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Agent-based Modeling of Microglia Behavior in the Context of Alzheimer's Disease

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Agent-based Modeling of Microglia Behavior in the Context of Alzheimer's Disease

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Overview

Whether immune cells protect or harm the brain is an open question depending on context, and their role is implicated in many diseases. Alzheimer's Disease (AD), the most common cause of dementia, currently affects 24 million people worldwide, a number expected to double over the next 20 years [5]. Recent key findings have been made connecting dysfunctional microglia cells to the progression of AD [1, 4, 6]. This project uses an agent-based model (ABM) to simulate relationships between microglia, neurons and signaling proteins to address open biological questions related to AD progression.

Figures

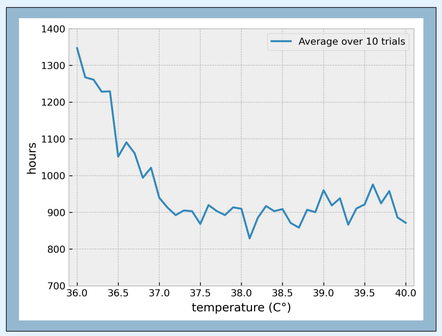


Figure 1: Average time for microglia to clear damaged neurons with varying environmental temperature. Variance in movement speed relative to temperature is multiplied by a factor of 10.

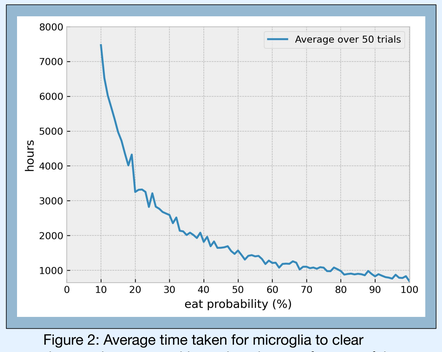


Figure 2: Average time taken for microglia to clear damaged neurons, with varying chance of successful phagocytosis.

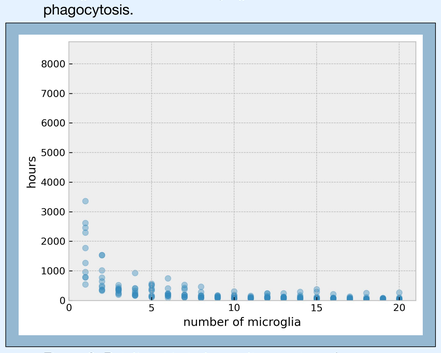
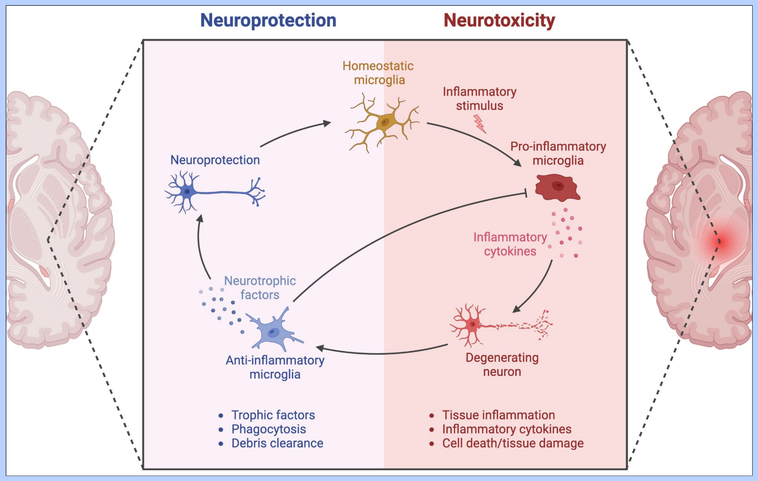


Figure 3: Relationship between the number of microglia in the ABM and the ticks it took for the microglia to clear all damaged neurons. Each dot in scatter plot represents one trial run.

Background

Microglia are immune cells in the central nervous system (CNS), and are able to survey their environment to mount an immune response [3] or clear debris and damaged cells. This is done through phagocytosis, a process of engulfing and digesting these substances [7]. Microglia are aided in their jobs through sensing a group of signalling proteins released by damaged cells, which are called cytokines [2]. However, dysfunctional microglia can facilitate the progression of Alzheimer's disease by being less efficient at sensing and phagocytosing damage [1, 4, 6].



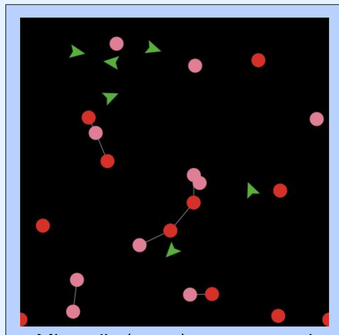
The dual-natured roles microglia play in the CNS.

Results

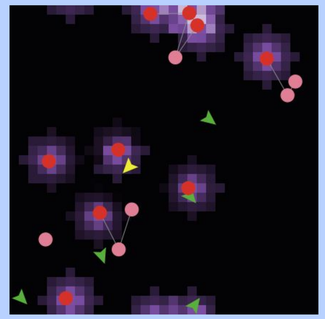
Automated, repeated model simulations highlight the impacts of varying different model parameters. The figures on left show results of three different simulations – one varying temperature, one varying the success rate of phagocytosis, and one varying the initial number of microglia. Each simulation tests these variables with time (in hours) to clear the damaged neurons as the dependency. Temperature variation showed minimal impact on clearance rate. Increasing the probability of successful phagocytosis reduced clearance time. Varying the initial microglia count led to a faster clearance with more microglia present. Some of these results support our model's potential for identifying therapeutic targets in treatment of AD, such as treatments targeting the enhancement of phagocytic capabilities.

Methodology

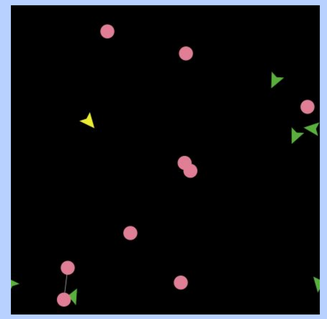
ABMs can simulate different types of agents (in this case, cells), and apply a ruleset that each type of agent needs to follow. Our ABM focuses on the ability for microglia to move, survey healthy neurons, and phagocytose damaged neurons. It also takes into account the effects that cytokine sensing have on these processes, represented by microglias' ability to move up greater concentrations of cytokines the simulation.



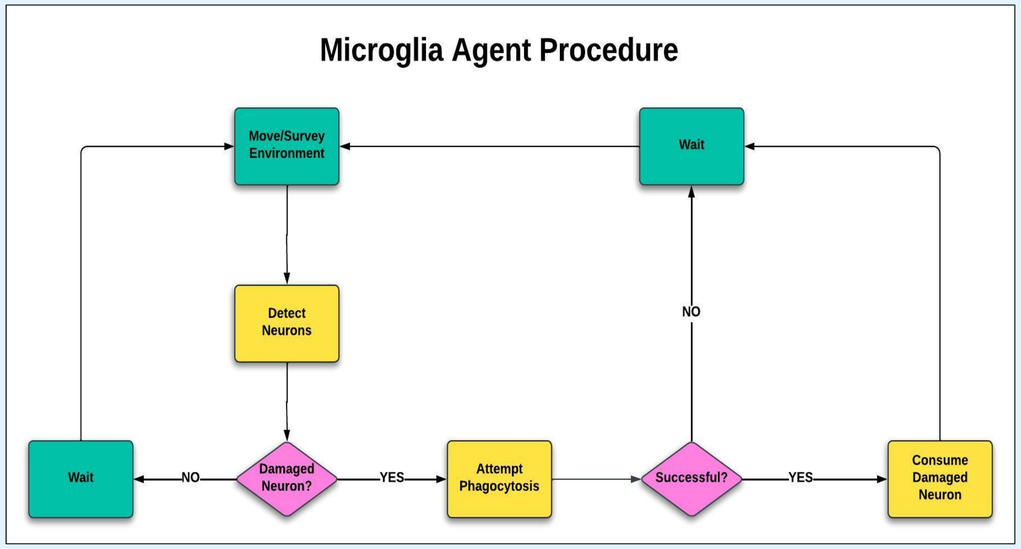
Microglia (green) move around in the ABM environment. Damaged neurons are red, and healthy neurons are pink.



Damaged neurons (red) release cytokines (purple), which microglia can sense and move towards.



Simulation ends when microglia phagocytose all damaged neurons in the environment.



Future Work / Acknowledgement

Because of the nature of an ABM, it is possible to build upon the work presented here to create a more detailed depiction of microglias' role in AD. For instance, knockout experiments could be replicated using a modified version of this ABM, allowing for meaningful experiments to be conducted without the use of a wetlab. Additionally, we hope to include more biological pathways that exist in the context of the hippocampus and AD. Microglia are complex, and behaviors such as communicating with other cell types and secreting cytokines can be implemented in future versions of our model.

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