Protein Folding Simulations

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Computational Physics 2007, Leipzig

Outline

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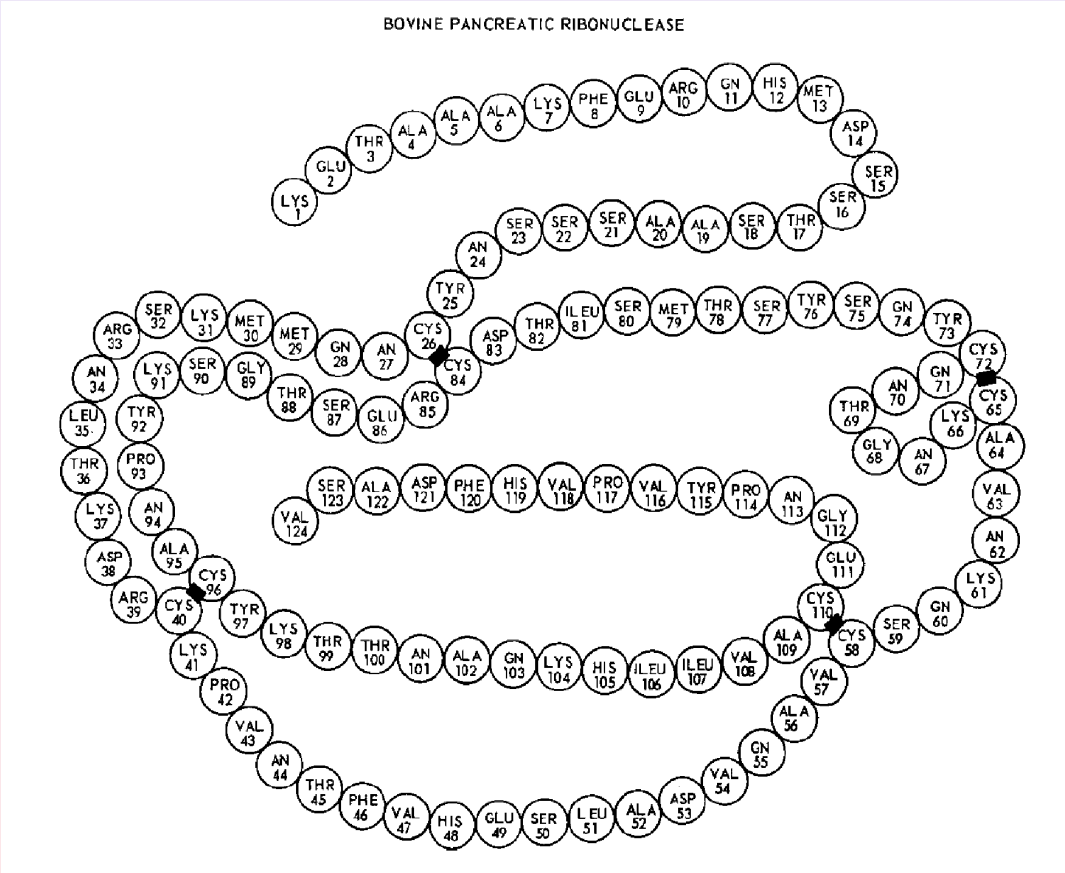
The Polypeptide Chain

Schematic structure of Bovine Pancreatic Ribonuclease[1]



[1] Christian B. Anfinsen, *Nobel Lecture*, 1972

Interaction between Aminoacids

Forces

- Repulsive forces between atoms and residues (LJ).
- Hidrogen bond bewteen NH-CO pairs.
- Dipole-Dipole interaction between NH-CO pairs.
- Water effects on Hydrophobic and Hydrophilic aminoacids.

$$V_T = V_{LJ} + V_{HB} + V_{DD} + V_{MJ} + V_{LocalHP}$$

The main problem in Protein Folding

Goal of Protein Folding Simulations

- Given a sequence of aminoacids one should predict the native structure.

Outline

Energy Landscape Paving

ELP

The Free-energy landscape is deformed to explore low- energy configurations while avoiding at the same time entrapment in local minima[a]. The weight of a configuration is,

$$\mathbf{w}(\tilde{\mathbf{E}}) = \mathbf{e}^{-\tilde{\mathbf{E}}/\mathbf{k_B T}} \text{ with } \tilde{\mathbf{E}} = \mathbf{E} + \mathbf{f}\left[\mathbf{H}(\mathbf{q}, \mathbf{t})\right]$$

$\mathbf{f}\left[\mathbf{H}(\mathbf{q}, \mathbf{t})\right]$ is a function of a histogram which keeps the record of Monte Carlo's process.

[a] PRL **88** 068105 (2002)

Outline

Wang-Landau Algorithm

W-L Algorithm

W-L is a method that calculates the density of states (DOS)[a]

1. Set the DOS to $\mathbf{g(E) = 1}$ and a function $\mathbf{H(E) = 1}$,
2. If $\mathbf{E_1}$ and $\mathbf{E_2}$ are the energies before and after some change, the transition probability is,

$$\mathbf{P(E_1 \rightarrow E_2) = \min \left[\frac{g(E_1)}{g(E_2)}, 1 \right]}$$

3. Each time the energy level $\mathbf{E}$ is visited, we modify the density of states $\mathbf{g(E) \rightarrow g(E) \times f}$, $\mathbf{f_{i+1} = \sqrt{f_i}}$.

[a] PRL **86** 2050 (2001)

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Thermodynamical Properties

Partition Function

$$\mathcal{Z}(\mathbf{T}) = \int \mathbf{g(E)e}^{-\beta \mathbf{E}}\, \mathbf{dE}$$

Free Energy

$$\mathbf{F(T)} = -\mathbf{k}_\beta \mathbf{T} \ln(\mathcal{Z}(\mathbf{T}))$$

Internal Energy

$$\mathbf{U(T)} = \frac{\int \mathbf{Eg(E)e}^{-\beta \mathbf{E}}}{\int \mathbf{g(E)e}^{-\beta \mathbf{E}}}$$

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Outline

Sequence:

Thr-Val-Thr-Phe-Thr-Gly-Gly-Thr-Leu-Lys-Val-Tyr

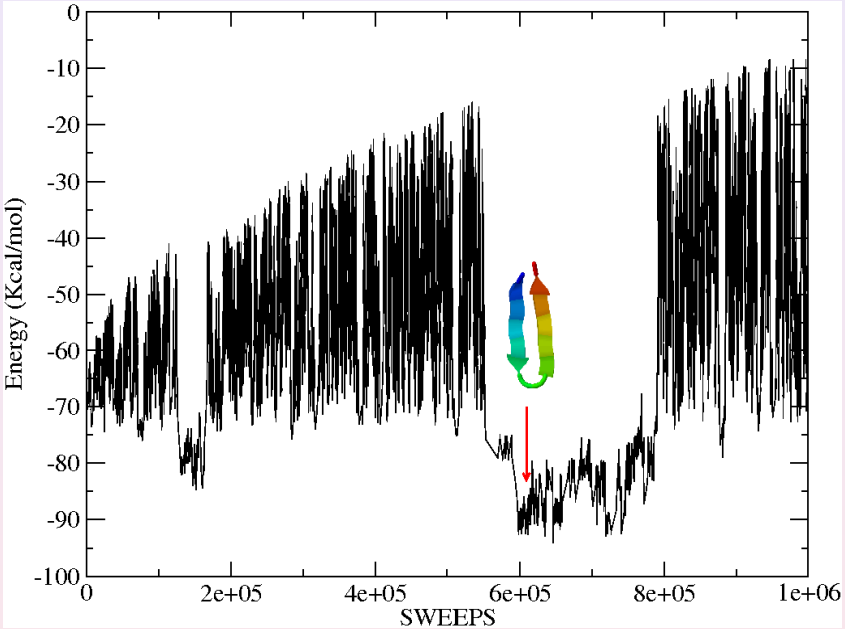

FIG. 7. Energy vs. MCS using the number of native contacts (Q) as a parameter in $f(Q, t)$.

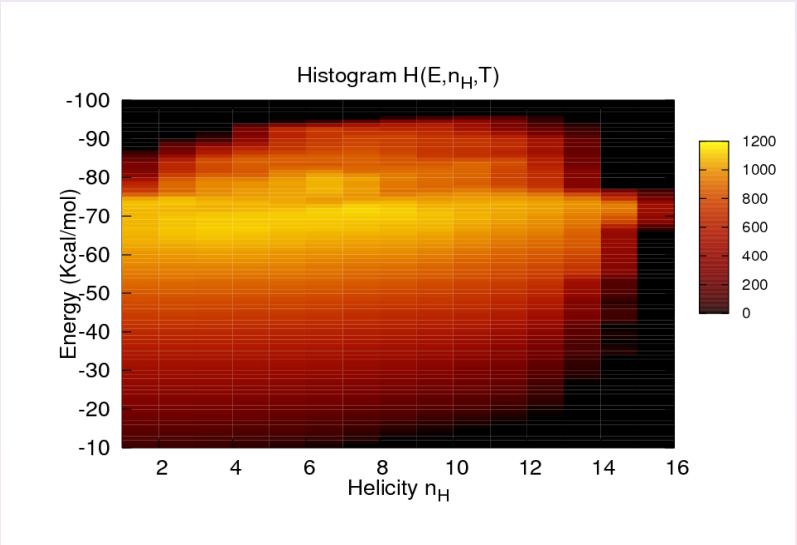

FIG. 8. Energy vs. MCS using the number of beta-sheet contacts (n_β) as a parameter in $f(n_\beta, t)$.

Sequence: Ala-Leu-Asn-Gln-Ala-Leu-Asn-Gln-Ala-Leu

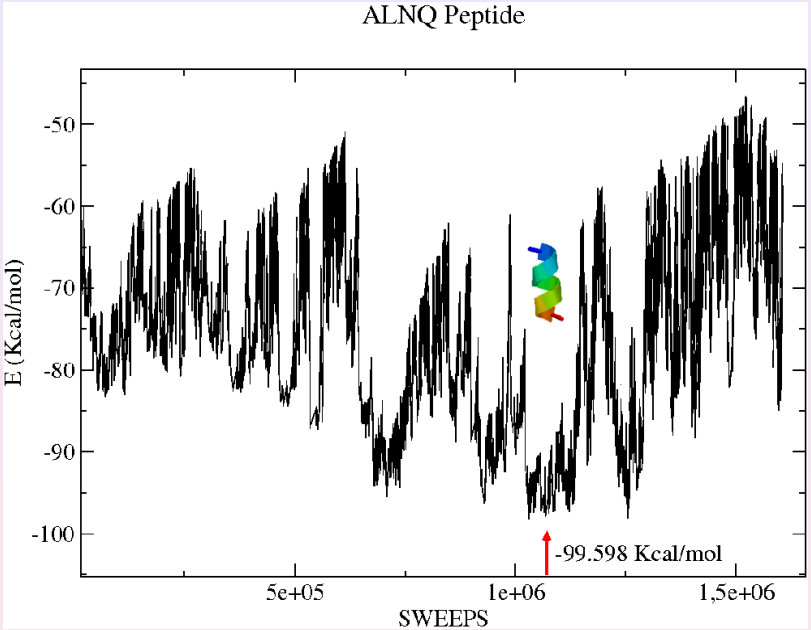

FIG. 9. Energy vs. MCS using the number of native contacts (Q) as a parameter in $f(Q, t)$.

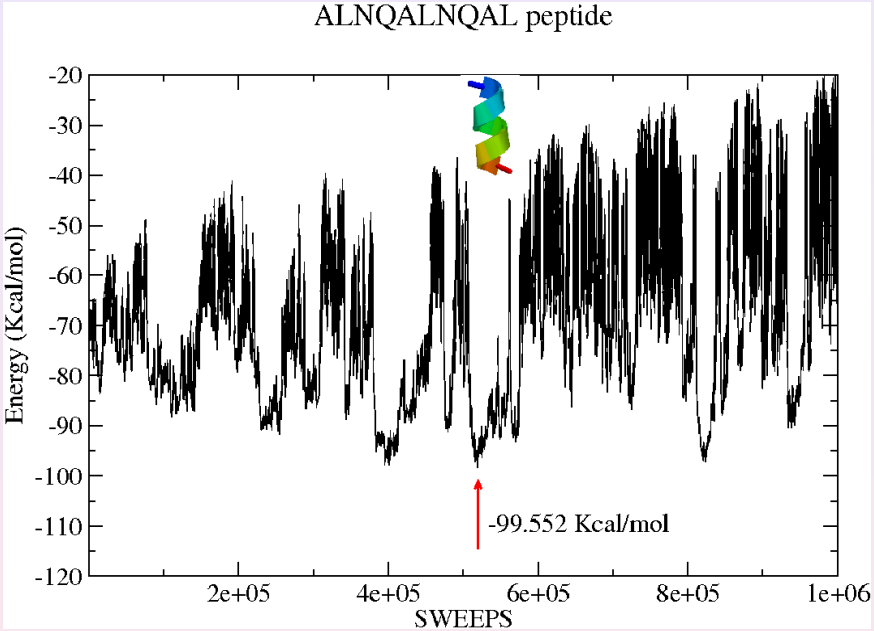

FIG. 10. Energy vs. MCS using the number of helical contacts (n_H) as a parameter in $f(n_H, t)$.

2G9P Peptide

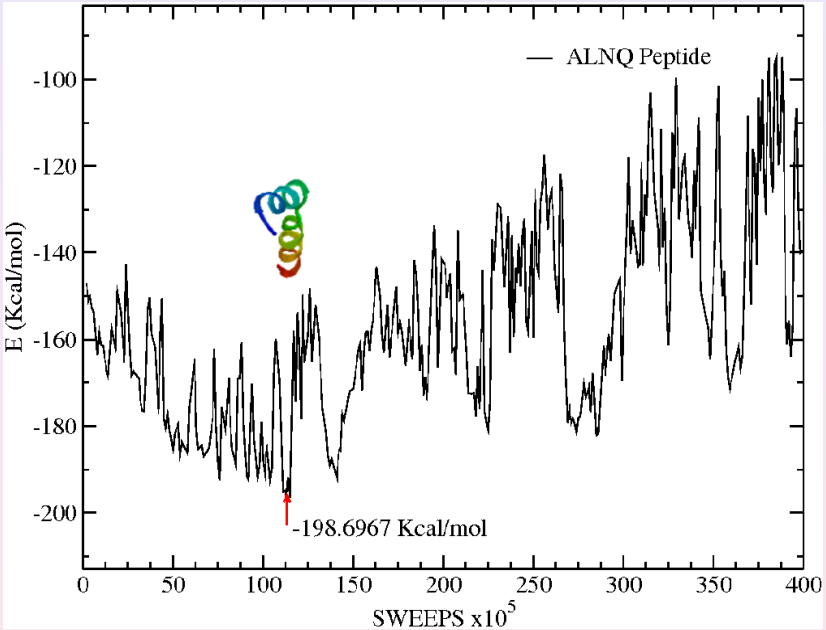

FIG. 11. Energy vs. MCS using the number of native contacts (Q) as a parameter in $f(Q, t)$.

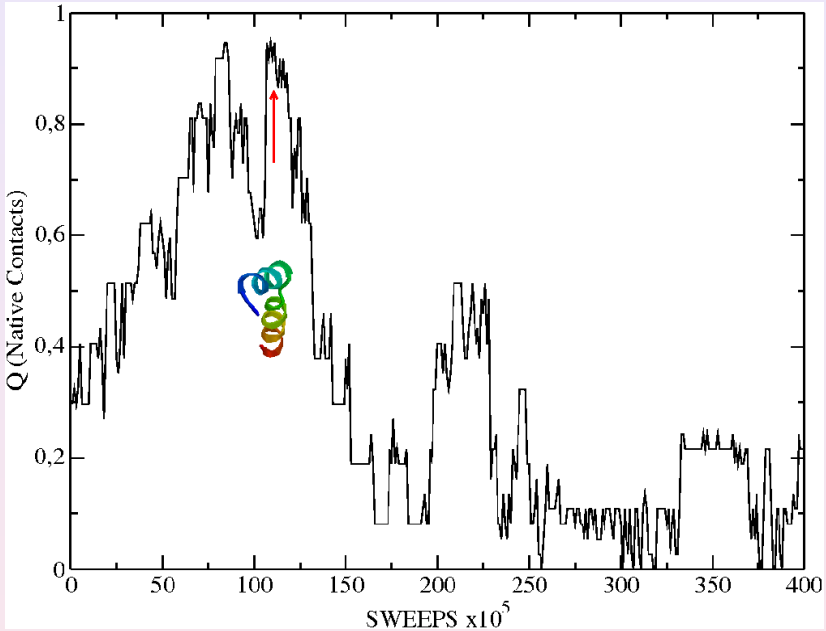

FIG. 12. Number of native contacts vs. MCS using the number of native contacts (Q) as a parameter in $f(Q, t)$.

Outline

Folding within a Chaperonin

Chaperonin

A Chaperonin is a protein with a cage form. The function of the Chaperonin is the regulation the folding process.

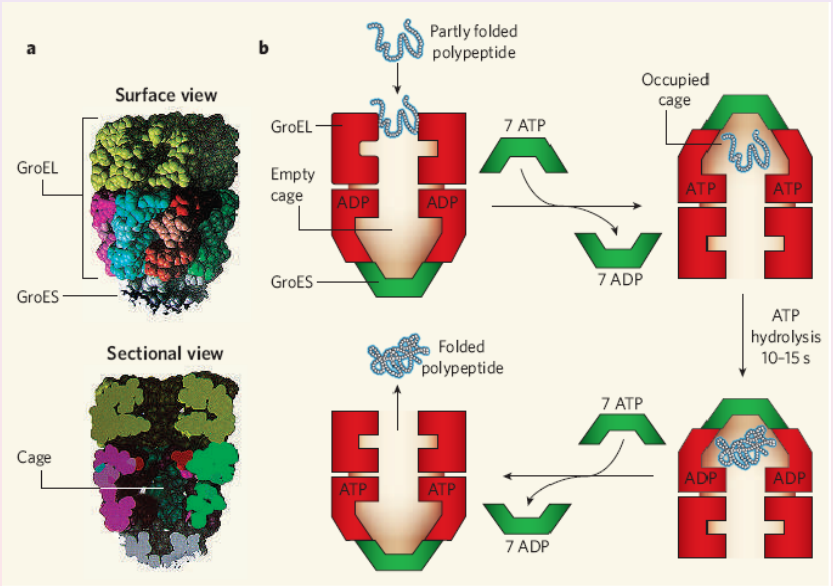

FIG. 13. Chaperonin structure.

Folding within a Chaperon

Simulation of the cage

We are taking a spherical potential with soft walls [a]

$$V_1 = \frac{0.01}{R_c}\left[e^{r-R_c}(r-1) - \frac{r^2}{2}\right]$$

[a] J. Chem. Phys. **118** 8042 (2003), Biophys. Jour. **90** 1767 (2006)

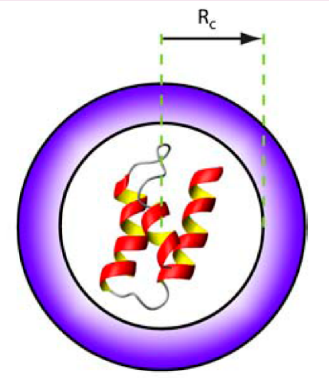

FIG. 14. Confinment potential.

1NJ0 Peptide 16 aminoacids

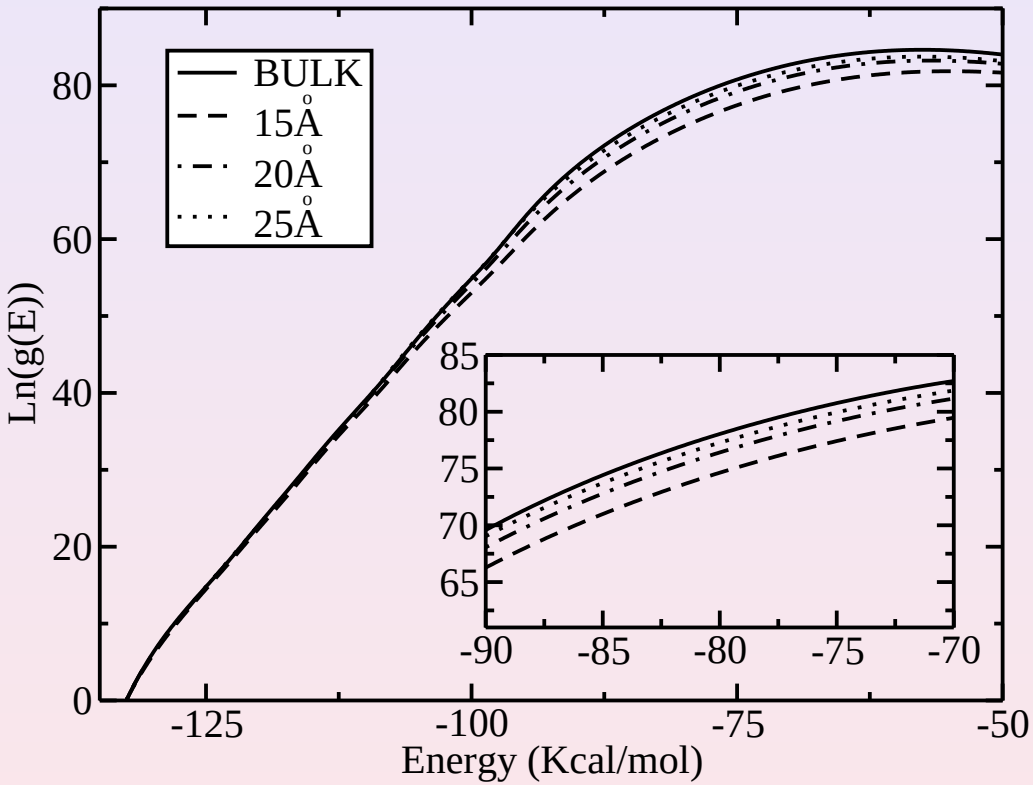

FIG. 15. Log of the DOS for different radii of the barrier.

1NJ0 Peptide 16 aminoacids

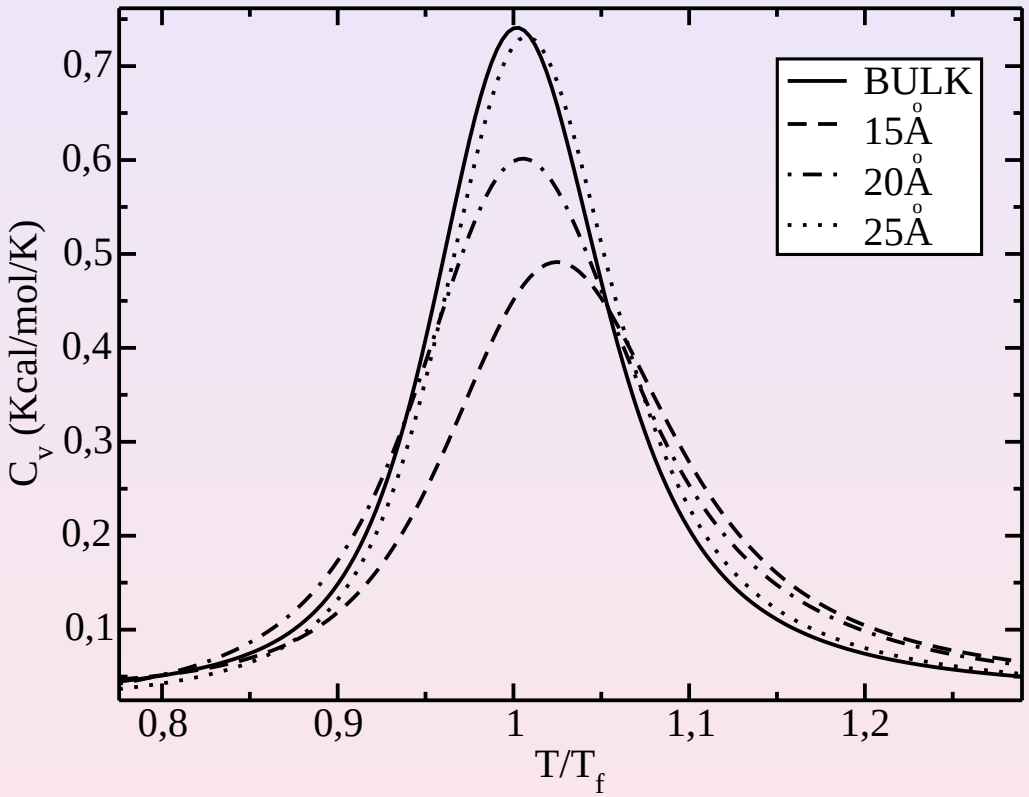

FIG. 16. Specific heat for different radii of the barrier.

Folding within a Chaperon

Simulation of the cage

We have considered also the hydrophobic effects of the chaperone surface by using the potential, [a]

$$\mathbf{V_2} = \mathbf{4}\epsilon_\mathbf{h}\frac{\pi \mathbf{R_c}}{\mathbf{r}}\left(\frac{\mathbf{1}}{\mathbf{5}}\left[\left(\frac{\sigma}{\mathbf{r}-\mathbf{R_c}}\right)^{\mathbf{10}}-\left(\frac{\sigma}{\mathbf{r}+\mathbf{R_c}}\right)^{\mathbf{10}}\right]\right.$$
$$\left.-\frac{\epsilon}{\mathbf{2}}\left[\left(\frac{\sigma}{\mathbf{r}-\mathbf{R_c}}\right)^{\mathbf{4}}-\left(\frac{\sigma}{\mathbf{r}+\mathbf{R_c}}\right)^{\mathbf{4}}\right]\right)$$

Rc is the radious of the cage, $\epsilon_\mathbf{h} = \mathbf{2.54Kcal/mol}$

[a] J. Chem. Phys. **118** 8042 (2003), Biophys. Jour. **90** 1767 (2006)

Potential barriers

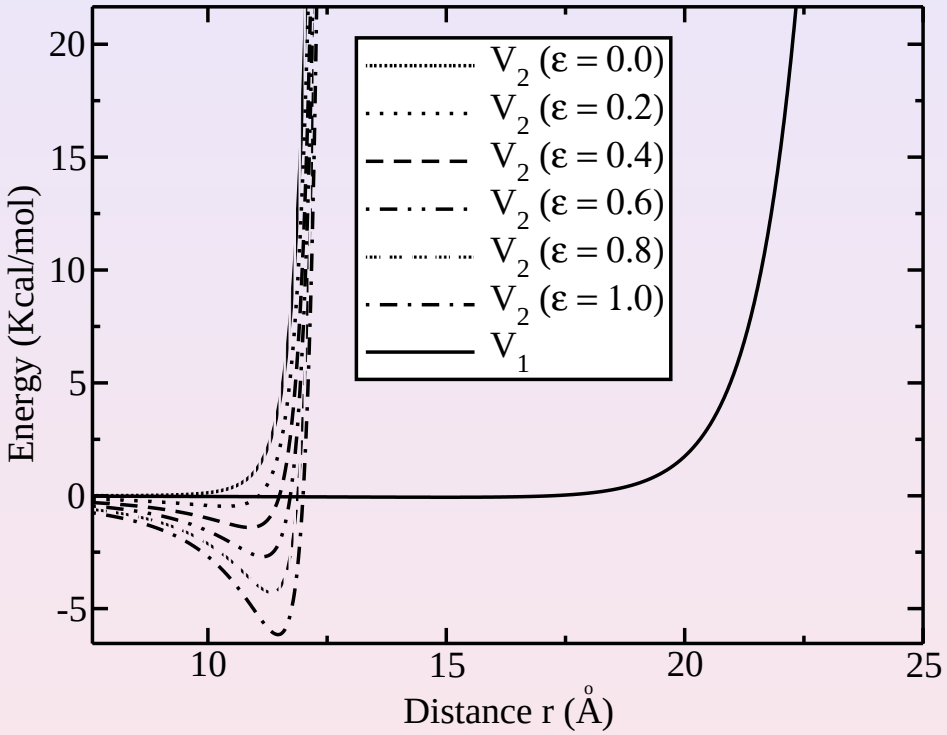

FIG. 17. Potentials used to study the confinment effects. $R_c = 15$ Å. V_1 simulates the confinment purely but V_2 takes into account also the hydrophobicity inside the chaperone.

1NJ0 Peptide 16 aminoacids

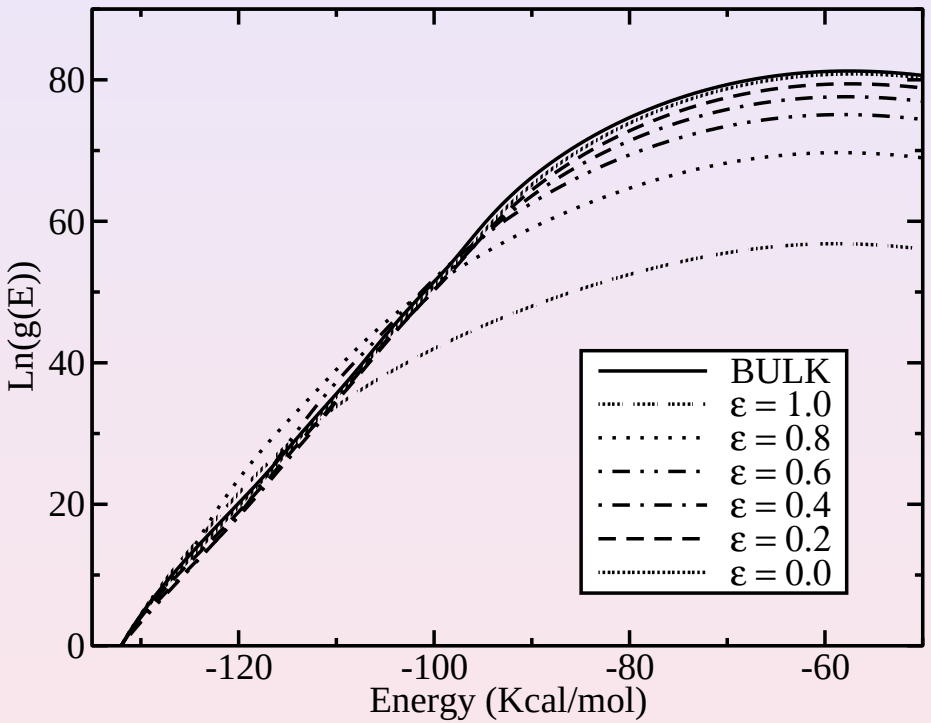

FIG. 18. Log of the DOS for different radii of the barrier.

1NJ0 Peptide 16 aminoacids

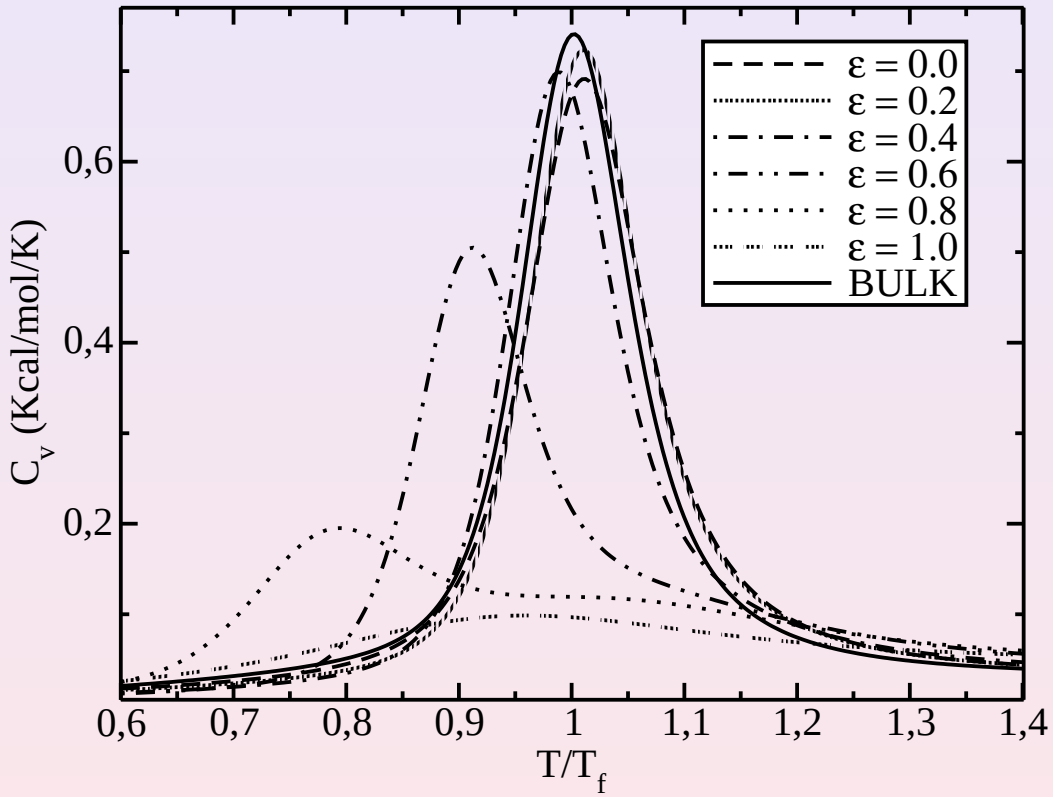

FIG. 19. Specific heat for different radii of the barrier.

Summary

- We can obtain the lest energy structures given a sequence using the potentials as in the Yow's model[a].
- To obtain the ground state structure we perform ELP simulations. The obtained structures are in good agreement with the models in the Protein Data Bank.
- We have found that the Chaperones have influence on the folding process. We have observed a reduction in the number of accesible states when a potential barrier is present.

[a] PRL **96** 078103 (2006)

THANKS FOR YOUR ATTENTION!