A simple model for protein mechanical unfolding

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Motivations

- Mechanical unfolding experiments on biopolymers (Nucleic Acids, Proteins)

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- Information about the internal structure of the molecules
- simple model of proteins to study the relations between the experimentally observed unfolding kinetics and the molecular structure

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- connected by C–N peptide bonds,
- with a well–defined low–energy, low–entropy native state,
- whose native structure is thought to be important for the kinetics

The Wako-Saitō-Muñoz-Eaton model

WSME model

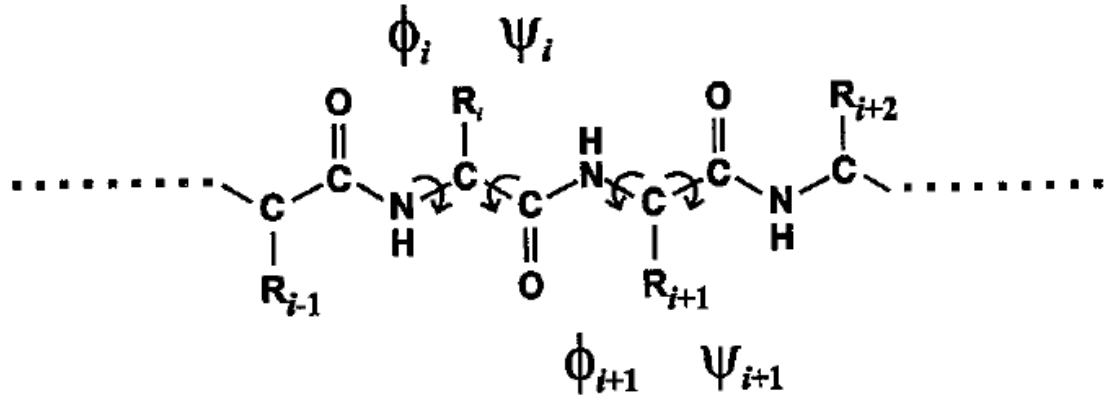


FIG. 1. Schematic of peptide backbone showing that fixing the orientation of the CO-NH peptide plane by defining the two dihedral angles (ψ_i, ϕ_{i+1}) also defines the relative orientation of the C_α-C_β bond vectors of residues R_i and R_{i+1}.

(*Wako and Saitô J. Phys. Soc. Jpn (1978), Muñoz and Eaton, PNAS (1999)*)

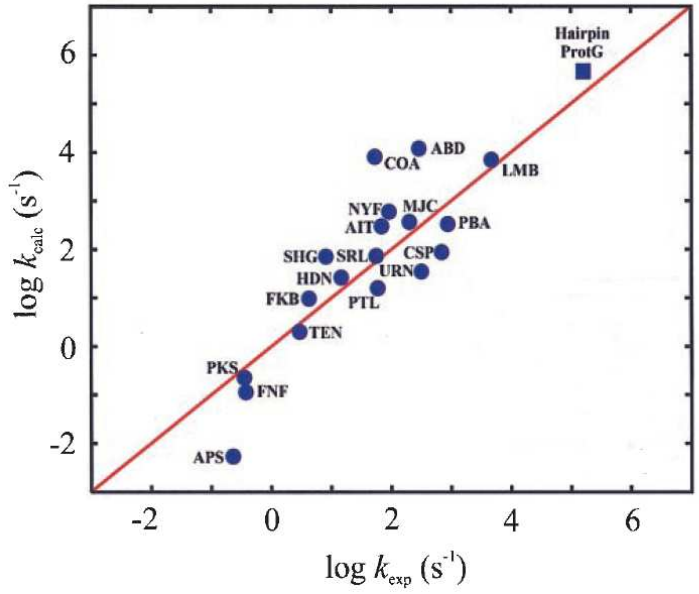
Details

- A binary variable $m_i = 0, 1$ is associated to each peptide bond $i = 1, \ldots N$.
- $m_i = 1$ for a native peptide bond, 0 otherwise
- an entropy $q_i > 0$ is associated to each non–native bond
- two aminoacids can interact only if
  - they are in contact in the native state
  - all the peptide bond between them are ordered (native)
- Effective free energy (“Hamiltonian”)

$$H = -\sum_{i<j} \epsilon_{ij} \Delta_{ij} \prod_{k=i}^{j} m_k - T \sum_i q_i (1 - m_i)$$

WSME model vs. experiments

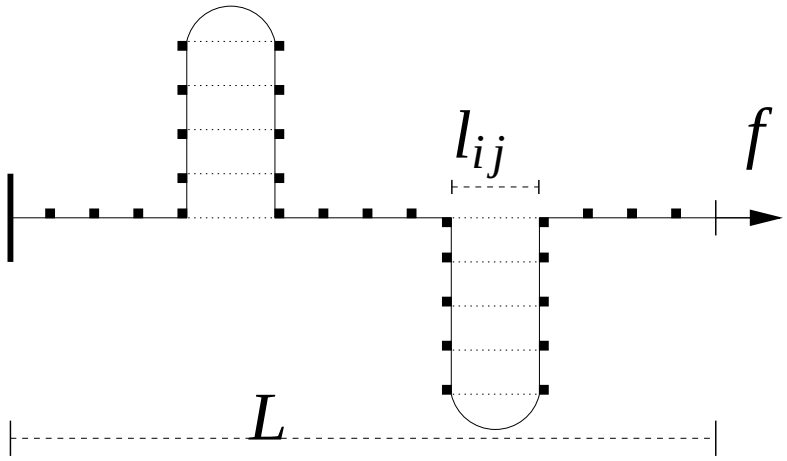
The model predicts quite well the experimental (thermal) folding rates of a large number of proteins



V. Muñoz and W.A. Eaton, Proc. Natl. Acad. Sci. U.S.A. **96**, 11311 (1999).

WSME model under force

Generalization of the WSME model of proteins (A.I., A. Pelizzola, M. Zamparo, cond-mat 2006, to appear in PRL)



$$\mathcal{H}(\{m_k\},\{\sigma_{ij}\}) = \sum_{i=1}^{N-1}\sum_{j=i+1}^{N} \epsilon_{ij}\Delta_{ij}\prod_{k=i,j} m_k - fL(\{m_k\},\{\sigma_{ij}\}).$$

$$L(\{m_k\},\{\sigma_{ij}\}) = \sum_{0\le i<j\le N+1} l_{ij}\sigma_{ij}(1-m_i)(1-m_j)\prod_{k=i+1}^{j-1} m_k.$$

$m_k = 0, 1$, k-th peptide bond in nonnative–native state;

$\sigma_{ij} = \pm 1$, stretch l_{ij} parallel-antiparallel to the force

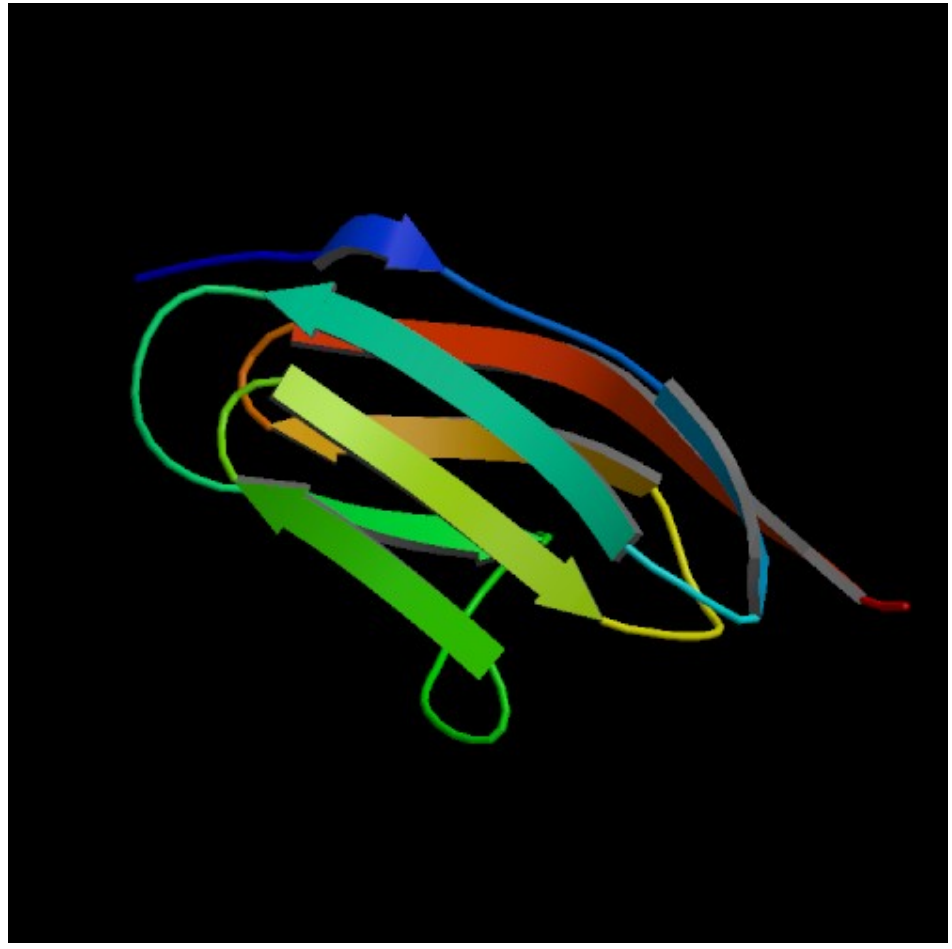
Equilibrium properties

The WSME model can be solved exactly

Bruscolini P., Pelizzola A. (2002) *Phys. Rev. Lett.* 88:258101.

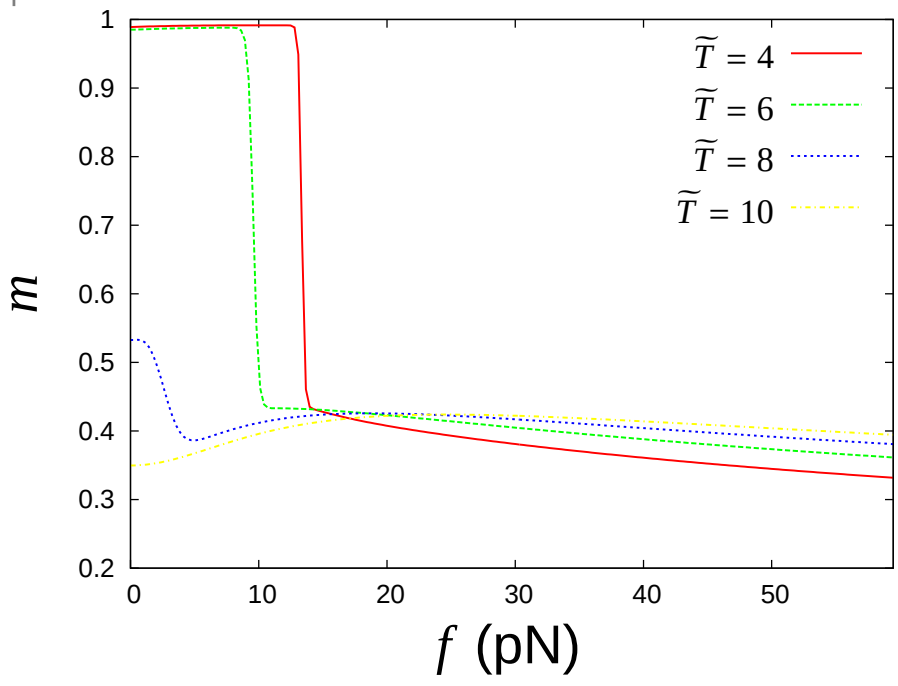
Pelizzola A. (2005) *J. Stat. Mech.-Theory Exp.* P11010

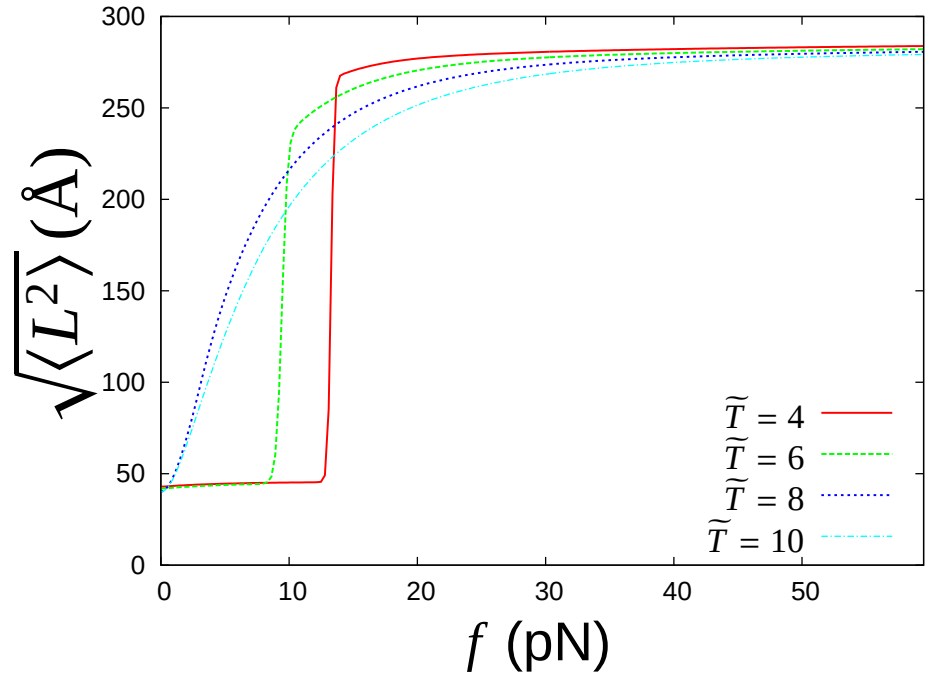
The I27 module of titin, pdb code 1TIT



89 aminoacids, $\epsilon/k_B = 43$ K, $\widetilde{T} = k_B T/\epsilon$

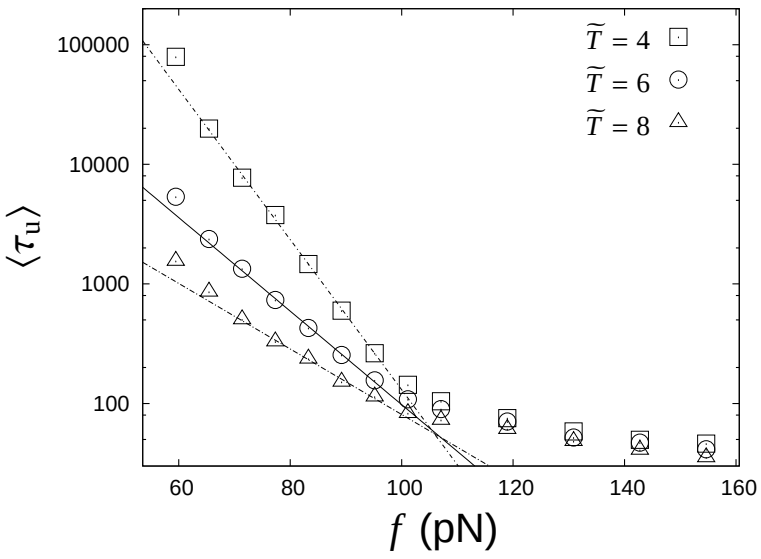
Equilibrium properties (1TIT)

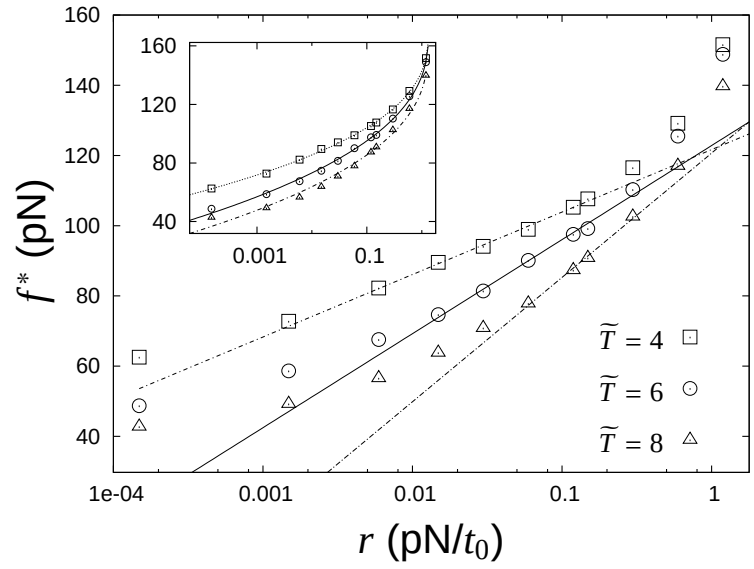




$\widetilde{T} = k_B T/\epsilon$, $m = \frac{1}{N}\sum_{i=1}^{N} m_i$

Force clamp and dynamic loading (1TIT)





$$\langle\tau_{\mathrm{u}}\rangle = \omega_0^{-1} \exp\left[\beta\left(\Delta E_{\mathrm{u}} - f x_{\mathrm{u}}\right)\right]$$

$$f^* = \frac{k_B T}{x_u} \ln[\beta r x_u \tau_0]$$

From the fits $x_u = 3\text{Å}$, agreement with the experimental value $x_u = 2.5\text{Å}$ Carrion-Vazquez M. *et al.* PNAS (1999).

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- $\mathcal{H}_\mu(x)$, x microscopic state (e.g. $x = \{r_i, p_i\}$), $\mu = \mu(t)$ manipulation parameter

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- Target: unperturbed free energy as a function of Y

$$\mathcal{F}_0(Y) = -\beta^{-1} \ln \int \mathrm{d}x\, \delta(Y - Y(x))\, \mathrm{e}^{-\beta \mathcal{H}_0(x)}$$

$\beta = 1/(k_B T)$

Extended Jarzynski equality

Evaluation of $\mathcal{F}_0(Y)$ from experiments

$$\mathrm{e}^{-\beta\mathcal{F}_0(Y)} = \mathrm{const} \cdot \mathrm{e}^{\beta U_{\mu(t)}(Y)} \left\langle \delta(Y - Y(x_t))\mathrm{e}^{-\beta W} \right\rangle_t$$

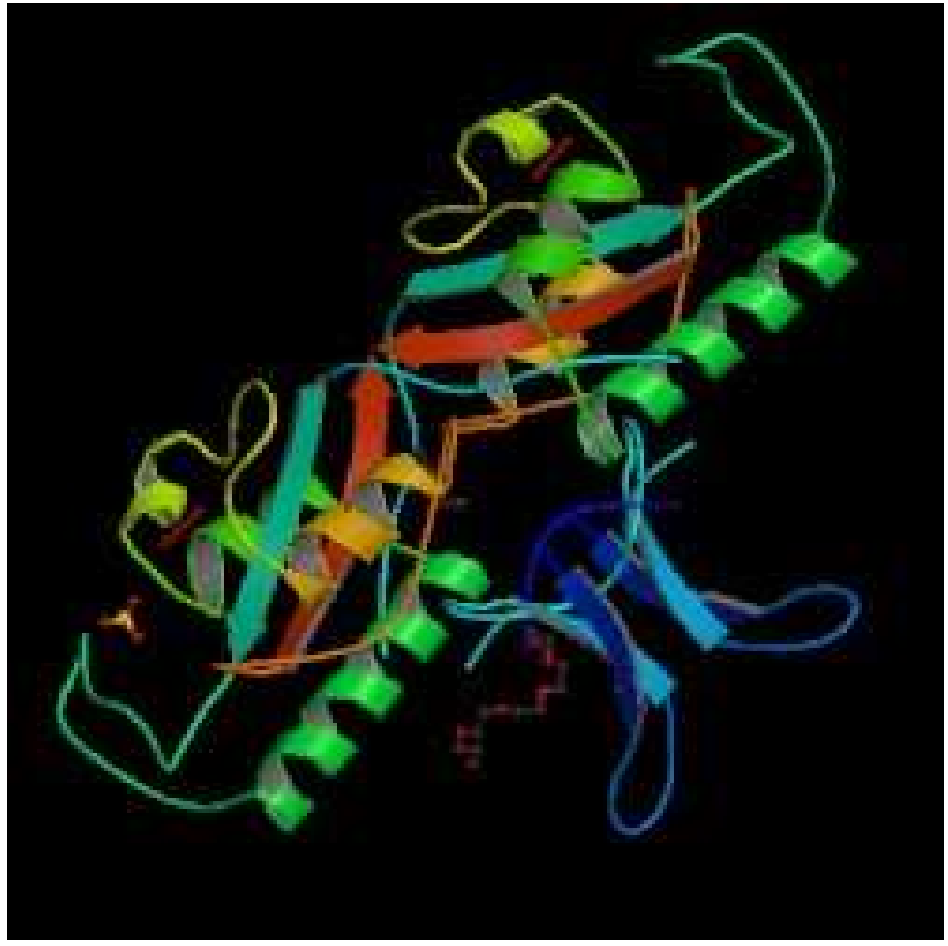
Crooks 1999, Hummer and Szabo 2001, Imparato and Peliti 2006

- Typical value of the work associated to the unfolding of 1TIT $\sim$ hundreds of $k_B T$.
- The JE involves the exponential of the work.
- We consider a smaller protein, the PIN1

For an illuminating discussion on the range of applicability of the JE to microscopic systems see Ritort F., in *Seminaire Poincare* **2** (2003) 193–226.

The PIN1 protein

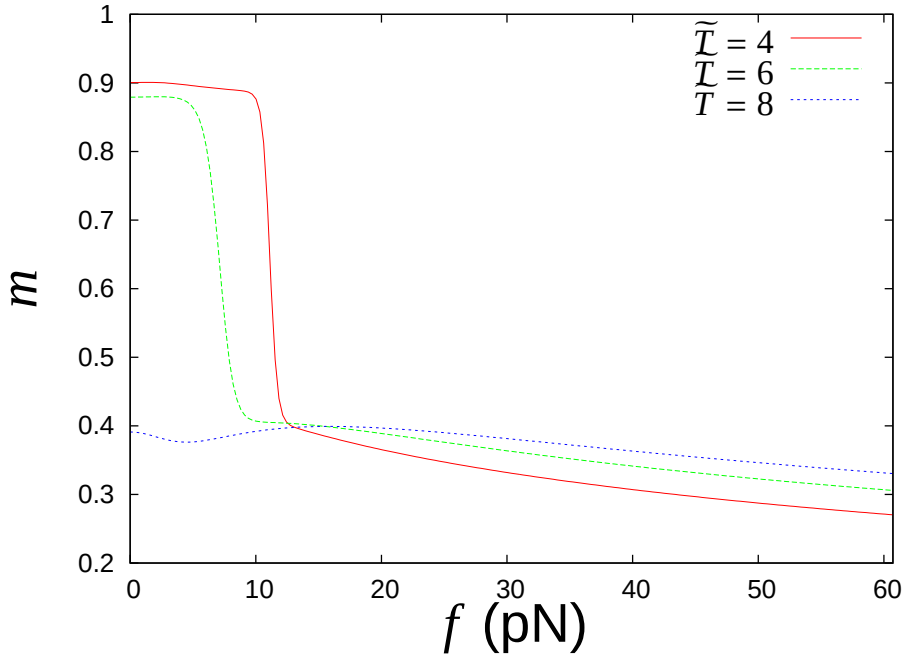
PIN1 protein (1I6C, Protein Data Bank, http://www.pdb.org/)

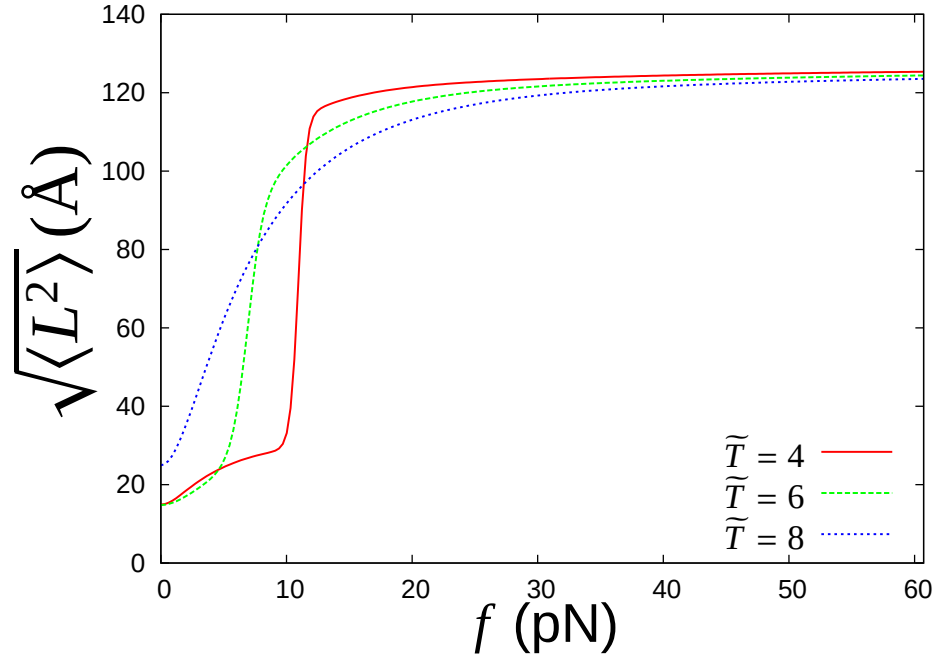


39 aminoacids, $\epsilon/k_B \simeq 44$ K.

Equilibrium Properties (PIN1)

$\widetilde{T} = Tk_B/\epsilon$ reduced temperature.



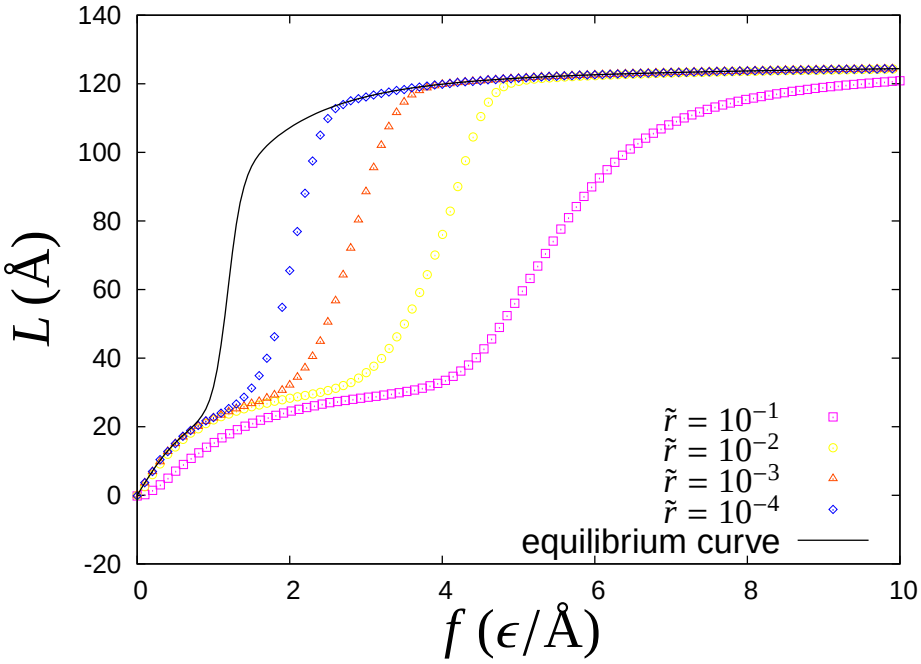


Free energy landscape of the PIN1 protein

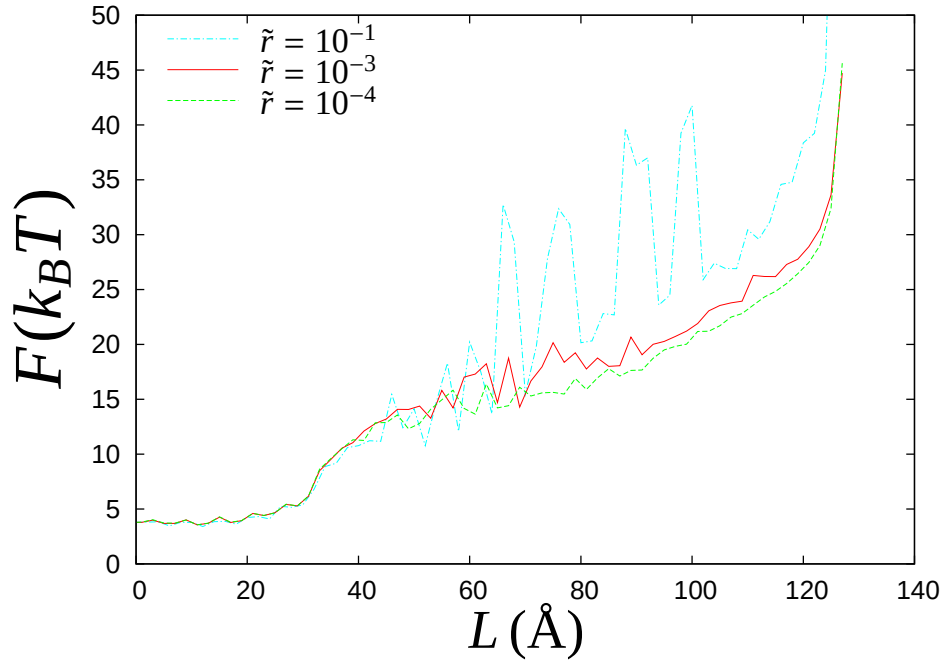
$$f(t) = r \cdot t$$

$\widetilde{T} = 6$, $\tilde{r} = r \cdot (t_0/\epsilon)$Å

"average trajectory"

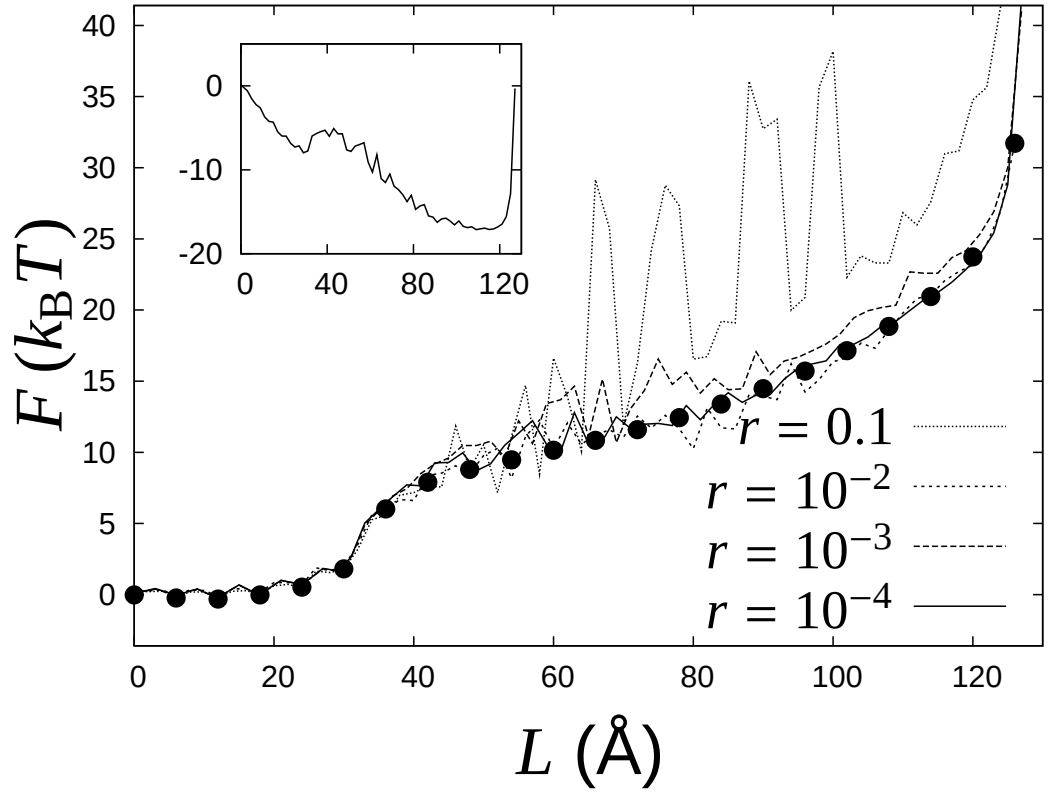


JE output



As the pulling rate r decreases the estimated curves collapse onto a single one.

Comparison with exact result

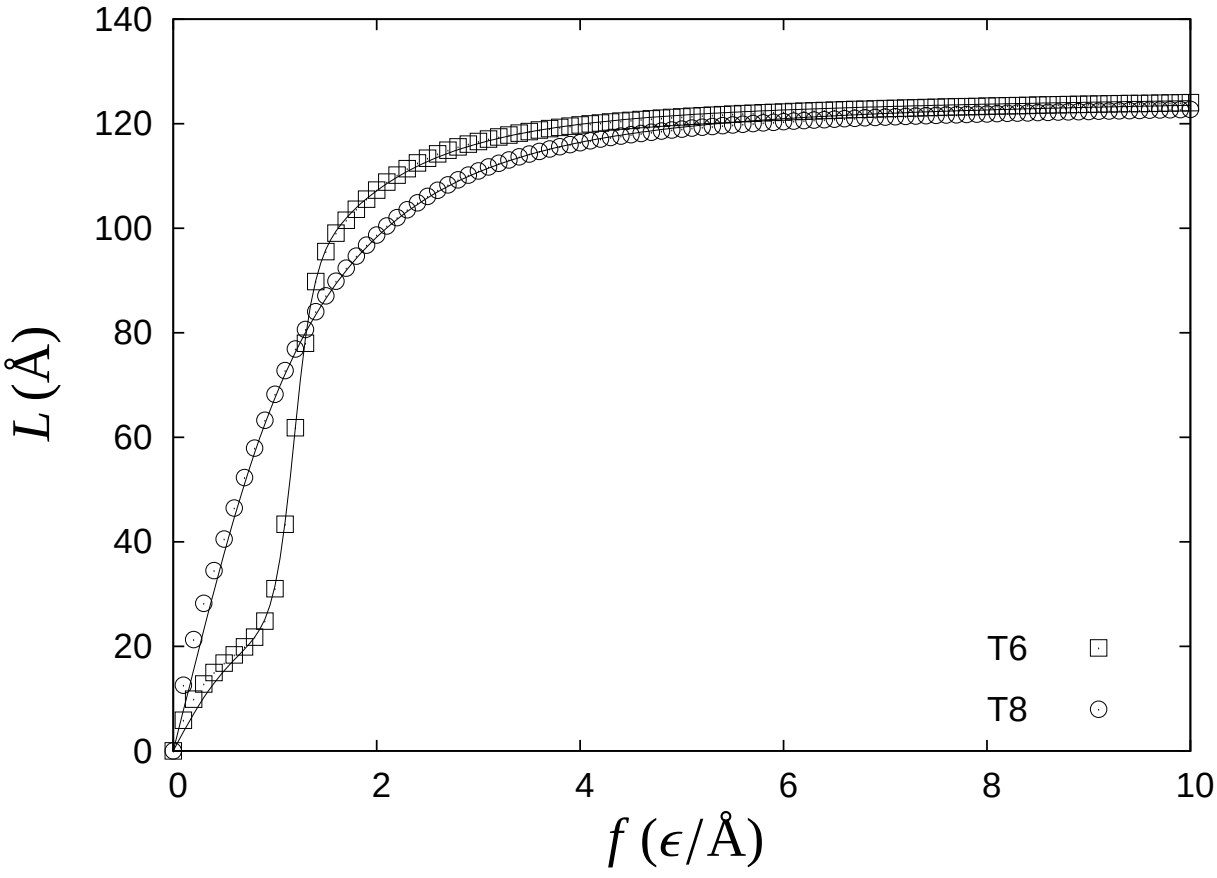


Free energy vs. L for PIN1. $\widetilde{T} = 6$; Pulling rates r. Dots: equilibrium values. Inset: Tilted free energy $F(L) - fL$ at $f = 12$ pN

Reliability of the $F(L)$ estimate

$$\langle L \rangle_f = \frac{1}{Z_0} \int dL \exp\left[-\beta(F(L) - fL)\right] L,$$

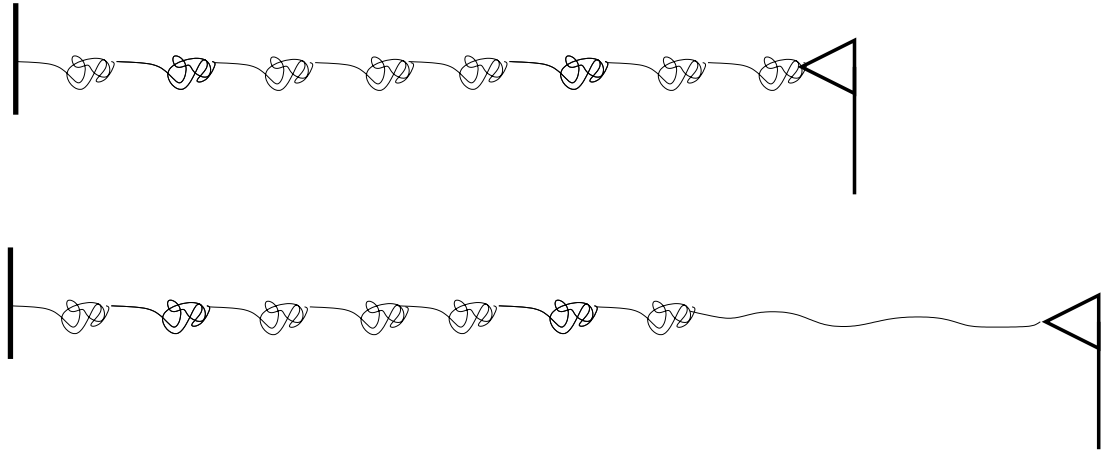
$$Z_0 = \int dL \exp\left[-\beta(F(L) - fL)\right].$$



Real Protein

Ig-like octamer from Titin protein

collaboration with F. Sbrana, M. Vassalli, Florence, Italy.



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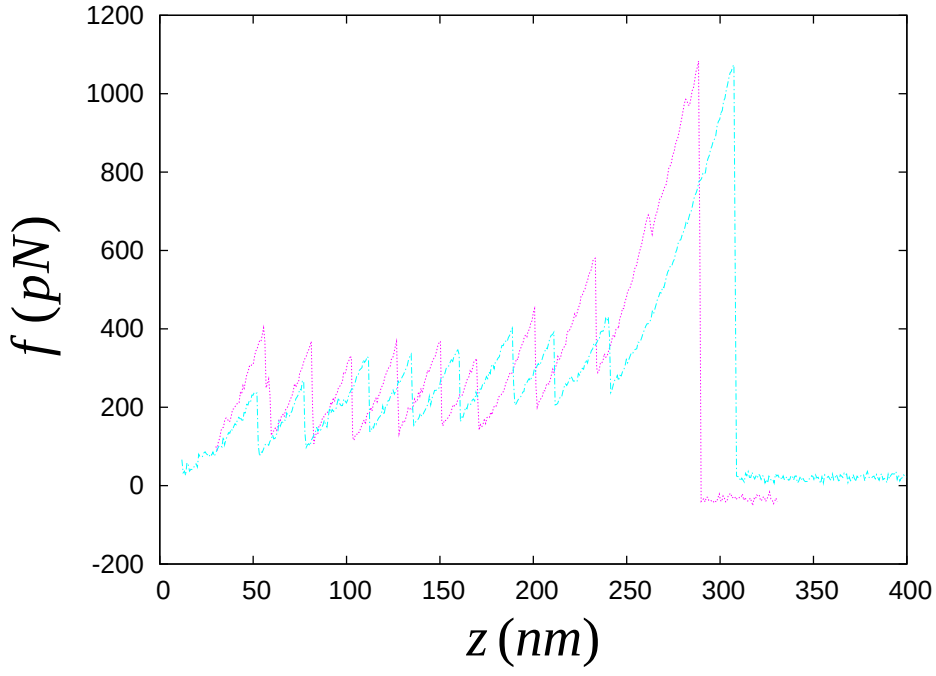

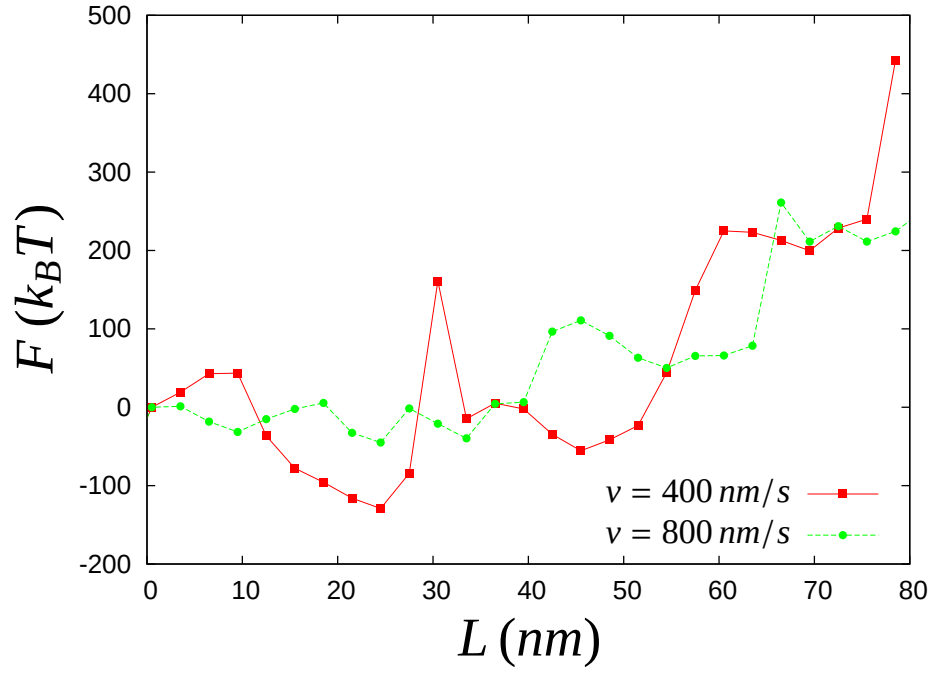

still in progress...

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- RNA under force

References

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