Modeling Neuroinflammation in Individuals with Parkinson's Disease

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Abstract

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra, which progressively manifests into in a movement disorder. We propose a mechanism that describes the role that aggregated α-synuclein and neuroinflammation play in perpetuating a vicious cycle of neurodegeneration. A system of autonomous Ordinary Differential Equations (ODEs) is derived. Given that the percentage decay of neurons that leads to the onset of the disease is unknown, the time it takes for the population of dopaminergic neurons to be reduced to various levels is obtained through numerical simulations. A sensitivity analysis reveals that the decay rate of cytokines is the most important parameter of the system. The effect that the decay rate of cytokines has on the time is explored.

1 Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) is considered the second most common neurodegenerative disease after Alzheimer's disease [34]. PD is characterized with the early prominent death of neurons that release dopamine, known as dopaminergic neurons, in the substantia nigra pars compacta (SNpc). The resultant dopamine deficiency then manifests into a movement disorder, classified as the most common neurodegenerative movement disorder [26, 34]. Some of the symptoms include the following: bradykinesia, akinesia, rigidity, tremor, and gait dysfunction. Postmortem examinations of human brains of cases diagnosed with PD with an average age of 75.25 years revealed a total loss of 55.8% of neurons present in the SNpc [4]. There is currently no known cure for PD, nor is there a treatment that delays the progressive neurodegenerative process [26]. Existing data shows that the prevalence of PD increases with age; therefore, with a growing senior population in the United States, further studies need be implemented to come up with treatment options to ameliorate the detrimental effects of the disease [27, 36].

The diagnosis of PD is made with the onset of motor symptoms; however, the biological process of the disease begins well before any clinical symptoms begin to appear [14]. It has been postulated that PD develops from a complicated interplay of both genetics and the environment. Environmental risk factors include the following: prior head injury, rural living, pesticide exposure and well-water drinking. The contribution of genetics to PD was suggested by an increased risk seen in individuals who had a family history of PD. This was proven with the discovery of various genes that are now known to cause the monogenic form of the disease. A gene called $SNCA$, which codes for a protein, α-synuclein, was the first gene identified [28]. The exact functions of normal α-synuclein remain to be fully elucidated, but it is suggested that it may play a role in synaptic plasticity and trafficking of cargo within the neuron [37].

With most neurodegenerative diseases, including PD, there is an abnormality in protein aggregation. Each neurodegenerative disease is categorized based on the most abundant protein present in the associated protein inclusions. For PD, a mutation or the overexpression of $SNCA$, causes the protein to fold abnormally and becomes insoluble, leading to an accumulation of misfolded proteins [3]. Diagnostic tests for PD do not exist, but the gold standard for a diagnosis has been the presence of SNpc degeneration and Lewy pathology in most cases at postmortem examination. Lewy bodies are made by intracellular inclusions formed by an accumulation of misfolded α-synuclein [14].

It has been postulated that one of the reasons why proteins begin to aggregate is due to a decrease in the function of autophagy with age [6]. Aside from other functions, autophagy allows for the removal of protein aggregates before they become toxic [29]. In eukaryotic cells, autophagy is the only mechanism known to degrade aggregated proteins that cannot be processed by the proteasome [22]. Unlike other cells in our body, neurons are postmiotic and do not have the potential to replicate [32]. Therefore, this may predispose neurons to the accumulation of toxic proteins and damage that otherwise could not be diluted through cell division. Studies have shown that the loss of autophagy in the central nervous system (CNS) of mice has led to neurodegeneration, emphasizing the essential role of autophagy [17]. Once the function of autophagy subsides, aggregation of α-synuclein induces the neuron to secrete aggregated α-synucelin [15].

1.2 Neuroinflammation

Epidemiological findings have suggested that inflammation may be involved in the pathogenesis of PD due to the elevated presence of pro-inflammatory cytokines found in the cerebrospinal fluid (CSF) of PD cases at postmortem examination [2]. Chronic neuroinflammation is primarily controlled by microglia, the resident innate immune cells and the main immune responsive cells in the CNS, with their density the highest in the substantia nigra (SN) [16]. Microglia are sensitive to changes in their microenvironment, so any subtle

change in the inflammatory status of an individual may amplify the process of neurodegeneration [26].

Microglia are found in a resting state continually screening the brain tissue when no injury is involved. In response to injury or toxins, they change morphology and become activated. Once activated, they are able to phagocytose and remove pathogens in the brain as a defense mechanism [13]. Aggregated α-synuclein is known to activate microglia [15, 33, 37]. Upon activation, microglia secrete various cytokines, some of which include IL-1β, IL-6, and TNF-α, in order to recruit other microglia to the site of injury [33]. Dopaminergic neurons appear to be the most sensitive to TNF-α [24]. Histological analysis of the SN in PD patients demonstrates that factors released from activated microglia further enhance oxidative stress, protein misfolding, and aggregation to promote degeneration of dopaminergic neurons, leading to a self-perpetuating vicious cycle of neurodegeneration [35]. Studies have shown that microglia of aging mice display an altered inflammatory profile with increased mRNA expression of pro-inflammatory factors. This suggests that microglia become over-responsive with age [30].

The goal of the paper is to model the contribution of genetics and neuroinflammation in PD. The percentage of dopaminergic neurons lost at the point at which an individual begins to show clinical symptoms is unknown; therefore, we asses the time it takes to reduce a population of healthy neurons down to various levels. We then determine which parameters are the most influential on the time to those respective reductions with the intention of identifying possible areas for effective intervention.

2 Model Description and Methods

We propose a model of Ordinary Differential Equations (ODEs) that describes the dynamics between aggregated α-synuclein and neuroinflammation, and how both factors contribute to the progressive loss of dopaminergic neurons in PD.

2.1 Assumptions

The following list describes the assumptions made for the simplicity of the model.

- We assume that the individual is already genetically predisposed to PD. This assumption is made because our model implements the course of neuroinflammation perpetuated by aggregated α-synuclein. Additionally, studies suggest that aggregation facilitates the protein's release from neurons [15].
- A compartment for resting microglia was not considered in the model, due to their very low turnover rate, the rate at which they are depleted and replaced [11]. We assume that microglia become activated from a stock of resting microglia.

- There are no births of neurons in the system. The only neurons in the brain known to have the potential to replicate are found in the dentate gyrus of the hippocampus, a brain structure that is important for memory function [9].
- For our model, it is important to know exactly when aggregated protein is released. Literature states that aggregated protein is released when the neuron is dying or dead [26, 37]. Both of these scenarios will be included in the model.

2.2 ODE Model Framework

Consider a system composed of healthy neurons (H), damaged neurons (D), aggregated protein (A), activated microglia (M), and pro-inflammatory cytokines (C). The model of ordinary differential equations that describes the dynamics of neuroinflammation in PD is given by

$$\begin{aligned}
\frac{dH}{dt} &= -(\mu_H + gC)H, \\
\frac{dD}{dt} &= (\mu_H + gC)H - \mu_D D, \\
\frac{dA}{dt} &= q_1(\mu_H + gC)H + q_2\mu_D D - rAM, \\
\frac{dM}{dt} &= \left(\beta A + \frac{\gamma C}{f + C}\right) f(M) - \mu_M M, \\
\frac{dC}{dt} &= drAM + nM - \mu_C C.
\end{aligned} \tag{1}$$

Where

$$f(M) = \begin{cases} e^{-\frac{M}{k-M}}, & M < k \\ 0, & \text{otherwise} \end{cases} \tag{2}$$

or

$$f(M) = \begin{cases} k - M, & M < k \\ 0, & \text{otherwise.} \end{cases} \tag{3}$$

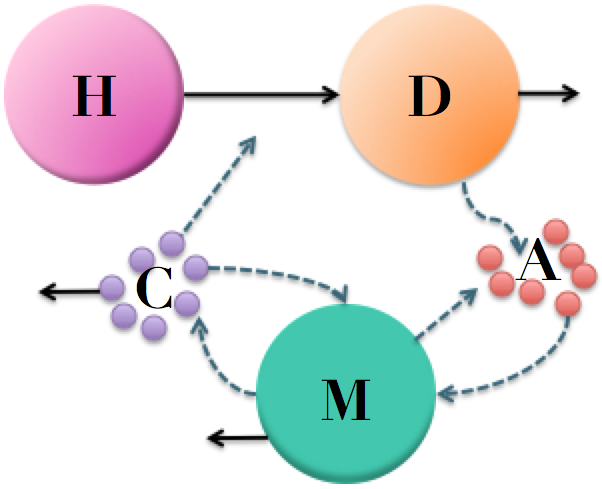

Figure 1: The interaction between the five classes, healthy neurons (H), damaged neurons (D), aggregated protein (A), activated microglia (M) and cytokine, TNF-α (C).

The model considers a population of healthy neurons, H. Over time, healthy neurons become damaged, D, due to natural decay or due to decay mediated by the concentration of cytokines, C. Damaged neurons will release aggregated protein, A, upon entry into the damaged compartment or upon exiting the damaged compartment. When microglia come in contact with the aggregated protein, they will become activated from a stock of resting microglia, k. M represents the compartment of activated microglia. Microglia may also become activated upon contact with cytokines, C. More cytokines get produced by activated microglia depending on how much aggregated protein is around and this is done to recruit more microglia to the site of injury. A constant production of cytokines may also be produced by activated microglia. Much of our attention is directed to the factors that transform healthy neurons into damaged neurons. A simple visual representation of the model is seen in Figure 1. The state variables and model parameters are summarized in Table 1.

There are two candidates for the $f(M)$ function. In both functions, k is a constant and cannot be larger than M.

Table 1: Description of the parameters and state variables.

Variables & Parameters	Description	Units
H	Healthy neurons	neurons
D	Damaged neurons	neurons
A	Concentration of aggregated protein	ng/ml
M	Activated microglia	microglia
C	Concentration of the cytokine TNF-α	ng/ml
μ	Natural decay rate	1/time
g	Cytokine mediated decay rate of H	1/time/ng/ml
q_1	Secretion rate of A upon entry into D	ng/ml/neuron
q_2	Secretion rate of A upon exiting D	ng/ml/neuron
r	Clearance rate of A per M	1/time/microglia
β	Microglia activation rate by A	1/time/ng/ml
γ	Microglia activation rate by C	1/time
k	Stock of resting microglia	microglia
f	Half-max concentration constant for the recruitment of M by C	ng/ml
d	Proportion of C:A	unitless
n	Constant cytokine production rate by M	ng/ml/microglia/time

2.3 Parameter Estimates

Since the function of macrophages in the peripheral nervous system is similar to the function microglia have in the CNS, some parameter estimates were obtained from data found on macrophages [10]. Additionally, given that dopaminergic neurons are most sensitive to the cytokine, tumor necrosis factor alpha (TNF-α), the parameters related to cytokines were used from data found only on TNF-α [24]. The following describes initial conditions and the estimates of the parameters in the model. Refer to Table 2 and Table 3 for parameter estimates and the initial conditions used for the simulations and the sensitivity analysis.

- μ_H: It has been postulated that neurons are the longest lived of all cells in the body. Furthermore, their lifespan is only limited by the maximum lifespan of the organism [23]. A study revealed that neurons transplanted from a species of mice to another, did not die, but survived long enough to double the lifespan of the donor [23]. This information lead us to consider using the age of the longest live

human being as the average lifespan of a neuron [18].

- k: The number of neurons present in the SNpc was found in the literature [7]. Microglia are not uniformlly distributed in the brain; the density of microglia in the SN is the highest of any region in the brain [16]. The number of resting microglia was not found in the literature, but it is known that they constitute around 15% of all the cells in the CNS [11]. With this information, k was obtained.

- μ_C: The decay rate of TNF-α was found in the literature where it was assumed that the decay rate was approximately equal to the rate of binding to the cell-surface receptors of neurons and other cells [20].

- n: The constant production of the cytokine, TNF-α, was calculated from experimental *in vitro* data [19, 20]. The information used for the calculation was the concentration of TNF-α produced from a known number of microglia at a fixed time interval. In the experiment, the stimulating factor was lipopolisacchardie (LPS), a common inflammogen.

- μ_M: The decay rate of activated microglia was difficult to find. Instead, a decay rate for activated macrophages was found, taking into consideration the assumption that microglia are similar to macrophages [5].

- β: The rate at which resting microglia become activated upon contact with aggregated α-synuclein was found in an article where the authors modeled an acute inflammatory response to an endotoxin by macrophages, as the main immune effector cells [8].

- γ: The rate at which resting microglia become activated by cytokines produced by other activated microglia was found in the same article from which β was estimated, again assuming macrophages are similar to microglia [8].

- r: The rate at which aggregated protein get cleared was obtained from a mathematical paper in which one of their parameters was described as bacterial clearance by macrophages [31].

- d: The conversion parameter d made sure the units in the concentration of cytokines compartment corresponded to the units of the state variable, C. This value was assumed.

- μ_D, g, q_1, q_2, and f: Some of the parameter values for microglia were attained based on data found on macrophages. However, a comparable cell that can be used in the case for neurons does not exist. For this reason, parameters μ_D, g, q_1, q_2, and f had to be assumed to the best of our knowledge. Existing data on the percentage of dopaminergic neurons lost at postmortem examination of PD cases who lived for an average of 75.25 years was used [4]. When compared to age-matched controls, there

was a 55.8% loss of dopaminergic neurons in PD brains. The parameters were assumed at the point at which they ensure that it would take ∼75.25 years to reduce the population of healthy neurons down to 44.2%.

For the initial conditions, the system starts with a population of healthy neurons. We assume that the process starts once one healthy neuron becomes damaged; therefore, the initial values of the other state variables are 0 as seen in Table 3.

Table 2: Parameter estimations based on existing knowledge and data.

Parameters	Estimated Values	Units	Ref
μ_H	$1/(122*365)$	1/day	[23]
μ_D	$1/(13*365)$	1/day	assumed
μ_M	0.4	1/day	[5]
μ_C	0.432	1/day	[20]
g	0.00013	1/day/cytokine	assumed
q_1	0.001	ng/ml/neuron	assumed
q_2	0.01	ng/ml/neuron	assumed
r	0.0001344	1/day/microglia	[31]
β	0.000833	1/day/ng/ml	[8]
γ	0.24	1/day	[8]
k	15,406 ± 1,593	microglia	[11]
f	0.2	ng/ml	assumed
d	0.2	unitless	assumed
n	0.000012	ng/ml/microglia/day	[19]

Table 3: Initial conditions based on data.

Initial Conditions	Estimated Values	Units	Ref
H_0	102,707 ± 10,622	neuron	[7]
D_0	0	neuron	–
A_0	0	ng/ml	–
M_0	0	microglia	–
C_0	0	ng/ml	–

3 Analysis

For our stability analysis, we chose the following:

$$f(M) = \begin{cases} k - M, & M < k \\ 0, & \text{otherwise.} \end{cases}$$

In order to determine the existence of equilibria, the right-hand side of system (1) is set to zero and solved for H^*, D^*, A^*, M^*, C^* as follows:

$$\begin{aligned} -(\mu_H + gC)H &= 0 \rightarrow H^* = 0 \\ -\mu_D D &= 0 \rightarrow D^* = 0. \end{aligned}$$

From $-rAM = 0$, we can see that either $A = 0$ or $M = 0$. If we consider the case where $A^* = 0$, we obtain the following

$$nM - \mu_C C = 0 \rightarrow C^* = \frac{n}{\mu_C} M$$

and,

$$\begin{aligned} \frac{\gamma \frac{n}{\mu_C} M}{f + \frac{n}{\mu_C} M}(k - M) - \mu_M M &= 0, \text{ or} \\ M\left(\frac{\gamma \frac{n}{\mu_C}}{f + \frac{n}{\mu_C} M}(k - M) - \mu_M\right) &= 0. \end{aligned}$$

At this point, we can see that either $M^* = 0$ or $\frac{\gamma \frac{n}{\mu_C}}{f + \frac{nM}{\mu_C}}(k - M) - \mu_M = 0$. If we consider the case where $H^* = 0$, $D^* = 0$, $A^* = 0$, and $M^* = 0$, we obtain that $C^* = 0$, and thus we have the equilibrium (0, 0, 0, 0, 0).

From $\frac{\gamma \frac{n}{\mu_C}}{f + \frac{nM}{\mu_C}}(k - M) - \mu_M = 0$, we observe the following

$$\begin{aligned} \mu_M &= \frac{\gamma \frac{n}{\mu_C}}{f + \frac{nM}{\mu_C}}(k - M), \text{ or} \\ \frac{n\gamma}{\mu_C}(k - M) &= \mu_M(f + \frac{nM}{\mu_C}), \text{ or} \\ \left(\frac{n\gamma}{\mu_C} k - \mu_M f\right) &= M\left(\frac{\gamma n}{\mu_C} + \frac{\mu_M n}{\mu_C}\right), \text{ and} \\ M^* &= \frac{\frac{n\gamma k}{\mu_C} - \mu_M f}{\frac{\gamma n}{\mu_C} + \frac{\mu_M n}{\mu_C}} \end{aligned}$$

Therefore, $M^* = \frac{n\gamma k - \mu_M f \mu_C}{\gamma n + \mu_M n}$ and in order for this to be biologically relevant, we need to assume that $\mu_M \mu_C < \frac{nk\gamma}{f}$. With these assumptions, we have that $C^* = \frac{n}{\mu_C} M^*$ and we obtain a second equilibrium, (0, 0, 0, M^*, C^*).

The general Jacobian matrix is as follows

$$J(H,D,A,M,C) = \begin{bmatrix} -\mu_H - gC & 0 & 0 & 0 & -gH \\ \mu_H + gC & -\mu_D & 0 & 0 & gH \\ q_1\mu_H + q_1 gC & q_2\mu_D & -rM & -rA & q_1 gH \\ 0 & 0 & \beta(k-M) & -\beta A - \frac{\gamma C}{f+C} - \mu_M & \frac{\gamma f}{(f+C)^2}(k-M) \\ 0 & 0 & drM & drA + n & -\mu_C \end{bmatrix}.$$

We evaluate the Jacobian at the equilibrium point (0, 0, 0, 0, 0) and solve for the eigenvalues of the resulting matrix

$$J(0,0,0,0,0) = \begin{bmatrix} -\mu_H & 0 & 0 & 0 & 0 \\ \mu_H & -\mu_D & 0 & 0 & 0 \\ q_1\mu_H & q_2\mu_D & 0 & 0 & 0 \\ 0 & 0 & \beta k & -\mu_M & \frac{\gamma k}{f} \\ 0 & 0 & 0 & n & -\mu_C \end{bmatrix}.$$

We obtain five eigenvalues, of which, one is zero and four are negative if $\mu_M\mu_C > \frac{nk\gamma}{f}$. Thus, the equilibrium (0, 0, 0, 0, 0) is locally asymptotically stable if $\mu_M\mu_C > \frac{nk\gamma}{f}$.

If $\mu_M\mu_C < \frac{nk\gamma}{f}$, the (0, 0, 0, 0, 0) is unstable and the equilibrium (0, 0, 0, M^*, C^*) exists. In order to determine the stability of (0, 0, 0, M^*, C^*), we evaluate the Jacobian at the equilibrium point and solve for the eigenvalues of the resulting matrix

$$J(0,0,0,M^*,C^*) = \begin{bmatrix} -\mu_H - gC^* & 0 & 0 & 0 & 0 \\ \mu_H + gC^* & -\mu_D & 0 & 0 & 0 \\ q_1\mu_H + q_1 gC^* & q_2\mu_D & -rM^* & 0 & 0 \\ 0 & 0 & \beta(k-M^*) & -\frac{\gamma C^*}{f+C^*} - \mu_M & \frac{\gamma f}{(f+C^*)^2}(k-M^*) \\ 0 & 0 & drM^* & n & -\mu_C \end{bmatrix}.$$

We obtain five negative eigenvalues if the condition, $\big(\frac{\gamma C^*}{f+C^*} + \mu_M\big)\mu_C - \frac{n\gamma f}{(f+C^*)^2}(k-M) > 0$ is met. The condition can be simplified as follows:

$$\begin{aligned} (\gamma C^* + \mu_M(f+C^*))\mu_C(f+C^*) &> \gamma f(nk - \mu_C C^*) \text{ or,} \\ (\mu_M f + (\mu_M+\gamma)C^*)(\mu_C f + \mu_C C^*) &> \gamma f(nk - \mu_C C^*). \end{aligned}$$

By using $C^* = \frac{n\gamma k - \mu_M \mu_C f}{\mu_C(\gamma + \mu_M)}$, we obtain the following expression

$$\begin{aligned}
\left[\mu_M f + \frac{n\gamma k - \mu_M \mu_C f}{\mu_C}\right]\left[\mu_C f + \frac{n\gamma k - \mu_M \mu_C f}{(\gamma + \mu_M)}\right] &> \gamma f\left(nk - \frac{n\gamma k - \mu_M \mu_C f}{\gamma + \mu_M}\right) \text{ or,} \\
\left(\frac{n\gamma k}{\mu_C}\right)\left(\frac{\mu_C f\gamma + n\gamma k}{\gamma + \mu_M}\right) &> \gamma f\left(\frac{n\mu_M k + \mu_M \mu_C f}{\gamma + \mu_M}\right) \text{ or,} \\
\frac{n\gamma k(n\gamma k + \mu_C f\gamma)}{\mu_C(\gamma + \mu_M)} &> \frac{\gamma f \mu_M}{\gamma + \mu_M}(nk + \mu_C f) \text{ or,} \\
nk\gamma(n\gamma k + \mu_C f\gamma) &> f\mu_M(nk + \mu_C f)\mu_C \text{ or,} \\
nk\gamma &> \mu_M \mu_C f.
\end{aligned}$$

Thus, (0, 0, 0, M^*, C^*) is locally asymptotically stable if $f\mu_M\mu_C < n\gamma k$.

The following summarizes our analytical analysis. If $\frac{n\gamma k}{f\mu_M\mu_C} < 1$, all the equilibrium (0, 0, 0, 0, 0) is locally asymptotically stable. If $\frac{n\gamma k}{f\mu_M\mu_C} > 1$, the equilibrium (0, 0, 0, M^*, C^*) exists and is locally asymptotically stable.

3.1 Biological Interpretation of the Condition

It is important to be able to interpret the analytical results and describe what they infer biologically. Consider the following

$$\underbrace{\frac{n}{\mu_C}}_{\substack{\text{production rate of C by M} \\ \times \text{ average lifespan of C}}} \qquad \underbrace{\frac{\gamma}{f\mu_M}}_{\substack{\text{activation rate of M by C} \\ \text{mediated by f} \\ \times \text{ average lifespan of M}}} \qquad \underbrace{k}_{\text{pool of resting microglia}}.$$

The trivial equilibrium is stable and all the trajectories tend to zero if the cytokines and activated microglia die faster than the rate at which they are introduced into the system. On the other hand, in order for the trajectories to tend to the equilibrium (0, 0, 0, M^*, C^*), the population of activated microglia and the concentration of cytokines must persist in the system, while H, D, and A tend to zero. This will occur if the decay rate of the activated microglia and the cytokines is less than their respective activation, resting pool size, and production.

The results indicate that the dynamics between M and C solely determine existence and stability of the equilibria. There is a constantly activated microglia population if the cytokines are able to start a positive feedback loop. Furthermore, if the above condition is satisfied, then any production of A will ultimately trigger microgliosis, when microglia remain chronically active.

4 Results

4.1 Transcritical Bifurcation

When choosing estimates for the parameters such that we attain ∼75.25 years to reduce the population of healthy neurons down to 44.2%, we noticed that changes in f, the half-max concentration constant, played a large role in determining the flow of the trajectories. Since f is one of the unknown parameter values, we used f as our bifurcation parameter as seen in Figure 2. We can see that a switch in stability of the system depends on how well the concentration of cytokines can recruit and activate microglia. When f is small, only a low concentration of cytokines is needed for microglia to be activated at $\gamma/2$, and thus the trajectories tend to the positive equilibrium. On the other hand, when f is large, a larger concentration of cytokines is needed and the cytokines don't recruit microglia efficiently. Thus, when f is large, the trajectories will tend to the trivial equilibrium.

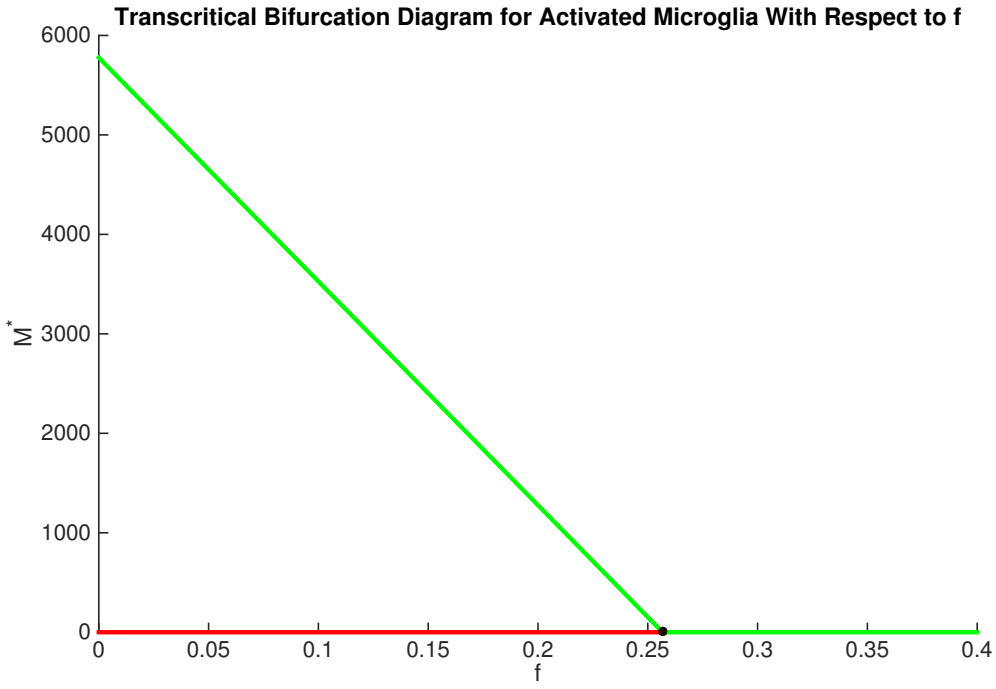

Figure 2: A transcritical bifurcation diagram for activated microglia with respect to parameter f.

4.2 Numerical Results

The following are the numerical simulations for each of the five compartments in our model using the parameters that ensure a duration of approximately 75.25 years to reduce the healthy neuron population

down to 44.2% as suggested by data [4]. Both, an individual with PD and without PD was simulated. For the case with PD, the secretion rates of aggregated protein, q_1 and q_2 were non-zero. For the case without PD, the secretion rates of aggregated protein were set to zero, since an individual without a mutation or overexpression of the gene, *SNCA*, forms insignificant quantities of aggregated protein.

The change in the population of healthy neurons over time is seen in Figure 3 and most of our time is focused on analyzing changes in this population with respect to the effect the parameters have on the time it takes to reduce the population to various levels. With the numerical simulations, we were able to obtain the time it takes for there to be a 55.8% decrease in the healthy neuron population, H, for the PD and non-PD individual, which was 72.73 years and 99.58 years, respectively. The time is denoted as $t_{44.2}$, which may also be described as the time it takes for the population to be reduced to 44.2% due to a loss of 55.8% of the healthy neurons.

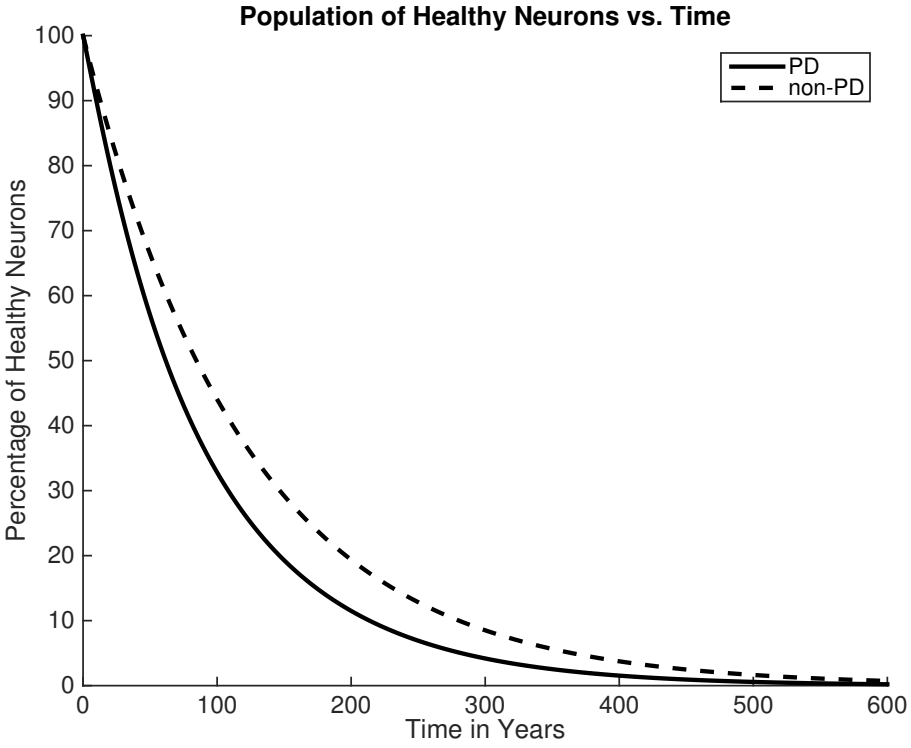

Figure 3: The numerical simulation of the population of healthy neurons, H. PD case: $q_1 = 0.001$, $q_2 = 0.01$ and $t_{44.2} = 72.73$ years. Non-PD case: $q_1, q_2 = 0$ and $t_{44.2} = 99.58$ years.

The numerical simulations of the rest of our compartments are seen in Figure 4. We see a peak in the population of damaged neurons, which then subsides and approaches zero when there are no more healthy

neurons available to enter the compartment, for both the PD and non-PD individual. However, we see that the peak is smaller in the individual without PD. When q_1 and q_2 are 0.001 and 0.01 respectively, a nontrivial amount of aggregated protein is released, which then approaches zero. In Figure 5, we see that there is an initial spike in the concentration of aggregates, which may indicate why there is an initial rise in the population of activated microglia, as well as an instant secretion of cytokines. However, once the activated microglia clear up the aggregates, the concentration of aggreagates quickly declines, then increases at a lower rate and eventually tends to zero. In the PD individual, we see that all trajectories tend to the equilibrium $(0, 0, 0, M^*, C^*)$.

When q_1 and q_2 are set to zero, since there is no secretion of aggregated protein, resting microglia do not get activated, and thus there is no production of cytokines. According to our simulations, in an individual without PD, all the trajectories tend to the zero equilibrium.

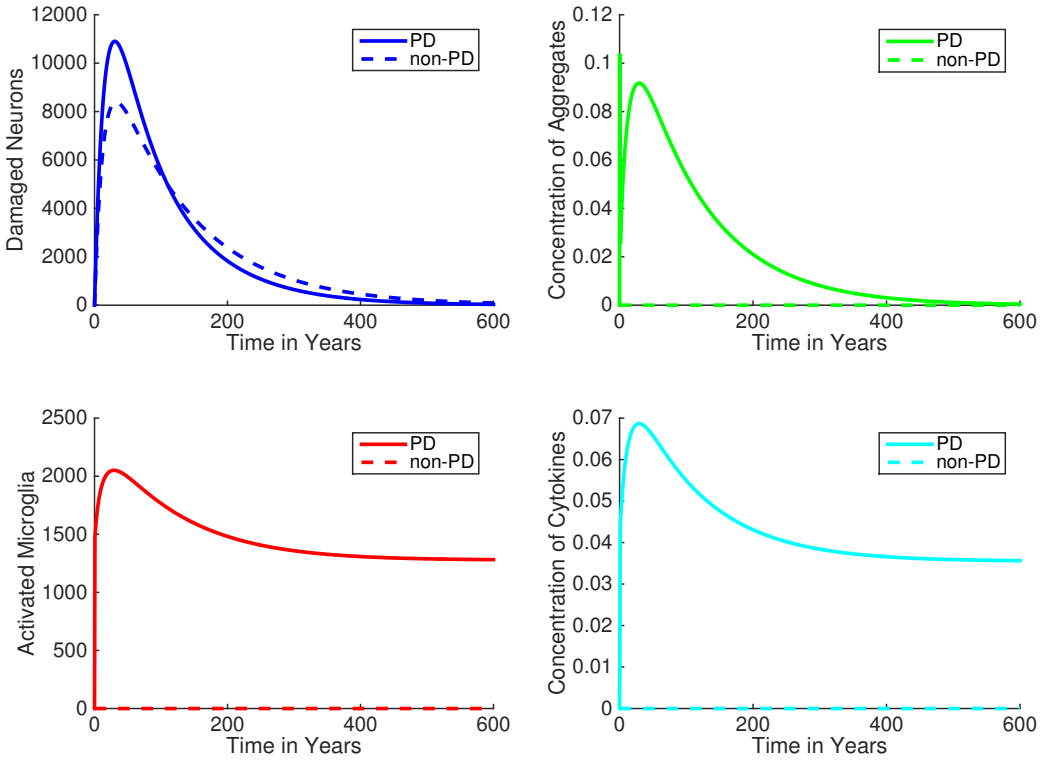

Figure 4: The numerical simulations of D, A, M, and C with respect to time for an individual with PD and an individual without PD.

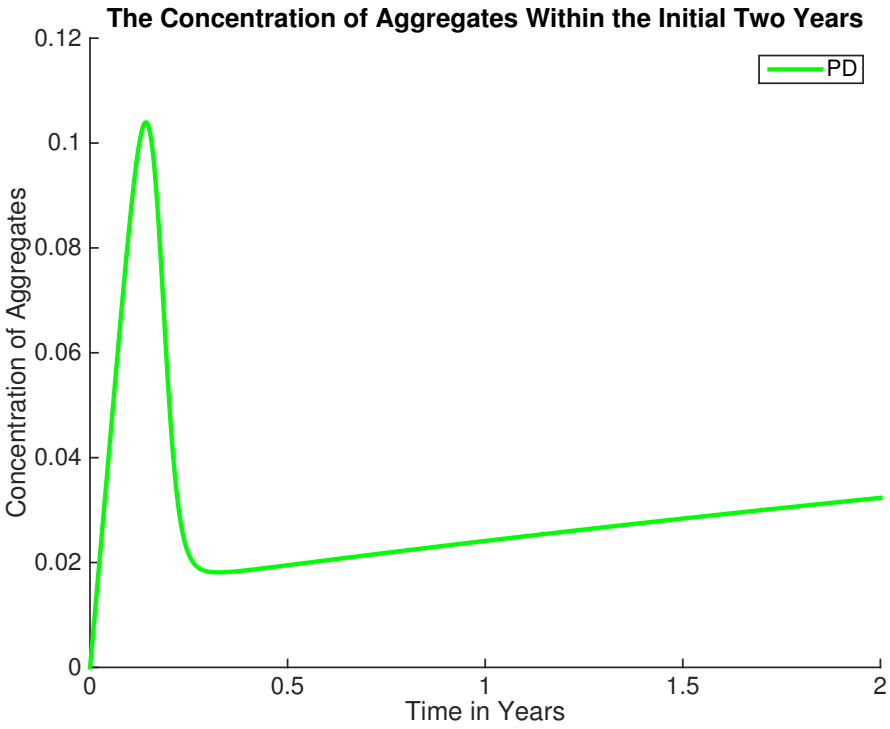

Figure 5: An initial peak observed within the first two years in the concentration of aggregates.

4.3 Sensitivity Analysis

Sensitivity analysis is used to determine the influence that parameter values have on the outcome of a model. Furthermore, with sensitivity analysis, one is able to determine which parameter values are the most important in the system. For our analysis, we use a forward sensitivity analysis that introduces perturbations to the input of the parameters and the resulting perturbations on the outcome are calculated. We are interested in what conditions affect the time to decrease to a certain level in the population of healthy neurons.

Let the time to reach a desired level in the population, z, be illustrated by t_z, which is our function of interest. Now, in order to determine which parameters affect t_z, the following derivative is used [1]:

$$\frac{dt_z}{dp} = -\frac{\frac{\partial H}{\partial p}\Big|_{t=t_z}}{f(zH_0, t_z; p)}.$$

We determine the sensitivity of s_p of the time t_z to the parameter p using the formula,

$$s_p = \frac{\partial t_z}{\partial p}.$$

Then after normalization, the sensitivity indices, e_p, are obtained with the following equation:

$$e_p = \frac{p}{t_z}\frac{\partial t_z}{\partial p}.$$

We observe the effect the parameters have on the time the healthy neuron population decreases to 99% and 44.2% as shown in Figures 6 and 7. When the population of healthy neurons is reduce down to 99%, the parameters that are beneficial to the system are μ_M, μ_C, and f, while the parameters that are detrimental to the system are μ_H, γ, k, and n. There are very little differences observed on the influence the parameters have on the time to reduce the population down to 44.2%. The main difference is a slight increase in the sensitivity index for the decay rate of cytokines. This implies that the same mechanism is at play throughout the course of PD. The numerical representations of the sensitivity indices corresponding to Figures 6 and 7 can be viewed in Table 4.

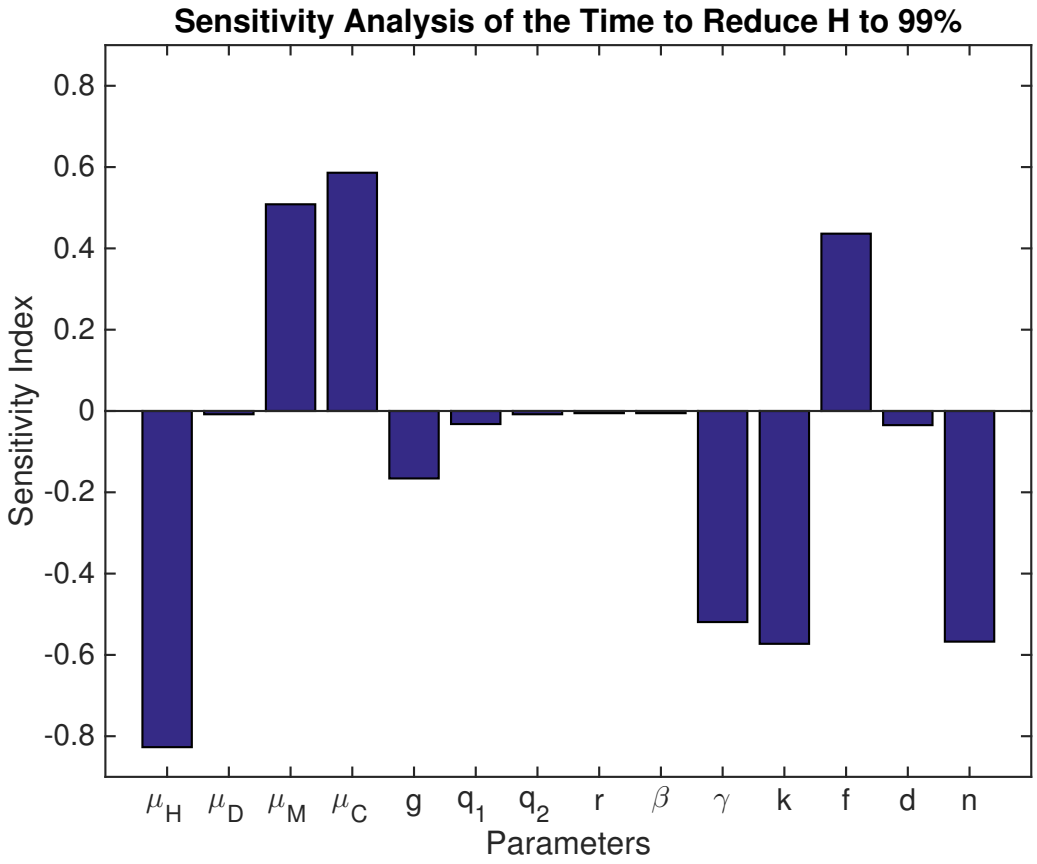

Figure 6: Sensitivity analysis of the effect the parameters have on the time it takes for the healthy neuron population to decrease to 99%.

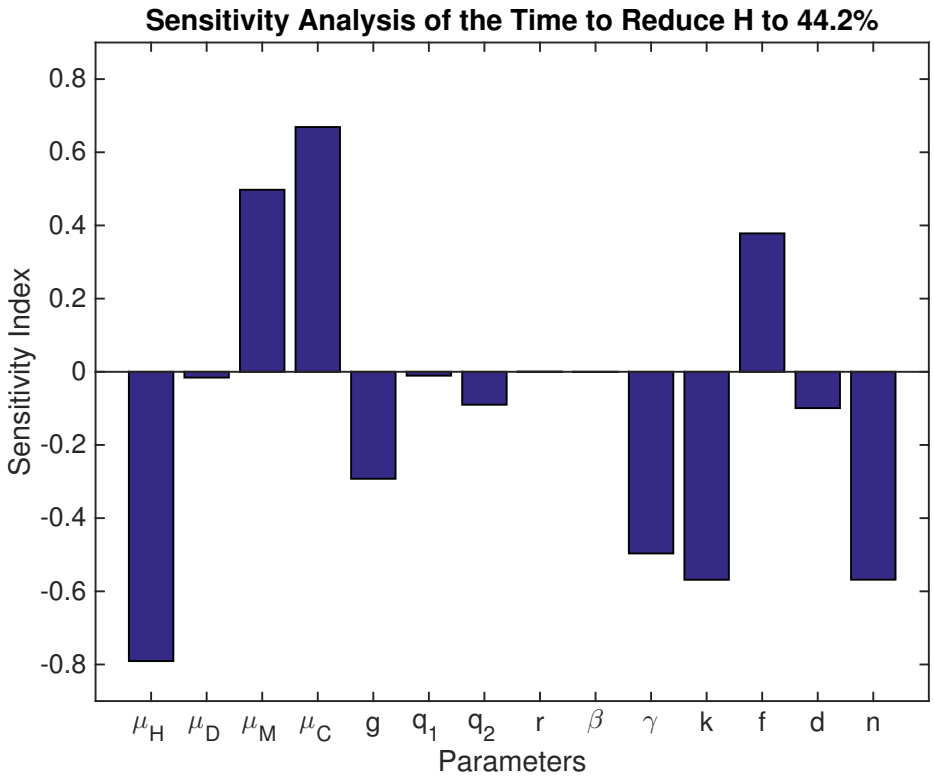

Figure 7: Sensitivity analysis of the effect the parameters have on the time it takes for the healthy neuron population to decrease to 44.2%.

Table 4: Sensitivity indices for the time to reduce H to 99% and 44.2%.

Parameters	Sensitivity Index	
	99%	44.2%
μ_H	-0.8269	-0.7905
μ_D	-0.0080	-0.0157
μ_M	0.5085	0.4970
μ_C	0.5861	0.6684
g	-0.1659	-0.2923
q_1	-0.0321	-0.0107
q_2	-0.0080	-0.0898
r	-0.0054	0.0003
β	-0.0054	-0.0004
γ	-0.5192	-0.4958
k	-0.5727	-0.5678
f	0.4362	0.3778
d	-0.0348	-0.0991
n	-0.5674	-0.5678

4.4 The effect of the decay rate of cytokines on $t_{44.2}$

Although the sensitivity analysis revealed, several important players at $t_{44.2}$, it is necessary to consider only the parameter in which one is able to potentially impact. In our case, the decay rate of cytokines could serve as a target for anti-inflammatory therapies. The following plot (Figure 8) describes the effect that a range on the value for the decay rate of cytokines has on the time to have a loss of 55.8% of the neurons present in the SN. A new $t_{44.2}$ was generated for 20 iterations, with its corresponding new $\bar{\mu}_C$, which was generated by adding $\epsilon = 0.01$ to it at each iteration. When we use the baseline of μ_C, we get that it takes 72.73 years to for the healthy neuron population to decrease to 44.2%. In the last iteration, when $\bar{\mu}_C = 0.6320$, we get that it takes 88.32 years to for the healthy neuron population to decrease to 44.2%. Notice that as μ_C goes to infinity, the time to reduce H to 44.2% goes to the same time it takes for an individual without PD (99.58 for our parameters).

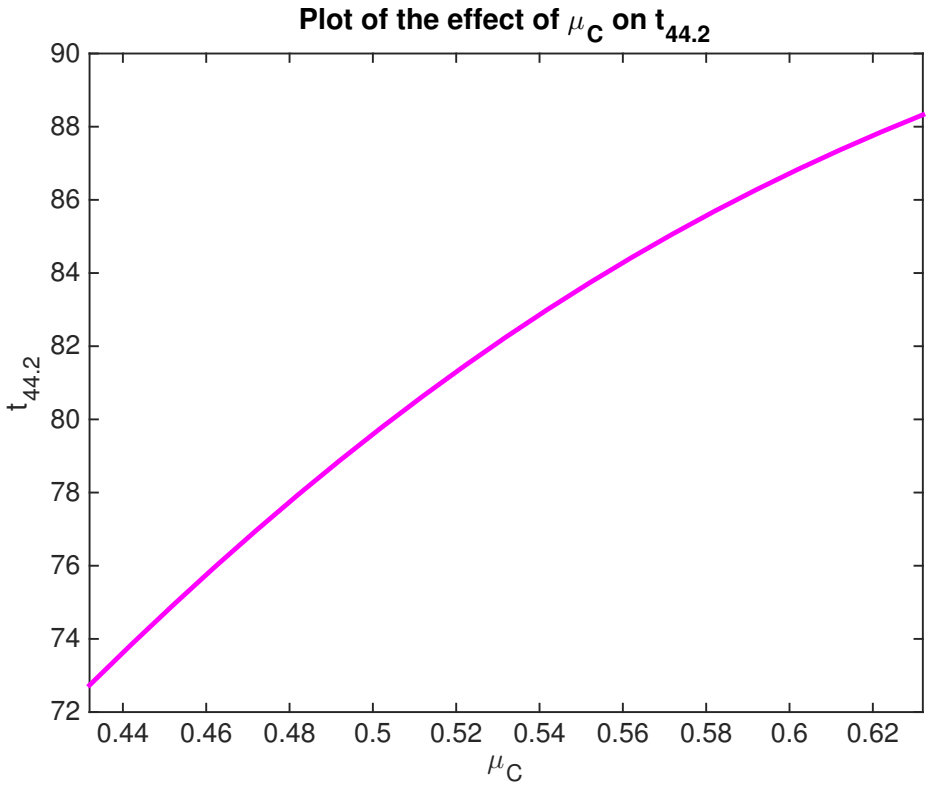

Figure 8: As you increase the decay rate of cytokines, the time it takes to reduce the healthy neuron population to 44.2% increases.

5 Discussion

The main hallmark of PD is the loss of dopaminergic neurons over time. In our model, the population of healthy neurons present in the SN eventually goes to zero. A postmortem examination revealed that the brains of individuals who had lived an average of 75.25 years and were diagnosed with PD had lost 55.8% of their dopaminergic neurons [4]. The results of our model indicated that it takes 72.73 years in the case with PD for the population of neurons to decrease to 44.2% and the major players driving this decrease are μ_M, μ_C and f. For the case without PD, the time to reduce the population of neurons to 44.2% was greater (99.58 years).

Given that there has been emerging and compelling evidence that neuroinflammation contributes to the pathogenesis of neurodegenerative disease, neuroinflammation was incorporated into our model. The hallmark of neuroinflammation is the activation of microglia, the resident CNS immune cells [16]. In a healthy normal brain, microglia are present in a resting and downregulated state; however, microenvironmental

alterations may induce microglia to become activated and change in morphology [25, 33]. Once activated, microglia are able to phagocytose, meanwhile secreting inflammatory mediators such as cytokines to recruit other microglia to become activated and attend to the site of injury. The activation of microglia is a defensive feature used to uptake any debris present in the brain, such as aggregated α-synuclein; however, an excessive inflammatory response can result in a source of additional injury to neurons [11]. In our simulations for an individual with PD, we see an immediate response of activated microglia as well as an increase in the concentration of cytokines present in the brain. In addition, we see that M^* and C^* approach an equilibrium over time. Postmortem analysis of cases with PD has revealed increased presence of activated microglia and pro-inflammatory factors [11]. According to the mathematical analysis, we can see that our simulation results correspond to when $\frac{n\gamma k}{f\mu_M\mu_C} > 1$ and (0, 0, 0, M^*, C^*) exists, meanwhile the equilibrium (0, 0, 0, 0, 0) is unstable.

The results of the sensitivity analysis revealed that when one begins to lose healthy neurons, the same parameters affect the system, when compared to a reduction of 55.8%. A detrimental effect on the system is due to the natural decay rate of healthy neurons, the cytokine mediated decay rate of neurons, the microglia activation rate by cytokines, the stock of resting microglia, and the constant release rate of cytokines by activated microglia. The beneficial effect on the system is due to the decay rate of microglia, the decay rate of cytokines, and the half-max concentration constant for the recruitment of microglia to become activated. These results may be interpreted as an early stage of reactive microgliosis, when microglia remain chronically active [21]. Microglia seem to have lost their neuroprotective defense mechanism, since the decay rate of activated microglia is actually beneficial to the system.

Given that increasing the decay rate of cytokines prolongs the time that it takes to reduce the healthy neuron population to a certain level, cytokines may be targeted as an intervention therapy. Chronic neuroinflammation occurs from an inbalance between the neuroprotective and protective factors [34]. Perhaps implementing anti-inflammatory factors may prolong t_z. Anti-inflammatory steroids have already been tested in animal models, which has shown to reduce the production of pro-inflammatory cytokines [12]. Reducing the concentration of cytokines in the brain may enhance the lifecycle of those that are predisposed to PD.

6 Conclusion

Our model demonstrated that uncontrolled inflammation forms a vicious cycle causing disease progression in PD. Once microglia escape the strict control normally imposed on them, they lose their neuroprotective role as their production of inflammatory factors becomes detrimental to the neurons.

Since the life expectancy of humans is increasing, it is essential to focus on producing more experimental

studies on pathologies of the aging brain. The lack of data in this field certainly does not help the potential that mathematical models can have on the understanding of neurodegenerative diseases. For future work, it would be interesting to be able to incorporate more accurate data in order to obtain more predictive results. In addition, it would be optimal to find the percentage of neurons lost when an individual begins to show clinical symptoms. Then, the effect the parameters have on the time to reach this loss can be explored with the intention of understanding the core trigger of PD. Lastly, our model can be improved by implementing autophagy in the neurons, since it is known to decrease with age.

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8 Appendix

8.1 MATLAB Code

8.1.1 ODE Model

```
function dydt = PD_model(~,y,p)
% vector of parameters p=(p(1),...,p(9))
muH=p(1);
muD=p(2);
muM=p(3);
muC=p(4);
g=p(5);
q1=p(6);
q2=p(7);
r=p(8);
beta=p(9);
gamma=p(10);
k=p(11);
f=p(12);
d=p(13);
n=p(14);


% vector of variables y=(y(1),y(2))
 H = y(1);
 D = y(2);
 A = y(3);
 M = y(4);
 C = y(5);

% ODE Model
      % [H]  Healthy neurons
    healthy = -H*(muH+g*C);
```

```
29        % [D] Damaged neurons
30      damaged = H*(muH+g*C)- muD*D ;
31        % Concentration of aggregated protein
32    aggregate = H*q1*(muH + g*C)+ q2*muD*D -r*A*M;
33        % Activated Microglia
34    microglia = (beta*A + (gamma*C)/(f+C))*max(0,(k-M))- muM*M;
35        % Concentration of cytokine: TNF-alpha
36     cytokine = d*r*A*M + n*M - muC*C;
37
38  dydt = [healthy;damaged;aggregate;microglia;cytokine];
```

8.1.2 Simulations

```
1  clear all; close all; clc;
2  %% Solving the ODE system
3  time = 0:1:600*365;
4  H_0=102707;
5  y0=[102707 0 0 0 0];
6  tspan = time;
7
8  vLD_x=44.2/100;
9
10 % Parameter Values
11 muH=1/(122*365);% 122 142
12 muD=1/(13*365);%
13 muM=0.4;
14 muC=0.432;
15 g=0.00013;% g=0.00013 g=0.000186
16 q1=0.001;%0.001
17 q2=0.01;%0.01
18 r=.0001344;
19 beta=.000833;
20 gamma=.24;
21 k=15406;
```

```
22 f=.2;%
23 d=.2;%
24 n=0.000012;
25 %f=n*k*gamma/muM/muC
26
27
28 % Vector of Parameter Values
29 p=[muH,muD,muM,muC,g,q1,q2,r,beta,gamma,k,f,d,n];
30
31
32 % Solving the model given in il6-free model by using ode45
33 [t,y] = ode23s(@PD_model,tspan,y0,[],p);
34
35       H_out    = y(:,1);
36       D_out    = y(:,2);
37       A_out    = y(:,3);
38       M_out    = y(:,4);
39       C_out    = y(:,5);
40
41 ind=find(H_out-H_0*vLD_x<= 0.000001,1);
42 t_k = t(ind)/365 % time of (1/2)H when all p are fixed
43
44 %%
45
46 figure(1),
47 hold on;
48 plot(t/365,(H_out/H_0)*100,'k','LineWidth',2.5);
49 set(gca,'FontSize', 14);
50 % set(gca,'XLim',[0 56]);
51 xlabel('Time in Years');
52 ylabel('Percentage of Healthy Neurons');
53 title('Population of Healthy Neurons vs. Time');
```

```
54
55 figure(2)
56 subplot(2,2,1);
57 hold on;
58 plot(t/365,D_out,'b','LineWidth',2.5);
59 set(gca,'FontSize', 14);
60 %set(gca,'XLim',[0 600]);
61 xlabel('Time in Years');
62 ylabel('Damaged Neurons');
63
64 subplot(2,2,2);
65 %figure(1);
66 hold on;
67 plot(t/365,A_out,'g','LineWidth',2.5);
68 set(gca,'FontSize', 14);
69 %set(gca,'XLim',[0 600]);
70 xlabel('Time in Years');
71 ylabel('Concentration of Aggregates');
72 %title('The Concentration of Aggregates Within the Initial Two Years');
73
74 subplot(2,2,3);
75 hold on;
76 plot(t/365,M_out,'r','LineWidth',2.5);
77 set(gca,'FontSize', 14);
78 %set(gca,'XLim',[0 600]);
79 xlabel('Time in Years');
80 ylabel('Activated Microglia');
81
82 subplot(2,2,4);
83 hold on;
84 plot(t/365,C_out,'c','LineWidth',2.5);
85 set(gca,'FontSize', 14);
```

```
%set(gca,'XLim',[0 600]);
xlabel('Time in Years');
ylabel('Concentration of Cytokines');
```

8.1.3 Sensitivity Analysis

```
clear all; %close all; clc;

%% Solving the ODE system
eps=0.001;
time = 1:0.001:400;
H_0=102707;
y0=[102707 0 0 0 0];
tspan = time;

vLD_x=99/100;%(98:-1:97)

parms2vary=1:14;

% Parameter Labels
paramlabel={'\mu_H', '\mu_D', '\mu_M','\mu_C','g', ...
    'q_1','q_2', 'r','\beta', '\gamma','k',...
    'f','d','n'};

for j=1:length(vLD_x)
    LD_x=vLD_x(j);

% Parameter Values
muH=1/(122*365);% 122 142
muD=1/(13*365);%
muM=0.4;
muC=0.432;
g=0.00013;% g=0.00013 g=0.000186
q1=0.001;%0.001
```

```
29 q2=0.01;%0.01
30 r=.0001344;
31 beta=.000833;
32 gamma=.24;
33 k=15406;
34 f=.2;%
35 d=.2;%
36 n=0.000012;
37
38 % Vector of Parameter Values
39 p=[muH,muD,muM,muC,g,q1,q2,r,beta,gamma,k,f,d,n];
40
41 % Solving the model by using ode23s
42 [t,y] = ode23s(@PD_model,tspan,y0,[],p);
43
44       H_out    = y(:,1);
45       D_out    = y(:,2);
46       A_out    = y(:,3);
47       M_out    = y(:,4);
48       C_out    = y(:,5);
49
50 ind=find(H_out-H_0*LD_x<= 0.000001,1);
51 t_k = t(ind) % time of (1/2)H when all p are fixed
52
53 i=1;
54 vecs_k=[];
55 for i=1:length(parms2vary)
56     p(parms2vary(i))=p(parms2vary(i))+eps*p(parms2vary(i));
57     % s is new vector of time
58     % z are the new outputs with p+eps
59     [s,z] = ode23s(@PD_model,tspan,y0,[],p);
60     ind=find(z(:,1)-H_0*LD_x<= 0.000001,1);
```

```
61        s_k = s(ind)
62        vecs_k=[vecs_k,s_k];
63        p(parms2vary(i))=p(parms2vary(i))-eps*p(parms2vary(i));
64    end
65
66    plotts=(vecs_k-t_k)./(eps)./t_k % change in t_k wrt p
67    LD=LD_x*100
68
69    figure(j),
70    %subplot(3,1,j)
71    plot1=bar(plotts);
72    set(gca,'FontSize', 14);
73    set(gca,'YLim',[-0.9  0.9]);
74    set(gca,'XTick',1:length(paramlabel));
75    set(gca,'XTickLabel',paramlabel);
76    title(['Sensitivity Analysis of the Time to Reduce H to ',num2str(LD),'%']);
77    ylabel('Sensitivity Index');
78    xlabel('Parameters');
79
80    % savename=['figures/image',num2str(j),'.eps'];
81    % print(gcf,'-dpsc2',savename);
82    end
```

8.1.4 Plot: Change in t_z with respect to μ_C

```
1   clear all; %close all; clc;
2
3   %% Solving the ODE system
4   eps=0.01;
5   time = 1:0.1:690*365;
6   H_0=102707;
7   y0=[102707 0 0 0 0];
8   tspan = time;
9
```

```
parms2vary=[4];

vLD_x=44.2/100;

% Parameter Values
muH=1/(122*365);% 122 142
muD=1/(13*365);%
muM=0.4;
muC=0.432;
g=0.00013;% g=0.00013 g=0.000186
q1=0.001;%0.001
q2=0.01;%0.01
r=.0001344;
beta=.000833;
gamma=.24;
k=15406;
f=.2;%
d=.2;%
n=0.000012;

% Vector of Parameter Values
p=[muH,muD,muM,muC,g,q1,q2,r,beta,gamma,k,f,d,n];

% Solving the model by using ode23s
[t,y] = ode23s(@PD_model,tspan,y0,[],p);

        H_out    = y(:,1);
        D_out    = y(:,2);
        A_out    = y(:,3);
        M_out    = y(:,4);
        C_out    = y(:,5);

```

```
ind=find(H_out-H_0*vLD_x<= 0.000001,1);
t_k = t(ind) % time of (1/2)H when all p are fixed


vt_k=[];
vp=[];
for i=1:20
    p(parms2vary(1))=p(parms2vary(1))+eps;
    % s is new vector of time
    % z are the new outputs with p+eps
    [s,z] = ode23s(@PD_model,tspan,y0,[],p);
    ind=find(z(:,1)-H_0*vLD_x<= 0.000001,1);
    s_k = s(ind)
    vt_k=[vt_k,s_k];
    vp=[vp,p(parms2vary(1))];
end

newvt_k = [t_k,vt_k];

newvp = [muC,vp];


figure(1),
plot(newvp,newvt_k/365,'m','LineWidth',2.5);
set(gca,'FontSize', 14);
%set(gca, 'YLim', [2.8808e+03 4.0828e+03]);
set(gca,'XLim',[0.4320 0.6320]);
ylabel('t_{44.2}');
xlabel('\mu_C');
title('Plot of the effect of \mu_C on t_{44.2}');
```