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Review

Molecular dynamics simulations of amyloid fibrils: an *in silico* approach

Wei Ye[1], Wei Wang[1], Cheng Jiang[1], Qingfen Yu[1], and Haifeng Chen[1,2*]

[1]State Key Laboratory of Microbial Metabolism, Department of Bioinformatics and Biostatistics, College of Life Sciences and Biotechnology, Shanghai Jiaotong University, Shanghai 200240, China
[2]Shanghai Center for Bioinformation Technology, Shanghai 200235, China
*Correspondence address. Tel: +86-21-34204348; Fax: +86-21-34204348; E-mail: haifengchen@sjtu.edu.cn

Amyloid fibrils play causal roles in the pathogenesis of amyloid-related degenerative diseases such as Alzheimer's disease, type II diabetes mellitus, and the prion-related transmissible spongiform encephalopathies. The mechanism of fibril formation and protein aggregation is still hotly debated and remains an important open question in order to develop therapeutic method of these diseases. However, traditional molecular biological and crystallographic experiments could hardly observe atomic details and aggregation process. Molecular dynamics (MD) simulations could provide explanations for experimental results and detailed pathway of protein aggregation. In this review, we focus on the applications of MD simulations on several amyloidogenic protein systems. Furthermore, MD simulations could help us to understand the mechanism of amyloid aggregation and how to design the inhibitors.

Keywords amyloid fibrils; prion; protein aggregation; MD simulation

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Introduction

Research on protein misfolding in human diseases has been a hot topic among a broad spectrum of disciplines. In living cells, the conversion of proteins from their normal soluble forms to misfolded insoluble amyloid fibrils was discovered as key reasons for a number of neurodegenerative diseases [1–5], such as Alzheimer's disease (AD), Parkinson's disease (PD), prion diseases (transmissible spongiform encephalopathies, TSEs) and its variant Creutzfeldt–Jakob disease, Huntington's disease (HD), as well as several famous unsolved non-neuropathic diseases, such as type II diabetes and cataract.

With the development of molecular biology and crystallographic technologies, a number of research articles with crystal structures have partially clarified the structure of misfolded amyloid fibrils, which also provides strong help in exploring the pathogenesis of these diseases. The rule that higher-order structure of protein is determined by its primary sequence, which has been considered as a dogma for years, has been challenged [6,7]. A protein could have distinctly different conformations without any changes in primary sequence [8,9]. In prion diseases, one of the most widely accepted views on the mechanism of infection and propagation of prion is the protein-only hypothesis [1,10]. It suggests that TSEs are caused only by the infectious protein (PrP^{Sc}) that is identical to the host protein (PrP^{C}) in primary sequence but different in conformation [1,2,11–13]. PrP^{C} contains plenty of α-helices (>40%), while PrP^{Sc} includes many β-sheets (>43%). Meanwhile, different from PrP^{C}, PrP^{Sc} is insoluble but has partial PK resistance [14]. Similar observations have also been reported in Aβ polymers induced AD, which adopt β-sheet conformation [15–17]. However, this protein tends to be intrinsically disordered in folded state [7,18]. Therefore, the research on the conversion of protein conformations has great significance to probe the mechanisms of pathogenesis and therapeutics of this kind of diseases.

However, current experimental technologies, both in molecular biology and crystallography, could hardly observe the process and pathway of the conformational conversion and transition. The appearance of molecular dynamics (MD) simulations [19–21] provides us an alternative method on this issue.

Based on force fields calculated from classical Newton's laws or quantum mechanics, MD simulation can simulate the atoms' movements of biomolecules [20,22] to study the structures and functions of solvated systems. With the robust development of computational capability, the simulation results are consistent with those of traditional 'wet' experiments. Therefore, MD simulations are important supplement for experiments. Here we focus on the applications of MD simulations on protein misfolding and aggregation which could hardly be explored with traditional experiments.

Principles and Methods

Recently, force field of AMBER (Assisted Model Building with Energy Refinement) [23] and GROMOS (GROningen MOlecular Simulation) [24], as well as CHARMM (Chemistry at HARvard Macromolecular Mechanics) [25] and OPLS (Optimized Potential for Liquid Simulations) [26], are widely used in biomolecules simulations. Several basic concepts are illustrated here. First, the start structures are preferred to be real. That is, MD results originated with X-ray or nuclear magnetic resonance (NMR) structures from Protein Data Bank (PDB, http://www.pdb.org/pdb/home/home.do) are more convincing than those from modeling structures. However, MD simulations are currently restricted to timescales of <1 μs, which is much shorter than folding and misfolding half-time of most proteins (at least 1 ms) [27,28]. The common approaches are: (i) taking the most important part that has the closest relationship with the project as MD system and (ii) pulling dynamics [29–31], and high-temperature MD simulations [32,33] could be employed to speed up the misfolding and folding. Certainly, parallel trajectories of MD simulations could generate more conformations in solvent and provide more observations.

MD Simulations in Prion Diseases

TSEs and relative diseases are considered to be attributed to the structural transition of PrP protein (PrP^C to PrP^{Sc}) normally encoded and expressed by gene *Prnp* [1]. In this transition, the primary structure of PrP protein does not undergo any changes, but the secondary and tertiary structures in PrP^{Sc} are distinctly different from those in PrP^C. Normal structure of PrP protein is shown in **Fig. 1**. As one of the hottest topic in protein misfolding and amyloid aggregation, much progress has been made in the mechanism of PrP protein aggregation and infections.

It is well known that transition from PrP^C to PrP^{Sc} can be induced by infectious PrP^{Sc}, or an external factor, such as low pH [1,2,34]. Many MD simulations have demonstrated the role of pH. It has been observed that the transition from PrP^C to PrP^{Sc} is pH dependent [35,36]. MD simulations on $PrP_{125-228}$ were carried out in neutral, weakly acidic and strongly acidic solutions, respectively [36]. It was confirmed that acidic environment could facilitate the aggregation of PrP protein, helices unfolded, and β-sheets extended. In high-temperature (350 K) simulations on the same system, unfolding pathways induced by heat and low pH were considered different. Additionally, it was concluded that the intramolecular salt-bridges were critical in the stabilization of PrP^C.

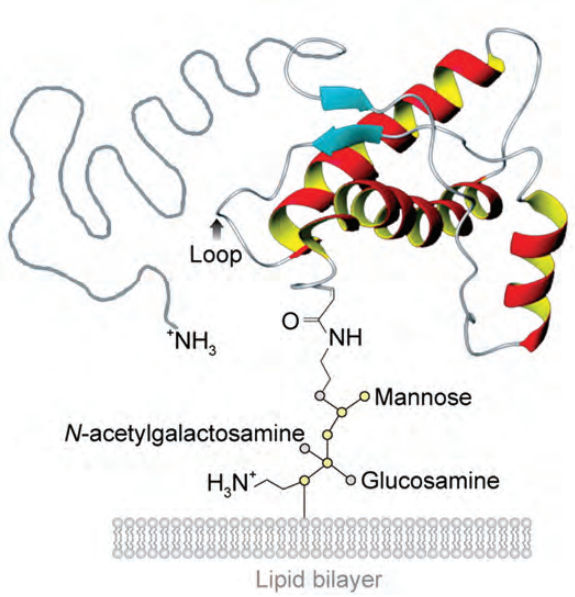

Figure 1 Structure of normally folded human prion protein High content of α-helix is shown in red, β-sheets are shown in cyan, and unstructured N-terminal is shown in gray. Glycosyl-phosphatidyl-inositol (GPI) anchor is also shown.

Besides infectious PrP^{Sc} and low pH, glycosylation of PrP protein is also critical to the prion protein's transition [37,38]. This post-translational modification appears to protect PrP^C from its transition. Zuegg *et al.* [39] performed MD simulations on the structured region of PrP (Res. 127–227) which had several glycosylation sites on Asn residues and shown in **Fig. 2(A)**. They found that glycosylation could indeed stabilize the prion protein, indirectly through reducing the mobility of the surrounding solvents. Recently, several research teams have observed that the low pH-induced PrP transition could possibly be reversible, both in experiments and MD simulations [34,40,41]. Even in the strongly acidic environment of pH = 1.7, the misfolding process could be reversed.

Progress has also been made in the polymerization mechanisms of prion proteins. In 2002, the dimerization of PrP protein was found to play a key role in the transition [42]. In the same year, through MD simulations, it was discovered that the octamer of short prion peptides could be stable enough to be an oligomerization seed [43]. In the misfolding process, consistent results were obtained that most populated intermediate states in MD simulations are partially unfolded with relatively high α-helix content [44]. And β-sheets may form between molecules, rather than from intra-molecule.

MD Simulations in AD

It was demonstrated in many recent researches that the overexpression, aggregation, and deposition of Aβ protein, which constitutes plaques in brain tissue in AD patients,

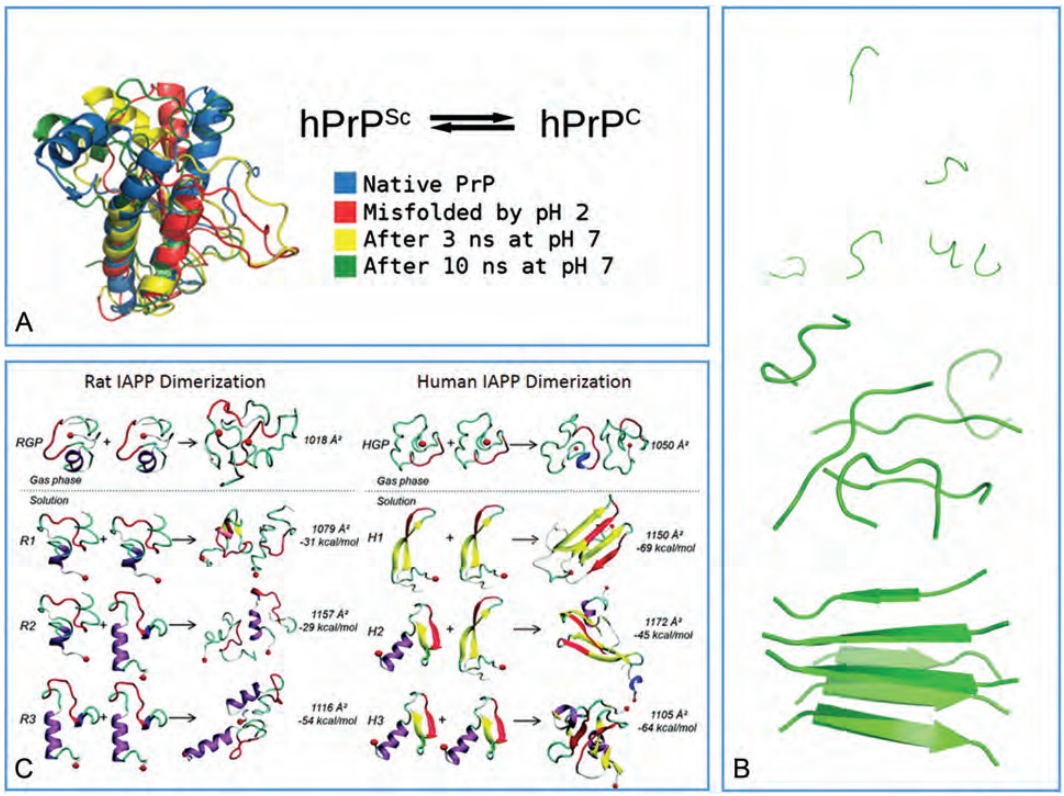

Figure 2 Applications of MD simulations on different amyloid fibrils (A) The reversibility of human PrP protein. (B) Predicted aggregating pathway of amyloid peptide GIFQINS, from unfolded monomer to intermediate 2-2 tetramer to the most stable 3-3 hexamer. (C) Secondary structure changes in the dimerization of rIAPP and hIAPP.

may be critical in the exploring of mechanism of AD and the relative drugs and therapeutics [3,45]. With the progress of solid-state NMR methods, MD simulations have contributed to protein misfolding topic. $A\beta_{40}$ and $A\beta_{42}$ are two major products of the cleavage of amyloid-β precursor protein (APP), whose original functions are important in cell adhesion, neuronal mobility, and transcriptional regulation [46,47]. The oligomerization of Aβ proteins may be the key step in the formation of amyloid fibrils. Standard MD simulations, pulling dynamics, and umbrella sampling on structured region of Aβ were performed in 2010 [48]. Buchete *et al.* [49] reported the same observation that the salt bridge between D23 and K28 stabilized the protofibrils. Furthermore, packing of I32 and aliphatic portion of K28 could in turn stabilize this salt bridge. So compounds that can interrupt these interactions might inhibit AD.

The two important types of Aβ monomers, $A\beta_{40}$ and $A\beta_{42}$ with only two amino acids different, show distinctly different conformations. Surprisingly, $A\beta_{40}$ could inhibit the aggregation of $A\beta_{42}$ [50]. Several MD simulations and NMR experiments have confirmed the importance of Met35 [51] and the hydrophobic turn located at C-terminal Gly37–Gly38 [52] in the aggregation. Also, different dynamics of the hydrophilic residues at N-terminal of $A\beta_{42}$ are critical for the oligomerization [52]. In 2005, 12 trajectories of long-time MD simulation of 12 on $A\beta_{40}$ got the consistent results [53].

In 2005, the crystal structure of amyloid-like fibril from a yeast prion-derived peptide was determined through X-ray microcrystallography [16]. This research was considered as a milestone in this field. Then a set of crystal structures from different protein precursors were also determined using the same method [54]. These atomic-resolution structures make it possible to investigate the common characters of amyloid formation by atomic MD methods, and directly compared with the experimental results. Chen *et al.* [55] have done a set of works on the mechanism of amyloid-like fibrils oligomerization using MD simulations. In 2008, cross-β Gly-Asn-Asn-Gln-Gln-Asn-Tyr (GNNQQNY) peptide in yeast protein Sup35, which could be converted to PrP^{Sc}-like fibrils, was carried out to simulate at several different temperatures. The tetramer of this peptide was found to be the probable transition state (TS) in the aggregation from the disaggregation landscape. 2-2 and 3-1 arrangements were found to be dominant in the TS. In 2009, several other Aβ relative peptide oligomers with modeled structures were further simulated and studied. For the Gly-Ile-Phe-Gln-Ile-Asn-Ser (GIFQINS) peptide, its dissolution is thermodynamically more difficult than aggregation. And the hexamer of GIFQINS is highly stable.

Furthermore, the intermediate of 2-2 tetramer and two TSs of 2-1 trimer and 3-2 pentamer were discovered through high-temperature MD simulations [56]. Aggregating pathway for GIFQINS was shown in **Fig. 2(B)**. Chen *et al.* [57] and Ye *et al.* [58] performed MD simulations on the stability of amyloid-like oligomer peptides. Among eight peptides from five classes [54], short peptides MVGGVV-1 and VEALYL were observed to be the most stable ones. Hydrophobic interactions play key roles in the oligomers stabilization. M1 and V2 in MVGGVV-1 and V1, L4 and Y5 in VEALYL are key residues. For MVGGVV-1, intermediate states may be 3-0 trimer and 2-2 tetramer. For VEALYL, 3-0 trimer and 3-2 pentamer may constitute the intermediate states.

MD Simulations in Other Diseases

Islet amyloid polypeptide (IAPP) has been identified as the primary component of the deposits in and around pancreas islet β-cells in type II diabetes [4]. Through MD simulations on core peptide of IAPP, Asn-Phe-Gly-Ala-Ile-Leu (NFGAIL), the fiber organization was confirmed to be sequence dependent and the inter-sheet hydrophobic and aromatic interactions are dominant [59,60]. This may be common in many other amyloid proteins aggregations. NFGAIL has also been used in further researches. Colombo *et al.* [61] demonstrated a core-recognition motif in the aggregation of IAPP. Before the formation of the whole cluster, the peptides would form a locally parallel alignment stabilized by inter-molecular aromatic interactions. This was consistent with findings of the previous work [59]. Further MD simulations were performed on 37-mer peptides of amyloidogenic human IAPP (hIAPP) and non-amyloidogenic rat IAPP (rIAPP) which is different from hIAPP by six residues [62] [**Fig. 2(C)**]. Besides inter-molecular interactions stabilizing hIAPP dimers, it was also observed that β-strand can recruit helix or coil in dimerization. These MD simulations could provide better understanding on the mechanism of type II diabetes.

PD is one of the most widespread progressive neurodegenerative diseases. Lewy bodies (LBs) in substantia nigra pars compacta, which consist of aggregated α-synuclein proteins, are considered as the main pathogenic signs in PD [5,12,63]. α-Synuclein is disordered in solution, but on lipid membrane it adopts conformation of partial α-helix. Transition from its normal conformation to β-sheet amyloid aggregations is the key to the understanding of PD mechanisms. Copper ions binding may trigger the aggregations of α-synuclein [64,65], and mutations of A30P and A53T were found to accelerate the aggregation of α-synuclein [66,67]. In recent years, several investigations on the aggregations of wild-type and mutant α-synuclein have been conducted. Comparison between A53T mutant and wild-type α-synuclein through NMR and MD simulations showed that the mutant α-synuclein had higher hydration level, leading to more favor on protein–protein interactions [68]. This difference disappeared in amyloid state, suggesting the independence between polymer and monomer. It was also found that both wild-type and mutant α-synucleins kept their global conformations during nanosecond timescale of the simulation; while A30P mutant of α-synuclein was found to have a transient change near the mutation site to form a kink-like conformation, which would influence the self-assembly of α-synuclein [69].

MD Simulations in Developing Amyloid Fibrils Inhibitors

The therapeutics of amyloid fibril-related diseases is another hot issue, especially on the aggregation inhibitors of Alzheimer's Aβ proteins. MD simulations could be used to explain the structure–affinity relationship [70]. MD simulation can be started from either cocrystallized structure of the receptor and ligand, or from drug candidates docking results at the binding site. In their docking results, Tell *et al.* [71] could have the explanation of the high activity of drug candidate 4f in the serie of 1-aza-9-oxafluorenes as an inhibitor of AD relative kinases. To study the binding mode of the novel inhibitor, MD simulations on Aβ protein with and without drug bindings were performed [72]. There are critical hydrophobic interactions between drug and Aβ protein. C-terminal fragments (CTFs) of Aβ protein were found to inhibit the Aβ toxicity. Discrete MD simulations were performed on Aβ protein in the absence and presence of CTFs [73]. CTFs decreased the β-sheet content and reduced the solvent accessibility in D1-R5, which could also explain the higher toxicity level of $A\beta_{42}$ than that of $A\beta_{40}$.

Concluding Remarks

In this review, a number of MD simulation cases were discussed, providing a general view of computational research on the aggregation mechanism of amyloid fibrils. The *in silico* approach could be employed as a highly complementary and synergistic tool in researching amyloid fibril-related diseases, such as prion diseases, AD, type II diabetes, and PD, and could widen the concept of amyloid fibrils inhibitors and the therapeutics of amyloid fibril-related diseases. Although more effort is still needed in the force field improvement, MD simulations will become more and more important in addressing variety of biological questions in the future. In summary, the cooperation between experimentalists and theorists should be very productive in scientific researches.

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