Text S2.

Employing reweighted aMD trajectories in the principal component analyses

The principal component analysis (PCA) plots presented in this work follow the procedure outlined by Pierce et al. and employ a 2D histogram across the PC1 and PC2 coordinates [1]. PC space is divided into bins of dimension 1Å x 1Å, and points sampled during the aMD simulations are placed into their respective bins. To facilitate this procedure computationally, we utilize an indicator function, $\delta_{k,ij}$, that accounts for whether each point in PC space, (PC1, PC2), falls into the bin (PC1$_i$, PC2$_j$) for a given trajectory frame, k (Eq. 1).

\[
(1) \quad \delta_{k,ij} = \begin{cases} 
1, & (PC1_k,PC2_k) \in (PC1_i,PC2_j) \\
0, & \text{otherwise}
\end{cases}
\]

Using $\delta_{k,ij}$, the histogram at bin (PC1$_i$, PC2$_j$) can be reweighted using Eq. 2, where K is the total number of trajectory frames and $\Delta V_k$ is the total boost potential applied at frame k.

\[
(2) \quad H_{ij} = \sum_{k=1}^{K} \delta_{k,ij} \exp(\beta \Delta V_k)
\]

In our analyses, we perform this reweighting using a tenth-order Maclaurin series expansion of the exponential (Eq. 3).
\[
\exp(\beta \Delta V_k) \approx 1 + \frac{\beta \Delta V_k}{1!} + \frac{(\beta \Delta V_k)^2}{2!} + \frac{(\beta \Delta V_k)^3}{3!} + \ldots + \frac{(\beta \Delta V_k)^{10}}{10!}
\]

After reweighting all the histograms in PC space, we obtain the PC1-PC2 free energy plot shown in Figure 5 using Eq. 4,

\[(4) W_{ij} = -k_BT \ln H_{ij} + W_0 ,\]

where \(k_B\) is the Boltzmann constant, \(T\) is temperature (taken to be 300K) and \(W_0\) is a constant chosen to set the free energy minimum to zero.

References