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Examining Electrostatic Influences on Base-Flipping: A Comparison of TIP3P and GB Solvent Models

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Abstract. Recently, it was demonstrated that implicit solvent models were capable of generating stable B-form DNA structures. Specifically, generalized Born (GB) implicit solvent models have improved regarding the solvation of conformational sampling of DNA [1, 2]. Here, we examine the performance of the GBSW and GBMV models in CHARMM for characterizing base flipping free energy profiles of undamaged and damaged DNA bases. Umbrella sampling of the base flipping process was performed for the bases cytosine, uracil and xanthine. The umbrella sampling simulations were carried-out with both explicit (TIP3P) and implicit (GB) solvent in order to establish the impact of the solvent model on base flipping. Overall, base flipping potential of mean force (PMF) profiles generated with GB solvent resulted in a greater free energy difference of flipping than profiles generated with TIP3P. One of the significant differences between implicit and explicit solvent models is the approximation of solute-solvent interactions in implicit solvent models. We calculated electrostatic interaction energies between explicit water molecules and the base targeted for flipping. These interaction energies were calculated over the base flipping reaction coordinate to illustrate the stabilizing effect of the explicit water molecules on the flipped-out state. It is known that nucleic base pair hydrogen bonds also influenced the free energy of flipping since these favorable interactions must be broken in order for a base to flip-out of the helix. The Watson-Crick base pair hydrogen bond fractions were calculated over the umbrella sampling simulation windows in order to determine the effect of base pair interactions on the base flipping free energy. It is shown that interaction energies between the flipping base and explicit water molecules are responsible for the lower base flipping free energy difference in the explicit solvent PMF profiles.

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Key words: TIP3P, generalized Born, flipping, implicit solvation, potential of mean force, DNA, DNA damage.

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1 Introduction

Base flipping is the process of a DNA base moving out of the base stack, breaking the Watson-Crick (WC) base pair hydrogen bonds, and being completely exposed in the solvent medium. The process is known to be energetically unfavorable since base pair interactions are stronger than base interactions with solvent [3,4]. However, base flipping has been shown to occur spontaneously [5], and in some cases enzymes utilize base flipping for catalysis [6]. For example, uracil DNA glycosylase enzymes target the exposed base, and stabilize the flipped-out state for the purpose of base excision repair [7,8].

Several studies have investigated the effects of the base flipping conformational transition on enzyme function [5,7,9]. Experimental and theoretical methods have both been used to study the base flipping conformational change. The imino proton exchange with solvent during the base flipping can be measured with NMR, and is a common technique for evaluating the transition experimentally [7]. These experiments yield base opening rates as well as the equilibrium constant ($K_{flip} = k_{op}/k_{clsd}$) between flipped-in and flipped-out state. Umbrella sampling [10,11] is a computational method that is commonly used to examine base flipping free energy differences. The method is used to construct a potential of mean force (PMF) with respect to a progress variable of some known path or reaction coordinate [10,11]. An umbrella biasing potential is applied to sample across the chosen reaction coordinate, from one end-point to the other. The reaction coordinate for the path between the flipped-out and flipped-in states has been the focus of several studies [12–14].

When molecular dynamics is used to describe conformational changes of proteins or nucleic acids, a suitable force field is critical [15,16]. Priyakumar *et al.* [17] tested the performance of three force fields (CHARMM27 [18], AMBER4.1 [19], and BMS [20]) for the construction of DNA base flipping PMF profiles. Profiles for the GC base pair were generated with umbrella sampling, using a center of mass (COM) pseudodihedral angle [12] as the reaction coordinate. The duplex dodecamer sequence $d(GTCAGCGCATGG)_2$ was used for the base flipping. Along with the umbrella sampling, the WC base pair interaction energies were calculated. The interaction energy calculated with CHARMM was 21.9 kcal/mol, which is similar to the literature value [21] for the GC base pair interaction energy. However, the AMBER (26.3 kcal/mol) and BMS (26.2 kcal/mol) force fields overestimated the experimental value for the GC base pair interaction energy [21]. Equilibrium constants for base flipping measured with NMR proton exchange [22] were compared with the free energy difference results from the force fields. The results indicated that free energies generated with CHARMM and AMBER were more similar to experimental values than those generated with BMS [17].

Along with finding an optimal force field, another challenge when modeling DNA conformational changes has been accurately representing the solvent environment, while also maintaining computational efficiency. The conformational equilibria of nucleic acids in particular are strongly influenced by the solvent environment [16,23], thus highlighting the importance of accurately modeling the solvent during free energy calculations.