Supporting Information

for "Improved Reweighting of Accelerated Molecular Dynamics Simulations for Free Energy Calculation" by Yinglong Miao, William Sinko, Levi Pierce, Denis Bucher, Ross C. Walker and J. Andrew McCammon

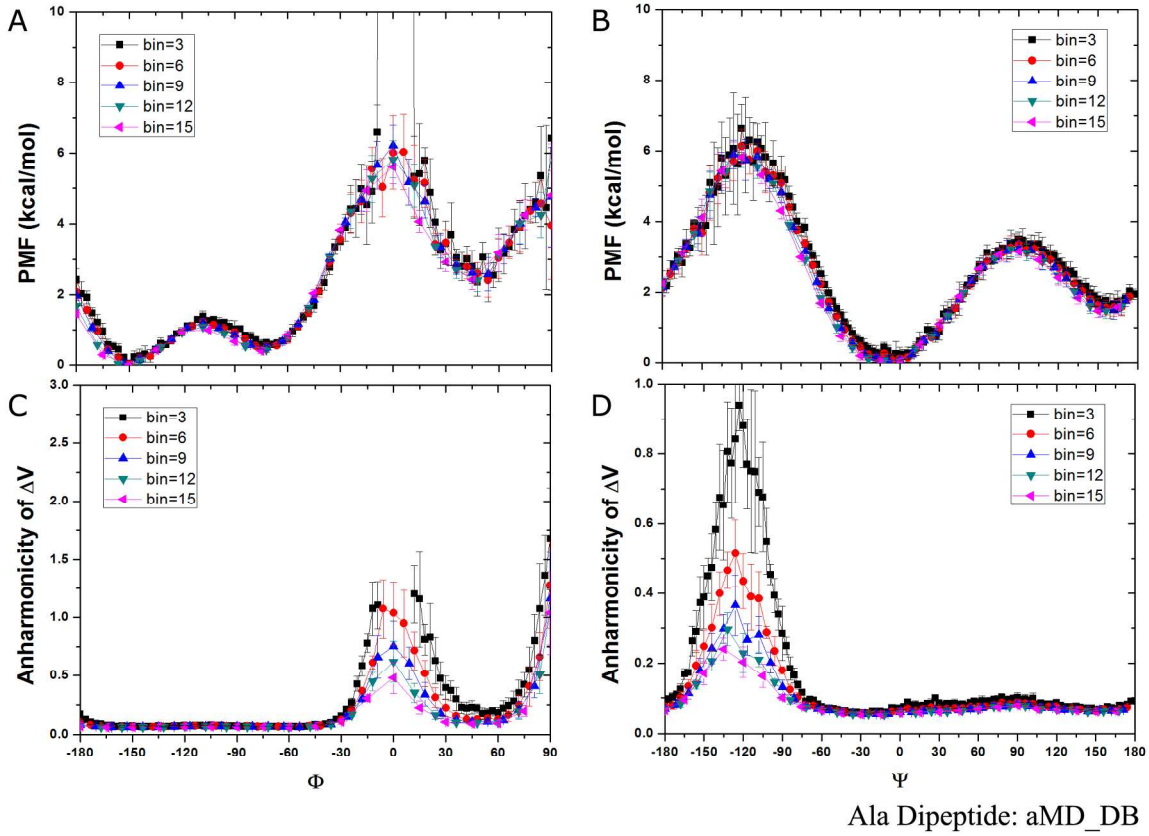

Fig. S1 Free energy profiles of backbone dihedrals (A) Φ and (B) Ψ in alanine dipeptide calculated by reweighting five independent 20 *ns* dual-boost aMD simulations using cumulant expansion to the 2nd order, and the corresponding anharmonicity of boost potential in (C) and (D), respectively.

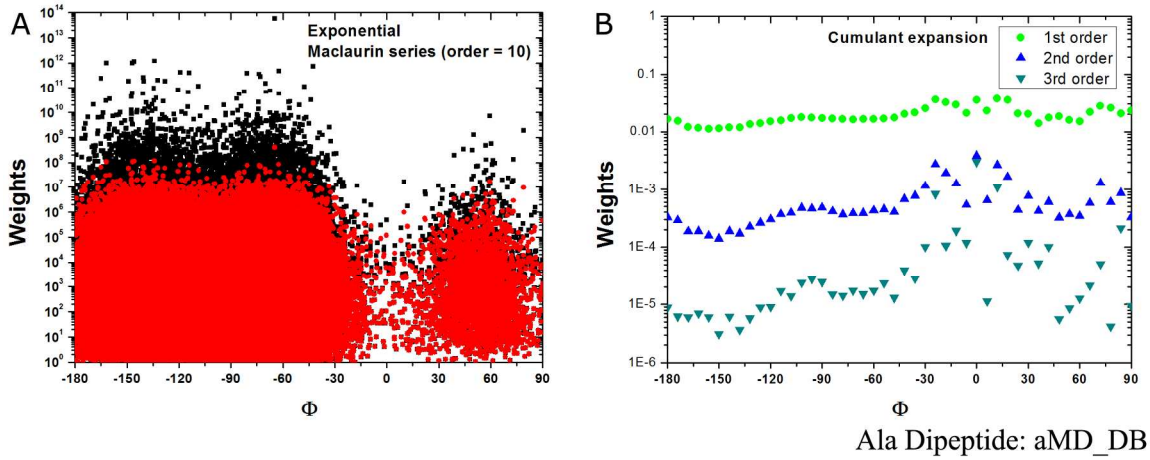

Fig. S2 The reweighting factors of backbone dihedral Φ in alanine dipeptide calculated from a representative 20 *ns* dual-boost aMD simulation: (A) the exponentials and Maclaurin series expansion to the 10th order, and (B) cumulant expansion to the 1st, 2nd and 3rd order, respectively.

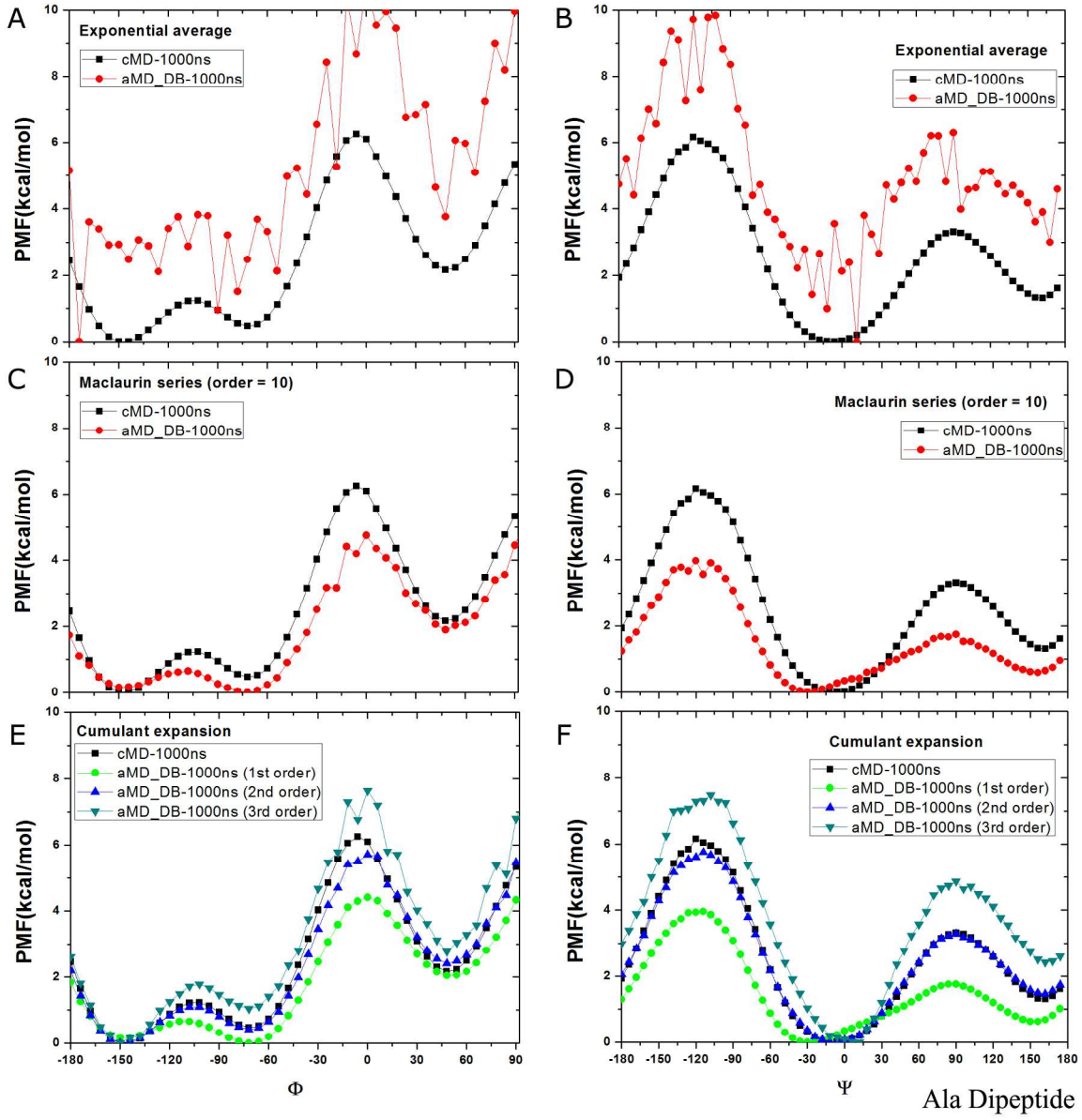

Fig. S3 Free energy profiles of backbone dihedrals Φ and Ψ in alanine dipeptide calculated by reweighting a 1000 *ns* dual-boost aMD simulations using: (A-B) exponential average, (C-D) Maclaurin series expansion to the 10th order, (E-F) cumulant expansion to the 1st, 2nd and 3rd orders. The free energy profiles obtained from a 1000 *ns* cMD simulation are plotted in black for comparison. The PMF profiles are closely similar to those obtained from the 20 *ns* dual-boost aMD simulations as shown in **Fig. 3**.

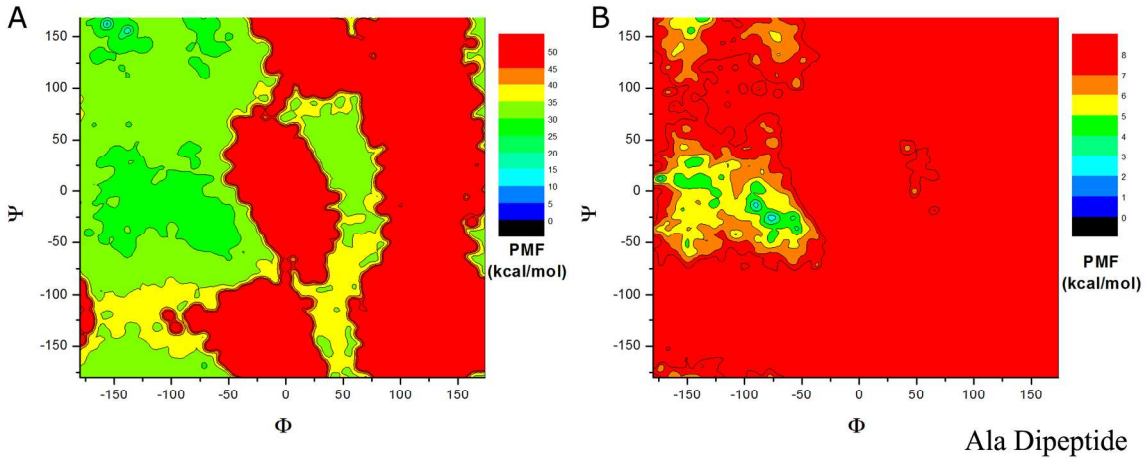

Fig. S4 Two-dimensional free energy profiles of backbone dihedrals (Φ, Ψ) in alanine dipeptide calculated from reweighting of (A) 20 *ns* and (B) 1000 *ns* dual-boost aMD simulation using exponential average. Overall, the exponential average reweighting produces highly fluctuating PMF, notably with large magnitudes of 20-40 kcal/mol in the 20 *ns* aMD simulation.

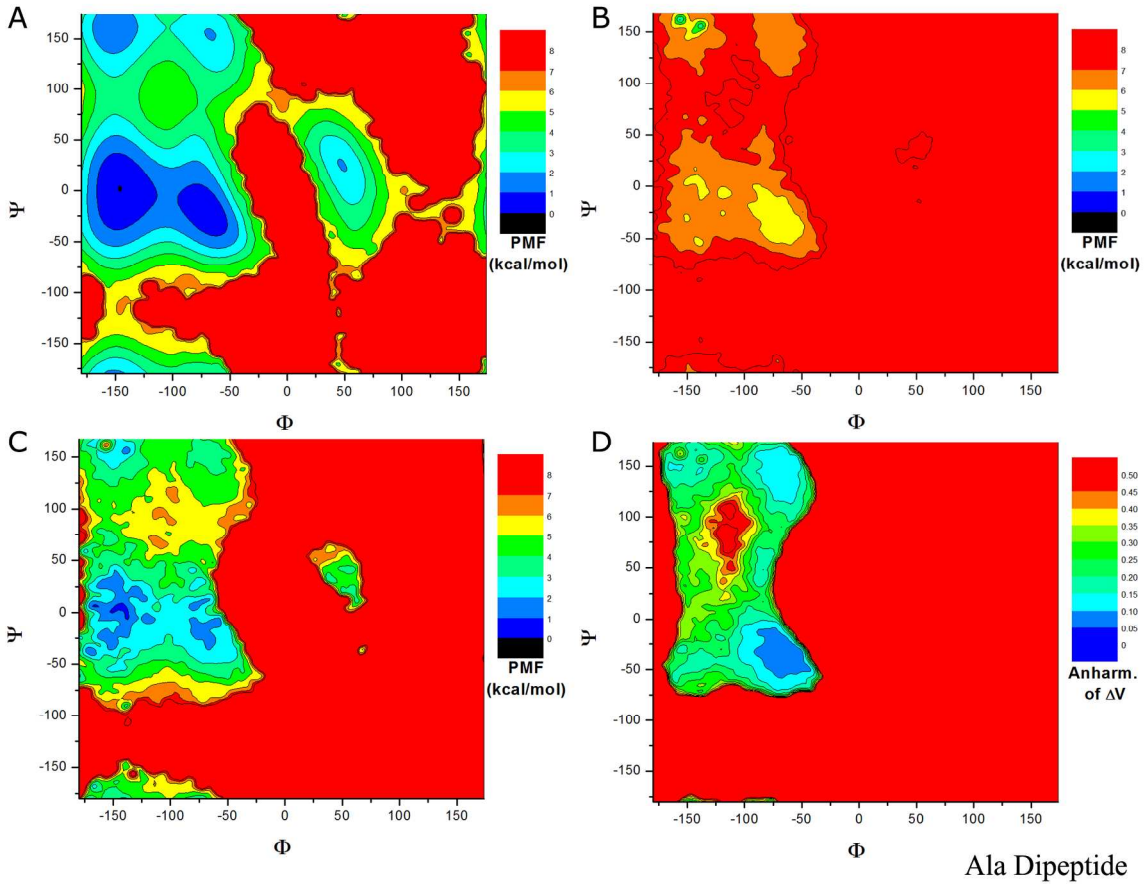

Fig. S5 Two-dimensional free energy profiles of backbone dihedrals (Φ, Ψ) in alanine dipeptide calculated from (A) 1000 ns cMD simulation and reweighting of a 20 *ns* dual-boost aMD simulation using (B) Maclaurin series to the 10th order and (C) cumulant

expansion to the 2nd order. (D) The distribution anharmonicity of ΔV of frames found in each bin of (Φ, Ψ) in the 1000 *ns* dual-boost aMD simulation. The 20 *ns* dual-boost aMD simulation appears to lack converged sampling compared with the 1000 *ns* simulation as shown in **Fig. 5**.

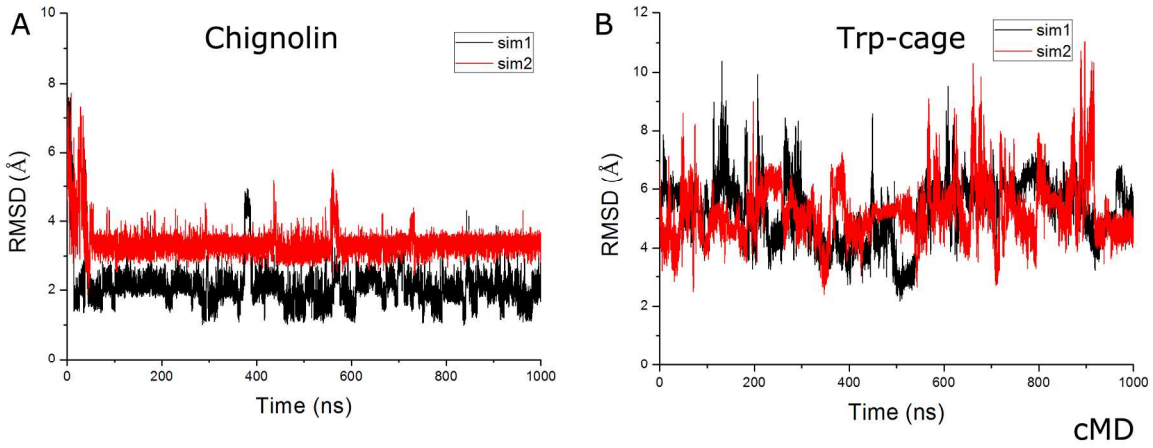

Fig. S6 The root-mean-square deviation (RMSD) of the protein C_α atoms relative to the experimentally-determined folded structure calculated from 1000 *ns* cMD simulations: (A) Chignolin and (B) Trp-cage.

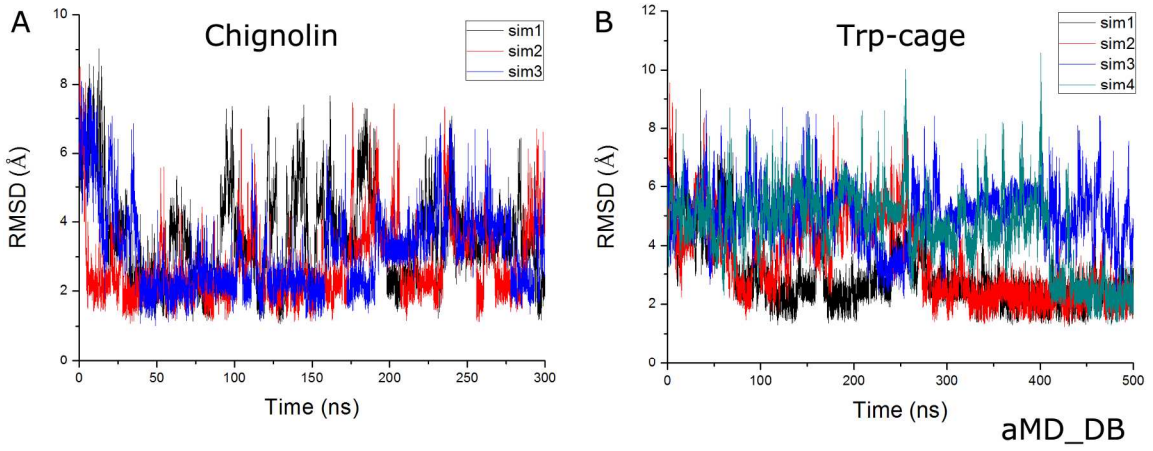

Fig. S7 The root-mean-square deviation (RMSD) of the protein C_α atoms relative to the experimentally-determined folded structure calculated from dual-boost aMD simulations: (A) Chignolin and (B) Trp-cage.