

TGD based model for anaesthetic action

M. Pitkänen

Email: matpitka6@gmail.com.

<http://tgdttheory.com/>.

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Abstract

The mechanism of anaesthetic action has remained mystery although a lot of data exist. The Meyer-Overton correlation suggests that the changes occurring at lipid layers of are responsible for anaesthesia but this model fails. Another model assumes that the binding of anaesthetics to membrane proteins is responsible for anaesthetic effects but also this model has problems. The hypothesis that the anaesthetics bind to the hydrophobic pockets of microtubules looks more promising.

The model should also explain hyperpolarization of neuronal membranes taking also place when consciousness is lost. The old finding of Becker is that the reduction or reversal of voltage between frontal brain and occipital regions correlates with the loss of consciousness. Microtubules and DNA are negatively charged and the discovery of Pollack that so called fourth phase of water involves generation of negatively charged regions could play a role in the model. Combining these inputs with TGD inspired theory of consciousness and quantum biology one ends up to a microtubule based model explaining the basic aspects of anaesthesia.

1 Introduction

The mechanism of anaesthetic action [J3] (http://en.wikipedia.org/wiki/Theories_of_general_anaesthetic_action) has remained mystery although a lot of data exist.

Typically anaesthetics induce analgesia, amnesia, and immobility. Some anaesthetics cause amnesia (brain) but no immobility (spinal cord). I have heard also about anecdotal evidence that anaesthetics do not always cause amnesia nor even analgesia.

The first question what comes in mind is whether anaesthetics indeed cause a loss of consciousness? In TGD framework self dies when the first state function reduction to the opposite boundary of CD occurs and time reversed self is generated [K9, K1]. Could also anaesthetics have the same effect? If so, anaesthesia would be like sleep, which need not be unconscious state but could represent time reversed self at "our" level of self hierarchy. This would explain also why we do not have memories about the period during sleep.

The Meyer-Overton correlation suggests that the changes occurring at lipid layers of are responsible for anaesthesia but this model fails. Another model assumes that the binding of anaesthetics to membrane proteins is responsible for anaesthetic effects but also this model has problems. The hypothesis that the anaesthetics bind to the hydrophobic pockets of microtubules looks more promising.

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2 Background

2.1 Some facts about anaesthesia

To begin with, it is could to list some facts about anaesthetics.

1. Very different substances act as anaesthetics. No clear correlation with the chemical properties of substance. Even noble gases can act as anaesthetics. Short range van der Waals interaction involving induction of electric dipoles are the most natural candidates for the interaction. The increase of atmospheric pressure is known to reduce anaesthetic action.
2. The anaesthetic potency correlation or Meyer-Overton correlation [J2] (<https://paulingblog.wordpress.com/2009/06/04/the-meyer-overton-theory-of-anaesthesia/>) serves as an important guideline when one tries to imagine mechanisms of anaesthetic action. The potency of anaesthetist is proportional to the solubility to lipids. This led to the proposal that anaesthetics are solved into lipids and induce perturbation of lipid layer. Anaesthetics causes a fluidization of membrane. So does also a slight temperature increase but is not followed by anaesthesia. Several mechanisms along these lines have been proposed [J3] (http://en.wikipedia.org/wiki/Theories_of_general_anaesthetic_action). Further objection is that stereoisomers of anaesthetics have very different anaesthetic effects. Some drugs highly soluble to lipids have a convulsive effect instead (they are called non-immobilizers). A small increase in body temperature affects membrane density and fluidity as much as anaesthetics but does not cause anaesthesia. The reason why polar anaesthetics are less effective is that they have to cross blood-brain barrier. The effect of anaesthetist also vanishes above certain chain length in the case of homologous series of any general anaesthetic. For instance, for n-alcohols carbon chain length of 13 units serves as a cutoff raising the question whether the anaesthetic effect occurs at microtubular surface having this kind of periodicity. The solubility to lipids does not display this kind of effect.

The conclusion is that lipid solubility is only a necessary condition (allowing the anaesthetist to get through the membrane) and the lipids in question need not be associated with cell membrane but be hydrophobic pockets of proteins.

3. Second proposal is that anaesthetics could bind to membrane proteins. Some anaesthetics are indeed stereospecific. This hypothesis led to the observation that general anaesthetics can also interact with the hydrophobic proteins sites of certain proteins. It is known that lock-key mechanism is not the general mechanism. Rather, it seems that anaesthetics affect protein dynamics in microsecond-millisecond time scale.

What one can conclude?

1. Effects on lipid layers do not explain the findings. Anaesthetist must be able to traverse neuronal membrane. High solubility to lipids certainly helps here. Different anaesthetic effect of stereoisomers suggests that the process involves further step(s).
2. Chemical bind and lock-key mechanism does not explain all findings: noble gases serve as a good example and suggests that also van der Waals interactions are important in some cases at least. The ability of anaesthetics prefer to bind to hydrophobic pi rings might be important. This kind of rings are associated with tubulin dimers, which suggests that the action of anaesthetist takes place at the level of microtubules.

2.2 Some basic facts about microtubules

1. Microtubules have been proposed to be central for consciousness. In [J1] <http://phys.org/news/2015-04-quantum-criticality-life-proteins.html> Stuart Hameroff discusses this hypothesis in light of the recent findings of Stuart Kauffmann, Gabor Vattay et al [J6] supporting the view that quantum criticality is a general property of biomolecules. Quantum criticality is the key notion of not only TGD inspired view about life [K13] but of entire TGD and realized in terms of hierarchy of sub-algebras of super-symplectic algebra represented as conformal gauge transformations [K2].

Hameroff argues that the hydrophobic regions are seats of consciousness and the interaction of anaesthetics with them leads to a non-conscious state. The view discussed below is not so simple but assumes that this interaction is central in the process leading to a loss of consciousness.

2. A related proposal [J12, J11] is that in the case of microtubules ferro-electric phase explaining the polarization of microtubules makes possible signalling along microtubule highly relevant to consciousness. Also this view is in accord with TGD based vision where resonant communications using dark photons with large Planck constant and having universal energy spectrum in the range of visible and UV energies is central. This gives connection also with quantum gravitation but in a manner very different from that in the model of Penrose and Hameroff [J9]. Quantum coherence in even astrophysical scales is essential.

The stabilization of microtubules is due to the negative charge density along them.

1. Microtubular carry negative charge density due to the binding of 2 GTP molecules to each tubulin dimer (<http://arxiv.org/pdf/1206.4400.pdf>). The article estimates the potential experience by given tubulin dimer and coming from the other dimers. It is assumed that microtubular alpha and beta proteins have positive charge, which cannot be true. The charge density is negative.

The article of Jack Tuszyński [J12, J11] provides a good view about non-linear liquid crystal model for ferro-electric phase of microtubules and also contains illustration about the average negative charge density of tubulin dimer.

2. Where does the positive charge reside? TGD interpretation for the fourth phase of water suggests that it resides outside microtubules at magnetic flux tubes as dark protons with large value of h_{eff} [K11, K10]. Huping and Wu [J10] have observed that proton pairs with members at opposite sides of cell membrane have spin-spin interaction frequencies in ELF scale, I have proposed that these protons are dark: TGD inspired model of super-conductivity suggests that they form a super-conducting phase. Also electrons and fermionic ions could be super-conducting with same binding energies for Cooper pairs [K8]. On basis of a model for dark protons I have proposed that they give rise to a representations of DNA, RNA, amino-acids and perhaps even tRNA and that also genetic is naturally realized [K4] and that dark proton sequences accompany DNA: this might make sense since also DNA is negatively charged with 2 negative charges per nucleotide.
3. The empirical rule for the direction of electric polarization is that the neuronal ends of axonal microtubules correspond to minus ends of the microtubule. Remarkably, in the case of dendrites there is fifty-fifty distribution in polarity in the case of vertebrates but for invertebrates the the dendrites have positive neuronal end [J7] (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2555934/>). This could tells something very deep about consciousness.

In TGD selves has time reversed variants born when self dies as the first state function reduction to the opposite boundary of CD takes place. Since electric potential changes sign in time reversal, the presence of two kinds of dendrites could relate to memory. Electric voltage changes its sign in time reversal and indeed leads to a loss of consciousness in the scales studied by Becker [J5]. Could the dendrites correspond to sensory dendrites and memory dendrites? Memories would involve signalling in reversed time direction and memory dendrites. The important conclusion would be that invertebrates would not have memory at this level of self hierarchy.

3 TGD based model for anaesthesia

In TGD based model for anaesthesia magnetic body, supra currents [K7, ?], and dark matter [K3, K13] should be involved. Besides this the findings of Pollack [I1], Becker's discoveries [J5], and microtubules, in particular the latest findings [J4, J8] are expected to be in a central role in the model.

1. The fourth phase of water discovered by Pollack [I1] involving charge separation creating negatively charged regions with sizes up to $100 \mu\text{m}$ and $H_{1.5}O$ stoichiometry inside negatively charged regions might be involved. Negatively charged linear structures populate living matter: for instance, DNA has 2 negative charges per nucleotide, tubulin dimers have 2 negative charge per nucleotide. Cell interior is also negatively charged. TGD based model [K11, K10] assumes that part of protons go to the magnetic flux tubes and become dark having large non-standard value of effective Planck constant $h_{eff} = n \times h$.
2. Becker's DC currents consist of electrons and are generated in wounds and lead to healing of the wound. What happens that wound gets in negative potential with respect to environment. For instance, frontal lobes are in negative potential with respect to the occipital regions and brain injury generates positive polarization. This means the presence of longitudinal electric fields and ferro-electric phase is a good guess. Becker's discoveries are discussed in TGD framework in [K8, K12]. It is proposed that electronic Becker currents are supra currents: this assumption is not necessary but possible. It is also proposed that the currents flow along microtubules.
3. Microtubular ferro-electric property could be the mechanism generating the electric potentials and the action of anaesthetics could weaken or destroy these potentials. There is an old discussion of ideas related to microtubules in [K6] and the latest findings are Bandyopadhyay et al are modelled in in [K12].

3.1 Mostly questions

It is good to start with a list of questions.

1. Could the mechanisms inducing anaesthesia and sleep have something in common? Could also anaesthetics induce hyperpolarization so that nerve pulses are not generated so much? How the hyperpolarization would be induced?
2. Could there be a connection with DC currents of Becker [J5]? Could anaesthesia reduce the strengths of the electric fields of Becker or maybe even reverse their direction. For instance, the electric field between frontal lobes and occipital lobes could change its direction or get weaker.
3. Healing by DC currents means that the damaged body part generates negative potential. DC currents of Becker consisting of electrons make this possible. Could one say that the damaged body part becomes conscious? Could also cell interior, DNA, microtubules negatively charged be conscious. In TGD framework it is difficult to think how they could avoid of being conscious.
4. Could there be a connection with microtubules and their ferroelectric phase transition? Could the microtubular longitudinal electric fields be responsible for these electric fields and could DC currents of Becker accompany microtubules? Is the phase transition destroying microtubular ferro-electricity responsible for the loss of consciousness induced by anaesthetics? Could the phase transition change the direction of electric field? Could this mean change of the arrow of time generating time reversed mental images? Could these two kinds of mental images be assigned with the dendrites with opposite directions of electric field?
5. Could anaesthetics act on microtubules and induce a phase transition destroying their ferroelectric character? Could Becker's DC currents [J5] flow along microtubules as proposed [K8, K12]? Consciousness would be lost, when ferroelectricity of microtubules is reduced or disappears. Longitudinal electric field of microtubule associated with its negative charge density would become radial and would induce hyperpolarization.
6. Is there a connection with TGD view about self? Could the change of the sign of voltage be a space-time correlate for time reversal for self [K5] - in the usual interpretation loss of consciousness? Could amnesia about period of "non-consciousness" be due to time reversal changing the sign of the potential.

3.2 What could happen in the ferro-electric phase transition?

What could happen in the phase transition making microtubule ferro-electric and in the reverse phase transition leading to a loss of consciousness?

1. Coherent orientation of the microtubular dipoles in longitudinal direction can generate a longitudinal electric field which for long microtubules is proportional to the electric charge at the second end. If the orientations of tubulin dipoles are random, the net electric field is also random. The effect of anaesthetist would be to randomize the directions of dipoles so that the potential between the ends of microtubule would be random. One can wonder whether this field is really strong enough to explain the experimental findings [?].
2. Microtubule carries non-vanishing constant negative charge density. Charge density is due to the presence of two GTPs differing from ATPs only in that A is replaced with G attached to the tubulin dimer and stabilizing it.

The non-topological half of Maxwell's equations also in TGD framework at the level of space-time surfaces. One can however assume it at QFT limit. Consider the solutions to the Maxwell equation $\nabla^2\Phi = -\rho_q$ for constant charge density ρ_q concentrated on long linear structure, say microtubule. The standard ansatz is that outside of a very long microtubule the potential depends on the radial coordinate ρ only. Φ satisfies Laplace equation $\partial_\rho^2\Phi + \partial_\rho\Phi/\rho = 0$ giving a potential of form $\Phi = az + k\log(\rho/\rho_0)$ creating a slowly varying radial electric field and constant electric field inside microtubule. For this option microtubule would be analogous to a conductor for which the tangential electric field at microtubular surface vanishes. The value of k is proportional to the surface charge density.

3. In the article of Tuzcinsky et al [?] it is assumed that inside microtubular surface the potential restricted to the microtubular surface satisfies the equation $\partial_z^2\Phi = \rho_q$. A more general ansatz reads as $\Phi = az + bz^2 + c\rho^2$ with $2b + 3c = \rho_q$. The electric field increases along the microtubule and voltage between ends can be larger than the voltage solely due to a coherent polarization. One can indeed pose this kind of condition as a boundary condition in Maxwell's theory although it makes solution numerically complex.

The physical picture would be that the electric flux created by the electric flux decomposes to two parts. The first part flows along the microtubule and second part flows in good approximation in the radial direction. The electric field generated by microtubule would be at large distances that of a point like charge but nearby radial field would be weaker than for the solution carrying maximal radial flux and there would be longitudinal electric field. If a phase transition to a situation in which the electric field is radial occurs, the value of radial flux becomes maximal and could lead to a hyperpolarization of the cell membrane and reduce neuronal activity. At the same time the longitudinal electric field would be reduced and would lead to a loss of consciousness in accordance with the findings of Becker. Becker's findings and basic fact from neuroscience would have common explanation.

4. One can ask whether a phase transition could in some situation change the sign of the longitudinal electric field of microtubule. Could this occur for the dendritic microtubules of vertebrates for which both directions of electric field are present? The direction of electric field correlates with the structure of the microtubule so that the reversal very probably cannot occur for an existing microtubule.
5. How the anaesthetist bound to hydrophobic pi resonance rings generates the phase transition from ferro-electret to non-ferro-electric phase or to a phase with weaker longitudinal electric field? Anaesthetist should induce a phase transition in which the electric field transforms from longitudinal to radial. How could this happen and how it is possible to have large several phases?

Quantum criticality which in TGD framework is basic characteristic of life. It is basically due to the huge vacuum degeneracy of Kähler action inducing 4-dimensional spin glass degeneracy, which predicts that a given induced Kähler field allows all symplectic transforms of the space-time surface as its representations. Only classical gravitational fields differ for these representations.

Also classical gravitation would be relevant and TGD predicts macroscopic quantum gravitational coherence [K13] highly relevant for the model of bio-photons as decay products of dark photons defining key element of quantum control also at microtubular level. The universality also predicts that bio-super-conductivity is universal and possible for all charged particle involved and is characterized by same binding energies of Cooper pairs associated with pairs of flux tubes. Also bosonic analogs of supra-currents acting also as spin currents and associated with single flux tube are predicted [K8].

The model could generalize to other important biopolymers.

1. The presence of negative charge density due to GTP and ATP could provide biopolymers with negative charged density generating the stabilizing electric fields. The negative charge could be due to the generation of fourth phase of water discovered by Pollack [I1] transforming part of protons to dark protons and providing the electron for the molecules. This suggests a very close connection with metabolism.
2. Denaturation of basic biopolymers such as DNA and proteins could rely on a phase transition reducing the longitudinal electric fields. In TGD framework one could say that biopolymer loses consciousness. The presence of GTP and ATP is essential for element of the mechanism and their negative charge could be also due to the Pollack's mechanism.
3. The two strands of DNA could represent sub-selves with opposite time directions. Something similar might be realized at the level of brain. Brain hemispheres could have opposite arrow of time. The other hemisphere would remember and the other hemisphere would precognize (remember in reverse time direction).

3.3 Why some anaesthetes do not prevent motor actions?

Some anaesthetes do not prevent motor actions. This piece of data could provide a test for the model. The two kinds of dendrites are expected to be similar. The interaction of anaesthetes with the microtubules of dendrites could prevent memories as negative energy signals to past. The assumption that the two kinds of dendrites correspond to sensory experience and memories and have opposite arrows of time would explain that sensory experiences - including pain- and memories are prevented. Interaction with axonal microtubules would prevent motor actions. If given anaesthetist can bind only to dendrites or to microtubules inside them, one could explain the finding.

What could distinguish between inside dendrites and motor axons? Size scale is different and could prevent the interaction of some anaesthetes with the microtubules of motor axons. Also the microtubules could be somehow different inside dendrites and axons.

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