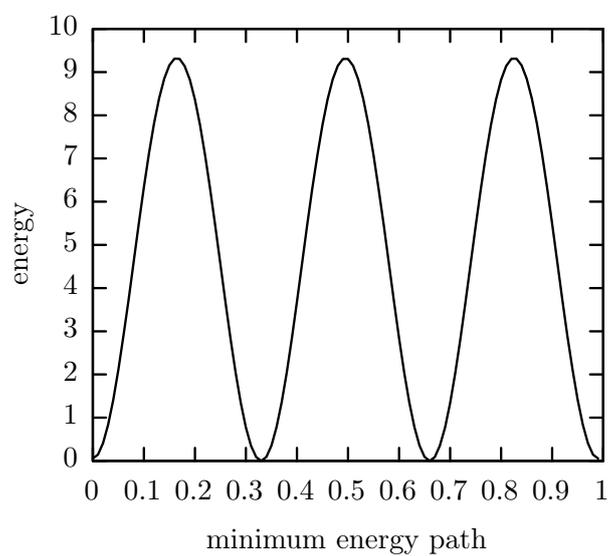
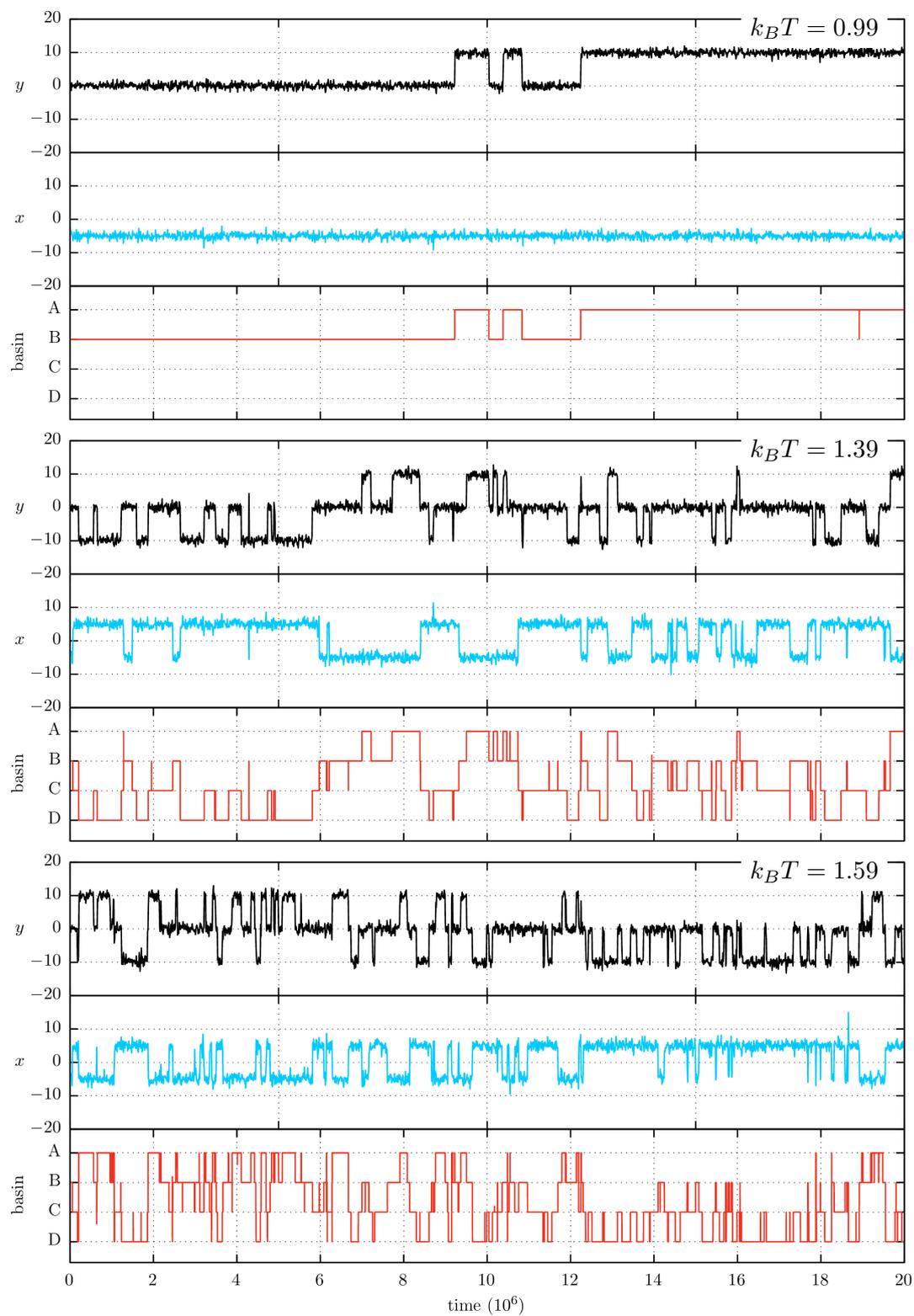


# Supplementary Materials: Testing Convergence of Different Free-Energy Methods in a Simple Analytical System with Hidden Barriers

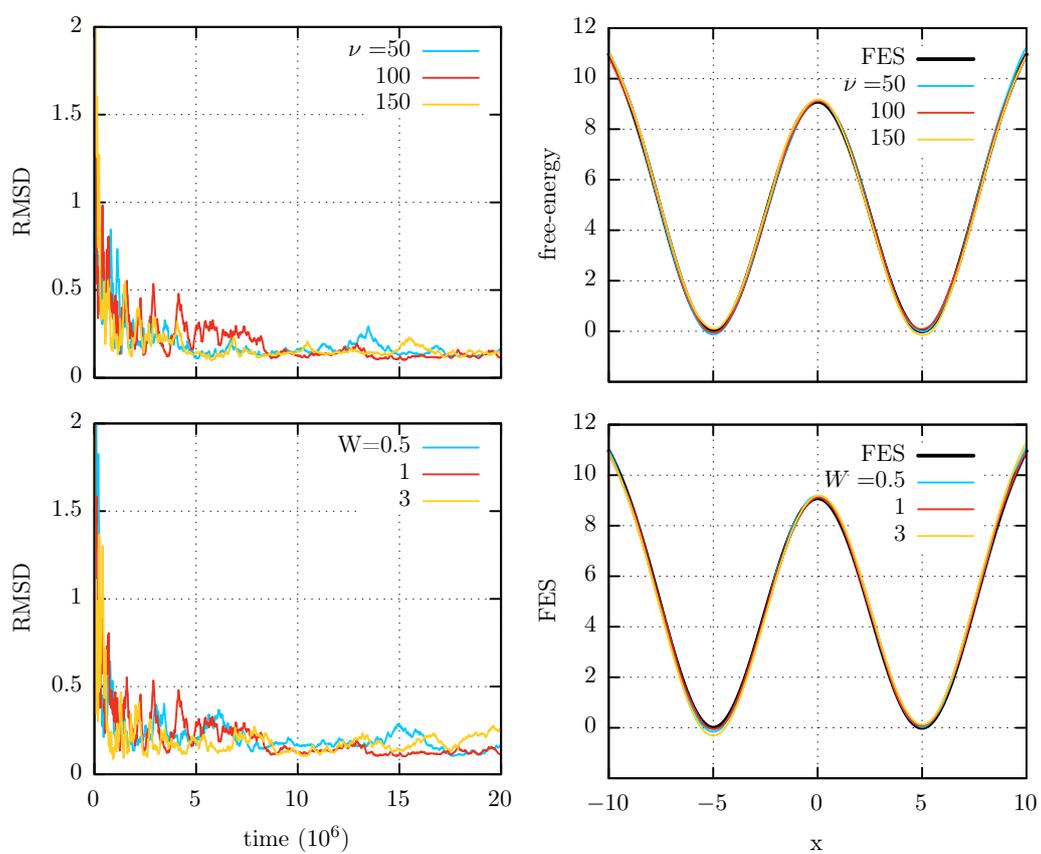
S. Alexis Paz<sup>1,2</sup>  and Cameron F. Abrams<sup>3</sup> \*



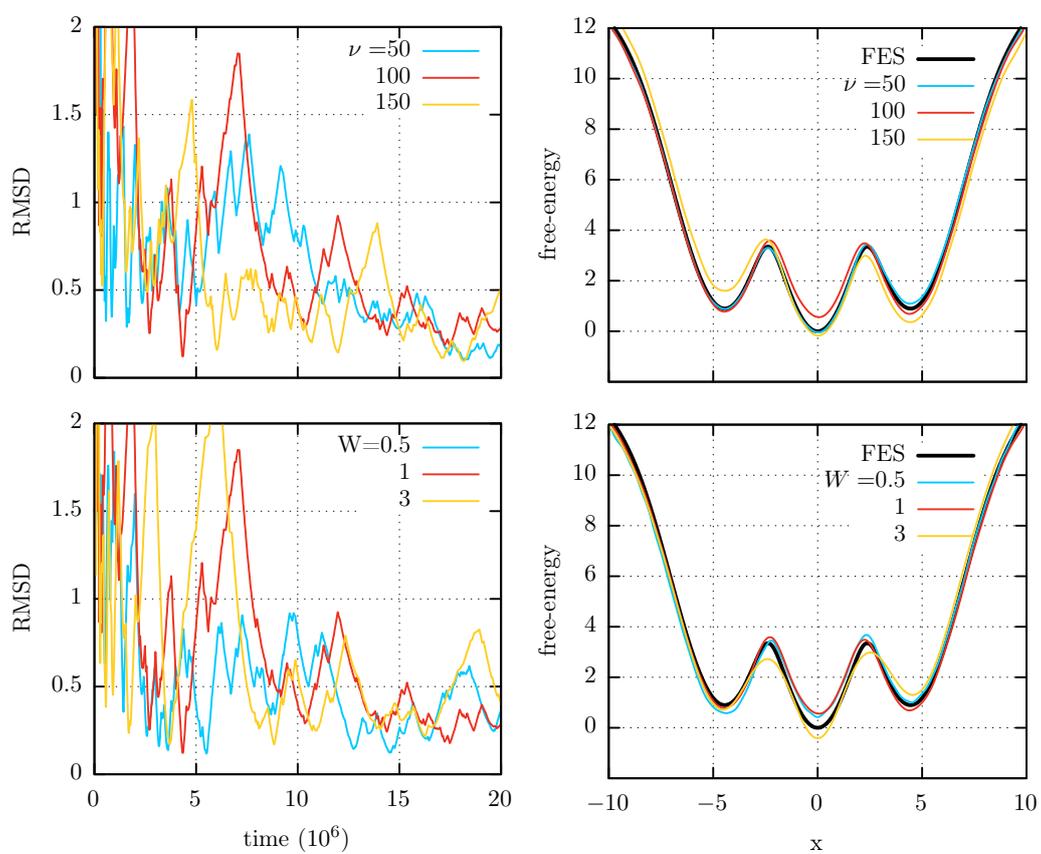
**Figure S1.** Minimum energy path for the PES used in this work.



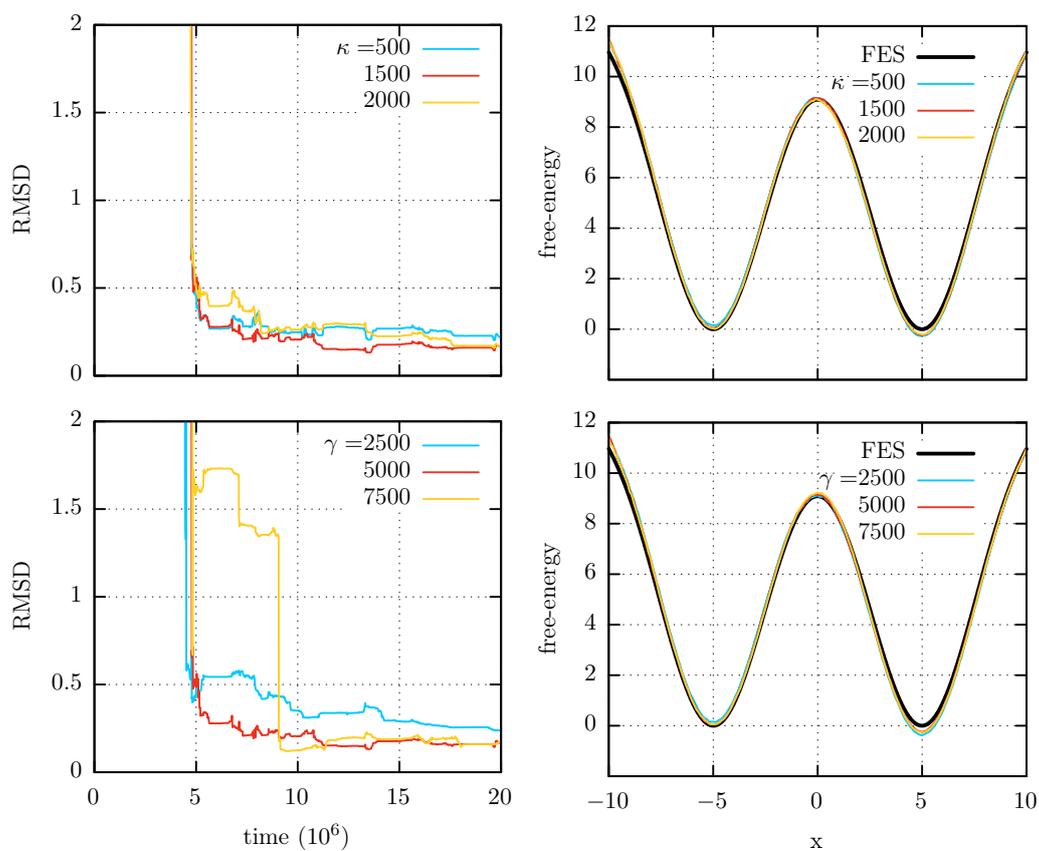
**Figure S2.** MD trajectory at different temperatures other than the  $k_B T = 1.19$  shown in figure 2 of the manuscript.



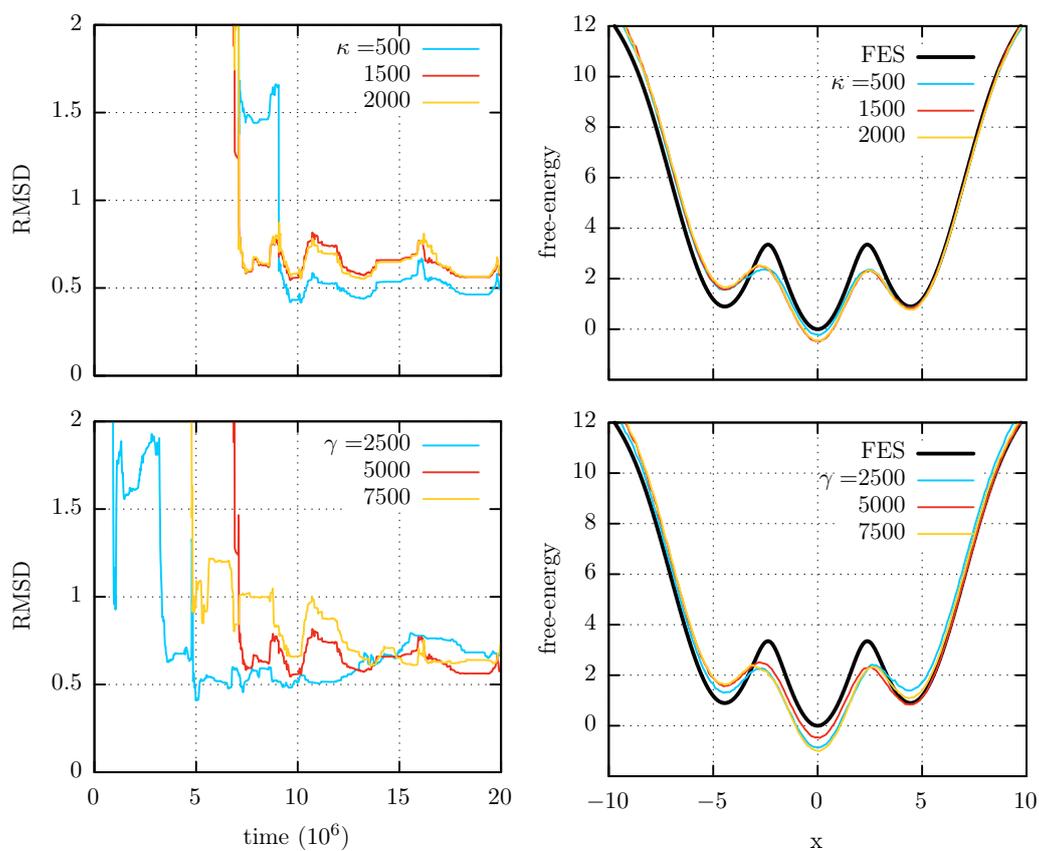
**Figure S3.** Convergence trace (left) and FEP (right) for WTMD simulations using  $x$  CV and different hill deposition frequency ( $\nu$ ) and hill width ( $W$ ) parameters.



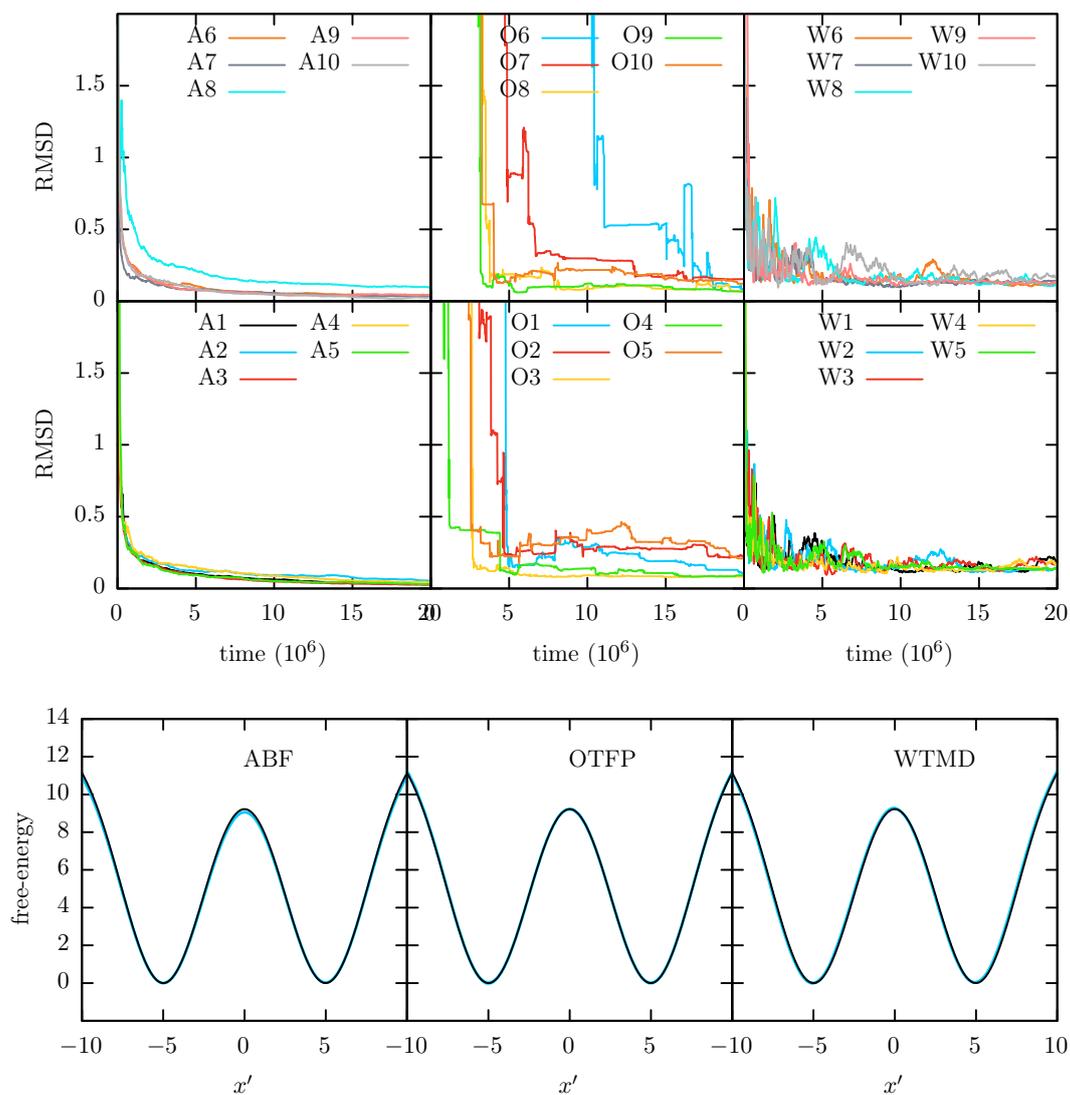
**Figure S4.** Convergence trace (left) and FEP (right) for WTMD simulations using  $x'$  CV different hill deposition frequency ( $\nu$ ) and hill width ( $W$ ) parameters.



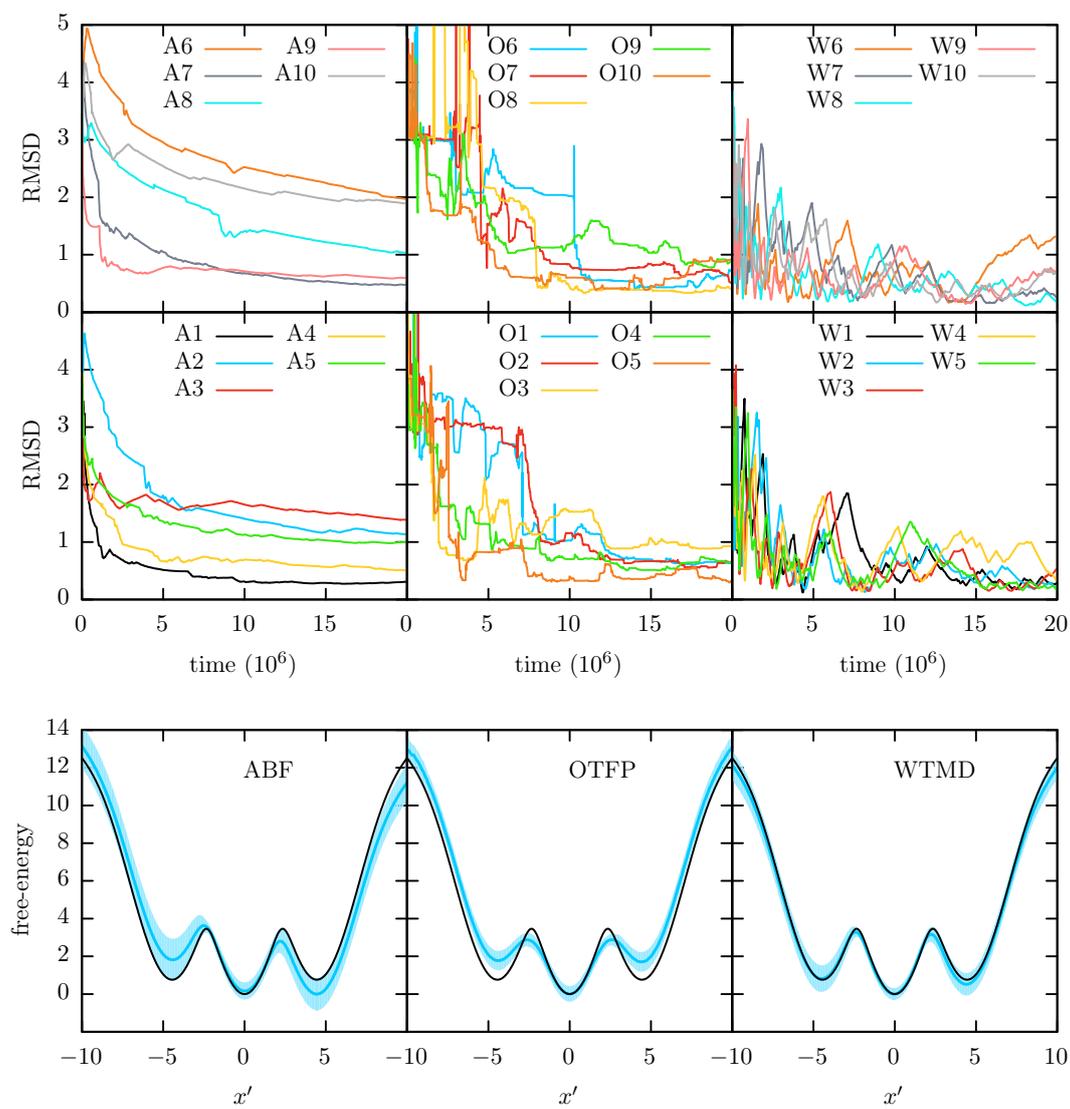
**Figure S5.** Convergence trace (left) and FEP (right) for OTFP simulations using  $x$  CV and different spring constant ( $\kappa$ ) and auxiliary friction ( $\bar{\gamma}$ ) parameters. The  $\bar{\gamma}$  values are the number of times the auxiliary friction is greater than the system friction.



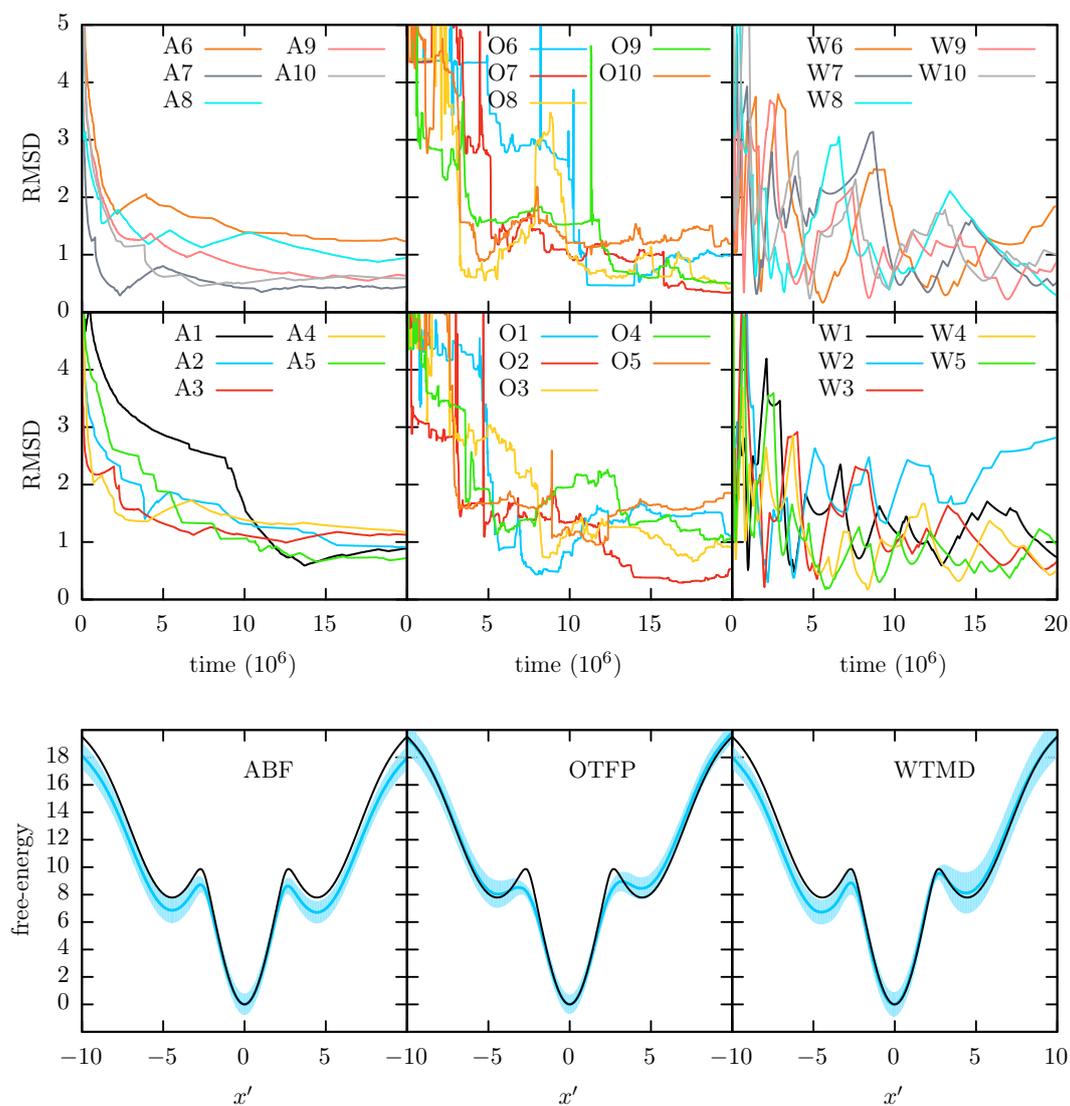
**Figure S6.** Convergence trace (left) and FEP (right) for OTFP simulations using  $x'$  CV and different spring constant ( $\kappa$ ) and auxiliary friction ( $\bar{\gamma}$ ) parameters. The  $\bar{\gamma}$  values are the number of times the auxiliary friction is greater than the system friction.



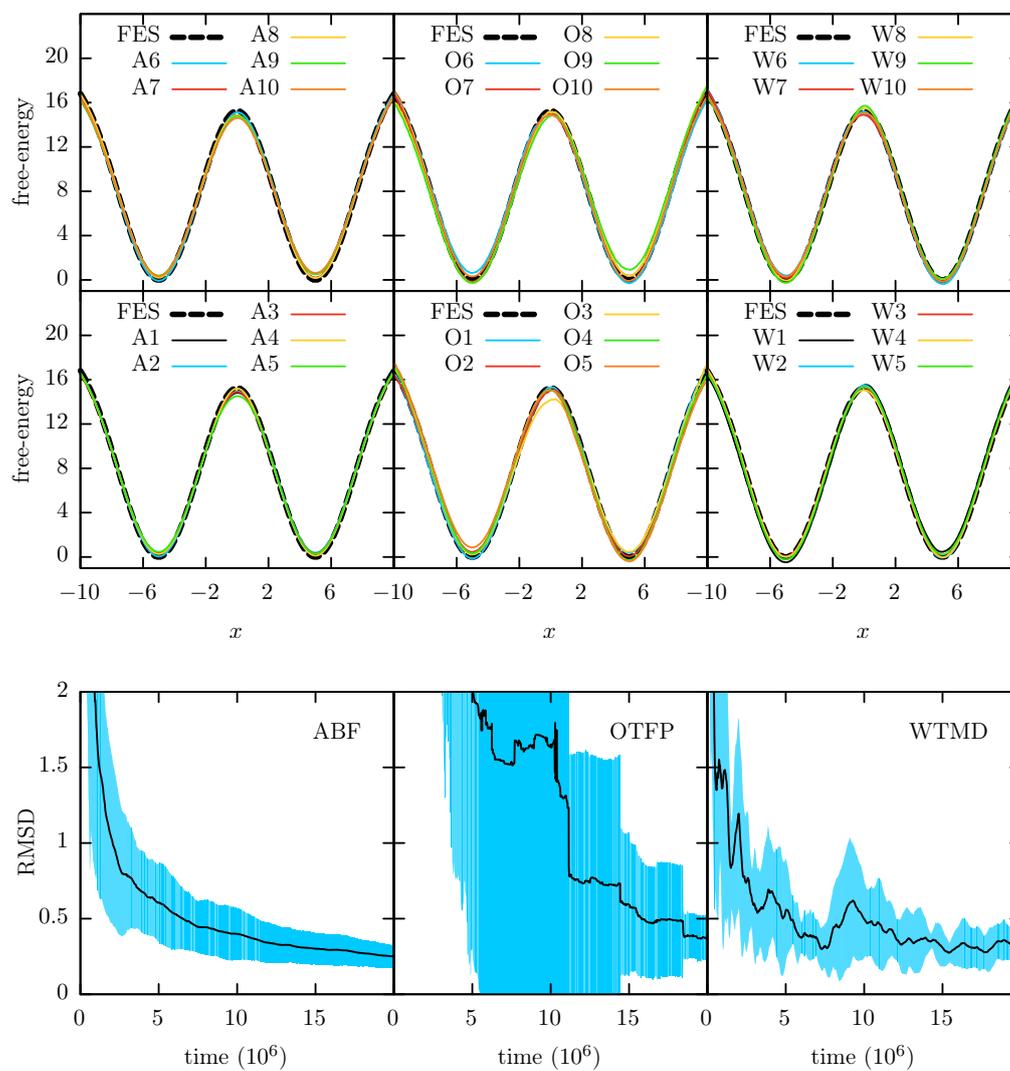
**Figure S7.** Individual RMSD profiles for the 10 simulations of each accelerated method shown in Figure 3 of the manuscript. Average FEP are also shown at the bottom of the figure. The blue shadow corresponds to one standard deviation.



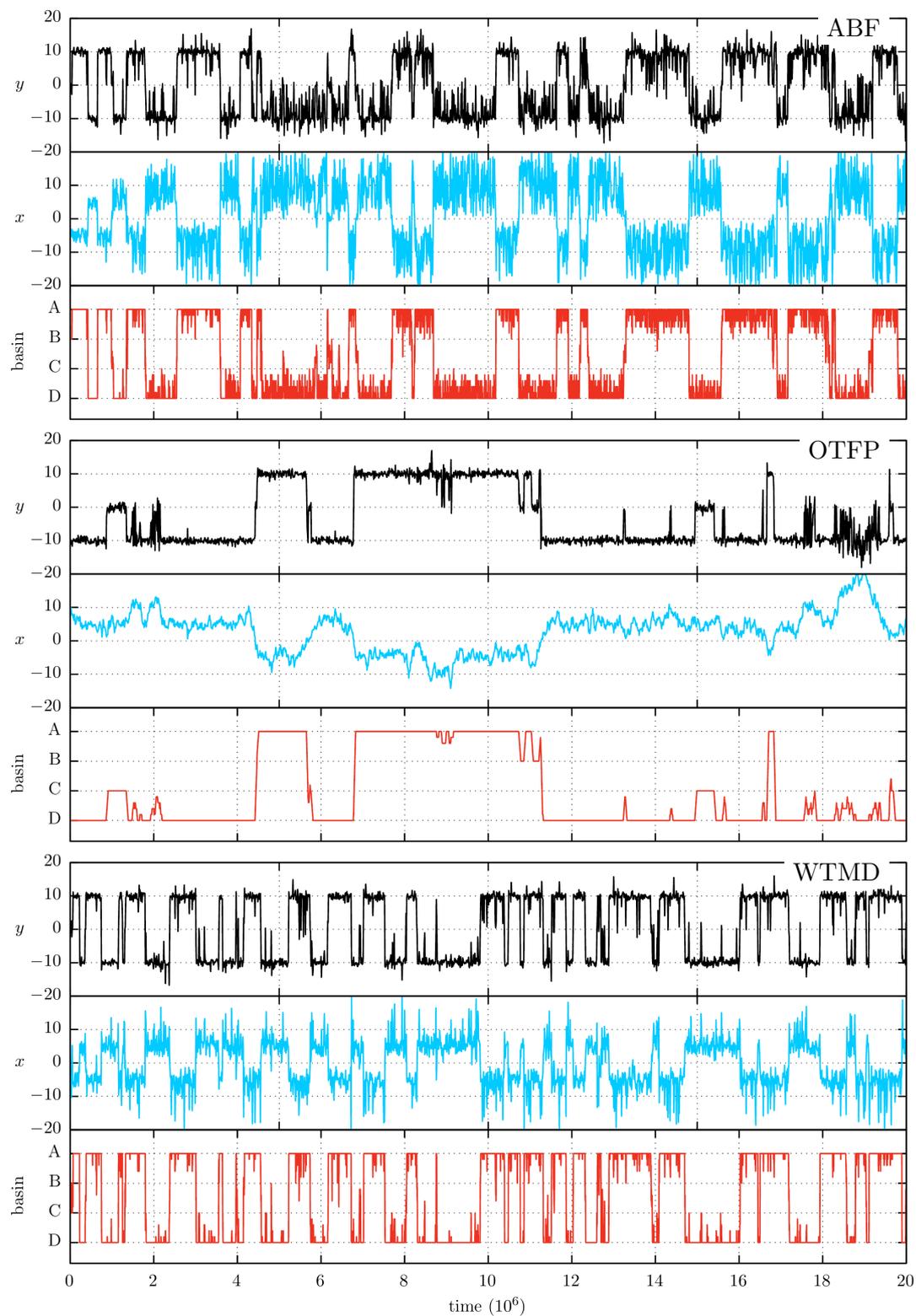
**Figure S8.** Individual RMSD profiles for the 10 simulations of each accelerated method shown in Figure 6 of the manuscript. Average FEP are also shown at the bottom of the figure. The blue shadow corresponds to one standard deviation.



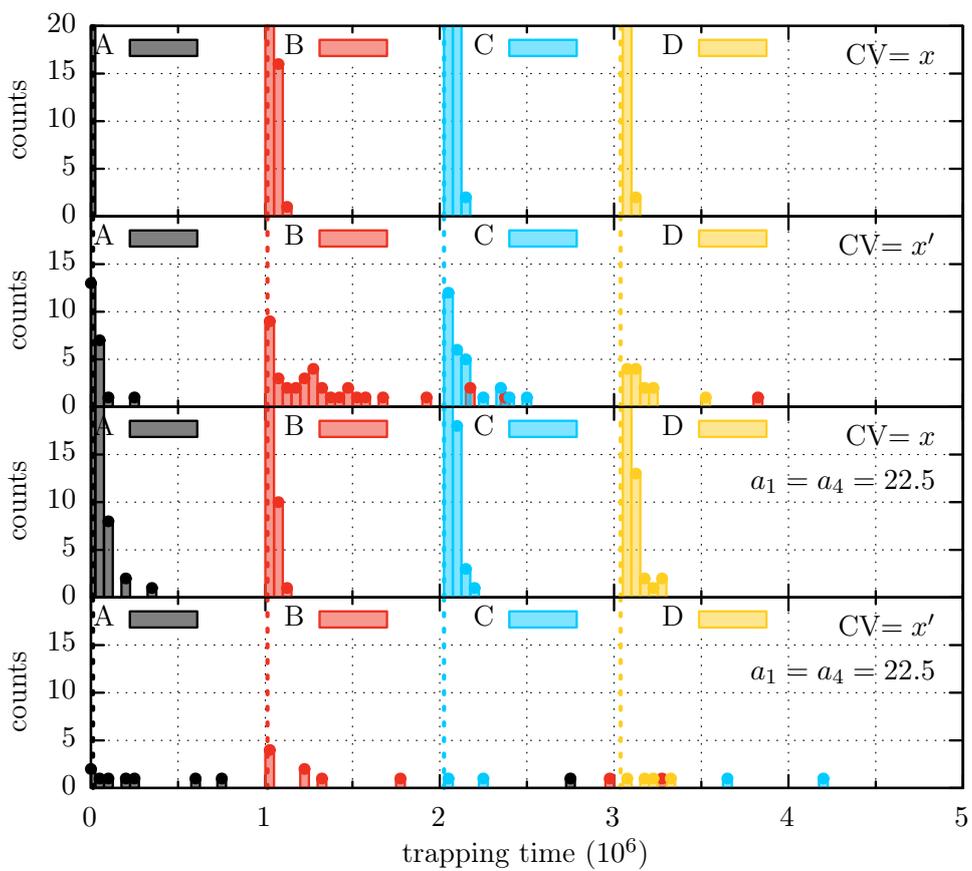
**Figure S9.** Individual RMSD profiles for the 10 simulations of each accelerated method shown in Figure 9 of the manuscript. Average FEP are also shown at the bottom of the figure. The blue shadow corresponds to one standard deviation.



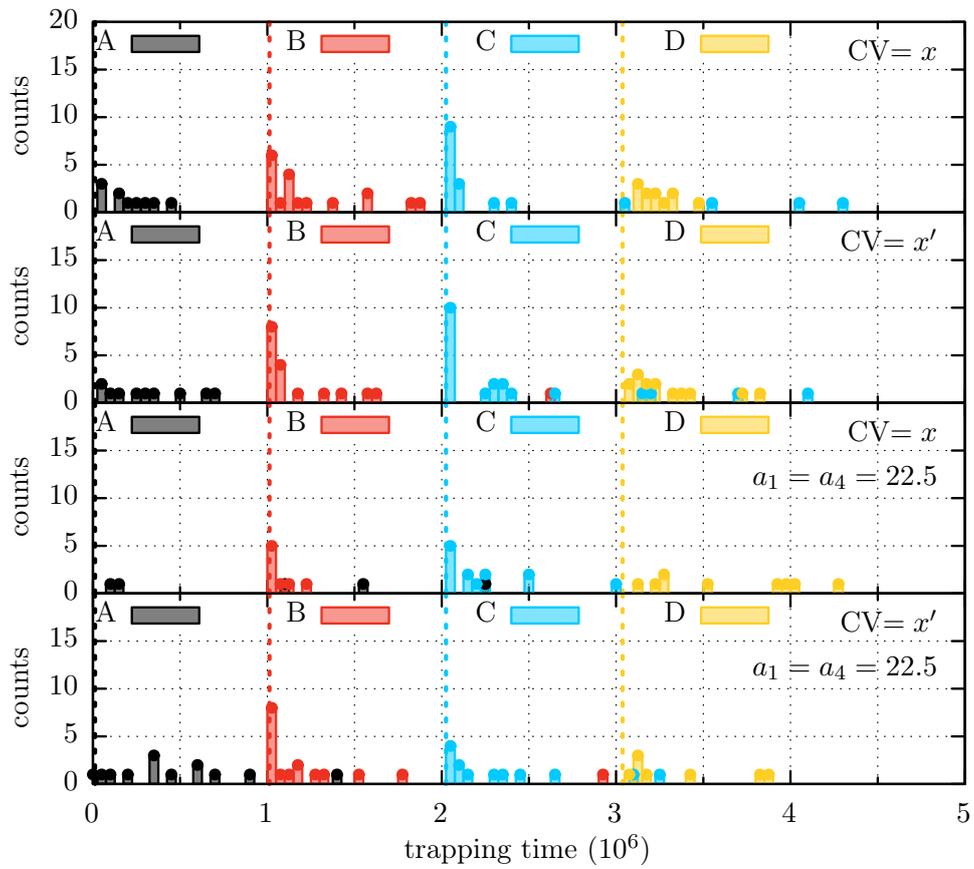
**Figure S10.** FEPs obtained using  $x$  as CV, a deeper A and D PES minima ( $a_1 = a_4 = 22.5$ ) and 10 different simulations for each free energy method as indicated: A1-A10 for ABF, O1-O10 for OTFP and W1-W10 for WTMD. The average convergence profiles are also shown in the bottom of the figure. The light blue region corresponds to one standard deviation. This profiles shows the expected convergence of each individual simulation and should not be confused with the convergence of the average FEP profile.



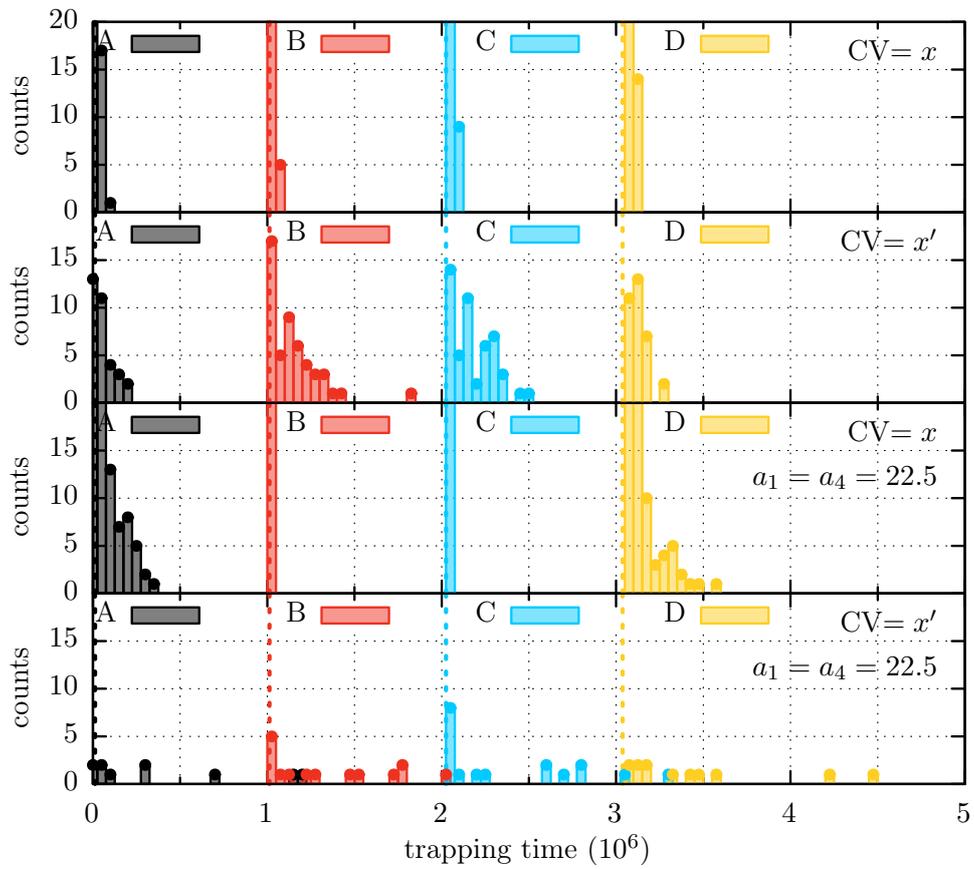
**Figure S11.** The position trace of representative ABE, OTFP and WTMD simulations associated with the results shown in Figure S10. For each method,  $x$ ,  $y$  and basin assignments are shown in black, blue and red respectively.



**Figure S12.** Histograms of “trapping times” for the simulations made with ABF and all the system used in this work. The trapping time are measured using the basin trace shown in figure 4,7,10 and S11.



**Figure S13.** Histogram of “trapping times” for the simulations made with OTFP and all the system used in this work. The trapping time are measured using the basin trace shown in figure 4,7,10 and S7.



**Figure S14.** Histogram of “trapping times” for the simulations made with WTMD and all the system used in this work. The trapping time are measured using the basin trace shown in figure 4,7,10 and S7.