Project Report

On

# MATHEMATICAL MODELLING ON ALZHEIMER'S DISEASE AND THE EFFECT OF DRUGS

*Submitted*

*in partial fulfilment of the requirements for the degree of*

MASTER OF SCIENCE

*in*

MATHEMATICS

*by*

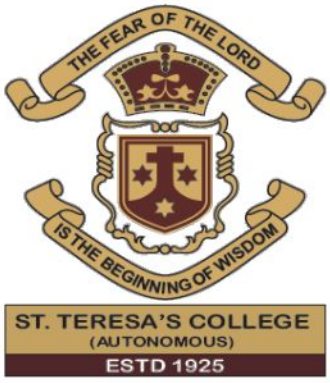
JOSNA VARGHESE

(Register No. SM20MAT007)

(2020-2022)

*Under the Supervision of*

DHANALAKSHMI O.M.




DEPARTMENT OF MATHEMATICS

ST. TERESA'S COLLEGE (AUTONOMOUS)

ERNAKULAM, KOCHI - 682011

APRIL 2022

ST. TERESA'S COLLEGE (AUTONOMOUS), ERNAKULAM

# CERTIFICATE

This is to certify that the dissertation entitled, **MATHEMATICAL MODELLING ON ALZHEIMER'S DISEASE AND THE EFFECT OF DRUGS** is a bonafide record of the work done by Ms. **JOSNA VARGHESE** under my guidance as partial fulfillment of the award of the degree of **Master of Science in Mathematics** at St. Teresa's College (Autonomous), Ernakulam affiliated to Mahatma Gandhi University, Kottayam. No part of this work has been submitted for any other degree elsewhere.

Date: 26/05/2022
Place: Ernakulam

**DHANALAKSHMI O.M.**
Assistant Professor,
Department of Mathematics,
St. Teresa's College(Autonomous),
Ernakulam.

ST. TERESA'S COLLEGE DEPT. OF MATHEMATICS ERNAKULAM

**Dr.Ursala Paul**
Assistant Professor and HOD,
Department of Mathematics,
St. Teresa's College(Autonomous),
Ernakulam.

**External Examiners**

1: DIVYA MARY DAISE S 26/05/2022

2: MARY RUNIYA 26/05/2022

# DECLARATION

I hereby declare that the work presented in this project is based on the original work done by me under the guidance of **DHANALAKSHMI O.M.** , Assistant Professor, Department of Mathematics, St. Teresa's College(Autonomous), Ernakulam and has not been included in any other project submitted previously for the award of any degree.

Ernakulam. **JOSNA VARGHESE**

Date: 26/05/2022 **SM20MAT007**

# ACKNOWLEDGEMENTS

First and foremost, I thank God with my whole heart for being able to complete my project with success.I would like to express deep gratitude for my guide Ms. Dhanalakshmi O.M. for her extraordinary guidance and support in completing my project.

I would like to extend my sincere gratitude to all the teachers of the Department of Mathematics and Statistics of St.Teresas College, Ernakulam and a special gratitude for the Head of the Department, Dr. Ursala Paul and my class teacher Ms. Nisha Oommen.

I would like to thank my parents and brother for their excellent support for completing my project.

Last but not the least I would like to thank my classmates who support.

Ernakulam. JOSNA VARGHESE

Date: 26/05/2024 **SM20MAT007**

# Contents

# Chapter 1

# INTRODUCTION

**In 1901, Karl Deter, a railway worker admitted his fifty-one-year-old wife, Auguste, to a psychiatric institution with symptoms of memory loss, confusion, violent outbursts, and inability to use language. According to Karl, Auguste's symptoms began to emerge in the late 1890s and were quite uncommon for the person he had come to know. She had become increasingly fearful and anxious and would sometimes scream loudly for several hours. Her condition became so overwhelming and debilitating that her family could no longer manage her care. For the next five years until she passed away, auguste remained at the institution and was observed by an German psychiatrist, Alois Alzheimer. After her death, Alzheimer performed histological studies on Auguste Deter's brain tissue. In the process, he discovered two abnormalities: Large abnormal clumps had formed between neurons and ropelike tangles had formed inside neurons. Calling these abnormalities, a peculiar disease of the cortex, Alzheimer presented his findings at a 1906 psychiatric conference in Germany, marking the first documented case of what is now known as Alzheimer's disease. Over the next five years, eleven similar cases were reported in medical journals. Today more than on hundred years later, there are approximately 35.6 million people suffering from Alzheimer's disease worldwide. To the shock of many, the 2010 world Alzheimer report projected that this number will almost double to 65.7 million cases by 2030 and will more than triple to 115.4 million cases by 2050.**

Dementia is a clinical syndrome characterized by a progressive decline in our cognitive skills such as memory, language, thinking and personal behavior. Alzheimer's is a common form of dementia that accounts for 50- 80 % of all dementia cases. Sometimes we interchangeably use both terms, but Alzheimer's one of, but, most notorious among the forms of dementia. Alzheimer's disease majorly affects people included in the age group above 65 years. According to the reports more women are affected by this disease twice than men. But this disease is observed in people in the age group of 35 to 50 years as an early onset Alzheimer's disease.

According to the studies, Alzheimer's disease which is short formed into AD is an irreversible disease. But this is not most shocking aspect of this disease. Even though, the medical field so advanced, but we are failed to find a cure for this disease. drugs and immunizations through vaccinations became a failure.

Alzheimer's is due to two pathological hallmarks: extracellular plaques formed by the accumulation of a protein called Amyloid beta peptide and the intracellular tangles formed by the Tau proteins.

If we try to learn any mechanism or any concept with the help of mathematics, then the it will be more clearly and precisely understandable.so, here we discuss the reason, progression of Alzheimer's disease and the effect of drugs that once invented but failed due to safety concerns and also the drugs that are still on clinical trials with the help of mathematics. We develop a mathematical model on Alzheimer's disease and the effect of drugs and this will be a dynamic model.

The content will be divided into three chapters. The first chapter will give a precise idea about the cause and progression of Alzheimer's disease mathematical modelling, mathematics and theoretical biology.in the second chapter we will introduce models for factors causing Alzheimer's

**disease using partial differential equations. The third chapter will discuss about the drugs that are invented but, failed and also on clinical trials. We will discuss the reason for the failure of drugs mathematically.**

# Chapter 2

# PRELIMINARIES

## 2.1 INTRODUCTION

In this chapter we will discuss about the notorious form of dementia, it's causes and progression. Since we want to explain the Alzheimer's diseases with the help of mathematics we will discuss about various mathematical models. Since we are dealing with some biological concepts here, we will also discuss about mathematics and theoretical biology.

## 2.2 ALZHEIMER'S DISEASE

Dementia is a clinical syndrome that is characterized by a progressive decline the cognitive skills such as memory, language, thinking and personal behavior. Alzheimer's is a common form of dementia that accounts for 50-80 % of dementia cases. Alzheimer's disease commonly known as AD. Sometimes people interchangeably use both dementia and AD. So, we should remember that Alzheimer's disease is a common form of dementia among so many other brain related diseases.it majorly affects the people belonging to the age group above 65 years old. But, majority of the people believe that Alzheimer's disease is only an age-old disease, because it is common among the age- old group and sometimes we forget to give much attention to the age-old people showing low memory issues. But these may be symptoms to Alzheimer's disease. Alzheimer's can be affected people belonging to age group of 30 to 50 as an early onset of Alzheimer's disease. Alzheimer's disease is an

irreversible and incurable disease. Even though our medical field is so advanced worldwide, our inability to invent a medication without any failure makes the causes for Alzheimer's disease notorious. Alzheimer's disease can be genetically inherited. Alzheimer's disease is mainly due to two proteins: extracellular plaques formed by the accumulation of a protein called amyloid beta peptide and intracellular neuro fibrillary tangles formed by the deposition of a protein called tau protein.

### 2.2.1 TAU PROTEINS

Tau protein is predominantly found in brain cells (neuron). Among tau's multiple functions in healthy brain cells, a very important on aid stabilization of the internal microtubules. Tau is a small protein with a short name but a large reputation because of its association with multiple brain diseases. The accumulation of amyloid beta in the brain of a person with AD is largely completed at an earlier clinical stage known as mild neurocognitive disorder. However, tau accumulation continues throughout the course of the disease. The aggregation of hyperphosphorylated tau proteins leads to the formation of neurofibrillary tangles. Beginning in the parts of the brain called the entorhinal cortex and hippocampus, brain tau continues to accumulate as AD progresses. Tau PET scans may in the future provide a biomarker measurement that will meaningfully indicate disease progression. The first of the tau PET tracers to be approved by the US FDA is F-18 flortaucipir. Many new AD clinical trials are including tau PET scans as a potential biomarker of disease severity.

### 2.2.2 MACROPHAGES

Macrophages are a type of white blood cell of the immune system that engulfs and digests anything that does not have, on its surface, proteins that are specific to healthy body cells including cancer cells, microbes, cellular debris, foreign substances etc.

### 2.2.3 MICROGLIAS

Microglia are a type of neuroglia located throughout the brain and spinal cord. Microglia and other neuroglia including astrocytes are distributed in large non- overlapping regions throughout the central nervous system. Microglia are key cells in overall brain maintenance they are constantly scavenging the central nervous system for plaques, damaged or unnecessary neurons and synapses and infectious agents.

## 2.3 PROGRESSION OF THE DISEASE

There is a strong correlation between amyloid beta peptide and tau proteins in the progression of disease. The neurofibrillary tangles are formed by aggregation of tau proteins.so, let's take a look at the progression of this disease.

Reactive oxygen species are highly reactive chemicals formed from oxygen($O_2$). The build-up of reactive oxygen species may cause damage to DNA, RNA and proteins and even cell death. The presence of these chemicals can be observed in the early stages of progression. We have already mentioned the amyloid precursor protein (APP) releases the amyloid beta peptide and this deposition becomes abnormal when the reactive oxygen species becomes high level. Tau proteins are mainly seen in the neurons and they promote the microtubules assembly and their stability. There is an enzyme called Glycogen synthase kinase - type 3 (GSK 3) which will be activated by the abnormal production of amyloid beta peptides. They mediate the hyperphosphorylation of tau proteins which lead to the microtubule depolymerization and destruction and they aggregate to form the neurofibrillary tangles. Due to this action the neuronal death happens and finally leads the neurofibrillary tangles to the extracellular environment since all these events happens inside the intraneural environment.

There is another pathway for the progression of the diseases and that

is via some non-neuronal cells. Non- neuronal cells support the neurons directly.

Microglias are the resident macrophages which helps in the conversations between the neurons, transportation of nutrients from blood to brain. Microglias are activated by the soluble $A\beta$ oligomers which are formed from the $A\beta$ deposits in the brain.

Macrophages are highly efficient in phagocytosis action when compared to microglias in the clearance of $A\beta$ .

Astrocytes are activated by $TNF-\alpha$ but in a small amount when compared to the neurons and also Monocyte Chemoattractant Protein-1 (MCP-1) which attracts monocytes from blood into the plaques. The monocytes then differentiated to form proinflammatory macrophages, $\overline{M_1}$ and then to anti- inflammatory macrophages $\overline{M_2}$.

Microglias are activated to form proinflammatory $M_1$ and then to anti-inflammatory $M_1$.

The combination of $M_1$ and $\overline{M_1}$ macrophages which are neurotoxic in nature to produce the proinflammatory cytokines $TNF-\alpha$, $IL-6$, $IL-12$,$IL-1\beta$. The combination of $M_1$ microglias and $\overline{M_2}$ macrophages produce the anti-inflammatory cytokines $IL-10$, $IL-13$, $IL-4$, $TBF-\beta$.

The proinflammatory cytokines causes neuronal stress and the anti-inflammatory cytokines will resist the stress and this results in the neuronal damage and neuronal death. There is a controversary in the action of $TBF-\beta$.It provides the protection that is needed from the neuron inflammation and neurodegeneration and also it supports in the formation of plaques and helps in the progression of the disease.

So, we have discussed the both pathways in the progression of the disease. So, we will be making a mathematical model for the Alzheimer's disease by making use of the partial differential equations. We consider each the components that will lead to the diseases in both the pathways.

Since, there is no cure is found for the disease we will try to examine some of the drugs that are once and also the ones that are still on clinical trials. We will also try to give some suggestions and predictions for the drug that has to be developed.

## 2.4 MATHEMATICAL MODELLING

Mathematical model is a description of a system using mathematical concepts and mathematical language. The process of constructing a mathematical model is called mathematical modelling. A model may help in understanding a system, explaining it, studying the effects and predicting the behaviour.

Mathematical models can take any forms including dynamical systems, differential equations, statistical models or game theoretic models. all these types of models can also overlap in the construction of the desired model.

A mathematical model is usually consisting of relationships and variables. Relationships can also be defined as operators like algebraic operators, functions, differential operators etc. variables are the abstractions of the parameters of the system of our interest.

### 2.4.1 CLASSIFICATION OF MATHEMATICAL MODELS

**Linear and Non- Linear-** if all the operators or relationships in a mathematical model shows the linearity, then the model will be linear. otherwise, the model is said to be non- linear.

**Dynamic and Static-** a dynamic model accounts for the time dependent changes in the state of the system and it is represented by differential equations. A static model calculates the system in equilibrium and thus it is time- invariant.

**Explicit and implicit-** if all the input parameters of the overall model are known, and the output parameters can be calculated by finite series of computations the model is said to be explicit. If the output parameters which are known, and the corresponding inputs must be solved by an iterative procedure, then the model is said to be implicit.Discrete and continuous- a discrete model treats objects and continuous model represents the objects in a continuous manner.

**Deterministic and probabilistic-** a deterministic model is one in which every set of variable states is uniquely determined by parameters in the model and by sets of previous states of these variables. In a stochastic model randomness is present and the variable states are not described by unique values, but rather by probability distributions.

Here, we consider the dynamic mathematical model for our study about the Alzheimer's disease.

### 2.4.2 MATHEMATICS AND THEORETICAL BIOLOGY

Mathematical and theoretical biology or biomathematics is a branch of biology which employs theoretical analysis, mathematical models and abstractions of the living organisms to investigate the principles that govern the structure, development and behaviour of the of the systems as opposed to experimental biology which deals with the conduction of experiments to prove and validate the scientific theories. The field is sometimes called mathematical biology or biomathematics to stress the mathematical side or theoretical biology to stress the biological side.

# Chapter 3

# MATHEMATICAL MODELLING ON ALZHEIMER'S DISEASE

**In this chapter we will discuss and construct mathematical models for various factors related to Alzheimer's disease.**

## 3.1 MATHEMATICAL MODEL

**In the intracellular environment, we demonstrate the partial differential equations for Amyloid beta peptide and tau proteins.**

### 3.1.1 FOR AMYLOID BETA PEPTIDE

**Let $A_\beta^i$ be number of Amyloid beta peptide in the intracellular environment. Let the Amyloid precursor protein (APP) release at the rate of $\lambda_\beta^i$.An abnormal production of these peptides happens by the reactive oxidation process and let it be R.So, the rate of peptides produced during this process will be $R\lambda_\beta^i$.**

**Therefore, the total production of Amyloid beta peptide is $\lambda_\beta^i + R\lambda_\beta^i$.**

**We also mentioned that these peptides degrade in a small amount. So let it be at the rate of $d_{\lambda_\beta^i}$**

**Let $N_0$ be the total density of neurons and $N$ be the neurons at the time of measurement.**

$\frac{\partial A^i_\beta}{\partial t} = [(\lambda^i_\beta + R\lambda^i_\beta) - d_{\lambda^i_\beta} A^i_\beta]\frac{N}{N_0}$

$\lambda^i_\beta$= **9.51 X $10^{-6}$ g/ml/day estimated**

$d_{\lambda^i_\beta}$ = **9.51/day**

$N_0$ = **0.14 g/cm$^3$ (Reference density)**

### 3.1.2 FOR TAU PROTEINS($\tau$)

**Under reactive oxidation process the abnormal production of Amyloid beta peptides activates the enzyme Glycogen Synthase kinase – type 3 (GSK- 3) and that mediates the hyperphosphorylation of tau proteins.**

**Let the production of tau proteins is at the rate of $\lambda\tau^0$ .**
**The abnormal production of Amyloid beta peptide leads to the activation of GSK 3 and then to the hyperphosphorylation of tau proteins.**

**When $A^i_\beta$ produced abnormally, then after a certain stage like a threshold value of $A^{i0}_\beta$ .During the oxidative process R ,the tau proteins are produced at a rate of $R\lambda_\tau$**

**Therefore, the total production of tau proteins is $\lambda\tau^0$+$R\lambda_\tau$**

**The tau proteins are degraded at a rate of $d_\tau$**

**Let the original density of neurons be $N_0$ and let the density of neurons at the time of measurement be N .**

**The rate of change of tau proteins is,**

$\frac{\partial \tau}{\partial t} = [(\lambda_{\tau_0} + R\lambda_\tau) - d_{\lambda_\tau}\lambda_\tau]\frac{N}{N_0}$

### 3.1.3 FOR NEUROFIBRILLARY TANGLES ($\mathbf{F}_i$)

**The NFTs in neurons ($F_i$) are formed by hyperphosphorylation of tau proteins and when neurons die, they are released to the extracellular region ($F_O$).**

**Let $\frac{\partial F_i}{\partial t}$ be the rate of change of intracellular NFTs and let $\frac{\partial F_O}{\partial t}$ be the rate of change of extracellular NFTs.**

**Extracellular NFTs are formed by the hyperphosphorylation of tau proteins. Let $\lambda_F$ be the production rate of neurofibrillary tangles by the hyperphosphorylation of tau proteins.**

**The production of NFTs will be $\lambda_F \tau$**

**Let $d_{F_i}$ be the degradation rate of $d_{F_i} F_i$.**

**Then, the corresponding equation is,**

$$\frac{\partial F_i}{\partial t} = (\lambda_F \tau - d_{F_i} F_i) \frac{N}{N_0}$$

**Let N be the number of neurons and let $|\frac{\partial F_i}{\partial t}|$ be the value of rate of change of neurons.**

**Then, the corresponding equation for the $F_O$**

$$\frac{\partial F_O}{\partial t} = F_i |\frac{\partial F_i}{\partial t}| - d_{F_O} F_O$$

$d_{F_O}$ **= 2.77 X $10^{-4}$/day**

### 3.1.4 FOR NEURONS

**There are two reasons that lead to the neuronal death.**

**1. Hyperphosphorylated tau proteins leads to the formation of neu-**

rofibrillary tangles (NFTs) and that lead to the depolymerisation of microtubules and that finally leads to the neuronal death.
2. The neuronal stress caused by the proinflammatory cytokines (we represent the proinflammatory cytokines by $TNF-\alpha$ )is resisted by the anti- inflammatory cytokines (we represent the anti-inflammatory cytokines by $IL-10$).However, it leads the neuronal damage and death.

Let $d_{NF}$ be the death rate of neurons by NFTs and let $d_{NT}$ be the death rate of neurons by $TNF-\alpha$.

Let $N$ be the number of neurons.

Let $F_i$ be the NFTs inside neurons and let $T_\alpha$be the $TNF-\alpha$.

$$\frac{\partial N}{\partial t} = -d_{NF}\frac{F_i}{F_i+K_{F_i}}N - d_{NT}\frac{T_\alpha}{T_\alpha+K_{T_\alpha}}\frac{1}{1+\gamma I_{10}/K_{I_10}}N$$

( In the sequel, in an expression of the form $\frac{X}{X+K_X}$ in the context of activation, the half saturation parameter $K_X$ is taken to be the steady state of the species $X$, provided $X$ tends to a steady state. Hence, in a steady state equation this factor is equal to $\frac{1}{2}$. If $X$ doesn't tend to a steady state, then the parameter $K_X$ will be taken to be the estimated average of X over a period of 10 years, the average survival time of AD patients. In an expression of the form $\frac{1}{1+\gamma x/K_X}$ where,$\gamma=\gamma(X)$ in the context of inhibition, $K_X$ is again the half- saturation of X, so that in steady state the inhibition is $1/(1+\gamma)$. If cells Y phagocytose species X, then the clearing rate is proportional to $Y\frac{X}{X+K_X}$ where the Michaelis-Menten constant $\overline{K}_X$ depends only on the 'eating capacity' of Y, has no relation to the half-saturation of X.)

### 3.1.5 FOR ASTROCYTES($A$)

Astrocytes are formed by $TNF-\alpha$ ($T_\alpha$) and also by $A\beta$ oligomers ($A_\beta^O$).

Let $\frac{\partial A}{\partial t}$ be the rate of change of astrocytes with time t.

**The production rate of astrocytes is $\lambda_{AA^O_\beta} A^O_\beta + \lambda_{AT_\alpha} \mathbf{T}\alpha$ and the death rate of astrocytes is $d_A A$.**

**Then, the corresponding equation is,**
$\frac{\partial A}{\partial t} = \lambda_{AA^O_\beta} A^O_\beta + \lambda_{AT_\alpha} \mathbf{T}\alpha - d_A A$

### 3.1.6 FOR DEAD NEURONS($N_d$)

**Let the rate of change of dead neurons be $\frac{\partial N_d}{\partial t}$ and the production rate of dead neurons is $-d_{NF} \frac{F_i}{F_i + K_{F_i}} N - d_{NT} \frac{T_\alpha}{T_\alpha + K_{T_\alpha}} \frac{1}{1+\gamma I_{10}/K_{I_1 0}} N$**
**The dead neurons are cleared out by both microglias ($M_1$ & $M_2$) and and macrophages ($\overline{M_1}$ & $\overline{M_2}$).**

**Let $d_{N_d M}$ the clearance rate of dead neurons by the macrophages.**

**Let $\overline{K_{N_d}}$ be the Michaelis- Menten coefficient for $N_d$.**
**( $\overline{K_{N_d}} = 10^{-3}$ g/ml )**

**Then, the corresponding equation will be,**

$$\frac{\partial N_d}{\partial t} = d_{NF} \frac{F_i}{F_i + K_{F_i}} + d_{NT} \frac{T_\alpha}{T_\alpha + K_{T_\alpha}} \frac{1}{1+\gamma I_{10}/K_{I_1 0}} N -$$

$$\mathbf{d}_{N_d M}(M_1 + M_2) \frac{N_d}{N_d + \overline{k}_{N_d}} - d_{N_d \overline{M}} (\overline{M_1} + \overline{M_2}) \frac{N_d}{N_d + \overline{K}_{N_d}}$$

### 3.1.7 FOR $A\beta$ OLIGOMERS (A$\beta$O)

**The soluble Aß oligomers can diffuse throughout the brain.**

**Let $A_O$ be the density of $A\beta$ oligomers and let $\frac{\partial A_O}{\partial t}$ be the rate of change of density of Aß oligomers.**

**Let $D_{A_O}$ be the diffusion coefficient of Aß oligomers and let $\Lambda_{A_O}$ be a small portion of the Aß oligomers.**

**Let $\lambda_{A_O}$ be the production rate of Aß oligomers.**

**The production of Aß oligomers will be $\lambda_{A_O} A_\beta^O$ and the degradation rate will be $d_{AO} A_O$.**

**Then the corresponding equation is,**

$\frac{\partial A_O}{\partial t} - D_{A_O} \lambda_{A_O} = \lambda_{A_O} A_\beta^O - d_{AO} A_O$

### 3.1.8 FOR HMGB-1 (H)

**When the cell death occurs through necrosis, the dying cells release the HMGB-1 (take part in the inflammatory actions inside the body). In the progression of Alzheimer's disease, the dying neurons release the HMGB-1.**

**Let $\frac{\partial H}{\partial t}$ be the rate of change of HMGB-1.**

**Let $D_H$ be the diffusion coefficient of HMGB-1 and let $\Delta H$ be a small portion of HMGB-1.**

**The production of HMGB-1 is mainly due to the dead neurons. Let $\lambda_H$ be the production rate of HMGB-1 and the production of HMGB-1 will be $\lambda_H N_d$.**

**The degradation of HMGB-1 will be equal to $d_H H$.**

**Then, the corresponding equation is,**
$\frac{\partial H}{\partial t} - \Delta H D_H$-=$\lambda_H N_d - d_H H$

### 3.1.9 FOR MICROGLIAS

**Microglias are activated by extracellular NFTs ($F_O$) and also by the soluble Aß oligomers ($A_O$).**

**There are proinflammatory microglia,$M_1$ and anti-inflammatory microglia,$M_2$.**

**Activated microglias are chemoattracted to dead neurons and then mainly to the HMGB-1.**

**Microglias become $M_1$ by proinflammatory $TNF-\alpha$ and $M_2$ by anti-inflammatory $IL-10$.**

**Let $\frac{\beta\epsilon_1}{\beta\epsilon_1+K\epsilon_2}$ be the ratio at which activated microglia into $M_1$ ( $\beta$ represents the proinflammatory/ anti- inflammatory environment) and let $\frac{\epsilon_1}{\beta\epsilon_1+K\epsilon_2}$ be the ratio at which the activated microglia into $M_2$.**

**There is a transition from $M_1 \longrightarrow$M$_2$ by $TGF-\beta$.**

**Then, the corresponding equation is,**

$$\frac{\partial M_1}{\partial t} - \nabla(M_1\nabla H) = M_G^O[\lambda_{MF}\frac{F_O}{F_O+K_{FO}} + \lambda_{MA}\frac{A_O}{A_O+K_{AO}}]\frac{\beta\epsilon_1}{\beta\epsilon_1+K\epsilon_2} - \lambda_{M_1}T_\beta\frac{T_\beta}{T_\beta+K_{T\beta}} -$$

$$\mathbf{d}_{M_1}M_1$$

$$\frac{\partial M_2}{\partial t} - \nabla(M_2\nabla H) = M_G^O[\lambda_{MF}\frac{F_O}{F_O+K_{FO}} + \lambda_{MA}\frac{A_O}{A_O+K_{AO}}]\frac{\beta\epsilon_1}{\beta\epsilon_1+K\epsilon_2} - \lambda_{M1}T_\beta\frac{T_\beta}{T_\beta+K_{T\beta}} -$$

$$\mathbf{d}_{M_2}M_2$$

### 3.1.10 FOR CYTOKINES

**The proinflammatory microglia and macrophages are neurotoxic but they form the proinflammatory cytokines $TNF-\alpha, IL-6, IL-12, IL-1\beta$. The anti-inflammatory microglia and macrophages form the anti-inflammatory cytokines $IL-10, IL-13, IL-4, TGF-\beta$.**

#### FOR TNF $-\alpha$

**The proinflammatory cytokine $TNF-\alpha$ is produced by both proinflammatory microglia, $M_1$ and the macrophage,$\overline{M_1}$.**

**Let $\lambda_{T_\alpha M_1}$ be the production rate of $TNF-\alpha$ by microglia and let $\lambda_{T_\alpha \overline{M}_1}$ be the production rate of $TNF-\alpha$ by macrophages.**

**Let $D_{T\alpha}$ be the death rate of $TNF-\alpha$ in the portion $\Delta_{T\alpha}$.**

**Let $d_{T\alpha}$ be the degradation rate of $TNF-\alpha$.**

**Then, the corresponding equation is,**

$$\frac{\partial T_\alpha}{\partial t} - D_{T\alpha}\Delta_{T\alpha} = \lambda_{T_\alpha M_1} M_1 + \lambda_{T_\alpha \overline{M}_1}\overline{M_1} - d_{T\alpha}T_\alpha$$

**FOR IL-10 ($I_{10}$)**

**The anti-inflammatory cytokine, $I_{10}$ is produced by both anti-inflammatory microglia, $M_2$ and the macrophage, $\overline{M}_2$.**

**Let $\lambda_{I_{10}M_1}$ be the production rate of IL-10 in the portion $\Delta I_{10}$.**
**Let $d_{10}$ be the degradation rate of IL-10.**

**Then, the corresponding equation is,**

$$\frac{\partial I_{10}}{\partial t} - D_{I10}\Delta I_{10} = \lambda_{I_{10}} M_2 M_2 + \lambda_{I_{10}\overline{M}_2}\overline{M_2} - d_{I10}I_{10}$$

**FOR TGF$-\beta$**

**The anti-inflammatory cytokine $TGF-\beta$ is produced by both anti-inflammatory microglia $M_2$ and the macrophage $\overline{M_2}$.**

**Let $\lambda_{T\beta}M_2$ be the production rate of $TGF-\beta$ by microglia $M_2$ and let $\lambda_{T_\beta \overline{M}_2}$ be the production rate of $\overline{M}_2$.**

**Let $D_{T\beta}$ be the death rate of $TGF-\beta$ in the portion $\Delta_{T\beta}$.**

**Let $d_{T_\beta}$ be the degradation rate of $TGF-\beta$.**
**Then, the corresponding equation is,**

$$\frac{\partial T_\beta}{\partial t} - D_{T\beta}\Delta_{T\beta} = \lambda_{T_\beta M_2} M_2 + \lambda_{T_\beta \overline{M}_2}\overline{M_2} - d_{T\beta}T_\beta$$

**FOR MCP-1**

**The activated astrocytes produce the Monocyte Chemo attaractant Protein (MCP-1) attracts the monocytes from blood to the plaques. The monocytes differentiate the proinflammatory macrophages $\overline{M}_1$ into anti-inflammatory $\overline{M}_2$.**

**MCP-1 is produced by both activated astrocytes(A) and the anti-inflammamtory microglia $M_2$.**

**Let $\lambda_{PA}$ be the production rate of MCP-1 by the activated astrocyte A and let $\lambda_{PM_2}$ be the production rate of MCP-1 by microglia $M_2$.**

**Let $D_P$ be the death rate of MCP-1 in the portion, $\Delta P$.**

**Let $d_P$ be the degradation rate of MCP-1.**

**Then, the corresponding equation is,**

$$\frac{\partial P}{\partial t} - D_P\Delta_P = \lambda_{PA}A + \lambda_{PM_2}M_2 - d_P$$

# Chapter 4

# THE EFFECT OF THE DRUGS

**There is no cure found for Alzheimer's disease but, there are medications which are on clinical trials. The drugs and immunizations in the form of vaccines that have been invented became a failure. There are some drugs which can only control the symptoms for a short time. Let's take a look at those.**

Table 4.1: Example of Table in Latex

| DRUG NAME | DRUG TYPE AND USE | HOW IT WORKS |
|---|---|---|
| ADUCANUMAB | Immunotherapy that modifies the disease that will treat the early-stage Alzheimer's disease. | Removes the abnormal production of Amyloid beta peptide so that the number of plaques can be reduced. |
| DONEPEZIL | Cholinesterase inhibitor prescribed to treat the symptoms of Alzheimer's disease ranging mild, moderate and severe | Prevents the breakdown of acetylcholine. |
| RIVASTIGMINE | Cholinesterase inhibitor prescribed to treat the symptoms of Alzheimer's disease ranging mild, moderate and severe | Prevents the breakdown of acetylcholine and butyrylcholine in the brain. |
| MEMANTINE | N- methyl D- aspartate antagonist prescribed to treat6 symptoms of moderate to severe Alzheimer's | Blocks the toxic effects associated with excess glutamate and regulates glutamate activation. |
| MANUFACTURED COMBINATION OF MEMANTINE AND DONEPEZIL | NMDA antagonist and cholinesterase inhibitor prescribed to treat symptoms of moderate to severe Alzheimer's disease | Blocks the toxic effects associated with excess glutamate and prevents the breakdown of acetylcholine in the brain. |
| GALANTAMINE | Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's disease | Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain. |

**The main cause for the progression of the disease is the degradation of the neurons. If we can control the cell death, we can slower the progression and thereby controlling the symptoms. The drugs that are prescribed for the AD patients are only meant to control the symptoms but not to slower the progression.**

**The main reason for the progression of the disease is due to the plaque formation by the accumulation of Aß deposits and the tangles formed by the aggregation of tau proteins. So, we need an anti- amyloid and anti- tau drug. Inflammation is also a reason for the progression of the disease which leads to the need of a drug that can prevent the inflammation.**

**So, we consider the drugs that are once failed and still in the clinical trials. We are going to check its efficacy among the affected with the help of partial differential equations. The main failure of the drugs is because of the safety concerns.**

## 4.1 TNF $-\alpha$ INHIBITOR

**When the $TNF-\alpha$ get increased, it will lead to the enhancement of $A\beta$ and reduces the $A\beta$ clearance. Then, it will lead to the neuron death and make way for the progression of the disease. So, it is needed to inhibit the production of $TNF-\alpha$.The medical field has invented some $TNF-\alpha$ Inhibitors (TNFIs). Etanercept is a TNFI which delivers a cognitive improvement effect and Infliximab is another TNFI which effects in the cognitive improvement conducted on humans. The main hindrance is due to the limitation in blood-barrier penetration.**

**To study the effect of $TNF-\alpha$ Inhibitor, we will apply the mathematical model.**

**Let us consider the equation for $TNF-\alpha$ by considering the TNFI, Etanercept.**

$\frac{\partial T_\alpha}{\partial t} - D_{T\alpha}\Delta_{T_\alpha} = \lambda_{T_\alpha M_1} M_1 + \lambda_{T_\alpha \overline{M}_1}\overline{M_1} - d_{T\alpha}T_\alpha$

**Etanercept is TNFI and this drug act as a soluble TNF receptor that binds $TNF-\alpha$ and $TNF-\beta$.**

**We will try to determine the effect in the amount of $TNF-\alpha$ when the AD patient take TNFI for 10 years after 300 days of the diagnosis of the disease.**

**To represent the Etanercept, let f proportional to the amount of Etanercept. Since, Etanercept is an inhibitor it reduces the amount of $TNF-\alpha$ with time, t.**

$\frac{\partial T_\alpha}{\partial t} - D_{T\alpha}\Delta_{T_\alpha} = \lambda_{T_\alpha M_1} M_1 + \lambda_{T_\alpha \overline{M}_1}\overline{M_1} - d_{T_\alpha}T_\alpha - fT_\alpha$

**$TNF-\alpha$ will diminish at the rate of $fT_\alpha$.**

## 4.2 TGF $-\beta$ INJECTION

**The anti- inflammatory microglia $M_2$ and macrophage $\overline{M_2}$ produces the anti- inflammatory cytokine $TGF-\beta$. $TGF-\beta$ leads to change of proinflammatory macrophages to anti- inflammatory macrophages and leads to the production of $TNF-\alpha$ and to the progression of the disease.**

**When we inject the $TGF-\beta$ decreases the proinflammatory microglia $M_1$ and the macrophage $\overline{M_2}$ and that leads to the decrease in $TNF-\alpha$.**

**Let us consider the equation for the $TGF-\beta$.**

$\frac{\partial T_\beta}{\partial t} - D_{T\beta}\Delta_{T\beta} = \lambda_{T_\beta M_2} M_2 + \lambda_{T_\beta \overline{M}_2}\overline{M_2} - d_{T\beta}T_\beta$

**When a person affected with AD takes the $TGF-\beta$, it reduces the production of $TNF-\alpha$.**

**Let g be proportional to the amount of $TGF-\beta$ injected.**

**Then, the corresponding equation is,**

$$\frac{\partial T_\beta}{\partial t} - D_{T\beta}\Delta_{T\beta} = \lambda_{T_\beta M_2} M_2 + \lambda_{T_\beta \overline{M}_2}\overline{M_2} - d_{T\beta}T_\beta + g$$

## 4.3 MCP-1 INHIBITOR

**The activated astrocytes produce the Monocyte chemo attractant Protein (MCP-1 ). The monocytes differentiate to form proinflammatory macrophages to anti- inflammatory macrophages.**

**So, if we can inhibit the MCP-1 ,we can decrease the neuronal death.**

**Bindarit is an MCP-1 inhibitor which is on clinical trials.**

**This inhibitor decreases $\overline{M_2}$ and that leads to the decrease in the proinflammatory cytokine, $TNF-\alpha$ which ultimately leads to the decrease in neuronal death.**

**When an affected patient takes MCP-1 inhibitor (K ), then the MCP-1 will be degraded at the rate of $d_P PK$.**

**Then, the corresponding equation will be,**

$$\frac{\partial P}{\partial t} - D_P\Delta_P = \lambda_{PA}A + \lambda_{PM_2}M_2 - d_P P(1+K)$$

# Chapter 5

# CONCLUSION

Alzheimer's disease which is a common form of dementia which accounts upto 80 % of all dementia cases. It causes a decline in some cognitive skills and personality behaviour of the affected persons and causes inability in doing even basic tasks for our daily living. The cause behind this disease is mostly unknown and the disease is irreversible. This disease strikes mostly people above 65 and affects twice more women than men. The disease can also affect younger people as an early onset case. Even though our medical field is so advanced, but we are unable to find a complete cure for the disease.

The main reason for the progression of the disease due to the accumulation of a 42-amino acid called Amyloid Beta Peptide in the extracellular environment and also due to the neurofibrillary tangles formed due to the hyperphosphorylation of the tau proteins.

There are two pathways for the progression of the disease.

The first one is, there are highly reactive chemicals called Reactive Oxidation Species (ROS). When the level ROS becomes high that leads to the abnormal production of $A\beta$ peptides which activates an enzyme called Glucose Synthase Kinase type-3(GSK-3) leading to the hyperphosphorylation of tau proteins which causes microtubule depolymerisation and aggregation and ultimately leading to the formation of

**neurofibrillary tangles. The second one is, the cytokine $TNF-\alpha$ activates the astrocytes and produces $A\beta$ in a smaller amount.The activated astrocytes also produces Monocyte Chemoattractant Protein 1(MCP-1) which attracts monocytes from blood into the plaques and monocytes differentiated to form proinflammatory macrophages and anti-inflammatory macrophages. Microglias are also get differentiated to form proinflammatory microglias and anti-inflammatory microglias. The proinflammatory microglias and macrophages combined produce proinflammatory cytokines and the anti-inflammatory microglias and macrophages produces anti-inflammatory cytokines.**

**The proinflammatory cytokines causes neuronal stress which is resisted by anti-inflammatory cytokines but, however it leads to the neuronal damage and neuronal death.**

**So, it is important inhibit the production of $A\beta$,$TNF-\alpha$ and MCP-1 and also to increase the anti-inflammatory cytokine $TGF-\beta$.We have formulated partial differential equations for factors that leads to the progression of the disease and also for factors that resist the progression of the disease. Also, we have formulated the partial differential equations for the drugs like $TNF-\alpha$ inhibitor,$TGF-\beta$ injection and MCP-1 inhibitor.**

**Inventing the drugs for Alzheimer's is very important and medical associations all over the world should take immediate steps to find the cure for this disease. A complete cure is essential for the disease but, more than that it is the love, affection and care from the close ones is needed for AD affected patient.**

# REFERENCES


[1] Rosis, Svetlana. "ALZHEIMER'S DISEASE". Scitable.

[2] Puri, Ishwar K, and Liwu Li. "Mathematical modelling for the pathogenesis of Alzheimer's disease."PloS one vol. 5,12 e15176. 14 Dec. 2010, doi:10.1371/journal.pone.0015176.

[3] Wang, Wen-Ying et al. "Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease." Annals of translational medicine vol. 3,10 (2015): 136. doi:10.3978/j.issn.2305-5839.2015.03.49.

[4] Huang, LK., Chao, SP et al. " Clinical trials of new drugs for Alzheimer disease".J Biomed Sci27,18 (2020). https://doi.org/10.1186/s12929-019-0609-7.

[5] Chang, Rudy et al. "Tumor necrosis factor Inhibition for Alzheimer's Disease."Journal of central nervous system disease vol. 9 1179573517709278. 15 May. 2017, doi:10.1177/1179573517709278.

[6] Pan A, Gerriets V. Etanercept. [Updated 2021 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK545252/

[7] Craft, David L. The novel impact of Aß burden in Alzheimer's disease. Switzerland : Springer

[8] Medeiros, Rodrigo et al. "The role of tau in Alzheimer's disease and related disorders." CNS neuroscience & therapeutics vol. 17,5 (2011): 514-24. doi:10.1111/j.1755-5949.2010.00177.

[9] Verkhratsky, Alexei et al. "Astrocytes in Alzheimer's disease." Neurotherapeutics : The journal of the American Society for Experimental NeuroTherapeutics vol. 7,4 (2010): 399-412. doi:10.1016/j.nurt.2010.05.017

**[10] Hayden Hayden, Eric Y, and David B Teplow. "Amyloid $\beta$-protein oligomers and Alzheimer's disease." Alzheimer's research & therapy vol. 5,6 60. 29 Nov. 2013, doi:10.1186/alzrt226**

**[11] Croft,Cara L.et al. (2020), Elucidating the relationship between TGF- signaling and Alzheimer's disease. Alzheimer's Dement., 16: e043570. https://doi.org/10.1002/alz.043570**