A Proposal for Memory Code

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Abstract

In an article in the March 8 issue of the journal PLoS Computational Biology, physicists Travis Craddock and Jack Tuszynski of the University of Alberta, and anesthesiologist Stuart Hameroff of the University of Arizona propose a mechanism for encoding synaptic memory in microtubules, major components of the structural cytoskeleton within neurons. The self-explanatory title of the article is Cytoskeletal Signaling: Is Memory Encoded in Microtubule Lattices by CaMKII Phosphorylation? [6]. The basic ideas of the model are described and criticized and after than TGD inspired model is discussed.

1 Basic ideas of the model of memorycode

The hexagonal cylindrical lattice of microtubule suggests the possibility of lattice consisting of bits and probably very many proposals have been made. One such idea is that bit is represented in terms of the two basic conformations of tubulin molecules called α and β. The recent proposal is that bit corresponds to the phosphorylation state of tubulin. Also a proposal that the bits form 6-bit bytes is considered: 64 different bytes are possible which would suggest a connection with the genetic code.

The motivation for the identification of byte is that CaMKII enzyme has in the active state insect like structure: 6 + 6 legs and the legs are either phosphorylated or not. This geometry is indeed very suggestive of connexion with 6 inputs and 6 outputs representing genetic codons representable as sequences of 6 bits. The geometry and electrostatics of CaMKII is complementary to the microtubular hexagonal lattice so that CaMKII could take care of the phosphorylation of microtubulins: 6 tubulins at most would be phosphorylated at one side. The presence of Ca^{+2} or calmodulin flux flowing to the neuron interior during nerve pulse is responsible for self-phosphorylation of CaMKII: one can say that CaMKII takes itself care that it remains permanently phosphorylated. I am not sure whether this stable phosphorylation means complete phosphorylation.

It is however difficult to imagine how Ca^{+2} and calmodulin flux could contain the information about the bit sequence and how this information could be coded in standard manner to phosphorylation pattern of legs. The only possibility which looks natural is that phosphorylation is a random process and only the fraction of phosphorylated legs depends on Ca^{+2} and calmodulin fluxes. Another possibility would be that the subsequence process of phosphorylation MT by completely phosphorylated CaMKII manages to do it selectively but it is very difficult to imagine how the information about codon could be transferred to the phosphorylation state of MT.

For these reasons my cautious conclusion is that phosphorylation/its absence cannot represent bit. What has been however found is a mechanism of phosphorylation of MTs, and the question is what could be the function of this phosphorylation. Could this phosphorylation be related to memory but in different manner? The 6+6 structure of CaMKII certainly suggests that the analog of genetic code based on 6 bits might be present but realized in some other manner.

1.1 What does one mean with memory?

Before proceeding one must make clear what one means with memory in the recent context. The articles of New Scientists with - almost as a rule - sensationalistic titles, do not pay too much attention for the fact this kind of proposals are always based on some philosophical assumptions which might be wrong.

1. What one means with "memory" in the recent context? The memory in question is behavioral memory. Conditioning producing reflect like reaction is a typical example of behavioral memory and need not have anything to do with conscious memory such as episodal memory in which one literally re-lives an event of past. Electric stimulation of some regions of temporal lobes can indeed induce this kind of memories. The idea about coding would suggest the identification of this memory with a highly symbolic computer memory based on "carving in stone".

2. The proposal is inspired by the idea of brain or cell as computer and can be criticized. There is no pressing need for coding since behavioral memory can be reduced to the formation of associations and associative learning by computers is standard example of this kind of behavioral memory. One can of course consider the coding for declarative and verbal memories and genetic code provides an attractive candidate for a universal code. This kind of code might be behind the natural languages as a kind of molecular language.

3. Behavioral memories can be defined as changes of behavior resulting from a continued stimulus. The understanding of behavioral memory relies on the notions of synaptic strength, synaptic plasticity, and long term potentiation. Synaptic strength tells how strongly the postsynaptic neuron responds to the nerve pulse pattern arriving along pre-synaptic axon and mediated by neurotransmitter over the synaptic gap. For instance, glutamate acts as excitatory neurotransmitter and binding to receptor. At neuronal levels long term potentiation means increase of the synaptic strength so that post-synaptic neuron becomes "more attentive" to the firing of pre-synaptic neuron.

   Hebb's rules [2]- not established laws of Nature and plagued by exceptions - state that the effectiveness of synaptic receptors increases, when the two neurons fire simultaneously: it is important to notice that these firings need not have any causal connection with each other. The simultaneous firing activates NMDA receptors in the post-synaptic neuron and generates Ca^{+2} flux which correlates with the increase of the synaptic strength. NMDA obeys same chemical formula $C_5H_9NO_4$ as glutamate: in fact, glutamate and asparagin the two acidic amino-acids. It is also known that the presence of CaKMII is necessary for the increase of the synaptic strengths.

4. There is however an almost-paradox involved with this view about memory if assumed to explain all kinds of memories - in particular episodal memories. Long term conscious memories can be lifelong. Synaptic structures are however highly unstable since the synapses and proteins involved are cycled. To my view this argument is somewhat naive. There could be a flow equilibrium. The flow pattern of fluid flow in flow equilibrium can be stable although the fluid is replaced with new one all the time. The proposal of authors is that memories are stored to some more stable structures and that microtubules are these more stable structures making possible short term memories. Post-synaptic microtubules, which differ from presynaptic microtubules in several manners are indeed stabilized by MAPs. Authors also propose the thin filaments associated with the cytoskeleton are responsible for long term memories.

   Authors believe on computationalism and they apply standard view about time so that their conclusion is that long term memories are stored elsewhere and remain able to regulate synaptic plasticity. In this framework the notion of memory code is very natural.

1.2 LTP and synaptic plasticity

From Wikipedia one can read that synaptic plasticity [5] means possibility for changes in function, location and/or number of post-synaptic receptors and ion channels. Synapses are indeed very dynamical and synaptic receptors and channel proteins are transient, which does not seem to conform with the standard view about long term memory and indeed suggest that the stable structures are elsewhere.

Long term potentiation [3], briefly LTP, involves gene expression, protein synthesis and recruitment of new receptors or even synapses. The mechanism of LTP is believed to be following. The glutamate from pre-synaptic neuron binds to post-synaptic receptors, which leads to the opening of Ca^{+2} channels and influx of Ca^{+2} ions to dendritic spines, shafts and neuronal cell body. The inflow of Ca^{+2} induces activation of multiple enzyme including protein kinase A and C and CaMKII. These enzymes phosphorylate intra-neuronal molecules.

It is known that the presence of CaMKII is necessary for long term potentiation. This supports the proposal of authors that microtubules are involved in an essential manner in memory storage and processing and regulation of synaptic plasticity. The observation about the correspondence between the geometries of CaMKII and microtubular surface is rather impressive support for the role of MTs. To my opinion, the hypothesis about memory code is however un-necessary.

1.3 Microtubules

Quite generally, microtubules (MTs) are basic structural elements of cytoskeleton. They are rope like polymers and grow as long as 25 micrometers long. They are highly dynamical. The standard view identifies their basic function as maintaining of cell structures, providing platforms for intracellular transport, forming the spindle during mitosis, etc..

Microtubules [4] are extremely rich in eukaryotic biology and brain neurons. They are believed to connect membrane and cytoskeletal levels of information processing together. MTs are the basic structural elements of axons and MTs in axons and dendrites/neuronal cell bodies are different. Dendrites contain antiparallel arrays MTs interrupted and stabilized by microtubule associated proteins (MAPs) including MAP_2. This difference between dendritic and axonal microtubules could be relevant for the understanding of the neuronal information processing. Microtubules are associated also with long neural pathways from sensory receptors, which seem to maximize their length.

For these reasons it would not be surprising if MTs would play a key role in the information processing at neuronal level. Indeed, the more modern view tends to see microtubules as the nervous system of the cell, and the hexagonal lattice like structure of microtubuless trongly suggests information processing as a basic function of microtubules. Many information processing related functions have been proposed for microtubules. Microtubules have been suggested role as cellular automatons and also quantum coherence in microtubular scale has been proposed.

The proposal of the article is that short term memory is realized in terms of a memory code at the level of MTs and that intermediate filaments which are much more stable could be responsible for long term memory.

1.4 CaMKII enzyme

According to the proposal the key enzyme of memory would be Calcium/calmodulin-dependent protein kinase II: briefly CaMKII [1]. Its presence is known to be necessary for long term potentiation.

In passive state CaMKII has snowflake shape. The activated kinase looks like double sided insect with six legged kinase domains on both sides of a central domain. Activation means phosphorylation of the 6+6 legs of this "nano-insect". In the presence of Ca^{+2} or calmodulin flux CaKMII self-actives meaning self-phosphorylation so that it remains permanently active.

There are however grave objections against phosphate=1–no-phosphate=0 coding.

1. Only the fluxes of Ca^{+2} and/or calmodulin matter so that it is very difficult to imagine any coding. One would expect that the fraction of phosphorylated legs depends on these fluxes in equilibrium but it is very difficult to image how these fluxes could carry information about a specific pattern of phosphorylation for legs. If all legs are phosphorylated the coding to microtubular phosphorylation would require that 6 bits of information is fed at this stage by

telling which leg actually gives its phosphate to tubulin. This does not look two plausible but one must be very cautious in making too strong conclusions.

2. Since metabolic energy is necessary for any information processing, the more plausible interpretation would be that phosphorylation makes bit active. Bit itself would be represented in some other manner. The 6+6 leg structure of CaMKII is very suggestive of a connexion with 6 incoming bits and 6 outgoing bits - possible same or conjugated. The interpretation in terms of DNA codon and its conjugate is what comes first in mind.

One should not however throw away child with the wash water. The highly interesting discovery discussed in the article [6] is that the spatial dimensions, geometric shape, and electrostatic binding of the insect-like CamKII and hexagonal lattices of tubulin proteins in microtubules fit nicely together. The authors show how CaMKII kinase domains can collectively bind and phosphorylate MTs. This alone could be an extremely important piece of information. There is no need to identify bit with phosphorylation state.

2 TGD view about the situation

TGD based view about memory could have been developed by starting from the paradox related to long term memories. Memories are long lasting but the structures supposed to be responsible for their storage are short-lived. TGD based solution of the paradox would be based on new view about the relationship between geometric time and experienced time.

1. According to this view brain is 4-dimensional and primary memories are in the time-place, where the neural event took place for the first time. In principle there would be no need to store memories by "carving them in stone". To remember would be to see in time direction: this view is indeed possible in zero energy ontology. Time-like entanglement and signaling to the geometric past using negative energy signals would be the basic mechanisms of memory.

2. Stable memories require copies also for another reason. The negative energy signal to geometric past is not expected to allow a precise targeting to a one particular moment of time in past. To circumvent the problem one must make the target large enough in time direction. The strengthening of memory would mean building up large number of copies of memory. These copies are produced in every conscious memory recall and learning would be based on this mechanism. The neuronal mechanism would produce large number of copies of the memory and one can ask whether CaMKII indeed generates phosphorylated sections of MT somehow essential for the representation of long term symbolic memories as names for experiences rather than experiences themselves.

3. Metabolism must relate also to conscious memory recall. Since negative energy signals are involved, there is great temptation to assume that de-phosphorylation liberating metabolic energy corresponding to the absorbed negative energy accompanies memory recall. Large $\hbar$ for the photons involved would allow very low frequencies -expected to characterize the time span of memory recall - and make communications over very long time intervals possible. This would mean that the original memory representation is destroyed in the memory recall. This would conform with the spirit of quantum no-cloning theorem [1]. Several copies of the memory representation would be needed and also feed of metabolic energy to generate new copies. In this framework conscious memory recall would be dynamical event rather than stable bit sequence in accordance with the vision about quantum jump as moment of consciousness.

2.1 Braiding as a universal model for memory

This leaves a lot of freedom to construct more detailed models of symbolic memories.

1. Braiding of magnetic flux tubes would make possible not only topological quantum computation [1] but also a universal mechanism of long term memory. In the model of DNA as topological quantum computer the flux tubes connect DNA nucleotides and lipids of cell membrane. It turned out that the flux tubes carrying dark matter - identified as ordinary particles

but with non-standard value of Planck constant [2] - could connect all kinds of biomolecules and that braiding and reconnection could serve as basic quantum mechanisms in the functioning of biomolecules. Flux tubes could also connect the tubulins of microtubules and lipids of axonal or dendritic membrane.

2. Two kinds of braidings are present: the lipid flow defines braiding in time direction as the analog of dance and the fact that lipids are like dancers with threads from shoes the wall - now microtubule surface - so that the dance induce braiding of these threads storing the dynamics of the dance to memory. The presence of both space-like and time-like braiding and the fact that they are in well-defined sense dual has become central idea of quantum TGD itself. Originally it was however discovered in the model for DNA as topological quantum computer [1].

3. Both active memory recall by sending negative energy dark photon to geometric past and spontaneous memory recall by receiving a positive energy photons from geometric past require metabolic energy. Therefore the presence of phosphate in braid strands is necessary. The flux tubes defining braid strands can be therefore assumed to be active only if they have phosphate at the other end. A more appropriate TGD based interpretation is that this makes possible negentropic entanglement, which is one of the basic predictions of the number theoretic vision about life. High energy phosphate bond would thus a signature of negentropic entanglement, which could serve as a correlate for the experience of understanding. One could relate ATP-ADP process as a basic process of life directly to cognition. The presence of phosphate would tell that there is magnetic flux tube - actually pair of them- beginning from the molecule.

2.2 TGD variant of the microtubular model for memory

The finding of the authors inspires a more detailed formulation for the vision for how memories could be realized at microtubular level.

1. The phosphorylation of tubulins would generate active braids strands and their presence would make possible memory recall. Note that memories as such could be stored to the braiding in any case if the microtubule-lipid flux tubes are present always. Every nerve pulse pattern would induce a flow of lipids at neuronal membrane if the membrane is in a phase corresponding to 2-D liquid crystal. This flow pattern would be stored to the braiding of the flux tubes.

2. In the model of DNA as topological quantum computer one assigns to braid strands connecting DNA nucleotides to lipids 4 different states representing the nucleotides A,T,C, G. In the original model the A,T,C,G were mapped to four states defined by quarks u,d and their antiquarks at the ends of braid strands. This proposal can be of course accused of being quite too science fictive. TGD however predicts the possibility of scaled up variants of QCD type physics even in the scale of living matter and there are some indications for this.

   A more down-to-earth realization of the genetic code proposed quite recently [3] is that braid states correspond to pairs of magnetic flux tubes. To the ends of both flux tubes one assigns electron so that the electrons form spin triplet and spin singlet state defining 3+1 states representing A,T,C,G. This gives also a connection with electronic super-conductivity which is fundamental assumption in the model of nerve pulse based on Josephson currents: nerve pulse corresponds to a simple perturbation of the ground state in which all Josephson current along axon are oscillating in the same phase. Mathematically the phase difference behaves like gravitational pendulum [4].

   The 6=2+2+2 legs could correspond to flux tube pairs and each flux tube pair would represent DNA nucleotide in terms of the spin state of electron pair. Phosphorylation would activate the braid strand by making possible negentropic entanglement and information storage and recall. This conforms with the fact of life is that metabolic energy is needed for all kinds of information processing including also information storage.

   If all 6 tubulins to which bits are assigned are indeed phosphorylated in the active state and if the memory recall involves use of metabolic energy as proposed, then the reading of the memory would mean complete de-phosphorylation of 6-tubulin sequences. The prediction would be the presence of phosphorylated 6-tubulin sequences at microtubular surface and their disappearance in memory recall. I do not know whether there is any manner to test these predictions.

3. For this proposal LTP would involve a generation of active braid strands. The post-synaptic neuron would be in "wake-up" state and would pay attention to the nerve pulse patterns arriving from the pre-synaptic neuron. This activation would be induced by simultaneous firing of post-synaptic and pre-synaptic neurons. As a consequence, the lipid flow would generate braidings providing memory representations and defining in temporal domain quantum computation like processes.

4. This does not yet explain why CaMKII is necessary for LTP. There is a high temptation to regard the increase of the synaptic sensitivity as a property of synaptic connection. One can imagine several mechanisms.

   (a) For instance, active flux tube connections between presynaptic lipids and postsynaptic microtubuli could be generated by phosphorylation, and the flux tubes might increase the flow of glutamate between pre- and post-synaptic neurons and in this manner increase synaptic strength. Flux tubes might make possible a continual flow of dark particles between pre- and post-synaptic neurons. They could also make possible negentropic entanglement between the two neutrons binding the neurons to single coherent quantum whole.

   (b) The strength of this connection could be affected also by the presence of active braid strands making possible quantum memory and topological quantum computation. Also more complex processes assigned with LTP would become possible since microtubules might be seen as conscious intelligent structures able to modify their nearby environment.

Books related to TGD

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