Brownian Dynamics simulation of calcium channels

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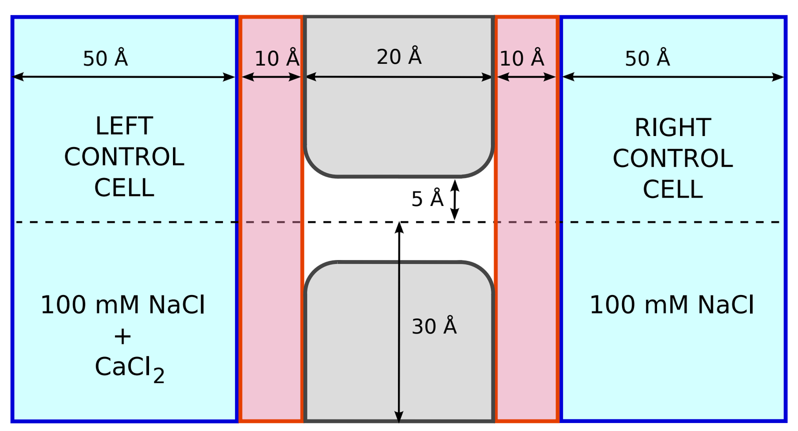
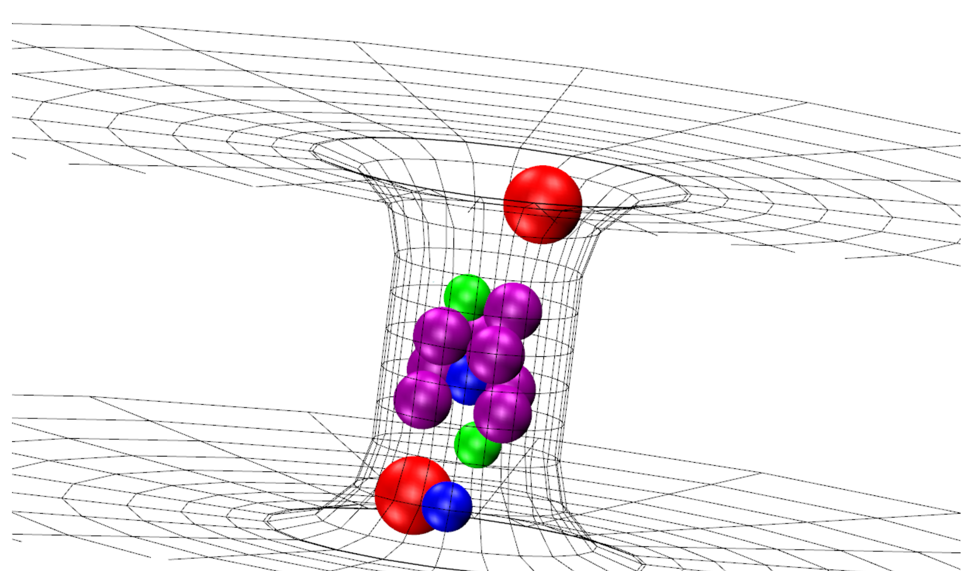
Introduction and methods

Calcium-selective ion channels play a crucial role in many biological functions allowing the selective flux of calcium ions into the cytoplasm from storage sites inside the cell or from the extracellular environment. They feature high selectivity for calcium ions even if the calcium concentration is hundreds of times smaller than other monovalent cations (sodium, potassium).
We studied ion permeation properties through calcium channels, using a simplified channel model and Brownian Dynamics simulations with Grand Canonical-Monte Carlo control regions in the baths.
The Brownian Dynamics approach was used to describe ion motion in the simulation domain.
The transmembrane potential and the ion concentrations were imposed by a Grand Canonical Monte-Carlo algorithm.
The electrostatic forces impinging on the ions were evaluated at run-time, solving Poisson's equation with the Induced Charge Computation method (ICC) that provided an accurate description of the electrostatics.

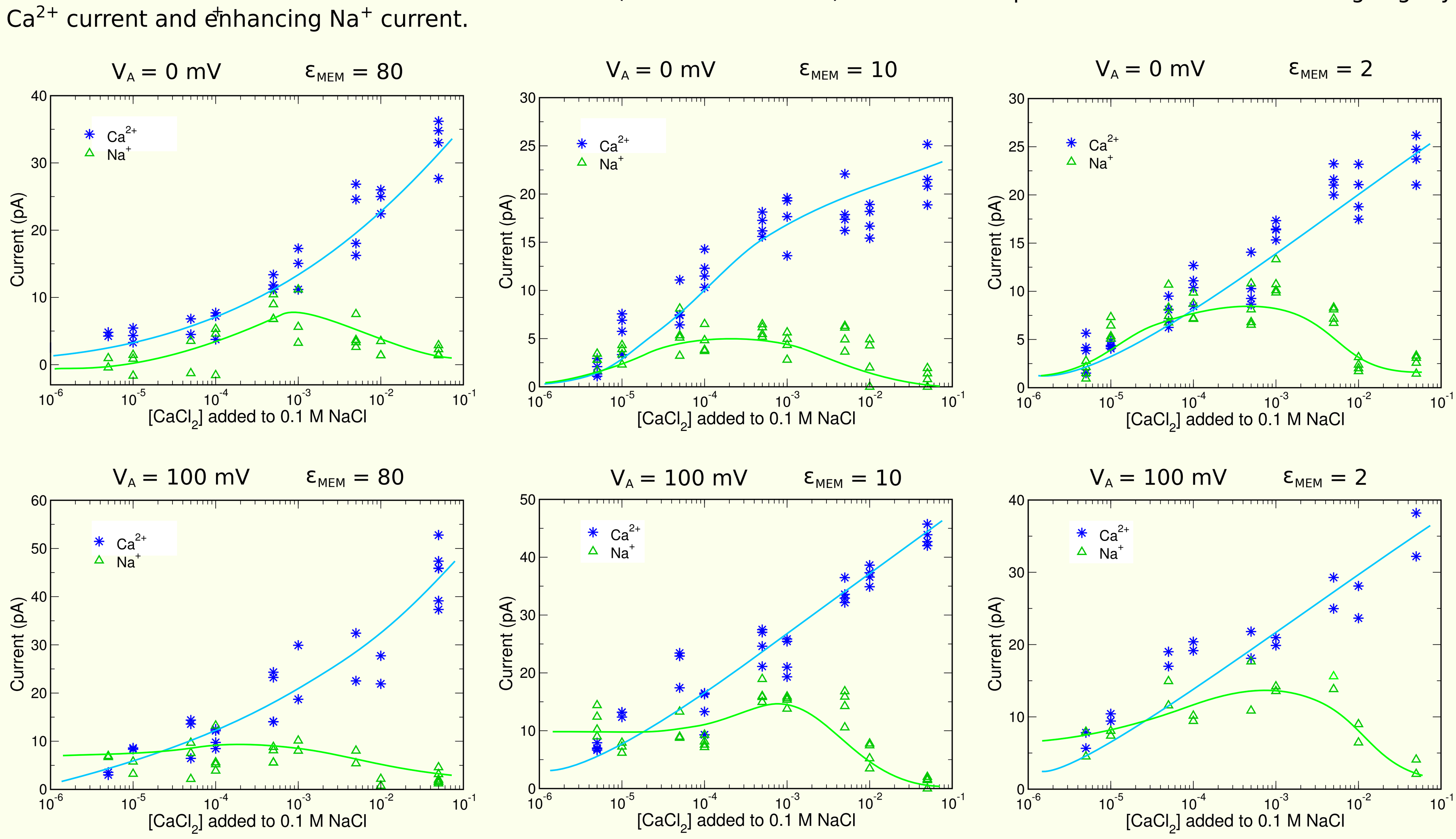


Our model featured two ionic baths with 100 mM NaCl connected by a cylindrical pore in a 20 Å thick membrane. Different concentrations, from 5 μM to 50 mM, of $CaCl_2$ were added to the left bath only.
The carboxylate-rich selectivity filter of calcium channels was modeled with eight independent half-charged oxygens. They were treated as ions, but they were confined in the central region of the pore.
The physical mechanisms related to ion permeation were investigated under different conditions of $CaCl_2$ concentrations, transmembrane potential (V_A) and dielectric constant of the membrane.



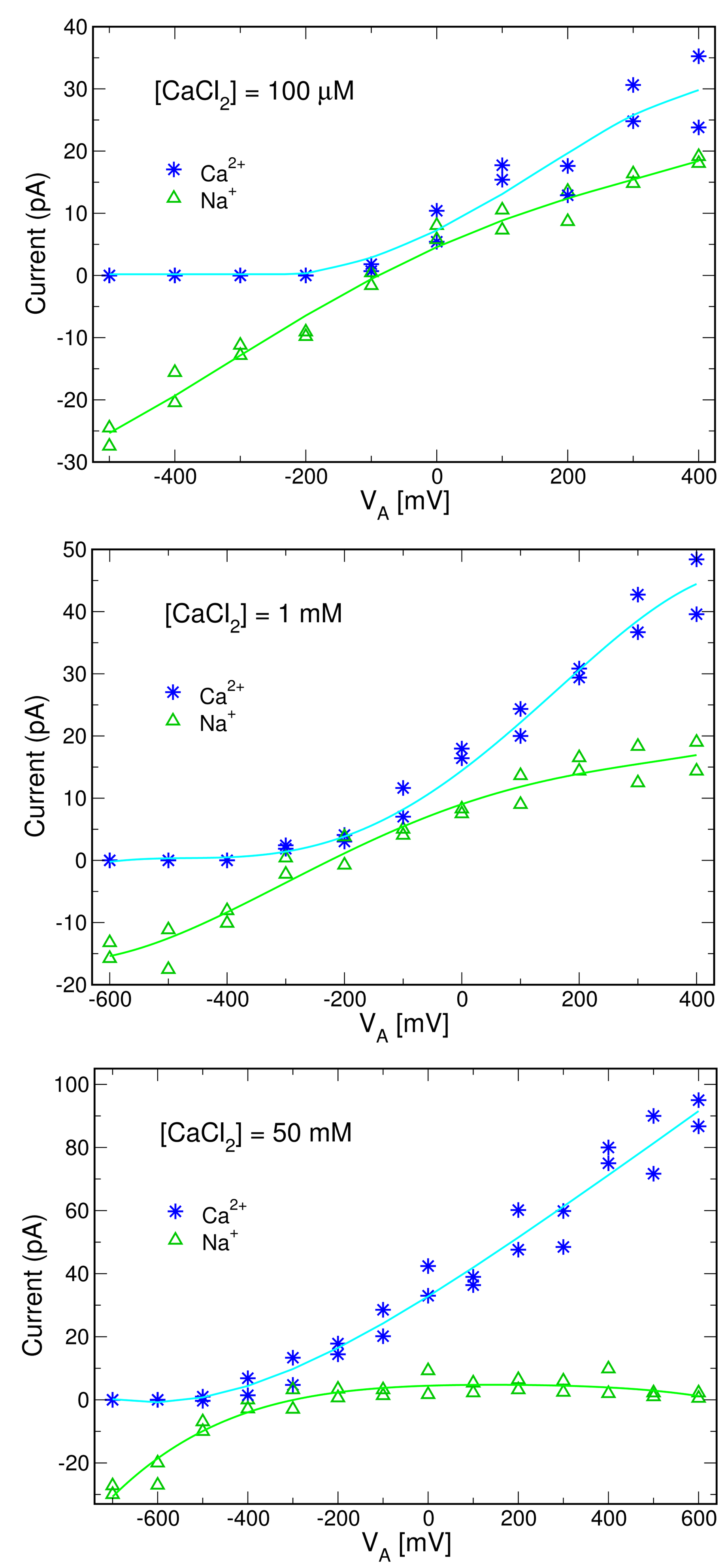
Currents vs. [$CaCl_2$]

We studied channel conductance as a function of the calcium concentration in the left control cell for two distinct transmembrane potential (V_A) values, 0 mV and 100 mV (left to right side), and for different values of the dielectric constant of the membrane ε_{MEM}. In any case, the channel features high selectivity for calcium ions even if its concentration is hundreds of times smaller then sodium concentration. Ca^{2+} current increase fairly linearly with calcium concentration in the left bath. Na^+ current increase slightly as [$CaCl_2$] increases up to ~1 mM. A further increase in [$CaCl_2$] determines a strong reduction of Na^+ current. A transmembrane potential of 100 mV helps the conductance of both Ca^{2+} and Na^+ (first row vs. second row). The reduction of the dielectric constant of the membrane (from 80 to 10 to 2) has a small impact on ionic currents reducing slightly Ca^{2+} current and enhancing Na^+ current.



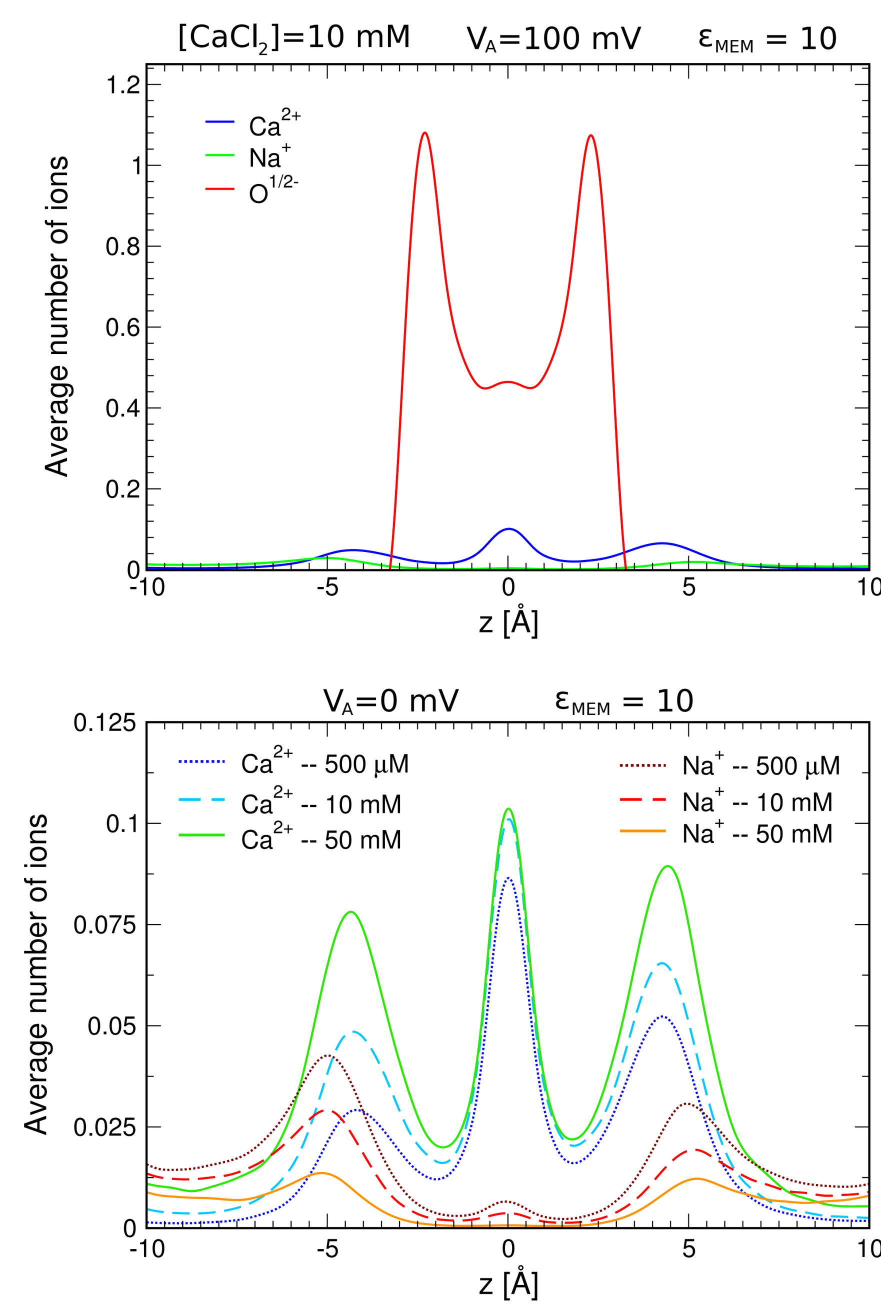
I-V relationship

The ionic currents flowing through the channel arises from the calcium concentration gradient and the applied transmembrane potential (V_A).
For very negative values of V_A, the calcium concentration gradient is unable to overcome the applied potential difference, resulting in a null Ca^{2+} current and in a negative Na^+ current proportional to V_A.
When the effect of the calcium concentration gradient and the transmembrane potential balances the channel becomes conductive for Ca^{2+}. We denote V* this threshold voltage. For V_A above V*, Ca^{2+} and Na^+ current grows with V_A. The slope ratio of Ca^{2+} and Na^+ currents depends on the calcium concentration in the left bath. The higher [$CaCl_2$] the larger the difference between
The value of V* shifts towards more negative values as the calcium concentration increases due the higher concentration gradient that opposes the potential difference.

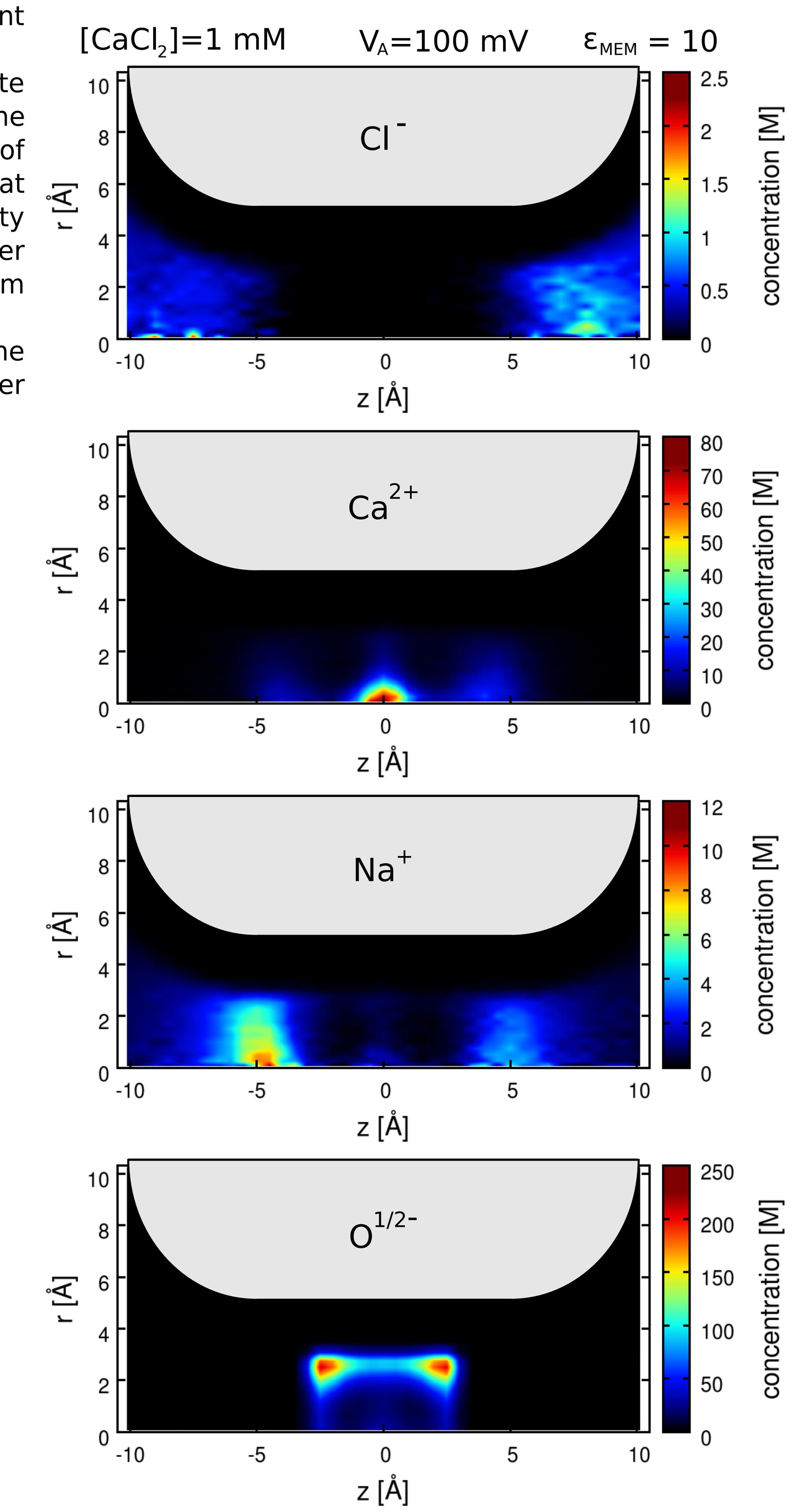


Ion concentration in the channel

The ion concentration in the channel helps elucidate the characteristics of ion permeation through our model of calcium channel. The longitudinal, cross sectionally averaged profiles of ion concentrations in the channel (below) and the radially averaged concentration maps (left) are not significantly influenced by the calcium concentration in the left cell, by the transmembrane potential and by the dielectric constant of the membrane (ε_{MEM}). The packing of the particles in the pore features always the same pattern as these parameters are changed, thus we show only few cases. Similar or indistinguishable figures can be obtained for different values of [$CaCl_2$], V_A or ε_{MEM}.
The structural ions of the selectivity filter accumulate mainly at z=±3 Å. Both Ca^{2+} and Na^+ permeate the channel as they are attracted by the eight half-oxygens of the selectivity filter. Ca^{2+} accumulates more favorably at the center of the pore and at either sides of the selectivity filter while Na^+ tends to be excluded from it. The number of Ca^{2+} and Na^+ in the pore depends on the calcium concentration in the left bath.
A higher [$CaCl_2$] results in an increase (decrease) of the number of Ca^{2+} (Na^+) that packs by the selectivity filter and at the center of the channel.



Concentration maps (below) show spatial ion distribution in the channel. The negatively charged selectivity filter does not let Cl^- ions permeate while allows the permeation of both Ca^{2+} and Na^+.
Ca^{2+} always packs near the pore axis and accumulates strongly at the center of the pore, whereas Na^+ is more spread out over the cross section and accumulates mainly at the left end of the filter.
$O^{1/2-}$ occupy the central section of the pore and packs more favorably ~3 Å off the channel axis.



Conclusion

We investigated ion permeation through calcium ion channels with Brownian Dynamics simulations. Boundary conditions for ionic concentrations was ensured by a Grand Canonical-Monte Carlo algorithm that enabled us to study ion conductance with sub-millimolar calcium concentrations.
Our results elucidate the impact of calcium concentrations, transmembrane potential and dielectric constant of the membrane on the conductance of calcium channels.
The selective conduction of divalent cations over monovalent cations are determined by the competition between electrostatic forces and steric repulsion due to charge crowding in the pore. Furthermore, transport properties depends on the contribution of the calcium concentration gradient and the applied transmembrane potential