ADVANCING MOLECULAR DYNAMICS SIMULATIONS OF GLYCANS THROUGH CHARGE SCALING

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Electrostatic interactions are fundamental to biomolecular processes, particularly in glycan-mediated recognition and binding. However, traditional nonpolarizable molecular dynamics (MD) force fields struggle to accurately model these interactions, often leading to overbinding and unrealistic ion pairing. We designed the prosECCo75 force field to overcome this limitation, a charge-scaled variant of the widely used CHARMM36 force field [1]. Our newly developed force field incorporates the missing electronic polarization in a mean-field manner, refining the description of charged and polar biomolecules such as glycans, lipids, and proteins without additional computational cost.

Glycosaminoglycans (GAGs), highly charged polysaccharide polymers forming the extracellular matrix, interact with ions and other biomolecules such as proteins primarily through electrostatics. Due to their numerous carboxyl and sulfate/sulfamate groups, the accuracy of MD simulations in describing these electrostatic interactions is critical for understanding their biological roles. Using charge-scaled models, we demonstrate substantial improvements in simulating glycan-ion [1-2] and glycan-peptide interactions [3], revealing, for example, that solvent-shared ion pairing is the dominant binding mode of calcium to sulfated GAGs [2]. Our approach outperforms conventional force fields, mitigating overestimated contact ion pairing and improving agreement with experimental data.

Extensive validation across diverse biomolecular systems highlights the broader applicability of charge scaling in improving force field accuracy. By refining partial charges without significantly modifying molecular topologies, our method aligns better with experimental observations while maintaining the same computational efficiency. These advancements enhance the reliability of large-scale biomolecular simulations involving glycans, enabling more precise insights into glycan-mediated interactions.

References:

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3. M. Riopedre-Fernandez et al., *Carbohydr. Polym.* **2024**, *325, 121568*