Brownian Dynamics study of current and selectivity of calcium channels

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Introduction and methods

Brownian Dynamics (BD) simulation is a powerful approach to investigate ion permeation properties through protein ion channels. BD does not require the explicit evaluation of the motion of all the particles in the system. Only ions' trajectories are computed. This results in a small computational burden that allows us to perform micro-seconds scale simulations, long enough for the reliable estimate of ionic currents.

We studied ion permeation properties and estimated ion currents through calcium channels, using a simplified channel model and Brownian Dynamics.

Our model featured two ionic baths separated by a 20 Å thick impermeable membrane and connected by a cylindrical pore.

We modeled the carboxylate-rich selectivity filter of calcium channels with 8 independent half-charged oxygens confined in the central region of the pore.

We computed ions' trajectories self-consistently evaluating the electrostatic forces impinging on the ions at every timestep. Such forces were evaluated solving Poisson's equation with a Boundary Element Method called the Induced Charge Computation method (ICC).

Ion permeation was investigated imposing, with the GCMC algorithm, a total concentration of cations (Na^+ and Ca^{2+}) of 100 mM in the left bath and changing the Ca^{2+} mole fraction. The solution in the right bath had 0 M ion concentration. Concentration imbalance between either side of the membrane determines a driving force that allows ions to flow through the channel. We studied ion permeation through different channel structures varying the radius of the pore.

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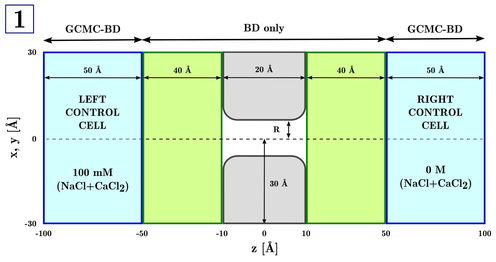

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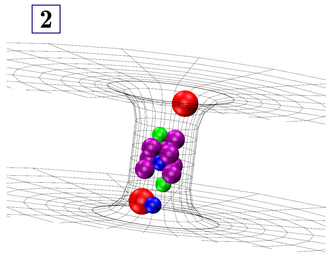

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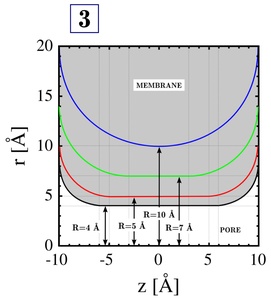

Comparison with Dynamical Monte Carlo simulations

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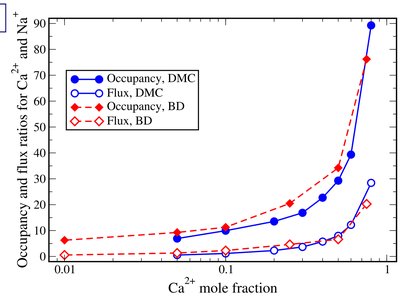

The adopted toy model of calcium channel (with pore radius equal to 4 Å) has been previously used by Rutkai et al. to investigate binding affinity and dynamical selectivity with the Dynamical Monte Carlo (DMC) technique (1). Binding selectivity is described by the ion concentration profile in the channel, while dynamical selectivity is described by ion flux.

Firstly, we checked BD simulation results in term of both binding affinity and dynamical selectivity with those in (1). Figure 4 shows the occupancies (upper curves) and flux (lower curves) ratios of Ca^{2+} and Na^+ as functions of the Ca^{2+} mole fraction.

For this model calcium channel, binding affinity is always larger than dynamical selectivity.

The good agreement between BD and DMC results is a strong consistency double-check for both types of simulation.

The agreement between BD and DMC data holds for ion concentration profiles inside the pore for calcium (Figure 5) and sodium (Figure 6) at different Ca^{2+} mole fraction.

For any Ca^{2+} mole fraction value, a Ca^{2+} ion occupies the center of the selectivity filter. The Ca^{2+} density in this binding site is substantially independent of the Ca^{2+} mole fraction. On the other hand an increase of Ca^{2+} produces a noticeable increase of calcium density in the remainder of the pore. Analogous results were obtained for different Ca^{2+} mole fraction (data not shown).

Na^+ density profiles in the pore decrease more evenly from left to right and their magnitude decreases everywhere along the pore axis as the Ca^{2+} mole fraction increases. In this case, 1 µs BD simulations are not able to provide a perfect fitting of DMC results due to the small number of Na^+ ions inside the channel. Longer simulations will provide better statistical accuracy.

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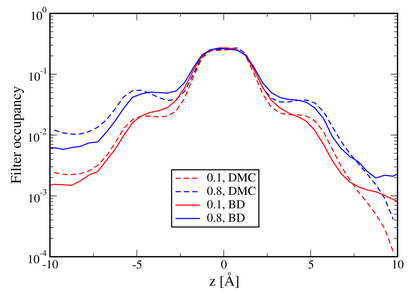

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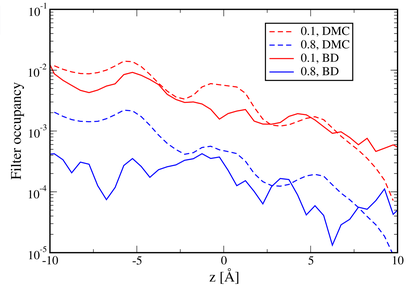

Current and Selectivity - Transmembrane potential dependence

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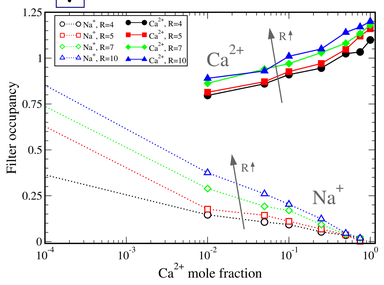

We investigated the influence of pore radius on binding affinity and dynamical selectivity of the model calcium channel. Figure 7 illustrates the average number of Ca^{2+} (upper curves) and Na^+ (lower curves) in the selectivity filter as function of the Ca^{2+} mole fraction.

Ion density increases as the pore radius increases. For any pore radius, Ca^{2+} (Na^+) density in the filter increases (descreases) as the Ca^{2+} mole fraction increases.

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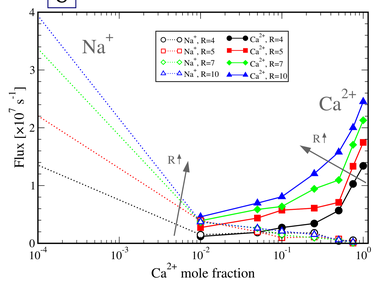

The increase of pore radius does not alter the binding affinity of the pore resulting in a higher Ca^{2+} density in the channel even for very low mole fractions.

Ion flux through the pore as a function of Ca^{2+} mole fraction for different pore sizes is displayed in Figure 8. For any pore radius, Ca^{2+} (Na^+) flux increases (decreases) as the Ca^{2+} mole fraction increases.

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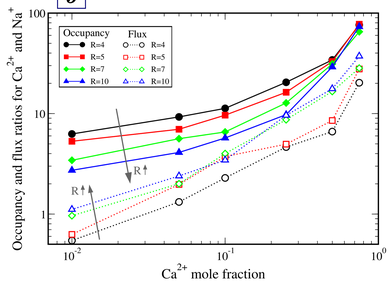

Larger pores provide larger fluxes, both for Ca^{2+} and Na^+.

Notice that for any pore radius, the Ca^{2+} maximum flux (obtained for Ca^{2+} mole fraction equal to 1) is always smaller than the correspondent Na^+ maximum flux (obtained for Ca^{2+} mole fraction equal to 0).

Figure 9 summarizes the effect of pore radius on binding affinity and dynamical selectivity of the model calcium channel: Occupancy and flux ratios for Ca^{2+} and Na^+ are plotted as functions of the Ca^{2+} mole fraction for different pore radii.

Notice that black curves are those displayed in Figure (4). For any channel radius, the binding affinity is always larger than the dynamical selectivity. They both increases as the Ca^{2+} mole fraction increases.

Binding affinity decreases as the pore radius increases, and on the contrary, the dynamical selectivity increases as the pore radius increases. This means that, as the volume of the pore increases, the negatively charged selectivity filter becomes weaker. This results in a smaller binding capability that allows cations to flow through the pore easily and provides larger ion fluxes. This mechanism, much more evident for the divalent $Ca2^+$ rather than for the monovalent Na^+, determines the opposite trends for binding affinity and dynamical selectivity as the pore radius increases.

Conclusion

Brownian Dynamics have been used to investigate ion permeation through a toy model of calcium channel.

Electric forces impinging on the ions were evaluated solving Poisson's equation at each timestep employing the ICC Boundary Element Method.

Boundary conditions for ion concentration were assured using a Grand Canonical-Monte Carlo algorithm.

BD simulations provide results in good agreement with Dynamical Monte Carlo simulations (1). This provides a strong consistency double check for the investigation of ion permeation through model ion channels.

Our results confirm that, for this model channel, the binding affinity is always larger than the dynamical selectivity.

Furthermore we studied the dependence of both binding affinity and dynamical selectivity on the pore radius. The main conclusion is that larger pores feature weaker selectivity filters that are less able to tightly bind cations, and as a consequence, provide larger ion fluxes.

This aspect is much more evident for divalent cations like Ca^{2+} then for monovalent cations like Na^+.

This results in a decreasing binding affinity and an increasing dynamical selectivity for Ca^{2+} over Na^+ as the pore radius increases.

(1) Rutkai, G., Boda, D., and Kristóf, T. (2010). Relating Binding Affinity to Dynamical Selectivity from Dynamic Monte Carlo Simulations of a Model Calcium Channel. J. of Phys. Chem. Lett. 1 (23), 2179-2184