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Role of repulsive forces on self-assembly behavior of amyloid β-peptide (1-40): Molecular dynamics simulation approach

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HIGHLIGHTS

- A new method was presented for studying Aβ-amyloid self-assembles.
- The change zones in the secondary and tertiary structures are different.
- The percentage of turn secondary structure in the LJ 6-12 has the highest value.
- Sensitivity of the OPLS-AA/L force field to the potential change is more.

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ABSTRACT

Aβ-amyloid self-assembly is related to the changing the structure of the β-amyloid from the helix to the sheet. This structural change is one of the main reasons for developing Alzheimer's disease. Usually, the addition of non-polar solvents to water is used to study the role of hydrophobic forces in the self-assembly behavior. However, adding non-polar solvents also causes unwanted structural changes. Here, by changing the Lennard-Jones potential repulsion expression, structural changes in Amyloid β-peptide (1-40) (Aβ40) have been studied using molecular dynamics simulation. For this purpose, in the Lennard-Jones potential $n = 6$ and $m = 8, 9, 10, 11, 12$ were placed in attractive and repulsion terms, respectively. Then this change in the potential was applied to the GROMOS96 and OPLS-AA/L force fields. Molecular dynamics simulations of Aβ40 were performed based on these 10 potentials. The results show that the change in the Lennard-Jones repulsion term in both of the applied force fields does not have a regular impact on the structure and dynamics of the Aβ40. For example, with the change of $m = 12$ to $m = 11$ in the GROMOS96 force field, the diffusion coefficient of Aβ40 decreases, while with the change of $m = 11$ to $m = 10$, the diffusion coefficient increases in this force field. The change zones in the secondary and tertiary structures are also different. However, the results indicate that the OPLS AA/L force field is more sensitive to the change in the Lennard-Jones potential repulsion term.

1. Introduction

Alzheimer's disease is one of the most common causes of mental deterioration in human societies [1]. One of the main causes of the disease is the aggregation of beta-amyloid peptide plaques (Aβ) outside the neuronal cell. Aβ monomers are in a dynamic equilibrium of various conformations with beta sheets that accumulate as oligomers or larger structures. The soluble oligomers of Aβ peptides which are poorly folded, increase the risk of developing Alzheimer's disease than amyloid

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fibrils [2]. In fact, the poor folding of Aβ protein is the most important factor in causing this disease. Aβ40 and Aβ42 are one of the most important beta-amyloid peptides [3]. Aβ40 beta-amyloid peptide is known to be the most abundant peptide present in neurons in a person with Alzheimer's disease [4,5]. The process of aggregation of Aβ40 protein has been investigated both through *in vivo* and *in vitro* studies. However, for different reasons, experimental studies in this area are difficult, and designing drugs fails to reduce the progression of Alzheimer's disease one after another [6]. The most important reasons include the heterogeneity of the aggregates, the sensitivity of the process to agitation, pH, temperature, surfactants, ionic strength, sample preparation and metal ion concentration [7,8]. On the other hand, due to the high tendency of amyloid for aggregation, the study of the structure of monomer and small oligomers of beta amyloid are not amenable to X-rays and NMR. Thus, our information on Aβ has been obtained from various complementary experimental methods. AFM and EM experimental methods were used to obtain the size of amyloid and its fibril [9–12]. Their molecular masses are obtained from the scanning TEM method [13]. Information about the secondary structure, especially on beta sheets, is derived from the FTIR method [14,15]. Information about the three-dimensional structure is obtained from various experimental methods, such as hydrogen/deuterium exchange, mutagenesis, proteolysis, EPR, and SS-NMR [9,15–19]. Thus, pure computational methods have been the basis of many studies on Aβ [20–23].

One of the most interesting theoretical methods is the change in potential expression. Since the refolding process is affected by the solvent hydrophobic forces in the system, much research has been done to strengthen or weaken the hydrophobic forces. For example, for myoglobin protein, a Monte Carlo-based method using a physical model and variations in hydrophobic forces was used, in which amino acid residues were considered as spheres of Van der Waals radius, and the hydrophobic forces among all residues were considered to be long range. Hydrophobic forces were created by changing the solvent energy and Van der Waals forces; accordingly, the attraction section of the Lennard-Jones potentials term was eliminated and the repulsion index of the rigid sphere was changed, and it was found that in the interaction intervals less than 4 angstroms, the structure is more compact and in the interaction intervals more than 4 angstroms, it is less compact. These results showed that the Lennard-Jones repulsion potential section blocks the transformation of the helix structure into beta sheets, and the attraction section caused folding of the myoglobin structure [24]. In another study, the role of Van der Waals forces was investigated in non-polar solvation model and the way of changes in Lennard-Jones potential terms was described, and then solvation free energy was compared in the presence and absence of the attraction statement and the Van der Waals repulsion [25].

The models naturally use the Lennard-Jones potential and lead to inevitable collisions between the parts of the repulsion. In order to solve this problem, a research task introduced a new contact potential, a combination of attraction section based on the Gaussian model and a separate repulsion statement section for protein flexibility, which simplified the studies [26].

In another study based on the same results, with the aim of examining available configurations coming from the modified repulsion statement, configurations of unfolded protein state were compared with the transient states by examining contact maps. The repulsion of unconnected sections had a severe impact on the folding prevention process. Simulation results with various contact potentials confirmed the structural model of protein folding and indicated that this new potential, coming from the changes in the attraction and repulsion terms, increases the flexibility of the protein [27].

Here, the molecular dynamics simulation of the Aβ40 peptide was done by changing the repulsion term exponent at the Lennard-Jones potential. The two force fields, GROMOS96 and OPLS-AA/L, were used in the simulation, and the effect of repulsion term on the results of these force fields was compared.

2. Molecular dynamics simulation details

2.1. Background

All simulations were performed with the Gromacs software version 5.1.2. In general, the force fields used in biomolecular systems are introduced with an empirical potential energy term, which is as follows:

$$E = \sum_{bondes} \frac{k_i}{2}(l_i - l_{i,0})^2 + \sum_{angeles} \frac{k_i}{2}(\theta_i - \theta_{i,0})^2 + \sum_{dihedrals} \frac{V_n}{2}(1 + \cos(n\omega - \gamma)) + \sum_{i=1}^{N}\sum_{j=i+1}^{N} \left\{ 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^m - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^n\right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \right\} \quad (1)$$

In which the first three terms show short-range interactions indicating that the bonds and angles are represented by a simple harmonic term and that changes in the distances between the first and third atoms are taken out. Dihedral energies expressed by the third term. Van der Waals interactions and electrostatic interactions are modeled with the Lennard-Jones potential and Coulomb potential, respectively. The Lennard-Jones (LJ) potential represents the statistical average of non-bonded interactions between system particles on a molecular scale [28]. It has been shown that the separation of attraction and repulsion expressions in the LJ potential helps to understand the fluid's behavior [29]. The separation of attraction and repulsion terms of the Lennard-Jones potential is as follows:

$$u_{LJ}(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \quad (2)$$