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Peptide folding and aggregation

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Outline

All-atom model with a simplified energy function

Calibration

- Folding of a set of well characterized peptides

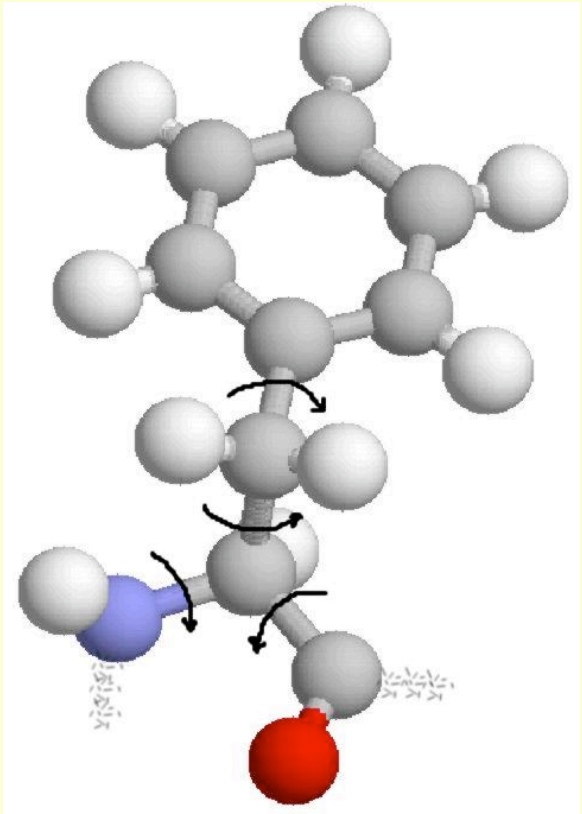
Applications

- Mechanical vs thermal unfolding of ubiquitin
- Aβ(16-22) aggregation
- Solution behavior of 4 semiconductor-binding peptides

Chain representation

- All atoms (including H atoms)
- Torsional degrees of freedom
  - backbone angles φ,ψ
  - side-chain angles χ_i

No explicit water molecules



Energy function

$$E=E_{\mathrm{loc}}+E_{\mathrm{ev}}+E_{\mathrm{hb}}+E_{\mathrm{hp}}$$

- E_{loc}: electrostatic, neighboring backbone dipoles
- E_{ev}: excluded volume, $1/r^{12}$ repulsion
- E_{hb}: H bonds; 12-10 LJ, angular dependence
- E_{hp}: hydrophobicity; effective, pairwise additive attraction between nonpolar side chains

– The amino acid sequence is the only input.

[Irbäck & Mohanty, Biophys. J., 2005]

Monte Carlo methods

- Simulated tempering
- Metropolis updates of individual angles
- Semi-local backbone update, BGS [Favrin et al., JCP, 2001]

PROFASI (PROtein Folding and Aggregation Simulator)

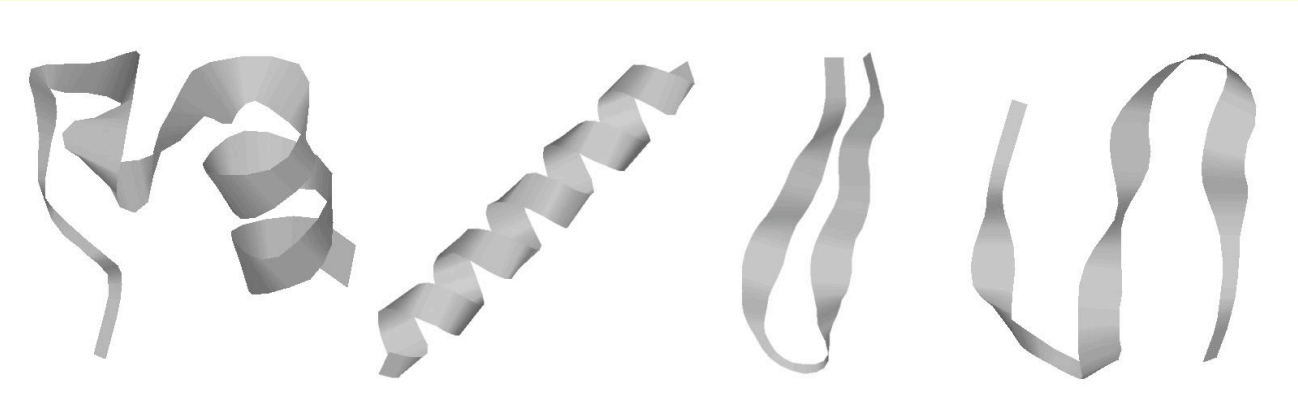
Program package written in C++

Available at http://cbbp.thep.lu.se/activities/profasi

[Irbäck & Mohanty, J. Comp. Chem., 2006]

Peptide folding

Trp cage	helical `miniprotein'	20 aa
F_s	α-helix	21 aa
GB1p	β-hairpin (from G B1 domain)	16 aa
GB1m2/3	GB1p mutants	16 aa
Betanova	3-stranded β-sheet	20 aa
LLM	Betanova mutant	20 aa



[Irbäck & Mohanty, Biophys. J., 2005]

Peptide folding

- For these sequences, the model gives a good description of both structure and thermo-dynamics.
- There are further peptides that the model is able to fold (unpublished results). There are also peptides that the model fails to fold, e.g. trpzip (β-hairpin with 12 residues).

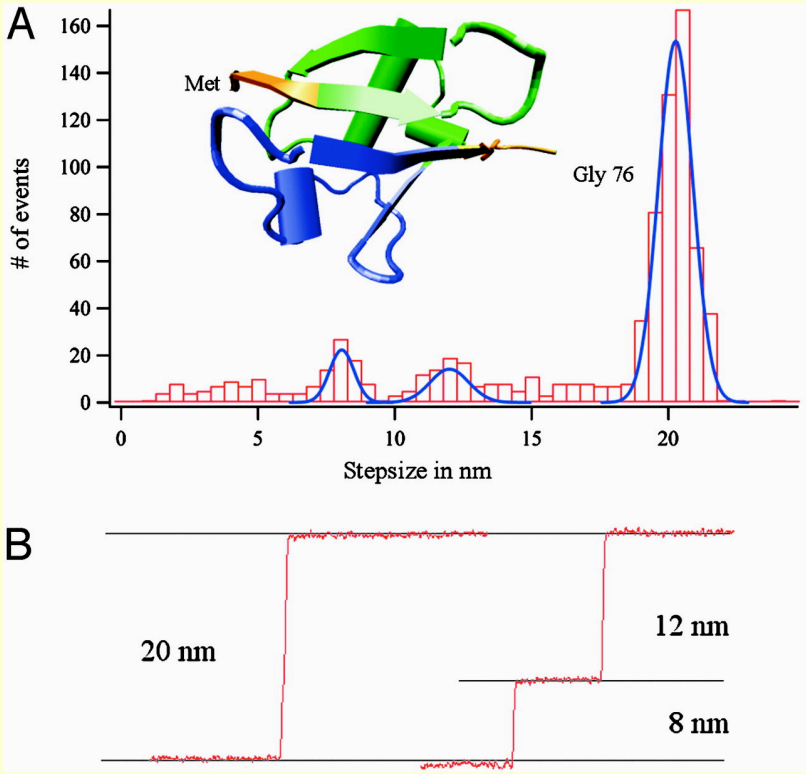
Mechanical unfolding of ubiquitin

α/β protein with 76 residues

Single-molecule study of (poly)ubiquitin at constant force

- In most cases, unfolding occurred in one step.
- In some cases, intermediate states were observed.

[Schlierf et al., PNAS, 2004]



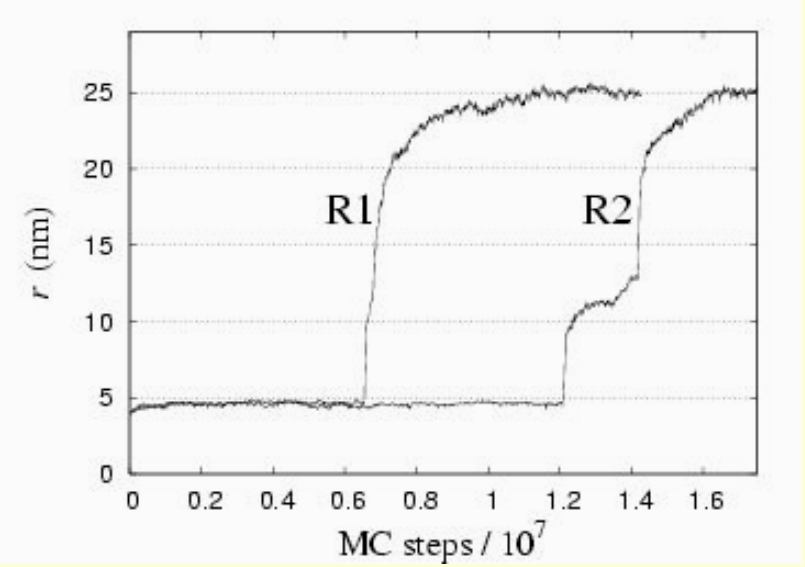
Simulations to characterize the unfolding pathway.

MC simulations of ubiquitin unfolding

Mechanical unfolding

- both one- and two-step unfolding
- native structure elements break in a definite order, which is not the same as in thermal unfolding exp.

[Irbäck et al., PNAS, 2005]



(100pN)

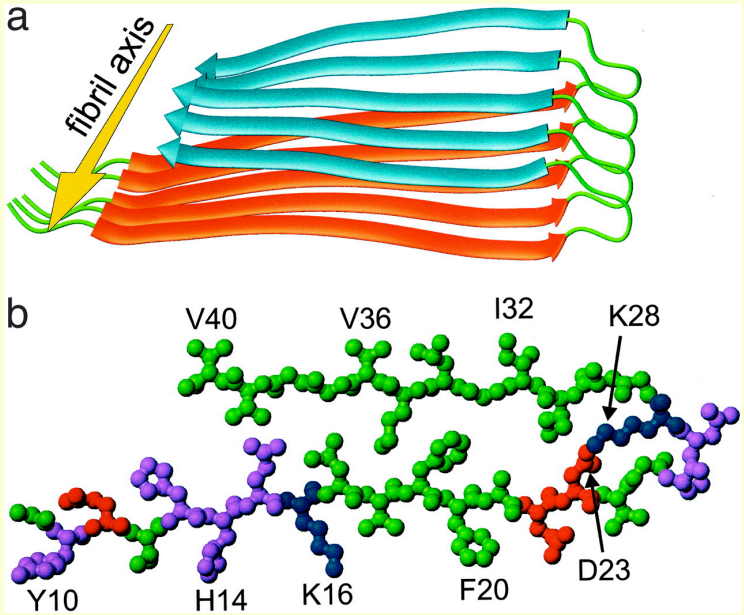
Calculated thermal unfolding order

Different than the calculated mechanical unfolding order, and consistent with experiments.

[Irbäck & Mitternacht, Proteins, 2006]

Peptide aggregation

- Peptide aggregation into amyloid fibrils occurs in several diseases.
- Aβ with ~40 residues makes fibrils in AD.
- There is evidence linking small Aβ assemblies to neurotoxicity.
  [e.g., Lesné et al., Nature, 2006]
- Barrel-like aggregates could create pores in cell membranes.
  [e.g., Lansbury, Q. Rev. Biophys., 2006]

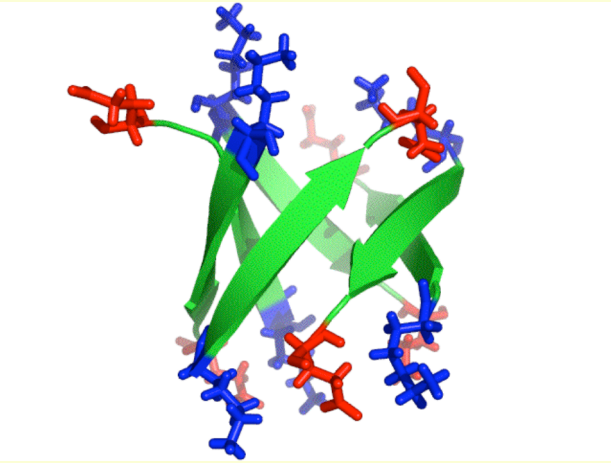


Aβ(1-40) fibril
[Petkova et al., PNAS, 2002]

Aβ(16-22) aggregation

- Aβ(16-22) makes fibrils with antiparallel β-sheets.
  [Balbach et al., Biochemistry, 2000]
- Sequence KLVFFAE (K & E oppositely charged).

- Unbiased simulations of 6 Aβ(16-22) peptides.
- Antiparallel β-structure, without Coulomb interactions between side-chain charges.
  [Favrin et al., Biophys J, 2004]
- With these interactions, spontaneous assembly into a β-barrel.
  [Irbäck & Mitternacht, work in progress]



Semiconductor-binding peptides

Recent experiments identified peptides with adhesion affinity for GaAs and Si surfaces.

Peptides in solution in contact with (100) GaAs and Si surfaces. After washing and drying, surface coverage was measured by AFM.

		GaAs	Si	
S1	AQNPSDNNTHTH	25%	1%	
S2	AQNPSDNNTATA	14%	3%	(H→A)
S3	TNHDHSNAPTNQ	17%	15%	(random perm.)
S4	AQAPSDAATHTH	21%	6%	(N→A)

[Whaley et al., Nature, 2000; Goede et al., Nano Lett., 2004; Goede et al., Langmuir, 2006]

Mode of binding

- Aggregates or one by one?

  Aggregation seems unlikely, because of dilute solutions (nanomolar) and low hydrophobicity.

- Docking or unstructured peptides?

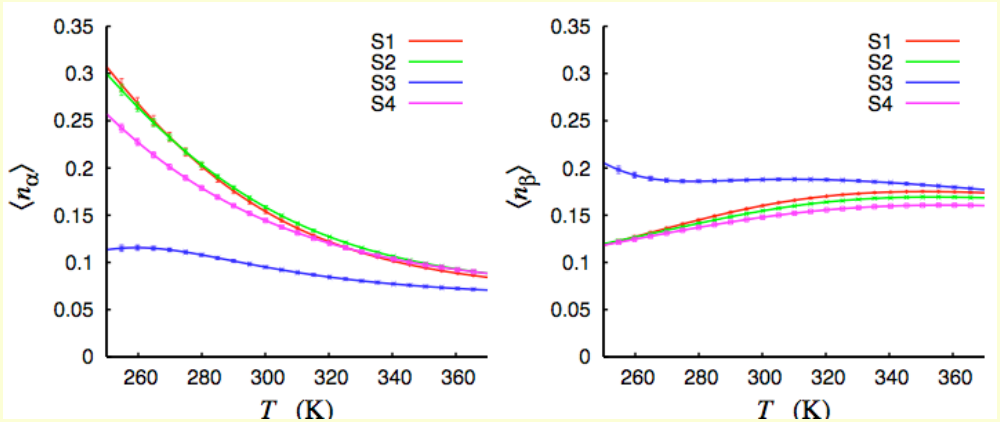
  CD analysis suggests that all the four peptides are largely unstructured.

  [Goede at al., Langmuir,2006]

Are there structural differences, not seen by CD, between the 4 peptides that could explain their different adhesion properties?

[Mitternacht, Schnabel, Bachmann, Janke & Irbäck, submitted]

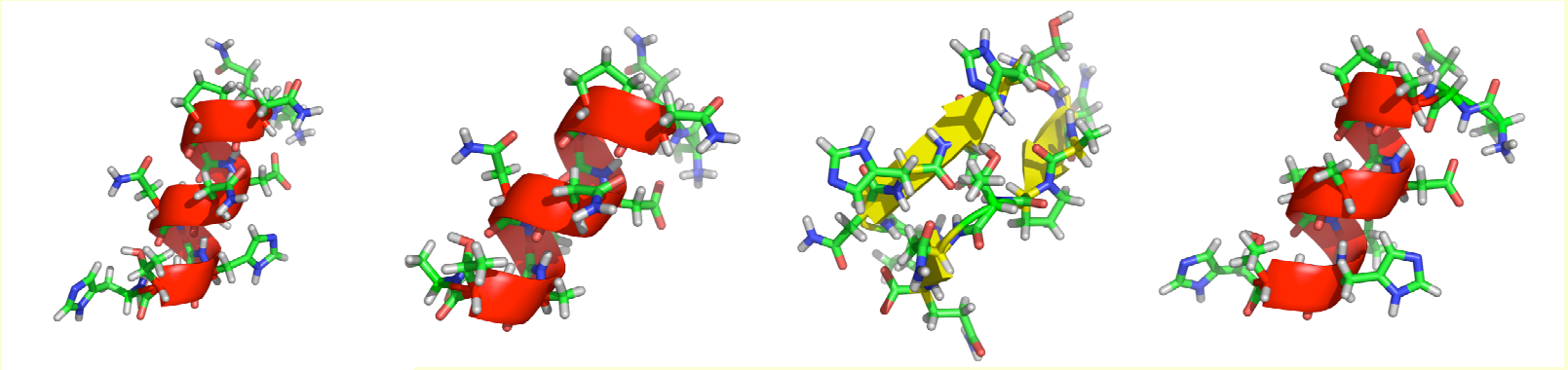
Secondary structure



α-helix and β-strand contents against *T*

- The α- and β-contents are both low for all the 4 sequences, which is consistent with CD data.
- The results for S1, S2 and S4 are very similar, but S3 (with relatively good adhesion to Si) is different.

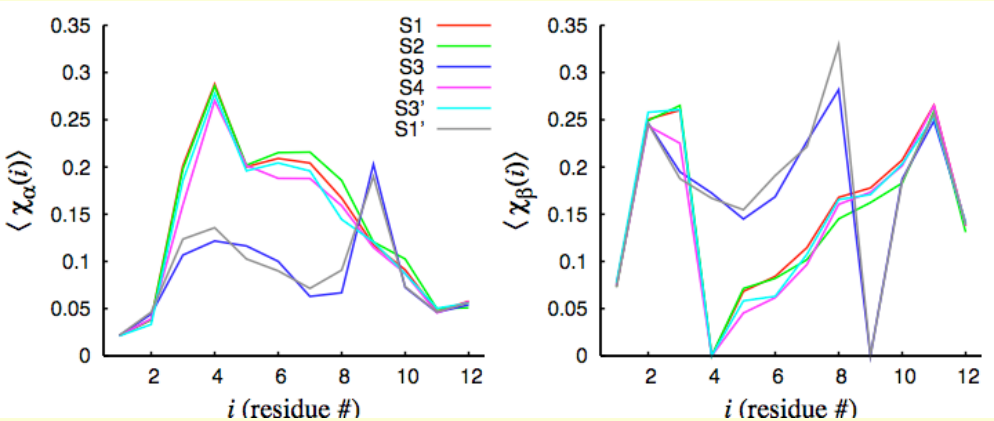
Minimum-energy structures



S1 S2 S3 S4

- Simulated annealing.
- Note that these states are only weakly populated at room temperature.

Secondary-structure profiles



α-helix and β-strand profiles (T=299K)

- Proline at position 4 for S1, S2 and S4, but at position 9 for S3.
- S3': S3 with Asp4↔Pro9. Behaves as S1,S2 & S4.
- S1': S1 with Pro4↔Thr9. Behaves as S3.

Summary

- S1-S4 are all largely unstructured, as in the CD experiments.
- S3 is structurally different from S1, S2 & S4, which could explain its different adhesion properties.
- It would be interesting to measure the adhesion properties of S1’ and S3’.
- Do the adhesion properties of S3’ resemble those of S1, S2 and S4 (with similar structure) or those of S3 (with 83% sequence identity)?

Poster by Simon Mitternacht & Stefan Schnabel.