Characterization and Dynamics of Imidazole-Based Channels in Membranes

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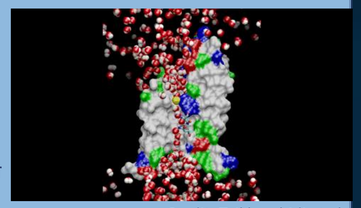
Introduction

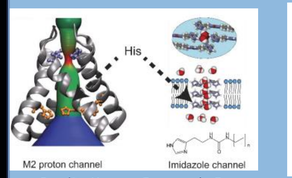
Biomimetic Motivation

- In nature, molecules like aquaporin serve as passive salt excluding channels in biological membranes
- Pore diameter needs to be smaller than 3 angstroms in diameter for salt exclusion

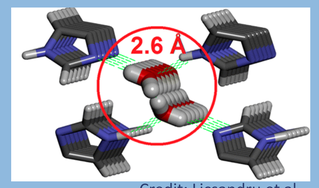


Credit: Tajkhorshidi et al.

- Current synthetic channels are ~30 angstroms in diameter
- Histadine in M2 proton channels utilize imidazole to create a water wire (an organized one-molecule-wide structure), ensuring a 2.6 angstrom gap.



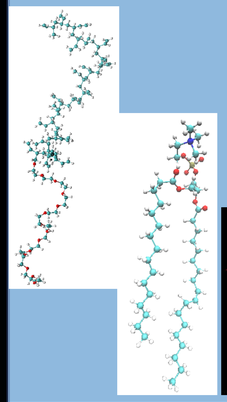
Credit: Kumar Research Group



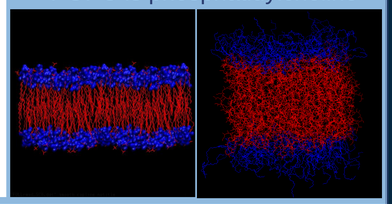
Credit: Licsandru et al.

- The water wire stabilizes the channel.
- It is unknown how many imidazole rings stack together in membranes and whether it is dependent on the identity of the membrane.

Membranes Investigated



- The membranes analyzed are
  - **$(PB)_{22}$-$(PEO_{1,2})_{14}$** (Left)
  - **POPC** (Right)
- **$(PB)_{22}$-$(PEO_{1,2})_{14}$** is referred to as block co-polymer
- POPC is phosphatidylcholine

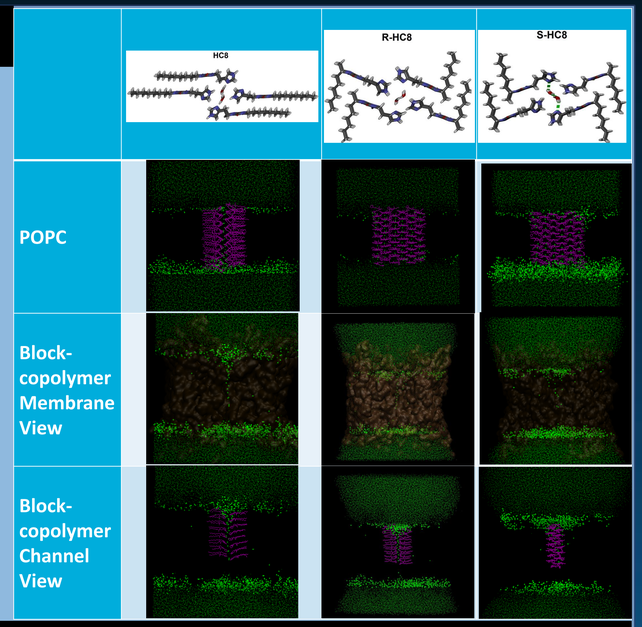


Objectives

- Understand why the experimental permeabilities obtained are different from channel to channel
- Evaluate if existing models are stable under CHARMM forces
- Investigate and quantify large-scale torsion
- Find out how many ”I-Quartets” stack in various membranes by “fine-tuning the number of ”I-Quartets” in a membrane simulation.

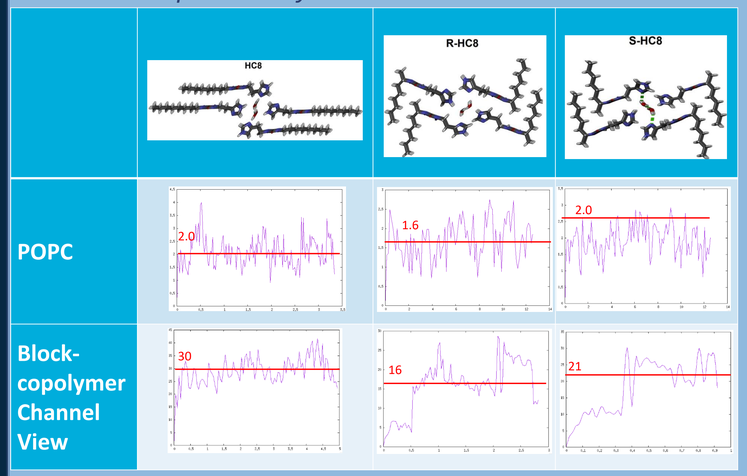
Methods

- Initial structures of channels were provided from experimentally obtained crystal structures and force field parameters were found through quantum calculations through Gaussian.
- Software packages utilized were **V**isual **M**olecular **D**ynamics (for building files from plugins), **Na**noscale **M**olecular **D**ynamics (for molecular dynamics simulations), and Gaussian (for force field parameters and quantum mechanics calculations).
- POPC membrane structures are supplied by VMD. Block-copolymer membranes were made and supplied by D. Ryan Barden.
- Large, two-channel complexes of the three channel types were inserted in both membranes using the method described at http://www.ks.uiuc.edu/Training/Tutorials/science/membrane/mem-tutorial.pdf
- Small, equilibrium-based simulations were initially carried out on *premise.sr.unh.edu* to equilibrate the stitched-together structures and long-scale simulations were then carried out on *comet.sdsc.xsede.org*.

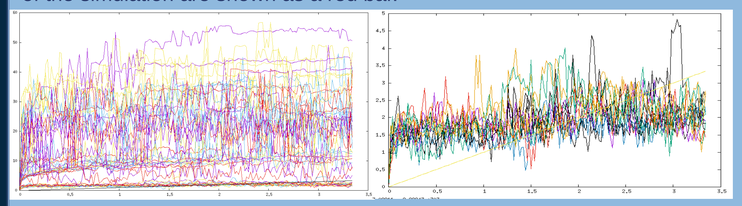


Results

Root Mean Square Analysis

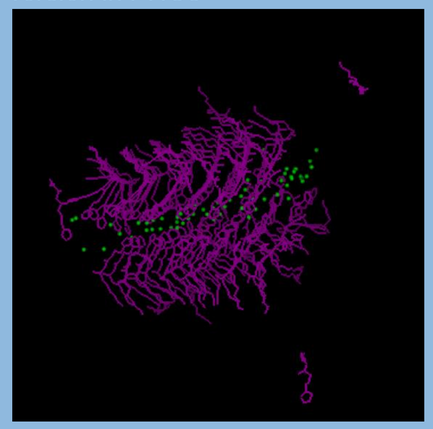


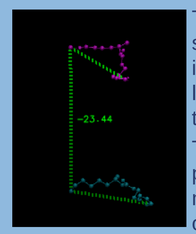
Above, the ensemble root mean square displacement (RMSD) over the course of the simulations are plotted. As a rule, the more novel block-copolymer runs have higher RMSDs. The average values over the course of the simulation are shown as a red bar.



The snapshot on the left shows the RMSD of each residue, and to the right are shown RMSDs of the remaining residues

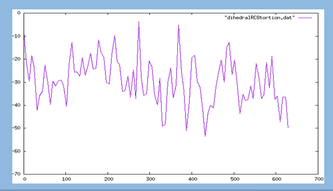
Torsion in r-HC8





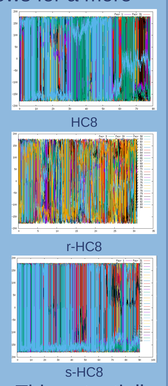
The figure above shows the spread of the r-HC8 channel in POPC. The figure to the left shows the dihedral angle that quantifies torsion.

The figure below details the progression of this measurement over the span of this simulation.



Conclusions

- Iterative method for channel thickness allows for a more stable structure (lower ensemble RMSD)
- Individual dihedral measurements (shown at the right) are inconclusive and show no pattern. What appears to be large-scale torsion observable in r-HC8 and s-HC8 is not quantifiable by a dihedral angle.
- r-HC8 is, by far, the most static (having the lowest RMSD), agreeing with the findings of the experimental findings. However, in opposition to experiment, s-HC8 has even larger RMSDs than HC8 (experiment found that chiral enantiomers of HC8 functioned best).
- POPC runs had lower RMSDs on average. This potentially was because
  - the phospholipid bilayer (POPC) is a well known and equilibrated system
  - channel clumping is occurring which was found experimentally.



Future Work

- Longer runs of all existing simulations with functional channel thickness in mind
- Permeability calculations (would do well to replicate Licsandru et al.)
- More work on channel clumping
- Charged solution simulations

References

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