Concerted Dynamic Motions of FABP4 Model and Ligands Revealed by Microsecond Molecular Dynamics Simulations

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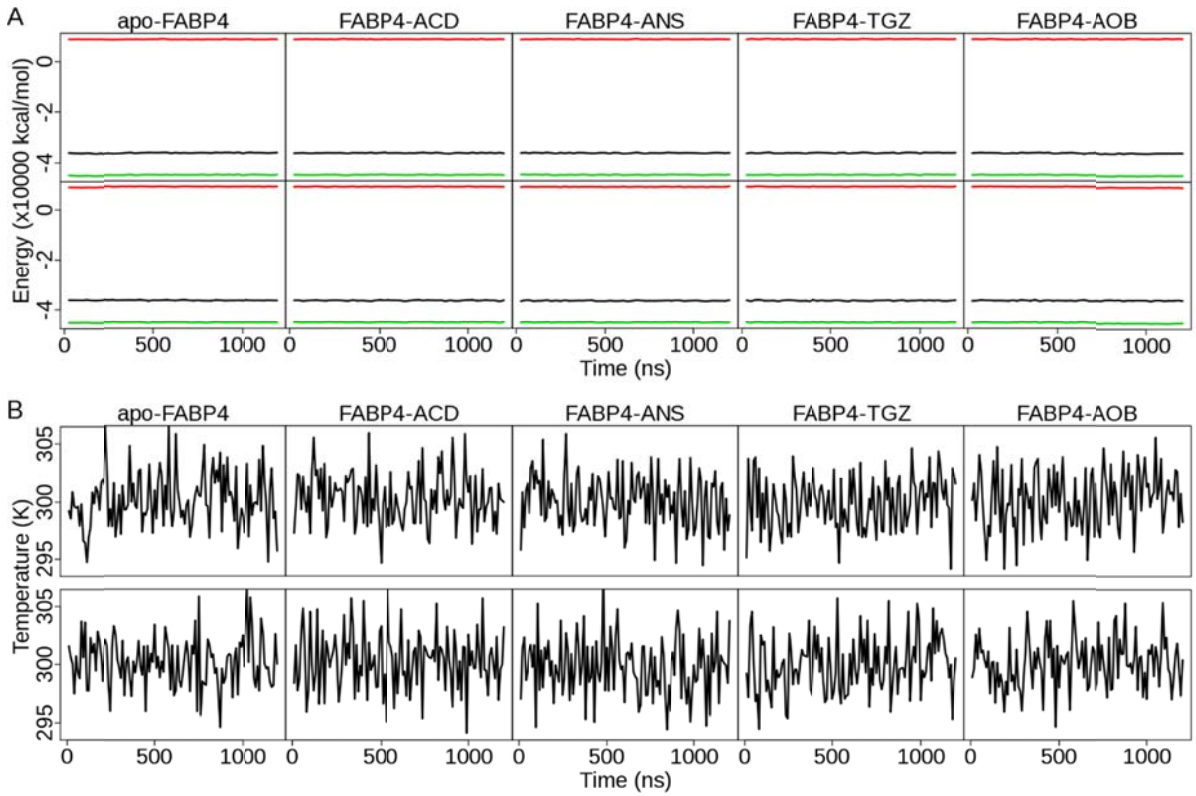

Figure S1. Time evolution of system energy and temperature in MD simulations. A) Fluctuation of system energy. Total Energy is in black, potential energy is in green and kinetic energy is in red. B) Fluctuation of simulation temperature. Data from all ten MD trajectories are presented.

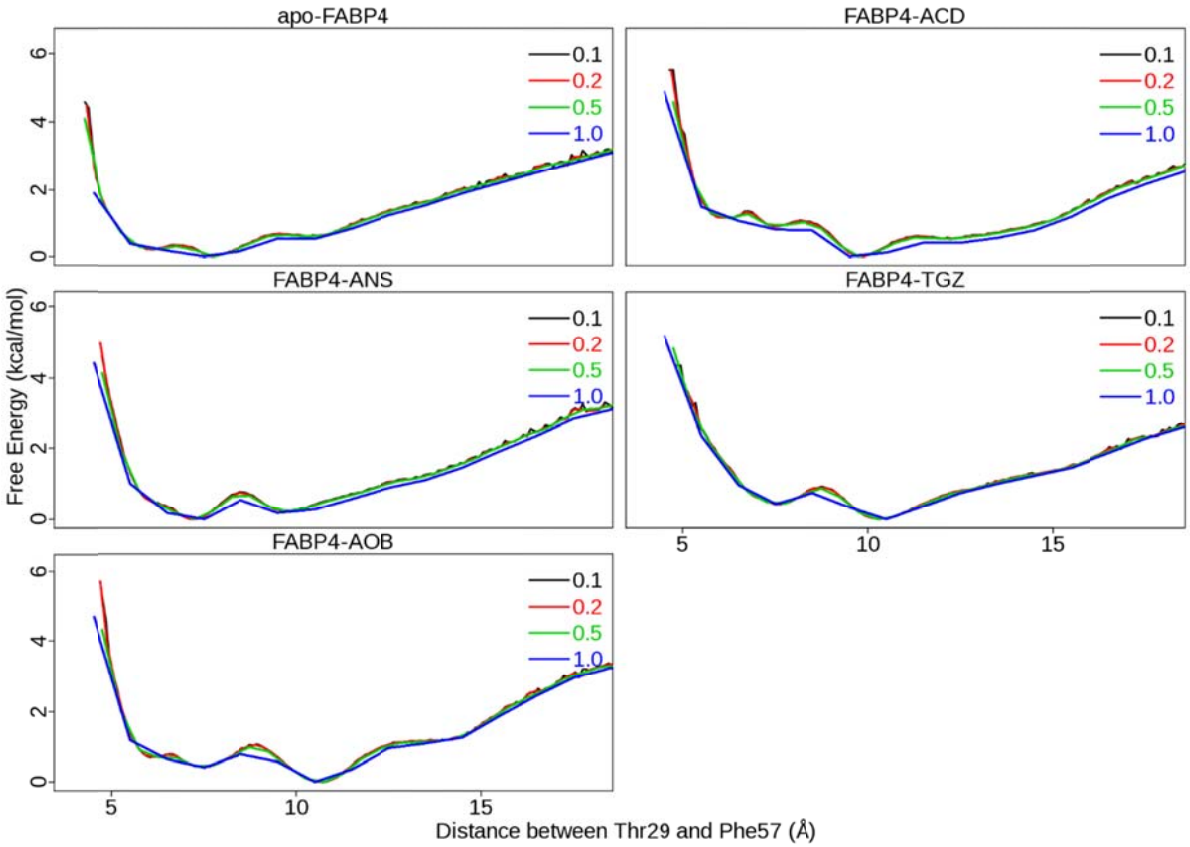

Figure S2. Effect of bin width on the free energy surface. The distribution function is computed with the procedure of HIST implemented in R v3.0. With Sturges algorithm, the bin width is set to 1.0 Å. With Freedman-Diaconis algorithm, the bin width is set to 0.1 Å. With Scott algorithm, the bin width is set to 0.2 Å. The 1D free energy on Thr29-Phe57 distance is calculated with a bin width of 0.1, 0.2, 0.5 and 1.0 Å, respectively. The bin width has little effect on the free energy when it is between 0.1 and 0.5 Å. Considering that narrow bins give greater precision to the density estimation than wide bins do, Freedman-Diaconis algorithm is used and the bin width is 0.1 Å (Figure 4B).

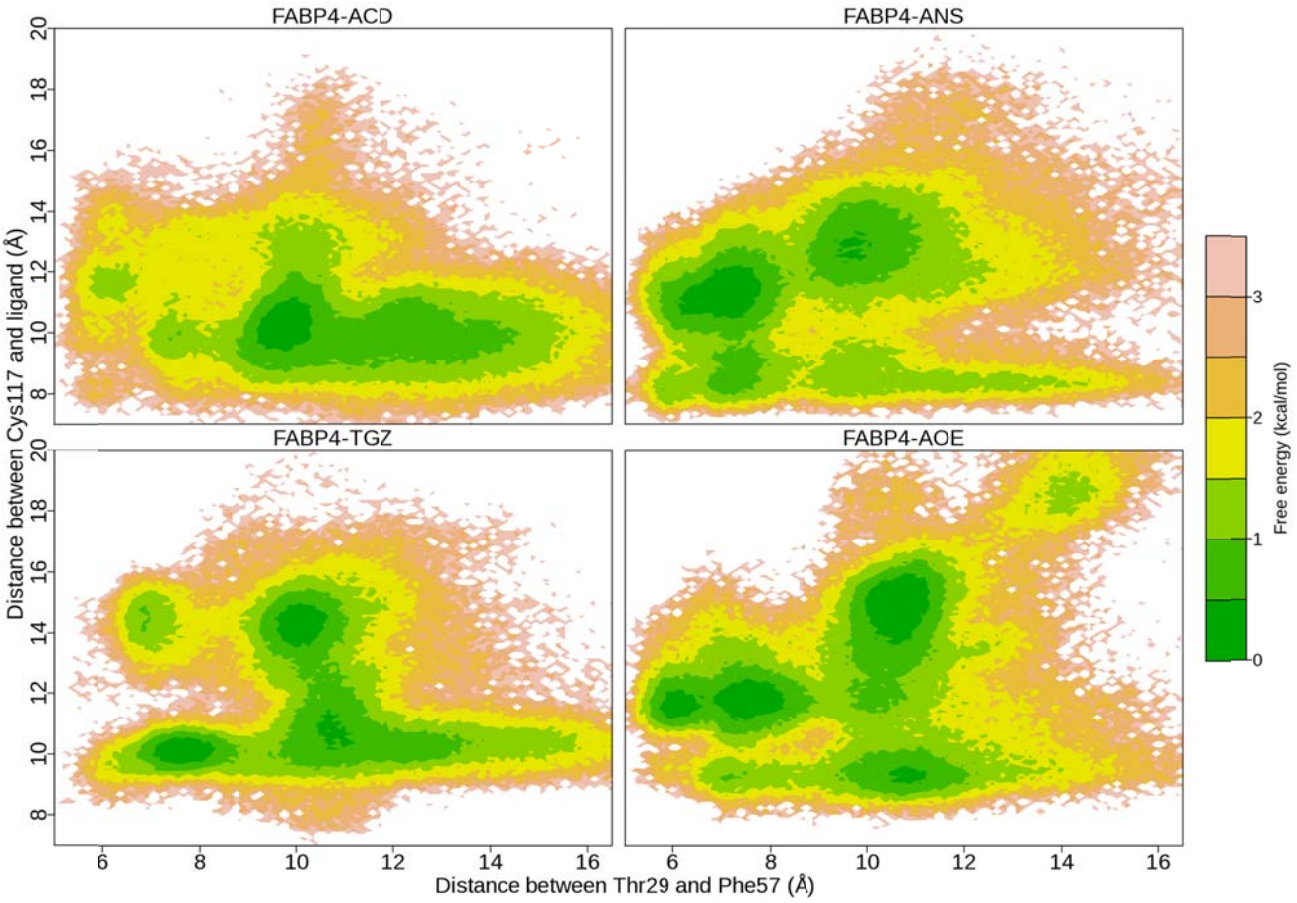

Figure S3. Effect of bin area on the free energy surface. The distribution function is computed with the procedure of HIST2D in the package of GPLOTS. The 2D FES is calculated with a bin area of 0.1 Å × 0.1 Å. The 2D FES with a bin area of 0.2 Å × 0.2 Å, 0.5 Å × 0.5 Å and 1.0 Å × 1.0 Å is shown in Figure S4, S5 and S6, respectively. With big bin area, the surface cannot be described very well. With small bin area, the surface is not very smooth. Therefore, the bin area of 0.3 Å × 0.3 Å is chosen (Figure 6).

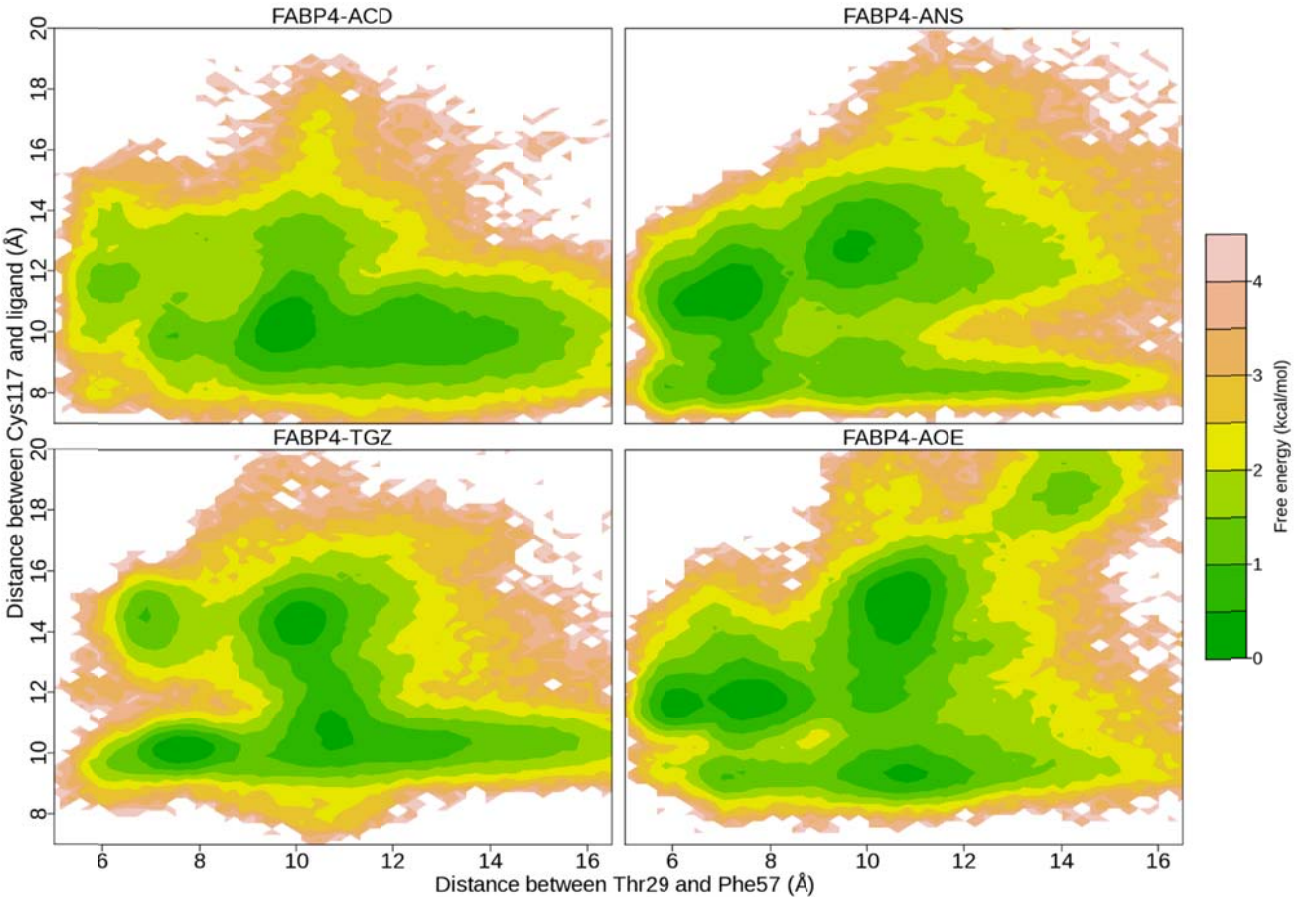

Figure S4. Effect of bin area on the free energy surface. The 2D FES is calculated with a bin area of 0.2 Å × 0.2 Å.

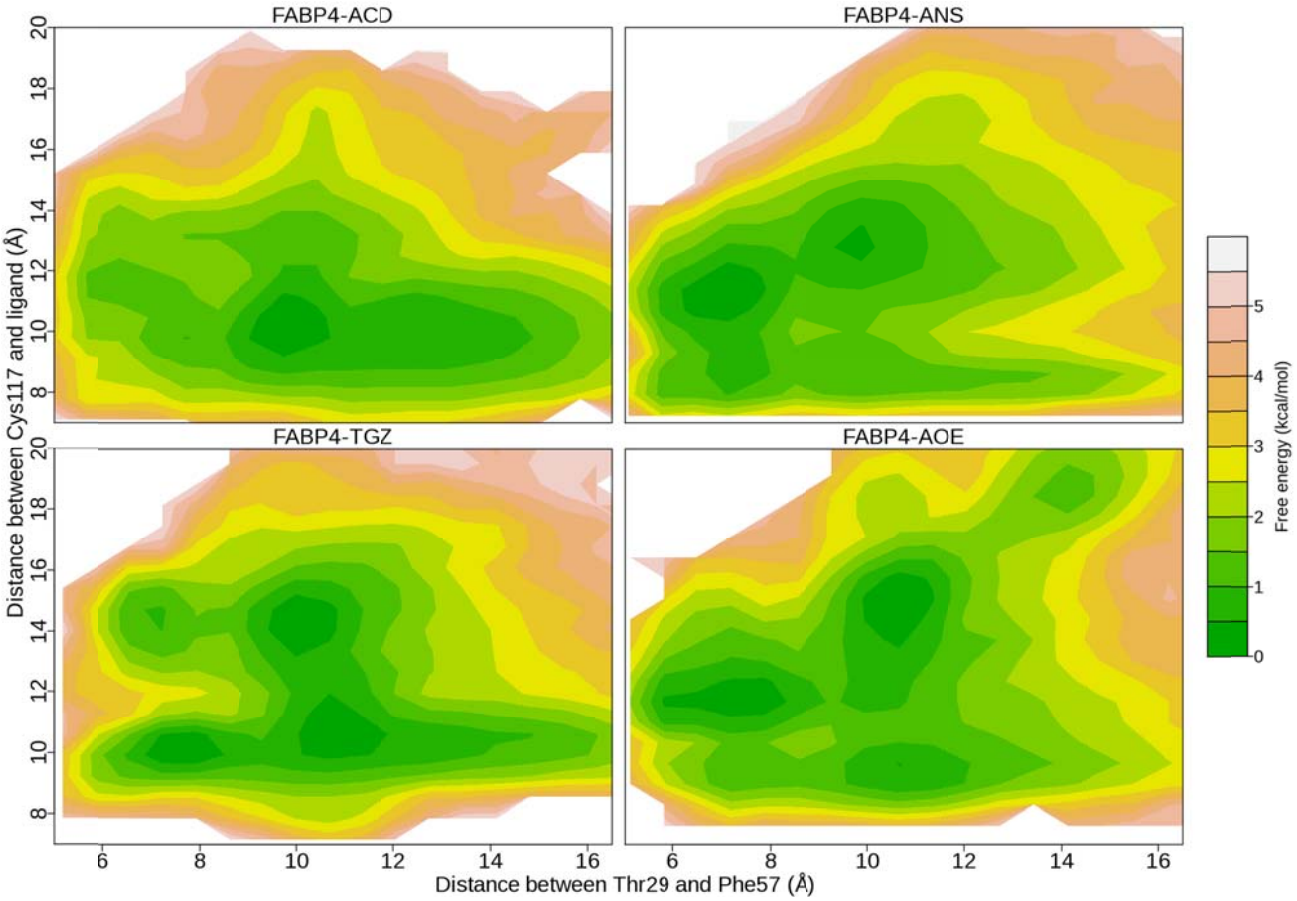

Figure S5. Effect of bin area on the free energy surface. The 2D FES is calculated with a bin area of 0.5 Å × 0.5 Å.

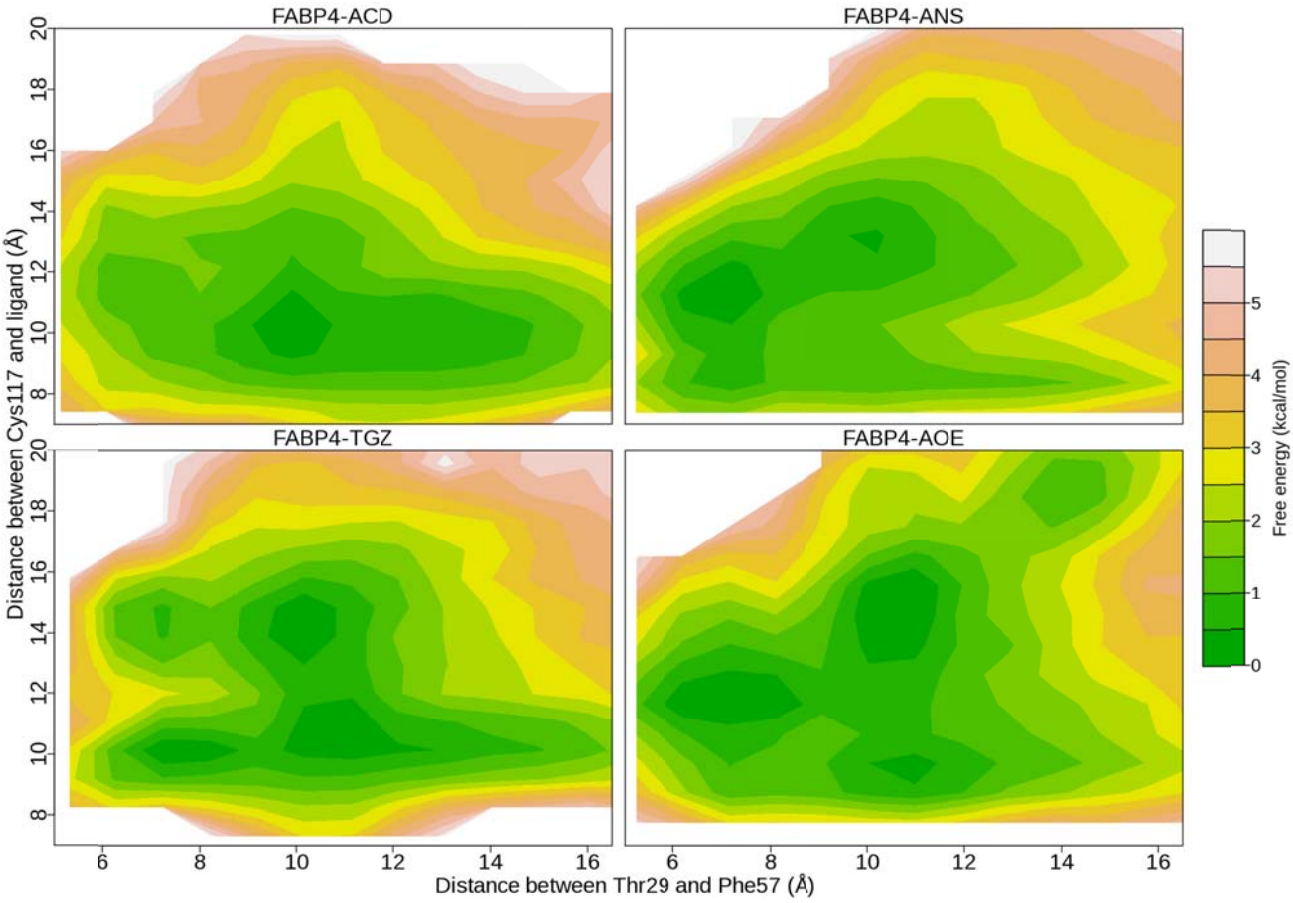

Figure S6. Effect of bin area on the free energy surface. The 2D FES is calculated with a bin area of 1.0 Å × 1.0 Å.

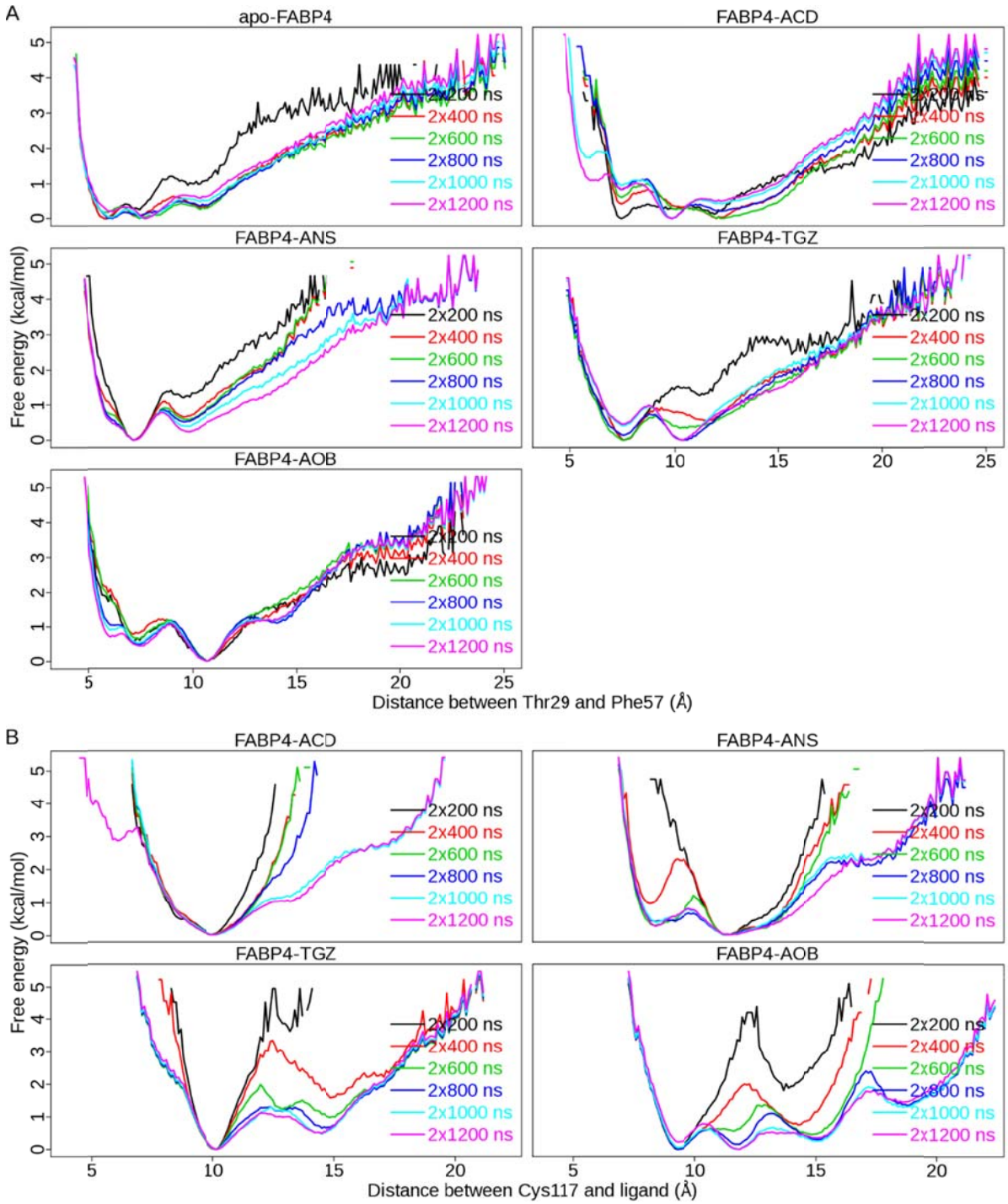

Figure S7. Convergence of free energy calculations. A) 1D free energy surface on the distance between Thr29 and Phe57. B) 1D free energy surface on the distance of Cys117 and ligand. For each structure, two MD trajectories are employed in free energy calculation. The free energy curve is calculated at an interval of 200 ns of simulation time.

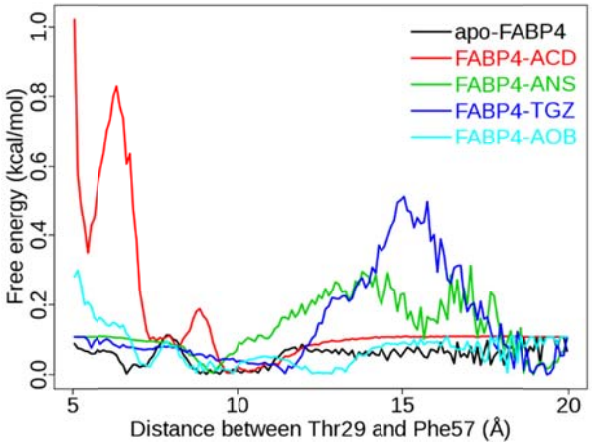

Figure S8. Variation of free energy along the distance between Thr29 and Phe57 during the last 200 ns MD simulation. The variation curves are computed with a bin width of 0.1 Å. The uncertainty on the calculation of free energy in Figure 4B is estimated by the largest variation observed during the last 200 ns MD simulations. The largest variation (about 1.0 kcal/mol) occurs in the simulation of FABP4-ACD complex because the shallow basin near 5 Å (Figure S7A) is not adequately sampled in the first 1 μs simulations. For other simulations, the largest variation is not more than 0.6 kcal/mol. In the most interesting range of 7 – 15 Å, the largest variation is below 0.4 kcal/mol.

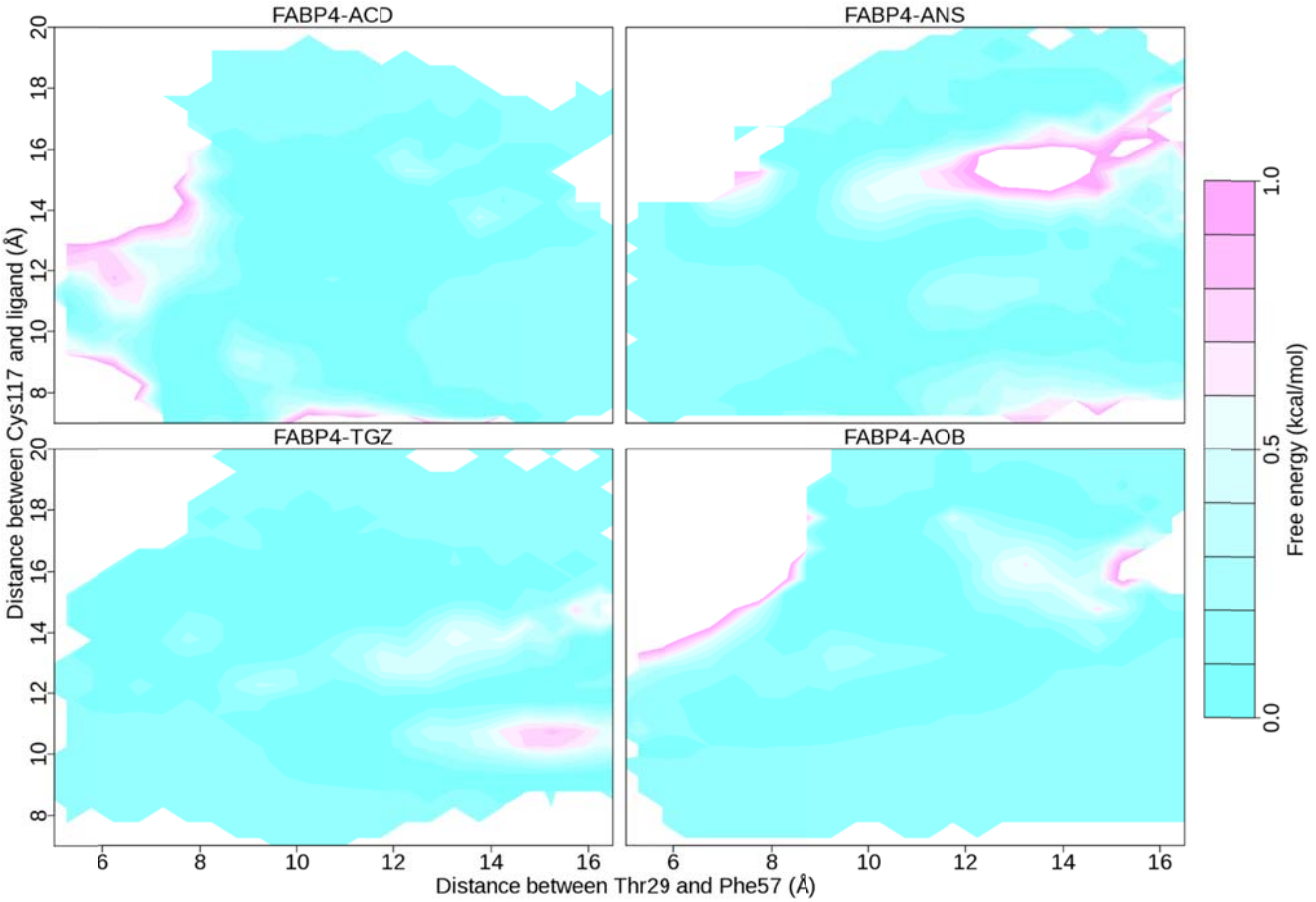

Figure S9. Variation of free energy on 2D FES during the last 200 ns MD simulation. The variation of free energy is computed with a bin area of 0.3 Å × 0.3 Å. The uncertainty on the calculation of free energy in Figure 6 is estimated by the largest variation observed during the last 200 ns MD simulations. The largest variation (about 1.0 kcal/mol) happens on the edges of the surface because of inadequate sampling. In most areas the largest variation is below 0.5 kcal/mol.

Appendix: Input parameter file for MD simulations

```
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  ntx=5, irest=1,
  ntpr=500000, ntwx=5000,
  ntwr=500000,
  iwrap=1, ioutfm=1,
  temp0=300.0, ntt=3, gamma_ln=2, ig=-1,
  ntb=1,
  ntp=0,
  ntc=2, ntf=2,
&end
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