Overview of Techniques for Various Aspects of the C. elegans Modeling Project

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Introduction

A project as ambitious as realistically emulating the nervous system of an entire organism necessarily consists of many parts and stages. In addition, in our project, there are multiple promising technologies that can serve each of these. In this document, I've identified four main areas, which correspond roughly to the phases of the scientific method—observation, the collection of data about what is happening in the neurons; modeling, the synthesis of this data into predictive models of neuronal function; stimulation, the perturbation of the nervous system so as to collect more nuanced data about its functional relationships; and finally, verification, the techniques for determining the accuracy or fitness of the models produced by the coaction of the other parts of the project.

Contents

1 Observation

1.1 Optics

It has been suggested that a spinning-disk confocal microscope is the best platform for imaging flourescence in individual *C. elegans* cells. Other possibilities include two-photon microscopy and scanning-laser confocal microscopy. As I know rather little about optics and understand only the basic principles of operation of these devices, I leave it to others—or better, to empirical trial—to determine which of these is the most promising.

1.2 Sensor Molecules

Many calcium- and voltage-sensitive dyes are commonly referred to in the literature, including:

- RH-155 *(voltage-sensitive)*
- RH-414 *(voltage-sensitive)*
- RH-482 *(voltage-sensitive)*
- Cameleon *(calcium-sensitive, ratiometric, commonly used in worms)*
- G-CaMP2 *(calcium-sensitive)*
- G-CaMP3 *(calcium-sensitive, 3 times brighter than G-CaMP2)*
- G-CaMP5 *(calcium-sensitive, not shown to work in worms)*

For the time being, G-CaMP3 is being considered as the leading candidate, but this may change due to new information or as novel molecules are introduced.

1.3 Image Analysis

As nearly all of the data collected by these means will consist of images, it will be necessary to apply some computer vision techniques, at least in the initial stages of analysis.

1.3.1 Straightening

The first step to processing these images will be to straighten and register the posture of each animal on a common anterior/posterior/left/right/dorsal/ventral coordinate system. Parts of this can be done manually, but work is underway to implement the algorithm of [?] and apply it to the preliminary data of October 6.

1.3.2 Signal Separation

In addition, it would be desirable to separate the time-varying signals of each neuron algorithmically. However, a full labeling of neurons may prove intractable, and depending on the performance of the straightening algorithm, it may be possible to run modeling techniques directly on the straightened and registered image data. Intermediate approaches are also possible.

2 Modeling

This is probably the least developed section in my current thinking. A great deal of discussion and learning will need to take place before this part of the project is well characterized. Some initial scattered thoughts are represented below.

2.1 Correlation Matrix

2.2 Kernel Methods

2.3 Control Theory

3 Stimulation

3.1 Rhodopsins

3.2 Optics

3.3 Genetic Mosaic

4 Verification

"How will you know when you are done?" is a question I am commonly asked regarding this project. Below is my current thinking on this subject.

4.1 Quantifying Behavior

One possible approach is to make well-known behavioral assays (in chemotaxis, thermotaxis, etc.) testable algorithmically and quantitatively from vision tracking data. We could then reproduce these assays in a virtual environment with our modeled worms and see that the numbers fall well within the standard distribution of a population of real wild-type worms.

4.1.1 Biophysical Simulation

To do this, we must model not only the nervous system, but also, to a certain degree, both the body and the environment of *C. elegans*. Suzuki and Ohtake [?] have a simplified body model of *C. elegans*, as does Lockery [?]. One of these might form a good starting point.

4.2 Predictable Perturbations

Perhaps a more tractable approach than quantifying the wild-type behavior is to produce predictive results regarding defective animals.

4.2.1 Mutants

Several mutants, such as *unc-3*, *unc-6*, *unc-30*, *unc-76*, and *unc-86*, have well-characterized behavioral defects in addition to well-characterized defects in neural morphology (the presumptive cause). Ideally, given these defects in neural morphology, our model should be able to predict the behavioral defects.

4.2.2 Laser Ablation

In addition to the relatively small space of genetic mutants with well-known behavior and neural defects, we can also introduce arbitrary neural defects by killing neurons with laser ablation, and performing behavioral assays to see if the behavior of such animals matches a prediction by our models.

4.2.3 Laser Inhibition (Halorhodopsin)

If we can genetically and/or optically isolate a given neuron for optogenetic stimulation during behavior (see section 3), then it may be more desirable to transiently inhibit the activity of such a neuron than to kill it, for the purpose of generating more nuanced data to be matched against a model's prediction.