DISCRETE AND CONTINUOUS STOCHASTIC MODELS FOR NEUROMORPHOLOGICAL DATA

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ABSTRACT

Mathematical modeling of axonogenesis started in the 1980's and is a growing field of research. Early theoretical apporaches to understanding axonogenesis utilized stochastic walk models [1]. Since then, there have been improvements in biological data collection procedures and computing power has and continues to increase. These facts encourage more detailed explorations of complex biological mechanisms of axonogenesis and in parallel require the building, improving and refining of mathematical models for axonogenesis.

There are important unanswered questions regarding axonogenesis that can benefit from theoretical investigations. Limited work has been done on incorporating the biochemical and molecular intracellular processes responsible for guiding the axon into mathematical models without using the dependance of an external guidance cue. The general goal of this research is to discover a model of the axon growth process which connects the microscale processes of molecular dynamics and lamellipodia and filopodia formation to axon network dynamics density and direction with and without the presence of guidance cues. This will allow the entire axon system to be quantitatively studied as a function of intracellular mechanisms at a larger length scale. This is important since little is known about the biological components responsible for axonogenesis which ultimately lead to neuronal connections [2].

This work builds towards developing a simulation tool, which takes as input two-dimensional in-vitro data, and outputs 'expected' axonal responses to specific experimental treatments. While we have not tested our model with the effects of a diffusible growth factor, we have been able to answer many questions about axonogenesis, particularly how positive axon elongation and growth cone kinematics are coupled processes but require very different theoretical descriptions. Preliminary results have been achieved through collaborations with Dr. Tara Lindsley at Albany Medical College, Center for Neuropharmacology and Neuroscience, who conducts a series of experiments aimed at isolating axons' responses to controlled gradient

exposures to guidance cues and the effects of ethanol and similar substances. With the data from Dr. Lindsley's lab we have been able to accomplish the following tasks:

1. Development of a filtering strategy to obtain data sets truly representative of the axon trail formation, leading to a coarse graining method which establishes an optimal parameter estimation technique.

2. Derivation of a mathematical model which is stochastic in nature, parameterized by arc length. This model allows for the comparison of experimental and theoretical *mean square displacement* (MSD) of the developing axon.

3. Development of a second filtering strategy to capture the growth cone velocity statistics by approximating the growth cone jump size distribution and correlation with respect to the experimental time of capture.

4. Synthesis of a novel mathematical model combining the previous three approaches. This model, ultimately leading to a simulation tool incorporates the wide range of variation of the growth cone dynamics as it traces the arclengths of the axons via a discrete approach.

This thesis will discuss the synthesis for each of the four topics listed above, as well as preliminary work on the Fokker Planck equation as part of #2 above. Current results include renewal process analysis and simulation, and future development will show how our results differ with the presence of guidance cues and experimental treatments. Qualitative and quantitative predictions of the model show encouraging results and capture experimental behaviors well.