C. ELEGANT

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Draft 1 compiled 02:19, Wednesday 15th September, 2010

1 Introduction

We propose a novel program to fully model the relationship between the neural circuits and behavioral dispositions of the organism *Caenorhabditis elegans* (*C. elegans*). This program is well matched to the current level of technological development, and is poised to provide important basic insights into systems neuroscience, with likely implications for artificial intelligence research in the future. At least, it provides a unique opportunity to establish an upper bound on the level of detail in neural simulation that is necessary to make predictions about the behavior of an entire organism; as a side product, the project may also contribute some degree of understanding about intermediate levels of abstraction between neurons and organism behavior.

2 Initial *in silico* work

We will begin with the closest current result to our eventual goal, a 2004 paper by Suzuki and Ohtake in which 18 *C. elegans* neurons involved in gentle touch response were modeled, using a real-coded genetic algorithm to tune the unknown parameters of a very simple sigmoidal neuron model to a predetermined mathematical model of the expected system behavior. There are a number of improvements that can be made to this approach immediately: using a more principled optimization technique, a more sophisticated model of behavior, and incorporating more interneurons in the model.

3 Behavioral and environmental modeling

Since our goal is to replicate the behavior of an organism—its interaction with its environment—a critical component of the project is to accurately model the environment and develop a quantitative assessment of the behaviors of interest. Fortunately, the environment in which *C. elegans* is usually observed is quite simple (a dish of agar). However, a literature search and possibly some new behavioral experiments will be necessary to establish a quantitative description of *C. elegans* behavior.

4 Optimization and meta-optimization

With a neural topology and a quantitative description of behavior, quite a bit of new work can be done using global optimization techniques to determine the parameters of a neural model to match the behaviors described. However, it is not necessarily the case that these parameters would have any biological meaning. Thus, some physical experiments on *C. elegans* are necessary to source this information. However, since most combinations of parameters would, in simulation, produce dramatically different behavior from that expected, it may be possible to apply a "meta-optimization" technique to generate experiments that would provide the most information about which set of parmaters represents biological reality.

5 Experimental technologies

Such a project as this would not have been feasible five years ago. Without the tools to directly probe functional relationships between neurons, any computer- generated theories about how behavior emerges from neural circuits would essentially be guesses. This project involves significant biological work, and the experimental tools that enable such work are briefly discussed below.

5.1 Optogenetics

In 2005, Ed Boyden and collaborators published a technique for optical control of neural potential, through transgenic rhodopsins. It is now possible to stimulate or inhibit individual neurons through a purely optical experimental setup. This has enabled a wide variety of neuroscientific research that previously would have been impractical.

5.2 Calcium dyes

As optogenetics provide optical input to neural circuits, calcium dyes, such as G-CaMP3, provide optical output from neural circuits, by activating flourescent proteins when calcium is present. The Ramanathan lab at Harvard has demonstrated simultaneous stimulation via optogenetics and readout via calcium dye, in *C. elegans*, to determine the functional relationship of certain neurons to other neurons.

5.3 Genetic mosaic

Although the Samuel lab at Harvard has developed a DLP-based targetting system for optically stimulating specific neurons, it is difficult to prevent this stimulation from affecting nearby neurons with optogenetic proteins expresed. One possible workaround is the FLP/FRT system of genetic mosaics, which causes the expression of a transgene in the descendants of only one cell during the development of the organism. It would be possible to sort out those mosaics in which exactly one neuron is labeled, and perform experiments on these to determine the effect of stimulating that single neuron on all the other neurons in the organism.