VIET NAM NATIONAL UNIVERSITY HCMC
UNIVERSITY OF TECHNOLOGY

THE SOCIALIST REPUBLIC OF VIETNAM

INFORMATION OF DOCTORAL DISSERTATION

Name of PhD Student: **Nguyen Hoang Linh**
Title: **STUDY STRUCTURE AND PHYSICOCHEMICAL PROPERTIES OF AMYLOID BETA OLIGOMERS USING MOLECULAR DYNAMICS SIMULATIONS**
Major: Engineering physics
Major Code: 9520401
Academic year: 2018
Supervisor:

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1. SUMMARY:

Despite of many years of intensive research, little is known about cause and mechanism of Alzheimer's disease (AD). Excess accumulation of amyloid beta (Aβ) peptides and their aggregation leads to ruin the neuronal cells being the basis of an amyloid cascade hypothesis, which attempts to explain the causes of AD. Therefore, the structure of Aβ aggregations play crucial role in the knowledge about mechanism of AD. It was initially thought that fibrils were toxic, but recent experiments have shown that oligomers are more toxic. Due to intrinsically disordered character of Aβ monomers and the high aggregation rate and transient life time of Aβ oligomers, their structures are virtually impossible to solve using experimental methods. The trimer, tetramer, hexamer, and dodecamer of $A\beta_{1-42}$ have more neuronal toxicity than other aggregation forms of Aβ. The molecular dynamics method has succeeded to obtain dynamic and structural properties of monomer Aβ as well as the interaction of dimer Aβ and neuronal membrane. For this reason, we used molecular dynamics simulations to extensively search for the conformational space of $A\beta_{1-42}$ tetramer and trimer. Obtained structures were subsequently tested for stability and compared with proposed experimental fibril models. The neuronal membrane pore forming is one of the neuronal toxicities caused by oligomer Aβ. Therefore, the impact of dodecamer Aβ42 and mature fibril Aβ42 on the structural stability of neuron membrane from patients of AD is also investigated in this dissertation.

Our results show that $A\beta_{1-42}$ tetramer can form multiple stable structures with polymorphism property, which may explain different aggregation pathways of Aβ. Obtained models are composed of outer and core chains, and therefore, are significantly different than the structure of mature fibrils. The interactions with water are the reason why the tetramer Aβ42 is more compact and less dry inside than fibrils. Physicochemical properties of the proposed all-atom structures are in agreement with the available

experimental observations and theoretical expectations. Therefore, this dissertation provides possible models for further studies and design of higher order oligomers.

For $A\beta_{1-42}$ trimer, we performed extended all-atoms molecular dynamics simulations, both canonical and replica-exchange, of $A\beta_{1-42}$ trimer starting from two different initial conformations: i) the pose produced by the best docking of a monomer aside of a dimer (simulation **1**), representing oligomers freshly formed by assembling monomers; ii) a configuration extracted from an experimental mature fibril structure (simulation **2**), representing settled oligomers in equilibrium with extended fibrils. The results show that simulation **1** of $A\beta_{1-42}$ trimer populates regions consistent with small β-barrels, indicating the chance of spontaneous formation of domains resembling channel-like structures. These structural domains are alternative to those more representative of mature fibrils (simulation **2**), the latter showing a stable bundle of C-termini that is not sampled in simulation **1**. For the first time, the spontaneous existence of β-barrel structure in the results is observed from simulation works. Moreover, trimer of $A\beta_{1-42}$ can form internal pores that are large enough to be accessed by water molecules and Ca2+ ions.

The effect of $A\beta_{1-42}$ dodecamer and fibril on a multiple lipid types membrane, which is similar to that observed in AD patients, using all-atom molecular dynamics simulations. Due to short simulation times, the formation of pores is not observed but, useful insight on the early events of this process has been obtained. Namely, we showed that dodecamer distorts the lipid membrane to a greater extent than fibril, which may indicate that ion channels can be more easily formed in the presence of oligomers. Based on this result we anticipate that oligomers are more toxic than mature fibrils, as observed experimentally. Moreover, the Aβ- membrane interaction was found to be governed by the repulsive electrostatic interaction between Aβ and ganglioside GM1 lipid. We calculated the bending and compressibility modulus of the membrane in the absence of Aβ and obtained good agreement with experiment. We predict that the $A\beta_{1-42}$ dodecamer will increase the compressibility modulus, but has little effect on the bending modulus. Due to the weak interaction with the membrane, $A\beta_{1-42}$ mature fibrils insignificantly change the membrane elastic properties.

The results for $A\beta_{1-42}$ tetramer, trimer and dodecamer indicate that the used simulation methods are reasonable to study the structure and interaction between $A\beta_{1-42}$ oligomer and neuronal membrane. These oligomers are disordered which is consistent with experimental data. Based on physicochemical properties of $A\beta_{1-42}$ tetramer and trimer, the author proposed a hypothesis about the structural difference between oligomer and mature fibril. Although the interaction between $A\beta_{1-42}$ dodecamer, fibril and membrane is captured at the early events, but the molecular mechanism shed some lights on the role of neural toxicity of oligomerization.

1. NOVELTY OF DISSERTATION:

In this dissertation, we obtain the following new results:

- Obtained 3 dimensions structures of Aβ42 tetramer using multiscale simulations. The structures can be used in future works to generate higher order Aβ42 oligomers

or design potential compounds inhibiting amyloid beta assembly. Furthermore, the reason why structure of Aβ42 oligomer is different from mature fibril is answered using simple model.

- Obtained 3 dimensions structures of Aβ42 trimer using all-atoms molecular dynamics simulations. For the first time, we obtained the Aβ42 trimer structures containing beta barrel using random initial configuration. The structural and physicochemical properties are also obtained from simulations.
- We shown that Aβ42 dodecamer impacts on the neuronal membrane more strongly than mature fibril at the early events of the interaction between amyloid beta aggregations and neuronal membrane.

The main results of this thesis are synthesized from 3 papers published in peer-reviewed ISI journals which is the ACS Physical Chemistry B (Q1 as scimago).

2. APPLICATIONS/ APPLICABILITY/ PERSPECTIVE

Based on the obtained results in the thesis, we would like to propose the following potential research directions:

- Using multiscale simulation protocol for high order of Aβ42 oligomers;
- Simulate Aβ42 oligomer in different environments;
- Elongate simulation time for interaction between Aβ42 oligomer and neuronal membrane.

Scientific Advisors		**PhD student**
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