Evolution and analysis of minimal neural circuits for klinotaxis in *Caenorhabditis elegans*
Overview

Spatial orientation is one of the most fundamental adaptive behaviors in motile organisms.

*C. elegans* performs a diverse set of orientation behaviors, including chemotaxis to tastants, odors, osmolarity, electrotaxis, thermotaxis, etc.

Nearly all work on *C. elegans* chemotaxis was based on *klinokinesis* (biased random walk).

Recently, Iino and colleagues have described a complementary strategy, called *klinotaxis*.

This work combines neural network modeling and evolutionary algorithms to identify simple circuit motifs for klinotaxis. It then uses dynamical systems analysis to understand how they function.
C. elegans as a model organism

Compact nervous system, with 302 neurons.

Full anatomical connectivity known.

Amenable to genetic manipulations and electrophysiological analysis.

Microfluidics and fluorescent proteins are allowing freely-moving worm recordings.

Neurons do not fire, they display graded potentials.

Body and locomotion are well understood.

Large behavioral repertoire, including several forms of learning.
Chemotaxis in *C. elegans*

*C. elegans* chemotaxis is based in part on a biased random walk.
Recent finding

The worm curves during forward locomotion in the direction of the peak.
Constraints

Muscular contraction initiated at the neck travels posterially. Each body segment follows the one anterior to it.

Pair of sensory cells detect changes in attractant concentration (ON, OFF cells).

Dorsal / ventral symmetry.
Theoretical challenge

attractant peak

worm

State-dependence.
Computational neuroethology approach

Idealised nervous system and body

Population

Behavioral assay on idealised environment

Recombination

Mutation

Dynamical system analysis of successfully evolved networks
Idealized nervous system

Pair of sensory cells detect changes in attractant concentration:

\[ D(t) = c_N(t) - c_M(t) \]

Two neck motor neurons (RMD), modeled as CTRNN nodes.

\[ \tau \frac{dy}{dt} = -y + w_s \sigma(y + \theta) + I(t), \]

Oscillatory element driving sinusoidal body waves (but no CPG assumed).

The network is bilaterally symmetric across the dorsal/ventral dimension.

No interneurons.
Turning is proportional to the difference between the two neck motor neurons.

\[ \phi = \frac{d\mu}{dt} = w_{\text{NMJ}}(\sigma(y_D + \theta) - \sigma(y_V + \theta)) + \zeta, \]

Constant speed.

The path must contain convex and concave curvatures, otherwise speed drops.

White noise on the turning.
Idealized environment

Conical chemical gradient, not Gaussian.

Fixed initial distance away from peak.

Random steepness.

Random initial orientation.

Neural activity initialized to random values.

Worm allowed to crawl for 500 secs.

Orientation changed at random with some probability.

Each individual tested 50 times.

\[ I^{che} = 1 - \left( \frac{1}{T} \int_0^T \frac{d(t)}{d_i} dt \right) \]
Results

Gradient shape

<table>
<thead>
<tr>
<th></th>
<th>Conical</th>
<th>Gaussian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotaxis index (CI)</td>
<td>0.88 ± 0.005</td>
<td>0.87 ± 0.007</td>
</tr>
<tr>
<td>Reliability (%)</td>
<td>99.99 ± 0.01</td>
<td>99.94 ± 0.25</td>
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Klinotaxis

Model

Worm

Turning bias (degrees)

Average curving rate (deg/mm)

Bearing (degrees)
Evolved network motifs

8D parameter space.

Two distinct clusters:
- Biases have different sign.
- Weights from sensor to motor neurons also have different sign.

Sensory neurons with opposing sensitivities always had antagonistic synaptic effects.

The magnitude of the OFF weight was on average 3 times stronger.

The self-connection was always less than 4, which meant motor neurons were not bistable.
Two parameters define the dynamics of the sensors.

No systematic relationship between motifs and sensory dynamics.

On average, reaction times were around the duration of a head sweep.

Turning bias modulated within an individual head sweep.
Dynamical systems analysis, step by step.

1

2

3

4

\[ [0.1, 1.0] \text{ mM} \]
Strategy

Given that turning angle is proportional to the difference in motor neuron output, we arrive at an extremely simple strategy:

**ON cell activation reduces turning angle.**

**OFF cell activation increases turning angle.**

Interestingly, the exact same simple strategy applies to both Motif 1 and 2, despite the anatomical differences.

How do those simple rules at the level of the internal dynamics lead to klinotaxis when embodied and situated?
Brain-body-environment interaction

1. Sensory response lasts around an individual head sweep.
2. ON reduces turning; OFF increases it.

Orientation response to single stepwise changes in concentration at key phases of the locomotion cycle.

The instantaneous velocity vector at the time of an upstep signals the direction of the implied peak.

Points b and d exemplify how crucial the duration of the sensory dynamic is.
Generalized strategy

1. Turning response is a sinusoidal function of where in the locomotion cycle the step occurs.

2. The amplitude of the orientation response is proportional to the amplitude of the concentration step.

3. The worm’s response to a downstep of a given size is greater than the response to an upstep of the same size.
Revisiting the theoretical challenge

Identical chemosensory signals sent simultaneously to dorsal / ventral motor neurons.

Effects are asymmetrical, allowing dorsal or ventral turning bias.

Three key principles:

1. Biased motor neurons.
2. Antagonistic synaptic connections from sensory neurons to motor neurons.
3. Timing of sensory dynamics related to head-sweep duration, such that it cancels out at the appropriate time.
Ablation study

Model

Worm

Normal weights

Chemotaxis Index

Control
ASEL ablation
ASER ablation
Joint ablation

no gradient
N2
sham ablation
ASEL ablation
ASER ablation
RIA ablation
ttx-3
AIZ ablation
AIZ ablation
The role of the ON and OFF cells

The reason for the difference in the behavioral effect is not due to the OFF cell being more strongly connected to the motor neurons than the ON cell.

The functional asymmetry cannot be fully deduced from the individual components of the network.
The role of the environment on the role of the ON and OFF cells

A simple geometrical argument is sufficient to account for the difference in effectiveness of the ON cell and OFF cell during klinotaxis.
C. elegans chemotaxis specific predictions

1. Neck motor neurons need not be bistable.

2. Interneurons could be acting as passive conduits of activity.

3. Model suggests an antagonistic pathway between sensory and neck motor neurons.

4. ON/OFF cell activation during forward locomotion should reduce/increase the worm’s curvature (respectively).
   4a. Turning should be sinusoidal function of locomotion phase.
   4b. Turning should be bigger for OFF than for ON cell activation.

5. In ablation studies,
   5a. Worms without ON cells should reach the gradient peak reliably, and do so in long, spiral shaped trajectories;
   5b. Whereas worms without OFF cells should reach the peak infrequently, and do so with short, relatively straight trajectories.
Proposed mechanism and analysis may be useful in different *C. elegans* behaviors (e.g., thermotaxis, electrotaxis).

Model provides an example of the same mechanism from different network parameters.

Model provides an illustration of different roles for neurons depending on geometry of environment.

Example of how modeling can be used as a cheap and quick way to test the usefulness of an experiment.