mitoses) although specific interference modes decreased the number of micronuclei. It may be concluded that nonspecific, low intensity laser illumination enhances centriole replication and promotes cell division (the opposite of a desired cancer therapy). On the other hand if centrioles are sensitive to coherent light, then higher intensity laser

Table 2. Quantum superposition, reduction and entanglement for electron pairs (top), tubulin pairs (middle), and centrioles (bottom).



illumination (still below heating threshold) may selectively target centrioles, impair mitosis and be a beneficial therapy against malignancy.

However laser illumination may also be used in a more elegant mode. If centrioles utilize quantum photons for entanglement, properties of centrosomes/centrioles approached more specifically could be useful for therapy. Healthy centrioles for a given organism or tissue differentiation should then have specific quantum optical properties detectable through some type of readout technology. An afflicted patient's normal cells could be examined to determine the required centriole properties which may then be used to generate identical quantum coherent photons administered to the malignancy. In this mode the idea would *not* be to destroy the tumor (relatively low energy lasers would be used) but to "reprogram" or redifferentiate the centrioles and transform the tumor back to healthy well differentiated tissue.

Stem cells are totipotent (or pluripotent) undifferentiated cells with a wide variety of potential applications in medicine. Zygotes, or fertilized eggs are totipotent stem cells, and embryonic cells in general are relatively undifferentiated. Thus fetal embryos have been a source for stem cells though serious ethical considerations have limited availability. Perhaps normally differentiated cells could be undifferentiated ("retrodifferentiated") by laser therapy as described above, providing an abundant and ethical source of stem cells for various medical applications.

Conclusion: Quantum entanglement and cancer

It is suggested here that normal mitosis is organized by quantum entanglement and quantum coherence among centrioles. In particular, quantum optical properties of centrioles enable entanglement in normal mitosis which ensures precise mirror-like activities of mitotic spindles and daughter chromatids, and proper differentiation, communication and boundary recognition between daughter cells.

Defects in the proposed mitotic quantum entanglement/coherence can explain all aspects of malignancy. Analysis and duplication of quantum optical properties of normal cell centrioles could possibly lead to laser-mediated therapeutic disruption and/or reprogramming of cancerous tumors as well as abundant, ethical production of stem cells.

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