Coarse grained Constant-pH protein dynamics

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***Short Abstract* — Protein's environment is critical to define its structure and function. One critical variable is pH and some constant pH molecular dynamics methods already exist. In our work we want to systematically study long timescale events. To achieve this we implemented and tested a constant pH module to the existing coarse grained potential AWSEM. We obtain the parameters of our model, calculate native state pKa shifts of proteins and study changes in stability as a function of pH. Our results show a promising tool to study global behaviour of proteins coupling dynamics and pH.**

***Keywords* — Constant-ph, Dynamics, Coarse-grained, AWSEM, LAMMPS**

Based on the energy landscape theory [1], protein structure fluctuates among minimal frustrated conformations. The dynamics between these conformers and the relative stability depend on the protein sequence and the surrounding media. Just like temperature, pH is a key macroscopic variable that living systems regulate and take advantage from. Some of the protein residues are titratable making these macromolecules coupled to pH.

To study the coupling between the energy landscape and pH, several constant pH molecular dynamic methods have been implemented in recent years [4-8]. However these tools aren't well suited to systematically study long timescale events because of the restrictive computer time required. To tackle this problem we implemented and tested a constant-pH module in the transferable potential AWSEM [2] which has been previously used to predict many unknown protein structures and to describe protein's energy landscapes. It is inside LAMMPS [9], a molecular dynamics suite written in C++, which gives many advantages at the hour of developing new features.

Our main goal is to couple long scale conformational changes in proteins with pH and use this as a tool to explore pH stability, dynamics and protein-protein interactions.

The existing AWSEM code has an electrostatic module which enables the use of Debye Huckel screened interaction [3]. We added to this a Monte Carlo discrete charge sampling algorithm to account for pH behaviour. We modelled each residue behaviour with local and long range contributions to the free energy [11].

To refine our method we optimized our parameters with an analytical version of the model exploring different approximations and approaches to test its limits. We compared our method with an already existent Go-model [10] and classical MD constant-pH and with experimentally determined pKa. We found that this method improves the Go-model constant-pH pKa prediction and, in the worst of the cases, the difference between experimental and predicted value is around 1.5 pH units.

This method would aid in the study of the coupling between protein thermodynamics, kinetics and pH.

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