The Effects of Hyper-phosphorylated Tau Proteins Through the Blood Brain Barrier Using Molecular Dynamics Simulations

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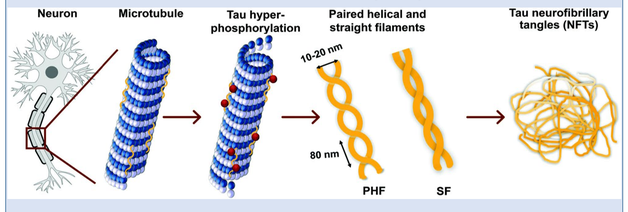
Introduction

- ❑ Purpose of Tau Proteins
  - Binds and stabilize microtubules
  - Commonly found in neurons
- ❑ Purpose of the Blood Brain Barrier (BBB)
  - The BBB is a highly selective semipermeable border that separates the circulating blood from the brain and extracellular fluid in the central nervous system (CNS).

Tau hypothesis of Alzheimer's Disease (AD)

Excessive or abnormal phosphorylation of tau results in the transformation of normal adult Tau proteins into paired helical filaments and neurofibrillary tangles(NFTs). In (AD), at least 19 amino acids are phosphorylated. All six tau isoforms are present in an hyper phosphorylated state in paired helical filaments in (AD).



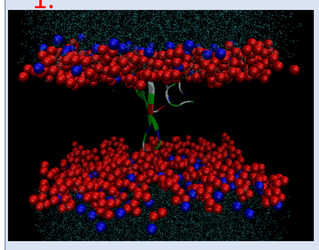
Method

- ❑ Produce Initial Structure
  - **CHARMM** membrane builder
- ❑ Equilibrate
  - Get to correct temperature and pressure
- ❑ Umbrella Sampling
  - Pull Tau Protein out of membrane in steps
  - Run simulation at each step

Configuration Used

- ❑ DOPC Membrane
- ❑ Tau 2N4R & Hyper-phosphorylated 2N4R
- ❑ Configurations
  1. Tau 2N4R in Membrane
  2. Tau 2N4R in pulled out of membrane
  3. Hyper-phosphorylated Tau 2N4R in Membrane
  4. Hyper-phosphorylated 2N4R pulled out of Membrane

1.



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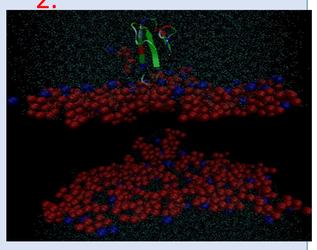

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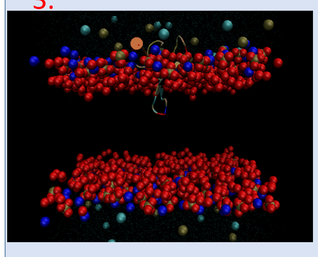

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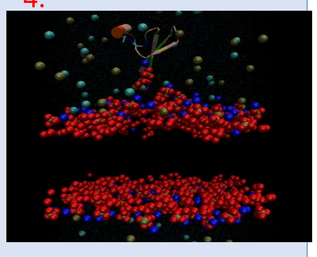


Understanding the Simulation

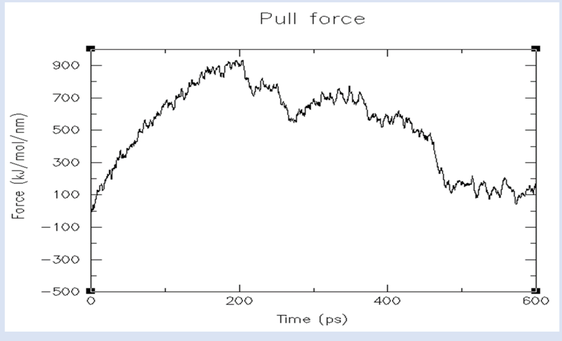
- ❑ Protein color:
  - Green polar, white non polar, blue basic, red acidic
- ❑ Lipid biliary color:
  - Red is oxygen, blue is nitrogen
- ❑ Water Molecules:
  - Transparent light blue
- ❑ phosphorylation:
  - Orange on protein

Pulling Simulation

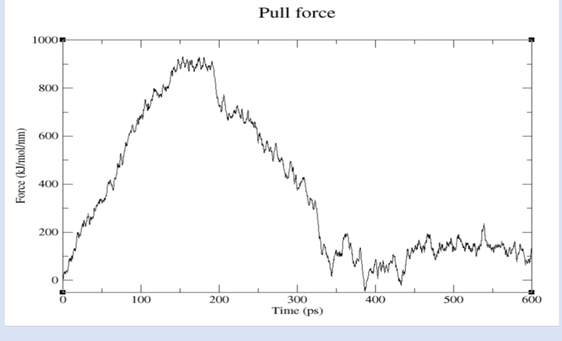
- ❑ Pull Tau away from the center of mass of membrane
  - Distance between center of mass of membrane and Tau used for measurements
  - Imaginary spring with spring constant 1000$\frac{kJ}{mol*nm^2}$
    - ❖ Expanded at constant rate 0.01 $\frac{nm}{ps}$
    - ❖ Pulls protein away from membrane
- ❑ Equilibrate at each step as pulling progresses and protects the system

Results

Tau 2N4R



Hyper-phosphorylated Tau 2N4R



Conclusion

- ➢ The simulations confirm that the Hyper-phosphorylated Isoform Tau 2N4R moves through the Blood Brain Barrier easier than less phosphorylated 2N4R.
- ➢ Our data supports the idea that excess Tau levels within spinal fluid could potentially be used as a bio marker for the degradation of the Blood Brain Barrier as well as the early stages of Alzheimer's Disease.

References

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