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Supporting Information

The Amber ff99 Force Field Predicts Relative Free Energy Changes for RNA Helix Formation

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Error Estimation in calculating the nearest neighbor free energies

The errors calculated in Table 2 and elsewhere in the main text follow the common rules of error propagation,[1] except when calculating the free energy change from the enthalpy and entropy changes. These three quantities are connected by the well known relationship $\Delta G^0(T) = \Delta H^0 - T\Delta S^0$ and the propagation of the uncertainties σ follows the well known relationship:

$$\sigma^2_{\Delta G^0(T)} = \sigma^2_{\Delta H^0} + T^2\sigma^2_{\Delta S^0} - 2Tr\sigma_{\Delta H^0}\sigma_{\Delta S^0} \quad (1)$$

where r is the correlation coefficient between ΔH^0 and ΔS^0. r, however, has a value of 0.9996 for duplexes in the database of available experiments[2] indicating a high correlation between these two values. The equation 1 can then be rewritten as $\sigma^2_{\Delta G^0(T)} = (\sigma_{\Delta H^0} - T\sigma_{\Delta S^0})^2$ showing that the errors of ΔH^0 , ΔS^0 and ΔG^0 are related in a same way as the quantities themselves and producing a much smaller overall error then when using common error estimation rules.

References

1. Bevington, P. R.; Robinson, D. K., *Data reduction and error analysis for the physical sciences*. 3rd ed.; McGraw-Hill: Boston, 2003.
2. Xia, T.; SantaLucia, J., Jr.; Burkard, M. E.; Kierzek, R.; Schroeder, S. J.; Jiao, X.; Cox, C.; Turner, D. H., Thermodynamic parameters for an expanded nearest-neighbor model for formation of RNA duplexes with Watson-Crick base pairs. *Biochemistry* **1998,** *37* (42), 14719-35.

Figure S1. RMSD of all heavy atoms to the NMR structure versus simulation time for native (a), mutant1 (b) and mutant2 (c) hairpins. Each hairpin had three independent simulations run.

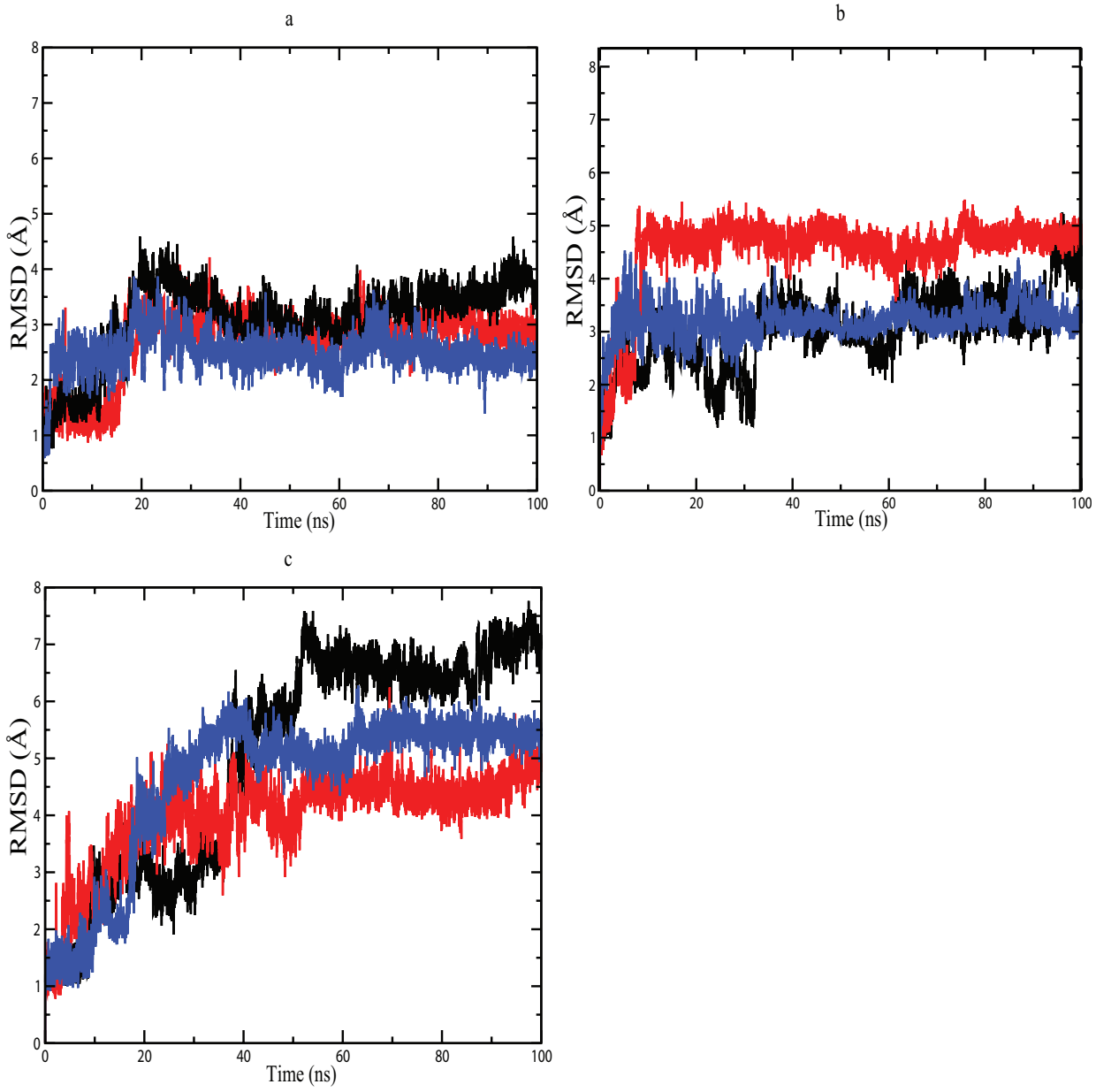

Figure S2. Plots of RMSD from the initial frame as a function of time for the whole mutant2 hairpin and stem (panel a) and the stem region (panel b), where the end-to-end distance was fixed to 17 Å using the harmonic restraint of 5 kcal/mol (identical to the production umbrella sampling simulations). This demonstrates that the structure is stable when the umbrella sampling restraints are applied. The simulation time was 30 ns, which is longer than any single window simulation time.

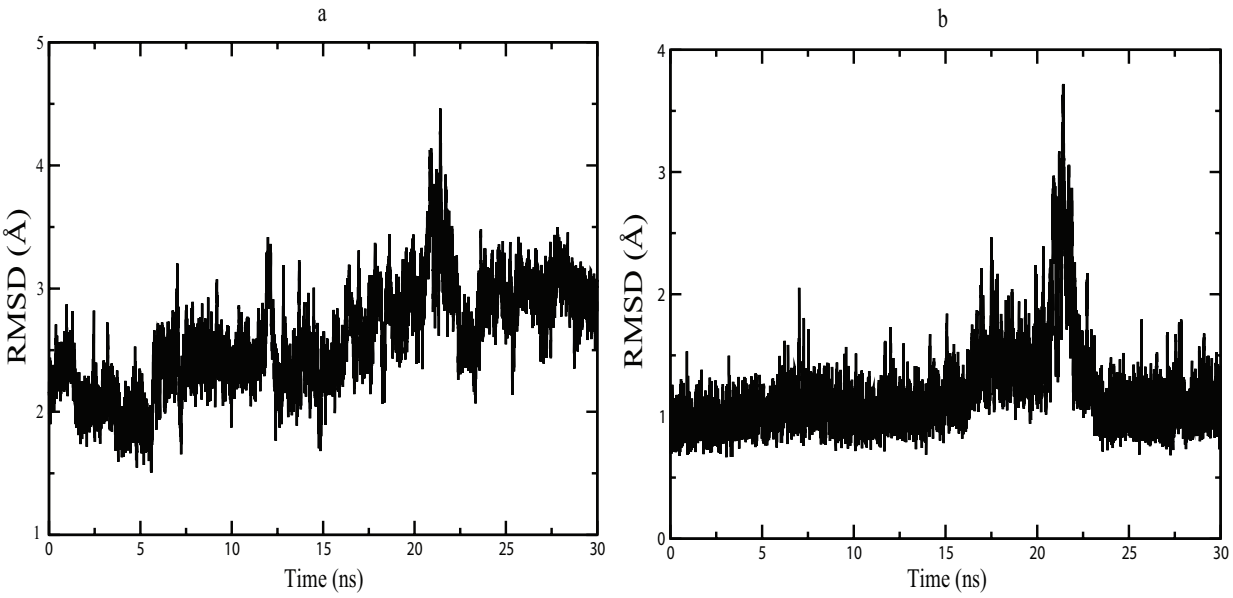

Figure S3. PMF as a function of end-to-end distance for native hairpin for three independent umbrella sampling calculations as a function of sampling time.

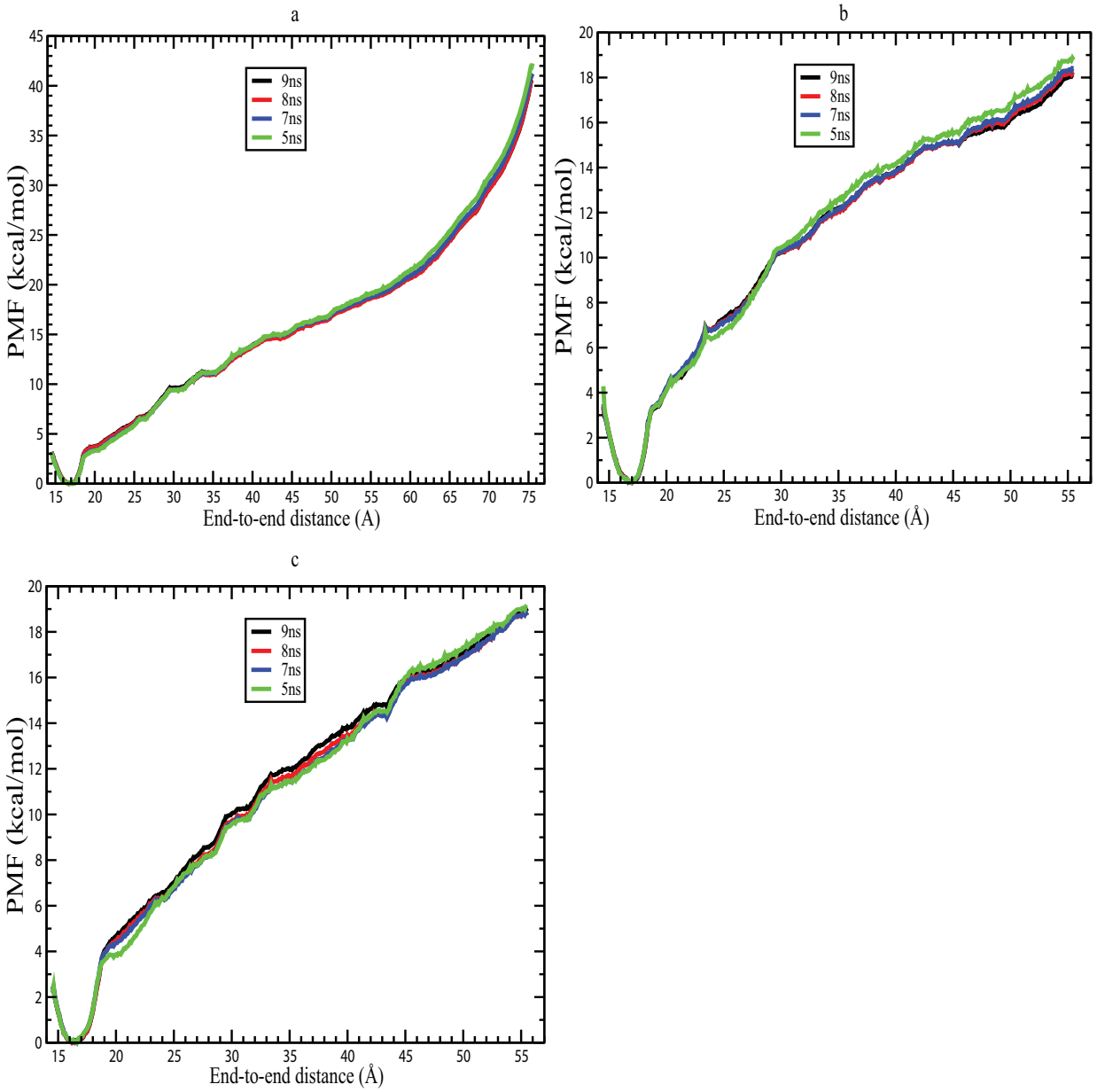

Figure S4. PMF as a function of end-to-end distance for mutant1 hairpin for four independent umbrella sampling calculations as a function of sampling time.

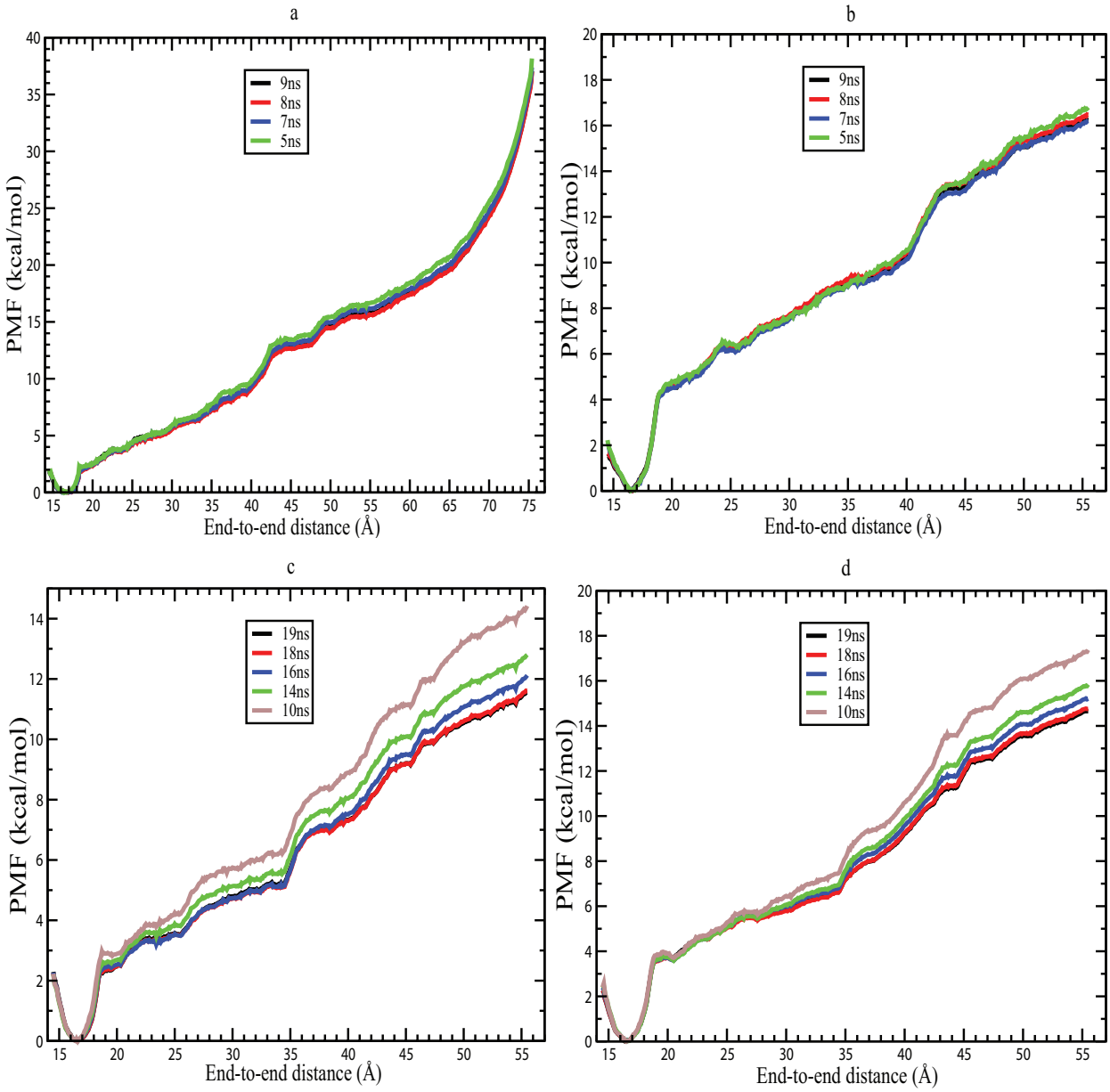

Figure S5. PMF as a function of end-to-end distance for mutant2 hairpin for four independent umbrella sampling calculations, as a function of sampling time.