

The Honeycomb-like Biomembrane and Bioprotonics

Lev Verkhovsky (Moscow)

levver@list.ru

ABSTRACT

The hypothesis of Dr Raik Mikelsaar (Tartu) about the honeycomb-like structure of the lipid layer of biomembranes is briefly presented. Then the author of the article considered some possible consequences of it in bioenergetics and other aspects.

From the author: *The hypothesis of Dr. R.-H.N. Mikelsaar (Tartu University, Estonia) about the honeycomb-like structure of the lipid biomembrane was published in a scientific journal `Molecular Crystals and Liquid Crystals`, Vol. 152, pp. 229—257 (1987)*
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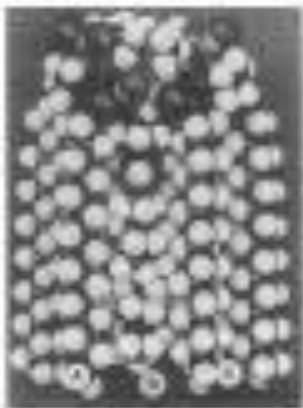
Then he published an article in the Soviet popular science magazine "Chemistry and Life" (1990, No. 4) in Russian, and after that I wrote a short paper "Bioprotonics", in which I tried to develop the Mikelsaar hypothesis in relation to bioenergetics. It was published in the same magazine (1990, No. 10).

Now I am presenting a translation of my paper into English (with minimal changes).

First, I briefly outline the essence of the Mikelsaar hypothesis about the honeycomb-like structure of the lipid biomembranes.

Working (= playing) with Tartu plastic atomic-molecular space-filling models (made under his leadership) Dr. Mikelsaar discovered that the three phospholipid molecules can form a right hexagonal prism. Every prism is closed above by `a hat` of three polar groups (heads of lipids) — they are bound by electrostatic interactions. According to Mikelsaar`s hypothesis, **such hexagonal trimeric units cover all the surface of the membrane** — it looks like the floor of a room with the parquet hexagonal tiles. And it is similar to a honeycomb.

But inside prisms, there are cavities which must be filled with some substance. It turned out that the three molecules of cholesterol perfectly fit it (on the photo); however, the quantity of this steroid in the lipid layer can vary and be not enough to fill all prisms. In this case, the prisms can contain -- and this is a clue point -- **tubes of structured (ice-like) water** (they are named shafts); thus, so-called a hydrophobic lipid



membrane may contain significant amounts of water. It is important that in the hydrophobic environment of lipid tails, this water (shafts) will freeze not at zero by Celsius but at a higher temperature. Ice`s melting will cause greater mobility of lipids, and that`s **the physical meaning of the membrane phase transition** (it is known, the high amount of cholesterol diminishes phase transition, now it becomes clear, why: the absence of water – the absence of transition).

A very interesting opportunity this honeycomb model opens for the molecular mechanism of **nerve impulses**. There is opinion (I. Tasaki), that Na^+ flow through the membrane occurs not by using special protein channels, but directly through the lipid bilayer, which changes its state under the action of a potential jump. The proposed model implements this idea. And what is the role of ion channel protein? Apparently, they perform some other (possibly, regulatory functions). There is evidence that in the axons of some organisms the density of these proteins in the membrane is very low, so they most likely cannot provide a large flow of sodium ions through the membrane.

It is established that this process is accompanied by the shift of charged atomic groups (gate current). One can imagine such a picture: at the potential jump on the membrane polar heads of lipids will rise, turn at a

certain angle and fall into new positions, forming connections with the heads of neighboring prisms; in this membrane's domain, the quasi-crystalline state will arise. The gates open and each prism will become a channel for sodium ions — the geometry of the holes at the top will allow Na^+ (but not K^+) to pass through.

The model also gives a new understanding of **general anesthesia**: molecules of anesthetics (it may be even inert gases) form clathrate structures in water shafts and close them.

Usually, as an objection to the proposed model, it was pointed out that an ordered (honeycomb-like) structure was not detected experimentally. Perhaps advances in experimental technique will help solve this problem.

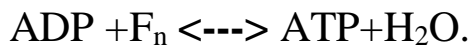
These are the main provisions of the Mikelsaar hypothesis. Below I present my article.

As the membranologists themselves admit, they have accumulated so much experimental data that it has become difficult to navigate; some new generalizing ideas are required. An interesting attempt was the hypothesis published in «ХИМИЯ И ЖИЗНЬ» (Chemistry and Life, 1990, No. 4) by a researcher from Tartu Dr. Raik Mikelsaar about the honeycomb-like structure of the membrane.

An unexpected and even at first glance paradoxical feature of it is that the so-called hydrophobic layer of the membrane (where lipid tails are enclosed) can, it turns out, to a large extent consist of water. However, not ordinary -- liquid, but structured, ice-like. The tubes of interconnected H_2O molecules inside phospholipid prisms were called "shafts". Since lipid matrices already limit the mobility of water in the shafts, as if they freeze it, the change in the aggregate state of the "water — ice" type in them and the associated phase transition of the entire lipid film will be observed not at zero Celsius, but at a higher, possibly physiological temperature (it primarily depends on the specific composition of lipids).

The phase transition of the membrane, in turn, will affect the membrane enzymes -- new cascades of reactions will turn on, which will change the properties of the cell as a whole. As a result, the very weak initial signal that caused the phase rearrangement will be amplified many times. In other words, such a membrane will serve as a very sensitive biosensor -- chemical, when the transition is induced even by single molecules, say, hormone or prostaglandin (this was discussed in the Mikelsaar's article), or physical, for example, with thermal radiation.

In general, the aggregate state of the water in the shafts will be influenced by a variety of factors, including, of course, the membrane potential. This circumstance, apparently, is able to shed light on one of the key mysteries of bioenergetics: how the universal cellular fuel is formed — the famous ATP. The chemiosmotic theory proposed by Peter Mitchell (Nobel Prize for 1978) states that during the oxidation of fats and carbohydrates by enzymes of the respiratory chain, electric charges are transferred through the membrane, and then the created electrochemical gradient of protons is used by another enzyme -- ATP synthetase, which attaches inorganic phosphate to ADP:



It has already been firmly established, that the membrane potential is the link between oxidation and phosphorylation. But at the same time, it is still unclear how this potential leads to the synthesis of ATP. Some researchers believe that first it causes a conformational change in the enzyme, and then the internal energy of the protein is used to form a chemical bond. However, this idea seems too general and explains little.

Let's take another look at the above reaction of synthesis-hydrolysis of ATP. It is clear that its equilibrium can be shifted to the right if one of its final products (water) is diverted. Moreover, it is not necessary to physically transfer it somewhere, but it is enough only to lower its chemical activity. Well, for example, by transferring to ice, that is, freezing. And this function could be performed by the membrane potential. We can suppose that the change in the aggregate state of water

in the membrane is the desired link between the membrane potential and the synthesis-hydrolysis of ATP.

In fact, let the respiratory circuit work, the membrane is charged. As a result, structural changes and phase changes are taking place in it. When the membrane is charged, the water in it will become liquid (this is reported by the fluorescent probes built into the membrane). But if now in some place several protons pass through it down the gradient of their concentration, then locally, for a moment, the membrane will discharge and the water in the shafts will freeze. This means that the equilibrium will shift to the right -- to the synthesis of ATP. And in the opposite direction: the membrane is not charged, the water in it is in a crystalline state. But if we throw a few protons across the membrane (outward), then the ice will melt locally and our reaction will go to the left (hydrolysis) -- in this case, the enzyme operates in the ion pump mode.

In addition to this protein, there are other ion pumps in different membranes (sodium-potassium, calcium) that transport ions through the membrane or, conversely, synthesize ATP when the membrane capacitor is discharged. It is natural to assume that they operate on the same principle, which, probably, could be called "aquachemiosmotic".

It is important that protons can migrate through ice-like water by the "relay" mechanism (known also as the de Grotthuss proton "hopping" mechanism) -- this conduction has nothing to do with ion diffusion.

The presence of ice shafts in the membrane allows us to return to a new level to the analogy that was pointed out in 1958 by the future Nobel laureate Manfred Eigen and a Belgian Leo De Maeyer. They drew attention to the fact that the "relay" mechanism of proton conduction resembles the movement of electrons and "holes" in conventional semiconductors. An electronic, *n*-type semiconductor corresponds to ice with an excess of protons, and *p*-type -- with an excess of hydroxyls,

which are also like "holes" in water molecules that have lost one hydrogen atom.

If you connect two pieces of ice with different types of carriers, then a shut—off potential arises at the boundary separating them -- an analog, an *n-p* junction in semiconductors, that is, a proton rectifier, a diode, will turn out. Eigen and De Maeyer noticed that since there are ice-like structures in the "pores of protein membranes", this would be important for biology, where combinations of such elements could give systems similar to those studied by technical cybernetics.

In a honeycomb-like membrane, the shafts are able to pass protons in one direction -- in accordance with their orientation, and for other ions, the lipid membrane can be considered an impenetrable barrier. On the other hand, individual compartments of a cell can vary greatly in the concentration of hydrogen ions (in their pH). An acidic environment is possible in one compartment, an alkaline one in the other. According to the gradient of their concentration, excess carriers will begin to seep into neighboring compartments, and a shut-off potential will appear on the membrane separating them.

It is clear that such a membrane will be very susceptible to electric fields: in a certain way, the applied field will enrich the close to membrane zone with current carriers, current will flow through the boundary, the potential will be removed. And this will cause a phase transition in it with all the consequences that follow from this. A very important, but still poorly understood role of electric fields in the body is being clarified.

But there is a complex, branched network of membranes in the cell — the endoplasmic reticulum. This means that complexes of three compartments separated by two membranes are possible there -- an analog of *n-p-n*-- or *p-n-p*--junctions in semiconductors that form a triode -- the main element of electronic circuits. And if so, what prevents a radio receiver or a computing device from being assembled in a cell from such proton transistors?

Another Nobel laureate, Albert St. Gyorgy, wrote a small book called "Bioelectronics" (1968). If the hypothesis about the honeycomb-like structure of biomembranes is confirmed, then, apparently, it will be possible to start writing "Bioprotonics".

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