Available online at www.sciencedirect.com

ScienceDirect

Physics Procedia 68 (2015) 61 – 68

Physics Procedia

28th Annual CSP Workshop on "Recent Developments in Computer Simulation Studies in Condensed Matter Physics", CSP 2015

All-atom simulation of amyloid aggregates

Workalemahu M. Berhanu, Erik J. Alred, Nathan A Bernhardt, and Ulrich H. E. Hansmann*

Department of Chemistry & Biochemistry, University of Oklahoma, Norman, Oklahoma 73019, United States

Abstract

Molecular simulations are now commonly used to complement experiments in the investigation of amyloid formation and their role in human diseases. While various simulations based on enhanced sampling techniques are used in amyloid formation simulations, this article will focus on those using standard atomistic simulations to evaluate the stability of fibril models. Such studies explore the limitations that arise from the choice of force field or polymorphism; and explore the stability of *in vivo* and *in vitro* forms of Aβ fibril aggregates, and the role of heterologous seeding as a link between different amyloid diseases.

Peer-review under responsibility of The Organizing Committee of CSP 2015 Conference

Keywords: molecular dynamics, amyloid, cross seeding, heterologous seeding, oligomer and polymorphism

Introduction

Peptides in the amyloid state are (**Figure 1**) highly ordered structures stabilized by networks of hydrogen bonds between β-strands within a single β-sheet (intra-sheet) and cross-β-sheet packing (steric zipper-like interactions) of extended intermolecular β-sheets into multi-sheet proto-filaments (inter-sheet) (Knowles et al., 2014). Deposits of amyloids are associated with a growing number of human diseases, possibly caused by toxic

* Corresponding author. Tel.: +1 405-325-2386; fax: +1 405-325-6111

E-mail address: uhansmann@ou.edu

Peer-review under responsibility of The Organizing Committee of CSP 2015 Conference
doi:10.1016/j.phpro.2015.07.110

aggregates that are thought to be not the final fibril themselves but transient pre-fibril oligomer species. These oligomers are believed to damage cells by disruption of cell membranes and/or through dislocation of other proteins in the cell membrane (Knowles et al., 2014). Hence, characterization of the mechanisms by which amyloids form and become toxic may allow for design of small molecules which can disrupt these processes, potentially leading to new drug candidates (Baral et al., 2014). Molecular dynamics simulations starting from or guided by experiments are a way to extrapolate possible conformations of molecular systems and the different paths between them, thereby complementing experiments in probing protein folding, aggregation; and such predictions can guide further experiments (Shea and Urbanc, 2012).

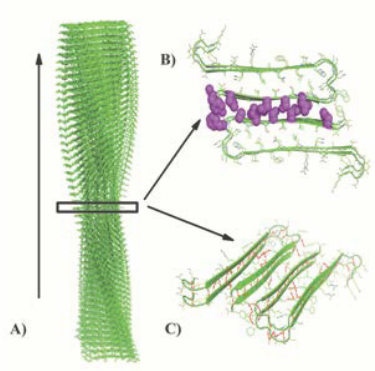

Figure 1 Amyloid structure. A) Structural model of amyloid fiber. B) Side chain steric zipper interaction (magenta) of adjacent β-sheets. C) Strong backbone interaction (backbone hydrogen bonds shown in red dots).

A number of enhanced sampling methods have been reported for atomistic simulations of the early stages of aggregation, and have been reviewed previously (Straub and Thirumalai, 2010), (Straub and Thirumalai, 2011). These methods enhance sampling of conformations but cannot provide a realistic path of folding and aggregation (Berhanu and Hansmann, 2014a). Coarse-grained simulations have been utilized to gain insight into the crucial intermediate steps between small oligomers and mature fibrils, and were recently reviewed by the Shea group (Morriss-Andrews and Shea, 2014). This article focuses on computational stability studies of given fibril structures (derived from experimental data). They are based on the notion that when during a sufficiently long simulation model aggregates do not dissociate, they can be considered stable (Berhanu and Hansmann, 2014a), (Berhanu and Hansmann, 2012b). Even though amyloid assembly is not probed directly in such studies, indirectly factors can be identified which add to or moderate fibril formation (Berhanu and Hansmann, 2014a). We will show that such simulations can both explain and guide experimental findings (Shea and Urbanc, 2012). In the following, we will describe some of our recent findings.

2. Force field choice for simulation of preformed oligomer

The choice of force field is critical in a molecular dynamics including that for the formed amyloid fibrils (Berhanu and Hansmann, 2012a). A comparative simulation of Aβ16–22 aggregates using frequently used force fields, showed that two recent versions of AMBER force fields have consistently smaller root mean square deviations to the initial configuration (Berhanu and Hansmann, 2012a). While the force field-induced bias becomes smaller as the size of the aggregates increases, suggesting that the selection of a force field becomes less of a problem with increasing size of the system, there is a need for carefully choosing an acceptable force field in simulations of amyloids. This has been also recognized in other simulations. For instance, Nguyen *et al* (Nguyen et al., 2011) noted the force field dependence of oligomer formation of Aβ.

3. Amyloid polymorphism

Understanding oligomer formation is critical for rational design of therapeutics; however, usually there is not a single structure for such aggregates but polymorphism controlled by the physicochemical environment. This polymorphism could be fibril variability through simple side-chain rotations or segmental polymorphism (Wiltzius