PARACELLULAR ION TRANSPORT

Allocation: GLCPC/590 Knh
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EXECUTIVE SUMMARY

Permeation of water, ions, and small molecules through the space between neighboring cells is controlled by macromolecular structures known as tight junctions. Tight junctions seal the paracellular space and act as barriers that limit diffusion of molecules down their electrochemical gradient. Claudins are one of the major components of tight junctions and play a key role in determining paracellular permeability. Little is known about the assembly of claudins and the architecture of tight junction pores. The research team built an atomic model of claudin pores and verified its function using molecular dynamics (MD) simulations. The team then used the MD simulations to build a simple model of tight junction networks and simulate their transport properties. However, the architecture of tight junctions at the cellular level is still unknown.

RESEARCH CHALLENGE

Claudin pores are one of the major components of the tight junctions that control the transport of ions and small molecules in paracellular space between neighboring cells [1,2]. Little is known about the molecular architecture of tight junctions and the assembly of components into ion channels. The research team used all-atom MD simulations to determine: (1) the structure of claudin pores and their functional mechanism, and (2) the mechanical properties of tight junction strands at the cellular level.

The simulations carried out in this project are among the largest simulations of ion channels to date. The tight junction networks consist of a few hundred ion channels assembled into linear strands of tiny pores in two parallel lipid membranes.

METHODS & CODES

The researchers ran atomic-scale MD simulations of claudin pores in two parallel lipid membranes. The highly scalable MD program NAMD was used to build and refine the model and to simulate its ion transport function. Moreover, to investigate the macroscopic properties of tight junctions at relevant length scales (micrometers), the team ran simulations of the system using a hybrid resolution representation using the PACE force field, in which the protein was represented atomically and its environment, including lipid membranes and solvent, were coarse-grained. The size of the systems simulated in this project range from 350,000 atoms to two million particles.

RESULTS & IMPACT

In this project, the team developed the first atomic model of a new class of ion channels: claudin pores. They used MD simulations to build and refine an atomic model based on a recently proposed architectural model [3,4] and to assess its stability. Furthermore, they verified this structural model by simulating its ion transport function. The simulations verified functional characteristics of claudin pores such as their charge and size selectivity and predicted mutations that reversed the charge selectivity of the channel. These mutations were further verified in electrophysiology experiments in the collaborator's laboratory. In addition, these simulations identified the molecular nature of ion selectivity in paracellular pores, which was again verified by experiments [5].

To investigate ion transport across tight junctions—the parallel networks of claudin pores that span the cell membrane—the team developed systems consisting of more than 180 claudins (44 pores) in two parallel membranes. Initial simulations of the system at equilibrium indicate that claudins form flexible strands with persistence lengths comparable to those obtained experimentally (approximately 200 nm). Furthermore, the simulations determined the origin of this flexibility and pairwise protein–protein interactions that are responsible for the formation of strands and their shape.

These are the first simulations of ion transport in paracellular pores ever conducted, and they have opened up new opportunities for studying the functional mechanism of these channels as well as the physical properties of tight junctions at the cellular level. Future studies could result in the development of possible inhibitors for this class of ion channel in the small intestines or kidneys, or enable the delivery of drugs across the blood–brain barrier.

WHY BLUE WATERS

Access to Blue Waters was essential in running simulations consisting of the assembly of several hundreds of proteins into functional ion channels. These simulations, which reached a few micrometers in length, were only possible through access to the large number of nodes available on Blue Waters. Equally important was the knowledge of the Blue Waters staff in compiling the codes and helping the research team to identify performance issues.

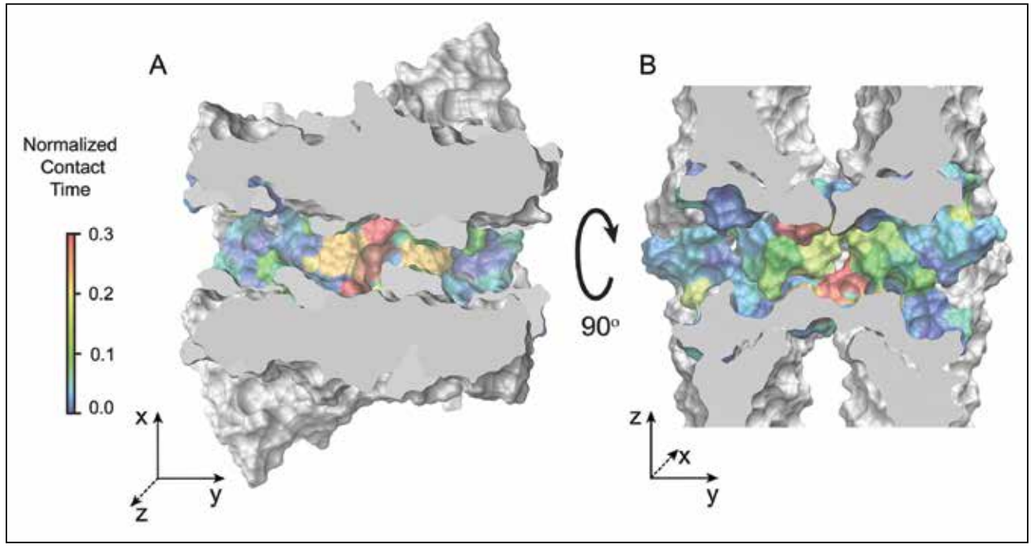

Figure 1: Ion transport pathway in claudin pore. Cross-section of a claudin pore across two parallel planes: (A) the plane parallel to the cellular membrane, and (B) the plane perpendicular to the cellular membrane. The amino acids on the pore surface are colored based on their contact time with permeating cations.

PUBLICATIONS & DATA SETS

P. Samanta *et al.*, "Molecular determination of claudin-15 organization and channel selectivity, "*J. Gen. Physiol.*, vol. 150, no. 7, pp. 949–968, Jun. 2018, doi: 10.1085/jgp.201711868.