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 $12\,\text{Å}$, with a switching distance of $10\,\text{Å}$. 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 $300\,\text{K}$ 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 $0.1\,\text{kcal/mol}$ 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:

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

where $\Delta G_{m,n}$ is the free energy value at (Φ_m, Ψ_n) in the original map, and $\Delta G_{i,j}^{\dagger}$ is the free energy value at (Φ_i, Ψ_j) in the new map.
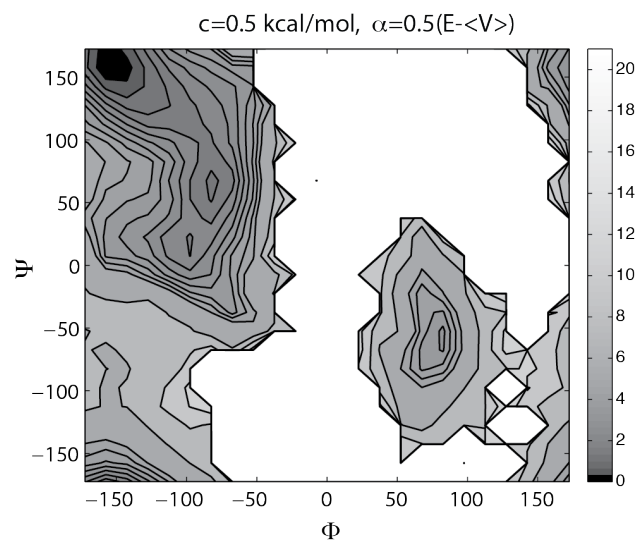
Figure S1: Replica simulation of the gas-phase alanine dipeptide aMD simulation with c=0.5 kcal/mol and $\alpha=0.5(E - \langle V \rangle)$ (see Fig 4).