Reconstructing the free energy landscape of a mechanically unfolded model protein

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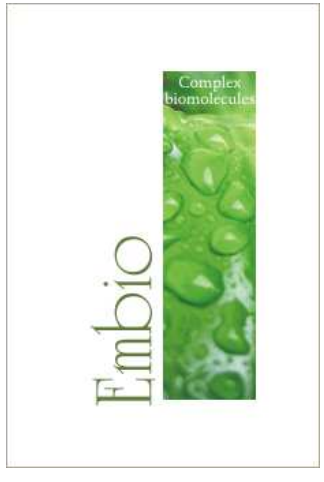

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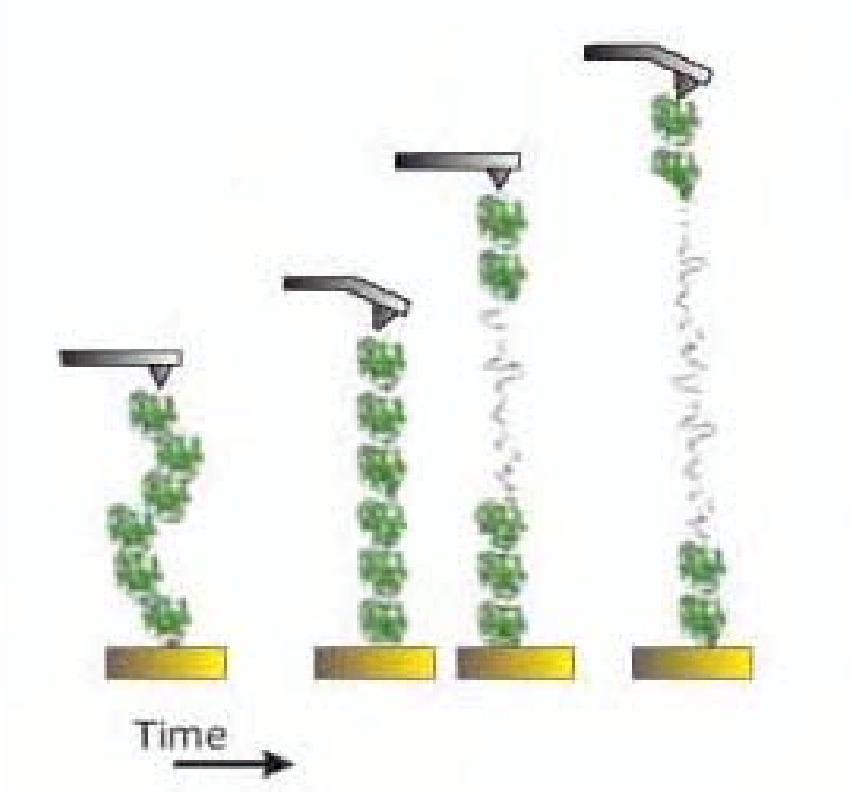
Introduction



Reconstruction of the free energy landscape of a simple protein model via two methods:

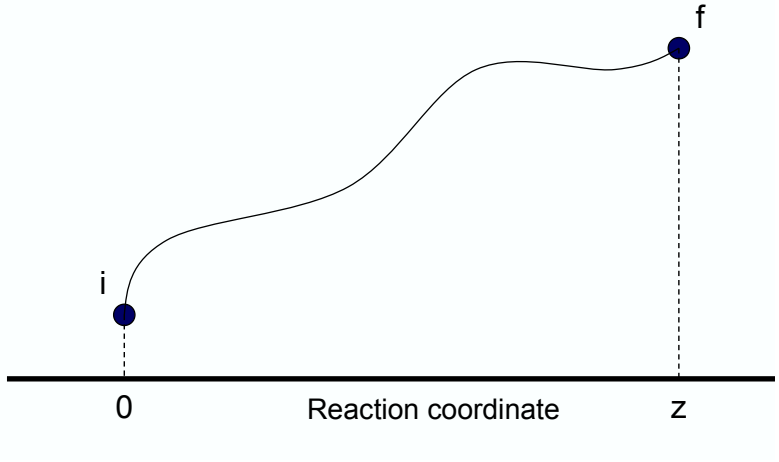
- mechanical unfolding manipulations (extended Jarzynski equality) → unzipping experiments on real proteins (AFM)
- thermodynamics of the protein inherent structures (IS=local minimum of the potential energy)

Summary

- Jarzynski equality (JE)
- Extended Jarzynski equality (EJE)
- The protein model
- Pulling protocol
- EJE reconstruction
- EJE: various temperatures
- Inherent structures (ISs)
- EJE versus ISs reconstruction
- Conclusions and perspectives

Jarzynski equality (JE)

Jarzynski equality [a] relates the work in an out of equilibrium process to the difference of equilibrium free energy.



$$\text{(1)} \qquad \langle e^{-\beta W_{if}} \rangle_{t_f} = e^{-\beta(F_{z(t_f)} - F_0)} \qquad \beta = 1/kT, \qquad F_0 = F_{z(0)}$$

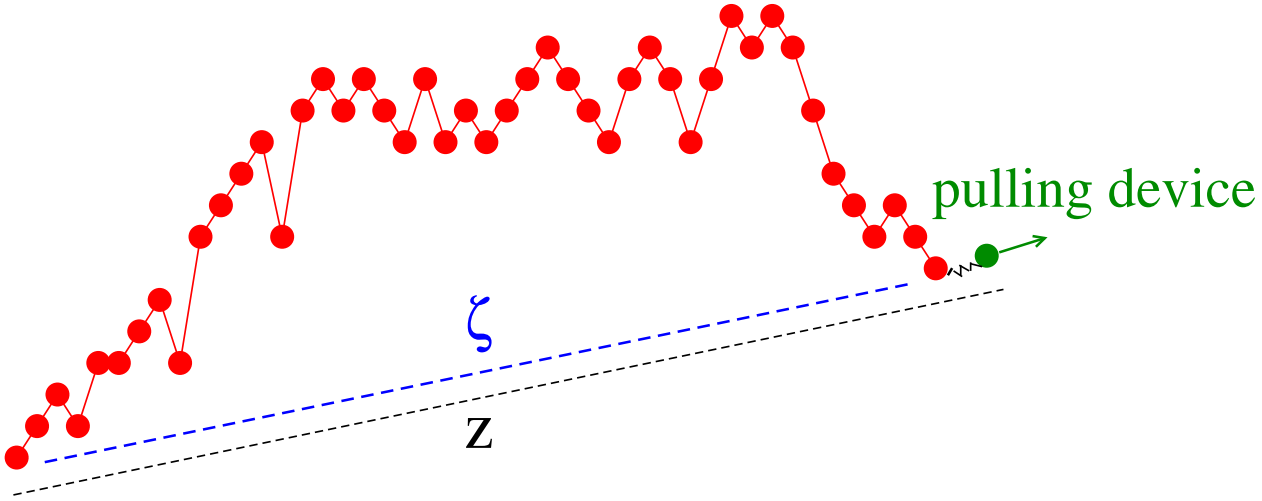
where:

- $\langle ... \rangle_{t_f} \rightarrow$ average on repetitions of the same experiment
- $W_{if} \rightarrow$ work done on the system
- $z \rightarrow$ reaction coordinate (manipulation parameter) $\rightarrow$ initial and final equilibrium states $\rightarrow$ externally controlled
- $z = z(t) \qquad t \in [0, t_f]$ manipulation protocol

[a] C. Jarzynski *Phys. Rev. Lett.* 78, 2690 (1997)

Extended Jarzynski equality (EJE)

stretching of a polypeptidic chain



(2) $$e^{\beta U_{z(t)}(\zeta)} \langle \delta(\zeta - \zeta(x)) e^{-\beta W} \rangle_t = e^{-\beta(F(\zeta) - F_0)}$$

where: [a]

- $F(\zeta) = -kT \ln \int dx \delta(\zeta - \zeta(x)) e^{-\beta H(x)}$
- $U_{z(t)}(\zeta) = c(z(t) - \zeta)^2/2 \rightarrow$ coupling potential
- ζ=end-to-end-distance $\rightarrow$ internal collective coordinate
- $z \rightarrow$ distance between the first bead and the pulling device

[a] G. Hummer and A. Szabo, *PNAS* **98**, 3658 (2001), A. Imparato and L. Peliti, *J. Stat. Mech.* 03005 (2006)

The protein model

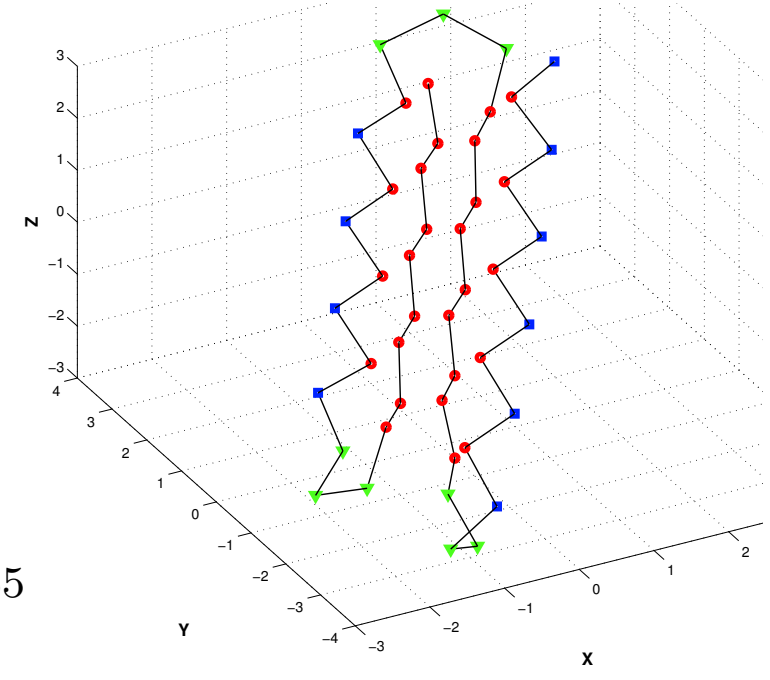
Model BPN (B=hydrophobic, P=polar, N=neutral) $N = 46$

Sequence: $B_9N_3(PB)_4N_3B_9N_3(PB)_5P$

(3) $$V = \sum_{i=1}^{N-1} V_i^{harm} + \sum_{i=2}^{N-1} V_i^{ang} + \sum_{i=2}^{N-2} V_i^{dih} + \sum_{i=1}^{N-3} \sum_{j=i+3}^{N} V_{ij}^{LJ}$$

where: [a]

$$V_i^{harm} = \alpha(r_{i,i+1} - \sigma)^2$$
$$V_i^{ang} = A\cos(\theta_i) + B\cos(2\theta_i)$$
$$V_i^{dih} = A_i[1 + \cos(\phi_i)] + B_i[1 + \cos(3\phi_i)]$$
$$V_{ij}^{LJ} = C_{ij}[(\frac{\sigma}{r_{ij}})^{12} - D_{ij}(\frac{\sigma}{r_{ij}})^6)]$$

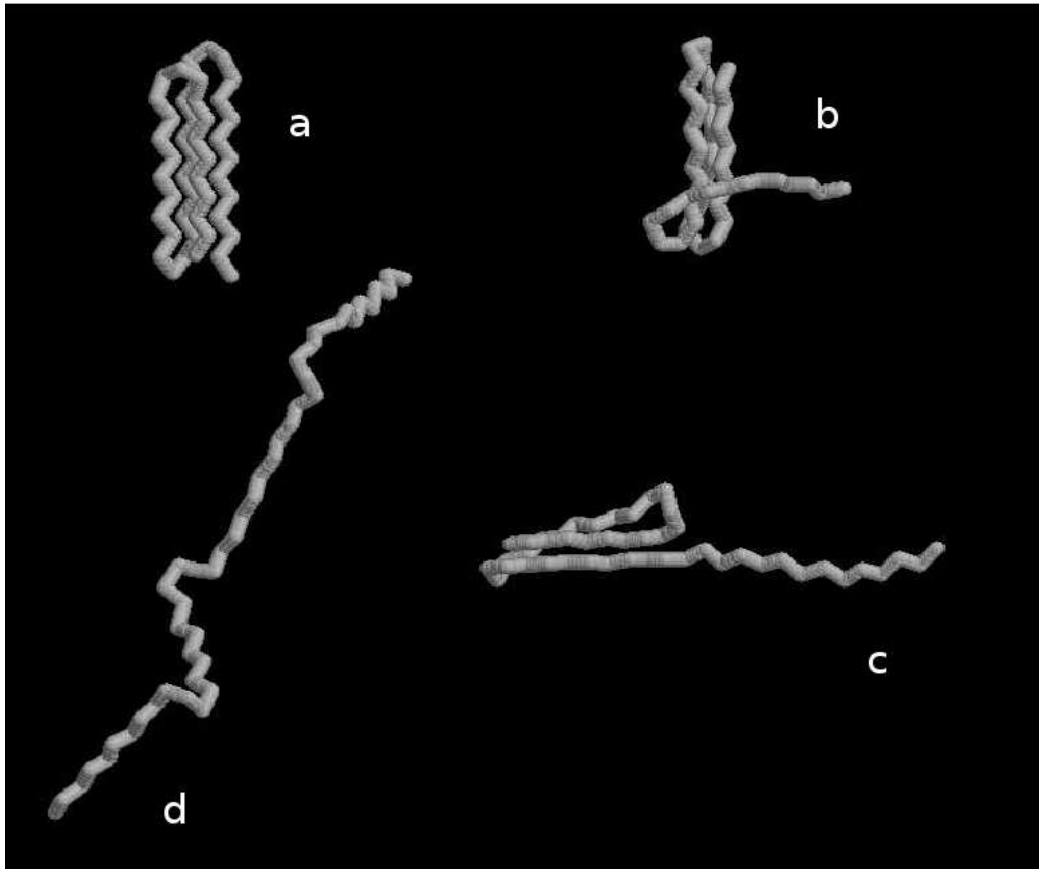


Thermodynamics:

- folding temperature $\rightarrow T_f = 0.28$
- hydrophobic collapse temperature $\rightarrow T_\theta = 0.65$

[a] J.D. Honeycutt and D. Thirumalai, *PNAS* **87**, 3526 (1990), R.S. Berry *et al*, *PNAS* **94**, 9520 (1999)

Pulling protocol



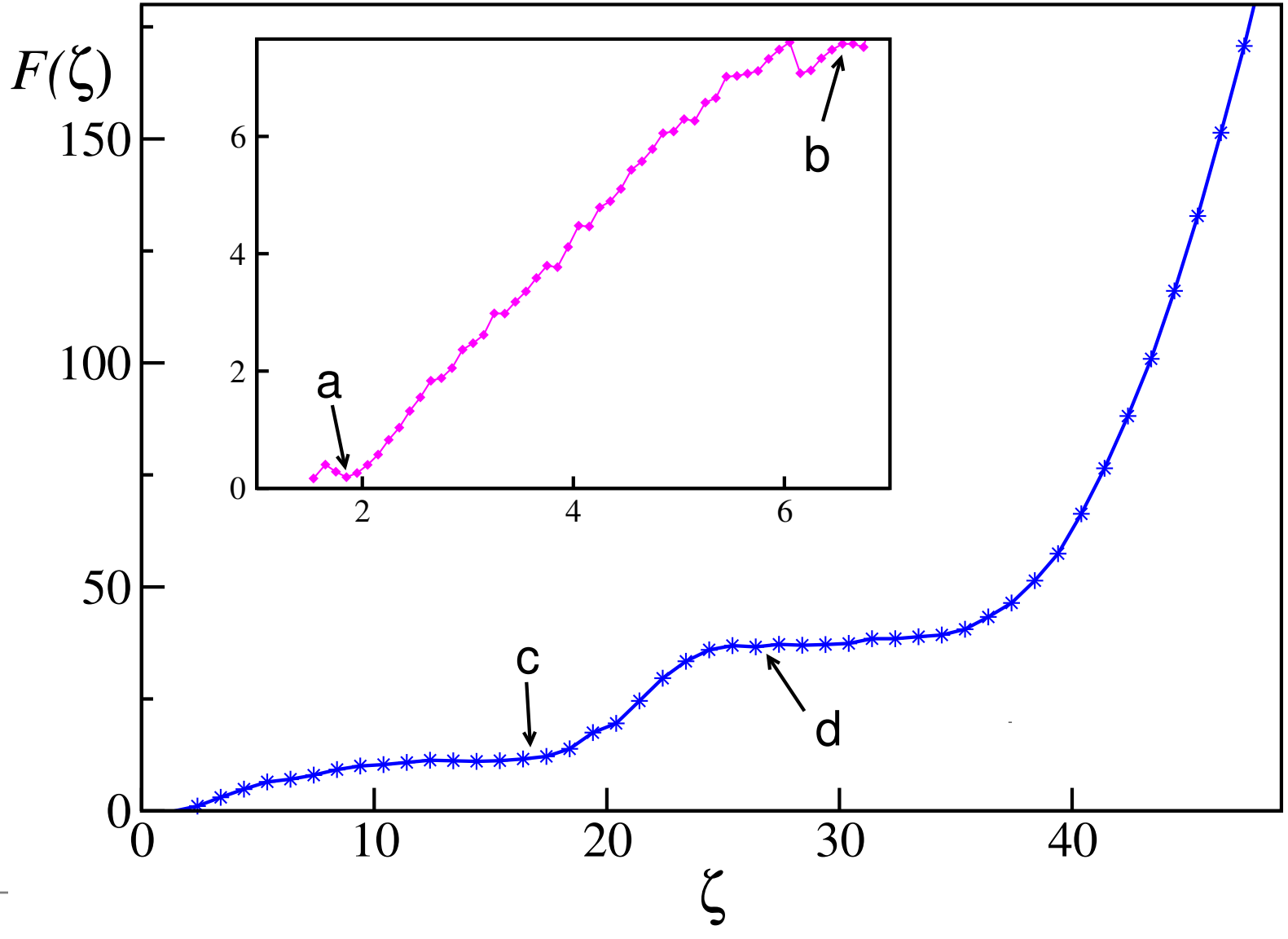
- the first bead is kept fixed and the last is attached to the pulling device moving along a fixed direction with the law:

  $z(t) = z(0) + v_p t \qquad t \in [0, t_f]$ linear protocol (v_p=constant velocity)

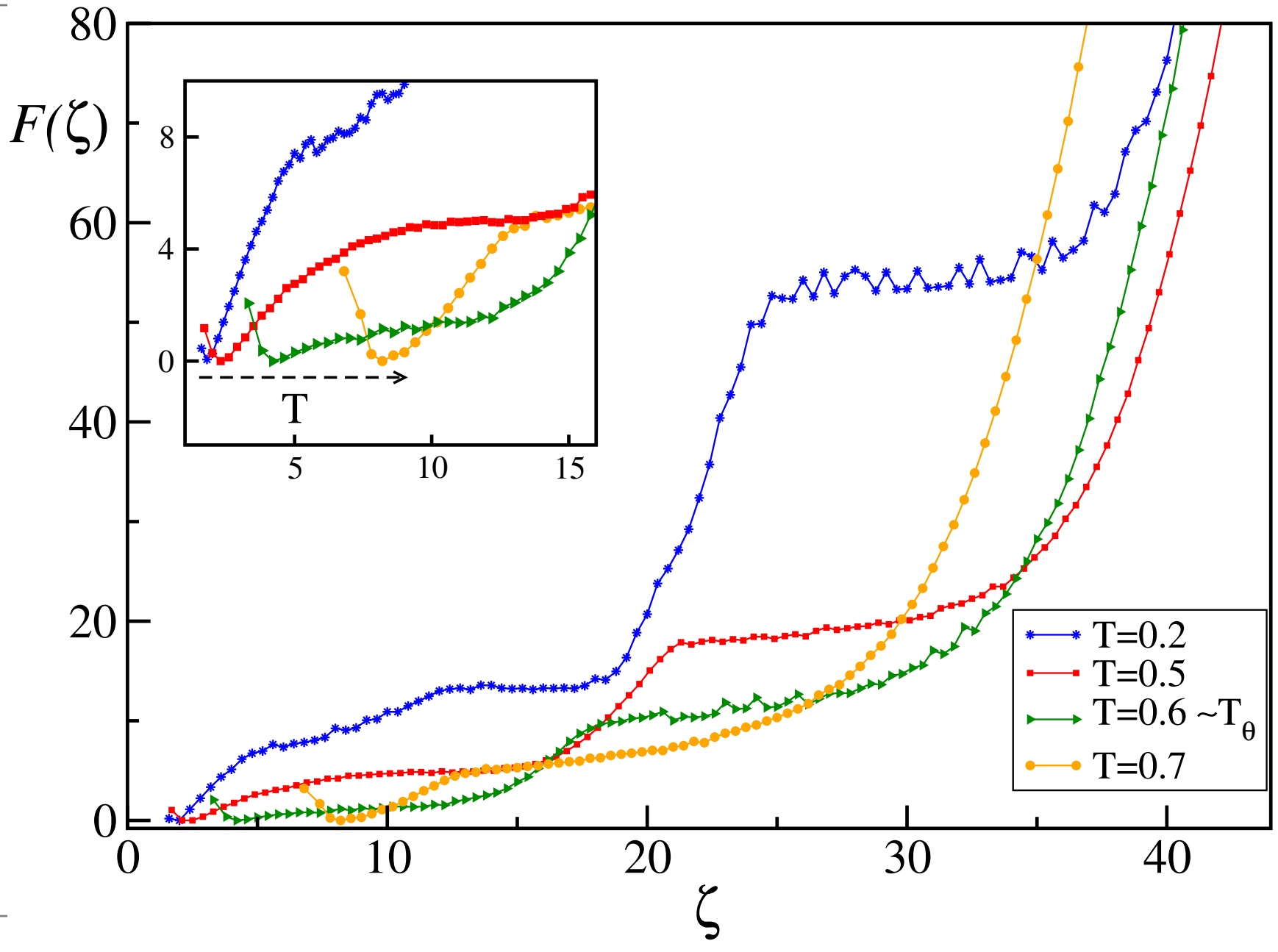
- forced unfolding performed at constant temperature via a Langevin dynamics

EJE reconstruction

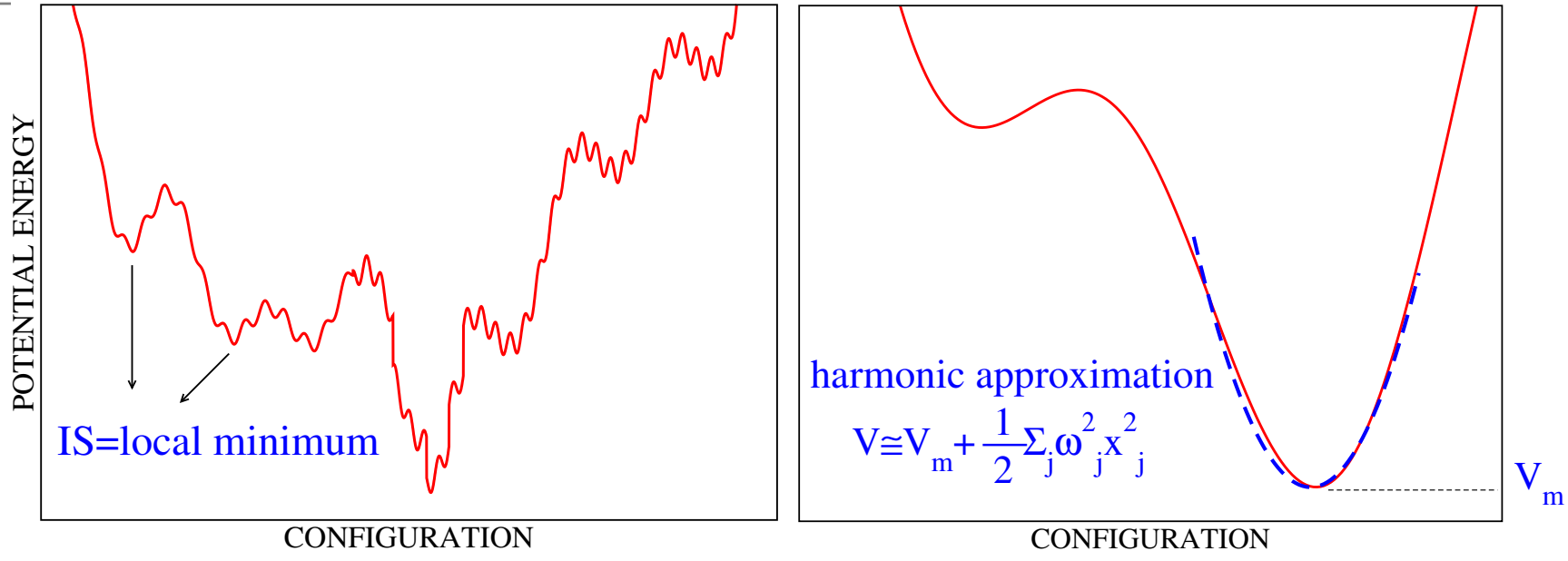
$T=0.3 \sim T_f$



EJE: various temperatures



Inherent structures (ISs)

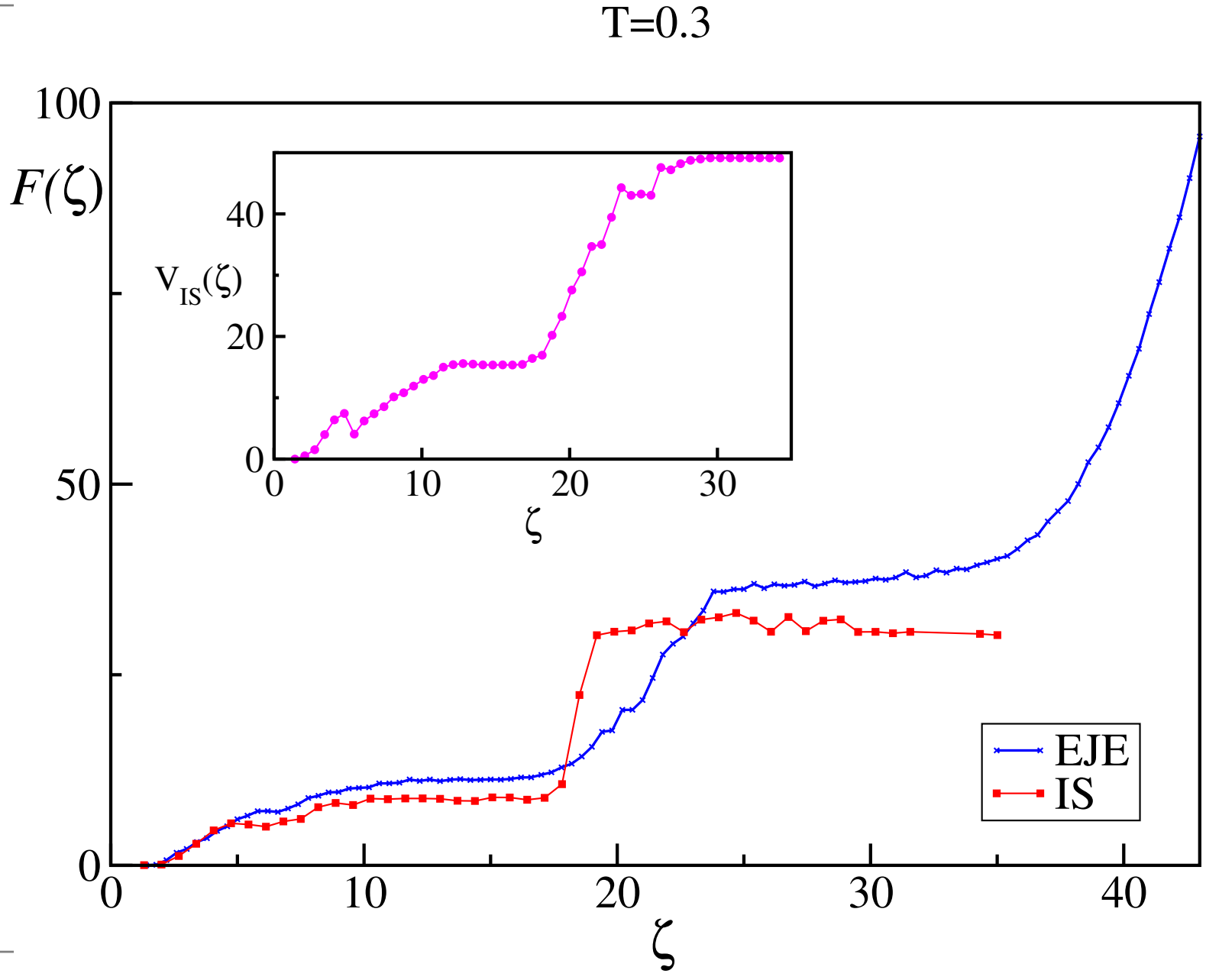


Within the IS formalism and assuming harmonic basins of attraction

(4) $$\mathrm{e}^{-\beta F_{IS}} = \sum_m \mathrm{e}^{-\beta(V_m+W_m)} \simeq \sum_m \mathrm{e}^{-\beta V_m} \prod_{j=1}^{3N-6} (T/\omega_m^j) \qquad \text{where :}$$

- V_m (resp. W_m) $\rightarrow$ potential (resp. vibrational free) energy of the IS;
- $\{\omega_m^j\} \rightarrow$ frequencies of the vibrational modes.

EJE versus ISs reconstruction



Conclusions and perspectives

We have used two different approaches for reconstructing the free energy landscape of a protein model (good folder) as a function of an internal coordinate of the system (end-to-end distance):

- agreement between ISs and EJE reconstruction $\longrightarrow$ integration of the two methods provides complementary information on the protein landscape.

Future plans:

- application of the two methods for reconstructing the free energy landscape of a bad folder (same number and types of residues of the good folder but random sequence).