Table S-I: Details for the MSB REXAMDtT simulations. [a]The accelerated molecular dynamics nomenclature follows that in Hamelberg et al.[10] Units are kcal mol$^{-1}$. [b]The effective number of reweighted and uncorrelated instantaneous $dV/d\lambda$ values was calculated using the method of Shen et al. [8] The total number of effective points from the ten $\lambda$ 0.11/0.89 and the 0.50 simulation when using the reweighted runs strategy are reported.

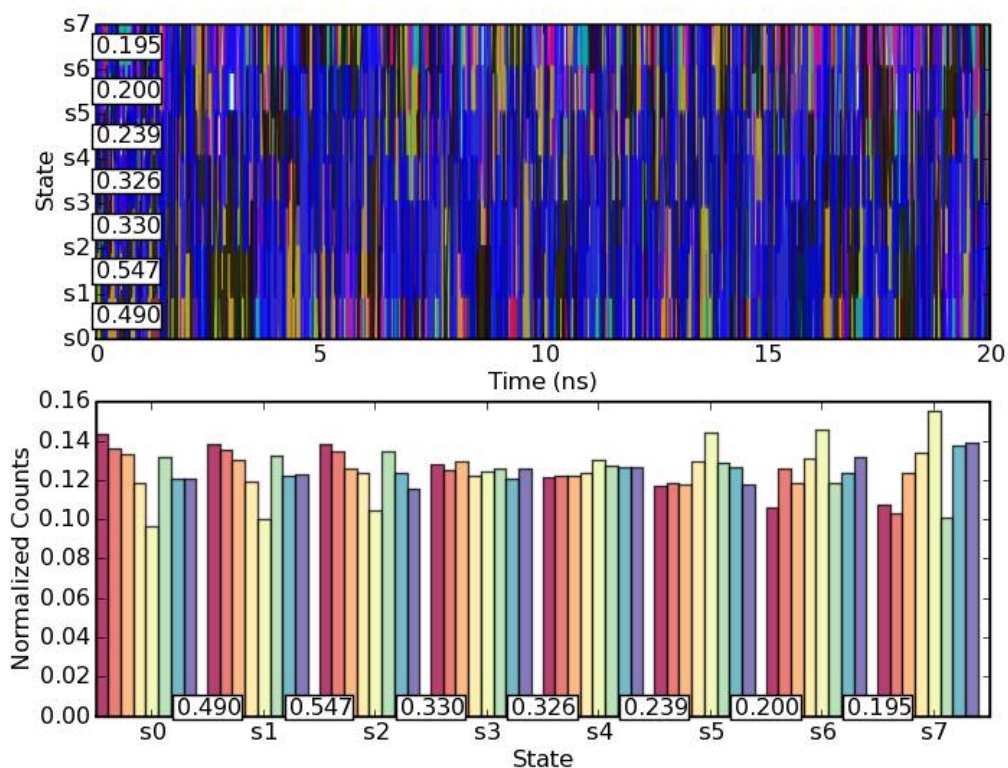| State Index | Boost Parameters [a] | | | | Avg. ΔV | | Approx. N$_{eff}$ [b] |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | $E_t$ | $\alpha_t$ | $E_T$ | $\alpha_T$ | $\lambda$ 0.11, 0.89 | $\lambda$ 0.50 | |
| s0 | n/a | n/a | n/a | n/a | 0.0±0.0 | 0.0±0.0 | 200000 |
| s1 | 70 | 1024 | 350 | 2048 | 29.8±0.7 | 11.6±0.4 | 3700; 8340 |
| s2 | 70 | 512 | 350 | 1024 | 51.9±1.4 | 20.9±0.7 | 1130; 3700 |
| s3 | 70 | 256 | 350 | 512 | 81.8±2.7 | 34.5±1.3 | 330; 1300 |
| s4 | 70 | 154 | 350 | 307 | 105±4 | 46.5±2.1 | 160; 530 |
| s5 | 70 | 92 | 350 | 184 | 123±7 | 58.3±3.1 | 70; 260 |
| s6 | 70 | 55 | 350 | 111 | 131±10 | 67.5±4.2 | 40; 150 |
| s7 | 70 | 33 | 350 | 66 | 129±13 | 73.0±5.4 | 30; 100 |

Figure S-I: A representative example of the replica exchange details for the MSB REXAMDtT simulations. The top plot shows a time series of the replicas (different colors) traveling through the various states. The boxed numbers between the states are the overall acceptance probability for the pairs of states. For example, the acceptance probability over the 20 ns simulation for the s0-s1 pair was 49.0%. The bottom plot shows the observed relative frequency of each replica (different colors) in each state. The overall acceptance probability is also shown between the state pairs.
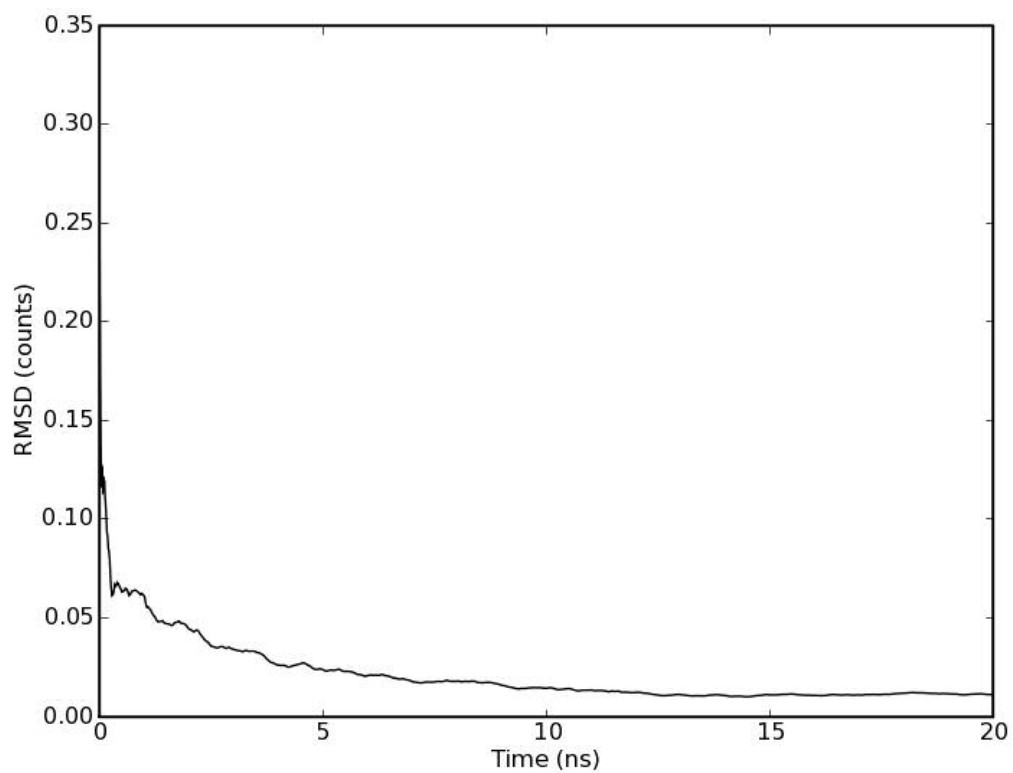
Figure S-II: A representative time series of the RMSD of the relative occupancy of the M replicas over the M states for the MSB REXAMDtT simulations, as defined by Abraham *et al.*[11]