Biophysical neuroscience

Neurons and Neural Networks

•Absorb information through sensory perception.

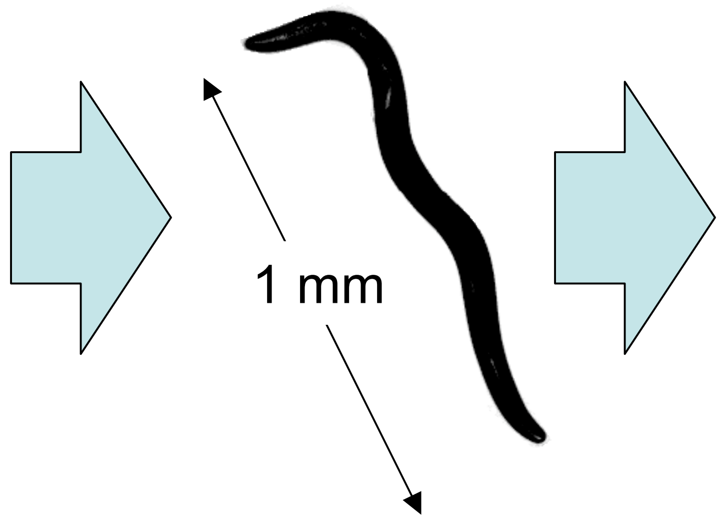
•Store information in long & short term memories

•Process information & calculate decisions

•Output behavioral responses through muscle and movement

Caenorhabditis elegans

Sensory input
- Taste
- Smell
- Touch
- Temperature
- Voltage



Behavioral output
- Movement
- Egg laying
- Feeding

How do neurons give rise to behavior?

Sensorimotor integration

Memory & experience dependent plasticity

Brain size

C. elegans

302 neurons

Mus musculus

~10^8 neurons

Rhesus macaque

~10^{11} neurons

Drosophila melanogaster

~10^4 neurons

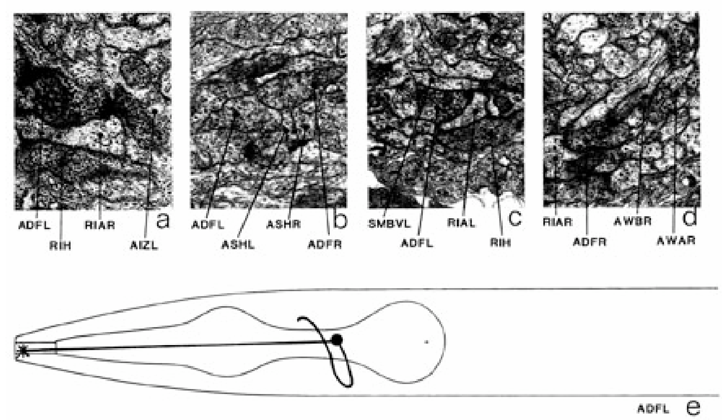
It's even worse:
Complexity grows combinatorically with brain size in wiring patterns of synaptic connectivity.

Wiring diagram

THE STRUCTURE OF THE NERVOUS SYSTEM OF THE NEMATODE *CAENORHABDITIS ELEGANS*

BY J. G. WHITE, E. SOUTHGATE, J. N. THOMSON AND S. BRENNER, F.R.S.

Serial section electron microscopy



Connectivity pattern

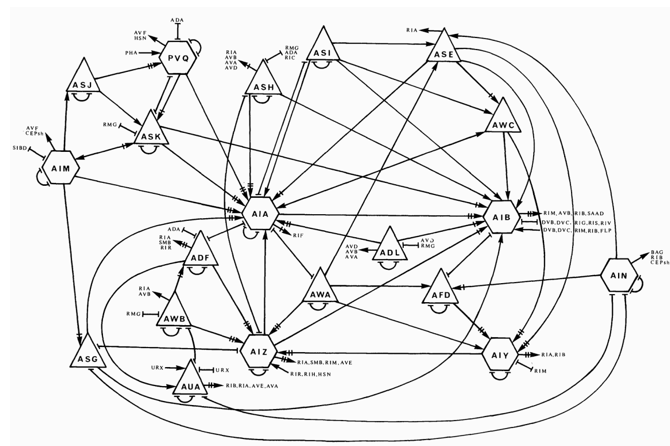


FIGURE 21. (a) Circuitry associated with amphids.

Strategy

Focus on movement responses to physical stimuli

Straightforward to quantify & automate

Establish patterns in behavior

Reduce behavior to specific rules

Find analogous patterns in neural structure and function

Manipulate neural connectivity

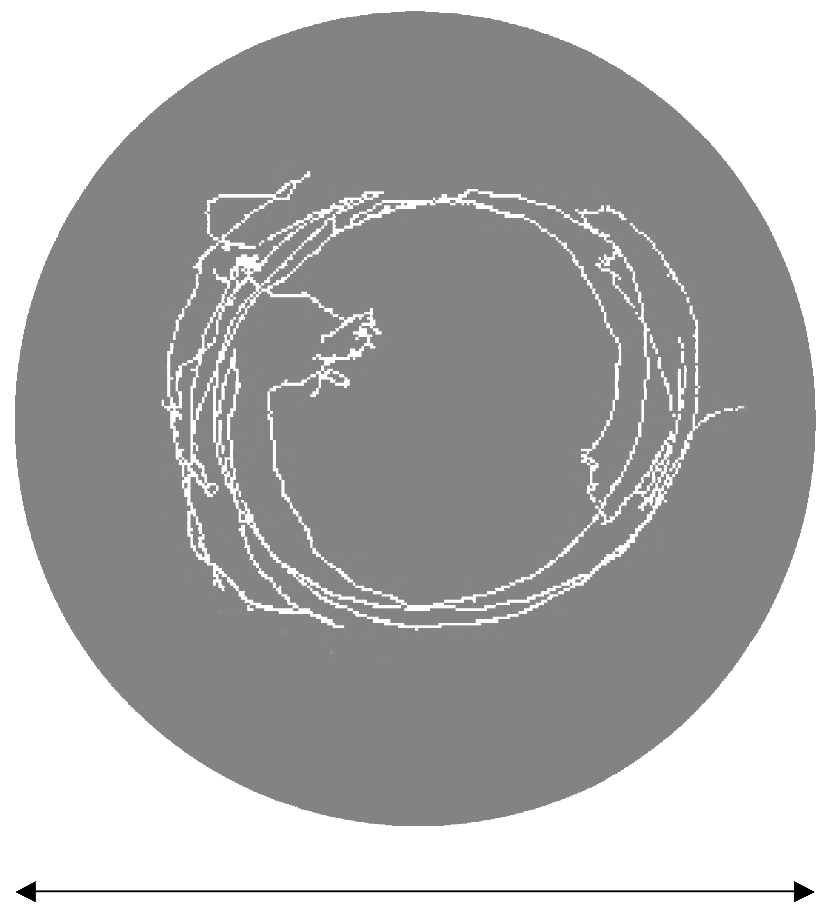
Monitor neural function

Long-term memory in thermotaxis

Associative learning between food and temperature.

Track of single worm grown overnight at 20ºC navigating radial thermal gradient that is 15ºC at center and 25ºC at edge.

Worm tracks isotherms near 20ºC

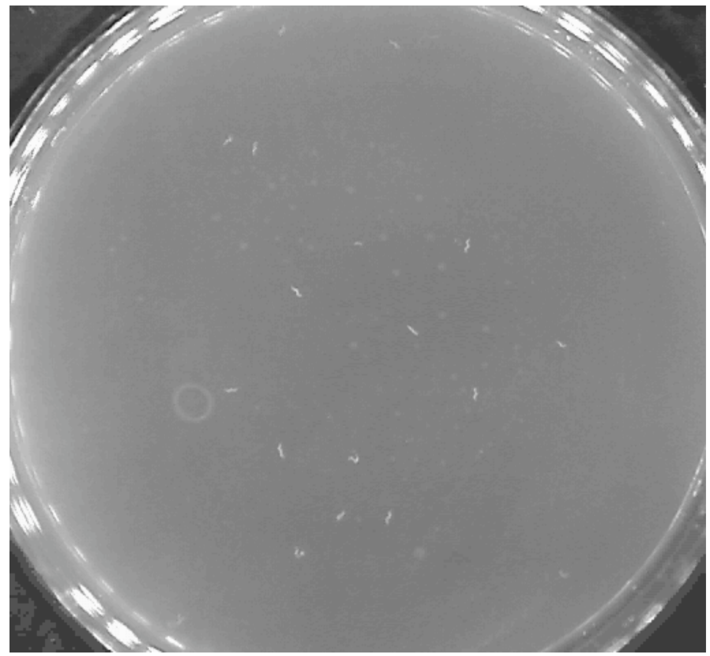


9 cm

Isothermal tracking

Worms
Young adult worms that had been cultivated overnight at 20ºC

Conditions
Linear spatial thermal gradient of ~0.5ºC/cm on NGM plate without food



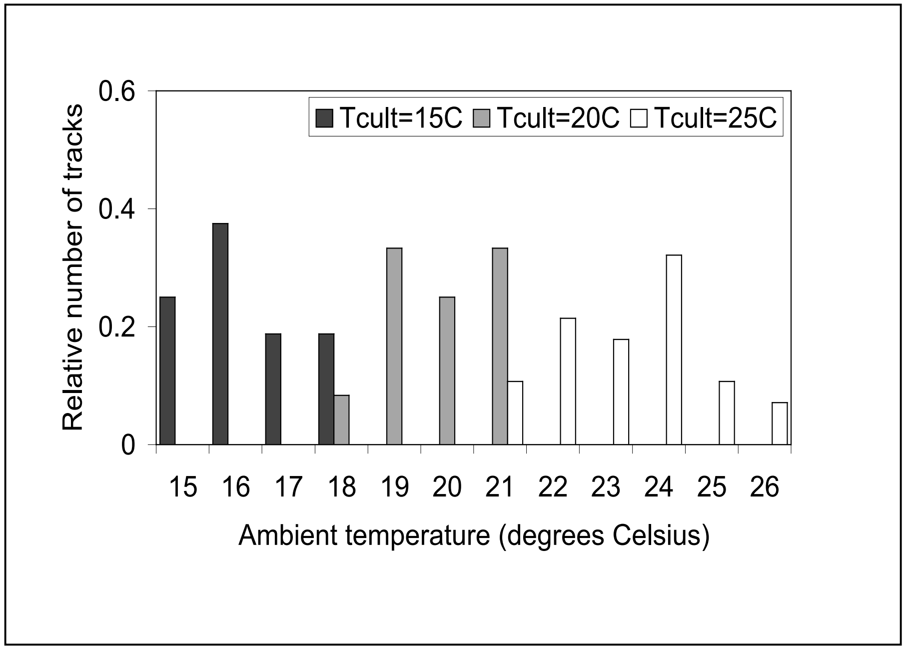
18ºC 20ºC 22ºC

Worms track isotherms near their cultivation temperature

Distribution of tracks is a measure of internal memory

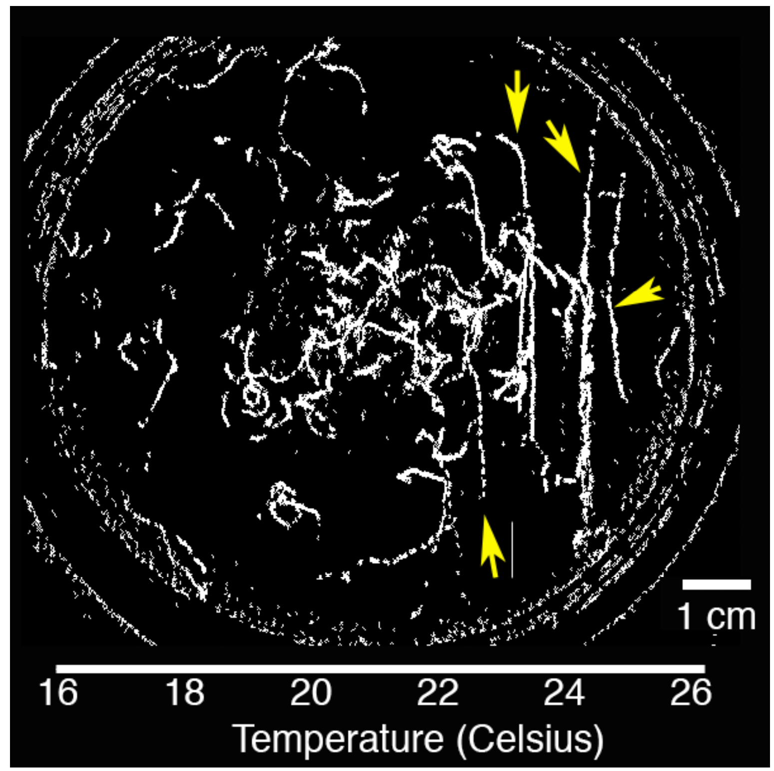
Cultivate worms overnight at 15, 20, or 25ºC

Record positions of isothermal tracks on linear spatial thermal gradients



Simple assay for thermotactic memory

- Impose linear thermal gradient on cultivation plate
- Record tracks for ~5 min
- Positions of tracks reveals thermotactic memory
- Return plate to incubator

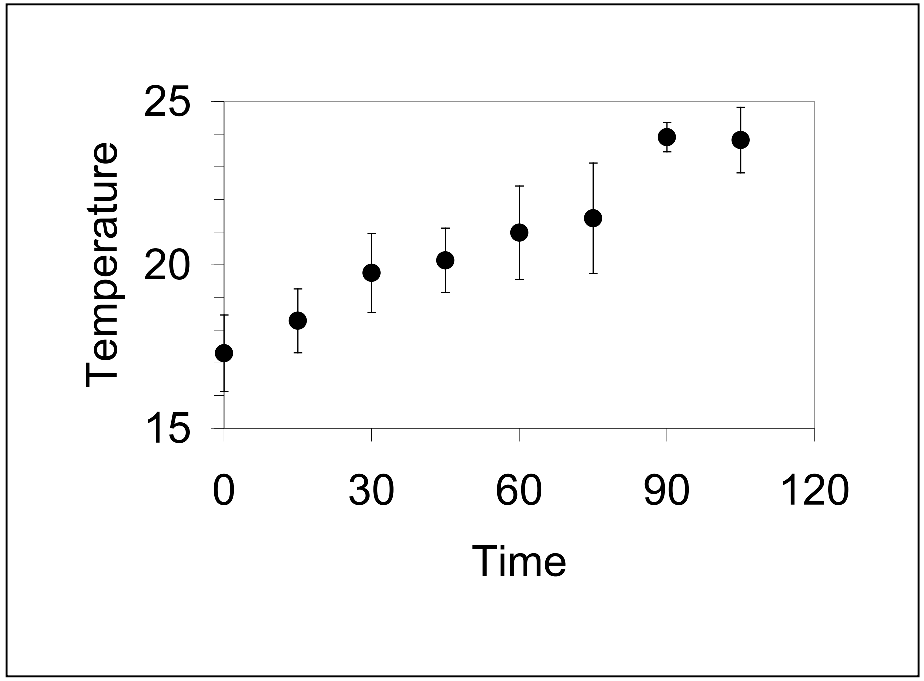


How quickly do worms learn?

Memory dynamics

UPSHIFT

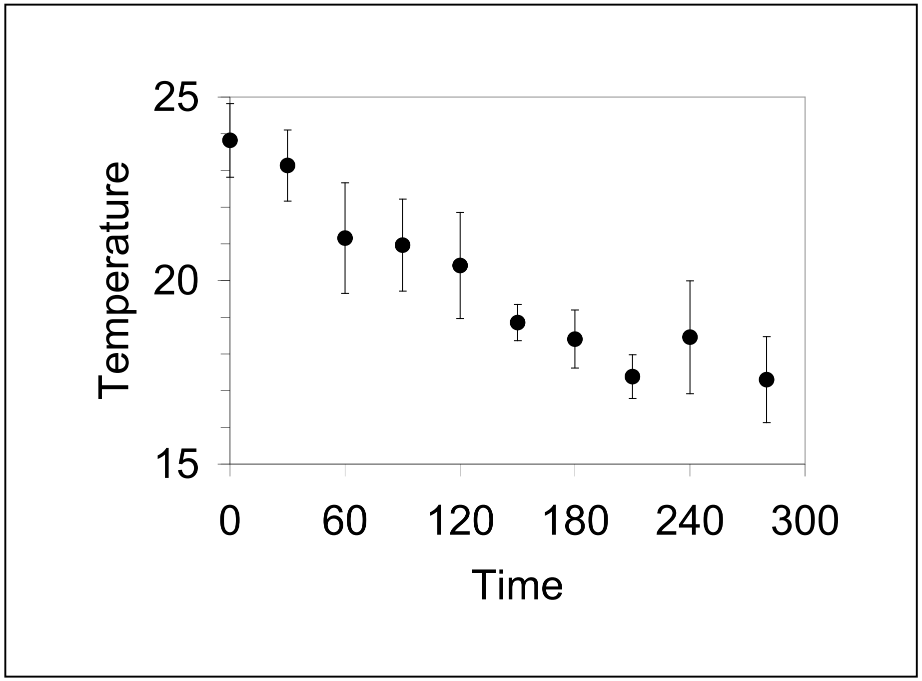
- Grow worms overnight at 15ºC
- At t=0, shift worms to 25ºC
- Positions of isothermal tracks at subsequent time intervals are measured



Memory dynamics

DOWNSHIFT

- Grow worms overnight at 25ºC
- At t=0, shift worms to 15ºC
- Positions of isothermal tracks at subsequent time intervals are measured



Memory dynamics

Cycling Temperature of Cultivation

Step 1: T_{cult}=15°C for $_{15ºC}$=5, 10 or 15 min

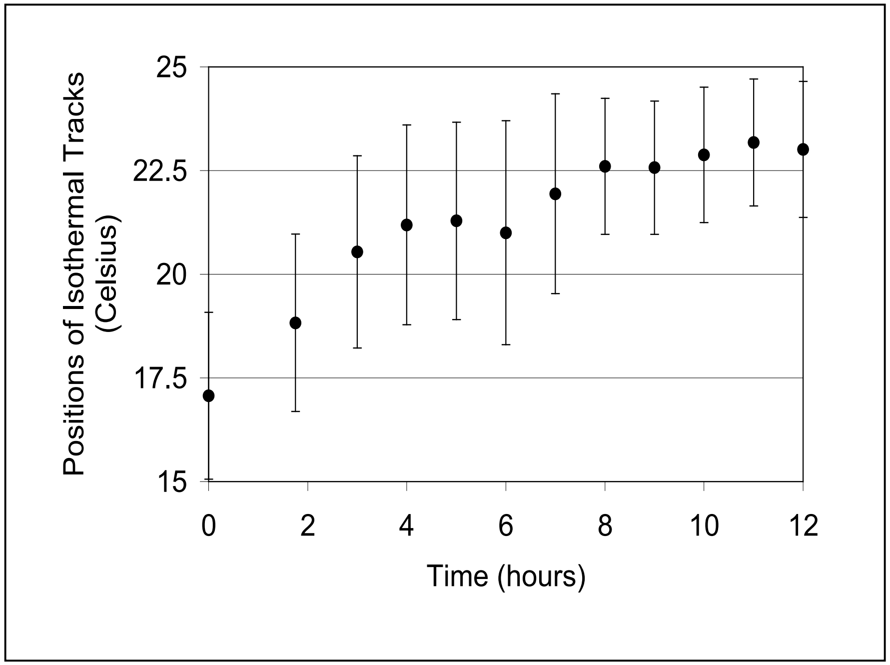
Step 2: T_{cult}=25°C for $_{25ºC}$=5 min

Step 3: Goto Step 1, continue overnight

$_{25ºC}$: $_{15ºC}$	Positions of tracks
1:1	21.4±1.4 C
1:2	20.7±1.0 C
1:4	19.1±1.0 C

Passive thermophilic drift

Grow worms overnight at 15ºC
At t=0, place on spatial thermal gradient from 15ºC to 25ºC with food
Measure positions of isothermal tracks at subsequent time intervals



Calculation of memory of cultivation temperature

Memory is single-valued.

Formed by an integral over time of measurements of ambient temperature while in the presence of food.

An integral has desirable properties for long-term memory: an accumulation of experience; insensitive to transients.

“Memory” neuron

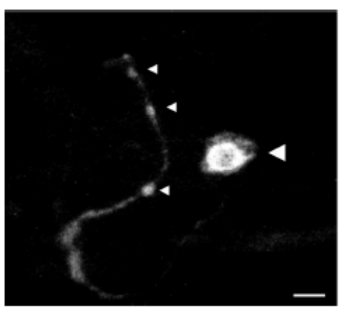
The Journal of Neuroscience, January 15, 2003 • 23(2):373–376 • 373

Brief Communication

Synaptic Activity of the AFD Neuron in *Caenorhabditis elegans* Correlates with Thermotactic Memory

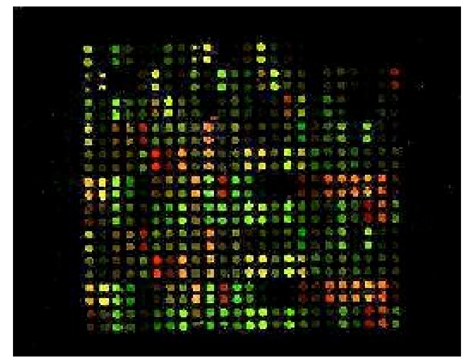
Aravinthan D. T. Samuel, Ruwan A. Silva, and Venkatesh N. Murthy
Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts 02138

Quantify synaptic activity using pH-sensitive GFP localized to synaptic vesicles



$T_{amb} > T_{cult}$	*ON*
$T_{amb} \sim T_{cult}$	*OFF*
$T_{amb} < T_{cult}$	*ON*

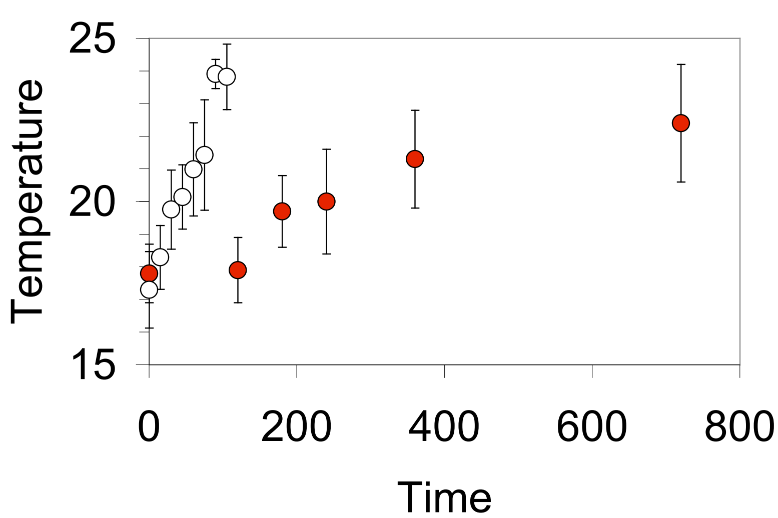
Single-celled DNA microarray analysis of AFD



dgk-3
diacylglycerol kinase

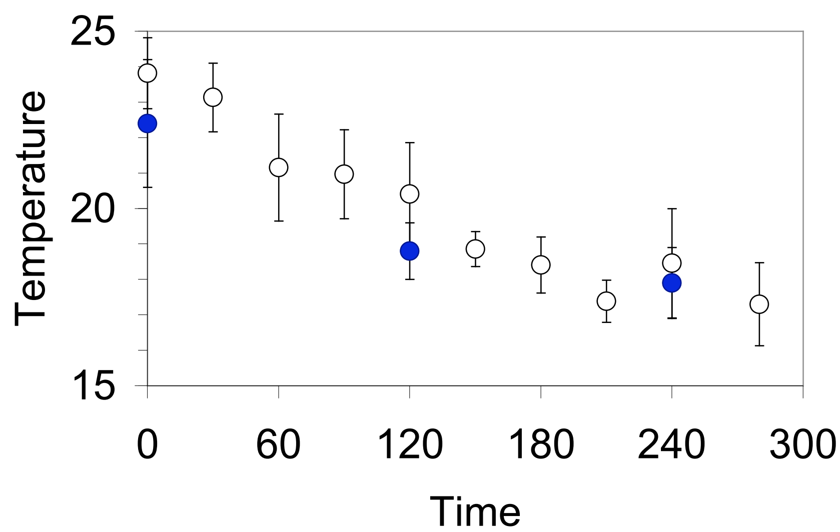
dgk-3: Learning mutant

UPSHIFT



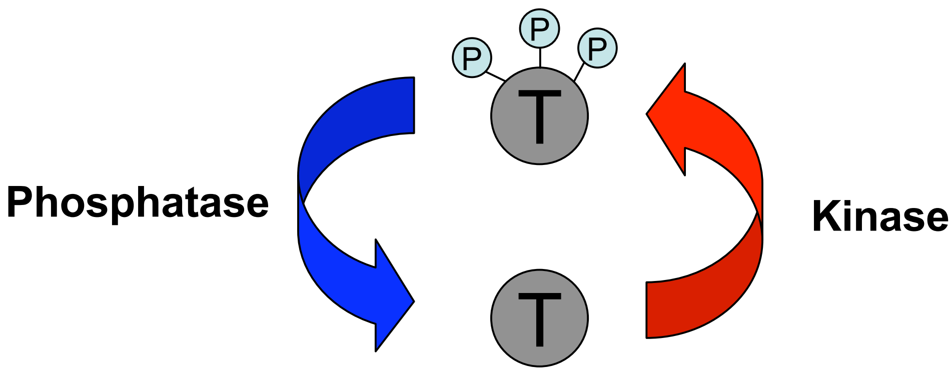
dgk-3 (red) learns 25C ~4x more slowly than wild-type worms (clear)

DOWNSHIFT

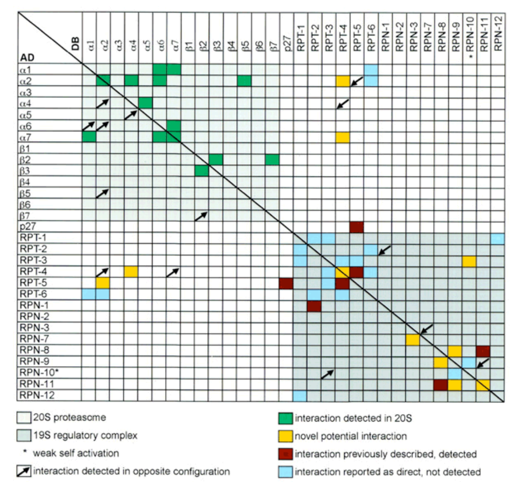


dgk-3 (blue) learns 15C as rapidly as wild-type worms (clear)

Memory tuning



Interaction map

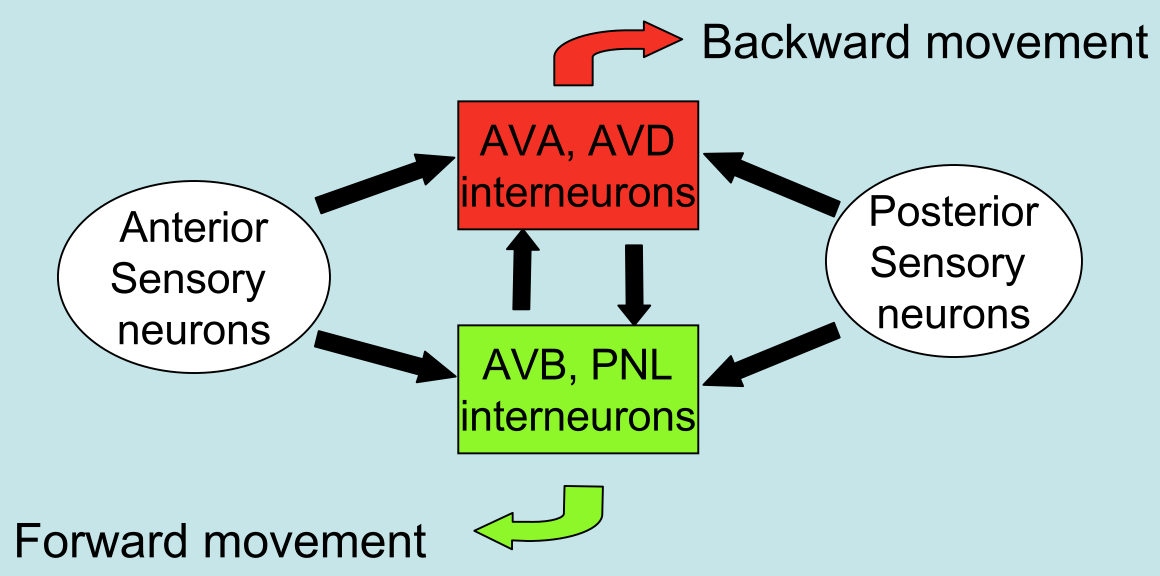


Mechanosensory behavior

Touch a worm's nose   Backward movement

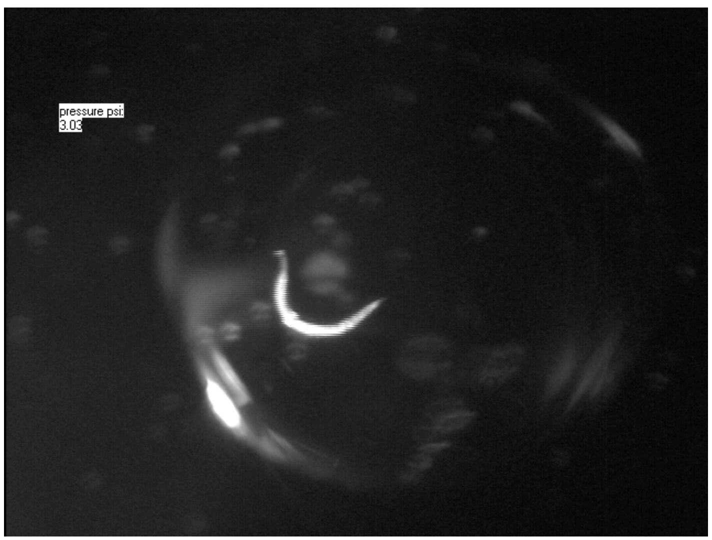
Tap a worm's tail   Forward movement

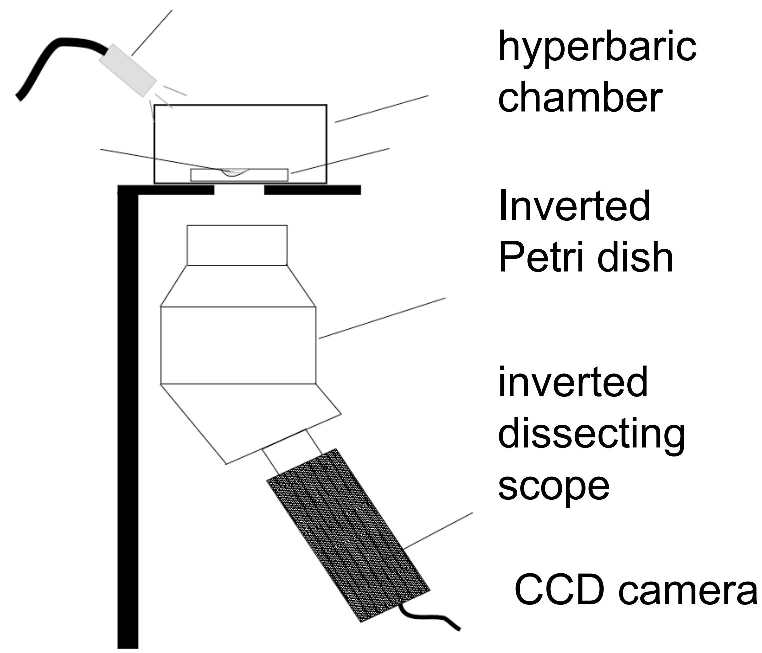
Reflex arc encoded in a well-studied neural circuit



What happens when you touch it all over at once?

Subject worm swimming in a microdroplet to variations in hydrostatic pressure

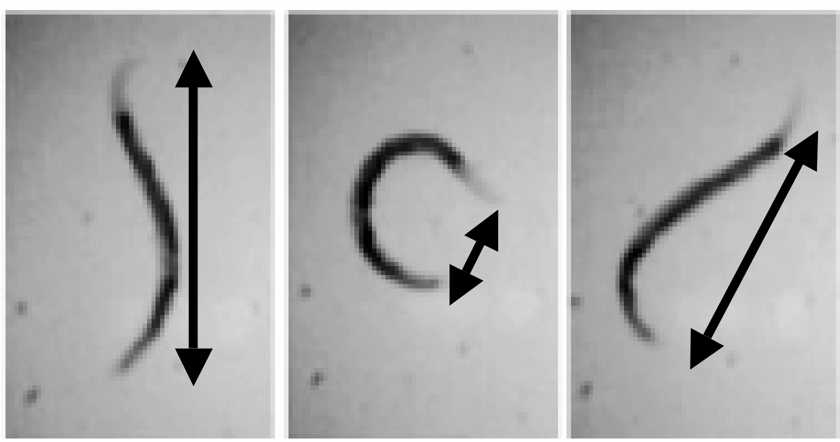




Behavioral analysis

Forward movement: End-to-end distance is large

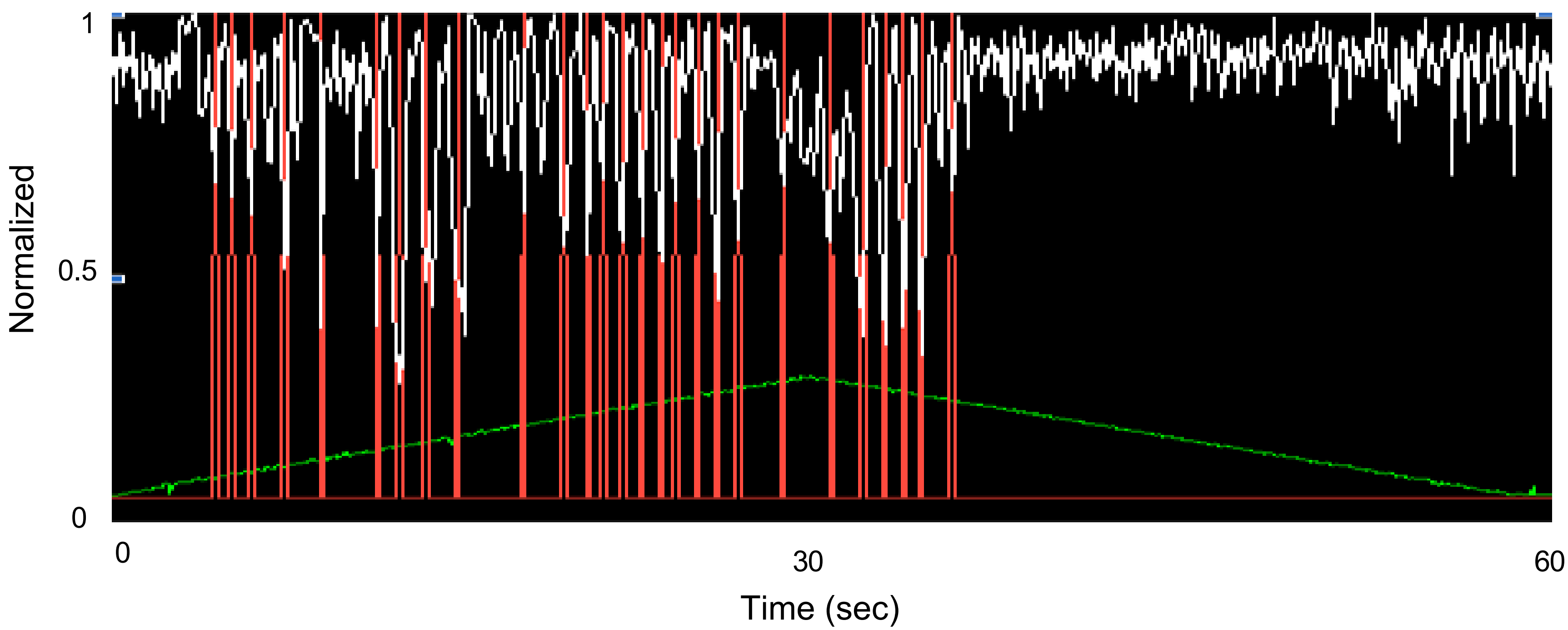
Backward movement and turns: End to end distance drops



Custom-written computer algorithm measures the end-to-end distance of a swimming worm in real-time

Raw Data

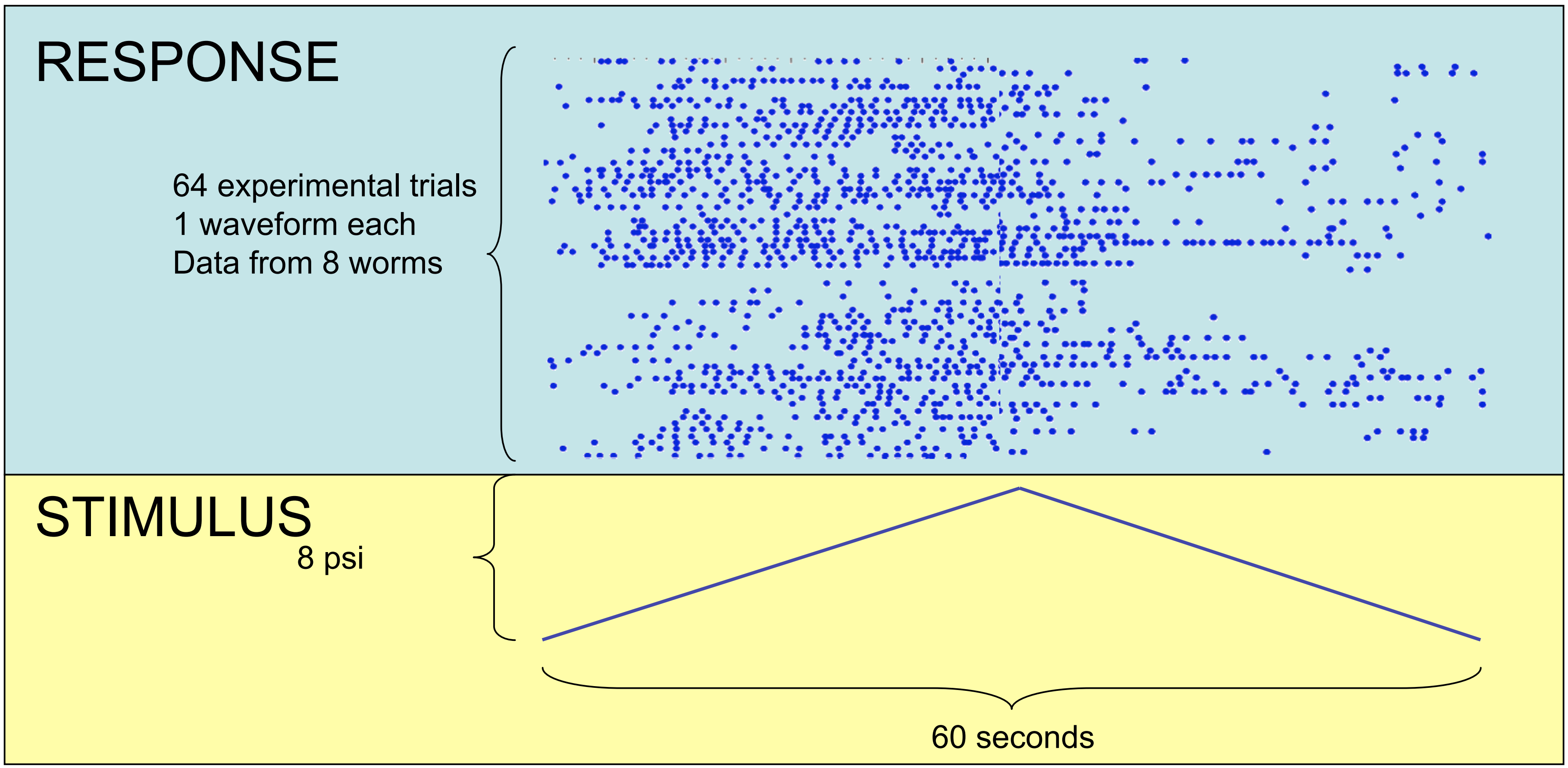
One waveform's worth of data of a cycling triangle wave stimulus (amplitude 8 psi, wavelength 60 sec)



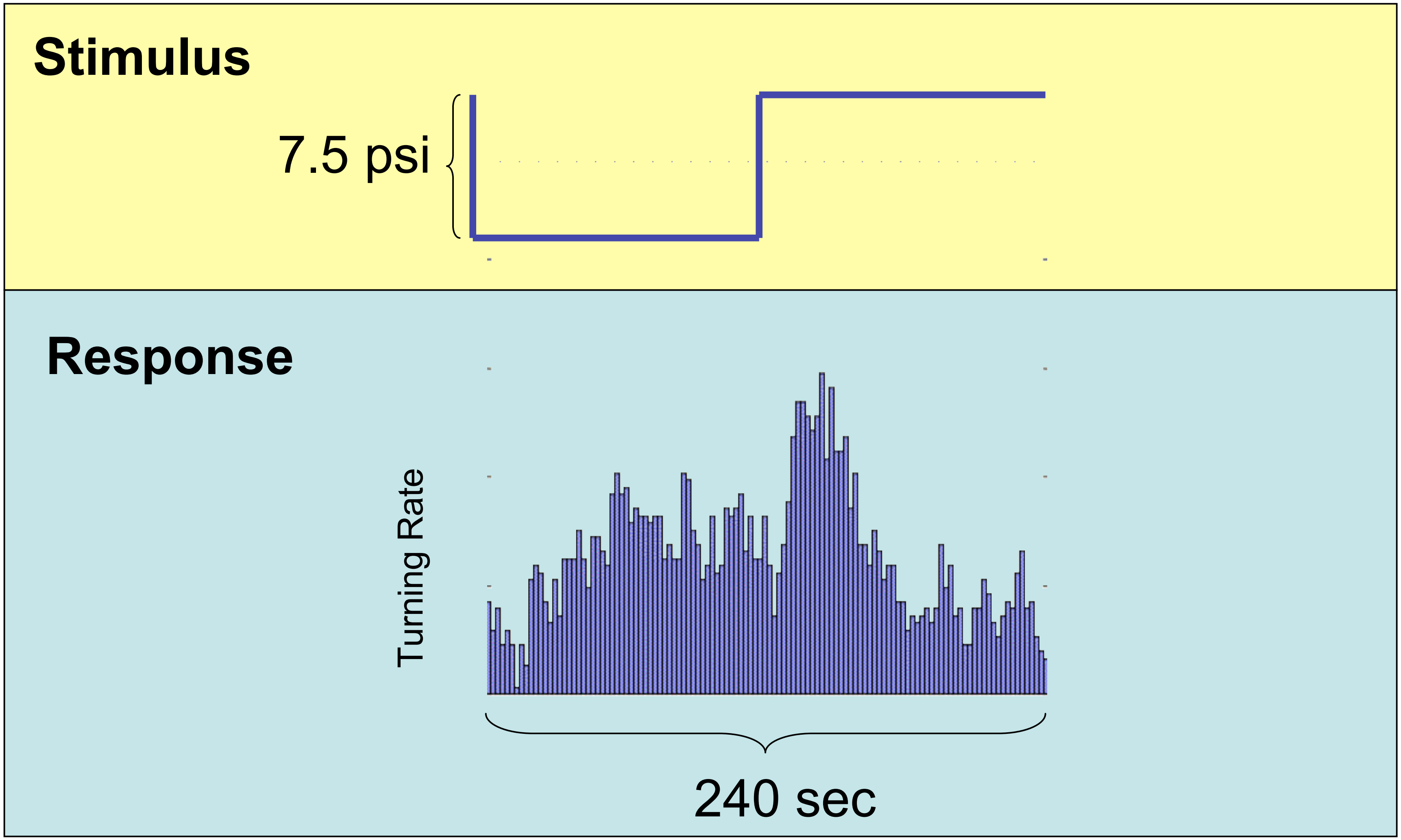
White = worm end to end distance
Red = turns flagged
Green = pressure stimulus

Behavioral analysis

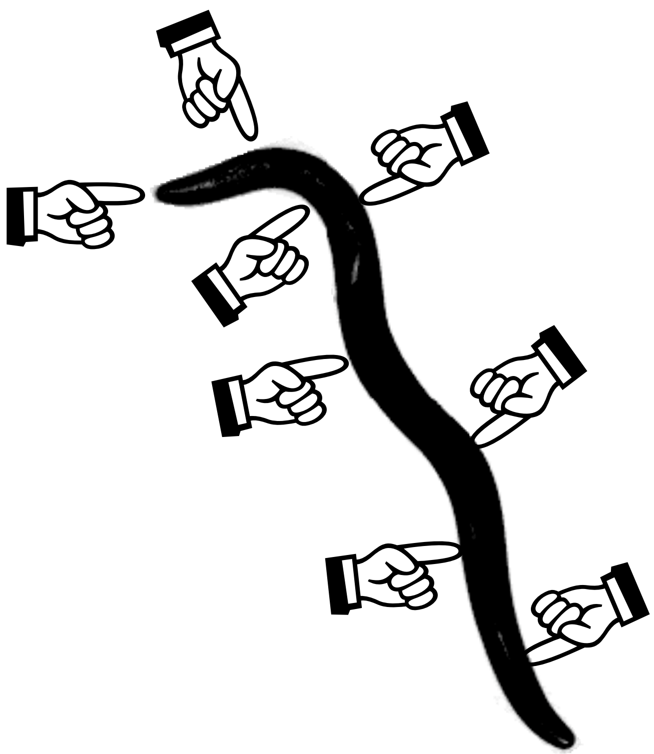
Raster Plot, The courses of each trial is distributed along the x-axis. Blue dots flag turns. Different trials are distributed along the y-axis



Square wave statistics



What does pressure *feel* like?



Pressure is *not* like being touched everywhere.

Water is nearly incompressible (150 atm gives 1% change in volume).

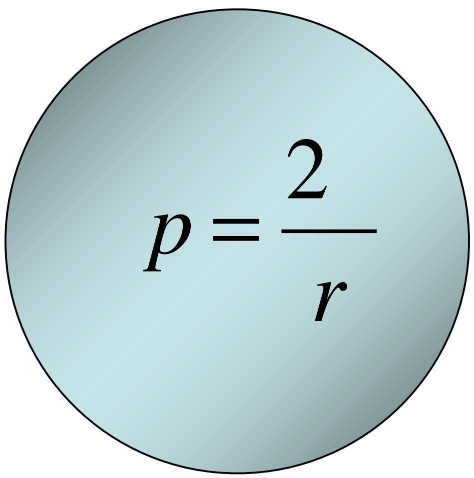
Gas is very compressible. Eardrums pop with changes in elevation.

Does the worm have ears?

Pressure & Tension

surface tension

r radius of curvature

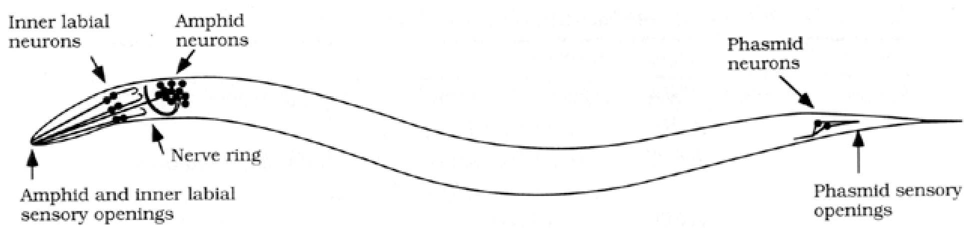


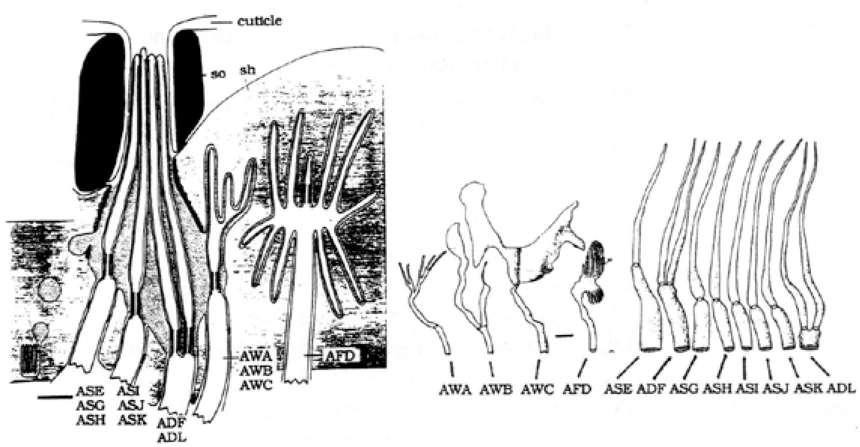
$$p = \frac{2}{r}$$

To measure pressure, all you need is a radius of curvature & a way to detect interfacial tension.

The worm is internally pressurized, so a sensor must be at the interface between inside and outside.

Amphid & Phasmid Neurons

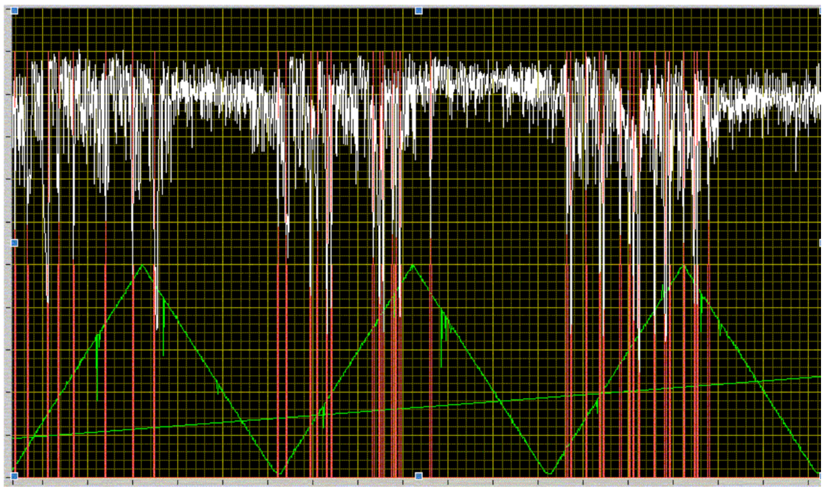




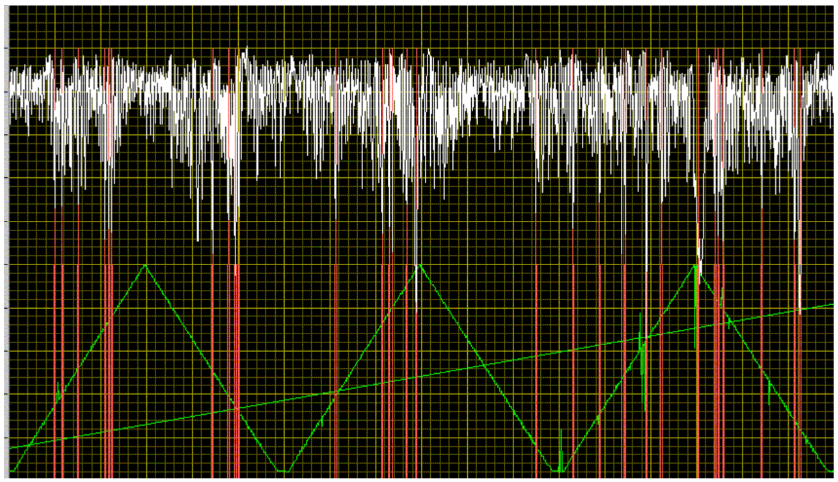
This family of sensory neurons contacts the external environment. The pressure gradient between the inside and outside of the worm must be held in membrane tension at the tips of the ciliary projections.

Popping their ears

Before sudden vacuum



After sudden vacuum



Now that we can pop their ears, perhaps we can find their ears.

Acknowledgments

HEPL
Chris Gabel (PD)
Damon Clark (G)
Alex Dahlen (U)
Ares Perides (U)
Steven Lin (U)

Brandeis
Piali Sengupta (PI)
Adam Brown (G)