Molecular Dynamics Simulation of Amyloid Beta in Alzheimer's Disease

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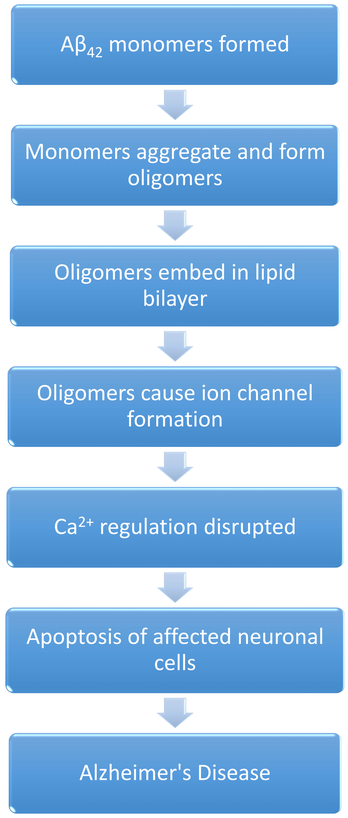
Background

- ❑ Amyloid beta (Aβ) peptides are formed by improper cleavage[1]
  - Most toxic form is 42 amino acids
  - Plaques are a hallmark of Alzheimer's Disease, but oligomers cause disease and progression

Ion Channel Hypothesis of Alzheimer's Disease[2]

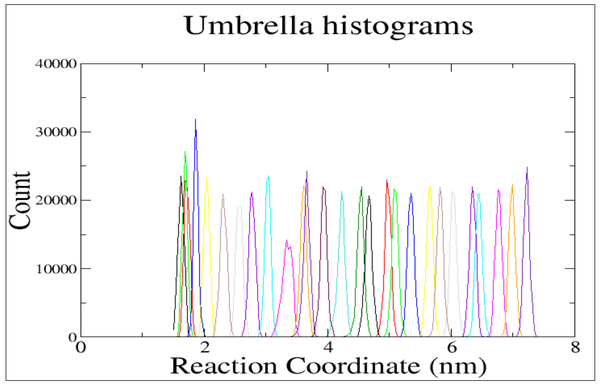


Introduction

- ❑ Modeling the neuronal membrane and $A\beta_{42}$ oligomers
- ❑ Simulating pore formation in the membrane
- ❑ Replicate results found by Xiang, et al.[3]
- ❑ Run additional simulations
- ❑ Find binding energies

Methods

- ❑ Utilize CHARMM-GUI membrane builder
  - Model the membrane
  - Implant oligomer
- ❑ Run simulation using GROMACS
- ❑ Visualize using VMD
- ❑ Use umbrella sampling
  - Pulling simulation now frames
  - Individual simulations for frames



Simulation

- ❑ Pulls $A\beta_{42}$ oligomer away from the center of the mass of the membrane
- ❑ Force generated using a spring with a constant of 1000$\frac{kJ}{mol*nm^2}$
- ❑ Spring expanded at a constant rate 0.01 $\frac{nm}{ps}$

Simulation Components

- ❑ $A\beta_{42}$
  - PDB: 2MXU[4]
    - Homo-oligomer
    - Colored regions are amino acids
- ❑ Membrane
  - POPC[3]
    - Not showing lipid tails
    - Red is O, blue is N, gold is P
- ❑ Solution
  - 0.15M KCl[3]
    - Water shown as blue points
    - KCl ions not shown

Results

Figure 1

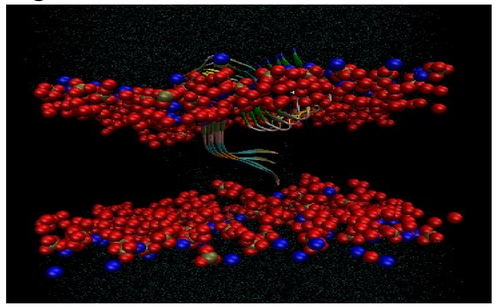


Figure 2

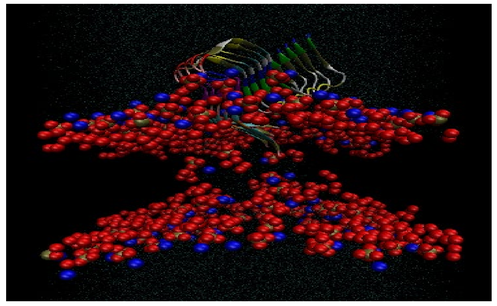


Figure 3

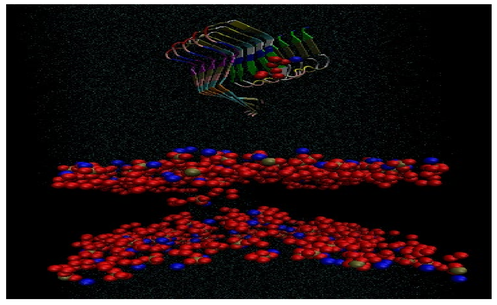
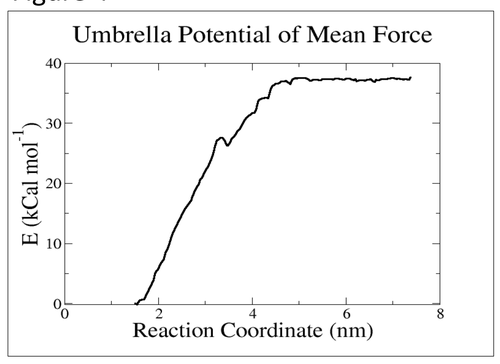


Figure 4



Conclusions

- ➢ 2MXU caused deformation in all configurations
  - Largest deformation with amine terminus inside membrane, shown progressing from fig. 1 – fig. 3
- ➢ Binding energy of 2MXU to membrane, ΔG_{bind} in fig. 4
  - $\Delta G_{bind} = 37.3 \pm 0.2 \frac{kCal}{mol}$

Future Work

- ➢ Literature search on binding energies of $A\beta_{42}$
- ➢ Apply umbrella sampling to all $A\beta_{42}$ configurations that have completed the pulling simulation

References

1. Pearson, H. A., & Peers, C. (2006). Physiological roles for amyloid beta peptides. The Journal of physiology, 575(Pt 1), 5–10. doi:10.1113/jphysiol.2006.111203
2. Shirwany, N. A., Payette, D., Xie, J., & Guo, Q. (2007). The amyloid beta ion channel hypothesis of Alzheimer's disease. Neuropsychiatric disease and treatment, 3(5), 597–612.
3. Xiang, N., Lyu, Y., Zhu, X., & Narsimhan, G. (2018). *PCCP*, **20**(10), 6817-6829.
4. Xiao, Y., et al. (2015). *Nat. Struct. Mol. Biology.*, **22**(6), 499-505.

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