Stability of full-length amyloid-β (1–42) dimer in solvating water: Replica exchange molecular dynamics and *ab initio* molecular orbital calculations

Akisumi Okamoto [1], Atsushi Yano [1], Kazuya Nomura [1], Shin'ichi Higai [2] and Noriyuki Kurita [1,*]

[1] *Department of Computer Science and Engineering, Toyohashi University of Technology*

[2] *Murata Manufacturing Co., Ltd.*

1. Introduction

The amyloid-β (Aβ) peptide plays a key role in pathogenesis of Alzheimer's disease. Since the aggregation of Aβs is involved in the pathogenesis, the conformations of Aβ aggregates have been investigated by many experimental and computational studies. Previously, it has been found experimentally that Aβs form stable dimers in solvating water [1]. However, it is extremely difficult to determine conformations of these Aβ aggregates in early stage through only experiments, due to their very fast aggregation [2]. In this aspect, molecular dynamics (MD) calculations have been expected to be very powerful technique to clarify the secondary structures of Aβs. We performed replica exchange MD (REMD) calculations to obtain various conformations of full-length Aβ(1–42) dimer in water and determined the most stable conformation of the solvated Aβ dimer by *ab initio* fragment molecular orbital (FMO) calculations. Further, we investigated the specific interactions between Aβ monomers, in order to elucidate which residues of Aβ are important in the dimerization of Aβs.

2. Details of molecular simulations

We first performed REMD calculations on Aβ dimer in explicit water molecules to search for stable conformations, starting from the β-sheet conformation created based on the NMR structure. We created 52 replicas, whose temperatures are exponentially spanned in the range of 270.0–363.8 K. REMD calculations were done for 50 ns per replica. The representative conformations sampled from the trajectories of the thirteen replicas in the range 289.6–310.7 K were optimized in water by the molecular mechanics (MM) method. In the REMD and MM calculations, we used the FF99SB force field in combinations with the TIP4P-Ew water model. Finally, the total energies for the optimized conformations of solvated Aβ dimer were evaluated by the *ab initio* MP2/6-31G method in FMO, and the most stable conformation was determined. From the FMO results, the specific interactions between Aβ monomers were examined.

3. Results and discussion

We made clear the most stable conformation of the solvated Aβ dimer by the *ab initio* FMO method, which is shown in Figure 1. In this conformation, the Lys16–Phe19 regions of two monomers (M1 and M2) form an intermolecular parallel β-sheet structure. Moreover, the Ile32–Met35 region of M1 forms a zipper-like β-sheet structure through hydrogen bonds with the Ile31–Met35 segment of M2. The Glu22–Asn27 region of M2 also forms a β-hairpin structure. We explain the specific interactions between Aβ monomers in detail and discuss the effects of solvating water molecules on their stability at this conference.

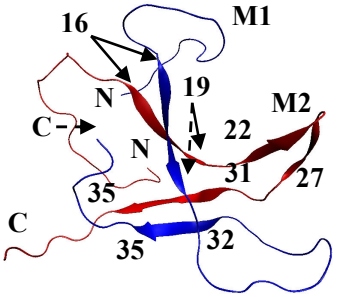

Figure 1
Most stable conformation of solvated Aβ(1-42) dimer (Solvating water molecules are not shown.)

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* Corresponding author: Tel. +81-532-44-6875, e-mail: kurita@cs.tut.ac.jp

[1] Soreghan, B., *et al., J. Mol. Biol.* 269 (**1994**) 28551. [2] Hou, L., *et al., J. Am. Chem. Soc.* 126 (**2004**) 1992.