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Molecular Dynamics Study of Ion Conduction through Voltage-Gated Ion Channels

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INTRODUCTION

- Voltage-gated ion channels are key transmembrane proteins that open after a voltage change and allow the transport of ions.
- Ion transport generates a voltage change that opens neighboring channels, generating an action potential.

MOTIVATION

- Channels play an essential role in various physiological processes in our body, such as muscle contraction and signal transduction, among others.
- Studying the mechanism of permeability and selectivity is fundamental for understanding the function of cells and for the discovery of new drugs.

SYSTEMS AND SETUP

SYSTEMS: $hNa_V1.4$, $hNa_V1.5$, Na_VPas, $EeNa_V$

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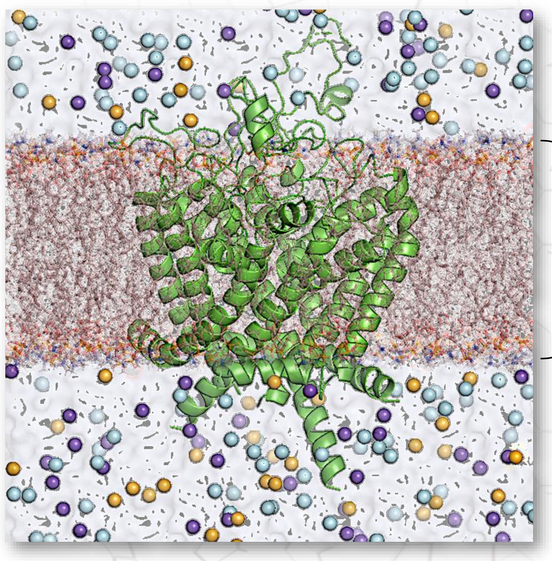
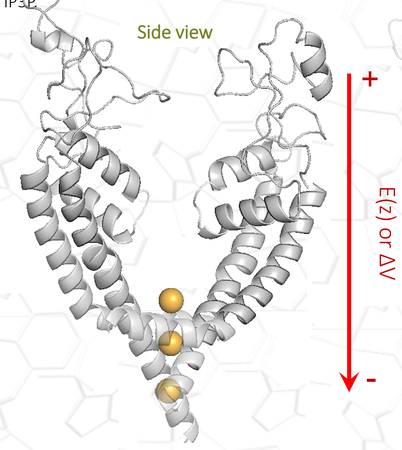
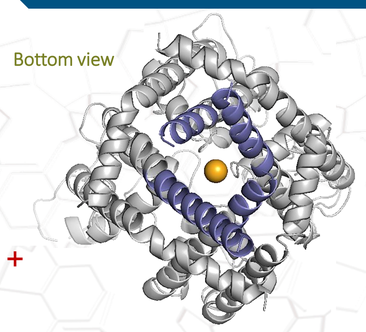


CLASSICAL MOLECULAR DYNAMICS (200ns)

- Biased dynamics → electric filed along z direction.
- Potential difference of 1V, 750mV, 500mV and 250mV.
- Ion concentration: 0.15 M Na^+Cl^- + 0.15M K^+Cl^-
- Force Fields :
  - Ions → Joung2008.
  - Protein and Lipids → Charmm36m.
  - Water → TIP3P.





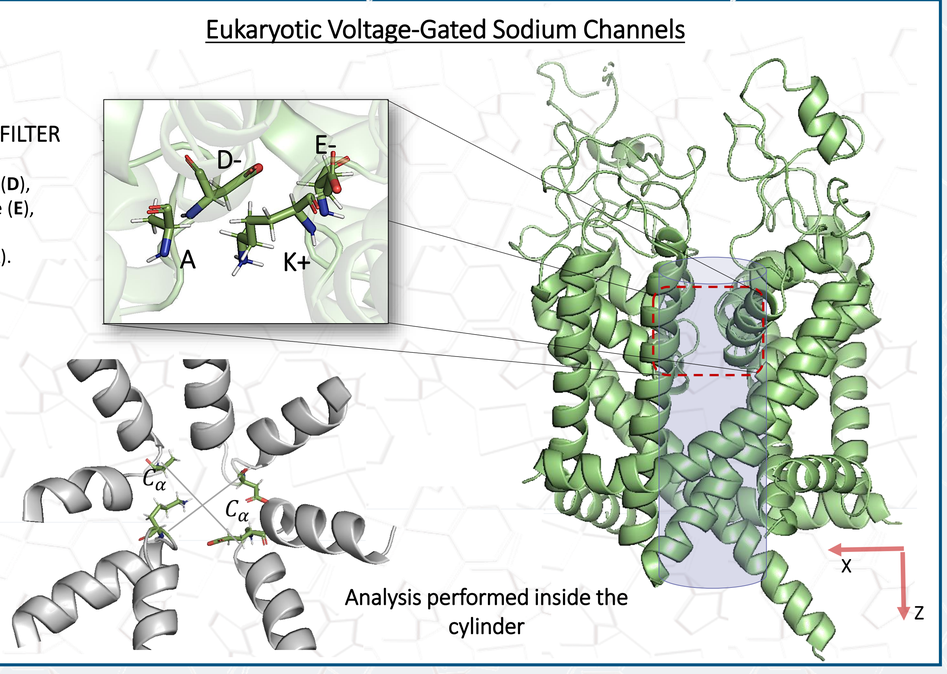
Open Gate region

- Calculation of the COG of gate residues.
- Three atoms with charge zero are placed along the gate region.
- Run dynamics increasing slowly the vdW radii from 0.25 to 5.00 Å.
- Gate region is frozen during the simulation.

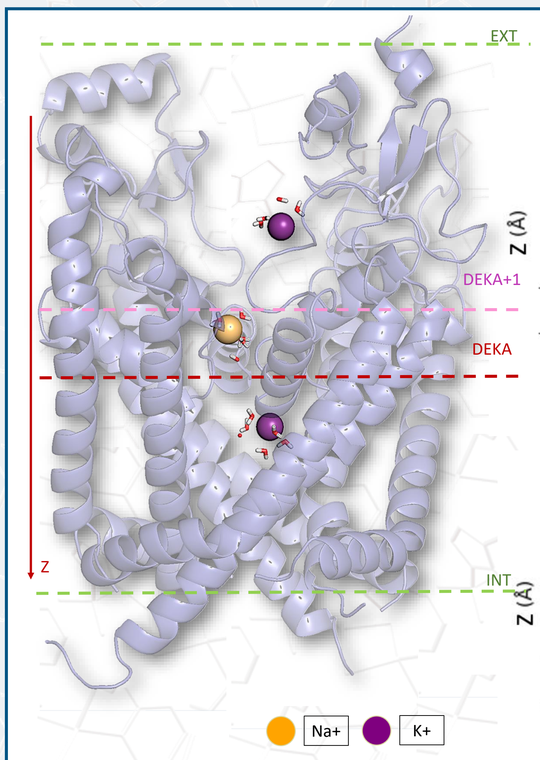
Eukaryotic Voltage-Gated Sodium Channels

SELECTIVITY FILTER

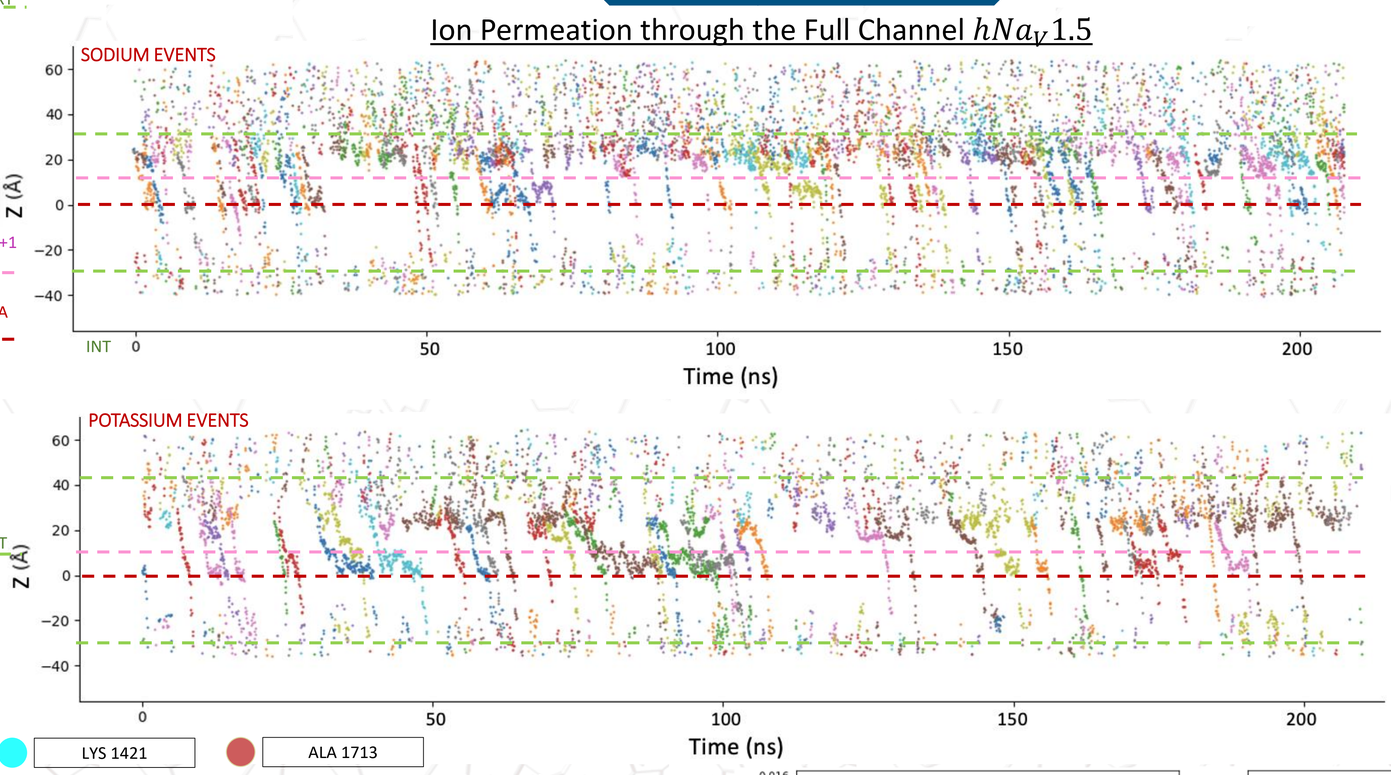
Aspartate (**D**), Glutamate (**E**), Lysine (**K**), Alanine (**A**).



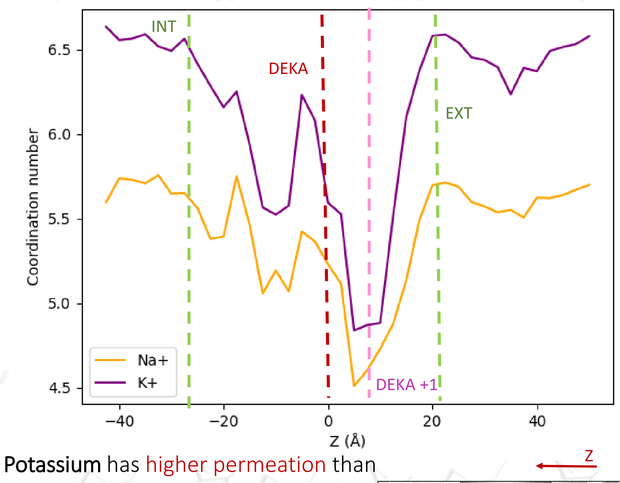
RESULTS



Ion Permeation through the Full Channel $hNa_V1.5$

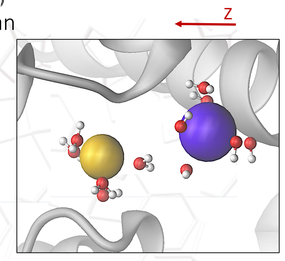


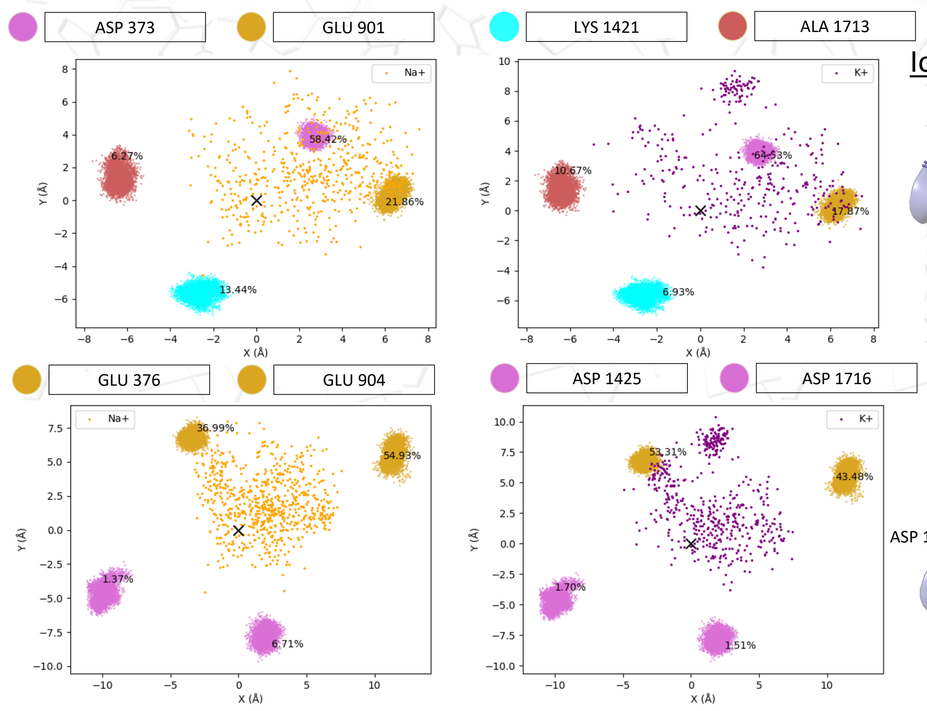
Hydration numbers for $hNa_V1.5$



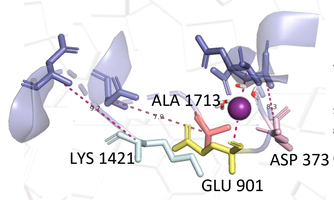
Potassium has higher permeation than sodium ions in a sodium channel.

Around the selectivity filter, K^+ ions lose 1.5 water molecules from the solvation shell. However, Na^+ ions lose 1 water molecule.

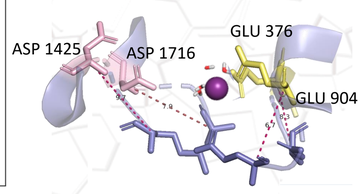


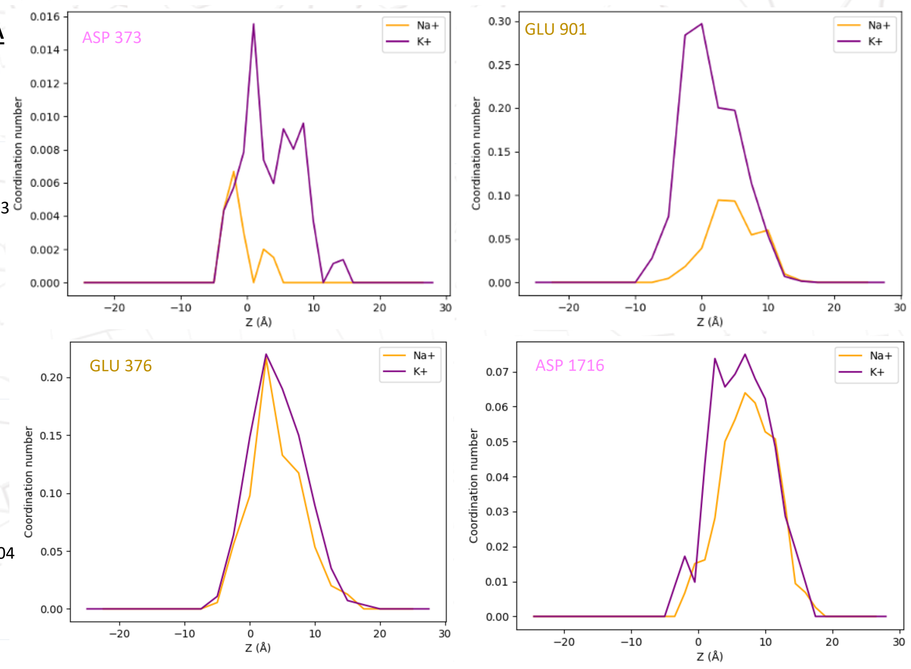


Ion Distribution in DEKA



Ion Distribution in DEKA+1





CONCLUSIONS

- Conduction for K^+ is higher than for Na^+, contrary to the expected behaviour.
- K^+ ions has higher dehydration than Na^+ ions.
- Interaction with DEKA and DEKA+1 does not compensate the dehydration penalty for Na^+ → failure of the force field?

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