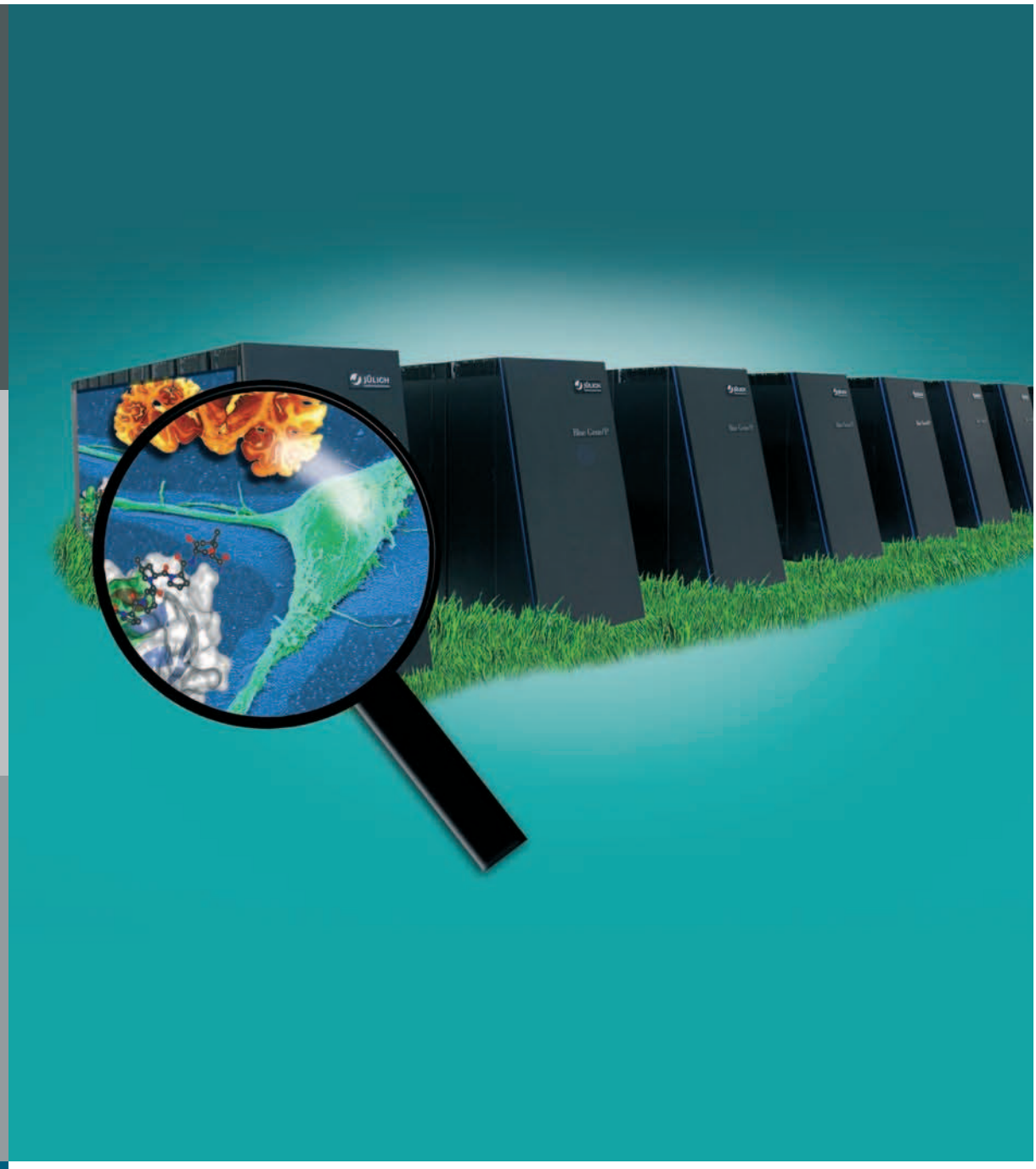

From Computational Biophysics to Systems Biology (CBSB11) – Celebrating Harold Scheraga's 90th Birthday

Proceedings, 20 – 22 July 2011 | Jülich, Germany

Paolo Carloni, Ulrich H.E. Hansmann, Thomas Lippert,
Jan H. Meinke, Sandipan Mohanty, Walter Nadler,
Olav Zimmermann (Editors)

JÜLICH
FORSCHUNGSZENTRUM

Member of the Helmholtz Association

Schriften des Forschungszentrums Jülich
IAS Series Volume 8

Forschungszentrum Jülich GmbH
Institute for Advanced Simulation (IAS)
Jülich Supercomputing Centre (JSC)

From Computational Biophysics to Systems Biology (CBSB11) – Celebrating Harold Scheraga's 90th Birthday

Proceedings, 20 – 22 July 2011 | Jülich, Germany

edited by Paolo Carloni, Ulrich H.E. Hansmann, Thomas Lippert, Jan H. Meinke, Sandipan Mohanty, Walter Nadler, Olav Zimmermann

Schriften des Forschungszentrums Jülich
IAS Series Volume 8

ISSN 1868-8489 ISBN 978-3-89336-748-1

Bibliographic information published by the Deutsche Nationalbibliothek.
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at http://dnb.d-nb.de.

Publisher and Distributor: Forschungszentrum Jülich GmbH
Zentralbibliothek
52425 Jülich
Phone +49 (0) 24 61 61-53 68 · Fax +49 (0) 24 61 61-61 03
e-mail: zb-publikation@fz-juelich.de
Internet: http://www.fz-juelich.de/zb

Cover Design: Grafische Medien, Forschungszentrum Jülich GmbH

Printer: Grafische Medien, Forschungszentrum Jülich GmbH

Schriften des Forschungszentrums Jülich
IAS Series Volume 8

ISSN 1868-8489
ISBN 978-3-89336-748-1

The complete volume is freely available on the Internet on the Jülicher Open Access Server (JUWEL) at http://www.fz-juelich.de/zb/juwel

Persistent Identifier: urn:nbn:de:0001-2011112819
Resolving URL: http://www.persistent-identifier.de/?link=610

Effects of Confinement on the Thermodynamics of a Model Protein

Mustafa Bilsel[1], **Buket Taşdizen**[1], **Handan Arkin**[1,2], **and Wolfhard Janke**[2]

[1] Department of Physics Engineering, Faculty of Engineering, Ankara University
Tandoğan, Ankara, Turkey
[2] Institut für Theoretische Physik, Universität Leipzig, Postfach 100 920, 04009 Leipzig, Germany
E-mail: Handan.Arkin@itp.uni-leipzig.de

We report the results of computer simulations of a model protein confined in a cage like a sphere to investigate the dynamics of the folding mechanism. The problem of whether proteins are misfolded or aggregated or on the contrary are folded properly more promptly in these confining media is of great interest in our study. Therefore our aim is to analyze the thermodynamics of the folding mechanism and also to investigate whether the folding mechanism is controlled or not in the confining media. To do so we have employed exhaustive multicanonical Monte Carlo simulations by using a minimalistic AB model approach. A detailed understanding of this subject plays a key role for finding treatments to diseases caused by misfolding of proteins.

1 Introduction

Protein folding is one of the most intensively studied and still unsolved problems in biology. The process by which a protein folds into its biologically active state cannot be traced in all details solely by experiments. Therefore, many theoretical and experimental studies focus on determination of the three-dimensional structure of these molecules. Recently, molecular modelling has attracted considerable attention for applications in designing and fabrication of nanostructures leading to the development of advanced materials. In a newly growing field of research, synthetic peptides are investigated for their use in nano-devices, by exploiting their self-assembly properties[1,2]. The self-assembly of biomolecular building blocks plays an increasingly important role in the discovery of new materials, with a wide range of applications in nanotechnology and medical technologies such as drug delivery systems[3]. In these studies, several types of biomaterials are developed, ranging from models for studying protein folding to molecular materials for producing peptide nanofibers, peptide surfactants by designing various classes of self-assembling peptides[4]. These experiments reveal many different interesting and important problems, which are related to general aspects of the question why and how proteins fold. In this context, modern simulation techniques have opened another window to give a new insight to the protein folding problem[5].

In this study, we focus on the folding of the model protein $BA_6BA_4BA_2BA_2B_2$ under the influence of a confining potential which simulates a cage being composed of rigid walls.

2 Model

The polymer chains are described by a coarse-grained hydrophobic-polar model which also helped to understand protein folding channels from a mesoscopic perspective[6]. A manifest

off-lattice variant of the HP model[7] is the AB model[8], where the hydrophobic monomers are labeled by A and the polar or hydrophilic ones by B. As on the lattice, the adjacent monomers are connected by rigid covalent bonds. Thus, the distance is fixed and set to unity. The contact interaction is replaced by a distance-dependent Lennard-Jones type of potential accounting for short-range excluded volume repulsion and long-range interaction. An additional interaction accounts for the bending energy of any pair of successive bonds. This model was first applied in two dimensions[8] and generalized to three-dimensional AB proteins[9], partially with modifications taking implicitly into account additional torsional energy contributions of each bond.

The AB model as proposed in Ref. 9 has an energy function

$$E = -\kappa_1 \sum_{k=1}^{N-2} b_k.b_{k+1} - \kappa_2 \sum_{k=1}^{N-3} b_k.b_{k+2} + 4 \sum_{i=1}^{N-2} \sum_{j=i+1}^{N} C(\sigma_i, \sigma_j) \left(\frac{1}{r_{ij}^{12}} - \frac{1}{r_{ij}^{6}} \right) \quad (1)$$

where b_k is the bond vector between the monomers k and $k+1$ with length unity. The second term in Eq. (1) takes torsional interactions into account without being an energy associated with the pure torsional barriers in the usual sense. The third term contains now a pure Lennard-Jones potential, where the $1/r_{ij}^6$ long-range interaction is attractive whatever types of monomers interact. The monomer-specific prefactor $C(\sigma_i, \sigma_j)$ only controls the depth of the Lennard-Jones valley:

$$C(\sigma_i, \sigma_j) = \begin{cases} +1, & \sigma_i, \sigma_j = A, \\ +1/2, & \sigma_i, \sigma_j = B \quad \text{or} \quad \sigma_i \neq \sigma_j. \end{cases} \quad (2)$$

Simulations of this model were performed with the multicanonical algorithm[10] and the update mechanism is a spherical update which is described in Ref. 11 in detail.

3 Confining Potentials

The focus of this study is to comprehend the folding mechanism of proteins in their cellular environments. To emulate this effect, the following potentials are used:

$$V_1(r) = \frac{0.01}{R_c} \left[e^{r-R_c}(r-1) - \frac{r^2}{2} \right], \quad (3)$$

$$V_2(r) = 4\epsilon_c \frac{\pi R_c}{r} \left(\frac{1}{5} \left[\left(\frac{\sigma}{r-R_c} \right)^{10} - \left(\frac{\sigma}{r+R_c} \right)^{10} \right] \right), \quad (4)$$

$$V_3(r) = 4\epsilon_c \frac{\pi R_c}{r} \left(\frac{1}{5} \left[\left(\frac{\sigma}{r-R_c} \right)^{10} - \left(\frac{\sigma}{r+R_c} \right)^{10} \right] - \frac{\epsilon}{2} \left[\left(\frac{\sigma}{r-R_c} \right)^{4} - \left(\frac{\sigma}{r+R_c} \right)^{4} \right] \right) \quad (5)$$

where R_c is the sphere radius which is a measure of the cage size, $r = (x^2 + y^2 + z^2)^{1/2}$ is the distance of a monomer to the origin and x, y, z are the coordinates of monomers, $\sigma = 1.0$ and $\epsilon_c = \epsilon = 1.0$. For our simulations, we set R_c large enough to enclose the protein inside the sphere.

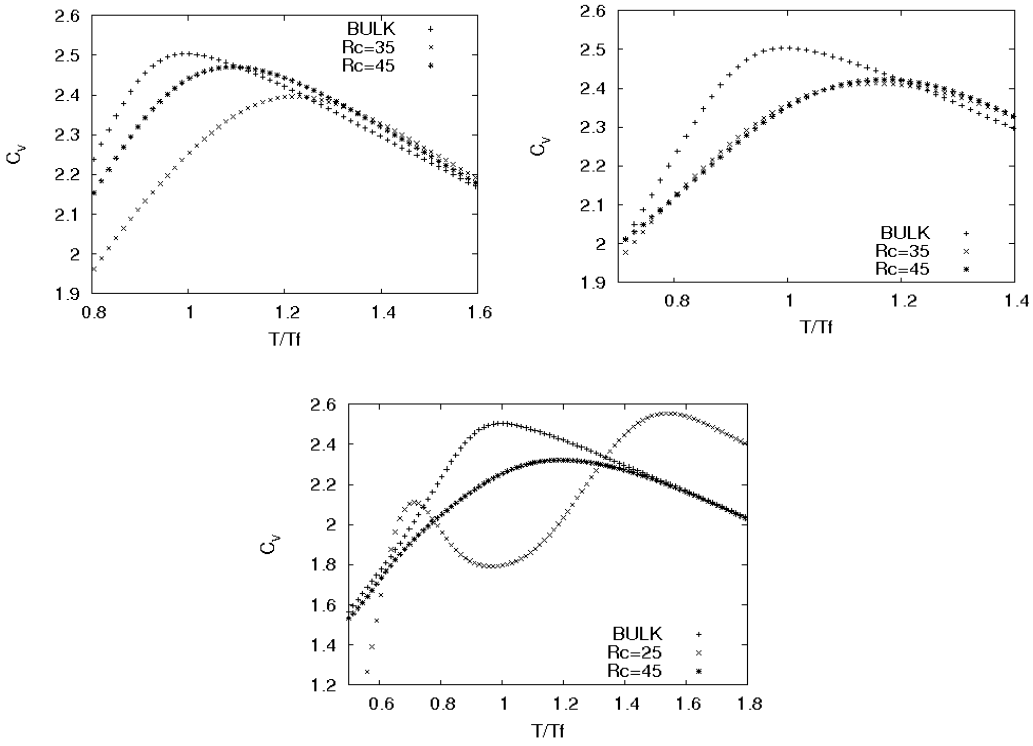

Figure 1. Specific-heat plots under the influence of potential a) V_1, b) V_2, and c) V_3.

4 Results and Discussion

The effect of confinement on the thermodynamic properties of the model protein was investigated by multicanonical simulations. We have chosen appropriate radii such that proteins are not allowed to move outside the sphere. The results are compared to a bulk protein which folds at $T = T_f$. After calculating multicanonical weights, 5×10^7 iterations were performed in the production run. We computed the transition temperature for the bulk protein and protein in cages with different radii. The results are plotted in Fig. 1. When the radius increases the effect of the confining potential decreases so that $R_c = 100$ behaves like a bulk environment.

The specific heats of potential V_1, V_2 and V_3 as a function of temperature are plotted in Fig. 1a), b) and c), respectively. Generically, increase in the radius of the sphere causes a decrease of the transition temperature. On the other hand, the situation for V_3 is different. The V_3 potential contains an attractive part so the model protein feels the effect of attractiveness of the potential at small radius ($R_c = 25$), and is adsorbed by the surface of the sphere in a first stage and in a second stage it arranges its structure. By increasing the radius up to $R_c = 45$ the influence of the potential starts to decrease and so adsorption disappears.

As a result, for all cases specific-heat plots were broadened when the radius of the sphere decreases. Narrower graph means states close to native ones appear more often than in the bulk situation. We can conclude that the protein becomes more stable when the radius of the sphere decreases. These results are compatible with the previous ones[12–14].

Acknowledgments

H.A. acknowledges support by the Alexander von Humboldt Foundation under a Fellowship for Experienced Researchers. M.B. acknowledges support by The Scientific and Technological Research Council of Turkey under the project number 109T730 and W.J. thanks the DFG for support under Grant No. JA483/24-3.

References

1. S. Santosa, W. Hwang, H. Hartman, and S. Zhang, *Self-asembly of surfactant-like peptides with variable glycine tails to form nanotubes and nanovesicles*, Nano Lett. **2**, 687–691, 2002.
2. S. Vauthey, S. Santosa, H. Gong, N. Watson, and S. Zhang, *Molecular self-assembly of surfactant-like peptides to form nanotubes and nanovesicles*, Proc. Nat. Acad. Sci. USA **99**, 5355–5360, 2002.
3. J. A. Hubbell, *Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering*, Curr. Opin. Biotechnol. **10**, 123–128, 1999.
4. T. Holmes, S. De Lacalle, X. Su, A. Rich, and S. Zhang, *Extensive neurite outgrowth and active synapse formation on self-assembling peptide scaffolds*, Proc. Natl. Acad. Sci. USA **97**, 6728–6733, 2000.
5. H. Arkin, *Searching low energy conformations of two elastin sequences*, Eur. Phys. J. B. **37**, 223–228, 2004.
6. S. Schnabel, M. Bachmann, and W. Janke, *Two-state folding, folding through intermediates, and metastability in a minimalistic hydrophobic-polar model for proteins*, Phys. Rev. Lett **98**, 048103-1–4, 2007. *Identification of characteristic protein folding channels in a coarse-grained hydrophobic-polar peptide model*, J. Chem. Phys. **126**, 105102-1–6, 2007.
7. K. A. Dill, *Theory for the folding and stability of globular proteins*, Biochemistry **25**, 1501–1509, 1985.
8. F. H. Stillinger and T. Head-Gordon, *Collective aspects of protein folding illustrated by a toy model*, Phys. Rev. E **52**, 2872–2877, 1995.
9. A. Irbäck, C. Peterson, F. Potthast, and O. Sommelius, *Monte Carlo procedure for protein design*, Phys. Rev. E **58**, R5249–R5252, 1998.
10. B. A. Berg and T. Neuhaus, *Multicanonical ensemble: A new approach to simulate first-order phase transitions*, Phys. Rev. Lett. **68**, 9–12, 1992.
11. M. Bachmann, H. Arkin, and W. Janke, *Multicanonical study of coarse-grained off-lattice models for folding heteropolymers*, Phys. Rev. E **71**, 031906-1–11, 2005.
12. F. Takagi, N. Koga, and S. Takada, *How protein thermodynamics and folding mechanisms are altered by the chaperonin cage: molecular simulations*, Proc. Natl. Acad. Sci. USA **100**, 11367–11372, 2003.
13. N. Rathore, T. A. Knotts, and J. J. de Pablo, *Confinement effects on the thermodynamics of protein folding: Monte Carlo simulations*, Biophys. J. **90**, 1767–1773, 2006.
14. D. Lu, Z. Liu, and J. Wu, *Structural transitions of confined model proteins: molecular dynamics simulation and experimental validation*, Biophys. J. **90**, 3224–3238, 2006.