Bringing a molecular system out of equilibrium:

Mechanical unfolding Steered Molecular Dynamics (SMD)
WHAM Free-Energy reconstruction analysis

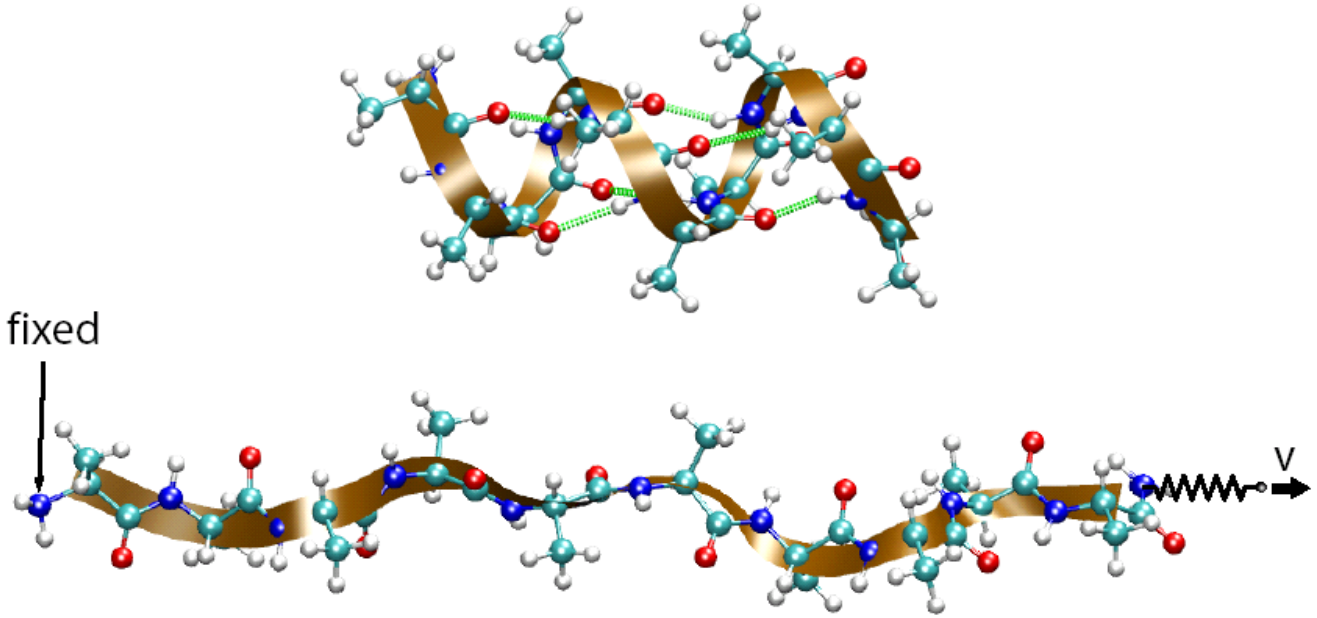
Thermal unfolding-refolding Simulated Annealing technique (SA)

Readings:

Bernardi RC, Melo MC, Schulten K. Enhanced sampling techniques in molecular dynamics simulations of biological systems. Biochim Biophys Acta. 2015 May;1850(5): 872-7. doi: 10.1016/j.bbagen.2014.10.019.

Hao GF, Xu WF, Yang SG, Yang GF. Multiple Simulated Annealing-Molecular Dynamics (MSA-MD) for Conformational Space Search of Peptide and Miniprotein. Sci Rep. 2015 Oct 23;5:15568. doi: 10.1038/srep15568.

Helix-Coil Transition of Deca-Alanine in Vacuum



Main purpose:

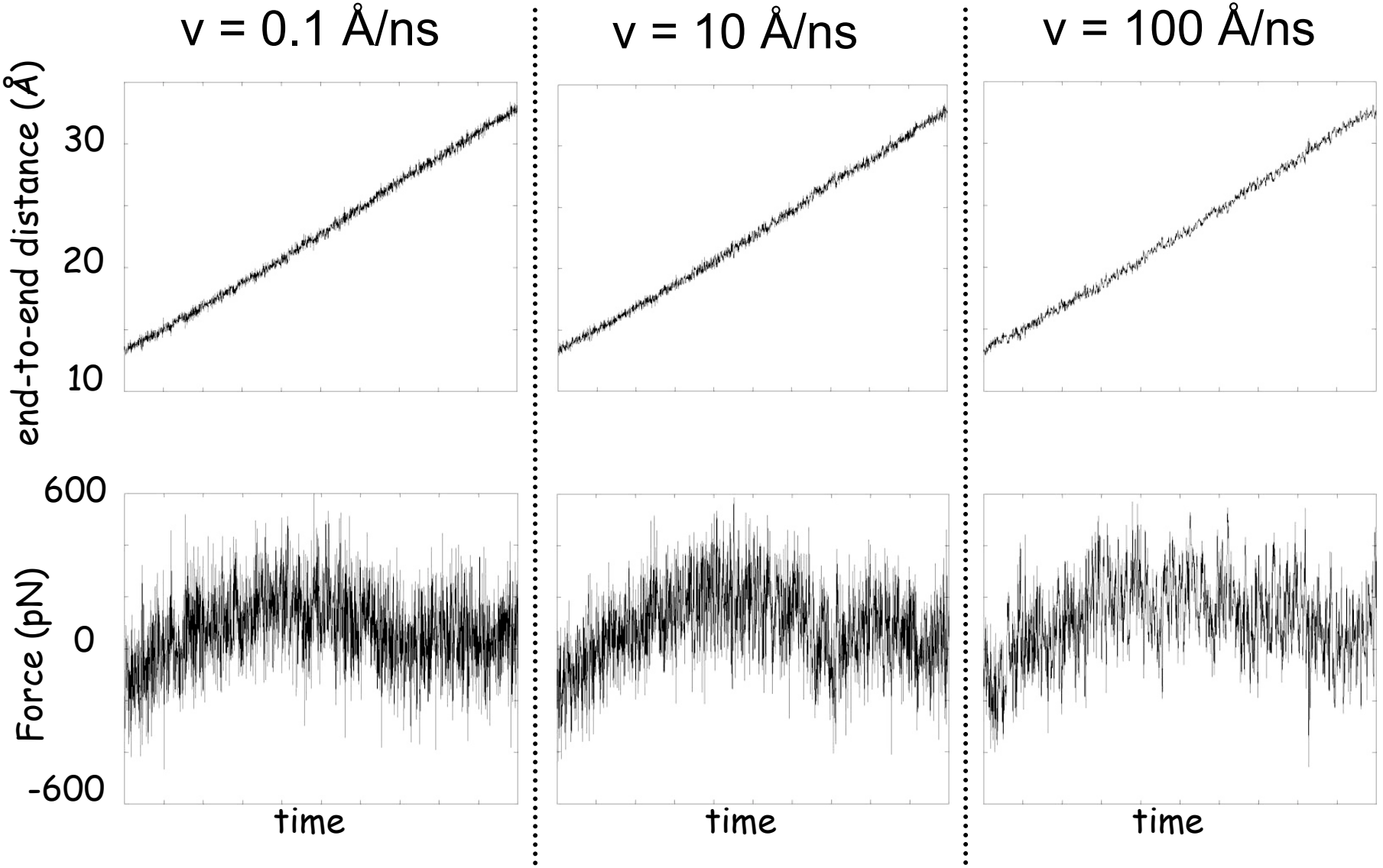
Systematic study of the methodology of free energy calculation

- Which averaging scheme works best
  with small number (~10) of trajectories ?

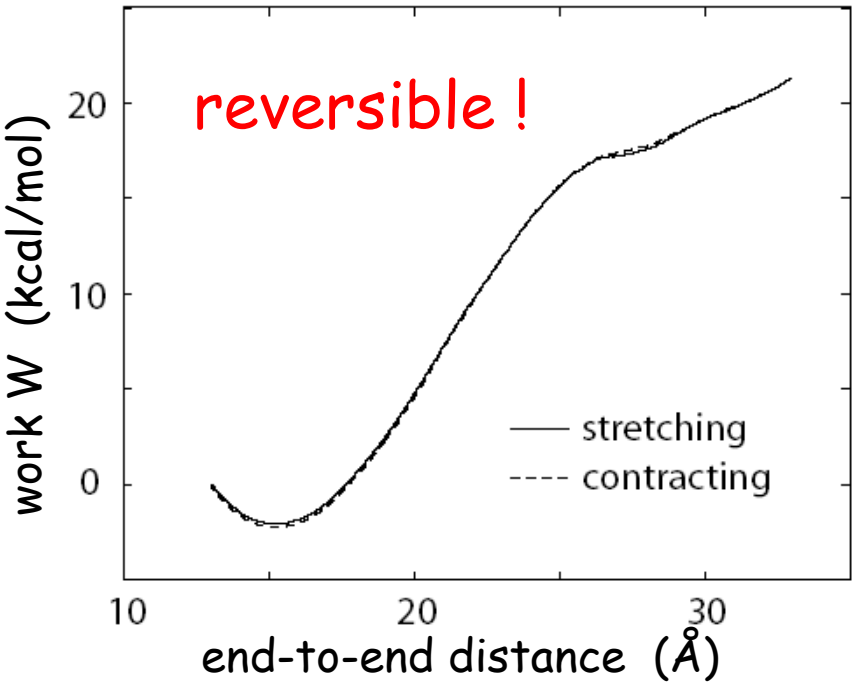
Why decaalanine in vacuum?

- small, but not too small: 104 atoms
- short relaxation time → reversible pulling → exact free energy

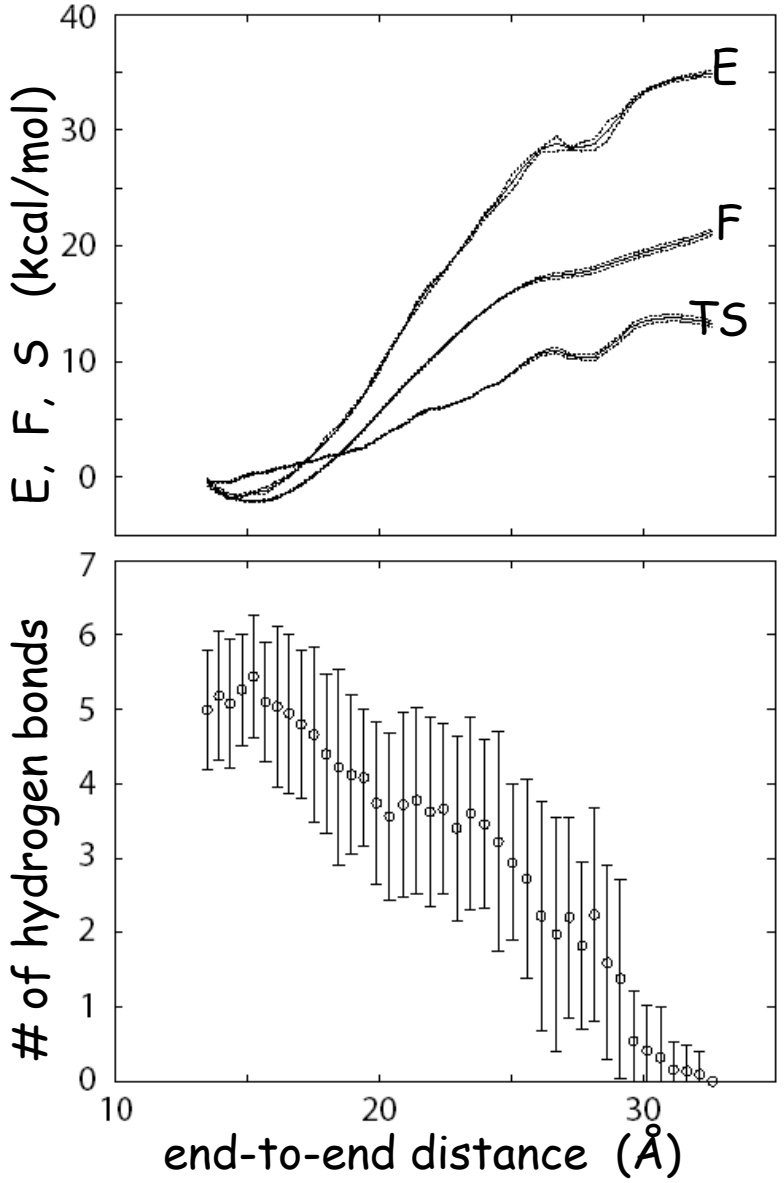
Typical Trajectories



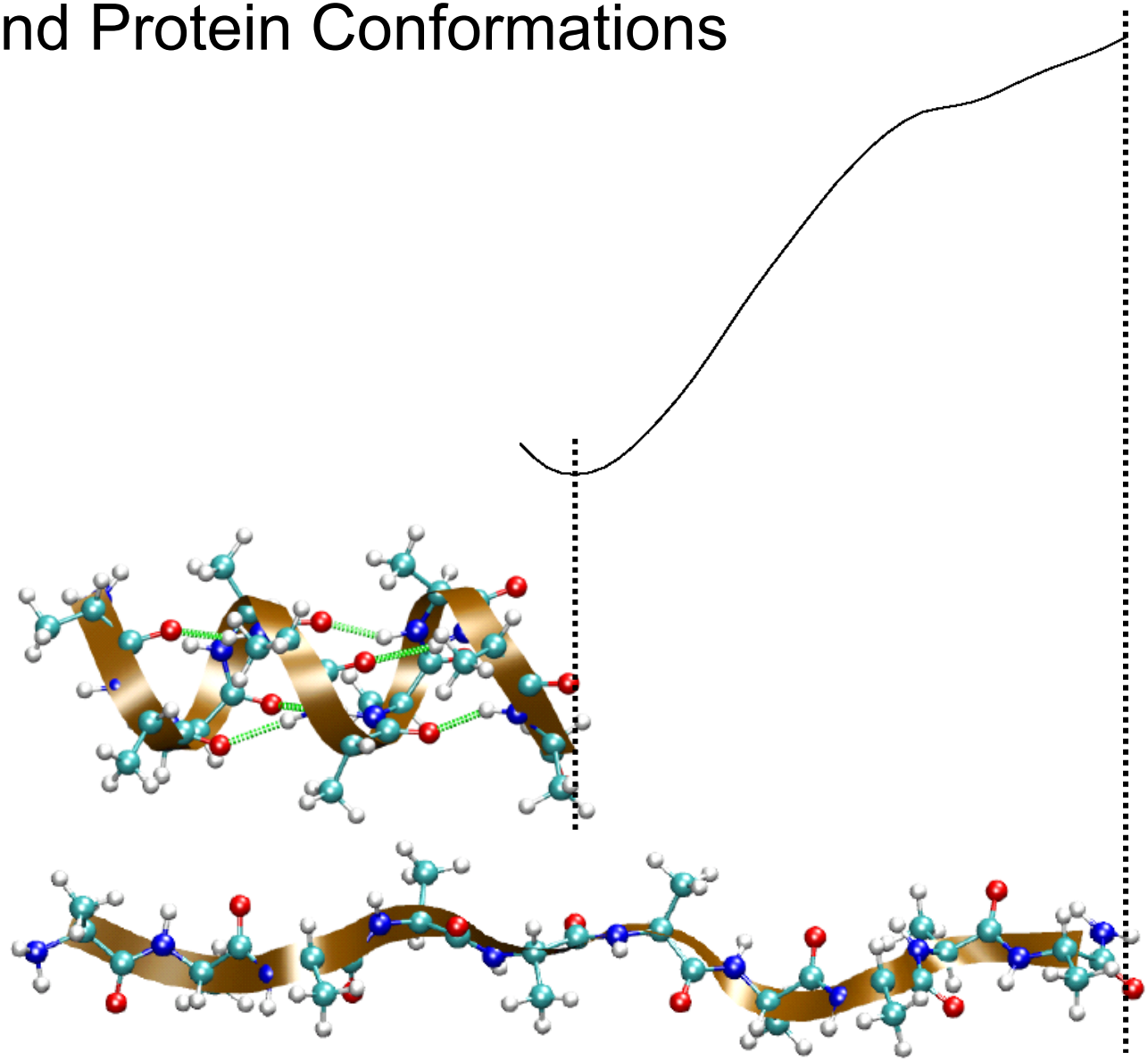
Reversible Pulling (v = 0.1 Å/ns)



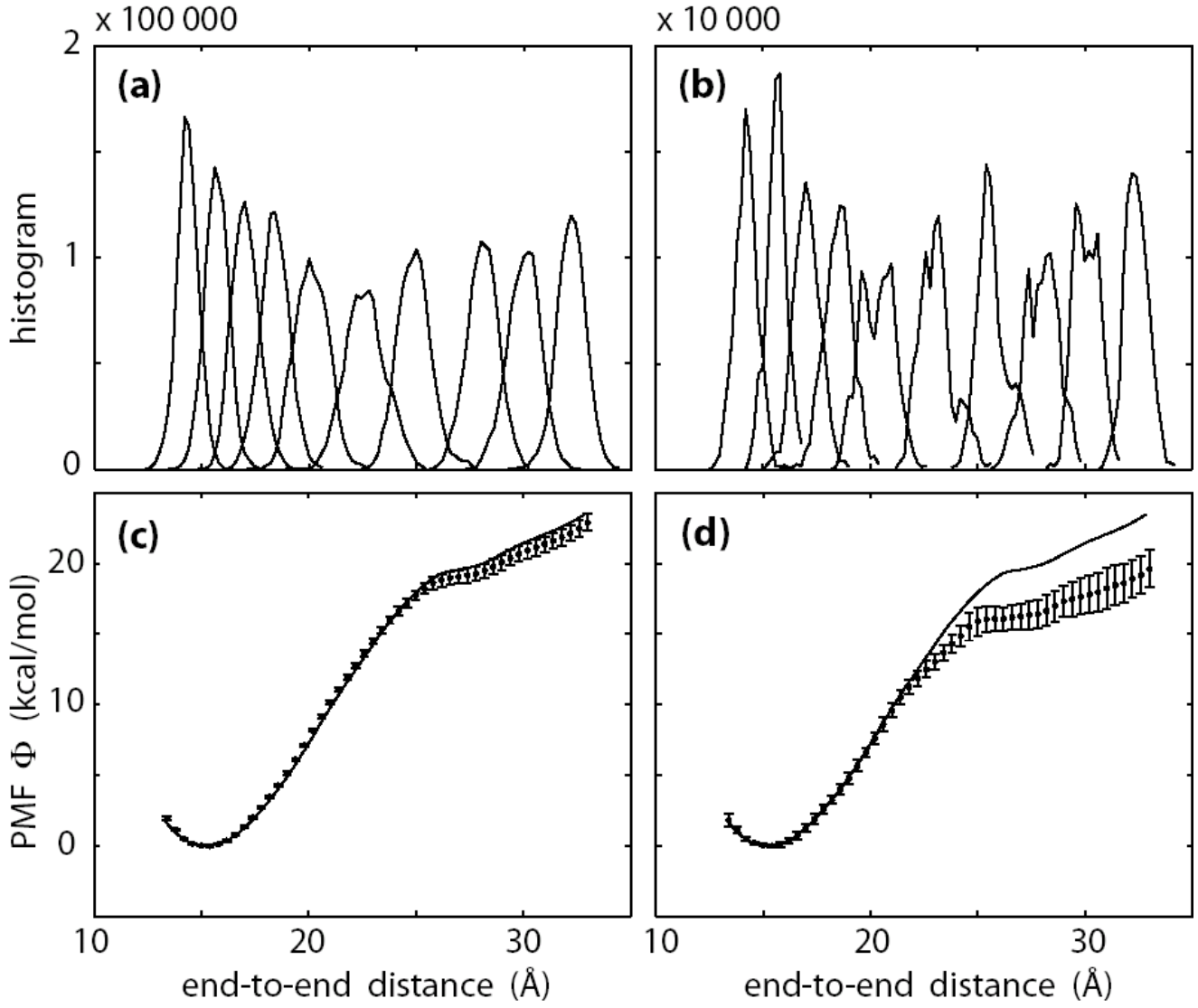
$$\Delta F = \langle W \rangle$$
$$TS = E - F$$



PMF and Protein Conformations

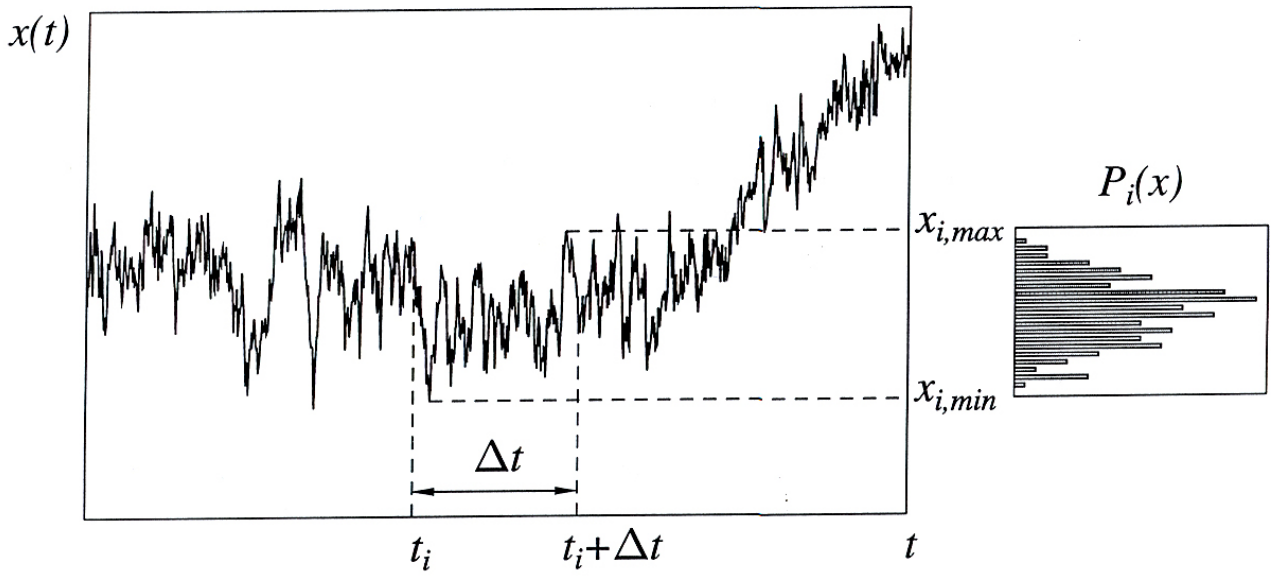


Umbrella Sampling w/ WHAM



Weighted Histogram Analysis Method

SMD trajectory



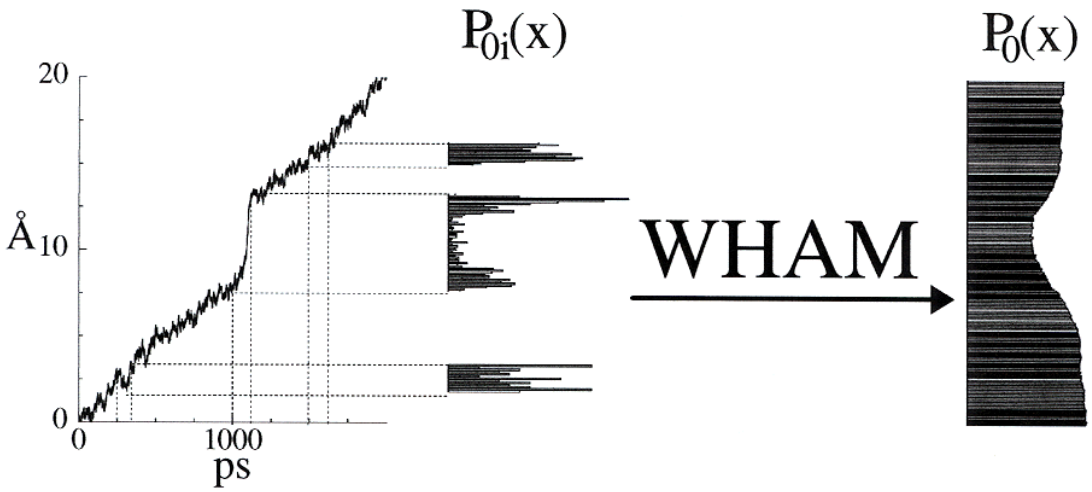
Biasing potential:

$$U_i(x) = \frac{1}{\Delta t}\int_{t_i}^{t_i+\Delta t} \frac{k}{2}(x - vt)^2 dt = \frac{k}{2}\left(x - vt_i - \frac{v\Delta t}{2}\right)^2 + \frac{k(v\Delta t)^2}{24}$$

Choice of Δt:

$$v\Delta t = \delta x, \quad \text{such that} \quad \exp\left(-\frac{k\,\delta x^2}{2k_B T}\right) \leq \varepsilon \to 0$$

Weighted Histogram Analysis Method



$P_{0i}(x)$, i = 1,2,…,M: overlapping local distributions

$P_0(x)$: reconstructed overall distribution

Underlying potential:
$U_0(x) = -k_B T \ln P_0(x)$

To reconstruct $P_0(x)$ from $P_{0i}(x)$ (i=1,2,…,M)

$$P_0(x) = \frac{\Sigma_{i=1}^{M} P_{0i}(x) N_i}{\Sigma_{i=1}^{M} \frac{Z_0}{Z_{0i}} P_i(x) N_i} \; ; \qquad \frac{Z_0}{Z_{0i}} = \int_{x_0}^{x_f} P_0(x) P_i(x) dx \; ,$$

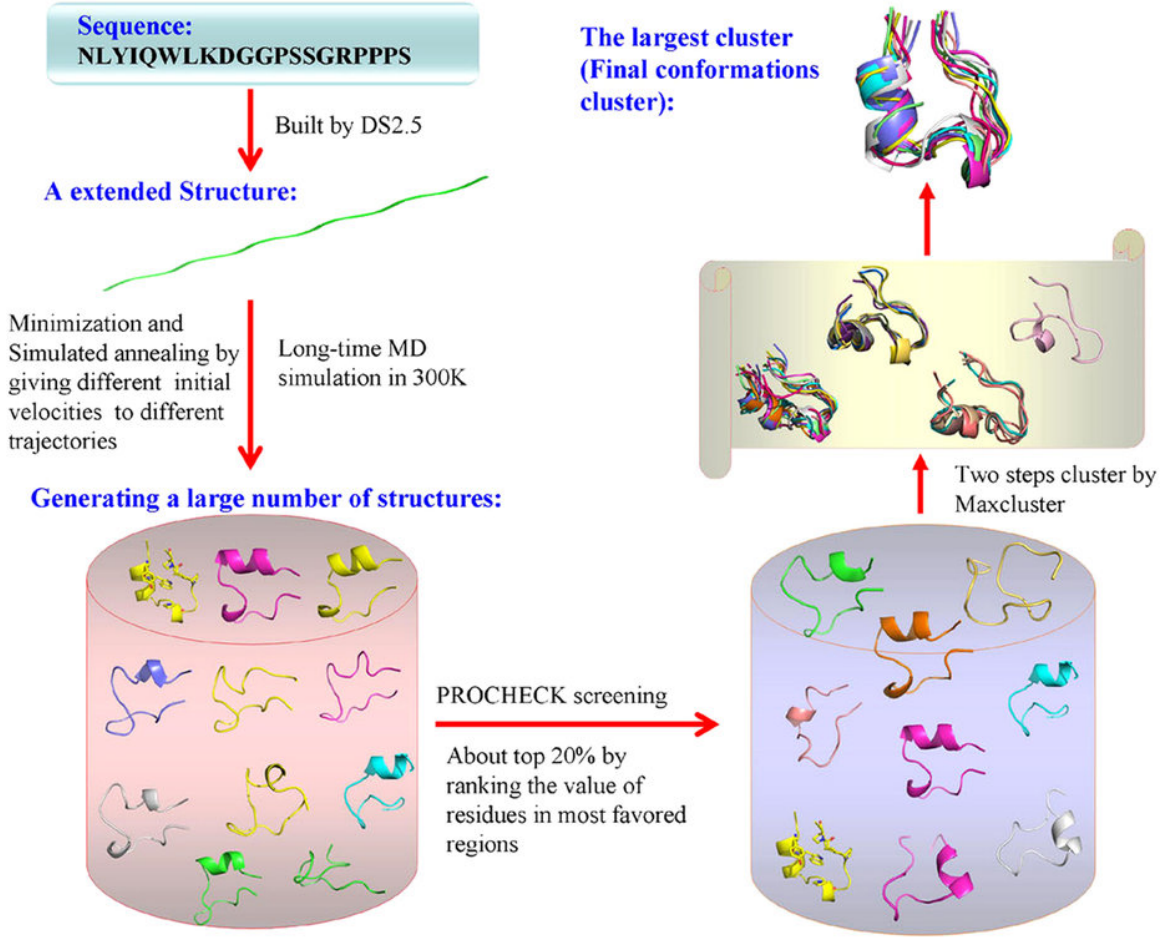
N_i = number of data points in distribution i,

$$P_i(x) = \frac{1}{\Delta t} \int_{t_i}^{t_i + \Delta t} \exp[-U_s(x,t)/k_B T] dt$$

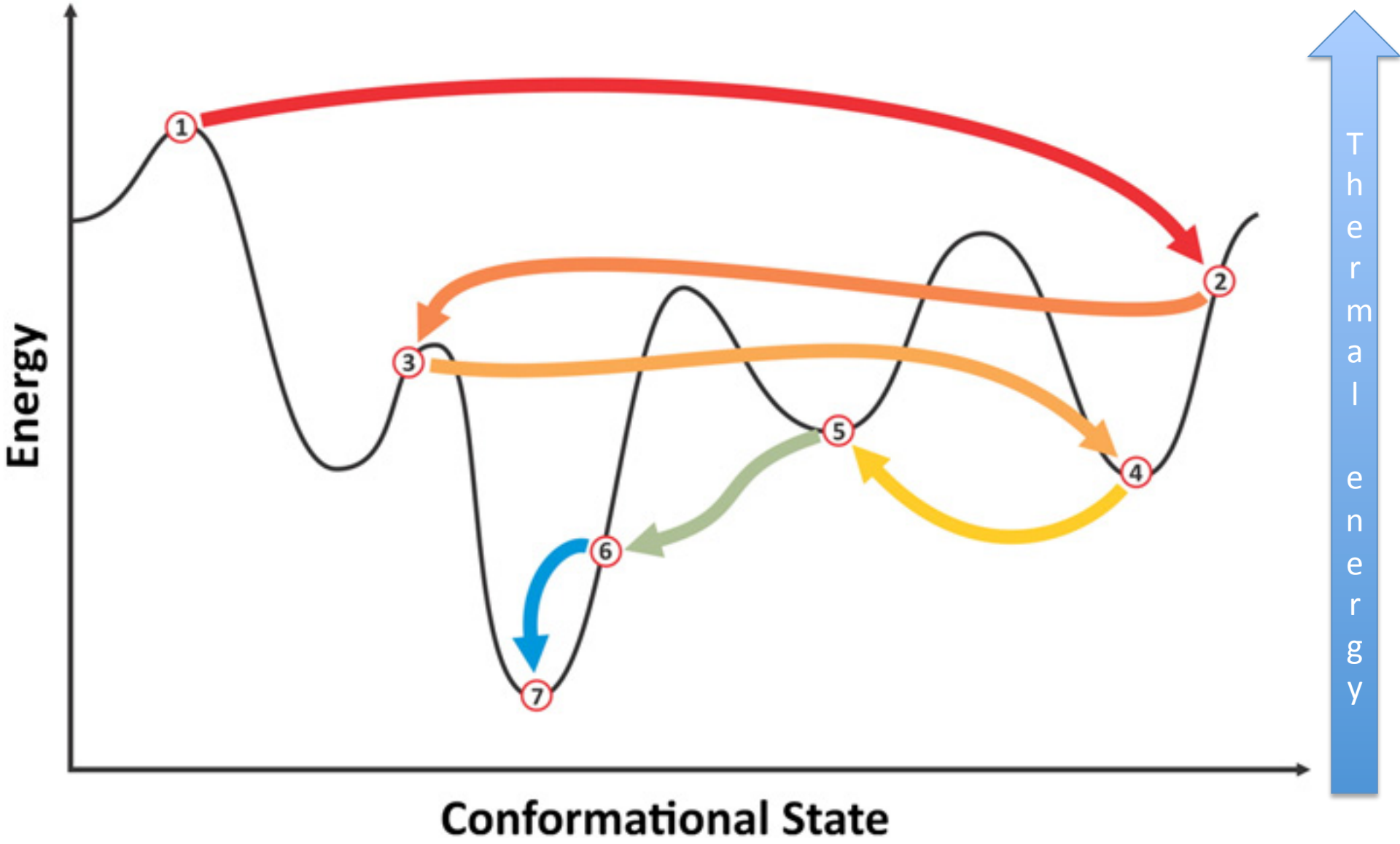
Biasing potential: $U_s(x,t) = k(x-vt)^2$

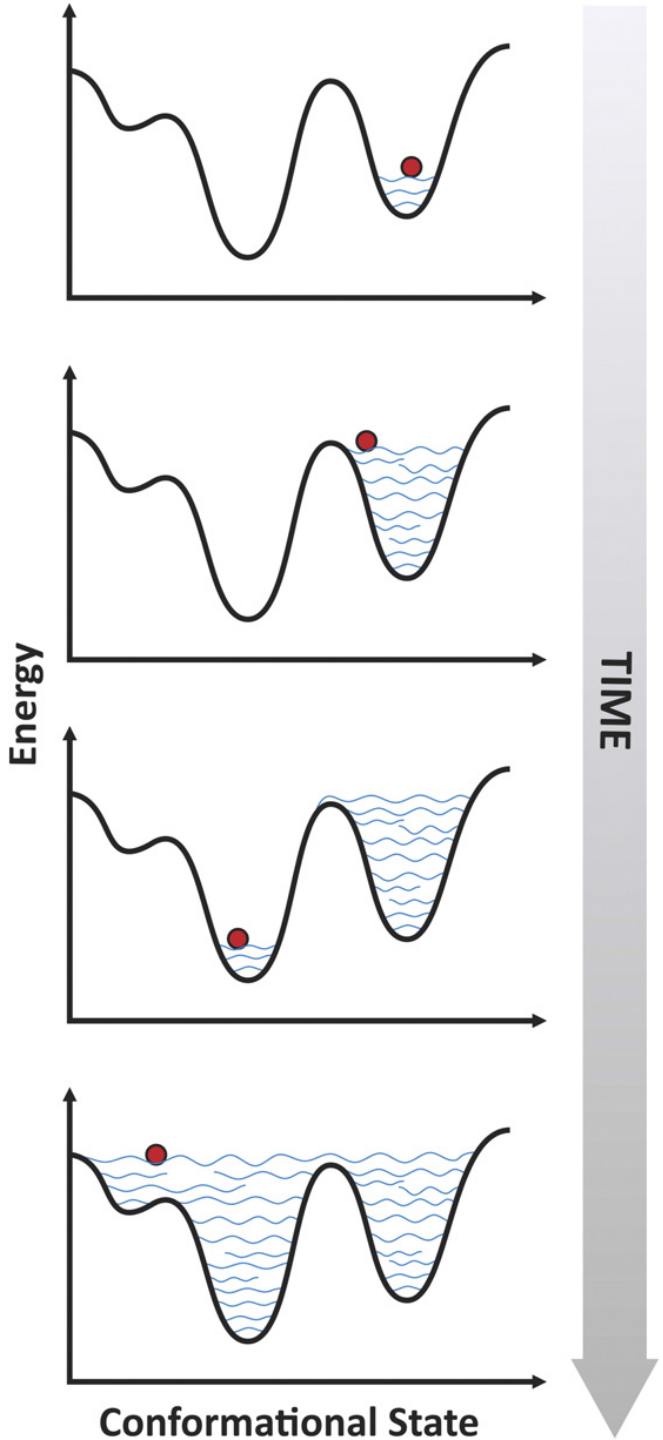
Simulated Annealing-MD

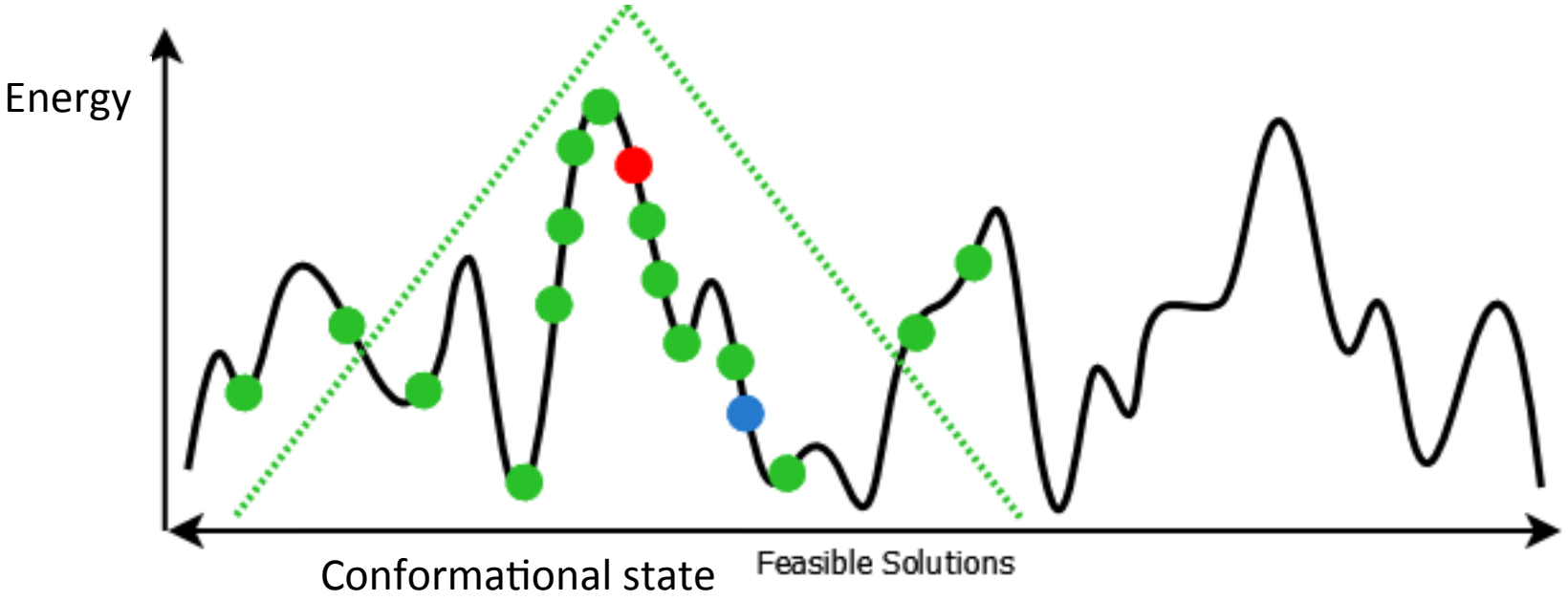
Refolding



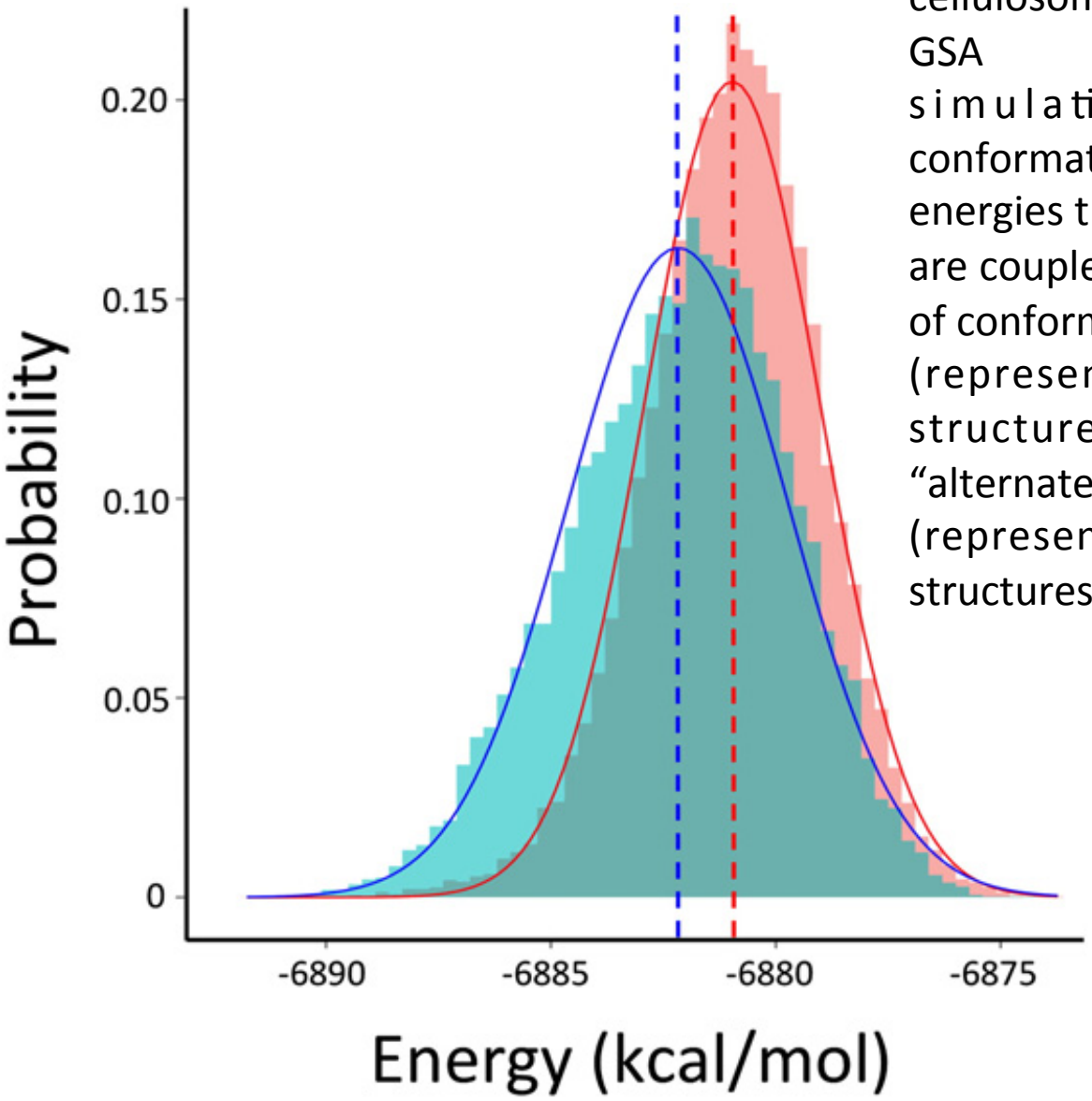
Hao GF, Xu WF, Yang SG, Yang GF Sci Rep. 2015 Oct 23;5:15568. doi: 10.1038/srep15568.


Energy
Conformational State
Thermal energy
1
2
3
4
5
6
7


Energy
TIME
Conformational State

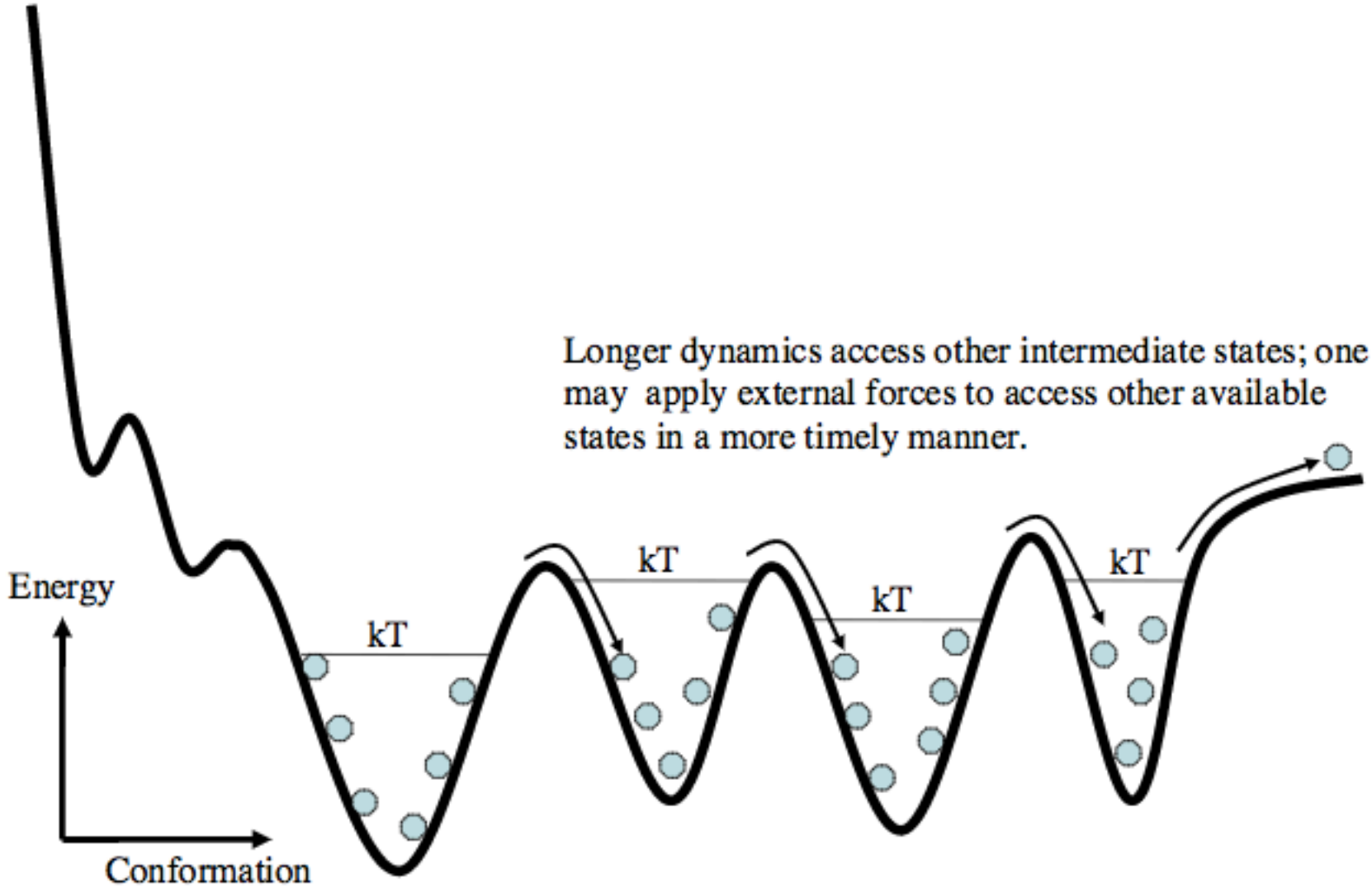


Collect ‘related’ states: clustering

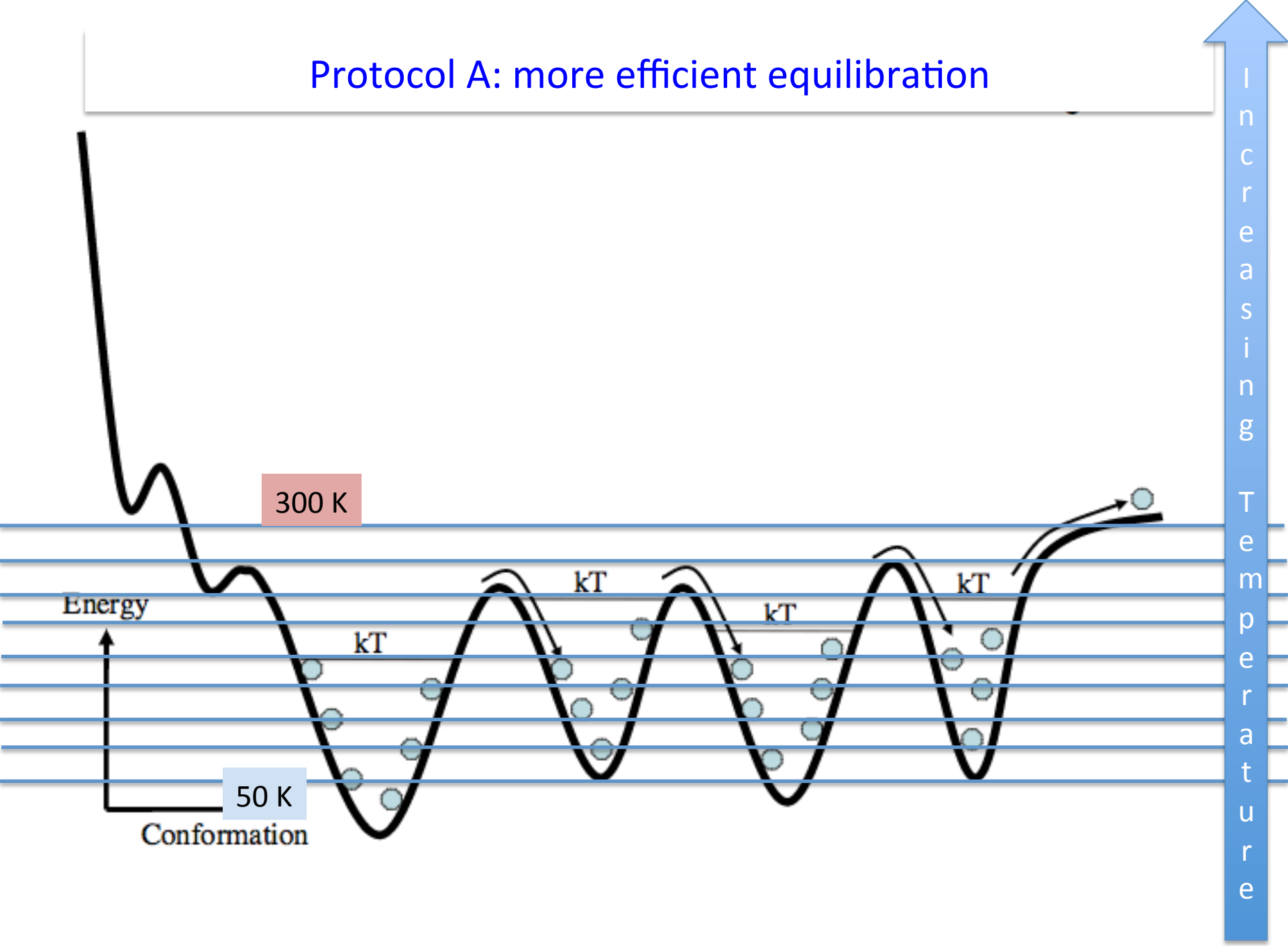


Potential energy distribution of the cellulosome fragment after 10,000 steps of GSA simulations. The 51,200 different conformations resulted in 51,200 different energies that are coupled according to the two main clusters of conformations. The “native” cluster (represented in red) occurs in 34,936 structures, or 68% of the cases. The “alternate” cluster (represented in blue) occurs in 16,264 structures, or 32% of the cases.

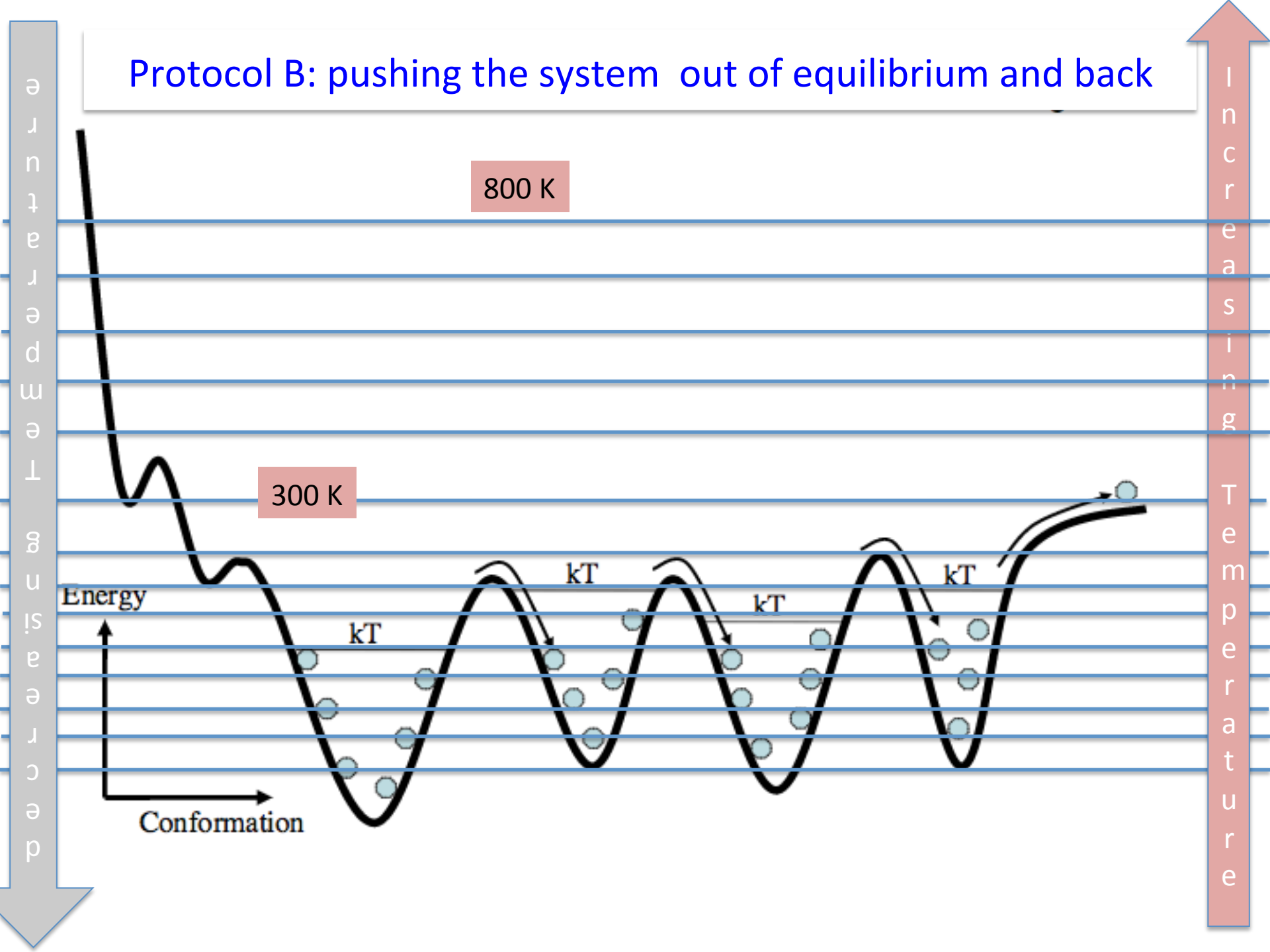
From the Mountains to the Valleys



Protocol A: more efficient equilibration



Protocol B: pushing the system out of equilibrium and back



A word of caution:

Force Fields are optimised for the temperatures around 300K!!!

The system can be ‘pushed out of equilibrium’ but the states we need to collect have to be ‘equilibrium-like’ from the 300K distribution.