

# MODELING CALCIUM INFLUXES THROUGH NEURONAL SYNAPSES HIGHLIGHTING NMDA RECEPTORS

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**Abstract.** -- Dendritic spines are small, membranous protrusions from a neuron's dendrite which are the hub for receiving signal inputs from axons at areas called synapses. The synaptic plasticity, or strength, of a synapse depends on its ability to perform synaptic signaling through second messenger Calcium ions. Ionotropic membrane receptors, such as N-methyl-D-aspartate receptors (NMDARs), located on the post synaptic cell play a key role in Long Term Potentiation and Depression affecting the memory retention of cells. To consider the effect of NMDAR on calcium dynamics, varying parameters, blocked Magnesium ion concentrations in NMDARs, membrane voltage and extracellular calcium concentrations, were used to model calcium dynamics mathematically. Ordinary differential equations were used to solve the system of equations which looked at a calcium influx with a timescale of 20 milliseconds. Using this model, we were able to focus on how important these specific parameters were in regulating the rate of flow of calcium ions into the post synaptic cell. The results indicated that with increases in the concentrations of Magnesium and extracellular-calcium ions, and probabilities of opening receptors, there was an overall increase in the rate of flow of calcium ions into the cell. To implement the results on a 3D model, realistic geometries of dendritic spines were created through the smoothing of meshes. Then, the ODE model of calcium influx through NMDAR can be converted to a full spatial, PDE model in these realistic 3D geometries to allow for a visual representation of the diffusion of calcium ions in dendritic spines.

## Introduction

Dendritic spines are small, protein- and actin-rich protrusions located on the dendrites of neurons, and have emerged as a critical hub for learning, memory, and synaptic plasticity in both short-term and long term synaptic events (Bourne and Harris 2008, Rangamni et al., 2016). The spines and the sub compartments provide space for the cell to cell interaction at synapses to help promote chemical and electrical activity and share signals. Previous studies have showed connections between many memory retention related, and different brain disorders that are associated with the different abnormal dendritic spines. This is because dendritic spines are buzzing with electrical and chemical activity that transmit signals throughout the body and down to crucial biological mechanisms of the body. The signaling network is controlled by hundreds of different types of membrane proteins, signaling molecules, and ions that create the difference in voltage at these sites. All of these parameters work together to help transmit the information and signals down the [pathway](#). Many different types of changes between the parameters of the synapse can cause changes in the strength and different electrical properties of the dendrites. The constant changing features of the synaptic site and the electrical signals in the dendrite gives it the neuronal plasticity of the dendrite which plays a large role in the brain plasticity, learning, and [memory](#).

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Calcium, or the  $\text{Ca}^{2+}$  molecule, is one of the most important molecule part of this complex signaling system. Calcium temporal dynamics are important signals that flow into the postsynaptic terminal.  $\text{Ca}^{2+}$  acts as important signal messenger that helps to trigger signaling cascades that can lead to long-term depression, long term potentiation, actin cytoskeleton rearrangement, and many other things. (Holmes, 1990; Bourne and Harris, 2008; Rangamani et al., 2016). Recent evidence showed that neuronal calcium signaling is abnormal in many of neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease (HD) and Parkinson's disease (PD) which is why it is important to study the effects of them and track changes in the signaling [pathways](#).

However, like a domino chain reaction, calcium influxes are only possible with neurotransmitters that enter the synaptic site. Neurotransmitters, like glutamate help, activate ionotropic flux sources like the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) and N-methyl-D-aspartate receptors (NMDARs). These neurotransmitters activate the surface cell membranes by creating a concentration gradient which changes the voltage potential of the system. However, the activation of AMPARs is fast while the activation of NMDARs are slow and take time. At resting potentials, NMDARs are blocked by external magnesium ( $\text{Mg}^{2+}$ ) ions and prevent any other ions from entering through the receptor. This is why the depolarization of the surrounding system is required to release the trapped  $\text{Mg}^{2+}$  from the pore of the receptor. High-frequency synaptic inputs from neurotransmitters, like Glu molecules, allow the excitatory postsynaptic potentials (EPSPs) by AMPAR activation to build over time. With Long Term Potentiation and Long Term Depression, the frequency input is strengthened or weakened depending on the signal received by the synapse. Since voltage dependency is so crucial to determine synaptic strength and NMDARs potential of opening for calcium influxes, AMPA should be studied and tested with different variables. Previous research has proven how there is a correlation between postsynaptic density (PSD) surface area and PSD-core volume. This signaling pathway (Fig. 1) is common between many different molecules, not just glutamate as well.

These signaling activities happen down to the millisecond time scale since the calcium enters the spine once neurotransmitters, like Glutamate, are released from the presynaptic cell. As stated before, these dynamics are influenced by different parameters that determine the rate of flow of calcium into the post synaptic cell. Computational models, using experimental data have been shown to provide insight into the signaling dynamics of the calcium molecules travelling through the dendritic spines. Most current models have only described the various calcium fluxes from and into the cytoplasm but not many have focused on seeing what affects changes in parameters around the signaling pathways have on the rate of flow of calcium into the cytosolic space. They usually focus on looking at the concentration of calcium into the ER and the different mitochondrial and buffer [fluxes](#).

The purpose of this study is to determine whether changes in extracellular Calcium Concentration, blocked Magnesium concentration, steepness variability and the NMDAR opening probability affects the rate of change of calcium ions in the volume at synapse sites on dendritic spines. In general, we are asking, do parameters that play key roles in the signaling pathway positively or negatively affect the rate of flow of calcium into the cell. By quantifying the differences in the rate of flow of calcium into the cytosolic cell, we hypothesize that (1) increases in concentrations, of the extracellular calcium, and also the blocked magnesium

concentrations will cause a decrease in the rate of flow of calcium into the cell and (2) as the probability of the NMDA receptor channel to open increases, the rate of flow of calcium into the cell will also increase.

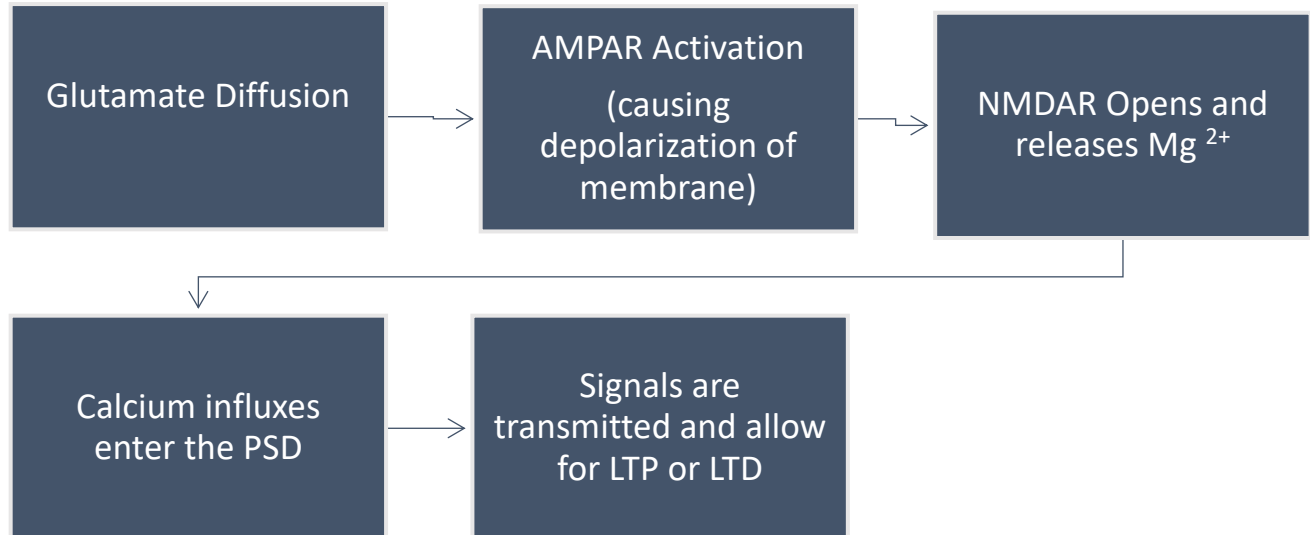


Fig. 1. Pathway of the calcium signaling pathway that happens in the dendritic cells. The neurotransmitter, glutamate is released from the presynaptic cell which causes the AMPA receptor to activate. Once AMPA receptors are activated, the cell membrane is depolarized as it is an ionotropic receptor. After a certain threshold is reached, this change in voltage allows for the NMDA receptor to open and then release the blocked magnesium molecule(s) to be released. The open NMDAR and AMPAR allow for calcium molecules in the synaptic cleft to flow into the postsynaptic cell and continue down the dendrite.

## Materials and Methods

### *Creating Realistic Geometry Meshes*

This study had two parts with each one being crucial to understanding the calcium signaling pathways deeper. The first part included creating the realistic geometries with the use of Blender and the BlendGAMeR addon from Lee, Christopher T et al. (2020): Marking boundaries using BlendGAMeR. This program allows for generating a tetrahedral, realistic mesh that can be used for further spatiotemporal modeling from a volume electron microscopy (EM) dataset. This study used the raw electron micrographs and segmentations from Wu et al. paper "Contacts between the endoplasmic reticulum and other membranes in neurons (2017)." The electron micrograph comes in various dimension images, 2D, 3D, 4D; however, Wu (2017) provided 3D preliminary meshes of the ER.

As preliminary meshes from different segmentations of data are poor quality for computation, they can lead to many errors in the computation and lots of times uncertainty and inefficiency when trying to create models. With the use of triangulated meshes, accurate evenness around the mesh edges and also vector distribution helps to model better. The quality of a mesh

is determined by the mesh topology and the ratio of different types of triangles which is why a higher quality of mesh contains more segmented triangles.

This study went through the BlendGAMeR methodology to smooth and refine the meshes. First, the raw data was imported into the Blender software. We started off with segmentation and connecting parts of the ER (Fig. 2) and plasma membrane(PM) (Fig. 3) which had been disconnected due to the electron microscopy process. This was done manually using the “Fill” function of the initial Blender program. (To be noted: Human error was possible in these steps however it was done to the best of knowledge)

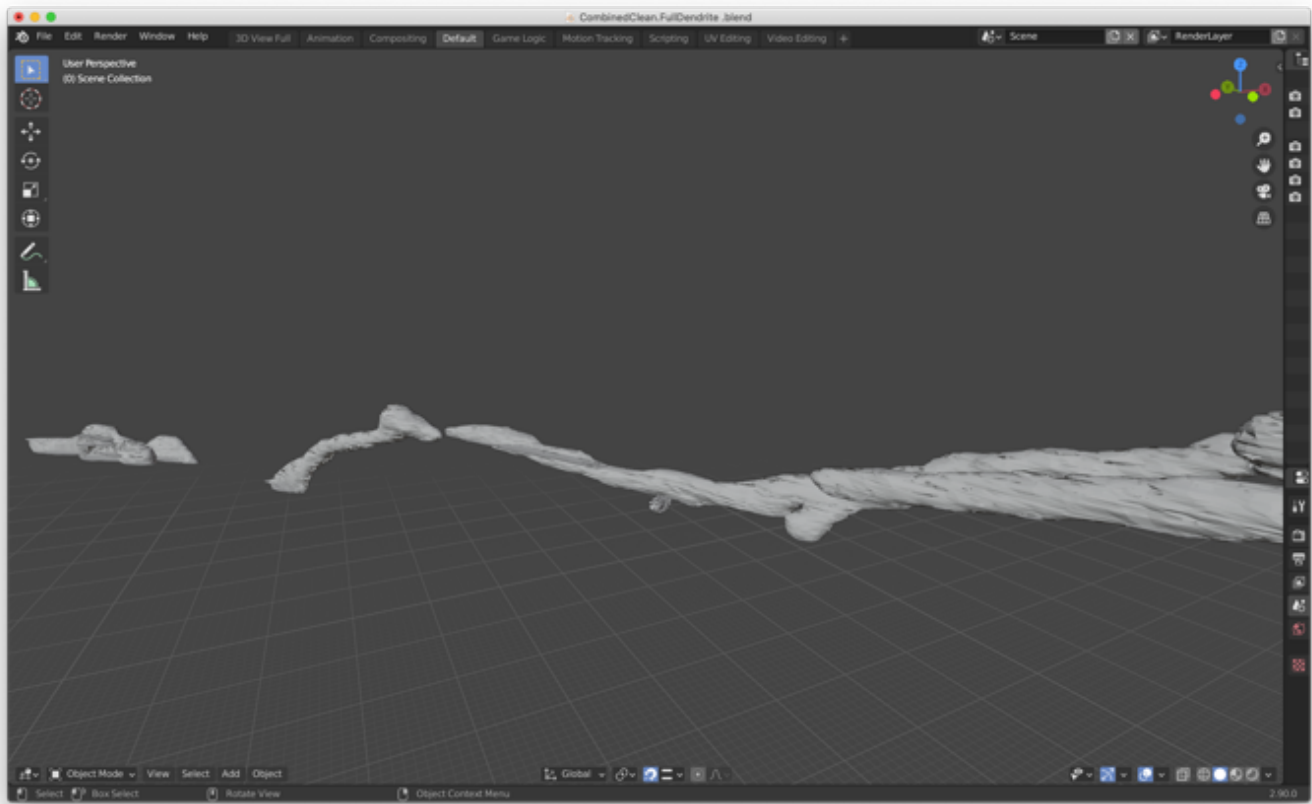


Fig. 2. Raw electron microscopy cuts and preliminary mesh of the Endoplasmic Reticulum(ER). The image was produced through the Blender software and no smoothing algorithms were implemented at this stage. The different sections of the volume were not combined because they were determined to be far enough to be declared another part of the plasma membrane

After the entire mesh was connected and produced a hollow 3D volume, the mesh was checked for holes. The GAMeR tab had a Mesh Quality Reporting panel which produced a summary of report features of the mesh. This included volume, surface area, Number of Wagon Wheels and more features that help to determine the quality of the mesh. Then, the non-manifold topology was cleaned up, which is irregular geometry that may exist in the real world which is why it is important to not smooth out the proper volumes that are found in cells. This helped clean up the intersecting faces that were produced due to the slices of images and also the triangles from the mesh were cleaned. Once the holes are also cleaned up and the volume

becomes a watertight mesh, a final triangulating function can be applied to evenly make all the faces into triangles.

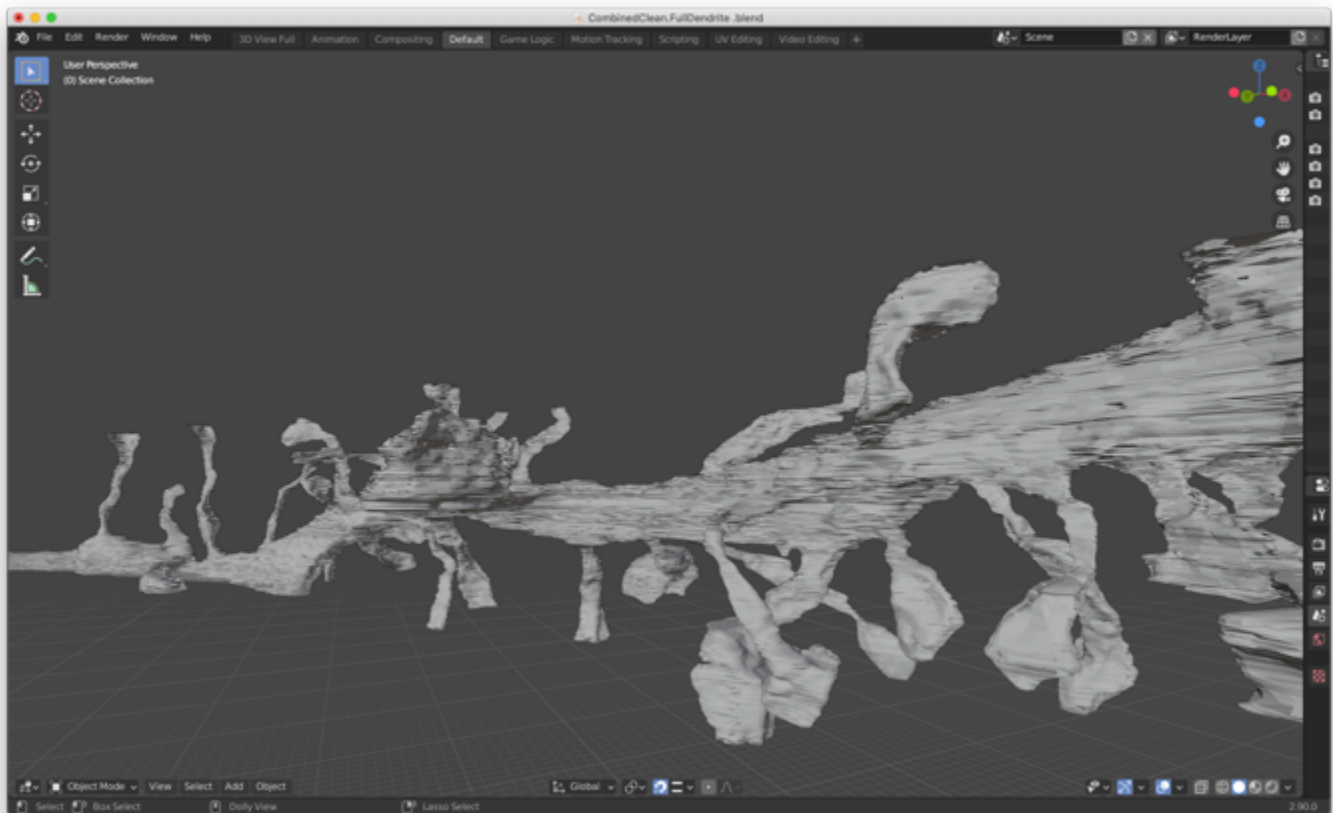


Fig.3.This is the preliminary mesh of the plasma membrane(PM). The layers were due to the different electron microscopy images stacked together and segmented for the specific PM model.

Then, the clean mesh was ready for the BlendGAMeR algorithm to condition the mesh. This was done through the Surface Mesh Conditioning panel which provides functions to smooth the surface, fill holes, reduce the number of triangles in regions of the mesh and also smooth the vertices between the triangles. The Smooth algorithm was run several times with different thresholds for the vertices of sharp faces to create a smoother mesh. Then the GAMeR addon detected no more sharp faces. The Smooth was first set to 15, then the Coarse dense was set to 5, then the Smooth was run at 15 again and the Coarse Dense was set to CD\_r,1; CD\_Iter,5. The Smoothing threshold was then increased to S\_Iter 20 and then finally Normal Smooth was run multiple times to smooth out the triangles. The Normal Smooth function found the average of different triangles which is why some information about the volumes might have been lost at this step.

Lastly, for creating the realistic geometries, the boundary box was added which is used to model the diffusion in the cytosol. The boundary box, which helps to set the cytosolic domain, was created when a cube was added to the mesh and positioned in the middle of the mesh and then subdivided into many different triangles. Finally, the realistic geometries, for the spatiotemporal models were created and ready. This entire process required the Blender Software, BlendGAMeR addon, dataset from Cell Image Library and lastly a computer. Due to

the convenience of the computational biology project, this was also possible through a virtual machine.

### *Solving ODE to Model Calcium Influxes*

Once the realistic geometries were created, the ODE model could be solved with the specified volumes that were determined with the realistic geometries. Literature searches helped to find and compile the necessary equations to solve the Ordinary Differential Equations (ODEs) that modeled the rate of flow of calcium into the post synaptic cell. To determine the rate of flow of calcium influxes into the post-synaptic cells, we created a diffusion ODE model as described by

$$\frac{dc}{dt} = \left( \frac{J_{NMDAR}}{nPMr} \right) - c/20 \quad (1)$$

where  $dc/dt$  describes the rate of change of the concentration of calcium molecules over time in the cytosolic area.  $J_{NMDAR}$  is a flux term with the units  $moles/\mu m^2$  and describes the rate of flow of calcium ions across the membrane. Since we wanted to know the rate of change of calcium ions in the volume,  $moles/\mu m^3$ , we used  $nPMr$ , which is a unit of  $\mu m$  as a unit converter. The flux of calcium that is dependent of the conductance and the dynamics of the receptor opening, or the  $J_{NMDAR}$  is given by

$$J_{NMDAR} = \gamma_i \frac{(N_{NMDAR})}{(\beta_{NMDAR} \cdot A_{PSD})} \quad (2)$$

In the equation above,  $\beta$  is a constant as describe in Table 1.  $\gamma_i$  describes the relationship between the voltage and current of the membrane and the opening of the membrane receptors and combines all of the paramteres together.

$$\gamma_i = P_0 G_{NMDAR} \left( I_f H(t) e^{-\frac{t}{\tau_f}} + I_s H(t) e^{-\frac{t}{\tau_s}} \right) B(V_m)(V_m - V_r) \quad (3)$$

Where  $H(t)$  is the Heaviside function and the  $N_{NMDAR}$  is the number of open receptors in the system.  $G_{NMDAR}$  is the conductance of the NMDAR which describes the rate that ions flow across the membrane.

$$G_{NMDAR} = \frac{(\zeta_i \times 10^{19})}{(2 \times 1.602) \times 6.022 \times 10^{23}} \left[ \frac{Ca^{2+} \text{ moles}}{V \cdot s} \right] \quad (4)$$

$\zeta_i$  is the single channel conductance of NMDAR which is described by

$$\zeta_i = \frac{G_0 + n_0 h}{1 + \frac{n_0 h}{g_\infty}} \quad (5)$$

$G_0$  and  $g_\infty$  are the limiting conductance for the varying levels of  $Ca^{2+}$ .  $h$  sets how fast the different cases are reached and then lastly  $n_0$  describes the concentration of the extracellular calcium. As

$$n_0 = r[Ca^{2+}]_{extracellular}$$

Furthermore,  $B(V)$  describes the unblocking of the magnesium ion that is normally in the NMDAR opening. In usual (basal) conditions, NMDAR is not open for two reasons. When it needs glutamate to bind to it and second, when there is a magnesium ion sitting in the channel opening. The Mg ion is there because of the charge difference (therefore the membrane potential  $V_m$ ). When the membrane voltage changes, the Mg ion is no longer held in place and moves out of the channel, allowing other ions (like  $Ca^{2+}$ ) to flow into the neuron.  $B(V)$  is described as

$$B(V) = \frac{1}{1 + e^{-K_m V_m} ([Mg]/Mg_{scale})} \quad (6)$$

Lastly, the membrane voltage, which is dependent on the time and also the relationship between the membrane and conductance of the membrane is given by

$$V_m(t) = V_{rest} + BPAP(t) + EPSP(t) \quad (7)$$

In which

$$BPAP(t) = maxBPAP(I_{bsf} e^{\frac{-(t-delay_{bp})}{t_{bsf}}} + I_{bss} e^{\frac{-(t-delay_{bp})}{t_{bss}}}) \quad (8)$$

and

$$EPSP(t) = s_{terms} (e^{\frac{-(t-delay)}{t_{ep1}}} - e^{\frac{-(t-delay)}{t_{ep2}}}) \quad (9)$$

Parameters for the membrane voltage are given in Table 2. These equations are based upon the assumption that there will be the maximum depolarization at the membrane meaning the NMDA receptor will be completely open.

*Table 1. Specific parameters to model NMDAR*

| Variable    | Value    | Units           |
|-------------|----------|-----------------|
| $N_{NMDAR}$ | 1        | # of Receptors  |
| $A_{psd}$   | Variable | Micrometers     |
| $G_0$       | 65.6     | $pS$            |
| $P_0$       | 0.5      |                 |
| $h$         | 11.3     | $\frac{pS}{mM}$ |

|              |       |           |
|--------------|-------|-----------|
| $g_{inf}$    | 15.2  | pS        |
| $r$          | 0.5   |           |
| $K_m$        | 0.092 | $mV^{-1}$ |
| [Mg]         | 1     | $mM$      |
| $Mg_{scale}$ | 3.57  | $mM$      |
| $V_r$        | 90    | $mV$      |
| $I_f$        | 0.5   |           |
| $I_s$        | 0.5   |           |
| $T_f$        | 50    | $Ms$      |
| $T_s$        | 200   | $Ms$      |

*Table 2: Parameters for the membrane Voltage Equations:*

|            |      |      |
|------------|------|------|
| $V_r$      | -65  | $mV$ |
| maxBPAP    | 38   | $mV$ |
| tdelaybp   | 2    | $ms$ |
| $I_{bsf}$  | 0.75 |      |
| $I_{bss}$  | 0.25 | $ms$ |
| $I_{bsf}$  | 3    | $ms$ |
| $I_{bss}$  | 25   | $ms$ |
| $I_{term}$ | 25   | $ms$ |
| tdelay     | 0    | $ms$ |
| Tep1       | 50   | $ms$ |
| Tep2       | 5    | $ms$ |

\*These were all chosen based on trying to get the maximum depolarization

To briefly summarize, all of the equations listed above were used in the ODE in a cascading manner. They all fit into Equation 1. And they are all cascading functions that fit inside of each other. Once the equations were set, and also the units for the equations were decided, we created a python script to model the control. The time scale used was 0-100 ms and the rest of the parameters, such as  $Ca^{2+}$  concentration and the  $Mg^{2+}$  concentrations were based off of experimental data. (Froemke et al., 2006; Fuenzalida et al., 2007; Griffith et al., 2016). The first step was to list all of the parameters above as variables in a function called *model*. Then, each of the unknown variables, that had expressions was assigned its own expression inside of *model*. Finally, the expression returned from function *model* was the overall Equation 1, showing the rate of flow of calcium over time. The Python script used `scipy.integrate.odeint` to solve the function as described in Equation 1. Then, the ode function output was plotted against time, meaning, if  $c$  described the ode output, script plotted  $c(t)$  ( $t$  being time, and  $c$  being the ODE function) as shown in Fig 4.

Once the control graph was outputted, the different varying parameters were determined. In this study, we focused on the affects of varying extracellular Calcium concentrations, blocked Magnesium concentration,  $P_0$  values (the probability of NMDA receptor opening up) and lastly,

$K_m$  or the steepness parameter used to adjust the probabilistic function to resemble the relationship between voltage and conductance of the synaptic site.

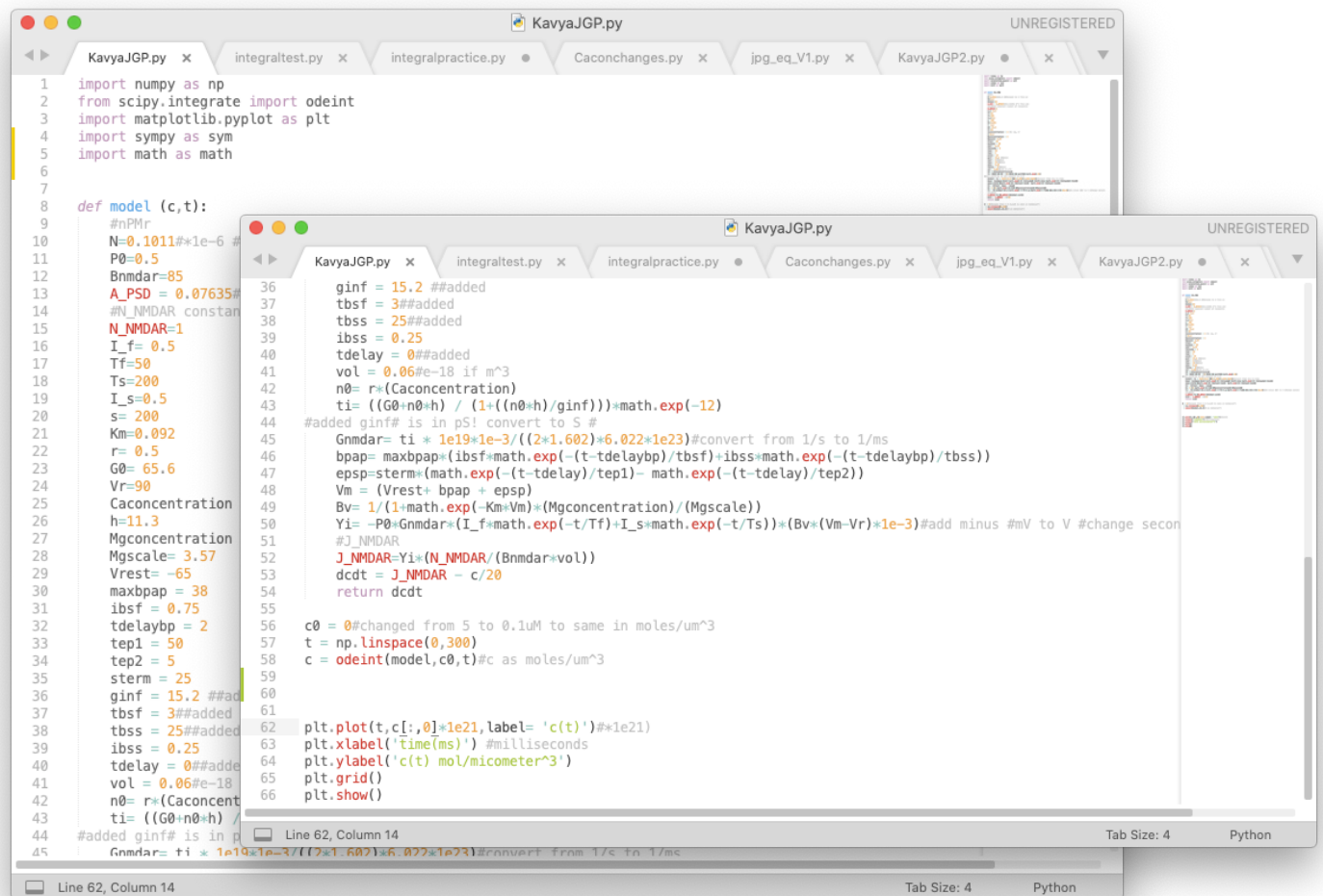


Fig 4. Script of the ODE model with the first image showing the different parameters and the second image showing the ode.int function used to solve the function. Text editor Sublime text was used as the python compiler which was later run on the MacOS terminal.

Once the control was model was produced, the script for the varying parameters was created. To create a varying parameter, a new variable to a function was created. Then the Loop was called and a new ode.int function was called with the arguments set as the varying parameter. Add labels for the graph and complete with the same plt.plot functions. Each of the parameters had five

## Results

### *Creating Smooth Meshes of the Realistic Geometries*

The BlendGAMeR procedure helped to create smooth, watertight meshes and volumes which could be used for further Partial Differential Equation Modeling. The meshes were all connected at all of the seams and created a recognizable, 3D model of the Endoplasmic Reticulum and the Plasma Membrane (Figure 5).

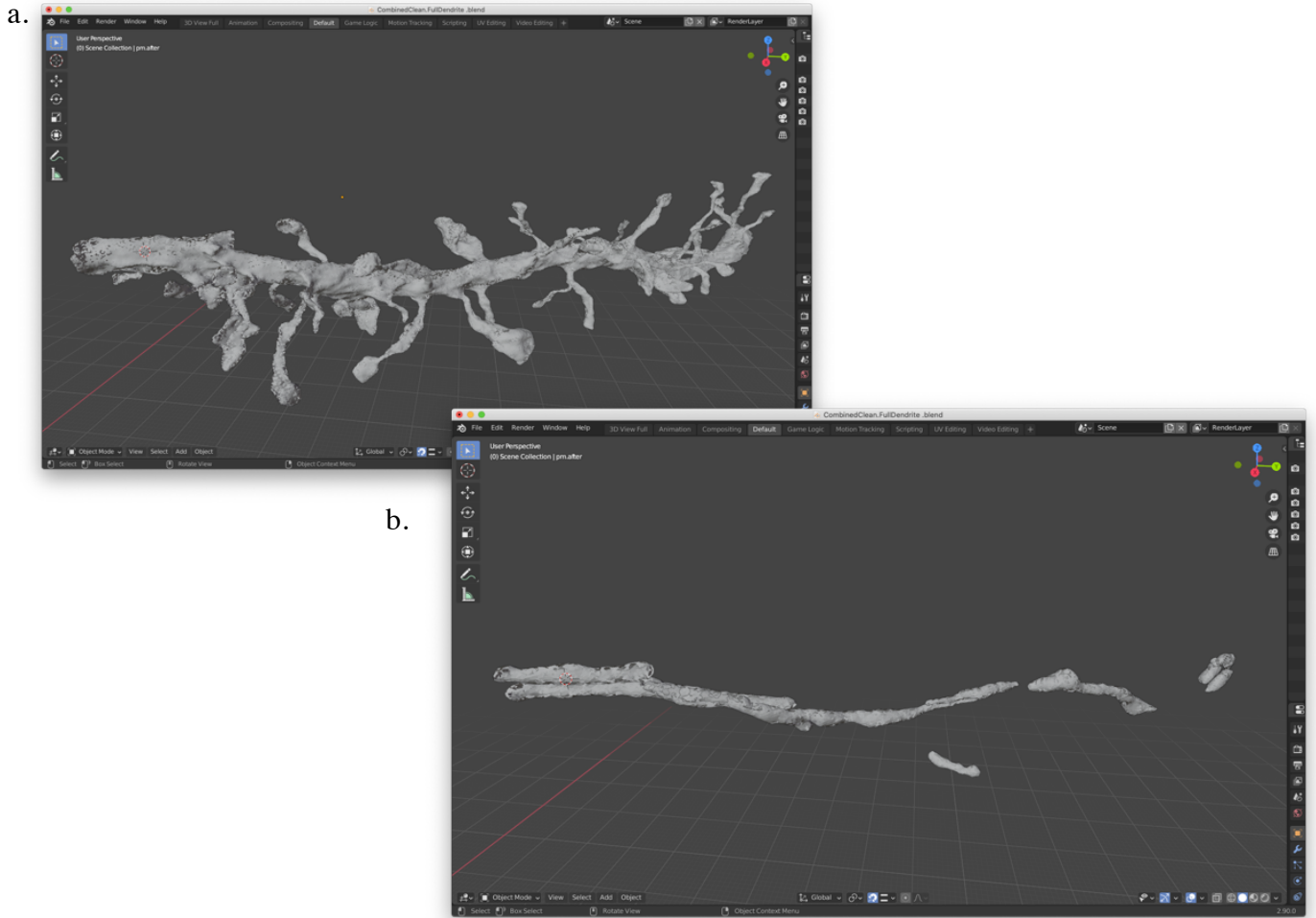


Fig. 5. a) Shows the cleaned and smoothed mesh of the plasma membrane. Compared to the original mesh, the layers between the images produced from the electron microscopy layers have been smoothed and now has a smooth surface. The volume is also preserved and did not lose key components of the shape of the PM. b) The smoothed EM shows similar results as the PM. The mesh overall is smoothed and does not show the layers between each of the image slices.

### *Creating ODE Model Comparing Different Values of Parameters*

Using the model from above, we investigated how differences in carrying parameters of the calcium dynamics model affect the rate of flow of calcium into the post synaptic cell.

Analysis of the varying parameters showed large differences between each of the increasing parameters. The control graph, with no varying parameters, showed a spike in the greatest rate of flow of calcium into the cytosolic area at around 16 ms. (Figure 6a) When the Extracellular Calcium concentration was increased at intervals of 2 mol, the peak rate of flow of calcium into the cell decreased starting at 0 mol of extracellular  $\text{Ca}^{2+}$ . (Figure 6b) The integrals of all of the different concentrations of the extracellular calcium showed similar data. ( $0 \text{ ms} \leq t \leq 40 \text{ ms}$ ). (Figure 6c) The integral of  $c(t)$  meaning, the rate of flow of calcium into the cytosolic area decreased as extracellular calcium concentrations increased. With varying Magnesium concentrations that are in the NMDA receptors, there was also a decrease in the rate of flow of the calcium molecules into the cell. As the magnesium concentrations blocking the NMDA receptors increased, the rate of flow of calcium into the post-synaptic cell also increased. (Figure 6d). This data was supported by the areas calculated under the curve. The integral of  $c(t)$  from 0 to 40 ms when the blocked Mg concentration was 0 mol was  $7.73 \times 10^{-38}$  while the integral of  $c(t)$  from 0 to 40 ms when Mg was 7 mol was  $1.07 \times 10^{-39}$  (Figure 6e).

For varying probabilities of the NMDA receptor to open up, as the probability, or P0 value, increased, the rate of flow of calcium into the post-synaptic cell increased (Figure 7c). Figure 7d also backed up this data since the integral of  $c(t)$ , for a 40 ms time interval with increasing probabilities of the NMDA receptor to open had increasing integrals. When there was a 5% chance for the NMDA receptor to open up, the total rate of flow of calcium into the post-synaptic cell was  $4.93 \times 10^{-40}$ . When there was a 72.5 % chance of the NMDA receptor to open up, the integral of  $c(t)$  in a 40 ms time interval was  $7.15 \times 10^{-39}$ , therefore increasing. Lastly, the varying  $K_m$  values, or relationship indicator between voltage and conductance of the membrane showed that with increasing  $K_m$  values, there was an decrease in the rate of flow of calcium into the post synaptic cell (Figure 7a). The integrals of the graphs shown in Figure 7b, with the varying  $K_m$  values, at 0.02 mV-1 increases showed a large peak at the  $K_m$  value of 0.0505 mV-1 and then had an exponential decay.

## Discussion

The results from the GAMeR smoothing techniques have showed that it is possible to use raw EM stack data to successfully create a full smoothed mesh of a realistic model of a dendritic spine. Some patterns I saw in the modeling section was how the different slices of the model were smoothed out with the help of the GAMeR software. The produced mesh would be helpful in creating 3D stochastic models of the calcium influxes to see the visuals of how the molecules diffuse throughout the dendritic spine head. Previously, using the algorithms from software, such as Blender, would not have been sufficient for keeping in shape the volume and of the mesh. Thus, previous methods and ways of smoothing 3D models of the realistic geometries created by the electron, microscopy graphs would not have been accurate. Some limitations that probably were produced due to the GAMeR smoothing algorithms was that since human judgments needed to be used when connecting the raw volumes, inaccuracies may have arrived. Also, even with the complex algorithms that help GAMeR run, there is no guarantee that the averaging techniques that the software uses is always accurate. There may be some overestimates which do not preserve the raw images of the EM and PM.

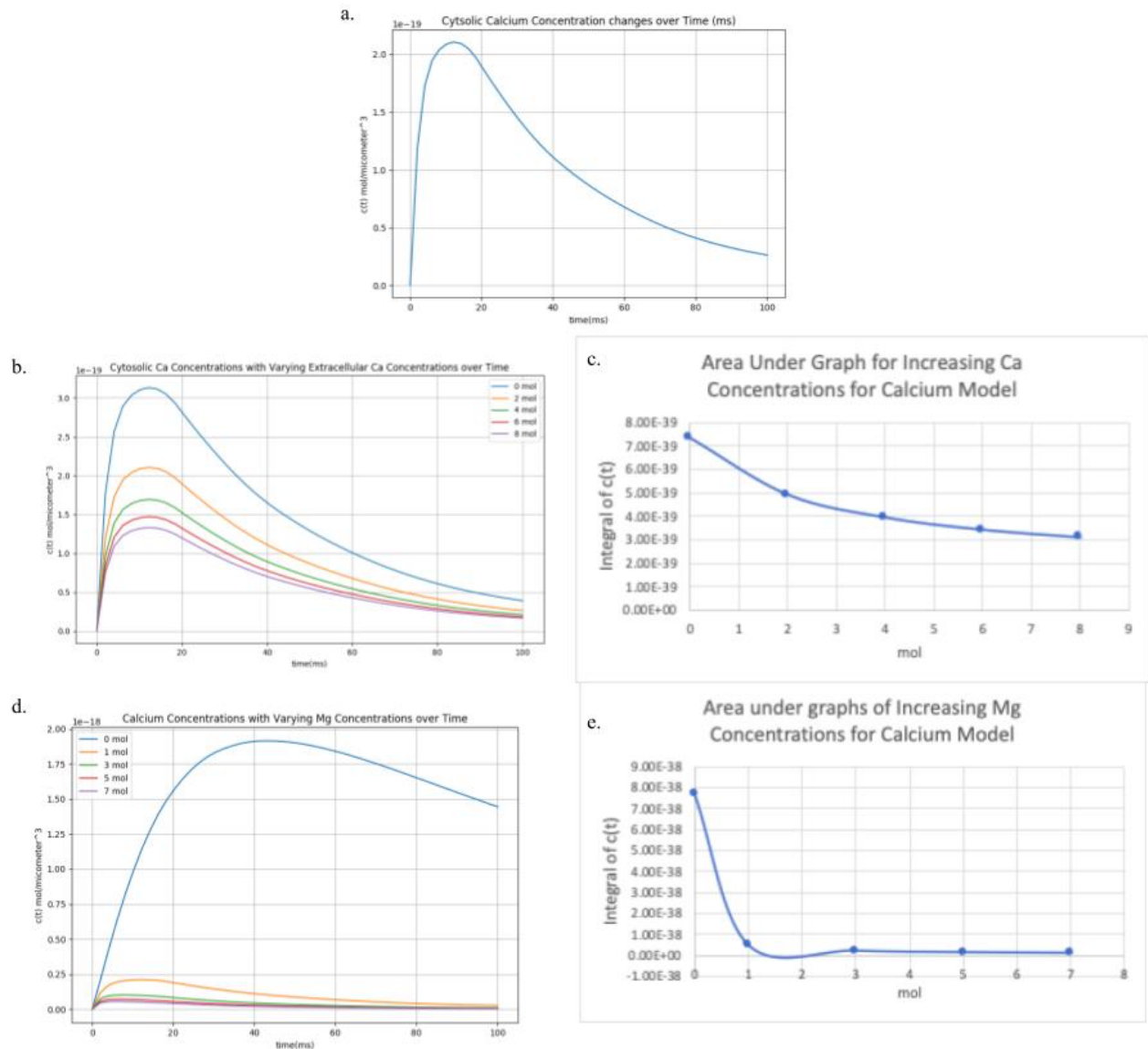


Fig.6. a) This is the control ODE model which does not have any varying parameters. This means that the values inputted for the parameters in this Calcium Model was what previous research deemed somewhat accurate representations of the values of molecules, concentrations, and fully open receptors produced. There was a peak around 16 ms showing the place of the fastest rate of flow of calcium into the cytosol. b) Rate of flow of calcium molecules into the cytosol with increasing extracellular (ECS) calcium concentrations, 0 to 8 mols. c) Integrals of graphs, of  $c(t)$  from 0 to 40 ms with varying ECS calcium concentrations. d) Rate of flow of calcium into rate of flow of Calcium ions into cell with increasing blocked magnesium concentrations. Time is in ms and  $c(t)$  is in  $\text{mol}/\mu\text{m}^3$  e) Integrals (total rate of flow of calcium into the cytosol from 0 to 40 ms) of varying blocked Mg concentrations in calcium pathway.

As the hypothesis predicted, the varying parameters did have a large difference between each other, as they increased, they affect the rate of flow of calcium into the cell. The decreased rate of flow of calcium into the cytosol with increased concentrations of calcium molecules in the ECS is logical because the synaptic cleft would become more crowded and make it harder for the calcium molecules to flow into the post synaptic cell through the NMDA receptor. Because it

is more crowded in the synaptic cleft, the total decreased rate of flow from 0 to 40 ms is probable since less calcium molecules are able to flow through, for every 1 ms. The increased magnesium blocked concentrations cause a slower rate of flow of calcium through the NMDA receptors

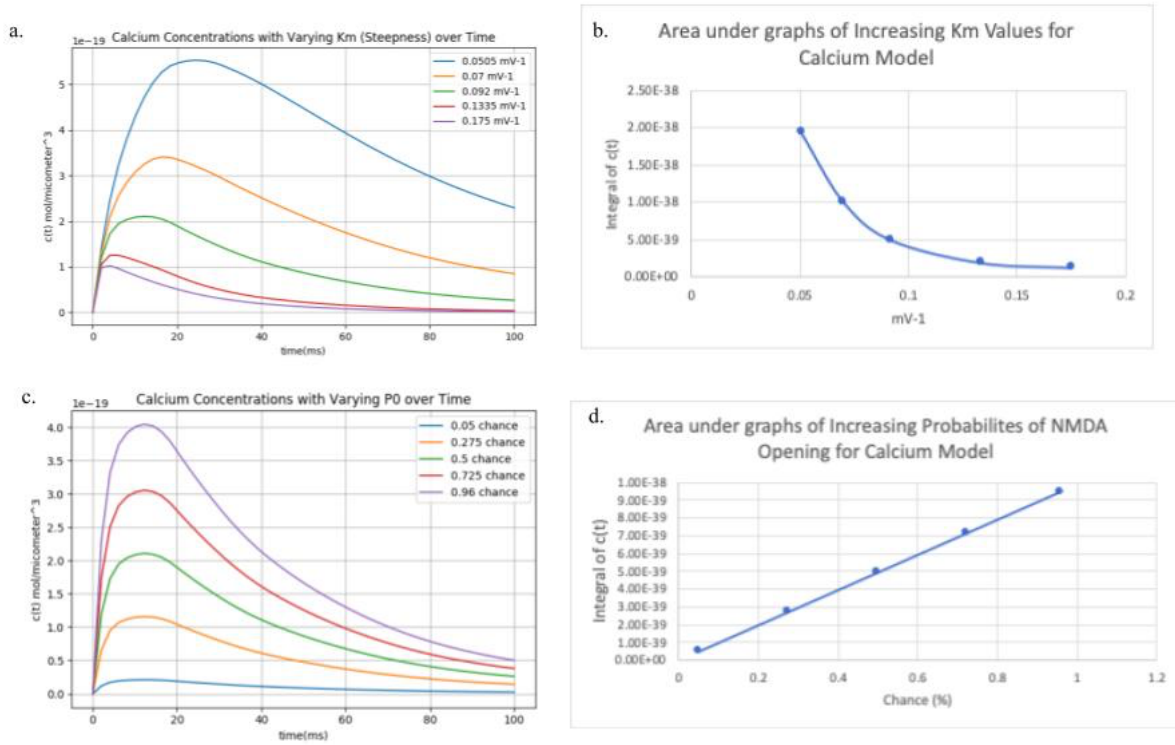


Fig. 7. a) Varying  $K_m$  values, or the steepness. The  $K_m$  values were changed from 0.0505  $\text{mV}^{-1}$  to 0.175  $\text{mV}^{-1}$  at constant  $\sim 0.02 \text{ mV}^{-1}$  intervals. b) Integrals of  $c(t)$  graphs of varying  $K_m$  values with a time interval of 0 to 40 ms. c) Varying  $P_0$  or probabilities of NMDA receptor chances in the calcium models. The chances ranged from 0.05-0.96 with  $\sim 0.25$  interval changes. d) Integrals, or the total rate of flow of calcium into the cytosol, with varying probabilities of the NMDAR opening up.

because it requires a higher amount of voltage displacement to clear out all of the magnesium molecules from the NMDA receptors. This may be explained by the results which show a slower total rate of flow of calcium molecules into the cytosol from a 0 to 40 ms time interval when there is more magnesium blocking the NMDA receptors. With an increased probability of the NMDA receptor to open up, that means more NMDA membrane receptors are free to allow an influx of calcium molecules into the post synaptic cell. The results align with the hypothesis since the total rate of flow of calcium molecules into the post-synaptic cell would increased and be larger over the same time interval with a lower chance of the NMDA receptor opening up. Lastly, the  $K_m$ , or steepness relationship between the voltage and conductance of the membrane, results prove how the threshold of depolarizing the membrane helps to regulate more calcium molecules into the post-synaptic cell. Once the certain threshold of voltage is met, and successfully depolarizes the synaptic site, there is a increase in the rate of flow of calcium into the post-synaptic site since all of the receptors on the membrane would be fully open to let in the calcium molecules.

Some limitations that might have come up may have been due to the simplified models that were used. In the future, programs like COSMOL and MCell might help to plot this data into a 3D model by using Partial Differential Equations to make a heat map like model to show the

exact flow of calcium ions into the cell. This would be helpful to also take into account boundary conditions that were assumed in this model. These studies showed similar results to previous research as new computational models have shown how volumes and morphologies of the dendritic spine also played a large role in the rate of flow of calcium molecules into the spine. Instead of varying chemical factors in the models, the previous research modeled the size and shape of the area of interest which was a constant in this study.

These results show how understanding the relationship for the small parameters in these calcium signaling pathways is very important because these small changes are prevalent in the diseases that affect the neurons in humans. This study is important to figure out the optimal values of these parameters (ECS calcium concentrations, magnesium concentrations,  $P_0$  values, and the  $K_m$  values) since they affect the rate of flow of calcium into the dendritic spine head. As stated above, the calcium signaling pathways affect the synaptic plasticity of the neurons which plays a key role in memory retention. This is why better understanding of the topic can help to understand why age related diseases such as Alzheimer's, worsen over time. Synaptic plasticity helps to understand many of the biological signaling pathways in the body and first looking at the key players in these pathways is extremely important. In conclusion, as the site of calcium influxes became more crowded and busy, the rate of flow of calcium into the post-synaptic cell decreased. This preliminary investigation suggests further research into visual models of these calcium influxes on realistic geometries that this study created in order to understand the diffusion of calcium molecules once they have crossed the membrane of the post-synaptic cell.

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### Literature Review

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