Simulating the Spread of Misfolded Tau Proteins in a Three-Dimensional Model of the Brain

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Introduction

Tau Proteins

- Tau proteins, or tubulin associated units, are proteins in the central nervous system that **stabilize microtubules**
- When these proteins **hyperphosphorylate** and misfold, they detach from microtubules and slowly aggregate into **neurotoxic neurofibrillary tangles (NFTs)**
- The widespread and rapid accumulation of NFTs are **heavily implicated** in neurodegenerative diseases such as Alzheimer's Disease and Chronic Traumatic Encephalopathy (CTE)

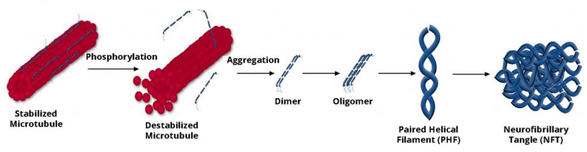

Figure 1. Evolution of misfolded tau[5]

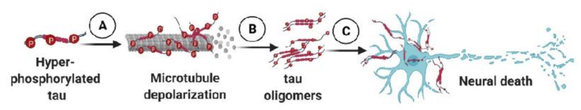

Figure 2. Effect of misfolded tau on neurons[3]

Spread

- Misfolded tau proteins spread through neuronal connections to different regions of the brain depending on the disease
- In Alzheimer's, tau spreads from neuron to neuron in a **prion-like way**, with factors like neuron activity affecting the pattern of spread
  - Tau accumulation typically starts in the transentorhinal and entorhinal cortices, before spreading to the hippocampus
- In CTE, tau clusters clump around blood vessels near injury sites, leading to inflammation
  - Tau **preferentially aggregates** in perivascular spaces

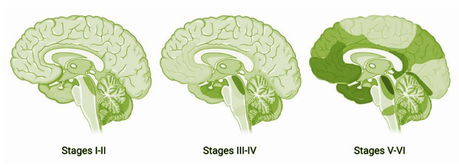

Figure 3. Proliferation of tau throughout different stages of Alzheimer's Disease[6]

Visualization

- Simplified mathematical models of misfolded tau spread exist but are specific to localized regions
- It is possible to visualize tau in individuals patients *in vivo* using PET scans, but this technology is still **new, expensive, and not widely accessible**
- For neurodegenerative diseases such as CTE, proper **diagnosis can only be made postmortem**
- Our goal is to create a **new 3D Visualization** of the spread of misfolded tau across the entire brain

Results

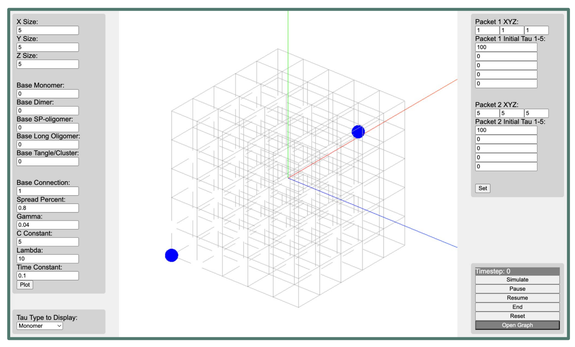

Figure 6. Initial 3D Visualization of concentration of misfolded tau monomers in a 5 x 5 x 5 grid, at (1, 1, 1) and (5, 5, 5) with example parameter inputs and associated GUI

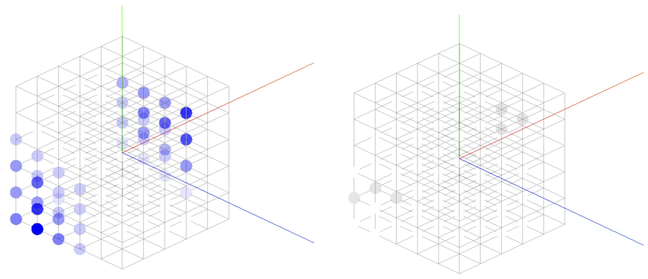

*Figure 7. Concentration after 5 timesteps of the simulation. Tau monomers are beginning to spread while **tangles** are just starting to form*

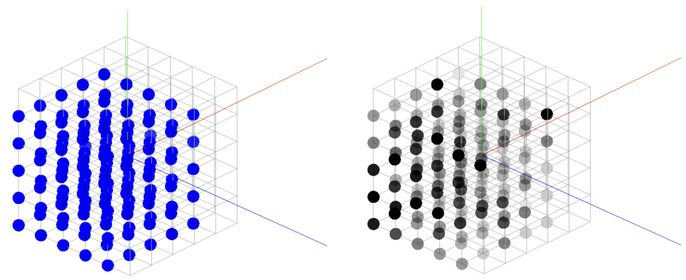

*Figure 8. Concentration after 20 timesteps of the simulation. Tau monomers are fully concentrated while **tangles** are forming*

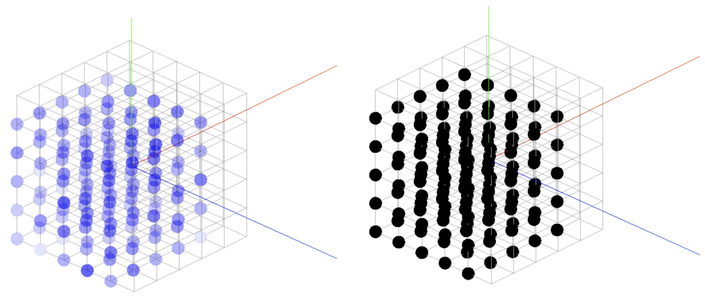

*Figure 9. Concentration after 40 timesteps. Tau monomers are fading while **tangles** are growing increasingly more concentrated*

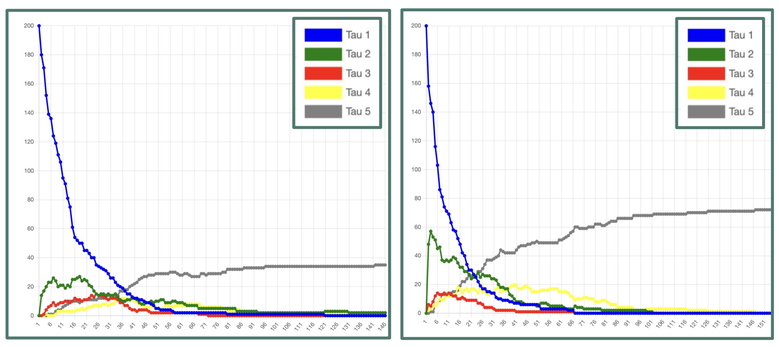

Figure 10. Misfolded tau concentration vs time graph, accounting for different axon connection strengths (0.4 and 0.8 respectively).

Discussion

Conclusions

- Our 3D model **accurately displays** the patterns in the canonical spread of tau throughout the brain
  - The square root shape of our tau 5 curve (*Figure 10*) **matches previous data** examining the progression of tau in neurodegenerative diseases, indicating we made a roughly accurate model
- Through simulations of all five forms of tau, the graphs (*Figure 10*) suggest that **a stronger axonal connection leads to higher concentration** of tau over time
  - This indicates that misfolded tau proteins will proliferate and aggregate more in highly interconnected areas of the brain
- In our simulations of multiple injuries—injections of tau concentrations into specific neuron packets—we observed that a **closer proximity of tau packets increases the concentration of tau aggregates within a localized region**
  - This suggests that multiple traumatic head injuries, which are known to lead to CTE, in close proximity increase one's risk for brain atrophy within a given region

Limitations

- We did not account for tau production induced by amyloid-beta, as this varies in different neurodegenerative diseases
- The mathematical model that we based our visualization off of does not account for extracellular tau proteins
- We assumed **homogeneity of neurons** within and across neural packages
- Our model does not represent the spread of tau with a rate relative to an accurate period of time
- Our model does not account for disease specific patterns, such as tau isoforms or genetic factors in Alzheimer's Disease

Application

- Although our model is preliminary, we intend to publish our visualization online with the hope that scientists can apply it to future research in medicine
- By cross-examining the expected diffusion of tau with real neurodegenerative patterns, scientists can reach a greater understanding of the relationship between **tau proliferation and brain atrophy**
- Analyzing spread patterns can help with the development of **targeted medicines**
- Determining factors that most contribute to the spread of misfolded tau can aid with **identifying at-risk patients** for neurodegenerative diseases

Methods

- Adapted a series of three partial differential equations[1] based off the Smoluchowski equations
  - Categorizes the spread of tau into **5 sections**: monomers, dimers, short proto-oligomers, long oligomers, and plaques/tangles
- Combined with a modified Fisher-Kolmogorov model[2]
  - Models circulation of tau throughout the brain

$$\frac{\partial \tau_1(x_m,t)}{\partial t} = \underbrace{-d_1 \tilde{\Delta}_G \tau_1(x_m,t)}_{\text{diffusion}} \underbrace{-\gamma \tau_1(x_m,t) \sum_{j=1}^{5} \tau_j(x_m,t)}_{\text{aggregation}}$$

$$\underbrace{+cs_\tau(x_m,t)}_{\text{production}} + \underbrace{C_\tau\left(\sum_{i=2}^{4} u_i(x_m,t) - \bar{U}\right)^+}_{\text{production induced by A}\beta}$$

Figure 4. Original equation used for tau monomer

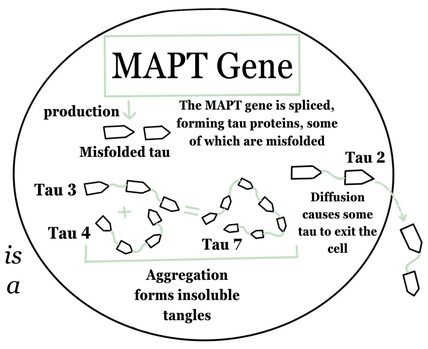

Figure 5. Diagram depicting how tau diffuses, aggregates, and is produced within a singular cell

- Translated this mathematical model into Python to **model the diffusion, aggregation, and production** of misfolded tau proteins
- Connected the Python code to an online server that communicates with our JavaScript code
  - JavaScript code outputs **real-time** 3D visualization of the spread of tau
- Simulated model to observe the effect of different factors
  - Modified parameters, such as initial tau concentration, size, and connection strength, and graphed results to examine the effect on the spread of tau

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