Control Measures for Alzheimer Disease: A Mathematical Approach

Thesis submitted in partial fulfillment of the requirement for the award of the degree of

Masters of Science

In

Mathematics and Computing

Submitted by:
Abhilasha Ahuja
301703001

Under the guidance of
Dr. Parimita Roy
(Assistant Professor)

THAPAR INSTITUTE
OF ENGINEERING & TECHNOLOGY
(Deemed to be University)

Certificate

I hereby certify that the work which is being presented in the thesis entitled "**Control Measures for Alzheimer Disease: A Mathematical Approach**" in partial fulfilment of the requirements for the award of degree of Master of Science, School of Mathematics, Thapar Institute of Engineering and Technology, Patiala is an authentic record of my own work carried out under the supervision of Dr. Parimita Roy.

The material submitted in this thesis has not been submitted for the award of any other degree of this or any other university.

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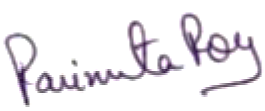
301703001

This is to certify that the above statement made by the candidate is correct and true to the best of my knowledge.



Dr. Parimita Roy

Assistant Professor(SoM)

Thapar Institute of Engineering and Technology, Patiala

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(Abhilasha Ahuja)

301703001

Abstract

Mathematical models can give us good understanding of how diseases progress, and provide us useful prevention, control strategies and guidance. To investigate the dynamics of Alzheimer's disease (AD) we proposed a model system. The proposed model is solved analytically to plan and prepare most effective control measure. We also perform numerical simulation using Runge-Kutta method and finite difference scheme. The dissemination of thesis results will be particularly directed toward scientists and to biological decision-makers, to raise awareness on the potential risks associated with drugs and promote gamma waves therapy as an alternative AD therapy. By the end of this work a policy piece will be prepared to discuss the relevance of the project's findings for designing rehabilitation or therapeutic strategies and might provide promising prospects for clinical interventions for Alzheimer's disease.

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Chapter-1

INTRODUCTION AND LITERATURE REVIEW

"It is a strange, sad irony that so often,
in the territory of a disease that robs an individual
of memory, caregivers are often the forgotten."
— *Karen Wilder*

1.1. Introduction

Alzheimer's disease (AD) is the most frequent form of dementia that affects senior age. It is identified by loss of neurons and neuro-muscular junction in the cerebral cortex. Alzheimer's is an intensifying disease in which dementia symptoms worsen over years. People suffering from this disease find it difficult to communicate and to respond to their environment. According to a recent report, the number of people suffering from dementia will be nearly 65.7 million in 2030 and 115.4 million in 2050 (Alzheimer's Disease International, 2013). Apart from the social dysfunction of patients, economic cost of this disease is also a remarkable consequence (Wimo and Prince, 2010). Therefore, there is a need to identify neuroimaging biomarkers that can grant accurate and early diagnosis of dementia. The cause of this neurodegenerative disorder is still unknown.

Many people have heard of Alzheimer's disease but not many are sure about what it is. Some facts about this condition are as listed below:

1. Alzheimer's is a chronic progressive condition which affects the brain causing slow decline.
2. Currently, there is no cure for Alzheimer's. However, its progression can be slowed by proper treatment.
3. Alzheimer's disease is a type of dementia.
4. People over age of 65 are prone to this disease. It might also occur to those having a family history of this disease.
5. This disease doesn't have same outcome for everyone. Some people suffer a quick onset of symptoms and disease progression while other suffer for a long time with slow damage.

The brain consists of 100 billion nerve cells that are called neurons. These nerve cells are connected to each other through networks. Every Group of neurons has some special jobs. Some of them are occupied in thinking, learning and remembering. Others work on how do we see, hear and smell. Scientists have discovered that Alzheimer's disease prevents parts of a cell from functioning properly. They are not sure in which part the trouble starts. Cells lose their ability to follow their jobs as the damage spreads and they eventually die. This causes irreparable changes in the brain.

Alzheimer’s disease is characterized by the presence of two types of neuropathological structures: extracellular plaques and intracellular neurofibrillary tangles (NFTs). These two structures called plaques and tangles are responsible for damaging and killing neurons. Plaques are the deposits of a protein fragment called beta-amyloid. This builds up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that build up inside the cells. Memory failure, change in personality, problems carrying out daily activities are the primary symptoms of Alzheimer's disease. All of these are caused by death and destruction of nerve cells. The extracellular plaques mainly consist of amyloid-beta peptide (Aβ) deposits. These peptides are acquired from the amyloid protein precuror (APP). Different forms of β-amyloid occurs in different forms which include soluble monomers and insoluble fibrillar aggregates. AD is usually confirmed by diagnosing the behavioural assessments and cognitive tests which are followed by a brain scan. Many advanced medical imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have been used as diagnostic indicators for AD. Extensive research has been done to understand the causes and to develop preventive therapies. Although the deposition of amyloid-beta (Aβ) peptides is considered as the main feature characterizing this disease, studies also suggest that microglia activation also plays an important role in the progression of this disease. In a healthy brain, microglia in a state of rest is in its anti-inflammatory state. This along with astroglia in a quiescent state, stimulates neuron survival. Microglia may adopt pro-inflammatory state which can further lead to astroglia proliferation and neuron death. These cells might have a positive or negative effect on the brain and hence they can alter the functioning of brain during the progression of AD.

1.2. Biological Preliminaries

1. Neurons

A neuron is a type of brain cell that sends, receives, processes, and transfers information through electrical and chemical signals. The central nervous system is mainly made up of neurons. It also includes the brain and spinal cord. At birth, the human brain consists of 100 billion neurons. These cells can't be replaced once they die because they don't have the ability to regenerate. Two states of neurons are considered in this model i.e. neuron survival and neuron death.

2. Microglia

Microglia are a type of glial cells located throughout the brain and spinal cord. Nearly 10-15% of population of cells in the brain is covered by microglia. These cells ingest foreign bodies like dead cells and bacteria. Microglia are present in two states: normal microglia which is in an anti-inflammatory state of rest and reactive microglia which is in an active pro-inflammatory state. These cells form an immune system in the central nervous system.

3. Astroglia

Astroglia is a type of microglia. Most of the cell population is covered by astroglia. Microglia is the defense system whereas astroglia is the support structure. Its main feature is to main the chemical environment around a neuron. The two states of this cell type are quiescent astroglia and proliferating astroglia.

4. β-amyloid

Senile plaques are the major component in identifying Alzheimer's. These plaques are formed from amyloid. The deposition of amyloid-beta generates signals which can activate microglia to a pro-inflammatory state resulting in astroglia proliferation and neuron death.

1.3. Tools of Analysis

1.3.1 Definition of Stability

In most cases, ordinary differential equations are used in mathematical models to describe physical phenomena. These are of the form $x' = F(t, x)$ with the initial data $x(t_0) = x_0$.

Definition 1: The solution $x(t)$ is said to be stable if, for each $\in > 0$, there exists a $\delta = \delta(\varepsilon) > 0$ such that for any solution $\bar{x}(t) = x(t, t_o, \bar{x}_0)$ of the given equation , the inequality$\| \bar{x}_0 - x \| < \delta \Rightarrow \| \bar{x}(t) - x(t) \| < \varepsilon \ \forall t > t_0$.

Definition 2: The solution $x(t)$ is said to be asymptotically stable if it is stable and if $\exists$ a $\delta_0 > 0$, such that $\| \bar{x}_0 - x \| < \delta_0 \Rightarrow \| \bar{x}_0(t) - x(t) \| \rightarrow 0$ as $t \rightarrow \infty$.

1.3.2 Hurwitz Theorem

A necessary and sufficient condition for the real parts of all the roots of the polynomial with real coefficients

$L(\lambda) = \lambda^n + a_1\lambda^{n-1} + ...+ a_n$

To be negative is the positivity of all the principal diagonals of the minors of the Hurwitz matrix

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & 0 & 0 & .... & 0 \\ a_3 & a_2 & a_1 & 1 & 0 & 0 & .... & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & 0 & .... & 0 \\ . & . & . & . & . & . & & . \\ 0 & 0 & 0 & 0 & 0 & 0 & .... & a_n \end{pmatrix}$$

It should be noted that the principal diagonal of the matrix H_n exhibits the coefficients of the polynomial $L(\lambda)$ in the order of their numbers from a_1 to a_n. The principal diagonal minors of the matrix are

$$D_1 = |a_1|, D_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix}, ..., D_n = |H_n|.$$

This theorem is not applicable for large values of '*n*'. To observe this, let us apply it to polynomials of the second, third and fourth degrees:

1. $\lambda^2 + a_1\lambda + a_2$

The Hurwitz conditions reduce to $a_1 > 0$ and $a_2 > 0$.

2. $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$

The Hurwitz conditions reduce to $a_1 > 0, a_2 > 0, a_3 > 0$ and $a_1a_2 - a_3 > 0$

3. $\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$

The Hurwitz conditions reduce to $a_1 > 0,\ a_2 > 0,\ a_3 > 0,\ a_4 > 0$ and $a_1a_2a_3 - a_3^2 - a_1^2 a_4 > 0$

From the Hurwitz conditions it follows that all the $a_i > 0,\ i = 1, 2, 3......n$; however, the positivity of all the coefficients is not enough for the real part of all the roots of $L(\lambda)$ to be negative.

1.4. Motivation/State of the Art

At present, there are no drugs to cure or stop the progression of Alzheimer's. It can only be treated by medications that can treat the symptoms of this disease. Possible ways for treating AD include preventing the plagues to build up. It can reduce the inflammation. The prevention and removal of amyloid-beta has not been of much use clinically. The main drugs which have been used are only helpful in preventing symptoms to worsen up. These drugs are anxiolytic and antipsychotic, along with drugs such as cholinesterase inhibitors and memantine. These drugs partially help in controlling some behavioural symptoms.

Most of the people takes music for granted, but it has been proved that it affects the quality of life by regulating emotions in day to day life. Another therapeutic target for AD prevention and treatment is using gamma waves. Recently, the MIT researchers Iaccarino et. al. (2016) used light flickering at 40 hertz and found that gamma wave treatment caused a notable drop in the level of beta amyloid plaques. It was also seen that the treatment raised the activity of immune cells called microglia.

But the question arises how does it work? Now Neuroscientists have brain scanning technology and have recommenced their interest in investigating how different therapies affect our neural circuits. Magnetic resonance imaging was used by a research group in Finland. They discovered that listening to music improves the auditory areas of the brain. Observations implies that the music and gamma wave therapy reduces some behavioral features of AD patients in an effective manner providing a large approval in considering music therapy at least as an effective supplemental non-pharmacological strategy in AD.

1.5. Problem Description and Solution Strategies

To better understand the exact effects of music and gamma waves on Alzheimer's disease further research is needed. Looking into these facts, we formulate mathematical model that can explain brain structural variability very well and provide most cost effective control measure for prevention of disease. The goal this thesis is to implement a framework to determine how these therapies helps to prevent Alzheimer's disease. Mathematical models which are both structurally and dynamically complex will be designed and the following will be answered.

i) What are the social factors associated with Alzheimer's disease?

ii) Which AD therapy is better in terms of cost and effectiveness?

To achieve these objectives, firstly, I will identify those regions where music and gamma waves affects the brain by extensive literature survey and data from advanced medical imaging and pattern recognition techniques. I will then built a robust model based on the study with minimum assumptions and more reality. The existence, uniqueness as well as the qualitative properties of the solution behavior will be analyzed.

Chapter-2

MATHEMATICAL MODELLING AND ANALYSIS

“Man's memory shapes its own eden within.”

-Jorge Luis Borges

Alzheimer's disease is currently known to be the sixth leading cause of death in older people in the United States. Recently, it has been estimated that it can become the third leading cause, just after cancer and heart disease. Having a look at the economic cost of AD, the approximate healthcare costs are of $172 billion per year in the US alone. Even after a lot of research carried out on AD, the exact mechanism of the progression of this disease still remains unknown. Scientists are conducting studies to learn more about plaques, tangles, and other biological features of Alzheimer’s disease. Some of the risk factors that are estimated include obesity, severe brain injury, family history and smoking. With the help of advanced brain imaging techniques, researchers have been able to see the transitions in the functioning of brain and the spread of amyloid peptides in the brain. Efforts are being made to know the symptoms of this disease at a very early stage.

Generally, it is known that music calms the soul and relieves a person from stress and tension. Some common benefits of music include: optimistic approach, positive transition in moods, memory recall, control over life, improving interest where other things prove to be ineffective, speaking fluently, being confident to interact with people etc. Research has estimated that by listening to music, a person suffering from Alzheimer's disease can obtain emotional and behavioral benefits (Smith, 1990). Patients are capable of remembering the music they listened to earlier. This happens because this disease is unable to damage those areas of brain which are linked to musical memories. Music can be used to maintain a person’s social, mental, physical, and emotional functioning (Matrone and Brattico, 2015). Music can treat the brain of those people who are in their early stage of dementia. It can improve their overall functioning of brain.

To better understand the effect of music on amyloid beta and its removal from the brain, we have made an attempt by constructing a mathematical model of Alzheimer’s disease.In this chapter, we propose a mathematical model to describe the role of different components of brain and the deposition of amyloid-β plaques. The deposition of amyloid-β (Aβ) generate inflammatory signals that activate microglia to a pro-inflammatory state. Normal microglia is at rest while it is in anti-inflammatory state. This activation of microglia further results in astroglia proliferation. The state of astroglia is relevant to that of microglia. Microglia in resting state can prevent astroglia proliferation and further promote neuron survival. Whereas activation of microglia leads to astroglia proliferation and intensifies neuron death.

2.1. Formulation of Mathematical Model

Puri and Li, (2010) presented a mathematical model to define major components of AD pathogenesis using ordinary differential equations. The four types of brain structures and cells that were studied and represented in the system of equations were astroglia, microglia, neurons (nerve cells), beta-amyloid. The mathematical model consists of the biological process involved in the formation of amyloid-β which is responsible for the cause of alzheimer's disease. i)The deposition of amyloid-β (Aβ) generate inflammatory signals that activate microglia to a pro-inflammatory state. ii)Normal microglia is at rest while it is in anti-inflammatory state. This activation of microglia further results in astroglia proliferation. iii) The state of astroglia is related to the state of microglia. Resting Microglia can prevent astroglia proliferation and further increase neuron survival. iv)Whereas microglia in an active state leads to proliferating astroglia and an expansion in neuron death.

The system of equations that model different states of astroglia, microglia, and neuron population are given by seven coupled differential rate equations.

1. $\frac{dN_s}{dt} = \alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1$

2. $\frac{dN_d}{dt} = -\frac{dN_s}{dt}$

3. $\frac{dA_q}{dt} = \alpha_4 M_2 - \alpha_5 M_1$

4. $\frac{dA_p}{dt} = -\frac{dA_q}{dt}$

5. $\frac{dM_2}{dt} = (\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta$

6. $\frac{dM_1}{dt} = -\frac{dM_2}{dt}$

7. $\frac{dA\beta}{dt} = \alpha_{15}N_s - \alpha_{16}M_2$

Further the factors involved in the above mentioned process are stated as following variables.

N_s = Population of neuron that has survived at a particular time.

N_d = Population of neuron that has died at a particular time.

A_q = Population of astroglia in quiescence state.

A_p = Population of astroglia in proliferation state.

M_2= Population of normal microglia in the resting state.

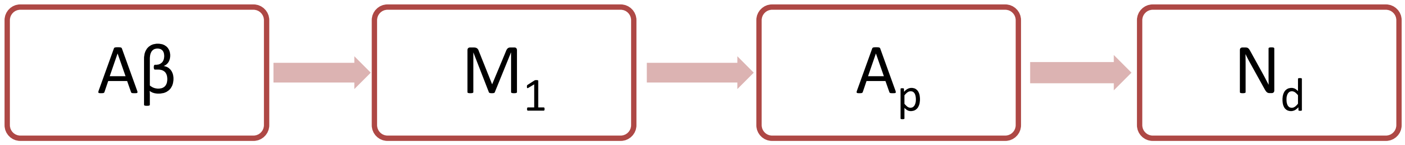
M_1= Population of reactive microglia in the active state.

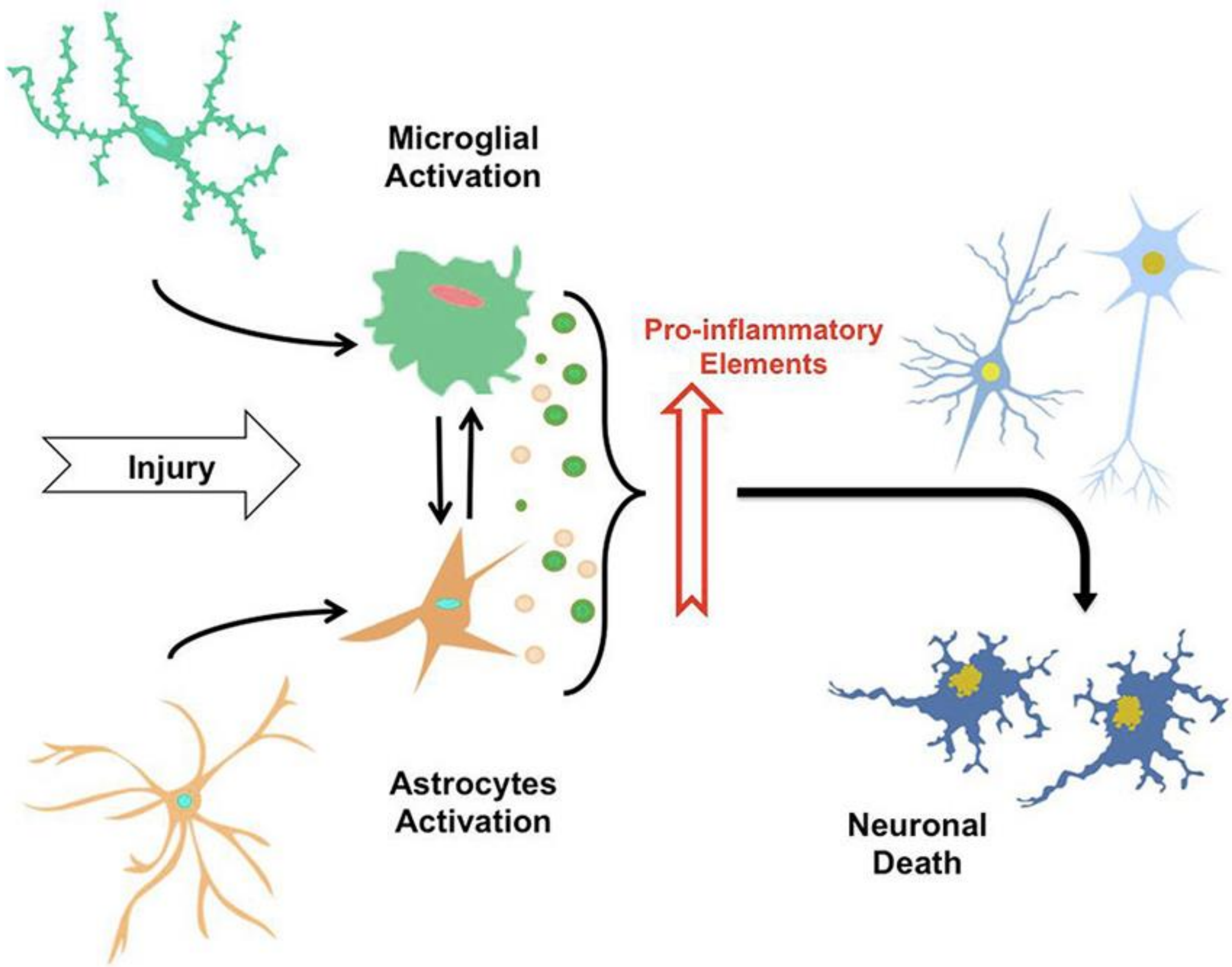
Aβ = Number of amyloid-β peptide molecules

Table 2.1. Model parameters values with description of the functional interactions among various cell types (Puri and Li, 2010).

Rate	**Pathway**	**1/year**
α_1	**$A_q \rightarrow N_s$**	**10^{-5}**
α_2	**$A_p \rightarrow N_d$**	**10^{-3}**
α_3	**$M_1 \rightarrow N_d$**	**10^{-2}**
α_4	**$M_2 \rightarrow A_q$**	**10^{-4}**
α_5	**$M_1 \rightarrow N_d$**	**10^{-2}**
α_6	**$N_s \rightarrow M_2$**	**10^{-2}**
α_7	**$A_q \rightarrow M_2$**	**10^{-4}**
α_8	**$A\beta \perp M_2$**	**10^{-2}**
α_9	**$M_1 \perp M_2$**	**10^{-2}**
α_{10}	**$N_d \rightarrow M_1$**	**10^{-2}**
α_{11}	**$N_s \perp M_1$**	**10^{-2}**
α_{12}	**$A_q \perp M_1$**	**10^{-4}**
α_{13}	**$A\beta \rightarrow M_1$**	**10^{-2}**
α_{14}	**$M_2 \perp M_1$**	**10^{-4}**
α_{15}	**$N_s \rightarrow A\beta$**	**1**
α_{16}	**$M_2 \perp A\beta$**	**10^{-2}**
α_r	**$M_2 \perp A\beta$**	**1**

2.2. Flow Chart





2.3. Analysis of Behavior of the Model

In this section, we calculate all feasible steady states for the model.

2.3.1. Possible Equilibrium

To find the equilibrium point, we solve the following equations simultaneously.

- $\alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1 = 0$
- $-(\alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1) = 0$
- $\alpha_4 M_2 - \alpha_5 M_1 = 0$
- $-(\alpha_4 M_2 - \alpha_5 M_1) = 0$
- $(\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta = 0$
- $-[(\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta] = 0$
- $\alpha_{15} N_s - \alpha_{16} M_2 = 0$

Following solutions are obtained:

$$\mathbf{N_s} = \frac{(M_1 \alpha_{16} \alpha_5)}{(\alpha_{15}\alpha_4)}$$

$$\mathbf{N_d} = \frac{(A_q \alpha_{15}\alpha_4 (\alpha_{12} + \alpha_7) - A\beta\ \alpha_{15}\alpha_4 (\alpha_8 + \alpha_{13}) + M_1(\alpha_{14}\alpha_{15}\alpha_5 + \alpha_{16}\alpha_5 (\alpha_6 + \alpha_{11}) - \alpha_{15}\alpha_4\alpha_9)}{(\alpha_{10}\alpha_{15}\alpha_4)}$$

$$\mathbf{A_p} = \frac{(A_q \alpha_1 - M_1 \alpha_3)}{\alpha_2}$$

$$\mathbf{M_2} = \frac{M_1 \alpha_5}{\alpha_4}$$

2.3.2. Stability Analysis of the Model

Now, we perform the stability analysis of the model system. To analyze the stability of our model, we write the system of equations in matrix form. The system of equations can be written in matrix form as:

$$\frac{dX}{dt} = \begin{bmatrix} 0 & 0 & \alpha_1 & -\alpha_2 & -\alpha_3 & 0 & 0 \\ 0 & 0 & -\alpha_1 & \alpha_2 & \alpha_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_5 & \alpha_4 & 0 \\ 0 & 0 & 0 & 0 & \alpha_5 & -\alpha_4 & 0 \\ \alpha_{11}+\alpha_6 & -\alpha_{10} & \alpha_{12}+\alpha_7 & 0 & -\alpha_9 & \alpha_{14} & -\alpha_{13}-\alpha_8 \\ -\alpha_{11}-\alpha_6 & \alpha_{10} & -\alpha_{12}-\alpha_7 & 0 & \alpha_9 & -\alpha_{14} & \alpha_{13}+\alpha_8 \\ \alpha_{15} & 0 & 0 & 0 & 0 & -\alpha_{16} & 0 \end{bmatrix} X$$

where $X = \begin{bmatrix} N_s \\ N_d \\ A_q \\ A_p \\ M_2 \\ M_1 \\ A\beta \end{bmatrix}$

The characteristic polynomial is given as:

$$\lambda^7 + a_4\lambda^6 + a_3\lambda^5 + a_2\lambda^4 + a_1\lambda^3 = 0 \ ,$$

$$\Rightarrow \lambda^3(\lambda^4 + a_4\lambda^3 + a_3\lambda^2 + a_2\lambda + a_1) = \ 0,$$

$$\Rightarrow \lambda^4 + a_4\lambda^3 + a_3\lambda^2 + a_2\lambda + a_1 = \ 0 \ , \qquad (1)$$

with $a_i > 0$, $i = \ 1,2,3,4$.

Where

$$a_1 = \ -(\alpha_1\alpha_{13}\alpha_{15}\alpha_4 + \ \alpha_{13}\alpha_{15}\alpha_2\alpha_4 + \ \alpha_1\alpha_{13}\alpha_{15}\alpha_5 + \ \alpha_{13}\alpha_{15}\alpha_2\alpha_5 + \ \alpha_1\alpha_4\alpha_{15}\alpha_8 + \ \alpha_{15}\alpha_2\alpha_4\alpha_8 + \ \alpha_1\alpha_8\alpha_{15}\alpha_5 + \ \alpha_{15}\alpha_2\alpha_5\alpha_8)$$

$$a_2 = -(\alpha_{13}\alpha_{15}\alpha_3 - \alpha_1\alpha_{10}\alpha_4 - \alpha_1\alpha_{11}\alpha_4 - \alpha_{10}\alpha_2\alpha_4 - \alpha_{11}\alpha_2\alpha_4 - \alpha_1\alpha_{10}\alpha_5 - \alpha_1\alpha_{11}\alpha_5 - \alpha_{10}\alpha_2\alpha_5 - \alpha_{11}\alpha_2\alpha_5 - \alpha_1\alpha_4\alpha_6 - \alpha_2\alpha_4\alpha_6 - \alpha_1\alpha_5\alpha_6 - \alpha_2\alpha_5\alpha_6 \ + \alpha_{15}\alpha_3\alpha_8)$$

$$a_3 = \alpha_{13}\alpha_{16} + \alpha_{10}\alpha_3 + \alpha_{11}\alpha_3 + \alpha_{12}\alpha_4 + \alpha_{12}\alpha_5 + \alpha_3\alpha_6 + \alpha_4\alpha_7 + \alpha_5\alpha_7 + \alpha_{16}\alpha_8$$

$$a_4 = \alpha_{14} + \alpha_9$$

Since three eigen values are equal to zero, we can’t guarantee its stability. But, in our case, for the parameter values given in table 2.1, the Routh-Hurwitz criteria is:

$$a_1a_2a_3 > a_3^{\ 2} + a_1^{\ 2}a_4$$

Therefore, by Routh-Hurwitz criterion, all the roots of the characteristic polynomial are negative. Thus, the equilibrium is locally asymptotically stable.

Example 1. For the parameter values provided in Table 1, we found that $a_1 a_2 a_3 = 2.04531 \times 10^{-14} < a_3^2 + a_1^2 a_4 = 2.52024 \times 10^{-7}$. Hence the system for the given parameter value is unstable and may not settle at equilibrium point for $t \to \infty$.

2.4. Music can Improve Memory?

Observations imply that the music therapy reduces some behavioral features of epileptic patients in an effective manner providing a large possibility to consider music therapy as an effective non-pharmacological strategy in treating Alzheimer's disease. To better understand the exact effects of music on Alzheimer further research is needed. According to the systematical review provided by Moreira (2018) music promotes neural survival. Looking into these facts, we formulated a mathematical modeling which is a simple extension of model proposed by Puri and Li (2010) as follows:

1. $\frac{dN_s}{dt} = \alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1 + \mu N_s$
2. $\frac{dN_d}{dt} = -\frac{dN_s}{dt}$
3. $\frac{dA_q}{dt} = \alpha_4 M_2 - \alpha_5 M_1$
4. $\frac{dA_p}{dt} = -\frac{dA_q}{dt}$
5. $\frac{dM_2}{dt} = (\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta$
6. $\frac{dM_1}{dt} = -\frac{dM_2}{dt}$
7. $\frac{dA\beta}{dt} = \alpha_{15} N_s - \alpha_{16} M_2$

where μ is effect of music on neuron survival.

2.5. Numerical Simulation

The effect of music on amyloid-beta count and neuron survival is investigated numerically. The ODEs were integrated using Runge-Kutta method in the MATLAB R2017a software environment.

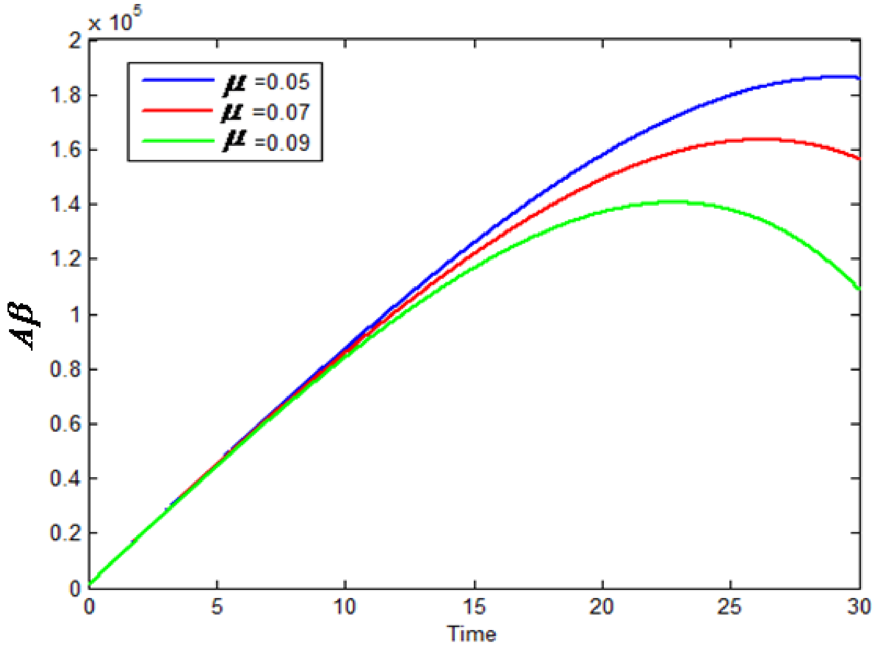


Figure 2.1: Number of amyloid-beta peptides versus time at different rates of music.

In Fig. 2.1, we observe that on increasing the effect of music the number of amyloid-beta peptides go on decreasing. The effect of music was increased from 0.05 to 0.09 which showed a drop in amyloid-beta population from 1.8 X 10^5 to 1.1 X 10^5.

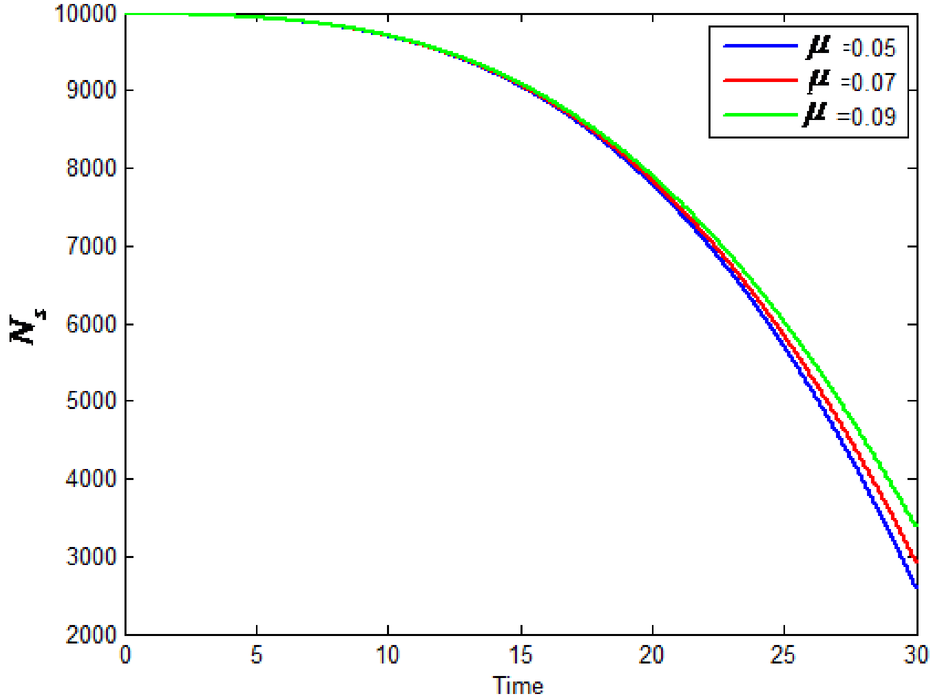


Figure 2.2: Neuron survival versus time at different rates of music.

Fig. 2.2 represents the plot between time and neuron survival showed an increase in neuron survival rate after introducing the effect of music. As a result of these numerical observations, it is observed that music has a notable effect on the decrement of this disease because it leads to decrement of amyloid-beta which is the primary component serving as a growth to this disease.

2.6. Discussion and Conclusions

Alzheimer's disease is a progressive and irreversible disease. This neurodegenerative disease destroys memory and causes cognitive decline. Expected duration for a person to live after the diagnosis of this disease is 10 years. Abnormal aggregations of beta-amyloid are seen in AD patients which is harmful to neurons as we have discussed previously. Modest advances in preventive strategies that cause even small effect in the onset and progression of Alzheimer's disease can help to reduce the global burden of this disease.

We have presented this model for the onset and evolution of AD. The model allows to simulate different modeling hypotheses. We have chosen some specific aspects of the illness, such as the aggregation and removal of Aβ. There are multiple future research developments regarding the evolution of disease and the control measures in different directions, which requires substantial research efforts. We mention some of them. The model that we have studied, can be used to explore the efficacy of music, gamma waves, some drugs or other possible factors that can help reduce the progression of this disease. In this model, we have focused on the progression of AD due to neuron death and deposition of amyloid-beta plaques. Further development of the model is needed. The true challenge is a breakthrough which allows one to develop effective therapies to stop or slow down the evolution of AD, possibly in an early stage of the illness. In further research we have implemented the effect of gamma waves on brain and how they are necessary for the removal of amyloid-beta. A mathematical model can give a contribution in this direction. Finally, some mathematical effort is necessary to check the validation of the model.

Chapter-3
GAMMA WAVES FOR CLEARING ALZHEIMER'S PLAQUES?

"To put it simply our brain span
should match our lifespan."
-Meryl Comer

In this chapter, we will focus on the affect of gamma waves on Alzheimer's disease. A gamma wave is a pattern of electrical activity that takes place in the brain when several neurons get activated at the same time. For a gamma wave an average frequency is of 40 Hertz or 40 oscillations per second. Gamma waves are fundamental to our ability to make sense of the world around us. People with Alzheimer's disease are also found to have impaired gamma oscillations. Gamma waves range from 25 to 80 hertz. It has been estimated that these brain waves promote brain functions. Such activities include attention, recognition and memorizing. Previous research shows that gamma waves are decreased in people with Alzheimer's disease. It was assumed that this was a result of the damage that occurs to brain cells (neurons) due to beta amyloid plaques. Gamma waves work in two ways: they reduce the production of amyloid beta in the first place, and they also activate microglia cells that clear away the damaged beta protein. Microglia are special kind of immune cells that clear away toxic debris in the brain and are increasingly implicated in the development of Alzheimer's disease. When gamma waves are artificially boosted in the memory centre of the brain, it lessens the production of amyloid-beta. Theoretically, this could prevent the onset of dementia symptoms.

Researchers found a way to ascertain whether gamma waves can affect Alzheimer's disease. Some initial studies were done using the technique called optogenetics. They genetically programmed mice to develop AD and later by studying some activities of brain, found that they also had impaired gamma oscillations. After that the hippocampus region of the brain was brought in contact with gamma oscillations at 40 hertz. This region is the area where memory is formed and retrieved. It was found that the beta amyloid protein levels had reduced by a 40-50 percent rate after one hour of stimulation at 40 hertz. This stimulation was done at 40 hertz and other frequencies were found to be ineffective. Tsai and Emery Brown, the Edward Hood Taplin Professor of Medical Engineering and Computational Neuroscience, a member of the Picower Institute, and an author of the paper, figured out a lesser invasive technique. They used light to drive gamma oscillations in the brain. They made a device constituting a strip of LEDs that can be programmed to flicker at different frequencies. What gamma waves do in Alzheimer's disease and what causes them to be disrupted in the first place is not clear, but this study highlights that it is an important area for further research. In this chapter, we have made an attempt to apply the results of this research on our mathematical model.

3.1. Formulation of Mathematical Model

This mathematical model that we have developed consists of effect of gamma waves on the factors that were already present in the previous mathematical model. We noted that flickering light of gamma waves affected the production of microglia, which is further incorporated in the mathematical model as follows:

1. $\frac{dN_s}{dt} = \alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1,$
2. $\frac{dN_d}{dt} = -\frac{dN_s}{dt},$
3. $\frac{dA_q}{dt} = \alpha_4 M_2 - \alpha_5 M_1,$
4. $\frac{dA_p}{dt} = -\frac{dA_q}{dt},$
5. $\frac{dM_2}{dt} = (\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta - \alpha_{17} G,$
6. $\frac{dM_1}{dt} = - \frac{dM_2}{dt},$
7. $\frac{dA\beta}{dt} = \alpha_{15} N_s - \alpha_{16} M_2 - \alpha_{18} G,$
8. $\frac{dG}{dt} = r\,G,$

3.2. Analysis of Behavior of the Model

In this section, we calculate all feasible steady states for the model with effect of gamma waves.

3.2.1. Possible Equilibrium

To find the equilibrium point, we solve the following equations simultaneously:

- $\alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1 = 0$
- $-(\alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1) = 0$
- $\alpha_4 M_2 - \alpha_5 M_1 = 0$
- $-(\alpha_4 M_2 - \alpha_5 M_1) = 0$
- $(\alpha_6 + \alpha_{11})\, N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12})\, A_q - \alpha_9 M_1$
  $+ \alpha_{14} M_2 - (\alpha_8 + \alpha_{13})\, A\beta - \alpha_{17} G = 0$
- $-[(\alpha_6 + \alpha_{11})\, N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12})\, A_q - \alpha_9 M_1$
  $+ \alpha_{14} M_2 - (\alpha_8 + \alpha_{13})\, A\beta - \alpha_{17} G] = 0$
- $\alpha_{15} N_s - \alpha_{16} M_2 - \alpha_{18} G = 0$
- $r\, G = 0$

and obtained the following solutions:

$$\mathbf{N_s} = \frac{(M_1 \alpha_{16} \alpha_5)}{(\alpha_{15} \alpha_4)}$$

$$\mathbf{N_d} = \frac{(A_q \alpha_{15} \alpha_4 (\alpha_{12} + \alpha_7) - A\beta\ \alpha_{15} \alpha_4 (\alpha_8 + \alpha_{13}) + M_1(\alpha_{14} \alpha_{15} \alpha_5 + \alpha_{16} \alpha_5 (\alpha_6 + \alpha_{11}) - \alpha_{15} \alpha_4 \alpha_9)}{(\alpha_{10} \alpha_{15} \alpha_4)}$$

$$\mathbf{A_p} = \frac{(A_q \alpha_1 - M_1 \alpha_3)}{\alpha_2}$$

$$\mathbf{M_2} = \frac{M_1 \alpha_5}{\alpha_4}$$

$$G = 0$$

3.2.2. Stability Analysis of the Model

Now, we perform the stability analysis of the model system. To analyze the stability of our model, we write the system of equations in matrix form .The system of equations can be written in matrix form as:

$$\frac{dX}{dt}=\begin{bmatrix} 0 & 0 & \alpha_1 & -\alpha_2 & -\alpha_3 & 0 & 0 & 0 \\ 0 & 0 & -\alpha_1 & \alpha_2 & \alpha_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\alpha_5 & \alpha_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_5 & -\alpha_4 & 0 & 0 \\ \alpha_{11}+\alpha_6 & -\alpha_{10} & \alpha_{12}+\alpha_7 & 0 & -\alpha_9 & \alpha_{14} & -\alpha_{13}-\alpha_8 & -\alpha_{17} \\ -\alpha_{11}-\alpha_6 & \alpha_{10} & -\alpha_{12}-\alpha_7 & 0 & \alpha_9 & -\alpha_{14} & \alpha_{13}+\alpha_8 & \alpha_{17} \\ \alpha_{15} & 0 & 0 & 0 & 0 & -\alpha_{16} & 0 & -\alpha_{18} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & r \end{bmatrix} X$$

where

$$X=\begin{bmatrix} N_s \\ N_d \\ A_q \\ A_p \\ M_2 \\ M_1 \\ A\beta \\ G \end{bmatrix}$$

The characteristic polynomial is given as:

$$\lambda^8 + b_4\lambda^7 + b_3\lambda^6 + b_2\lambda^5 + b_1\lambda^4 + b_0\lambda^3 = 0$$
$$\Rightarrow \lambda^3(\lambda^5 + b_4\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0) = 0$$
$$\Rightarrow \lambda^5 + b_4\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0 \qquad (1)$$

with $b_i > 0, i = 0,1,2,3,4.$

where

$$b_1 = \mathrm{r}\alpha_1\alpha_{13}\alpha_{15}\alpha_4 + \mathrm{r}\alpha_{13}\alpha_{15}\alpha_2\alpha_4 + \mathrm{r}\alpha_1\alpha_{13}\alpha_{15}\alpha_5 + \mathrm{r}\alpha_{13}\alpha_{15}\alpha_2\alpha_5$$
$$+ \mathrm{r}\alpha_1\alpha_4\alpha_{15}\alpha_8 + \mathrm{r}\alpha_{15}\alpha_2\alpha_4\alpha_8 + \mathrm{r}\alpha_1\alpha_8\alpha_{15}\alpha_5 + \mathrm{r}\alpha_{15}\alpha_2\alpha_5\alpha_8$$

$$b_2 = r\alpha_{13}\alpha_{15}\alpha_3 - r\alpha_1\alpha_{10}\alpha_4 - r\alpha_1\alpha_{11}\alpha_4 - \alpha_1\alpha_{13}\alpha_{15}\alpha_4 - r\alpha_{10}\alpha_2\alpha_4$$
$$- r\alpha_{11}\alpha_2\alpha_4 - \alpha_{13}\alpha_{15}\alpha_2\alpha_4 - r\alpha_{10}\alpha_1\alpha_5 - r\alpha_{11}\alpha_1\alpha_5 - \alpha_1\alpha_{13}\alpha_{15}\alpha_5 - r\alpha_{10}\alpha_2\alpha_5$$
$$- r\alpha_{11}\alpha_5\alpha_2 - \alpha_{13}\alpha_{15}\alpha_2\alpha_5 - r\alpha_1\alpha_4\alpha_6 - r\alpha_2\alpha_4\alpha_6 - r\alpha_1\alpha_5\alpha_6 - r\alpha_2\alpha_5\alpha_6 + \mathrm{r}\alpha_{15}\alpha_3\alpha_8$$
$$- \alpha_1\alpha_{15}\alpha_4\alpha_8 - \alpha_{15}\alpha_2\alpha_4\alpha_8 - \alpha_1\alpha_{15}\alpha_5\alpha_8 - \alpha_{15}\alpha_2\alpha_5\alpha_8)$$

$$b_3 = -r\alpha_{13}\alpha_{16} - r\alpha_{10}\alpha_3 - r\alpha_{11}\alpha_3 - \alpha_{13}\alpha_{15}\alpha_3 + \alpha_1\alpha_{10}\alpha_4 + \alpha_1\alpha_{11}\alpha_4 - r\alpha_{12}\alpha_4$$
$$+\alpha_2\alpha_{10}\alpha_4 + \alpha_2\alpha_{11}\alpha_4 + \alpha_1\alpha_{10}\alpha_5 + \alpha_1\alpha_{11}\alpha_5 - r\alpha_{12}\alpha_5 + \alpha_2\alpha_{10}\alpha_5 + \alpha_2\alpha_{11}\alpha_5$$
$$-r\alpha_3\alpha_6 + \alpha_1\alpha_4\alpha_6 + \alpha_2\alpha_4\alpha_6 + \alpha_1\alpha_5\alpha_6 + \alpha_2\alpha_5\alpha_6 - r\alpha_4\alpha_7 - r\alpha_5\alpha_7 - r\alpha_{16}\alpha_8 - \alpha_{15}\alpha_3\alpha_8$$

$$b_4 = \mathrm{r}\alpha_{14} + \alpha_{13}\alpha_{16} + \alpha_{10}\alpha_3 + \alpha_{11}\alpha_3 + \alpha_{12}\alpha_4 + \alpha_{12}\alpha_5 + \alpha_3\alpha_6 + \alpha_4\alpha_7 + \alpha_5\alpha_7 + \alpha_{16}\alpha_8 - r\alpha_9$$

$$b_5 = -r + \alpha_{14} + \alpha_9$$

Out of all eigenvalues, three eigenvalues are equal to zero. Since these eigen values are equal to zero, we can't guarantee its stability. But, in our case, for the parameter values given in table 2.1, the Routh-Hurwitz criteria is:

$$-b_5[b_4(-b_1b_2b_3 + b_3^2 + b_1^2b_4) + (-b_2b_3 + b_1(b_2^2 - 2b_4))b_5 + b_5^2] > 0$$

Therefore, by Routh-Hurwitz criterion, all the roots of the characteristic polynomial are negative. Thus, the equilibrium is locally asymptotically stable.

3.4. Movement of Microglia

In our modeling we have considered a system of eight ordinary differential equations where each equations describes the rate of increase or decrease in the cells. Neurons, astroglia and microglia are the different kind of cells each of which have two states. That is, neurons have two states: neuron death and neuron survival. Astroglia are in proliferating and quiescent state. Microglia are in normal and reactive state. It has been observed that the total amount of each cell type remains constant over time but their proportions may vary. The proportion of reactive microglia and normal microglia changes over time. Further it has been observed that microglia cells show certain movement with change of time. In fact they are the fastest-moving cells in healthy adult brains. Thus, we infer this result in the system of equations and perform a 2-dimensional analysis to see the effect on microglia with and without effect of gamma waves. The distribution of reactive microglia over different times were studied.

1. $\frac{\partial N_s}{\partial t} = \alpha_1 A_q - \alpha_2 A_p - \alpha_3 M_1$,
2. $\frac{\partial N_d}{\partial t} = -\frac{\partial N_s}{\partial t}$,

3. $\frac{\partial A_q}{\partial t} = \alpha_4 M_2 - \alpha_5 M_1,$

4. $\frac{\partial A_p}{\partial t} = -\frac{\partial A_q}{\partial t},$

5. $\frac{\partial M_2}{\partial t} = (\alpha_6 + \alpha_{11}) N_s - \alpha_{10} N_d + (\alpha_7 + \alpha_{12}) A_q - \alpha_9 M_1 + \alpha_{14} M_2 - (\alpha_8 + \alpha_{13}) A\beta - \alpha_{17} G + D_{M_2} \Delta M_2,$

6. $\frac{\partial M_1}{\partial t} = -\frac{\partial M_2}{\partial t},$ (2)

7. $\frac{\partial A\beta}{\partial t} = \alpha_{15} N_s - \alpha_{16} M_2 - \alpha_{18} G,$

8. $\frac{dG}{dt} = r\,G,$

the model system (2) is analyzed under zero flux boundary condition

$\frac{\partial M_2}{\partial n} = 0,\ z \in \partial\Omega, t > 0,$ and under the initial conditions given by

$M_2(z,0) = M_{20} > 0,$ **where** $z = (x, y) \in \Omega = [0, L] \times [0, L].$

D_{M_2} is diffusion-coefficient of reactive microglia. In the above, *n* is the outward unit normal vector of the boundary $\partial\Omega$ and the homogeneous Neumann boundary condition is being considered. The Laplacian operator $\Delta = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}$, is used to describe the local Brownian random motion in two-dimensional space.

3.5. Numerical Simulation

3.5.1. Without Diffusion

Gamma waves work in reducing the production of amyloid beta and they also activate microglia cells that clear away the damaged beta protein. By introducing the effect of gamma waves in the mathematical model, it was observed numerically that on increasing the effect of gamma waves, neuron survival increased with a remarkable rate. Thus, it is verified by means of numerical simulations that gamma waves have a positive effect on neuron survival which in turn is beneficial to decrease the risk of Alzheimer's disease.

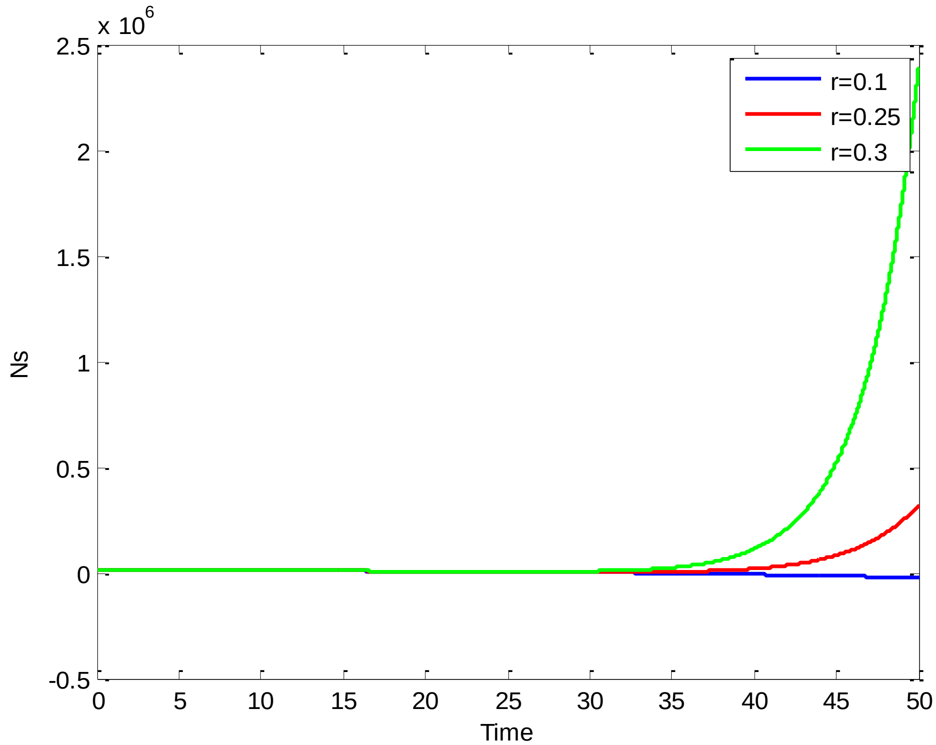


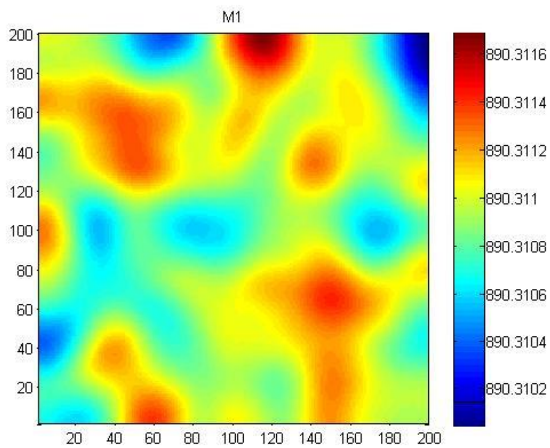
Figure 3.1: Neuron survival versus time at different values of *r*.

3.5.2. With Diffusion

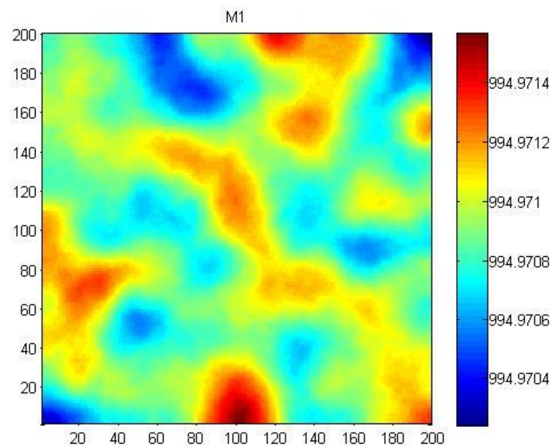
In this section, we perform simulations of diffusive model system in two dimension. All our numerical simulations use non-zero initial condition and zero-flux boundary conditions having system size of 200×200 discretized through $(x_0, x_1, x_2 \ldots x_N)$ and $(y_0, y_1, y_2 \ldots y_N)$, with N = 300. The spacing between the lattice points is defined using lattice constant Δh. For $\Delta h \to 0$, the differences approach the derivatives. In the present study, we set $\Delta t = 0.001$; $\Delta h = 0.25$. We employ explicit and standard five-point approximation for the 2D Laplacian with the Neumann (zero-flux) boundary conditions. The plots gives spaces vs. population densities.

3.5.2.1 Effect of Gamma Waves on Distribution of Microglia

Figure 3.2 show the distribution of reactive microglia at time 1000 hours with effect of gamma waves. But no remarkable change was observed on the pattern distribution of microglia while the density of microglia increases uniformly as predicted. However, on further increasing the time of simulation to 10000 and 50000 hours (Figures 3.3 and 3.4) we found that the distribution of reactive microglia increases on the entire domain with the effect of gamma waves i.e. the microglia increases in all parts of brain. Our mathematical model is a small step towards understanding the distribution of microglia under the effect of gamma rays and ultimately clearing amyloid beta plaques responsible for Alzheimer's disease.

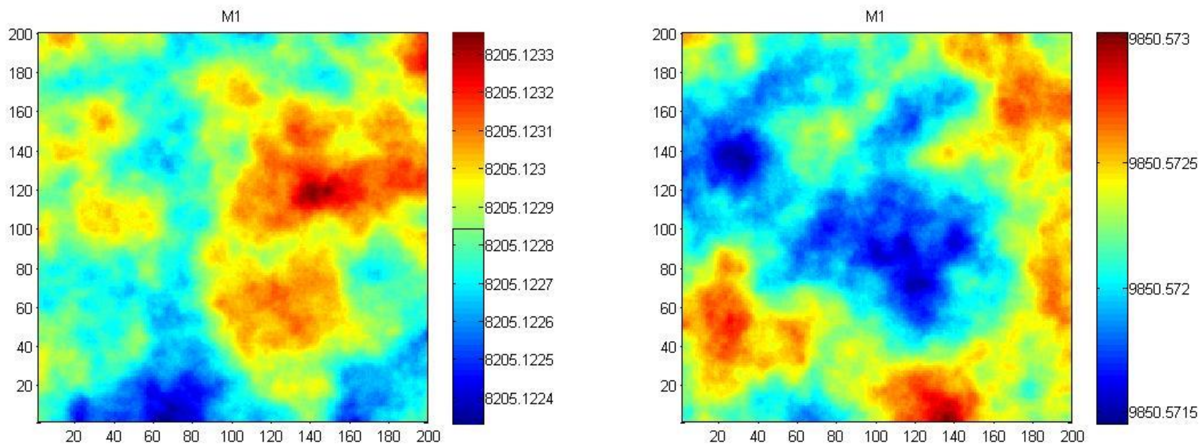


(a)



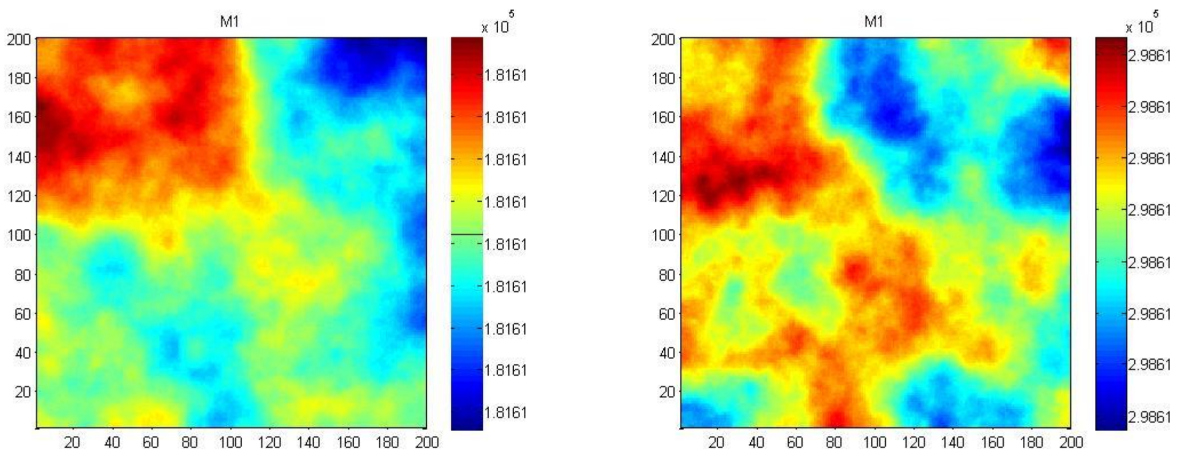
(b)

Figure 3.2: Distribution of reactive microglia after 1000 hours (a) without effect of gamma waves (b) with effect of gamma waves.



(a) (b)

Figure 3.3: Distribution of reactive microglia after 10,000 hours (a) without effect of gamma waves, (b) with effect of gamma waves.

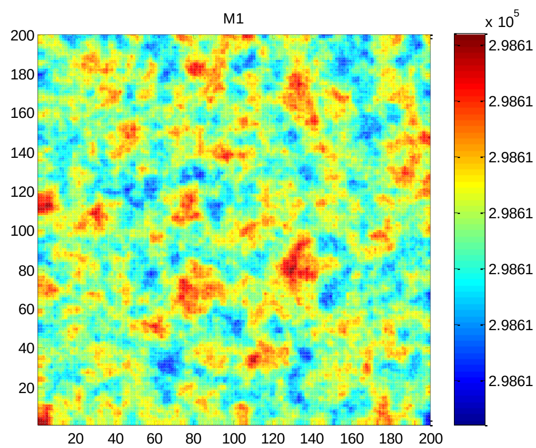


(a) (b)

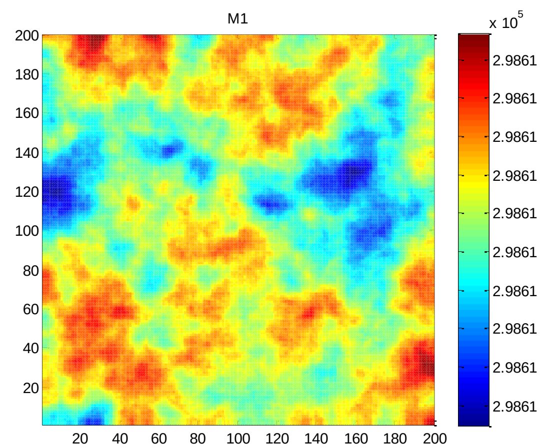
Figure 3.4: Distribution of reactive microglia after 50,000 hours (a) without effect of gamma waves, (b) with effect of gamma waves.

3.5.2.2. Effect of Diffusion Coefficient

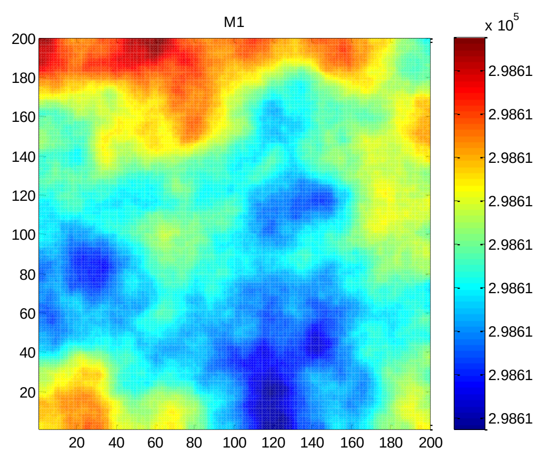
In this section, the spatiotemporal dynamics of system (2) is observed by changing the diffusion coefficient D_{M_2}. The diffusion coefficient D_{M_2} is increased from 0.01 to 10. From simulations, we observe that the density of microglia remains almost the same in all the cases but the scattered distributed microglia gets clustered on increasing the diffusion coefficient (c.f. Figure 3.5). From this we suggest that chemical which increases the microglia diffusion should be avoided to cross brain blood barrier to break its clusterization. It is yet to be known how these brain macrophages gather, store, and carry out their various functions under normal and disease conditions and further study is required.



(a)



(b)



(c)

Figure 3.5. Patterns produced through simulating model system (2) varying D_{M_2} at $t = 50$ days with (a) $D_{M_2} = 0.01$, (b) $D_{M_2} = 1$, (c) $D_{M_2} = 10$.

3.6. Discussion and Conclusions

It has been observed clinically that people suffering from Alzheimer's disease have impaired gamma oscillations. In a study of mice with Alzheimer's disease, the researchers have investigated that gamma wave treatment for a longer duration could reduce amyloid-beta plaques in mice. Both plaques and amyloid-beta were found to be markedly reduced after seven days treatment of the mice for one hour a day. So the concept of gamma waves in brain is something that needs more research. Thus, we have made an attempt to capture the effect of gamma waves on brain through our mathematical model. The stability analysis of our model is done. Further, it was verified numerically that effect of gamma waves increases the neuronal survival in brain. It has been found that beta amyloid formation rate depreciates after gamma wave therapy. Thus, we conclude microglia clears out beta amyloid proteins from the brain. Gamma waves actually benefit the whole process in two ways (i) They reduce beta amyloid levels in brain and, (ii) they increase the rate of clearance of amyoid beta. The role of microglia in this disease is debatable, because although they produce harmful cytotoxins that promotes neuronal death (Barron, 1995; Angelov et al., 1998), they may also secrete factors that enhance neuronal survival (Barron, 1995; Elkabes et al., 1996) .

Chapter-4

SUMMARY AND CONCLUSIONS

"Never let the brain idle. 'An idle mind is the devil's workshop.'
And the devil's name is Alzheimer's."
-George Carlin

The thesis consists of four chapters in which second and third chapter discusses the mathematical models for Alzheimer's disease and shows the impact of control measure if implemented. *Chapter 2* explains the extended mathematical model of the disease and its stability. Further it consists of numerical simulation that also shows the effect of music on neuron survival and amyloid-beta peptides. In *Chapter 3*, we tried to model the disease by introducing effect of gamma waves. Gamma waves have effect on both microglia as well as amyloid beta. We try to identify the change in neuron count with the effect of flickering light.

Both models are analyzed using different tools of dynamical system theory, namely, Routh-Hurwitz criteria, etc. We found conditions as to when the equilibrium point is locally asymptotically stable. Numerical experimentation has been performed for the proposed system of equations by considering biologically relevant values. The model indicates that the disease will decline by increasing the rate of music because it causes an increase in neuron survival and decrease in amyloid-beta. Also, the model in Chapter 3 indicates that neuron survival increases on a better rate when gamma wave therapy is introduced. We have inferred this result in the system of equations and performed a 2-dimensional analysis to see the effect on microglia with and without effect of gamma waves. We also observed the distribution of microglia cells, with change of diffusion coefficient.

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