An Efficient Enhanced Sampling Strategy for Magnesium-Phosphate Interactions in Biological Systems

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Many biological molecules contain phosphate groups, including nucleic acids and modified proteins involved in diseases like Alzheimer's. These phosphate groups are key interaction sites with ions, including divalent ions such as Mg^{2+} and Ca^{2+}. These interactions play an important role in numerous biomolecular processes, such as RNA folding.

Modeling these interactions accurately in molecular dynamics (MD) simulations comes with two major challenges: traditional force fields poorly describe these interactions, often requiring polarization effects to be included, and there are significant sampling challenges due to the extremely slow exchange (> µs) of ligands in the Mg^{2+} solvation sphere. These limitations make it difficult to properly characterize ion binding modes and sites from standard MD simulations, and limit our understanding of their impact on biomolecular structures and dynamics.

Here, we introduce an efficient and general enhanced sampling approach for studying divalent ion binding to biomolecules, demonstrated on the most challenging case of Mg^{2+} binding to phosphate-rich DNA. Our method leverages Hamiltonien Replica Exchange molecular dynamics (HREX), strategically scaling charge and van der Waals parameters across replicas to promote ion exchanges and explore different binding modes. Applied to a Dickerson’s DNA dodecamer with 11 Mg^{2+} ions, our approach achieves full convergence in just a few hundreds of nanoseconds, whereas standard MD shows no ion exchanges, even after microseconds. It is straightforward to implement and compatible with standard MD engines capable of running Hamiltonian Replica Exchange (HREX). This efficient sampling exposes serious limitations in standard force fields which tend to overestimate binding free energies and cause ion accumulation near DNA.

On-going work aims to combine this strategy with HREX-based (REST2) enhanced sampling for biomolecules, opening the way for accurate simulations of complex ion-related processes, such as RNA folding with Mg^{2+}.

Key Words: Enhanced Sampling method, Magnesium-Phosphate interactions, Hamiltonian Replica Exchange, Biomolecules