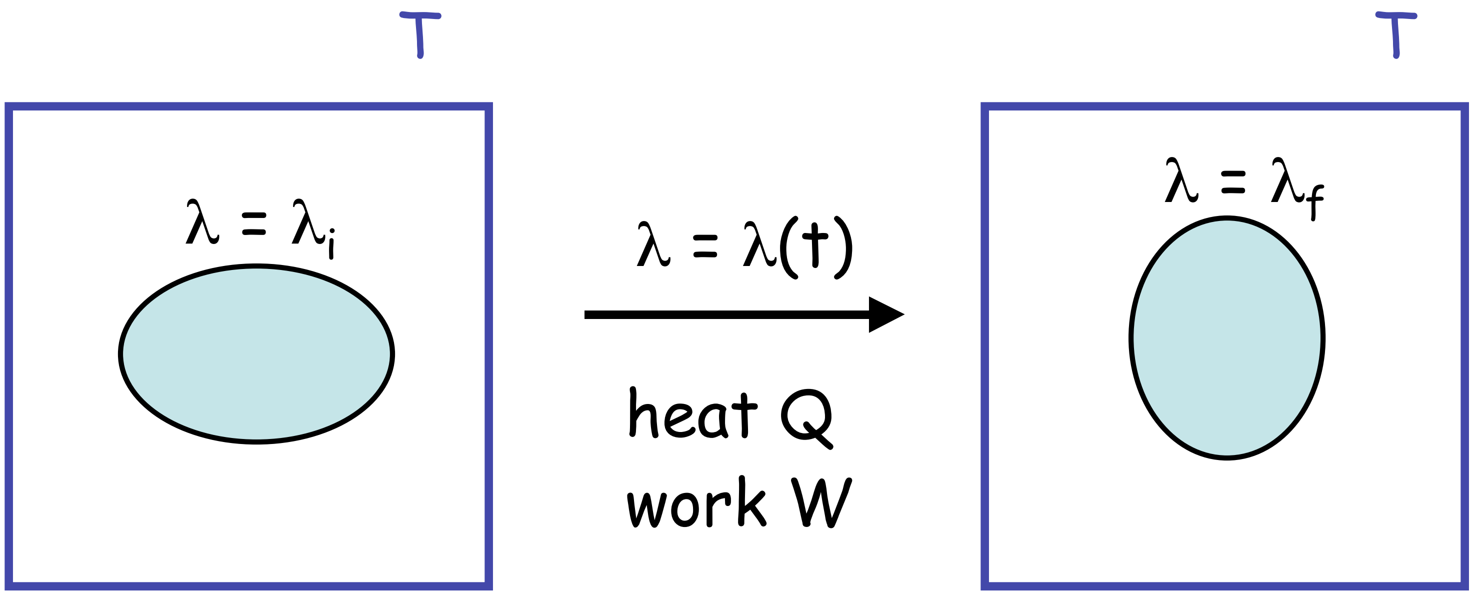
Free Energy Calculations

- Non-equilibrium SMD simulations
  using Jarzynski equality

- Equilibrium MD simulations
  Umbrella Sampling (WHAM)

Jarzynski Identity



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

Jarzynski (1997): $\langle \exp(-\beta W) \rangle = \exp(-\beta \Delta F)$

difficult to estimate

$e^{-\beta\langle W \rangle} \leq \langle e^{-\beta W} \rangle = e^{-\beta \Delta F}$

$\langle W \rangle \geq \Delta F$ JE $\Rightarrow$ 2nd law

Jarzynski, *Physical Review Letters* **78**, 2690 (1997)

Derivation of Jarzynski Identity

- Hamiltonian systems:

  energy conservation, Liouville's theorem

- Stochastic systems:

  Markov property, balance condition

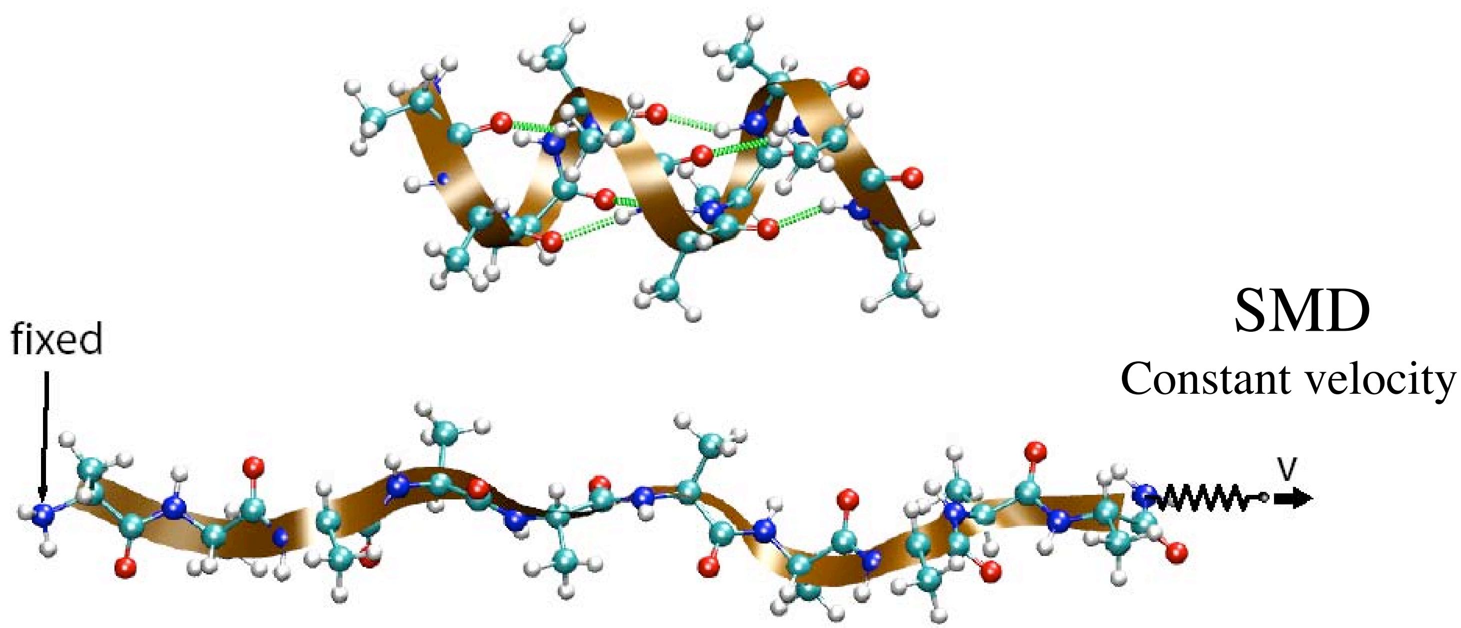
Stochastic algorithms in MD:

- NVT (Nose-Hoover)
- NpT (Langevin piston)   (Gibbs free energy)

markovian (no History)
Balance Condition   => Jarzynski Identity

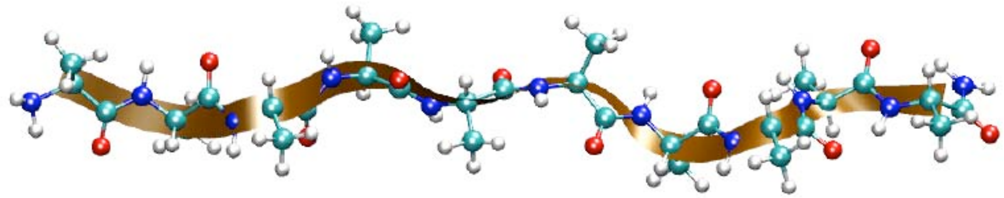
Helix-Coil Transition of Deca-alanine in vacuum

- Small, but not too small: 104 atoms
- Short relaxation time → reversible pulling → exact PMF



A system with Hamiltonian H_0

ϕ free energy along the reaction pathway



External potential: $h(r) = k(r - \lambda)^2/2$

$$H(r, p) = H_0(r, p) + h(r, \lambda)$$

$$\Delta F = -(1/\beta) \log \langle e^{-\beta W} \rangle$$

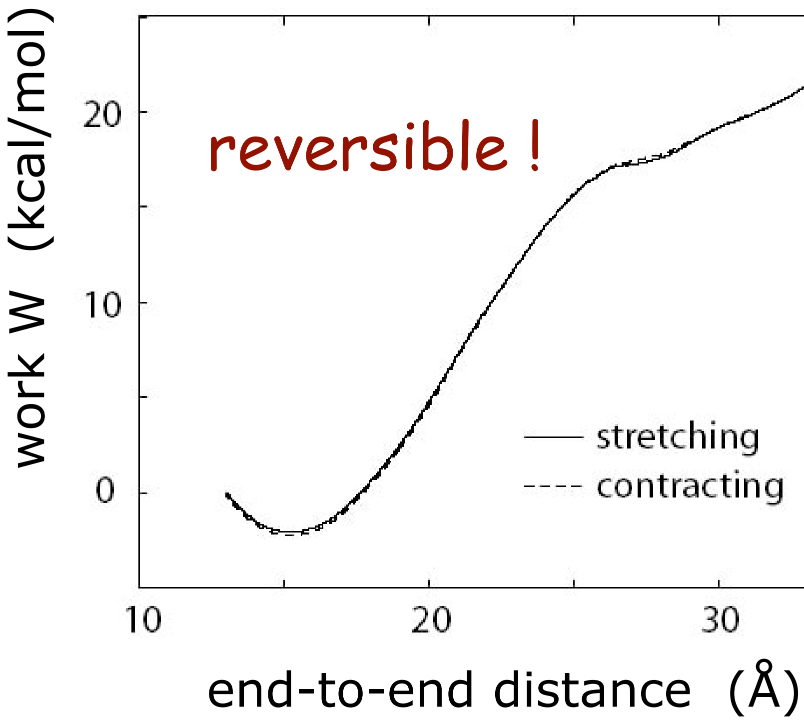
For stiff springs
(large spring constant)

$$\Delta F \approx \Delta \phi$$

here we have used 500pN/A,
Covalent bond strength 3500pN/A **Stiff!**

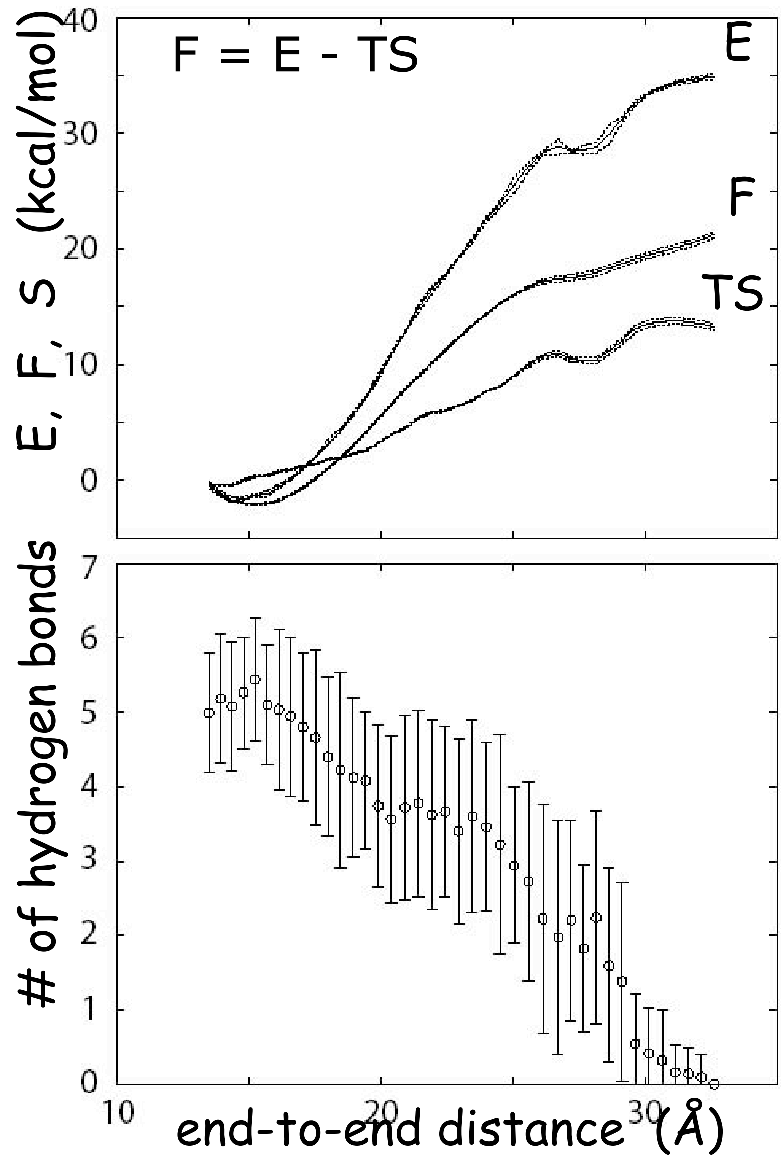
Reversible Pulling (v = 0.1 Å/ns)

Park, Khalili-Araghi, Tajkhorshid & Schulten, J Chem Phys 119, 3559 (2003)



$$\Delta F = \langle W \rangle$$

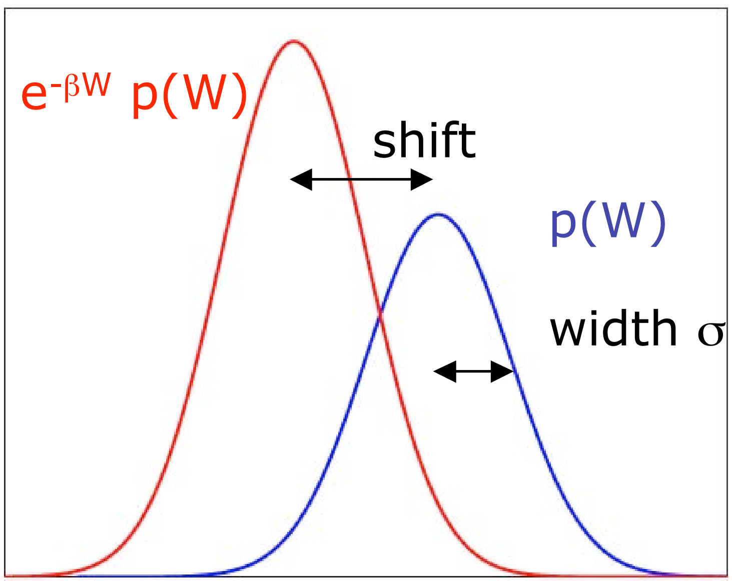
$$TS = E - F$$



Sampling Error and Truncation Error

$$\Delta F = -(1/\beta) \log \langle e^{-\beta W} \rangle$$
$$= \langle W \rangle - (\beta/2) (\langle W^2 \rangle - \langle W \rangle^2)$$
$$+ (\beta^2/6) (\langle W^3 \rangle - 3\langle W^2 \rangle\langle W \rangle + 2\langle W \rangle^3) + \cdots$$

Gaussian distributions



W

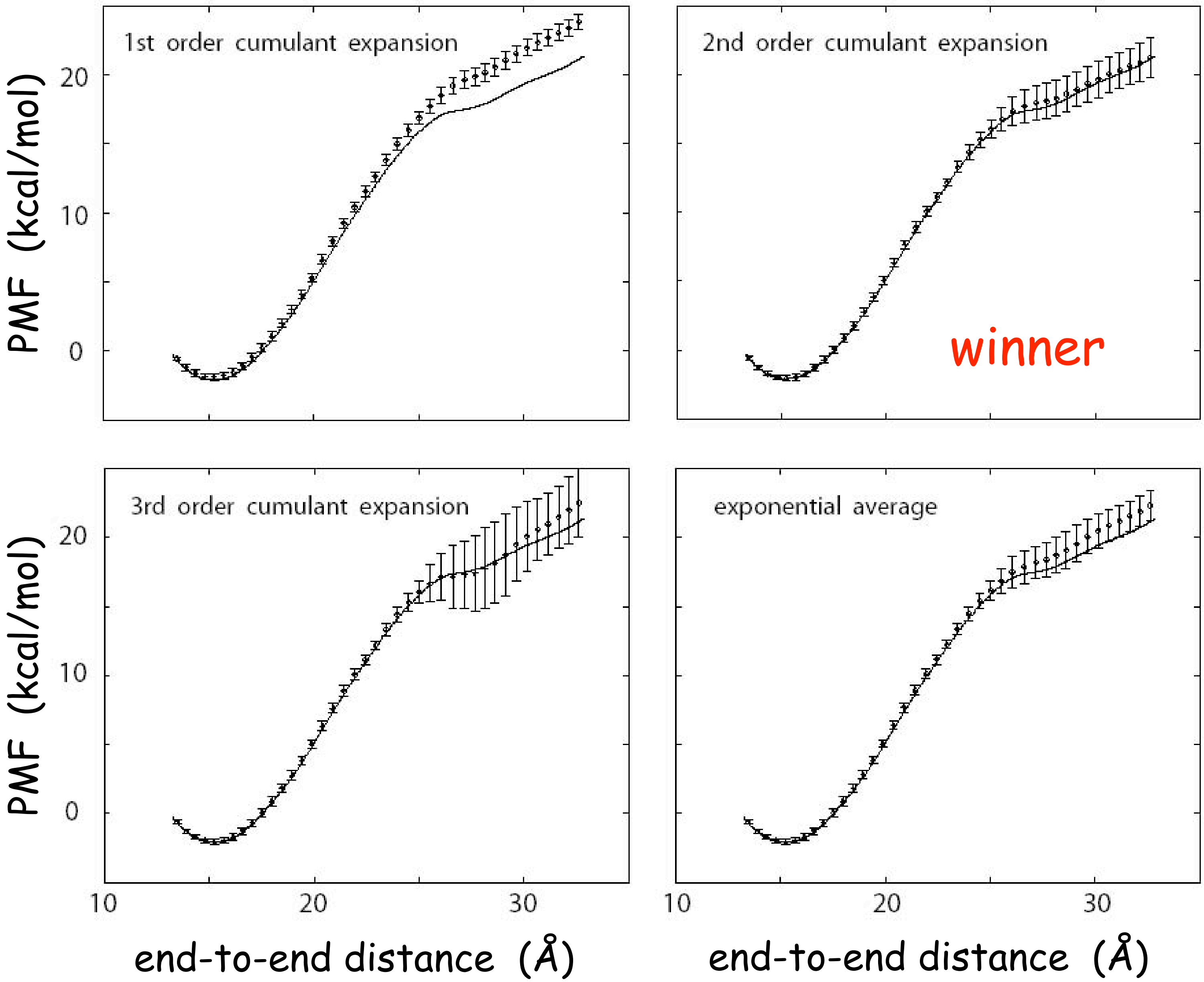
Example: Guassian
Shift = $\sigma^2 / k_B T$
shift/width ~ $\sigma / k_B T$

big in strong nonequilibrium

Biggest contribution to ΔF comes from small values of work, far from its average value, which requires ample sampling

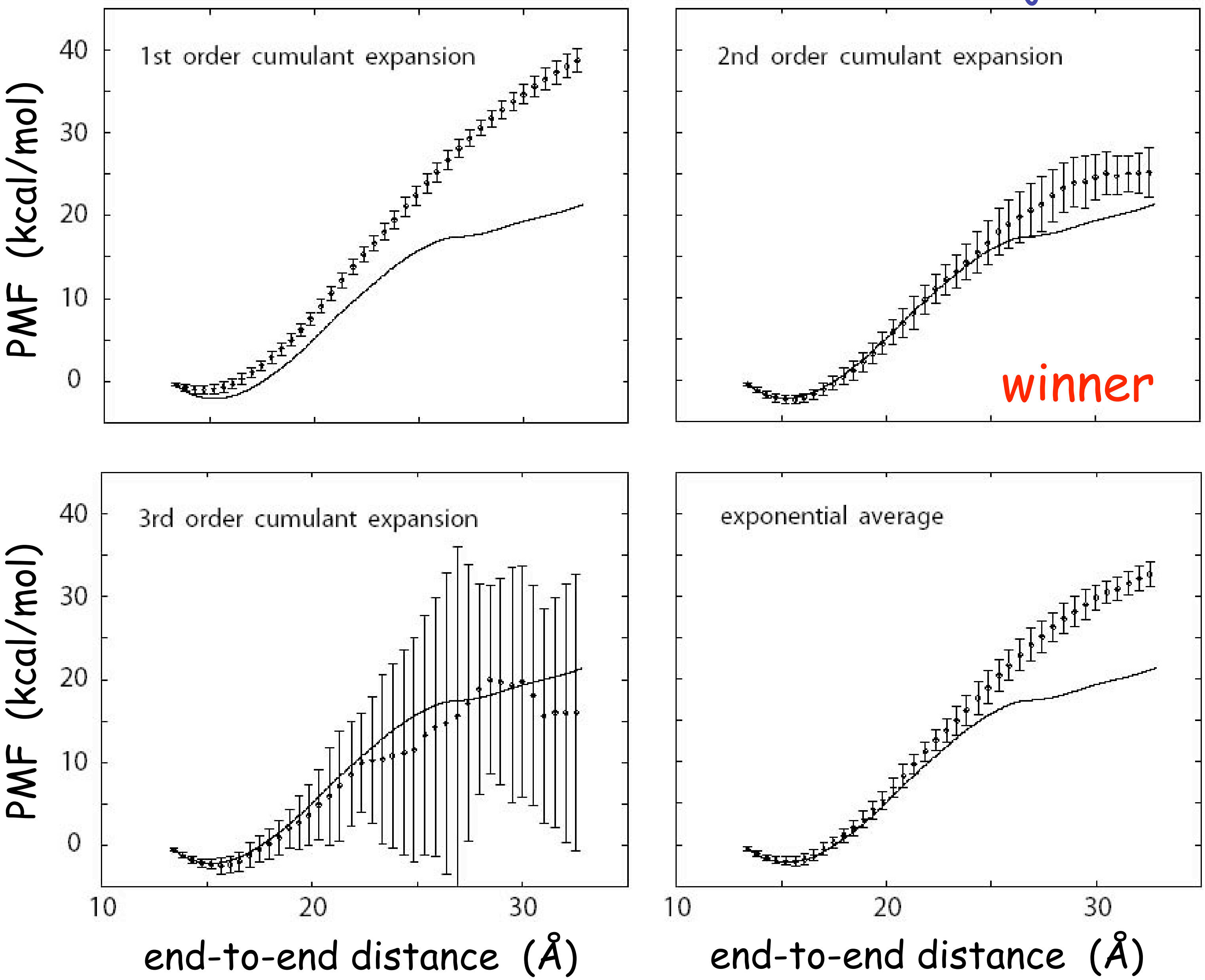
Irreversible Pulling (v = 10 Å/ns)

10 blocks of 10 trajectories



Irreversible Pulling (v = 100 Å/ns)

10 blocks of 10 trajectories



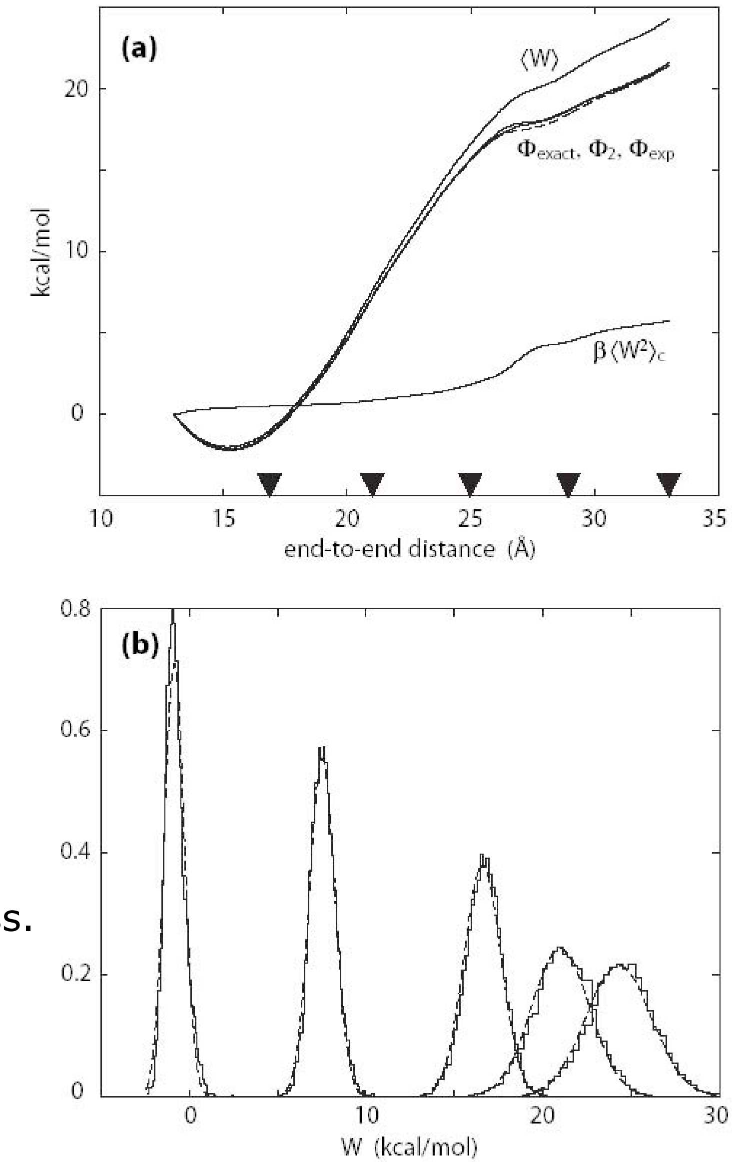
Guassian Work Distribution

- Langevin dynamics
- Harmonic guiding potential
- Stiff spring approximation

Guassian Work Distribution

v = 10 Å/ns

Park & Schulten, J Chem Phys, in press.



PMF from Umbrella Sampling

Equilibrium sampling of the configuration space.

Takes very long time

Confine the system to a small region, by applying a biasing potential

$$E_i = E_0 + V_i\,(x) \qquad P_i\,(x) \sim e^{\beta V_i(x)}\, h_i(x)$$

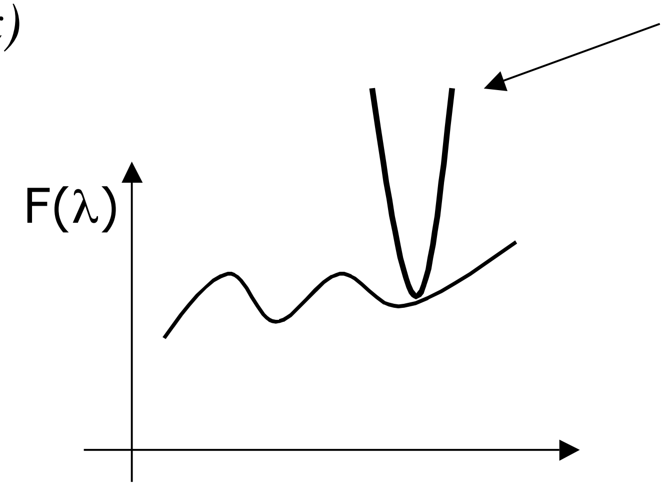
$$= Z_i\, e^{-\beta H\,(x)}$$

h_i : Histograms built from equilibrium MD simulations

$$V_i\,(x) = k\,(x - x_i)^2 / 2$$

Choice of biasing harmonic potential

$$k\,\Delta x^{\,2} \approx k_B\,T$$



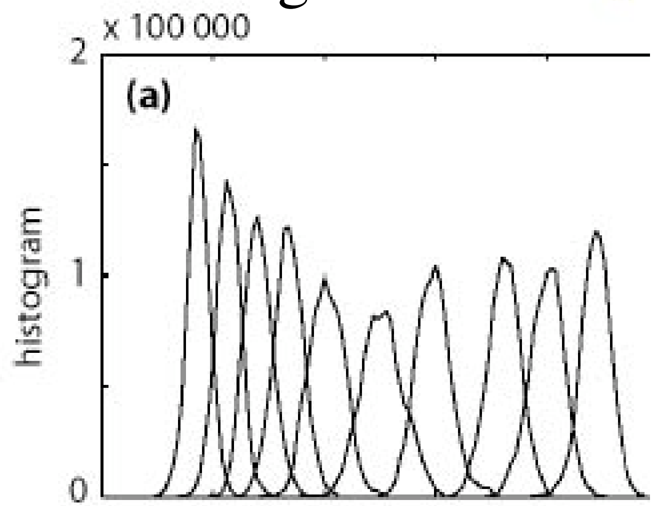
WHAM

Weighted Histogram Analysis Mehtod

Histogram

Biasing potential => free energy difference in each region

Free energy in the overlapping regions has to be matched.



$$P_0^{est} = \sum_i w_i(x) \exp[V_i / (k_B T)] Z_i / Z_0 P_i (x)$$

To minimize the statistical error, a **weight function** is used.

Weight function that minimizes the error:

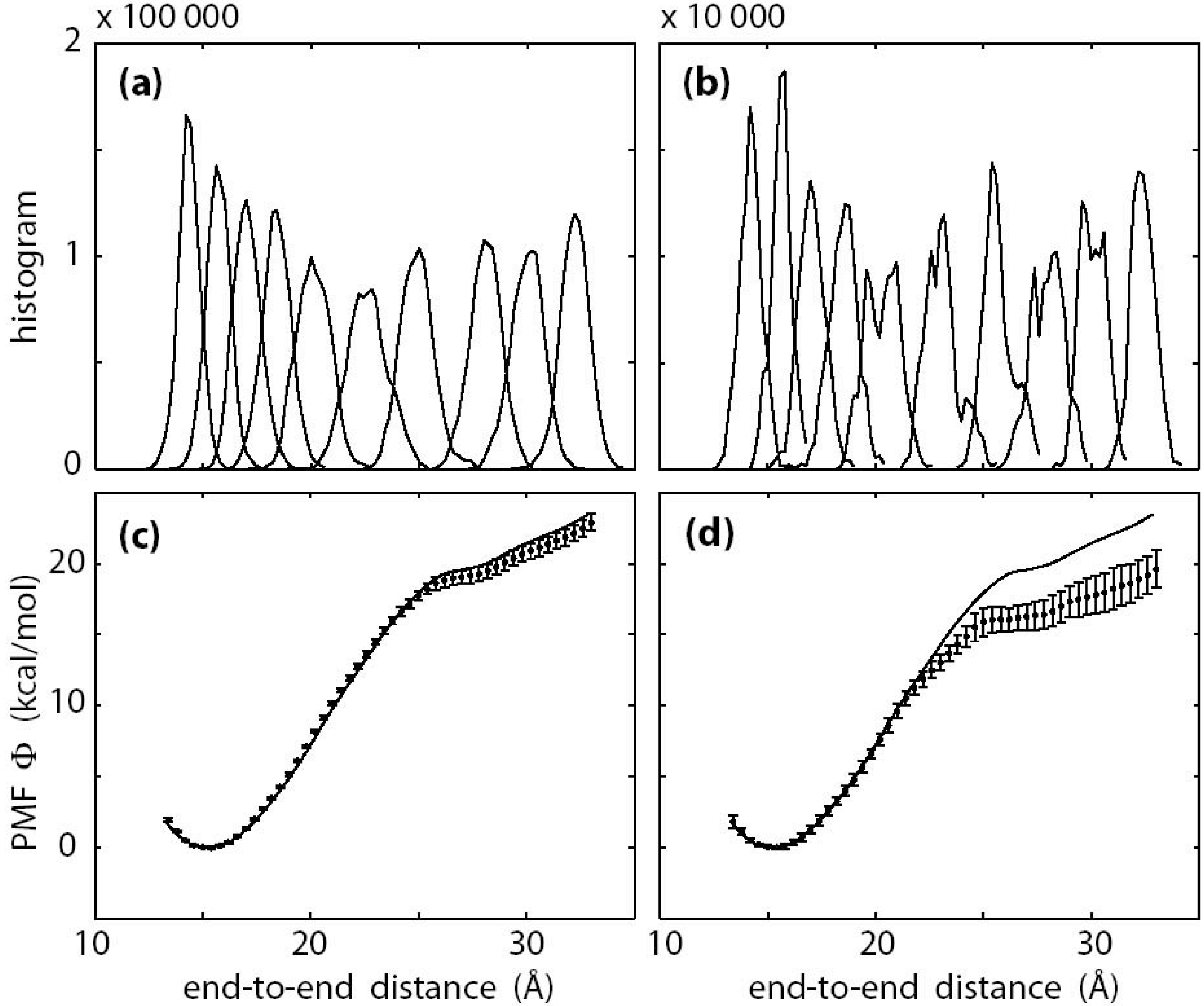
$$w_i(x) = [\exp(-V_i(x)/ k_B T) Z_0/Z_i] / \sum_i \exp(-V_i(x)/ k_B T) Z_0/Z_i$$

This results in a set of equations that has to be solved self consistently for Z_i

$$P_0^{est} = \sum_i w_i(x) \exp[V_i / (k_B T)] Z_i / Z_0 P_i (x)$$

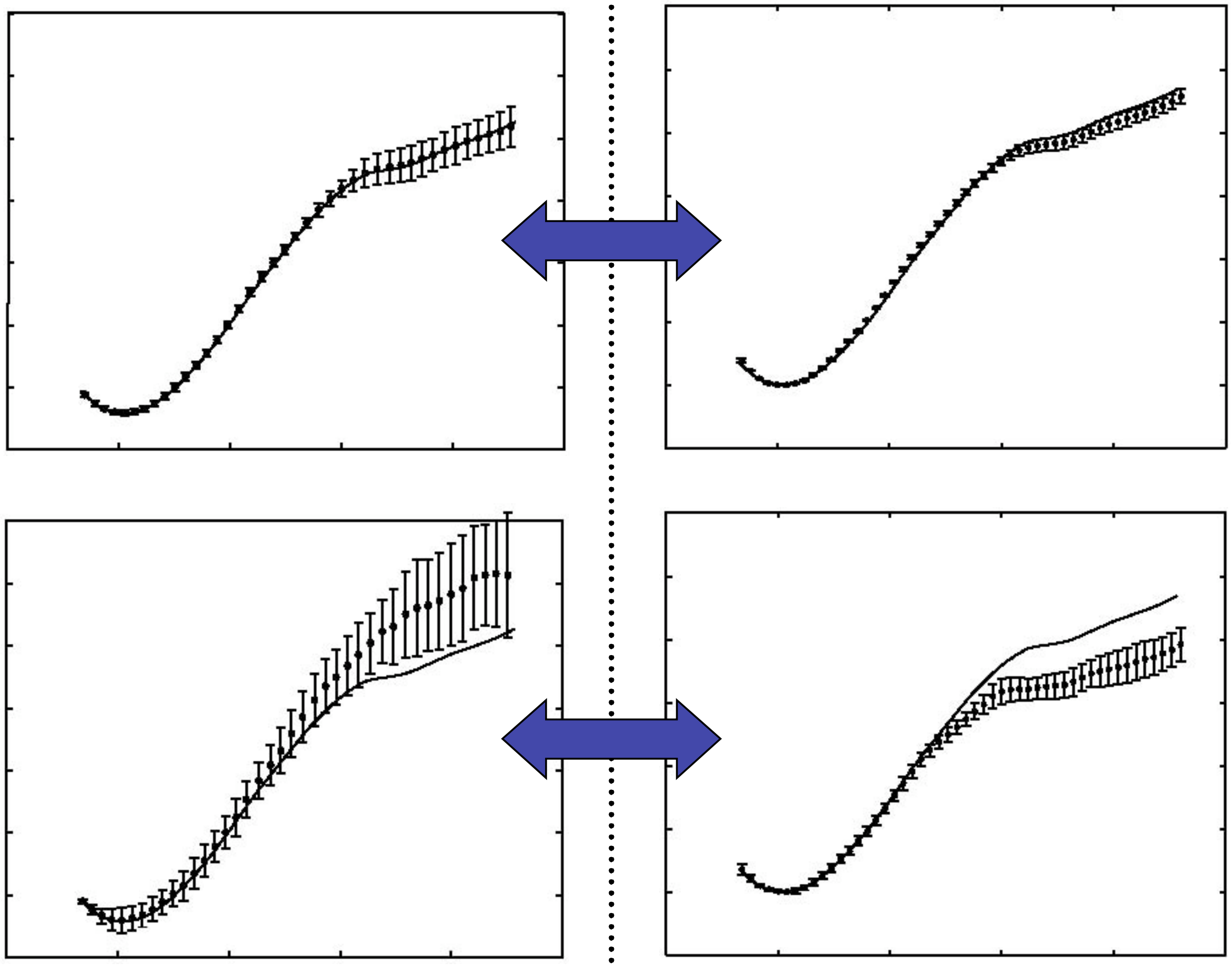
$$F(x) = -k_B T \log (P_0^{est} (x))$$

Umbrella Sampling w/ WHAM



SMD-Jarzynski | Umbrella Sampling

(equal amount of simulation time)



SMD-Jarzynski	Umbrella Sampling
simple analysis	coupled nonlinear equations (WHAM)
uniform sampling of the reaction coordinate	nonuniform sampling of the reaction coordinate