



## Aggregation of the Amyloid- $\beta$ Protein: Monte Carlo Optimization Study

S. M. Gopal, K. V. Klenin, W. Wenzel

published in

*From Computational Biophysics to Systems Biology (CBSB07),  
Proceedings of the NIC Workshop 2007,*  
Ulrich H. E. Hansmann, Jan Meinke, Sandipan Mohanty,  
Olav Zimmermann (Editors),  
John von Neumann Institute for Computing, Jülich,  
NIC Series, Vol. 36, ISBN 978-3-9810843-2-0, pp. 177-180, 2007.

© 2007 by John von Neumann Institute for Computing

Permission to make digital or hard copies of portions of this work for personal or classroom use is granted provided that the copies are not made or distributed for profit or commercial advantage and that copies bear this notice and the full citation on the first page. To copy otherwise requires prior specific permission by the publisher mentioned above.

<http://www.fz-juelich.de/nic-series/volume36>

# Aggregation of the Amyloid- $\beta$ Protein: Monte Carlo Optimization Study

Srinivasa M. Gopal, Konstantin V. Klenin, and Wolfgang Wenzel

Institut für Nanotechnologie,  
Forschungszentrum Karlsruhe, 76021 Karlsruhe, Germany  
*E-mail:* {gopal, klenin, wenzel}@int.fzk.de

The free-energy approach has delivered promising results for protein folding and structure prediction in recent years. The native state is found as the global minimum of an all-atom free-energy forcefield. Now, we used this approach to simulate the aggregation of A $\beta$  fragment 16-22. This aggregation is believed to be associated with the Alzheimer's disease. The model system contained 2 polypeptide chains. The obtained structures of the aggregates consisted of either parallel or anti-parallel  $\beta$ -sheets, the latter were preferable.

## 1 Introduction

The Alzheimer's disease is associated with misfolding of the amyloid protein. In the functional native form, this small protein, of 42 amino acids, has globular structure with two  $\alpha$ -helices. However, under certain conditions, it can form aggregates of  $\beta$ -sheets that, on a larger scale, are arranged as long insoluble fibrils<sup>3</sup>. The resulting fibrils have toxic effects in the extracellular space of the brain of patients with the Alzheimer's disease. The amyloid protein in this form is known as A $\beta$  peptide.

This protein has been extensively studied by both experimental and computational methods<sup>8,7</sup>. The experimental techniques such as solid-state NMR, X-diffraction and electron microscopy were used for characterizing the structure of aggregates<sup>8</sup>. Most of the computational studies were focused on short polypeptide fragments of this protein, such as *LYS*<sub>16</sub> – *LEU* – *VAL* – *PHE* – *PHE* – *ALA* – *GLU*<sub>22</sub><sup>4</sup>. This fragment is believed to play a key role in the formation of the aggregates. In the present work, we study the systems of one and two chains of A $\beta$ <sub>16–22</sub> peptide<sup>2</sup>.

## 2 Methods and Results

The free-energy approach has delivered promising results for protein folding and structure prediction in recent years. Following Anfinsen's hypothesis<sup>1</sup> the native state is postulated to be the global minimum of a all-atom free-energy function. This minimum can be found by optimization methods<sup>9</sup> including the Monte Carlo procedure. This approach was successfully used to fold  $\alpha$ -,  $\beta$ - and mixed proteins of moderate length<sup>10,12,5</sup>.

This approach requires an accurate, transferable protein free-energy forcefield. In this study we used Protein Force Field (PFF02)<sup>6,11</sup>. In our model, all the atoms are explicitly represented (the apolar group  $CH_n$  is considered as a single atom). The bond angles and the bond lengths are fixed. The degrees of freedom considered are the backbone ( $\psi, \phi$ ) and the sidechain ( $\chi_i$ ) dihedral angles.

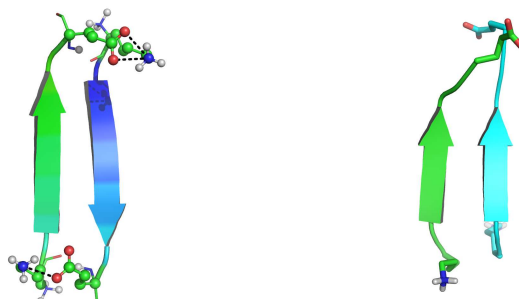


Figure 1. **Left:** The lowest energy structure is an anti-parallel  $\beta$ -sheet. The polar contacts between side-chain atoms N of *LYS*<sub>16</sub> and O of *GLU*<sub>22</sub> are shown explicitly. **Right:** The energy of the best parallel  $\beta$ -sheet structure is higher by 10 kcal/mol.

The energy function contains the following terms: (1) the standard Lennard-Jones potential, (2) the Coulomb energy of electrostatic interaction with group specific dielectric constants, (3) a term for the hydrogen bonding, (4) a SASA-based solvation term that implicitly takes into account the influence of the solvent. We used several optimization methods used to find the global minimum of the energy function: (1) basin hopping technique (BHT), (2) parallel tempering, and (3) evolutionary strategies<sup>9</sup>.

Recently, our protein simulation package, POEM, has been modified to treat multiple polypeptide chains. In the present study, we simulated the systems of one and two chains of  $A\beta_{16-22}$  using a modified version of BHT<sup>12</sup>. In the simulations of a single chain, no specific unique structure was formed, in agreement with the earlier studies<sup>4</sup>. In contrast, the system of two chains formed an anti-parallel  $\beta$ -sheet in most of the cases. The lowest energy structure is shown in Fig. 1. The main reason for the antiparallel orientation has been much debated in the literature, the two options being the salt bridges<sup>7</sup> and the efficient sidechain packing<sup>4</sup>.

Analysis of the simulations shows the overwhelming preference for the anti-parallel orientation. The free energy surface of the two-chain system is presented in Fig. 2. The lowest energy structures are the anti-parallel  $\beta$ -sheets. However, in the simulations the parallel orientation was also observed. The parallel  $\beta$ -structure with the lowest energy is shown in Fig. 1. The anti-parallel orientation is stabilized by the efficient sidechain packing as well as by the polar interactions between the sidechains of *LYS*<sub>16</sub> and *GLU*<sub>22</sub>.

## Acknowledgments

We thank the BMBF, the Deutsche Forschungsgemeinschaft (grants WE 1863/10-2, WE 1863/14-1) and the Kurt Eberhard Bode Stiftung for financial support. We are grateful to S. Gregurick and J. Moulton for parts of code that was used in our simulations. We are thankful to the Barcelona Supercomputer Center for computational resources.

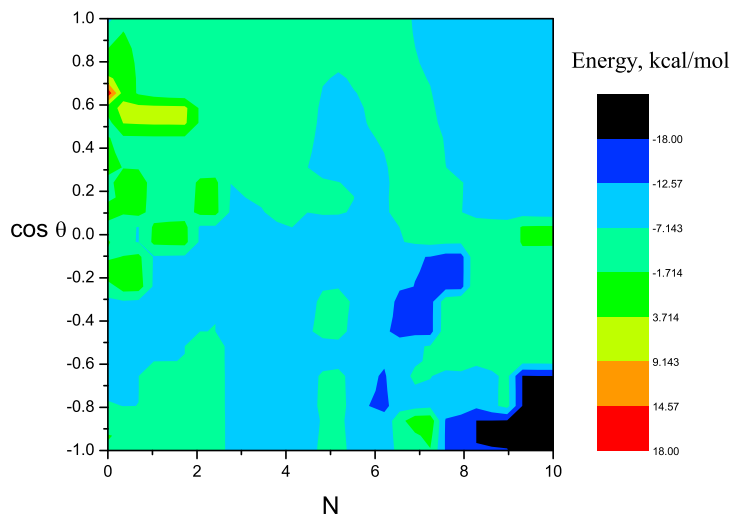


Figure 2. The free energy surface of the two-chain system. The co-ordinates are the number  $N$  of the residues in the  $\beta$ -conformation and the cosine of the angle  $\theta$  between the two end-to-end vectors.

## References

1. C. B. Anfinsen, *Principles that govern the Folding of Protein Chains*, Science **181**, 223, 1973.
2. J. J. Balbach and Y. Ishii and O. N. Antzutkin and R. D. Leapman and N. W. Rizzo and F. Dyda and J. Reed and R. Tycko, *Amyloid fibril formation by A beta 16-22, a seven-residue fragment of the Alzheimer's beta-amyloid peptide, and structural characterization by solid state NMR*, Biochemistry **39**, 13748, 2000.
3. C. M. Dobson, *The structural basis of protein folding and its links with human disease*, Phil. Trans. R. Soc. Lond. B **356**, 133, 2001.
4. G. Favrin and A. Irbäck and S. Mohanty, *Oligomerization of amyloid A $\beta_{16-22}$  peptides using hydrogen bonds and hydrophobicity forces*, Biophysical Journal **87**, 3657, 2004.
5. S. M. Gopal and W. Wenzel, *De Novo Folding of the DNA-Binding ATF-2 Zinc Finger Motif in an All-Atom Free-Energy Forcefield*, Angew. Chemie Int. **45**, 7726, 2006.
6. T. Herges and W. Wenzel, *An All-Atom Force Field for Tertiary Structure Prediction of Helical Proteins*, Biophysical Journal **87**, 3100, 2004.
7. D. K. Klimov and D. Thirumalai, *Dissecting the assemble of A $\beta_{16-22}$  amyloid peptides into antiparallel  $\beta$  sheets*, Structure **11**, 295, 2003.
8. T. Lührs and C. Ritter and M. Adrian and D. Riek-Loher and B. Bohrmann and H. Döbeli and D. Schubert and R. Riek, *3D structure of Alzheimer's amyloid-beta(1-42) fibrils*, Proc. Nat. Acad. Sci. **102**, 17342, 2005.
9. A. Schug, A. Verma, W. Wenzel, and G. Schoen, *Biomolecular structure prediction*

- with stochastic optimization methods*, Adv. Eng. Materials **7**, 1005, 2005.
10. A. Verma and S. Murthy and K. H. Lee and E. Starikov and W. Wenzel, *De novo all atom folding of helical proteins*, NIC Series **34**, 45, 2006.
  11. A. Verma and W. Wenzel, *Towards a universal Free Energy Forcefield for All atom Protein Folding*, (Submitted) 2007.
  12. W. Wenzel, *Predictive folding of a  $\beta$  hairpin in an all-atom free-energy model*, Europhys. Letters **76**, 156, 2006.