Time-Varying Network Models of Neurodegenerative Disease Spread in Biological Neural Networks

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***Abstract*— Although some cognitive decline over time is considered normal, neurodegenerative diseases such as dementia can exacerbate loss of memory and physical functionality, and even lead to death, especially within the elderly population. Currently, clinical understanding of these types of diseases is limited by inadequate knowledge of how they progress throughout the brain. Emerging studies show that the spreading and buildup of beta-amyloid proteins in certain grey matter regions of the brain could be a possible indicator of disease progression, specifically in Alzheimer's. In order to address a debate on the method of protein spreading, we created two dynamic spreading models that could predict the progression of Alzheimer's disease by looking at the brain as a network throughout which proteins can spread along varying pathways. The hope is that these models will predict the progress of neurodegeneration throughout the brain network of people diagnosed with Alzheimer's and perhaps identify the underlying process for protein spreading. Future studies into the buildup of proteins that affect grey matter density could use this model to target the specific areas for intervention with potential treatments. Our model could also be applied to the spreading processes of other diseases and be used to help patients and families better understand and prepare for the progression of their illness.**

***Index Terms*—Alzheimer's, dementia, neural networks, predictive models, disease spread, dynamic models**

INTRODUCTION

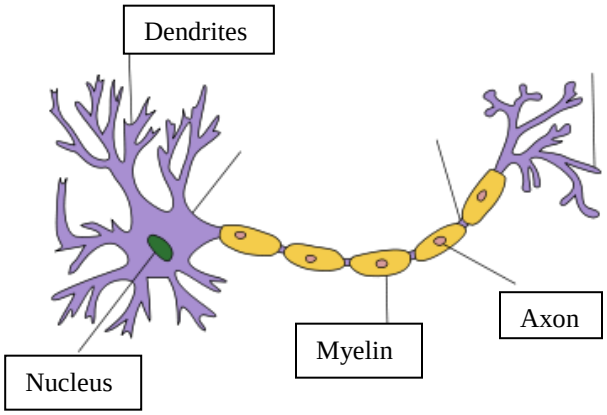
As mapping of nervous systems becomes easier and more feasible, many questions arise about the network structure of neurons in the brain and information flow within this network. Therefore, neural network modeling and analysis has become a more prominently researched topic. This has also become an interdisciplinary field, bringing together computer science and medicine in order to predict, analyze, and interpret the effects on disease on the human brain. Those diseases that are particularly interesting to network analysts are those that affect the structure and functionality of the biological neural network including dementia and multiple sclerosis. Approximately 25 million people worldwide suffer from dementia [1]; therefore, it is a prominent disease worthy of the research directed at reducing its impact on our population.

The neural network of patients with a neurodegenerative disease can be used a basis for modeling disease dynamics throughout the brain. This project focused on fitting two network models to neural networks extracted from MRI data of affected patients in order to predict Alzheimer's disease progression over time. The MRI data used came from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database of standardized data collections from 3T scans [2]. Previous studies done in the area look at the progression of dementia through the use of the second and third eigenvalues collected from static networks created from diffusion MRI images. These values have been found to be associated with different latency of disease progression in Alzheimer's versus frontotemporal dementia [1]. Other studies look at the co-variance between brain regions in order to determine the influences of one part of the brain on another [3]. Our goal is to determine how to better predict protein spread in Alzheimer's and how to better encode the spreading pathways they travel along. This will be helpful not only in possible medicinal alteration of disease progression but also in patient care as patients will be better able to plan their lives with the knowledge of how the disease will affect them.

I. BACKGROUND

A. The Brain

The brain is comprised of billions of neurons which consist of a single axon and many dendrites. The dendrites receive an electrical signal created by chemical gradients and the axons carry the signal. They connect to each other through synapses, which transmit signals using neurotransmitters, or specialized



chemicals for the brain.

Figure 1. The layout of a neuron. [4]

Axons are covered in myelin sheaths (pictured in Figure 1 in yellow), which are cells that help propagate the signal more efficiently down the axon. These myelin covered axons make up what is called white matter. The white mater creates what is considered the fibrous tracts of the brain or the connective network pathways, pictured in Figure 2.

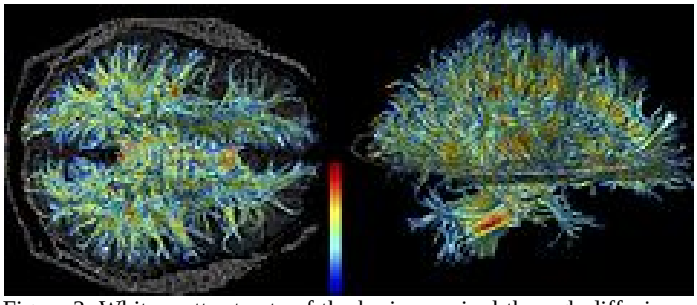


Figure 2. White matter tracts of the brain acquired through diffusion tensor imaging (DTI). The colors represent the vector direction of water flow within the neurons, allowing for mapping of their connections. [5]

Grey matter is everything else that makes up the brain, mostly consisting of the cell bodies. In network analysis, the brain can be thought of as a network of nodes and connections which are wholly defined as a biological neural network to differentiate them from computer created artificial neural networks.

The anatomical layout of the brain is made up of the ventricles, white and grey matter, and the brainstem which contains the cerebellum and eventually turns into the spinal cord. The ventricles can be subdivided into several different lobes, as seen in Figure 3, which are associated with different ideas and functions such as speech, vision, motor function, or higher level thinking.

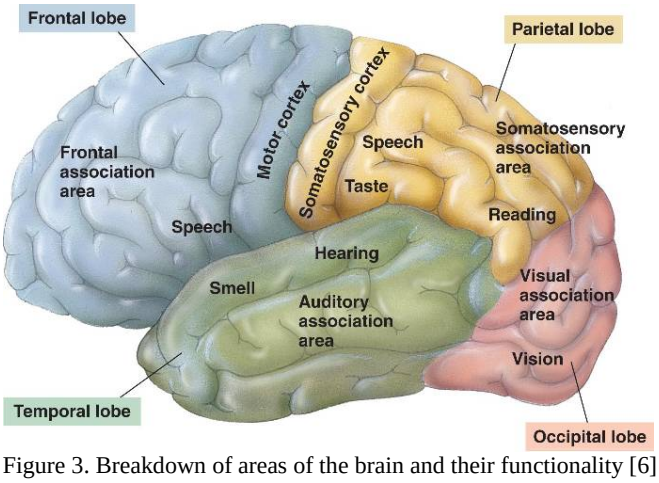


Figure 3. Breakdown of areas of the brain and their functionality [6]

B. *Neurodegenerative diseases*

Neurodegenerative diseases are characterized by the death of neurons and synapses in the brain. Examples of such are Alzheimer's, Parkinson's, and Huntington's. They are caused by several factors including but not limited to genetics, membrane damage, protein pathway degradation, or protein misfolding [7]. Typical symptoms of such diseases are memory loss, loss of coordination and motor function, and slow loss of the ability to take care of oneself. These symptoms are correlated to which area of the ventricles the cell death occurs in. Dementia is simply defined as the global decrease of cognitive function beyond that of normal and can encompass all of the above [8]. It is most prevalent in elderly people and it is estimated to affect 25 million people worldwide [1].

1) *Disease Progression*

Neurodegenerative diseases work by disrupting normal electrical transmissions between neurons. Slowly over time, these connections start to atrophy, or decay, and become no longer functional. Within the neurons, this is caused by a misfolding of the protein tau leading to a buildup called neurofibrillary tangles. Without this tau protein the links for the nutrient transport system of the neuron falls apart causing the cell to die. Beta amyloid proteins are also known to misfold outside of the neuron and become what are known as amyloid plaques. This leads to memory loss and a decrease in functional ability as well as a physical decrease in the size of the brain [9]. This corresponding decrease in grey matter is what is used in our models to indicate the progression of protein spread.

The disease spread of dementia can in one sense be defined as "prion-like". This simply means there the proteins previously defined will travel along the white matter pathways to different parts of the brain. The deposition of these proteins and the atrophy they cause is thought to be a major process leading to Alzheimer's disease [1]. This method of protein spread tested in our first predictive model.

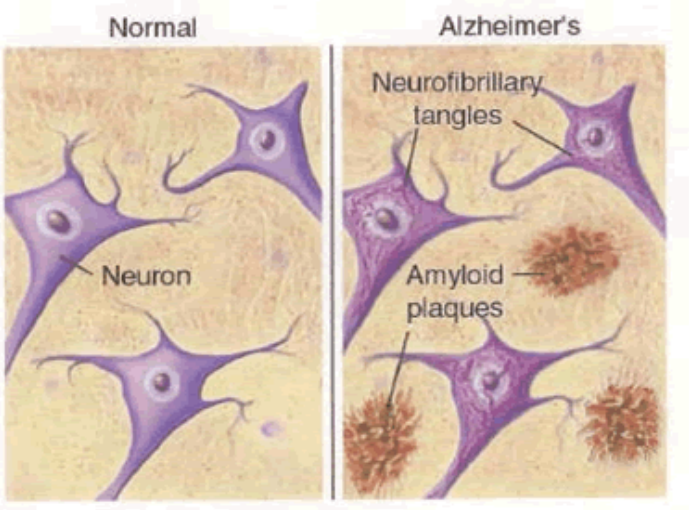


Figure 4. Beta amyloid and tau protein buildup within and around neurons [10]

2) Structural Covariance

In healthy individuals, certain areas in the brain exhibit structural covariance – that is, they are similar in grey matter density and cortical thickness as well as other parameters. There is also usually a connection between the functions of the two areas that co-vary or a similarity of metabolic load in those regions.

It is thought that because of this phenomenon, neuron loss of covarying brain regions could be a predictor of disease progression in Alzheimer's. This is because certain regions of the brain are thought to be more susceptible to protein invasion based on this covariance and studies suggest grey matter loss overlaps with regions where grey matter volumes co-vary in healthy individuals [2]. In terms of prediction modeling, this implies it is possible a different spreading pattern for these proteins exists if they are able to move from one region of the brain to another, even if they are not directly connected by white matter tracts. Therefore, we take this into account with our second covariance based model.

C. Magnetic Resonance Imaging

Magnetic Resonance imaging is one of the most common techniques for brain imaging because of its ability to differentiate the structures of the brain. It is based on the premise that when brain matter is placed in a strong magnetic field the hydrogen nuclei align with that magnetic field. Then a quick radio pulse of a specific frequency will be absorbed by said nuclei and cause them to spin and create a magnetic field detectable by the scanner. This secondary pulse is measured by a receiver and the matter is differentiated based on the variations in the signal due to the changing spin states of the hydrogen nuclei in diverse regions of the brain.

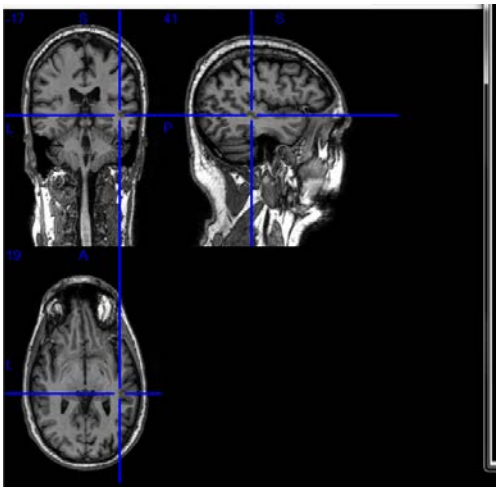


Figure 5. MRI of patient with Alzheimer's disease [3]

This imaging method is used in our study in order to create a structural representation of the brain of people with Alzheimer's from which we can extract a network of grey matter densities usable in our prediction models.

D. Network Representation of Biological Neural Networks

1) Structural Connectomes

A structural connectome is a representation of the white matter connections in the brain, usually acquired using diffusion tensor imaging. This imaging modality tracks the movement of water along the neurons and displays a colored image based on the vector movement of the water molecules (See figure 2). The image it produces is what is used to determine where the connections between the neurons are located and which areas of the brain are more or less connected to one another. Connectomes are unique to individuals; no two people have the same connections because the formation of these is highly dependent on the experiences and memory of the individual person. That being said, there is a great deal of universality between them allowing for generalizations over a range of people [11].

For network analysis purposes, the structural connectome can be represented by and undirected, weighted adjacency matrix, or a matrix whose numbers represent the strength of connections between a set of neurons. These matrices typically are non-directional, meaning direction of travel between any two nodes can progression in either direction, and weighted to represent variations in connection strength [12].

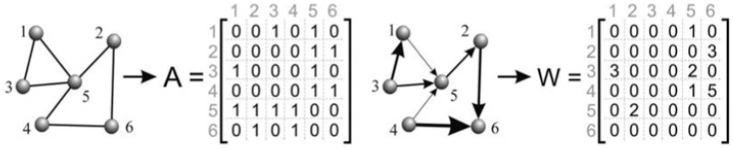


Figure 6. A) A non-directional, un-weighted network translated into its adjacency matrix (A). Where there is a 1 it represents a connection between the two points represented by the row and column (i.e. Points 1 and 3 are connected and vice versa.) B) A weighted directional network translated into its adjacency matrix (W). It is no longer symmetric (or mirrored along the diagonal) due to the directionality. The larger the number representation of the connection the stronger the connection is. [13]

2) Parcellation

Since there are billions of neurons in the human brain, it is impossible to deal with every single connection between them. Therefore it is necessary to come up with a way to combine them and create a network of manageable size for analysis. In a process called parcellation, a network of nodes is extracted from MRI images. Nodes are centers of communication, or hubs, from which the connection pathways can be said to come and go. Physically they can be represented as dots connected by lines (called edges) as seen in Figure 6.

In order to parcellate, one must first acquire a high resolution MRI image. This image is then run through a computer program called DRAMMS which does the following: strips the brain from the head and skull, segments the ventricular brain regions into visible white and grey matter maps, creates regions that have easily recognized anatomical landmarks, and individually subdivides each region into smaller regions of interest (ROIs) which become the nodes of the network [12].

F. Previous Spreading Models

Since it seems as though patterns in dementia target specific brain networks, previous work has be done on a diffusion model created using the Eigen modes of the Laplacian matrix of the brain network to predict the migration

of proteins in future disease states. The Laplacian matrix is the difference between the degree and adjacency matrices. The degree matrix is a diagonal matrix whose values represent the number of connections each node has and the adjacency matrix was described above. The Laplacian is used because it encodes information about the structure of a network by describing how one node differs from its neighbors. In simple terms, the Eigen modes represent different patterns of diffusion that can occur within the network defined by the Laplacian. The main focus of the study was to see if this prion (misfolded protein) diffusion model was consistent with actual disease patterns in dementia.

The first Eigen mode was found to correlate with normal age degeneration. The second was found to be involved with the medial and lateral temporal lobes which correlate to memory and AD. The third Eigen mode agrees with the FTD data. The fourth and higher Eigen modes are correlated possibly to more rare diseases such as Huntington's [1]. Ideas from this model are applied to our tractography based model.

II. Procedure for Dynamic Modeling

A. Data

In order to create networks from human brains we used MRI images from people with varying levels of dementia. The MRI images we used for analysis were downloaded from the "Standardized MRI Data Sets" image collection of the Alzheimer's Disease Neuroimaging Initiative (ADNI) which is part of the Laboratory of Neuro Imaging (LONI) at University of California Los Angeles [2]. For this project we used only those patients who were diagnosed with AD but it could be possible to run the model with any neurodegenerative disease that has protein spreading related to degeneration. An example of an MRI used in this study is seen above in Figure 5.

For each MRI image there is also an associated cognitive score that describes the functionality of the patient whose brain was imaged. These scores come from a range of tests used to assess the progression of Alzheimer's disease including the Alzheimer's Disease Assessment Scale (ADAS), the Mini-Mental State Examination (MMSE), and the Functional Assessment Questionnaire (FAQ). These scores were used as time steps in defining real neurodegenerative data to provide a basis on which to compute the accuracy of the predictive models. The scores ranged from 0-30 for example using the MMSE. Therefore, a person with a score of 0 was said to be starting disease progression and 30 would be end stage Alzheimer's. Each step in score then corresponds to a time step of degeneration and can be matched to time steps of prediction from the models.

B. Network Extraction

In order to create a network usable for our models, we needed both a set of nodes extracted from the ADNI MRI images as well as an adjacency matrix which describes the network connections from a structural connectome created by DTI. To extract the parcels and related grey matter densities for the nodes, a program from the Section of Biomedical Image Analysis (SBIA) at the University of Pennsylvania called DRAMMS (Deformable registration via attribute matching and mutual-saliency weighting) was used. The program takes an MRI image as its input and separates the actual brain matter from the skull first and then deforms the brain to fit a template so that all the networks acquired are on the same scale. Once this is complete, an overall grey and white matter intensity map is made over the entire brain. The brain is also segmented into 73 regions of interest (ROIs) based on an algorithm that takes into account identifiable ventricular structures within the brain. This segmentation of ROIs is overlaid onto the map of grey and white matter intensities. For each region, an average based on the intensities of the image voxels contained in that region is made to give us a network of nodes with each node corresponding to a particular grey matter density [12].

The structural connectome was also acquired from the SBIA lab. The DTI image was segmented into the same 73 ROIs and the connections going into and out of those regions were then determined. These connections then were overlaid with the nodes with the grey matter intensities to create a biological neural network that we can then fed into our first predictive model.

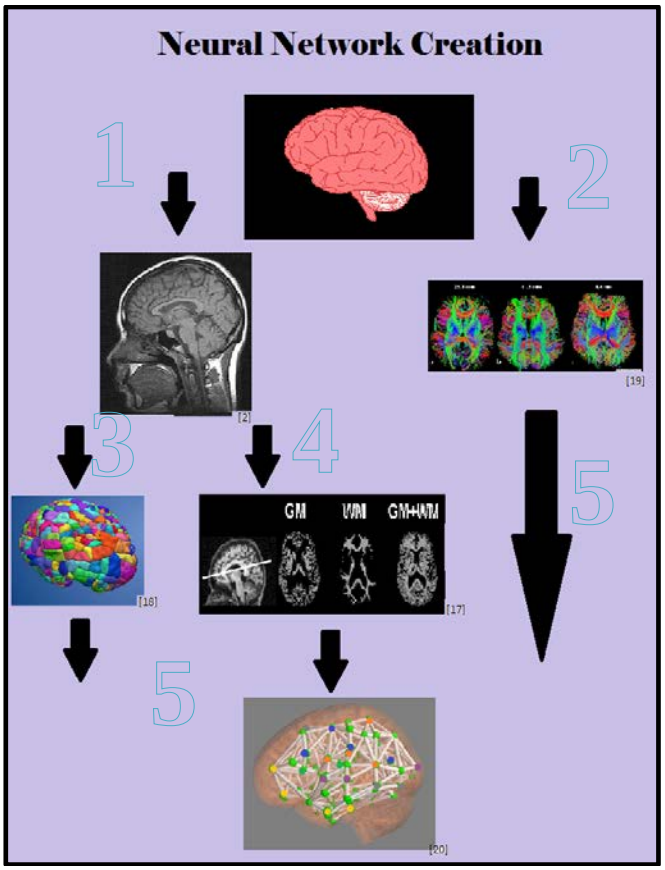


Figure 7. A biological neural network is created according to the following steps: 1) A MRI image is taken of the brain. 2) A DTI image of the brain is taken. 3) The MRI is parcellated into 73 ROIs. 4) A grey matter intensity map of the MRI is created. 5) The ROIs are overlaid with the grey matter map to determine nodes for the network. The color correspond to differences in grey matter intensities. The ROIs are also overlaid on the connectome to

determine the connectivity between the nodes or the edges of the network.

C. Models

We have come up with two spreading models, one that takes into account the white matter adjacency matrix, and one which defines the connections between nodes based on covariance of parameters such as grey matter intensity and cortical thickness at each node. We will compare the output of both spreading models against each other and against real time varying data to see how well they work and which, if either, is better a predictor the spread of proteins within the network.

Our first model takes into account the adjacency matrix (connections between brain regions) created via the white matter tracts (physical neuron connections) of the brain determined from a diffusion tensor image (DTI). Since this matrix is weighted, the strength of connections between nodes, or points of connection, is already predefined [21]. Therefore, we can use equation (1) to simulate spreading within the neural network,

$$X_i(t+1) = \sum_{j \in Ni} A_{ij} X_j + cX_i(t) \qquad (1)$$

where Xi is the grey matter intensity at any node *i* at time t and *j* is in the neighborhood (N) of *i*. The density at node *i* in the next time step (X_i (t+1)) is dependent on the density of a neighboring node X_j multiplied by the strength of connection between nodes *i* and *j* defined in the weighted adjacency matrix A and added to the density of that node at its current state in time X_i (t). The entire list of X_i's from 73 regions of interest (ROIs) is placed into a column vector which is run through the model all at once so that it predicts the decrease of grey matter intensities (spreading of proteins) to any or all adjacent nodes at each time step.

Our second model replaces the weighted adjacency matrix, which indicates the strength of connections between different regions of interest, with a matrix P which defines edges by capturing the strength of connection based on pairwise covariances across all ROI. This covariance is determined by correlations found between the grey matter intensities of each node as well as other parameters obtained from the magnetic resonance image (MRI) analysis such as cortical thickness, which is a known indicator of covariance in brain regions. With this replacement, the new equation of the spreading model becomes the following:

$$X(t+1)=P(t)\ X + cX(t) \qquad (2)$$

where X is a vector of grey matter densities for the different regions of interest (or the 93 regions of interest), and c is a scalar less than zero to indicate reduction in grey matter density over time caused by spreading and building up of proteins.

The spreading based predictive models described here are based on the known fact that Alzheimer's is caused by the buildup of beta-amyloid plaques as well as neurofibrillary bundles that cause a decrease in grey matter density due to atrophy of neurons. Since it is unknown which path these proteins, our models embrace various ideas in order to better show the pattern of degeneration and disease movement throughout the neural network. We chose to use network analysis tools such as the adjacency matrix instead of the Laplacian that was used in previous models [1] because our model focuses more on disease movement as a selective spreading process rather than on simple, undirected diffusion.

D. Prediction

Once the initial networks are run through our spreading models, we receive an output that depicts the state of the network at each time step based on probabilistic predictions of disease spread. The outputs of these models are compared to one another as well as real data extracted from MRI images of patients with varying levels of degeneration from the ADNI database. In order to represent change over time, these real data images are ordered based on cognitive scores that are known to be correlated to more or less cognitive function and disease progression. For each time step (incremental increase or decrease in cognitive score), the output of both models is compared to the real data in order to evaluate which model was better able to predict the state of disease at that time.

III. Experimental Results

This study is ongoing pending the analysis of the models with the data recently received from the SBIA. Due to numerous roadblocks in obtaining access to computers with the processing power to run DRAMMS, as well as amount of time necessary to analyze each image, we only received the necessary grey matter densities and parcellations at the end of the 10-week SUNFEST program, and were not able to analyze them in time for the conclusion. All coding for the models was completed in MATLAB and what is left is to feed the data into the two models and analyze the results.

IV. Discussion and Conclusion

We believe the two models will differ in their prediction of protein spreading. Our preliminary intuition is that the tractography based model will show local spreading over each time step, whereas the covariance model will show a wider region of spreading due to the greater length of connections between brain regions defined by covariance. Our hope is to show which method better encodes spreading pathways or perhaps discover an unknown method of protein spreading, not yet defined by previous studies.

Future studies into the buildup of proteins that affect grey matter density could use this model to target the specific areas for intervention with future treatments. The model could be modified and applied to spreading processes of other types of dementia or be used to help patients and families better understand and prepare for the progression of their illness.

Acknowledgment

Many thanks the National Science Foundation for their generous funding without which the SUNFEST Program would not be possible, as well as Jan Van der Spiegel PhD and Linda Kalb for their tireless efforts in organizing the program. Another thanks to George Pappas PhD for allowing her access to the GRASP lab as well as its resources and people. Thank

you to the Section of Biomedical Image Analysis, specifically Christos Davatzikos Ph.D and Da Xiao (Steve) M.S, for access to imaging data for the project. Finally, thank you to Chinwendu Enyioha, Danielle S. Basset PhD, and Victor Preciado PhD for their complete dedication and persistent efforts to move the project forward.

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