



Assessing the influence of solvation models on structural characteristics of intrinsically disordered protein



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ABSTRACT

Intrinsically disordered proteins are associated with functions of signaling and regulation as well as with a number of diseases such as cancer and neurodegenerative conditions. Molecular dynamics simulation is potentially a powerful tool to study those protein conformational disorders in full atomic details that would be difficult to gain from experimental measurements. However, the accuracy of the simulation critically relies on the quality of underlying potential energy functions or force fields. In particular, structural properties of intrinsically disordered proteins are expected to depend more sensitively on protein–water interactions because of their increased solvent exposure than folded globular proteins. Here, we investigate the impact of solvation models on structural characteristics of full-length amyloid-beta ($A\beta$) protein, an intrinsically disordered protein whose aggregation is linked to Alzheimer's disease. For this purpose, we performed extensive molecular dynamics simulations by combining AMBER ff99SB force field for protein with differing solvent water models as well as solvation procedures with different solvent box sizes. We find that the structural characteristics of $A\beta$ protein differ remarkably depending on the water model adopted as well as on the solvent box size. Our results demonstrate the significant sensitivity on the solvation procedure including the solvent force field in characterizing structural properties of intrinsically disordered proteins.

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1. Introduction

Recent efforts to refine force fields for biomolecules have contributed to develop molecular dynamics (MD) simulations into a more reliable tool for studying structure and dynamics of proteins associated with their functions [1–3]. However, relatively less attention has been paid to the validity of models for solvent water. Several deficiencies have been reported for standard three-site water models such as TIP3P [4] and SPC [5], in particular, concerning the temperature dependence of various water properties [6,7]. These models may therefore be inadequate in simulating protein behavior at thermodynamic conditions other than standard temperature and pressure. Furthermore, it is expected that more accurate models for water are necessary to elucidate structural and dynamic properties of intrinsically disordered proteins (IDPs) [8]. This is because IDPs are more solvent-exposed than folded globular proteins reflecting the unfolded nature, and their conformational fluctuations may depend more sensitively on protein–water interactions. In fact, recent simulation studies have demonstrated that the use of more refined water models such as TIP4P-Ew [9] and TIP4P/2005 [10] yields more accurate conformational ensembles,

particularly of disordered peptides [11–14]. However, these studies focused on model peptides or shortened fragments of disease-related proteins. In this paper, we investigate the effects of solvation models on the structural characteristics of full-length, 42-residue form of amyloid-beta protein ($A\beta_{42}$), an IDP whose aggregation is associated with Alzheimer's disease [15].

Several groups have carried out explicit-water MD simulations for $A\beta_{42}$ protein [16–27], but dissimilar results among those simulations are reported concerning, e.g., representative conformations, distribution of the radius of gyration, and average secondary-structure populations. These inconsistencies in the reported results may partly arise from the heterogeneous conformational ensemble of disordered $A\beta_{42}$ protein and an insufficient sampling due to limited computational times. Another contribution to the discrepancies would be the sensitivity of $A\beta_{42}$ conformational fluctuations on protein–water interactions since those simulations have been performed with a variety of different combinations for protein force fields and water models. But would this be all? Among characteristic features of IDPs is the large net charge that is primarily responsible for their inability to fold into well-defined structures [8]. In view of the long-range nature of the electrostatic interaction as well as of possible sensitivity of IDPs' structure on their interaction with water, the solvation procedure such as a choice of the solvent box size in the preparation stage of

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simulations can be another source of discrepancies. It would therefore be important to examine how the solvation procedure affects structural characteristics of IDPs.

Here we report extensive explicit-water MD simulations to investigate the impact of solvation models on the structural characteristics of A β 42 protein. Three distinct sets of simulations that differ in the treatment of solvent water were carried out with the force field for protein fixed to AMBER ff99SB [28]. The first set of simulations was performed employing the TIP4P-Ew water model with a larger solvent box size than the one in the previous simulation studies for A β 42. The second set of simulations differs from the first set only in that the standard TIP3P water model is adopted. The third set of simulations was conducted also with the TIP3P water model, but with a smaller solvent box size that is comparable to the one in the previous simulations. For IDPs such as A β 42, how to efficiently sample their potentially wide conformational space is a challenging issue. Replica-exchange method [29] is a powerful tool in this regard, and has often been adopted in the explicit-water MD simulations for A β 42 [18,23–26]. However, explicit handling of solvent water molecules requires a large number of replicas since the energetic fluctuation becomes relatively smaller for larger systems. This is problematic especially for the first and the second sets of our simulations that include a large number of explicit water molecules, which will significantly limit the length of the simulation at a desired temperature. In the present work, we conducted multiple independent simulations that start from carefully prepared protein structures obtained by heating and conformational annealing simulations. We then examined the performance of the water model and the dependence on the solvation procedure in characterizing structural features of A β 42 through the comparison with available experimental data.

2. Material and methods

2.1. MD simulations

Three distinct sets of MD simulations for A β 42 protein were carried that differ in the water model and the solvation procedure detailed below and summarized in Table 1. The sequence of A β 42 protein is ⁽¹⁾DAEFR HDSGY EVHHQ KLVFF AEDVG SNKGA IIGLM VGGVV IA⁽⁴²⁾, and the protein force field employed here is fixed to ff99SB. All the simulations were performed at 300 K and 1 bar using AMBER11 simulation package [30]. Each set of simulations consists of ten independent production runs of 100 ns length (i.e., an accumulative simulation time of 1 μ s). The simulations were done under neutral pH, where Lys and Arg residues are positively charged and Glu and Asp are negatively charged, and A β 42 is in the -3 charged state. The particle mesh Ewald method [31] was applied for treating long-range electrostatic interactions, while a 10 Å cutoff was used for the short-range non-bonded inter-

actions. The hydrogen atoms were constrained to the equilibrium bond length using the SHAKE algorithm [32], which enables simulations with a 2-fs time step. Temperature and pressure were controlled by Berendsen's thermostat and barostat with coupling constants of 1.0 and 2.0 ps, respectively [33].

2.2. A β 42/TIP4P-Ew system

We employed the TIP4P-Ew model for solvent water in the first set of our simulations, and this system is referred to as A β 42/TIP4P-Ew in the following. Since A β 42 protein in the monomeric state is intrinsically disordered and no atomic-level structure in aqueous environment is available experimentally, the initial conformations for independent production runs were carefully prepared as follows. The starting conformation was taken from the NMR structure determined in an apolar solvent (PDB ID: 1IYT [34]), which was solvated by explicit water and neutralized by counter Na⁺ ions. The starting system was initially subjected to 500 steps of steepest descent minimization followed by 500 steps of conjugate gradient minimization while A β 42 protein was constrained by 500 kcal/(mol Å²) harmonic potential. Then, the system was minimized using 1000 steps of steepest descent minimization followed by 1500 steps of conjugate gradient minimization without harmonic restraints. The system was subsequently subjected to 20 ps equilibration process in which the temperature was gradually raised from 0 to 300 K with a constant volume. This is followed by 200 ps constant-pressure (NPT) ensemble simulation of 1 bar to achieve the correct water density. We then heated the system to 600 K and carried out 20 ns canonical (NVT) ensemble simulation. From this 600-K simulation of 20 ns length, we took ten protein structures with 2 ns time interval. The C α RMSD (root-mean-squared deviation) between any pair of these ten structures was \sim 10 Å, and they were considered as independent configurations. Each of the ten structures was then gradually annealed to 300 K: the temperature was decreased from 600 K with 50 K interval, and 1-ns NVT simulation was performed at each of the intervening temperatures between 600 K and 300 K. Subsequently, additional 5-ns equilibration NPT simulation was performed at 300 K and 1 bar. The final structures obtained from the annealing simulations starting from the ten different 600-K structures were used as the initial structures for the ten independent NPT production runs of 100 ns each at 300 K and 1 bar. The length of the production run was chosen in view of the estimation in Ref. [24], where it was suggested that the simulation longer than \sim 60 ns/replica is necessary to achieve the convergence in the ensemble for A β 42. The minimization, heating, annealing, and production runs were all carried out under the fully hydrated condition with 13,417 water molecules dissolved in the cubic periodic box of the average side length of 74.3 Å. The size of the solvent box is larger than a typical one (\sim 50 Å) in the recent simulation studies for A β 42 [24–27].

Table 1
Summary of simulation procedures for the systems studied.

Systems	Preparation protocols	Production runs	# of water	Box size ^a (Å)
A β 42/TIP4P-Ew	1. Heating in water at 600 K 2. Annealing to 300 K 3. Equilibration at 300 K (5 ns)	100 ns \times 10	13,417	74.3
A β 42/TIP3P-I	1. Heating in water at 600 K 2. Annealing to 300 K 3. Equilibration at 300 K (5 ns)	100 ns \times 10	13,666	75.0
A β 42/TIP3P-II	1. Heating <i>in vacuo</i> at 600 K 2. Solvation by explicit water 3. Equilibration at 300 K (5 ns)	100 ns \times 10	4290 ^b	51.3

^a Average side length of the cubic simulation box in the production runs.

^b Average number of water molecules upon solvating A β 42 protein with 10 Å buffer.

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