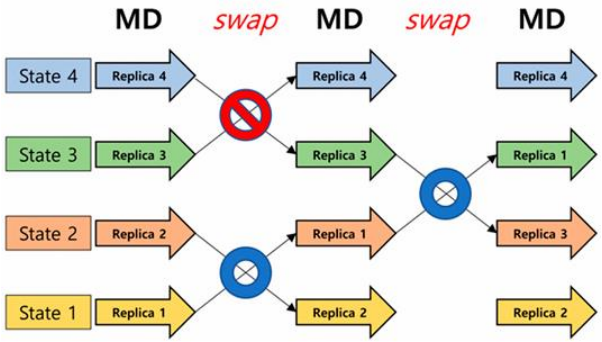
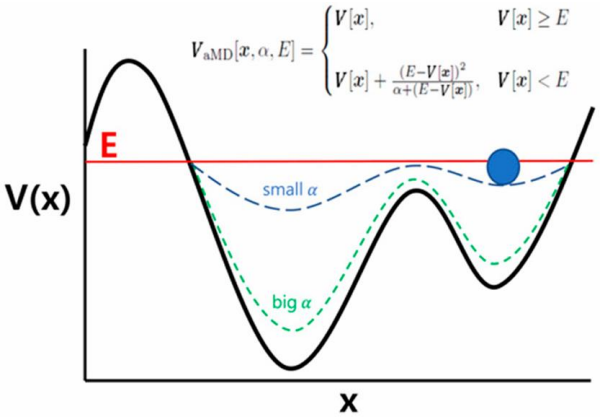
Free energy Calculation





2024 Winter Son Lab Seminar

February 22th, 2024

SeungBin Hong

Front. pharmacol., ***2018***, 9, 00923

Content

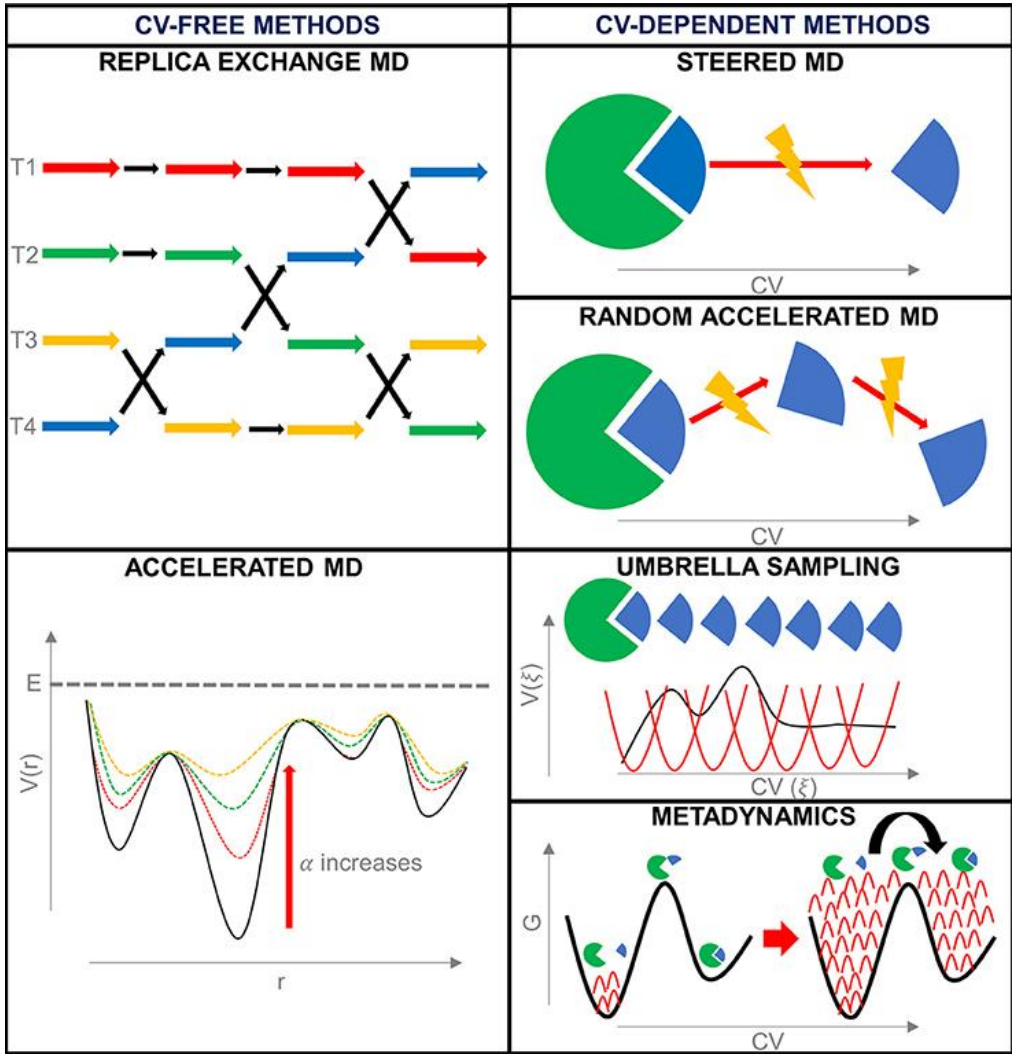
Common Concept

Unbiased Enhanced sampling

Take-home Massage

Common Concept

What is “ Unbiased Enhanced Sampling” ?



Front. pharmacol., ***2018***, *9*, *00923*

Biased sampling Methods

Steered Molecular Dynamics

The free energy change between two different coordinated states, each states are λ_0, λ_1

$$\Delta F = \Delta F_{\lambda_1} - \Delta F_{\lambda_0} = -\frac{1}{\beta}\ln\left(\frac{Z_{\lambda_0}}{Z_{\lambda_1}}\right)$$

Free energy change between two states can be exactly related to the ensemble average of the Boltzmann-weighted work performed in many non-equilibrium transformations from the initial to final states.

$$\Delta F = -\frac{1}{\beta}\ln\langle e^{-\beta W}\rangle$$

sMD restrain to a particular center that changes according to a constant velocity v during a simulation of the irreversible transformation from λ_0 to λ_1

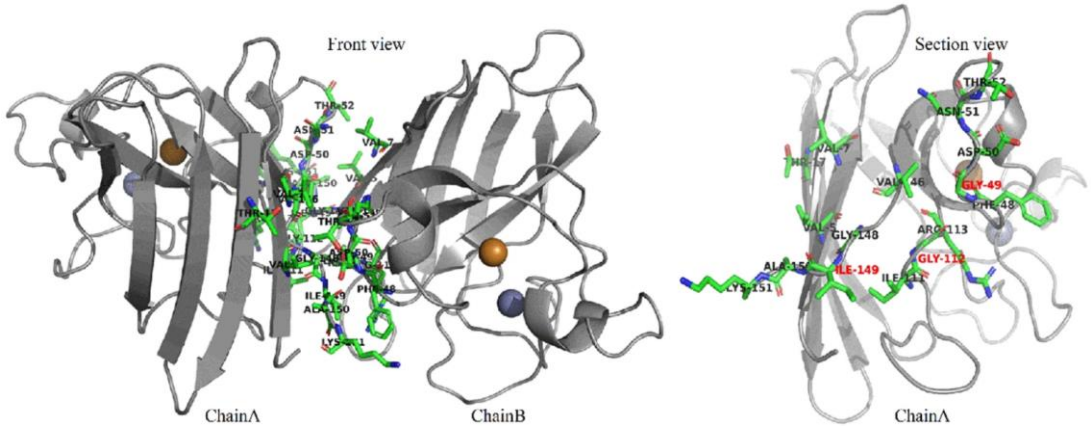
$$V(q,t) = \frac{1}{2}k[\lambda(t) - \lambda'(q)]^2 \quad where\ \lambda(t) = \lambda_0 + vt$$

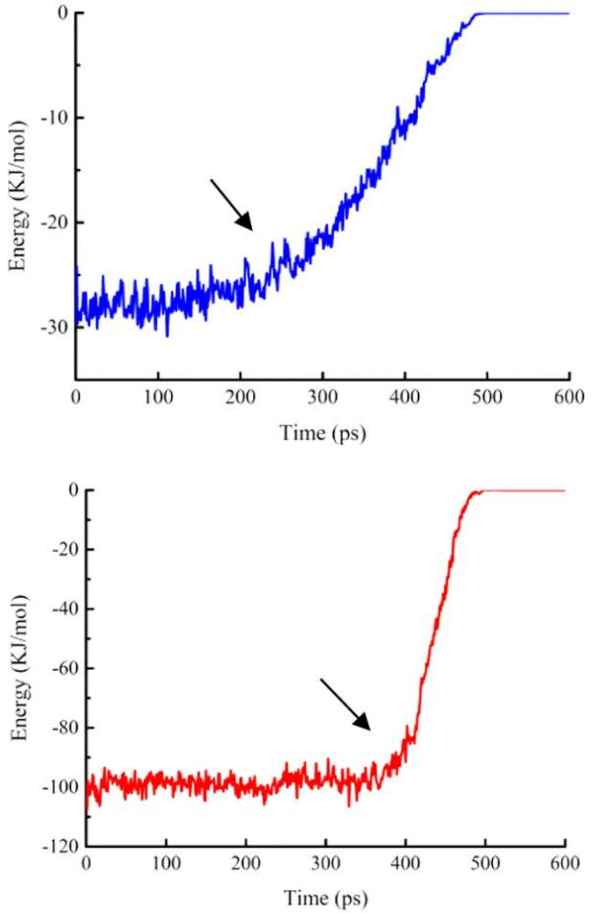
*JCTC, **2013**, 9, 7, 2887-2899*

Biased sampling Methods

Steered Molecular Dynamics

Three amino acid residues (Gly49, Gly112 and Ile149) are affected by the restrained force $F = -k\left[x_{pull}(t) - x_{pull}(0) - vt\right]$.



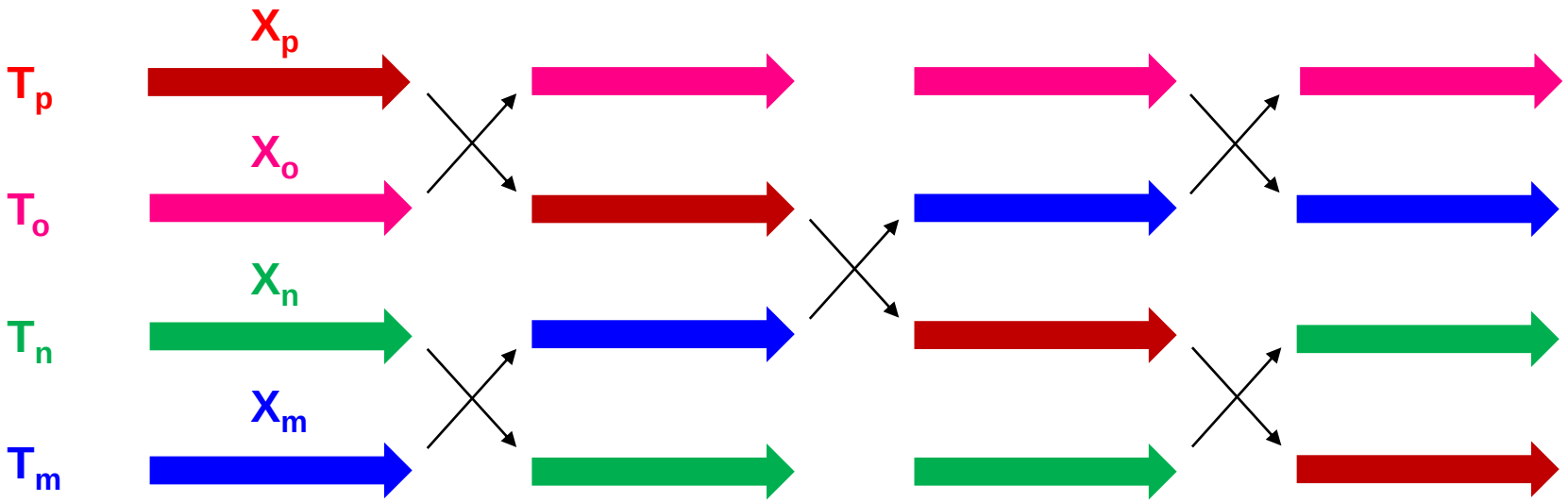


Replica Exchange Molecular Dynamics

There are much types of REMD (Temperature REMD, Hamiltonian REMD, etc….).

Several replicas of the system are evolved at different temperatures.

A pair of replicas with adjacent temperatures is tried to exchange.



JCP, ***2002***, *116, 9058*

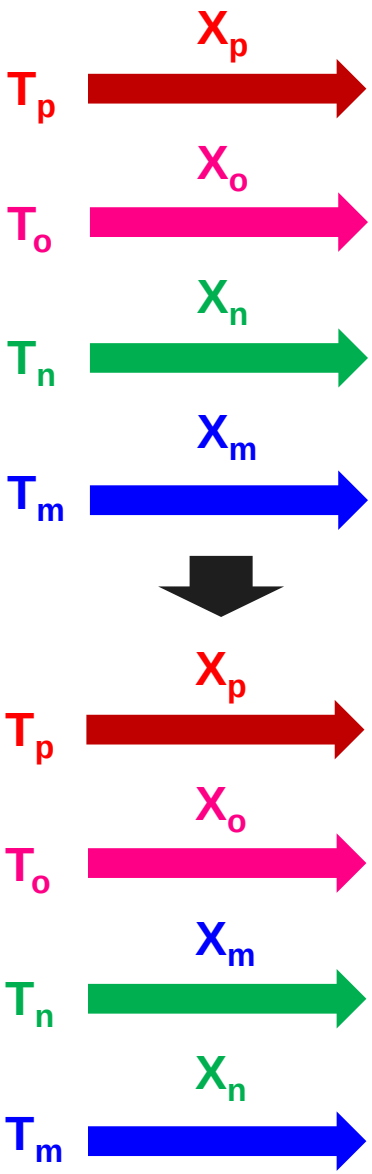
Replica Exchange Molecular Dynamics

The probability of populating configuration X_m in the m^{th} replica obeys the Boltzmann distribution at T_m

$$P_m(X_m) = \frac{e^{-\beta_m E(X_m)}}{Z_m} \qquad \beta_m = (k_B T_m)^{-1}$$

$$P_{all} = \prod_i^M P_i(X_i)$$

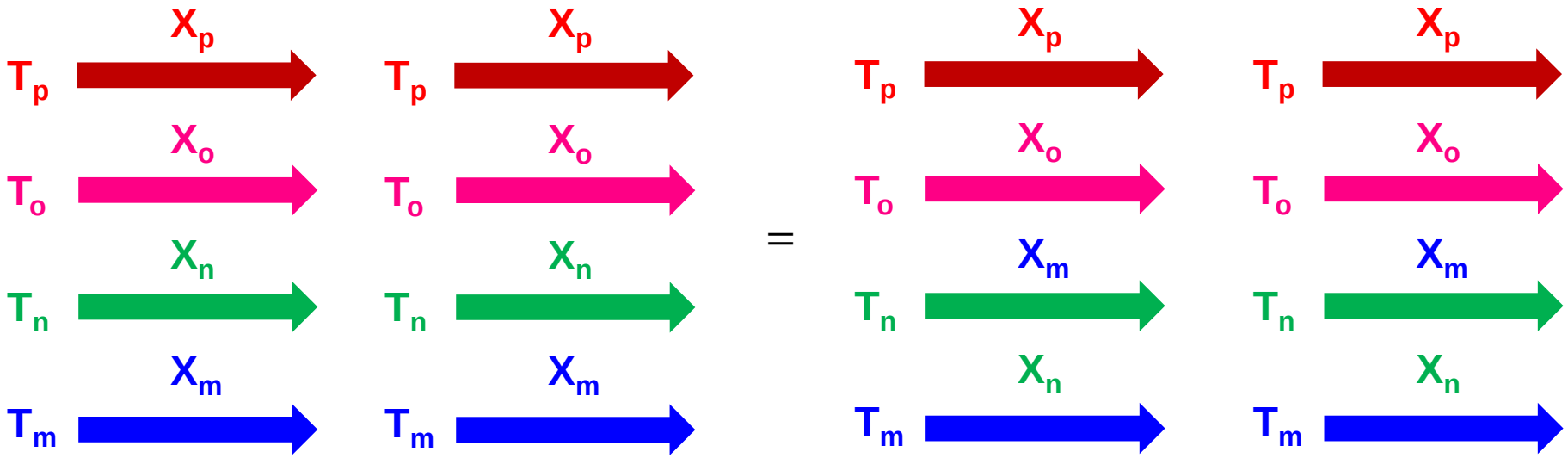
Probability that configuration X_m,X_n in the m,n replicas are exchanged by configuration X_n, X_M in the n,m.



Replica Exchange Molecular Dynamics

For a system in thermal equilibrium the detailed balance condition holes:

$$P_{all}(X_m, T_m; X_n, T_n; X_o, T_o; X_p, T_p)W(X_m, T_m; X_n, T_n) =$$
$$P_{all}(X_m, T_n; X_n, T_m; X_o, T_o; X_p, T_p)W(X_m, T_n; X_n, T_m)$$



Replica Exchange Molecular Dynamics

$$P_{all}\left(X_m, T_m; X_n, T_n; X_o, T_o; X_p, T_p\right) W(X_m, T_m; X_n, T_n) = P_{all}\left(X_m, T_n; X_n, T_m; X_o, T_o; X_p, T_p\right) W(X_m, T_n; X_n, T_m)$$

$$\Rightarrow \frac{W(X_m, T_m; X_n, T_n)}{W(X_m, T_n; X_n, T_m)} = \frac{P_m(X_m, T_m) P_n(X_n, T_n)}{P_m(X_n, T_m) P_n(X_m, T_n)} = \frac{\frac{e^{-\beta_m E(X_n)}}{Z_m} \frac{e^{-\beta_n E(X_m)}}{Z_n}}{\frac{e^{-\beta_m E(X_m)}}{Z_m} \frac{e^{-\beta_n E(X_n)}}{Z_n}}$$

$$\frac{W(X_m, T_m; X_n, T_n)}{W(X_m, T_n; X_n, T_m)} = e^{-(\beta_m - \beta_n)(E(X_n) - E(X_m))} = e^{-\Delta} \quad , \qquad \beta_m = (k_B T_m)^{-1}$$

The exchange between replica is accepted according to **Metropolis criteria**:

$$W(X_m, T_m; X_n, T_n) = 1 \quad for \quad \Delta \leq 0$$

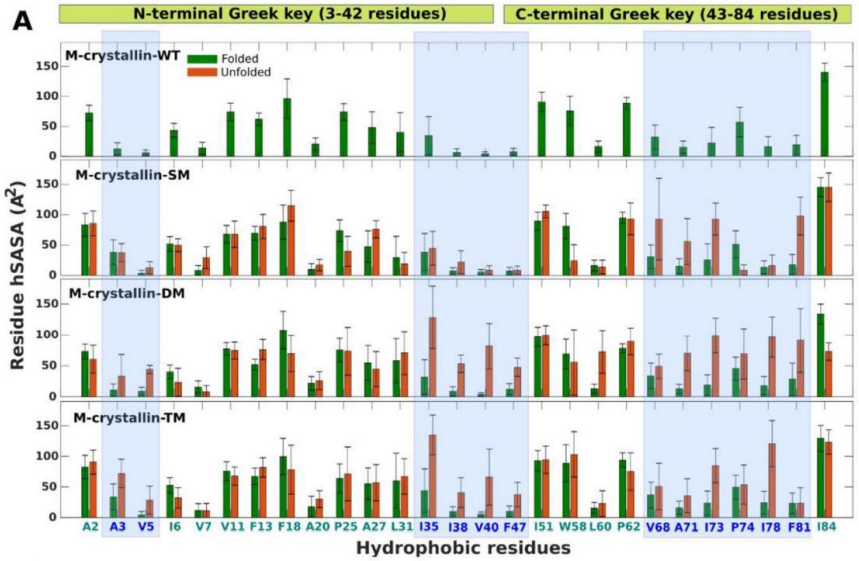
$$W(X_m, T_m; X_n, T_n) = e^{-\Delta} \quad for \quad \Delta > 0$$

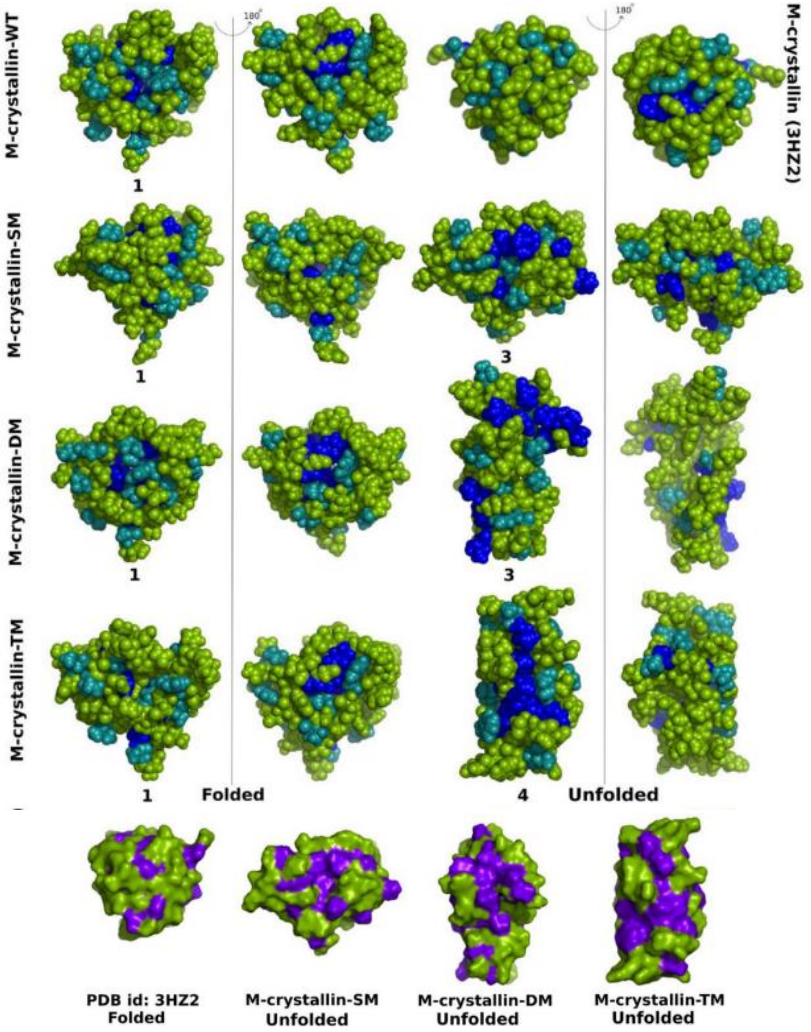
Exchange between replicas is accepted when **the energy of the high temperature configuration is smaller than the energy of the low-temperature configuration**.

Unbiased sampling Methods

Replica Exchange Molecular Dynamics

M-crystallins are long-lived and structural intactness is required for maintaining lens transparency and protein solubility.





Sci Rep, ***2021***, *11*, 23270

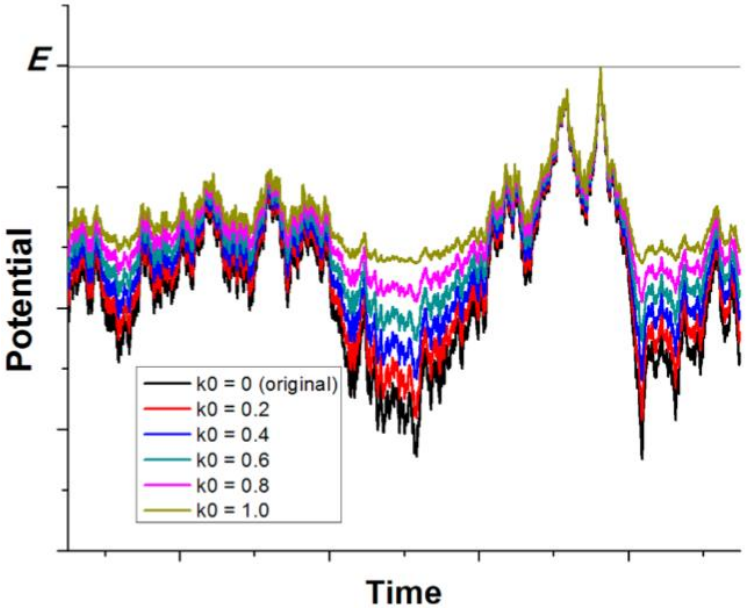
Accelerated Molecular Dynamics & Gaussian accelerated molecular dynamics

With adding a boost potential /harmonic boost potential to smoothen the system potential energy surface.

$$\Delta V(\vec{r}) = \frac{1}{2}k\left(E - V(\vec{r})\right)^2 \; for\; V(\vec{r}) < E \qquad \Delta V(\vec{r}) = \frac{\left(E - V(r)\right)^2}{a + (E - V(r))} \; for\; V(\vec{r}) < E$$

The modified system potential is given by

$$V^*(\vec{r}) = V(\vec{r}) + \frac{1}{2}k\left(E - V(\vec{r})\right)^2 \quad for\; V(\vec{r}) < E$$
$$V^*(\vec{r}) = V(\vec{r}) \quad for\; V(\vec{r}) \geq E$$



If $V_1(\vec{r}) < V_2(\vec{r})$

$$\frac{1}{2}[V_1(\vec{r}) + V_2(\vec{r})] < E < \frac{1}{2}[V_1(\vec{r}) + V_2(\vec{r})] + \frac{1}{k}$$

With $V_{min} \leq V_1(\vec{r}) < V_2(\vec{r}) \leq V_{max}$, we need to set the **Threshold energy** in the following range.

$$V_{max} \leq \boldsymbol{E} \leq V_{min} + \frac{1}{k}$$

Problem of accelerated Molecular Dynamics

$$\Delta V(\vec{r}) = \frac{1}{2}k\left(E - V(\vec{r})\right)^2 \; for\; V(\vec{r}) < E \quad \Delta V(\vec{r}) = \frac{\left(E - V(r)\right)^2}{a + (E - V(r))} \; for\; V(\vec{r}) < E$$

$$\Delta U = U' - U = \Theta(E_0 - U) \times \frac{(E_0 - U)^2}{a + E_0 - U}$$

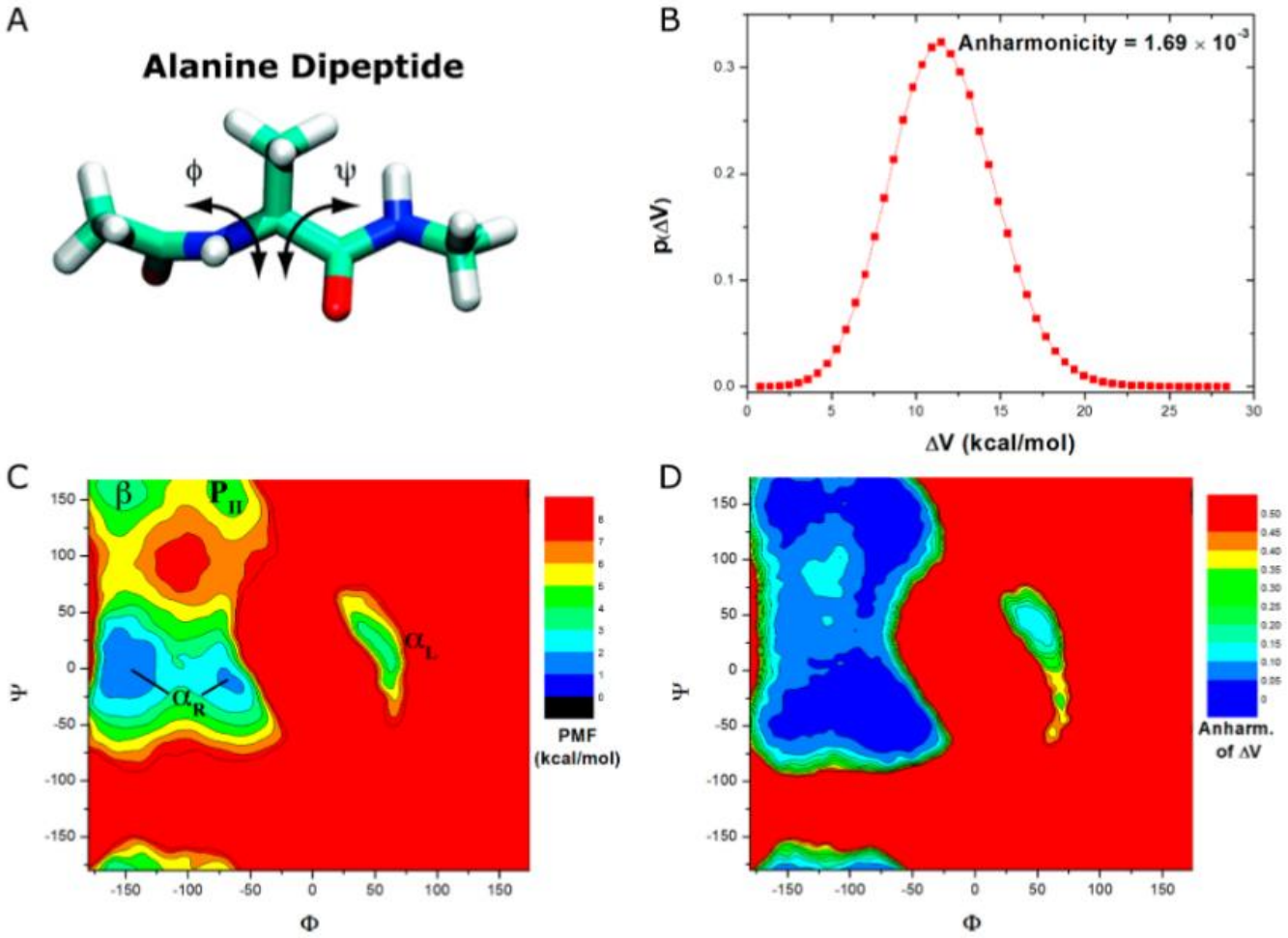
The type of Heaviside function

1) This function form was designed to alter the original energy function efficiently at the same time keeping the **smoothness up to the second order derivative of the energy**.

2) Variance of potential energy's order of tens-to-hundreds of kilocalories per mole.

So , if we can use same exponent with usual harmonic equation , we can avoid this problem !

Gaussian accelerated molecular dynamics



Takeaways

- Take Home Message 1

Use adequate tool for each systems

- Take Home Message 2

Always keep conscious about thermodynamics