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Folding of β-Structures via the Polarized Structure-Specific Backbone Charge (PSBC) Model

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Abstract : Proteins are the biological machinery that executes specific vital functions in every cell of the human body by folding into their 3D structures. When a protein misfolds from its native structure, the machinery will malfunction and lead to misfolding diseases. Although in vitro experiments are able to conclude that the mutations of the amino acid sequence lead to incorrectly folded protein structures, these experiments are unable to decipher the folding process. Therefore, molecular dynamic (MD) simulations are employed to simulate the folding process so that our improved understanding of the folding process will enable us to contemplate better treatments for misfolding diseases. MD simulations make use of force fields to simulate the folding process of peptides. Secondary structures are formed via the hydrogen bonds formed between the backbone atoms (C, O, N, H). It is important that the hydrogen bond energy computed during the MD simulation is accurate in order to direct the folding process to the native structure. Since the atoms involved in a hydrogen bond possess very dissimilar electronegativities, the more electronegative atom will attract greater electron density from the less electronegative atom towards itself. This is known as the polarization effect. Since the polarization effect changes the electron density of the two atoms in close proximity, the atomic charges of the two atoms should also vary based on the strength of the polarization effect. However, the fixed atomic charge scheme in force fields does not account for the polarization effect. In this study, we introduce the polarized structure-specific backbone charge (PSBC) model. The PSBC model accounts for the polarization effect in MD simulation by updating the atomic charges of the backbone hydrogen bond atoms according to equations derived between the amount of charge transferred to the atom and the length of the hydrogen bond, which are calculated from quantum-mechanical calculations. Compared to other polarizable models, the PSBC model does not require quantum-mechanical calculations of the peptide simulated at every time-step of the simulation and maintains the dynamic update of atomic charges, thereby reducing the computational cost and time while accounting for the polarization effect dynamically at the same time. The PSBC model is applied to two different β-peptides, namely the Beta3s/GS peptide, a de novo designed three-stranded β-sheet whose structure is folded in vitro and studied by NMR, and the trpzip peptides, a double-stranded β-sheet where a correlation is found between the type of amino acids that constitute the β-turn and the β-propensity.

Keywords : hydrogen bond, polarization effect, protein folding, PSBC
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