Microtubules: from classical properties to quantum effects in human cognition

Ivan Kukuljan
Supervisor: Prof. Dr. Rudolf Podgornik

Faculty for Mathematics and Physics
University *of Ljubljana*

January 2013

Abstract

The underlying text is a seminar paper written for the master level Seminar class at the Faculty for Mathematics and Physics of University of Ljubljana. It deals with microtubules, Microtubules are highly dynamical hollow cylindrical protein polymers. They are one of the components of the cytoskeleton of eukaryotic cells and have many important biological functions. Because of their interesting crystal-like structure, they have many interesting properties. The paper presents some of these properties, such as dynamic instability, mechanical properties, higher order assemblies and goes on to discuss the role of microtubules in human cognition. Here, it deals with the two most mainstream models, Cellular Automata and Orch-OR. The latter suggest a mechanism for quantum computation within microtubules. The paper also presents some of the critiques of the two models and the most recent experimental evidence.

Contents

1 Introduction

This seminar paper was motivated by the talk of Professor Dr. Sir Roger Penrose about the Orchestrated objective reduction theory and the potential role of quantum mechanics and quantum gravity in conscious mentality, that he gave on the 4th of April 2012 at the ETH Zurich*. The brilliant speaker inspired the author of the underlying work to take a closer look at microtubules, the structure that was supposed to be the medium for the quantum effects in human cognition. The microtubules turned out to be an amazing structure, not only because the extravagant theory Prof. Penrose presented, but because of their important role in living cells and interesting properties arising from their crystal-like structure, alone.

The goal of this work is to inform the reader about different properties, functions and open questions on microtubules and then lead him through the theories explaining the role of this protein polymer in cognition. The text is divided into two sections. The first one presents the classical properties of microtubules. It includes their role in living cells, structure, dynamic instability, mechanical properties and higher order assemblies. The second section presents two computational theories of microtubules, Cellular automata and Orchestrated objective reduction, and discusses whether the theories are to be expected to be correct. It has to be stressed that both theories are still very weakly supported by experimental evidence. They are included in the seminar paper not because the author would believe them to be true but because he finds them *interesting* - compositions of different areas of physics (and biology) that try to address a difficult question of cognition.

*A video of the lecture can be found at http://www.youtube.com/watch?v=M5XYf1GJBhg

2 Classical properties

2.1 Role in living cells

Microtubules together with actin filaments and intermediate filaments build the *cytoskeleton* of the cells. This is an organizational substructure of eukaryotic cells, a network of protein filaments extending throughout the cytoplasm. The cytoskeleton provides a structural framework for the cell. It serves as the scaffold that determines the shape of the cells and organizes the cytoplasm. It is also responsible for movements inside the cells. This includes the movement of organelles and other structures inside the cells but also the movement of the entire cells. It has an important role in cell division.

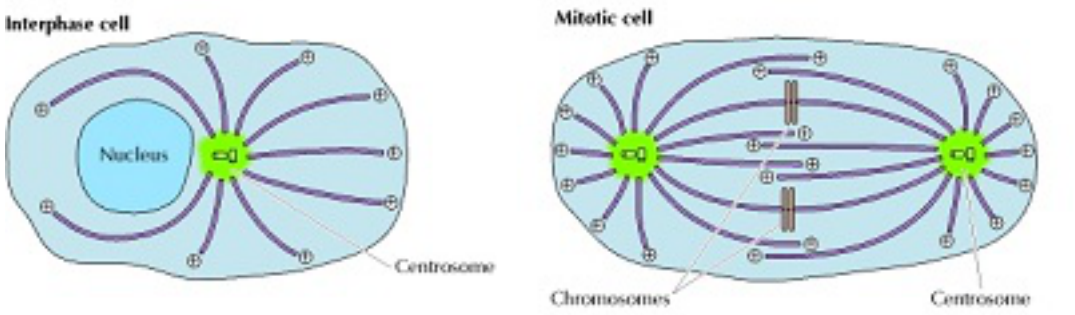

Figure 1: Arrangement of microtubules in an interphase and a mitotic cell. [1]

Microtubules, more particularly, are a highly dynamical polar filaments. In animal cells, they are during the interphase (non-dividing phase) anchored with their (-) ends to the centrosome, located adjecent to the nucleus. Other types of cells have different microtubule-organizing centers, which will be discussed a bit later. Apart from the structural task, they serve, because of their polarity, as "motorways" for the movement of the *motor proteins*. The major ones are *kinesin* that moves towards the (+) ends and *dynein* that moves towards the (-) ends of the microtubules. They help transporting different materials within the cells and are also used by the viruses that need to reach the nucleus in order to reproduce their genetic material. During the mitosis, microtubules form the *mitotic spindle*, which helps decide the cell, in particular to divide and distribute the chromosomes to daughter cells. [1, 3]

2.2 Structure

Microtubules are hollow cylindrical polymers whose building blocks are *tubulin heterodimers.* [3, 11]

Tubulin heterodimers are composed of α- and β-tubulins. The word *heterodimer* means consisted of two (*di*) different (*hetero*) units (*mer*). The aforementioned α- and β-tubulins are proteins with a diameter of 4 nm and weight of 55000 dalton (atomic mass unit) [18]. They are homologous but not identical, mainly consisting of bacterial GTPase, called FtsZ [2]. The main difference between the two is in the *guanosine triphosphate* (GTP) nuclide they are bound to. The GTP molecule bound to α-tubulins is stable. That is why α-tubulins are often denoted as N (non-exchangeable) site. The GTP molecule bound to β-tubulins is labile. It can be hydrolyzed to *guanosine diphosphate* (GDP). Because of that are β-tubulins denoted as E (exchangeable) site. [3, 12] Both, α- and β-tubulins, are produced in cells using the standard protein production mechanism by transcription of genes. However it is doubtful that the two types can be found in cells as individual proteins - they spontaneously bind one to another to form 4 nm long heterodimers.[4] The tubulin heterodimers are polarized. The (-) pole of a heterodimer normally corresponds to the α-tubulin and (+) pole to the β-tubulin. The electric dipole moment of a heterodimer is about 10^{-26} Cm. [3, 11] The polarization of tubulin heterodimers, as we are about to learn in this work, plays a very important role for physical properties and biological functions of microtubules. One more among the important properties of tubulin heterodimers is that they have a hydrophobic pocket at the stitch between the two monomers [18].

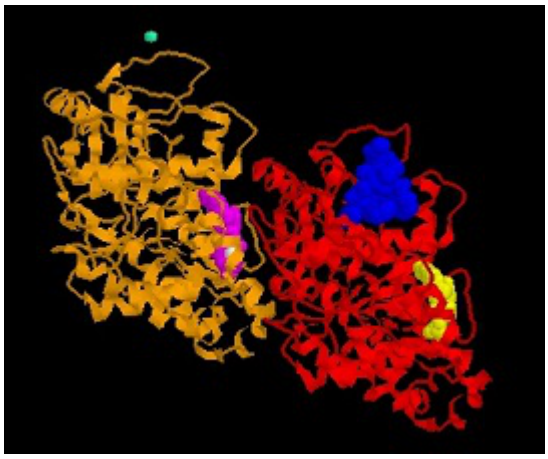

Figure 2: Computer model of the structure of a tubulin heterodimer [12]. Legend:α-tubulin in orange, β-tubulin in red, GTP in magenta, GDP in yellow.

Tubulin heterodimers bind one to another with oppositely charged ends touching so that GTP (or GDP) molecule of every tubulin is covered by the next monomer (see Fig. 2). In this way they form *protofilaments.* The monomers in a protofilaments are $4.0 - 4.2$ nm apart [12].

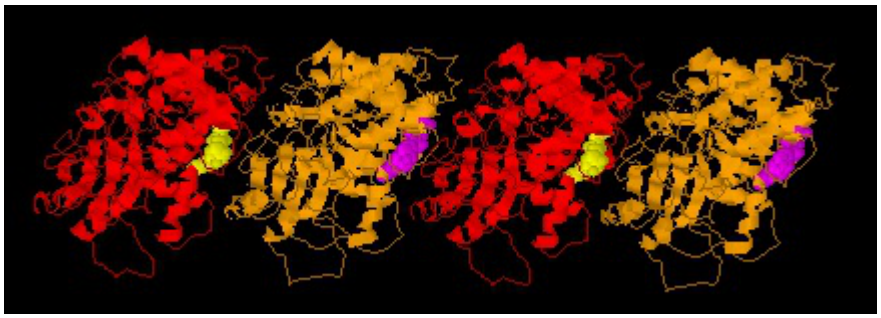

Figure 3: A short protofilament consisting of only two heterodimers (computer model) [12].

The protofilaments, furthermore, bind laterally one to another in sheets which eventually bend to form microtubules. These usually consist of 13 protofilaments but microtubules consisting of 10 - 16 protofilaments have been observed. The structure of microtubules is more precisely a left-handed 3-start helix - if we follow

the nearest neighbor heterodimers around a microtubule, we meet the third subunit up from the starting one after completing the circuit. In other words, we need to start three independent helices to cover the whole microtubule.[12] The surface of the microtubule, seen as a two dimensional crystalline structure, has a slightly twisted hexagonal lattice - each subunit has six nearest neighbors [18]. The inner and the outer diameter of microtubules are 17 nm and 25 nm, respectively [11]. The microtubules can grow as long as 25 μm [3]. Because of the way they are formed, microtubules have a (+) and a (-) end, first ending in a β-tubulin, second in an α-tubulin. Such a polymer built of polarized proteins is called *electret polymer* [18].

Tubulin heterodimers in a microtubule can exist in two different conformation states: the α *state* and the β *state* (not to be mixed with α- and β-tubulin). In the α state the electron negative charge, located in the hydrophobic pocket between the monomers, is shifted more to the α-tubulin side, while in the β state it is shifted to the β-tubulin side [18]. Because of this, is the heterodimer in the β state tilted by 29° with respect to the microtubule axis [11]. The energy of the β conformation state is by 0.4 eV higher than of the α state [12].

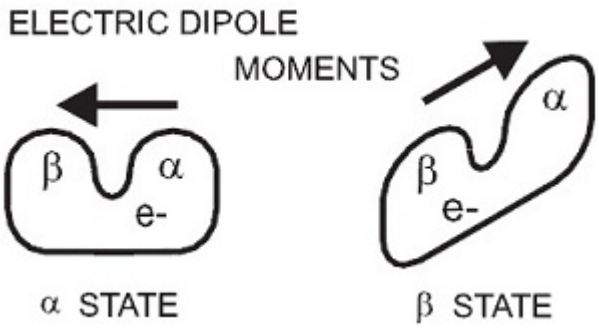

Figure 4: Conformation states of tubulin heterodimers in a microtubule. The axis of the microtubule is horizontal, lying below the tubulins. The arrows denote the electric dipole moment. [11]

2.3 Dynamic instability

Microtubules are a highly dynamic polymer. Because the GTP molecules bound to the β-tubulins are prone to hydrolyze to GDP, there is a coexistence of assembly and disassembly at the microtubule's (+) end. The GTP bound tubulin units are tightly bound to the structure and at the tip of the microtubule they favor its further assembly. The GDP bound units at the tip of the microtubule tend to fall off. The GDP bound tubulins in the middle of the microtubule cannot simply pop out but they increase the radial tension on the microtubule's wall and locally deform its cross section [12]. Because only the GTP bound ones among the tubulins floating in the cytoplasm can attach to the microtubule, there is a cap of GTP tubulins at its tip, protecting it from disassembly. If the β-tubulins at the tip hydrolyze at a faster rate than the new tubulins attach, the microtubule begins to depolymerize rapidly. This process is called *catastrophe*. It can be terminated if a new cap of GTP tubulins is added to the tip. This is called *rescue*. [3] Because of the dynamic instability, microtubules have half-lives of only several minutes within cells [1].

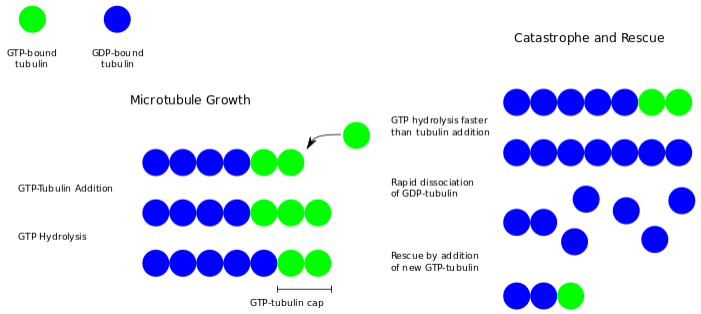

Figure 5: Dynamic instability of microtubules. On the left hand-side, a microtubule in the growing regime, stabilized by a GTP tubulin cap. On the right hand-side, a microtubule in the shrinking regime, also called *catastrophe*. [3]

The process of dynamic instability can be highly influenced by drugs. For example, the *taxanes* and *epothilones* block dynamic instability by stabilizing GDP-bound tubulin in the microtubule and preventing it from falling off the tip. As a result, even when completely hydrolyzed, the microtubule cannot switch into shrinking regime. *Nocodazole*, *vincristine*, and *colchicine* have the opposite effect, blocking the polymerization of the microtubules. *Eribulin* binds to the growing end of the microtubules. These effects are used in medicine, for example for cancer fighting.[3]

In vitro experiments with unattached microtubules reveal a similar process to dynamic instability, called *threadmilling*. Threadmilling adds to dynamic instability a slow disassembly of microtubules at their unattached (-) ends. [1]

The mechanism of microtubule dynamic instability was discovered by Mitchinson and Kirschner [5] back in 1984, but it is still not completely understood and is a matter of many experimental and theoretical present-day research projects. The research questions are mostly related to the effect of microtubule natural environment in biological cells on its growth and the behavior of microtubules in different phases of cell division [10].

2.4 Mechanical properties

Mechanical properties of microtubules for all of their functions as a building block of cytoskeleton. They have been extensively studied during last few decades. Several techniques have been used: atomic force microscopy (AFM), thermal bending, oscillatory and shearing modes, osmotic stress combined with synchrotron X-ray diffraction and most recently, molecular dynamics simulations [6, 9, 7].

It is not a trivial task to experimentally determine mechanical properties for two reasons. Firstly, because of the small size of the microtubules and their rigidity, mechanical properties, such as Young's modulus cannot be measured directly. Instead, they are modeled and estimated out of some parameters that can be measured, such as flexural rigidity and radial indentation. [7] Secondly, because of microtubule very short half-lives, they have to be stabilized by taxol in order tube experimented on. It has been discovered that taxol, such as other drugs, alters the mechanical properties of the microtubules. Most studies of this effect report a decreased Young's modulus and therefore "softer" microtubules, but there are reports of the opposite effect. [6] At the present time, when the atomic structure of tubulins and microtubules is well known due to cryo-electron microscopy, computer simulations can, in turn, give very good results about mechanical properties of microtubules and a closer insight on the functioning of this structure. A combination of experimental and simulation techniques will probably provide us with very precise knowledge about the properties of the microtubules.

Here are some of the results for microtubule mechanical properties. Young's modulus for axial deformations: 1.3 GPa (experimental, osmotic stress method combined with synchrotron X-ray diffraction [9]) and 1.2 GPa (molecular dynamics simulation by Wells and Aksimentiev [7]). The same molecular dynamics simulation predicts the following stress-strain curve for axial deformations of a finite microtubule:

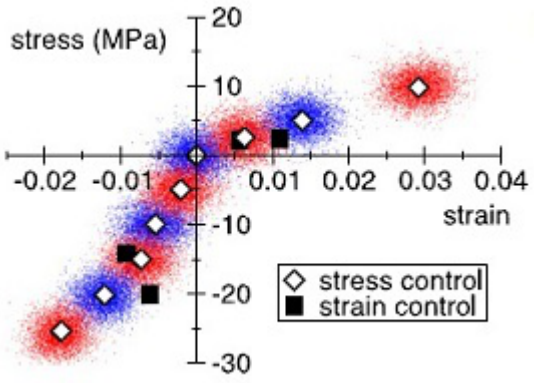

Figure 6: Stress-strain curve for a finite microtubule. [7]

Shear modulus: 5 Pa (experimental [11]).

Stretching reduces microtubule radius, as expected. Molecular dynamics gives the average radius of 111.57 ± 0.07 Å at -20MPa stress, 110.45 ± 0.06 Å at zero stress and 110.45 ± 0.06 Å at +5 MPa stress. [7]

Needledman et al [9] have discovered that increasing the osmotic pressure above 600 Pa causes the microtubule to buckle from a circular cross section with a diameter of $\sim 25\,\text{nm}$ to a noncircular shape with a short dimension of $\sim 19\,\text{nm}$. Further increasing of the osmotic pressure to 200 kPa only decreases the short dimension to $\sim 16\,\text{nm}$. Molecular dynamics simulation gives the following behavior of microtubules when exposed to the radial stress:

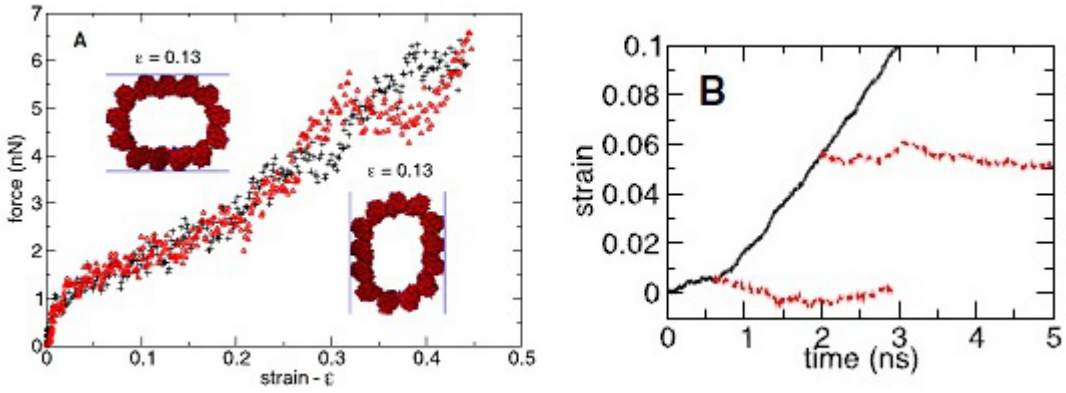

Figure 7: Response of a microtubule on radial stress. On the hand left side, force-strain curve. Strain was estimated by the eccentricity of the ellipse fitted to the microtubule cross section. Triangles and crosses represent two directions of force application (slight asymmetry of the microtubules). The graph gives the effective spring constant of $\sim 0.3\,\text{N/m}$. On the right hand side, relaxation of a microtubule after being deformed to certain strain. [7]

An AFM experiment finds the effective spring constant to be $\sim 0.07\,\text{N/m}$ and the radial deformation to be reversible up to 15% deformation [7].

Wells et al [7] also explain the behavior of microtubules if they are twisted around their axis. They predict asymmetrical behavior with regard to the direction of twisting. This is due to the helical structure of the microtubules.

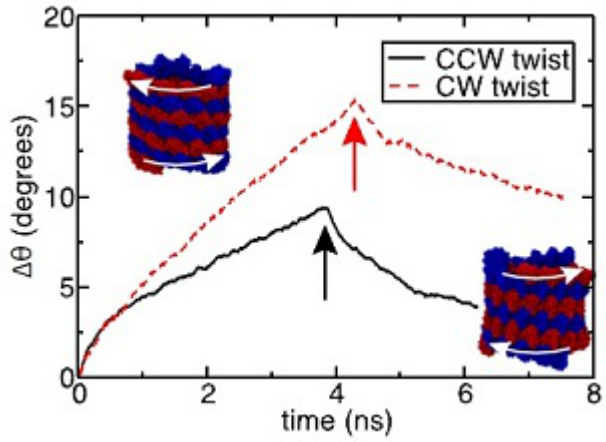

Figure 8: Angular displacement of a finite length microtubule as a function of time, given by a molecular dynamics simulation. The microtubule was twisted in the opposite directions (denoted clockwise and anti-clockwise and presented by the sketches) in both cases with the same persistent torque of $\sim 89\,\text{nN nm}$ turned on at the time 0. The torque was slightly increasing ($< 3\%$) due to increasing microtubule radius. It was set to zero at the certain moment indicated by the arrows on the plot so that the structure was allowed to relax. The graph shows that microtubules are slightly "softer" when twisted in the clockwise than in the anti-clockwise direction. [7]

2.5 Higher order assemblies

Within living cells, microtubules are organized by microtubule-organizing centers (MTOCs), which have the function to nucleate the microtubule assembly. In animal cells the MTOC is a centrosome, a lattice of microtubule-associated proteins that sometimes but not always contains a pair of centrioles. In other types of eukaryotic cells, there can be many MTOCs freely floating in the cytoplasm. The structure inside the MTOCs that enables the nucleation of the microtubule assembly are γ-tubulin ring complexes. The third, not yet discussed, type of tubulins, γ-tubulin, can be found only in MTOCs. It forms rings of 13 which serve as bases to which tubulin heterodimers from the surrounding cytoplasm can attach. [2]

During mitosis, the microtubule array present in interphase dissasembles and the free tubulin subunits reassemble to form the mitotic spindle. This process is directed by duplication of the centrosome. The task of the mitotic spindle is to help divide the cell, in particular to divide and distribute the chromosomes to daughter cells (Fig. 1). [1]

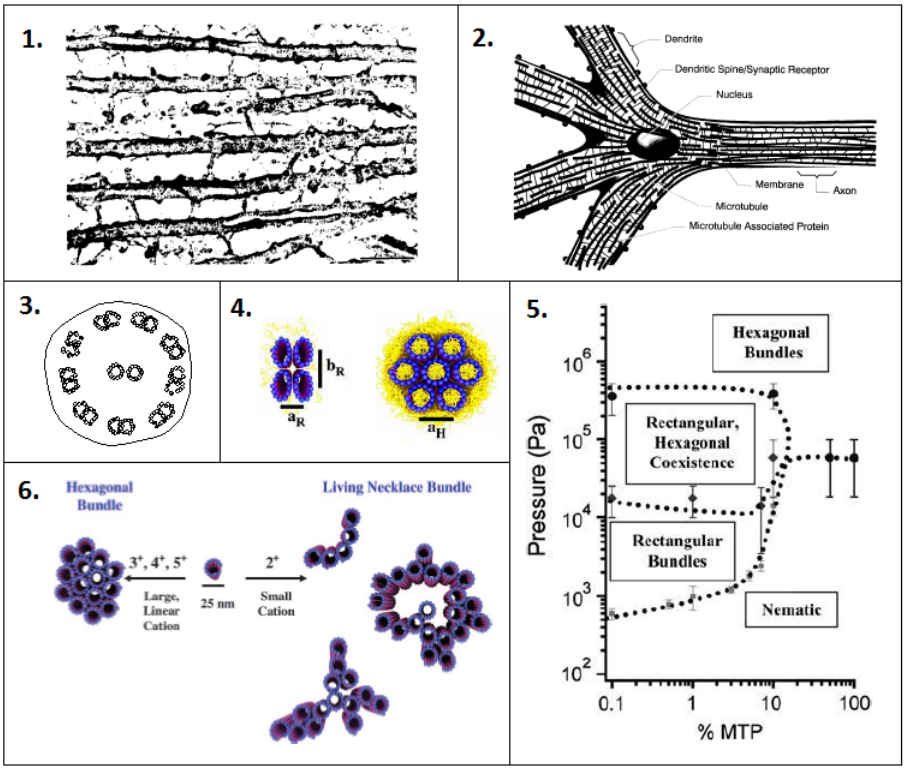

Figure 9: 1. Immunofluorescent micrograph of neuronal microtubules interconnected by MAPs [18]. 2. Organization of microtubules within neurons [18]. 3. The so called 9-1 structure of microtubules in cilia and flagella with 9 doublets surrounding the central one (cross section) [4]. 4. Rectangular (with radially compressed microtubules) and hexagonal bundle phases [9]. 5. Phase diagram (a log-log graph of pressure as a function of microtubule concentration) for phases reported by [9]. 6. Higher order assembling of microtubules is governed by the size of the cations in the solution used in the *in vitro* experiment [8].

There are a whole bunch of other proteins associated to microtubules, the so called microtubule-associated proteins (MAPs). The function of most of them is to interconnect microtubules in order to increase their stiffness, stabilize the dynamic instability and therefore determine the shape of the cells. MAPs have many other important functions, such as motor activities and the control of the microtubules. [1] The process of the cell division and the organization of the mitotic spindle is one of the open questions in cell biology and associated sciences. [10]

Apart from doublet microtubules in *cilia* and *flagella* (structures that help in locomotion and movement of fluids across the surface of tissue cells in animals; an example is the tail of a sperm cell), and triplet

microtubules in centrioles and basal bodies, there were other types of microtubule assemblies observed. Needleman et al. [9] report transition from nematic to rectangular bundle to hexagonal bundle phases of microtubules with the increase of osmotic pressure. In their other work [8] the same authors report a transition of the hexagonal phase to the "living necklace" bundle in the presence of small divalent cations. This bundle phase is an experimental example of nematic membranes. The results of Needleman et al. are experimental and there is a lack of theoretical models of the observed phase transitions [8].

A bit specific is also the organization of microtubules within neurons. In axons, they are lengthy and continuous, whereas in dendrites they are interrupted and of mixed polarity. They are connected by MAPs to membranes and receptors on dendritic spines. Microtubules within neurons are highly involved in maintaining synaptic connections and other essential tasks. [18]

3 Theories describing information processing and signaling in microtubules

Microtubules serve not only as "bone-like" support and circulatory system of living cells but also as their nervous system. The latter includes information processing, signaling and regulating its environment, for example MAP architecture and synaptic formation. Several experimental observations even suggest that cytoskeleton might be involved in cognition. For example, MAP-2, a dendrite specific, MT-cross linking MAP, has an important position in models of learning and memory in mammalian hippocampal cortex. It has been observed that MAP-2 in cat visual cortex dephosphorylates when visual stimulus occurs. In rats, MAP-2 is involved in strengthening of specific synaptic pathways. Auditory Pavlovian conditioning stimulates MAP-2 activity in temporal cortex in rats. The degree of cognitive damage correlates with decrease of measured levels of MAP-2 in animals whose brains are temporarily deprived of oxygen.

There is also evidence that more directly links microtubules with cognitive functions. For example, microtubule activity and tubulin production correlate with peak learning, memory and experience in baby chick brains. Vast quantities of tubulin begin to be produced in visual cortex of baby rats after they first open their eyes. Selective damage of microtubules in animal brains by the drug colchicine causes defects in learning and memory which mimic the symptoms of Alzheimer's disease. Alzheimer's disease itself is caused by entanglement (in the classical, everyday-life, meaning) of neuronal cytosceleton which is suggested to be a result of microtubule dysfunction.

There are a few different theories that try to explain how information is processed, signaled in microtubules and incorporated into the functioning of the nervous system.

3.1 Cellular automata

Cellular automata was one of the first mechanisms to explain the information processing and signaling abilities of microtubules. It was born from the suggestion by Herbert Fröhlich, a German-born British physicist and an important contributor to the theory of superconductors, that sets of protein dipoles in a common electromagnetic field undergo coherent conformational excitations if energy is supplied. Fröhlich's coherent pumped phonons are a type of Bose-Einstein condensate. His theory could apply for example to proteins within a polarized membrane, but also to subunits of an electret polymer like microtubule [18]. In microtubules, energy to pump coherent excitations could be provided by thermal energy of the surrounding "heath bath", as originally proposed by Fröhlich [18], phosphorylation [18] or by hydrolysis of GTP to GDP [11, 18].

Coherent pumped phonons are used to predict that microtubules act as *cellular automata*. These are computational systems in which complex signaling and patterns emerge from local activities of simple subunits (cells). This takes place under the following conditions:

1. At a given time, each subunit is in one of a finite number of possible states (usually two possible states are considered for simplicity).

2. The subunits are organized according to a fixed geometry, the size and shape of the neighborhood are the same for all cells.

3. Each subunit communicates only with neighboring subunits.

4. Changes happen in coherent discrete time - each subunit can change its state only at "clock ticks".

5. Transition rules for changing state depend on each subunit's "present" state and those of its neighbors;

Depending on starting patterns, simple transition rules can lead to complex, dynamic patterns capable of computation. John Von Neumann proved mathematically that cellular automata could function as Turing machines.

There were several simulations of microtubules acting as cellular automata performed. They used Fröhlich excitations as discrete clocking mechanism and electrostatic dipole forces for transition rules. The α and β states introduced in 2.2 were used as the possible states of the subunits.

The simulations conformational pattern behaviors including standing waves, oscillators and gliders traveling one heterodimer length (8 nm) per time step ($10^{-9} - 10^{-11}$ s), which gives the velocity range of $8 - 800$ m/s. This is consistent with the velocity of propagation of nerve action potentials.

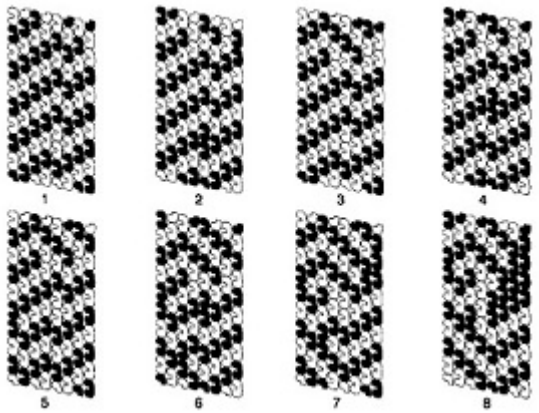

Figure 10: A result of a microtubule cellular automaton simulation. The starting pattern evolves through 8 ns time steps. White and black tubulins correspond to α and β states, correspondingly, eight drawings represent eight consecutive time steps.

Cellular automata provide a broad range of possibilities for information processing and signaling in microtubules. The information processed in microtubules could be transmitted into the surrounding using several different mechanisms. Gliders could convey signals which could then regulate synaptic strengths. They could transport materials. Different could determine binding sites for MAPs and thus neuronal and synaptic architecture. [18]

3.2 Orchestrated objective reduction

Orchestrated objective reduction (Orch OR) is a model of microtubule information processing mechanism, proposed by Stuart Hameroff and Roger Penrose in 1996 [18], which is based on quantum computation, in particular on the notion of quantum coherence.

The theory is motivated by Penrose-Lucas argument (which Penrose presented in his earlier works [13, 14] and soon became an intensely controversial claim) that human consciousness is non-computable. The argument is based on the famous Gödel incompleteness theorem that states that any effectively generated theory capable of expressing elementary arithmetic cannot be both consistent and complete. Further to that, for any consistent formal theory that proves certain basic arithmetic truths, there is an arithmetical statement that is true, but not provable in the theory. [15] Expressed in a more simple manner, no formal proof system of any consistent theory can prove all the (true) mathematical statements arising from that theory. Penrose claims that, on the other hand, human mathematicians indeed can prove such statements. This means that the human consciousness can preform "non-computable" (defined in *[13]*) functions, furthermore, no computable theory can describe it. [15] Hameroff and Penrose argue that the modern approaches to describing human brain, based on classical physics, have too little computational power and are therefore unfounded. They propose that the non-computable component could be introduced to the theory of the functioning of the

brain by quantum computation. Because even quantum mechanics is computable, they suggest the non-computability to be provided by the collapse of the wave function driven by the quantum-gravitational effect, the so called *objective reduction* (OR). The idea is again based on Penrose's earlier work [16].

In search for the structure inside the brain suitable for long range coherent quantum states Hameroff, after having dealt with microtubules for a long time, proposed that they might be the best candidate. In particular, they satisfy all the requirements for such a structure:

1. High prevalence.
2. Functional importance (for example regulating neural connectivity and synaptic function).
3. Periodic, crystal-like structure with long range order.
4. Ability to be transiently isolated from external interaction.
5. Functionally coupled to quantum-level events.
6. Suitable for information processing.

There are some other biological structures that satisfy some of these conditions, for example membrane proteins, synapses and DNA, but none satisfies all six of them. It is evident from the preceding sections why microtubules satisfy conditions 1, 2, 3 and 6. Conditions 4 and 5 will be discussed slightly later in the text, when Orch OR is presented into details. But first we need to introduce some concepts that may help the reader understand the idea.

3.2.1 Quantum computation

Quantum computation is a sub domain of quantum information theory. It has developed out of the question to what extend and how can quantum systems be used for information processing and storing. The fundamental difference between quantum objects and classical objects, which conventional present-day computation utilizes, is in the property of quantum objects that they can be in a superposition of the allowed states, the eigenstates of their Hamilton operator, while classical objects can be only in one of their possible states at a time. For a discrete spectrum $\{(E_i(t), |\psi_i(t)\rangle)\}$ the general *superposed state* $|\psi(t)\rangle$ writes as

$$|\psi(t)\rangle = N \sum_i c_i(t) \, |\psi_i(t)\rangle \, , \tag{1}$$

where $c_i(t)$ are complex coefficients and N a normalization coefficient. Superposed states are also referred to as *coherent states*.

Another feature of quantum objects is that they can become *entangled* one with another. This means that they can no longer be regarded as individual separate systems but have to be treated as a whole. Mathematically speaking, the state of the system of m entangled objects is a vector in the space which is the tensor product of the state spaces of individual objects. If $\{|\psi_{ij_i}(t)\rangle\}_{j_i=1,\dots n_i}$ is the basis for the i-th object, then the basis of the whole system is given by

$$\{|\psi_{1j_1}(t)\rangle \otimes \ldots \otimes |\psi_{mj_m}(t)\rangle\}_{j_1,,\dots j_m} \, . \tag{2}$$

It is obvious that the dimension of the tensor product is $n_1 \cdot \ldots \cdot n_m$. [17]

Quantum theory allows two possible types of time evolution of superposed states. The first one, *unitary evolution* (in the Orch OR model denoted with U), is how the system evolves, undisturbed, in the potential it is surrounded with, governed by Schrödinger's equation. It is called unitary, because as a consequence of the linearity of Schrödinger's equation, the norm of such state is preserved at all times and the evolution is time reversible. The most important properties of unitary evolution of quantum states are that it is deterministic (therefore computable) and continuous.

The second type of system evolution is the so called *measurement*. Our attempt to measure a physical quantity of a quantum system is mathematically described as us acting on the system with the quantum mechanical operator corresponding to the measured quantity. What happens is one of the most controversial open questions in quantum theory. The conventional approach, the Copenhagen interpretation, says that the outcome of the measurement will be us measuring one of the eigenvalues of the measurement operator. We will find the system in the eigenstate that corresponds to the measured value, which means that the

measurement has caused the wave function of the system to instantaneously collapse to a single end state (classical state). This collapse mechanism is called *reduction* (R) in the Orch OR theory. The nature of the process is random (or probabilistic), meaning that the probabilities to find the system in the possible states is given by the squares of the absolute values of the coefficients standing in front of the states if the initial wave function is written in the eigenbasis of the measurement operator. Why human interaction with the quantum system should be something special and have different (non-unitary) evolution rules disturbed many physicists. There were several alternative interpretations developed where only unitary evolution is aloud. An example is the theory of *Parallel universes*, where measurement is described as a change of the Hamiltonian. At the time when the measurement begins, the system is coupled with the measurement apparatus so the evolution of the complete system has to be taken into account. Because the measurement apparatus is much larger than the measured system and has many more degrees of freedom, the unitary evolution causes the measured system to decohere into a classical state. The measurement in this interpretation does not happen instantaneously but continuously in a very short time. This type of reduction is called *subjective reduction* (SR) in the Orch OR theory. Different interpretations of the measurement differ in the philosophical point of view but they all agree in the measurable predictions. The important properties of the measurement for us will be that it is probabilistic but computable (we know hot to compute the probabilities). This makes the time evolution in quantum mechanics altogether computable. [18, 16]

Quantum computation utilizes coherent states of quantum objects with discrete spectra and both types of time evolution to process information. The theory and the resulting technology promise a huge progress in the computational abilities of our civilization but perhaps they have already been used by the evolution itself. [17, 18]

3.2.2 Penrose's objective reduction

One of the most puzzling open questions in present day physics is the one of quantum gravity, namely there is no consistent physical theory that would describe all four fundamental forces observed so far - electromagnetic, weak, strong and gravitational force. At the present time, there are two ground physical theories, quantum mechanics (quantum field theory being its strongest version) which describes electromagnetic, weak and strong force and general relativity which describes gravitation, that no-one has succeeded to unify yet. Among many technical difficulties the obstacle lies in the fundamental difference between the two theories: general relativity is a deterministic geometrical (nonlinear) theory, whereas quantum mechanics is probabilistic theory adequate only for flat space-times. To illustrate the problem imagine a ball-like object, say a neutron, that is in a superposition of two spatially displaced states. Relativistically this means that the space-time, as well, has to be in the superposition of two curvatures and we do not know how to proceed. Quantum mechanically this means that one state has to evolve in the curved spacetime because of the presence of the other state and we do not know how to proceed. There have been many attempts to unify the two theories, from super-symmetries, M theories, non-commuting geometries to string theories, but until now none has given good results.

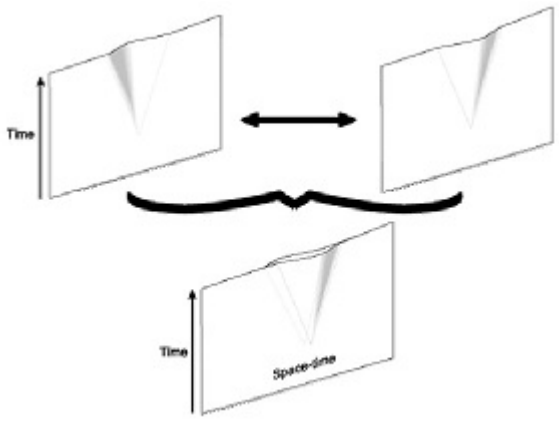

Figure 11: How do we treat superposed states that cause a differently curved space-time each? As a superposed spacetime? [14]

In his work from 1996 [16] Penrose does not try to give a theory of quantum gravitation as he shares the view that the uniting theory will involve a major change in our physical world-view, extending and generalizing our knowledge, rather than just making the two theories consistent with one another. According to his view, quantum gravity will prove to be non-computable. Instead, he merely uses the basic features of both theories to discuss why superposed states of microscopical objects are not very likely to be observed - he predicts a collapse of superposed wave function under the influence of gravity. He begins his argument with the fact that the superposed system of two spatially displaced states has some gravitational energy (called gravitational self-energy E_Δ) as a consequence of one state being in space curved by the mass distribution of the other state. He uses quantum estimate for characteristic lifetime T of system with energy E_Δ:

$$T \simeq \hbar / E_\Delta \tag{3}$$

The author claims that without knowing the precise mechanism, we can predict, using the basic phenomenology of quantum mechanics, that a coherent wave function with the gravitational self-energy $E_\Delta$would decohere (collapse into a classical state) in the characteristic time T.[16] Because Penrose believes that quantum gravity will be a non-computable theory, he predicts the gravitationally driven collapse of a wave function to be non-computable [18].

A bit more difficult than the above estimate is the question how to compute E_Δ, to which the major part of [16] is dedicated. The difficulty arises from the facts that there is no consistent way to identify points in two different space-times and therefore to compute the energy of a state in the space-time of another state. After very carefully argumentation why classical approximation can be taken, Penrose derives the following expression:

$$\Delta = -4\pi G \int \int (\rho(\mathbf{x}) - \rho'(\mathbf{x}))(\rho(\mathbf{y}) - \rho'(\mathbf{y}))/\left|x - y\right| d^3x d^3y, \tag{4}$$

where ρ and ρ' are the mass densities of the two displaced states and G the gravitational constant. The author suggests that the correct E_Δ should be a multiple of Δ.

Finally the author uses these results to calculate what the characteristic lifetimes of various objects would be. For a single protons he finds the expected lifetime to be of the order of a million years, for a water speck 10^{-5}m in radius of the order of one hour and for the water speck 10^{-3}m in radius of the order of a microsecond. These results show why macroscopic bodies are not likely to be found in superposed states. Of course, OR is on the very speculative level and experimental evidence has to be found if its predictions are to be taken seriously. [16]

3.2.3 Orch OR: The model

Hameroff and Penrose extend the computational model of cellular automata. They use the fact that the conformational states of tubulin heterodimers (α and β states) are functionally coupled to state of the electron in the hydrophobic pocket of the heterodimers. They suggest that these electrons of different heterodimers could get entangled one with another. More precisely, they imagine the computation in microtubules to happen in cycles. Heterodimers in a microtubule that is in the beginning in some (classical) conformational pattern start to entangle. With time, the number of entangled heterodimers grows and a unitary quantum computation is performed on the entangled state, driven by the Hamiltonian of the whole system. After the characteristic lifetime specified by the gravitational self-energy of entangled heterodimers (being in a superposition of conformational states tilted by 29°), the gravitationally driven OR occurs and the heterodimers end again in some classical state. The information produced by the cycle is processed and transmitted using the cellular automata mechanism and a new cycle starts in the meanwhile.

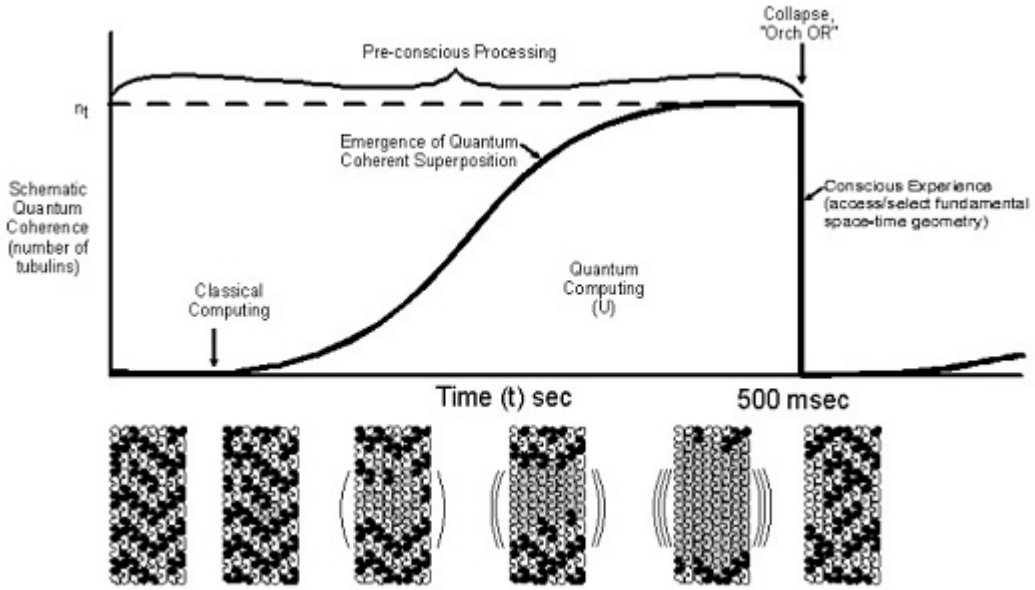

Figure 12: A cycle in the computational mechanism proposed by the Orch OR model. Starting from a classical conformation of a tubulin heterodimers, they start to entangle and quantum computation is preformed on the entangled state. When a certain threshold is reached, the entangled state OR collapses into a new classical conformation pattern. Above, the number of entangled heterodimers as a function of the time. The maximum number n_t is the number of entangled heterodimers in cycles with period t. Bellow, a sketch of the process on the microtubule wall. White and black tubulins represent the α and β states, correspondingly, gray tubulins represent the entangled (and superposed) tubulins. [19]

The idea of computation in cycles is supported by the observations of coherent synaptic vesicle release (firings) of certain neuronal groups with frequencies $40-80\,\mathrm{Hz}$ and suggestions that our conscious experience occurs in cycles with periods in the range of $100-500\,\mathrm{ns}$. The latter is based on the former and other observations of processes in our brains that are periodic. According to these proposals our brain does not process the information continuously but in cycles. The end of each cycle provides us with a processed piece of information and represents a conscious experience. The periods of such cycles are not fixed but depend on the cerebral parts and the mental activity. When the neurons are highly stimulated by the incoming impulses (visual information, for example), the cycles get shorter and they get longer when we are asleep. The authors of the Orch OR theory suggest that the cyclic processes could for example control neuron firings and so provide to cognition. The produced patterns could also determine MAP attachment sites and thus govern intra-neuronal architecture and synaptic function by modulating sensitivity of membrane receptors, ion channels, exoplasmic transport and communication with genetic material. The authors map the entangled phase of the cycles to the per-conscious processing and the collapse of the coherent state to the conscious events (conscious experience or "now" experience). Moreover, because the OR is irreversible, this mechanism could explain our perceived flow and direction of time.

Hameroff and Penrose calculate how many tubulins have to be involved in coherent computation to have $500\,\mathrm{ns}$ cycles. They find that this number should be of the order of 10^9. Combined with the measured concentration of 10^7 tubulins per neuron, this means about 100 neurons. If further not all of the tubulins took part in a coherent process at all times but say only 1% of them, 10000 neurons would be required to elicit Orch OR. This number is comparable with the number of neurons in functional groups of neurons in human cognition. The shorter the cycles the bigger the number of tubulins involved. This is consistent with the observations that less developed organisms, for example worms, that have a smaller number of neurons, are only capable of modest brain functions, in the language of this theory, very long cycles. It would also infer that during more intensive mental activity bigger parts of our brain are involved.

To conclude the model and link to the discussion about the feasibility of such processes, it has to be stressed that one of the biggest difficulties of the Orch OR proposal is that superposed and entangled quantum states are usually realized only if extremely strict conditions are provided. Usually these superconductors cooled to the temperature close to the absolute zero or ions in ion traps with precisely controlled potentials using lasers. The quantum coherent states are extremely delicate in the sense that they decohere if they are coupled with a

noisy environment. How can we then expect to find coherent quantum states in microtubules that are located in the "noisy" random environment inside living cells? The authors of the theory suggest several mechanisms that could isolate or protect the microtubules from the decohering influence of their environments:

- **Ordered water.** Water on microtubule surface can be highly ordered, expanding up to 9 layers (3 nm) around the microtubule. Because decoherence influence of the neighborhood involve also short range interactions like hydrogen bonds, this layer of ordered water would act as a shield blocking them. Some models show that the thermal energy received from the surroundings could be accumulated in coherent modes of the ordered water layers manifesting as electromagnetic energy beams of radius 15 nm inside the microtubule.
- **Isolation inside microtubule hollow core.** Models based on quantum field theory predict a specific collective dynamics called super-radiance in which the microtubule can transform incoherent, disordered energy into coherent photons within its hollow core. Time for generation of such photons is much shorter than the time needed for the environment to decohere the microtubule thermally.
- **Sol-gel states.** There are two phases of the cytoplasm: sol (solution) and gel (gelatinous). It can be converted from one phase to the other reversibly under the influence of calcium ions bound to actin and other cytoskeletal polymers. Hameroff and Penrose suggest that the microtubule could control the phase of the surrounding cytoplasm so that it would be in the gel phase during the coherent part of the Orch OR cycle and in the sol phase in the classical part of the cycle. The gel phase could help isolate the microtubule while it is in a coherent state.
- **Orchestration by MAPs.** MAPs that are bound to the microtubules at several sites are the medium that is most likely to transmit the incoherent thermal energy to the microtubule. The authors of the Orch OR proposal suggest that this effect could "orchestrate" the computation in microtubules. MAPs would prevent the heterodimers to become coherent at the binding sites and therefore act as the "nodes" for computation. In this way, the computation would not be completely random, it would be orchestrated by the MAPs instead. That is where the word Orchestrated in the name Orch OR comes from.

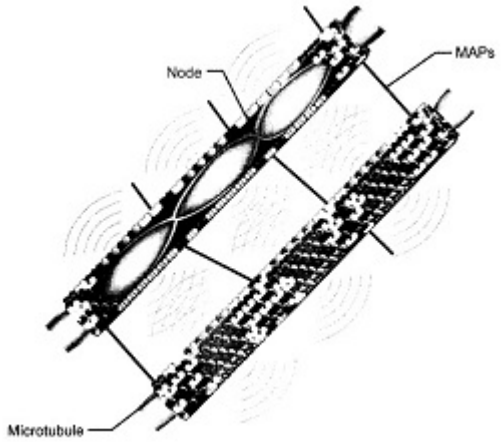

Figure 13: MAP attachment sites act as nodes that orchestrate the quantum computation. In the upper microtubule, the curves symbolically denote the number of superposed heterodimers per unit of length. In the lower microtubule, gray heterodimers again represent the superposed ones. [18]

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