Simulation of Proteins and Protein Interactions

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Supported by research grants of the National Science Foundation (CHE-0313618) and the National Institutes of Health (GM62838)

MichiganTech

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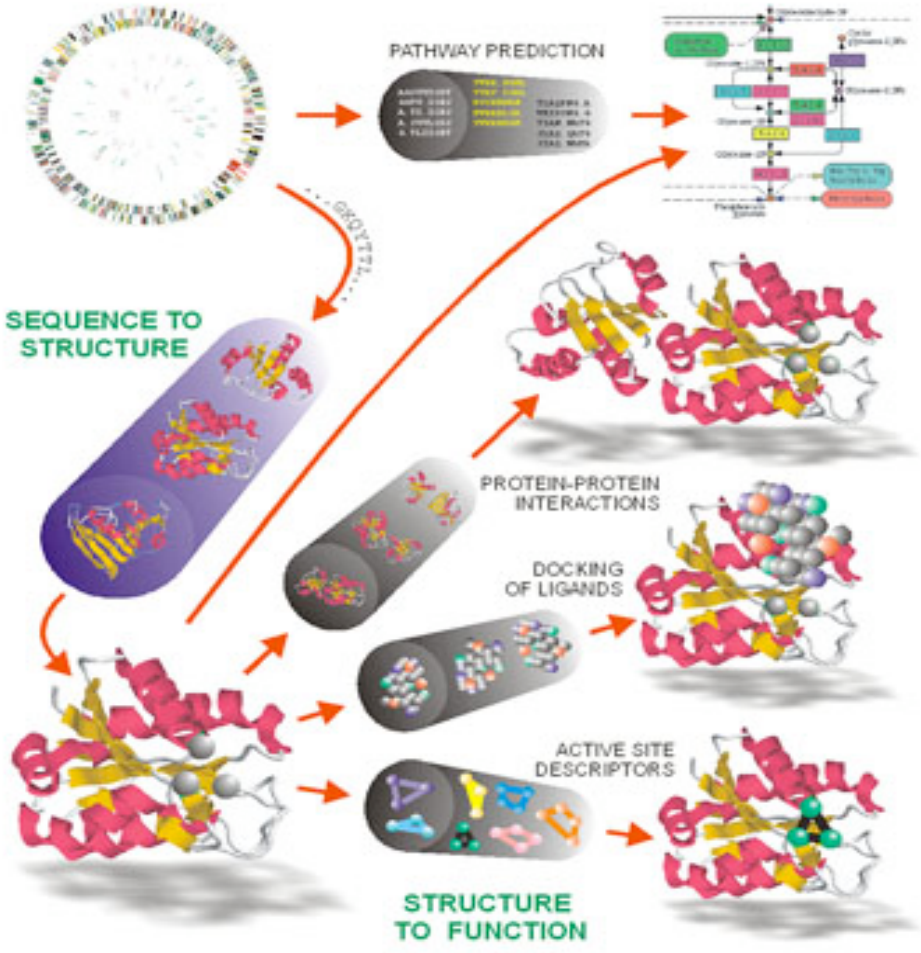
- **Wolfgang Nadler** (MTU)
- **Siegfried Hoefinger** (MTU)

- **Xiaolin Xiao** (FZJ)
- **Liang Han** (MTU)
- **Parimal Kar** (MTU)
- **Yanjie Wei** (MTU)

The Protein Folding Problem

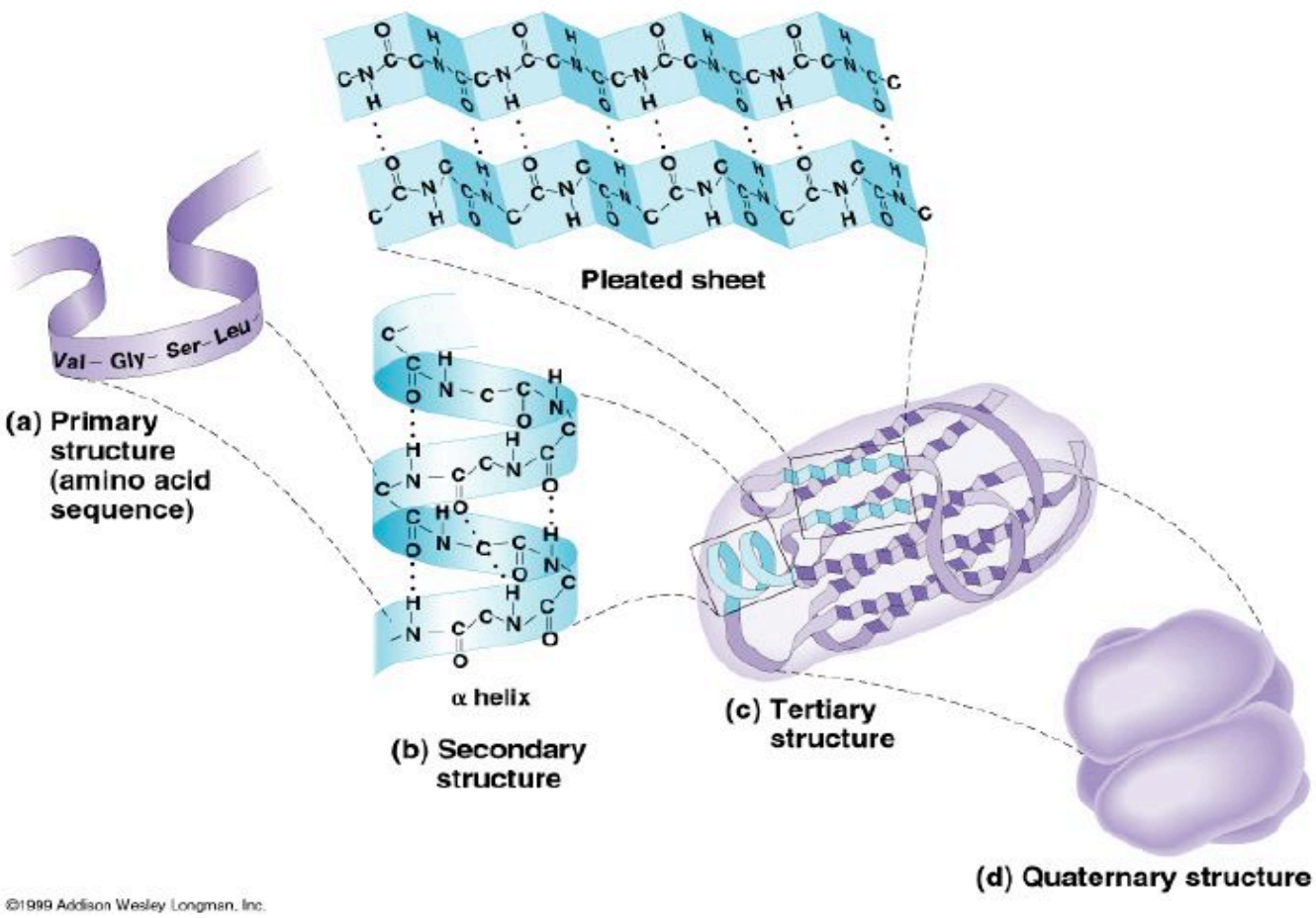
- **> 50,000** different kinds of proteins in human body
- Muscles, antibodies, enzymes, … (“**nanomachines**”)
- Proteins are **polymers** built up from **amino acids**
- The sequence of amino acids is specified in the genome → we know in principal the **chemical composition** of all proteins in the human body
- **Function** of these proteins?
- Sequence – structure – function **relationship**?
  - Understanding (mal)function of enzymes and their role in diseases
  - Design of new drugs

Protein Science



http://cssb.biology.gatech.edu/skolnick/

Structure Prediction



Dihedral region prediction using SVMs

O. Zimmermann and U.H.E. Hansmann, Bioinformatics, in press

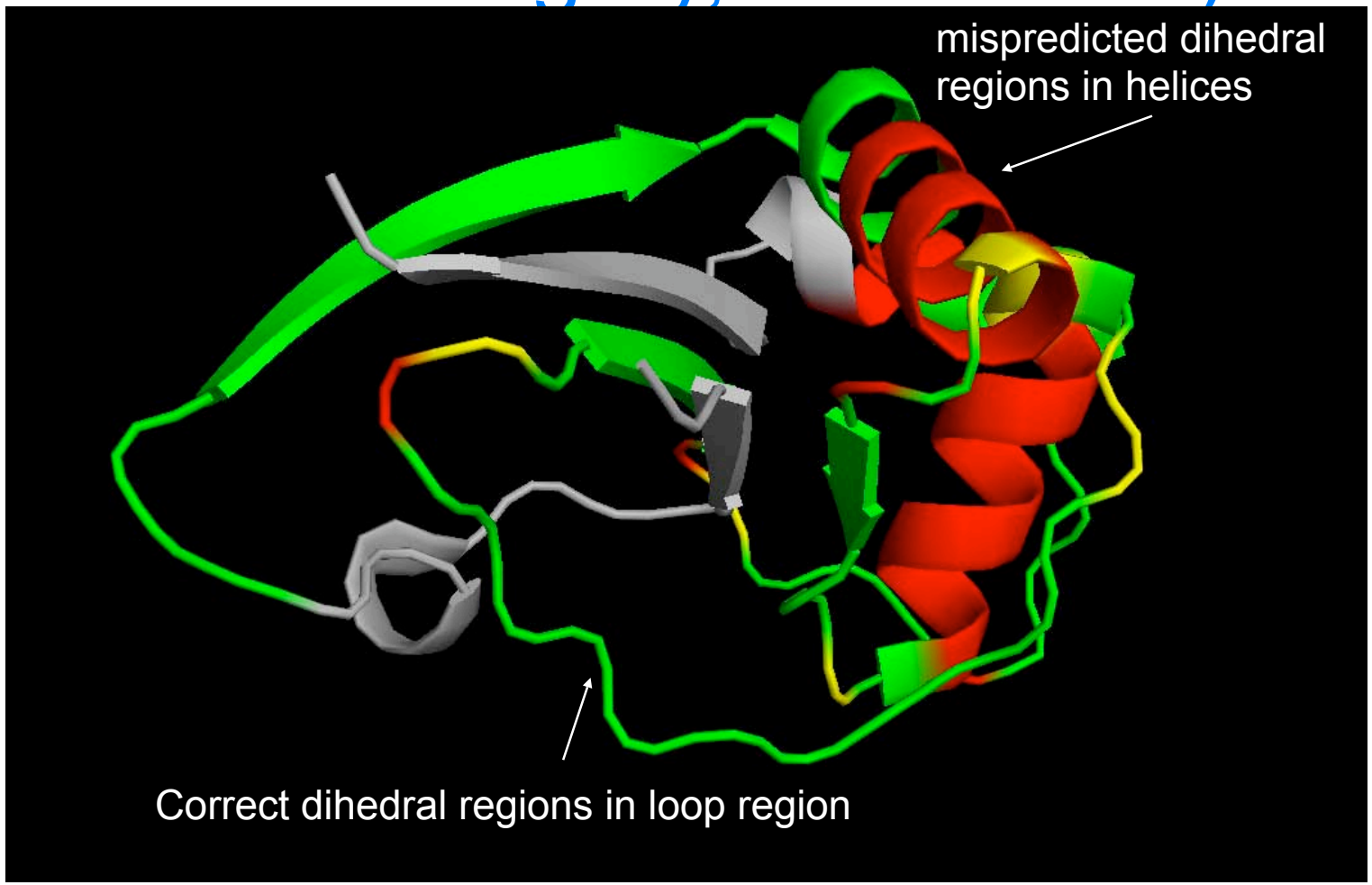
- **Secondary structure** prediction: helix, sheet, coil
- **Dihedrals** of “coil” residues?
- Mostly in the α and β regions of the Ramachandran plot.
- Additional information for **structure prediction** algorithms.
- **No** multiple sequence alignments!

Dihedral region prediction using SVM

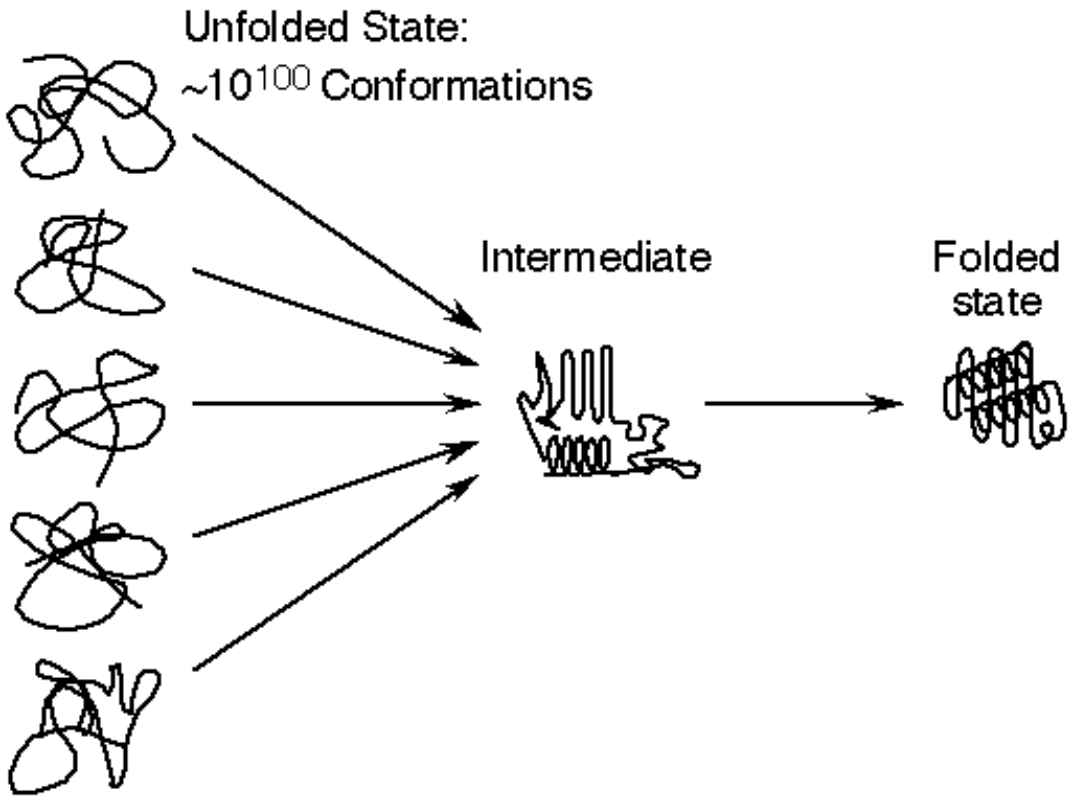
O. Zimmermann and U.H.E. Hansmann, Bioinformatics, in press

- **SVM** based multistep method
- **encoding** of sequences as vectors of **amino acid properties** (e.g. volume, hydrophobicity etc.)
- Prediction correct for **~70%** of all residues in protein cores including residues in “coil“ regions.
- Current work in progress:
  - include **additional** information,
  - understand **clustered mis-predictions**,
  - **optimize** parameters

Example: CASP6 target T0242 (new fold category, PDB:2blkA)



Mechanism of Folding

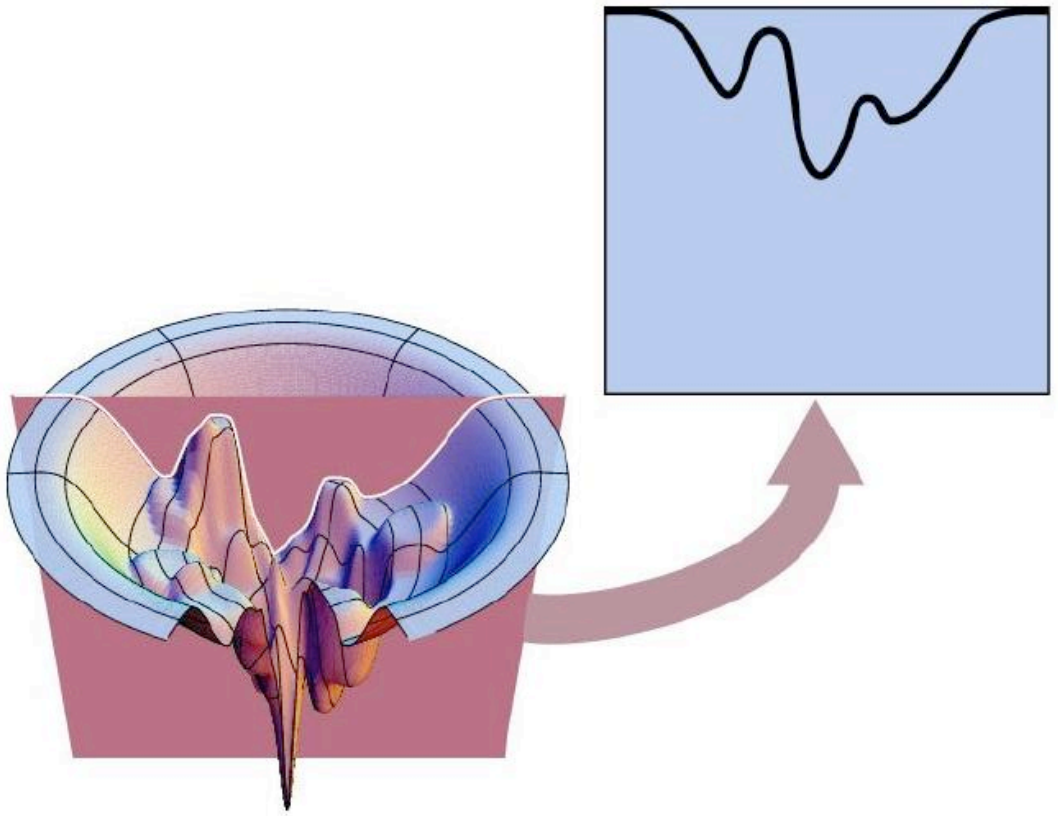


www.pitb.de/ nolting/prot00/

Simulations

- Proteins are only **marginal stable**: ≈ 10 kcal/mol
- **Approximations** necessary
- Interaction with **solvent**?
- **Rough** energy landscape
- **Slow convergence** at room temperature

Energy Landscape of Proteins



http://www.dillgroup.ucsf.edu/energy.htm

Energy Function

- Sum of ***in vacuo*** energy and **solvation** energy
- The ***in vacuo*** energy is modeled by **force fields**
  Example: ECEPP/2
  (Nemethy et al., *JPC* **87** (1983) 1883)
- How to model best **protein-water** interaction?

$$E_{tot} = E_{es} + E_{vdW} + E_{hb} + E_{tors}$$

$$E_{es} = \sum_{(i,j)} \frac{332 q_i q_j}{\varepsilon r_{ij}}$$

$$E_{vdW} = \sum_{(i,j)} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right)$$

$$E_{hb} = \sum_{(i,j)} \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right)$$

$$E_{tors} = \sum_{l} U_l \left(1 \pm \cos\left(n_l \alpha_l\right)\right)$$

To Address Problems of Simulations

Minimal protein models

- Capture only **predominant** interactions in proteins (chain connectivity…)
- Allow only study of the **general characteristics** of folding
- **Review**: K.A. Dill & H.S. Chan, *Nature Str. Biol.* **4** (1997) 10

Elaborated simulation techniques

- **Global optimization** techniques
- Evaluating **thermodynamic quantities** requires new **sampling techniques**
- **Review:** U.H. & Y. Okamoto, *Curr. Opp. Str. Biol*, **9** (1999) 177

New Algorithms for Protein Simulations

- **Generalized-ensemble** techniques
  U.H.E. Hansmann & Y. Okamoto, *JCC* **14** (1993) 1333

- Algorithms relying on **Tsallis-like** weights
  U.H.E. Hansmann & Y. Okamoto, *PRE*, **56** (1997) 2228

- **Stochastic tunneling** and related methods
  W. Wenzel & K. Hamacher, *PRL.* **82** (1999) 3000
  U.H.E. Hansmann, *Eur. Phys. J. B* **12** (1999) 607

- Energy Landscape Paving (**ELP**)
  U.H.E. Hansmann & L. Wille, *PRL.* **88** (2002), 068105

- Multiple Markov Chains (**Parallel Tempering**, REM)
  C.J. Geyer *et al.*, *J. Am Stat Assn* **90** (**431**) (1995) 909;
  U.H.E. Hansmann, *Chem. Phys. Lett.* **281** (1997) 140
  W. Kwak and U.H.E. Hansmann, *Phys. Rev. Lett.* **95** (2005) 138102

Simulation in Generalized Ensembles:

- **Idea:** choose ensemble that allows **better sampling**
- **Earliest realization**: umbrella sampling
  G.M. Torrie and J.P. Valleau, J. Comp. Phy. **23** (1977) 187
- Re-discovered in the 90's: multicanonical sampling, …
- Energy **barriers** can be crossed → **enhanced** sampling
- Problem: **Weights** are not *a priori* known
- What is the **optimal** ensemble?
- **Review:**
  U.H. & Y. Okamoto, in: D. Stauffer (ed), *Annual Reviews in Computational Physics VI*, World Scientific 1999, p.129

Multicanonical Ensemble:

B.A. Berg and T. Neuhaus, Phys. Lett. , **B267** (1991) 249

- All **energies** enter with **equal probability**:

$$P_{mu}(E) \propto n(E) w_{mu}(E) = const$$

- The **multicanonical weight** factor has the form:

$$w_{mu}(E) \propto n^{-1}(E)$$

- Connection to the canonical ensemble by **re-weighting** :

$$P_B(T,E) \propto P(E) w_{mu}(E) e^{-E/k_B T}$$

- Expectation values of **physical quantities**:

$$< O >= \frac{\int dx\, O(x) w_{mu}^{-1}(E(x)) e^{-E(x)/k_B T}}{\int dx\, w_{mu}^{-1}(E(x)) e^{-E(x)/k_B T}}$$

Part of a Multicanonical Simulation of PTH(1-34)

Department of Physics
Michigan Technological University

Parallel Tempering (also known as REM)

U.H.E. Hansmann, *Chem. Phys. Lett.*, **281** (1997) 140

- N copies of the molecule at **different temperatures** T
- Parallel tempering uses two kinds of **updates**:
  1. Standard MC moves which effect only **single** copy
  2. **Exchange** of configurations between two copies i and j

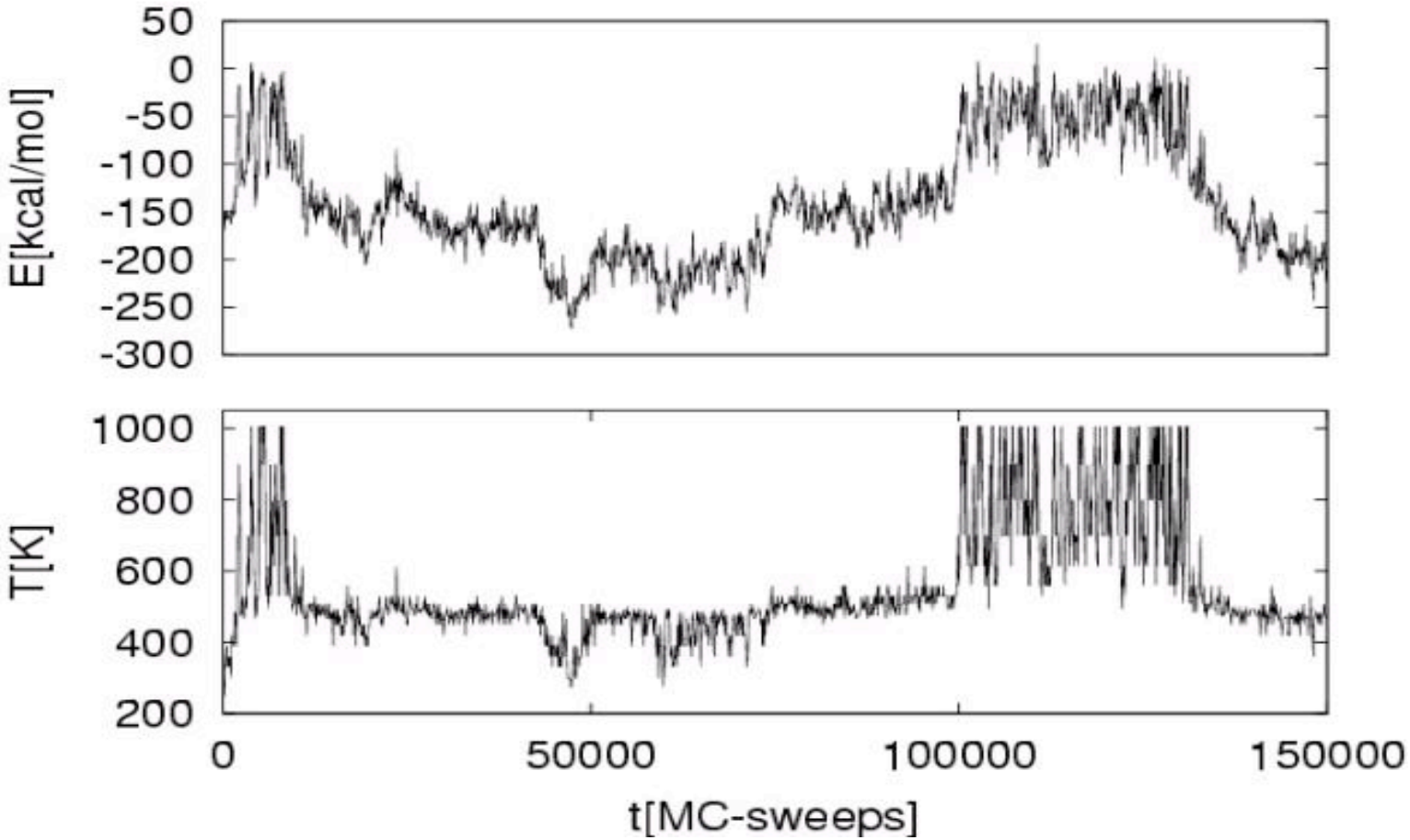
$$w(C \to C') = \min\left(1, \exp\left\{-\frac{E(C_j)}{k_B T_i} - \frac{E(C_i)}{k_B T_j} + \frac{E(C_i)}{k_B T_i} + \frac{E(C_j)}{k_B T_j}\right\}\right)$$

C.J. Geyer *et al., J Am Stat Assn* **90** (431) (1995) 909;
K. Hukushima *et al, J. Phys. Soc (Japan)* **65** (1996) 1604

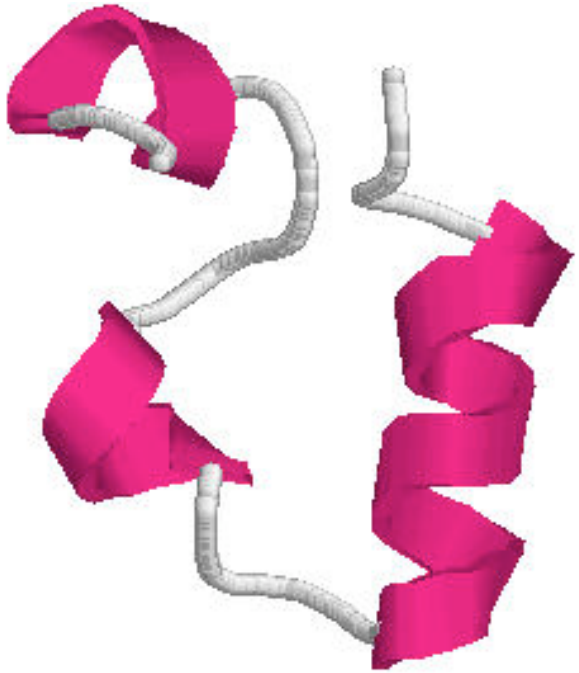
- No restriction to **Boltzmann weights** or **temperature** ladders!

Parallel Tempering Simulation of HP-36

C.-Y. Lin, C.-K. Hu and U.H., *Proteins* **52** (2003) 436



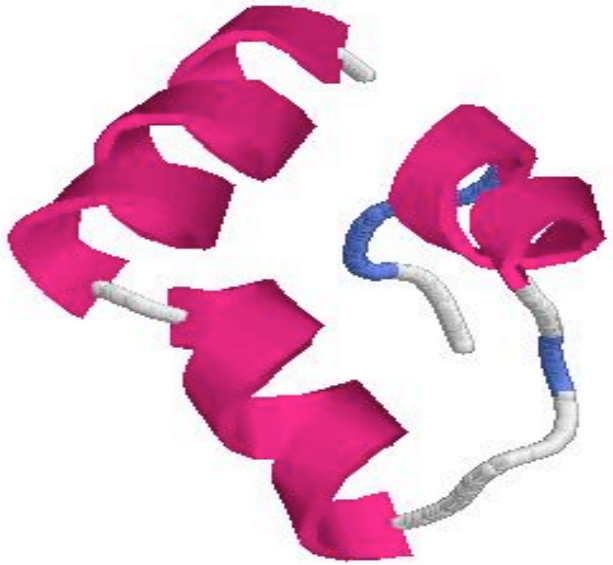
PDB-structure of HP-36



Lowest-energy configuration of HP

C.-Y. Lin, C.-K. Hu and U.H., *Proteins* **52** (2003) 436

(simulation with solvent-accessible surface area term)



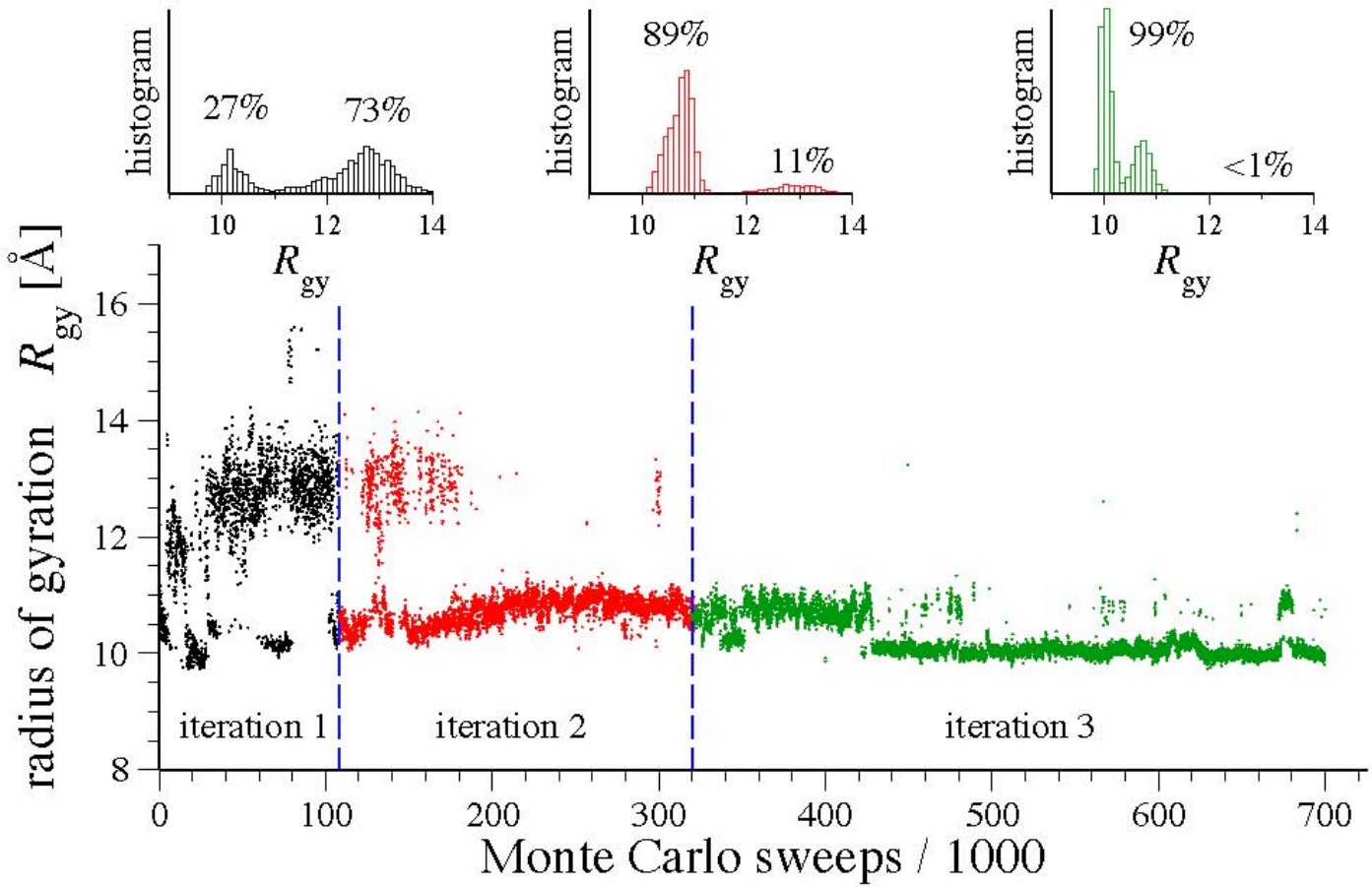
Low-energy configuration of HP-36

C.-Y. Lin, C.-K. Hu and U.H., *Proteins* **52** (2003) 436

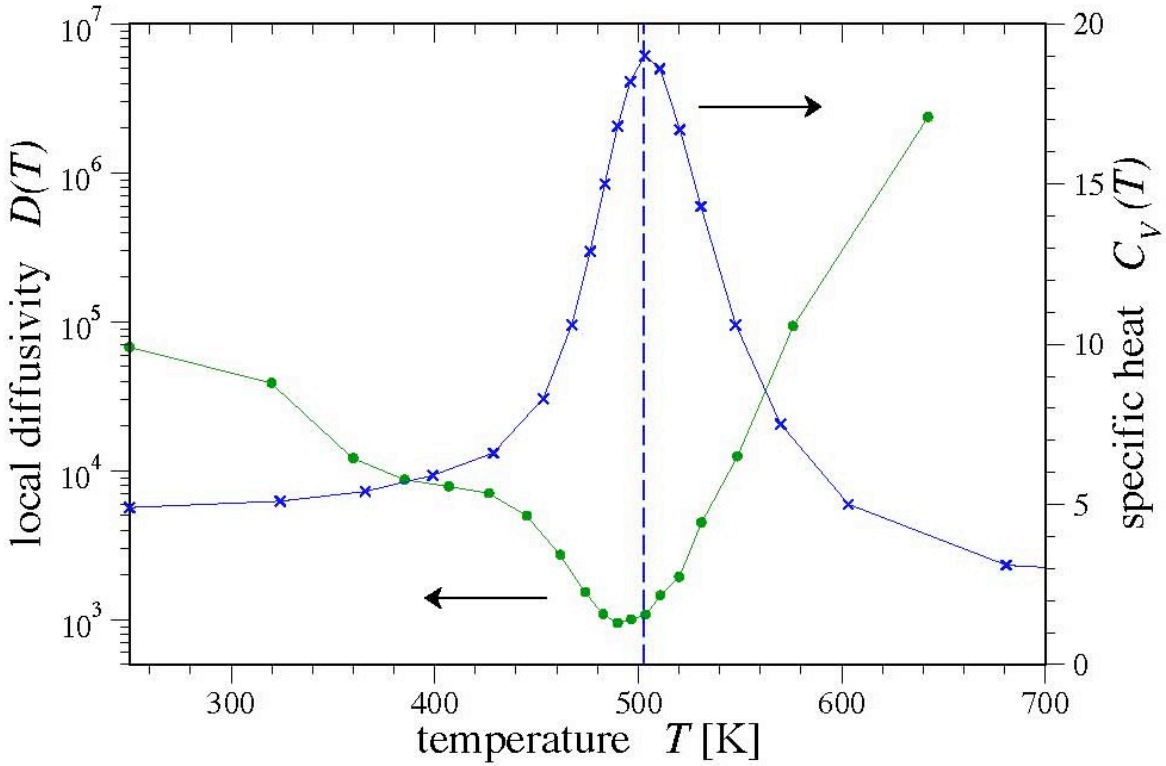
(simulation with solvent-accessible surface area term)

Time series of RGY

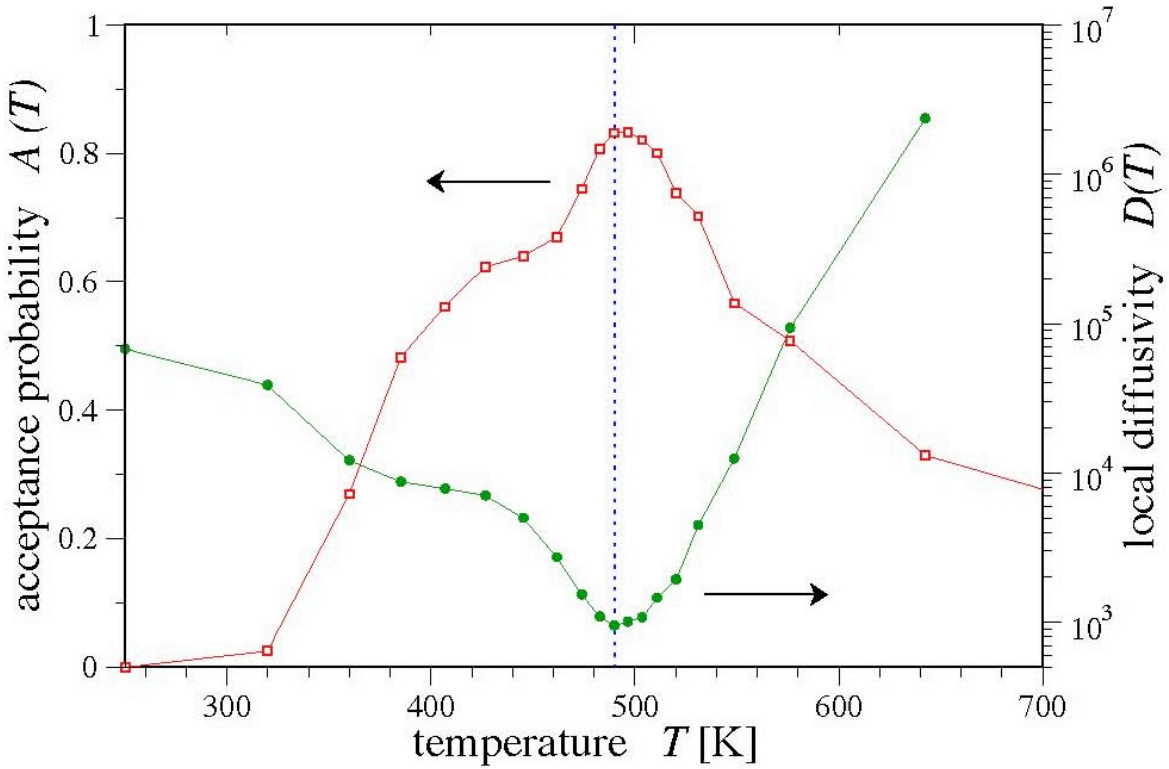
S.Trebst, M. Troyer and U.H.E.Hansmann, J. Chem. Phys. 124 (2006) 174903



Local Diffusitivity

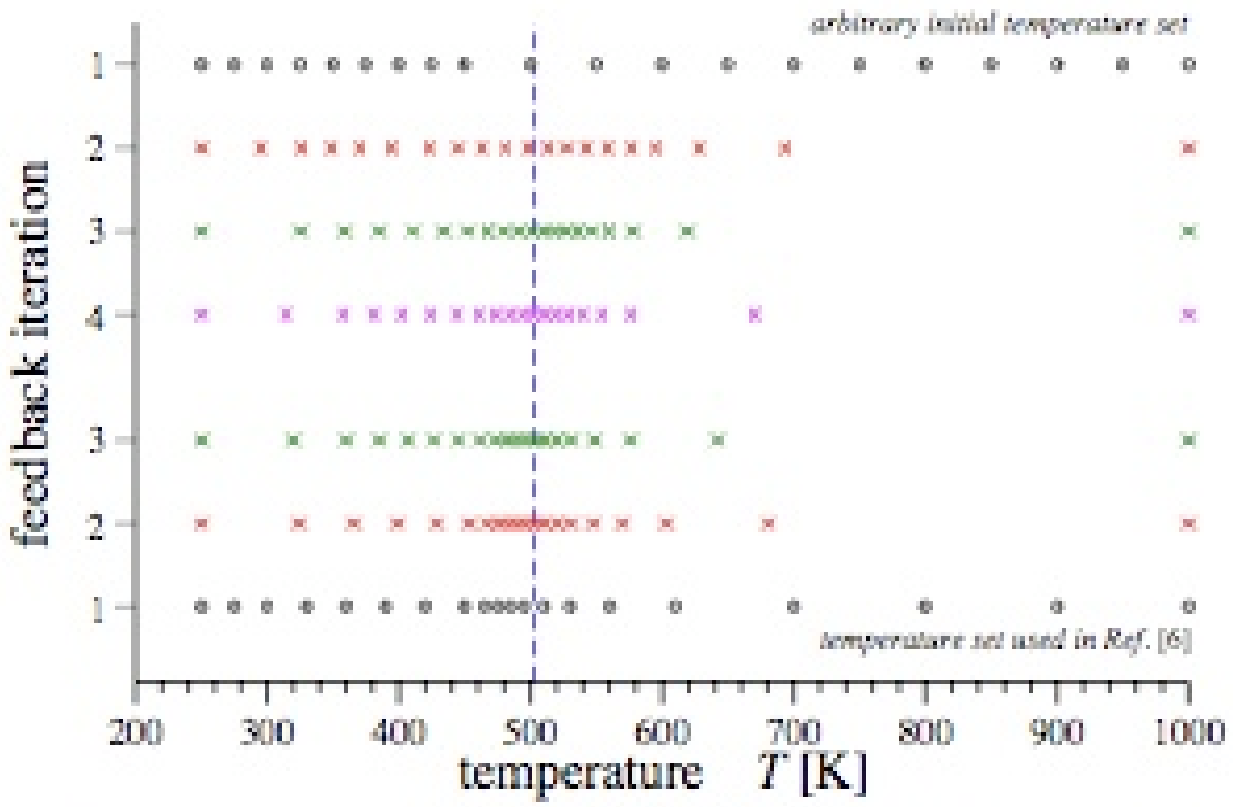


Acceptance probabilty



Iteration of Temperature Distribution

S.Trebst, M. Troyer and U.H.E.Hansmann, J. Chem. Phys. 124 (2006) 174903

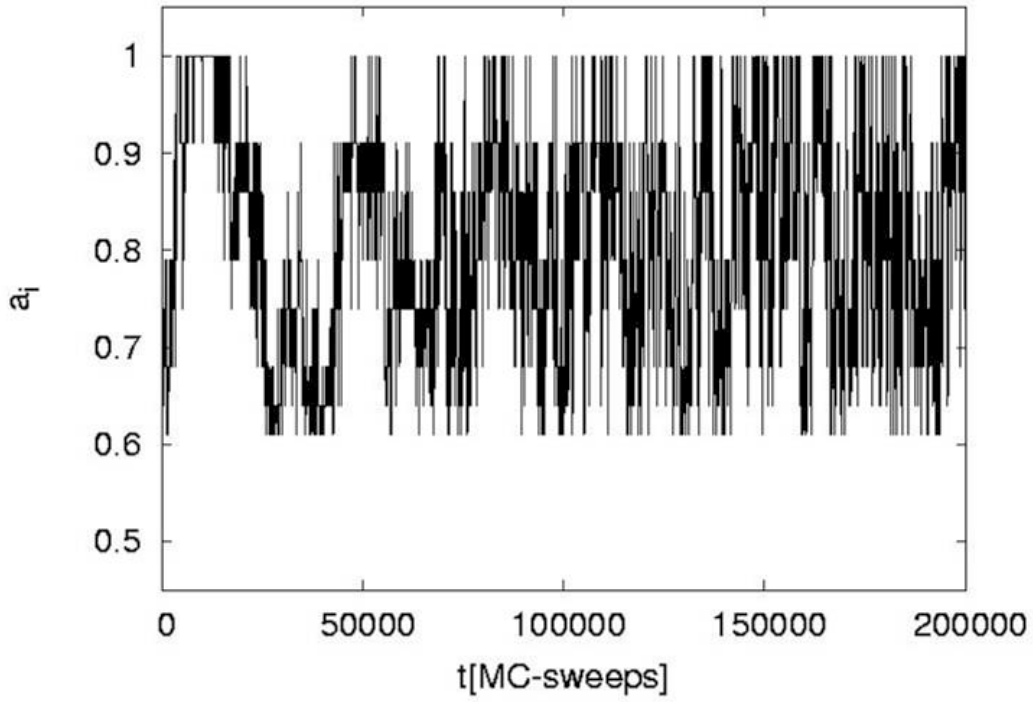


“Model Hopping” in Protein Simulations

W. Kwak & U.H.E. Hansmann, PRL **95** (2005) 138102

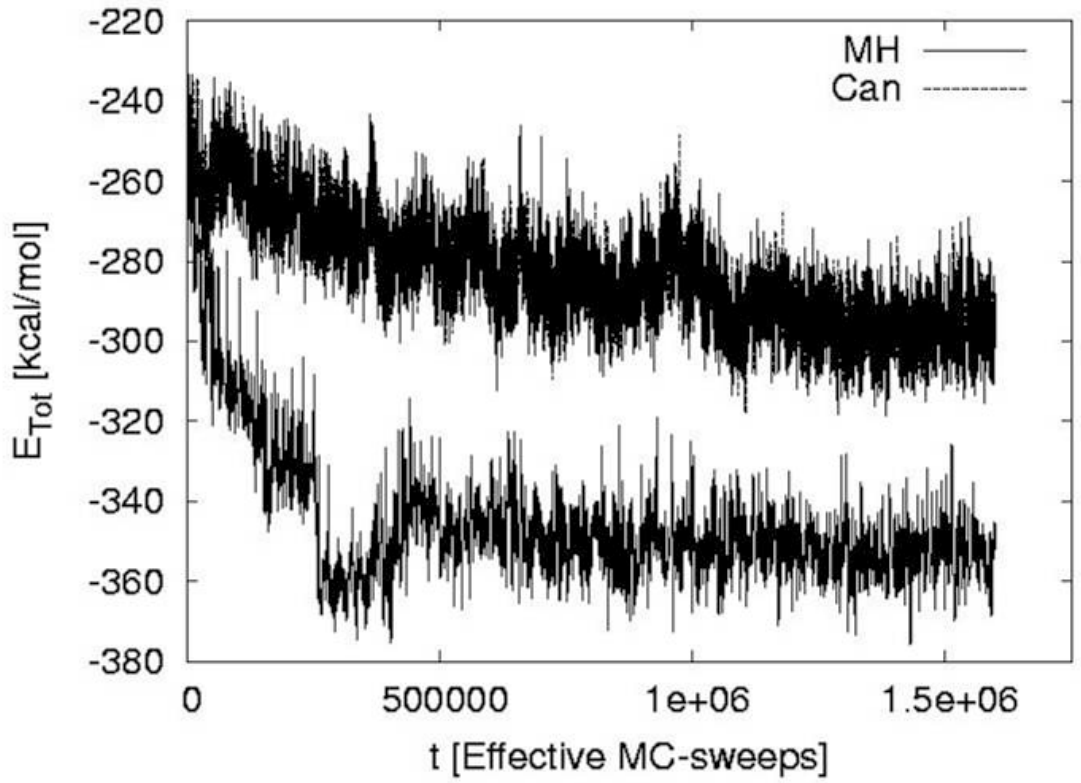
- Energy barriers often due to **vdW**-repulsion
- **Model Hopping** (MH) “tunnels” through barriers by random walk over non-physical models
- $E = E_{Rest} + E_{vdW} \rightarrow E_i = E_{Rest} + a_i E_{vdW}$
- $W(i,j) = \min(1,\exp(\Delta a \; \Delta E_{vdW}))$
- First test: **HP-36** and **protein A** fragment (48 AA)
- Other realization: **multiscale** modeling (in preparation)

Time Series of Coupling Parameter in a Simulation of HP-36

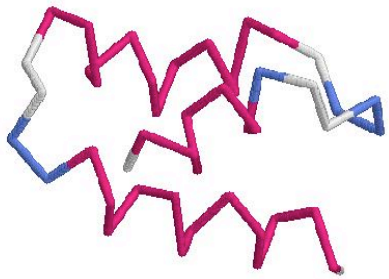


Comparison of MH with Canonical Simulation

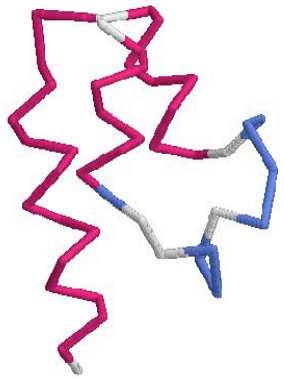
HP-36:



Protein A configurations (OONS solvent)



PDB - structure



Lowest energy structure
Rmsd: 3.9 **d**

Energy Landscape Paving

U.H.E. Hansmann, L. Wille, *Phys. Rev. Let.* **88** (2002), 068105;
H.P. Hsu, S.C. Lin, U.H.E. Hansmann, *Act Cryst*. **A 58** (2002) 254

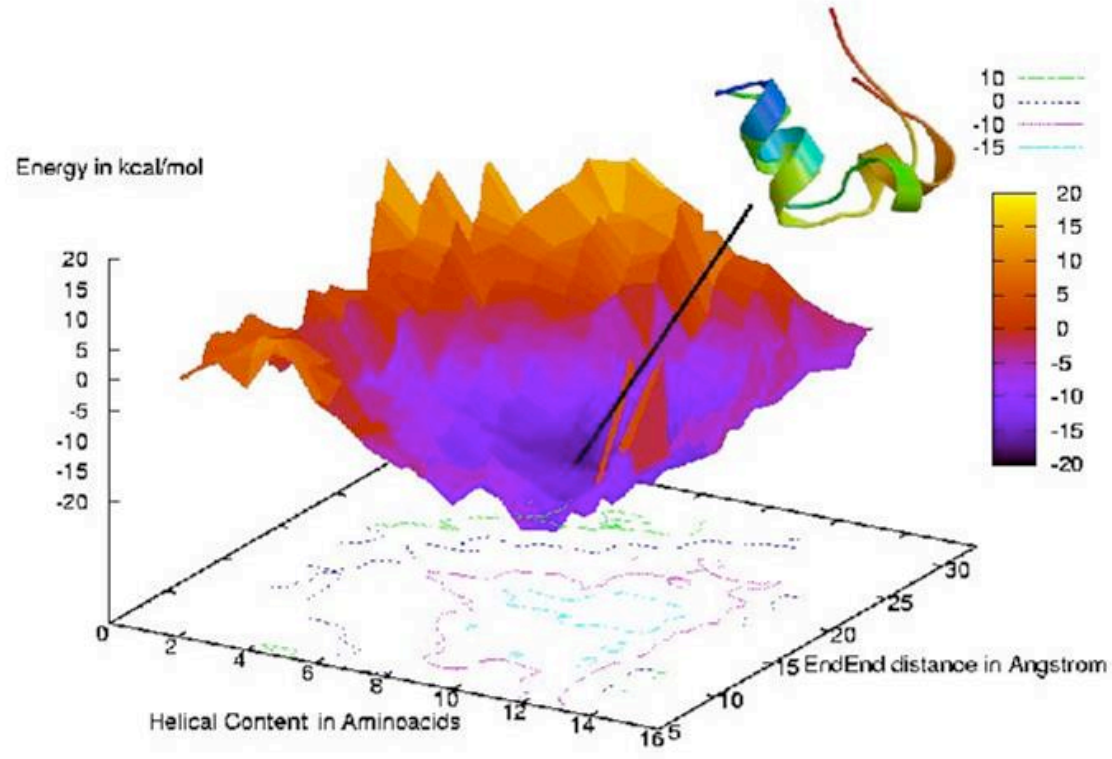
- **ELP** combines ideas from **tabu search** and **energy landscape deformation** approaches.
- Configurations are searched with **time-dependent** weights

$$w(E,q,t) = e^{-(E + f(H(q,t)))/k_B T}$$

- The low temperature *T* leads to drive toward **low energies**.
- The function ***f(H(q,t))*** drives simulation **out** of local minima.
- Often: ***f(H(q,t))= H(q,t),*** or even *f(H(q,t)) = H(E,t)*

Trp-cage protein (20 residues)

A. Schug, W. Wenzel & U.H.E. Hansmann, *J. Chem. Phys.*, **122** (2005) 194711.



Program Package SMMP

- **SMMP** (**S**imple **M**olecular **M**echanics for **P**roteins) is a modern package for simulation of proteins.
- Contains **generalized-ensemble** algorithms and other sophisticated simulation techniques.
- Runs also **parallel** computers
- Written in **FORTRAN**, a **C++** version is in preparation
- The program package is **freeware** and **open source** (http://www.phy.mtu.edu/biophys/smmp.htm)

Reference:

F. Eisenmenger, U.H.E.Hansmann, S.Hayryan & C.K.Hu
[SMMP] - A modern package for simulation of proteins
Computer Physics Communications **138** (2001) 192

Helix vs. Sheet Formation

Y.Peng and U.H.E. Hansmann, *PRE*, **68** (2003) 041911.

- **α-helices** and **β-sheets** are common motifs in proteins
- "Mis-folding" → **aggregation**, often associated with **diseases**
- What **factors** govern formation of secondary structure?
- Our model: **EKAYLRT**, which forms both **α-helices** and **β-sheets**

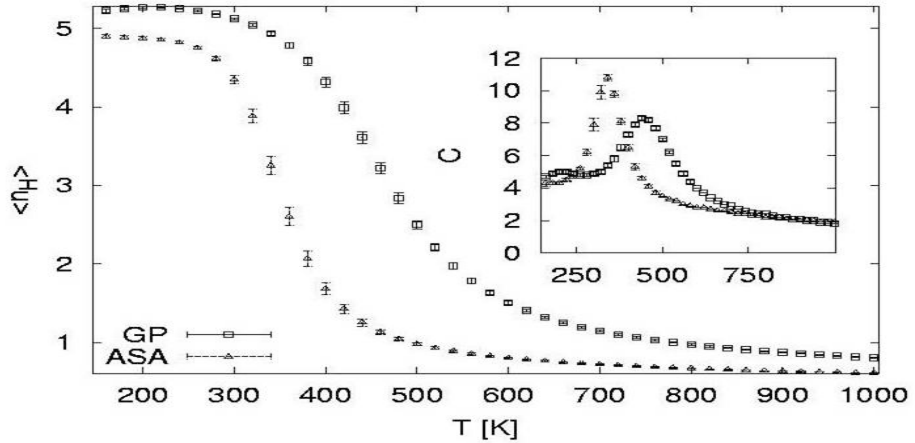
  S. Sudarsanam, *Proteins* **30** (1998) 228
- **Isolated** molecule and **interacting** with a β-strand.
- Simulations in **gas phase** and with an **implicit solvent**

  T.Ooi, *et al.*, *PNAS (USA)* **84** (1987) 3086

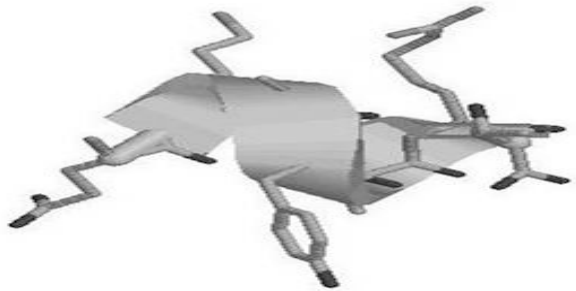
Isolated EKAYLRT Molecule

Y.Peng and U.H.E. Hansmann, *PRE*, **68** (2003) 041911.

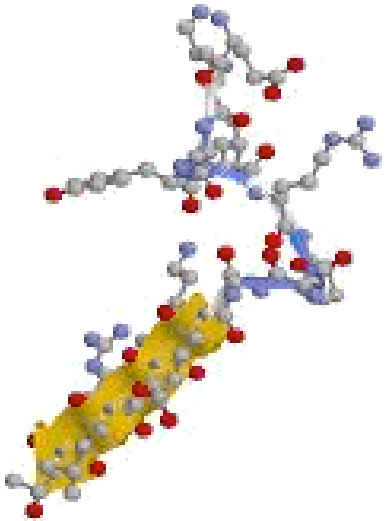
Helicity as function of temperature:



Ground-state structure of EKAYLRT:

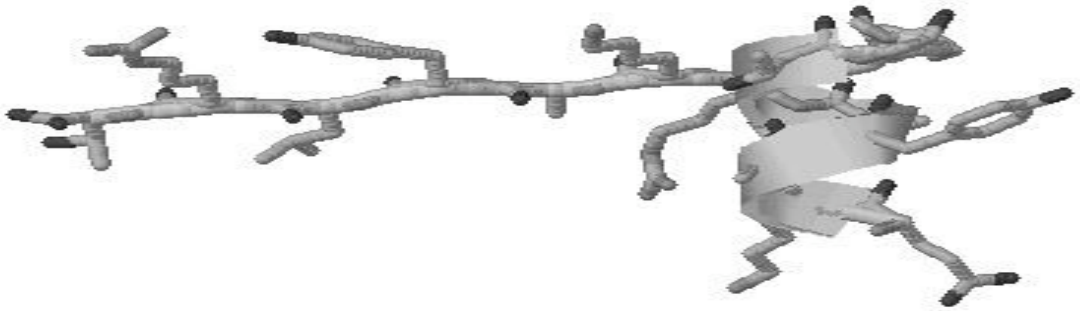


Simulation of the Peptide Sequence EKAYLRT Interacting with a β-Strand

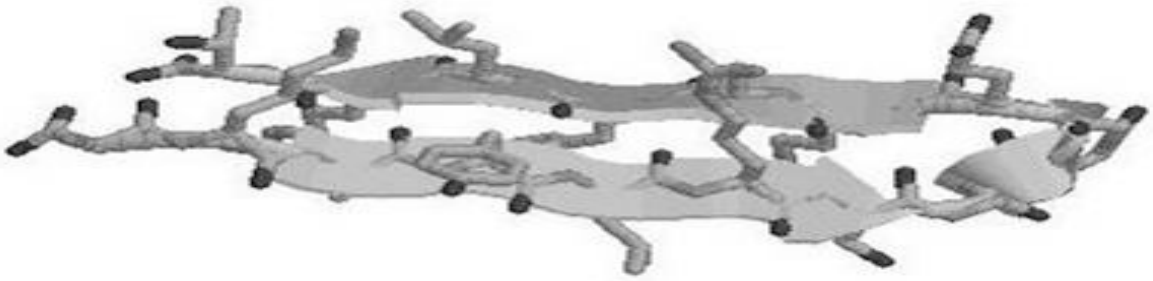


Low-energy structures of EKAYLRT interacting with a β-strand

Large end-to-end distance $d_{e\text{-}e}$:



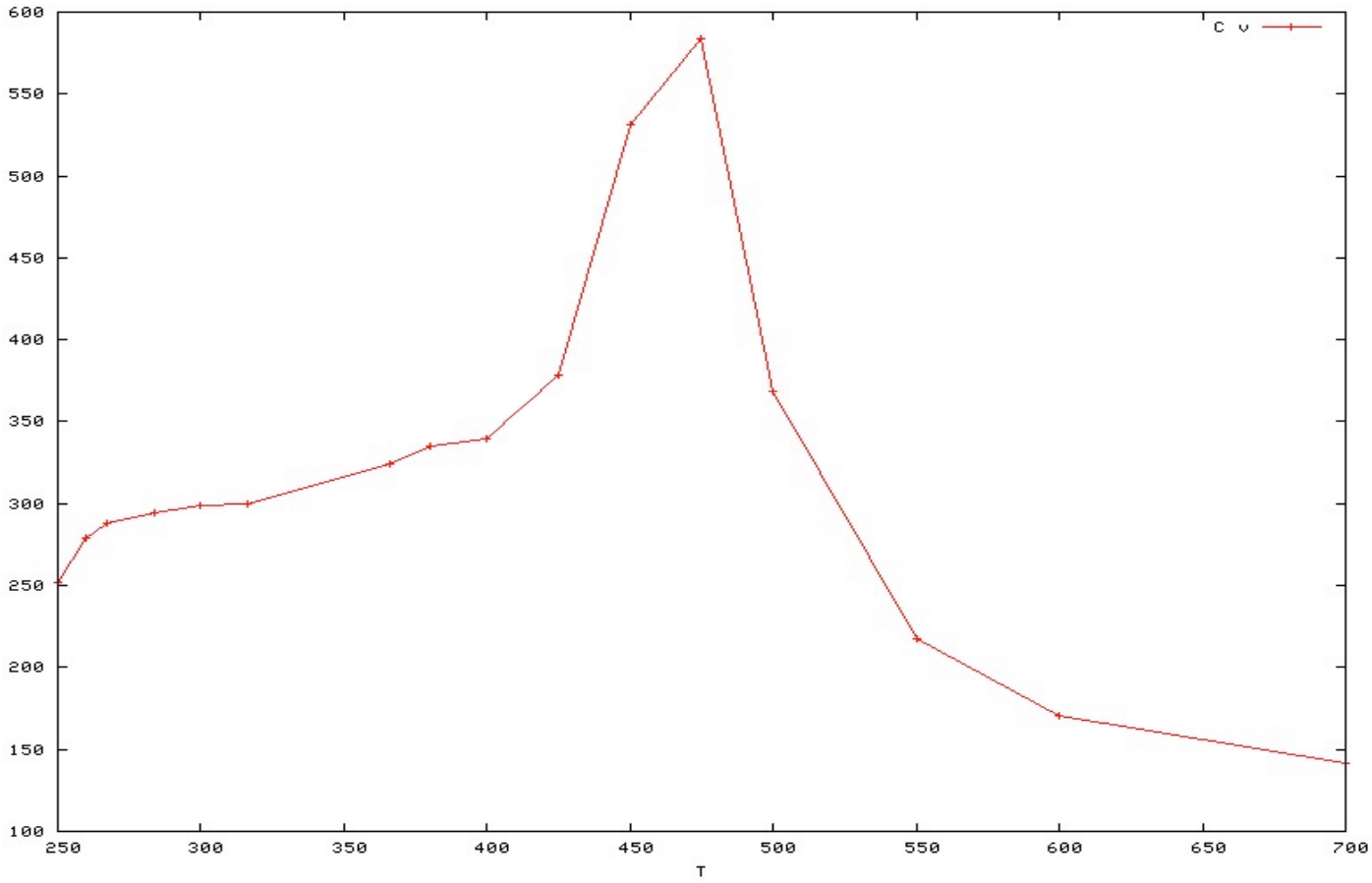
Small end-to-end distance $d_{e\text{-}e}$:



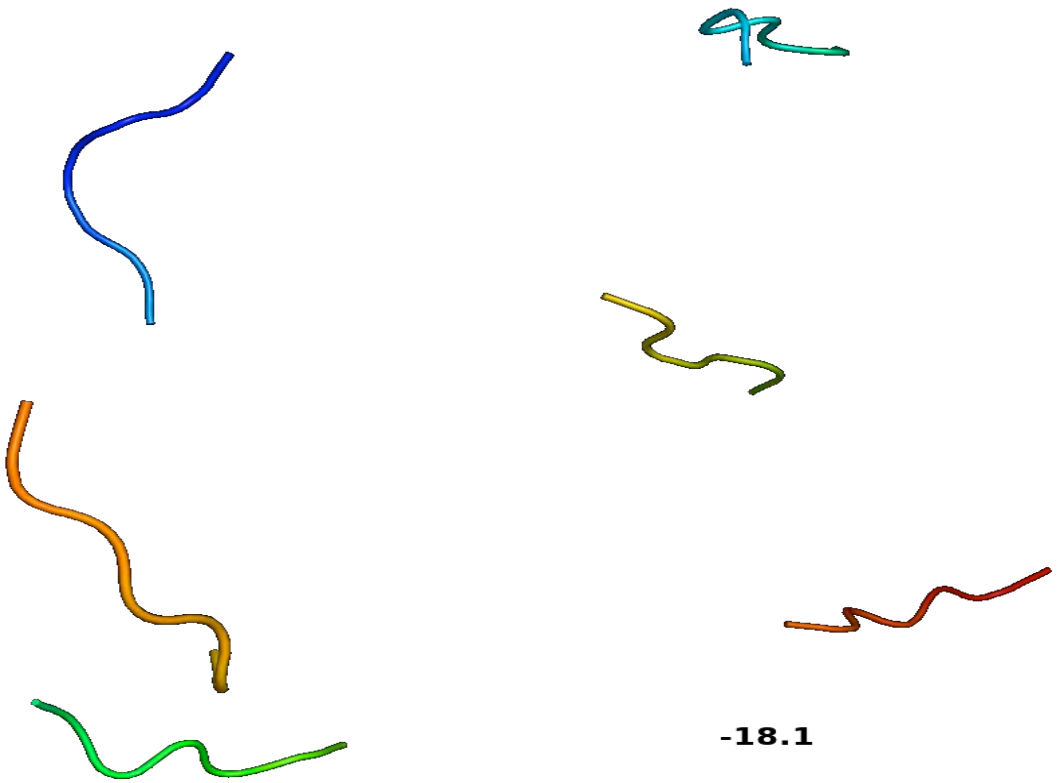
Aggregation of β -Amaloyd 16–22

- **Fibrils** build out of mis-folded β - Amaloyd peptides are related to outbreak of **Alzheimer disease**.
- Aggregated peptides show **high β - strand** content
- We focus on **segment 16-22** which has high β - strand propensity
- Can we observe fibril formation ***in silico***?

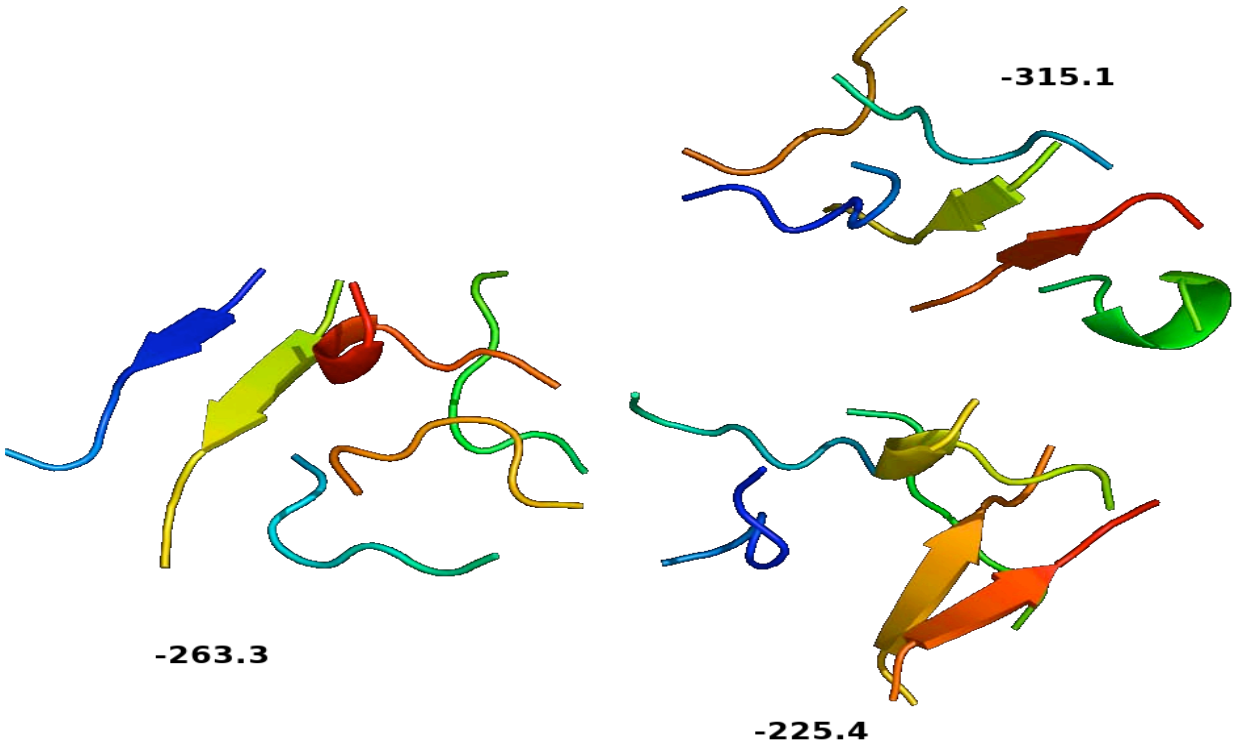
Spec. Heat



“Free” chains

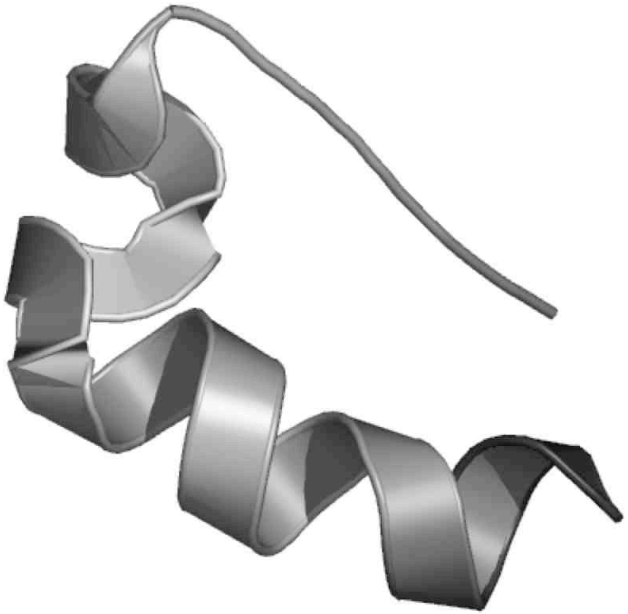


Low-energy configurations

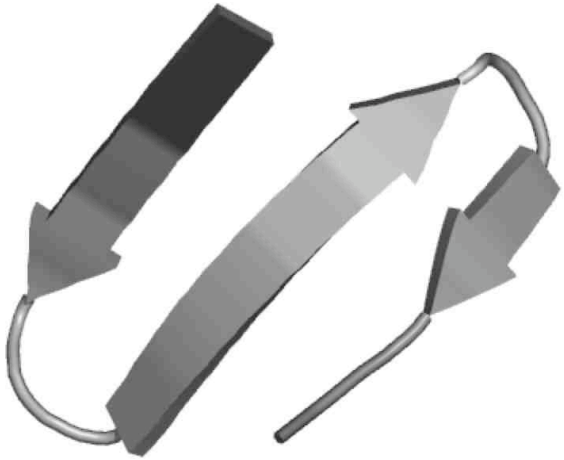


Three small proteins

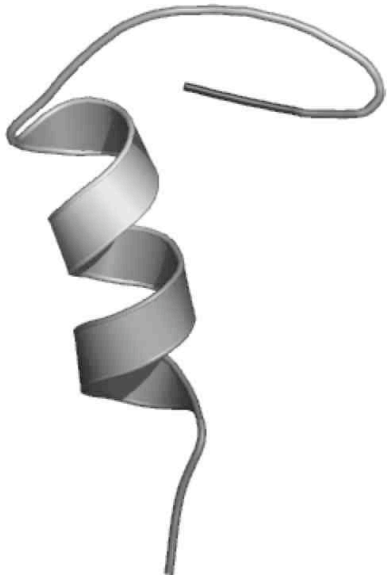
S. Mohanty and U.H.E. Hansmann, Biophysical Journal, in press



1RIJ



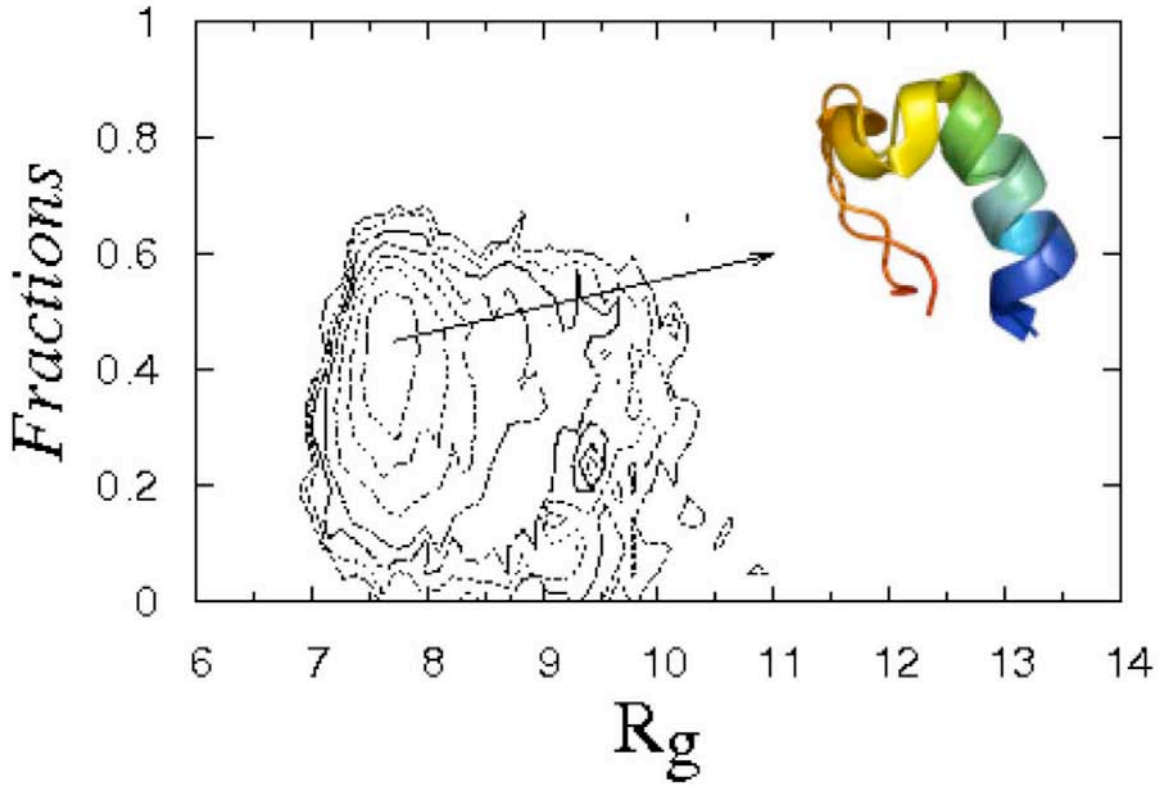
beta3s



bba5

Energy Landscape of 1RIJ

S. Mohanty and U.H.E. Hansmann, Biophysical Journal, in press



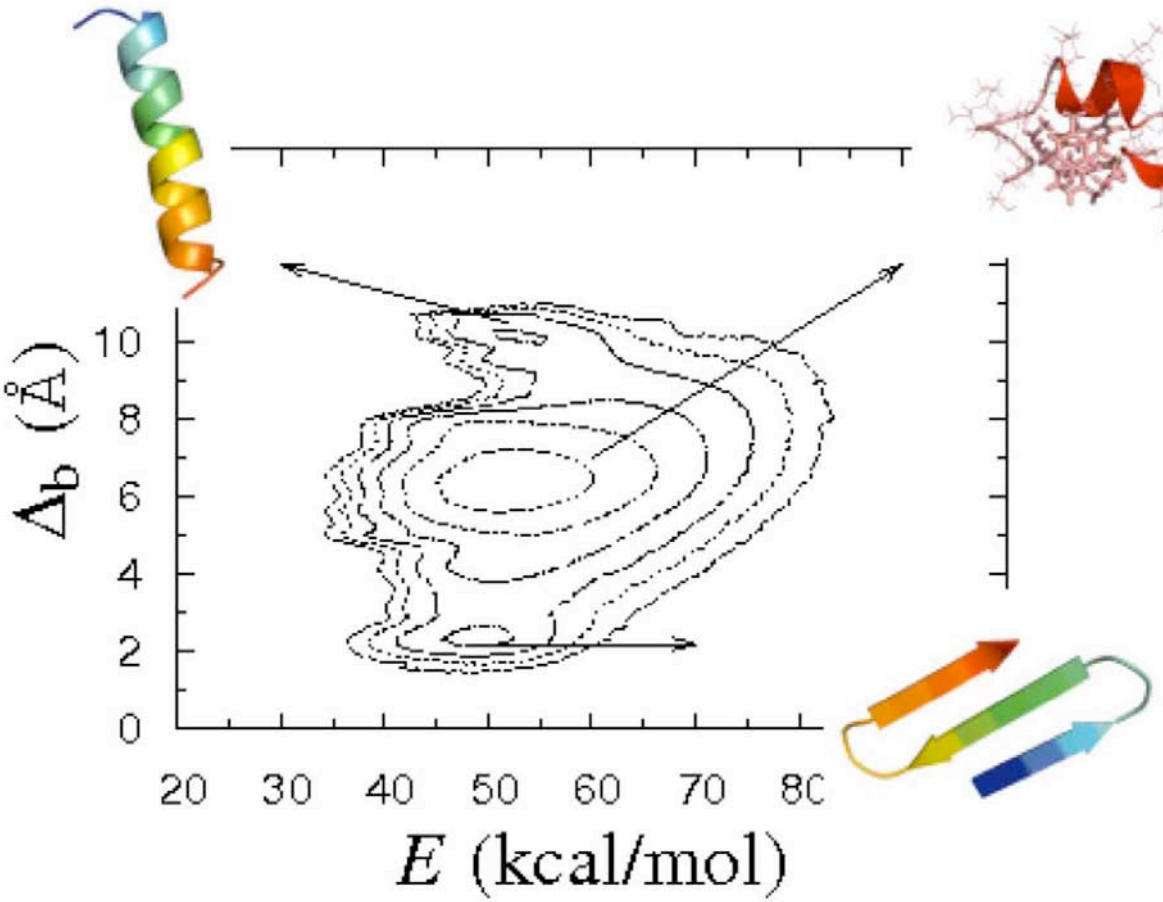
RMSD= 2.7Å

50% at T=274K
(Exp. Value: 90%)

Synchronous
Collapse and
Helix-formation

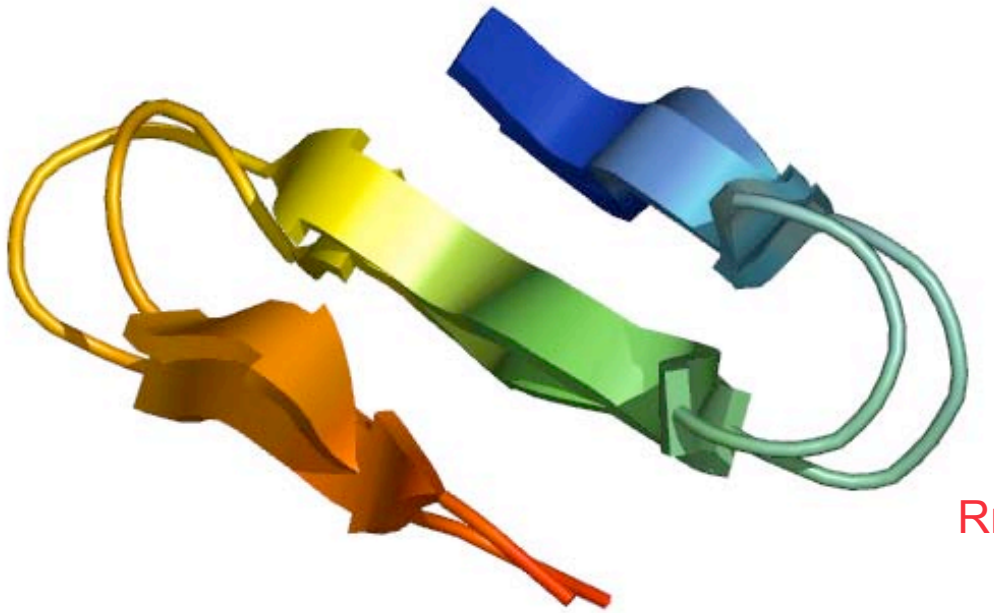
Energy landscape of beta3s

S. Mohanty and U.H.E. Hansmann, Biophysical Journal, in press



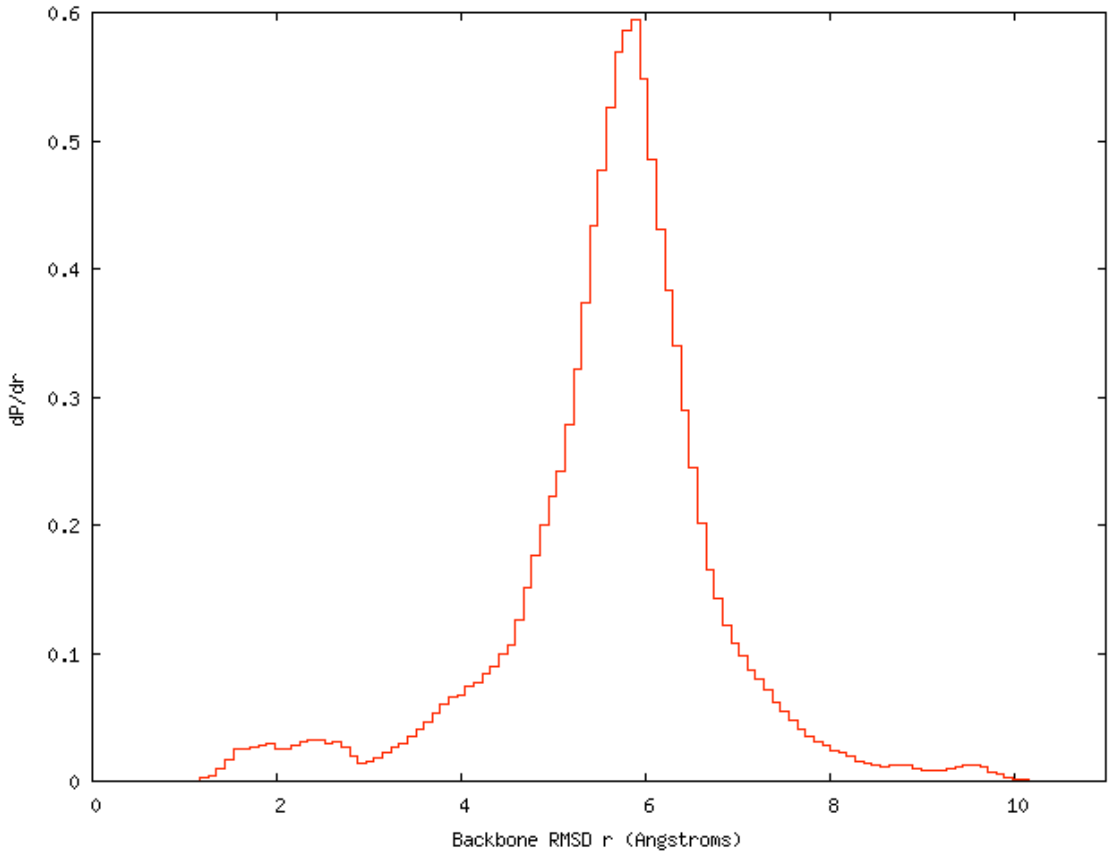
Lowest energy configuration

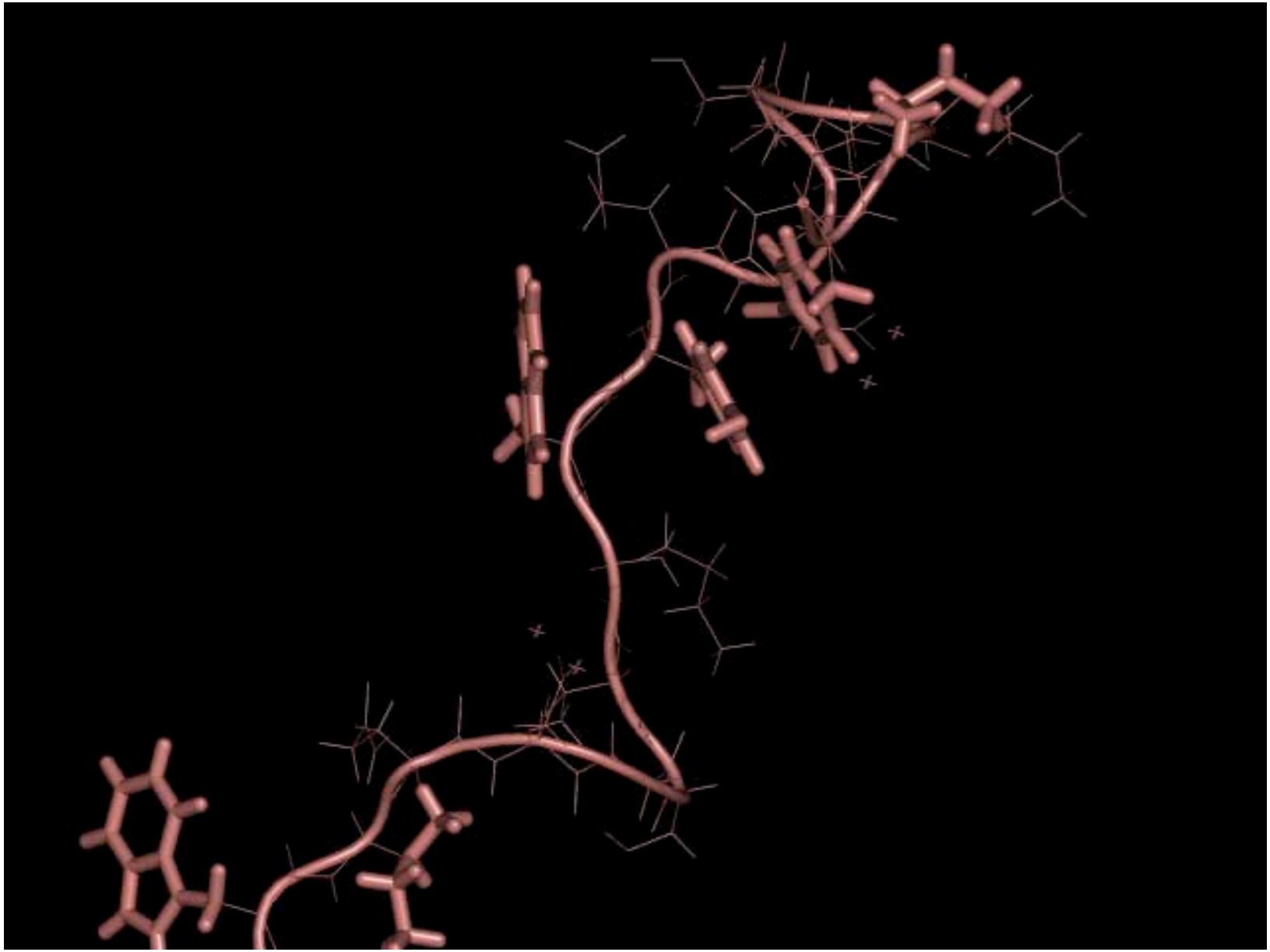
S. Mohanty and U.H.E. Hansmann, Biophysical Journal, in press



Rmsd: 2 Å

Propensity of configurations



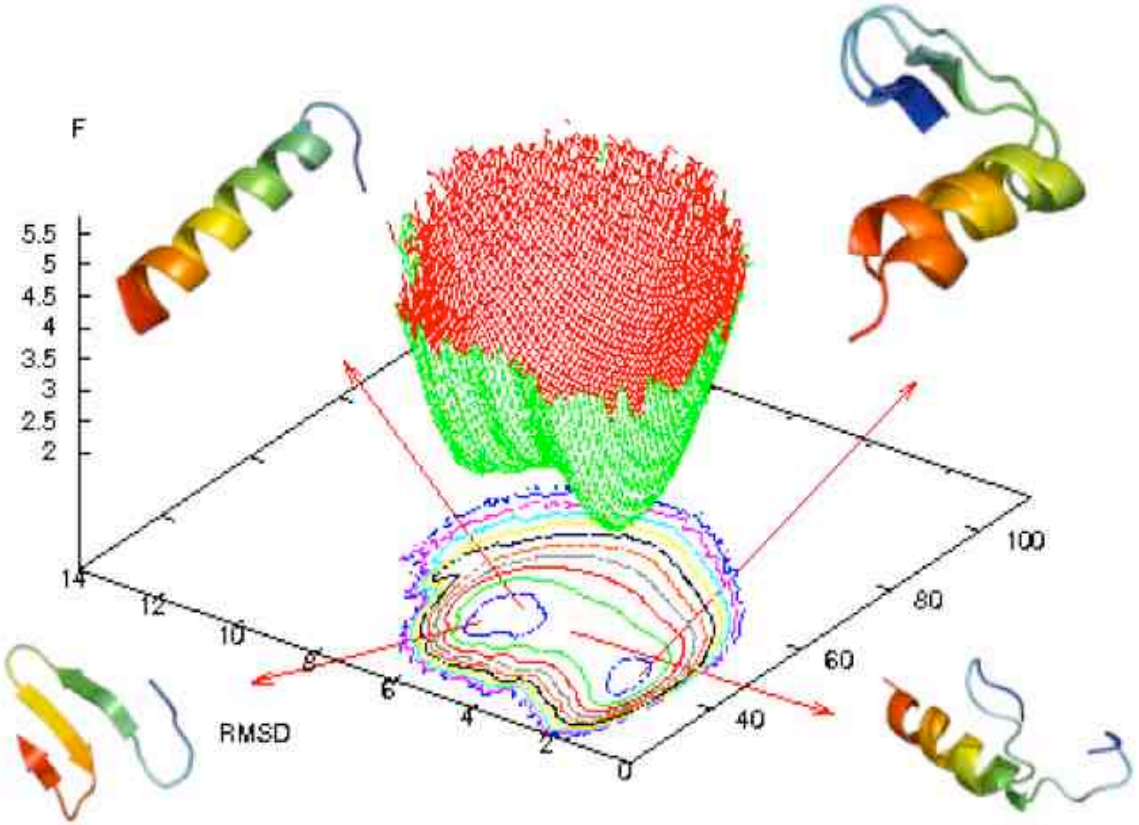


Folding of Beta3s

- Collapse **precedes** secondary-structure formation
- **Zipper**-like formation of hairpins
- No particular order in that hairpins are formed
- Once formed it **catalyzes** formation of second hairpin

Energy landscape of BBA5

S. Mohanty and U.H.E. Hansmann, Biophysical Journal, in press



RMSD = 2.2 Å

Folding of BBA5

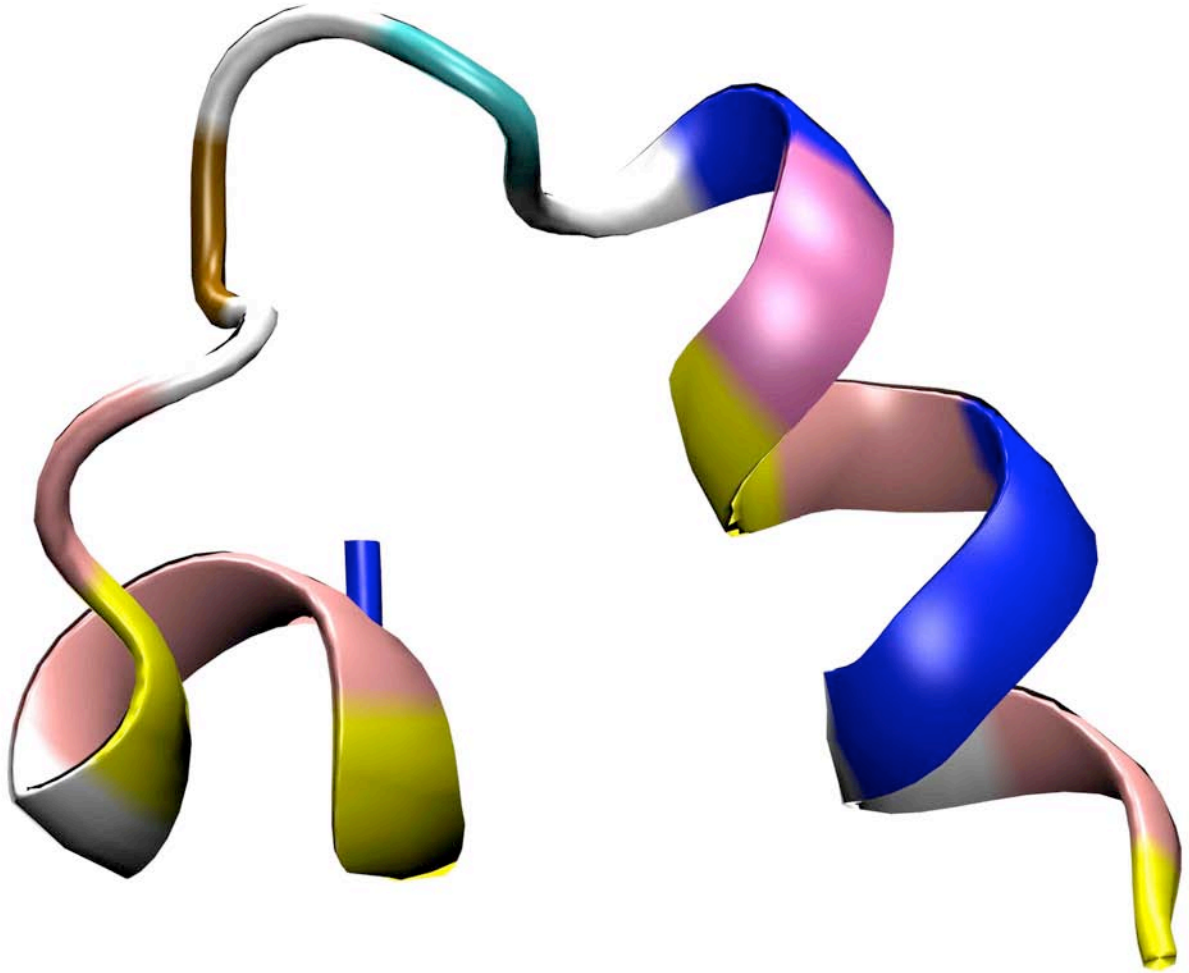
- Both **helix** and **sheet**
- Secondary structure elements form **independently**
- Both formed **before** folding into final shape

PTMD of a Signal Peptide

S. Höfinger and U.H.E. Hansmann, submitted for publication

- Signal peptides have strong **hydrophobic** character
- Folding only in **membran** environment?
- But biological considerations suggest folding in **aqueous** environment
- **22-residue** signal peptide of rat liver aldehyde dehydrogenase
- NMR analysis shows a **helix-loop-helix** motif
- Parallel tempering molecular dynamics in **explicit water**

Lowest-energy configuration of the SP



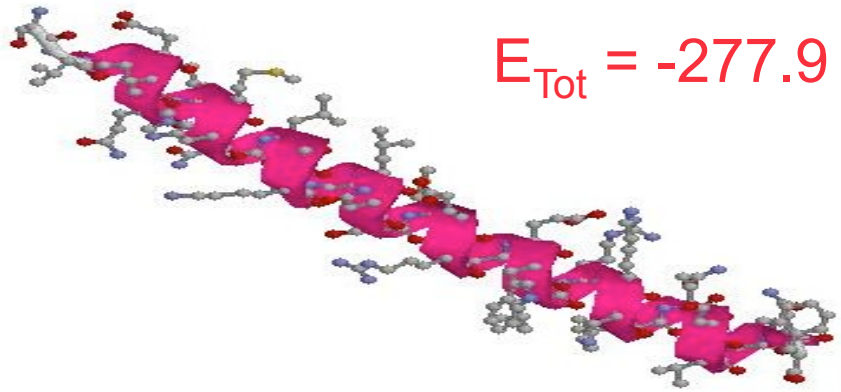
Structure Prediction of Small Proteins

- Goal is **folding** of **stable domains** (50 – 200 residues)
- The **sampling techniques** exist now
- But are the force-fields **accurate** enough?

Systems:

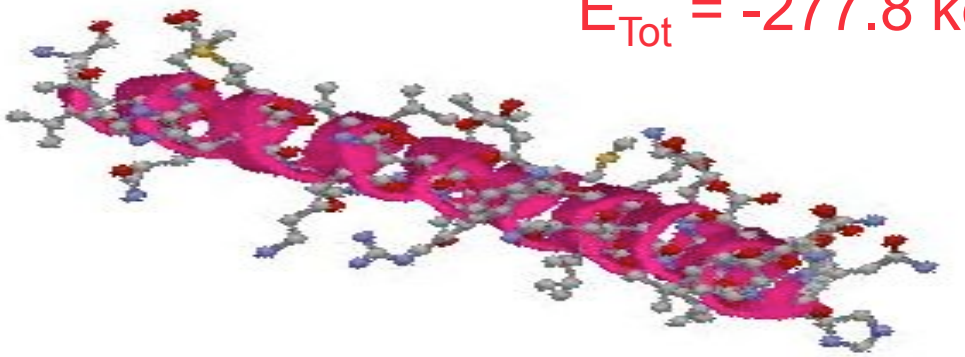
- Fragment **PTH(1-34)** of human parathyroid hormone
  U.H.E. Hansmann, J. Chem. Phys. **120** (2004) 417
- Villin headpiece subdomain **(HP-36)**
  U.H.E. Hansmann and L.Wille, *PRL* **88** (2002) 068105
  C.-Y. Lin, C.-K. Hu and U.H., *Proteins* **52** (2003) 436
- B domain of **protein A**
  W. Kwak and U.H.E. Hansmann, *PRL* 95 (2005) 138102
- Artificial three-stranded sheet-peptide **beta3s**

Crystal Structure (1ET1) of PTH(1-34)



E_{Tot} = -277.9 kcal/mol

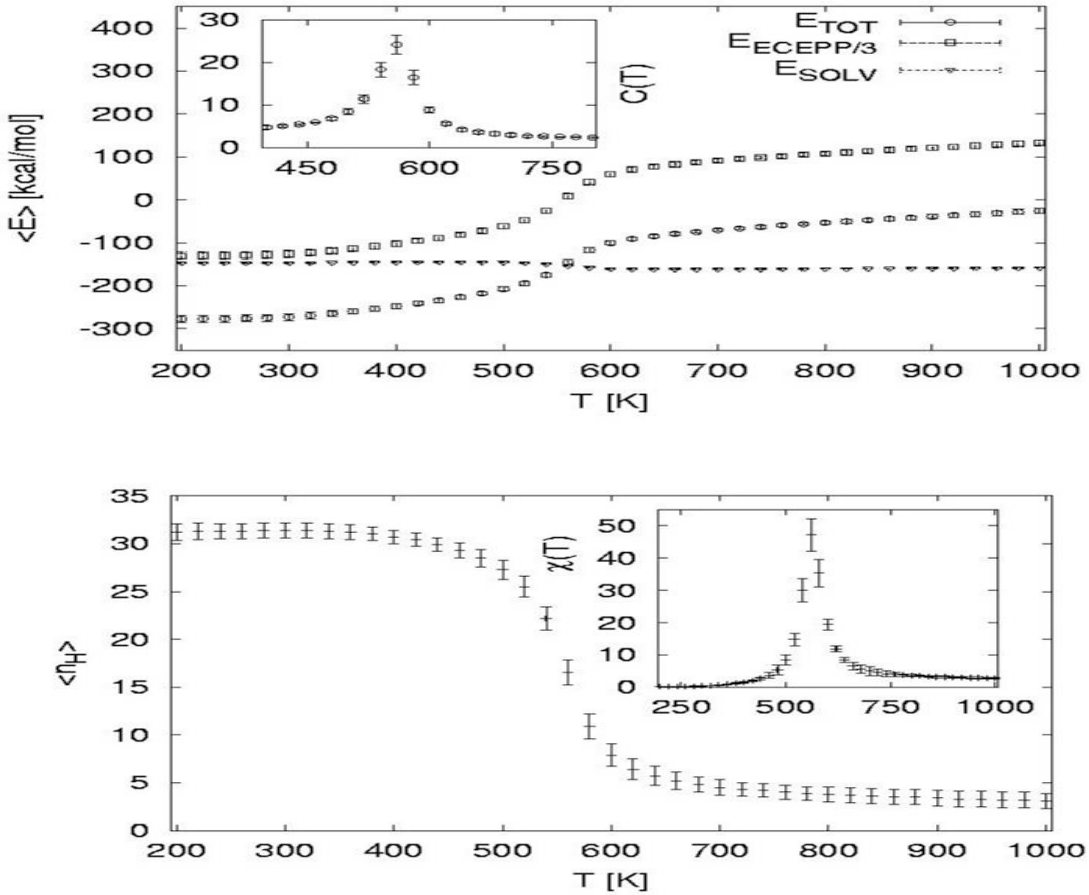
Lowest-energy structure



E_{Tot} = -277.8 kcal/mol

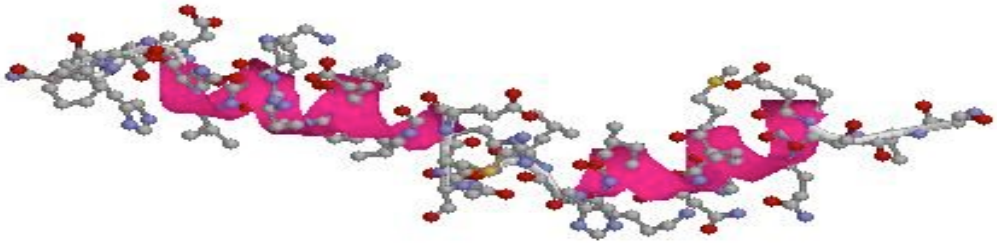
RMSD: 0.9 Å

Thermodynamics of PTH(1-34)

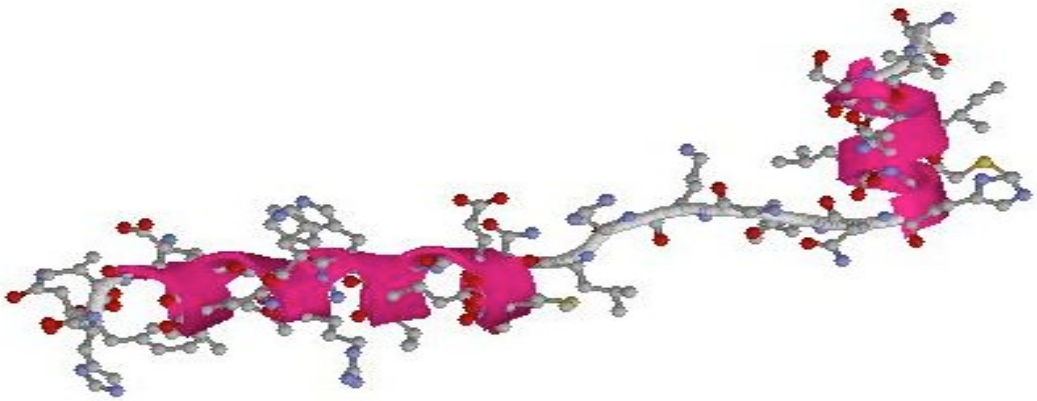


Transition Temperature: T_θ = 560 ± 20 K

NMR Structure (1HPY) of PTH(1-34)



Structure found at T=540 K



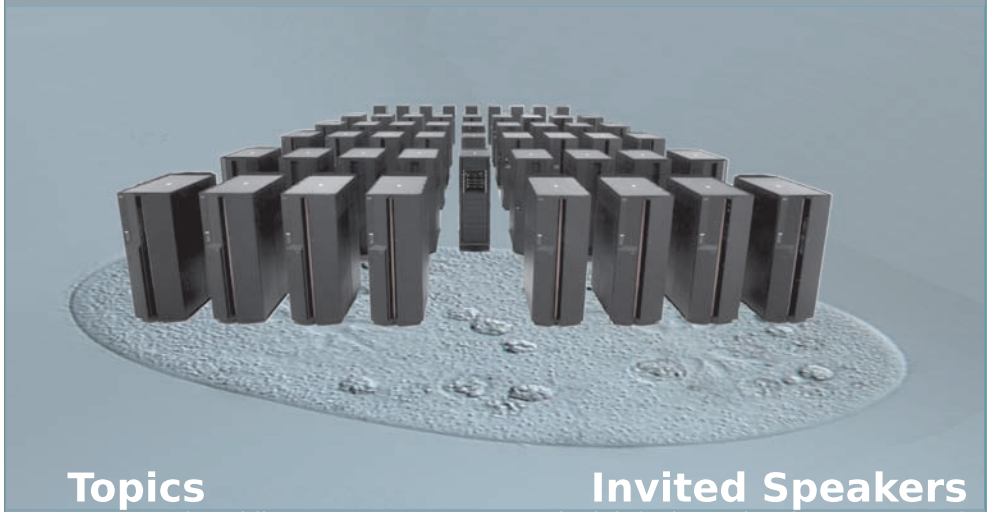
Conclusion

- We have now **efficient** simulation techniques
- **Experimental results** can be reproduced for small proteins
- What happens for **larger molecules** (protein L)?
- **Limitations** of protein models?

From Computational Biophysics to Systems Biology (CBSB07)

Celebrating 20 years Neumann Institute for Computing (NIC)

02 to 04 May 2007, Jülich, Germany



Topics

- Protein Folding
- Multi Protein Complexes
- Nanostructures
- Cellular systems at the molecular level

Invited Speakers

M. Cieplak (Pol. Acad. Science, Warsaw)
Ch. Floudas (Princeton)
J. Langowski (DKFZ, Heidelberg)
B. Lesyng (U. Warsaw)
A. Liwo (U. Gdansk)
J. Onuchic (UCSD, La Jolla)
A. Roitberg (UF, Gainesville)
R. Russell (EMBL, Heidelberg)
K. Takahashi (tMSI, Berkeley)
D. Thirumalai (UM, College Park)
R. Wade (EML, Heidelberg)

http://www.fz-juelich.de/cbsb07

Organizers: U. Hansmann, J. Meinke, S. Mohanty, T. Neuhaus, O. Zimmermann

GRADUATE STUDENT AND POSTDOC POSITIONS AVAILABLE!

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