A Spatiotemporal Simulation for Alzheimer's Disease

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***Abstract*—This paper introduced Alzheimer's disease (AD) simulation with a brain network simulator. Several AD models about the time course of structural and functional changes of the human brain are firstly reviewed. Then, a spatiotemporal model for AD simulation is proposed. By applying the model, we can observe structural and functional dynamics of the human brain affected by AD with the brain network simulator. This research helps the studies of the changes of the human brain correlated to AD.**

Alzheimer's disease; brain networks; spatiotemporal dynamics; simulation

I. INTRODUCTION

In 2010, we proposed and designed the structure of a brain simulator as a tool for investigate the human brain [1]. Since Alzheimer's Disease (AD) shows complex structural and functional dynamics with the human brain, it is potentially a suitable case for demonstrating how the brain network simulator works. In this paper, we firstly review several models about the developmental process of AD. These models include neuropathological stages which present distribution patterns of amyloid deposits and neurofibrillary changes; network damage model which describe the behavior of preferential attack in large complex networks; and an AD treatment that shows how neurotransmitter acetylcholine and cholinergic neurons take effects on AD. Then, we integrate these models and propose a spatiotemporal model of AD that considers both space and time dimension. Finally, we provide a simple case and algorithmic steps to demonstrate how we apply the model and the brain network simulator to simulate the AD development.

II. ALZHEIMER'S DISEASE

Alzheimer's disease is a common dementia usually seen on the elder over 65 years of age. It is currently incurable and the causes of AD are still unknown. It is considered as a protein misfolding disease. One type of protein which called Amyloid Precursor Protein (APP) embeds on the cell membrane. APP is possibly hydrolyzed by three different kinds of enzymes: α-, β-, and γ-secretase. Under normal procedure, APPs are hydrolyzed by α- and γ-secretase. The fragments cut by secretase outside the cell membrane are called beta-amyloid protein 40 (Aβ40). These fragments are easy to be decomposed in the brain. However, when APPs are hydrolyzed by α- and β-secretase, the long fragments called beta-amyloid protein 42 (Aβ42) are produced. This kind of fragment is hard to be decomposed and easy to polymerize with other amyloids into plaques. On the other hand, AD is also considered as a tauopahty. Tau proteins reside in the neurons. They are responsible for microtubule fixation. Microtubules are important parts of cytoskeleton. The main functions of microtubules are cytoarchitecture support and substance transport. When the mutation occurs, tau protein will be distorted and started to separate from microtubules. The formation of NeuroFibrillary Tangles (NFT) will present, making the collapse of microtubules and leading to neuron deaths [2].

III. MODELS OF ALZHEIMER'S DISEASE

Three AD related models are reviewed in this section.

A. Network Damages

The general framework proposed by Callaway *et al.* [4] describes an intentional attack to the nodes with highest degree is commonly seen in most real-world network. A study by Albert and Barabási [5] describes this phenomenon as "target attack" and has experiment results in agreement with works of Callaway *et al*. The "target attack" shows that the nodes with higher degree in a network have a higher probability to be attacked. This phenomenon can be mathematically described as follow

$$q_k = \theta(k_{max} - k) = \begin{cases} 1 & if \quad k \le k_{max} \\ 0 & if \quad k > k_{max} \end{cases} \qquad (1)$$

where q_k is the probability that a node will be occupied (in physics, a node is occupied means it is stay in the network, otherwise it is unoccupied which means it is removed from the network). θ is the Heaviside function. This function shows that if a node with degree k higher than k_{max}, then the node will be unoccupied. In other word, the node will be removed from the network. When a node with highest degree (hub) is removed from a network, the network breaks into several fragments (cluster) as shown in Figure 3. This may reduce the number of shortest paths and lead to difficulties in information transmission. "Target attack" is also found in the human brain suffered from AD. A study by Buckner *et al.* shows that highly active regions which imply hubs of the human brain may cause preferential accumulation of β-amyloids. Another study by Stam *et al.* [6] which applies target attack model to construct networks damaged by AD brain shows lacking of shortest paths. This result is similar to the brain networks of AD subjects, suggesting that the highly

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connected ‘hubs’ of neural network may also be in highly risk for AD.

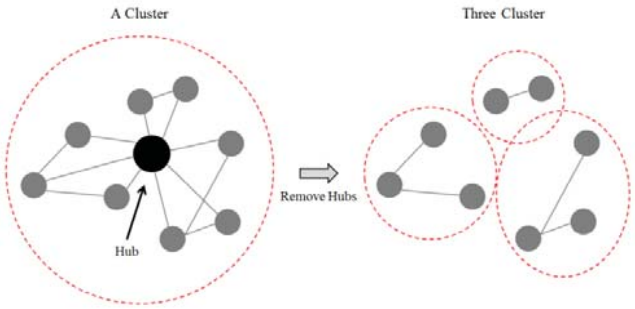

Figure 3. Phenomenon of Target Attack

B. *Neuropathological Stages*

Braak et al. [3] define neuropathological stages of AD by post-mortem. They examine patterns of amyloid deposits and neurofibrillary changes (neurofibrillary tangles and neurofibrillary changes) distribution to differentiate clinical stages of AD. The result is that three stages of amyloid deposits and six stages of neurofibrillary changes are defined. As shown in Figure 1, the amyloid deposits start from basal portion of isocortex, then to isocortical association areas, and finally all areas of isocortex. On the other hand, as shown in Figure 2, neurofibrillary changes initiate from transentorhinal section to limbic part of brain, and finally all over the isocortex.

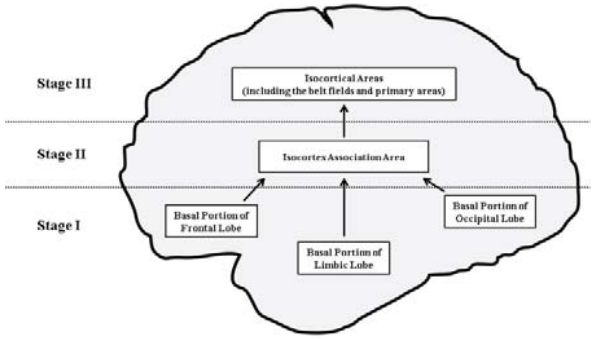

Figure 1. Distribution pattern of amyloid deposits

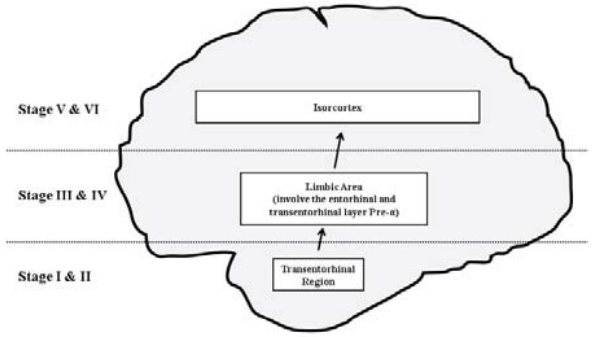

Figure 2. Distribution Pattern of Neurofibrillary changes

C. *Treatments of Alzheimer’s Disease*

One of well-known features of AD is the reduction of the amount of cholinergic neurons [7]. Most of current treatments of AD employed the acetylcholinesterase inhibitors to prevent the cholinesterase enzyme from breaking down acetylcholine (ACh), thereby increasing concentration of ACh in the human brain, helping patients to keep their cognitive functions at a certain level. Figure 8 shows the chemical reactions caused by acetylcholine between presynaptic neurons and postsynaptic neurons. At the very beginning, an enzyme which is called choline acetyltransferase (ChAT) helps to activate the reaction between Acetyl-CoA and choline, resulting in the formation of the ACh. These acetylcholine molecules are wrapped in vesicles and stored at the end of the presynaptic neurons. After the nerve impulse happens, the presynaptic neurons release calcium ions, causing the vesicles empty their contents to the synaptic cleft. Most of the acetylcholine will bind to the ACh receptors and absorbed by the postsynaptic neurons. Some of the acetylcholine molecules will be hydrolyzed by acetlcholinesterase (AChE) and reproduced to choline molecules. These choline molecules will be recycled by presynaptic neurons. By using AChE inhibitor, the process of acetylcholine hydrolysis will be reduced, leading to a higher concentration of acetylcholine. This avoids the tau proteins separating from the microtubules, stabilizing the structure of microtubule, and resulting in the reduction of neurofibrillary tangles. It also reduces secretion of soluble amyloid precursor proteins (APP), avoiding the creation of β-amyloids.

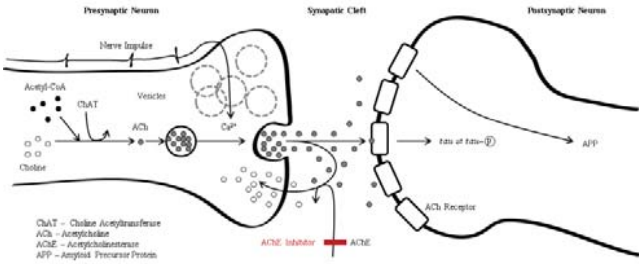

Figure 4. Neurochemical Reactions in Alzheimer’s Brain

On the other hand, McGeer *et al*., Woolf, and Mesulam *et al.* [8], have defined the cholinergic cells and pathways in the mouse brain. Most of their experiment results are consistent, giving us an insight into the relationship between cholinergic neurons and AD.

IV. The Spatiotemporal Model for AD Simulation

In order to have a comprehensive simulation for spatiotemporal dynamics of AD, we integrate models mentioned above. Firstly, we define the global and the local view of distribution patterns of AD related features as shown in figure 7.

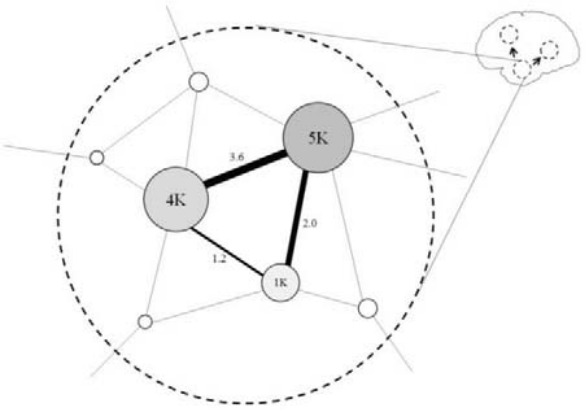

Figure 5. Global and Local View of the Brain Network

In a global view, we follow the works of Braak *et al*. [3], defining different stages of amyloid deposits and neurofibrillary changes in the brain network simulator. This will control the order of affected regions by AD. For example, neurofibrillary changes begin at the transentorhinal section in stage I and II, then the changes will spread to the limbic part of the brain in stage III and IV, and finally cover all over the isocortex in stage V and VI. In a local view, we apply target attack models to simulate the behavior of the preferential attack of AD. In the original framework of Callaway *et al*. [4], the target attack model can be described as earlier in (1) which describes that any nodes with degree lager than k_{max} will be removed from the networks. Here we modify the equation, making k_{max} as a function of time, that is, the value of k_{max} will decrease as time changes to simulate the continuous attack by AD. The equation then is modified as follow

$$\theta(k_{target} - k_i) = \begin{cases} 1 & if \quad k_i \le k_{target} \\ 0 & if \quad k_i > k_{target} \end{cases} \tag{2}$$

Let

$$k_{target} = f(t) = k_{max} - \left\lceil \frac{t - t_0}{p} \right\rceil \tag{3}$$

where p is the parameter that denotes the duration of attacks on certain nodes with degree higher than k_{max}. Following the equation, the brain network simulator can decide which nodes should be marked as the attacking targets with the AD progressing.

After deciding which nodes will be attacked at time *t*, the brain network simulator will next compute the function $f(t)$ to determine decreased number of neurons. Function $f(t)$ can be a linear or non-linear function to describe the behavior of amount of neuronal death caused by AD. Here we assume that $f(t)$ is a non-linear function with a constant velocity v_c and the amount of acetylcholine a_n to control the speed of neuronal loss. The function is described as follow

$$\begin{aligned} f(t) &= N(t_0) - N(t_n) \\ &= \int_{t_0}^{t_n} V(t)dt \\ &= \int_{t_0}^{t_1} v_1 dt + \int_{t_1}^{t_2} v_2 dt + \cdots + \int_{t_{n-1}}^{t_n} v_n dt \\ &= v_1(t_1 - t_0) + v_2(t_2 - t_1) + \cdots + v_n(t_n - t_{n-1}) \\ &= v_c \left[\frac{(t_1 - t_0)}{a_1} + \frac{(t_2 - t_1)}{a_2} + \cdots + \frac{(t_n - t_{n-1})}{a_n} \right] \\ &= v_c \sum_{i=1}^{n} \frac{(t_i - t_{i-1})}{a_i} \end{aligned} \tag{4}$$

In order to simulate the effect of treatment of AD by acetylcholine, we must predefine the cholinergic neurons and pathways in the brain network simulator. Here we refer to the works done by McGeer *et al*., Woolf, and Mesulam *et al*. [8]. This work shows similarities on brain structure between mice and humans. Therefore we try to create mappings of cholinergic neurons and pathways from a mouse brain to the human brain as shown in figure 8. In the human brain, each neuron groups from ch1 to ch6 has its own projections to different targets. For example, one of cholinergic neuron groups is horizontal limb nucleus which projects to the olfactory bulb. Another one is pedunculopotine nucleus which projects to the thalamus and the brain stem. These cholinergic neurons and pathways are predefined in the brain-component module. When the simulation starts, the acetylcholine takes effects on these predefined components, helping to decrease the speed of neuronal loss.

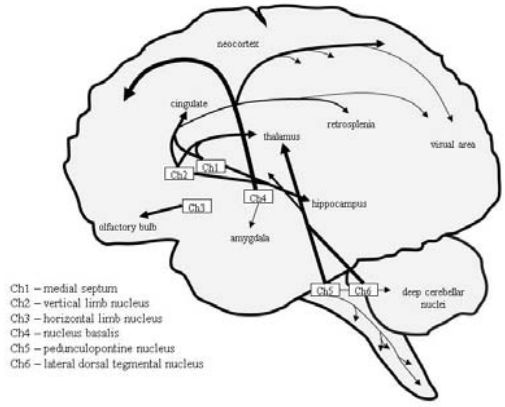

Figure 6. Cholinergic Neurons and Pathways

The death of neurons will lead to reduction of connections. This effect will also be reflected on the brain network simulator. Before the simulation starts, the brain network simulator will first construct a brain network with nodes and edges that are defined by the brain-component module. Each edge has a weight determined by the number of connections and corresponding path length. Because the brain network is currently design to be constructed at macroscopic scale, an edge between two macroscopic brain

components is composed by numerous connections. So for each edge in the brain network that connect from source S to target T, following equation defines the weight of the edge at time t_n

$$W(t_n) = \frac{\beta}{\alpha} \times \frac{C(t_n)}{10^4} \times \frac{1}{l} \quad (5)$$

Where $C(t_n)$ is the number of connections that compose an edge at time t_n. l is the length of an edge. α and β are parameters to determine the ratio between $C(t_n)$ and l. Note that $0 < \alpha, \beta < 1$. From the equation, we can see that the value of a weight will be change only determined by $C(t_n)$ because l is a constant. Hence, $C(t_n)$ can be described as follow

$$C(t_n) = \begin{cases} N_s(t_n) \times 10^4 \times \frac{y}{x+y} \times \frac{N_T(t_n)}{\sum_{i=0}^{y} N_{T_i}(t_n)} & if \quad n = 0 \\ C(t_{n-1}) \times \begin{cases} 1 - \frac{\Delta n_S}{N_S(t_{n-1})} & if \quad \Delta n_S \geq \Delta n_T \\ 1 - \frac{\Delta n_T}{N_T(t_{n-1})} & if \quad \Delta n_S < \Delta n_T \end{cases} & if \quad n > 0 \end{cases} \quad (6)$$

where x and y are the number of afferent and efferent edges of S respectively. $N_s(t_n)$ and $N_T(t_n)$ are the number of neurons of S and T respectively at time t_n. Δn_S and Δn_T describe the decreased number of neurons of S and T respectively from time t_{n-1} to t_n. Because there are about 10^{11} neurons and 10^{15} synapses in the human brain, we assume that each neuron has 10^4 connections in average. When n is equal to 0, that is, at the initial state of a simulation, the number of connections composed of an edge is determined by the number of neurons S contains, the ratio between efferent edges and all edges, and the ratio between number of neurons T contains and the number of neurons all project targets of S (other components who are connected with S) contains. When n is larger than 0, that is, after the initialization of a simulation, the number of neurons the attack targets contain will be decreased, leading to a loss of connections which attach to the target nodes. For simplicity, the computation of decreased number of connections considers only the ratio between decreased number of neurons and the number of neurons before decrease happens at one end (source or target, determined by the amount of neuronal loss, pick the higher one). Figure 7 shows the steps of the computation on the number of neurons and the weight. Here we assume that α, β, l are all equal to 1, v_c is 2 per unit time, and a is a factor of 2. The red circles mark up the attacking targets while the yellow circle denotes the brain component which is on the acetylcholine pathways.

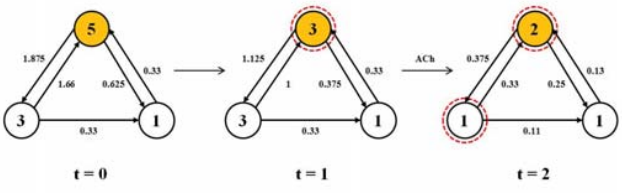

Figure 7. Steps of Brain Network Simulation for Alzheimer's Disease

In summary, the simulation of AD can be formulated as algorithmic steps: Given a network *s* which contains nodes and edges and a time *t*, if *t* is less than t_{end}, then the brain network simulator will firstly choose the global regions affected by AD according to *t*. Next, the brain network simulator will choose attacking targets for each region and compute their decreased number of neurons. Finally, for each edge that attaches to the attacking targets, the brain simulator computes the decreased number of connections and updates the weight of the edge. These steps will keeps executing until time *t* is large than t_{end}.

V. CONCLUSION

In this paper, we review several models that describe the developmental process of Alzheimer's Disease in space and time. Each model describes an aspect of AD in different time scale and different perspective of view (global or local). However, none of them can be applied alone to simulate the developmental process of AD in the brain network simulator. This research tries to integrate these models and propose a spatiotemporal model. This model presents most aspects of AD in the developmental process, helping us to know much more about AD. With current technology, a comprehensive and accurate brain simulation is still not feasible. However, we believe simulation will be a crucial methodology for future human brain researching. It will greatly help us to discover unknown mysteries of the human brain.

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