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# Protein's native structure is dynamically stabilized by electronic polarization

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In this paper, molecular dynamics (MD) simulations were performed for a number of benchmark proteins using both the standard assisted model building with energy refinement (AMBER) charge and the dynamically adjusted polarized protein-specific charge (DPPC) from quantum fragment calculations to provide accurate electrostatic interactions. Our result shows that proteins' dynamic structures drifted away from the native structures in simulations under standard (nonpolarizable) AMBER force field. For comparison, proteins' native structures were dynamically stable after a long time simulation under DPPC. The free energy landscape reveals that the native structure is the lowest energy conformation under DPPC, while it is not under standard AMBER charge. To further investigate the polarization effect on the stability of native structures of proteins, we restarted from some decoy structures generated from simulations using standard AMBER charges and then carried out further MD simulation using DPPC to refine those structures. Our study shows that the native structures from these decoy structures can be mostly recovered using DPPC and that the dynamic structures with the highest population in cluster analysis are in close agreement with the corresponding native structures. The current study demonstrates the importance of electronic polarization of protein in stabilizing the native structure.

*Keywords*: Polarization; polarized protein-specific charge (DPPC); force field; decoy structure; native structure; stabilization.



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## 1. Introduction

Hydrogen bonds (H-bonds) are important to the specificity of intramolecular and intermolecular interactions in protein and protein–ligand complex. The vast majority of H-bonds in proteins formed between the backbone amide NH group (as a donor) and the backbone carbonyl CO group (as an acceptor) play a critical role in determining the structures of proteins.[1,2] The precise role of H-bonds in protein folding, protein stability, and protein recognition[3–5] has been studied for decades and continues to be a focus of many recent studies. Hence accurate description of H-bond interactions is critical to protein structure prediction, protein–protein docking, and protein design and protein–ligand interactions. H-bonds are dominated by electrostatic interaction and polarization is important in determining the interaction energy of H-bonds. Previous study found that electronic polarization is often critical to the stability of H-bonds and secondary structures including $\alpha$-helix and $\beta$-sheet.[6–9]

Simulation of biomolecules using the standard force fields such as AMBER,[10] CHARMM,[11] OPLS,[12,13] etc. has led to many useful insights into the structural and dynamical properties of biomolecules. The description of electrostatic interaction that employs a system of fixed point charges interacting via Coulomb's law is reasonable at a certain extent and has been widely applied to many biological systems. Some recent studies demonstrated the need to include polarization in accurate description of hydrogen bonds.[14] Limitations in the force field could drive the system away from its native state in MD simulation. The inclusion of polarization in the force field should largely improve the accuracy of MD simulation result, and many researchers have been working intensively to develop polarizable or polarized force fields. Since the application is much more complicated than that of the conventional force field, it is still a challenge to develop a simple and practical polarizable force field for more accurate descriptions of H-bond in MD simulations.

A polarized protein-specific charge (PPC)[15] has recently been developed based on a linear scaling quantum method termed molecular fractionation with conjugate caps (MFCC).[16–21] PPC is protein-specific which distinguishes it from amino acid-specific charge typically used in existing force fields such as standard AMBER. This feature of PPC implies that it is capable of giving more accurate description of electrostatic interactions for proteins. Some recent work that includes polarization has demonstrated the advantage of PPC over standard AMBER charge.[6,7,15,22–28] However, application of PPC is usually limited to cases in which the native structure is available and protein does not deviate far away from the native structure. When protein undergoes large conformation changes, applying a fixed PPC calculated from a pre-fixed structure is not ideal. In order to make it applicable for vast majority of molecules, the dynamically adjusted polarized protein-specific charge (DPPC) scheme is proposed in which PPC is periodically updated in MD simulation to properly account for the impact to the charge from the dynamic fluctuation of protein structure.

Recently, Wroblewska *et al.* evaluated the energies of many decoy structures for 150 proteins using standard AMBER plus (Generalized Born) GB potential and found none of the native structures had the lowest energy among decoys.[29] When PPC is employed to evaluate energy, the native energy is found to be the lowest in nearly all of the refined "50-set" proteins.[22] This means that PPC can pick native-like structures from decoy ensemble and the native structure may be driven away from the native conformation to some of these decoy states due to their lower energies in MD simulation using standard AMBER. The MD simulation performed using AMBER and DPPC for six proteins 1a19A, 1bb9, 1c1yB, 1c4zD, 1cskA, 1ctf have obvious differences in the average energy gap between the native and the lowest-energy decoy structures.[22]

In the present work, we carried out MD simulations utilizing both standard AMBER force field and DPPC and investigated the protein structures, especially the hydrogen bonds. We also carried out MD simulations utilizing DPPC to refine the partially distorted protein structures from the simulations utilizing standard AMBER force field. The result is consistent and it shows that DPPC can stabilize the native structure of protein.

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## 2. Theoretical Methods

The initial structures of six proteins are taken from the protein date bank (PDB: 1a19A, 1bb9, 1c1yB, 1c4zD, 1cskA, 1ctf) and H-bonds are added to their proper positions using leap module in AMBER10.[30] All MD simulations are performed using the AMBER10 package with AMBER99 force field and DPPC, respectively, at room temperature. The solvent is treated as a continuous dielectric medium approximated by the GB model, denoted as IGB1[31] in AMBER package. The initial structure is first optimized with steepest descent minimization method for 1000 steps followed by conjugate gradient method until convergence. Then the system is heated up to 300 K in 300 ps. Finally MD simulation is performed to further relax the system for 5 ns due to large expense of CPU time for QM calculation using DPPC. But the simulation has reached equilibrium. The dielectric constants of the protein interior and of the solvent are set to, respectively, 1.0 and 78.5. The nonpolar contribution to solvation free energy is given by a surface area term employing the LCPO model.[32] The interior and solvent dielectric constants are set to, respectively, 1.0 and 78.5. The Langevin dynamics with a collision frequency of 1.0 $ps^{-1}$ is used to regulate the temperature. Nonbond interactions are all counted without any cutoff. SHAKE[33] algorithm is used to constrain all the bonds involving hydrogen atoms. The calculation is performed in NPT ensemble with 2 fs time step. Snapshots of the MD trajectories are collected every 1 ps for analysis.

The details in computing PPC in MD simulation can be found elsewhere.[6,15] Atomic charges are initially taken from AMBER force field, but are periodically updated. DPPC is derived from quantum mechanical calculation for a protein solution in which the atomic charges of all residues are fitted at regular intervals.

In principle, updating charges of all atoms at every MD step is indispensable but is very demanding. Because such frequent updating needs great computational costs. To balance the computational efficiency and accuracy, PPC is updated every 100 ps.

## 3. Results and Discussion

### 3.1. *RMSD analysis*

Since standard partial atomic charges of proteins[34] are mean field like and do not include polarization, a long time MD simulation could drive the protein away from its native structure. Thus MD simulation provides an opportunity for direct comparisons of dynamical stabilities between standard AMBER and DPPC. In this work, MD simulation is carried out for six proteins employing separately standard AMBER and DPPC. The RMSD of the backbone atoms of the simulated protein structure from that of the native structure, which is useful in discriminating the native structure from decoys, is depicted in Figs. 1(a)–1(f) for six proteins. As shown in the figures, the use of standard atomic charge drove these proteins away from their native states, with the RMSD ranging from 2.9 Å to 4.8 Å. For comparison, the use of DPPC is shown to give more dynamically stable structures with RMSD in the range of 1.0 Å to 2.2 Å. In all the cases, the backbone atoms under DPPC are more stable and remain close to the native structures.

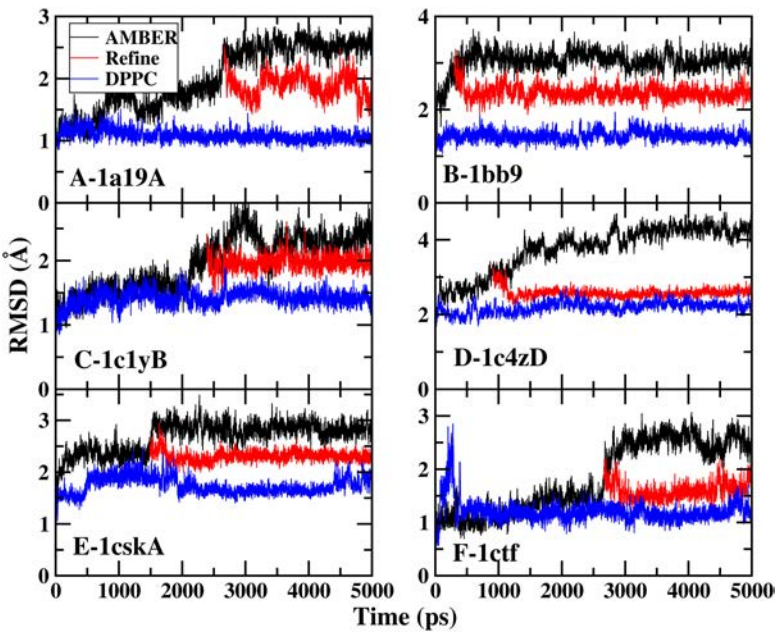


Fig. 1. RMSD of backbone atoms of six proteins as a function of MD simulation time using standard AMBER and DPPC starting from the native state, and from DPPC starting from intermediate (decoy) structures from AMBER simulations.



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Next we try to refine decoy structures by performing MD simulations using DPPC to see if they can be optimized toward the native structures. These decoy structures were generated from simulations using standard AMBER charge and they have RMSD (from the native structure) values ranging from 2.1 Å to 3.4 Å. These refined structures from the decoy structures are compared to the corresponding native structures to evaluate the capability of the DPPC refinement. As shown in Fig. 1, the RMSDs of these DPPC refined structures undergo precipitous drops first and then stabilize with RMSD values generally around 2.0 Å. The RMSD of these refined structures are closer to the native structures than that from the AMBER simulations. The RMSDs of refined structures are improved by up to 0.9 Å from those of the decoy structures from which the refinement started. The result demonstrates that DPPC can help refine the protein decoy structures and make them closer to the native structures. This result demonstrates the important effect of electronic polarization in the stability of protein's dynamical structure.

### 3.2. *H-bond analysis*

When the polarized charge is employed, the H-bonds should be more stable during MD simulation. We performed statistical analysis of backbone H-bonds to examine the percentage occupancy of them from MD simulation. The percent occupancy is calculated in the same way as in Ref. 7. The fractions of these H-bonds versus their occupancy are plotted using a histogram. Figures 2(a)–2(f)

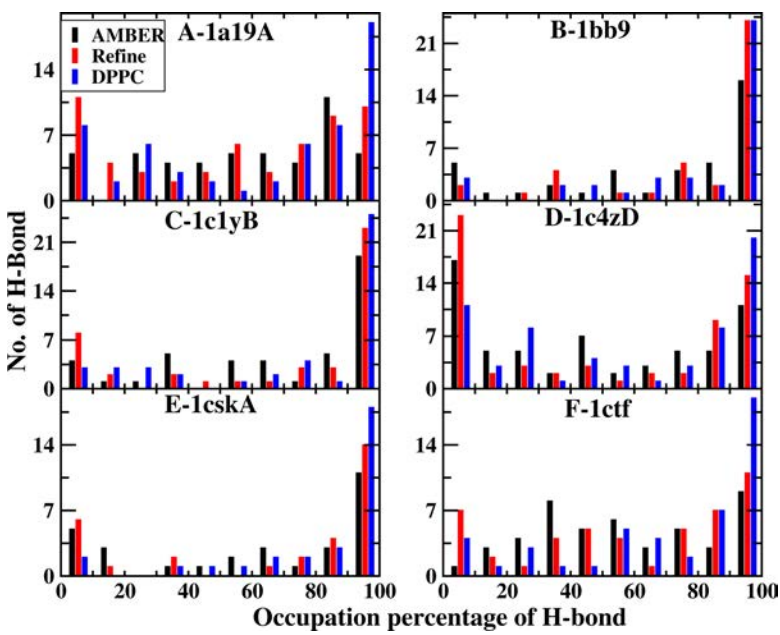


Fig. 2. The occupancy of the backbone H-bonds in MD simulations using AMBER, DPPC and refinement simulations for the six proteins, respectively.

shows the comparison of H-bonds percentage occupation during MD simulation between AMBER and DPPC for the six systems. The distribution of high occupancy H-bonds are higher with DPPC charge than with standard AMBER charge, in good agreement with an early study.[7] Next, we examine the efficacy of refinement with using DPPC. As shown in Fig. 2, the high occupancy H-bonds increases in the refined structures. This indicates that some broken H-bonds are quickly rebuilt and thus the secondary structure could be recovered with DPPC. Although the refined H-bonds have equal or lower populations compared to those directly obtained from DPPC simulation starting from the native structure, they are far more than that obtained from simulations using standard AMBER charge. The result demonstrates that DPPC is more accurate in stabilizing the H-bonds, and it can also restore some decoy structures toward nature structures. The H-bonds are more stable using DPPC and the stable H-bonds help maintain the protein nature structure better.[35]

Next, we further analyze the variety of average charges for NH and CO group forming H-bonds in DPPC simulation for 1c4zD protein. For comparison, the corresponding charges from AMBER are also shown in Fig. 3. The structure has 62 backbone H-bonds, in which the average charges of N, H, C and O are −0.42, 0.28, 0.61 and −0.57 respectively in AMBER. It is illustrated in Fig. 3 that absolute values of DPPC charges of C, H and O atoms are larger (by about 0.04) than the corresponding AMBER charges and the DPPC charge of N atom fluctuates around −0.42. The polarized charges enhance the Coulomb interaction, so the H-bonds become stronger which is properly described by DPPC charges.

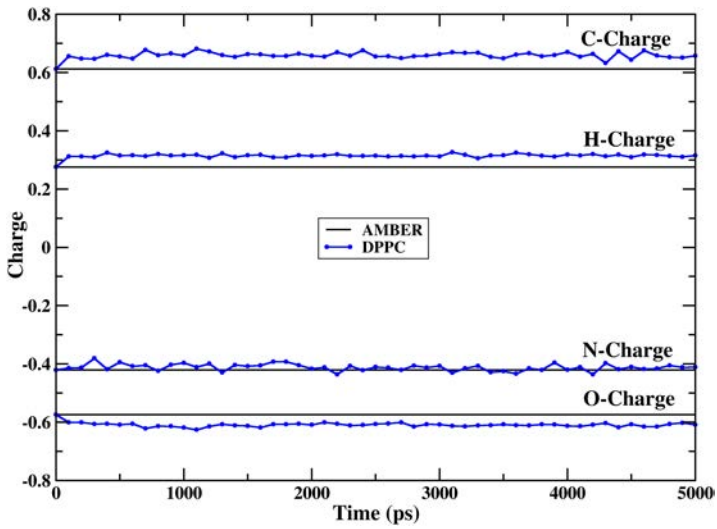


Fig. 3. The average charges of NH and CO group forming H-bonds as a function of MD simulation time using AMBER and DPPC for 1c4zD protein.



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### 3.3. *Cluster analysis*

The trajectories are analyzed by K-means clustering[36] and the representative structures of the most populated clusters are shown in Fig. 4. The most populated conformation is the one closest to the experimental structure with the backbone RMSD in a range between 0.9 Å and 2.2 Å and the population between 25.2% and 51.7% for six proteins under DPPC. Thus the native conformation is the most favorable. While under standard AMBER charge, the most populated cluster is only partially folded, with a high backbone RMSD of 2.6, 3.0, 2.3, 4.3, 2.8 and 2.4 Å respectively. After refining the structure using DPPC, the backbone RMSDs in the most populated cluster drop to 1.7, 2.4, 1.9, 2.5, 2.3 and 1.7 Å. Since secondary structures are stabilized by H-bonds between backbone carbonyl oxygen atom and the amide hydrogen atom, the breaking of backbone H-bonds can lead to large conformational change in protein structure and thus could drive the protein away from its native state in MD simulation. The higher overall stability of H-bonds under DPPC should better preserve or help restore stability of secondary structures.

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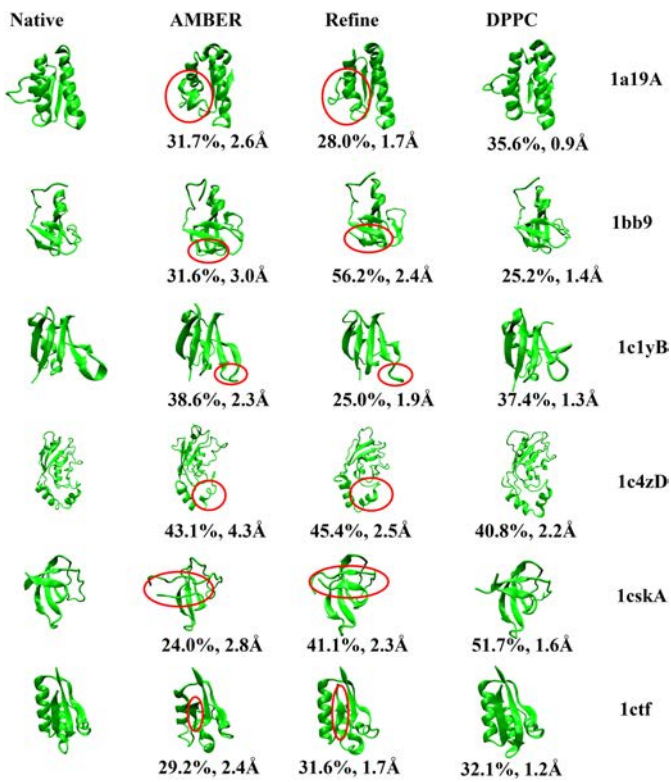


Fig. 4. Representative structures of six proteins selected from the most populated cluster using AMBER, DPPC and refinement simulation, respectively. The population of clusters and the backbone RMSD of the cluster centers is indicated. The different structure between AMBER and refinement simulation is shown in red circle.

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The partially denatured or disappeared structures obtained from the most populated cluster are given in Fig. 4. Clear differences are observed that those proteins are disordered under standard AMBER charge while match well with those native structures using DPPC. For 1a19A under AMBER charge, one helix is only partially formed and its position deviated from that in the native structure. After refinement, the position of helix is corrected and the broken helix is reformed. For 1bb9 under AMBER charge, one $\beta$-sheet is destroyed and the structure of the loop region is far away from the native one. After DPPC refinement, the destroyed $\beta$-sheet is completely restored and the overall topology is in excellent agreement with the native structure. However, the broken turn region in 1c1yB is not repaired under DPPC, but the refined tertiary structure is still closer to the native state than that of decoy structure. For 1c4zD, the broken secondary structure and the overall topology are rebuilt by DPPC with an RMSD drop from 4.3 Å to 2.5 Å. For 1cskA, the $\beta$-sheet is completely unfolded in AMBER simulation, while the recovered $\beta$-sheet is found in refined structure. For 1ctf, again, the partially denatured helix is recovered in the refined structure. These results indicate that the DPPC simulation can be applied to restore the deformed structure of the protein.

### 3.4. *Free energy landscape analysis*

In order to obtain a more detailed view of the protein simulation picture, the two-dimensional free energy landscapes using the RMSD and radius of gyration (Rg) of backbone as the reaction coordinates are constructed in Fig. 5. Rgs of the native structures are 11.7, 11.7, 11.4, 15.4, 9.7 and 10.5 Å respectively for the six proteins. The free energy landscapes are determined by calculating the normalized probability from weighted histogram analysis method (WHAM)[37–39] from state density. The relative free energy can then be easily expressed as $G(X2)-G(X1) = -RT\ln[P(X2)/P(X1)]$.[40] The free energy landscapes under AMBER charge and DPPC are dramatically different. In AMBER, the conformation with the lowest free energy or the pseudo-native structure is located around (RMSD = 2.5 Å, Rg = 11.7 Å), (RMSD = 3.0 Å, Rg = 11.8 Å), (RMSD = 2.3 Å, Rg = 11.4 Å), (RMSD = 4.3 Å, Rg = 15.5 Å), (RMSD = 2.9 Å, Rg = 10.0 Å) and (RMSD = 2.4 Å, Rg = 10.4 Å) for the six proteins respectively, which are far away from the native structures. In contrast, in DPPC simulation, the native state is correctly located in its local minimum (RMSD = 1.1 Å, Rg = 11.8 Å), (RMSD = 1.4 Å, Rg = 12.0 Å), (RMSD = 1.4 Å, Rg = 11.3 Å), (RMSD = 2.3 Å, Rg = 15.5 Å), (RMSD = 1.6 Å, Rg = 9.8 Å) and (RMSD = 1.1 Å, Rg = 10.5 Å). Only 1bb9 has a slightly higher Rg than that of the native state. In comparison, the refined structures also give good results. The local minima are (RMSD = 1.8 Å, Rg = 11.8 Å), (RMSD = 2.3 Å, Rg = 11.8 Å), (RMSD = 2.0 Å, Rg = 11.5 Å), (RMSD = 2.5 Å, Rg = 15.7 Å), (RMSD = 2.2 Å, Rg = 9.7 Å) and (RMSD = 1.4 Å, Rg = 10.5 Å), which are closer to their corresponding native states than that of the decoy structures.

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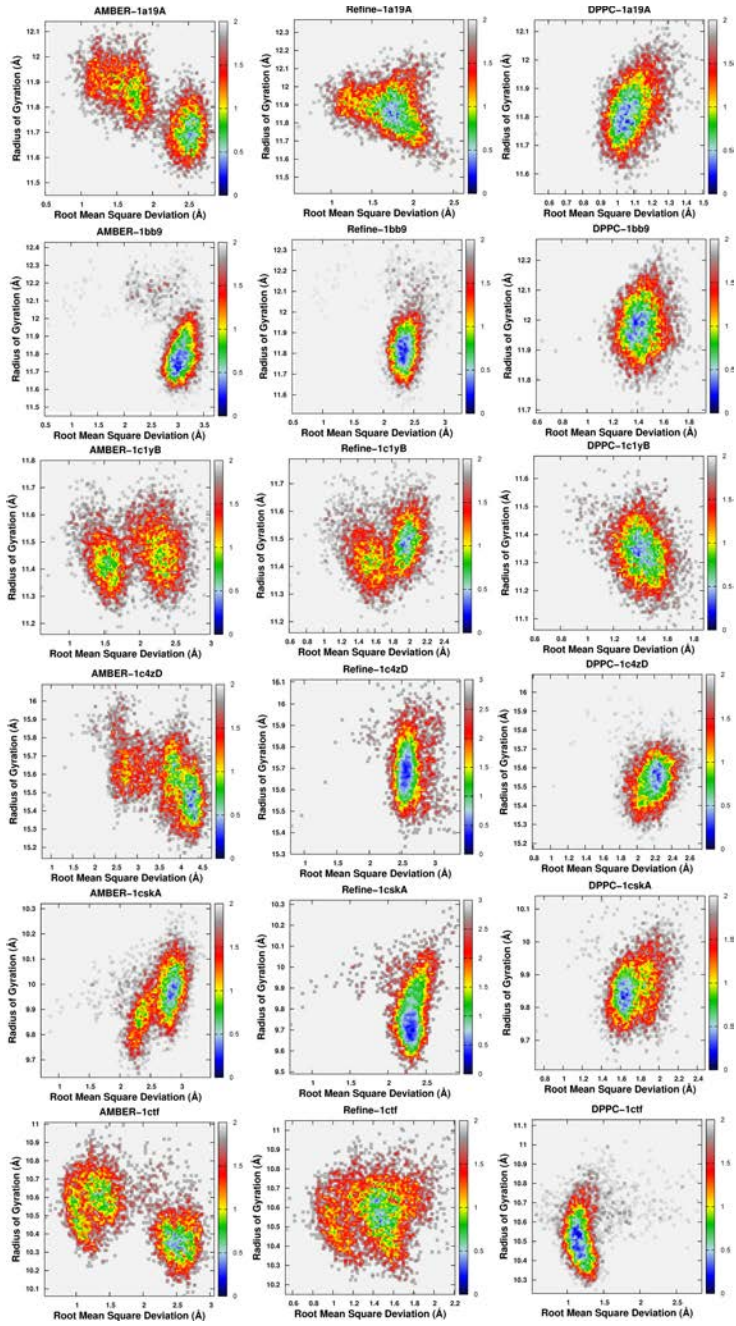


Fig. 5. Free energy landscape as a function of RMSD and radius of gyration from standard AMBER, DPPC and refinement simulation for the six proteins, respectively.

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## 4. Conclusion

Although mean-field like force fields have enjoyed great success in modeling many of the dynamical properties of proteins, they lack the polarization effect which plays a significant role in protein's dynamical structures. In this paper, we employed the recently developed MFCC approach coupled with an implicit solvent model to generate PPCs and update the charge at regular intervals in MD simulation. This new charge model, which is termed DPPC, is protein-specific and can correctly delineate the polarized electrostatic state of the protein. Detailed analysis and comparison of these MD results show that DPPC gives MD results that are in better agreement with experiment than standard AMBER charge, both in terms of structures and dynamics. Specifically, H-bonds and secondary structure are better preserved using DPPC than standard AMBER charge. More importantly, DPPC can correct the biased/deformed structure of the protein. While with AMBER charge broken backbone hydrogen bonds result in some secondary structure deformation or elimination, thereby drive protein away from its native state in MD simulation. These partially unfolded structures could somehow be recovered to certain extent by DPPC simulation. The current study provides strong evidence that electronic polarization of protein plays an important role in protein's dynamical structures.

It should be mentioned that there is a new version of polarizable force field (induced dipole method) in AMBER12 package. To examine the effect of using different polarizable models, further MD simulation for protein 1bb9 is performed using AMBER02 and AMBER12 polarizable force fields with the POL3 water model. The RMSD from three sets of MD simulations using DPPC, AMBER02 and AMBER12, respectively, are shown in Fig. 6. The result in Fig. 6 shows that the

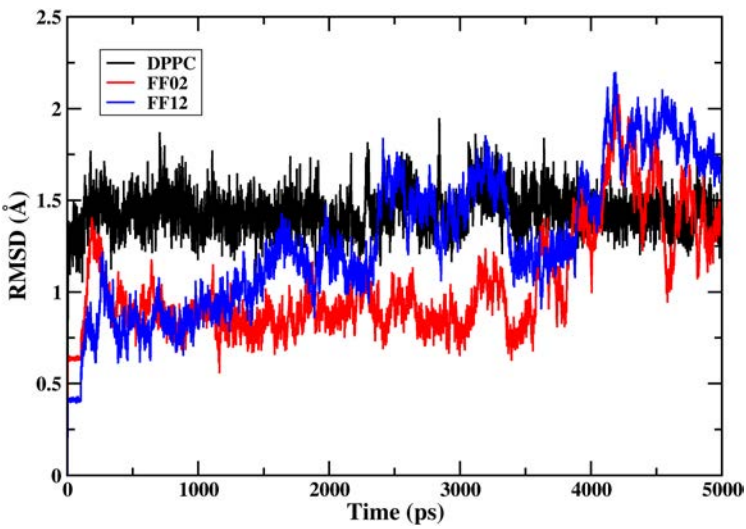


Fig. 6. RMSD of backbone atoms of 1bb9 proteins as a function of MD simulation time using DPPC, AMBER02, AMBER12 polarizable force field respectively.

simulation using DPPC gives more stable structures than the other two polarizable force fields.

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