Mesoscopic Modeling of Protein Folding and Aggregation

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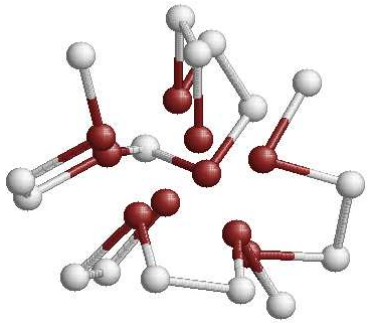

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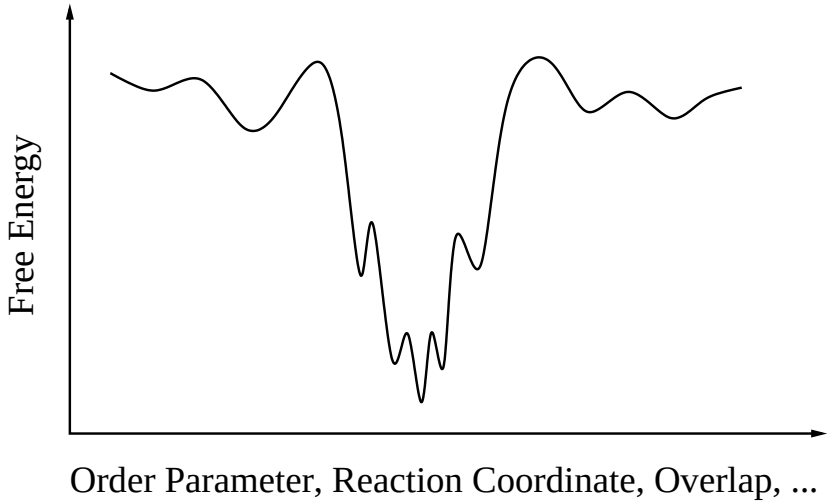
1/3 Proteins – Intro

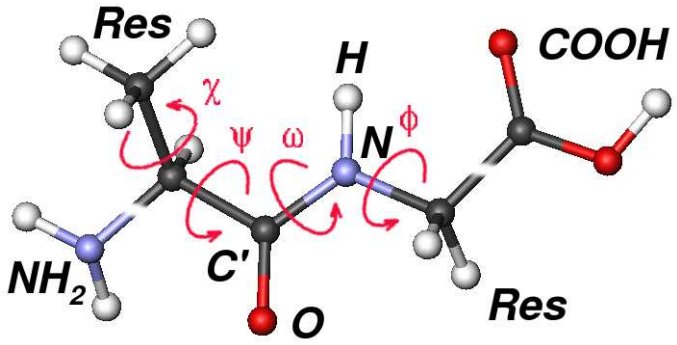
Sequence
⇓
Conformation
⇓
Function

Sequence determines structure.

- **Spontaneous folding** into native conformation (Anfinsen's experiments)
- **Path(s) to the fold:** energy-driven stochastic search
- Time scale of protein folding: **milliseconds to seconds**
- **Metastability** (function-dependent)

Free energy landscape: rugged, with deep funnel-like global minimum.





NH_2– . . . –Ala–Gly– . . . –COOH

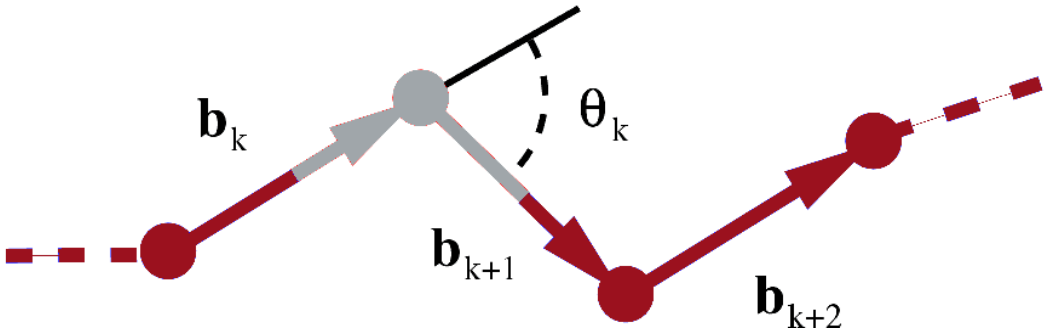
2/3 AB Model – Mesoscopic Model for Heteropolymers

AB off-lattice proteins:

Two types of monomers:

hydrophobic (A)

hydrophilic (B)



AB model: [F. Stillinger, T. Head-Gordon, C. L. Hirshfeld, PRE (1993)]

$$E_{\mathrm{AB}} = \frac{1}{4}\sum_{k=1}^{N-2}(1-\cos\theta_k) + 4\sum_{i=1}^{N-2}\sum_{j=i+2}^{N}\left(\frac{1}{r_{ij}^{12}} - \frac{C_I(\sigma_i,\sigma_j)}{r_{ij}^{6}}\right)$$

$\Longrightarrow$ **Bending energy: "ferromagnetic" coupling**

$\Longrightarrow$ $C_I(A,A), C_I(A,B) > 0$ **(attractive),** $C_I(B,B) < 0$ **(repulsive)**

2/3 AB Model – Mesoscopic Model for Heteropolymers

"Order parameter"

[U. H. E. Hansmann, M. Masuya, Y. Okamoto, PNAS (1997)]

Angular overlap between conformation X and reference conformation (e.g., native fold) X':

[M.B., H. Arkın, W. Janke, PRE (2005)]

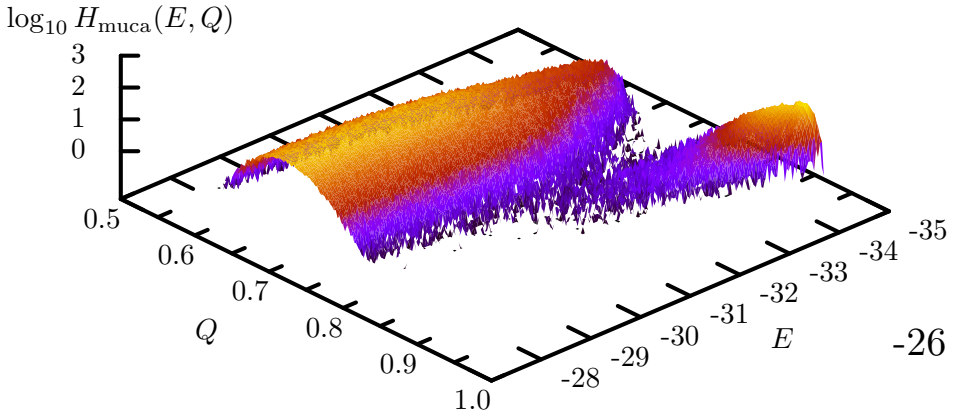
$$Q(\mathrm{X},\mathrm{X}') = \frac{N_t + N_b - d(\mathrm{X},\mathrm{X}')}{N_t + N_b},$$

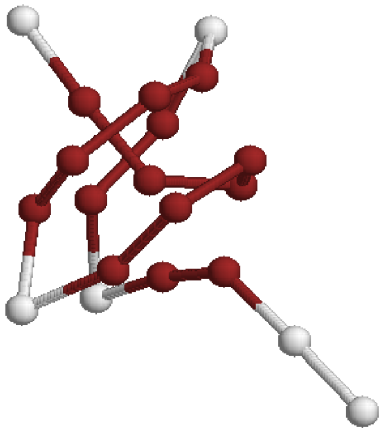
$N_t = N - 3$ **and** $N_b = N - 2$ **numbers of torsional angles** Φ_i **and bond angles** Θ_i**, respectively**

$$\begin{aligned} d(\mathrm{X},\mathrm{X}') &= \frac{1}{\pi}\left(\sum_{i=1}^{N_t} d_t\left(\Phi_i,\Phi_i'\right) + \sum_{i=1}^{N_b} d_b\left(\Theta_i,\Theta_i'\right)\right), \\ d_t(\Phi_i,\Phi_i') &= \min\left(|\Phi_i - \Phi_i'|, 2\pi - |\Phi_i - \Phi_i'|\right), \\ d_b(\Theta_i,\Theta_i') &= |\Theta_i - \Theta_i'|. \end{aligned}$$

In any case: $0 \le Q \le 1$.

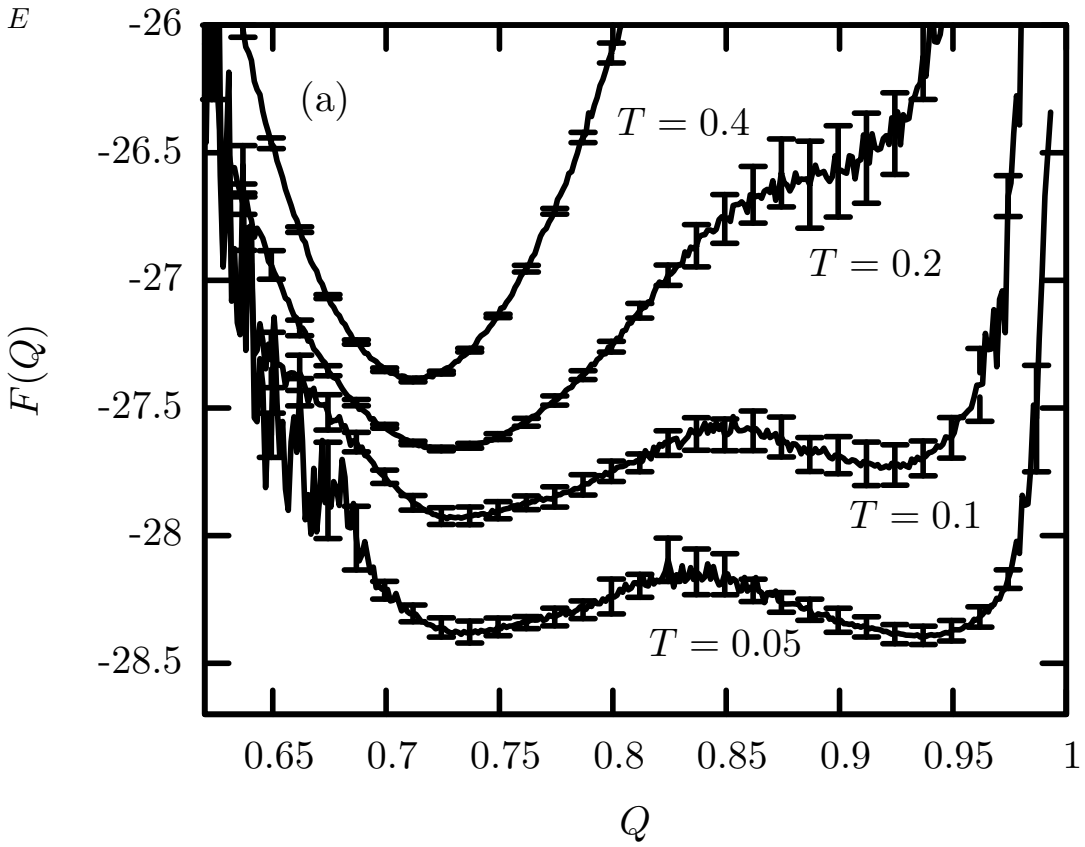
2/3 AB Model – Mesoscopic Model for Heteropolymers



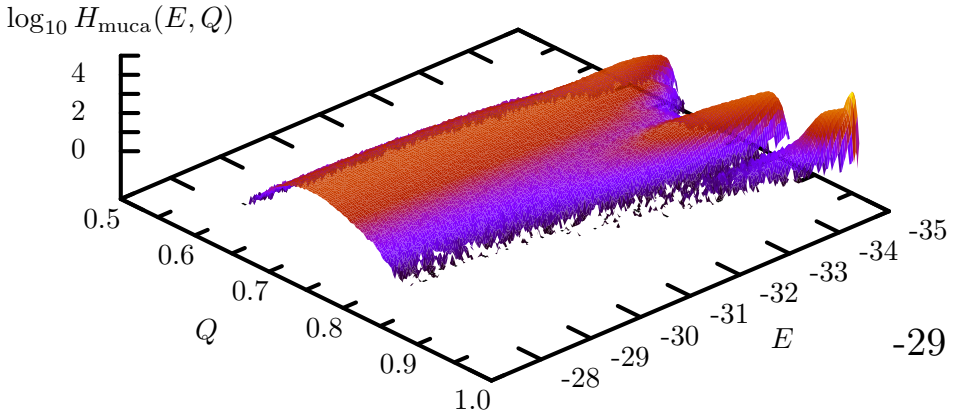


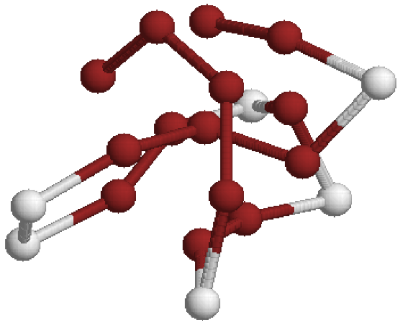
global energy minimum

"Classical" two–state folding:
sequence: $BA_6BA_4BA_2BA_2B_2$



2/3 AB Model – Mesoscopic Model for Heteropolymers

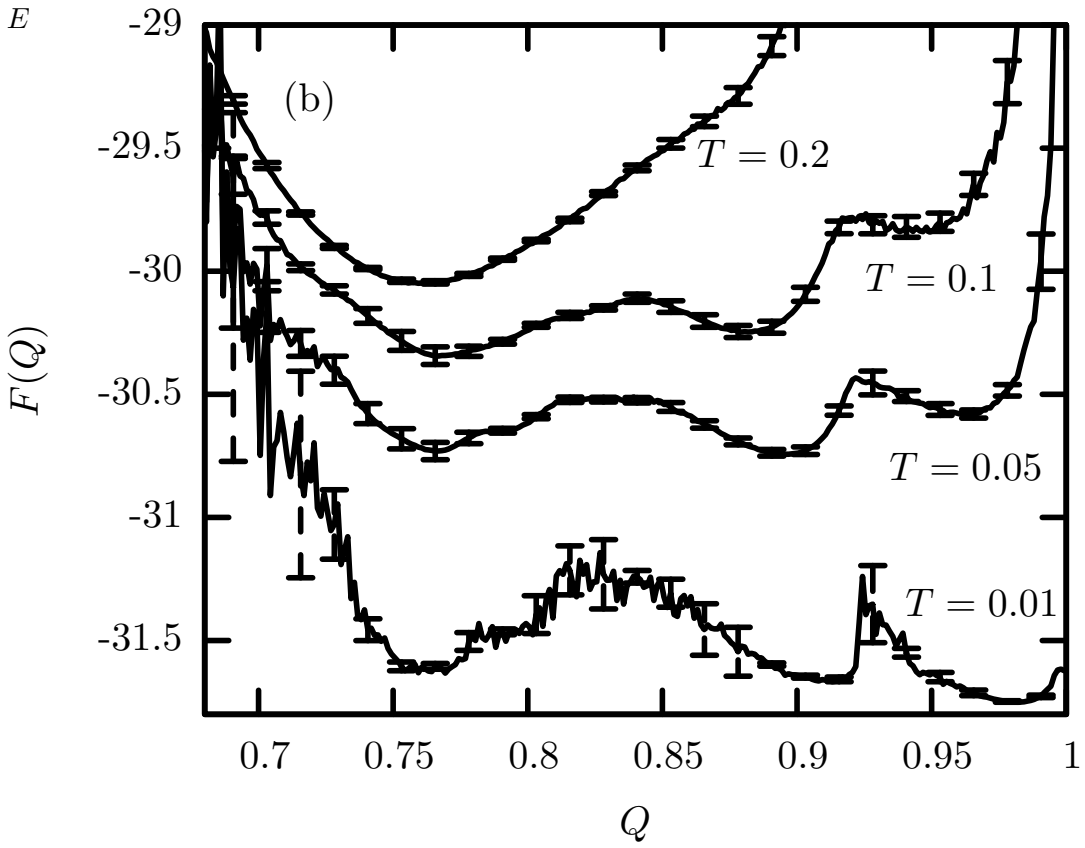




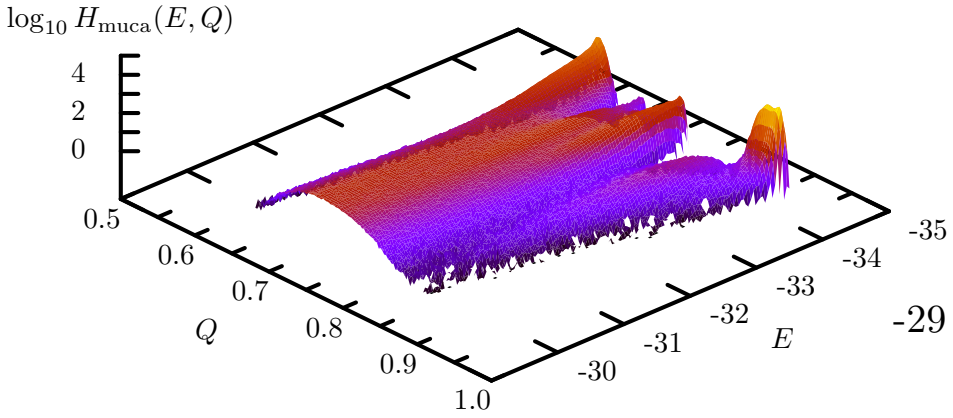
global energy minimum

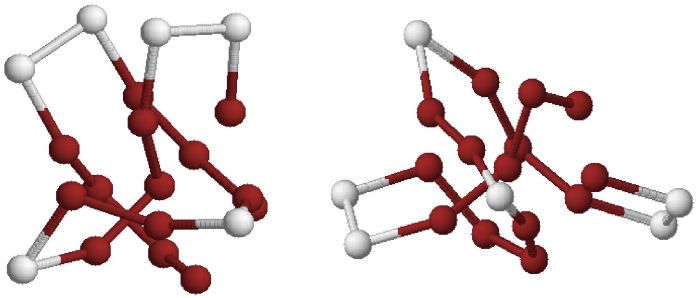
Folding through intermediates:

$A_4BA_2BABA_2B_2A_3BA_2$



2/3 AB Model – Mesoscopic Model for Heteropolymers



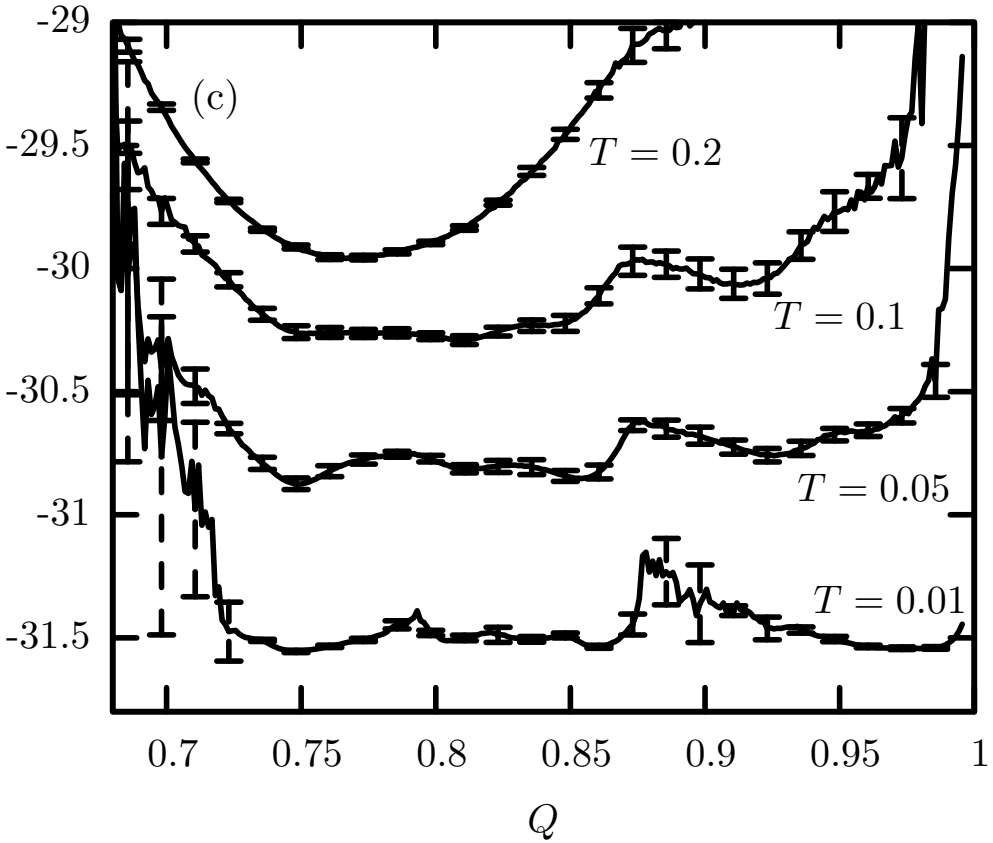


$Q = 1$ $\quad$ $Q \approx 0.75$

global energy minima

Metastability:

sequence: $A_4B_2A_4BA_2BA_3B_2A$



[S. Schnabel, M.B., W. Janke (2006)]

2/3 Conclusions & Outlook

Conclusions:

- Indications of characteristic tertiary folding properties of coarse-grained hydrophobic-polar heteropolymer models
- Suitable definition of "cooperativity" parameter that allows the discrimination between different conformational phases
- Central objective revisited: alternative view of the *path to fold*

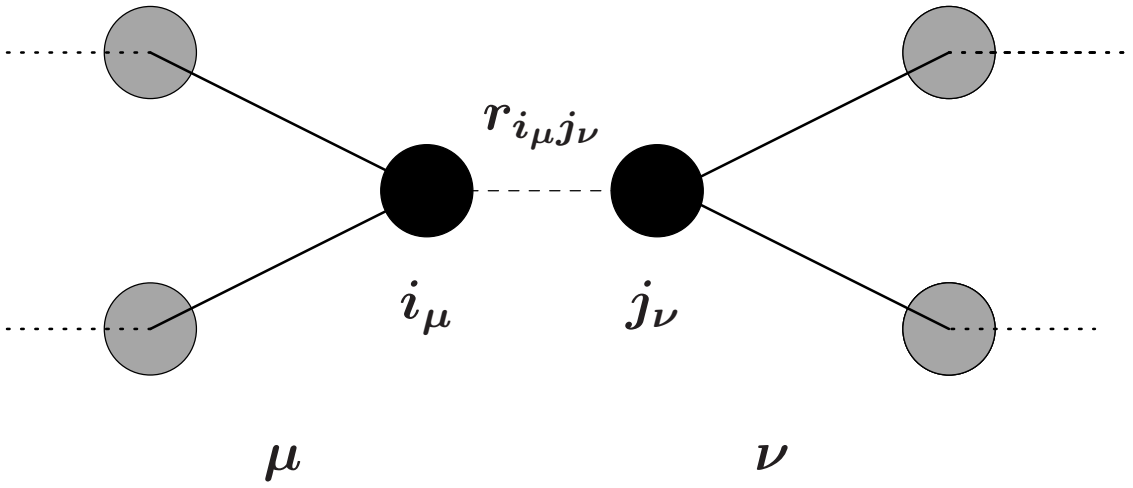
Outlook:

- Understanding tertiary folding paths in the contact-ordering framework
- Kinetic studies of hydrophobic-polar and effective Gō-like models; problem: folding-unfolding cycles
- Molecular dynamics studies of coarse-grained models: folding/unfolding events?

3/3 Heteropolymer Aggregation at Mesoscopic Scales

Aggregation: Simple extension of the AB model

$$E = \sum_{\mu} E_{\mathrm{AB}}^{(\mu)} + 4 \sum_{\mu<\nu} \sum_{i_\mu, j_\nu} \left[r_{i_\mu j_\nu}^{-12} - C(\sigma_{i_\mu}, \sigma_{j_\nu}) r_{i_\mu j_\nu}^{-6} \right]$$



Periodic boundary conditions: Box with edge length L

3/3 Heteropolymer Aggregation at Mesoscopic Scales

Aggregation transition: "Order" parameter

$$\Gamma^2 = \frac{1}{2M^2} \sum_{\mu,\nu=1}^{M} \left(\vec{r}_\mu^{\,\mathrm{COM}} - \vec{r}_\nu^{\,\mathrm{COM}} \right)^2_{\mathrm{per}}$$

- Center of mass: $\vec{r}_\mu^{\,\mathrm{COM}} = \sum_{i=1}^{N} \vec{r}_{\mu_i}/N$
- Definition similar to gyration radius $r_{\mathrm{gyr}}^2 = \sum_{i,j}^{N} (\vec{r}_i - \vec{r}_j)^2/(2N^2)$
- Statistical average: $\langle \Gamma \rangle = Z^{-1} \prod_{\mu=1}^{M} \left[\sum_{\{\vec{X}\}_\mu} \right] \Gamma \exp(-E/k_B T)$
- Fluctuations

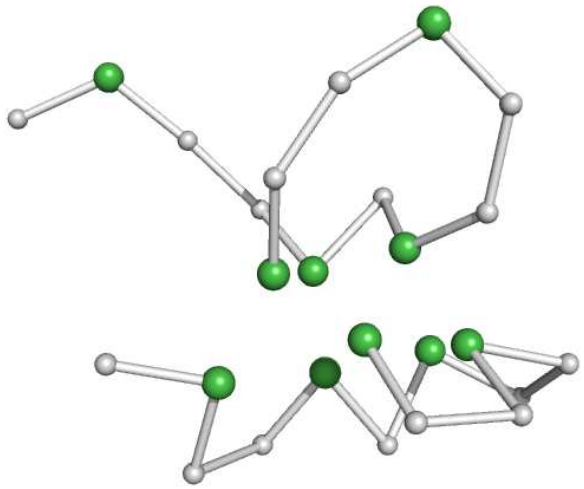
$$\frac{d\langle \Gamma \rangle}{dT} = \frac{1}{k_B T^2} \left(\langle E\,\Gamma \rangle - \langle E \rangle \langle \Gamma \rangle \right)$$

should signalize aggregation transitions, if any!

3/3 Heteropolymer Aggregation at Mesoscopic Scales

A simple, but instructive example:

$M = 2$ identical chains with $N = 13$ monomers each

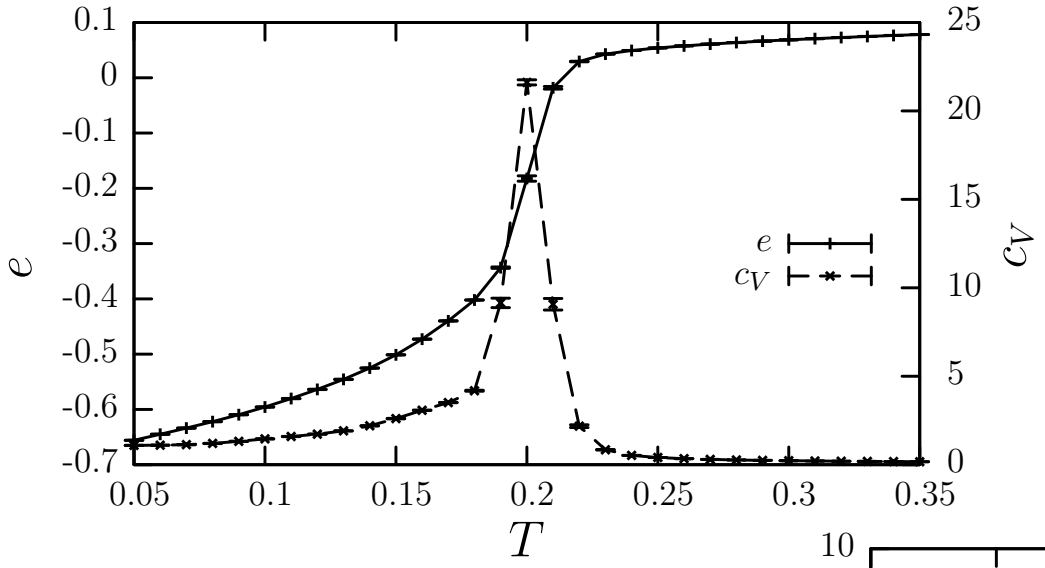


Sequence:
$AB_2AB_2ABAB_2AB$

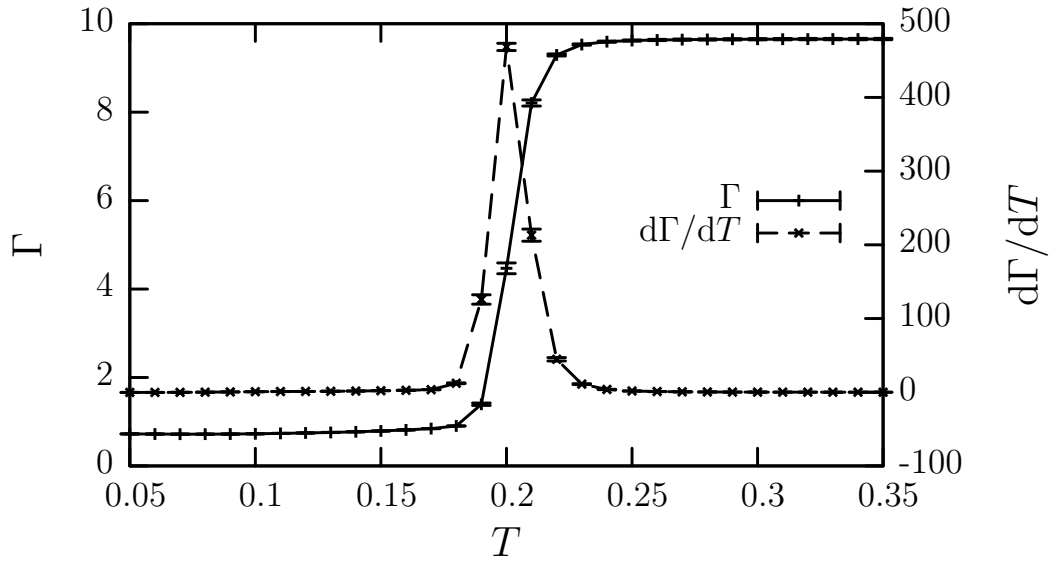
Cubic periodic box
with edge lengths $L = 40$

3/3 Heteropolymer Aggregation at Mesoscopic Scales

Thermal fluctuations: Indications for conformational activity



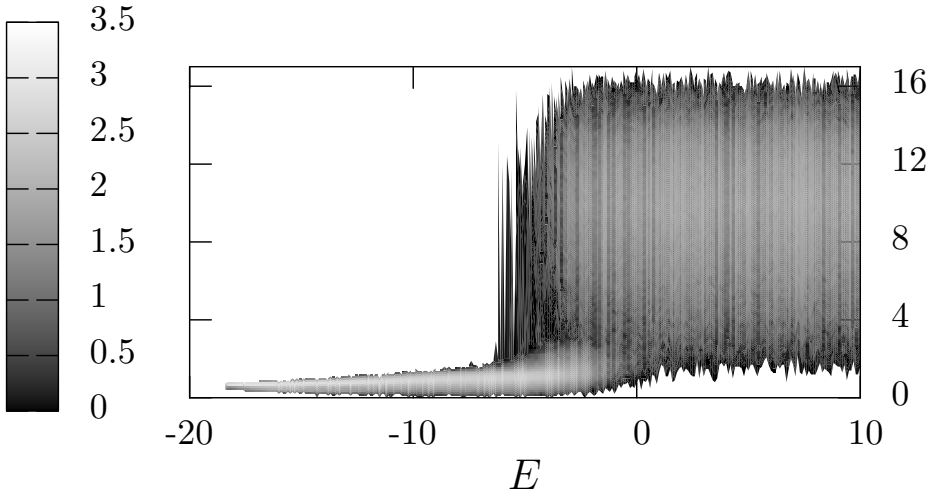
Energy



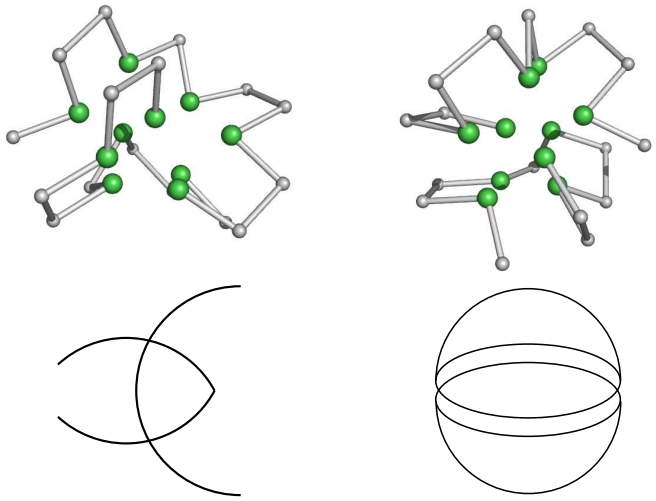
"Order" parameter

3/3 Heteropolymer Aggregation at Mesoscopic Scales

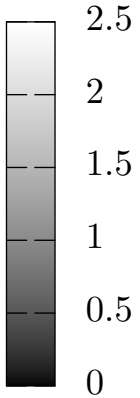
The multicanonical transition channels

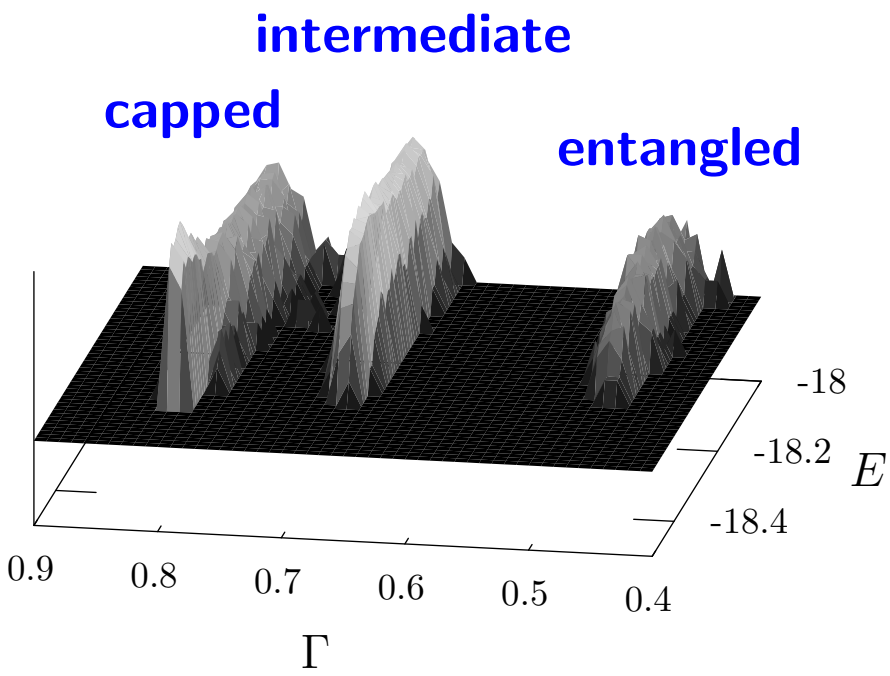


$$H_{\mathrm{muca}}(E,\Gamma) \sim \sum_{t_{\mathrm{muca}}} \delta_{E,E_{t_{\mathrm{muca}}}} \delta_{\Gamma,\Gamma_{t_{\mathrm{muca}}}}$$



entangled capped

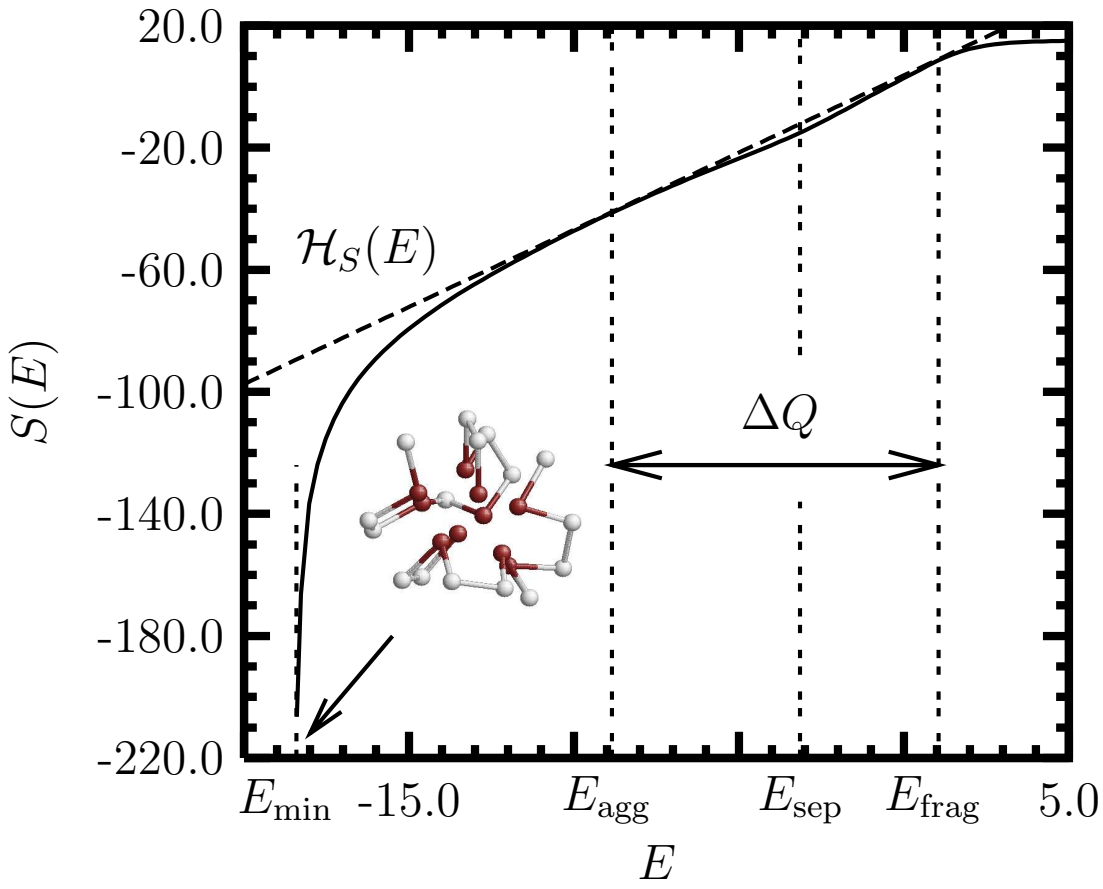




3/3 Heteropolymer Aggregation at Mesoscopic Scales

Canonical vs. microcanonical interpretation

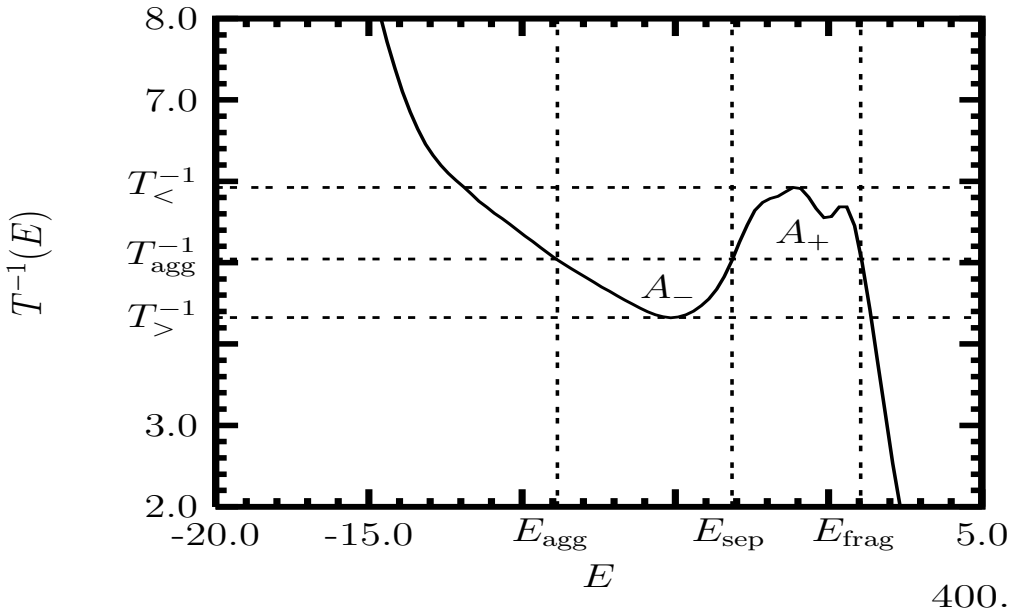
Entropy: $S(E) = k_B \ln g(E)$ **with** $g(E)$**: density of states**



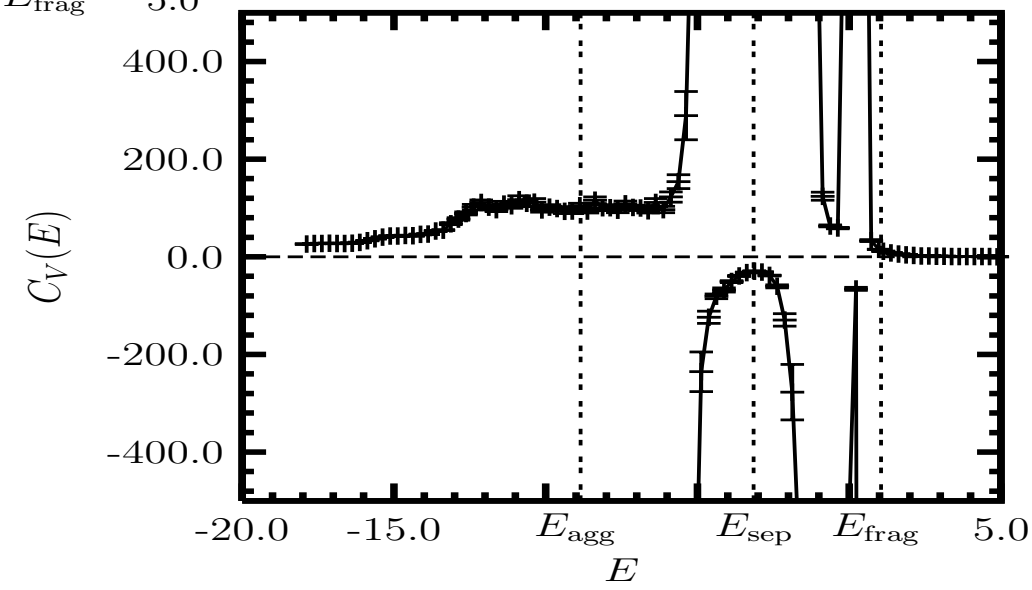
- **Convex region:**
  $E_{\rm agg} < E < E_{\rm frag}$
- **Phase coexistence,**
  latent heat ΔQ
- **Gibbs construction**
  $$\mathcal{H}_S(E) = S(E_{\rm agg}) + \frac{E}{T_{\rm agg}}$$
- **Transition temperature**
  $$T_{\rm agg} = \left(\frac{\partial \mathcal{H}_S(E)}{\partial E} \right)^{-1}$$
- **Phase separation,**
  surface entropy
  $\Delta S = \mathcal{H}_S(E_{\rm sep}) - S(E_{\rm sep})$

3/3 Heteropolymer Aggregation at Mesoscopic Scales

Consequences for the transition regime



- **Backbending effect:** Aggregate becomes **colder** with **increasing** total energy
- **No bijective mapping $T \leftrightarrow E$,** T is no suitable external control parameter



- Microcanonical specific heat can be **negative**
- Canonical **interpretation** of the aggregation transition (at least) **questionable**

[C. Junghans, M.B., W. Janke, PRL (2006)]

3/3 Conclusions

The backbending effect

- is in our model also observed in the aggregation transition of systems with more than two chains
- vanishes in the thermodynamic limit – but, there is no thermodynamic limit for proteins and protein-like heteropolymers!
- accompanies – sequence-dependently – also protein folding processes
- is a "fact" and should therefore be seen in experimental studies – still pending for polymers/proteins
- was recently observed in experiments of small clusters of sodium ions