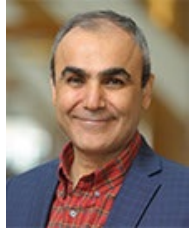
BLUE WATERS
SUSTAINED PETASCALE COMPUTING



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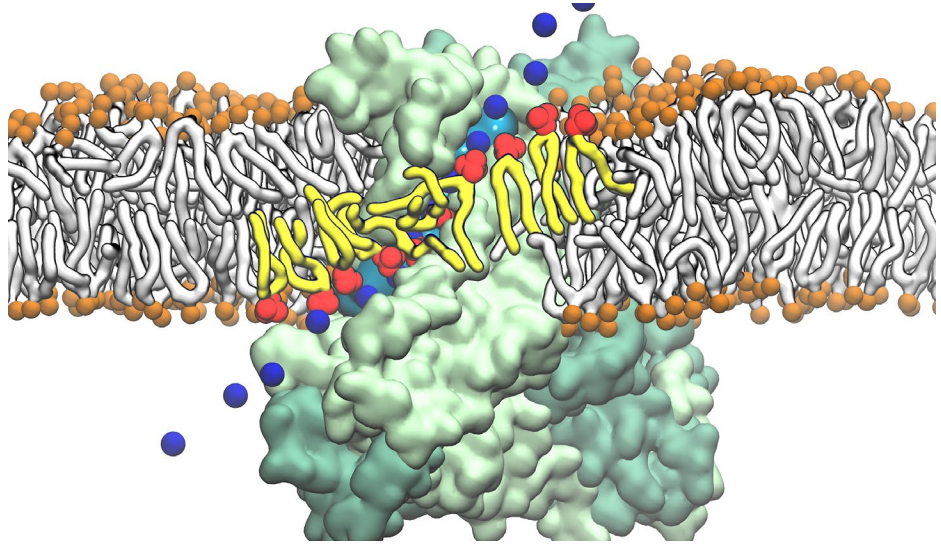
MOLECULAR MECHANISM OF LIPID AND ION TRANSPORT IN A PHOSPHOLIPID SCRAMBLASE



An ion-conducting “proteolipidic” pore formed at the interface of the channel protein TMEM16 (green) and lipid head groups (red) providing a pathway for ions (blue) to cross the membrane.

Research Challenge

Nature distributes different phospholipid species asymmetrically between the two leaflets of the cellular membrane. Dissipation of this asymmetry in response to the elevation of cytoplasmic Ca^{2+} concentration is a ubiquitous signaling mechanism critical for diverse cellular events including blood coagulation, bone mineralization, and cell–cell interaction. Phospholipid scramblases mediate the phospholipid scrambling process. The absence of phospholipids and ionic substrates in their solved structures leaves unanswered the question of how they conducts both lipids and ions.

Methods & Codes

The team conducts extensive MD simulations on the atomic models of the lipid scramblase in asymmetric lipid bilayers in the presence and in absence of Ca^{2+} ions at the activation binding sites. Application of multiple levels of transmembrane voltage to the equilibrated Ca^{2+}-activated structure allows to examine the ion permeation properties and to compute the ionic conductivity across the membrane. All MD simulations employ the NAMD package.

Results & Impact

Simulations explain that thinning and deformation of the lipid bilayer drives lipid translocation. The team detected one spontaneous full lipid scrambling event through the membrane-spanning lipid translocation track under equilibrium conditions, and four full scrambling events in the presence of voltage. Simulation determined key amino acids that enhance scrambling. Experimentally engineered scramblase activity in a homologous Ca^{2+}-activated ion channel confirmed that prediction.

Why Blue Waters

The high-performance architecture of Blue Waters makes it an excellent computing resource for the present study. The project employs the GPU-accelerated simulation program NAMD that has been extensively tested and optimized for Blue Waters. The large number of GPU-accelerated XK nodes significantly increases our computational productivity. Finally, the technical support provided by the Blue Waters team greatly facilitates the achievement of research goals.