MOSCOW, June 18, 2018 - **Research led by Oleg Batishchev and conducted jointly by scientists from NUST MISIS, the A.N. Frumkin Institute of Physical Chemistry & Electrochemistry (Russian Academy of Sciences), and the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry**

The lipid membrane of a cell is the basis of every living organism. This membrane is an amazingly intuitive "fence" through which the cell communicates with the body, eats, protects against foreign invaders, and controls the flow of substances into and out of the cell. The complexity of it all is mind-boggling. Pores - optional holes in membrane - are the main tools of this biochemical "communication". Pores act as a kind of gateway where scientists can actively study and describe cells and their functions.

(Photo: https://mma.prnewswire.com/media/707074/ModelNUST.jpg)

(Logo: http://mma.prnewswire.com/media/484501/NUST_MISIS_Logo.jpg)

The essence of the study and what has been done:

For the first time ever, scientists have accurately described the process of pore formation in lipid membranes and carried out computer simulations of their formation and evolution. The research team has created a large-scale theoretical model that explains the inconsistences in previously obtained experimental data from other studies, resolving the contradictions that plagued previous findings.

The research results, led by Oleg Batishchev and conducted jointly by scientists from NUST MISIS, the A.N. Frumkin Institute of Physical Chemistry & Electrochemistry (Russian Academy of Sciences), and the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, were published in two parts in the Scientific Reports journal.

https://www.nature.com/articles/s41598-017-12127-7 https://www.nature.com/articles/s41598-017-12749-x

Lipid membranes are membranes that separate cells and their organelles from the external environment. These structures perform a number of important life functions, most notably becoming a barrier that controls a cell's metabolism. Possible violations of this barrier mechanism have been actively studied in relation to drug development and therapeutic strategies such as drug delivery, considering that it is the membrane that eventually determines whether a substance does or doesn't enter a cell. Accordingly, the algorithm of getting a substance through the membrane is by creating a pore, which functions like an ID-card for a living cell.

There has not been a physical model that describes the formation, growth, and resistance of such pores yet, although there are many experimentally-proven methods in the world to create pores in membranes to allow a drug to enter a cell (for example, to let an antibiotic kill a bacteria or an anti-tumor toxin to destroy cancer cells).

How the research was done:

Now the researchers have set a goal to create a theoretical model that will describe every stage of a pore's evolution in lipid membrane. This task is complicated by the fact that any attempt to present the membrane as an ideal elastic shell without taking the peculiarities of the internal structure of the living "fence" into account only leads to a simplified and therefore rough description of this system. To eliminate such problems, scientists have started with the most complete theoretical description of the membrane, and then by using a number of transformations they received expressions for the energy of the pores, which will allow them to describe the state of the pores depending on their geometric parameters.

With the help of a new computer model, scientists were able to explain the inconsistencies observed in previous research on this topic. This new model not only explainsÂÂ *the mechanism of pore formation in the membrane*
, but also makes it possible to describe how exactly the membrane will react to a mechanical (injection, puncture) or electromagnetic action (point indication by the field). In some cases, these actions lead to the controlled formation of pores of certain sizes, and in others - to

irreversible ruptures of the membrane and the cell's death. This option needs to be excluded in the case of therapy and vice versa, as it can be widely used for the direct elimination of injected cells.

In order to verify the validity of this proposed theory, the research team conducted computer simulation with methods of molecular dynamics where the lipid membrane was recreated on the scale of individual molecules. The results of these studies typically coincided with the theoretical model's prediction and the available experimental data, making it possible to "see" how the pore develops (arises, grows, and expands) in the virtual membrane.

"This work required a lot of effort from everyone on the project and a large amount of machine time for calculating the methods of molecular dynamics conducted by our colleagues from the Laboratory for Biomolecular Systems at the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry. [It also required the] tedious work of creating the models to observed the processes, and most importantly, the huge array of calculations which were conducted by Sergey Akimov, the A.N. Frumkin Institute of Physical Chemistry and Electrochemistry (Russian Academy of Sciences), and the NUST MISIS Department of Theoretical Physics and Quantum Technologies," said **Timur Galimzyanov, a co-author of the research article and a**

researcher at the NUST MISIS Department of Theoretical Physics & Quantum Technologies.

Why was it done:

The researchers believe that their work will become the foundation of future research on controlled delivery of various drugs into a cell. Roughly speaking, the computer model of a complex organic system - a lipid membrane - will help to select optimal modes of action for the successful passage through the "gateway" of the cell to introduce the necessary concentrations of substances inside. The new model will also likely help to describe the processes associated with the violation of the integrity of the membranes observed in the course of many complex and as yet untreatable neurodegenerative diseases such as Alzheimer`s, Parkinson`s, Peak, and Huntington`s chorea.

"We have never conducted such detailed and sequential theoretical research. The results have completely justified the efforts we put in: for the first time ever, we have managed to create a complete model of the process of pore formation in membranes, allowing us to make not only qualitative, but also quantitative predictions,"

Galimzyanov mused.

Source: http://en.misis.ru/university/news/science/2018-06/5445/