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
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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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- sequence of **aminoacids**,
- connected by C–N **peptide bonds**,
- with a well–defined low–energy, low–entropy **native state**, and
- whose **native structure** is thought to be important for the **kinetics**.
The Wako-Saitô-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 ($\psi_i$, $\phi_{i+1}$) also defines the relative orientation of the $C_\alpha-C_\beta$ bond vectors of residues $R_i$ and $R_{i+1}$.

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 amino acids 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

**WSME model under force**

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

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

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

\[m_k = 0, 1, \ k\text{-th peptide bond in nonnative–native state;}
\]

\[\sigma_{ij} = \pm 1, \ \text{stretch } l_{ij} \text{ parallel-antiparallel to the force}
\]
Equilibrium properties

The WSME model can be solved exactly
The I27 module of titin, pdb code 1TIT

89 aminoacids, $\epsilon/k_B = 43$ K, $\tilde{T} = k_B T / \epsilon$
Equilibrium properties (1TIT)

$\tilde{T} = 4$
$\tilde{T} = 6$
$\tilde{T} = 8$
$\tilde{T} = 10$

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

$\sqrt{\langle L^2 \rangle}$ (Å)
\[ \langle \tau_u \rangle = \omega_0^{-1} \exp[\beta (\Delta E_u - f x_u)] \]

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

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).
Free energy landscape

- $H_\mu(x)$, $x$ 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 $Y$

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

$$\beta = 1/(k_B T)$$
Extended Jarzynski equality

Evaluation of $F_0(Y)$ from experiments

$$e^{-\beta F_0(Y)} = \text{const} \cdot e^{\beta U_{\mu(t)}(Y)} \left\langle \delta(Y - Y(x_t))e^{-\beta W} \right\rangle_t$$


- 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, $\epsilon/k_B \approx 44$ K.
Equilibrium Properties (PIN1)

\[ \tilde{T} = \frac{T k_B}{\epsilon} \] reduced temperature.

\[ \tilde{T} = 4 \]
\[ \tilde{T} = 6 \]
\[ \tilde{T} = 8 \]
Free energy landscape of the PIN1 protein

\[ f(t) = r \cdot t \]

\[ \tilde{T} = 6, \tilde{r} = r \cdot (t_0/\epsilon) \text{Å} \]

"average trajectory"

As the pulling rate \( r \) decreases the estimated curves collapse onto a single one.
Free energy vs. $L$ for PIN1. $\tilde{T} = 6$; 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.
Real Protein

still in progress...
Conclusions

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- RNA under force
References
