SI2-SSE: Software Tools for Biomolecular Free Energy Calculations

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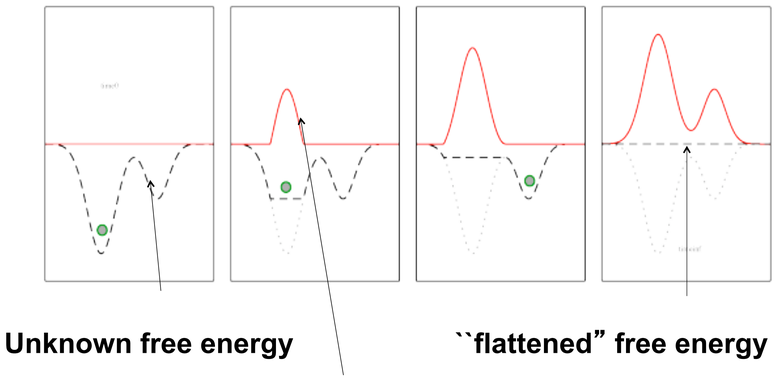
INTRODUCTION:

- The free energy is perhaps the single-most important quantity for describing biomolecular systems at equilibrium, determining such characteristics as molecular coformations, binding, chemical reactions, etc
- Free energy surfaces of biomolecular systems are typically rugged and complx, requiring very long time scales to explore – typically precluded in a regular molecular dynamics (MD) simulation
- to address issue, we developed the Adaptively Biased Molecular Dynamics (ABMD) method, which belongs to the general category of umbrella sampling methods with a time-dependent potential [Babin et al, JCP (2008)]
- ABMD calculates accurate Landau free energies as a function of suitable set of collective variables
- advantages include a linear-scaling in time, and few parameters
- Implemented with multiple-walker and replica exchange enhancements
- implemented along with Steered Molecular Dynamics (SMD) in AMBER v.10-12
- our SI2 programs aims to develop software tools around this program

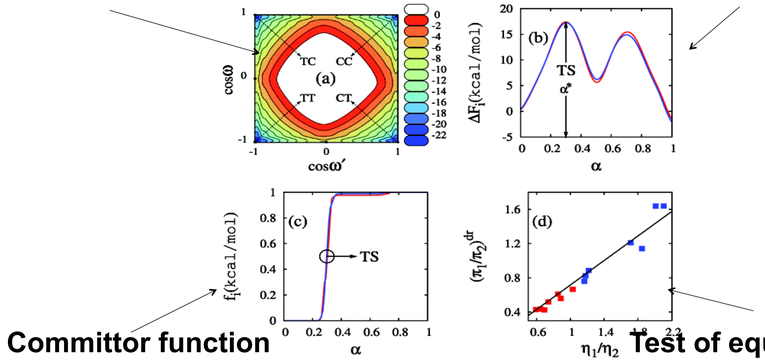


SI2-SSE EXTENSTIONS:

(a) Transition rates from driven nonequilibrium simulations

- Study f reactions and transitions is hampered by need to probe rare events
- by combining elements of Transition Path Theory (TPT) with results based on the nonequilibrium work theorem, we are able to relate equilibrium and driven reaction rates – may be obtained from SMD [Moradi et al, CPL (2011); JCP (2014)]
- test by probing chiral transition of proline dipeptide

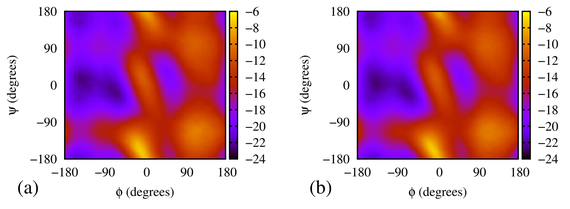
Free energy landscape PMF



Committor function Test of equations

(b) Interacting walkers for enhanced sampling

- Multiple-walker enhancements lead to speed-up of code
- Can do better by implementing a strategy based on the birth/death cycle of interacting walkers
- Not all walkers are equally effective in sampling phase space – sometimes they ``bunch up
- To increase efficiency, one kills walkers that bunch together and restart them elsewhere

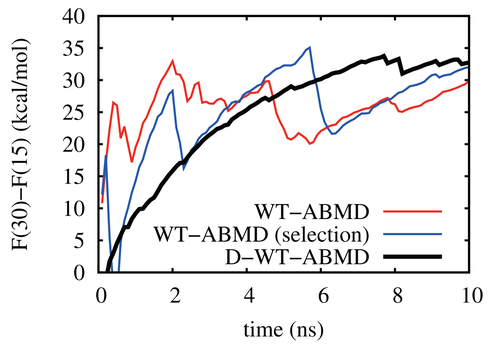


- Free energy of dialanine peptide (selection mechanism leads to speedup)

Without Selection Mechanism With Selection Mechanism

(c) Well-tempered and Driven ABMD (WT-ABMD, D-ABMD)

- Well-tempered ABMD updates biasing potential in a nonuniform way as to enhance convergence and stability
- Driven ABMD combines SMD and ABMD thereby ensuring early exploration of the most important pathways, again for enhanced stability and more uniform convergence along most important pathways (Moradi et al, JPC Lett. (2013).



(d) ``Swarms of trajectories String method" for multi-dimensional free energy calculations

- Because of high computational costs, its difficult to calculate free energy landscapes in more than 2 dimensions
- rather than full landscapes, String method focuses on calculating the Minimum Free Energy Path (MFEP) which is deemed to be the most important
- This enables calculating MFEP in multidimensional space
- Ref.: Pan et al, JPC (2008)

ALL SOFTWARE HAS BEEN WRITTEN AND IS CURRENTLY AVAILABLE AS ``BUGFIXES" TO AMBER SOFTWARE PACKAGE – PLAN TO FINISH ALL ASPECTS BY END OF SUMMER 2015.