John von Neumann Institute for Computing

Inhibition of Fibril Formation of Beta-Amyloid Peptides

N. S. Lam, M. Kouza, H. Zung, M. S. Li

published in

From Computational Biophysics to Systems Biology (CBSB08),
Proceedings of the NIC Workshop 2008,
Ulrich H. E. Hansmann, Jan H. Meinke, Sandipan Mohanty,
Walter Nadler, Olav Zimmermann (Editors),
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. **40**, ISBN 978-3-9810843-6-8, pp. 121-124, 2008.

http://www.fz-juelich.de/nic-series/volume40

Inhibition of Fibril Formation of Beta-Amyloid Peptides

Nguyen Sy Lam[1], Maksim Kouza[2], Hoang Zung[1], and Mai Suan Li[2]

[1] Computational Physics Lab, Vietnam National University,
Ho Chi Minh city, 227 Nguyen Van Cu, Dist. 5, Vietnam

[2] Institute of Physics, Polish Academy of Sciences,
Al. Lotnikow 32/46, 02-668 Warsaw, Poland
E-mail: masli@ifpan.edu.pl

Alzheimer's, Parkinson's, Huntington's, type II diabetes, and Mad Cow disease, or Cystic fibrosis, these apparently unrelated diseases, the so-called protein structural diseases, are found to be a result of protein misfolding. Understanding the role of molecular inhibitors in formation of amyloid fibrils plays an important role in finding proper treatments to those structural diseases. In the case of Alzheimer's disease, experiments showed that the fibrillation of full-length $A\beta$ peptides is disrupted by the peptide fragment $A\beta_{16-20}$ (KLVFF). In this contribution, we studied the kinetics of oligomerization of the system of two $A\beta_{16-22}$ and one $A\beta_{16-20}$ peptides, using all-atom simulations with the GROMOS96 force field 43a1 in explicit water. In agreement with experiments, $A\beta_{16-20}$ peptide was found to slow down the aggregation process.

1 Introduction

In many cases protein aggregates take the form of amyloid fibrils, which appear as unbranched rod-like nanostructures with the diameter of an order of 10 nm and varying length[1]. A large body of evidence suggests that amyloid fibrils and associated oligomeric intermediates are related to a number of diseases, including Alzheimer's, Parkinson's, Huntington's, and prion diseases[1]. For example, in the case of the Alzheimer's disease the memory decline may result from the accumulation of the amyloid β-proteins (Aβ) present in two forms - 40 (Aβ_{1-40}) and 42 (Aβ_{1-42}) amino acids of which are produced through endoproteolysis of the β-amyloid precursor transmembrane protein. Since structural diseases affect a significant portion of senior population, it is vital to develop therapeutic approaches to combat the amyloid assembly. One of possible ways is to design molecular inhibitors, which interfere with this process. For example, the peptide fragment Aβ_{16-20} KLVFF[2] and the peptide LPFFD derived from Aβ_{17-21} fragment by V18P and A21D mutations[3] can disrupt fibrillation of full-length Aβ peptide. An insertion of prolines also inhibits amyloid formation. An another powerful strategy for inhibition is a peptide N-methylation. It was demonstrated that themembrane-permeable NN-methylated pentapeptide A$\beta 16-20$m is an effective fibrillogenesis inhibitor, capable of both preventing fibril growth and disassembling existing fibrils[4]

In this contribution, we study the influence of a pentapeptide Aβ_{16-20} on the kinetics of oligomerization of longer Aβ_{16-22} peptides, using all-atom simulations with the GROMOS96 force field 43a1 in explicit water[5]. Since the fibril formation time t_{fibril} of a system of two Aβ_{16-22} and one Aβ_{16-20} peptide is much longer than that for three Aβ_{16-22} peptides, one can expect that, in agreement with experiments[2], Aβ_{16-20} fragment slows down the fibril growth process.

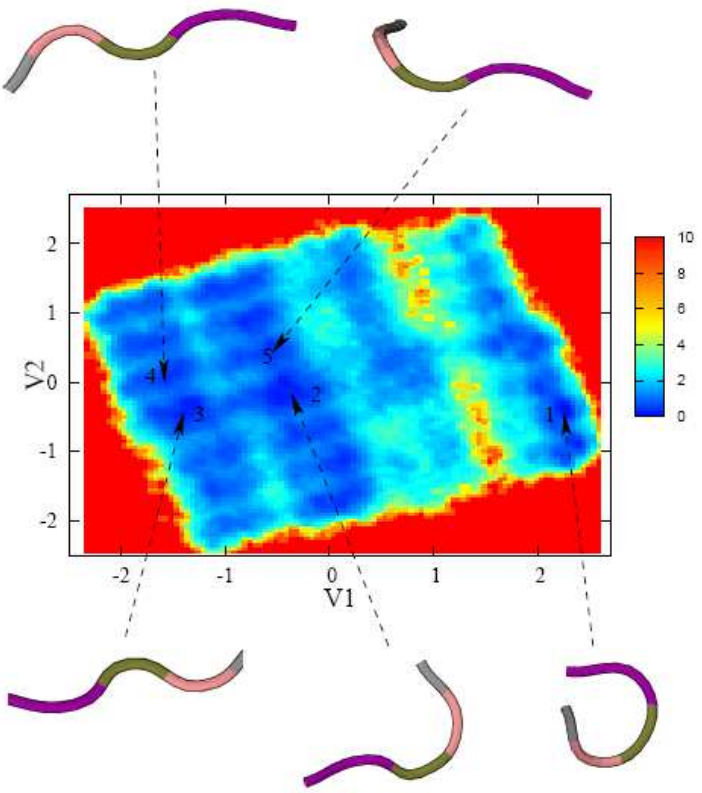

Figure 1. The free energy landscape as a function of V_1 and V_2. Typical conformations of some local minima are shown.

2 Method and Results

The structures of monomeric Aβ_{16-20} and Aβ_{16-22} were extracted from the structure of Aβ_{10-35} peptide available in the Protein Data Bank (ID: 1hz3). In order to study conformation changes of a monomer Aβ_{16-20}, one trajectory of 150 ns was generated. The initial configuration of the system of two Aβ_{16-22} and one Aβ_{16-20} was created by randomly placing these peptides in a periodic box of volume 78 nm^3 which corresponds to the peptide concentration of 64 mM. For this system, four runs of 300, 343, 453, and 484 ns were carried out. All simulations were performed at $T = 300$ K.

We used the dihedral principal component analysis[6] to compute the free energy landscapes (FEL), using the first two eigenvectors V_1 and V_2. In order to monitor the fibril formation process, we use the "liquid crystal" order parameter P_2. If $P \geq 0.9$ then the system is considered to be in the fibril-like state[6].

Fig. 1 shows the free energy of a monomer Aβ_{16-20} as a function of V_1 and V_2. The existence of many shallow local minima separated by low barriers (of only a few k_BT)

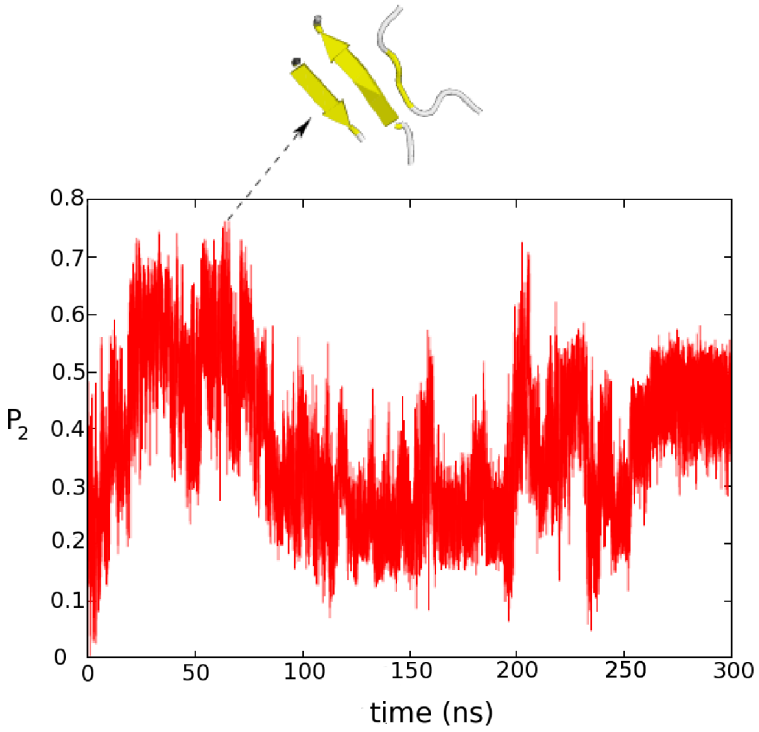

Figure 2. Time dependence of P_2 for the (2Aβ_{16-22}+Aβ_{16-20}) system. Shown is the structure at the largest $P_2 \approx 0.75$. Interestingly, one Aβ_{16-22} and one Aβ_{16-20} adopt anti-parallel arrangement.

suggests that the system is not stable under thermal fluctuations. As evident from typical snapshots (Fig. 1), the monomer adopts mainly coil conformations. Comparing with the free energy landscape of Aβ_{16-22}[6], one can see that the pentapeptide Aβ_{16-20} is less stable than Aβ_{16-22}. This may be a reason why Aβ_{16-20} can serve as an inhibitor for oligomerization of Aβ_{16-22} peptides, because in some situations proteins which have a more ordered structure in the monomeric state, are expected to be more prone to aggregation.

The time dependence of the order parameter P_2 for the (2Aβ_{16-22}+Aβ_{16-20}) system is shown in Fig. 2. Since the largest value $P_2 \approx 0.76$, found at $t \approx 64$ ns, is lower than 0.9, a fibril-like state does not occur in this run. This state was also not observed for three other trajectories (results not shown). Therefore, for the (2Aβ_{16-22}+Aβ_{16-20}) system, $t_{fibril} > 400$ ns, which is larger than $t_{fibril} \approx 200$ ns for a system of three Aβ_{16-22} peptides[6]. This result suggests that, in agreement with the experiment[2], Aβ_{16-20} can interfere with the oligomerization process. There are two possible reasons for this:
(a) Aβ_{16-20} does not contain the negatively charged glutamic acid (E) as Aβ_{16-22} does.
(b) The replacement of Aβ_{16-22} by KLVFF reduces hydrophobicity of the whole system.

In conclusion, we have shown that a short peptide KLVFF can inhibit the oligomerization of a system of Aβ_{16-22} peptides. It is expected to prevent the fibril growth of full-length $A\beta$ peptides, due to charge imbalance.

Acknowledgments

This work was supported by the Ministry of Science and Informatics in Poland (grant No 202-204-234).

References

1. F. Chiti, and C. M. Dobson, *Protein misfolding, functional amyloid, and human disease*, Annual Rev. Biochemistry **75**, 333–366, 2006.
2. L. O. Tjernberg *et al.*, *Arrest of β-amyloid fibril formation by a pentapeptide ligand*, J. Biol. Chem. **271**, 8545-8548, 1996.
3. C. M. Soto, S. Kindy, M. Baumann, and B. Frangione, *Inhibition of Alzheimer's amyloidosis by peptides that prevent β-sheet conformation*,Biochem. Biophys. Res. Commun. **226**, 672-680, 1996.
4. D. J. Gordon, R. Tape, and S. C. Meredith, *Design and characterization of a membrane permeable N-methyl amico acid-containing peptide that inhibit Aβ_{1-40} fibrilogenesis*, J. Pep. Res. **60**, 37-55, 2003.
5. H. J. C. Berendsen, D. van der Spoel and R. van Drunen, *A message-passing parallel molecular dynamics implementation*, Comp. Phys. Comm. **91**, 43–56, 1995.
6. P. H. Nguyen, M. S. Li, G. Stock, J. E. Straub, and D. Thirumalai, *Monomer adds to preformed structured oligomers of Aβ-peptides by a two-stage dock-lock mechanism*, Proc. Natl. Acad. Sci. USA **104**, 111–116, 2007.