# **Deca-Alanine Stretching**

Free Energy Calculation from Steered Molecular Dynamics Simulations Using Jarzynski's Eqaulity

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 $\lambda$  = end-to-end distance, position of substrate along a channel, etc.

2nd law of thermodynamics:  $\langle W \rangle \geq \Delta F = F(\lambda_f) - F(\lambda_i)$ 

Jarzynski (1997):  $\langle \exp(-\beta W) \rangle = \exp(-\beta \Delta F)$ difficult to estimate Derivation of Jarzynski's Equality

Process described by

a time-dependent Hamiltonian H(x,t)

Trajectory  $\mathbf{x}_{t} \implies$  External work  $\mathbf{W} = \int_{0}^{\tau} d\mathbf{t} \partial_{t} \mathbf{H}(\mathbf{x}_{t}, \mathbf{t})$ 

If the process

- (1) is Markovian:  $\partial_{\dagger} f(\mathbf{x}, \mathbf{t}) = L(\mathbf{x}, \mathbf{t}) f(\mathbf{x}, \mathbf{t})$
- (2) satisfies the **balance** condition:  $L(x,t) \exp[-\beta H(x,t)] = 0$

Then,  $\exp \{-\beta [F(\tau) - F(0)]\} = \langle exp(-\beta W) \rangle$ 

Isothermal MD schemes (Nose-Hoover, Langevin, ...) satisfies the conditions (1) and (2).

#### Cumulant Expansion of Jarzynski's Equality





## 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  $\rightarrow$  reversible pulling  $\rightarrow$  exact free energy



## Reversible Pulling (v = 0.1 Å/ns)









## Umbrella Sampling w/ WHAM

![](_page_10_Figure_1.jpeg)

## Weighted Histogram Analysis Method

![](_page_11_Figure_1.jpeg)

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  $\Delta t$ :

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

## Weighted Histogram Analysis Method

![](_page_12_Figure_1.jpeg)

 $P_{0i}(x), i = 1, 2, ..., M$ : 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  $P_{0i}(x)$   $(i=1,2,...,M)$   

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

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

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![](_page_13_Figure_0.jpeg)

## **II. Finding Reaction Paths**

## **Typical Applications of Reaction Path**

Chemical reaction

Protein folding

Conformational changes of protein

### **Reaction Path**

## steepest-descent path for simple systems

![](_page_16_Figure_3.jpeg)

?

Reactions are **stochastic**: Each reaction event takes a different path and a different amount of time.

 $\Rightarrow$  Identify a representative path, revealing the reaction mechanism.

Reaction Path Based on the Mean-First Passage Time

Reaction coordinate r(x): the location of x in the progress of reaction

 $r(x) = MFPT \tau(x)$  from x to the product

MFPT  $\tau(\mathbf{x}) \leftarrow$  average over all reaction events

reaction path //  $-\nabla \tau$ 

### **Brownian Motion on a Potential Surface**

![](_page_18_Figure_2.jpeg)

Smoluchowski equation:  $\partial_{+}p = D\nabla \cdot (e^{-\beta U} \nabla (e^{\beta U} p))$ 

 $\rightarrow$  -D $\nabla \cdot (e^{-\beta U} \nabla \tau) = e^{-\beta U}$ 

#### **Brownian Motion on a Potential Surface**

β = 1

β = 8

![](_page_19_Figure_4.jpeg)

#### Brownian Motion on a Potential Surface

![](_page_20_Figure_2.jpeg)