Math 153 – Project Proposal

[redacted]

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1 Field of interest

Neuroscience is a diverse field of research due to its interdisciplinary nature. From molecular mechanisms and pathways to neural circuits and cognitive functions, there are multiple levels of analysis that may lend themselves to a mathematical approach. In my project, I would like to investigate the dynamics of neurodegenerative diseases, such as Alzheimer's (AD).

The molecular pathology of AD is known to propagate through the brain via circuits, producing stereotypical patterns of disease progression [2, 5]. I would like to expand on this model of disease progression and model the brain as a population of neurons which can contain pathological proteins such as tau that are transmissible between neurons.

2 Specific questions

2a Constructing a network model of the AD brain

I would like to investigate the dynamics of AD progression in the brain. My first step would be to convert biologically relevant pathways and circuits into a network model, i.e. a weakly connected directed graph where strongly connected subgraphs represent the neuronal populations of each brain region, and directed edges exist between neurons. As a simplification, we will model all neurons as monosynaptic (i.e. each upstream neuron projects to one and only one other neuron).

To further explore the effect of structure on evolutionary dynamics, I could vary graph parameters such as connectedness in- and outside of each brain region. I could also compare my graph to a fully connected graph, to establish whether my simple model is a suppressor of disease progression [4]

2b Finding time to "fixation" of pathological tau

Given my model of the brain as a structured population, I would then model disease progression as a Moran process. Because neurons in the adult brain do not divide, only diseased cells have the ability to be selected for "reproduction," which is taken here to mean "transfer of pathological tau between neurons" [5]. In each time-step, the important event becomes the selection of a connected cell (either within the subgraph or connected via circuit) to receive the pathological tau. If a healthy neuron is selected, the population number of diseased neurons increases. If a diseased neuron is selected, the population number of diseased neuron remains the same.

In this simple model, the disease can only progress. I would be interested in calculating the time to fixation of the diseased phenotype within the initial brain region subgraph, as well as time to "escape" of the diseased phenotype from the initial brain subgraph to other subgraphs of the brain. Analogizing this neurodegenerative model to an infectious disease model, I could quantify "incubation time" and vary "infectiousness" of diseased tau protein [3] by manipulating the birth rate of diseased neurons.

2c Including the resident immune system: microglia

Consider the innate immune system and its potential to reverse the course of AD. Microglia, the resident immune cells of the brain, have diverse functions in AD [6], ranging from uptake of pathological tau to *propagation* of pathological tau [1]. I would augment my simple model by updating the birth and death probabilities of normal and diseased neurons according to a composite parameter that reflects microglial activation and protein clearance ability. Microglial activation increases proportionally to number of diseased neurons, but protein clearance ability decreases after a maximum threshold is reached. While this model is highly reductive, it can illustrate some basic features of the pro- and anti-inflammatory functions of microglia.

I am most interested in finding a way to model the ability of microglia to "jump" between subgraphs. Because microglia are highly motile cells, they are free to travel across the brain, and can transport tau between neurons that are not directly connected within a subgroup or by a directed circuit connection [1]. This allows for the "seeding" of tau across the brain regardless of circuit connections. I would model this as implicit "migration" of diseased neurons, where the limitations on death selection are lifted with some rate corresponding to microglia migration rate [7].

3 Approaches

I plan to model neurons as belonging to a finite, constant population in a Moran process. With further development of my model, "birth" and "death" rate will be analogized to biological phenomena that are relevant to the disease model at hand. I also plan to simulate this dynamical system with representative graphs of varying connectedness and with varying parameters to support the development of a biological intuition of disease progression.

References

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