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MODELING CHEMOTAXIS IN THE NEMATODE *C. elegans*

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ABSTRACT

To elucidate the neural mechanisms of chemotaxis in the nematode C. elegans, we constructed a model based on the anatomically defined neural circuitry associated with identified chemosensory neurons. The model combines the temporal derivative of chemosensory input with an internal representation of behavioral state to produce a duty-cycle controller of head angle during swimming movements. The model reproduces observed chemotactic behavior and suggests that separate control circuitry is required when moving up as opposed to down the concentration gradient.

The problem of the neural basis of chemotaxis in *C. elegans* raises important issues in sensorimotor integration. The exposed tips of its chemosensory neurons are too close, and at the wrong orientation during locomotion, for the animal to take an instantaneous spatial derivative of concentration [1]. Rather, it is believed the worm computes the temporal derivative of concentration, a task containing an inherent memory component. Moreover, the behavioral significance of the temporal derivative depends upon the action performed at the time the derivative is computed. Derivative information must be integrated with behavioral state to compute the correct response.

As a first step in understanding the neural basis of chemotaxis in *C. elegans*, we analyzed the anatomical circuitry database [2] for connections that could contribute to this behavior. For simplicity, we focussed on the pathways from the chemosensory neuron ASER, whose ablation produces the greatest deficit in chemotaxis [3], to motor neurons projecting predominantly to either dorsal or ventral muscles. ASER connects directly to 11 first-order sensory and interneurons which connect in turn to

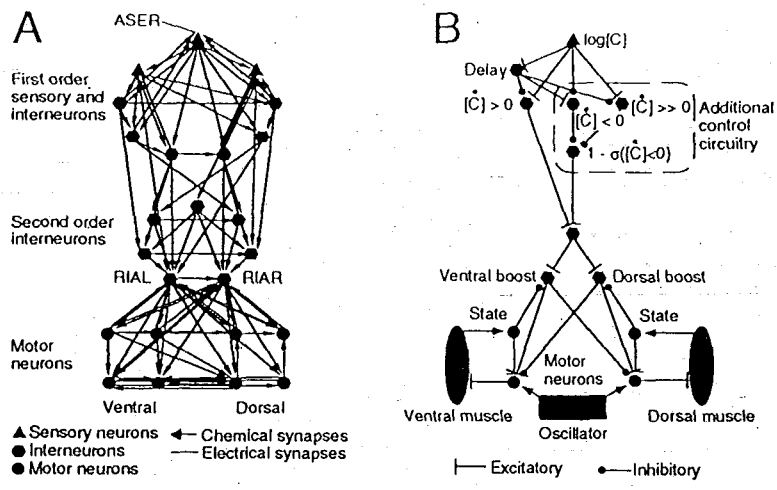

Figure 38.1. A. Anatomically defined connections from a chemosensory neuron (ASER) to motor neurons innervating dorsal or ventral muscles of the head and neck. The connections shown are those mediated by interneurons RIAL and RIAR, which uniquely connect to both dorsal and ventral motor neurons. Sensory neurons are shown as triangles, interneurons as hexagons, and motor neurons as circles. Lines with arrows indicate chemical synapses; lines without arrows indicate electrical synapses. B. Neural network model based on the anatomical connections in A. In Model 1, the derivative of concentration is computed by the unit labeled $\dot{C}>0$, which receives direct and delayed input from the chemosensory neuron. The derivative is combined with behavioral state by the dorsal and ventral boost neurons, which provide duty-cycle control of head movements driven by an oscillator. Model 2 is similar to Model 1 except that additional control circuitry (dashed box) has been added for moving down the gradient.

an additional 22 second-order interneurons. Two first-order and 10 second-order interneurons make direct connections to dorsal or ventral motor neurons. Chief among these are interneurons RIAL and RIAR which are presynaptic to 8 and 7 motor neurons, respectively, and are unique in contacting both dorsal and ventral motor neurons. Restricting the analysis to the motor effects of these interneurons yields a simplified circuit (Fig 38.1A) with 8 first-order neurons that have connections to RIAL, RIAR, or the 5 second-order interneurons presynaptic to them.

A simple yet plausible model for chemotaxis in *C. elegans* assumes the normal oscillatory swimming movements of the head are biased in the direction of increasing attractant concentration. To explore this possibility, we constructed a model worm having a head and tail joined by a single flexible segment. The area of the flexible segment is constant, representing the constant volume constraint imposed by the hydrostatic skeleton of the worm. Head angle is controlled by muscles, represented as spring-dash pot systems, on either side of the flexible segment. Rather than model the biomechanics of sinusoidal swimming movements in detail [4], we

assume a constant and appropriately scaled tangential velocity in the direction given by the head angle. The muscles receive out-of-phase sinusoidal inputs resulting in characteristic, quasi-sinusoidal swimming movements whose amplitude matches those of previously published worm tracks [1].

The purpose of Model 1 was to determine whether swimming movements could be biased appropriately by a simple neural network (Fig. 38.1B) that computes the temporal derivative of attractant concentration and integrates this information with behavioral state. The model was constrained by the connections in the biological network (Fig. 38.1A). Neurons were represented as single electrical compartments with a sigmoidal synaptic transfer function [5] and a realistic time constant (10 ms) derived from anatomical measurements of typical *C. elegans* neurons [6] and standard values for specific membrane capacitance and resistivity [7]. The derivative was computed using a three-neuron circuit that takes the difference between the current chemosensory input and a delayed version of the same signal. Direct and delayed sensory inputs are a common feature of first-order interneurons in the biological network. Behavioral state was represented by a stretch receptor on each side of the model. However, other representations of behavioral state such as motor neuron activity would serve as well. Derivative and state information were integrated by dorsal and ventral boost neurons. RIAL and RIAR are candidate boost neurons.

Model 1 operates as a duty cycle controller of head angle. For example, if the derivative is made positive by a head sweep to the dorsal side, the ventral boost neuron is inhibited while the dorsal boost neuron is excited. The main effect of exciting the dorsal boost neuron is to inhibit the contralateral motor neuron. This delays the next contraction on the ventral side, shifting the duty cycle of head sweeps in favor of the dorsal side (Fig. 38.2A), resulting in movement biased toward higher attractant concentration. Each boost neuron also excites the ipsilateral motor neuron, but this effect is comparatively small relative to contralateral inhibition.

Model 1 orients successfully as it approaches the center of the gradient (the "x" in Fig. 38.2B), then fails in an instructive way. As it moves away from the center the amplitude of its swimming movements is reduced, and it never turns back toward the center. Analysis of the problem revealed that the primary source of derivative information is not the side-to-side head movements, but simply the forward motion through the gradient. This means that as the model worm moves away from the center of attractant the temporal derivative of concentration is strongly negative and three-neuron derivative circuit, which is specifically tuned for positive derivatives, is shut down.

The failure of Model 1 when moving away from the center of the gradient was corrected in Model 2 by additional circuitry that takes over when the overall derivative is negative. Model 2 includes a neuron that responds only when the derivative is negative ($\dot{C}<0$, Fig. 38.1B). The output of this neuron is subtracted from the activity of a neuron with a strong positive bias ($1-\sigma(\dot{C})<0$). The result is a pathway

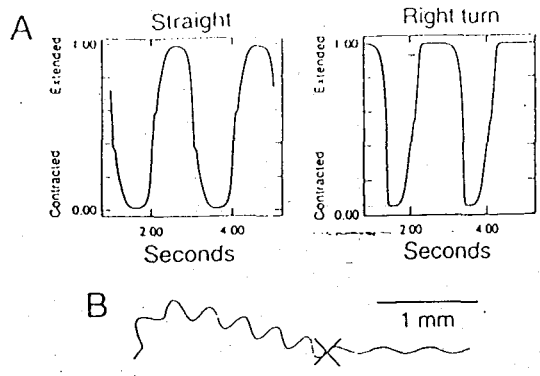

Figure 38.2. A. Duty-cycle control of orientation. The state of the left muscle in the model network is shown during straight-ahead movement (top) or a right turn (bottom). Straight-ahead movement involves a 50% duty cycle. In turns, however, the extension phase is longer on the side opposite the turn. B. Chemotaxis of Model 1 in response to a gradient centered at the "x". The model passes through the center of the gradient, but fails to turn back. This problem was solved in Model 2 by additional control circuitry.

that detects the direction in which the derivative is decreasing most slowly, the appropriate control signal when the overriding derivative is negative. Balance between the positive and negative derivative pathways is achieved by a neuron that shuts off the negative pathway when the derivative is strongly positive ($|\dot{C}| >> 0$). Thus, chemotaxis in this system uses separate control circuitry for moving up and down the gradient, and a means of switching between these circuits.

With its additional control circuitry, plus noise added to each neuron, Model 2 successfully reproduces chemotactic behavior in a variety of conditions (Fig. 38.3). First, in the presence of a gradient model worms, like the real ones, swim toward the center of the gradient and hover there for extended periods. Second, in the absence of a gradient, the animals wander in confined regions. Finally, with the addition of a bias in head angle, the model reproduces the spiraling trajectories of a strain of worms in which the head is permanently bent to one side.

These preliminary models provide the basis for construction of more realistic models of *C. elegans* chemotaxis. The high degree of convergence and divergence of both sensory and motor information suggested by the anatomical circuitry (Fig. 38.1A) points to a distributed processing mechanism for the integration of sensory and motor state.

Using neural network training algorithms like backpropagation [8], such a model can now be constructed by optimizing a model with the anatomically correct connections to reproduce the sensory and motor neuron activity produced by Model 2 as it successfully negotiates the gradient. This procedure can be expected to reveal novel means of computing the derivative of chemosensory information. Moreover, it

provides a theoretical basis for the interpretation of experiments in which identified chemosensory neurons and interneurons are ablated in living worms.

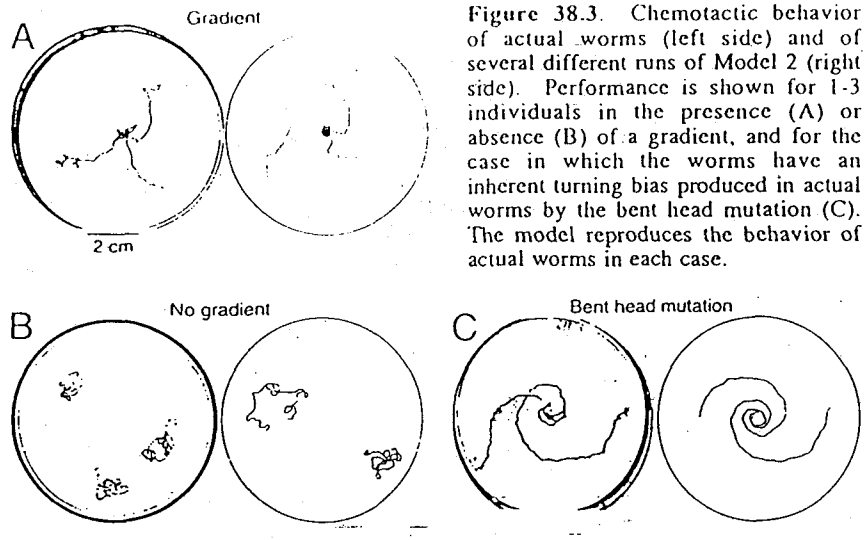

Figure 38.3. Chemotactic behavior of actual worms (left side) and of several different runs of Model 2 (right side). Performance is shown for 1-3 individuals in the presence (A) or absence (B) of a gradient, and for the case in which the worms have an inherent turning bias produced in actual worms by the bent head mutation (C). The model reproduces the behavior of actual worms in each case.

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