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An Agent-Based Model of Microglia and Neuron Interaction: Implications in Neurodegenerative Disease

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ABSTRACT

Whether immune cells protect or harm the brain is an open question depending on context, and their role is implicated in multiple diseases such as Alzheimer's disease, dementia, and other neurological disorders. Microglia, a specific type of immune cell in the central nervous system, play a key role in homeostasis, and genes associated with an elevated risk of Alzheimer's disease correspond with deficiencies in their behavior. We created an agent-based model that incorporates inflammatory signaling, chemotaxis, and phagocytosis of damaged neurons and allows the exploration of crucial pathways in the maintenance of brain health. We specifically investigated pathways related to Alzheimer's risk variants of the gene *TREM2*, which results in impaired microglia phagocytosis and sensing.

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Alzheimer's disease, microglia, neuron, agent-based model

1 Introduction

Whether immune cells protect or harm the brain is an open question depending on context, and their role is implicated in multiple diseases such as Alzheimer's disease (AD), dementia, and other neurological disorders. AD is the most common type of dementia currently afflicting 24 million people worldwide, a number expected to double over the next 20 years [41]. Several key findings have been made in the last few years connecting microglia (a type of immune cell) dysfunction to the progression of AD [40, 45, 10], and yet few mathematical models of this system exist. We present and analyze an agent-based model (ABM) to simulate a complex system including neurons, immune cells, and signals to understand how deficiencies in microglia function relate to the clearance of damaged neurons, which relates to the progression of AD.

Microglia are the resident immune cells of the central nervous system (CNS) that survey their environment via the abundant receptors on their surfaces. Upon sensing danger, they mount a specialized response [34], destroying pathogens and signaling other immune cells via cytokines, a class of signaling proteins [22]. In addition to serving as immune sentinels, they phagocytose (eat) cellular debris [47]. They are dynamic custodians and are highly plastic when responding to environmental cues that alter their function [5].

Recently, it has been demonstrated that a rare but potent genetic mutation that alters a protein (TREM2) on microglia triples an individual's risk of developing AD [48]. The mutation causes microglia to exhibit reduced debris clearance and less responsiveness to signals– for example, microglia with this mutation are less likely to move towards a damaged neuron. Therefore, understanding the role of impaired response and phagocytosis is necessary to elucidate the pathology of AD.

Agent-based modeling (ABM) is a useful modeling paradigm to explore a system that involves spatial heterogeneity and stochasticity (randomness). ABMs simulate the actions and interactions of agents which follow specific rules. What is especially relevant is that mechanistic rules understood at the level of the cell can be implemented, and one can observe behavior of the system as a whole [2], thus linking spatial scales. Chance plays an important role in biological systems, particularly at the level of the cell [8], and this can be directly implemented into the model. Stochasticity manifests in the model as some decision-making rules can be based on chance, such as random walk movement of cells. ABMs have been successfully applied to systems

as diverse as bird foraging behavior [30], development of cancer [60] and the transmission of COVID-19 [14]. Moreover, ABMs have been shown to yield patterns not seen in deterministic systems (e.g., emergent behavior) [17, 18]. This suggests that they have the potential to yield a different or complementarypicture of microglia function in the context of neurodegeneration, particularly when coupled with a deterministic model. Given the mechanistic understanding of specific behaviors microglia exhibit when responding to their environment and to neurons, and because we wish to include a spatial component and elements of randomness to represent imperfect signal-receptor binding, an ABM is an appropriate paradigm to explore the system.

2 Biological Background

Microglia switch to an activated phenotype in the presence of damaged neurons and promote an inflammatory response which further engages the immune system [19]. For example, in AD, microglia release pro-inflammatory mediators such as tumor necrosis factor α (TNFα) and interleukin 1β (IL-1β) [1]. This response is often due to the presence of amyloid-β plaques [11], the accumulation of which is a sign of developing AD. Systemic inflammation is often accompanied by a fever [7], and in the case of AD, there is some evidence that core body temperature increases due to neuroinflammation in the brain [35]. Microglia exhibit temperature-dependent movement [44] due to thermosensitive signaling channels and might have an important role during brain injury, infection, or disease [50].

Phagocytosis is the process by which certain cells recognize, engulf, and digest biological matter. Microglia commonly phagocytose damaged or stressed neurons [59] as well as amyloid-β protein (present in AD) and aging microglia [56] and those with genetic mutations (e.g., *APOE* and *TREM2*) [21] exhibit impaired phagocytosis and sensing which is linked with the development of AD.

A synapse is the small gap at the end of a neuron that allows a signal to pass from one neuron to the next. Microglia regularly perform synaptic pruning [47], since pruning synapses not in regular use allows the brain to function well. This process is most active during the earliest years of development, but remains in effect for life, and might relate to cognitive impairment seen in pathologies like AD. Thus, in addition to the death of neurons, inappropriate pruning which impairs connectivity between neurons could also contribute to cognitive impairment [15].

Chemotaxis refers to the movement of cells in response to a concentration gradient. For microglia, one such gradient is seen with cytokines, a class of signaling proteins. An example of a cytokine important in microglial function is fractalkine (CXCL1), which can be secreted by damaged neurons [6]. Cytokines like fractalkine guide microglia towards damaged neurons in order to find and phagocytose them. In particular, fractalkine is closely linked to microglial phagocytosis and chemotaxis, but its role in the context of AD is complex [38, 58]. If the ability for microglia to sense cytokines is impaired, they will miss crucial environmental signals and not perform necessary processes. This can be seen when the microglial receptor for fractalkine is absent or malformed, causing greater neuronal death and damage due to microglia not being able to phagocytose existing damage [58]. Since cytokines are important environmental signals that inform microglia how to best protect the brain, impaired cytokine detection may lead to greater damage and the progression of neurodegenerative diseases, like AD. Additionally, there is some evidence that the movement speed of microglia can change depending on the temperature of their current environment, with higher temperatures indicating faster movement [44]. Since disease-associated microglia can release higher levels of pro-inflammatory cytokines which can induce fever [52], we aim to see if this change in speed affects the rate at which microglia perform their functions.

In knockout experiments of the *TREM2* gene in human brains, microglia showed impaired phagocytosis and inhibited chemotaxis [42]. This is significant because AD is linked with deficiencies in expression of the TREM2 gene [37]. Understanding how microglia phagocytosis and sensing relates to the clearance of damaged neurons is a goal of our model.

Our ABM seeks to address questions related to the ability of microglia to maintain the health of the CNS and to understand how their impairment can lead to the progression of AD. Specifically, we interrogate how deficiencies in microglia sensing and phagocytosis relate to the clearance of damaged neurons, as well as how microglia movement as a function of temperature impacts clearance rate.

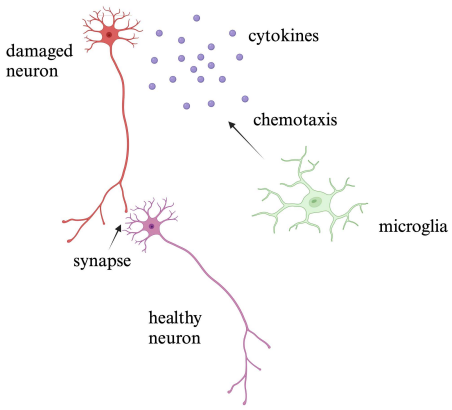

Figure 1: Schematic depicting potential interaction between microglia and neurons. Damaged neurons secrete cytokines, which diffuse through the extracellular space and are sensed by microglia. In response microglia perform chemotaxis and move towards the damaged neurons. Upon encountering a damaged neuron, they perform phagocytosis and cleanly remove it from the system. Figure created with BioRender.

3 Model Description

The following subsections constitute the steps of the Overview, Design concepts, Details (ODD) protocol used in ABM descriptions [20, 62]. This format is helpful in making a model understandable and reproducible.

3.1 Purpose

This model aims to investigate the dynamic interplay between microglia and both healthy and damaged neurons. Our simulation encompasses diverse aspects of microglia behavior, including their movement, surveillance activities, and their ability to phagocytose damaged neurons. The overarching goal of this model is to gain insights into the impact of microglia sensing and responding in the hippocampus, an area of the brain where memories are stored, and very related to the progression of AD. To accomplish this goal, this model is used to investigate how varying microglia sensing capabilities, movement, and clearance ability impacts the clearance rate of damaged neurons, taken as a proxy for the pathology of AD. Damaged neurons are an appropriate proxy for the pathology of AD [43, 12], and measurements of the destruction of circuits, regional brain volume loss, and damage to axons, dendrites and synpases in postmortem brains are used along with the presence of amyloid or tau proteins to classify the disease. Recent advances, such as the ability to measure protein fragments (e.g., neurogranin), representative of damaged neurons and synapses, in cerebral spinal fluid provide a specific biomarker for neurodegeneration in AD [61].

3.2 Entities, state variables, and scales

This ABM contains two main types of agents: agents representing microglia, and agents representing neurons. Neuron agents are further specified as either being healthy or damaged, and two nearby neurons of either type can form a synapse link, indicating the neurons can be in communication. The model's environment consists of a 33×33 grid of patches, with each patch representing an area of approximately $18\times18\,\mu m$ in the adult human hippocampus. This number was approximated using Balena's et al. [4] average size of a neuron, which was estimated to be $18.71\pm0.26\,\mu m$. The environment's edges wrap, so agents moving across one edge will reappear on the opposite edge of the environment. Thus, the environment's topology is a torus. Each tick (a time unit) within the model represents a time step of approximately 10 hours. This estimate takes into account how it takes five ticks for a simulated microglia to phagocytose a neuron in our model, and how the average measured phagocytosis time was 46.06 ± 7.86 hours [4]. The estimates for environment size and time scale coincide with the findings of Nimmerjahn et al., where a microglia in a typical temperature moved at approximately 1–2 µm per hour [44].

Default values for each variable used in experiments are shown in Table 1. Microglia are characterized with the following state variables: *eat-probability*, *sensing-efficiency*, and *wait-ticks*. Both variables

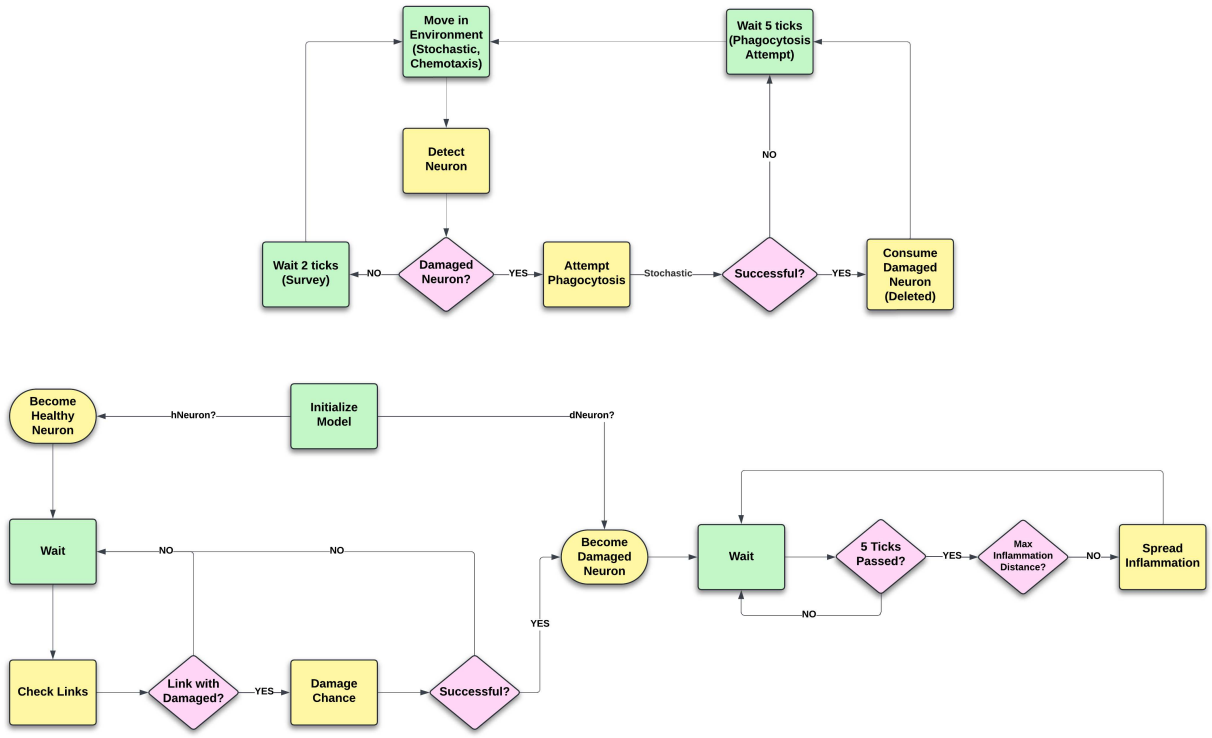

Figure 2: Flowchart depicting the procedure and decisions made by microglia agents (top) and neuron agents (bottom) in the ABM. Microglia move in the environment by following a concentration gradient of chemokines when they are sensed, and moving randomly in their absence. When a microglia detects a neuron, it ascertains whether it is damaged, and if so, attempts phagocytosis, whose success is probabilistic. Healthy and damaged neurons are initialized, and if a healthy neuron is linked with a damaged neuron, it has a chance of becoming damaged. Damaged neurons secrete cytokines which diffuse through the space.

Table 1: Default values used for parameters in the model that can be varied by the user. Each variable is followed by its corresponding name in the model. Distances are measured in units of patches.

Default Values for Parameters		
Initial Populations		
Microglia	*init-microglia*	5
Healthy Neurons	*init-hNeuron*	10
Damaged Neurons	*init-dNeuron*	15
Microglia Variables		
Eat Probability	*eat-probability*	70%
Sensing Efficiency	*sensing-efficiency*	50%
Neuron Variables		
Damage Chance	*damage-chance*	0.5%
Neuron Distance	*neuron-distance*	5
Patch Variables		
Inflammation Radius	*inflam-radius*	3
Global Variables		
Temperature	*temperature*	37° C

eat-probability and *sensing-efficiency* are global variables and have a constant value throughout any given simulation. The variable *eat-probability* is a user-designated numeric value that represents the probability that an individual microglia agent will successfully phagocytose an encountered damaged neuron. The variable *sensing-efficiency* is another user-designated numeric value representing the percentage chance that an individual microglia will move in the direction of a surrounding patch with the highest value of *inflam-val*. The variable *wait-ticks* changes per individual microglia depending on the subroutines it has performed, designating the number of ticks a microglia will wait during those subroutines. Microglia are also influenced by the global variable *temperature*. The value of *temperature* reflects a value of temperature of the hippocampus in degrees Celsius. This variable influences the distance a microglia agent can move per tick, with faster movement occurring at higher *temperature* values.

Patches in the environment are characterized by the variable *inflam-val*, which keeps track of the amount of inflammation that is present on an individual patch. For the purposes of our model, the amount of inflammation present is correlated to the amount of pro-inflammatory cytokines secreted by damaged neurons. There are also four additional variables that help facilitate the spread of inflammation: *curr-spread*, *inflam-radius*, *dismantling*, and *residence*. The *residence* variable indicates whether a damaged neuron currently resides on the patch. The *curr-spread* variable determines the radius to which a patch spreads inflammation to surrounding patches. The maximum radius that any given patch can spread inflammation to is determined by the global variable *inflam-radius*. The *dismantling* variable indicates that the patch no longer has a damaged neuron, triggering the dismantling of inflammation. The sole purpose of these variables is to facilitate the dismantling of inflammation within the model.

Both healthy and damaged neurons are represented by stationary agents. Damaged neurons affect the environment by setting the *residence* variable of the patch they inhabit to true. This indicates to the patch to start spreading inflammation, mimicking the effect that cytokines emitted by neurons have on surrounding cells and tissue. Neuron agents of either type can share an undirected link representing a synapse, mirroring the biology of neurons. The maximum distance between two neurons that can be linked is dictated by the global variable *neuron-distance*. Healthy neurons that share a synapse link with a damaged neuron can become a damaged neuron themselves, and the process by which this occurs is affected by the global variable *damage-chance*.

3.3 Process overview and scheduling

This model proceeds in time steps called ticks, where each tick represents 10 hours. Microglia move semi-randomly throughout the simulation and will perform different procedures depending on what they encounter in the environment. If adjacent patches have differing levels of inflammation, microglia have a chance to move towards patches with a greater concentration, employing chemotaxis. When moving to a patch that contains a healthy neuron, microglia will survey the neuron to check and maintain its health. During this procedure, the microglia agent will be stationary until surveying is completed. When moving to a patch that contains a damaged neuron, microglia will attempt to phagocytose the neuron (i.e., phagocytosis will be successful with some probability). If successful, the damaged neuron is deleted from the simulation, and the patch it was on will start to dismantle inflammation. If the microglia fails to phagocytose the neuron, the neuron will not be deleted. Regardless of the outcome, the microglia will be stationary before resuming typical behavior, which represents the amount of time this process takes.

3.4 Design concepts

3.4.1 Sensing

Microglia agents are able to identify differing concentrations of pro-inflammatory cytokines and will tend to move towards greater concentrations of these cytokines with some probability. The range in which microglia are able to distinguish cytokine levels is highly restricted, and only encompasses the patches it is adjacent with as well as the patch it is currently on. This is because cytokines must form a bond with its associated receptor on a cell, and therefore only direct contact with cytokines lead to microglia sensing them [36].

3.4.2 Interaction

Microglia agents interact with both damaged and healthy neurons upon entering the patch on which the neuron resides. Damaged neurons can interact with nearby healthy neurons by giving them the chance to

become damaged [53]. There is some evidence that inflammation can spread from one neuron to another via crosstalk involving ATP [25], and our model simplifies this process and allows neurons with a synaptic link to share inflammation with some probability.

3.4.3 Stochasticity

The initialization of the model results in both neuron and microglia agents being arbitrarily placed throughout the model environment, introducing variation in the state of the model upon each initialization. The microglia agents are the only motile agents in our model, and move randomly when cytokines are absent. If an individual microglia encounters a patch where cytokines are present, the microglia has a chance to move up the cytokine concentration gradient in accordance with the user-designated probability determined by the agent variable *sensing-efficiency*. This represents the imperfect binding between cytokines and their corresponding receptors and the subsequent signal transduction, which can differ especially in the case of aged or disease-associated microglia [52]. Microglia agents that encounter damaged neurons attempt phagocytosis, and the chance that this succeeds depends on a fixed, global probability. This further allows for the exploration of disease-associated microglia, as these forms of microglia often have impaired phagycytosis capabilities [52].

3.4.4 Collectives

Microglia do not belong to any aggregation, and interact with their environment on an individual level. Neurons can belong to either the healthy or damaged collective. A healthy neuron that shares a synapse link with a damaged neuron can switch and become part of the damaged collective. This behavior captures the crosstalk involving ATP that allows inflammation to spread among neurons [25]. The number of neurons belonging to either category can be set upon initialization of the model.

3.4.5 Observation

The total runtime of the model is collected once all damaged neurons within the model have been phagocytosed. The values used for certain parameters, such as *sensing-efficiency* or *eat-probability*, are also recorded. This allows for the aggregation of multiple runs with differing values for parameters, revealing patterns that may emerge as parameters are varied.

3.5 Initialization

During the model's initialization, microglia and neuron agents are randomly placed onto patches in the environment. Only one agent can occupy any given patch upon initialization. The initial number of microglia, healthy neurons, and damaged neurons are decided by the global variables *init-microglia*, *init-hNeuron*, and *init-dNeuron*, respectively. After all agents have been created, synapse links between nearby neurons are initialized. Patches on which damaged neurons reside start with 1 *inflam-val*, and will be set as *residence* patches that diffuse inflammation values throughout a given trial.

3.6 Input data

The environment that is modeled is constant, with changes occurring only due to agent behavior. Therefore, there is no input data to be read for this model.

3.7 Submodels

Microglial chemotaxis. Microglia are the only motile agents in our model, and their ability to move using chemotaxis reflects their behavior in the in vivo hippocampal environment. For every tick in the model, microglia agents either undergo undirected movement or actively move towards higher concentrations of cytokines, represented by varying levels of *inflam-val* within patches. The probability that a microglia decides to move towards higher concentrations of cytokines is determined by the global variable *sensing-efficiency*. Additionally, microglia will always choose to perform undirected movement if the current and all adjacent patches have equal values for *inflam-val*.

For undirected movement, a microglia agent will first rotate left or right by a random amount, up to 25°. They will then advance a certain distance, which can be affected by the temperature within the hippocampal environment. At a neutral temperature of 37° C, microglia will move a distance of one patch. Using results from a study conducted by Nishimoto et al. [44], we found that the approximate change in speed was around ±5% patches per degree above or below 37° C, respectively. Therefore, the distance in patches that a microglia agent can move is determined by the following equation:

$$distance = 1 + 0.05 * (temperature - 37).$$

If a microglia agent successfully senses a higher concentration of cytokines in any of the eight patches it is adjacent to, it will move to the adjacent patch that has the highest value for *inflam-val*. If there are multiple patches with the same highest value, the patch to move to is selected from these at random. The microglia agent will be relocated to the center of the patch, and facing in the direction of its movement to the patch.

Surveillance and phagocytosis. If a microglia agent moves to a patch that contains a neuron, it will perform one of two actions depending on the specific type of neuron. If the neuron is healthy, the microglia agent will spend two ticks "waiting" on the current patch to simulate the time it takes for an in vivo microglia to survey the health of neurons. This rule captures behavior of microglia in the CNS [13]. While in a waiting state, microglia cannot perform any other subroutines.

If the neuron is damaged, the microglia will attempt to phagocytose the neuron. The chance for successful phagocytosis is dictated by the *eat-probability* global variable. If the microglia is successful, the damaged neuron agent is deleted, simulating phagocytosis. The microglia will then wait 5 ticks, simulating the amount of time it takes to phagocytose the neuron. If the microglia is not successful, the damaged neuron is unaffected. The microglia will still wait 5 ticks in this case, since that is the time taken per phagocytosis attempt. So, no matter the outcome of a phagocytosis attempt, a microglia will wait 5 ticks to simulate the time taken for the attempt.

The time a microglia waits for both surveillance and phagocytosis are mediated by the *wait-ticks* variable, stored within each microglia agent. These subroutines add values to *wait-ticks*, and microglia can only proceed with other subroutines if their value for *wait-ticks* is zero.

Neuronal damage. Upon initializing the model, neurons check to see if there are any nearby neurons within a radius set by the global variable *neuron-distance*. If so, the neuron creates a synaptic link with up to one other nearby neuron through the creation of a synapse object.

There is no special interaction between two healthy or two damaged neurons that are linked by a synapse. However, a healthy neuron sharing a link with a damaged neuron can cause damage to spread to the healthy neuron. Every tick, the chance that a healthy neuron becomes damaged due to sharing a synapse with a damaged neuron is governed by the global variable *damage-chance*. If a healthy neuron becomes damaged in this way, it will turn into a damaged neuron agent, and the patch it is on will become a *residence* patch. Following this, the newly-damaged neuron will behave identically to neurons that were damaged upon initialization of the model. Because the only variable affecting neurons becoming damaged is *damage-chance*, there is no set time in which a healthy neuron becomes damaged through this subroutine.

Inflammation diffusion and decay. Inflammation is spread as the model progresses, and originates from *residence* patches. These patches have a variable called *curr-spread*, which tracks the distance in patches inflammation has spread. The maximum value for *curr-spread* is stored in the global variable *inflam-radius*. If a *residence* patch's value for *curr-spread* is equal to *inflam-radius*, it will no longer diffuse inflammation. This simulates the diffusion of proinflammatory cytokines by damaged neurons, as well as the cytokine gradient they generate.

Every 5 ticks, all *residence* patches with a value for *curr-spread* less than *inflam-radius* will diffuse inflammation. This is done by adding 1 *inflam-val* to all patches within *curr-spread* radius, including the *residence* patch itself. After this is done, the *residence* patch's *curr-spread* value is incremented by 1. This subroutine results in the surrounding patches around the *residence* patch having differing inflammation values, where the patches closest to the *residence* patch have higher values for *inflam-val*. The result of this subroutine is illustrated in Figure 3.

Patches that are near several damaged neurons will be affected by the inflammation spread subroutine called by each damaged neuron. Therefore, these patches will have a higher cumulative inflammation values than if they were near only one damaged neuron.

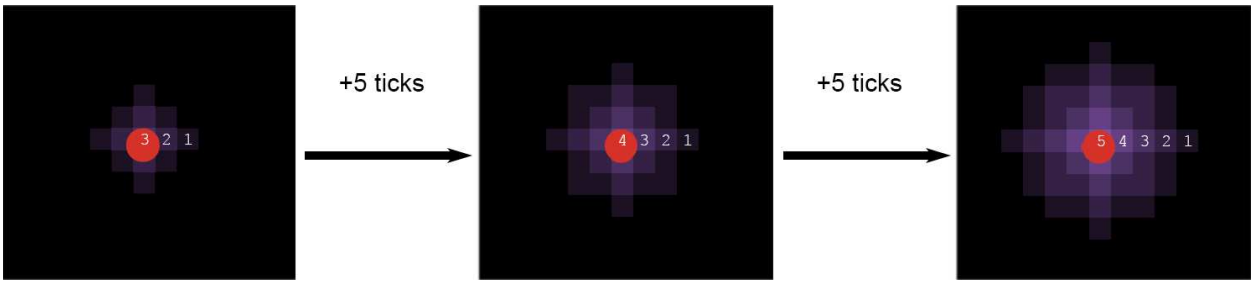

Figure 3: The spread of inflammation within the model, with values for *inflam-val* superimposed to illustrate the resulting cytokine gradient. Inflammation levels are higher the closer the patch is to the damaged neuron, signified through a brighter, lighter purple coloration. The numbers depicted are directly related to the strength of inflammation.

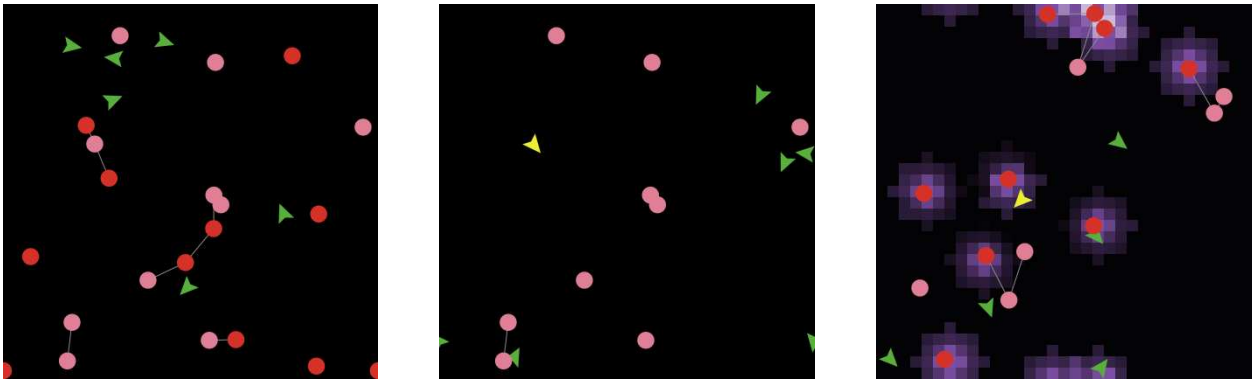

Figure 4: Images of the ABM simulation. The left image shows the microglia (green), healthy neurons (pink), and damaged neurons (red) upon initialization. The middle image depicts the end of the simulation, where all damaged neurons have been phagocytosed. The yellow arrow represents a microglia currently in the process of phagocytosis. The right image shows our sub-model that includes microglia sensing. Purple areas represent inflammation from damaged neurons, with lighter shades indicating higher concentrations. Microglia are able to sense inflammation levels, and move towards higher inflammation concentrations.

After a damaged neuron is phagocytosed, pro-inflammatory cytokines will no longer be produced since the neuron no longer exists. This causes the amount of pro-inflammatory cytokines and inflammation in the area to decrease to baseline environmental levels. When a damaged neuron is phagocytosed by a microglia agent, the patch it was occupying will no longer be a *residence* patch. Instead, this patch will be set as *dismantling* and will call a different subroutine that simulates the decay of inflammation. This subroutine acts as the opposite of the subroutine facilitating the spread of inflammation. Therefore, *dismantling* patches will subtract 1 *inflam-val* from all patches within *curr-spread* radius every 5 ticks, including itself. Afterwards, the value for *curr-spread* decrements by 1. This subroutine is called every 5 ticks until the value for *curr-spread* reaches 0. After this, the patch will no longer be considered *dismantling*.

3.8 Implementation

This model was implemented in NetLogo 6.4.0 [62], a software designed specifically for the creation and execution of ABMs. Simulations were automated through NetLogo's built-in BehaviorSpace feature, and data from simulations was collected through this feature automatically. BehaviorSpace runs a model multiple times, systematically varying the model's parameters and recording the results of each model run. This allows the user to explore the parameter space and understand the relationship between parameter values and model outcome. Graphical analysis of data was conducted through JupyterLab [32], distributed as part of Anaconda [16]. Python packages used were pandas [55], NumPy [24], and Matplotlib [29]. Code to reproduce our results is provided in the Supplemental Information.

4 Results

To analyze the effects that microglia behavior and genetically induced deficiencies can have on the progression of AD, we selected parameters to vary in simulations that correspond to microglia behavior and the environment. These parameters included temperature, the probability of a microglia successfully removing a damaged neuron through phagocytosis, sensing, and the initial number of microglia in the system. In the simulation which varied the initial number of microglia in the system, two separate BehaviorSpace experiments were conducted – the first of which had microglia agents lacking the ability to sense nearby damaged neurons and the second where the microglia had this sensing ability. This allows us to consider the impacts of a *TREM2* variant, which impairs microglia sensing ability. The outcome of interest of each individual trial in all three simulations was the time it took the microglia agents to clear all damaged neurons, providing insights into the efficiency of microglia in potentially restoring the system to a healthy state or delaying disease progression.

Temperature variation. We conducted an experiment to determine the effect of hippocampal temperatures on the microglia's ability to clear damaged neurons. To ensure that the clearance rates observed were purely the result of a change in temperature, the parameters *sensing-efficiency* and *damage-chance* were set to 0%. We varied the temperature from 36° to 40° Celsius. Although human core body temperature is on average 37° Celsius and does not vary greatly from this range in healthy individuals (hypothermia sets in at 35° Celsius and hyperthermia is 40° Celsius or higher), recent experiments indicate that human brains routinely maintain a temperature that would be considered a fever elsewhere in the body, with some areas deep in the brain reaching 40° Celsius regularly [51]. When varying the ambient temperature of the hippocampus (Figure 5), minimal overall impact was observed on the removal rate of damaged neurons by microglia. As a consequence of these results, we have concluded that a variation in brain temperature does not have a significant impact on the rates of clearance and therefore can be removed as a variable in our model. (Identical simulations were run twice more, resulting in similar graphs indicating no association between the variables. The data, code and graphs of these repeated runs are provided in the repository linked to in Supplemental Information.)

Phagocytosis variation. The varied probability of a microglia successfully performing phagocytosis when encountering damaged neurons was another key parameter examined (Figure 6). This simulation showed a clear relationship between increased clearance probability and reduced time needed for the clearance of damaged neurons. Specifically, as the probability of successful phagocytosis increased, the duration required for the microglia agents to clear all damaged neurons decreased significantly. The results of this simulation are noteworthy recalling that microglia in an AD afflicted CNS exhibit impaired abilities to successfully perform phagocytosis [42]. This suggests that enhancing the phagocytic capability of microglia could be a potential therapeutic strategy for accelerating the removal of damaged neurons.

Sensing and initial microglia population size. We conducted two distinct experiments to examine the effects of varying the initial number of microglia in the system (Figure 7). The first scenario prohibited the ability of microglia to sense nearby damaged neurons, mimicking the impaired abilities of microglia observed in AD afflicted brains, particularly related to the *TREM2* genetic variant [42, 58]. Even in this compromised state, increasing the initial number of microglia resulted in faster clearance. The second simulation allowed microglia to have full sensing ability, corresponding to fully functional microglia. Microglia with the ability to sense damaged neurons exhibited even faster removal rates than the sensing-disabled scenario. In both cases, a higher initial number of microglia led to a more rapid clearance of damaged neurons.

5 Discussion

In this work, we developed an ABM that includes pathways for microglia sensing, chemotaxis and phagocytosis, as well as the secretion of inflammation from damaged neurons. We also conducted several in silico experiments with the ABM. For each experiment, we considered the time required to clear damaged neurons as the outcome of interest.

The first experiment varied temperature, which in turn increases the velocity of microglia. Temperature is a meaningful variable in the context of AD and other neurodegenerative pathologies, because inflammation present from neurodegeneration can increase the temperature of the brain through the febrile response [31].

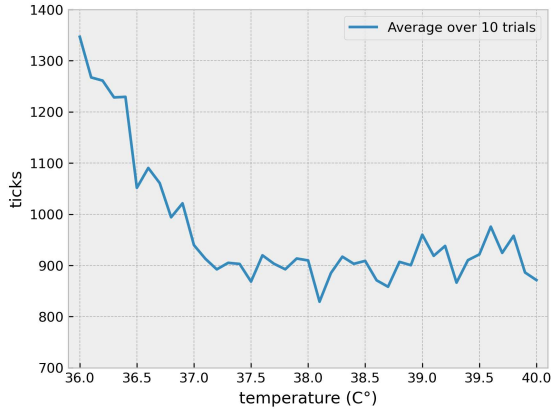

Figure 5: Average number of ticks (10-hour intervals) taken for microglia to clear damaged neurons with variation in environmental temperature with sensing set to zero. The experimental results indicate there is no association between hippocampal temperature and the time required to clear damaged neurons.

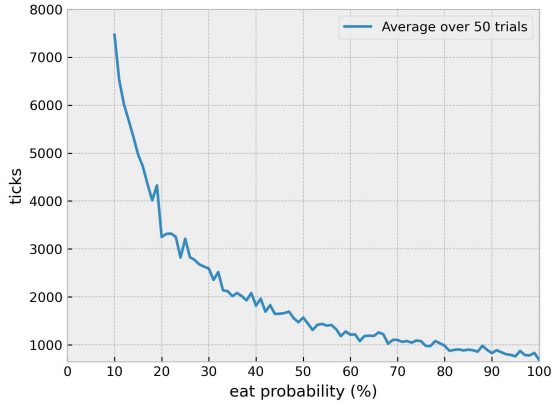

Figure 6: Average number of ticks (10-hour intervals) taken for microglia to clear damaged neurons, with varying percent chance of successfully eating a damaged neuron. Probabilities below 10% not included due to limitations in the ABM software.

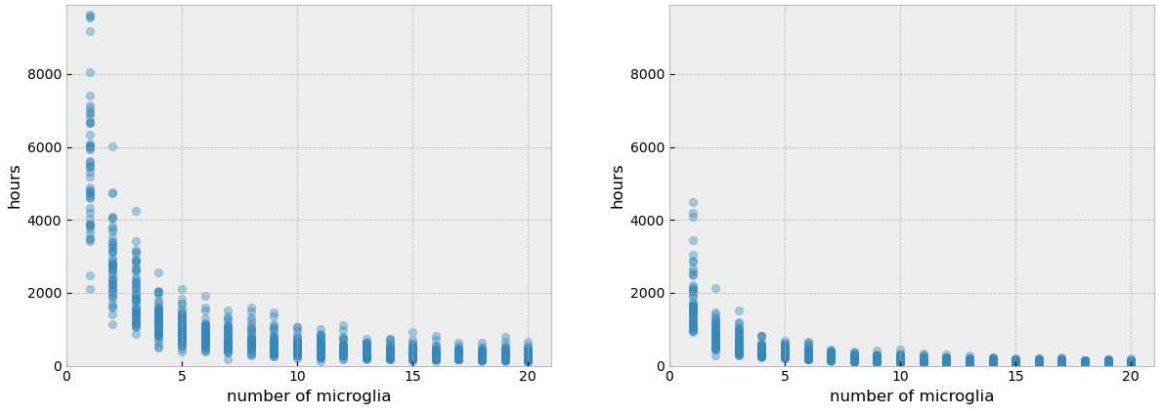

Figure 7: Plots showing the relationship between the number of microglia in the ABM and the ticks (10-hour intervals) it took for the microglia to clear all damaged neurons (50 runs per number of microglia). In the left plot, microglia are not able to sense; whereas in the right plot, microglia are able to sense damaged neurons.

Our experiments indicate that a variation in temperature had no correlation with the time it takes for the microglia to clear all of the damaged neurons. From this, we conclude that temperature does not impact clearance of damaged neurons through the mechanisms we have included in our model. It is important to note that fever can work through other mechanisms, such as augmenting the performance of immune cells or inducing stress on pathogens and damaged cells directly [63]. Additionally, higher body and brain temperatures can drive the activity of certain proteins (transcription factors) that in turn control genes which are responsible for a more general immune response [23]. So, although our model does not indicate a significant impact of temperature, it could be that more pathways should be included to capture this effect. A future iteration of our ABM should include more detailed pathways to fully investigate the impact of fever on damaged neuron clearance.

Our second experiment varied the success rate of a microglia phagocytosing a damaged neuron it encounters. TREM2 is a surface receptor protein (coded by the *TREM2* gene) required for various microglia responses, including phagocytosis. It is well established that many AD patients carry a risk variant of this gene, leading to impaired phagocytosis [57]. This experiment indicates that the time to full damaged neuron clearance is a function of successful phagocytosis, and there appears to be a decaying exponential relationship. This results highlights the importance of successful phagocytosis in maintaining brain health, and suggests that therapies targeting and enhancing phagocytosis could be effective in neurodegenerative diseases. This is in line with recent work [49] which identified that the inhibition of CD22 restores phagocytosis in a murine model and is a promising strategy to restore homeostasis in the aging brain. Of note, this therapy targets the phagocytic cell (microglia) rather than the target of phagocytosis, which is a paradigm shift in the treatment of AD.

Our third experiment probed the importance of sensing in microglia's ability to clear damaged neurons. This behavior was selected because it also relates to deficiencies in *TREM2* variants. This experiment shows that sensing is important for clearance of damaged neurons. However, it also showed that impaired sensing can be mitigated with a larger initial population of microglia. We interpret this to mean that if a therapy can increase recruitment and proliferation of microglia, this could be a viable way to offset the impairment caused by *TREM2* variants. There are currently immunotherapies (e.g., leukocyte Ig-like receptor B4 (LILRB4) specific antibody) [28] which can better activate and recruit microglia in the brains of individuals with AD.

These results suggest potential therapeutic targets in AD. For instance, treatments that increase the phagocytic efficiency of microglia or expand their sensing radius could significantly improve the clearance of damaged neurons. By enhancing these aspects of microglial function, it may be possible to develop more effective treatments for AD. Ultimately, these avenues of investigation provide hope for the development of interventions that could mitigate the progression of AD by promoting more efficient clearance of neuronal debris and maintaining a healthier brain environment.

6 Future Work

Amyloid β (Aβ) protein is formed by the breakdown of a precursor protein, and some forms are especially toxic. In AD, abnormal levels of this naturally occurring protein bind to form plaques which can disrupt cell function. A number of treatments have been developed which target these plaques (e.g., monoclonal antibodies such as aducanumab and lecanemap) [33], but the repeated failure of Aβ-targeted clinical trials has cast doubt on the previously prevailing "amyloid cascade hypothesis" which suggests that Aβ deposits in the brain are the initiating event in AD. Indeed, aducanumab has been discontinued as of 2024 [26], and the limitations of an anti-Aβ therapy for a complex disease which includes many pathways beyond plaque formation has been recognized. Focus has shifted from Aβ plaques to other dynamic players in this complex ecosystem, such as microglia [39, 27]. For this reason, our model prioritizes microglia-neuron interaction, but a future iteration of our model should include Aβ plaques. Additionally, our model groups many cytokines into inflammation, when in reality, there are a variety of signals released by damaged neurons, microglia themselves, and other immune cells not included in our model (e.g., T cells can interact with microglia during AD progression [54]). Microglia also express receptors for a variety of signals and can respond to these signals in a variety of ways not included in our model (e.g., metabolic reprogramming [3], phenotype switching [64]). Future work will incorporate more specific pathways and behaviors.

We will also consider additional pathways related to temperature, such as the creation and action of heat shock proteins (Hsp) [9], a type of molecular chaperone that can mediate protein folding, signaling and is induced by heat stress. Interestingly, Hsp90 can influence microglia phagocytosis [46], which could

link temperature to clearance rate through a mechanism not yet explored and suggests a new avenue of investigation.

Our ABM provides a solid first step in modeling microglia-neuron interaction in the hippocampus, and allows us to probe deficiencies in microglia behavior related to genetic variants of *TREM2* commonly found in individuals with AD and to understand how these deficiencies relate to their ability to clear damaged neurons. An advantage of the ABM framework is that it is extremely conducive to iterative refining of rules and pathways considered in the model. Our model can be expanded in future iterations to include specific pathways that capture more refined cross-talk between neurons and microglia, different cell types which are also present in the brain, as well as Aβ plaques.

7 Supplemental Information

The Netlogo model has been published to the NetLogo Model Library and can be found at this link: https://www.netlogoweb.org/launch#http://ccl.northwestern.edu/netlogo/community/Microglia%20Model.nlogo. Users are free to download and modify the code as they desire, or to run the code in the web interface. The data collected from the repeated simulations of the model as well as the Python code used to create Figures 5–7 is available on a public repository found at this link: https://github.com/cjt101/microglia-spora24.

Author Contributions

All authors contributed to the conceptualization of the agent-based model, coding, visualization and the interpretation of the results. All authors contributed to drafting, finalizing and revision of the manuscript.

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