CHAPTER 1

MOTIVATION & OUTLINE OF THE THESIS

Motivation & outline of the thesis

1.1. Motivation of the present work:

Alzheimer's disease (AD) is the most common form of progressive irreversible dementia, affecting large numbers of elderly worldwide [1-3]. It is caused by brain cell death wherein the total brain size shrinks leading to tissues with fewer nerve cells and connections. The accumulation of Aβ peptides [4, 5] in the brain produces plaques that are the pathological hallmarks of the AD. Just as plaques in arteries can harm the heart, plaques on the brain have alarming consequences for brain function.

According to the Alzheimer's Association, AD most commonly affects people at the age of 65 years and above. However, recently it has been reported that people in their late 30s or 40s have also been affected with AD. Worldwide, nearly 44 million people are suffering from AD and the figure may go up to131.5 million without any cure. AD and dementia are most common in Asian and Western European population and least prevalent in Sub-Saharan African population [6].

According to the National Institute on Aging till date there is no prevention to AD. Recently, it has been highlighted [7] that detecting the disease at an early stage can lead to better treatment options. One of the most important clinical trials under way at this moment involves 5,000 members of a large Colombian family who may carry an early-onset Alzheimer's gene. According to the proposed diagnostic layout three hundred family members shall receive a drug that has been shown to decrease the misfolded production of $A\beta_{1-42}$ peptides and the other half shall be administered a placebo thereby comprising the control group. The information from the proposed trial could be applied to millions of people worldwide who suffer from the more conventional, late-onset form of AD [7].

Since there are no effective treatments for AD and the only medications available are analgesic in nature, the developments of drugs that actually prevent the production of misfolded $A\beta_{1-42}$ peptides are critical. The normal function of $A\beta_{1-42}$ peptide which is generated from the sequential cleavage of the APP is not well understood [8]. Noticeable loss of physiological function has not been observed in the absence of $A\beta_{1-42}$ peptide. Some studies have reported quite a few possible activities of $A\beta_{1-42}$ peptide like activation of kinase enzymes, protection against oxidative stress and regulation of cholesterol transport [9-11].

The potential mechanism of $A\beta_{1-42}$ peptide aggregation suggests that $A\beta_{1-42}$ peptide misfolds by undergoing changes in its native secondary structures from α-helical form to random coils and β-sheet rich structures. The misfolded $A\beta_{1-42}$ peptides then aggregate to form toxic dimers and oligomers finally leading to the mature fibrils which then accumulate in the grey matter of brain as senile plaques [12, 13]. Many researches have been carried out in the past with respect to $A\beta_{1-42}$ peptide and its involvement in AD. However, the flexible, disordered and transiently dynamic nature of the insoluble $A\beta_{1-42}$ peptide raises some questions that remain unanswered. Although current Alzheimer's treatments cannot stop Alzheimer's from progressing, there is a widespread effort going on worldwide to find better ways to treat the disease, delay its onset, and prevent it from developing. Likewise, in order to design potential therapeutics and combat AD, we have used MD simulation and tools to answer some of the questions regarding the $A\beta_{1-42}$ peptide, the major risk factor of AD, which are: (i) the probable initial seed structure responsible for aberrant aggregation; (ii) driving forces that hold the monomeric units together to form intermediate aggregates and (iii) how the $A\beta_{1-42}$ peptide aggregation can be prevented in the early and later stages?

1.2. Outline of the thesis:

Chapter 2 introduces Alzheimer's disease, its diagnosis and the $A\beta_{1-42}$ peptide in details.

Chapter 3 presents the methods and the key principles of MD simulation, force field development and the principles of the other MD tools and softwares used in this thesis.

Chapter 4 features study on the structural characterization of the probable initial seed structure of $A\beta_{1-42}$ peptide that may initiate aggregation. We have charted down the development of secondary structure in $A\beta_{1-42}$ peptide right from its initial linear structure that has been built from its amino acid sequence to the formation of stable 3-D structure.

Chapter 5 presents the dimerization study of $A\beta_{17-42}$ peptide and studies to investigate the interaction profile of the monomeric units that hold together the $A\beta_{17-42}$ dimer complex. This study can be helpful in understanding the fibrillation process and

might be used to design potential therapeutics to combat the aggregation process of $A\beta_{1-42}$ peptide at its initial stage.

Chapter 6 presents cross-seeding study of $A\beta_{25-35}$ peptide with $Tau_{273-284}$ using the free energy analysis. Our results demonstrated here may be useful to design different strategies to prevent the interaction of $A\beta_{1-42}$ peptide and Tau.

Chapter 7 presents the disordered regions in $A\beta_{1-42}$ peptide predicted by disorder predictors AMYLPRED2 and DisEMBL.

Chapter 8 features interaction study of the $A\beta_{1-42}$ peptide oligomers and $A\beta_{1-42}$ fibril polymorphs that are found in the senile plaques.

Chapter 9, 10 and 11 focuses on the computational approach to design inhibitors to prevent the aggregation of $A\beta_{1-42}$ peptide at early and later stage. In order to gain insight into the mechanisms involved in inhibiting the aggregation process, ss-oligonucleotide, $A\beta_{1-40}$ an isoform of $A\beta_{1-42}$ peptide and 6-mer peptide IGLMVV were used.

The conclusions are summarized in Chapter 12.