Evaluating Molecular Mechanics Force Fields with a Quantum Chemical Approach

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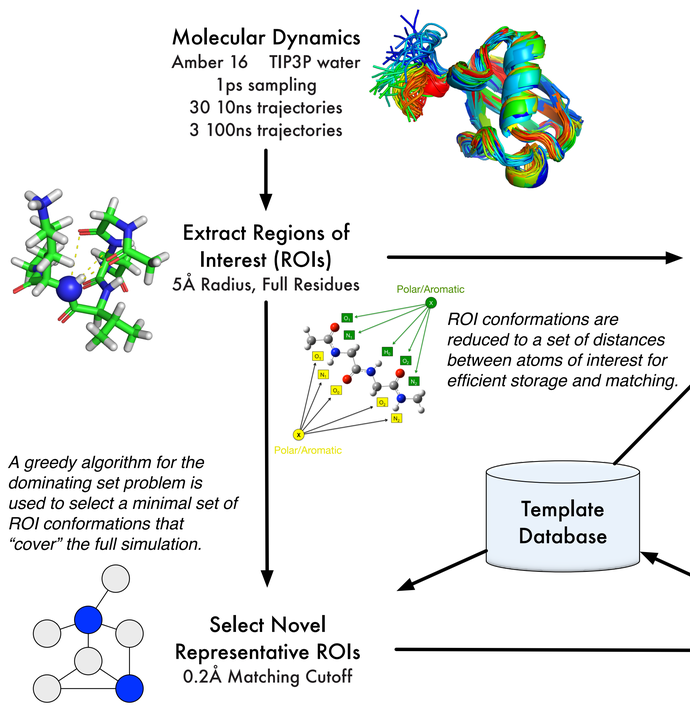
http://github.com/dkoes/MD2NMR

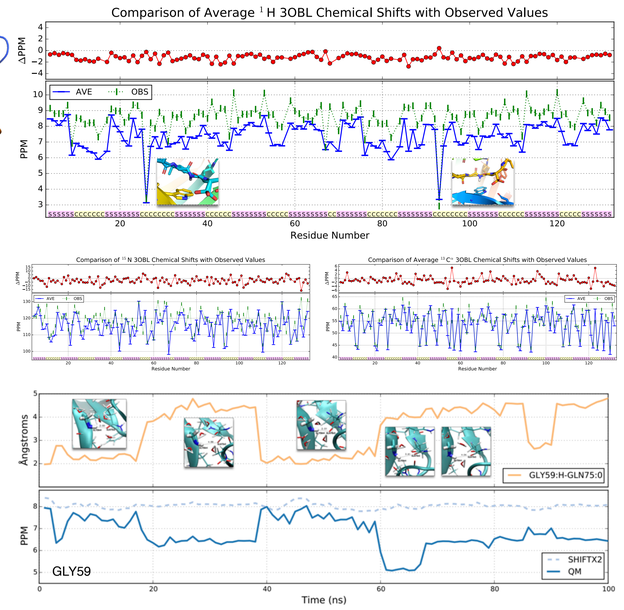
Introduction

The chemical shifts of a molecular dynamics trajectory can be obtained from de novo quantum mechanical (QM) calculations performed on localized regions surrounding the atoms of interest. The ensemble average of these calculated chemical shifts can be compared to the chemical shifts obtained from NMR spectroscopy to get an estimate of the accuracy of the simulation [1].

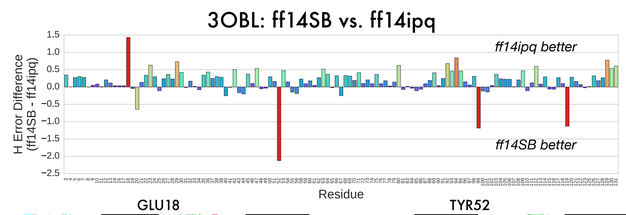
We quantify the errors associated with the backbone atoms in MD simulations of seven model proteins. A library of regional conformers containing 261,587 members was constructed from molecular dynamics simulations of the model proteins. The chemical shifts associated with the backbone atoms in each of these conformers was obtained from QM calculations using density functional theory at the B3LYP level with a 6−311+G(2d,p) basis set. Chemical shifts were assigned to each backbone atom in each MD simulation frame using a template matching approach. The ensemble average of these chemical shifts was then compared to chemical shifts from NMR spectroscopy.

All force fields exhibit errors, and 1H atoms display a particularly prominent systematic error. Different force fields exhibit consistent differences in errors that map directly to residue specific differences in conformational sampling. We find that recent force fields developed with the implicitly polarized charge model generate trajectories with the lowest average error, but no single force field is clearly best.



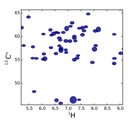


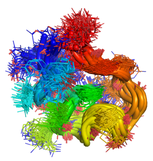
The computed chemical shift can serve as a sensitive indicator variable of the local chemical environment.



Background

Chemical Shifts. The chemical shift of an atom is the change in resonant frequency of the nuclei with respect to a standard. As the resonant frequency is determined by the local electronic environment, chemical shift values provide an experimentally measurable indicator of the local chemical environment of individual atoms of a protein.





Molecular dynamics. Molecular dynamics simulations numerically integrate Newton's equations of motion to derive a trajectory of atomic coordinates.

Force fields. Molecular mechanics force fields determine the potential energy of a molecular system and usually consist of covalent (bond/angle/dihedral) and noncovalent (electrostatic/van der Waals) terms. If a force field accurately estimates the potential energy of a system, then molecular dynamics simulations computed using the force field will have realistic dynamics that correspond to experimental observables. In this work we evaluate force fields from the **Amber** family of force fields (in approximate chronological order): ff94[2], ff96[3], ff03[4], ff99SB[5], ff99SBildn[6], ff99SBnmr[7], ff14SB[8], ff14ipq[9], and ff15ipq[10].

References

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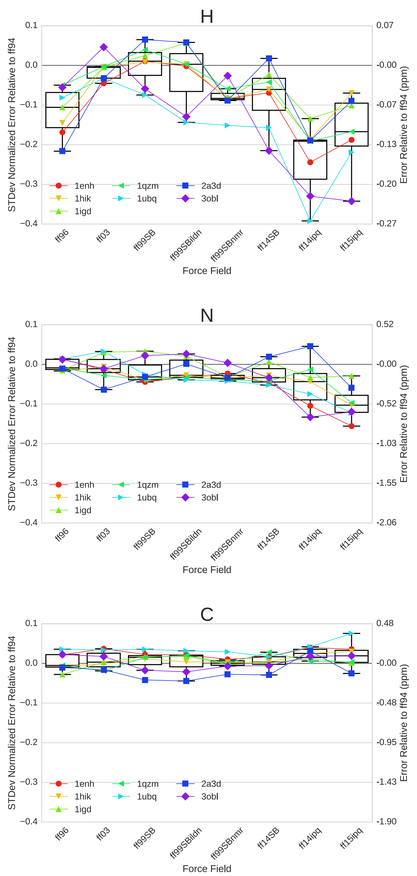
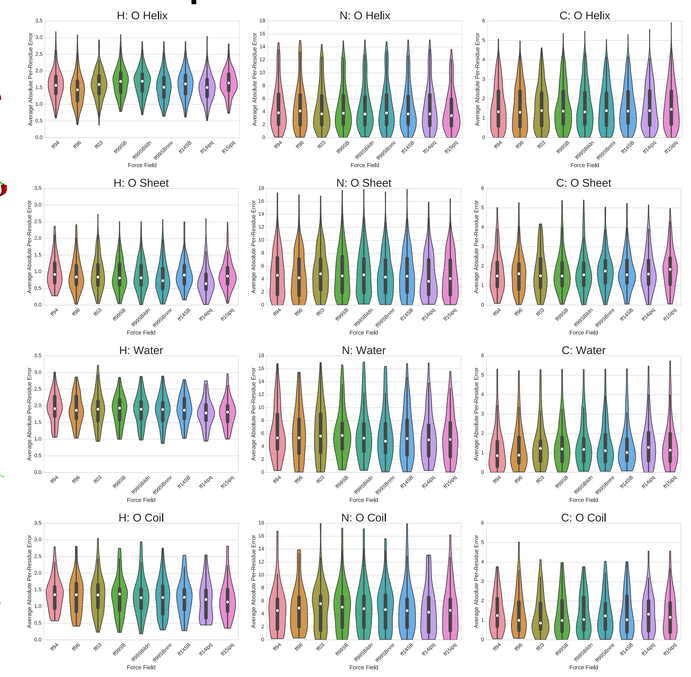
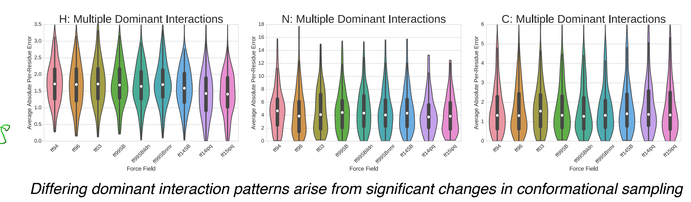
Force Fields Compared



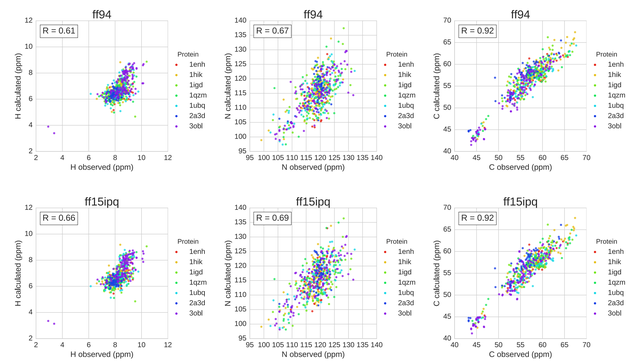


75% of residues display the same dominant interaction pattern across all force fields (examples above).



Differing dominant interaction patterns arise from significant changes in conformational sampling

Correlation With Experiment



Conclusion

Force fields are typically validated on larger systems using statistical analysis of secondary structure, NMR relaxation times, and J-couplings. Ab initio chemical shift prediction provides an additional metric for validation that provides detailed information about atomic environments.

ff14ipq and **ff15ipq** perform best in our evaluation. Neither is clearly superior to the other, but both generally outperform the other considered force fields.

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