Modeling Associative Memory Deficits in Alzheimer's Disease with NFT-Induced Synaptic Degradation Using an Asymmetric Hopfield Network

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Introduction

- **Neural networks**, inspired by the brain, consist of interconnected nodes analogous to the biological neuron
- Many neurological process such as dementia can be modeled by neural networks
- **Alzheimer's disease (AD)**, the most prevalent form of dementia, is characterized by **neurodegeneration** and impaired **associative memory** in the presence of excess neurotoxic β-amyloid plaques and **tau neurofibrillary tangles (NFTs)** (Fig. 1.)

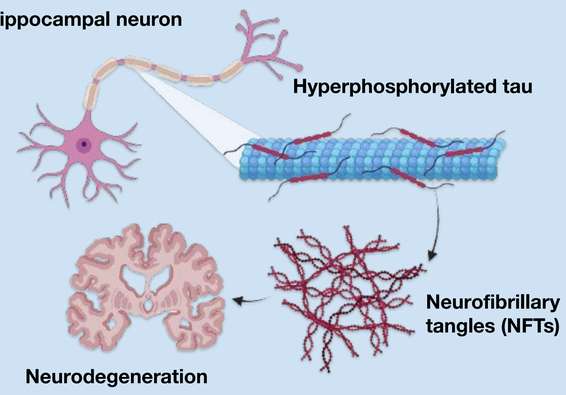
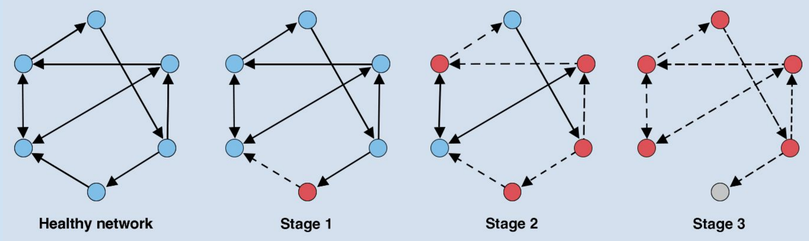


Fig. 1. NFT-induced neurodegeneration

- Existing neural network models have attempted to simulate the deterioration of associative memory in AD yet fall short in incorporating biologically accurate algorithms for neurodegeneration and neural pathways
- To address this gap, we aim to develop a modified, **asymmetric Hopfield network** that is more biologically plausible than other neural network models of AD
- Our network aims to simulate NFT-induced synaptic degradation while maintaining the pattern recognition properties of a traditional Hopfield network

Methods



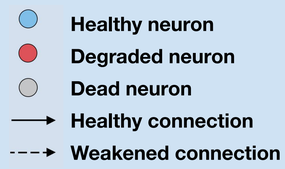


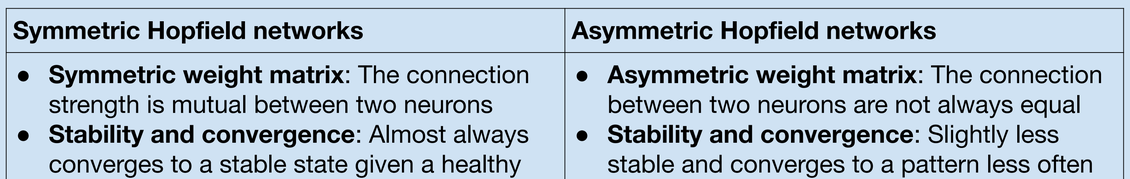
Fig. 2. Synaptic degradation in an asymmetric Hopfield network

- We employ a modified **asymmetric Hopfield network** to model AD
- A **Hopfield network** is a recurrent neural network that functions as an associative memory model

Symmetric Hopfield networks	Asymmetric Hopfield networks
• **Symmetric weight matrix**: The connection strength is mutual between two neurons • **Stability and convergence**: Almost always converges to a stable state given a healthy network • **Less biologically feasible**: Oversimplification of synaptic connections and memory	• **Asymmetric weight matrix**: The connection between two neurons are not always equal • **Stability and convergence**: Slightly less stable and converges to a pattern less often • **More biologically feasible**: Many synaptic connections are asymmetric (i. e. the influence from one neuron to another is not necessarily equal in both directions)

Designing Our Model

- Our model was developed in VS Code using Python with NumPy, Matplotlib, and PIL
- Our network simulates **neurofibrillary tangles (NFT)-induced synaptic degradation** while maintaining the pattern recognition properties of an **asymmetric Hopfield network**
- To simulate the progression of AD, we increased the number of nodes affected by NFT
  - Research indicates that affected neurons release NFT which can be taken up by other neurons
  - Propagation is dependant on how damaged a neuron is (i. e. the more tangles within the system, the more likely it is to propagate)
  - Our propagation threshold was chosen based on informed speculation
  - Propagation of NFT increases at an exponential rate
- We modeled how synapse strength changes as a function of time post-NFT infliction
  - $S_{Synapse} = 1 - (\frac{t}{6})^2$
  - Where t represents how many years have progressed since initial NFT affliction
  - The time it takes for moderate to severe memory recall deficits to appear is roughly 8-10 years after onset of AD[1]
  - Based on this, the model assumes that a neuron will be completely dead within 6 years of propagation
- Our model roughly aligns with the timeline of AD attributing for propagation and deterioration



Simulating Associative Memory Deterioration

- We initially encoded 3 binary $(-1, 1)$ patterns into our Hopfield network
- We assessed our Hopfield network's ability to recall these original patterns by presenting similar stimuli and observing if the network is able to converge back to the original pattern
- To emulate the progression of AD, we initiated the accumulation of NFTs and reevaluated recall ability over time, representative of different stages of AD (Fig. 2.)

References

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Results

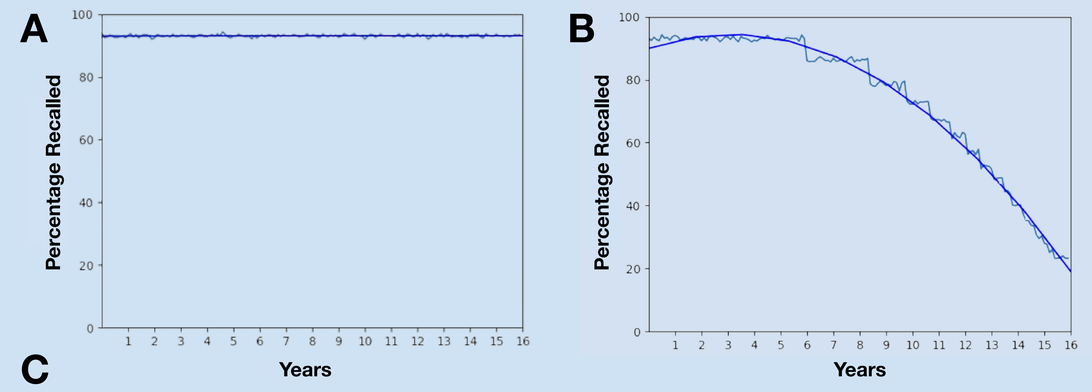

Fig. 3. Visualization of associative memory deficits

(A) Healthy Hopfield network has constant average percent recall of ~93% (100 iterations with 5 samples per year); Line fitted to data

(B) AD Hopfield network displays progressive decline in average percent recall over time (100 iterations with 5 samples per year); Curve fitted to data

(C) Representation of associative memory deficits and neuron health in AD network trained with 3 distinct patterns

- In a healthy network, the average percentage recall is consistent over time (Fig. 3A)
- However, in an AD network, the average percentage recall declines exponentially over time with the accumulation of NFTs (Fig. 3B)
  - The fitted curve ($-.45548x^2 + 2.86022x + 89.92901$) is plotted
  - It is notable that during the early years (1-5 years) of NFT-induced synaptic degradation, the average percentage recall is comparable to that of the healthy network
  - Time is necessary for NFTs to degrade synapses and accumulate within the network
- Our AD network successfully models associative memory deficits via NFT-induced synaptic degradation (Fig. 3C)

Discussion

Model Limitations

- **Quantity of neurons and memories**
  - Our Hopfield network used merely 256 nodes to represent the neurons involved in a multitude of memories
  - The recollection of memories in the human brain requires thousands to millions of neurons
- **Limitations in NFT-induced synaptic degradation**
  - We developed a simple exponential decay equation to represent the rate of NFT-induced synaptic degradation based on our understanding of tauopathy
  - While based on scientific observation, the equation created is merely speculation: It is subject to change as new data emerges
  - NFT is not the only factor that contributes to synapse degradation
- **Randomized asymmetry**
  - To make our Hopfield network more biologically feasible, we assigned random weights to 0; however, overdoing this resulted in the destabilization of the network's recall ability
  - The asymmetry of our model is very limited and not akin to the complexity of the human brain

Applications

- **Development of treatments**
  - Our network can serve as a platform to test potential treatments for AD by simulating different stages of neurodegeneration and observing the effects of NFT-targeted interventions on memory recall and synaptic strength
- **Educational tool**
  - Our network serves as a simplified multi-scale model of the AD, NFT-induced synaptic degradation, and associative memory decline that can be used by students

Future Directions

- We could enhance biological accuracy by scaling and integrating our modified Hopfield network with other AD models
- Synaptic degradation is a complex process, so including additional neurotoxic factors such as β-amyloid aggregation and inflammation would strengthen our model

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