The World of Amyloids, Explored by Simulation

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Amyloids are found in the brain of patients with Alzheimer's disease and those with BSE, and are considered to be a cause of these diseases. Although amyloids have a fibrous cross-β structure, it is difficult to reveal the detailed structure of amyloids by X-ray crystallographic analysis or solution NMR, because of difficulties in crystallization and insolubility. At AIST, we are studying the formation process of amyloid fiber by computer simulation. Simulation has some advantages, including high resolution time (about 1 femtosec) and spatial resolution (about 1Å), and is therefore very useful for studying amyloid formation processes that are difficult to observe.

The article "The World of Amyloids, Explored by Simulation"[1] describes the results of a study on the amyloid-forming ability of tetrapeptides. Johansson *et al*.[2] prepared FF (di-phenylalanine) flanked by various charged amino acids to study the amyloid-forming ability. They found that KFFE having both positively charged residue (K, lysine) and negatively charged residue (E, glutamic acid) forms amyloid fibrils, whereas peptides with only positive charges (KFFK), only negative charges (EFFE), or no charge (FFF) do not form fibrils. Moreover, an equimolar mixture of a positively charged peptide and a negatively charged peptide (KFFK + EFFE) forms amyloid fibrils, suggesting that "formation of salt bridges between charged residues is important." We investigated this phenomenon, by molecular dynamics (MD) simulation, substantially accelerated using the Generalized Born energy[3] to approximate the hydration effect.

We simulated 3 different peptides, KFFE, KFFK and KFFK+EFFE for 100 nanosec at 315 K. KFFE (Fig. 1) and KFFK+EFFE formed an oligomer made by antiparallel b-sheets, which was consistent with the experimental results. Interestingly, KFFK (Fig. 2) did not form a large aggregate, but formed two or three stranded b-sheets. This finding appears to be consistent with the experiment, which Johannson et al. showed that KFFK does not form amyloids but that b-structure is present as seen with CD spectrum.[2]

On the basis of this finding, the simulation results suggest that "KFFK can form β stranded dimers or trimers by hydrophobic interaction between F side chains, but do not form oligomers higher than trimer because of the strong Coulomic repulsion between side chains at terminal residue." This suggestion does not conflict with the experimental results.

Currently, this method is applied to disease-related proteins, including the Aβ protein, to study the development of amyloid formation inhibitors by simulation of systems involving drug candidates.

References

*1 Kameda, T.: "The World of Amyloids, Explored by Simulation", *Seibutsukougakkaishi*, **84**(10), pp.407-409 (2006).
*2 Tjernberg, L. *et al.*: *J. Biol. Chem.*, **277** (45), pp.43243-43246 (2002).
*3 Still, W.C. *et al.*: *J. Am. Chem. Soc.*, **112**, pp.6127-6129 (1990).

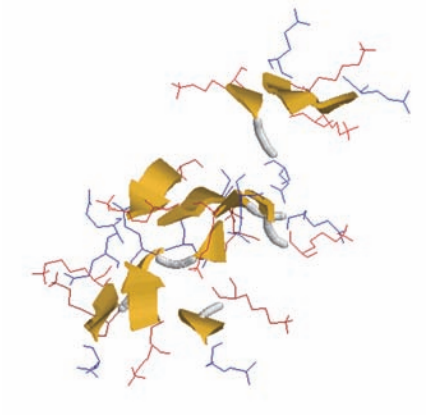

Fig.1 Structure after 100 nanosec (KFFE)

Fig.2 Structure after 100 nanosec (KFFK)
(Magnified figure showing only 8 peptides)