Long time scale molecular simulations for understanding ion channel function

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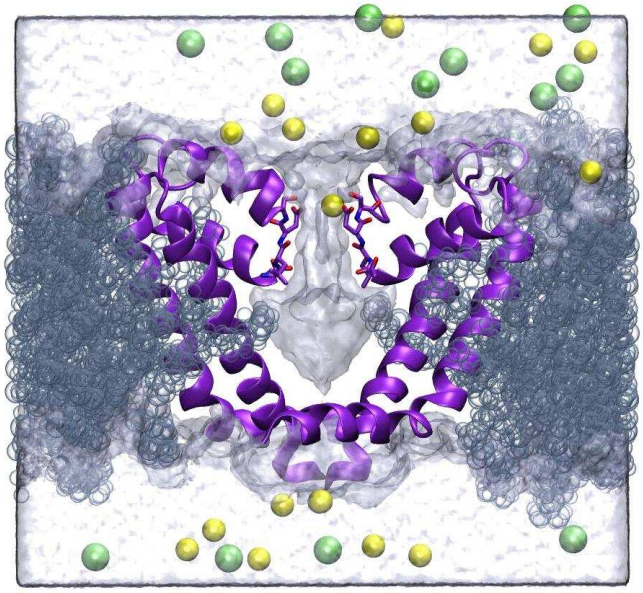
In the past, the size and time scale of molecular simulations of macromolecules has been limited by the available computational power. As a consequence it has been difficult to include the full complexity of the natural environment of proteins and to simulate for long enough to capture biological processes taking longer than 10s of nanoseconds. However, recently the steady increase in computer power has allowed for much longer simulations to be conducted, with a few cutting edge studies reporting simulations of millisecond duration. Thus, it is now possible to directly investigate global conformational changes of proteins that are responsible for protein function as well as to quantify the energetics of physiological processes.



The simulation system used to study ion transport and selectivity in the bacterial voltage gated sodium channel NavAB.

Recent work in our laboratory and others illustrates how the increasing power of molecular simulation is being used to understand the fundamental operation of ion channels. In particular, we have been using long simulations to quantify the energetics of ion transport and selectivity in sodium channels. Using long simulations it is possible to show that ion conduction involves two loosely coupled hydrated ions, and that selectivity between sodium, potassium and calcium involves the detailed balance of interactions between the protein, ions and accompanying water. The direct simulations of the gating of mechanosensitive and voltage gated channels is shedding light on molecular mechanisms. For example, experimentally restrained simulations show how the gating motion is assymetric and postulate a role of the periplasmic loop in sensing membrane tension. In a second case, motion of the voltage sensor is seen to involve a sliding and rotation that is directly coupled to the activation gate.