Lecture 14: Advanced Conformational Sampling

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Multidimensional Rough Energy Landscapes

MD ~ ns, conformational motion in macromolecules ~μs to sec

Interconversions between basins are infrequent at room temperature. Barriers are poorly sampled.
Biased Sampling

Thermodynamic properties can be “unbiased”:

\[
\langle A \rangle_{w(x)} = \frac{\int dx \, A(x) e^{-\beta U(x)}}{\int dx \, e^{-\beta U(x)}} = \frac{\int dx \, A(x) e^{+\beta w(x)} e^{-\beta U(x)} e^{-\beta w(x)}}{\int dx \, e^{+\beta w(x)} e^{-\beta U(x)} e^{-\beta w(x)}} =
\]

\[
\frac{Q_{U+w} \langle A(x) e^{\beta w(x)} \rangle_{U+w}}{Q_{U+w} \langle e^{\beta w(x)} \rangle_{U+w}} = \frac{\langle A(x) e^{\beta w(x)} \rangle_{U+w}}{\langle e^{\beta w(x)} \rangle_{U+w}}
\]
Biased Sampling Methods

- Umbrella sampling
- Targeted/Steered MD
- Local elevation, conformational flooding, metadynamics, essential dynamics
- ...

Statistical Thermodynamics

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Generalized Ensembles

Microcanonical Ensemble

\[ \Omega(E) = \text{density of states} = \int d\Gamma \delta [H(\Gamma) - E] \quad S(E) = k_B \ln \Omega(E) \]

Canonical ensemble

\[ Q_c(\beta) = \int dE \Omega(E) e^{-\beta E} \quad p_c(E) = \frac{\Omega(E)e^{-\beta E}}{Q_c} \]

\[ e^{-\beta E} = \text{canonical weight} \]

Multicanonical ensemble

\[ Q_{\mu} = \int dE \Omega(E) W(E) \quad \text{generalized weight function} \]

Set so that: \[ p_{\mu}(E) = \frac{\Omega(E)W(E)}{Q_{\mu}} = \text{constant} \]

\[ W(E) \propto \frac{1}{\Omega(E)} = e^{-S(E)/k_B} \quad \text{Often expressed as:} \quad W(E) = e^{-\beta M(E, \beta)} \]
Multicanonical ensemble (cont.)

\[ Q_{\text{mu}} = \int dE \Omega(E) e^{-\beta M(E, \beta)} = \int dE d\Gamma \delta[H(\Gamma) - E] e^{-\beta M(E, \beta)} = \int d\Gamma e^{-\beta M[H(\Gamma), \beta]} \]

MD/MC with modified Hamiltonian \( M(\Gamma) = M[H(\Gamma)] \)

The \( M \) function (spline) is adjusted by trial and error until the distribution of energies is constant within a given range \([E_{\text{min}}, E_{\text{max}}]\)

The multicanonical ensemble samples both low energy and high energy conformations – barrier crossing.

Unbiasing:

\[
\langle A \rangle_{\text{canonical}} = \frac{\langle A(\Gamma) e^{-\beta[H(\Gamma) - M(\Gamma)]} \rangle_{\text{mu}}}{\langle e^{-\beta[H(\Gamma) - M(\Gamma)]} \rangle_{\text{mu}}} 
\]
Generalized Ensembles

Canonical ensemble

\[ Q_c = \int d\Gamma \ e^{-\beta H(\Gamma)} \quad p(\Gamma) = \frac{e^{-\beta H(\Gamma)}}{Q_c} \]

Extended Ensemble: a parameter \( \lambda \) becomes a dynamical variable

\[ Q = \int d\lambda \int d\Gamma \ e^{f(\lambda)} e^{-\beta H(\Gamma|\lambda)} = \int d\lambda e^{f(\lambda)} Q_c(\lambda) \]

\[ p(\Gamma, \lambda) = \frac{e^{f(\lambda)} e^{-\beta H(\Gamma|\lambda)}}{Q} \]

\[ p(\lambda) = \int d\Gamma \ p(\Gamma, \lambda) = \frac{e^{f(\lambda)}}{Q} \int d\Gamma e^{-\beta H(\Gamma|\lambda)} = \frac{e^{f(\lambda)} Q_c(\lambda)}{Q} \]

When \( p(\lambda) = \text{constant} \)

\[ f(\lambda) = -\ln Q_c(\lambda) + \text{const.} \]

Dimensionless free energy at \( \lambda \)
Extended Ensemble example: Simulated Tempering

\[ \lambda = \text{temperature} \]
\[ Q = \int dT \ d \Gamma \ e^{f(T)} e^{-H(\Gamma)/k_B T} = \int dT \ e^{f(T)} Q_c(T) \]

Want to sample temperature uniformly within a range:

\[ p(T) = \int d \Gamma \ p(\Gamma, T) = \frac{e^{f(T)} Q_c(T)}{Q} = \text{constant} \]

Therefore we seek: \( f(T) = -\ln Q_c(T) + \text{const.} \)

In actual applications sample a discrete set of temperatures \( T_m \)

\[ Q = \sum_m \int d \Gamma \ e^{f_m(T_m)} e^{-\beta_m H(\Gamma)} \]

Generalized Hamiltonian is:

\[ H_m(\Gamma) = H(\Gamma) - f_m(T_m)/\beta_m \]
Conformational sampling in Simulated Tempering

**MC**

Velocities are not considered ($Q \rightarrow Z$ above).

Generalized energy function: $U_m(x) = U(x) - f_m(T_m) \beta_m$

Sampling distribution: $\rho(x, T_m) \propto e^{-\beta_m U_m(x)}$

Two kinds of MC moves:

1. Change of coordinates at constant temperature:

   $$(x, T_m) \rightarrow (x', T_m) \quad \frac{\rho'}{\rho} = e^{-\beta_m [U(x') - U(x)]}$$

2. Change of temperature at fixed coordinates:

   $$(x, T_m) \rightarrow (x, T_m') \quad \frac{\rho'}{\rho} = e^{-(\beta_m - \beta_m) U(x) + (f_m - f_m)}$$
Conformational sampling in Simulated Tempering

MD

Sampling distribution: \( \rho (p, x, T_m) \propto e^{-\beta_m[K(p)+U(x)]+f_m} \)

1. Constant temperature MD for \( n \) steps at \( T_m \) with potential function \( U(x) \)
   think of it as a move: \( (p, x, T_m) \rightarrow (p', x', T_m) \)

2. Attempt to temperature move at constant positions + rescaled velocities:

\[
(p, x, T_m) \rightarrow ((T_m'/T_m)^{1/2} p, x, T_m')
\]

\[
\beta_m' K' = \beta_m' \frac{p'^2}{2M} = \beta_m' \frac{\beta_m}{\beta_m} \frac{p^2}{2M} = \beta_m \frac{p^2}{2M} = \beta_m K
\]

So:

\[
\frac{\rho'}{\rho} = e^{-[\beta_m' K - \beta_m K + (\beta_m' - \beta_m) U(x)] + (f_m' - f_m)} = e^{-[(\beta_m' - \beta_m) U(x)] + (f_m' - f_m)}
\]

Same as in MC
Simulated Tempering (cont.)

The weight factors $f_m(T_m)$ – a.k.a. dimensionless free energies - are adjusted by trial and error until all of the temperatures are visited approximately equally. This can be a time consuming and tedious process.

Temperatures can not be spaced too far apart to keep MC acceptance probabilities at a reasonable level.
Simulated Tempering (cont.)

When the system is visiting high temperatures, barrier crossings are more likely. Then new conformations may “cool down” and reach the temperature of interest.

The samples at the temperature of interest can be used directly to compute thermodynamic averages; each $T$-ensemble is canonical

$$\langle A \rangle_T = \frac{1}{n_T} \sum_{\text{samples at } T} A(x_k)$$

(can also unbias from other temperatures – WHAM/MBAR, later)
Temperature Replica Exchange
(a.k.a. Parallel Tempering)

In Simulated Tempering equal visitation of temperatures is ensured by the free energy weights $f_m$.

In Parallel Tempering the same is ensured by having each temperature correspond to an individual replica of the system.

$$Q_{RE} = Q_1 Q_2 Q_3 \cdots Q_n$$

We consider the generalized canonical ensemble of the collection of replicas.

Because the replicas are not interacting, the partition function of the RE ensemble is the product of the individual partition functions.

$$Q_i = \int d \Gamma_i e^{-\beta_i H(\Gamma_i)}$$

$$Q_{RE} = \int d \Gamma_1 \cdots d \Gamma_n e^{-\sum_i \beta_i H(\Gamma_i)}$$
The state of the RE ensemble is specified by an ordered sequence of momenta/coordinate pairs:

\[(\Gamma_1, \Gamma_2, \ldots \Gamma_n)\]

Two kinds of moves:

1. Change of coordinates in one replica (MC or MD):

\[(\Gamma_1, \ldots, \Gamma_i, \ldots, \Gamma_n) \rightarrow (\Gamma_1, \ldots, \Gamma'_i, \ldots, \Gamma_n)\]

2. Exchanges of state between a pair of replicas:

\[(\Gamma_1, \ldots, \Gamma_i, \ldots, \Gamma_j, \ldots, \Gamma_n) \rightarrow (\Gamma_1, \ldots, \Gamma_j, \ldots, \Gamma_i, \ldots, \Gamma_n)\]

2a. MC: exchange coordinates (no velocities)
2b. MD: rescale velocities at the new temperature
Recall Metropolis MC algorithm:

probability of accepting move = \( \min \left( 1, \frac{\rho_j}{\rho_i} \right) = \min \left( 1, e^{-\beta \Delta U_{ij}} \right) \)

\[ \rho_{RE}(\text{before}) \propto \exp \left( -\beta_1 U_1 \ldots -\beta_i U_i \ldots -\beta_j U_j \ldots -\beta_n U_n \right) \]

\[ \rho_{RE}(\text{after}) \propto \exp \left( -\beta_1 U_1 \ldots -\beta_i U_i \ldots -\beta_j U_j \ldots -\beta_n U_n \right) \]

\[ \frac{\rho_{RE}(\text{after})}{\rho_{RE}(\text{before})} \propto \exp \left[ -(\beta_j - \beta_i)(U_i - U_j) \right] \]

Accept or reject exchange attempt based on this quantity
\[
\rho_{\text{R.E.}}(\text{before}) \propto \exp\left[... - \beta_i (K_i + U_i) ... - \beta_j (K_j + U_j) ...ight]
\]
\[
\rho_{\text{R.E.}}(\text{after}) \propto \exp\left[... - \beta_i \left(\frac{\beta_j}{\beta_i} K_j + U_j\right) ... - \beta_j \left(\frac{\beta_i}{\beta_j} K_i + U_i\right) ...ight]
\]
\[
\frac{\rho_{\text{R.E.}}(\text{after})}{\rho_{\text{R.E.}}(\text{before})} \propto \exp\left[-(\beta_j - \beta_i) (U_i - U_j)\right]
\]

Same as in MC
Exchange will be accepted with 100% probability if lower temperature gets the lower energy.

Otherwise the exchange has some probability to succeed if either the temperature difference is small or if the energy difference is small, or both.

On average larger systems require smaller spacing of temperatures:

\[
\langle U_i - U_j \rangle \approx \frac{\partial U}{\partial T} (T_j - T_i) = C_v (T_j - T_i) \quad \text{and} \quad C_v \propto N
\]
Replica exchange molecular dynamics

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Replica exchange molecular dynamics

Temperature trajectory of a walker
Hamiltonian Replica Exchange (HREM)

A RE method in which different replicas correspond to (slightly) different potential functions rather than temperature.

\[ U(x, \lambda) = U_0(x) + V(x, \lambda) \]

“Base” energy \( \rightarrow \) “Perturbation” energy

\[
\rho_{\text{HREM}} \propto \exp \left\{ -\beta \left[ U(x_1, \lambda_1) + \ldots + U(x_n, \lambda_n) \right] \right\}
\]

The probability of exchange between two replicas in HREM

\[
U_{\text{before}} = U(x_1, \lambda_1) + U(x_2, \lambda_2) + \ldots \quad U_{\text{after}} = U(x_2, \lambda_1) + U(x_1, \lambda_2) + \ldots
\]

\[
\frac{\rho_{\text{after}}}{\rho_{\text{before}}} = \exp \left[ -\beta \left( \Delta U_1 + \Delta U_2 \right) \right]
\]

where

\[
\Delta U_1 = U(x_1, \lambda_2) - U(x_1, \lambda_1) \quad \Delta U_2 = U(x_2, \lambda_1) - U(x_2, \lambda_2)
\]

(proposed change in energy of conformation \( x_i \)) (proposed change in energy of conformation \( x_2 \))
Two examples of HREM applications

- **REUS: Replica Exchange Umbrella Sampling**
  
  \[ V(x, \lambda) = w(x; d_{\lambda}) \quad w(x) = \text{biasing potential} \]

  Originally proposed to compute the end-to-end distance PMF of a peptide, in which case the biasing potentials are harmonic restraining potentials of the end-to-end distance \( d \).

- **BEDAM: Binding Energy Distribution Analysis Method**
  
  \[ V(x, \lambda) = \lambda V_{RL}(x) \quad V_{RL}(x) = \text{ligand-receptor interaction energy} \]

  Replicas are distributed from \( \lambda = 0 \) (unbound state) to \( \lambda = 1 \) (bound state). Replicas at small \( \lambda \) provide good sampling of ligand conformations whereas replicas at larger \( \lambda \)'s provide good statistics for binding free energy estimation.

- In either case the Weighted Histogram Analysis Method (WHAM) is used to merge the data from multiple replicas
  
  \[ [\text{Gallicchio, Andrec, Felts, Levy, 2005}] \]