Supporting Information Available

Energy conservation in MD

To examine the conservation of the energy and force stability, we carried out ∼3.5 ns of constant energy MD simulations using the protein HP36 (which has 36 residues) at 300K starting from the equilibrated NMR structure. The time step was 0.5 fs and SHAKE constraints were removed. Mixed precision GPU version (pmemd.cuda_SPFP) of Amber 20 and our program were used for GB and dSASA GB/SA simulations, respectively. For GB/SA simulations, surface tensions varied from 5, 10 and 20 cal/(mol· Å^2). The energy terms were

printed out every 100 steps. The total energy deviations from the respective starting point were recorded to evaluate the energy conservation and force stability of the GPU code with and without the SASA term. As shown in Figure 13 and Table 1, the inclusion of dSASA produces comparable energy drift and standard deviation (SD) in the total energy. We can conclude that inclusion of the nonpolar term does not result in additional significant force instability.
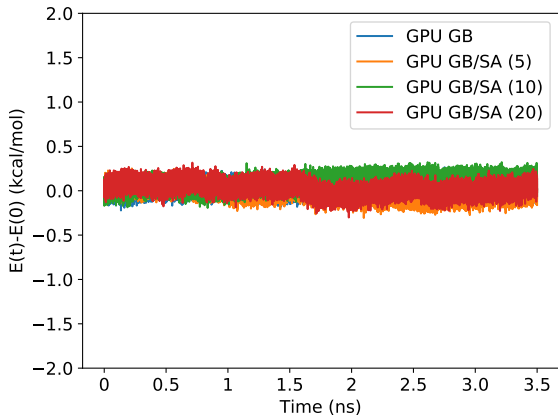

Figure 13: Energy deviation in constant energy simulations for HP36 from initial energy for GB and dSASA GB/SA with different surface tension parameters.

Table 1: The averages, the average deviations and standard deviations of the total energies in constant energy simulations for HP36 with GB and dSASA GB/SA.

Surface tension cal/(mol· $Å^2$)	Etot Mean (kcal/mol)	E(t)-E(0) Mean (kcal/mol)	SD (kcal/mol)
0	-397.46215	0.0404465	0.05769035
5	-380.55516	-0.0185640	0.07033996
10	-363.58555	-0.0903457	0.06883961
20	-329.35631	-0.0302929	0.07151965

Trajectories of proteins in REMD

In the main text, we showed the computed thermal stability profiles for Trp-cage and the fraction of folded for homeodomain from REMD, here we provide the detailed trajectories for Trp-cage Fig. 14, Fig. 15 and for homeodomain Fig. 16, Fig. 17 at various temperatures.
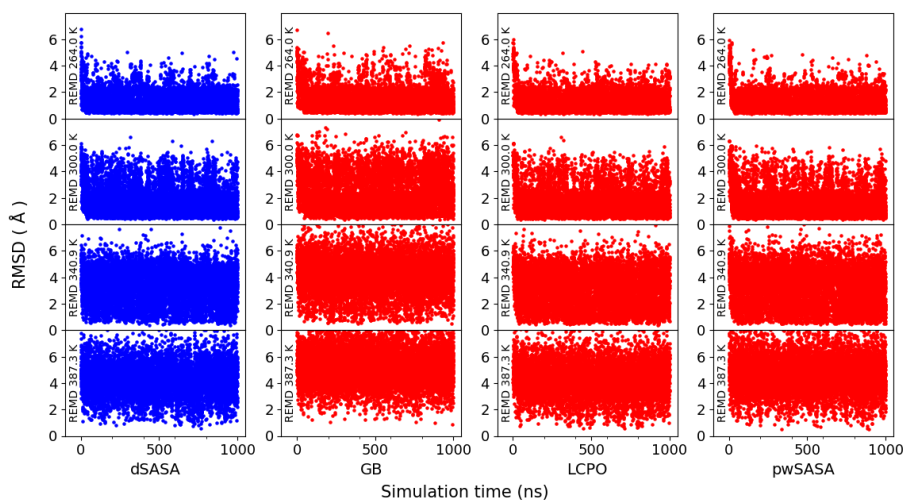

Figure 14: Trajectories at selected temperatures starting from extended state of Trp-cage with surface tension 5 cal/(mol· Å^2) in GB and GBSA simulations.
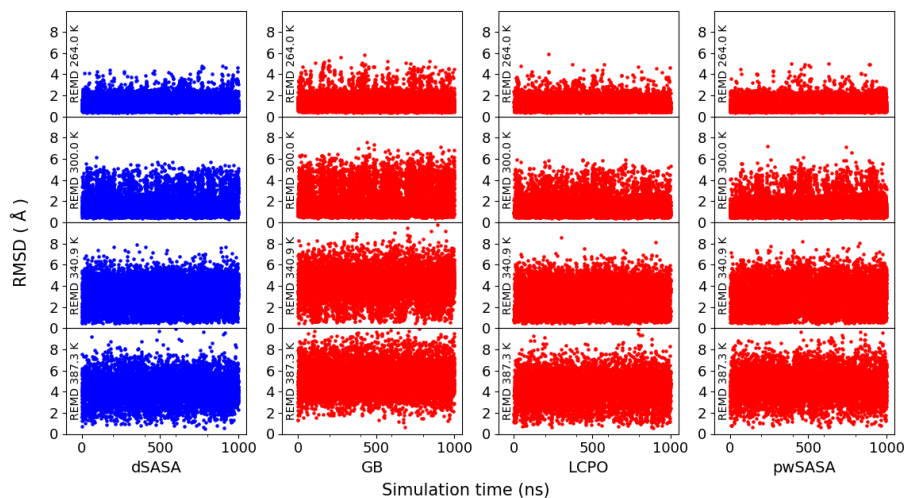
Fraction of folded for the second test of homeodomain

Figure 15: Trajectories at selected temperatures starting from native state of Trp-cage with surface tension 5 cal/(mol· Å²) in GB and GBSA simulations.
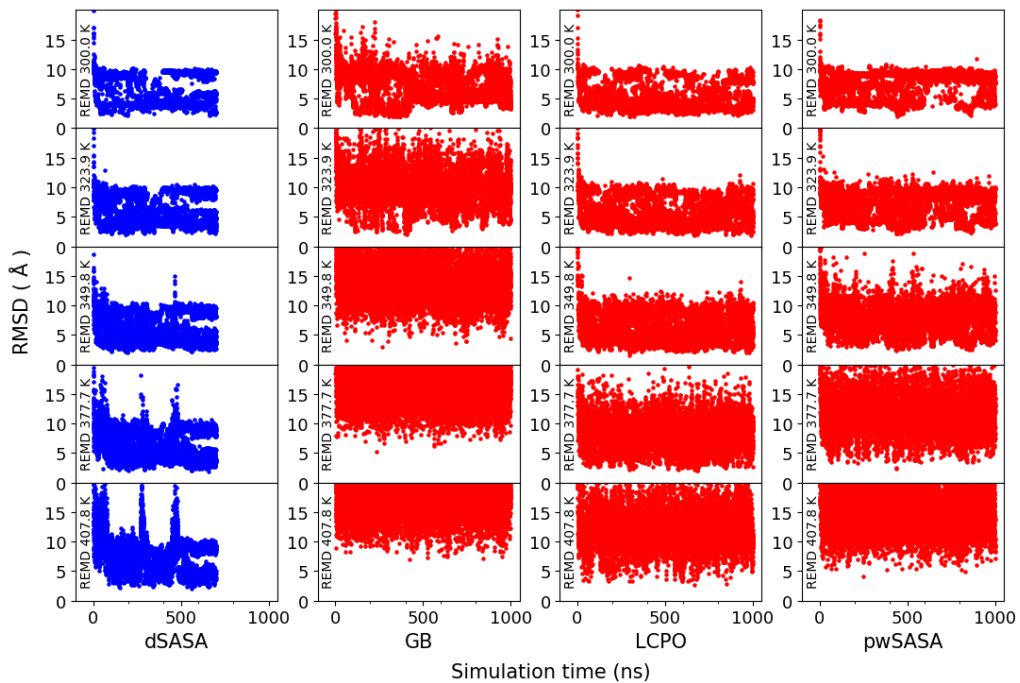

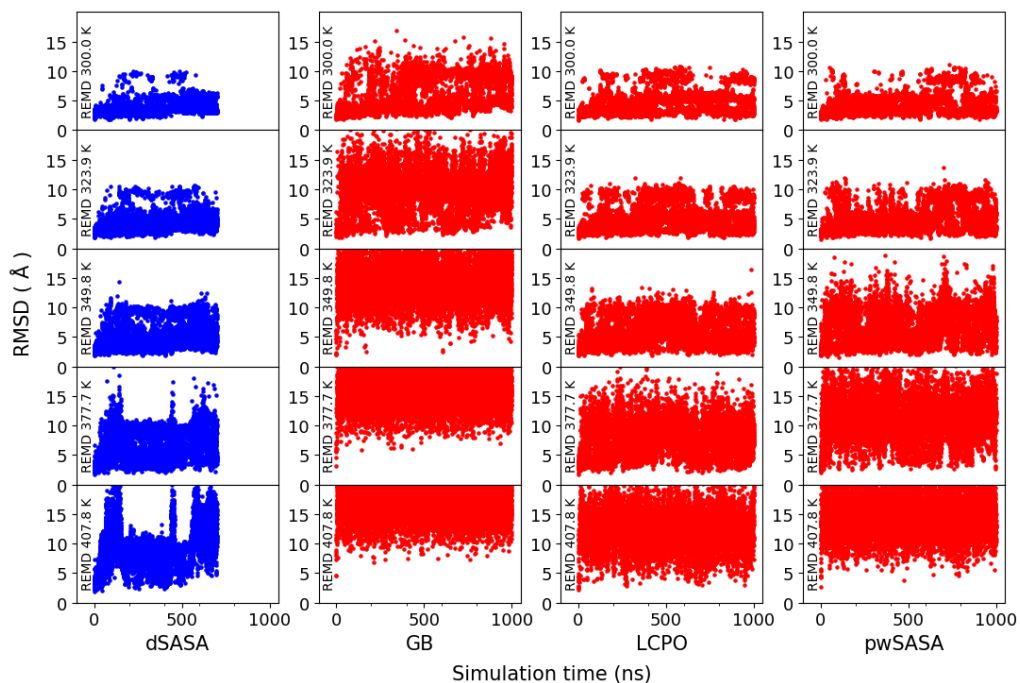Figure 16: Trajectories at selected temperatures starting from unfolded state of home-odomain with surface tension 7 cal/(mol· Å²) in GB and GBSA simulations.

Figure 17: Trajectories at selected temperatures starting from native state of homeodomain with surface tension 7 cal/(mol· Å²) in GB and GBSA simulations.
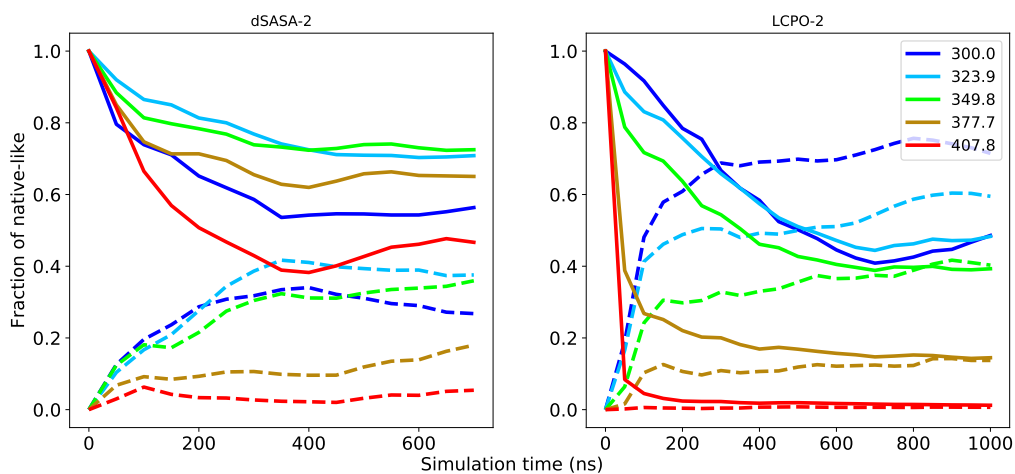

Figure 18: Fraction of native-like for homeodomain starting from native (solid lines) and extended (dashed lines) at 5 selected temperatures. Left: dSASA. Right: LCPO.