Computer Evolution of Chemotaxis in Model Nematodes

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The nematode worm *Caenorhabditis elegans* is a remarkable organism for behavioral neuroscience. Not only does this millimeter-long soil-living animal exhibit a rich behavioral repertoire (including withdrawal reflexes, crawling, swimming, a variety of taxes, social feeding, egg-laying, habituation and associative conditioning), but it does so with a nervous system containing only 302 neurons, for which the anatomical connectivity is completely known from serial section electron microscopy [White et al., 1986]. Despite the small size and pressurized body of *C. elegans*, progress is also being made on electrophysiological analysis of its nervous system using genetic and developmental manipulations, optical imaging, and whole-cell patch-clamp techniques [Schäfer, 2006]. However, we are still a very long way from knowing even which of the over 6,000 synaptic connections that make up this nervous system are excitatory or inhibitory.

A recent paper by Izquierdo and Lockery [2010] in the *Journal of Neuroscience* demonstrates a new way to use computational techniques to compensate for missing electrophysiological data. The paper focuses on a model of salt klinotaxis, a recently-discovered form of chemotaxis in *C. elegans* in which orientation is continuously adjusted along a line of steepest ascent in a salt gradient [Iino and Yoshida, 2009]. The environment is modeled as a static cone-shaped gradient of salt concen-

tration. Since each segment follows the one in front of it during sinusoidal locomotion, the nematode body is represented by head location and velocity, with head direction controlled by the action of 2 opposing neck muscles. Finally, the model neural circuit consists of 2 chemosensory neurons and 2 neck muscle neurons, each representing identified classes of neurons in *C. elegans*, whose synaptic connections are consistent with the known anatomical connectivity. This circuit is driven by a sinusoidal oscillation representing the nematode locomotion system.

In order to set the electrophysiological parameters of the neural circuit model, an evolutionary algorithm was used. An evolutionary algorithm is a search technique loosely based on biological evolution [Mitchell, 1998]. A search begins with a random population of genetic strings that encode the unknown phenotypic characteristics of interest (here, the parameters of the neural circuit model). Each individual is then assigned a fitness based on the quality of its performance on the given task (here, the chemotactic success of the entire brain-body-environment model averaged over multiple trials). Individuals are then selected to serve as parents for the next generation with a probability related to their fitness. From the selected parents, a new generation of children are then produced by randomly swapping portions of 2 parents (crossover) and making small modifications (mutation). Once a new

population has been constructed in this manner, the entire process of evaluation, selection and reproduction repeats until the population converges on highly fit individuals.

Using this approach, a set of 100 model nematodes were evolved, 77 of which were particularly successful and robust. These models utilized a klinotaxis strategy whose features were qualitatively identical to those observed in the worm, even though this was not explicitly selected for during evolution. Interestingly, within the set of evolved networks, 2 distinct network motifs could be identified which differed by the pattern of excitation and inhibition among a set of electrophysiological parameters. In both motifs, the nonlinear responses of the motor neurons were utilized to achieve a state-dependent sensory response asymmetry necessary for the asymmetric turning that is characteristic of klinotaxis, but in somewhat different ways. In addition, analysis of the evolved neural circuits led to an understanding of the mechanisms of orientation which, among other things, can explain the observed effects of ablating 1 class of chemosensory neurons in the worm (an effect that the model reproduces) [Iino and Yoshida, 2009]. Finally, the model makes testable predictions regarding the effect of activating chemosensory cells on path curvature and additional consequences of ablating these sensory neurons for trajectory shape and chemotactic reliability.

One sometimes hears the argument that there is not yet enough data available to begin modeling some biological system. However, as Izquierdo and Lockery's work clearly shows, modeling can play a vital role at any stage of understanding. Of course, many things have been left out of this preliminary model. For example, it does not yet incorporate interneurons that are known to mediate between chemosensory and neck motor neurons, nor does it explain how the klinotaxis circuit is neurally integrated into the locomotion

and klinokinesis circuits. But this model does suggest a plausible mechanism by which klinotaxis might operate in *C. elegans*, and it makes a number of experimentally testable predictions. Evolutionary algorithms are particularly well-suited for this kind of modeling because they can be used to explore the space of possible models that are consistent with the known anatomy, physiology and behavior, 'filling-in' for currently missing data in a variety of plausible ways. Analysis of such an ensemble of models can then lead

to general insights and focus the design of crucial experiments that distinguish between the different possibilities. Indeed, evolutionary approaches are increasingly being employed in behavioral neuroscience and related areas, including studies of locomotion [Beer et al., 1999; Bryden and Cohen, 2008; Ijspeert, 2001], neuromodulation in *Aplysia* [Deodhar and Kupfermann, 2000], path integration in ants [Vickerstaff and Di Paolo, 2005], and even selective attention in humans [Ward and Ward, 2008].

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