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Thomas Howard graduated in May 2012 from BSU with a BS in Mathematics and is currently a graduate student earning an MS in Computer Science at BSU. This research was developed as part of an ATP Summer Research Grant under the direction of Dr. Irina Seceleanu. Tom presented his research at the Joint Mathematics Meeting, the largest annual mathematics meeting in the world, and at the National Conference on Undergraduate Research in the spring of 2012. Tom is looking forward to completing his MS and joining the work force as a programmer.

Alzheimer's disease is a condition linked to plaque aggregation in the brain. Despite being the focus of many studies, current treatments are of questionable significance in the overall improvement of a patient's condition. In recent years, computer models have been used to better understand complex biological systems and simulate the effects of various treatments. In the following paper we present a mathematical model studying the effects of plaque aggregation on the neuronal pathways of the human brain. To create our mathematical model we employ tools from the theory of dynamical systems and stochastic processes, and simulate the passage of a signal through a healthy and a plaque-affected brain. Moreover, our model simulates the increased resistance of the neuronal network to plaque disruption as a result of cognitive stimulation through learning and cerebral exercises, and measures the increased connectivity in a plaque-affected neuronal network when cognitive stimulation is present. Our mathematical model shows promise as a first step in modeling the complex interactions of plaque deposits in the human brain and studying the influence of behavioral treatments on Alzheimer patients.

Alzheimer's disease is a condition linked to plaque aggregation in the brain which has a great impact on the population in the United States and worldwide. Projections show that fifty percent of Americans over 85 will suffer from dementia, and fifty million Americans are expected to have some form of dementia by 2030 according to the Alzheimer's Association (2012). The debilitating effects on patients include memory disturbances, high incidence of emotional outbursts, communication difficulties, daytime wandering, hallucinations, delusions, physical violence, and incontinence. Moreover, Alzheimer's disease impacts the vast number of caregivers, linked to their higher incidence of alcoholism, anger, sadness, fatigue, and depression. Care giving increases likelihood of disease and familial conflict (Rabins, Mace, & Lucas, 2008). In 2012, an estimated $200 billion dollars will be spent on Alzheimer's disease alone, not to mention the variety of other forms of dementia. However, the current medicines have had questionable significance in the overall improvement on patients' conditions, and side effects vary from mild incontinence to severe liver damage (Qaseem et al., 2008).

Effective pharmacotherapeutic treatments for Alzheimer's disease have been difficult to find despite being the focus of many studies. Most drugs used for dementia are limited by side effects, restricted duration of efficacy, and

the need for frequent monitoring of blood levels or other laboratory values to prevent toxicity. In recent years, the creation of computer simulations of the human brain to investigate the interaction of plaque granules and the neural network has become a target for researchers. In the following, we present a mathematical model of this complex biological system using tools from the field of dynamical systems to better understand the aggregation of these undesirable proteins and their interference with neurons. This type of computer modeling has potential for evaluating drug and behavioral interventions.

The Theory Of Dynamical Systems

The study of dynamical systems seeks to describe structures which change with respect to time. An abundance of examples exist: blood pumped by the atria and ventricles flowing through the chambers of the heart, planetary motion, a pendulum swinging back and forth from its axis, a population of rabbits growing and declining in a field, etc. Many dynamical systems can be described via mathematical models allowing for the prediction of state information (Devaney, 2003).

Figure 1. Henri Poincaré

Sir Isaac Newton (1642-1726) is credited with the development of the study of dynamical systems as an articulated field. Newton was driven to develop methods of calculus to describe the motion of the planets over time, which he introduced in his *Principia.* Henri Poincaré (1854-1912) contributed to the study of dynamical systems by introducing a wide variety of tools and methods for the advancement in this area. Through work on the three-body problem (introduced by Newton), Poincaré noted the complexity of the behavior which could arise from simple nonlinear systems. Famously stating, "…small differences in the initial conditions produce very great ones in the final phenomena" (Poincaré, 1914), Poincaré is considered one of the forebears of Chaos Theory, a field focused on this high sensitivity to the starting circumstances.

Gaston Julia in his work, *Mémoire sur l'itération des fonctions rationnelles* (1881), and Pierre Fatou helped explain the orbits of particles using recursively iterated functions. A recursively iterated function is of the type $f_{n+1}(x) = f(f_n(x))$; that is the input to the subsequent iteration of the function is the current output.

Figure 2. Julia Set

By analyzing the dynamics of iterated complex polynomials, Julia introduced a geometric object of particular interest called the Julia Set (see Figure 2), which gives rise to beautiful graphs exhibiting properties of self-similarity, and an accessible, intuitive way to understand the behavior of chaotic systems.

In the 1960s, Edward Norton Lorenz set off to make a computer modeling program for meteorological forecasting. Truncating a variable to save time in his computations, Lorenz noticed how dropping a seemingly insignificant portion of a number led to a great discrepancy in the resultant. His discoveries contributed greatly to the modern theory of chaos. His observations led him to popularize the Butterfly Effect, the notion that "The fluttering of a butterfly's wing in Rio de Janeiro, amplified by atmospheric currents, could cause a tornado in Texas two weeks later (Krützmann, 2008)." Along with the rise in computer processing speeds, a renaissance to the field of dynamical systems took place, in that previously intractable problems could be approached with processing power which standard analytics could not match. The iteration of functions at a very fast rate led self-described "nomad-by-choice" (Gleick, 1987) of the sciences Benoit Mandelbrot to begin his investigation into visualizations of certain mathematical sets using computers. Mandelbrot saw the regular in the irregular objects often found in nature and developed fractal geometry, allowing for the description of many complex patterns in a systematic way.

Mathematical Model

Computer simulations have been indispensable in understanding of the dynamics of various complex phenomena (Anderson, 1986). Computer models are now used in diverse scientific are-

nas from physics, to astrophysics, biology, and chemistry. In the following, we describe our mathematical model created to study the effects of plaque deposits on the neuronal pathways of the human brain. To start, a recursive algorithm is used to generate a set of points to graph a fractal image resembling the complex neural network. Given that plaque deposits exhibit clustering patterns of formation, a probabilistic model using a non-homogeneous Markov process is employed to simulate their aggregation. To study the effects of the plaque granules on the neuronal network, we integrate the two models into one and identify the neurons affected by the plaque. Moreover, graph theoretical tools are used to measure the number of neuronal connections that a signal travels before and after plaque deposition. To emphasize the resemblance of our model to reality, we present computer generated graphs, from our simulations, in juxtaposition to the actual image of plaque deposits in the human brain. Finally, we model the increased connectivity in a plaque-affected neuronal network as a result of learning and cognitive exercises, by making the neuronal connections more resistant to plaque disruption when cognitive stimulation is present. We then contrast this improvement in signal passage through the neuronal network to the reduced connectivity of a brain affected by plaque without cognitive stimulation. Our mathematical model shows promise as a first step in modeling the complex interactions of plaque deposits in the human brain and studying the influence of different pharmacological and behavioral treatments while weighing these results against side effects.

Generating The Neuronal Network

To model the neuronal network in the human brain we employ a fractal generating algorithm. Fractal, a term coined in 1975 by Benoit Mandelbrot from the Latin *fractus* (derived from the past participle of *frangere* to break apart), describes a type of geometry which is self-similar at different scales. Mathematicians are able to model complex systems by "breaking" these complex structures into simple pieces using properties of self-similarity. In wide-ranging arenas, from computer graphics to cellular data transmissions to noise cancellation, fractals have provided insights and have led to new engineering solutions. In modern cell-phone antennas bandwidth has increased while size has diminished by incorporating the self-similar structure known as the Sierpinski Carpet (see Figure 3). In our model of the neuronal network, we use a recursive algorithm to generate a fractal tree acting as a topological map of the human brain. By modeling the neuronal network as a symmetric geometric object with regular plots, we are able to use relatively simple algorithms to simulate the flow of signal in the network and measure the effects of the deposits. The fractal generating algorithm uses the following steps (see also Figure 4):

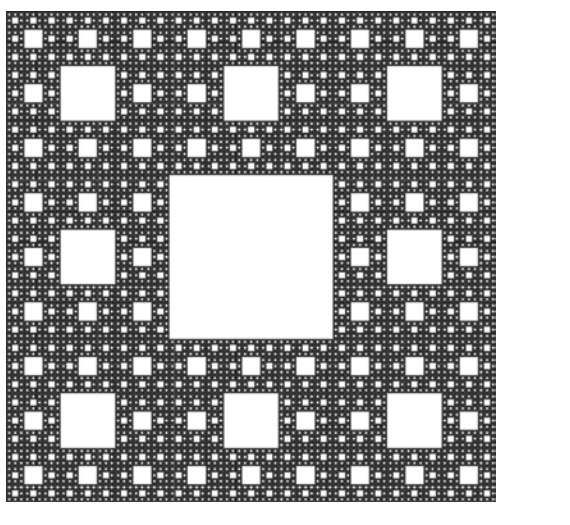

Figure 3. Sierpinski Carpet

1. The first stage graphs a horizontal line.

2. In the next step, three more lines are drawn, two perpendicular to and one straight out from the original segment. At each step, the new lines drawn are half the length.

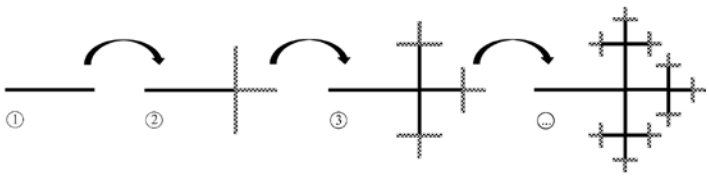

Figure 4. Generating the Fractal Tree

3. In the n^{th} iteration, each new line branches off to produce 3^{n-1} new lines of length $\frac{1}{2^{n-1}}$ relative to the first line. For instance, the first stage produces 3^0=1 of length 1; the second 3^1 = 3 of length 1/2; the fifth 3^4 = 81 lines of length 1/16.

The output of our fractal tree program is transformed into a directed graph (see Figure 5). Each vertex (representative of a neuron) and edge is numbered. A signal flows across a directed graph in one direction, similar to the signal firing across the neural networks of the human brain.

We model the flow of a signal in a healthy neuronal network using the Bernoulli distribution, a discrete probability assignment designating low and high receptor values to the vertices in the fractal tree. In a biological setting, the action potential is more likely transmitted the higher the number of receptors on the dendritic side of the synapse. Similarly, in our model, the success of the signal passing is related to the receptor value associated with each vertex.

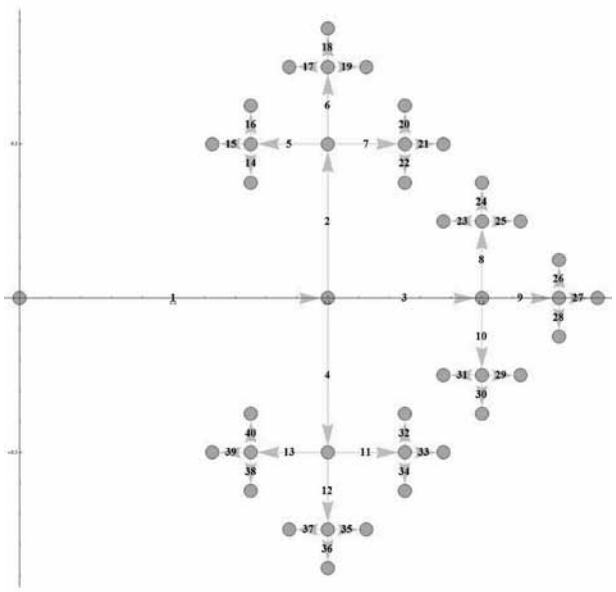

Figure 5. Fractal Tree in the form of a directed graph

After Swiss scientist and mathematician Jacob Bernoulli, the Bernoulli distribution gives the probability that a value will take one of two (discrete) predetermined values, be it high or low receptors; 0 or 1; success or fail. The probability for success is given as variable p and failure is given as $q=1-p$. The q and p values in this type of assignment will always total 1, meaning that a discrete value will be defined in every case. For instance if a p value is given as .6 the q value will be equal to .4. Moreover, the mean of assigned "successful" values will be around 60% and the mean of the failure value will be around 40%. In the receptor distribution portion of our model a high count of receptors is denoted by a 1, and a low count by a 0. We can formalize this as $P(X = 1) = 1 - P(X = 0) = 1 - q = p$.

For our model, the starting p value is .9; in this stage, about 90% of vertices get assigned a high receptor value, represented as 1, and in 10% of cases, the vertex would be assigned a low receptor value or 0. The assigned Bernoulli distribution value is descriptive of either a high, 1, or low, 0, number of receptors located at the terminus of the dendrites. A high number of receptors will increase the likelihood a vertex will receive the signal, whereas a low number of receptors has a lower probability of signal reception. A successfully transmitted signal represents an action potential (signal firing) being received, consequently passing through the neuron and triggering the release of neurotransmitters at the axon terminals, and further signal propagation. Since downstream neurons receive signal less frequently in the human brain, our model incrementally decreases the probability p of having high receptor values for vertices at each stage of the fractal tree. Consequently, q increases at each stage and further downstream vertices are more likely to have a low receptor values.

Once the receptor values have been assigned to each neuron in the fractal tree, we now simulate the passage of a signal through the fractal tree by using another Bernoulli distribution. The assigned probability that the signal passes through a neuron depends on the number of receptors: a relatively higher p-value (lower q-value) for those vertices with a high receptor value and a relatively lower p-value (higher q-value) for those with a low receptor value. Figure 6 shows an example of how the high (upper half of ring in black) and low (lower half of ring in black) receptor values end up being disbursed throughout the graph. The figure also depicts the passage of a signal over this network of a healthy brain, where signal reception is depicted by a shaded inner circle.

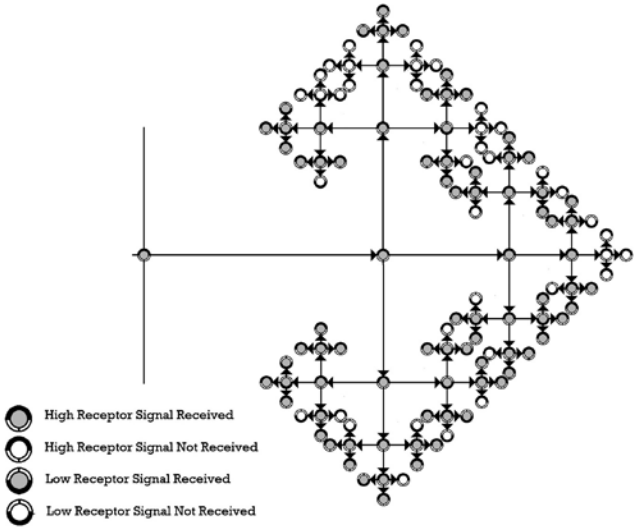

Figure 6. Distribution of neurons with High and Low number of receptors and signal passage through network

Modeling Plaque Formation

Plaque formation, a major contributing factor to Alzheimer's disease and neuronal decay, is the second component of our model. In the human brain, plaques form in clusters posited to disrupt neuronal connections. After defining an n x n matrix, the first of our plaque deposits is randomly chosen from the entire field; any cell $a_{i,j}$ has a $1/n^2$ chance of being chosen in the first iteration. Next, a high probability box is defined around the initial grain ($a_{i,j}$) along with its eight adjacent cells. The next grain is

	$a_{i-1,j-1}$	$a_{i-1,j}$	$a_{i-1,j+1}$		
	$a_{i,j-1}$	$a_{i,j}$	$a_{i,j+1}$		
	$a_{i+1,j-1}$	$a_{i+1,j}$	$a_{i,j+1}$		

Figure 7. High Probability Box defined around initial deposit

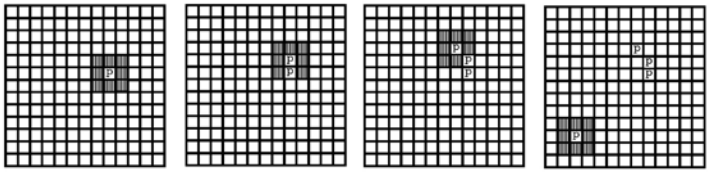

Figure 8. Iteration for plaque deposition

selected with 9/10 chance of being in the high probability box (each cell has a 1/10 possibility of being utilized). The remaining 1/10 of a chance is divided over the rest of the field (the complement to the high probability box), yielding a $1/(10n^2 - 90)$ likelihood of being chosen for the next placement. In the next step, a new high probability box is created around the new grain. We continue this process of generating a new granule at each stage recording its position in the two-dimensional matrix which, consequently, is layered onto the directed graph. As a result of the probability model employed, the granules generally form in clusters (see Figure 9).

Modeling The Effects Of Plaque On The Network

To measure the effects of the granules on the network, we measure the distance between each plaque deposition and the closest edge on the directed graph. If the particle and segment fall within a predetermined distance threshold of each other, the edge is considered affected by the deposit. Once a certain number of plaque granules fall within this distance, the edge is considered interrupted and signal passage is not allowed to downstream vertices. The number of plaques required to disrupt an edge is proportional to the length of the edge.

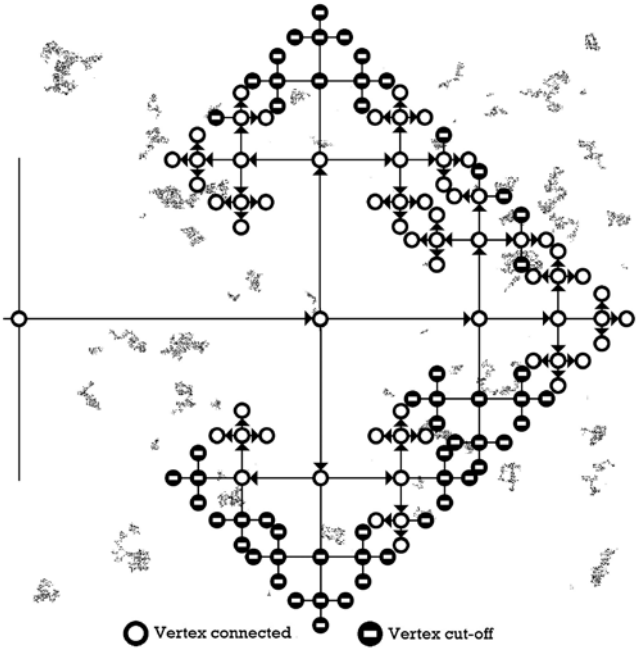

Figure 9. Plaque disrupted network

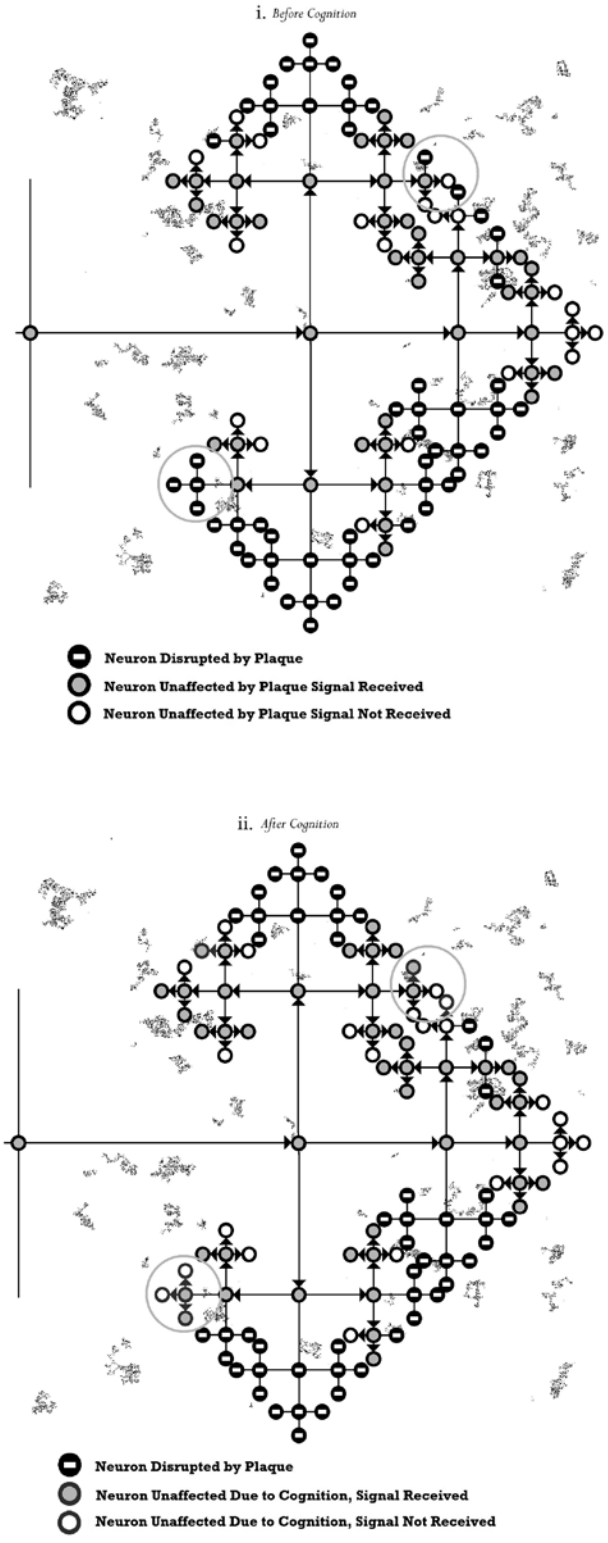

Figure 10. Path of signal through neuronal network affected by plaque degradation (i) without memory and learning exercises (ii) with memory and learning exercises.

In figure 9, we see the network after damage done by plaque deposition. Where plaque gets to within a predetermined proximity of the network, in great enough numbers, the signal does not reach the downstream neuron (depicted with shaded circle and white rectangle). The unfilled circles denote vertices connected to the network, ready to receive a signal; their preceding pathways have not been interrupted by the proteins. In figure 10(i), we see the signal passage through the network which has been degraded by plaque. The darkened circles with white rectangles are blocked; neurons ringed by circles are passable: the ones which are shaded in have successfully received a signal while the ones with white centers have not been reached by the signal. We contrast this graphic with figure 6 and easily see that the network without plaque degradation allows a substantially increased signal passage throughout the network.

Plaque disrupts signal flow on the neural network like downed trees interfere with traffic on a roadway. Signals, accustomed to traveling on a certain path, can still be delivered via a re-organization of available healthy neural branches. A variety of the brain's regions are pooled together to form a behavioral output. If the connection between these regions is disrupted, a person can possibly relearn a different way to connect the regions using a different neural substrate (set of neurons), resulting in an overall similar type of behavior. Certain modularity of basic tasks is common to many theories of neural branch configuration (Mogensen, 2011). Furthermore, mature astrocytes transform into radial glial cells to guide immature neurons to form fresh neural substrate (Pelvig, Pakkenberg, Stark, & Pakkenberg, 2008). Otherwise, factors, present in the adult brain, promote axon regeneration over more complicated trajectories, which may aid in finding new connections (Becker, et al. 2012). Like drivers taking detours to avoid road debris, the new routes are less direct. Passage of a signal across a network degraded by the influx of these plaque proteins results in fewer neurons being activated than in a disruption-free system.

Simulating The Impact Of Learning

The frequent use of neurons through cerebral exercises (Sudoku, playing piano, complex housing, physical tasks, and learning) decreases the impact of plaque deposits (Kolb, Arif, & Gibb, 2011). The effects of cognitive training have been shown to have a variety of implications on the health of the neural network. This long-lasting enhancement in signal transmission between two neurons that results from simulating them synchronously is called *Long Term Potentiation* (Cooke & Bliss, 2006). LTP enhances the ability of a signal to be received after crossing the synaptic cleft by adding new glutamate receptors to the membrane surface. As learning occurs, the successful signal passage across the synchronous neurons promotes the likelihood of future propagation; LTP is a positive feedback loop. In addition, mice given learning tasks show delays in the onset of extracellular amyloid beta plaque and tau protein synthesis (Billings, Green, McGaugh, & LaFerla, 2007). Furthermore, preconditioning (learning prior to the arrival of deleterious effects) provides greater long term benefits compared to conditioning beginning in the pathological stages of Alzheimer's; plaque burdens are best reduced by lifelong learning regimens. On top of this, lacking the cognitive stimulation, plaque levels tend to return to their normal pathological state rapidly, suggesting learning enhances protective mechanisms. Moreover, learning increases the amount of synaptic connections; from postmortem autopsies, people who engage in mentally stimulating jobs have an average of seventeen percent more neuronal connections than those with less cerebrally demanding career paths.

In our model, we simulated the effect of learning by increasing the threshold values for the number of plaque granules needed to disrupt a neuronal connection, which resulted in the signal being able to pass through some regions previously disrupted by plaque. In figure 10(ii), we depict the signal passage through such a neuronal network after cognitive training. Contrasting this to the brain without cognitive stimulation represented in figure 10(i), we see areas (circled in grey) which are now reached due to the introduction of the cognitive exercises, but were disrupted in the other model.

	Path of Signal	Average Proportion of Neurons Reached
A	without Plaque	0.378
B	after Plaque	0.255
C	with Learning	0.301

Figure 11 Average proportion of neurons reached in 50 simulations

To quantify the effects of plaque on the neuronal network in each of the three models (healthy brain without plaque; brain affected by plaque; and brain affected by plaque with learning), we ran a large number of simulations and averaged the number of neurons reached by the signal. To allow for a valid comparison of how the signal travels through the neuronal network in the three different models, we ran our simulations with the same fixed parameters for the neuronal network and plaque formation. That is, all three models had the same underlying distribution of low/high receptor values for the neurons throughout the network. Moreover, we used the same plaque formation affecting the brain in both models

b and *c*. In figure 11, we show the result of our 50 trials on the network, and report the mean proportion of the 1093 neurons in our neuronal network that were reached in the 50 simulations for each of the three models. When the variables for each of the three programs are fixed, we note that $b = 0.255 = 279/1093$ (network after plaque deposition) is a substantially less than $a = 0.378 = 413/1093$ (before plaque deposition), and $c = 0.301 = 329/1093$ (network ameliorated by cognition) is a slight improvement on *b*.

Conclusion

In figure 12, we illustrate the results of *(i)* our computer generated model by juxtaposing it next to a picture of the *(ii)* human hippocampus affected by plaque deposits. Our model shows resemblance to reality and can be manipulated using several variables to better reflect the actual conditions seen in Alzheimer's patients and the clustering characteristics (amount and pattern) of the proteins. From our studies on the

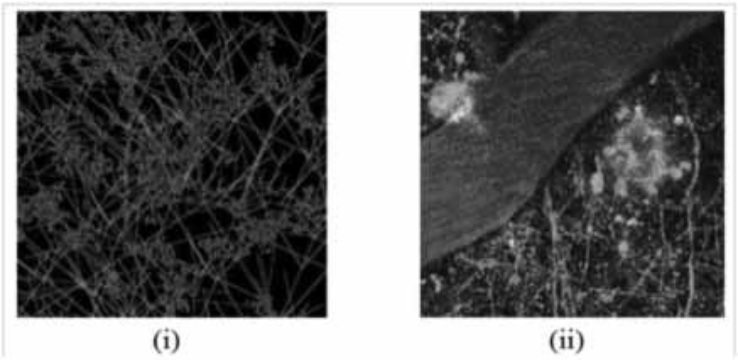

Figure 12 (i) Our computer generated model juxtaposed with (ii) biological network in the human hippocampus (Hampton, 2008).

model, strengthening the resiliency of the neural connections, such as occurs through learning, ameliorates the deleterious effects of plaque deposits on the network. We hope we have produced a rudimentary tool to better predict the outcomes of using certain treatments, possibly weighing them against any potential adverse side effects, and providing a framework to add features which enhance realism. Our model is the basis to which a variety of nuances could be added to more completely explain the system: Long Term Potentiation on the synaptic conductivity, differentiability of intraneuronal vs. extra cellular plaques, regeneration of axonal fibers, neurogenesis, etc. The complexity of the human brain is astounding, having roughly 1 quadrillion synaptic connections; our model consists of merely one thousand. In a subject which branches between mathematics; programming, neuroscience; and behavioral psychology; we hope to have made an inroad into a gigantic problem.

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