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

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. They 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 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 Orch OR model and the most recent experimental evidence.
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 of the extravagant theory Prof. Penrose presented, but because of their important role in living cells and interesting properties arising from their crystal-like structure, as well.

The goal of this work is to inform the reader about different properties, functions and open questions on microtubules and then lead him or her 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 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=M5XYfIgJBhg

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.
Microtubules, more particularly, are highly dynamical polar filaments. In animal cells, they are during the interphase (non-dividing phase) anchored with their (-) ends to the centrosome, located adjacent 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 divide the cell, in particular to divide and distribute the chromosomes to daughter cells. [1, 2]

2.2 Structure

Microtubules are hollow cylindrical polymers whose building blocks are tubulin heterodimers. [2, 3]

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) [4]. They are homologous but not identical, mainly consisting of bacterial GTPase, called FtsZ [5]. 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. [2, 6] 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. [10] 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. [2, 3]

The polarization of tubulin heterodimers, as we are about to learn, 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 [4].
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. The surface of the microtubule, seen as a two dimensional crystalline structure, has a slightly twisted hexagonal lattice - each subunit has six nearest neighbors. The inner and the outer diameter of microtubules are 17 nm and 25 nm, respectively. The microtubules can grow as long as 25 µm (with persistence length of 1.4 mm they are quite stiff). 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.

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. Because of this, is the heterodimer in the β state tilted by 29° with respect to the microtubule axis. The energy of the β conformation state is by 0.4 eV higher than of the α state.

![Figure 3: 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.](image)

**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. 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. Because of the dynamic instability, microtubules have half-lives of only several minutes within cells.

![Figure 4: 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.](image)
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. [2]

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 [8] back in 1984, but it is still not completely understood and is a matter of many experimental and theoretical present-day research projects. [9]

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 [11, 12, 13].

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. [12] 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. [11] 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.

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 [13]) and 1.2 GPa (molecular dynamics simulation by Wells and Aksimentiev [12]). The same molecular dynamics simulation predicts the following stress-strain curve for axial deformations of a finite microtubule:

![Stress-strain curve for a finite microtubule.](image)

Figure 5: Stress-strain curve for a finite microtubule. [12]

Shear modulus: 5 Pa (experimental [3]).

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. [12]

Needledman et al [13] have discovered that increasing the osmotic pressure above 600 Pa causes the microtubule to buckle from a circular cross section with a diameter of ~25 nm to a noncircular shape with a short dimension of ~19 nm. Further increasing of the osmotic pressure to 200 kPa only decreases the short dimension to ~16 nm. Molecular dynamics simulation gives the following behavior of microtubules when exposed to the radial stress:
Figure 6: 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. [12]

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 [12].

Wells et al [12] also explain the behavior of microtubules if they are twisted about their axis. They predict asymmetrical behavior with regard to the direction of twisting. This is due to the helical structure of the microtubules.

Figure 7: 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 $\sim 89 \text{nN mm}$ 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. [12]

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 $\gamma$-tubulin ring complexes. The third, not yet discussed, type of tubulins, $\gamma$-tubulin, can be found only in MTOCs. It forms rings of 13 units which serve as bases to which tubulin heterodimers from the surrounding cytoplasm can attach. [5]
During mitosis, the microtubule array present in interphase dissassembles and free tubulin subunits reassemble to form the mitotic spindle. This process is directed by duplication of the centrosome (Fig. 1). [1]

There is 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. [9]

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. Needlemen et al. [13] report transition from nematic to rectangular bundle to hexagonal bundle phases of microtubules with the increase of osmotic pressure. In their other work [14] 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 Needlemen et al. are experimental and there is a lack of theoretical models of the observed phase transitions [14].

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. [4]

---

**Figure 8:** 1. Immunofluorescent micrograph of neuronal microtubules interconnected by MAPs [4]. 2. Organization of microtubules within neurons [4]. 3. The so called 9-1 structure of microtubules in cilia and flagella with 9 doublets surrounding the central one (cross section) [10]. 4. Rectangular (with radially compressed microtubules) and hexagonal bundle phases [13]. 5. Phase diagram (a log-log graph of pressure as a function of microtubule concentration) for phases reported by [13]. 6. Higher order assembling of microtubules is governed by the size of the cations in the solution used in the *in vitro* experiment [14].
3 Theories describing information processing and signaling in microtubules

Several experimental observations suggest that microtubules serve not only as “bone-like” support, circulatory and kinematic 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. There are a few different models 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 [4]. In microtubules, energy to pump coherent excitations could be provided by thermal energy of the surrounding “heath bath”, as originally proposed by Fröhlich [4], phosphorylation [4] or by hydrolysis of GTP to GDP [3, 4].

Based on the coherent pumped phonon theory, microtubules are predicted 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 global discrete time - each subunit can change its state only at “ticks” of a global clock.

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.

Figure 9: A result of a microtubule cellular automaton simulation. The starting pattern evolves through 8 ns time steps. White and black tubulins correspond to $\alpha$ and $\beta$ states, correspondingly, eight drawings represent eight consecutive time steps.
There were several simulations of microtubules acting as cellular automata performed. The discrete clocking mechanism was given by the Fröhlich excitation model and the transition rules determined by the electrostatic dipole interaction between the tubulins. The $\alpha$ and $\beta$ 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.

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. Different patterns could determine binding sites for MAPs and thus neuronal and synaptic architecture. [4]

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 [4], 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 [15, 16] 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. [17] 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 [15]) functions, furthermore, no computable theory can describe it. [17] 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 [18].

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.

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 extent 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

\[
|\psi(t)\rangle = N \sum_i c_i(t) |\psi_i(t)\rangle,
\]

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 \( \{|\psi_{ij}(t)\rangle\}_{j=1,...,n_i} \) is the basis for the \( i \)-th object, then the basis of the whole system is given by

\[
\{|\psi_{1j_1}(t)\rangle \otimes \ldots \otimes |\psi_{mj_m}(t)\rangle\}_{j_1,...,j_m}.
\]

It is obvious that the dimension of the tensor product is \( n_1 \cdot \ldots \cdot n_m. \) \([19]\)

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 in the potential it is surrounded with, governed by Schrödinger’s equation. It is called unitary, because the norm of a state evolved in this way 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. It disturbed many physicists, why human interaction with the quantum system should be something special and have different (non-unitary) evolution rules. There were several alternative interpretations developed where only unitary evolution is aloud. An example is quantum decoherence, 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. Unitary evolution causes the measured system to decohere into a classical state or in other words the density matrix of the measured system is diagonalized during the time evolution by the entire hamiltonian. 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 how to compute the probabilities). This makes the time evolution in quantum mechanics altogether computable. \([4, 18]\)

Quantum computation utilizes coherent states of quantum objects with discrete spectra (usually two-level systems) 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. \([4, 19]\)

### 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 in unifying 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 supersymmetries, M theories, non-commuting geometries to string theories, but until now none has given good results.

**Figure 10:** How do we treat superposed quantum states that cause a differently curved space-time each? As a superposed spacetime? [16]

In his work from 1996 [18] 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 $E_\Delta$) 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 $E_\Delta$:

$$T \simeq \hbar/E_\Delta$$

(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 $T$.[18] Because Penrose believes that when quantum gravity is discovered, the gravitationally driven collapse of a wave function will be shown to be non-computable [4].

A bit more difficult than the above estimate is the question how to compute $E_\Delta$, to which the major part of [18] is dedicated. The difficulty arises from the facts that there is no consistent way to identify points in two different space-times (curved manifolds) 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:

$$\Delta = -4\pi G \int \int (\rho(x) - \rho'(x))(\rho(y) - \rho'(y))/|x - y| d^3x d^3y,$$

(4)

where $\rho$ and $\rho'$ are the mass densities of the two displaced states and $G$ the gravitational constant. The author suggests that the correct $E_\Delta$ should be a multiple of $\Delta$.

Finally the author uses these results to calculate what the characteristic lifetimes of various objects would be. For a single proton 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. [18]
3.2.3 Orch OR: The model

Hameroff and Penrose [4] 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), 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 11](image)

**Figure 11:** A cycle in the computational mechanism proposed by the Orch OR model. Starting from a classical conformation of a tubulin heterodimers, these 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, a plot of 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.

Hameroff and Penrose calculate how many tubulins have to be involved in coherent computation to have 500 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.

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 very quickly 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 also involve 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 by regulating the calcium-ion concentration 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 12](image.png)

**Figure 12:** 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. [4]
3.2.4 Critiques of the model and experimental evidence

The Hameroff-Penrose Orch OR has been intensively discussed and polemicized since its publication in 1996. There have been many critiques mostly regarding the small probability for quantum coherence at physiological temperatures (the so called (too) “warm and wet” argument [22]) and excessive range of entanglement required by the Orch OR model [23]. There have been several theoretical treatments and simulations, giving a variety of answers whether Orch OR is possible or not. In one of the first serious critiques, Tegmark [17, 24] modeled coupled tubulin heterodimers and obtained that if the coherent tubulin states were possible, the decoherence time would only be of the order of magnitude of femtoseconds. This is indeed much shorter than 25 ms required by Penrose and Hameroff. In response, Hagan, Tuszynski and Hameroff [17, 25] argued that Tegmark was not using the Orch OR model but a model of his own construction. They showed that decoherence times, if all the shielding mechanisms stated in 3.2.3 are taken into account, would be of seven orders of magnitude Greater than Tegmark’s. This is still short of the required 25 ms. There are also more recent theoretical works, such as [6, 21, 22, 26, 27] or by Reimers et al [17], that mainly focus on certain aspects or details of the Orch OR proposal. For example, Georgiev [6] argues that GTP hydrolisis cannot provide enough energy for transition between $\alpha$ and $\beta$ conformational states of tubulin heterodimers. Or in another paper [27] the same author claims that the actual number of neurons in a typical brain neuron is $10^9$ and not $10^7$ as estimated by Penrose and Hameroff. This is actually in favour of the model, because it reduces the required number of coherent neurons from 10000 to 1500, which means that Orch OR could be possible in smaller systems than first estimated by the authors of the theory.

Regarding the experimental evidence, there have recently been direct observations of coherent quantum states in biological systems - in structures responsible for photosynthesis (not in microtubules) [26]. However, the decoherence times observed in photosynthetic systems are about 660 fs [17]. In microtubules, Bandyopadhyay has measured coherent resonance peaks, indicating coherent quantum processes. He also reports ballistic electronic transport in microtubules and some other phenomena that indicate their quantum behavior [26]. There have also been some observations that directly reveal errors in the details of the Orch OR model. For example, Kikkawa et al showed that cortical dendrites have ‘B’ type lattice and not mainly ‘A’ type, as predicted by Hameroff [17]. De Zeeuw et al showed that dendritic lamellar bodies are actually located micrometers away from gap junctions which indicates a mistake in the Penrose’s and Hameroff’s model of synaptic firings.

To sum up, there is too little evidence to either confirm or reject the Orch OR hypothesis. The theoretical results oppose one another and more importantly, sufficient experimental evidence is missing. This leaves Orch OR as a controversial theory. A reason for this also lies in the fact that it is a complex model on the edge of what is plausible and it is based on numerous nontrivial and unjustified assumptions. This are certainly not qualities of a robust theory.

References


