Argonne Leadership Computing Facility

Argonne NATIONAL LABORATORY

INCITE Project:
Breaking New Ground in Membrane Protein Research

Discipline: Life Sciences

INCITE CONTRIBUTION

"Being able to run on these top computers is essential for this work. The time and energy scales of the underlying molecular processes are just within reach of the computational capabilities of such leadership-class computers."
-- Benoit Roux

PROBLEM

Many biological processes are controlled by proteins in cell membranes. Large-scale gating motions are essential for the function of many important membrane proteins such as transporters and channels. Voltage-activated ion channels are literally electric switches that are turned "on" by a change in the cellular potential. Malfunction of those channels can lead to cardiac arrhythmia and neurological pathologies.

Researchers are modeling the molecular function of a voltage-gated potassium ion channel at leadership-class facilities, including Argonne National Laboratory. The long-term goal of this study is to understand how the membrane-associated molecular protein-machines are able to carry out their functions.

APPROACH

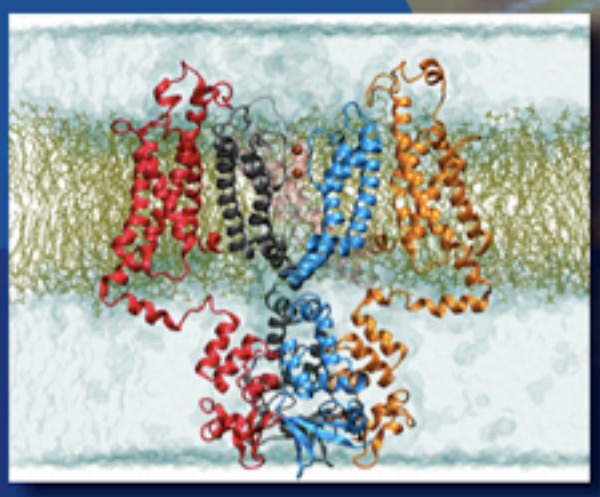
A research team from Argonne, The University of Chicago, the University of Illinois at Chicago, and the University of Wisconsin used high-performance computing to break new ground in understanding how these membrane proteins work. Exploiting state-of-the-art developments in molecular dynamics and protein modeling, the team constructed models of voltage-gated potassium channels and ran them on leadership-class computers, including Argonne's Blue Gene/P.

RESULTS

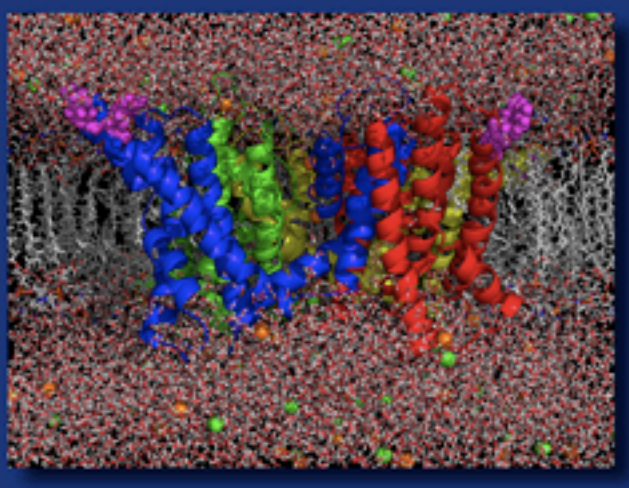
An important result of these simulations concerns the properties of the electric field responsible for the voltage activation. The calculations show that this electric field is indeed more intense than at other equivalent positions across the membrane far away from the protein. These results from simulations open up the possibility of better-designed therapeutic drugs, as well as the construction of artificial biomemetic electro-mechanic nano-switches.

FUTURE DIRECTION

The next challenge to be addressed will be the conformational pathway for the open and closed gating transition of the channel. Advanced and novel strategies will be essential in determining the reaction pathway and the interconversion rate by describing the transition process through a chain of states.



Complete model of the Kv1.2 channel (350K atoms) assembled using the Rosetta method. The simulations were generated by using NAMD on the Cray X-T (Jaguar) at Oak Ridge National Laboratory and the BG/P at the Argonne Leadership Computing Facility.



Atomic model for the simulation of the KvAP channel in a lipid membrane (113K atoms). The model represents the channel in an open activated state as determined by EPR experiments of Eduardo Perozo et al. (The University of Chicago). The positively charged arginine residues of the voltage sensors are colored magenta. The simulations of about 50 ns were performed by using NAMD with up to 512 processors on the BG/L at the Argonne Leadership Computing Facility.

CONTACT

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