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### MEETING ABSTRACT

#### A1.5

##### **Ca<sup>2+</sup> vs. Na<sup>+</sup>: How come Ca<sup>2+</sup> ion channels are so specific?**

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**Background:** Cations, such as H<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and Mg<sup>2+</sup>, are essential for a variety of biological processes in every cell. Several of these processes depend on a discrimination between different ions with a very high accuracy. Ion channels are membrane proteins that allow ion flow through an otherwise ion-impermeable cell membrane upon a specific signal. These channels discriminate different ion types at their so called selectivity filter. Calcium and sodium channels share a rather similar selectivity filter, based on their amino acid sequence. However, calcium channels are highly selective towards calcium, with a ratio of 1000 : 1. This is intriguing, given the fact that the sodium concentration in the extracellular lumen is 70-fold higher than the calcium concentration and calcium and sodium ions are of approximately the same size. How this high selectivity can be achieved is a fundamental and long-standing question in this field.

**Methods:** With our first aim of studying the coordination sphere of different ions in the context of the selectivity filter, we limited the Ca<sub>v</sub>1.1 structure [1] to its selectivity filter (four times TxExW) and parts of the P-helices for running the QM/MM MD simulations. Three systems were built: one with the Ca<sup>2+</sup> ion, one with a Na<sup>+</sup> and one with a K<sup>+</sup> ion. The extension of the self-consistent-charge density-functional tight-binding method DFTB3 was used to treat the QM region in these initial studies (PM6 for Na<sup>+</sup>) [2]. All the QM/MM MD simulations were run for 20 ps and only the ion was included in the QM region. This region was polarized by the environment within the electrostatic embedding scheme. The positions of all the alpha carbons were restrained with a harmonic constant (5 kcal mol<sup>-1</sup> Å<sup>-2</sup>) except for those residues that define the selectivity motif.

**Results:** The coordination sphere of Ca<sup>2+</sup> remains similar to the cryo-EM model along the MD simulation: Glu292 and Glu1014 bind to the cation with one carboxylic oxygen and Glu614 binds with both oxygens. Four water molecules complete the first coordination shell (coordination number of 8). Two of these water molecules bridge the cation with Glu1323. In contrast, for K<sup>+</sup> we observe significant changes in the coordination sphere. The coordination sphere is a distorted octahedron where the side chain of Glu1014 has moved apart from the monovalent ion. Additionally, one of the water molecules has been substituted by the backbone oxygen of Gly1322.

**Discussion:** This study gives mechanistic insights into Ca<sup>2+</sup> vs. Na<sup>+</sup> selectivity at the highly selective ion binding sites in a calcium channel and their water hydration shell throughout the conduction process.

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#### References

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