Brownian dynamics simulation of ion channel block by polypeptide toxins

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Toxins derived from the venoms of various creatures form a particularly rich source of potent ion channel blockers. There is an intense research effort directed at modifying or mimicking these toxins to develop drugs capable of treating ion-channel related diseases. The difficulty and expense of experiments, coupled with exponentially growing computer power, ensure that computational studies will form an increasingly important research method. While classical molecular dynamics is the default tool for such calculations, the computational demands are huge, with many tens of thousands of processor hours being typically required to derive a single binding affinity, for example. Clearly, a faster computational tool is needed in order to test dozens or hundreds of different candidate blockers. Existing molecular docking programs only perform some of the functions that would be useful in such a tool.

With this in mind, we have developed a Brownian dynamics program that is capable of simulating toxin binding and blockade of ion channels. The channel is fixed and water is implicit. Ions and the toxin are explicitly simulated. The toxin is modelled using coupled rigid bodies, allowing a degree of side-chain flexibility. To simulate the tumbling stochastic motion of the toxin, we have incorporated our own algorithm for rigid-body Brownian motion (Gordon, Hoyles & Chung, 2009). We use continuum electrostatics in the presence of dielectric materials to describe the polar interactions between charged objects in the system, with lookup tables being used to speed up the simulation. Other forces include steric forces between atoms and phenomenological pair potentials that are used to describe hydrophobic forces, water mediated van der Waals forces, and interactions such as salt bridges between charged groups.

We demonstrate the model using the NavAb sodium channel with the μ-conotoxin PIIIA blocker (see Figure 1). A molecular dynamics study has shown that this toxin is expected to exhibit multiple binding modes with the channel (Chen & Chung, 2012). We reproduce this finding using our Brownian dynamics simulation, and show how our program could be useful for investigating binding poses (docking), deriving binding affinities and potentials of mean force, and investigating the effect of the blocker on channel permeation. In future, we expect that such a tool could form an extremely useful tool for drug discovery and other theoretical investigations.

Gordon D, Hoyles M & Chung SH (2009). Algorithm for rigid-body Brownian dynamics. *Physical Review E* **80,** 066703–1–066703–12

Chen R & Chung SH (2012). Binding modes of μ-Conotoxin to the bacterial sodium channel (NavAb). *Biophysical Journal* **102,** 483-488.

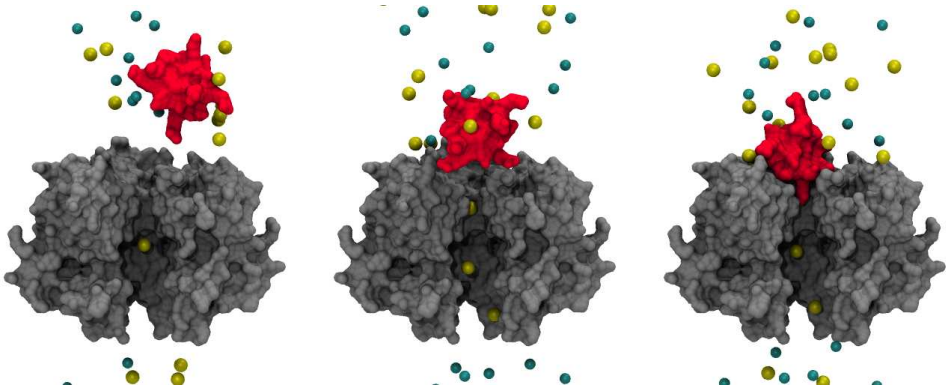

Figure 1. Brownian dynamics simulation showing the μ-conotoxin PIIIA blocker binding to the NavAb bacterial voltage gated sodium channel. ***Left:*** *the positively charged blocker is drawn to the negatively charged extracellular vestibule of the channel.* ***Middle:*** *the blocker tumbles in the vestibule.* ***Right:*** *the blocker binds tightly to the pore, inserting a lysine into the selectivity filter and thereby blocking ionic current.*