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Study of the Alzheimer's Aβ40 peptide in SDS micelles using molecular dynamics simulations

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ABSTRACT

The interaction of the Alzheimer's amyloid beta peptide, Aβ40, with sodium dodecyl sulfate (SDS) micelles, together with the self-assembly of SDS molecules around the peptide from an initial random distribution were studied using atomistic and coarse-grained (CG) molecular dynamics simulations. In atomistic simulations, the peptide structure in the micelle was characterized by two helical regions connected through a short hinge. The initial structure of the system was shown to affect the simulation results. The atomistic self-assembly of SDS molecules resulted in a 38-molecule micelle around the peptide, along with some globules and individual molecules. Coarse-grained simulation results, however, did not show such a difference, and at the end of all CG simulations, a complete 60-molecule micelle was obtained, with the peptide located at the interface of the micelle with water. The obtained CG radial density profiles and SDS micelle size and shape properties were identical for all CG simulations.

1. Introduction

The major component of the senile plaques found in the brain of Alzheimer's disease (AD) patients is a 4 kDa peptide called amyloid-β (Aβ) peptide, containing 39–43 amino acid residues. Aβ peptides are proteolytically cleaved from a transmembrane protein known as the amyloid precursor protein (APP). According to the amyloid cascade hypothesis, the fibrillization of these peptides leads to the formation of the extracellular senile plaques in AD [1]. Later, however, soluble oligomers of Aβ were found to be more strongly correlated with the severity of AD symptoms than fibrillar aggregates [2]. One mechanism for the toxicity of Aβ oligomers is the formation of pores or ion channels in cell membranes which causes an increased level of calcium ions in neurons. Secondary structure predictions by Durell et al. indicated that the 40-residue β-peptide (Aβ40) can form an ion channel in a bilayer environment with six subunits in each leaflet [3]. Later experiments using atomic force microscopy confirmed the existence of these multimeric ion channels for Aβ42. The tetramers or hexamers were shown to form after the insertion of Aβ monomers in lipid bilayers [4].

Structure investigations of Aβ peptides in membrane-mimicking environments, such as the aqueous solutions of fluorinated alcohols, detergent micelles, and explicit lipid bilayers, all report a high degree of helical content in the peptide. In aqueous solutions of trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP), there are two α-helical regions that are connected by a flexible hinge or kink [5,6]. Molecular dynamics (MD) simulation of Aβ42 in a 40% (v/v) solution of TFE shows helical regions between residues 14–24 and 28–36, which are connected through a loop involving residues 25–27 [7]. Similar structures have been observed for the peptide in sodium dodecyl sulfate (SDS) micelles [8–10].

Despite the agreement on the structure of Aβ peptides in different membrane-mimicking media, there is a discrepancy about the positioning of Aβ in these environments. Whereas some people suggest that the C-terminal helix of Aβ is embedded in the core of SDS micelles [6,8,10], others report that the peptide resides on the micelle surface and do not insert into its hydrophobic core [9]. Similar inconsistencies have been observed in the simulation studies of Aβ in lipid bilayers. Xu et al. showed that the Aβ40 exited DPPC bilayers [11], while Lemkul and Bevan reported that the peptide is partially inserted into the bilayer [12].

The presence of such inconsistencies among the experimental studies motivated us to study the positioning of Aβ in SDS micelles using MD simulations. Knowledge about the structure and positioning of Aβ monomers in SDS micelles is essential for an understanding of the initial events in the oligomerization process of Aβ in biological membranes. Micelles are excellent mimics for biological membranes; the small size of micelles makes them suitable for NMR experiments. Moreover, their faster time scale of motion allows the simulation studies for these systems to be run for longer times and/or larger systems. The simulation methods have been successfully used for the study of detergent micelles [13,14] and their interaction with proteins and peptides [15,16]. The results of such simulations are directly

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comparable with bilayer simulations [17,18] and experimental observations.

In addition to atomistic simulations, we have also performed coarse-grained (CG) simulations on our systems. CG models, in which the description of biomolecules is simplified through the integration of a large number of degrees of freedom into a few one, enable us to extend the timescale of our simulations up to one order of magnitude, which is more relevant for biomolecular and membrane processes. CG descriptions have been used to study several protein–micelle and protein–bilayer systems [19–21]. Despite the loss of some structural details, the results of CG models are comparable to atomistic simulations.

2. Methods

Atomistic simulations of Aβ40 peptide in preformed SDS micelles were performed using two different initial positions for the peptide: one in the micelle core (S1) and one in water phase (S2), far from the micelle. In the 3rd simulation (S3), the process of spontaneous self-association of SDS molecules around the peptide was followed.

Initial coordinates of the peptide were taken from the most representative conformer of an ensemble of 10 lowest energy NMR structures (PDB id, 1BA4), determined in SDS micelle [8]. The charges of titrable amino acids were chosen for pH = 7, with a net charge of −3*e* on the peptide. Both termini were charged.

The initial coordinates of the SDS micelle with 60 detergent molecules were obtained from MacKerell simulations [13]. After removing water molecules from this structure, the peptide was added to it. For simulation S1, the peptide was directed along the diameter of the micelle, with its center of mass superimposed on that of the micelle (Fig. 1A). The spherical symmetry of the micelle precluded the need for considering further initial orientations. For simulation S2, the peptide was removed away from the micelle. Each of these systems was placed in the center of a 7.0 nm cubic box. The starting configuration for the self-assembly simulation (S3) was prepared by placing 60 SDS molecules in all-trans conformation in random positions in a 7.5 nm cubic simulation box surrounding the peptide. Each box was filled with appropriate amounts of SPC water molecules [22]. Three sodium ions were added to each system to neutralize them. The ionic strength of the systems was set at ~30 mM using 6 Na^+ and 6 Cl^- additional ions at random positions in the box. The sizes of the systems are given in Table 1. The SDS concentration in each system was ~0.3 M, well above the critical micelle concentration (cmc) of SDS, which is ~8 mM at room temperature [13].

Table 1
Summary of atomistic (AT) and coarse-grained (CG) simulations.

Simulation	No. of water molecules	No. of particles	Box length (nm)	Simulation time (ns)
S1 (AT)	10344	32515	7.0	50
S2 (AT)	10211	32116	7.0	50
S3 (AT)	12769	39790	7.5	50
S1c (CG)	10344	10747	7.0	500
S2c (CG)	10211	10614	7.0	500
S3c (CG)	12769	13172	7.5	1000

All MD simulations and subsequent analyses were performed on a Beowulf cluster of 16 CPUs using the GROMACS 4.0 simulation package [23]. The GROMOS96 force field with the 43a2 parameter set was used in atomistic simulations [24]. The SDS charges and bonded parameters were taken from the previous simulations [25]. Every system was first energy minimized, using 1000 steps of the steepest descent algorithm, followed by 1 ns NVT simulation for equilibration. During this run, the coordinates of the peptide and micelle were harmonically restrained with a force constant of 1000 kJ mol^{-1} nm^{-2}. The production runs were performed for 50 ns at constant temperature, pressure and number of particles (NPT) and the coordinates of the system were saved every 10 ps. The temperature of the system was maintained at 300 K, using the Nose–Hoover thermostat [26,27] with a coupling constant of 0.1 ps. The pressure coupling was performed at 1 bar with the Parrinello–Rahman barostat [28], using a coupling constant of 1.0 ps and a value of 4.5×10^{-5} bar^{-1} for the isothermal compressibility. Long range electrostatic interactions were treated using the PME method with a real space cutoff of 1 nm [29]. Periodic boundary conditions were applied with a van der Waals cutoff of 1 nm. All bond lengths were constrained using the LINCS algorithm [30], allowing an integration time step of 2 fs.

CG parameters were taken from the MARTINI 2.1 force field of Monticelli et al. [31], which is an extension of their original force filed [32] which includes protein parameters and has been validated for use in peptide–bilayer systems [31]. In this force field, each amino acid is represented by one backbone site and up to 4 interaction sites for side chains. SDS molecules were described using one Qa site for head group and three C_1 sites, each representing four CH_2/CH_3 groups of the hydrophobic tail (Fig. 1B). Solvent molecules are modeled by a single polar site with a mass of 72 amu, which is equivalent to four real water molecules.

CG simulations are summarized in Table **1**. In accordance with atomistic simulations, three different initial conditions were chosen

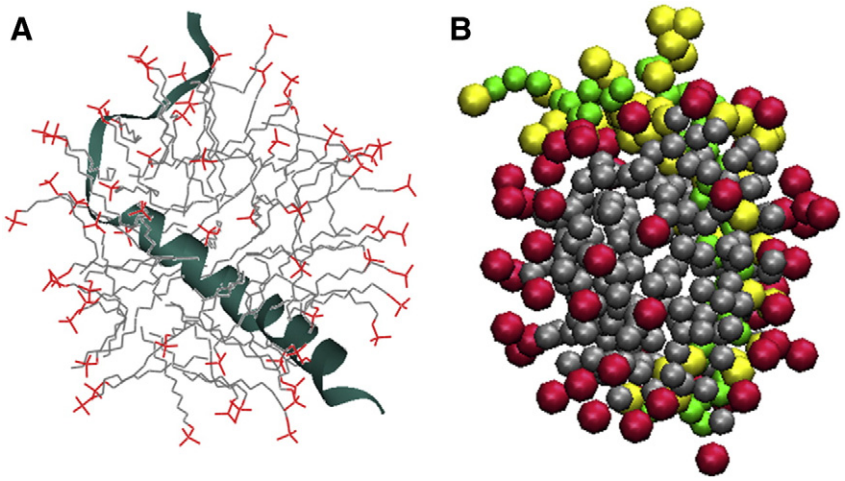

Fig. 1. Initial atomistic (A) and coarse-grained (B) structures of the Aβ40–SDS complex, with the peptide in micelle core. The micelle head groups and tails are shown in red and gray, respectively. In (B), backbone sites of the peptide are in green and side chains are in yellow.

(S1c, S2c and S3c simulations). Each system was first energy minimized and equilibrated for 5000 steps of NPT simulation using a time step of 0.2 fs. The production runs were conducted with a time step of 25 fs and the configurations were saved every 25 ps. Other simulation conditions were chosen as described elsewhere [33].

3. Results and discussion

3.1. Interaction of Aβ40 with preformed micelles: Peptide position and conformation

3.1.1. Atomistic simulations

The interaction of Aβ40 with preformed micelles was studied using two different initial positions for the peptide: one in the micelle core (S1) and one in aqueous phase (S2). In the limit of large sampling times, the results from these two simulations must be identical. However, due to the practical limitations in atomistic simulation times, the convergence may not be achieved. In order to examine the convergence, one can compare the time variations of the center-of-mass (COM) distance between the peptide and the micelle in S1 and S2 simulations, Fig. 2A.

In S1 simulation, the initial center-of-mass distance of about 0.5 nm increases to 1 nm during the first 5 ns and then fluctuates around this value. For S2, the peptide is initially at a distance of ~3.5 nm from the micelle, in aqueous phase. This distance increases in the first 6 ns and then falls. At the end of both simulations, the peptide's center of mass reaches to a distance of ~1.5 nm from the micelle's COM, which is approximately equal to the micelle's radius of gyration [13]. In order to avoid the effect of unfavorable fluctuations on the results, the ensemble averages for both simulations are evaluated from the last 5 ns.

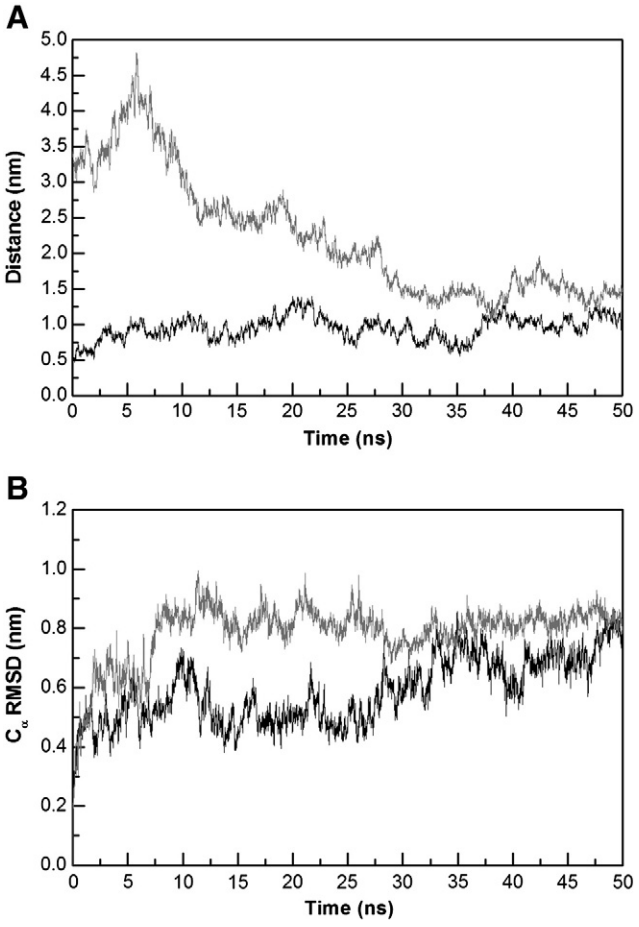

Fig. 2. Variations of (A) peptide-micelle COM distance and (B) peptide's C_α RMSD with time in S1 (black) and S2 (grey) simulations.

The convergence may also be examined on the basis of the peptide's root mean square deviation (RMSD) from the initial energy-minimized structure. Fig. 2B shows the time variations of C_α RMSD for the peptide in S1 and S2 simulations. The RMSD values are nearly constant in the last 5 ns of both simulations. For S2, after the initial approach of the peptide to the micelle (which takes a time of about 30 ns), the system reaches to a rather stable condition and the changes in RMSD become small. However, in S1, the fluctuations stabilize only in the last 10 ns and in the last 3 ns, the RMSD increases along with a decrease in the COM distance (Fig. 2A). The final RMSD is about 0.8 nm for both simulations, which shows the large flexibility of peptide structures. Similar large values for RMSD have been observed in atomistic simulations of Mistic protein in lauryl dimethylamine oxide (LDAO) micelles [34].

The time evolution of the peptide's secondary structure in S1 and S2 simulations is shown in Fig. 3. According to these graphs, there are two helical regions in the peptide, which are connected through a structureless link. The first 14 residues are nearly unstructured in both simulations and appear as coils or bends. This structure is in agreement with the experimental studies in aqueous solutions of TFE [5] and HFIP [6], as well as in SDS micelles [8–10]. For S1 system, there are two α-helices between residues 15–24 and 29–36, connected by residues 25–27. This is similar to the results of atomistic simulations of Aβ42 in TFE/water mixtures [7]. For S2, the helical regions are mainly of 5-helix type. A notable event is that for S2, a β-sheet structure appears in the peptide within the time range of 10–30 ns. As shown in Fig. 2, the peptide is approaching the micelle during this time period. As the peptide becomes closer and closer to the peptide, the amount of the β-sheet structure decreases and when the interaction completes, the helical structures reappear. In this regard, experimental studies show that when the peptide is at the interface of micelle with water, it adopts mainly a β structure, but upon insertion to the micelle core, it attains helical structures [35].

Final structures obtained from S1 and S2 simulations are shown in Fig. 4. There is a difference between two systems in the position of the peptide relative to the micelle. In S1, the C-terminal helix of the peptide is located in the micelle core, whereas in S2 this section is outside the core and can interact with micelle head groups and water. This difference is more obvious in radial density profiles of Fig. 5. In this figure the average densities of different groups over the last 5 ns of each simulation are plotted against the distance from the micelle's center of mass. These diagrams show the amphiphilic nature of the micelle with separate regions of high density for head groups and tails. In S1, the peptide's peak is completely located in the region corresponding to the micelle core, while for S2, the insertion of the peptide in micelle core is lower and the peptide's curve has a significant overlap with the distribution of head groups.

More information about the peptide positioning relative to the micelle may be obtained from Fig. 6, which shows the radial probabilities for different groups. The positions of the peaks for head group distributions are in the range of 1.9–2.0 nm, in agreement with atomistic simulations of a pure SDS micelle [13]. The peptide distribution is plotted for three regions (which are selected based on the experimental studies [10,13]). These three regions are (1) first 10 amino acids, (2) the region between residues 15–24 (helix I), and (3) the region between residues 29–35 (helix II). In both simulations, from N- to C-terminus, the maximum of the probability distribution shifts to closer distances from the micelle's COM. The distribution for helix II in S1 system is located completely inside the hydrocarbon distribution, extending to a distance of 1.5 nm. Moreover, the major part of the helix I distribution is in the same region. By contrast, in S2 system, helix I is mainly located in the interface region of the micelle and the helix II is only slightly buried in the micelle. Radial

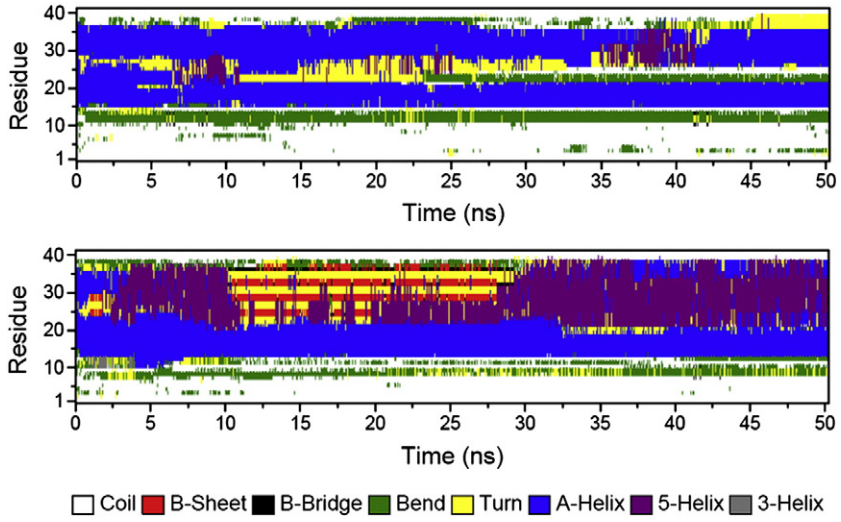

Fig. 3. Time evolution of the peptide's secondary structure in S1 (top) and S2 (bottom) simulations.

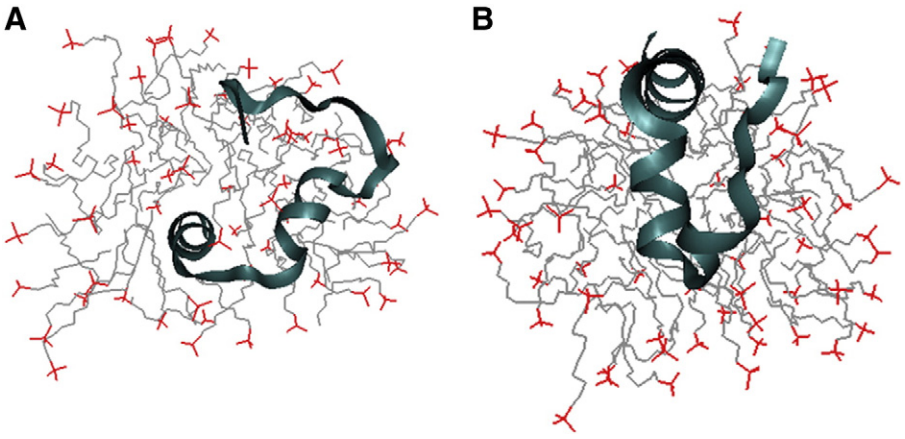

Fig. 4. Final atomistic structures from S1 (A) and S2 (B) simulations.

distribution functions show that in the case of S1, the interaction of helix II with water is very weak, which is a result of its burial in the micelle (data not shown).

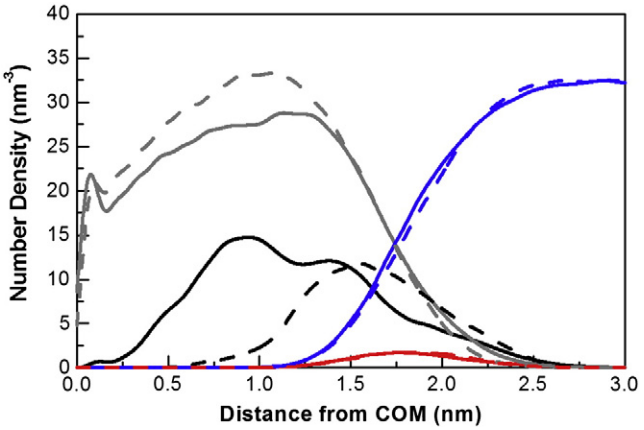

Fig. 5. Radial density profiles relative to distance from the micelle's COM for the peptide (black), micelle sulfur atoms (red), micelle tails (gray) and water oxygens (blue) in S1 (solid lines) and S2 (broken lines) systems.

3.1.2. Coarse-grained simulations

The results of atomistic simulations were shown to depend on the initial positioning of the peptide relative to the micelle. This difference may be caused by insufficient sampling and convergence problems. Examination of the energetics of S1 and S2 simulations showed that the S1 is probably the less stable system that is not converged. Extending the simulation time for S1 to 100 ns did not make any difference in the results. To decide which result is probably more reliable, which is not possible solely on the basis of energetics, we performed coarse-grained simulations for 500 ns on these two systems (S1c and S2c simulations, Table 1). This is equivalent to an effective time of 2 μs, which is four times larger than the actual simulation time, because the CG potentials are much smoother than the atomic potentials and the dynamics is faster. This factor was chosen based on the comparison of diffusion constants for atomistic and CG simulations of water [32].

Fig. 7 shows the final structures obtained from S1c and S2c simulations. Examination of these figures shows that in both cases, the peptide is located at the interface of micelle with water, with the C-terminal part (shown in dark blue) in more contact with the micelle tails. However, these contacts are made through the motions of micelle tails and the peptide is not buried into the micelle core. From the radial density profiles of Fig. 8, which are averaged over the last 200 ns of trajectories, it is clear that the results obtained from two

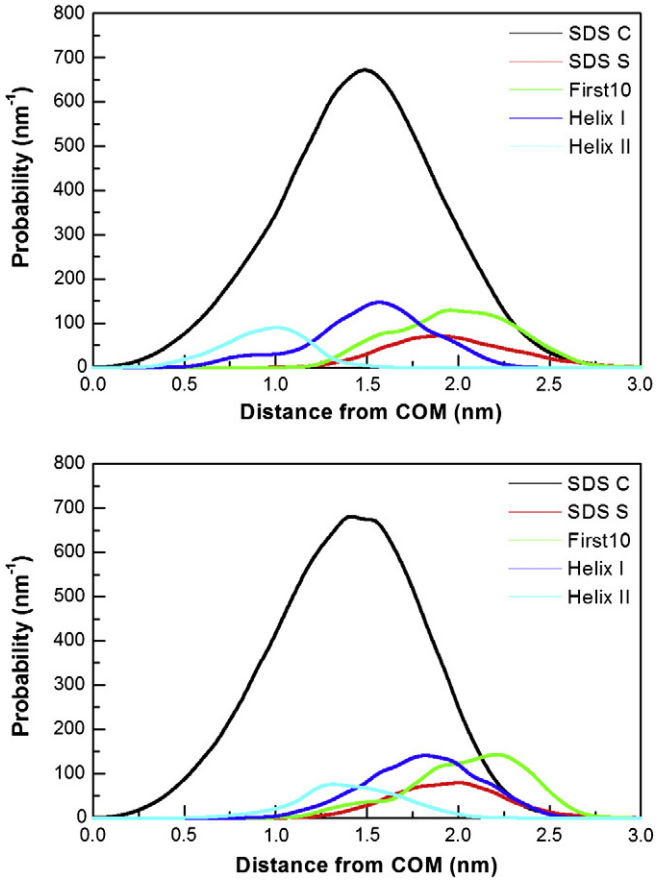

Fig. 6. Radial probability distributions for different groups in S1 (top) and S2 (bottom) simulations.

simulations are identical, irrespective of the initial conditions. The position of the maxima for head group distributions is ~2.0 nm, which is in agreement with atomistic simulations. Apart from a four-fold difference in the carbon and water densities, which is a result of the four-to-one mapping of CG representation, the density profiles of Fig. 8 are similar to the profiles of S2 simulation in Fig. 5. Examination of the time variations of the peptide-micelle COM distance in CG simulations (data not shown) reveals that it takes about 100 ns for the two simulations to have a same COM distance. This time, which is equivalent to an effective time of 400 ns of atomistic simulation, is obviously beyond the scope of our atomistic simulations.

3.2. SDS self-assembly around Aβ40

In the atomistic simulations of the Aβ peptide with preformed micelles we showed that the initial position of the peptide is important for final results. Here, we describe the process of SDS self-assembly around the peptide, from a random initial distribution. Fig. 9 shows the main steps of the spontaneous self-assembly of SDS molecules around the peptide, for atomistic (upper row) and CG (lower row) simulations.

For atomistic simulation at zero time, when the equilibration of the system is completed, there exist sparse collections of 10–15 dodecyl sulfate molecules at different locations around the peptide in the simulation box. These collections are joined together during the simulation and eventually form a 38-molecule micelle around the peptide at the end of simulation. The association of these assemblies normally proceeds via head group interactions. The other 22 SDS molecules are ordered in the form of two 7-molecule globules and some individual molecules. The formation of a main micelle and a few of globules has been also observed in the simulation of dodecylphosphocholine (DPC) self-assembly around the peptides [36]. The properties that are calculated for the "micelle" in atomistic simulation all correspond to the 38-molecule main micelle.

CG simulation shows a similar trend in the steps for the SDS self-vhassembly. After a time of 6 ns, partially ordered associations of SDS molecules are formed around the peptide. These associations join together and form a small micelle attached to the peptide, together with two independent globules. Later, these globules are fused together to form two larger micelles. At 115 ns, these two micelles are both attached to the peptide. Finally, after 150 ns, a complete micelle with 60 SDS molecules is formed around the peptide. Formation of a complete micelle from the association of globules in long CG simulations is also reported in the study of GpA and OmpA proteins with DPC micelles [19].

The peptide structure in S3 simulation has the basic properties of Aβ in membrane-mimicking environments, with two helical regions (Fig. 10). The C-terminal helix is mainly a 5-helix, as in S2. The RMSD changes (Fig. 10) show that after 6 ns, the RMSD values stabilize and fluctuate around 0.8 nm, similar to S1 and S2 simulations. The peptide position relative to the micelle is similar to the S2 simulation, as revealed from radial density plots (Fig. 11, top). The main part of the peptide is located at the interface of the micelle with water (at a distance of about 1.5–2.0 nm). The observation that the peptide

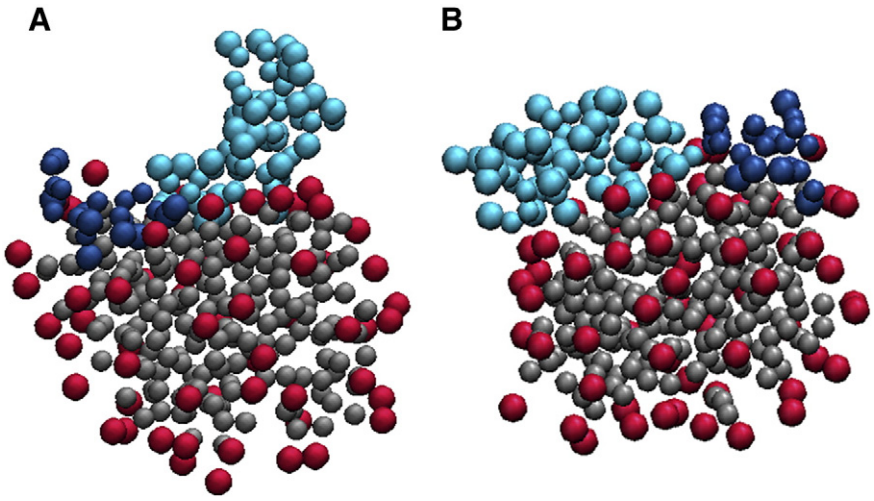

Fig. 7. Final coarse-grained structures for S1c (A) and S2c (B) simulations.

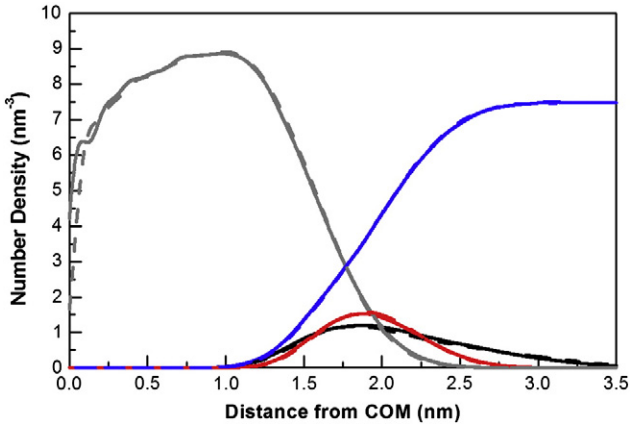

Fig. 8. Radial density profiles for S1c (solid lines) and S2c (broken lines) simulations. The color codes are black for peptide, red for micelle head groups, gray for micelle tails and blue for waters.

resides on the micelle surface may be supported by the results of recent MD simulations of the Aβ peptide in phospholipid bilayers, which show that the peptide remains on the bilayer surface [37].

For CG simulation of the self-assembly process (S3c), the radial density profiles (Fig. 11, bottom), averaged over the last 500 ns, are very similar to the profiles for the preformed micelles of Fig. 8. This shows the independence of CG results to the initial conditions. Comparison of atomistic and CG simulations in Fig. 11 shows that the position of head groups and the location of the micelle-water interface are similar in two simulations. This shows that the CG model is successful in modeling the amphiphilic character of the micelles and the distribution of peptides in micelles.

3.3. Dynamic properties of the micelles

Table 2 summarizes the properties of the micelle calculated from the atomistic simulations. The initial value of the radius of gyration (R_g) for the preformed micelle used in S1 and S2 simulations is 1.64 nm. The average values of R_g for the last 5 ns of these two systems are similar to this value and have small fluctuations, especially for S2, which has an average R_g of 1.65 nm. This shows that the micelle maintains its integrity during these simulations. The calculated R_g for S2 agrees well with the atomistic simulations of SDS micelles [13,14,38] and it seems that the peptide does not disturb the micelle structure, as noted in experimental studies [10]. The average distance of the sulfur atoms from the micelle's COM, R(S), which is a measure of its radius, is 1.96 and 1.94 nm in S1 and S2 systems, respectively, which are very close to the initial value of 1.99 nm for the preformed micelle. The same value is obtained in the simulation of the transmembrane protein GpA with SDS micelles [15]. For CG simulations, the initial value of the R_g in S1c and S2c simulations is 1.56 nm, which is similar to the values obtained for pure SDS micelles [33]. The average value of R_g over the last 200 ns of these two simulations is 1.61 nm. The similarity of the final results of S1c and S2c is evident from these data. For the S3 simulation, the aggregation number of the produced micelle is only 38. The micelle's radius of gyration is also small (1.46 nm), with a small fluctuation that is a result of the formation of a whole 38-molecule micelle after 20 ns (Fig. 9). In the case of S3c, the average radius of gyration is 1.61 nm, similar to S1c and S2c simulations.

Table 2 contains the average values of the three moments of inertia for the micelle along its principal axes, calculated from the atomistic

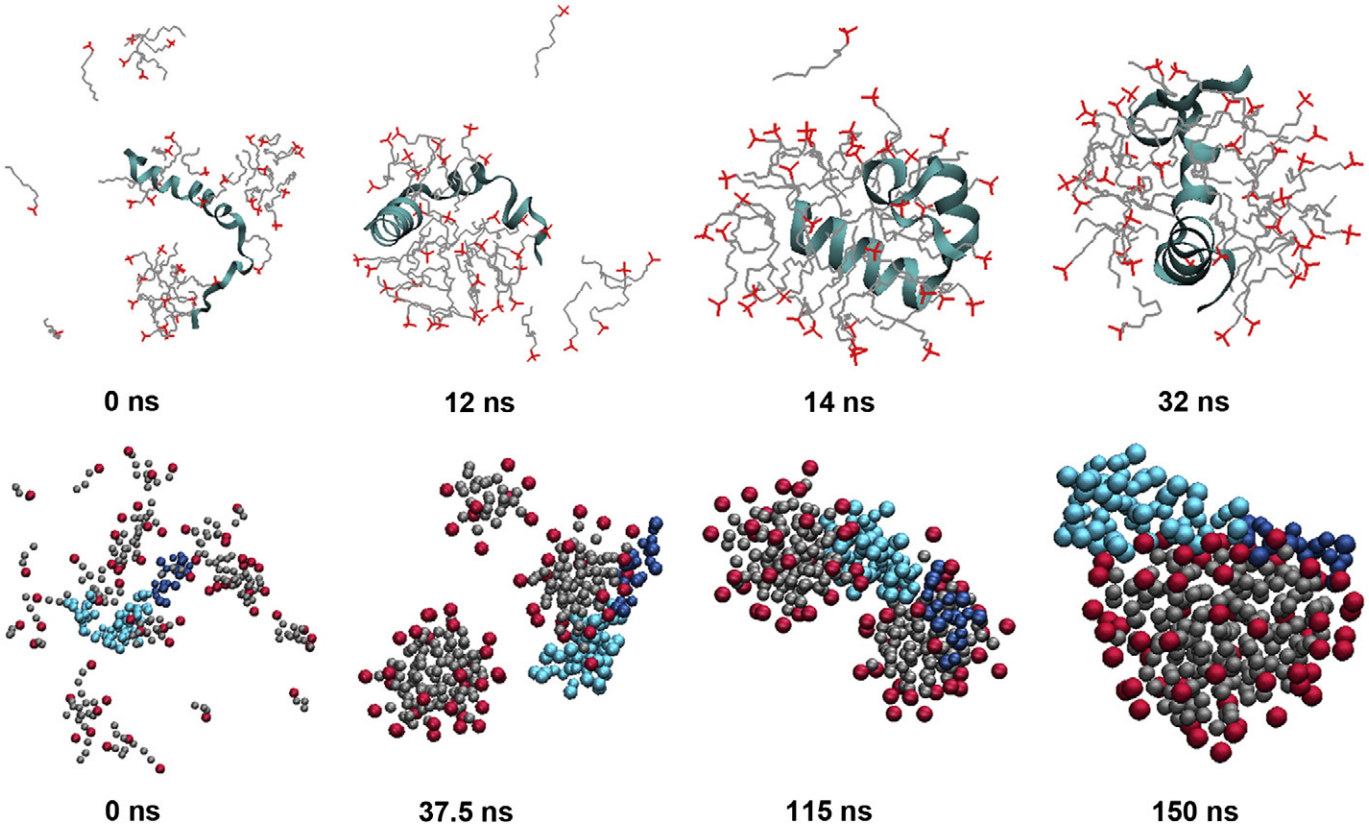

Fig. 9. Formation of the peptide–SDS complexes. Snapshots from the atomistic simulations (S3, top) are shown for the main (38-molecule) micelle. In the coarse-grained simulation (S3c, bottom), the C-terminal (28–40) amino acids of the peptide are in dark blue.

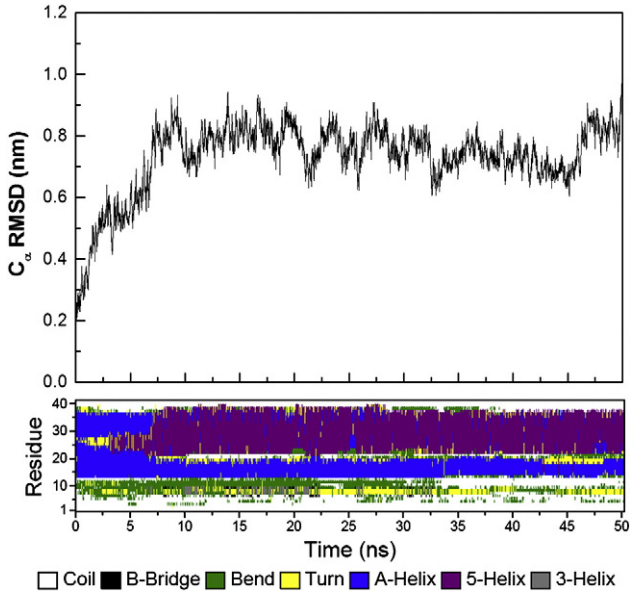

Fig. 10. Time variations of C_α RMSD (top) and the secondary structure (bottom) for the peptide in S3 simulation.

trajectories. In S1, the ratios of three moments of inertia (I_1:I_2:I_3) is 1.6:1.5:1.0, whereas for S2 and S3 the ratios is 1.5:1.4:1.0. It turns out that in all three cases, the micelle shape is a prolate ellipsoid. The deviation of the micelle shape from its initial spherical shape in S1 and S2 (with the ratios of 1.1:1.0:1.0) may be attributed to its interactions with the peptide. Similar moments of inertia ratios have been observed in the simulations of OmpA protein in DPC micelles [17].

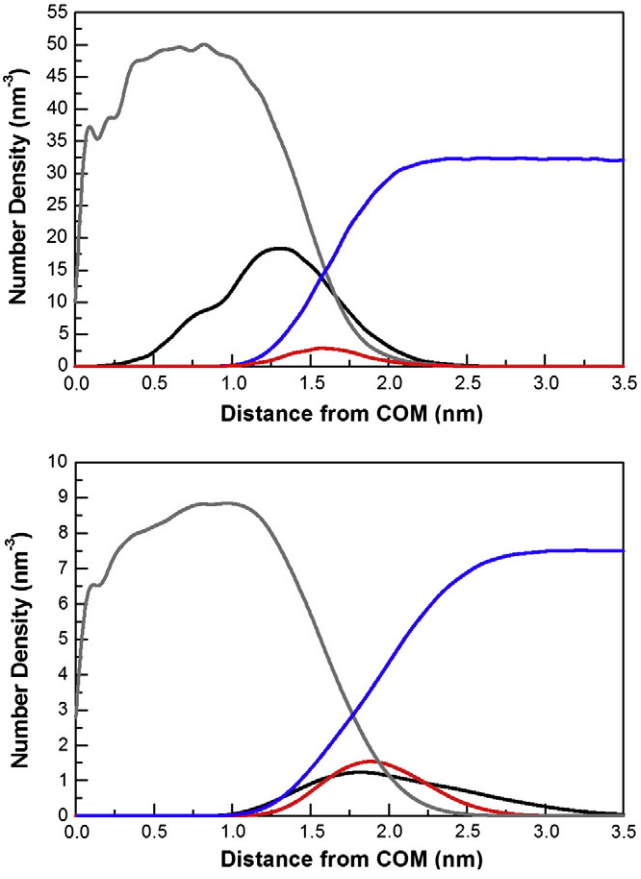

Fig. 11. Radial density profiles for S3 (top) and S3c (bottom) simulations.

Table 2
The properties of micelle (averaged over last 5 ns) in atomistic simulations.

	N_{agg}	R_g (nm)	R(S) (nm)	I_1/I_3	I_2/I_3	e
S1	60	1.71 ± 0.03	1.96 ± 0.02	1.60 ± 0.19	1.50 ± 0.21	0.26 ± 0.07
S2	60	1.65 ± 0.03	1.94 ± 0.02	1.48 ± 0.20	1.35 ± 0.19	0.21 ± 0.08
S3	38	1.46 ± 0.03	1.71 ± 0.19	1.48 ± 0.15	1.35 ± 0.16	0.21 ± 0.06

Another criterion for the micelle shape is its eccentricity, which is defined by $e = 1 - I_{min}/I_{avg}$. I_{min} is the smallest moment of inertia (I_3) and I_{avg} is the average of three moments. A complete sphere has an eccentricity value of zero. Table 2 shows that in all atomistic simulations, the eccentricity is larger than the initial value (0.05), but the deviation is larger for the S1 system. The deviation from sphere is a result of the interaction with protein and is also reported in the study of the interaction of antimicrobial peptides with SDS micelles [16]. For CG simulations, the amount of eccentricity is 0.23 for all three cases, which is very close to our atomistic results and the results of atomistic simulations of GlpF in an Octyl glucoside (OG) micelle [18]. The ratios of moments of inertia in CG simulations are 1.6:1.1:1.0, corresponding to a oblate ellipsoid shape.

4. Conclusions

In this paper, we studied the interaction of the Alzheimer's Aβ40 peptide with SDS micelles. Although SDS micelles are not as good as lipid bilayers to mimic biological membranes, they are widely used in this regard, because of their amphiphilic nature. Our results showed that the experimental conformation of the peptide in SDS micelles is well reproduced using atomistic molecular dynamics simulations. However, the position of the peptide relative to the micelle was shown to depend on the initial conditions. Coarse-grained (CG) simulations were performed to resolve this discordance. Despite some limitations of the CG model, such as the loss of some atomic details and its lack to simulate the secondary structure changes of the peptide, it enables us to extend our simulation times by an order of magnitude and still reproduce the main structural and dynamics properties of our systems. Comparison of our CG results to available atomistic results shows that this model is sufficient for studies of protein–surfactant systems and may be used for simulation of more complex systems, such as lipid bilayers. In the CG process of SDS self-assembly around the peptide, it was shown that the formation of a complete 60-molecule micelle requires a simulation time of about 150 ns (equivalent to an effective time of 600 ns), which is much more than the typical times available for atomistic simulations, i.e. ~100 ns.

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