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"Everything should be made as simple as possible, but not simpler."
A. Einstein

Biomimetic Membranes without Proteins but with Aqueous Nanochannels and Facilitated Transport. Minireview

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Abstract—Imitation of biological membranes and aqueous channels attracts more and more attention. In this review, we mention both the early and very recent papers in this area. Still, we concentrate our attention on less known biomimetic membranes, which are commercial nitrocellulose ultrafilters, impregnated by esters of fatty acids. Pores in filters are filled with lipid-like oils, but aqueous nanochannels are spontaneously formed on the inner pore surfaces with carboxylic groups fixed on nitrocellulose. This combination imitates the most fundamental barrier properties of biological membranes, including specific (per unit thickness) permeability of respiratory gases, transport of nonelectrolytes, water, and ions, cation/anion selectivity, electric impedance, etc. The activation energy for water transport in nanochannels is similar to that in aquaporin. In the presence of fatty acids and other carriers, it is possible to observe facilitated and coupled active counter transport of different metal cations in exchange to H^+ and without any transmembrane pressure, voltage or ATP. When quinones are dissolved in oils, light-sensitive co-transport of electrons and H^+ through oil is possible. In this case, redox-active substances are separated by the membrane. They are not mixed, but they still react. Small biomimetic membranes can be used as electrochemical drug sensors in drug detection and screening, medium size membranes—for smart transdermal drug -delivery, and large membranes—for industrial separation and purification. For example, after small modifications, they can be used for metal recovery, including radioactive strontium removal from nuclear waste accumulated and stored since the Cold War.

Keywords: biomimetic membranes, aqueous nanochannels, passive and active transport, transmembrane reactions, transport regulation, applications

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INTRODUCTION

Biomimetics (Greek *mimetikos* = imitative) is one of the hot areas of modern science with the purpose to model and thus to understand fundamental ideas or principles from biology, and then based on these ideas/principles to create something artificial and useful. Biological membranes are playing a critical role in live organisms because they not only lead to compartmentalization in cells, but they also have selective permeability and catalytic activity, which can be regulated by different signals, including chemical and biochemical (pH, Ca^{2+}, neuro mediators, etc.), electric (transmembrane voltage) and physical factors (mechanical stress, light, temperature). Biomimetic membranes are based on biological principles; they are easy to make, cheap but simple, and stable enough to be used again and again. They could find many practical applications, including small membranes in sensors, medium-sized membranes in drug delivery, and large membranes in chemical separation and purification processes, including water purification [1–31].

The most well-known models of biological membranes are lipid-based monolayers at air/water interface, Langmuir-Blodgett multilayer films on different supports, bilayer lipid membranes (well-known abbreviation BLM), and liposomes [32–34]. The more recent development is lipid-protein nanodiscs [35]. In some cases, synthetic polymers are used to imitate their biological analogs, for example, polyhydroxyalkanoates imitate bacterial poly(3-hydroxybutyrate) [36]. Bulk liquid membranes, which can find applications in chemical separations and wastewater treatment, also mimic some aspects of biological membranes, as described in the books [37, 38]. These books also describe supported liquid membranes.

As we can see, several good reviews are describing biomimetic membranes and their applications. Instead, we will mainly discuss one specific example

of much less known biomimetic membranes, which are simple nitrocellulose ultrafilters, initially impregnated by organic solvents [39–43], and then by fatty acids, their esters, and some other lipid-like substances [44–52]. These membranes investigated in our group do not look like biological membranes, but their characterization shows that they have many of fundamental similarities. We will also briefly mention our related publications describing supported liquid membranes and some possible biophysical implications. Thus, we will summarize our major results and show how modeling of biological processes and new applications can be closely related. A hundred sixty years ago, Michael Faraday published a book "The Chemical History of a Candle" [53]. Candles are made of stearin, paraffin, tallow, or bee wax. This short paper describes the chemical history of an oily filter paper, which can be used as a biomimetic membrane.

Oil-Impregnated Nitrocellulose Filters as a Model of Biological Membranes

It is known that Alfred Nobel was using nitrocellulose impregnated by nitroglycerin in one of his dynamites. Ashless nitrocellulose filters were developed after the Second World War for micro- and ultrafiltration, for example, to remove microbiological weapons from water wells. It looks like a bright flash when these filters are burnt, and no ash is left behind. In 1963–1973 Asher Ilani found another possible application for these filters. He demonstrated that Millipore filters after impregnation with different organic solvents have not only cation/anion but also cation/cation selectivity. In addition, their capacitance was frequency-dependent, reminding one of the fundamental properties of biomembranes. The electric resistances of such filter-based membranes could be changed by 100–1000 times by simple changes of a solvent, such as chloroform, toluene, bromobenzene, etc. As a result, Ilani suggested that these membranes have "fixed negative sites in an aqueous channel, surrounded by a medium of low dielectric constant" [39–43].

Impregnating liquid fills the pores, which is easy to see by measuring the membrane weight before and after impregnation. It is possible to impregnate filters by dissolving lipids in organic solvents and then removing the solvent from the pores, but in this case, lipids do not fully fill the pores [54, 55].

Trying to imitate biological membranes instead of lipids we decided to use simple and cheap esters of fatty acids available at that time in the former USSR and nitrocellulose Synpor filters produced in the former Czechoslovakia. The filters were impregnated by liquid esters of fatty acids, like iso-propyl laurate or methyl myristate, which are much cheaper than lecithin from eggs or soya. Previously oil-impregnated paper was used as an insulator in paper capacitors [56]. Now methyl esters of fatty acids are produced in large volumes and are used as biodiesel. In medicine iso-propyl myristate is used as a penetration enhancer for pharmaceutically active substances [57].

Impregnated filters are very easy to make, and they are stable enough to separate different systems, including gas/gas, gas/water, and water/water. Our experiments demonstrated that although these membranes are approximately 10000 times thicker than biological membranes (50–100 μ and ~50 Å), many of their physicochemical properties are very similar to the typical properties of biomembranes [44–48]. When the membrane separated air and aqueous solutions, important for respiration gases could penetrate through it. CO_2/O_2 selectivity was similar to a lung wall, which is explained by solubility and direct diffusion of gases through the impregnating oil [47]. When the membrane separated two aqueous solutions, the permeability of organic molecules was proportional to their hydrophobicity. Still, some small molecules like water and methanol went through the membrane much better than expected [44, 50]. This phenomenon is similar to the well-known tendencies of biological membranes, which are explained by the existence of aqueous channels [58].

Pretreatment of impregnated filters with water could lead to the dominant role of the "channel"-based process, and activation energy for water transport decreased from typical value for liposomes to observed in erythrocytes. The content of water in membranes was measured using calorimetry, impedance, and tritium-labelled water [44]. It became clear that there are narrow aqueous channels in our membranes, so that water is penetrating simultaneously both through oil and these channels. The channels are formed by nanolayers of water, adsorbed on the inner surface of the filter pores. They separate nitrocellulose and oil, which fills the pores [44]. At that time, the channel-forming protein aquaporin was not known yet.

Nitrocellulose is made from wood by treatment with concentrated nitric acid, and it has impurities of fixed carboxylic groups. If the pH is greater than 5, these groups have a negative charge, which leads to cation/ anion selectivity of the aqueous nanochannels. Moreover, related to K^+/Na^+ selectivity, bi-ionic K^+/Na^+ potential is thickness independent. It could be above 20 mV, comparable to the resting potential through some nerve membranes [46].

As usual [59], permeability in our experiments was inversely proportional to the membrane thickness but recalculated to the thickness of biomembranes it was comparable to that of erythrocytes. Direct current resistance R of the membrane, which characterizes ion transport, is proportional to the membrane thickness l, $R = (\chi_i + \rho l)/S$, and the specific resistivity ρ, calculated per unit of area and unit of thickness also is comparable to the one for biomembranes [45]. In comparison, nonmodified lecithin-based BLMs have a thickness of biomembranes, but without channels their resistivity is 4–5 orders of magnitude higher [33].

Moreover, using a stack of two, three, etc., impregnated filters and extrapolating results to zero thickness, it was possible to estimate the resistivity χ_i of unstirred aqueous layers and interfaces, which is undoubtedly important for thin biological membranes.

In the case of electrical capacitance, which characterizes membrane polarity, instead of dividing by thickness, one must multiply by the ratio of thicknesses, and thus calculated effective dielectric constant was higher than both dielectric constants of oil and nitrocellulose [60, 61]. This again confirmed the presence of aqueous nanostructures and was supported by direct measurement of water in the membrane using tritium labeling.

Thus, we had to divide by 10000 for comparison of specific electric resistivity, to account for thickness. For electric capacitance, which is inversely proportional to the thickness, we had to multiply by this number. Transmembrane voltage or activation energy of transport are not thickness-dependent, and scaling was unnecessary, but the values are still similar to those in biology. See the table with all these comparisons in paper [45].

Differential scanning calorimetry demonstrated that the freezing temperature of water in nitrocellulose-based membranes is below 0°C and depends on the pore size in a filter (0.05–0.45 μ) [62]. Note that heat of water adsorption on Whatman paper due to specific interactions is 114 *KJ/mol*, and it is much higher than that of medium-sized hydrocarbons [63].

Inorganic ions can penetrate into and then through aqueous nanochannels. As a result, after the addition of salts, the resistance of aqueous channels decreased with time, changing the membrane impedance. This is reminiscent of known processes on a frog skin. Dispersion of dielectric properties as a function of frequency depends both on resistivity and electric capacitance, reminding known for nerve membranes. This dispersion is not observed on nonmodified BLMs [33, 60].

In other words, using simple oil-impregnated filters, it is possible to imitate the transport of gases, nonelectrolytes and ions because our membrane is based on the same fundamental principles, which determine barrier properties of biomembranes. In terms of material science, we can say that the barrier properties both of biomembranes and impregnated filters are formed by liquid crystals or similar structures, which was confirmed by nitroxide spin probes and DSC [62, 64]. The ordering of impregnating oils is distorted by nitrocellulose polymer chains penetrating through the membrane. These polymers (not only proteins but also polysaccharides) carry ion-exchange groups and interact with water [63, 65], thus forming ion-selective aqueous channels with a thickness of a few nm. Polysaccharides are a common component of biological membranes, especially those of plant cells, including wood. Hydrophobic Teflon or PVDF impregnated membranes are often used as biomimetic membranes, but they have orders of magnitude higher resistivity because they do not have aqueous channels. It should also be understood that if dry porous cellulose first is impregnated by fatty acids, which are then converted into a solid phase, the material's surface becomes more hydrophobic [66–69].

Facilitated Active Transport and its Applications

It should be remembered that ion transport through biological membranes is possible both due to direct transport through channels and facilitated transport via carrier molecules. The most well-known carriers of H^+ ions are free fatty acids. Note that *stratum corneum*, which is the main barrier in natural skin, has many free fatty acids. Free fatty acids also play an essential role as uncouplers of oxidative phosphorylation in mitochondria bioenergetics [70]. Brown fat in polar bears during hibernation has a lot of free fatty acids so that chemical energy is used for heating and not for movement. Biomimetic membranes can be further modified to have some more specific properties due to inserted carriers. For example, it is possible to use a mixture with free fatty acids [48, 49]. Our experiments demonstrated that if the impregnating liquid has fatty acids, they can carry H^+ through the membrane from a more acidic solution to a more alkaline solution, and Na^+ or K^+ ions are carried in the opposite direction. The process is described by $H^+(2) + Na^+(1) \rightleftarrows H^+(1) + Na^+(2)$, and its equilibrium constant is equal to one for two separated by the membrane aqueous solutions. As a result, if H^+ concentration in the second (strip) solution is higher than in the feed, this facilitated by fatty acids coupled counter transport can be used for active transport of alkaline metals from less concentrated to the more concentrated solution [49]. The process stops only when the ratio of Na^+ concentrations in two solutions becomes equal to that for H^+. If the donor solution has pH 7, and the acceptor side has 1 M strong acid, theoretically, it is possible to transport Na^+ from a large volume of aqueous solution and accumulate it in a small volume of an acid so that the ratio of concentrations is 10^7 in equilibrium. Recently it was suggested that protocells at intermediate stages of evolution could have acquired electrochemical K^+/Na^+ ion gradients with the participation of fatty acids but in the absence of any macromolecular transport machinery or pumps [71].

Measurements of the main physico-chemical parameters of the process, such as diffusion coefficient D of the mobile fatty acids in the membrane, ion exchange constants, distribution coefficients, etc., allowed explaining on a quantitative level the H^+ leakage in resting mitochondria [49]. When we increased membrane thickness l using two, three, etc., filters

together, the resulting mass transfer resistance was proportional to the thickness. Still, extrapolation to the zero thickness demonstrated that in addition to the membrane resistance, there is an additional resistance of two unstirred stagnant aqueous layers near the membrane. This interface resistance can play a dominant role in biology, where the membrane thickness is much less.

Based on similar phenomena but with other ion-selective carriers it is possible to conduct active transport of heavy metals like Cu^{2+} from etching solutions after printed board production in microelectronic industry. Copper is accumulated in sulfuric acid up to saturation and precipitation of a commercially valuable product copper sulfate pentahydrate [72]. We should mention that engineering aspects of membrane-based solvent extraction and facilitated transport, especially with hollow fiber membranes, were described by K. Sirkar in the well-known handbook [73].

Another application is radioactive Sr removal from the alkaline waste accumulated and stored at Hanford Site, Washington State, after atomic bomb production during the Cold War [74]. It is considered the most expensive project in the history of civil engineering. Similar problems exist in Russia. Current purification of this waste with pH 14 is based on water evaporation, i.e., removing large volumes of water from small volumes of radioactive materials. The biomimetic membrane-based process does the opposite. It involves the removal of small amounts of Sr from large storage tanks. The process is fast, safe, and energy-efficient. The whole spontaneous process is coupled counter-transport of two H^+ ions and a metal cation facilitated by the carrier. Transmembrane pressure, voltage difference, and energy of ATP hydrolysis are not necessary for this so-called secondary active transport as it is called in biology. It would allow practically 100% of radioactivity removal and should be two orders of magnitude cheaper than existing technology.

An interesting phenomenon demonstrated the role of interactions of a mobile ion carrier and carboxylic groups on nitrocellulose matrix. In a simple situation, according to the Barrier-Einstein relation, characteristic time lag τ to reach the steady—state transport rate is $\tau = l^2/6D$, and it does not depend on the concentration of the carrier. Contrary to this, in experiments with biomimetic membranes, the increase of fatty acid concentration not only leads to the flux increase but also to a sharp increase of τ [75]. This effect was explained by the possibility of H^+ ion exchange between carboxylic groups of the carrier and immobile carboxylic groups on the nitrocellulose matrix. Large molecules of the carrier have a diffusion coefficient in oil two-three orders of magnitude less than that of small H^+ jumping in the aqueous channels from one carboxylic group to another. When the fatty acid concentration is high, the facilitated by fatty acids transport is dominant and τ is high. In the opposite situation, H^+ is mainly transported in aqueous channels, so that τ is much less, but simultaneously transmembrane flux without the carrier also is much less.

Not only ions but even electrons can be transferred through the membrane. If the membrane has some quinones dissolved in the oil, it is possible to have facilitated coupled co-transport of electrons and H^+ ions in the same direction through the oil. For example, it was possible from ascorbic acid (vitamin C) through the membrane with the quinone as the carrier to an oxidant ferricyanide. The process imitates some steps in mitochondrial respiration related to the coenzyme Q. If the quinones are light-sensitive, the process can be regulated by light [52], reminding some aspects of photosynthesis in chloroplasts.

It is well-known that acid-doped polyaniline has high electric conductivity due to electron transport along polyconjugated polymer chains. To imitate electron transport with the participation of proteins, we suggested using polyaniline-based membranes. Even at physiological pH, it was possible to observe transmembrane redox reactions. Transport of electrons s case was coupled with counter-transport of chloride anions via aqueous nanochannels. Note that after recalculation to the thickness of biological membranes the rate of electron transport was much higher than that in mitochondria [76].

Usually, in chemical technology, for two chemicals to react, they must be mixed. Not so in biology, where cellular compartmentalization plays a crucial role. With biomimetic membranes it is possible to conduct redox reactions between non mixed species separated by a membrane [77], which potentially means the elimination of expensive final separation and purification steps in chemical production.

Membrane-Based Drug Sensors and Drug Screening

Transport of drugs is essential for transdermal drug delivery, absorption in the gastrointestinal tract, and penetration through the blood-brain barrier. For drug screening pharmaceutical companies often use Parallel Artificial Membrane Permeability Assay (known as PAMPA), where egg lecithin or even hexadecane is immobilized in porous polymer support, and kinetics of transport is characterized by measurements of a drug concentration in the acceptor solution [22]. The polymer support usually is inert, hydrophobic, and it does not have aqueous channels with ion-exchange groups. What happens with the membrane stays unknown.

It was natural to test some drugs using our biomimetic membranes. A lot of medicines are salts of organic nitrogen-based cations. Experiments demonstrated that these drugs are not only extracted into the oil but also interact with carboxylic groups on nitrocellulose. An interesting example is rimantadine hydrochloride, which is not toxic and is recommended as an

antiviral drug to prevent flu. A cation of protonated rimantadine is adsorbed on a membrane and binds to carboxylic groups, but chloride anion stays in the solution [78]. Similar processes are possible in biological membranes and should influence membrane permeability. As a result of this charge separation, the cell surface becomes positively charged. It also repels positively charged viruses, which now cannot penetrate through the membrane into the cell. Note that based on its iso-electric point COVID-19 virus also is positively charged at physiological pH, and it seems that rimantadine could be repurposed for this case [79].

Charge separation in this and other similar cases leads to a transmembrane voltage, which is easy to measure. The slope of electric potential versus log of drug concentration was almost ideally described by the Nernst equation when concentration was changed by 1000 times. The sensitivity of this potentiometric sensor for many other drugs, including some antioxidants [80], cardiotropic, psychotropic, antibiotics, methamphetamine, and some other drugs of abuse, often is better than 1 μM. As long as the membrane resistance is not high (a few megaΩxcm^2), the measurements may be conducted using a simple pocket-size mV-meter instead of pH-meter, and the instrument could be called a 'drug-meter'.

When we conducted similar measurements with chlorpromazine hydrochloride, which is used to treat schizophrenia or manic depression in adults, the initial increase of concentration in solution also resulted in transmembrane voltage, but when concentration was above 10^{-4} M, which is comparable to CMC, this voltage suddenly disappeared, the membrane resistance dropped to several kΩ cm^2, and the membrane lost its barrier properties for ions [81]. As a surface-active molecule, chlorpromazine at high concentration was acting as a surfactant, washing out impregnating liquid from the pores. In biology, this effect is called membrane lysis. It is known that when taken by patients for a long time, chlorpromazine is accumulated in chromaffin granules of hepatocytes, and local concentration there may be above 10^{-4} M, which leads to liver cirrhosis and then to necrosis and possible lethal effects.

When we looked at a dozen different depressants, those which resulted in biomimetic membrane lysis, all had clinical side effects, damaging the liver. For those like rimantadine, which even at high concentration leads only to changes of transmembrane voltage, liver side effects such as cirrhosis and then necrosis could not be found in the literature. Thus, our biomimetic membranes can be used for fast and cheap prebiological screening of potentially liver-toxic chemicals.

Another phenomenon we have observed with surface-active and positively charged glycine esters, which have fungicidal activity. As usual, added into a solution on one side of the membrane, they gave transmembrane potential. Still, when their concentration was further increased, not far from a critical micelle concentration we observed downward fluctuations of transmembrane voltage up to 50 mV, which soon disappeared because impregnating oil was washed out from the membrane, reminding the effect observed with chlorpromazine [82]. Similar results were observed with cationic surfactants [83]. The whole process imitates the washing of cellulose fabric in washing machines. It may be used not only for drug screening and prediction of nonspecific liver toxicity but also for the optimization of laundry processes.

Implications for Biology

Our experience with biomimetic membranes has helped to formulate a hypothesis regarding some key biophysical membrane processes. Facilitated ionic transport through the membrane is relatively slow. Lateral transport with the carrier along the membrane surface may be much faster and play an essential role for a nonhomogeneous membrane. Both high interface resistance, the possibility of H^+ exchange between fixed and mobile ion-exchange groups [75], and even coupled transport of H^+ and electrons through oil by mobile carriers [52], all supported our hypothesis that coupling of electron transport and ATP synthesis is possible not necessary due to transmembrane H^+ transport, as it is in chemiosmotic mechanism. Instead, it may be due to the much faster lateral transport of H^+ from proteins in the respiratory chain to ATP-synthase, mainly facilitated by cardiolipin and other acidic lipids [84–86].

Another related hypothesis is that interactions of acidic lipids and proteins lead to the distortions of the usual bilayer orientation of lipids and to the selective ionic channel formation [87]. This channel is formed not in the protein but at the protein/lipid interface, similar to the nitrocellulose/oil interface in our biomimetic membranes. Later this idea was supported by experiments [88, 89]. This formation of aqueous channels certainly is possible due to strong interactions of carboxylic groups of acidic lipids with positively charged lysine or arginine groups of polypeptide chains. Moreover, this mechanism leads to the simple physical interpretation of not yet explained numeric coefficients in famous Hodgkin-Huxley equations, describing voltage-sensitive K^+ and Na^+ channels [87].

Future Prospects

We have described basic biomimetic membranes, which could be used in education, science, and technology. The membrane has a matrix of polysaccharides with carboxylic groups, narrow water channels, and fatty acid-based components (Fig. 1). It is possible to chemically modify the nitrocellulose matrix and add positively charged amino groups, which would

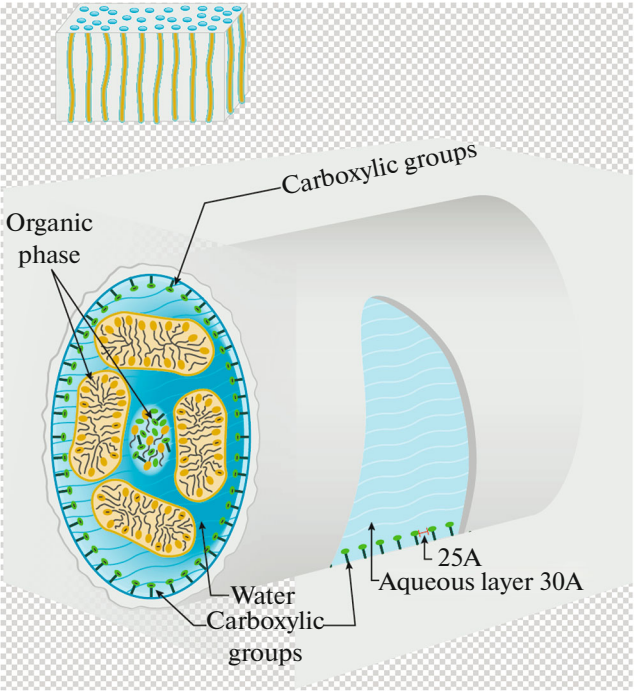

Fig. 1. A schematic structure of the impregnated pore in biomimetic membrane.

lead to anion/cation selectivity. Further potential developments could include more complicated systems based on biological components. It is easy to immobilize enzymes [66] and even antibodies on the membrane. This may be done either by the simple adsorption on a lipid-like surface or by covalent binding to nitrocellulose. Immobilized on the biomimetic membrane, enzymes stay active, leading to the membranes with specific functions. The membrane after that should not be called biomimetic but rather biofunctional [90]. Due to high antibody-antigen affinity, it could be used as a fast and selective electrochemical sensor for COVID-19 and similar tests. The time for this pocket-size test should be a couple of minutes.

Summarizing, we can say that a simple and old material, similar to the ones used in paper capacitors in early radios, oil-impregnated filters, after some modifications and a closer look may be considered as a new nanomaterial with tailorable interfaces, which could be used both in fundamental modelling of biological membrane processes, and as a biomimetic membrane in many new potential applications, including pharmacology and pharmaceutical industry, analytical chemistry, heat, and energy storage, and even in large scale chemical and environmental technology. Our subsequent publication will show that it is possible to observe large spontaneous oscillations both of transmembrane voltage and current at the melting point of fatty acids in filter pores [91]. The effect is observed even when the membrane separates two aqueous solutions with the same composition and can be essential both for our understanding of biological channels and for the conversion of thermal energy to electrical energy.

Finally, we should mention that the imitation of biological membranes and aqueous channels attracts more and more attention. See, for example, recent reviews which give a broader view of mimicking biological membranes [92, 93], bioinspired nanochannels [94, 95] and their possible applications as sensors [96], separation, and purification, including desalination [97–99]. We hope that nitrocellulose-based biomimetic membranes will find a proper place in this research and its applications.

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