A Winter Short Course on Statistical Mechanics for Molecular Simulations

Lecture 5: Free Energy Calculations

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Good Practices in Free-Energy Calculations

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As access to computational resources continues to increase, free-energy calculations have emerged as a powerful tool that can play a predictive role in a wide range of research areas. Yet, the reliability of these calculations can often be improved significantly if a number of precepts, or good practices, are followed. Although the theory upon which these good practices rely has largely been known for many years, it is often overlooked or simply ignored. In other cases, the theoretical developments are too recent for their potential to be fully grasped and merged into popular platforms for the computation of free-energy differences. In this contribution, the current best practices for carrying out free-energy calculations using free energy perturbation and nonequilibrium work methods are discussed, demonstrating that at little to no additional cost, free-energy estimates could be markedly improved and bounded by meaningful error estimates. Monitoring the probability distributions that underlie the transformation between the states of interest, performing the calculation bidirectionally, stratifying the reaction pathway, and choosing the most appropriate paradigms and algorithms for transforming between states offer significant gains in both accuracy and precision.

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Perspective

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Practical Aspects of Free-Energy Calculations: A Review

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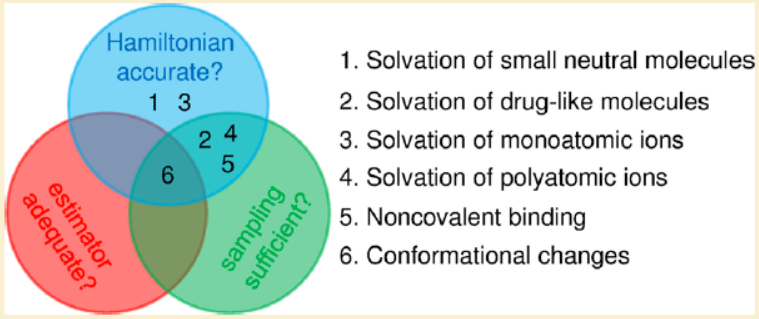
ABSTRACT: Free-energy calculations in the framework of classical molecular dynamics simulations are nowadays used in a wide range of research areas including solvation thermodynamics, molecular recognition, and protein folding. The basic components of a free-energy calculation, that is, a suitable model Hamiltonian, a sampling protocol, and an estimator for the free energy, are independent of the specific application. However, the attention that one has to pay to these components depends considerably on the specific application. Here, we review six different areas of application and discuss the relative importance of the three main components to provide the reader with an organigram and to make nonexperts aware of the many pitfalls present in free energy calculations.



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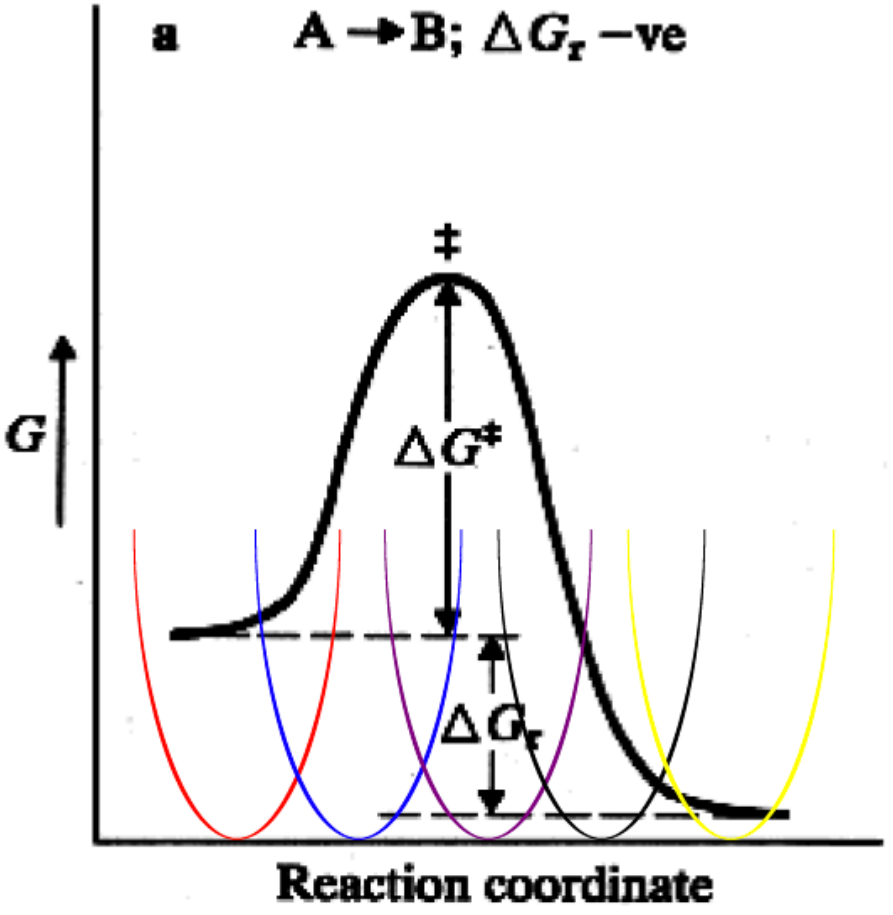
Enhanced Sampling Methods

- Biasing potential methods
  - Umbrella sampling
  - Metadynamics
  - Steered MD/Local elevation/Conformational flooding/adaptive force bias…
- Multicanonical methods
  - Parallel Tempering (Replica exchange)
  - Integrate-over-temperature (Yi Qin Gao)
- Transition path methods…

Umbrella Sampling

- Sample with umbrella potential U'(x)
- Compute biased probability P'(x)
- Estimate unbiased free energy
  $A(x) = -k_B T \ln P'(x) - U'(x) + F$
- F is undetermined
- Multiple biasing potentials can be used (multiple windows)



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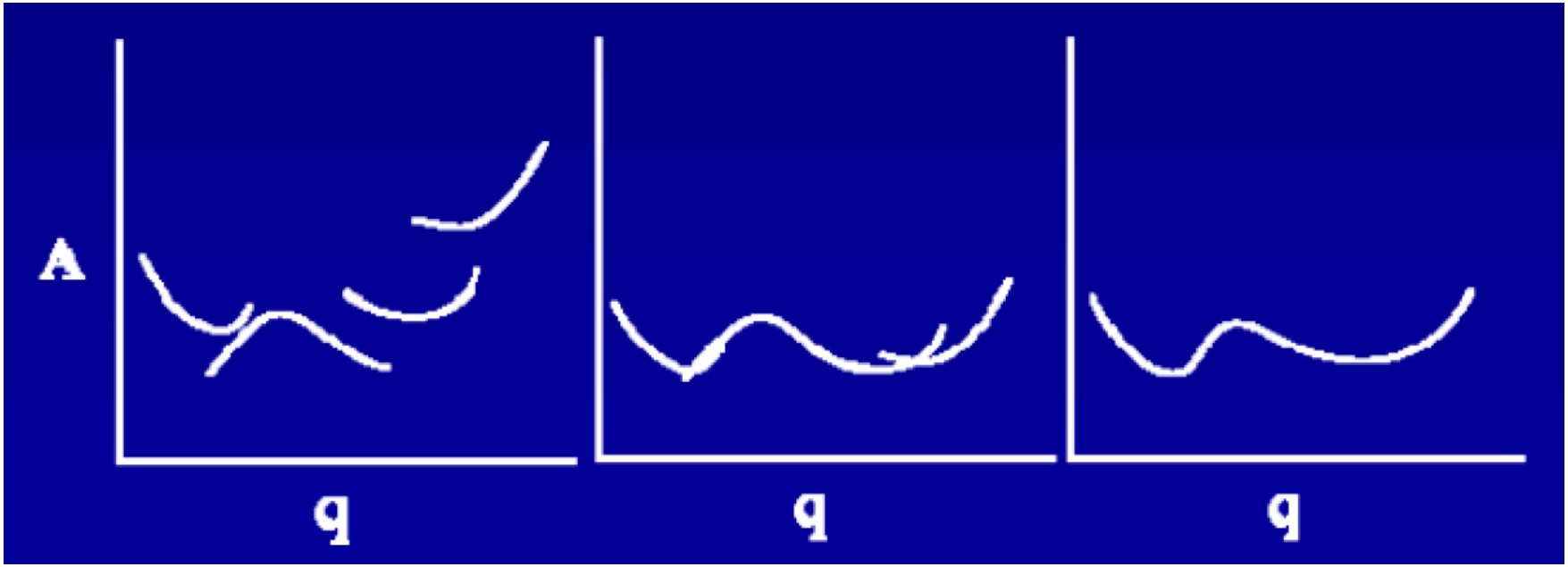
Weighted Histogram Analysis Method

- Potentials can be combined using WHAM (Kumar, et al. J Comput Chem, 13, 1011,1992)



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Running US simulation

- Choose the reaction coordinate
- Choose the number of windows and the biasing potential
- Run the simulations
- Compute time series for the value of the reaction coordinate (histograms)
- Apply the WHAM equations

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- Convergence is probed by two criteria:
  - Convergence of individual windows. The statistical error can be measured through block-averaging over sub-runs
  - Appropriate overlap of free energy profiles between adjacent windows
- The approaches to estimate errors for the different methods based on a single simulation only reflect the statistical precision of the method
- Statistical accuracy can be derived from an ensemble of simulations starting from different regions in phase space

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Example

- Translocation of C60 into DPPC bilayer
- Reaction coordinate : Distance between the COM of C60 and COM of DPPC membrane
- 9 windows : 0 – 32 Å, 4 Å spacing
- Harmonic constraint force
- k = 0.5 kcal/mol/Å^2

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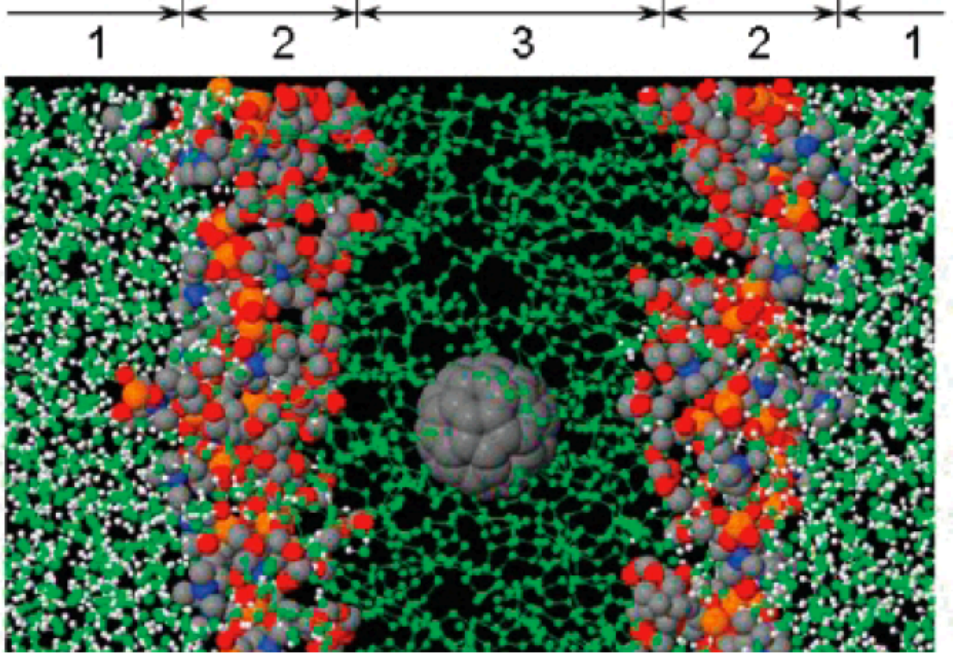
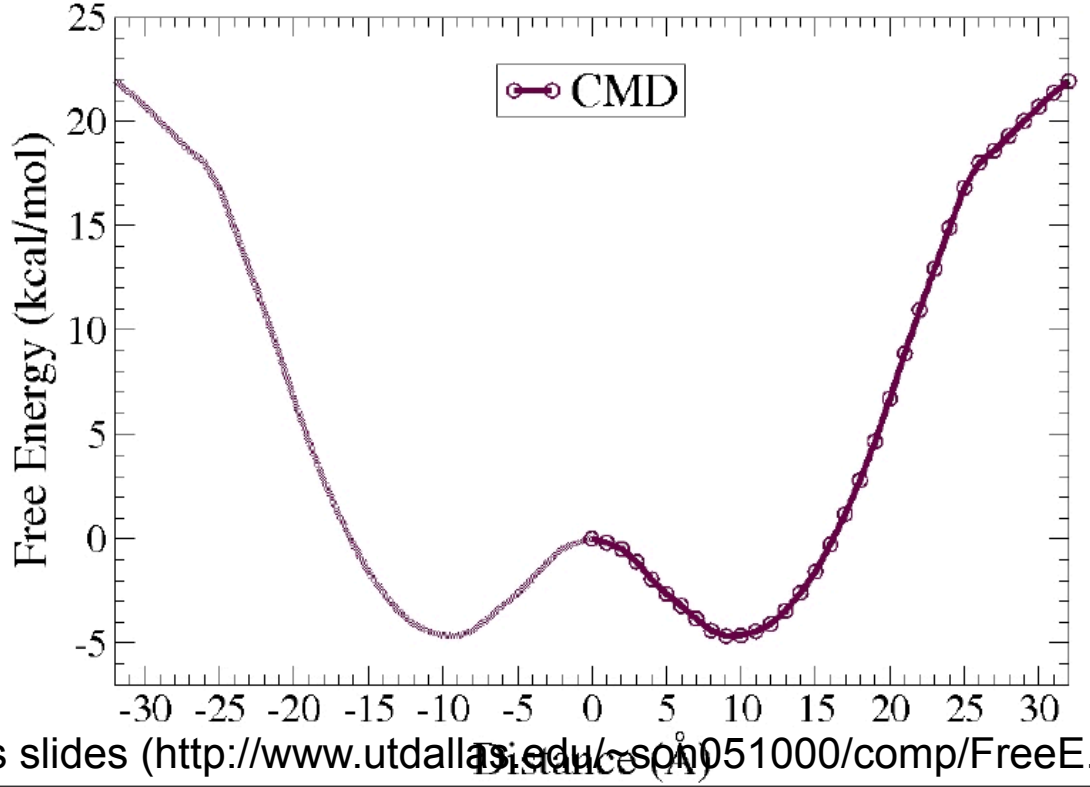


Potential of mean force from constrained MD simulations



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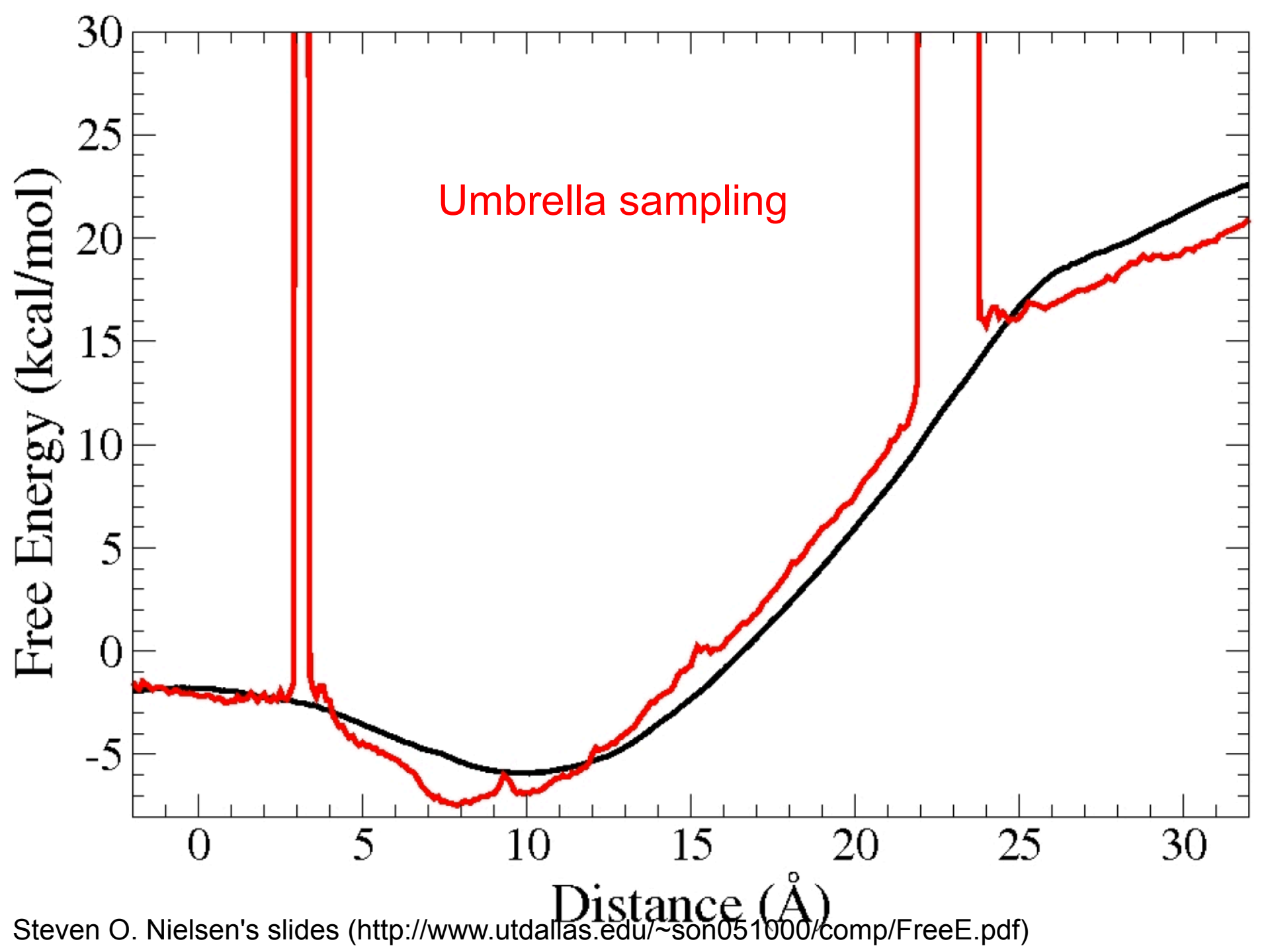

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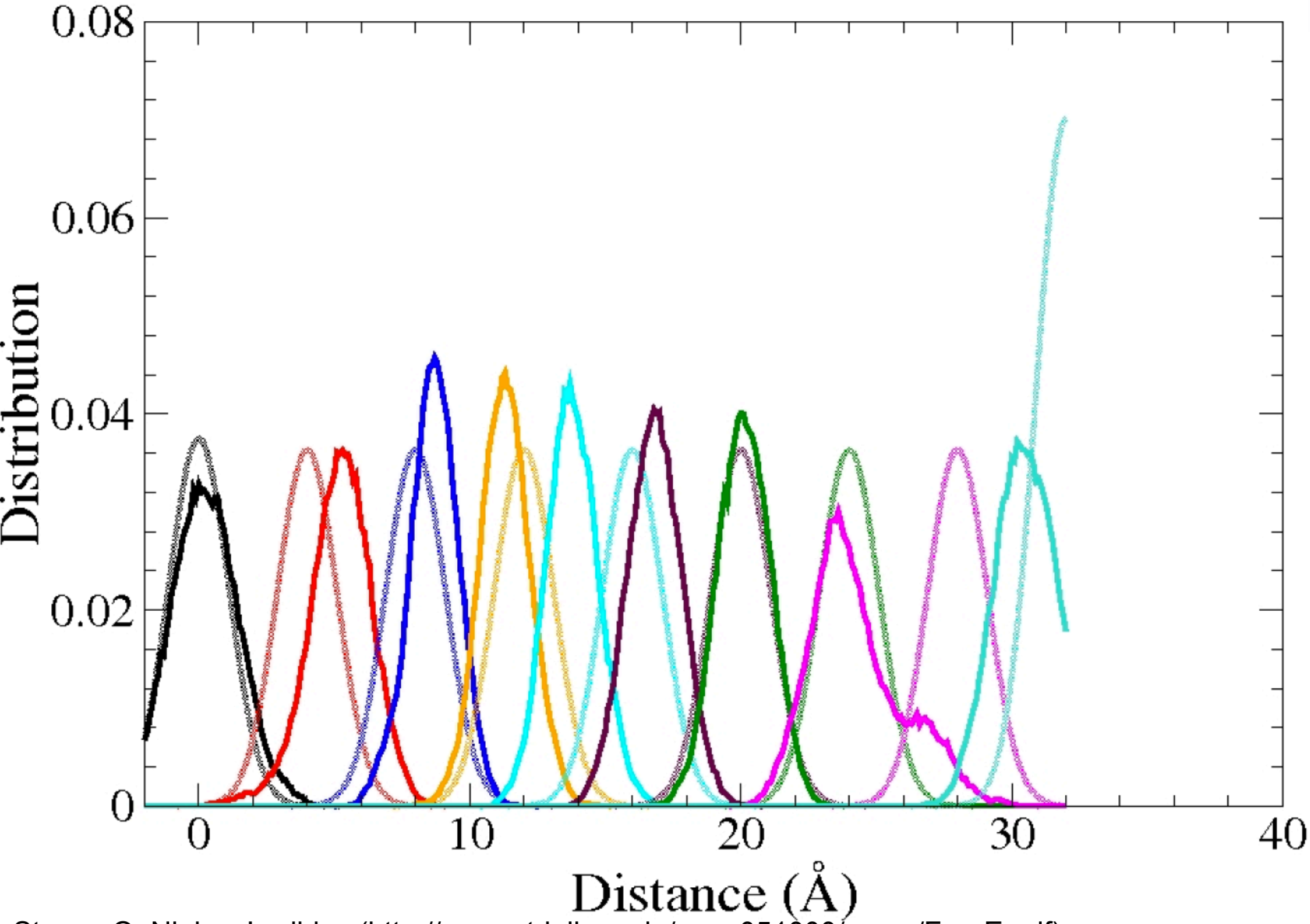

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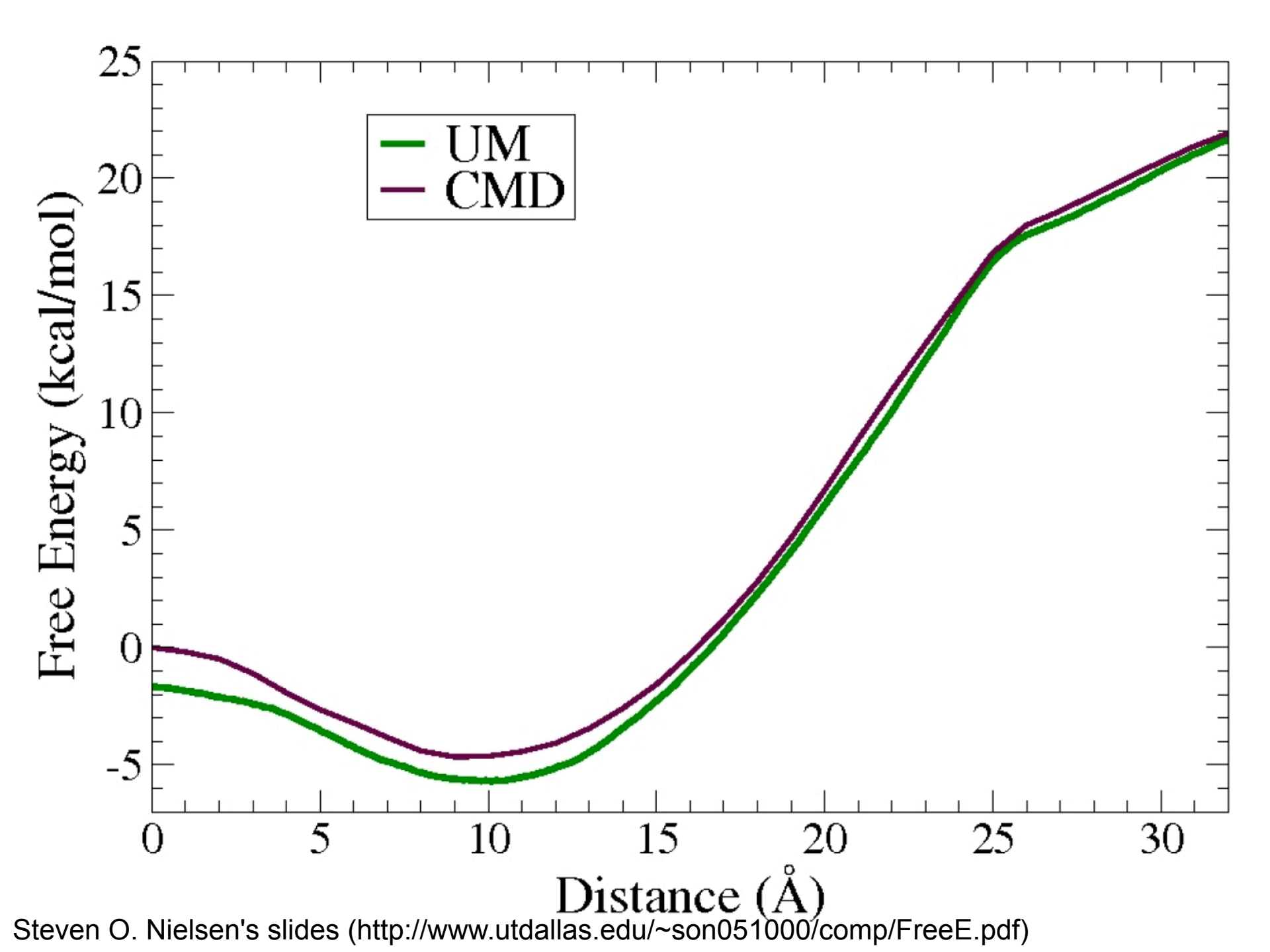

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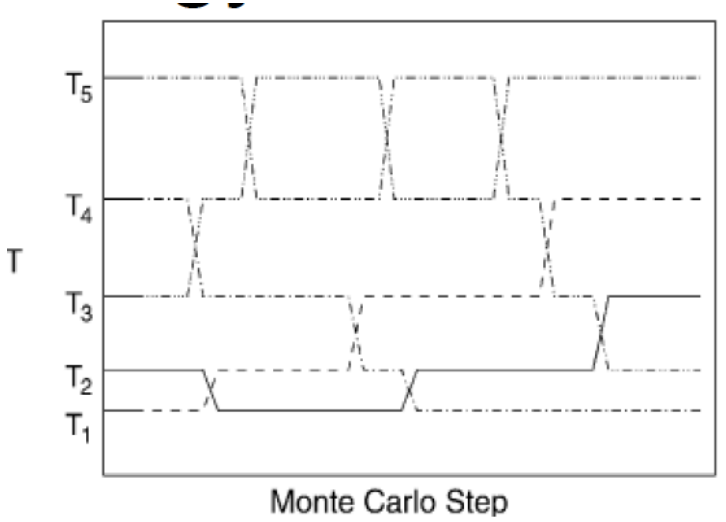
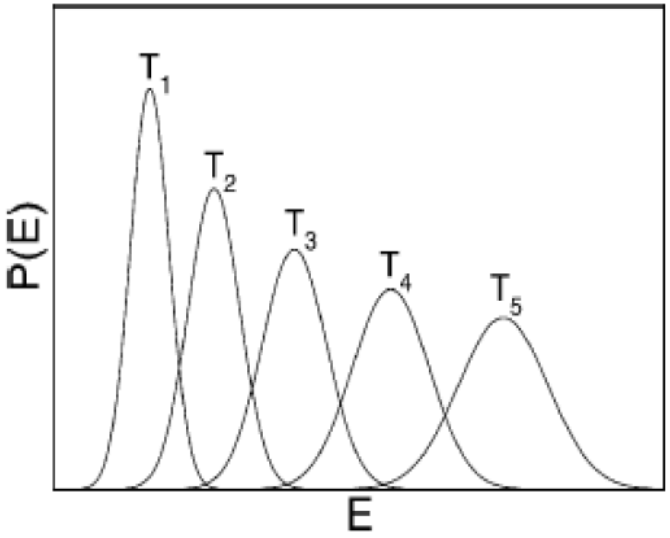
Replica Exchange - Overcoming Free Energy Barrier

- Non-directed method (no reaction coordinate)
- How to sample unfavorable states?
- At high T, barriers are easier to overcome.
- Heat and cool the system to push it over barriers to sample new configurations





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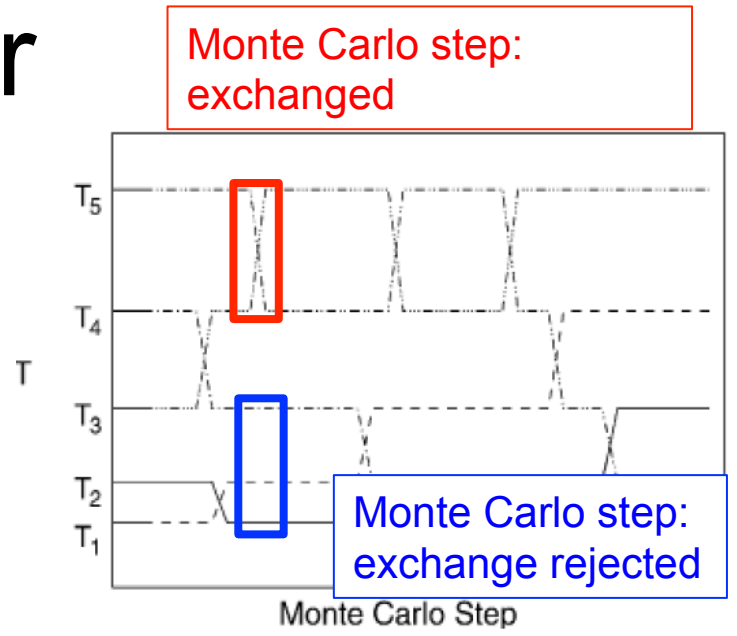
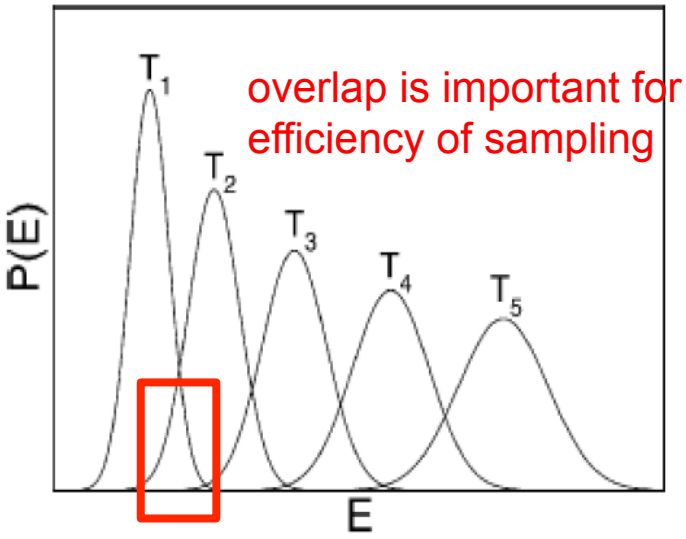
Replica Exchange - Overcoming Free Energy Barrier

- Launch simulations at different temperatures
- Swap configurations based on the metropolis criterion:

$$p = \min\left(1, \frac{\exp\left(-\frac{E_j}{kT_i} - \frac{E_i}{kT_j}\right)}{\exp\left(-\frac{E_i}{kT_i} - \frac{E_j}{kT_j}\right)}\right) = \min\left(1, e^{(E_i - E_j)\left(\frac{1}{kT_i} - \frac{1}{kT_j}\right)}\right),$$

- The lowest temperature "trajectory" samples from the Boltzmann distribution.
- Swapping configurations effectively improves sampling





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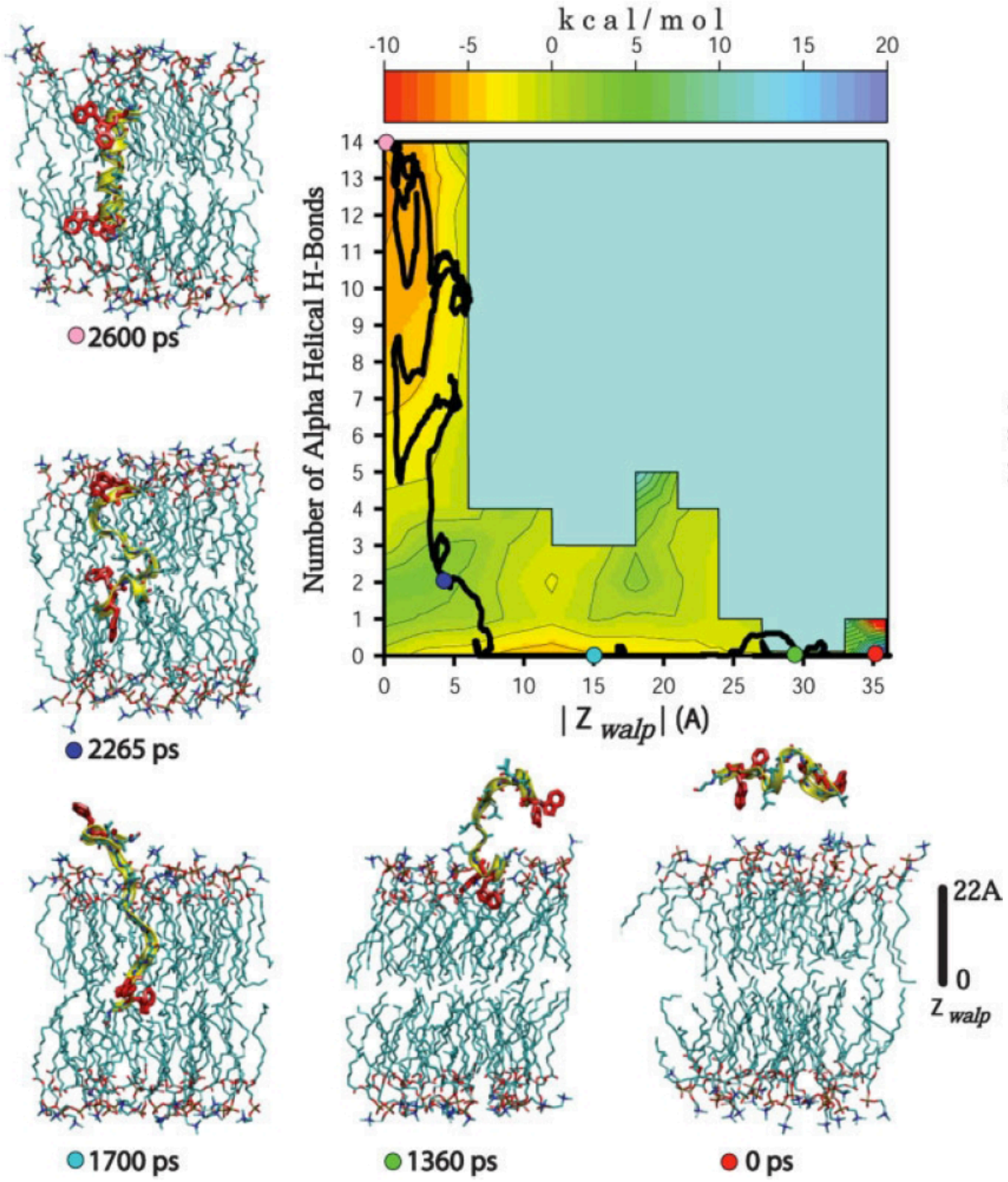

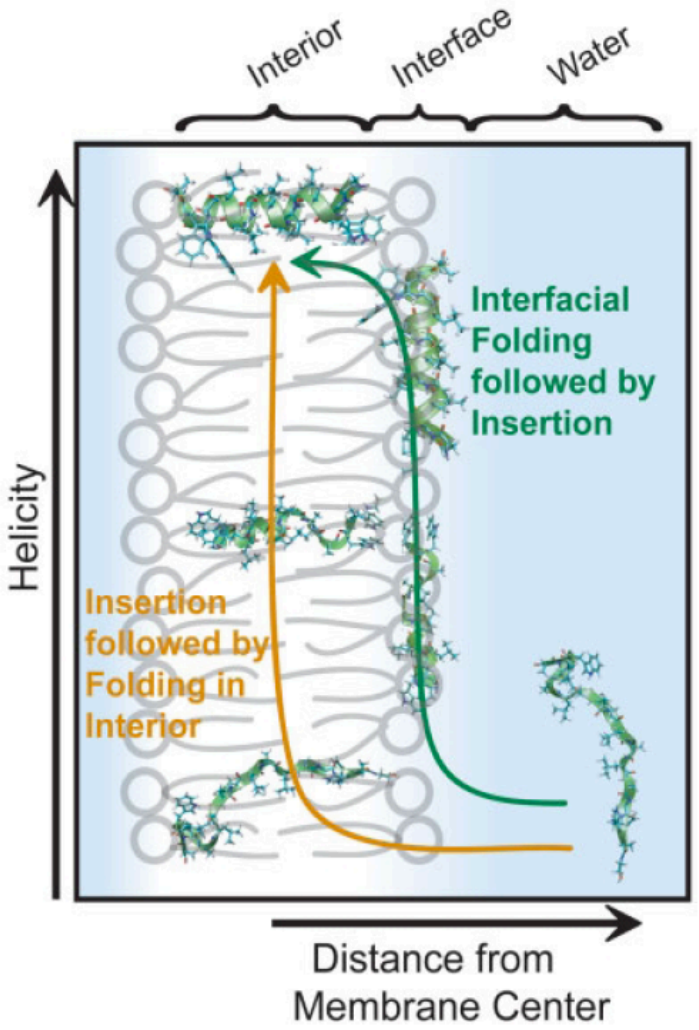

Garcia et al.
PROTEINS: Structure, Function, and Bioinformatics 59:783–790 (2005)