Supplementary Material

aMD input and output parameters

The aMD module in NAMD uses the following parameters:

aMD	turn on/off aMD, default off.
aMDE	the acceleration threshold energy E
aMDalpha	the acceleration factor α, must be a positive number
aMDdihe	turn on/off the aMDd mode, default on.
aMDskip	skip the first aMDskip steps, default 0.
aMDOutFreq	aMD output frequency, default 1.

When *aMD* is turned on, an aMD output line is added to the log file, which contains the the boost potential (dV) at the current timestep and the average boost potential ($dVAVG$) since the last aMD output. By default, the aMDd mode is used and the boost is applied to the dihedral potential. When the parameter *aMDdihe* is turned off, aMD is switched to the aMDT mode and the boost is applied to the total potential.

Benchmark simulation protocols

Benchmark simulations were performed on the protein RmlC (pdb code 1nxm), a 388-residue enzyme from the bacterium *Streptococcus suis*. The simulation system, containing 60,298 atoms in total, include 6168 protein atoms, 18038 TIP3P water molecules, and 16 Na^+ ions. All the benchmark simulations were performed on the supercomputer Ranger at Texas Advanced Computing Center. Each node on Ranger consists of four quad-core AMD opteron processors. All nodes are interconnected using InfiniBand. The benchmark simulations were performed using 2, 4, 5, 6 and 8 nodes, respectively. Each simulation was repeated three times, and benchmark data provided in the log files were averaged to give the benchmark performance (ns/day). All the simulations were performed under NVT conditions using a 2-fs timestep, and a 1-1-2 multiple-time-stepping algorithm.

The cutoff for short-range non-bonded interactions was 12 Å, with a switching distance of 10 Å. Long-range electrostatic forces were calculated using the Particle Mesh Ewald (PME) method (31) with a grid density of at least $1/\text{Å}^3$. The temperature was maintained at 300 K for all simulations using Langevin dynamics.

Metadynamics simulation protocols

A 100-ns metadynamics simulation was performed for the gas-phase alanine dipeptide using the collective variable module in NAMD (14). The same conditions in gas-phase cMD and aMD simulations were used here. A bin width of 5° and a Gaussian biasing potential of width 10° and height 0.1 kcal/mol were chosen, resulting a free energy map with a resolution of 5°. For comparison with the rest of the simulations, we converted the resolution of the free energy map to 15° by combining data from nine neighboring bins:

$$\Delta G^{\dagger}_{i,j} = -k_B T ln\Bigg[\sum_{3i-2,3j-2}^{3i,3j} exp(-\beta \Delta G_{m,n})/9\Bigg]$$

where $\Delta G_{m,n}$ is the free energy value at (Φ_m, Ψ_n) in the original map, and $\Delta G^{\dagger}_{i,j}$ is the free energy value at (Φ_i, Ψ_j) in the new map.

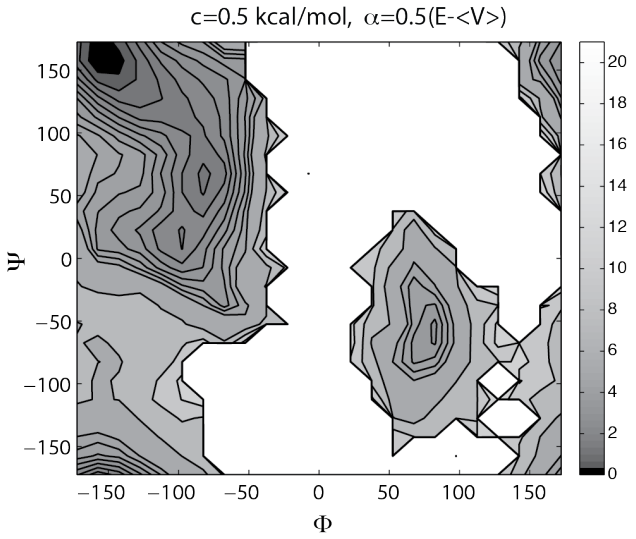

Figure S1: Replica simulation of the gas-phase alanine dipeptide aMD simulation with c=0.5 kcal/mol and α=0.5($E - \langle V \rangle$) (see Fig 4).

Sample aMD configuration file

```
structure    wtdia.psf
coordinates    wtdia.pdb

set temperature    300
set outputname     sample-aMD
set inputname      mineq-wtdia-01

bincoordinates     $inputname.coor
binvelocities      $inputname.vel
extendedSystem    $inputname.xsc
firsttimestep      0

paraTypeCharmm      on
parameters          par_all27_prot_lipid.prm

wrapWater           on
wrapAll             on

exclude             scaled1-4
1-4scaling          1.0
cutoff              12.
switching           on
switchdist          10.
pairlistdist        13.5
```

```
timestep            2.0
rigidBonds          all
nonbondedFreq       1
fullElectFrequency  2
stepspercycle       10

PME                 yes
PMEGridSizeX        30
PMEGridSizeY        30
PMEGridSizeZ        30

langevin            on
langevinDamping     1.0
langevinTemp        $temperature
langevinHydrogen    off

outputName          $outputname
restartname         $outputname.restart
dcdfile             $outputname.dcd
xstFile             $outputname.xst

restartfreq         500
dcdfreq             50
xstFreq             50
outputEnergies      50
outputPressure      50
```

```
# AMD Settings
aMD             on
aMDdihe         on
aMDE            14.
aMDalpha        5.5
aMDOutFreq      50

run 50000000
```