Interaction of Alpha Beta and Tau Proteins in the Brain

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1 Introduction

1.1 Motivation

Alzheimer's disease is a neurodegenerative disease that affects 5 million Americans and 44 million people worldwide. The disease currently has no cure or treatment. Alzheimer's typically starts with difficulty with memory and recognition of faces. Eventually, motor functions and spacial orientation begin to degrade and as progression furthers bodily functions are lost; leading to death. Moreover, it can be economically and emotionally straining for families and caregivers, costing over a trillion dollars every year in healthcare and support costs. It is also the seventh leading cause of death worldwide. There has been extensive research on the how Alzheimer's effects patients, but its growth and progression is still not well understood. By modeling the spread of Amyloid-Beta and Tau proteins (2 proteins thought to cause Alzhgeimer's) we may be able to get a better understanding of how this disease spreads in the human brain, and potentially how to curb its development.

1.2 Background

Since the development of Alzheimer's is not well understood, we wanted to model how the disease can spread between parts of the brain. We decided to focus on two proteins in the brain, that through research, have been shown to affect neuro-degenerative diseases. These two proteins are Amyloid-Beta and Tau.

The Amyloid-Beta protein is a peptide that groups together to form plaques outside neurons in the brain. These plaques make it hard for the neurons to send signals; triggering inflammation and leading to dysfunction and the death of neurons. This impairs memory and cognitive abilities as well. Because neurons are responsible for sending signals across the body and the brain, neuron death and dysfunction lead to improper communication which can cause memory loss and inconsistencies in behavior.

The Tau protein is a microtubule-associated protein that stabilizes a neuron's microtubules , intracellular structures that are essential for neuronal structure and transport of nutrients and other cellular components. In Alzheimer's disease, tau proteins group together and tangle within neurons. These tangles alter the neurons' function, which leads to additional miscommunication and cell death.

The interaction between A_β and Tau is complex and not yet fully understood. It is hypothesized that the deposition of A_β plaques may facilitate Tau pathology, creating a detrimental cycle that accelerates neuronal damage. This relationship is central to many current research studies aiming to elucidate the mechanisms of AD and find potential targets for intervention (Puri and Li, 2010)

Modeling Focus: Given the complexity of the brain and the multifaceted nature of AD, our model aims to simulate the spread and interaction of A_β and Tau within a simplified network of brain regions. This approach allows us to study the dynamics of these proteins under controlled conditions, potentially revealing insights into their pathogenic roles and interactions across different parts of the brain.

To construct our mathematical model of potential Alzheimer's disease progression, we base our simulations on several key assumptions. These assumptions are necessary to reduce the complexity of the biological processes involved, allowing us to focus on the core dynamics of Amyloid-Beta (A_β) and Tau interactions and their impact on neuronal health and function.

2 Assumptions

1. **Beta-amyloid accumulation triggers Tau pathology:** This assumption is supported by a wealth of research suggesting that the accumulation of A_β may precede and facilitate the aggregation of Tau proteins, exemplifying the primary effects of the beta-amyloid protein in Alzheimer's disease pathogenesis. This interaction suggests a cascading effect where A_β plaques contribute directly to the formation and exacerbation of Tau tangles within neurons (Hyman etal., 2012; Jack et al., 2013).

2. **Association with inflammation and neural communication:** Both A_β and Tau pathologies are associated with the activation of microglial and astrocytic cells, which leads to a chronic inflammatory response. This inflammation is known to contribute significantly to neuronal dysfunction and degeneration. The inflammatory response not only exacerbates the existing pathology but also accelerates the progression of the disease by damaging neuronal communication and impairing cellular function (Heneka et al., 2015; Wyss-Coray, 2006).

3. **Homogeneous neuron susceptibility:** For the purposes of simplification, we assume that all neurons have an equal susceptibility to A_β and Tau pathology. This assumption disregards potential regional variations in neuronal vulnerability, which are often observed in more detailed pathological studies of Alzheimer's disease. This simplification allows us to model the disease progression in a more uniform and controlled manner Serrano-Pozo et al., 2011).

3 Mathematical Models

3.1 Overview of the Model

The mathematical model developed aims to simulate the interactions between (A_β) and Tau proteins across different brain regions using a network-based approach. Differential equations

are employed to model the dynamics of protein aggregation and their effects on neuronal health.

3.2 Variables and Parameters

- A_β^i **and** A_β^o**:** Amyloid-Beta inside and outside the neurons, respectively.
- τ**:** Tau proteins within neurons, involved in microtubule stabilization.
- F_i **and** F_o**:** Neurofibrillary tangles inside and outside neurons.
- N**:** Total neuron count within a brain region.
- M**:** Macrophages that interact with extracellular A_β and influence inflammatory responses.

These variables are chosen based on their significant roles in the pathology of Alzheimer's disease, reflecting the biological processes crucial for the disease's progression and effects on neural networks.

3.3 Model Equations

The following ordinary differential equations (ODEs) are used to describe the dynamics of the model:

$$\frac{dA_\beta^i}{dt} = \lambda_{\beta_i}(1+R) - d_{\beta_i}A_\beta^i, \tag{1}$$

$$\frac{dA_\beta^o}{dt} = A_\beta^i\frac{dN}{dt} + \lambda_N\frac{N}{N_0} - \theta\mu, \tag{2}$$

$$\frac{d\tau}{dt} = (\lambda_{\tau_o} + \lambda_{\tau_R} - d_\tau)\frac{N}{N_0}, \tag{3}$$

$$\frac{dF_i}{dt} = (\lambda_{F\tau} - d_{Fi}F_i)\frac{N}{N_0}, \tag{4}$$

$$\frac{dN}{dt} = -d_{NF}\frac{F_i}{F_i + K_{Fi}}N, \tag{5}$$

$$\frac{dM}{dt} = \lambda_M A_\beta^o - d_M + \sum_{j\in\text{neighbors of } i} \alpha_{ij}, \tag{6}$$

where λ, d, and α parameters represent the rates of production, degradation, and interaction strengths, respectively. The equations model the rate of change of each component over time, capturing the complex interactions between cellular and molecular components in Alzheimer's disease pathology.

4 Graphical Simulations

4.1 Simulation Setup

Our model of Alzheimer's disease progression is constructed using a network approach, where each node represents a specific region of the brain. The nodes are interconnected in various configurations to simulate the neural pathways through which A_β and Tau can spread. Each node contains a dynamic model governed by ordinary differential equations that describe the production and clearance rates of A_β and Tau, their aggregation into plaques and tangles, and the impact on neuronal health.

4.2 Results of Simulations

4.2.1 Fully Connected Network

In a fully connected network, every node is directly connected to every other node. This configuration represents a scenario where every brain region can directly influence every other region through the rapid spread of pathological proteins.

Observations: In this setup, the spread of A_β and Tau is fastest due to the high connectivity, leading to a quicker onset of widespread neurodegeneration across all simulated brain regions. The results indicate a rapid increase in both protein concentrations, suggesting that high interconnectivity can exacerbate the progression of Alzheimer's disease.

4.2.2 Partially Connected Network

A partially connected network simulates a more realistic scenario where only certain brain regions have direct pathways to others, reflecting the actual anatomical connections of the human brain.

Observations: The progression of pathological proteins is slower compared to the fully connected model. This setup shows delayed onset of symptoms and a more gradual increase in protein aggregation, aligning more closely with the observed progression of Alzheimer's disease in clinical settings.

4.2.3 Disjoint Network

In the disjoint network configuration, nodes are isolated or grouped into small clusters with no connections between them. This model explores the impact of highly localized disease progression.

Observations: The disjoint setup results in very localized and uneven progression of Alzheimer's pathology. Some regions show significant degradation while others remain relatively unaffected. This can help in understanding how Alzheimer's might progress in cases where the disease is initially localized to specific brain areas.

4.2.4 Unconnected Network

When the network is fully unconnected, the nodes do not have any effect on each other. This model then explores how each node behaves on it's own without any outside factors.

Observations: It seems that the network's behavior does not change drastically in this case. The Tau protein rises extremely fast, but the end behaviors of all of the variables end up being similar to the previous starting conditions.

5 Conclusion

Overall, throughout this paper we have created a model to simulate Amyloid-Beta and Tau proteins throughout different starting conditions in the brain. Although we were able to gather some interesting results on A_β, Tau and the other variables within the brain we chose to explore, we found that many of the results were very similar even with the different initial conditions.

A Fully Connected Graphs

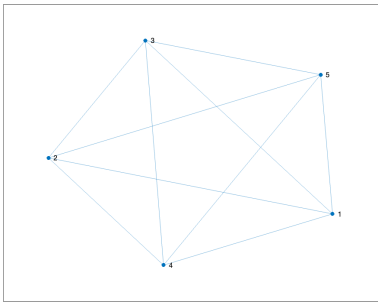

Figure 1: Brain Node Connectivity in a Fully Connected Network

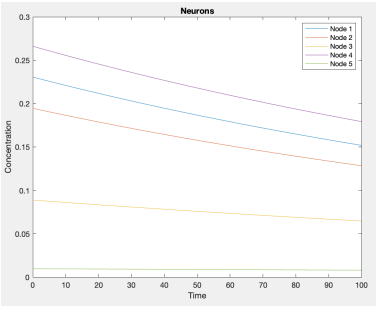

Figure 2: Neuron Concentrations in a Fully Connected Network

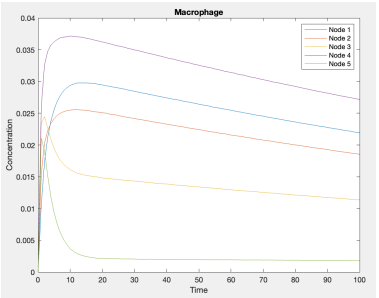

Figure 3: Macrophage Concentrations in a Fully Connected Network

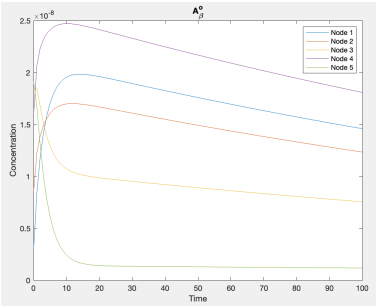

Figure 4: A_β^o Concentrations in a Fully Connected Network

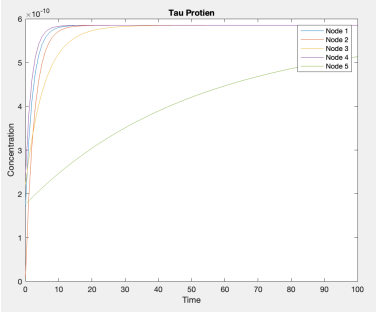

Figure 5: Tau Protein Concentrations in a Fully Connected Network

B Partially Connected Graphs

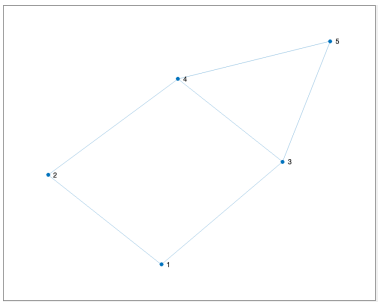

Figure 6: Brain Node Connectivity in a Partially Connected Network

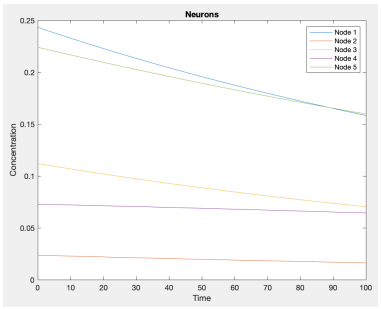

Figure 7: Neuron Concentrations in a Partially Connected Network

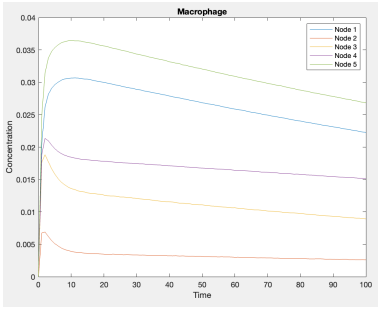

Figure 8: Macrophage Concentrations in a Partially Connected Network

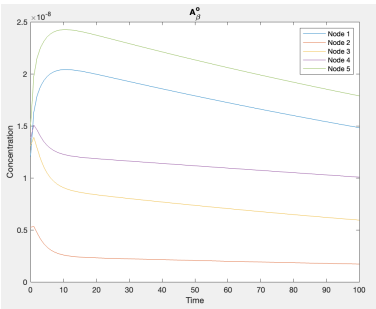

Figure 9: A_β^o Concentrations in a Partially Connected Network

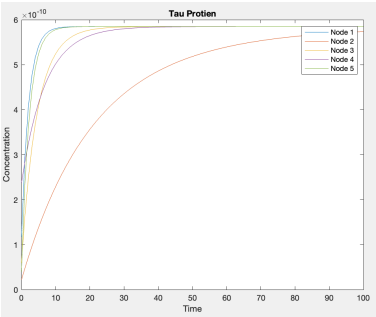

Figure 10: Tau Protein Concentrations in a Partially Connected Network

C Disjoint Network Graphs

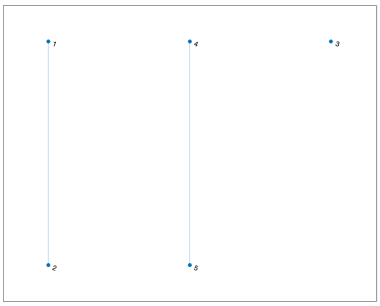

Figure 11: Brain Node Connectivity in a Disjoint Network

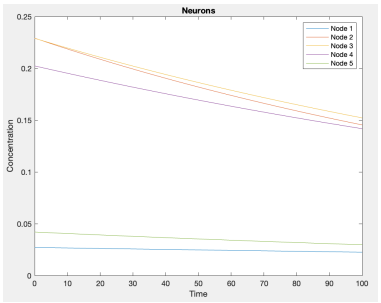

Figure 12: Neuron Concentrations in a Disjoint Network

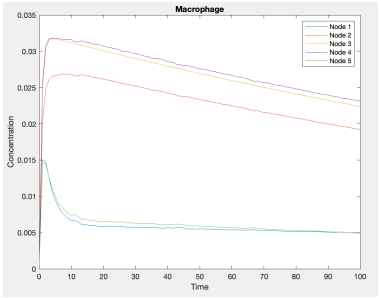

Figure 13: Macrophage Concentrations in a Disjoint Network

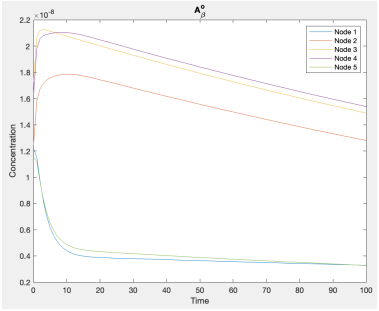

Figure 14: A_β^o Concentrations in a Disjoint Network

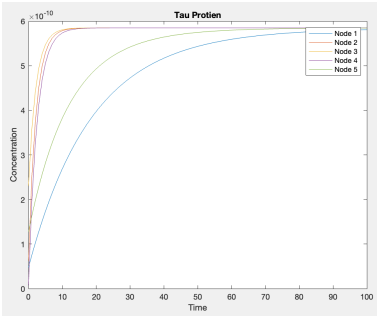

Figure 15: Tau Protein Concentrations in a Disjoint Network

D Unconnected Network Graphs

Figure 16: Brain Node Connectivity in an Unconnected Network

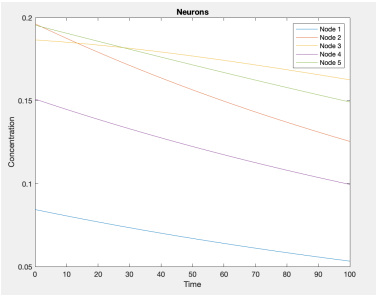

Figure 17: Neuron Concentrations in an Unconnected Network

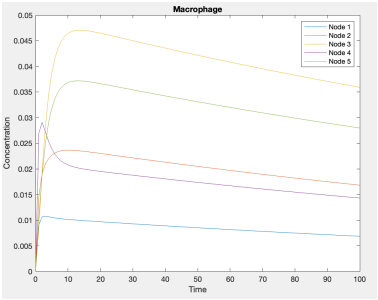

Figure 18: Macrophage Concentrations in an Unconnected Network

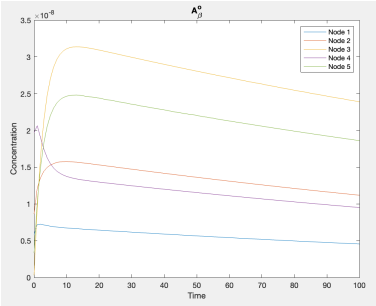

Figure 19: A^o_β Concentrations in an Unconnected Network

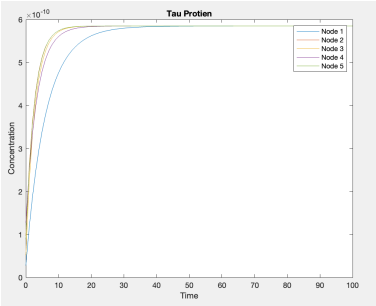

Figure 20: Tau Protein Concentrations in an Unconnected Network

E Matlab Code

```
clc; clear; close all;

Q = 5;
p = 0.5;
% symmetric adj matrix
matrix = zeros(Q, Q);
for i = 1:Q
     for j = i+1:Q
         if rand <= p
            matrix(i, j) = 1;
         end
     end
end

adj = matrix + matrix.';

% Initialize - 7 per variable

y0 = 2*rand(Q*7, 1);

% Fill in real values

lBi = ones(Q, 1)*(9.51*10^(-6));
R = ones(Q, 1)*6;
dAiB = ones(Q, 1)*9.51;
No = ones(Q, 1)*0.14;
lN = ones(Q, 1)*(8*10^(-9));
lto = ones(Q, 1)*8.1*10^(-11);
lt = ones(Q, 1)*1.35*10^(-11);
dt = ones(Q, 1)*0.277;
lF = ones(Q, 1)*(1.662*10^(-3));
dFi = ones(Q, 1)*(2.77*10^(-3));
dFo = ones(Q, 1)*(2.77*10^(-9));
dNF = ones(Q, 1)*(3.4*10^(-4));
KFi = ones(Q, 1)*3.36*10^(-10);
lM = 0.3;
theta = 0.5;
d = 0.2;
alpha = 0.2;

fun = @(t, y)der(t, y, Q, lBi, R, dAiB, No, lN, lto, lt, dt, lF
   , dFi, dFo, dNF, KFi, theta, d, lM, alpha, adj);
```

```
[t, y] = ode45(fun, 0:50, y0);

figure(1);
plot(t, y(: ,1), 'DisplayName', 'Node 1');
hold on;
for i = 2:Q
    plot(t, y(: ,i), 'DisplayName', ['Node ' num2str(i)]);
end
xlabel("Time");
ylabel("AiB amounts")
legend;
hold off;

figure(2);
plot(t, y(: ,6*Q+1), 'DisplayName', 'Node 1');
hold on;
for i = 2:Q
    plot(t, y(: ,6*Q+i), 'DisplayName', ['Node ' num2str(i)]);
end
xlabel("Time");
ylabel("Macrophage Populations")
legend;
hold off;

figure(3);
plot(t, y(: ,5*Q+1), 'DisplayName', 'Node 1');
hold on;
for i = 2:Q
    plot(t, y(: ,5*Q+i), 'DisplayName', ['Node ' num2str(i)]);
end
xlabel("Time");
ylabel("Brain Cells")
legend;
hold off;

function dxdd = der(t, y, Q, lBi, R, dAiB, No, lN, lto, lt, dt,
    lF, dFi, dFo, dNF, KFi, theta, d, lM, alpha, adj)
    AiB = y(1:Q);
    AoB = y(Q+1:2*Q);
    tau = y(2*Q+1:3*Q);
    Fi = y(3*Q+1:4*Q);
    Fo = y(4*Q+1:5*Q);
    N = y(5*Q+1:6*Q);
    M = y(6*Q+1:7*Q);
```

```
    % dont know how to send dN/dt forwards so I am just gonna
       use the newly
    % calculated one to make dFo/dt and dAoB/dt. This means dFo
       /dt and dAoB/dt will be calculated
    % last but still before dM/dt. Also using w instead of "d"
       for deriv

    wAiB = zeros(Q,1);
    wAoB = zeros(Q,1);
    wtau = zeros(Q,1);
    wFi = zeros(Q,1);
    wFo = zeros(Q,1);
    wN = zeros(Q,1);
    wM = zeros(Q,1);

    for i=1:Q
        wAiB(i) = (lBi(i)*(1+R(i)) - dAiB(i)*AiB(i))*N(i)/No(i)
           ;
        wtau(i) = (lto(i) + lt(i)*R(i) - dt(i)*tau(i))*N(i)/No(
           i);
        wFi(i) = (lF(i)*tau(i) - dFi(i)*Fi(i))*N(i)/No(i);
        wN(i) = -dNF(i)*(Fi(i)/(Fi(i)+KFi(i)))*N(i);
        wAoB(i) = AiB(i)*wN(i) + lN(i)*N(i)/No(i) - theta*M(i);
        wFo(i) = Fi(i)*wN(i) - dFo(i)*Fo(i);
        wM(i) = lM*AoB(i) - d*M(i);
        for j=1:Q
            if adj(i, j) == 1 && AoB(j)/M(j) > AoB(i)/M(i)
                wM(i) = wM(i) - alpha;
            elseif adj(i, j) == 1 && AoB(j)/M(j) < AoB(i)/M(i)
                wM(i) = wM(i) + alpha;
            end
        end
    end

    dxdd = [wAiB; wAoB; wtau; wFi; wFo; wN; wM];
end
```

References

[1] Clara H. Mulder. *The relationship between population and housing.* University of Amsterdam. Department of Geography, Planning and International Development Studies. https://unece.org/fileadmin/DAM/hlm/archive/Key%20note%20population%20and%20housing.pdf.