Influence of Hydrophobicity on Anion Selectivity

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1. Introduction

- Crystal structures of a number of ion channels and membrane transport proteins suggest chloride ions may form favourable interactions with hydrophobic sidechains that line these transmembrane pores (Fig.1) [1].
- Here, we use MD simulations of model systems to provide insight into the localisation of chloride ions to hydrophobic surfaces.
- This contributes to our understanding of anion permeation and selectivity in biological ion channels.

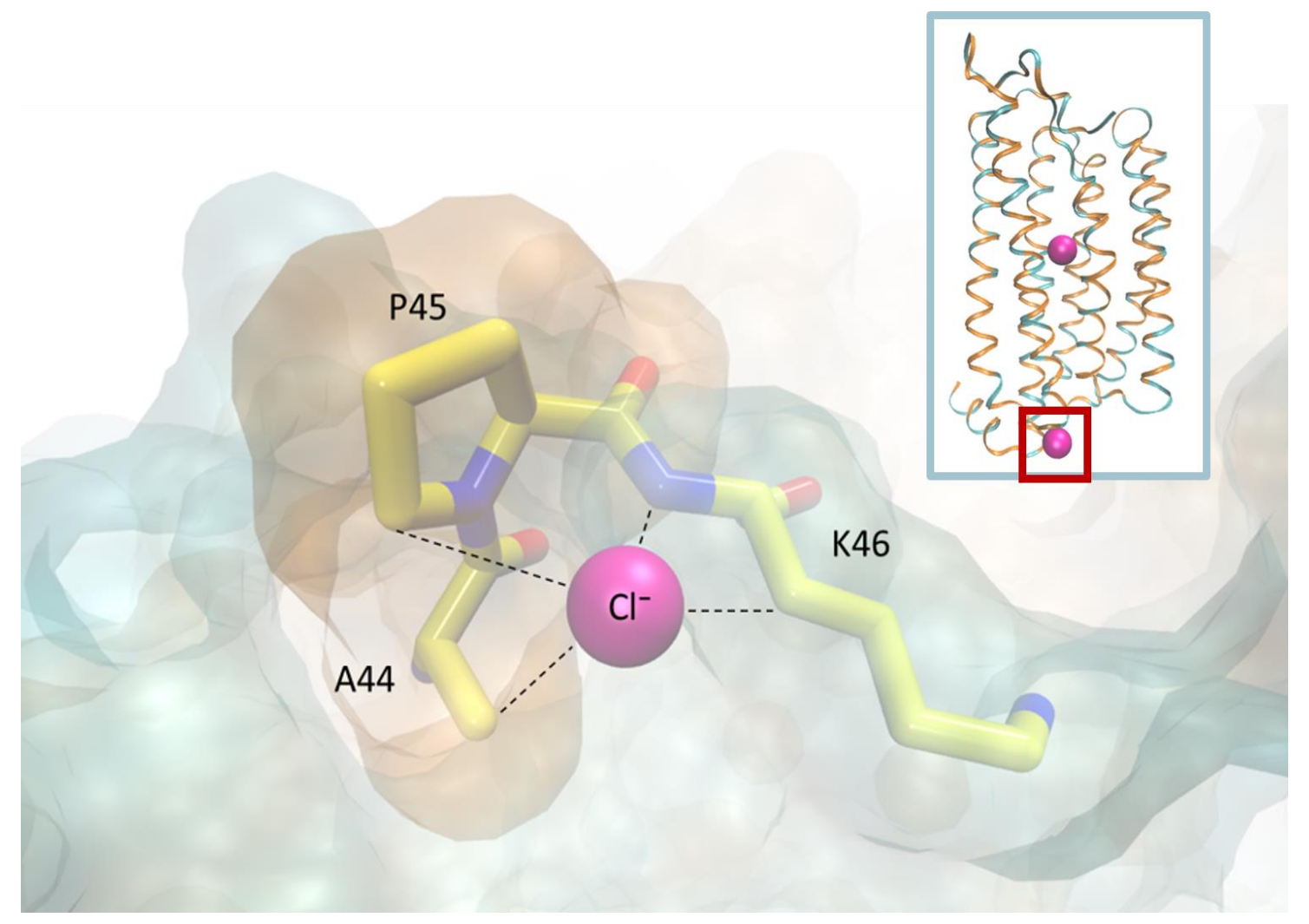


Fig 1. PDB:5G28. Surface hydrophobic (orange) and polar (cyan) regions around Cl⁻ cytosolic binding site [1].

2. Anions at a Water/Hydrophobic Interface

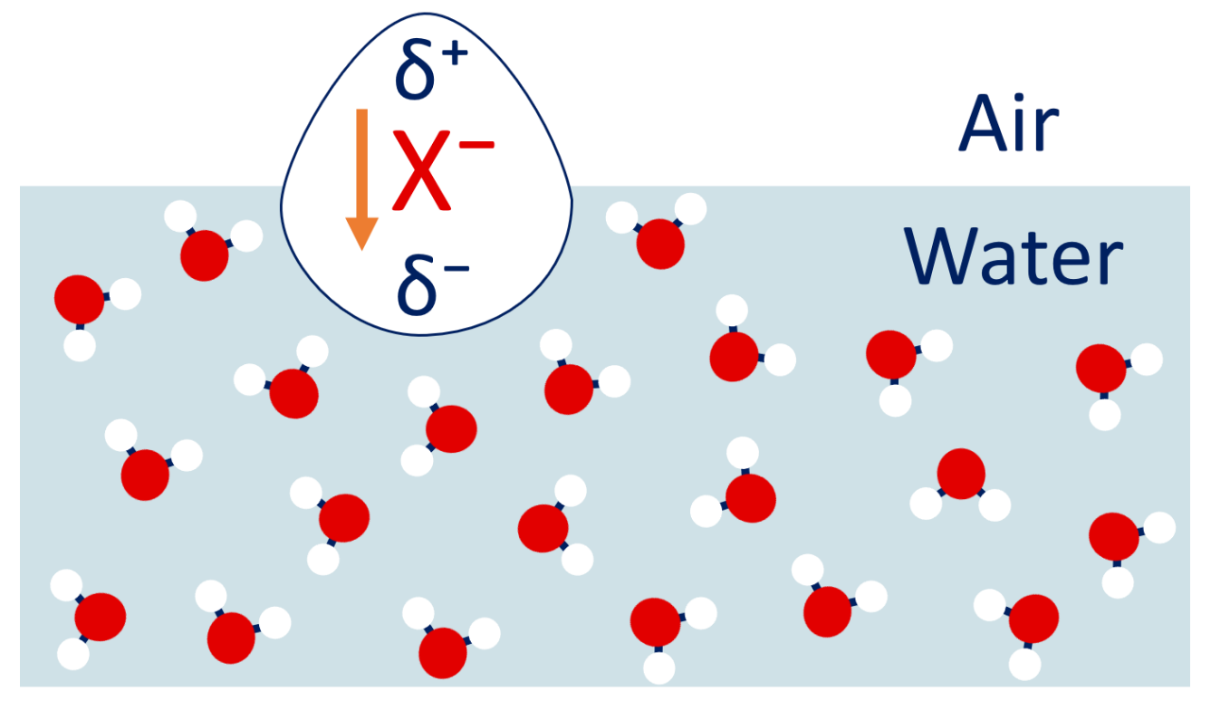


Fig 2. An anion ion at the air-water interface, adapted from [4].

- At air/water interfaces, dipoles are induced in large anions. The attractive interaction between dipole and surrounding water molecules compensates for the loss of solvation at the interface (fig.2) [2].
- Affinity for anions at the surface follow the series $F^- < Cl^- < Br^- < I^-$ [3].
- Similar effects are seen at water/alkane interfaces [3].

3. Water Models

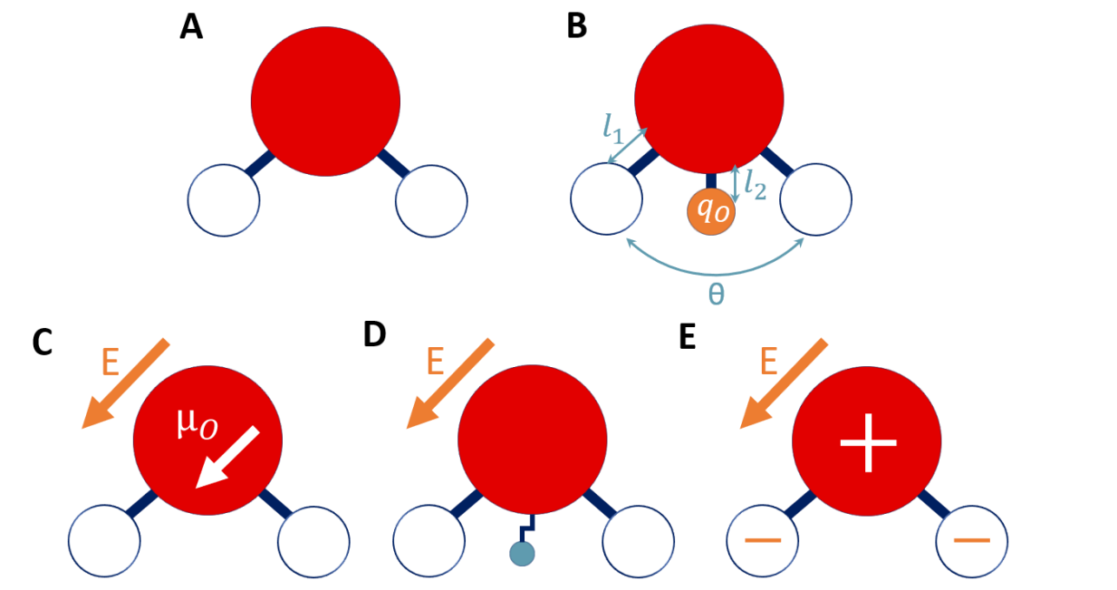


Fig 3. Water models. Rigid fixed point water models – **A** 3-point and **B** 4-point. Polarisable water models – **C** Polarisable multipole, **D** Classical Drude oscillator and **E** Fluctuating charge.

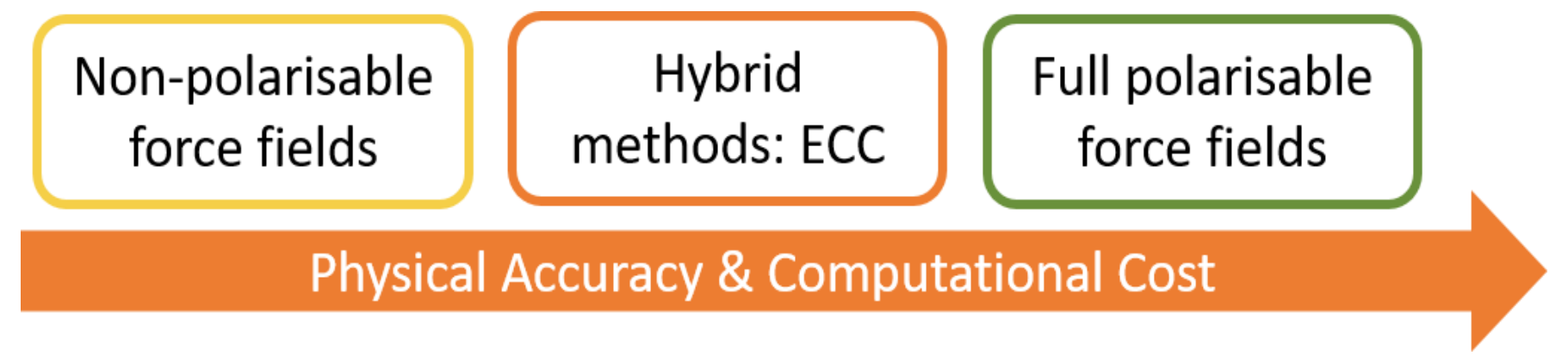
- The dynamic behaviour of water within nanopores and at interfaces emphasises the need for accurate models.
- Some water models are developed to describe particular physical properties better than others.
- Polarisable water models account for variation in charge distribution and fluctuation (fig.3).

4. Electronic Continuum Correction (ECC)

The ECC method introduces some electronic polarisability effects to the force field whilst maintaining computational efficiency.

$$Q^{ECC} = f_q \cdot Q = \frac{1}{\sqrt{\varepsilon_{el}}} \cdot Q$$

Eq. 1: ECC method; f_q= scaling factor, Q = charge on ion, ε_{el} = high frequency dielectric constant



Non-polarisable force fields
Hybrid methods: ECC
Full polarisable force fields
Physical Accuracy & Computational Cost

The ECC approach accounts of electronic polarisation in a mean-field way by means of ionic charge rescaling (Eq.1) [2][5].

5. Simulations of Water-Alkane Interfaces

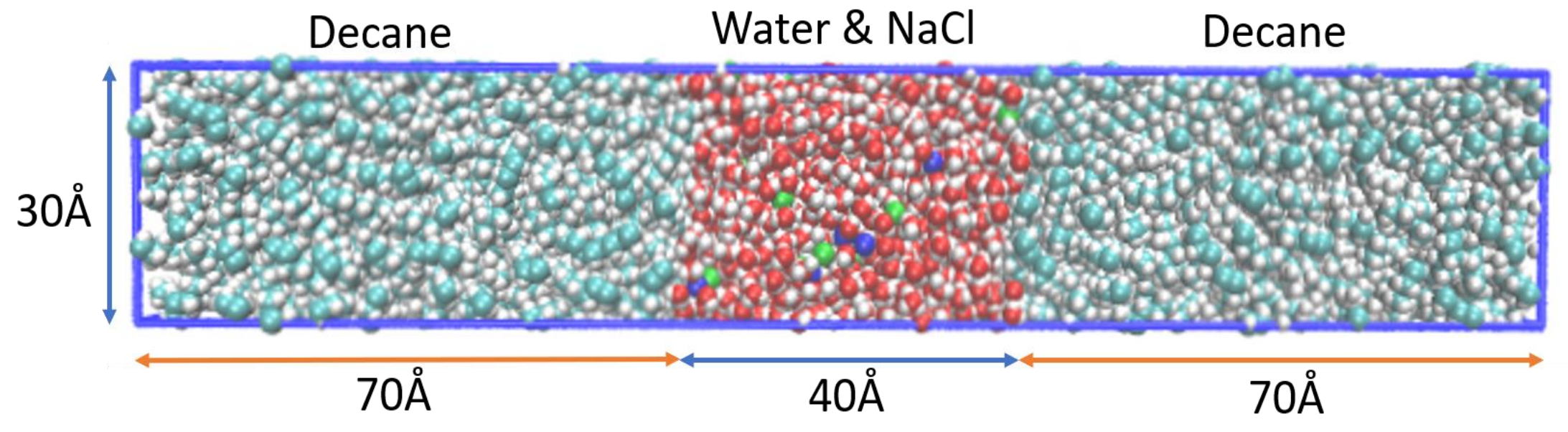


Fig 4. Water/alkane system set up. Carbon atoms are represented by cyan, hydrogen by white, oxygen by red and sodium and chloride ions are represented by blue and green respectively.

Simulation Details

- Force field: OPLS-AA
- GROMACS 2018
- SPC/E water model
- 50 ns simulation
- Simulations with NP FF & ECC

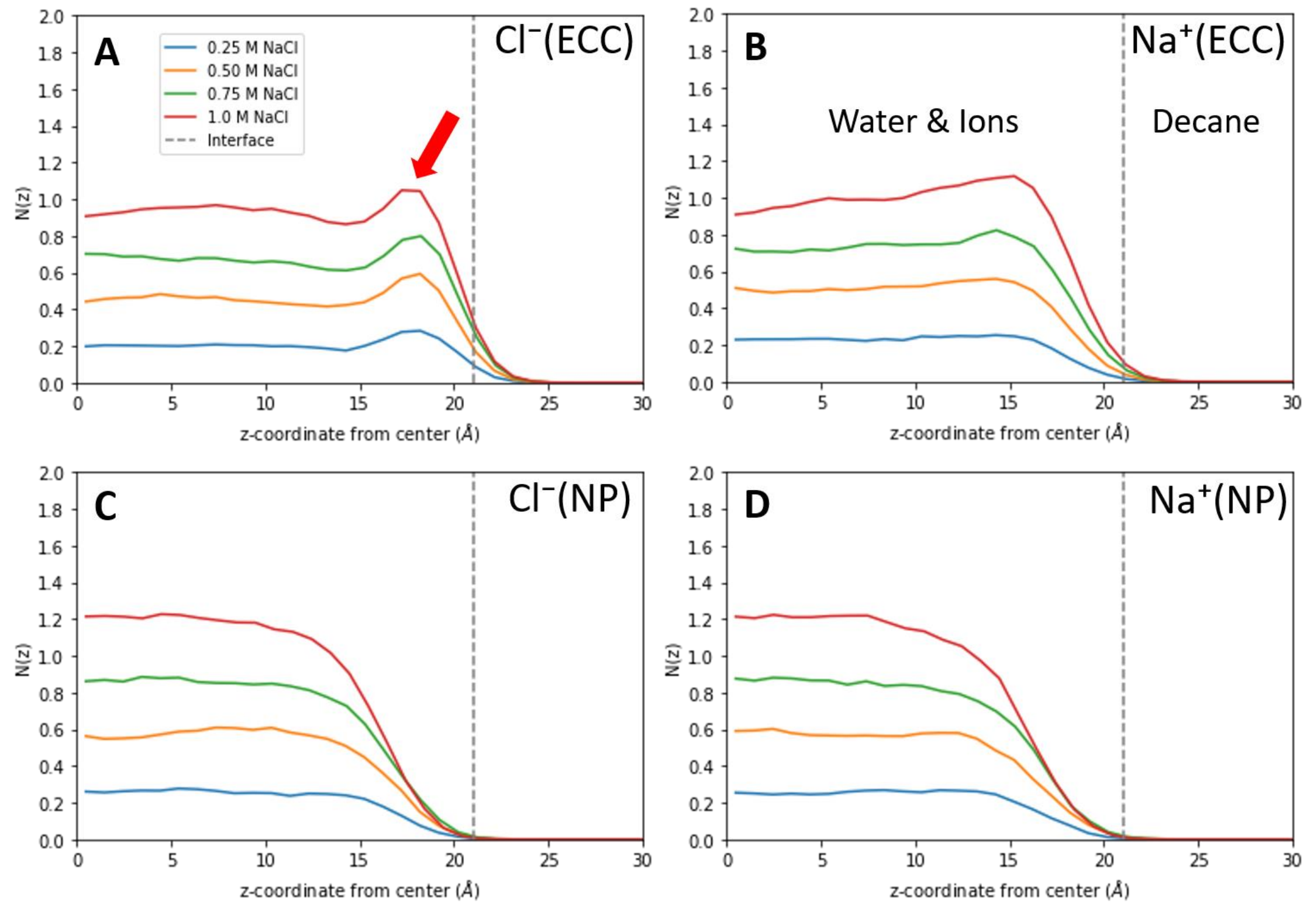


Fig 5. Symmetrised number density profiles. N(z) represents number density normalised by bulk water density and the ions are scaled by the water/ion ratio. **A** Cl⁻ ions with ECC method **B** Na⁺ ions with ECC method **C** Cl⁻ ions with NP FF & **D** Na⁺ ions with NP FF.

Results

- Cl⁻ ions adsorb to the hydrophobic interface with ECC. This is indicated by peak and shifting towards interface (fig 5. **A** red arrow).
- Na⁺ ions are repelled from the surface.
- These effects are not seen with a standard additive FF.
- Effects are consistent across several salt concentrations.

6. Simulations of a Model Nanopore

Simulation Details

- Hydrogen capped carbon nanotubes (CNT) were generated in Avogadro1.2.
- Water molecules were distance restrained to the insides of the CNT pore walls to create two polar regions (fig. 6A & 6C).
- The structure was inserted into a POPC bilayer and solvated with water (SPC/E) and NaCl (fig.6B).
- Samples from a 1 nm thick segments taken from the hydrophobic region were used for analysis.
- Simulation details – same as above.

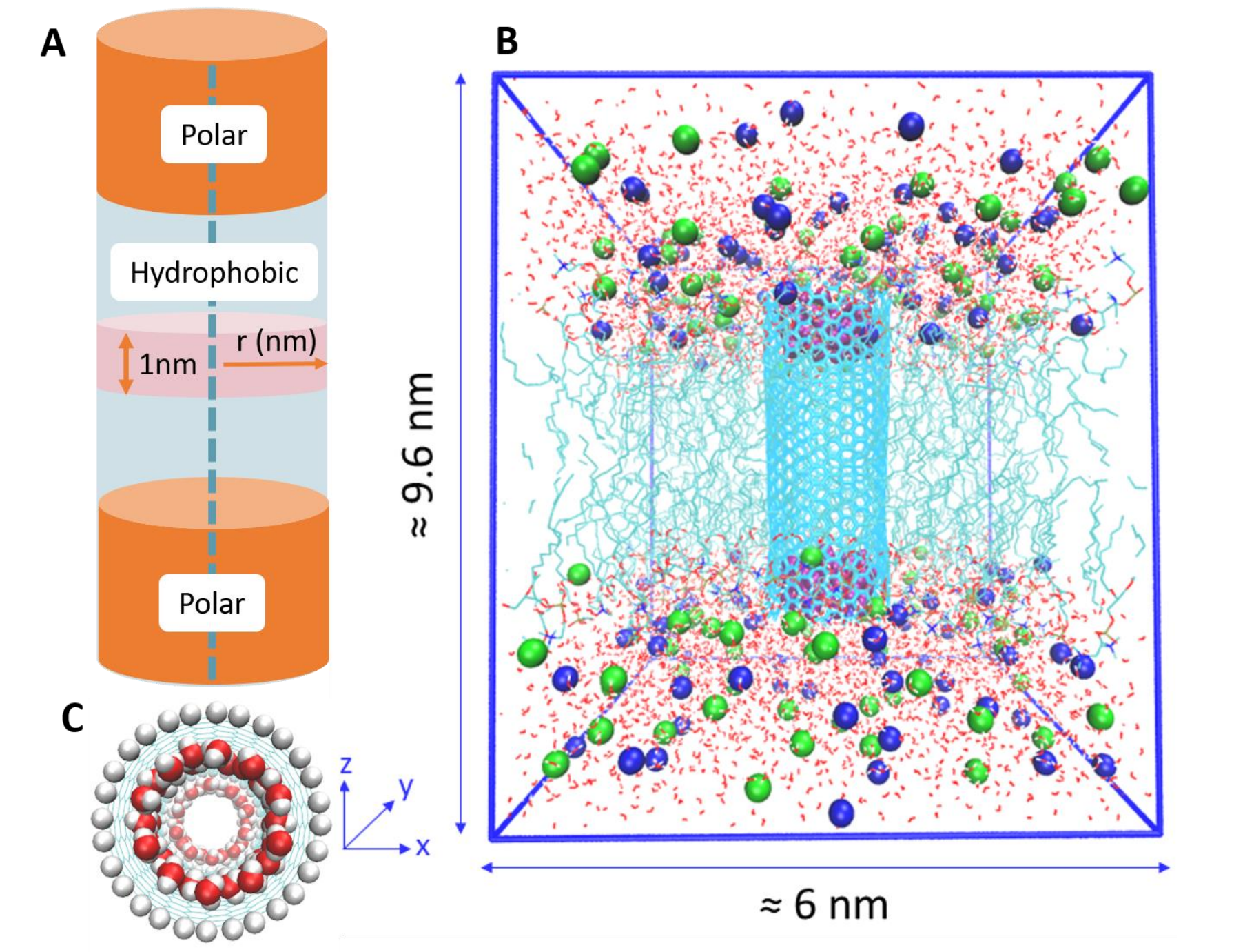


Fig 6. Model CNT Pore. **A** Schematic diagram of the model pore. **B** Simulation box with model CNT embedded in a POPC bilayer and solvated with NaCl and water. **C** Top-down view of pore.

References

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7. Exploring a Model Nanopore

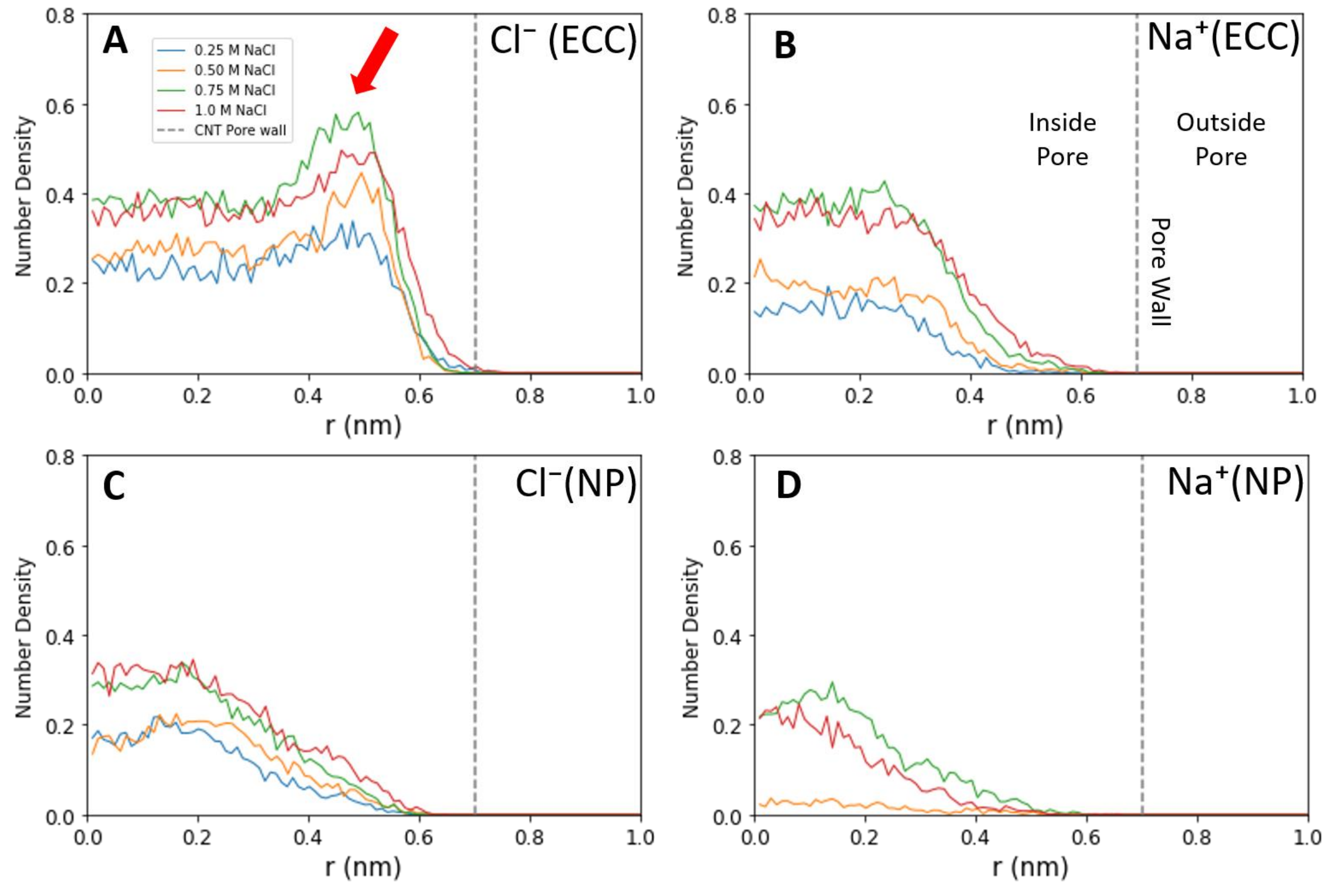

Fig 7. Symmetrised number density profiles normalised by bulk water density from 1 nm thick sample from hydrophobic region of CNT pore (fig. 6A). **A** Cl⁻ ions with ECC method **B** Na⁺ ions with ECC method **C** Cl⁻ ions with NP FF & **D** Na⁺ ions with NP FF.

Concentration Dependence

- Similar Cl⁻ adsorption to the hydrophobic CNT wall as seen with the interfacial system.
- Na⁺ prefers to remain close to the pore axis (fig.7).
- These interfacial effects are not seen when employing a non-polarisable force field.

Radius Dependence

- Cl⁻ adsorption to the hydrophobic CNT wall consistent across different sized CNTs (fig.8).
- Greater area under Cl⁻ curve than Na⁺ suggests more ions are presents therefore suggests some selectivity for Cl⁻ ions.

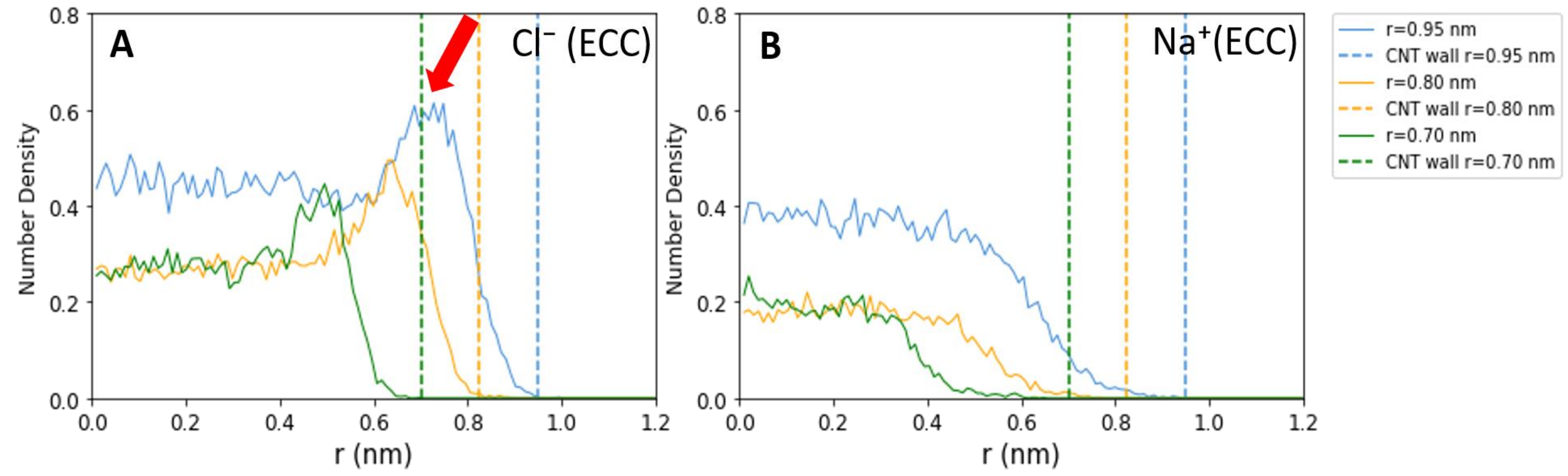

Fig 8. Symmetrised number density profiles normalised by bulk water density from 1 nm thick sample from hydrophobic region of CNT pore (fig. 6A). **A** Cl⁻ ions with ECC method **B** Na⁺ ions with ECC method. Radii found using CHAP.

8. Summary & Conclusions

- Simulations of water/alkane interfaces reveal characteristic adsorption to the hydrophobic interface by the anion only when using the ECC method/ inclusion of polarisability effects.
- Model CNT pores were simulated to explore anion behaviour in hydrophobic nanoconfinement and revealed a some chloride selectivity.

Acknowledgements

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