Increasing CREB impacts memory recall in a computational model of Hippocampal CA1 neurons affected by Alzheimer's Disease

Ali Chaudhry[1,6], Marshall Graves[2,6], Aaron Kahn[3,6], Samuel Korff [4,6], Inesh Parikh[5,6], Marianne Bezaire, PhD[6]

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Introduction

- 46,000,000+ worldwide suffer from Alzheimer's Disease (AD).
- The abnormal buildup of Amyloid-Beta (Aβ) plaques causes AD by impairing memory and learning and damaging neurons in the hippocampus.

Inspiration: increasing Cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) may enhance Long Term Potentiation (LTP)—the strengthening of synapses—to create more excitable neurons and ultimately improve AD-affected memory.

Goal: contribute to AD research by modeling realistic stages of AD and analyzing the amount of CREB expression that is most effective therapeutically.

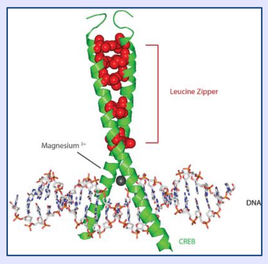


Figure 1: CREB

Neveu, C. (2014, January 29) from https://commons.wikimedia.org/wiki/

Results

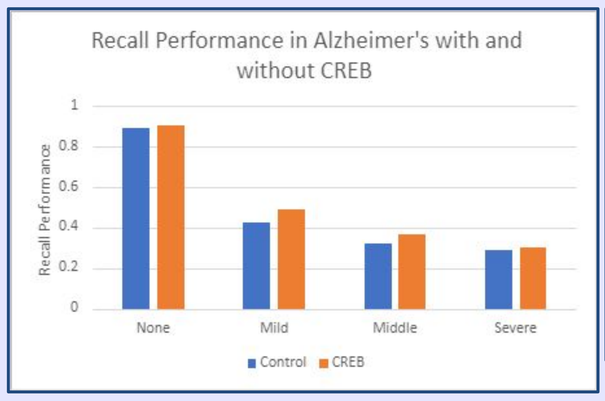


Figure 3: The 3 stages of AD and a control (healthy) with and without CREB. Recall performance is measured.

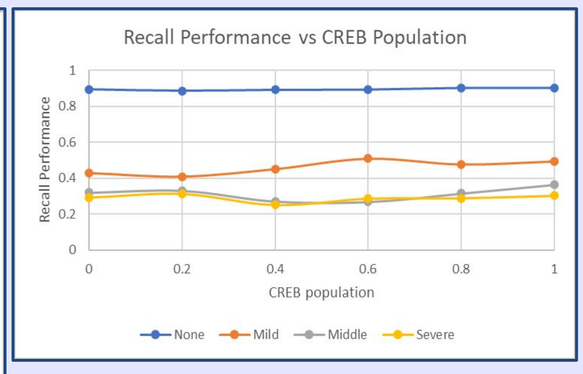


Figure 4: The effect of changing the neuron population affected by CREB on recall performance for all stages of AD. CREB level is set to 1.

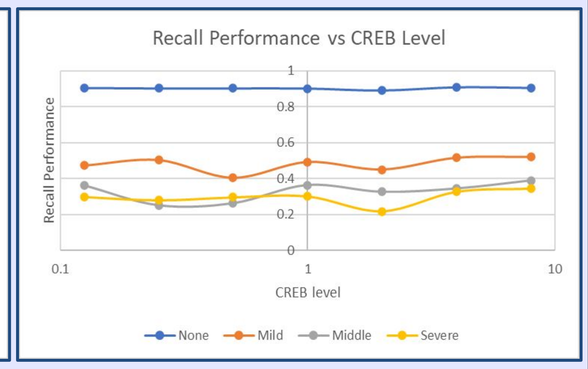


Figure 5: The effect of changing the CREB level factor on recall performance for all stages of AD. The CREB level factor affects the CREB value that was shown in Table 2, and CREB population is set to 1.

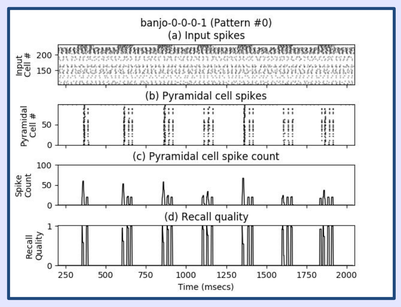
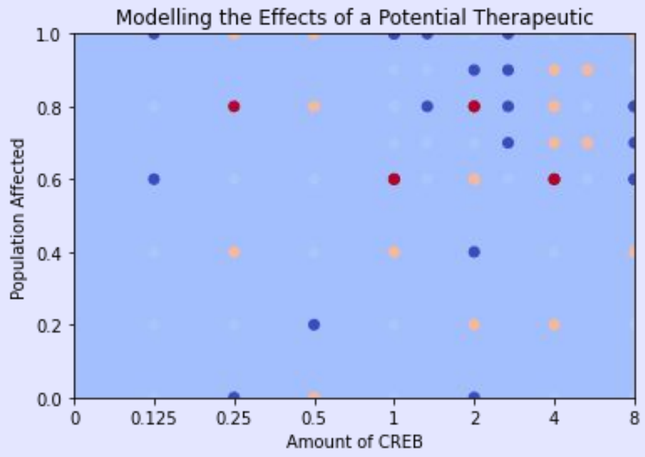


Figure 7. Visualization of one output graph that the model gives per simulation.



Class of Therapeutic	Recall Quality
Class A	0.35-0.4
Class B	0.3-0.35
Class C	0.25-0.3
Class D	0.2-0.25

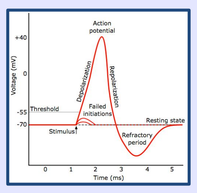
Figure 6: SVM analyzing the effects of varying the population affected by CREB and the amount of CREB. **It was not able to determine a certain area of CREB level and population that is most effective.**

Discussion/Conclusions

- Our research yielded a modified model of a CA1 neuronal network that represents AD and the addition of CREB. **As Alzheimer's became worse, overall recall performance became worse.**
- The simulations showed that **CREB slightly alleviated** the effects of AD in all stages and barely improved recall without AD**. CREB had the least effect without AD and when AD was the most severe** because in more severe stages there are not enough neurons and synapses to receive CREB's impact.
- Through varying the population affected by CREB and the level of CREB in each cell, we observed that both parameters, especially CREB level, **did not significantly impact the cells**. However there is the possibility that the methodology of programming these parameters in the CA1 model was not effective and thus further research could show that these parameters do have an effect.
- Our hypothesis that CREB would significantly ameliorate Alzheimer's, and that a higher CREB level and higher population would further this effect **was not proven true.**
- Our model can be used to further the development of therapeutics to combat AD. While most research is focused on Aβ and Tau, work on CREB and other mitigating factors is also crucial to AD research.
- Bianchi et al. created a similar model of CREB in the CA1 circuit which inspired our experiment
  - Major differences between our work and theirs include:
    - We present a more accurate and specific portrayal of AD including the killing off of neurons and synapses
    - We use **SVM** to model the characteristics of a potential CREB-based therapeutic
  - Their model showed CREB to have stronger effects than our model. **One possible explanation is that CREB is less effective at mitigating memory loss if significant amounts of neurons and synapses are already lost.** Our finding has significant implications for computing the effect of CREB in future studies.
- Our future work will focus on improving and optimizing our code, specifically the code used to simulate AMPA and NMDA receptors.
- Future work in this field could increase the complexity of AD models to include more detail than the loss of synaptic connections and neuronal death and represent the issue at its source (such as including propagation of Tau and buildup of Aβ)
- A major limitation to our study was the **lack of understanding of the intrinsic properties of on CREB and its exact effects.** Better understanding of CREB's neurobiological properties could aid in making our model more realistic.

Methods

- We modified an existing model of the hippocampal CA1 microcircuit (through Python using NEURON) to illustrate the impacts of CREB and AD on processes involved in memory. This model included 100 CA1 pyramidal cells and few inhibitory interneurons.
- We simulated the effects of no, early, middle, and late stage Alzheimer's by varying the percentage of cell death and the connections lost between synapses (see table 1).
- **To simulate CREB in each of these models, we considered 4 methods: increasing the conductance of AMPA channels, increasing the conductance of NMDA channels, decreasing the conductance of voltage gated potassium channels, and doing all together** (details about changes in values to the code in table 2).
  - Increased conductance of AMPA and NMDA channels represents CREB's ability to increase synaptic weight through those channels.
  - **Decreased conductance of voltage gated potassium channels** - models CREB's ability to lower the after-hyperpolarization (AHP) duration of firing neurons.



AHP is the period in which the voltage potential level remains below the resting membrane potential; thus, a lower AHP duration produces more excitable neurons.

Figure 2. Kurzweil, R. (Ed.). (2016, August 3). *IBM scientists emulate neurons with phase-change technology*. Retrieved August 9, 2022, from https://www.kurzweilai.net/ibm-scientists-emulate-neurons-with-phase-change-technology

- After considering the effects of each type of CREB, we decided on only modeling AHP due to the accuracy of the code used in the model
- **We used a support vector machine (SVM) to compare the population of cells affected by CREB and the individual effect of CREB on each neuron to determine the variable that was most significant in treatment.**
- For each simulation, we utilized Boston University's Shared Computing Cluster (SCC) which took our simulation time from 50 minutes to less than 1 minute.

Stage of AD	Cell death	Synapse Connection Loss
None	0%	0%
Early	15%	9%
Middle	46%	26%
Late	65%	35%

Table 1. **Modeling Different Stages of AD (based on real data)**

Level of CREB	1*
Population Affected	1*
mAHP	0.52
sAHP	0.64
AMPA	1.62
NMDA	1.5

Table 2. **Modeling the Effect of CREB Induction**
*The population affected and CREB level factor is then changed for the SVM analysis. CREB level goes from a logarithmic factor of 0.125 to 8 and population level goes from 0 to 1.

References

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Introduction

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- Unknown true cause: The abnormal buildup of Amyloid-Beta (Aβ) plaques cause AD by impairing memory and learning and damaging neurons in the hippocampus

Inspiration: increasing Cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) may enhance Long Term Potentiation (LTP)—the strengthening of synapses—to create more excitable neurons and ultimately improve AD

Goal: contribute to AD research by modeling realistic stages of AD and analyzing the amount of CREB expression that is most effective therapeutically.

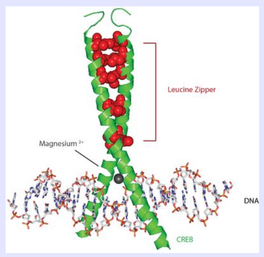

Figure 1: CREB

Neveu, C. (2014, January 29). [The overall structure of the CREB transcription factor. The region in red is the dimerization domain called the leucine zipper. The magnesium ion is in grey and the DNA is multicolored. Rendering of PDB 1DH3]. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:CREB_protein.png

Results

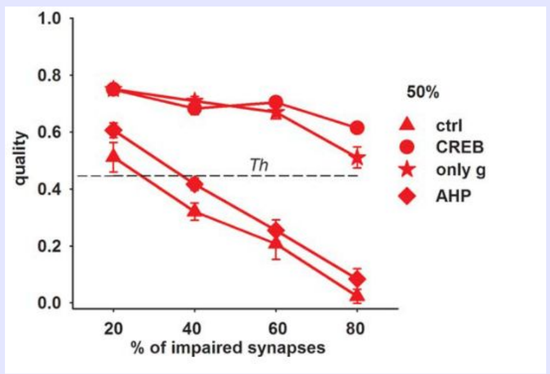

Figure 3: The 4 stages of AD (including no AD) with and without CREB. Recall performance is measured. CREB is either modeled by using AHP, AMPA, NMDA

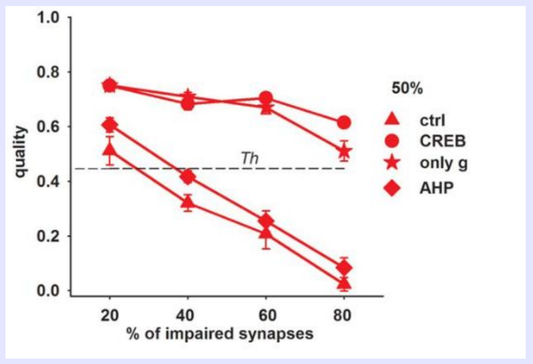

Figure 4: The effect of change in the neuron population affected by CREB on recall quality for all stages of AD. CREB level is set to 1

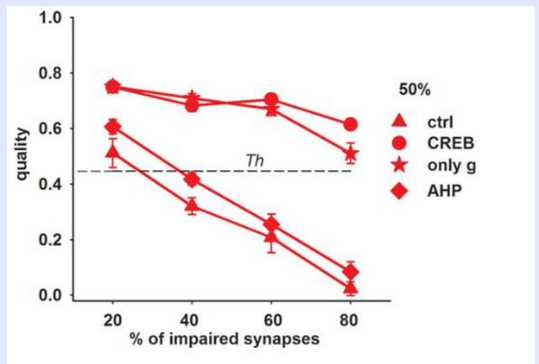

Figure 5: The effect of change in the CREB level factor on recall quality for all stages of AD. The CREB level factor affects the AHP value, and CREB population is set to 0

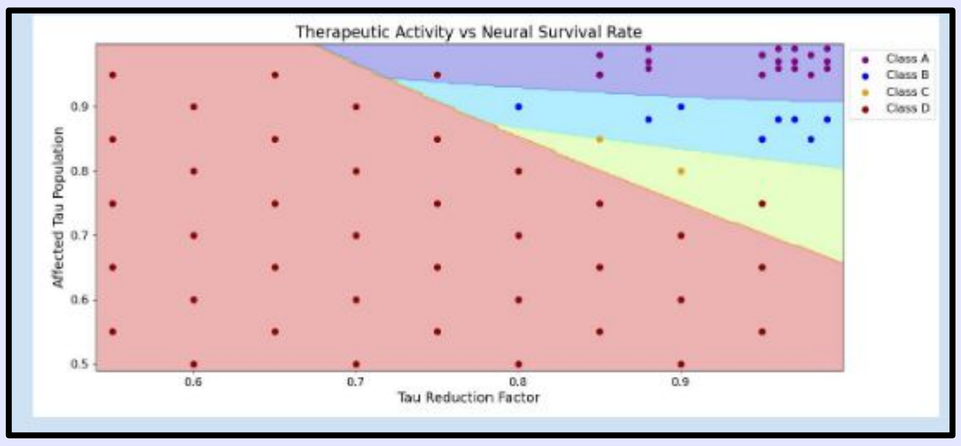

Figure 6:

Discussion/Conclusions

- The simulations showed that CREB **helped ameliorate the effects of AD in all stages**. On the other hand, CREB seemed to have minimal effect on the model without any AD.
- By varying the population affected by CREB and the factor of CREB level in the population, we determined that an effective therapeutic _____
- Bianchi et al. created a similar model of CREB in the CA1 circuit however we did not use the same methods and code
  - Major differences between our works include:
    - Possibly a more accurate/specific portrayal of AD including the killing off of neurons and synapses
    - The use of SVM to model the characteristics of a potential CREB-based therapeutic
  - Importantly, both studies concluded that CREB alleviated AD-like conditions.
- Our model can be used to further the development of therapeutics to combat AD. While research is primarily focused upon Tau and Aβ reduction, ameliorating therapeutics such as CREB can be useful for treatment.
- Future work in this model could increase the complexity of AD models to include more detail than the loss of synaptic connections and neuronal death
- We only changed AHP to model CREB for the SVM. Future studies could attempt to combine all effects of CREB, including more than just AHP, AMPA, and NMDA.

Methods

- We modified an existing model of the hippocampal CA1 microcircuit (through Python using NEURON) to illustrate the impacts of CREB and AD on processes involved in memory. This model included 100 CA1 pyramidal cells and few inhibitory interneurons
- We simulated the effects of no, early, middle, and late stage Alzheimer's by varying the percentage of cell death and the connections lost between synapses (see table 1)
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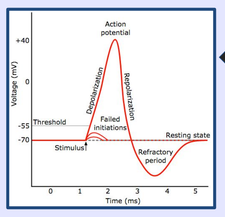

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- For each simulation, we utilized Boston University's SCC (Shared Computing Cluster) which took our simulation time from 50 minutes to 1 minute.

Stage of AD	Cell death	Synapse Connection Loss
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Table 2. **Modeling the Effect of CREB Induction**
*The population affected and CREB level factor is then changed for the SVM analysis. CREB level goes from a logarithmic factor of 0.125 to 8 and population level goes from 0 to 1.

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INTRO

- More than 46,000,000 worldwide suffer from invariably fatal Alzheimer's Disease (AD)
- AD impairs memory and learning abilities on structural level by damaging neurons in the hippocampus
- While there is no established cause, the general notion regards abnormal build up of proteins in and around brain cells as the predominant link. For example, Amyloid Beta Precursor Proteins (AβPP) ensure synaptic plasticity and synapse formation throughout life; however, proteolysis may occur with life's progression, and the new misfolded Amyloid Beta (Aβ) prion causes formation of amyloid plaques, indicating AD
- This study explores a potential therapeutic that uses cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) because it can restore Long Term Potentiation (LTP)—the strengthening of synapses—and create more excitable neurons
- Konowing this, we hypothesize that increasing CREB may improve memory in neurodegenerative cases.
- We ultaimtely aim to contribute to AD research by **modeling realistic stages of AD and analyzing the amount of CREB expression that is most effective therapeutically.**

Methods

- We modified an existing model of the hippocampal CA1 microcircuit (through Python using NEURON) to illustrate the impacts of CREB and Alzheimer's on processes involved in memory.
  - 20 of the 100 CA1 pyramidal neurons in the network were chosen to remember a pattern. The synaptic conductances changed to learn the "memory." When the memory was recalled, we measured the quality with which the network remembered the pattern over a simulation period of 2050 ms and took the average performance
- We simulated the effects of no, early, middle, and late stage Alzheimer's by varying the percentage of cell death and the connections lost between synapses (see table 1)
- **To simulate CREB we considered 4 methods: increasing the conductance of AMPA channels, increasing the conductance of NMDA channels, decreasing the conductance of voltage gated potassium channels, and doing all together**
  - Increased conductance of AMPA and NMDA channels represents CREB's ability to increase synaptic weight through those channels
  - **Decreased conductance of voltage gated potassium channels** - models CREB's ability to lower the after-hyperpolarization (AHP) duration of firing neurons
    - AHP is the period in which the voltage potential level remains below the resting membrane potential; thus, a lower AHP duration produces more excitable neurons
- We first ran the model for the 4 stages of AD under 5 CREB conditions: No CREB, and the 4 aforementioned methods
- We then ran our model such that CREB impacted between 0-100% of the population with the effects of CREB ranging from ⅛ to 8 times those in the initial model. This was done only on Middle AD.
- **We used a support vector machine (SVM) to compare the population of cells affected by CREB and the individual effect of CREB on each neuron to determine the variable that was most significant in treatment**
-

Results

Graph 1 - The 4 stages of AD (including no AD) with and without CREB. Recall performance is measured. CREB is either modeled by using AHP, AMPA, or NMDA.

The results show that:

Graph 2-3 - Show the effect varying population and CREB level factor have on recall performance.

This information was then put into the SVM which resulted in:

AD Methods Table

Stage of AD	Cell death	Synapse Connection Loss
None	0%	0%
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CREB Methods Table

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Figure 2. **Modeling the Effect of CREB.**
***The population affected and CREB level factor is then changed for the SVM analysis. CREB level goes from a factor of 0.125 to 8 and population level goes from 0 to 1.**

Discussion

- Our research yielded a modified model of a CA1 neuronal network that represents AD and the addition of CREB
- The simulations showed that CREB helped ameliorate the effects of AD in all stages. On the other hand, CREB seemed to have no effect on the model without any AD
- By varying the population affected by CREB and the factor of CREB level in the population, we determined that an effective therapeutic _____
- Bianchi et al. created a similar model of CREB in the CA1 circuit which inspired our experiment
  - Major differences between our works include:
    - Possibly a more accurate/specific portrayal of AD including the killing off of neurons and synapses
    - The use of SVM to model the characteristics of a potential CREB-based therapeutic
  - Importantly, both studies concluded that CREB alleviated AD-like conditions.
- Our model can be used to further the development of therapeutics to combat AD. While a lot a research is focused on Aβ and Tau, work on CREB or other mitigating factors could aid treatment.
- Future work in this field could increase the complexity of AD models to include more detail than the loss of synaptic connections and neuronal death and represent the issue at its source
- Our use of the Cutsuridis model prevented us from actually implementing CREB, and we could only simulate its impacts
- Our experiment was further limited by values we approximated instead of scientifically determining (ask Marshall)

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- Our experiment was further limited by values we approximated instead of scientifically determining (ask Marshall)

Discussion

- Our research yielded a modified model of a CA1 neuronal network that represents AD and the addition of CREB. As Alzheimer's became worse, overall performance became worse.
- The simulations showed that CREB helped ameliorate the effects of AD in all stages slightly. The biggest effect was in Early Stage Alzheimer's
  - This could be because there is less cell and synapse death.
- By varying the population affected by CREB and the factor of CREB level in the population, we saw that there was not much of a difference in their effects as CREB level ended up not affecting the cells too much
- Our hypothesis that CREB would significantly ameliorate Alzheimer's, and that a higher CREB level and more population would further this effect was not proven true.
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    - Possibly a more accurate/specific portrayal of AD including the killing off of neurons and synapses
    - The use of SVM to model the characteristics of a potential CREB-based therapeutic
  - They got more significant amelioration than our model, however due to the killing of neurons and synapses, maybe CREB does not have as much of an ameliorating effect if those connections are already gone.
- Our model can be used to further the development of therapeutics to combat AD. While a lot a research is focused on A**β** and Tau, work on CREB or other mitigating factor are important to analyze.
- Future work from us will be to re-analyze the code and modify and expand on CREB to see if it can have any difference. We will modify the AMPA and NMDA code. We can also try to see if synapse death can be replaced with synapse weakening to generate better results
- Future work in this field could increase the complexity of AD models to include more detail than the loss of synaptic connections and neuronal death and represent the issue at its source
- Our model ran 3 simulations per data point which could lead to randomness (however this was not deemed to significant)

- Our research yielded a modified model of a CA1 neuronal network that represents AD and the addition of CREB. As Alzheimer's became worse, overall performance became worse.
- The simulations showed that CREB slightly alleviated the effects of AD in all stages and barely improved recall without AD. CREB had the least effect without AD and when AD was the most severe because there is little CREB can do to improve an already healthy brain or a brain that is lacking as many synapses and neurons as a brain with severe AD.
- Through varying the population affected by CREB and the factor of CREB level in the population, we observed a minimal difference in their effects because CREB level did not signficantly impact the cells. Thus, we determined that a therapeutic was not effective.
- Our hypothesis that CREB would significantly ameliorate Alzheimer's, and that a higher CREB level and higher population would further this effect **was not proven true.**
- Bianchi et al. created a similar model of CREB in the CA1 circuit which inspired our experiment
  - Major differences between our works include:
    - Possibly a more accurate/specific portrayal of AD including the killing off of neurons and synapses
    - The use of SVM to model the characteristics of a potential CREB-based therapeutic
  - Their model showed CREB to have stronger effects than our model. One possible explanation is that CREB is less effective at mitigating memory loss if significant amounts of neurons and synapses are already lost. Our finding has significant implications for computing the effect of CREB in future studies
- Our model can be used to further the development of therapeutics to combat AD. While a lot a research is focused on Aβ and Tau, work on CREB or other mitigating factors is crucial to analyze.
- Our future work will focus on re-analyzing our code, specifically the code used to simulate AMPA and NMDA receptors. We will also try to see if synapse death can be replaced with synapse weakening to generate better results
- Future work in this field could increase the complexity of AD models to include more detail than the loss of synaptic connections and neuronal death and represent the issue at its source.
- Our model ran 3 simulations per data point which could lead to randomness

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