A mathematical model for inhibitor drugs in the treatment of Alzheimer's disease

By

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Recent studies reveal that from the pathological standpoint, Alzheimer's disease (AD) is described by the cerebral deposition of aggregated amyloid beta (AB) polymers in the form of amyloid plaques. This thesis introduces a new mathematical model for the treatment of AD in the presence of inhibitory drugs. Two types of drugs are considered: monomer inhibitors of AB aggregation and anti-aggregate drugs. First, the model is analyzed with only one of the two drugs and then the two drugs are tested in the presence of one another. The numerical simulations of models show that the first type of drug is able to reduce the steady state value of the number bonded monomers into aggregated polymers, but it does not reduce the rate of these monomers bonding to zero; thus, this type of drug can be used as a way to control but not treat AD. The second drug is able to reduce the steady state value while reducing the number of bonded monomers. This kind of drug can be used as an effective tool for treating AD, on at least the formation of AB plaques.

Key words: Alzheimer’s Disease, Amyloid Beta-40 Protein Monomer, Amyloid Beta-42 Protein Monomer, β-Amyloid Precursor Protein, Presenilin-1 and Presenilin-2

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NOMENCLATURE

AD	*Alzheimer's Disease*
Aβ-40	*Amyloid Beta-40 Protein Monomer*
Aβ-42	*Amyloid Beta-42 Protein Monomer*
APP	*Amyloid Precursor Protein*
PSEN1	*Presenilin-1*
PSEN2	*Presenilin-2*

CHAPTER I

INTRODUCTION

In 2015 the Center for Disease Control and Prevention rated AD as the sixth leading cause of death for the year 2012 [1]. Several studies have been conducted in order to shed light on three major questions regarding AD: What are its causes? Is there a commonality on the cellular level between the biological structure of neurodegenerative diseases like AD and Parkinson's Disease (another top leading cause of death in 2012)? And, which neurons in the brain are affected by the disease [2]? The first of these questions is the main theme of the current study.

Depicted in Fig. 1, the central hypothesis of this paper posits the cause of AD to be the Amyloid Cascade Process, which is described as the mutation of the APP and/or the PSEN1 and then PSEN2 genes [3]. APP, the transmembrane protein undergoes a cleavage process by certain enzymes present in the brain. Under normal conditions, APP is cleaved by α-secretase, which does not produce an amyloid monomer, but when the APP is mutated, there is a heightened likelihood that it is cleaved by β-secretase. Similarly, if the PSEN1 and PSEN2 genes are mutated, there is a heightened chance that the APP is cleaved by the γ-secretase. Both of these processes produce Amyloid-β protein peptides as shown in Fig. 2 [4]. This Amyloid-β protein peptide will be referred to as an Aβ-42 monomer. Experimental studies have shown that the concentration of the soluble Aβ species has a direct correlation to the cognitive impairment associated with AD [3].

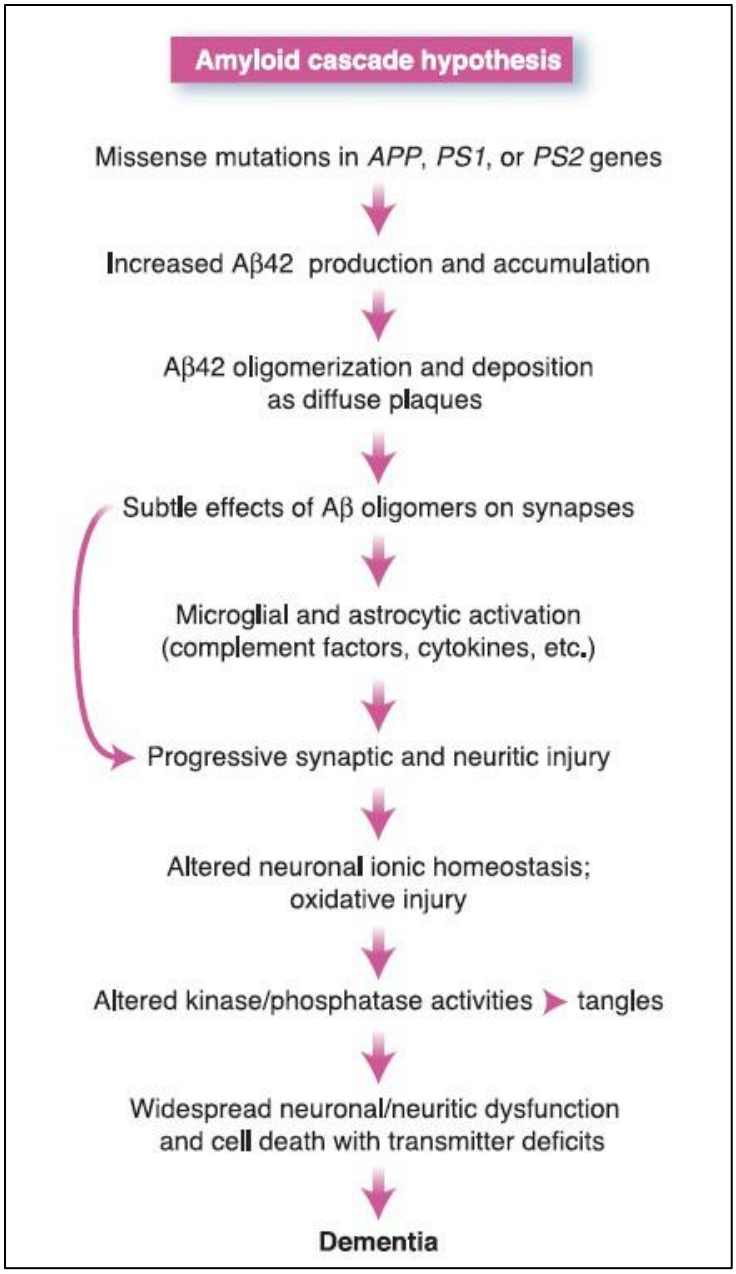


Figure 1

Amyloid Cascade Process

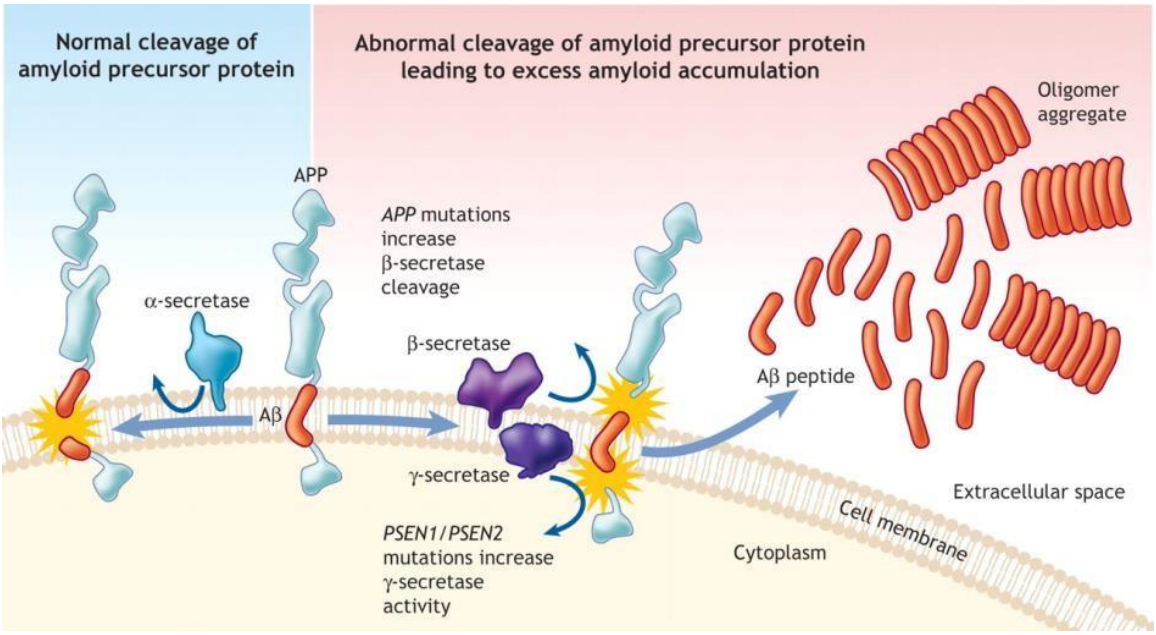


Figure 2

Cleavage Process Illustration

In regard to the treatment of AD, prior research alludes to drugs being able to react with Aβ-42 monomers and prevent them from going through the nucleation and elongation processes [9]. Current research is focused on finding ways to break up and even completely clear polymers from creating tangles around neurons. Certain research shows many drugs having this ability in vitro including non-steroidal anti-inflammatory medicines like ibuprofen [10], nordihydroguaiarectic acid [11], and nicotine [12]. The major problem with transitioning these in vitro findings into in vivo results is how to allow these drugs to cross over the blood brain barrier in order to interact with the polymers. Other research has been conducted using focused ultrasound waves on rats in order to create micro bubbles that create openings in their blood brain barrier [13].

Although a number of experimental studies have studied the progression of AD with and without possible treatment [5, 6, 7], none identified how the fibrillogenetic

process would be affected with the possible treatment. This research takes the idea of the two types of drugs which are mentioned above and models their interactions to discover how they would affect the process of aggregation. In this regard, a prior mathematical model [8] has been developed, which utilized a summation of first order reactions between monomers, oligomers, and fibrils to capture how the concentrations of the monomers and the fibrils interacted. Then, three novel models are introduced to include the interaction of the monomer-inhibitor and polymer-inhibitor drugs with the Aβ-42 monomer and with aggregated polymers.

The rest of the thesis is organized as follows. In chapter 2, the mathematical model for studying the effect of monomer-inhibitor drugs is developed, which leads to the master equation in section 2.1 and the closed system of kinetic equations describing the dynamic of the chemical reactions, which is presented in 2.2. Numerical simulations for this case are presented in section 2.3. The mathematical model for studying the effect of polymer-inhibitor drugs is developed in chapter 3, master equations in section 3.1, and numerical simulations in section 3.3. In chapter 4 the simultaneous impact of the two drugs is simulated and analyzed. The chapter following describe the implications of the findings including applications and future research.

CHAPTER II

MATHEMATICAL MODEL FORMULATION

In this chapter, a mathematical model to study the effect of inhibitors on the polymerization of the amyloid fibrils is developed. This model is based on situations depicted in Fig. 3, which describes the nucleation and elongation of the Aβ fibrils in the presence of the monomer/polymer-inhibitors. The figure gives a schematic representation of the Aβ nucleation, elongation, and fragmentation in the presence of the inhibitory drugs [8]. The first three rows represent reactions and interactions that occur independently from the presence of either drug. The fourth row represents the monomer-inhibitory drug reaction, and the fifth row represents the polymer-inhibitory reaction. Each reaction has an inverse reaction except for the nucleation and fragmentation reactions. By applying the law of mass-action to the reactions in Fig. 3, these reactions will result in a closed system of ordinary differential equations describing the kinetic equations of the system.

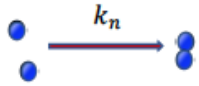
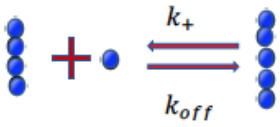
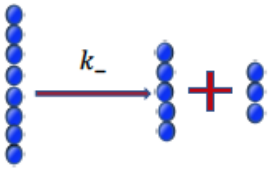
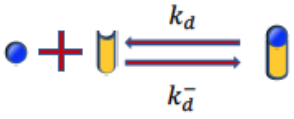
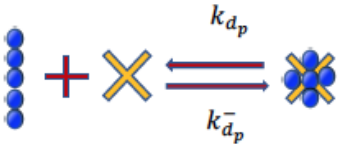
Microscopic Process	Chemical Reactions	Reaction Rate	Explanation
	$A + A \longrightarrow A_2$	k_n	Primary Nucleation
	$A_n + A \rightleftarrows A_{n+1}$	k_+/k_{off}	Elongation/Dissociation
	$A_n + A_m \longleftarrow A_{n+m}$	k_-	Fragmentation
	$A + D \rightleftarrows AD$	k_d/k_d^-	Monomer Inhibition Drug
	$A_i + D \rightleftarrows AD_i$	$k_{d_p}/k_{d_p}^-$	Polymer Inhibition Drug

Figure 3

Monomer and Polymer Reactions

2.1 Master Equations for the Monomer-Inhibitor Drug

To base of the model begins with the model proposed by Cohen et. al. in [8], which captures essentially the events of nucleation and elongation. These reactions show how the concentration of polymers of a specific length, *j*, is changing with respect to time. Coefficients of 2 are added to the elongation and dissociation events to account for Aβ-42 monomers interacting with both ends of each polymer. As such, if *f(t,i)* is the concentration of the polymers with length *i* at a time *t* and *m(t)* represents the concentration of free Aβ

proteins at time *t*, the master equation governing the evolution of Aβ filaments [8] is given by:

$$\frac{df(t,j)}{dt} = 2k_+\big(m(t)f(t,j-1) - m(t)f(t,j)\big) + 2k_{off}\big(f(t,j+1) - f(t,j)\big) + k_-\left(2\sum_{i=j+1}^{\infty} f(t,i) - -(j-1)f(t,j)\right) + k_n m(t)^{n_c}\delta_{j,n_c} \quad \textbf{(2.1)}$$

In equation 2.1, $k_n m(t)^{n_c}\delta_{j,n_c}$ represents the primary nucleation, and n_c is the minimum number of monomers needed to be bonded to form a polymer. In our model $n_c = 2$.

$$2k_+ m(t)f(t,j-1) - 2k_+ m(t)f(t,j)$$

describes the elongation event.

$$2k_{off}f(t,j+1) - 2k_{off}f(t,j)$$

denotes the polymerization of the fibrils, and

$$2k_-\sum_{i=j+1}^{\infty} f(t,i) - k_-(j-1)f(t,j)$$

characterizes the breakage of the longer filaments into smaller filaments [8]. To describe the interaction of monomers and/or polymers in the presence of drugs, two additional reactions must be considered, which are listed in the last two rows of the table depicted in Fig. 3.

2.2 Closed System of Equations for Monomer-Inhibitor Drug

In order to capture the time-evolution of the concentration of monomers and the polymerized fibrils, it is required to find the first two moments of $f(t,j)$. These moments $P(t)$ and $M(t)$ are defined by equation 2.2. By summing over j on both sides of equation

2.1, the kinetic equations for the first two moments can be derived. In this regard, $P(t)$ described the total concentration of aggregated filaments $f(t,j)$ of all lengths $j \geq n_c$, and $M(t)$ denotes the total number of bonded protein monomers (See [8] for details of derivation).

$$P(t) = \sum_{i=n_c}^{\infty} f(t,i) \qquad M(t) = \sum_{i=n_c}^{\infty} i\, f(t,i) \tag{2.2}$$

Now, since the drug acts on free monomers, based on the chemical reactions described in Fig. 3, the inhibition process is modeled by adding two equations describing the variation of drug and drug-monomer complex creations, which are represented by $d(t)$ and $d_a(t)$, respectively. Since the drug does not have any impact on the fibrils, equations for $P(t)$ and $M(t)$ are the same as what is described in [8]. Regarding the free proteins concentration $m(t)$, conservation of mass accounts for the bracketed terms which are equivalent to $\frac{dM(t)}{dt}$. Then the conservation of mass with respect to the drug produces the un-bracketed terms of $\frac{dm(t)}{dt}$ along with the last two equations in Equations 2.3-7.

$$\frac{dP(t)}{dt} = k_{-}[M(t) - (2n_c - 1)P(t)] + k_n m(t)^{n_c} \tag{2.3}$$

$$\frac{dM(t)}{dt} = 2\left(m(t)k_{+} - k_{off} - \frac{k_{-}n_c(n_c-1)}{2}\right)P(t) + n_c k_n m(t)^{n_c} \tag{2.4}$$

$$\frac{dm(t)}{dt} = -\left[2\left(m(t)k_{+} - k_{off} - \frac{k_{-}n_c(n_c-1)}{2}\right)P(t) + n_c k_n m(t)^{n_c}\right] - k_d m(t)d(t) + k_{d_a} d_a(t) \tag{2.5}$$

$$\frac{dd(t)}{dt} = -k_d m(t)d(t) + k_{d_a} d_a(t) \tag{2.6}$$

$$\frac{dd_a(t)}{dt} = k_d m(t)d(t) - k_{d_a} d_a(t) \tag{2.7}$$

2.3 Numerical Simulations

Numerical simulations are performed for the different initial values for the concentration of protein and drug. The parameters for both sets of simulations are set at

$$k_+ = 5 * 10^4 \;\; k_- = 5 * 10^{-8} \;\; k_{off} = 10^{-10} \;\; k_n = 2 * 10^{-5} \;\; k_d = 10 \;\; k_{d_a} = 10^{-10}$$

These parameters are selected from [8] and the new parameters are selected based on the discussions in [9]. All simulations use an embedded fourth order Runge-Kutta method within the Mathcad software. The first set varies the initial value for the concentration of drug, so the initial conditions for $P(t)$ and $M(t)$ are set to zero, and the initial condition of $m(t)$ is set to $5 * 10^{-6}$. The results of these simulations are shown in Fig. 4. The second set varied the initial time by varying the initial mass concentration of polymers, $M(t)$, and the concentration of monomer, $m(t)$. The sum of $M(t)$ and $m(t)$ for all simulations is $5 * 10^{-6}$ due to the conservation of mass. The results of these simulations are shown in Fig. 5.

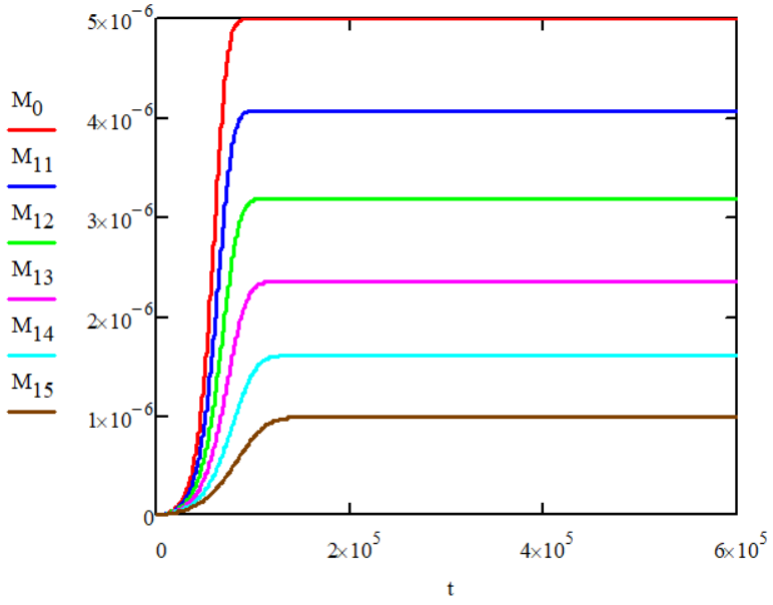


Figure 4

Numerical Simulations with Monomer-Inhibitor Drug (Concentration)

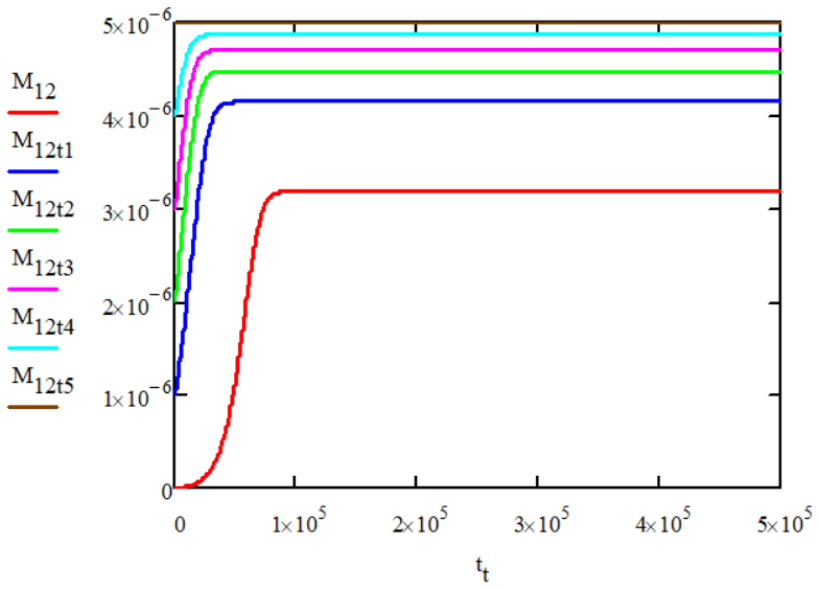


Figure 5

Numerical Simulations with Monomer-Inhibitor Drug (Time)

In Fig. 4 and Fig. 5, the subscripts of M represent initial concentrations of the monomer inhibitor drug $d(t)$. M_0 represents the control with no drug present. The first digit of the subscript represents which drug is being tested where 1 represents the monomer-inhibitor drug. The second digit represents the coefficient, n, of drug concentration used in the form $n * 10^{-6}$. The subscript t signifies a time delay, and the digit following the t represents n for the initial concentration of $M(t)$. If no t is in the subscript, this means that the initial condition for the mass concentration of polymers, $M(t)$, was set at zero. An example of this labeling method would be M_{12t4}, which is the plot that shows the numerical solution of the mass concentration of polymers, $M(t)$, with initial conditions of

$$d(0) = 2 * 10^{-6} \quad M(0) = 4 * 10^{-6}$$

2.4 Discussion

The numerical simulations show that an implementation of the monomer-inhibitor drug creates a decrease in the steady state value of the mass concentration of polymers, $M(t)$. The first set of simulations show that the amount of decrease in this steady state value is strictly dependent upon the amount of drug that is introduced to the concentration in the beginning time step. The second set of simulations shows how ineffective the drug is after the polymerization process has begun. Once these polymers have begun forming, this drug does not have the capability to force the function $M(t)$ to decrease, which would signify the number of monomers in filaments decreasing or the disease getting better.

CHAPTER III

POLYMER-INHIBITOR DRUG MODEL

In this section, the model is developed further to capture the impact of polymer-inhibitor drugs on the progress of Aβ fibrils formation. In this regard, it is assumed that the drug is acting on the filaments of different length, $f(t,i)$, which results in the formation of drug-filament complex $d_A(t,j)$.

3.1 Master Equations for Polymer-Inhibitor Drug

In this simulation, two master equations are involved. The first describes the time-evolution of the filaments as before with $f(t,j)$. The second explains the formation of the drug filament complexes, $d_A(t,j)$. Because of this, in addition to chemical reactions describing nucleation, elongation, dissociation, and fragmentation, the last equation in Fig. 3 is now included in the model. This equation describes the inhibition of the fibrils of different length by the drug. The system of master equations is written as follows in equations 3.1 and 3.2.

$$\frac{df(t,j)}{dt} = 2k_+\big(m(t)f(t,j-1) - m(t)f(t,j)\big) + 2k_{off}\big(f(t,j+1) - f(t,j)\big) \tag{3.1}$$

$$+ k_-\left(2\sum_{i=j+1}^{\infty} f(t,i) - -(j-1)f(t,j)\right) + k_n m(t)^{n_c}\delta_{j,n_c}$$

$$+ \big(1-\delta_{j,1}\big)[k_{d_p}^- d_A(t,j) - k_{d_p} f(t,j)d(t)]$$

$$\frac{dd_A(t,j)}{dt} = \big(1-\delta_{j,1}\big)[k_{d_p} f(t,j)d(t) - k_{d_p}^- d_A(t,j)] \tag{3.2}$$

3.2 Closed System of Equations for Polymer-Inhibitor Drug

Similar to the monomer-inhibitor drug case, $P(t)$ and $M(t)$ are defined via summations on $f(t,j)$ for all filament lengths j; however, in this case there are two additional moments involved which are related to the drug-filament complexes. These, too, are found via a summation for all filament lengths j, but are associated with the filaments that have been reacted on by the drug. These moments are denoted as $P_D(t)$ and $M_D(t)$, and are seen with $P(t)$ and $M(t)$ in the system of equations in equation 3.3.

$$P(t) = \sum_{i=n_c}^{\infty} f(t,i) \quad M(t) = \sum_{i=n_c}^{\infty} i\, f(t,i)$$

$$P_D(t) = \sum_{i=n_c}^{\infty} d_A(t,i) \quad M_D(t) = \sum_{i=n_c}^{\infty} i\, d_A(t,i) \tag{3.3}$$

Then, by adding in equation 3.3, the closed system of equations can be written as seen in equations 3.4-9.

$$\frac{dP(t)}{dt} = k_{-}[M(t) - (2n_c - 1)P(t)] + k_n m(t)^{n_c} - k_{d_p} P(t) d_p(t) + k_{\bar{d}_p} P_D(t) \quad \textbf{(3.4)}$$

$$\frac{dM(t)}{dt} = 2\left[m(t)k_{+} - k_{off} - \frac{k_{-}n_c(n_c - 1)}{2}\right] P(t) + n_c k_n m(t)^{n_c} - k_{d_p} M_D(t) d_p(t) + k_{\bar{d}_p} M_D(t) \quad \textbf{(3.5)}$$

$$\frac{dP_D(t)}{dt} = k_{d_p} P(t) d_p(t) - k_{\bar{d}_p} P_D(t) \quad \textbf{(3.6)}$$

$$\frac{dM_D(t)}{dt} = k_{d_p} M_D(t) d_p(t) - k_{\bar{d}_p} M_D(t) \quad \textbf{(3.7)}$$

$$\frac{dm(t)}{dt} = -[2\left(m(t)k_{+} - k_{off} - \frac{k_{-}n_c(n_c - 1)}{2}\right) P(t) + n_c k_n m(t)^{n_c}] \quad \textbf{(3.8)}$$

$$\frac{dd_p(t)}{dt} = -k_{d_p} M_D(t) d_p(t) + k_{\bar{d}_p} M_D(t) \quad \textbf{(3.9)}$$

3.3 Numerical Simulations

Similar to the previous analysis conducted on the governing differential equations for the monomer-inhibitor drug, the polymer-inhibitor drug will be analyzed by varying two initial conditions. The first analysis varies the initial drug concentration. Starting with the control where the initial drug concentration is zero, each trial increases the initial drug concentration by $1 * 10^{-6}$. The method of solving the system of differential equations is still the embedded fourth order Runge-Kutta method. The results are shown in Fig. 6.

The second analysis tests how the polymer-clearing drug reacts to higher initial concentrations of polymers. This, like the analysis on the monomer-inhibitor drug, simulates how effective the drug is after the onset of the disease or once polymers have begun forming. The initial concentration of drug is held constant at

$$d_p(0) = 2 * 10^{-6}$$

In order to maintain an accurate model that abides by physical constraints, $P(0)$ must have a value greater than zero. This value is assumed to be equal to the fraction of total number

of bonded monomer to the average length of polymer. The average length of polymers is assumed to be 5000, so

$$P(0) = \frac{M(0)}{5000}$$

The rate of polymer-drug attachment is

$$k_{d_p} = 10$$

and the rate of polymer-drug detachment is

$$k_{d_p}^{-} = 10^{-10}$$

The rest of the k parameters are equivalent to those in the previous analysis. The results of this analysis are shown in Fig. 7. The subscripts of Fig. 6 and Fig. 7 are equivalent to those of Fig. 4 and Fig. 5.

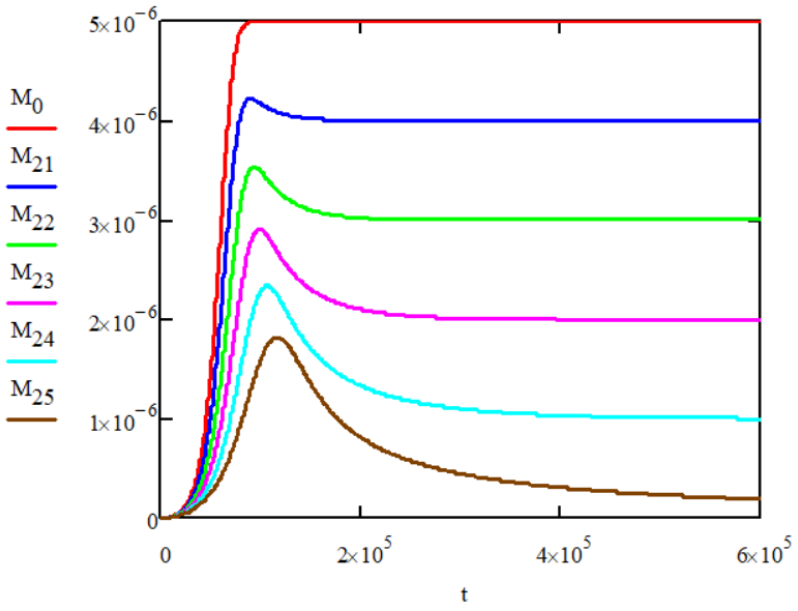


Figure 6

Numerical Solutions with Polymer-Inhibitor Drug (Concentration)

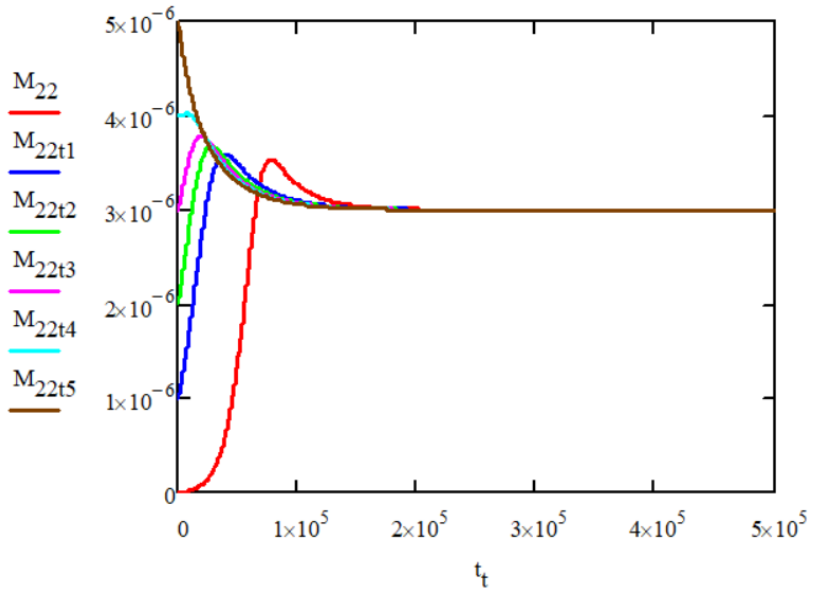


Figure 7

Numerical Solutions with Polymer-Inhibitor Drug (Time)

3.4 Discussion

These results show how a drug that can work to clear polymers out of concentration could be used as a cure for AD. The polymer clearing drug, even at lower concentrations, both lowered the steady state and forced the mass concentration of polymers to decrease. This process equates to improved neural flow and a decrease symptoms as neural networks that were once closed are now reopened. The time delay simulation shows that this type of drug would provide equivalent relief to a patient no matter when it was administered so long as the increase of monomers going into concentration is maintained at negligible values. The time delay could still cause damage if the neurons were to experience irreversible damage from being cut off from neural networks for too long, but from a physical stand point, this type of drug could be used in order to cure AD.

CHAPTER IV

COMBINATION OF TWO DRUGS

To model the simultaneous impact of the two drugs, the master equations from both of the previous two cases, equations 2.1, 3.1, and 3.2, are considered. In this manner, both of the drugs are modeled as being present. In order to differentiate between the two drug concentrations, $d(t)$ is the concentration of the monomer-inhibitor drug, and $d_p(t)$ is the concentration of the polymer-inhibitor drug. The master equations for the combination of drugs are shown in Equations 4.1 and 4.2.

$$\frac{df(t,j)}{dt} = 2k_+\big(m(t)f(t,j-1) - m(t)f(t,j)\big) + 2k_{off}\big(f(t,j+1) - f(t,j)\big) \qquad \textbf{(4.1)}$$

$$+ k_-\left(2\sum_{i=j+1}^{\infty} f(t,i) - -(j-1)f(t,j)\right) + k_n m(t)^{n_c}\delta_{j,n_c}$$

$$+ \big(1-\delta_{j,1}\big)[k_{d_p}^- d_A(t,j) - k_{d_p} f(t,j)d(t)]$$

$$\frac{dd_A(t,j)}{dt} = \big(1-\delta_{j,1}\big)[k_{d_p} f(t,j)d(t) - k_{d_p}^- d_A(t,j)] \qquad \textbf{(4.2)}$$

Likewise, the closed system of equations for the combination of drugs is simply a combination of the terms from the two cases. The system of equations for this case is shown in Equations 4.3-10.

$$\frac{dP(t)}{dt} = k_{-}[M(t) - (2n_c - 1)P(t)] + k_n m(t)^{n_c} - k_{d_p} P(t) d_p(t) + k_{d_p}^{-} P_D(t) \quad \textbf{(4.3)}$$

$$\frac{dM(t)}{dt} = 2\left[m(t)k_{+} - k_{off} - \frac{k_{-} n_c(n_c - 1)}{2}\right] P(t) + n_c k_n m(t)^{n_c} - k_{d_p} M_D(t) d_p(t) + k_{d_p}^{-} M_D(t) \quad \textbf{(4.4)}$$

$$\frac{dP_D(t)}{dt} = k_{d_p} P(t) d_p(t) - k_{d_p}^{-} P_D(t) \quad \textbf{(4.5)}$$

$$\frac{dM_D(t)}{dt} = k_{d_p} M_D(t) d_p(t) - k_{d_p}^{-} M_D(t) \quad \textbf{(4.6)}$$

$$\frac{dm(t)}{dt} = -\left[2\left(m(t)k_{+} - k_{off} - \frac{k_{-} n_c(n_c - 1)}{2}\right) P(t) + n_c k_n m(t)^{n_c}\right] - k_d m(t) d(t) + k_{d_a} d_a(t) \quad \textbf{(4.7)}$$

$$\frac{dd(t)}{dt} = -k_d m(t) d(t) + k_{d_a} d_a(t) \quad \textbf{(4.8)}$$

$$\frac{dd_a(t)}{dt} = k_d m(t) d(t) - k_{d_a} d_a(t) \quad \textbf{(4.9)}$$

$$\frac{dd_p(t)}{dt} = -k_{d_p} M_D(t) d_p(t) + k_{d_p}^{-} M_D(t) \quad \textbf{(4.10)}$$

4.1 Numerical Simulations

Numerical simulations were performed in a fashion similar to the previous cases where the drugs were isolated. The parameters k_a all have the same values as they did in the isolated cases. The results of these simulations are shown in Fig. 8-17. The first subscript of "3" signifies a combination of the two was tested. The second digit corresponds to the coefficient n for the monomer inhibitory drug, and the third digit corresponds to the coefficient m for the polymer inhibitory drug.

In the simulations, both drugs help maintain a certain desirable behavior of $M(t)$, but each also has an undesirable effect as well. The monomer-inhibitor drug aids in lowering the rate of reaction of the monomer, but it cannot force the mass concentration of polymers to decrease, so the drug cannot affect the previously formed polymers. The polymer-inhibitor drug is able to force the mass concentration of polymers to decrease, but

it has a delay where $M(t)$ reaches a local maximum, which can lead to permanent damage in the neurons. The idea in combining the two types of drugs is to see how the perks and weaknesses of each drug interact together. Based on the results, a threshold maximum for $M(t)$ can be maintained by adding in more of the monomer inhibitor drug, while the overall progression of the disease can be reversed by adding in more of the polymer-inhibitor drug.

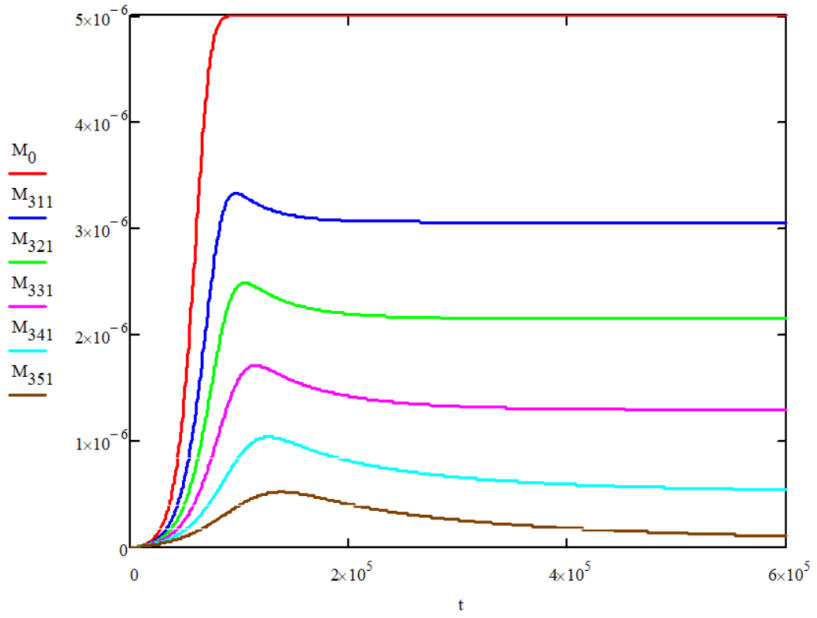


Figure 8

Numerical Solutions of Combination of Drugs 1

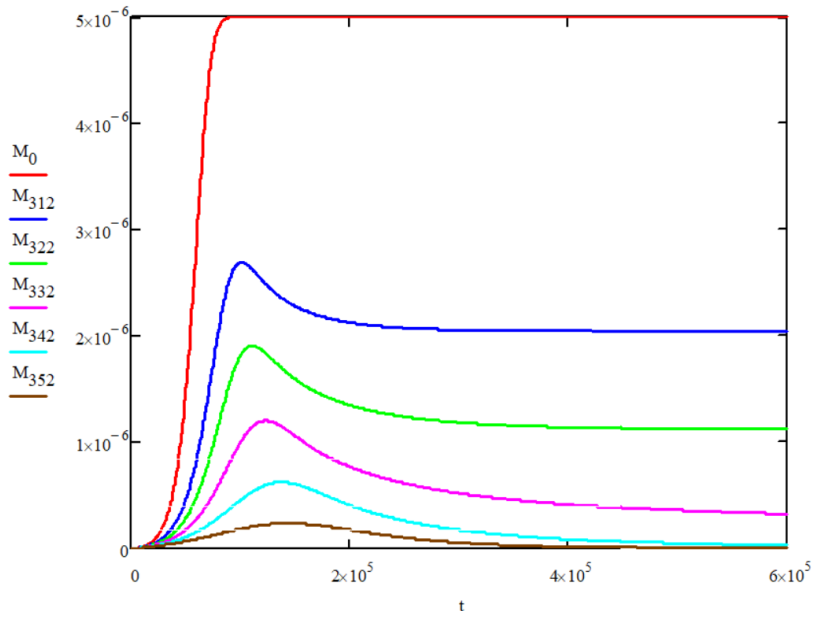


Figure 9

Numerical Solutions of Combination of Drugs 2

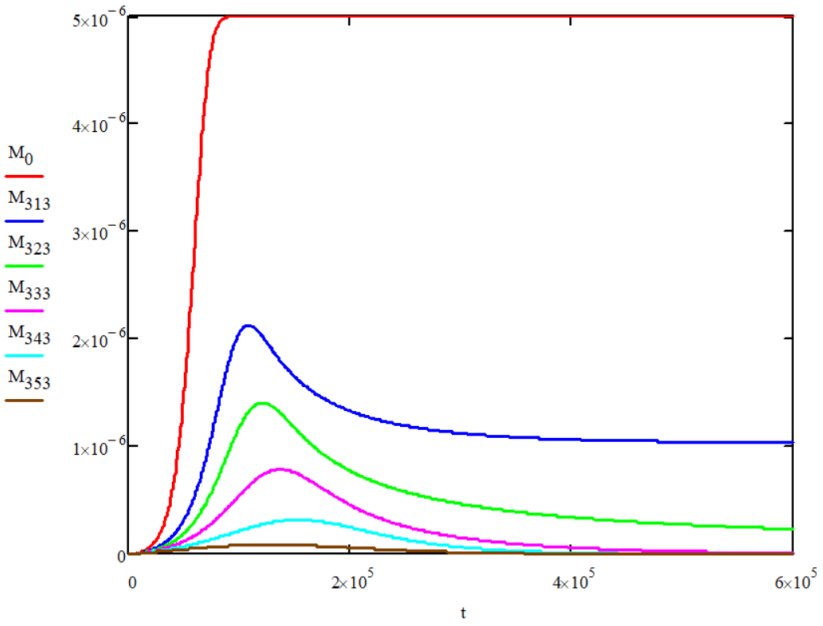


Figure 10

Numerical Solution of Combination of Drugs 3

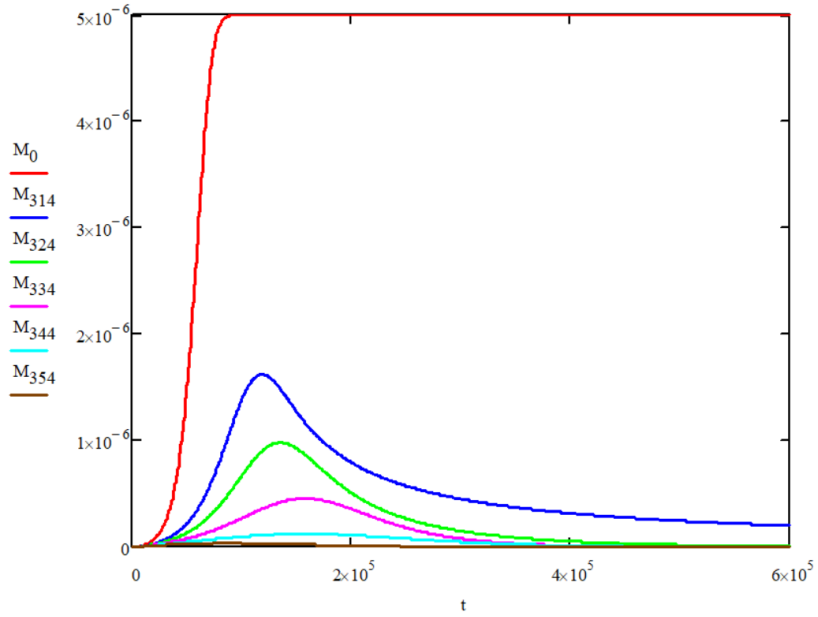


Figure 11

Numerical Solution of Combination of Drugs 4

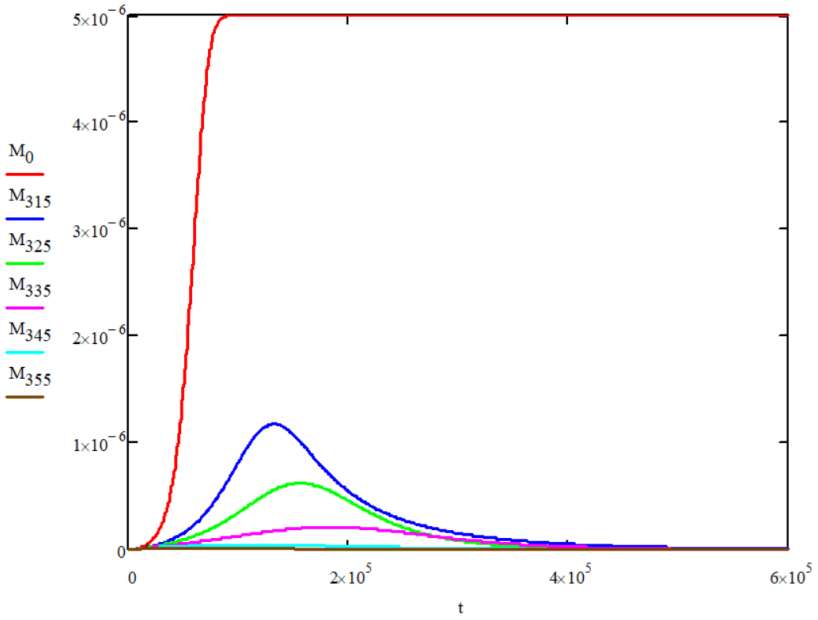


Figure 12

Numerical Solution of Combination of Drugs 5

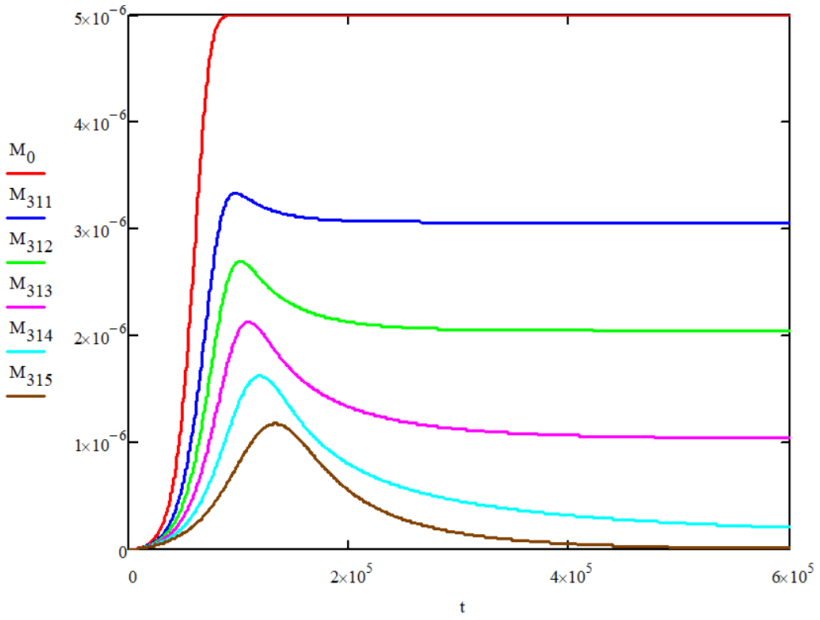


Figure 13

Numerical Solution of Combination of Drugs 6

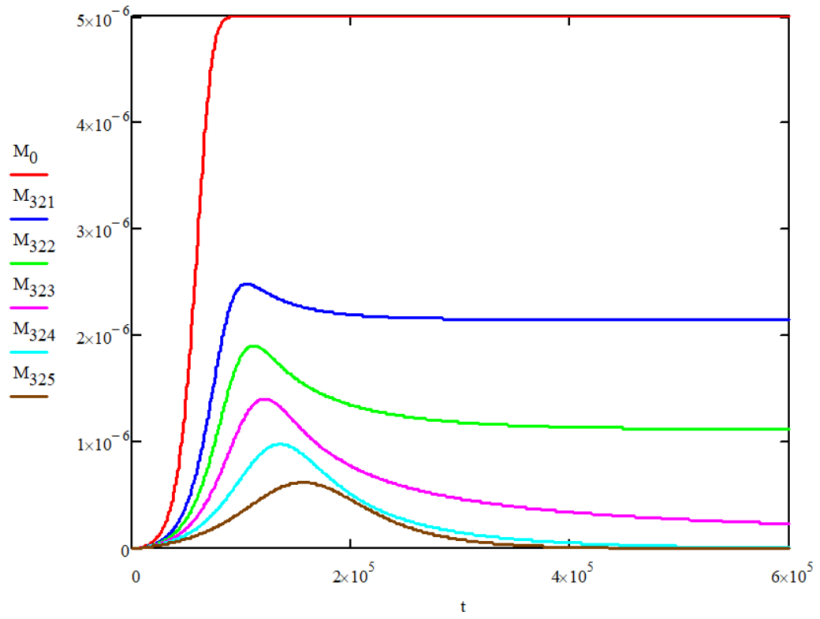


Figure 14

Numerical Solution of Combination of Drugs 7

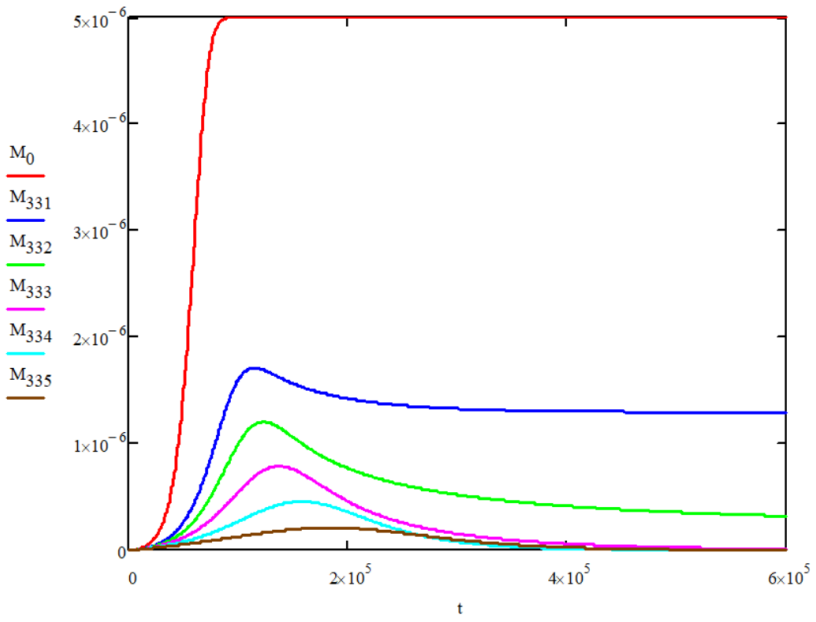


Figure 15

Numerical Solution of Combination of Drugs 8

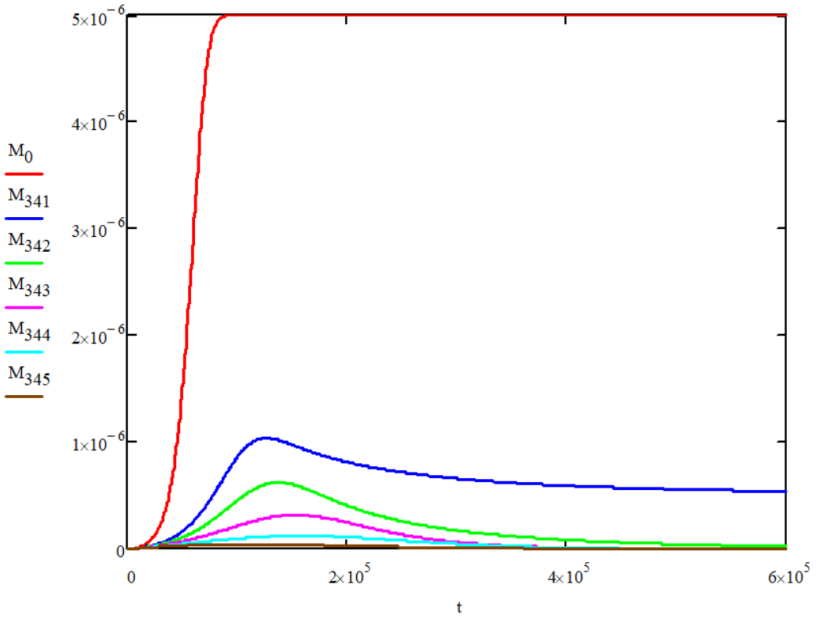


Figure 16

Numerical Simulation of Combination of Drugs 9

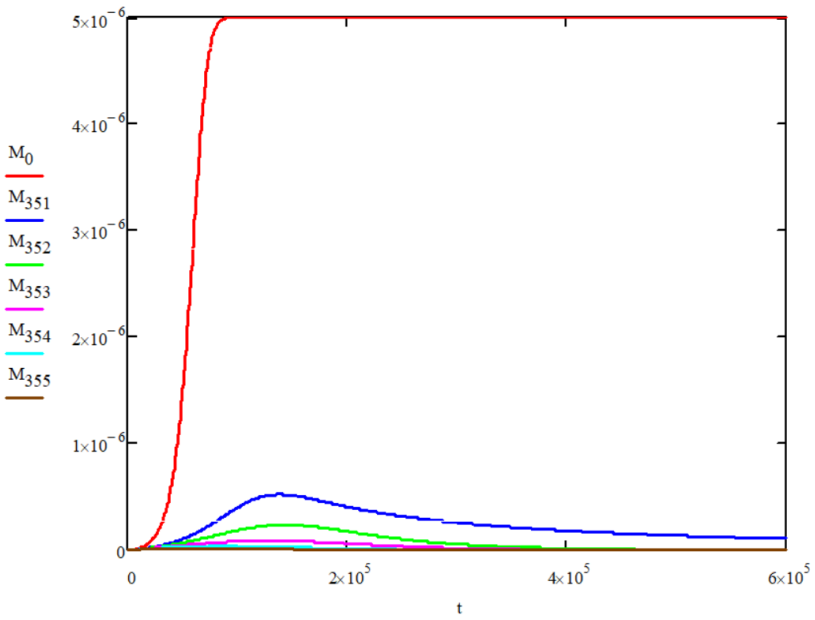


Figure 17

Numerical Simulation of Combination of Drugs 10

4.2 Discussion

The results of the simulations show that when the two drugs are combined, the monomer-inhibiting drug produces a maximum value for the mass concentration of polymers, $M(t)$ while the polymer-inhibiting drug forces the mass concentration of polymers to decrease therefore reversing the progression of the disease. The higher the initial concentration of the monomer-inhibitor drug, $d(0)$, the lower value of the steady state of the mass concentration of polymers. This means the initial spike of $M(t)$ is lowered and the progression of the disease is slowed. The higher the initial value of the polymer-inhibitor drug, $d_p(t)$, the lower the steady state value of $M(t)$. Although this is also true for the monomer-inhibitor drug, the effects of the polymer-inhibitor drug are true for any time delay; whereas, the monomer-inhibitor drug only has that effect if the drug is introduced with few polymers already formed.

CHAPTER V

CONCLUSION

5.1 Summary

In this research, three novel models were introduced that can be used to study the impact of two important types of drugs on AD. The monomer-inhibitor drug is a way to slow down the progression of the disease, but the drug lacks of ability to reverse the polymerization process and reduce the number of monomers contained in polymers. These characteristics limit the effectiveness of the monomer-inhibitor drug to applications in the early stages of the disease. The second type of drug, the polymer-inhibitor, is more effective in the more progressed cases of AD. The polymer-inhibitor drug has its fault in that it has a time delay which allows a spike in number of monomers that have been polymerized before this number begins to decrease. The benefits and faults of both types of drug can be combined in order to produce a reversal in the trend of polymerization while keeping the maximum value of the mass concentration of polymers below a threshold that is deemed adequate.

5.2 Future Research

Future research in this area is an interdisciplinary endeavor. If the model were to be further analyzed, the time dependence of the combination of drugs could be analyzed to see if there was an ideal time to introduce the polymer-inhibitor drug into concentration. Another aspect would be to apply control theory to the model to analyze the stability. The

k_a parameters for the two drugs were approximated in this research. Thus, further study on what would be ideal reaction constants would progress the model as well as give an insight as to how an actual drug could be designed for this application. The other k_a parameters that came from prior work [8] could also be researched and confirmed. Once the mathematical model is sufficiently tuned and the rate of monomer development within AD patients is found, the model can be used to develop clinical trials that can be used to treat AD patients.

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