Rigid body Brownian dynamics simulations of ion channels and channel blockers

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Ion channels allow cells to regulate the flow of ions across cell membranes in a controlled manner. This ionic flow is responsible for a host of key functions in the organism, including nerve signaling, muscle contraction, chemical signaling, and the regulation of metabolism. The presence of various kinds of channel blocker molecules can impede the normal flow of ions through ion channels, leading to important physiological consequences, both beneficial (*e.g.* calcium channel blocker drugs for high blood pressure) and detrimental (*e.g.* various polypeptide toxins). Therefore, it is important to be able to computationally model the dynamics and energetics of various channel blockers interacting with channels. We report on the development of a system that uses rigid body Brownian dynamics to simulate the interaction between blockers, ion channels, and ions. This allows us to elucidate binding, unbinding and blocking mechanisms, and to directly simulate the effects that blocker molecules have on ionic currents. The use of Brownian dynamics, rigid body dynamics and macroscopic electrostatics means that our simulation can be run on long timescales, allowing the direct measurement of ionic currents.

Our model system contains an ion channel embedded in a lipid bilayer membrane as well as one or more channel blocker molecules, and is solvated by water and ions. The channel is represented as a fixed rigid body and the blocker molecules as mobile rigid bodies. The ions are explicitly represented as spherical charged particles, whereas the water is implicit. The force field for the system contains various terms for short range interactions between the ions, channel and blocker molecules, frictional and random forces that drive the Brownian motion of the ions and blockers, and long range electrostatic forces which are given by the solution to Poisson's equation. The latter are the most challenging to model, and we have developed new methods for efficiently solving Poisson's equation in our molecular system and applying these solutions to our simulation.

The other major component of our simulation is the motion algorithm. We have developed a new algorithm for simulating the rigid body Brownian motion of the blockers (Gordon, Hoyles & Chung, 2009). A rotational and translational Langevin equation is formulated, and a numerical solution algorithm is proposed, based on the velocity Verlet algorithm, with additional steps being needed to handle the more complicated rotational algebra and extra frictional terms.

We have tested our simulation in various applications involving voltage gated potassium channels. We have examined a number of candidate blockers, including small classical blocker molecules like 4-aminopyridine (4AP) and tetraethylammonium (TEA), polypeptide toxins such as charybdotoxin (CTX), and other small charged molecules. Our aim is to elucidate the binding, unbinding and blocking mechanisms for a range of different channels and blockers.

Gordon D, Hoyles M, Chung SH. (2009) An algorithm for rigid-body Brownian dynamics. *Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics* **80,** 066703-1 - 066703-12.