Broadening the bilayer

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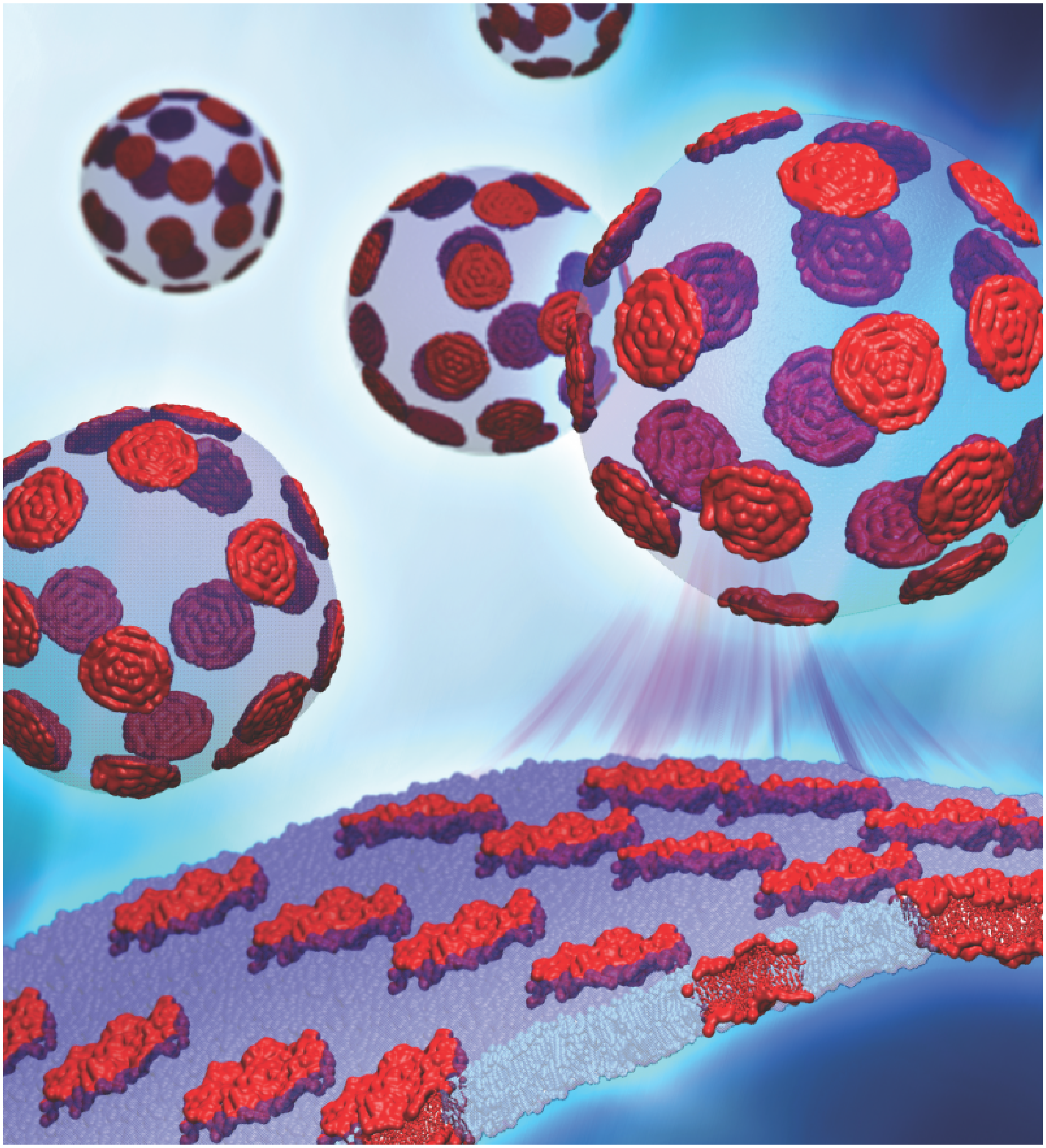

The dynamics of “contrast enhanced” unilamellar lipid vesicles reveal the local mechanical properties of nanoscopic domains. Image Credit: Barmak Mostofian, John Nickels, and Renee Manning

Lipid molecules have split personalities—one part loves water, whereas the other avoids it at all costs. Lipids make up cell membranes, the frontline defense in preventing cellular access to bacterial and viral invaders.

Many researchers believe that the membrane is not just a scaffold where proteins reside, but instead actually plays an important role in a number of biological processes. Researchers are also starting to see that lipids and proteins can form small patches, similar to a mosaic. This patchiness seems to have a functional role in the life of a cell and in regulating its different processes. Functional patches of lipids are commonly referred to as lipid rafts.

To better understand the biological processes that govern lipid raft formation—processes with broad implications for research ranging from how cells regulate proteins to how viruses invades healthy human cells—researchers at the US Department of Energy's (DOE's) Oak Ridge National Laboratory (ORNL) are using two world-class research facilities to study the presence and formation of these nanoscale lipid patches.

"Without having access to high-speed computing and neutron experiments, this study would be impossible," said ORNL researcher Xiaolin Cheng. Cheng, ORNL researcher John Katsaras, and their respective research groups are collaborating to use the Cray XK7 Titan supercomputer at the Oak Ridge Leadership Computing Facility (OLCF) and the beam lines at the Spallation Neutron Source (SNS)—both DOE Office of Science User Facilities located at ORNL—to understand membrane organization and how it affects biology. In the near term, the larger team seeks to determine the presence or absence of lipid rafts.

Despite efforts over 40 years, no experiment has conclusively shown the existence of lipid rafts in a living system because the rafts are very small and highly dynamic. In fact, these properties are believed to impart their unique biological functions. Understanding the size, lifetime, and connectivity of rafts is crucial to understanding their functional significance in cells. However, these parameters are poorly understood and are the focus of much of the current biomembranes research.

Biomembranes are also known to be asymmetric, meaning that the inward- and outward-facing parts of the membrane are made up of different lipids. However, this added complexity increases the difficulty of experiments and simulations. Importantly, researchers are still trying to prove whether membrane patches (rafts) form across the asymmetric bilayer.

The combination of neutron research at SNS and high performance computing on Titan offers the team leading-edge research tools to help address questions that have stymied others. Access to SNS has allowed Katsaras' researchers to perform neutron spin echo experiments to observe the bending properties of the lipid patches that populate the membrane. "The neutron spin echo experiments allowed us, for the first time, to measure the mechanical properties of isolated, individual patches of lipids," Cheng said. "No other technique can do this. We basically measured the mechanical properties of this tiny patch by probing the undulation motion of the bilayer."

Measuring undulations that take place many millions of times per second at the nanoscale, however, is not without challenges. Even with the spin echo experiment, researchers must be able to precisely assign a signal to molecular motions in the membrane and understand from where in the membrane these signals originate.

This is difficult when using only experimental data, but by introducing Titan, the researchers were able to simulate how the atoms' motions contribute to the signal. In essence, supercomputing was the only method for the team to verify its world-class experiments.

Rapid calculations

Although charting the trajectories of lipids may sound straightforward, it requires serious computational power to gain meaningful insights. The Cheng group runs molecular dynamics (MD) simulations on Titan to observe the trajectories of the atoms.

The main challenges for MD simulations come from the length and time scales needed for each simulation. "If you want a realistic picture of the bilayer's undulation motions, you need a system big enough to capture these motions," Cheng said. "Most of these simulations use hundreds of lipids, so you typically need a 10 nanometer by 10 nanometer grid, but for us, this number of lipids is too small. We had more than 2,000."

That means that each 2,000-lipid simulation contains millions of individual atoms the researchers must track, and each time step is 1–2 femtoseconds (one quadrillionth of a second). Typically, the team's simulations span hundreds of nanoseconds, or, in some cases, a full order of magnitude increase to a full microsecond (one millionth of a second).

Access not just to a supercomputer, but specifically to a supercomputer with a hybrid architecture, helped the team run its simulations efficiently. In fact, it took roughly 2 months of time to produce the data; the work would have taken more than 3 times longer on a traditional

CPU-only machine.
Cheng's team was able to verify its experimental data successfully with simulations, laying the groundwork for bigger simulations moving forward. The team was able to simulate simplified lipid bilayers containing three different types of lipids. As supercomputing power continues to increase, Cheng and his collaborators will be able to increase the complexity of their simulations.

"In terms of length, the system we're studying has thousands of lipids," Cheng said. "If we want to do the same system for a human cell, it would contain millions. I think the next-generation supercomputers like Summit [the OLCF's next-generation supercomputer, set to be ready for production in late 2017] will be able to push this forward in the length scale, which will become more biologically relevant, but also in time, because it will allow us to observe phenomena that we can't observe currently."

More information: J. Nickels, X. Cheng, B. Mostofian, et al., "Mechanical Properties of Nanoscopic Lipid Domains." *Journal of the American Chemical Society* 137, no. 50 (2015), DOI: 10.1021/jacs.5b08894

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