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IB Physics, pd 5  
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## Science Fair Literature Review and Research Plan

### Research Question;

What is the optimal combination and dosage of Lecanemab and Cromolyn across different genetic backgrounds (APOE3, APOE4, and TREM2 R47H mutation, combination of the two) to maximize neuronal survival and minimize neuroinflammation in Alzheimer's disease and where will it the benefits be most pronounced?

### Hypothesis;

Due to their complementary effects on factors of Alzheimer's, it is hypothesized that Lecanemab and Cromolyn's synergistic effects will be most prevalent in APOE4 carriers. Conversely, in TREM2 R47H mutation carriers, the efficacy of Lecanemab-dependent microglial clearance will be reduced, requiring higher doses of Cromolyn to compensate for the microglia's impaired function.

### Introduction;

More than 7 millions Americans live with Alzheimer's disease, a progressive brain disorder that destroys memory and cognitive processes. On a larger scale, 50 million people have the disease across the world. Every 65 seconds, someone else develops the disease. If we're solely judging by the amount of people infected, Alzheimer's may seem relatively inconsequential: after all, every year there are an estimated 1 billion flu cases, yet the flu is not considered to be too dangerous. The concern with Alzheimer's stems from the fact that there is no cure for it. There is treatment, but it doesn't rid people of (nor does it reverse) the effects of Alzheimer's; treatment only mitigates and slows the symptoms. But what are the specific symptoms? And why does Alzheimer's function the way it does? Why don't we have a cure?

Alzheimer's is characterized by the degeneration of brain cells starting in the hippocampus and the entorhinal cortex (the parts of the brain responsible for memory). Then, the degeneration spreads to other parts of the cerebral cortex, which is responsible for higher-level functions such as language, reasoning, and social skills. The degeneration itself has no clear cause: only a number of contributing factors. The two most credited factors consist of amyloid-beta plaques and neuroinflammation.

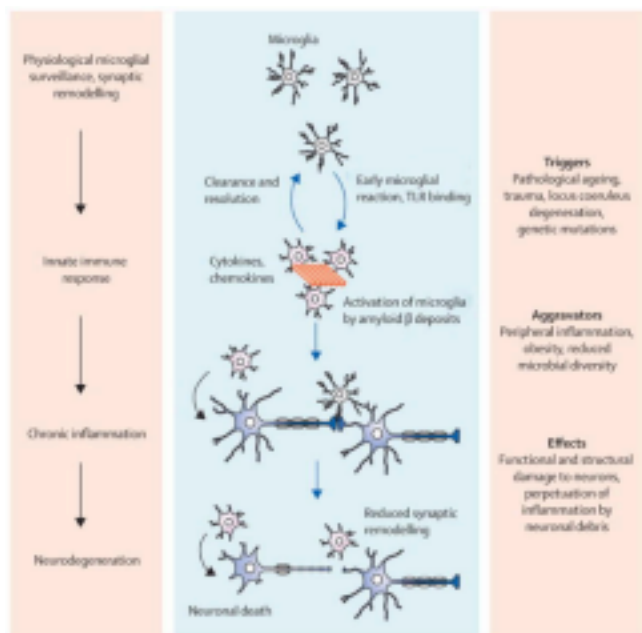
Let's break the factors down, starting with amyloid-beta plaques: abnormal deposits of the amyloid-beta protein, formed between neurons. Amyloid-beta is created through the cleaving of the Amyloid Precursor Protein (APP) by enzymes called secretases. There are two existing processing systems, one with a beneficial effect and the other with a detrimental effect: a non-amyloidogenic pathway consists of  $\alpha$ -secretase and  $\gamma$ -secretase and produces fragments which promote neuroplasticity and reduce neuroinflammation. An amyloidogenic pathway, however, cleaves the APP with the help of  $\beta$ -secretase and  $\gamma$ -secretase, producing the amyloid-beta plaques which are a marker of Alzheimer's. These plaques block neural connections by settling between neurons, rendering that pathway useless and prohibiting information and signaling from passing through. This leads to neuronal dysfunction and eventually neuronal death.

Neuroinflammation is an inflammatory response in the brain and spinal cord with a dual nature: it has the capacity to be either helpful or harmful. For a short duration, acute neuroinflammation promotes injury repair. To understand the cause of neuroinflammation, we first have to understand what a cytokine is. Cytokines are small proteins that balance neuroinflammation and coordinate immune response. Cytokines come in two types: pro-inflammatory and anti-inflammatory. As stated in their name, cytokines have a dual nature, as they can both mitigate neuroinflammation and purport it. Neuroinflammation itself can be both beneficial and detrimental, as the intensity and duration of inflammation is responsible for immune signals becoming supportive or destructive; slight inflammation in the brain is an immune response system that clears cellular debris and promotes cellular repair after injury of infection, but inflammation to a larger degree begins to destroy healthy cells. Chronic neuroinflammation is characterized by an overproduction and dysregulation of cytokines which creates a toxic cycle as it shifts cells such as the brain's immune cells, the microglia, to a destructive, pro-inflammatory state.

The microglia is a glial cell found in the brain and spine. It acts as a macrophage, engulfing and digesting pathogens such as plaques, damaged neurons, and infectious agents. It is essential for cerebral and cognitive homeostasis. Microglia are regulated by and release cytokines. Under healthy conditions, a balance between pro-inflammatory and anti-inflammatory cytokines maintains brain homeostasis. In Alzheimer's, the accumulation of amyloid-beta chronically activates microglia, leading them to secrete excessive pro-inflammatory cytokines such as IL-1 $\beta$ ,

TNF- $\alpha$ , and IL-6. This creates a toxic environment that accelerates neuron loss. Below is a diagram illustrating microglia's process:

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Despite decades of research, scientists still debate which factor is the true origin of this cycle. The long-standing amyloid cascade hypothesis argues that amyloid buildup is the initiating event, setting off inflammation as downstream effects. Yet recent studies have challenged this idea, noting that some patients with heavy amyloid accumulation exhibit minimal cognitive decline, while others with moderate amyloid load show severe symptoms. Alternative models propose that neuroinflammation may precede amyloid accumulation, or that genetic and metabolic factors disrupt immune regulation first, making the brain more susceptible to amyloid toxicity. Most current theories describe Alzheimer's as a system-wide breakdown where there's no single cause. Instead, each factor acts as a feedback loop, feeding the others.

Genetics play a crucial role in determining Alzheimer risk and progression. Two of the most significant genetic factors are the variance in the APOE and TREM2 genes. The APOE (Apolipoprotein E) gene, located on the 19th chromosome, exists in three forms:  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ . The APOE2 gene, present in approximately 8% of people, is associated with positive benefits and a reduced risk of Alzheimer's (Li et. al 2020). The APOE3 gene is classified as the neutral gene, with approximately 78% of the world's population carrying it. About 14% of the world's population has the APOE4 gene, which is associated with a dramatically increased risk of developing Alzheimer's. APOE4 is widely regarded as one of the most influential factors that causes Alzheimer's. But how does APOE4 actually affect the disease and the brain itself? First, APOE4 impairs amyloid-beta clearance. The APOE protein binds to amyloid-beta to encourage its removal. However, the APOE4 variant is less efficient at binding and clearing amyloid-beta compared to APOE3 or APOE2. This means that amyloid-beta accumulates more rapidly in APOE4 carriers, leading to earlier and more plaque formation [16]. Second, APOE4 affects microglial function. APOE4 shifts microglia toward a more pro-inflammatory state, with increased production of inflammatory cytokines and reduced capacity for beneficial functions like debris clearance. Third, APOE4 affects lipid metabolism and neuronal membrane integrity. The APOE protein plays a key role in transporting cholesterol and other lipids to neurons, which need these molecules to maintain healthy cell membranes and synaptic connections. APOE4 is less effective at this function, making neurons more vulnerable to damage [17]. Those who have one allele are two times more likely to develop Alzheimer's than those without, while those with two alleles are twelve times more likely (Li et. al 2020).

The TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) gene encodes a receptor on the surface of microglia that helps them identify and engulf cellular debris and amyloid plaques. Mutations in TREM2 prevent this process, reducing the microglia's ability to clear amyloid-beta. Several variants of TREM2 have been identified that increase Alzheimer's risk. The most well-studied is the R47H variant, which increases Alzheimer's risk about 2-4 times. Other risk variants include R62H and D87N. These mutations impair TREM2 function, reducing its ability to bind to molecules it recognizes and activate signaling pathways. This allows plaques to accumulate and continue activating inflammatory signaling, worsening neuronal damage. In the experiment of Kotredes et al. (2021), they combined humanized APOE4 with the TREM2 R47H mutation in a mouse model, allowing researchers to study how these two genetic risk factors interact. TREM2 R47H mutation reduced microglial clustering around amyloid plaques, decreased phagocytic uptake of amyloid, and altered microglial gene expression patterns. Importantly, the combination of APOE4 and TREM2 R47H produced more severe pathology than either variant alone, suggesting that their effects worked in synergy.

Currently, there are many contended treatments that slow the progression of Alzheimer's. For the sake of this experiment, the two important ones are Lecanemab and Cromolyn.

Lecanemab is a monoclonal antibody that binds to soluble amyloid-beta protofibrils (the precursors to plaques). Unlike earlier treatments that primarily targeted mature plaques, Lecanemab's focus on protofibrils aims to prevent plaque formation before it occurs. By attaching to these protofibrils, Lecanemab marks them for destruction by microglia, promoting amyloid clearance and preventing further plaque growth. The

CLARITY-AD trial, published in 2023, proved the efficacy of Lecanemab. The trial had almost two thousand patients with early

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Alzheimer's disease and the confirmed presence of accumulated amyloid-beta. Participants received either Lecanemab (10 mg/kg every two weeks) or a placebo for 18 months. The primary endpoint was change in the Clinical Dementia Rating-Sum of Boxes (CDR-SB), a comprehensive measure of cognitive and functional abilities. Results showed that Lecanemab reduced cognitive and functional decline by 27% compared to those who didn't take the treatment. Willis et al. (2023) developed an exposure-response model to describe how Lecanemab affects brain amyloid

levels. Their model linked serum Lecanemab concentrations to the rate of amyloid clearance from the brain, quantifying the elimination rate constant (Kout) and the concentration-dependent effect of Lecanemab on amyloid removal. This model provides a mathematical framework for predicting how different dosing regimens would affect amyloid levels over time. However, despite its benefits, the treatment does not reverse neuronal death, and in high concentrations, Lecanemab may lead to an increased risk of severe side effects such as amyloid-related imaging abnormalities (ARIA), which comes in two forms: ARIA-E (brain swelling) and ARIA-H (hemorrhage). In the CLARITY-AD trial, 12.6% of Lecanemab-treated patients developed ARIA-E and 17.3% developed ARIA-H, compared to 1.7% and 9.0% respectively in the placebo group. Most cases were asymptomatic, but about 2.8% of treated patients experienced symptoms including headaches, confusion, visual disturbances, and in rare cases, seizures. APOE4 carriers appear to be at higher risk for ARIA, with APOE4 homozygotes (two copies) showing particularly elevated risk. How Lecanemab causes ARIA is not fully understood, but it likely stems from the speed at which amyloid is removed from blood vessel walls and how this affects the strength and integrity of the vessels. Van Olst et al. (2025) investigated the microglial mechanisms involved in antibody-mediated amyloid clearance, finding that anti-amyloid immunization activates microglia to attack antibody-bound amyloid, but this process can trigger inflammatory responses that may contribute to vascular damage. This finding suggests that combining anti-amyloid therapy with anti-inflammatory agents might reduce ARIA risk.

Cromolyn, on the other hand, addresses the inflammatory aspect of the disease by targeting microglial hyperactivation and excessive cytokine production. Cromolyn sodium (also known as cromoglicic acid) was originally used for treating asthma and allergies, but researchers have discovered that it also balances immune cell function in the brain. By maintaining microglia in a more balanced activation state, Cromolyn may preserve the beneficial functions of microglia (such as amyloid clearance and debris removal) while reducing their excessive inflammatory responses. Preclinical studies in mouse models of Alzheimer's disease have shown that Cromolyn treatment reduces microglial activation markers, decreases pro-inflammatory cytokine levels, improves synaptic density, and in some studies, reduces cognitive deficits [13]. However, it's important to keep in mind that clinical evidence for Cromolyn in Alzheimer's disease is limited. Large-scale clinical trials in humans have not yet been completed.

The reasoning for combining Cromolyn and Lecanemab stems from the fact that these drugs address complementary aspects of Alzheimer's. Lecanemab removes the amyloid which triggers microglia, and Cromolyn targets neuroinflammation (and while it can be caused by amyloid, it can also overact under conditions.) More importantly, the success of either treatment may depend heavily on a patient's genetic background. For example, a therapy that relies on microglial activity (like Lecanemab) may perform poorly in individuals with TREM2 mutations, where microglial phagocytosis is impaired. Likewise, anti-inflammatory therapies may yield limited benefits in APOE4 carriers, whose microglia are chronically overactive. The interplay between these genetic factors and treatment responses represents a major knowledge gap in current Alzheimer's research.

#### **Computational Models in Alzheimer's Research;**

In order to conduct research in the field of neuroscience, scientists would usually need access to a biological lab, or to a brain. However, with recent developments in computational ability, researchers can simulate biological processes that would be impossible or unethical to study directly in humans, and to quickly test hypotheses that would usually require trial over years to see the results of. Three main types of approaches have been developed to study Alzheimer's disease: agent-based models, ordinary differential equations models, and hybrid multiscale frameworks. Agent-based models (ABMs) simulate individual cells as independent and autonomous "agents" that follow programmed rules and interact with each other and their environment. This approach has been used to focus on specific factors of Alzheimer's before. For example, in the experiment of Weathered et al. (2023), an agent-based model was utilized to explore microglial roles in the disease, focusing on how microglia interacts with amyloid-beta plaques. They focused on specific behaviors including chemotaxis (movement toward chemical signals), phagocytosis (engulfing and digesting cellular debris), and barrier formation around plaques. By systematically enabling and disabling these and additional functions, the researchers found that loss of phagocytosis produced the largest increase in plaque size, and that delayed microglial arrival at plaque sites correlated with larger plaques [1]. This finding supports the hypothesis that impaired microglial clearance function is a critical driver of amyloid accumulation. Ty et al. (2025) created another agent-based model focusing on microglia-neuron interactions during neurodegeneration. This model incorporated multiple microglial states of passive surveillance and active inflammation and simulated how they affect neuronal survival. The model demonstrated that the balance between pro-inflammatory and anti-inflammatory microglial states determines whether microglia provide neuroprotection or contribute to neurotoxicity [2]. This work provides computational support for the dual nature of neuroinflammation described in clinical observations, where microglia can either help clear pathology or accelerate neuronal damage depending on their activation state. Ordinary Differential Equation (ODE) models represent populations or concentrations of molecules and cells as continuous variables that change over time according to preset mathematical equations. These models are often chosen for their ability to simulate network and system dynamics and can be altered to represent different genetic backgrounds or disease stages. Duchesne et al. (2024) developed a comprehensive 19-equation ODE model that spans from molecular processes (amyloid-beta monomer aggregation) to cellular processes (microglial activation, neuronal death). Importantly, their model incorporated the APOE genotype as a parameter that affects multiple processes simultaneously, such as amyloid clearance rates, microglial reactivity, and inflammatory signaling. When they simulated disease progression in virtual patients with different APOE variants, the model predicted that APOE4 carriers would experience earlier neuronal loss and earlier transitions to pro-inflammatory microglial states compared to those with APOE3 [3]. This prediction aligns with clinical observations that

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APOE4 carriers develop symptoms earlier and progress faster than non-carriers. Hybrid multiscale models combine elements of both agent-based and equation-based approaches, often using random elements to simulate biological variability. Abi Nader et al. (2022) developed SimulAD, a multiscale model that combines biomarker dynamics (how amyloid spreads through brain regions) with clinical outcomes (cognitive test scores). Using real patient data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), they calibrated their model to predict how interventions at different disease stages would affect long-term outcomes. Their results suggested that anti-amyloid treatments should be introduced much, much earlier than expected to have a much more tangible effect. These computational modeling approaches demonstrate that Alzheimer's disease progression emerges from complex interactions across multiple biological scales, and that genetic variants like APOE4 and TREM2 mutations alter the very dynamics of how the amyloid-plaques, microglia, neuroinflammation, and neurodegeneration interact with each other.

### **Machine Learning as a Calibration Method;**

While the previously mentioned models (like ABMs and ODE models) simulate the biological processes underlying Alzheimer's disease, machine learning is solely driven off of data, learning patterns from clinical data to predict disease progression without simulating or understanding the underlying mechanisms. As large datasets of patient data (including but not limited to brain imaging, cognitive assessments, genetic information, and biomarker measurement) become available, the accuracy and power of machine learning has developed as well. Machine learning models for Alzheimer's progression use baseline measurements (initial brain scans, cognitive test scores, etc.) as inputs to predict the future of the disease. There are many algorithms that can be utilized for different purposes, including deep neural networks, and specialized time-series models like recurrent neural networks. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has been the primary data source for many of these studies, providing standardized data from thousands of participants at various disease stages [6]. Deep learning using convolutional neural networks has been particularly successful at getting predictive features directly from brain imaging data. These models identify subtle patterns in MRI or PET scans that point to future cognitive decline, sometimes detecting changes before they are apparent to human radiologists.

### **Objective;**

This project aims to determine the optimal combination and dosage levels of Lecanemab and Cromolyn across different genetic backgrounds (Normal/APOE3, APOE4, and TREM2 mutation) to maximize neuronal survival. To achieve this goal, the experiment uses a computational modeling approach that combines machine learning and agent-based simulation. This experiment would be impossible to implement in a traditional biological laboratory under such conditions due to ethical constraints, time limitations, and the inherent difficulty of controlling multiple variables simultaneously in living systems.

### **Methods;**

This experimental approach consists of five steps:

**1. Machine Learning Model Development:** A deep learning model using a recurrent neural network will be built using open-access Alzheimer's datasets from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Its function will be to learn patterns of disease progression from patient data, mapping how cognitive function, amyloid burden, and inflammatory markers evolve across time and genetic backgrounds. This model will map how cognitive function, brain imaging markers, and biomarker levels typically change over time in patients with different genetic backgrounds. The trained model provides reference trajectories for amyloid accumulation and neuronal loss used to calibrate the subsequent ABM.

**2. Agent-Based Model Construction:** The agent-based model approach is chosen for this experiment because The agent-based model approach is chosen because it captures cell-level interactions (such as microglial activation and neuron death) that cannot be represented in purely mathematical ODE models, allowing dynamic simulation of localized feedback loops between amyloid and inflammation. It will simulate the biological interactions between neurons (which can transition between healthy, stressed, and dead states based on local toxicity and inflammation), microglia (which exist in three states: resting, pro-inflammatory, and anti-inflammatory), and amyloid beta plaques (which will specifically be measured in concentration and spatial distribution and orientation). Each agent will follow biologically validated rules derived from published parameters.

Neurons: Neurons will have the ability to exist in two states, those being healthy or dead. Death probability increases nonlinearly with local amyloid concentration and pro-inflammatory cytokine levels, following the sigmoidal toxicity relationship defined in Duchesne et al. (2024). Amyloid-Beta: Amyloid aggregation rate and clearance rate depend on APOE genotype. This will be simulated not as its own agent, but as a blockage of the connection between neurons. With APOE4, clearance rate is reduced by 40% (Castellano et al., 2011). Microglia: The microglia can exist in three states, those being Resting (M0), Anti-inflammatory (M2), Pro-inflammatory (M1). Transition probabilities are adapted from Weathered et al. (2023), where chronic amyloid exposure increased M1 transition rate by 60%. Microglial phagocytosis efficiency is reduced by 60–70% in the TREM2 R47H condition, consistent with findings of Kotredes et al. (2021). Drug effects are modeled as changes to these rules:

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Lecanemab increases amyloid clearance rate by a dose-dependent multiplier (80% at 10 mg/kg) and raises local inflammation risk to reflect ARIA side effects. The model includes a 5–10% increase in cytokine release (van Olst et al., 2025).

Cromolyn decreases cytokine release by up to 50% and reduces microglial transition to the M1 state.

All simulations will run in Mesa, a Python-backed framework tuned towards ABMS, and will run 1,000 simulated time steps representing approximately 10 years of disease progression.

### **3. Model Calibration**

To tune the ABM properly, the model's results must fit the results of the deep learning model. Three quantitative data points will be used: amyloid accumulation, microglial activation timelines, and neuronal survival rates. The values will be compared between the deep learning model and the ABM. Additionally, a loss function (mean squared error between simulated and predicted trajectories) will determine adjustment until an accuracy of 80% or above has been achieved.

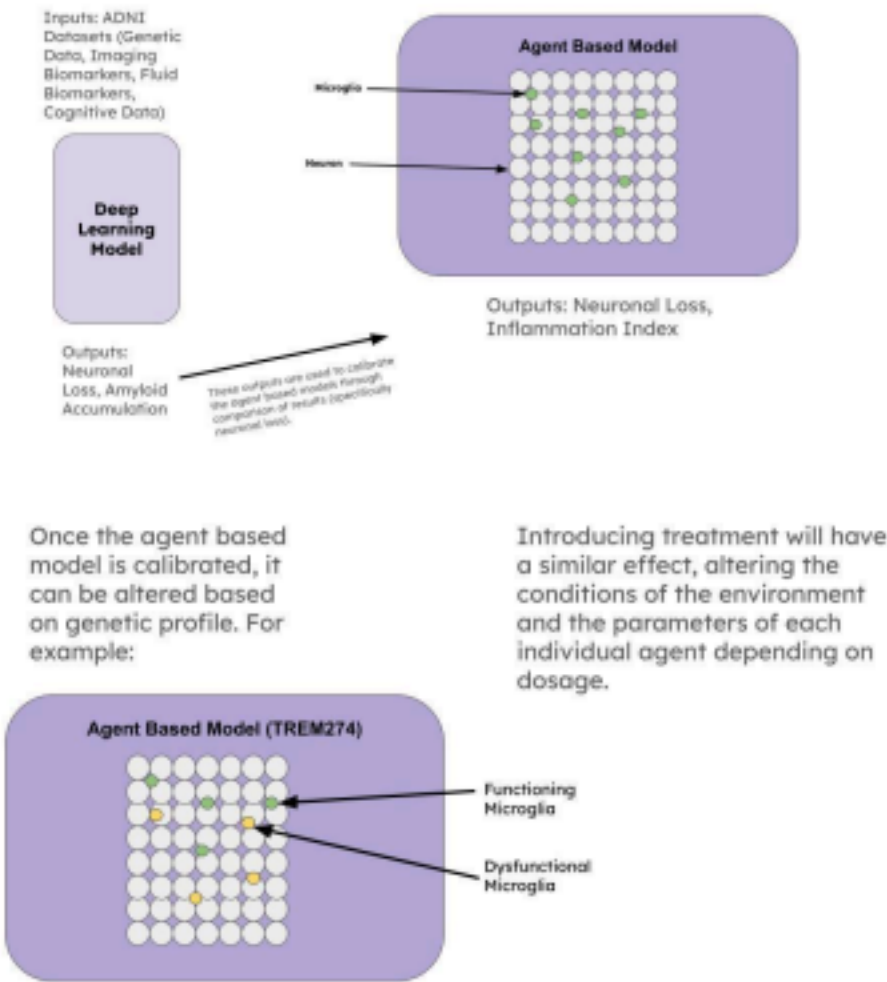
### **4. Treatment Simulation**

For each genetic background (APOE3, APOE4, TREM2 R47H), the model will simulate disease progression under 25 unique Lecanemab–Cromolyn

dose combinations:

- Lecanemab: 0, 2.5, 5.0, 7.5, 10.0 mg/kg
  - Cromolyn: 0, 25, 50, 75, 100 mg/kg
- Each simulation will be repeated 30 times to account for variability in agent-based behavior. The output will specifically focus on:
- Final neuron survival (%)
  - Resultant inflammation level (Arbitrary Units, AU)

Here's a diagram for the first four steps:



5. Optimization and Deep-Learning Surrogate Model

A deep learning surrogate model/feedforward network will learn to predict the ABM's output metrics, reducing the need for full simulation runs. The optimizer will use the surrogate to rapidly screen thousands of potential dose pairs and identify the combination yielding maximal neuron survival and minimal inflammation.

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An important note regarding this third model: This may be scrapped depending on the ability of the computer to run the agent-based model and record the results for many iterations.

Variables;

Variable	Role	Type Description	Values
Genetic Background	Independent	Categorical The specific genetic profile being simulated to test differential treatment response.	1. APOE3 (Baseline/Control), 2. APOE4, 3. TREM2 R47H, 4. APOE4 + TREM2 R47H

Lecanemab Dosage	Independent	Discrete The simulated concentration of Lecanemab administered in the model.	0, 2.5, 5.0, 7.5, 10.0 mg/kg
Cromolyn Dosage	Independent	Discrete The simulated concentration of Cromolyn administered in the model.	0, 10, 20, 30, 40 mg/kg
Neuronal Survival	Dependent (Primary Outcome)	Continuous The percentage (%) of neuron agents that remain in the 'healthy' state at the end of the simulation.	N/A
Neuroinflammation Level	Dependent (Secondary Outcome)	Continuous A measure of the overall inflammatory state in the simulation, derived from M1 microglial population. Measured in Arbitrary Units (AU).	N/A
Microglial State	Mediating Agent State	Categorical The functional state of microglial agents, which determines their behavior (phagocytosis vs. cytokine release).	Resting (M0), Pro-inflammatory (M1), Anti-inflammatory (M2)
Neuronal State	Mediating Agent State	Categorical The status of individual neuron agents. Death probability is influenced by local amyloid and cytokine levels.	Healthy, Dead
Amyloid-Beta (A $\beta$ )	Mediating Environmental Factor	Continuous Modeled as a concentration/blockage.	N/A
Microglial Phagocytosis	Mediating Agent Behavior	Continuous (Efficiency) The ability of microglia to clear A $\beta$ .	N/A
Cytokine Release	Mediating Agent Behavior	Continuous (Rate) The rate of pro-inflammatory cytokine release from M1 microglia.	N/A
Simulation Time	Controlled Parameter	Discrete The duration over which the simulation runs.	1,000 time steps (representing ~10 years)

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### Safety and Ethical Statement;

This project poses no ethical risks to human or animal subjects, as all experiments are computational. The models rely exclusively on de-identified public datasets (e.g., ADNI), with full compliance with data privacy standards. All work occurs digitally.

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