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Original Article

Neuron modelling for Alzheimer's neuron condition in early, intermediate, and advanced stage using amyloid-beta and tau protein as parameters

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Abstract

Neurons are basic units of our nervous system used for communication between the brain and the body. Any disruption in their structures or communication can result in several disorders like Dementia and Alzheimer's disease (A.D.). In this paper, we explore the alterations in neurons causing A.D. Due to specific genetic mutations, neurons release and accumulate tau protein and beta-amyloid protein, thus hampering the communication process, leading to neuron death known as brain atrophy, and eventually shrinking the brain is the case in A.D. This paper discusses neuron modeling of a typical neuron and an Alzheimer's neuron to understand the difference and progression of A.D. and the fact that once these equations are concluded, they could be used to control the brain through a brain-computer interface. Modeling of neurons enables exploring different parameters and understanding the behavior of a particular system, and finally, concluding to represent a biological activity mathematically.

Keywords: Alzheimer's disease, beta-amyloid protein, genetic mutation, neurons, tau protein

1. Introduction

Alzheimer's disease (A.D.) is a devastating and eventually incurable form of neurodegeneration characterized by progressive loss of cognition and disruption of essential functions, such as swallowing, walking, attention, and memory. Various symptoms and problems include depression, social withdrawal, mood swings, irritability and aggres siveness, and many more (Ozben & Ozben, 2019).

According to various theories and hypotheses, there are multiple reasons which are responsible for it. Nevertheless, there is no validation that each of them is true. However, some things can be observed and can be derived after doing a literature study. The main protein responsible is tau protein and amyloid beta-protein which causes neuron abnormality like the formation of amyloid plaques, neurofibrillary tangles, and which causes loss of neuronal connection and results in cell death (Zott, Busche, Sperling, & Konnerth, 2018). The effect of this, in brief, will be explained later in this section. Also, considering all these parameters and based on the hypothesis, we derived equations describing the relationship mathematically, which can be simulated and verified further.

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2. Literature Review

The Modelling Neurons article (Graham & Van Ooyen, 2006) discusses various types of modeling. These techniques include compartmental modeling, detailed compartmental modeling, rate-based neuron modeling, etc.

While in the Modelling Neural Activity article (van Drongelen, 2013), we explored an overview of different models for studying the activity of nerve cells and their networks, neuronal models based on the Hodgkin and Huxley. Also, the network models can exclusively contain individual network nodes that model the neurons or are found in representations of compound population activity.

In the article Mathematical Modeling of Neural Activity (Einevoll, 2006), we discovered the remarkable properties of the brain that are due to an intricate interplay

between billions of neurons, i.e., nerve cells connected in a complex network. The main challenge is understanding this neural network behavior, establishing connections between their properties at the microscopic level (single neurons), and observing brain activity at the macroscopic systems level. Various mathematical models describing single neurons are outlined in this paper. Biophysically realistic compartmental models, simplified spiking neuron models, and firing-rate models are part of the same. In the Mathematical model on Alzheimer's disease article (Hao & Friedman, 2016), we learned about the advances made to give a mathematical model of A.D. that includes neurons, astrocytes, microglia, and peripheral macrophages, amyloid β aggregation, and also hyper phosphorylated tau proteins. The model then simulates the effect of drugs that failed in clinical trials or are currently in clinical trials. The model was a bit more accurate because it overcomes the limitations of the previous models. It also has an amount of data with respective parameters. It is also running continuously. It also has a production rate and degradation rate of specific hallmarks. Treatment can be predicted by increasing or decreasing the inhibitors of the distinctive hallmarks. The model shows the network within a neuron, leading from ROS to NFTs and the destruction of the microtubule. This model is given by a system of Partial differential equations (PDEs).

While in Mathematical modeling and numerical simulation of the morphological development of neurons (Graham & Van Ooyen, 2006), a wide range of mathematical models are reviewed for (1) neurite initiation, (2) neurite elongation, (3) axon pathfinding, and (4) neurite branching and dendritic shape formation. The different mathematical techniques employed in the paper are also presented. The results indicate some comparison of modeling results with experimental data. The report concludes that a unified mathematical and numerical simulation framework should eventually expand work on neuronal development models, as has also occurred with compartmental models of neuronal electrical activities.

Mathematical Modeling for the Pathogenesis of Alzheimer's Disease by (Puri & Li, 2010) shows a Schematic model of A.D. It intakes various feedback mechanisms from live and dead neurons, aims for significant factors, and considers astrocytes and microglia's action. It is not practical because of the unknown elements and lack of variables depicted in this model. This model also evaluates the dynamic network involving multiple cross-talking among distinct states of microglia, astroglia, and neurons which has led to an insight that microglia activation and threshold for amyloid-beta may be a critical initiator for A.D.

3. Materials and Methods

3.1 Identify, research, and collect idea

3.1.1 Plan of work

1. Review different types of neuron models
2. Select one neuron model
3. Study A.D. and what causes the change in neuron
4. Study the equations related to those changes
5. Consider a neuron model for A.D. using a standard neuron model as a base
6. If accurate can be used in BCI (Brain-Computer Interface)

3.2 Method opted

There are two main hallmarks considered in our model, amyloid-beta and tau protein, responsible for the prognosis of A.D. Amyloid-beta and tau are both tracked inside and outside the neuron. There are two primary thresholds ROS and GSK which play their role as abnormality arises in nerve cells. ROS Reactive Oxygen Stress forms chemical bonds that lead to the destruction of RNA and DNA followed by neuron death GSK-3 is a serine protein kinase that controls various biological activities. When the amount of amyloid-beta hits a threshold, GSK-3 promotes hyper phosphorylation of tau. This model comprises elements from model A which is model by (Puri & Li, 2010b), and modified equations by model B, Model by (Hao & Friedman, 2016a).

3.3 Equations formulated

3.3.1 Amyloid-beta inside the neuron

$$\frac{\partial A_\beta^i}{\partial t} = (\lambda^i{}_\beta(1+\mathrm{R}) - d_{A_\beta^i}\, A^i{}_\beta)\frac{N}{N_o}$$

The amyloid-β within neurons, $A^i{}_\beta$, is constitutively released from APP at a rate $\lambda^i{}_\beta$ and are degraded at a rate $d_{A_\beta^i}$. Under Reactive Oxidative Stress, R, $A^i{}_\beta$ is overproduced.

3.3.2 Amyloid-beta outside the neuron)prominent(

$$\frac{\partial A_\beta^o}{\partial t} = A_\beta^i\left|\frac{\partial N}{\partial t}\right| + \lambda_N\frac{N}{N_o} + \lambda_A\frac{A}{A_o} - [\left(d_{A_\beta^o M}(M_1+\theta M_2)\right)\frac{A_\beta^o}{A_\beta^o + \bar{K}_{A_\beta^o}}$$

The extracellular amyloid-β peptides satisfy the above equation. Neurons die at a rate $\frac{\partial N}{\partial t}$, thereby releasing their $A^i{}_\beta$. Hence, they contribute $A_\beta^i\left|\frac{\partial N}{\partial t}\right|$ to the growth rate of A_β^o. The second term on the right-hand periphery of the equation represents Aβ constitutively released from APP, and the third term accounts for Aβ liberated by activated astrocytes. A_o is the reference density of the astrocyte cells in the brain. A_β^o is cleared primarily by peripheral macrophages but also by activated microglia.

3.3.3 Tau and NFT pathology

$$\frac{\partial \tau}{\partial t} = (\lambda_{\tau o} + \lambda_\tau R - d_\tau \tau)\frac{N}{N_o}$$

Tau protein is constitutively produced at some rate $\lambda_{\tau 0}$. We suppose that when A_β^i production exceeds a threshold A_β^{i0} GSK-3 becomes activated, and it mediates hyperphosphorylation of tau.(Weingarten, Lockwood, Hwo, & Kirschner, 1975)

$$\frac{\partial F_i}{\partial t} = (\lambda_F \tau - d_{F_i} F_i)\frac{N}{N_o}$$

$$\frac{\partial F_o}{\partial t} = F_i \left|\frac{\partial N}{\partial t}\right| - d_{F_o} F_o$$

The NFTs in neuron (F_i), are formed from the hyper phosphorylated tau proteins, and they are released to the extracellular space (F_0) when the neurons die.

3.3.4 Live neuron

$$\frac{\partial N}{\partial t} = -d_{NF}\frac{F_i}{F_i + K_{F_i}}N$$

Hyperphosphorylated tau proteins, forming neurofibrillary tangles, cause microtubules depolymerization and destruction, resulting in neuron death. Neuron death is also caused by trauma from pro-inflammatory cytokines, which are resisted by anti-inflammatory cytokines. (Hao & Friedman, 2016b)

3.4 Workflow

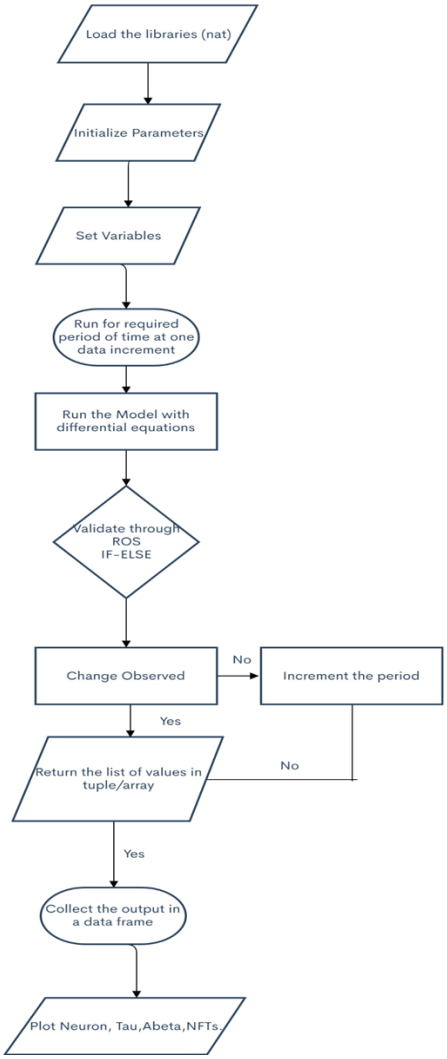


Figure 1. Flowchart of work

This model included various parameters which could help us study the different stages of Alzheimer's disease. Typically, there can be 3 to 7 stages based on their progression. For simplicity, this paper discusses three different sets of Alzheimer's, namely Early Stage (Onset), Moderate Stage (Mild), and Advance Alzheimer's Stage (Severe). As and when the disease progresses, it shrinks the Hippocampus situated in the Medial Temporal Region of the Brain. Thereby simultaneously increasing the size of Ventricles and Cortical severe shrinkage.

The variables for analysis and their variations between stages are mentioned from Table 1 to 3, which are taken after studying the research from (Roher et al., 2009) and also with the help of ("GitHub - Megparks/Alzheimers-Disease-Model: A Differential Equation Model of Neuron Death in Alzheimer's Disease Patients Developed in R," n.d.). Simulation performed for the fundamental analysis of the disease's progression is in R Studio with the help of R language and subsequent libraries, including deSolve, rootSolve, nat, etc. R Studio allows users to develop and edit programs in R by supporting many statistical packages, higher-quality graphics, and the ability to manage your workspace. Being excellent for statistical computing and analysis made us select the R language to run our simulations and data analysis.

To check the changes in graphs in 3 different stages, we changed the following parameters:

- Variation in years by multiplying the number by 365
- Increased the rate of degradation of amyloid-beta.
- Decreased the rate of production of tau protein.

4. Results and Discussion

The graphs are plotted to follow the concentration of parameters in the mild cognitive or the primitive stage. We cannot accurately predict the tendency to develop Alzheimer's at later stages because some individuals tend to be cumbersome in their daily lives. At the same time, others feel difficult to remember things from the past. These graphs show us that the concentration of live neurons is decreasing but at what rate would be precisely specified when compared the reference with later stages. Thus, the need to identify the parameters in healthy to mild impaired brain emerges.

Table 1. Initial values (Mice) ("GitHub - Megparks/Alzheimers-disease-model: A differential equation model of neuron death in Alzheimer's disease patients developed in R," n.d.)

Amyloid beta $d_{A_\beta^i}$	Tau protein λ_τ
9.51/day	1.35 * 10^{-11} g/ml

Table 2. Variation in parameter according to a period

Stages	$d_{A_\beta^i}$ (per day)	λ_τ (g/ml)
Onset (3 Year)-early stage	13.314	1.0125 * 10^{-11}
Mild (5 Year)-moderate stage	12.363	1.1475 * 10^{-11}
Advanced (10 Year)-severe	11.412	1.28 * 10^{-11}

Table 3. Initial values (Human) (Hampel & Blennow, 2004; Randall, Mosconi, Leon, & Glodzik, 2013; Roher *et al.*, 2009)

Variable-description	g/ml
A_β^i-Amyloid beta made inside neurons	$350.12 * 10^{-8}$
A_β^o- Amyloid beta outside neurons	$380.12 * 10^{-10}$
T-Tau protein	$660 * 10^{-12}$
F_i-NFTs inside neurons	$3.36 * 10^{-10}$
F_o-NFTs outside neurons	$3.36 * 10^{-11}$
A-Astroglias	0.14
M1-Proinflammatory microglias	0.02
M2-Anti-inflammatory microglias	0.02
N-Neurons	0.14

The concentration of Amyloid Beta inside the neuron increase and then reaches a steady-state, while concentration outside the neuron increase exponentially, suggesting the rise in the amount of amyloid-beta plaque and sheets formation.

The concentration of NFT, on the other hand, is decreasing exponentially, which is the case to be considered in a person with no signs of dementia to mild cognitive impairment, showing that the communication is not disrupted. In contrast, NFT outside the neuron lies in a minimal range that doesn't affect the process.

Activated microglia have two phenotypes: pro inflammatory M1 Type 1 and anti-inflammatory M2 Type 2. They travel in the brain, as are the immune cells in the active brain region. Activated microglia are chemo attracted to dead neurons, more precisely to the cytokines HMGB-1 produced by dead neurons. They are also activated by the extracellular NFTs and by soluble oligomers.

Similarly, astrocytes are activated by extracellular A_β^o. The tau protein concentration within the neuron increases and reaches a steady-state in a normal condition depicted here in the graph.

The concentration of live neuron density, as hypothesized by us, that the neuron death rate increases, which means the amount of live neuron density decrease shown in the graph as linearly, might change but has been linear fitted to the curve obtained.

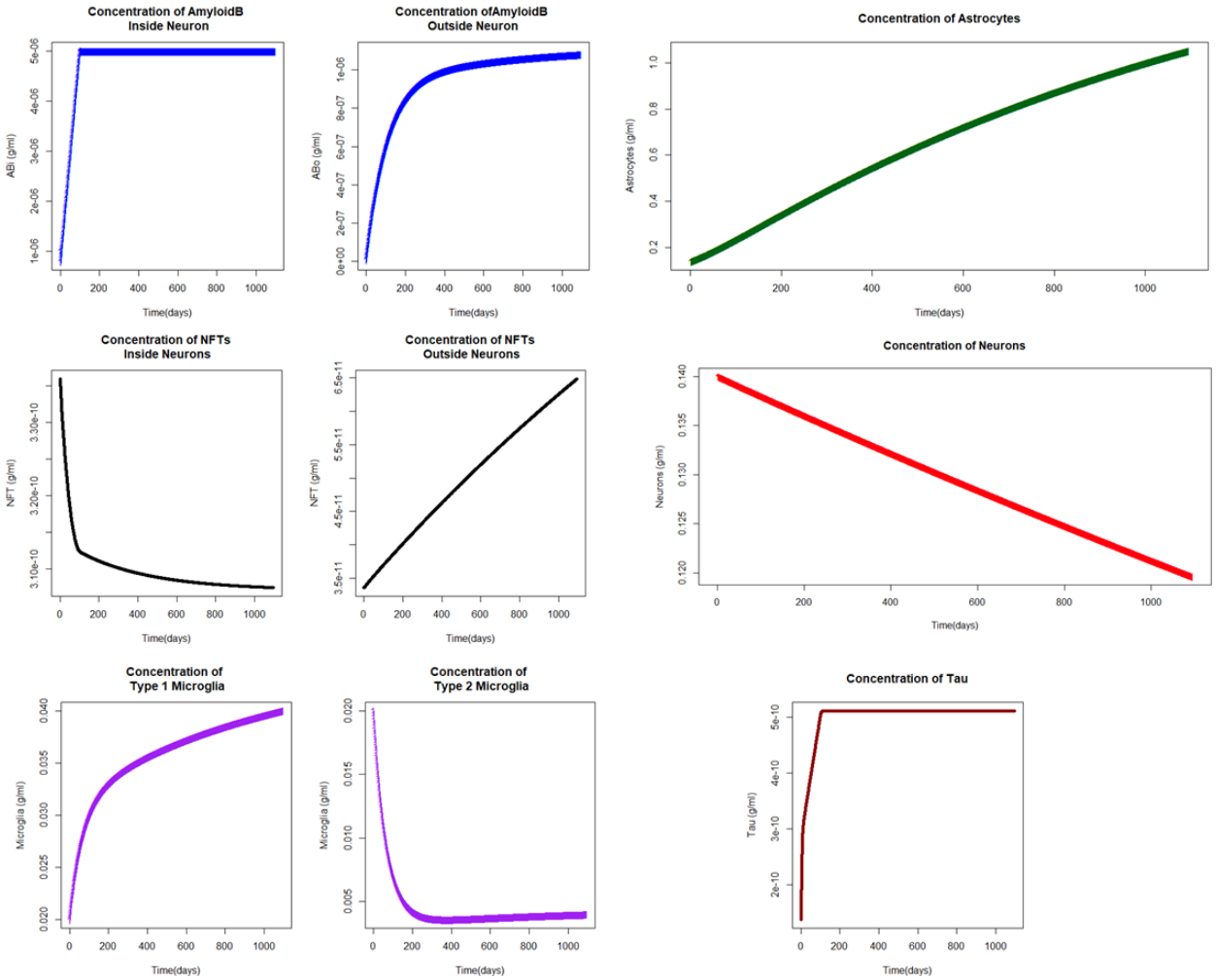


Figure 2. Concentration of parameters

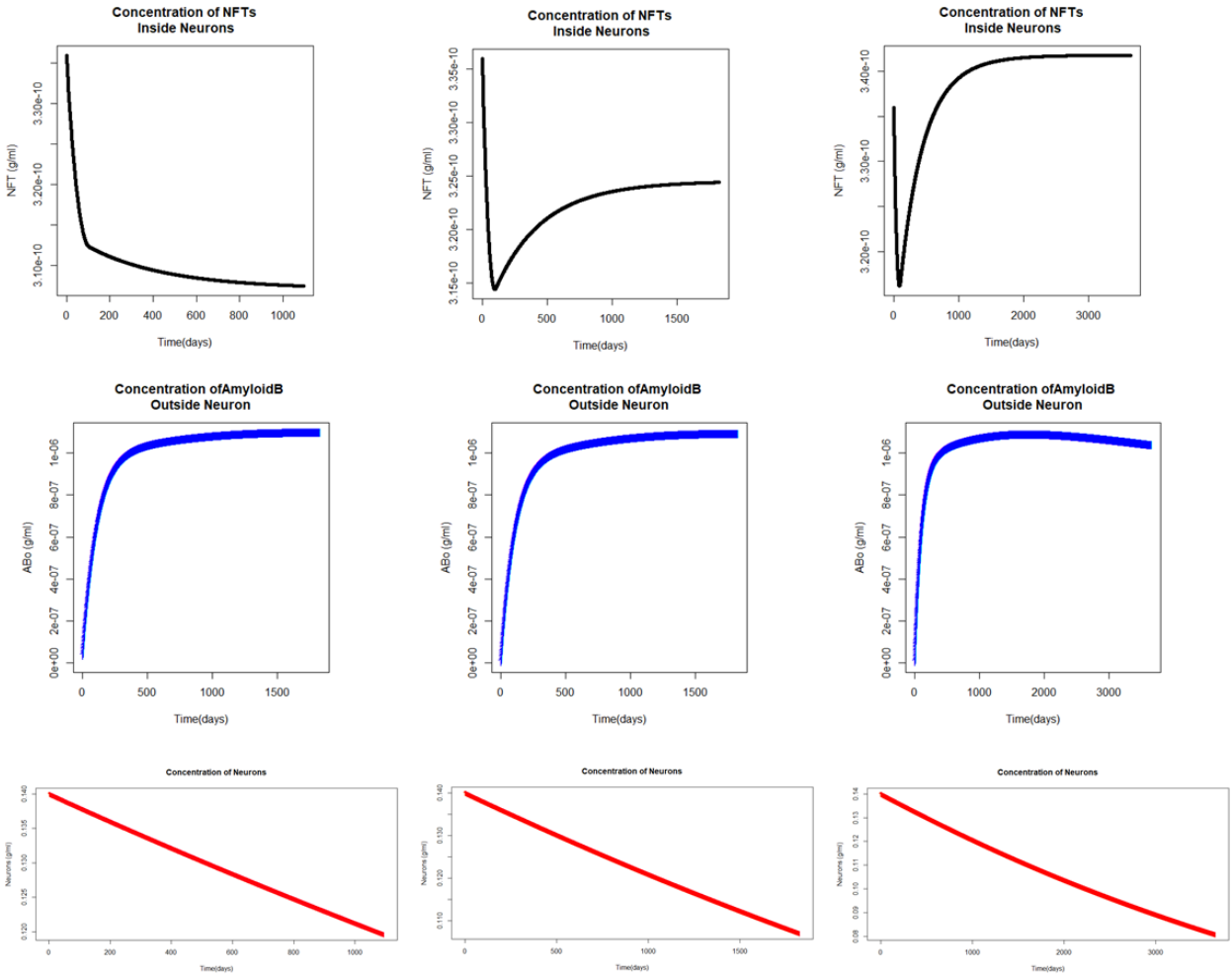
The rise in the level of NFT concerning increase in a year shows the progression of Alzheimer's, resulting in an increase in intracellular tangles, which disrupts the communication between soma and axon and the bubble terminals. Visualization of the progress of NFT concerning consecutive years shows us how the ROS (Reactive Oxygen Species) saturates healthy communication. With the change in a year, microglia and astrocytes that play a crucial role in developing and maintaining neurons are activated and behave abnormally. Their phagocytic part or wall of the damaged areas decreases, and thus, tangles are formed within the soma. Formation of these tangles at early stages is not much crucial but as. When tau protein becomes hyper phosphorylated, it leads to the formation of NFT, hence the progression of Alzheimer's.

The rise in the level of Amyloid Beta concerning an increase in a year shows the progression of Alzheimer's. This process increases extracellular plaques forming sheets surrounding the neuron dendrites and cell body, which is prominent as time changes, disrupting the communication between the current and the next neuron, interrupting the rate at which nerve cells receive the nutrients.

The concentration of live neurons decreases as the neuron death rate increases, clearly seen from the graphs. However, we can see that the decrease is a little sharp in year 10, suggesting that AD is progressing significantly.

To prove our hypothesis, we took the slope of the graph to obtain values. The difference in the slope values gave us the 5% rate of neuron death initially assumed, hence verifying our initial hypothesis.

At last, we tried to identify if an inevitable change of 5% neuron death occurs in the human body between subsequent stages of the disease, would a similar result be generated from the mice model. For this, we followed the initial values from Table 1 and simulated on the same model used for the human being. The results obtained are very similar, having a 5.023% death rate of live neurons, approximately equal to 5%. At later stages, we focus on trying the model for the treatment of the drug also to vary the model according to the different concentrations of parameters extracted from various species of mice which are ideal for observation.



3 Years 5 Years 10 Years

Figure 3. Comparison

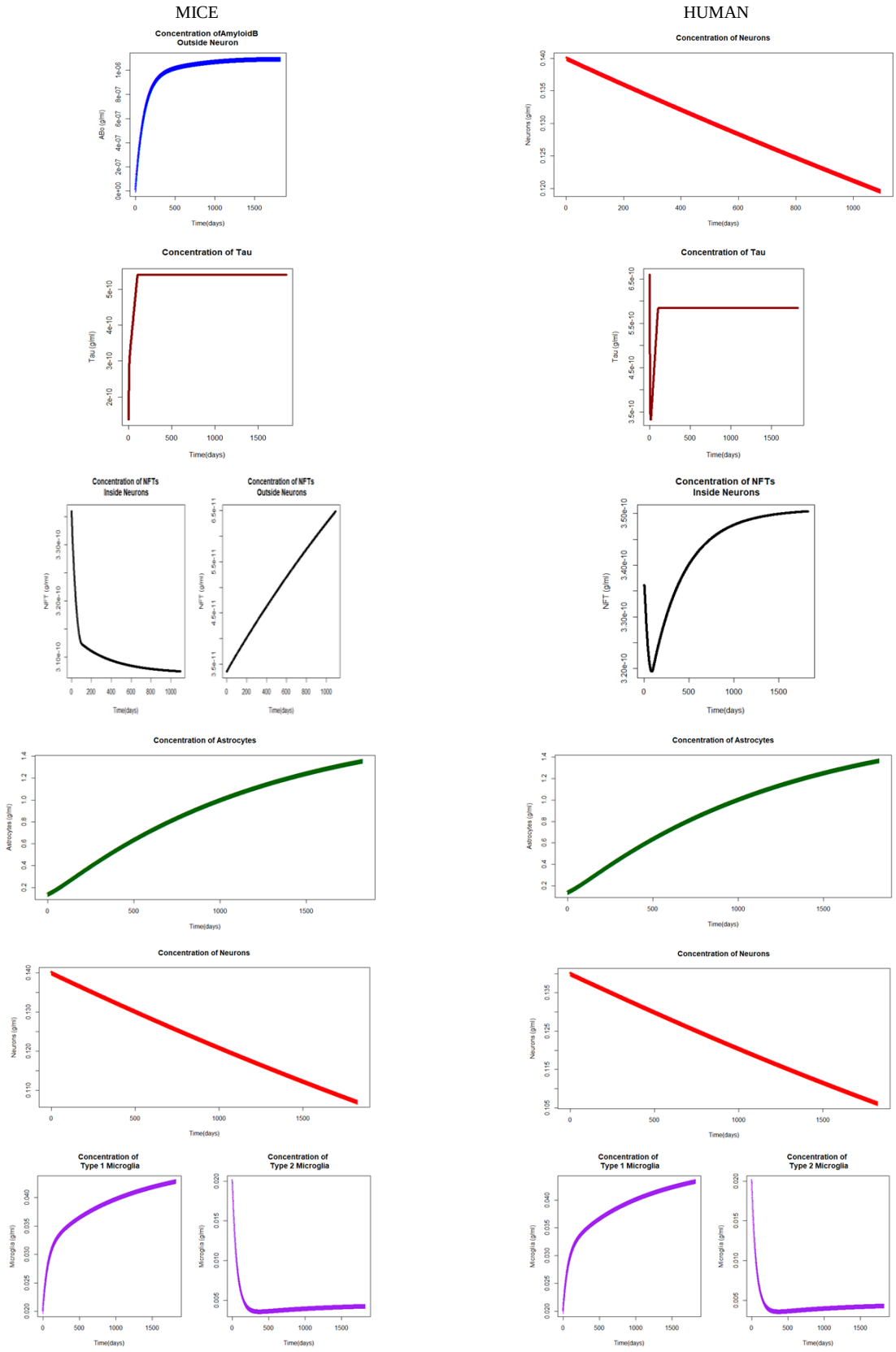


Figure 4. Similarity between human and mice values for the five years

5. Conclusions

We can conclude that A.D. is a progressive disorder that slowly destroys memory and thinking skills and can even do the simplest tasks. Many trials are undergoing to find drugs as well as proper treatment for A.D. One in ten people age 65 have Alzheimer's disease. We observed many reasons for the patient's developing accumulation of beta-amyloid and tau protein. ("Cognitively Stimulating Activities Delay Alzheimer's by 5 Years," n.d.)After studying various hypotheses and claims, we attended to some standard parameters that can support forming a mathematical model of A.D. The mathematical model developed will be based on assumptions on various interactions between amyloid, tau, and other neuro-filaments in A.D.

We achieved the following outcomes:

- Study of different mathematical models of neurons and examine its relationship between various parameters
- Selection of the primary model and do literature and background study for Alzheimer's
- Study various trials, their results, as well as the hypothesis of Alzheimer's disease.
- Derive the relationship between the parameters and the hallmarks causing Alzheimer's

There is still not enough and precise data to sort out complete assumptions and develop a model which will be accurate. Still, we surely can make some assumptions about the role of amyloid and tau proteins in A.D. to observe the progression of the disease.

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