Sex-based computational analysis of microglial initiation and impact of estrogen in progression of Alzheimer's disease

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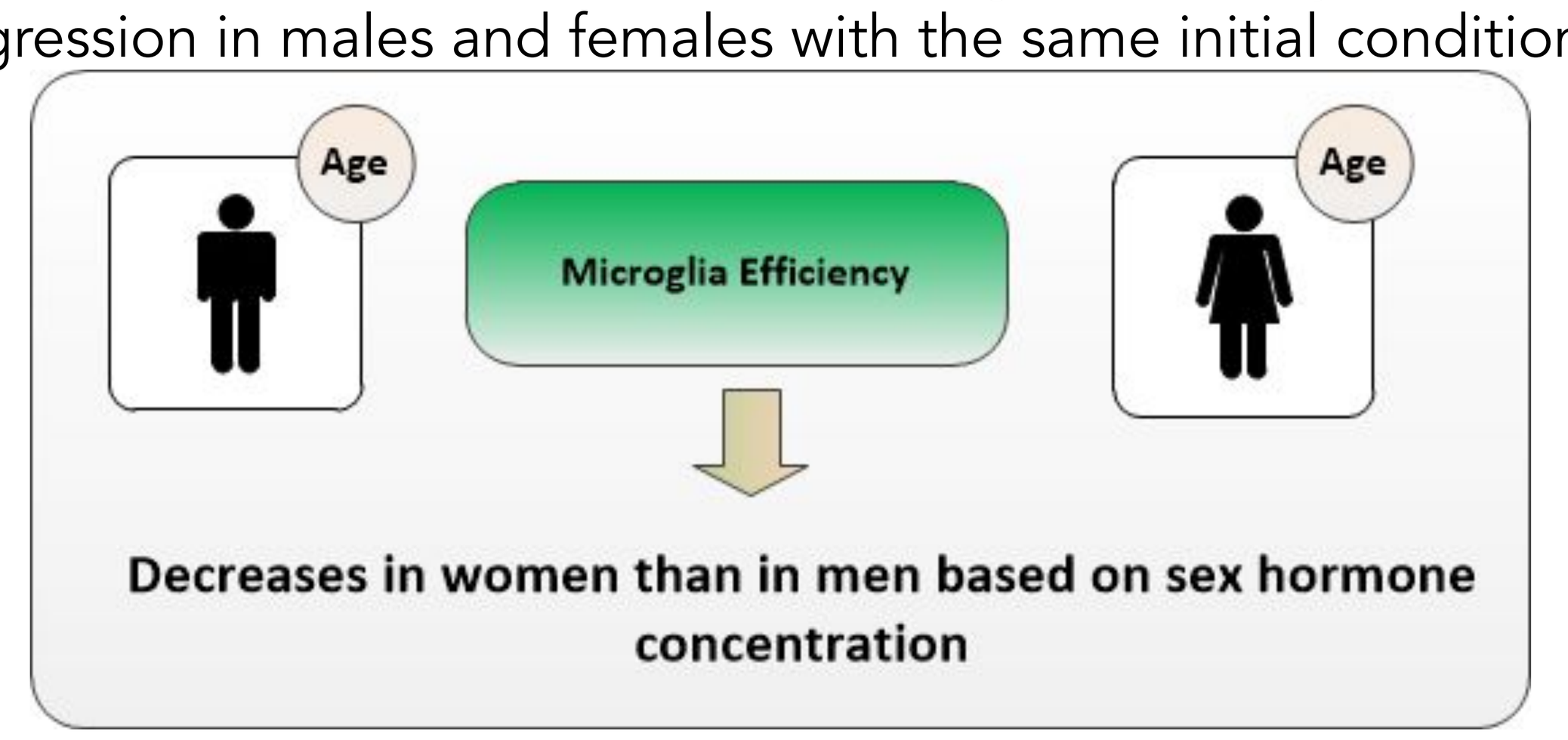
Introduction

- Alzheimer's Disease (AD) is a neurodegenerative disease impacting thought, language, and memory and is the most common cause of dementia.
- Today, nearly ⅔ of AD patients are females, who experience a more rapid cognitive decline after diagnosis. AD symptoms might not be as easily detected in females.
- Historically, most AD research was done exclusively on males, causing a considerable knowledge gap when it comes to diagnosis and treatments for females.
- Microglia are the resident immune cells of the brain and regulate proper brain activity. They are responsible for clearing up abnormal protein accumulation (such as tau and amyloid-β), which is a hallmark of AD.
- Research has shown that microglial initiation and function is heavily impacted by sex hormones, specifically estrogen. Estrogen is known for … glial initiation.
- The APOE … on the variant (AP… compared to APOE variant 1).

Sex Hormones impact Microglia efficiency

What is our proposed solution?

Create a computational model that can highlight this gap in the field and be used to simulate differences in microglia efficiency and AD progression in males and females with the same initial conditions.



Model Interface

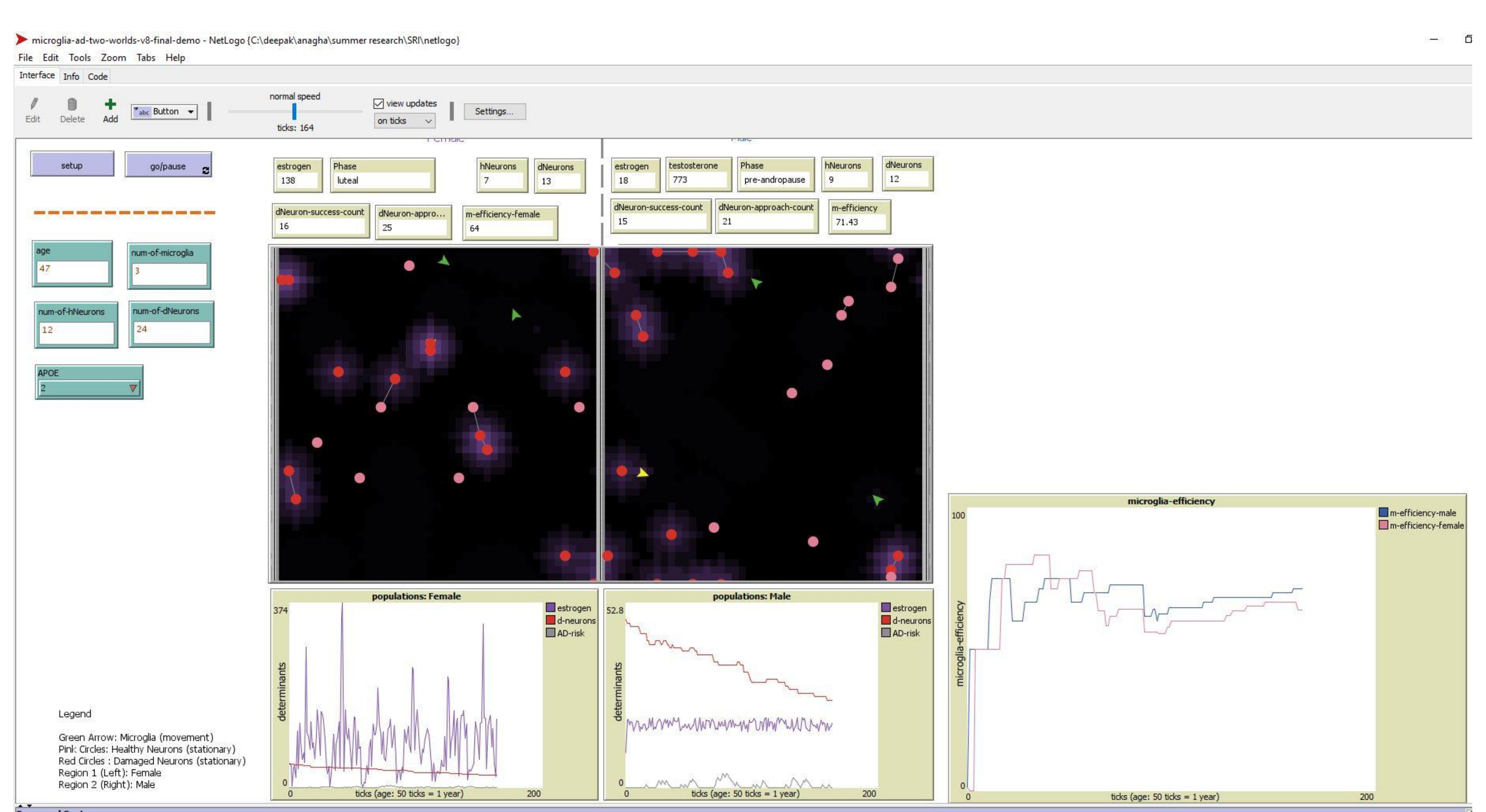


Figure 1: NetLogo interface with male and female regions

Model Workflow

- **Setup** initializes our model and generates random agents in the interactive interface environment based on the parameters outlined in our code

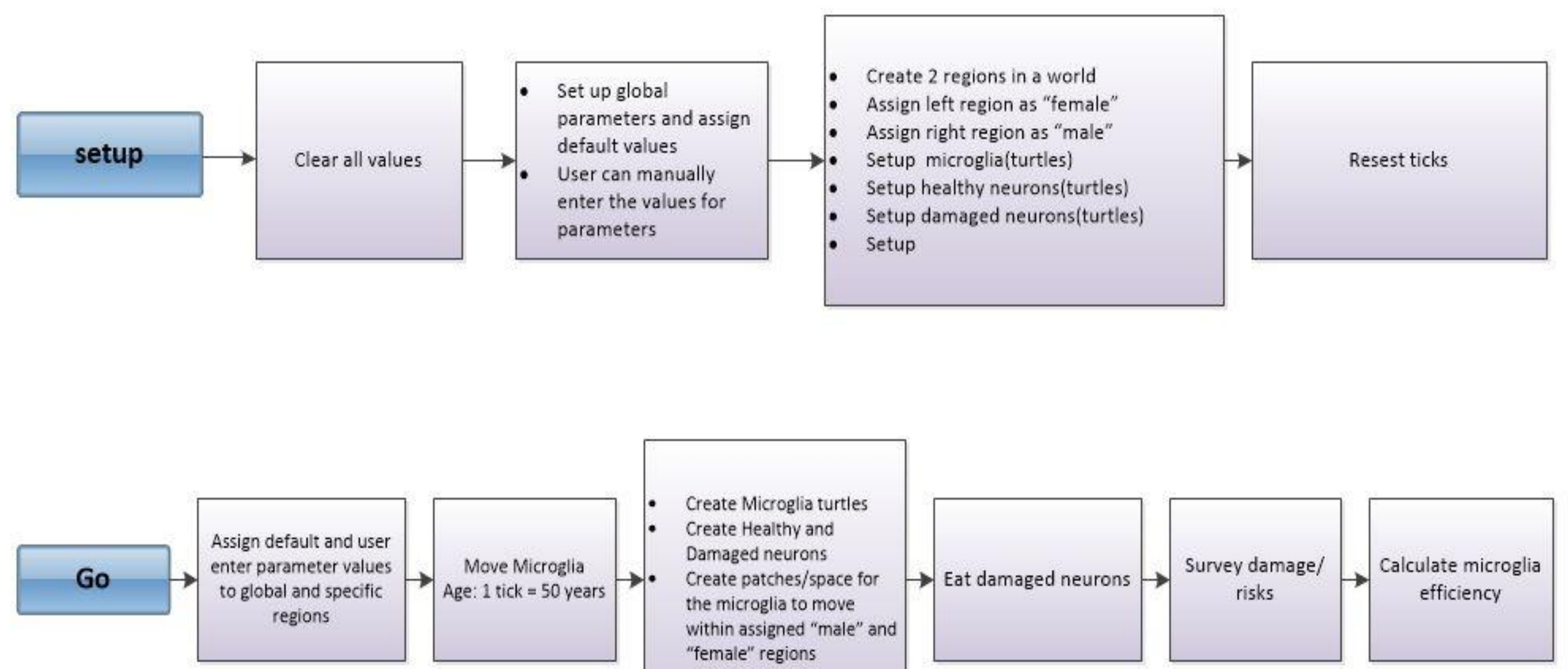


Figure 2: Workflow of the "Setup" and "Go" buttons to establish and run the simulation

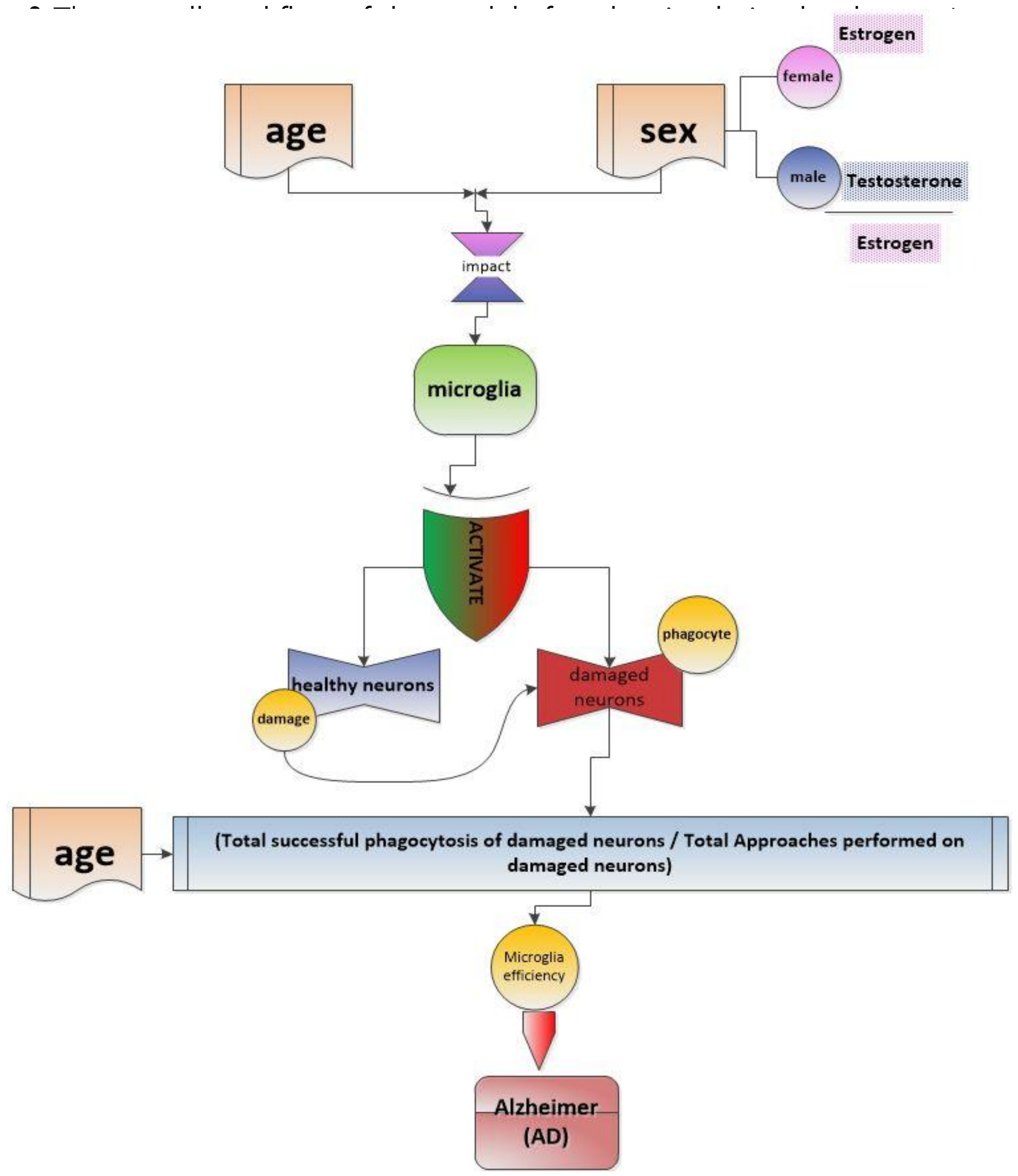


Figure 3: Overall NetLogo model workflow and interdependencies of functions in the model

Simulation Analysis

- Microglia's efficiency at destroying diseased neurons is impacted by estrogen concentration and APOE status, which is then used as a measure to determine differences between males and females with the same initial conditions.
- The NetLogo simulation was initialized and ran ten times (n=10) for a given APOE status until there were no healthy neurons left or all diseased neurons were cleared. The age where microglia efficiency reached its lowest point was recorded for males and females in each run. A two tailed t-test was then used to determine statistical significance of microglia efficiency between males and females with varying AD risk (determined by APOE status).

Initial Conditions: Age= 45, Number of Microglia= 3, Number of Healthy Neurons= 24, and Number of Damaged Neurons= 12. APOE Status was variable.

$$\text{Microglia Efficiency} = \%\left(\frac{\text{number of times microglia destroyed a damaged neuron}}{\text{total number of times microglia approached a damaged neuron}}\right)$$

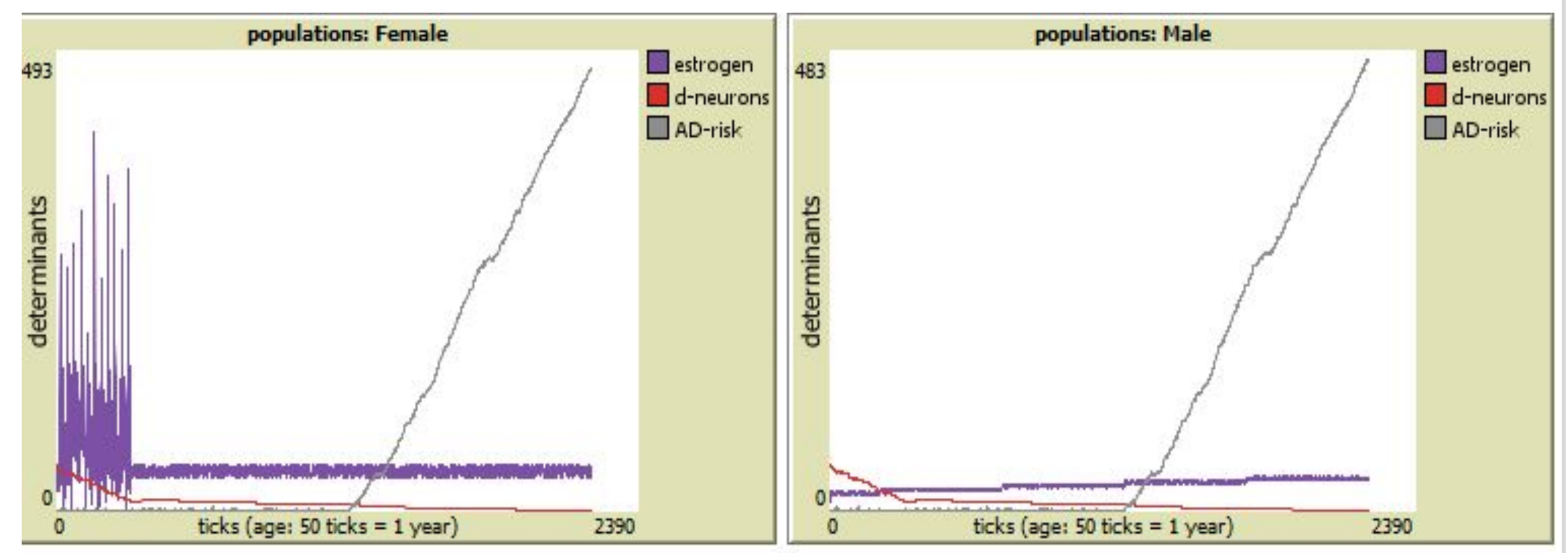


Figure 4: Sample simulation run with "healthy" (low AD risk, APOE1) females (left) and males (right). Where the starting age is 45 years and every 50 ticks= 1 year. Estrogen concentration fluctuations are represented by the purple line, the number of damaged neurons in the simulation over time is represented by the red line, and AD risk (determined by increased microglia activation) is represented by the gray line

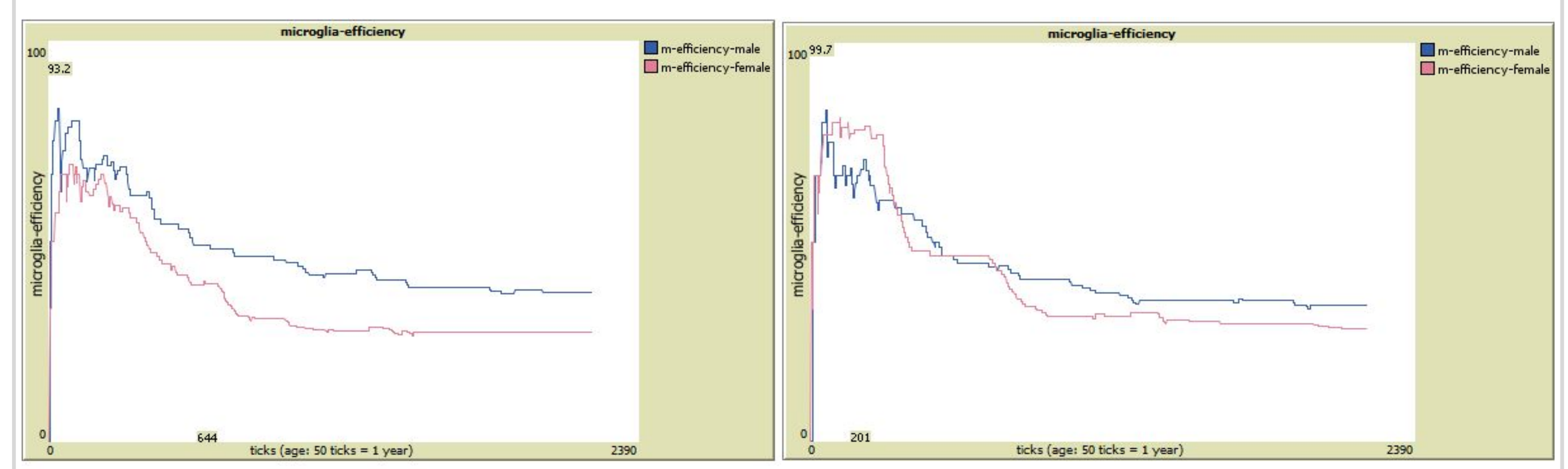


Figure 5: Sample plots of microglia efficiency over time in a simulation run with "healthy" individuals (low AD risk, APOE1; left) and high AD risk individuals (APOE4d; right)

	APOE1 (Low AD Risk)		APOE4d (High AD Risk)	
Simulation Run	Women	Men	Women (A4)	Men (A4)
1	83	71	59	64
2	81	83	81	80
3	89	80	83	87
4	84	84	80	80
5	85	89	76	87
6	80	82	81	84
7	79	87	85	84
8	83	58	36	87
9	83	79	73	82
10	83	79	73	82
	Women (APOE1)	Men (APOE1)	Women (APOE4d)	Men (APOE4d)
Average:	83	79.2	72.7	81.7
Standard Deviation:	2.79	8.94	14.89	6.78

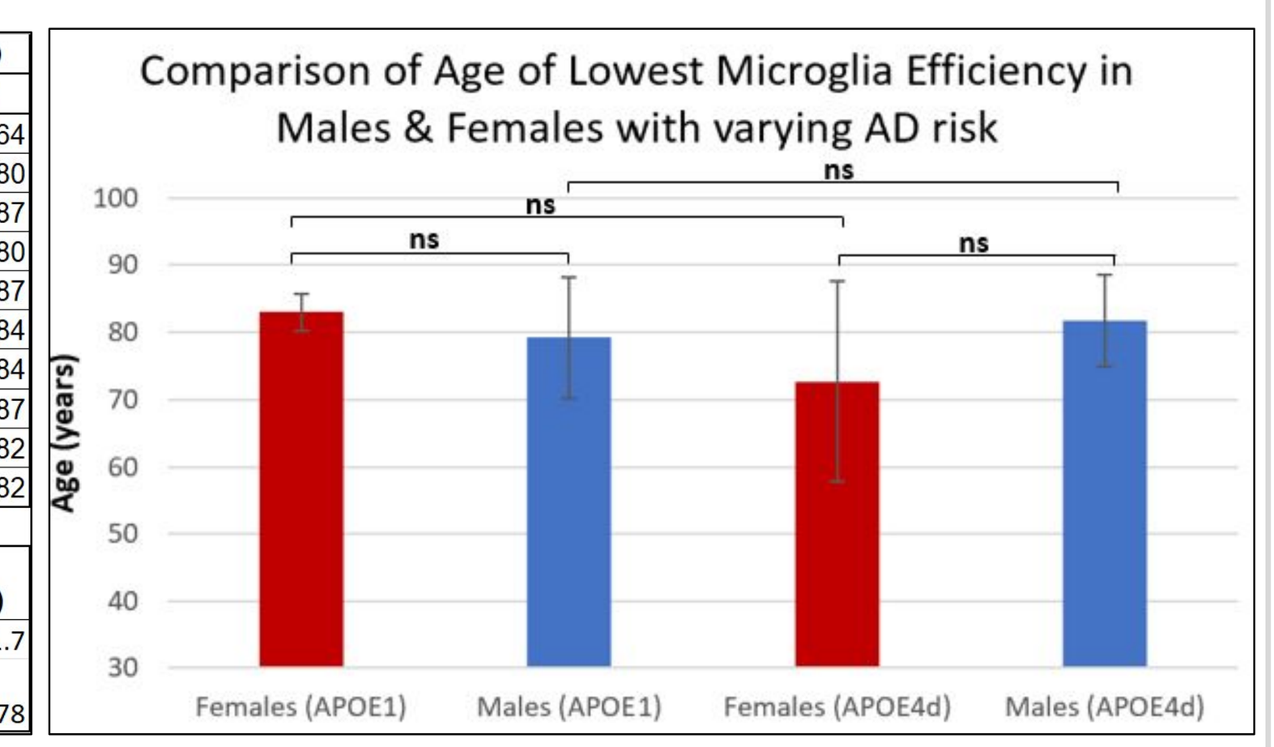


Figure 6: Comparison of age where microglia efficiency reached its minimum between males and females with varying AD risk (n=10 runs per APOE status). No significant difference in age of lowest microglia efficiency was found when alpha= 0.05. There is a significant difference in microglia efficiency between Women with varying AD risk (APOE1 and APOE4d) when alpha > 0.05.

Discussion / Conclusion

- Our model was able to capture differences in microglia function and efficiency based on sex in individuals with varying AD risk.
- Our model showed that healthy (APOE1) individuals had a higher minimum microglial efficiency than high risk AD (APOE4d) individuals.
- Low AD risk (APOE1) individuals' microglial efficiency reached its lowest point at an older age than high AD risk (APOE4d) individuals.
- While our research did not show a significant difference in the age at which microglia efficiency reached its lowest point when alpha= 0.05, there is a significant difference in the age of lowest microglia efficiency between women with low and high AD risk (APOE1 and … alpha > 0.05

Next Steps

- Re-structure the process by which neuron damage spreads
- Include temperature (representative of neuroinflammation) as a deterministic parameter and study the impact of temperature change on microglia initiation
- Use differential equations to more accurately capture the dynamic interaction of variables (such as estrogen concentration and APOE status) and their impact on microglia function and efficiency in males and females
- Collaborate with individuals that have real world data regarding estrogen's effect on microglia to increase model relevance

References

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This model is openly available at https://github.com/teenie3/SexEffect_Microglia_AD

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