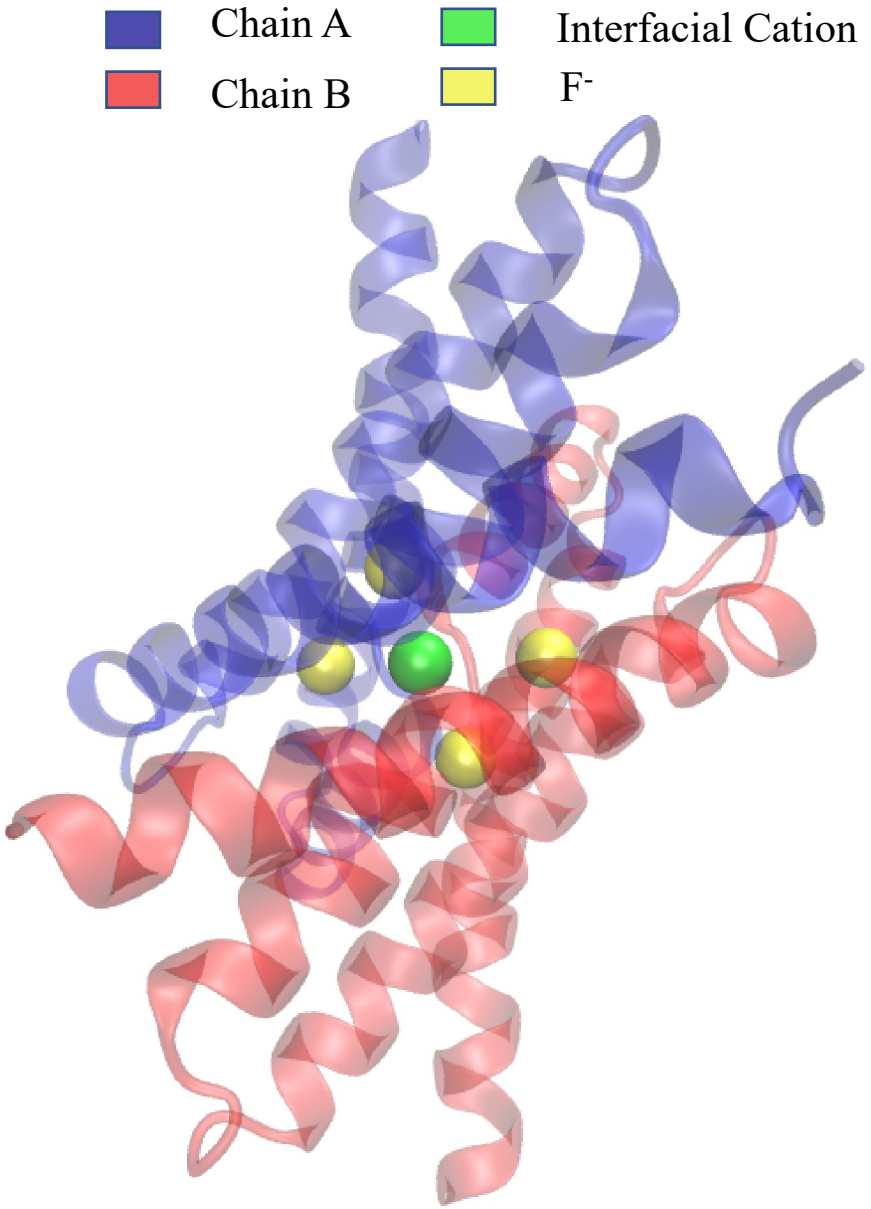
Exploring the role of interfacial cation in F ion channel using MD simulation: Application of computational chemistry

Aru Chezhian, Zabin Momin, Hedieh Torabifard*
University of Texas at Dallas

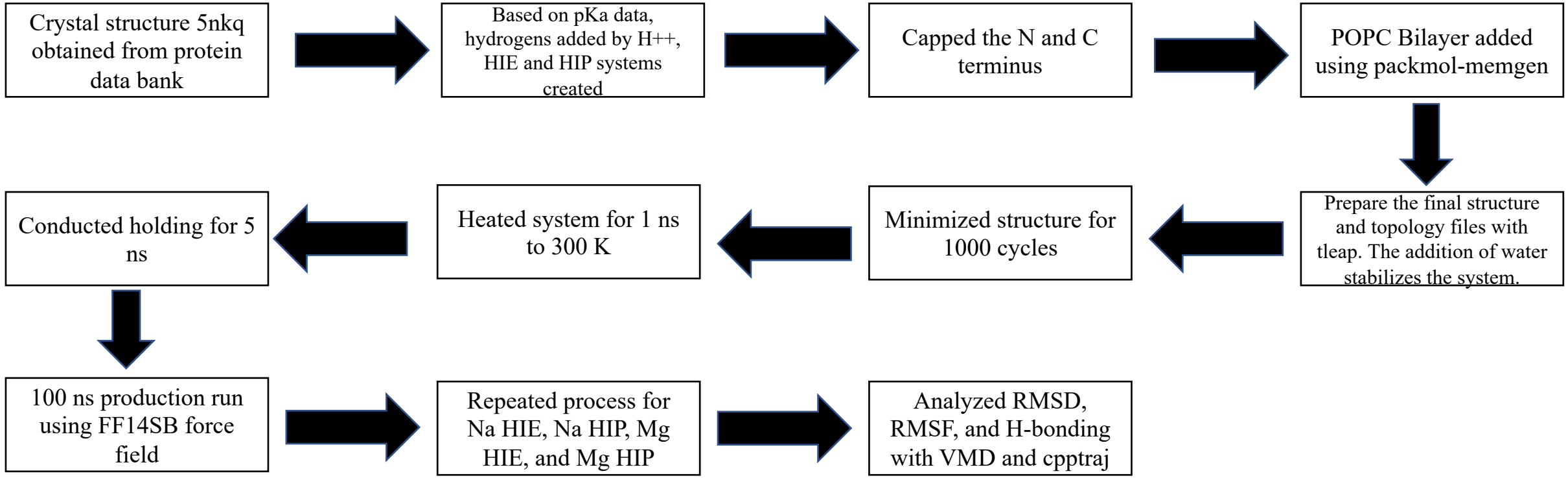
Introduction:

- Fluoride ion channel, called Fluc is a selective towards F^- that has evolved in many microbes to combat F^- toxicity
- Fluc has a dual topology dimeric architecture
- Previous crystallography work has proposed that a Na^+ ion is located at the interface of the dimer
    - Na^+ usually coordinates with 5/6 ligands, but the Fluc interfacial cation is tetrahedrally coordinated
- We are modelling Fluc with alternate cations Mg^{2+} and Li^+ to compare structural stability and conformational changes
- This work could have larger implications for future study of this channel and other cation-coupled transporters for antimicrobial drug design



Stockbridge, R., Kolmakova-Partensky, L., Shane, T. *et al.* Crystal structures of a double-barrelled fluoride ion channel. *Nature* **525,** 548–551 (2015)

Methods:

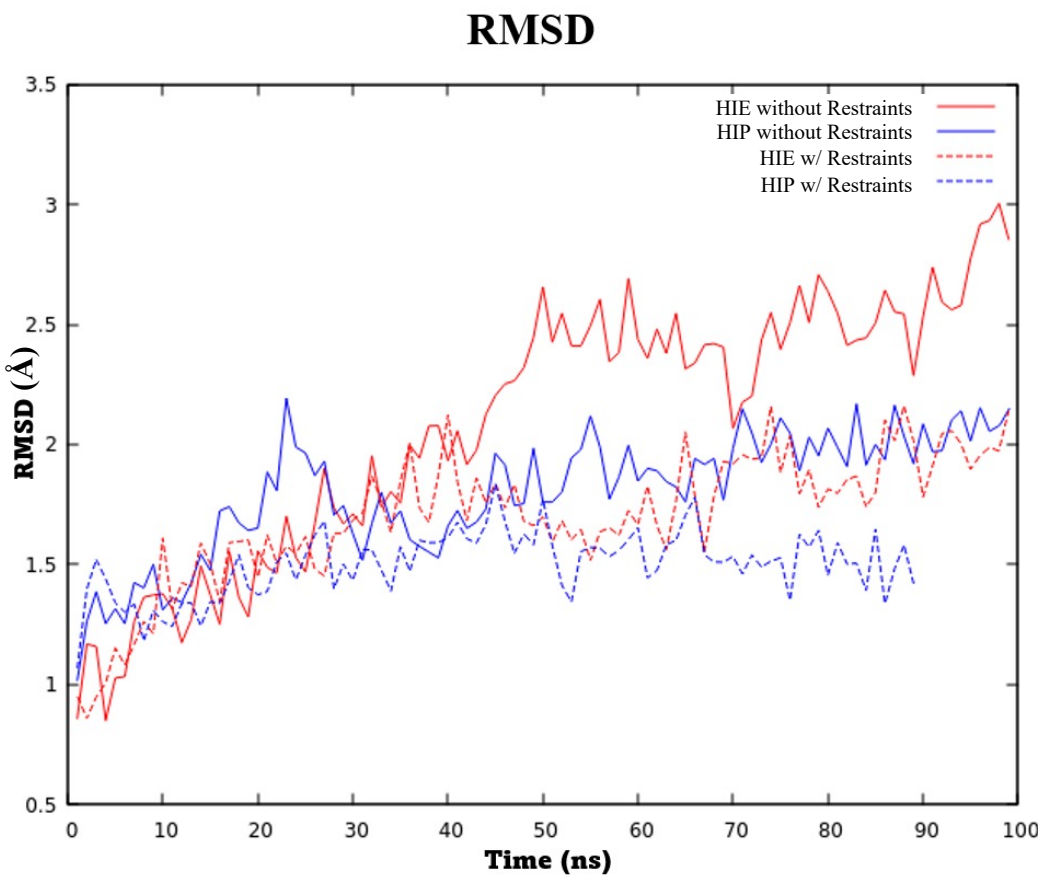


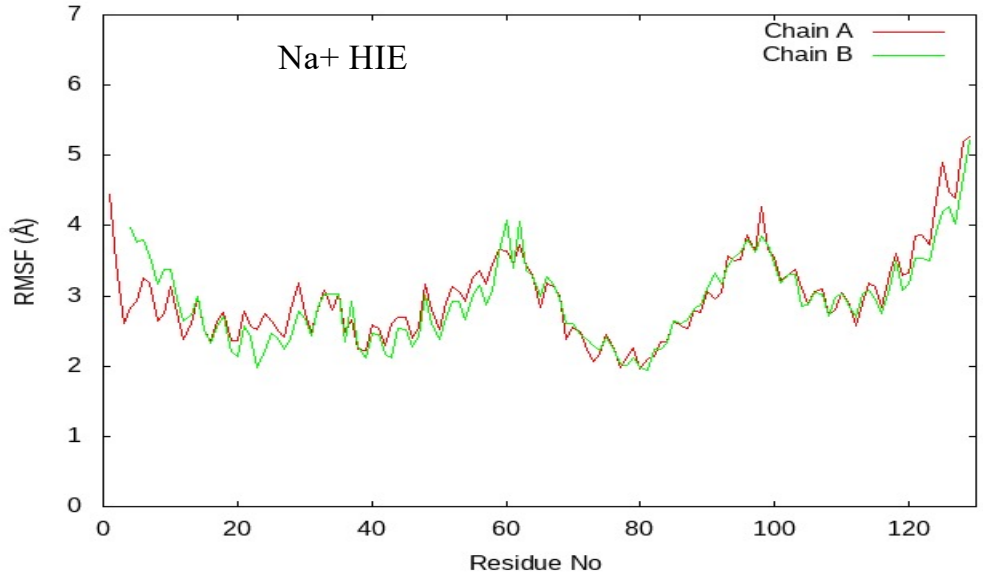
D.A. Case, K. Belfon, I.Y. Ben-Shalom, S.R. Brozell, D.S. Cerutti, T.E. Cheatham, III, V.W.D. Cruzeiro, T.A. Darden, R.E. Duke, G. Giambasu, M.K. Gilson, H. Gohlke, A.W. Goetz,R Harris, S. Izadi, S.A. Iz- mailov, K. Kasavajhala, A. Kovalenko, R. Krasny, T. Kurtzman, T.S. Lee, S. LeGrand, P. Li, C. Lin, J. Liu, T. Luchko, R. Luo, V. Man, K.M. Merz, Y. Miao, O. Mikhailovskii, G. Monard, H. Nguyen, A. Onufriev, F. Pan, S. Pantano, R. Qi, D.R. Roe, A. Roitberg, C. Sagui, S. Schott-Verdugo, J. Shen, C.L. Simmerling, N.R. Skrynnikov, J. Smith, J. Swails, R.C. Walker, J. Wang, L. Wilson, R.M. Wolf, X. Wu, Y. Xiong, Y. Xue, D.M. York and P.A. Kollman (2020),

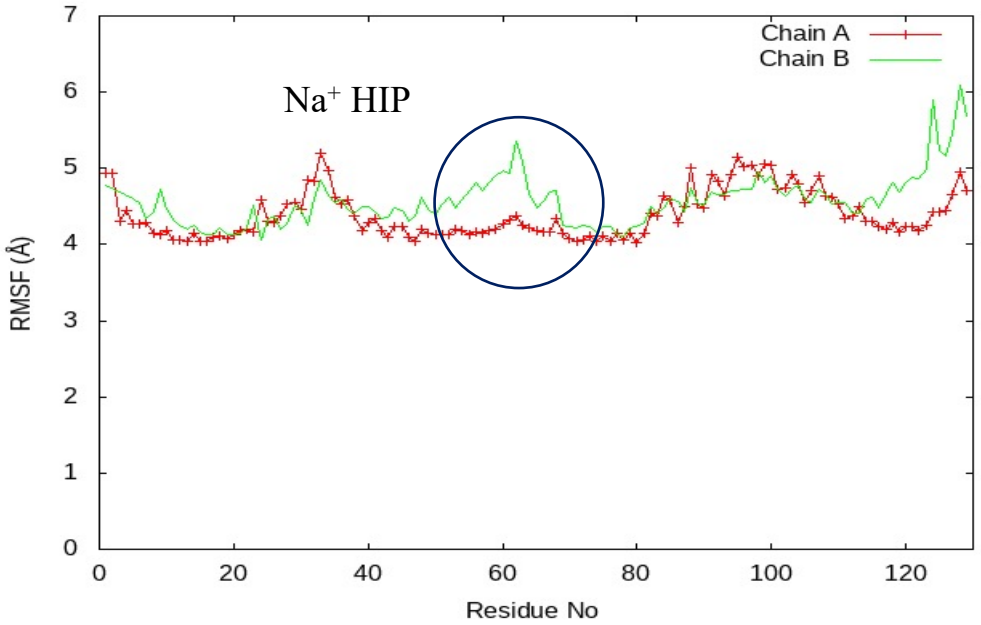
Results:

Na^+ RMSD/RMSF

Na Cation Fluc

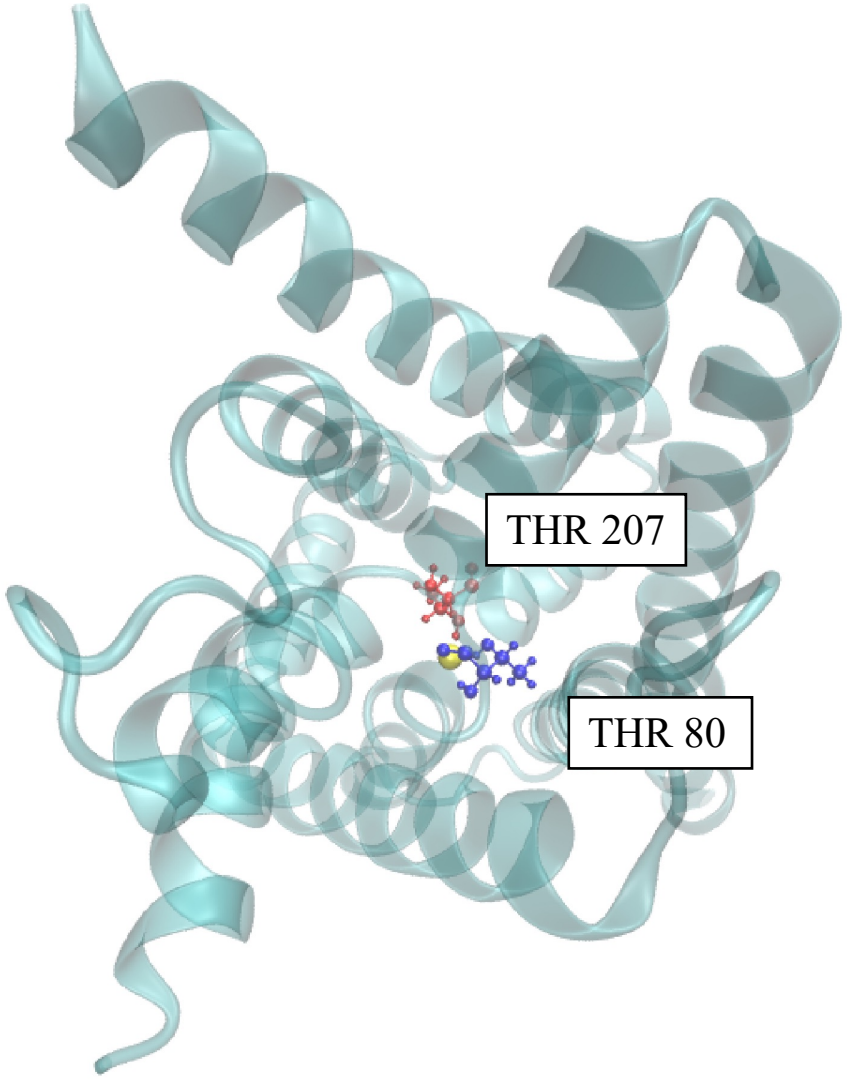






The significant difference in RMSF in the HIP system corresponds to the loop where HIS 60 is located.

Na^+ HIE Coordination



System	# of intracellular F^-
Na^+ HIE	2

Bonded Residues	Fraction of Time Bonded
F260 – THR 80	0.9968
F260 – THR 207	0.9572

The H-bonding analysis shows that THR 207 and THR 81 form an H-bond network with F 260 and hold it in place

Humphrey, W., Dalke, A. and Schulten, K., "VMD - Visual Molecular Dynamics", J. Molec. Graphics, 1996, vol. 14

Na^+ HIP Coordination

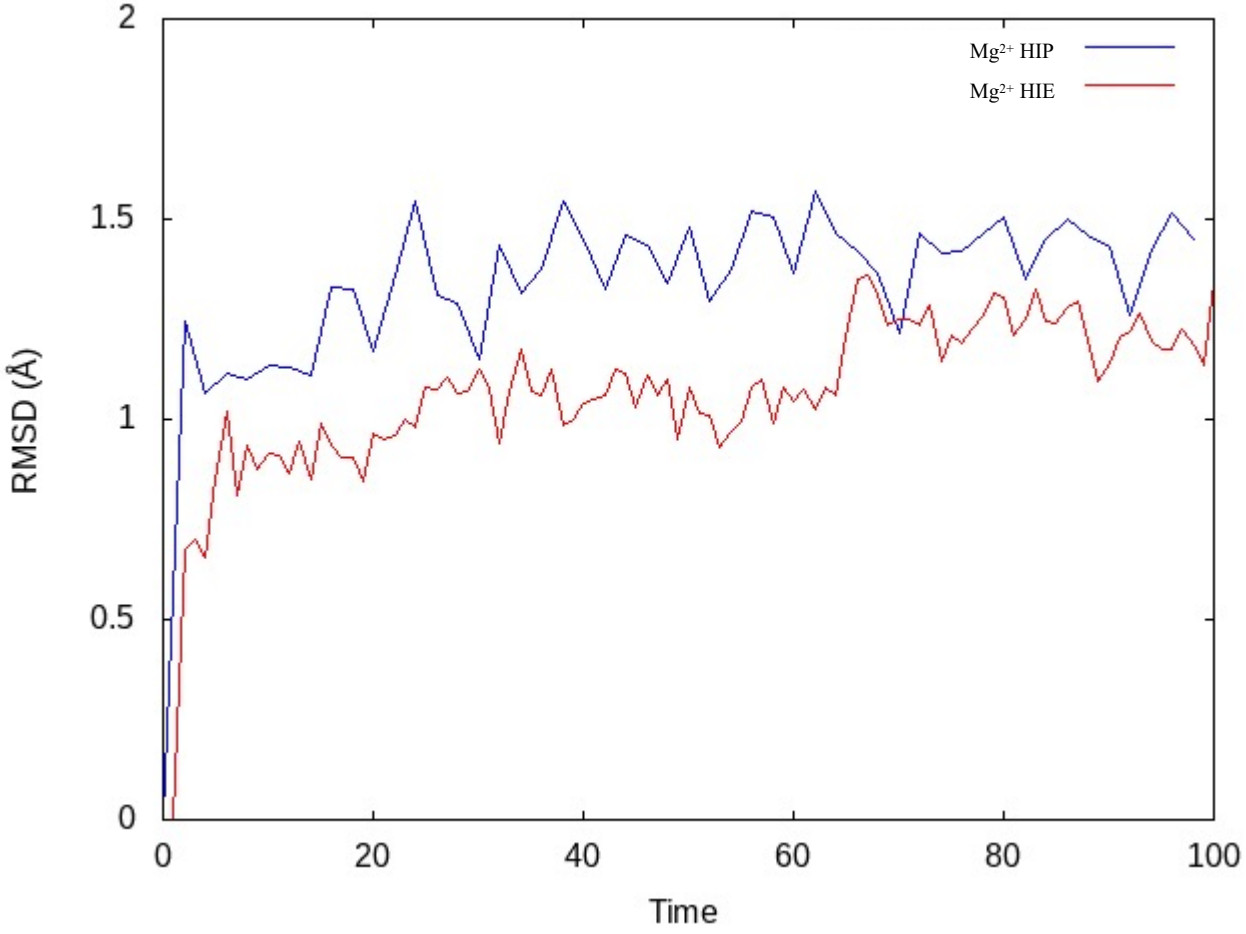
The H-bonding analysis shows that ARG 23 has interactions with GLY 78. ARG 23 is potential interest since this specific residue has not had prolonged hydrogen bonding in Na^+ HIE system. Also, the fluoride ions have no H-bond interactions with the neighboring residues. Yet, 2 of them remained inside the pore.

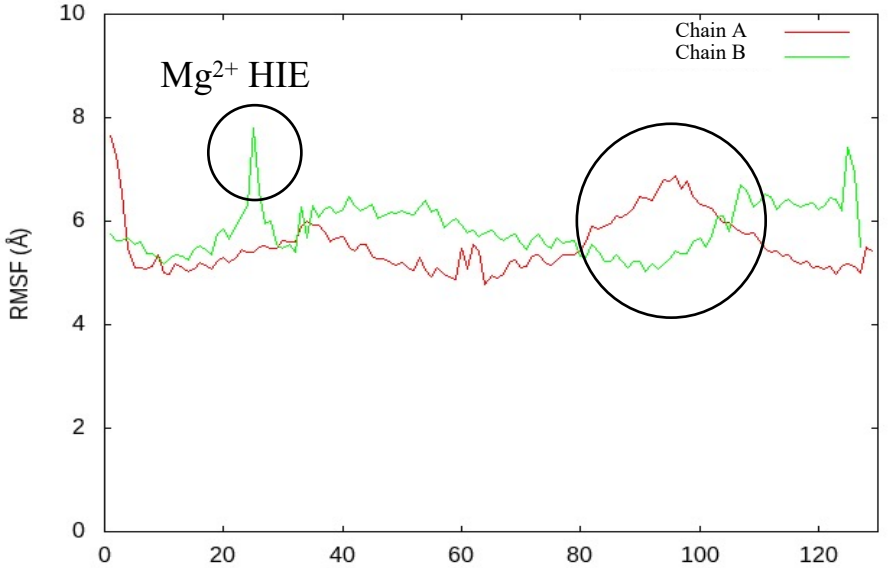
System	# of intracellular F^-
Na^+ HIP	2

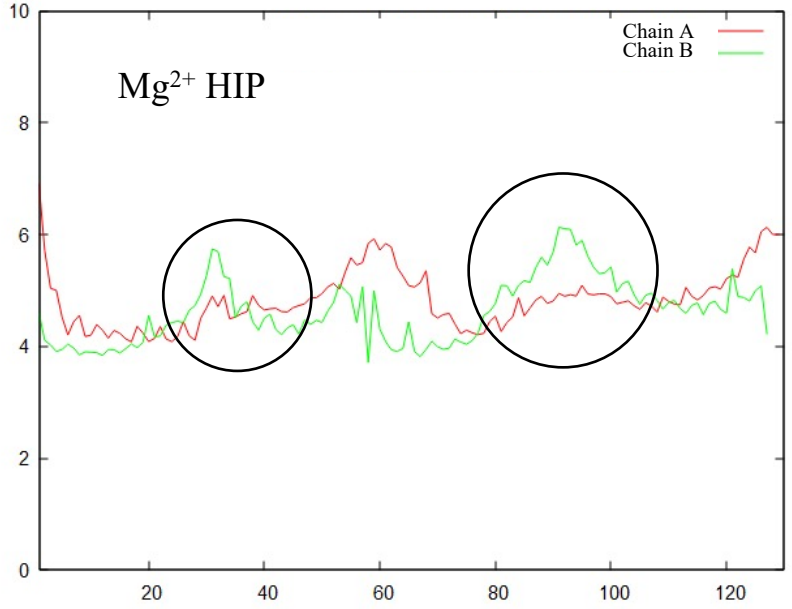
Bonded Residues	Fraction of Time Bonded
GLY 78 – ARG 23	0.9493
TRP 37- THR 41	0.9451

Humphrey, W., Dalke, A. and Schulten, K., "VMD - Visual Molecular Dynamics", J. Molec. Graphics, 1996, vol. 14

Mg^{2+} RMSD/RMSF

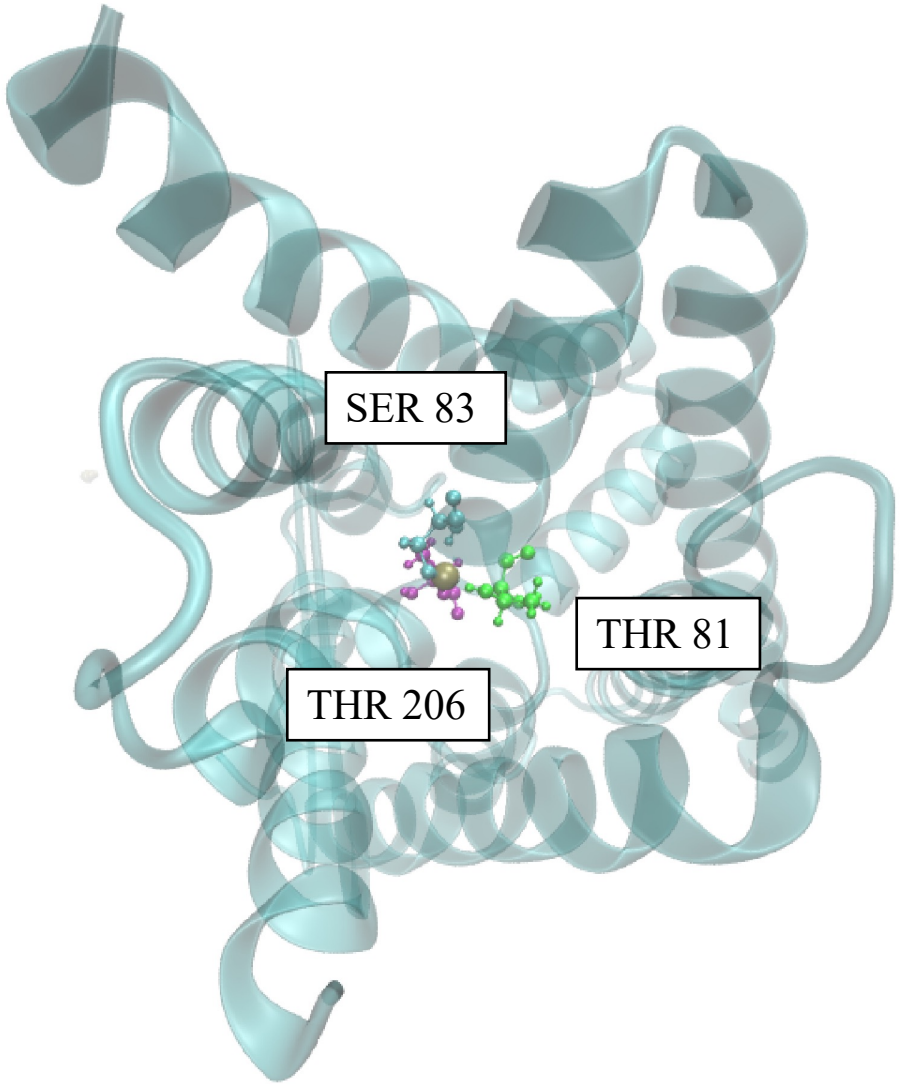






ARG 23, specifically its conformational changes, are of interest. Residues 80-100 are also of interest, because of the unique wide peak.

Mg^{2+} HIE H-Bonding and Coordination



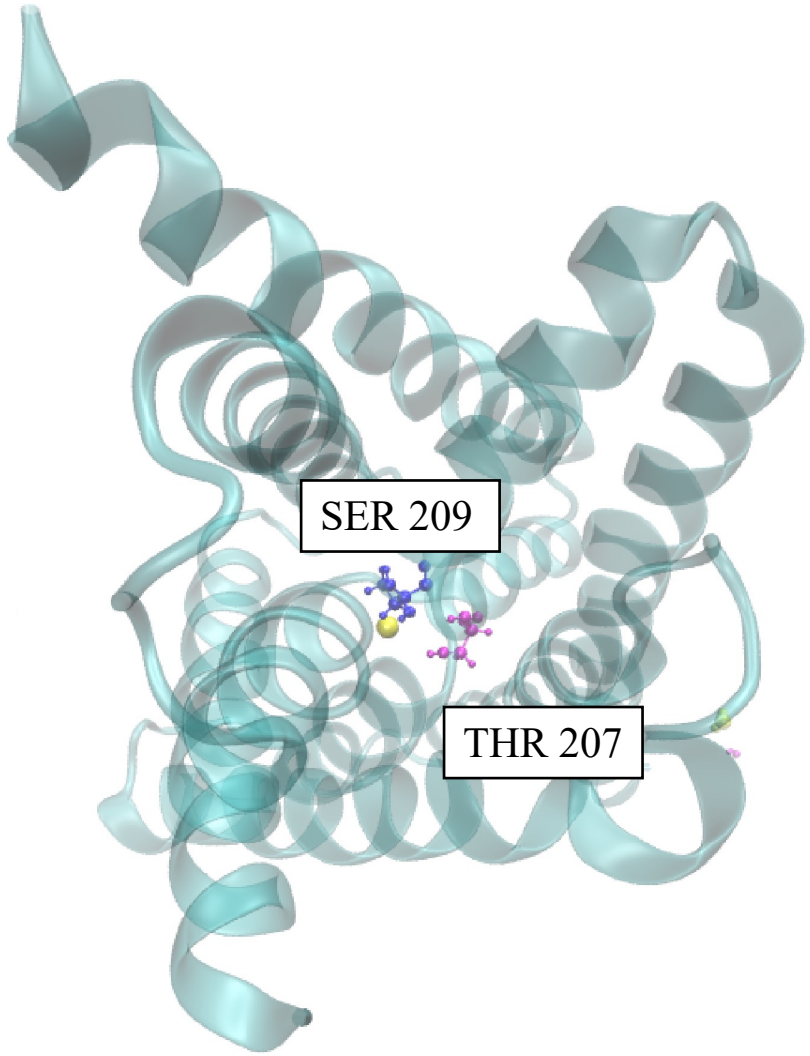
System	# of intracellular F^-
Mg^{2+} HIE	3

Bonded Residues	Fraction of Time Bonded
F 258 – THR 81	0.9988
F 258 – SER 83	0.9985
F 258 – THR 206	0.9948

The H-bonding analysis shows that THR 206 and THR 81, and SER 83 form an H-bond network with F 258 and hold it in place

Humphrey, W., Dalke, A. and Schulten, K., "VMD - Visual Molecular Dynamics", J. Molec. Graphics, 1996, vol. 14

Mg^{2+} HIP H-Bonding and Coordination



System	# of intracellular F^-
Mg^{2+} HIP	2

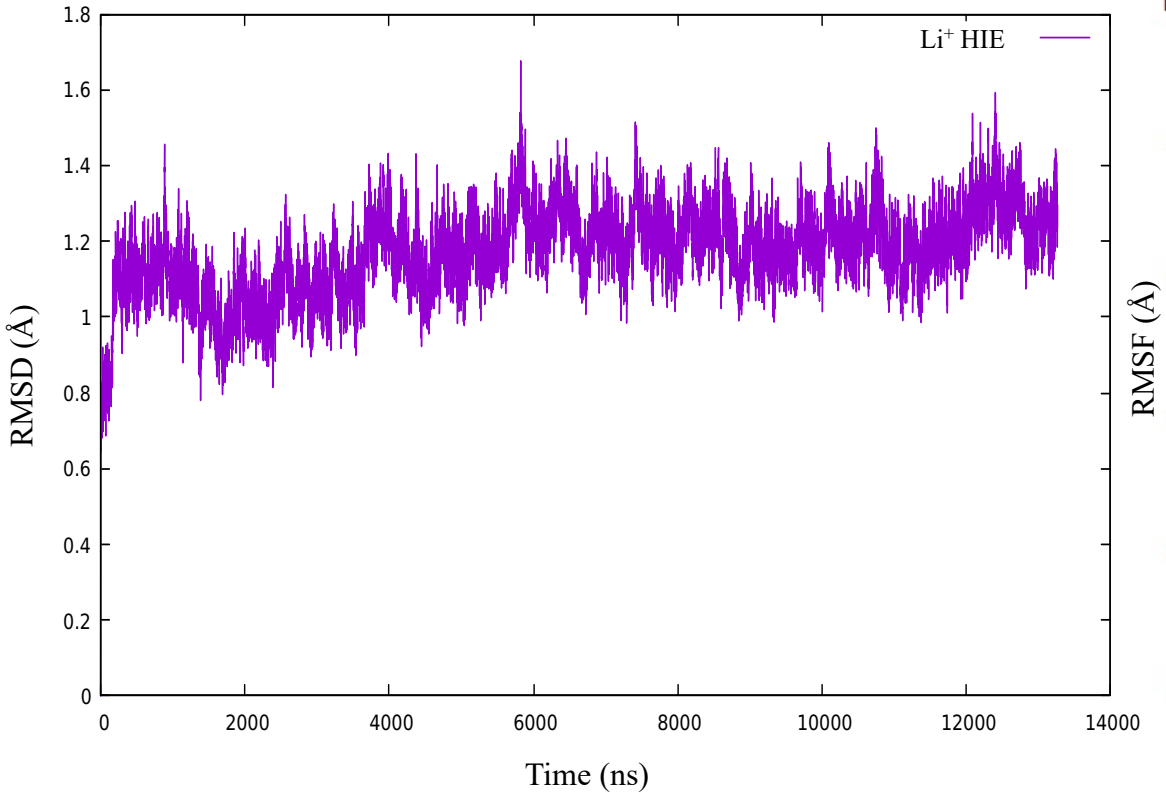
Bonded Residues	Fraction of Time Bonded
F 260 – SER 209	1.0000
F 260 – THR 207	0.9800

The H-bonding analysis shows that SER 209 and THR 209 form an H-bond network with F 260 and hold it in place

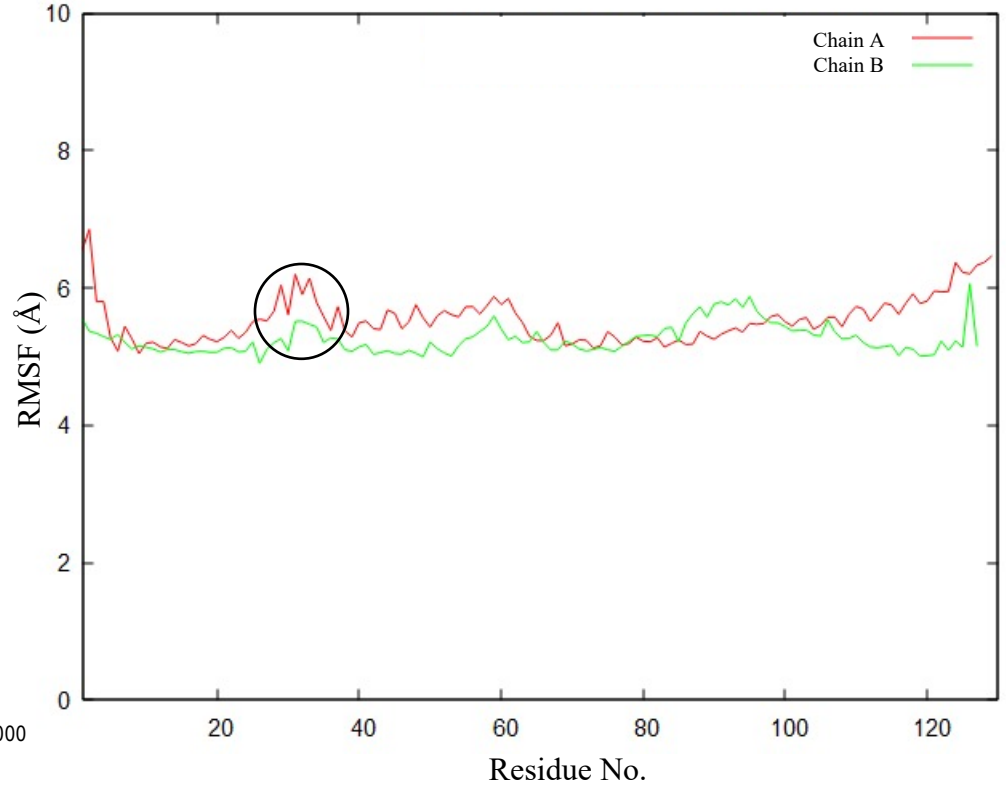
Humphrey, W., Dalke, A. and Schulten, K., "VMD - Visual Molecular Dynamics", J. Molec. Graphics, 1996, vol. 14

Li^+ RMSD/RMSF

Li^+ RMSD

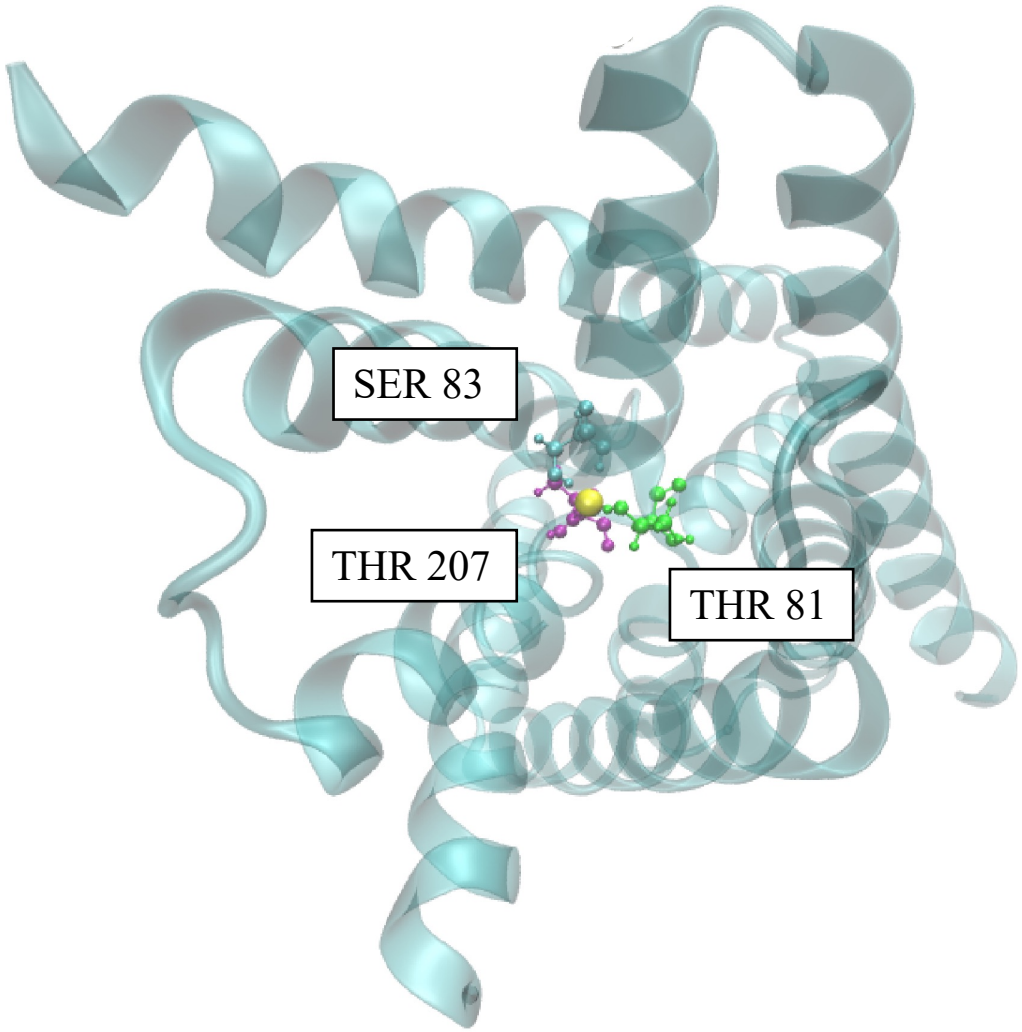


Li^+ RMSF



The first peak coincides with ARG 33, a residue of interest. The second peak corresponds to the loop where HIS 60 is located

Li^+ HIE H-bonding and Coordination



System	# of intracellular F^-
Li^+ HIE	2

Bonded Residues	Fraction of Time Bonded
F 258 – SER 83	0.9996
F 258– THR 206	0.9993
F 258– THR 81	0.9992

The H-bonding analysis shows that THR 206 and THR 81, and SER 83 form an H-bond network with F 258 and hold it in place

Humphrey, W., Dalke, A. and Schulten, K., "VMD - Visual Molecular Dynamics", J. Molec. Graphics, 1996, vol. 14

Conclusion:

- The Mg^{2+} HIE system had the most stable backbone. However, the Na^{+} HIE system had the lowest residual movement. These two systems seem to be the most stable.
- The Mg^{2+} HIE and Li^{+} HIE systems had the most complex hydrogen bond networks involving fluoride ions. These hydrogen bond networks held those ions in place during the entire simulation.
- We plan to run these systems for a longer period and replace the anions with Cl-, nitrate, and guanidinium.

Thank You!

- **Texas Advanced Computing Center (TACC)** for the large computing services and allowing us to run and analyze simulations
- All members of the **Torabifard Lab**: Dineli, Kira, Tejas, Abiola, Andre, Sahar, and Dr. Torabifard, for their advice and guidance
- **The University of Texas at Dallas** for allowing us to conduct our research