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High-performance molecular dynamics at constant pH and constant redox potential using AMBER

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Abstract: Protein function is intrinsically related to structure and dynamic. Solution pH often has a dramatic impact on protein systems, since pH can affect the charge distribution within these biomolecules.[1] Understanding how pH-dependent conformation changes take place is key to the development of drugs targeting pH sensors, to the success of computational drug discovery strategies, and so forth.[2] Hence, accurate computational models designed to treat such systems must somehow account for pH effects. While the traditional approach of assigning a fixed protonation state for each titratable residue at the beginning of the simulation is still the most common approach, numerous methods have been developed in an attempt to treat pH effects in biomolecules more quantitatively.[1] For this purpose, Swails et al.[1] presented a new method of performing Constant pH Molecular Dynamic simulations in explicit solvent using discrete protonation states, which predicted pK_a values agreed well with experiment.

On the other hand, redox reactions, like protonation reactions, represent the simplest chemistry, involving only transfer of electrons. The source of the pH dependence of protein stability is the changing ionization state of protein residues. Redox reactions are usually coupled to some redistribution of protons within the protein, as the charge change at the redox center modifies the pK_as of the surrounding residues. In the same way, modifications of protonation states with pH influence redox site midpoint redox potential (E^0).[3]

A group of versatile and important proteins incorporate hemes as cofactors (heme-proteins). The *in situ* heme E^0 determines the role the protein will play. Many of the methods that analyze heme E^0 in proteins are conceptually similar to those that calculate residue pK_as in proteins, analyzing how the protein shifts the proton affinity of a site. However, proteins are found to shift heme E^0 over a much larger range than amino acid pK_as.[4]

Thus, the aim of this study was to extend replica exchange molecular dynamics for constant pH and electrochemical potential calculations. The implementation was done on AMBER Computational Package and have been tested and validated with some model systems (Figure 1), including the microperoxidase-8 peptide (Bis-His-NAcMP8), an 8-residue peptide with one heme c as cofactor. By making use of CUDA implementation, we obtain a high-performance code that can be used in simulations of large systems. We also show how our results are in agreement with theoretical/experimental expectations, and how computational benchmarks show the high-performance of calculations using GPU in comparison with serial or MPI calculations for large systems.

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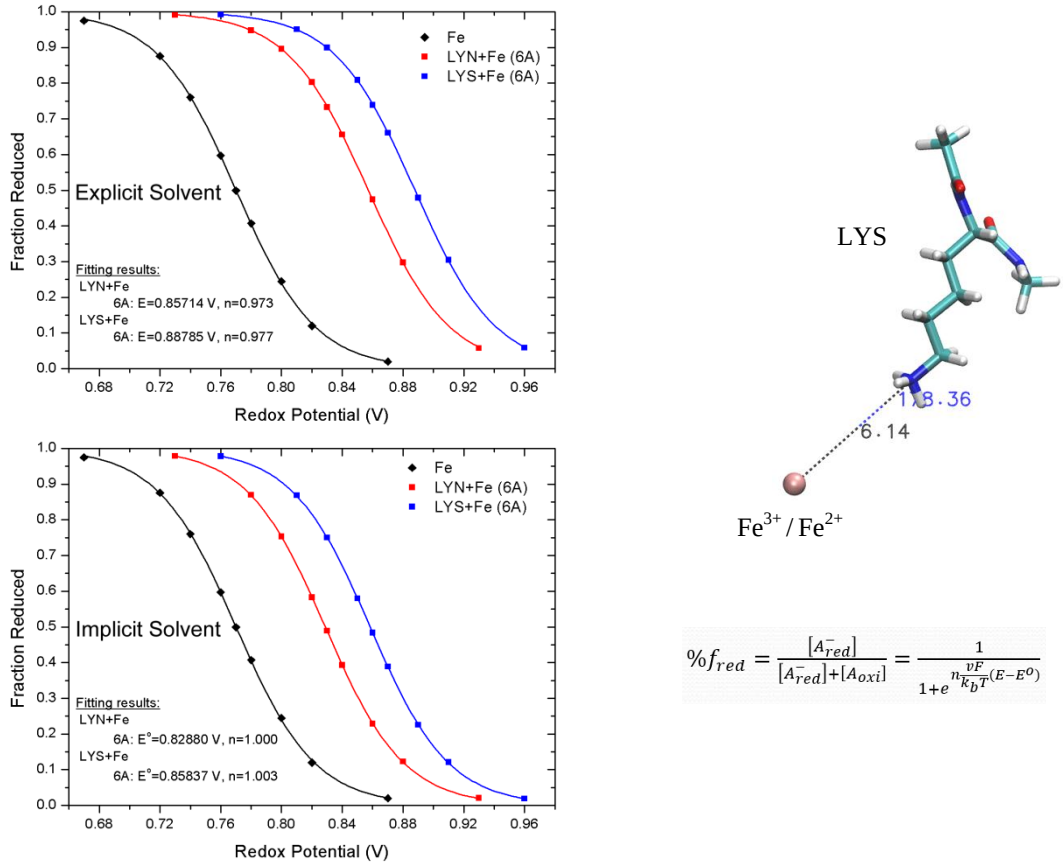

Figure 1. Computational results and graphical representation for an iron ion in the presence of lysine peptide. The figure shows the fraction of reduced species ($\%f_{red}$) as a function of the redox potential by using explicit and implicit solvent representations, with the respective fittings by equation for $\%f_{red}$. Results in blue are for when the peptide is protonated (LYS), and results in red are for the deprotonated peptide (LYN).

Key-words: Molecular Dynamic; cytochrome; CEMD; REMD; CpHMD
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